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Systematic Review

Acute respiratory infection case definitions for young children: a systematic review of community-based epidemiologic studies in South Asia

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Abstract

OBJECTIVE To explore the variability in childhood acute respiratory infection case definitions for research in low-income settings where there is limited access to laboratory or radiologic investigations.

METHODS We conducted a systematic review of community-based, longitudinal studies in South Asia published from January 1990 to August 2013, in which childhood acute respiratory infection outcomes were reported. Case definitions were classified by their label (e.g. pneumonia, acute lower respiratory infection) and clinical content 'signatures' (array of clinical features that would be always present, conditionally present or always absent among cases). Case definition heterogeneity was primarily assessed by the number of unique case definitions overall and by label. We also compared case definition-specific acute respiratory infection incidence rates for studies reporting incidence rates for multiple case definitions.

RESULTS In 56 eligible studies, we found 124 acute respiratory infection case definitions. Of 90 case definitions for which clinical content was explicitly defined, 66 (73%) were unique. There was a high degree of content heterogeneity among case definitions with the same label, and some content signatures were assigned multiple labels. Within studies for which incidence rates were reported for multiple case definitions, variation in content was always associated with a change in incidence rate, even when the content differed by a single clinical feature.

CONCLUSION There has been a wide variability in case definition label and content combinations to define acute upper and lower respiratory infections in children in community-based studies in South Asia over the past two decades. These inconsistencies have important implications for the synthesis and translation of knowledge regarding the prevention and treatment of childhood acute respiratory infection.

keywords respiratory infections, pneumonia, bronchiolitis, children, South Asia, developing countries, diagnosis, epidemiology

Introduction

Acute respiratory infections (ARIs) are among the most important contributors to childhood illness and mortality throughout the world [1, 2]. ARIs present with a diverse constellation of symptoms and signs [3]. Most children have one or more symptoms of mucosal irritation or inflammation (e.g. rhinorrhea, cough). Children with infections of the lower respiratory tract (e.g. pneumonia, bronchiolitis) may demonstrate signs of compensation for impaired gas exchange (e.g. elevated respiratory rate, chest indrawing), and those with severe ARI (e.g. associated with sepsis or hypoxaemia) often display 'danger signs' (e.g. cyanosis, altered mental status) [4, 5]. However, even among children with the same ARI subtype, clinical presentations are highly variable; for example, some children with chest radiograph-confirmed pneumonia do not have cough [6].

To mitigate the toll of childhood acute lower respiratory infections (ALRIs) in low-income countries, in 1990, the World Health Organization (WHO) introduced a standardized approach to case management of children with 'cough and/or difficulty breathing'. Simple symptom- and sign-based case definitions (CDs) are used to identify children with 'pneumonia' in need of antibiotics or hospital referral. Since 1997, the ARI classification algorithm has been iteratively updated as part of the Integrated Management of Childhood Illness (IMCI) program [7]. Classical clinical pneumonia CDs have not been well suited for research (e.g. vaccine trials [8, 9]), yet there remains a lack of standardized CDs for epidemiologic studies and trials, particularly for use in low-income community settings with limited access to laboratory or radiologic investigations [10–12]. This absence of uniform research-oriented ARI CDs may limit the validity of between-study comparisons and meta-analyses that form the basis for practice-based guidelines and policies. In particular, estimates of the incidence of childhood ARI depend on the CD, leading to challenges in comparing the public health burden of ARI across regions or over time using epidemiologic studies that have applied different CDs [12].

To explore the extent of childhood ARI CD variation in the published literature, we conducted a systematic review of ARI CDs used in the implementation and analysis of longitudinal, community-based, epidemiologic studies of children in South Asia, a region that accounts for a substantial burden of the global under-five mortality related to ARI [2]. Numerous community-based childhood ARI studies have been conducted in South Asia over the past two decades, highlighting the relevance of ARI CDs to research in this region. Moreover, we expected that a focused analysis of CDs applied in South Asia would provide a conservative estimate of the heterogeneity in childhood ARI CDs across all low-income regions worldwide.

The primary aim of the review was to quantify the heterogeneity in reported ARI CDs. Using a novel approach to CD characterization and analysis, we first deconstructed each CD into its 'label' (e.g. 'pneumonia') and 'content' (i.e. coded array of clinical features that would determine whether an individual child fulfilled the CD criteria). We then compared the number of unique CDs (label–content combinations) to the total number of CDs, and assessed the degree of CD label–content discordance (i.e. discrepancies in content among CDs with the same label, or content that corresponded to multiple labels). The second aim was to demonstrate the potential effect of CD variability on epidemiologic inferences, by describing CD-related variations in ARI incidence rate (IR) estimates, for the subset of studies in which IR was reported (or estimable) using multiple ARI CDs applied to the same study population.

Methods

Study inclusion and exclusion criteria

We sought to include primary reports of all community-based, longitudinal studies published in the peer-reviewed literature from January 1990 to August 2013, in which ARI outcomes were reported and participants were children from birth to 5 years (any age span) in Bangladesh, Bhutan, India, Nepal, Pakistan or Sri Lanka. To maintain a primary focus on ARI CDs in the community setting, we excluded studies in which recruitment occurred only through healthcare facilities; the study population was restricted to children with a particular underlying chronic condition (e.g. HIV, cystic fibrosis); or, respiratory outcomes were limited to chronic infections (e.g. tuberculosis) or primarily non-infectious conditions (e.g. asthma). Multiple studies involving the same cohort were eligible for inclusion, as CDs may have differed across the published reports. There were no language restrictions placed on studies included in this review.

Search strategy

We searched MEDLINE and EMBASE electronic databases initially in November 2012 and updated the search in August 2013 to capture all relevant peer-reviewed studies. Our search syntax included a comprehensive list of keywords, medical subject headings (MeSH) (MEDLINE) and Emtree terms (EMBASE) identifying the geographic regions, participant age groups, study designs and outcomes of interest (Appendix Figure A1). Additionally, we screened the reference lists of all relevant reviews that were returned by the electronic search and cross-referenced our personal libraries.

