The epidemiology of Legionnaires' disease in Switzerland: A re-emerging disease

Inauguraldissertation

zur

Erlangung der Würde einer Doktorin der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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Basel, 2024

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von
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Basel, 18. Oktober 2022

Prof. Dr. Marcel Mayor
Dekan der Philosophisch-
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Acknowledgements

Over the past years, I had the chance to cross paths with many great people, researchers, collaborators, and fellow students. Deepest thanks to all of you, who supported me during this rewarding experience.

First and foremost, I am deeply grateful to my supervisor Professor Daniel Mäusezahl for his guidance throughout my PhD. Your continued trust in me has enabled me to take on and overcome many challenges and grow professionally. I would like to thank my second supervisor, Professor Günther Fink, and the external examiner of this thesis, Professor Werner C. Albrich, for their support as part of my doctoral committee. Many thanks to Melina Bigler, who took over the *SwissLEGIO* project from me. Since you joined, I was happy to have gained an ally and to know that the project is in the very best hands. I would like to thank all colleagues that have joined our *SwissLEGIO* team for their work and enthusiasm to bring this large study to life. Furthermore, I thank all our collaborators within the *LeCo* project, specifically Franziska Rölli for our weekly discussions, and patience to explain me the ins-and outs of household plumbing systems. Moreover, to Dr. Timothy Julian and Dr. Frederik Hammes for their collaboration and expertise. I would also like to thank Dr. Valeria Gaia from the National Reference Centre for *Legionella* for always being approachable and our collaborations, starting with my first manuscript until *SwissLEGIO*. My thanks go also to Dr. Adrian Egli from the 'applied microbiology research lab' for the collaboration. I am very grateful to the Federal Office of Public Health for the funding of most of the studies in this thesis, and Marianne Jost, Mirjam Mäusezahl-Feuz, Dr. Sabine Basler, Nicole Gysin, Dr. Monica Wymann and Ornella Luminati, for many successful collaborations. My gratitude extends to the Federal Food Safety and Veterinary Sciences and Federal Office of Energy for funding part of the work presented in this thesis and various exchanges, in particular Dr. Françoise Fridez and Stefanie Bertschi. I would like to acknowledge our many partners, without whom *SwissLEGIO* would not be possible, particularly all the hospitals across Switzerland.

A special thanks to Giuliana Sanchez-Samaniego, who has been my PhD buddy at Swiss TPH from the start and has become a dear friend inside and outside the office. Many thanks also to Dr. Christian Schindler and Dr. Jan Hattendorf for being always available for statistical and practical advice. Many thanks to Danielle Vieanneau for introducing me to the world of spatial epidemiology and for her support. I'd also like to thank Eliane Kobel supporting me in all administrative issues with patience and kindness. Many thanks to all my colleagues at Swiss TPH for exchanges, collaborations, and great company! Specifically, to Aliya Karim, Carmen Sant Fruchtman, Claudia Schmutz, Doris Osei Afriyie, Jordyn Wallenborn, Marina Antillon, Maryam Tavakkoli, Michael Deml, Stella Hartinger and Tamsin Lee.

I would like to address a big thank you to my friends that have been with me during the last years; Tina, Tsering, Patrick, Alonso and Wanda. Many thanks to Apolline, for not only being a great scientist

but also friend. Laura, for unwavering friendship and for granting refuge in Ticino. Shannay, for ice cream, walks and companionship not just in the happiest of times. Sarah, for jointly letting of steam at the rock or over a glass of wine and letting me into the bus made of dreams. And my deepest thanks to Lydia and Theresa who had to see me almost every day for nearly five years, thank you for being there. An additional special thanks to those that helped me with the big and little things for the final steps of this thesis: Lydia, Theresa, Sarah, Shannay, Melina, Giuliana, Lucie, Jenny and Jakob for providing scientific, linguistic and moral support.

Last but not least, my deepest gratitude to my mom and sister: Ohne euch hätte ich es nicht gewagt. Danke, dass ihr immer für mich da seid.

There were many people along this path that I could not name, but thank you to everyone that contributed to this work in every possible way.

Summary

For almost two decades, the number of Legionnaires' disease cases, a severe pneumonia caused by the bacterium *Legionella* spp., has been increasing in Switzerland. An increase in the number of cases has also been observed in many other countries for which case estimates are available, such as countries in Europe, the United States of America and Canada. After the discovery of Legionnaires' disease in 1976 and a subsequent period of low observed case numbers and little public health attention, the disease has now been described as a re-emerging infectious disease: In 2021, about seven times as many cases were reported in Switzerland as in 2000. However, as with many (re-)emerging infectious diseases, little is known about its epidemiology, specifically the various risk factors and sources of infection. The latter is a particular conundrum because *Legionella* spp. are ubiquitous in our everyday environment and suspected infection sources are numerous and diverse. The lack of knowledge on the aetiology and population health dynamics of Legionnaires' disease poses severe challenges for evidence-based prevention and control measures – and to research itself.

The overall aim of this thesis was to provide a comprehensive description of the epidemiology of Legionnaires' disease in Switzerland to guide and support future research, and to provide a basis for evidence-based decision-making.

The analysis of Legionnaires' disease national notification data regarding temporal and spatial patterns and data quality marked the starting point of this research. To better understand and interpret this data, we then investigated the processes involved in the diagnosis and reporting of cases. The positivity rate, which relates the number of positive *Legionella* findings to the number of diagnostic tests performed in Swiss medical laboratories, was determined for a ten-year period. Using a qualitative approach, we further explored physicians' decision-making pathways and case management of community-acquired pneumonia. These studies were complemented by a comprehensive review of existing recommendations, guidelines and legislation on or in the management of Legionnaires' disease and *Legionella*. We looked at four different topics: environmental prevention and control, clinical case management, disease surveillance, and outbreak management. Furthermore, we explored large- and small-scale risk factors for population exposure. For this purpose, we used an ecological model to investigate spatial and environmental infection determinants at the district level and a case-crossover design to identify the short-term associations between the onset of Legionnaires' disease and the preceding weather and air pollution levels.

The development of a research study to investigate small-scale risk factors and exposure sites for community-acquired and sporadic Legionnaires' disease is particularly challenging. Legionnaires' disease remains comparatively rare even today. Rare diseases are usually investigated with case-control studies;

however, case-control studies must rely on self-reporting by study participants to evaluate exposure. The challenges and limitations of working with self-reported data are exacerbated by the variable and long incubation period of Legionnaires' disease and the often-poor health status of patients, resulting in data being collected long after the relevant exposure. Beyond the case-control study, comparative genomics, in conjunction with epidemiological data, provides the most conclusive evidence of a source of infection. It involves comparing *Legionella* isolates from the lower respiratory tract of patients and the suspected source of infection using whole genome sequencing. However, clinical isolates are rarely available, as lower respiratory tract samples are often not collected or tested for *Legionella* . The procedure for collecting and analysing environmental samples presents further difficulties. Due to the ecology of *Legionella* (e.g. their intracellular persistence in amoebae), they cannot always be detected consistently in the environment. In addition, *Legionella* are difficult to culture. Therefore, the design and implementation of a national prospective case-control and molecular source-attribution study to identify host, behavioural and environmental risk factors and individual exposure sites concludes this thesis.

This thesis synthesizes existing knowledge and generates new evidence on the epidemiology of Legionnaires' disease in Switzerland. The analysis of the national notification data showed that between 2000 and 2020 the annual crude notification rate for legionellosis cases increased from 1.1 cases (confidence interval (CI): 0.9–1.4) to 5.6 cases (CI: 5.1–6.1) per 100,000 inhabitants. Despite the overall increase, the case numbers in 2020 have been slightly lower than in previous years. Fewer clinical reports were sent in in 2020, likely due to an overburdening of reporting physicians during the COVID-19 pandemic. The lack of clinical notifications may have led to an underestimation of cases, as the case definition only classifies cases with clinically proven pneumonia as Legionnaires' disease. Additionally, in 2020 we observed a short-term 35% decline in reported cases, which was associated with COVID-19 containment measures, such as travel restrictions and/or related behavioural changes. In 2021, the number of cases increased again; the latest reports from the Federal Office of Public Health show a notification rate of Legionnaires' disease of now 6.5 per 100,000 inhabitants - one of the highest in Europe.

Apart from the long-term temporal development, Legionnaires' disease in Switzerland is subject to a pronounced seasonality, with 37% of all cases occurring between June and August. This contrasts with the number of diagnostic tests for Legionnaires' disease, which generally peaks in winter. The overall number of diagnostic tests more than doubled between 2007 and 2016. The urinary antigen test has been reported as the most widely used test, continuously reflected in over 80% of all reported case diagnoses.

Clinical guidelines for the diagnosis and treatment of community-acquired pneumonia do not recommend aetiological testing of pneumonia in outpatient settings. Hence, the largest proportion of reported Legionnaires' disease cases stems from hospitals and the hospitalisation rate for notified cases is generally high (89.9%). In our qualitative study, physicians working in hospitals indicated a high level of awareness of Legionnaires' disease and its diagnostic and treatment approaches. In contrast, general practitioners

indicated lower levels of awareness, reflecting the fact that they treat pneumonia cases empirically without identifying the causative agent. Thus, clinical guidelines and shape physicians' level of awareness. Furthermore, physicians reported concerns about the urinary antigen test's sensitivity and coverage limited to the detection of *Legionella pneumophila* serogroup 1. The availability of diagnostic tests and the physicians' perception of the reliability of the testing procedures also influenced their preference for targeted treatment approaches with antibiotics or the use of broad-spectrum antibiotics. Finally, external constraints such as financial and time considerations also affected physicians' testing and treatment preferences.

The extent and public health relevance of undetected, mild Legionnaires' disease cases and the proportion of avoidable severe cases through earlier detection remains unknown. The case fatality rate of Legionnaires' disease decreased between 2000 and 2020 from 7.7% to 3.6%. A comparison with hospital statistics, however, shows that the case fatality rate is underestimated by 30% on average. Despite this underestimation, the 'true' case fatality rate of about 5.1% seems to be somewhat lower than the European average of 8%.

Regarding regional distribution within Switzerland, the canton of Ticino in southern Switzerland consistently reported higher per capita Legionnaires' disease case numbers than the rest of Switzerland, with a standardised notification rate of 14.3 cases per 100,000 inhabitants (CI: 12.6-16.0). It was also identified as a statistically significant regional hotspot for 2017-2021. However, in recent years, case numbers have decreased in Ticino and increased in all other regions of Switzerland.

We argue that the overall increase in Legionnaires' disease case numbers is at least partly due to changes in the underlying disease incidence and does not represent only a surveillance artefact. The clinical guidelines for aetiological testing of pneumonia cases, which affect case detection and thereby the observed number of cases, have long been standardised for hospitalised pneumonia patients. Similarly, diagnostic test methods remained largely unchanged. Another hypothesis explaining the increase as a surveillance artefact has been that increasing physician awareness of *Legionella* as a cause of pneumonia may have led to increased case detection. However, it is reasonable to assume that the testing protocols from the clinical guidelines have been followed in the past, even when the level of awareness of the disease was not as high as it is today. Furthermore, the influence of growing awareness among physicians should diminish over time and lead to a plateau of notified cases. However, after 20 years of sustained increase, the increase in the number of Legionnaires' disease cases shows no sign of slowing down.

Despite an improved understanding of the Legionnaires' disease burden in Switzerland, the drivers for infection and causes of regional heterogeneity remained unclear. Using two different methodologies (an ecological regression model and a case-crossover study), we found evidence for the short-term association of elevated daily mean temperature (odds ratio (OR): 2.83; CI: 1.70-4.70) and mean daily vapour pressure (OR: 1.52; CI: 1.15-2.01) 6-14 days before Legionnaires' disease onset. In the ecological model, we also found

a strong association between Legionnaires' disease incidence and air pollution levels, but no significant results in the case-crossover study. However, as the ecological model can be subject to ecological bias and the case-crossover study was limited in power, future studies are needed to further investigate the association. Knowledge of these large-scale risk factors, such as the impact of weather conditions and air pollution on the occurrence of Legionnaires' disease, is essential. It contributes to the understanding of regional differences, provides information on the vulnerability of certain at-risk populations/regions and ultimately helps to anticipate disease trends.

The investigation of small-scale risk factors and exposure sites is of central importance for targeted prevention and control measures. However, due to the disease dynamics and the role of water supply systems in the transmission of *Legionella* , the investigation is complex and requires suitable research methodologies and a broad range of expertise. The studies summarised in this thesis have informed the design of a prospective one-year national case-control and molecular source attribution study. The study set-up includes the establishment of a network of 20 university and cantonal hospitals to facilitate and expedite recruitment of patients with Legionnaires' disease and promote the sampling of material from the lower respiratory tract to obtain clinical *Legionella* isolates. In a subset of cases and controls (from the general population), water samples are collected from the shower and kitchen tap, which are then analysed and processed to obtain isolates of *Legionella* from the environment. In a last step, the clinical and environmental isolates are genetically matched using whole genome sequencing to support infection source attribution. The environmental component of this study has been developed and implemented jointly with experts in water hygiene in buildings and environmental microbiology. The study, thus, provides the framework for a wide range of research on Legionnaires' disease and *Legionella* , including clinical aspects, such as long-term health effects, as well as the identification of household characteristics conducive to *Legionella* contamination. The implementation of this national research project strengthens intersectoral and multidisciplinary collaboration and capacity building to address the ongoing increase in Legionnaires' disease case numbers.

In light of climate change, and demographic changes, the number of observed cases of Legionnaires' disease is expected to increase further in Switzerland and abroad. To stop this trend, comprehensive research is needed to allow targeted and evidence-based action. Although Switzerland benefits from strong government support to combat this disease, data gaps remain an obstacle and, in many other countries, the data gap is even larger. The lack of data and, thus, estimates on the disease burden does not translate into the absence of a public health problem and efforts should be made to investigate the attributable Legionnaires' disease burden globally. In the context of climate change and urbanisation, public health should advocate for healthy (built) environments to curb Legionnaires' disease and other (re-)emerging infectious diseases.

Zusammenfassung

Seit fast zwei Jahrzehnten steigt die Zahl der Fälle der Legionärskrankheit in der Schweiz an. Die Legionärskrankheit ist eine schwere Lungenentzündung, welche durch die Bakterien *Legionella* spp. verursacht wird. Auch in den meisten anderen Ländern, für welche Schätzungen der Fallzahlen vorliegen, wie in Ländern Europas, den Vereinigten Staaten von Amerika und Kanada, wurde ein Anstieg der Fallzahlen beobachtet. Nach der Entdeckung der Legionärskrankheit im Jahr 1976 wurden bis zur Jahrtausendwende nur geringe Fallzahlen gemeldet, und die öffentliche Gesundheit befasste sich wenig mit Legionellosen im Allgemeinen. Heute wird die Legionärskrankheit als eine wieder aufkommende Infektionskrankheit bezeichnet: Im Jahr 2021 wurden in der Schweiz etwa siebenmal so viele Fälle gemeldet als noch zu Beginn des Jahrtausends. Wie bei vielen (wieder-)aufkommenden Infektionskrankheiten ist nur wenig über die Epidemiologie bekannt, insbesondere über die verschiedenen Risikofaktoren und Quellen einer Infektion. Letzteres ist ein fundamentales Problem, da Legionellen in unserer alltäglichen Umgebung omnipräsent und die vermuteten Infektionsquellen zahlreich und vielfältig sind. Der Mangel an Wissen über die ursächlichen Zusammenhänge und die Dynamik der Legionärskrankheit in der öffentlichen Gesundheit stellt eine erhebliche Herausforderung für evidenzbasierte Präventions- und Kontrollmassnahmen dar.

Das übergeordnete Ziel dieser Doktorarbeit war eine umfassende Beschreibung der Epidemiologie der Legionärskrankheit in der Schweiz zu erstellen um die zukünftige Forschung zu orientieren und zu unterstützen, und um eine Faktengrundlage für evidenzbasierte Entscheidungsprozesse zu schaffen.

Die Analyse der nationalen Meldedaten zur Legionärskrankheit hinsichtlich zeitlicher und räumlicher Merkmale und der Datenqualität bildete den Ausgangspunkt dieser Arbeit. Um die Meldedaten der Legionärskrankheitsfälle besser zu interpretieren, wurden Prozesse untersucht, die zur Diagnose und Meldung von Krankheitsfällen beitragen. Die Positivitätsrate, welche die Anzahl der positiven Legionellenbefunde mit der Anzahl der in schweizerischen medizinischen Laboratorien durchgeführten diagnostischen Tests in Relation setzt, wurde über einen Zeitraum von zehn Jahren bestimmt. Die Entscheidungsabläufe von Ärzten und das Fallmanagement bei ambulant erworbenen Lungenentzündungen wurde mit Hilfe eines qualitativen Forschungsansatzes erforscht. Ergänzt wurden diese Studien durch eine umfangreiche Überprüfung bestehender Empfehlungen, Richtlinien und der Gesetzgebung zum oder im Umgang mit der Legionärskrankheit und Legionellen. Wir untersuchten hierbei vier verschiedene Themenbereiche: die Prävention und Kontrolle in der Umwelt, das klinische Fallmanagement, die Krankheitsüberwachung, sowie den Umgang mit Krankheitsausbrüchen. Darüber hinaus wurden die gross- und kleinräumigen Risikofaktoren und die Legionellenexposition der Schweizer Bevölkerung untersucht. Räumliche und umweltbedingte Determinanten für eine Legionelleninfektion auf Bezirksebene wurden mittels eines ökologischen Regressionsmodells untersucht. Die unmittelbaren Zusammenhänge zwischen dem Auftreten der Legionärskrankheit, und dem

vorhergehenden Wetter und der Grad der Luftverschmutzung wurden in einer case-crossover Studie (ein Studiendesign ähnlich einer Fall-Kontroll-Studie) ermittelt.

Die Entwicklung einer Forschungsstudie zur Untersuchung von kleinräumigen Risikofaktoren und Infektionsquellen von ambulant erworbenen und sporadisch auftretenden Legionärskrankheitsfällen stellte sich als besonders herausfordernd dar. Die Legionärskrankheit ist auch heute noch vergleichsweise selten. Seltene Krankheiten werden üblicherweise mit Fall-Kontroll-Studien untersucht, da hierbei gezielt Fälle in die Studie eingeschlossen werden. Allerdings müssen sich Fall-Kontroll-Studien auf Selbstauskünfte der Studienteilnehmer stützen, um die Exposition zu ermitteln. Selbstauskünfte sind allerdings oft abhängig von der Wahrnehmung und dem Erinnerungsvermögen der Teilnehmer. Diese Problematik wird durch die Inkubationszeit der Legionärskrankheit, welche bis zu 14 Tage dauern kann, verschärft. Somit ist der Zeitpunkt der Datenerhebung zeitlich weit nach der relevanten Exposition, was die Erinnerung erschwert. Zudem ist der Gesundheitszustand der Patienten oft schlecht. Über die Fall-Kontroll-Studie hinaus, liefert die vergleichende Genomanalyse, besonders und ausschliesslich in Verbindung mit epidemiologischen Daten, den aussagekräftigsten Hinweis auf eine Infektionsquelle. Dabei werden Legionellenisolate aus den unteren Atemwegen der Patienten und der vermuteten Infektionsquelle mittels Ganzgenomsequenzierung verglichen. Klinische Isolate sind jedoch nur selten vorhanden, da Proben der unteren Atemwege oft nicht entnommen oder nicht auf Legionellen getestet werden. Das Vorgehen zur Entnahme und Analyse von Umweltproben birgt weitere Schwierigkeiten in sich. Durch die Ökologie der Legionellen (z.B. ihrem intrazellulären Vorkommen in Amöben) können sie nicht immer gleich gut in der Umwelt nachgewiesen werden. Zudem lassen sich Legionellen nur schwer kultivieren. Diesen Herausforderungen stellten wir uns indem wir eine einjährige, nationale Fall-Kontroll-Studie konzipierten, die wir mit einer molekularen Untersuchung der Infektionsquellen kombinierten. Die Studie hat zum Ziel, die patienten-, verhaltens- und umweltbedingten Risikofaktoren sowie die einzelnen Infektionsquellen zu ermitteln. Die Implementierung dieser prospektiven Fall-Kontroll-Studie bildet den Abschluss dieser Arbeit – die Studie wird gegenwärtig in der gesamten Schweiz bereits in Zusammenarbeit mit anderen Forschungspartnern umgesetzt.

Die vorliegende Arbeit fasst bestehende und neu gewonnene Erkenntnisse über die Epidemiologie der Legionärskrankheit in der Schweiz zusammen. Die Analyse der nationalen Meldedaten ergab, dass zwischen dem Jahr 2000 und 2020, die jährliche Melderate der Legionellosefälle von 1.1 (Konfidenzintervall (KI): 0.9-1.4) auf 5.6 (KI: 5.1-6.1) pro 100‘000 Einwohner stieg. Im Jahr 2020 wurden weniger klinische Meldeformulare eingesandt, so dass die Zahl der erfassten Fälle leicht zurückging. Wahrscheinlich ist dies auf eine Überlastung der meldenden Ärzte durch die COVID-19 Pandemie zurückzuführen. Der Mangel an klinischen Meldungen könnte zu einer Unterschätzung der Krankheitsfälle geführt haben, da die Falldefinition nur Krankheitsfälle mit einer klinisch nachgewiesenen Pneumonie als Legionärskrankheit einstuft. Überdies wurde im Jahr 2020 ein vorübergehender Rückgang der gemeldeten Fälle um 35% beobachtet. Dieser Rückgang wurde mit COVID-19-Eindämmungsmassnahmen wie Reisebeschränkungen und/oder damit ver-

bundenen Verhaltensänderungen in Verbindung gebracht. Im Jahr 2021 stiegen die Fallzahlen wieder an; die jüngsten Berichte des Bundesamtes für Gesundheit weisen eine Melderate der Legionärskrankheit von nunmehr 6.5 pro 100,000 Einwohner aus – eine der höchsten in Europa.

Abgesehen von der langfristigen zeitlichen Entwicklung unterliegt die Legionärskrankheit in der Schweiz einer ausgeprägten Saisonalität; 37% aller Fälle ereignen sich zwischen Juni und August. Demgegenüber steht die Anzahl der diagnostischen Untersuchungen auf die Legionärskrankheit, die im Winter ihren Höhepunkt erreicht. Die Gesamtzahl der diagnostischen Tests hat sich zwischen 2007 und 2016 mehr als verdoppelt. Der Urin-Antigentest wird Meldungen zufolge am häufigsten verwendet und wurde in den letzten 20 Jahren stets in über 80% aller gemeldeten Legionärskrankheitsfällen in der Diagnostik eingesetzt.

In den klinischen Leitlinien für die Diagnose und Behandlung der ambulant erworbenen Lungenentzündung wird eine ätiologische Untersuchung im ambulanten Bereich nicht empfohlen. Daher stammt der grösste Teil der gemeldeten Legionärskrankheitsfälle aus Krankenhäusern. Die Hospitalisierungsrate der gemeldeten Fälle ist für gewöhnlich hoch (89.9%). Die klinischen Leitlinien und folglich das Testverhalten im Falle einer Pneumonie beeinflusst auch das Bewusstsein der Ärzte für die Legionärskrankheit. In der qualitativen Studie gaben im Krankenhaus tätige Ärzte an, dass sie die Legionärskrankheit und die Diagnose- und Behandlungsmethoden gut kennen. Im Gegensatz dazu waren Hausärzte weniger auf die Legionellenthematik sensibilisiert. Dies ist darauf zurückzuführen, dass Pneumoniefälle von Hausärzten empirisch behandelt werden, ohne vorab den Erreger zu identifizieren. Die klinischen Leitlinien prägen somit den Sensibilisierungsgrad der Ärzte. Darüber hinaus äusserten Ärzte Bedenken hinsichtlich der Sensitivität des Urin-Antigentests und dessen, auf den Nachweis von *Legionella pneumophila* Serogruppe 1 beschränkte, Anwendung. Die Verfügbarkeit von Diagnosetests und die Einschätzung der Ärzte hinsichtlich der Zuverlässigkeit der Testverfahren beeinflussten auch ihre Präferenz für gezielte Behandlungsansätze mit Antibiotika oder dem Einsatz von Breitbandantibiotika. Nicht zuletzt wirkten sich auch äussere Anforderungen wie finanzielle und zeitliche Erwägungen auf die Test- und Behandlungspräferenzen der Ärzte aus.

Das Ausmass und die Bedeutung von unerkannten, leichten Legionärskrankheitsfällen für die öffentliche Gesundheit bleibt weiterhin unbekannt. Der Anteil der schweren Fälle, die durch eine frühere Erkennung verhindert werden könnten, ist ebenfalls unbekannt. Die Sterblichkeitsrate der gemeldeten Legionärskrankheitsfälle ist zwischen 2000 und 2020 von 7.7% auf 3.6% gesunken. Ein Vergleich von Krankenhausstatistiken zeigt indessen, dass die Sterblichkeitsrate im Durchschnitt um 30% unterschätzt wird. Aber selbst unter Berücksichtigung dieser Unterschätzung scheint die Todesfallrate von ca. 5.1% in der Schweiz etwas niedriger zu sein als der europäische Durchschnitt von 8%.

Hinsichtlich der regionalen Verteilung innerhalb der Schweiz meldete der Kanton Tessin in der Südschweiz mit 14.3 Fällen pro 100,000 Einwohner (KI: 12.6-16.0) kontinuierlich höhere Pro-Kopf-Fallzahlen der Legionärskrankheit als andere Kantone. Für die Jahre 2017-2021 wurden weite Teile des Kantons überdies

als statistisch signifikanter, regionaler Hotspot identifiziert. In den letzten Jahren sind die Fallzahlen im Tessin allerdings rückläufig, während sie in den übrigen Regionen der Schweiz zunehmen.

Wir sind der Ansicht, dass der Gesamtanstieg an gemeldeten Legionärskrankheitsfällen zumindest teilweise auf Veränderungen in der tatsächlichen Krankheitsinzidenz zurückzuführen sind und nicht nur einen Überwachungsartefakt darstellen. Die klinischen Leitlinien für die ätiologische Untersuchung von Pneumoniefällen, die sich auf die Fallerkennung und folglich auf die gemeldeten Zahlen auswirken, sind seit langem für hospitalisierte Pneumoniepatienten standardisiert. Ebenso sind die verwendeten diagnostischen Testmethoden weitgehend unverändert geblieben. Die Klassifizierung des Anstieges als Überwachungsartefakt ist laut einer Hypothese potentiell auf die zunehmende Sensibilisierung der Ärzte für Legionellen und einer daraus folgenden erhöhten Fallerkennung zurückzuführen. Es ist jedoch anzunehmen, dass die Testprotokolle aus den klinischen Leitlinien auch in der Vergangenheit angewandt wurden. Ausserdem sollte der Einfluss der wachsenden Sensibilisierung der Ärzte mit der Zeit abnehmen und zu einem Plateau der gemeldeten Fälle führen. Doch auch nach 20 Jahren zeigt der Anstieg der Fallzahlen der Legionärskrankheit jedoch keinerlei Anzeichen einer Verlangsamung.

Trotz eines verbesserten Verständnisses der Legionärskrankheitslast in der Schweiz blieben die Treiber der Infektion und die Ursachen der regionalen Heterogenität bisher unklar. Wir fanden Hinweise auf einen unmittelbaren Zusammenhang von erhöhter Tagesmitteltemperatur (Odds ratio (OR) 2.83; KI: 1.70-4.70) und mittlerem Tagesdampfdruck (OR: 1.52; KI: 1.15-2.01) 6-14 Tage vor Krankheitsausbruch mit der Legionärskrankheit. Diese Risikofaktoren wurden mit Hilfe eines ökologischen Regressionsmodells und einer case-crossover Studie ermittelt. Im ökologischen Regressionsmodell wurde zudem eine deutliche Assoziation zwischen dem Auftreten der Legionärskrankheit und dem Grad der Luftverschmutzung gefunden. Dieser Zusammenhang konnte jedoch in der case-crossover Studie nicht nachgewiesen werden. Das ökologische Regressionsmodell kann jedoch mit systematischen umweltbedingten Verzerrungen behaftet sein, und die case-crossover Studie hatte nur wenig Datenpunkte zur Analyse des Einflusses der Luftverschmutzung zur Verfügung. Demnach sind zukünftige Studien erforderlich, um den potentiellen Zusammenhang zwischen der Inzidenz der Legionärskrankheit und der Luftverschmutzung weiter zu untersuchen. Das Wissen um diese grossräumigen Risikofaktoren, wie z.B. die Auswirkungen der Witterungsbedingungen und der Luftverschmutzung auf das Auftreten der Legionärskrankheit ist essenziell. Es trägt zum Verständnis regionaler Unterschiede bei, gibt Aufschluss über die Vulnerabilität bestimmter Risikobevölkerungen und -regionen und hilft letztlich bei der Vorhersage epidemiologischer Trends.

Die Untersuchung kleinräumiger Risikofaktoren und Expositionsorte ist für zielgerichtete Präventions- und Bekämpfungsmassnahmen von zentraler Bedeutung. Aufgrund der Erkrankungsdynamik und der Bedeutung von Wasserversorgungssystemen bei der Übertragung von Legionellen, ist die Untersuchung jedoch äusserst komplex und erfordert geeignete Forschungsmethoden sowie ein breites Spektrum an Expertenwissen. Die in dieser Arbeit zusammengefassten Studien dienten als Grundlage für die Planung der ein-

gangs erwähnten, nationalen, einjährigen Fall-Kontroll-Studie gepaart mit einer molekularen Zuordnung der Infektionsquellen. Die Studie umfasst den Aufbau eines Spitalnetzwerks von 20 Universitäts- und Kantonsspitälern, um die Rekrutierung von Patienten mit Legionärskrankheit zu erleichtern und die Entnahme von Proben aus den unteren Atemwegen zur Gewinnung klinischer Legionellenisolate zu fördern. Bei einer Auswahl von Fällen und Kontrollen, die aus der Allgemeinbevölkerung rekrutiert werden, werden Wasserproben aus der Umwelt (z.B. in der Wohnung, aus der Dusche und dem Wasserhahn in der Küche der Teilnehmenden) entnommen, analysiert und aufbereitet, um Legionellenisolate zu erhalten. In einem letzten Schritt werden die klinischen Isolate und die Isolate aus Haus und Umwelt mit Hilfe der Ganzgenomsequenzierung genetisch abgeglichen, um die Zuordnung der Infektionsquelle zu unterstützen. Die Umweltkomponente dieser Studie wurde gemeinsam mit Experten für Wasserhygiene in Gebäuden und Umweltmikrobiologie entwickelt und implementiert. Die Studie bildet somit den Rahmen für eine Vielzahl von Forschungsarbeiten zur Legionärskrankheit und zu Legionellen. Diese umfassen klinische Aspekte wie beispielsweise die langfristige Krankheitsbelastung einzelner Patienten bis hin zur Ermittlung von Haushaltsfaktoren, die eine Kontamination mit Legionellen begünstigen. Die Umsetzung dieses nationalen Forschungsprojekts stärkt die intersektorielle und multidisziplinäre Zusammenarbeit sowie den Aufbau von Kompetenzen und Kapazitäten, um dem anhaltenden Anstieg der Fallzahlen der Legionärskrankheit zu begegnen.

Angesichts des Klimawandels, der Urbanisierung und den demographischen Veränderungen wird die Zahl der beobachteten Legionärskrankheitsfälle in der Schweiz und im Ausland voraussichtlich weiter ansteigen. Um diese Entwicklung zu stoppen, ist eine ganzheitliche Betrachtung erforderlich, die ein gezieltes und evidenzbasiertes Handeln ermöglicht. Obwohl die Schweiz von einer starken staatlichen Unterstützung bei der Bekämpfung dieser Erkrankung profitiert, bleiben Defizite in der Einschätzung der tatsächlichen Krankheitslast ein Hindernis. In vielen anderen Ländern sind diese Defizite noch grösser. Das Fehlen von Einschätzungen der Krankheitslast impliziert jedoch nicht, die Abwesenheit einer Legionellen-Problematik für die öffentliche Gesundheit. Es bedarf vielmehr weiterer Anstrengungen, um die der Legionärskrankheit zuschreibbare, - attributable - Krankheitsbelastung zu untersuchen. Vor dem Hintergrund des Klimawandels und der Urbanisierung sollte sich die öffentliche Gesundheit für eine gesunde (gebaute) Umwelt einsetzen, um die Legionärskrankheit und andere (neu) auftretende Infektionskrankheiten einzudämmen.

Synthèse

Depuis près de deux décennies, le nombre de cas de la maladie du légionnaire, une pneumonie grave causée par la bactérie *Legionella* spp. (les légionelles), est en augmentation en Suisse et dans la plupart des pays où l'on dispose d'estimations sur cette maladie, comme en Europe, aux États-Unis et au Canada. Après sa découverte en 1976, suivie d'une période de faible taux de cas et de peu d'attention par la santé publique, la maladie du légionnaire est aujourd'hui décrite comme une maladie infectieuse réémergente. En 2021, environ sept fois plus de cas ont été déclarés en Suisse qu'en 2000. Cependant, comme pour de nombreuses maladies (ré)émergentes, on sait peu de choses sur son épidémiologie, en particulier sur les facteurs de risque et les sources d'infection. Ce dernier point est particulièrement problématique, car la bactérie responsable de la maladie du légionnaire, *Legionella* spp. est omniprésent dans l'environnement quotidien et les sources d'infection suspectés sont nombreuses et variées. Le manque de connaissances sur l'étiologie et la dynamique de santé de la population atteinte de la maladie du légionnaire pose des défis de taille à la prévention et aux mesures de contrôle fondées sur des preuves - et à la recherche elle-même.

L'objectif global de cette thèse est de mener une enquête exhaustive sur l'épidémiologie de la maladie du légionnaire en Suisse afin d'orienter les recherches futures et, en fin de compte, de fournir une base de données probantes pour l'élaboration des politiques.

L'analyse des données nationales de notification de la maladie du légionnaire, en termes de tendances temporelles et spatiales et de qualité des données, a été le point de départ de cette enquête. Pour mieux comprendre et interpréter ces données, nous avons ensuite analysé les processus impliqués dans le diagnostic et la notification des cas. Nous avons recherché le nombre de tests de diagnostic de *Legionella* effectués dans les laboratoires de diagnostic médical de toute la Suisse et calculé le taux de positivité sur une période de dix ans. À l'aide d'une approche qualitative, nous avons exploré les voies de décision des médecins et la gestion des cas de pneumonie communautaire. Ces études ont été complétées par un examen complet des recommandations, lignes directrices et législations existantes sur la maladie du légionnaire et la gestion de la maladie du légionnaire pour la prévention et le contrôle, la gestion des cas cliniques, la surveillance de la maladie et les épidémies. En outre, nous avons exploré les facteurs de risque à grande et petite échelle pour l'exposition de la population. À cette fin, nous avons utilisé un modèle écologique pour étudier les déterminants de l'infection au niveau du district et de l'environnement, et un plan de croisement des cas pour identifier l'association à court terme entre l'incidence de la maladie du légionnaire, le climat et la pollution atmosphérique.

La conception d'une étude visant à étudier les facteurs de risque et les sites d'exposition à petite échelle ou de la maladie du légionnaire sporadique et communautaire est particulièrement difficile. La maladie du légionnaire reste relativement rare et nécessite donc une approche cas-témoin. Cependant, les études cas-témoins doivent s'appuyer sur des données autodéclarées pour évaluer l'exposition des participants. Ce

défi est aggravé par la période d'incubation variable et longue de la maladie du légionnaire et par l'état de santé des patients, de sorte que le moment de la collecte des données est très éloigné du moment de l'exposition à la bactérie. En outre, associée aux données épidémiologiques, la génomique comparative fournit la preuve la plus concluante des sources d'infection, en comparant les isolats de *Legionella* provenant à la fois des voies respiratoires inférieures du patient et de la source suspectée, grâce au séquençage du génome entier. Cependant, les isolats cliniques sont rarement obtenus et le protocole d'obtention et d'analyse des échantillons environnementaux présente ses propres défis. La thèse est conclue avec la conception et la mise en œuvre d'une étude nationale prospective cas-témoins et d'une étude d'attribution de source moléculaire pour identifier les facteurs de risque liés à l'hôte, au comportement et à l'environnement ainsi que les sites d'exposition individuels.

Cette thèse synthétise les preuves existantes et génère de nouvelles preuves sur l'épidémiologie de la maladie du légionnaire en Suisse. L'analyse des données de déclaration nationales a montré que le taux brut annuel de déclaration des cas de la maladie du légionnaire est passé de 1.1/100,000 habitants (Intervalle de confiance (IC): 0.9-1.4) en 2000 à 5.6/100,000 habitants (IC: 5.1-6.1) en 2020. Le nombre de cas en 2020 a été légèrement inférieur à celui des années précédentes. Moins de rapports cliniques ont été envoyés en 2020, probablement en raison d'une surcharge de travail pour les médecins déclarants. La définition de cas classant les symptômes cliniques de la pneumonie dans la catégorie de la maladie du légionnaire, l'absence de rapports cliniques peut avoir conduit à une sous-estimation des cas en 2020. En outre, nous avons observé une baisse temporaire à court terme de 35% des cas en 2020, qui a été associée à des mesures de confinement de la pandémie de COVID-19, telles que des restrictions de voyage et/ou des changements de comportement connexes. Le nombre de cas a repris en 2021; l'Office fédéral de la santé publique rapporte récemment un taux de notification de la maladie du légionnaire de 6.5/100,000 habitants.

En plus du schéma temporel général, la maladie du légionnaire en Suisse est soumise à une forte saisonnalité, avec 37% des cas survenant entre juin et août. Ce chiffre contraste avec le nombre de tests de diagnostic de la maladie du légionnaire, qui connaît généralement un pic en hiver. Le nombre total de tests de diagnostic a plus que doublé entre 2007 et 2016. Le test de l'antigène urinaire a été signalé comme le test le plus fréquemment utilisé, ce qui se reflète systématiquement dans plus de 80% de tous les diagnostics de cas rapportés.

Les directives cliniques pour le diagnostic et le traitement de la pneumonie communautaire ne recommandent pas de tests étiologiques pour la pneumonie en milieu ambulatoire. Par conséquent, la plupart des cas déclarés de la maladie du légionnaire proviennent des hôpitaux et le taux d'hospitalisation des cas déclarés est généralement élevé (89.9%). Le respect des directives cliniques et, par conséquent, le comportement en matière de dépistage influent également sur la sensibilisation des médecins à la maladie. Dans notre étude qualitative, les médecins travaillant dans les hôpitaux ont indiqué un niveau élevé de sensibilisation à la maladie du légionnaire et des approches diagnostiques et thérapeutiques comparables. En revanche, les

médecins généralistes ont indiqué des niveaux de sensibilisation plus faibles, reflétant le fait qu'ils traitent les cas de pneumonie de manière empirique sans identifier l'agent causal. Par conséquent, le niveau de sensibilisation est dicté par les directives cliniques. En outre, les médecins ont exprimé des inquiétudes quant à la sensibilité du test de l'antigène urinaire et à la couverture limitée pour la détection de *Legionella* pneumophila sérogroupe 1. La disponibilité des tests de diagnostic et la perception de l'efficacité des tests par les médecins ont également influencé leur préférence pour les approches thérapeutiques à large spectre ou ciblées. Enfin, des contraintes extrinsèques, telles que des considérations financières et de temps, ont également influencé les préférences des médecins en matière de tests et de traitements.

L'ampleur et l'importance pour la santé publique des cas légers non détectés et la proportion de cas graves qui peuvent être évités par un diagnostic plus précoce restent inconnues. Le taux de mortalité des cas de la maladie du légionnaire a diminué entre 2000 et 2020, passant de 7.7% à 3.6%. Cependant, la comparaison avec les statistiques hospitalières montre que le taux de mortalité est en moyenne sous-estimé de 30%. Toutefois, même en tenant compte de cette sous-estimation, le taux de mortalité des cas en Suisse semble être légèrement inférieur à la moyenne européenne de 8%.

En termes de répartition régionale au sein de la Suisse, le canton du Tessin, dans le sud de la Suisse, a toujours enregistré un nombre de cas de la maladie du légionnaire par habitant plus élevé que dans le reste de la Suisse. Entre les années 2017-2021, il a également été identifiée comme un point chaud régional statistiquement significatif, avec un taux de notification standardisé de 14.3 cas/100,000 habitants (IC: 12.6-16.0). Ces dernières années, cependant, le nombre de cas a diminué au Tessin et augmenté dans toutes les autres régions de Suisse.

Nous soutenons que cette augmentation globale du nombre de cas de la maladie du légionnaire est au moins partiellement due à des changements dans l'incidence réelle de la maladie et n'est pas un artefact de la surveillance. Les directives cliniques pour l'analyse étiologique des cas de pneumonie, qui influencent la détection des cas et donc le nombre de cas observés, sont depuis longtemps standardisées pour les patients hospitalisés atteints de pneumonie et les méthodes d'analyse diagnostique utilisées sont restées largement inchangées. Une autre hypothèse expliquant l'augmentation comme un artefact de la surveillance est que la sensibilisation accrue des médecins à la *Legionella* comme cause de pneumonie peut avoir conduit à une détection accrue des cas. Cependant, il est raisonnable de supposer que les protocoles d'analyse des directives cliniques étaient suivis dans le passé, même lorsque le niveau de sensibilisation à la maladie n'était pas aussi élevé qu'aujourd'hui. En outre, l'effet de la sensibilisation croissante des médecins devrait diminuer avec le temps, jusqu'à atteindre un plateau. Cependant, après 20 ans d'augmentation soutenue, le nombre de cas de la maladie du légionnaire ne montre aucun signe de ralentissement.

Cependant, les déterminants de l'infection et les causes de l'hétérogénéité régionale sont restés obscurs. Néanmoins, en utilisant deux méthodologies différentes (un modèle de régression écologique et une étude cas-

croisé), nous avons trouvé des preuves d'une association à court terme entre une température quotidienne moyenne élevée (odds ratio (OR): 2.83; IC: 1.70-4.70) et une pression de vapeur quotidienne moyenne (OR: 1.52; IC: 1.15-2.01) 6-14 jours avant l'apparition de la maladie du légionnaire. Dans le modèle écologique, nous avons également trouvé une forte association entre l'incidence de la maladie du légionnaire et la pollution atmosphérique, mais aucun résultat significatif dans l'étude cas-croisé. Cependant, comme le modèle écologique peut être sujet à un biais écologique et que l'étude de croisement de cas avait une puissance limitée, des études futures sont nécessaires pour approfondir l'association. La compréhension de ces facteurs de risque à grande échelle, tels que l'impact des conditions météorologiques et de la pollution atmosphérique sur l'apparition de la maladie du légionnaire, permet de mieux comprendre les différences régionales, donne un aperçu de la vulnérabilité de certaines populations/régions au risque et, en fin de compte, aide à anticiper les tendances de la maladie.

La recherche des facteurs de risque et des sites d'exposition à petite échelle est essentielle pour des mesures de prévention et de contrôle ciblées, mais elle est complexe en raison de la dynamique de la maladie et du rôle des systèmes d'eau artificiels dans la transmission des légionelles. Elle nécessite donc des méthodologies de recherche appropriées et un large éventail de compétences. Les études résumées dans cette thèse ont servi de base à la conception d'une étude nationale prospective d'un an sur l'attribution de sources moléculaires et de cas-témoins. Le plan de l'étude prévoit la mise en place d'un réseau hospitalier de 20 hôpitaux universitaires et cantonaux afin de faciliter et d'accélérer le recrutement de patients atteints de la maladie du légionnaire et de promouvoir le prélèvement de matériel dans les voies respiratoires inférieures pour obtenir des isolats cliniques de légionelles. Dans un sous-ensemble de cas et de témoins (issus de la population générale), des échantillons d'eau sont prélevés dans la douche et le robinet de la cuisine, qui sont ensuite analysés et traités pour obtenir des isolats de légionelles dans l'environnement. Dans une dernière étape, les isolats cliniques et environnementaux sont appariés génétiquement par séquençage du génome entier (Whole Genome Sequencing) afin d'étayer l'attribution de la source d'infection. Le volet environnemental de cette étude a été élaboré et mis en œuvre en collaboration avec des experts en hygiène des eaux de construction et en microbiologie environnementale. L'étude fournit ainsi le cadre d'une série de recherches sur la maladie du légionnaire et les légionelles, depuis les aspects cliniques, tels que la charge à long terme de la maladie sur les patients individuels, jusqu'à l'identification des caractéristiques domestiques favorisant la contamination par les légionelles. La mise en œuvre de ce projet de recherche national renforce la coopération intersectorielle et multidisciplinaire ainsi que le renforcement des capacités pour faire face à l'augmentation constante des cas de la maladie du légionnaire.

Compte tenu des changements climatiques et démographiques, on s'attend à une nouvelle augmentation du nombre de cas de la maladie du légionnaire signalés en Suisse et à l'étranger. Pour enrayer cette tendance, des recherches approfondies sont nécessaires pour permettre une action ciblée et fondée sur des preuves. Bien que la Suisse bénéficie d'un fort soutien gouvernemental dans la lutte contre cette maladie,

le manque de données reste un obstacle. Dans de nombreux autres pays, le manque de données est encore plus prononcé. Le manque de données et d'estimations sur la charge de morbidité ne se traduit pas par l'absence d'un problème de santé publique, et des efforts doivent être faits pour étudier la charge attribuable à la légionellose dans le monde. Dans le contexte du changement climatique et de l'urbanisation, la santé publique doit promouvoir un environnement (bâti) sain pour contenir la maladie du légionnaire et d'autres maladies infectieuses (ré)émergentes.

Sintesi

Sintesi Da quasi due decenni il numero di casi della malattia del legionario, una grave polmonite causata dal batterio *Legionella* spp., è in aumento in Svizzera e nella maggior parte dei Paesi in cui sono disponibili stime di questa malattia, come Europa, Stati Uniti e Canada. Dopo la sua scoperta, avvenuta nel 1976, susseguita da un periodo con un tasso basso di casi e scarsa attenzione da parte della sanità pubblica, la malattia del legionario è ora descritta come una malattia infettiva riemergente. Nel 2021 in Svizzera è stato segnalato un numero di casi circa sette volte superiore a quello dell'anno 2000. Tuttavia, come per molte malattie (ri)emergenti, si sa poco sulla sua epidemiologia, in particolare dei fattori di rischio e delle fonti d'infezione. Quest'ultimo aspetto rappresenta un particolare enigma, poiché il batterio che causa la malattia del legionario, la *Legionella* spp., è onnipresente nell'ambiente quotidiano e le fonti di infezione sospette sono numerose e varie. La mancanza di conoscenze sull'eziologia e sulle dinamiche sanitarie della popolazione affetta dalla malattia del legionario pone dure sfide alla prevenzione e alle misure di controllo basate sull'evidenza – e alla ricerca stessa.

L'obiettivo generale di questa tesi è stato quello di eseguire un'indagine completa sull'epidemiologia della malattia del legionario in Svizzera per orientare la ricerca futura e, in ultima analisi, fornire una base di evidenza per la definizione delle politiche.

L'analisi dei dati nazionali di notifica della malattia del legionario, per quanto riguarda i modelli temporali e spaziali e la qualità dei dati, ha rappresentato il punto di partenza di questa indagine. Per comprendere e interpretare meglio questi dati, abbiamo poi analizzato i processi coinvolti nella diagnosi e nella notifica dei casi. Abbiamo ricercato il numero di test diagnostici per la *Legionella* eseguiti nei laboratori medici diagnostici in tutta la Svizzera e calcolato il tasso di positività in un periodo di dieci anni. Utilizzando un approccio qualitativo, abbiamo esplorato i percorsi decisionali dei medici e la gestione dei casi di polmonite acquisita in comunità. Questi studi sono stati integrati da una revisione completa delle raccomandazioni, delle linee guida e della legislazione esistenti sulla gestione della malattia del legionario e della *Legionella* per la prevenzione e il controllo, la gestione dei casi clinici, la sorveglianza della malattia e le epidemie. Inoltre, abbiamo esplorato i fattori di rischio su larga e piccola scala per l'esposizione della popolazione. A tal fine, abbiamo utilizzato un modello ecologico per indagare i fattori decisivi dell'infezione a livello distrettuale e ambientale e un disegno di case-crossover per identificare l'associazione a breve termine tra l'incidenza della malattia del legionario, il clima e l'inquinamento atmosferico.

La progettazione di uno studio di ricerca per indagare i fattori di rischio e i siti di esposizione su piccola scala o la malattia del legionario sporadica e acquisita in comunità è particolarmente impegnativa. La malattia del legionario rimane relativamente rara e richiede quindi un approccio caso-controllo. Tuttavia, gli studi caso-controllo devono basarsi su dati autodichiarati per valutare l'esposizione dei partecipanti. Questa sfida è aggravata da un periodo di incubazione variabile e lungo della malattia del legionario e dallo

stato di salute dei pazienti, di conseguenza il momento della raccolta dati è molto lontano dal momento dell'esposizione al batterio. Inoltre, insieme ai dati epidemiologici, la genomica comparativa fornisce la prova più conclusiva per le fonti di infezione, confrontando gli isolati di *Legionella* provenienti dal tratto respiratorio inferiore del paziente e dalla fonte sospetta mediante il sequenziamento dell'intero genoma. Tuttavia, raramente si ottengono isolati clinici e il protocollo per ottenere e analizzare i campioni ambientali presenta di per sé delle sfide. Pertanto, la progettazione e l'implementazione di uno studio prospettico nazionale caso-controllo e molecolare di attribuzione della fonte per identificare i fattori di rischio dell'ospite, del comportamento e dell'ambiente e i siti di esposizione individuale conclude questa tesi.

Questa tesi sintetizza le prove esistenti e ne genera di nuove sull'epidemiologia della malattia del legionario in Svizzera. L'analisi dei dati di notifica nazionali ha mostrato che il tasso di notifica grezzo annuale dei casi della malattia del legionario è aumentato da 1.1/100,000 abitanti (intervallo di confidenza (IC): 0.9-1.4) nel 2000 a 5.6/100,000 abitanti (IC: 5.1-6.1) nel 2020. Il numero di casi nel 2020 è stato leggermente inferiore rispetto agli anni precedenti. Nel 2020 sono state inviate meno segnalazioni cliniche, probabilmente a causa di un sovraccarico di lavoro per i medici segnalatori. Poiché la definizione del caso classifica i sintomi clinici della polmonite come malattia del legionario, la mancanza di rapporti clinici potrebbe aver portato a una sottostima dei casi nel 2020. Inoltre, abbiamo osservato un calo temporaneo a breve termine dei casi nel 2020, pari al 35%, che è stato associato alle misure di contenimento della pandemia di COVID-19, come le restrizioni ai viaggi e/o i relativi cambiamenti comportamentali. Il numero di casi è ripreso nel 2021; i rapporti recenti dell'Ufficio federale della sanità pubblica riportano un tasso di notifica della malattia del legionario di 6.5/100.000 abitanti.

Oltre all'andamento temporale generale, la malattia del legionario in Svizzera è soggetta a una forte stagionalità, con il 37% dei casi che si verificano tra giugno e agosto. Questo dato è in contrasto con il numero di test diagnostici per la malattia del legionario, che in genere ha un picco in inverno. Il numero complessivo di test diagnostici è più che raddoppiato tra il 2007 e il 2016. Il test dell'antigene urinario è stato segnalato come il test più utilizzato, che si riflette costantemente in oltre l'80% di tutte le diagnosi di casi segnalati.

Le linee guida cliniche per la diagnosi e il trattamento della polmonite acquisita in comunità non raccomandano test eziologici della polmonite in ambito ambulatoriale. Di conseguenza, la maggior parte dei casi della malattia del legionario segnalati proviene dagli ospedali e il tasso di ospedalizzazione dei casi notificati è generalmente elevato (89.9%). L'aderenza alle linee guida cliniche e, di conseguenza, il comportamento in materia di test influisce anche sulla consapevolezza della malattia da parte dei medici. Nel nostro studio qualitativo, i medici che lavorano negli ospedali hanno indicato un alto livello di consapevolezza della malattia del legionario e approcci diagnostici e terapeutici comparabili. Al contrario, i medici generici hanno indicato livelli di consapevolezza più bassi, che riflettono il fatto che trattano empiricamente i casi di polmonite senza identificare l'agente causale. Pertanto, il livello di consapevolezza è dettato dalle linee

guida cliniche. Inoltre, i medici hanno espresso preoccupazioni riguardo alla sensibilità del test dell'antigene urinario e alla copertura limitata alla rilevazione di *Legionella* pneumophila sierogruppo 1. La disponibilità dei test diagnostici e la percezione dell'efficacia del test da parte dei medici hanno anche influenzato la loro preferenza per approcci terapeutici ad ampio spettro o mirati. Infine, anche i vincoli estrinseci, come le considerazioni finanziarie e di tempo, hanno influenzato le preferenze dei medici in materia di test e trattamento.

L'entità e l'importanza per la salute pubblica dei casi lievi non rilevati e la percentuale di casi gravi evitabili grazie a una diagnosi più precoce rimangono sconosciuti. Il tasso di mortalità dei casi della malattia del legionario è diminuito tra il 2000 e il 2020 dal 7.7% al 3.6%. Tuttavia, il confronto con le statistiche ospedaliere mostra che il tasso di mortalità è in media sottostimato del 30%. Anche tenendo conto di questa sottostima, il tasso di mortalità in Svizzera sembra essere leggermente inferiore alla media europea dell'8%.

Per quanto riguarda la distribuzione regionale all'interno della Svizzera, il Canton Ticino, nella Svizzera meridionale, ha costantemente registrato un numero di casi della malattia del legionario pro capite più elevato rispetto al resto della Svizzera. Tra gli anni 2017-2021, è stato inoltre identificato come un hotspot regionale statisticamente significativo, con un tasso di notifica standardizzato di 14.3 casi/100,000 abitanti (IC: 12.6-16.0). Negli ultimi anni, tuttavia, il numero di casi sta diminuendo in Ticino e aumentando in tutte le altre regioni della Svizzera.

Noi sosteniamo che questo aumento complessivo del numero di casi della malattia del legionario sia almeno in parte dovuto a cambiamenti nell'incidenza effettiva della malattia e non rappresenti un artefatto della sorveglianza. Le linee guida cliniche per l'analisi eziologica dei casi di polmonite, che influenzano l'individuazione dei casi e quindi il numero di casi osservati, sono da tempo standardizzate per i pazienti ospedalizzati con polmonite e i metodi di analisi diagnostica utilizzati sono rimasti in gran parte invariati. Un'altra ipotesi che spiega l'aumento come artefatto della sorveglianza è che l'aumento della consapevolezza tra i medici della *Legionella* come causa di polmonite possa aver portato a una maggiore individuazione dei casi. Tuttavia, è ragionevole supporre che i protocolli di analisi delle linee guida cliniche siano stati seguiti in passato, anche quando il livello di consapevolezza della malattia non era così elevato come oggi. Inoltre, l'effetto della crescente consapevolezza dei medici dovrebbe diminuire nel tempo, fino a raggiungere un plateau. Tuttavia, dopo 20 anni di aumento sostenuto, il numero di casi della malattia del legionario non mostra segni di rallentamento.

Tuttavia, i fattori che determinano l'infezione e le cause dell'eterogeneità regionale sono rimasti poco chiari. Ciononostante, utilizzando due diverse metodologie (un modello di regressione ecologico e uno studio case-crossover), abbiamo trovato prove dell'associazione a breve termine tra l'elevata temperatura media giornaliera (rapporto di odds (OR): 2.83; IC: 1.70-4.70) e la pressione media di vapore giornaliera (OR: 1.52; IC: 1.15-2.01) 6-14 giorni prima dell'insorgenza della malattia del legionario. Nel modello ecologico, abbiamo

anche trovato una forte associazione tra l'incidenza della malattia del legionario e l'inquinamento atmosferico, ma nessun risultato significativo nello studio case-crossover. Tuttavia, poiché il modello ecologico può essere soggetto a bias ecologici e lo studio case-crossover aveva una potenza limitata, sono necessari studi futuri per approfondire l'associazione. La comprensione di questi fattori di rischio su larga scala, come l'impatto delle condizioni meteorologiche e dell'inquinamento atmosferico sull'insorgenza della malattia del legionario, favorisce la comprensione delle differenze regionali, fornisce indicazioni sulla vulnerabilità di alcune popolazioni/regioni a rischio e, in ultima analisi, aiuta ad anticipare le tendenze della malattia.

La ricerca di fattori di rischio e siti di esposizione su piccola scala è fondamentale per misure di prevenzione e controllo mirate, ma è complessa a causa della dinamica della malattia, del ruolo dei sistemi idrici artificiali nella trasmissione della *Legionella* e, pertanto, richiede metodologie di ricerca appropriate e un'ampia gamma di competenze. Gli studi riassunti nella tesi hanno informato la progettazione di uno studio prospettico nazionale caso-controllo e di attribuzione molecolare della fonte, della durata di un anno. L'impostazione dello studio prevede la creazione di una rete ospedaliera di 20 ospedali universitari e cantonali per facilitare e accelerare il reclutamento di pazienti con la malattia del legionario e promuovere il campionamento di materiale dal tratto respiratorio inferiore per ottenere isolati clinici di *Legionella* . In un sottoinsieme di casi e controlli (provenienti dalla popolazione generale), vengono raccolti campioni di acqua dalla doccia e dal rubinetto della cucina, che vengono poi analizzati ed elaborati per ottenere isolati di *Legionella* dall'ambiente. In un'ultima fase, gli isolati clinici e ambientali vengono fatti corrispondere geneticamente mediante il sequenziamento dell'intero genoma (Whole Genome Sequencing) per supportare l'attribuzione della fonte di infezione. La componente ambientale di questo studio è stata sviluppata e realizzata in collaborazione con esperti di igiene dell'acqua negli edifici e di microbiologia ambientale. Lo studio fornisce quindi il quadro per una serie di ricerche sulla malattia del legionario e sulla *Legionella* , dagli aspetti clinici, come l'onere della malattia a lungo termine sui singoli pazienti, all'identificazione delle caratteristiche domestiche che favoriscono la contaminazione da *Legionella* . L'attuazione di questo progetto di ricerca nazionale rafforza la cooperazione intersettoriale e multidisciplinare e la creazione di capacità per affrontare il continuo aumento dei casi della malattia del legionario.

Alla luce dei cambiamenti climatici e demografici, si prevede un ulteriore aumento del numero di casi riportati della malattia del legionario in Svizzera e all'estero. Per arrestare questa tendenza, è necessaria una ricerca completa che consenta un'azione mirata e basata su dati concreti. Sebbene la Svizzera benefici di un forte sostegno governativo nella lotta a questa malattia, le lacune nei dati rimangono un ostacolo. In molti altri Paesi, il divario di dati è ancora maggiore. La mancanza di dati e stime sull'onere della malattia non si traduce nell'assenza di un problema di salute pubblica, e occorre impegnarsi per indagare sull'onere attribuibile alla malattia del legionario a livello globale. Nel contesto del cambiamento climatico e dell'urbanizzazione, la sanità pubblica dovrebbe promuovere un ambiente sano (costruito) per contenere la malattia del legionario e altre malattie infettive (ri)emergenti.

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Abbreviations

AIDS	Acquired Immunodeficiency Syndrome;
aOR	adjusted Odds Ratio;
ATS	American Thoracic Society;
BAG	Bundesamt für Gesundheit, Schweiz;
BAL	Bronchoalveolar Lavage;
BLV	Bundesamt für Lebensmittelsicherheit und Veterinärwesen, Schweiz;
BTS	British Thoracic Society;
CALD	community-acquired *Legionella* spp. infections;
CAP	Community-Acquired Pneumonia;
CAPNETZ	Competence Network Community Acquired Pneumonia;
CI	Confidence Interval;
CDC	Centers for Disease Control and Prevention, USA;
CFR	Case Fatality Rate;
CFU	Colony Forming Units;
cgMLST	core genome Multi-Locus Sequence Typing;
COVID-19	Coronavirus Disease 2019;
DALY	Disability-Adjusted Life Year;
DFA	Direct Fluorescent Antibody;
DIN	Deutsches Institut für Normung e.V.;
DLNM	Distributed Lag Linear and Non-Linear Models;
DWBSO	Drinking Water and Water in Public Baths and Shower Facilities Ordinance;
ECDC	European Centre for Disease Prevention and Control;
eCFR	electronic Case Report Form;
EEA	European Economic Area;
EID	(Re-)Emerging Infectious Disease;

EKNZ	Ethics Committee Northwest and Central Switzerland;
ELDSNet	European Legionnaires' Disease Surveillance Network;
EpidA	Swiss Epidemics Act;
EPIS	Epidemic Intelligence Information System;
ERS	European Respiratory Society;
ESCMID	European Society for Clinical Microbiology and Infectious Diseases;
ESGLI	European Study Group for *Legionella* Infections;
EU	European Union;
EWGLI	European Working Group for *Legionella* Infections;
FOE	Federal Office of Energy, Switzerland;
FOPH	Federal Office of Public Health, Switzerland;
FSO	Federal Statistical Office;
FSVO	Federal Food Safety and Veterinary Office, Switzerland;
GIS	Geographic Information System;
GNI	Gross National Income;
GP	General Practitioner;
HIV	Human Immunodeficiency Virus;
HRA	Human Research Act;
HUS	Hemolytic Uremic Syndrome;
ICU	Intensive Care Unit;
IDSA	Infectious Diseases Society of America;
ISO	International Organization for Standardization;
LD	Legionnaires' Disease;
L. pneumophila	*Legionella pneumophila*;
LMIC	Low- and Middle Income Country;
LRTI	Lower Respiratory Tract Infection;
MAb	Monoclonal Antibodies;
MALDI-TOF MS	MALDI-TOF Mass Spectrometry;

MeSH	Medical Subject Heading;
MeteoSwiss	Federal Office for Meteorology, Switzerland;
NENT	National Centre for Enteropathogenic Bacteria and Listeria, Switzerland;
NNDSS	National Notifiable Diseases Surveillance System, USA;
NNSID	National Surveillance System for Infectious Diseases, Switzerland;
NO_2	Nitrogen Dioxide;
NCBI	National Center for Biotechnology Information;
NRCL	National Reference Centre for *Legionella*, Switzerland;
NTD	Neglected Tropical Disease;
NUTS	Nomenclature of Territorial Units for Statistics;
ODK	Open Data Kit;
OR	Odds Ratio;
OxCGRT	Oxford Covid-19 Government Response Tracker;
PCR	Polymerase Chain Reaction;
$PM_{2.5}$	Particular Matter smaller or equal to 2.5μm;
PM_{10}	Particular Matter smaller or equal to 10μm;
PSI	Pneumonia Severity Index;
QFE	measured air pressure on the ground (meteorological station);
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus type 2;
SBT	Sequence-Based Typing;
SDG	Sustainable Development Goal;
SDI	Socio-Demographic Index;
SEP	Socio-Economic Position;
sg	serogroup;
SIA	Schweizerischer Ingenieur- und Architektenverein;
SLDSS	Supplemental Legionnaires' Disease Surveillance System, USA;
SNP	Single Nucleotide Polymorphism;
spp.	*species plurimae*;

SPSP	Swiss Pathogen Surveillance Platform;
SSI	Swiss Society for Infectious Diseases;
ST	Sequence Typ;
STEC	Shiga toxin-producing *Escherichia coli*;
Stx	Shiga toxin;
SVGW	Schweizerische Verein des Gas- und Wasserfaches;
Swisstopo	Federal Office of Topography, Switzerland;
Swiss TPH	Swiss Tropical and Public Health Institute;
SWKI	Schweizerische Verein von Gebäudetechnik-Ingenieuren;
TALD	Travel Associated Legionnaires' Disease;
TESSy	The European Surveillance System;
UAT	Urinary Antigen Test;
US	United States;
VBNC	Viable But Non-Culturable;
WGS	Whole Genome Sequencing;
WHO	World Health Organisation.

Glossary

antibiotic stewardship. '[...] A coherent set of actions which promote using antimicrobials in ways that ensure sustainable access to effective therapy for all who need them.'[1]

'The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance.'[2]

artifact. Surveillance artifacts are events such as heightened awareness of a disease, introduction of new diagnostic tests, and changes in the method of conducting surveillance. These events change the sensitivity of a surveillance system to capture disease cases and therefore can lead to changes in the observed case numbers. 'A search for such surveillance "artifacts" is often an initial step in outbreak investigations.'[3]

case fatality rate. As a measure of disease fatality, it represents 'the proportion of (diagnosed) cases of a specified condition which are fatal within a specified time.'[4] The case fatality rate is usually expressed as a percentage:

$$\text{CFR } [\%] = 100 \times \frac{\text{number of deaths from a disease (in a given period)}}{\text{number of diagnosed cases that disease (in the same period)}}$$

emerging infectious disease. Emerging infectious diseases are defined as infectious diseases that are newly recognized in a population or have existed but are rapidly increasing in incidence or geographic range. They may be new infections resulting from changes or evolution of existing organisms, known infections spreading to new geographic areas or populations, previously unrecognized infections appearing in areas undergoing ecologic transformation, or old infections reemerging because of antimicrobial resistance in known agents or breakdowns in public health measures.[5]

National Notification System for Infectious Diseases. As a basis for the reporting of infectious diseases, an obligatory national notification system was established in Switzerland and is explicitly described in the Epidemics Act (SR 818.101.1) in Switzerland in its newest revision since 2016. It is operated by the

[1] O Dyar et al. [2017]. "What is antimicrobial stewardship?" In: *Clinical Microbiology and Infection* 23.11, pp. 793–798.
[2] TH Dellit et al. [2007]. "Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship". In: *Clinical Infectious Diseases* 44.2, pp. 159–177.
[3] DN Klaucke et al. [1988]. "Guidelines for evaluating surveillance systems". In: *Morbidity and Mortality Weekly Report.*
[4] M Porta [2014]. *A Dictionary of Epidemiology.* Oxford University Press.
[5] DB McArthur [2019]. "Emerging infectious diseases". In: *Nursing Clinics* 54.2, pp. 297–311.

Federal Office of Public Health in collaboration with the cantonal medical services, analytical laboratories and doctors.

'Doctors, hospitals and other public and private public health institutions notify observations regards infectious diseases with all information necessary to identify the sick, infected or exposed persons and the transmission pathway to the cantonal authorities and for specific pathogens additionally to the Federal Office of Public Health. Additionally, laboratories notify analytical findings with information necessary to identify the sick or infected person to the cantonal authorities and the Federal Office of Public Health.'[6]

Legionnaires' disease. Legionnaires' disease is a severe and atypical pneumonia caused by the gram-negative *Legionella* bacteria which is found in natural and artificial aquatic environments including cooling towers or water systems in buildings. After exposure, the incubation period is roughly 2–14 days.[7]

notification rate. The notification rate represents the proportion of notified cases of a specified condition within a population of a defined size under surveillance. If the surveillance of the disease manages to capture all cases, the notification rate approximates the incidence rate. It is usually expressed as per 100,000 population.[8]

$$\text{notification rate} = \frac{\text{number of notified cases (in a given period)}}{\text{population under surveillance (in the same period)}} \times 100{,}000$$

passive surveillance. 'A system by which a health jurisdiction receives reports submitted from hospitals, clinics, public health units, or other sources. Passive surveillance is a relatively inexpensive strategy to cover large areas, and it provides critical information for monitoring a community's health. However, because passive surveillance depends on people in different institutions to provide data, data quality and timeliness are difficult to control.'[9]

Pontiac fever. 'Pontiac fever is a febrile and generally benign, non-pneumonic disease associated with exposure to *Legionella* bacteria. Its pathogenesis remains obscure and there is no agreed-on definition, nor any specific clinical findings or laboratory tests for its diagnosis. [...] Pontiac fever is produced by inhalation of an environmental water aerosol containing microorganisms and their toxins, including *Legionella* spp.'[10]

[6] The Federal Assembly of the Swiss Confederation [2016]. *Federal Act on Controlling Communicable Human Diseases (Epidemics Act, EpidA)*. https://www.fedlex.admin.ch/eli/cc/2015/297/en. Legal Rule or Regulation. SR 818.101.
[7] BA Cunha, A Burillo, and E Bouza [2016]. "Legionnaires' disease". In: *The Lancet* 387.10016, pp. 376–385.
[8] M Porta [2014]. *A Dictionary of Epidemiology*. Oxford University Press.
[9] P Nsubuga et al. [2006]. "Public health surveillance: a tool for targeting and monitoring interventions". In.
[10] BA Cunha, A Burillo, and E Bouza [2016]. "Legionnaires' disease". In: *The Lancet* 387.10016, pp. 376–385.

positivity rate. The positivity rate represents the proportion of all tests for a condition within a specified period of time which are positive. The positivity rate is a measure of disease spread within a population but dependent on additional factors such as the indications for testing, and specificity and sensitivity of laboratory methods. The positivity rate is usually expressed as a percentage:

$$\text{positivity rate [\%]} = 100 \times \frac{\text{number of positive tests from a disease (in a given period)}}{\text{number of performed tests for that disease (in the same period)}}$$

recall bias. 'Recall bias in a case-control study is the increased likelihood that those with the outcome will recall and report exposures compared to those without the outcome. In other words, even if both groups had exactly the same exposures, the participants in the cases group may report the exposure more often than the controls do. Recall bias may lead to concluding that there are associations between exposure and disease that do not, in fact, exist. It is due to subjects' imperfect memories of past exposures. If people with Kaposi's sarcoma are asked about exposure and history (e.g., HIV, asbestos, smoking, lead, sunburn, aniline dye, alcohol, herpes, human papillomavirus), the individuals with the disease are more likely to think harder about these exposures and recall having some of the exposures that the healthy controls.'[11]

underestimation. 'Underestimation [...] can be understood as the many ways in which surveillance systems fail or are unable to reflect all infections in a given population. Mathematically, underestimation is the number of infections estimated to have occurred in a population that have not been captured by the surveillance system for every reported case over a given time period.'[12]

whole genome sequencing. Sequence determination of the near-complete (typically 95–99% of the total) length of the full genome of a microorganism. '[Whole genome sequencing] has become the reference microbial typing method in outbreak studies and is increasingly applied to national surveillance of infectious diseases in EU/EEA countries and beyond. [...] The advantages of whole genome sequencing-based typing over other pathogen typing methods includes the optimal resolution of the near-complete genomic sequence comparison for measuring inter-genomic sequence similarity, and inferring the most probable phylogenetic lineages of descent between isolates to infer the direction and route of pathogen transmission, from environmental, animal or human sources and reservoirs [...]. However, work on how to translate genomic data into meaningful information for public health decision-making is still incomplete.'[13]

[11] S Tenny, CC Kerndt, and MR Hoffman [2017]. *Case control studies*. https://www.ncbi.nlm.nih.gov/books/NBK448143/. Website. Accessed: 2022-09-17.

[12] CL Gibbons et al. [2014]. "Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods". In: *BMC Public Health* 14.1, p. 147.

[13] European Centre for Disease Prevention and Control (ECDC) [2016]. *Expert opinion on whole genome sequencing for public health surveillance*. Report.

Preamble

My engagement with Legionnaires' disease began in 2017 with a research mandate to establish positivity rates for *Legionella* infections and Shiga toxin-producing *Escherichia coli*. At the time, I could not have imagined the scale of the research endeavour I had embarked on and the portfolio of work that I would create in the framework of a dissertation on Legionnaires' disease. With this thesis, I would like to take the reader on a journey similar to my own. We begin as I did, with studies on Legionnaires' disease notification data and a deep dive into the data and literature. From this initial and mostly desk research, I moved into the field, interviewing both health care providers and patients with Legionnaires' disease. Along my way, I was fortunate enough to meet and collaborate with many actors involved in Legionnaires' disease research, treatment and mitigation. Through these collaborations, we managed to bring together diverse expertise, in both research and application, which has charted the next phase of Legionnaires' disease research in Switzerland. As one journey ends, another begins and I am excited that the end of this dissertation marks the beginning of a national research project on Legionnaires' disease that is likely unprecedented in its scope and ambition.

I hope that this thesis will be a useful reference tool for professionals and researchers working on Legionnaires' disease in Switzerland and a source of motivation for a joint, multi-sectoral response to this public health concern.

The layout and formatting of published articles were adapted for the purposes of this thesis. This includes tables, figures and supplementary material numbering. Supplementary materials of published articles are included in the appendix at the end of the thesis (page iii). Materials from other sources (e.g. the various notification forms), which are provided in the appendix for ease of reference, have not been adapted for the purposes of this thesis, including the layout. Abbreviations which are repeatedly used, are included in the list of abbreviations (page XXXI) and are marked with an '*'. All references, including from published articles, are jointly listed in the bibliography (page 294).

Part I

Introduction, Objectives and Methodology

Chapter 1

Introduction

1.1 (Re-)emerging diseases: new challenges to tackle

Legionnaires' disease (LD)* was discovered and gained worldwide recognition after an outbreak in the United States (US)* in 1976 resulted in the deaths of 29 out of 182 infected people [Fraser et al. 1977]. Many attendees of a convention of the American Legion, an organization of US war veterans in Philadelphia, fell ill with severe pneumonia, which was later attributed to a bacterial infection with *Legionella* species (spp.)*. The outbreak attracted considerable attention and encouraged intensive research [Winn Jr 1988]. In the same year of the outbreak, the US introduced LD into their passive surveillance system[1] requiring LD cases to be reported to the health authorities. In the subsequent years, several other countries followed suit. However, this interest was short-lived, as the lack of (observed) cases led to a perception of low public health relevance. At the same time, the arrival of other devastating diseases captured the public's attention, such as the human immunodeficiency virus (HIV)*/the acquired immunodeficiency syndrome (AIDS)* in the 1980s [Greene 2007] and the recognition of non-communicable diseases such as Alzheimer's disease and bulimia nervosa in the 1970s and 1980s. These factors led to a loss of interest and slowed LD-specific research endeavours [Winn Jr 1988]. In recent years, an increase in LD case numbers [ECDC 2022; Fischer, Mäusezahl, and Wymann 2022] and repeated outbreaks with up to 380 infected individuals (such as in Portugal, 2014 [Hamilton et al. 2018; Russo et al. 2018]) have increased the visibility of LD and exemplify the threat of emerging or re-emerging diseases (EIDs)*. The former refer to previously undescribed diseases, the latter to known diseases that suddenly gain public health relevance [Herwaldt and Marra 2018; Morse 1995].

Globally, but especially in high- and middle-income countries, public health focus shifted away from infectious diseases following a steady decline in the global burden of infections since 1990 [Vos et al. 2020]. Today, four out of five main causes of death globally are non-communicable diseases [Vos et al. 2020] and the main burden of infectious diseases is borne by low and lower-middle income countries[2] (LMICs)*. The

[1] 'Passive surveillance systems are systems through which a health jurisdiction receives reports submitted from hospitals, clinics, public health units, or other sources' [Nsubuga et al. 2006]

[2] The Global Burden of Disease study stratifies countries by socio-economic strength using the socio-demographic index (SDI)*, a 'composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates' [Vos et al. 2020]. Many central and western European countries have a high SDI; Switzerland is the country with the highest SDI. For the remainder of this thesis, income levels are usually referred to by the definition of the World Bank based on the gross national income (GNI)* [World Bank 2022]

leading causes of death in LMICs are diarrheal diseases, lower respiratory tract infections and ischemic heart disease followed by malaria and tuberculosis, but diseases such as Schistosomiasis or Dengue, summarized under the term neglected tropical diseases (NTDs)* also account for a significant burden [IHME 2019]. These diseases have been largely eradicated and eliminated in high-income countries and while infectious diseases accounted for 17% of disability-adjusted life years (DALY)* and 14% of deaths in 2019 globally [Vos et al. 2020], the proportion of DALYs attributable to infectious diseases has reduced to 3% in high-income countries, and the proportion of deaths to 5%. Therefore, infectious diseases have largely shifted out of focus in these countries. Yet, the threat posed by infectious diseases is far from resolved: an outbreak of Ebola, a disease discovered in the same year as LD (1976), caused 11,000 deaths between 2013 and 2016 in West Africa [Rojas et al. 2020]. An epidemic of the Zika virus spread throughout the Americas (primarily Middle and South America) since 2015, with an estimate of 132.3 million infected people by 2018 [Moore et al. 2020]. Still, high-income countries could remain largely unconcerned towards these threats. Recently, the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)* pandemic has shown that, even for the affluent countries, new infectious diseases pose a persisting threat that can have debilitating effects [Islam et al. 2021].

There are several reasons for the emergence of new, or the spread of known infectious diseases that were previously thought to be under control, that can be broadly categorized into changes in disease control and changes in environment and demographics. Pathogens for which effective treatments exist may develop drug-resistance, as is the case for tuberculosis [Suk and Semenza 2011]. Vaccine-preventable diseases may re-emerge as a consequence of dropping vaccination rates, as seen recently when Croatia [Tomljenovic et al. 2020] or Italy [Andrianou et al. 2019] had to combat outbreaks of measles. Climate change is also widening the geographic range of some disease vectors, such as the mosquito species transmitting malaria or dengue, while rising sea levels and extreme weather events promote the spread of water-borne diseases such as cholera [Patz et al. 1996; Semenza and Menne 2009]. Rapid urbanization and increasing population density promote zoonotic and foodborne diseases such as listeriosis. Lastly, changes in migration, tourism, and human trafficking are thought to globalize sexual networks and promote the transmission of sexually transmitted diseases, such as gonorrhoea and chlamydia [Suk and Semenza 2011].

Considering the range of possible sources of EIDs, it becomes apparent that the problems they cause are likely to exacerbate in the future. Currently, the focus of combatting EID is on surveillance and rapid and effective response [McCloskey et al. 2014]. This approach can be strengthened by improved epidemiological surveillance, better case detection through faster and cheaper diagnostics and the development of new or improved antimicrobial treatments [Bloom, Black, and Rappuoli 2017]. Arguments have also been made to shift focus to combat EIDs upstream i.e. from surveillance and response to prevention [McCloskey et al. 2014]. However, this reorientation necessitates an integrated strategy for healthy living and a combination

of classical epidemiology with other disciplines, such as sociology, economics and ecology [Suk and Semenza 2011].

Vulnerability to EIDs is exacerbated by the lack of disease knowledge. The recent SARS-CoV-2 pandemic is an example of the difficulty involved with policy-making and planning of prevention and control measures in the absence of scientific evidence to guide decisions. Successful management of EIDs hinges on a comprehensive understanding of the disease, from pathogen, over patient to the health system [Fears, Meer, and Meulen 2011]. To make effective evidence-based policy for LD prevention and control, the knowledge base must first catch up with the last 50 years, during which LD has received little attention: Little is known about the epidemiology of this disease and the disease system as a whole; a comprehensive understanding of major exposures sources, transmission pathways, the exposure-response relationship and risk factors is lacking.

1.2 A short introduction to Legionnaires' disease and *Legionella* spp.

Diseases caused by *Legionella* spp. are summarized under the term legionellosis [Cordes and Fraser 1980]. The majority of recognized legionellosis cases are LD, which is typically characterized by pneumonia, but can be accompanied by a wider range of diffuse symptoms such as confusion and diarrhoea [Cunha, Burillo, and Bouza 2016]. Nowadays, the case fatality rate (CFR)* of LD is with approximately 10% similar to estimates from other community-acquired pneumonia (CAP)* in adult hospitalised patients [Phin et al. 2014; Baum et al. 2008], but higher than reported CAP fatality rates in outpatients (3%) [Restrepo, Faverio, and Anzueto 2013]. With comorbidities and other risk factors, LD fatality rates can be much higher [WHO 2007]. Pontiac fever is the other clinically distinct presentation of a *Legionella* spp. infection. Pontiac fever remains largely undescribed beyond its definition as a self-limiting flu-like *Legionella* infection [Cunha, Burillo, and Bouza 2016; Glick et al. 1978]. In rare instances, *Legionella* spp. can cause severe extrapulmonary infections such as myocarditis or wound infections [Cunha, Burillo, and Bouza 2016; Marrie and Hoffman 2011]. There is compelling evidence that LD can lead to long-term consequences and debilitated health status due to symptoms of fatigue or compromised general self-reported quality of life [Gamage et al. 2021; Lettinga et al. 2002; Loenhout et al. 2014].

1.2.1 Transmission, exposure and risk factors of Legionnaires' disease

Legionella spp. are ubiquitous in freshwater ecosystems. Therefore, almost all water sources that release droplets into the air (through evaporation or mechanical sheering) are potential sources of infection. Yet, the number of LD cases remains on a much lower level than the presumably frequent exposure to the

ubiquitous bacteria would suggest. The attack rate[3] for LD is estimated at approximately 0.01-6.4% [Phin et al. 2014] and 70-95% for Pontiac fever [WHO 2007; Doebbeling and Wenzel 1987; Glick et al. 1978; Pancer and Stypułkowska-Misiurewicz 2003; Stypułkowska-Misiurewicz and Czerwiński 2016]. However, these rates are primarily based on estimates from outbreak investigations; neither the exposure-response relationship, nor the most important drivers of infections are known.

Several sources of exposure, ranging from residential showers, to car washing facilities, cooling towers and compost and soil have been described as causing *Legionella* infections [Orkis et al. 2018; Heijnsbergen et al. 2015]. Most of these sources were identified during the investigation of an outbreak. However, 90% of all LD cases are sporadic, i.e. occurring as a single case not associated with any identified outbreak [Rockswold and Bernier 2021]. It is uncertain whether the same infection sources described for outbreaks also cause the majority of sporadic infections.

The investigation of infectious sources is complicated by the sophisticated biology and ecology of *Legionella* bacteria. While *Legionella* bacteria proliferate best in warm (25-42 degree Celsius [°C]) and stagnant water, they can also survive in a wider range of temperatures (5-63 °C) [Fliermans 1996]. Additionally, they exist free-living in the water, hidden in biofilms, encapsulated as a viable but non-culturable (VBNC)* state, and within protozoa (such as amoeba) [Borella et al. 2005]. The ability of *Legionella pneumophila* to replicate within host cells is central to their pathogenesis and ecology. Due to this diverse ecology, most of the known detection methods encounter difficulties in determining the actual extent of *Legionella* contamination. The detected level of *Legionella* may vary depending on the day and place of sampling and testing and the analytical methods used to detect *Legionella* (such as agar plate treatment). Lastly, even if the bacteria is found in a suspected infectious source, due to the ubiquitous nature of *Legionella*, it still might not be responsible for the illness case. Several methods are available to identify the strain or serogroup of *Legionella*, such as (multiplex) polymerase chain reaction (PCR)*, MALDI-TOF mass spectrometry (MALDI-TOF MS)* or agglutination tests. Subtyping below strain or even serogroup level has been found especially useful to support the identification of enviornmental sources [Cunha, Burillo, and Bouza 2016; Lück et al. 2013]. Various methods exists to sub-type including detection of lipopolysaccharide epitope patterns using monoclonal antibodies (MAb)* to subtype *Legionella pneumophila* sg 1 and genomic subtyping methods, such as sequence-based typing (SBT)* [Lück et al. 2013]. A high degree of differentiation between *Legionella* supporting source attribution can be achieved by whole genome sequencing (WGS)* *Legionella* spp.

Currently more than 60 *Legionella* species with more than 80 serogroups habe been described [Miyashita et al. 2020]. The majority of human illness cases are attributed to *Legionella pneumophila* , especially *L.*

[3] 'The proportion of a group that experiences the outcome under study over a given period (e.g., the period of an epidemic)' [Porta 2014].

pneumophila * serogroup (sg)* 1, which accounts for over 80% of the disease burden worldwide [Yu et al. 2002] and over 90% in Switzerland [Fischer, Mäusezahl, and Wymann 2022]. Yet, there appears to be some regional variability in the occurrence of *Legionella* strains, e.g. in Australia and New Zealand, *Legionella longbeachea*, a strain that is predominantly found in soil and compost, is commonly detected in clinical samples [Yu et al. 2002].

In addition to local differences in the causative strains, which might influence regional variability in LD incidence, incidence is also variable over time. Weather, for example, appears to have a strong influence on infection rates [Pampaka et al. 2022; Walker 2018]. Case numbers increased following hot and humid days or after heavy rainfall events [Gleason et al. 2016]. Consequently, LD cases primarily occur in summer [ECDC 2022]. In contrast to environmental factors, host-specific risk characteristics have been relatively well described. Men are twice as likely to be diagnosed with LD as women and the risk increases after 50 years of age [Cooley et al. 2020; Marston, Lipman, and Breiman 1994]. Other risk factors include smoking, alcohol consumption, and comorbidities such as diabetes mellitus, chronic lung disease, renal failure, various types of cancer, and immunosuppression. Most other risk factors are behavioural such as recent travel history (exposure to stagnated water or compromised plumbing systems) and/or related to suspected exposure to contaminated aerosols, such as exposures to cooling towers or wastewater treatment plants or, particularly in Australia and New Zealand, gardening and soil exposure [Boer, Nijhof, and Friesema 2006; Emma et al. 2017; O'Connor et al. 2007].

1.2.2 Clinical management of Legionnaires' disease

Once *Legionella* spp. has entered the lower respiratory tract, they attack alveolar macrophages and multiply intracellularly before inducing apoptosis and before killing the host cell [Fields, Benson, and Besser 2002]. LD symptoms usually develop after 2 to 14 days [Cunha, Burillo, and Bouza 2016]. The primary clinical characteristic of LD is pneumonia, which is usually confirmed by imaging procedures such as chest X-ray or computer tomography [Ott 2018]. It often seems difficult to distinguish *Legionella* pneumonia clinically from other types of pneumonia, such as pneumococcal pneumonia. Common symptoms associated with both types of pneumonia include high fever, cough, chills, and dyspnoea [Cunha, Burillo, and Bouza 2016]. *Legionella* pneumonia is additionally associated with gastrointestinal (such as diarrhoea and nausea) and neurological symptoms (such as headache and confusion). Attempts to establish clinical criteria and scores to differentiate LD from other types of pneumonia have been either unsuccessful, are currently being validated or not yet widely used [Bolliger et al. 2019; Cunha 2008; Fiumefreddo et al. 2009]. Pontiac fever manifests after a few hours, but appears to remains benign without needing antimicrobial treatment, even though the pathogenesis is still not well understood.

There are five main diagnostic methods for the clinical detection of *Legionella* spp. infections, each with strengths and limitations: culture, urinary antigen test (UAT)*, PCR, direct fluorescent antibody (DFA)*

staining and serological testing. Culturing is considered the gold standard for *Legionella* identification with a 100% specificity [Diederen 2008]. Isolation from culture also allows genotyping and can, therefore, be used for source attribution. However, *Legionella* spp. are fastidious bacteria, onerous and slow to grow, allowing proper diagnosis only after approximately 7-10 days after the respiratory sample has been obtained. This wait can delay the prescription of an effective antimicrobial treatment and worsen the health outcome of the patient [Viasus et al. 2022]. Additionally, sensitivity i.e. successful culturing *Legionella* spp. is dependent on the sample material obtained from the patient and can vary between 20% and 80% [Cunha, Burillo, and Bouza 2016]. The highest sensitivity is obtained with samples from the lower respiratory tract. Yet, the availability of these samples proves to be a bottleneck: sputum samples are not always available, as LD causes mostly non-productive cough and broncheo-aelovar lavage is only applicable for severely ill (and intubated) patients. Samples from the upper respiratory tract (such as nasopharyngeal swaps) provide less sensitivity [Cho et al. 2012]. In the 1990s the UAT was developed, allowing *Legionella* antigens to be detected in urine. Due to its ease of use, the obtainability of sample material without compromising patient comfort, and the fast turnaround, the UAT has revolutionized clinical management of pneumonia and LD. Nowadays, the majority of *Legionella* cases are diagnosed using the UAT (90% in Europe [ECDC 2022]). The major drawback is coverage, which is limited to *L. pneumophila* sg 1. As the majority of human illness cases are caused by *L. pneumophila* sg 1, one could assume that this limitation is not of great importance. However, this would be an oversimplification: if the most commonly used diagnostic test detects only one strain, it seems likely that the reported frequency of that strain overestimates the true (relative) prevalence of this strain in human cases. Additionally, sensitivity seems to be based on disease severity, whereby mild cases might be false-negative. Overall, test sensitivity is only 74%, while specificity is 99% [Shimada et al. 2009]. Detection with PCR is becoming more frequently used for diagnosis and has several important advantages: sensitivity and specificity is higher than UAT and culture with 97% and 99%, respectively, and it is able to detect strains other than *L. pneumophila* sg 1. Yet, it suffers the same drawback as culture (limited availability of a suitable sample), and could provide false-positive results by detecting non-culturable/dead *Legionella* and is more expensive. Most recently, molecular diagnostics for *Legionella pneumophila* has been added to syndromic multiplex PCR panels. Until the 2000s, DFA staining was a popular method but has been largely replaced by the UAT, which has both improved sensitivity and specificity [Murdoch 2003]. Serological methods for diagnostic testing are also rarely used any more, as their suitability for clinical evaluation is limited. In summary, the diagnostic methods used heavily impact the observed epidemiological features of LD: mild cases and non-*pneumophila* strains are likely underrepresented.

Legionella infections are treated with antibiotics exerting intracellular antibiotic activity. The guidelines from the Swiss Society for Infectious Diseases (SSI)* recommend quinolones [Albrich et al. 2021]. Macrolides are also effective, and recommended by various other guidelines [Boyles et al. 2017; Wiersinga et al. 2018]. A systematic review on quinolones versus macrolides for the treatment of *Legionella* spp. infec-

tions showed a trend in decreased mortality and shorter hospital stay when using quinolones [Burdet et al. 2014]. Treatment duration for *Legionella* spp. infections have generally been longer than for other types of pneumonia [Laifer, Flückiger, and Scheidegger 2006]. Though in recent years, the recommended therapy duration has been shortened and aligned to other pneumonia treatment durations of 5 to 7 days [Albrich et al. 2021; Viasus et al. 2022]. Fast diagnosis of LD and prompt treatment with effective antibiotics are essential for beneficial health outcomes. Yet diagnosis is contingent on the physicians' awareness of LD and the success of diagnostic tests, whose shortcomings have been described above. An alternative, to ensure the best health outcome, would be empirical treatment with extra-and intracellular active antibiotics. This generalised broad-spectra treatment approach, however, is not in line with antibiotic stewardship efforts. Overall, diagnosis and diagnostic methods are not only essential for adequate treatment for individual patients, but also for case detection. Improvement in these areas will contribute to a more accurate evaluation of the disease burden and better inform public health policy and resource allocation.

1.3 Public health of infectious diseases in Switzerland and Europe

In Switzerland, LD case reporting is mandatory since 1988. Infectious disease notification is regulated in the Epidemics Act (EpidA)* [Federal Assembly 2016], in particular by the ordinance on combating communicable human disease and the ordinance on notification of communicable diseases by physician and laboratories [Bundesrat 2015; EDI 2015]. The latest update of the EpidA has come into force in 2016. Diseases covered in the surveillance system need to fulfil one of the following criteria: they (i) may cause epidemics; (ii) may result in serious consequences; (iii) are novel or unexpected; or (iv) their monitoring is internationally agreed upon. *Legionella* spp. and LD fulfils all of these .

In Europe, LD is monitored in a European-wide network since 1987 with the establishment of the European Working Group on *Legionella* Infections (EWGLI)*[4] [ECDC 2017a]. In 2010, surveillance activities were transferred to the European Center for Disease Control and Prevention (ECDC)* which is mandated to detect, control and prevent cases and outbreaks. Specifically and with regard to LD, the activities of ECDC were threefold: (i) collect and disseminate routine surveillance data from all member states; (ii) collect and disseminate clusters and outbreaks and (iii) facilitate the control of travel-associated LD cases, which require multi-country coordination. The two former activities were carried out within the European Surveillance System (TESSy)* managed by ECDC. To enable multi-country coordination, ECDC manages also an Epidemic Intelligence Information System (EPIS)* under the name 'European Legionnaires' disease Surveillance Network' (ELDSNet)*. The international infectious disease surveillance in Europe is currently in transition: By the end of 2022 TESSy and ELDSNet will be replaced by the 2021-launched 'EpiPulse

[4] Around 2012, EWGLI was replaced by a new working group of the European Society of Clinical Microbiology and Infectious disease (ESCMID)*, called European Study Group for *Legionella* Infections (ESGLI)*

- European surveillance portal for infectious diseases'. The platform is a means to harmonize infectious disease surveillance and integrates multiple tools, including WGS as a one-stop shop. Switzerland is neither part of the European Union (EU)*, nor the European Economic Area (EEA)* and, therefore, not included in TESSy or ELDSNet. Consequently, no Swiss notifiable disease including LD is reflected in ECDC dissemination reports. However, in the interest of public health, there seems to be a limited exchange between Switzerland and ELDSNet on travel-associated LD cases. The degree of Switzerland's inclusion in EpiPulse currently remains unclear. Outside of the EU, the World Health Organization (WHO)* has recently organised a Pan-European expert meeting on the prevention and control of legionellosis, which Switzerland attended [WHO 2022].

The Swiss Notification System for Infectious Diseases (NNSID)* provides the data basis for most of the studies presented in this thesis and is, therefore, briefly explained here. The NNSID is managed by the Federal Office of Public Health (FOPH)*. There are two pathways for notification of a *Legionella* infection: Through the diagnostic laboratory providing a laboratory notification form (Appendix F-3) and through the treating physician providing a clinical notification form (Appendix F-4). The diagnostic laboratories report any positive test result for *Legionella* spp. to the cantonal[5] physician/cantonal medical services ('Kantonsärztlicher Dienst') of the patient's canton of residence and to the NNSID directly. Physicians who diagnose a case are asked to report to the cantonal physician only. The cantonal physician is responsible for acquiring the patients' information on exposure and risks and to initiate the environmental investigation if deemed necessary. This information is provided by the cantonal physician on the clinician's form to the NNSID. The notification period for both physicians (treating and cantonal) and laboratories is seven days after identifying a positive finding. This means that theoretically up to two weeks (one week each for the treating and cantonal physician) may elapse between the identification of the case and the complete notification to the FOPH. At the FOPH, laboratory and clinical notifications are entered into an electronic database and compiled to one entry for each case.

Although all laboratory-confirmed infections with *Legionella* spp. are required to be reported, only cases that present with pneumonia are classified as either confirmed or probable LD cases and are disseminated in official reports. The current case definition of LD in Switzerland differs slightly from that of the ECDC (see Table 1.1) [Gysin 2018]. While the ECDC recognizes *Legionella pneumophila* sg 1 seroconversion in a paired sample as a confirmed case, the FOPH classifies it as a probable case. The NNSID includes a 'possible case' category for all individuals who meet the laboratory criteria but not the clinical criteria. Only confirmed and probable cases count towards the official FOPH reporting on LD, hence, *Legionella* infections not presenting with a pneumonia are excluded. There are two additional notification requirements

[5] A canton is an administrative sub-division within Switzerland. There are 26 cantons. The Federal Constitution states that 'the cantons are sovereign except to the extent that their sovereignty is limited by the Federal Constitution' [Swiss Confederation 1999]

concerning *Legionella* spp. and LD. First, a notification form to report a 'cluster of cases' (Appendix F-7) to be filled out by the cantonal physician. Second, since 2006, all laboratories are required to provide the aggregated total number of tests performed for *Legionella* spp. once per year [Federal Assembly 2016; Gysin 2018]. This information can be used as denominator data to contextualize the notification numbers. Last, all *Legionella* isolates obtained from patients are required to be sent for typing to the National Reference Centre for *Legionella* (NRCL)* in Bellinzona [BAG 2020a].

Table 1.1: Case definition for Legionnaires' disease as defined by the Swiss Federal Office of Public Health since 2012

Clinical criteria	**Microbiological criteria A:** Laboratory evidence of at least one of the following:	**Microbiological criteria B:** Laboratory evidence of at least one of the following:	**Definition for a Legionnaires' disease case**
Confirmed diagnosis of pneumonia	Isolation (culture) of *Legionella* species from respiratory secretions or any normally sterile site	Detection of *Legionella pneumophila* antigen in respiratory secretions or lung tissue e.g. by DFA staining using monoclonal-antibody derived reagents	A confirmed case should be one that meets clinical and microbiological criteria A.
	Detection of *Legionella pneumophila* antigen in urine	Detection of *Legionella* spp. nucleic acid in respiratory secretions, lung tissue or any normally sterile site	A probable case should be one that meets clinical and microbiological criteria B
	Significant rise in specific antibody level to *Legionella pneumophila* serogroup 1 in paired serum samples	Significant rise in specific antibody level to *Legionella pneumophila* other than serogroup 1 or other *Legionella* spp. in paired serum samples	A possible case should meet any of the laboratory criterion.
		Single high level of specific antibody to *Legionella pneumophila* serogroup 1 in serum	
		Significant rise in specific antibody level to *Legionella pneumophila* serogroup 1 in paired serum samples	

Source: Gysin [2018]

1.4 The burden of Legionnaires' disease in Switzerland and worldwide

The global burden of LD has not yet been quantified [Prüss-Ustün et al. 2014]. Disease estimates are mostly based on the notification numbers from the countries with established passive surveillance systems incorporating LD notification. The implementation of such a passive disease surveillance system necessitates an integrated healthcare system with an effective data flow, policy commitment to institutionalize such a system, and sufficient human and diagnostic resources. Many of these countries providing such data are, therefore, high-income countries. There is a striking lack of case estimates from other countries, especially from LMICs which typically do not have effective disease surveillance systems. Based on the ecological niche of *Legionella* spp. (warm and stagnant water) and climate factors affecting case numbers, it is reasonable to expect legionellosis to also occur in (sub-) tropical and tropical regions, which often coincide with low levels of per capita income. In addition, limited availability of appropriate antimicrobial treatment could increase the burden of disease even further in these countries without effective health care systems.

Even if a country formally monitors LD cases, the surveillance system might be poorly functioning. For example, countries in the eastern parts of Europe (Bulgaria, Romania, Greece and Poland) report strikingly low case numbers with less than 1 case per 100,000 population. Evidence from infected travellers returning from Greece [Beauté, Zucs, and De Jong 2012] and evidence from a cluster in Bulgaria point towards underdiagnosis [Tomova, Marinov, and Maeva 2007], and hence, the local health systems being unable to pick up cases [Beauté, Robesyn, and Jong 2013]. Therefore, even in countries with a established surveillance system, the incidence of disease is likely to be underestimated. Every step from infection to the registration of the case in the surveillance system can contribute to an underestimation of population exposure or disease burden. These different steps are often illustrated using the burden of illness pyramid as shown in Figure 1.1 for LD. The different levels are exemplified here: Starting on the mid-level of the pyramid, only patients that are seeking biomedical treatment have the potential to be reflected in the notification data, i.e. at the tip of the pyramid. Concerning LD, patients with Pontiac fever and mild cases of LD are not likely to seek care. Moving up on the pyramid, even at the health care provider level, pneumonia cases are often treated without aetiological testing. If a diagnostic attempt is made, the etiological pathogen might not be identified [Fischer, Deml, and Mäusezahl 2022]. Lastly, on the top level of the pyramid, once the pathogen has been identified, the finding must be reported to the health authorities. The case counts from the notification system are the closest estimates available to population level incidence in Switzerland.

The fundamental problem in estimating the burden of disease is differentiating LD from other types of pneumonia. As outlined in Chapter 1.2.2, it is difficult to clinically distinguish LD from other pneumonia cases. A microbiological assessment is often not performed for mild pneumonia cases treated in an outpatient

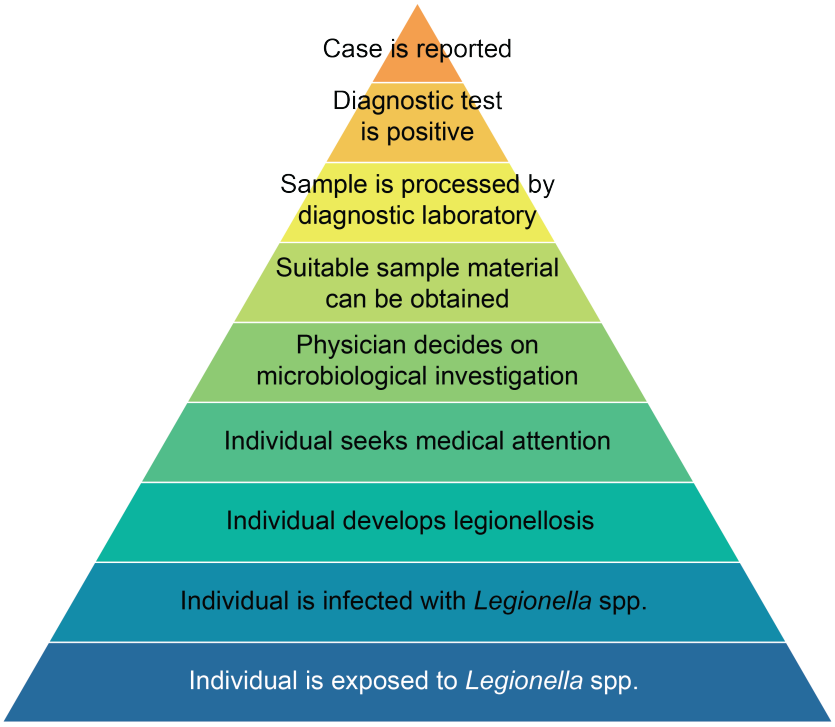

Figure 1.1: The burden of illness pyramid for food- and waterborne pathogens on the example of Legionnaires' disease and *Legionella*. Adapted from Allos et al. [2004], Gibbons et al. [2014], and MacDougall et al. [2008]

setting. Moreover, even if microbiological investigation is attempted, a causative agent cannot be found for more than half of all pneumonia cases [Carugati et al. 2018; Shoar and Musher 2020].

In Switzerland, 530 LD cases were reported in 2019, 435 cases in 2020 and 568 in 2021 [BAG 2022c]. This puts Switzerland among the countries with the highest notification rate per 100,000 population with 6.1/100,000 in 2019, 5.0/100,000 in 2020 and 6.5/100,000 in 2021. In Europe in 2020, only Slovenia reported a higher notification rate with 5.7/100,000 population. Several attempts have been made to estimate the true disease burden of LD at the national and global level, for example in the US, New Zealand or Europe. These attempts provide insights and context to the extent of underestimation in Switzerland. Active case finding over one year in New Zealand showed three times as many cases as in the previous years [Priest et al. 2019]. A study from the US in 2019 and from the ECDC in 2011 estimated that only approximately 10% of LD cases were captured in the respective notification systems [Cassell et al. 2019; Zucs 2011]. A global review of the seroprevalence for *Legionella* found a seroprevalence rate in the general population of 10.5% (95% CI: 11.3–16.5) [Graham et al. 2020]. With 8.6 million inhabitants in Switzerland in 2019, this would imply that 903,000 people were exposed at one point to *Legionella* spp. With an attack rate of 5% for LD, this would translate to 45,150 cases. However, the interpretation of seroprevalence is difficult, as single high levels of antibodies are not an indication of a clinically-relevant infection and high antibodies levels can persist for years. Therefore, such inferences need to be carefully evaluated. The bottom line, however, is that the number of LD cases in Switzerland is likely to be underestimated considerably.

1.5 Why has interest in Legionnaires' disease increased?

1.5.1 The reported cases of Legionnaires' disease are increasing

Apart from an uncertain disease burden, case numbers have been rising in Switzerland and other European countries, as well as the US, since the turn of the century. In the last 10 years, the notification rate of all countries covered by ELDSNet has increased. The average notification rate in 2009 was 1.1/100,000 population and in 2019, 2.2/100,000 population [ECDC 2021b; Zucs 2011]. Switzerland reported the largest increase (from 2.4 to 6.2) after Slovenia. The cause of this increase is unclear. However, there are two opposing hypotheses ascribing the increase in LD case numbers either to an artefact[6] of surveillance or to an actual increase in incidence: The first hypothesis proposes that the increase in the case numbers does not correspond to an actual increase in the burden of disease. Rather, it reflects changes in the processes that lead to the reporting of cases as depicted in the burden of illness pyramid, e.g. increased awareness or new diagnostic testing methods. At each level of the burden of disease pyramid, a potential loss of reported cases is possible. If this 'rate of loss' changes at any level, it affects the number of reported cases and the degree of underestimation, while the incidence remains stable. The most common narrative for the increase in the number of LD cases is that heightened awareness (among physicians and the public) leads to more diagnostic testing. The impact of the testing behaviour on the case numbers and the importance of the 'positivity rate' has become evident during the Coronavirus Disease 2019 (COVID-19)* pandemic, when the positivity rate was disseminated daily (FOPH 2021a). Since 2006, diagnostic laboratories are legally required to provide annual reports on aggregated testing data (i.e. total tests performed in a calendar year (by diagnostic method and month) and thereof the number of positive findings). This applies to 15 diseases, including legionellosis, hepatitis C and chlamydia [BAG 2020b; Federal Assembly 2016]. Unfortunately, previous efforts to analyse these reports showed data quality to be severely impaired to the extent that a meaningful analysis would hardly be possible [Schmutz 2018].

The second hypothesis attributes the increase in reported cases to a true increase in incidence of LD, yet the reason for this increase remains speculative. Three main factors have been described for the re-emergence of infectious diseases: (i) factors increasing the number of susceptible individuals; (ii) factors increasing the risk of exposure; and (iii) factors increasing infectiousness [Lindahl and Grace 2015]. All three factors can be elaborated for LD: Based on the current knowledge on the host risk factors (Chapter 1.2.1), it is plausible that the number of susceptible individuals in Switzerland has increased. Since 2000, the proportion of people aged 65 years and above has increased from 12 to 19% [BFS 2020a]. The prevalence of

[6] Surveillance artefacts are events such as heightened awareness of a disease, introduction of new diagnostic tests, and changes in the method of conducting surveillance. These events change the sensitivity of a surveillance system to capture disease cases and therefore can lead to changes in the observed case numbers. 'A search for such surveillance 'artefacts' is often an initial step in outbreak investigations.'Klaucke et al. [1988]

smoking reduced only marginally [BFS 2020b], while the proportion of overweight people in the population increased until 2012 before stabilizing [BFS 2020c]. The increasing risk of exposure is more difficult to assess as the main exposure source remains unknown. Yet, based on current evidence, there are several arguments for an increase in exposure. As *Legionella* spp. proliferates in the water supply system of buildings, it is plausible that with ageing infrastructure, the contamination of *Legionella* spp. increases. Furthermore, considering energy efficiency, the temperature of hot water boilers could be lowered to a temperature range where *Legionella* spp. are not instantly killed (below 60 °C). The most compelling argument, however, is on-going climate change towards warmer and more humid weather promoting *Legionella* spp. proliferation. With climate change the likelihood of more extreme weather events, such as heavy rainfall, also increases, which have previously been associated with an increased incidence of LD [Miho et al. 2020; Walker 2018]. The third factor thought to contribute to increased risk of infection is still the least known: Knowledge about the infectivity, virulence and exposure-response relationship of *Legionella* is so limited that it is effectively impossible to determine whether these factors have changed (e.g. whether virulence has increased). These uncertainties pertain to the exposure-response relationship, the role of aerosols (e.g. size and composition) in the transmission process, the infectivity and virulence of different *Legionella* strains, the overall prevalence of *Legionella* strains in the environment or the (relative) number of pathogenic strains [Whiley et al. 2014]. Of all three factors, only one lends itself to addressing the growing LD incidence in the short and medium term: By identifying the main sources of exposure, it will be possible to assess whether any recent changes in this exposure have promoted LD incidence. This will support evidence-based decision-making for prevention and control measures. Thus, the identification of exposure risks and exposure sites has received most attention on part of various actors and stakeholders.

1.5.2 The stakeholder landscape in Switzerland is multi-facetted

A multitude of actors is involved in *Legionella* prevention and control in Switzerland. The Federal Council and the FOPH define all reporting procedure and all upstream ('who reports, when and what') and downstream ('what happens after a case has been reported') processes. The FOPH maintains the NNSID for LD, disseminates current epidemiological developments and is central to all public health prevention efforts.

LD can be described as a 'consequence of human action' [Lindahl and Grace 2015]. If not for the invention and development of intricate water systems, or in the concrete example of the first outbreak in Philadelphia, without the invention of air cooling systems, it might never have emerged as a public health concern [Fraser et al. 1977]. Hence, there is a responsibility and incentive to do better. In 2017, potable shower and bath water in public buildings were included in the food safety law and thresholds for *Legionella* spp. contamination were set [EDI 2017]. With this step, the Federal Food Safety and Veterinary Office (FSVO)* has resumed responsibility to ensure clean potable water and prevent LD cases. Furthermore, as *Legionella* spp. grows best in warm and stagnate water, management of water sanitation systems in

buildings are crucial for the prevention and control of LD. Chemical disinfection, e.g. chlorination, is possible and is pursued in several countries (such as the US or Spain), but not in Switzerland. Therefore, the most essential measure of control remains the regulation of water temperature to be either above or below the temperature range that *Legionella* spp. prefers. Such a regulation could require maintaining a temperature of above 60 °C for hot water at the source (i.e. the boiler in most buildings) and at least 55 °C at the point of use and below 25 °C for cold water at every point in the system [Van Kenhove et al. 2019]. Yet, for most residential buildings, 55°C hot water at the point of use is not needed and even poses the danger of scalding. Additionally the production and maintenance of hot water requires energy. In view of climate change and in the pursuit of energy efficiency, the Swiss Federal Office of Energy (FOE)* has drawn up the Energy Strategy 2050, which strives for energy efficient buildings. Therefore, the FOE advocates energy savings, including the reduction of hot water temperatures below the current standard of 60 °C. The FOPH's and FVSO's primary interest is the prevention of LD and *Legionella* growth in the water systems. Currently, only health concerns seem to require higher hot water temperatures in buildings, yet this argument is not fully supported scientifically: it is not known whether most cases of LD are caused by contact with contaminated water in homes, whether there is a threshold level of contamination below which the risk of infection is low, and whether other measures are sufficient to prevent contamination.

As a result, the three Federal Offices and their respective mandates are in conflict: On the one hand, public health is to be preserved and, on the other hand, energy efficiency is to be increased and energy saved in the long term. The lack of evidence on the main drivers of infection and effective prevention and control measures is hindering discourse and decision-making. The three Federal Offices have long been individually investing in *Legionella* spp. research. Yet, the Federal Offices recognized the need for consorted action and in 2019, the FOPH, FSVO and FOE established a Federal action plan to combat LD ('Aktionsplan Legionellenbekämpfung Bund') to promote collaboration within and between Federal Offices and to improve LD prevention and control efforts through research and evidence generation for policy making [Bertschi 2021]. The steering committee decided for 2021 and 2022 to develop and implement an 'action plan': The three Federal Offices stipulated individual actions, which primarily consists of the promotion of research efforts to generate evidence for policy-making.

Enforcement of legislation on surveillance and control is regulated at the cantonal level. The cantonal medical services work closely with the FOPH and the cantonal food safety authorities (cantonal laboratories, 'Kantonale Labore') with the FSVO. The cantonal medical services are responsible for reporting LD cases to the FOPH and for involving the cantonal laboratories in the investigation and identification of infectious sources. This is particularly important when cases occur in clusters or outbreaks. However, these processes are not standardised. Investigation primarily concerns the environmental sampling of potential exposures to identify infectious sources. Yet, while some cantons investigate every single *Legionella* case, others reported that they had never investigated a case. The cantonal laboratories are also organised in a specific working

group for *Legionella*: The 'Arbeitsgruppe Legionellen in der Kommission Trink- und Badewasser' ('Working Group on *Legionella* in the Drinking and Bathing Water Commission') within the Swiss Association of Cantonal Chemists.

Since the revision of the food safety law in 2017, building managers, too, have been under increasing pressure to contribute to LD control. Several trade associations established building maintenance guidelines, which include *Legionella* control and prevention guidelines, such as the 'Schweizerische Verein des Gas- und Wasserfaches' (SVGW)*, Suissetec and the Swiss Society of Engineers and Architects (SIA)*. Since the enforcement of the food safety law is the responsibility of the cantons, they requested the SVGW as well as Suissetec to develop documents with which the owners and operators of building drinking water installations could be supported in the implementation of the legally required self-monitoring.

Overall, the marked increase in LD case numbers has prompted several government offices to take action, which has also led to increased awareness of *Legionella* among the general public. For instance, the results from intensified research efforts were also taken up by news agencies, which brought them to the attention of the public (selected examples are shown in Appendix K). The activities of the FSVO and the FOE in the area of hot water management in buildings have attracted the attention of building managers and homeowners in particular. Most recently, the current energy crisis in connection with the Russian-Ukrainian war has again brought *Legionella* to the fore, as the question arises whether it is possible to lower the hot water temperature in order to save energy. *Legionella* and LD are, therefore, not only a health policy issue, but also have significance for our day-to-day lives.

Chapter 2

Rationale, aims and objectives

2.1 Rationale

In contrast to other emerging infectious diseases dominating the contemporary public health discourse (namely COVID-19 and monkeypox), the (observed) case number of LD is still low, but the increase in cases has been persisting for almost two decades. Furthermore, the ecology of the causative pathogen *Legionella* spp., as well as demographic and climate changes, all suggest that the disease threat will further increase in the future. However, due to low cases numbers and perceived low public health relevance, little progress has been made in the last 50 years. The introductory chapter outlines the prevailing LD knowledge gaps which hinder evidence-based policy making for disease prevention.

The impulse for this thesis was the continuous increase in case numbers observed in the Swiss national notification system over the past two decades. Although concerning, the interpretation of this observed increase and the accuracy of the LD disease estimates remained uncertain. Specifically, there were questions regarding the extent to which LD has been and currently is underestimated in the notification system and whether the increase in notified cases represents merely a surveillance artefact. The latter question in particular could be essential to determine the public health relevance of the observed increase of notified cases, which in turn would guide a future course of action. At the same time, with the introduction of limits for *Legionella* spp. in the Food Safety Act and the FOE's advocacy of energy saving, the need to identify the main sources of infection for sporadic, community-acquired LD has grown. Overall, there was a lack of knowledge and evidence on the epidemiology of this re-emerging infectious disease to guide a response to the continued increase in reported cases.

