

Epidemiology, etiology, x-ray features, importance of co-infections and clinical features of viral pneumonia in developing countries

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Pneumonia is still the number one killer of young children globally, accounting for 18% of mortality in children under 5 years of age. An estimated 120 million new cases of pneumonia occur globally each year. In developing countries, management and prevention efforts against pneumonia have traditionally focused on bacterial pathogens. More recently however, viral pathogens have gained attention as a result of improved diagnostic methods, such as polymerase chain reaction, outbreaks of severe disease caused by emerging pathogens, discovery of new respiratory viruses as well as the decrease in bacterial pneumonia as a consequence of the introduction of highly effective conjugate vaccines. Although the epidemiology, etiology and clinical characterization of viral infections are being studied extensively in the developed world, little data are available from low- and middle-income countries. In this paper, we review the epidemiology, etiology, clinical and radiological features of viral pneumonia in developing countries.

KEYWORDS: acute respiratory infections • adult • children • developing countries • pneumonia • viral

Despite significant reductions in child mortality over the last decade, pneumonia remains the leading cause of childhood mortality worldwide, accounting for 18% of deaths in children under 5 years of age [1]. An estimated 120 million new cases of pneumonia occur globally each year [2]. In addition, an estimated 14.9 million (95% CI: 12.4–18.1 million) episodes of severe and very severe acute lower respiratory infections (ALRI) in young children result in hospital admissions [3]. In developing countries, management and prevention efforts against pneumonia have traditionally focused on bacterial pathogens, known to cause between 30 and 77% of the most severe pneumonia cases [4–6]. Among these pathogens, two bacteria stand out as the major causes of disease: *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) [5–9]. The scarcity of routine microbiology facilities in most resource-constrained settings and the low sensitivity of current bacterial identification

methods hinder adequate surveillance, which may in turn contribute to an underestimation of the real burden of these pathogens. The relevance and impact of bacteria as a cause of pneumonia was clearly established prior to the introduction of the pneumococcal and Hib conjugate vaccines [8–11]. More recently, however, attention has shifted toward non-bacterial causes of pneumonia, namely, to viral respiratory infections. Respiratory syncytial virus (RSV), widely studied in both developed and developing countries, is estimated to cause over 22% of all ALRI and up to 200,000 deaths annually [12]. In addition to RSV, other viruses have emerged as major causes of pneumonia and other potentially life-threatening respiratory syndromes. Viral pathogens have gained recent interest as a result of improved diagnostic methods such as PCR, outbreaks of severe disease caused by emerging pathogens such as avian influenza A (H5N1) and pandemic influenza A (H1N1) and the discovery

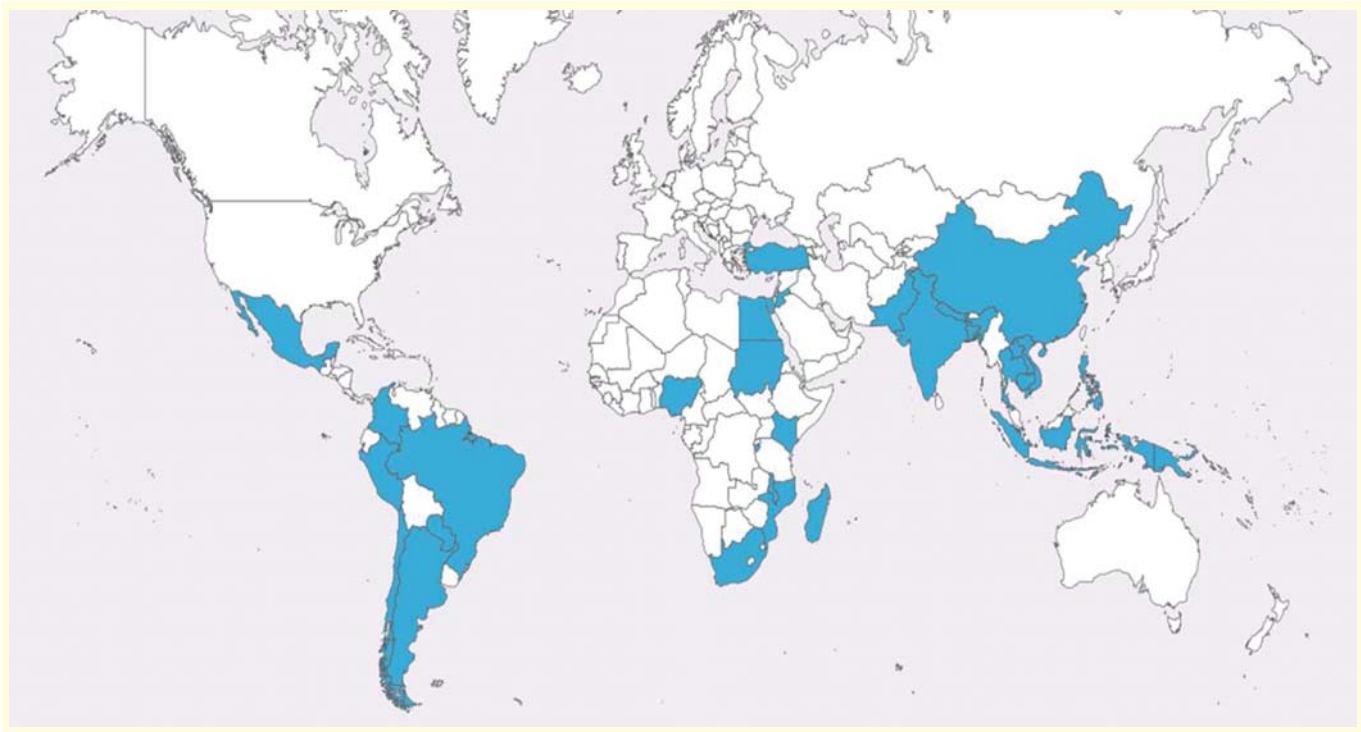


Figure 1. Countries with data on viral pneumonia included in the review.

of new respiratory viruses such as human metapneumovirus (hMPV), human coronavirus (hCoV), human bocavirus (hBoV) and human rhinovirus (HRV) species C. Furthermore, the introduction of highly effective conjugate vaccines globally has led to a decrease in bacterial pneumonia, and consequently, a rise in the prominence of viruses. Although the epidemiology, etiology and clinical characterization of such infections in children are currently being studied extensively in the developed world, very little microbiologically confirmed data are available from low- and even middle-income countries [13]. In this paper, we review the epidemiology, etiology, clinical and radiological features of viral pneumonia in developing countries. Data have been retrieved from countries highlighted in **FIGURE 1**.

