Impact factor 6.4

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 25 | Weekly issue 33 | 20 August 2020

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Three infection clusters related with potential pre-symptomatic transmission of coronavirus disease (COVID-19), Shanghai, China, January to February 2020

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Citation style for this article:
Gong Xiaohuan, Xiao Wenjia , Cui Yan , Wang Yuanping , Kong Dechuan , Mao Shenghua , Zheng Yaxu , Xiang Lunhui , Lu Lu , Jiang Chenyan , Yu Xiao , Zhu Yiyi , Fang Qiwen , Pan Hao , Wu Huanyu . Three infection clusters related with potential pre-symptomatic transmission of coronavirus disease (COVID-19), Shanghai, China, January to February 2020. Euro Surveill. 2020;25(33):pii=2000228. https://doi.org/10.2807/1560-7917.ES.2020.25.33.2000228

Article submitted on 01 Mar 2020 / accepted on 28 May 2020 / published on 20 Aug 2020

We report three clusters related with potential pre-symptomatic transmission of coronavirus disease (COVID-19) between January and February 2020 in Shanghai, China. Investigators interviewed suspected COVID-19 cases to collect epidemiological information, including demographic characteristics, illness onset, hospital visits, close contacts, activities' trajectories between 14 days before illness onset and isolation, and exposure histories. Respiratory specimens of suspected cases were collected and tested for SARS-CoV-2 by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) assay. The interval between the onset of illness in the primary case and the last contact of the secondary case with the primary case in our report was 1 to 7 days. In Cluster 1 (five cases), illness onset in the five secondary cases was 2 to 5 days after the last contact with the primary case. In Cluster 2 (five cases) and Cluster 3 (four cases), the illness onset in secondary cases occurred prior to or on the same day as the onset in the primary cases. The study provides empirical evidence for transmission of COVID-19 during the incubation period and indicates that pre-symptomatic person-to-person transmission can occur following sufficient exposure to confirmed COVID-19 cases. The potential pre-symptomatic person-to-person transmission puts forward higher requirements for prevention and control measures.

Background

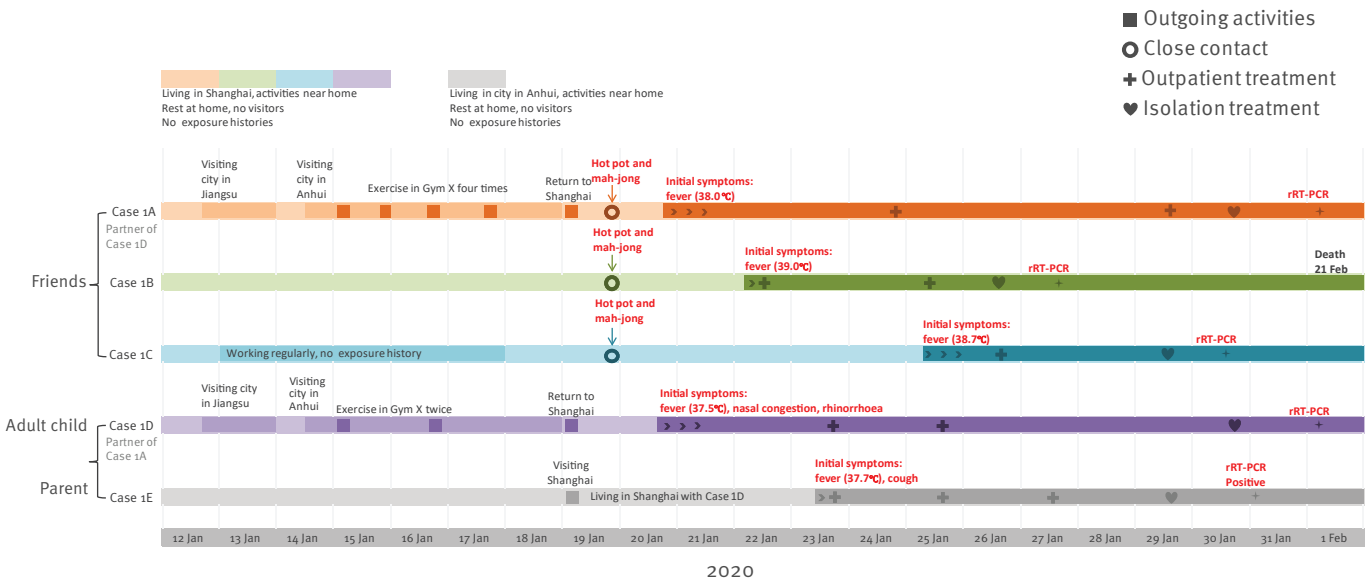
An outbreak of pneumonia of unknown aetiology occurred in Wuhan, Hubei Province, China, in December 2019 [1,2]. The first cases were linked to exposure at Wuhan's Huanan Seafood Wholesale Market. A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the causing infectious agent [3] and the World Health Organization (WHO) declared a public health emergency of international concern on 30 January and a pandemic on 11 March 2020 [4,5]. As at 29 March 2020, there were 82,356 coronavirus disease 2019 (COVID-19) confirmed cases in China and 634,813 confirmed cases globally [6]. The COVID-19 pandemic has since continued to progress rapidly worldwide [7,8].

As at 21 January 2020, Hubei Province reported 375 confirmed cases and Shanghai had reported nine confirmed cases [9]. On 24 January, the Shanghai Municipal Government declared the first-level response for a major public health emergency to firmly curb the spread of the epidemic [10]. Stringent prevention and control measures were implemented, including strengthening health screening and quarantine, cancelling various large-scale public activities, encouraging people to stay at home and to wear a mask in unavoidable outside activities.

There was early evidence for human-to-human transmission among close contacts, such as in hospital, family and community settings [11-14]. Although evidence of pre-symptomatic transmission accumulated [15-17], the infectivity and duration of transmission during the incubation period have been inconclusive.

Figure 1

Timeline of exposure to pre-symptomatic case and illness onsets of cases in Cluster 1 of COVID-19 outbreak, Shanghai, China, 12 January–1 February 2020 (n = 5)



These key epidemiological parameters, however, are important for outbreak control and to reduce virus transmission. Virus spread by pre-symptomatic cases poses great challenges to disease control and has an important impact on preventive strategies.

Outbreak detection

Between 26 and 30 January 2020, three hospitals in two districts of Shanghai city reported five suspected COVID-19 cases to the local district Centers for Disease Control and Prevention (CDC). The five cases (Cluster 1) were laboratory-confirmed 1–2 days later by the Shanghai municipal CDC laboratory; two were index cases and three were close contacts, i.e. friends and close family members. Cases had histories of common activities, such as travelling and dining, or were living together.

On 1 February 2020, another hospital in Shanghai reported one suspected COVID-19 case and six of their close contacts to the local district CDC; four of the close contacts tested positive for SARS-CoV-2 by real-time reverse-transcriptase polymerase chain-reaction (rRT-PCR), 1–2 days later (Cluster 2). The seven persons were from one family, including four grandparents plus a young couple and their infant. Two grandparents had come to Shanghai from Wuhan on 21 January.

From 21–23 January 2020, a further hospital in Shanghai reported four suspected COVID-19 cases to the local district CDC. These four cases (Cluster 3), two index cases and two close contacts, were laboratory-confirmed 1 day later. They were from two couples and two of the four individuals were siblings. One couple had come to Shanghai from Wuhan on 15 January and had lived with the other couple since then.

Initial investigations revealed the epidemiological links in each of these thee clusters. Further epidemiological investigations, control measures and specimen collection were conducted by a joint field epidemiology team from the respective days when reports were received. We report the key findings of the field epidemiological investigations of the three infection clusters related with potential pre-symptomatic transmission of COVID-19.

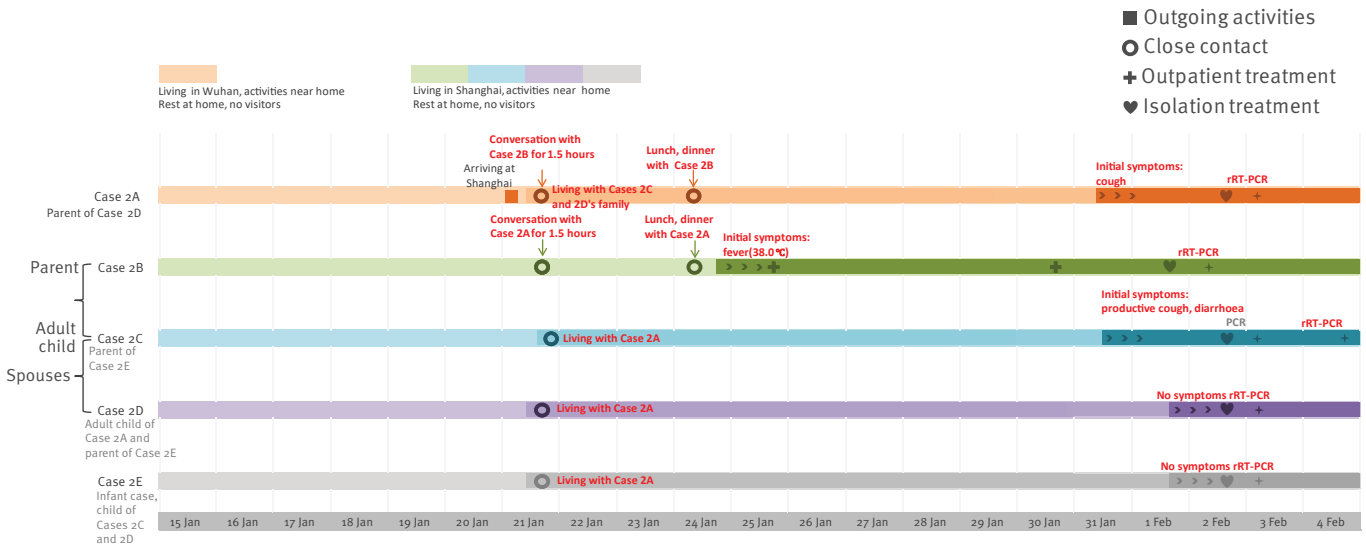
Methods

Epidemiological investigation

A joint field epidemiology team, comprising public health physicians from Shanghai municipal CDC and local district CDCs, was formed and conducted detailed field investigations from the day COVID-19 case reports were received. Investigators interviewed COVID-19 cases, close contacts and healthcare workers directly (face-to-face or over the phone) to collect epidemiological information including demographic characteristics, date of illness onset, hospital visits, close contacts, activities' trajectories between 14 days before illness onset and isolation and exposure histories (i.e. travel to or living in Wuhan or Hubei Province, visiting any other area with local sustained transmission of SARS-CoV-2, contact with persons with respiratory symptoms, contact with suspected or confirmed COVID-19 cases). In addition to interviews, medical records and travel records were checked, security cameras' videos were retrieved, and on-site investigation of key public settings were performed. The epidemiological information of cases from multiple sources was cross-checked to ensure the reliability of information. Once an infection cluster was identified, epidemiological links and transmission chains were analysed.

