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Epidemiology of respiratory syncytial virus associated acute lower respiratory infection in young children

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Declaration

I, Ting Shi, hereby declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where states otherwise by reference or acknowledgment, the work presented is entirely my own.

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Lay summary of thesis

Acute lower respiratory infection (ALRI) (chest infection), is still causing a large number of illness and deaths in young children. Viral ALRI is becoming more and more important because of a decreased proportion of bacterial contribution due to available vaccines. The global burden of disease due to ALRI related to respiratory syncytial virus (RSV) in young children has been recognised. This thesis aims to estimate the absolute contribution of RSV in causing ALRI cases, investigate risk factors for RSV associated ALRI, disease burden of RSV associated ALRI in children younger than five years old in different regions and in the global scale.

This thesis has used data from systematic reviews of studies published in the last 20 years supplemented by 76 unpublished data sets from RSV Global Estimates Network (RSV GEN) working group consisting of 45 leading researchers on childhood chest infections.

The thesis provides evidence that RSV contributed to children presenting with ALRI in a causal path and the absolute percentage of RSV resulting in RSV associated ALRI was around 90% (80%-95%). Eight risk factors were identified to have significant associations with RSV associated ALRI in young children: being born with gestational age <37 weeks, low birth weight (<2.5 kg), being male, having siblings, mothers smoking during pregnancy, family history of atopy, no breastfeeding and crowding - >7 persons in household. Globally in 2015 there were 33.0 (95% CI 20.6-53.2) million episodes of RSV associated ALRI occurring in children younger than 5 years old. Among them, 3.0 (95% CI 2.2-4.0) million cases were admitted to hospitals. Around 60,000 children died in the hospital settings with 99% of these deaths occurring in developing countries. The overall mortality from RSV associated ALRI was estimated about 131,000. RSV disease burden was particularly higher in infants during their early months of life and in developing countries.

RSV associated ALRI infections are common in young children and cause a substantial burden on family care-takers and hospital services worldwide. The population based evidence places essential basis for prompt prevention and vaccination strategies.

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Abstract

Introduction

Acute lower respiratory infection (ALRI) remains as a leading cause of childhood morbidity and mortality. With the continued universal vaccination campaign against bacterial pathogens, an increase in relative proportion of respiratory viruses contributing to ALRI is anticipated. Respiratory syncytial virus (RSV) has been recognised as the most common pathogen identified in young children presenting with ALRI as well as an important cause of hospital admission. This thesis aims to estimate the aetiological roles and attributable fractions of common respiratory viruses among ALRI cases and investigate the risk factors for RSV associated ALRI in young children. It also aims to estimate the global and regional incidence of RSV associated ALRI in both community and hospital based settings, and the possible boundaries for RSV associated ALRI mortality in children younger than five years old.

Methods

Systematic reviews were carried out separately for the following three research questions: aetiological roles of RSV and other common viruses in ALRI cases, risk factors for RSV associated ALRI and global/regional burden of RSV associated ALRI, formulating an overall picture of epidemiology of RSV associated ALRI in young children. They all focused on children younger than five years old. The identified studies were selected according to pre-defined inclusion and exclusion criteria. The whole process was conducted following the PRISMA guidelines for systematic review and meta-analysis. Unpublished data from RSV Global Estimates Network (RSV GEN) were collected from 45 leading researchers on paediatric pneumonia (primarily in developing countries). They either reanalysed data from their already published work with the pre-defined standardised case definitions or shared hitherto unpublished data from ongoing studies. Data from both systematic reviews and RSV GEN working group were included into further meta-analysis. Random effects model was consistently applied in all meta-analyses.

Results

There were 23 studies identified through literature search satisfying the eligibility criteria, investigated the viral aetiology of ALRI in young children. Strong evidence was observed for RSV in support of its causal contribution in children presenting with ALRI and the association was significant measured in odds ratio: 9.79 (4.98-19.27). Thus, the

corresponding attributable fraction among the exposed was estimated as 90% (80%-95%), which means around 90% of RSV associated ALRI cases were in fact attributed to RSV in a causal path.

In total, 27 studies (including 4 unpublished studies) were included and contributed to the analysis. Across these studies, 18 risk factors were described and 8 of them were observed to have significant associations with RSV infection: prematurity - gestational age <37 weeks, low birth weight (<2.5 kg), being male, having siblings, maternal smoking, history of atopy, no breastfeeding and crowding - >7 persons in household.

Overall, 304 studies met the selection criteria and were included to estimate the global and regional burden of RSV associated ALRI in young children. These included 73 published articles identified through Chinese language databases and 76 unpublished studies provided by RSV GEN working group, mainly from developing countries. It is estimated that in 2015, there were 33.0 (95% CI 20.6-53.2) million episodes of RSV associated ALRI occurring in children younger than 5 years old across the world. 30.5 (95% CI 19.5-47.9) million of them were in developing countries. 3.0 (95% CI 2.2-4.0) million cases were severe enough and warranted hospitalisation. Around 60,000 children died in the hospital settings with 99% of these deaths occurring in developing countries. The overall mortality from RSV associated ALRI was estimated about 131,000.

Conclusion

This thesis not only enhanced the epidemiological understanding of RSV in young children, but also provided important information for public health decision makers. It incorporated both data through systematic reviews of published articles in the past 20 years and more than 70 unpublished data sets shared by RSV GEN working group. The population based incidence, hospitalisation, mortality and risk factor data are essential to assess the various severity of illness in a specific age group and region, and inform local public health professionals regarding appropriate and prompt cases management, prevention and vaccine allocation strategies. National sentinel systems of RSV surveillance gathering structured and reasonably representative data are needed. Within the surveillance system, a universal definition regarding disease severity in various settings should be developed, and diagnostic methods with higher sensitivity and specificity should be applied.

Chapter 1 Introduction

1.1 Acute lower respiratory infection

Acute lower respiratory infections (ALRI), which include pneumonia and bronchiolitis, decreased from 3.4 million of all-age deaths to 2.8 million during the period from 1990 to 2010 (Lozano et al., 2012). However, it still remained as the second leading cause of years of life lost due to premature mortality (YLL) and global disability-adjusted life year (DALY) in 2010 and the fourth leading cause of death across all age groups (Murray et al., 2012a, Lozano et al., 2012).

Most of this disease burden occurred in children younger than 5 years old, resulting in a substantial burden of childhood morbidity and mortality, particularly within developing countries, like Southeast Asia and Africa (Walker et al., 2013). It was estimated that in 2010, there were about 120.4 million episodes of ALRI and 14.1 million episodes of severe ALRI in children younger than 5 years globally (Rudan et al., 2013). In hospital-based settings, globally, 11.9 million new episodes of severe ALRI and 3.0 million of very severe ALRI were estimated resulting in hospital admissions in children younger than 5 years in 2010 (Nair et al., 2013). Among them, around 265,000 deaths occurred in hospital and 99% of these deaths were from developing countries. It was also estimated that there were 1.4 million pneumonia deaths worldwide in this age group in the same year, which decreased to 936,000 in 2013 (Liu et al., 2015a). ALRI contributed to 6-8% of neonatal deaths (0-27 days), 20.1% of deaths occurred in post-neonatal period (28-364 days), and 12.4% of mortality in young children aged 1-4 years old (Lozano et al., 2012). A high proportion (around 81%) of childhood deaths due to pneumonia occurred in children during their first two years of life (Walker et al., 2013). Childhood pneumonia was postulated to induce several long-term respiratory sequelae. The most common one was restrictive lung disease and the risk of major respiratory sequelae was higher in children younger than 2 years (Edmond et al., 2012).

