swiss medical weekly

Original article | Published 20 February 2023 | doi:10.57187/smw.2023.40040
Cite this as: Swiss Med Wkly. 2023;153:40040

Detection of mostly viral pathogens and high proportion of antibiotic treatment initiation in hospitalised children with community-acquired pneumonia in Switzerland – baseline findings from the first two years of the KIDS-STEP trial

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Summary

AIMS OF THE STUDY: Globally, since the introduction of conjugate-vaccines against encapsulated bacteria, respiratory viruses have caused most hospitalisations for community-acquired pneumonia. The aim of this study was to describe pathogens detected and their association with clinical findings in Switzerland.

METHODS: Baseline data were analysed for all trial participants enrolled between September 2018 and September 2020 into the KIDS-STEP Trial, a randomised controlled superiority trial on the effect of betamethasone on clinical stabilisation of children admitted with community-acquired pneumonia. Data included clinical presentation, antibiotic use and results of pathogen detection. In addition to routine sampling, nasopharyngeal specimens were analysed for respiratory pathogens using a panel polymerase chain reaction test covering 18 viral and 4 bacterial pathogens.

RESULTS: 138 children with a median age of 3 years were enrolled at the eight trial sites. Fever (obligatory for enrolment) had been present for median 5 days before admission. Most common symptoms were reduced activity (129, 93.5%) and reduced oral intake (108, 78.3%). Oxygen saturation <92% was found in 43 (31.2%). Forty-three participants (29.0%) were already on antibiotic treatment prior to admission and 104 participants (75.4%) received antibiotic treatment on admission. Pathogen testing results were available from 132 children: 31 (23.5%) had respiratory syncytial virus detected, 21 (15.9%) human metapneumovirus. The pathogens detected showed expected seasonal and age preponderance and were not associated with chest X-ray findings.

CONCLUSIONS: In the context of the predominantly viral pathogens detected, the majority of antibiotic treatment is probably unnecessary. The ongoing trial, as well as other studies, will be able to provide comparative pathogen detection data to compare pre- and post-COVID-19-pandemic settings.

This trial is registered on https://clinicaltrials.gov (NCT03474991) and on the Swiss National Clinical Trials Portal (SNCTP000002864).

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Introduction

In Europe, community-acquired pneumonia accounts for 10 to 15% of paediatric hospital admissions [1]. Studies conducted in different settings since the introduction of conjugate vaccines for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b consistently found the majority of admissions due to acute respiratory infections and more specifically for community-acquired pneumonia to be caused by respiratory viruses, most prominently respi-

ratory syncytial virus (RSV) and influenza viruses [2–4]. Detection of individual respiratory viruses is not associated with increased severity or extended length of hospital stay [5], although some studies have shown increased length of stay for combinations of RSV and influenza or rhinoviruses [6, 7]. Current clinical guidelines for children hospitalised with CAP uniformly recommend antibiotic treatment in the presence of World Health Organization (WHO) danger signs but are incongruent regarding antibiotics in other children.

The KIDS-STEP trial enrols children at eight sites providing medical care to a large proportion of Switzerland's paediatric population [8]. The ancillary microbiology study has the aim to provide data for pathogen subgroup analyses of the effect of betamethasone for community-acquired pneumonia and to differentiate pathogen-driven effects on length of hospital stay from medication effects. The COVID-19 pandemic has disrupted the seasonality of acute respiratory infections in Switzerland and may result in changed patterns of aetiology of community-acquired pneumonia in the coming years [9]. We therefore conducted a preliminary pathogen analysis for the trial participants enrolled up to autumn 2020 to provide representative, high-quality and mostly prepandemic data on pathogen detection in children in Switzerland hospitalised for community-acquired pneumonia. The aim of this study was to describe the pathogens detected and their association with clinical findings at baseline in Switzerland.

