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REVIEW

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Can we distinguish respiratory viral infections based on clinical features? A prospective pediatric cohort compared to systematic literature review

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Summary

Studies have shown that the predictive value of "clinical diagnoses" of influenza and other respiratory viral infections is low, especially in children. In routine care, pediatricians often resort to clinical diagnoses, even in the absence of robust evidence-based criteria.

We used a dual approach to identify clinical characteristics that may help to differentiate infections with common pathogens including influenza, respiratory syncytial virus, adenovirus, metapneumovirus, rhinovirus, bocavirus-1, coronaviruses, or parainfluenza virus: (a) systematic review and meta-analysis of 47 clinical studies published in Medline (June 1996 to March 2017, PROSPERO registration number: CRD42017059557) comprising 49 858 individuals and (b) data-driven analysis of an inception cohort of 6073 children with ILI (aged 0-18 years, 56% male, December 2009 to March 2015) examined at the point of care in addition to blinded PCR testing. We determined pooled odds ratios for the literature analysis and compared these to odds ratios based on the clinical cohort dataset.

This combined analysis suggested significant associations between influenza and fever or headache, as well as between respiratory syncytial virus infection and cough, dyspnea, and wheezing. Similarly, literature and cohort data agreed on significant associations between HMPV infection and cough, as well as adenovirus infection and fever. Importantly, none of the abovementioned features were unique to any particular pathogen but were also observed in association with other respiratory viruses. In summary, our "real-world" dataset confirmed published literature trends, but no individual feature allows any particular type of viral infection to be ruled in or ruled out. For the time being, laboratory confirmation remains essential. More research is

List of Abbreviations: Ab, antibody; AE, asthma exacerbation; altered/LOC, altered or loss of consciousness; anorexia/DF, anorexia/difficulty feeding; ARI, acute respiratory infection; BALF, bronchoalveolar lavage fluids; BCL, bronchiolitis; CAP, community-acquired pneumonia; CC, case-control; CF, cystic fibrosis; CI, confidence interval; COH, (inception) cohort dataset; CS, cross-sectional; DB, difficulty breathing; DFA, direct immunofluorescence assay; EIA, enzyme immunoassay; EIFA, enzyme immunofluorescence assay; ETA, endotracheal aspirates; Flu, influenza; FS, febrile seizure; FRI, febrile respiratory illness; HAdV, human adenovirus; HBoV-1, human bocavirus type 1; HCoV, human coronavirus; HHP-6, human herpesvirus 6; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; HRV, human rhinovirus; IFA, (indirect) immunofluorescence assay; ILI, influenza-like illness; LIT, literature review dataset; LRTI, lower respiratory tract infections; NOS, number of studies; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; NS, nasal swabs/secretions; NW, nasal washing; OP, observational prospective; OPS, oropharyngeal swabs; OR, observational retrospective; PC, prospective cohort; PNA, pneumonia; (p)OR, (pooled) odds ratio; PPV, positive predictive value; PROSPERO, International Prospective Register of Systematic Reviews; PS, pharyngeal swabs; QI, quality improvement; RKI, Robert Koch Institute; RS, respiratory samples; SARI, severe acute respiratory infection; RT, rapid test,; RTI, respiratory tract infection; TA, tracheal aspirates; TS, throat swabs; URTI, upper respiratory tract infections; WHO, World Health Organization

needed to develop scientifically validated decision models to inform best practice guidelines and targeted diagnostic algorithms.

KEYWORDS

children, clinical symptoms, respiratory viruses

1 | INTRODUCTION

Influenza and acute respiratory infections (ARI) are major contributors to disease burden in the pediatric age group[1-4] with highest mortality rates in resource-limited settings.[5,6]

It has been shown that the positive predictive value of a "clinical" influenza diagnosis in children is as low as 32%.[7] In children in particular, influenza symptoms are often nonspecific, making it difficult to distinguish influenza infection from infection because of other respiratory viruses.[8] The ability to make accurate "clinical diagnoses" is further hampered by the frequent succession of different respiratorys infection during the winter months.[7]

For pediatricians in acute care settings, however, it may not always be possible to perform virus diagnostics. Even if diagnostic tests are widely available, presumptive clinical diagnoses will still be influencing clinical decision-making, such as the use of diagnostics, antivirals, and antibiotics. Clinical bias in the use of diagnostic testing may thus impair epidemiological surveillance and disease burden estimates.[9]

To address this question further, we explored which clinical features, according to the published literature, may be associated with ARI due to influenza, respiratory syncytial virus (RSV), human adenovirus (HAdV), human rhinovirus (HRV), human metapneumovirus (HMPV), human bocavirus-1 (HBoV-1), human parainfluenza virus (HPIV), and human coronavirus (HCoV). We then addressed the same question through analysis of a "real-world" dataset based on a prospective surveillance of 6073 children aged 0 to 18 years, where detailed clinical presentations and virus diagnoses were assessed and documented in all patients, independent from routine care.[10]

The objectives of this analysis are as follows:

1) To identify clinical features linked to specific respiratory viral infection in pediatric clinical trials and observational studies published in Medline
2) To explore the same question in a real-world dataset, derived from a pediatric inception cohort.

2 | METHODS

2.1 | Systematic literature review and meta-analysis

We searched the English language literature published in Medline (PubMed) from January 01, 1996 to March 21, 2017.

The search protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) No. CRD42017059557. The literature search was conducted on March 21, 2017. The search terms are listed in the following online document: https://www.crd.york.ac.uk/PROSPEROFILES/59557_PROTOCOL_20180419.pdf

The publications identified by the initial search were included only if (a) study participants were children 0 to 18 years of age; (b) studies were randomized/nonrandomized clinical trials, observational studies, and/or epidemiological reports; (c) ≥1 association between patients with confirmed viral infection and a clinical symptom had been reported; and if (d) a control group with patients testing negatively for the respective viruses was included.

We excluded animal or in vitro studies, adult studies, case series, studies lacking information on clinical features and outcomes, studies lacking virological data, studies lacking same virus-negative control groups, studies where data could not be reliably categorized and extracted, overlapping studies addressing chronic conditions or other nonrespiratory infection as well as meta-analyses, review papers, and conference papers.

