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Clinical presentation and microbiological diagnosis in paediatric respiratory tract infection:

a systematic review

Abstract

Background
Antibiotic prescribing decisions for respiratory tract infection (RTI) in primary care could be improved if clinicians could target bacterial infections. However, there are currently no evidence-based diagnostic rules to identify microbial aetiology in children presenting with acute RTIs.

Aim
To analyse evidence of associations between clinical symptoms or signs and detection of microbes from the upper respiratory tract (URT) of children with acute cough.

Design and setting
Systematic review and meta-analysis.

Method
A literature search identified articles reporting relationships between individual symptoms and/or signs, and microbes detected from URT samples. Associations between pathogens and symptoms or signs were summarised, and meta-analysis conducted where possible.

Results
There were 9984 articles identified, of which 28 met inclusion criteria. Studies identified 30 symptoms and 41 signs for 23 microbes, yielding 1704 potential associations, of which only 226 (13%) have presently been investigated. Of these, relevant statistical analyses were presented for 175 associations, of which 25% were significant. Meta-analysis demonstrated significant relationships between respiratory syncytial virus (RSV) detection and chest retractions (pooled odds ratio [OR] 1.9, 95% confidence interval [CI] = 1.6 to 2.3), wheeze (pooled OR 1.7, 95% CI = 1.5 to 2.0), and crepitations/crackles (pooled OR 1.7, 95% CI = 1.3 to 2.2).

Conclusions
There was an absence of evidence for URT pathogens other than RSV. The meta-analysis identified clinical signs associated with RSV detection, suggesting clinical presentation may offer some, albeit poor, diagnostic value. Further research is urgently needed to establish the value of symptoms and signs in determining microbiological aetiology and improve targeting of antibiotics in primary care.

Keywords
child; diagnosis; microbiology; point-of-care systems; primary health care; respiratory tract infections.

INTRODUCTION

Respiratory tract infection (RTI) is one of the most common reasons why children present to primary care. A recent review by the UK's National Institute for Health and Care Excellence (NICE) concluded that antibiotics do not confer a clinically significant reduction in the time needed to recover from an RTI, and recommended that antibiotics are not prescribed for RTI in children who are otherwise healthy.[1] However, despite this, prescribing rates remain high[2] and are increasing[3] in UK general practice. This results in the treatment of children who experience no clinical benefit, yet are exposed to the potential adverse effect of antibiotics. This practice increases the potential for development of antimicrobial resistance.[4]

No diagnostic or prognostic rule has been developed to distinguish bacterial from viral RTI that would be expected to respond to antibiotics. In the absence of this information, a diagnostic gap exists between the presentation of RTI and the appropriate management. This leads to diagnostic uncertainty, which is reflected in a wide variation in antibiotic prescribing rates between clinicians,[5] practices,[6] and countries.[7]

The aim of this review was to identify the extent of evidence-reporting associations between clinical presentation and the detection of microbes in the upper respiratory tract (URT) in children presenting to healthcare services with RTIs associated with acute cough — cough being the most common presenting symptom of RTI[8] — and to conduct meta-analysis where appropriate.

METHOD

Search strategy

The search strategy was designed to identify observational studies and reviews that reported the relationships between clinical presentation and microbes sampled from the URT in children presenting with cough. Included studies were required to present data at the level of individual patients, and could be conducted in any country and published in any language. MEDLINE, Embase, and the Cochrane database using the OVID platform were searched on 30 November 2012, and the search was updated on 12 April 2014.

The MEDLINE search strategy is presented in Appendix 1 and used combinations of MeSH terms and text words for clinical symptoms and signs, disease causation, microbes, and clinical diagnoses. The search strategy was adapted for use in both MEDLINE and Embase. The search was not limited to the English language,

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How this fits in

No diagnostic test is routinely available to help clinicians distinguish bacterial from viral respiratory tract infections (RTIs) in children in primary care. Using symptoms and signs to identify the microbiological aetiology of RTI could improve appropriate use of antibiotics. This systematic review reports an absence of evidence for the relationship between clinical symptoms or signs and upper respiratory tract pathogens in children with RTI. Only 13% of the potential relationships between clinical characteristics and microbiology have been investigated, with 25% of these reporting significant associations, most notably for respiratory syncytial virus. Further research is urgently needed to establish the value of symptoms and signs for making a microbiological diagnosis and improve the targeting of antibiotic treatment to children.

no time restrictions were applied, and translations were obtained where required. Reference lists of all full-text articles were also screened.

Study selection

Studies eligible for inclusion were all peer-reviewed, quantitative studies reporting microbiological and clinical data from children presenting to a healthcare service or research team with a diagnosis or symptoms of an RTI associated with cough. Studies recruiting from primary care, secondary care, and community settings were included. Studies were excluded if data presented were selected based on a subgroup of children with positive microbiology results, or if children were recruited from intensive care or from a population with a high prevalence of pre-existing chronic disease or immune incompetence. Full inclusion and exclusion criteria are listed in Box 1.

Titles and abstracts of all articles identified were reviewed by one author, and those that were not relevant were excluded. Twenty per cent of abstracts were independently reviewed by one of two other authors, with good agreement (κ 0.89). Full-text copies of all included articles were independently reviewed by three authors, and any eligibility disagreements resolved by discussion.

Data extraction and quality assessment

Data were extracted from studies included in the review using a purpose-designed Access form and Excel spreadsheet. Descriptive variables extracted were participant age, study setting, design, country of recruitment, URT sample site, laboratory methods, microbes identified, analysis methods, whether children with prior antibiotic use were included in the study, and whether study inclusion criteria specified any named RTIs. Outcome data extracted were any symptoms and signs reported that were related to the clinical presentation of RTI. Quality assessment was conducted for all included articles using a purpose-designed form containing criteria based on recommendations from the GRADE guidelines and QUADAS-2 checklist.[9,10]

Data synthesis and analysis

Visual representation of the number of relationships sought was achieved by cross-tabulation of reported symptoms and signs against the respiratory pathogens identified. Where three or more studies reported raw data for an association between a pathogen and a symptom or sign, data were extracted, results checked for homogeneity, and meta-analysis carried out.