Study selection

All titles and abstracts returned by the electronic search or identified in the reference lists of relevant reviews or personal libraries were independently assessed for relevance by at least two review authors (ESR, DER, SKM or TF) using a standardized screening form. Any disagreements were resolved by discussion among the screeners. The full-text reports of studies screened as relevant were then independently assessed for review eligibility by at least two review authors (ESR, DER, SKM or TF) applying the inclusion and exclusion criteria described above,

with any disagreements again resolved through discussion.

Data abstraction

Data from eligible studies were independently abstracted by at least two reviewers (ESR, DER, SKM, TF or MFG) using a standardized form designed to capture study design, population, CD characteristics and case ascertainment methods. Where possible, we abstracted ARI incidence data. If a reported IR was calculated according to our standard definition (i.e. number of episodes within an at-risk period of observation), we used the IR as reported by the authors. If the IR was not directly reported or was calculated using another definition, we calculated the IR for each CD using the reported number of episodes and the person-time, if such data were provided in the article. For controlled trials, we abstracted the IR for the control group only. Disagreements within any of the data abstraction fields were resolved through discussion among two or more authors.

Case definition ascertainment

To characterize and classify the diverse CDs, each extracted CD was deconstructed into two major semantic components: label and content. The CD label was the noun or brief phrase used by the study authors to identify a particular diagnosis or outcome measure (e.g. 'pneumonia'). The CD content primarily consisted of a set of clinical features – signs (observable) and/or symptoms (caregiver-reported) that were indicated by single words (e.g. 'cough') or brief phrases (e.g. 'difficult breathing'), combined with modal verbs (e.g. 'must' *vs.* 'may' be present) and conjunctions (e.g. 'and' *vs.* 'or' or 'and/or'). CD components were abstracted from text, tables and appendices. If a CD was labelled but no clinical criteria were reported, we considered the CD to be 'undefined.' We did not accept citations of published criteria (e.g. WHO) as substitutes for explicit descriptions. In some studies, an umbrella CD (e.g. 'ARI') was disaggregated into multiple additional CDs; in such scenarios, we included the umbrella CD as a distinct unit in our analysis if it was used by the authors to report study outcomes. Various CD content elements other than the core clinical features (Table 1) were not used in the analysis because these were inconsistently reported and would have invariably increased CD heterogeneity.

Data analysis

Label classification. Using all abstracted CD labels, we generated a 3-tier hierarchy of ARI categories by grouping study author-specified labels (Tier 3) that had closely related clinical interpretations into a more parsimonious set of reviewer-assigned labels (Tier 2). For example, the Tier 3 labels 'acute respiratory infection' and 'acute respiratory illness' were grouped together in Tier 2, with the most common Tier 3 label then used as the Tier 2 label. We further clustered Tier 2 labels into three broad categories (Tier 1): upper respiratory tract infections (URTIs), lower respiratory tract infections (LRTIs) or general/unspecified respiratory infections.

Table 1 Content elements of acute respiratory infection case definitions used in epidemiologic studies. Only the first two elements (clinical symptoms and signs) were used in the analysis of case definition heterogeneity

Element of case definition	Examples
Clinical features reported by parent/guardian (symptoms)	Cough, difficulty breathing
Clinical features observed directly by study personnel (signs)	Respiratory rate, chest wall indrawing
Subjective indicators of the severity of signs/symptoms	*Severe* lower chest wall indrawing
Specific cut-off values for quantitative signs	Respiratory rate thresholds to indicate fast breathing; body temperature cut-offs for fever
Minimum duration of reported clinical features	At least 3 consecutive days of symptoms
Minimum number of illness-free days between discrete episodes	At least 7 symptom-free days between preceding episode
Observed response to administered therapies	Positive response to a trial of an inhaled bronchodilator as an exclusion criterion
Results of diagnostic or point-of-care testing	Chest X-ray, laboratory tests, pulse oximetry
Designation, expertise or level of training of the individuals responsible for case ascertainment	Community health worker, physician
Referral and treatment algorithms that influence the representativeness of cases	Community health workers refer to hospital those children who meet a broad set of a criteria, but a physician makes the final case ascertainment based on a more limited set of criteria
Post hoc adjudication of cases	Two or more physicians conduct a retrospective review of clinical and ancillary data to determine whether the case definition is met

Content classification. To precisely characterize the clinical content of each CD, we aimed to acknowledge fine granularity (i.e. differences among CDs due to subtle yet critical differences in phrasing or terminology) while avoiding 'hair-splitting' (i.e. undue emphasis on negligible semantic distinctions). We considered fitting CDs into existing classification systems (e.g. WHO ARI algorithm), but found that this approach was practically unfeasible (most CDs lacked sufficient information for reliable matching) and sacrificed necessary granularity. Therefore, we developed a novel content classification system, whereby the content of each CD was summarized using a numeric 'signature'. First, for each abstracted (and defined) CD, we classified the function of each