Methods

Definitions

A major challenge of reviewing published literature on acute respiratory infections (ARI) in children is the lack of a gold standard, universally accepted case definition for pneumonia [14]. The lack of a gold standard definition has hampered a homogenous approach to pneumonia research for decades. Therefore, we decided to use a non-restrictive approach during this systematic literature search to incorporate the wide variety of utilized case definitions for pneumonia (**TABLE 1**).

We defined ‘developing country’ using the World Bank and International Monetary Found (IMF) classifications and included studies performed in countries in the newly industrialized category as of 2011, including Brazil, People’s Republic of

China, India, Mexico, Philippines, South Africa, Thailand and Turkey (IMF 2011).

Search strategy

We undertook a systematic literature review using various search terms in Medline and Embase (**APPENDIX 1**) as well as hand-searched online journals so as to include the different age ranges, inclusion criteria (ARI, ALRI, severe ALRI, very severe ALRI, influenza-like illness, radiologically confirmed pneumonia and WHO-defined pneumonia), the different detection techniques utilized for viral detection (PCR, immunofluorescent antibody test, enzyme-linked immunosorbent assay, shell-vial and viral culture); the different number of virus studied (from single virus detection studies to multiple-viral detection studies) and finally the different samples studied (nasopharyngeal aspirates [NPA], nasal and pharyngeal swabs, bronchial aspirates and lung punctures).

Epidemiology

To address public health issues, a thorough knowledge of the epidemiology of viral pneumonia is mandatory. While the epidemiology of ARI in the developed world has been adequately characterized, this is not the case for most developing countries where there is a scarcity of reliable surveillance data. In resource-constrained settings, incidence calculations are either roughly estimated or based on a limited number of geographically limited areas under demographic surveillance systems (DSS) set up in the context of research efforts. Furthermore in such settings, data from adults and elderly patients are

Table 1. Definitions of 'pneumonia' used in different studies.

Study (year)	Age group, years	Nomenclature	Case definition	Ref.
Turner <i>et al.</i> (2013)	<2	Pneumonia	WHO criteria [†]	[26]
Lamarao <i>et al.</i> (2012)	<3	CAP	Two clinical findings: cough, history of fever, pleuritic pain, crackles or bronchial breath sounds AND one radiological finding: focal airspace consolidation or patchy increased interstitial markings	[96]
Mathisen <i>et al.</i> (2010)	<3	Pneumonia	WHO criteria	[108]
Mathisen <i>et al.</i> (2009)	<3	Pneumonia	WHO criteria	[85]
Guerrier <i>et al.</i> (2013)	<5	LRTI	Cough or respiratory distress associated with tachypnea, with or without fever	[44]
Brooks <i>et al.</i> (2010)	<5	Pneumonia	Age-specific tachypnea AND crackles	[20]
Munywoki <i>et al.</i> (2013)	<5	Pneumonia	History of cough or difficulty breathing AND one of the following: age-specific tachypnea, lower chest indrawing, oxygen saturation $\leq 90\%$, or inability to feed, prostration or unconsciousness	[105]
Nokes <i>et al.</i> (2009)	<5	Pneumonia	History of cough or difficulty in breathing for less than 30 days	[109]
Katz <i>et al.</i> (2012)	All ages	LRTI	Patients <5 years: cough or difficulty breathing AND at least one of the following: oxygen saturation $\leq 90\%$, or maternal report of convulsions, or inability to drink/breast-feed, or lethargy, lower-chest indrawing or estridor Patients >5 years: cough, difficulty breathing or chest pain AND documented fever or oxygen saturation $\leq 90\%$	[30]
Fry <i>et al.</i> (2011)	All ages	ALRI	Fever or abnormal white blood cell count AND cough or abnormal breath sounds	[22]
Bagget <i>et al.</i> (2012)	All ages	ALRI	At least one of the following: reported fever, reported chills, measured temperature >38.2 or $<35^{\circ}\text{C}$, or abnormal white blood cell count or differential AND at least one of the following: abnormal breath sounds, documented tachypnea, cough, sputum production or dyspnea	[19]
Vong <i>et al.</i> (2013)	>5	ALRI	Symptoms onset ≤ 14 days AND fever $\geq 38^{\circ}\text{C}$ or history of fever during the last 3 days AND cough AND one of the following: dyspnea, chest pain or crackles on auscultation	[79]
Feikin <i>et al.</i> (2012)	>5	ALRI	Cough or difficulty breathing or chest pain AND fever $\geq 38^{\circ}\text{C}$ or oxygen saturation $\leq 90\%$ or hospitalization	[28]

Only studies including at least 1000 subjects published during the last 5 years have been considered.

[†]WHO case definition: age-specific tachypnea AND cough and/or difficulty in breathing.

ALRI: Acute lower respiratory infection; CAP: Community-acquired pneumonia; LRTI: Lower respiratory tract infection.

extremely scarce, if not, nonexistent. In developed countries, the incidence of ARI is highest among children younger than 5 years of age, decreasing greatly after 15 years of age and increasing again among adults older than 75 years of age [13]. The few available data from the developing world suggests similar age-distribution tendencies, although a rise in pneumonia incidence has been observed among young adults in settings with high HIV prevalence [15].

Incidence of ALRI & specific virus-related ALRI

A total of 21 studies from South America [16–18], Asia [19–27] and Africa [25,28–35] presented incidence data on ALRI and virus-specific associated ALRI, 4 of which presented incidences

in adults [19,22,24,30]. Incidence rates are summarized in TABLES 2–5. In the pediatric populations from African settings, the incidence of ALRI ranged from 90 to 1029 cases per 1000 children-year-at-risk (CYAR) for all ALRI, and from 13.2 to 560 cases per 1000 CYAR for severe ALRI. In Asian settings, the incidence of ALRI and severe ALRI ranged from 21.7 to 730 and from 16 to 210 cases per 1000 CYAR, respectively. In South America, only incidences of all ALRI cases (and not for severe cases) were available, ranging from 64 to 1710 cases per 1000 CYAR. Discrepancies between the different settings may in part be explained by differences in age groups, year of study and definitions hampering accurate epidemiological comparisons among regions. Children under 1 year of age have the

Table 2. Descriptors of studies reporting incidence of acute lower respiratory infection in children younger than 5 years of age from developing countries.