Statistical analysis was completed in STATA (version 12). Pooled odds ratios (OR) were obtained by fixed-effects meta-analysis to investigate the odds of pathogen detection in the presence of individual symptoms and signs. Heterogeneity was assessed using the I^2 statistic, and the possibility of publication bias was assessed using funnel plots.

RESULTS

Study characteristics

Searches identified 9984 articles of which 2502 were duplicates and 6378 excluded on the basis of title. There were 1104 abstracts screened and the full texts of 216 articles

Box 1. Inclusion and exclusion criteria for this systematic review

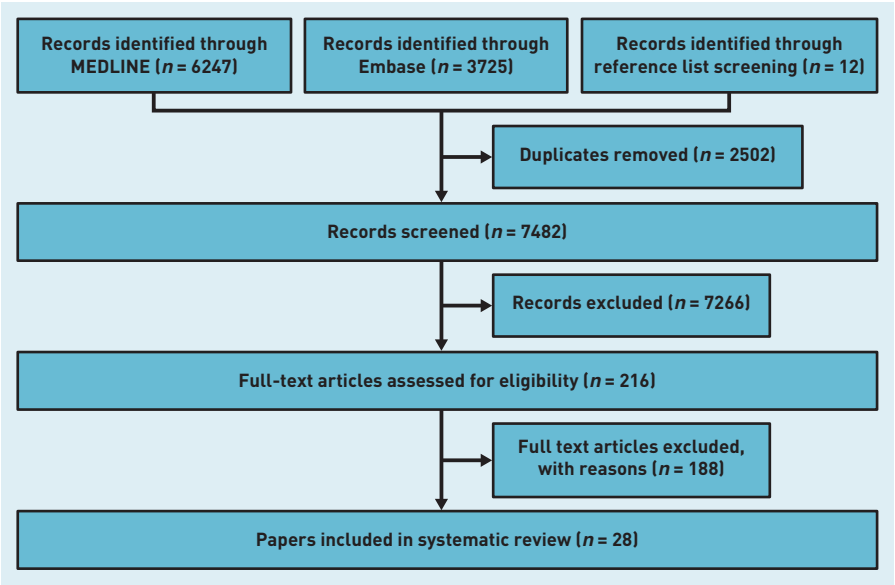
Inclusion criteria

1. Published peer-reviewed, quantitative studies reporting microbiological outcome.
2. Participants present to a healthcare service or research team with a diagnosis, or symptoms, of an RTI that includes (or is very likely to include) a cough.
3. Studies report either:
   a. The strength of associations between specific symptoms and/or signs and pathogens identified from respiratory tract samples; or
   b. Raw data cross-tabulating the incidence of specific symptoms and/or signs against pathogens identified from respiratory tract samples.
4. Studies report data from children; studies that recruit both adult and child participants must report child data separately from adult data.

Exclusion criteria

1. Studies where children are selected for entry into the study on the basis of positive microbiology results.
2. Studies where data is not presented from the whole cohort, but from a subgroup selected on the basis of microbiology results.
3. Microbiology results from pulmonary, blood, urine, or faecal samples.
4. Study participants recruited from intensive care.
5. Study participants recruited from a population of children with a high prevalence of pre-existing chronic disease or immune incompetence.

Figure 1. Flow chart showing inclusion and exclusion stages for articles in the review.



were read. Twenty-eight articles were eligible for inclusion in the review (Figure 1).

Raw data were presented by three or more studies for the associations between six individual clinical signs and pathogen detection, and this data, extracted from 10 studies, were included in the meta-analysis.

Study characteristics are summarised in Table 1. Half of studies (14 out of 28, 50% of total) recruited only infants aged 0–1 years, 1 out of 28 (4%) recruited only children aged from 2–17 years, and 3 out of 28 (11%) recruited infants and children aged from 0–17 years. All studies used samples taken from the nasopharynx, with the majority (18 out of 28, 64%) using nasopharyngeal aspirates. Laboratory methods of pathogen identification varied within and between studies, and included polymerase chain reaction (PCR) (used in 18 out of 28 studies, 65%), bacterial culture (4 out of 28 studies, 14%), assays (real-time analyte specific reagent or enzyme-linked immunoassay) (4 out of 28, 14%), and direct immunofluorescence (5 out of 28, 18%). The majority of studies (20 out of 28, 71%) were set in high-income countries.[11]

Quality assessments are summarised in Appendix 2. Studies were found to be of generally good quality and no study was excluded from this review on the basis of poor quality.

Symptoms, signs, and microbes investigated in the literature

Data were sought for 24 individual pathogens and were identified for 71 symptoms and signs, yielding 1704 potential comparisons (Appendix 3). Of the potential comparisons 226 (13%) were investigated by one or more study, within which 19% showed statistically significant associations; 58% showed no significant association; and 23% presented no relevant statistical analysis (Figure 2).

Signs associated with RSV detection

Six associations were identified that were examined by three or more studies presenting raw data. All six associations described the relationships between respiratory syncytial virus (RSV) and clinical signs. Raw data were extracted, and meta-analysis found significant associations between RSV detection and chest retractions (OR 1.9, 95% CI = 1.6 to 2.2, I^2 = 48%, *P*-value for I^2 statistic 0.074), wheeze (OR 1.7, 95% CI = 1.5 to 2.0, I^2 = 37%, *P* = 0.134), and crepitations/crackles (OR 1.7, 95% CI = 1.4 to 2.2, I^2 = 0%, *P* = 0.842) (Figure 3). Rales were not significantly associated with RSV (OR 1.2, 95% CI = 0.98 to 1.4, I^2 = 0%, *P*<0.669), and nor was fever (OR 0.97, 95% CI = 0.7 to 1.3, I^2 = 0%, *P* = 0.507). Results

Figure 2. Summary of Appendix 3: evidence for the 1704 potential associations between pathogens and clinical presentation investigated by studies in this review.