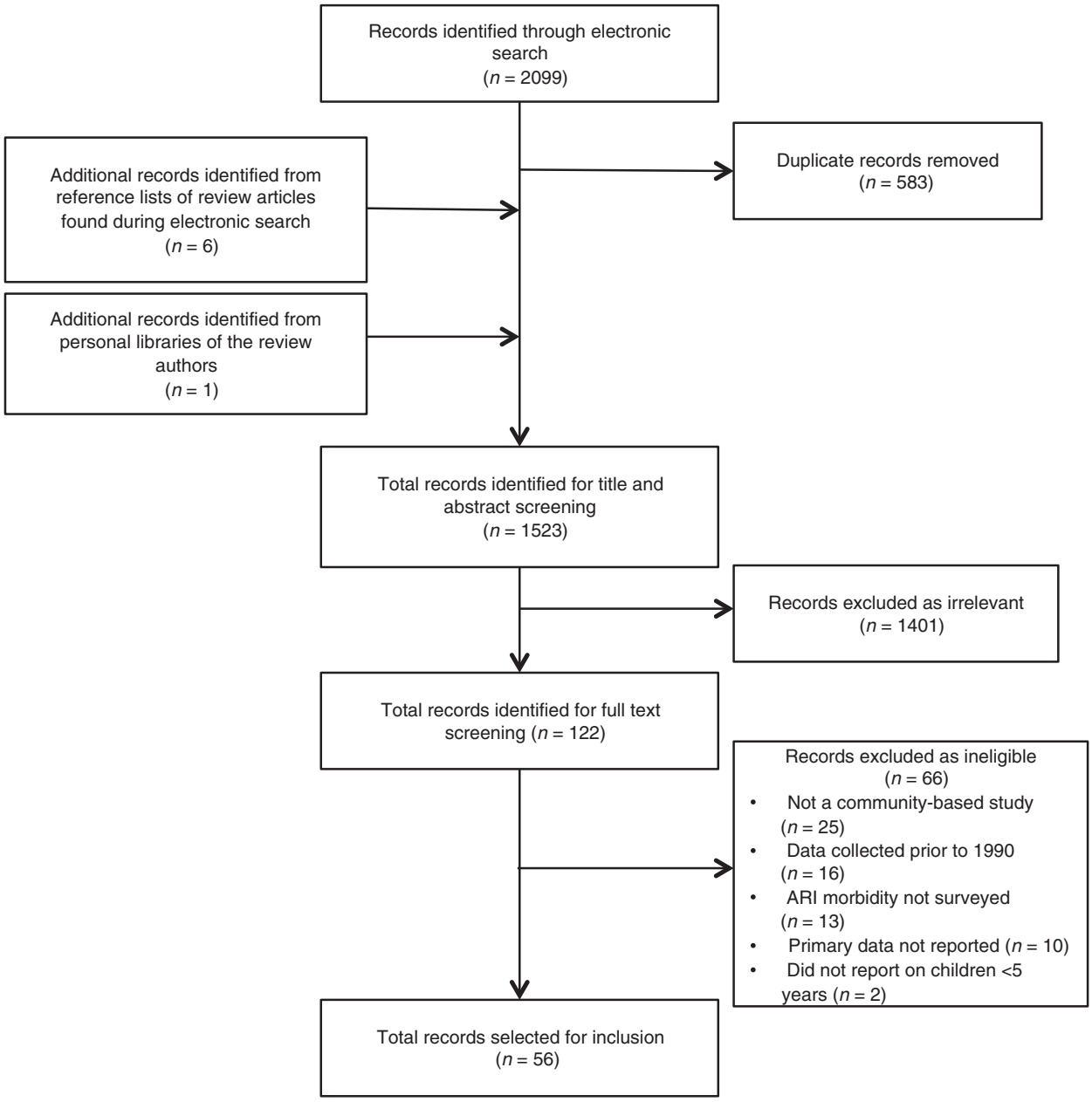

Figure 1 Flow of study selection.

component clinical feature that would be used to identify cases: a feature that must be present among all identified cases was classified as 'always present' (coded as '1'); a feature that must be present among all identified cases in the absence of another specified feature (e.g. 'cough' if the CD included 'cough and/or difficult breathing') or within a particular age band was classified as 'conditionally present' ('2'); and a feature that must not be present among any identified cases was classified as 'always absent' ('3'). Clinical features that were either not mentioned or were listed but were non-functional (e.g. 'with or without fever') were classified as 'non-contributory' ('0'). To represent the full clinical content of each CD, we generated numeric signatures by concatenating the functional codes of a series of clinical features, whereby a single digit represents a feature. We generated a 31-digit signature for each CD based on the full set of signs and symptoms abstracted from all eligible studies (Appendix Figure A2), and a 9-digit signature based on the following common features: cough, difficulty breathing, cough and/or difficulty breathing, fast breathing (reported), tachypnea (observed), lower chest indrawing (observed), crackles on auscultation, fever and danger signs. For example, 'cough' is represented by the first digit in both the 31- and 9-digit signatures, with '0' indicating that cough is not mentioned or is a non-contributory symptom in the CD, a '1' indicating that cough is always present among cases identified by the CD, a '2' indicating it is conditionally present among cases (e.g. must be present if 'difficult breathing' is absent), and a '3' indicating it is never present among cases. Synonymous features were combined even if the terms differed; for example, if 'fast breathing' was based on direct measurement of respiratory rate by study personnel, it was coded as 'tachypnea (observed)'. However, parent-/caregiver-reported features were distinguished from their directly observed correlates (e.g. 'fast breathing' reported by a parent was deemed distinct from tachypnea observed by study personnel). In the 9-digit signature, coding of 'danger signs' was based on study authors' use of the generic term 'danger signs' or reference to at least one specific feature conventionally considered as a danger sign (i.e. cyanosis, lethargy, inability to drink, feeding difficulty, abnormal sleepiness, irritability, convulsions, unconsciousness, vomiting). In the 9-digit signatures, chest indrawing was considered as a separate feature even if it was branded a danger sign by study authors. In the 31-digit signature, all danger signs were individually represented.