In the first round of review, the following data were extracted independently: (1) study location (country), (2) study design, (3) age range, (4) cohort size/number of subjects, (5) sampling and laboratory method, and (6) presenting symptoms including respiratory and extrarespiratory symptoms. Full-text publications were accessed for a second round of review. XM and BR independently reviewed studies against the predefined inclusion and exclusion criteria, and any eligible discrepancy was resolved by discussion among the reviewer team

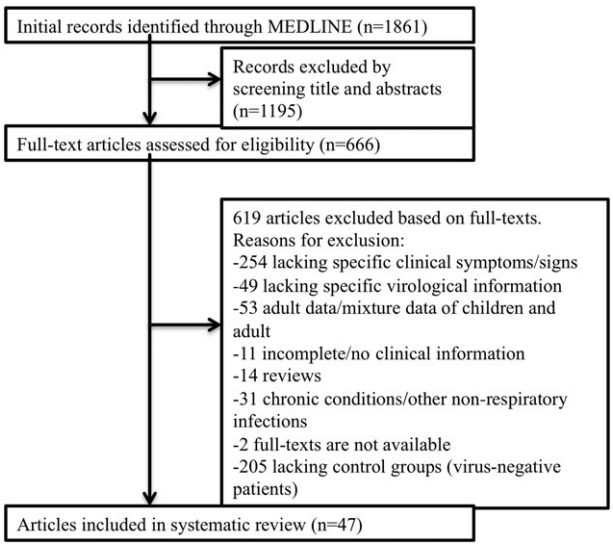

FIGURE 1 Flow chart describing the systematic literature search and selection of eligible publications

TABLE 1 Characteristics of 47 eligible published studies

Author, Year, Reference	Country	Design	Size	Age	Sample Type	Type of RTI	Lab Method	Pathogen
Ahn 2014[24]	Korea	OP	1528	≤18 years	NPA	ARI	PCR	HBoV-1
Akhras 2010[25]	USA	OR	256	<18 years	NPS	ARI	DFA, culture, PCR	RSV, HMPV
Ali 2010[26]	Jordan	OP	728	<5 years	NS, TS	ARI	PCR	HMPV
Annamalay 2016[27]	Mozambique	OP	277	≤10 years	NPA	RTI	PCR	HRV
Bhandary 2016[28]	India	CS	100	≤5 years	NPA	RTI	DFA	RSV
Broor 2014[29]	USA	OP	245	<5 years	NS, TS	ARI	PCR	Flu A/B, RSV
Bryant 2010[30]	Australia	OP	446	≤16 years	NPA, NS, TS	ILI	DFA, PCR	Flu A
Carballal 2002[31]	Argentina	OR	168	<2 years	NPA	Acute LRTI	IFA, culture	HAdV
Chang 2012[32]	USA	OP and CC	5066	≤18 years	NS	ILI	PCR	Flu A
Chano 2005[33]	Canada	CC	1132	≤18 years	NPA, BAL, ETA	RTI	DFA, culture, EIA, PCR	HMPV
Chen 2010[34]	China	OP	6296	≤18 years	NPA	Acute LRTI	PCR	RSV, HMPV
Cuevas 2003[35]	Brazil	OP	111	<3 years	NS	Acute LRTI	PCR	RSV, HMPV
Esposito 2016[36]	Italy	OP	307	≤18 years	NS	RTI	PCR	HAdV
Fairchok 2010[37]	USA	Cohort	318	≤30 months	NS	RTI	PCR	Flu A
Farng 2002[38]	China	OR	48	≤18 years	TS, serum	PNA	IFA	HAdV
Fischer Langley 2013[39]	Guatemala	OP	2413	<5 years	NPS, OPS	ARI	PCR	RSV
Flores 2004[40]	Portugal	OP	225	<3 years	NS	Acute BCL	PCR	RSV
Giamberardin 2016[41]	Brazil	CS	250	24-59 months	NS, OPS	RTI, asthma	PCR	Flu A/B, HRV, HAdV, HPIV, HCoV
Halasa 2015[42]	Jordan	OP	3173	<2 years	NS, TS	RTI, others	PCR	RSV
Hite 2007[43]	UK	CC	411	≤18 years	NS	ILI	RT, culture	Flu A/B
Hombrouck 2012[44]	Belgium	OP	139	<5 years	NPS, TS	ILI	PCR	Flu A, RSV, HRV, HMPV, HPIV
Hsieh 2014[45]	China	OP	1062	≤18 years	Serum	Flu season	Ab	Flu A
Huai 2017[46]	China	OP	14479	<15 years	NS	SARI	PCR	Flu A/B
Jevsnik 2012[47]	Slovenia	OP	741	<6 years	NPS, TS, TA, BAL, sputum	ARI	PCR	HCoV
Jin 2010[48]	China	OP	645	<16 years	NPA	ARI	PCR	HCoV
Khamis 2012 [49]	Oman	OP	259	≤5 years	RS	RTI	PCR	RSV
Kuo 2011[50]	China	CC	308	≤18 years	NPS, TS	ILI	RT, PCR	Flu A
Lamarao 2012[51]	Brazil	CS	1214	≤18 years	NPS	CAP	DFA, PCR	RSV
Landa-Cardena 2012[52]	Mexico	CS	124	<6 years	NS	RTI	PCR	HRV
Leung 2009[53]	China	OP and OR	1981	<18 years	NPA	ARI	IFA, PCR	HCoV
Martin 2015[54]	Canada	OP	219	≤2 years	Oral fluid	HHP-6 history	PCR	HBoV-1
Moreno-Valencia 2015[55]	Mexico	OP	432	<12 years	NPS	ARI	PCR	Flu A, RSV, HRV, HMPV, HPIV, HAdV
Nitsch-Osuch 2013[56]	Poland	OP	59	≤59 months	NS, PS	ILI	RT, PCR	Flu A/B
Nokes 2009[57]	Kenya	OP	6026	1 day-59 months	NS	PNA	DFA	RSV
Nyawanda 2016[58]	Kenya	OP	4714	<5 years	NPS, OPS	ARI	PCR	RSV

(Continues)

TABLE 1 (Continued)

Author, Year, Reference	Country	Design	Size	Age	Sample Type	Type of RTI	Lab Method	Pathogen
Pecchini 2008[59]	Brazil	OP	455	<5 years	NPS	Acute LRTI	IFA	RSV
Pierangeli 2012[60]	Italy	OP	231	≤16 years	PS, nasal washing	ILI	PCR	Flu A, RSV, HRV
Ramagopal 2016[61]	India	OP	80	1 month-3 years	NPS	BCL	PCR	RSV
Saha 2010[62]	India	OP	69	10 months-12 years	NS, TS	Acute FRI	PCR	Flu A
Schuster 2015[63]	Jordan	OP	3175	<2 years	NS, TS	TRI, AE, CF, FS	PCR	HMPV
Smit 2012[64]	Netherlands	OP	423	≤17 years	OPS, NW	ILI	PCR	Flu A
Smuts 2011[65]	South Africa	OP	220	2 months-5 years	NS	Cough, DB, wheezing	PCR	HRV
Tresoldi 2011[66]	Brazil	Cohort	61	≤18 years	NPS, PS	ILI	PCR	Flu A
von Linstow 2004[67]	Denmark	OP	374	≤2 years	NPS	TRI	IFA, EIFA, PCR	RSV, HMPV
Weigl 2003[68]	Germany	CC	1316	≤2 years	NPA	LRTI	PCR	RSV
Yan 2017[69]	China	OP	387	8 days-15 years	NPA	Acute LRTI	PCR	RSV, HMPV
Zimmerman 2014[70]	USA	CC	662	<2 years	NS, OPS	URTI	PCR	Flu A/B, RSV, HRV, HMPV, HCoV

Ab, antibody; AE, asthma exacerbation; ARI, acute respiratory infection; BALF, bronchoalveolar lavage fluids; BCL, bronchiolitis; CAP, community-acquired pneumonia; CC, case-control; CF, cystic fibrosis; CS, cross-sectional; DB, difficulty breathing; DFA, direct immunofluorescence assay; EIA, enzyme immunoassay; EIFA, enzyme immunofluorescence assay; ETA, endotracheal aspirates; Flu, influenza; FS, febrile seizure; FRI, febrile respiratory illness; HHP-6, human herpesvirus 6; IFA, (indirect) immunofluorescence assay; ILI, influenza-like illness; LRTI, lower respiratory tract infection; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; NS, nasal swabs/secretions; NW, nasal washing; OP, observational prospective; OPS, oropharyngeal swabs; OR, observational retrospective; PC, prospective cohort; PNA, pneumonia; PS, pharyngeal swabs; RS, respiratory samples; SARI, severe acute respiratory infection; RT, rapid test; RTI, respiratory tract infection; TA, tracheal aspirates; TS, throat swabs; URTI, upper respiratory tract infection.