Figure 2

Timeline of exposure to pre-symptomatic case and illness onsets of cases in Cluster 2 of COVID-19 outbreak, Shanghai, China, 15 January–4 February 2020 (n = 5)



Laboratory detection

Upper respiratory specimens (nasopharyngeal swab, throat swab and/or nasopharyngeal-throat swab) and/or lower respiratory specimens (sputum) of suspected cases were collected and tested for SARS-CoV-2 by rRT-PCR assay in the Shanghai municipal CDC laboratory. The viral target included open reading frame 1ab (ORF1ab) and nucleocapsid protein (N). The specimen was positive for COVID-19 only if both viral targets were positive [18,19].

Definitions of cases and contacts

We used the 3rd version of Prevention and Control Guidelines for Novel Coronavirus Pneumonia by the National Health Commission of the People's Republic of China's case definition [18]. A suspected case was defined as any person meeting clinical signs of COVID-19 and/or with epidemiological histories. A confirmed case was any suspected case with respiratory samples testing rRT-PCR-positive for SARS-CoV-2.

Epidemiological histories were defined as (i) history of travelling or residing in Wuhan or any other areas where local sustained transmission of COVID-19 existed within 14 days before illness onset, (ii) history of contact with patients with fever or respiratory symptoms from Wuhan or any other area where local sustained transmission of COVID-19 existed within 14 days before illness onset, and (iii) clustering of illness onsets, or having an epidemiological association with cases rRT-PCR-positive for SARS-CoV-2.

Clinical and laboratory signs included were (i) fever, (ii) radiological evidence of pneumonia, (iii) normal or under normal white blood cell count in early stage, or under normal lymphocyte count.

An infection cluster was identified if more than one SARS-CoV-2 rRT-PCR-positive case was found in a confined environment or group (such as a family, a company, etc.) within 14 days, and there was a possibility of interpersonal transmission because of close contact or co-exposure.

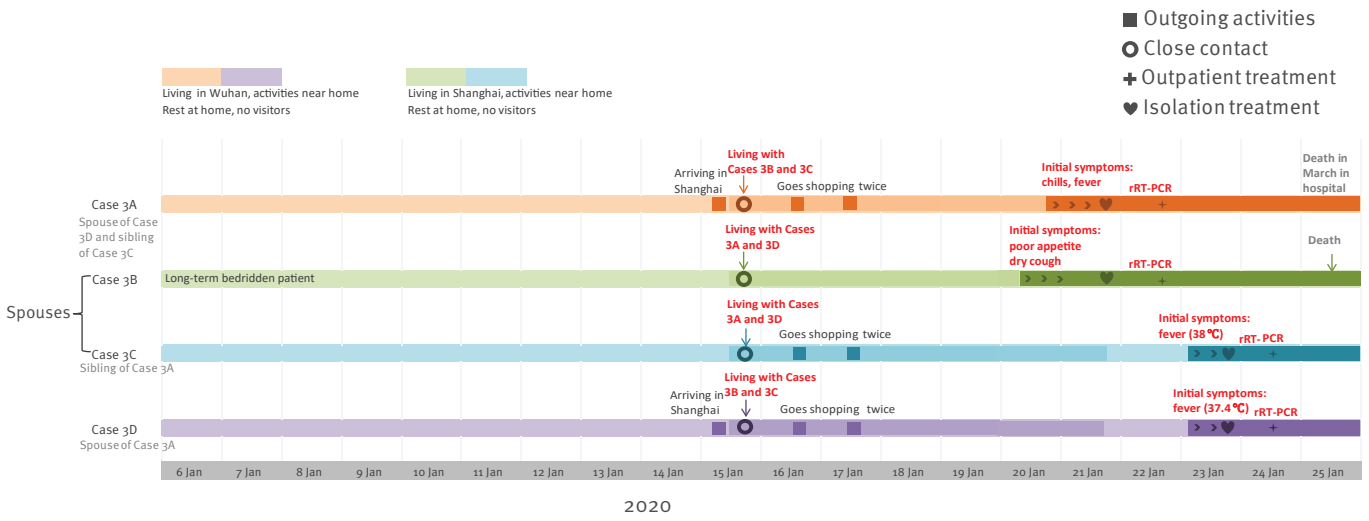
A close contact was anyone who was closely in contact with a suspected, confirmed and asymptomatic case without effective personal protection (classified protection according to the contact situation, including gloves, medical protective masks, protective face screens, isolation clothing, etc.) since onset of symptoms in the suspected case and confirmed case or the day asymptomatic case's specimens were collected. The close contact included: (i) living, working, or studying in one house or classroom, (ii) diagnosing, treating, or visiting cases in hospital ward, (iii) being within short distance in the same vehicle, (iv) other situations assessed by the field investigators.

Ethical statement

The epidemiological investigations were carried out according to the Law of the People's Republic of China on prevention and control of infectious diseases [20]. Ethical approval was not required because the CDCs are able to access and use personal identifiable information for infectious disease outbreak investigation according to the Law of the People's Republic of China on prevention and control of infectious diseases [20]. All cases were informed about the related rights and obligations and oral consent was obtained from all cases. Details were anonymised to protect the individual's privacy.

Figure 3

Timeline of exposure to pre-symptomatic case and illness onsets of cases in Cluster 3 of COVID-19 outbreak, Shanghai, China, 6 January–25 January 2020 (n = 4)



Results

Description of clusters

Cluster 1

Cluster 1 involved five confirmed COVID-19 cases; three females and two males. Cases 1A to 1C, two males and one female, all in their 20s, were friends. Case 1D also in their 20s was the partner of Case 1A whereas Case 1E, who was in their 50s, was parent of Case 1D.

Cases 1A to 1D lived in Shanghai. On 12 January, Case 1D went on duty travel to a city in Jiangsu Province, accompanied by Case 1A, where Case 1A went for a haircut and to a gym for exercise. Two days later, Cases 1A and 1D travelled to a city in Anhui Province, where Case 1E lived. Here, Cases 1A and 1D participated in a wedding and then a family dinner with relatives. Case 1A exercised with Case 1D twice and exercised alone twice in Gym X. Five days after their arrival, Cases 1A, 1D and 1E returned to Shanghai. Cases 1A dined with Cases 1B, 1C and two friends in a hotpot restaurant between 17:00 and 20:00 on the same day. Then they played mah-jong in a separate room with poor ventilation in the chess and cards parlour, between 20:00 and 23:00. These five people went home separately and had no further contact with each other before illness onset.

Case 1A became symptomatic with fever (38.0 °C) at night on 20 January. They presented to hospital accompanied by a parent on 24 January and were diagnosed with bronchitis. The examination showed: body temperature was 38.5 °C, white blood cell count was 6.02 x 10^9/L (norm 4.0–10.0 x 10^9/L). Influenza A and B antigen tests were both negative. Case 1A visited the hospital again, accompanied by their parent, on 29 January because of persisting symptoms. Chest computed tomography (CT) scan showed scattered patches and increased density in both lungs. They went back home that day. Following Case 1E's detection as suspected COVID-19 case on 29 January, Case 1A returned to hospital alone and was suspected as COVID-19 case one day later, when they were isolated and treated. The nasopharyngeal-throat swab was rRT-PCR positive for SARS-CoV-2 on 1 February.

Case 1B developed fever (39.0 °C) at 02:00 on 22 January. They developed headache, productive cough (bloodshot) and myalgia subsequently during 23 and 25 January. They presented to hospital accompanied by their parent on 22 January and 25 January, respectively. Influenza B antigen test was positive and influenza A antigen test was negative. On 26 January, they went to hospital again, accompanied by their parent, were suspected as COVID-19 case, were isolated and received treatment at the hospital. The examination showed: white blood cell count was 4.0 x 10^9/L. Chest CT scan showed multiple ground glass opacities in both lungs. The nasopharyngeal-throat swab and sputum specimen were both rRT-PCR positive for SARS-CoV-2 on 27 January. Case 1B died in February at the treating hospital.

Case 1C had a fever (38.7 °C) at 09:00 on 25 January. They visited the hospital accompanied by their parent on 26 January, got symptomatic treatment and went back home. As Case 1B's close contact with symptoms, Case 1C visited the hospital again, alone; they were suspected as COVID-19 case, they were isolated and received treatment at hospital on 29 January. The examination showed: body temperature was 37.6 °C, white blood cell count was 3.6 x 10^9/L. Chest CT scan showed infection in the left lung. The sputum specimen was rRT-PCR positive for SARS-CoV-2 on 30 January.

Cases 1D and 1E became symptomatic on 20 January and 23 January, respectively. Case 1E was isolated and received treatment on 29 January. As Case 1E's close contact with symptoms, Case 1D was isolated and

Table 1

Demographic and clinical characteristics of confirmed COVID-19 cases related with potential pre-symptomatic transmission in three infection clusters, Shanghai, China, January–February 2020 (n = 8)

Cluster	Case	Age (years)	BMI	Smoking	Comorbidity	Fever (°C)	Other respiratory symptoms	Influenza antigen test	White blood cell (x 109/L, (norm 4.0–10.0)	Chest computed tomography scan	Clinical outcome
Cluster 1	Case 1A	20–30	30.4	No	None	38.0–38.5	NA	Influenza A and B negative	4.1–6.0	Scattered patches and increased density in both lungs	Recovery
	Case 1B	20–30	35.5	No	None	37.6–39.0	Headache, productive cough, myalgia	Influenza B positive	4.0	Multiple ground glass opacities in both lungs	Death
	Case 1C	20–30	22.9	No	None	37.3–38.7	NA	NA	3.6	Infection in left lung	Recovery
Cluster 2	Case 2A	50–60	NA	Yes	None	NA	Cough	NA	NA	NA	Recovery
	Case 2B	60–70	22.6	Yes	Diabetes mellitus	37.3–38	NA	NA	3.8–4.2	Infectious lesions of both lungs and thin nodular shadow of left lung	Recovery
	Case 2C	30–40	28.7	No	None	37.7	Light productive cough, diarrhoea	NA	NA	NA	Recovery
Cluster 3	Case 3A	60–70	19.7	No	None	37.6–38.5	Chills	NA	4.4	Two patchy ground glass opacity high-density shadows in right lung	Death
	Case 3B	80–90	19.8	No	Hypertension, cardiac disease, COPD	38.2	Poor appetite, dry cough	Influenza A and B negative	7.2	Interstitial hyperplasia and infection of both lungs	Death

BMI: body mass index; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease; NA: not available.

received treatment on 30 January. Respiratory specimens of Cases 1D and 1E were rRT-PCR positive for SARS-CoV-2 on 1 February and 31 January, respectively (Figure 1).

All five cases of Cluster 1 wore masks during their visits to hospital. In addition to the confirmed cases, there were seven close contacts of Cluster 1 cases: Case 1A's parents and a close family member, as well as Case 1B and 1C's parents. The close contacts were all living together with cases in respective households. None of them had symptoms or signs compatible with COVID-19 during the 14-day medical observation at home.

Among the five cases in Cluster 1, Cases 1A and 1D travelled outside of Shanghai, and Case 1E lived outside Shanghai. Cases 1A, 1D and 1E did not have contact with persons known to have fever or respiratory symptoms in the cities they had recently visited. During the wedding and family dinners, there were no participants from Hubei Province or any other areas with local sustained transmission of SARS-CoV-2 at the time. Gym X turned out to be the most probable source of infection of Cases 1A and 1D. From 11 January to 19 January, five persons exercised in Gym X on several occasions, who were confirmed as COVID-19 cases by the local CDC in early February. This time period overlapped with the time period when Cases 1A and 1D exercised in Gym X. None of the five cases in Cluster 1 had contact with other persons known to have fever or respiratory symptoms in Shanghai. Close contact between Cases 1A, 1B and 1C when Case 1A was asymptomatic was the likely infection source for Cases 1B and 1C.