Data Analyses. We quantified ARI CD heterogeneity in several ways. First, for all groups based on Tier 1, 2 and 3 labels, we tabulated the number of CDs retrieved (i.e. CDs included in a label group), the number of defined CDs and the number of unique CDs (i.e. the number of distinctive 9-digit content signatures within the label group). Further analyses focused on four major Tier 2 LRTI labels (pneumonia, severe pneumonia, ALRI and severe ALRI) because these are of most public health importance and were well represented in the pool of defined CDs. We devised a 'Similarity Index' (SI) with exact binomial 95% confidence intervals as a standardized summary measure of CD content heterogeneity within each label group, using both the 31- and 9-digit signatures:

$$SI = (\text{total defined CDs retrieved} - \text{total unique CDs})/(\text{total CDs retrieved} - 1),$$

where by $0 \leq SI \leq 1$, such that 0 indicates complete dissimilarity (i.e. each CD in the group had its own unique content signature) and 1 indicates complete similarity (i.e. all CDs in the group had the same signature). To display the variability in the functional role ascribed to specific clinical features, we plotted the frequency distributions of the codes (0, 1, 2 or 3) for each feature in the 9-digit signature, by major Tier 2 LRTI label. To further examine label-to-content concordance, we constructed a

Table 2 Characteristics of studies included in the systematic review of childhood acute respiratory case definitions in epidemiologic studies in South Asia, 1990–2013

Study characteristics	*n* (%)
Total	56 (100)
Country	
Bangladesh	20 (35)
Bhutan	1 (2)
India	21 (38)
Nepal	7 (13)
Pakistan	7 (13)
Sri Lanka	0
Setting	
Urban	7 (13)
Slum/peri-urban	21 (38)
Rural	28 (50)
Study design	
Trial	20 (36)
Observational cohort	36 (64)
Publication year	
1994–99*	10 (18)
2000–06	16 (29)
2007–13	30 (54)

*There were no eligible studies published from 1990 to 1993.

matrix of the 9-digit content signatures by major Tier 2 LRTI label. Lastly, to demonstrate the effect of CD heterogeneity on epidemiological inferences, we compared CD-specific IRs for studies with reported IR for multiple defined CDs.

Results

Among 1523 articles screened, we found 56 published reports of community-based longitudinal childhood ARI studies that met criteria for inclusion in the review (Figure 1; and Appendix Table A1). Studies were primarily conducted in India and Bangladesh, and spanned the years 1994–2013 (Table 2). The number of CDs per study ranged from 1 to 7 (median = 3).

Overall, 124 CDs were abstracted, of which 90 (73%) were explicitly defined. We identified 37 distinct author-specified (Tier 3) ARI labels, of which 20 (54%) referred to LRTI (Figure 2). The most commonly used Tier 3 labels were 'pneumonia' (18 uses), 'severe pneumonia' (16), 'acute respiratory infection' (14) and 'acute lower respiratory infection' (14). We collapsed the Tier 3 labels into 20 reviewer-assigned (Tier 2) labels, of which 11 (55%) were classified as LRTI.

Among all defined CDs (n = 90), there were 53 (59%) unique 9-digit content signatures and 66 (73%) unique 31-digit signatures (Figure 2). The most common 9-digit signature (100000100; 'cough and fever'), used in six studies, was linked to four Tier 3 labels (acute respiratory infection, non-severe acute respiratory infection, severe acute respiratory infection, upper respiratory infection). The next most frequent 9-digit signature (221010000; 'cough and/or difficulty breathing and tachypnea'), used in five studies, was linked to three Tier 3 labels (acute