Streptococcus pneumoniae and *Haemophilus influenza* type b (Hib) have been established as the principal aetiological agents of severe pneumonia and pneumonia mortality, especially in developing countries. It was estimated that in 2000, there were 14.5 million episodes of serious streptococcus pneumococcal disease occurring in children aged 1-59 months worldwide (O'Brien et al., 2009). Among them, there were 13.8 million episodes of pneumococcal pneumonia, resulting in around 741,000 deaths globally (82,700 deaths in HIV-positive children and 658,000 deaths in HIV-negative children). Pneumococcal

pneumonia contributed to 95.6% of all pneumococcal cases and 90% of pneumococcal deaths. It accounted for 8% of clinical pneumonia and 36% of chest radiography (CXR) positive pneumonia according to the meta-analyses results of several trials assessing the efficacy of pneumococcal conjugate vaccines against clinical and CXR confirmed pneumonia (O'Brien et al., 2009). It was also reported to cause around 18.3% of severe pneumonia episodes and 32.7% of all pneumonia deaths in young children (Walker et al., 2013). Similarly, in 2000, there were around 8.13 million episodes of serious Hib disease occurring in children aged 1-59 months globally (Watt et al., 2009). Among all Hib cases, there were 7.91 million Hib pneumonia, leading to 292,000 deaths among these young children (6,400 in HIV-positive and 286,000 in HIV-negative). It accounted for 5% of clinical pneumonia and 21% of pneumonia with radiographic consolidation based on results from several vaccine trials assessing the efficacy of Hib vaccine (Watt et al., 2009). Hib also contributed to about 4.1% of severe pneumonia cases and 15.7% of pneumonia mortality (Walker et al., 2013).

There are effective interventions available to prevent pneumonia cases caused by *Streptococcus pneumoniae* or Hib, such as pneumococcal conjugate vaccine and Hib conjugate vaccine. With the continued widespread of universal vaccination campaign against these two bacteria (World Health Organization, 2013b), a substantial reduction in childhood morbidity and mortality from bacterial ALRI and an increase in relative proportion of respiratory viruses contributing to ALRI are anticipated. Respiratory viruses played a more substantial part in causing ALRI deaths in infants compared to the age group of 1-4 years (Lozano et al., 2012). Therefore, subsequent research is expected to focus increasingly on understanding the role of viral pathogens in the remaining ALRI cases.

1.2 Respiratory syncytial virus

1.2.1 Molecular characteristics of RSV

Respiratory syncytial virus (RSV) has been found to be an important cause of childhood ALRI. It is a single-stranded negative-sense RNA enveloped virus and belongs to the family *Paramyxoviridae* and the subfamily *Pneumovirinae* (Acheson, 2011). It has two antigenic groups - subtype A and B. RSV-A is more prevalent than RSV-B (Meng et al., 2014). The subtypes contain different nucleotide sequences and amino acids. The RSV virion has two different shapes and sizes under electron microscopy: one is a spherical particle with diameter of 150-250 nm and the other one is a filament with length up to 10 μm (Bachi and Howe, 1973). Both of them are infectious. The virus particles are enveloped by a lipid bilayer where the attachment glycoprotein (G) and fusion glycoprotein (F) are inserted

(Figure 1). They serve to bind RSV particles to the cell surface components and mediate the fusion of virus and cell membranes respectively. Both of them can be observed under electron microscopy in the form of spikes around the virion. The F glycoprotein has two conformations: functional pre-F in a metastable form and non-functional post-F in a stable form (Graham et al., 2015, McLellan et al., 2013). A third small hydrophobic (SH) glycoprotein, is expressed on the surface of virus particles. A larger amount of it is produced on the surface of infected cells. Inside the virion, the virus nucleocapsid consists of RNA genome and nucleoprotein (N). They bind to each other tightly, forming a helical morphology. There are other viral proteins incorporated into the nucleocapsid: RNA-dependent RNA polymerase (L protein), phosphoprotein (P) and 22k protein (M2-1). P protein plays a central role in the RSV synthesis, interacting with N, L and 22k proteins. Another three non-structural proteins are also encoded by RSV: NS1, NS2 and M2-2. They are only expressed in virus-infected cells (not in the virus particles) (Cane, 2006). Among all the proteins which make up the RSV virion, only G and F glycoproteins are targeted by neutralising antibodies.

Activated by G glycoprotein, RSV virion binds to the target cell surface glycosaminoglycans (GAGs). Then, F protein is triggered and mediates the fusion of membranes from virus and target cell on the cell surface in the following process: the highly hydrophobic fusion peptide of F protein is exposed and subsequently it is inserted into the host cell membrane; this F protein intermediate is refolded, which brings the viral and cell membranes into close proximity; a stable structure is formed; lipids of these two membranes are mixed; the fusion pore that connects the interior of viral particles and the cytoplasm of target cells is produced. This makes the viral nucleocapsids enter into the host cell. Subsequent transcription and replication of the viral genome are activated to generate mRNAs followed by translation of relevant gene products and antigenome cRNA with opposite polarity but the same full-length as the RSV genome respectively. The transcription process requires the coordination of the following proteins: N, P, L and 22k proteins, while replication process needs similar proteins except from 22k protein. Afterwards, RSV gene products accumulate near the host cell membrane and they are assembled into new virions which are then released from the infected cells by budding. The matrix protein (M) coordinates this process: it binds to the nucleocapsids, which leads them to become transcriptionally inactive before packaging; it mediates the association of the nucleocapsid with the newly synthesised viral envelope (Cane, 2006).

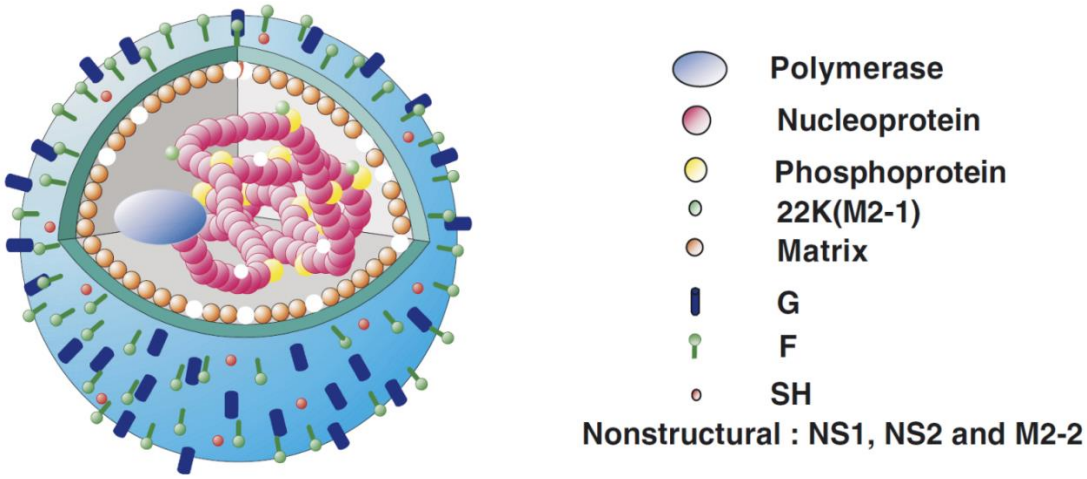

Figure 1: Schematic diagram of RSV virion (Cane, 2006)

G=attachment glycoprotein: bind virus to cell surface. F=fusion glycoprotein: mediate fusion of the viral and cell membranes. SH=small hydrophobic glycoprotein: express on the surface of infected cells with low amounts incorporated on the surface of virus particles. 3 non-structural proteins are produced in infected cells without incorporation in the virus particles.

