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Epidemiology of Respiratory Syncytial Virus Lower Respiratory Tract Infection (RSV-LRTI) In Children in Developing Countries

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Abstract

The global estimate in 2005 indicate that at least 33.8 million episodes of respiratory syncytial virus (RSV) associated acute lower respiratory infection (ALRI) occurred worldwide in children younger than 5 years and most of these deaths occurred in developing countries. The review aimed to analyze published epidemiological data on RSV lower respiratory tract infection in young children in developing countries to ascertain the burden of the disease for evidence-based public health priorities. Articles in English published between 2002 and 2014 were identified through literature searches in PubMed, Web of knowledge, and Embase. The incidence of RSV-LRTI in Asian countries were lower than African countries except Bangladesh. Rate of hospitalized LRTI was similar in magnitude across all studies. Despite an increasing number of epidemiological studies of RSV-LRTI published over the past 13 years in developing countries, there are still clearly many areas that merit further study. There is still a need to establish further RSV surveillance studies to improve the incidence estimates and to explore the extent to which national and regional variation in RSV infection rates exist in countries where there is a high burden and high mortality attributable to LRTI but lack of understanding of local RSV epidemiology.

Keywords: Respiratory syncytial virus; RSV; Lower respiratory tract infection; Children; Developing countries

Introduction

Lower respiratory tract infection (LRTI) is the leading global cause of death in children between 1 month and 5 years of age. Nearly 70% of LRTI deaths under five years old are among children in developing countries [1-4]. Clinical characteristics of RSV infection include upper respiratory infection with rhinorrhea and nasal congestion lasting between 7 and 12 days. Re-infection rates vary between 6% and 83% each year, showing that initial infection does not confer immunity to succeeding infection [5]. By the age of 2 years, nearly all children have had RSV infection [6]. More serious disease involving the lower respiratory tract may develop in older children especially in immunocompromised and cardiopulmonary disease patients [7,8]. The review aimed to systematically aggregate and analyze published epidemiological data on RSV lower respiratory tract infection in young children in developing countries, in order to ascertain the burden of the disease for evidence-based public health priorities and to summarize the currently available data and identify the gaps and scope for further epidemiological study of RSV lower respiratory tract infection in developing countries.

Literature Reviewed

Potentially relevant published articles were identified through literature searches of the following bibliographic database: Pubmed database, Web of knowledge, and Embase. To access publications from developing countries that might not be included in those databases, searches in Scielo, Indian Medlars Centre, Bioline International, and African Journals online were also performed. The following combination of MesH terms (Medical Subject Heading term) and individual search terms were used: (Respiratory Syncytial Viruses OR pneumonia OR bronchiolitis OR respiratory tract infections) AND (developing country OR each individual country of developing countries) for the epidemiological review, and (Respiratory Syncytial Viruses AND vaccine) for the review of vaccine development updates. The searches were restricted to studies of human subjects that were published in English between 2002 and 2014. For the purpose of this review, the developing countries were defined as the ones designated as such by either World Bank (low, lower middle and upper middle-income countries) or World Health Organization. For the results of epidemiological review, data extracted from original articles describing incidence, prevalence, and demographic distribution, comorbidities, complications and outcomes, and case fatality rates of RSV infection were tabulated and presented in descriptive form.

Results and Discussion

Pneumonia is one of the leading causes of childhood mortality. Of the 6.3 million children who died before age 5 years in 2013, infectious diseases caused 51.8% (3.257 million) of them, with the largest percentage due to pneumonia 935,000 deaths (817,000-1,057,000; 14.9% of total deaths, 13.0-16.8%), followed by diarrhea 578,000 deaths (448,000-750,000; 9.2%, 7.1- 11.9) [9] (Figure 1). The global estimate in 2005 indicate that at least 33.8 million episodes of respiratory syncytial virus (RSV) associated acute lower respiratory infection (ALRI)

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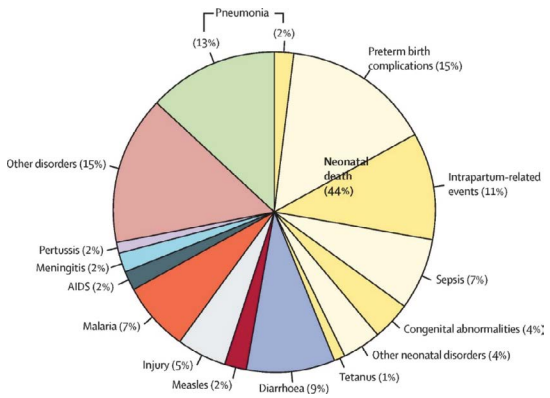

Figure 1: Global causes of child deaths [9].

occurred worldwide in children younger than five years. This estimate represents approximately 22% of all episodes of ALRI in young children, and 96% of them were in developing countries (where 90% of the world's population aged younger than 5 years reside).The global estimates also have shown that 3.4 million young children worldwide developed RSV-associated severe ALRI necessitating hospital admission, of which 91% occurred in developing countries. And 66,000-199,000 children younger than 5 years died from RSV associated ALRI, with 99% of these occur in developing countries [10]. Ninety-three studies were included in the review, 20 were community-based studies and 52 were hospital-based studies. The other studies discussed complications and outcomes of RSV-LRTI. The main outcome of 52 of the studies included was to identify the viral etiology of LRTI while the main outcome of the other studies was to identify the incidence of RSV-associated LRTI. PCR was the diagnostic method used by over 60% of the studies. Other diagnostic methods included ELISA, immunofluorescence and viral isolation. Countries included in the study and the corresponding number of studies for each are as follows:

Countries included in the study

Countries included in the study and the corresponding number of studies for each are as follows:

Africa: Madagascar (1), Kenya (13), Egypt (3), South Africa (4), Nigeria (2), Mozambique (3), Ghana (2), The Gambia (1), Tunisia (1).

Asia: Bangladesh (4), Nepal (5), Vietnam (4), China (5), India (6), Iran (1), Turkey (3), Thailand (10), Myanmar (1), Philippines (1), Indonesia (4), Malaysia (1), Jordan (1), Yemen (1), Russia (1) (borders European and Asian countries as well as the Pacific and Arctic oceans but for the purpose of this review is included here).

Latin America: Brazil (13), Argentina (1), Mexico (1), Guatemala (2).

A review of the community-based studies revealed that 39.7% to 84% of LRTI were positive for viral etiology and 11.8% to 80.8% of total viral LRTI were confirmed as RSV infection using PCR or ELISA (Table 1).