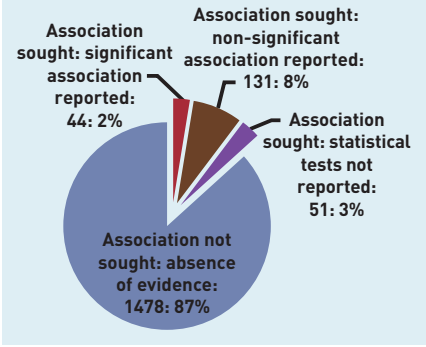


Table 1. Study characteristics

Author and year	Sample size	Country of recruitment	Setting	Design	Participant age	URT sample site	Type of RTI	Lab methods	Excluded children with prior antibiotic use?	Pathogen(s)	Analysis
Abu Raya 2013[25]	309	Israel	Secondary care: inpatients	Observational prospective	<1 year	NPA	Acute bronchitis	PCR	NR	BP	Univariable
Akhras 2010[26]	256	US	Secondary care: inpatients	Observational retrospective	<18 years	NPS or NPW	Any RTI	Assay	NR	RSV and hMPV	NR
Al-Toum 2009[16]	200	Jordan	Secondary care: inpatients	Observational prospective	<1 year	NPA	Any RTI	Culture	NR	AdV	Univariable
Berman 1990[27]	90	US	Secondary care: outpatients	Observational prospective	<1 year	NPA	Any RTI	Immunofluorescence or culture	NR	RSV, CP, BP, PIV, RV	NR
Chen 2010[28]	878	China	Secondary care: inpatients	Observational prospective	<18 years	NPA	Any RTI	PCR	NR	RSV, hMPV	Univariable
Durani 2008[29]	197	US	Emergency department	Observational prospective	<1 year	NPW	Bronchiolitis	Assay	NR	RSV	Multivariable
Esposito 2010[30]	69	Italy	Secondary care: inpatients	Observational prospective	<1 year	NPS	Bronchiolitis	PCR	NR	RSV	Univariable
Flores 2004[14]	225	Portugal	Secondary care: inpatients and emergency department	Observational prospective	<1 year	NPS	Bronchiolitis	PCR	Yes	RSV	Univariable
Gagliardi 2009[31]	262	Brazil	Secondary care: inpatients	Observational prospective	<18 years	NPA	Any RTI	PCR	NR	RSV, hMPV, CV, IA, IB, PIV	Univariable
Ghafoor 1990[32]	1492	Pakistan	Secondary care: inpatients and outpatients	Observational prospective	<18 years	NPA	Any RTI	Immunofluorescence or culture	NR	RSV, PIV, IA, IB, AdV	Univariable
Harnden 2007[33]	425	UK	Primary care	Observational prospective	<18 years	NPA	Any RTI	PCR	NR	IA, IB, RSV, hMPV, PIV, AdV	Multivariable
Heininger 1993[34]	3629	Germany	Primary care	Observational prospective	<18 years	NPS	Any RTI	Immunofluorescence	NR	BP	Univariable
IJpma 2004[35]	137	South Africa	Secondary care: inpatients	Observational prospective	<18 years	NPA	Any RTI	PCR	NR	hMPV, RSV, I	Univariable
Kellner 1989[36]	519	Austria	Secondary care: inpatients. Secondary care: outpatients	Observational prospective	<18 years	NPA	Any RTI	Assay or culture	NR	RSV, RV	Univariable
Khamis 2012[37]	259	Oman	Secondary care: inpatients	Observational prospective	<18 years	NPA	Any RTI	PCR	NR	RSV, AdV,PIV, IA IB, RV, hMPV, hBOV	Univariable
Lamarão 2012[38]	1050	Brazil	Secondary care: inpatients	Observational prospective	<18 years	NPA	Community-acquired pneumonia	DFA	NR	RSV	Multivariable

... continued

Table 1 continued. Study characteristics

Author and year	Sample size	Country of recruitment	Setting	Design	Participant age	URT sample site	Type of RTI	Lab methods	Excluded children with prior antibiotic use?	Pathogen(s)	Analysis
Mansbach 2008[15]	277	US	Emergency department	Observational prospective	<1 year	NPA	Bronchiolitis	PCR	NR	RSV, RV, hMPV, I	Univariable
Mathisen 2010[39]	2219	Nepal	Community	Observational prospective	<18 years	NPA	Any RTI	PCR	Yes	RSV, IA, IB, PIV, hMPV	Multivariable
Nuolivirta 2010[40]	142	Finland	Secondary care: inpatients	Observational retrospective	<1 year	NPA	Bronchiolitis	Immunofluorescence or PCR	NR	RSV, IA, IBAdV, PIV, hMPV, hBOV	Univariable
Papadopoulous 2002[41]	118	Greece inpatients	Secondary care	Observational prospective	<1 year	NPW	Any RTI	PCR	NR	RSV, CV, IA, IB, PIV, AdV, CP	Multivariable
Pecchini 2008[42]	455	Brazil	Secondary care: inpatients	Observational prospective	<1 year	NPA	Any RTI	Immunofluorescence	NR	RSV, AdV, IA, IV, PIV	Univariable
Pierangeli 2012[43]	231	Italy	Emergency department	Observational prospective	<18 years	Pharyngeal swab and nasal wash	Bronchiolitis, pneumonia, influenza-like illness, 'wheezing'	PCR	NR	RSV, IA, RV	Univariable
Regamey 2008[44]	112	Switzerland	Community	Observational prospective	<1 year	Nasal swab	Any RTI	PCR chain	Yes	RV, CV, PIV, RSV, hMPV, hBOV, IA, IB, AdV, EV	Univariable
Rhedin 2014[45]	209 (data extracted from case patients only)	Sweden	Emergency department	Matched case-control	<18 years	NPA	Any RTI	Real-time PCR	NR	IA, IB, AdV, hBOV, CV, EV, hMPV, RV, PIV, RSV	Multivariable
Teeratakulpisarn 2007[46]	170	Thailand	Secondary care: inpatients	Observational prospective	<1 year	NPA	Bronchiolitis	Real-time PCR	NR	RSV, hMPV	Univariable
von Linstow 2004[47]	383	Denmark	Secondary care: inpatients	Observational retrospective	<1 year	NPA	Bronchiolitis	PCR or assay	NR	RSV, hMPV	Univariable
Weigl 2003[48]	700	Germany	Secondary care: inpatients	Retrospective case-control	<18 years	NPA	Any RTI	PCR	NR	IA, IB,PIV, AdV, EV, MP, CP	Multivariable
Xepapadaki 2004[13]	56	Greece	Secondary care: inpatients	Observational prospective	<1 year	NPW	Bronchitis	PCR	NR	hMPV and RSV	Univariable