However, viral particles with a missing G gene can also bind to the target cells, in spite of the attenuated function. Activation of the F glycoprotein is independent of the presence of the G glycoprotein. This indicates that alternative factors might exist and mediate binding of RSV virion to the host cell surface (Cane, 2006). This remains further investigation.

1.2.2 Pathogenesis of RSV

RSV was first discovered in a group of chimpanzees in 1956 and isolated in humans one year later (Chanock and Finberg, 1957).

RSV is transmitted by contact with nasal or oral secretions from infected persons. It infects the ciliated epithelial cells of the upper airways at first. Viral replication in the nasopharynx produces a high virus load in the upper respiratory tract. In 30-50% of infants, the upper airway infection spreads to the lower respiratory tract after 1-3 days (Hall, 2001). This is mediated by direct spread of RSV along the respiratory epithelium or aspiration of infected nasopharyngeal secretions. The manifestations following RSV infection result from the function of direct viral cytotoxicity from viral replication and from the host immune response to infection. Immune response to infection includes innate and adaptive immunes. The innate immune response triggers the release of cytokines and recruits relevant molecules and phagocytic cells to the infection site; while the adaptive immune response consists of protective humoral immunity with production of IgG, IgM and IgA antibodies and cellular response to clear virus (CD4+ T-helper and CH8+ cytotoxic T lymphocytes) (Cane, 2006). Innate immune cells could have an influence on the subsequent adaptive immune response.

Crucial factors in response to RSV infection, such as dendritic cells and macrophages, may impact on both innate and adaptive immune cells. Therefore, it is important to take into account the interaction between innate immune and adaptive immune while assessing the role of each one.

Epithelial cells respond to the RSV infection by producing molecules and proteins that have direct effects against RSV, such as defensins, collectins and mucus (Diamond et al., 2000). Also, they recruit inflammatory cells and phagocytic cells to enhance the inflammatory response, which is achieved by secretion of inflammatory cytokines and chemokines (after activation of NF-κB) that increase capillary permeability and recruit inflammatory cells from the blood to the site of infection, such as neutrophils, eosinophils and NK cells (McNamara and Smyth, 2002). This leads to airway inflammation and bronchoconstriction. The majority of inflammatory cells are neutrophils and alveolar macrophages. In response to RSV infection, macrophages also play an important role in activating various immune responses, for example, interaction with T helper cells and cytotoxic T cells, and producing cytokines and phagocytic cells augmenting the immune response. Dendritic cells also activates the innate immune response against RSV infection (Cane, 2006). They are antigen-presenting cells to activate RSV specific naïve T cells. The sloughing of infected epithelial cells, airway inflammation, impaired ciliary beating and mucus accumulation lead to obstruction of airways and air trapping, and result in the clinical manifestation of severe bronchiolitis associated with RSV infection. This has a particularly significant effect in young infants and premature children who have small airways. The pathogenesis process of RSV bronchiolitis is shown in Figure 2.

Even though there are antibodies (limited magnitude and poor durability) and T-cell responses produced after a natural RSV infection and there is no antigenic change on RSV surface glycoproteins, re-infection with RSV occurs frequently (Meissner, 2016). The mechanisms of how RSV evades or inhibits host defences still remain unknown and require further research.

Children inhale droplets containing the virus from infected persons and after 4-6 days of incubation, they start to develop respiratory symptoms, such as fever (in about 50% infected infants), nasal congestion and rhinorrhea. After the virus spreads to the lower respiratory tract, it infects the ciliated epithelial cells of the bronchioles and pneumocytes (Meissner, 2016). Figure 3 displays the clinical progression of RSV as well as pathogenesis of RSV.

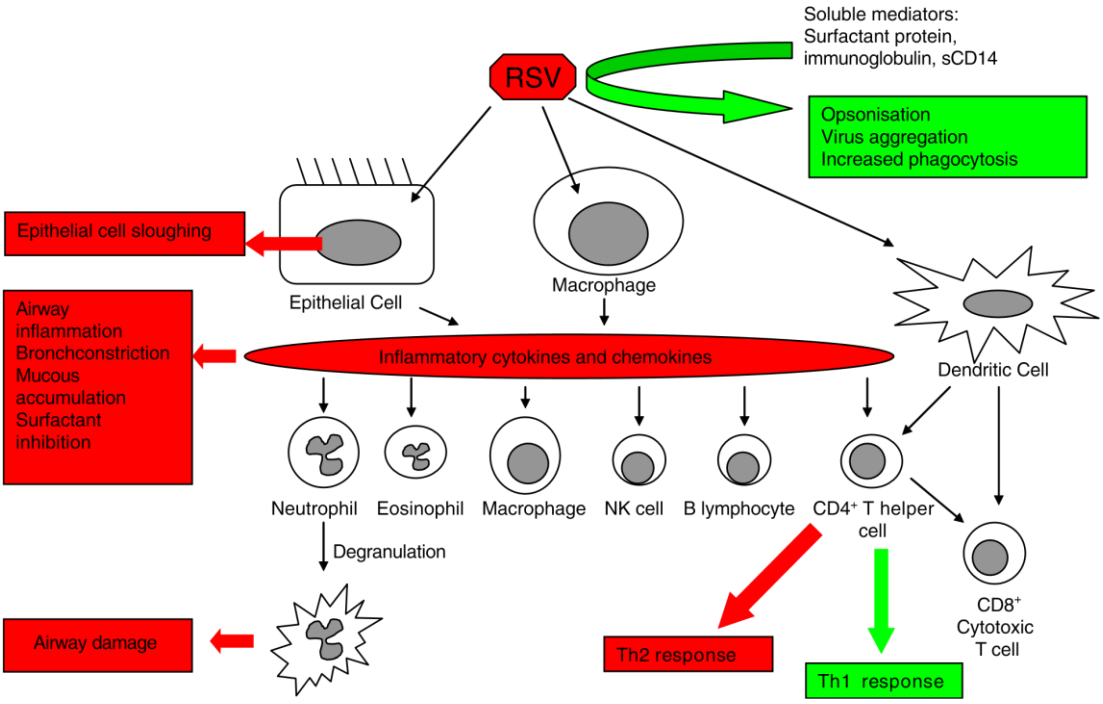

Figure 2: Pathogenesis of RSV bronchiolitis (Cane, 2006)