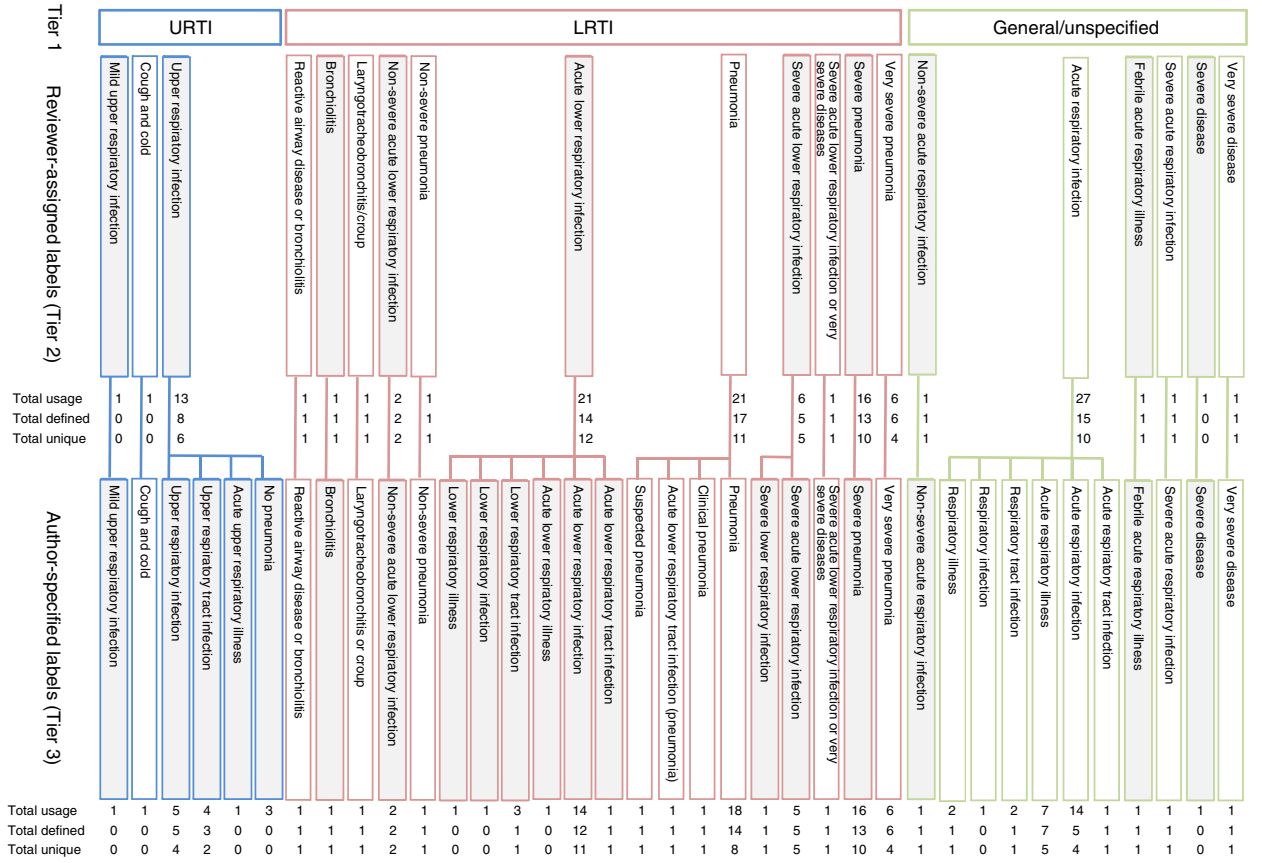

Figure 2 Classification tree of acute respiratory infection case definition labels used in published community-based longitudinal studies of children in South Asia. Tier 3 labels are shown exactly as written in the original published study, whereas Tier 2 and Tier 1 labels were reviewer-assigned. For Tier 2 and Tier 3 groupings, the column of numbers below each label group shows the number of studies in which the label was used, the number of studies in which the label was used for which the content was explicitly defined, and the number of unique definitions to which the label was linked. Connecting lines between Tier 2 and Tier 3 indicate the set of Tier 3 labels that comprise each Tier 2 group.

lower respiratory infection, acute respiratory tract infection, pneumonia).

There was a high degree of content heterogeneity among CDs with the same label, regardless of whether Tier 3 (author-specified) or Tier 2 (reviewer-assigned) labels were used (Figure 2). Among CDs classified with one of the four major Tier 2 LRTI labels, SI values were generally low (closer to 0 than 1), were not consistently higher within each label group compared to a pooled analysis and were not markedly higher using 9-digit *vs.* 31-digit signatures (Figure 3). Across studies, many features were assigned contradictory functional roles despite similar CD labels (Figure 4). Label-to-content discordance was due primarily to the variability of content signatures within label groups (reflected by low SI values), but some CD signatures were used in conjunction with multiple labels (Figure 5). In the subset of studies in which IRs were reported (or could be calculated) according to multiple defined CDs, variation in CD content was always associated with a change in the IR (Table 3). Overall, the IRs for CDs classified as URTI/unspecified (n = 12) ranged from 0.26 to 12.32 episodes per child-year, and for LRTI (n = 23) were 0.008–2.56 episodes per child-year (Table 3).

Discussion

Consistent and coherent clinical CDs for childhood ARIs are lacking in the epidemiologic literature. We found wide variability in ARI label and content combinations to define episodes of acute upper and lower respiratory infection in children participating in community-based studies in South Asia over the past two decades. In many studies, CDs were undefined, leading to uncertainty about the clinical phenotype that was ascertained or analysed. These observations were based on selected field studies in a defined geographic region with a high burden of LRTI, but the conclusions are likely generalizable and have substantial implications for synthesis and translation of knowledge about childhood ARIs, particularly in low-income communities.

Because of the greater clinical significance of LRTIs *vs.* URTIs, we focused our analysis on CDs that were presumably intended to target lower respiratory illness. Even among studies that adopted similar LRTI labels (e.g.

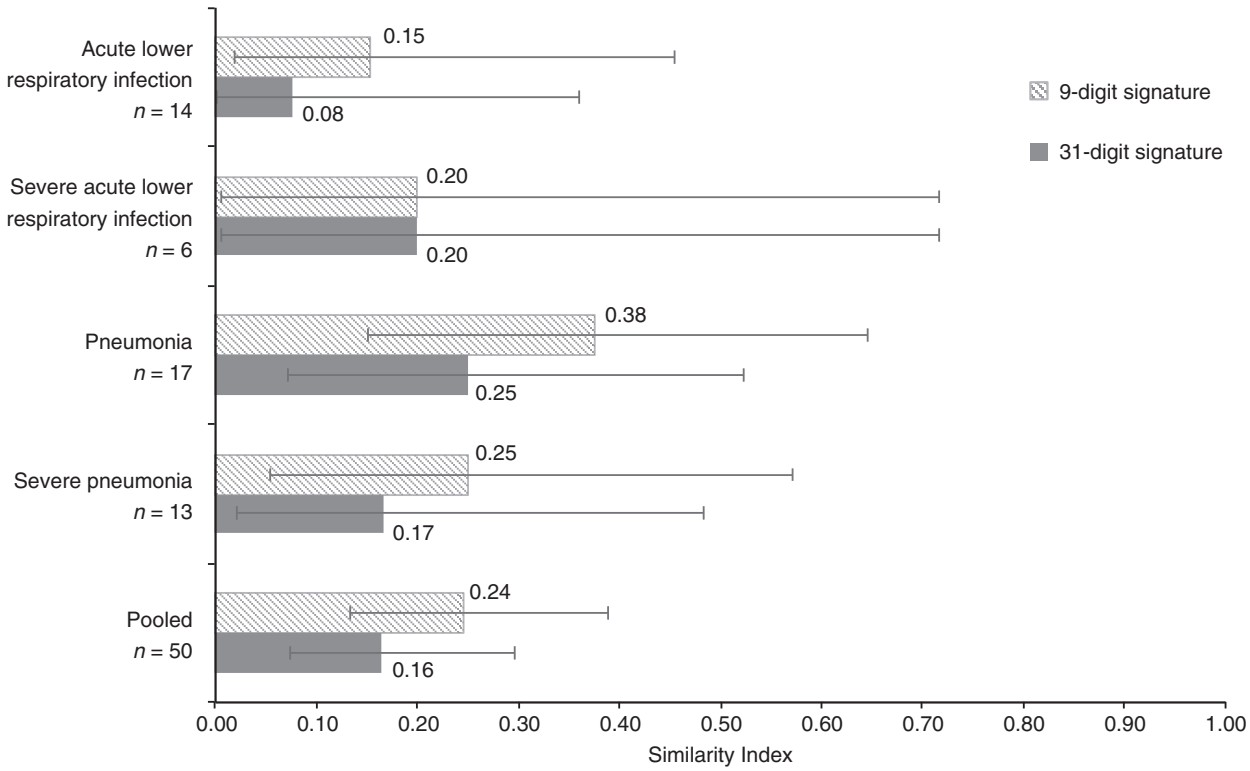

Figure 3 Similarity indices for the major reviewer-assigned lower respiratory tract infection label groups, using 9- *vs.* 31-digit case definition content signatures. Error bars indicate the 95% confidence intervals on the similarity index value. 'Pooled' refers to the combined analysis of all CDs in the four label groups.