For hospital-based studies (Table 2), 11.2% to 94.3% of LRTI were positive for viral etiology and RSV accounted for 8% to 91% of total viral LRTI cases. The majority of hospital-based studies and all of community-based studies have shown that RSV was the most frequently detected virus in children with bronchiolitis, LRTI, pneumonia and severe pneumonia, suggesting that RSV was one of the major contributors of respiratory illnesses regardless of geographic location, disease studied, severity and setting of study. Only in one study from Iran and in two studies from Brazil and Mozambique, RSV is reported as being the second (Iran) and the third (Brazil and Mozambique) more frequently detected virus in locally conducted studies.

a) Study recruited children aged 1 month to 13 years, but identified viral etiology in children aged ≤ 3 years.

b) Study recruited children, adults and elderly up to 76 years old, but identified viral etiology in children aged ≤ 5 years.

c) Study recruited children aged 2 months to 13 years, but identified viral etiology in children aged ≤ 5 years.

d) Study recruited children and adults up to 50 years old, but identified viral etiology in children aged <5 years.

e) Study recruited children aged 2 months to 14 years, but identified viral etiology in children aged <5 years.

Among community-based studies, a Nepalese study reported the lowest percentage of RSV among LRTI cases (14.3%) This might be due to age of study populations, as the study excluded young infants <2 months of age, who are considered to be the population at higher incidence. Frequency of viral detection depends on a variety of factors including the characteristics of study like study site, case definition, disease severity, duration of the study, season of the year, age range for study inclusion, patients selection criteria, health care and hospitalization setting or laboratory and specimen management like sampling method (nasopharyngeal aspiration/wash and nasal wash vs. nasal swab, nasopharyngeal swab or throat swab technique), quality of specimen samples, transport and storage condition of the samples, time of collection in relation to onset of illness, methodology applied to establish the diagnosis (e.g. RT-PCR, immunofluorescence, serology, culture), quality of reagents, laboratory technician experience, inter- and intra-laboratory standardization.

Besides the aforementioned factors, the proportion of viral LRI cases among enrolled subjects and the proportion of RSV cases among viral LRTI depend also on the number of etiologic agents in diagnostic panels. More virus types included in diagnostic panel can contribute to higher proportion of viral LRTI cases, thus to lower proportion of RSV cases among the viral LRTI cases identified. Viral LRTI cases tend to be detected more in studies using PCR method and diagnostic panel including various types of viruses. On the contrary, studies using diagnostic panel with less viral types (e.g. excluding rhinovirus, one of the common respiratory pathogen and human metapneumovirus) identified RSV in > 70%of viral LRTI cases. However, this is not necessarily the case, as inconsistent findings were demonstrated in some studies with fewer etiologic agents in the diagnostic panel but modest percentage of RSV in viral LRTI cases.

Incidence of RSV-associated LRTI in young children aged ≤ 5 years

Incidence rates were available mainly from two regions, Africa and Asia with one study from Latin America. The RSV-associated LRTI incidences reported by community-based studies in children aged <1 year ranged from 86.9-154/1000 child-years (Africa) and 333-125/1000 child-years (Asia). The incidence rates of RSV-associated LRTI in children aged <5 years reported were 90-94/1000 child-years (Africa) and 34-95/1000 child years in Asia (Table 3).

a) Study recruited children aged 1 month to 13 years, but identified viral etiology in children aged ≤ 3 years.

b) Study recruited children, adults and elderly up to 76 years

Country	Age	Sample size	Disease studied	Study period	Mode of sampling	Diagnostic method	% Viral LRI of enrolled subjects	% RSV of viral LRI
Madagascar [11]	2 to 59 mos	295	ARI	Feb 10 to Feb 11	NP swab	PCR	74.60%	11.80%
Kenya [12]	< 5 yo	2,973	SARI	Mar 07 to Feb 10	NP / OP swab	PCR	84%	22%
Kenya [13]	< 5 yo	1,815 (ILI) 4,449 (SARI)	ILI, SARI	Sept 07 to Aug 10	NP / OP swab	PCR	49.80%	12.50%
Kenya [14]	>1; <13 yo	451	LRI	2009 to 2010	NP aspirate	PCR	N / A	38%
Kenya [15]	< 5 yo	4,012 (R) 2,744 (U)	ILI, SARI	Mar 07 to Feb 11	NP / OP swab	PCR	N / A	12.5% 11.7%
Bangladesh [16]	≤ 2	252	LRI	1993 to 1996	NP aspirate	ELISA	44.80%	80.80%
Bangladesh [17]	< 2	515	pneumonia	Apr 09 to Mar 11	NP wash	PCR	77.50%	29.00%
Nepal [18]	2mos to <3 yo	1,909	pneumonia	Jul 04 to Jun 07	NP aspirate	PCR	40.00%	37.70%
Nepal [19]	2 to 35 mos	2,230	pneumonia severe pneumonia	Jun 04 to Jun 07	NP aspirate	PCR	39.7% 44.3%	14.3% 27.5%
Vietnam [20]	< 24 mos	4,800	ARI	2006 to 2007	NP aspirate	PCR	64%	20.10%
China [21]	< 5 yo	511	SARI	2010 to 2011	NP aspirate	PCR	51.40%	33.10%

LRI/LRTI = lower respiratory tract infection, NP wash = nasopharyngeal wash, NP aspirate = nasopharyngeal aspirate, NP secretion = nasopharyngeal secretion, OP = oropharyngeal, BAL = bronchoalveolar lavage, PCR = polymerase chain reaction, ELISA = Enzyme-linked immunosorbent assay, IF = immunofluorescence, IFA = indirect immunofluorescent antibody test, ILI = Influenza-like Illness, DFA = direct fluorescent antibody test. RSV = respiratory syncytial virus, N / A = not available, SARI = severe acute respiratory illness, R = rural site, U = urban site

Table 1: Viral etiology of LRTI in community-based studies.