This work contributes to closing the gaps in knowledge and gaining a better understanding of the epidemiology of LD in Switzerland. Thereby, it could serve as a basis and guidance for future research. The thesis also provides actionable knowledge of the disease system and supports current governmental efforts to plan and implement effective prevention and control strategies to combat the spread of LD. Lastly, we hope that this thesis illustrates the complexity of the topic for actors from all sectors and disciplines while providing a basis for trans-sectoral and trans-disciplinary exchange.

2.2 Aims and objectives

The primary aims of this thesis were to contribute to a better understanding of the epidemiology of LD in Switzerland. This work provides a thorough synthesis of the available knowledge. It also generates new knowledge on the interpretation of available disease estimates, the processes involved in case detection and the extent of underestimation of LD in Switzerland. Additionally, we aimed to generate new evidence on large-scale risk factors and drivers of infection and set up a framework to study host, behavioural and small-scale environmental risk factors and further LD characteristics.

Objective 1: To investigate the recent increase of Swiss Legionnaires' disease case numbers and Legionnaires' disease surveillance data at large

(a) To investigate the temporal trend of Legionnaires' disease notifications and determine whether the increase in notification numbers reflects a test artefact or a true increase in incidence

(b) To explore temporal and spatial/regional Legionnaires' disease patterns in the Swiss national notification data

(c) To investigate the development of data quality in the Swiss national notification data for Legionnaires' disease

Objective 2: To investigate the health care context in which Swiss Legionnaires' disease notification numbers are generated

(a) To conduct a literature review and provide a global overview on the prevention and control, clinical case management, surveillance and outbreak management for Legionnaires' disease *Legionella*

(b) To explore clinical case management of community-acquired pneumonia and the involved decision-making processes of physicians practising in Switzerland

Objective 3: To investigate risk factors and exposure sites for Legionnaires' disease in Switzerland at population level

(a) To investigate the seasonal and regional heterogeneity of Legionnaires' disease notification rates in relation to weather and air pollution factors

(b) To conceive, design and implement a national case-control study integrating a molecular source attribution approach to determine risk factors and infection sources of Legionnaires' disease

Chapter 3

Research concepts and methodological overview

The research presented in this thesis was conducted at the Swiss Tropical and Public Health Institute (Swiss TPH)*, an associated institute of the University of Basel, in the Household Economics and Health Systems Research Unit, part of the Department of Epidemiology and Public Health. The thesis is part of a broader research portfolio on the Swiss health system's research on food- and waterborne diseases in Switzerland. This work constitutes the third volume in this portfolio. The first volume investigated the epidemiology of campylobacteriosis and acute gastroenteritis from a human and health system's perspective in Switzerland [Bless 2017]. The second volume expanded on the previous thesis to investigate foodborne diseases as a whole and focused on the surveillance system and the burden of illness period to understand underestimation [Schmutz 2018]. This thesis and the third volume constitutes now the move from food- to waterborne diseases with the focus on LD and *Legionella* in Switzerland.

3.1 Overview of study designs, methodologies and methods used

The following chapter provides an overview of the different methodologies and methods used for the work summarised in this thesis. The objectives that the different methods address are indicated in the grey boxes.

3.1.1 Positivity studies incorporating denominator into notification data

Contributing to Objective 1a.

To investigate the contribution of surveillance artefacts, specifically changes in diagnostic testing frequencies, to the observed increasing LD disease trend, denominator data needs to be evaluated. By dividing the number of cases by the number of diagnostic tests performed, the positivity rate can be calculated, which provides additional insights into disease trends. Both positivity studies, shown in Chapter 6 and 7 on LD and Shiga toxin-producing*Escherichia coli* (STEC)* were mandated by the FOPH, as a similar increase in case numbers was observed for LD and STEC infections. As testing data is not routinely available, testing data needed to be collected from 14 diagnostic laboratories across Switzerland for LD and 11 for STEC. We then calculated the positivity rate for the period of 10 years. Additionally, we used mixed-effect logistic regression models to investigate the determinants for a positive test result.

Both studies were conducted through the FOPH under the enactment of EpidA [Federal Assembly 2016]. According to Article 20 letter a of the EpidA of 29 April 2015, the FOPH may order that notifications contain information on the identification of persons if a particular threat to public health is imminent or exists, so that measures can be ordered in accordance with Articles 15 and 33-38 EpidA. Under Article 20 letter b EpidA, the FOPH may also order that selected physicians, hospitals and other public or private healthcare institutions and laboratories subject to the reporting obligation must report certain information.

3.1.2 Time series and interrupted time series designs

Contributing to Objectives 1b and 1c.

The Swiss LD notification data have previously been described for 2000-2016 [Gysin 2018]. Since the number of cases has continued to increase considerably, the analysis of temporal trends was extended to LD notification from 2000-2020 and the analytical methods were refined to include a time series approach (Chapter 4). Longitudinal routine health data, such as LD notification data, are generally a composite of trends, cyclical components, seasonal variance and randomness ('noise'). Using a time series analysis allows to disentangle these components and support the interpretations of the epidemiological curve. Additionally, data were analysed in a descriptive manner to explore potential effects of case demographics, diagnostic methods, clinical features, reported exposures and risks, strain information, and assess data quality in terms of internal validity, completeness and timeliness of the notifications.

Subsequently, an analysis of the COVID-19 pandemic and containment measures' impact on LD notifications was added employing an interrupted time series (or quasi-experimental time series) approach [Bernal, Cummins, and Gasparrini 2017]. An interrupted time series allows the evaluation of an intervention's effect by comparing time trends before and after the intervention. The intervention events we chose were the implementation of travel restrictions and the resumption of use of previously closed buildings/facilities. Both factors have previously been hypothesised to impact LD case numbers. Information on COVID-19 case numbers were obtained from publicly available data, such as the COVID-19 dashboard from the FOPH for quantitative data (cases, hospitalisation and tests) [FOPH 2021a]. Qualitative data on the containment measures were obtained from the publicly available Oxford COVID-19 Government Response Tracker (OxCGRT) [Hale et al. 2021] modified for Switzerland and supplemented by an additional information on containment measures in Switzerland [Dünner 2020].

Since the study includes secondary personalised health data, it needed to be clarified whether ethical approval was required . The study was submitted to the Ethics Committee Northwest and Central Switzerland (EKNZ)*, who decided that the study does not fall under the scope of the Human Research Act (HRA)* and did not require further authorisation.

3.1.3 Spatial and environmental epidemiology: mapping of cases and exposures, hot spot analysis, ecological model and case-crossover study design

Contributing to Objectives 1b and 3a.

As an environmental pathogen, differences in the environment could explain regional variations in LD incidence and disease trends. Regional LD notification data have not yet been investigated beyond cantonal level, which could lead to a loss of small-scale patterns and associations. To investigate the regional and spatial patterns of LD cases in Switzerland on a residential address resolution, we received LD notification data including address information from the FOPH for 2017 to 2021. The analyses were split in three parts and summarised in Chapter 10: the exploration of the spatial and regional distribution of LD cases, followed by two different approaches to investigate spatial determinants for LD incidence.

First, we used a descriptive analysis and mapped LD cases on a 'greater region' (Nomenclature of Territorial Units for Statistics (NUTS)*-2 level), cantonal, district and municipality level. Additionally, we used Geographic Information Systems (GIS)* for two global statistics (Getis-Ord General G and Global Moran's I) and two local statistics (Getis-Ord Gi* and Local Moran's I) to identify hot spots of sex- and age-standardised notification rates for LD on district level. The spatial statistics are able to identify regions with higher than expected notification rates based on their surrounding regions.

Second, we applied an ecological model to identify environmental determinants on case frequency at the district level. For this purpose, all case and exposure data were aggregated in space (district) and time. The ecological model is particularly useful for estimating ecological effects and for their simplicity in analysis and presentation to guide further investigations. Individual-level analysis would have been additionally limited by the lack of appropriate control group. For the model, we collected information on the location of known or suspected *Legionella* exposure sources or risk factors, e.g. wastewater treatment plant location, weather conditions or mean socio-economic position (SEP)*. We used univariable and multivariable negative binomial regression models to explore associations between LD case counts per district (adjusted for the population size) and exposure source densities.

Third, to strengthen the previous analysis, which is subject to ecological bias, and identify short-term associations of weather conditions, we employed a case-crossover approach. The case-crossover is a self-matched study design where each exposure level during the 'hazard period' (the period before the adverse outcome occurred) is compared with exposure levels in other periods where the case did not occur (disease-free period).

We investigated the effect of seven weather parameters on LD occurrence. We used distributed lag non-linear models (DLNM)* [Gasparrini and Armstrong 2013], to capture potential non-linear and delayed effects. As both LD case data with residential addresses and air pollution data at a fine spatial scale were only available for the year 2019, a sensitivity analysis restricted to that year was performed. The sensitivity analyses allowed the evaluation of the overall association of air pollution with LD incidence and the role of air pollution as a confounder in weather-related associations.

The study has been submitted to the EKNZ for a clarification of responsibility. They decided that it does not fall under the scope of the HRA and an authorization is not required.

3.1.4 Literature review

Contributing to Objective 2a.

To improve the understanding of the interplay of policies and LD, we conducted a scoping review exploring the landscape of guidelines, regulations and legislation for four topics on *Legionella* and LD: (i) prevention and control in the environment; (ii) clinical case management; (iii) surveillance and (iv) outbreak management (Chapter 8). The focus was on Swiss national guidelines, regulations and legislation. Yet by comparison with international documents, deviations and areas for improvements could be identified. The results of this review were summarised and presented to the FOPH in a narrative report, which also included the main messages on each topic.

As no individual health data were used, this study did not need ethical approval.

3.1.5 Qualitative study with in-depth interviews

Contributing to Objective 2b.

We used qualitative methods to assess the awareness of LD among physicians and the diagnostic pathway for LD patients from first contact with a physician to entry in the notification system (Chapter 9). Qualitative methods are useful to support interpretation of quantitative data, such as the LD notification data and lends itself particularly well to understand concepts, opinions or experiences.

The selection of participants was designed to cover physicians from all language-regions (French, Italian, German) in Switzerland and different health care levels from primary health care physicians and general practitioners to physicians at regional and cantonal hospitals and physicians at university hospitals. Qualitative face-to-face interviews were conducted using a semi-structured interview guide until saturation was reached. A coding tree was prepared a priori based on the interview guide and the research objectives. Interview transcripts were analysed using thematic analysis. The coding tree was expanded with additional

themes identified during the first coding round. The themes and conclusions of this study were validated in a workshop with the data collectors.

Ethical approval was obtained from the EKNZ (ID 2019-01708).

3.1.6 A prospective national case-control and molecular source attribution study

Contributing to Objective 3b.

Identifying host, behavioural and small-scale environmental risk factors is essential for adopting effective prevention and control measures. However, the study of these risk factors on the population-level is subject to several design and implementation challenges (such as limited LD case numbers, self-reported data or difficulties in source attribution due to the ubiquitous nature of *Legionella*. We conceptualised and developed a national prospective case-control and molecular source attribution study (project-acronym *SwissLEGIO* to specifically address and overcome these challenges. The study protocol and rational for the design is presented in Chapter 12.

The study was centred around a prospective case-control study design: In collaboration with 20 university- and cantonal hospitals, 205 newly diagnosed LD patients and 205 healthy controls matched for age, sex and region of residence (district level) will be recruited across Switzerland over one year. A questionnaire to investigate host, behavioural and environmental risk factors for LD is applied to cases and controls. For LD patients, additional data on the clinical presentation and disease severity of LD and the patients' case management is extracted from electronic medical records. Risk factors will then be identified using univariable logistic and multivariable (unconditional) regressions. A sub-set of cases will be followed-up with an investigation, where *Legionella* isolates from the lower respiratory tract will be used for genomic comparison with isolates sampled from the patient's home.

The study received ethical approval from the EKNZ for the pilot study (ID 2019-01708), as well as the actual *SwissLEGIO* case-control and molecular source attribution study (ID 2022-00880).

3.2 Collaborations

The research projects presented in this thesis were realized in collaboration with several partners. As this thesis is part of a series of works on Swiss Health System's Research on Food- and Waterborne Diseases in Switzerland, it was built on a long-standing and fruitful partnership with the FOPH. Chapters 4, 6, 7, 8, 9 and 10 were funded as specifically mandated federal policy research ('Ressortforschung') with which the FOPH can address questions outside of the routine mandate scope. The FOPH provided the funding for *SwissLEGIO* (Chapter 12). The FOPH was also directly involved in the work on the notification data

(Chapters 6, 7, 4 and 10) providing insights into the national notification system and advising in regard to the interpretation and the Swiss health system's perspective.

The FSVO, FOPH and FOE jointly funded the *LeCo* project and thereby also supported the *SwissLEGIO* study (Chapter 12). All Federal Offices are on the advisory board for the *LeCo* project and provide feedback on progress on a quarterly basis.

The *LeCo* '*Legionella* control in buildings' project is conducted by a consortium comprising of the Eawag (lead), Swiss TPH, the University of Applied Sciences Lucerne and the cantonal laboratory Zurich. They are key scientific collaborator for the ongoing *SwissLEGIO* study. Swiss TPH is responsible for one out of eight working packages within *LeCo* related to the question 'How can the new investigation tools for identifying *Legionella* be promoted?' - this question is addressed through the usage of WGS for source attribution. Through *LeCo*, the sampling, analytics and WGS of the environment are funded. Funding for WGS for clinical isolates is provided under *SwissLEGIO*. Further, the *LeCo* consortium facilitates and jointly implements the environment-related components of *SwissLEGIO* , from the planning of sampling and analytics, supporting the development of data collection tools for housing attributes, over training of Swiss TPH staff, to support for the laboratory analysts during data collection. In this capacity, *SwissLEGIO* and *LeCo* are closely linked and benefit from bringing together different expertise. However, as *SwissLEGIO* provides the framework of the study, for simplicity, we refer to the overall project as *SwissLEGIO* (Chapter 12).

Throughout the thesis, the NRCL provided advice on *Legionella* biology, strain monitoring, current diagnostics and the practical day-to-day management of *Legionella* in Switzerland. Specifically, the NRCL was a key collaborator for the LD positivity study (Chapter 6) supporting the interpretation of the data. For *SwissLEGIO* (Chapter 12), we collaborated closely with the NRCL to process clinical samples from the hospitals up until WGS.

A collaboration with the 'applied microbiology research lab' at the Institute of Medical Microbiology, University of Zurich (formerly at the University Hospital Basel) was established to perform WGS analysis on clinical and environmental *Legionella* isolates.

The hospital network, established within the framework of the *SwissLEGIO* study (Chapter 12), consists of 20 hospitals across Switzerland. Beyond the immediate scope of the study (recruitment of patients and respiratory sample collection), the key partners in the hospitals were involved in the finalisation of the study protocol and act as scientific partners. The established network also facilitates further research, such as a planned study on clinical parameters for LD identification, radiology in LD diagnostics or a study on antibiotic stewardship and LD.

Part II

The Swiss national notification data on Legionnaires' disease

Chapter 4

Temporal trends in legionellosis national notification data and the effect of COVID-19, Switzerland, 2000–2020

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This article was published in:
International Journal of Hygiene and Environmental Health (2022), 113970
doi: 10.1016/j.ijheh.2022.113970

International Journal of Hygiene and Environmental Health 247 (2023) 113970

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Temporal trends in legionellosis national notification data and the effect of COVID-19, Switzerland, 2000–2020

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ARTICLE INFO

Keywords:
Legionnaires' disease
Legionellosis
Switzerland
COVID-19
Disease surveillance
Communicable diseases

ABSTRACT

The notification rate of legionellosis in Switzerland and other European countries has markedly increased over the last 20 years. Here, we investigated the Swiss notification data on legionellosis from 2000 to 2020 in regards of overall time trend, content and data quality. We further explored the impact of the COVID-19 pandemic on the reported case numbers using an interrupted time series approach. Between 2000 and 2020, 5980 cases were included in our analysis. The annual crude notification rate for legionellosis cases increased from 1.1/100,000 population (CI: 0.9–1.4) in 2000 to 5.6/100,000 population (CI: 5.1–6.1) in 2020. In recent years, the summer peaks have been more pronounced and some shifted earlier in the year. The highest notification rate was recorded in 2018 with 6.7/100,000 population (CI: 6.2–7.3). The hospitalisation rate for notified cases remained high across all study years (89.9%), while the case fatality rate slightly decreased (from 7.7% to 3.6%). COVID-19 containment measures, such as travel restrictions and/or related behavioural changes, are associated with a temporary decline in cases of 35%. Overall, the quality of the notification data was good. Clinical data were more susceptible to interferences than data from laboratory reporting, which could be observed most clearly in the decline of clinical reports by 4.3 percentage points in 2020. As the case classification for Legionnaires' disease includes pneumonia symptoms, this decline could lead to an underestimation of Legionnaires' disease cases, yet the continuous reporting though the diagnostic laboratories suggested a robust surveillance system for legionellosis in Switzerland.

1. Introduction

The term legionellosis comprises all diseases caused by *Legionella* spp. The majority of the known burden of disease stems from Legionnaires' disease (LD), which presents as pneumonia often requiring hospitalisation. Legionellosis is caused by inhalation or aspiration of aerosols from contaminated water sources, and has the potential to occur as larger outbreaks, even though most cases are sporadic. To detect such outbreaks, monitor disease trends, and take appropriate public health measures, legionellosis is included in the passive disease surveillance system of many, mostly high-income, countries (Thacker et al., 1983).

In the last two decades, the notification rate of legionellosis steadily increased in Switzerland, other European countries and the US (Centers for Disease Control and Prevention (CDC), 2020; European Centre for Disease Prevention and Control (ECDC), 2021). Several hypotheses for the increase in disease incidence were formulated such as changes in weather and climate, changes in energy policy and buildings/water systems infrastructure, both thought to promote *Legionella* spp. growth, and, demographic changes with an increasing susceptible population for LD (European Centre for Disease Prevention and Control (ECDC), 2021; Fukushima et al., 2021). Yet, the observed disease trend is not only shaped by changes in incidence, but also prone to react to any changes in the processes leading up to the case being reported, e.g. health-seeking behaviour, diagnosis and reporting procedures (Schmutz, 2018).

In Switzerland, cases of legionellosis are notifiable to the National Notification System for Infectious Diseases (NNSID) since December 1987. The NNSID is managed by the Federal Office of Public Health (FOPH). Trigger for a mandatory notification is a positive confirmation for a *Legionella* spp. infection. The diagnostic laboratory has to notify simultaneously to the cantonal health authorities and the FOPH with the "reporting form on laboratory findings". The treating physician must

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https://doi.org/10.1016/j.ijheh.2022.113970
Received 19 January 2022; Received in revised form 31 March 2022; Accepted 4 April 2022
Available online 2 May 2022

Abstract

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Keywords: Legionnaires' Disease; Legionellosis; Switzerland; COVID-19; Disease Surveillance; Communicable Diseases

Introduction

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In Switzerland, cases of legionellosis are notifiable to the National Notification System for Infectious Diseases (NNSID)* since December 1987. The NNSID is managed by the Federal Office of Public Health (FOPH)*. Trigger for a mandatory notification is a positive confirmation for a *Legionella* spp. infection. The diagnostic laboratory has to notify simultaneously to the cantonal health authorities and the FOPH with the 'reporting form on laboratory findings'. The treating physician must also submit a 'reporting form on clinical findings' to the cantonal health authorities. The cantonal health authorities check for completeness of the clinical information provided and if immediate measures are necessary. They then forward the information to the FOPH. At the FOPH, the paper-based clinical and laboratory notification forms are recorded electronically and are matched by patient. The timeframe for reporting of both laboratory and clinical findings for legionellosis is one week [BAG 2020a].

Before 2000, there were substantial changes to the notification process, hampering the evaluation of prior disease trends. Since then, there were only few adjustments made to the notification form and to the case classification for LD, which was last updated in 2012 (see Table 4.1) [Gysin 2018]. Cases classified as 'possible' were either without pneumonia or without clinical information on pneumonia. They count towards legionellosis cases, but not as LD. Since 2006, the FOPH also requested diagnostic laboratories to report the annual number of tests performed for *Legionella* spp. to obtain complementary denominator data to improve contextualisation of the surveillance data [Gysin 2018]. The quality of this reporting, however, was insufficient; therefore, a research study investigated the positivity for the years 2007-2016 [Fischer et al. 2020b]. The authors found a strong and parallel increase of the test volume and the number of positive

Table 4.1: Case definition for Legionnaires' disease in Switzerland since 2012 [Gysin 2018].

Case classification	
Confirmed case	Any person meeting the clinical criterion AND at least one laboratory criteria for a confirmed case
Probable case	Any person meeting the clinical criterion AND at least one laboratory criteria for a probable case
Possible case	Any person meeting at least one of the laboratory criteria for either a confirmed or probable case AND missing information on the clinical criterion OR clinical criterion not met
Criteria	
Clinical criterion	Any person with pneumonia
Laboratory criteria for a confirmed case	Either isolation of *Legionella* spp. from respiratory secretion or any normally sterile site OR detection of *Legionella pneumophila* antigen in urine
Laboratory criteria for a probable case	Detection of *Legionella* spp. nucleic acid in clinical samples (using for example PCR) OR detection of *Legionella pneumophila* antigen for example by DFA staining using monoclonal-antibody-derived reagents OR significant rise in specific antibody level to *Legionella pneumophila* or other *Legionella* spp. in paired serum samples OR single high level of specific antibody to *Legionella pneumophila* serogroup 1 in serum.

cases. However, without an assessment of the reasons for the increase in test volume, a conclusion on the observed notification trend could not be made.

The COVID-19 pandemic in 2020 has affected the notification rates of almost all mandatory notifiable diseases in Switzerland, including LD [BAG 2021a]. LD cases in 2020 reduced by one third compared to the expected number of LD cases based on the five years prior to the pandemic. Multiple mechanism could explain the impact of the pandemic on LD: First, changes in people's behaviour could affect incidences and health-seeking behaviour; second, the clinical presentation of LD being similar to COVID-19 [Cassell, Davis, and Berkelman 2021] could lead to higher testing rates and third, the heavy burden on the health care system could affect testing and reporting behaviours. In particular, the ubiquitous travel and entry restrictions were hypothesised to have reduced cases of travel-associated Legionnaires' disease (TALD)* [Steffen, Lautenschlager, and Fehr 2020]. Additionally, the closure of public buildings for leisure activities e.g. sport centres, shopping malls, office buildings, and schools might have reduced exposure during the closure but could have led to increased proliferation of *Legionella* spp. in the then stagnant water in unused buildings. Upon re-opening and without thorough flushing of the pipes, the risk for an infection is thought to be increased [Dey and Ashbolt 2020; ESCMID ESGLI 2020; Palazzolo et al. 2020; Proctor et al. 2020]. However, as of now, there has been no quantification of this effect.

Additionally, in 2017, thresholds of *Legionella* spp. contamination in potable, publicly accessible water were regulated in the Food Safety Law [Bundesversammlung 2014b]. Consequently, *Legionella* spp. became

a new concern for the Federal Food Safety and Veterinary Office (FSVO)*. Due to these developments in the past years, the increasing attention towards legionellosis and efforts to understand and prevent illness cases, an analysis of the past 20 years of LD notification in Switzerland is timely. The first aim of this study is to describe the Swiss notification data for LD for the two decades between 2000 and 2020, specifically the content of the notification data (i.e., cases per week and their characteristics), and the quality of the data (i.e., completeness, validity and timeliness). The second aim is to explore the impact of the COVID-19 pandemic on the content and the quality of these data.

Material and methods

Study design and setting

This is a retrospective longitudinal study utilising routinely collected health data for legionellosis from the NNSID in Switzerland between 01.01.2000 and 31.12.2020. The year 2000 was chosen as the starting time point, as there have been significant changes to the notification system earlier on, rendering older data incomparable.

Legionellosis notification data sources, access and processing

The raw data presented by the NNSID [BAG 2022e] reports all legionellosis notifications before case classification, including cases later classified as possible and 'no case', irrespective of their residency. After classification based on the case definition shown in Table 4.1, the FOPH retains only confirmed and probable cases, i.e., LD cases, with residency in Switzerland or the Principality of Liechtenstein, in their reports. For the purpose of this study, we used the same inclusion criteria for residency, but kept confirmed, probable and possible cases in the dataset and only excluded 'no cases'.

The legionellosis notification data underwent the routine cleaning processes at the FOPH. For data confidentiality reasons, variables like date of birth and place of residence are stored in separate files and deleted after three years. For the years 2000 to 2016, we therefore, obtained only the age in years and the canton of residence. We did not exclude case records that violated the internal validity (illustrative example: an observation with the hospitalisation date after the death date), in order to present the full dataset and explore its quality.

The legionellosis notification dataset contained cases notified on any given day. Due to low case numbers and to eliminate the effect of the day of the week on health-seeking behaviour and case confirmation, we aggregated data on a weekly level. The case notification further contains information on the patient's demographics (date of birth, sex, residential address, nationality), clinical information (date of disease onset and diagnosis, hospitalisation status, death), diagnostic information (sample material and diagnostic

method), information about exposures prior to disease onset (locations, activities, installations), risk factors for development of LD, and information about the notification process (date of data entry, case classification, number of received notification forms).

Age categories were pre-set by the FOPH according to the standard of the European Centre for Disease Prevention and Control (ECDC)*. The FOPH further categorises cases based on the most probable exposure in the 2-10 days prior to onset of illness: travel-associated, retirement-home-associated, nosocomial, professional-associated, and community-acquired [BAG and BLV 2018]. Community-acquired cases include both, cases with a probable or confirmed infection in the community and cases, without another exposure category indicated.

Quantification of the impact of the COVID-19 pandemic on legionellosis cases

To address the second aim, the exploration of the impact of the pandemic, we collected information on the development of the COVID-19 pandemic, either quantitative (case numbers, hospitalisations, deaths and tests) or qualitative (non-pharmaceutical interventions implemented).

Information on the evolution of the COVID-19 pandemic in Switzerland were taken from the Oxford COVID-19 Government Response Tracker (OxCGRT)* [Hale et al. 2021], which has been adapted for the Swiss context [Dünner 2020]. This information was complemented with our own compilation of events. Data on the number of COVID-19 cases, hospitalisation, deaths and testing is publicly available and was extracted on 4 February 2021 [FOPH 2021b]. Data on the COVID-19 pandemic contains daily information from the start of the pandemic in Switzerland (early February 2020) until end of December 2020 and was also aggregated by week.

Linkage of legionellosis case data and COVID-19 data

For the legionellosis data, to identify events and cases on the timeline, we used the variable 'case date', which is generated within the NNSID. The case date denotes the earliest date available from a series of date-related variables per case. Ideally, and in most cases, this is the date of symptom onset. The OxCGRT and COVID-19 case database had unique time identifiers, which allowed linkage with the LD database on the timeline.

We used population statistics from the Swiss Federal Statistical Office (FSO)* to calculate crude and adjusted notification rates. At the time of the analysis, these statistics were not yet available for 2020; therefore, we used the statistic from 2019 instead.

Statistical methods

Descriptive analyses

Data were descriptively analysed in terms of data content and data quality using the statistical software R (Version 4.0.3 [R Core Team 2020]). Notification rates, defined as the number of notified cases per 100,000 resident population, were calculated using population statistics from the FSO. Confidence intervals for crude rates were calculated using the package *propCIs* using the function exactci to apply the Clopper-Pearson exact CI approach. Confidence intervals for adjusted rates have been calculated using the package *dsrTest* to apply the Gamma Method proposed by Fay and Feuer [1997].

Interrupted time series analysis

To address the second aim, we used an interrupted time-series analysis approach as outlined by Bernal, Cummins, and Gasparrini [2017] to estimate the effect of selected measures on the legionellosis case numbers. The selected events were i) the implementation and lifting of travel restrictions, on 16th March (week 12) and 15th June (week 25), and ii) the opening of schools and leisure activity facilities on 11th of May (week 20) after almost two months of closure [The Swiss Federal Council 2020]. As there has been stepwise openings, we excluded the data points during the opening phase from week 20 until week 24. We assumed a lagged level change for both events. With count data available, we modelled the weekly number of cases between 2016 and 2020 using a quasi-Poisson regression model with the log-transformed standardised population as the offset. We incorporated harmonic functions to account for seasonality and a lag-time of one week (incubation time) into the model [Berkelman 2020].

Results

Time trend in legionellosis cases

Figure 4.1 shows the increasing weekly case numbers since 2000 until 2018, followed by a small drop in 2019 and 2020. The annual crude notification rate for legionellosis cases ranged from 1.1/100,000 population (CI: 0.9 - 1.4) in 2000 to 5.6/100,000 population (CI: 5.1 - 6.1) in 2020. The highest notification rate was recorded in 2018 with 6.7/100,000 population (CI: 6.2 - 7.3).

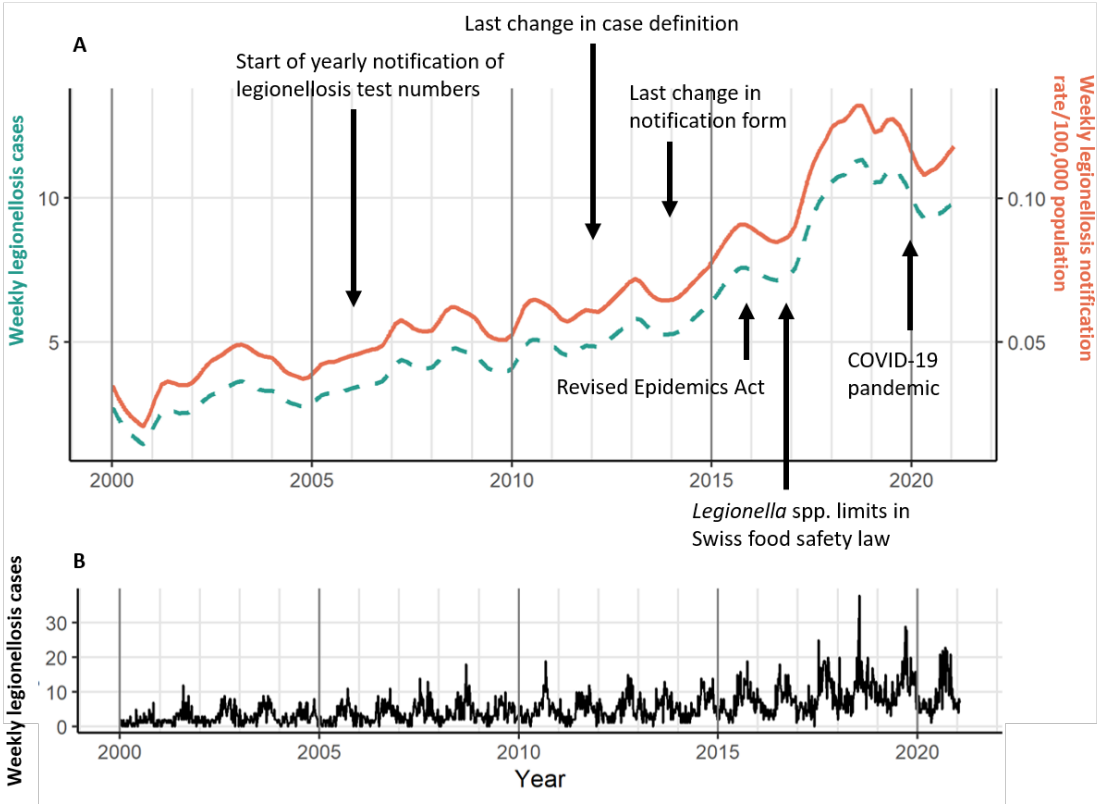

Figure 4.1: Time trend of legionellosis cases in Switzerland, 2000-2020. (A) Time trend (without seasonality and randomness). (B) Complete times series of legionellosis cases including trend, seasonality and randomness.

There is a strong annual seasonality in the data peaking around calendar week 36 (Figure 4.2). The record-high year of 2018 showed a strong summer peak, which however, shifted to June instead of August. Since 2000, the increase of cases in the summer months has been more pronounced than the increase during the winter months. Comparing the period 2010-2015 with the period 2016-2020, the number of cases increased most strongly in spring (Mar - May) by 85.1%. The cases during summer (Jun - Aug) increased by 75.3%, compared to an increase of 53.3% during autumn (Sept - Nov) and 58.7% during winter (Dec – Feb).

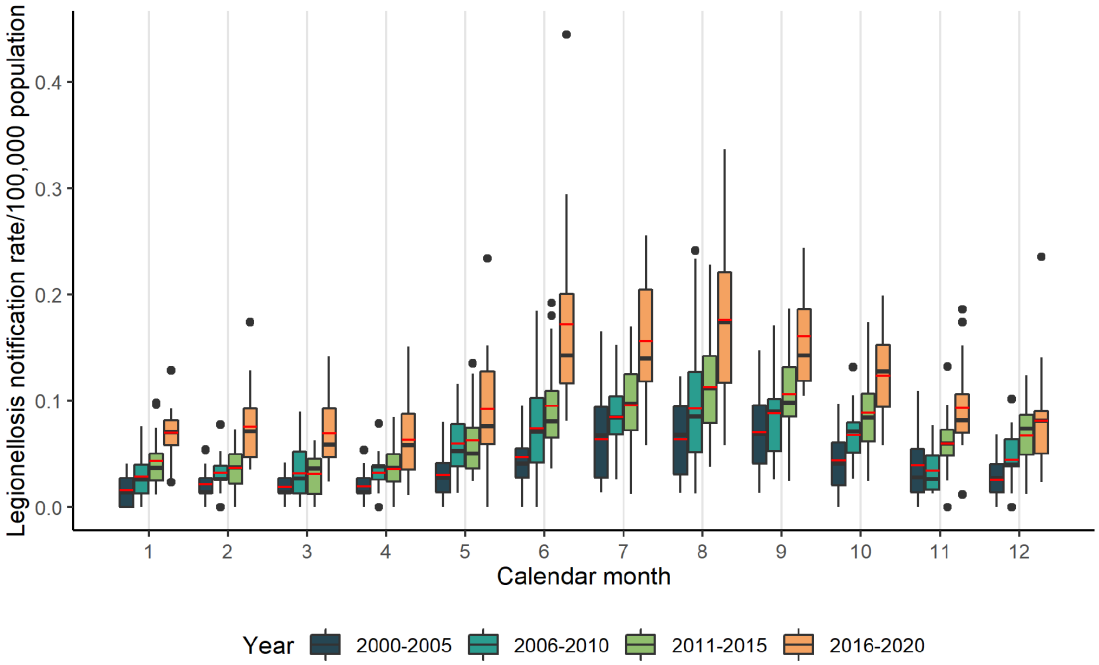

Figure 4.2: Seasonality of legionellosis cases in Switzerland, 2000-2020. The red line in the boxplot denotes the mean, the black line the median. The black dots denote outliers.

Content of notification

Demographics

Between 2000 and 2020, the database of the NNSID included 5,980 legionellosis cases. Table 4.2 shows a comparison of the key variables across the years. Cases comprised of 68.9% (N=4,120) men, the median age was 64 years (1st and 3rd quartile: 53-76). The age group of 60 to 69-year olds made up for one quarter of the legionellosis cases (22.7%). The notification rate of the whole period (2000-2020) was highest for the 80 to 89 years olds (13.3/100,000 population, Appendix A, Table 1). The proportion of men among all cases was high over all years (range: 54.3%-73.6%) and the overall and all period notification rates were more than double than those for women (5.0/100,000 versus 2.2/100,000 population). Over all study years, the canton of Ticino accounted for 15.0% of all cases, followed by the cantons of Zurich (14.0%) and Berne (10.2%). Yet, the notification rate in Ticino was found to be three to four times higher than the average of the other greater regions (Appendix A, Table S1 and Figure S1). In 2020, fewer cases were reported from the cantons of Geneva (3.4%) and Neuchatel (1.5%) compared to their overall means (7.0% and 2.6%). In contrast, the canton of Valais reported more cases in 2020 (6.1%) than its overall mean (3.5%).

Table 4.2: Key variables across the years for notification of legionellosis in Switzerland, 2000-2020.

	2000-2005		2006-2010		2011-2015		2016-2020		Overall	
	[%]	N	[%]	N	[%]	N	[%]	N	[%]	N
Notification										
Confirmed case of LD[a]	89	784	87	978	90.9	1,353	92.1	2,288	90.4	5,404
Probable case of LD	4.5	40	3.9	44	4.3	64	1	26	2.9	174
Possible case of LD	6.5	57	9.1	102	4.8	72	6.9	171	6.7	402
Clinical criteria fulfilled	93.6	825	91.7	1,031	95.5	1,421	93.6	2,325	93.7	5,603
Laboratory criteria fulfilled	100	881	99.8	1,122	99.7	1,484	99.1	2,462	99.5	5,950
Demographics										
Median age (1^{st}-3^{rd} quartile)	63	(51-75)	63	(51-75)	64	(53-75)	65	(54-77)	64	(63-76)
Female	32.5	286	29.4	330	30.4	452	31.8	791	31.1	1,858
Swiss nationality	72.2	636	65.2	733	71.8	1,068	69.7	1,733	69.8	4,171
Seasonality										
Spring (Mar, Apr, May)	14.2	125	18.4	207	14.9	222	16.6	411	16.1	965
Summer (Jun, Jul, Aug)	37.6	331	37.2	419	35.7	531	37.5	931	37	2,212
Autumn (Sep, Oct, Nov)	34.5	304	28.8	324	31.2	465	28.7	713	30.2	1,806
Winter (Jan, Feb, Dec)	13.7	121	15.6	174	18.1	270	17.2	428	16.6	993
Region										
Central Switzerland	4.2	37	6.3	71	6.8	101	7.6	189	6.7	398
Eastern Switzerland	8.4	74	6.9	78	11.4	169	9.5	237	9.3	557
Espace Mittelland	22.2	196	20.8	234	22.3	332	20.4	506	21.2	1,268
Lake Geneva	20.3	179	19.7	221	21.6	321	18.5	459	19.7	1,180
Northwestern Switzerland	14.6	129	16.3	183	11.1	165	13.9	346	13.8	823
Ticino	14.9	131	15.7	176	13.9	207	15.3	379	14.9	894
Zurich	15	132	14	157	12.6	188	14.5	360	14	838
Clinic										
Hospitalisations	86.5	762	86.9	977	89.3	1,329	84.7	2,104	86.5	5,173
Deaths	6.4	56	6.9	78	4.4	66	4	100	5	300
Exposition										
Old-age home	2.7	24	2.8	32	3.3	49	2.6	64	2.8	169
Community-acquired	72.5	639	80.9	909	76.9	1,144	80	1,987	78.3	4,681
Nosocomial	6	53	3.8	43	3.5	52	3.4	84	3.9	231
Occupational	1.7	15	1.4	16	1.6	24	2.1	51	1.8	106
Travel-associated	17	150	11	124	14.7	219	12	299	13.3	793
Risk factors for LD										
Reported as 'No risk'	29.5	260	10.5	118	14.9	221	14.9	371	16.2	971

Key variables across the years for notification of legionellosis in Switzerland, 2000-2020 (continued).

	2000-2005		2006-2010		2011-2015		2016-2020		Overall	
	[%]	N	[%]	N	[%]	N	[%]	N	[%]	N
Tobacco smoking	17.1	151	40.7	458	44.9	669	40.2	998	38.1	2,276
Alcohol consumption	4	35	3.1	35	2.5	37	1.4	35	2.4	142
Immune suppression	8.5	75	13.7	154	12	178	12.2	304	11.9	710
Diabetes	8.1	71	13.1	147	14.9	222	14.3	356	13.3	796
Cancer	5.6	49	11.7	131	9.1	135	10.3	255	9.5	570
Pneumopathy	2.3	20	2.8	31	2.4	35	0.4	11	1.6	97
Nephropathy	0.2	2	1.5	17	0.9	14	0.4	10	0.7	43
Cardiopathy	1	9	2.8	31	1	15	1.4	34	1.5	89
Age 80+ years	15	132	16	180	17.5	261	19.4	482	17.7	1,055
Diagnosis										
Urinary antigen test	86.4	761	83.2	935	85.6	1,274	82	2,036	83.8	5,010
Culture	7.3	64	6	67	4.7	70	4.6	114	5.3	314
PCR	3.3	29	7.4	83	8.6	128	10.6	263	8.4	503
Serology	4.7	41	2.9	33	2.2	32	0.7	17	2.1	123
Strains										
L. pneumophila	95.5	840	95.2	1,072	96	1,429	95.4	2,371	95.5	5,712

[a] Legionnaires' disease
[b] Confidence interval

Notification process

Of all cases, 91.9% (N=5,494) were classified as confirmed cases of LD, 1.3% (N=80) as probable and 6.8% (N=406) as possible cases. Congruently, 93.5% (N=5,574) of all cases had both, a notification from the physician and from the diagnostic laboratory; 3.8% (N=227) had only a laboratory notification and 0.1% (N=4) were recorded with a clinical notification only. This proportion remained largely stable, however, in 2020, 8.1% (N=39) of all cases were notified to the FOPH without a clinical notification form. This is in line with only 89.6% clinically confirmed LD cases in 2020, the lowest since 2000 (mean 2000- 2020: 93.7%); and the highest number of cases classified as probable (11.2%, mean: 6.7%).

Clinical information

Among all cases with a clinical notification form (N=5,753), 85.8% were hospitalised in 2020 and in 2019 (mean: 89.9%). The median number of days from case date to hospitalisation was 3 days. The overall case fatality rate (CFR)* was 5.2% (N=300). The annual CFR decreased from 7.7 % (CI: 2.5% - 17.0%) in 2000 to 3.6% (CI: 2.1% – 5.8%) in 2020. The CFR was highest in 2001 (10.2%, CI: 5.6% – 16.9%) and

lowest in 2016 (2.8%, CI: 1.4% – 5.1%). The median duration from the reported case date to death was 7 days (10^{th} and 90^{th} percentile: 2 - 24 days). On average 97.4% of cases with a clinical report form were diagnosed with a pneumonia, thereby fulfilling the clinical criteria for diagnosing a LD.

Exposure

If clinical reports were available, the highest proportions of reported risk factors for LD were tobacco smoking (39.6%), age 80 and over (17.7%) and diabetes (13.8%). These proportions remained stable over the years after 2005. Most cases were classified as community-acquired (77.4%, N=4,454) followed by travel-associated LD (13.8%, N=793), nosocomial (4.0%, N=231), related to a retirement home (2.9%, N=169) and occupation-related (1.8%, N=106). All exposure classifications except retirement home-related cases exhibited a comparable relative seasonality with most cases occurring in summer. Travel-associated cases peaked in August and September. Among all travel-associated cases, the majority was traveling abroad (78.1%).

The proportion of travel-associated legionellosis cases most prominently decreased in 2020 (8.3%, mean: 13.8%), while the number of occupation-associated cases increased to 3.6% (mean: 1.8%). Further, the proportion of travels abroad decreased to 64.9% (mean: 78.1%).

Diagnostics

Most cases were diagnosed using a urine sample (89.5%); sputum (6.4%), bronchoalveolar lavage fluid (6.5%) and serum (2.2%) were significantly less often used. Consequently, the urinary antigen test (UAT)* was used for most diagnostics (91.2%), followed by PCR (9.4%) and culture-based diagnostics (7.1%), and serological testing (3.2%). The proportion of PCR tests used increased continuously over the years. Of all 5,927 cases with the test specified, 642 (9.2%) had at least two different kinds of tests; the combinations of an UAT with a culture (N=315) and an UAT with a PCR test (N=281) were most frequently recorded.

***Legionella* species**

Among all cases, *Legionella pneumophila* has been indicated as the causative agent for 95.5% (N=5,712). This proportion remained high across all years. If a culture or a PCR was indicated in the records, the species could be identified for 82.3% (730 out of 887). Of these, a significant proportion were identified as *Legionella pneumophila* (87.4%), among which serogroup 1 accounted for 21.5%. Only 7 cases of *L. bozemanii*, 4 cases of *L. longbeachae*, 3 cases of *L. micdadei* and 1 case of *L. brunensis* infection were recorded.

Data quality of the NNSID database

Completeness

The data between 2000 and 2020 was generally complete. In 2020, due to the reduced reporting of the clinical notification form, more clinical information was missing compared to previous years: the hospitalisation status was given only for 89.9% of all cases and the manifestation date (i.e. the date of disease onset) for 82.0%. A detailed overview is provided in the Appendix A, Table S2.

Internal validity

Overall, the internal validity of the data was high and only a few inconsistencies were found. In 37 records (0.6%), the case classification and the entries of the clinical and laboratory criteria were discordant. From the cases with known disease onset date (N=5,111), 102 (2%) records indicated an onset date after the notification date. Similarly, in a few cases, the entries of date of death preceded the date of testing. We could not be evaluate the indicated exposure classification in relation to the incubation timeline.

Timeliness

The median number of days between the case date to the hospitalisation date was 2 days (10 and 90 percentiles: 0-7 days). The median number of days between hospitalisation and reception of the notification at the FOPH was 5 days (10 and 90 percentiles: 1-16 days). On average, there was no delay between reception and data entry at the FOPH (0 days; 10^{th} and 90^{th} percentiles: 0-1 days).

In 2020, the median days between events has remained stable, however, the spread, i.e. the 90% percentile, increased, particularly during the peaks of the pandemic (spring and autumn 2020). Table S3 in Appendix A shows the overall median number of days from case date to notification entry at the FOPH.

Legionellosis notifications during 2020

The first cases of COVID-19 were identified in Switzerland in week 8 of 2020 (Figure 4.3A). The first wave of the pandemic peaked in week 12 with 7,118 cases and the second wave in week 44 with 56,093 cases. The most stringent non-pharmaceuticals measures (closure of schools, shops, sport centres and travel-restrictions) were set in place on March 16th (week 13) and were then gradually removed until week 25. However, daily life was not resumed to levels before the pandemic between the first and second wave as some measures, such as quarantining if traveling from 'risk countries' or limiting capacities at certain venues, persisted.

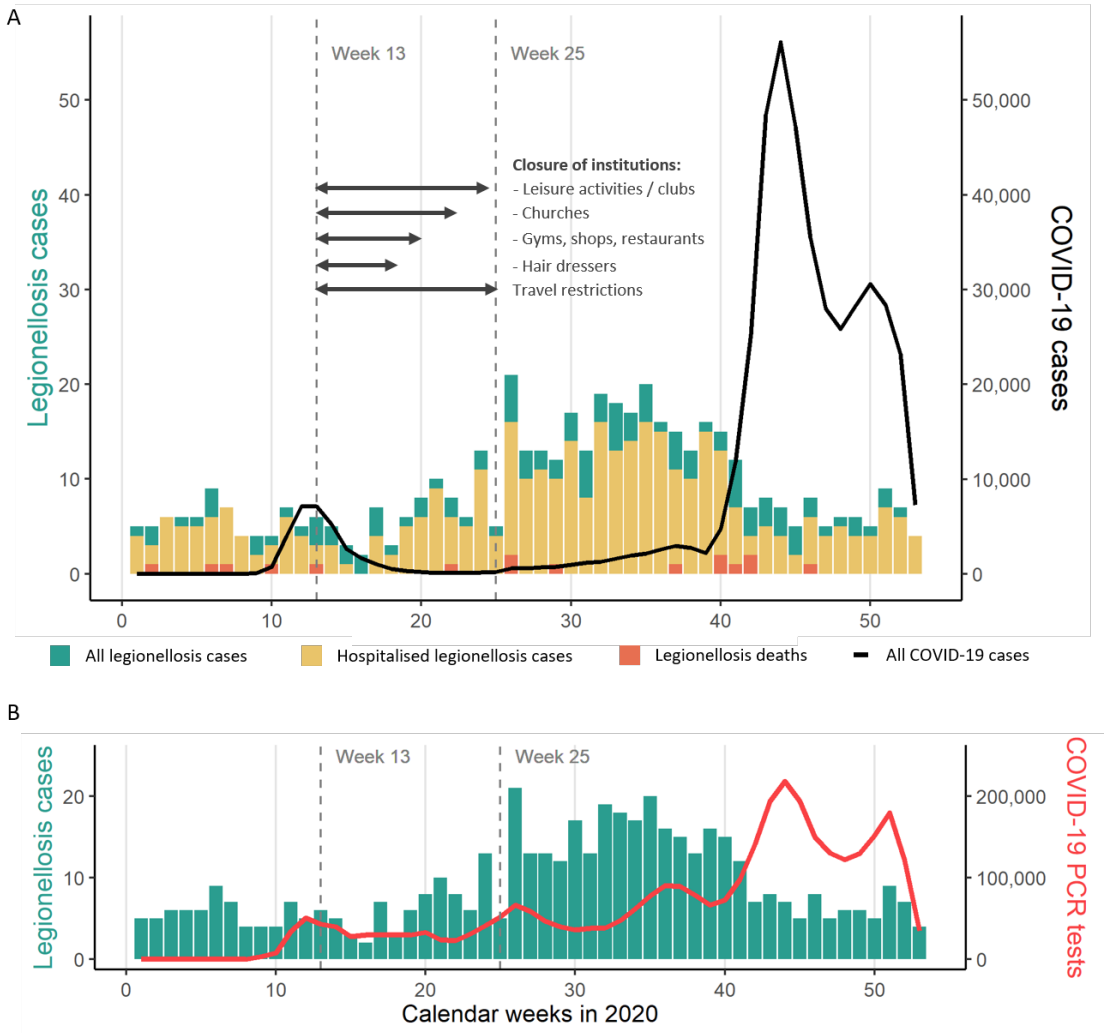

Figure 4.3: Legionellosis cases in the context of the COVID-19 pandemic in 2020. (A) Weekly number of legionellosis cases (left y-axis, scale 0-50) and COVID-19 cases (right y-axis, 0-50,000) in 2020, Switzerland. (B) Weekly number of legionellosis cases (left y-axis, scale 0-20) and COVID-19 PCR tests (right y-axis, scale 0-200,000) in 2020, Switzerland.

In total 483 legionellosis cases (among them 429 LD cases) were reported in 2020. In week 26 an early peak in legionellosis cases could be seen (21 cases), followed by the expected seasonal increase in cases by week 30/32. The number of legionellosis cases followed the usual seasonality with more cases occurring in summer than in winter. This contrasted with the period of relatively low COVID-19 incidence before the surge of the second wave.

Figure 4.3B illustrates the number of legionellosis cases and the frequency of COVID-19 PCR tests performed, which are weakly correlated (Spearman's rank correlation=0.38, $p < 0.01$). Figure 4.4 shows

the results from the interrupted time-series analysis. The time of the implementation of travel restrictions is associated with a decrease in notification rate of 35% (95% CI: 0.47-0.90; $p < 0.01$), the re-usage of buildings such as gyms, shops and restaurants (week 20) is statistically non-significantly associated with an 11% increase in notification rate (95% CI: $0.85 - 1.46$; p=0.44). Also all other opening steps were not associated with an increase in cases.

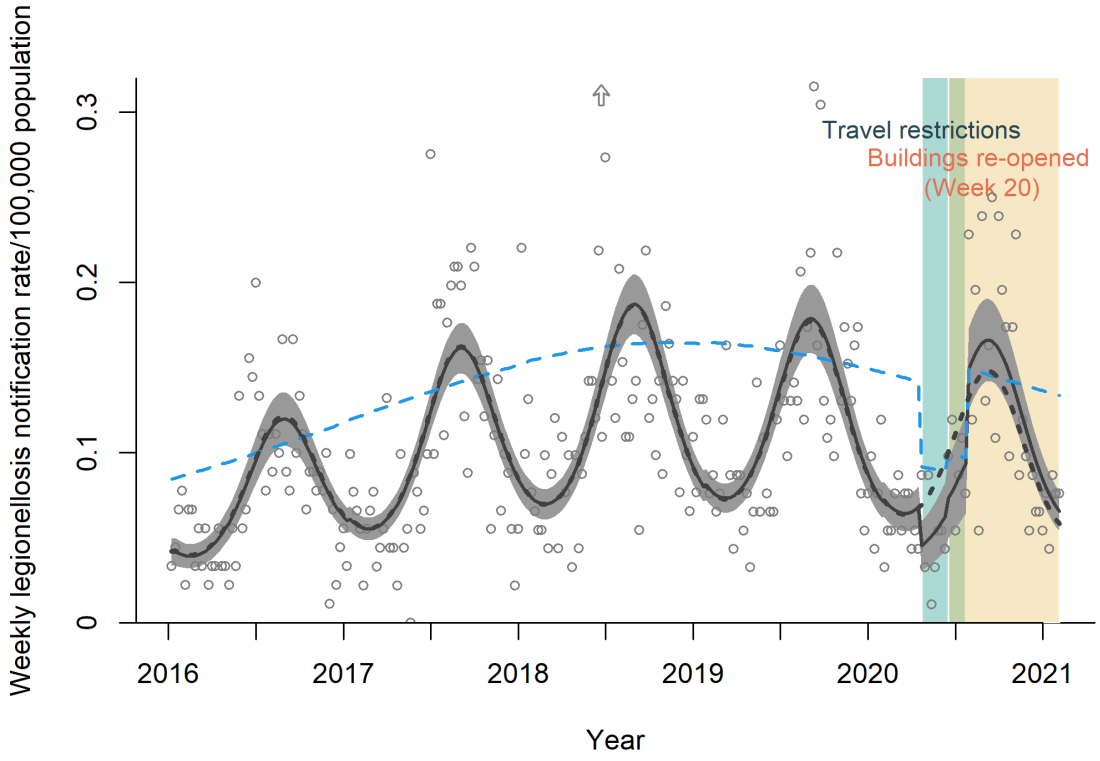

Figure 4.4: Interrupted time series analysis using Quasi-Poisson regression model on the number of weekly cases of legionellosis in Switzerland, 2016-2020. The blue line denotes the deseasonalised trend. The dotted black line represents the counterfactual if no interventions took place. The grey arrow denotes a point out of bounds (week 25, weekly notification rate per 100,000 population=0.42).

Discussion

Interruption of the upwards disease trend since 2018

We evaluated the Swiss legionellosis notification data over two decades. The upward trend since 2000 peaked in 2018 and plateaued thereafter. In 2018, the summer peak was also particularly strong and shifted into June instead of late summer time. This shift was most notably visible in Central Switzerland, Espace Mittelland, Northwestern Switzerland and to a lesser extent in the southern Swiss canton of Ticino. Therefore, this seasonal shift is unlikely driven by a cross-regional outbreak of legionellosis.

Comparing the most recent published European estimates on LD from 2019, Switzerland has one of the highest notification rates; Only Slovenia (9.4/100,000) reported higher rates [ECDC 2021b]. While in about half of the European countries the upward trend in case notification after 2018 persisted, the strong and early summer peak in 2018 could be observed across all the EU/EEA and has been unmatched in 2019. The fact that also the US reported a similar high notification rate in 2018, suggest larger-scale (such as weather and climate) effects impacted LD occurrence [Han 2021]. The impact of climate, weather, relative humidity, and rainfall events in particular promoting LD infection and rising incidences has been highlighted before [Gleason et al. 2016; Sakamoto 2015; Walker 2018].

The latest published data from the FOPH show that legionellosis case numbers in 2021 exceeded those of 2018 with a notification rate of 7.8 per 100,000 inhabitants compared to 6.7 [BAG 2022d]. As such, data following the post-pandemic years with their extraordinary circumstances need to be closely monitored.

Stable risk groups and high level of data quality

There has been no remarkable shift in legionellosis case demographics and risk groups across the years. The CFR for LD has been fluctuating throughout the years, but has been lower in recent years than at the start of the century. The overall CFR of 5% calculated from the NNSID data in our study is slightly lower than the average in the EU/EEA of 7% [ECDC 2021b]. However, this figure needs to be interpreted with care: mandatory notification requires the information on the diagnostic (laboratory) findings and a report on clinical findings including exposure data and condition at time of reporting, but a follow-up reporting of the disease outcome including death is not mandatory. Given that notification often occurs early in the disease progression the LD-related CFR of 5% from NNSID data may be underestimated. Vital statistics are consistently collected at the FSO. The ICD-10 code A481 'Legionnaires' disease' has been reported as primary or secondary cause of death for on average 23 cases per year (range $12 - 35$ cases) in the decade from 2008 to 2018; (data provided by the FSO to the FOPH). Because the death reports do not always provide the underlying disease leading to respiratory or cardiovascular failure, they tend to underestimate the importance of infectious diseases as cause of death. Still, based on these estimates and for the reasons above, the number of deaths in the NNSID was generally underestimated by an average of 30% (range $1\% - 58\%$).

Overall, the extent of data incongruities and missing data in the NNSID database is low, and notifications and data entry are made in a timely manner. Similar to the death status, other post-notification information on the development of the cases, such as the discharge date cannot be universally captured in the surveillance system. As a result, e.g. discharge date was removed from the reporting form in 2014. The median duration from requesting a diagnostic test for *Legionella* infection and legionellosis notification to the FOPH is 5 days and in due-time of the one week time limit for legionellosis notifications [Federal Assembly 2016] and comparable to the Norwegian timeliness [Wolff et al. 2019]. The variable 'case date',

which fixes the case on the timeline does hamper the interpretation slightly as it can relate to various dates that were recorded within the disease progression. Finally, the current structure of the database is in part marginally user-friendly and/or has been changed (with little readily available documentation) over the years, impeding access to the information. For some reported information (e.g., exposure classification), the database does not allow automatic verification. Electronic reporting could support this process and facilitate data evaluation in the long term. Additionally, some of the incongruities might be avoidable if automated data checks would be included in such an electronic system at entry points with the laboratories and the physicians.

Lastly, the amount of information on each case has been decreasing in recent years with the omission of variables of the clinic progression and risk factors (e.g. occupation). Decreasing the requested information and streamlining the notification process to the data that is essential for the purpose of the surveillance, lowers the workload on the notifying physicians and might further improve (the already high) adherence and quality of the information provided.

The impact of COVID-19 on LD case numbers

In 2020, the first year of the SARS-CoV-2 pandemic, the number of reported legionellosis cases was similar to 2017 (see Appendix A, Figure S2). A recent report from the FOPH noted a decline of LD cases of 32% compared to the expected case numbers based on the years 2015 to 2019 [BAG 2021a]. In our model, starting in 2016, the expected case numbers without the containment measures (the counterfactual) was lower than the actual case numbers. Forward prediction was dependent on the inclusion of years; however, the estimated effect of the investigated measures remained stable. The CFR was lowest in 2020, and a temporal pattern within 2020 could not be observed. We found a weak correlation between the number of COVID-19 tests performed and the number of LD cases identified.

It is difficult to disentangle the effects of the pandemic on legionellosis notification rates. The pandemic itself had an influence on a multitude of aspects of our life and the main causes of LD are not well understood yet. A notable difference in 2020, however, was a 4-percentage-point reduction of clinical notification forms submitted to the NNSID. The clinical notification is sent by the treating physician to the cantonal physicians, who processes and forwards the notification to the FOPH [Schmutz 2018]. In case, the cantonal physician receives a laboratory but no clinical notification, they request a clinical notification from the treating physician. These clinical notification forms are most prominently missing in April and October 2020, suggesting (hospital) physicians and/or cantonal authorities were preoccupied with the consequences and the control of the COVID-19 pandemic. As cases without clinically confirmed pneumonia are counted as legionellosis cases, but not as LD, this leads to an underestimation of LD cases.

The number of both domestic and international travel-associated cases decreased during the pandemic [Steffen, Lautenschlager, and Fehr 2020]. Concurrently, the interrupted time series analysis showed a marked drop in legionellosis cases at the implementation of travel restrictions; and a corresponding increase in cases after they were lifted. Yet, on average only 13.3% of all cases were travel-associated, indicating that either this number is underrepresented or the effect of the travel-restrictions is confounded. We saw only a small effect associated with the reopening of buildings and the presumed exposure to higher concentrations of *Legionella* spp. from extended water stagnation in the buildings' pipes and plumbing. According to a recent publication, water stagnation-related issues following closure of buildings might have overstated the respective risk for LD [Rhoads and Hammes 2021]. Yet, there is no concluding evidence for either side. The lack of effect could also be due to staggered re-opening of buildings, spreading the new cases and diluting the effect, or flushing recommendations in anticipation of the risk through stagnation have been taken seriously by buildings owners/management and cases were successfully prevented.

Conclusion

In Switzerland, the notification rate of LD continuously increased since 2000 to one of the highest rates in Europe, yet the upwards trends was interrupted in 2018, the reason remains unclear. The COVID-19 pandemic seemed to have affected the case numbers mainly through the travel restrictions, which has notably decreased the number of travel-associated cases. Additionally, while physicians seemed to lack resources to keep up with their obligations to notify, the notifications were reported through the diagnostic laboratories in similar frequency and quality compared to previous years, suggesting a robust surveillance system.

Limitations

As this study was based on information from passive disease surveillance, we were limited to cases that were reported. Therefore, we could only approximate the true incidence of the disease. Further, the main drawback on studies involving surveillance data is the lack of denominator data. However, a study on this additional data for the years 2007-2016 has been published previously [Fischer et al. 2020b].

Acknowledgements

We thank Dr. Jan Hattendorf (Swiss TPH), Anja Orschulko (Swiss TPH), Julia Fanderl (Swiss TPH) and Dr. Monica Golumbeanu (Swiss TPH) for their support in the statistical analysis, data acquisition, data cleaning and advice. We also thank the Federal Office of Public Health, in particular Marianne Jost, Ornella Luminati and Dr. Ekkehardt Altpeter for providing the data and their support.

Statements and Declarations

Funding

This study was funded by the Federal Office of Public Health (FOPH, contract number 142003961/334.0-85/53).

Competing Interests

The authors have no conflicts of interest to declare that are relevant to the content of this article. Monica N. Wymann is staff of the FOPH and participated in her capacities as public health specialist and her function as scientific collaborator within the organisation.

Author contributions

Fabienne B. Fischer and Daniel Mäusezahl conceived and designed the study. Material preparation and data collection were performed by Fabienne B. Fischer and Monica N. Wymann. Analysis and interpretation was performed by Fabienne B. Fischer with support of Daniel Mäusezahl and Monica N. Wymann. The first draft of the manuscript was written by Fabienne B. Fischer and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

The study was conducted under the Epidemics Act (SR 818.101) [Federal Assembly 2016]. The study team received the legionellosis notification data from the FOPH. Other data (COVID-19 cases, non-pharmaceutical measures, and population statistics) are publicly available from the FOPH, the FSO or third parties.

Chapter 5

When infectious diseases (re-)emerge: Transferable experiences from COVID-19 to Legionnaires' disease

From Public Health Policy to Impact for COVID-19: A Multi-Country Case Study in Switzerland, Spain, Iran and Pakistan

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This article was published in:
International Journal of Public Health (2022), 67
doi: 10.3389/ijph.2022.1604969

Did COVID-19 policies have the same effect on COVID-19 incidence among women and men? Evidence from Spain and Switzerland

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This article was published in:
International Journal of Public Health (2022), 67
doi: 10.3389/ijph.2022.1604994

One of the through-lines of this thesis is the interplay between the Swiss health system with Legionnaires' diseases (LD)* case numbers: In particular, we address how disease estimates are generated within the healthcare system and captured within the disease surveillance system. In Chapter 4, we look specifically at the impact of health policy for COVID-19 containment on the number of LD cases. This theme is expanded in this chapter, exploring the interactions between health systems and policies and COVID-19 incidence.

COVID-19 emerged at the end of 2019 and rapidly spread around the world [Ryan 2021]. At the time, we had requested the LD reporting data for 2000-2020 from the FOPH with the aim of creating a detailed overview of the data and epidemiology in Switzerland, resulting in the two studies on the temporal (Chapter 4) and spatial patterns (Chapter 10) of LD. COVID-19 quickly took hold in Switzerland too, affecting nearly every aspect of our daily lives, from recommendations to stay at home to travel restrictions and school closures. It became clear that a comparison of the temporal developments in 2020 with earlier years without taking into account the COVID-19 pandemic itself would not be appropriate. We, therefore, conducted a sub-analysis on the effects of selected COVID-19 containment measures on LD reporting rates (Chapter 4).

By embedding part of the study on LD notification data in the context of COVID-19, opportunities arose to engage in two further research studies, both of which had the COVID-19 policies as their starting point. Both studies are reproduced in full in the Appendices B and C. The content of these studies is briefly summarised here and discussed in context with LD.

5.1 The interplay between policies and infectious disease case numbers

The first study 'From Public Health Policy to Impact for COVID-19: A Multi-Country Case Study in Switzerland, Spain, Iran and Pakistan' focused on the comparison of COVID-19 related policies implemented by selected countries and how these policies shaped the beginning of the COVID-19 pandemic [Tavakkoli et al. 2022]. For this purpose, the chronology of containment measures for the analysis in Chapter 4 was expanded with the collection of qualitative data between February and July 2020 according to 17 indicators based on 16 COVID-19 recommendations from the WHO [WHO 2020]. These 17 measures comprised multiple health systems domains: governance, financing, health workforce, information, medicine, and technology and service delivery.

The study showed that the landscape of policies in Switzerland at the beginning of the COVID-19 pandemic was complex and fast changing. Whenever new knowledge about COVID-19 became available or the epidemiological situation changed, rapid decision-making was required. In Switzerland, decision-making

is highly decentralised among the 26 cantons. At the height of the first 'wave' (spring 2020), decision-making based on the EpidA was centralised to the Federal Council to facilitate and expedite the management of this crisis. When decision-making was decentralised and responsibility was given back to the cantons, legislation changed sometimes within a few days. The rapidly changing policies make it difficult to disentangle the impact of policies on COVID-19 case numbers and choose the most beneficial mitigation measures. One of the conclusions from the study was that retrospective analysis of the dynamic interaction between polices and public health requires transparency in publicly available information and a comprehensive compilation of information of different legalisation.

We further showed that policy decisions may not always be motivated by health concerns alone. During the first wave, wearing surgical or hygiene masks was not recommended to the general public. Today, it appears that wearing hygiene masks is one of the most effective measures to contain the disease when they are used almost universally [Howard et al. 2021]. However, a report from 2021 indicates that there was a significant shortage of masks in spring of 2020, which may have been part of the rationale for this recommendation [Tavakkoli et al. 2022]. The study suggests that trust in and acceptance of mitigation measures influences their success. Initial communication about the effectiveness of hygiene masks seemed to have generated some scepticism about future recommendations.

The comparison of Swiss policy with that of Pakistan or Iran showed that the health system and economic context had a strong influence on the measures that could be implemented. The robust economic situation in Switzerland and the functioning healthcare system provided broad access to diagnostic tests and treatment and made it possible for Switzerland to avoid a complete 'lockdown'.

Many of these findings bring transferable insights for the policy context of LD. The initial phase of the pandemic was complicated by a lack of knowledge about the emerging disease and thus a paucity of evidence about effective mitigation measures. This led not only to problems in averting the burden of disease, but also to changing policy recommendations, public confusion or non-acceptance of the interventions. It highlights the need for an evidence base for policy-making. In the case of LD, the implementation of prevention and control measures is impeded by the lack of evidence on the main sources of infection: Many of the efforts to prevent LD, target hot water systems in buildings, from legislating *Legionella* limits in public buildings to advising the public to keep the minimum boiler temperature at 60 °C. However, it is not known whether these measures are effective in preventing cases. Some circumstantial evidence, such as the seasonality of *Legionella* cases (Chapter 4), suggests that the source of infection may be elsewhere, as the hot water temperature in buildings remains largely constant regardless of the ambient temperature. An evidence base for policies is not only important for the decision-making process itself, but also for the public acceptance of the policy. Similarly, the introduction of 60 °C at boiler level receives the most push back from energy reduction advocates when public health benefits have not been demonstrated. However, in the absence of evidence for, but also against, the effectiveness of hot water temperature limits, the severity of LD and the

widespread exposure of the population to their domestic drinking water justify precautionary measures to avoid a major public health burden.

The economic background and the generally good condition of the healthcare system in Switzerland have not only shaped the handling of the COVID-19 pandemic, but probably also continues to shape the number of observed LD cases and the handling of LD and *Legionella* as a whole: Switzerland has one of the highest LD notification rates in Europe, which can be partly attributed to a well-functioning healthcare system, i.e. good access to health care and to diagnostic methods leading up to LD case detection. In addition, research on LD and *Legionella* has received strong government support and funding in recent years. These resources are needed to address the growing public health concern, but may not be available for a disease with relatively low case numbers in resource-limited settings.

5.2 Policy impact on vulnerable populations

The second publication titled 'Did COVID-19 policies have the same effect on COVID-19 incidence among women and men? Evidence from Spain and Switzerland' focused on the differential impact COVID-19 containment measures had on COVID-19 incidence among women and men [Sant Fruchtman et al. 2022]. We applied a retrospective longitudinal study design using data from the FOPH and the Spanish epidemiology surveillance site between February 2020 and June 2021 to explore sex and age differences in COVID-19 cases, testing rates and deaths. The female-male incidence rate ratios were estimated for each week of the pandemic.

The study showed that the COVID-19 incidence was larger among women of working age than men during the time of highest incidence in both Switzerland and Spain. These time points also coincided with the most stringent COVID-19 containment measures. The disparity in incidence among women and men grew the more stringent the implemented measures were, both in comparison between waves and between Switzerland and Spain. In Switzerland, the biggest difference in incidence was observed in women aged 20 to 29, where the excess from March to May 2020 reached 94%. The difference in incidence could not be attributed to different testing behaviour and case finding either, because although women got tested more often, the positivity rate remained similar in men and women. The findings suggest that the COVID-19 containment policies affected women and men of working age differently. We hypothesised that part of the disparity was due to the women's over-representation in essential jobs with human contact (e.g. in retail or healthcare) and their stronger involvement in unpaid care work increasing their exposure to SARS-CoV-2.

The study illustrates that health policies do not always benefit all population groups equally and, in some cases, exacerbate existing inequalities. In terms of LD, the burden of disease is borne proportionately more by men, a finding which is consistent across most countries, e.g. on average 70% of all European LD cases and 68.9% of all Swiss cases were male [ECDC 2022; Fischer, Mäusezahl, and Wymann 2022]. The

proportion of (hospitalised) patients with pneumonia also appears to be predominantly male, but the sex distribution is more balanced than for LD. For example, 59% of all hospitalised CAP patients in Switzerland and 56% of all hospitalised CAP patients in New Zealand, were men [Corica et al. 2022; Garbino et al. 2002; Priest et al. 2019]. The cause for this disparity is poorly understood. Based on the ubiquitous exposure to *Legionella* in the environment, there is little to suggest that the exposure is higher in men than in women, with the exception of occupational exposures [Principe, Tomao, and Visca 2017]. There are some occupations with elevated risk for LD infection due to increased exposure to water aerosols. For example, industrial facilities equipped with cooling towers or coolant systems have been implicated with occupational LD cases [Principe, Tomao, and Visca 2017]. A review of occupation-associated LD cases from 2021 found that most occupational cases were associated with employees in hazardous or service industries [Hunter et al. 2022].

Another explanation could be that some risk factors for LD are more common in men, such as alcohol consumption, smoking or certain comorbidities [Corica et al. 2022]. Finally, the underlying biological mechanism of disease could be different in men than in women. For example, animal studies show that there is a clinically stronger reaction to infections in males than females [Mege, Bretelle, and Leone 2018]. Thus, the course of disease in women could be more often benign enough so that they do not appear in the health care system. Similarly, a review on sex distribution of CAP found that the proportion of women increases if mild CAP cases are considered [Falagas, Mourtzoukou, and Vardakas 2007].

Apart from sex (biological) and gender (societal) differences, evidence on subgroups who are particularly vulnerable to LD due to social and economic determinants is limited. Studies suggest that areas with higher poverty rates show higher LD incidences [Hunter et al. 2022]. Yet, this association seems to not be unique to LD, but holds for pneumonia in general. Studies from the US have further shown that there is a disproportionally higher incidence of LD among Black communities, which has been attributed to their disadvantages in social determinants of health, such as income stability or lack of medical access [Hunter et al. 2022]. The evidence on socio-economic inequalities concerning LD morbidity and mortality in Switzerland is likewise limited. In the ecological model, we found that a lower mean socio-economic position per district was associated with higher LD case numbers (Chapter 10). The analysis of the national notification data also showed that the proportion of Swiss nationals is smaller among LD cases (approx. 69.7%) [Fischer, Mäusezahl, and Wymann 2022] than the general population (75%) [BFS 2022a]. However, the cause of these differences have not been explained. Generally, foreign nationals are overrepresented in the low-income population [BFS 2002]. Furthermore, they are less likely to visit a physician or seek biomedical care [Tzogiou, Boes, and Brunner 2021]. The delay in seeking medical care could lead to an exacerbation of symptoms, which then results in hospitalisation and the detection of LD; in other words, the proportion of Swiss nationals among mild LD cases could be more even.

The *SwissLEGIO* study incorporates questions to better understand social determinants of health on LD incidence such as income or education level. The thorough assessment of housing attributes should further allow insights into the factors related to socioeconomic inequality associated with LD incidence. These factors include the age of the building and last renovation date, the layout of the bathroom (e.g. with or without window) and defects or maintenance of the drinking water system (e.g. corrosion, problems with water pressure). Understanding these risk factors allows for the planning of better prevention strategies. For example, if deficiencies in drinking water installations were associated with the occurrence of LD, measures and preventive actions should be taken to strengthen and protect low-income neighbourhoods with insufficient building maintenance.

Finally, our experience with LD patients from the pilot study and the first patients from the actual *SwissLEGIO* study (Chapter 12) has shown that knowledge about the domestic drinking water system is partly limited. In addition, access to comprehensible information for the required steps to avoid *Legionella* contamination (e.g. the temperature of 60 °C) or the channels to take if contamination is suspected is difficult or not equally available. We devoted a section in the *SwissLEGIO* questionnaire to collect and explore the patients' disease experience and their available knowledge of their disease but also the pathogen. Until these concepts have been explored, it remains important to provide accessible and understandable information on *Legionella* prevention and control to the public. This regained some urgency with the recent energy crisis, where people might be tempted to save money and lower the water temperatures of their boilers to critical levels. The recently launched information campaign 'Energy is scarce. Let's not waste it.' of the Federal Department of the Environment, Transport, Energy and Communications and the Federal Department of Economic Affairs, Education and Research advises the public on energy saving methods. It includes a section on hot water [EnergieSchweiz 2022] that is currently lacking information on *Legionella* and should be expanded in the near future.

In summary and in the most simplified terms, the steps in dealing with such a (re-)emerging infectious disease are similar: (i) recognise the problem; (ii) assess the extent of the problem; and (iii) understand the causes of the infection. COVID-19 and LD face similar systemic and political challenges, albeit COVID-19 in a much larger scale and public setting. These challenges stem from a lack of knowledge about these emerging diseases and a shortage of evidence. Given the severity of the public health problem, the advances in research and knowledge about COVID-19 are remarkable and arguably exceed the available knowledge about many diseases that have been known for much longer, including LD. As new evidence became available, mitigation policies could be adapted, e.g. the wearing of hygiene masks. Such evidence is urgently needed for LD. The COVID-19 pandemic has also raised general awareness that population health does not refer to 'one uniform population'. As we make progress in public health, we need to be aware of sub-populations and how they are affected by the disease and interventions. A shared commonality between COVID-19 and LD that was not covered in the two studies was the different interests of policy-makers and the fact that health policy

is not exclusively driven by public health. The predominant discussion during the COVID-19 pandemic was the trade-off between preventing COVID-19 infections and economic stability and social and mental well-being. The LD analogy would be the opposing interests of preventing LD infections while remaining energy efficient and heating hot water sources in buildings to the minimum required temperature. In this respect, too, new evidence can contribute to finding common ground.

Chapter 6

Legionnaires' disease on the rise in Switzerland: A denominator-based analysis of national diagnostic data, 2007–2016

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This article was published in:
International Journal of Environmental Research and Public Health (2020), 17, 7343
doi: 10.3390/ijerph17197343

International Journal of
Environmental Research and Public Health

MDPI

Article

Legionnaires' Disease on the Rise in Switzerland: A Denominator-Based Analysis of National Diagnostic Data, 2007–2016

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Received: 14 September 2020; Accepted: 3 October 2020; Published: 8 October 2020

Abstract: The risk of falling ill with Legionnaires' disease (LD) is suggested to increase, but the global burden of disease is unknown due to a lack of appropriate diagnosis and surveillance systems. In Switzerland, the number of LD cases, captured by the National Notification System for Infectious Diseases, has more than doubled since 2008. This study aims to investigate this increase, contextualizing disease surveillance data with denominator data, which is not routinely available, i.e., the number of tests performed for *Legionella* spp. We collected the testing data for *Legionella* spp. of 14 Swiss diagnostic laboratories and calculated the positivity, defined as the proportion of the number of positive tests to the number of tests performed. The number of positive tests increased proportionally to the number of tests performed; hence, the positivity remained stable. However, the cause of the increase in test volume is unclear and has a large impact on the interpretation of the positivity curve. Further, the test outcome was found to be dependent on regional determinants, and the diagnostic method applied. The lack of understanding if and at which stage LD is considered in current case management of pneumonia patients limits the interpretation of observed heterogeneities in incidence or underestimation of LD in Switzerland. The absence of (or non-adherence to) existing guidelines and the heterogeneity in diagnostic testing hampers the comparison of data in the Swiss public health context. Therefore, diagnostic procedures should be harmonised across Switzerland and adherence to national LD management guidelines supported.

Keywords: *Legionella* spp.; disease surveillance; underestimation; Legionnaires' disease; diagnostics; denominator data

1. Introduction

Legionella spp. are the cause of a group of diseases termed "legionellosis" ranging from mild and self-limiting Pontiac fever to potentially fatal Legionnaires' disease (LD), characterized by pneumonia [1,2]. Infections with *Legionella* spp. occur through inhalation or aspiration of contaminated water or aerosols. In recent years, person-to-person transmission was also suspected [3]. Cases can occur sporadically, in clusters and large outbreaks.

Although *Legionella* spp. occur worldwide, the global burden of disease is unknown due to the lack of appropriate diagnosis and/or surveillance systems in many countries. In Europe in 2017, 1.8 cases per 100,000 population were estimated, corresponding to 9238 cases in total. In the same year, the US reported 7500 cases, corresponding to 2.3 cases per 100,000 population [4,5]. Case numbers have been increasing in European countries and the US in the past years.

Abstract

The risk of falling ill with Legionnaires' disease (LD)* is suggested to increase, but the global burden of disease is unknown due to a lack of appropriate diagnosis and surveillance systems. In Switzerland, the number of LD cases, captured by the National Notification System for Infectious Diseases, has more than doubled since 2008. This study aims to investigate this increase, contextualizing disease surveillance data with denominator data, which is not routinely available, i.e., the number of tests performed for *Legionella* spp. We collected the testing data for *Legionella* spp. of 14 Swiss diagnostic laboratories and calculated the positivity, defined as the proportion of the number of positive tests to the number of tests performed. The number of positive tests increased proportionally to the number of tests performed; hence, the positivity remained stable. However, the cause of the increase in test volume is unclear and has a large impact on the interpretation of the positivity curve. Further, the test outcome was found to be dependent on regional determinants, and the diagnostic method applied. The lack of understanding if and at which stage LD is considered in current case management of pneumonia patients limits the interpretation of observed heterogeneities in incidence or underestimation of LD in Switzerland. The absence of (or non-adherence to) existing guidelines and the heterogeneity in diagnostic testing hampers the comparison of data in the Swiss public health context. Therefore, diagnostic procedures should be harmonised across Switzerland and adherence to national LD management guidelines supported.

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Introduction

Legionella spp. are the cause of a group of diseases termed 'legionellosis' ranging from mild and self-limiting Pontiac fever to potentially fatal Legionnaires' disease (LD)*, characterized by pneumonia [Fraser et al. 1977; Glick et al. 1978]. Infections with *Legionella* spp. occur through inhalation or aspiration of contaminated water or aerosols. In recent years, person-to-person transmission was also suspected [Correia et al. 2016]. Cases can occur sporadically, in clusters and large outbreaks.

Although *Legionella* spp. occur worldwide, the global burden of disease is unknown due to the lack of appropriate diagnosis and/or surveillance systems in many countries. In Europe in 2017, 1.8 cases per 100,000 population were estimated, corresponding to 9238 cases in total. In the same year, the US reported 7500 cases, corresponding to 2.3 cases per 100,000 population [ECDC 2019; Centers for Disease Control and Prevention (CDC) 2018]. Case numbers have been increasing in European countries and the US in the past years.

In Switzerland, infections with *Legionella* spp. need to be reported to the National Notification System for Infectious Diseases (NNSID)*, which is managed by the Federal Office of Public Health (FOPH)*, since 1988. While all laboratory-confirmed infections are notifiable, only LD cases- cases with pneumonia— are considered as confirmed or probable cases, which are reflected in the numbers published in official statistics. The case numbers continuously increased from 219 in 2008 to 464 cases in 2017 [BAG 2018].

The increase of LD cases in Switzerland, the rest of Europe and the US is not well understood. It has been hypothesised that the increase in incidence is due to augmented susceptibility in the population, climate change or changes in energy policies [ECDC 2019; BAG 2018]. Common risk factors for LD are age >40 years, being male, tobacco smoking, travelling abroad or having chronic conditions, e.g., diabetes mellitus or a compromised immune system [Boer, Nijhof, and Friesema 2006; WHO 2007]. Furthermore, several studies link weather and climate, namely warm and humid conditions, to LD incidence [Gleason et al. 2016; Beauté et al. 2016; Sakamoto 2015; Conza et al. 2013]. Efforts in energy saving, resulting in recommendations to lower temperature thresholds of potable warm water, could have the drawback to promote conditions which favour *Legionella* spp. proliferation [Völker and Kistemann 2015].

Conversely, the increase in case numbers could also be an artefact. Increased awareness of physicians could lead to increased testing and hence, to more cases found. The incidence of legionellosis is generally thought to be underestimated; a study from Germany in 2008 estimated about 15,000 to 30,000 cases of sporadic LD annually [Baum et al. 2008]. Improvements in diagnosis and surveillance could lead to higher but more accurate case numbers [Campèse et al. 2013; Van Hest et al. 2008].

We collected testing data of 14 Swiss diagnostic laboratories between 2007 and 2016 to evaluate the effect of changes in test numbers and diagnostic procedures on the notification numbers in Switzerland. Using this data, we calculated the positivity of *Legionella* spp. testing, emphasising on temporal trends, and assessed the determinants for a positive test outcome.

Methods

The methods of a positivity study have been described in detail elsewhere [Fischer et al. 2020a]. In brief, we collected testing data from 14 Swiss diagnostic laboratories. The laboratories were selected in 2016, based on providing most LD notifications in the prior 10 years.

We collected data on all tests performed for *Legionella* spp. regardless of the test outcome, between January 2007 and December 2016. Information requested included 'date of test', test result (binary; 0=negative, 1=positive), diagnostic test method, sample material used, patient identification number, and patients' date of birth, sex and canton (a political and administrative subdivision of Switzerland, in total 26 cantons) of residence. The test result was reported by the laboratories and not assigned by the study team, hence the application and description of the case definition were not needed in this study.

We excluded tests of patients with residency outside of Switzerland, inconclusive test results, duplicated entries as well as 'repeated tests'. Repeated tests were defined as more than one test performed per patient and disease episode. The definition of a disease episode was complex given the laboratory data available; the process is described in the supplementary material (see Appendix D for details).

We use the term positivity as the proportion of the number of positive tests to the total number of tests performed for *Legionella* spp. [Schmutz et al. 2012; Bless et al. 2017]. The analysis was planned a priori and was conducted using STATA 15 (StataCorp., College Station, TX, USA). The positivity was calculated for different age and sex groups, test methods, sample materials, spatial (region and laboratory) and temporal (annual and seasonal) trends. The main outcome, the annual positivity, was age- and sex-adjusted using direct standardisation with the sample population (2007–2016) as the reference population.

We used mixed-effect logistic regression to account for clustered data to analyse the determinants for a positive test result. The significance level was defined as α=5%. Univariable logistic regression was used to test the association between the test result and test year, season, time trend, sex, age group, laboratory, test method, sample material and greater region (Table 6.1). 'Season' was modelled using sine and cosine functions with an annual period. The time trend was a continuous variable combining test month and test year. The age groups were based on categories (standard in ECDC publications), but we used a higher level of differentiation in older people, due to the known risk factor 'age' for LD. The greater regions correspond

to the Nomenclature of Territorial Units for Statistics (NUTS)*-2-level. Categories with most observations were chosen as reference categories, except for the seasonality (first month of the year).

We constructed two multivariable mixed-effect logistic regression models, both including the variables sex, age group, season, time trend, and test method. One model included the region and the other the laboratory as random effect. This partition was necessary due to collinearity and bias between the two variables and the outcome variable, which is shown in the results 'Regional differences' and discussed in the discussion section 'Regional differences across Switzerland'.

Table 6.1: Overview of the variables used in the regression models on a positive test result for *Legionella* spp. in Switzerland, 2007-2016.

Variable	**Format**	**Content**
Age group	Categorical	0–4, 5–14, 15–24, 25–44, 45–64, 65–74, 75–84, 85+ years old
Greater region	Categorical	Lake Geneva region, 'Espace Mittelland', Northwestern Switzerland, Zurich, Eastern Switzerland, Central Switzerland, Ticino
Laboratory	Categorical	14 selected Swiss diagnostic laboratories (11 hospital-associated and 3 private)
Method	Categorical	PCR, UAT, culture
Sample material	Categorical	Bronchial-liquid, urine, blood, biopsy, sputum, swab, paracentesis, liquid, other
Season	Numeric (float)	$sin((d \times 2 \times \pi)/T)$ and $cos((d \times 2 \times \pi)/T)$; d = time period (e.g., January, February), T=number of time periods (e.g. 12 months)
Sex	Binary	Male, female
Test result	Binary	Negative, positive
Time trend	Numeric (float)	Combination of month and year, e.g., January 2007=1, February 2007=2, February 2008=14

Ethical Statement

The study was conducted under the Epidemics Act (SR 818.101). The data, provided by laboratories, were anonymised for analysis. Other data (notification data, population statistics) are publicly available from the FOPH or the Swiss Federal Statistical Office.

The data that support the findings of this study are available from the corresponding author, DM, with the permission of the FOPH and the Federal Food Safety and Veterinary Office (FSVO)*, upon reasonable request.

Results

Data Received

The 14 laboratories provided a total of 154,851 observations, including 2808 positive tests. Three laboratories could not provide data for the entire study period (2007–2016) due to changes in their laboratory information system and data storage.

Exclusion

Applying pre-defined exclusion criteria (residence outside of Switzerland, inconclusive test results, tests performed outside of the study period), we excluded 6721 observations (134 positives and 968 with an inconclusive or missing test result). Additionally, 762 (13 positives) entries were excluded, for which information on either sex or age was missing.

We excluded 7287 duplicates (412 positives) from the dataset. It was further decided to exclude all serological tests due to their limited utility in a clinical/diagnostic setting (see Appendix D for details). In total 2558 (1.8%) serological tests (108 positives) were performed. Lastly, 13,196 repeated tests (383 positives) were excluded. The final dataset comprised 126,422 (1638 positives) observations.

National Notification System for Infectious Diseases

We compared the number of positive test results in our dataset to the NNSID notification numbers as notified by our selected laboratories. As noted above, the published notification numbers only reflect LD cases while the positive test results in our dataset reflect all legionellosis cases. The biggest difference in numbers was observed in 2009 with a relative difference of 54.9% (91 LD cases in the NNSID compared to 141 positive test results in our dataset; Figure 6.1). The average relative difference was 23.0%. Generally, the annual case number from all participating laboratories combined was higher in our dataset than in the NNSID data.

The LD cases notified to the NNSID from the 14 selected laboratories account for 54% of all notified cases nationwide between 2007 and 2016 according to the NNSID database. This proportion remained constant across the years.

The number of tests performed increased by 131% from 7366 in 2007 to 17,027 in 2016 and the number of positives by 71% from 114 to 195 (Figure 6.2a). The yearly age- and sex-adjusted positivity decreased marginally from 1.5% to 1.1% (Figure 6.2b).

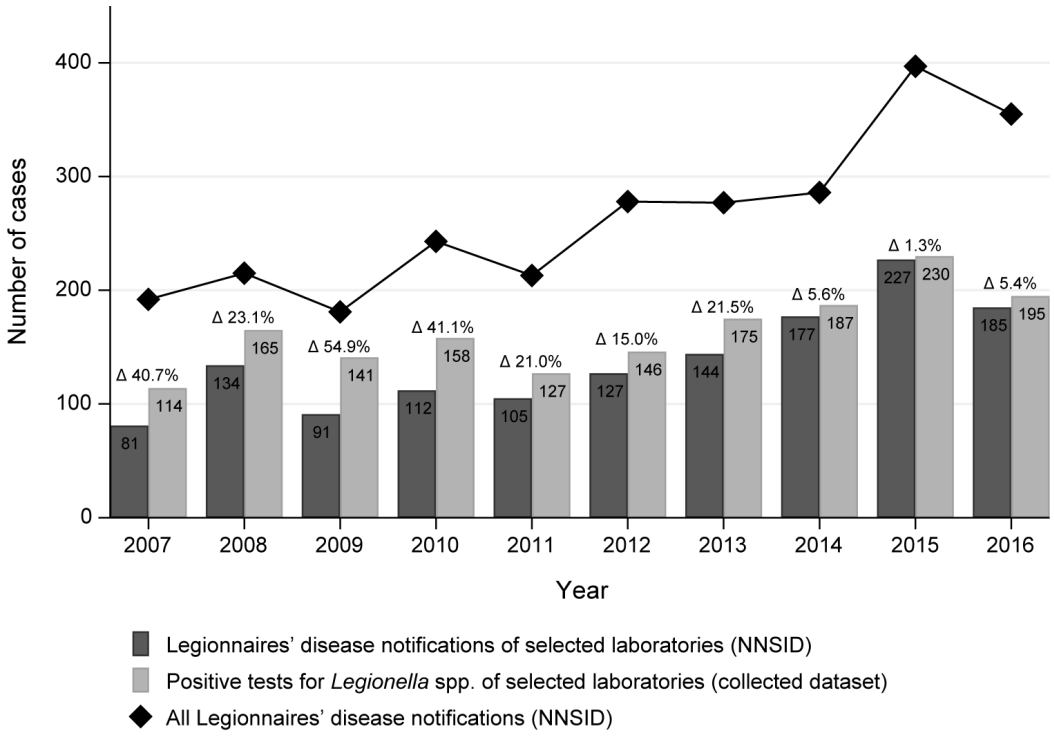

Figure 6.1: Number of Legionnaires' disease (LD) notifications of the 14 selected laboratories as reported in the Swiss National Notification System for Infectious Diseases (NNSID) and the number of positive tests of the selected laboratories, as well as the total number of LD notifications reported in the NNSID per year, 2007–2016, Switzerland. The figures in the bars correspond to the number of observations; the relative difference between them is denoted as the percentages above the bars.

Positivity

Across all years, the positivity started increasing in May and peaked in August and September reaching 2.6%, then decreased in October to reach an all-year low in February with 0.5%. The seasonality of the positivity is a direct result of the contrasting seasonality of the number of tests performed and the number of positive test results obtained (Appendix D, Figure S2). Most tests were performed during the winter months; on average 62% more tests were conducted in February than in August. Conversely, more than three times as many cases were reported in September compared to February.

The seasonality persisted across all age groups, both genders and all regions. It is most strongly reflected in tests performed using urinary antigens. PCR and culture-based tests do not show any clear seasonal pattern for the number of tests performed and the number of positive cases, also explained by small numbers.

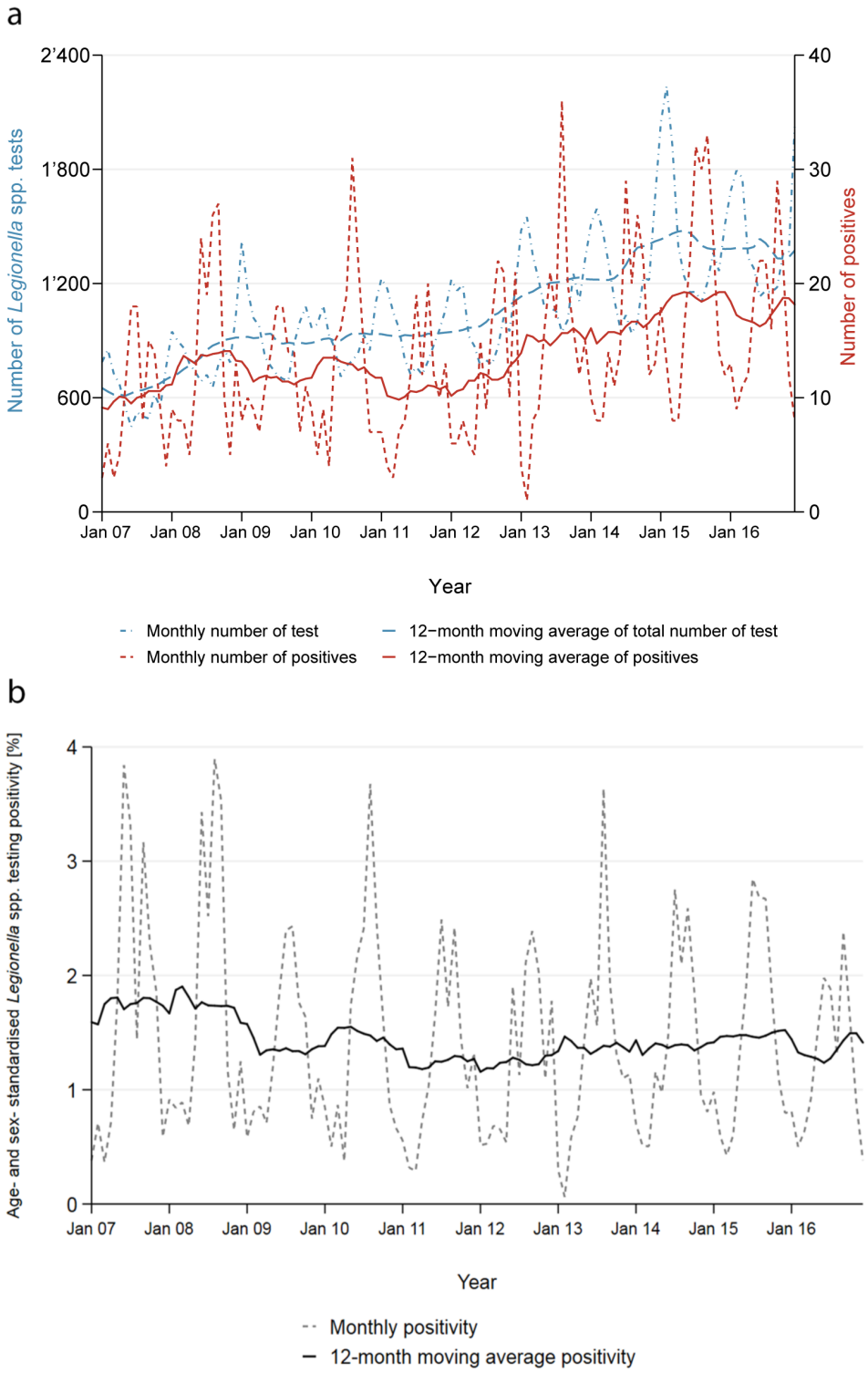

Figure 6.2: Time trend in test volume, cases and positivity. (a) Twelve-months moving average (solid lines) and monthly (dashed lines) number of *Legionella* spp. tests performed and number of positive tests, for the entire study period (2007–2016) by 14 diagnostic laboratories in Switzerland. (b) Twelve-months moving average (solid line) and monthly (dashed line) age- and sex-standardised positivity of *Legionella* spp. testing, Switzerland, 2007-2016.

Gender and Age

The positivity varies strongly by gender and age group. Males have an overall higher positivity compared to females (1.6% to 0.9%). The positivity increases with age and is highest among 45–64-year-olds (2.5% for males and 1.3% for females) and then decreases gradually again; this pattern is similar for both genders (Appendix D, Figure S3a). The positivity of males aged 5–14 years old is the only exception to this pattern with a positivity of 1.4%. No female in the age groups '0–4' and '5–14' was tested positive.

The majority of patients tested were males (57.9%, N=73,224). This proportion remained stable across the study period (2007–2016). The overrepresentation of males in the tested population was seen in all age categories, except in the oldest (85+ years old), where 48.7% of all tested patients were male (chi-square test: $p<0.01$, Appendix D, Figure S3b).

Overall, most tests were performed in the age group of 75–84-year-olds (25.6%, N=32,349), closely followed by the age group of 45–64-year-olds (24.5%, N=30,956). Least tests were performed in the age groups of infants (0–4), adolescents (5–14) and young adults (15–24) with 0.3%, 0.4% and 2.3%, respectively. During the study period, the age distribution of tested patients remained similar and the median age increased only marginally from 69 years old in 2007 to 71 in 2016 (Kruskal–Wallis test: $p<0.01$).

The difference in sex distribution was small but statistically significant for all greater regions (range 57.5% to 60.4% males, chi-square test: $p<0.01$) and slightly more variable between laboratories (53.3% to 64.4% males, chi-square test: $p<0.01$). Similarly, the median age only differed marginally, but significantly between regions (range of medians 68–73 years old, Kruskal–Wallis test: $p<0.01$) and more strongly between laboratories (range 59–74 years old, Kruskal–Wallis test: $p<0.01$).

Regional Differences

Of the 14 laboratories in our dataset, 11 were hospital laboratories accounting for 86.2% (N=109,016) of all observations included in this analysis. However, the three private laboratories may also perform diagnostics for hospitalised patients. The laboratories performed diagnostics mainly for patients with residency in proximity to the laboratory site. Therefore, the variable 'laboratories' is correlated with the variable 'greater region' (Appendix D, Figure S4). Hence, any information on regions is heavily influenced by the selection of laboratories.

The positivity in the greater regions across all years ranged from 0.9% in 'Northwestern Switzerland' to 2.4% in the region 'Zurich' (Figure 6.3). The positivity for all regions decreased from 2007 to 2016 except in 'Northwestern Switzerland', where there was a relative increase of 44%. The positivity fluctuates throughout the years, most notably in 'Zurich' (range 1.1% to 4.5%).

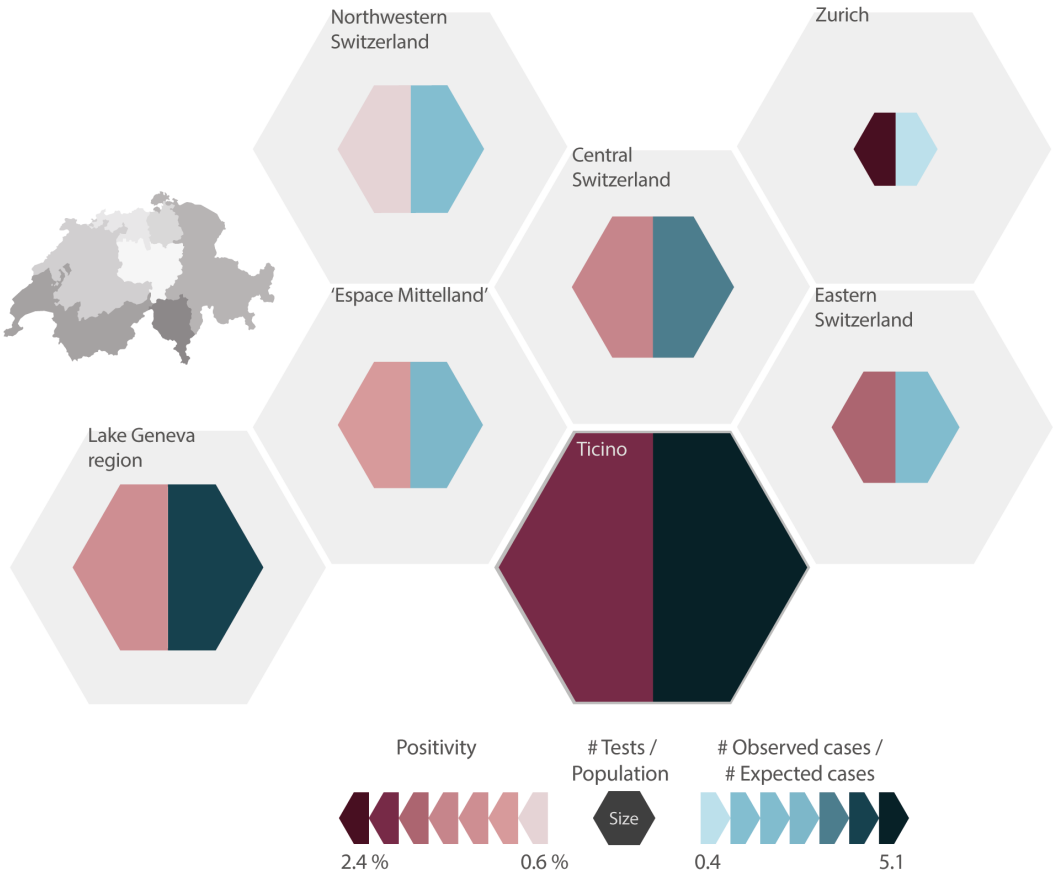

Figure 6.3: Representation of the seven greater regions of Switzerland (displayed as grey area) of the positivity for *Legionella* spp. testing (colour of left part of the smaller hexagon), the number of tests performed in relation to the resident population (size of smaller hexagon) and the ratio of the number of observed cases to expected cases (colour of right part of the smaller hexagon), based on the testing data of 14 Swiss diagnostic laboratories (2007–2016). The expected cases were calculated based on the relative population size of each region to the overall Swiss population and the proportion of each region of all cases (in our dataset).

Over the entire study period (2007–2016), most tests were performed in the 'Lake Geneva' region, followed by 'Espace Mittelland' and 'Ticino'. The least amount of tests was reported from the region 'Zurich'. In relation to the average population of the regions (2007–2016), much more tests were conducted in 'Ticino' with 6493 tests per 100,000 population compared to 'Zurich' with 377 tests per 100,000 population (Figure 6.3). The average for all greater regions was 2028 tests per 100,000 population.

The number of tests performed increased in all regions between 2007 and 2016 (Appendix D, Figure S5). The biggest relative increase (129 in 2007 to 1698 in 2016) was observed for 'Northwestern Switzerland', followed by 'Espace Mittelland' (544 to 3055) and 'Eastern Switzerland' (455 to 1332). 'Zurich' had the smallest relative increase (536 to 585). This distribution remained stable, even when disregarding the laboratories not providing data for the entire study period.

Diagnostic Method and Sample Material

The process of exclusion of repeated tests could already provide first insights on the diagnostic procedures used in the laboratories; hence, we shortly describe the raw data set here. In the raw dataset, 7.7% (N=10,809) of all patients were tested at least twice during the same disease episode; 4.3% (N=6022) of the patients were tested more than once on the same day. After excluding tests performed on the same day— as the order of test could not be assessed- 3.4% of all urinary antigen tests (UATs), 14.8% of all culture-based tests and 14.7% of all PCR tests were excluded as repeated tests. The positivity among the repeated tests was 2.9%.

All results henceforth stem again from the analysis of the cleaned dataset (omitting repeated tests). The positivity of *Legionella* spp. tests performed using UATs was 1.3%, using culture-based tests it was lower (0.8%) and using PCR higher (3.1%). The positivity of UATs varied based on the exact test used (Fisher's exact test: $p<0.01$): The UATs from lowest to highest positivity were, Binax™ *Legionella* Urinary Antigen EIA (Alere) (0.9%), BinaxNOW® *Legionella* ICT (Alere) (1.2%), Biotest *Legionella* Urinary Antigen Enzyme Immunoassay (EIA, Biotest) (1.7%) and Sofia *Legionella* Fluorescent Immunoassay (FIA, QUIDEL) (2.2%).

The positivity of UATs decreased during the study period from 1.6% in 2007 to 1.1% in 2016. The positivity of culture-based tests remained below 1% except for three years (2008: 1.5%; 2012: 1.6%; and 2014: 1.4%). The positivity of diagnostic tests using PCR increased gradually since 2011 from 2.8% to 4.8%.

The majority of diagnostic tests performed was UATs with 90.1% (N=113,863) followed by culture-based methods (6.6%, N=8373) and PCR (3.3%, N=4169). This distribution remained stable at large between 2007 and 2016. Only PCR slightly gained importance (0.8% in 2007 to 2.5% in 2016) at the costs of UATs (92.4% to 88.3%). UATs performed were mostly BinaxNOW (71.4%), Binax (11%), Biotest

(10.1%) and Sofia *Legionella* FIA (7.6%). The Sofia *Legionella* FIA test was introduced only in 2014 and increased its market share since to 28.6% of all UATs in 2016. For BinaxNOW market shares decreased from 75.7% of all UATs in 2007 to 52.3% in 2016.

Almost all of the nine laboratories performing PCR used a different type of test. Four laboratories reported to outsource PCR diagnostics to other laboratories and, therefore, could not provide detailed information. Three laboratories had communicated to use respiratory multiplex PCR panels; however, for two of three, the distinction between single and multiplex PCR could not be made in our dataset (personal communication, May-July 2017). Due to this heterogeneity and lack of accuracy, we did not further quantify the different types of PCR tests performed.

As the test method is dependent on the laboratories and their diagnostic procedures, the variable 'method' is correlated with the variable 'laboratory' and therefore also with 'region' (see Appendix D, Figure S4). Twelve of the 14 laboratories predominantly or exclusively performed UATs. One laboratory performed 76.3% PCRs and another 79.3% culture-based diagnostics. The proportion of PCR increased in the former between 2007 and 2016 replacing UATs, while in the latter the proportion of culture-based tests and UATs increased replacing PCR. UATs comprise at least 80.6% of all tests performed in all greater regions. The biggest proportion of culture-based tests was performed in 'Espace Mittelland' (11.5%), 'Lake Geneva region' (9.8%) and 'Northwestern Switzerland' (8.9%). Most PCR tests were performed in 'Northwestern Switzerland' (10.5%) and 'Lake Geneva region' (3.2%). In four of the seven regions, the diagnostic methods used over the years remained overall unchanged (Ticino, Central Switzerland, Eastern Switzerland, Zurich).

Determinants for a Positive Test Result of *Legionella* spp.

The univariable model showed a significantly increased odds ratio (OR)* for a positive test outcome for the test years 2007 and 2008 compared to the latest test year 2016. The time trend variable showed a marginal downward trend, with a rounded OR of 1 (exact OR 0.998, CI 0.9970–0.9998, $p = 0.03$). Further, all calendar months from May to December had significantly increased odds for a positive test outcome compared to February. The highest odds were calculated for August and September (OR 4.02, $p < 0.01$ for both).

Females were almost half as likely as males to be tested positive for a *Legionella* spp. infection (OR 0.56, $p<0.01$). Compared to the reference group of 75–84 year olds, the age groups '15–24' and '85+' had significantly decreased odds for a positive test outcome (OR 0.41, $p<0.01$ and OR 0.76, $p<0.01$), and the age groups '45–64' and '65–74' showed increased odds (OR 2.06, $p<0.01$ and OR 1.36, $p<0.01$).

'Northwestern Switzerland' showed 20% lower probability for a positive test result compared to the 'Lake Geneva' region (OR 0.81, p=0.04), while 'Zurich' had more than double the odds and 'Ticino' a 50% increased chance for a positive test result (OR 2.22, p<0.01 and OR 1.47, p<0.01).

Culture-based tests had lower odds for a positive test outcome compared to UATs (OR 0.63, p<0.01). In contrast, PCR tests had 2.5-fold increased odds for a positive test (OR 2.47, p<0.01).

The univariable regression using the sample material as an explanatory variable was stratified by culture-based tests and PCR. For culture-based tests, using material obtained through paracentesis or using sputum showed the highest OR (OR 10.32, p=0.03 and OR 5.12, p<0.01). Using PCR, material obtained through paracentesis (OR 4.47, p=0.05) or swabs (OR 3.91, p<0.01) or using sputum (OR 3.24, p<0.01) had elevated odds for a positive test outcome.

Figure 6.4 shows the ORs for different UATs before and after inclusion of 'laboratory' as a random effect. Univariable models including other variables showed no significant effect on the ORs and are therefore not shown.

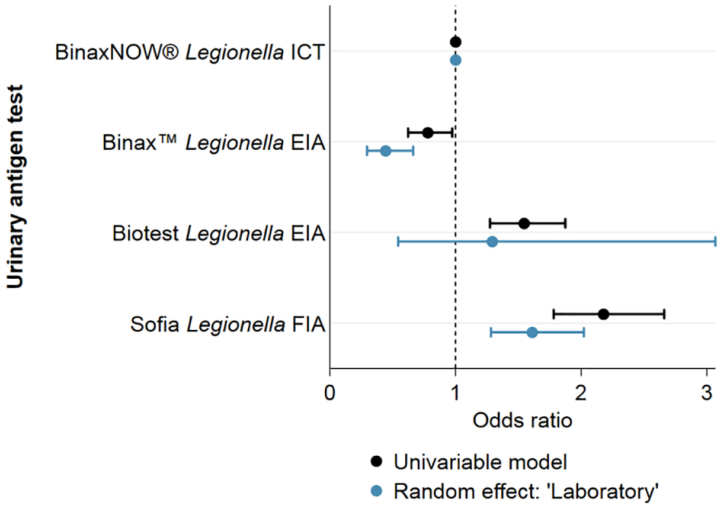

Figure 6.4: Differences in positivity across UAT test kits. Univariable regression results with and without random effect on 'laboratory' for the outcome of having a positive test result for *Legionella* spp. in Switzerland, 2007–2016.

Both multivariable mixed-effect logistic regression models (with the inclusion of 'region' or 'laboratory' as random effect, respectively) are shown in Figure 6.5 together with the results of the univariable models. The estimates are comparable for all variables. The marginal but statistically significant negative OR for the time trend-variable, however, lost its statistical significance in both multivariable models.

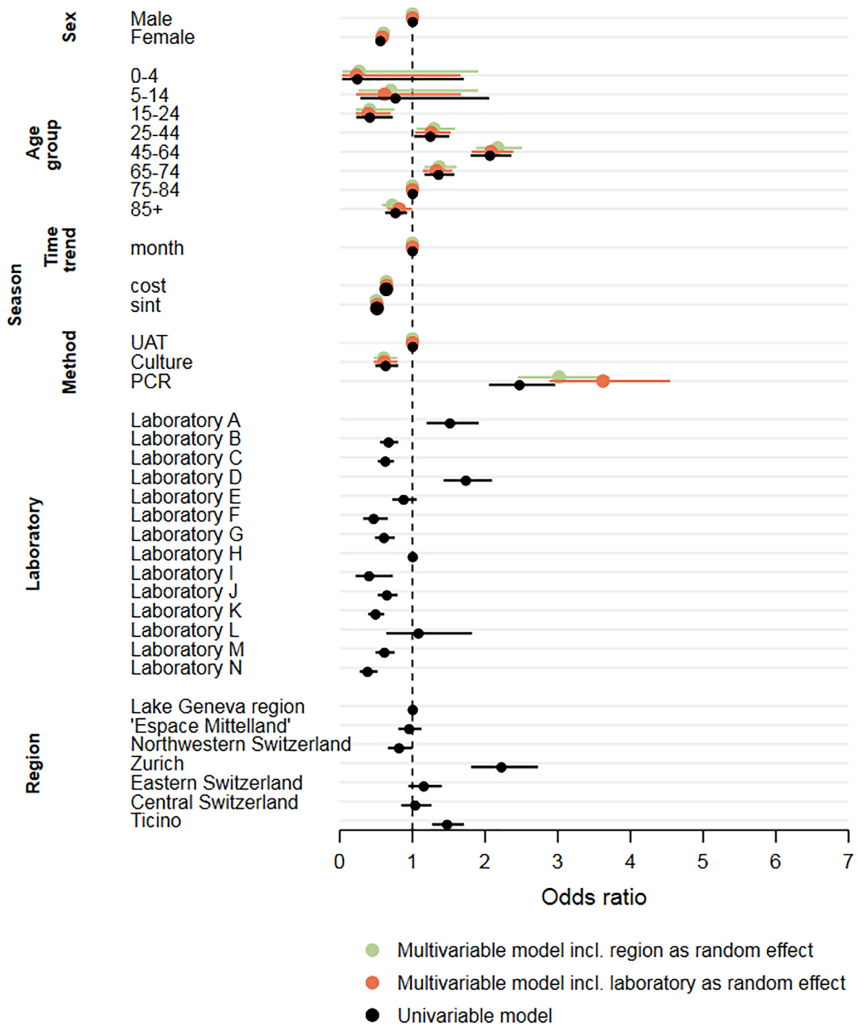

Figure 6.5: Determinants for a positive test result for *Legionella* spp. Multivariable mixed-effect logistic regression compared with the univariable regression results for the outcome of having a positive test result for *Legionella* spp. in Switzerland, 2007–2016.

Discussion

We collected the testing data of 14 Swiss diagnostic laboratories and calculated the positivity, i.e., the proportion in the number of positive tests to the number of tests performed to investigate the increase observed in case numbers of LD in official disease surveillance.

Time Trend in Positivity 2007–2016

The number of *Legionella* spp. tests performed increased more strongly than the number of cases found, resulting in a marginally decreasing positivity between 2007 and 2016 from 1.5% to 1.1%. However,

no temporal trend was found in the multivariable regression models. The strong increase in test numbers for *Legionella* spp. cannot be explained given that contextual information on health-seeking, test behavior of physician and on diagnostic methods and procedures applied by laboratories are essential for a correct interpretation of trends in positivity.