Methods

The KIDS-STEP Trial is a randomised controlled superiority trial on the effect of betamethasone on clinical stabilisation of children hospitalised with community-acquired pneumonia. The full trial protocol has been published [8]. In brief, children are screened following a clinical diagnosis or differential diagnosis of community-acquired pneumonia and the decision to admit as an inpatient and are eligible if they are between 6 months and 14 years of age and fulfil a clinical case definition of community-acquired pneumonia at eight paediatric emergency departments across Switzerland. The clinical case definition is a temperature ≥38°C and at least two from a list of signs and symptoms of a lower respiratory tract infection. Detailed eligibility criteria are presented in table 1. Co-primary outcomes of the main trial are (1) clinical stabilisation defined as normalisation of initially deranged vital signs or discharge from hospital and (2) re-admission to hospital within 4 weeks from randomisation. Enrolment into the main trial has been delayed owing to the COVID-19 pandemic and is currently ongoing [9].

All parents or legal guardians gave written informed consent including the ancillary study presented here. The trial and ancillary study were approved by the local ethics committee of the trial centre (Ethikkommission Nordwest- und Zentralschweiz (EKNZ), study no. 2018-00563), other local ethics committees in Switzerland for participating sites and the regulatory authority Swissmedic (2018 DR 3070). The trial is registered on https://clinicaltrials.gov (NCT03474991) and on the Swiss National Clinical Trials Portal (SNCTP000002864).

For this interim baseline analysis, we included participants enrolled over the first two years since opening of the trial, i.e., from September 2018 until calendar week 36 in 2020. Clinical data at presentation, management during the first 24 hours after admission and pathogen detection results from standard of care samples taken on the day of admission were collected prospectively for the main trial and were extracted from the trial database held at the University of Basel's clinical trials unit. Positive pathogen detection results from standard of care testing were collected through the trial's case report forms with specific fields for RSV, influenza viruses, *S. pneumoniae*, *H. influenzae* and *Mycoplasma pneumoniae* and free text for other respiratory pathogens. SARS-CoV-2 test results were collected in amended case report forms from 19 May 2020 onwards. Standard of care samples were obtained according to routine procedures at the trial sites, local materials were used and the analyses performed in local laboratories.

Randomised treatment allocation to betamethasone or placebo remained concealed. The interim analysis was exploratory and sample size and endpoints were not pre-specified. For the current report, use and release of clinical follow-up data from the main trial needed to be limited in order to prevent jeopardising the integrity of the trial.

As an ancillary study offered to all trial participants, nasopharyngeal swabs are taken on the day of admission. Nasopharyngeal swabs were collected on the day of randomisation using swabs (FLOQSwab®) and transferred to 3 ml universal transport medium (UTM®) by Copan (Brescia, Italy). The suspended swabs were processed within 48 hours. After vortexing for 30 seconds, UTM was transferred to sterile storage tubes in aliquots of 900 µl. Aliquots were stored at −80°C until analysis. One aliquot per patient was used for pathogen detection with Filmarray BIOFIRE® Respiratory Panel 2.1 *plus* (bioMérieux, Marcy-l'Étoile, France). The panel detects the following targets: adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63, Middle East respiratory syndrome coronavirus (Mers-CoV), human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A/H1, influenza A/H1-2009, influenza A/H3, influenza B, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, RSV, *Bordetella pertussis*, *Bordetella parapertussis*, *Chlamydophila pneumoniae* and *M. pneumoniae*. The analyses were done before addition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to an updated version of the panel.

Data management and statistical operations were performed in Stata 15 (College Station, Texas). C-reactive protein values were grouped into lower than 80 mg/l and equal to or higher than 80 mg/l [12]. For comparisons between groups Wilcoxon rank-sum test or Kruskal-Wallis tests were used for continuous variables and chi-square tests for categorical variables. The alluvial plot for figure 1 was drawn using the online tool RawGraphs 2.0 beta.

Ethics

The trial and ancillary study were approved by the local ethics committee of the trial centre (Ethikkommission Nordwest- und Zentralschweiz (EKNZ), study no. 2018-00563), other local ethics committees in Switzerland for participating sites and the regulatory authority Swissmedic (2018 DR 3070).

Results

The first 138 children enrolled in the trial were included in the current analysis. The majority of participants were enrolled in autumn and winter 2019/20 (detailed in supplementary figure S1 in the appendix). Thirty (21.7%) were enrolled after detection of the first case of COVID-19 in Switzerland, mostly in March 2020 and only 6 were enrolled between April and September 2020.