Country	Age	Sample size	Disease studied	Study period	Mode of sampling	Diagnostic method	% Viral of enrolled subject	%RSV out of viral LRI
Egypt [22]	< 5 yo	450	LRI	Nov 06 to Dec 07	NP aspirate	DFA, PCR, virus isolation	59.90%	23.80%
Egypt [23]	< 5 yo	427	LRI	Dec 06 to Nov 07	NP aspirate	IFA	21%	77%
South Africa [24]	3 mos to 2 yo	114	bronchiolitis	Jun 99 to May 00	NP aspirate	IF, viral isolation	48.30%	74.60%
South Africa [25]	< 5 yo	4,293	LRI	Jan 10 to Dec 11	NP aspirate	PCR	n/a	27%
Nigeria [26]	< 5 yo	122	pneumonia	N / A	NP aspirate	IFA	50.00%	45.90%
Mozambique [27]	< 5 yo	807	severe pneumonia	Sep 06 to Sep 07	NP aspirate	PCR	48.80%	12.70%
Ghana [28]	< 5 yo	128	severe pneumonia	Jan 08 to Dec 08	NP swab	PCR	25.80%	54.50%
Ghana [28]	< 5 yo	128	LRI	Jan 08 to Dec 08	NP aspirate / swab	PCR	25.90%	14.10%
Kenya [29]	1 mo to < 5 yo	810	severe pneumonia	Jan 10 to Dec 10	NP swab	PCR	60.40%	43.80%
Kenya [29,30]	< 5 yo	2,143	ARI	May 02 to Apr 04	NP swab	IF	N / A	8.00%
Kenya [31]	1 mo to 59 mos	805	pneumonia	Jan 10 to Dec 10	NP swab, OP swab, IS	PCR	60.80%	12.50%
Brazil [32]	6mos to < 5 yo	472	pneumonia	Jun 94 to Jun 95	NP swab	DFA	11.20%	45.00%
Brazil [33]	< 5 yo	336	LRI	Jan 03 to Dec 03	nasal wash	PCR	55.60%	43.30%
Brazil [34]	< 5 yo	184	pneumonia	Sep 03 to May 05	NP aspirate and paired serum	IF, ELISA serology	66.30%	25.30%
Brazil [35]	< 5 yo	455	LRI	Feb 05 to Sep 06	NP aspirate	IFA	30.20%	73.00%
Brazil [36]	< 2 yo	77	bronchiolitis	Mar 06 to Jul 07	NP aspirate	PCR	93.50%	68.00%
Brazil [37]	0 to 3 yo	1,050	pneumonia	Nov 06 to Oct 07	NP aspirate	IFA, PCR	n/a	23.10%
Brazil [38]	0 to 12 yo	12,160	RTI	2007 to 2010	NP aspirate	IFA	n/a	81.5% (07), 61% (08), 37.7% (09), 53.5% (10)
Argentina [39]	< 5 yo	18561	LRI	Jan 98 to Dec 02	NP aspirate	IFA	32.80%	78.80%
Mexico [40]	0 to 18 yo	2,797	RTI	Jan 04 to Dec 08	Nasal secretion, bronchial aspirate	IFA	12.70%	74.70%
India [41]	1 mo to 1 yo	245	bronchiolitis	Jan 07 to Dec 07	NP aspirate, NP swab, throat swab	viral isolation, ELISA, PCR	46.10%	63.70%
China [42]	≤3 (a)	29183	LRI	Jan 01 to Dec 06	NP aspirate	IFA	36.30%	74.80%
China [43]	<5 (c)	688	pneumonia	Oct 04 to Oct 05	NP aspirate and paired serum	DFA, ELISA serology	44.20%	43.40%

China [44]	< 6 yo	370	SARI	May 08 to Mar 10	NP aspirate or blood or IS	Virus spin kit	94.30%	51.08%
China [45]	< 14 yo	720	LRI, URTI	Jul 09 to Jun 10	NP aspirate, NP swab, BAL	PCR	55.80%	9.91%
Iran [46]	1 mo to 5 yo	202	LRI	Oct 01 to May 02	NP secretion	IFA	54.00%	23.80%
Turkey [47]	1mo to 5 yo	147	LRI	Oct 06 to Mar 07	NP swab	DFA	36.70%	55.60%
Turkey [48]	< 2 yo	671	LRI	N / A	NP swab	Respi-Strip	n/a	38%
India [49]	1mo to ≤ 5 yo	301	LRI	Apr 05 to Mar 07	NP aspirate	PCR	35.20%	57.60%
India [50]	0 to 14 yo	188	LRI	Jun 11 to May 12	NP aspirate	PCR	45.70%	21.30%
India [51]	< 2 yo	77	ALRI	Sept 08 to Mar 09	NP aspirate	DFA	22.10%	22.10%
Nepal [52]	2 mos to < 3 yo	627	severe pneumonia	Jan 06 to Jun 08	NP aspirate	PCR	30.00%	46.80%
Nepal [53]	< 5 yo	772	pneumonia	Jul 08 to Aug 11	NP aspirate	Culture, viral isolation	N / A	12.60%
Bangladesh# [54]	< 2 yo	29	bronchiolitis	Jul-10	NP swab, throat swab	PCR	91%	91%
Vietnam [55]	≤ 5 yo (c)	295	LRI	Nov 04 to Jan 08	NP aspirate, NP swab, throat swab	PCR	72.50%	33.60%
Vietnam [56]	0 to 12 yo	1,082	ARI	Apr 10 to May 11	NP swab	PCR	63.80%	23.80%
Thailand [57]	< 5 yo	467	LRI	Nov 98 to Feb 01	NP aspirate	IFA	36.00%	71.80%
Thailand [58]	< 5 yo (d)	1325	pneumonia	Sep 03 to Dec 05	NP swab	ELISA, PCR	74.80%	50.20%
Thailand [59]	1 to 12 mos	354	LRI	Dec 07 to Aug 09	NP swab	PCR	36.70%	29.40%
Thailand – Myanmar [60]	< 5 yo	708	pneumonia	Apr 09 to Sept 11	NP aspirate	PCR	53.70%	24.90%
Philippines [61]	< 13 yo	819	severe pneumonia	May 08 to May 09	NP swab	PCR	61.20%	20.10%

LRI/LRTI = lower respiratory tract infection, NP wash = nasopharyngeal wash, NP aspirate = nasopharyngeal aspirate, NP secretion = nasopharyngeal secretion, BAL = bronchoalveolar lavage, IS = induced sputum, PCR = polymerase chain reaction, ELISA = Enzyme-linked immnunosorbent assay, IF = immunofluorescence, IFA = indirect immunofluorescent antibody test, DFA = direct fluorescent antibody test. RSV = respiratory syncytial virus, N / A = not available, SARI = severe acute respiratory infection, # = outbreak investigation

Table 2: Viral etiology of LRTI in hospital-based studies.

old, but identified viral etiology in children aged ≤ 5 years.

c) Study recruited children aged 2 months to 13 years, but identified viral etiology in children aged ≤ 5 years.