(3 researchers). The clinical symptoms were grouped into the following 19 distinct symptom categories: altered or loss of consciousness (altered/LOC), anorexia/difficulty feeding, apnea, conjunctivitis, cough, hypoxia, diarrhea, dyspnea, fever, headache, malaise, myalgia, rash, rhinitis, seizures, sore throat, signs of upper respiratory tract infection, vomiting, and wheezing/bronchoconstriction/signs of lower respiratory tract infection (henceforth labeled "wheezing").

2.2 | Inception cohort analysis

The literature review was compared to a well-described clinical inception cohort[11-15]: From December 2009 to April 2015, a specifically trained quality improvement (QI) team performed predefined clinical assessments of 6073 influenza-like illness (ILI) patients aged 0 to 18 years at the point of care.[11-15] Influenza-like illness case criteria were defined as evidence of fever with a body temperature ≥38°C and ≥1 respiratory symptom (including cough, rhinitis/coryza, red/sore throat, ear ache, dyspnea, tachypnea, labored breathing, wheezing) or a documented clinician diagnosis of ILI. Clinical assessments were as described previously.[10] Nasopharyngeal swabs were collected in universal transport medium (Copan™, Copan Diagnostics, Murrieta, CA) and investigated at the National Reference Centre for Influenza at the Robert Koch Institute, Berlin, for 8 respiratory viruses. The QI program was approved by the institutional review board (Charité EA 24/008/10). Informed consent procedures were waived for the purpose of enhanced quality of care and infection control.[10-15]

Nucleic acid was extracted by MagNA Pure 96 DNA and Viral NA Small Volume Kit (Roche Deutschland Holding GmbH, Mannheim, Germany), MagAttract Viral RNA M48 Kit (Qiagen, Hilden, Germany), or RTP DNA/RNA Virus Mini Kit (Invitek, Germany) according to the manufacturer's instructions using a specimen volume of 200, 300, and 400 µL, respectively. Twenty-five microliters of extracted RNA were subjected to cDNA synthesis applying 200 U M-MLV Reverse Transcriptase (Invitrogen, USA) in a total reaction volume of 40 µL.

Specimens were analyzed for influenza A and B, RSV, HMPV, HAdV, and HRV by real-time PCR as published previously.[10,11,16-19] Investigation of HCoV (NL63, 229E, OC43, and HKU1), HPIV1-4, and HBoV-1 was performed in a total reaction volume of 15 µL containing 1× PCR buffer, 4 mM $MgCl_2$, 0.2 mM dNTP with dUTP, 40 ng/µL BSA, 0.3 U Platinum Taq Polymerase primers and probes (as specified in Supporting Information 1) and 5 µL of cDNA (or nucleic acid for HBoV-1). Amplification was carried out at 95°C for 300 seconds, followed by 45 cycles at 95°C for 15 seconds and 60°C for 30 seconds.

In summary, the QI program used an unbiased approach where all 19 predefined clinical features were assessed at the point of care, and all 8 viruses were tested in all ILI patients.

2.3 | Comparative analysis

The comparative statistical analysis was performed using R with the Metaphor Package software.[20] Clinical features associated with viral pathogens were determined independently using pooled odds ratios (pOR), with 95% confidence intervals (CI) for the literature review

dataset (LIT) and odds ratio (OR) for the real-world (inception cohort) dataset (COH). We used 2 × 2 contingency tables to analyze the association between a virus-positive (versus virus-negative) case and an individual clinical feature (present/absent) in the literature and inception cohort, respectively. If lower/upper limits of 95% CI were within 1 decimal point of 1.0, we did not consider these OR as significant.

Random effect models for meta-analysis were applied.[20] Heterogeneity testing was done using I^2 statistics. I^2 values <25% were considered low, 25% to 75% as moderate, and values >75% indicated high levels of heterogeneity.[21] Publication bias was assessed using funnel plots. A symmetrical plot indicates a lack of publication bias.[22] For each used OR calculation, we estimated the exact CI using the mid-p method.[23]

3 | RESULTS

3.1 | Characteristics of the literature review

The initial Medline search yielded 1861 potentially relevant publications. After manual screening of all titles and abstracts, 666 publications were relevant to the topic. Of these, 47 eligible publications were included into the final analysis according to the predefined inclusion and exclusion criteria (Figure 1).

The 47 eligible publications are listed in Table 1.[24-70] One quarter of these studies included children aged 0 to 5 years, and 6.4% and 12.8% of studies recruited children aged 0 to 3 years and aged 0 to 2 years, respectively. The systematic literature review yielded 9960 individual cases of laboratory-confirmed ARI and 39 898 cases with negative test results for the same virus, respectively. The virology methods varied considerably: PCR was used in the majority of studies (88.9%), followed by enzyme-linked immunoassays (14.9%), direct/indirect immunofluorescence (21.3%), and culture methods (6.4%). The geographic representation was rather broad, with 34.0% of study subjects stemming from the World Health Organization (WHO) region of the Americas, followed by the European Region (21.3%) and Western Pacific Region (21.3%). Fewer studies represented the WHO African Region (8.5%), the Eastern Mediterranean Region (8.5%), and the Southeast Asian Region (6.4%).

3.2 | Associations between clinical features and viral infections based on literature review (LIT)

3.2.1 | Fever and wheezing in influenza and RSV infections

In clinical practice, fever is often considered a hallmark of influenza disease, whereas wheezing is viewed as "typical" for RSV infections. Therefore, we studied these clinical associations in detail in the published literature (Figures 2 and 3). Of note, the pooled sample sizes in studies of influenza and RSV were highest (N = 24 661 and N = 29 426, respectively). The funnel and forest plots for other significant associations discussed below are provided in the Supporting Information 2 and 3.

Indeed, fever was the single most highly associated feature with regards to influenza infection (pOR = 3.0; 95% CI [2.0, 4.3]; I^2 = 66%) (Figures 2A and 4A). As evident from detailed literature analysis, most studies agreed on a *positive correlation*, with 1 exception.[66] No evidence of publication bias was observed. There was no significant association in the meta-analysis between fever and RSV (pOR 1.1; 95% CI [0.9, 1.3]; I^2 = 76%), albeit individual studies suggested (positive or negative) associations (Figure 2B).

The meta-analysis (Figure 3B) also yielded a significant association between wheezing and RSV infection (pOR = 2.2; 95% CI [1.7, 2.8]; I^2 = 86%). In-depth analysis of individual studies showed positive associations for most RSV studies, with 2 exceptions.[35,40] There was some publication bias in the RSV studies. Of note, wheezing was *not* significantly associated with influenza (pOR = 1.0; 95% CI [0.7, 1.4]; I^2 = 35%) (Figure 3A).