We hypothesise that changes in the diagnostic methods influenced the number of tests performed: Especially, the introduction of the UAT revolutionised the diagnosis of legionellosis. In 2015, 78.2% of all LD cases in Europe were detected using UATs [Beauté and ESGLI 2017]. In Switzerland, UATs were introduced to the routine diagnostic in 1997 and are now predominantly used [Gysin 2018]. However, the UAT is unlikely to have influenced the most recent increase in test numbers, as the introduction of this test occurred almost 20 years ago and the proportion of UATs performed remained stable or declined during the study period. Therefore, changes in testing behaviour of physicians, health-seeking behaviour of patients, prevalence of risk factors and of disease frequency need to be considered to explain the increase in test volume.

Symptom-based testing explains the inverse seasonality in the number of tests performed and the number of cases found. Community-acquired pneumonia (CAP)* peaks during the winter months but is predominantly caused by agents other than *Legionella* spp. [Murdoch et al. 2014]. Therefore, the testing volume is higher in winter than in summer even if the physicians are aware of a summer peak for *Legionella* spp. [Cherrie et al. 2018].

The Swiss Society of Infectious Diseases (SSI)* provides guidelines for the management of CAP, which were adapted from European guidelines. The guidelines state that microbial testing is not indicated in primary care settings, and even in hospital settings, *Legionella* spp. testing may only be useful for selected risk patients based on clinical or epidemiological features [Laifer, Flückiger, and Scheidegger 2006]. These recommendations leave room for interpretation and can, thus, be applied differently by the treating physician, depending on his/her awareness of LD and knowledge of its epidemiological and clinical features. Failure to diagnose LD has previously been attributed to a lack of awareness of LD [Fields, Benson, and Besser 2002]. Heightened awareness of physicians and consideration of LD in their differential diagnosis of patients presenting with pneumonia would lead to more LD tests ordered over time. However, there is a lack of information on adherence to the CAP guidelines, the awareness level among Swiss physicians and the case management of LD in Switzerland.

An increasing number of patients in Switzerland seek care for non-urgent or non-life-threatening conditions at emergency departments rather than at primary care level [Diserens et al. 2015]. These 'new' patients presenting at the emergency department could contribute to a higher number of LD tests conducted: According to SSI guidelines, microbiological investigation of pneumonia is recommended earlier in the hospital compared to the primary care setting. Increased awareness and change in health-seeking

behaviour as potential causes for increased testing are independent of disease incidence, but rather represent a shift in test practices. More cases are found if a larger part of the population is being screened for LD, hence, reducing the extent of underestimation.

However, an important alternative explanation for the increase in test volume is that, actually, more ill patients present with signs and symptoms of LD (i.e., pneumonia). In this scenario, the increase in test numbers would be explained by an increase in incidence rather than a decrease in the extent of underestimation. According to the 'medical statistic of hospitals' ('Medizinische Statistik der Krankenhäuser') published annually by the Federal Statistical Office, the number of hospitalised patients with pneumonia recorded as 'main diagnosis' in over 14-year-olds has increased by one third between 2007 and 2016, while the number decreased for patients younger than 15 [Diserens et al. 2015]. Hence, these statistics support the hypothesis of increased pneumonia incidence leading to higher test volumes.

However, the lack of information and understanding of the trajectory from health-seeking to LD diagnosis does not allow conclusive interpretation of the 10-year-trend in positivity. The number of reported LD cases is not only rising in Switzerland but also in the EU/EEA countries, which are members of the European Legionnaires' Disease Surveillance Network (ELDSNet)* and in the US [ECDC 2019; Shah et al. 2018]. Nevertheless, Switzerland had the highest notification rate per 100,000 population in 2017 (5.8), followed by Slovenia (5.7), Denmark (4.8) and Italy (3.3) and the second largest increase in notification rate between 2013 and 2017 [ECDC 2019; BAG 2022e]. However, we are not aware that data from these national surveillance systems were evaluated considering denominator data. Furthermore, notification rates are heavily influenced by the health system itself, and hence, comparability between countries is limited.

Male and Elderly People at Risk

We found that men were more often tested for *Legionella* spp. than women were, and positivity was significantly higher for males than for females. This suggests that the higher case numbers for men are actually due to a higher incidence in the male population or a diverging health-seeking behaviour rather than more thorough testing due to male sex being a known risk factor [Marston, Lipman, and Breiman 1994].

Regardless of gender, adults over 25 years showed an increased positivity, peaking at 45–64 years of age and declining again in older age groups. The difference in positivity for the middle-aged patients (25–64) compared to the older patients (over 65) is likely due to a more thorough testing approach for the older patients compared to younger patients (testing elderly earlier, presenting with less severe acute respiratory infections). The difference in test volume could also be due to the knowledge that older age is a risk factor for LD or CAP being more prevalent in older age [BAG 2018; WHO 2007; Garbino et al. 2002].

Regional Differences Across Switzerland

It is difficult to estimate regional differences based on our data, as it is heavily dependent on the laboratories included in the study. The interaction of these variables ('laboratory' and 'greater region') is not straightforward to assess. Apart from the collinearity of these variables, we found that the positivity of tests performed in one laboratory differed substantially depending on the residency of the patient, especially if the patient lived outside of the usual catchment area of said laboratory. We assume this is due to different pre-test probabilities for a positive test outcome, e.g., only the samples of immunosuppressed patients (with an assumed higher probability of an actual infection with *Legionella* spp.) would be sent to another laboratory for confirmation. However, it is impossible to control our dataset for these 'outsourced' tests. For this reason, we decided to construct two multivariable logistic regression models. These limitations should be kept in mind when interpreting the results on the greater regions.

The calculated positivity and the logistic regression models show heterogeneity across regions. The regions of 'Zurich' and 'Ticino' seem to identify more positive cases per number of tests performed. Additionally, the two regions show opposite test frequency: relative to the resident population, in 'Ticino' many people are tested for LD while the inverse applies for 'Zurich'. Further, 'Ticino' has the highest notification rate amongst all Swiss cantons, which might not only result from the highest testing volume but from an actually increased incidence, as indicated by the increased positivity and suggested by other studies focusing on the impact of climate at regional level (2018) [Conza et al. 2013]. In contrast, in 'Zurich', where the number of reported cases and case rate is similar to the national average (2008–2017), either testing is more targeted to the 'correct' patients, resulting in a higher positivity or incidence is actually higher, but underestimated due to the small test number [BAG 2018]. In 'Northwestern Switzerland' the reporting rate is also on the national average, but the region has significantly decreased odds for a positive test outcome. The number of tests performed increased most strongly in this region. At the same time, it was the only region with an increasing positivity.

As has been mentioned before, the SSI guidelines are subject to the interpretation of the health personnel, and the level of adherence is unknown. Hence, who is tested is likely very heterogeneous across Switzerland.

Heterogeneity in the Diagnostic Methods

Not all diagnostic test methods for *Legionella* detect the same pathogens and strains. The application of UAT is limited mainly to *Legionella pneumophila* serogroup 1, culture-based techniques can detect all *Legionella* species, while PCR techniques can either detect only *L. pneumophila* or all species, depending on the type of test. The positivity also varies depending on the test method used, on the application of the chosen test method and on the specific kind of test kit or manufacturer.

Using PCR increased the odds of obtaining a positive test result significantly compared to UAT and cultures. This could be attributed to the higher sensitivity of PCR compared to UAT, but it could also result from false-positives due to cross-reaction or contamination [Peci, Winter, and Gubbay 2016]. A systematic review comparing UAT and PCR found PCR to be preferable. However, PCR is limited by the availability of appropriate sample material from the patient [Avni et al. 2016]. Culture is still regarded as the gold standard, as it allows the cultivation of strains but exhibits an overall lower sensitivity, which corroborates with our results [Peci, Winter, and Gubbay 2016]. However, in our study, the differences in positivity between UAT, PCR and culture could also be attributed to different testing behaviours, rather than to features inherent to the test. In some hospitals/laboratories, PCR and culture-based tests may only be performed in high-risk patients (e.g., immunocompromised patients), which might affect the positivity and introduce bias.

Double-testing with different diagnostic methods is often seen as advantageous [Peci, Winter, and Gubbay 2016; Avni et al. 2016; Pierre et al. 2017; Jespersen et al. 2009]. The European Study Group of *Legionella* Infections (ESGLI)* further recommends that all samples positive by UAT should be retested after heat treatment of the urine for confirmation unless the initial sample was already boiled [Pontoizeau et al. 2014; Rota et al. 2014]. However, in our raw dataset, only 1 in 12 patients got tested at least twice during the same disease episode. UATs are most often used as a stand-alone test, and only in 194 cases, a positive UAT was repeated during the same disease episode. However, it is likely that not all secondary tests for confirmation are registered in the individual laboratory information systems and, hence, are possibly not reported.

Lastly, the choice of test kit manufacturer for the widely used UAT also influences the positivity of *Legionella* spp. testing: the Sofia *Legionella* FIA test has a significantly increased positivity compared to the most commonly used UAT BinaxNOW. In comparison, the former has a higher sensitivity but also a lower specificity especially without heat treatment of the urine, which could lead to false-positive results [Beraud et al. 2015]. The Swiss national reference centre for *Legionella* (NRCL)* recommends heat treatment of all urine samples if Sofia *Legionella* FIA is used. If the initial urine sample was not boiled, a confirmation test needs to be performed on positive samples. However, it is unclear how many laboratories adhere to these recommendations of the NRCL. Hence, differences in positivity of the various test kits might not only be inherent to the kit itself but also to the performance of the test. It should be noted that due to the correlation of the test method (kit) and region, these differences could also be impacted by differences in regional incidence. However, the calculated positivities and the distribution of methods do not all point in the same direction and performance differences of test kits have been demonstrated before.

It is evident that diagnostic test practices, including patient selection for testing, choice of test method and the performance of the diagnostic test influence test outcomes. From our dataset, heterogeneity between preferred diagnostic test methods is observed. There is a high degree of uncertainty linked to physicians'

testing behaviours and also test performance in the laboratories, or rather the physicians' adherence to existing guidelines. An assessment of current practices and the harmonisation across Switzerland could improve public health surveillance and decrease heterogeneity (e.g., of levels of underestimation) between regions.

Limitations

For feasibility reasons, considering over 106 laboratories are either authorised or accredited in Switzerland [Swissmedic 2019], the analysis had to be limited to a selection of laboratories. We chose to base the selection on the volume of notifications during the study period, therefore, favouring laboratories with the highest notification rates. With the 14 selected laboratories, 54% of all notifications between 2007 and 2016 could be covered. Detailed information on the selected laboratories, e.g., laboratory coverage, testing volume by greater region and laboratory identifiers, are in parts restricted for data confidentiality reasons.

Conclusion

We found a stable positivity for *Legionella* spp. testing between 2007 and 2016 analysing the testing data of 14 Swiss diagnostic laboratories. There is a proportional increase in the number of cases identified in relation to the number of diagnostic tests performed. However, it is not clear why the number of tests performed more than doubled in the 10-year study period. The interpretation of the positivity curve and the implications on disease incidence can be vastly different depending on the reason for the increase in testing volume.

The assessment is further complicated, as large variations in positivity and test volume across the seven greater regions of Switzerland exist. We assume that these differences are only partly explained by differences in actual disease incidence; they seem to also stem from different CAP case management and diagnosis plans and represent different degrees of underestimation. The scarcity of data impedes evaluation of the different hypotheses. The diagnostic method greatly influences the test outcome. Culture-based methods, PCR and UATs perform differently and have their own limitations; particularly as in the case of the latter compliance with the recommendations and standard operating procedure for boiling of the urine are suspected to vary.

The lack of national (or adherence to existing) guidelines and the heterogeneity of the diagnostic tests and testing procedures applied hampers the diagnosis of LD as well as comparison of data in a public health context. Therefore, diagnostic procedures should be harmonised across Switzerland to follow recommendations from the national reference centre for *Legionella* .

Statements and Declarations

Supplementary Materials

The following are available online at https://www.mdpi.com/1660-4601/17/19/7343/s1, Figure S1: Different example scenarios based on the definition of disease episode to exclude repeated tests for *Legionella* spp. in Switzerland, 2007–2016. Text file S2: Descriptive analysis of the serological tests performed for *Legionella* spp. in Switzerland (2007–2016) as provided in the raw dataset by 14 Swiss laboratories and argumentation for their exclusion for further analysis. Figure S2: Seasonality in test volume and cases. The average and interquartile range (IQR) per calendar month of the total number of *Legionella* spp. tests and number of positive tests, Switzerland, 2007–2016. The seasonality has been incorporated into the mixed effect logistic regression using sine and cosine functions, in the form of $sin((d \times 2 \times \pi)/T)$ and $cos((d \times 2 \times \pi)/T)$, where d is the time period (e.g. January, February) and T is the number of time periods (e.g. 12 months), as described by Stolwijk, A. M., et al. (1999). Figure S3: Age distribution in test volume and positivity (a) Positivity of *Legionella* spp. testing by sex and age groups, Switzerland, 2007–2016. (b) Number of *Legionella* spp. tests performed by sex and age groups in Switzerland (2007–2016) and permanent resident population in Switzerland (2016) by sex and age groups. Figure S4: Correlation between the variables 'greater region' and 'laboratory' included in the *Legionella* spp. positivity study, Switzerland, 2007–2016. Figure S5: Trends of the total number of tests performed per greater region by 14 diagnostic laboratories included in the *Legionella* spp. positivity study, Switzerland, 2007–2016. References [Pedro-Botet and Yu 2006; Amsden 2005; Steele and Bragg 2016; Hall et al. 1994; Sanders, Walker, and Lee 1980; Kohler, Winn, and Wheat 1984; Diederen 2008; Sopena et al. 2002; Harrison and Taylor 1988; Waterer, Baselski, and Wunderink 2001; Delgado-Viscogliosi, Solignac, and Delattre 2009; Plouffe et al. 1995] are cited in the supplementary materials.

Author contributions

C.S. and D.M. conceived and designed the study. Data collection and processing was performed by F.B.F., with C.S. F.B.F. conducted the analysis. F.B.F., C.S., V.G. and D.M. interpreted the results. F.B.F. wrote the first draft of the manuscript. All authors contributed to the revisions of the manuscript and approved the final version.

Funding

This study was funded by the Swiss Federal Office of Public Health (FOPH, grant number 16.015253) and the Swiss Federal Food Safety and Veterinary Office (FSVO, grant number 307.2/2014/00158).

Acknowledgments

The authors thank Apolline Saucy (Swiss Tropical and Public Health Institute, Swiss TPH) for support during the data collection and data cleaning. Christian Schindler (Swiss TPH) and Jan Hattendorf (Swiss TPH) provided statistical advice. Various staff of the Federal Office of Public Health (FOPH) provided detailed insights to the Swiss surveillance system and information on the notification data. We specifically thank Mirjam Mäusezahl (FOPH) and Nicole Gysin (FOPH) for reviewing and commenting to the manuscript and Andreas Baumgartner (Federal Food Safety and Veterinary Office [FSVO]) for supporting this research from the start. The authors much appreciate the support of the following laboratories providing data for the study: ADMed Microbiologie/Lienhard Reto (La Chaux-de-Fonds); EOLAB–Dipartimento di medicina di laboratorio, Ente Ospedaliero Cantonale (Bellinzona); Institut für Infektionskrankheiten (IFIK, Bern); Institut für Labormedizin soH AG (Solothurn); Institut für medizinische Mikrobiologie (IMM, Luzern); Kantonsspital Aarau AG (Aarau); Laboratoire de Bactériologie des HUG/Jacques Schrenzel (Geneva); Spitalzentrum Biel AG (Biel); Universitätsspital Basel/Adrian Egli (Basel); Viollier AG (Allschwil); Zentrum für Labormedizin (St. Gallen); and three other Swiss diagnostic laboratories. The FOPH and the FSVO are gratefully acknowledged for providing the funding and the framework for this study.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Chapter 7

Do changes in STEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity, 2007 to 2016

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This article was published in:
Eurosurveillance (2020), 25, 33
doi: 10.2807/1560-7917.ES.2020.25.33.1900584

Do changes in STEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity, 2007 to 2016

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Citation style for this article:
Fischer Fabienne Beatrice, Saucy Apolline, Schmutz Claudia, Mäusezahl Daniel. Do changes in STEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity, 2007 to 2016. Euro Surveill. 2020;25(33):pii=1900584. https://doi.org/10.2807/1560-7917.ES.2020.25.33.1900584

Article submitted on 19 Sep 2019 / accepted on 22 Apr 2020 / published on 20 Aug 2020

Background: Laboratory-confirmed cases of Shiga toxin-producing *Escherichia coli* (STEC) have been notifiable to the National Notification System for Infectious Diseases in Switzerland since 1999. Since 2015, a large increase in case numbers has been observed. Around the same time, syndromic multiplex PCR started to replace other diagnostic methods in standard laboratory practice for gastrointestinal pathogen testing, suggesting that the increase in notified cases is due to a change in test practices and numbers. **Aim:** This study examined the impact of changes in diagnostic methods, in particular the introduction of multiplex PCR panels, on routine STEC surveillance data in Switzerland. **Methods:** We analysed routine laboratory data from 11 laboratories, which reported 61.9% of all STEC cases from 2007 to 2016 to calculate the positivity, i.e. the rate of the number of positive STEC tests divided by the total number of tests performed. **Results:** The introduction of multiplex PCR had a strong impact on STEC test frequency and identified cases, with the number of tests performed increasing sevenfold from 2007 to 2016. Still, age- and sex-standardised positivity increased from 0.8% in 2007 to 1.7% in 2016. **Conclusion:** Increasing positivity suggests that the increase in case notifications cannot be attributed to an increase in test numbers alone. Therefore, we cannot exclude a real epidemiological trend for the observed increase. Modernising the notification system to address current gaps in information availability, e.g. diagnostic methods, and improved triangulation of clinical presentation, diagnostic and serotype information are needed to deal with emerging disease and technological advances.

Introduction

Infections caused by Shiga toxin (Stx)-producing *Escherichia coli* (STEC) are generally mild and self-limiting or even asymptomatic. However, particularly in children and elderly people, STEC infections can lead to severe gastroenteritis with haemorrhagic diarrhoea and life-threatening conditions, e.g. haemolytic uraemic syndrome (HUS) [1,2].

STEC transmission can occur through the consumption of contaminated food and drinks, or by direct contact with infected individuals or animals shedding the bacterium* [1,3-5]. STEC infections are endemic in Europe, including Switzerland [6,7]. Cases occur sporadically or in outbreaks; a large outbreak attributed to contaminated sprouts occurred in Germany in 2011 [8]. Smaller outbreaks have also been reported, e.g. there was an outbreak in Italy in 2013 and in Romania in 2016, both were suspected to be caused by contaminated dairy products [9,10]. Considering 22 years of population-based data up to 2012, Majowicz et al. estimated in 2014 that STEC leads to an estimated 2.8 million illness cases per year, including 3,800 cases of HUS, globally [11].

The National Notification System for Infectious Diseases (NNSID) of the Swiss Federal Office of Public Health (FOPH) has been receiving all notifications of laboratory-confirmed STEC infections since 1999. Case numbers were generally constant until 2010, with only a few laboratories reporting STEC cases in Switzerland. An increase in cases was observed in 2011 following the outbreak in Germany, before returning to expected yearly fluctuations, and then markedly increasing since 2015 [12]. Given that this increase was observed around the same time as the introduction of syndromic multiplex PCR panels for stool analyses in standard laboratory practice in Switzerland [12], it was hypothesised that these panels were the cause of the increase in notified STEC cases. Traditionally, routine testing of stool samples for bacterial pathogens involved only *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. using culture-based techniques. With syndromic multiplex PCR panels, stool samples can be tested for

Abstract

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Aim: This study examined the impact of changes in diagnostic methods, in particular the introduction of multiplex PCR panels, on routine STEC surveillance data in Switzerland.

Methods: We analysed routine laboratory data from 11 laboratories, which reported 61.9% of all STEC cases from 2007 to 2016 to calculate the positivity, i.e. the rate of the number of positive STEC tests divided by the total number of tests performed.

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Conclusion: Increasing positivity suggests that the increase in case notifications cannot be attributed to an increase in test numbers alone. Therefore, we cannot exclude a real epidemiological trend for the observed increase. Modernising the notification system to address current gaps in information availability, e.g. diagnostic methods, and improved triangulation of clinical presentation, diagnostic and serotype information, are needed to deal with emerging disease and technological advances.

Keywords: STEC/EHEC/VTEC; surveillance; multiplex PCR; diagnostics; notification system

Introduction

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STEC transmission can occur through the consumption of contaminated food and drinks, or by direct contact with infected individuals or animals shedding the virus [WHO 2018; Chart 1998; Grif et al. 2005; Vernozy-Rozand 1997]. STEC infections are endemic in Europe, including Switzerland [ECDC 2020; Schmutz 2018]. Cases occur sporadically or in outbreaks; a large outbreak attributed to contaminated sprouts occurred in Germany in 2011 [Buchholz et al. 2011]. Smaller outbreaks have also been reported, e.g. there was an outbreak in Italy in 2013 and in Romania in 2016, both were suspected to be caused by contaminated dairy products [Germinario et al. 2016; Usein et al. 2017]. Considering 22 years of population-based data up to 2012, Majowicz et al. estimated in 2014 that STEC leads to an estimated 2.8 million illness cases per year, including 3,800 cases of HUS, globally [Majowicz et al. 2014].

The National Notification System for Infectious Diseases (NNSID)* of the Swiss Federal Office of Public Health (FOPH)* has been receiving all notifications of laboratory-confirmed STEC infections since 1999. Case numbers were generally constant until 2010, with only a few laboratories reporting STEC cases in Switzerland. An increase in cases was observed in 2011 following the outbreak in Germany, before returning to expected yearly fluctuations, and then markedly increasing since 2015 [BAG 2015]. Given that this increase was observed around the same time as the introduction of syndromic multiplex PCR panels for stool analyses in standard laboratory practice in Switzerland [BAG 2015], it was hypothesised that these panels were the cause of the increase in notified STEC cases. Traditionally, routine testing of stool samples for bacterial pathogens involved only *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. using culture-based techniques. With syndromic multiplex PCR panels, stool samples can be tested for up to 22 pathogens, including STEC, in one single run [BAG 2015; Binnicker 2015].

Prior to the gradual introduction of multiplex PCR to the routine diagnostics between 2014 and 2015, STEC was only specifically tested for in Switzerland upon physician request, and this rarely happened. Current testing practice includes the use of small syndromic enteric bacterial panels for testing in patients without a travel history or a larger gastrointestinal panel if travel history is reported on the test order form [Schmutz 2018].

A qualitative assessment found that Swiss laboratory experts uniformly agreed that the increase in STEC case numbers was because of the introduction and increasing use of multiplex PCR panels [Schmutz 2018]. We set out to conduct a quantitative investigation as to whether an increase in the STEC testing

rate associated with the use of the panels is was what led to the increased notification of cases. Our study assesses the development of the STEC positivity in the Swiss population between 2007 and 2016 using routine laboratory data, and gives insight into the epidemiology and notification numbers of STEC infections in Switzerland.

Methods

The study uses pre-existing records from the routine work of diagnostic laboratories. Swiss regulatory authorities report 106 authorised or accredited diagnostic laboratories, but not all of them perform STEC diagnostics [Swissmedic 2019]. Therefore and for feasibility reasons, we decided in 2016 to purposively select 11 diagnostic laboratories to be included in our study. First, the laboratories with the most STEC notifications the year before were selected and their coverage of Swiss regions was checked. For underrepresented regions, we added the top reporting laboratories of these regions to the sample. Our final sample included all regions of Switzerland, and both hospital and private diagnostic laboratories. The organisation of infectious disease diagnostics in Switzerland does not allow for estimating the population covered by the laboratories.

Anonymised, individual-based testing data on STEC from the laboratories' pre-existing records were received from the FOPH. Data collected comprised all tests performed for STEC between January 2007 and December 2016, including positive and negative test outcomes. Our resulting database included date of test, test result, test method, patient identification number, and patients' date of birth, sex and canton of residence.

Test records indicating a patient resided outside of Switzerland and those without a conclusive test result were omitted. Duplicate entries, defined as identical values for all variables, and repeated tests were excluded from the analyses. Repeated tests were defined as more than one test performed for the same patient during a single disease episode.

The analysis was planned a priori and was performed using STATA version 14.0 (StataCorp, Texas, United States (US)*). A statistical significance level of alpha 0.05 was chosen for all tests and models. We use the term positivity as the rate of number of positive tests to the total number of tests performed for STEC [Schmutz et al. 2012; Bless et al. 2017]. Positivity was calculated for different demographic groups, test methods, spatial (i.e. patients' canton of residence) and temporal (annual and seasonal) trends. The main outcome, annual positivity, was age- and sex-adjusted using direct standardisation with the sample population (2007–2016) as reference population.

We calculated odds ratios (ORs)* for the association between test result and test year, test month, season, a discrete time trend variable, sex, age group, laboratory, test method and greater region using

univariable logistic regression. Season was modelled using a sine and cosine function with an annual period. The time trend was a discrete variable constructed of all test months combining the test month and test year variables. The greater regions correspond to the seven regions of Switzerland as specified by the Nomenclature of Territorial Units for Statistics (NUTS)*-2. Categories with most observations were chosen as reference categories, except for the seasonality (first month of the year).

We defined a multivariable mixed-effect logistic regression model a priori, independent of the outcome of the univariable regression, to calculate adjusted ORs (aORs)*. The model's explanatory variables included sex, age group, seasonality, time trend, greater region, diagnostic test method, and an interaction term for sex and age group. Laboratories were included as a random effect variable to account for clustering. Clustering on patient level (same identification number) was omitted.

Finally, we compared the fully adjusted multivariable model to a multivariable model without adjustment for test method in order to validate the results and ensure the consistency of the time trend, independently from the diagnostic method. Based on multivariable regression results, we computed predicted probabilities for a positive test result, and plotted them for direct visualisation and comparison of categories and models.

We also performed a sensitivity analysis, omitting laboratories not providing data for the entire study period to account for the impact of the missing data. For relevant figures, both the complete dataset referring to data from all 11 laboratories, and the reduced dataset, referring to only the laboratories providing data for the entire study period, are shown.

Ethical statement

The study was conducted under the Epidemics Act (SR 818.101). The study team received anonymised laboratory data from the FOPH, who had received already-anonymised data directly from the laboratories. Other data (notification data, population statistics) are publicly available from the FOPH or the Swiss Federal Statistical Office.

Results

Number of test records and STEC-positives

The 11 participating laboratories provided 91,685 STEC test records, of which, 1,366 were positives. Five laboratories (laboratories B, G, H, I and J) provided data for the entire study period of 2007 to 2016 (n=61,916). Three laboratories (C, D and F) started performing STEC testing between 2014 and 2015 with the introduction of multiplex PCR panels, two laboratories (A and E) could not extract all data requested

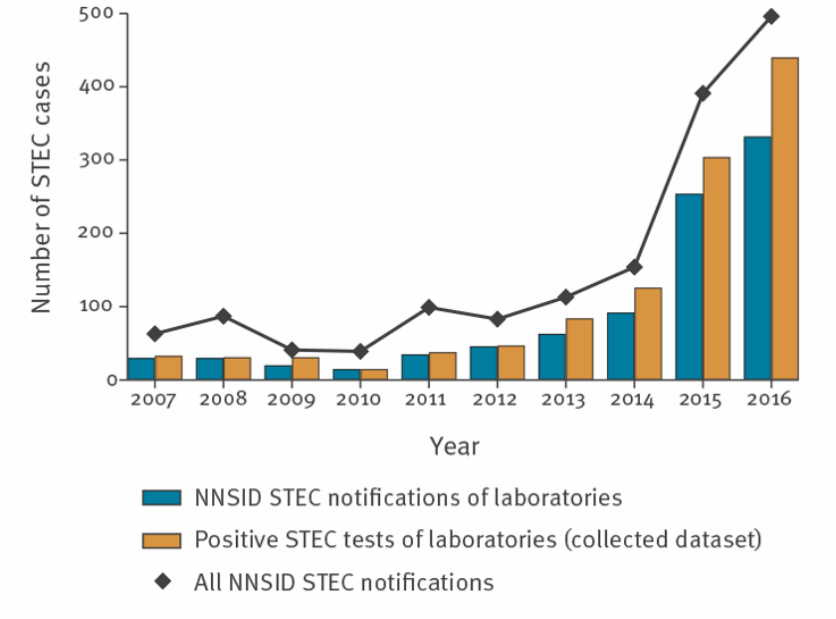

Figure 7.1: Number of STEC notifications to NNSID versus number of positive STEC tests of 11 diagnostic laboratories, and total number of STEC notifications to NNSID per year, Switzerland, 2007–2016. NNSID: National Notification System for Infectious Diseases; STEC: Shiga toxin-producing *Escherichia coli*.

because of changes in their data storage system and one laboratory (K) did not specify a reason for missing years of data. Sensitivity analyses omitting laboratories not providing data for the entire study period showed that observed trends were robust. Therefore, the complete dataset without omission is presented and discussed. Relevant figures show the data with and without omission.

Following our exclusion criteria, 1,407 records, including 22 positives, were excluded. Further, 71 records (3 positives) with missing sex or age, 1,110 duplicated entries (31 positives) and 3,054 repeated tests (96 positives) were excluded. The final dataset comprised 86,043 records, of which, 1,149 were positives.

Figure 7.1 shows the number of notified STEC cases in the NNSID and in our dataset. In concert, the laboratories selected for this study reported 61.9% of all cases registered in the NNSID between 2007 and 2016 (range 39.4% in 2011 to 73.2% in 2009).

Characteristics of the tested and STEC-positive population

Median age of the tested population increased significantly from 30 to 43 years between 2007 and 2016 (test for trend: $p<0.01$, Appendix E, Table S1). The proportion of females tested in this period was 55.6% on average and remained level throughout the test years. The median age of the tested population differed significantly between laboratories (Kruskal-Wallis test: $p<0.01$, range: 27–55, overall median: 40; data not shown) and greater regions (Kruskal-Wallis test: $p<0.01$, range: 37–44; data not shown).

Similarly, among the STEC-positive population, the median age increased significantly from 2007 to 2016, while the proportion of females remained stable (test for trend: $p<0.01$, Appendix E, Table S1). Median age differed significantly between laboratories (Kruskal-Wallis test: $p<0.01$, range: 2.5–55, overall median: 36; data not shown), but not between regions (Kruskal-Wallis test: $p=0.399$, range: 34–68; data not shown). The average number of disease episodes per person was one, with a maximum of four for 122 persons (data not shown).

Laboratories, diagnostic methods and greater regions

The variables laboratory, greater region and test method were strongly correlated (see Appendix E, Figure S2).

The diagnostic methods performed included multiplex PCR (66.5%, n=57,168), antigen test (26.3%, n=22,588), single PCR, i.e. PCR panels targeting STEC/pathogenic *E. coli* only (7.3%, n=6,247), and culture-based diagnostics (<0.1%, n=4). Sixteen (<0.1%) tests did not have a test method specified (outsourced tests). Multiplex PCR panels used were mainly BD MAX (normal or extended) Enteric Bacterial Panel (BD, Franklin Lakes, US) (51.6%), xTAG Gastrointestinal Pathogen Panel (Luminex, Austin, US) (36.1%), BioFire FilmArray Gastrointestinal Panel (BioFire, Salt Lake City, US) (5.9%) and Seegene, not specified whether Allplex Gastrointestinal Panel or Seeplex Diarrhoea ACE Detection (Seegene, Seoul, South Korea) (4.6%). All available information on the test methods applied as reported by the laboratories is presented in Appendix E, Table S2.

The number of tests performed using the antigen test, single PCR or culture remained stable between 2007 and 2016, while the number of multiplex PCR panels performed increased by 42% (Figure 7.2A). The five laboratories providing data for the entire study period were using single PCR or antigen tests before the introduction of multiplex PCR (Figure 7.2B). Only one of these five laboratories continued using primarily antigen tests for the entire study period.

Positivity

The number of tests for STEC increased sevenfold from 2007 to 2016 (3,711 to 26,639) while the number of positive test results increased 13-fold (33 to 440). The age- and sex-standardised positivity of STEC testing increased from 0.8% in 2007 to 1.7% in 2016 (Figure 7.3). Positivity increased for all age categories. The positivity calculated over the entire study period was highest for children aged 1–4 years (192/8,855, 2.2%) and increased from 1.4% (11/809) in 2007 to 2.9% (51/1,734) in 2016. The largest relative increase was in individuals $\geq$ 80 years of age, from no case among 146 in 2007 to 1.8% (45/2,449) in 2016. The overall positivity is similar for men (518/38,209, 1.4%) and women (631/47,834, 1.3%) and increased from 0.6 (11/1,705) and 1.1% (22/2,006) to 1.7% (198/11,682) and 1.6% (242/14,957), respectively, from 2007 to 2016.

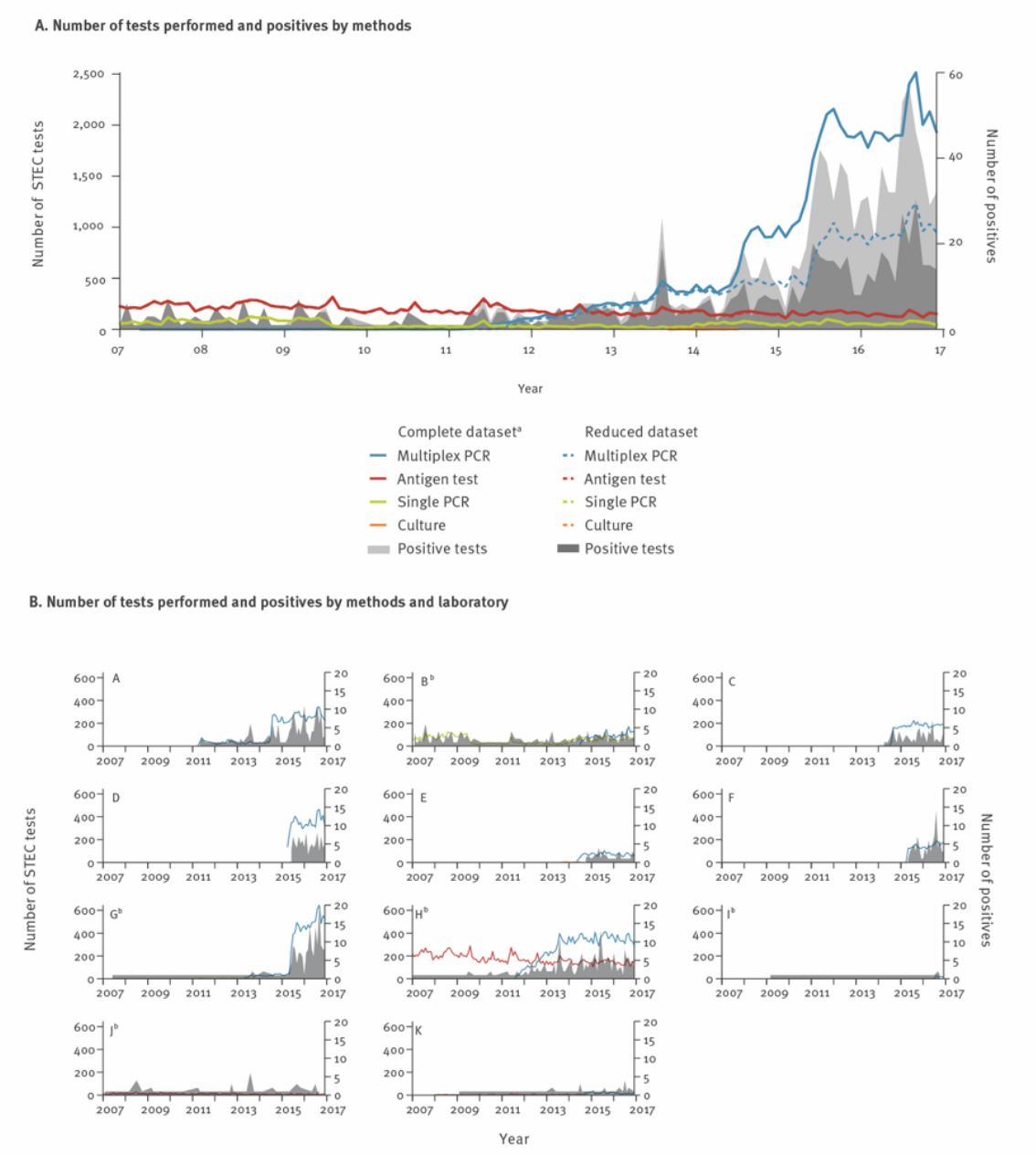

Figure 7.2: Total number of STEC tests performed and number of positive tests by test method (A) and by laboratory (B), 11 diagnostic laboratories, Switzerland, 2007–2016. STEC: Shiga toxin-producing *Escherichia coli*.
[a]Complete dataset refers to data from all 11 laboratories, while reduced dataset refers to only the five laboratories providing data for the entire study period.
[b]The five laboratories providing data for the entire study period. For laboratories G and I, the numbers starting at 2007 are too small to appear on the figure.

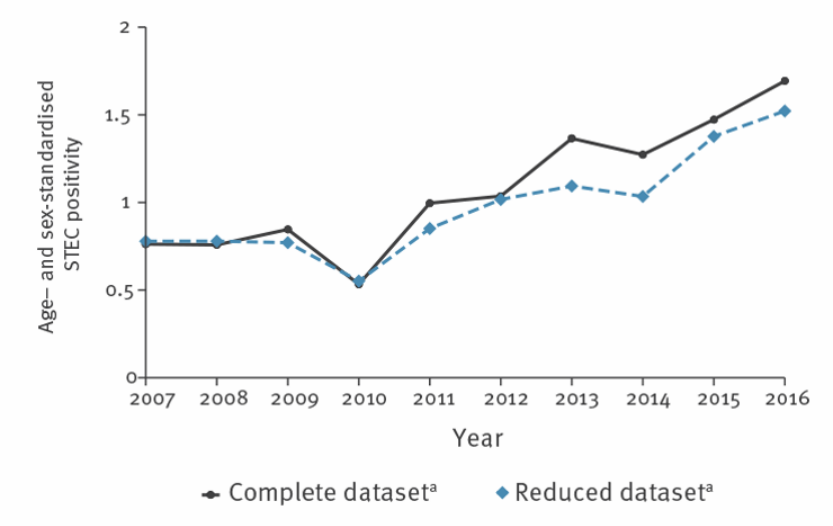

Figure 7.3: Age- and sex-standardised positivity of STEC testing, 11 diagnostic laboratories, Switzerland, 2007–2016. STEC: Shiga toxin-producing *Escherichia coli*. [a]Complete dataset refers to data from all 11 laboratories, while reduced dataset refers to only the five laboratories providing data for the entire study period.

The positivity and trend in positivity differed across laboratories (Figure 7.4). The overall positivity ranged from 0.6% (245/38,796) to 5.8% (7/121). There were large fluctuations in positivity for some laboratories because of small testing numbers.

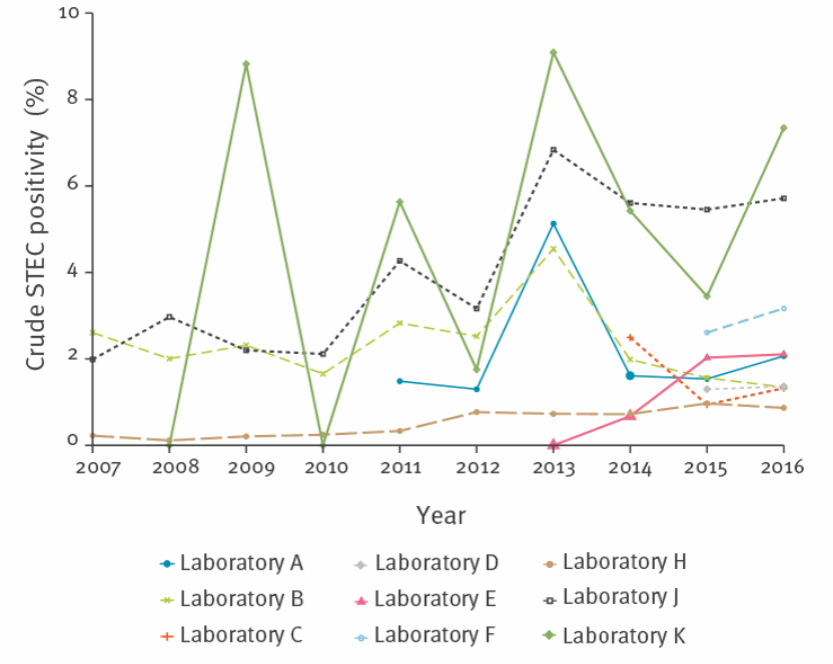

Figure 7.4: STEC positivity by laboratory, nine diagnostic laboratories[a], Switzerland, 2007–2016. STEC: Shiga toxin-producing *Escherichia coli*. [a] Two of the 11 laboratories comprising the dataset are not shown because of the large fluctuations in positivity (range: 0–50%) because of small testing numbers

Positivity further differed by test method. We did not calculate the positivity of culture-based tests because there were few observations and because of our exclusion process for repeated tests (observations excluded if used as confirmation tests). The positivity across all test years was highest for tests using

single PCR (147/6,247, 2.4%) and lowest for the antigen test (129/22,588, 0.6%); positivity of multiplex PCR panels was at 1.5% (870/57,168). The positivity of multiplex PCR increased from 1.1% (80/7,617) in 2014 to 1.7% (418/24,190) in 2016. In contrast, the positivity of single PCR and antigen tests started to decrease in 2014 and 2015 respectively, after PCR peaking at 4.3% (11/256) in 2013 and antigen tests at 1.4% (27/1,896) in 2014.

Predictors of a positive diagnostic test result

The univariable regressions showed a marginal but significant trend for the time trend variable (OR: 1.003, $p<0.01$, Table 7.1). All test years except 2013 showed decreased odds for a positive test outcome compared with the reference year 2016. All calendar months except July have smaller odds for a positive test outcome than the reference month August.

Table 7.1: Odds ratios for a positive STEC test result of the uni- and multivariable logistic regression models, Switzerland, 2007–2016 (n=86,043)

Variable	n	OR	95% CI	aOR	95% CI
Age group (year)					
Under 1	2,915	0.97	0.67–1.40	1.28	0.72–2.28
1–4	8,855	1.88	1.56–2.27	3.38	2.56–4.45
5–9	2,593	1.80	1.34–2.43	1.66	1.07–2.58
10–19	5,898	1.03	0.79–1.35	1.03	0.71–1.49
20–39	21,971	Ref	NA	Ref	NA
40–59	19,404	1	0.84–1.20	1.03	0.81–1.31
60–79	17,685	1.1	0.92–1.32	1.05	0.82–1.34
Over 79	6,722	1.14	0.89–1.45	1.11	0.81–1.52
Sex					
Male	38,209	1.03	0.91–1.16	0.93	0.72–1.20
Female	47,834	Ref	NA	Ref	NA
Male, age group (year)					
Under 1	1,582	NA	NA	1.14	0.52–2.47
1–4	4,962	NA	NA	0.92	0.62–1.36
5–9	1,325	NA	NA	1.23	0.67–2.27
10–19	2,827	NA	NA	1.14	0.66–1.95
20–39	9,080	NA	NA	Ref	NA
40–59	8,833	NA	NA	1.02	0.70–1.47
60–79	7,408	NA	NA	1.27	0.88–1.84
Over 79	2,192	NA	NA	1.17	0.69–1.95
Greater region					
Lake Geneva region	15,526	0.79	0.66–0.93	1.2	0.89–1.60
Espace Mittelland	20,000	Ref	NA	Ref	NA

Variable	n	OR	95% CI	aOR	95% CI
Northwestern Switzerland	15,273	0.39	0.32–0.49	0.69	0.53–0.89
Zurich	14,439	0.79	0.66–0.94	0.75	0.58–0.98
Eastern Switzerland	6,474	0.70	0.55–0.90	0.88	0.67–1.16
Central Switzerland	10,015	0.9	0.74–1.09	0.92	0.70–1.21
Ticino	1,008	0.74	0.43–1.30	1.3	0.73–2.32
Test method					
Multiplex PCR	57,168	Ref	NA	Ref	NA
Antigen test	22,588	0.37	0.31–0.45	0.34	0.26–0.44
Single PCR	6,247	1.56	1.31–1.86	2.31	1.55–3.45
Culture	24	NC	NC	NC	NC
Time trend	86,043	1.00	1.00–1.01	1.00	1.00–1.01
Test month					
January	6,040	0.50	0.37–0.68	NA	NA
February	5,529	0.59	0.44–0.80	NA	NA
March	6,137	0.58	0.43–0.77	NA	NA
April	5,872	0.76	0.58–0.99	NA	NA
May	6,357	0.69	0.53–0.90	NA	NA
June	7,084	0.77	0.60–0.99	NA	NA
July	7,321	1.08	0.86–1.35	NA	NA
August	9,154	Ref	NA	NA	NA
September	8,919	0.68	0.54–0.87	NA	NA
October	8,098	0.78	0.61–0.99	NA	NA
November	8,000	0.71	0.55–0.91	NA	NA
December	7,532	0.62	0.47–0.81	NA	NA
Seasonality					
sin((d*2*π)/T)	86,043	0.84	0.77–0.91	0.89	0.82–0.98
cos((d*2*π)/T)	86,043	0.83	0.76–0.90	0.81	0.75–0.89
Test year					
2007	3,711	0.53	0.37–0.76	NA	NA
2008	3,978	0.47	0.32–0.67	NA	NA
2009	3,421	0.54	0.38–0.79	NA	NA
2010	2,536	0.35	0.21–0.59	NA	NA
2011	3,393	0.67	0.48–0.94	NA	NA
2012	4,483	0.63	0.47–0.85	NA	NA
2013	6,152	0.82	0.65–1.04	NA	NA
2014	10,246	0.74	0.61–0.90	NA	NA
2015	21,484	0.85	0.74–0.99	NA	NA
2016	26,639	Ref	NA	NA	NA
Laboratory					

Variable	**n**	**OR**	**95% CI**	**aOR**	**95% CI**
A	8,712	2.98	2.44–3.64	NA	NA
B	8,861	3.15	2.59–3.83	NA	NA
C	5,102	2.09	1.60–2.75	NA	NA
D	7,181	2.13	1.68–2.70	NA	NA
E	2,197	2.84	2.02–4.00	NA	NA
F	2,904	4.80	3.75–6.16	NA	NA
G	9,852	2.86	2.36–3.48	NA	NA
H	38,796	Ref	NA	NA	NA
I	121	9.66	4.46–20.94	NA	NA
J	1,438	6.14	4.55–8.28	NA	NA
K	879	8.09	5.81–11.27	NA	NA

aOR: adjusted odds ratio; CI: confidence interval; NA: not applicable; NC: not calculated; OR: odds ratio; Ref: reference group for comparison; STEC: Shiga toxin-producing *Escherichia coli*.

[a] Adjusted for sex, age group, method, temporal trend and seasonality (refer to Appendix E for details). Interaction between age and sex. Random effect of laboratory.

[b] $p<0.001$

[c] $p<0.05$

[d] $p<0.01$

[e] The estimates for culture-based tests could not be calculated because of small testing numbers.

The age groups 1 to 4 years and 5 to 9 years were almost twice as likely to have a positive test outcome (OR 1.88, $p<0.001$ and OR 1.80, $p<0.001$) than the reference category 20 to 39 years. No difference was observed between sexes. Compared with multiplex PCR panels, the use of the antigen test had a 63% lower probability to generate a positive test outcome (OR 0.37, $p<0.001$), while the use of single PCR showed 56% higher chance for a positive test outcome (OR 1.56, $p<0.001$). The ORs and significance levels from the fully adjusted multivariable model, presented in the Table, varied only marginally from the univariable models and do not alter the interpretation; therefore, they are not commented here.

Predicted probabilities based on the fully adjusted multivariable model showed an increasing time trend for all test methods and regions. Comparison of the fully adjusted multivariable model to a multivariable model excluding the adjustment for test method showed increasing predicted probabilities for both models, but with a smaller slope for the fully adjusted model (Figure 7.5).

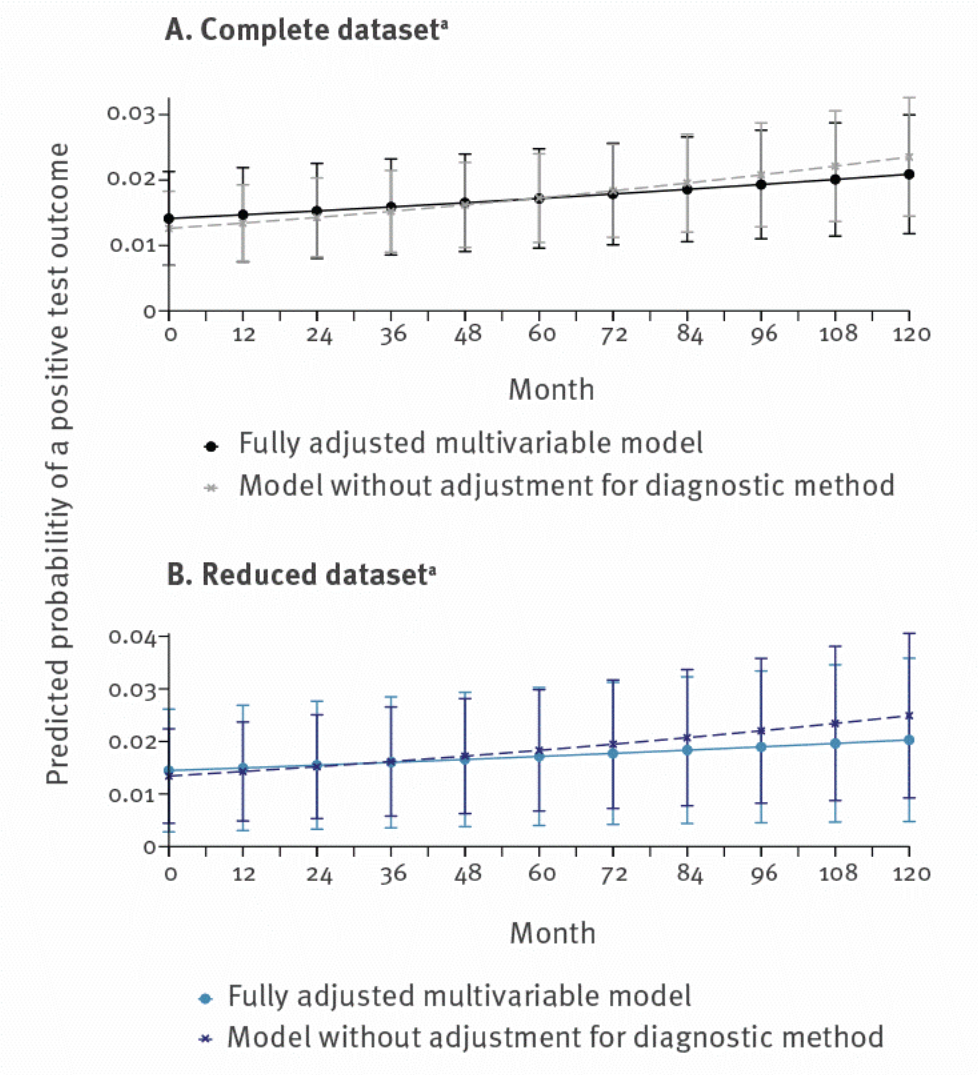

Figure 7.5: Predicted probability for a positive STEC test outcome for the fully adjusted multivariable model and the model excluding adjustment for test method for the complete (A) and reduced (B) dataset, 11 diagnostic laboratories, Switzerland, 2007–2016. STEC: Shiga toxin-producing *Escherichia coli*. [a]Complete dataset refers to data from all 11 laboratories, while reduced dataset refers to only the five laboratories providing data for the entire study period.

Discussion

We investigated the apparent epidemic increase of STEC infections seen in the rise of case notifications in the Swiss NNSID. We calculated positivity as the rate of all positive diagnostic STEC tests to the total number of STEC tests performed. The 11 laboratories in our study reported almost two-thirds (61.9%) of all STEC cases in the NNSID between 2007 and 2016. Positivity increased since 2007.

Culture-independent diagnostic tests for STEC

The increase of STEC cases in Switzerland coincides with the introduction of multiplex PCR panels as a new diagnostic method for STEC detection. The impact of changes in diagnostic approaches on public health surveillance has been highlighted before, especially concerning the switch from culture-dependent to culture-independent diagnostics for food-borne diseases [Kehl 2002; Cronquist et al. 2012; Moran-Gilad 2019]. This switch is particularly important for STEC, as the case definitions for STEC in the European Union/European Economic Area (EU/EEA)* and Switzerland are not limited to culture-confirmed cases, but include the detection of the Stx1 or Stx2 antigen or their respective genes [Parliament and Council 2018]. Increases in STEC notifications in Ireland were explained by the shift from culture-dependent to culture-independent diagnostic methods; the latter showing higher sensitivity and ability to detect non-O157 STEC [Johnson et al. 1996; Rice et al. 2016].

The 11 Swiss diagnostic laboratories included in our study switched to culture-independent methods for STEC detection before 2007; hence, the impact thereof cannot be assessed using our data.

Considerations when using multiplex PCR panels for STEC diagnosis

The introduction of multiplex PCR panels for gastrointestinal pathogens is the next paradigm shift in diagnostics for food-borne diseases after switching to culture-independent tests.

In most of our study laboratories, the use of multiplex PCR panels as routine diagnostic methods was introduced between 2011 and 2015. Since then, multiplex panels comprise the largest proportion of all diagnostic tests performed for STEC and have led to an increase in test numbers. The increase in test volume, resulting in more positives notified, originates from a larger proportion of the population being automatically screened for STEC. This screening happens for two reasons: (i) the testing for a specific gastrointestinal pathogen, e.g. Campylobacter spp., now also implicitly leads to a STEC test or (ii) the physician orders a gastrointestinal panel when the patient presents with diarrhoea, i.e. syndromic testing. Previously, a test for STEC was predominantly ordered if the patient was a child and/or reported a bloody stool and/or reported a history of travel because of higher probabilities to develop severe complications such as HUS [Clogher et al. 2012; Rivas et al. 2014; Bless et al. 2016]. We hypothesised that if the increase in new STEC cases was a result of the introduction of multiplex PCR only (leading to less targeted screening) there

would be a decrease in positivity because of a lower pre-test probability for a positive test outcome. But this decrease in positivity is not reflected in our data. Instead, the increase in STEC cases is disproportionally higher compared with the increase in test volume, resulting in the observed increase in positivity.

Part of the increased testing could also stem from a change in physicians' test-ordering behaviour following the raising of public awareness for STEC infections. However, laboratory experts reported that tests specifically for STEC are rarely ordered by treating physicians [Schmutz 2018]. Therefore, STEC tends to largely be an unintentional finding and its clinical relevance for the individual patient may be arguable. Questions on reporting to the patient and appropriate treatment, see Davis et al. [Davis, Kar, and Tarr 2014], and mandatory notification still need to be addressed.

Furthermore, using multiplex PCR increases the number of cases found because of the higher sensitivity of PCR compared with other conventional diagnostic methods, and the increased probability of detecting co-infections [Khare et al. 2014; Buss et al. 2015; Stockmann et al. 2015; Harrington et al. 2015]. A study among staff members of meat-processing companies in Switzerland found 3.5% asymptomatic carriers of STEC [Stephan, Ragettli, and Untermann 2000]. Assuming a similar prevalence of asymptomatic carriers in the general population and the possibility that such asymptomatic STEC carriers become infected with another diarrhoeagenic pathogen, multiplex PCR would detect both the symptom-causing pathogen and the asymptomatic STEC co-infection.

While it is clear that changes in the diagnostic landscape can influence surveillance data and trend monitoring, we believe that this change only explains part of the increase in STEC case notifications in Switzerland.

From our analyses, indications for a real increase in STEC incidence independent of the diagnostic test method are threefold: (i) Our logistic regressions and predicted probabilities for a positive STEC test outcome showed an increasing trend between 2007 and 2016 even after adjusting for the diagnostic method, (ii) the predicted probabilities for a positive STEC test show an increasing trend for all methods (multiplex PCR, single PCR and antigen test) and (iii) an increase in positivity was also seen in two laboratories introducing multiplex PCR panels late, i.e. in the second half of 2016, or not at all. Based on these three findings, we argue that the increase in notified STEC cases is a combination of changing test practices and a real increase in incidence of STEC infections among the Swiss population.

Rising incidence of STEC infections

Age and sex distributions of STEC patients in Switzerland remained unchanged since the observation period 2007 to 2016. We conclude that the observed incidence increase is independent of potential changes in STEC risk groups.

If our findings suggest a true increase in STEC, the epidemiology of HUS also needs to be considered. In Switzerland, the number of HUS cases remained relatively constant from 1999 to 2015 in terms of absolute numbers; hence, there was a relative decrease of HUS among notified STEC cases [BAG 2015]. Thus, the increase in STEC notifications observed is likely to represent mainly mild cases and/or asymptomatic co-infections that might have been present but undetected in the past.

We propose that a changing distribution of STEC serogroups among cases could be an explanation for the change in disease severity. In other studies, O157 STEC cases were found to mostly be associated with the development of severe disease, i.e. HUS, although the importance of non-O157 infections as a cause for HUS is being increasingly recognised [Käppeli et al. 2011; Kuehne et al. 2016; Freedman et al. 2016].

STEC culture and subsequent analysis of isolates are not routinely performed in Switzerland; the proportion of culture-based tests in our raw dataset of routinely conducted tests in 11 laboratories was only 0.1% (78/89,081, raw dataset). The scarce information on serotype distribution primarily comes from studies published by the Swiss National Reference Centre for Enteropathogenic Bacteria and Listeria (NENT)* [Fierz et al. 2017; Nüesch-Inderbinen et al. 2018]. Analysing 2017 data, Nüesch-Inderbinen et al. [2018] indicated that an isolate for further characterisation could be successfully obtained from less than 30% of multiplex PCR positive samples, suggesting limited information on serotypes in Switzerland compared with other countries. Still, using these studies and the results from research in similar contexts abroad, we can discuss the epidemiology of rising STEC incidence within Switzerland.

The two studies out of NENT reported a decrease in the proportion of STEC stx2 carrying and eae carrying variants, which are both associated with severe disease in Switzerland [Fierz et al. 2017; Nüesch-Inderbinen et al. 2018]. Over the course of several years, the proportion of non-O157 STEC associated with human disease increased in Switzerland, other European countries and the US [Fierz et al. 2017; Marder Mph et al. 2018; ECDC 2018d]. On the other hand, a 2013 study found that healthy people can shed stx-carrying bacteriophages that might lead to stx-positive multiplex PCR test results [Martínez-Castillo et al. 2013].

No EU/EEA country reported an increase in STEC notification numbers to the extent observed in Switzerland (eightfold increase, 2012–2016), except Romania, where 1 case was reported in 2012 while 29 were found in 2016 following an intensified testing after a HUS outbreak [ECDC 2018d]. In Finland, the increase in reported cases between 2012 and 2016 was fourfold, with multiplex PCR screening introduced in 2013 [ECDC 2018d; Antikainen et al. 2013]. In Norway, the notification rate increased from 0.6 to 7.6 per 100,000 population between 2007 and 2017, noting that this increase occurred mostly after 2014 and coinciding with the introduction of multiplex PCR diagnostics [Jenssen et al. 2019]. STEC patients associated with a recent outbreak in Finland were classified as rather mild cases [Kinnula et al. 2018]. The increasing STEC notifications in Norway were associated with an increasing proportion of cases classified

as low-virulent while case numbers of HUS were generally constant [Jenssen et al. 2019]. The US also reported an increased incidence of STEC cases in 2017 compared with 2014 to 2016, although not to the extent observed in Switzerland [Marder Mph et al. 2018]. Further, the incidence of HUS in children in the US remained similar in 2016 compared with 2013–2015, while non-O157 infections increased, resulting in a relative decrease of O157 cases. This again supports the hypothesis of an association between disease severity and serogroup, with a trend of culture-independent diagnostic tests increasing detection of less virulent strains.

Information on co-infections is neither available from the notification system nor from the data collected by the laboratories. However, up to 10% of the STEC strains obtained from clinical samples of ill individuals and identified by Nüesch-Inderbinen et al. [2018] were the same as strains isolated from the faecal samples of healthy individuals suggesting that not the identified STEC, but another pathogen was causing the symptoms. This is in line with earlier reports that 3.5% of meat factory workers were asymptomatic STEC carriers [Stephan, Ragettli, and Untermann 2000]. In Norway, co-infections were observed in 15% of notified STEC cases detected using multiplex PCR [Jenssen et al. 2019]. Hence, it is likely that a minor but relevant proportion of the newly identified infections by multiplex PCR are asymptomatic co-infections.

Implications of changing disease patterns on STEC surveillance in Switzerland

Current disease surveillance for STEC in Switzerland neither is designed to account for changes in diagnostics nor systematically distinguish between strains (particularly O157 and non-O157) that could reflect differences in virulence.

From a health systems perspective, monitoring the usage of diagnostic methods and testing algorithms applied for each notifiable pathogen among authorised and accredited diagnostic laboratories could complement surveillance data.

Since the implementation of a revised Epidemics Act in Switzerland in 2016, diagnostic laboratories are required to report the number of tests conducted for certain notifiable diseases (but excluding STEC) to the FOPH once a year. This annual reporting of summary statistics was established in the hope of improving interpretation of routine surveillance data through the incorporation of denominator data similar to that here in our study; without the need to mandate resource-intensive research for each pathogen. However, analyses of these summary statistics indicate that data quality is rather poor and that too many factors play a role to conclude on reasons for changes in test and case numbers based on summary statistics [Schmutz 2018].

The increase of STEC cases, which are mostly mild, and the shift in serotype distribution as shown by others, changes the interpretation of STEC notifications as clinical and public health relevance needs to be considered. We believe it is critical that all cases of STEC infections, regardless of clinical relevance, are

reported in order to identify clusters and sources and thus support outbreak control. However, the current effectiveness of the surveillance system for STEC could be improved incorporating strain typing information that would guide intervention and control measures, yet this also depends on achieving higher success rates of STEC isolation after PCR-positive results. The federal public health authorities recognise the need to modernise the current notification system toward electronic reporting which addresses the current issues of information availability, including more information on the diagnostic test methods used, and data inconsistency, ensuring more harmonisation between laboratory-based notifications of test results with clinical information obtained from physicians' mandatory notifications (personal communication, Daniel Koch (FOPH), August 2019).

Limitations

First, we selected our sample of 11 laboratories based on their contribution to the latest NNSID notifications. This choice favoured laboratories that had switched to multiplex PCR and may therefore not be representative of all laboratories in Switzerland. However, we adjusted for test method in our main trend analysis, thereby accounting for bias towards an over-representation of multiplex PCR. Second, our study only uses the actual information available to the laboratories; clinical information could not be obtained. Third, as partly evident from the data, culture-based tests and typing of STEC was very rarely performed by the participating laboratories; hence, microbiological data were not available for analysis. However, analysis of pre-existing (routine) data from laboratories can support the evaluation of surveillance data in a time- and resource-efficient manner, which could potentially be harnessed for other pathogens. Fourth, we noted that in recent years, NNSID case numbers differed from the number of positive test results recorded in the laboratories' individual datasets. This means that positive cases were either under-reported to the NNSID, or the NNSID excluded certain reports from their official statistics or the number of positive test results in our sample was overestimated because of, for example, an insufficient exclusion of repeated tests. Finally, the correlation of laboratory, greater region and test method hampered the evaluation of spatial trends. Differences in testing and positivity rates between greater regions in Switzerland largely depend on the laboratories chosen. The differences can either relate to true differences in tests ordered by physicians between regions or they could be because the laboratories selected for our sample under-, over- or misrepresent the laboratories within their region.

Conclusion

Since 2015, the notification numbers for STEC markedly increased in Switzerland. Meaningful interpretation of such surveillance data requires that every aspect of the disease trajectory, from changes in awareness (among physicians and patients) and testing behaviour to the choice of diagnostic method, are taken into consideration.

STEC surveillance has been heavily impacted by recent changes in diagnostic methods given the lack of culture-based confirmative testing and previously infrequent, but targeted testing for STEC. The switch from targeted STEC testing to co-testing of virtually all stool samples submitted for basic stool bacteriology using multiplex PCR panels has notably increased the test volume for STEC in Switzerland. However, we have found a rise in STEC cases that is disproportionally high compared to the increase in test volume, suggesting that there has been a real increase in STEC infection incidence in Switzerland.

The recently observed changes in the frequency of different serogroups and the stability of HUS cases suggests that the trend observed for STEC is mostly attributable to rather mild cases. Surveillance systems should be adapted to include information on diagnostic methods used considering the rapid development of new laboratory techniques. Modernising the notification system should also allow for a better triangulation of notified information on clinical presentation, diagnostic approaches and serotypes, provided the success rate of isolating multiplex PCR-positive samples increases.

Acknowledgments

The authors thank Christian Schindler (Swiss Tropical and Public Health Institute) for statistical advice, Adrian Egli (University Hospital Basel) for feedback on repeated testing and Angelika Fruth (Robert Koch Institute) for sharing experience on STEC surveillance in Germany. Roger Stephan (Institute for Food Safety and Hygiene, University of Zurich) provided feedback on the manuscript. Various staff of the Swiss Federal Office of Public Health (FOPH) provided detailed insights to the Swiss surveillance system and information on the notification data; we appreciate the contributions made by Daniel Koch and Mirjam Mäusezahl-Feuz, Department of Communicable Diseases, FOPH. The authors much appreciate the support of the following laboratories providing data for the study: ADMed Microbiologie / Reto Lienhard (La Chaux-de-Fonds), Analytica Medizinische Laboratorien AG (Zurich), Bioanalytica (Lucerne), Dianalabs (Geneva), Laboratoire de bactériologie des HUG / Jacques Schrenzel (Geneva), IFIK / Sara Droz (Bern), MCL Medizinische Laboratorien (Niederwangen), Labor Synlab / André Burnens and Marcel Brandenberger (Lucerne), Viollier AG (Allschwil) and two other Swiss diagnostic laboratories.

Funding statement

This study was funded by the Swiss Federal Office of Public Health (FOPH). The FOPH provided the framework of the study which was carried out under the Epidemics Act (SR 818.101). FOPH were not involved in the data processing, analysis and interpretation of the results.

Statements and Declarations

Conflict of interest

None declared.

Authors' contribution

CS and DM conceived and designed the study. Data collection and processing was performed by AS, with FBF and CS. FBF conducted the analysis. FBF, AS, CS and DM interpreted the results. FBF and AS wrote the first draft of the manuscript. All authors contributed to the revisions of the manuscript and approved the final version.

Part III

The role of the health (care) system in case detection

Chapter 8

Literature review on global recommendations, guidelines and legislation for Legionnaires' disease and *Legionella* management

This technical report constitutes the deliverable of a literature review mandated by the Federal Office of Public Health. (2020)

Preamble

This document constitutes the final narrative report for literature study, which is part of the project 'Literatur- und Vorstudien zur Legionärskrankheit 2018-20' (contract no 18.008688) mandated by the Federal Office of Public Health (FOPH)*.

The report consists of two parts: First, we report on the search process and present a so-called literature profile. In the second part, we highlight and discuss the identified literature. Overall, we looked at four different topics concerning *Legionella* guidelines/ recommendations and legal regulations: (i) diagnosis, (ii) surveillance, (iii) prevention and control and (iv) outbreaks.

This report was preceded by a reporting on 'Meilenstein 1a: Suchstrategie Literaturstudie'[1] to the FOPH. In this report, we defined the search strategy for the literature screening. For consistency, we present the search strategy applied in the Chapter 'Methods' on page 105. Differences in the proposed and applied search strategy are highlighted. Throughout the document, we use the term publication, which encompasses scientific literature (original research articles, reviews, commentaries etc.), poster presentations, and other forms of presentation, official government documents, and all other published documents.

[1] This report is available upon request.

Background

Legionnaires' disease (LD)* is characterised by pneumonia and non-productive cough, but belongs to a wider group of diseases termed legionellosis, which are all caused by the gram-negative bacteria *Legionella* spp. [Fraser et al. 1977; Woodhead et al. 2011; Berkelman 2020; Ewig et al. 2016]. Other disease manifestations are Pontiac fever, a mild and self-limiting fever episode, as well as in more rare occasions extra pulmonary infections, such as infections of the heart.

LD though severe, has been shown to not present clinically different from other pneumonias. Pneumonias are further often empirically treated, without the assessment of the aetiology. However, the microbiological cause is important (i) for a more targeted therapy approach to better the health outcome of the patient, (ii) for epidemiological surveillance. To understand the extent of LD among pneumonias, it is needed to understand the **diagnostic pathway** from a patient presenting with symptoms to an LD diagnosis. These pathways are often informed by guidelines.

Legionella spp. is a ubiquitous environmental bacterium, mainly found in water, soil and other environs. Transmission occurs through inhalation or aspiration, however, in recent years person-to-person transmission has also been suspected [Correia et al. 2016]. *Legionella* spp. prefers stagnant and warm (25 to 42° C) water, thus, man-made water systems with aerosolisation of water, such as showers, whirlpools, fountains or cooling towers are ideal for proliferation and transmission of *Legionella* spp. and hence, LD [Fields, Benson, and Besser 2002; Orkis et al. 2018]. For this reason, **prevention and control** mechanism are especially important to decrease the burden of disease of legionellosis. There are numerous guidelines, recommendations and legal regulations on such prevention and control measures.

Lastly, *Legionella* spp. does not only sporadically cause disease cases, but can also be the cause for **small clusters and large outbreaks**. It is important to be able to distinguish between sporadic cases or true clusters and respond appropriately. Once a cluster/ outbreak has been detected, it is crucial that the infectious source is identified rapidly and further infections can be prevented.

For the reasons above LD has been added to the national passive **surveillance** system in various countries. An effective surveillance is highly dependent on the case identification by physician and their reporting and, in turn, informs public health officials of outbreaks and guides prevention and control measures. Therefore, all these guidelines are not autonomous entities but are dependent on each other for successful management of LD.

Overall approach/Overview

The aim of the study was to explore and map the national and international literature on *Legionella* spp. with regard to prevention and control of cases, diagnosis, surveillance, and disease outbreaks. A literature research in scholarly databases acted as the foundation to identify further relevant literature, also from the grey literature. Identified literature consisted mostly of the recommendations, guidelines and legal regulations, but also included scientific publications demonstrating the use of these regulations in the daily life and current research as well as publications commenting on the regulations.

To manage the wealth of literature, we divided the search and discussion in four chapters (i) 'Epidemiology and environment: Prevention and Control', (ii) 'Health services and clinical aspects: Diagnosis of LD', (iii) 'Surveillance of LD' and (iv) 'Outbreaks'.

Methods

We followed the methodological process of a scoping review, but did not adhere to in all detail all formal steps (e.g., we had one assessor (FF) instead of two). An essential part of the study was the documentation of all steps during the literature search. We followed the structure proposed by Arksey and O'Malley [2005] with some alterations suggested by Levac, Colquhoun, and O'Brien [2010]. In concert, they describe the process as a five-step approach:

1. Identifying the research question;
2. identifying relevant studies;
3. study selection for analysis;
4. charting the data;
5. collating, summarising and reporting the results.

While we did chart all selected articles, these lists were working documents and have not been cleaned for dissemination, due to the unexpected wealth of literature and information found. However, they can be made available upon request.

In a first step several search enquiries to scholarly databases were performed. The publications retrieved were reviewed for relevance and inclusion. After identifying relevant literature, the publications were analysed for content on recommendations, guidelines and legal regulations. If such content was found, the publications were collected in a separate list. All publications identified were indexed with country of origin, year and keywords to facilitate further analysis.

For handling the publications retrieved, we used the software package EndNote X8 (Clarivate Analytics), Microsoft Excel 2010 and Stata/IC 15.

Research question

We formulated four research questions to cover all aspects of LD management. Each research question led to their own literature research, cleaning and charting of literature and discussion of the content.

1. **Epidemiology/Environment**: What are the current guidelines, recommendations and legal regulations on the prevention and control of *Legionella* spp. infection and contamination on national country and international level?
2. **Health services/Clinical**: What are the current guidelines, recommendations and legal regulations on the diagnostic pathway and case management of pneumonia patients (including potential LD patients) on national country and international level?
3. **Surveillance**: What are the processes involved for case notification of *Legionella* spp. infections?
4. **Outbreak**: How are outbreaks/clusters of LD and sources of infection identified and handled?

For each research questions, we looked at Swiss and international regulations and discuss common features and discrepancies among them.

Definitions

Keywords

We have previously defined a list of keywords to be used for the literature research. The keywords were grouped into different topics:

Topic-1 covers the target disease 'legionellosis';
Topic-2 explores all variants of 'recommendation, guidelines and legal regulation';
Topic-3 addresses all the topics around 'prevention and control';
Topic-4 deals with 'diagnosis and case management';
Topic-5 with 'surveillance';
Topic-6 with 'outbreaks and source identification'.

For example, to retrieve literature on 'Diagnosis of LD', the search terms (1), (2) and (4) are combined (Table 8.1). Two changes have been made to the search strategy as proposed in a previous report[2]: We reduced the search terms for the topic 'disease' (1) to just 'legionellosis', instead of lower respiratory tract

[2]This report is available upon request.

infection (LRTI)* and pneumonia in general. After an initial search, we received too many irrelevant hits. It was observed that search for LD provided a breadth results on pneumonia and community-acquired pneumonia. In addition, we included 'Switzerland' as search term but omitted to add a regional search component given that a vast number of individual searches would have been necessary to obtain all articles. The same changes were applied to the Medical Subject Headings (MeSH)*[3] terms.

Table 8.1: Keywords and search combinations by topic for the literature search in scientific databases for *Legionella* spp. and legionellosis guidelines.

Search components		**Search terms**
1: Disease	legionellosis	'legionnaires disease' OR legionellosis OR *Legionella* OR 'pontiac fever'
2: Type of document	recommendation, guideline, legal regulation	recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order
3: Topic 'Prevention and control'	prevention, control	prevention OR action OR counteraction OR control OR regulation OR management OR measure
4: Topic 'Case management and diagnosis'	diagnosis, case management	diagnosis OR 'clinical decision-making' OR diagnoses OR diagnostics OR 'health care' OR 'case management' OR 'patient care planning'
5: Topic 'Surveillance'		surveillance OR monitoring OR notification OR notice OR report OR reporting OR 'case definition'
6: Topic 'Outbreaks'		outbreak OR cluster OR source OR 'outbreak investigation' OR 'source identification' OR epidemic OR exposure OR 'environmental source' OR investigation OR exposure

Next to common keywords, we had previously also compiled a list of MeSH terms for all the identified topics. We used this list of MeSH terms searching databases such as PubMed (Table 8.2). Search terms were combined using Boolean operators, such as AND, OR, NOT.

Databases

Here we provide a short overview on the databases.

[3]MeSH terms are constructed by the National Center for Biotechnology Information (NCBI)* in order to cover a large array of potentially related search terms

Table 8.2: MeSH terms and search combinations by topic for the literature search in PubMed for *Legionella* spp. and legionellosis guidelines.

Search components		**MeSH terms**
1: Disease	legionellosis	'legionellosis' [MeSH Terms] OR '*Legionella* '[MeSH Terms]
2: Type of document	recommendation, guideline, legal regulation	('Health Planning'[MeSH Terms] OR 'Health Planning Guidelines'[MeSH Terms] OR 'Legislation as Topic'[MeSH Terms])
3: Topic 'Prevention and control'	prevention, control	'prevention and control' [Subheading]
4: Topic 'Case management and diagnosis'	diagnosis, case management	('Diagnosis'[MeSH Terms] OR 'Patient Care Planning'[MeSH Terms])
5: Topic 'Surveillance'		'Disease Notification'[MeSH Terms] OR 'Epidemiological Monitoring'[MeSH Terms]
6: Topic 'Outbreaks'		'Disease Outbreaks'[MeSH Terms] OR 'Environmental Exposure'[MeSH Terms]

Scientific literature. As databases for the search of scientific literature, **Embase**[4], **PubMed**[5] (including MEDLINE), **Web of Science** (Core Collection[6]) and **Google Scholar**[7] were used [Bramer et al. 2017]. These databases have their own advantages and disadvantages and a combination of these should result in an optimal search output [Shultz 2007]. Embase, PubMed and Web of Science have a defined set of journals they cover and, therefore, a defined denominator. PubMed focuses on clinical, biomedical and health-related journals, similar to Embase, which has an additional focus on drug/pharmacology and clinical medicine, while Web of Science has a broader scope. In contrast, the databases and resources Google Scholar searches are not known. However, for this reason Google Scholar is also able to find more grey literature. Yet, considering the before mentioned the completeness (and quality) of Google Scholar-generated hits cannot be assessed. A major difference might be that Embase, PubMed and Web of Science only search the citation data for the search terms, while Google Scholar scans the entire body of text. We used the software 'Publish or Perish 7' to download hits from Google Scholar searches.

'Grey literature'. We used Google as a generic search engine to retrieve grey literature, as Google Scholar focuses on scholarly literature. Google possesses similar features as Google Scholar, and has been used in the same manner.

[4]https://www.embase.com
[5]https://www.ncbi.nlm.nih.gov/PubMed
[6]https://www.webofknowledge.com/
[7]https://scholar.google.ch/

We also looked at known stakeholders for relevant documents. European guidelines and the network for *Legionella* in Europe is rather comprehensive and has been used as a starting point for the identification of national guidelines. Similarly, agencies from overseas, known to publish on *Legionella* spp. were explored for each of the research questions. This includes the agencies from countries such as the US, Canada, Australia and New Zealand. Scientific literature was often a valuable resource and starting point to identify grey literature. Publications on *Legionella* often refer to official documents from the respective country, where the study took place, and hence, we could discover guidelines from China, Taiwan, South Africa and other nations, which are generally not prominent in the discussions around *Legionella* spp.

Inclusion and exclusion criteria

We excluded all documents published before 1999 given guidelines of two decades ago are likely outdated. We have not restricted the search to any language and all languages were retained in the database of collected publications. However, only publication in English and German language were evaluated and discussed in detail. Some mostly technical documents from engineering societies were not free of charge at reasonable costs and were thus, excluded. However, as the evaluation of such documents is beyond the scope of this project, we do not see any loss in not obtaining these documents. When scanning the publications for relevance, we only included publications, which were either regulations, reviews thereof, discussed actual guidelines, or referenced guidelines.

Processes

Selection of relevant publications

The cleaning was done in several steps, including automated charting, sorting and removing of entries in Stata/IC, as well as manual screening and marking of publications in Microsoft Excel, before re-importing into Stata/IC.

The cleaning processes were also done in a stratified manner. The hits of the databases Embase, PubMed and WoS were cleaned together, while the hits of Google Scholar were cleaned separately; at a later stage, both cleaned databases were merged. The rationale for this division was twofold: (i) It proved to be more time efficient: while Embase, PubMed and WoS provided instant search results, which were downloadable, the Google scholar searches took processing time until the list of hits was generated; (ii) While Embase, PubMed and WoS are 'traditional', well defined databases for literature search, Google Scholar is not. Hence, searching Google Scholar generated more, but also less relevant hits.

Cleaning was divided among the topics 'Prevention and control', 'Diagnosis and case management', 'Surveillance' and 'Outbreak', and in iterative steps merged and divided again. The stratification per subject had the advantage to divide the massive number of hits into manageable portions, especially for the manual

screening steps. The merging was done to remove any duplicates across the different topics. The screening was done in several steps: First, publications were removed based on the title of the publication; second, abstracts were checked and finally individual publications were checked for any reference to regulations.

Charting the data

We did not anticipate the extreme wealth of information and publications for this literature study. The aim of the study was to cover four different topics ('Prevention and control', 'Diagnosis and case management', 'Surveillance' and 'Outbreak') - each provided sufficient material for an independent literature review. We deviated from charting the data as proposed in the previous report[8] using the categories accuracy, objectivity, currency and coverage of the publications, as this would not provide additional value. The main body of literature that we reviewed were government documents; while their validity might be debatable, they reflect the current state-of-the-art in LD management. In this report, we discuss similarities and differences between the different publications. Topicality has been noted by the date published and outdated publications will be highlighted in the report. Lastly, coverage is mostly implicit in the agency releasing the guidelines. For all publication selected, we retained the title, author, abstract, year of publication, country, publisher and the source information (URL). We further added keywords to each publication to better sort by content. Lastly, each publication was indexed to facilitate a tracing back to the original search inquiry and retrieval.

While checking the publications identified we generated an additional list (database) compiling all regulations, which were referenced in the publications. Hence, in the end we had a list of all relevant publications, including scientific articles, reviews, posters, letters, guidelines and another lists limited only to regulations.

Output/literature profile

The initial research has been performed in four scientific databases. The literature search could include publications up until 24 June 2019. In total 20'470 hits were returned by all four scholarly databases combined.

A detailed overview of the cleaning processes for all searches for the different topics and the resulting pool of literature can be found in Appendix F-1. All search terms and specifications are shown in Appendix F-2.

[8]This report is available upon request.

Content analysis

Prevention and control of legionellosis and Legionnaires' disease

As *Legionella* spp. are ubiquitous environmental bacteria, the possible infectious sources are numerous. On the one side this complicates the identification of the actual infectious site for cases and clusters; on the other side there is no 'one-fit-all' solution for prevention and control of *Legionella* spp. Guidelines have been developed for drinking water, spa and pool water, hotels, cruise ships, cooling towers, buildings in general, nursing and elderly homes and hospitals. Additionally, there are often governmental guidelines at national and at local level, as well as guidelines from private institutions and societies. For Germany, we found 18 documents. Among them are 6 Deutsches Institut für Normung e.V. (DIN)* norms, the German equivalent of the International Organisation of Standardisation (ISO)*. Most guidelines were American: 50 guidelines were found.

A review on regulation for *Legionella* prevention worldwide was recently published by Van Kenhove et al. [2019]. Therefore, we do not duplicate their effort. However, we will discuss their findings within the context of the Swiss regulations and other publications on this topic. The review provides tables charting the regulations of different countries; we recommend consulting this document for further details. A pertinent article, by Yu et al. published in 2002 summarises references of internet resources on the subject of *Legionella* [Yu, Bassetti, and Widmer 2002].

Switzerland

In Switzerland, an updated reference document on *Legionella* and legionellosis was published in 2018 by the FOPH and the Federal Food Safety and Veterinary Office (FSVO)*: 'Legionellen und Legionellose BAG-/BLV-Empfehlungen' [BAG and BLV 2018]. The legal basis for these recommendations is given in several documents. Basis for prevention and control of LD and legionellosis are given in either:

- Federal Act on Foodstuffs and Utility Articles (Foodstuffs Act, FSA) SR 817.0 [Bundesversammlung 2014b];
  - Ordinance of 16 December 2016 on Foodstuffs and Utility Articles (FUAO) SR 817.02 [Bundesrat 2016];
  - Ordinance of 16 December 2016 on Drinking Water and Water in Public Baths and Shower Facilities (DWBSO)* SR 817.022.11 [EDI 2017];
- Federal Act of 15 December 2000 on the Protection against Dangerous Substances and Preparations (Chemicals Act, ChemA) SR 813.1 [Bundesversammlung 2000];
- Federal Act of 21 March 2014 on Construction Products (ConProdA) SR 933.0 [Bundesversammlung 2014a];

- Ordinance of 25 August 1999 on Protection of Employees from Dangerous Microorganisms (PEMO) SR 832.321 [Bundesrat 1999];

The DWBSO SR 817.022.11 ordinance became effective as of 1st of May 2017 and stipulates limits for *Legionella* spp. contamination for public shower- and bathing water (Table 8.3). These limits do not apply to water in private institutions. The cantons have the authority to control public institutions for adherence to these guidelines and to order measures to limit the level of contamination. However, other than this contamination limit stated in the new food safety law, the recommendations of the FOPH and FSVO are not legally binding.

Table 8.3: Limits of *Legionella* spp. contamination in Switzerland [BAG and BLV 2018]

Category	**Limit**	**Test method**	**Legislation/ source**
Public bath- and shower water			
Water in whirlpools or water in pools over 23°C with a circulation promoting aerosolation	100 CFU/L	EN/ISO 11731	DWBSO SR 817.022.11
Steam bath: water production with aerosol formation	100 CFU/L	EN/ISO 11731	
Water in shower facilities	1000 CFU/L	EN/ISO 11731	
Cooling towers			
Aerobic and facultative anaerobic mesophilic bacteria	10^3 cfu/ml	EN/ISO 6222:1999	SWKI BT102-01 and SWKI VA104-01 in accordance to ESGLI recommendations
Legionella spp.	10^3 CFU/L	ISO 11731: 2017	
Hospitals/Nursing homes			
Vulnerable departments (oncology/transplantation/ICU)	100 CFU/L	EN/ISO 11731	Adapted from Ruef C, Pagano E, Raeber PA, Gaia V, Peduzzi R. Legionellen im Spital. Praktische Hinweise für das Screening. Swiss-Noso 1998; 5(2):12-14. Tabelle 2 S. 13.
Other departments	1000 CFU/L	EN/ISO 11731	DWBSO SR 817.022.11

If contamination of 1'000-10'000 colony forming units per litre (CFU/L)* of *Legionella* has been observed, the source needs to be identified and eliminated, the system needs to be decontaminated and sustainable measured need to be taken to avoid further contamination; the system needs to be retested after two and six months. During that time, it is usually possible to continue using the facility. If a contamination of more than 10'000 CFU/L has been found, it is likely that the whole system needs to be renewed; facilities cannot be used after this level has been observed.

The FOPH and FSVO recommend differentiating between health care and nursing facilities and general facilities regarding contamination limits. Due to the susceptibility and vulnerability of people in hospitals and nursing homes a maximal limit of 100 CFU/L in shower water and other aerosol forming water is recommended, while outside of the hospital, the recommendation is in line with the limit in DWBSO SR 817.022.11 (ref modul 11, chapter 3). In contrast, modul 12 recommends a level of 100 CFU/L only in departments with highly vulnerable patients (e.g. oncology, after transplantations), while 1'000 CFU/L is acceptable for other exposure settings within hospitals.

Hospitals and nursing homes are public institution and are, therefore, under the control of the cantonal laboratories, according to DWBSO SR 817.022.11. However, the periodicity of the monitoring is not stipulated and the focus is on self-control. It is recommended that hospitals with high vulnerability departments test their level of *Legionella* contamination twice a year; for all other hospitals once a year suffices.

In Swimming pools and spas, only the water which comes in contact with the clients and forms aerosols is to be tested. In the beginning testing should be performed every three months, if no problems are detected the period can be extended to six or 12 months. There is no recommendation on the timeframe of monitoring for cooling towers. The EN/ISO 11731 is a standard published by the ISO in 2017 on the enumeration of *Legionella* [ISO 2017].

Numerous of other standards have been published by the Swiss Society of Engineers and Architects[9] (SIA)*), the 'Schweizerische Verein von Gebäudetechnik-Ingenieuren (SWKI)*'[10], the 'Verein Deutscher Ingenieure e.V. (VDI)'[11] and the 'Schweizerische Verein des Gas- und Wasserfaches (SVGW)*'[12]. SWKI is a technical association of the SIA, focusing on heating- and air conditioning, among other things. The discussion of the content of these guidelines on the construction and maintenance of sanitation systems is outside the scope of this review.

Discussion

Almost all guidelines have the same key elements of *Legionella* prevention and control: Risk assessment; monitoring of the water system; control measures; establishing of a sustainable hygienic system. The striking shortfall in all guidelines is the paucity of information on the trajectory from *Legionella* spp. contamination to LD infection. Whiley H. et al. discuss this paucity and uncertainties and how this impacts public health decisions [Whiley et al. 2014]. In their publication (of 2014) they named three major knowledge gaps:

[9]http://www.sia.ch/en/the-sia/, accessed 22 July 2019
[10]https://die-planer.ch/, accessed 22 July 2019
[11]https://www.vdi.de/, accessed 22 July 2019
[12](http://www.svgw.ch/, accessed 22 July 2019

1. **Risk assessment**: The identification of high-risk sites is difficult, partly driven by the fact that LD incidence is assumed to be underestimated and cases not captured in the system could potentially be infected via unknown sources
2. **Hazard assessment**: The pathogenicity of *Legionella* leading either to a Pontiac fever or LD is largely unknown. This includes the dose-response relationship for *Legionella* spp. for disease expression. Virulence factors of various *Legionella* strains are not well understood.
3. **Exposure assessment**: Exposure and risk factor patterns for Pontiac fever and LD are not well understood. They differ and the fact that aerosols containing *Legionella* spp. can travel large distance hampers the identification of sources. Additionally the quantification of *Legionella* spp. in environmental samples is difficult, due to their ability to be alive, dead (destroyed or intact), viable but non-culturable (VBNC)* or even live intracellular in amoeba.

Despite these unknowns, public health officials do issue guidelines to limit LD infections and protect the public; the interpretations of these gaps or the limited body of evidence can be quite different and leads to different results. We highlight the most important points of discussion identified here:

1. Implementation of a contamination threshold and monitoring: The Centers for Disease Control and Prevention (CDC, US)* does not recommend routine monitoring for *Legionella* spp. in the absence of an outbreak. Consistently the CDC does also not provide a quantitative limit for *Legionella* spp. contamination [Van Kenhove et al. 2019]. Similarly, the World Health Organisation (WHO)*, also does not provide quantitative thresholds, but rather focuses on controlling the proliferation of *Legionella* and the production and release of aerosols [Van Kenhove et al. 2019]. In contrast, the guidelines of the European Study Group for *Legionella* Infections (ESGLI)* do recommend quarterly *Legionella* testing in cooling towers and spas, and testing of hot and cold water systems under specific circumstances [ESCMID ESGLI 2017]. They also provide the thresholds for *Legionella* quantification (Table 8.4). These limits are comparable to the Swiss limits. Likely, due to the influence of ESGLI many European countries do have regulations on limits and monitoring. In 2011, Germany introduced mandatory testing of public water systems (including apartment buildings), next to providing limits for *Legionella* spp. contamination [Parr, Whitney, and Berkelman 2015].

However, there are several arguments against routine monitoring and the recommendations of thresholds. Most countries, including Switzerland use the ISO 11731 as the reference method for the isolation and enumeration of *Legionella* in environmental samples. However, this method is not without limitations; it cannot detect VBNC *Legionella* , and is, therefore, thought to underestimate the contamination of *Legionella* in water systems [Borges et al. 2012; Whiley 2017]. Additionally the thresholds are thought to be arbitrary due to the lack of knowledge on the dose-response relationship [Meyer 2017]. In this article from 2017, the routine monitoring of *Legionella* in Germany is cited as 'not effective, not evidence-based and expensive and should therefore be stopped' [Meyer 2017]. Lastly, the testing of water systems and evaluating the contamination based on a threshold is thought to convey a false sense of security (if the *Legionella*

Table 8.4: ESGLI recommendations on the limits of *Legionella* spp. contamination [ECDC 2017b]

Category	**Limit**	**Action**
Hot and cold water systems	100 to 1000 CFU/L	Refer to contact person/water management plan and ensure real-time monitoring (biocide levels, temperature) is within limits
	1000 to 10000 CFU/L	Resample/Review of control measures and risk assessment, consider disinfection
	10000 CFU/L	Resample, and review of control measures and risk assessment, consider disinfection of the whole system
Spas	100 to 1000 CFU/L	Resample/Review of control measures and risk assessment, advice to drain and disinfect
	1000 CFU/L	Close pool to the public; drain and disinfect, review control measures and risk assessment
Cooling towers	1000 CFU/L	Refer to contact person/water management plan and ensure real-time monitoring (biocide levels, temperature) is within limits
	1000 to 10000 CFU/L	Resample/Review of control measures and risk assessment, consider disinfection
	10000 CFU/L	Turn cooling tower of; review of control measures and risk assessment, disinfection

count is below the threshold) and leads stakeholders to put less emphasis on appropriate risk management strategies (such as water management plans, maintenance of piping and water systems) [Whiley et al. 2014; Whiley 2017].

Almost all guidelines agree that the maintenance of the water system in general should take highest priority as a risk management strategy and helps curtail *Legionella* contamination. This includes the identification and management of critical spots, and avoiding water stagnation and dead ends in the system [Van Kenhove et al. 2019]. The most common *Legionella* contamination prevention measure is the usage of high water temperatures to stop *Legionella* from proliferation [Van Kenhove et al. 2019]. Table 8.5 shows a compilation of the different temperature recommendations published by Van Kenhove et al. [2019] with the recommendations for Switzerland added. Swiss recommendations are similar to other international recom-

mendations, at point of use though European Working Group for *Legionella* Infection(EWGLI)*/ESGLI[13] recommends at temperature 5°C higher than Swiss recommendations.

Table 8.5: Temperature recommendations for warm water systems to curtail *Legionella* spp. contamination. Adapted from Van Kenhove et al. [2019]: Recommendations of Switzerland added to the table.

	Water heater	**Return loop**	**Point of use**
WHO	60°C	55°C	$\geq$ 50 °C[a]
EWGLI/ESGLI	$\geq$ 60 °C[b]	$\geq$ 55 °C	$\geq$ 55 °C[c]
Switzerland	$\geq$ 60 °C	$\geq$ 55 °C	$\geq$ 50 °C
UK	$\geq$ 60 °C	$\geq$ 50 °C/loop	$\geq$ 55 °C[d]
France	55°C[e]	50°C	$\geq$ 50 °C
USA	$\geq$ 60 °C	$\geq$ 51 °C	$\geq$ 43.3 °C to 49°C[d]
Asia	$\geq$ 60 °C	NA[f]	$\geq$ 50 °C/$\leq$ 43 °C[d]

[a] after 1 minute
[b] 1 hour/d/wk
[c] 70°C should be possible
[d] health care
[e] recommendation $\geq$ 60 °C
[f] Not included in regulations

2. Registration of cooling towers: Another point of discussion for *Legionella* prevention and control is the registration of cooling towers. In Switzerland, this registration is currently not mandatory. However, EWGLI/ESGLI suggests that wet cooling systems should be one of the primary targets of prevention efforts [Ricketts et al. 2009]. Several countries, such as Andorra, Belgium, France, Malta, The Netherlands, Norway, Singapore, Spain, the United Kingdom, and Russia, already require registration of all cooling towers since as long as 1992 [Ricketts et al. 2009]. Such a registration system supports monitoring of cooling towers, but more importantly, it facilitates the investigation of outbreaks and shortens the time to trace the infections back to a contaminated cooling tower.

3. Considerations for the regulation of prevention and control of *Legionella* spp.: Prevention and control efforts have a wide-ranging impact in decreasing the burden of disease of Legionellosis at the population level. This evidence at hand, moral, and ethical obligations becoming ever more discussed, the necessity for *Legionella* control at national levels is still questioned. A pragmatic costing study from Canada amounts the costs for a single case of legionellosis to 24'000 Canadian dollars (medical costs plus productivity costs) [Vinson 2012] . These comprise the second highest costs of all waterborne illnesses in Canada next to Toxoplasmosis. The costs are likely to be conservative, as only the costs of hospitalised patients have been

[13]EWGLI was succeeded by ESGLI, more information can be found in '5.4.1 LD outbreak investigation toolbox'. In this report we will use mostly refer to ESGLI or both, according to the source material

calculated. A similar study from the US found LD to have with a total of 33'000 US dollars the highest cost per episode among all primarily waterborne diseases [Collier et al. 2012]. Hence, the costs associated with this disease are non-negligible. Such information from Switzerland is currently not available; however Switzerland has a higher notification rate than both the USA and Canada and as another high-income country, it can be assumed that costs will be comparably high. At his point, it should also be mentioned, that the introduction of more guidelines has an impact on liabilities. Even though the legislative basis for *Legionella* spp. is limited in Switzerland, it has been suggested that more actors are likely to be held liable if recommendations of the SWKI are not followed [Leiblein et al. 2018].

Key points

- A universal assessment of prevention and control efforts for *Legionella* is challenged through a vast number of guidelines available and the heterogeneity of their contents targeting a variety of water system.
- Risk assessment is highlighted as an integral part of all prevention efforts. Water systems should be assessed and critical points, such as dead ends, stagnant water, biofilm formation, temperature levels). A well-maintained water system without critical points is likely to pose a low risk for *Legionella* infections. The 'Legionellen und Legionellose BAG-/BLV-Empfehlungen' (from 2018) provides a guide for performing a risk assessment [BAG and BLV 2018].
- Limits for *Legionella* contamination and routine monitoring are not globally applied. Switzerland harmonises with the European recommendations supporting comparisons of intervention impacts among neighbouring countries. However, further research on dose-response relationships and thresholds is needed.
- Water temperature is still the main measure to control *Legionella* proliferation. The consensus on temperature levels worldwide is high. Changes to this recommendation should be carefully considered.
- Switzerland lacks a systematic monitoring of cooling towers. The introduction of a mandatory registration could be beneficial for prevention efforts, but more so for outbreak investigations.

Case management of pneumonia and diagnosis of LD

Going through the selected publications, thirty-six (36) guidelines on the management of pneumonia and the diagnosis of LD could be identified, together with four recommendations, five reviews and four papers on clinical scores. The guidelines and recommendation are presented together; the scores will be discussed separately. Six (6) guidelines were targeting nosocomial pneumonias; 30 were about community-acquired pneumonia (CAP)*. The majority of these guidelines were written for immune competent adults. Only one guideline was written for infants and children older than three months [Bradley et al. 2011]. The amount of information and guidance for inpatient treatment is generally greater than outpatient treatment. Fourteen guidelines were from Europe, seven each from North America and Asia, one from Africa, five from South America and two were international.

During the literature review it became clear, that two guidelines were the most referenced in regards to CAP and various other guidelines are adaptions of these: 'The BTS guidelines for the management of community acquired pneumonia in adults' by the British Thoracic Society (BTS)*, last updated in 2009 and the 'Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults' by the Infectious Diseases Society of America (IDSA)* and the American Thoracic Society (ATS)*, last updated in 2007 [Mandell et al. 2007; Lim et al. 2009]. The additional third important guideline is the 'Guidelines for the management of adult lower respiratory tract infections' by the Joint Taskforce of the European Respiratory Society (ERS)* and European Society for Clinical Microbiology and Infectious Diseases (ESCMID)*, last updated in 2011 [Woodhead et al. 2011].

The detail of the guidelines varied throughout but general features were often comparable. The benefit of incorporation of new research throughout the years, was clear when comparing older to newer guidelines. Newer guidelines also most often followed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [Guyatt et al. 2008].

Almost all guidelines started with a description of the local epidemiology, including aetiologies for CAP of different severities (inpatient/ outpatient) and antibiotics resistances. Guidelines should be locally adapted to account for such differences, e.g. an endemic pathogen in one country, might be hardly present in another, which has implications on testing and empirical treatment [Mandell et al. 2007]. Additionally guidelines should be adapted to the possibilities and realities of the local health system. Often guidelines referred to so-called 'atypical' pneumonia. Most often, these refer to pneumonia caused by *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella* spp. or respiratory viruses. However, with the exception of *Legionella* species, these microorganisms are common causes of pneumonia, especially among outpatients [Mandell et al. 2007].

We present here a short overview on the guidelines, a detailed list can be found in Appendix F-9. We assessed only the parts of the guidelines relevant for legionellosis and LD diagnosis.

The assessment of the disease severity of CAP seems to be the most important step in the subsequent diagnosis and therapy. Several scores have been developed to assist the physicians in this decision. However, it has been highlighted that the clinical judgement of the physician is most important and should not be overruled by the scores.

Clinical scores

Clinical scores were shown to be not universally applicable, but country-dependent [Filmer and Pritchett 2001]. However, the most used scores nowadays are the CURB-65, CRB-65 and the Pneumonia Severity Index (PSI)* [Lim et al. 2003], which are both endorsed by the BTS and the IDSA and ATS respectively. The CURB-65 score has been developed in 2002 to predicted mortality of CAP in the next 30 days. For this purpose, only five parameters need to be assessed:

- Confusion of new onset (defined as an abbreviated mental test score (AMTS) of 8 or less)
- Blood Urea nitrogen greater than 7 mmol/l (19 mg/dL)
- Respiratory rate of 30 breaths per minute or greater
- Blood pressure less than 90 mmHg systolic or diastolic blood pressure 60 mmHg or less
- Age 65 or older [Lim et al. 2003]

The CRB-65 is a reduced version of CURB-65, which can be used without the need to draw and analyse blood. Each parameter gives one point to the score – the higher the score, the higher the risk of mortality [Lim et al. 2009].

The PSI was developed in 1997 and validated afterwards with even more patients [Fine et al. 1997; Mandell et al. 2007]. It consists of 20 variables and stratifies the patients into five groups with different predicted mortalities. The CURB-65 and PSI have comparable predictive powers, even though the PSI seems to be better at identifying low risk patients [Aujesky et al. 2005]. However, it has also been noted that CURB does not predict mortality equally well for all cohorts, as e.g. comorbidities are neglected which are an important contributor to mortality in the elderly [Ananda-Rajah et al. 2008]. The PSI has been suggested to underestimate the severity of the disease, especially in younger patients without concomitant diseases [Menendez et al. 2010].

A study in 2012 showed that in Switzerland the CRB-65 is not routinely assessed, even though the score is mentioned in the current guidelines of the Swiss Society of Infectious Diseases (SSI)* from 2006 [Laifer,

Flückiger, and Scheidegger 2006; Widmer and Bachli 2012]. The study suggests that it might be due to a lack of assessment of the respiratory rate and the confusion criteria.

Two other scores that were mentioned were Smart-COP (Australia, 2008) and SCAP (Spain, 2006). Both aim to identify severe CAP, which requires admission to the ICU [Bantar et al. 2010; Ribeiro et al. 2013; Cao et al. 2018].

Microbiological aetiology

None of the guidelines recommend to routinely assessing the microbiological aetiology for mild CAP, which can be treated ambulatory. Exceptions should be made even in an outpatient setting, if the pathogen is suspected due to clinical or epidemiological cues/risks. The description of these risks varies greatly. Further indicators for *Legionella* infection include symptoms, such as confusion or non-drug induced diarrhoea [Mandell et al. 2000; Menendez et al. 2010; Athlin et al. 2018; Cao et al. 2018]; travel or alcohol abuse [Mandell et al. 2000; Wiersinga et al. 2012] or patients from an endemic setting; during an outbreak [Mandell et al. 2000; Lim et al. 2009] or non-responding to β-lactam antibiotics [Athlin et al. 2018; Cao et al. 2018].

If microbiological investigation is warranted (i.e. the patient is hospitalised), all guidelines recommend an investigation using the urinary antigen test. The information provided is varied, some guidelines give information on the sensitivity and specificity and the limitation to *Legionella pneumophila* serogroup 1. One guideline even incorporated the heat treatment of the urine samples for an improved specificity into their guidelines [Menendez et al. 2010]. Serology is often still mentioned, but not recommended for use in a clinical setting. Culture is seldom mentioned specifically. It is recommended to obtain sputum samples, ideally before the beginning of the treatment [Wiersinga et al. 2018], but mostly for gram staining and not specified for *Legionella* spp. Culturing (gram staining is a laboratory test used to identify several different bacteria (e.g. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*) and guide antibiotic treatment). Newer guidelines also support the use of PCR diagnostics, especially if a *Legionella* spp. other than *pneumophila* is suspected [Ewig et al. 2016]. For PCR the ideal sample would be sputum, however one guideline even highlighted the potential to perform the test on nasopharyngeal samples or nasal swabs if sputum is not available [Lee et al. 2018]. However, as the evidence for the appropriateness of these samples is limited, sample choice should be made carefully.

Treatment

Empirical treatment is recommended in all guidelines, as soon as CAP has been diagnosed. Treatment should ideally start not later than four hours (or even one hour [Woodhead et al. 2011]) after diagnosis; hence the aetiology is mostly not identified [Fally et al. 2017]. The recommendation for antibiotics is based on the

local prevalence of certain pathogens in the different disease severity groups and on antibiotic resistance. Good antibiotic stewardship has become increasingly important to avoid the generation of resistances.

The most prevalent causes for mild CAP are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumonia*, hence treatment should be adapted to those pathogens [Aleva and Boersma 2005]. First line treatment for mild cases, that can be treated ambulant are often β-lactams (amoxicillin, amoxicillin-clavulanate, cefditoren, cefpodoxime). Those can be supplemented with a macrolide (azithromycin, clarithromycin, roxithromycin). A macrolide is often indicated if atypical pneumonia is suspected [Lee et al. 2018]. However, macrolides were found to have some cardiovascular toxicity; if no atypical pathogen could be identified, it should been withdrawn after three days [Ewig et al. 2016]. Additionally, monotherapy with a macrolide is discouraged due to growing resistance of pneumococci [File and Tan 2003; Wiersinga et al. 2018]. Similarly, fluorquinolones should not be prescribed if tuberculosis is suspected [Boyles et al. 2017; Froes, Pereira, and Póvoa 2018; Lee et al. 2018].

Moderate to severe cases should be treated with a respiratory fluoroquinolones (gemifloxacin, levofloxacin, moxifloxacin). Because *Legionella* spp. are important in severe CAP, the empirical treatment must be targeted to include *Legionella* spp. antibiotics. Broad-spectrum antibiotics such as amoxicillin-clavulanate, cefuroxime, ceftriaxone are not recommended for the suspected pathogens in this severity group [Wiersinga et al. 2018].

The JRS guidelines recommend pathogen-oriented treatment as the initial appropriate therapy in cases in which an etiologic diagnosis is established or strongly suspected [Miyashita, Matsushima, and Oka 2006]. A study from 2004 in Switzerland showed that the *Legionella* Urinary Antigen test (UAT)* had a strong impact on the patient management: Non-*Legionella* targeted antibiotics were promptly withdrawn. The addition of active antibiotics was of less importance, because *Legionella* was mostly covered already in the empiric treatment regimen [Garbino et al. 2004].

B-lactams are ineffective against *Legionella* spp., which is a parasitic microorganism in cells; hence, β-lactam treatment failure should result in testing and treatment for *Legionella* spp. The recommended treatment by the 2016 S3-guidelines, the 2009 BTS-guidelines and the 2011 ERS/ESCMID guidelines all recommend fluoroquinolone antibiotics for a *Legionella* infection [Lim et al. 2009; Woodhead et al. 2011; Ewig et al. 2016]. Macrolides, are also effective, and recommended by various guidelines [Boyles et al. 2017; Wiersinga et al. 2018]. A systematic review (from 2014) on quinolones versus macrolides for the treatment of *Legionella* spp. infections showed a trend in decreased mortality and shorter hospital-stay when using quinolones, but a randomized-trial must be conducted to confirm these findings [Burdet et al. 2014].

In March 2019, the website of the British government has issued precautions using fluoroquinolone antibiotics[14]. Rare reports of disabling and potentially long-lasting or irreversible side effects have been received and therapy should be discontinued at the first sign of adverse reactions. National Institute for Health and Care Excellence (NICE) is reviewing recommendations relating to fluoroquinolone antibiotics for their guideline.

Treatment duration for *Legionella* spp. infections are generally longer than for other types of CAP. The termination of therapy needs to be guided by clinical judgement, but most often between 7 and 14 days of therapy are recommended. In general, improvements in antibiotic therapy seemed to have resulted in shorter treatment durations. A review of the previous IDSA guidelines, states that therapies longer than 14 days are no longer indicated [Yu et al. 2004]. The new 2007 IDSA/ATS does not state therapy duration for *Legionella* spp. explicitly.

Reporting and case investigation

The 2009 BTS guideline and the 2007 IDSA/ATS guideline both mention the implications of a legionellosis diagnosis: The case has to be reported to the national authorities and the source of the infections will be investigated [Mandell et al. 2007; Lim et al. 2009]. The guidelines further mention the benefit of obtaining a sputum sample for culturing and typing. Additionally, the 2009 BTS guideline discuss Pontiac fever and that no treatment is warranted for such a finding [Lim et al. 2009].

Switzerland

The current guidelines of Switzerland were published in 2006 by the SSI [Laifer, Flückiger, and Scheidegger 2006]. This guideline were also endorsed in the latest document on legionellosis of the Swiss Government [BAG and BLV 2018]. The Swiss guidelines are based on the ERS/ESCMID Guidelines of 2005 [Woodhead et al. 2005].

The diagnosis of LD and the test indication is stipulated in a similar manner and in line with other guidelines [Woodhead et al. 2011; Ewig et al. 2016; Wiersinga et al. 2018]: Mild pneumonia treated in outpatients, does not warrant microbiological investigation. Exemptions are for subgroups with severe co-morbidities and a high probability of unusual microorganism or resistance problems or in immunocompromised patients. These patients would explicitly need to be tested for *Legionella* spp. infection.

Microbiological testing of patients is indicated for all those admitted to the hospital. Blood cultures and sputum gram stain should be obtained for all hospitalised patients. A *Legionella* UAT should be

[14]https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-new-restrictions-and-precautions-for-use-due-to-very-rare-reports-of-disabling-and-potentially-long-lasting-or-irreversible-side-effects, accessed 22 July 2019

performed for patients with severe CAP or where it is clinically or epidemiologically indicated. If sputum could be obtained, sputum gram stain is recommended. Serological testing is not recommended due to a lack of clinical relevance. PCR (amplification tests) may be considered if therapeutically relevant. Hence, the testing behaviour is highly dependent on the decision to treat in- or outpatient. The CURB-65 or PSI score are recommended to be used to support the decision. Treatment should be started as soon as possible; in case of uncertain aetiology, the patient will be empirically treated. Mild outpatient cases should be primarily treated with Amoxiciline/Clavulanate or Doxycycline. Moderated, hospitalised patients should be treated with Amoxiciline/Clavulanate +/- Clarithromycine. Severe cases, admitted to the ICU should receive Ceftriaxone + Clarithromycine. Treatment is recommended to last for seven to ten days. If *Legionella* spp. has been identified the patients should be treated with a macrolide or quinolone. Treatment should last at least 14 days.

Discussion

In 2011, there has been an update to the ERS/ESCMID guidelines [Woodhead et al. 2011] published on their website[15]. The newer guidelines incorporated new information about prevalence antibiotic resistance and patients outcomes.

The CRB-65 is now recommended for the assessment of pneumonia severity. Biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT), as well as proadrenomedullin (pro-ADM) could be used to assess severity; however, their usefulness still needs to be fully evaluated.

The *Legionella* UAT is still indicated for hospitalised patients or if clinically or epidemiologically suspected. Some more information on the UAT is given, adding the relevance of concentrated or heat-treated urine samples. Serological testing is not recommended. More information about PCR could be incorporated in 2011: PCR for *Legionella* spp. is useful in combination with the UAT, if sputum could be obtained. Recommendations regarding sputum staining have not changed.

The recommendations of antibiotic therapy have changed between 2005 and 2011: Newer broad-spectrum antibiotics (such as Amoxiciline/Clavulanate) are reserved for second-choice escape medication when the traditional well-known agents cannot be used. For *Legionella* spp. treatment respiratory quinolones should be preferred over macrolides.

In 2016, an update of the 2009 guidelines for CAP and LRTI management of several German societies (German Respiratory Society, the Paul-Ehrlich-Society for Chemotherapy, the German Society for Infectious Diseases, the Competence Network CAPNETZ), was published [Hoffken et al. 2010; Ewig et al. 2016]. This

[15]https://www.escmid.org/escmid_publications/medical_guidelines/jointly_developed_guideline/, accessed 22 July 2019

update widened its scope to also be applicable for Austria and Switzerland and authors from respective Societies (Austrian Respiratory Society, Austrian Society for Infectious and Tropical Diseases and the Swiss Respiratory Society) were, therefore, participating in the generation of the update.

These guidelines are very extensive; a few highlights are mentioned here.

- The CRB-65 score is recommended to assess the severity of pneumonia in concordance of clinical judgement, assessment of comorbidities and the oxygenation.
- Microbiological investigation is not indicated for outpatients. All hospitalised patients should have an UAT performed; if possible sputum for gram staining and culture should be obtained. Multiplex PCR is not routinely recommended. Single PCR should be performed if there is a suspicion of other *Legionella* spp. other than *pneumophila* , otherwise they are not recognized as therapeutically relevant. The anamnesis for *Legionella* spp. should consider the epidemiological situation and previous travel with hotel stays.
- Empirical treatment is decided upon disease severity. Mild cases should be treated with Amoxicillin; inpatients with co-morbidities receive Clavulanic acid in addition. Severe cases should be treated with Piperacillin/Tazobactam and a macrolide. In case *Legionella* spp. could be identified, patients should be given a fluoroquinolone (Moxifloxacin or Levofloxacin). Due to changing from a macrolide to a fluoroquinolone, a shorter therapy duration, has been observed (<14 days).

Due to these international adaptations to the guidelines and the epidemiological changes of LD in Switzerland, an update to the Swiss guidelines might be warranted.

Over time, more information on LD has been incorporated in the guidelines, recognising their contribution to the burden of disease on CAP. However, the level of detail varies through the guidelines. If a guideline only recommends testing on clinical and epidemiological suspicion, it expects the physician to know those clinical and epidemiological signs or to gather them from another source. It allows for more variety in the actual case management depending on the physician acting on the guideline. However, even if the guidelines were perfect, the adherence of health care providers to follow them is critical to their success.

A study in 2011, investigated the proportion of pneumonia patients tested for *Legionella* and the adherence to the IDSA/ATS guidelines in the US [Hollenbeck, Dupont, and Mermel 2011]. Fifty-nine percent (59%) of all investigated LD cases warranted testing according to these guidelines; hence, the guideline does not manage to detect all patients, which should be tested. At the same time only 44% percent of the patients, for which bronchosopic specimen were sent for microbiologic testing, had *Legionella* testing by UAT or culture, which suggest an underutilisation of the available diagnostic methods.