Study (year)	Country (study site) Date of the study	Denominator (age group)	Diagnostic tests	Control group	Ref.
Weber <i>et al.</i> (2002)	Gambia (Western region) 1994	20,338 (<1 y)	IFA, serology	None	[34]
Robertson <i>et al.</i> (2004)	Mozambique (Manhiça) 1999	1342 (<1 y)	ELISA	None	[25]
	Mozambique (Manhiça) 1999	6020 (<5 y)	ELISA	None	
	Nigeria (Ibadam) 1999	1579 (<5 y)	ELISA	None	
	South Africa (Agincourt) 1999	8258 (<5 y)	ELISA	None	
Nokes <i>et al.</i> (2008)	Kenya (Kilifi) 2002	655 (birth cohort [†] , 4 y)	IFA	None	[31]
Nokes <i>et al.</i> (2004)	Kenya (Kilifi) 2002	338 (birth cohort, 1 y)	IFA	None	[32]
O'Callaghan <i>et al.</i> (2011)	Mozambique (Manhiça) [‡] 2006	807 (<5 y)	PCR	None	[33]
Onyango <i>et al.</i> (2012)	Kenya (Kilifi) 2007	2002 (<13 y)	PCR	None	[35]
Feikin <i>et al.</i> (2013)	Kenya (Western region) 2007	2973 (<5 y)	PCR	Asymptomatic outpatients who presented for immunizations or medicine refills	[29]
Berman <i>et al.</i> (1983)	Colombia (Cali) 1977	8748 (<5 y)	Culture, serology	None	[16]
Borrero <i>et al.</i> (1990)	Colombia (Cali) 1986	340 (birth cohort, 17 months)	IFA, culture	None	[17]
Sutmoller <i>et al.</i> (1995)	Brazil (Rio de Janeiro) 1987	262 (<5 y)	IFA, culture	None	[18]
Robertson <i>et al.</i> (2004)	Indonesia (Bandung) 1999	1420 (<5 y)	ELISA	None	[25]
Djelantik <i>et al.</i> (2003)	Indonesia (Lombok Island) 2000	30,000 (<2 y)	ELISA	None	[21]
Brooks <i>et al.</i> (2010)	Bangladesh (Kamalapur) 2004	2370 (<5 y)	Culture	None	[20]
Turner <i>et al.</i> (2013)	Thailand (Myanmar Border) 2007	1067 (<2 y)	PCR	None	[26]
Yoshida <i>et al.</i> (2013)	Vietnam 2007	1992 (<2 y)	PCR	Community controls randomly selected	[27]
Hasan <i>et al.</i> (2013)	Thailand (SaKaeo) 2005–2010	28,523 (<5 y)	PCR	Outpatients without ALRI	[23]

[†]Birth cohort: study participants recruited in the maternity ward and monitored over the specified period.

[‡]Results in HIV-infected children are presented in the first line, whereas results in HIV-uninfected children are in the second line.

IFA: Immunofluorescent antibody analysis; y: Years.

Table 3. Incidence of ALRI and specific virus-associated ALRIs in children younger than 5 years of age from developing countries.

Study (year)	ALRI incidence	RSV-associated ALRI incidence	Influenza-associated ALRI incidence	RSV-associated ALRI incidence	ADV-associated ALRI incidence	hMPV-associated ALRI incidence	PIV-associated ALRI incidence	Case fatality rate	Ref.
Weber <i>et al.</i> (2002)	96	8							[34]
Robertson <i>et al.</i> (2004)	509	30							[25]
	126 [†] (<1 y) 68 [†] (<5 y)	15 [†] (<1 y) 5 [†] (<1 y)							
	323 (<1 y) 270 (<5 y)	116 (<1 y) 94 (<5 y)							
	332 [†] (<1 y) 80 [†] (<5 y)	15 [†] (<1 y) 9 [†] (<5 y)							
Nokes <i>et al.</i> (2008)	90/43 [†] (<2.5 y)	12/8 [†] (<2.5 y)						RSV 0%	[31]
Nokes <i>et al.</i> (2004)	1029/463 [†] (<1 y)	154/100 [†] (<1 y)						RSV 0%	[32]
O'Callaghan <i>et al.</i> (2011) ^{††}	45.6–125 [¶] 7.8–8.3 [¶]	3.3–9.1 1.4–1.5	4.1–11.4 0.5–0.6	24.9–68.2 3.5–3.7	11.6–31.8 2.1–2.3	6.6–18.2 0.8–0.9	3.3–9.1 0.7–0.8	Viral ALRI 3%	[33]
Onyango <i>et al.</i> (2012)	39 [§] (<1 y) 13.2 [§] (<5 y) 5.9 [§] (<13 y)		1.5 [§] (<1 y) 0.6 [§] (<5 y) 0.3 [§] (<13 y)					Influenza 4%	[35]
Felkin <i>et al.</i> (2013)	560 [†]	71 [†]	58 [†]						[29]
Berman <i>et al.</i> (1983)	70	6						RSV 0.94%	[16]
Borrero <i>et al.</i> (1990)	1710 (<1.5 y)	198 (<1.5 y)							[17]
Sutmoller <i>et al.</i> (1995)	64	14							[18]
Robertson <i>et al.</i> (2004)	178/25 [†] (<1 y) 191/22 [†] (<5 y)	41/16 [†] (<1 y) 34/10 [†] (<5 y)							[25]
Djelantik <i>et al.</i> (2003)	60	16						RSV 1.9%	[21]
Brooks <i>et al.</i> (2010)	511		102					Influenza 0%	[20]
Turner <i>et al.</i> (2013)	730/210 [†]	284						RSV 0%	[26]
Yoshida <i>et al.</i> (2013) [#]	21.7	4.3	2.6						[27]
Hasan <i>et al.</i> (2013)	57.7	11	4.6	10.8				Viral ALRI 0.1%	[23]

All incidences are expressed in cases per 1000 person-years at risk unless indicated otherwise.

[†]Severe ALRIs.

[‡]All ALRIs/severe ALRIs.

[§]Severe and very severe ALRIs.

[¶]Viral pneumonia.