3.2.2 | Clinical associations across all types of respiratory infection

Associations with fever or wheezing however are neither unique to influenza nor to RSV. When we studied the meta-analyses across all 8 types of respiratory viral infection, multiple overlapping associations were easily identified for different types of respiratory viral infections (Figure 4A). In fact, most associations were shared across multiple types of viral infection, and no clinical feature stood out as unique to any specific type of infection.

In addition to influenza, fever was also significantly associated with HMPV (pOR = 1.7; 95% CI [1.2, 2.3]; I^2 = 45%) and HAdV infections (pOR = 2.2; 95% CI [1.2, 4.1]; I^2 = 11%). Additional features significantly associated with influenza infection included malaise (pOR = 2.4; 95% CI [1.5, 4.0]; I^2 = 48%), headache (pOR = 1.9; 95% CI [1.2, 3.3]; I^2 = 76%), cough (pOR = 1.6; 95% CI [1.3, 2.0]; I^2 = 19%), and rhinitis (pOR = 1.4; 95% CI [1.3, 1.6]; I^2 = 0%).

Wheezing was not only linked to RSV infections but also to HMPV (pOR = 1.6; 95% CI [1.1, 2.2]; I^2 = 54%) and HBoV-1 infections (pOR = 1.4; 95% CI [1.1, 2.0]; I^2 = 0%). The strongest association with RSV infection in the literature was seen with cough and dyspnea (pOR_{cough} = 2.9; 95% CI [1.8, 4.6]; I^2 = 77% and $pOR_{dyspnea}$ = 2.3; 95% CI [1.7, 3.0]; I^2 = 84%). Cough and dyspnea were also shared with HMPV infection (pOR_{cough} = 4.6; 95% CI [2.5, 8.6]; I^2 = 18% and $pOR_{dyspnea}$ = 1.7; 95% CI [1.1, 2.4]; I^2 = 39%), and cough was also linked to influenza and HBoV-1 infections.

3.3 | New associations revealed in the inception cohort (COH)

The same clinical features were now tested in the clinical cohort (Figure 4B). The most striking difference was that associations in the COH dataset yielded narrower CI compared to the LIT dataset.

Several new (positive and negative) associations were revealed in the COH dataset that were not previously observed in the meta-analysis. For example, influenza was positively linked to myalgia (OR 3.1; 95% CI [2.3, 4.3]) and sore throat (OR = 1.8; 95% CI [1.5, 2.1]). Wheezing (OR = 0.4; 95% CI [0.3, 0.5]) as well as hypoxia (OR = 0.4; 95% CI [0.4, 0.6]), dyspnea (OR = 0.5; 95% CI [0.4, 0.6]), rash, and diarrhea (both OR = 0.7; 95% CI [0.6, 0.9]) were *negatively* linked to influenza in the COH dataset.

With respect to RSV, anorexia/difficulty feeding and apnea were positively linked to that pathogen (OR = 1.6; 95% CI [1.4, 1.8] and

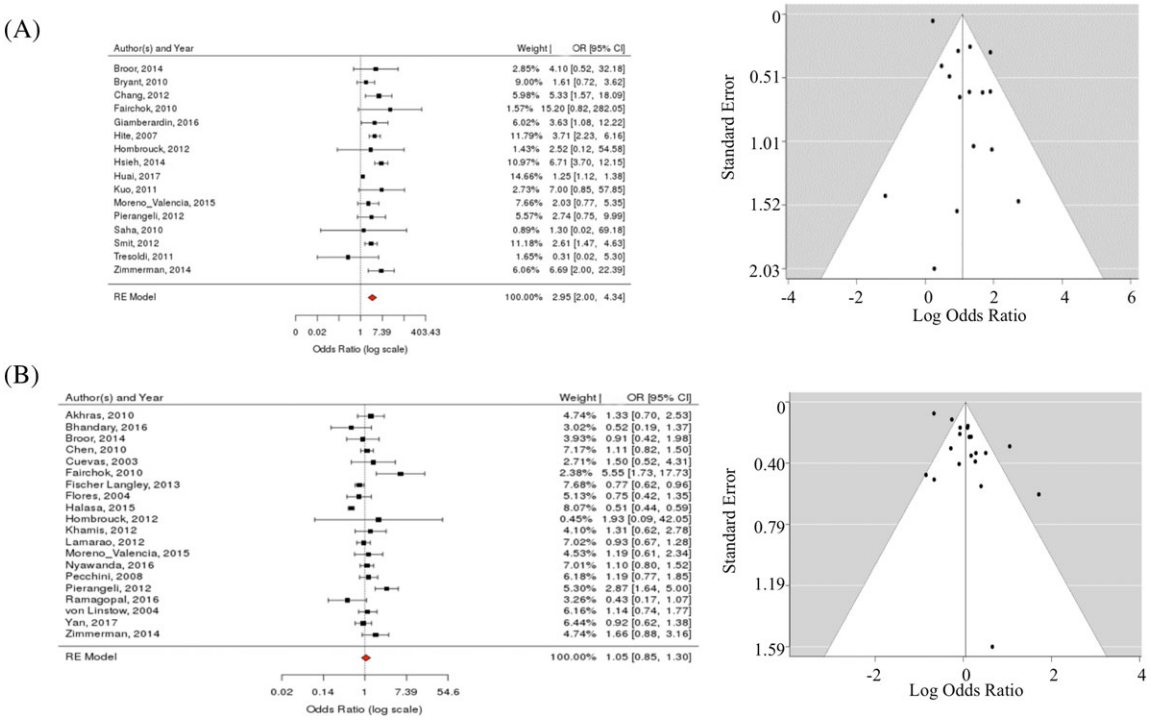

FIGURE 2 Relationship between fever and A, influenza versus B, RSV: LIT forest and funnel plots