Key points There are numerous guidelines for the management of CAP. No other infectious disease had exhibited such a variety in therapeutic approaches [Cunha 2004]. Key points relevant for the Swiss context:

- There is a need to update and harmonise the Swiss guidelines for the treatment of CAP concerning *Legionella* assessment and prevention efforts: (i) Swiss guidelines issued by the SSI [Laifer, Flückiger, and Scheidegger 2006] on the management of pneumonia as endorsed by the FOPH [BAG and BLV 2018] are based on the ERS/ESCMID guidelines from 2005 [Woodhead et al. 2005]. The latter were since updated in 2011 [Woodhead et al. 2011]; (ii) a new guideline pertinent for Switzerland was published in Ewig et al. [2016].
- The 2006 Swiss guidelines published by the SSI are rather brief and present limited background of the epidemiology of CAP in Switzerland (e.g. the prevalence and distribution of the major infectious pathogens) compared to other guidelines available. The regional setting is of importance for the testing and therapy approach. The guideline by Ewig et al. [2016] could potentially fill this gap.
- Guidelines should be as complete as possible: Information on the mandatory notification of infections based on the microbiological testing could be incorporated, notably for *Legionella* . Similarly, relevant information on the correct usage of UAT (heating of urine) should be added.
- Accessibility of guidelines: The state-of-the-art guideline on CAP management; key information should be clear to all physician, and should be presented in ways that can be easily and rapidly reviewed, e.g. in form of tables or illustrations [Cunha 2004; Flanders and Halm 2004; Postma, Werkhoven, and Oosterheert 2017].

Surveillance of legionellosis/Legionnaires' disease

Disease surveillance can be differentiated in accelerated - national active, national passive or sentinel [WHO 2019b]. Active surveillance has been defined as visiting health care providers sites and actively looking for cases (talks with health care providers or reviews medical charts); it is useful when every single case should be identified, e.g. when a disease is short before eradication, or in case of an outbreak. Sentinel surveillance consist of a selection of reporting units doing surveillance. It can provide high quality data, and estimates of prevalence. However, it is not representative. National passive surveillance consists of a reporting process, which is embedded in the routine management of the disease under surveillance and mandatory for all institutions that see patients. Passive surveillance is mostly indicated for diseases that are (i) dangerous, i.e. with a high morbidity or mortality and (ii) where actions can be taken to protect the public. Hence, the passive disease surveillance of legionellosis respectively LD is appropriate.

Using the surveillance data, we can estimate disease trends; detect single cases and respond appropriately and most importantly detect clusters and outbreak and take appropriate measures, to avoid further infections. However, a passive disease surveillance system is only functional in a well-established health system. Additionally, LD is a rare disease and the diagnosis is not straightforward. Hence, passive surveillance for LD is only implemented in few countries – mostly in high-income countries. We subsequently discuss passive disease surveillance about *Legionella* , but highlight other findings, when appropriate. The literature search in the scientific databases could only identify a very limited amount of guidelines on national passive disease surveillance, as this information is often directly (i.e. not as downloadable content) accessible on the website of the individual countries. Hence, we listed all countries from where it is known, that a national passive surveillance system for LD exists and attempted to gather information indirectly.

However, accessing this information has proven to be difficult. Navigating the websites is often confusing; information hidden or not available or in the worst case contradicting. For Public Health England, two different case definitions are available: Once directly on their website[16] and, once in a published guideline [Public Health England 2019a]. From their respective publication dates in July 2016 and January 2019, it can be assumed that the latter is the current version, nevertheless both information are simultaneously available. Similarly, the only case definition for Canada was found on a website stating, 'We have archived this page and will not be updating it. You can use it for research or reference. Last updates May 2008'[17], but an update could be found. Nevertheless, we provide an overview of the passive disease surveillance systems in Appendix F-10.

[16] https://www.gov.uk/guidance/legionnaires-disease-case-definitions, accessed 22 July 2019

[17] https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2009-35/definitions-communicable-diseases-national-surveillance.html, accessed 22 July 2019

Switzerland

In Switzerland, cases of LD must be reported to the National Surveillance System for Infectious Diseases (NNSID)* since 1988. The NNSID is managed by the FOPH. The legal basis of the mandatory notification is the Epidemics Act, which is in force since 2016 [Federal Assembly 2016] and in particular the ordinance on combating communicable human disease and the ordinance on notification of communicable diseases by physician and laboratories [Bundesrat 2015; EDI 2015]. All information on *Legionella* spp. and legionellosis, including surveillance has been compiled in a report provided by the FOPH and the FSVO (from 2018) [BAG and BLV 2018].

In summary: The diagnostic laboratories are requested to report a positive finding of *Legionella* spp. to the cantonal physician of the canton of residence of the patient and to the NNSID directly. The physicians are requested to report to the cantonal physician only. Hence, there are two notification forms for LD – the clinical and laboratory form (Appendices F-3 and F-4). The forms are usually provided via Fax. The notification period for both clinicians and laboratories is seven days after identifying a LD case. It is important to note, that even though all infections with *Legionella* spp. are reported (as per microbiological findings of the diagnostic laboratories), only cases which presented with pneumonia, hence LD, are reported in the official notification numbers of Switzerland.

The cantonal physician is responsible to acquire the patients' information on exposure and risks and to initiate the environmental investigation. This information is provided by the cantonal physician on the clinician form to the FOPH. All isolates obtained from patients should be sent to the National Reference Centre for *Legionella* in Bellinzona (NRCL)*. Additionally, since 2006 all laboratories are requested to provide the aggregated total number of tests they performed for *Legionella* spp. once a year. This should allow better contextualisation of the notification data.

The current case definition of LD in Switzerland differs slightly from the case definition of European Centre for Disease Prevention and Control (ECDC*, see Table 8.6) [Gysin 2018]. While the ECDC recognises *Legionella pneumophila* serogroup 1 seroconversion in a paired sample as a confirmed case, the FOPH

classifies it as a probable case. The FOPH also has the category of a 'possible case', which is indicated for any person meeting the laboratory criteria.

Table 8.6: Case definition for Legionnaires' disease in Switzerland since 2012.

Clinical criteria	**Microbiological criteria A:** Laboratory evidence of at least one of the following:	**Microbiological criteria B:** Laboratory evidence of at least one of the following:	**Definition for a case**
Confirmed diagnosis of pneumonia	Isolation (culture) of *Legionella* species from respiratory secretions or any normally sterile site	Detection of *Legionella pneumophila* antigen in respiratory secretions or lung tissue e.g. by DFA staining using monoclonal antibody-derived reagents	A confirmed case should be one that meets clinical and microbiological criteria A.
	Detection of *Legionella pneumophila* antigen in urine	Detection of *Legionella* spp. nucleic acid in respiratory secretions, lung tissue or any normally sterile site	A probable case should be one that meets clinical and microbiological criteria B
	Significant rise in specific antibody level to *Legionella pneumophila* serogroup 1 in paired serum samples	Significant rise in specific antibody level to *Legionella pneumophila* other than serogroup 1 or other *Legionella* spp. in paired serum samples	A possible case should meet any of the laboratory criterion.
		Single high level of specific antibody to *Legionella pneumophila* serogroup 1 in serum	
		Significant rise in specific antibody level to *Legionella pneumophila* serogroup 1 in paired serum samples	

Source: Gysin [2018]

Discussion

The earliest known passive surveillance system has been introduced in the US in 1976 (in light of the seminal outbreak in Philadelphia in the same year) [Fraser et al. 1977]. Most countries incorporated LD to their routine surveillance in the 1980ies. However, for some countries the exact year when *Legionella* surveillance was introduced cannot be allocated with certainty given some countries list the date when

policies are introduced others when surveillance was made mandatory (or a policy updated). Switzerland started surveying LD in 1988.

Switzerland[18], Germany and South Africa do only survey LD, while Australia, New Zealand, the UK, Japan, Ireland, Singapore and Poland have all *Legionella* spp. infections incorporated into their surveillance systems (most importantly Pontiac fever). The US has two surveillance systems: The National Notifiable Diseases Surveillance System (NNDSS)* and the Supplemental Legionnaires' Disease Surveillance System (SLDSS)*. The notification to the NNDSS is mandatory, while the reporting to the SLDSS is voluntary; in reporting to the SLDSS additionally information on the case is provided, which support environmental investigation. (We note as an aside that the Swiss cantonal authorities, - partly of various disciplines – investigate outbreaks but these data are not centralised.)

In most countries, the notification process includes both the clinician and the diagnostic laboratories. There are a few exemptions. In Australia, all physicians are required to report, as well as the laboratories (with the exception of the laboratories in Western Australia). In Germany, all laboratories are required to report –not so physician expect those form the Bundesland 'Sachsen' who must report cases and deaths.

The case definition differs by country. The most used one is based ECDC's case definition (Table 8.6) [Parliament and Council 1998]. Specifically, Austria, Latvia, Scotland, and Ireland all state explicitly that they are using the case definition provided by the ECDC. Switzerland has adapted this case definition but changing seroconversion as an indicator for a probable case instead of a confirmed case [Gysin 2018]. Poland uses this definition as well but adds the laboratory finding of a single high titre of antibodies against *Legionella* to the confirmed cases. The US uses a similar case definition, and includes immune-histochemical analyses in their diagnosis of a probable case.

The confirmation of *Legionella* using PCR is only seen as a probable case. PCR has proven to have higher sensitivity than conventional techniques (UAT and culture) [Avni et al. 2016; Peci, Winter, and Gubbay 2016]. Compared to the UAT, it also has the added benefit that it is not restricted to *L. pneumphila* serogroup 1. Through the widespread use of UATs, it is likely that LD caused by other *Legionella* strains is underestimated. New Zealand has conducted a sentinel surveillance of LD between 2015/2016, where every patient presenting with pneumonia and able to provide a lower respiratory sample, was tested using a PCR for *Legionella* spp. [Priest et al. 2019]. They found a fourfold increase in estimated incidence. They name PCR 'arguably the test of choice for diagnosing Legionnaires' disease' [Priest et al. 2019]. In line with this findings laboratory findings of *Legionella* using PCR is also classified as a confirmed case in New Zealand. This is also the case in England and Wales, Denmark, Germany, Israel and Japan. The ECDC considers the

[18] In Switzerland laboratory tests positive for *Legionella* spp. have to be reported to the NNSID, implying that all *Legionella* infections will be captured. However, officially communicated cases are limited to pneumonia cases, i.e. LD cases.

seroconversion of the antibody titre against *Legionella pneumophila* sg1 as a confirmed finding. However, to observe the seroconversion, a fourfold increase in titre between two samples over approx. 3 to 12 weeks must be observed. The time needed for this test renders it of little value for clinical application. Additionally, a study from Taiwan reports that a titer >1:256 or fourfold elevation in paired sera could not adequately define an LD aetiology, which has led to a reduction in case rates [Lay et al. 2005]. In fact, in Switzerland, serological tests for *Legionella* spp. are not covered in the 'Analyseliste', listing the remuneration for each test, since 2009 [BAG 2009].

Information on the timeframe between case finding and notification was difficult to find. Latvia and Germany request that not more than 24 hours should pass and England and Wales request notification 'as soon as possible'. Immediate notification is requested in New Zealand. The US has two different standards; mandatory reporting to the NNDSS should be done 'routinely' (assumed to be weekly based on other sources), and the voluntary notification to the SLDSS can be done in 30 days, expect for travel associated LD (TALD)*, where it should be done within seven days. In Switzerland, the reporting of both the laboratory and the physician needs to be done within seven days. In reality, the physician will need to wait for the confirmation of the laboratory and then report to the cantonal physician within seven days, who then in turn has additional seven days to report to the NNSID. This could potentially add up to a lag of 14 days until the clinical notification is recorded.

We also looked at the notification form of England and Wales, New Zealand and the SLDSS form of the US and compared it to the Swiss notification forms (Appendix F-5). All countries except Switzerland seemed to have only one form to collect information, albeit in Germany each 'Bundesland' has their own form. The collected information can be divided in several sections: Reporting source, demographics, disease severity, clinical features, laboratory diagnostics, risk factors, exposition, information on outbreaks and information on measures taken. The level of detail varied greatly. All countries except Switzerland collected information on the occupation. The timeframe of exposition also varied between ten (US and England and Wales) and 14 days (New Zealand and Switzerland). All countries' notification forms, except Switzerland's had the option to put free text at the end of the notification form. The English notification form provided some information and recommendation in their form, e.g. when to send a sample to the reference centre.

Europe has a unified notification system: The ECDC manages surveillance systems including all 28 EU Member States and two of the three remaining EEA countries (Iceland and Norway). All countries are asked to submit their notification data to the ECDC, which are then analysed and disseminated. The common platform is called 'The technical platform for web-based data submission, data storage and dissemination is The European Surveillance System (TESSy)*'. The ECDC further manages a network for TALD: European Legionnaires' disease Surveillance Network (ELDSNet)*. More details to this network is provided on page 8.

The ECDC published yearly the 'Legionnaires' disease - Annual Epidemiological Report'. The last report has been published in January 2019, covering TESSy data from 2017 [ECDC 2019]. Switzerland is not part of the EU and not part of TESSy, hence, Swiss data is not reflected in these reports. This is unfortunate, as the contextualisation of European data is more complicated; especially in the light of Switzerland having almost the same notification rate per 100'000 population (5.8) as Slovenia (5.7), which is the highest rate of all TESSy countries in 2017. Also in the two years before, only Slovenia had higher notification rates than Switzerland [ECDC 2017c; ECDC 2018b; ECDC 2019]. However, while part of the differences in notification rate across countries is due to differences in incidence, they can also be attributed to differences in the performance and fidelity of the surveillance system. Southeastern European countries hardly report any cases [ECDC 2017c; ECDC 2018b; ECDC 2019]. Most likely this can be attributed to deficits in the disease surveillance and hence is an underestimation of the actual incidence [Beauté, Robesyn, and Jong 2013].

Even those countries with well-documented surveillance systems are assumed to vastly underestimate the true incidence of *Legionella* . The ECDC has made two attempts to estimate the true incidence of LD: The first estimate from 2004 generated an incidence of 20 per million inhabitants, based on the notification rate of Denmark [Beauté and ESGLI 2017]. Denmark is thought to have a rather accurate estimation due to their small size, the rather rigorous testing of pneumonia patients and the fact that they have a single reference centre. Extrapolating this estimate of 20 cases per million inhabitants to the Swiss situation would equal 170 cases in Switzerland (for 8.5 million people in 2017 [BFS 2020a]). In 2017, Switzerland counted approx. 500 cases, clearly the Danish estimate does not apply well for Switzerland. In 2011, ECDC published a new estimate: 103 cases per million inhabitants; this would equal 876 cases in Switzerland in 2017 [Zucs 2011]. In that scenario, Switzerland would strongly underestimate its true number of cases; however the accuracy of ECDC's estimate is unclear; the estimate stems from a theoretical incidence of pneumonia and the estimated proportion LD of 4%.

Underreporting originates from a variety of sources: non-reporting of cases i.e. a lack of completeness in notification. There have been several studies of countries or regions assessing their level of completeness of LD notifications. Most often, the capture-recapture method was applied, where the notification statistics are compared to some other independent statistics, such as hospital statistics. In Ireland 87% of all hospitalisations were reported to its computerised infectious disease reporting (CIDR) [Kelly, O'Donnell, and O'Flanagan n.d.]. A study (from 2012) from Wallonia (Southern region of Belgium) found the reporting rate to be 65% [Jacquinet et al. 2015]. Italy estimates the notification rate to be 79% in 2002 [Rota et al. 2007]. In 2010, the French estimated a rate of 89%, compared to 1998 where they estimated a sensitivity of 33% [Nardone et al. 2003; Campèse and Che 2012]. Lastly, The Netherlands in 2001/2002 estimated a notification rate of 41% [Van Hest et al. 2008]. Almost all countries have room for improvement; however, it seems likely, especially based on the French repeat of the estimate that the notification completeness

has improved in the past years. Reasons for non-reporting are;- the lack of knowledge of the mandatory reporting of the disease, the belief that a colleague will notify, lack of time, cumbersome processes or lack of knowledge on the importance of notifications and the refusal to report [Brabazon et al. 2015; Jacquinet et al. 2015].

France published an analysis of the development of their surveillance system during ten years (1998-2008) [Campèse et al. 2006]. They attribute the improvement of the LD surveillance to several factors: (i) the introduction of the UAT; (ii) the strict monitoring and control of cooling towers (mandatory registry for cooling towers); (iii) the publishing of guidelines standardising all processes from surveillance to investigation; (iv) publishing guidelines on the organisation of outbreak investigation. The French national reference centre for *Legionella* has also been listed as beneficial to the surveillance. In France, it is also recommended to follow up with a culture for all patients with a positive UAT [Campèse et al. 2006]. Lastly, the estimation of the LD incidence is heavily dependent on the disease ascertainment. Likely LD is underdiagnosed. Following the guidelines for CAP management, (see page 118) only severe CAP cases are tested for *Legionella* . Empiric treatment is likely – and under ascertainment of *Legionella* species other than L. *pneumophila* serogroup 1, due to the heavy utilisation of UAT is equally likely.

Several countries, such as Austria, the US, Ireland, England and Wales and New Zealand have switched to an electronic notification process. This has several added benefits: (i) it facilitates the process for physicians; (ii) it shortens the time until the notification reaches the relevant health department; (iii) it can enforce filling of fields and therefore increase reporting quality. A study in the US has incorporated notifications into an electronic health record, which would inform the physician of relevant notification, once he entered appropriate symptoms, e.g. during an LD outbreak, once 'cough' has been entered, the system recommends sputum culture or UAT to the physician [Lurio et al. 2010].

Another proposition to improve LD surveillance that has been mentioned several times was the implementation of education activities. Austria organises training for public health officers (cantonal physicians) and other employees of public health offices and associated institutions. Ireland and Italy also propose educational courses for physicians on the notification process and the importance of notifications respective the identification of causal pathogens for pneumonia [Rota et al. 2013; Brabazon et al. 2015]. Lastly, it has also been suggested to educate the public and the lay media on *Legionella* spp. [Yu 2002]

The disease surveillance of Switzerland is well-developed. The high notification rate can be attributed in part to a higher capture rate than in other countries. Similar to France and other countries, the surveillance system has profited from the introduction of the UAT and from guidelines on surveillance procedures. However, there is a lack of knowledge on the actual capture rate within Switzerland. Additionally, Switzerland experiences the same drawback as all countries surveying LD: The low ascertainment of *Legionella* infections among all pneumonia cases. Guidelines for the management of CAP need to be in line with the

demand of the surveillance system. Based on the development of new diagnostic tools for LD, case definitions might need to be revisited. Lastly, LD management in Switzerland could profit from a mandatory surveillance scheme for all cooling towers (see page 8).

Key points

- Electronic notification of *Legionella* infections could improve capture rate, timeliness and quality of the reports.
- The timeframe for notification of LD cases in Switzerland is long compared to other countries. Timely notification is important for a rapid detection of clusters and implementation of outbreak control measures; hence, the timeframe for reporting could be optimised.
- Case definition might need to be adapted based on the recent development of diagnostics for legionellosis. Serology might be removed from the case definitions, while PCR counts towards a confirmed case. However, ideally adaptations should be made at European level.
- Routine education for physicians, laboratory staff and public health office staff (e.g. cantonal chemists and physicians and associated staff) on notifiable diseases, the notification process and the importance of notification, could improve the capture and ascertainment rate.

Outbreaks of legionellosis

Identifying guidelines for outbreaks of legionellosis was less straightforward that for the case management and diagnosis. Only seven institutions, which might have been issuing guidelines, could be identified, when scanning the scientific literature. Hence, we were purposefully looking first into the most well known publications on these topics and specific outbreak disseminations and lessons learned. In 2018, a review on the outbreaks of LD and Pontiac fever between 2006 and 2017 was published [Hamilton et al. 2018]. While this review is very informative on the properties of the outbreaks, it contains little information on outbreak management.

LD outbreak investigation toolbox

In 1986, EWGLI was formed. Around 2012, EWGLI was replaced by a new working group of ESCMID, ESGLI. EWGLI has also formed the surveillance platform EWGLINET, which has been renamed in 2010 to the ELDSNet and is now managed by the ECDC. It operates as a disease-specific network in accordance with the decisions 2119/98/EC [Parliament and Council 1998] and 2000/96/EC [Parliament and Council 1999; ECDC 2017a]. ELDSNet and ESGLI are one of the most important resources for *Legionella* prevention, surveillance and outbreak control in Europe. They have released a series of guidelines, support documents and tools on these issues. Many of the above-mentioned European guidelines were drafted by this group.

Thirty-two European countries are members of ELDSNet (Appendix F-6). Due to Switzerland not being part of the European Union, it does not officially belong to this network [ECDC 2017c; ECDC 2018b; ECDC 2019]. ELDSNet provides an outbreak investigation toolbox[19]. The website states that it provides tools that 'Member States, Iceland, Liechtenstein and Norway and ECDC can use' in order to support LD outbreak investigation in the EU context. The main page also links to the EWGLI website[20], which seems outdated.

[19] https://legionnaires.ecdc.europa.eu/; accessed 22 July 2019
[20] http://www.ewgli.org/, accessed 22 July 2019

The toolbox gives recommendations and guidelines for each step involved in an outbreak investigation:

Pre-outbreak planning - training and safety. Roles and responsibilities of the different actors should be clarified before an outbreak. People should be trained in understanding disease expression (of LD) and infection (with *Legionella*); implementing risk assessments on site; sampling; safety aspects and legal aspects including ramifications of law. Ideally, an outbreak response team should exist.

Data collection. Information on the descriptive epidemiology of the outbreak obtained from patients is usually the first step. ELDSNet provides a trawling questionnaire (hypothesis-generating questionnaire)(to obtain this information, it is recommended using a standardised questionnaire. The recommended timeframe for investigation is 14 days prior to disease onset. Samples from environmental investigations should be taken. Microbiological findings of cases and the environment should be matched.

Case definition. Cases can be defined as (i) individual cases (ii) part of a cluster or outbreak, using case definition. The case definition for outbreaks is very similar to the case definition used in routine surveillance. However, it can be adapted through the course of the outbreak, if carefully documented. The surveillance case definition in the 'Legionnaires' disease outbreak investigation toolbox' is based on the Commission Decision of 28 April 2008 amending Decision 2002/253/EC under Decision No 2119/98/EC, however there has been an update in 2012 and 2018 and the case definition has slightly changed.

Cluster and outbreak definition. ELDSNet defines clusters as linked in space and time and outbreaks as special cases of clusters, where a common source is suspected. A cluster or outbreak is suspected when two or more cases are linked in space and time and each cluster/outbreak should be investigated. Cluster can also be defined as linked in time, but not in space (e.g. due to meteorological influences on the incidence. If a cluster is investigated and no common source is found, cases should be classified as community-acquired. The proximity of time and space is not fixed and should be adapted to the setting (e.g. densely populated areas different to rural areas.) For international consideration, i.e. travel-associated LD two or more cases within two years at the same accommodation can be considered a cluster.

Questionnaires. ELDSNet differentiates between three questionnaire: (i) the surveillance questionnaire, which should be routinely applied to all cases (Appendix F-11); (ii) The trawling questionnaire, which should be applied when a cluster/outbreak is suspected (Appendix F-12); (iii) the analytical questionnaire, which should be applied in an outbreak situation to test a clearly defined hypothesis on the source of infection.

ELDSNet does further provide recommendations on data management and data sharing.

Analysis. Basic descriptive epidemiology might be enough to deduce a source and take appropriate measures. If not, analytical studies, such as cohort or case-control studies might be needed. Spatial statistical analysis using GIS might provide additional information. The best evidence for the identified source is the successful matching of clinical and environmental strains.

End of the outbreak/dissemination. The outbreak investigation should be analysed to identify lessons learned to improve future outbreak management. The findings should be disseminated. Templates for communication with the outbreak control team and the general public are provided by ELDSNet.

International outbreak control

Since 2017, 28 EU Member States plus Iceland, Norway and Switzerland contribute data on TALD. Since 2016, neighbouring countries to the EU or EU enlargement countries can appoint contact person to communicate on TALD information. Currently, over 50 countries are involved in ELDSNET surveillance activities, countries not included are notified through collaboration of ELDSNet with the WHO. In 2017, an update to the procedures of ELDSNet in relation to TALD was published [EWGLI 2011]. The case definition of the EU is applied (Table 8.6) [European Commission 2018].

A cluster is defined according to the outbreak toolbox: Two or more cases staying in the same accommodation two to ten days prior to onset illness within two years. The clusters are also categorised as (i) rapidly evolving; (ii) complex; (iii) active and (iv) expired.

Each country has a contact person appointed to ELDSNet – data from national surveillance are reported to ELDSNet after applying the EU case definition. Information is submitted on a secure section of the ECDC web portal to the surveillance database. Countries can report both, cases that were infected inland and TALD infected abroad. Only confirmed cases, residing in or being associated with public accommodation (e.g. hotel; Airbnb) should be reported; Cases residing in private accommodations should not. However, ELDSNet members can exchange directly, if cases from private places have been reported. Similarly, occupational exposure or day visits to thermal resorts, which do not have accommodation sites, should not be reported to ELDSNet TALD. If a single case is reported to ELDSNet TALD, it will be checked against the database. If no other case appeared in this database and geographical site in the two years prior, the reporting agency will be notified of a 'single-site notification'; the reporting agency will also receive information on all cases in the five years prior at this location. The 'single-site notification' will also be reported to the country of travel with copy to the reporting agency. The reporting agency should forward a checklist to minimise *Legionella* infection risk to the suspected accommodation site. Investigation reports can be voluntarily submitted to ELDSNet TALD.

Cluster detection. If a cluster is detected, ECDC will notify all ELDSNet members and the WHO, as well as the country of travel if they do not have a contact person for ELDSNet. The ELDSNet member/country of travel should investigate the source according to the European technical guidelines [ECDC 2017b]. The national authorities should draw up recommendations against future risks for LD. ECDC will support the ELDSNet member/country of travel to access technical expertise, if needed. The results of the assessment and the actions taken should be reported to the ECDC using a standardised form within six weeks. If the country of travel is located within the EU/EEA and this report is not received, the accommodation will be published on the ECDC website.

EWGLI has published a guideline 'EWGLI Technical Guidelines for the Investigation, Control and Prevention of Travel Associated Legionnaires' Disease' in 2011 [EWGLI 2011]. It has received an update in 2017 now called 'European Technical Guidelines for the Prevention, Control and Investigation, of Infections Caused by *Legionella* species' [ESCMID ESGLI 2017]. The website of the ECDC[21] and the new document does not make it entirely clear that this is the update of the previous guideline. However, the guidelines are endorsed by the ECDC and one of the most referenced guidelines on this topic. The 2017 guideline has expanded the two previous chapters (i) 'Procedures for the risk assessment, environmental investigation and the control and prevention of *Legionella* in water systems' and (ii) 'Methods for the investigation and control of an outbreak of LD in a hotel, other accommodation sites or other public buildings' with two new chapters: (iii) 'Technical guidelines for the control and prevention of *Legionella* in Water systems' and iv) 'Treatment methods for different water systems'. Here, we discuss the second chapter, related to the management of outbreaks.

If a cluster is detected a network of different actors needs to be involved: The local health authorities in accordance to national communicable disease control arrangements; an accredited laboratory (according to ISO/IEC 17025) for the sampling analysis of the environmental samples; the engineer responsible for the water system in question; experts on water systems and microbiology for interpretation of the findings. Results from cluster investigations must be reported back to ELDSNet at one, two and six weeks, using the forms provided.

The EWGLI Sequence-Based Typing (SBT)* Database for *Legionella pneumophila* [22] is another often-used resource. It supports the typing of clinical environmental strains using SBT and therefore helps to find matching strains and sources for human illnesses. It is frequently used in outbreak investigations. The CDC of the US also provides a comprehensive guide on outbreaks on its website[23].

[21] https://ecdc.europa.eu/en/publications-data/european-technical-guidelines-prevention-control-and-investigation-infections, accessed 22 July 2019
[22] http://bioinformatics.phe.org.uk/Legionella/Legionella_sbt/php/sbt_homepage.php, accessed 22 July 2019
[23] https://www.cdc.gov/Legionella/index.html, accessed 22 July 2019

Switzerland

The governmental document 'Legionellen und Legionellose BAG-/BLV-Empfehlungen' (from 2018), specifies how an outbreak should be handled [BAG and BLV 2018]. In Switzerland, a suspected cluster or outbreak must be reported to the cantonal medical officer within 24 hours. The FOPH provides a specialised form for this (Appendix F-7). A cluster can also be suspected by the FOPH, based on notification dynamics observed in the NNSID database. A cluster is defined as two or more cases that originate from the potentially same source during their incubation time within 6 months (Table 8.7).

Table 8.7: LD cluster definition for selected countries

Cluster definition	**Country**
≥ 2 persons from the same potential source during incubation period within 6 months	Australia [CDNA 2017]
More cases in a period than usual AND the suspicion of a common source	Germany [Robert Koch-Institut (RKI) 2018]
≥ 2 persons from the same potential source during incubation period within 6 months	Switzerland [BAG and BLV 2018]
A location cluster: ≥ 2 persons from the same potential source during incubation period within 2 years; Geographic cluster: ≥ 3 persons living1 km apart within 6 months	The Netherlands [Den Boer, Nijhof, and Friesema 2006]
Health-care associated: ≥ 2 persons staying at the same health facility during the incubation time within 24 months; TALD: ≥ 2 persons staying at the same accommodation during the incubation time within 24 months; CAP: ≥ 2 persons within 6 km of each other during incubation time within 6 months	UK [Public Health England 2019b]
≥ 2 persons from the same potential source within 12 months	USA [CDC 2021b]
≥ 2 persons from the same potential source during incubation period within (e.g.) 6 months	ECDC [ECDC 2018a]

In case of a suspected cluster and a common source, the cantonal health departments need to perform a risk assessment, inspect the technical installations and perform the environmental investigation. In order to identify the source of the outbreak the environmental strains samples should be typed and matched with the clinical strains. If remedial measures are taken, this must be documented, but not centrally reported.

The FOPH supports to the cantonal physicians in providing advice, sharing of the weekly notification data and the coordination of intercantonal actions. Similarly, the NRCL is available for analysis and technical advice. Environmental samples can be sent to them for analysis, prices and information can be

found on their website[24]. The protocol on which actions needs to be taken, differs slightly, depending on the category of LD. Hospital-acquired LD needs to be investigated even if only a single case has been detected. If more than one case has been observed, the spatial and temporal distribution of the cases needs to be assessed (also graphically) and the common source needs to be identified and investigated. Eventually a case- control study needs to be considered.

If a case was likely infected in its canton of residence during travels (also called travel-associated), the cantonal physician is responsible for taking actions, and informs the FOPH. If a case acquired an infection outside its canton of residence but within Switzerland, the cantonal physician informs the colleague of the canton where the infection likely had occurred. If a case was infected abroad, the cantonal physician informs the FOPH, which in turn informs ELDSNet. If a cluster was identified within Switzerland, the respective cantonal physician takes actions and the FOPH will be reporting to ELDSNet. If a cluster of community-acquired pneumonia is observed, an investigation has to be conducted, including the inspection of the suspected site, inspection of the technical plans of the water-supply system, inspection of the maintenance, and temperature, and testing for *Legionella* .

Discussion

Before the discussion of the guidelines, we will consider two real examples of outbreak investigations in 2017 [Zanella et al. 2018; Wüthrich et al. 2019].

> An outbreak in Geneva was detected when the local University hospital notified the Public Health Service (likely the cantonal physician) of eight cases which appeared within seven days. On the day of notification, an outbreak control team was formed with members of the university hospital and the Public Health service. Active surveillance to identify LD was initiated and local physicians (general practitioners (GP)* and clinicians) were informed by letter. The Public Health Service reviewed cases in the region of the three months prior and within ELDSNet. Cases were defined according to Swiss and European (ELDSNet) case definition with the additional epidemiological criteria of a likely infection within the canton of Geneva. All cases were interviewed using a standard questionnaire regarding the 14 days prior to illness onset. Geographical distribution of the residence of the patients was illustrated using the R software package. The Public Health Service and the Official Food and Veterinary Control Authority (we assume the FSVO, or the cantonal chemist) conducted the environmental investigations. Meteorological data covering one month before and one month after the cluster detection were obtained and analysed. Clinical and environmental isolates were sent to NRCL, who performed monoclonal antibody subtyping and SBT. First measures were taken seven day after the outbreak was reported and after an additional two

[24]https://microbiologia.eoc.ch/Legionella/CNRL-deutsch.html, accessed 22 July 2019

days, the first disinfection control procedures were performed. Two months after reporting the outbreak was contained. The outbreak study team listed the lack of registering of water systems at risk as a possible reason that matching of clinical environmental strain could not be achieved [Zanella et al. 2018].

In 2017, there was another outbreak in the area of Basel, Switzerland [Wüthrich et al. 2019]. The outbreak management is not as well documented in the publication as for the Geneva outbreak. It is reported that the health authorities of Basel-City did not initiate active case findings after an increase of case numbers was identified; however epidemiological investigations were performed using a standardised questionnaire on all patients. After initial analysis a spatial temporal cluster was found; a follow-up investigation was attempted to identify the suspected source. Whole genome sequencing (WGS)* was performed on the clinical isolated and three isolated with the same type were found. Environmental investigation was performed to find the source of infection for these three patients. Eventually the source could be tracked down to an air-conditioner cooling towers [Wüthrich et al. 2019].

The two examples from Switzerland show that the procedures to contain an outbreak are not harmonised. The guidance in the 'Legionellen und Legionellose BAG-/BLV-Empfehlungen' (from 2018) does lack the detail in that regard [BAG and BLV 2018].

Lessons can be learned from previous international outbreak investigations. Major shortfalls in the fast identification of the infectious sources and implementing control measures were difficulties in the cooperation between different stakeholders and unclarities of each stakeholders' role and responsibility [Hyland et al. 2008]]. Additionally, depending on the size and duration of the outbreak, a considerable amount of resources is required, which should be taken into account, when developing a generic plan for LD outbreak control [Hyland et al. 2008]. However, while guidelines for outbreak management are beneficial to streamline processes, to achieve faster implementation of outbreak control measures and to protect the public from further infections, it has also been highlighted that control teams and agencies should have enough degree of freedom to respond to each outbreak individually [Smith, Wild, and Law 2003; Buckley et al. 2018]. It has further been proposed that a database is generated, identifying governmental, para-governmental, private and public organisation with expertise for on the *Legionella* disease system. This database can be used in a case of outbreak to rapidly recruit the necessary knowledge, as well as human resources [Trudel et al. 2014]. This could be useful e.g. if the cantonal chemists does not have the capacity to perform all environmental investigations possible, such that not only public but also other agencies can be engaged, to support the cantonal chemists. Engaging other partners outside of a core response team has also shown to improve planning and preparedness activities [Buckley et al. 2018].

The use of graphical representation of outbreaks (such as timelines and maps) proofed as advantageous in identifying the source [Hyland et al. 2008]. In the 'Legionellen und Legionellose BAG-/BLV-Empfehlungen' (from 2018) the use of such graphical assessments is explicitly mentioned only in the chapter regarding hospital-acquired LD, while it is relevant for all outbreaks, especially community acquired.

There has also been a report of a pseudo-outbreak of Legionnaires' disease [Regan et al. 2000]. The study team recommends the confirmation of positive UAT test, whenever possible, due to the false positive results (which in this particular case have been due to cross-reactions). This is also in line with the recommendations of ESGLI that all samples positive by UAT should be retested after heat treatment of the urine for confirmation, unless the initial sample was already boiled. It was suspected early from contradicting clinical and epidemiological evidence that this was not a *Legionella* -associated outbreak, hence when investigating a cluster of LD a strong index of suspicion should be emphasized [Regan et al. 2000]. Another publication from a hospital reports that they have been unnecessarily burdened with additional *Legionella* prevention and control efforts, due to a suspected hospital-acquired LD case, which in the end proved to be community-acquired [ECDC 2018a]. Currently, in most countries, a single case of hospital-acquired LD leads to a full investigation, similar to an outbreak investigation. The study suggests using the threshold of at least two cases to merit epidemiological investigations also within hospitals. While, this might not necessarily appropriate it shows that choosing the appropriateness of an epidemiological investigation is difficult. Further, if LD case numbers continue to increase, the definition of clusters in an attempt to separate them from sporadic cases might needs to be revisited.

Another study reported delay of appropriate control measures, due to initial confusion on the scale of the outbreak and when the outbreak should be declared [Smith, Wild, and Law 2003]. Switzerland has defined the event of a cluster and measures should be taken, when this definition applies. The definition of Switzerland is in line with those of other countries and the ECDC. In comparison, the German definition of a cluster is vaguer. It should be noted however, that almost all guidelines that recommend a timeframe between cases (e.g.) six months, state that the timeframe is no strict threshold and can be adapted. The UK provides an additional definition for hospital-acquired cases. The definition of ELDSNET for TALD is likely applicable in all member states (as well as Switzerland).

Several publications also stressed the importance of communication with the public during an outbreak. In case of a large outbreak, constant and accurate information to the public should be provided, best predefined according to a communication plan [Buckley et al. 2018].

Lastly, WGS appears to revolutionise outbreak management. WGS provides better discrimination between strains and a more definite description of outbreaks and relevant strains [Taylor 2016]. WGS for *Legionella* was successfully applied in the outbreak in Basel [Wüthrich et al. 2019]. Another outbreak study from Germany also demonstrated the usefulness of WGS in outbreaks; however, traditional epidemiological

description and investigation of the events are essential to anchor the information from the WGS in space and time [Petzold et al. 2017; Wüthrich et al. 2019].

Key points

- The section on guidelines for outbreak management and control as described in 'Legionellen und Legionellose BAG-/BLV-Empfehlungen' (from 2018) [BAG and BLV 2018] is not as detailed and implementation-oriented as other sections in the 'Empfehlungen'. There is paucity on guidance on how to proceed with control measures after a cluster of cases is detected. The way cantonal authorities collaborate best e.g. cantonal physicians and chemists is not formalised and not clearly stipulated.
- An investigative control team should ideally be predefined and readily operational, in case of an outbreak, as has been described in the Geneva outbreak in 2017. The members of this team and their expertise should be defined in advance as an essential part of an outbreak control guideline.
- A database listing all national actors with legionellosis/LD expertise could assist in acquiring the necessary human resources for outbreak response and control.
- A communication plan with the public and media should be part of outbreak control guidelines.
- While the definition of a cluster seems helpful to trigger fast responses to outbreak situations, each cluster suspicion should be evaluated carefully not to waste resources on pseudo-clusters.

Conclusion

Research on *Legionella* spp. and LD has made significant advances in the past 20 years and guidelines concerning all topics covered in this report have been continuously developed and improved the management of LD. However, the breadth of information is extremely wide and can easily be overwhelming, when not familiar with the topic. One criterion for good and effective guidelines is accessibility; hence, harmonisation of the guidelines should be generally improved. At the same time, out-dated information or contradictory statements can still be found.

Switzerland does have a well-developed LD management system. Yet, other countries advance in research and guidelines in some topics; such as The Netherlands on outbreaks and France on surveillance research. The cooperation within Europe on *Legionella* and legionellosis is certainly a benefit for all European countries. Advances in other countries thus, foster mutual learning. Conversely, it is also necessary that the European countries act according to similar standards and regulations. The Swiss regulations are generally in line with the European regulations. However, this can also be a disadvantage as the decision to improve a regulation might be harder to make, if it means a deviation from international standards.

The compilation of almost all relevant information on LD management in one document makes Switzerland stand out from other (European) countries [BAG and BLV 2018]. Nonetheless, an update on the case management of CAP and outbreak management may be needed in due time.

Chapter 9

Legionnaires' disease – a qualitative study on Swiss physicians' approaches to the diagnosis and treatment of community-acquired pneumonia

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This article was published in:
Swiss Medical Weekly (2022), 152:w30157
doi: 10.4414/smw.2022.w30157

Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 02 May 2022 | doi:10.4414/SMW.2022.w30157
Cite this as: Swiss Med Wkly. 2022;152:w30157

Legionnaires' disease – a qualitative study on Swiss physicians' approaches to the diagnosis and treatment of community-acquired pneumonia

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Summary

BACKGROUND: The number of reported cases of Legionnaires' disease has increased significantly over the last decade in Switzerland and abroad. Along with the number of cases, the volume of testing has increased as well, which has been partially attributed to a change in awareness of the disease. Yet, while there are numerous guidelines and recommendations for the case management of community-acquired pneumonia, little is known about how physicians in Switzerland perceive and manage Legionnaires' disease.

METHODS: This study aimed to investigate physicians' awareness of Legionnaires' disease, their information resources and their approach to the diagnosis and treatment of pneumonia (and thus Legionnaires' disease). Using a semi-structured interview guide, we conducted in-depth interviews with physicians from different levels of care and from the German-, French- and Italian-speaking regions of Switzerland.

RESULTS: We conducted 46 interviews with physicians from university, cantonal and regional hospitals as well as with general practitioners (GPs) from all three language regions. Overall, the physicians working in hospitals indicated a similar level of awareness of Legionnaires' disease, and comparable diagnosis and treatment approaches. The *Legionella* urine antigen test (UAT) was reported to be routinely performed in inpatients. In contrast, GPs indicated lower levels of awareness, reflecting the fact that they treat pneumonia cases empirically without identification of the causative agent, in accordance with current guidelines. The value of the diagnostic tests in general and the *Legionella* UAT in particular was considered to be dependent on the (preferred) antibiotic treatment approach. Some physicians saw the test as redundant, as its result would not influence treatment. This was tied to concerns about the UAT's sensitivity and its limited use for the detection of *Legionella pneumophila* serogroup 1. Lastly, extrinsic constraints, such as financial and time considerations also affected physicians' testing and treatment preferences.

CONCLUSION: Awareness of Legionnaires' disease is overall high, yet cases are mainly diagnosed and reported by hospitals. Improved diagnostic tools are needed to support physicians in reducing underestimation of Legionnaires' disease and optimise antibiotic stewardship without compromising patient health outcomes.

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Background

Legionnaires' disease is characterised by severe pneumonia and caused by the gram-negative *Legionella* spp. bacteria. In Switzerland, reporting cases of Legionnaires' disease to the National Notification System for Infectious diseases (NNSID) managed by the Federal Office of Public Health (FOPH) is mandatory [1]. Between 2008 and 2019, the number of reported cases has more than doubled, reaching an annual incidence of 6.5 cases per 100,000 population in 2019 [2]. At the same time, the burden of disease for Legionnaires' disease might be underestimated [3–5], due to under-ascertainment or underdiagnosis through lack of testing or limitations of the various diagnostic methods [6].

We previously investigated the trend of diagnostic test frequency for Legionnaires' disease and showed that the number of tests performed increased between 2007 and 2016, along with the number of reported cases [7]. During this period, the *Legionella* urinary antigen test (UAT) was most widely applied throughout all study years. Based on these data alone, the increase in testing and notified cases could not be explained. Particularly, there was no information available in the notification database to describe and contextualise these findings with regard to physician-related factors. The underdiagnosis of Legionnaires' disease has been partially attributed to a lack of awareness about the

Abstract

Background: The number of reported cases of Legionnaires' disease (LD)* has increased significantly over the last decade in Switzerland and abroad. Along with the number of cases, the volume of testing has increased as well, which has been partially attributed to a change in awareness of LD. Yet, while there are numerous guidelines and recommendations for the case management of community-acquired pneumonia, little is known about how physicians in Switzerland perceive and manage LD.

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Results: We conducted 46 interviews with physicians from university, cantonal and regional hospitals as well as with general practitioners (GPs)* from all three language regions. Overall, the physicians working in hospitals indicated a similar level of awareness of LD and comparable diagnosis and treatment approaches. The *Legionella* urine antigen test (UAT)* was reported to be routinely performed in inpatients. In contrast, GPs indicated lower levels of awareness, reflecting the fact that they treat pneumonia cases empirically without identification of the causative agent, in accordance with current guidelines. The value of the diagnostic tests in general and the *Legionella* UAT in particular was considered to be dependent on the (preferred) antibiotic treatment approach. Some physicians saw the test as redundant, as its result would not influence treatment. This was tied to concerns about the UAT's sensitivity and its limited use for the detection of *Legionella pneumophila* serogroup 1. Lastly, extrinsic constraints, such as financial and time considerations also affected physicians' testing and treatment preferences.

Conclusion: Awareness of LD is overall high; yet LD cases are mainly diagnosed and reported by hospitals. Improved diagnostic tools are needed to support physicians in reducing underestimation of LD and optimise antibiotic stewardship without compromising patient health outcomes.

Keywords: Legionnaires' disease; *Legionella* , pneumonia; diagnostics; treatment; antibiotics; decision-making; qualitative study; health care

Background

Legionnaires' disease (LD)* is characterised by severe pneumonia and caused by the gram-negative *Legionella* spp. bacteria. In Switzerland, reporting cases of LD to the National Notification System for Infectious diseases (NNSID)* managed by the Federal Office of Public Health (FOPH)* is mandatory [Federal Assembly 2016]. Between 2008 and 2019, the number of reported cases has more than doubled, reaching an annual incidence of 6.5 cases per 100,000 population in 2019 [BAG 2021b]. At the same time, the burden of disease for LD might be underestimated [Fastl et al. 2020; Cassell et al. 2019; ECDC 2021b], due to under-ascertainment or underdiagnosis through lack of testing or limitations of the various diagnostic methods [Beauté, Robesyn, and Jong 2013].

We previously investigated the trend of diagnostic test frequency for LD and showed that the number of performed tests increased between 2007 and 2016 along with the number of reported cases [Fischer et al. 2020b]. During this period, the *Legionella* urinary antigen test (UAT)* was most widely applied throughout all study years. Based on this data alone, the increase in testing and notified cases could not be explained. Particularly, there was no information available in the notification database to describe and contextualize these findings with regard to physician-related factors. The underdiagnosis of LD has been partially attributed to a lack of awareness about the disease among physicians, while growing case numbers likely represent increased awareness (and hence, testing and case detection). For example, Ticino, a canton in the south of Switzerland has a notification rate four times higher than the rest of Switzerland, which is often attributed to a heightened awareness of local physicians leading to a cycle of confirmation biases. In other words, high case numbers lead to increased awareness and intensive testing, which in turn results in more cases identified [Gysin 2018]. Indeed, we have found that most diagnostic tests are performed in Ticino, yet there the positivity rate was also found to be the highest [Fischer et al. 2020b]. Hence, to explain the growing legionellosis test numbers, we need to understand the processes leading to diagnoses and diagnostics.

The diagnosis of LD is dependent on pneumonia case management. Pneumonia is often classified as nosocomial pneumonia or community-acquired pneumonia (CAP)*. For the purpose of this study, we focused on CAP. Current case management is rooted in numerous available guidelines for CAP. The Swiss guidelines on the management of CAP in use at the time of the study (2019-2020), were published in 2006 by the Swiss Society of Infectious Diseases (SSI)* [Laifer, Flückiger, and Scheidegger 2006]. This guideline is based on the European Respiratory Society (ERS)*/European Society for Clinical Microbiology and Infectious Diseases (ESCMID)* Guidelines from 2005 [Woodhead et al. 2005] and was endorsed in the Swiss Government's latest document on legionellosis [BAG and BLV 2018]. In 2016, an update of the German CAP and lower respiratory tract infection (LRTI)* management guideline was published, which widened its scope to the Austrian and Swiss contexts [Hoffken et al. 2010; Ewig et al. 2016]. In 2021, these

guidelines received another update, with the SSI among its authors [Ewig et al. 2021]. The SSI updated the CAP guideline in their online collection as well [Albrich et al. 2021].

Most guidelines agree that microbiological investigation is generally only recommended for hospitalised patients or patients with severe CAP. CAP severity is frequently based on the CURB-65 or Pneumonia Severity Index (PSI)* score but should be individually assessed. There are minor differences in this recommendation, e.g. the SSI guideline from 2006 associating severe CAP, warranting a *Legionella* UAT, with intensive care unit (ICU)* admission [Laifer, Flückiger, and Scheidegger 2006]. LD testing is also recommended when clinically and epidemiologically suspected. Since the clinical presentation of LD does not differ from other atypical pneumonias, both indications for LD testing (disease severity and suspicion) are subject to interpretation. Therefore, efforts were made to develop a scoring system to identify *Legionella* infections based on clinical parameters, some of which have proven useful in recent validation studies [Miyashita et al. 2019; Bolliger et al. 2019; Ito et al. 2017; Cunha 2008; Fiumefreddo et al. 2009]. The causative pathogen guides the pneumonia treatment. For *Legionella* infections, antibiotic treatment that can reach high intracellular concentrations (e.g. fluoroquinolones or macrolides) significantly decreases mortality from 60-70% to 10-20% [Phin et al. 2014; Velazco 2020].

Physicians' acceptance and uptake of recommendations for the management of LD and their use of subjective testing guidelines has been largely unexplored. It is unclear what factors influence decision-making from the assessment of a patient with symptoms of LRTI to the initiation of detailed clinical investigations for LD. The aim of this study is to explore physicians' awareness of LD and their decision-making processes regarding the clinical management and of CAP in Switzerland. Investigating the decision-pathway for diagnosis (or diagnostics in particular) of LD and the role of corresponding guidelines and other influencing factors provides essential insights into explanations for the increase in testing and determinants of LD underestimation to further contextualise increasing reported case numbers.

Methods

Study design

We conducted qualitative face-to-face in-depth interviews with Swiss physicians using a semi-structured interview guide (Table 9.1). We asked physicians about (1) their diagnosis and management of CAP, (2) awareness and knowledge about LD in Switzerland, and (3) their approaches to diagnosing and managing LD. The interview guide was designed following a review of national and international guidelines for the management of CAP. It was purposively designed to allow for a general discussion of pneumonia before prompting participants to discuss LD specifically. We collected feedback from the FOPH and tested the

interview guide with selected physicians. The interview guide was further refined with the data collection team and during the interviews, e.g. to prioritise questions in case the interview was running over time.

Table 9.1: Overview of the semi-structured interview guide for in-depth interviews on pneumonia and Legionnaires' disease (LD)* with physicians in Switzerland.

Topics	Sample questions
Information sources and guidelines	• Do you consult guidelines to diagnose and treat pneumonia? If so, which ones? • Assuming that you have enough time and that all costs are covered, would you like additional training? What should this training cover?
Pneumonia diagnosis	• Could you walk me through a typical approach for diagnosing and treating a patient presenting with an acute respiratory infection/pneumonia? • Do you initiate aetiological testing? When? Why? How often?
Experience with Legionnaires' disease	• LD may not be so common in daily practice – What do you know about LD? Have you ever treated a patient with LD? Could you describe this instance(s)?
Opinions on Legionnaires' disease	• Could you describe the main challenges in obtaining adequate information on LD? • Do you think we miss LD cases in Switzerland? Why?

Additionally, we collected participants' demographic data including location, years of clinical practice and current position.

Sampling strategy

Physicians who encounter pneumonia patients in daily practice were eligible for participation. We purposively sampled a wide variety of physicians of all care levels in order to examine an array of possible diagnostic pathways. We aimed to enrol six physicians per language region and health care level. To recruit hospital physicians, we compiled a list of primary, secondary and tertiary hospitals and aimed to cover most cantons. First contact was made with the hospital secretariat, which distributed the recruitment letter, and informed consent forms in their departments. We started with the interviews at the largest institutions, typically the university hospitals. We randomly selected GPs at family medicine practices

from a publicly available registry and contacted them directly. The selection of GPs was based on the same regional stratification criteria as for hospital-based clinicians. After the initial interviews, we recruited more physicians using the snowball system in accordance to the strata defined above. We stopped data collection upon reaching data saturation.

Data collection and processing

Data was collected between October 2019 and February 2020. We obtained written informed consent from all participants before conducting the interviews. The interviews were audio recorded. Six female interviewers, from backgrounds in medicine, biomedicine, sociology and ethnology were trained in qualitative data collection. They conducted interviews in German, French, and Italian. The interviews lasted between 30 and 60 minutes and took place in the physicians' offices and workplaces (N=41) or online/ telephonically (N=5).

We transcribed interviews verbatim and translated them to German or English (depending on the data collectors' language skill). For quality control reasons, four interviews were translated independently by two researchers. The interviews were organised and processed applying the framework method [Gale et al. 2013]. We used MAXQDA to analyse the transcripts. We used the consolidated criteria for reporting qualitative research (COREQ) to organise and report our results [Tong, Sainsbury, and Craig 2007].

Data analysis

We analysed the interview transcripts using thematic analysis, which involves coding excerpts of transcripts and identifying common themes in the data [Braun and Clarke 2006]. A coding tree was prepared a priori based on the interview guide and the research objectives, e.g. level of awareness of physicians or the different steps taken in the case management of pneumonia (such as anamnesis, aetiological testing and mandatory reporting). This tree was used to code three interviews independently by two researchers: FBF (doctoral researcher in epidemiology) and JF (MSc student in epidemiology). The coding of these interviews was discussed and the code tree adapted iteratively. One researcher (JF) then coded all interviews with the adapted coding tree. FBF and JF repeatedly met during this process to clarify any uncertainties or disagreements.

During this process, we identified several themes, which were not directly linked to the interview guide or our pre-existing knowledge and assumptions, but nonetheless came up repeatedly. We reiterated the coding process using the newly generated and developed, data-driven themes and codes (e.g. diagnostic uncertainty). This inductive analysis of the data allowed us to further consider the (unexpected) processes behind the interplay between diagnostics and treatment. In a final step, we held a workshop with the data collectors to validate the themes and conclusions of this study. MJD (postdoctoral medical sociologist) and

DM (senior epidemiologist) supervised the conduct of the study and the analysis and interpretation of the results.

Compliance with ethical standards

Ethical approval was obtained from the "Ethikkommission Nordwest- und Zentralschweiz" (ID 2019-01708). We do not identify any study participants by name to ensure participant confidentiality and anonymity.

Results

Study participants and themes

We interviewed 46 physicians. The sample of physicians was well-balanced based on language-region and employment at different health care levels (see Table 9.2 for details). More than 65% of interviewed physicians were male. At the time of the interview, participants' average years of medical practice was 23 years. On average, the physicians practicing at a university hospital had about ten years less medical practice than physicians working elsewhere did. Six physicians practiced at multiple health-care levels, e.g. working part-time in a cantonal hospital and in their own family medicine practice. Two of the interviewed GPs were part of a Sentinella study on LD [BAG 2019b].

Table 9.2: Characteristics of physicians included in the study on pneumonia and LD case management in Switzerland.

		N	**%**
Language region	German	12	26.1
	French	20	43.5
	Italian	14	30.4
Sex	Female	13	28.3
	Male	33	71.7
Health care level	GP	19[a]	41.3
	(Median years of medical practice: 23)		
	Regional hospital	13	28.3
	(Median years of medical practice: 29)		
	Cantonal hospital	12	26.1
	(Median years of medical practice: 28)		
	University hospital	9	19.6
	(Median years of medical practice: 13)		

Characteristics of physicians included in the study on pneumonia and LD case management in Switzerland. (continued)

		N	%
Speciality	Pulmonology	7	15.2
	Infectiology	11	23.9
	Emergency medicine	7	15.2
	General medicine	17	37
	Other	8	17.4
Years of medical practice	0-5 years	1	2.2
	5-10 years	3	6.7
	10-20 years	12	26.7
	20-30 years	16	35.6
	Over 30 years	13	28.9
Total		46	100

[a] Two (2) GPs participated in the LD Sentinella study [BAG 2019b]

In the following sections, we discuss five inter-related themes we identified during data analysis. These include (1) awareness of LD, (2) underestimation of LD, (3) treatment approaches, (4) the interdependency of diagnostics and treatment approaches and (5) the enablers and barriers affecting all other identified themes. In Figure 9.1, we visualise the relationship between the themes. For example, physicians' education and awareness of the guidelines strongly influenced their awareness about LD. Awareness around LD and/or existing pneumonia guidelines impacted both clinical and public health aspects. On the clinical side, awareness informed the diagnostic testing and treatment approaches, which are mutually dependent on each other.

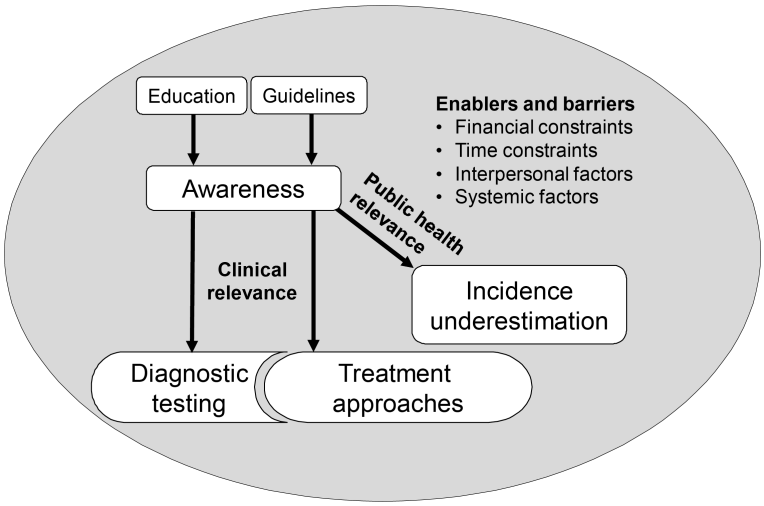

Figure 9.1: Overview of the themes and their relationships with each other which emerged from the in-depth interviews with 46 Swiss physicians on pneumonia and Legionnaires' disease.

Hospital physicians and GPs reported different levels of awareness about *Legionella* as a possible cause for pneumonia

Overall, physicians demonstrated a high level of awareness of LD by including it in their considerations for pneumonia diagnosis, before we specifically prompted them about it during the interviews. Additionally, many physicians were able to provide details on host and exposure risks, the clinical presentation, treatment and the transmission routes and prevention efforts. Physicians from Ticino were also well aware of the high LD incidence in their region. Physicians working in hospitals demonstrated the highest level of awareness and in-depth knowledge. They reported a large emphasis on LD during their education, both initial medical school training and in continuing education. One hospital physician described:

> "I feel that there is enough knowledge about LD. Somehow, as a medical student, pneumonia is drummed into you. If you have something less typical, then it is always *Legionella* -not Coxiella or tularaemia. Tuberculosis or *Legionella* are the big two to think about when you do not have a normal bacterial pneumonia. I have the feeling that it is also somewhat a mystified disease. You know [that it is LD], I think, even if you haven't had anything to do with it for a very long time." (University hospital in the German-speaking part of Switzerland, female, 13 years medical practice)

The few physicians that self-reported being unaware were all GPs. Most GPs stated never having encountered a LD case in their practice, or would likely not be aware if they had. After referral of patients with severe pneumonia to the hospital, GPs explained that thereafter they often do not learn about patients' outcomes in detail. Due to this lack of feedback and the rarity of LD, after several years of practice, some physicians might fail to recall LD. One physician explained:

> "There are things that I learned in medical school that I just never saw again. In addition, to be honest, I don't even know what [LD] is and I don't really have the intellectual concepts available anymore either. [...] If I am no longer exposed to these things, then they disappear from my professional life. However, I am aware that I don't know some things. And if [the patient] doesn't really make progress, then I'm pretty quick with referrals." (GP in the French-speaking part of Switzerland, male, 23 years of medical practice)

However, GPs did not perceive this lack of in-depth knowledge as problematic. They saw their responsibility in triaging patients (i.e. referring them to the hospital or specialists when necessary) and initiating timely empirical antibiotic treatment in pneumonia patients, which did not necessarily entail identifying the causative pathogen.

Physicians overall agreed that the incidence of Legionnaires' disease in Switzerland is underestimated

Despite the high awareness for LD, most physicians believed that the incidence is underestimated in Switzerland. Three main reasons for underestimation were named. First, many physicians agreed that

LD cases presenting with mild pneumonia on an outpatient basis would be missed due to omission of the etiological investigation. Second, few cases might be missed due to oversights in ordering the diagnostic tests or limitations of the tests themselves. Third and foremost, for a large proportion (estimated to 30-50%) of pneumonia cases no causative agent can be found even if etiological investigation is attempted. One physician explained:

> "Unfortunately, for probably the vast majority of our pneumonia patients, even if we do good diagnostics or standard good diagnostics, - not scientifically good diagnostics -, but routine diagnostics, we find no pathogen. That's more common [among pneumonia patients] than pneumococcus [laughs]." (Cantonal hospital in the German-speaking part of Switzerland, male, 37 years of medical practice)

Even considering the underestimation, most physicians did not consider *Legionella* spp. as an important pathogen for pneumonia. In this regard, some physicians mentioned a limited clinical relevance of *Legionella* as it can be treated appropriately and a minor public health relevance due to the low case numbers.

Physicians demonstrated diverging viewpoints for treatment approaches of pneumonia

Appropriate antibiotic prescription for pneumonia in general and LD in particular was perceived as a highly relevant topic. Many physicians steered the discussion toward the issue of antibiotic treatment. Depending on their treatment approach, interviewed physicians could be divided into two groups: 1) those who encourage testing and targeted antibiotic treatment and 2) those who promote empirical treatment with less testing.

The physicians in the first group, primarily hospital physicians, perceived the results of diagnostic tests as an opportunity to initiate targeted antibiotic treatment to reduce antibiotic resistance. While, most physicians were aware of this need, these physicians working in hospitals exhibited more ownership of that responsibility as part of their professional roles. Apart from impeding antimicrobial resistance, they also reported clinical considerations with fewer antibiotics prescribed resulting in fewer side effects and less negative effects on the microbiome. Especially macrolides, which are often used to treat LD, were noted to have adverse effects. One physician summarised the importance of diagnostic testing:

> "Unfortunately, too little emphasis is placed on carrying out regular diagnostics. In my opinion, doctors too often use a combination therapy with a macrolide or a quinolone and also use it for a relatively long period [...]. [With good diagnostics] we can deescalate the treatment, and we can use a narrow-spectrum antibiotic with a clear conscience. This means less side effects, less negative effects on antimicrobial resistance and less negative effects on the microbiome. That's why it's important to me personally, that we put microbial diagnostics in the foreground again. [...] In many cases, it is only a viral pneumonia [...]. Then you don't have to treat with antibiotics. Viral pneumonia has a more severe progression if treated with antibiotics. Patients and especially the treating physicians need to be made aware of this, so nobody says, 'I gave an antibiotic to be on the safe

> side. It won't do any harm.' We know that it does harm." (Cantonal hospital in the German-speaking part of Switzerland, male, 37 years of medical practice)

In the second group of physicians, there was one primary through-line in favour of empirical treatment, whereby physicians favoured a pragmatic and maximalist approach to improve patients' health quickly. Most GPs belonged to this group, stating that improving the patient health was their priority. One physician commented:

> "You have to ask yourself the question: Will I provide better care if I do [diagnostic testing] than if I don't? And other doctors will answer you differently, but as an infectiologist with my experience, I tell you I don't need that most of the time. I do a good job with an empirical approach." (Cantonal hospital in the French-speaking part of Switzerland, male, 34 years of medical practice)

Physicians discussed how treatment and diagnostics for pneumonia are mutually dependent

In our interviews, questions about appropriate treatment could not be explored without discussing diagnostics. The *Legionella* UAT belongs to the standard tests for inpatient diagnostics. According to several physicians, their hospitals made adapted guidelines available, which supported the use of UAT for patients admitted to or presenting at the emergency ward with pneumonia symptoms. In contrast, GPs reported generally not testing for LD. If patients need to be referred to the hospital, GPs assumed that testing is initiated there. Regardless of the setting, the *Legionella* UAT was well known and the initial test of choice to diagnose LD to all physicians. While the test was primarily appreciated for its ease of use and rapid results, some hospital physicians and GPs expressed that the UAT was too costly and time-consuming to receive results, when it should and could be a point-of-care test. There were also concerns about the test's sensitivity, which closely tied together with the physicians' awareness of the limitations of the UAT to only reliably detect *Legionella pneumophila* serogroup 1 and their trust in the diagnostic tests. To address the UAT's limitations, hospital physicians in particular mentioned the usage of PCR diagnostics, but considered PCR mostly as a second line test if patients were severely ill or the UAT returns negative but the suspicion for LD is strong. Many physicians recognised problems in determining the aetiology, but they felt that this could only be solved by innovating in diagnostics rather than through adjustments on their case management side.

Physicians expressed two contrasting perspectives regarding the influence of an LD test result on treatment. These perspectives were contingent upon physicians' trust in diagnostics. On the one hand, some physicians reported that the result of a diagnostic test does not affect treatment. These physicians were particularly conscious of diagnostic uncertainty and would not deescalate the antibiotic treatment even if the UAT tested negative. One physicians described his decision-making process:

> "Given a [pneumonia] patient has a good disease progression what we don't know is when to stop a macrolide therapy? If I haven't confirmed [the diagnosis] with the UAT, that doesn't mean that I have ruled out an atypical pathogen. Because the test is too unspecific. Or it could be that I didn't look for [the pathogen] before starting the antibiotics, then it's possible that it can't be detected. I can't do a PCR on every patient due to cost reasons. So one treats perhaps a bit broader - empirically. [...] I think there is a small need for improvement; after all it depends on the diagnostics. And when microbiological diagnostics become more accessible, perhaps also cheaper and more precise, then this problem will be solved. [...] With *Legionella* if you have a negative UAT, other serotypes are not excluded. We have enough guidelines. I think it's the precision of the diagnostics [that need improvement]." (Regional hospital in Italian-speaking part of Switzerland, male, 13 years medical practice)

They also highlighted that a high degree of suspicion of LD should overrule the test result. On the other hand, some physicians reported to deescalate the antibiotic treatment if the UAT tests negative, as one physician explained:

> "We rely on these *Legionella* UATs and I think that if the UAT is negative, you [should] stop the *Legionella* therapy. I personally want to prescribe as few antibiotics as possible. If you already have a negative test result, then I rely on that. And I think - I checked - about 90% of the strains are covered [by the UAT]. It's not 100%, but it's very high." (Cantonal hospital in the German-speaking part of Switzerland, female, 19 years medical practice)

Physicians reported only a few instances, where they would add antibiotic prescriptions after a positive test result, since treatment would most often be initiated with an LD-active antibiotic. We also observed some uncertainty concerning the correct approach, which the comment below illustrates:

> "Recently, due to one or two pneumonia cases that were presented and discussed [in the internal hospital seminars], I became a little unsure. [...] We often say 'Ok, if the UAT is negative, then you can stop [the therapy] again'. I think that's not quite right." (University hospital in the German-speaking part of Switzerland, male, 6 years of medical practice)

Physicians recognised the existence of guidelines regarding pneumonia but described a complex decision-making path in clinical practice

Apart from adhering to guidelines and the clinical considerations physicians made when met with patients presenting with pneumonia/ LD, we noted during interviews that other more distal factors shaped the decision-making process in clinical practice. The factors most often mentioned were cost concerns (for both patients and the health systems), time constraints, lack of resources/equipment, and patients' expectations.

Most physicians were highly cost aware toward diagnostic testing. They believed that currently testing is not sufficiently targeted to at-risk patients resulting in a perceived unnecessary burden on the health system. As one interviewee said:

> "The aim is to focus more on [targeted] diagnostic tests. [We should be] really focusing on severe patients, as testing is worthwhile there, but for all others it is not needed. I think there is an overuse of diagnostic tests; we could save money if we would do it in a certain way... targeted to patients where the pre-test probability [of a positive finding] is higher." (University hospital in the French-speaking part of Switzerland, female, 17 years medical practice)

Yet, at hospitals, even though the physicians were cost conscious, they estimated testing accounts for a small portion of total hospitalisation costs only. Mostly GPs felt the need to save resources, which discouraged testing. They voiced concerns about being sanctioned or seen as a 'bad doctor', if they increased the diagnostic test volume. One GP noted:

> "I'm sure I missed legionellosis cases, but the problem is that there is so much pressure from the health insurance companies not to do examinations [i.e. aetiological tests], that I prefer saving my laboratory resources for follow-ups or other diagnoses [than LD]. Since the treatment is not going to be changed, there is just no point in making a specific diagnosis. [...] They should pay us for these diagnostic tests, and stop bothering us with cost issues. We can't be asked to work more and do more examinations and at the same time be punished for doing so. It just does not make any sense." (GP in the French-speaking part of Switzerland, male, 35 years of medical practice)

Overall, physicians saw antibiotics as too cheap and diagnostic testing as too expensive, which encouraged treatment with broad-spectrum antibiotics. Many physicians, in particular GPs, saw conflicting interests in promoting microbiological investigations for public health benefits (such as improved surveillance activities of pathogens and antimicrobial resistance), and the need for cost-effective and resource-saving treatment of patients.

Congruously, a lack of time was the next major consideration affecting testing and treatment decisions. Some physicians, particularly GPs, noted a lack of time to pursue continuing education and stay on top of current medical and public health advancements. Further, GPs noted that the prescription of broad-spectrum antibiotics was time-efficient, as it would lessen the need for follow-up with the patients. Overall, they saw a conflict in devoting time to continued education, the in-depth investigation of cases, the efficient care of many of their patients and timely referral once a case becomes complicated. As one interviewee put it:

> "I don't think [most doctors have enough knowledge on pneumonia], me included. We don't have enough time [to know everything]. As primary care providers, if we have patients with pneumonia, we just give Augmentin and wait and see what happens. And if it doesn't work, maybe we add a Klacid and that's how we do medicine. However, I'm convinced that's wrong and I'm convinced we don't have the time [to do better]. If I want to take good care of my patients, as a primary care provider, I have to draw a line somewhere and say 'I can treat uncomplicated pneumonia here in my clinic. If it gets difficult, I know exactly where to turn to.' However, I really think the body of knowledge has grown so much [...] I think we have a conflict there. We don't have that time anymore." (Regional hospital in Italian-speaking part of Switzerland, male, 31 years medical practice)

The lack of resources was exemplified by GPs generally not being able to perform the *Legionella* UAT in-house. In addition, hospital physicians questioned why the UAT was slow in delivering a test result and not more accessible, which they would see as an improvement in the LD diagnosis:

> "[The UAT] is a standard test, it's not particularly difficult. It can be carried out in almost every laboratory, even in small laboratories or in private laboratories. It is like a pregnancy test. I think it can be done as a point of care test by a clinician in the emergency ward. But it has to be done in an accredited laboratory and so the barrier to do it is actually large. If we could make it possible for the test to be carried out by GPs or in the emergency wards, then we would certainly improve diagnostics. In our laboratory, for *Legionella* , the 'tolerance time', the time until we get the result, is much too long. The test takes 15 minutes and if you send it to the laboratory, the result should be there in an hour. Now we only receive the result after four hours or even the next day. Then it's no longer a point of care test, that's our frustration." (Cantonal hospital in the German-speaking part of Switzerland, male, 37 years of medical practice)

Lastly, GPs reported prescribing antibiotics based on patients' wishes. They did note, however, that the frequency of patient requests for antibiotic treatment seemed to have declined over time. They also explained the need to justify expensive diagnostics for patients, which prevented them from costly testing. One GP gave an example:

> "When you are in a practice you are much more cost-conscious not only for yourself but also for the patients, because in the hospital everything is included in the flat rate but in the practice everything is charged separately. And you don't want to scare the patient [with the laboratory costs]; or you have to explain it to them because then patients come back to you and say 'I have received an 850 francs invoice from the laboratory!' Then you have to be able to justify it." (GP in Italian-speaking part of Switzerland, female, 22 years medical practice)

Overall, many physicians reported taking a variety of considerations and factors into account when deciding on a diagnosis and treatment pathway. However, GPs seemed to be most affected by constraints beyond clinical considerations.

Discussion

Through analysis of 46 in-depths interviews with physicians, we provide an in-depth, qualitative understanding of physicians' awareness on Legionnaires' disease (LD)* and practices for diagnosis and treatment in Switzerland. While we did not observe major regional differences, we found physicians working at hospital level regardless of regional, cantonal or university hospitals were comparable in their views and opinions, while GPs differed in comparison to hospital physicians in most aspects.

Previous research on the 'true' burden and the trend of LD suggested a lack of awareness or changing awareness as causes [Fastl et al. 2020; Cassell et al. 2019; ECDC 2021b]. However, we found no evidence supporting this hypothesis in our study; awareness about LD was generally high. Swiss physicians in our

sample see LD neither as a major public health threat nor as an emerging disease. This assessment seems to be based on the low number of contacts with LD patients and the fact that appropriate treatment for LD is available, regardless of whether the pathogen has been identified. Indeed, annually 'only' 6 to 7 cases per 100,000 inhabitants are notified. However, due to the on-going increase in case numbers, LD is now among the ten most notified disease among the 52 infectious diseases under surveillance in Switzerland [BAG 2020a]. Additionally, Switzerland has the second highest LD notification rate in Europe behind Slovenia (9.4 in 2019) [ECDC 2021b]. Nevertheless, almost all physicians in this sample agreed that LD is likely underestimated, primarily due to a small proportion of pneumonia cases, for whom microbiological investigation are initiated and an even smaller proportion, where it is successful [Carugati et al. 2018; Shoar and Musher 2020].

Additionally, diagnostic work-up of pneumonia and, therefore, *Legionella* seems to be limited to the hospital setting. Many physicians stated following internal hospital guidelines, where, in line with current Swiss guidelines, UATs were listed as standard test procedures for patients presenting at the emergency ward with pneumonia symptoms or for patients admitted to the hospital [Laifer, Flückiger, and Scheidegger 2006].

In contrast, GPs were well aware that aetiological testing is not recommended for outpatients presenting with mild pneumonia symptoms. Considering that GPs often do not know the causative agent of a pneumonia they treat and are, therefore, not consciously confronted with LD cases, they tend to be less sensitised to LD than doctors working in hospitals. It is likely that most notified LD cases in Switzerland are treated in the hospitals. Yet, this also implies that patients with mild symptoms being treated in an outpatient setting will not be diagnosed and LD cases could potentially be missed. Hence, disease severity (and its assessment) and health-seeking behaviour likely influence testing and, therefore, case numbers.

Several assessment scores exist to assist the physicians in determining the disease severity of CAP, such as the PSI and the CURB-65 respective CRB-65 score, all of which are listed in the 2006 SSI guideline [Laifer, Flückiger, and Scheidegger 2006; Widmer and Bachli 2012; Lim et al. 2009]. In the last decade, several additional scores were developed and validated to differentiate LD from pneumonias of other origins based on clinical parameters [Miyashita et al. 2019; Bolliger et al. 2019; Fiumefreddo et al. 2009]. Yet, none of these scores were specifically mentioned in the interviews and were not at the forefront of the physicians' considerations. Consistent with the low emphasis on these scores, a 2012 study showed that the CRB-65 is not routinely assessed in Switzerland [Widmer and Bachli 2012]. Without objective parameters to assess disease severity, the decision for testing is subject to the physicians' empirical intuition. While most of the hospital physicians in our study demonstrated high awareness of the clinical signs and risk factors for LD, and reported that their current level of education and training was adequate, there was considerable uncertainty about narrowing down the population-at-risk who warrant testing.

In our interviews, we found two contrasting attitudes toward treatment and diagnosis: (1) low confidence in diagnostics and a preference for empirical treatment; and (2) a preference for diagnosis in favour of narrow-spectrum antibiotics. The UAT is the most commonly used diagnostic test for *Legionella* infections in Switzerland [Fischer et al. 2020b]. The physicians from this study highlighted several features that they appreciated about these tests. Nonetheless, confidence in the accuracy of the UAT is interlinked with its use and the approach to antibiotic treatment. Some physicians would continue treatment even with a negative test result, as they were cautious regarding the sensitivity of the UAT and its limitation of only detecting *Legionella pneumophila* serotype 1.

Indeed, a systematic review found a sensitivity of 0.74 for the UAT and reported a rate of 26% false negatives [Shimada et al. 2009]. A more recent study found an even higher false negative rate of 44.4% [Muyldermans et al. 2019]. Several publications suggested that the UAT should be used solely to confirm (the presence of) *Legionella* , but not for ruling it out [Shimada et al. 2009; Rojas, Naqvi, and Balakrishnan 2021]. Therefore, from a clinical perspective and in cases where antibiotics with *Legionella* spp. coverage has already been administered, it could be argued that an UAT need not be performed at all if it does not further influence the treatment. However, a single centre study from Switzerland highlighted that in 90% of hospitalised cases, macrolide therapy was discontinued, once a UAT tested negative [Piso, Arnold, and Bassetti 2013]. Another Swiss study in 2004 showed that a negative UAT would lead to a shorter treatment duration than recommended, but not to withdrawal of macrolides or quinolones [Garbino et al. 2004]. After a positive UAT, non-*Legionella* targeting antibiotics were discontinued. The addition of antibiotics was of less importance, because *Legionella* was mostly covered already in the empiric treatment regimen. The 2006 SSI guideline does not specifically mention the de-escalation of therapy, but the 2021 S3 update devotes a chapter to this topic and antibiotic stewardship in general [Laifer, Flückiger, and Scheidegger 2006; Ewig et al. 2021].

Ideally, physicians could base their choice of appropriate treatment for a patient on scientific evidence, but the literature seems to be inconclusive. Some studies conclude that respiratory fluoroquinolones or a combination of a β-lactam with a macrolide is a superior empirical treatment strategy compared to β-lactam monotherapy [Garin and Marti 2016]. Similarly, it was found that the initial therapy with an antibiotic active against *Legionella* (quinolones or macrolides) reduces the likelihood of transfer to the ICU [Falcone et al. 2021] and treatment failure in severe CAP cases [Ott et al. 2012]. The latter study, however, cautions against the excessive use of fluoroquinolones. This is supported by Dutch researchers, who recently advised against the excessive use of quinolones in view of the low incidence of LD cases and recommended a diagnostic workup for *Legionella* based on the CURB-65 score [Henegouwen et al. 2017]. Other studies found that the increased use of narrow-spectrum antibiotics following an antibiotic stewardship intervention did not compromise patients' health outcomes [Schweitzer et al. 2021]. There was also the recommendation to use narrow-spectrum antibiotics for all patients except those with severe

pneumonia or a high risk for an adverse outcome [Piso, Arnold, and Bassetti 2013]. Harmonisation of the clinical implications of *Legionella* UATs could facilitate the decision-making for physicians and lead to more consistent testing and treatment approaches.

Previous research demonstrated a wide range of intrinsic (such as fear of negative health outcomes) and extrinsic (such as time pressure) factors that influence antibiotic prescribing behaviour [Rodrigues et al. 2013]. In our study, we found similar effects influencing not only treatment but also diagnostic approaches. In previous sections, we discussed the influence of extrinsic (patient-related) clinical considerations and intrinsic diagnostic uncertainty on physicians' decision-making. Other reported factors that affected diagnostic and treatment approaches were often systems-related, such as cost and time constraints.

For most physicians, financial considerations were paramount. Antibiotics are less costly than diagnostic tests, which account for the majority of hospital costs [Spoorenberg et al. 2014; Vestjens et al. 2018]. A Dutch study reported potential health care cost reductions from de-escalation of antibiotic treatment for a negative LD test result. However, such antibiotic de-escalation based on a negative UAT result is not always recommended according to Dutch guidelines [Vestjens et al. 2018; Wiersinga et al. 2012; Wiersinga et al. 2018]. In our study, hospital physicians - while cost-conscious - appeared less constrained by financial considerations than GPs.

The GPs' empirical approach to care (in line with current guidelines) likely accounts partially for the underestimation of LD cases, yet it is noteworthy that GPs felt the need to reconcile various demands. They reported lacking time for continuous education and in-depth investigation of individual patients, lacking the resources to perform diagnostic testing, and being under pressure to be cost-effective for patients and the health care system. The concern of being reprimanded or considered a "bad doctor" for overuse of diagnostic tests, could originate from the revised (and lowered) tariffs/reimbursement GPs can claim following tariff point revisions in the 2000s. Additionally, in Switzerland, the UAT may only be performed in accredited laboratories, which does not allow their use in in-house diagnostics of family medicine practices. Lastly, GPs seemed to be more affected by interpersonal factors and communication with their patients than hospitalists. GPs placed more emphasis on a diagnosis and treatment approach that was agreeable with the patient's wishes and expectations.

Diagnosing LD, i.e. using a diagnostic test, should serve two purposes: to improve patient outcomes and to promote public health by gaining knowledge on the spread of pathogens and their contribution to the burden of disease. The impact on individual and public health of not diagnosing LD is not obvious to assess. There is a lack of knowledge about the spectrum of disease severity in LD, since primarily severe i.e. hospitalised cases are detected. It can only be speculated how large the pool of mild cases is. Results from the German CAPNETZ study suggest that the numbers of hospitalised and ambulatory cases with *Legionella* infection are similar [Baum et al. 2008]. Furthermore, we do not know how many of the severe

cases could have been prevented through earlier detection at the GP level. From a public health perspective, diagnosing LD at the primary care level, which would reduce underestimation, supports accurate monitoring. It further guides future case management and potentially facilitates the identification of infectious sources, which allows the implementation of accurate prevention and control measures. However, rolling out the UAT to primary health care levels would be hampered by the lower test sensitivity in patients with mild symptoms [Blazquez et al. 2005]. In hospital settings, improved diagnostic methods is the most obvious approach to reduce the underestimation of cases, e.g. by heavily relying on PCR diagnostics as has been done in New Zealand [Priest et al. 2019]. The utility of *Legionella* clinical scores should also be further investigated. For individual health, empirical treatment might be sufficient, if there is little transition of undetected mild cases to severe hospitalised cases. If the burden of mild cases is found to be high, CAP guidelines should be adjusted.

Strength and limitations

To minimise bias, we aimed to limit LD prompts before and during the first part of the interview. Due to the purposive sampling, physicians who were either aware of LD or had a special interest in the topic might be overrepresented. Hence, the generally high level of awareness found might not be representative. However, this qualitative study aimed at uncovering realities and opinions that shape the awareness and testing (and case detection) approaches for legionellosis. The study was not designed to quantify our findings. We note however, that several GPs reported having limited knowledge which shows that, at least for them, knowledge and previous information was not a barrier to participation, but rather that these GPs saw the study as a platform to express their experiences and constraints.

Conclusion

Physicians in Switzerland showed high awareness of *Legionella* spp. and the LD disease system, suggesting that we should broaden the discussion of LD underestimation beyond a lack of awareness. A majority of LD notifications originate in the hospital settings since GPs rarely perform aetiological testing, which is as currently recommended. This implies that mild cases may not be detected. Physicians uniformly agreed that LD is underdiagnosed, largely due to a general difficulty in identifying the causative agent of pneumonia. Most study participants were aware of and reported testing and treatment decisions in adherence to the current guidelines. There are challenges in balancing multiple interests and constraints that affect physician practices. Specifically, this relates to clinical benefit to the patient, antibiotic stewardship, and time and cost efficiency for both the patient and the health care system. Physicians reported uncertainties towards the reliability of the UAT for LD and the correct approaches towards antibiotic stewardship and de-escalation of therapy. There is a need for better diagnostics to help physicians reduce underestimation of LD and improve antibiotic stewardship without compromising patients' health outcomes. Additionally, questions about the extent of missed mild LD cases and cases transitioning from mild to severe due to

non-diagnosing and ineffective treatment need to be answered to assess the public and individual health impact of non-testing at GP level and, therefore, the appropriateness of current guidelines.

Acknowledgments

We gratefully acknowledge the contributions of the following persons: Audrey Lanyan, Amélie Viret, Anja Orschulko, Deniz Dogan and Linda Eggs for supporting the data collection and the validation of the findings. Jean-Baptiste Puginier supported the translation of the interviews. We thank Julia Fanderl for supporting the coding and analysis of the data and Melina Bigler for reviewing the manuscript.

Statements and Declarations

Financial disclosure

This study was funded by the Swiss Federal Office of Public Health.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

Part IV

Who contracts Legionnaires' disease and why? Determinants of infection at population-level

Chapter 10

Impacts of weather and air pollution on Legionnaires' disease in Switzerland: a national case-crossover study

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This article was published in:
Environmental Research (2023), 233, 116327.
doi: 10.1016/j.envres.2023.116327

Environmental Research 233 (2023) 116327

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

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ARTICLE INFO

Handling Editor: Jose L Domingo

Keywords:
Legionnaires' disease
Legionellosis
Legionella
Weather
Climate
Air pollution

ABSTRACT

Background: The number of reported cases of Legionnaires' disease (LD) has risen markedly in Switzerland (6.5/100,000 inhabitants in 2021) and abroad over the last decade. *Legionella*, the causative agent of LD, are ubiquitous in the environment. Therefore, environmental changes can affect the incidence of LD, for example by increasing bacterial concentrations in the environment or by facilitating transmission.
Objectives: The aim of this study is to understand the environmental determinants, in particular weather conditions, for the regional and seasonal distribution of LD in Switzerland.
Methods: We conducted a series of analyses based on the Swiss LD notification data from 2017 to 2021. First, we used a descriptive and hotspot analysis to map LD cases and identify regional clusters. Second, we applied an ecological model to identify environmental determinants on case frequency at the district level. Third, we applied a case-crossover design using distributed lag non-linear models to identify short-term associations between seven weather variables and LD occurrence. Lastly, we performed a sensitivity analysis for the case-crossover design including NO_2 levels available for the year 2019.
Results: Canton Ticino in southern Switzerland was identified as a hotspot in the cluster analysis, with a standardised notification rate of 14.3 cases/100,000 inhabitants (CI: 12.6, 16.0). The strongest association with LD frequency in the ecological model was found for large-scale factors such as weather and air pollution. The case-crossover study confirmed the strong association of elevated daily mean temperature (OR 2.83; CI: 1.70, 4.70) and mean daily vapour pressure (OR: 1.52, CI: 1.15, 2.01) 6–14 days before LD occurrence.
Discussion: Our analyses showed an influence of weather with a specific temporal pattern before the onset of LD, which may provide insights into the effect mechanism. The relationship between air pollution and LD and the interplay with weather should be further investigated.

1. Introduction

Legionnaires' disease (LD), caused by inhalation or aspiration of the bacteria *Legionella* spp., is a severe form of pneumonia with a high case-fatality rate of 10% (Phin et al., 2014). Reported LD case numbers have been increasing in many countries, where the disease is surveyed. In the EU the notification rate increased from 1.4 cases per 100,000 population in 2015 to 2.2 in 2019 (ECDC, 2021). The US reported an increase from 1.9 to 2.7 cases per 100,000 population between 2015 and 2018. The reason for this widespread increase in case numbers remains unclear. Apart from improved disease surveillance, the design and maintenance of building infrastructure, and an ageing and increasingly susceptible population, Barskey et al. suggest that the geographical distribution and increasing seasonal frequency of reported cases in summer indicate weather patterns may play a role in increasing LD incidence (Barskey et al., 2022). Studies from the European Centre for Disease Prevention and Control (ECDC) and others also consider climate change as one of the potential drivers of the increasing temporal trend (ECDC, 2021; Walker, 2018).

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https://doi.org/10.1016/j.envres.2023.116327
Received 26 October 2022; Received in revised form 3 May 2023; Accepted 2 June 2023
Available online 22 June 2023

Abstract

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Introduction

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Legionella spp. are ubiquitous in the environment, particularly water, and grow optimally in stagnant, warm water (25 to 42 °C) [Fields 2008]. Therefore, most water reservoirs that aerosolise or evaporate are potential risk sources for infection [Orkis et al. 2018]. Numerous infectious sources have been reported ranging from residential drinking water [Buchholz et al. 2020], cooling towers, whirlpools, potting soil/compost, to fountains and wastewater treatment plants. Evidence stems mostly from outbreak investigations by mapping of cases and potential exposure sites using Geographic Information Systems (GIS) [Hammami et al. 2019; Nygård et al. 2008]. However, the largest part of all LD cases are community-acquired and not related to an outbreak. The few studies that have spatially investigated sporadic cases focused on cooling towers [Dunn et al. 2013; Ricketts et al. 2009]. As such the main sources of infection for sporadic cases remain unknown [Klamer et al. 2021; Heijnsbergen et al. 2015]. Apart from localised point sources in the environment, there are other population-level (i.e. environmental) determinants impacting LD incidence, such as neighbourhood characteristics (e.g. the percentage of poverty or vacant housing) [Gleason et al. 2016; Hunter et al. 2022]. Most of these environmental determinants have, however, not yet been explored in the Swiss context.

Weather, one of the better-researched environmental determinants, has been strongly associated with the occurrence of LD [Pampaka et al. 2022; Walker 2018]. Precipitation, high relative humidity [Braeye et al. 2020; Fisman et al. 2005; Gleason et al. 2016; Halsby et al. 2014; Karagiannis, Brandsema, and Van Der Sande 2009; Ricketts et al. 2009; Simmering et al. 2017] and warm temperatures [Beauté et al. 2016; Brandsema et al. 2014; Conza et al. 2013; Halsby et al. 2014; Karagiannis, Brandsema, and Van Der Sande 2009; Park et al. 2019; Simmering et al. 2017] before the disease onset were often reported as important risk factors. Other relevant risk factors that were less often identified included atmospheric pressure [Beauté et al. 2016; Gleason et al. 2016], low wind speed [Braeye et al. 2020; Gleason et al. 2016], high dew point

and low daily visibility [Gleason et al. 2016]. High vapour pressure was reported as a significant risk factor by Conza et al. [2013]. Yet, temperature, relative humidity and vapour pressure are all closely interlinked and most studies included relative humidity in their investigation rather than vapour pressure. Most of the studies faced similar limitations: Vapour pressure and temperature are almost perfectly correlated strongly hampering disentangling individual association with LD incidence. In addition, most of them had to accept limitations in spatial resolution, as the exposure data came from a limited number of weather stations and/or were averaged over a larger area. Lastly, the variable incubation period of LD of 2 to 14 days [Cunha, Burillo, and Bouza 2016], together with the high correlation between consecutive days' temperature and similar weather variables, make it difficult to select an appropriate timeframe for which an association with weather may be relevant. Most studies either calculated the odds ratio separately for each day or calculated the odds ratio averaged over a given time window. While the a priori definition of these windows can affect the observed associations, these models are also subject to exposure misclassification and autocorrelation [Braeye et al. 2020].

Despite the evidence that ambient air pollution has both short- and long-term effects on respiratory health [US EPA 2016; US EPA 2019] and the risk of respiratory infections [WHO 2021], the role of air pollution in LD incidence has received little study, both, alone and in association with weather [US EPA 2016; US EPA 2019]. One previous study investigated the short-term impact of particulate matter (PM)* on LD in Portugal and attributed part of a larger LD outbreak to a Saharan dust storm that yielded high PM_{10} concentrations and favoured aerosol formation [Russo et al. 2018]. As ambient air pollution is a complex mixture of compounds including PM and volatile pollutants, such as NO_x or ozone (O_3), it is often difficult to disentangle the harmful effects of different pollutants individually. Similarly, the strong association between weather and air pollution makes it difficult to estimate interaction and causal associations concerning LD infections [Bäumer and Vogel 2007; De Sario, Katsouyanni, and Michelozzi 2013].

In Switzerland, LD is included in the national surveillance system for infectious diseases and case numbers doubled in the last decade reaching approximately 560 cases in 2021 [BAG 2022d]. Similar to other countries, the cause for the increase remains widely unknown, but distinct epidemiological features such as a pronounced seasonality with most cases occurring between June and September are observed [Fischer, Mäusezahl, and Wymann 2022]. There is also a clear regional distribution of cases in Switzerland [Fischer, Mäusezahl, and Wymann 2022] with the southern canton of Ticino constantly reporting the highest notification rates in the country. The reason for this divergence is unclear, yet studies on the positivity rate and physicians' testing behaviour suggest that this is not due to a difference in testing and reporting behaviour alone [Fischer et al. 2020b; Fischer, Deml, and Mäusezahl 2022]. In Switzerland, the Alps act as a barrier between the South and the North of the country. Hence, the regions north of the Alps are influenced by the Atlantic Ocean resulting in mild, humid winters and drier summers, while the southern region is influenced

by the Mediterranean Sea resulting in even milder winters and warm and humid summers. One study investigated the difference in incidence and weather between Ticino and a region north of the Swiss Alps and found that higher vapour pressure in Ticino significantly increased the risk of developing LD [Conza et al. 2013]. While air pollution has strongly decreased in Switzerland since 1985 [BAFU 2021], ground level concentration limits are still surpassed regularly, particularly for tropospheric ozone [BAFU 2021]. The daily thresholds for PM are also exceeded multiple times each year, and the highest measurements are being recorded in Ticino. Gaining evidence on the potential role of air pollution in LD incidence is therefore particularly relevant to inform future public health policies.

The aim of this study was to understand the role of environmental factors on the reported number of community-acquired LD cases in Switzerland. We conducted a series of comprehensive analyses exploiting the Swiss LD notification database in conjunction with detailed spatial data to: (1) understand the spatial distribution of LD cases at cantonal and district levels and identify spatial clusters of LD; (2) elucidate the ecological determinants of LD and (3) study the association of short-term weather and air pollution on LD incidence. The latter used a case-crossover design with unaggregated case and exposure data as well as distributed non-linear lag models (DLNMs)* to address the common shortfalls of weather-association studies and to achieve high temporal and spatial resolution across Switzerland. An overview of the analytical approaches is depicted in Figure 10.1.

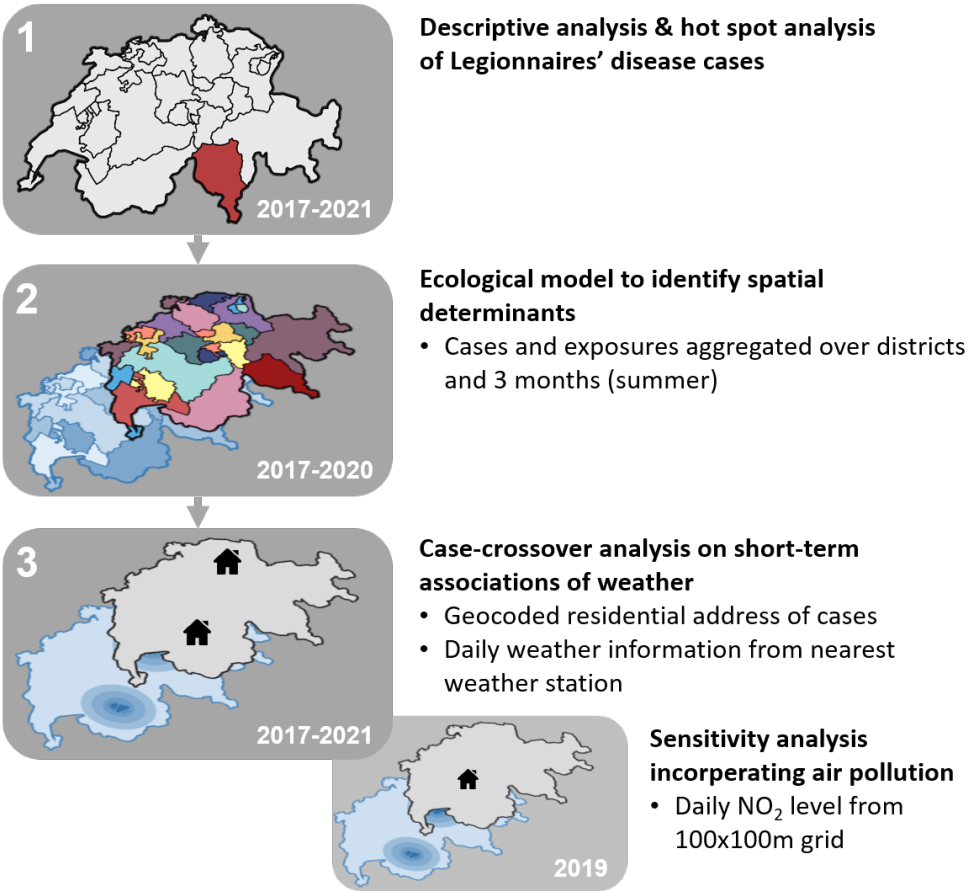


Figure 10.1: Overview of the analytical approaches presented in this paper. All analysis were based on the Swiss national notification data for Legionnaires' disease from 2017 to 2021. The first analyses comprised of a descriptive and hot spot analysis. The second analyses was an ecological regression model using various environmental exposures (such as wastewater treatment plant locations or degree of urbanisation). The third analysis was a case-crossover analysis on the short-term association of weather with LD cases. The third study incorporated a sensitivity analysis restricted to 2019 but incorporating air pollution data (daily NO_2 levels).

Methods

Study design, Legionnaires' disease notification data sources, access and processing

This is a longitudinal retrospective study utilising routinely health data for LD collected from the National Notification System for Infectious Diseases (NNSID)* in Switzerland. While notification rates also measure case capture, these estimates are usually the closest approximation to the true incidence of the disease, and the terms are, therefore, often used interchangeably in this context [Braeye et al. 2020; BAG

2022e; Conza et al. 2013]. We considered disease notifications from 1 January 2017 to 19 November 2021. We applied the case definition of the Federal Office of Public Health (FOPH)* [Gysin 2018] and included only confirmed and probable community-acquired LD cases for the analysis as a proxy for disease incidence. As our analyses ultimately lead to an individual-level analysis in relation to environmental exposures around the home location, we excluded cases where the suspected exposure occurred elsewhere, such as travel-associated, nosocomial and occupational LD cases. Further, we excluded all cases with residency outside of Switzerland and cases with missing demographic information (age and sex). Residential information was geocoded using the geocoding tool of the Federal Office of Topography (swisstopo)* [swisstopo 2019], and cases without known residency at district-level were excluded.

Exposure data

Environmental and population-level determinants

For the ecological model, we compiled the geolocations of the following suspected LD exposure sources and population-level determinants and calculated the average 'exposure' levels aggregated at district-level: freshwater bodies, air pollution and weather, wastewater treatment plants, composting plants, socio-economic position and age of the population, degree of urbanisation, land use and population density. More details on the data used for the ecological model is summarised in Appendix H, Table S1, including data source, temporal and spatial resolution.

Meteorological and air pollution data

Meteorological data were obtained from the Federal Office for Meteorology (MeteoSwiss)* for daily mean air temperature 2 m above ground, daily mean relative air humidity 2 m above ground, daily total precipitation, daily mean vapour pressure 2 m above ground, daily mean wind speed (scalar), daily maximal gust peak (one second), and daily mean atmospheric pressure at barometric altitude (QFE)*. Data were obtained for 191 weather stations in Switzerland for the timeframe from 1 November 2016 until 19 November 2021. Meteorological data were checked for implausible values and outliers. Outliers were defined as measured values that deviated more than a predefined cut-off value (e.g. 20 °C for temperature) from predicted values. The prediction models were based on spatial coordinates, altitude and the daily median of the respective weather parameter across all weather stations included in the study as fixed effects and the site id of the weather station as random intercept.

We omitted monitoring stations with less than 75% data availability for precipitation and 80% data availability for all other weather variables. For the remaining stations, missing daily values of each variable were imputed using information from the meteorological stations with complete data (Appendix H, Table S2). To impute missing daily exposure values, we fitted separate linear regression models for each monitoring station and variable using daily values from all stations with complete data and including month, year and

Julian day as fixed effects (Equation 1). The models' performance was assessed by calculating the R^2 and adjusted R^2 comparing the imputed and measured variable values. In addition, temporal evolution of the imputed values were visually assessed for each monitoring station (example in Appendix H, Figure S1). Finally, all missing weather values were replaced by the imputed values.

$$W_{imp} = \beta_0 + \beta_1 \times month + \beta_2 \times year + \beta_3 \times ordinal\_day + \beta_4 \times W_4 + \ldots + \beta_n \times W_n \quad (10.1)$$

Where W_{imp} is the imputed parameter value, and W are the parameter values at monitoring stations with complete data.

All weather estimates were extracted at the home location of LD cases, defined as the values from the weather station closest to their home location for each weather variable individually. If the altitude difference between the home location and weather station was over 500 m, the second-closest weather station was selected. Only, if the second-closest station also had more than 500 m in altitude difference, the closest station remained selected.

Mean daily NO_2 concentrations were extracted for each case's home location from the spatio-temporal model estimating historical NO_2 concentrations in Switzerland at a fine resolution (100 × 100 m; daily estimates from 2005-2016, and 2019) described by Hoogh et al. [2019]. As the address-level information for LD cases was only available for 2017-2021, we could investigate the association between NO_2 concentration and LD incidence only for the year 2019.

Statistical methods

Descriptive and hot spot analyses

Descriptive analysis of data content and data quality were performed with the statistical software R Version 4.0.3 [R Core Team 2020], Stata Version 16 [StataCorp. 2019] and ArcGIS Version 10.6.1 [Esri 2011]. Notification rates, defined as the number of notified cases per 100000 resident population, were calculated using publicly available population statistics from the Federal Statistical Office (FSO)* [BFS 2021]. We used the Pearson correlation to assess correlation between the weather variables. P-values <0.05 were considered statistically significant.

The hot spot analysis was conducted using two global statistics (Getis-Ord General G and Global Moran's I) and two local statistics (Getis-Ord Gi* and Local Moran's I) and was based on the sex- and age-standardised notification rates for LD on district level (n= 143). Hot spots denote regions, where the notification rate is higher than the expected rate if the rates would be randomly distributed. Relationships

between districts were determined via 'zone of indifference', and distance bands selected using 'Incremental Spatial Autocorrelation' to ensure each district had at least one neighbour. The Local Moran's I analysis was conducted with 9'999 permutations. A false discovery rate (FDR) correction accounted for multiple testing in both local analyses.

Ecological model (district level)

An exploratory analysis using an ecological model was performed to investigate the association of LD case frequency with various environmental factors, including weather, air pollution ($PM_{2.5}$ and NO_2), data on the built environment (compost facilities, wastewater treatment plants, land use, urbanisation grade, population density), natural spaces (total shoreline and river length), and social environment (area-level Swiss socioeconomic position (Swiss-SEP)* and mean population age). We used univariable and multivariable negative binomial regression models to explore associations between LD case counts per district (adjusted for the population size) and exposure source densities (for count data; e.g. infrastructural exposure sources) or values (e.g. mean age of the population) using the log-transformed population size as offset (Appendix H, Table S1). Separate models were developed for $PM_{2.5}$ and NO_2. All models were adjusted for the number of compost facilities and wastewater treatment plants, length of shoreline and rivers per district. As well as the mean age, mean $PM_{2.5}$ and NO_2 levels, mean temperature, mean relative humidity and mean precipitation per district and land coverage ratio and category of degree of urbanisation and Swiss-SEP.

Case-crossover design (individual level)

The ecological model described above is based on aggregated data at the temporal and district levels, which help inform about relevant characteristics of the regions with increased LD notification rates and potential environmental candidates that can drive these differences. However, remaining bias resulting from regional differences not captured in the models cannot be avoided with this approach. To address this issue, we used LD infection data at the individual level and conducted a case-crossover study investigating the short-term impact of a set of meteorological (and air pollution) exposures at fine spatial and temporal resolution. The case-crossover is a self-matched study design where each exposure levels during the 'hazard period' (the period before the adverse outcome occurred) is compared with exposures in other periods where the case did not occur (disease-free period) (Figure 10.2). The self-matching procedure limits the risk of potential confounding by time-invariant characteristics (e.g. sex, socio-economic position, chronic comorbidities and other unknown regional confounding suggested by the high heterogeneity in regional notification rates), which are typical sources of bias in other observational study designs and ecological studies.

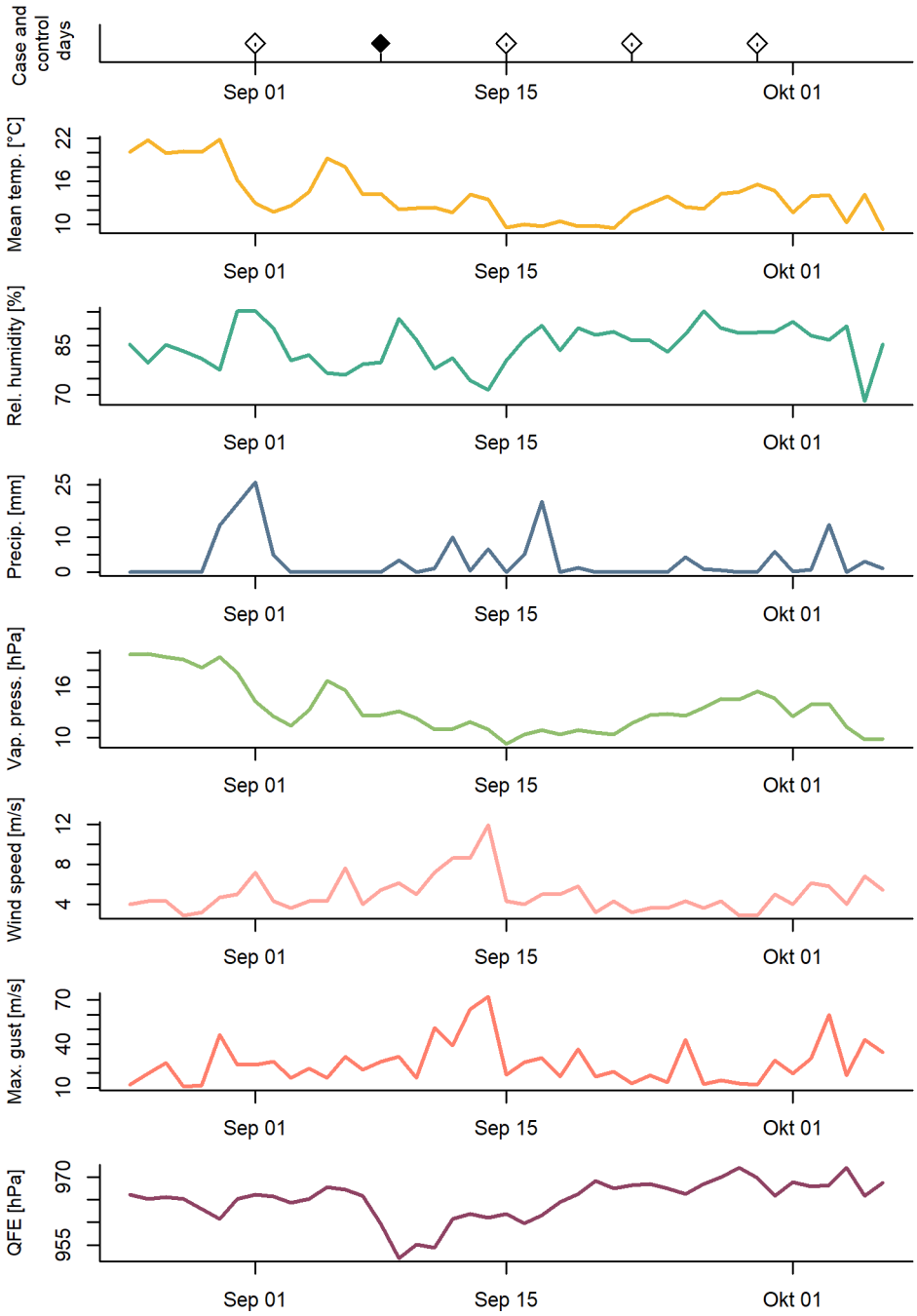


Figure 10.2: Illustrative example of the time-stratified case-crossover study design and the data. The first panel shows the case (black) and three control windows (white), which were chosen randomly before or after the case within the same month, for one individual. The lower panels show the time series of the weather at the residential address of this case.

To avoid any risk of bias due to seasonality and time-trends, the control periods were selected using a time-stratified sampling approach matched on the same weekday within the same month, leading to four to five control events for each case event, as previously described by Janes, Sheppard, and Lumley [2005].

We conducted single- and multi-exposure conditional logistic regression to estimate the association between individual weather exposures and the risk of infection by *Legionella* . First, we fit single-exposure DLNMs to estimate the association between individual exposures and the risk of infection up to 21 days prior to the onset of clinical manifestations (using the R package dlnm [Gasparrini 2011; Gasparrini and Armstrong 2013]). These lag periods were chosen as 21 days are a typical lag used when analysing temperature and weather effects on hospital admission and mortality [Gasparrini et al. 2015; Zhai, Zhang, and Chai 2021]. Further, it captures the typical incubation days for LD of 2 to 14 days [Cunha, Burillo, and Bouza 2016].

The lag functions were specified as a natural spline with one to three equally spaced knots on the logarithmic scale. The exposure-response functions were specified as: (i) a linear term for exposures with an expected linear association with LD (precipitation, gust, atmospheric pressure, relative humidity); (ii) a b-spline with two knots (50^{th} and 75^{th} percentiles of the annual distribution) for mean temperature; and (iii) a b-spline (1 knot at the median of the annual distribution) for vapour pressure. Models with the best fit were selected as the combination of lag- and exposure-response functions that led to the lowest value for the Akaike information criterion (AIC)*. Given the high correlation between mean daily temperature and mean daily vapour pressure (Pearson's correlation r=0.90), we constructed two separate multi-exposure models. All models were adjusted for regional school holidays, defined as the total number of days of holidays during the incubation period to account for travelling. We did not add a variable adjusting for the effects of the COVID-19 pandemic, as seasonal time-trends are naturally accounted for by the study design.

For easier interpretation, we estimated the odds ratio (OR)* of infection as the ratio between the odds at 0 and the odds at a sensible value: for mean temperature 20 °C, precipitation 10 mm, wind speed 20 m/s and maximal gust 20 m/s. For variables that only take positive values (atmospheric pressure, mean relative humidity and vapour pressure), we estimated the OR as the deviation from the median to the 5^{th} and 95^{th} percentiles of the annual distribution. To disentangle the role of environmental and weather conditions on different phases of the disease transmission, we present the overall odds ratios for three a priori selected exposure windows: 'Early incubation/ shortly before disease onset' (lag 2-6), 'Prolonged incubation period' (lag 6-14) and 'Before incubation' (lag 14-21).

Sensitivity analyses

We conducted the following three sensitivity analyses: (i) to validate the estimates from our DLNM models, we built 'simple' models using each weather variable's average over the most relevant lag days (as identified by the DLNM) as exposure variable and conducted single and multi-exposure conditional logistic

regression adjusted for school holidays. Further, these simple models provided estimates of the variation inflation factor and overall correlation between the different exposures, and helped inform and verify the validity of our DLNM multi-exposure models. (ii) Air pollution can change rapidly over time and is partly correlated with meteorological conditions, making it a possible confounding factor for our analyses. To rule out this potential bias and explore the effect of air pollution on LD, we considered data from 2019 for which individual daily NO_2 estimates were available. We compared our results from the DLNM and 'simple' models with and without additional adjustment for NO_2; and, (iii) Ticino has reportedly the highest LD notification rates and unique weather conditions. To ensure that no other time-variant factors special to Ticino bias our results, we ran a sensitivity analysis excluding all cases from Ticino.

Ethical approval

The study was conducted under the Epidemics Act (SR 818.101) [Federal Assembly 2016]. The study was submitted to the Ethics Committee Northwest and Central Switzerland (EKNZ), and was evaluated to be outside the scope of the Human Research Act (SR 810.30) [The Swiss Federal Council 2013] and, therefore, does not require ethical approval.

Results

Legionnaires' disease cases 2017-2021, description and hot-spot-analysis

Between 2017 and 2021, 2,854 cases of LD were reported in Switzerland. We excluded 376 cases with a 'possible' (N=151) or missing case definition (N=135), and 405 cases due to being categorised as 'travel-associated', 'nosocomial' or 'occupation-associated'. An additional 20 cases were excluded for the following reasons: missing sex (N=1), district (N=11) or non-Swiss residency (N=8). Six cases occurred after 19 November 2021 and were, thus, excluded from the analyses. In total, 2,047 cases of LD with an onset between 1 January 2017 and 19 November 2021 were included in the study (Table 10.1). Among the cases,

68.5% were males and 84.9% were over the age of 50 years. Most cases occurred in the summer months between June to August (40.3%).

Table 10.1: Legionnaires' disease cases and annual crude and age-and sex adjusted notification rates in Switzerland, 2017 - 2021

	Total (N=2,047)	**Annual notification rate per 100,000 population**	
		Crude	**Age- and sex-adjusted**
Sex			
Female	644 (31.5%)	3.0 (2.8, 3.2)	2.8 (2.6, 3.0)
Male	1,403 (68.5%)	6.6 (6.2, 6.9)	7.0 (6.7, 7.4)
Year			
2017	412 (20.1%)	4.9 (4.4, 5.4)	4.9 (4.5, 5.4)
2018	410 (20.0%)	4.8 (4.4, 5.3)	4.8 (4.4, 5.3)
2019	428 (20.9%)	5.0 (4.5, 5.5)	5.0 (4.5, 5.5)
2020	351 (17.1%)	4.1 (3.6, 4.5)	4.0 (3.6, 4.5)
2021	446 (21.8%)	5.1 (4.7, 5.6)	5.1 (4.6, 5.6)
Age in years			
20	3 (0.1%)	0.03 (0.01, 0.1)	0.03 (0.01, 0.1)
20- 49	306 (14.9%)	1.8 (1.6, 2.0)	1.7 (1.6, 2.0)
50- 79	1,315 (64.2%)	8.9 (8.4, 9.4)	8.9 (8.5, 9.4)
80	423 (20.7%)	18.8 (17.1, 20.7)	21.2 (19.1, 21.3)
Season[a]			
Spring (Mar- May)	340 (16.6%)	3.2 (2.8, 3.5)	-
Summer (Jun- Aug)	825 (40.3%)	7.7 (7.2, 8.2)	-
Fall (Sep- Nov)	557 (27.2%)	5.2 (4.8, 5.6)	-
Winter (Dec- Feb)	325 (15.9%)	3.0 (2.7, 3.4)	-
Greater region			
Central Switzerland	168 (8.2%)	4.1 (3.5, 4.8)	3.8 (3.5, 4.7)
Eastern Switzerland	183 (8.9%)	3.1 (2.7, 3.6)	3.0 (2.6, 3.5)
Espace Mittelland	431 (21.1%)	4.6 (4.2, 5.0)	4.4 (4.0, 4.9)
Lake Geneva Region	375 (18.3%)	4.5 (4.1, 5.0)	4.8 (4.4, 5.4)
Northwestern Switzerland	329 (16.1%)	5.6 (5.0, 6.3)	5.5 (4.9, 6.1)
Zurich	274 (13.4%)	3.6 (3.2, 4.0)	3.8 (3.4, 4.3)
Ticino	287 (14.0%)	16.3 (14.5, 18.3)	14.3 (12.6, 16.1)

[a] Notification rates were calculated using the annual population, hence there is no age- or sex difference between the seasons and only the crude rates are shown.