[#]Incidence expressed in cases per 1000 persons.

^{††}Results in HIV-infected children are presented in the first line, whereas results in HIV-uninfected children are in the second line.

ALRI: Acute lower respiratory infection; y: Years.

Table 4. Descriptors of studies reporting incidence of acute lower respiratory infection from developing countries (studies including adults).

Study (year)	Country (study site) date	Denominator (age group)	Diagnostic tests	Control group	Ref.
Katz <i>et al.</i> (2012)	Kenya (Kibera, Lwak) 2007	10,873 (children and adults)	PCR	None	[30]
Feikin <i>et al.</i> (2012)	Kenya (Western region) 2007	3406 (>5 y)	PCR	Asymptomatic outpatients who presented for immunizations or medicine refills	[28]
Fry <i>et al.</i> (2011)	Thailand (SaKaeo) 2003	1919 (children and adults)	PCR	Outpatients without fever, cough, sore throat or diarrhea within the previous 3 days	[22]
Olsen <i>et al.</i> (2010)	Thailand (2 rural provinces) 2003	1730 (children and adults)	PCR, culture	None	[24]
Bagget <i>et al.</i> (2012)	Thailand (SaKaeo, Nakhon) 2009	7207 (children and adult)	PCR	None	[19]

highest incidence of ALRI and severe ALRI. This declines with age and is lowest between 15 and 65 years, increasing again in the elderly although never attaining the figures observed in the under one populations. This trend was observed in influenza and HRV-related ALRI [19,22], but not in RSV-related ALRI [24]. Few studies presented incidence rates for viruses other than RSV and influenza [22,23,33].

Seasonality

Before 2000, few studies recruited for more than 12 consecutive months and hence seasonality could not always be inferred [36]. Since then, there have been several reports on site-specific virus

seasonality, especially for RSV, influenza virus and hMPV (TABLE 6). RSV and hMPV in particular seem to be more frequently detected during the rainy season in America, Africa and Asia, with the exception of Nigeria and South Africa where RSV showed higher incidence during the dry season [25] and Kenya where several peaks of epidemics occurred without following any clear seasonal pattern. HRV and adenovirus (ADV) were detected throughout the year. Influenza viruses showed different seasonal patterns (throughout the year in Vietnam in 2004–2008, or restricted to the cool season in 2007–2008; cool season in Chile, and during the rainy season in India, Mozambique and Kenya). Limited data are available for

Table 5. Incidence of ALRI and specific virus-associated ALRIs in studies from developing countries.

Study (year)	ALRI incidence	RSV-associated ALRI incidence	Influenza-associated ALRI incidence	HRV-associated ALRI incidence	Case fatality rate	Ref.
Katz <i>et al.</i> (2012)			36.7 (<1 y) 25.3 (5–17 y) 8.1 (18–34 y) 3 (≥50 y)		Influenza 0.3%	[30]
Feikin <i>et al.</i> (2012)	120	4.4	26		RSV 3% Influenza 0% HRV 2%	[28]
Fry <i>et al.</i> (2011)	36.2 (<1 y) 16 (1–4 y) 3.1 (20–65 y) 18 (≥65 y)			10.4 (<1 y) 4.6 (1–4 y) 0.3 (20–65 y) 1.6 (≥65 y)	HRV 1.6%	[22]
Olsen <i>et al.</i> (2010)		4.2 (<5 y) 0.03 (5–49 y) 0.12 (≥50 y)	1.5 (<5 y) 0.06 (5–49 y) 0.4 (≥50 y)	2.4 (<5 y) 0.07 (5–49 y) 0.37 (≥50 y)		[24]
Bagget <i>et al.</i> (2012)			4.8 (<5 y) <1 (15–60 y) 4.1 (≥75 y)		Influenza 0.4%	[19]

Studies including adults; all incidences are expressed in cases per 1000 person-years at risk.
ALRI: Acute lower respiratory infection; y: Years.

parainfluenza virus (PIV), hCoV and hBoV. Interestingly, seasonality of RSV, hMPV and PIV in Chile differed from that of the other countries, most likely due to its temperate instead of tropical climate with two distinctive seasons.

Diagnosis, detection rates & attributable causes of viral pneumonia

Microbiologic confirmation of viral pneumonia relies on the detection of a specific virus, usually in upper respiratory samples using either culture, antigen detection by immunofluorescence microscopy or, more recently, PCR methods. In developing countries, lower respiratory samples such as induced sputum or lung aspiration are seldom collected because health facilities are rarely equipped for such invasive, often iatrogenic procedures. In a study of 95 cases of pediatric radiologically confirmed pneumonia in Malawi, PCR on lung aspirates identified *S. pneumoniae* in 41% of samples, Hib in 6%, ADV in 16% and hBoV in 4% [37]. Pneumothorax occurred in two children, consistent with previously reported complication rates related to lung punctures [38]. Establishing the etiology of pneumonia is challenging because viral–viral and viral–bacterial coinfections are frequently identified in upper respiratory samples and the pathogenic role of each microorganism is difficult to determine. Viruses identified in NPA samples of patients with pneumonia could either be pathogenic, bystanders or the cause of initial damage in the respiratory epithelium leading to a subsequent bacterial infection. The recent adoption of highly sensitive methods such as PCR could overestimate the etiologic role of respiratory viruses if causality is inferred in all positive results. Prolonged shedding of viruses is poorly understood and could overestimate the relevance of viral identification in pneumonia cases. In a study in Wisconsin, 285 children were followed-up during their first year of life and serial NPAs were obtained during moderate to severe respiratory illnesses and during pre-scheduled visits. The authors reported that while ADV was frequently detected more than 2 weeks after the initial onset, HRV rarely caused persistent infection [39]. In a study of healthy adults who underwent experimental inoculation of HRV-16, viral shedding was still detectable in 54% subjects 2 weeks after inoculation [40]. Detection of respiratory viruses in a control group with asymptomatic nasopharyngeal infection could be useful in clarifying the burden of virus-specific attributable disease at a population level, but only 12 studies have used this approach [5,22,27–29,41–47].

Pediatric studies

In the majority of pediatric studies, the detection of at least one virus among ALRI cases was a common finding. In studies where culture or antigen detection were the only diagnostic methods used, 19–35% of the samples were positive for at least one virus [4,7]. However, when PCR methods were utilized, detection rates increased to 35–85% in all ALRI cases and to

Table 6. Seasonality of specific viruses.