AdV = adenovirus. BP = Bordetella pertussis. CP = Chlamydia pneumoniae. CV = coronaviruses. DFA = direct immunofluorescence assay. EV = enterovirus. hBOV = human bocavirus. hMPV = human metapneumovirus. I = influenza (type not specified). IA = influenza A. IB = influenza B. IV = influenza virus. MP = Mycoplasma pneumoniae. NPA = nasopharyngeal aspirate. NR = not reported. NPS = nasopharyngeal swab. NPW = nasopharyngeal wash. PCR = polymerase chain reaction. PIV = parainfluenza virus. RSV = respiratory syncytial virus. RTI = respiratory tract infection. RV = rhinovirus.

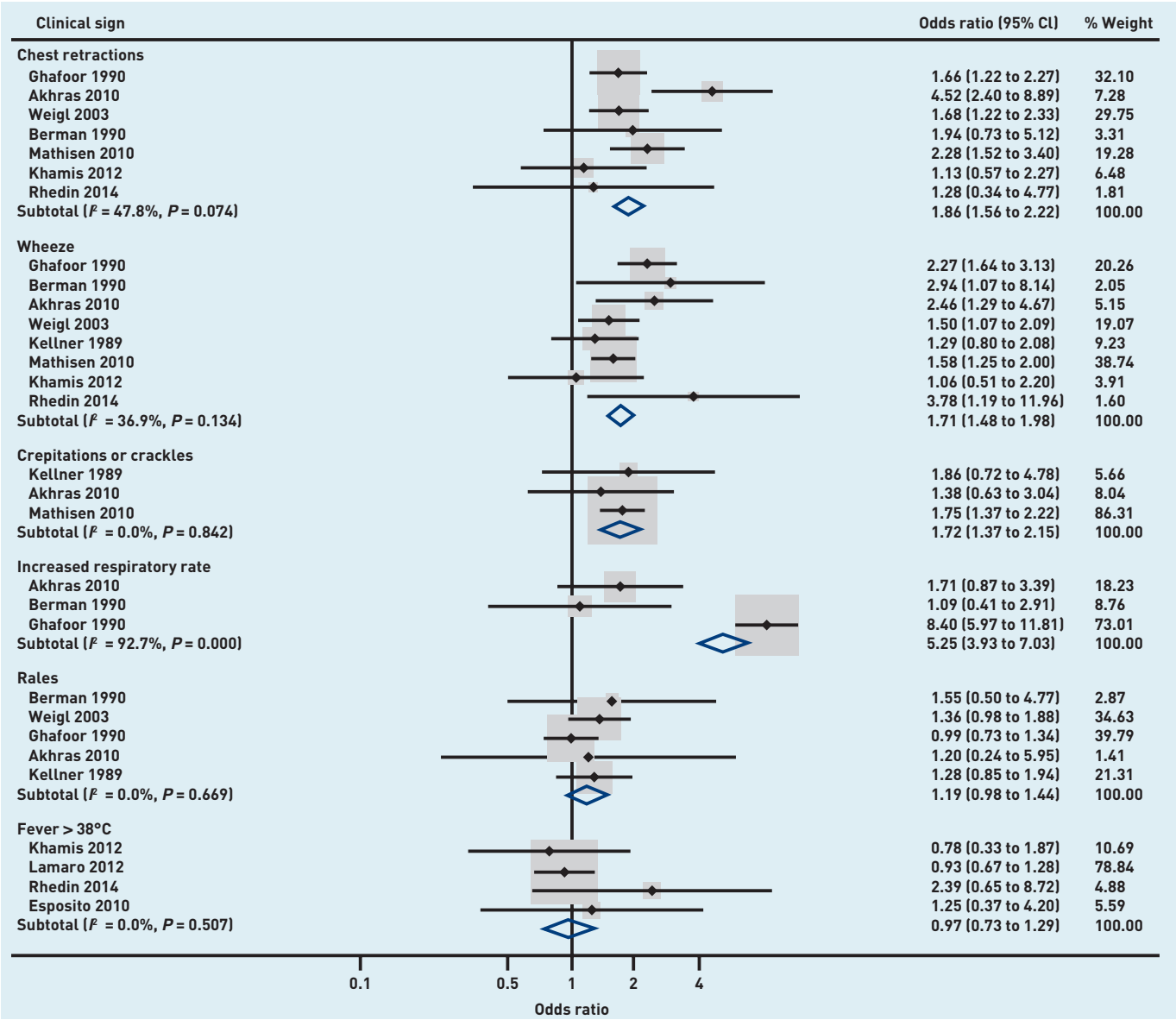


Figure 3. Evidence for the 1704 potential associations between pathogens and clinical presentation investigated by studies in this review.

of meta-analysis could not be considered for increased respiratory rate, as the data showed considerable heterogeneity (OR 5.3, 95% CI = 3.9 to 7.0, I^2 = 93%, P<0.001).