In general, hospital-based studies reported lower incidence of both RSV-LRTI and RSV-severe LRTI than community-based studies. Although RSV-severe LRTI cases are expected to be hospitalized, different studies from the same district in Kenya reported hospital-based estimates 5-6 times lower than community-based estimates (Table 4).

a) Incidence of RSV-LRTI in children aged <2 years

b) Incidence of RSV LRTI/severe LRTI in children <2.5 years

c) Incidence of RSV LRTI/severe LRTI in children aged <3 years

d) Incidence of RSV severe LRTI in urban (8.7), rural (17.7) settings

e) Incidence of RSV LRTI during the first (12.6) and second studied year (5.8)

Few epidemiological studies reported RSV incidence stratified by comparable age groups. The highest incidence rates were found in young infants aged < 6 months in 2 studies and even younger aged <3 months in 1 study [68]. Interestingly, studies from Indonesia found the lowest incidence in infants younger than 6 months of age [64] and lack of RSV-LRTI in infants aged less than 3 months [63,64]. In another study from the same country (Indonesia), the presence of RSV-LRTI in infants younger than 3 months old was reported but the incidence was not found to be the highest rate [70]. Incidence studies were mainly from Africa and Southeast Asia, which are the world regions with the highest incidence of pneumonia. It should be noted, however, that those studies are largely from only some countries such as Nigeria, Kenya, Mozambique, South Africa, Gambia, Indonesia, Bangladesh, India. Other countries with highest estimated absolute number of new cases of pneumonia such as China, Pakistan, Ethiopia, Democratic Republic of Congo, Vietnam, Philippines, Sudan, Afghanistan, United Republic of Tanzania, Myanmar, and Brazil are not proportionally represented in this review. It is crucial to generate data from countries where child pneumonia incidence is highest. No incidence studies were identified from the Eastern Mediterranean, the Western Pacific, Latin Americas, and developing European Regions. This may be due to the use of English language as one of the inclusion criteria. Fourteen studies reported underlying conditions known to be risk factors for serious RSV infection among young children with RSV-LRTI. History of premature birth was found in 4.6% to 27.0% of children with RSV-LRTI. 1.0% to 17.7% of cases had congenital heart disease and chronic lung disease was found in 1.0% of the cases.

Rates of hospitalized LRTI were similar in magnitude across all studies. But in the South African study, there was a documented drop in clinic attendance rates during the study period due to a shortage of medications. Thus, the findings represent minimum estimates of the burden of severe LRI. The Indonesian study stated that most acute respiratory illness deaths in the study villages occurred at home, thus the hospitalization incidences reported here should be considered a fraction of the true incidence of RSV cases that resulted in hospitalizations.

Co-morbidities of RSV-LRTI cases

Malaria: Four studies from Africa reported malaria parasitemia in

Country	Study Period	Study denominator	Diagnostic method	RSV-LRTI (per 1,000 child-years of observation)		RSV severe LRTI (per 1,000 child-years of observation)	
				<1 yo	<5 yo	<1 yo	<5 yo
Nigeria [62]	Jun 99 - May 01	Defined population based	ELISA	116	94	n/a	n/a
Kenya [63]	Jan 02 - Jan 03	Defined population based	DFA	154	n/a	104	n/a
Kenya [64]	2002 - 2005	Defined population based	DFA	104	90 (b)	66	43 (b)
Kenya [15]	Mar 07 - Feb 11	Defined population based	DFA	86.9 (R) 62.8 (U)	n/a	n/a	n/a
Indonesia [65]	Feb 99 - Jan 01	Defined population based	ELISA	41	34	16	1000%
Indonesia [66]	Feb 99 - May 01	Defined population based	ELISA and PCR	n/a	95	n/a	n/a
Bangladesh [17]	Apr 09 - Mar 11	Defined population based	PCR	125 (a)	n/a	n/a	n/a
India [67]	Oct 01 - Mar 05	Defined population based	DFA, viral isolation	33	39 (c)	14	9(c)
Guatemala [68]	Nov 07 - Dec 12, Feb 09 - Dec 12, Nov 09 - Apr 11	Defined population based	PCR	58	n/a	n/a	n/a

RSV = respiratory syncytial virus, LRTI = lower respiratory tract infection, IP = inpatient, OP = outpatient, PCR = polymerase chain reaction, ELISA = Enzyme-linked immnunosorbent assay, IF = immunofluoresecence, DFA = direct fluorescent antibody test, cyo = child-years of observation, n/a = not available, R = rural site, U = urban site

Table 3: Incidence of RSV-associated LRTI and severe LRTI in community-based studies.

Country	Study period	Study denominator	Diagnostic method	RSV-LRTI (per 1,000 child-years of observation)		RSV severe LRTI (per 1,000 child-years of observation)	
				<1yr	<5yr	<1yr	<5yr
Gambia [69]	Oct 93 to Dec 97	Defined population base	IF	N/A	N/A	8.7-17.7 (d)	n/a
Kenya [70]	Jan 02 to Dec 07	Defined population base	DFA	N/A	N/A	11.1	290.00%
Kenya [71]	Jan 07 to Dec 07	Defined population base	PCR	N/A	N/A	20.4	540.00%
Mozambique [72]	Feb 99 to Jan 00	Defined population base	ELISA	30	N/A	15	500.00%
South Africa [72]	Apr 00 to Mar 01	Defined population base	ELISA	N/A	N/A	15	900.00%
Indonesia [59]	Jan 00 to Dec 01	Defined population base	ELISA	N/A	N/A	25	n/a
Thailand [73]	Nov 98 to Feb 01	Defined population base	IF	N/A	5.8-12.6 (e)	N/A	N/A
Thailand [74]	Sep 03 to Dec 07	Census derived estimate	PCR, ELISA serology	10.9	8.8	N/A	N/A
Thailand [75]	Sep 03 to Dec 05	Census derived estimate	PCR, viral isolation, ELISA serology	n/a	8.2	N/A	N/A
Thailand [76]	Jan 08 to Dec 11	Census derived estimate	PCR	15.43	9.8	N/A	N/A
India [77]	Aug 09 to Jul 11	Census derived estimate	PCR	346	N/A	N/A	N/A
Guatemala [78]	Nov 07 to Jul 10	Defined population based	PCR	5.9	2	45.9	1370.00%

RSV = respiratory syncytial virus, LRTI = lower respiratory tract infection, IP = inpatient, OP = outpatient, PCR = polymerase chain reaction, ELISA = Enzyme-linked immnunosorbent assay, IF = immunofluoresecence, DFA = direct fluorescent antibody test, cyo = child-years of observation, N / A = not available

Table 4: Incidence of RSV-associated LRTI and severe LRTI in hospital-based studies.

children with RSV-LRTI. Malaria co-occurred in 2.0% to 28.4% of children with RSV-LRTI. A prospective population-based surveillance study from Kenya reported that concurrent malaria parasitemia were significantly less common among RSV-positive children than RSV-negative children (Relative Risk, RR=0.36; 95%CI 0.26-0.49). Similarly, a study from Mozambique reported the association of malaria with a lower prevalence of RSV infection (Odd Ratio, OR=0.5; 95%CI 0.20-0.90). Two African studies reported a negative association between malaria and RSV. Suppression of malaria parasitemia has been observed with another on-going viral infection (measles and influenza). However, a study from Mozambique found that the prevalence of malaria parasitemia among RSV-positive patients is similar to that seen in community surveys (30%), therefore suggesting that this negative association may be an artifact resulting from the high prevalence of malaria parasitemia among other admitted children.