Virus	General pattern	Reported exceptions (country)
Respiratory syncytial virus	Rainy season	Dry season (Nigeria, South Africa) Peaks without clear pattern (Kenya)
Influenza virus	Rainy season	Cool season (Chile, Vietnam) Throughout all year (Vietnam)
Human rhinovirus	Throughout all year	
Adenovirus	Throughout all year	
Human metapneumovirus	Rainy season	Cool season (Chile)

47–60% in severe ALRI [45,48–50]. Overall among the 21 studies reviewed, RSV was the most frequently detected virus, especially in children under the age of 2, with detection rates of 15–64 and 15–34% in all ALRI and severe ALRI, respectively (TABLE 7) [51,52]. Interestingly, 30% of lung samples from 98 fatal pneumonia episodes in children under the age of 2 from Mexico were positive for RSV [53]. HRV was the second more frequently reported virus, although in some studies it ranked first, especially in children over the age of 2 [52]. In all ALRI and in severe ALRI, HRV was detected in 21–40 and 20–41%, respectively. In studies that further typed HRV, HRV-A was the most frequently identified species in both severe and non-severe ALRI while HRV-B was rarely detected [47,54–59]. HRV species distribution was consistent among African, Asian and American settings, although recent reports from non-developing settings, namely Australia, have highlighted the pathogenic role of the newly described HRV-C and its potential impact as a cause of pediatric severe respiratory disease and hospital admissions [60]. ADV, influenza and PIV were recorded in 4–37, 3–16 and 5–23% of ALRI cases, respectively. However, ADV was consistently more frequently identified than RSV in samples from Mozambique in three large studies [33,48,61], two of which were in severe ALRI cases in children under the age of 5. This trend was not confirmed by other studies with the exception of a Malawian study where 16% of the lung puncture samples in radiologically confirmed pneumonia were

Table 7. Detection rates for specific viruses in pediatric population.

Virus	ALRI (%)	Severe ALRI (%)
Respiratory syncytial virus	15–64	15–34
Human rhinovirus	21–40	20–41
Adenovirus	4–37	
Influenza virus	3–16	
Parainfluenza virus	5–23	
Human metapneumovirus	3–27	
Human coronavirus	0–9	
Human bocavirus	0.7–5	

ALRI: Acute lower respiratory infection.

positive to ADV. In those populations, there is a high burden of HIV and the importance of this condition needs to be further investigated. Of the newly described respiratory viruses, hMPV was recorded in 3–27.2% of ALRI cases, hCoV in 0–9% and hBoV in 0.7–5%. Finally, only two studies reported polyomavirus infection in 3.6 and 25% of ALRI in children under 13 years of age in Philippines, and in children younger than 12 years of age in Thailand, respectively [57,59]. When considering only the most comprehensive studies (detection by PCR of at least 10 viruses in study populations larger than 500 patients over a minimum 12-month period), the general prevalence of viral infections ranged from 47 to 69%, with HRV, RSV, influenza, ADV and hMPV being the most commonly detected pathogens [29,33,42,44,45,48,59,62].

Viral etiology can only be inferred if proper case–control studies including healthy and/or asymptomatic children are conducted to compare the prevalence of viral pathogens between both groups and to calculate the attributable fraction. Such a study design, currently being utilized by the Pneumonia Etiology Research for Child Health (PERCH) study [63], could help clarify the role of some respiratory viruses such as HRV in viral pneumonia. Eleven studies conducted in countries including the Gambia, Kenya, Nepal, Thailand and Vietnam included control groups to compare virus prevalence in patients with either pneumonia, severe pneumonia or radiologically confirmed pneumonia. The only virus indisputably associated with pneumonia was RSV, which was significantly more prevalent in all three pneumonia case definitions and for different age groups. Influenza was related to hospitalized pneumonia in children under the age of 3 [27], but not in children younger than 12 years of age with severe pneumonia. Two studies conducted in Kenya with 810 and 2973 patients with severe pneumonia under the age of 5, respectively, demonstrated variable results with a significant association between influenza and severe pneumonia in the larger study [29,45]. HRV, hMPV and PIV were mostly unrelated to pneumonia in different case–control studies, although a significant association was found between HRV and pneumonia in the 1–4 age group (odds ratio [OR]: 2.3; 95% CI: 1.0–5.2) with the exception of one study of infants from Thailand [22]. In this study, HRV genotypes were typed and significance was only attained for species A and C, but not B. Interestingly, hMPV was only related to pneumonia in children older than 5 years of age, but not in those younger than 5 or in those younger than 12 [28]. Only PIV-3 was associated with an increased risk of pneumonia (OR: 13; 95% CI: 6.0–28.0) in children under the age of 3 [46]. ADV, hCoV and hBoV were not related to pneumonia in any of the case–control studies that included their detection [27–29,41,43,45].

Viral pneumonia in human immunodeficiency virus-infected children

Pneumonia is a major cause of death and hospital admissions in HIV-infected children [64]. In sub-Saharan Africa, where the pediatric HIV epidemic is essentially circumscribed, studies

describe singularities in HIV-associated pneumonia. Cytomegalovirus (CMV), a viral pathogen responsible for mononucleosis-like or influenza-like illnesses in immunocompetent children, is a leading cause of pneumonia in HIV-infected children. In a study of children with severe ALRI from South Africa, CMV was identified in 36% of HIV-infected children (and in 15% of uninfected children, most of whom were severely malnourished). Furthermore, CMV was more common than *Pneumocystis jirovecii* pneumonia (27%) and other viral-associated pneumonia (19%) [65]. In another study, hMPV was identified as the only infection in 3.7% of HIV-infected and 9.1% of HIV-uninfected children [66]. Other respiratory viruses are also commonly identified among HIV-infected patients with severe ALRI, although less frequently than among HIV-uninfected children. One likely explanation for this is the role of other pathogens in severe pneumonia in such immunocompromised patients. In a large study of children younger than 2 years of age admitted for severe pneumonia, viruses and bacteria were identified in 15.7 and 12.5% of HIV-infected patients compared with 34.8 and 5.8% of HIV-uninfected cases, respectively [67]. *P. jirovecii* was only detected among HIV-infected children. In this study, CMV and hMPV were not tested for, possibly resulting in an underestimation of the relevance of viral pathogens causing ALRI in HIV-infected patients. In such children, polymicrobial infections were more common than in HIV-uninfected patients and also appeared to be associated with a worse prognosis [68]. Clinical features were similar in hMPV-associated ALRI [66], but not in PIV and influenza-associated ALRI where wheezing was less frequent and alveolar consolidation was more frequent in HIV-infected than in HIV-uninfected children [69,70]. Fatal outcome was recorded in 0–35% of HIV-infected and in 0–11% of HIV-uninfected children with viral pneumonia, with CMV causing worse prognosis than any other virus (TABLE 8) [65,67,69,70]. Lymphoid interstitial pneumonitis (LIP) is a lymphoproliferative response to HIV and/or Epstein–Barr virus common in HIV-infected children older than 2 years of age without proper antiretroviral treatment [71–73]. Although LIP is a chronic lung disease, it may present intermittent episodes of ALRI with fever and tachypnea mostly due to bacterial superinfections [74]. Digital clubbing, generalized lymphadenopathy and hepatomegaly are common in children with LIP, and the characteristic radiological findings include persistent, diffuse bilateral reticulonodular pattern [74,75].