Clinical characteristics of the participants at trial entry are presented in table 2. The median age was 3 years with an even distribution between sexes. A high proportion of participants had signs of more severe disease, including 65.2% with chest retractions and 31.2% with an oxygen saturation below 92%.

Forty-three participants (29.0%) were already on antibiotic treatment prior to admission and 104 participants (75.4%) received antibiotic treatment on admission. Figure 1 shows antibiotic treatment of trial participants before and after admission. The most common antibiotics used were aminopenicillins (58.7% of those receiving antibiotic treatment after admission). When antibiotics were used, 85.6% were Access group antibiotics according to the WHO's Essential Medicines List AWaRe classification [13]. Six of the 27 participants (22.2%) initially treated with an aminopenicillin plus a beta-lactamase inhibitor were switched to an aminopenicillin only within the first 24 hours after admission.

Within the first 24 hours, 91 participants (65.9%) received supplemental oxygen and four (2.9%) were placed on some form of respiratory support.

Respiratory specimens for pathogen testing were obtained from 132 of 138 participants (95.7%). These were either part of the standard of care or nasopharyngeal swabs obtained as study samples. Eighty-four participants (60.9%) had both kinds of sample taken, 25 (18.1%) only standard of care samples, 23 (16.7%) only study samples, and 6 (4.3%) had no sample taken.

Standard of care samples were obtained from 109 participants (79.0%). Except for one tracheal aspirate, all other respiratory standard of care samples were nasopharyngeal swabs or nasopharyngeal aspirates. Seventy-two (66.1%) were tested for viruses and bacteria, 16 (14.7%) for viruses and 21 (19.3%) for bacteria only. Testing for bacteria was most commonly done by bacterial culture. The respiratory pathogens detected on standard of care samples are listed in table 3. No positive SARS-CoV-2 tests were reported. Blood cultures were obtained in 86 patients but yielded no positive results.

Study nasopharyngeal swabs at trial entry were obtained from 107 participants (77.5%). Table 3 shows the respiratory pathogens detected on nasopharyngeal swabs in these

Table 1:
Eligibility criteria for the KIDS-STEP trial [8].

Inclusion criteria (all must be fulfilled)	
At least 6 months of age and less than 14 years of age	
Body weight between 5 kg and 45 kg	
Admission to hospital (i.e., assignment of an inpatient case number or receipt of in-hospital treatment in a designated short stay unit)	
Clinical diagnosis of CAP	*A. Temperature ≥ 38 °C measured by any method or history of fever in last 48 hours reported by parents*
	AND
	B. at least two of the following signs and/or symptoms:
	Presence of cough (observed or reported in last 72 to 96 hours)
	Increased age-specific respiratory rate as defined by American Heart Association Accredited Pediatric Advance Life Support guidelines during assessment in the paediatric emergency department (first or second triage or clinical examination)
	Hypoxaemia (<92% arterial oxygen saturation) in room air as measured by pulse oximetry (SpO_2) [10, 11]
	Signs of laboured/difficult breathing, including nasal flaring, chest retractions, grunting, abdominal breathing and shortness of breath
	Clinical signs of lobar pneumonia including focal dullness to percussion, focal reduced breath sounds, crackles with asymmetry
Parent and/or child (as age-appropriate) willing to accept all possible randomised allocations and to be contacted for three telephone follow-up visits up to and including at 4 weeks after randomisation	
Informed consent form for trial participation signed by participants and/or caregivers	
Exclusion criteria (excluded if of the following are present)	
Presence of local complications (empyema or pleural effusion with clinically identified need for drainage, pneumothorax and pulmonary abscess).	
Chronic underlying disease associated with an increased risk of very severe CAP or CAP of unusual aetiology, such as sickle cell disease, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis.	
Bilateral wheezing without focal chest signs AND clinical indication for primary administration of steroids (most likely to represent respiratory tract infection affecting the medium airways, i.e., not pneumonia).	
Admission to hospital with a primary clinical diagnosis of bronchiolitis.	
Inability to tolerate oral medication.	
Documented allergy or any other known contraindication to any trial medication.	
Subacute or chronic conditions requiring higher betamethasone equivalent or known primary or secondary adrenal insufficiency.	
Known diabetes mellitus (type 1).	
Hospitalisation within the last two weeks preceding current admission with the possibility that pneumonia could be hospital-acquired or healthcare-associated.	
Completion of a course of systemic corticosteroids within 2 weeks from enrolment for courses of >5 days.	
Transfer for any reason to a non-participating hospital directly from the paediatric emergency department.	
Parents are unlikely to be able to reliably participate in telephone follow-up because of significant language barriers.	
Participation in another study with an investigational drug within the 30 days preceding and during the present study.	
Previous enrolment into the current study.	
Enrolment of the investigator, his/her family members, and other dependent persons.	