HIV infection: Two studies from Africa found that 10.0% to 13.6% of RSV-LRTI children were HIV-positive. A study from South Africa reported higher rates of concomitant bacteremia in HIV-positive children with RSV LRTI than HIV-negative children. (HIV vs. non-HIV; 6.9% vs. 1.4%). Case fatality rate of HIV-infected children was higher than for HIV-uninfected children (7.4% vs. 0.6%, respectively). Of note, this study could not exclude that concurrent PCP (Pneumocystis carinii pneumonia) might have contributed to a higher mortality rate in HIV-infected children as the investigation for Pneumocystis carinii pneumonia was not done in every HIV-infected children who died.

Malnutrition: Five studies reported a proportion of malnourished condition in children with RSV-LRTI by using various definition of malnutrition. Overall, 6.6% to 24.8% of children with RSV-LRTI had malnutrition. A study from Kenya reported that severe malnutrition was significantly less common among RSV-positive children (RR=0.47; 95%CI 0.36-0.61). A study from Mozambique reported that mild or moderate and severe malnutrition were associated with a lower risk for

RSV infections, (OR=0.50; 95%CI 0.30-0.80 and 0.20; 95%CI 0.10-0.60), respectively). Malnutrition is a well-known cause of immunodeficiency and has been shown to be associated with increased incidence and mortality of respiratory illness, but this risk is not common to all acute respiratory and seems to be low for RSV. The negative association found between malnutrition and RSV infection is in agreement with other previous studies in Nigeria and the Gambia, where RSV was found less frequently in malnourished children with pneumonia.

Malaria may result in fever and raised respiratory rate, therefore, it could be another confounding infection mimicking LRTI in countries where malaria is endemic [76,77]. Moreover, the common practice of treating children with respiratory symptoms with antimalarial drugs causes delays in care seeking for children with pneumonia. Most children who died from pneumonia were reportedly first treated at home with antimalarial drugs [78]. Hence, malaria endemicity affects the estimation of RSV prevalence/incidence among LRTI cases and case fatality rate of RSV-LRTI. Increasing awareness is important for healthcare workers who should provide adequate diagnosis and treatment of both pneumonia and malaria. The contribution of RSV-LRTI differs between HIV-infected and HIV-uninfected children. HIV-infected children have greater evidence of bacterial co-infection and greater mortality than HIV-uninfected children, as previously described [79,80]. In a lot of the health facilities in developing countries, a moderate degree of malnutrition is so common that it is frequently not recorded as an admission diagnosis, and the increased risk of death is not appreciated. Moreover, the clinical signs such as fast breathing and retractions have poor predictive values in malnourished children [81]. Thus, the difference and consequences of malnutrition should not be neglected.

Limitations of the current literature review

Despite various literature databases utilized to make this review as exhaustive as possible, some limitations exist. Only English literature was searched. This likely biased the findings by excluding some studies from certain regions such as China, and some countries in Latin America, Russia, and the Middle East where there may be substantial information in local language publications. The comparability of various findings from the reviewed literature included is problematic for a number of reasons including dissimilar case finding procedures, variable study year, and non-uniform classification schemes for age. Studies that were published before 2002 have been excluded, and this may have led to an underestimation of some results. However, it does ensure that the most current epidemiological data was focused and previous studies, in which conventional virological diagnostic techniques were used, have most likely underestimated rates of RSV infection. The possibility of excluding relevant studies because the published studies were screened by abstract review and were excluded if the abstract did not indicate that the paper contained information on RSV epidemiology. Some papers may have contained relevant information, even if this was not apparent from the abstract.

Conclusions

Despite the increasing number of epidemiological studies of RSV-LRTI published over the past 13 years in developing countries, there are still clearly many areas that merit further study. There is still a need to establish further RSV surveillance studies to improve the incidence estimates and to explore the extent to which national and regional variation in RSV infection rates exist in countries where there is a high burden and high mortality attributable to LRTI but lack of understanding of local RSV epidemiology. Studies of RSV disease burden should ideally be prospective, community-based, with a known population denominator, with standardized case definition, with specimens collected by nasopharyngeal aspirate or nasal wash and tested by sensitive viral detection method (preferably using PCR assay), and with active surveillance by dedicated research staffs who can obtain specimens at the household level. To strengthen the available body of evidence for RSV epidemiology, future incidence studies should be conducted in compliance with the existing WHO protocol to be standardized and facilitate international comparisons. Specifically, in areas of disease severity in various age groups, reinfection and age-specific incidence which have implications for vaccine development and immunization strategies, have been incompletely reported. Reporting of information on underlying illnesses, prematurity, complications and therapy administered to RSV-LRTI cases should be encouraged and harmonized to permit a valid comparison of RSV-LRTI epidemiology across studies. Furthermore, these data would supplement the basis of a cost-effectiveness quantification to justify the cost and effort of introducing a vaccine and of sustainability when a vaccine becomes available. Given the importance of HIV and malaria on RSV epidemiology, their impact on RSV should be further explored in HIV and malaria endemic countries.

A number of important challenges remain including: (1) in community-based studies, case ascertainment would be difficult in communities where a variety of different sources of medical care are utilized, for example, use of private practitioners, over-the-counter drugs, or household remedies; (2) morbidity and mortality is likely to be under-recognized due to delayed healthcare seeking behavior and limited healthcare access; (3) diagnosis of bacterial pneumonia secondary to RSV infection in young children with community-acquired pneumonia is difficult to establish, (4) funding and resources are needed to enable studies with adequate study design and adequate study methodologies to be conducted. The high burden of RSV-LRTI in developing countries justifies the investment of resources for wide-scale epidemiologic studies, and investments to fund such studies should be considered by international organizations. At a national level, governments must give high priority to the fight against RSV-LRTI and should identify centers to be equipped with laboratory facilities. Investigations of epidemiology as recommended above and systematic data collection will help decision-makers in understanding RSV epidemiology, thereby avoiding delays in vaccine deployment in developing nations with tremendous need. Good quality data from countries and regions will facilitate precise global estimation of RSV-LRTI burden. Such estimates are useful to motivate international efforts such as vaccine development or financing.