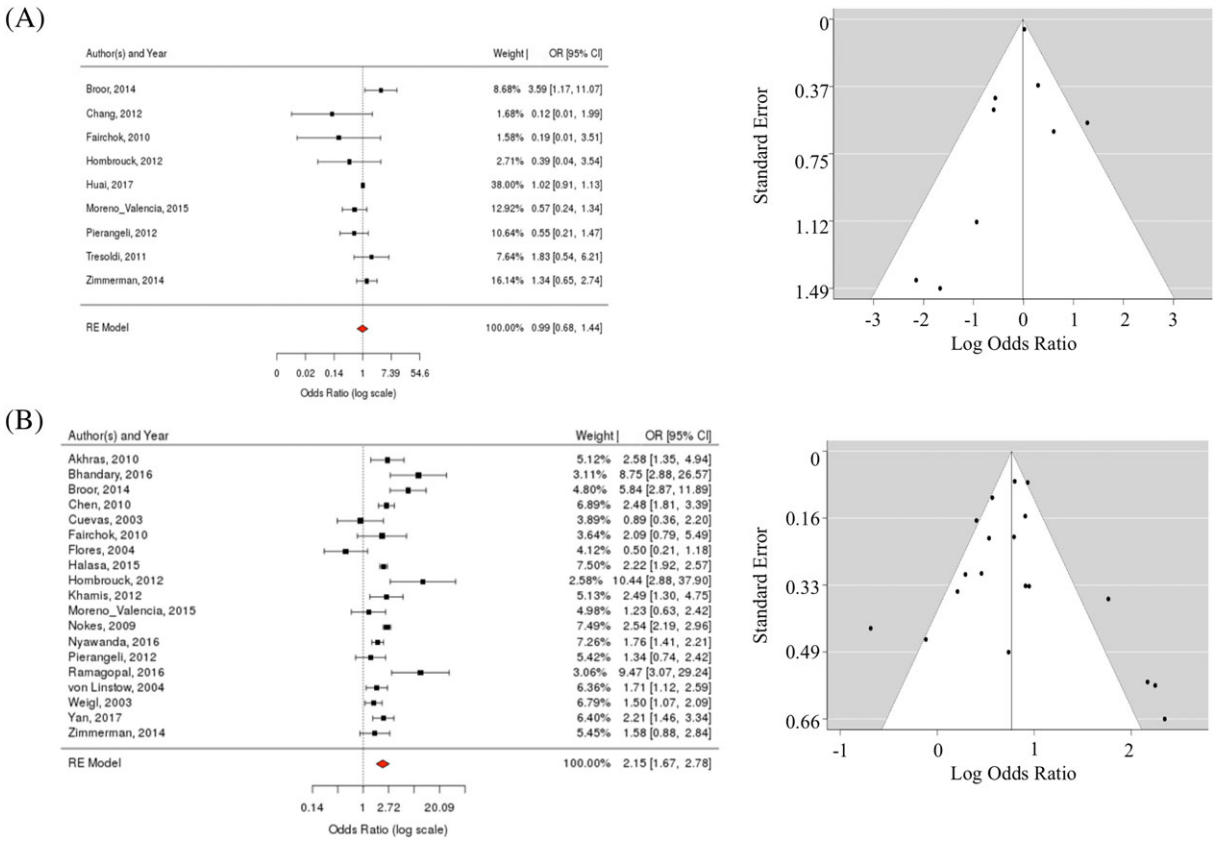

FIGURE 3 Relationship between wheezing and A, influenza versus B, RSV: LIT forest and funnel plots

OR = 1.5; 95% CI [1.1, 2.1] respectively). Additional *negative* associations were also revealed for RSV, namely fever (OR = 0.5; 95% CI [0.4, 0.6]), headache and myalgia (OR = 0.2; 95% CI [0.1, 0.2] and OR = 0.2; 95% CI [0.1, 0.3] respectively), seizures (OR = 0.4; 95% CI [0.3, 0.5]), rash, and sore throat (OR = 0.8; 95% CI [0.6, 0.9] and OR = 0.8; 95% CI [0.7, 0.9], respectively).

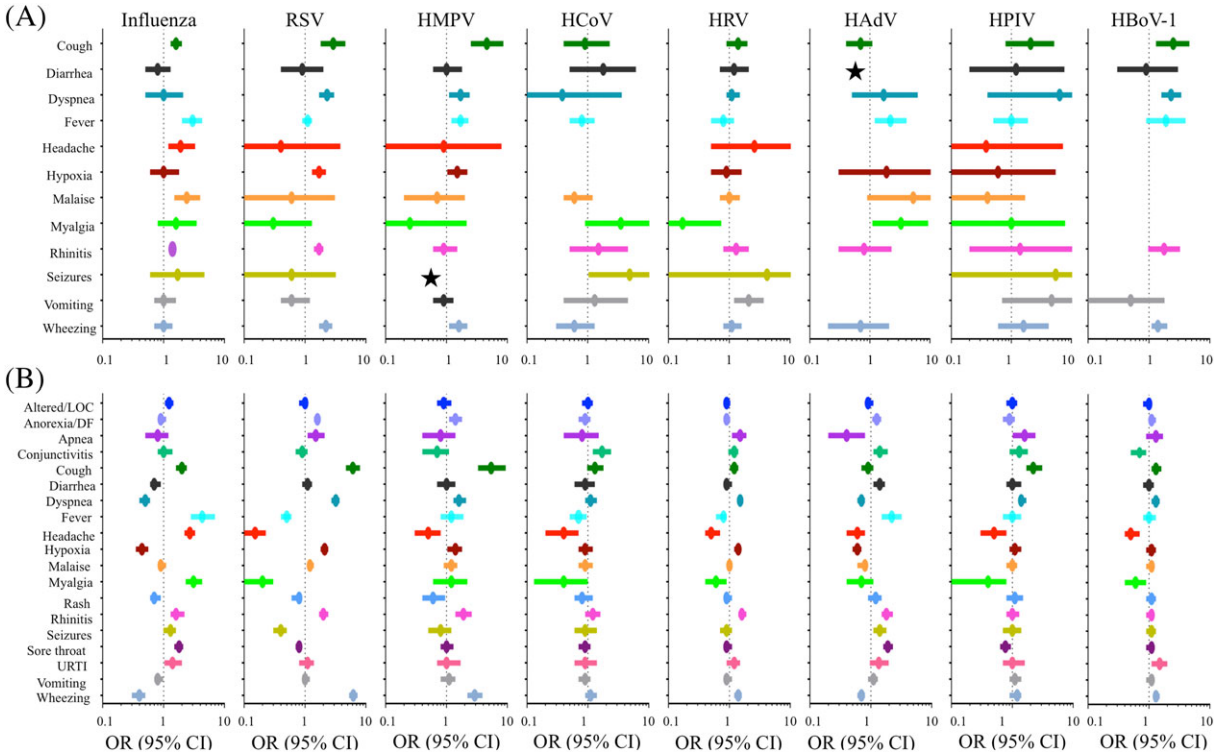

FIGURE 4 Summary of statistically significant ($P < .05$) features identified in A, the LIT dataset and in B, the COH dataset. ★ 95% CI exceeding scale: for seizure/HMPV, OR (95% CI) =16.6 (0.6, 438.1) and for or diarrhea/HAdV OR (95% CI) OR = 14.4 (2.5, 82.1)

Of note, headache was *negatively* associated with all respiratory viral infections, except for influenza.

3.4 | Agreements and disagreements between literature and cohort data (LIT/COH)

Figure 5 provides a "matrix view" of clinical features in relation to the 8 different types of viral infection, in direct comparison between LIT and COH data. This synopsis confirms that in most instances, COH data agreed with published literature trends, usually with higher OR and higher confidence levels (ie, narrower 95% CI) despite a smaller sample size. Exceptions were malaise/influenza, fever/HMPV, vomiting/HRV, and malaise/HAdV, which could not be confirmed in the COH data.

The matrix view in Figure 5 also provides an overview of new *negative (red)* as well as *positive (green)* associations in the COH column/analysis that were not evident in the LIT column/analysis. Individual clinical features were not distinctive but shared among multiple types of viral infection, even if OR were not always significant.