participants. The most frequently detected pathogen was human rhinovirus/enterovirus, followed by RSV and hMPV.

Twenty-one of the 24 participants where multiple pathogens were detected in study samples carried multiple (up to four) different viruses. In the other three participants, *M. pneumoniae* was found in combination with a virus (one adenovirus, two rhinovirus).

When information from standard of care and study samples was combined, 5 (3.8%) participants had co-detection of bacteria and viruses. Ninety-seven participants (73.5%) had at least one respiratory virus detected in any sample and 92 (69.7%) had one or more viruses but no bacteria detected. All co-detections of different pathogens including study and standard of care samples are detailed in supplementary table S1 in the appendix.

Detection of respiratory pathogens showed age- and season-related patterns (table 4). RSV was more commonly found in younger children and during the peak acute respiratory infection season from October to March. Influenza virus was equally more common during the acute respira-

Table 2:
Clinical characteristics at presentation and antibiotic treatment.

All		**138 (100%)**
Demographics		
Sex, n (%)	Female	66 (47.8)
	Male	72 (52.2)
Median age in years (IQR)		3.04 (1.67–4.67)
Season of inclusion n (%)		
Season	April to September	29 (21.0)
	October to March	109 (79.0)
Signs at presentation n (%)		
Wheeze	Present	29 (21.0)
	Not present	104 (75.4)
	Unknown	5 (3.6)
Crackles	Present	88 (63.8)
	Not present	48 (34.8)
	Unknown	2 (1.5)
Retractions	Present	90 (65.2)
	Not present	46 (33.3)
	Unknown	2 (1.5)
Reduced oral intake	Present	108 (78.3)
	Not present	27 (19.6)
	Unknown	3 (2.2)
Reduced activity	Present	129 (93.5)
	Not present	7 (5.1)
	Unknown	2 (1.5)
Oxygen saturation <92%	Present	43 (31.2)
	Not present	95 (68.8)
	Unknown	0 (0.0)
C-reactive protein >80 mg/l	Present	32 (23.2)
	Not present	71 (51.5)
	Unknown	35 (25.4)
Chest X-ray	Lobar consolidation and patchy infiltrates	7 (5.1)
	Lobar consolidation only	46 (33.3)
	Patchy infiltrates only	47 (34.1)
	Inconclusive infiltrates	8 (5.8)
	Not suggestive of pneumonia	4 (2.9)
	Not done	26 (18.8)
Chest sonography	Done	14 (10.1)
	Not done or not documented	124 (89.9)
Days coughing before presentation	Median (IQR)	5 (3–8)
	Unknown	0 (0.0)
Days of fever before presentation	Median (IQR)	5 (2–6)
	Unknown	0 (0.0)
Antibiotic treatment n (%)		
Decision to treat with antibiotics on admission	Yes	104 (75.4)
	AP only	61 (44.2)
	AP + BLI	27 (19.6)
	Ceph	9 (6.5)
	BL + M	4 (2.9)
	Other	3 (2.2)

IQR: interquartile range, AP: aminopenicillin, AP + BLI: aminopenicillin + beta-lactamase inhibitor, Ceph: cephalosporin, BL + M: beta-lactam + macrolide

tory infection season, and *M. pneumoniae* was more commonly detected in older children.

Patchy changes on chest X-ray were found in a higher proportion of children than lobar consolidations with any of the listed pathogens detected, but this finding was not supported by statistical evidence.