Author Contributions

SS, EP, FLP contributed to the design and interpretation of data for this manuscript. SS, MS were responsible for drafting the work and revising it critically for intellectual content. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work and read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Global Burden of Disease (2010) Compare. In: Compare G (eds.) Institute for Health Metrics and Evaluation (IHME).
2. Liu L, Johnson HL, Cousens S, Perin J, Scott S, et al. (2012) Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 379: 2151–2161.
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, et al. (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and

2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380: 2095–2128.

4. Simoes EAF, Cherian T, Chow J, Shahid-Salles SA, Laxminarayan R, et al. (2006) Acute Respiratory Infections in Children In: Jamison, D.B.; Measham, A.R., et al., editor. Disease Control Priorities in Developing Countries (2nd edn). Washington (DC): World Bank.
5. Tregoning JS, Schwarze J (2010) Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. Clin Microbiol Rev 23: 74-98.
6. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, et al. (2009) The burden of respiratory syncytial virus infection in young children. N Engl J Med 360: 588-598.
7. American Academy of Pediatrics (2009) Respiratory syncytial virus. In: Red Book: Report of the Committee on Infectious Diseases, (28th edn) Pickering LK (Ed), American Academy of Pediatrics pp: 560.
8. Center for Disease Control and Prevention. Respiratory syncytial virus (RSV).
9. Liu L, Oza S, Hogan D, Perin J, Rudan I, et al. (2015) Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 385: 430-440.
10. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, et al. (2010) Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 375: 1545-1555.
11. Hoffmann J, Rabezanahary H, Randriamarotia M, Ratsimbasoa A, Najjar J, et al. (2012) Viral and atypical bacterial etiology of acute respiratory infections in children under 5 years old living in a rural tropical area of Madagascar. PLoS One 7: e43666.
12. Feikin DR, Njenga MK, Bigogo G, Aura B, Aol G, et al. (2013) Viral and bacterial causes of severe acute respiratory illness among children aged less than 5 years in a high malaria prevalence area of western Kenya, 2007 - 2010. Pediatric Infect Dis J 32: e14-e19.
13. Ahmed JA, Katz MA, Auko E, Njenga MK, Weinberg M, et al. (2012) Epidemiology of respiratory viral infections in two long-term refugee camps in Kenya, 2007-2010. BMC Infect Dis 12: 7.
14. Munywoki PK, Koech DC, Agoti CN, Lewa C, Cane PA, et al. (2014) The source of respiratory syncytial virus infection in infants: a household cohort study in rural Kenya. J Infect Dis 209: 1685-1692.
15. Bigogo GM, Breiman RF, Feikin DR, Audi AO, Aura B, et al. (2013) Epidemiology of respiratory syncytial virus infection in rural and urban Kenya. J Infect Dis 208 Suppl 3: S207-216.
16. Hasan K, Jolly P, Marquis G, Roy E, Podder G, et al. (2006) Viral etiology of pneumonia in a cohort of newborns till 24 months of age in rural Mirzapur, Bangladesh. Scand J Infect Dis 38: 690-695.
17. Homaira N, Luby SP, Petri WA, Vainionpaa R, Rahman M, et al. (2012) Incidence of respiratory virus associated pneumonia in urban poor young children of Dhaka Bangladesh 2009 -2011. PloS One 7: 1-6.
18. Mathisen M, Strand TA, Sharma BN, Chandyo RK, Valentiner-Branth P, et al. (2009) RNA viruses in community acquired childhood pneumonia in semi urban Nepal: a cross sectional study. BMC Med. 7: 1-12.
19. Mathisen M, Strand TA, Sharma BN, Chandyo RK, Valentiner-Branth P, et al. (2010) Clinical presentation and severity of viral community acquired pneumonia in young Nepalese children. Pediatr Infect Dis J 29: e1-e6.
20. Yoshida LM, Suzuki M, Thiem VD, Smith WP, Tsuzuki A, et al. (2014) Population Based Cohort Study for Pediatric Infectious Diseases Research in Vietnam. Trop Med Health 42: 47-58.
21. Huo X, Fang B, Liu L, Yu H, Chen H, et al. (2013) Clinical and epidemiologic characteristics of respiratory syncytial virus infection among children aged <5 years, Jingzhou City, China, 2011. J Infect Dis 208:S184-S188.
22. Shafik CF, Mohareb EW, Yassin AS, Amin MA, El Kholy A, et al. (2012) Viral etiologies of lower respiratory tract infections among Egyptian children under five years of age. BMC Infect Dis 12: 350.
23. Fattouh AM, Mansi YA, El-Anany MG, El-Kholy AA, El-Karaksy HM. (2011) Acute lower respiratory tract infection due to respiratory syncytial virus in a group of Egyptian children under 5 years of age. Ital J Pediatr 37: 1-6.
24. Jeena PM, Ayannusi OE, Annamalai K, Naidoo P, Coovadia HM, et al. (2003) Risk factors for admission and the role of respiratory syncytial virus specific cytotoxic T- lymphocyte responses in children with acute bronchiolitis. S Afr Med J 93: 291-294.
25. Moyes J, Cohen C, Pretorius M, Groome M, von Gottberg A, et al. (2013) Epidemiology of respiratory syncytial virus-associated acute lower respiratory tract infection hospitalizations among HIV-infected and HIV-uninfected South African children, 2010-2011. J Infect Dis 208: S217-S226.
26. Johnson AW, Osinusi K, Aderele WI, Gbadero DA, Olaleye OD, et al. (2008) Etiologic agents and outcome determinants of community-acquired pneumonia in urban children: A hospital based study. J Natl Med Assoc 100: 370-385.
27. O'Callaghan-Gordo C, Bassat Q, Morais L, Díez-Padrisa N, Machevo S, Nhampossa T, et al. (2011) Etiology and epidemiology of viral pneumonia among hospitalized children in rural Mozambique: a malaria endemic area with high prevalence of HIV. Pediatr Infect Dis J 30: 39-44.
28. Kwofie TB, Anane YA, Nkrumah B, Annan A, Nguah SB, et al. (2012) Respiratory viruses in children hospitalized for acute lower respiratory tract infection in Ghana. Virol J 9: 78.
29. Hammitt LL, Kazungu S, Morpeth SC, Gibson DG, Mvera B, et al. (2012) A preliminary study of pneumonia etiology among hospitalized children in Kenya. Clin Infect Dis 54: S190-S199.
30. Okiro EA, Ngama M, Bett A, Nokes DJ. (2012) The incidence and clinical burden of respiratory syncytial virus disease identified through hospital outpatient presentations in Kenyan children. PLoS One 7:e52520.
31. Nacul LC, Kirkwood BR, Carneiro AC, Pannuti CS, Magalhaes M, et al. (2005) Aetiology and clinical presentation of pneumonia in hospitalized and outpatient children in northeast Brazil and risk factors for severity. J Health Popul Nutr 23: 6-15.
32. Thomazelli LM, Vieira S, Leal AL, Sousa TS, Oliveira DB, et al. (2007) Surveillance of eight respiratory viruses in clinical samples of pediatric patients in southeast Brazil. J Pediatr (Rio J) 83: 422-428.
33. Nascimento-Carvalho CM, Cardoso MR, Barral A, Araújo-Neto CA, Oliveira JR, et al. (2010) Seasonal patterns of viral and bacterial infections among children hospitalized with community-acquired pneumonia in a tropical region. Scand J Infect Dis 42: 839-844.
34. Pecchini R, Berezin EN, Felício MC, Passos SD, Souza MC, et al. (2008) Incidence and clinical characteristics of the infection by the respiratory syncytial virus in children admitted in Santa Casa de Sao Paulo hospital. Braz J Infect Dis 12: 476-479.
35. Nascimento MS, Souza AV, Ferreira AV, Rodrigues JC, Abramovici S, et al. (2010) High rate of viral identification and coinfections in infants with acute bronchiolitis. Clinics (Sao Paulo) 65: 1133-1137.
36. Lamarão LM, Ramos FL, Mello WA, Santos MC, Barbagelata LS, et al. Prevalence and clinical features of respiratory syncytial virus in children hospitalized for community-acquired pneumonia in northern Brazil. BMC Infect Dis 12: 119.
37. De-Paris F, Beck C, Pires MR, dos Santos RP, Kuchenbecker Rde S, et al. (2014) Viral epidemiology of respiratory infections among children at a tertiary hospital in Southern Brazil. Rev Soc Bras Med Trop 47: 223-226.
38. Viegas M, Barrero PR, Maffey AF, Mistchenko AS (2004) Respiratory viruses seasonality in children under five years of age in Buenos Aires, Argentina: a five-year analysis. J Infect 49: 222-228.
39. Rodríguez-Auad JP, Nava-Frías M, Casasola-Flores J, Johnson KM, Nava-Ruiz A, et al. (2012) The epidemiology and clinical characteristics of respiratory syncytial virus infection in children at a public pediatric referral hospital in Mexico. Int J Infect Dis 16: e508-e513.
40. Kaur C, Chohan S, Khare S, Puliyel JM (2010) Respiratory viruses in acute bronchiolitis in Delhi. Indian Pediatr 47: 342-343.
41. Tang LF, Wang TL, Tang HF, Chen ZM (2008) Viral pathogens of acute lower respiratory tract infection in China. Indian Pediatr 45: 971-975.
42. Zhang Q, Guo Z, MacDonald NE (2011) Vaccine preventable community-acquired pneumonia in hospitalized children in northwest China. Pediatr Infect Dis J 30: 7-10.
43. Zhang C, Zhu N, Xie Z, Lu R, He B, et al. (2013) Viral etiology and clinical profiles of children with severe acute respiratory infections in China. PLoS One 8: e72606.