Cluster 2

Cluster 2 involved five confirmed COVID-19 cases, three males and two females aged between 9 months and their early 60s. Cases 2A and 2B are parents of Case 2D and 2C, respectively. Case 2C and 2D are Case 2E's (infant case) parents.

Case 2A and their spouse lived in Wuhan, Hubei province. They stayed at home except for purchasing food items in market. They had not been to Wuhan's Huanan Seafood Wholesale Market or been in contact with wild animals in Wuhan. Case 2B had diabetes as underlying disease. Cases 2C, 2D and 2E lived together in an apartment in Shanghai. Case 2B lived together with their spouse in another apartment in Shanghai and their daily activities were purchasing food items at the

Table 2

Contact situations of three infection clusters related with potential pre-symptomatic transmission, Shanghai, China, January–February 2020

Cluster	Case	Residence city	Close contact with primary cases (Cases 1A, 2A, 3A)								Time of onset of illness
			Type of contact	Persons	Duration (hours)	Contact distance (meters)	Contact frequency	Mask wearing	Surroundings	Contact period	
Cluster 1	Case 1A	Shanghai	NA	NA	NA	NA	NA	NA	NA	NA	20 Jan; night
	Case 1B	Shanghai	Hot pot dinner, mah-jong game	5	6	<1	Frequently within 6 hours	None	Inside a restaurant, a poorly ventilated room	19 Jan; 17:00 – 23:00	22 Jan; 02:00
	Case 1C	Shanghai	Hot pot dinner, mah-jong game	5	6	<1	Frequently within 6 hours	None			25 Jan; 09:00
Cluster 2	Case 2A	Wuhan	NA	NA	NA	NA	NA	NA	NA	NA	31 Jan; noon
	Case 2B	Shanghai	Conversation / lunch and dinner	7	11.5	<1	Commonly / frequently	None	In 2C and 2D's apartment	21 Jan; 09:30 – 11:00 24 Jan; 09:30 –19:00	24 Jan; 19:00
	Case 2C	Shanghai	Living together with Case 2A	5	241	<1	Frequently	None	In 2C and 2D's apartment	21 Jan; night until 2 Feb (isolation)	31 Jan; noon
Cluster 3	Case 3A	Wuhan	NA	NA	NA	NA	NA	NA	NA	NA	20 Jan; 22:00
	Case 3B	Shanghai	Living together with Case 3A	4	114	<1	Frequently	None	In their own apartment	15 Jan; 16:00 until 21 Jan (isolation)	20 Jan; morning

NA: not available.

market and cooking in Case 2C and 2D's home. They had lunch and dinner with the young family and went back to their own home every day. Case 2C commuted to and from work regularly. Case 2D took care of Case 2E at home.

Case 2A and spouse drove from Wuhan to Shanghai on the morning of 21 January and lived in Case 2C and 2D's apartment since then. Case 2B and their spouse arrived in Case 2C's apartment soon afterwards. Case 2B went back home after having a conversation with Case 2A and their spouse for ca 1.5 hours. Case 2A, their spouse, Case 2B's spouse and Case 2D talked to each other, had lunch and had dinner together until evening. Case 2C joined dinner after work in the evening. Case 2B's spouse went back home that evening. On 22 January and 23 January, Case 2B and their spouse stayed at their own apartment. At 09:30 on 24 January, Case 2B and their spouse arrived in Case 2C and 2D's apartment. The seven persons stayed together, had lunch and dinner, celebrating the spring festival until almost 19:00 that evening. Case 2B and their spouse went back home that evening. After 24 January, Case 2B and their spouse stayed at their own apartment and did not go outside. After 24 January, Case 2A and their spouse, Cases 2C, 2D and 2E stayed at Cases 2C and 2D's apartment and did not go outside.

Case 2A developed cough around noon of 31 January. As Case 2B's close contact with symptoms, they presented to hospital, were suspected as COVID-19 case, and were admitted to hospital for isolation and treatment on 2 February. The nasopharyngeal swab was rRT-PCR positive for SARS-CoV-2 on 3 February.
Case 2B developed fever (38.0 °C) at 19:00 at their own home on 24 January. They presented to hospital on 25 January and 30 January, twice, wearing mask, accompanied by their spouse. Because Case 2B had fever, they visited hospital again, accompanied by their spouse, were suspected as COVID-19 case, and were admitted to hospital for isolation and treatment on 1 February. The examination showed: body temperature was 37.3 °C, white blood cell count was 3.9 x 10^9/L. Chest CT scan showed infectious lesions of the upper lobe of both lungs and thin nodular shadow of the upper lobe of the left lung. The nasopharyngeal swab was rRT-PCR positive for SARS-CoV-2 on 2 February.

Case 2C became symptomatic with a light productive cough and diarrhoea around noon of 31 January, 1 hour after illness onset of Case 2A. As Case 2B's close contact with symptoms, they presented to hospital, were suspected as COVID-19 case, were isolated and received treatment on 2 February. The nasopharyngeal-throat swabs were rRT-PCR negative for SARS-CoV-2 on 3 February and positive on 4 February.

As Case 2B's close contacts, Cases 2A and 2B's spouses, as well as Cases 2D and 2E had been asymptomatic and were admitted to hospital on 2 February. The nasopharyngeal swabs of cases 2D and 2E were both rRT-PCR positive for SARS-CoV-2 on 3 February. The nasopharyngeal swabs of Cases 2A and 2B's spouses were both twice rRT-PCR negative for SARS-CoV-2 at an interval of 24 hours (Figure 2).

Except for confirmed cases and Cases 2A and 2B's spouses, there were no other close contacts of Cluster 2.

Among the five cases in Cluster 2, only Case 2A had a history of living in Wuhan. Cases 2B, 2C, 2D and 2E had not travelled outside Shanghai. In Shanghai, none of these five cases had known contact with other persons with fever or respiratory symptoms and other persons coming from Hubei Province or any other areas where local sustained transmission of SARS-CoV-2 existed. Before Case 2B's onset of symptoms, Case 2B went to a market and Case 2C went to work regularly. Considering the COVID-19 situation in Shanghai and Wuhan at that time, close contact with pre-symptomatic Case 2A was the most likely infection source of Cases 2B and 2C. The likelihood of Cases 2B and 2C's exposure to other sources in Shanghai was considered much lower.

Cluster 3

Cluster 3 involved four confirmed COVID-19 cases, two males and two females, aged between 60 and 80 years. Case 3A is Case 3D's spouse. Case 3C is Case 3B's spouse. Case 3A and Case 3C are siblings.

Cases 3A and 3D lived in Wuhan, Hubei Province. They stayed at home except for purchasing food items in the market. They had not been to Wuhan's Huanan Seafood Wholesale Market or been in contact with wild animals in Wuhan. Cases 3B and 3C lived in Shanghai. Case 3B was a long-term bedridden patient with several comorbidities (hypertension, cardiac disease and chronic obstructive pulmonary disease). Case 3C purchased food items, cooked meals and took care of Case 3B at home.

Cases 3A and 3D arrived in Shanghai by train on 15 January and stayed in Case 3B and 3C's apartment since 16:00 that day. On 16 January and 17 January, Cases 3A, 3C and 3D went shopping at a nearby supermarket twice. Apart from this, the four cases stayed at home and did not go outside.

Case 3A became symptomatic with chills and fever at 22:00 on 20 January. They presented to hospital, were suspected as COVID-19 case, and were admitted to hospital for isolation and treatment on 21 January. The examination showed: body temperature was 38.5 °C, white blood cell count was 4.37 x 10^9/L. Chest CT scan showed two patchy ground glass opacity high-density shadows in the right lung. The throat swab was rRT-PCR positive for SARS-CoV-2 on 22 January. Case 3A died in hospital in March.

Case 3B developed poor appetite and dry cough on the morning of 20 January and fever (38.2 °C) on 21

January. They presented to hospital, were suspected as COVID-19 case, and admitted to hospital for isolation and treatment on 21 January. The examination showed: white blood cell count was 7.16 x 10^9/L. Influenza A and B antigen tests were both negative. Chest CT scan showed interstitial hyperplasia and infection of both lungs. The nasopharyngeal swab and throat swab were both rRT-PCR positive for SARS-CoV-2 on 22 January. Case 3B died in hospital on 25 January.

As close contact of Cases 3A and 3B, Case 3C developed fever (38.2 °C); Case 3D also developed fever (37.4 °C), both at 09:00 on 23 January, and they were both admitted to hospital on the same day. The nasopharyngeal swabs and sputum specimens of Cases 3C and 3D were both rRT-PCR positive for SARS-CoV-2 on 24 January (Figure 3).

Except for confirmed cases, there were three close contacts of Cluster 3 cases, including Case 3B and 3C's child, their spouse and grandchild, who had visited Case 3B. They did not have any symptoms or signs during the 14-day medical observation at home.

Cases 3A and 3D had histories of living in Wuhan. Cases 3B and 3C had not travelled outside Shanghai. In Shanghai, none of the four cases had known contact with other persons with fever or respiratory symptoms and persons coming from Hubei Province or any other areas where local sustained transmission of COVID-19 existed. Case 3B was a long-term bedridden patient. Close contact with Case 3A when they were pre-symptomatic was the most likely infection source of Case 3B.

Analysis of clusters

In these three infection clusters, 14 confirmed cases developed symptoms and visited hospitals when they were in Shanghai and eight of these confirmed cases were related with potential pre-symptomatic transmission (Table 1). CDCs' public health physicians conducted field epidemiological investigations and communicated with the cases directly; contact situations of three infection clusters are shown in Table 2. In each of the clusters, the primary cases were identified (Cases 1A, 2A, 3A) and in total five cases (Case 1B, 1C, 2B, 2C, 3B) were secondary cases who got infected by being in close contact with the primary cases. The primary cases 1A, 2A and 3A, had no clinical symptoms or signs when they were in contact with these five secondary cases, and there were no contacts after the illness onset of the primary cases. In Cluster 1, illness onset in the five secondary cases was 2 to 5 days after the last contact with the primary case. In Cluster 2 and Cluster 3, illness onset in secondary cases occurred prior to or on the same day as the onset in the primary cases. The interval between the onset of illness in the primary case and the last contact of the secondary case with the primary case in our report was 1 to 7 days. No other relevant exposure histories of the secondary cases were found.

Outbreak control measures

Multiple control measures were implemented immediately once these three clusters were detected. First, isolation and treatment was performed immediately when patients were suspected to have COVID-19 according to doctors' judgment based on the existing guidelines [18]. Suspected cases were transferred by ambulance to a municipal-designated hospital once their respiratory specimens were rRT-PCR positive for SARS-CoV-2. Second, close contacts were put under centralised or home medical observation for 14 days since the last day of contact with cases, under supervision of a team including clinical physicians, nurses, CDC physicians, and community workers. During observation, body temperature and respiratory symptoms or signs were recorded twice every day. Third, disinfection measures were implemented in cases' homes, visited hospitals, work places and other places where cases had spent time, to prevent secondary infections. Fourth, surveillance in fever clinics and health education for the population were strengthened especially in areas where the infection clusters occurred. Fifth, people arriving to Shanghai from other provinces or foreign countries were health quarantined for 14 days in a centralised isolation location, and observed medically with body temperature and respiratory symptoms or signs being recorded twice every day.