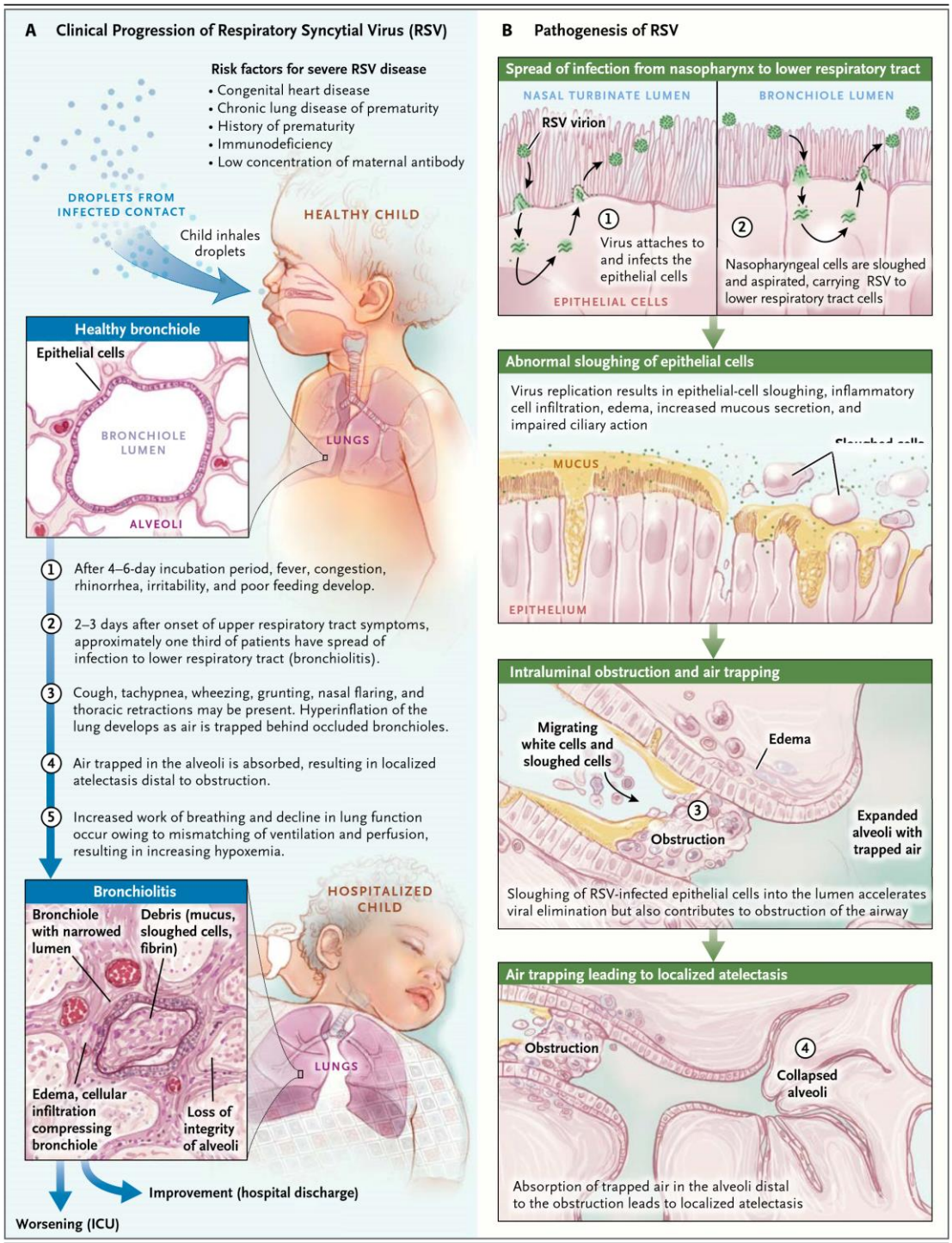

Figure 3: Clinical progression and pathogenesis of RSV (Meissner, 2016)*

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1.2.3 Epidemiology of RSV

RSV has been recognised as the most common pathogen identified in young children presenting with ALRI as well as an important cause of hospital admission (Nair et al., 2010). Globally, 33.8 million new episodes of ALRI which were RSV positive were estimated to occur in children younger than 5 years old in 2005. Among them, at least 3.4 million episodes represented severe cases which required hospitalisation. It was also estimated that RSV attributable in-hospital mortality in children younger than 5 years old was around 53,000 deaths and up to 199,000 overall deaths in community settings worldwide in 2005, with 99% of these occurring in developing countries. A population-based surveillance study carried out in 3 counties of the US showed that approximately 2.1 million children younger than 5 years old required medical attention every year due to RSV infection (around 10% of all under five-year-old children). Among them, around 57,000 children were hospitalised and the rest of children were treated in emergency rooms or by paediatric practices (Hall et al., 2009). A few more studies conducted in US also indicated a very large burden of RSV posed in both inpatient and outpatient settings (Stockman et al., 2012, Jain et al., 2015). There is also a high burden of RSV disease in HIV infected or exposed children. A hospital-based surveillance carried out in 4 provinces from South Africa manifested that the hospitalisation rate of RSV associated ALRI in HIV-infected infants less than 6 months was around 67.1 per 1000 children per year, 50.0 in HIV-exposed but uninfected infants, and 35.1 in infants with HIV-unexposed and uninfected (Cohen et al., 2016). The hospitalisation rate ratios for infants with HIV infection and HIV-exposed but uninfected were 1.9 (95% CI 1.3-2.7) and 1.4 (95% CI 1.3-1.6) respectively, compared to infants with HIV-unexposed and uninfected. The in-hospital case fatality ratio of RSV associated ALRI among infants with HIV infection was around 19%, 2% in infants with HIV-exposed but uninfected, and 0 in infants with HIV-unexposed and uninfected. The magnitude of RSV incidence or hospitalisation rate varies across different study years (months) and geographical areas. Its seasonality pattern will be discussed later in detail.

RSV is known to be more likely to have a severe outcome in children with certain pre-existing chronic medical conditions, resulting in a higher rate of hospitalisation and a higher risk of death. A case control study in southwest Alaska indicated that underlying medical conditions, such as prematurity, chronic lung disease and heart disease, were associated with an increased risk of RSV hospitalisation (Bulkow et al., 2002). Several other studies also confirmed similar results (Hall et al., 2013, Hall et al., 2009). Another systematic review reported that the case fatality ratio among children hospitalised with RSV infection was higher in children with chronic lung disease, congenital heart disease or prematurity,

compared to otherwise healthy children (Welliver et al., 2010). The association between RSV illness and other chronic conditions (e.g. Down's syndrome) is difficult to quantify due to the low incidence of RSV disease among this specific population. It was reported that the rate of RSV hospitalisation among these high-risk children declined after the implementation of RSV immune-prophylaxis in these high-risk populations (Homaira et al., 2014). A nationwide database derived study in US – the Kids' Inpatient Database (KID), indicated that the RSV hospitalisation rate in all high-risk infants (chronic lung disease, congenital heart disease, congenital airway anomalies, Down syndrome and other conditions), decreased from 62.9 per 1000 children per year to 39.1 (37.9% reduction) during the study period from 1997 to 2012 (Doucette et al., 2016). The main contribution to rate reduction came from infants with chronic lung disease and infants with higher-risk congenital heart disease (based on its rate in different ICD-9 codes). Hospitalisation rate among infants with the other comorbid conditions were not observed to decline.