Publication bias

Publication bias was assessed in the data for wheeze and chest retractions using funnel plots (Appendices 4 and 5). Some evidence of positive publication bias was seen for chest retractions, but there was no evidence of publication bias for wheeze. There were insufficient data to assess publication bias for rales, crepitations/crackles, fever, or increased respiratory rate.

DISCUSSION

Summary

There is an absence of evidence evaluating the link between many clinical symptoms or signs and URT respiratory pathogens in children presenting to healthcare services with RTI-associated acute cough. Meta-analysis shows that some clinical signs (chest retractions, wheeze, and crepitations/crackles) are associated with URT detection of RSV. These results are applicable to children presenting to primary or secondary care with cough. However, caution should be taken in applying them beyond this population due to the effect of age on both URT flora and symptomatic presentation.

Strengths and limitations

This systematic review and meta-analysis of published literature without language or geographical restrictions was conducted and reported according to the MOOSE

guidelines.[12] Included are studies reporting either raw data or statistical results for associations between clinical presentation and URT respiratory pathogen detection, and have presented a unique overview of current knowledge. URT samples were selected for this review as this is the most accessible and acceptable site for primary care microbiological sampling. It is here that future point-of-care tests would most easily sample respiratory tract pathogens.

Reference lists of included articles were hand-searched, but it was beyond the scope of this investigation to search grey literature or conference proceedings.

Absence of multivariable analysis in the published literature means that, while no clear pattern is demonstrable between individual symptoms and signs, important independent associations may have been confounded by the presence of other symptoms and signs. Similarly, studies that failed to test for, or analyse, a broad range of respiratory pathogens may be affected by confounding due to the presence of an untested, or unadjusted for, microbe. Furthermore, the possibility of asymptomatic 'carrier states' was not investigated by these studies.

A lack of consensus was identified regarding the definition of continuous objective signs such as 'hypoxia' and 'fever'. For example, some studies defined 'hypoxaemia' as a blood oxygen saturation level of <92%,[13–15] while in others the cut-off limits were <95%.[16] In the interest of brevity, results for multiple definitions of these signs were combined into a single row in the tables. The use of international guidelines to define such terms in research, or the reporting of raw data, would increase the potential for meaningful comparisons between studies, and quantitative synthesis.

A wide variety of laboratory methods are employed to detect microbes in URT samples, and in many publications little or no validation data or standardisation of methods were described. Further to this, the use of URT samples as the diagnostic reference standard in this review may represent a poor measure of aetiology.

Comparison with existing literature

Previous work has demonstrated that clinicians use symptoms and signs to inform prescribing decisions in patients with RTI.[17] Evidence from existing meta-analyses suggests that *Mycoplasma pneumoniae* and influenza A and B may be associated with symptoms and signs; however, settings were not limited to primary care and reference standards included serological diagnosis.[18,19] Additionally, a recent study demonstrated that clinical features are moderately diagnostic for the detection of streptococci from the throat in patients presenting to primary care with tonsillitis.[20]

Implications for research and practice

Clinical guidelines in the UK and Europe advise that prescribing decisions are made based on the severity of disease or potential for complications.[1,21,22] Despite these recommendations, however, previous research has demonstrated that European clinicians use clinical presentation to help them assess the likelihood of bacterial aetiology in their decision making.[17,23] Overall, given the absence of evidence in this area, clinicians should be cautious about using clinical features to distinguish the 'bacterial' or 'viral' status of RTI in children in primary care. In the absence of a gold-standard aetiological test, further research is needed to establish whether URT microbes are associated with clinical presentation and, more importantly, with prognosis. High-quality, large-scale observational studies investigating a broad panel of respiratory pathogens are lacking, particularly in the primary care setting.

Future research should include other causality metrics in study design, for example, investigating the relationship between microbe quantification and clinical presentation, which could be used to help distinguish microbial aetiology from incidental carriage or asymptomatic infection. Other biomarkers, such as C-reactive protein and procalcitonin, have also been investigated as potential diagnostic aids in RTI[24] and their use could be considered in conjunction with URT samples.

This review demonstrates a significant gap in the evidence for using clinical presentation to make a microbiological diagnosis for children presenting with RTI. That said, the meta-analysis shows that clinical presentation is associated with the detection of RSV from the URT. This suggests that clinical presentation could be associated with the detection of other easily accessible URT microbes, which could be used to develop future diagnostic strategies and improve targeting of antimicrobials.

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Ethical approval

Not applicable.

Provenance

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Competing interests

Peter Muir reports grants from Mast Group Ltd, grants from Nanosphere Inc., and travel expenses from Nanosphere Inc. to attend and present data on above point-of-care test evaluation at a European conference and user group meeting, outside the submitted work. Peter Muir reports frequent discussion with commercial companies who market diagnostic microbiology products during the course of his work, some of which may be relevant to the subject of this manuscript. All other authors declare no competing interests.