Discussion

The study provides empirical evidence for transmission of COVID-19 in the pre-symptomatic phase. It supports the 5th version of Prevention and Control Guidelines for Novel Coronavirus Pneumonia published by the National Health Commission of the People's Republic of China on 21 February [21] which refers to close contacts as those in close contact with cases without effective protection from 2 days before the onset of symptoms. In their research, Zou et al. showed that the viral load detected in asymptomatic COVID-19 cases was similar to that in symptomatic ones [22], which suggests the transmission potential of asymptomatic or minimally symptomatic patients.

In April 2020, WHO interim guidelines also suggested that individuals who had contact with a confirmed case from 2 days before symptom onset should be identified and traced [23]. These changes to the earlier WHO interim guidelines emphasised the importance of looking for contacts in their pre-symptomatic stage. The longest interval between the onset of illness in the primary case and the last contact of the secondary case with the primary case in our report was 7 days, which was longer than 2 days and within the ranges of published mean incubation period (5.1–11.5 days) according to recent research [11,24,25]. An alternative explanation could be that the initial symptoms of the primary case of Cluster 2 were too mild to self-recognise. Both explanations of this study provide clues for further research on pre-symptomatic transmission of COVID-19.

Unlike SARS-CoV-1, where almost all onward transmissions occur after symptom onset [26], published evidence of pre-symptomatic transmission has been accumulating for SARS-CoV-2 [14-16,27,28]. Transmission before symptom onset has a marked effect on control and prevention of infectious diseases. It increases the probability for the population to get infected, and weakens the power of isolation because contacts may have got infected already before isolation of the cases [29]. In the study by Mizumoto et al., the estimated asymptomatic proportion was 17.9% (95% credible interval: 15.5–20.2%) [27]. The clinical spectrum and infection spectrum of COVID-19 still need to be studied deeper to help public health decision making.

Among the three infection clusters, pre-symptomatic transmission appeared to take place when (i) the exposure time was sufficiently long i.e. equal to or more than 6 hours, (ii) the exposure distance was short i.e. less than 1 m, (iii) the exposure frequency was high and the distance was short i.e. living together in one house, dining or playing together at one table, and (iv) no masks were worn when in contact. This indicates that pre-symptomatic person-to-person transmission can happen when there is sufficient exposure with a confirmed COVID-19 case. However, we do not know whether shorter or less intense exposures to pre-symptomatic cases might also lead to transmission.

There are two main limitations that need to be acknowledged. First, the evidence case reports provide is less persuasive than results of well-designed studies where information is obtained following a specific protocol. Second, even with detailed field investigation and information that was cross-checked from multiple sources, considering recall bias, there is still chance that not every possibility for transmission was recorded, such as whether there were alternative sources for Cluster 2.

This report also showed that COVID-19 can be transmitted between families, friends and cities. Transmission has taken place all over the world [30,31]. Strict measures were adopted in the early stage of the COVID-19 epidemic in Shanghai, which resulted in decreasing numbers of reported confirmed and suspected cases. In the past months people have been returning to Shanghai for work from all over China and people have been arriving in Shanghai from all over the world; Shanghai is facing great challenges in preventing imported cases. Medical observation and centralised isolation of people from abroad was strengthened. Health quarantine for 14 days in centralised isolation location for every traveller returning from other countries is crucial in preventing imported COVID-19 cases, which can lead to imported cases in this pandemic. The potential pre-symptomatic person-to-person transmission puts forward higher requirements for research and prevention and control measures. Until the infectivity and duration of incubation period transmission are conclusive, more research is needed for optimising prevention and control strategies, including seroprevalence studies, natural history studies based on population in epidemic areas, and studies about efficiency of asymptomatic transmission. The incubation period should be taken into consideration in epidemiological investigations and the identification of close contacts. Moreover, the importance of pre-symptomatic transmission in outbreak evolution needs to be in far wider and deeper consideration.

Acknowledgements

The authors of this study thank all the cases and the cases' relatives, the public health physicians from Baoshan, Huangpu, Putuo, Pudong district CDCs and Shanghai municipal CDC, the nurses and the clinical physicians from hospitals for the strong support during the epidemiological investigations.

Funding: This work was supported by Science and Technology Commission of Shanghai Municipality (Study on the seroepidemiology and transmission risk of COVID-19, grant number 20JC1410200; Shanghai Sailing Program, grant number20YF1441700; The Epidemiological study on COVID-19 in Shanghai, grant number 20411950100).

Conflict of interest

None declared.

Authors' contributions

Xiaohuan Gong and Wenjia Xiao analysed the infection clusters, drafted the manuscript and acquired the funding. Yan Cui and Yuanping Wang participated in the manuscript revision and epidemiological investigation. Xiaohuan Gong, Wenjia Xiao, Dechuan Kong, Shenghua Mao, Yaxu Zheng, Yan Cui, Yuanping Wang, Lunhui Xiang and Lu Lu collected the information and participated in the epidemiological investigation. Chenyan Jiang, Xiao Yu, Yiyi Zhu and Qiwen Fang analysed the data. Huanyu Wu and Hao Pan conceived the study, gave valuable instruction and acquired the funding, in epidemiological investigation and in laboratory test and analysis, respectively.

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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

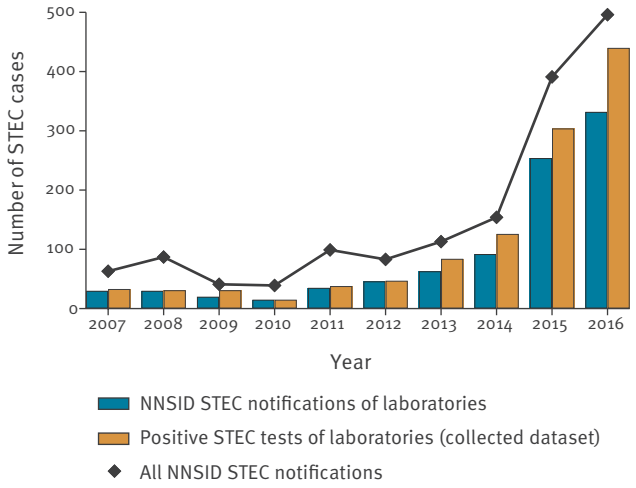
Infections caused by Shiga toxin (Stx)-producing *Escherichia coli* (STEC) are generally mild and self-limiting or even asymptomatic. However, particularly in children and elderly people, STEC infections can lead to severe gastroenteritis with haemorrhagic diarrhoea and life-threatening conditions, e.g.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

Figure 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*.

up to 22 pathogens, including STEC, in one single run [12,13].

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 [7].

A qualitative assessment found that Swiss laboratory experts uniformly agreed that the increase in STEC case numbers was due to the introduction and increasing use of multiplex PCR panels [7]. 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 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 [14]. 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.

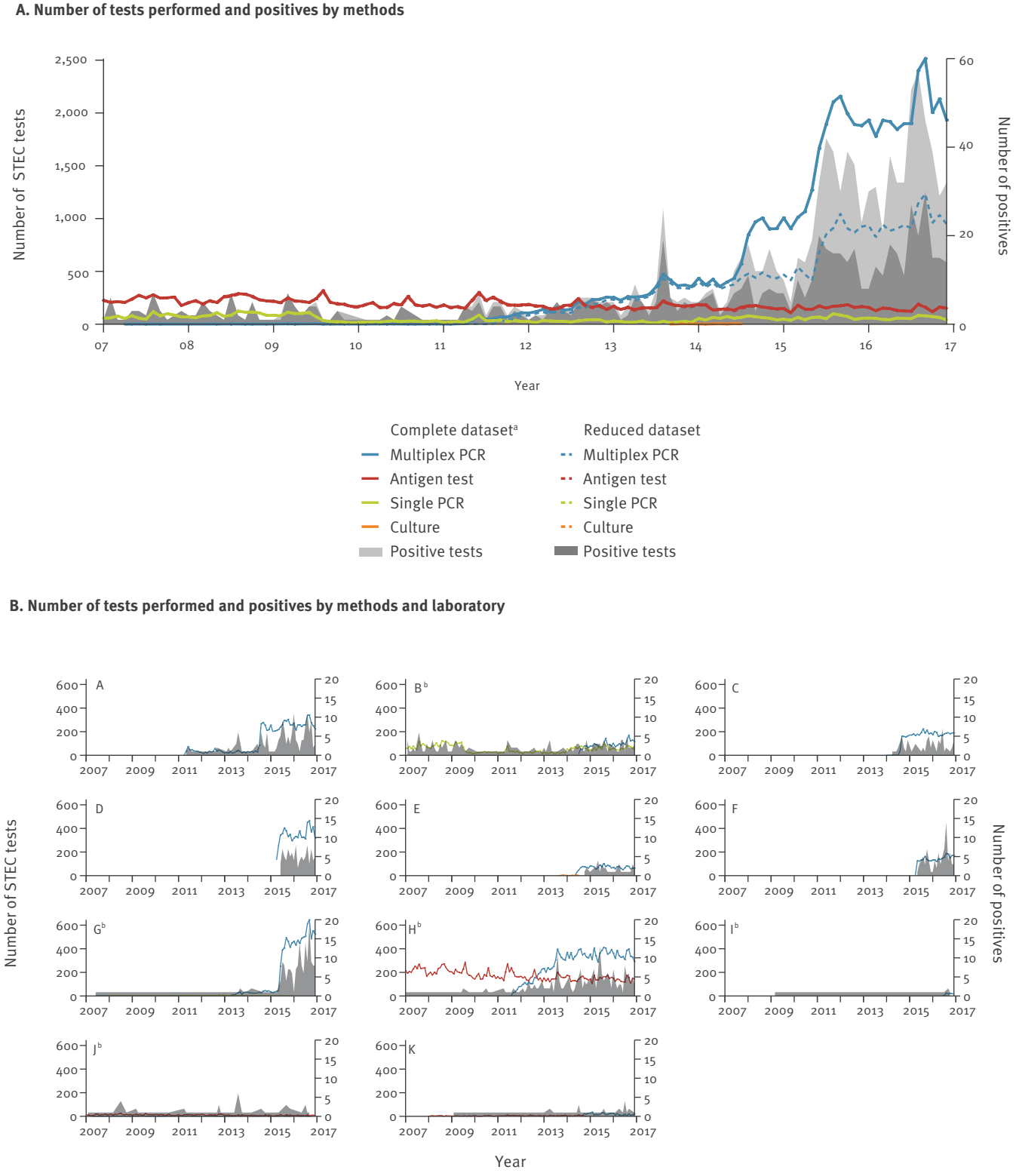
We use the term positivity as the rate of number of positive tests to the total number of tests performed for STEC [15,16]. Positivity was calculated for different demographic groups, test methods, spatial (i.e. patients' canton of residence) and temporal (annual and seasonal) trends. The main outcome, 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

Figure 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



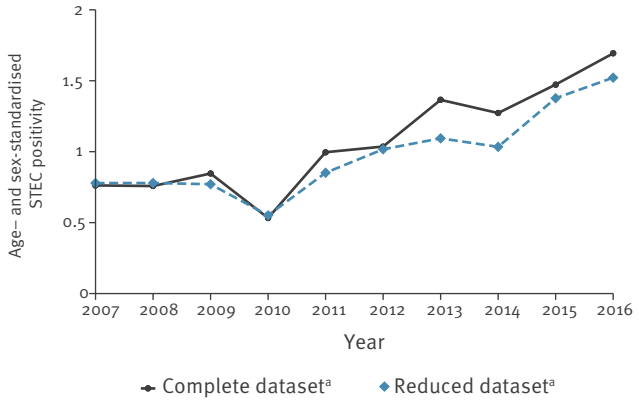
STEC: Shiga toxin-producing Escherichia coli.