Before this thesis, there had been only one systematic review published over one decade ago that assessed the associations between various risk factors and RSV associated ALRI and the magnitude of the associations (Simoes, 2003). Male gender, age group of less than 6 months during acquisition of RSV, birth during the first half of the RSV season, crowding or having siblings, and day care attendance were reported to have significant associations with severe RSV associated ALRI; while the roles of race or ethnicity, smoking exposure, low maternal education, lack of breastfeeding and malnutrition remained unclear or unknown. However, this review was a descriptive study, listing different studies reporting the risk factors of interest without carrying out an analysis assessing the overall magnitude of the association between each risk factor and RSV associated ALRI. In addition to the risk factors which might enhance the risk of obtaining RSV infection, genetic susceptibility to RSV disease is also proposed based on several lines of evidence: family studies show that children are at higher probability of getting respiratory illness if parents were previously infected in early life; aboriginal populations have higher hospitalisation rates of RSV disease; great variations of phenotypic traits between laboratory mice of different strains (Cane, 2006). Therefore, genetic variation might also affect individual risk to RSV disease, which remains under further investigation.

1.2.4 RSV associated subsequent respiratory morbidity

Whether or not RSV infection is associated with subsequent wheezing and asthma morbidity in young children remains controversial. A randomised double-blind clinical trial carried out across multiple centres in Netherlands demonstrated that healthy preterm infants (gestational

age of 33-35 weeks), who received monthly monoclonal antibody for RSV prevention (palivizumab) during the RSV season, were observed to have less total days of wheezing in their first year of life reported by parents, compared to those who received placebo, with a relative reduction of 61% and an absolute reduction of 2.7% in the rate of wheezing (Blanken et al., 2013). This effect existed in infants with or without a family history of atopy, and it persisted even after prophylaxis and outside the RSV season. A reduction of recurrent wheezing was also shown in the palivizumab group. The result is consistent with some previous observational studies, where an increased rate of asthma and recurrent wheezing was identified in early adulthood after they were hospitalised with RSV infection during infants (Sigurs et al., 2010). These studies provide some evidence in support of RSV playing a role in the pathogenesis of recurrent wheezing. It is hypothesised that RSV infection early in life causes direct pulmonary epithelial damage and alterations of the pulmonary environment and local immunologic responses. This leads to remodelling of the airway which contributes to long-term airway hyper-responsiveness to respiratory viruses (and other stimuli) and wheezing. Nevertheless, several other possible mechanisms might exist: there is a pre-existing alteration of immune response and pulmonary abnormality in infants which predispose them to both subsequent RSV infection and recurrent wheezing; there is a genetic tendency to both illnesses.

Moreover, in another more recent randomised double-blind phase 3 clinical trial, based on healthy term Native American infants, infants receiving motavizumab did not present a lower rate of medically attended wheezing compared to infants who received placebo after a 3-year follow up (O'Brien et al., 2015). A similar result was observed in previously healthy term infants hospitalised with RSV associated ALRI after a 12-month follow up (Ramilo et al., 2014). Therefore, the role of RSV infection in the development of subsequent asthma and respiratory morbidity remains unclear. It requires further investigation and the mechanisms remain to be clarified. This highlights the importance of understanding the occurrence and magnitude of RSV disease in young children in order to estimate its potential impact posed in later life.

1.2.5 Seasonality of RSV

The seasonality of RSV varies across the world. Seasonal epidemics occur throughout the year in tropical and subtropical regions, while RSV outbreaks in temperate regions often occur during the winter and spring. Appropriate preparation and management within healthcare facilities according to seasonality data is critical to coordinate an appropriate response to the rising demand during peak seasons.

In temperate regions, annual epidemics of RSV usually occur in the cold and dry winter period. The mechanisms are not well elaborated. A retrospective study in Greece investigated the relationship between RSV activity and several climate parameters during a 12-year study period (Sirimi et al., 2016). This study focused on children younger than 15 years old hospitalised with respiratory tract infection who were tested RSV positive. More than 95% of them were infants. The annual epidemic of RSV activity was observed from December to April with a peak in February. Statistically significant correlations were found between monthly RSV activity and mean monthly relative humidity (positive) as well as RSV activity and mean monthly temperature (negative). After multivariable analysis, mean monthly temperature remained in a negatively significant association with RSV activity. Similar results were observed in other temperate regions. In Netherlands, RSV outbreaks in children were observed consistently and positively associated with relative humidity and cloud cover as well as negatively associated with minimum temperature throughout the study period from 1998 to 2005 (Meerhoff et al., 2009b). Weekly RSV incidence among children younger than 2 years old during winter seasons (from 2007 to 2010) in Bologna (Italy) was correlated negatively with mean minimum temperature during the same week or with at least one-week time lag (Vandini et al., 2013). No correlation was found for the mean relative humidity. The weekly RSV detection was also significantly associated with mean PM_{10} (air pollutants) concentration of the week before. The associations between RSV infection rate and these meteorological parameters mentioned above could be used to predict RSV seasonal pattern in these areas (Tang and Loh, 2014). The negative correlation between RSV outbreaks and temperature could be due to the fact that as a lipid-enveloped virus, RSV survival decreases as the temperature rises affecting the state of viral proteins and the virus genome integrity (Tang, 2009).

However, the seasonality of RSV in subtropical and tropical regions presents a more complicated picture. The associations between RSV infection rate and climate factors are variable and inconsistent (Tang and Loh, 2014). A 15-year (1998-2012) retrospective epidemiological study conducted in Hong Kong (subtropical area) revealed that RSV was predominant in the spring and summer (from April to August) among hospitalised patients (Chan et al., 2015). Thus, RSV immune-prophylaxis for children in Hong Kong who are at high risk should cover recipients at least during this period. The presence of RSV was associated with several meteorological factors: RSV activity was significantly lower with mild temperature (20°C) while higher at cold and warm temperatures; high RSV activity was also observed during short sunshine duration (4-6 hours); virus activity was lower when there was a low level of rainfall (0-50 mm/day). Although there is variation of RSV

incidence year by year, the seasonality of RSV in Hong Kong and other subtropical areas is still relatively predictable. One article investigated the monthly RSV activity and its associations with several meteorological parameters (average monthly minimum temperature, average monthly maximum temperature, relative humidity, precipitation) in 7 subtropical and tropical areas: Bangladesh, China, Egypt, Guatemala, Kenya, South Africa and Thailand (Haynes et al., 2013). The month of onset, peak month, and duration of RSV infection varied across different countries, but, in general, were consistent within each country during the multiple year surveillance period. However, their associations with climate factors varied across both geographical sites and study years. There were one or two annual epidemic periods of RSV circulation in each study site. In countries where there is a generally high annual precipitation (>14 inches by month), such as in Bangladesh, Guatemala and Thailand, the RSV peak was usually observed in wet and warm months during the rainy season (above average temperature and relative humidity). In countries where they have moderately hot and arid climates (China and Egypt), RSV infection rate was highest in cooler months (below average temperature). RSV peaked during autumn in South Africa and there was no clear association with weather seasonal patterns observed in the Kenya site. However, these observations of correlations between climate parameters and RSV activity are limited to the participating surveillance sites and may not be generalisable to other areas. The high RSV activity after the precipitation peak was also observed in other study sites with high annual precipitation. This might be because during rainy seasons, people tend to stay indoors which contributes to indoor crowding and facilitates RSV transmission. This hypothesis was discussed in a study in Bangladesh where some evidence of the association between rainfall and risk of acute respiratory infection was observed in a 3-month surveillance in young children (Murray et al., 2012b). Although the mechanism of the association between temperature and RSV activity was well described in temperate areas (as mentioned above), there is no conclusive explanation to this in subtropical and tropical regions.