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Appendix 1. MEDLINE search strategy

1	characteristic*.tw.
2	manifest*.tw.
3	symptom*.tw.
4	cough*.tw.
5	headache.tw.
6	"Chest pain".tw
7	Breathlessness.tw
8	"runny nose".tw.
9	"Chest tightness".tw
10	clinical sign*.tw.
11	fever.tw.
12	temperature.tw.
13	"head bobbing".tw
14	Cyanosis.tw
15	"pursed lip*".tw
16	"nasal flaring".tw.
17	coryza*.tw
18	stridor.tw.
19	mucus.tw
20	sputum.tw
21	dyspnoea.tw
22	"Short* of breath".tw
23	"intercostal recession".tw.
24	tachypnoea.tw
25	hyperpnoea.tw
26	wheez*.tw.
27	crepitation*.tw.
28	"pleural rub".tw
29	"bronchial breathing".tw
30	crackles.tw
31	ronchi.tw
32	"vocal resonance".tw
33	fremitus.tw
34	"peak flow".tw
35	"oxygen saturation".tw
36	sats.tw
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38	diagnos*.tw.
39	role.tw.
40	cause.tw.
41	effect.tw.
42	significance.tw.
43	importance.tw.
44	predict*.tw.
45	rule.tw.
46	manifest*.tw
47	judgement.tw
48	judgment.tw
49	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50	bacterial infections/
51	"chlamydia pneumonia*".tw.
52	"chlamydophila pneumonia*".tw.
53	"c pneumonia*".tw.
54	"mycoplasma pneumonia*".tw.
55	"m pneumonia".tw.
56	"bordetella parapertussis".tw.
57	"b parapertussis".tw.
58	"bordetella pertussis".tw.
59	"b pertussis".tw.
60	"staphylococcus aureus".tw.
61	"staph aureus".tw.
62	"s aureus".tw.
63	beta haemolytic streptococc*.tw.
64	"beta hemolytic streptococc*".tw.
65	"moraxella catarrhalis".tw.
66	"m catarrhalis".tw.
67	"influenza*".tw.
68	"streptococcus pneumonia*".tw.
69	"strep pneumonia*".tw.
70	"s pneumonia*".tw.
71	virus diseases/
72	rsv.tw.
73	"respiratory syncytial virus".tw.
74	parainfluenzavirus.tw.
75	metapneumovirus.tw.
76	adenovirus.tw.
77	coronavirus.tw.
78	rhinovirus.tw.
79	enterovirus.tw.
80	parechovirus.tw.
81	bocavirus.tw.
82	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81
83	croup.tw.
84	respiratory tract infection/
85	bronchitis.tw.
86	common cold/
87	cough.tw.
88	bronchiolitis.tw.
89	sinusitis.tw
90	rhinitis.tw
91	pertussis.tw
92	"whooping cough".tw38 diagnos*.tw.
93	pneumonia.tw
94	flu.tw
95	Influenza.tw
96	tracheitis.tw
97	empyema.tw
98	broncopneumonia.tw
99	83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 01 or 02 or 93 or 94 or 95 or 96 or 97 or 98
100	37 and 49 and 82 and 99
101	limit 100 to (English language and humans and all child [0 to 17 years])

Appendix 2. Quality assessment

Author	Selection criteria clearly defined?	Population/demographics well described?	Aims clearly defined?	Study design described?	Consistent clinical examination?	Examination results recorded prospectively?	Swab type clearly reported?	Lab methods clearly reported?	Lab and clinical investigators blinded?	Analysis methods clear and appropriate?	Possible to extract raw data for sign/symptom and microbe detection?
Abu Raya 2013	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓
Akhras 2010	✗	–	✓	✓	–	–	✗	✓	✓	✓	✓
Al-Toum 2009	✓	–	✓	–	–	✗	–	✓	–	✓	✓
Berman 1990	–	–	✓	–	✓	✓	✓	✓	–	–	✓
Chen 2010	✓	✓	✓	✓	–	✗	✓	✓	✓	✓	✗
Durani 2008	✓	✓	✓	✓	✓	✓	–	✓	–	✓	✗
Esposito 2010	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓
Flores 2004	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✓
Gagliardi 2009	✓	–	✓	✓	–	–	✓	✓	–	✓	✗
Ghafoor 1990	–	✗	–	–	✓	✓	–	✓	✓	✓	✓
Harnden 2007	✓	✓	✓	✓	✓	✓	✓	✓	–	✓	✗
Heiniger 1993	✓	✓	✓	✓	–	✓	✓	✓	–	✓	✓
IJpma 2004	✓	✓	✓	✓	–	–	✓	✓	–	✓	✗
Kellner 1989	–	✗	✓	–	–	✗	✓	✓	–	✓	✓
Khamis 2012	–	✓	✓	✓	–	✓	✓	✓	✗	✓	✓
Lamarão 2012	✓	✗	–	–	–	✓	✓	✓	–	✓	✓
Mansbach 2008	✓	✓	✓	✓	✓	✗	✓	✓	–	✓	✓
Mathisen 2010	✓	✓	✓	–	✓	✓	✓	✓	–	✓	✓
Nuolivirta 2010	–	✓	✓	✓	–	✗	–	–	✓	–	✓
Papadopoulos 2002	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✗
Pecchini 2008	✓	✓	✓	–	✓	✓	✓	✓	–	✓	✓
Pierangeli 2012	✓	✗	✓	✓	–	✓	✓	✓	✗	✓	✗
Regamey 2008	✓	✗	✓	✓	✓	✓	✓	✓	–	✓	✓
Rhedin 2014	✓	✓	✓	✓	✓	✓	–	–	✗	✓	✓
Teeratalkulpisarn 2007	–	✓	✓	–	–	–	✓	✓	–	✓	✗
von Linstow 2014	–	✓	✓	–	✗	✗	✓	–	✓	✓	✗
Weigl 2003	✓	✗	✓	✓	✓	✓	✓	–	✓	✓	✓
Xepapadaki 2004	✓	✓	✓	–	–	✓	✓	✓	–	✓	✗

Appendix 3. Associations sought between symptoms or signs and microbes reported by studies in this review