The annual age-and sex adjusted notification rates were highest in the greater region (NUTS-2 level, N=7 in Switzerland) of Ticino with 14.3 cases/100,000 population (CI: 12.6, 16.0). The lowest notification rates were observed in the region of Zurich (3.8, CI: 3.3, 4.3). In the canton of Ticino, the district of Lugano (20.6, CI: 17.7, 24.0) had a 33% higher notification rate than the district of Mendrisio with the second highest notification rate (14.0, CI: 10.0, 19.3) (10.3 A and B). Hot spot analyses, with the two local statistics Local Moran's I and Getis-Ord Gi*, both showed a significantly elevated notification rate in Ticino (10.3 C and D).

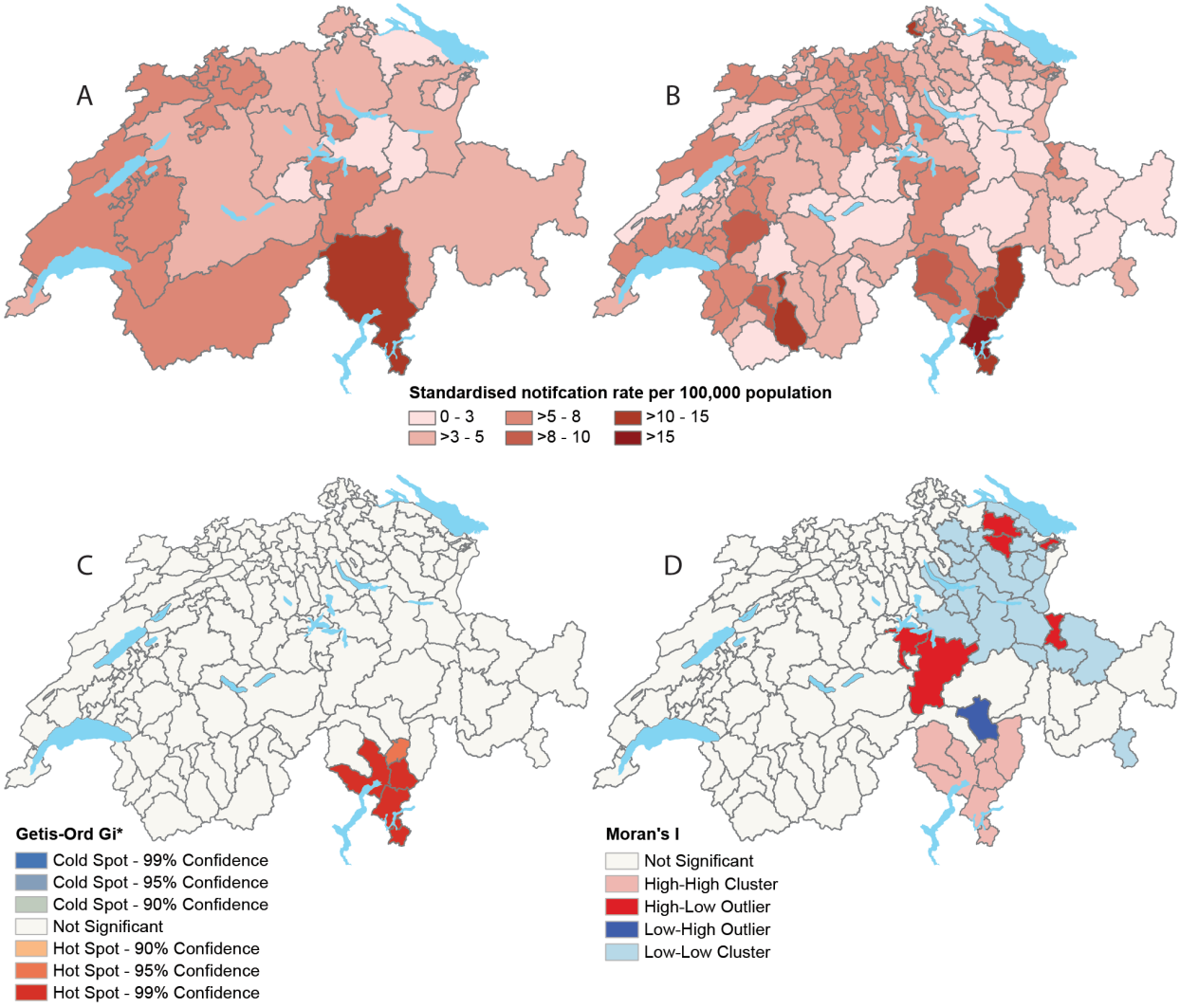


Figure 10.3: Distribution of Legionnaires' disease cases in Switzerland from 2017 to 2021. (A) Average annual notification rate across cantons (n=26). (B) Average annual notification rate across districts (n= 143). (C) Cluster analysis using Getis-Ord Gi* based on sex- and age- adjusted notification rates per district. (D) Cluster analysis using Local Moran's I based on sex- and age- adjusted notification rates per district.

Ecological model to identify spatial determinants (2017-2020)

We included 1,603 LD cases between 2017 and 2020. Since both $PM_{2.5}$ and NO_2 were statistically significant in the univariable model, and there is limited existing literature on the association of air pollution and LD occurrence, we developed one separate model for each air pollutant. Results from both multivariable regression analyses suggest that the relative humidity is negatively associated with LD occurrence (Appendix H, Figure S3). Higher air pollution concentrations ($PM_{2.5}$ and NO_2) were strongly associated with LD occurrence. Further, lower socio-economic position and older age were positively associated with LD occurrence on a district-level. Infrastructural and environmental exposures (e.g. wastewater treatment plants, lakes) were not found to be associated with LD case numbers, but effects could have been masked by aggregation across a larger area.

Case-crossover analysis on short-term determinants

Weather in Switzerland (2017-2021)

Weather data were linked to cases' individual locations based on proximity. For most cases (88.5%), a residential address was reported and used. If not available (11.5%), the geometric centroid of the reported residential municipality was used as address.

From the data of the seven weather variables of the 191 stations, only one value was implausible and set to missing. On average, the imputation models for missing weather data performed well (0.91 adjusted R^2) and only a few stations for the variables 'gust' and 'maximal relative humidity' scored an R^2 lower than 0.6 (Appendix H, Table S2). The median distance and median altitude difference of individual cases to the linked station was 5.4 km (range 0.1 to 32.6 km), respective 37 m (range: 0 to 630 m) (Figure 10.4).

In general, temperatures are cooler in the alpine regions all-year. Across Switzerland, Ticino is subject to most heavy rain events. The year 2018 was exceptionally warm with heat periods above 30° C across Switzerland and notable lack of rain during summer. The year 2019 had an equally hot summer but with more precipitation. The year 2020 was characterised by a mild winter, another hot summer and heavy rain events in Ticino (August and October) and the Lake Geneva region, Berne, and parts of Graubünden (October only). In 2021, June and July were exceptionally wet across Switzerland with heavy rainfall in Ticino and several flooding north of the Alps. Table S3 in Appendix H provides an overview of the weather conditions from the stations included in our study.

At address-level resolution, daily values of (i) mean vapour pressure and mean temperature and (ii) gust and wind speed (r=0.79) were strongly correlated with each other (Pearson's correlation r=0.90). Weaker correlated were mean temperature and mean relative humidity (r=-0.31), atmospheric pressure and vapour pressure (r=0.31), and precipitation and relative humidity (r=0.31).

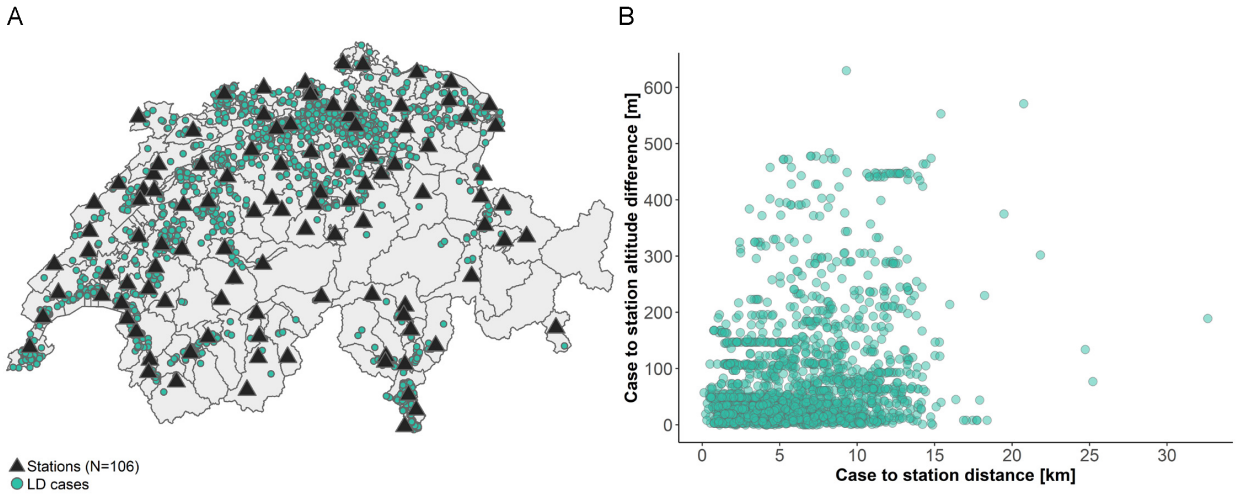


Figure 10.4: Assignment of weather exposure to Legionnaires' disease cases (2017-2021) on the example of mean daily temperature. (A) Map of all included Legionnaires' disease cases (2017-2021) in green and included weather stations measuring temperature (black triangles). (B) Linear distance and altitude difference of each case to the selected weather station measuring temperature.

The association between weather and Legionnaires' disease case occurrence (2017-2021)

We estimated the risk of *Legionella* infection for seven weather variables using single-exposure DLNM models (Table 10.2). Six of these variables were included in a multi-exposure model which also included either mean temperature (Model 1) or mean vapour pressure (Model 2), due to their high collinearity. We validated the models running simple conditional logistic regressions over either the statistically significant lag days or selected lag periods if no significant lag days were observed: For wind speed and maximum gust, we tested the lag windows proposed by Fisman et al. [2005] and selected the one with the best model fit

according to the AIC (1-5 days) (Appendix H, Table S4 and Figure S4). Overall, the results of the DLNM and simple models were consistent.

Table 10.2: Output for DLNM models using conditional logistic regression. Odds ratios and 95% confidence intervals for single-exposure and multi-exposure models for each weather variable. Due to collinearity, two models were constructed, once with temperature and the other with vapour pressure. All estimates stem from the mean temperature model (Model 1), except vapour pressure, which is based on the vapour pressure model (Model 2). The centre depicts the reference value selected for the prediction. The value depicts the value for which the overall odds ratio are estimated.

				Single-exposure		**Multi-exposure**	
Parameter	**Centre**	**Value**	**Lag period**	**OR**	**95% CI**	**OR**	**95% CI**
Temperature	0 °C	20 °C	2-6 days	0.91	(0.59, 1.42)	1.1	(0.69, 1.74)
			6-14 days	1.93	(1.20, 3.10)	2.83	(1.70, 4.70)
			14-21 days	1.77	(1.13, 2.79)	1.67	(1.01, 2.75)
Relative humidity	0.762	0.952	2-6 days	1.11	(1.01, 1.22)	1.08	(0.95, 1.23)
			6-14 days	1.43	(1.22, 1.68)	1.38	(1.11, 1.72)
			14-21 days	0.9	(0.78, 1.05)	1.06	(0.86, 1.31)
Precipitation	0 mm	10 mm	2-6 days	1.11	(1.01, 1.21)	1.05	(0.93, 1.19)
			6-14 days	1.47	(1.25, 1.73)	1.21	(0.98, 1.49)
			14-21 days	1.04	(0.88, 1.21)	1.01	(0.82, 1.24)
Vapour pressure[a]	9.2 hPa	18.1 hPa	2-6 days	1.02	(0.87, 1.20)	1	(0.84, 1.19)
			6-14 days	1.59	(1.22, 2.08)	1.52	(1.15, 2.01)
			14-21 days	1.3	(1.01, 1.68)	1.31	(1.00, 1.71)
Wind speed	0 m/s	20 m/s	2-6 days	0.97	(0.72, 1.31)	-	
			6-14 days	0.99	(0.59, 1.67)	-	
			14-21 days	0.87	(0.53, 1.43)	-	
Maximal gust	0 m/s	20 m/s	2-6 days	0.98	(0.90, 1.06)	0.95	(0.85, 1.05)
			6-14 days	1.03	(0.90, 1.19)	0.97	(0.82, 1.16)
			14-21 days	0.99	(0.86, 1.13)	1.04	(0.88, 1.23)
Atmospheric pressure	964.6 hPa	986.8 hPa	2-6 days	0.96	(0.78, 1.18)	0.89	(0.70, 1.15)
			6-14 days	0.59	(0.42, 0.83)	0.7	(0.47, 1.05)
			14-21 days	1	(0.70, 1.42)	0.94	(0.62, 1.42)

[a] Model 2 instead of model 1

Figure 10.5 shows the lag structure of 21 days for each weather variable in both the single-exposure and multi-exposure model (left-hand panel), and the cumulative odds ratio of the multi-exposure model for the different lag periods (right-hand panel). For example, Figure 10.5D shows the DLNM outputs for daily mean vapour pressure. The left-hand panel depicts the OR for an increase from 9.2 to 18.1 hPa across lags

0 to 21. Both the single-exposure and multi-exposure model show that vapour pressure has increased ORs 7 to 17 days before disease onset. The right-hand panel depicts the cumulative OR for each lag period '2-6 lag days before disease onset', '6-14 lag days' and '14-21 lag days'. The strongest associations can be seen for 6-14 lag days before the exposure, where the OR is around 1.3 (CI: 1.1-1.4) at 15 hPa daily mean vapour pressure.

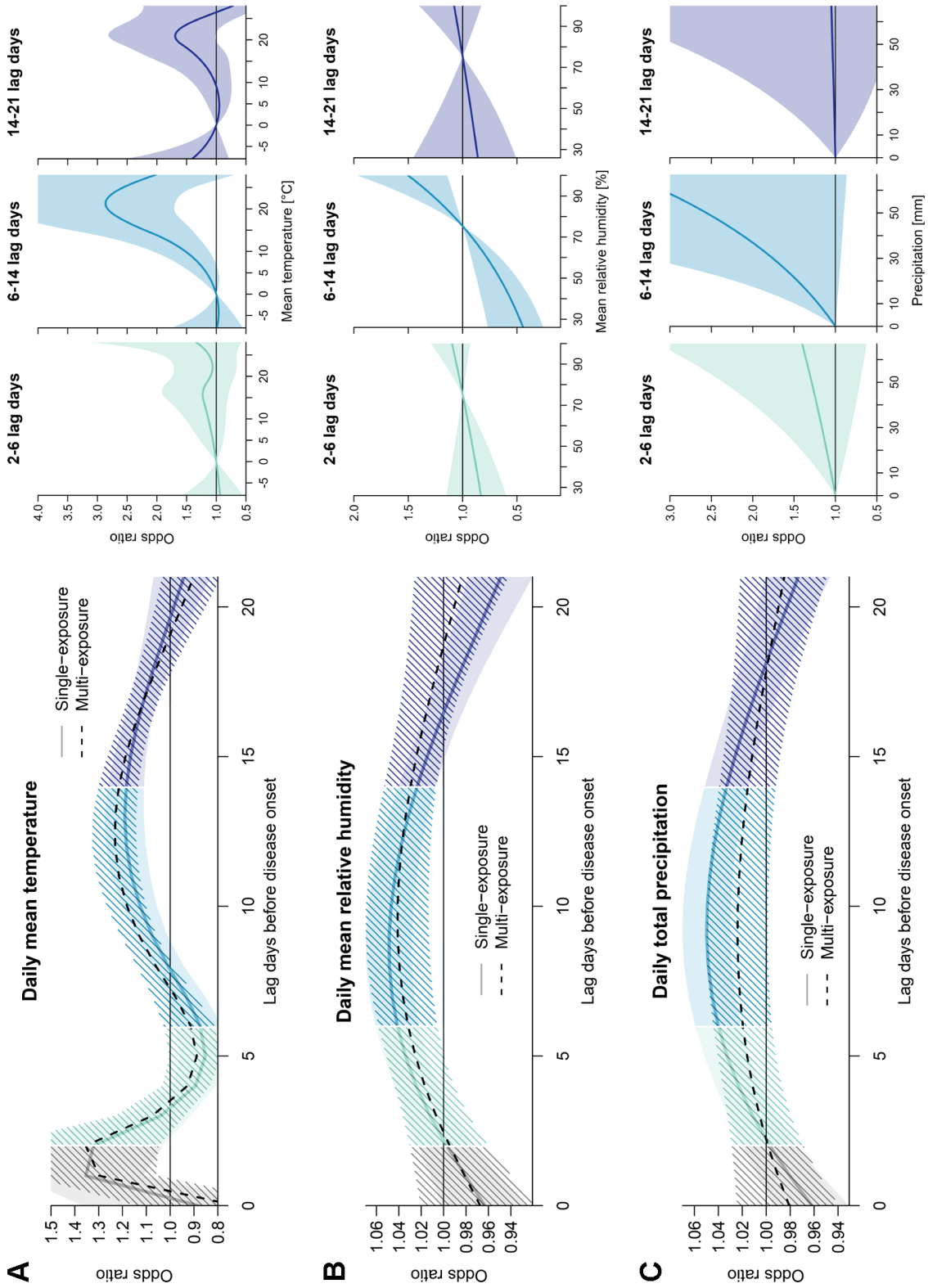
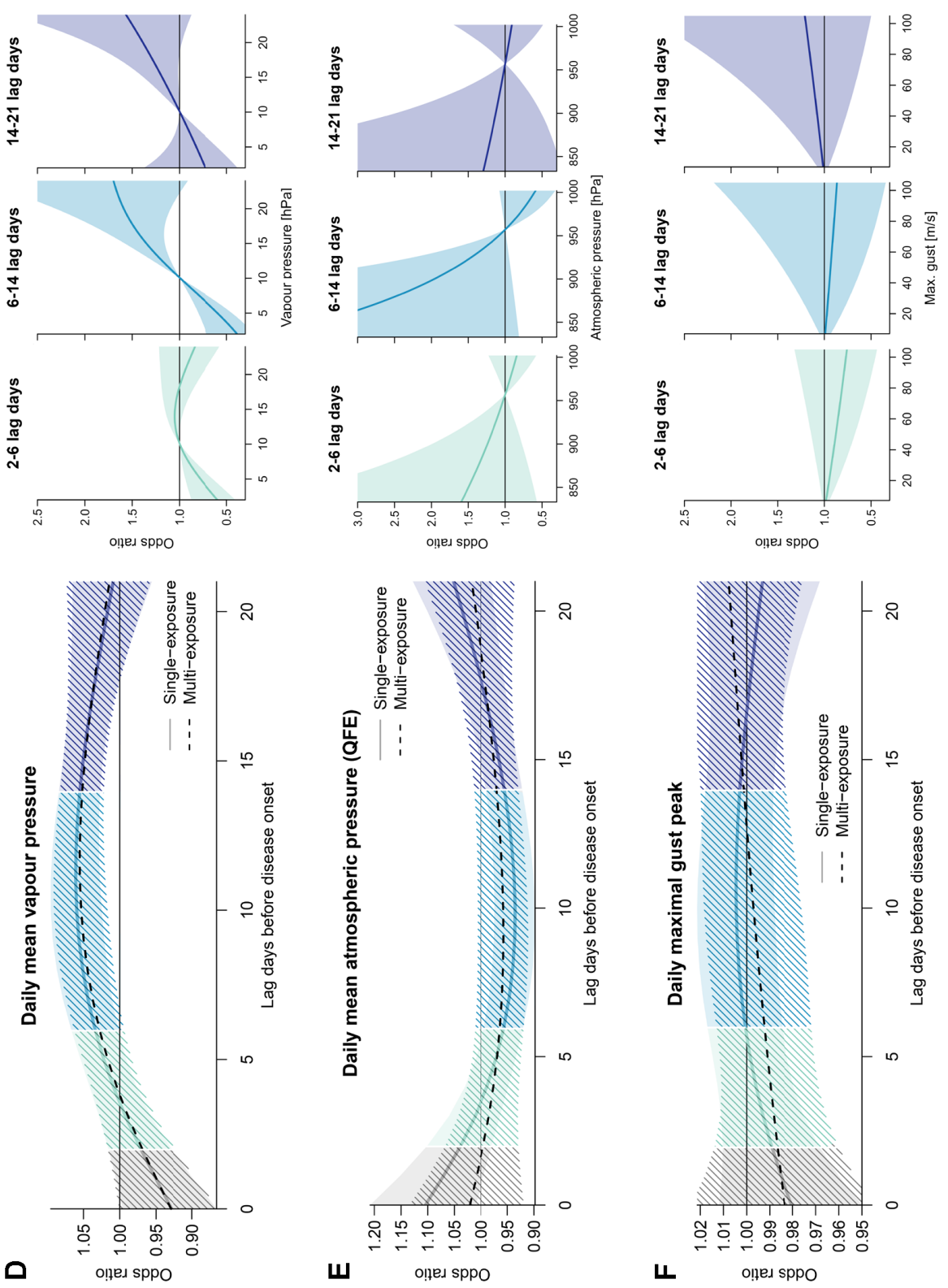


Figure 10.5: Short-term associations of seven weather variables with Legionnaires' disease onset (2017-2021). DLNM model output for (A) daily mean temperature, (B) daily mean relative humidity, (C) daily total precipitation, (D) daily mean vapour pressure, (E) daily maximal gust peak and (F) daily mean atmospheric pressure (QFE). The right-hand figure always depicts the lag structure across 21 days before the Legionnaires' disease onset. The left-hand figure depicts the overall odds ratio (OR) for three exposure windows: early incubation (lag 2-6), late incubation (lag 6-14) and before incubation (lag 14-21). The multi-exposure models included daily mean relative humidity, daily total precipitation, daily maximal gust peak and daily mean atmospheric pressure (QFE) and either daily mean temperature or daily mean vapour pressure, as well as a term adjusting for regional school holidays.


D
Daily mean vapour pressure
Odds ratio
Lag days before disease onset
Single−exposure
Multi−exposure
2-6 lag days
6-14 lag days
14-21 lag days
Vapour pressure [hPa]
E
Daily mean atmospheric pressure (QFE)
Atmospheric pressure [hPa]
F
Daily maximal gust peak
Max. gust [m/s]

The mean temperature showed a significantly increased OR at 20 °C compared to the baseline at 0 °C (OR 1.58, CI: 1.05, 2.37) shortly before the disease onset (lag 0-2 prior to first symptoms). Followed by stronger and longer lasting associations at the higher end of the incubation period (lag 6-14) and before the incubation period (lag 14-21) (Appendix H, Figure S5). Vapour pressure showed the largest OR in the single-exposure models in the 6 to 21 days before onset of the disease. Relative humidity and precipitation were significantly associated with LD notifications during the whole incubation time. Atmospheric pressure was only found statistically significant late in the incubation time (6-14 lag days) and the only weather variable that was negatively associated with LD relative risk.

The estimated direction of association remained consistent in the multi-exposure model. Mean temperature showed a large increase in effect size (OR 2.83, CI: 1.70-4.70), while precipitation and atmospheric pressure were no longer significantly associated.

Sensitivity analysis including daily mean NO_2 (2019)

Only for the year 2019, data for both, LD case residential addresses and NO_2 concentrations, were available. Therefore, for a subset of 426 LD cases, the associations with air pollution could be analysed using the same methodology as for the weather variables.

With data restricted to 2019, the analysis (including weather) does not have enough data points to lead to a conclusive result and should be interpreted with caution (Appendix H, Table S5). NO_2 was most strongly correlated with temperature (r=-0.4) and vapour pressure (r=-0.36). In the single-exposure models, only relative humidity and precipitation remained significant with relative humidity having an OR of 1.23 (CI: 1.00, 1.52) 2-6 lag days before disease onset and an OR of 1.75 (CI: 1.24, 2.47) 6-14 days before disease onset. Ten millimetres of precipitation corresponded to an OR of 1.69 (CI: 1.12, 2.54) 6-14 days before disease onset. The direction of association, however, remained consistent with the analysis of the full dataset. The 95% percentile of NO_2 (37.3 µg/m^3) was negatively associated, though statistically not significant, during the incubation time, but positively associated before the incubation, compared to the median (16.5 µg/m^3).

In the multi-exposure model, the association of relative humidity and precipitation with LD diminished, yet atmospheric pressure showed an OR of 0.29 (CI: 0.10, 0.89) for the 95^{th} percentile compared to the median. NO_2 was consistently but non-significantly associated with LD occurrence (Appendix H, Figure S5).

Sensitivity analysis excluding all cases from Ticino (2017-2021)

The sensitivity analysis excluding Ticino (1,760 LD cases) showed largely consistent estimates with the full data analyses. The largest change was the increasing association of precipitation with LD case

reporting in the multi-exposure model at lag 6-14 with a 58% (CI: 19-110%) increase in the odds in LD notification per 10 mm increase in daily precipitation (Appendix H, Table S6).

Discussion

In this study, we provide a comprehensive overview of the spatial distribution and the environmental determinants of reported LD cases in Switzerland for the years 2017-2021. Overall, our models supports the notion that a specific sequence of weather events - warm weather followed by high humidity, leads to the highest risk for contracting LD [Ricketts et al. 2009; Beauté et al. 2016; Brandsema et al. 2014]. Understanding the impact of weather on infectious diseases, such as LD supports the interpretation of regional distribution or seasonality of disease. It also opens opportunities for climate- and weather driven early warning systems [Morin et al. 2018] and could guide diagnostic testing and treatment preferences for pneumonia patients.

The impact of weather on Legionnaires' disease notification rates

Overall, temperature, relative humidity and vapour pressure were associated with the highest risk increase on case occurrence. These observations are in line with previous studies identifying wet and warm weather to be associated with LD case occurrence [Pampaka et al. 2022; Ricketts et al. 2009; Fisman et al. 2005; Braeye et al. 2020]. In particular, our findings confirm the observations of Conza et al. [2013], who analysed the weather conditions in relation to LD incidence of two Swiss regions aggregated by month . Our study contributes in translating these local conclusions to the national level and by using DLNM models allows a more detailed understanding of the time-lagged response of the different weather variables.

Weather can affect case numbers in various ways, such as (i) increasing the susceptibility of the population towards an infection with *Legionella* spp. on the long term; (ii) increasing the current transmission rates through increased bacteria concentrations in the environment or increased exposure (e.g. more air droplets or change in behaviour) or (iii) worsening of symptoms, which results in increased health-seeking or referral and, therefore, detection and reporting, as LD is usually only diagnosed in hospital. The 'worsening of symptoms scenario' is expected to present the most immediate impact on LD notifications (increased OR on the case day or shortly before). An increased transmission rate could result in an increased OR during or before the incubation period, when the bacteria start to proliferate in the environment. An increase in susceptibility would likely show larger ORs during the incubation period or on the longer term. Therefore, while our analyses are unable to establish any causality, the specific (lag) days for which an association with LD incidence is observed can provide meaningful insights into the mechanisms by which weather affects the LD case occurrence.

Temperature was found to have the strongest association with disease onset early in the incubation period and just before. Consistent with our study, Ricketts et al. [2009] observed an increased risk of LD associated with increasing temperatures with long lag periods, up to three months preceding LD infections, which is much longer than our investigated time frame. This would align with the hypothesis that sustained high temperature can warm up small water sources up to *Legionella* 's ideal growth temperatures of 25-45 °C. We observed the highest OR at 21- 22 °C during and before the early incubation period. Other studies also found a maximal association at this temperature range [Beauté et al. 2016; Simmering et al. 2017] that is below Legionella's ideal growth temperature. However, the mean daily temperature used in our study is measured in the ambient air 2 m above ground and might not represent the actual temperatures in e.g. plumbing and piping. Additionally, higher ambient temperatures, i.e. over 24 °C seem to reduce airborne bacterial survival [Fernstrom and Goldblatt 2013].

We also observed an increased association of elevated temperature with LD case occurrence just before the case date, which is likely too close to the disease onset to fall into the incubation time. The same association has also been reported by others [Dunn et al. 2013]. These short-term relationships have rarely been investigated, but could be explained by a worsening of symptoms in previously infected people due to hot weather - the highest OR was seen at a mean daily temperature of 28 °C likely prompting people to seek care and leading to LD case detection. Mean daily vapour pressure showed similar, yet slightly weaker associations than temperature. Vapour pressure is highly correlated with temperature; it is, therefore, difficult to disentangle the individual contributions of these two weather variables.

Relative humidity showed the strongest association with LD incidence throughout the incubation time, consistent with the existing literature [Conza et al. 2013; Fisman et al. 2005]. This shorter lag period compared to temperature suggests that humidity may indeed increase LD transmission rates. Daily total precipitation was also found to be linearly associated with LD occurrence in the single-exposure model. Also consistent with our findings, heavy rainfalls were previously found to be associated with LD occurrence [Miho et al. 2020]. However, the association between precipitation and LD incidence reduced in the multi-exposure model. It is likely that the estimated risk of precipitation may be confounded by daily mean relative humidity. In turn, the association of relative humidity with LD remained significant in both, the single-exposure and multi-exposure models.

Lastly, we found that increasing atmospheric pressure was associated with a decrease in the odds of LD infection in the single-exposure model but not in the multi-exposure model. This association is likely confounded by humidity, which lowers atmospheric pressure [Gleason et al. 2016]. Furthermore, lower atmospheric pressure is also associated with more storms and precipitation. These findings highlight the strong interconnection of the different weather variables, which, in turn, complicate effect attribution to specific weather variables. It is interesting, however, that another Swiss study found only vapour pressure to be associated with LD cases but not relative humidity [Conza et al. 2013]. We found a significant association

for all three in the multi-exposure models: temperature, relative humidity and vapour pressure. While we did not investigate the cumulative effect of different weather variables, weather types, i.e. a combination of weather conditions might be the most suitable predictor for LD incidence in practice.

To date, the dynamics by which weather affects the occurrence of cases are poorly understood. Further studies are needed to test our hypotheses and identify the mechanisms at work.

The role of air pollution

Given the sparse literature on the association of air pollution with LD, we aimed to include air pollution in the case-crossover study as we found strong association with LD case numbers per district for both NO_2 and $PM_{2.5}$ in the ecological model.

We did not find any significant association between daily air pollution and LD incidence, using a highly resolved spatiotemporal NO_2 model to estimate exposure. This finding is in part due to a lack of power, as only data from 2019 could be investigated. Even other investigated weather conditions, such as temperature, that showed statistically significant results using data of five years remained inconclusive when only using data of a single study year. Additionally, we could only use NO_2, as a proxy for traffic-related air pollution. Even though $PM_{2.5}$ and NO_2 showed a similar strength of association in the ecological model, other pollutants (PM or ozone) may play a more important role in LD incidence than NO_2. A recent study on the effect of air pollutants on LD case occurrence observed the strongest effect for SO_2 six days and two days, and PM_{10} nine days before case occurrence in two different cities [Graham et al. 2020]. Data on NO_2 was not available for this study.

In contrast to the rather immediate effects observed by Graham et al. [2020], we found that the associations between NO_2 and LD cases in the multi-exposure model were stronger at the beginning of the 21-day period under study than immediately before the onset of the disease. Coupled with the large and significant association observed in the aggregated analysis of the ecological model, this finding could suggest that the impact of NO_2 on detected LD cases is more relevant in mid- and long term compared to the more transient effects investigated using our case-crossover design. Among the possible mechanisms, exposure to NO_2 could (i) increase the susceptibility to pneumonia in general (e.g. through inflammation and epithelial cell damage [Neupane et al. 2010]); or (ii) increase disease severity, and lead to hospitalisation and consequently case detection and notification. Yet, the strong observed association of air pollution with LD incidence in the ecological model could also stem from an unknown confounder, which occurs primarily in Ticino, as this canton has both the highest air pollution and the highest LD notification rates in Switzerland [Hoogh et al. 2019]. Such confounding was, however, avoided in our case-crossover analyses.

Based on the large body of evidence of the impacts of weather and air pollution on human health including their possible synergetic or confounding effects [Vanos et al. 2015], we recommend that future

studies continue including air pollution in the assessment of weather events on LD incidence with a larger time series, and several pollutants including NO_2, PM and ozone.

Topography and the regional distribution of Legionnaires' disease in Switzerland and abroad

The Ticino region in the South of Switzerland shows the highest notification rate of all regions and has been marked a hot spot in the spatial hot spot analysis. However, while the notification rate of LD has been consistently elevated in Ticino and the discrepancy grew stronger in 2015, in recent years the notification rate in Ticino declined, contrary to the rates in the other regions across Switzerland [BAG 2022e].

The weather in Switzerland is characterised by the Alps dividing the country, leading to strong weather differences even within our small country. In the ecological model, we saw a negative association of relative humidity and LD incidence, which contrasted with the existing literature[Fisman et al. 2005; Ricketts et al. 2009; Karagiannis, Brandsema, and Van Der Sande 2009; Gleason et al. 2016]. In the case-crossover study however, our results concurred well with the available literature. This discrepancy between both study designs could be explained by regional confounding in the ecological model using aggregated data at the regional level, which is absent in the case-crossover design. Since the alpine regions have an overall higher humidity than the rest of Switzerland, but also the lowest notification rates, this particular topography of Switzerland is likely to have driven this unexpected negative association in the ecological model.

The higher LD notification rate in Ticino could also be explained by the higher humidity in this region, together with the more frequent occurrence of heavy rainfall events and warmer temperatures. Ticino also lies in the area of influence of the Italian Po-valley with one of the highest air pollution measurements in Europe, particularly for PM and ozone [EEA 2022]. Whether this special geographical and environmental situation explains the LD hotspot in Ticino will need further inquiry alongside the assessment on the general effects of air pollution on LD using fine-scale air pollution data over several years.

Weather phenomena and air pollution as potential drivers of LD incidence should lead to cross-border effects on the notification numbers of LD. While Switzerland stands out with higher notification rates than the adjacent neighbouring countries, the clustering of higher rates lies towards the area south of the Alps. In addition, Switzerland's case numbers are not reported through the European Surveillance System managed by the ECDC and are, therefore, missing in the annual epidemiological reports. Looking at the newest report of 2020, only Slovenia, being also part of the alpine belt, had a higher notification rate than Switzerland [ECDC 2022]. Part of this variation is probably depend on health systems factors, such as in Southern Italy where underdiagnosing and underreporting have been previously reported [Rota et al. 2013; Riccò et al. 2021].

Since extreme weather conditions such as increasing warm weather and heavy rain events are expected to become more frequent [Hoegh-Guldberg et al. 2018], LD infections are likely to increase in future years. It is, therefore, important that the drivers of LD and their interactions are being understood, especially focussing on the interplay of various correlated weather conditions and air pollution. Future environmental and public health policies focussing on the mitigation of air pollution, together with effective climate actions will be essential to reduce the burden of non-communicable diseases, but also of infectious diseases such as LD.

Strengths and limitations

Similar to other studies on *Legionella* epidemiology, all our analyses use the notification data as a proxy for LD incidence, which may influence findings on regional differences in case of differential testing strategies. The interpretation and validity of the Swiss notification data on LD has previously been discussed in several studies on the positivity rate [Fischer et al. 2020b], physician case finding [Fischer, Deml, and Mäusezahl 2022] and the notification data itself [Fischer, Mäusezahl, and Wymann 2022]. Based on these works, we presume that regional differences in incidence are real. Nevertheless, discussing our results and their implications, we are mindful that our estimates represent a combination of case detection and incidence. Furthermore, our results on the impact of meteorological factors resulting from the case-crossover approach (objective 3) are unlikely to be affected by potential regional differences, which supports the plausibility of our findings. In addition, we performed a sensitivity analysis excluding cases from Ticino, where detection bias is most likely, yielding robust estimates.

The combination of several analytical approaches compensated for limitations of a single study design. The ecological design is useful to understand geographical distributions and LD clusters over time, the association between long-term environmental exposures and case numbers might be confounded by further regional, geographic or topographic characteristics, such as health systems performance or altitude. The case-crossover study removed between-individual exposure variability and potential confounding through time-invariant characteristics. DLNMs are particularly useful to study the association of weather with LD incidence due to the models' ability to investigate sequences and different time delays (lags) [Braeye et al. 2020]. Yet, while DLNMs were found to be well suited for these types of analyses, they might be subject to overfitting. To validate our model fit, we built ordinary simple models aggregating over the significant lag days and using a conditional logistic regression.

The case-crossover study design required the assumption that the place of residency is the source of infection for all community-acquired LD cases. However, the spatial scale of meteorological variables limits the exposure misclassification. Further, while the case-crossover design inherently takes into account time-invariant confounders, time-variant confounders need to be specifically adjusted for. While we did include

a term in the model to approximate changes in LD notification rates due to travels, we cannot exclude that other varying environmental factors may influence our results.

The incubation time of up to 14 days for LD is rather long. Adding some additional time to account for changes in the environment before the incubation the time under investigation was expanded to 21 days. With such a long timeframe, meaningful associations could be diluted. Therefore, we decided to group the 21 days into three periods: 'early incubation/ shortly before disease onset', 'prolonged incubation period' and 'before incubation'. While the grouping does influence the presented numbers, the most influential lag days can be visually identified from the DLNM results.

Unfortunately, we did not have data on air pollution on a comparable temporal and spatial level as the meteorological data. However, in doing the sensitivity analysis, we accounted for daily NO_2 exposure for a subset of LD cases, demonstrating the individual influence of meteorological factors on LD independent of air pollution levels, which has rarely been addressed in the past. Additional studies covering a broader range of air pollutant exposures and stratified by long-term pollutant concentrations are needed to further investigate differences in susceptibility to LD infection and symptom severity.

Conclusion

Our study based on individual weather estimates with high spatio-temporal resolution confirms that weather conditions such as warm temperature and increasing humidity are likely to increase the risk of LD case occurrence. At the same time, Switzerland's summers are setting repeatedly new temperature records and the number of rainstorms seems to be increasing. Against the backdrop of climate change, there is a high risk that the burden of LD will aggravate in the future years. Future research should aim to disentangle the main drivers of LD occurrence. In particular, understanding the interplay of temperature and humidity with air pollution and other regional characteristics could explain hotspots of infection and provide guidance on measures to prevent the conducive effect of warm and humid weather on LD incidence. Environmental policies to combat air pollution and climate change must be afforded due consideration in order to limit the progression of LD infections in Europe in the coming years.

Acknowledgments

We thank the Federal Offices (Federal Office of Public Health, Federal Office for the Environment, Federal Office of Energy, Federal Office for Agriculture, Federal Statistical Office, Federal Office of Topography and the Federal Office of Meteorology) and all third parties for providing data. The data that support the findings of this study are available on request from the corresponding author with permission of the respective data holders.

We further thank Benjamin Flückiger (Swiss TPH) for support in the air pollution data acquisition and general R support and Melina Bigler (Swiss TPH) for reviewing the manuscript. This study was funded by the Federal Office of Public Health (contract number 142003961).

Declaration of conflicts of interest

The authors declare they have nothing to disclose.

Funding source

This study was supported by the Federal Office of Public Health (FOPH, contract number 142003961).

Chapter 11

SwissLEGIO pilot study: development and piloting of a questionnaire and interview for patients with Legionnaires' disease

Context

The number of reported Legionnaires' diseases (LD)* cases in Switzerland has been increasing for two decades, yet little is known about the main drivers of infection. Most investigations on the risk factors and exposure sources are conducted in an outbreak setting, which might not represent sporadic cases which constitute the majority of all reported cases. Such outbreak investigations have been performed and disseminated by public actors (e.g. health authorities) [ECDC 2018a; CDC 2018] or in the form of research studies [Den Boer, Nijhof, and Friesema 2006; O'Connor et al. 2007; Emma et al. 2017; Buchholz et al. 2020].

To identify risk factors and environmental exposures on a national scale for sporadic community-acquired LD, we developed a prospective case-control and molecular source attribution study (*SwissLEGIO* , see Chapter 12). In a first planning phase, and as a proof of concept, we clarified the feasibility of the interview process with patients with LD, specifically addressing the following challenges: (i) The incubation time (2-10 days [WHO 2007]), and the required notification timeline is long (up to 14 days (2018), prolonging the time between exposure and interview and hampering recall. (ii) *Legionella* spp. is ubiquitous and requires the questionnaire to cover a multitude of exposures leading to a long interview. (iii) Information pathways are not standardized nationally to facilitate uniform recruitment procedures across Switzerland. (iv) Patients with LD are often elderly [Cunha, Burillo, and Bouza 2016] and severely compromised in their health, complicating the interview.

Here we present the findings from the first piloting phase and proof of concept of the recruitment and interview processes of patients with LD at a large University hospital in Switzerland.

Aim of the pilot

The aim of the first phase of the pilot was to (i) assess and, if needed, shorten the time between case onset and enrollment in our study, (ii) test the collaborative recruitment of cases through the hospitals

and the study team in place of recruitment through the national surveillance system, (iii) test and improve the interview process and the questionnaire. The questionnaires are designed to identify host risk factors (e.g. age, comorbidities), and transient risk factors (e.g. behaviours and exposures) during the incubation time and finally, (iv) gain experience as data collectors, which would then be implemented into a training manual for future staff.

Pilot overview

We interviewed 9 patients with LD. The average age was 68 years (range 43-79) and 2 out of the 9 patients were women. On average the interview lasted 52 minutes (range 32-75 minutes), all participants were able to complete the interview. Figure 11.1 shows the recruitment timeline for each pilot participant. The median time between the onset of the disease and the interview was 13 days. The median time between the notification to our study team and the interview was 3 days. The majority of the interviews could be conducted at the hospital bedside (5/8 interviews). Regarding the disease severity of the interviews patients, 1 out of the 9 patients had been admitted to the intensive care unit (and moved back to the general ward) prior to the interview.

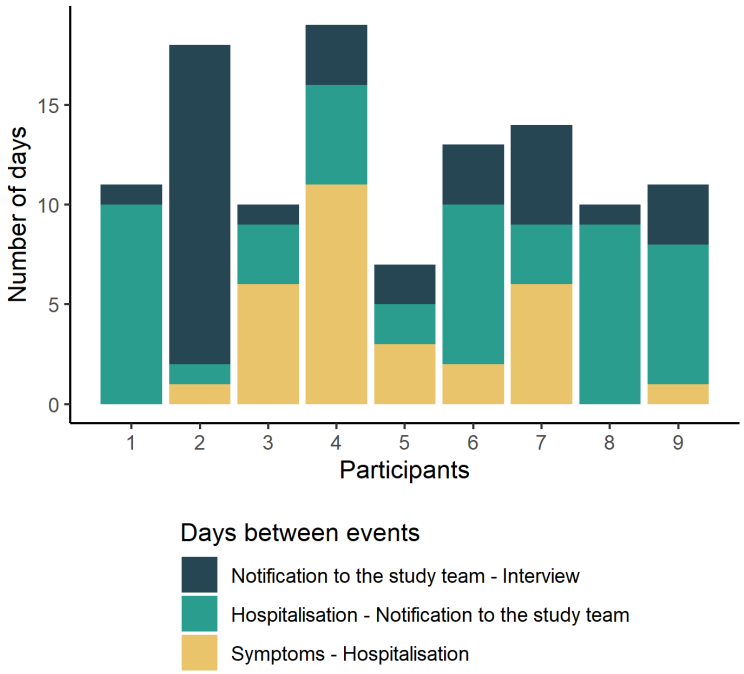


Figure 11.1: Overview of recruitment timeline for pilot participants (patients with Legionnaires' disease)

Lessons learned

Recruitment

- The recruitment of LD cases through the hospital could cut the time until the interview, such that the majority of the interviews could be conducted while the patient was still hospitalised. This facilitated planning and access to the patient.
- The involvement of the nursing team in the planning of the interview team ensured that the interview was aligned with the hospital routine and increased acceptance of the study among the nursing staff and the patient.

Interview and rapport

- We have included a series of open-ended questions about the illness perception early in the interview, which, apart from providing information, improved rapport with the patient.
- Questions about various sources in the patient's close environment, could lead to the patient feeling insecure. Therefore, we developed guidelines for data collectors how to wrap up the interview. The objective was to leave the participants feeling good about the interview process and not insecure about potential exposure sources.

Recall

- Including an open-ended question, where the patient is asked to narrate the 14 days of exposure time, improved recall. To help the patients identify the time point of events, we used vignettes or events from the narration to center the exposure period around, e.g. 'Was this before or after your sister visited?' or if during the chronological narration the patient reports walking their dog, questions about exposures to fountains or open water sources, can be prompted supporting the patient's memory, e.g. ('Were you close to an outdoor fountain? – What about the route where you walk your dog?').
- Apart from personal events, we used a 'cultural calendar' / landmark events to situate occurrences, e.g. 'was this when all the shops were still closed for COVID-19?'.
- The interviewer carried a calendar to clearly mark out the exposure period, we also encouraged participants to check their own calendar as well. This seemed to work particularly well for the younger participants that used their phone as their calendar. Approximately half of the respondents also consulted their calendar as an aid, which impproved recall.
- Questions regarding the infrastructure of the housing were most difficult to answer for many respondents (e.g. on the warm water heating system). To improve efficiency, we have removed overly technical questions from the questionnaire. Instead, we introduced questions targeting the user experience, e.g. about problems with the water pressure. Key questions on the knowledge about the water

heating system (e.g. 'To which temperature is the warm water/ boiler temperature pre-set?') were kept in the questionnaire providing us important insights in the health literacy of the respondents and knowledge of their own water installation systems.

- If an answer to an event e.g. 'visit to a dentist' comes faster than expected based on the rest of the interview, probe them on the date 'so which day was it?' to ensure correct recall.
- To facilitate discussion surrounding the exposure to several aerosol-producing devices, we have developed a booklet with pictures of all the devices that are questioned.

Compliance

- The participants noted that although long, the interview was feasible to finish. It helped that the interview was divided into chapters, which were introduced individually, giving a sense of progress. The interviewer also announced certain hallway marks, i.e. half of the questionnaire has been answered.

Conclusion and outlook

The pilot helped establish recruitment processes and the questionnaire and showed that the case-control study was feasible in regards to the case interviews, which were seen as a bottleneck of the study due to the need to fast access to the patients and their compromised health.

This first pilot phase will be followed up with further pilot activities to expand on the interview with patients to include other processes, such as recruitment communication pathways and environmental sampling and analytics. Future piloting will be carried out within the mandate for the case-control and molecular source attribution study (*SwissLEGIO*).

Chapter 12

Legionnaires' disease in Switzerland: Rationale and study protocol of a prospective national case-control and molecular source attribution study (*SwissLEGIO*)

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This article was published in:
Infection (2023), 51, 1467–1479
doi: 10.1007/s15010-023-02014-x

Infection
https://doi.org/10.1007/s15010-023-02014-x

RESEARCH

Legionnaires' disease in Switzerland: rationale and study protocol of a prospective national case–control and molecular source attribution study (*SwissLEGIO*)

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Received: 31 October 2022 / Accepted: 23 February 2023

Abstract

Switzerland has one of the highest annual Legionnaires' disease (LD) notification rates in Europe (7.8 cases/100,000 population in 2021). The main sources of infection and the cause for this high rate remain largely unknown. This hampers the implementation of targeted *Legionella* spp. control efforts. The *SwissLEGIO* national case–control and molecular source attribution study investigates risk factors and infection sources for community-acquired LD in Switzerland. Over the duration of one year, the study is recruiting 205 newly diagnosed LD patients through a network of 20 university and cantonal hospitals. Healthy controls matched for age, sex, and residence at district level are recruited from the general population. Risk factors for LD are assessed in questionnaire-based interviews. Clinical and environmental *Legionella* spp. isolates are compared using whole genome sequencing (WGS). Direct comparison of sero- and sequence types (ST), core genome multilocus sequencing types (cgMLST), and single nucleotide polymorphisms (SNPs) between clinical and environmental isolates are used to investigate the infection sources and the prevalence and virulence of different *Legionella* spp. strains detected across Switzerland. The *SwissLEGIO* study innovates in combining case–control and molecular typing approaches for source attribution on a national level outside an outbreak setting. The study provides a unique platform for national Legionellosis and *Legionella* research and is conducted in an inter- and transdisciplinary, co-production approach involving various national governmental and national research stakeholders.

Keywords *Legionella* spp. · Legionnaires' disease · Case–control study · Whole genome sequencing · Surveillance · Switzerland

Background

Legionnaires' disease (LD) is a severe form of pneumonia with a case fatality of 5–10% [1, 2]. The disease is caused by Gram-negative *Legionella* spp. bacteria, ubiquitously

Members of The *SwissLEGIO* Hospital Network are listed in the Acknowledgement section.

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Published online: 11 March 2023

Abstract

Switzerland has one of the highest annual Legionnaires' disease (LD)* notification rates in Europe (7.8 cases/100,000 population in 2021). The main sources of infection and the cause for this high rate remain largely unknown. This hampers the implementation of targeted *Legionella* spp. control efforts. The *SwissLEGIO* national case–control and molecular source attribution study investigates risk factors and infection sources for community-acquired LD in Switzerland. Over the duration of one year, the study is recruiting 205 newly diagnosed LD patients through a network of 20 university and cantonal hospitals. Healthy controls matched for age, sex, and residence at district level are recruited from the general population. Risk factors for LD are assessed in questionnaire-based interviews. Clinical and environmental *Legionella* spp. isolates are compared using whole genome sequencing (WGS)*. Direct comparison of sero- and sequence types (ST)*, core genome multilocus sequencing types (cgMLST)*, and single nucleotide polymorphisms (SNPs)* between clinical and environmental isolates are used to investigate the infection sources and the prevalence and virulence of different *Legionella* spp. strains detected across Switzerland. The *SwissLEGIO* study innovates in combining case–control and molecular typing approaches for source attribution on a national level outside an outbreak setting. The study provides a unique platform for national Legionellosis and *Legionella* research and is conducted in an inter- and transdisciplinary, co-production approach involving various national governmental and national research stakeholders.

Keywords: *Legionella* spp., Legionnaires' disease, case-control study, whole genome sequencing, surveillance, Switzerland

Background

Legionnaires' disease (LD)* is a severe form of pneumonia with a case fatality of 5-10% [Burillo, Pedro-Botet, and Bouza 2017; Fischer, Mäusezahl, and Wymann 2022]. The disease is caused by Gram-negative *Legionella* spp. bacteria, ubiquitously found in freshwater environments and soil. The bacterium is facultative intracellular and replication in amoeba is likely the predominant mechanism for its proliferation. This interaction with amoeba plays an important role in the persistence and release of *Legionella* spp. from its environmental reservoirs [Greub and Raoult 2004; Boamah et al. 2017]. Transmission to humans occurs through inhalation of aerosols or aspiration of water containing *Legionella* spp. In the lung, *Legionella* spp. is phagocytosed into alveolar macrophages, where it replicates intracellularly [Cunha, Burillo, and Bouza 2016]. Human-to-human transmission is a rare exception [Correia et al. 2016].

In Switzerland, LD is notifiable to the Federal Office of Public Health (FOPH)* [BAG 2020a]. Similar to trends observed in other European countries [ECDC 2022], notification rates for LD in Switzerland continue to rise. In 2021 the notification rates reached a new high of 7.8 cases per 100,000 population [Fischer, Mäusezahl, and Wymann 2022]. About 70% to 80% of all reported LD cases in Europe, including Switzerland, are community-acquired, about 15 to 20% of cases are travel-associated, and only about 5% are nosocomial acquired [Fischer, Mäusezahl, and Wymann 2022; Beauté and ESGLI 2017]. Additionally, the majority of LD cases are occurring sporadically, in contrast to outbreaks or clusters. To date, numerous sources including showerheads, dental units, cooling towers, and fountains have been linked to community-acquired *Legionella* spp. infections (CALD)* [Amemura-Maekawa et al. 2018; Schönning et al. 2017; Wüthrich et al. 2019; Faccini et al. 2020], yet little is known about their contribution to the overall disease burden [Whiley et al. 2014; BAG and BLV 2018].

Estimating the impact of infection sources on the overall disease burden is difficult. In order to draw any significant conclusions on the contribution of a potential infection source to the disease burden, a sizable proportion of LD patients must be screened as LD remains relatively rare[1] [BAG 2022e]. Regional variability in notification rates additionally suggests that infection sources might differ between regions [BAG 2022f], hampering the generalisability of results to different geographic areas. To link a LD case to an infection source, genomic comparison of *Legionella* spp. isolates recovered from patients with LD and from the environment is required. Such molecular epidemiological investigations are resource-intensive and challenging for multiple reasons: First, clinical *Legionella* spp. isolates are recovered from only about 5 to 10% of patients in routine surveillance [Fischer, Mäusezahl, and Wymann 2022; ECDC 2022]. Second, the ubiquity of the *Legionella* bacteria and the variable incubation period of 2 to 14 days for LD [Cunha, Burillo, and Bouza 2016] requires consideration of multiple potential infection sources for a single LD case [Den Boer

[1] Despite the strong increase in notification rates, only 678 cases were reported in Switzerland in 2021.

et al. 2015; Den Boer et al. 2007]. The incubation time may also create an inherent delay of up to 14 days between the time a patient is infected and the time environmental samples can be collected. The delay between infection and environmental source investigation might be further prolonged based on reporting timelines set for case notifications by public health authorities[2] [BAG 2020a]. This prolongation of the period between the time of infection and the investigation of the environmental source may reduce the chances to successfully recover the disease-causing *Legionella* spp. strains from a suspected infection source. Finally, the recovery of *Legionella* spp. isolates may depend on the chosen sampling approaches (e.g. exact sampling location but also procedures) and sampling time points as the detachment of bacteria from biofilms and their release from amoeba may vary over time [Wang et al. 2017; Schoen and Ashbolt 2011]. Additionally, culture isolation of *Legionella* spp. from environmental samples is labour intensive. It requires careful selection of culture plates and pre-treatment conditions prior to plating (e.g. filter concentration, heat treatment) to optimise growth conditions for *Legionella* spp. and minimise overgrowth of plates by competing organisms. As a result, molecular source attribution of sporadic CALD are primarily reported in single case studies. From such studies is difficult to conclude on a source's contribution to the overall disease burden [Orkis et al. 2018; Heijnsbergen et al. 2015].

Conducting a combined case-control and molecular source attribution study allows to address some of the challenges outlined above. The case-control study design enables the exploration of various (including transient) host, behavioural, and environmental exposure risk factors for CALD [Den Boer, Nijhof, and Friesema 2006; Kenagy et al. 2017; O'Connor et al. 2007; Che et al. 2008]. Data obtained from case-control questionnaires can inform the sampling of potential environmental infection sources, in turn, facilitating molecular source attribution [Faccini et al. 2020; Buchholz et al. 2020]. For now, combined case-control and molecular source attribution studies in Europe focused primarily on urban settings or were part of outbreak investigations and, thus, did not investigate any regional variability of infection hazards [Faccini et al. 2020; Buchholz et al. 2020; Löf et al. 2021]. The potential of combined molecular and epidemiological approaches to investigate infection sources for sporadic CALD cases at a national and general population level has not yet been realised.

Herein, we present the study design of a national case-control and molecular source attribution study (*SwissLEGIO*). The study aims at investigating risk factors and possible exposure sites for community-acquired, mainly sporadic, LD cases across Switzerland. Engaging with a network of 20 participating university and cantonal hospitals, and collaborating closely with the Swiss National Reference Centre for *Legionella* (NRCL)*, the project creates a framework that enables timely, nationwide recruitment of patients with LD, and facilitates the collection and processing of clinical *Legionella* spp. isolates. Together

[2]Currently 7 days in Switzerland.

with the *Legionella* Control in Buildings (*LeCo*) research consortium [Eawag 2022], environmental source investigations are conducted within days after case detection.

Methods

Study design and objectives

This research comprises of a one-year, prospective, national case-control study applying whole genome sequencing (WGS)* to link LD patients to potential exposure sources in Switzerland. Host, behavioural and exposure risk factors are investigated by conducting interviews with newly diagnosed LD patients (cases) and healthy control subjects. For patients, further parameters on the clinical, radiological and laboratory characteristics, the clinical case management, disease severity, and health outcomes are extracted from electronic medical records. For a subset of cases and controls, clinical and environmental *Legionella* spp. isolates are collected and sequenced (Fig. 12.1).

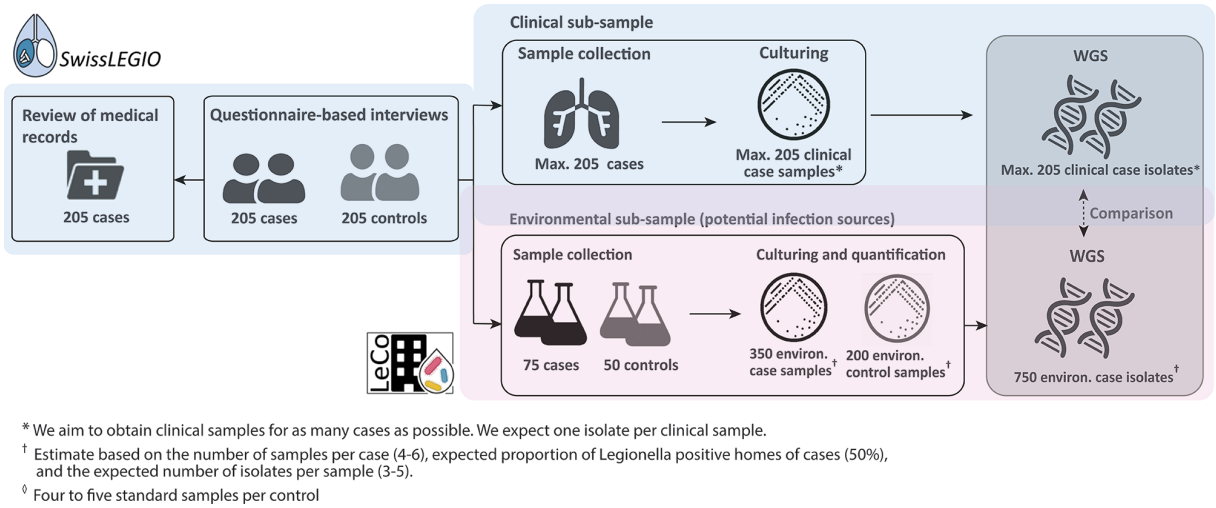

Figure 12.1: Study design for the national case-control and molecular source attribution study on Legionnaires' disease in Switzerland, *SwissLEGIO*. The environmental sampling and sample analytics is conducted in collaboration with the *LeCo* Consortium.

The objectives of the *SwissLEGIO* study are: (i) To identify host, behavioural, and environmental risk factors for LD; (ii) To attribute infection sources to LD cases by comparing clinical and environmental *Legionella* spp. isolates using WGS; (iii) To assess the genome sequence of *Legionella* spp. differing in virulence and to identify potential traits of more virulent strains; (iv) To assess strain diversity and concentration of *Legionella* spp. in standard household and other environmental samples[3]; (v) To ex-

[3]A primary objective of the *LeCo* consortium.

plore the illness experiences of patients with LD, their health-seeking and long-term quality of life, and, (vi) To describe clinical, laboratory, and radiological characteristics of LD and the patient's clinical case management.

The study involves multiple governmental and research stakeholders. Since its inception, the FOPH, the NRCL, and the Federal Food Safety and Veterinary Office (FSVO)* are involved as advisory and strategic planning partners. For the implementation, we closely collaborate with a hospital network consisting of 20 university and cantonal hospitals, the NRCL, the Institute of Medical Microbiology (IMM) at the University of Zurich, and the *LeCo* consortium led by Eawag[4] [Eawag 2022].

Study setting, recruitment process and participation eligibility

Cases of Legionnaires' disease

The study includes newly diagnosed CALD patients from all of Switzerland over a one-year period to account for seasonal and meteorological impacts on infections [Conza et al. 2013; Gysin 2018]. Patients are recruited through a hospital network representing a significant proportion of diagnosed LD patients (the network collectively reported about 55% of all LD cases between 2018 and 2020) (Fig. 12.2). The decision to recruit through hospitals and the selection of the participating hospital sites were informed by previous research: in Switzerland, diagnostic testing for *Legionella* spp. is mainly limited to the hospital setting and, therefore, most reported cases are identified at the hospital. In outpatient care, patients with pneumonia are primarily treated empirically or are referred to the hospital for further clinical and diagnostic evaluations [Fischer, Deml, and Mäusezahl 2022]. An in-depth analysis of LD notification data in Switzerland was used to identify hospitals notifying the most LD cases and also showed that LD notification rates regionally differ across Switzerland [Fischer, Mäusezahl, and Wymann 2022], highlighting the importance to include patients from all seven greater regions (NUT-2 level).

For participating hospitals, individualised recruitment procedures were developed to ensure that the study is embedded optimally in each hospital's existing workflows and in order to help minimise the risk of missing any admitted patients with LD and to optimise efforts to obtain clinical *Legionella* spp. isolates from LD patients as part of their routine clinical case management. In brief, the central study team at the Swiss Tropical and Public Health Institute (Swiss TPH)* is immediately informed by the hospital's clinical laboratory in case of a positive diagnostic *Legionella* spp. test result. The central study team then coordinates with the hospital's appointed study physician or the attending physician on the pre-assessment of the patient's eligibility for participation (the eligibility criteria are summarised in Table 12.1) and the subsequent enrolment. Written study-specific informed consent is obtained by the study physician, a study

[4]Eawag – Swiss Federal Institute of Aquatic Science and Technology, ETH Zurich

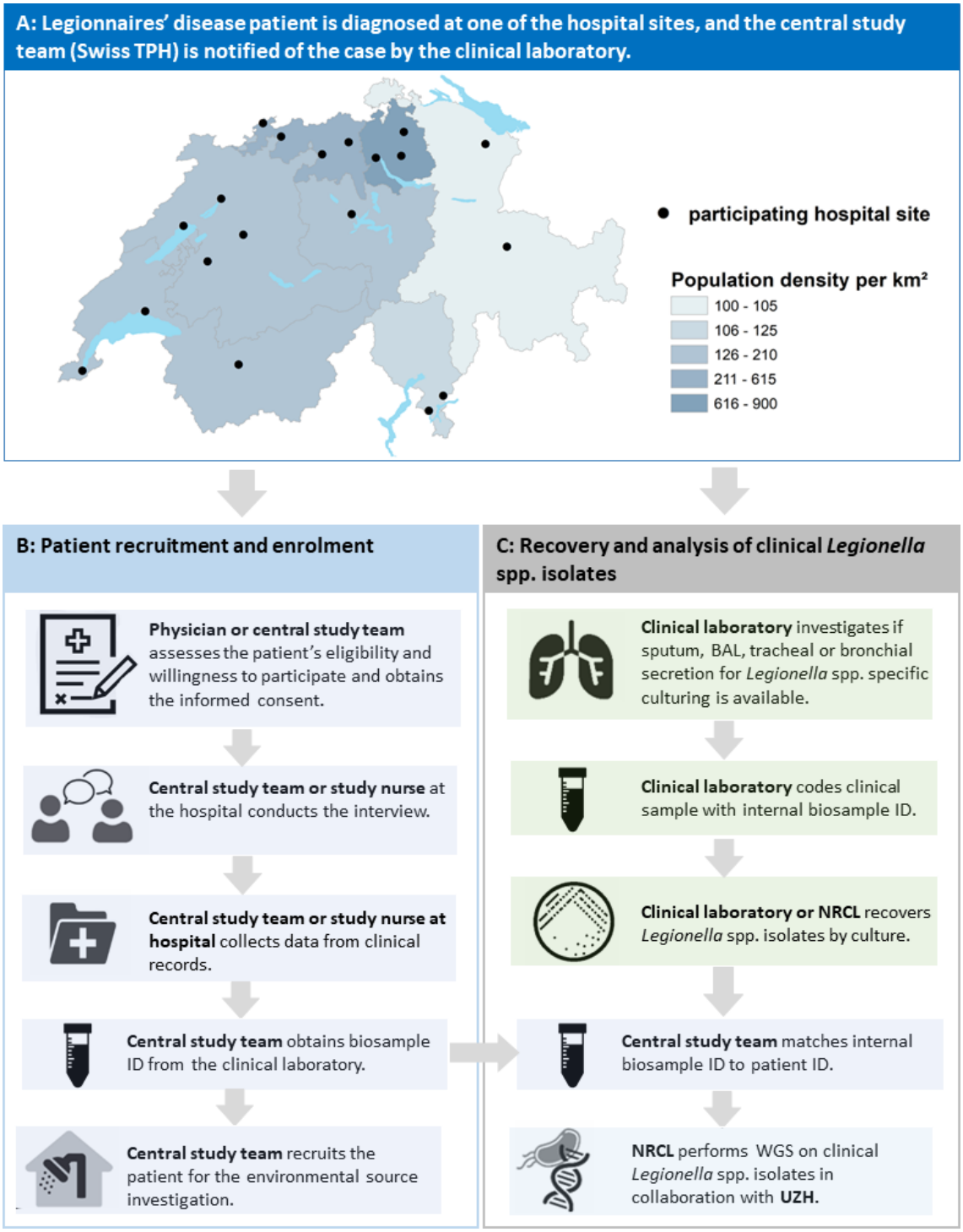

Figure 12.2: *SwissLEGIO* operational flowchart for the recruitment and the collection of data from patients with Legionnaires' disease: (A) Overview of the *SwissLEGIO* hospital network, (B) Data collection upon enrolment, (C) Collection and analytics for clinical samples as part of routine case management. BAL: Bronchoalveolar lavage; NRCL: National Reference Centre for *Legionella* ; WGS: Whole genome sequencing; UZH: University Hospital Zurich.

nurse or the central study team before the questionnaire-based interview is conducted by the study physician or the central study team (Fig. 12.2). The study does not interfere with the case management of enrolled patients.

Table 12.1: Summary of eligibility criteria (inclusion and exclusion) for participation in *SwissLEGIO*

	Inclusion criteria	**Exclusion criteria**
Cases	• living in Switzerland; • speaking German, French, Italian or English; • age≥18 years; • health status (assessed by physician) well enough to provide informed consent and to participate in the study; • clinical signs and symptoms suggestive of Legionnaires' disease (confirmed pneumonia); • laboratory confirmed Legionella spp. infection (according to case definitions of a probable or confirmed case by the Federal Office of Public Health)[a]	• overnight stay at a hospital or rehabilitation facility for at least one night during the 14 days prior to onset of first symptoms; • stay at a hotel, hostel, campground, Airbnb or similar for more than seven nights during the 14 days prior to onset of first symptoms; • positive laboratory test result was available 7 days before study team was notified of case
Controls	• living in Switzerland; • speaking German, French, Italian or English; • age≥18 years; • health status well enough to provide informed consent and to participate in the study;	• overnight stay at a hospital or rehabilitation facility for at least one night during the 14 days prior to onset of first symptoms; • stay at a hotel, hostel, campground, Airbnb or similar for more than seven nights during the 14 days prior to onset of first symptoms; • flu-like symptoms or fever during the 14 days incubation time of the corresponding case

[a] Isolation of *Legionella* spp. from respiratory secretions or any primarily sterile site OR detection of *L. pneumophila* antigen in urine OR detection of *Legionella* spp. nucleic acid in clinical samples (using for example PCR) OR detection of *L. pneumophila* antigen e.g. by Direct Fluorescent-Antibody Staining using monoclonal-antibody-derived reagents OR significant rise in specific antibody level to *L. pneumophila* or other *Legionella* spp. in paired serum samples OR single high level of specific antibody to *L. pneumophila* serogroup 1 in serum.

Controls

One control per enrolled case is recruited from the general Swiss population. Controls are selected from a dataset based on the national census list, which comprises a random population sample. The dataset is provided by the Swiss Federal Statistical Office [BFS 2022b]. A control matched to a LD case for age (+/- 5 years), sex, and location of residence (district level/ "Bezirksebene") is chosen and contacted by e-mail or postal mail as soon as a case has been enrolled. Following the written invitation, the study team assesses the control's eligibility (Table 12.1), ability and willingness to participate in the study by phone. Informed consent from controls is obtained prior to the interview.

Sample size calculation

Calculation of the sample size was performed using Epi Info™ 7 (Centers for Disease Control and Prevention, USA). We consider the ubiquitous nature of *Legionella* spp. in the environment and assume that 60% of controls are exposed to a risk factor during the period of potential risk exposure [Buchholz et al. 2020; Casati, Gioria-Martinoni, and Gaia 2009]. Therefore, a sample size of 205 cases and 205 controls is required to detect an odds ratio (OR)* of 2 with 90% power and alpha=0.05. We adjusted the size of the hospital network to reach the required sample size within one year.

Data collection and piloting

For cases, data and biological samples are collected at three different time points: (i) the treating physician obtains clinical samples suitable for *Legionella* -specific culturing prior to enrolment of the patient in the study, (ii) after informed consent is obtained, a questionnaire-based interview on potential risk exposures is conducted and electronic medical records are reviewed, and (iii) thereupon environmental samples from potential risk exposure sites are collected for a subset of cases. Preference for the environmental sampling is given to cases from whom clinical *Legionella* spp. isolates are available. For controls, the questionnaires-based interview is conducted and environmental samples are collected from a subset of controls matched to a LD case (for whom environmental samples were also collected) (Fig. 12.1).

Data and biological sample collection were carefully piloted in a two-step approach: in a first step, between October 2020 and October 2021, direct recruitment of patients with LD through the hospital was tested in collaboration with the University Hospital Basel. Moreover, by interviewing newly diagnosed LD patients, the manageability and comprehensibility of the questionnaire-based case-control interview were assessed. In a second piloting step, from March to June 2022, the participant invitation process, the electronic data collection tools, the coordination of the case-control interview, and the subsequent environmental sample collection, shipment, and analysis were pretested with healthy volunteers. Additionally, data collectors and laboratory staff of the central study team were trained on the data collection and laboratory

processing of environmental samples. Finally, the manageability and comprehensibility of the interview completion guidelines and study-specific standard operating procedures (SOPs) on participant recruitment, sampling and sample analysis were tested.

Clinical samples

Clinical samples suitable for *Legionella* -specific culturing (such as sputum, Bronchoalveolar lavage (BAL)*, tracheal or bronchial secretion, or pleural fluid in case of pleural effusion) are collected by the treating hospital physician as part of the routine clinical management of the patient and, hence, prior to patient enrolment. To enhance and promote the isolation of *Legionella* spp. from LD patients, the participating hospitals reviewed and, if required, refined their standardised diagnostic procedures to ensure clinical samples for *Legionella* -specific culture are collected promptly for suspected or confirmed LD cases; the collection of clinical samples can either be triggered by a positive Urinary Antigen Test (UAT)* for *Legionella* or may occur prior to the LD diagnosis. After LD is confirmed, hospitals' clinical laboratories initiate a *Legionella* spp.-specific culture on charcoal-based agar. The isolates obtained are subsequently sent to the NRCL as described in the guidelines for notifiable infectious diseases from the FOPH [BAG 2020a]. [BAG 2020a]. If a clinical laboratory cannot perform *Legionella* -specific culturing, clinical samples can be sent directly to the NRCL for further processing (i.e. culturing and serotyping). Upon enrolment, the study team enquires if *Legionella* spp. could be isolated from clinical samples and obtains written informed consent from the patient for the use of the *Legionella* spp. isolates in the study. *Legionella* spp. isolates are sent from the NRCL to the IMM for WGS analysis (Fig. 12.2). To maximise the number of clinical Legionella spp. isolates that can be obtained in the hospitals' routine assessments, treating physicians are encouraged to collect clinical samples for *Legionella* -specific culture from every patient, irrespective of whether antibiotic therapy has already been initiated. We expect to obtain clinical samples suitable for *Legionella* -specific culturing for about 50–60% of all patients (since LD is often associated with dry cough, we assume insufficient sputum for some patients) and to successfully isolate *Legionella* spp. from about half of these samples [Cunha, Burillo, and Bouza 2016]. We anticipate to analyse one *Legionella* spp. isolate per patient [David et al. 2018].

Case-control questionnaire and patient records

Upon completion of the informed consent, the central study team or a study nurse conducts questionnaire-based interviews with LD patients and controls. The questionnaire is based on information from published LD data collection tools (either for routine assessment [ECDC n.d.; CDC 2021a] or other case-control studies [Kenagy et al. 2017; Buchholz et al. 2020]) and current literature on risk factors and exposure sites for LD. Swiss federal stakeholders in *Legionella* spp. control namely the FOPH, the FSVO, the Federal Office of Energy (FOE)* and collaborating researchers from the *LeCo* consortium were consulted for inputs on the questionnaire design.

The questionnaire consists of 20 sections and focuses on the 14 days before the onset of illness for cases and the same (matched) time period for controls. The questionnaire covers potential predisposing host risk factors for LD (e.g. age, sex, co-morbidities), potential behavioural risk factors for LD (e.g. regularly showering at sports facilities, gardening habits) and investigates exposure to potential environmental infection sources (e.g. housing water installation, public artificial water sources, natural water sources). For cases, the questionnaire further covers the illness experiences of patients with LD and their health-seeking (Table

12.2). Pretested interviews lasted approximately 60 minutes and were well received by patients and healthy control volunteers in content, length, and flow.

Table 12.2: Structure of the *SwissLEGIO* case-control questionnaire for Legionnaires' disease

Set-up	1	Administrative information (e.g. participant ID, interview location, interviewer name)
	2	Screening for inclusion (including assessment of symptoms and illness onset for cases)
Core interview part 1[a]	3	Demographic information (e.g. age, sex, occupation, income)
	4	Cases only: Disease manifestation and illness experience (including perceived severity and the patients' understanding of their diagnosis and the disease in general)
	5	Cases only: Health-seeking
	6	Medical history and medical history
	7	Assessment of potential LD infections/ signs of LD infection (e.g. diarrhoea, fever, dry cough or pneumonia) amongst cohabitants and work colleagues in the recent past
Core interview part 2[b]	8	Chronological narration of the 14 days prior to symptom onset: assessments of the general activity level of the participant and establishment of reference points to guide the interviewee through the second core part of the interview
	9	Housing infrastructure (e.g. year of construction and renovations, specifications on the plumbing system)
	10	Housing – habits (e.g. use of water taps, showering habits)
	11	Housing – pets
	12	Workplace (e.g. assessment of potential exposure to infection sources at the participant's workplace)
	13	Indoor contacts with water aerosols (e.g. with a dishwasher, an indoor ornamental fountain, a humidifier, a whirlpool, steam during cosmetic treatment)
	14	Gardening and plants (e.g. assessment of gardening activities and contact with soil or compost)
	15	Outdoor contacts with water aerosols (e.g. with fountains, lakes, rivers, car wash facilities, water mist from food displays)
	15	Street and transportation (e.g. assessment of mobility and exposure to busy streets)
Wrap-up	17	Cases only: Perceived causes on the LD infection
	18	Option for future contact: Can we contact you in case we have any follow-up questions?
	19	Remaining open questions/ general remarks from the participant
	20	General remark (internal use)

[a] Illness experience, health seeking and intrinsic risk factors for LD

[b] Behavioural risk factors and potential infection sources for LD

For cases, parameters on the patients' clinical case management and the disease severity are extracted from the electronic medical records. The parameters include the medical history, the timespan between onset of symptoms and admission to the hospital, length of hospital stay, CURB-65 parameters [Lim et al. 2003], radiological findings (e.g. consolidation, crazy paving, bronchial wall thickening, pleural effusions), ICU admission and length of ICU stay, disease progression within 48h after admission, performed diagnostics, laboratory parameters and prescribed treatment.

Environmental samples

Environmental source investigation is triggered if either a clinical *Legionella* spp. isolate is available or the *Legionella* -specific culturing is confirmed to be ongoing at the time of case enrolment. Environmental samples and information on residential building and water installation are collected for these cases and their matched controls.

Up to six environmental samples from approximately 75 cases within 14 days following the questionnaire-based interview are collected (Fig. 12.1). Up to five of these samples are standardised water samples collected in the patient's home: (i) first flush (1 L, mix of cold and warm water) kitchen tap water (ii) first flush (1 L, mix of cold and warm water) shower head water from the most used shower, (iii) sequential sample from the hot water line collected at the most-used shower/ bathtub[5], (iv) sequential sample from the cold water line collected at the shower/ bathtub[6] of the most-used shower, and (v) first flush (1 L, mix of cold and warm water) from the second-used shower. The detailed procedures for water sampling are found in the supplementary file). Prior to this sampling, the participant is instructed to refrain from using the taps for four hours. In addition to the standard samples, up to two samples are collected from other likely environmental risk exposure sites reported in the patient interview. These exposure sites are sampled from private locations (e.g. garden hose, water dispenser or humidifier) or public locations (e.g. spas, car wash facilities, decorative fountains, air-conditioners or cooling towers of hotels or supermarkets in proximity of patient's residency, permissions provided). For a subset of approximately 50 healthy controls, only standard household water samples are collected (Fig. 12.1).

Environmental samples are cultured and the number of colony-forming units (cfu)* of *Legionella* spp. in the original water sample are estimated according to ISO 11731 guidelines. For the ISO culturing of standard household water samples, we prepare three plates per sample using the following pre-treatment conditions: filtration only, filtration plus heat treatment, and filtration plus acid treatment. Culture plates are regularly checked for growth for one week and up to three suspected *Legionella* spp. colonies of each morphology

[5] 10 times 100 mL, flow-proportional: 1 L representative sample from 10 L hot water line after flushing for 5 s prior to taking first sequential sample.
[6] 10 times 100 mL, flow-proportional: 1 L representative sample from 10 L cold water line after flushing for 5 s prior to taking first sequential sample.

are culture-confirmed by direct plating of the colony on charcoal agar plates with and without L-cysteine. Isolates showing no growth on plates without L-cysteine are considered *Legionella* spp. (Fig. 12.3a). All culture-confirmed *Legionella* spp. isolates will be characterised by MALDI-TOF mass spectrometry (MS)* (to differentiate strains) and agglutination tests (to differentiate serogroups of *L. pneumophila*). All *Legionella* spp. isolates recovered from potential infection sources of cases that are matching the strain and/ or serogroup of the case's clinical *Legionella* spp. isolate are sent to the IMM for further strain characterisation using WGS (Fig. 12.3b). Finally, flow cytometry (for total cell count), IDEXX Legiolert (quantification of culturable *L. pneumophila*), and digital PCR (quantification of the ssrA gene for *Legionella* spp., mip gene for *L. pneumophila* and the wzm gene specific to *L. pneumophila* serogroup 1) are performed for quality control (Fig. 12.3c). The digital PCR protocol was developed by adapting the qPCR assay from Benitez and Winchell [Benitez and Winchell 2013].

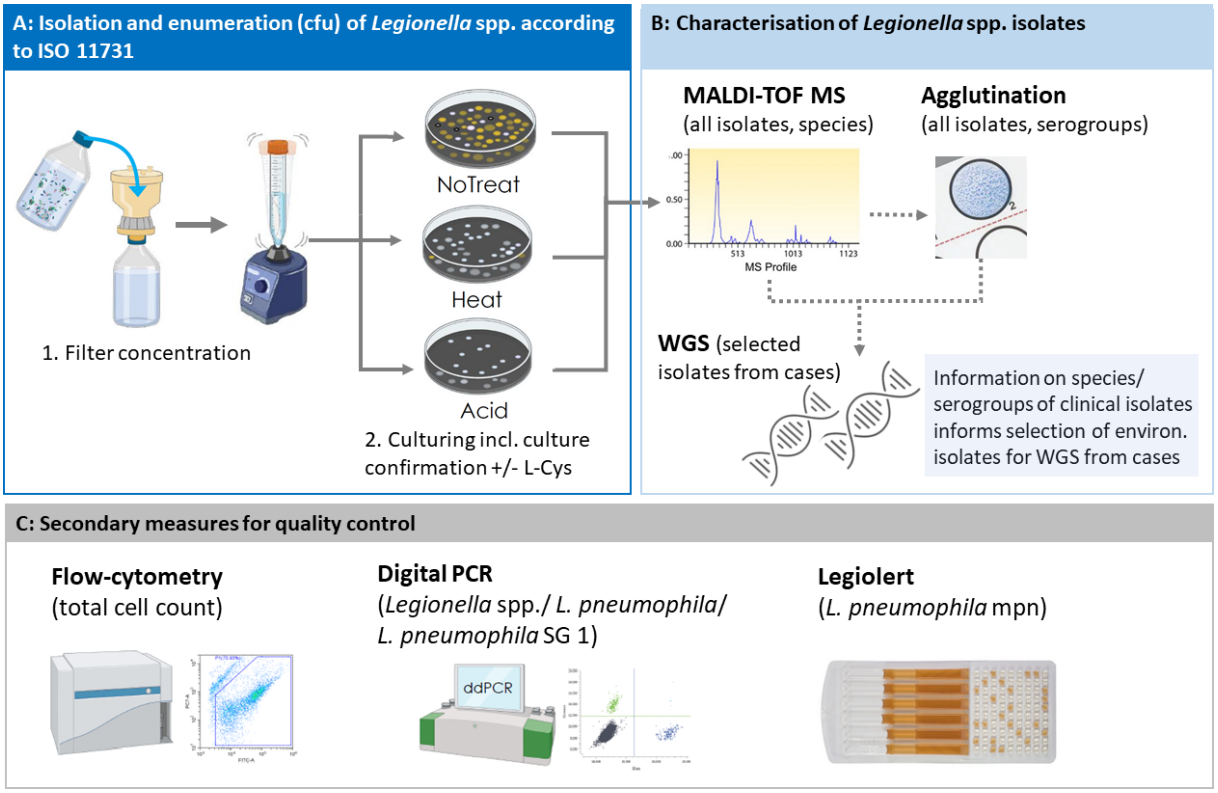

Figure 12.3: Overview of the laboratory analytics pipeline for the isolation and characterisation of environmental *Legionella* spp. strains from standard household and other environmental samples: (A) Summarises the isolation and enumeration of *Legionella* spp. according to ISO 11731, (B) Culture-confirmed *Legionella* spp. isolates are characterised by MALDI-TOF MS and agglutination tests and are selected for WGS, (C) For quality control, flow-cytometry, digital PCR and Legiolert are performed for all samples. cfu: colony-forming units; L-Cys: L-Cysteine; MS: mass spectrometry; WGS: whole genome sequencing; SG: serogroup; mpn: most probable number

For additional samples from potential exposure sources of patients, sample processing approaches are assessed on a case-by-case basis in consultation with researchers and external research partners from the *LeCo* consortium. The characterisation pipeline for such isolates will remain the same as for the standard household water samples. Based on rough estimates from the literature [Wüthrich et al. 2019; Buchholz et al. 2020; Boss et al. 2020], we expect to sequence a total of 750 environmental *Legionella* spp. isolates recovered from potential exposure sources of cases (Fig. 12.1).

Data management

Data are collected on standardised electronic Case Report Forms (eCRF)* using the data collection software Open Data Kit (ODK*, getodk.org). Forms are identified by subject IDs. Automated validation tools in the eCRF check for data completeness and plausibility during data entry. During data collection, the data collected is continuously checked by the research team for completeness, plausibility, and accuracy. Additionally, random source data verification is performed. Data are stored on a secured network drive accessible only to authorised study team members. Data on the network drive are backed up regularly, according to Swiss TPH institutional policy. Radiological images are coded and securely shared between hospitals via a secure data exchange platform, and the images are securely stored on two password protected hard drives.

Quality control measures for the analysis and storage of biological samples are performed according to the study laboratories' routine standard operation procedures.

Statistical methods and analysis

Epidemiological analysis

Cases and controls are characterised in terms of demographics, illness experience (only cases), health-seeking (only cases), and co-morbidities. Crude OR for LD will be calculated by running univariable logistic regressions on single risk factors. Based on results of the univariable logistic regression and biological or epidemiological plausibility, variables will be subsequently selected for a multivariable (unconditional) regression to calculate adjusted OR (aOR). The population attributable fraction (PAF) is calculated for each statistically significant risk factor of the multivariable model as the difference of observed cases and expected cases in absence of the risk factor. The analysis will be conducted with the statistical software R [R Core Team 2020]. Potential exposure sites of cases will be geocoded using geographic information systems (GIS)* to assess regional distributions of LD cases and to identify clustering of potential infection sources.

Additionally, analysis of radiological imaging is performed independently by at least two experienced radiologists. All chest X-rays or CT scans are evaluated blinded from clinical and microbiological information

for lung involvement, distribution (e.g. upper vs. lower lobes, uni- versus multilobar), radiological patterns (e.g., consolidation, ground glass opacities, cavitation, nodules, crazy paving, bronchial wall thickening), pleural effusion, and lymphadenopathy.

Analysis of biological samples

WGS is performed using the IMM's internal ISO accredited (ISO/IEC 17025) sequencing workflow and analytical pipeline for the characterisation of the *Legionella* spp. strains. This workflow and the analytical pipeline are already in use for the characterisations of *Legionella* spp. isolates currently performed for the NRCL [BAG 2020a]. For library preparation, the Illumina NextFlex assay is used and sequencing is performed batch wise at a NextSeq 1000i with 150nt paired end sequencing. After sequencing, the data is quality controlled, raw reads are assembled, and analysed using SeqSphere (Ridom) and the CLC workbench. Only genomes with an average minimal coverage of 40-fold or more will be further evaluated. The sequence type (ST)* of all isolates will be determined and the genomic relatedness will be visualised with a series of phylogenetic tools such as core genome multilocus sequence typing (cgMLST)* e.g. as neighbour joining tree or as a single nucleotide polymorphism (SNP)* tree. Fig. 12.4 illustrates such visualisation for a *Legionella* spp. outbreak investigation conducted in Basel: allelic differences between *L. pneumophila* isolates shown in the figure are based on a published cgMLST scheme for *L. pneumophila* using 1'521 allelic loci [Moran-Gilad et al. 2015].

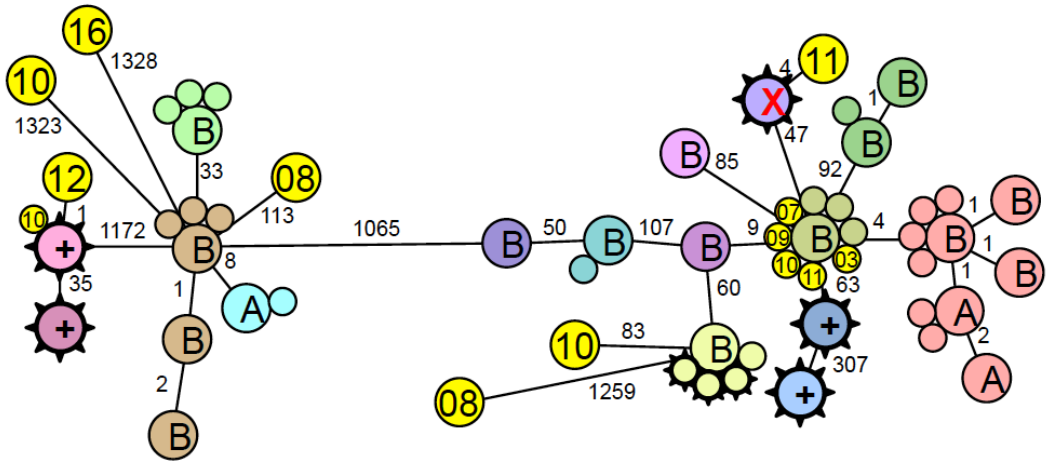

Figure 12.4: Environmental source of *L. pneumophila*. Isolates labelled with A and B are from two air conditioning cooling towers. Isolates with spikes are human isolates from the same seasons. Circles with numbers are human isolates from previous years. The small numbers between the circles indicate the number of allelic differences between two isolates (data from Egli-lab, IMM).

All successfully sequenced strains will be contextualised with previously sequenced isolates from the Swiss database and with global available sequences from public data repositories such as the National Center for Biotechnology Information (NCBI)*. In addition, we will compare the human and environmental isolates

using a bacterial genome wide association study approach. We will link clinical phenotypes (e.g. LD, disease severity) to potential enriched sequence types, genes, k-meres, or SNP in isolates causing invasive disease [San et al. 2020]. We aim to identify genes and annotate potential functionalities linked to the clinical phenotypes. All sequenced genomes are shared according to FAIR principles [Wilkinson et al. 2016] on the Swiss Pathogen Surveillance Platform (http://www.spsp.ch). The usage of the platform further eases data exchange between the different research partners [Egli et al. 2018].

Strengths and limitations

The *SwissLEGIO* study enrolls patients with LD from all seven greater regions of Switzerland. To our knowledge, this is the first national case-control and molecular source attribution study that is conducted outside of an outbreak setting in Switzerland. The study design innovates in (i) minimising the timespan between LD symptom onset and enrolment of cases in the study, (ii) enhancing and promoting the collection of clinical *Legionella* spp. isolates, and (iii) ensuring a high sensitivity of the molecular source attribution approach. All three aspects are crucial to ensure a successful linking of clinical isolates to an infection source. The direct recruitment of cases through an established hospital network instead of the Swiss National Notification System of Infectious Diseases (NNSID)* - as in previous studies [Den Boer, Nijhof, and Friesema 2006; Kenagy et al. 2017]- significantly reduces the timespan between the patient's diagnosis and enrolment in the study. When piloting the recruiting process, the time between patient's hospitalisation and case notification to the study team averaged at three days. This is significantly shorter than the Swiss legal requirements to report an LD case within seven days to the NNSID [BAG 2020a]. The recovery of clinical *Legionella* spp. isolates was a major limitation in environmental source investigations in previous studies [Den Boer et al. 2015; Petzold et al. 2017]. By directly recruiting LD patients through the hospital network, and by exchanging closely with hospital partners on an ongoing basis, we believe to address this challenge by promoting and facilitating the collection of clinical *Legionella* spp. isolates.

We ensure a high sensitivity of the molecular source attribution approach by applying WGS, which has a strong discriminatory power between different *Legionella* spp. strains and, therefore, allows a direct comparison of environmental and clinical isolates [Petzold et al. 2017]. During LD outbreak investigations, WGS analysis was successfully used to trace clinical *Legionella* spp. strains in the environment [Wüthrich et al. 2019; Reuter et al. 2013; Graham et al. 2020]. Yet, such outbreak investigations also highlighted the complexity of developing sensitive environmental sampling, culturing and isolate selection strategies to account for high *Legionella* spp. strain diversities in environmental samples [Wüthrich et al. 2019; Löf et al. 2021]. The challenges of obtaining and subsequently selecting appropriate environmental *Legionella* spp. isolates for WGS in a streamlined manner and the applicability of WGS for the investigations of sporadic LD cases remain largely unexplored. For the *SwissLEGIO* study we developed streamlined processes for the collection and processing of standard environmental household and other environmental samples and

carefully implemented *Legionella* spp. isolates characterisation measures that will inform the selection of isolates for WGS analysis. Finally, the genomics of *Legionellae* is very complex: genetically highly similar *Legionella* spp. strains from different parts of the world have been described without apparent epidemiological link and studies have shown that also recombination events must be considered when interpreting similarities of WGS data between different clinical and environmental *Legionella* spp. strains [Petzold et al. 2017; Schjørring et al. 2017]. Epidemiological context information is, therefore, essential for a reliable interpretation of observed similarities between different environmental and clinical *Legionella* spp. strains and, hence, for infection source attribution. A key strength of the *SwissLEGIO* study is that it combines both epidemiological metadata and WGS data.

Data collected during the questionnaire-based interviews might be subject to reporting biases. The selective memory effect of participants (recall bias) was accounted for by the design of the questionnaire: during the interview, the participant is guided in a structured manner through a wide range of potential exposure sources. To improve recall, participants are interviewed as soon as possible after the LD diagnosis is confirmed. Using an established hospital network, the time between diagnosis, interview and environmental sampling of risk exposures can be kept short. Additionally, any cases for which the diagnostic assessment occurred more than seven days before the study team is notified are excluded. The number of environmental samples collected and isolates analysed is limited due to financial and other resource constraints. Some non-standardised environmental samples may not be collected if access is difficult and/or permissions cannot be obtained.

Future perspectives and impact on policy

Large-scale studies combining molecular and epidemiological methods are sorely needed to investigate predominant infection sources of CALD, to explore their risk magnitude and to inform *Legionella* infection prevention and control measures in Switzerland. The current knowledge gaps regarding predominant infection sources for CALD is reflected in the Swiss *Legionella* spp. control guidelines. The guidelines mainly target shower and bathing water defining thresholds for *Legionella* spp. contamination for portable water and recommendations of hygienically optimally operating water temperatures [BAG and BLV 2018]. However, the relative importance of potable water as infectious source has not been conclusively clarified. In contrast, for cooling towers, which have previously been described as infection sources for LD [Wüthrich et al. 2019], no register exists in Switzerland as yet. The *SwissLEGIO* study investigates potential infection sources for Switzerland and aims to provide a foundation for evidence-based and targeted *Legionella* spp. prevention and control. The study draws on a unique range of scientific and policy expertise on *Legionella* spp. and LD in Switzerland. Through close collaboration with national partners in aquatic science and building-technology research, we harness expertise in environmental sampling and sample analysis, bridging the gap between human health and environmental exposure. The recruitment through the hospital network

and the close collaboration with the NRCL and IMM aligns the study with *Legionella* spp. surveillance activities enacted by the FOPH [BAG 2020a]. The support from and regular consultations with the Federal Offices (FOPH and FSVO) further ensures that the project aligns with governmental research needs, facilitating research uptake and policy improvement.

The study contributes to capacity building for future national *Legionella* surveillance and LD case management. Through the hospital network, the study raises awareness for LD and promotes the collection and analysis of clinical *Legionella* spp. isolates as part of the routine surveillance. Clinical, radiological and laboratory data from the *SwissLEGIO* study will be used in satellite projects to validate the *Legionella* score developed by Fiumefreddo et al. [2009] and to systematically assess radiological characteristics of pneumonia caused by *Legionella* spp. in a large LD patient population that is representing a significant proportion of reported LD cases in Switzerland. For both of these assessments we will use a control group of suspected pneumonia cases tested negative with the *Legionella* UAT. This analysis of clinical, laboratory and radiological characteristics of LD together with data that is collected on patients' health-seeking and recovery from LD may inform revisions of current pneumonia management guidelines. Experiences gained from processes established during this study will also aid the effort to introduce a nationally standardised questionnaire for future case and outbreak investigations. As of today, Switzerland lacks such a comprehensive LD outbreak investigation toolbox [BAG and BLV 2018]. This results in procedures applied to address LD clusters or outbreaks within Switzerland being heterogeneous and, hence, the responsibilities of different stakeholders not being well defined [Wüthrich et al. 2019; BAG and BLV 2018; Zanella et al. 2018]. In turn, this hampers a successful and timely detection of the cluster's infection source. Lastly, the study will, as part of the *LeCo* consortium's research portfolio, play an important role in assessing and informing stakeholders and authorities of the applicability of WGS for single case and cluster investigations during routine surveillance activities.

The *SwissLEGIO* study also provides a unique platform for future research on *Legionella* and LD, including a more in-depth exploration of the bacteria's complex ecology, of virulence factors, of antimicrobial susceptibility of clinical and environmental *Legionella* spp. strain, of clinical and laboratory characteristics and also on disease progression and long-term sequelae of LD. Additionally, the *SwissLEGIO* study data is contributing towards the establishment of a nationally centralised biobank for clinical and environmental *Legionella* spp. strains and associated epidemiological metadata on the spsp.ch platform. Similar to EpiPulse, which is currently implemented by the European Centre for Disease Prevention and Control (ECDC)* [ECDC 2021a], the spsp.ch platform will allow researchers and policy makers to exchange epidemiological and genomic data on LD. Such platforms promote research on LD to be conducted in inter-and transdisciplinary collaborations that are highly needed to address the complex pathway from environmental exposure to *Legionella* spp. to the clinical presentation of LD. Finally, the experiences gained conducting this study, and the data foundation *SwissLEGIO* is providing on LD may provide an opportunity to link

Switzerland through LD on a scientific level to the international data sharing initiatives and EpiPulse, which connect European research and public health community.

Statements and Declarations

Acknowledgments

We thank William Rhoads and Frederik Hammes for their valuable advice during the development and validation of the sampling and analytics protocols. We also would like to acknowledge the valuable inputs from all other *LeCo* consortium members supporting the implementation of these protocols. We also thank the cantonal laboratory Basel-Stadt for sharing their experiences on sampling and sample analytics approaches applied by the lab for routine surveillance and source investigations. At the Federal Office of Public Health, we gratefully acknowledge the various inputs and discussions surrounding the case–control study with Sabine Basler, Marianne Jost, Simone Graf, Nicole Gysin, Mirjam Mäusezahl-Feuz, Ornella Luminati and Ekkehardt Altpeter. We also thank the University Hospital Basel (USB) namely Sarah Dräger and Michael Osthoff for supporting the piloting study that informed the *SwissLEGIO* study. We acknowledge the Federal Statistical Office for providing the data for the recruitment of controls from the general population.

Funding

Open access funding provided by University of Basel. The *SwissLEGIO* project is funded by the FOPH (grant nr.: 142004673). For the molecular source attribution we acknowledge financial support from the FSVO, the FOPH and the SFOE through the project *LeCo* (*Legionella Control in Buildings*; Aramis nr.: 4.20.01).

Availability of data and materials

Not applicable.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose. Monica Wymann, Françoise Fridez Fridez and Stefanie Bertschi are staff of the FOPH, FSVO and SFOE, respectively and participated in their capacities as experts and their function as scientific collaborator within their organisation.

Ethics approval

Ethical approval for the study was obtained from the Ethics Commission of Northwestern and Central Switzerland (EKNZ, 2022-00880). This study is conducted in accordance with the principles of Good Epidemiological Practice[Altpeter et al. 2005] and the Declaration of Helsinki. Data are stored in concordance with Swiss data protection laws.

Contributions

FBF and DM conceived the study concept. FBF, MB and DM further developed the study design and coordinated the operational implementation with partners. JH contributed to the design of the statistical analysis plan. AE and VG contributed to the design of the WGS component. TRJ and FR contributed to the design of the collection, the processing and the analysis of environmental samples. The *SwissLEGIO* Hospital Network members and VG contributed to the implementation of the data collection procedures within the hospitals. All authors provided their expertise to the overall study design, the study protocol and the data collection instruments. All authors participated in the revisions of earlier versions of the manuscript and approved the final version.

Part V

Discussion

Chapter 13

General discussion

One of the biggest challenges in the control of (emerging and re-emerging) infectious diseases is the lack of knowledge about the disease system and disease ecology, which impedes the adoption of appropriate prevention and control measures. Although Legionnaires' disease (LD)* has been a known public health concern since 1976, knowledge around its epidemiology in Switzerland remained limited until recent years. This thesis provides a thorough synthesis of the current epidemiology of LD in Switzerland to serve as a basis for informed discourse, future research and decision-making. Finally, the thesis showcases how the Swiss health system is impacted by and addresses infectious diseases more broadly, referencing examples from SARS-CoV-2 and STEC.

Given the government's commitment to improving LD prevention and control mechanisms and the overall robust notification system (Chapter 4), Switzerland provides a conducive setting for LD research. The burden of illness pyramid (Figure 13.1) is a useful tool to unravel the epidemiology of infectious diseases from the notification system level. The burden of illness pyramid depicts the steps leading from the exposure to *Legionella* spp. in the population up to the capture of an LD case in the passive disease surveillance system. It illustrates that the cases recorded in the surveillance system often represents only the tip of the iceberg of 'true' cases. To fully capture and understand the burden of disease, one must first understand and analyze the steps leading up to the notified case. The research presented in this thesis first reviews Swiss LD notification data collected over the last two decades, demonstrating a seven-fold increase in case numbers (Chapter 4). The extension of this review includes a positivity analysis showing that the number of diagnostic tests increased significantly in parallel with the number of LD cases (Chapter 6).

To understand the increase in diagnostic tests and observed LD case numbers, we examined the mid-levels of the burden of illness pyramid by investigating the role of the health (care) system in detecting LD cases. The analysis of national and international guidelines, recommendations and legislation on LD clinical case management, environmental prevention and control, surveillance and outbreak management (Chapter 8) and a qualitative study among physicians in Switzerland (Chapter 9) revealed that LD diagnostics are highly standardised and confined to the hospital setting only.

Following the principle 'prevention is better than cure'[1], we turned to the lowest level of the burden of illness pyramid to examine population exposure and individual risk to contract LD. In Chapter 10, an

[1]This expression has no clear origin, but is attributed to Desiderius Erasmus (1466–1536).

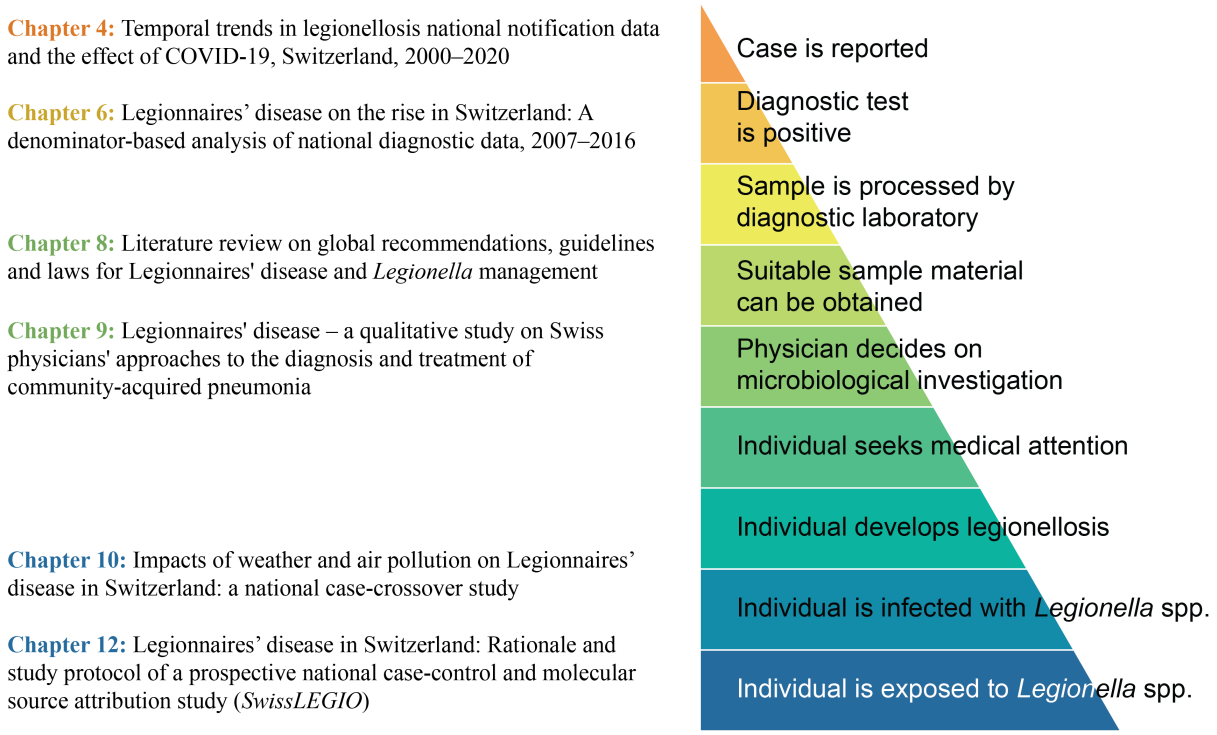

Figure 13.1: The pyramid of disease burden, with references to the individual chapters within this thesis that address specific levels of the pyramid in relation to Legionnaires' disease

association between an increased incidence of LD cases after warm and humid weather was identified, and a similar association was suggested for air pollution. Host, behavioural and environmental risk factors are currently being investigated through a large national case-control and molecular source attribution study that we developed in a trans-disciplinary manner involving actors at all levels. The research protocol for this study, which incorporates the results and lessons learned from the previous studies, concludes this thesis (Chapter 12).

Although the focus of this thesis focuses on LD, contributions on two other (emerging) infectious diseases, COVID-19 and STEC infections, are also included to provide comparative reflections on LD. One of the central themes of this thesis is the interplay between the Swiss health system with LD notification rates, where we specifically examine the role of the healthcare system in case detection and the role of the surveillance system in case capture. In Chapter 4, we studied the impact of COVID-19 containment policies on the number of LD cases. Therefore, this theme is expanded by two studies on COVID-19 from a health system's perspective. Chapter 5 provides a short synthesis of both studies[2] and discusses them in the

[2]Both studies are shown in full in the Appendices B and C.

context of LD. In Chapter 7, we present a positivity study for STEC infections utilizing the same methods as the research on the positivity rate of LD testing (Chapter 6), demonstrating that the interpretation of the results requires nuance.

This final chapter examines how the work presented in this thesis contributes to combatting EIDs, concluding with a reflection on the need to work across disciplines and borders to improve public health.

13.1 A re-emerging infectious disease: generating evidence

13.1.1 Identifying challenges and opportunities in the Swiss routine surveillance system

In recent years, approximately 450 to 550 LD cases were registered annually in Switzerland, with a reporting rate of 5 per 100,000 population in 2020 and 6.5 per 100,000 population in 2021 [BAG 2022c]. With this, Switzerland recorded the second highest notification rate in the entire EU/EEA region in 2020 (based on the latest available European case numbers [ECDC 2022]). Preliminary Swiss case numbers from 2022 are comparable with 2021. After influenza and invasive pneumococcal disease, LD is now the third most common notifiable disease in Switzerland (as of September 2022 [BAG 2022e]). The continuous increase in reported LD case numbers has long been attributed to an increased awareness [Cunha, Burillo, and Bouza 2016; Fields, Benson, and Besser 2002]. However, this assumption falls short of explaining the sustained increase in LD cases: While a qualitative assessment among physicians in Switzerland in 2019 did show significant awareness at all health care levels that LD is a source of atypical pneumonia (Chapter 9), diagnostic testing guidelines have remained largely unchanged since 2006. Under these guidelines, testing is standardised for hospitalised patients with pneumonia regardless of whether LD is suspected or not (Chapter 8). Furthermore, no new diagnostic methods have been introduced since the UAT around the year 2000[3] (Chapter 4), which could result in higher detection rates and, thus, could explain an increase. Overall, if the increase in the number of cases were due to increased awareness, eventually a plateau in observed number of cases would be expected as we converge on the 'true' burden of disease in the population. As of now, after 20 years of steadily rising case numbers, this plateau has not materialised.

Despite the increase in reported case numbers, it is likely that LD incidence in Switzerland is still underestimated. First, as diagnosis is limited to the hospital sector, the likelihood of a case being detected depends on the severity of the disease and the patient's health-seeking behaviour. Second, diagnostic

[3] While PCR was available and has been introduced into routine diagnostics in Denmark as early as 1995 [Uldum and Mølbak 2001], the introduction of PCR methods for clinical *Legionella* detection in Switzerland did not seem to get underway until the 2000s. The proportion of detected cases by PCR increased from 3.3% to 10.6% between 2000-2005 and 2016-2020 [Fischer et al. 2020b]. However the overall proportion remained comparatively low.

approaches for LD are not fully satisfactory: Sensitive PCR and culture-based approaches are rarely used in Switzerland, and the commonly used UAT only detects one serotype with a sensitivity rate of about 80% [Muyldermans et al. 2019; Kawasaki et al. 2022]. Overall, physicians estimate that a causative agent can only be identified in roughly half of all pneumonia cases, even if diagnostic efforts are made due to shortcoming in diagnostic methods, lack of sample material or delay in testing after antibiotic therapy has been initiated [Shoar and Musher 2020] (Chapter 9). Though reported cases represent only the visible burden of disease, i.e. the tip of the iceberg, Chapter 4 has shown that the capture of cases in the infectious disease surveillance system seems to be satisfactory once they have been detected in the health system: The internal validity, completeness and timeliness of reported LD cases in Switzerland are generally good.

Increases in cases have been noted in many other countries, but rarely addressed in a systematic manner. However, hypotheses and explanations for the increase largely remain similar to those made in Switzerland. For example, studies from Italy and Denmark could not rule out the possibility that the observed increase was merely a surveillance artefact [Riccò et al. 2021; Cassell et al. 2021]. However, similar to us, they also conclude that surveillance artefacts alone cannot fully explain the increase in cases. The study from Italy also reported that the UAT was introduced far earlier than the observed increase in cases and the positivity rate remained largely stable [Riccò et al. 2021]. Case detection in Denmark is different to the one from Switzerland, Italy and the majority of other countries: The primarily used diagnostic method is PCR rather than UAT, and PCR has already been introduced in routine diagnostics since 1995 [Cassell et al. 2021; Uldum and Mølbak 2001]. Nevertheless, Denmark shows an increase in the number of cases between 2014 and 2017, which suggests against the strong influence of the UAT on the growing number of cases. New Zealand has observed an increase in cases in 2010 and another one in 2015/2016 [ESR 2021]. Both increases coincides with the introduction of new testing strategies: First the replacement of culture with PCR for routine diagnostics of LD in one region and then the subsequent nation-wide roll-out in 2015/2016 [Priest et al. 2019]. Outside of these strong surges in case numbers, the notification rate seems stable, albeit high, which would suggest that the observed increase in cases might be attributable to a surveillance artefact. Overall, there is no universal answer to the increase in cases. Due to globalization, innovations in diagnostic tests are nowadays circulating rapidly around the world, and climate change and population ageing are also global phenomena – or at least in the countries where disease estimates of LD are available. However, as health policies determine a large part of the actual disease detection and generated disease estimates, an individual assessment of the processes is essential to draw conclusions on epidemiological trends, and surface-level comparison between countries is difficult (see Chapter 13.2.3).

Reliable disease estimates are essential for decision-making in public health [Murray and Lopez 1996]. They allow the tracking and monitoring of progress in alleviating disease burden and trends over time. Ultimately, they are a decisive factor in allocating resources for the implementation of public health measures to address specific problems. Disease estimates are also important for the allocation of research resources

and identification of meaningful research avenues that translate into public health benefit. The Swiss notification data, thus, provide a basis for further research or extended surveillance. Careful evaluation of this data is, therefore, essential to arrive at sensible decision-making. In this thesis, we have conducted several studies drawing on notification data, many of them integrating other data sources as well. In the following sections, we discuss the benefits of the specific data sources and how the institutionalized integration of all or some of them could systematically improve future infectious disease surveillance in Switzerland (and abroad).

13.1.2 The potential of integration of various data sources to strengthen infectious disease surveillance

Testing and denominator data

Infectious disease surveillance systems are primarily designed to monitor long-term disease trends and detect short-term deviations from the norm to enable timely reaction to outbreaks. Notification data alone, however, is insufficient to determine long-term epidemiological trends. Surveillance systems can only account for those cases that are visible to the health system. How can we account for the invisible likely larger proportion of cases lost in the steps up to notification? In part, by incorporating the numbers of diagnostic tests performed as denominator data for positive test results (- analogous to the inclusion of the underlying population to calculate incidence or mortality rates). This is particularly valuable if there is reason to believe that testing behaviour has changed, as was the case for COVID-19 and chlamydia, following updated testing recommendations [Schmutz et al. 2012], or for STEC infections after a new diagnostic test was introduced (Chapter 7). Such knowledge can reveal apparent increases in case numbers to be merely the result of changes in testing or detection. The FOPH has recognized the importance of such denominator data and institutionalised its collection [BAG 2020a; Federal Assembly 2016]: However, the data quality was not sufficient for an investigation [Schmutz 2018]. As long as the quality of the reported data is not assured, the analyses of the positivity rates using denominator data presented in Chapters 7 and 6 had to be carried out on the basis of a primary data collection, which requires additional time and costs.

The value, but also limitation, of analysing testing denominator data is illustrated when comparing the temporal trends of the positivity rates of two diseases we investigated, namely LD (Chapter 6) and STEC infections (Chapter 7). Both infectious diseases saw large increases in case numbers in previous years. For STEC infections, the positivity rate increased between 2007 and 2016 (Figure 7.3), while it remained stable for LD (Figure 6.2). In both cases, the number of diagnostic tests performed increased dramatically. The rise in STEC testing is attributed to the introduction of a new diagnostic test, the syndromic multiplex PCR panel [BAG 2015], to routine diagnostics in medical laboratories. Using these syndromic panels, the diagnostic workup of gastrointestinal infections automatically triggers a test for a multitude of gastrointestinal pathogens, including STEC. With the number of positive tests increasing more

strongly than the total number of performed tests, the increased notification rate of STEC infections cannot solely be attributed to expanded testing. Such context was not available for LD, hindering interpretation of the increasing test rate and the constant positivity rate for LD. Through our subsequent studies, we demonstrate that the UAT was introduced in routine diagnostics in Switzerland around 2000 (Chapter 4), well before the study time frame (2007–2016) and that the CAP testing guidelines remained unchanged between 2006 and 2021 (Chapter 8). These studies support the assumption that changes in testing behaviour were not driven by external factors, but are rather clinically motivated, i.e. by increased consultations with patients presenting with symptoms prompting a *Legionella* diagnosis.

Although increased testing intensity is often cited as a cause of rising LD reporting rates, to our knowledge no other study has examined testing behaviour. Generally, little attention has been paid to positivity studies by scientists and policy makers alike until the COVID-19 pandemic, when positivity rates were regularly used for decision-making. This development can strengthen support for improved annual reporting of aggregate test rates, which in turn supports the interpretation of notification data in a resource-efficient manner for decision-making.

Hospital statistics

To capture outbreaks in a timely manner, LD cases must be reported to the FOPH within one week of diagnosis (Federal Office of Public Health, 2020). Consequently, health outcomes occurring outside of this window are not captured in notification data. Comparing the number of LD-attributable deaths in hospital statistics[4] with the number of deaths reported in the NNSID, suggests that NNSID underreports LD-attributable deaths by an average of 30%. Considering this, the 3.6% CFR reported in Switzerland in 2020 is likely closer 5.1%, yet still lower than the European average CFR of 8%. The public health relevance of LD continues to be underestimated since underreported fatality rates are widely disseminated and the underreporting of deaths goes largely unnoticed. Other clinical variables, such as intensive care unit (ICU)* admission rate, or hospitalization duration (discharge date), which can not reliably assessed, have already been removed from the clinical notification form and are currently not systematically captured. Overall, information on clinical outcomes might be better extracted elsewhere, such as from hospital statistics, rather than the national notification system (or not at all).