There have been several possible mechanisms proposed to explain the seasonality of viral respiratory tract infection. One article discussed four potential mechanisms and proposed that the underlying mechanism is likely to be that the lower temperatures or host chilling may activate the viruses in the respiratory tract, which is compatible with the phenomenon that the virus arrives simultaneously across different geographical regions (Shaw Stewart, 2016).

Understanding RSV seasonality across widespread geographic regions and predicting the onset of RSV season based on meteorological parameters in these regions could provide evidence-based guidance. It could help to formulate a cost-effective strategy to implement

immune-prophylaxis or the targeted delivery of future efficacious and safe RSV vaccines on high-risk populations as well as to apply early antiviral treatment to minimise RSV transmission. Further monthly continuous surveillance data across large geographical locations during a long-term period are needed and would enable improved modelling of the associations between climate parameters and RSV activity, and description of the seasonal pattern of RSV circulation.

1.2.6 Clinical specimen and laboratory diagnosis of RSV

Diagnosis based on clinical features alone will not suffice because the presentation of RSV infection is indistinguishable from other viral respiratory infections. Timely diagnosis of the associated (or causal) pathogen in cases with respiratory infection is of great public health importance. It provides an evidence base for optimal RSV management and treatment. Health professionals could implement appropriate infection control measures to reduce child morbidity and mortality caused by RSV, and at the same time decrease excessive testing and antibiotic use.

The microbiologic confirmation of RSV infection is based on detection of the virus in samples obtained from nasopharyngeal cavity. Most samples come from nasopharyngeal aspirate (NPA), nasopharyngeal wash (NPW), nasopharyngeal swab (NPS), oropharyngeal swab (OPS), nasal swab, nasal wash or a mix of specimens. Nevertheless, virus detection in the nasopharyngeal cavity might also indicate a co-incidental upper respiratory infection. Thus, conducting aetiological studies comparing the virus detection in children with ALRI with control children might be able to elucidate the percentage of ALRI cases attributable to RSV in a causal way. Clinical specimens could also be obtained from the lower respiratory tract, such as induced sputum. However, it is difficult to get specimens from this site and it is hard to distinguish whether the virus detection is due to prolonged shedding or colonisation from infection (Ruuskanen et al., 2011). Using different specimens for RSV diagnosis might account for some variations in findings across different studies. Nasal swabs have been reported to have a lower sensitivity of detecting RSV compared to NPA, although the results were comparable to those for other common respiratory viruses (Heikkinen et al., 2002). Another study in adults showed that NPW, NPS and OPS sampling methods shared the same sensitivity for RSV identification. However, for detection of any respiratory virus or some other specific viruses, such as influenza, rhinovirus and coronavirus, NPW samples had a higher sensitivity than NPS, which was more sensitive than OPS (Lieberman et al., 2009).

There are various laboratory methods with differing sensitivity and specificity available to diagnose RSV infection, which include cell culture, antigen-based assays, serology and

molecular assays (polymerase chain reaction). Cell culture was the gold standard for the respiratory virus identification for many years. Since it has several disadvantages (listed in Table 1), molecular assays have now become the new gold standard (Henrickson, 2004, Henrickson and Hall, 2007). Table 1 displays the advantages and disadvantages of each diagnosis method. This supports one of the selection criteria that studies using serology as the only diagnostic test will be excluded, which was applied consistently in the following systematic reviews.

Table 1: Comparison of different diagnosis methods (Henrickson and Hall, 2007)

	Advantage	**Disadvantage**
Cell culture	Ability to detect coinfections; Monitor new mutations (genetic and antigenic change); Discover unknown viruses; High sensitivity (but lower than molecular assays);	Require special specimen handling procedures; Long assay time (2 to 5 days); Large financial and laboratory cost;
Antigen-based assays	Inexpensive; Easy to perform; Easy to interpret; Results ready within 2-4 hours;	Insufficient sensitivity and specificity, especially during off-season or in special population (immunocompromised, the elderly);
Serology	Provide sero-epidemiologic information;	Falsely negative (10-30%);
Molecular assays	High sensitivity and specificity; Relatively fast diagnosis (2-24 hours);	Risk of contamination; Not available in most clinical laboratories;

There are two different categories of antigen-based assays: immunofluorescence assays (IF) and commercially available rapid antigen-detection test (RADT). The former is based on microscopic detection of viral proteins via labelled antibodies and the latter one is based on macroscopic detection of colour change. IF includes direct immunofluorescent antibody test (DFA) and indirect immunofluorescent antibody test (IFA) depending on whether the observed signal is from the antibody binding directly on the viral protein or from the antibody targeted at the antibody binding viral protein. RADT is easy to use, does not require professional laboratory technicians, and the results can be ready within 30 minutes, which makes it widely used. RADT for RSV detection has three formats: immunochromatographic (ICR) tests, enzyme immunoassays (EIA) and optical immunoassays (OIA) (Prendergast and Papenburg, 2013). The principle underlying these three formats is similar. If the patient's clinical specimen contains viral proteins, a macroscopic colour change will be observed. The

colour change is incurred by the binding of viral antigen from the sample to the RSV specific antibodies in the test. The process of these three formats are displayed respectively in detail in Figure 4, Figure 5 and Figure 6. Generally, RADT has been reported to have a lower sensitivity compared to PCR or viral culture, but has a consistently comparable specificity (Kanwar et al., 2015, Tuttle et al., 2015). There were several other variables which might affect the performance of RADT: the age of children, quality of specimens and administration of palivizumab. The virus load from nasal secretions decreases with the age of children, which lowers its sensitivity. Palivizumab might interfere with the RSV detection by RADT (Prendergast and Papenburg, 2013). Therefore, children with a negative RADT result should be interpreted with caution and another more sensitive test (PCR) should be carried out to confirm those negative cases. In spite of these disadvantages, the feasibility of rapid diagnosis of RSV infection at the point of care has shown a few advantages of RADT: it can decrease the number of unnecessary tests, limit the use of antibiotics, lead to early implementation of infection control measures and decrease the RSV morbidity and mortality in infected children (shorter hospital stay). In addition, rapid multiplex point of care antigen detection tests for several respiratory viruses are becoming available.