Studies in adult population

We identified 13 studies that included adults, 4 of which reported detection rates for both adults and children (TABLE 9). Viral detection rates were 20–39% [76–79] in adult ALRI with the exception of a study in Laos of 34 patients hospitalized with ALRI where 67% of samples were positive to at least one virus [80]. This value must be considered with caution because of the small size of the study. HRV was the most frequently reported virus (6–11.5%) and was detected in all studies where it was tested for. Influenza was detected in 3.1–13% of ALRI

Table 8. Viral acute lower respiratory infection in HIV-infected children.

Study (year)	Country Study date	Study group age pathology n (HIV+/HIV-)	Prevalence of pathogen			Case fatality rate			Ref.
			HIV positive	HIV negative	OR (95% CI) or p-value	HIV positive	HIV negative	OR (95% CI) or p-value	
Zampoli <i>et al.</i> (2011)	South Africa Dec 2006–Jun 2008	<2 y Severe ALRI 200 (124/76)	CMV 36%	15%	OR: 3 (1.3–7.4)	Severe ALRI 35%	11%	OR: 4.5 (1.9–11.8)	[65]
Madhi <i>et al.</i> (2003)	South Africa Mar 2000–Sep 2000	<1 y ALRI 812 (326/486)	hMPV 3.7%	9.1%	p = 0.24	hMPV- ALRI 0%	0%	NA	[66]
Madhi <i>et al.</i> (2002)	South Africa Mar 1997–Mar 1999	<5 y Influenza severe ALRI 116 (25/91)				Influenza severe ALRI 8%	2.2%	p = 0.2	[69]
Madhi <i>et al.</i> (2002)	South Africa Mar 1997–Mar 1999	<5 y PIV severe ALRI 80 (24/56)				PIV severe ALRI 21%	0%	p = 0.001	[70]
Madhi <i>et al.</i> (2000)	South Africa Mar 1997–Mar 1998	<5 y Severe ALRI 946 (440/506)	Virus 15.7%	34.8%	p = 0.00001	Severe viral ALRI 7.5%	0%	p = 0.001	[67]
			Bacteria 12.5%	5.8%	p = 0.0001				

OR: Odds ratio; Y: Years.

adult cases and was usually the second most commonly identified virus after HRV, with the exception of a study conducted in Vietnam during the H1N1 pandemic where influenza was the most frequently detected virus [81]. RSV was documented in 0–13% of cases, hMPV in 0–11.5%, ADV in 0.7–3% and hBoV in 0.7% of adult ALRI cases [43]. Two studies reported data stratified according to age groups for influenza-related ALRI and HRV-related ALRI, showing a decrease of viral detection with age [22,30].

Viral co-infections

Since the advent of multiplex-PCR allowing the simultaneous detection of up to 18 respiratory viruses, multiple viruses in the same specimen have been increasingly identified in pneumonia etiological studies. Multiple viral infections were reported in 5.8–8% of adults and 11–56% of children [80,82–86]. Both the lowest and the highest co-infection rates in children were reported from studies using an 18-virus multiplex PCR in similar age groups (<5 years vs <3 years of age), so disparity may be due to epidemiological differences in the various settings. The most frequently detected combination usually included the most prevalent viruses identified in the study (RSV-hMPV, RSV-HRV, RSV-influenza and HRV-ADV). hBoV is frequently detected in association with other respiratory viruses (70–89%), followed by polyomavirus (73%), ADV, hCoV and PIV (60% each) and HRV, hMPV and RSV (50% each) [29,50,87]. The clinical relevance of those associations remains unclear and some studies did not find differences in severity due to viral co-detection compared with single virus identification [50,79,88]. However, two studies in Mozambique reported multiple viral infections in 11–20% of cases of severe pneumonia and found significant associations with nasal flaring (OR: 2.7; 95% CI: 1.1–6.5), lower chest indrawing (OR: 3.8; 95% CI: 1.4–9.9) and fatal outcome (OR: 2.2; 95% CI: 1.0–4.7) [33,61]. Other studies have reported increased risk of developing ALRI in children with RSV-HRV, RSV-hMPV and RSV-PIV-3 co-infections but not with RSV-influenza co-infection [27], and longer hospitalization length and oxygen requirements in RSV-HRV co-infected toddlers [49]. In a large study of children and adults with radiologically confirmed pneumonia in Thailand, single hBoV infection was not associated with ALRI hospitalization. However, hBoV co-detection with RSV, HRV and PIV was associated with wheezing and signs of respiratory distress more frequently than RSV, HRV and PIV single infections [43].

Clinical & radiological features

The WHO-proposed case definition for pneumonia, part of the integrated management of childhood illnesses (IMCI) strategy that has saved the lives of

Table 9. Detection rates for specific viruses in adult population.