Furthermore, clinical reporting is particularly vulnerable to non-compliance: we found that physician reporting declined at the start of the COVID 19 pandemic compared to laboratory reporting (Chapter 4). While laboratory notifications are often automated, clinical reporting forms are completed by hand.

[4] 'The hospital statistics primarily serve to describe the infrastructure and the activity of hospitals and maternity hospitals in Switzerland. The establishments required to provide information report annually on, among other things, the outpatient and inpatient services provided, staff and their operating accounts.' [BFS 2022]

This is in part necessary as some of the information requested can only be filled out in dialogue with the patient, which cannot be automated. This information primarily relates to risk factors and possible exposures (see Appendix F-3 for the current clinical notification form). The quality of these reports is difficult to judge without external validation. Nevertheless, in light of the COVID-19 pandemic and the overload of physicians, the clinical reporting may, thus, have been neglected. However, introducing electronic notification and simplifying the current notification form to variables which can be reliably captured, i.e. the minimal essential, would decrease the time needed to fill and could improve acceptability and compliance on part of the treating physician. Information gaps could then be filled from hospital statistics. A recent study from New Zealand showed how the integration of hospital statistics with routine surveillance data allowed estimating the length of hospital stay, the number of deaths and the direct costs of inpatient care related to LD [Graham and Baker 2022].

Geospatial (health) data

Geospatial methods can be used to determine spatial disease patterns, clusters and risk factors or exposure sources and visualize disease distributions. While spatial models for many other infectious diseases on the basis of human-to-human transmission are not applicable to LD, models typically used for abiotic environmental exposures like air pollution or pesticides, such as a case-crossover study or ecological model (Chapter 10) are better suited.

The NNSID records the residential addresses of LD cases, theoretically providing the basis for detailed geospatial analyses. Yet, routine analyses at the FOPH only report the spatial distribution of cases at cantonal or greater region (NUTS-2) levels. Furthermore, the FOPH is restricted to keep person-identifying data such as residential addresses for only three years for data protection reasons. After residential addresses are deleted, only the information of the case's municipality is retained for future analyses. It is likely for similar reasons that fine-scale spatial analysis are often only used for outbreak investigations [Bull et al. 2012; White et al. 2013], while analysis of routine surveillance data is performed on aggregated data. Yet, any aggregation of spatial information covers up small -scale associations.

The fact that the ecological model examining different spatial determinants of LD occurrence (such as number of wastewater treatment plants and mean socio-economic position per district) identified mainly large-scale determinants of LD occurrence is also due to methodological constraints and data limitations (Chapter 10). To spatially correlate point-source determinants to LD cases, we had to request data on potential determinants (exposures) from respective data holders, ranging from governmental entities (e.g. for wastewater treatment plants) to private registries (e.g. for public outdoor and indoor pools). If this data were not available with sufficient completeness, it could not be used for the study due to potential exposure misclassification. The limitations of this data scarcity are best illustrated with the example of cooling towers. These determinants were of great interest due to their previous association with LD outbreaks [Wüthrich

et al. 2019]. However, primary data collection for cooling towers is extremely resource-intensive: Cooling towers are numerous and not all of them evaporate water into the air, thereby posing a risk for *Legionella* infection. Differentiating between 'risky' and 'safe' cooling towers is virtually impossible from afar. Several countries already recognized the benefits of registering (LD) risk factors and have, therefore, established a national cadastre of cooling towers [Paschke, Schaible, and Hein 2019].

To maximize the potential of GIS for research but also outbreak investigations, geospatial case data and locations of potential sources (e.g. cooling towers) is essential [Bull et al. 2012]. Data protection has become increasingly important, for example, with the advent of large cohort studies with biobanking, and data security and storage procedures have become more sophisticated to meet data protection requirements. The problem with small-scale geospatial health data is that they require different anonymization methods than other data- a dot on a map always has the potential to be person-identifying [Curtis, Mills, and Leitner 2006]. Similar issues have been exemplified during the COVID-19 pandemic, where COVID-19 containment measures such as contact tracing posed problems to data privacy and solutions had to be found urgently. Therefore, a long-term strategy to harmonize data protection needs and data requirements for public health research (including spatial health data) is needed to facilitate research, but also to ensure preparedness for epidemics.

Pathogen genomic data

Another cornerstone of infectious disease surveillance is monitoring shifts in pathogen diversity, virulence and antibiotic resistance using genomic information. For *Legionella* in particular, understanding the degree of relatedness of *Legionella* spp. isolated from clinical and environmental samples, combined with epidemiologically plausible links, is currently the most reliable method for determining the infection source or whether a group of cases originates from the same source and should, therefore, be classified as an outbreak.

For typing of pathogens and pathogen monitoring, the FOPH commissions 15 national reference laboratories for selected diseases. The corresponding analyses require the availability of bacterial isolates from bacteriological culture. Nowadays, however, culture diagnostics for LD are rarely performed, as faster and cheaper diagnostic methods are available. In Switzerland, over 80% of LD cases are diagnosed using an UAT (Chapter 4). Consequently, isolates are only available for a small fraction of LD cases. If isolates are obtained, the diagnostic laboratories are required to send them to the NRCL. So far, around 50 *Legionella* isolates are sent to the NRCL annually. However, the information from these isolates (such as the strain) is not fed back into the NNSID or currently not yet collected in any other centralised database. Therefore, in the last 20 years only a handful of *Legionella* non-*pneumophila* strains were recorded in the NNSID (Chapter 4).

Compared to New Zealand [ESR 2021] or Denmark (personal communication), which use PCR diagnostics in over 90% of cases, Switzerland is lagging behind in assessing and monitoring the landscape of pathogenic *Legionella* strains, which has implications for prevention and control. As clinical isolates are typically not obtained from patients in Switzerland, the cantonal laboratories often have to rely on epidemiological evidence alone, which limits the identification of the source of individual cases or outbreaks, and, therefore, the ability to advocate for appropriate public health measures.

The *SwissLEGIO* study (Chapter 12) has fuelled the discussion on improving *Legionella* diagnostics in Switzerland. For example, at the time of the study initiation, one hospital in the network was able to establish *Legionella* bacterial cultures in their own laboratory with the guidance of other research partners. Increasing the yield of sputum seems to be possible through the increased sensitization of physician and diagnostic laboratories and intensified communication within hospitals: The set-up in *SwissLEGIO* currently often has staff from the diagnostic laboratories proactively asking the treating physicians for the availability of sputum if a UAT returns positive. Depending on the results of the study, efforts should be made to maintain the increased level of sputum yield and expand it to non-participating hospitals to improve pathogen surveillance through existing channels, such as the NRCL and the NNSID.

Apart from the availability of clinical sample materials, there have been large advances in molecular methods for typing, such as WGS. These methods have great discriminatory power between *Legionella* strains and subtypes and are becoming increasingly available in disease surveillance [ECDC 2018c]. Investigating the potential of applying WGS for routine outbreak investigation of food- and waterborne diseases is part of the FOPH's 2021–2024 research strategy [BAG 2019a]. The FOPH has mandated the NRCL with the promotion of culture-independent diagnostic methods and new methods for typing *Legionella* , and the *LeCo* project presented in Chapter 12 received the research mandate to evaluate the integration of next generation sequencing methods into routine source investigation.

Central management and storage of genomic surveillance data are essential to make them available for future (public) use. If available data are fragmented between different data holders, pattern detection will be severely hindered. The recently established 'Swiss Pathogens Surveillance Platform' (SPSP)* has assumed this role for COVID-19 and, in this capacity, closely collaborates with the FOPH to make data available. Now, the platform aims to centralize WGS data for several diseases, including LD. The isolates gained within the *SwissLEGIO* project will be centralised with SPSP and contribute to a larger library of *Legionella* sequences, important not only for future research but also for outbreak investigations. Additionally, since summer 2021, the ECDC has moved to a new infectious disease surveillance platform 'EpiPulse', integrating routine surveillance, global epidemic intelligence and WGS. The *Legionella* surveillance system, ELDSNet will move to EpiPulse at the end of 2022. With *SwissLEGIO* and the promotion of the SPSP platform for *Legionella* sequences, Switzerland can take a leading role on genomic surveillance for *Legionella* .

We have shown that the integration of different data sources holds much promise for public health. Several avenues, such as the promotion of WGS for disease surveillance, are currently being pursued. Until integration is institutionalised, the NNSID database provides a sound basis not only for the FOPH but also for researchers to fill the gaps or research needs for effective prevention and control of the 56 notifiable diseases. Therefore, strategic partnerships between the FOPH and researchers are mutually beneficial, ensuring strong governance to harmonize and integrate data from different sources while assuring data security, transparency and accessibility.

13.1.3 The health care providers' role in the notification process

The burden of illness pyramid is a good tool to investigate notifiable diseases and contextualize notification processes and, thus, the generation of notification data. The pyramid considers all steps in the care and diagnostic processes leading up to notification. In other words, using the pyramid as framework to understand reported cases adds setting-specific context to notification data. Adding such context supports the interpretation of the data and the drawing of correct conclusions.

For example, when comparing the positivity curves for STEC infections and LD, additional context on changes in the diagnostic landscape was available for STEC infections. As this information was unavailable for LD, no inferences could be drawn on why test volume increased while the positivity remained stable. We approached this knowledge gap from two angles. First, we investigated the clinical guidelines that guide diagnosis for lower respiratory tract infection (LRTI)* and, therefore, lead to aetiological testing (Chapter 8). Second, we explored how these guidelines are translated into practise by physicians across Switzerland in their daily routines (Chapter 9).

The importance of historical 'book keeping'

Clinical practice guidelines are recommendations that are systematically developed aiming at optimising patient care. Clinical management of LD is primarily addressed in pneumonia guidelines, which form the basis for all decisions that shape and inform the data we see. For example, aetiological testing for pneumonia is not recommended for outpatients (Chapter 8). Indeed, the majority of LD cases visible in the NNSID are hospitalised persons (Chapter 4). Only with the contextual knowledge of the test recommendations can we conclude that presumably not all LD cases end up in the hospital, but that primarily hospitalised cases are diagnosed and reported.

The most prominent clinical guidelines for CAP management, the SSI guideline mentioned by the Federal Offices in the document '*Legionella* Recommendations of the FOPH and FSVO' [BAG and BLV 2018], was updated in 2021 [Albrich et al. 2021], the previous version has been published in 2006 [Laifer, Flückiger, and Scheidegger 2006]. Hence, we can assume that testing standards have remained largely similar for 15 years. Even, when looking at other guidelines for the treatment of CAP, the recommended

diagnoses and treatments remained generally consistent. Therefore, the influence of clinical guidelines is likely not representing a surveillance artefact and did not contribute to the increasing number of reported LD cases. In contrast, however, there is no documentation of when the *Legionella* UAT was introduced in routine diagnostics in Switzerland, although its introduction is assumed to have revolutionised LD diagnosis and case finding. We can see in the data that by the year 2000, the earliest year in the time series, the UAT was already used in the largest proportion of all notified LD cases (76.2%). However, this data provides little insights in the absolute test number and the deployment of the UAT. Only from personal communication and exchanges with experts, we learned that the test was introduced around the 2000s – therefore, while it might explain some increases in test frequency and case numbers, the effect should not have continued on for 20 years. This contextual information has been critical for the discourse around the observed LD case increase.

Generally, retrospective interpretation of disease trends will profit from the diligent recording of current contextual information. On the most basic level, and most feasible to implement, changes in legislation or guidelines should be well documented and transparently disseminated, particularly if the notification data itself is freely available. The document '*Legionella* Recommendations of the FOPH and FSVO' [BAG and BLV 2018], last updated in 2018, covers in part the role of such a compendium, as it summarises current LD and *Legionella* case management in Switzerland. However, it does not capture contextual changes systematically. Ideally, compendia or repositories should be available for all existing notifiable diseases and should be initiated as soon as a new disease emerges. The need for the dissemination of such information has been recognised in the case of COVID-19, where the interpretation of the COVID-19 case numbers was strongly dependent on current containment measures and testing recommendations (Chapter 5). The FOPH has already realised such record keeping by providing a publicly available list of implementation dates of containment measures for COVID-19 [BAG 2022a].

The role of 'practical wisdom'

Guidelines are only functional if they are adhered to. When they are not, we may misinterpret data by relying too strongly on theoretical frameworks. Despite the guidelines recommending a *Legionella* UAT for hospitalised pneumonia patients, the widespread belief persists that a lack of awareness of LD among physicians led to underreporting and that the growing notification rate merely reflected a growing awareness among physicians leading to increased case detection [Fields, Benson, and Besser 2002; Cunha, Burillo, and Bouza 2016]. While it is difficult to establish retrospective awareness levels, we suggest that growing awareness of physicians' is likely not the primary factor driver of increasing case numbers (Chapter 9). The hospital physicians in our study were well aware of LD and reported that they ordered *Legionella* UAT tests regularly, as indicated by clinical guidelines. And, as mentioned above, these clinical guidelines regarding *Legionella* testing have remained largely unchanged between 2006 and 2021. In contrast, general practitioners (GP)* were less sensitised, as they do not perform aetiological investigations of pneumonia

and thus are not consciously exposed to LD. However, the lack of testing is not a result of poor awareness, but complies with the recommendations for empirical CAP treatment in the outpatient setting.

Furthermore, GPs expressed limited financial resources to order diagnostic tests. Diagnostic test reimbursement, controlled by the government and health insurance companies, was reduced in a 2008 reform, discouraging GPs with in-house practices from performing them. Therefore, part of the underestimation has been by design through tariff policies and clinical guidelines. Optimal and cost-efficient patient care and the promotion of public health may not always be achieved by the same means. Lastly, some physicians reported low confidence in the sensitivity of the available diagnostic test methods for LD, specifically in the UAT (Chapter 9). Where confidence was low, physicians favoured broad-spectrum antibiotics since testing would not impact their treatment preferences, rendering testing obsolete. Indeed, this lack of trust is not unfounded with a UAT sensitivity of 79% [Kawasaki et al. 2022] and reported false negative rates of up to 37.5% [Muyldermans et al. 2019]. For this reason, recent research suggests that the UAT should be used as a rule-in test rather than a rule-out test [Rojas, Naqvi, and Balakrishnan 2021].

For the reasons above, beyond keeping track of legislation and guidelines, their translation into lived reality should be regularly evaluated. Physicians' and and professionals' working in diagnostic laboratories knowledge on this translation is an example of what has been described as 'practical wisdom' [Robert and Fulop 2014]. Deviations from clinical management according to guidelines often result from the complexity in which physicians or other practitioners are required to make decisions [Gabbay and May 2016]. The adaption of clinical guidelines through experience has also been coined 'mindlines' - guidelines-in-the-head. Understanding the formation of these mindlines are important for understanding and fostering good clinical care. However, for public health, and particularly the interpretation of disease surveillance data, these mindlines become particularly important, when collective mindlines are formed, where practitioners align their practical approach through communication and exchanges [Gabbay and May 2016]. These can influence case detection as much as clinical guidelines. Yet an outsider is not privy to these collective guidelines or practical wisdom, and thus, might fail to understand processes leading up to case detection. Practical wisdom is often context-specific and contrasts with our primarily empirical and numbers-driven understanding of public health information systems [Sahay and Lewis 2010]. For this reason, it is often pushed to the side-lines or disregarded. However, the work in Chapter 9, aided by practical wisdom, could clarify three direct and actionable shortfalls in estimating the LD burden of disease: (i) the misconception that awareness campaigns are the best path to reducing LD underestimation, (ii) that clinical guidelines and diagnostic test reimbursement at the primary health care level need to be revisited if LD case detection should expand beyond the hospital setting and (iii) the need to invest in the development of better diagnostic tests, improving physician's trust in the test result and thereby, treatment approaches.

Currently, efforts to gather practical wisdom or understand mindlines in such depth as presented in Chapter 9 are often undervalued. Moreover, even if such studies are encouraged, it is understandably

difficult to conduct them for the entire notifiable infectious diseases portfolio (of 56 diseases) in Switzerland. Yet, valuable assessments could also be made on a smaller scale to remain feasible. For STEC, for example, the FOPH sent delegates to selected diagnostic laboratories across Switzerland to discuss recent increases in case numbers and their current diagnostic approaches [Schmutz 2018]. While not adhering to strict scientific methodology, this information was sufficient to interpret the results of the STEC study on testing denominator data (Chapter 7). The diagnostic laboratories also appreciated the direct contact and exchange with the FOPH [Schmutz 2018]. Such knowledge transfer should, therefore, be further encouraged and could be one of the first avenues to pursue when unexpected patterns are observed in surveillance data.

13.1.4 Population-level determinants of Legionnaires' disease

The bottom level of the burden of illness pyramid is likely the most difficult to assess, as we move out of the health care system and into population-level determinants. Despite the challenge, identifying these risk factors and exposure sites is probably the most essential step to guide prevention and control efforts.

Weather and air pollution: Large-scale determinants of Legionnaires' disease incidence

The risk factors assessed in this thesis can broadly summarized in two groups: Large-scale environmental promoters of LD incidence and small-scale sources of infection. The large-scale determinants are not exposure sources in and by themselves, but act as important risk modifiers, either by increasing the *Legionella* concentration in the environment or by facilitating transmission. The effects of specific weather conditions on LD case occurrence has been previously investigated [Beauté et al. 2016; Braeye et al. 2020; Brandsema et al. 2014; Conza et al. 2013; Gleason et al. 2016; Sakamoto 2015; Russo et al. 2018; Simmering et al. 2017; Walker 2018; Pampaka et al. 2022]. For Switzerland, we identified warm and humid weather as promoters of LD incidence (Chapter 10), in line with international literature [Pampaka et al. 2022]. The weather likely contributes to the observed seasonality (Chapter 4), with more cases in summer and the regional heterogeneity with highest per capita case numbers in Ticino. The mechanism of this observed effect remains unclear, but the time frame of lag effects can provide some insights: Temperature effects were most strongly associated with LD incidence before the incubation time, suggesting that temperature does not facilitate transmission but promotes changes in the environment, such as increasing *Legionella* concentrations. In contrast, vapour pressure showed the strongest associations during the incubation time. This would suggest that the infectious sources are water sources that vary in temperature based on ambient temperature. However, residential drinking water installations for hot water, one of the primary suspects for infection, remain relatively stable in temperature. And other questions remain: The seasonality is primarily observed in community-acquired LD or TALD cases, not among nosocomial cases. While the mechanism remains poorly understood, the finding of these associations could guide CAP management guidelines (e.g. intensive testing and LD-active treatment) following specific weather patterns.

In Chapter 10, we further argue for the potential association of LD incidence with air pollution. This association has received little attention until now, even though air pollution could act as an important confounder in the link of weather and LD [De Sario, Katsouyanni, and Michelozzi 2013; Vanos et al. 2015]. If air pollution indeed promotes LD incidence, it could explain at least part of the high LD notification rate in Ticino, which is severely affected by the air pollution from the Italian Po-valley [EEA 2020]. In our analysis, the association of air pollution was not confounded by the degree of urbanization, nevertheless the highest case burdens are concentrated in urban areas [Passer et al. 2020]. All of the above factors (weather and climate, air pollution and urbanization) are projected to globally worsen or intensify in the future. Understanding the attributable risk helps in understanding variations in disease incidence and in anticipating trends.

Showers, fountains, wet cooling towers or dentures? Sources of infection for Legionnaires' disease

Identifying small-scale sources of infection are paramount to identifying effective prevention and control measures. Current prevention measures, such as the recommended temperature guidelines for residential hot water systems in buildings, lack evidence of their effectiveness. Or, in other words, while high water temperature manages to stave off *Legionella* contamination, it remains unknown if residential drinking water is actually the main driver of LD infections. Not only does this lack of evidence impede the actual public health benefit, it also reduces the acceptability of these guidelines. The conflicting interests regarding hot water temperature in buildings and, therefore, LD and *Legionella* management, on the one hand towards protecting the health of people and safe potable water, and on the other hand towards economic and environmentally compatible energy consumption are further discussed in Chapter 13.2.1.

In Chapter 12, we present the protocol for *SwissLEGIO*, a case-control and molecular attribution study designed to identify host, behavioural and environmental risk factors and exposure sites. During the conception and planning of the study, we found that many processes in the data collection pipeline from patient recruitment to WGS of environmental samples have not yet been established. To account for this complexity, Chapter 13.2.2 is devoted to discuss the challenges in identifying population-level risk exposures for LD.

The need for multidisciplinary research to address population-level determinants

No single research discipline can explain the impact of the small and large determinants of LD infections alone; it requires the expertise of various fields, such as environmental biology and microbiology, (drinking) water hygiene and public health. All these research streams are essential to fill knowledge gaps in the LD disease system, but have been operating in silos more often than not. The results from public health research guide and provide the rationale for most research efforts of other disciplines. For example, the difficulties to obtain reliable environmental isolates to support the detection of infectious sources, may in part motivate

the research to investigate *Legionella* in biofilms and amoeba. Understanding these dynamics in ecology could support the development of more robust sampling and analytical methods. However, public health research and particularly observational epidemiology (in contrast to experimental epidemiology including randomized controlled trials) can hardly provide causal relationships of observed patters, as described on the example of the association of weather conditions and LD incidence. Conversely, the knowledge gained from molecular and microbiological research enhances our understanding of causal relationships and mechanistic pathways of transmission and pathogenicity in the LD disease system, and may help identify solutions for environmental control and prevention. In turn, the results of this research are sometimes difficult to translate into public health relevance.

Therefore, a principal design feature of the *SwissLEGIO* study (Chapter 12) is the integration of human and public health with environmental and microbiology and water hygiene through the involvement of a wide range of actors across disciplines and sectors.

13.2 Navigating a complex landscape: public health research across disciplines, sectors and regions

13.2.1 Policy-making for Legionnaires' disease management: A multitude of actors and a multitude of challenges

At the federal level, three Federal Offices are involved in policy-making for LD and *Legionella* prevention and control: The FOPH, the FSVO and the FOE. Concerning LD management, the pursue conflicting objectives: Both the FOPH and the FSVO call for strict plumbing system guidelines to ensure a sufficient hygienic standard to avoid the spread of LD. The FOE, responsible for buildings, energy and planning, pursues economic and energy-efficient management of residential buildings, which extends to the energy consumption for the production of drinking water, water distribution and hot water heating. Reducing the hot water temperature could save energy, while potentially compromising temperature-based *Legionella* control in plumbing and piping. High temperature for potable water is currently the primary preventive method to stave off *Legionella* contamination - at the cost of higher energy expenditures. The use temperature of hot water (e.g. the temperature at the tapping point for showering or cooking) in residential spaces could be lower (below 50 °C) than the current standard of at least 55 °C [BAG and BLV 2018]. Switzerland is not alone with this conundrum, the temperature treshholds for hot water at the point of the water heater (boiler) are largely aligned across the globe (Chapter 8). At time of writing, the discussion about energy savings is receiving renewed attention due to rising energy prices and the threat of gas shortages resulting from the Russian-Ukrainian war since February 2022. Particularly in Germany, this has led to a number of news reports about the energy saving potential of decreasing hot water temperatures [Heizsparer Redaktion

2022; Bund der Energieverbraucher 2022]. Currently, the risk posed by *Legionella* means that reductions below 55 °C are rarely recommended. Yet this could change as discussions around energy savings become more prominent in the public discourse, not least because of the looming threat of climate change. Evidence for or against the benefit of current recommendations for hot water and building maintenance are urgently needed to guide decision-making and also to improve the acceptability of policies for prevention measures.

Policies around building planning and maintenance are translated into practice by professional associations on *Legionella* and energy efficiency who are largely aligned with the FOE. In particular, suppliers and advocates of heat pumps and solar thermal systems feel that strict regulations on hot water temperature prevents these technologies from being used to their fullest potential [Haller and Ruesch 2019]. Moreover, these professional associations are also not at ease with such stringent requirements while the main source of infection has not yet been identified. On the other hand, wet cooling systems that have been shown to be responsible for multiple outbreaks are not considered an utility article in the food safety law and are free from these restrictions. This tension led to an initial rejection of a revised hot water norm in 2018 and sparked research on the safety of solar thermal systems [Haller and Ruesch 2019]. To strengthen acceptability of preventative measures, there is a need to identify *Legionella* prevention strategies that do not compromise energy-efficiency and that are backed by evidence.

Other actors influencing the discourse are private contract laboratories who offer testing services evaluating buildings for *Legionella* contamination. Contract laboratories can carry out sampling on behalf of the contract owner and thereby empower the public to take ownership of the quality and safety of drinking water in their own homes. However, as profit-oriented companies, the contract laboratories also have a vested interest in carrying out building inspections and water sampling. Germany is an example of how profitable this system can be: In Germany, large facilities like apartment buildings must be tested for *Legionella* every three years while public buildings such as schools must be tested annually [Meyer 2017]. Thus, these approx. 3.3 million public buildings in Germany provide inspectors and laboratories with a turnover of almost 400 million Euros per year [Meyer 2017].

The impact that different actors, including private contract laboratories, can have on the public discourse on *Legionella* prevention measures became apparent in early 2020. At the beginning of COVID-19 shutdown measures, warnings abounded that building closures would lead to water stagnation, increased proliferation of *Legionella* in plumbing systems and, thus, increased infections. These warnings came from ESCMID ESGLI [2020], the SVGW [2020] (which was also taken up in a press release of the FSVO), but also many private contract laboratories. However, scientific evidence on the dangers of shutdown measures was and is scarce: A study from Taiwan concluded that there was a stagnation effect by comparing the total number of cases from two years before the pandemic and two years after the pandemic [Chao and Lai 2022]. However, temporal nuances are lost in this aggregation: In Switzerland, a combined LD case count from 2020 and 2021 would not explain the decline in cases in 2020 nor the sharp increase in 2021.

Other research reports a primarily higher proportion of *Legionella* -positive water samples [Association 2021], but increased contamination does not necessarily translate into increased incidence and public health relevance. Conditions in the sanitation system are complex and stagnation does not always lead to the same contamination results [Rhoads and Hammes 2021]. In our study (Chapter 4), we did not find an increased incidence after buildings reopened compared to the same calendar weeks in the prior years. However, the reopening of buildings in Switzerland was gradual, meaning a potential effect could be spread over a longer period of time and, therefore, harder to detect. Alternatively, the intense warnings and education efforts might have paid off among building managers who regularly flushed their pipes. In the absence of evidence, these warnings followed the principle of 'better safe than sorry'. However, these warnings may not have been entirely driven by public health concerns, given that preventing stagnation comes at a cost, and that the warnings likely prompted some building managers to hire contract laboratories to assess the safety of their drinking water system. Fundamentally, the question if drinking water in buildings cause the largest proportion of LD cases remains unanswered.

13.2.2 The genesis of *SwissLEGIO* and the epidemiological research agenda in Switzerland at large

Almost five years passed between the conception of *SwissLEGIO* and the start of data collection in summer 2022. With LD notifications increasing strongly in the first half of the 2010s, suspicion grew that this increase might not be temporary, but likely the start of a trend that was not well understood. Without knowledge on the potential causes of the increase, evidence-based, targeted prevention and control efforts were difficult. In a scoping phase in 2015/2016, the FSVO, therefore, commissioned Swiss TPH to identify knowledge gaps in the epidemiology of LD in Switzerland and to develop a research concept including study proposals, to close these gaps. At the same time, the FOPH mandated a study to investigate whether the case increase was primarily a test artefact (Chapter 6).

To investigate risk factors and exposure sources, Swiss TPH proposed initially a case-control study with was then extended by the molecular source attribution to answer this complex research question. This research study entitled *SwissLEGIO* constitutes a research endeavour comprising several research methodologies and secondary objectives requiring careful preparation to manage the interdisciplinary study team with collaborators from four institutes, a network of 20 hospitals and 410 study participants (cases and controls). Many processes in the data collection pipeline - from participant recruitment and clinical and environmental sampling to isolate picking and WGS - had not yet been fully established in the framework of LD. This meant that we could not fall back on proven principles, but had to optimize each individual step. Therefore, following the initiation of *SwissLEGIO* endeavour in 2016, a set of pre-studies was developed in a joint effort with the FOPH to inform the final study design and assess feasibility before the funding for the case-control study could be approved. The pre-studies encompassed (i) a literature review (Chapter

8) and (ii) a physician survey to explore case recruitment avenues (Chapter 9) and (iii) a case-control pilot study to assess feasibility (Chapter 11). The insights from these pre-studies were incorporated into a revised case-control study proposal. This chapter summarizes several key learnings about the design and development of *SwissLEGIO*.

Scientific challenges

The framework: A case-control study to assess risk factors. Case-control studies are particularly well suited to investigate risk factors for rare diseases, as cases are actively recruited to increase sample size [Riffenburgh and Gillen 2020]. To date, numerous case-control studies on LD have been published [Storch et al. 1979; Den Boer, Nijhof, and Friesema 2006; O'Connor et al. 2007; Vermeulen et al. 2021; Emma et al. 2017; Buchholz et al. 2020] and generated most of the current knowledge on risk factors and exposures for LD. However, the majority of these studies were conducted in the framework of outbreaks and provide limited generalizability for sporadic cases, which constitute the majority of cases. Conducting a representative case-control study on sporadic community-acquired LD cases requires a sufficient sample size. However, in the early planning phases of *SwissLEGIO*, LD incidence in Switzerland was relatively low, with around 500 cases annually. Therefore, data collection was planned nationwide and prospectively, over the course of a year. Sample size assessment was rather conservative (maximalist) as there was little available evidence on the general public's exposure. Therefore, we used an exposure of 60% for the sample size calculations. Details of the methods chosen and the sample size are described in Chapter 12.

Establishing a hospital network to address recall bias. The initial idea was to recruit patients through the FOPH, which receives notification of all cases. However, the diagnostic laboratory, the attending physician and the cantonal medical services each have a period of one week to report a case to the FOPH [BAG 2020a]. This means that, in the worst case, the clinical report arrives at the FOPH two weeks after diagnosis. Adding in the incubation period (2–14 days [Cunha, Burillo, and Bouza 2016]), a few more days for the patient to seek medical care and diagnosis and the FOPH's notification to us, the time-lag between exposure and notification of Swiss TPH could amount to over a month. The 'Legionellen in der Trinkwasser-Installation' (*LeTriWa*) study, a case-control and molecular source attribution study conducted in Bern, Germany, was accessing LD cases through notification to district health authorities, yet still managed a rather short enrolment period[5] [Buchholz et al. 2020]. However, the notification timeline for LD in Germany is only 24 hours and therefore much shorter than in Switzerland [Deutsches Bundesamt 2000].

[5]The exact timelines until the interview are not stated, yet environmental sampling could be conducted on average 26 days after disease onset [Buchholz et al. 2020].

Recall bias is one of the most common and influential biases in case-control studies which rely on self-reported data. For LD exposure identification, overall recall can pose a substantial problem, as all possible exposures during the variable incubation period of up to 14 days have to be assessed, resulting in a lengthy questionnaire. While the time-frame covered in the questionnaire (i.e. the incubation period) cannot be shortened, decreasing enrolment time would be key to minimize recall bias and improve overall recall. Therefore, a direct link from the hospitals to the study team was proposed, eliminating reporting to the FOPH as an intermediary. With this approach, the proportion of LD cases not captured by the study was deemed negligible as the majority of cases (86.5%) are reported by hospitals (Chapter 4). To facilitate recruitment through hospitals, a network with collaborating hospitals was established. The selection of hospitals was based on the number of notifications in prior years and hospitals in all greater regions in Switzerland were considered. The final network consists of 20 hospitals operating in 14 out of 26 cantons.

Feasibility assessment of the interview. LD patients are usually over 50 years old and suffer from comorbidities [Cunha, Burillo, and Bouza 2016]. Even without previous health conditions, LD often compromises patient well-being immensely. Despite this, it is important to interview patients as early as possible. As lengthy questionnaires impact compliance and completion negatively, in-person bedside interviews were chosen. During the piloting of the interview processes in a university hospital (Chapter 11), several advantages of this approach became evident: The patient could be recruited for the study in a timely manner; scheduling the hour-long interview could be coordinated with nursing staff; and the patient could be pre-informed about the study by their physician, which increased acceptance of participation.

Optimising clinical and environmental sampling to obtain *Legionella* isolates for WGS. A match between clinical *Legionella* isolates obtained from a patient's lower respiratory tract and *Legionella* isolates from a patient's environment provides the strongest evidence for an infectious source, if coupled with epidemiological data [Petzold et al. 2017]. However, obtaining both a clinical and environmental sample where *Legionella* bacteria can be isolated and cultured poses a particular challenge.

Clinical isolates are obtained via a bacteriological culture of a lower respiratory tract sample. But these samples are hard to come by: Invasive sampling such as the broncheo-aleovar lavage are only performed when the patient is intubated. While non-invasive sputum sampling only requires the patient to cough up material from their lower respiratory tract, LD is characterized by a dry cough, hampering patients' ability to cough up material. Due to these limitations, culture diagnostics are performed on less than 10% of all patients in Switzerland (Chapter 4). Countries such as Denmark (personal communication) and New Zealand [ESR 2021], however, achieve PCR diagnostic rates of up to 90%, suggesting sputum yield can be improved by sputum induction [Maze et al. 2014]. Within the (*LeTriWa*) study, samples from the respiratory tract could be obtained for 56% of all enrolled cases [Lehfeld et al. 2022]. The establishment of the *SwissLEGIO* hospital network provides opportunities to strengthen physician efforts to collect sputum

cultures. By involving the NRCL as a backup laboratory for sputum sample analysis, we ensured that diagnostic laboratories without the capacities to culture and isolate *Legionella* themselves could participate.

Collecting and processing environmental samples also present challenges. To obtain samples, water sample collection from a subset of participants' residential buildings was planned. Sampling requires expertise and should ideally include an appraisal of the potable water installations. Additionally, a multitude of samples should be taken, varied both in space (to represent the whole piping system) and time (to account for contamination fluctuations). While strict adherence to sampling guidelines is important for individual investigations, in the context of a large-scale research project (sampling 125 households, a subset of the 410 study participants) demands a trade-off between thoroughness and scalability. After collection, sample processing (culturing) and isolate selection for WGS was further complicated by difficult-to-implement guidelines. ISO standard 11731 stipulates methods for processing *Legionella* sampled from the environment. These guidelines are broad, at times unspecific and challenging to scale up. For example, each sample is required to be processed with three different treatments (heat treatment, acid treatment and no treatment), which already proves cumbersome for individual case investigations, but very time and cost-intensive for larger-scale studies. Additionally, comparability of sample processing approaches is hindered by missing documentation in source investigation studies. After consultation with experts from public sector bodies (cantonal laboratories and NRCL) and together with our research partners at *LeCo* , we established a standard approach to water sample collection. Despite the considerable effort involved, this guarantees that cultures are obtained and processed according to ISO standards, ensuring the validity of the test results.

The challenges in source attribution are exemplified by two large research endeavours: The *LeTriWa* study also aimed to link a case-control study design with typing of isolates from the patients and the environment to identify presumptive infection sources [Buchholz et al. 2020]. They did not use WGS to compare the genomic sequence of clinical and environmental isolates, but also considered a presumptive source, if they could identify a MAb 3/1-positive strain in the environment. This subtype has been found in the majority of human cases but not the environment. The innovation of this study was the evidence categorization in microbiological, cluster and analytical-comparative evidence [Buchholz et al. 2020]. With this categorization, they report an overall identification of the infection source for 49% of all enrolled cases [Lehfeld et al. 2022]. However, microbiological matching using sequence-based typing was only achieved for 25.2%. The investigation of the largest outbreak to date (with 449 confirmed cases) in Murica, US, could eventually identify a cooling tower on a hospital as the infections source; however initial samples of the same tower returned either *Legionella* negative or the wrong strains, showing the high temporal sensitivity in environmental samples [García-Fulgueiras et al. 2003].

Scale-up of WGS for environmental isolates. Comparative genomics between environmental and clinical isolates requires comparatively more environmental than clinical isolates. While *Legionella* strain

diversity in clinical samples is low (limited to the disease-causing strain), the causative strain is likely obscured by other strains in environmental samples. If this diversity is not accounted for, the absence of a genomic match between clinical and environmental samples could also indicate inadequate scientific rigour rather than exclusion of the sampling site as a source of infection. To account for this entails picking several environmental isolates per cultured plate for WGS. Based on exchanges with collaborators and assuming *Legionella* positive households (60%) and strain diversity (3-5 strains per sample), we expect to find between 1,200 and 6,000 putative isolates from the total of 125 households [Wüthrich et al. 2019]. This exceeds the approximately 750 isolates the project budget allows to sequence. Therefore, a considerable effort was made to streamline the laboratory and analytics processes, including strain pre-selection for WGS. The established pre-selection consists of comparing environmental strains to clinical isolates using MALDI-TOF MS and agglutination methods. This challenge has only became evident when developing standard operating procedures for environmental sampling, analytics and preparation for WGS. Even in a research setting the scale-up proofed difficult regarding resources. This challenge needs to be carefully considered for the application of WGS in a routine case investigation.

Structural–organizational challenges

Harnessing existing and building new research synergies across disciplines. In early 2019, the FSVO launched a call for a research project to combat *Legionella* in buildings. One of the objectives of the call was investigating opportunities for new detection methods for *Legionella* control. The call from the FSVO and our previous LD research study proposal to the FOPH provided the opportunity to build new synergies. The *SwissLEGIO* project could implement a unique case-control and molecular source attribution study which, owing to the complexity and the resulting interdisciplinary scientific challenges, demanded the expertise of a wide array of stakeholders. The environmental component of this new study set-up was, therefore, embedded as one out of eight working packages in a larger proposal led jointly by the Eawag, the University of Applied Sciences Lucerne, the cantonal laboratory Zurich and Swiss TPH. In turn, the resulting project of this proposal, *LeCo* , was to access a data pool with public health relevance (i.e. LD case data). While the benefit of using synergies for better science and research is clear, aligning separate research projects is difficult from an operational and administrative point of view, e.g. in the harmonization of deliverables and timelines. Therefore, operational and administrative factors play a large role in the development and implementation of large research endeavours.

Apart from the *SwissLEGIO -LeCo* interface, existing collaborations and information pathways were harnessed for the study, such as outine surveillance activities require diagnostic laboratories to send *Legionella* isolates to the NRCL [BAG 2020a]. Upon reception and first analyses, the NRCL in turns forwards the isolates to the 'applied microbiology research lab' in Zurich for WGS. These existing information pathways could be used for WGS analysis of the clinical *Legionella* isolates collected within the framework of the study [BAG 2020a].

Through the diverse cooperation of different disciplines and sectors, the project is broadly supported and it can be ensured that the research objectives are aligned with the interests of the policymakers and are therefore transferable to practice.

Lessons learnt for multidisciplinary project planning. The involvement of so many collaborators and stakeholders rendered the structural and organisational aspects ever more complex. Researchers from four different institutions collaborated closely in the core team of *SwissLEGIO* and *LeCo* to shape the study design, data collection procedures and analytics. A clear set-up of research objectives was a central aspect for successful collaboration. Each party defined their minimal essential data and the final protocol that would integrate *SwissLEGIO* and all activities of *LeCo* pertaining to the environmental sampling and analytics was agreed upon by all partners. This provided a setup that incentivised all parties to invest in the project. Practically, this entailed navigating conflicting data collection requirements and leveraging data collection efforts.

With the launch of *SwissLEGIO* in summer 2022, the genesis of such a large multidisciplinary project can be summarized in four lesson learnt: First, the research goals of all partners need to be in agreement, and all partners should be able to provide feedback and influence data collection procedures and instruments. Second, close communication between partners is essential and administrative barriers need to be minimised. Third, patience, perseverance and trust are required. And a little luck doesn't hurt.

13.2.3 'Disease knows no borders': Legionnaires' disease worldwide

The previous chapters investigated the re-emergence of LD in Switzerland and contributed to building a national research portfolio to fill existing knowledge gaps. This chapter emphasizes the importance of broadening national research agendas and establishing international collaborations to foster collaborative knowledge generation. In the light of efforts to ensure clean drinking water and combat waterborne diseases globally, the chapter further encourages to look outwards to countries that have largely been neglected in the discourse surrounding LD.

The WHO lists legionellosis as one of the diseases contributing to the 4.6% of global DALYs in 2016 caused by inadequate water, sanitation and hygiene [WHO 2019a]. However, data scarcity prevents an accurate determination of the global burden of disease for LD [Prüss-Ustün et al. 2019]. This data gap is not equally distributed across the globe: Only a few countries have estimates of LD incidence from their (passive) surveillance systems including countries in the EU/EEA with the addition of Switzerland, the US, Canada, Australia, New Zealand, Japan, South Korea, and Singapore (Table 13.1). The trends of LD notification rates in monitoring countries are comparable across the globe: Similar to most European countries, case numbers in the US and Canada have increased since 2003 [ECDC 2022; Barskey, Derado,

and Edens 2022; Public Health Agency of Canada 2021]. In New Zealand, the LD notification rate rose as well, albeit considerably more slowly and potentially associated with reforms in LD diagnostics [ESR 2021].

Table 13.1: Most recent publicly available notification rates from selected countries and regions, where Legionnaires' disease is included in the passive surveillance system for infectious diseases.

Country/ region	**Notification rate[a]**	**Year**	**Reference**
Slovenia	5.2	2020	[ECDC 2022]
Switzerland	5.0	2020	[BAG 2022c]
Denmark	4.3	2020	[ECDC 2022]
New Zealand	3.4	2019	[ESR 2021]
Malta	3.0	2020	[ECDC 2022]
Italy	2.8	2020	[ECDC 2022]
USA	2.7	2018	[Barskey, Derado, and Edens 2022]
Austria	2.5	2020	[ECDC 2022]
Portugal	2.5	2020	[ECDC 2022]
Spain	2.5	2020	[ECDC 2022]
Netherlands	2.4	2020	[ECDC 2022]
Czechia	2.0	2020	[ECDC 2022]
France	1.8	2020	[ECDC 2022]
Slovakia	1.8	2020	[ECDC 2022]
Canada	1.7	2019	[Public Health Agency of Canada 2021]
*EU/EEA average	1.6	2020	[ECDC 2022]
Luxembourg	1.6	2020	[ECDC 2022]
Australia	1.5	2016	[Office of Health Protection, Australia 2021]
Hong Kong	1.4	2020	[CHP Hong Kong 2022]
Japan	1.4	2017	[Fukushima et al. 2021]
Germany	1.3	2020	[ECDC 2022]
Latvia	1.3	2020	[ECDC 2022]
Estonia	1.2	2020	[ECDC 2022]
Sweden	1.2	2020	[ECDC 2022]
Belgium	1.1	2020	[ECDC 2022]
Hungary	1.0	2020	[ECDC 2022]
UK	0.7	2019	[ECDC 2021b]
Norway	0.7	2020	[ECDC 2022]
Cyprus	0.5	2018	[ECDC 2021b]
Finland	0.4	2020	[ECDC 2022]
Lithuania	0.4	2020	[ECDC 2022]

Country/ region	Notification rate[a]	Year	Reference
Ireland	0.3	2020	[ECDC 2022]
Greece	0.2	2020	[ECDC 2022]
Singapore	0.3	2017	[MoH, Singapore 2017]
Bulgaria	0.1	2020	[ECDC 2022]
Poland	0.1	2020	[ECDC 2022]
Romania	0.0	2020	[ECDC 2022]

[a] Notification rate per 100,000 population. The list contains likely a mixture of crude and age-and sex-adjusted estimates.

New insights from cross-country research on Legionnaires' disease notification rates

Cross-country comparisons of LD notification data can be useful for disentangling factors that influence case numbers. Large-scale geographical risk factors, such as climate or weather and air pollution, would suggest similar disease patterns across borders. Indeed, regions with high LD notification rates correspond with high air pollution levels in the Italian Po-valley and surrounding Mediterranean regions (Figure 13.2) [De Sario, Katsouyanni, and Michelozzi 2013]. Given the suspected interplay of weather conditions with air pollution and their observed effect on LD incidence [Pampaka et al. 2022], these disease patterns warrant more attention, particularly in light of climate change.

Local determinants, such as differing communal water management plans and funding of the healthcare system, might explain differences between regions and neighbouring countries. For example, the north-south divide in Italy was partly explained by fewer LD diagnostic tests being performed in southern Italy due to an underfunded health system [Rota et al. 2013]. Switzerland reports continuously higher notification rates than all neighbouring regions, possibly reflecting lower LD underestimation likely attributable to a well-funded health system. Switzerland has one of the highest health expenditures in US dollar purchasing power parity per capita in Europe [De Pietro et al. 2015]. Similarly, the low case numbers from south-eastern European countries are potentially caused by deficits in disease surveillance and, as a result, an underestimation of the actual incidence [Beauté, Robesyn, and Jong 2013]. To illustrate, in 2014, Poland reported an incidence of only 0.04 cases per 100,000 population [Stypułkowska-Misiurewicz and Czerwiński 2016]. Yet, the strikingly high death rate of 25% might suggest severe underreporting [Stypułkowska-Misiurewicz and Czerwiński 2016]. Bulgaria further exemplifies the case detection deficit with its first culture proven LD case reported only in 2020 [Tomova and Nenova 2020]. And until 2022, no domestic LD case has been reported in Serbia [Djordjevic et al. 2022].

Despite all European countries officially reporting LD cases, it remains difficult to obtain accurate disease estimates. It is even more challenging to derive a comprehensive understanding of the (local) LD epidemiology from these estimates. Even if they were considered reliable, as deriving insights into

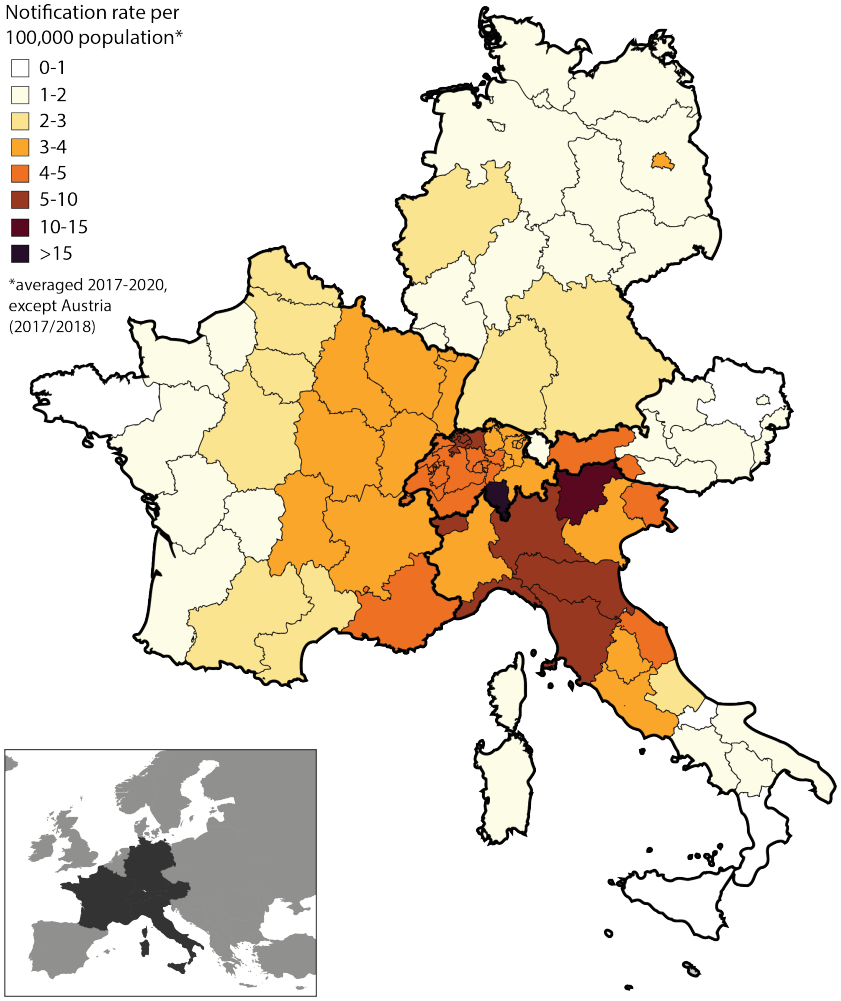

Figure 13.2: Annual Legionnaires' disease notification rates averaged over two (2017/2018) respectively four years (2017-2020) for France, Germany, Austria, Italy and Switzerland. Notification rates for France, Germany, Austria and Italy were compiled from publicly available surveillance reports of the national public health agencies.

epidemiology requires a firm understanding of the data quality (Chapter 4) and the processes leading to reporting of cases (Chapters 8 and 9). This raises the question of how countries without an infectious disease surveillance system which includes LD could approach assessing their LD burden and develop effective prevention measures.

The data gap: Available Legionnaires' disease incidence estimates from countries around the world

In countries where a passive infectious disease surveillance system is lacking, various research approaches are being used to assess the burden or risk of *Legionella* infections. These methodology can be categorized in three groups: (i) exclusively environmental analyses by screening water samples for *Legionella* contamination. (ii) seroprevalence studies and (iii) hospital-based observational studies. Table 13.2 shows an overview of published studies on LD estimates using these methodologies. Estimates on the country-

level burden of LD vary greatly across the globe and by methodology. The positivity of environmental samples ranged from 2% in Saudi Arabia, to 98% in Kuwait [Fakhri et al. 2019]. The seroprevalence was derived from a meta-analyses, compiling data for larger regions. The seroprevalence was highest in Asia with 18.9% [Ngeow et al. 2005] and lowest in Africa with 4.7% [Graham et al. 2020], which was significantly lower than the global mean. The highest LD proportion among CAP patient was reported in Argentina (20%) [Aguerre et al. 2018] and the lowest in South Africa (1.2%) [Wolter et al. 2016]. Yet, data remains scarce or is non-exitant for many countries and regions. It is telling that in Bangladesh the first *L. pneumophila* sg 1 was isolated from public water in 2016 [Haque et al. 2016].

Table 13.2: Overview of Legionnaires' disease estimates from countries without a passive surveillance systems. The estimates are derived from several different methodologies: (i) Environmental positivity refers to the proportion of tested water samples in which *Legionella* could be identified. (ii) Seroprevalence studies estimate the proportion of the tested population for which antibodies against *Legionella* were found in the blood. (iii) Hospital-based studies estimate the proportion of hospitalised patients with community-acquired pneumonia, which were tested positive for *Legionella* .

Country/ region	**Methodology**	**Estimate [%]**	**Year**	**Reference**
Kuwait	Environmental positivity[a]	98.0	2019[c]	[Fakhri et al. 2019]
China	Environmental positivity[a]	82.0	2019[c]	[Fakhri et al. 2019]
Egypt	Environmental positivity[a]	40.0	2019[c]	[Fakhri et al. 2019]
Japan	Environmental positivity[a]	38.0[d]	2019[c]	[Fakhri et al. 2019]
Austria	Environmental positivity[a]	34.0	2019[c]	[Fakhri et al. 2019]
Italy	Environmental positivity[a]	27.0[d]	2019[c]	[Fakhri et al. 2019]
Taiwan	Environmental positivity[a]	24.0[d]	2019[c]	[Fakhri et al. 2019]
Morocco	Environmental positivity[a]	20.0	2019[c]	[Fakhri et al. 2019]
Iran	Environmental positivity[a]	18.0[d]	2019[c]	[Fakhri et al. 2019]
South Korea	Environmental positivity[b]	16.2[f]	2021[c]	[Lee et al. 2021]
US	Environmental positivity[a]	16.0[d]	2019[c]	[Fakhri et al. 2019]
Turkey	Environmental positivity[a]	15.0[d]	2019[c]	[Fakhri et al. 2019]
South Korea	Environmental positivity[b]	13.5[f]	2021[c]	[Lee et al. 2021]
Greece	Environmental positivity[a]	11.0[d]	2019[c]	[Fakhri et al. 2019]
Jordan	Environmental positivity[a]	9.0	2019[c]	[Fakhri et al. 2019]
South Korea	Environmental positivity[a]	8.0[d]	2019[c]	[Fakhri et al. 2019]
Poland	Environmental positivity[a]	4.0	2019[c]	[Fakhri et al. 2019]
Saudi Arabia	Environmental positivity[a]	2.0	2019[c]	[Fakhri et al. 2019]
Asia	Seroprevalence study	18.9[d]	2005[c]	[Ngeow et al. 2005]
The Americas	Seroprevalence study	15.7[d]	2020[c]	[Graham et al. 2020]
European	Seroprevalence study	14.7[d]	2020[c]	[Graham et al. 2020]
Western Pacific	Seroprevalence study	13.0[d]	2020[c]	[Graham et al. 2020]

Overview of Legionnaires' disease estimates from countries without a passive surveillance systems (continued)

Country/ region	**Methodology**	**Estimate [%]**	**Year**	**Reference**
South East Asian	Seroprevalence study	12.4[d]	2020[c]	[Graham et al. 2020]
Eastern Mediterranean	Seroprevalence study	12.0[d]	2020[c]	[Graham et al. 2020]
Africa	Seroprevalence study	4.7[d]	2020[c]	[Graham et al. 2020]
Argentina	Hospital-based study	20.0	2015-2017	[Aguerre et al. 2018]
Manila, Philippines	Hospital-based study	16.9	2001/2002	[Ngeow et al. 2005]
Malaysia	Hospital-based study	16.2	2001/2002	[Ngeow et al. 2005]
Iran	Hospital-based study	9.6[d]	2000-2016	[Khaledi et al. 2019]
Kenya	Hospital-based study	9.2	2007	[Odera and Anzala 2009]
Thailand	Hospital-based study	8.2[g]	2001/2002	[Ngeow et al. 2005]
Kuwait	Hospital-based study	8.0	2005[c]	[Behbehani et al. 2005]
Asia	Hospital-based study	6.6	2001/2002	[Ngeow et al. 2005]
Thailand	Hospital-based study	5.4[h]	2001/2002	[Ngeow et al. 2005]
China	Hospital-based study	3.9	2014–2016	[Qin et al. 2019]
India	Hospital-based study	2.3	2015-2020	[Sreenath et al. 2021]
South Korea	Hospital-based study	2.0	2001/2002	[Ngeow et al. 2005]
South Africa	Hospital-based study	1.2	2012-2014	[Wolter et al. 2016]

[a] Proportion of *Legionella* positive environments
[b] Proportion exceeding 1,000 CFU/L
[c] Publication year
[d] Average over multiple studies
[e] Estimate from public facilities
[f] Estimate from apartment buildings
[g] Estimate from outpatients
[h] Estimate from inpatients

While the studies listed are a starting points for understanding the LD burden, they cannot provide population-based representative estimates. Environmental analyses suffer from the inherent problem of detecting *Legionella* in the environment. Further, the translation of environmental analyses to public health relevance is challenging. Seroprevalence studies can provide an assessment of the overall population exposure. However, seroprevalence values are unreliable in inferring active/symptomatic or even recent exposure to *Legionella* spp. [Graham et al. 2020; Mora-Sero et al. 2009], complicating their usefulness for deriving the public health burden. Hospital-based observational studies, such as testing pneumonia patients for *Legionella* face the major caveat of a biased sample: Assuming that the majority of LD cases are severe enough to require hospitalization, the bias may be small in countries with good access to health care (such as Switzerland). However, in countries with limited access to healthcare, the hospitalized LD population is much less representative of the general LD population.

Still, hospital-based studies provide the most concrete evidence of the public health relevance of LD in countries without passive surveillance systems. In Switzerland, 38,897 people were hospitalized with pneumonia (main and secondary diagnosis) in 2018 [BFS 2019]. Thus, we calculated that the proportion of *Legionella* pneumonia among all hospitalised pneumonia cases was 1.3%. Estimates from hospital-based studies range from 1.2 to 20% (Table 13.2), suggesting that LD represents a larger proportion of hospitalised pneumonia cases in many other countries compared to Switzerland. This indicates that countries without a surveillance system may bear a substantial undetected LD burden. Yet, due to limited data availability elsewhere, LD is primarily discussed in the context of high-income countries. We should be consciously aware that absence of data does not mean absence of a public health problem. Furthermore, worrying developments are obscured by these data gaps: Climate change and urbanization are global developments that particularly affect LMICs and both are thought to promote LD incidence [Walker 2018]. And while air pollution levels are decreasing in many high-income countries, including Switzerland, other countries, which account for over half of the global population, are facing increasing levels of air pollution [Shaddick et al. 2020].

Disease diagnosis is more than an addition to disease statistics

Hospital-based observational study estimates are often obtained from active case finding, which should not be confused with available routine diagnostics. In many countries, diagnostic tests for atypical pneumonia pathogens (such as *Legionella*) are not performed due to diagnostic possibilities. While about half of hospitalized CAP patients are tested for an atypical pneumonia pathogen in Europe, this number decreases to 5% in Africa or South America [Gramegna et al. 2018]. Non-diagnoses has repercussions not only for public health, but also for individual health.

The value of diagnosis and the danger of non-diagnosis depends on the empirical treatment approach: If LD-active antibiotics are included, non-diagnosis will have little effect on health outcomes. However, if empirical treatment does not include an LD-active antibiotic and LD is left undiagnosed, adequate, and timely treatment is unlikely. Delayed treatment leads to worse health outcomes, demonstrated by one study that showed the mortality rate increase from 10 % to 27 % without early macrolide therapy [Falcó et al. 1991]. However, recent research evidence advocates against empirical treatment of LD in low transmission settings on the basis of antibiotic stewardship [Henegouwen et al. 2017]. For example, fluoroquinolones, one of the main treatment options for LD, is not recommended as first-line treatment in settings with high tuberculosis burden (such as South Africa) due to the risk of developing fluoroquinolone resistant tuberculosis [Dlamini and Mendelson 2012; Boyles et al. 2017]. Community-acquired pneumonia guidelines in many high-income countries promote treatment with narrow-spectrum antibiotics for non-severe pneumonia cases and a step up approach (i.e. the escalation of treatment) in case of treatment failure (Chapter 8). Yet, step-up approaches recommended in high income countries might not be feasible in settings with limited access to health care [Aston and Rylance 2016] where broad-spectra treatment approaches should be prioritised. In

the absence of LD estimates, it is impossible to draw conclusions about the extent of transmission and the best empirical treatments for pneumonia.

Towards addressing Legionnaires' disease on a global level

There are short-, medium- and long-term goals to addressing LD at a global level. Targeted short- to medium-term research efforts in countries without an infectious disease surveillance system should aim to (i) establish a baseline understanding of the local public and individual health relevance of LD, and (ii) review current antibiotic treatment practices for pneumonia. If LD active agents are covered by empirical treatment approaches, undetected LD remains a limited threat to individual health.

In the long-term, overall health system strengthening efforts will beneficially impact not only the LD burden but also EIDs at large. The establishment of an institutionalised infectious disease surveillance system, the inclusion of LD in existing disease surveillance systems (if excluded), and improvements to the disease surveillance system are important for anticipating changes in disease patterns and making informed decisions on allocation of resources and mitigation measures. Once estimates of disease levels are established, they can inform the public health relevance of LD and whether investments contribute to an overall improvement in public health or would be better spent elsewhere. Disease estimates can also guide recommendations for CAP diagnosis and treatment. In low transmission settings, empirical LD treatment could be forgone, thereby saving resources without compromising health outcomes. Strengthening health care services also improves access to health care and diagnostic testing. New molecular diagnostics, such as PCR, remain inaccessible to many LMICs, particularly in rural settings [Naidoo et al. 2021]. Innovations in better LD diagnostics should, therefore, address accessibility and improve sensitivity and *Legionella* strain coverage in point-of-care diagnostics, such as the UAT.

Many of the above suggestions are mitigation measures once infection has occurred. Given current knowledge, it is difficult to give recommendations for LD prevention. First, infection sources are not well understood and sources might differ strongly based on possible water exposures or even local drinking water installations. This underlines the overall importance of initiatives for a healthy (built) environment, in line with Sustainable Development Goal (SDG)* target 6.1 (ensure safely managed drinking-water services) and SDG targets 3.3 and 3.9 (combat waterborne diseases and reduce deaths and illnesses from water contamination), as they will also alleviate risk factors for LD [United Nations 2015].

13.2.4 The future of Legionnaires' disease research

The work summarised in this thesis provided a strong foundation for and has made a tangible contribution to epidemiological LD research with the launch of a major multidisciplinary research project to identify risk factors and sites of exposure. Numerous findings on risk factors, exposure sites and clinical

features are expected in the near future. Yet, despite this progress substantial knowledge gaps in public health remain.

The extent of mild or asymptomatic LD cases remains unknown. The prevailing assumption is that LD presents so severely that almost all cases end up in hospital and are detected. However, a German CAPNETZ study suggests a substantial number of undetected LD cases outside of the hospital setting [Baum et al. 2008]. This issue is addressed by two ongoing studies. First, LD was added to the project portfolio of the Sentinella Surveillance System for one year in 2019 [BAG 2019b]. GPs were asked to test for and report LD cases among presenting pneumonia cases. Of 235 urine samples received 0.9% were *Legionella* UAT positive [BAG 2022b]. Additional findings of this study are to be disseminated. The cause of these low sample number, as well as positives remains unknown without further dissemination of the results. Second, a serological survey on *Legionella* was included in the pilot phase of the Swiss Health Survey[6]. The pilot phase of this study concluded at the end of 2021, the results are not yet available.

The second knowledge gap is the care-seeking behaviour of LD patients. Currently, choice of care impacts the probability of being detected as LD diagnosis is limited to the hospital setting. The relationship between notification and access rates to hospital-care remains unknown. Intuitively, this would align with the highest notification rates being observed in urban settings (Chapter 10). Additionally, it also remains unclear how many severe cases could have been prevented if detected earlier by a GP. Both these questions could be answered through an investigation of the patient journey including health-seeking behaviour, and the referral process from GPs to hospitals.

Third, the potential long-term effects of an LD infection on health and quality of life are unknown. Limited evidence that LD can have long-term effects, not dissimilar to the those attributed to a SARS-CoV-2 infection [Yang, Zhao, and Tebbutt 2020], has been published [Lettinga et al. 2002; Loenhout et al. 2014; Gamage et al. 2021]. However, it remains unclear if these effects are primarily consequences of staying at the ICU and artificial ventilation [Herridge et al. 2016]. Regardless, the LD-associated public health burden would grow considerably if LD caused long-term quality of life reductions. *SwissLEGIO* lays the basis for investigating these long-term effects. Patients will be asked to participate in a long-term follow up 6–12 months after the disease episode to collect longitudinal data on their convalescence.

Globally, much of the LD research interest focuses on laboratory detection methods, ecology and host–pathogen interaction and *Legionella* ecology at large [WHO 2022]. More efforts should be made to strengthen disease surveillance, reporting and outbreak management. The establishment of global burden of disease estimates should be of high priority to guide decision-making and allocation of public health resources. LD should be included in the discourse of EIDs and addressing LRTI burden particularly in

[6] https://www.schweizer-gesundheitsstudie.ch/, Last accessed: 2022-09-15.

countries with no LD data. Ultimately, identifying the main sources of infection is the most important step for effective prevention and control measures. However, the starting point of these efforts is the detection of LD cases. As such, the importance of a well-functioning, accessible healthcare system where diagnostics are available and cases can be monitored cannot be overstated.

Chapter 14

Conclusion

This thesis demonstrated how a re-emerging infectious disease with an inadequately characterised epidemiology can be confronted, emphasising the value of careful surveillance to assess the health burden and map disease patterns (Chapter 13.1.1). Furthermore, it has shown the importance of contextualising disease data by analysing the processes leading to notification to ensure educated interpretation and maximise the information value of data (Chapter 13.1.3).

To summarise, the work presented in this thesis suggests that the observed increase in Legionnaires' disease cases cannot be dismissed simply as a surveillance artefact. Furthermore, it is likely that Legionnaires' disease incidence is still underestimated in Switzerland. Physician awareness plays an important role in reducing underestimation, but testing recommendations in clinical guidelines, reimbursement practices for diagnostic tests and innovations in diagnostic test methods themselves should be also be considered. Finally, if the increase in incidence remains true, it will become even more important to understand the drivers of infections. In this thesis, we differentiated between large-scale risk factors, such as weather and air pollution, which can– if at all– only be influenced in the long-term. However, understanding these drivers helps to anticipate disease trends and identify vulnerable populations and regions. Small-scale risk factors are sources of infection which could be addressed by targeted prevention and control measures. Yet, researching these small-scale risk factors is riddled with challenges. By synthesising available evidence, generating new insights into Legionnaires' disease epidemiology and identifying knowledge gaps, the work presented in this thesis has laid the foundation for ongoing national Legionnaires' disease research that combines clinical, public health and environmental domains of this disease system to identify risk factors and ultimately inform prevention and control measures (Chapter 13.2.2).

After the discovery of Legionnaires' disease in 1976, interest waned over the following decade. Although public health interest in Legionnaires' disease is currently high, and although there is widespread support for research into the disease, interest may again wane as other public health issues take precedence, such as the current COVID-19 pandemic. Furthermore, despite the extensive expertise available, progress in research and policy is held back by the fragmentation of actors, institutions and funding, as well as divergent interests. We have seen, however, that continued and sustained commitment to Legionnaires' disease prevention and control as well as multisectoral and transdisciplinary collaboration is needed to ensure responsiveness to outbreaks and long-term trends of rising Legionnaires' disease cases.

This is particularly important as climatic and demographic changes and urbanisation are likely to exacerbate the Legionnaires' disease burden globally. Given these developments, health problems caused by low water quality, long regarded as problems in low-income countries, are regaining public health relevance also in higher-income countries. Therefore, and irrespective of the setting, Legionnaires' disease can only be effectively managed by striving for a healthy (built) environment.

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Part VI

Appendices

Appendix A

Supplementary materials from Chapter 4

Temporal trends in legionellosis national notification data and the effect of COVID-19, Switzerland, 2000–2020

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Temporal trends in legionellosis national notification data and the effect of COVID-19, Switzerland, 2000- 2020

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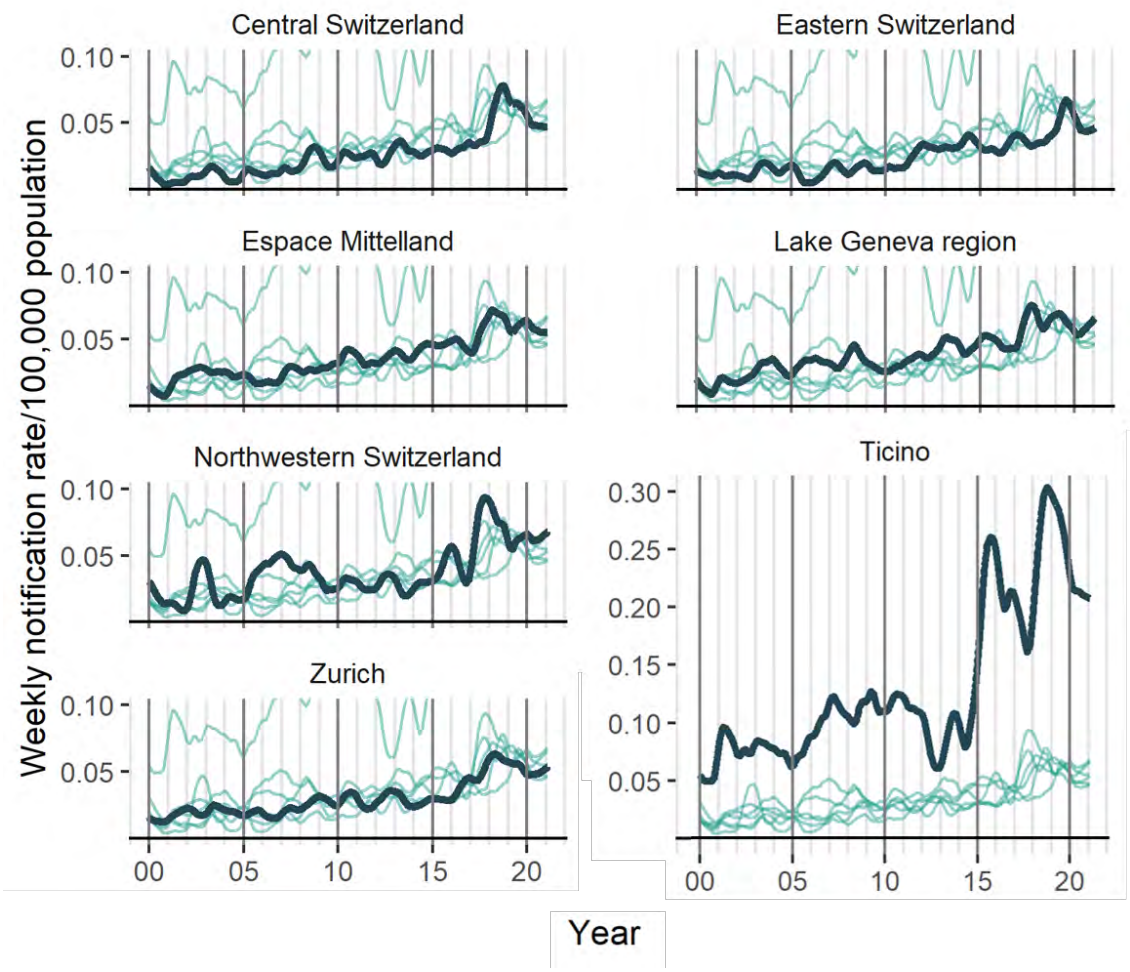
Supplementary information

Supplementary Table 1 Period notification rates and 20-year notification rate for legionellosis in Switzerland, 2000-2020

	Notification rate per 100,000 population for each period				
	2000-2005	2006-2010	2011-2015	2016-2020	Overall
Age category (years)					
0 to 19	0.1	0.1	0.1	0.1	0.1
20 to 29	0.2	0.6	0.4	0.9	0.5
30 to 39	0.8	1.0	1.2	1.9	1.2
40 to 49	1.9	2.4	2.7	3.7	2.6
50 to 59	3.0	4.3	5.5	8.0	5.3
60 to 69	4.1	6.3	7.9	12.3	7.8
70 to 79	6.4	8.6	9.7	14.9	10.1
80 to 89	7.3	10.0	12.7	21.9	13.3
90+	4.8	8.3	14.6	21.1	12.8
Sex					
Male	2.8	4.2	5.1	8.0	5.0
Female	1.3	1.7	2.2	3.7	2.2
Region					
Central Switzerland	0.0	0.1	0.1	0.3	0.1
Eastern Switzerland	0.1	0.1	0.2	0.2	0.1
Espace Mittelland	0.1	0.2	0.2	0.3	0.2
Lake Geneva	0.1	0.2	0.2	0.3	0.2
Northwestern Switzerland	0.1	0.2	0.2	0.3	0.2
Ticino	0.4	0.6	0.7	1.2	0.7
Zurich	0.1	0.1	0.1	0.3	0.2



Supplementary Figure 1 Weekly notification rate for legionellosis between 2000 and 2020 across the seven greater regions (NUTS-2 level) in Switzerland. The think green line denotes the notification rate of the specific region, while the thinner lines are the notification rate of all other six regions for easier visual comparison.

Supplementary Table 2 Completeness of key variables for the notification of legionellosis in Switzerland with 95% confidence interval across all years, for all cases in the database and confirmed and probable cases only, 2000-2020

	All cases (N=5,980)				**Confirmed and probable cases (N=5,578)**			
	Variable not empty		Variable not empty and not "unknown"		Variable not empty		Variable not empty and not "unknown"	
	%	*95% CI*	%	*95% CI*	%	*95% CI*	%	*95% CI*
Notification								
Case classification	100.0	*100-100*	-	-	100.0	*100-100*	-	-
Clinical information	100.0	*100-100*	-	-	100.0	*100-100*	-	-
Laboratory information	100.0	*100-100*	-	-	100.0	*100-100*	-	-
Name of reporting institution	81.7	*74.3-89.2*	65.2	*53.5-76.8*	86.2	*78.0-94.5*	68.2	*56-80.4*
Demographics								
Age	99.93	*99.85-100*	-	-	99.98	*99.94-100*	-	-
Sex	99.98	*99.94-100*	-	-	99.97	*99.94-100*	-	-
Canton of residence	99.6	*99.4-99.7*	-	-	99.7	*99.5-99.9*	-	-
Nationality	82.6	*80.0-85.1*	82.3	*79.8-84.9*	86.7	*84.8-88.7*	86.4	*84.44-88.45*
Clinic								
Hospitalisation	100	*100-100*	91.6	*88.9-94.4*	100.0	*100-100*	96.4	*94.8-98.0*
Hospitalisation date	98.4	*97.8-98.9*	-	-	98.4	*97.9-99*	-	-
Discharge date*	61.7	*57.1-66.3*	-	-	61.5	*56.8-66.1*	-	-
Death	100.0	*100-100*	-	-	100.0	*100-100*	-	-
Date of death	81.9	*77.4-86.4*	-	-	82.5	*78-87.1*	-	-
Manifestation date	84.7	*82.3-87.1*	-	-	89.5	*88.2-90.8*	-	-
Pneumonia	94.9	*93.1-96.6*	-	-	99.95	*99.9-100*	-	-

Exposure								
Risk factor	100.0	*100-100*	84.7	*82.4-86.9*	100.0	*100-100*	88.6	*86.6-90.5*
Modus	100.0	*100-100*	-	-	100.0	*100-100*	-	-
National or international travel if travel-associated LD	100.0	*100-100*	92.0	*88.6-95.4*	100.0	*100-100*	92.9	*89.6-96.3*
Diagnostic								
Diagnostic test	90.9	*89.4-92.5*	90.9	*89.4-92.5*	92.9	*91.5-94.3*	92.9	*91.5-94.3*
Sample material	93.8	*92.6-95.0*	93.8	*92.6-95.0*	93.6	*92.3-94.9*	93.6	*92.3-94.9*

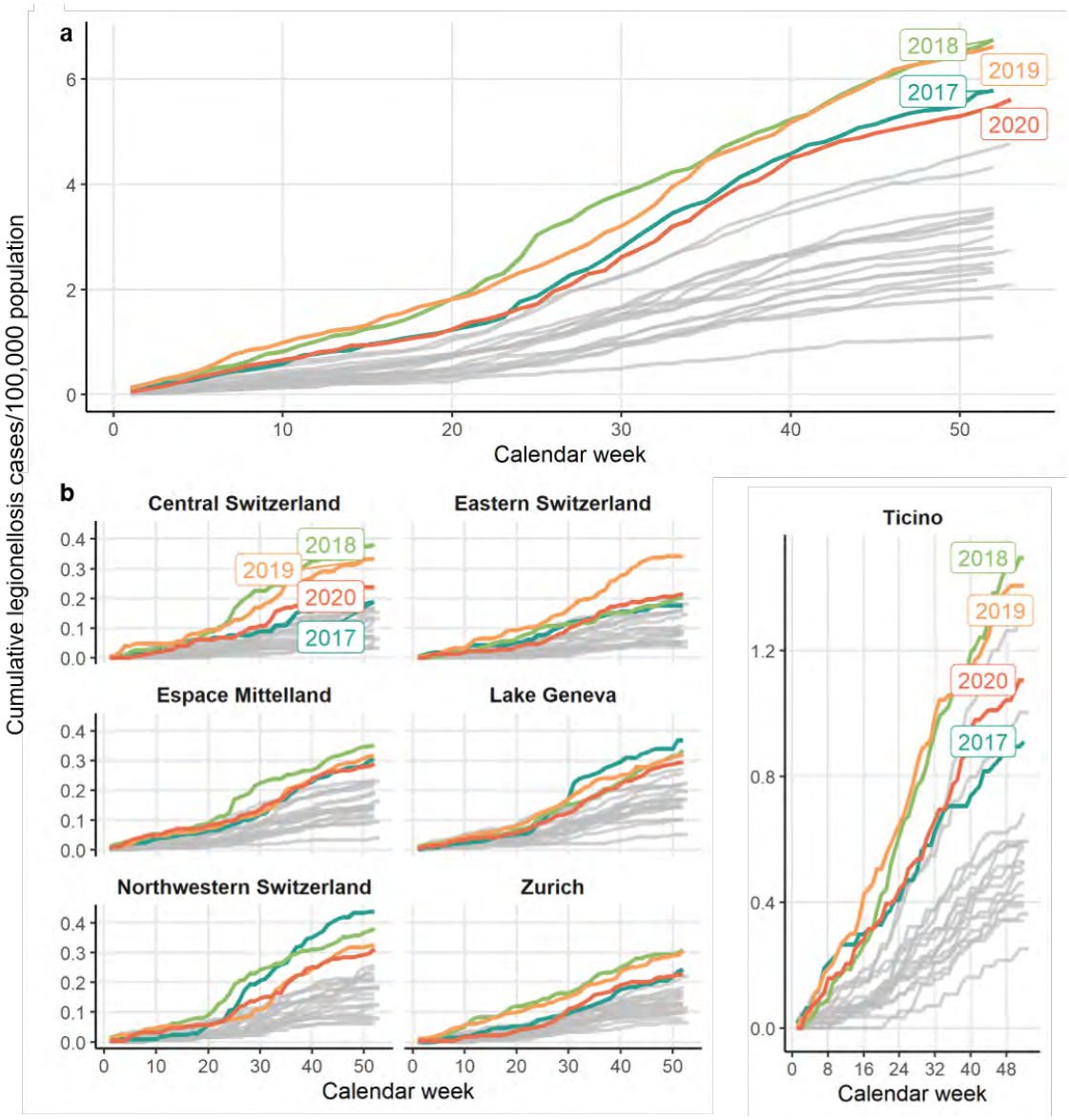
* Variable omitted from the notification form in 2014

Supplementary Table 3 Number of days between different steps to notification for legionellosis in Switzerland, 2000-2020

		2000-2005		2006-2010		2011-2015		2016-2020		Overall	
	N	p50[a]	(p10, p90)[b]	p50	(p10, p90)	p50	(p10, p90)	p50	(p10, p90)	p50	(p10, p90)
Case date to diagnostic sampling	3,782	0	(0, 0)	3	(0, 8)	3	(0, 8)	3	(0, 7)	3	(0, 7.9)
Diagnostic sampling to notification	3,782	3	(-1, 8.4)	7	(2, 20)	5	(1, 13)	4	(1,11)	5	(1, 13)
Reception of notification to data entry	5,976	0	(0, 0)	0	(0, 1)	0	(0, 0)	0	(0, 2)	0	(0, 1)
Case date to data entry	5,976	7	(0, 22)	10	(4, 26)	8	(3, 20)	8	(3, 19)	8	(2, 20)

[a] 50th percentile / median

[b] 10th and 90th percentile



Supplementary Figure 2 Cumulative legionellosis case number across the calendar year since 2000 across Switzerland (a) and stratified by greater region (NUTS-2 level, b). Highlighted are the last 4 years. The reference population for the notification rate is constant over the calendar year.

Appendix B

First publication from Chapter 5

From public health policy to impact for COVID-19: A multi-country case study in Switzerland, Spain, Iran and Pakistan

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International Journal of Public Health
ORIGINAL ARTICLE
published: 31 August 2022
doi: 10.3389/ijph.2022.1604969

From Public Health Policy to Impact for COVID-19: A Multi-Country Case Study in Switzerland, Spain, Iran and Pakistan

Maryam Tavakkoli[1,2], Aliya Karim[1,2], Fabienne Beatrice Fischer[1,2], Laura Monzon Llamas[3], Azam Raoofi[4,5], Shamsa Zafar[6], Carmen Sant Fruchtman[1,2], Don de Savigny[1,2], Amirhossein Takian[5,7], Marina Antillon[1,2†] and Daniel Cobos Muñoz[1,2†]*

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Objectives: With the application of a systems thinking lens, we aimed to assess the national COVID-19 response across health systems components in Switzerland, Spain, Iran, and Pakistan.

Methods: We conducted four case studies on the policy response of national health systems to the early phase of the COVID-19 pandemic. Selected countries include different health system typologies. We collected data prospectively for the period of January–July 2020 on 17 measures of the COVID-19 response recommended by the WHO that encompassed all health systems domains (governance, financing, health workforce, information, medicine and technology and service delivery). We further monitored contextual factors influencing their adoption or deployment.

Results: The policies enacted coincided with a decrease in the COVID-19 transmission. However, there was inadequate communication and a perception that the measures were adverse to the economy, weakening political support for their continuation and leading to a rapid resurgence in transmission.

Conclusion: Social pressure, religious beliefs, governance structure and level of administrative decentralization or global economic sanctions played a major role in how countries' health systems could respond to the pandemic.

Keywords: COVID-19, pandemic, governance, health system, public health, COVID-19 restrictions, cross-country comparison, policy responses

OPEN ACCESS

Edited by:
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This Original Article is part of the IJPH Special Issue "Responses to the COVID-19 Pandemic: International Comparisons."

Received: *31 March 2022*
Accepted: *22 July 2022*
Published: *31 August 2022*

Citation:
Tavakkoli M, Karim A, Fischer FB, Monzon Llamas L, Raoofi A, Zafar S, Sant Fruchtman C, de Savigny D, Takian A, Antillon M and Cobos Muñoz D (2022) From Public Health Policy to Impact for COVID-19: A Multi-Country Case Study in Switzerland, Spain, Iran and Pakistan. Int J Public Health 67:1604969. doi: 10.3389/ijph.2022.1604969

INTRODUCTION

Since the World Health Organization (WHO) announced SARS-COV-2 as a public health emergency of international concern on 31 January 2020, countries have applied various strategies to control the spread of the virus [1, 2]. Health systems are key to the response to COVID-19, but are also highly vulnerable to collapse due to the demands posed by the rapid

TABLE 1 | Health systems profile (Switzerland, Spain, Iran and Pakistan, 2019) [17, 67].

Country	Population	Income level	Healthy life expectancy at birth (years)	UHC: Service coverage index[a]	Density of medical doctors (per 10k population)	Density of nursing and midwifery personnel (per 10k population)	Current health expenditure (%of GDP)	Compulsory health insurance (CHI) as % of current health expenditure (CHE)
Switzerland	8591	High	72.5	83	43.3	178.9	11.29	44
Spain	46,737	High	72.1	83	40.3	60.8	9.13	4
Iran	82,914	Upper-middle	66.3	72	15.8	20.8	6.71	35
Pakistan	216,565	Lower-middle	56.9	45	11.2	4.8	3.38	1

[a]*Coverage of essential health services (defined as the average coverage of essential services based on tracer interventions that include reproductive, maternal, newborn and child health, infectious diseases, non-communicable diseases and service capacity and access, among the general and the most disadvantaged population). The indicator is an index reported on a unit-less scale of 0–100, which is computed as the geometric mean of 14 tracer indicators of health service coverage.*

TABLE 2 | List of selected Indicators and domains of public health policy response to Covid-19 (Switzerland, Spain, Iran and Pakistan, January-July 2020).

Governance
Coordination mechanism created
Level of decentralization in COVID response in the health sector
Finance
Introducing emergency legislation to finance response to COVD-19. source, e.g. mobilized emergency reserve funds; reallocated from other budget lines; etc.
Human resources
Mobilizing and repurposing health workforce (e.g. reserves, retired staff, staff from other specializations, trained students, etc.)
Information systems
Media briefing at regular intervals
Medical technologies and pharmaceuticals
Ensuring emergency mechanisms are in place for procurement and registration of medicines and health technologies
Service delivery
Contact tracing
Screening on entry
Preventive measures
Quarantine/home isolation of COVID-19 patients
Quarantine/home isolation of suspected cases and contacts of confirmed patients
Announcement of preventive activities (personal hygiene)
Physical distancing
Restrictions on congregation
Closure of schools and other teaching facilities
Closure of bars, restaurants, sports venues
Lockdown
Border closure/Travel restriction

expansion of the demand for services [3–5], yet it was not until 18 April 2020 that the WHO's Regional Office for Europe published its technical working guidance, Strengthening the Health System Response of COVID-19 [3], more than 4 weeks after the pandemic had been declared on March 11, 2020. However, many of its recommendations were similar to the principles in other documents for other outbreaks [6], and the recommendations were sufficiently generic to be adapted within different contexts.

However, both complexity theory and our experience tells us that there is no one-size-fits-all strategy. Inevitably, however, the WHO and country-level officials must glean the best approach from general principles of health and governance systems, past experience, and the demands of the population at the time, managing not only the expectations and principles mandated by their constituents and their constitutions, but also an unusual amount of uncertainty during an outbreak of an emerging pathogen [7–9].

The variability of responses to the pandemic and the interplay of different elements warrants approaches that account for complexities inherent to a country's political, economic, and social context; their existing health systems structures; and disease dynamics. Understanding and managing this complexity through a systems lens is essential to enable governments to better adapt and respond to threats like the current pandemic [10].

Since the onset of the pandemic, case studies have been carried out to monitor country-specific response to the pandemic [11, 12]. In a study reviewing the preparedness in 177 countries, environmental seasonality, altitude and GDP per capita were identified as the main contextual factors influencing the COVID-19 infections rate [13]. However much uncertainty still exists

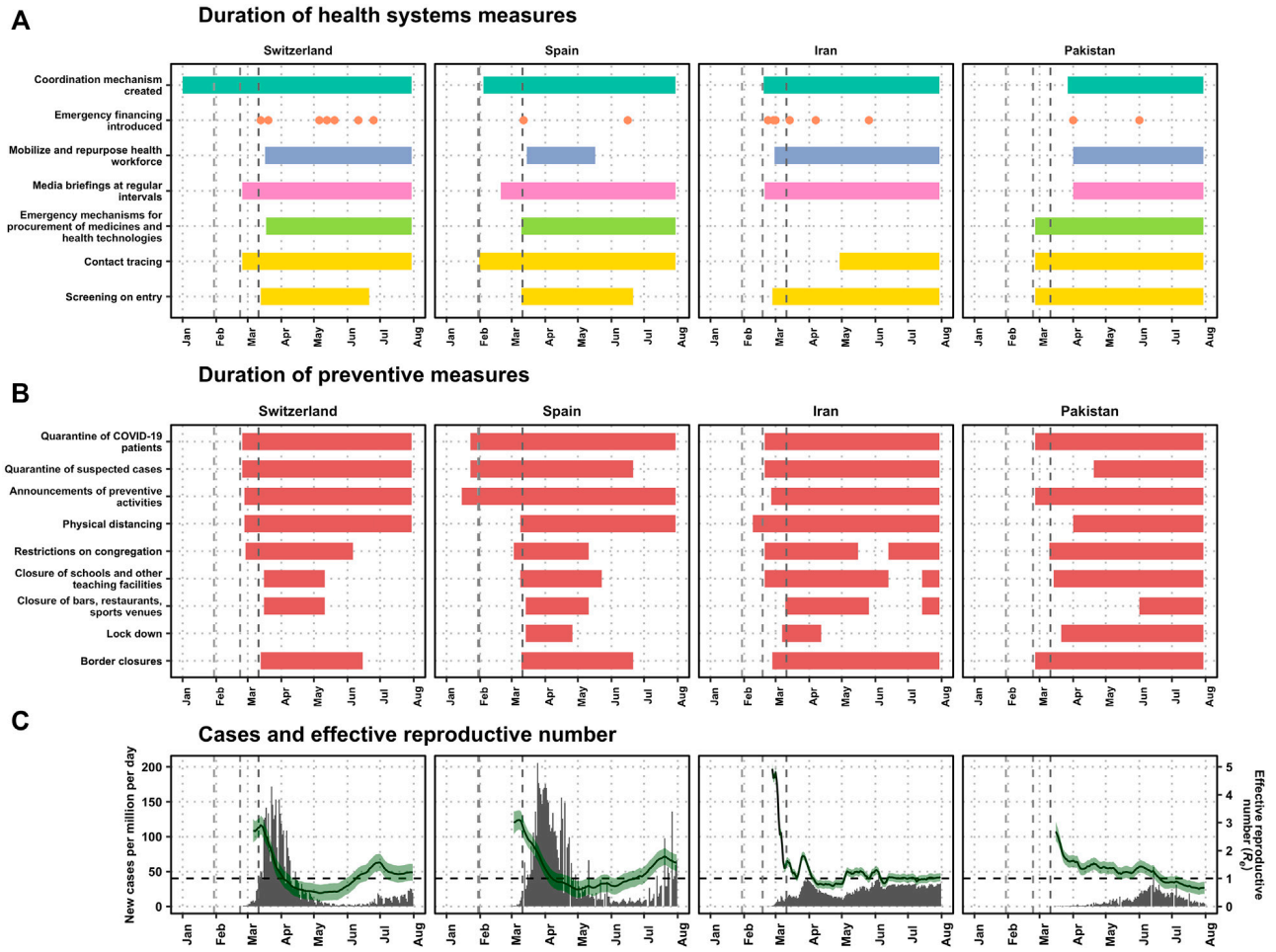

FIGURE 1 | Timeline for public health policy response over cases and number of cases per country (Switzerland, Spain, Iran and Pakistan, January–July 2020). **(A)** The duration of the measures, organized by the six building blocks of health systems (Switzerland, Spain, Iran and Pakistan, January-July 2020). The first gray dashed lines represent the day that the World Health Organization declared the pathogen a subject of international concern and the second line represents the first day of a COVID-19 case was detected in each country: 23 February in Switzerland, 31 January in Spain, 18 February in Iran, and 24 February in Pakistan. In Spain, the day that the WHO declared the pathogen of international concern was 1 day before the first case was found in Spain, and therefore the difference between the first two lines is indistinguishable in the graph. The third gray line shows the day when the WHO declared the pandemic: 11 March 2020. **(B)** The duration of preventive policies (Switzerland, Spain, Iran and Pakistan, January-July 2020). **(C)** The number of cases and effective reproductive number (Switzerland, Spain, Iran and Pakistan, January-July 2020). The number of cases (in gray bars) and the estimated effective reproductive number (R, in green) with 95% confidence intervals as estimated by [18], and assuming a serial interval of 7 days. The dashed horizontal line in black shows $R_e = 1$, the threshold above which the pandemic is growing.

about the extent to which these factors influence the desired outcome in countries [14–16].

We aimed to assess the influence of the political and health systems response on COVID-19 incidence in Switzerland, Spain (high-income countries in Europe region) and Iran, Pakistan (Middle-income countries in Eastern Mediterranean Region). The selected countries included different health system typologies (see countries' health system profile in **Table 1**), whose governance around health care ranges from extensively decentralized systems in Switzerland and Spain to more centralized systems in Iran and Pakistan [17].

In this article, we provide an assessment of the implementation of the measures recommended by the WHO within the six building blocks of health systems. We qualitatively investigated the effect of the system responses over time and the influence of context-specific factors on the measures put in place by governments to contain the pandemic. Our study sheds light on the dynamic interaction of the health, social, economic and cultural systems and how they influenced the ability to manage the pandemic.

METHODS

We conducted four case studies to explore the national response to the COVID-19 pandemic from January through July 2020, corresponding to the "first wave." To capture what measures were taken to prepare the system for the COVID-19 response in Switzerland, Spain, Iran, and Pakistan, we collected data on several interventions mentioned in the WHO's technical guidance document to support countries strengthening the

TABLE 3 | Describing selected Indicators and domains of public health policy response (Switzerland, Spain, Iran and Pakistan, January–July 2020).

Domain of response	Switzerland	Spain	Iran	Pakistan
Governance				
Coordination mechanism created	Legislation in place before the pandemic. The epidemics act "EpiA" clarifies the work-sharing and other coordination aspects between confederation and cantons during a crisis	The Inter-territorial Council of the National Health System, which is the government body of the health system, laid ground for the collaboration between the national and regional health authorities	In February 19,, the National Covid-19 Committee (NCC) led by the minister of health and medical education was established to achieve maximum coordination and inter-sectoral cooperation/ Establishing a joint committee (the scientific sub-committee of the NCC) consisting of some deputies of the Ministry of Health and members of the parliamentary health commission	A multi-sectoral response was designed through the creation of the National Coordinating Council (NCC) to manage the epidemic in March 13. The NCC was headed by the Prime Minister alongside representatives from all relevant ministries. Subsequently, on March 27 the National Command and Operations Center (NCOC) was established, this civil-military constellation proved to be critical in fast-tracking logistics, information gathering, real-time reporting and "smart" lockdowns
Level of decentralization in COVID response in the health sector	Policy-making in Switzerland is usually decentralized. Health care is mostly organized in cantonal level. During an epidemic, the epidemics act "EpiA", allows the transfer of decision-making from sub-national to national levels through escalating steps from "normal", over "special" to "extraordinary situation"	The state of alarm was declared on March 14, this conferred to the central Government full responsibility for implementing measures for COVID-19 crisis. Regional administrations retain operational management of health services	General regulations have been passed by the national committee, while provincial committees are obliged to pass specific regulations based on provinces' situation in line with national committee regulations. National committee also announced the need for continuous monitoring and control over the measures of the provinces	The response initially in February and March was decentralized, as the provinces were independent. But after NCOC was established on March 27 the response was mainly central
Finance				
Introducing emergency legislation to finance response to COVD-19. Briefly describe source, e.g. mobilized emergency reserve funds; reallocated from other budget lines; etc.	In 2020. mobilized estimated CHF 70 to 80 billion from high level of liquidity but also incurrence of debt	A Royal decree approved on March 12 2020 to implement measures that allow exceptional mobilization of structural and contingency funds; Release of extra funds to support the education sector for COVID-19 crisis	Mobilizing $1,127,770,000 from the National Development Fund; allocating $176,229,885 by the government to the country's health system; $62,362,297 foreign financial facilities to fight Corona; etc.	The initial shortage of health commodities and medical equipment in April and May was addressed by the disbursement of more than six billion Pakistani rupees (PKR) (US$ 37M) to buy equipment, ventilators and to upgrade hospital facilities. Additionally, state banks provided low-interest loans to hospitals to improve their case management capacity
Human resources				
Mobilizing and repurposing health workforce (e.g. reserves, retired staff, staff from other specializations, trained students, etc.)	National level: Non-emergency procedures have been prohibited March 21 - April 27, 2020. Other mobilization was organized largely on a cantonal or even hospital level. Cantons can request private institutions to provide their resources for COVID-19 support	Regulation to adopt measures for human resources management during the covid19 crisis. Some Autonomous Communities implemented measures to mobilize the health workforce to cope with the crisis	Reserving 5%–10% nursing staff from other wards of the hospitals for COVID-19 wards; Recruiting individuals who have capability for nursing, (i.e retirees, unemployed nurses, volunteers and interns); Invite nursing professionals, faculty members and post-graduate nursing students to counsel people via the 4030 hotline	A shortage of trained professionals in critical care units was observed in the beginning of the pandemic. Training programs were launched for health care staff
Information systems				
Media briefing intervals	Media releases/press conferences are done at irregular intervals, but several times a week. Special press conferences with specific topics (e.g. sport) are released additionally	From February, the Government released the latest update on the pandemic evolution and the implementation of different measures and policies, at daily press conferences	From February, ministry of health published daily reports of covid-19 statistics including new/total cases, deaths and laboratory tests	Daily media briefings by NCOC started in April and continued for a long time

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TABLE 3 | (*Continued*) Describing selected Indicators and domains of public health policy response (Switzerland, Spain, Iran and Pakistan, January–July 2020).

Domain of response	Switzerland	Spain	Iran	Pakistan
Medical technologies and pharmaceuticals				
Ensuring emergency mechanisms are in place for procurement and registration of medicines and health technologies	In General, the supply of essential medical products is organized in COVID-19 Ordinances 2/3. Some selected smaller scale measures: i) Procurement can be done on a federal level via the military; ii) exceptions are made concerning legal requirements of medical products; iii) essential medicines are given out only in limited amounts; iv) mandatory reporting of ICU availabilities, PPE stocks etc.	There were mechanisms in place but they did not ensure the access to specific health technologies and PPEs	Due to economic pressures from sanctions and the ban on foreign exchange transactions, the possibility of importing medicines and health equipment was minimized. Therefore, the country developed and implemented mechanisms to encourage Iranian companies and factories to increase domestic production lines and achieve self-sufficiency	The NCOC provided vital PPE, oxygen supply systems and established COVID-19 care and treatment centers through National Disaster Management Authority
Service delivery				
Identification of cases				
Contact tracing	Contact tracing done by the cantons. Contact tracing app "SwissCovid app" piloted in June 2020	The contact tracing protocol classified "close contacts" or as possible, probable or confirmed cases; On May 9, the MoH published new guidelines for early detection of cases and contact tracing. Tracing workers would track down people who were closer than 2 m and for more than 15 min to suspected or confirmed cases	A mobile app (mask app) was developed for this purpose. But it was not widely used All people in contact with cases should be screened within 14 days after contact	Contact tracing conducted by rapid response team, including primary healthcare doctors, nurses and paramedics
Screening on entry	Since March 13, travel from "risk countries" (neighboring Italy at the time) was restricted. This list was slowly expanded. On May 11, first travel restrictions were relaxed. Since June 2020, passengers from "risk countries" could have their temperature measured. From July 2020, travelers from "risk countries" need to quarantine for 10 days	Initially, after the detection of the first imported case on January 31, public health interventions were activated to detect cases coming from China; In March, travel bans were imposed from Italy and cruises from any origin; In May land borders closure measures were implemented	Inbound travelers from abroad were required to fill out an entry form/ Prohibition of passenger entry into the aircraft without a mask/ Screening before exist/airport public places disinfection, including terminals and aircraft/Develop a special procedure for protecting flight controllers/flight restriction	Initially screening only applied to travelers from China. Then extended to the pilgrims from Iran who were quarantined at Taftan border
Preventive measures				
Quarantine/home isolation of COVID-19 patients	Isolation of positive cases for 10 days	Cases with symptoms were isolated at home and followed up by a PHC team, or hospitalized if needed	Compulsory quarantine of infected people was approved by the NCC, its implementation was not monitored	Quarantine facilities were established in major cities in the early phases
Quarantine/home isolation of suspected cases and contacts of confirmed patients	Quarantine of close contacts of positive cases for 10 days	Initially, suspicious cases were isolated on arrival, and potential contacts investigated. During the state of alarm, symptomatic cases were isolated at home and potential contacts further investigated.	All people in contact with cases should be screened within 14 days after contact	Quarantine facilities were established in major cities in the early phases
Announcements of preventive activities (personal hygiene)	Public information campaign updated with new rules and recommendations (e.g., hand washing) at different intervals	Personal hygiene, physical distance and indoor preventive and hygienic measures	Personal hygiene protocols were recommended Since July 5 wearing face mask became mandatory in public places	After NCOC took the control national strategy for communication was developed
Physical distancing	Initially 2 m, scaled back to 1.5 m	When the first community outbreak was declared, progressive physical distancing measures were implemented. After the state of alarm declaration, citizens were required to stay at home and use public roads just	It was recommended but not mandatory Eid al-Fitr prayers was held outdoors of mosques Introducing staggered office hours	All preventive measures were communicated but not strictly followed

(Continued on following page)

TABLE 3 | (*Continued*) Describing selected Indicators and domains of public health policy response (Switzerland, Spain, Iran and Pakistan, January–July 2020).

Domain of response	Switzerland	Spain	Iran	Pakistan
		when carrying out specific activities		
Restrictions on congregation	Congregations banned at various levels of stringency, e.g. prohibiting gatherings of more than five people	On March 10, sports events were limited to closed doors and, in regions with community transmission, events with more than 1000 people were banned. When the state of alarm started, citizens were required to stay at home and congregation was not allowed	Issuance of regulations by the government regarding restrictions on gatherings in high risk areas	Non-essential services such as educational institutions, government offices, markets, business centers, parks, etc., were closed
Closure of schools and other teaching facilities	Schools on all levels closed for 2 months. Step-wise reopening (Secondary level II, tertiary level and further education last), shift of decisions to cantons	Schools and universities were closed, first in the regions with community transmission, followed by application country-wide on March 12th. When the de-escalation plan started to be implemented, during the state of alarm, educational centers could open under particular circumstances	In the metropolis of Tehran and other red-zone cities: Closure of all universities, seminaries, educational centers, and libraries (the NCC scientific committee has classified the country into five zones according to the COVID-19 situation in each city: red, orange, yellow, blue, and white. In this classification, white zone is where no new COVID-19 cases are found, and the red zones are the cities with the most infected cities)	In March all the educational institutions, were closed to reduce the spread of COVID-19
Closure of bars, restaurants, sports venues	Fully closed for 2 months, afterwards opening with restrictions (e.g. four people per table)	During the first months of state of alarm, hotels and restaurants had to close, except if they had been recruited to serve healthcare workers or truck drivers. In May, during the de-escalation plan, bars and restaurants in some regions could open with some restrictions. Professional sports competitions were allowed behind closed doors	Fully closed in red-zone cities. Re-opening with restrictions in lower risk zones	Fully closed during lockdown, afterwards opening with restrictions in lower risk areas
Lockdown	Not considered	Total lockdown started on March 14 and was progressively scaled back (with the de-escalation plan) until June 21	Lockdown was in place including closing businesses and government offices and inter-city and inter-province travel bans. Later, using a color coded scale, cities were classified into blue, yellow, orange, and red zones based on the COVID-19 infection rate. In red cities, only essential services were allowed to open. Inter-city travel was banned Blue was the lowest threat with minimum restrictions	After the low compliance with the initial decision on national lockdown for 2–3 months, prime minister ordered to reopen the economy and move to a strategy of contact tracing and "smart lockdown" in areas with high positivity ration
Border closure/Travel restriction	Closure of borders/travel restrictions and stepwise reopening (first neighboring countries, Schengen area, then other countries)	Closure of borders/travel restrictions and stepwise reopening (first neighboring countries, Schengen area, then other countries)	Partial closure of borders/travel restrictions and stepwise reopening	Initially only china but later included other countries. Since March 2020, Pakistan suspended domestic and international flight operations and reopened the borders in stepwise manner

health system response to COVID-19 [3] within each health system component. We tracked the presence of these measures weekly on the basis of 17 indicators. We also collected qualitative data on the rationale and the political support for these measures.

We developed the first version of the data collection tool in Microsoft Excel. We pilot-tested this version by collecting information for 1 week. After discussion with key informants, we selected 17 indicators (**Table 2**) and tracked

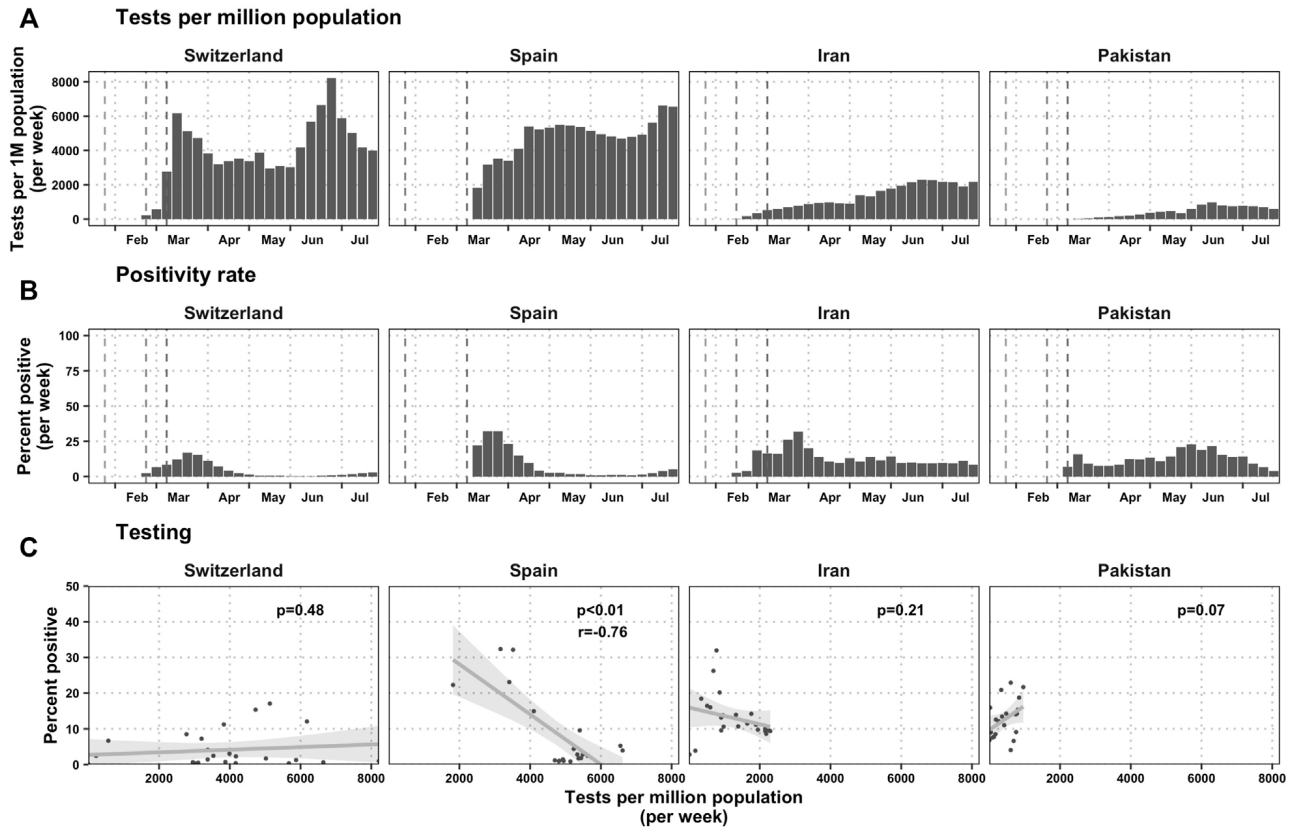

FIGURE 2 | Testing statistics per country (Switzerland, Spain, Iran and Pakistan, January-July 2020). **(A)** Tests per million population. The first gray dashed lines represent the day that the World Health Organization declared the pathogen a subject of international concern and the second line represents the first day of a COVID-19 case was detected in each country: February 23 in Switzerland, January 31 in Spain, February 18 in Iran, and February 24 in Pakistan. In Spain, the day that the WHO declared the pathogen of international concern was 1 day before the first case was found in Spain, and therefore the difference between the first two lines is indistinguishable in the graph. The third gray line shows the day when the WHO declared the pandemic: 11 March 2020. **(B)** Positivity rate, measured as the fraction of all tests that are positive each week. **(C)** The relationship between test intensity (measured as tests per million population) and the positivity rate each week. In Switzerland, the COVID-19 Datahub did not have testing numbers before epidemiological week 22, but the Swiss government provides those estimates for download, so we have combined both datasets [66]. In Iran, the COVID-19 Datahub did not have testing numbers before epidemiological week 15, but we knew that there would be 78,434 tests administered on week 16, and we found a publication that stated that there were about 600 tests per day done at the end of the first week after the first case, and 6000 tests performed by the end of the first month [53]. We therefore took a linear interpolant to calculate the number of tests that were done in those first 8 weeks.

their implementation prospectively; these indicators encompass the thematic domains of governance, financing, health workforce, information, medicine and technology and service delivery.

Teams of health systems researchers from Switzerland, Spain, Iran, and Pakistan volunteered to participate as key informants. We collected information on country responses from publicly available sources including official government documents (legislation, press releases, policy briefings); reports from different agencies in countries; and major media channels. Information was extracted in German, Spanish, Persian and Urdu in Switzerland, Spain, Iran and Pakistan respectively, and translated to English in the data matrices. Some data in all countries was available in English. Finally, two independent researchers performed data reviews and quality control for each country. To gain a comprehensive view of how the measures tracked with the case burden in each country, we developed a set of visuals side-by-side with two simple indicators of the epidemiological situation: the incidence and the basic or effective reproductive number (R_e) by day, sourced from the COVID-19 Datahub using the associated R Package as an interface [18, 19]. We also graphed the weekly number of tests and the percent positivity; we opted for the weekly statistics rather than the daily statistics because daily statistics can be noisy (i.e. fewer tests take place on weekends, more cases are reported on Mondays). To understand whether there was significant relationship between the tests per million population and positivity rate we ran a Pearson Chi2 test.

The information collected was structured and analyzed around the domains of the health system. To gain a detailed, holistic view of the development of the response in each country, each of our key informants gave a narrative overview of the health commodities, restrictions, and economic response to the pandemic framed around the centralized or decentralized nature of governance.

RESULTS

The data collection strategy yielded more than 100 data points over 8 months on the implementation of the different strategies. The detail of the sequence of the interventions in countries combined with the measures of disease progression can be seen in **Figure 1** for Switzerland, Spain, Iran, and Pakistan (see **Supplementary Appendix SA1** for list of information sources).

Visual inspection of the policy response in **Figure 1** is complemented by the information about the policy response in **Table 2** for the four countries. Our findings show that enactment of the public health policy responses coincided with the decrease in the transmission, expressed in terms of the effective reproductive number.

Multi-sectoral coordination committees began either before or immediately after the first case in all countries but Pakistan (**Figure 1**; **Table 3**). Initially the response was centralized at the national level in all four countries and then with increasing geographic heterogeneity in prevalence of COVID-19 cases within a country, more localized approaches were adopted.

Emergency financing measures were introduced in all countries within 1 month of the first case (**Figure 1**; **Table 3**). The healthcare workforce was repurposed in all countries within 3 weeks except in Pakistan, where it took more than 1 month. Media briefings at regular intervals began within 2 months of the WHO declaration of COVID-19 as a disease of international concern; it began in February 2020 and after the report of the first case in Switzerland, Spain and Iran, but more than 1 month after the first case in Pakistan.

Emergency mechanisms for the procurement of medicines and health technologies began on the day that the first case was reported in Pakistan, after 3 weeks in Switzerland, and 1 month after the first case in Spain; these mechanisms were never put in place in Iran (**Figure 1**). Contact tracing began in Spain, Switzerland, and Pakistan on the day that the first case was reported in the country, and in Iran more than 2 months after the first case was reported in the country. Screening on entry to the country—symptom screening and tracing services—was mandated on the day of the first detection in Pakistan, on the week of the first detection in Iran, and within 3 weeks in Spain and Switzerland. Preventive measures were in place at different time intervals and intensity in each country.

Corona virus testing intensity and outcomes are shown in **Figure 2**. Testing began to ramp up on the week after the first case was found in all countries. The testing rate was relatively high at 4-8 thousand tests per 1 million population per week in both Switzerland and Spain, but under 2000 per 1 million population in Iran and under 1000 per 1 million population in Pakistan. The positivity rate was highest in Switzerland, Spain, and Iran during March, and fell during April and subsequent months. In Pakistan the peak positivity rate was not reached until the last week of May and first week of June. The intensity of testing had no relationship with the positivity rate in Switzerland, Iran, and Pakistan, but it had a substantial and significant relationship in Spain (p=<0.01, correlation coefficient r = −0.76) indicating that the high positivity rate may be attributable to the low number of tests in the first weeks after the outbreak.

DISCUSSION

We discuss our findings by describing the application of responses to COVID-19 and their consequent influence on the evolution of the pandemic in Switzerland, Spain, Iran, and Pakistan. We found that while *a priori* many of the systems domains delineated by the WHO were addressed in each country's response (**Figure 1**; **Table 3**), the application of measures and their consequent influence on the evolution of the pandemic varied widely. Our findings show that the capacity of governments to sustain preventive measures was affected by different contextual factors, sometimes leading to quick resurgence in transmission.

Switzerland: The Swiss Journey From Decentralized to Centralized Decision-Making and Back

Policy-making is heavily decentralized in Switzerland's 26 cantons. However, during an epidemic, the Epidemics Act allows the transfer of decision-making from sub-national to national levels through escalating steps from "normal," over "special" to "extraordinary situation" [20].

Three days after the first confirmed case on 25 February 2020, the Federal Council declared the "special situation" and banned events with more than 1000 visitors [21]. After an initial lag, decisions were made in quick succession: when Ticino, the canton with the highest disease burden, declared a "state of emergency" on 11 March 2020, several other cantons introduced stricter measures and the national government announced the closure of schools and banned events of over 100 participants. After four more cantons declared a "state of emergency", the government escalated the national situation to "extraordinary" on 15 March 2020, enabling centralized decision-making and all shops, restaurants, entertainment facilities, and international borders were closed (**Figure 1**). This "extraordinary" situation allowed the government to decide on national matters without consultation of the cantons, thereby allowing for faster reactive policy-making. The centralization of the decision-making power was well received by some cantons: it provided support to contain the pandemic and required the government to take responsibility for the mandated measures and resulting economic consequences. On the other hand, some cantonal authorities criticized a lack of involvement in the strategic communication and little time to prepare before decisions were communicated to the public [22].

Even with centralized decision-making, cantons retained some decision-making capacity: they had the freedom to make their own policies if there was no national ordinance. The resulting, often complex, situation of decentralization can be exemplified by the governing council of the canton Uri, which decided on March 20 to ban people over 65 years old from leaving their houses but on the same day the Federal Council issued a new ordinance

rendering the canton's decision invalid and lifting the curfew [23, 24].

Stepwise re-opening began on 27 April 2020. On 19 June 2020, the situation was de-escalated from the "extraordinary" to "special," returning some autonomy back to the cantons. The opening and de-escalation steps were taken more quickly than expected; cantons criticized the short timeframes between discussion and decision-making, and between communication of the decisions and implementation [22].

In 2020, the government mobilized 74 billion Swiss Francs (CHF) for combatting the pandemic in the form of loans for companies and social welfare [25]. On 25 June 2020, the Federal Council fully subsidized all tests for symptomatic persons, persons in close contact with the positive cases, and persons that were in quarantine mandated by cantonal authorities.

At the height of the first wave, wearing masks was only recommended for cases, their care takers or risk groups. The public perceived this as a strategic decision due to a shortage of masks, which was disputed by the Federal Office of Public Health (FOPH) as the scientific basis for this mandate was not yet given [26]. A report from 2021 attests that there was a severe shortage of masks by the end of February 2020 [27]. Following an increase in cases in July 2020 (**Figure 1**), the first national mask mandate in public transport was issued. The Swiss NationaL COVID-19 Science Task Force (SN-STF) called for stricter measures (such as a mask mandate in shops). The public discourse was dominated by a sense of uncertainty by the statements of the SN-STF, the diverging actions of the Federal Council, and the cantons' sense of being overburdened and unsupported. At the end of July 2020, the FOPH proposed uniform national rules to avoid confusion among the public [28].