44. Lu Y, Wang S, Zhang L, Xu C, Bian C, et al. (2013) Epidemiology of human respiratory viruses in children with acute respiratory tract infections in Jinan, China. Clin Dev Immunol 2013: 210490.

45. Farshad N, Saffar MJ, Khalilian AR, Saffar H (2008) Respiratory viruses in hospitalized children with acute lower respiratory tract infection, Mazandaran province,Iran. Indian Pediatr 45: 590-592.

46. Hatipoğlu N, Somer A, Badur S, Unüvar E, Akçay-Ciblak M, et al. (2011) Viral etiology in hospitalized children with acute lower respiratory tract infection. Turk J Pediatr 53: 508-516.

47. Hacımustafaoğlu M, Celebi S, Bozdemir SE, Ozgür T, Ozcan I, et al. (2013) RSV frequency in children below 2 years hospitalized for lower respiratory tract infections. Turk J Pediatr 55: 130-139.

48. Bharaj P, Sullender WM, Kabra SK, Mani K, Cherian J (2009) Respiratory viral infections detected by multiplex PCR among pediatric patients with lower respiratory tract infections seen at an urban hospital in Delhi from 2005 to 2007. Virol J 6: 1-11.

49. Singh AK, Jain A, Jain B, Singh KP, Dangi T, et al. (2014) Viral aetiology of acute lower respiratory tract illness in hospitalised paediatric patients of a tertiary hospital: one year prospective study. Indian J Med Microbiol 32: 13-18.

50. Gupta S, Shamsundar R, Shet A, Chawan R, Srinivasa H (2011) Prevalence of respiratory syncytial virus infection among hospitalized children presenting with acute lower respiratory tract infections. Indian J Pediatr 78: 1495-1497.

51. Mathisen M, Basnet S, Sharma A, Shrestha PS, Sharma BN, et al. (2011) RNA viruses in young Nepalese children hospitalized with severe pneumonia. Pediatr Infect Dis J 30: 1032-1036.

52. Banstola A, Banstola A (2013) The epidemiology of hospitalization for pneumonia in children under five in the rural western region of Nepal: a descriptive study. PLoS One 8: e71311.

53. Haque F, Husain MM, Ameen KM, Rahima R, Hossain MJ, et al. (2012) Bronchiolitis outbreak caused by respiratory syncytial virus in southwest Bangladesh, 2010. Int J Infect Dis 16: e866-e871.

54. Do AH, van Doorn HR, Nghiem MN, Bryant JE, Hoang TH, et al. (2011) Viral etiologies of acute respiratory infections among hospitalized Vietnamese children in the Ho Chi Minh city 2004-2008. PLos One 6: 1-9.