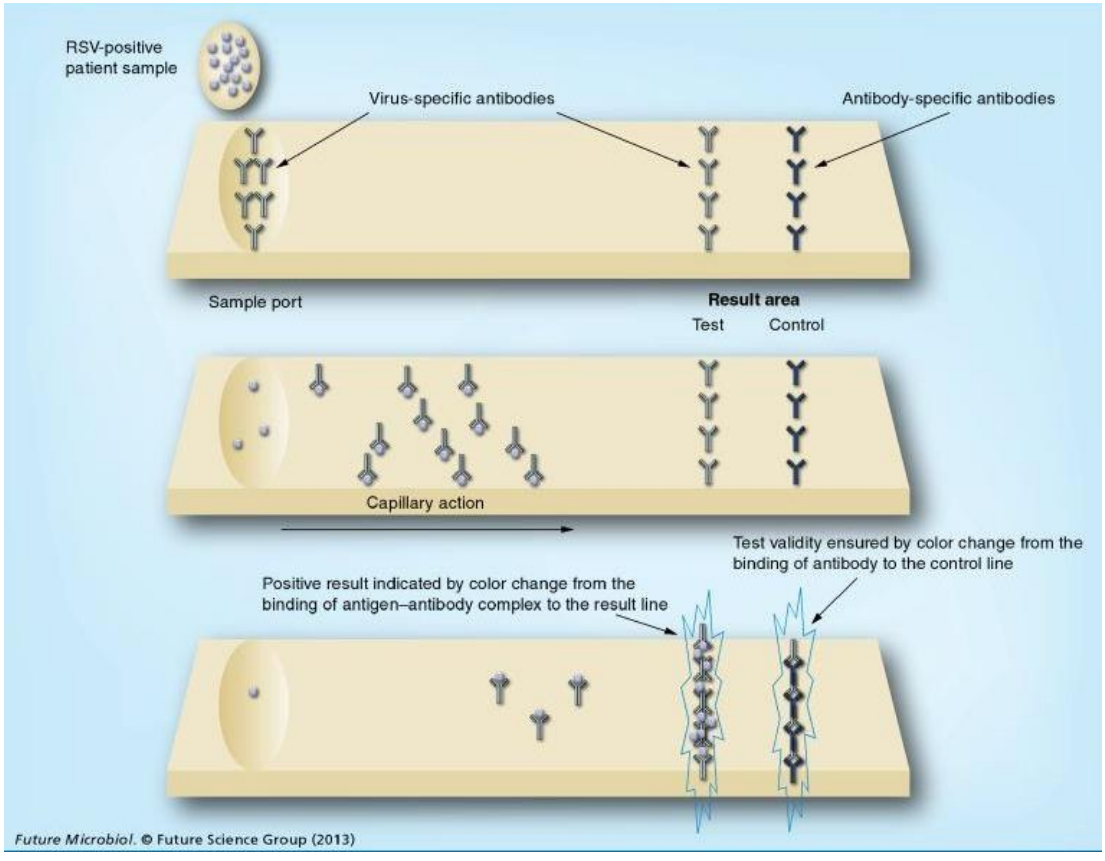

Figure 4: Immunochromatographic rapid diagnostic test for RSV (Prendergast and Papenburg, 2013)

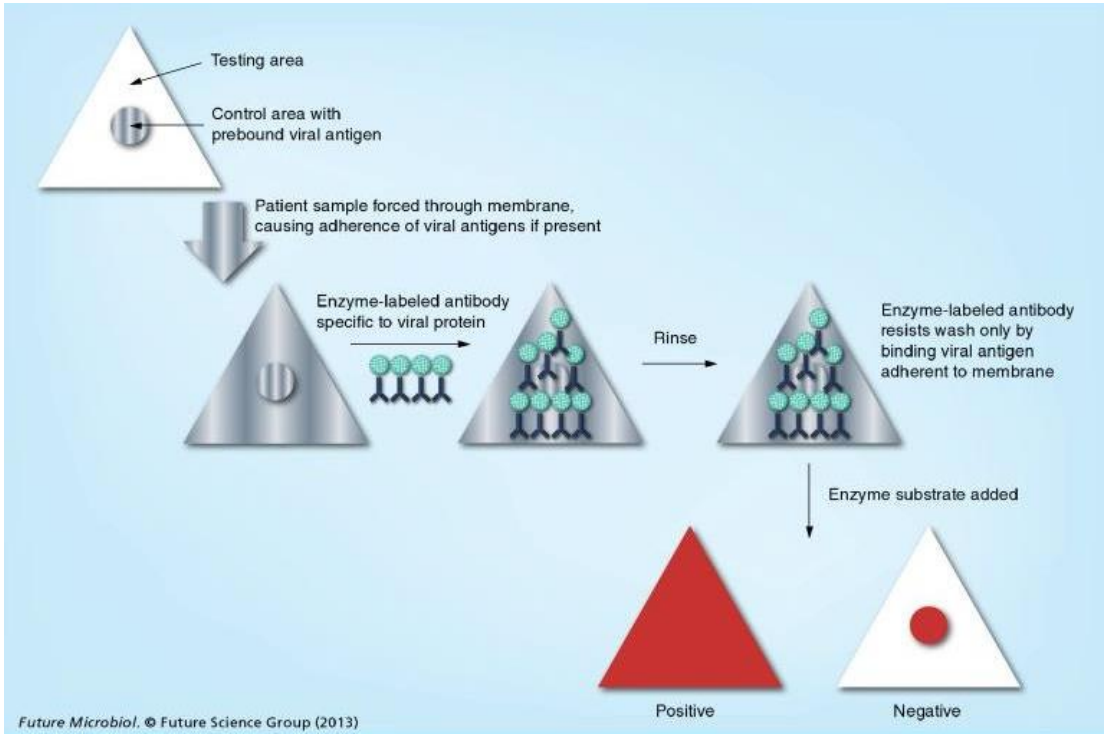

Figure 5: Enzyme immunoassay rapid diagnostic test for RSV (Prendergast and Papenburg, 2013)