[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 3

Age- and sex-standardised positivity of STEC testing, 11 diagnostic laboratories, Switzerland, 2007–2016

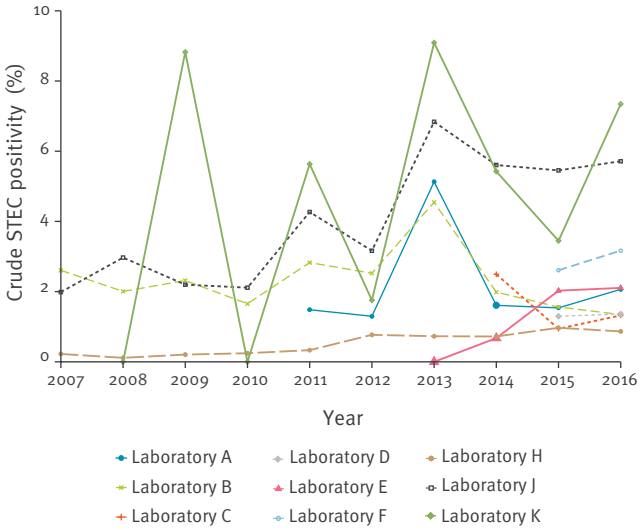


STEC: Shiga toxin-producing *Escherichia coli*.

[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.

Figure 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.

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 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 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).

Table A

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[a]	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[b]	1.56–2.27	3.38[b]	2.56–4.45
5–9	2,593	1.80[b]	1.34–2.43	1.66[c]	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	1.00	0.84–1.20	1.03	0.81–1.31
60–79	17,685	1.10	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[d]	0.66–0.93	1.20	0.89–1.60
Espace Mittelland	20,000	Ref	NA	Ref	NA
Northwestern Switzerland	15,273	0.39[b]	0.32–0.49	0.69[d]	0.53–0.89
Zurich	14,439	0.79[d]	0.66–0.94	0.75[c]	0.58–0.98
Eastern Switzerland	6,474	0.70[d]	0.55–0.90	0.88	0.67–1.16
Central Switzerland	10,015	0.90	0.74–1.09	0.92	0.70–1.21
Ticino	1,008	0.74	0.43–1.30	1.30	0.73–2.32
Test method					
Multiplex PCR	57,168	Ref	NA	Ref	NA
Antigen test	22,588	0.37[b]	0.31–0.45	0.34[b]	0.26–0.44
Single PCR	6,247	1.56[b]	1.31–1.86	2.31[b]	1.55–3.45
Culture	24	NC	NC	NC	NC

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 Supplement S1 and Supplementary Figure S1 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.

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, Supplementary 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, Supplementary 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 Supplementary 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=24). 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 Supplementary 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 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 2B). Only one of these five laboratories continued using primarily antigen tests for the entire study period.

Table B

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[a]	95% CI
Time trend	86,043	1.00[b]	1.00–1.01	1.00[c]	1.00–1.01
Test month					
January	6,040	0.50[b]	0.37–0.68	NA	NA
February	5,529	0.59[d]	0.44–0.80	NA	NA
March	6,137	0.58[b]	0.43–0.77	NA	NA
April	5,872	0.76[c]	0.58–0.99	NA	NA
May	6,357	0.69[d]	0.53–0.90	NA	NA
June	7,084	0.77[c]	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[d]	0.54–0.87	NA	NA
October	8,098	0.78[c]	0.61–0.99	NA	NA
November	8,000	0.71[d]	0.55–0.91	NA	NA
December	7,532	0.62[b]	0.47–0.81	NA	NA
Seasonality					
sin((d*2*π)/T)	86,043	0.84[b]	0.77–0.91	0.89[b]	0.82–0.98
cos((d*2*π)/T)	86,043	0.83[b]	0.76–0.90	0.81[c]	0.75–0.89
Test year					
2007	3,711	0.53[d]	0.37–0.76	NA	NA
2008	3,978	0.47[b]	0.32–0.67	NA	NA
2009	3,421	0.54	0.38–0.79	NA	NA
2010	2,536	0.35[b]	0.21–0.59	NA	NA
2011	3,393	0.67[c]	0.48–0.94	NA	NA
2012	4,483	0.63[d]	0.47–0.85	NA	NA
2013	6,152	0.82	0.65–1.04	NA	NA
2014	10,246	0.74[d]	0.61–0.90	NA	NA
2015	21,484	0.85[c]	0.74–0.99	NA	NA
2016	26,639	Ref	NA	NA	NA
Laboratory					
A	8,712	2.98[b]	2.44–3.64	NA	NA
B	8,861	3.15[b]	2.59–3.83	NA	NA
C	5,102	2.09[b]	1.60–2.75	NA	NA
D	7,181	2.13[b]	1.68–2.70	NA	NA
E	2,197	2.84[b]	2.02–4.00	NA	NA
F	2,904	4.80[b]	3.75–6.16	NA	NA
G	9,852	2.86[b]	2.36–3.48	NA	NA
H	38,796	Ref	NA	NA	NA
I	121	9.66[b]	4.46–20.94	NA	NA
J	1,438	6.14[b]	4.55–8.28	NA	NA
K	879	8.09[b]	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 Supplement S1 and Supplementary Figure S1 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.

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 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 ≥ 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.

The positivity and trend in positivity differed across laboratories (Figure 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.

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

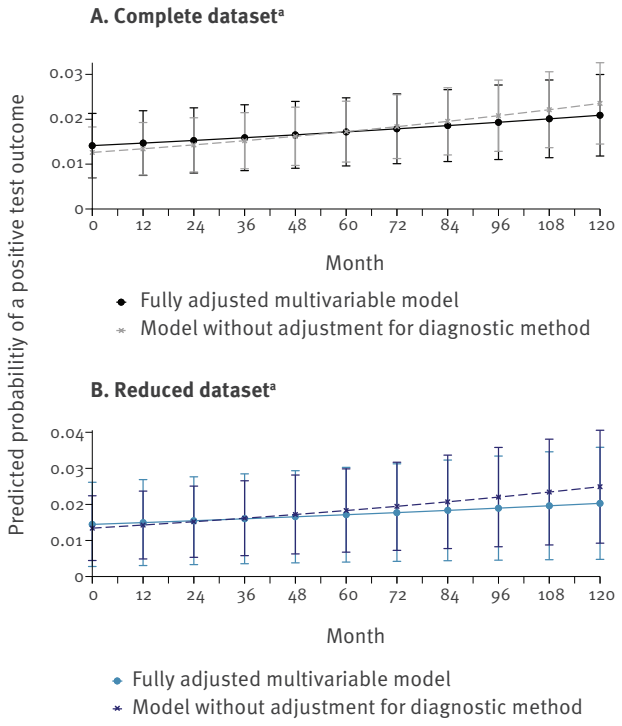
The univariable regressions showed a marginal but significant trend for the time trend variable (OR: 1.003, $p<0.01$, Table). All test years except 2013 showed decreased odds for a positive test outcome compared with the reference year 2016. All calendar months except July have smaller odds for a positive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

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

Figure 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.

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 5).

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 [17-19]. 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 [20]. 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 [21,22].

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 [23-25]. 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 [7]. 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. [26], 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 [27-30]. A study among staff members of meat-processing companies in Switzerland found 3.5% asymptomatic carriers of STEC [31]. 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 [12]. 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 [32-34].

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) [35,36]. Analysing 2017 data, Nüesch-Inderbinen et al. [36] 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 [35,36]. 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 [35,37,38]. 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 [39].

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 [38]. In Finland, the increase in reported cases between 2012 and 2016 was fourfold, with multiplex PCR screening introduced in 2013 [38,40]. 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 [41].

STEC patients associated with a recent outbreak in Finland were classified as rather mild cases [42]. 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 [41]. 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 [37]. 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. 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 [36]. This is in line with earlier reports that 3.5% of meat factory workers were asymptomatic STEC carriers [31]. In Norway, co-infections were observed in 15% of notified STEC cases detected using multiplex PCR [41]. 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 [7].

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 Swiss 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 notifications 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.

Acknowledgements

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.

Conflict of interest

None declared.

Authors' contributions

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.

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Accounting for indirect protection in the benefit–risk ratio estimation of rotavirus vaccination in children under the age of 5 years, France, 2018

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Citation style for this article:
Escolano Sylvie, Mueller Judith E , Tubert-Bitter Pascale . Accounting for indirect protection in the benefit–risk ratio estimation of rotavirus vaccination in children under the age of 5 years, France, 2018. Euro Surveill. 2020;25(33):pii=1900538. https://doi.org/10.2807/1560-7917.ES.2020.25.33.1900538

Article submitted on 23 Aug 2019 / accepted on 10 Jan 2020 / published on 20 August 2020

Background: Rotavirus is a major cause of severe gastroenteritis in children worldwide. The disease burden has been substantially reduced in countries where rotavirus vaccines are used. Given the risk of vaccine-induced intussusception, the benefit–risk balance of rotavirus vaccination has been assessed in several countries, however mostly without considering indirect protection effects. **Aim:** We performed a benefit–risk analysis of rotavirus vaccination accounting for indirect protection in France among the 2018 population of children under the age of 5 years. **Methods:** To incorporate indirect protection effects in the benefit formula, we adopted a pseudo-vaccine approach involving mathematical approximation and used a simulation design to provide uncertainty intervals. We derived background incidence distributions from quasi-exhaustive health claim data. We examined different coverage levels and assumptions regarding the waning effects and intussusception case fatality rate. **Results:** With the current vaccination coverage of < 10%, the indirect effectiveness was estimated at 6.4% (+/– 0.4). For each hospitalisation for intussusception, 288.2 (95% uncertainty interval: (173.8–480.0)) hospitalisations for rotavirus gastroenteritis were prevented. Should 90% of infants be vaccinated, indirect effectiveness would reach 57.9% (+/– 3.7) and the benefit–risk ratio would be 297.6 (95% uncertainty interval: 179.4–497.3). Indirect protection accounted for almost half of the prevented rotavirus gastroenteritis cases across all coverage levels. The balance remained in favour of the vaccine even in a scenario with a high assumption for intussusception case fatality. **Conclusions:** These findings contribute to a better assessment of the rotavirus vaccine benefit–risk balance.