The synopsis of meta-analysis and inception cohort suggests that fever is significantly associated with influenza and HAdV infections, but again, the presence of fever does not rule out any of the other types of viral infection. HAdV infections were also linked to diarrhea. Cough is most likely present in influenza, RSV, HMPV, and HBOV-1 infections but also observed in other respiratory infections. Wheezing was most prominent in RSV, HMPV, and HBOV-1 infections. Wheezing was less likely to be seen in influenza and HAdV infections in the cohort, whereas the literature review revealed inconclusive results in this regard. HCoV infections showed no agreement bewteen LIT and COH datasets with no data available in the literature on a number of nonrespiratory symptoms. The only negative association confirmed in both LIT and COH datasets was between malaise and HRV infections.

4 | DISCUSSION

We are presenting the first systematic literature review and meta-analysis coupled with the analysis of a matching inception cohort, addressing the question whether respiratory viral infections in children can be differentiated based on individual clinical features. The prospective cohort confirmed several trends that were also identified in the meta-analysis of the published literature. But the cohort dataset also established new significant associations between individual clinical features and viral infections.

Our matching analysis showed that systemic signs and symptoms such as fever and headache are more common in influenza and HAdV infections, whereas RSV, HMPV, and HBoV-1 are more likely to manifest with respiratory symptoms such as wheezing, cough, and dyspnea. This trend was observed in the meta-analysis and confirmed in the inception cohort. The approach of linking individual clinical features to specific viral infections however revealed a major diagnostic challenge to the clinician: None of the associations identified with either method were unique to any specific type of respiratory viral infection, but were shared across several types of infection. Individual clinical signs or symptoms can therefore *not* be used to reliably rule-in or rule-out any specific type of respiratory viral infection. For the time being, physicians need to be aware that clinical diagnoses are insufficiently sensitive, and laboratory testing will remain inevitable.