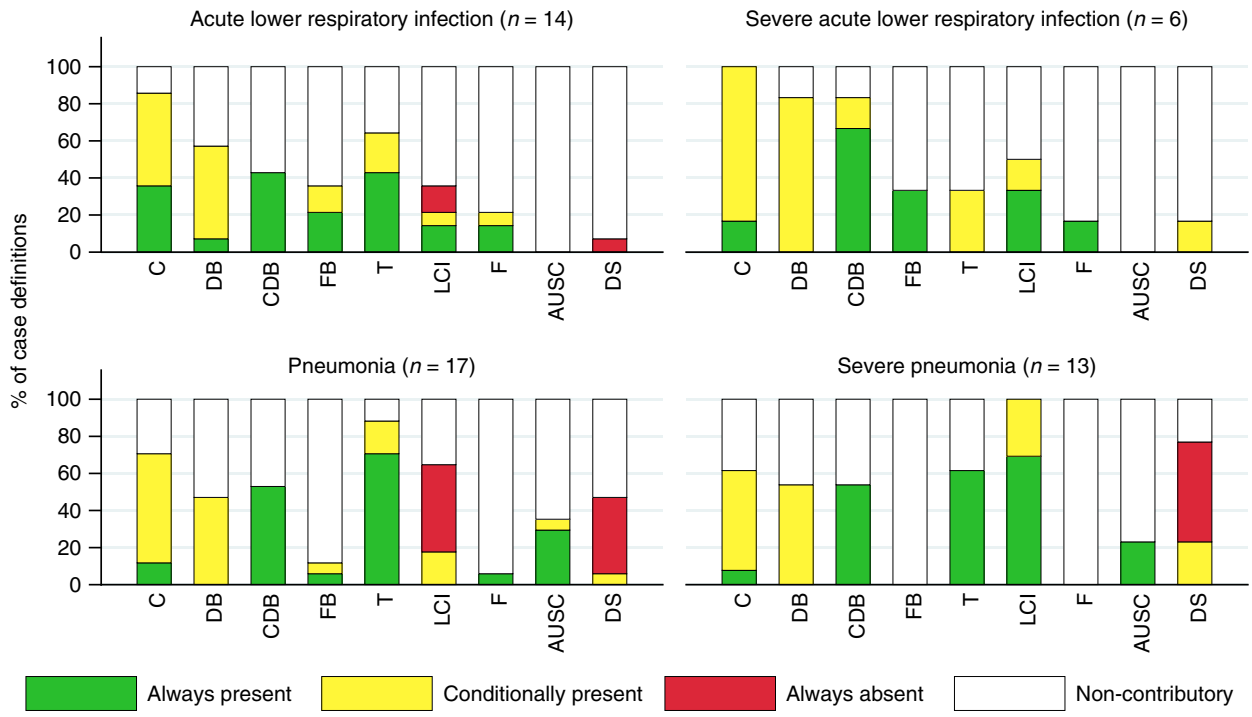

Figure 4 Distribution of the functional roles assigned by study authors to individual signs and symptoms that comprise the 9-digit content signature for acute respiratory infection case definitions. Non-uniformity of any column indicates that the function assigned to that particular features differed across studies, for example observed lower chest wall indrawing was highly variable among CDs that were labelled as 'acute lower respiratory infection', whereas it was universally considered essential (always present) or conditionally present for CDs labelled as 'severe pneumonia'.

'ALRI', 'pneumonia'), CD content differed widely. Limiting the comparisons to nine common clinical features did not substantially reduce the degree of heterogeneity, suggesting the variation was not primarily a result of differences in rare features (e.g. danger signs). Many authors referred to WHO pneumonia definitions, and the basic tenets of 'cough and/or difficulty breathing' and observed tachypnea were commonly adopted in LRTI CDs; however, we found inconsistencies in the application of WHO CDs. Heterogeneity that persisted among studies that purportedly used WHO classifications may have been partly attributable to the evolution of the WHO CDs over the past 20+ years (Appendix Table A2). WHO definitions are widely considered to lack sufficient specificity for use in epidemiologic research [11, 13] and are often modified rather than stringently applied [11].

The consequences of CD heterogeneity in ARI research have been largely underappreciated. In a recent study of global 'childhood pneumonia' incidence, Rudan *et al.* observed that 'the most fundamental uncertainty with measuring the incidence of childhood pneumonia in a community setting comes from the choice of case definition' and that 'great caution must be applied in making comparisons between studies or in combining data across studies to assure that only similarly designed and implemented case definitions are considered together' [12]. Nonetheless, incongruous CDs were pooled in their estimation of the median 'incidence of community-acquired childhood pneumonia in low- and middle-income countries'[12], which provided the basis for the pneumonia burden estimates in the recent Lancet Series on Childhood Pneumonia and Diarrhoea [14]. Unlike incidence rates, clinical syndromes (as represented by CDs) cannot be averaged; thus, the aggregation of data based on multiples studies that used disparate CDs yields summary estimates that do not correspond to any recognizable clinical phenotype.