Discussion

In line with international data, RSV is the most commonly detected pathogen that has been found to be strongly associated with hospital admission [2, 4]. Compared with other European settings, hMPV was detected more frequently in the Swiss population. This may either reflect differences in local aetiology or the winter season 2019/

Figure 1: Alluvial plot of antibiotic treatment prior to admission and on admission. No label: unknown; AMC: amoxicillin + clavulanic acid; AMX: amoxicillin; BL + M: beta-lactam + macrolide; CFX: cefuroxime; CLA: clarithromycin; CRO: ceftriaxone; DOX: doxycycline

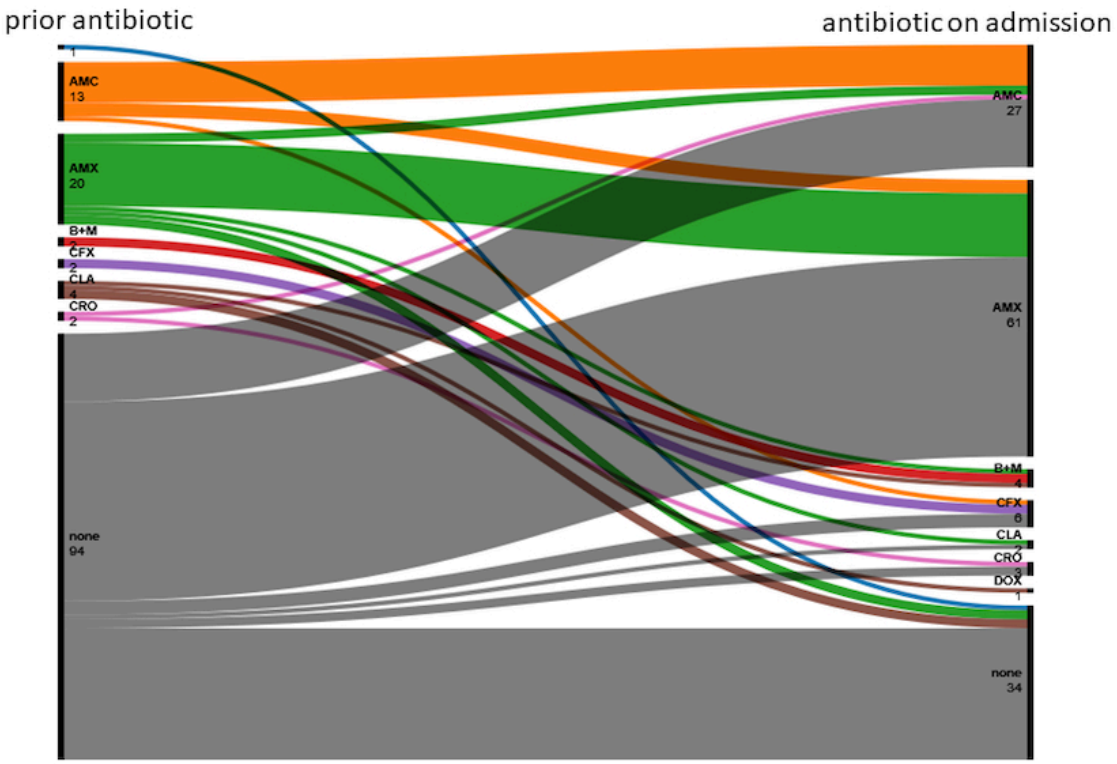

Table 3:
Pathogens detected in study participants. *S. pneumoniae* and *H. influenzae* were not tested for on study samples; data collected on standard of care samples and pathogens other than RSV, influenza viruses, *S. pneumoniae*, *H. influenzae* and *M. pneumoniae* was collected as free text and may be incomplete – numbers detected should be interpreted with care.