Spain: Decentralization and Citizens' Influence on the Response

Spain enacted surveillance and monitoring mechanisms before detecting the first confirmed case on 31 January 2020 [29]. The national government activated existing coordination mechanisms for an integrated response across ministries and regions, and created a communication strategy to raise awareness of the transmission risk and preventive measures. However, the false perception of low community transmission risk among the public resulted in low compliance with preventive measures in the initial phases of the pandemic [30]. Eventually when Spain became one of the epicenters of the health crisis in Europe, the public perception changed dramatically [31].

Despite a rapid increase in the number of cases in February, only on 3 March 2020, community transmission was declared in Madrid, Basque Country and La Rioja, and more restrictive measures (e.g., school closures and congregation restrictions) were introduced. The legal framework of the decentralized governmental system in Spain made it impossible to implement targeted lockdowns in autonomous regions and so the national government had to resort to the declaration of a nationwide lockdown on 14 March 14, 2020.

Initially, PCR tests were reserved for hospitalized patients, health professionals and workers in essential services. After 7 May 2020, testing was extended to all suspected cases and diagnosis, surveillance, and contact tracing were performed by the public health system.

Primary Health Care (PHC) was left outside of COVID-19 pandemic planning and management and the strategic focus on hospital care limited the potential of the PHC system to respond to the pandemic and led to a deficient contact tracing system in some regions [32, 33]. With the increased demand in hospitals and nursing homes, PHC providers were reallocated to provide treatment to COVID-19 patients [34]. With an overstretched PHC system and shortage of personal protective equipment (PPEs) by April 2020, Spain had the highest number of health professionals infected with COVID-19 worldwide [35].

Years of structural adjustment programs after the 2008 economic crisis in Spain left an under-resourced social and health care system [33]. Although structural and contingency funds were mobilized, and social measures to protect the most vulnerable populations were activated (e.g., guarantee home care for dependent persons), these measures could not fix the existing structural gaps. An under-resourced PHC and failing to monitor the quality of care and social services resulted in almost 20,000 deaths in nursing homes between January and June 2020 [36–39].

While public acceptance of preventive measures increased due to recognition of the epidemic's gravity, debate over the lockdown measures rose steadily since April 2020. The lockdown in Spain was one of the strictest lockdowns in Europe resulting in negative social and economic impacts [40]. Compared to the more proactive containment strategies (massive testing and contact tracing) taken by countries such as South Korea, in early stages of the pandemic, Spain's approach was criticized in the scientific literature as being unnecessarily restrictive in controlling the spread of the virus [41, 42]. Fear of economic slowdown and political polarization in parliament combined with social opposition to restrictive measures resulted in the loss of parliamentary support for the continued state of alarm [43, 44]. On 21 June 2020, all pandemic response competencies were fully devolved to the autonomous communities and the quick reopening resulted in deficient implementation of tracking and tracing systems, likely hindering the efficiency of the pandemic response [43–45].

Iran: Whole of Government Approach Under Economic Pressure

Iran was among the first countries to face the heavy burden of the COVID-19 outbreak. Immediately after officially detecting the first case of the disease on 19 February 2020, the National COVID-19 Committee (NCC) was established. Among the NCC's immediate decisions (between February 22–26, 2020) were suspending commercial flights from China, issuing health certificates for foreign travelers, closing schools and universities, banning public gatherings, congregation restrictions, and reducing working hours (**Table 3**).

Although all economies were significantly handicapped by the pandemic, Iran's economy faced a double burden due to pre-existing unilateral economic sanctions; therefore, timeliness and effectiveness of mitigation strategies were overshadowed by low economic resilience [46]. Despite the growing number of cases in February

2020, authorities hesitated to impose more restrictive measures such as national lockdown, which did not come into effect until early March 2020 (**Figure 1**). The continuous surge in daily reported new cases to over 1000 in March 2020, combined with concerns about the high risks of spread of the virus during the Persian New Year (Nowruz) holidays on 20 March 2020, led to imposing further restrictions, such as fines for travel ban violations [47].

Eventually economic concerns and frequent changes in the lead policy-makers in the most conflicted provinces led to the premature lifting of COVID-19 restrictions. By 3 April 2020, during the peak of the first wave, businesses, which had been closed since 18 March 2020 due to Nowruz holidays, reopened gradually. Easing the preventive measures continued with the reopening of mosques, allowing religious ceremonies during Ramadan (25 April–24 May 2020), and gatherings during the consecutive holidays of Eid —celebration of the end of the month of Ramadan— which likely instigated the rise of the second wave.

With the unilaterally imposed economic sanctions, adopting a whole of government (WOG) approaches has led to the self-sufficiency of Iran in the face of shortages of the basic prerequisites for managing COVID-19. The strong political support of the Supreme Council for National Security, within the framework of the WOG approach, allowed the government to launch various national campaigns and make use of the resources of the army and many other national organizations for conducting training programs, providing health support packages, monitoring and tracking the disease.

Given the state of the fragile economy, the risk of low compliance from public to restrictive measures at national level and differences in the prevalence of COVID-19 across provinces, the NCC delegated policy-making powers for re-imposing restrictions to the provincial COVID-19 Committees [48].

Despite the efforts to minimize the economic burden, as a result of COVID-19 restrictions, about 3 million Iranians lost their jobs between March and September 2020 and the government's financial aid to the affected businesses and households was insufficient to protect them from economic hardship [49, 50].

In response to the shortage of essential medical supplies, particularly at the outset of the pandemic, the government facilitated import, banned exports and incentivized the domestic industry to increase production capacity [51]. The capacity for real-time PCR tests increased from two centers to 190 laboratories by 22 July 2020 [52, 53], led by the Pasteur Institute of Iran, which began coordination on the first week a case was detected [53]. However, only symptomatic individuals were allowed to be tested free of charge and upon a physician's request [47], perhaps explaining the relationship low testing intensity in the country (**Figure 2**).

Pakistan: Multi-Sectoral Response for a Whole of Society Approach

A multi-sectoral response was designed through the creation of the National Coordinating Council (NCC) to manage the epidemic 3 weeks after the first case was detected—the slowest of any of the countries in our analysis [54].

Pakistan initiated preventive strategies in January 2020. One of the first containment actions taken was contact tracing of international travelers, designating quarantine houses in airports and near borders for individuals entering Pakistan to prevent community transmission; however, the state of the quarantine houses was questionable due to unsanitary conditions [55, 56].

Pakistan's risk communication strategies included using national television programming, mobile ringtone messaging, the development of a helpline, and daily-televised briefings by the Ministry. However rumors and misinformation from social media, framing the pandemic as a conspiracy theory hindered these efforts and the country faced the challenge of low compliance by the public to the preventive measures [55].

Implementing restrictive measures such as lockdown requires taking into account the country-specific circumstances such as population structure, health needs and resources. According to Patel et.al. economically disadvantaged people are more vulnerable to COVID-19 due to poor housing conditions, no possibility to work remotely, unstable work conditions and comorbidities [57]. Thus implementing a lockdown policy without a welfare support system in a low income country could increase the unemployment rate and further drive down compliance and increase the spread of the virus [58, 59]. This also accords with the situation in Pakistan when the government announced a national lockdown for 3 weeks starting on 15 March 2020. This decision did not receive public acceptance and was criticized and violated widely due to its economic impacts on a large portion of the population. Inefficiency in implementing the national lockdown resulted in lifting the measures after 2 weeks and introducing a "smart lockdown" strategy by enforcing the lockdown, only in places with higher positivity ratio [60].

Adopting a whole-of-society approach, the government worked with the existing social safety net "Ehsaas," to alleviate the economic burden associated with the pandemic by providing cash disbursements for daily wage earners starting in April 2020 [61].

Despite the concerns about maintaining social distancing during the prayers at mosques, the mosques were open to the public during the month of Ramadan (23 April–23 May 2020) [62]. The support of religious leaders during Ramadan was instrumental in gaining broad compliance in many areas of the country [63]. On 19 May 2020 and right before the religious festival of Eid which ends the month of Ramadan (23–24 May 2020), the Supreme Court decided to ease the measures and opened shopping centers and public transport, resulting in a sharp increase in cases in the following 2 weeks (**Figure 1**).

The initial shortage of health commodities and medical equipment in April and May 2020 was addressed by the disbursement of more than six billion Pakistani rupees (PKR) (USD 37M) to buy equipment, ventilators and to upgrade hospital facilities. Additionally, state banks provided low-interest loans to hospitals to improve their case management capacity [64]. While diagnostic testing was initially very scarce, Pakistan acquired increased testing capacity in late February 2020 when several testing sites across the country were established by the federal government under the supervision of Pakistan's National Institute of Health (NIH) [65]. However, within the 4-country case study

presented here, Pakistan observed a relatively low testing intensity (**Figure 2**), probably representative of the testing capacity of poorer countries around the world.

Limitations

Our study is subject to a number of limitations. The accuracy of the observed incidence might not be comparable as different countries had different testing and diagnostic policies (**Figure 2**). There were not enough jurisdictions examined across the 17 indicators to analyze the independent and synergistic effects of each policy in a quantitative manner, and therefore we decided to rely on a structured thematic periodization of the package of interventions. Data from more countries could have also improved the geographic representation of the sample, but as this was a volunteer-based data collection effort, we relied on available and willing colleagues. Despite the collection of 17 indicators for 7 months, the decentralized responses in any one country could not be fully captured, nor could shortcomings with the centralization of decision-making. Moreover, the indicators of the economic impact of lockdowns are not perfectly comparable across countries whose informal employment sector is substantial.

Conclusion

Health systems are complex adaptive systems embedded in a wider ecosystem of economic, social and cultural super-systems that influence each other. Disentangling the effects of this dynamic interaction to capture independent and synergistic effects of policies require both transparencies in publicly available information and a broad collection across jurisdictions of one country or several countries. The results illustrate that the functional boundaries of the health system do not stop at the edges of WHO's six building blocks of the health systems framework.

The policy responses to COVID-19 are largely dependent on the level of decentralization of the system, their social and cultural contexts and the economic forces that define them.

Health systems with chronically under-resourced primary care and public health services, weak governance mechanisms, and substantial fragmentation across services hampered the ability of governments to respond to the health needs of citizens in a timely manner. Primary health care is the first contact point of people with the health system, however during the pandemic it was overshadowed by prioritizing secondary care. An under-resourced primary health care slowed down preventive responses and led to increased transmission.

Overall economic context and the strength of social protection systems played a crucial role in the type of interventions that the different governments put in place. Access to COVID-19 tests and functional health infrastructures allowed Switzerland to take a proactive approach to "flatten the curve" using containment measures such as testing and contact tracing thus avoiding a national lockdown. On the other side of the spectrum, in Iran and Pakistan implementing a partial lockdown was an inevitable choice, not only because of limited access to diagnostic tests but also due to the low coverage of sick or unemployment benefits.

Another major finding was that in all countries compliance to the measures was a concern. This further reinforces the importance of effective communication strategies and the need to galvanize context-driven "trust" dynamics between population and centralized and decentralized governments.

AUTHOR CONTRIBUTIONS

MT: Project management and coordination, data synthesis AK: Data synthesis FF: Data collection and synthesis, LM: Data collection and synthesis, AR: Data collection and synthesis, SZ: Data collection and synthesis, MA: Data synthesis, visualization, DCM: Supervision and data synthesis, MA and DCM are senior authors. All authors contributed to conceptualizing the study, writing the first draft, preparing and approving the final article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the work of Seckin Boz, Anna Fesser and all individuals who supported COVID-19 health systems and policies observatory team throughout the project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/ijph.2022.1604969/full#supplementary-material

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Appendix C

Second publication from Chapter 5

Did COVID-19 policies have the same effect on COVID-19 incidence among women and men? Evidence from Spain and Switzerland

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International Journal of Public Health
ORIGINAL ARTICLE
published: 20 September 2022
doi: 10.3389/ijph.2022.1604994

Did COVID-19 Policies Have the Same Effect on COVID-19 Incidence Among Women and Men? Evidence From Spain and Switzerland

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Objective: This study aimed to investigate how COVID-19 prevention policies influenced the COVID-19 incidence in men and women.

Methods: We conducted a retrospective longitudinal study using the Swiss Federal Office of Public Health and the Spanish Ministry of Health surveillance data for February 2020–June 2021 to explore sex and age differences in COVID-19 cases and testing. The female-male incidence rate ratios (IRR) were estimated for each week of the pandemic. We complemented our analysis with qualitative information on relevant containment measures in each country.

Results: In Switzerland and in Spain, there was an excess of cases in women of 20–59 years old and 80+. This excess of cases was significant during the waves of the pandemic in both countries. In Switzerland, the biggest difference was observed for the age group 20–29, reaching an excess of 94% of cases compared to men during the first wave of COVID-19 (March–May 2020). The excess of cases in women was greater in Spain than in Switzerland, where it reached 159% for women aged 20–29 during the first wave (March–June 2020). In both countries, the age groups 60–79 had a significant excess of cases in men during the pandemic.

Conclusion: COVID-19 public health policies affect men and women in different ways. Our findings highlight the importance of gender-sensitive responses to address a public health crisis.

Keywords: public health, COVID–19, health policy, epidemiology, gender

OPEN ACCESS

Edited by:
Michael J. Deml,
Université de Genève, Switzerland

Reviewed by:
Daniela Anker,
Université de Fribourg, Switzerland

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This Original Article is part of the IJPH Special Issue "Responses to the COVID-19 Pandemic: International Comparisons"

†These authors have contributed equally to this work

Received: *05 April 2022*
Accepted: *19 August 2022*
Published: *20 September 2022*

Citation:
Sant Fruchtman C, Fischer FB, Monzón Llamas L, Tavakkoli M, Cobos Muñoz D and Antillon M (2022) Did COVID-19 Policies Have the Same Effect on COVID-19 Incidence Among Women and Men? Evidence From Spain and Switzerland. Int J Public Health 67:1604994. doi: 10.3389/ijph.2022.1604994

INTRODUCTION

Early in 2020, the first reports coming from China and Italy indicated the population group with the highest mortality risk due to the virus were men with comorbidities, which was confirmed globally as the pandemic spread [1, 2]. Numerous studies have shown that the impact of the COVID-19 pandemic is gendered: conferring differential risks attributable to both biological differences (sex), but also marked by social dynamics and socially constructed norms (gender) [3]. Given the differences in mortality, much research and academic commentary has

focused on explaining the increased mortality in men compared to women [4]. Such approaches, however, have failed to address how sex and gender differences affect COVID-19 incidence [5, 6].

Since early in the pandemic, few countries have routinely reported sex-disaggregated data on cases and deaths of COVID-19 [7]. The countries reporting cases and deaths disaggregated by sex show mostly higher death rates in men and similar incidence for men and women [5]. Unfortunately, incidence data describing the differential progress of the disease by gender is not routinely collected [8]. Gender has been described as a multidimensional variable that describes identity, norms and relations between individuals and that can influence access to health services, social support, as well as behaviour towards the prevention of the virus [9, 10].

A pre-print published in May 2020 examined the apparent equality between men and women in COVID-19 infection rates adding an age-disaggregated analysis in ten European countries [11]. The study used routine epidemiological data and reported a higher rate of infections among women compared to men of working-age (20–59 years old). The difference became non-significant in the population above 60 years of age. This finding illustrates the potential role that social norms could have in the spread of COVID-19.

As the pandemic was unfolding, countries worldwide tried to control its peak with strict public health policies that included lockdowns and other restrictions, which started in March 2020 [12]. Unfortunately, some of these policies reinforced pre-existing inequalities, including gender inequalities [9, 13].

Despite the growing body of evidence showing differences by gender and other social determinants in COVID-19, very few studies have examined how different phases of the pandemic have impacted men and women differentially with a specific focus on COVID-19 incidence and its policy drivers. We explore whether the overall case burden, even in age groups for whom COVID-19 is not usually fatal, shows a similar pattern between men and women and how COVID-19 prevention policies may have affected it.

For this study, we chose to focus on two European countries: Switzerland and Spain, which were among the European countries with the highest numbers of cases and deaths per capita in the first year of the pandemic [14, 15]. Additionally, the countries' policies represent different stringency to COVID-19 containment approaches, with Spain going into full "lockdown" (as in people were not allowed to leave their homes freely) for a considerable time, while Switzerland never went into full lockdown.

METHODS

We conducted a retrospective longitudinal study using quantitative COVID-19 case and testing data and qualitative data on the containment measures and policies between February 2020 and June 2021 in two European countries, Switzerland and Spain.

Study Setting

Switzerland is a small federal state in central Europe bordering France, Germany, Austria, the Principality of Liechtenstein and Italy. It is divided into 26 cantons (administrative entities). The Swiss health system is based on universally mandated private health insurance [16].

Spain, bordering Portugal and France and the microstate of Andorra, consists of 17 autonomous communities, including two island territories. It has a public, universally accessible National Health System complemented by voluntary private insurance policies.

Healthcare is more privatised in Switzerland than in Spain, where it is more socialised. Both countries have universal access to healthcare and a decentralised public health system. However, both had mechanisms to centralise decision making in times of an emergency like COVID-19. The per capita spending on health care in 2018 was 9,870 USD in Switzerland, the second highest in the world, while in Spain it was 2,736 USD [17].

Both countries ranked similarly in the latest Gender Gap Index: 10th (Switzerland) and 14th (Spain) place out of 156 [18]. However, despite this high ranking, there are prevailing differences in everyday lives for women and men in these countries. In recent years, men and women have achieved a more balanced participation in the labour market, however, in both countries, most domestic tasks and care work are still predominantly carried out by women in the family context [19, 20]. Even during the lockdown, many women had to consider quitting their jobs to be able to take care of their children, since schools were closed [21].

In both countries, women tend to have jobs that include physical interactions with people (teaching, childcare, health workers, supermarket employees, etc.), many of which were considered "essential", even when most workers were recommended to stay home [20, 22].

Data Collection and Analysis

To understand how COVID-19 incidence among men and women changed over time, we used publicly available case data stratified by sex and age. Data was collected from the Swiss Federal Office of Public Health (FOPH), as well as the Spanish Red Nacional de Vigilancia Epidemiológica (RENAVE). COVID-19 cases were mandatory to be notified to the FOPH since before the first case in Switzerland. The case definitions were adapted through time, based on the diagnostic possibilities (changing from PCR-confirmed to rapid test confirmations). Likewise, the definition of a case was updated in Spain according to the technical reports for the COVID-19 case management [23].

We explored the incidence between men and women from the outbreak of the pandemic (February 2020) until June 2021. We calculated the IRR of cases between women and men, stratified by age groups - for each week of the pandemic:

$$IRR_{women} = \frac{Cases\ among\ women\ of\ that\ age\ group\ in\ that\ week / Population\ of\ women\ in\ that\ age\ group}{Cases\ among\ men\ of\ that\ age\ group\ in\ that\ week / Population\ of\ men\ in\ that\ age\ group}$$

For convenience, excess cases per population are shown in two ways: 1) as IRR, 2) as a percentage deviation from equality between both sexes (IRR = 1):

$$Percent\ excess\ incidence = \begin{cases} {}^{1}/_{IRR_{women}} - 1, & IRR_{women} < 0\ (Excess\ of\ men) \\ IRR_{women} - 1, & IRR_{women} \geq 0\ (Excess\ of\ women) \end{cases}$$

To test for disparities, we used an exact test assuming that incidence is Poisson-distributed. "Waves" in the COVID-19 pandemic were defined as any time that the test positivity rate exceeded 5%, as defined by the World Health Organization (WHO) [24].

We collected information from policies (such as Royal Decree in Spain, or the COVID-19 Ordinance in Switzerland) published by the governments for the regulation of tele-working, school closures, which had been previously hypothesised as the biggest drivers behind gender differences, as well as testing strategies that were regularly updated by the Ministry of Health (MoH) in Spain and the FOPH in Switzerland to complement the case data [25, 26]. Two of the authors (FBF and LM) searched publicly available reports such as official government documents/websites or press releases and press conferences of national-level policies and their implementation at the second administrative level (cantons in Switzerland, autonomous communities in Spain) to create a harmonised timeline of policies in each country. This was an extension of the Health Observatory detailed in a previous manuscript [27]. These data were then visualised to show the duration of policies (for home office recommendations and school closures) and the changes in testing policies.

To account for differences in testing behaviour between men and women, supplemental analyses in Switzerland on testing rates by gender were included and the positivity rate was calculated, stratified by gender. In Spain, testing data stratified by gender was not available.

A simple simulation was performed to calculate the theoretical 95% confidence interval of the positivity rate for women had both genders had the same underlying incidence but women were testing at higher rates. This was done by taking 1,000 Monte Carlo samples from a gamma distribution with shape parameter equal to the cases among men and rate parameter equal to the population of men. Then we sampled from a Poisson distribution with rate parameter equal to the gamma distribution draw times the number of women in the population, and we calculated the simulated positivity-rate by the number of tests done on women in the population.

RESULTS

Switzerland

COVID-19 Policies Over Time

Switzerland has aimed to strike a balance between limiting the spread of COVID-19 and "normalcy" in social and economic life. A full lockdown, where leaving the house was legally restricted, has never been implemented. The most stringent measures were issued during the first wave from March to June 2020, which included a closure of schools, shops and all leisure and entertainment facilities [25]. Schools were closed from the week of 16 March to the week of 4 May 2020 and most of the remaining restrictions were lifted during summer 2020.

The second wave, which peaked at the end of October 2020, yielded more than seven times as many reported cases but had fewer restrictions and a more diverse response. At this stage, decision making was decentralised to the cantons, which contrasted with the first wave where centralization to the Federal Council was enabled after declaring an "extraordinary situation" as stated in the Epidemics Act [28].

During the second wave, schools remained open, with the exception of universities and other institutions of tertiary education. The second wave was accompanied by a semi-shutdown in which restaurants and other institutions for social activities remained closed for three months. Employers were mandated to enable home office for their employees, if possible. Despite these interventions, the case numbers decreased only slowly between January and March 2021.

During the first months of the pandemic, testing capacities were limited to high-risk groups or people with severe symptoms (**Supplementary Figure S1**) [29]. Over time and with the availability of more tests, these recommendations became more relaxed and all symptomatic people or people with suspected exposures were included in the testing strategy. From June 2020 onwards, the government would pay for tests if indicated by their testing criteria [30]. By the end of 2020, a rapid antigen test became available and from January 2021, the government agreed to pay for the tests also of asymptomatic people with suspected exposure [31].

Starting in March 2020, the Federal Council implemented a number of social support measures to lessen the impact of the pandemic on companies and employees, such as compensation of loss of earnings for childcare or quarantine/isolation or short time work compensation.

Incidence by Sex Over Time

In Switzerland, there were distinct peaks of increasing COVID-19 incidence ("waves"): the first wave in February–April 2020, and the second wave began in October 2020, peaking by the end of the month, and remaining at an overall high level until a third wave in 22 March, 2021.

We found that during the waves, women in working ages were significantly overrepresented among all COVID-19 cases (**Figure 1**). During the first wave, women were overrepresented with an excess of up to 58% among women of working age (20–59 years of age). The excess during the second wave remained at a lower level with a maximum of 23% among women of working age. In contrast, between the waves, little significant difference between the sexes was observed. This is largely attributable to lower case numbers but when the disparity was statistically significant, it disadvantaged men more than women. In an analysis stratified by age (**Supplementary Figure S2**), there was a tendency towards a higher excess in women aged 20–29 years old with 40–94% excess in the first wave,

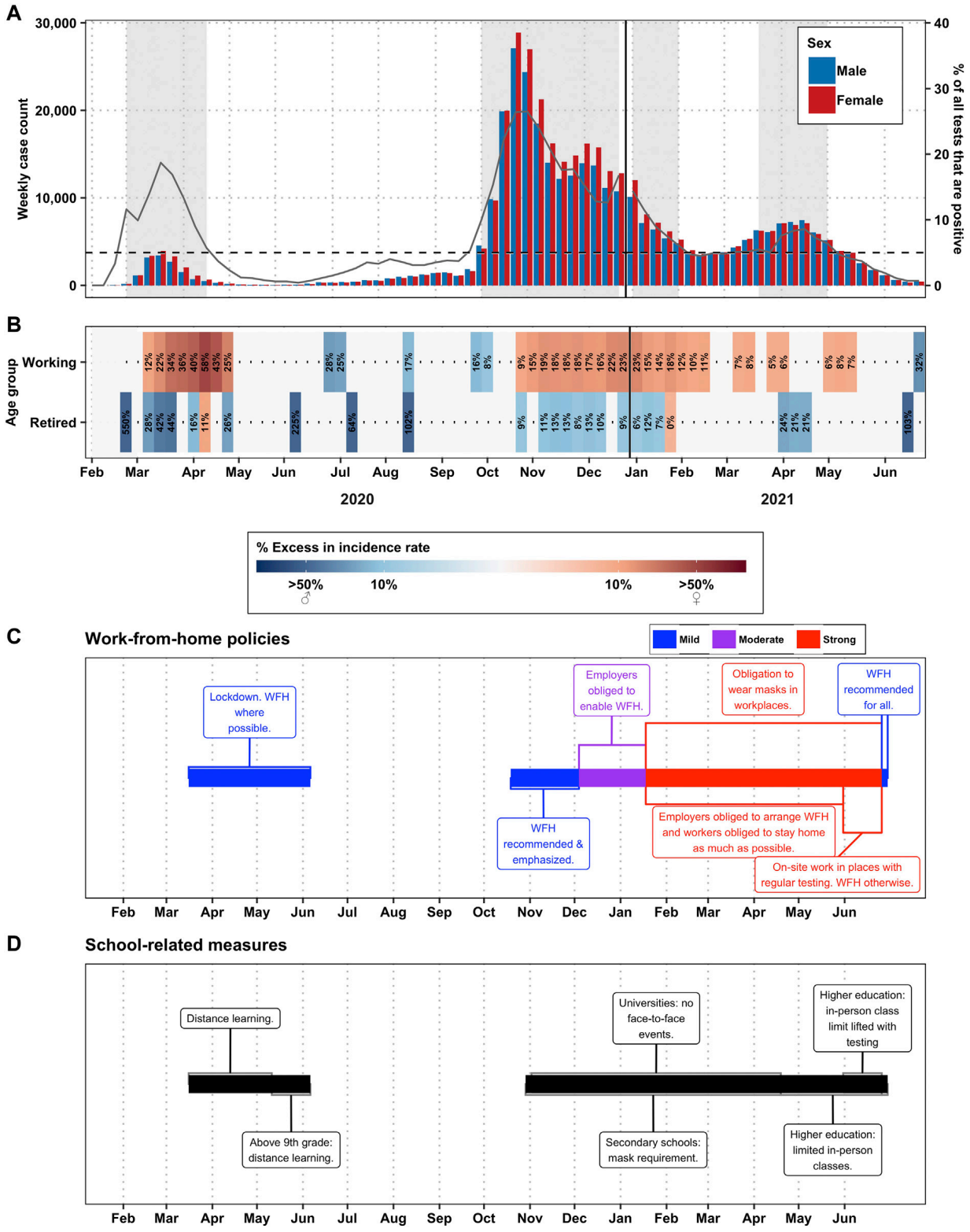

FIGURE 1 | Disparities by gender, in Switzerland (2020–2021)—**(A)** Total number of cases per sex per week. Weeks with backgrounds in grey are weeks where the positivity rate was >5%, the definition of a "wave" in this paper. The gray lines correspond to the % of tests that were positive for that week (right-axis). **(B)** Percent excess in incidence among men (in blue) or among women (in red) by week and by age group. The working age group constitutes ages 20–59 and the retired age group constitutes ages 60–79. People over age 80 were excluded. Weeks marked in white did not have statistically significant differences in the incidence rate ratio between the sexes. **(C)** Work from home policies, color-coded for stringency. **(D)** School policies.

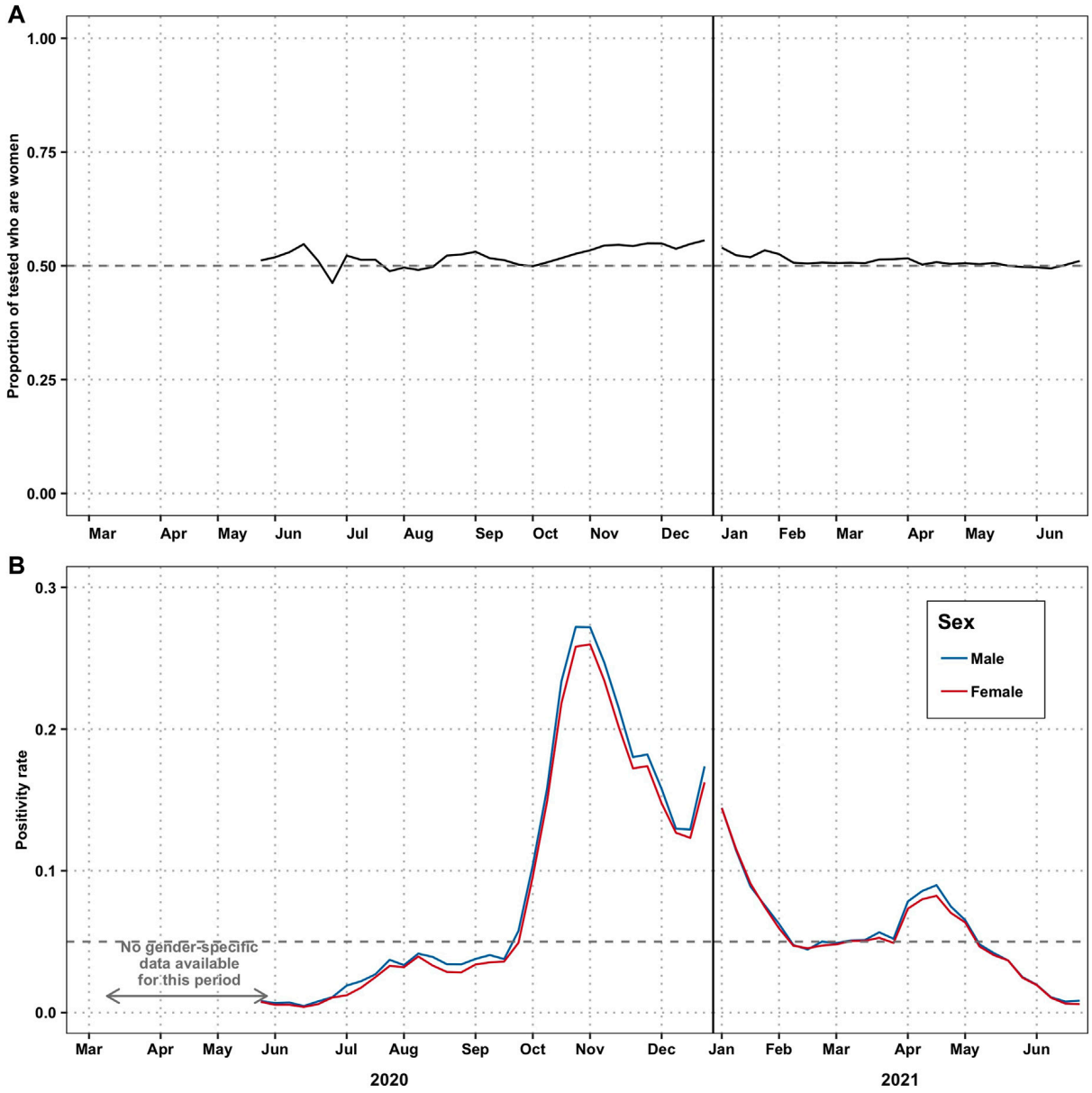

FIGURE 2 | Disparities in testing by gender—(Switzerland. 2020–2021). **(A)** Proportion of tests taken by women. The grey dashed line at 0.5 represents the line at which men and women are testing in equal numbers. **(B)** Proportion of tests among men and women that are positive for COVID-19. We could not perform this analysis from 24 February, when the first case was reported, until the week of 25 May when the positivity rate was first reported stratified by gender. The gray dashed line at 5% represents the WHO-recommended threshold for defining a wave.

10–30% in the second wave, yet only 1 week with a significant difference in the third wave. For older working age groups (30–39, 40–49 and 50–59 years old) the excess was milder than in the 20–29 years old age group. This pattern of changing disparity during the course of the pandemic was not observed for the population of retired age, where men were almost consistently overrepresented among the cases and the weeks with strong disparity were more sporadic and not associated with the waves (**Figure 1**; incidence rate ratios are shown in **Supplementary Figure S3**). In the more detailed age group analysis (**Supplementary Figure S2**), we note that among the retired age group (60–79 years of age), those above 80 years old, men show excess cases in the first wave of up to 80%, but in the second wave women show excess incidence of up to 28%.

In order to assess if our findings were due to testing bias, we analysed testing patterns by sex (**Figure 2**). The COVID-19 testing rate by sex was only available after the week of 25 May 2020, hence after the first wave. While women were being tested more often than men were, the positivity rate for both men and

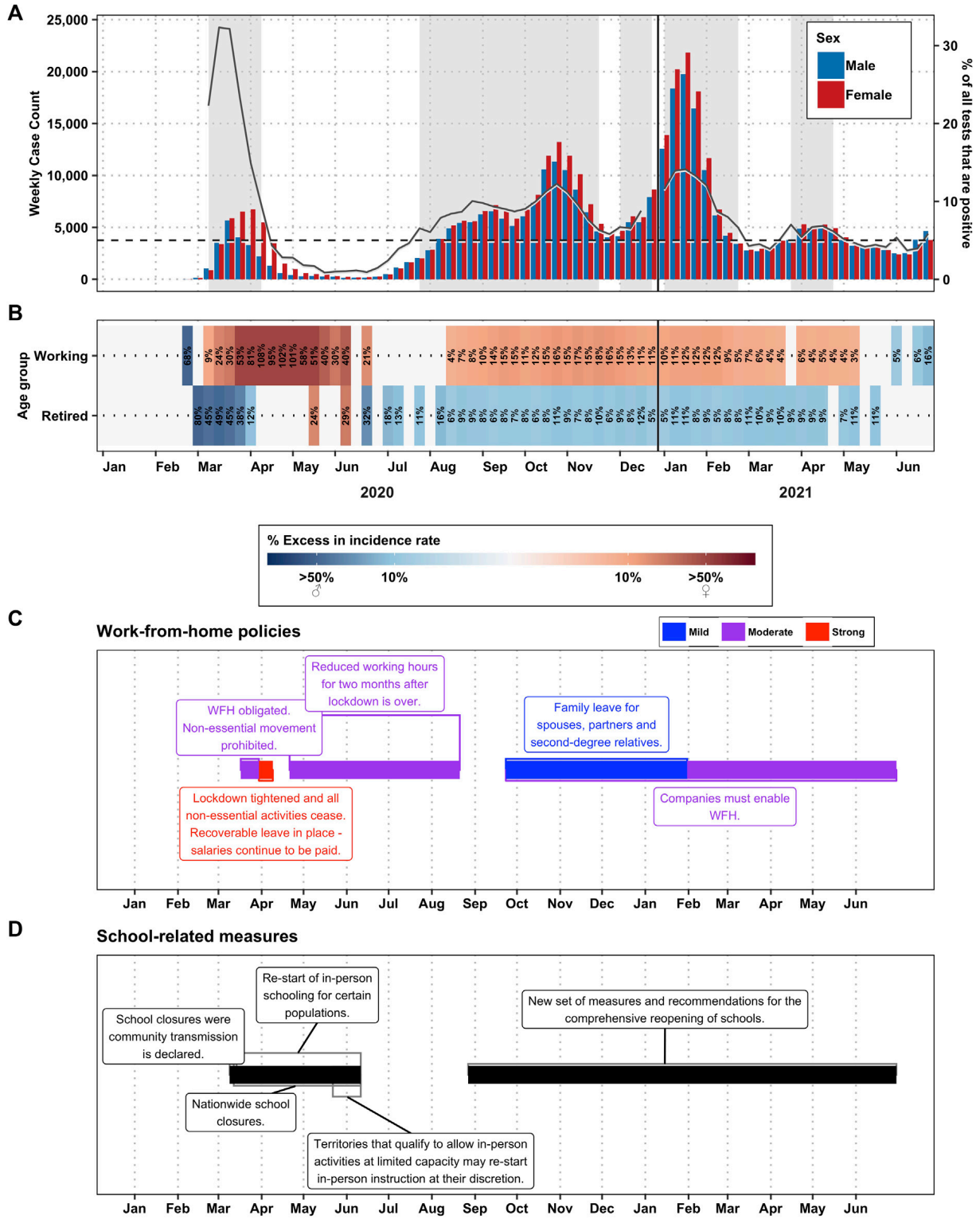

FIGURE 3 | Disparities by gender, in Spain (2020–2021)—**(A)** Total number of cases per sex per week. Weeks with backgrounds in grey are weeks where the positivity rate was >5%, the definition of a "wave" in this paper. The gray lines correspond to the % of tests that were positive for that week (right-axis). **(B)** Percent excess in incidence among men (in blue) or among women (in red) by week and by age group. The working age group constitutes ages 20–59 and the retired age group constitutes ages 60–79. People over age 80 were excluded. Weeks marked in white did not have any statistically significant differences in the incidence rate ratio between the sexes. **(C)** Work from home policies, color-coded for stringency. **(D)** School policies.

women was at a comparable level throughout our study period (**Figure 2**), and the women's positivity rate was higher than we would expect if the underlying incidence rate was equal to that of the men (**Supplementary Figure S4**).

Spain

COVID-19 Policies Over Time

In Spain, after the announcement of community transmission, several policy measures were put in place to contain the epidemic (**Figure 3**). Spain was one of the countries with the most stringent measurements during the first wave. Between March and April 2020 a full lockdown was implemented. Only workers in specific sectors (such as healthcare or retail sector) that were considered essential were allowed to leave their houses. From 9 March, face-to-face education was suspended until September 2020.

Starting on the week of 16 March, teleworking was generally recommended. Between the weeks of 30 March and 6 April, with a total lockdown, all non-essential activities ceased. At that time, health professionals were the most exposed to COVID-19 [32]. After this date, although home office was recommended, the law did not force companies to facilitate it, leaving this decision entirely up to the employer.

COVID-19 testing was implemented nationwide from 13 March (**Supplementary Figure S4**). However, until 7 May testing was only limited to severe cases of COVID-19 presenting at the emergency department or admitted to the hospital. Health professionals and workers in essential services were also classified as priority populations for testing. Patients with mild and moderate symptoms who were monitored at home or residents in nursing homes were not tested and thus not counted in official statistics of confirmed cases [33]. A study suggested that the lack of tests of non-hospitalized patients could lead to underreporting of cases in women [34]. After 4 May, PCR tests became available for all suspected cases.

Since 28 April 2020, the public health restrictions were slowly lifted and the responsibilities fully devolved to the autonomous communities in a co-governance system. Several waves have been reported since summer 2020: a second wave in October 2020, a third wave in January 2021, and a fourth wave after an intense vaccination campaign between January and June 2021.

Incidence by Sex Over Time

Our results show that the most significant gender disparity in relation to COVID-19 incidence was during the first wave in working age groups, reaching an excess of female cases of up to 108% (**Figure 3**; incidence rate ratios are shown in **Supplementary Figure S6**). In the detailed age group analysis, we note that the excess is even more pronounced in the 20–29 and 30–39 years-old age groups (**Supplementary Figure S5**). The excess of female incidence remained during the following peaks, albeit at a lower level, reaching a maximum excess of 18%. In contrast, in the retired age group (60–79 years of age) data shows an excess of male case incidence (reaching 87% of excess) before the week of 6 April 2020. However, this trend changes dramatically in the 80+ age group, where, between the weeks of 6 April through 15 June, the excess of female cases reached 102% (**Supplementary Figure S5**). After the first wave, there is no significant gender disparity among the retired age groups (less than 12% excess of male cases).

DISCUSSION

Gender differences in relation to COVID-19 incidence rates have been previously discussed, given the higher risk of mortality and hospitalisation in men [35]. However, less attention has been given to the sex-differential impact of public health response on COVID-19 case incidence rates. The COVID-19 burden goes beyond mortality and short-term illness [36]. Women have been shown to be four times as likely than men to suffer from at least one persisting symptom after a COVID-19 infection for an extended period [37].

Global data suggested a similar case burden in women and men during the first year of the pandemic [38]. Our study shows, however, that in Spain and in Switzerland, during the waves in 2020 and the first half of 2021, more women were diagnosed with COVID-19 than men. Testing data from Switzerland suggests that this phenomenon is not due to differential test-seeking behaviour between the genders, but rather different incidence (**Figure 2**), as the positivity rate was similar in both groups. Yet, higher infection rates in women are only present for the populations of working age (20–59 years old) and above 80 years old (**Supplementary Figure S2**). In a previous study, Sobotka et al. also found a higher rate of cases in women compared to men, for the working age group [11].

The difference in the stringency of the containment measures between the waves studied seemed to be associated with a different degree of disparity, which could be read similar to a "dose response" relationship. The more stringent the measures, the larger the gender disparity, which could explain the differences seen between Switzerland and Spain; in Switzerland, where the measures were less stringent, the gender disparity in cases was lower than in Spain.

The WHO's sex and gender in infectious diseases framework [39] describes the interaction of sex and gender with infectious diseases at three different levels: 1) vulnerability to the disease, 2) ability to prevent exposure and 3) decision-making power.

It has been hypothesised before that women are more exposed than men to COVID-19, be it in the domestic or professional setting [40]. Paradoxically, women also self-reported higher compliance with containment measures (namely social distancing and hygiene) [41]. Therefore, even though women aim to act responsibly, they are limited in their ability to prevent exposure. They are subject to more frequent or more precarious exposures than men, which would explain what we observed in Switzerland and in Spain. We discuss below the potential causal pathways between the implementation of COVID-19 prevention policies and the differential protective effect in men and women.

Women Were More Exposed to COVID-19 at Work

In Switzerland, when home office policies were established (recommended from 13 March–6 June, 2020, 19 October–4 December 2020, and starting on 26 June 2021; but moderately or strongly advised from 4 December 2020–26 June 2021) the excess of cases among women increased significantly. However, when we looked at the degree of stringency and the degree of excess cases among women, it suggests that it is the school closure during the first wave that is associated with the excess among women, whereas in the more severe second wave, schools remained open for younger children, and the excess among women was milder (**Figure 1**). A similar situation was observed in Spain, where an excess of cases was observed among the women of working age, and more marked among women of typically child-bearing age during the closure of schools and day care centres (**Figure 3**).

During the first wave the stringency of policies differed in Switzerland and Spain: while in Switzerland a "soft-lockdown" was applied, citizens in Spain were forced to stay at home. Face-to-face education at schools and universities were suspended in both countries. Exceptions to the norms of staying and working from home were issued in Switzerland as well as in Spain for workers in sectors considered "essential". Essential services included those ensuring supply of food and hygiene products, medicines, health care, transport or security [27, 42]. Workers in these sectors are predominantly women in both countries [22, 42, 43]. For context, in Switzerland 68% of the health workforce, 92% of childcare and 67% of retail positions are staffed by women [22]. Similarly, in Spain, more than 70% of the health professionals are women and they are also overrepresented in sectors like social work, retail, health and cleaning services [42]. Studies have shown that workers in some industries, such as meat factories, were predominantly male and at higher risk of contracting COVID-19 due to superspreading events [44]. However, in the case of Spain and Switzerland, these occupations account for a smaller volume of workers than the health, educational and care sectors, where women are overrepresented.

There is little to no evidence in both countries on case burden by sex and occupation. However, several studies have shown a higher case burden among the health workforce. Furthermore, Perez-Romero et al. found that most health and social care professionals in several high incidence areas in Spain were infected in their workplaces, while the general population were infected mostly at home [45]. One study in Switzerland found increased seroprevalence in hospitals treating COVID-19 patients compared to hospitals without COVID-19 patients, but overall only a small difference between healthcare workers and the general population was observed [46].

Care-Giving in Switzerland and Spain

Evidence suggests that women were not only more exposed at work, they were also more exposed to the virus at home compared to men. In Switzerland, women take on more of the unpaid care work than men (31.2% of women reported to take care of either children, adults or both compared to 11.6% of men) [47]. In both countries, if a family member gets ill, it has been shown that the closest care (with the highest infection risks) falls to the women of the household [48]. Additionally, most (known) transmissions in Switzerland happened within households [46].

The closure of schools and nursery homes implied that two out of three mothers had to stay at home in Spain, shouldering the highest burden of domestic and care work [21]. Moreover, the additional burden on women due to caregiving activities did not only increase their risk to contract the virus, but it also led to additional secondary effects, such as loss of jobs.

Over-Representation of Women in Nursing Homes

Finally, our results also show that women above 80 years old were at higher risk of contracting the disease than men in the same age group. The difference was, however, more prominent in Spain (**Supplementary Figures S2 vs. S6**), where the difference was maintained throughout the pandemic, reaching 102% of infections in April 2020. The Spanish MoH estimates that almost 20 thousand people died between January and June 2020 in nursing homes nationwide due to COVID-19, where most of the residents are women [21]. Several studies and media reports addressed the problem of nursing homes during the COVID-19 pandemic, as elderly people were abandoned by the State, leaving especially old women in a vulnerable situation [49].

Switzerland could have faced similar challenges, as there was an excess of COVID-19 cases in women above 80 years old during the second wave of the pandemic (November 2020–January 2021). According to the Swiss Federal Statistical Office, in 2020, 1.8% of the Swiss population lived in care homes (either short-term or long-term), and among those living in care homes 67% are women [50]. In a recently published report, an increase of 80% of deaths in care homes was reported during autumn of 2020 [51]. The press release does not differentiate, however, between deaths of men and women. Our study findings, which show an excess of cases in women over age 80 in the second wave (**Supplementary Figure S2**), highlight the importance of understanding if this increase of deaths was attributable to transmission within care homes.

We hypothesize that the reason for the overrepresentation of women in old-age nursing homes is partly an overall decline in the proportion of men with increasing age, but also that women of that age have often lost their partners, while men could potentially benefit from at-home care from their wives or partners [21, 52]. This circumstance could be attributed to the fact that men tend to have younger partners and a lower life expectancy.

The COVID-19 crisis has affected everyone, but in different ways. Social determinants and inequalities have been described as key factors behind the drivers of this pandemic. Social determinants have influenced the risk of contracting the disease, the outcomes of it, as well as the unintended effects of the containment measures [52]. Our findings for two exemplary countries, Spain and Switzerland, suggest that the differences in

the sex-ratio of cases are not only due to biological differences, but rather to social and gender norms and how policies affected population groups differently. These associations were seen despite both of our selected countries ranking high in the Global Gender Gap report; it is likely that our findings are transferable to many other countries.

Limitations

Our results are probably showing an underrepresentation of disparities, given changing testing policies. Until May 2020, the testing strategy only covered inpatients and severe cases, which were borne in a slightly higher proportion by elderly men. Furthermore, data on testing disaggregated by both age and sex were not available for either country.

Conclusion

Our study shows that while the mortality of COVID-19 is disadvantageous to men, the incidence of COVID-19 disproportionately burdens women, in particular women of child-bearing and working age (20–59 years old). This has long-term implications due to fourfold higher odds of developing "long COVID" borne by women.

Evidence is emerging about the protective benefits and effectiveness of certain policies and non-pharmaceutical interventions to reduce COVID-19 incidence. These studies are, however, often looking at overall numbers and may overlook how policies may reduce the risk differently among population groups, including those defined by gender. When different effects are observed this is often attributed to the levels of compliance, rather than structural exposures or risks that are unaddressed by the policies. We argue that there is a need to search for drivers beyond compliance and understand how policies enable certain groups to shield from the pandemic more than others.

Policy and decision-makers have embedded gender in their discourse, but this has often been limited to rhetoric or implementing policies to alleviate socioeconomic effects of the pandemic. Our study highlights that a gender perspective is also crucial to implement incidence-prevention measures, like non-pharmaceutical interventions.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study. CS and MA designed the data collection, FBF and LM conducted the data collection. MA led the analysis. CS wrote the first outline of the manuscript and all authors contributed to sections of it. All authors reviewed and approved the last version of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.ssph-journal.org/articles/10.3389/ijph.2022.1604994/full#supplementary-material

Supplementary Figure S1 | Testing policies in Switzerland. Dates are listed along the x-axis, and vertical lines indicate the date when the policy was implemented. RDT tests were available in Switzerland since 18 December 2020, but only for screening purposes. Confirmation of a case was only possible through PCR (Switzerland. 2020-2021).

Supplementary Figure S2 | Disparities by gender, detailed (Switzerland. 2020-2021). **(A)** Total number of cases per sex per week. Weeks with backgrounds in gray are weeks where the positivity rate was >5%, the definition of a "wave" in this paper. **(B)** Percent excess in incidence among men (in blue) or among women (in red) by week and by detailed age group. Weeks marked in white did not have any statistically significant differences in the incidence rate ratio between the sexes.

Supplementary Figure S3 | Incidence rate ratio for COVID-19 cases among women compared to men by week from February 2020–June 2021 and stratified for working age groups and retired age groups (Switzerland. 2020-2021). The solid lines represent the weeks for which the IRR is statistically significant ($p < 0.05$) and the shaded lines represent the weeks for which the IRR is not statistically significant.

Supplementary Figure S4 | Sensitivity analysis of testing positivity rate in Switzerland if men and women had the same incidence rate but different testing rates. The gray ribbon shows the expected positivity rate for women when men's incidence rates were applied (Switzerland 2020–2021).

Supplementary Figure S5 | Testing policies in Spain. Dates are listed along the x-axis, and grey vertical lines indicate the date when the policy was implemented. RDT tests were available in Spain since 7 December 2020, but only for screening purposes. Confirmation of a case was only possible through PCR. (Spain. 2020–2021).

Supplementary Figure S6 | Disparities by gender, detailed (Spain. 2020–2021). **(A)** Total number of cases per sex per week. Weeks with backgrounds in gray are weeks where the positivity rate was >5%, the definition of a "wave" in this paper. **(B)** Percent excess in incidence among men (in blue) or among women (in red) by week and by detailed age group. Weeks marked in white did not have any statistically significant differences in the incidence rate ratio between the sexes.

Supplementary Figure S7 | Incidence rate ratio for COVID-19 cases among women compared to men by week from February 2020–June 2021 and stratified for working age groups and retired age groups (Spain. 2020–2021). The solid lines represent the weeks for which the IRR is statistically significant ($p < 0.05$) and the shaded lines represent the weeks for which the IRR is not statistically significant.

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Appendix D

Supplementary materials from Chapter 6

Legionnaires' Disease on the Rise in Switzerland: A Denominator-Based Analysis of National Diagnostic Data, 2007–2016

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Legionnaires' disease on the rise in Switzerland: A denominator-based analysis of national diagnostic data, 2007-2016

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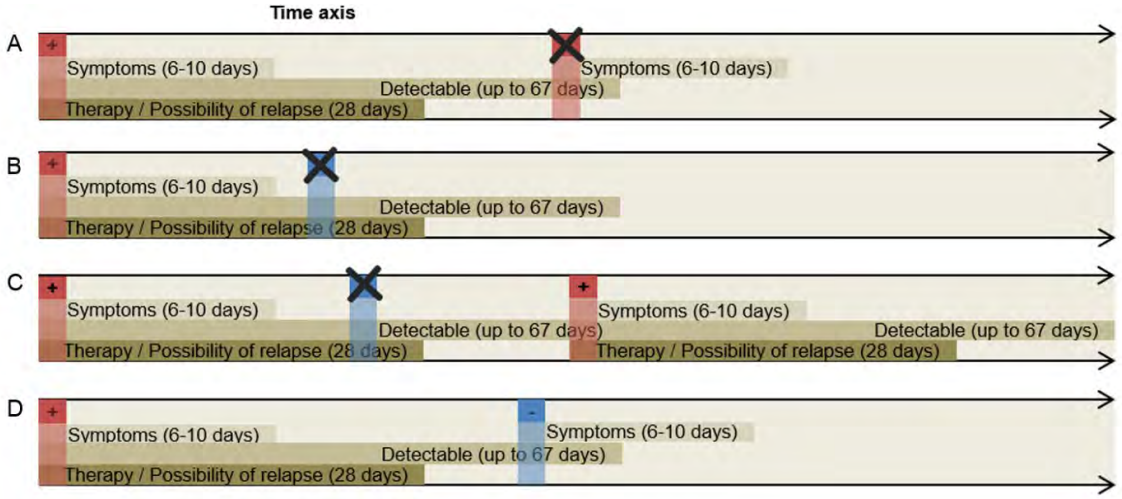
SUPPLEMENTARY MATERIAL: REPEATED TESTS

To calculate the positivity, i.e. the proportion of all positive tests among all tests performed, as a proxy for the incidence rate across the years, it is essential to limit the number of tests to one for each patient and disease episode. Otherwise, if one *Legionella*-infected patient is tested multiple times, the numerator will be inflated and skews the proportion.

Patients were identified by their identification number (given by the laboratory), sex and birthdate. The disease episode was defined as one single disease event from infection to curation/death. If a patient was re-infected at any later time point, this was counted as a second disease episode. However, as the dataset investigated is limited to laboratory data and lacks clinical information, the definition of a disease episode within our dataset was rather complex.

After reviewing the literature and consultation with an expert, we made several assumptions on timeframes: i) The duration of symptoms or hospitalisation is 6-10 days [39, 40]; ii) The duration of therapy and the possibility for a relapse is 28 days [41-43]; iii) The bacteria is detectable in any given test up to 67 days [31,44-49]. Those timeframes were then anchored to the only available information we have: diagnostic tests (positive and negative) using another set of assumptions: i) Each test indicates that the patient must have symptoms, otherwise no test would be ordered; ii) Each positive test indicates that (parts of) *Legionella* were found, hence, there is a possibility for a future relapse and the detection period of the test has to be considered.

Based on these assumptions, we constructed several scenarios, on which we based the exclusion of repeated tests, some examples are shown in Figure 1. In scenario A, the second (positive test) will be excluded, as the positive test could also result from continued detection of the pathogen causing the initial infection. In scenario B, the second (negative) test is excluded, as it is within the treatment period and assumed to be control of treatment. In scenario C, the second (negative) test is excluded for the same reason as in B (control of treatment); the third (positive) test is assumed to be a new disease episode, due to the previous negative test. In scenario D, it is assumed that the indication for testing (i.e. symptoms) are independent for both tests, hence represent two disease episodes. Therefore, both tests remain in the data set.



Supplementary Figure 1 Different example scenarios based on the definition of disease episode to exclude repeated tests for *Legionella* spp. in Switzerland, 2007-2016.

To avoid random exclusion of tests using different diagnostic methods for the same patients on the same day, we ordered the test methods by the total number of tests performed (i.e. urinary antigen test [UAT], culture, PCR).

The results from the exclusion based on these scenarios have been selectively and manually tested for plausibility. A sensitivity analysis has been performed alternating the timeframes, as well as the order of exclusion by test method to check the robustness of the results. The number of excluded positive and negative tests proofed to be stable.

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Legionnaires' disease on the rise in Switzerland: A denominator-based analysis of national diagnostic data, 2007-2016

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SUPPLEMENTARY MATERIAL: SEROLOGY

The initially cleaned dataset contained 2558 (1.8%) serological tests (108 positives). The frequency of serological tests performed decreased during the study period with 329 tests in 2007 and 162 in 2016. Using a serological test, 40 patients have been tested twice, three patients three times and one patient four times. In 10 cases the second serological test was done three to six weeks after the initial antibody test.

The Serological tests performed were either the RIDA®FLUOR Legionella IgG (r-biopharm, 84.8%), in-house methods (4.7%), IFA (Meridian Bioscience Inc., 4.6%), Legionella IFA (Focus Diagnostics, 2.7%), or unknown (3.21%).

Although serological test have their value for epidemiological studies, they are not suitable for clinical settings and acute diagnostics, due to their long turnover for a positive result [25,47]. Moreover a single high titer is only classified as a probable case by the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) (and accordingly the Swiss Federal Office of Public Health [FOPH]), and single acute phase antibody titers of 1:≥256 cannot distinguish between cases and non-cases [50]. Only a fourfold increase in titer between two tests with 3 to 12 weeks in-between is considered as a confirmed case by the FOPH. However, our data shows that only 45 patients (1.8% of all serological tests) have been tested twice and of those only 10 in the appropriate time period. Hence, a conclusive decision whether a test result was negative (0) or positive (1) could not be made, which would have hampered most of our analyses.

Lastly, since 2018, the titer does not need to be provided on the notification report. Thus, results from serological tests are difficult to interpret and serology is not promoted anymore amongst laboratories for diagnosis of acute LD cases. Therefore, we have decided to exclude these tests from the analysis.

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Legionnaires' disease on the rise in Switzerland: A denominator-based analysis of national diagnostic data, 2007-2016

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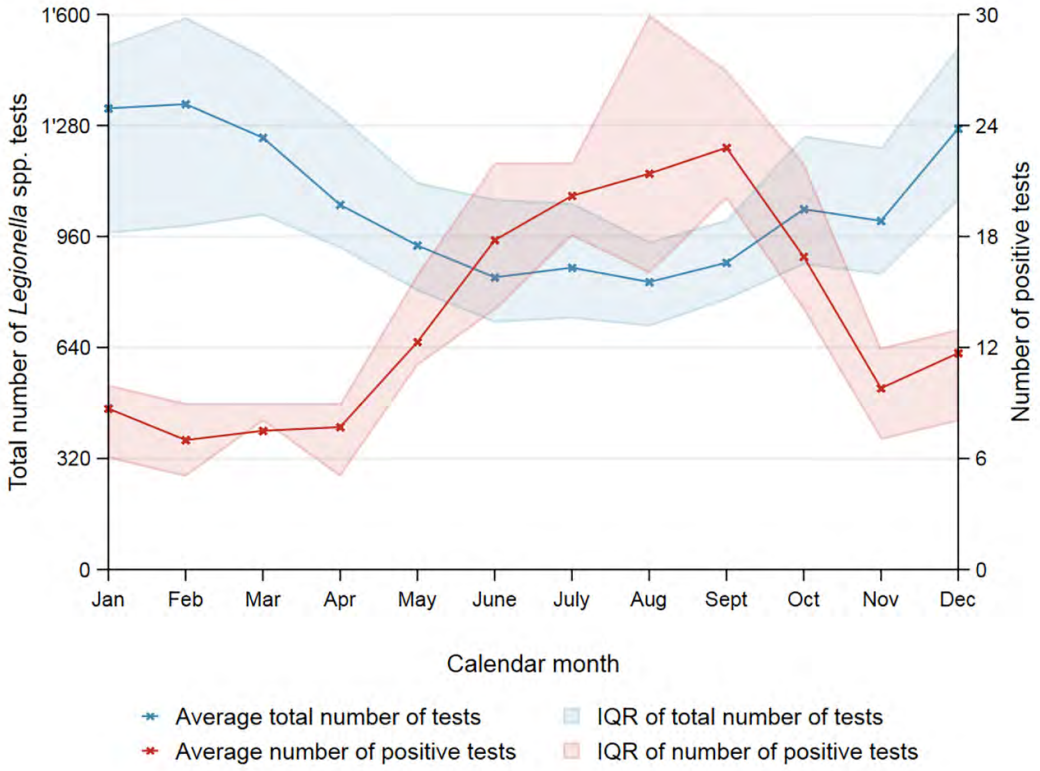
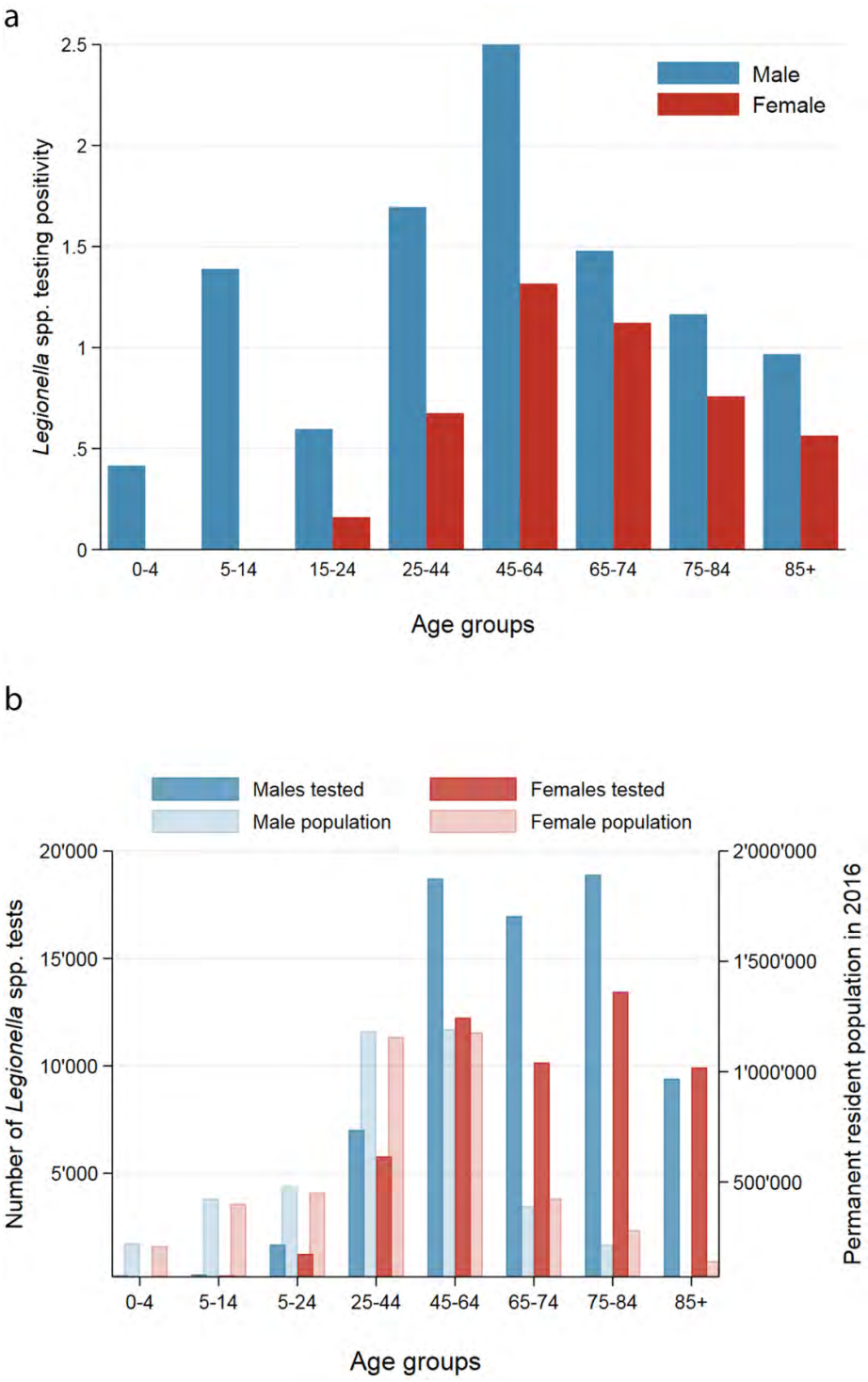
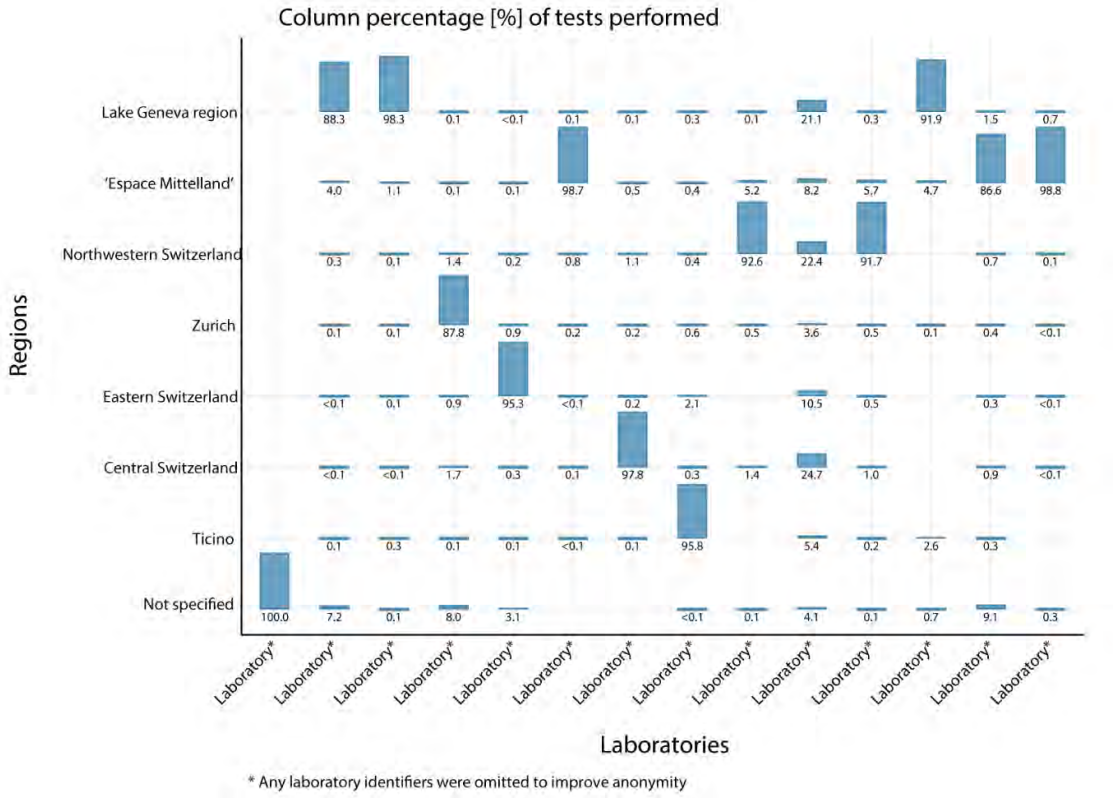
SUPPLEMENTARY MATERIAL: ADDITIONAL FIGURES



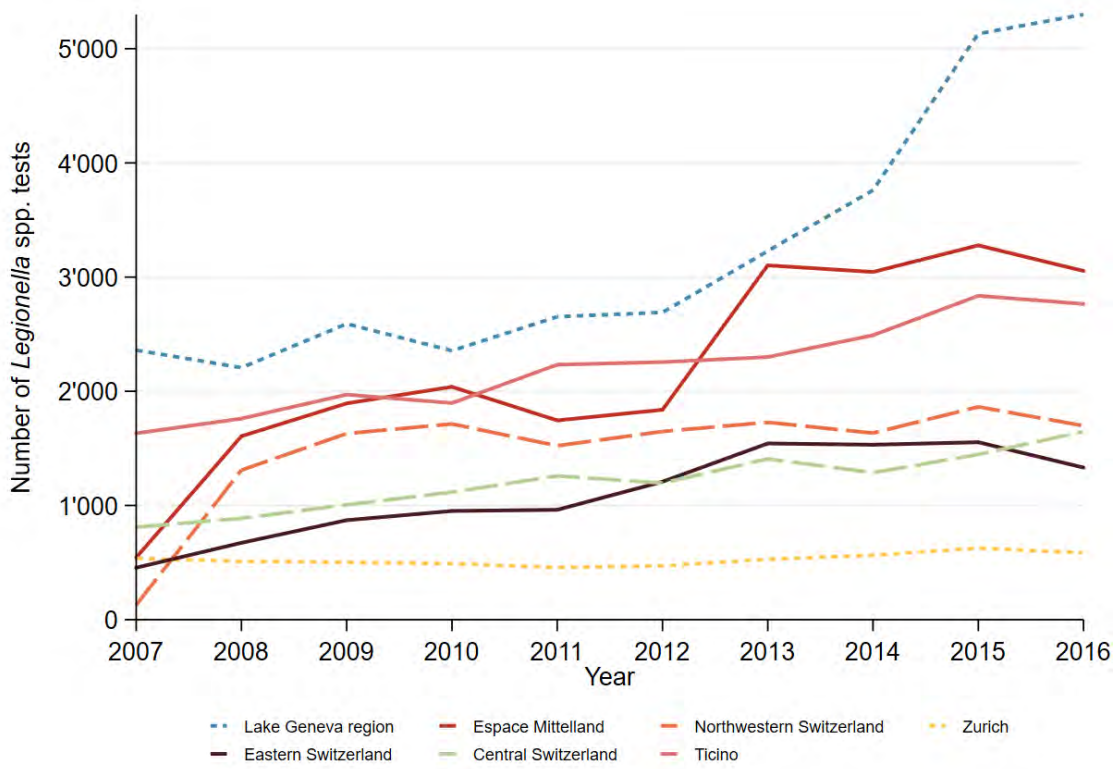
Supplementary Figure 2 Seasonality in test volume and cases. The average and interquartile range (IQR) per calendar month of the total number of *Legionella* spp. tests and number of positive tests, Switzerland, 2007-2016. The seasonality has been incorporated into the mixed effect logistic regression using sine and cosine functions, in the form of sin((d*2*π)/T) and cos((d*2*π)/T), where d is the time period (e.g. January, February) and T is the number of time periods (e.g. 12 months), as described by Stolwijk, A. M., et al. (1999).



Supplementary Figure 3 Age distribution in test volume and positivity (a) Positivity of *Legionella* spp. testing by sex and age groups, Switzerland, 2007-2016. (b) Number of *Legionella* spp. tests performed by sex and age groups in Switzerland (2007-2016) and permanent resident population in Switzerland (2016) by sex and age groups.



Supplementary Figure 4 Correlation between the variables "greater region" and "laboratory" included in the *Legionella* spp. positivity study, Switzerland, 2007-2016.



Supplementary Figure 5 Trends of the total number of tests performed per greater region by 14 diagnostic laboratories included in the *Legionella* spp. positivity study, Switzerland, 2007-2016

Appendix E

Supplementary materials from Chapter 7

Do changes in STEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity, 2007 to 2016

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SUPPLEMENTARY MATERIAL

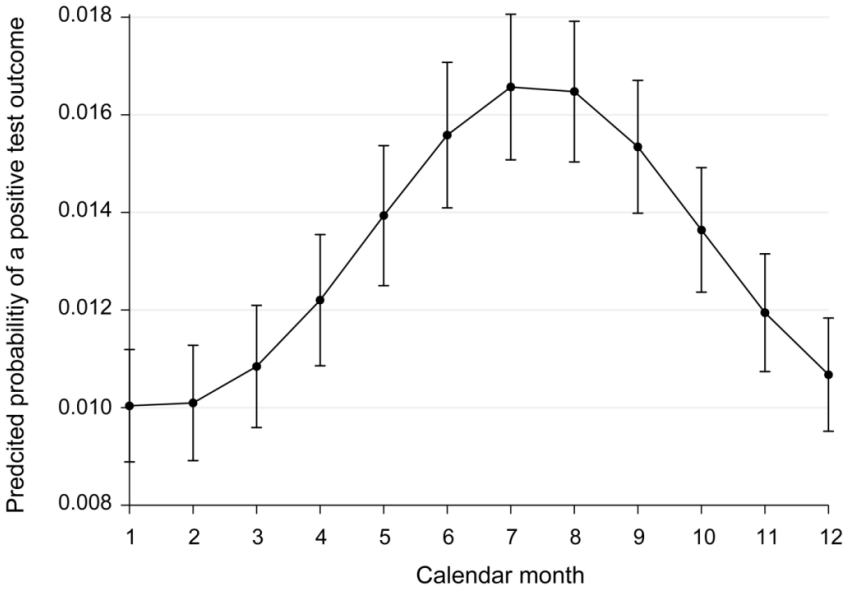
This supplementary material is hosted by *Eurosurveillance* as supporting information alongside the article “Do changes in STEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity from 2007 to 2016.” on behalf of the authors who remain responsible for the accuracy and appropriateness of the content. The same standards for ethics, copyright, attributions and permissions as for the article apply. Supplements are not edited by *Eurosurveillance* and the journal is not responsible for the maintenance of any links or email addresses provided therein.

Supplement S1. Seasonality of STEC testing and as a determinant for a positive test outcome

The positivity of STEC testing shows a strong seasonality. The seasonality of the total number of tests and the number of positives was calculated as the average number of tests (positives) of all test years (2007-2016) per calendar month. The number of total tests performed increased by 68% from February with 553 tests until September with 928 tests. The number of positively tested cases follows a similar seasonal pattern with 6 cases detected in February and 16 in August. Positivity peaked in July with 1.9%.

The seasonality has been incorporated into the mixed effect logistic regression using a sine and cosine functions, in the form of $\sin(d * 2 * \pi/T)$ and $\cos(d * 2 * \pi/T)$, whereas d is the time period (e.g. January, February) and T is one year, as described by Stolwijk, A. M., et al. [1]. The predicted probabilities for a positive test outcome of the univariable logistic regression are shown in Figure 1.

Supplementary Figure S1. Predicted probabilities with 95% confidence intervals per calendar month for a positive test outcome of an STEC infection for the univariable model using sine and cosine functions, 2007-2016, Switzerland



Reference

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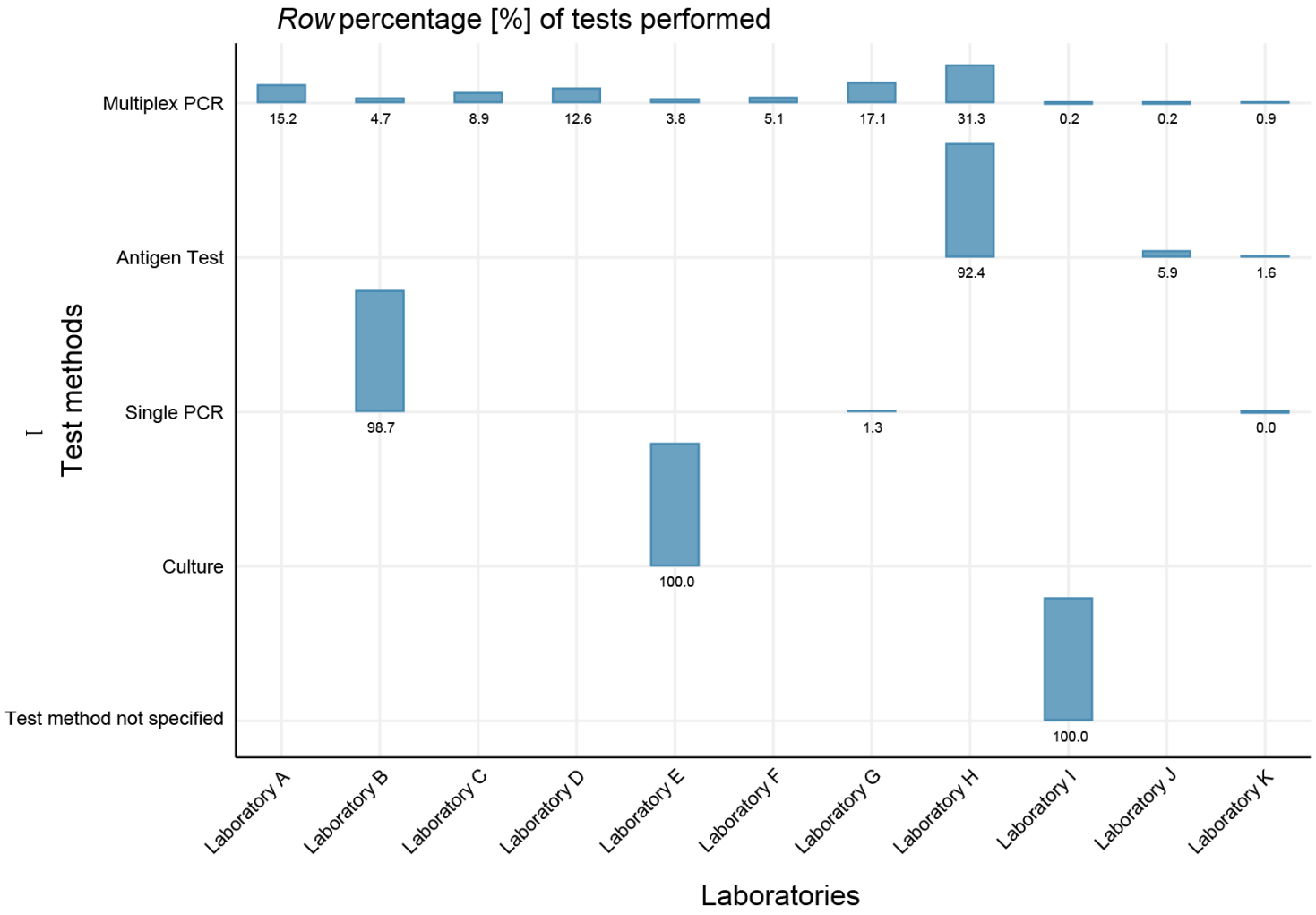
Supplementary Table S1. Age and sex of the population tested for STEC and of cases with a positive result over the entire study period, 2007-2016, Switzerland

	2007-2016	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	P-value test for trend
Tested												
Median age [years; (n)]	40 (86'043)	30 (3'711)	29 (3'978)	31 (3'421)	29 (2'536)	31 (3'393)	37 (4'483)	42 (6'152)	43 (10'246)	44 (21'484)	43 (26'639)	<0.01
Male	38 (38'209)	28 (1'705)	29 (1'872)	29 (1'618)	26 (1'177)	28 (1'598)	33 (2'027)	39 (2'668)	41 (4'489)	42 (9'373)	41 (11'682)	<0.01
Female	42 (47'834)	31 (2'006)	30 (2'106)	32 (1'803)	31 (1'359)	33 (1'795)	40 (2'456)	45 (3'484)	45 (5'757)	46 (12'111)	46 (14'957)	<0.01
Proportion of females [%]	55.6	54.1	52.9	52.7	53.6	52.9	54.8	56.6	56.2	56.4	56.2	<0.01
STEC-positive												
Median age [years; (n)]	36 (1'149)	23 (33)	33 (31)	25 (31)	23 (15)	16.5 (38)	37 (47)	30 (84)	40.5 (126)	38 (304)	41 (440)	<0.01
Male	35 (518)	2 (11)	41 (13)	25 (17)	12.5 (6)	4 (19)	34.5 (18)	27 (46)	40.5 (56)	38 (134)	37 (198)	<0.01
Female	38 (631)	25 (22)	27.5 (18)	25.5 (14)	27 (9)	34 (19)	37 (29)	30 (38)	41.5 (70)	38 (170)	43 (242)	<0.01
Proportion of females [%]	54.9	66.7	58.1	45.2	60.0	50.0	61.7	45.2	55.6	55.9	55.0	0.75

Supplementary Figure S2. Row percentages of the number of STEC tests performed by test method and laboratory, 2007-2016, Switzerland.[1]



[1] The information on the correlation of greater region and laboratory is purposively omitted to ensure the anonymity of the selected laboratories.

Supplementary Table S2. Overview of diagnostic methods performed for STEC as provided by participating laboratories, 2007-2016, Switzerland. PCR panels targeting STEC/pathogenic E. coli only are referred to as 'single PCR' in contrast to 'multiplex PCR'.

Method	**[%]**	**Details**	**[N]**	**[%]**
Multiplex PCR	66.45	BD MAX™ (Extended) Enteric Bacterial Panel	29'514	34.30
		BioFire FilmArray™ *Gastrointestinal Panel*	3'368	3.91
		Luminex xTAG® Gastrointestinal Pathogen Panel	20'610	23.95
		Seegene (not specified whether Allplex™ Gastrointestinal Panel or Seeplex®Diarrhea ACE Detection) and in house method	2'629	3.06
		Multiplex PCR, not further specified	1'047	1.22
Antigen Test	26.26	Premier® STEC	1'341	1.56
		NOVITEC® Verotoxin ELISA	20'882	24.27
		Antigen test not specified	365	0.42
Single PCR	7.26	PCR after MacConkey culture	6'165	7.17
		PCR performed by external laboratory	2	<0.01
		PCR, not further specified	80	0.09
Culture			24	0.03
Samples sent to NENT			16	0.02
				100.00

Legend: NENT, Nationales Zentrum für enteropathogene Bakterien und Listerien (National Reference Centre for Enteropathogenic Bacteria and Listeria)

Appendix F

Supplementary materials from Chapter 8

Literature review on global recommendations, guidelines and legislation for Legionnaires' disease and *Legionella* management

F-1: Search / Literature profile for LD

1.1 Prevention and control of legionellosis and LD

1.1.1 Embase, WoS, PubMed

Embase, WoS and PubMed returned 1'522 hits. 1'304 of those were unique entries, 210 duplicates, and 9 publications with multiplicities.

The initial round of manual screening resulted in 424 deleted articles and 241 articles marked as "relevant" and 176 as "very relevant". The second round of manual screening resulted in 115 additional deleted entries and 14 duplicates (which were identified after the titles of the publications have been cleaned). After reassigning the publications to the most fitting topic (e.g., a publication retrieved in the search for "outbreaks", but content fits the topic "prevention and control regulation" better), 332 publications were assigned to the topic of "prevention and control".

1.1.2 Google Scholar

In total, the Google Scholar search generated 3'991 hits, of those 1'549 were duplicates. All databases were merged, allowing additional entries to be removed as duplicates – after stratification Google Scholar identified 996 publications. After manual screening, 274 entries remained. After reassigning the publications to the most fitting topic, 397 publications were assigned to the topic of "prevention and control".

1.1.3 Final database / literature profile

The Embase/PubMed/WoS and Google Scholar databases were merged at this point. The final screening step was essential and helped to identify relevant publications, missing information (region and year), to assign keywords to the relevant publications and to identify guidelines.

The results of this step are shown in Table 8. In total 163 relevant and available articles were identified. Twelve publications were in languages other than English. Seventy-five publications were not available; either because the full-text could not be found or was behind a pay-wall.

Table 1 Cleaning steps of the merged databases (Embase/PubMed/WoS), Google Scholar, and final database stratified by topic: diagnosis, surveillance, prevention and control and outbreaks for legionellosis and Legionnaires' disease

Steps	Control	Diagnosis	Surveillance	Outbreak
Embase, PubMed, WoS	332	308	119	79
Google	397	311	272	149
Merged database	**729**	**619**	**391**	**228**
Published before 1999	32	50	11	9
Manual removal of duplicates	51	30	57	22
Manual removal of irrelevant publications	427	247	168	70
Publication not available	57	71	23	12
Remained	**162**	**221**	**132**	**115**

The number of publications identified per year ranged from one to 15, with a slight increase between 1999 and 2018 (Figure 1). For 77.8% of all articles the associated country or region

could be identified. The majority of articles were from the US, followed by Germany, the UK, Italy and Spain (Figure 3).The 158 publications with no region specified, discussed the global situation or were generic statements and findings.

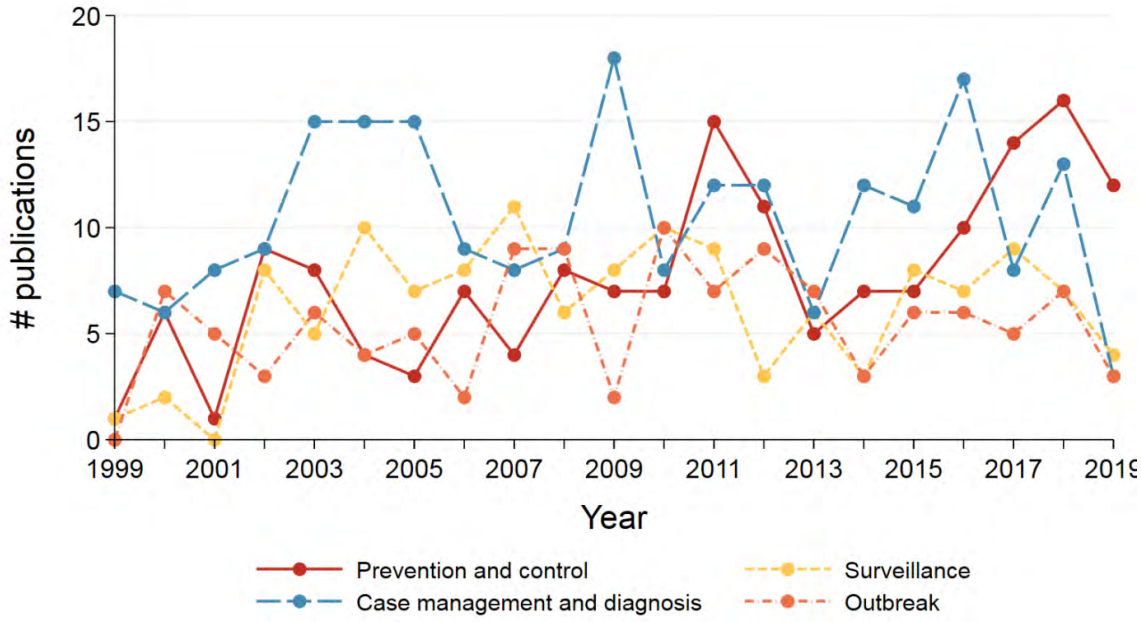


Figure 1 Number of publications found for each topic (diagnosis, surveillance, prevention and control and outbreaks) for legionellosis or Legionnaires' disease by year of publication, 1999-2019

The assigned keywords showed that most publications identified are published guidelines and not reviews or references to guidelines (Figure 2). There is also a breadth of publication on prevention and control of LD in hospitals and care facilities.

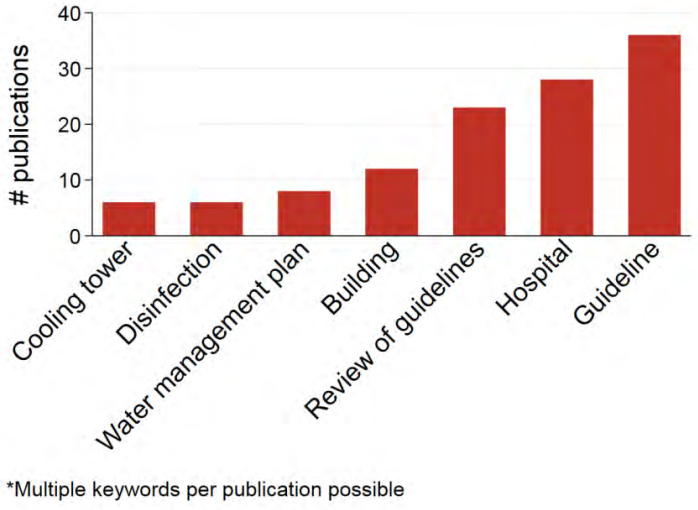


Figure 2 Selected publication on the topic of "prevention and control" of legionellosis and Legionnaires' disease, 1999-2019, by keyword as assigned by the study team

After checking each publication, we had listed 209 recommendation, guidelines and legal regulations, which were referenced in these publications.

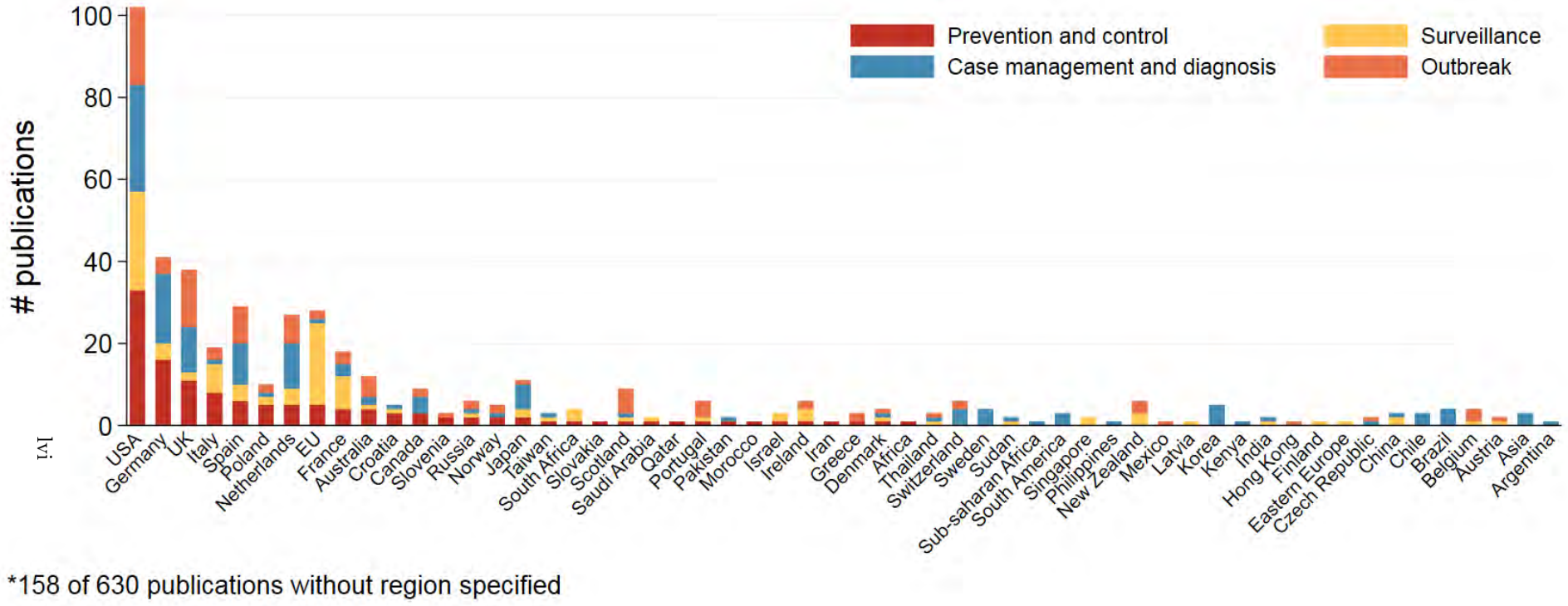


Figure 3 Number of publications found for each topic (diagnosis, surveillance, prevention and control and outbreaks) for legionellosis or Legionnaires' disease by country or region, 1999-2019

1.2 Diagnosis of Legionnaires' disease

1.2.1 Embase, WoS, PubMed

Embase, WoS and PubMed returned 836 hits, of which 727 were unique entries. The initial round of manual screening resulted in 61 articles deleted and 315 articles marked as "relevant" and 77 as "very relevant". The second round of manual screening resulted in 171 additional deleted entries and 13 duplicates (which were identified after the titles of the publications were cleaned), resulting in 208 remaining articles. After reassigning the publications to the most fitting topic, 308 publications were assigned to the topic of "diagnosis and case management".

1.2.2 Google Scholar

In total, the Google Scholar generated 3'215 hits, of those 241 were duplicates. Afterwards, all databases were merged, allowing additional 1'666 entries to be removed as duplicates – after stratification it showed that Google Scholar identified 1'308 unique publications. After manual screening, 308 entries remained. Some publications were reassigned to this topic from other searches; hence, finally 311 publications were identified by Google Scholar for "diagnosis and case management".

1.2.3 Final database

The merged database contained 619 entries, and after manual screening 222 available and relevant entries remained (Table 8).

The number of publications published between 1999 and mid-2019 fluctuated around ten per year (Figure 1). Of 37% of these articles, the respective country or region could not be identified. Most articles related to the US, Germany, the UK and The Netherlands (Figure 3). Twelve publications were in languages other than English.

The majority of the publications were assigned to the keyword "community-associated pneumonia", followed by LD specific publications (Figure 4). Around 50 publications were guidelines and some 40 reviewed published guidelines. In the 222 identified entries could identify 101 guidelines. Each of those 101 guidelines were checked individually. Only the newest update of the same guideline was retained.

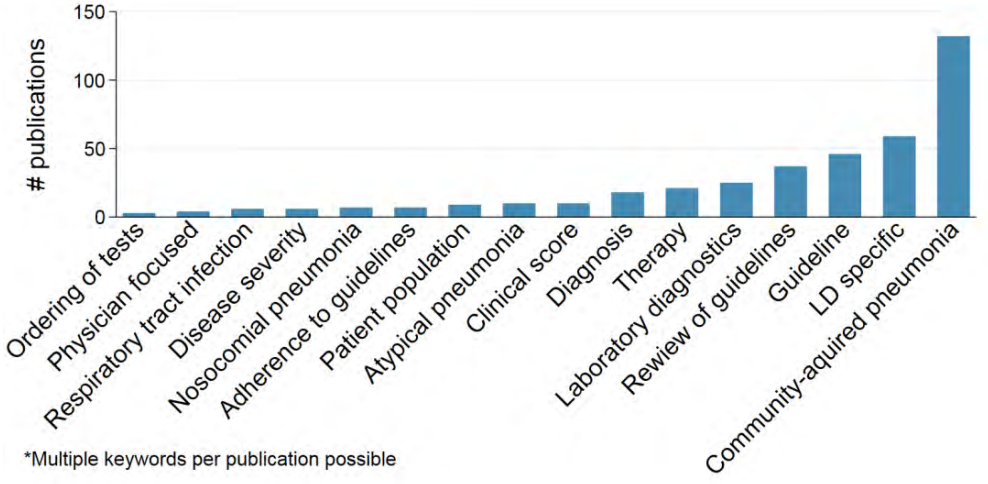


Figure 4 Selected publication on the topic of "diagnosis"of legionellosis and Legionnaires' disease, 1999-2019, by keyword as assigned by the study team

1.3 Surveillance of legionellosis and LD

1.3.1 Embase, WoS, PubMed

Embase, WoS and PubMed returned 984 hits and 845 of unique entries.

The initial round of manual screening resulted in 213 deleted articles and 160 articles marked as “relevant” and 97 as “very relevant”. The second round of manual screening generated 92 additional entries that were deleted and 4 duplicates (which were identified after the titles of the publications were cleaned). This process resulted in 257 articles. After reassigning the publications to the most fitting topic, 119 publications were assigned to the topic of “Surveillance”.

1.3.2 Google Scholar

In total, Google Scholar generated 3’993 hits, of those 1’707 were duplicates. Additional entries were removed as duplicates after the databases of all topics were merged – after stratification Google Scholar identified 1’231 unique publications. After manual screening, 246 entries remained. After reassigning the publications to the most fitting topic, 272 publications were assigned to the topic of “surveillance”.

1.3.3 Final database

The merged database contained 391 entries, and after manual screening 132 available and relevant entries remained (Table 8).

The number of publications selected has been highest in the period 2000-2010 and slightly lower in the decade afterwards (Figure 1).The majority of the publications are relevant to the USA and the EU (Figure 3). Further, France has been actively working on their surveillance for LD, which is reflected in the number of publications.

Most publications were reports relating to disease surveillance, such as “State of infectious diseases in The Netherlands, 2016” or “Cases of Legionnaires' disease in France in 2008” [119, 120]. Such articles were simply assigned to the keyword “disease surveillance” (Figure 5). Other publications were reviews of surveillance systems performance. A larger body of publications also looked at TALD, either as a review or case study.

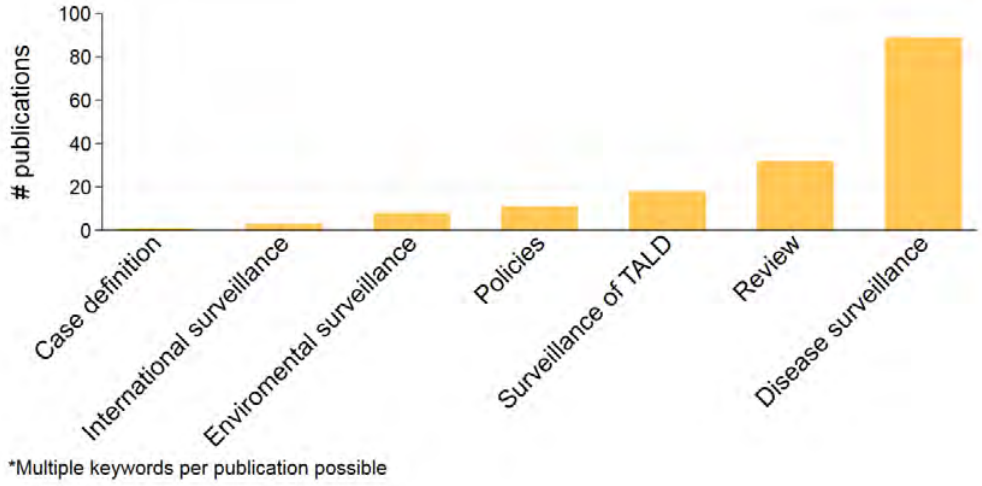


Figure 5 Selected publication on the topic of “surveillance” of legionellosis and Legionnaires’ disease, 1999-2019, by keyword as assigned by the study team; TALD: Travel-associated Legionnaires’ disease

1.4 Outbreaks of legionellosis and LD

1.4.1 Embase, WoS, PubMed

Embase, WoS and PubMed returned 1174 hits. One-thousand-twenty-one (1'021) of those were unique entries and 153 duplicates.

The initial round of manual screening resulted in 145 deleted articles and 360 articles marked as "relevant" and 103 as "very relevant". The second round of manual screening resulted in 257 additional deleted entries and duplicates (which were identified after the titles of the publications were cleaned). After reassigning the publications to the most fitting topic, 79 publications were assigned to the topic of "Outbreak".

1.4.2 Google Scholar

In total, the Google Scholar found 3'699 hits, of those 1'139 were duplicates. All databases were merged, allowing additional entries to be removed as duplicates (among the different topics) – after stratification, Google Scholar identified 961 unique publications. After manual screening, 246 entries remained. After reassigning the publications to the most fitting topic, 149 publications were assigned to the topic of "Outbreak".

1.4.3 Final database

The merged database contained 228 entries, and after manual screening 115 available and relevant entries remained (Table 8). The number of publications fluctuated between zero to ten publications per year (Figure 1). Again, the majority of the articles are of relevance to the US and the UK; however, due the higher number of outbreaks in Spain, almost 10 publications were related to Spain (Figure 3). The Netherlands has issued an outbreak control programme, which is also reflected in its publications numbers.

Most of the selected publications were review of regulations regarding guidelines (Figure 6). We also highlighted apublications with a section marked as "lessons learned".

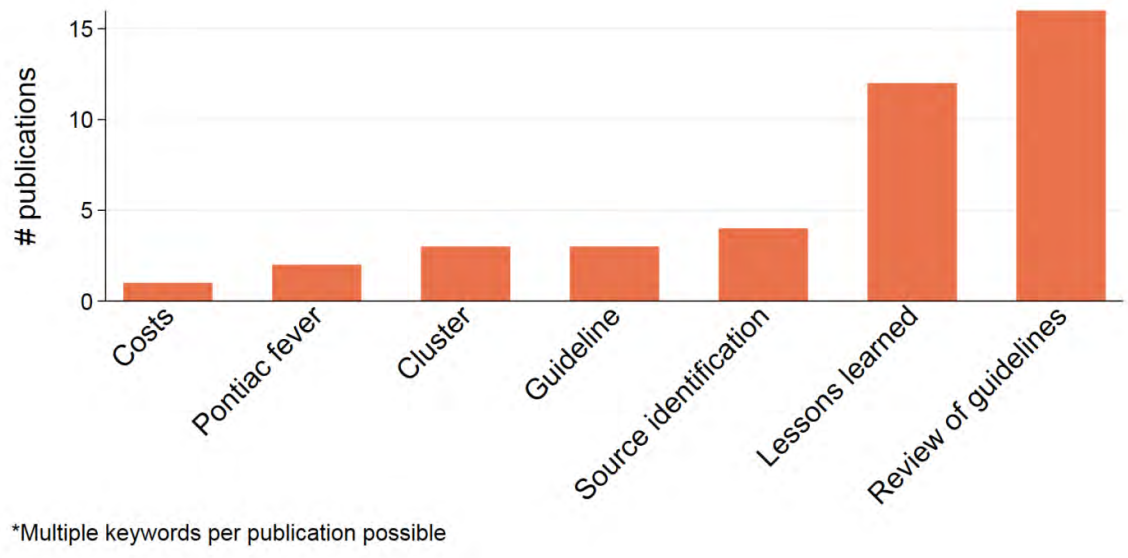


Figure 6 Selected publication on the topic of "outbreaks"of legionellosis and Legionnaires' disease, 1999-2019, by keyword as assigned by the study team

Appendix F-2: Search terms, hits and specifications for LD literature study

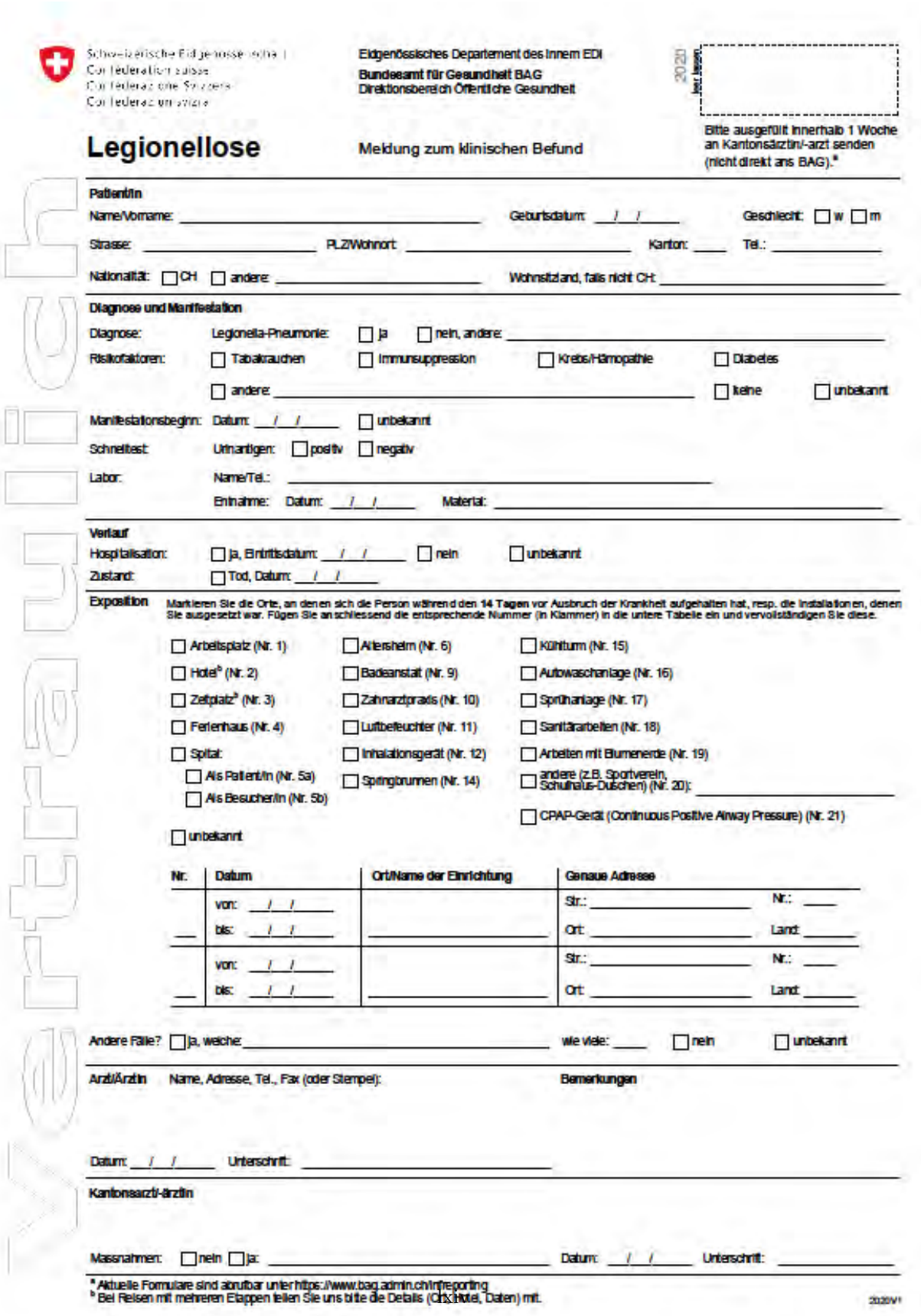
Prevention and control				
Database	**Query**	**Hits**	**Search fields**	**Timeframe**
Embase	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (prevention OR action OR counteraction OR control OR regulation OR management OR measure)	526	title, abstract, keywords	All years
PubMed	("legionellosis" [MeSH Terms] OR "*Legionella*"[MeSH Terms]) AND ("Health Planning"[MeSH Terms] OR "Health Planning Guidelines"[MeSH Terms] OR "Legislation as Topic"[MeSH Terms]) AND (prevention and control [Subheading])	25	all fields	All years
Web of Science	((("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (prevention OR action OR counteraction OR control OR regulation OR management OR measure))	971	title, abstract, author keywords, keywords plus	1900-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation) AND (prevention)	996	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND (prevention)	997	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (law) AND (prevention)	999	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND (control)	999	keywords	1999-2019

Diagnosis and case management				
Database	**Query**	**Hits**	**Search fields**	**Timeframe**
Embase	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (diagnosis OR "clinical decision-making" OR diagnoses OR diagnostics OR "health care" OR "case managment" OR "patient care planning")	384	title, abstract, keywords	All years
PubMed	("legionellosis" [MeSH Terms] OR "*Legionella*"[MeSH Terms]) AND ("Health Planning"[MeSH Terms] OR "Health Planning Guidelines"[MeSH Terms] OR "Legislation as Topic"[MeSH Terms]) AND ("Diagnosis"[MeSH Terms] OR "Patient Care Planning"[MeSH Terms])	4	all fields	All years
Web of Science	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (diagnosis OR "clinical decision-making" OR diagnoses OR diagnostics OR "health care" OR "case managment" OR "patient care planning")	448	title, abstract, author keywords, keywords plus	1900-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommedation) AND (diagnosis)	996	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND (diagnosis)	997	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (law) AND (diagnosis)	999	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND ("case management")	223	keywords	1999-2019

Surveillance				
Database	**Query**	**Hits**	**Search fields**	**Timeframe**
Embase	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (surveillance OR monitoring OR notification OR notice OR report OR reporting OR "case definition")	352	title, abstract, keywords	All years
PubMed	("legionellosis" [MeSH Terms] OR "*Legionella*"[MeSH Terms]) AND ("Health Planning"[MeSH Terms] OR "Health Planning Guidelines"[MeSH Terms] OR "Legislation as Topic"[MeSH Terms]) AND ("Disease Notification"[MeSH Terms] OR "Epidemiological Monitoring"[MeSH Terms])	3	all fields	All years
Web of Science	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (surveillance OR monitoring OR notification OR notice OR report OR reporting OR "case definition")	629	title, abstract, author keywords, keywords plus	1900-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation) AND (surveillance)	996	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND (surveillance)	996	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (law) AND (surveillance)	999	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND ("case definition")	706	keywords	1999-2019

Outbreaks				
Database	**Query**	**Hits**	**Search fields**	**Timeframe**
Embase	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (outbreak OR cluster OR source OR "outbreak investigation" OR "source identification" OR epidemic OR exposure OR "environmental source" OR investigation OR exposure)	419	title, abstract, keywords	All years
PubMed	("legionellosis" [MeSH Terms] OR "*Legionella*"[MeSH Terms]) AND ("Health Planning"[MeSH Terms] OR "Health Planning Guidelines"[MeSH Terms] OR "Legislation as Topic"[MeSH Terms]) AND ("Disease Outbreaks"[MeSH Terms] OR "Environmental Exposure"[MeSH Terms])	7	all fields	All years
Web of Science	("legionnaires disease" OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation OR proposal OR suggestion OR proposition OR guideline OR protocol OR instruction OR standard OR basis OR guidance OR program OR law OR requirement OR government OR jurisdiction OR rule OR decree OR legislation OR mandate OR code OR constitution OR act OR decision OR statute OR order) AND (outbreak OR cluster OR source OR "outbreak investigation" OR "source identification" OR epidemic OR exposure OR "environmental source" OR investigation OR exposure)	748	title, abstract, author keywords, keywords plus	1900-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (recommendation) AND (outbreak)	997	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND (outbreak)	999	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (law) AND (outbreak)	998	keywords	1999-2019
Google Scholar	(legionnaires disease OR legionellosis OR *Legionella* OR "pontiac fever") AND (guideline) AND (cluster)	997	keywords	1999-2019

Appendix F-3: Swiss notification form for clinicians for LD



Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Öffentliche Gesundheit

2020 Jetzt lassen

Bitte ausgefüllt innerhalb 1 Woche an Kantonsärztin/-arzt senden (nicht direkt ans BAG).[a]

Legionellose

Meldung zum klinischen Befund

Patient/in

Name/Vorname: _____ Geburtsdatum: __/__/____ Geschlecht: ☐ w ☐ m

Strasse: _____ PLZ/Wohnort: _____ Kanton: ____ Tel.: _____

Nationalität: ☐ CH ☐ andere: _____ Wohnsitzland, falls nicht CH: _____

Diagnose und Manifestation

Diagnose: Legionella-Pneumonie: ☐ ja ☐ nein, andere: _____

Risikofaktoren: ☐ Tabakrauchen ☐ Immunsuppression ☐ Krebs/Hämopathie ☐ Diabetes
☐ andere: _____ ☐ keine ☐ unbekannt

Manifestationsbeginn: Datum: __/__/____ ☐ unbekannt

Schnelltest: Urinantigen: ☐ positiv ☐ negativ

Labor: Name/Tel.: _____
Entnahme: Datum: __/__/____ Material: _____

Verlauf

Hospitalisation: ☐ ja, Eintrittsdatum: __/__/____ ☐ nein ☐ unbekannt

Zustand: ☐ Tod, Datum: __/__/____

Exposition Markieren Sie die Orte, an denen sich die Person während den **14 Tagen** vor Ausbruch der Krankheit aufgehalten hat, resp. die Installationen, denen Sie ausgesetzt war. Fügen Sie anschliessend die entsprechende Nummer (in Klammer) in die untere Tabelle ein und vervollständigen Sie diese.

☐ Arbeitsplatz (Nr. 1)
☐ Hotel[b] (Nr. 2)
☐ Zeltplatz[b] (Nr. 3)
☐ Ferienhaus (Nr. 4)
☐ Spital:
  ☐ Als Patient/in (Nr. 5a)
  ☐ Als Besucher/in (Nr. 5b)
☐ unbekannt

☐ Altersheim (Nr. 6)
☐ Badeanstalt (Nr. 9)
☐ Zahnarztpraxis (Nr. 10)
☐ Luftbefeuchter (Nr. 11)
☐ Inhalationsgerät (Nr. 12)
☐ Springbrunnen (Nr. 14)

☐ Kühlturm (Nr. 15)
☐ Autowaschanlage (Nr. 16)
☐ Sprühanlage (Nr. 17)
☐ Sanitärarbeiten (Nr. 18)
☐ Arbeiten mit Blumenerde (Nr. 19)
☐ andere (z.B. Sportverein, Schulhaus-Duschen) (Nr. 20): _____
☐ CPAP-Gerät (Continuous Positive Airway Pressure) (Nr. 21)

Nr.	Datum	Ort/Name der Einrichtung	Genaue Adresse
___	von: __/__/____ bis: __/__/____	_____	Str.: _____ Nr.: ____ Ort: _____ Land: _____
___	von: __/__/____ bis: __/__/____	_____	Str.: _____ Nr.: ____ Ort: _____ Land: _____

Andere Fälle? ☐ ja, welche: _____ wie viele: ____ ☐ nein ☐ unbekannt

Arzt/Ärztin Name, Adresse, Tel., Fax (oder Stempel): **Bemerkungen**

Datum: __/__/____ Unterschrift: _____

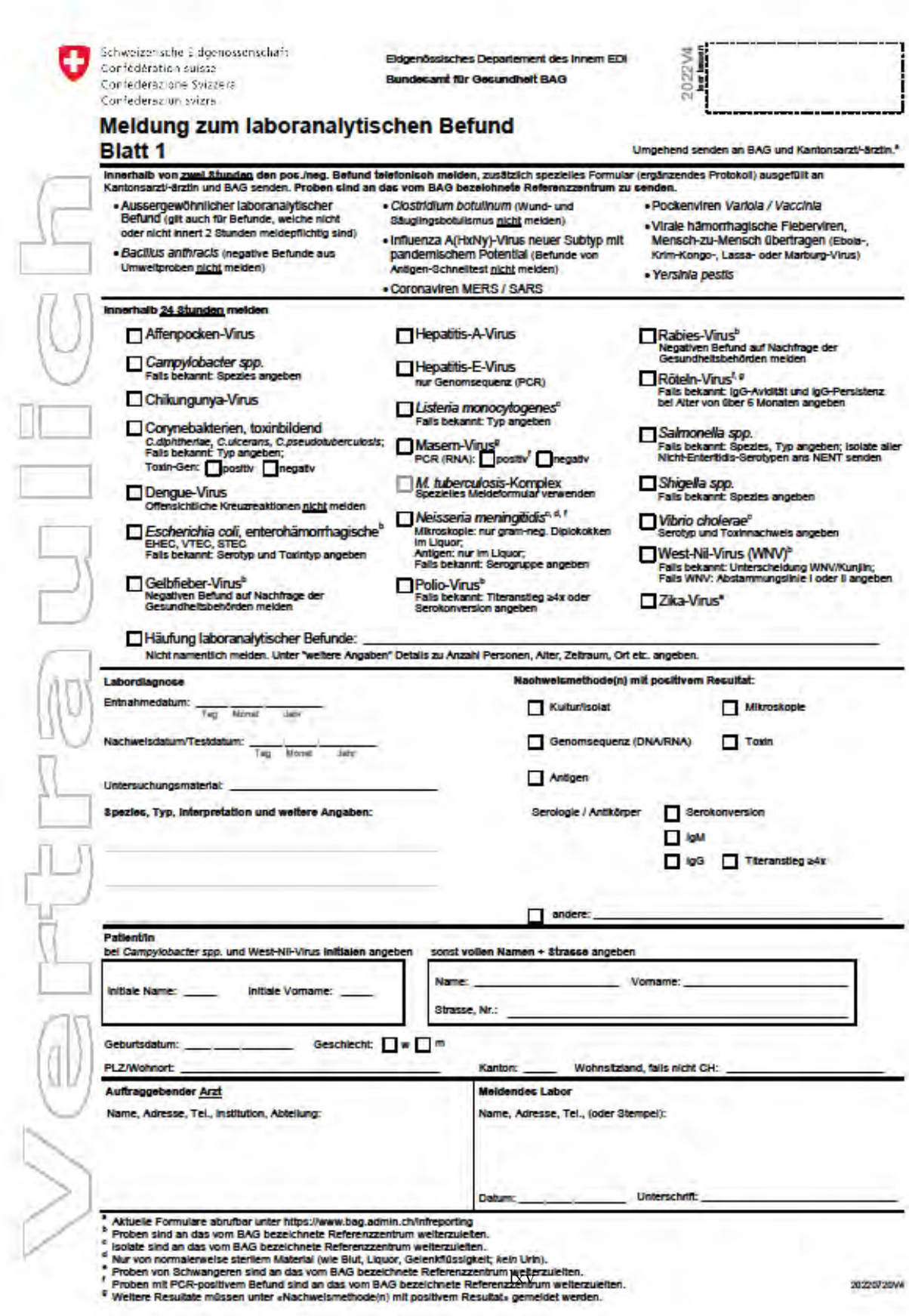
Kantonsarzt/-ärztin

Massnahmen: ☐ nein ☐ ja: _____ Datum: __/__/____ Unterschrift: _____

[a] Aktuelle Formulare sind abrufbar unter https://www.bag.admin.ch/infreporting
[b] Bei Reisen mit mehreren Etappen teilen Sie uns bitte die Details (Ort, Hotel, Daten) mit.