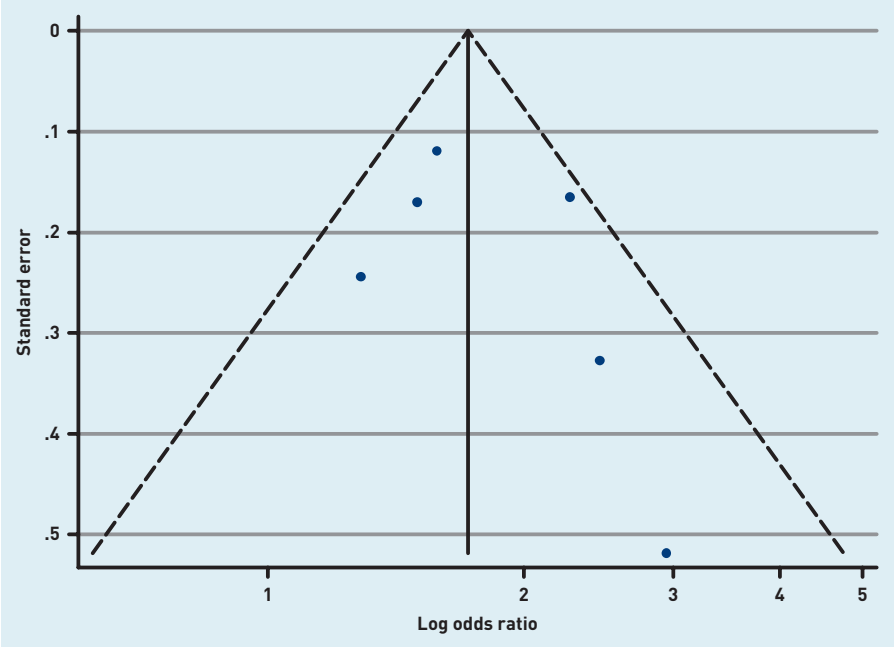
	Symptom or sign (bold text)	RSV	hMPV	Rhinovirus	Influenza A	Influenza B	Parainfluenza	*B.Pertussis*	Adenovirus	Influenza A/B	hBoV	Coronaviruses	*C. Pneumoniae*	*M. Pneumoniae*
Upper respiratory tract	Rhinitis	2	2	1	1	1	2	0	1	0	0	1	0	0
	Rhinorrhoea (symptom)	1 4 1	1 1 1	0	1	1	0	0	0	1	0	0	0	0
	Congestion	2 1	1	0	0	0	0	0	0	0	0	0	0	0
	'Runny nose, nasal obstruction or sneezes'	1	0	0	0	0	0	0	0	0	0	0	0	0
	Sneezing	0	0	0	0	0	0	0	0	0	1	0	0	0
	Nasal flare	1 1	0	1	0	0	0	0	0	0	0	0	0	0
	Coryza	0	0	0	0	0	0	0	0	0	1	0	0	0
	Rhinorrhoea (sign)	1 1	1	0	0	0	0	0	0	0	0	0	0	0
	Inspiratory stridor	1	0	0	0	0	0	0	0	0	0	0	0	0
	Stridor	1	0	0	0	0	0	0	0	0	0	0	0	0
	Expiratory stridor	1	0	1	0	0	0	0	0	0	0	0	0	0
Cough	Cough reported by parent	2 4 1	1 1 1	1	1	1	0	1	0	1	1	0	0	0
	Post-tussive vomiting	0	0	0	0	0	0	1	0	0	0	0	0	0
	Paroxysmal cough	0	0	0	0	0	0	1	0	0	0	0	0	0
	Cough	3 2	1	1	1	0	0	1	0	0	0	0	0	0
Lower respiratory tract	Tight chest	1	1	0	1	1	0	0	0	0	0	0	0	0
	Wheezing history	2	1	1	0	0	1	0	0	0	0	1	0	0
	Rapid breathing reported	1	1	0	0	0	0	0	0	0	0	0	0	0
	Difficulty breathing (maternal report)	1	1	0	0	0	0	0	0	0	0	0	0	0
	'Apnoea (symptom)	1 1	1	0	0	0	0	0	0	0	0	0	0	0
	Grunting	1 1 1	0	0	0	0	0	0	0	0	0	0	0	0
	Tracheal aspirate	1	0	1	0	0	0	0	0	0	0	0	0	0
	Chest retraction/indrawing	4 4 2	1 1 1	1	1	1	1	0	1	0	0	0	0	0
	Hyperinflation	1	1	0	0	0	0	0	0	0	0	0	0	0
	Crepitations or crackles	2 2 2	1 2 1	1 1	3	1	1	1	1	0	0	0	0	0
	Wheeze	4 4 2	1 3 1	2	1 3	3	2	1	1	0	0	0	0	0
	Ronchi	1 1 1	1 1 1	0	0	0	0	0	0	0	0	0	0	0
	Rales	3 2	1	1	0	0	0	0	0	0	0	0	0	0
	Reduced breath sounds	1 2	1	0	0	0	0	1	0	0	0	0	0	0
	Intensified breath sounds	1	0	1	0	0	0	0	0	0	0	0	0	0
	'Increased' respiratory rate	2 6 1	1 1 1	1 1	0	0	0	1	1	0	0	0	0	0
	Mean breath frequency	2	1	0	1	1	0	0	0	0	0	0	0	0
	Dyspnoea	1 1	0	0	0	0	0	0	0	0	1	0	0	0
	Respiratory distress	1	1	0	0	0	0	0	0	0	0	0	0	0
	Respiratory failure	2	1 1	0	0	0	0	0	0	0	0	0	0	0
	Hypoxia <92% or <95%	2 4	3	2	2	2	1	1	1	0	0	2	0	0
	Apnoea (not defined as symptom/sign)	0	0	0	0	0	0	0	0	0	1	0	0	0
	Prolonged expirium	1	0	1	0	0	0	0	0	1	0	0	0	0
Head & neck	Headache	0	0	0	1	1	0	0	0	1	0	0	0	0
	Earache	1 1	1	0	0	0	0	0	0	0	0	0	0	0
	Conjunctivitis (symptom)	1	1	0	1	1	1	0	1	0	0	0	0	0
	Watery eyes	1	1	0	0	0	0	0	0	0	0	0	0	0
	Red eyes	1	1	0	0	0	0	0	0	0	0	0	0	0