The effect of outcome definition specificity on epidemiological inferences is a well-known methodological issue. For example, in vaccine trials, efficacy estimates are

Content signature based on 9 signs and symptoms	ALRI	Pneumonia	Severe ALRI	Severe pneumonia	Total
000011000	1	0	0	1	2
000011013	0	0	0	2	2
000012000	0	0	0	1	1
000012012	0	0	0	1	1
000013000	0	1	0	0	1
000013013	0	3	0	0	3
000022000	0	1	0	0	1
010010000	1	0	0	0	1
100000010	0	1	0	0	1
100010000	1	0	0	0	1
100011003	0	0	0	1	1
100011100	1	0	0	0	1
100013003	0	1	0	0	1
100020200	1	0	0	0	1
100100000	1	0	0	0	1
120021100	0	0	1	0	1
120023100	1	0	0	0	1
200022000	1	0	0	0	1
200022022	0	1	0	0	1
201002002	0	0	1	0	1
201222000	0	1	0	0	1
221001000	0	0	1	1	2
221001003	0	0	0	3	3
221002002	0	0	0	1	1
221010000	1	3	0	0	4
221010010	0	1	0	0	1
221011003	0	0	0	1	1
221012002	0	0	0	1	1
221013003	1	3	0	0	4
221100000	2	0	2	0	4
221100100	0	1	0	0	1
221200000	2	0	0	0	2
222020000	0	0	1	0	1
Total	14	17	6	13	50

Figure 5 Case definition content signatures associated with major reviewer-assigned lower respiratory tract infection labels (using the 9-digit case definition content signatures). The variability of content signatures across case definitions (CDs) with the same label is reflected by the spread (*vs.* concentration) of CDs within a single column of the matrix. The specificity of a particular content signature for any given label is reflected by the spread (*vs.* concentration) of CDs within a single row. Shaded cells highlight CD usage in at least one study, and darker shading indicates increased frequencies of usage.

biased towards the null when lower-specificity clinical LRTI CDs are used as outcome measures instead of radiologically confirmed pneumonia [8, 9]. Considering studies included in the present review, multiple CDs led to highly divergent estimates of ARI incidence within the same study, indicating that the CD itself was the cause of the difference in IR. These within-study comparisons suggest that CDs likely contribute to substantial between-study variation in interventions effects or epidemiologic estimates [15]. For example, in a meta-analysis of the effect of routine zinc supplementation for the prevention of LRTI in children in low-income settings, we previously showed that between-study variation in effect measures was significantly associated with the ranked severity/specificity of clinical CDs [16].

There were several limitations of our study that must be acknowledged. In general, our analytical approach underestimated the true extent of CD heterogeneity. First, we intentionally reviewed studies that were expected to adopt similar CDs, because of restriction to studies with relatively robust designs (community-based cohort studies and trials) in a defined world region (South Asia). Given that WHO ARI CDs were revised in classification algorithms published in 2013 and 2014 (Appendix Table A2), we expect that inclusion of studies published after mid-2013 (end of the review period) would have further increased LRTI CD heterogeneity. Second, we focused our analysis on itemized clinical criteria that were explicitly mentioned in published articles, yet numerous other elements and qualifiers (e.g. respiratory rate cut-offs to define tachypnea) that we did not incorporate in our analysis would further differentiate the CDs (Table 1). To maintain a consistent approach to CD classification across all studies, we relied only on the wording in the published articles

Table 3 Within-study comparisons of childhood acute respiratory infection incidence rates in South Asia, by case definition

Study	Country, setting	Source of clinical information	Author-specified ARI label	Clinical features		Incidence rate (episodes per child-year)	Incidence rate ratio*
				Must/May be present	Must be absent		
Asling-Monemi 2009	Bangladesh, rural	Mother/ caregiver only	Acute respiratory infection	Cough + Fever		10.7	1
			Acute lower respiratory infection (pneumonia)	(Cough and/or 'breathing problem') + Fever + Fast breathing		2.2	0.21
Baqui 2003	Bangladesh, rural	Mother/ caregiver only	Acute lower respiratory infection	(Cough and/or difficulty breathing) + Fast breathing		2.56	1
			Non-severe acute lower respiratory infection	(Cough and/or difficulty breathing) + Fast breathing	Chest in drawing	1.06	0.41
			Severe acute lower respiratory infection	(Cough and/or difficulty breathing) + Fast breathing + Chest indrawing		1.49	0.58
Bhandari 2002	India, peri-urban	Mother/caregiver and study physician	Acute lower respiratory tract infection	Cough + (tachypnea or chest indrawing)		1.62	1
			Pneumonia	(a) Cough + (tachypnea or chest indrawing) + (chest indrawing or nasal flaring or a danger sign†) or (b) Cough + (crackles or bronchial breathing on auscultation)		0.32	0.20
Brooks 2005	Bangladesh, periurban	Mother/caregiver and Study physician	Upper respiratory infection	Cough + Rhinorrhea + Fever	Tachypnea	12.32	1
			Pneumonia	Tachypnea + Crackles	Chest indrawing, Danger signs‡	0.56	0.05
			Severe pneumonia	Tachypnea + Crackles + (Chest indrawing or a danger sign‡)		0.082	0.01

Table 3 (*Continued*)