2020V1

Appendix F-4: Swiss notification form for laboratories for LD



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Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG

2022VM

Meldung zum laboranalytischen Befund
Blatt 1

Umgehend senden an BAG und Kantonsarzt/-ärztin.[a]

Innerhalb von zwei Stunden den pos./neg. Befund telefonisch melden, zusätzlich spezielles Formular (ergänzendes Protokoll) ausgefüllt an Kantonsarzt/-ärztin und BAG senden. Proben sind an das vom BAG bezeichnete Referenzzentrum zu senden.

- Aussergewöhnlicher laboranalytischer Befund (gilt auch für Befunde, welche nicht oder nicht innert 2 Stunden meldepflichtig sind)
- *Bacillus anthracis* (negative Befunde aus Umweltproben nicht melden)
- *Clostridium botulinum* (Wund- und Säuglingsbotulismus nicht melden)
- Influenza A(HxNy)-Virus neuer Subtyp mit pandemischem Potential (Befunde von Antigen-Schnelltest nicht melden)
- Coronaviren MERS / SARS
- Pockenviren *Variola / Vaccinia*
- Virale hämorrhagische Fieberviren, Mensch-zu-Mensch übertragen (Ebola-, Krim-Kongo-, Lassa- oder Marburg-Virus)
- *Yersinia pestis*

Innerhalb 24 Stunden melden

- ☐ Affenpocken-Virus
- ☐ *Campylobacter spp.* — Falls bekannt: Spezies angeben
- ☐ Chikungunya-Virus
- ☐ Corynebakterien, toxinbildend — *C.diphtheriae, C.ulcerans, C.pseudotuberculosis*; Falls bekannt: Typ angeben; Toxin-Gen: ☐ positiv ☐ negativ
- ☐ Dengue-Virus — Offensichtliche Kreuzreaktionen nicht melden
- ☐ *Escherichia coli*, enterohämorrhagische[b] — EHEC, VTEC, STEC. Falls bekannt: Serotyp und Toxintyp angeben
- ☐ Gelbfieber-Virus[b] — Negativen Befund auf Nachfrage der Gesundheitsbehörden melden
- ☐ Hepatitis-A-Virus
- ☐ Hepatitis-E-Virus — nur Genomsequenz (PCR)
- ☐ *Listeria monocytogenes*[c] — Falls bekannt: Typ angeben
- ☐ Masern-Virus[g] — PCR (RNA): ☐ positiv / ☐ negativ
- ☐ *M. tuberculosis*-Komplex — Spezielles Meldeformular verwenden
- ☐ *Neisseria meningitidis*[c, d, f] — Mikroskopie: nur gram-neg. Diplokokken im Liquor; Antigen: nur im Liquor; Falls bekannt: Serogruppe angeben
- ☐ Polio-Virus[b] — Falls bekannt: Titeranstieg ≥4x oder Serokonversion angeben
- ☐ Rabies-Virus[b] — Negativen Befund auf Nachfrage der Gesundheitsbehörden melden
- ☐ Röteln-Virus[f, g] — Falls bekannt: IgG-Avidität und IgG-Persistenz bei Alter von über 6 Monaten angeben
- ☐ *Salmonella spp.* — Falls bekannt: Spezies, Typ angeben; Isolate aller Nicht-Enteritidis-Serotypen ans NENT senden
- ☐ *Shigella spp.* — Falls bekannt: Spezies angeben
- ☐ *Vibrio cholerae*[c] — Serotyp und Toxinnachweis angeben
- ☐ West-Nil-Virus (WNV)[b] — Falls bekannt: Unterscheidung WNV/Kunjin; Falls WNV: Abstammungslinie I oder II angeben
- ☐ Zika-Virus[a]

☐ Häufung laboranalytischer Befunde: _____
Nicht namentlich melden. Unter "weitere Angaben" Details zu Anzahl Personen, Alter, Zeitraum, Ort etc. angeben.

Labordiagnose

Entnahmedatum: ___ ___ ___ (Tag Monat Jahr)

Nachweisdatum/Testdatum: ___ ___ ___ (Tag Monat Jahr)

Untersuchungsmaterial: _____

Spezies, Typ, Interpretation und weitere Angaben:

Nachweismethode(n) mit positivem Resultat:

- ☐ Kultur/Isolat
- ☐ Mikroskopie
- ☐ Genomsequenz (DNA/RNA)
- ☐ Toxin
- ☐ Antigen

Serologie / Antikörper
- ☐ Serokonversion
- ☐ IgM
- ☐ IgG ☐ Titeranstieg ≥4x

☐ andere: _____

Patientin

bei *Campylobacter spp.* und West-Nil-Virus **Initialen** angeben

Initiale Name: ____ Initiale Vorname: ____

sonst vollen **Namen + Strasse** angeben

Name: _____ Vorname: _____

Strasse, Nr.: _____

Geburtsdatum: ___ ___ ___ Geschlecht: ☐ w ☐ m

PLZ/Wohnort: _____ Kanton: ____ Wohnsitzland, falls nicht CH: _____

Auftraggebender Arzt

Name, Adresse, Tel., Institution, Abteilung:

Meldendes Labor

Name, Adresse, Tel., (oder Stempel):

Datum: ___ ___ ___ Unterschrift: _____

[a] Aktuelle Formulare abrufbar unter https://www.bag.admin.ch/infreporting
[b] Proben sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[c] Isolate sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[d] Nur von normalerweise sterilem Material (wie Blut, Liquor, Gelenkflüssigkeit; kein Urin).
[e] Proben von Schwangeren sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[f] Proben mit PCR-positivem Befund sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[g] Weitere Resultate müssen unter «Nachweismethode(n) mit positivem Resultat» gemeldet werden.

2022/07/20/VM

Appendix F-5: Comparison of selected notification forms for legionellosis

		Switzerland	New Zealand	USA (SLDSS)	England and Wales
Specific form for legionellosis		[Only clinician form]	x	x	x
Reporting source	Physician	x	x	x	x
	GP		x		
	Hospital-based practitioner		x		
	laboratory	x	x		
	Self-notification		x		
	Outbreak investigation		x		
	Other		x		
	Usual GP		x		
Demographic	Name	x	x	x	x
	Birth date	x	x	x	x
	Sex	x	x	x	x
	Address	x	x	x	x
	Nationality	x			
	Ethnic group		x	x	
	Occupation		x	x	X [details inquired]
Disease severity	Hospitalisation	x	x	x	x
	Duration of hospitalisation	x	x	x	x
	ICU				x
	Death	x	x	x	x
Clincal Features	Start of symptoms	x	x	x	x
	Legionnaires' disease	x	x	x	x
	Pontiac fever			x	x
	Non-pneumotic legionellosis				x
	Chest pain				x
	Confusion				x
	Lethargy				x
	Cough				x
	Shortness of breath				x
	Diarrhoea				x
	Other	x		x	x
Laboratory diagnostics	Method	x	x	x	x
	Date sample taken	x		x	x
	Date analyses	x			
	Sample material	x		x	x
	Typ	x		x	x
	Sample sent to reference laboratory				x
Classification	Under investigation				
	Probable				
	Confirmed				
	Not a case				
Risk factors	Smoking	x	x		x
	Immunosupressed	x	x		x
	Cancer	x			

		Switzerland	New Zealand	USA (SLDSS)	England and Wales
	Diabetes	x			
	Other	x	x		x
	No	x			
	Unknown	x			
		14 days prior	2-14 days prior	10 days prior	10 days prior
Exposition	Means of regular transport		[free text]		x
	Usual place of grocery shopping		[free text]		x
	Work place	x	[free text]		
	Hotel	x	[free text]		
	Camping site		[free text]		
	Holiday home	x	[free text]		
	Nursing home	x	[free text]	x	
	Public pool	x	[free text]		
	Dentist	x	[free text]		x
	Humidifier	x	[free text]	x	
	Inhalation device	x	[free text]		
	Fountain	x	[free text]		x
	Cooling tower	x	[free text]		
	Car wash facility	x	[free text]		x
	Spray system	x	[free text]		x
	Plumbing	x	[free text]		x
	Working with soil	x	[free text]		x
	Other (e.g. sport club, school showers)	x	[free text]		
	CPAP device	x	[free text]	x	
	Hospital as patient	x	[free text]	x	x
	Hospital as visitor	x	[free text]	x	
	Health-care associated case		[free text]	x	x
	Whirlpool		[free text]	x	x
	Air conditioning		[free text]		x
	Shower other than home		[free text]		x
	Free text	x	x		x
	Overseas		x		x
	Patient history (diary)				x
Outbreak	Have there been other cases?	x	x	x	x
Have measures been taken?		x			x
Space for notes gives			x	x	x

Appendix F-6: ELDSNet members

Taken from https://www.ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/eldsnet, accessed 22 July 2019

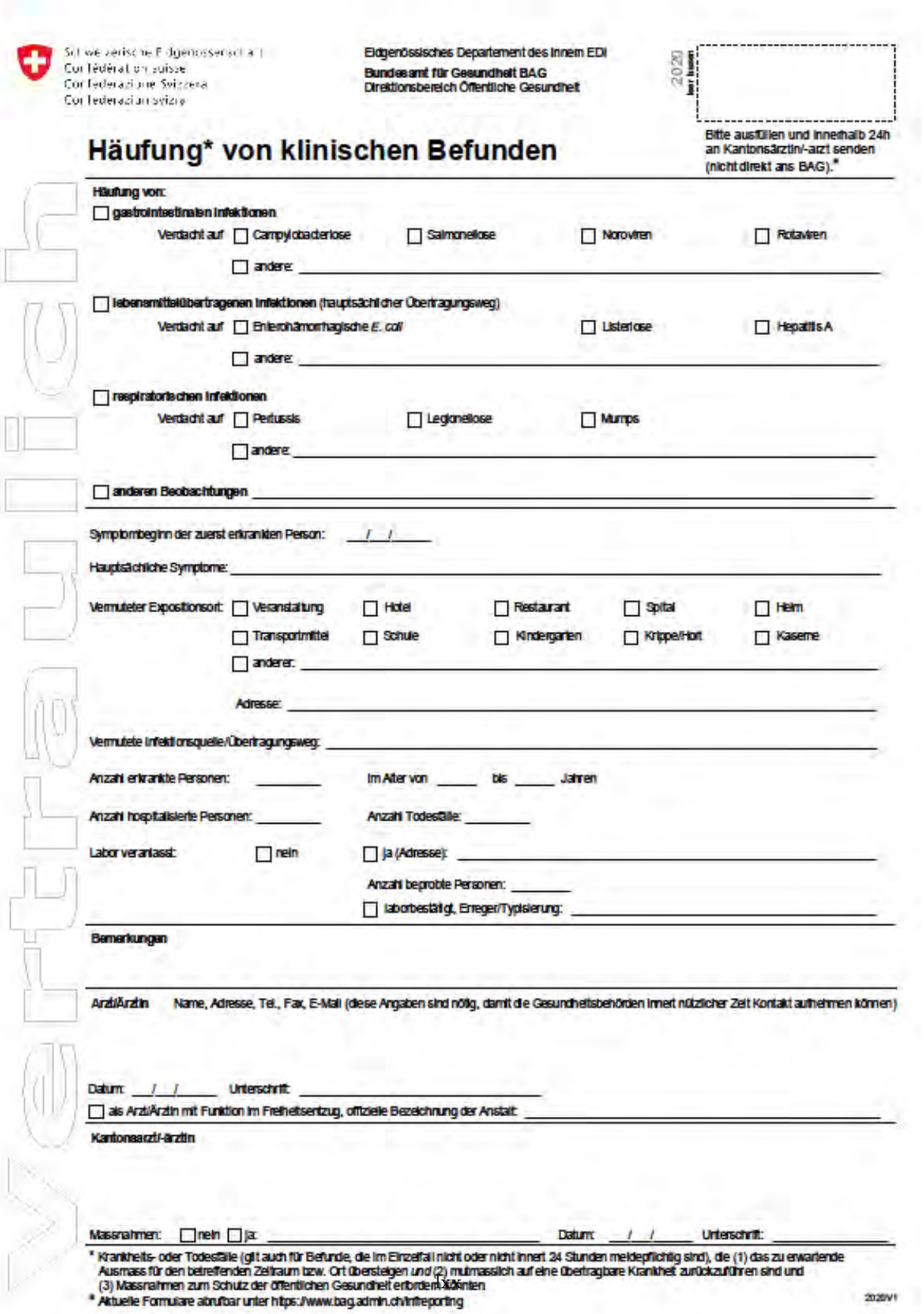
Institution		Address	Country	URL
Austrian Agency for Health and Food Safety	1	Beethovenstraße 6, AT-8010 Graz	Austria	http://www.ages.at/
Centre for Communicable Diseases and AIDS	1	Nugaletoju st. 14D, LT-10105 Vilnius	Lithuania	http://www.vvspt.lt/
Centre for Disease Prevention and Control	2	Duntes 22, 1005 Riga	Latvia	http://spkc.gov.lv/
Centre of Health Security and Communicable Disease Prevention	1	Barónsstíg 47, IS - 101 Reykjvík	Iceland	http://www.landlaeknir.is/
Croatian National Institute of Public Health	2	Rockefellerova 7, 10000 Zagreb	Croatia	http://www.hzjz.hr/epocetna.htm
Directorate General of Health	2	Alameda D. Afonso Henriques, 45- 2º, 1049-005 Lisbon	Portugal	http://www.dgs.pt/
Directorate of Medical and Public Health Services	2	1, Prodromou str, CY-1448 Nicosia	Cyprus	http://www.moh.gov.cy/moh/moh.nsf/index_en/index_en
Health Board	2	81 Paldiski Mnt, 10617 Tallinn	Estonia	http://www.terviseamet.ee
Health Protection Surveillance Centre	2	25-27 Middle Gardiner Street, IR-1 Dublin	Ireland	http://www.hpsc.ie/hpsc/default.aspx
Institute for Public Health Surveillance	1	12 rue du Val d'Osne, FR-94410 Saint-Maurice cedex	France	http://www.invs.sante.fr/
Ministry of Health	1	Villa Louvigny-Allée Marconi, 2120 Villa Louvigny-Allée Marconi	Luxembourg	http://www.ms.public.lu/fr/
National Center for Epidemiology	1	Gyali ut 2-6, Budapest	Hungary	http://www.oek.hu
National Centre of Epidemiology, Health Institute Carlos III	1	Monforte de Lemos, 5, ES-28029 Madrid	Spain	http://www.isciii.es/
National Centre of Infectious and Parasitic Diseases	2	26 Yanko Sakazov Blvd, 1504 Sofia	Bulgaria	http://www.ncipd.org/
National Institute for Health and Welfare	2	Mannerheimintie 166, (00)271 Helsinki	Finland	http://www.thl.fi
National Institute for Public Health and the Environment (RIVM)	2	Antonie van Leeuwenhoeklaan 9, PO Box 1, 3720BA Bilthoven	Netherlands	http://www.rivm.nl/
National Institute of Health	1	Viale Regina Elena 299, (00)161 Rome	Italy	http://www.iss.it/
National Institute of Public Health	2	Dr. Leonte Anastasievici 1-3, (0)50463 Bucharest	Romania	http://www.insp.gov.ro/

Institution		Address	Country	URL
National Institute of Public Health (NIJZ)	[2]	Trubarjeva 2, SL - 1000 Ljubljana	Slovenia	http://www.nijz.si
National Institute of Public Health/National Institute of Hygiene	[2]	24 Chocimska Street, (00)791 Warsaw	Poland	http://www.pzh.gov.pl/
National Public Health Organization	[2]	3-5 Agrafon St., EL-15123 Athens	Greece	http://www.keelpno.gr/
Norwegian Institute of Public Health	[2]	PO Box 4404 Nydalen, (0)403 Oslo	Norway	http://www.fhi.no/
Principality of Liechtenstein	[2]	Äulestrasse 51, 9490 Vaduz	Liechtenstein	http://www.ag.llv.li
Public Health Agency of Sweden	[2]	Nobels väg 18, Solna, 17182 Stockholm	Sweden	https://www.folkhalsomyndigheten.se/
Public Health Authority of the Slovak Republic	[2]	Trnavská cesta 52, SK-826 45 Bratslava	Slovakia	http://www.uvzsr.sk/en/
Public Health England	[2]	Colindale Avenue 61, NW9 5EQ London	United Kingdom	https://www.gov.uk/government/organisations/public-health-england
Regional Public Health Authority Moravian-Silesian Region in Ostrava	[1]	Na Belidle 7, 702 00 Ostrava	Czech Republic	http://www.szu.cz
Robert Koch Institute	[1]	DGZ Ring 1, 13086 Berlin	Germany	http://www.rki.de
Sciensano	[2]	Rue Juliette Wytsmanstraat 14, 1050 Brussels	Belgium	https://www.sciensano.be/en
Statens Serum Institut	[1]	5 Artillerivej, DK-2300 Copenhagen S	Denmark	http://www.ssi.dk/
Superintendence of Public Health	[1]	37-39 Rue D'Argens, MT-5 Msida MSD	Malta	http://ehealth.gov.mt

[1] Disease network member

[2] Coordinating Competent Body, disease network member

Appendix F-7: Swiss notification form for clusters of LD



Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Öffentliche Gesundheit

2020 leer lassen

Bitte ausfüllen und innerhalb 24h an Kantonsärztin/-arzt senden (nicht direkt ans BAG).*

Häufung* von klinischen Befunden

Häufung von:

☐ **gastrointestinalen Infektionen**
Verdacht auf ☐ Campylobacteriose ☐ Salmonellose ☐ Noroviren ☐ Rotaviren
☐ andere: _____

☐ **lebensmittelübertragenen Infektionen** (hauptsächlicher Übertragungsweg)
Verdacht auf ☐ Enterohämorrhagische *E. coli* ☐ Listeriose ☐ Hepatitis A
☐ andere: _____

☐ **respiratorischen Infektionen**
Verdacht auf ☐ Pertussis ☐ Legionellose ☐ Mumps
☐ andere: _____

☐ **anderen Beobachtungen** _____

Symptombeginn der zuerst erkrankten Person: __/__/____

Hauptsächliche Symptome: _____

Vermuteter Expositionsort: ☐ Veranstaltung ☐ Hotel ☐ Restaurant ☐ Spital ☐ Heim
☐ Transportmittel ☐ Schule ☐ Kindergarten ☐ Krippe/Hort ☐ Kaserne
☐ andere: _____

Adresse: _____

Vermutete Infektionsquelle/Übertragungsweg: _____

Anzahl erkrankte Personen: _____ Im Alter von _____ bis _____ Jahren

Anzahl hospitalisierte Personen: _____ Anzahl Todesfälle: _____

Labor veranlasst: ☐ nein ☐ ja (Adresse): _____
Anzahl beprobte Personen: _____
☐ laborbestätigt, Erreger/Typisierung: _____

Bemerkungen

Arzt/Ärztin Name, Adresse, Tel., Fax, E-Mail (diese Angaben sind nötig, damit die Gesundheitsbehörden innert nützlicher Zeit Kontakt aufnehmen können)

Datum: __/__/____ Unterschrift: _____
☐ als Arzt/Ärztin mit Funktion im Freiheitsentzug, offizielle Bezeichnung der Anstalt: _____

Kantonsarzt/-ärztin

Massnahmen: ☐ nein ☐ ja: _____ Datum: __/__/____ Unterschrift: _____

* Krankheits- oder Todesfälle (gilt auch für Befunde, die im Einzelfall nicht oder nicht innert 24 Stunden meldepflichtig sind), die (1) das zu erwartende Ausmass für den betreffenden Zeitraum bzw. Ort übersteigen *und* (2) mutmasslich auf eine übertragbare Krankheit zurückzuführen sind und (3) Massnahmen zum Schutz der öffentlichen Gesundheit erfordern könnten

* Aktuelle Formulare abrufbar unter https://www.bag.admin.ch/infreporting

2020V1

Appendix F-8: Publication by Van Kenhove et al. (2019)

Van Kenhove et al. have recently published an overview of the prevention of *Legionella* infections world-wide [12]. The publication can be accessed here: https://www.sciencedirect.com/science/article/pii/S0196655318309957?via%3Dihub (Last accessed 28 January 2020).

Appendix F-9: Overview of global guidelines on the diagnosis of LD

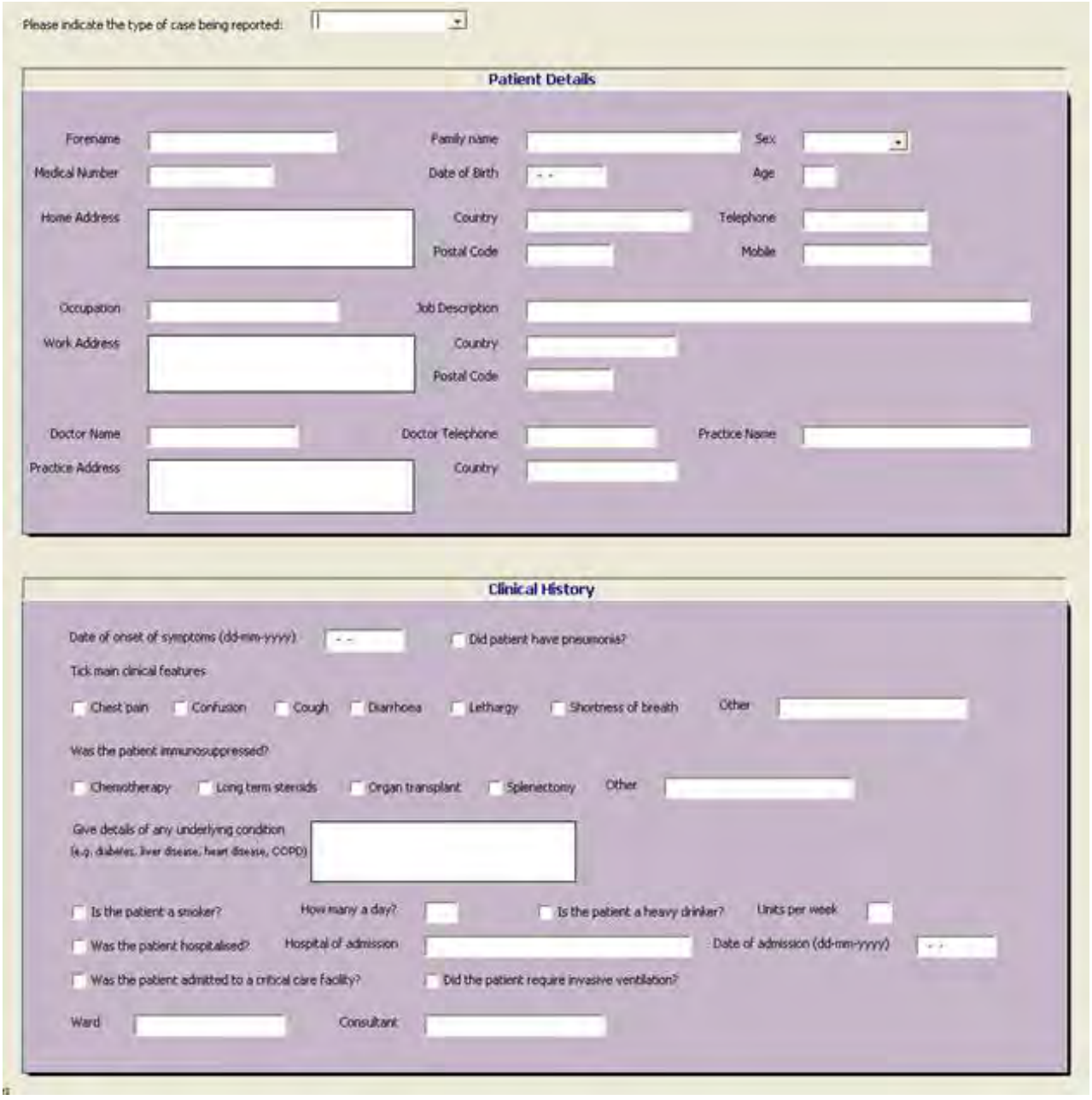
For the purpose of this review, we have collected information from various guidelines on the diagnosis of pneumonia and LD. All identified information has been charted and been made available in a separately provided excel-file. While every attempt was made to obtain a complete overview, we cannot guarantee that no information has been omitted or is outdated.

Appendix F-10: Overview of global surveillance for LD

Similarly, for the purpose of this review, we have collected information of various surveillance schemes for LD. This information has been charted and made available in a separately provided excel-file. While every attempt was made to obtain a complete overview, we cannot guarantee that no information has been omitted or is outdated.

Appendix F-11: ECDC's Legionnaires' disease outbreak investigation toolbox – surveillance questionnaire

The toolbox and questionnaire can be accessed on https://legionnaires.ecdc.europa.eu/?pid=210 (Last accessed 30 January 2020).



Patient Status

Current Status: Still ill | If dead, date of death (dd-mm-yyyy): - -

Please do NOT wait for the 30 day time period to be over before submitting the form. The form MUST be submitted as soon as possible with a response to the next question submitted as an update at the appropriate time.

30 day status: Recovered | If dead, date of death (dd-mm-yyyy): - -

Patient's Two Week Diary

Activities in the two weeks prior to onset

Means of regular transport

Route to work

Usual places of shopping

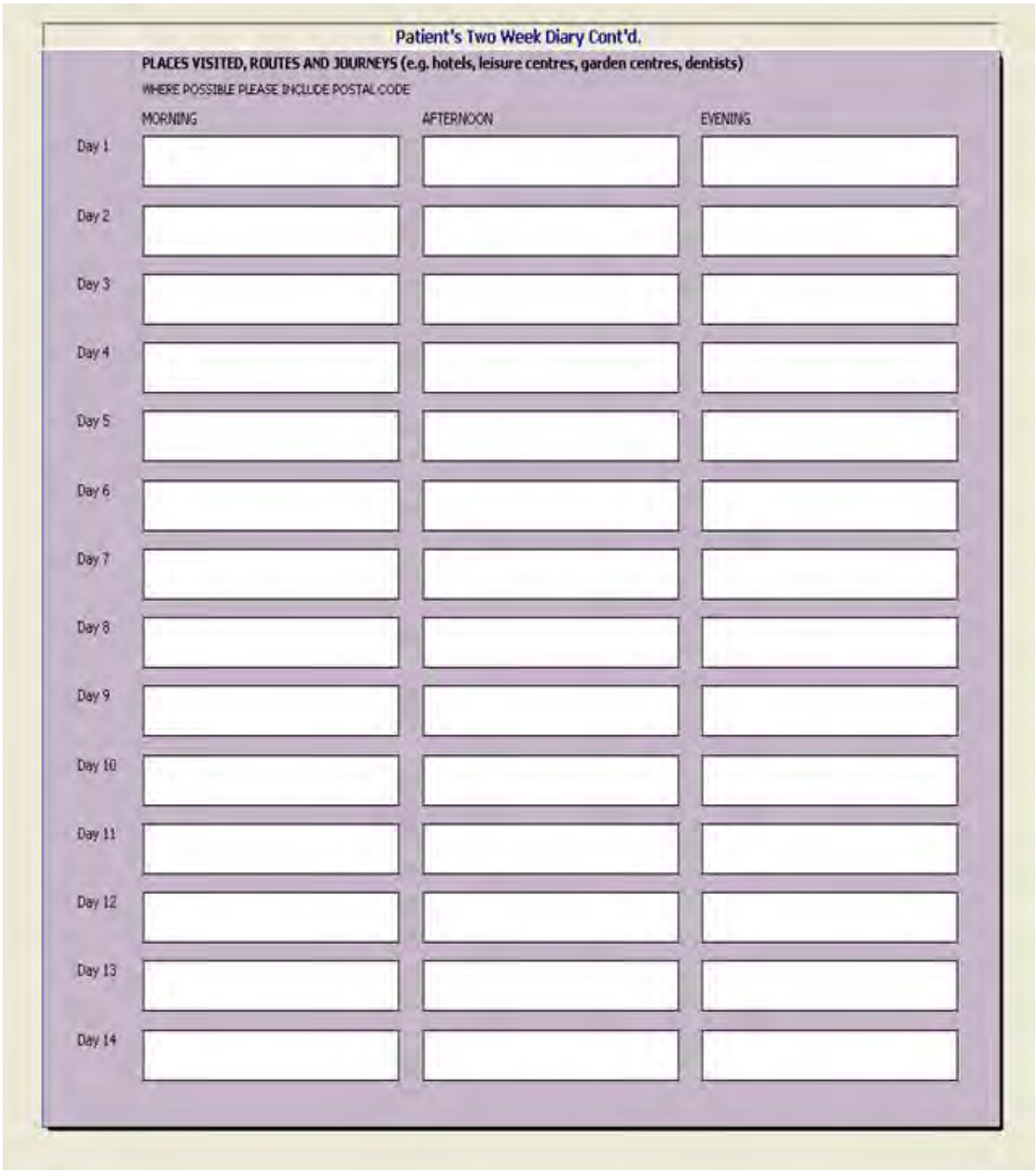
Was the patient exposed (in home country or abroad) to:

Exposure (Yes/No)	Details (e.g. name, location, postcode etc)	Exposure (Yes/No)	Details (e.g. name, location, postcode etc)
☐ Whirlpool spas/hot tub Natural thermal springs/ Natural spa pools		☐ Water displays in shopping or garden centre	
☐ Showers		☐ Food displays with water mists	
☐ Fountains		☐ Compost/potting mixes	
☐ Car Washes		☐ Cutting Fluids	
☐ Jet Washes		☐ Other 1	
☐ Air conditioning		☐ Other 2	

Any recent repairs on property/garden

Any other relevant information (e.g. smoker)

IF THE CASE HAS TRAVELLED EITHER WITHIN THE HOME COUNTRY OR OUTSIDE DURING THE INCUBATION PERIOD, OR VISITED A HOSPITAL, PLEASE COMPLETE THE APPROPRIATE SECTIONS ON PAGE 4



Patient's Two Week Diary Cont'd.

PLACES VISITED, ROUTES AND JOURNEYS (e.g. hotels, leisure centres, garden centres, dentists)

WHERE POSSIBLE PLEASE INCLUDE POSTAL CODE

	MORNING	AFTERNOON	EVENING
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			

Risk Factor Information

Cases are defined as hospital or travel-associated if they fulfil the criteria below

Definitions

Travel associated cases: One or more overnight stays in holiday accomodation in the UK or abroad in the 2-14 days before onset of illness.

Hospital associated cases: Patients who spent at least one night in hospital during the fourteen days prior to onset of symptoms.

Possible Hospital Associated Case

☐ Patient admitted to hospital at any time in the fourteen days BEFORE onset? Hospital of admission

Date of admission (dd-mm-yyyy) - - Ward or Unit

If the patient was transfered from another hospital within the incubation period, please give details:

Hospital prior to transfer Dates of stay - - to - -

☐ Did the patient VISIT a hospital at any time in the two weeks BEFORE onset?

Details (including dates)

Possible Travel Associated Case

ABROAD

Did the patient travel abroad in the two to fourteen days before onset?

Arrival Date	Departure Date	Town or Resort	Hotel or other Accommodation	Room No	Country

Tour Operator (if known)

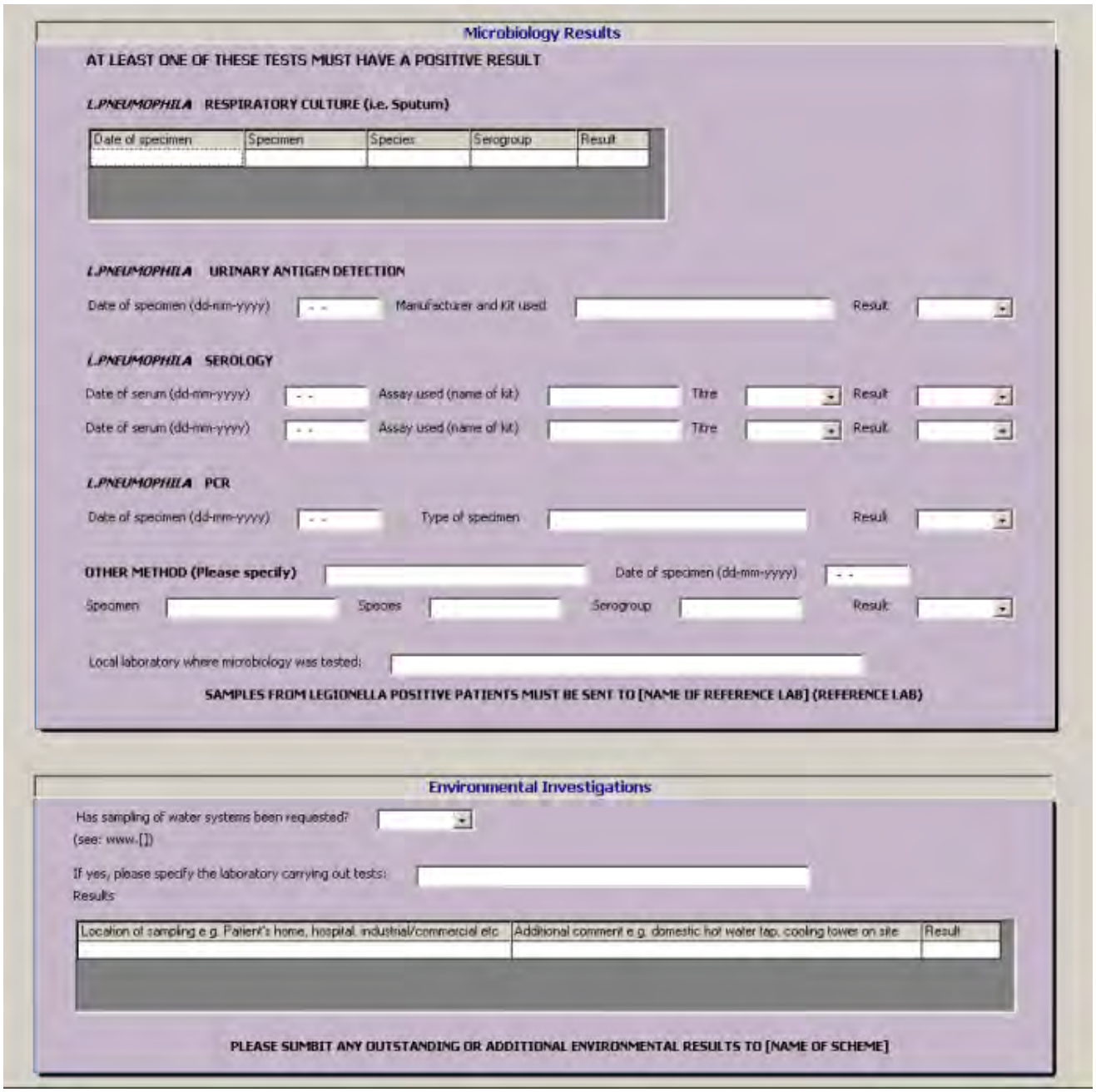
HOME COUNTRY

Did the patient travel within the home country in the two to fourteen days before onset?

Arrival Date	DepartureDate	Town or Resort	Hotel or other accommodation	Room No

Tour Operator (if known)

Additional information



Microbiology Results

AT LEAST ONE OF THESE TESTS MUST HAVE A POSITIVE RESULT

L.PNEUMOPHILA RESPIRATORY CULTURE (i.e. Sputum)

Date of specimen	Specimen	Species	Serogroup	Result

L.PNEUMOPHILA URINARY ANTIGEN DETECTION

Date of specimen (dd-mm-yyyy) - - Manufacturer and Kit used: Result:

L.PNEUMOPHILA SEROLOGY

Date of serum (dd-mm-yyyy) - - Assay used (name of kit): Titre: Result:

Date of serum (dd-mm-yyyy) - - Assay used (name of kit): Titre: Result:

L.PNEUMOPHILA PCR

Date of specimen (dd-mm-yyyy) - - Type of specimen: Result:

OTHER METHOD (Please specify): Date of specimen (dd-mm-yyyy) - -

Specimen: Species: Serogroup: Result:

Local laboratory where microbiology was tested:

SAMPLES FROM LEGIONELLA POSITIVE PATIENTS MUST BE SENT TO [NAME OF REFERENCE LAB] (REFERENCE LAB)

Environmental Investigations

Has sampling of water systems been requested?
(see: www.[])

If yes, please specify the laboratory carrying out tests:
Results

Location of sampling e.g. Patient's home, hospital, industrial/commercial etc	Additional comment e.g. domestic hot water tap, cooling towes on site	Result

PLEASE SUMBIT ANY OUTSTANDING OR ADDITIONAL ENVIRONMENTAL RESULTS TO [NAME OF SCHEME]

Appendix F-12: ECDC's Legionnaires' disease outbreak investigation toolbox – trawling questionnaire

The toolbox and questionnaire can be accessed on https://legionnaires.ecdc.europa.eu/?pid=210 (Last accessed 30 January 2020).

Questionnaire

Date questionnaire completed (dd/mm/yyyy)
Questionnaire completed by ..... (name, profession, department, hospital, address, telephone, fax)
Person interviewed (delete as appropriate): Patient themselves, Family Member, Friend/associate, Hospital Staff

A) Patient identification

Patients name	Family name:	First name:
Date of birth	**(**dd/mm/yyyy)	
Sex	M / F	
Residential Address	House number, Street name Town/municipality. Postal code (if appropriate):	
Telephone no.:		
Contact person details	Address: Telephone no.:	
Work address		
Employer's contact details		
Hospital name and address		
Date of Hospitalisation	**(**dd/mm/yyyy)	
Doctor's name		
Doctor's contact details	Address: Telephone no.:	

Date of legionellosis symptoms onset (dd/mm/yyyy)

Period of questioning (ideally 14 days before onset date of symptoms) from dd/mm/yyy/ to dd/mm/yyyy

B) Confirmation of diagnosis

Case of: Legionnaires' disease □ , Pontiac fever □ or asymptomatic *Legionella* infection □

Other clinical features: Chest pains □, Confusion □, Cough □, Diarrhoea □, Lethargy □, Shortness of breath□, other (please state ….)

Diagnostic test	**Done?**	**Test Result**		
		Not yet known	**Positive**	**Negative**
Strong clinical suspicion of pneumonia	NA	NA	□	□
X-ray confirmation of pneumonia	□	□	□	□
Urinary antigen	□	□	□	□

Culture - respiratory specimen		□	□	□	□
Serology	**Single titre serum**	□	□	□	□
	Paired serum	□	□	□	□

Microbiological detail:

Species	**Serogroup:** (if applicable)	**Subgroup:** (if applicable and known)	**Sequence type:** (if known)

Clinical Risk factors: Cancer □ (please state which type?), corticosteroids □, other immunosuppressants □, Smoking □, diabetes □, Chronic pulmonary disease (chronic bronchitis, emphysema….) □, Cardiovascular disease □, Renal failure □, dialysis □, Transplant □, Other (please state ….)

	Still ill	**Dead**	**Recovered**	**Unknown**
Current situation		Date of death (dd/mm/yyyy)	Date of discharge (dd/mm/yyyy)	
30 day follow up		Date of death (dd/mm/yyyy)	Date of discharge (dd/mm/yyyy)	

C) Exposures

Do you have an idea of where you may have contracted Legionellosis? yes □ no □ don't know □

If yes, please state where, when and how

1) Overnight stays outside of the house

In the 14 days BEFORE the first day of your illness, did you spend a night away from the residential address given above? yes □ no □ don't know □

If yes, was this spent at a:

Hospital yes □ no □ don't know □

Other health care institution yes □ no □ don't know □

Hotel yes □ no □ don't know □

Campsite yes □ no □ don't know □

Apartment or cottage yes □ no □ don't know □

Ship yes □ no □ don't know □

Private accommodation yes □ no □ don't know □

Second home yes □ no □ don't know □

Other yes □ no □ don't know □

If yes, please give details:

Name and address of temporary accommodation (including room number if known)*	**Town or resort**	**Country**	**Purpose of stay, if appropriate (i.e. visitor, patient, tourist, business)**	**Dates of stay** (dd/mm/yyyy)		**Possible contact with aerosols other than designated bathroom****
				From	**To**	

* If temporary accommodation is a hospital or health care institution then check they have not been transferred from another similar institution in the past 14 days and ensure this sites details are captured too.

** possible sources of contamination include: any system that might generate aerosols, for example but not limited to: water systems (showers), air cooling systems and cooling towers, whirlpool/spa/hot tubs/thermal baths, aerosol respiratory equipment, thermal waters, decorative fountains, biological treatment plants and cooling towers)

2) Other visits to Hospital settings

In section 1 you told me about any overnight stays in hospital or other health care institution and where and when these occurred. Could you now tell me of any day trips in the fourteen days BEFORE the first day of your illness, as patient or visitor in a hospital or similar institution?

Date of visit (dd/mm/yyyy)

Type of ward in which you were visitor/patient:

Name of institution

Room no.

Address:

Postal code (if relevant):

Did you visit other hospitals in the 14 day period not already stated above or in section 1? If so please give details?

If yes, please give details:

Name of hospital before transfer

Date of stay from (dd/mm/yyyy) to (dd/mm/yyyy)

When was your last visit to a hospital? (dd/mm/yyyy)

3) Possible sources at work or during regular activity

Occupation (or activity if retired):

Name and address of place of work (or place of regular activity):

During the 14 days before your first day of illness , have you taken one or more showers at your place of work? yes □ no □ don't know □

Do you work with pressurised water (water gun, cutting fluid)? yes □ no □ don't know □

If yes, please state:

At work, are you in contact with an air cooling system (air conditioning system, cooling tower)? yes □ no □ don't know □

If yes, please state:

If so is your air conditioning associated with a cooling tower? yes □ no □ don't know □

Are there temporary remedial works (i.e. road etc) near to your work? yes □ no □ don't know □

At approximately what distance from your place of work?

How do you make the journey between home and work?

On foot □, by car □, public transport □, other (example car plus train), don't know □

Can you share details about your normal route to work from place of residence? (Roads normally used, extraordinary deviations from typical route in 14 days prior to onset of symptoms)

Travelling to work, do you pass (f yes please provide specific geographical detail about areas and/or roads):

- **through urban areas?** yes □ no □ don't know □
- **industrial areas?** yes □ no □ don't know □
- **biological treatment plants?** yes □ no □ don't know □
- **temporary works (such as road maintenance etc)?** yes □ no □ don't know □

<u>If yes</u>, what type (construction, excavation)?

4) Leisure activities

During the 14 days before your first day of illness, have you done any gardening? yes □ no □ don't know □

<u>If yes</u>, what type?

- **Watering with hose pipe:** yes □ no □ don't know □
- **Handling soil or compost:** yes □ no □ don't know □
- **Have you used a water spray for treating plants (inside or outside)?** yes □ no □ don't know □

During the 14 days before your first day of illness, have you washed your car yes □ no □ don't know□

<u>If yes</u>, was this at home or at a car-wash? <u>If car-wash</u>, please state place and date:

During the 14 days before your first day of illness, have you been in contact with water systems such as:

System	Yes	No	Not sure	<u>If yes</u>, address and date of contact
Pressure/jet washers				
Water jets, fountains				
Showers away from residential and work setting				
Water sports (swimming, canoeing)				
Aquagym				
Jacuzzi/spa pool/thermal bath				
Sprayer or humidifier in public areas (service station, train station..)				

During the 14 days, have you visited

Venue	Yes	No	Not sure	<u>If yes</u>, addresses and dates of contact
A sports club				
A sports stadium				
A swimming pool				
Public baths				
Dentist				
Petrol Service Station				
A park with water games				
An exhibition or fair with water				
Any other place with water emission				
Any place where thermal water has been aerosolised?				
A shopping centre				
Other shopping outlet				
An industrial unit with cooling towers				

A Biological treatment plant				

5) Person's residence

Do you live in a: house □, block of flats □, Other □ please state:

If you live in a block of flats, is the hot water production of your home: individual □, collective □, not known □

Is the source of your domestic water: municipal □, individual (*e.g.* well) □, mixed □, not known □

<u>If individual</u>, is it from: a well □ a channel? □ don't know □

In your bathroom, is the hot water from:

- **Storage tank** yes □ no □ don't know □
- **Instant production (boiler, immersion)** yes □ no □ don't know □
- **Other** yes □ no □ **<u>if yes</u>, please state**:

Do you have air-conditioning at home yes □ no □ don't know □

<u>If yes</u>, was it used for at least on day during this period? yes □ no □ don't know □

Have you used a nebuliser at home? yes □ no □ don't know □

During the period, have you had any cuts to your water supply to your house? yes □, no □, not known □

Have there been any works/construction/excavation near to your house (i.e. same street)?

<u>If yes</u>, which type (construction/excavation)?

And at what distance from your house (or give road name)?

Is your house near an industrial unit, which produces fumes? yes □, no □, not known □

<u>If yes,</u> which factory and what does it produce?: Town:

6) Summary table of cases activities in the 14 days BEFORE onset of symptoms. Please complete as accurately as possible

Day	DATE (count back 14 days from start of illness)	MORNING	AFTERNOON	EVENING
14				
13				
12				
11				
10				
9				
8				
7				
6				
5				
4				
3				
2				
1				
Start				

D) Epidemiological links to other cases

Do you know people near to you who have recently been hospitalised with pneumonia? yes □, no □, not known □

<u>If yes</u>, please state which hospital

(Interviewer/outbreak control team to complete following parts, if necessary)

Have any other legionellosis cases visited the same places or areas within a period of 2 years? yes □ no □

<u>If yes</u>, give case numbers: date of symptom onset: (dd/mm/yyyy)

Summary of common areas/numbers exposed	Number exposed	Number of people with possible symptoms of pneumonia	Number of confirmed cases of Legionnaires' disease
Living/staying at same residence			
Visiting residence			
Working at same site			
Staying/visiting same temporary location (hospital/leisure sites etc)			

Other notes/comments:

Appendix G

Supplementary materials from Chapter 9

Legionnaires' disease – a qualitative study on Swiss physicians' approaches to the diagnosis and treatment of community-acquired pneumonia

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Appendix: Supplementary material

Details on antibiotic treatment

Recommendations for Community-acquired pneumonia (CAP) in Switzerland at the time of the study were to treat mild outpatient cases with Amoxiciline/Clavulanate or Doxycycline [51]. Moderately ill, hospitalised patientsshould be treatedwith Amoxiciline/Clavulanate +/– Clarithromycine. Severecases, admitted to the ICU shouldreceive Ceftriaxone + Clarithromycine. If *Legionella* spp. has been identified the patients should be treated with a macrolide or quinolone. Treatment is recommended to last at least 14 days for *Legionella* spp., but shorter duration are possible if the patient is afebrile. The Swiss guideline published by the Swiss Society of Infectious Diseases in 2006 is based on the European Respiratory Society (ERS) / European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines from 2005 [9, 10]. The ERS/ESCMID guidelines were updated in 2011 and recommendations slightly changed: Newer broad-spectrum antibiotics (such as Amoxiciline/Clavulanate) are reserved for thirdline treatment when the traditional well-known agents cannot be used [50]. For *Legionella* spp. treatment respiratory quinolones should be preferred over macrolides. The newest update of the S3 guideline, which was conceived together with the SSI, recommends a macrolide for all cases of severe pneumonia, which can be discontinued afterthree days and clinical stabilisation of the patient if no atypical pathogen could be identified [14]. Confirmed Legionnaires' disease cases should be treated with a quinolone. Treatment duration as short as five days might be possible.

Most of the physicians in our study mentioned antibiotic prescriptions in line with these recommendations. Nine different antibiotics belonging to four different antibiotic classes were named by the physicians for treating pneumonia: β-lactams, quinolones, macrolides and tetracycline. Macrolides were most often mentioned for Legionnaires' disease treatment – few physicians also mentioned their adverse effects. As GPs stated to hardly perform diagnostic tests, they were more in favour for empirical treatment with broad-spectrum antibiotics for patients presenting with pneumonia. GPs most frequently reported initiating treatment with β-lactams such as amoxicillin and penicillin. If the patient's clinical condition would not improve, clarithromycin is added. Yet, also a considerable number of GPs mentioned macrolide and quinolone treatment. In a hospital setting, macrolide and quinolone treatment prevailed.

Appendix H

Supplementary materials from Chapter 10

Impacts of weather and air pollution on Legionnaires' disease in Switzerland: a national case-crossover study

Fabienne B. Fischer[1,2,†], Apolline Saucy[3,†], Danielle Vienneau[1,2], Jan Hattendorf[1,2], Julia Fanderl[1,2], Kees de Hoogh[1,2], Daniel Mäusezahl[1,2]

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Short-term impacts of weather and air pollution on Legionnaire's disease in Switzerland: A national case-crossover study

Fabienne B. Fischer, Apolline Saucy, Julia Fanderl, Danielle Vienneau, Jan Hattendorf, Kees de Hoogh, and Daniel Mäusezahl

1 Supplementary material

Table S1 Overview of different exposure data sources and resolution included in the ecological model.

Dataset	Source	Year	Resolution
Compost facilities	CVIS, FOEN	2020 (CVIS), 2013 (FOEN)	N per district
Land use	FSO	2004	Percentage covered by agriculture, industry, settlement, unproductive area
Weather	MeteoSwiss	2017-2020	3-month mean of June, July, August by district
WWTP	FOEN	2020	N per district
SwissTLM	swisstopo	2016	N per district Total shoreline length (minus lake islands) Total river length (over ground)
Population density			
…per district	FSO	2018	1,000 people per km^2
…per settled area	FSO	2018	1,000 people per km^2 settled area
Age of population	FSO	2018	Mean population age per district
Swiss-SEP	SNC	2017	Mean Swiss-SEP per district
Air pollution	Meteotest	2017	Population-weighted mean $PM_{2.5}$ and NO_2 concentrations per district based on 200m^2 grid
Urbanisation	FSO	2017	Categories: densely populated areas, intermediate density areas and sparsely populated areas [212].

CVIS: Composting Inspectorate

FOEN: Federal Office for the Environment

FSO: Swiss Federal Statistical Office

MeteoSwiss: Federal Office of Meteorology and Climatology

N: Number

SNC: Swiss National Cohort

SwissTLM: Swiss topographic landscape model

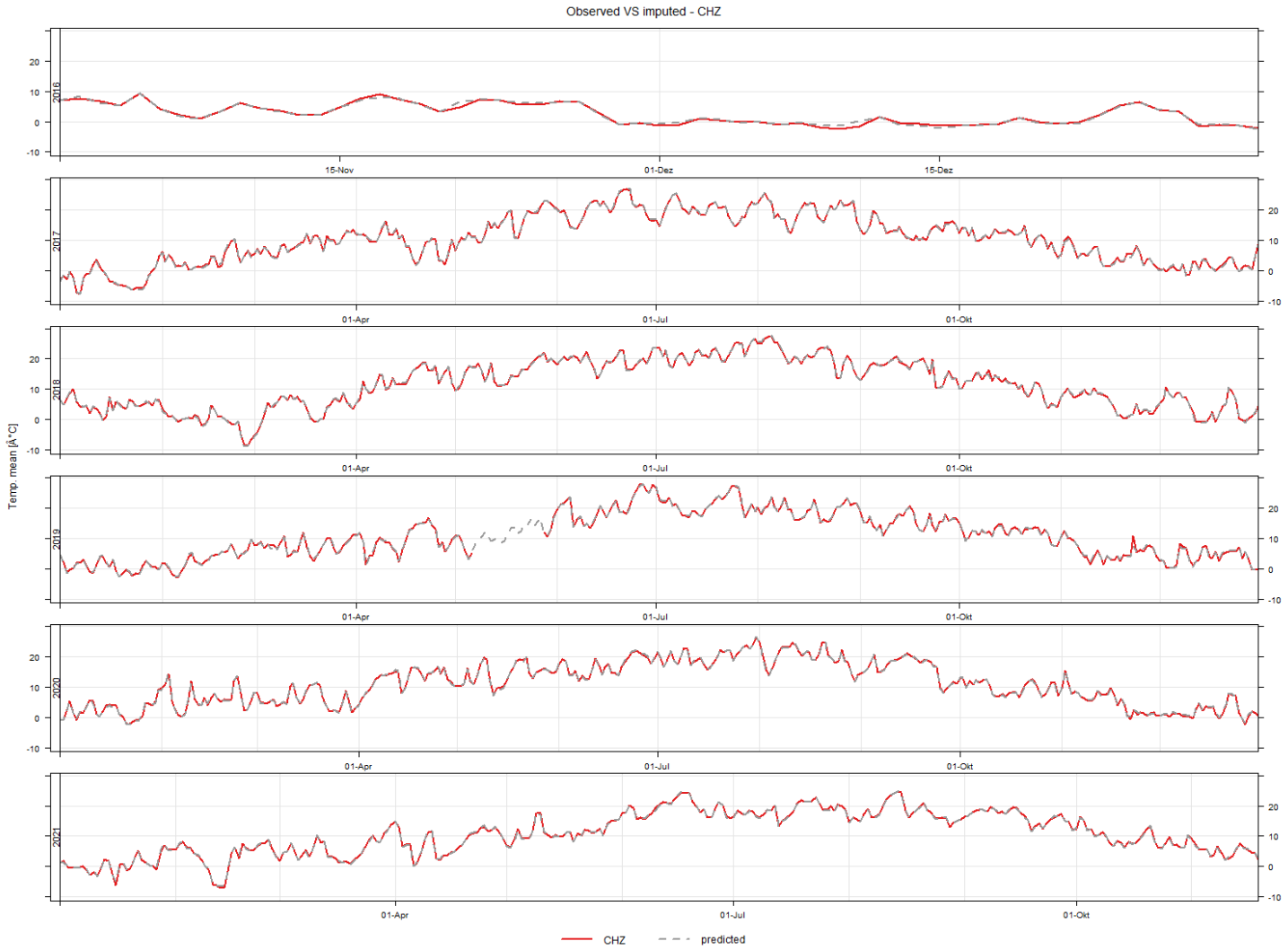

Figure S1 Illustrative example of the measured (continuous red line) versus imputed (dotted grey line) values of mean temperature over time (Nov 2016-Nov 2021) at one monitoring station (CHZ).

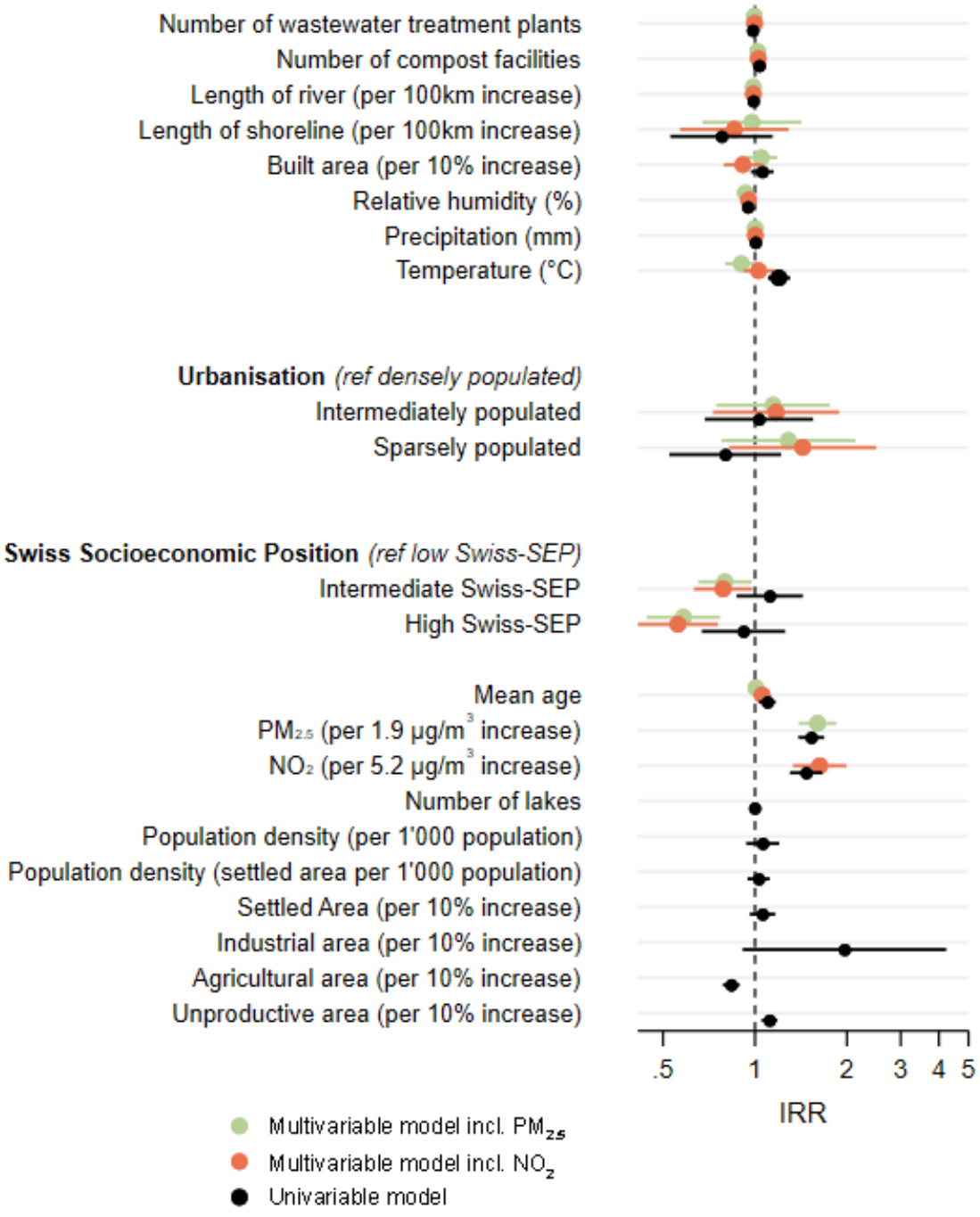

Figure S2 Incidence rate ratios (IRR) of the univariable and multivariable negative binomial regression analyses of exposure sources and determinants on Legionnaire's disease occurrence per district, 2017-2020.

Table S2 Summary statistics of the data availability and model performance for missing data imputation for each parameter for the case-crossover analysis, 2017-2021.

Parameter	**Mean R^2**	**Min. R^2**	**Max. R^2**	**Mean aR^2**	**Min. aR^2**	**Max. aR^2**	**Predictor stations (N)**	**Stations to predict (N)**	**Data availability threshold (%)**	**Total stations (N)**
Temperature (max)	0.991	0.968	0.998	0.990	0.966	0.997	82	24	80	106
Temperature (mean)	0.996	0.990	0.999	0.996	0.990	0.999	81	25	80	106
Temperature (min)	0.987	0.978	0.996	0.987	0.977	0.996	82	24	80	106
Rel. humidity (max)	0.728	0.336	0.884	0.719	0.314	0.880	55	51	80	106
Rel. humidity (mean)	0.938	0.883	0.971	0.935	0.877	0.970	79	27	80	106
Rel. humidity (min)	0.907	0.817	0.962	0.902	0.809	0.960	79	27	80	106
Precipitation	0.837	0.681	0.949	0.833	0.673	0.948	41	130	75	183
Vapour pressure	0.993	0.979	0.997	0.993	0.978	0.997	78	28	80	106
Wind speed	0.886	0.755	0.964	0.881	0.742	0.962	82	25	80	108
Max. gust	0.780	0.405	0.909	0.774	0.389	0.907	43	64	80	108
Atmospheric pressure	0.999	0.990	1.000	0.999	0.989	1.000	90	10	80	100
Summary statistics										
Mean	0.913	0.798	0.966	0.910	0.791	0.965				
Min	0.728	0.336	0.884	0.719	0.314	0.880				
Max	0.999	0.990	1.000	0.999	0.990	1.000				

Table S3 Descriptive statistics for weather conditions at station level in Switzerland from 1 November 2016 to 19 November 2021. The table shows the completed dataset using measured and imputed values. As summer, we defined June to August, and for winter December to February.

	Central Switzerland		Eastern Switzerland		Espace Mittelland		Lake Geneva Region		Northwestern Switzerland		Zurich		Ticino	
	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter
Daily mean temperature [°C] (N=105)														
Mean (SD)	17.7 (4.1)	1.2 (4.3)	18.1 (3.7)	0.9 (4.4)	17.3 (4.0)	1.0 (4.4)	17.8 (3.9)	1.0 (4.5)	19.6 (3.2)	2.6 (3.9)	18.5 (3.7)	1.64 (4.2)	18.7 (4.8)	1.8 (4.4)
Median (Min, Max)	18.0 (1.0, 28.1)	1.2 (-21.7, 17.2)	18.3 (2.8, 29.5)	0.9 (-21.0, 18.2)	17.0 (1.7, 28.6)	1.1 (-20.6, 15.9)	17.9 (4.7, 28.9)	1.2 (-18.7, 16.6)	19.6 (10.0, 29.1)	2.2 (-10.5, 13.8)	18.6 (7.0, 27.8)	1.5 (-15.3, 13.8)	19.6 (2.9, 29.6)	2.2 (-18.1, 15.1)
Daily mean relative humidity [%] (N=105)														
Mean (SD)	75.9 (11.1)	83.3 (14.2)	73.4 (11.5)	80.3 (15.3)	74.3 (11.3)	82.2 (14.6)	69.3 (11.9)	77.9 (14.7)	71.7 (11.5)	84.3 (10.8)	71.2 (12.3)	81.9 (13.2)	70.2 (13.1)	67.8 (20.7)
Median (Min, Max)	75.9 (34.5, 100.0)	86.4 (9.2, 100.0)	73.8 (27.0, 100.0)	83.3 (14.1, 100.0)	74.4 (30.8, 100.0)	85.7 (6.2, 100.0)	68.90 (24.1, 100.0)	80.9 (14.1, 100.0)	71.8 (36.5, 100.00)	86.2 (38.3, 100.0)	71.3 (40.8, 100.0)	84.5 (14.1, 100.0)	70.7 (24.9, 100.0)	70.3 (10.6, 100.0)
Daily total precipitation [mm] (N=162)														
Mean (SD)	5.3 (9.9)	3.3 (7.2)	4.3 (9.1)	2.8 (6.7)	3.9 (8.0)	2.9 (6.1)	3.1 (6.8)	3.0 (7.0)	3.3 (6.9)	2.8 (5.7)	4.0 (8.4)	2.9 (6.1)	5.4 (15.7)	2.2 (7.8)
Median (Min, Max)	0.1 (0, 9.8)	0 (0, 96.3)	0 (0, 106.5)	0 (0, 128.6)	0 (0, 82.3)	0 (0, 79.4)	0 (0, 8.6)	0 (0, 116.2)	0 (0, 72.5)	0 (0, 66.0)	0 (0, 71.1)	0 (0, 78.9)	0 (0, 185.4)	0 (0, 93.5)
Daily mean vapour pressure [hPa] [N=105]														
Mean (SD)	15.1 (2.9)	5.7 (1.7)	14.9 (3.0)	5.4 (1.7)	14.4 (2.8)	5.5 (1.8)	13.8 (2.9)	5.3 (1.8)	15.8 (2.6)	6.4 (1.7)	14.8 (2.5)	5.7 (1.6)	15.2 (4.2)	4.8 (1.9)
Median (Min, Max)	15.3 (4.2, 23.9)	5.7 (0.4, 13.2)	15.1 (5.3, 25.6)	5.4 (0.7, 13.2)	14.4 (4.3, 24.4)	5.50 (0.5, 13.6)	13.8 (4.0, 26.2)	5.2 (0.9, 12.0)	15.8 (8.3, 24.0)	6.1 (1.2, 13.2)	14.6 (6.9, 23.4)	5.6 (1.0, 11.5)	15.3 (3.6, 27.3)	4.7 (0.5, 11.3)
Daily mean wind speed (scalar) [m/s] (N=107)														
Mean (SD)	6.8 (3.1)	8.1 (6.8)	7.4 (3.1)	7.8 (6.1)	8.0 (5.1)	10.7 (10.1)	8.3 (3.8)	8.7 (6.8)	5.6 (2.4)	8.3 (6.0)	8.7 (4.3)	12.0 (8.7)	8.6 (5.7)	8.9 (8.3)
Median (Min, Max)	6.1 (1.1, 36.7)	5.4 (0.4, 51.5)	6.8 (1.4, 30.2)	5.8 (0, 49.7)	6.5 (1.1, 57.2)	7.2 (0.4, 78.8)	7.20 (1.8, 46.4)	6.1 (0, 51.8)	5.0 (1.1, 18.7)	6.8 (0.7, 45.7)	7.6 (1.8, 30.2)	9.4 (1.1, 58.7)	6.8 (1.8, 48.6)	5.8 (0, 60.8)
Daily gust peak (1 second) [m/s] (N=107)														
Mean (SD)	33.0 (15.8)	33.7 (25.2)	34.7 (13.6)	32.5 (20.5)	35.6 (14.9)	38.0 (25.6)	36.7 (13.8)	33.8 (20.5)	30.8 (12.0)	33.8 (20.3)	35.6 (14.9)	39.8 (23.8)	36.4 (15.9)	32.1 (21.6)
Median (Min, Max)	28.8 (6.1, 161.6)	23.8 (3.6, 195.1)	32.4 (7.9, 133.2)	26.3 (0, 139.0)	32.0 (9.0, 122.8)	30.2 (5.4, 183.6)	34.8 (9.0, 129.6)	28.4 (5.0, 147.6)	28.1 (8.3, 134.3)	29.2 (5.4, 147.6)	32.4 (11.2, 131.8)	34.6 (6.1, 163.1)	32.4 (7.6, 122.4)	25.2 (4.3, 133.6)
Atmospheric pressure (QFA) [hPa] (N=99)														
Mean (SD)	931.5 (49.1)	931.1 (52.5)	942.8 (41.7)	943.1 (44.9)	926.1 (46.3)	925.4 (49.7)	918.7 (47.7)	918.2 (51.1)	972.5 (11.5)	974.3 (15.6)	942.8 (28.2)	942.8 (31.5)	921.8 (71.1)	921.6 (75.7)
Median (Min, Max)	955.8 (776.5, 974.0)	948.7 (756.6, 988.8)	960.0 (798.4, 985.6)	959.0 (780.1, 1002.6)	948.5 (789.1, 981.2)	946.1 (768.5, 996.2)	929.0 (822.1, 980.1)	931.7 (805.0, 995.1)	976.3 (929.4, 988.8)	977.3 (912.2, 1004.0)	956.3 (873.5, 976.0)	955.0 (855.1, 990.7)	956.9 (768.8, 999.0)	959.9 (750.8, 1017.1)

Table S4 Output for simple conditional logistic regression for LD cases 2017-2021. Odds ratios and 95% confidence intervals for single-exposure and multi-exposure models for each weather variable (without NO_2). Due to collinearity, two models were constructed, once with temperature and the other with vapour pressure. All estimates stem from the mean temperature model (Model 1), except vapour pressure, which is based on the vapour pressure model (Model 2). The unit increase correspondence to the same increase from "center" to "value", that was used for the DLNM.

		Single-exposure		Multi-exposure	
Parameter	**Increase**	**OR**	**95% CI**	**OR**	**95% CI**
Temperature	20 °C	3.07	(1.92, 4.91)	2.92	(1.80, 4.71)
Relative humidity	19%	1.58	(1.37, 1.82)	1.39	(1.18, 1.64)
Precipitation	10 mm	1.46	(1.30, 1.63)	1.20	(1.05, 1.37)
Vapour pressure*	8.9 hPa	2.05	(1.58, 2.65)	1.89	(1.45, 6.56)
Wind speed	20 m/s	0.94	(0.61, 1.43)	.	
Maximal gust	20 m/s	0.94	(0.84, 1.06)	0.98	(0.87, 1.10)
Atmospheric pressure	22.2 hPa	0.45	(0.33, 0.62)	0.64	(0.46, 0.90)

*Model 2 instead of model 1

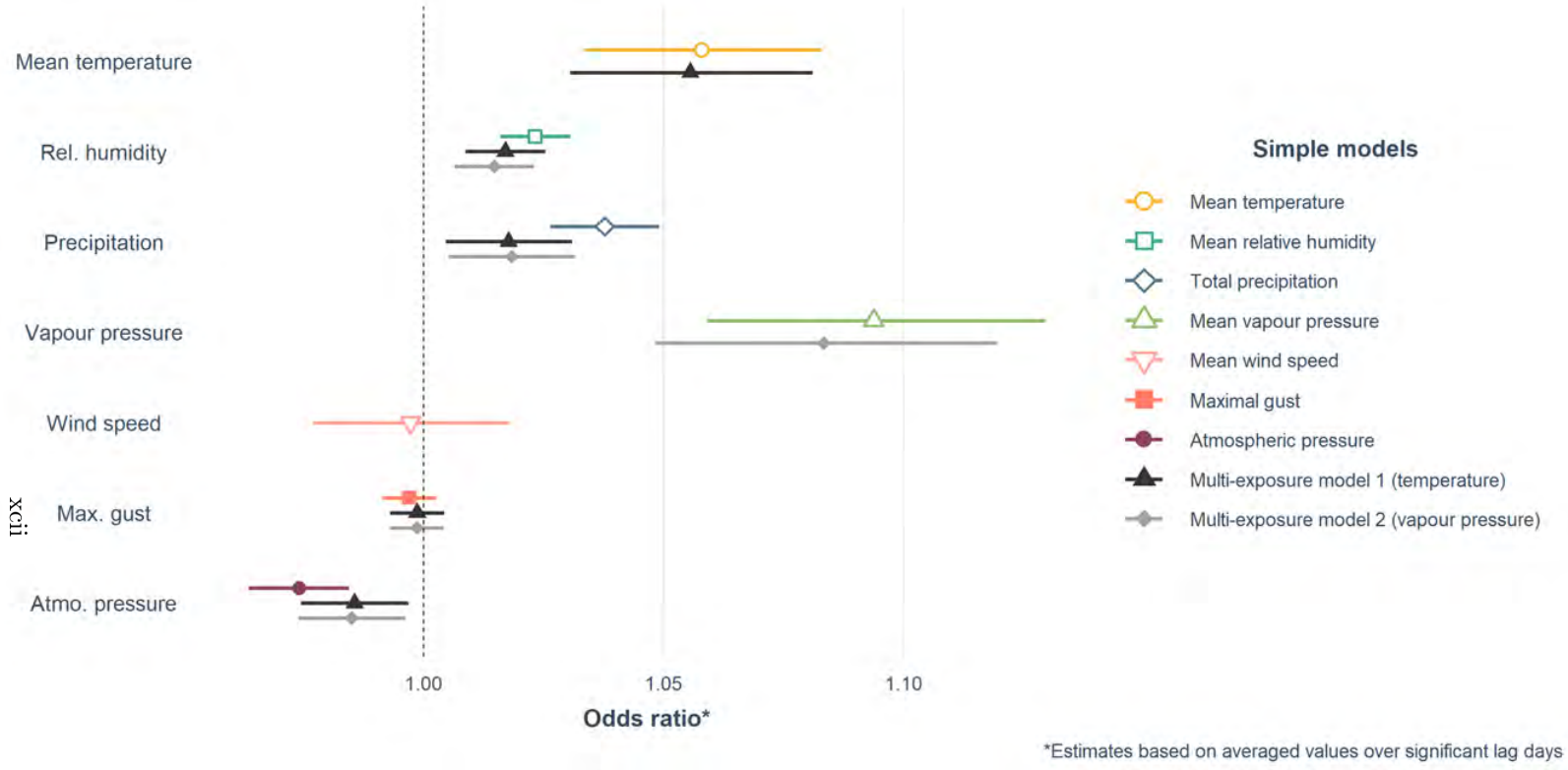

Figure S3 Forest plot showing the odds ratio and 95% confidence intervals from the single-exposure and both multi-exposure models for a single unit-increase.

Table S5 Output for DLNM models using conditional logistic regression for LD cases 2019. Odds ratios and 95% confidence intervals for single-exposure and multi-exposure models for each weather variable for data from 2019 only but in addition of mean daily NO_2. Due to collinearity, two models were constructed, once with temperature and the other with vapour pressure. All estimates stem from the mean temperature model (Model 1), except vapour pressure, which is based on the vapour pressure model (Model 2). The centre depicts the reference value selected for the prediction. The value depicts the value for which the overall odds ratio are estimates.

				Single-exposure		**Multi-exposure**	
Parameter	**Center**	**Value**	**Lag period**	**OR**	**95% CI**	**OR**	**95% CI**
Temperature	0 ℃	20 ℃	2-6 days	0.57	(0.2, 1.63)	1.22	(0.34, 4.36)
			6-14 days	1.49	(0.45, 4.88)	3.42	(0.58, 20.29)
			14-21 days	1.03	(0.31, 3.47)	2.46	(0.46, 13.08)
Relative humidity	0.762	0.952	2-6 days	**1.23**	**(1.00, 1.52)**	1.05	(0.77, 1.42)
			6-14 days	**1.75**	**(1.24, 2.47)**	1.17	(0.68, 2.01)
			14-21 days	1.04	(0.74, 1.47)	1.37	(0.82, 2.30)
Precipitation	0 mm	10 mm	2-6 days	1.04	(0.82, 1.34)	1.01	(0.73, 1.38)
			6-14 days	**1.69**	**(1.12, 2.54)**	1.63	(0.96, 2.77)
			14-21 days	0.99	(0.66, 1.49)	0.81	(0.45, 1.45)
Vapour pressure*	9.2 hPa	18.1 hPa	2-6 days	0.99	(0.71, 1.40)	1.03	(0.71, 1.50)
			6-14 days	1.13	(0.61, 2.07)	1.32	(0.67, 2.60)
			14-21 days	1.05	(0.58, 1.91)	1.35	(0.68, 2.66)
Wind speed	0 m/s	20 m/s	2-6 days	0.82	(0.43, 1.59)	.	
			6-14 days	0.58	(0.19, 1.73)	.	
			14-21 days	0.88	(0.30, 2.53)	.	
Maximal gust	0 m/s	20 m/s	2-6 days	0.91	(0.77, 1.07)	0.92	(0.72, 1.17)
			6-14 days	0.91	(0.68, 1.21)	0.93	(0.63, 1.38)
			14-21 days	0.97	(0.73, 1.29)	1.16	(0.78, 1.73)
Atmospheric pressure	964.6 hPa	986.8 hPa	2-6 days	1.03	(0.70, 1.53)	0.63	(0.33, 1.18)
			6-14 days	0.59	(0.33, 1.09)	**0.29**	**(0.10, 0.89)**
			14-21 days	0.87	(0.44, 1.7)	0.40	(0.14, 1.11)
NO_2	16.5 µg/m3	37.3 µg/m3	2-6 days	0.72	(0.44, 1.17)	1.00	(0.38, 2.65)
			6-14 days	0.76	(0.44, 1.34)	1.58	(0.52, 4.82)
			14-21 days	1.14	(0.56, 2.32)	2.50	(0.74, 8.43)

*Model 2 instead of model 1

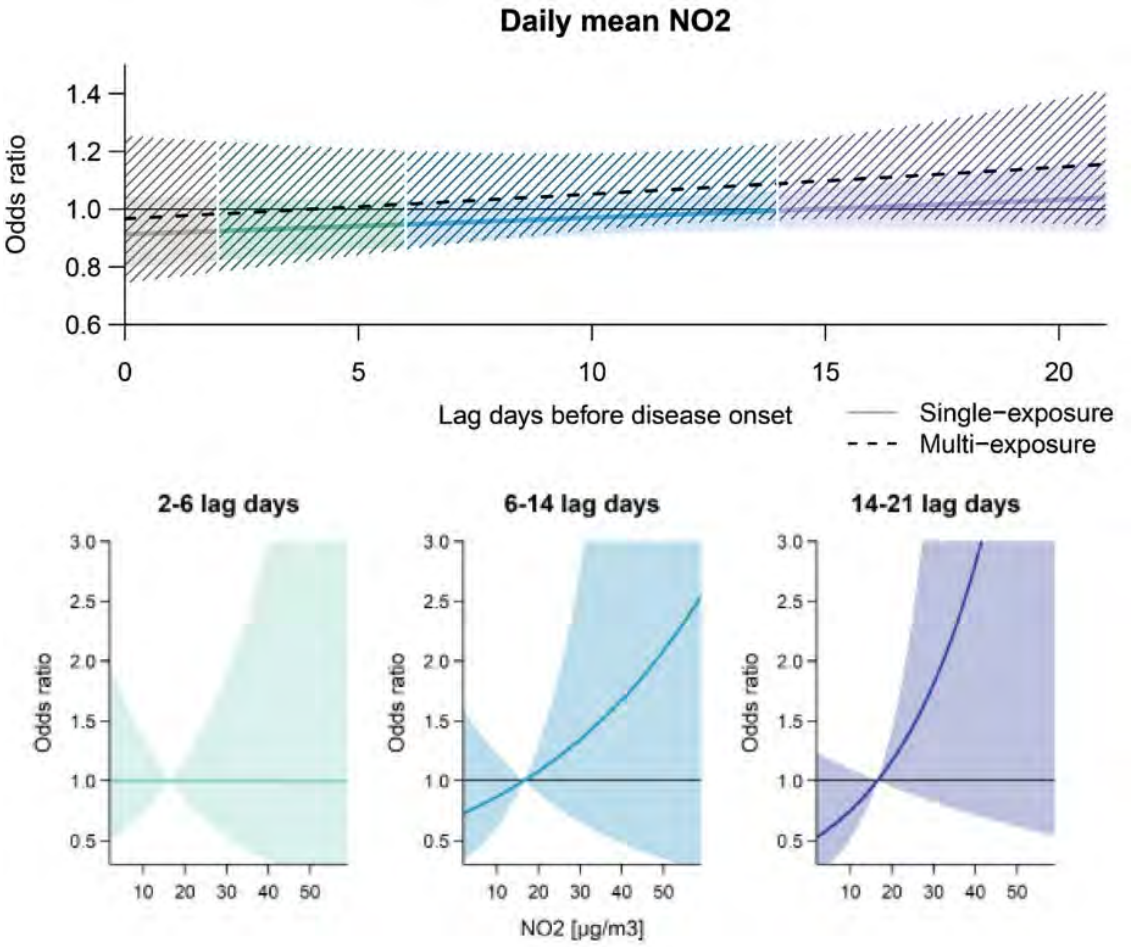

Figure 4 DLNM model output for daily mean NO_2 level for the year 2019. The upper figure depicts the lag structure across 21 days before the Legionnaires' disease onset. The lower figure depicts the overall odds ratio (OR) for three exposure windows: early incubation (lag 2-6), late incubation (lag 6-14) and before incubation (lag 14-21). The multi-exposure models included daily mean relative humidity, daily total precipitation, daily maximal gust peak and daily mean atmospheric pressure (QFE) and either daily mean temperature or daily mean vapour pressure, as well as a term adjusting for regional school holidays.

Table S6 Output for DLNM models using conditional logistic regression for LD cases excluding Ticino 2017-2021. Odds ratios and 95% confidence intervals for single-exposure and multi-exposure models for each weather variable for all cases excluding Ticino (and without NO_2). Due to collinearity, two models were constructed, once with temperature and the other with vapour pressure. All estimates stem from the mean temperature model (Model 1), except vapour pressure, which is based on the vapour pressure model (Model 2). The centre depicts the reference value selected for the prediction. The value depicts the value for which the overall odds ratio are estimates.

				Single-exposure		Multi-exposure	
Parameter	Center	Value	Lag period	OR	95% CI	OR	95% CI
Temperature	0 °C	20 °C	2-6 days	1.22	(0.76, 1.95)	1.48	(0.9, 2.43)
			6-14 days	**2.03**	**(1.34, 3.75)**	3.36	(1.93, 5.85)
			14-21 days	**1.77**	**(1.09, 2.87)**	1.47	(0.85, 2.55)
Relative humidity	0.762	0.952	2-6 days	1.11	(0.98, 1.23)	1.04	(0.89, 1.21)
			6-14 days	**1.52**	**(1.26, 1.83)**	**1.33**	**(1.02, 1.74)**
			14-21 days	0.88	(0.74, 1.04)	0.96	(0.74, 1.23)
Precipitation	0 mm	10 mm	2-6 days	**1.20**	**(1.06, 1.36)**	1.12	(0.95, 1.32)
			6-14 days	**1.92**	**(1.54, 2.38)**	**1.58**	**(1.19, 2.10)**
			14-21 days	1.16	(0.95, 1.41)	1.24	(0.95, 1.62)
Vapour pressure*	9.2 hPa	18.1 hPa	2-6 days	1.12	(0.97, 1.30)	1.09	(0.93, 1.28)
			6-14 days	**1.83**	**(1.43, 2.33)**	**1.66**	**(1.28, 2.14)**
			14-21 days	**1.27**	**(0.99, 1.63)**	1.24	(0.95, 1.61)
Wind speed	0 m/s	20 m/s	2-6 days	0.97	(0.70, 1.34)	.	
			6-14 days	0.86	(0.49, 1.51)	.	
			14-21 days	0.93	(0.55, 1.59)	.	
Maximal gust	0 m/s	20 m/s	2-6 days	0.98	(0.89, 1.07)	0.95	(0.85, 1.07)
			6-14 days	1.00	(0.86, 1.16)	0.92	(0.76, 1.11)
			14-21 days	0.99	(0.85, 1.15)	0.98	(0.82, 1.18)
Atmospheric pressure	964.6 hPa	986.8 hPa	2-6 days	1.04	(0.86, 1.26)	0.98	(0.77, 1.24)
			6-14 days	0.67	(0.48, 0.91)	0.76	(0.52, 1.12)
			14-21 days	0.96	(0.69, 1.33)	0.98	(0.66, 1.46)

*Model 2 instead of model 1

Appendix I

Supplementary materials from Chapter 12

Legionnaires' disease in Switzerland: Rationale and study protocol of a prospective national case-control and molecular source attribution study (*SwissLEGIO*)

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Supplementary information: Legionnaires' disease in Switzerland: Rationale and study protocol of a prospective national case-control and molecular source attribution study (*SwissLEGIO*)

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Protocol for sampling of standard household water samples

Kitchen tap; collection of first liter; cold and warm water mixed

- ❒ Determine how cold and hot water are mixed
- ❒ With an open 1-L glass bottle with narrow opening directly below the outlet, open the cold and hot outlet(s) to get approximately equal proportion of cold and hot water flowing through the outlet and fill the bottle

  Note: Open the outlet to medium flow rate (it should take approx. 5 s to fill the sample bottle)
- ❒ Remove the sample bottle from the flow (set aside) and immediately collect 250 mL in the 1000 mL plastic beaker (you may quickly turn off the water in between)
- ❒ Turn off the fixture
- ❒ Firmly close the sampling bottle, turn bottle twice upside down to mix the thiosulfate
- ❒ Read and record sample temperature in the beaker with 250 mL (highest temperature that is reached on the display)

Most used shower; collection of first liter from (most used) shower **through the shower head**; cold and warm water mixed

- ❒ Determine how cold and hot water are mixed
- ❒ Do not remove the shower head from the shower hose
- ❒ If the shower head is too large to direct all the water into the 1-L wide-mouth glass bottle, use a UV irradiated plastic bag to act as a funnel to direct the water into the sampling bottle
- ❒ With the shower head (or funnel if needed) directed into an open 1-L wide-mouth glass bottle, open the cold and hot outlet(s) to get approximately equal proportion of cold and hot water flowing through the outlet and fill the bottle

  Note: Open the outlet to medium flow rate (it should take approx. 5 s to fill the sample bottle)
- ❒ Switch the shower head from the 1 L sample bottle to the 1000 mL beaker and collect 250 mL (you may quickly turn off the water in between)
- ❒ Turn off the fixture
- ❒ Firmly close the sampling bottle, turn bottle twice upside down to mix the thiosulfate

- ❒ Read and record sample temperature in the beaker with 250 mL (highest temperature that is reached on the display)

Most used shower (same sampling location as for Sample B); composite sample of 100 ml from every subsequent 1L from the cold water line **through the existing shower hose**

- ❒ Remove the shower head
- ❒ Set water handle to cold position
- ❒ Turn on the tap and flush for 5 seconds, adjust flow rate so that a 100 mL bottle can be filled without splashing.
- ❒ Take sequential 100 mL samples – repeat 10 times in total so that a composite of 1 L water is collected in one autoclaved 1-L wide-mouth glass bottle:
    a) Collect 100 ml cold water via shower hose into one of the 100 mL autoclaved glass bottles.
    b) Move the hose to the plastic beaker and immediately collect 900 mL into the beaker
    c) Turn off the cold water
    d) Transfer the 100 mL from the 100 mL bottle to the autoclaved 1-L wide-mouth glass bottle
    e) **For the 1st, 2nd and 4th liter**: Measure and record water temperature in the beaker
- ❒ Firmly close the sampling bottle, turn bottle twice upside down to mix the thiosulfate
- ❒ Turn on the cold water to the maximum flow rate. Continue flushing cold water until water temperature no longer changes.

  Note: Coldwater temperature may continually decreases for long periods. Therefore flush the cold water until it is not changing by more than 0.1 °C for approx. 20 s or after a total time of 2 minutes flushing (whichever occurs first) and document it
- ❒ measure and record the amount of time required to reach steady temperature
- ❒ measure and record water temperature at steady state
- ❒ Continuing flushing the cold water (meaning: do not turn off the water between temperature and flow rate measurements) and measure the water flow rate: record the amount of time it takes to fill the 1000 mL (repeat to have 3 measurements in total)

Most used shower (same sampling location as for Sample B); composite sample of 100 ml from every subsequent 1 L sample from the hot water line

➔ If the shower hose was collected, this sample will be collected through the spout where the existing shower hose was installed.

➔ If the shower hose was not collected, this sample will be collected through the existing shower hose

- ❒ Set water handle to hot position
- ❒ Turn on the tap and flush for 5 seconds, adjust flow rate so that a 100 mL bottle can be filled without splashing.
- ❒ Take sequential 100 mL samples – repeat 10 times in total so that a composite of 1 L water is collected in one autoclaved 1-L wide-mouth glass bottle:
    f) Collect 100 ml hot water into one of the 100 mL autoclaved glass bottles.

g) Move the hose to the plastic beaker and immediately collect 900 mL into the beaker

Note: Here you can increase the flowrate when filling the beaker with 900 mL water to save some time during the sampling,

h) Turn off the hot water

i) Transfer the 100 mL from the 100 mL bottle to the autoclaved 1-L wide-mouth glass bottle

j) **For the 1st, 2nd, 4th and 10th liter:** Measure and record water temperature in the beaker

- ❒ Turn on the hot water to the maximum flow rate. Continue flushing hot water until water temperature no longer changes.

  Note: Flush the hot water until it is not changing by more than 0.1 °C for approx. 20 s or after a total time of 2 minutes flushing (whichever occurs first) and document it.

- ❒ Measure and record the amount of time required to reach steady temperature
- ❒ Measure and record water temperature at steady state
- ❒ Continuing flushing the hot water (meaning: do not turn off the water between temperature and flow rate measurements) and measure the water flow rate: record the amount of time it takes to fill the 1000 mL (repeat to have 3 measurements in total)
- ❒ Flush cold water over the sampling bottle to bring it below 50 °C (if applicable, depending on hot water temperature) to cool the sample down sufficiently such that it is not disinfected during transport.

Second used shower (if applicable); collection of first liter from shower **through the shower head**; cold and warm water mixed

- ❒ If the shower head is too large to direct all the water into the 1-L wide-mouth glass bottle, use a UV irradiated plastic bag to act as a funnel to direct the water into the sampling bottle
- ❒ With the shower head (or funnel if needed) directed into an open 1-L wide-mouth glass bottle, open the cold and hot outlet(s) to get approximately equal proportion of cold and hot water flowing through the outlet and fill the bottle

  Note: Open the outlet to medium flow rate (it should take approx. 5 s to fill the sample bottle)

- ❒ Switch the shower head from the 1 L sample bottle to the 1000 mL beaker and collect 250 mL (you may quickly turn off the water in between)
- ❒ Turn off the fixture
- ❒ Firmly close the sampling bottle, turn bottle twice upside down to mix the thiosulfate
- ❒ Read and record sample temperature in the beaker with 250 mL (highest temperature that is reached on the display)
- ❒ Discard the 250 mL water into the bathtub/shower

Additional measurements at the kitchen tap; constant hot water temperature and flow rate

- ❒ Turn on the hot water of the kitchen tap to the maximum flow rate. Continue flushing hot water until water temperature no longer changes.

  Note: Flush the hot water until it is not changing by more than 0.1 °C for approx. 20 s or after a total time of 2 minutes flushing (whichever occurs first) and document it.

- ❒ Measure and record the amount of time required to reach steady temperature

Note: You may use the stop watch and always switch it on 5 to 10 seconds before you open the tap and subtracts this time at the end when recording the time on the paper form.

- ❒ Measure and record water temperature at steady state
- ❒ Continuing flushing the hot water (meaning: do not turn off the water between temperature and flow rate measurements) and measure the water flow rate: record the amount of time it takes to fill the 1000 mL (repeat to have 3 measurements in total)

Appendix J

Contribution in the 'BAG-Bulletin'

Zeitliche Entwicklung und Einfluss verschiedener Faktoren auf die räumliche Verteilung der Legionärskrankheit in der Schweiz

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This article has been a contribution in the 'BAG-Bulletin' (3/2022) summarising the work presented in Chapter 10. The BAG-Bulletin is published weekly by the FOPH in French and German. We provide here the German version.

Zeitliche Entwicklung und Einfluss verschiedener Faktoren auf die räumliche Verteilung der Legionärskrankheit in der Schweiz

Die Legionärskrankheit ist eine schwere Form von Lungenentzündung, die durch das Einatmen des Bakteriums *Legionella* spp. verursacht wird. Die wichtigsten Infektionsquellen in der Schweiz und Gründe für die Häufung von Erkrankungen sind noch weitgehend unbekannt. Die Meldezahlen der letzten zwei Jahrzehnte zeigen eine Verfünffachung der schweizweiten Fallzahlen und eine Häufung von Legionärskrankheitsfällen im Süden der Schweiz auf. Eine Analyse der Fallzahlen auf Bezirksebene bezüglich möglicher Faktoren, welche die Melderate beeinflussen, deuten auf einen Einfluss der Bevölkerungszusammensetzung und auf Umweltfaktoren, wie Luftverschmutzung, hin.

1. EINFÜHRUNG

Die Legionärskrankheit ist eine schwere Form von Lungenentzündung, verursacht durch Bakterien der Gattung *Legionella* spp. Die Ansteckung erfolgt hauptsächlich über das Einatmen von zerstäubten Wassertröpfchen (Aerosole), die Legionellen enthalten. Bestätigte Infektionen mit Legionellen sind seit Dezember 1987 meldepflichtig und müssen über das obligatorische Meldesystem den kantonalen Gesundheitsämtern und dem Bundesamt für Gesundheit (BAG) gemeldet werden. Die jährlichen Fallzahlen haben sich in den letzten zehn Jahren mehr als verdoppelt und erreichten mit 567 Fällen im Jahr 2018 einen Höchstwert; im Jahr 2019 wurden 530 und 2020 435 Fälle gemeldet [1]. Die Fallzahlen und Melderaten sind regional sehr unterschiedlich. Die Gründe für die Zunahme der Häufigkeiten und deren regionaler Verteilung sind weitestgehend unbekannt. *Legionella* spp. kommen natürlicherweise in fast allen wässerigen und feuchten Umgebungen vor. Da die Bakterien sich in 25–45° C warmem, stehendem Wasser am besten vermehren, kommen sie auch in von Menschen geschaffenen Wassersystemen, zum Beispiel in Duschen, Whirlpools und Kühltürmen, vor [2]. Die Identifizierung der Infektionsquellen ist jedoch schwierig und gelingt auch in Ausbruchsuntersuchungen selten [3]. Über 80% der Fälle treten jedoch sporadisch, d. h. als Einzelfälle, auf [2]. Zusammen mit den spezifischen Herausforderungen beim Nachweis der Legionellen und dem verbreiteten Vorkommen der Bakterien in der Umwelt sind nur selten gesicherte Rückschlüsse auf die Infektionsquellen möglich. Das Infektionspotenzial vieler vermuteter Quellen, wie Abwasseranlagen und Kompostieranlagen, bleibt damit weitgehend unbekannt. Deshalb hat das Schweizerische Tropen- und Public Health Institut im Auftrag des BAG Legionellose-Fälle der letzten Jahre auf deren räumliche Verteilung bezüglich möglicher Infektionsquellen in der Umwelt hin untersucht sowie die zeitliche Entwicklung der Fallzahlen analysiert.

2. METHODEN

Zeitliche und räumliche Analysen wurden durchgeführt. Die Auswirkungen der Covid-19-Pandemie im Jahr 2020 wurden mittels einer «Interrupted time series»-Analyse untersucht. Der Einfluss potenzieller Infektionsquellen, umwelt- und bevölkerungsbezogener Faktoren, wurde ebenfalls untersucht. Dazu wurden die Daten auf Bezirksebene aggregiert und der Einfluss der Faktoren mittels einer Regressionsanalyse ermittelt. Diese Analyse erlaubt eine Übersicht über mögliche Zusammenhänge von Expositionen und Krankheitshäufigkeit, ermöglicht aber keine Schlussfolgerungen auf das Krankheitsrisiko einer Einzelperson.

3.3 RESULTATE UND DISKUSSION

3.1 Demografie der Fälle der letzten Jahre

Zwischen Januar 2017 und Dezember 2020 wurden 1603 sichere oder wahrscheinliche Legionärskrankheitsfälle registriert, welche die Einschlusskriterien der Studie erfüllten. Die Erkrankung betraf mehrheitlich Männer (69,1%). Das Durchschnittsalter aller Fälle betrug 65 Jahre (Bereich 17–99), der Altersmedian lag bei 66 Jahren. Der Grossteil der Fälle war zum Zeitpunkt der Meldung hospitalisiert (88,6%). Zum Meldezeitpunkt waren 73 Patientinnen bzw. Patienten bereits verstorben (4,6%). Eine Analyse der Fallzahlen der Legionärskrankheit bis ins Jahr 2017 wurde in einer früheren Ausgabe des BAG-Bulletins veröffentlicht [4].

3.2 Zeitliche Verteilung der Fälle (2000–2020)

Die Melderaten der Legionärskrankheit stiegen um mehr als das Fünffache von 0,9 Fällen pro 100 000 Einwohnerinnen und Einwohner im Jahr 2000 auf 5.0/100 000 im Jahr 2020 an. Nach einem Höchstwert im Jahr 2018 (6,3/100 000 Einwohnerinnen und Einwohner) sind die Melderaten in den Jahren 2019 und 2020 zurückgegangen. Die meisten europäischen Länder verzeichneten ebenfalls einen Anstieg der Fälle in den letzten Jahren, jedoch weist die Schweiz eine der höchsten Melderaten auf [5]. Global präsentiert sich ein starkes saisonales Muster mit den höchsten wöchentlichen Melderaten in der nördlichen Hemisphäre im August (Juni im Jahr 2018). Parallel zu dieser Studie durchgeführte Analysen des BAG zeigten auf, dass im Covid-19-Pandemie-Jahr 2020 weniger Fälle gemeldet wurden, als aufgrund der Vorjahre erwartet wurden [6]. In dieser Analyse nun wurde ein Rückgang der klinischen Fallmeldungen beobachtet. Vor allem im April und Oktober trafen weniger Meldungen zum klinischen Befund ein. Die Anzahl der Labormeldungen ging hingegen weniger stark zurück. Dies ist ein Indiz für die starke Belastung der Ärzteschaft durch die erste und zweite Welle der Pandemie. Zudem reduzierte die starke Einschränkung der Reisetätigkeit im Jahr 2020 die Häufigkeit der reiseassoziierten Fälle. Anders als prognostiziert scheinen sich die Nichtbenutzung von Gebäuden während des Covid-19-bedingten «Lockdowns» im Frühjahr 2020 und die anschliessende stufenweise Wiedereröffnung nicht in einem Anstieg der Fallzahlen widerzuspiegeln.

3.3 Räumliche Verteilung (2017–2020)

Die Fallzahlen und Melderaten weisen eine ungleiche regionale Verteilung auf (Abbildung 1, A [Kantone] und B [Bezirke]). Die über die vier Studienjahre gemittelte jährliche, nach Alter und Geschlecht standardisierte Melderate war im Kanton Tessin mit 15,8 Fällen pro 100 000 Einwohnerinnen und Einwohner am höchsten. Aufgrund unterschiedlicher Ausschlusskriterien (z. B. Ausschluss von reiseassoziierten Fällen) weichen die Melderaten in diesem Artikel geringfügig von jenen im aktuellen Bericht «Legionärskrankheit – Lagebericht Schweiz 2019–2020» [1] ab. Auf Bezirksebene sticht Lugano (TI) mit 22,9/100 000 als der Bezirk mit der höchsten Melderate heraus. Sieben von acht Bezirken des Kantons Tessin und ein angrenzender Bezirk des Kantons Graubünden wurden mithilfe der «Getis-Ord Gi»-Statistik* als «Hot Spots» identifiziert, während einzelne Bezirke in der Ost- und Zentralschweiz als «Cold Spots» identifiziert wurden, also als Bezirke mit besonders tiefer Melderate (Abbildung 1, C).

3.4 Faktoren, welche die Melderaten der Bezirke beeinflussen

Weder die Dichte an von Menschen geschaffenen möglichen Infektionsquellen wie Abwasserreinigungsanlagen und Kompostieranlagen noch jene an natürlichen Infektionsquellen wie Seen Flüssen zeigte einen signifikanten Einfluss auf die Melderaten. Hingegen scheint die Zusammensetzung der Bevölkerung in Bezug auf Durchschnittsalter, Siedlungsdichte und sozioökonomische Position eines Bezirks die Fallzahlen zu beeinflussen. In Bezirken mit einer tieferen durchschnittlichen sozioökonomischen Position wurden fast 40% mehr Fälle registriert. Das häufigere Vorkommen von Risikofaktoren, z. B. von Rauchern und chronischen Krankheiten in sozioökonomisch schwächeren Regionen, könnte das Vorkommen der Legionärskrankheit begünstigen und dieses Resultat erklären [7, 8].
Der Einfluss von Klima und Wetter auf die Inzidenz der Legionärskrankheit wurde bereits in mehreren internationalen Studien untersucht [9–11]. Unsere Analysen auf Bezirksebene konnten jedoch keinen Zusammenhang zwischen relativer

Datengrundlage

Meldedaten zur Legionärskrankheit des Nationalen Meldesystems für Infektionskrankheiten

Einschlusskriterien für die räumliche Analyse (N = 1603)

- Falljahr 2017–2020 (Adressangaben sind bei länger zurückliegenden Fällen anonymisiert)
- Im Alltag erworbene oder Altersheim-assoziierte Fälle
- Geschlecht, Alter und Kanton bekannt
- Fallklassifikation: sicherer oder wahrscheinlicher Fall einer Legionärskrankheit

Einschlusskriterien für die zeitliche Analyse (N = 5980)

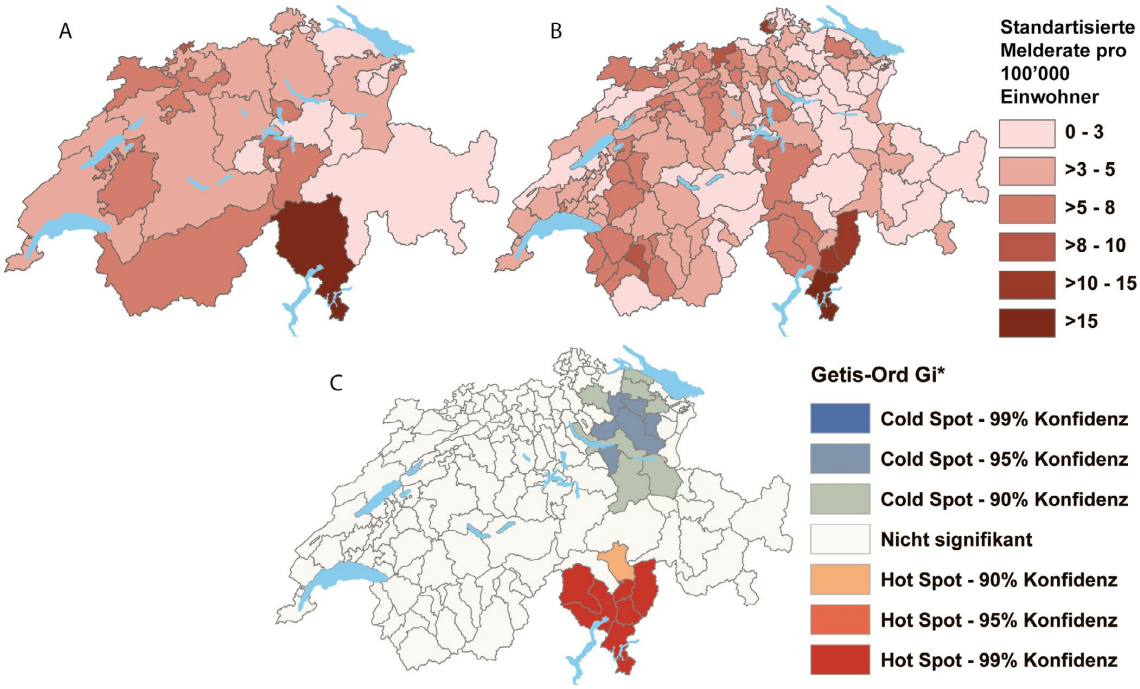
- Falljahr 2000–2020
- Fallklassifikation: sicherer, wahrscheinlicher oder möglicher Fall

Umweltfaktoren für die räumliche Analyse

Alle Umweltfaktoren wurden auf Bezirksebene aggregiert.

- Jahresmittel der Feinstaub-($PM_{2.5}$)- und Stickstoffdioxid-(NO_2)-Konzentrationen (Durchschnitt des Bezirkes)
- Durchschnitt der Temperatur, relativen Luftfeuchtigkeit und des Niederschlages während der Sommermonate
- Altersdurchschnitt der Bevölkerung
- Durchschnitt des sozioökonomischen Status der Bevölkerung
- Totale Länge der Flussläufe im Bezirk
- Total Anzahl Seen und Uferlänge
- Anzahl der öffentlichen Kompostieranlagen
- Anzahl der Abwasserreinigungsanlagen
- Urbanitätsindex (häufigster Wert pro Bezirk)
- Anteil der überbauten Fläche

Abbildung 1
Geschlechts- und altersstandardisierte Melderaten der Legionärskrankheit in der Schweiz zwischen Januar 2017 und Dezember 2020. A) Kantone, B) Bezirke, C) Resultate der Hot-Spot-Analyse nach Getis-Ord Gi*



Luftfeuchtigkeit und den Fallzahlen für die Schweiz bestätigen. Die Schweizer Geografie könnte dies erklären: In den Alpenregionen ist die Luftfeuchtigkeit höher, die Fallzahlen und Bevölkerungsdichte sind jedoch gering. Die Temperatur steht in keinem eindeutigen Zusammenhang mit der Meldehäufigkeit, was auch frühere Studien bekräftigen [9]. Ebenso hatte die durchschnittliche Niederschlagsmenge auf Bezirksebene keinen Einfluss auf die Schweizer Fallzahlen. Jedoch muss bei Rückschlüssen auf das Infektionsrisiko beachtet werden, dass die Expositionsorte und die Einflüsse auf die Fallzahlen auf Bezirksebene aggregiert wurden. Kurzzeitige und kurzlebige Risikofaktoren, z. B. Starkniederschläge (Platzregen), wurden somit nicht untersucht.
Die aktuelle Studie zeigt andererseits einen deutlichen Zusammenhang von Luftverschmutzung und Legionärserkrankung. Bei einer um 1,9 µg/m³ erhöhter Feinstaubkonzentration ($PM_{2.5}$) wurden 56% mehr Fälle registriert. Zum Vergleich, die Höchstgrenze für das Jahresmittel beträgt 10 µg/m³, die tatsächlichen Werte schwanken im Mittelland zwischen 8 und11 µg/m³ [12]. Es ist plausibel, dass eine erhöhte Luftverschmutzung Lungenerkrankungen wie die Legionärskrankheit begünstigt, jedoch wurde dieser Zusammenhang bisher kaum untersucht [13,14]. Da der Grad der Verstädterung in die Analyse miteinbezogen wurde, kann weitgehend ausgeschlossen werden, dass die Luftverschmutzung nur stellvertretend für andere (nicht untersuchte) städtische Faktoren steht und selbst keinen direkten Einfluss auf die Krankheitshäufigkeit hat.

3.5 Einschränkungen der Studie

Die Analyse der vorliegenden Meldedaten zur Legionärserkrankung erlaubt mögliche Zusammenhänge zu beschreiben, die gegebenenfalls Indizien und Hypothesen für allfällige kausale Verknüpfungen von Umweltfaktoren und Legionärserkrankung liefern können; kausale Zusammenhänge können in dieser Studie jedoch nicht hergeleitet werden. Weitere mögliche bekannte Infektionsquellen, z. B. Kühltürme und Brunnen, konnten nicht untersucht werden, da keine schweizweit verfügbaren Daten zu deren Lokalisation existieren.
Fälle mit einer bekannten Reiseexposition wurden explizit von der Analyse ausgeschlossen. Ansteckungen ausserhalb der Wohnkantone und insbesondere der Wohnbezirke sind jedoch möglich. Da die Ansteckungsorte meist unbekannt sind, konnten diese Fälle nicht aus diesen Analysen nach Wohnkanton und Wohnbezirk ausgeschlossen werden. Dies schwächt möglicherweise vorhandene Effekte ab.

4. FAZIT

Der ansteigende Trend der Fallzahlen der Legionärskrankheit wurde in den letzten beiden Jahren unterbrochen. Die bekannte ungleiche räumliche Verteilung von Legionärskrankheitsfällen konnte in dieser Studie erstmals auf Bezirksebene aufgezeigt werden. Insbesondere die tiefer als zu erwartenden Melderaten in einem grossen Teil der östlichen Schweiz sowie die «Hot Spots» im Süden sollten näher untersucht werden. Die Studie beschreibt einen starken Einfluss der Luftverschmutzung auf die Häufigkeit der Legionärskrankheit in der Schweiz. Dem sollte ebenfalls nachgegangen werden. Insgesamt scheinen grossräumig wirkende Faktoren die Fallzahlen zu beeinflussen, selbst wenn keine Punktquellen identifiziert werden konnten. Das Verständnis dieser Faktoren hilft bei der Vorhersage von Fallschwankungen und bei der Planung von Präventivmassnahmen.

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Appendix K

Selected examples of features on Legionnaires' disease in Swiss media

SRF, 7.2.2018: 'Legionellen auf dem Vormarsch - Die Gefahr lauert im lauwarmen Wasser' (https://www.srf.ch/news/panorama/legionellen-auf-dem-vormarsch-die-gefahr-lauert-im-lauwarmen-wasser)

Neue Zürcher Zeitung, 14.9.2019: 'Legionellose: Der Erreger, der aus der Wärme kam' (https://www.nzz.ch/wissenschaft/legionellose-der-erreger-der-aus-der-waerme-kam-ld.1507492?reduced=true)

St. Galler Tagblatt, 2.5.2022: 'Ist es der Klimawandel? Gefährliche Infektionen mit Legionellen nehmen zu' (https://www.tagblatt.ch/news-service/leben-wissen/legionaerskrankheit-ist-es-der-klimawandel-gefaehrliche-infektionen-mit-legionellen-nehmen-zu-ld.2283744). News feature of the research in this thesis.

Appendix L

Curriculum vitae

Fabienne Beatrice Fischer

Epidemiologist and public health specialist

Basel, Switzerland
Birthdate: 28.02.1991
Nationality: Swiss

Education

2018-2022	**PhD student at the Swiss Tropical and Public Health Institute (Swiss TPH). University of Basel.** Thesis «The epidemiology of Legionnaires' disease in Switzerland: a re-emerging disease»
2015-2017	**Master of Science in Epidemiology, Swiss TPH, University of Basel.** Thesis «Out-of-pocket expenditures in rural Tajikistan: Magnitude and perception and impact on patients with chronic diseases»; Stay in Tajikistan (April – June 2016)
2012-2015	**Bachelor of Science in Biotechnology ETH, ETH Zürich**
2011-2012	**Scientific Visualisation, Zürcher Hochschule der Künste**

Professional experience

2023-current	**Scientific project leader** at the Swiss Health Observatory (Obsan)
2019-2020	**Consultant** at Swiss TPH
2017-2018	**Scientific assistant** at Swiss TPH
2012-2017	**Editorial assistant** (part-time) at MDPI AG
2016	**Consultant** at Swiss TPH

Teaching experiences

2023-current	**Lecturer** for the course «Methods in Epidemiology», (11654-01, Daniel Mäusezahl)
2017-2022	**Teaching assistant** and **lecturer** for the course «Methods in Epidemiology», (11654-01, Daniel Mäusezahl)
2022	**Tutor** for the course «Research Data Management», (48613-01, Aurelio di Pasquale, Manuel Hetzel, Malin Michelle Ziehmer-Wenz)
2020-2021	**Co-supervisor** of a student in Master's in Epidemiology

Skills

Languages	German (native), English (fluent), French (intermediate), Russian (basic)
Programming	R (proficient), Stata (proficient), SAS (advanced), MATLAB (basic), Python (basic)
Computer (other)	Adobe (Illustrator, InDesign, Photoshop), Microsoft Office, LaTeX (Overleaf/ R Markdown), Version control (Git), ArcGIS

Extracurriculars, volunteering

- Enrolled in the Swiss School of Public Health (SSPH+, 2019-2024)
- Volunteering, with the University of Basel's Wissensbox' «Microscopy – the world of tiny things» (2022-2023)
- Member of the organising committee «SciFilmIt Hackathon Basel» (2019-2022)
- Student representative MSc in Epidemiology (Swiss TPH, 2015-2016)
- Active board member of the Biotechnology Student Association for media and communication (ETH, 2014-2015)

Scientific publications

For a full list please refer to https://orcid.org/0000-0001-9860-2242. † Shared first authorship.

- Fischer, F. B.†, Saucy, A.†, Vienneau, D., Hattendorf, J., Fanderl, J., de Hoogh, K. & Mäusezahl, D. (2023). Impacts of weather and air pollution on Legionnaires' disease in Switzerland: A national case-crossover study. *Environmental Research*, *233*, 116327.
- Fischer, F. B.†, Bigler, M.†, Mäusezahl, D.† et al. (2023). Legionnaires' disease in Switzerland: rationale and study protocol of a prospective national case–control and molecular source attribution study (*SwissLEGIO*). *Infection*, 51(5), 1467-1479.
- Fischer, F. B., Mäusezahl, D. & Wymann, M. N. (2023). Temporal trends in legionellosis national notification data and the effect of COVID-19, Switzerland, 2000–2020. *International Journal of Hygiene and Environmental Health*, *247*, 113970.
- Fischer, F. B., Deml, M. J. & Mäusezahl, D. (2022). Legionnaires' disease-a qualitative study on Swiss physicians' approaches to the diagnosis and treatment of community-acquired pneumonia. *Swiss Medical Weekly*, *152*, w30157.
- Fischer, F. B., Schmutz, C., Gaia, V. & Mäusezahl, D. (2020). Legionnaires' disease on the rise in Switzerland: A denominator-based analysis of national diagnostic data, 2007–2016. *International Journal of Environmental Research and Public Health*, 17(19), 7343.
- Fischer, F. B., Saucy, A., Schmutz, C. & Mäusezahl, D. (2020). Do changes in STEC diagnostics mislead interpretation of disease surveillance data in Switzerland? Time trends in positivity, 2007 to 2016. *Eurosurveillance*, *25*(33), 1900584.
- Fischer, F. B., Mengliboeva, Z., Karimova, G., Abdujabarov, N., Prytherch, H. & Wyss, K. (2020). Out of pocket expenditures of patients with a chronic condition consulting a primary care provider in Tajikistan: A cross-sectional household survey. *BMC Health Services Research*, *20*, 1-12.
- Sant Fruchtman, C.†, Fischer, F. B.†, Monzón Llamas, L. †, Tavakkoli, M., Cobos Muñoz, D. & Antillon, M. (2022). Did COVID-19 policies have the same effect on COVID-19 incidence among women and men? Evidence from Spain and Switzerland. *International Journal of Public Health*, *67*, 1604994.
- Tavakkoli, M., Karim, A., Fischer, F. B., Monzon Llamas, L., Raoofi, A., Zafar, S., Sant Fruchtman, C., de Savigny, D., Takian, A., Antillon, M. & Cobos Muñoz, D. (2022). From public health policy to impact for COVID-19: A multi-country case study in Switzerland, Spain, Iran and Pakistan. *International Journal of Public Health*, *67*, 1604969.