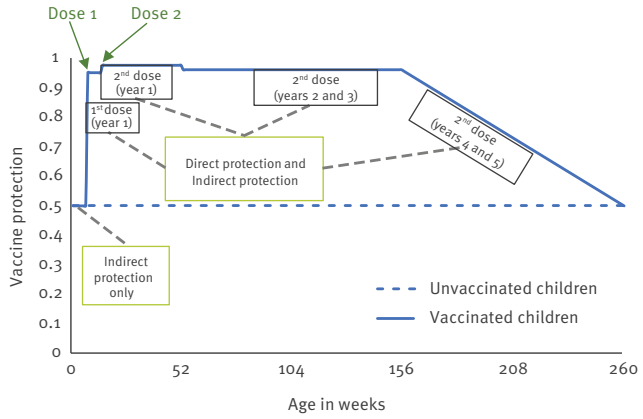
Introduction

Rotavirus infections are responsible for severe diarrhoea and vomiting in children, including substantial case fatality if appropriate care cannot be provided. The World Health Organization (WHO) estimated that during the pre-vaccination era, more than 2 million children worldwide were hospitalised each year for rotavirus gastroenteritis (RVGE) [1]. Oral live attenuated rotavirus vaccines have been introduced in more than 90 countries to date and substantial reductions in disease burden have been observed [2]. For high-income countries with high vaccine coverage (VC) such as some European countries and the United States (US), a large reduction in the number of hospitalisations for acute gastroenteritis is considered attributable to the vaccine [3,4]. Two vaccines are currently marketed globally: Rotarix (a monovalent, two-dose schedule vaccine) and Rotateq (a pentavalent, three-dose schedule vaccine), all doses being administrated before the age of 8 months. Post-marketing surveillance and analyses based either on epidemiological studies or on pharmacovigilance data have shown an increased but limited risk of intussusception, especially during the first week after administration of the first dose, but also possibly during the second and third weeks and after the second dose [5-10].

In the context of increasing coverage, the transmission of the virus to susceptible persons becomes a rarer event. In addition, because vaccinated children transmit the virus to contacts to a lesser extent, the vaccine has the potential to indirectly protect unvaccinated persons. Based on both effects, a vaccination programme with high VC can provide indirect or herd protection, and eventually herd immunity, a situation where no new cases occur. The importance of the indirect protection effect depends on various factors that

Figure 1

Illustration of rotavirus vaccine protection against gastroenteritis in children



This illustrative example corresponds to a fictitious population with 90% vaccine coverage, indirect protection of 50% and linear waning of antibodies, where all vaccinated children receive two doses of vaccines (in the 7th and 14th weeks of age), have direct effectiveness of 90% after dose 1, of 95% after dose 2 (during the 1st year) and 92% (during the 2nd and the 3rd year). Then, according to Formula (1), the total effectiveness for vaccinated children is 50% before week 7 and after week 260, 95% between weeks 7 and 14, 97.5% between weeks 14 and 52 and 96% between weeks 52 and 156.

are specific to the virus (transmissibility, asymptomatic forms of infection), the vaccine (level of serum antibody response and capacity to induce mucosal immunity) and the population (contact patterns, conditions of hygiene, VC). It is therefore difficult to estimate indirect protection effects in a vaccination programme. Analysis of population surveillance data in terms of incidence changes in out-of-target age groups and unvaccinated individuals following vaccine introduction may suggest the presence of indirection protection and allow a rough estimate of its strength. However, for precise estimates, clinical trials with specific designs are required [11].

Several studies in countries possessing long-term surveillance data and a range of high VC have reported substantial indirect protection effects, although the effect estimates varied between studies, countries and age groups [12-15]. Such variation makes it challenging to include vaccine-induced indirect protection effects in predictive modelling.

The public health impact of rotavirus vaccination has been assessed in several middle- and high-income countries by estimating benefit–risk (BR) ratios. These evaluations can be conducted for different vaccine scenarios, they can be used to quantify the current impact of vaccination or to predict the impact of immunisation programme changes. Therefore, they apply to the current local setting but also to hypothetical ones, typically with varying levels of VC. To provide uncertainty intervals (UI), BR studies may also involve model-generated simulations [16-20]. However, to assess the overall population impact of a vaccination, it is necessary to estimate the benefit including indirect protection effects. So far this has not been attempted in rotavirus BR studies, except for a recent analysis conducted in the Netherlands [21].

Rotarix and RotaTeq have been marketed in France since 2006 and 2007, respectively, but in the absence of a recommendation by health authorities or reimbursement, VC was estimated to be less than 10% according to a survey conducted between 2008 and 2013 [22]. In 2013, the French national technical committee on vaccination recommended rotavirus vaccination, conditional on a future cost-effectiveness evaluation. In 2015, however, two cases of intussusception with delayed care and fatal outcome were observed and the recommendation was withdrawn [23]. We previously estimated the BR ratio for rotavirus vaccination in the 2015 population in France at a median value of 214 for hospitalisations and 273 for deaths [20]. That analysis did not take the effects of indirect protection into account. In the present paper, we propose a new evaluation of this BR ratio that now includes it. Highly variable indirect effect estimates exist in high-income countries with medium-to-high VC and none is available for low-coverage settings, yet indirect effectiveness is expected to decrease with lower coverage levels. To circumvent these difficulties and to use realistic values in all scenarios, we used an approximated mathematical equation relating indirect effectiveness and VC that was proposed by Bauch et al. [24]. It involves an epidemiological metric: the basic reproduction number of an infection. In our approach, we considered this number as an additional parameter for which estimates for rotavirus infection are available in several high-income countries.

Overall, we aimed at estimating the BR ratio for the French population in various VC scenarios. We extended our model for BR ratio estimation to incorporate indirect protection in the algorithm and obtained corresponding predictions of indirect effectiveness. Finally, we also aimed at exploring the impact of assuming a higher case fatality of intussusception.

Methods

General study design and data sources

We developed an extended version of the model presented in Lamrani et al. [20]. The general purpose was to quantify the benefits of rotavirus vaccines (defined as the yearly number of prevented hospitalisations or deaths for RVGE in children under the age of 5 years), their risks (the yearly number of induced hospitalisations or deaths for intussusception in children under the age of 1 year), and then to calculate the ratio of these two estimates. This was done with a simulation study and applied to the French population in 2018. For parameterisation, we aimed at including French data wherever available or approached the situation in France with transposable data from other settings. Key parameters were (i) epidemiological and

Table 1

Estimated indirect effectiveness and annual benefits and risks of rotavirus vaccine, under various scenarios of vaccine coverage and efficacy waning, France, 2018 (n = 20,000 simulations)

Vaccine coverage	Waning scenario	Indirect effectiveness, mean (SD)	Benefit: number of prevented rotavirus gastroenteritis cases		Risk: number of induced intussusceptions		Benefit–risk ratio	
			Median	95% uncertainty interval [a]	Median	95% uncertainty interval [a]	Median	95% uncertainty interval [a]
10%	Linear	6.4% (0.4)	1,749 *2.4*	1,324 – 2,266 *2.1–2.7*	6.1 *0.006*	3.9–9.3 *0.001–0.02*	288.2 *384.2*	173.8 –480.0 *128.2 – 1,709*
	Accelerated	5.5% (0.3)	1,605 *2.2*	1,207–2,080 *1.9–2.5*			265.1 *354.5*	160.3 – 441.6 *116.5 – 1,634*
	Absence	7.3% (0.5)	1,873 *2.6*	1,411–2,419 *2.2–2.9*			309.1 *414.7*	185.1 – 520.4 *137.2 – 1,851*
50%	Linear	32.2% (2.0)	8,904 *12.3*	6,750–11,480 *10.8–13.7*	30.3 *0.03*	19.3–46.3 *0.007–0.09*	294.1 *391.5*	177.4 – 494.7 *127.3 – 1,771*
	Accelerated	27.7% (1.6)	8,200 *11.3*	6,250–10,600 *9.9–12.6*			270.3 *362.7*	163.0 – 455.3 *119.8 – 1,650*
	Absence	36.7% (2.4)	9,500 *13.1*	7,190–12,290 *11.4–14.7*			314.3 *427.6*	187.6 – 526.8 *139.2 – 1,920*
90%	Linear	57.9% (3.7)	16,280 *22.4*	12,380–20,840 *19.8–25.0*	54.6 *0.05*	35.0–83.8 *0.01–0.2*	297.6 *402.9*	179.4 – 497.3 *134.5 – 1,810*
	Accelerated	49.9% (3.0)	15,080 *20.8*	11,470–19,340 *18.4–23.1*			276.0 *370.8*	166.2 – 462.8 *121.8 – 1,700*
	Absence	65.9% (4.3)	17,350 *23.9*	13,230 –22,350 *21.1–26.7*			317.9 *428.1*	191.3 – 536.5 *141.7 – 1,977*

SD: standard deviation.

[a] 2.5%–97.5% percentiles.

All simulations assumed a mixture of 70% Rotarix and 30% Rotateq vaccines. Benefits, risks and benefit–risk ratios are given for hospitalisation (standard font) and for death (italic font).

demographical features (i.e. number of children under 1 year and under 5 years of age living in France and VC), (ii) relative risk (RR) of intussusception in the 3 weeks following administration of a vaccine dose and (iii) vaccine efficacy, including direct and indirect effects.

Although the main difference with our previous work was that we took the effects of indirect protection into account [20], other enhancements were made. Firstly, to fit the underlying age distribution of RVGE and of intussusception, we used exhaustive data from the French national health care system, rather than a sample. Together with patient age, this database included all hospitalisations occurring in children under the age of 5 years from 2009 to 2015 in France that were coded as K56.1 (for intussusceptions) and A08.0 (for RVGE) according to the ICD-10 classification. Secondly, we introduced a multiplicative correction factor for the incidence of RVGE and intussusception, taking into consideration the fact that the national estimates comprised a (small) number of vaccinated cases, whereas we wanted to estimate the background incidences (Supplementary Methods SM1 and SM2). Without these correction factors, the incidence of intussusception would have been slightly overestimated and the incidence of RVGE would have been slightly underestimated because vaccination induces some intussusception cases and prevents some RVGE cases. Thirdly, we modified the assumption about the long-term duration of protection after immunisation by exploring several waning scenarios after the 3rd year of life, as main or sensitivity analyses. Finally, we updated demographical data using 2018 values for French populations of children under 1 year of age and under 5 years of age (711,904 and 3,726,091, respectively [25]).

Three levels of VC were explored: 10%, the current approximate coverage which is considered as the base scenario in this work, 50%, a coverage level reached in many countries where the vaccine is recommended and realistic for rotavirus vaccine introduction without specific communication or reinforcement, and 90%, the observed coverage of recommended infant vaccines in France. Based on French pharmacy sales data, we assumed that 70% of administered doses were Rotarix and 30% Rotateq in the base scenario [22].