Pathogen		Participants tested		
		Standard of care samples	Study samples	On any sample
All samples		109 (100%)	107 (100%)	132 (100%)
Adenovirus		1 (0.9)	11 (10.3)	12 (9.1)
RSV		19 (17.4)	29 (27.1)	31 (23.5)
hMPV		4 (3.7)	19 (17.8)	21 (15.9)
Influenza viruses		12 (11.0)	11 (10.3)	15 (11.4)
PIV		3 (2.8)	8 (7.5)	11 (8.3)
Human rhinovirus/enterovirus		11 (10.0)	32 (29.9)	35 (26.5)
Endemic coronaviruses		4 (3.7)	7 (6.5)	10 (7.6)
S. pneumoniae		2 (1.8)	-	2 (1.5)
H. influenzae		1 (0.9)	-	1 (0.8)
B. pertussis		0 (0.0)	0 (0.0)	0 (0.0)
B. parapertussis		0 (0.0)	0 (0.0)	0 (0.0)
C. pneumoniae		0 (0.0)	1 (0.9)	1 (0.8)
M. pneumoniae		5 (4.6)	6 (5.6)	10 (7.6)
Number detected	0	49 (45.0)	13 (12.2)	26 (19.7)
	1	58 (53.2)	70 (65.4)	78 (59.1)
	>1	2 (1.8)	24 (22.4)	28 (21.2)

RSV: respiratory syncytial virus; hMPV: human metapneumovirus; PIV: parainfluenza viruses; endemic coronaviruses: coronavirus 229E, coronavirus HKU1, coronavirus OC43, coronavirus NL63

20 may have seen uncommonly large numbers of hMPV infections. Both RSV and influenza showed the expected seasonality. Since very few participants were enrolled after the onset of the COVID-19 pandemic, we were unable to capture possible changes in seasonality of pathogens. As expected, *M. pneumoniae* was more commonly detected in older children [14]. Human rhinovirus was overall the most frequently detected pathogen, but previous studies have shown that detection of human rhinovirus in upper respiratory tract samples is only very weakly associated with pneumonia or hospital admission due to acute respiratory infection [2, 4].

Of the children admitted with community-acquired pneumonia, 75.4% received antibiotic treatment. Antibiotics were selected mostly in accordance with international treatment guidelines and from the AWaRe classification's Access group [11, 13]. Assessed against the pathogen testing results, it is likely that a large proportion of these antibiotic prescriptions were unnecessary. German guidelines advise withholding antibiotics in children without WHO danger signs, whereas current UK guidelines advise treating and reviewing in due course, especially after receiving pathogen testing results. The proportion of children receiving antibiotics on admission in our study is broadly comparable to recent studies from the USA and Europe [4, 15, 16]. Future analyses of the trial will show if antibiotics were stopped during the participants' hospitalisation. Earlier availability of results from rapid syndromic pathogen testing may prevent antibiotic prescriptions in children with acute respiratory infections including pneumonia, but results from single-centre or retrospective studies have so far been disappointing [17, 18]. Judicious prescribing can be aided by the implementation of Antimicrobial Stewardship programmes, which have so far not been extended to Swiss paediatric emergency departments [19].

Overall, 81.2% of patients had a chest X-ray. This is surprising because German language guidelines that were written with participation of Swiss members do not routinely recommend a chest X-ray in children without WHO danger signs [11]. The PERCH study demonstrated that abnormal chest X-ray findings were associated with severe or very severe pneumonia and slightly longer duration of symptoms [20]. However, 46% of children with clinically severe or very severe pneumonia had a normal chest X-ray, demonstrating that radiology alone is insufficient to iden-

Table 4:
Age, season and chest X-ray findings by detection of respiratory pathogens.