... continued

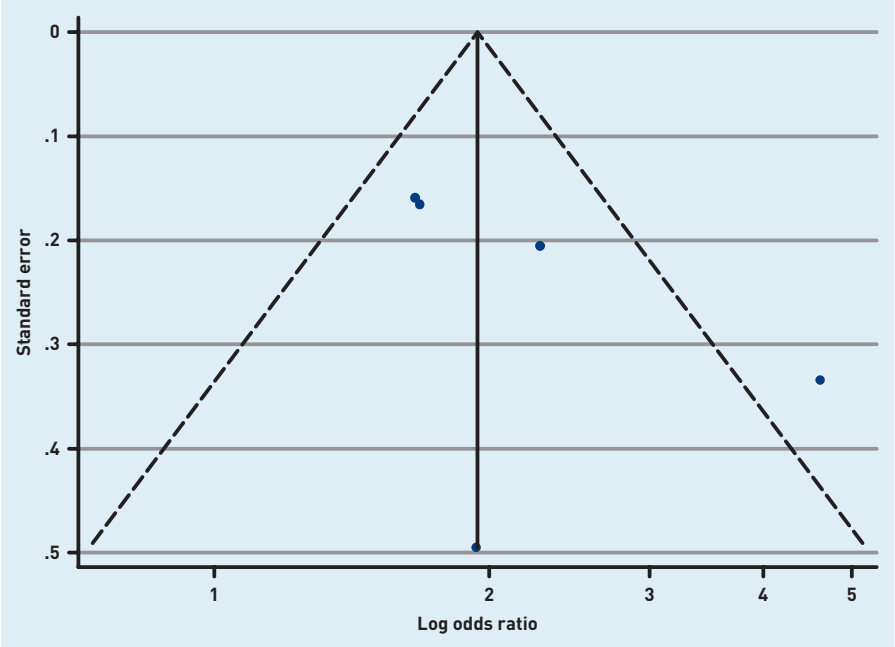
Appendix 3 continued. Associations sought between symptoms or signs and microbes reported by studies in this review

	Symptom (cells not shaded) or sign (cells shaded)	RSV	hMPV	Rhinovirus	Influenza A	Influenza B	Parainfluenza	*B.Pertussis*	Adenovirus	Influenza A/B	hBoV	Coronaviruses	*C. Pneumoniae*	*M. Pneumoniae*
Head & neck	Red eyes	1	1	0	0	0	0	0	0	0	0	0	0	0
	Sore throat	1 1	1	0	0	0	0	0	0	1	0	0	0	0
	Signs of otitis media	2	1	0	0	0	0	0	0	0	0	0	0	0
	Conjunctivitis (sign)	1 1	1	0	0	0	0	0	0	0	0	0	0	0
	Red throat	1	0	1	0	0	0	0	0	0	0	0	0	0
	Swollen occipital/cervical glands	1 2	1	1	0	0	0	0	0	0	0	0	0	0
CV	**Increased heart rate**	2 2 1	1 1	1	0	0	0	1	0	0	0	0	0	0
Gastrointestinal	Vomiting	1 1	1	0	0	0	0	0	0	0	0	0	0	0
	Abdominal pain	0	0	0	0	0	0	0	0	1	0	0	0	0
	Diarrhoea	1 1	1	0	0	0	0	0	0	1	0	0	0	0
	Difficulty feeding	1 1	1	0	0	0	0	0	0	0	0	0	0	0
	'Gastrointestinal symptoms'	1 2	1 1	0	0	0	0	0	0	0	0	0	0	0
Other	Activity disruption	1	1	1	0	0	1	0	0	0	0	1	0	0
	Reported severity/overall symptom score	1	1	1	0	0	1	0	0	0	0	1	0	0
	Reported fever	0	2 1	1	0	0	1	1	1	0	0	1	0	0
	Fatigue	1	1	0	0	0	0	0	0	0	0	0	0	0
	Rash	1	1	0	0	0	0	0	0	0	0	0	0	0
	Myalgia	0	0	0	0	0	0	0	0	1	0	0	0	0
	Decreased urine output	1	1	0	0	0	0	0	0	0	0	0	0	0
	Duration of symptoms prior to presentation	2 1	1	1 1	0	0	0	0	0	0	0	0	0	0
	Overall duration of symptoms	1 1	1	1	1	1	1	1	0	0	0	0	0	0
	Fever>37.5˚C	4	3	1	0	0	0	0	0	0	0	0	0	0
	Fever>38˚C	1 4	2	1	2 2	1 1	1	1 2	0	0	0	0	0	0
	Fever (threshold not defined)	4 2	0	1	0	0	0	0	0	0	0	0	0	0
	Cyanosis	3	1	0	0	0	0	0	0	0	0	0	0	0
	Poor perfusion	1	1		0	0	0	0	0	0	0	0	0	0
	Clinically assessed severity/severity score	2 3	2	2	1	1	2	1	2	0	1	2	1	1
	Acute symptom onset	1	0	0	0	0	0	0	0	0	0	0	0	0
	Length of stay	2 1	1 1	0	0	0	0	0	0	0	0	0	0	0

The numbers in each cell indicate the number of studies in this review which investigated each potential association between a symptom (left hand column, standard text) or sign (bold text) and a microbe (top row). Brown circles (●) represent studies reporting statistically significant associations. Blue circles (●) represent studies reporting non-statistically significant associations. Yellow circles (●) indicate studies in which raw data was presented, but no statistical analysis was performed. Red circles (●) indicate that no data were found for the relationship.



Appendix 4. Funnel plot with pseudo 95% CIs for studies reporting the relationship between wheeze and respiratory syncytial virus detection.



Appendix 5. Funnel plot with pseudo 95% CIs for studies reporting the relationship between chest retractions and respiratory syncytial virus detection.