Table 2

Estimated annual benefits and benefit-risk ratios of rotavirus vaccine, under various scenarios of vaccine coverage and efficacy waning, scenario without indirect protection, France 2018 (n = 20,000 simulations)

Vaccine coverage	Waning scenario	Benefit: Number of prevented rotavirus gastroenteritis episodes		Benefit–risk ratio[a]	
		Median	95% uncertainty interval[b]	Median	95% uncertainty interval[b]
10%	Linear	998.4 *1.4*	756.1 – 1,280 *1.2 – 1.5*	164.4 *221.5*	98.5 – 272.6 *73.4 – 1,003*
	Accelerated	956.9 *1.3*	728.1 – 1,230 *1.2 – 1.5*	158.0 *214.9*	95.4 – 261.7 *70.6 – 967.2*
	Absence	1,018 *1.4*	772.9 – 1,310 *1.2 – 1.6*	167.8 *223.7*	101.1 – 281.9 *73.7 – 1,031*
50%	Linear	4,990 *6.9*	3,800 – 6,420 *6.1 – 7.7*	[a]	[a]
	Accelerated	4,780 *6.6*	3,630 – 6,140 *5.8 – 7.3*		
	Absence	5,100 *7.0*	3,890 – 6,560 *6.2 – 7.8*		
90%	Linear	8,970 *12.4*	6,830 – 11,540 *10.9 – 13.8*	[a]	[a]
	Accelerated	8,610 *11.9*	6,550 – 11,070 *10.5 – 13.2*		
	Absence	9,160 *12.6*	6,960 – 11,820 *11.1 – 14.1*		

[a] Benefit–risk ratio does not depend on vaccine coverage in the event that there is no indirect protection.

[b] 2.5%–97.5% percentiles.

All simulations always assumed a mixture of 70% Rotarix and 30% Rotateq vaccines. Benefits, risks and benefit–risk ratios are given for hospitalisation (standard font) and for death (italic font).

Using Monte Carlo simulations, we sampled parameters independently according to their distribution (Supplementary Tables S1 and S2) and generated simultaneous estimates of the number of cases avoided and induced, and the according benefit-risk ratios. Simulations were iterated 20,000 times. With this approach, point estimates are given as the 50% percentiles (i.e. median values) and UI are given as the 2.5% and 97.5% percentiles of the distributions resulting from the simulations. The model was written in SAS language and we used SAS 9.4 version to perform the simulations.

Modelling

Vaccine benefit assessment accounting for indirect protection

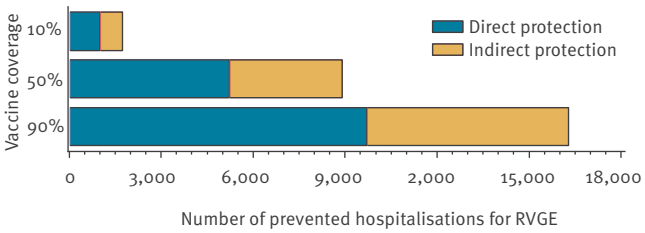
At the population level, the benefit of an immunisation programme is due to direct and indirect protection. In this work, the indirect protection was accounted for by introducing a 'pseudo-vaccine', which we assumed covered the entire child population with equal benefit and without any adverse event. Among unvaccinated children, this indirect effectiveness E^I applied homogeneously regardless of age. Among vaccinated children, it applied alone before receipt of the first dose of vaccine, while after the first dose, it applied in combination with direct efficacy E^D . Thus, vaccinated children benefitted from total effectiveness E^T [11], where

$$1 - E^T = (1 - E^D)(1 - E^I) \quad (1)$$

The parameter for direct protection corresponded to the vaccine efficacy estimated in clinical trials, with vaccine protection decreasing during the first 3 years following immunisation [26]. Consequently, we assumed that children were protected by the vaccine as soon as the first dose was administered and that this protection remained constant until another dose was administered or until the end of the first year of life. During the 2nd and 3rd years of life, children continued to benefit from direct protection, albeit at a lower level because of waning of antibodies. During the 4th and 5th years of life, we assumed in the base scenario that vaccine efficacy linearly waned to zero (Figure 1).

Figure 2

Number of hospitalisations prevented by direct and indirect protection, obtained under several scenarios of rotavirus vaccine coverage, France, 2018 (n = 20,000 simulations)



RVGE: rotavirus gastroenteritis.

Built-in indirect effectiveness

The estimates of the indirect protection effect available in the literature were observed in populations with a coverage of ca 50% or higher. In Germany, a 48% indirect effectiveness was estimated given a coverage of 47.6% (mean values over the observed period 2007–2017 [12]). In a meta-analysis, the VC ranged from 54.1% (in 2007–2008, US) to 93% (in 2013–2014, United Kingdom (UK)) [14]. In France, the VC is substantially lower and no pre-vaccine data are available to estimate the indirect protection effect. Therefore, for the three levels of VC, indirect protection levels were derived from Formula (2) which proposes an approximation of indirect effectiveness E^I from the VC, the direct efficacy E^D and the basic reproduction number R_0 (average number of secondary infections per primary case in a susceptible population) for universal vaccination against a paediatric infectious disease [24]:

$$E^I \approx \frac{R_0 \times VC \times E^D}{R_0 - 1} \qquad (2)$$

According to Formula (2), E^I decreases with R_0 (for $R_0 > 1$) with minimum VC × EDED . Rotavirus is highly infectious with R_0 estimates ranging from 11 to 54 in children younger than 5 years in high-income countries [27,28]. Although in Formula (2), the value of R_0 has a modest impact on E^I , as opposed to VC and E^D , we chose an overdispersed discrete distribution of R_0 to cover this range of estimates (Supplementary Table S1, last line). As for E^D in Formula (2), an average direct efficacy over both vaccines, doses and ages $\overline{E^D}$ was used (Supplementary Method SM1). We used this value E^I for unvaccinated children and in Formula (1) for vaccinated children.

Benefit–risk ratio calculation

Details on formulas for benefit and risk calculations are given in the Supplementary Methods. The benefit is the annual number of prevented hospitalisations for RVGE and depends on the background number of infants hospitalised at age w (w=1 to 261 weeks), on the proportion of the population newly vaccinated by dose d of either vaccine at age w, on E^T for either vaccine at dose d in week t of vaccination and on E^I . The risk is the annual number of vaccine-induced hospitalisations for intussusception and depends on the background number of infants experiencing the adverse event at age w (w=1 to 52 weeks), the proportion vaccinated by dose d of either vaccine at age w and the RR of intussusception in week t after dose d of vaccination with either vaccine. Finally, the BR ratio is simply obtained by dividing the benefit by the risk. Similar calculations apply for deaths.

Sensitivity analyses

Concerning the duration of protection, we considered two opposite scenarios: (i) accelerated waning, meaning that direct efficacy was not maintained beyond the 3rd year of life, so that the protection of a vaccinated child fell back to the indirect protection level by the age of 4 years and (ii) absence of waning, so that direct efficacy at 2 years of age was maintained until the age of 5 years.

For purposes of comparison, we performed a set of simulations without any indirect protection. We performed another set of simulations based on an assumption that only Rotarix or only Rotateq were available in the market.

Finally, we considered the conservative assumption where the case fatality rate for intussusceptions would reach the highest value among the countries covered by the review paper on childhood intussusception (i.e. 0.7%, observed in Spain) [29]. For this scenario, we made the most conservative choice for the persistence of vaccine efficacy, assuming accelerated waning.

Ethical statement

Because this was a simulation study, ethical approval was not needed.

Results

Background incidences

The annual background number of hospitalised RVGE in France was estimated at a median of 11,400 (95% UI: 8,770–14,500) and the annual background number of hospitalised intussusceptions at 192 (95% UI: 167–218). Age distributions are displayed in Supplementary Figures S2 and S3. Thus, the corresponding incidences were 3.1 per 1,000 for RGVE in children younger than 5 years and 2.8 per 10,000 for intussusceptions in children younger than 1 year.

Built-in indirect effectiveness estimates

With the three chosen VC rates (10%, 50% and 90%), the indirect effectiveness E^I as calculated from Formula (2) was estimated at a mean of 6.4% (standard deviation (SD): +/−0.4), 32.2% (SD: +/−2.0) and 57.9% (SD: +/−3.7), respectively (Table 1). The distributions

obtained after 20,000 simulations are displayed in Supplementary Figure S1.

Benefit–risk ratio estimates

In the base scenario where coverage was 10% with an assumption of linear waning of antibodies, we estimated a median BR ratio of 288.2 (95% UI: 173.8–480.0) for hospitalisations and 384.2 (95% UI: 128.2–1,709) for deaths (Table 1). The BR ratio increased with VC: for 50%, we estimated a BR ratio of 294.1 (95% UI: 177.4–494.7) for hospitalisations and 391.5 (95% UI: 127.3–1,771) for deaths and for a coverage of 90%, a BR ratio of 297.6 (179.4–497.3) for hospitalisations and 402.9 (95% UI: 134.5–1,810) for deaths (Table 1). While the estimated indirect effectiveness increased a lot with larger VC, predicted BR ratios in our model increased only modestly.

Estimated impact of indirect protection

Without including any indirect protection effect, we estimated a BR ratio of 164.4 (95% UI: 98.5–272.6) for hospitalisations and 221.5 (95% UI: 73.4–1,003) for deaths (Table 2). The proportion of prevented hospitalisations for RVGE thanks to indirect protection slightly decreased with larger VC levels, ranging from 43% (for 10% coverage) to 40% (for 90% coverage) (Figure 2).

Sensitivity analyses

The estimates for indirect effectiveness were slightly lower when assuming accelerated waning. For 10%, 50% and 90% VC, we obtained 5.5%, 27.7% and 49.9%, respectively (Table 1 and Supplementary Figure S1). Likewise, BR ratios were slightly lower; for 10% coverage for example, they were 265.1 (95% UI: 160.3–441.6) for hospitalisations and 354.5 (95% UI: 116.5–1,634) for deaths (Table 1). In case of absence of waning, the corresponding estimates were slightly higher: 7.3%, 36.7% and 65.9% for indirect effectiveness in the three CV scenarios, and 309.1 (95% UI: 185.1–520.4) and 414.7 (95% UI: 137.2–1,851) for the BR ratios for hospitalisations and deaths, respectively, with 10% coverage.

The whole set of simulations was also run for scenarios where only Rotarix or only Rotateq were available and the corresponding results are displayed in Supplementary Tables S4a and S4b for simulations with indirect protection and in Supplementary Tables S5a and S5b for simulations without indirect protection effect. We observed very marginal changes compared with the results of the scenario with a mixture of Rotarix and Rotateq vaccines.

In addition, assuming a 0.7% case fatality rate, accelerated waning and 10% coverage, the annual number of prevented deaths from RVGE was 2.2 (95% UI: 1.9–2.5) with an annual number of vaccine-induced deaths from intussusception of 0.042 (95% UI: 0.027–0.065) (Figure 3). The BR ratio for deaths in this scenario was 52.2 (95% UI: 33.4–83.3, declining to 30.9 (95% UI: 19.9–48.9) if no indirect protection effect was included.