		Not detected	Detected	p-value
RSV				
Age, median (IQR)		3.33 (1.75–5.08)	2.42 (1.42–3.17)	0.015
Season, n (%)	Apr to Sep	28 (96.6)	1 (3.5)	0.006
	Oct to Mar	79 (72.5)	30 (27.5)	
CXR, n (%)	Consolidation	47 (88.7)	6 (11.3)	0.068
	Patchy	33 (70.2)	14 (29.8)	
	Not suggestive	9 (75.0)	3 (25.0)	
Influenza virus				
Age, median (IQR)		2.92 (1.58–4.5)	4.08 (2.33–5.75)	0.100
Season, n (%)	Apr to Sep	29 (100.0)	0 (0.0)	0.034
	Oct to Mar	94 (86.2)	15 (13.8)	
CXR, n (%)	Consolidation	49 (92.5)	4 (7.6)	0.211
	Patchy	42 (89.4)	5 (10.6)	
	Not suggestive	9 (75.0)	3 (25.0)	
hMPV				
Age, median (IQR)		3.17 (1.92–4.75)	2.17 (1.58–3.17)	0.066
Season, n (%)	Apr to Sep	25 (86.2)	4 (13.8)	0.810
	Oct to Mar	92 (84.4)	17 (15.6)	
CXR, n (%)	Consolidation	46 (86.8)	7 (13.2)	0.280
	Patchy	36 (76.6)	11 (23.4)	
	Not suggestive	11 (91.7)	1 (8.3)	
Seasonal (endemic) coronaviruses				
Age, median (IQR)		3.13 (1.67–4.75)	2.33 (1.25–3.17)	0.123
Season, n (%)	Apr to Sep	29 (100.0)	0 (0.0)	0.090
	Oct to Mar	99 (90.8)	10 (9.2)	
CXR, n (%)	Consolidation	49 (92.5)	4 (7.6)	0.341
	Patchy	41 (87.2)	6 (12.8)	
	Not suggestive	12 (100.0)	0 (0.0)	
M. pneumoniae				
Age, median (IQR)		2.92 (1.58–4.50)	6.75 (4.50–8.83)	<0.001
Season, n (%)	Apr to Sep	26 (89.7)	3 (10.3)	0.469
	Oct to Mar	102 (93.6)	7 (6.4)	
CXR, n (%)	Consolidation	51 (96.2)	2 (3.8)	0.131
	Patchy	41 (87.2)	6 (12.8)	
	Not suggestive	12 (100.0)	0 (0.0)	

IQR: Interquartile range; CXR: chest X-ray; p-values obtained by Wilcoxon rank-sum test or chi-square test as applicable and shown to describe distribution patterns of the data (not for formal hypothesis testing)

tify children with more severe disease [20]. In a high-resource setting, the decision on antibiotic treatment taken before chest X-ray was altered in less than half of cases where radiological findings were discordant (i.e., not suggestive of pneumonia in children with a pre-X-ray plan for antibiotics and vice versa), indicating that care providers are aware of the limited predictive value of chest X-ray [21]. Pleura and lung sonography have demonstrated a high negative predictive value for pathological findings on chest X-ray in paediatric community-acquired pneumonia and can help to avoid unnecessary irradiation in settings where sufficient resources for ultrasound are available [22].

The presented study has some important limitations. Pathogen testing both on study and routine samples was mostly limited to upper respiratory tract samples. A strong association of detection of pathogens in upper respiratory tract samples with hospitalisation for acute respiratory infection is only seen with some respiratory viruses (RSV, influenza virus, hMPV and parainfluenza viruses) but not in bacteria or human rhinovirus/enterovirus [4]. Lower respiratory tract samples may be better suited for detection of aetiologically relevant bacteria [23, 24]. Additionally, for standard of care samples only positive findings were collected. However, in paediatric clinical routine, sampling is most commonly limited to upper respiratory tract samples [25]. Because more than a quarter of children had already received antibiotic treatment prior to inclusion in the trial, a higher proportion of detection of typical bacteria may have been missed [26]. The test method applied to study samples did not include *S. pneumoniae* or *H. influenzae*. It is likely that *S. pneumoniae* would otherwise have been detected in a substantial proportion of participants, but the relevance of this finding to establish a causal agent for the community-acquired pneumonia episode would have been questionable [2, 4, 27].

A second important limitation is the small sample size. Although we were able to sample more than 10% of children admitted for community-acquired pneumonia at the participating centres during the study period, we were not able to assess pathogen interactions or seasonality, age preponderance or association with length of hospital stay for rarer pathogens.

The trial was designed to capture a real-world patient population and is thus using a pragmatic clinical case definition [28]. Patients were selected for screening for the trial based on the clinician's diagnosis of community-acquired pneumonia.