Clinical Features	LIT	COH	LIT	COH	LIT	COH	LIT	COH	LIT	COH	LIT	COH	LIT	COH	LIT	COH
	Influenza		RSV		HMPV		HCoV		HRV		HAdV		HPIV		HBoV-1	
Altered/LOC	1.1 (0.4, 3.5)	**1.2 (1.05, 1.4)**	0.6 (0.2, 2.0)	1.0 (0.8, 1.1)	1.8 (0.2, 19.5)	0.9 (0.7, 1.2)		1.0 (0.8, 1.2)	1.5 (0.1, 15.7)	**0.9 (0.8, 1.03)**		0.9 (0.8,1.1)	0.7 (0.0, 15.6)	1.0 (0.8, 1.2)		1.0 (0.8, 1.1)
Anorexia/DF	1.4 (0.9, 2.3)	0.9 (0.8, 1.1)	**1.4 (0.96, 1.9)**	**1.6 (1.4, 1.8)**	0.9 (0.6, 1.2)	**1.4 (1.1, 1.8)**		0.9 (0.7, 1.1)	0.9 (0.2, 3.0)	**0.9 (0.8, 1.03)**		**1.2 (1.05, 1.5)**	1.1 (0.3, 4.5)	0.9 (0.7, 1.1)		**1.1 (0**.99, 1.3)
Apnea	0.5 (0.2, 1.7)	0.8 (0.5, 1.2)	0.3 (0.0, 2.4)	**1.5 (1.1, 2.1)**	2.1 (0.4, 13.3)	0.8 (0.4, 1.4)		0.8 (0.4, 1.5)		**1.5 (1.1, 1.9)**	1.9 (0.5, 7.3)	**0.4 (0.2, 0.8)**		**1.6 (1.02, 2.4)**		1.3 (0.9, 1.7)
Conjunctivitis	1.6 (0.5, 5.3)	1.0 (0.8, 1.4)	1.6 (0.2, 14.1)	0.9 (0.7, 1.1)	1.2 (0.2, 7.6)	0.7 (0.4, 1.1)	0.7 (0.1, 5.1)	**1.7 (1.2, 2.4)**	0.3 (0.0, 5.4)	**1.2 (0.96, 1.4)**	1.4 (0.5, 4.0)	**1.4 (1.1, 1.9)**	2.2 (0.4, 13.1)	1.3 (0.9, 1.8)		**0.7 (0.5, 0.9)**
Cough	**1.6 (1.3, 2.0)**	**2.0 (1.6, 2.4)**	**2.9 (1.8, 4.6)**	**6.1 (4.7, 8.0)**	**4.6 (2.5, 8.6)**	**5.4 (3.3, 9.4)**	0.9 (0.4, 2.3)	**1.3 (0.97, 1.8)**	1.4 (0.9, 2.0)	**1.2 (1.02, 1.4)**	0.7 (0.4,1.1)	0.9 (0.7,1.1)	2.1 (0.8, 5.2)	**2.2 (1.7, 3.1)**	**2.5 (1.3, 4.6)**	**1.3 (1.1, 1.6)**
Diarrhea	0.8 (0.5, 1.3)	**0.7 (0.6, 0.9)**	0.9 (0.4, 2.0)	1.1 (0.9, 1.3)	1.0 (0.6, 1.8)	1.0 (0.7, 1.4)	1.8 (0.5, 6.2)	0.9 (0.6, 1.3)	1.2 (0.7, 2.1)	0.9 (0.8, 1.1)	**14.4 (2.5, 82.1)**	**1.4 (1.1, 1.7)**	1.2 (0.2, 7.7)	1.0 (0.8, 1.4)	0.9 (0.3, 3.0)	1.0 (0.8, 1.2)
Dyspnea	1.0 (0.5, 2.1)	**0.5 (0.4, 0.6)**	**2.3 (1.7, 3.0)**	**3.2 (2.7, 3.7)**	**1.7 (1.1, 2.4)**	**1.6 (1.3, 2.1)**	0.4 (0.0, 3.6)	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)	**1.5 (1.4, 1.7)**	1.7 (0.5, 6.3)	**0.7 (0.6, 0.8)**	6.4 (0.4, 112.5)	**1.4 (1.1, 1.7)**	**2.3 (1.6, 3.4)**	**1.3 (1.1, 1.5)**
Fever	**3.0 (2.0, 4.3)**	**4.3 (2.8, 7.0)**	1.1 (0.9, 1.3)	**0.5 (0.4, 0.6)**	**1.7 (1.2, 2.3)**	1.2 (0.8, 1.9)	0.8 (0.5, 1.3)	**0.7 (0.5, 0.95)**	0.8 (0.5, 1.2)	**0.8 (0.6, 0.9)**	**2.2 (1.2, 4.1)**	**2.2 (1.5, 3.2)**	1.0 (0.5, 1.9)	1.0 (0.7, 1.4)	1.9 (0.9, 4.0)	1.0 (0.8, 1.3)
Headache	**1.9 (1.2, 3.3)**	**2.7 (2.2, 3.3)**	0.4 (0.1, 3.8)	**0.2 (0.1, 0.2)**	0.9 (0.1, 8.0)	**0.5 (0.3, 0.8)**		**0.4 (0.2, 0.7)**	2.6 (0.5, 12.2)	**0.5 (0.4, 0.7)**		**0.6 (0.4, 0.8)**	0.4 (0.0, 7.3)	**0.5 (0.3, 0.8)**		**0.5 (0.4, 0.7)**
Hypoxia	1.0 (0.6, 1.8)	**0.4 (0.4, 0.6)**	**1.7 (1.3, 2.2)**	**2.1 (1.8, 2.4)**	**1.5 (1.03, 2.2)**	**1.4 (1.03, 1.8)**		0.9 (0.7, 1.2)	0.9 (0.5, 1.6)	**1.4 (1.2, 1.5)**	1.9 (0.3, 10.9)	**0.6 (0.5, 0.7)**	0.6 (0.1, 5.5)	1.1 (0.9, 1.4)		1.1 (0.9, 1.3)
Malaise	**2.4 (1.5, 4.0)**	0.9 (0.8, 1.1)	0.6 (0.1, 3.1)	**1.2 (1.1, 1.4)**	0.7 (0.2, 2.0)	1.2 (0.9, 1.5)	0.6 (0.4, 1.2)	0.9 (0.7, 1.2)	1.0 (0.7, 1.5)	1.0 (0.9, 1.1)	5.3 (0.9, 30.2)	**0.8 (0.6, 0.9)**	0.4 (0.1, 1.7)	1.0 (0.8, 1.2)		1.1 (0.9, 1.2)
Myalgia	1.6 (0.8, 3.5)	**3.1(2.3, 4.3)**	0.3 (0.1, 1.3)	**0.2 (0.1, 0.3)**	0.3 (0.0, 2.1)	1.2 (0.6, 2.2)	3.5 (0.9, 13.6)	**0.4 (0.1, 0.99)**	**0.2 (0.0, 0.7)**	**0.6 (0.4, 0.9)**	**3.3 (1.1, 9.4)**	0.7 (0.4,1.1)	1.0 (0.1, 7.9)	**0.4 (0.1, 0.8)**		**0.6 (0.4, 0.9)**
Rash		**0.7 (0.6, 0.9)**	0.4 (0.1, 3.0)	**0.8 (0.6, 0.9)**	1.2 (0.1, 9.9)	**0.6 (0.4, 0.95)**		0.8 (0.6, 1.2)		0.9 (0.8, 1.1)		1.2 (0.9,1.5)		1.1 (0.8, 1.5)	1.2 (0.3, 5.2)	1.1 (0.9, 1.3)
Rhinitis	**1.4 (1.3, 1.6)**	**1.6 (1.3, 1.9)**	**1.7 (1.4, 2.0)**	**2.0 (1.7, 2.4)**	0.9 (0.6, 1.5)	**1.9 (1.4, 2.6)**	1.5 (0.5, 4.6)	1.2 (0.9, 1.6)	1.3 (0.8, 2.1)	**1.6 (1.4, 1.9)**	0.8 (0.3, 2.3)	**1.8 (1.5, 2.3)**	1.4 (0.2, 10.5)	1.0 (0.8, 1.3)	**1.8 (0.97, 3.2)**	1.1 (0.9, 1.2)
Seizures	1.7 (0.6, 4.7)	**1.3 (0**.99, 1.6)	0.6 (0.1, 3.2)	**0.4 (0.3, 0.5)**	16.6 (0.6, 438.1)	0.8 (0.5, 1.2)	**4.9 (1.03, 23.0)**	0.9 (0.6, 1.4)	4.2 (0.1, 222.1)	0.9 (0.7, 1.1)		**1.4 (1.1, 1.8)**	5.5 (0.1, 295.9)	1.0 (0.7, 1.4)		1.1 (0.9, 1.3)
Sore throat	1.4 (0.8, 2.4)	**1.8 (1.5, 2.1)**	0.7 (0.3, 1.9)	**0.8 (0.7, 0.9)**	0.7 (0.3, 2.1)	1.0 (0.8, 1.3)	0.7 (0.4, 1.2)	0.9 (0.7, 1.1)	0.7 (0.4, 1.1)	0.9 (0.8, 1.1)		**1.9 (1.6, 2.3)**		**0.8 (0.6, 0.95)**		1.1 (0.9, 1.2)
URTI	0.6 (0.2, 1.5)	**1.4 (1.03, 2.0)**	0.6 (0.3, 1.3)	1.1 (0.8, 1.4)	1.3 (0.7, 2.4)	1.0 (0.7, 1.7)	1.8 (0.1, 31.8)	0.9 (0.6, 1.4)	0.7 (0.2, 2.8)	1.2 (0.9, 1.5)		1.4 (0.96,2.0)	3.0 (0.3, 25.7)	1.0 (0.7, 1.6)		**1.5 (1.1, 2.0)**
Vomiting	1.0 (0.7, 1.6)	**0.8 (0.7, 0.98)**	0.6 (0.4, 1.2)	1.0 (0.9, 1.2)	0.9 (0.6, 1.3)	1.1 (0.8, 1.4)	1.3 (0.4, 4.6)	0.9 (0.7, 1.1)	**2.1 (1.2, 3.7)**	0.9 (0.8, 1.1)		1.1 (0.9,1.3)	4.7 (0.7, 33.0)	1.1 (0.9, 1.4)	0.5 (0.1, 1.8)	1.1 (0.9, 1.2)
Wheezing	1.0 (0.7, 1.4)	**0.4 (0.3, 0.5)**	**2.2 (1.7, 2.8)**	**6.2 (5.3, 7.3)**	**1.6 (1.1, 2.2)**	**2.9 (2.2, 3.9)**	0.6 (0.3, 1.3)	1.1 (0.9, 1.4)	1.1 (0.8, 1.6)	**1.4 (1.2, 1.6)**	0.7 (0.2, 2.1)	**0.7 (0.6, 0.8)**	1.6 (0.6, 4.2)	1.2 (0.9, 1.4)	**1.4 (1.1, 2.0)**	**1.3 (1.2, 1.5)**
Case numbers	N=24661	N=6073	N=29426	N=6073	N=14010	N=6073	N=4597	N=6073	N=2653	N=6073	N=1523	N=6073	N=1139	N=6073	N=1747	N=6073

FIGURE 5 Comparison between literature review (LIT; pOR) and cohort data (COH; OR): Dark green color: positive agreement with statistically significant positive associations in both LIT and COH datasets. Dark red color: negative agreement with statistically significant negative associations in LIT and COH. Light green color: significant positive association in either LIT or COH, but not the other; light red color: significant negative association in either LIT or COH, but not the other; gray color: borderline-significant associations (ie, CI values close to 1). N: number of study subjects with diagnostic testing and clinical data

The results in our matched analysis are broadly in line with literature reviews by Ebell et al[71] confirming the suspected association between fever and influenza. The findings by Ebell et al[71] however are limited by the fact that viruses other than influenza (such as adenoviruses for example) were not studied. Thornton et al,[72] the second literature review in this area, found that wheezing is associated with RSV infections, but this study again lacked associations with other respiratory viral pathogens tested in this study (such as HMPV and HBoV-1). The latter also differed from the current study in that it was restricted to children with acute cough. Compared to previous reviews, our meta-analysis included more recent literature sources and lager sample sizes (49 858 versus 6790 and 15 069, respectively) and a slightly greater number of countries (24 versus 4 and 20, respectively). This current meta-analysis is also the only one linking to a prospective dataset.

Overall, literature data on RSV and influenza (and to a lesser degree, HMPV) seemed more readily available than literature on other respiratory viruses, which remain understudied in children. With the advent of new vaccines and antivirals against various respiratory viruses however, it will soon become critical to distinguish respiratory viral infections and to study the associated disease burden, including in the acute care setting.