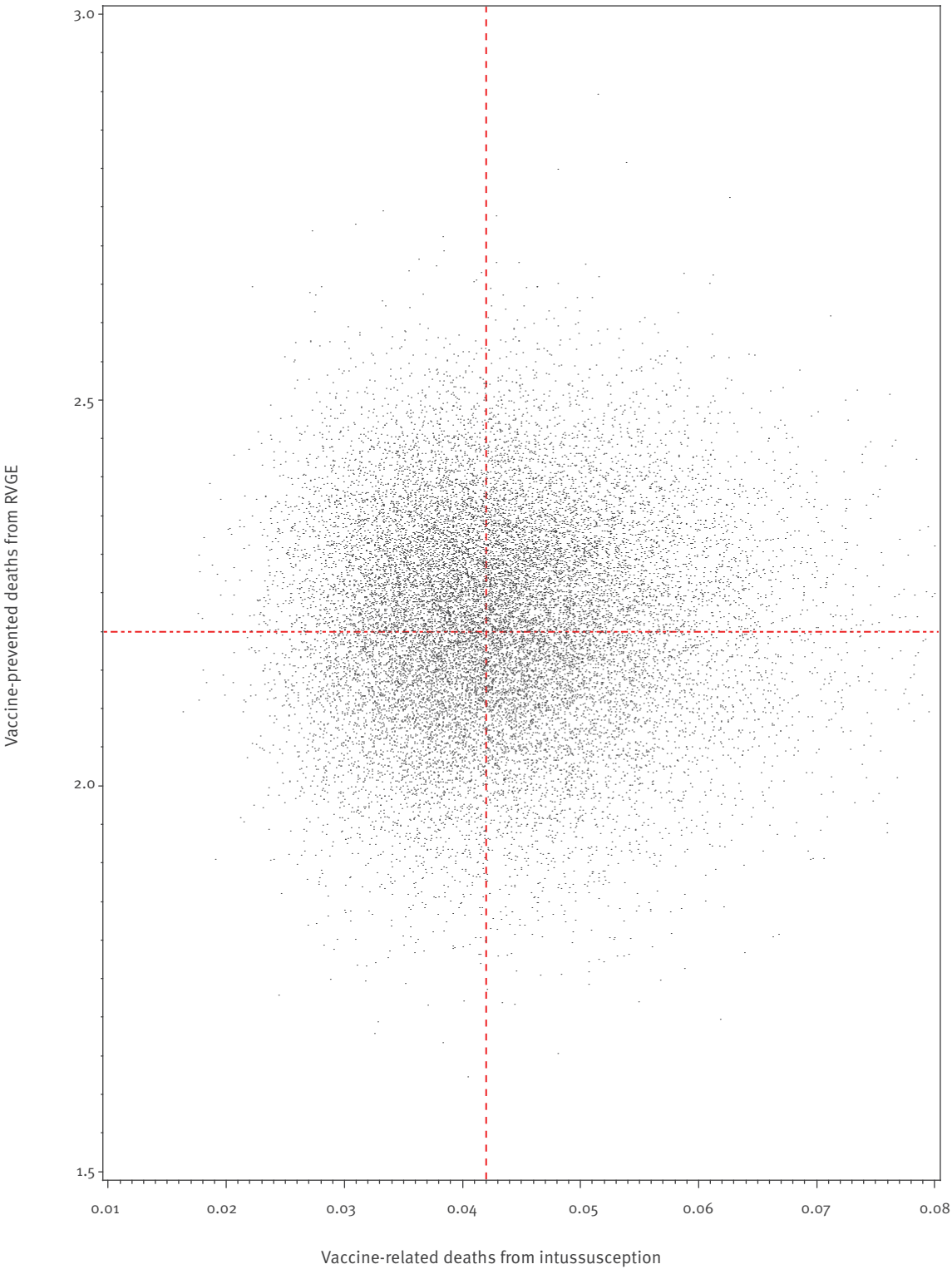
Discussion

The goal of this study was to provide an accurate and comprehensive BR assessment of rotavirus vaccination in France, by comparing the number of RVGE hospitalisations (or deaths) prevented by the vaccination with the number of hospitalisations (or deaths) induced by intussusception as an effect of the vaccination; we also included an indirect protection effect as a specific model component that varied across a range of VC scenarios. For VC of 10% (current), 50% and 90% (potential coverage rates), we found that the BR ratio ranged from 288 to 298 for hospitalisations and from 384 to 428 for deaths. Our results indicate that it increases with VC, whereas the contribution of indirect protection effects to the benefit is slightly but inversely related with VC. Indirect protection accounted for almost half of the prevented cases hospitalised for RVGE in all coverage scenarios. Sensitivity analyses showed that the alternative assumptions on waning only marginally impacted the results. Furthermore, a substantial BR ratio persisted under the unfavourable assumption of higher case fatality associated with intussusception, with a lower BR ratio uncertainty interval limit at 33.4. Another specificity of this work is that background incidences of RVGE and intussusceptions were calculated by using exhaustive data from the French national healthcare system and corrective factors, and that it mimics the French context (market distribution between Rotarix and Rotateq).

Because no indirect effect had been included in our previous work [20], the benefits and the BR ratios resulting from the present analyses are greater than those already published, even for more conservative assumptions about the waning of antibodies. The BR ratio without indirect immunity obtained in the present work could be considered as the lower limit of the BR, in case indirect protection would be negligible. The only available BR study accounting for indirect protection found a BR ratio estimate of 685 hospitalisations with a hypothetical 86% VC in the Netherlands [21]. This ratio is larger than what we observed in our study (318 with no waning and 90% coverage), even though the authors applied an indirect effectiveness of 30% maximum, which is lower than the 66% estimated in our approach for this coverage. The gap between these results is mainly driven by the choice in the risk component: Bruijning et al. used one excess case of intussusception per 50,000 vaccinated children, which is by far more optimistic than ours. Of note, they also ran simulations using one excess intussusception case per 20,000 vaccinated children and obtained then a much lower BR value of 274. Compared with estimates from other countries (see Table 3 in reference [19] for example), our BR ratio estimates without indirect protection effects were lower than the range of published values for hospitalisations (from 282 in Mexico to 1,265 in Brazil) and fall within the range of published values for deaths (from 71 in the US to 395 in Latin America).

Figure 3

Number of vaccine-prevented deaths from rotavirus gastroenteritis in children under 5 years of age (benefit) vs vaccine-related deaths from intussusception in infants under 1 year of age (risk), France, 2018 (n = 20,000 simulations)



RVGE: rotavirus gastroenteritis.

Assumptions: a high estimate of case fatality (0.7%) for intussusceptions, 10% coverage and accelerated waning effect.

In the present study, we approximated indirect effectiveness by using a formula including coverage, direct effect and R_0. Although the dynamics of rotavirus infection are not fully understood and R_0 estimates vary widely, there is evidence that the basic reproduction number for rotavirus is high. Another difficulty is that the approximation proposed by Bauch et al. assumes lifelong vaccine-derived and natural immunity, which may not be met for rotavirus. At the same time, as mentioned by the authors, this approximation only partially accounts for indirect protection or herd immunity [24]. Despite these challenges, the indirect effectiveness estimates that we produced and used fall within the range of estimates derived from real-life surveillance data in populations with ca 50% VC (e.g. in the US) or 90% VC (e.g. in Belgium, Australia or Great Britain) [12-15].

In mathematical modelling, indirect protection effects are usually taken into account by using dynamic transmission models, which produce indirect effects depending on hypotheses about age-specific mixing patterns and risk of transmission [27]. Such a model was developed for evaluating the cost effectiveness of Rotateq vaccination in France [30], assuming 75% VC, but the indirect effectiveness was not explicitly quantified in that work. In addition, results from some mathematical modelling studies on rotavirus predict a limited indirect protection effect that contrasts with the large reductions in incidence in unvaccinated age groups observed in countries with high coverage levels ([31], p. 32).

In this work, we had to make several simplifying assumptions. Firstly, the pseudo-vaccine approach supposes that the vaccine has been on the market long enough and the coverage is stable. Secondly, the possible interactions of children younger than 5 years with other age groups, whether with older children (6–10 years) or with adults, were not taken into account. Thirdly, the population of children under the age of 5 years was considered as a whole, which means that we did not introduce age-specific indirect effects. However, a clear relationship between age and the amount of indirect protection has not yet been established. Comparing the results of studies performed in three high-income countries among children under 5 years of age, estimates from the US were highest for the youngest and decreased with age, estimates in Great Britain were constant across age groups, while estimates in Australia were high in the middle-aged group (36–47 months) and low in other age groups [14]. Fourthly, estimation of RVGE and intussusception incidences and age distributions were not based on epidemiological surveillance but on national drug claims and hospital discharge data, by identifying cases through specific ICD10 codes. Fifthly, for some of the input parameters, we could not find values resulting from French studies. Wherever possible, we tried to input results from studies performed in Europe or at least in high-income countries. Finally, the approximation proposed by Bauch et al. was obtained with a pseudo-dynamic model by including the basic reproduction number R_0, a transmission feature of the rotavirus [24]. We acknowledge that this static approach oversimplifies the likely complex pattern of the disease. In sensitivity analyses, the BR ratio estimation was overall robust and not dependent on assumptions of efficacy persistence. Additional knowledge about the effectiveness of rotavirus vaccines would help refine the proposed modelling framework.

BR ratios without indirect protection effects may be the most relevant for vaccine decision by families and doctors for individual children. However, as soon as the goal of protecting vulnerable persons or eliminating rotavirus disease is established, the BR ratio including indirect protection becomes more relevant, even for individual decision-making. From the perspective of national decision makers, BR estimates including indirect protection are the most relevant, and our results suggest that the benefits of recommending vaccination against rotavirus outweigh the risks. However, some additional considerations may be required before implementing nationwide recommendations or obligations. Firstly, for currently recommended or mandatory infant vaccines in France, the risk of a severe and possibly fatal side effect can be estimated at 0.0003% for the paediatric hexavalent vaccine (anaphylactic shock) and 0.0022% for the measles-mumps-rubella vaccine (adding up risk estimates for anaphylactic shock, encephalitis and thrombocytopenic purpura) [32-36]. This is substantially lower than our estimate of ca 0.0086% for the rotavirus vaccine. As French people are keenly aware of vaccine safety [37], they may not agree with the claim that 'rotavirus vaccine is safe'. Secondly, the tendency of parents to attribute a more negative value to vaccine-induced than disease-induced deaths, also known as the omission bias, has been described for several recommended vaccinations [38,39]. Similarly, averting the side effects of vaccines was found to dominate judgments in vaccine decision-making among adults in the UK [40]. Such an individual preference could limit acceptance of the rotavirus vaccine despite official recommendations. As safety concerns interact with the perception of disease risk [41], BR analyses give structure to the implicit reasoning of individuals and society at large. In any case, national decisions about vaccine recommendations need to be based not only on scientific data but also on political and societal priorities.

Conclusion

The BR ratio estimates for rotavirus vaccination are substantially impacted by taking into account indirect protection effects. We have simulated indirect protection effects from rotavirus vaccination with simple techniques, yielding estimates that are roughly comparable to those obtained with data from surveillance studies. Given the major uncertainty about the exact level of indirect protection effects, these modelling techniques have helped to mitigate knowledge gaps

about the full impact of vaccination at the population level for different coverage scenarios. We used a simulation framework to incorporate the uncertainty of the model parameters into the estimation and carefully considered relevant sources of uncertainty. Addressing these issues is an important step towards an unbiased assessment of the BR ratios of vaccination. This adds stronger evidence on which decision-making and communication in vaccination programmes can be based.

Acknowledgements

The authors would like to thank R. Dray-Spira (Epidemiology Department, French Drug Medicine Agency) for providing aggregate hospitalisation data.

Conflict of interest

None declared.

Authors' contributions

SE, JEM and PTB designed the study, contributed to the interpretation of the results, manuscript writing and approved its final version. SE and PTB conceived and implemented the mathematical model. SE performed the analyses.

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