All patients admitted for community-acquired pneumonia at the participating sites were recorded as pre-screened patients and more than a third of these fulfilled the eligibility criteria. Although this proportion is arguably higher than in most medication trials, it is still likely that some patient groups are disproportionately affected by the exclusion criteria. These may likely include children with *M. pneumoniae* infection, who often present without fever, and older children who would often only be hospitalised in the presence of respiratory or immunological comorbidities that would result in exclusion from the trial. The demographics of included children nonetheless closely resemble those of all children admitted for community-acquired pneumonia in similar settings [1]. We therefore believe that the data we present are generalisable to children admitted with community-acquired pneumonia in Switzerland and largely transferable to similar European settings. Most participants were enrolled in the winter season before the start of the COVID-19 pandemic. In this way, the findings can provide information for pre-post pandemic comparisons on pathogen detection and management of paediatric community-acquired pneumonia.

Data availability statement

Raw data can be obtained from the sponsor (UKBB) upon request to the Trial Steering Committee via the corresponding author once the trial has been completed. Any requests for access to raw data will be welcomed as long as they are scientifically valid, appropriate consent for the requested level of data sharing has been obtained from participants and as long as the planned data use does not conflict with ongoing analyses by the trial team.

Acknowledgements

The authors thank the families participating in the KIDS-STEP trial and the contributing staff at all trial sites.

The authors thank Angela Huttner and Theoklis Zaoutis (Independent Data Monitoring Committee and the Trial Steering Committee) for advice on focus and delimitation of the current report against the planned final report on the clinical trial.

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Financial disclosure

KIDS-STEP is funded by the Swiss National Science Foundation (SNSF) under the IICT call. Project title: "A randomised controlled trial of adjunct corticosteroid therapy in hospitalised children with community acquired pneumonia (CAP): THE KIDS-STEP STUDY" (SNSF-ID 173532).

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. PMMS was supported by a Walter und Gertrud Siegenthaler Fellowship and the career development programme "Filling the Gap" of the University of Zurich. No other potential conflict of interest was disclosed.

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Appendix: Supplementary data

Figure S1: Inclusion over time.

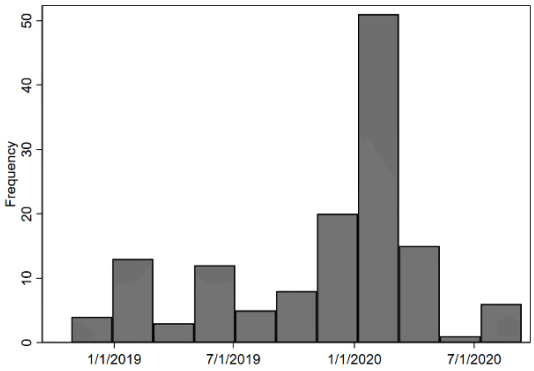

Table S1:
Pathogen combinations.

Infl	hMPV	CoV	Mp	Sp	Hi	PIV	AdV	R/EV	Cpn		Count co-detections
1	2	3	0	0	0	0	1	5	0	**RSV**	12
–	0	0	0	0	0	1	0	2	0	**Infl**	4
–	–	6	0	1	0	1	0	2	0	**hMPV**	12
–	–	–	0	0	0	0	0	2	0	**CoV**	5
–	–	–	–	0	0	0	1	2	1	**Mp**	4
–	–	–	–	–	0	0	0	0	0	**Sp**	1
–	–	–	–	–	–	0	0	0	0	**Hi**	0
–	–	–	–	–	–	–	0	3	0	**PIV**	5
–	–	–	–	–	–	–	–	3	0	**AdV**	5
–	–	–	–	–	–	–	–	–	0	**R/EV**	19
–	–	–	–	–	–	–	–	–	–	**Cpn**	1

RSV: respiratory syncytial virus; Infl: influenza viruses; hMPV: human metapneumovirus; CoV: endemic coronaviruses; Mp: *Mycoplasma pneumoniae*; Sp: *Streptococcus pneumoniae*; Hi: *Haemophilus influenzae*; PIV: parainfluenza viruses; AdV: adenovirus; R/EV: human rhinovirus or enterovirus; Cpn: *Chlamydophila pneumoniae*