55. Tran DN, Pham TMH, Ha MT, Tran TTL, Dang TKH, et al. (2013) Molecular Epidemiology and Disease Severity of Human Respiratory Syncytial Virus in Vietnam. PLoS ONE 8: e45436.

56. Siritantikorn S, Puthavathana P, Suwanjutha S, Chantarojanasiri T, Sunakorn P, et al. (2002) Acute viral lower respiratory infection in children in a rural community in Thailand. J Med Assoc Thai 85: s1167-s1675.

57. Olsen SJ, Thamthitiwat S, Chantra S, Chittaganpitch M, Fry AM, et al. (2010) Incidence of respiratory pathogens in persons hospitalized with pneumonia in two provinces in Thailand. Epidemiol Infect 138: 1811-1822.

58. Suntarattiwong P, Sojisirikul K, Sitaposa P, Pornpatanangkoon A, Chittaganpitch M, et al. (2011) Clinical and epidemiological characteristics of respiratory syncytial virus and influenza virus associated hospitalization in urban Thai infants. J Med Assoc Thai 94 Suppl 3:S164-S171.

59. Turner P, Turner C, Watthanaworawit W, Carrara V, Cicelia N, et al. Respiratory virus surveillance in hospitalised pneumonia patients on the Thailand-Myanmar border. BMC Infect Dis 13: 434.

60. Suzuki A, Lupisan S, Furuse Y, Fuji N, Saito M, et al. (2012) Respiratory viruses from hospitalized children with severe pneumonia in the Philippines. BMC Infect Dis 12: 267.

61. Suwanjutha S, Sunakorn P, Chantarojanasiri T, Siritantikorn S, Nawanoparatkul S, et al. (2002) Respiratory syncytial virus-associated lower respiratory tract infection in under-5-year-old children in a rural community of central Thailand population based study. J Med Assoc Thai 85: s1111-1119.

62. Nokes DJ, Okiro EA, Ngama M, White LJ, Ochola R, et al. (2004) Respiratory syncytial virus epidemiology in a birth cohort from Kilifi district, Kenya: infection during the first year of life. J Infect Dis 190: 1828-1832.

63. Nokes DJ, Okiro EA, Ngama M, Ochola R, White LJ (2008) Respiratory syncytial virus infection and disease in infants and young children observed from birth in Kilifi District, Kenya. Clin Infect Dis 46: 50-57.

64. Simões EA, Mutyara K, Soh S, Agustian D, Hibberd ML, et al. (2011) The epidemiology of respiratory syncytial virus lower respiratory tract infection in children less than 5 years of age in Indonesia. Pediatr Infect Dis J 30: 778-784.

65. Broor S, Parveen S, Bharaj P, Prasad VS, Srinivasulu KN, et al. (2007) A prospective three-year cohort study of the epidemiology and virology of acute respiratory infection of children in rural India. PLoS One 2: 1-6.

66. McCracken JP, Prill MM, Arvelo W, Lindblade KA, López MR, et al. (2013) Respiratory syncytial virus infection in Guatemala, 2007-2012. J Infect Dis 208 Suppl 3:S197-S206.

67. Weber MW, Milligan P, Sanneh M, Awemoyi A, Dakour R, et al. (2002) An epidemiological study of RSV infection in the Gambia. Bull World Health Organ 80: 562-568.

68. Nokes DJ, Ngama M, Bett A, Abwao J, Munywoki P, et al. (2009) Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. Clin Infect Dis 49: 1341-1349.

69. Berkley JA, Munywoki P, Ngama M, Kazungu S, Abwao J, et al. (2010) Viral etiology of severe pneumonia among Kenyan infants and children. JAMA 303: 2051-2057.

70. Robertson SE, Roca A, Alonso P, Simoes EA, Kartasasmita CB, et al. (2004) Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ 82: 914-922.

71. Djelantik IG, Gessner BD, Soewignjo S, Steinhoff M, Sutanto A, et al. (2003) Incidence and clinical features of hospitalization because of respiratory syncytial virus lower respiratory tract illness among children less than two years of age in a rural Asian setting. Pediatric Infectious Disease Journal 22: 150-157.

72. Fry AM, Chittaganpitch M, Baggett HC, Peret TC, Dare RK, et al. (2010) The burden of hospitalized lower respiratory tract infection due to respiratory syncytial virus in rural Thailand. PLoS One 5: e15098.

73. Naorat S, Chittaganpitch M, Thamthitiwat S, Henchaichon S, Sawatwong P, et al. (2013) Hospitalizations for acute lower respiratory tract infection due to respiratory syncytial virus in Thailand, 2008-2011. J Infect Dis 208 Suppl 3:S238-S245.

74. Broor S, Dawood FS, Pandey BG, Saha S, Gupta V, et al. (2014) Rates of respiratory virus-associated hospitalization in children aged <5 years in rural northern India. J Infect 68: 281-289.

75. Fischer Langley G, McCracken J, Arvelo W, Estevez A, Villarruel G (2013) The epidemiology and clinical characteristics of young children hospitalized with respiratory syncytial virus infections in Guatemala (2007-2010). Pediatr Infect Dis J 32: 629-635.

76. English M, Punt J, Mwangi I, McHugh K, Marsh K (1996) Clinical overlap between malaria and severe pneumonia in Africa children in hospital. Trans R Soc Trop Med Hyg 90: 658-662.

77. O'Dempsey TJ, McArdle TF, Laurence BE, Lamont AC, Todd JE, et al. (1993) Overlap in the clinical features of pneumonia and malaria in African children. Trans R Soc Trop Med Hyg 87: 662-665.

78. Källander K, Hildenwall H, Waiswa P, Galiwango E, Peterson S, et al. (2008) Delayed care seeking for fatal pneumonia in children aged under five years in Uganda: a case-series study. Bull World Health Organ 86: 332-338.

79. Madhi SA, Schoub B, Simmank K, Blackburn N, Klugman KP (2000) Increased burden of respiratory viral associated severe lower respiratory tract infections in children infected with human immunodeficiency virus type-1. J Pediatr 137: 78-84.

80. Madhi SA, Venter M, Madhi A, Petersen MK, Klugman KP (2001) Differing manifestations of respiratory syncytial virus-associated severe lower respiratory tract infections in human immunodeficiency virus type 1-infected and uninfected children. Pediatr Infect Dis J 20: 164-170.

81. Chisti MJ, Tebruegge M, La Vincente S, Graham SM, Duke T (2009) Pneumonia in severely malnourished children in developing countries - mortality risk, aetiology and validity of WHO clinical signs: a systematic review. Trop Med Int Health 14: 1173-1189.