Virus	ALRI (%)
Human rhinovirus	6–11.5
Influenza virus	3.1–13
Respiratory syncytial virus	0–13
Human metapneumovirus	0–11.5
Adenovirus	0.7–3
Human bocavirus	0.7

ALRI: Acute lower respiratory infection.

millions of children in the developing world [89], is a highly sensitive albeit poorly specific case definition aimed to maximize the detection of potentially life-threatening ALRI episodes and prompt the rapid initiation of life-saving antibiotic therapy. Respiratory and non-respiratory illnesses might both fulfill this all-embracing definition, but not all patients with this clinical presentation may benefit from antibiotic therapy, particularly if the cause of their ALRI is exclusively a viral infection. Furthermore, in malaria-endemic countries, severe malaria might also present with respiratory distress or tachypnea [48]. For these reasons, given the scarcity of antibiotics (particularly wide-spectrum ones such as third-generation cephalosporins) in many developing settings, together with the emergence of antimicrobial resistance to those commonly available [90], it is important to identify features that could reliably distinguish viral from bacterial pneumonia, which could clearly have relevant management and public health implications for clinicians and policy makers in developing countries.

Radiological features

In developed countries, the diagnosis of pneumonia relies on a combination of clinical signs and symptoms, radiological results and laboratory tests [91,92]. In developing countries, hospitals outside urban areas rarely have x-ray facilities or access to laboratory tests such as procalcitonin (PCT) or C-reactive protein (CRP) and diagnostic biomarkers are usually limited to clinical research. Thus, in such contexts, diagnosis is often purely clinical, although standardized x-ray-based case definitions have been proposed by WHO for their use in epidemiological studies or clinical trials [93]. A study in Sweden with 346 pediatric cases with confirmed pneumonia who underwent extensive microbiological tests concluded that x-ray features had no relation to etiology [94]. Authors described hyperinflation and interstitial infiltrates more frequently in viral pneumonia and more alveolar infiltrates in bacterial pneumonia, but those descriptions were not specific. However, they found a relation with age and concluded that age might be a confounder in x-ray interpretation. A study carried out in China describing the x-ray features of 210 pediatric cases less than 15 years of age with viral pneumonia reported that 63% of patients had patchy areas of consolidation, 15% had interstitial infiltrates and 7%

had lobar consolidation [95]. Bilateral affectation of lower lobes was frequent. The authors found that ADV-related pneumonia was associated with interstitial infiltrates and seasonal influenza A (H1N1) with diffuse areas of air space consolidation. They found no specific features related to influenza B or PIV pneumonia. However, respiratory viruses commonly causing viral pneumonia were not tested for. Another study in Thailand of 1067 children under the age of 2 years described a significant relationship between RSV-associated pneumonia and interstitial infiltrates [26]. Interestingly, 30% of the pneumonia cases showing lobar consolidations were positive for RSV. In a similar study from Brazil, 54% of RSV-positive patients and 51% of RSV-negative patients had identical interstitial infiltrates and no relation could be established between clinical features and etiology [96]. Most of the studies carried out in a large variety of settings have reported similar results; the most frequent pattern of viral pneumonia (with RSV being the most studied virus) includes interstitial or peribronchial infiltrates, but alveolar or lobar consolidation is not a rare finding (7–30% of viral pneumonias), and mixed patterns are frequent both in viral and bacterial-confirmed pneumonia episodes [21,97–100]. Thus, it is fair to conclude that etiologic diagnosis (specific respiratory virus or virus vs bacteria) cannot and should not be made on the basis of x-ray features alone in pediatric pneumonia [101,102].

In adults, radiologic findings in viral pneumonia are variable and highly overlapping [103]. Moreover, the corroboration of a lobar consolidations and/or pleural effusion is not rare in adult viral pneumonia [79,81]. In a series of Kenyan adult patients with viral pneumonia, lobar and multilobar consolidation patterns were seen in 15 patients while patchy consolidation was seen only in one [78]. Although the study was small, it is noteworthy that lung aspirates were performed to rule out bacterial disease. However, 11 patients were HIV-infected and the radiological pattern could have been altered by this condition.

Clinical features

Most clinicians in developing countries rely on their clinical evaluation for an initial orientation of the probable etiology of their patients, despite the poor specificity of clinical symptoms for that purpose. A study carried out at Turku University Hospital (Finland) of 4277 children with laboratory-confirmed viral respiratory infections compared clinical features of eight different respiratory viruses (HRV, RSV, ADV, PIV-1, PIV-2, PIV-3, influenza virus A and influenza virus B), and found that overlapping symptomatology was frequent [13]. Overlapping clinical presentation is also common in developing countries, and more importantly, viral pneumonia signs and symptoms seem to overlap with those of bacterial pneumonia. In a study of 226 children less than 5 years of age with ALRI from Thailand, the authors were unable to identify clinical signs to differentiate viral from bacterial etiology [100]. This was also observed in a study of 214 children under 14 years of age in Sudan [104]. Other studies have compared virus-positive

pneumonia versus virus-negative pneumonia and failed to identify significant differences. Low sensitivity of bacterial diagnosis, mostly based on blood cultures, may underestimate viral-bacterial co-infections in the virus-positive group leading to conflicting results [44,105]. However, wheezing has shown significant association with viral pneumonia in some studies, and was present in 17–64% of children and 32% of adults [79,106]. RSV-related ALRI usually presents with crackles, wheezing, nasal flaring, lower chest indrawing, rhinorrhea and nasal obstruction more frequently than other viruses [96,107–109]. Unfortunately, none of those clinical features are clearly specific of RSV infection and wheezing has also been associated with HRV (particularly to HRV-C), hMPV and hBoV [43,58,60,61,110]. Reactive airway disease as a sequel of previous viral infections leading to repeated wheezing episodes and readmissions has been described in RSV infections, but also after influenza-related ALRI [20,105]. In most studies, RSV has been characterized as having more severe presentation in terms of oxygen requirements, hypoxemia and signs of respiratory distress [50,58,108], but other studies found HRV infections to be more severe in both children and adults [49,79], and finally some studies concluded severity was not associated with any virus [44,111,112]. Case fatality rates have been reported for RSV-associated ALRI (1.9–7.5% in children from different settings), severe influenza-associated ALRI (4% in <12 years in rural Kenya), influenza-associated ALRI (0.3–0.4% in children and adults series in Kenya) and hMPV-associated ALRI (5.9% in Indonesia) among the most pathogenic respiratory viruses [35,59,106–108]. In addition, avian influenza A (H5N1) may be associated with a case fatality rate as high as 33% with early antiviral treatment or 80–93% without treatment [113–116].