The individual studies in our meta-analysis showed high levels of heterogeneity, especially with regards to inclusion criteria and/or cut-off criteria for specific symptoms such as fever and hypoxia. For instance, 7 studies used a hypoxia definition of oxygen saturation <90% while 2 studies used higher thresholds of <92%[29] and <95%[60]. Similarly, 11 studies defined fever as body temperature ≥38°C, 6 studies used cutoff values at 37.5°C,[27,35,37,40,52,65] and 1 study 38.2°C[73], while 22 studies did not define fever at all. Various clinical data collection methods, including phone interviews[24,29,37,39,41] questionnaires,[26,27,36,40,45,49,52,58,68] and surveys,[70] were used to obtain information on clinical features; clinical data collection for these studies may thus have been subject to recall bias, interviewer bias, or misclassification bias. Additional issues may arise in the design of control groups in observational and cohort studies[33,68,70] Among 6 case-control studies, merely 2 used age-matched or sex-matched control groups[43,73] and 1 was randomized.[50] Publication bias was also of concern in literature studies as funnel plots indicate that negative associations may have been missed in the published literature.

By contrast, the design of the inception cohort limited the risk of bias and heterogeneity through standardized clinical assessments in a predefined group of patients followed by independent laboratory and data analysis. In inception cohorts, the same data are solicited from all patients, and the same definitions/cutoff criteria for symptoms such as fever and hypoxia are used consistently. Standardized clinical and laboratory data collection in the QI program included predefined positive and negative findings, yielding a complete dataset for the analysis of positive and negative associations. Commonly referenced symptoms such as headache and myalgia may be underreported in infants and toddlers compared to older children. Headache and myalgia can only be elicited when age-appropriate examination techniques are applied. To avoid observer bias in the inception cohort, a trained QI team elicited these symptoms accurately in all patients, regardless of age.

In clinical routine care in most settings, it will not be feasible to obtain virus diagnostics on the 8 most common respiratory viral pathogens in all patients with ILI, as was the case in this inception cohort.

However, it will be important for clinicians to be conscious of awareness bias. One of the greatest challenges may lie in preconceived notions of "typical clinical presentations" in children with specific viral infections. The literature analysis may have revealed some of these inherent biases.

Clinical judgment is not only influenced by the lecture of journal articles: One may speculate that textbook knowledge (as acquired during medical school and residency training) also influences clinical decision-making. The most commonly referenced pediatric textbook (Nelson's textbook of pediatrics), for example, states that influenza infection is dominated by systemic symptoms such as fever, myalgia, chills, headache, malaise, and anorexia.[74] It also suggests that the onset of RSV infections is associated with rhinorrhea, cough, and wheezing, sometimes concomitant with a low-grade fever.[75] For these 2 diseases however, there are no literature references provided, nor specific guidance on the differential diagnosis in clinical practice. Nelson's textbook also states that symptoms of HAdV infection may be difficult to distinguish from similar illnesses caused by other pathogens, such as RSV, HPMV, or HRV.[76] However, it does not mention the difficulty in differentiating influenza infections from HAdV and other respiratory viral infections in children, as identified in the current work.

It may be of interest that the mass media have recently picked up on the fact that "not all that looks like the flu may indeed be influenza": Media reports by CNN, NBC News, and New York Daily News during the recent flu season emphasized that adenovirus infections may mimic symptoms otherwise attributed to influenza.[77-79] This recent media attention underlines the importance of health messages to the general public, for example to avoid the false impression that "flu vaccines don't work."

The current work has several strengths and limitations. The systematic review was restricted to publications in English and available in PubMed. Articles published elsewhere may have been missed. PubMed and the English language were chosen as they represent the most commonly accessed publications by clinicians.

A total of 205 literature studies had to be excluded because of lack of a "virus-negative" control groups (Figure 1). In the inception cohort, each patient was simultaneously tested (+/−) for the same viral pathogens using highly sensitive and specific RT-PCR assays at the National Reference Centre for Influenza at the Robert-Koch Institute. Even though sample sizes were usually smaller in the inception cohort, prospective data collection resulted in higher confidence levels, because of a comprehensive dataset with predefined variables (8 viruses/19 clinical features) determined in all subjects.

The inception cohort dataset was derived from a single center and 6073 subjects, limiting the generalizability of these findings to other settings with different patient populations or health care systems. The literature meta-analysis was more global in reach. Overall, cohort sizes were higher in the literature meta-analysis focusing on influenza (N = 24661), RSV (N = 29462), and HMPV (N = 14010).

As mentioned above, the available literature data on HRV, HAdV, HPIV, and HBoV-1 infections in children are relatively sparse, with sample sizes ranging from 1139 for HPIV to 2653 for HRV indicating selection bias. Published articles often focused on no more than 1 to 3 viral pathogens at a time and optional reporting of symptoms. The literature review is also limited by the inconsistency of laboratory methods used to detect respiratory viruses: Each published study used slightly different laboratory methods. In the inception cohort, a trained QI team obtained clinical specimens and delivered these to 1 National Reference Center.

Lastly, the effect of antiviral treatment or vaccination status on clinical features was not assessed in this analysis. Among the 6073 patients included in the inception cohort, only 3.3% received antivirals and influenza vaccination rates were 8.2% (data not shown). Future prospective studies or QI programs in different settings (for example in countries with universal influenza vaccination and treatment recommendations) may allow for the analysis of medical interventions.[80]

5 | CONCLUSIONS

We showed that point-of-care clinical assessments via mobile application represent a powerful mechanism to identify "typical clinical features" likely to be associated with a specific viral infection.

Many clinical features are shared across different types of respiratory viral infection. This means that even though significant associations between individual clinical features and viral infections have been identified, clinical symptoms alone cannot be used to predict specific respiratory viral infections in a particular patient. Clinicians should be aware that clinical features alone will not "rule-in" or "rule-out" any specific type of viral infection. Diagnostic testing for respiratory viruses will remain the cornerstone of accurate diagnoses. Testing should be encouraged to prevent unnecessary prescriptions of antivirals in "similar-looking" noninfluenza cases, where neuraminidase inhibitors would be ineffective.[81,82]

Methodologically, prospective data collection may be more effective in identifying clinical associations than large-scale meta-analyses of the medical literature. While some trends in the literature are confirmed, additional features were identified through the inception cohort. In the future, complex decision models considering combinations of symptoms rather than individual features may be more useful to inform best practice. Machine-learning algorithms may show the way toward "smart" decision software and the targeted use of diagnostics and antivirals.

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AUTHOR CONTRIBUTIONS

XM wrote the initial draft of the manuscript and contributed significantly to the laboratory data collection. BR designed the QI program and the literature review and supervised the writing of the manuscript. BS supervised the laboratory work and contributed significantly to the

writing of the manuscript. TC conducted the statistical analysis and contributed to the writing of the manuscript. JR supported the laboratory work and contributed significantly to the writing of the manuscript. MA as a key member of the QI staff contributed to the clinical data collection and to the writing of the manuscript. All authors have seen and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare with regards to the work presented.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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