Study	Country, setting	Source of clinical information	Author-specified ARI label	Clinical features		Incidence rate (episodes per child-year)	Incidence rate ratio*
				Must/May be present	Must be absent		
Brooks 2010	Bangladesh, periurban	Mother/caregiver and study physician	Upper respiratory infection	Cough + Rhinorrhea + Fever		1.54	1
			Pneumonia	Tachypnea + Crackles	Chest indrawing, Danger signs§	0.47	0.31
			Severe pneumonia	Tachypnea + Crackles + Chest indrawing	Danger signs§	0.035	0.02
			Very severe pneumonia	Tachypnea + Crackles + Chest indrawing + Danger sign§		0.008	0.01
Broor 2007	India, rural	Mother/caregiver and study personnel	Acute respiratory infection	Cough and/or difficulty breathing		2.97	1
			Acute lower respiratory infection	(Cough and/or difficulty breathing) + Tachypnea	Chest indrawing, Danger signs¶	0.54	0.18
			Severe acute lower respiratory infection or very severe disease	(Cough and/or difficulty breathing) + (Chest indrawing or nasal flaring or grunting or danger sign¶)		0.043	0.01
			Upper respiratory infection	Cough and/or difficulty breathing	Tachypnea, Chest indrawing, Danger signs¶	2.39	0.80
Homaira 2012	Bangladesh, urban	Mother/caregiver and physician	Acute respiratory infection	Cough or runny nose		1.25	1
			Pneumonia	(Cough and/or difficulty breathing) + Tachypnea + Wheeze + Crackles		0.52	0.42
Khan 2009	Pakistan, rural	Mother/caregiver and study personnel	Pneumonia	(Cough and/or difficulty breathing) + Tachypnea		0.30	1
			Severe pneumonia	(Cough and/or difficulty breathing) + (Chest indrawing or stridor or danger sign**)		0.081	0.27

Table 3 (*Continued*)

Study	Country, setting	Source of clinical information	Author-specified ARI label	Clinical features		Incidence rate (episodes per child-year)	Incidence rate ratio*
				Must/May be present	Must be absent		
Osendarp 2001	Bangladesh, urban	Mother/caregiver only	Upper respiratory tract infection	(Cough and/or difficulty breathing) or (Cough + nasal discharge)	Fast breathing, Chest indrawing	8.16	1
			Acute lower respiratory infection	(Cough and/or difficulty breathing) + (Fast breathing or chest indrawing)		1.42	0.17
Osendarp 2002	Bangladesh, urban	Mother/caregiver only	Upper respiratory tract infection	(Cough and/or difficulty breathing) or (Cough + nasal discharge)	Fast breathing, Chest indrawing	9.02	1
			Acute lower respiratory infection	(Cough and/or difficulty breathing) + (Fast breathing or chest indrawing)		1.34	0.15
Rahman 2001	Bangladesh, periurban	Mother/caregiver and study personnel	Acute lower respiratory infection	Cough + Difficult/rapid breathing + Fever	Chest indrawing	0.79	1
			Severe acute lower respiratory infection	Cough + Difficult/rapid breathing + Fever + Chest indrawing		0.32	0.41
Tielsch 2007b	India, rural	Mother/caregiver only	Acute respiratory illness (1)	Cough + Fever	Difficulty breathing	1.9	1
			Acute respiratory illness (2)	Difficulty breathing + Fever	Cough	0.35	0.18
			Acute respiratory illness (3)	Cough + Fever + Difficulty breathing		0.26	0.14

*Within-study comparison of incidence rates, whereby the reference case definition for each study is that for which the rate was highest (indicated as '1').
†Extreme lethargy, inability to drink, inability to feed, abnormal sleepiness, restlessness or irritability, convulsions.
‡Cyanosis, lethargy, inability to drink.
§Cyanosis, lethargy, inability in drink, convulsions.
¶Lethargy, inability to drink, poor feeding, convulsions, unconscious, vomiting.
**Lethargy, inability to drink, convulsion, unconscious, vomiting.

(rather than contacting authors), yet we frequently had to adjudicate ambiguous grammar (e.g. comma placement affected the designation of a particular feature as 'always' or 'conditionally' present). Our proposed 'similarity index' (SI) provided a quantitative metric of CD variability; however, the low number of CDs in each label group reduced the precision of the SI estimates. To increase the number of CDs in each grouping, we used reviewer-assigned labels that avoided minor semantic distinctions among author-specified labels; doing so did not increase heterogeneity, suggesting that the original study authors did not select specific label variants intentionally.

The present study was not designed to identify a set of optimal ARI CDs. Distinct CD sets may be suited to particular research questions (e.g. microbial aetiology studies *vs.* efficacy trials). However, there is a practical benefit of consensus on core CDs among studies targeting similar clinical conditions [17]. The 'pneumonia' label in particular has emerged as a particular focus of confusion in the literature [18]: the paediatrician's concept of pneumonia is a lower respiratory tract infection of known or suspected bacterial aetiology, typically confirmed by alveolar consolidation on chest X-ray, and thus distinct from acute small airways disease (i.e. viral bronchiolitis), whereas the conventional WHO case management definition of pneumonia conflates viral/airway and bacterial/alveolar ALRI [19]. Therefore, a more generic label (e.g. ALRI) may be preferred in research in which the aggregate outcome of interest encompasses a range of phenotypes including viral bronchiolitis and bacterial pneumonia. For most of the community-based studies, we reviewed, suitable clinical CDs may be those that are most predictive of adverse outcomes (e.g. need for hospitalization, death), rather than those that differentiate among specific microbial aetiologies, pathological mechanisms or chest X-ray findings [20, 21].

Conclusion

We found substantial childhood ARI CD variation among epidemiological studies conducted in South Asia between 1990 and 2013. Within studies for which IRs were reported for multiple CDs, variation in CD content was always associated with a change in IR, even when the content differed by a single clinical feature. These findings highlight the need to generate standardized CDs that will improve the rigour and comparability of studies of childhood ARI incidence, prevention and treatment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix Figure A1 Literature search strategy
Appendix Figure A2 Clinical content signatures
Appendix Table A1 Studies included in the review
Appendix Table A2. Acute respiratory infection case definitions according to the World Health Organization (WHO), 1990–2014. All case definitions include a reported history of "cough and/or difficult breathing". The case definitions are mutually exclusive, whereby a child is assigned to the most severe case definition for which criteria are met.

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