Serum biomarkers

In developed countries, serum biomarkers such as PCT and CRP are used for distinguishing viral from bacterial infections, especially in children. Serum PCT and CRP levels increase in bacterial infections above a cutoff of 1–5 ng/ml and 15–100 mg/l, respectively [117]. Other commonly studied biomarkers, including IL-6, IL-8, IL-18, IFN- α , TNF- γ , lipopolysaccharide-binding protein or heparin-binding protein have not shown higher sensitivity, specificity or predictive value than PCT or CRP for that purpose [118–120]. In a meta-analysis comparing PCT and CRP for differentiating bacterial from viral infections, PCT was more sensitive and specific and had a higher false discovery rate (Q value) than CRP [117]. In developing countries, affordable, rapid and simple diagnostic tools for that purpose are crucial to assure adequate management of antibiotics, especially in view of the low specificity of clinical features. PCT and CRP have proved to be useful markers for bacterial diagnosis in African settings [121–124]. However, serum levels of PCT and CRP increase in patients with malaria infection and hence may compromise their utility in malaria-endemic settings [125–127]. Further research in this area should be undertaken with the aim of developing a rapid diagnostic test, ideally a point-of-care test that is capable of identifying

the underlying etiology of infection in severely ill patients at admission.

Treatment & prevention

Antivirals are rarely used in developing countries, except for avian influenza A (H5N1) cases where oseltamivir, amantadine, rimantadine and rimbavirin have been tested with good results if initiated promptly [116]. Lack of rapid etiologic diagnosis renders this option unsuitable for clinicians from resource-constrained areas. Following WHO recommendations [128], antibiotics are initiated in patients fulfilling the WHO clinical pneumonia case definition.

Passive immunization through the use of specific monoclonal antibodies has been used in developed countries for the management of RSV infections, particularly among highly selected high-risk populations such as extreme preterms and congenital heart defect patients during epidemics. Its prohibitive price, however, makes it an unrealistic option in developing countries. Thus, prevention and control of viral respiratory diseases should primarily be focused on vaccines. Unfortunately, there are no registered vaccines against respiratory viruses suitable for use in children younger than 6 months of age, which is the population at highest risk [31,129]. For older children and adults, the only available vaccine in the market is that against seasonal influenza, although this vaccine has not been included in the expanded program of immunization for children. Immunization of pregnant women relying on the protectiveness of mother-to-child transferred antibodies, and immunization of post-partum mothers and household contacts have been studied as a strategy to reduce influenza virus burden in young children with promising results [130–132]. A polyvalent vaccine against RSV and PIV-3 (MEDI-534) is being evaluated in Phase I trials with good safety profile [133]. Vaccines against hMPV and HRV are still in pre-clinical stages and their widespread availability cannot be expected in the short-term [134,135].

Expert commentary & five-year view

In developing countries, similar to what occurs in more developed settings, respiratory viruses are an important cause of pneumonia, particularly among young children. However, their real burden is presumably heavily underestimated. The pathogenic role of specific viruses (or viral subtypes) detected in the upper respiratory tract of patients with pneumonia still requires further clarification. Thus, well-designed case-control studies providing robust data and pathogen-specific attributable disease fractions are required, in addition to new diagnostic methods or biomarkers clearly differentiating pathogens which colonize from pathogens which cause disease. Homogenization in clinical and radiological definitions, inclusion criteria and laboratory tests are also necessary to allow comparisons among studies and clearly detect priorities for public health policy makers. Only then, the real and underexposed burden of viral pneumonia in resource-constrained settings will emerge in its true magnitude and significance.

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Key issues

- Despite great reductions in child mortality over the last decade, pneumonia remains the major killer of young children globally, accounting for 18% of the under-5 mortality. In recent years, attention has shifted toward non-bacterial causes of pneumonia, and more specifically, to viral-attributable respiratory infections. Data of viral pneumonia from developing countries are scarce.
- In developed countries, the highest incidence of acute respiratory infections (ARIs) is evidenced among children younger than 5 years of age, falling dramatically after 15 years of age and increasing again among adults older than 75 years of age. The few available data from the developing world suggests similar age-distribution tendencies.
- When considering only the most comprehensive studies (detection by PCR of at least 10 viruses in study populations larger than 500 patients over a minimum 12-month period), the prevalence of viral infections in pediatric pneumonia cases ranged from 47 to 69%, with human rhinovirus, respiratory syncytial virus, influenza virus, adenovirus and human metapneumovirus being the most commonly detected pathogens. In adult pneumonia cases, human rhinovirus and influenza are the most frequently detected viruses.
- Causality cannot be inferred from a positive viral isolate in a respiratory sample, especially from upper respiratory tract samples, given lack of controls in most studies.
- Overlapping clinical and radiological presentation is common in viral pneumonia cases caused by different respiratory virus, and more importantly, viral pneumonia signs and symptoms seem to overlap with those of bacterial pneumonia.
- Serum biomarkers used in developed countries to distinguish between viral and bacterial infection such as procalcitonin and C-reactive protein increase in patients with malaria infection compromising their utility in malaria-endemic settings.
- There are no registered vaccines against respiratory viruses suitable for use in children younger than 6 months of age, which is the population at highest risk.

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Appendix 1. Search strategy in Medline (Ovid) and Embase (Ovid) (number of references retrieved).

- (pneumonia or respiratory infection* or respiratory tract infection* or bronchiolitis).mp (202,707 and 192,748).
- (adenovirus or bocavirus or citomegalovirus or coronavirus or enterovirus or influenza or metapneumovirus or parainfluenza or picornavirus or respiratory syncytial virus or rhinovirus or RSV).mp or virus pneumonia/ (154,170 and 225,549).
- (developing countries or developing world or Africa or South Asia or Southeast Asia or “South and Central America” or Latin America).mp (155,984 and 284,753).
- 1 and 2 and 3 (391 and 542).
- Limit 4 to human and (English, French, Portuguese, Spanish) and year = 1990-Current and article (323 and 281).

We included all studies regardless of sampling and detection methods. After exclusion of duplicates (140), we further excluded guidelines, studies focused on specific population (e.g., leukemia patients, ventilator-associated pneumonia, travellers, nosocomial pneumonia) and small series of cases. Data was extracted for study location, period of study, study design, sample size, clinical diagnosis, sample type, diagnostic test, aetiological agents investigated, and incidence of viral infections. Studies that did not report data on a complete year (or multiples of a year) were not included in the Epidemiology section.