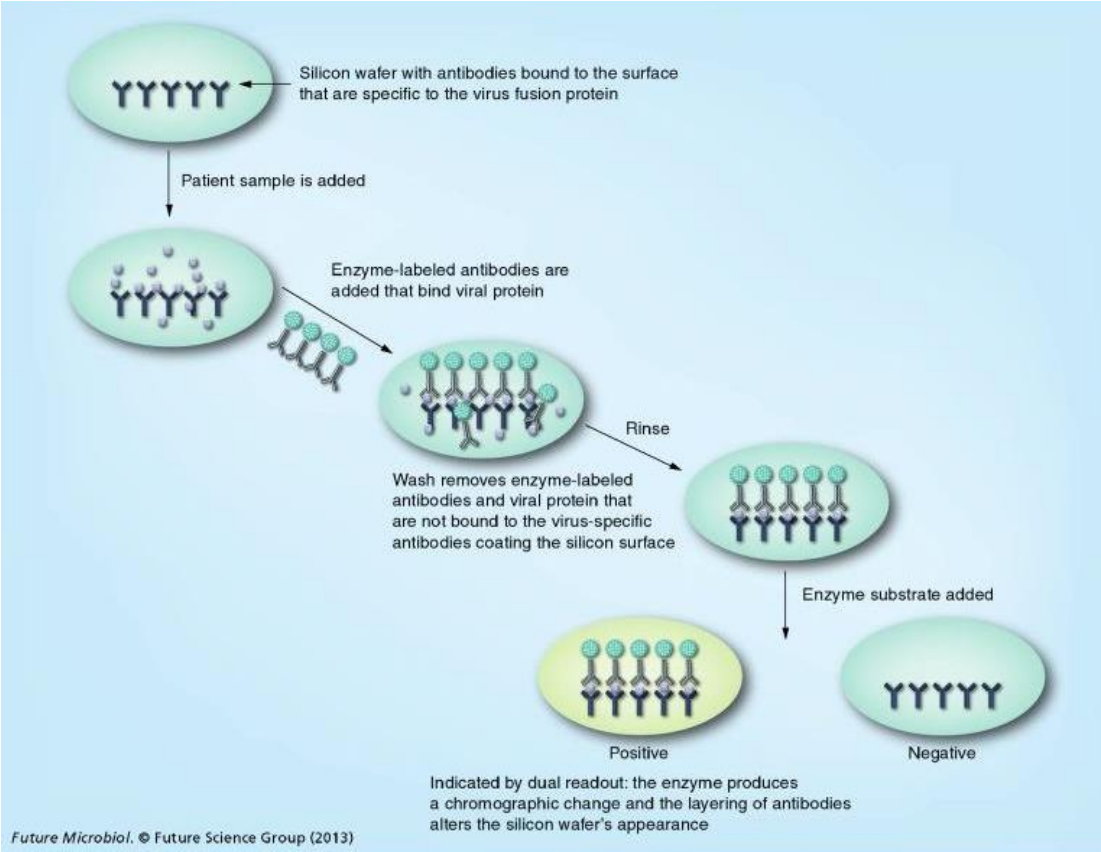

Figure 6: Optical immunoassay rapid diagnostic test for RSV (Prendergast and Papenburg, 2013)

1.3 Other common respiratory viruses

RSV is the most commonly identified virus in young children with ALRI, contributing to a substantial morbidity and mortality (Nair et al., 2010). However, at least 25 other viruses have been described to be associated with community-acquired pneumonia, most notably – influenza, PIV, hMPV, rhinovirus, bocavirus, adenovirus and coronavirus (Ruuskanen et al., 2011).

Influenza, parainfluenza (PIV) and human metapneumovirus (hMPV) are also frequently identified in children hospitalised with respiratory infection (Nair et al., 2011, Feikin et al., 2013, Singleton et al., 2010). Globally 20 million new episodes of influenza associated ALRI were estimated to occur in children younger than 5 years in 2008, and around 1 million of them were severe enough to warrant hospitalisation (Nair et al., 2011). PIV was the second most commonly detected virus after RSV in young Alaskan children hospitalised with respiratory infection, and hMPV was associated with a higher severity of respiratory infection (Singleton et al., 2010). The hospitalisation rate of hMPV infection among children younger than 5 years old from three counties in the US was estimated to be around 1 per 1000 children per year (Edwards et al., 2013). This was translated into approximately 20,000 hospitalisation cases with hMPV infection in young children. The hospitalisation rate was 3 and 2 per 1000 children per year for infants aged 0-5m and 6-11m respectively. Compared to children hospitalised without hMPV infection, children with hMPV disease were older, more likely to have diagnosis of pneumonia or asthma, more likely to require oxygen supplementation and to have a longer length of intensive care unit (ICU) stay. The rates of hMPV illness associated with outpatient visits and emergency department visits were 55 and 13 per 1000 children per year, which meant there were around 1 million outpatient visits and 263,000 emergency department visits associated with hMPV infection every year. The hospitalisation rate of PIV associated acute respiratory illness was estimated as 1 per 1000 children per year in children less than 5 years old based on New Vaccine Surveillance Network (NVSN) (Weinberg et al., 2009). The rates were 3.0 and 1.7 per 1000 children per year respectively in younger age groups (0 to 5 months and 6 to 11 months). This was projected to around 23,000 hospitalisations associated with PIV infection among young children.

However, their aetiological roles in young children with ALRI remain uncertain and there have been no systematic reviews published that investigated this before this thesis. Moreover, co-infection of multiple viruses has been commonly described in childhood ALRI, which

necessitated the supportive research into other common viruses to have a better estimation of RSV disease burden in young children.

1.4 Clinical significance of this study

Therefore, it is important to understand the attributable roles of these common respiratory viruses to ALRI. This thesis aims to conduct a thorough review to identify available case control studies investigating the potential roles of respiratory viruses in the aetiology of ALRI in children younger than five years old. The high incidence of RSV infection as well as its potentially severe outcome, make it important to identify and prioritise children at high risk of developing RSV associated ALRI. There have been no recent comprehensive systematic reviews exploring studies in the recent years which investigated the risk factors for RSV associated ALRI in young children. Understanding children at increased risk will provide an evidence basis to inform policy makers about prevention strategies and priority for vaccine allocation. Moreover, the global and regional burden of RSV disease in the younger age groups, especially in neonates and children in their first six months of life, has not yet been reported. Prompt and up-to-date estimates of key parameters of RSV epidemiology, such as incidence pattern and mortality by age and in different geographical settings, is critical to inform prevention and management strategies. Resource allocation and political support for the introduction of prevention strategies will also depend on good-quality local epidemiological data. Therefore, it is necessary and important to study the epidemiology of RSV associated ALRI in young children to better inform national and international policy making. This thesis aims to focus on children younger than five years old since this is the age group where most RSV cases occur and this represents a large disease burden as discussed above.

1.5 Aim

To estimate the epidemiology (incidence, mortality, risk factors etc.) of RSV associated ALRI in children younger than 5 years old.

1.5.1 Specific objectives

- Investigate the aetiological role and attributable fraction of common respiratory viruses among ALRI cases (including RSV) in young chidlren
- Investigate the risk factors for RSV associated ALRI in children younger than 5 years old
- Estimate the incidence rate and number of new cases of RSV associated (severe) ALRI in children younger than 5 years old in community settings, stratified by different regions and age groups
- Estimate the number of hospitalised cases of RSV associated ALRI in children younger than 5 years old in hospital settings, stratified by different regions and age groups, using two different approaches:
    - A hospitalisation rate-based approach using hospital-based studies with a clear and well defined denominator population reporting hospitalisation rate;
    - A proportion-based approach using hospital-based studies without a clear and defined denominator population reporting proportion of hospitalised ALRI cases which are RSV positive coupled to population-based estimates of ALRI hospitalisation rates
- Estimate the hospitalisation rate and number of cases of RSV associated very severe ALRI, cases with hypoxemia, cases requiring ICU admission or mechanical ventilation in children younger than 5 years old in hospital settings
- Estimate in-hospital case fatality ratio and mortality from episodes of RSV associated hospitalised ALRI in children younger than 5 years old in hospital settings, stratified by different regions and age groups
- Estimate number of deaths in community from episodes of RSV associated ALRI in children younger than 5 years old
- Estimate the disease burden associated with RSV-A and RSV-B separately

Chapter 2 Overall methods

2.1 Literature search

Systematic reviews were carried out separately for the following three research questions: aetiological roles of common viruses in ALRI, risk factor of RSV associated ALRI and global burden of RSV associated ALRI. They all focused on children younger than five years of age, formulating an overall picture of epidemiology of RSV associated ALRI in young children. The searches were conducted across several databases based in different languages (English, Spanish and Chinese): Medline (Ovid), Embase, Global Health, LILACS, CINAHL, Web of Science, WHOLIS, IndMed, grey literature (SIGLE), and three Chinese language based databases: China National Knowledge Infrastructure (CNKI), Wanfang data and Chongqing VIP. Another researcher was involved in the process of each systematic review (except the three Chinese language databases), according to PRISMA guidelines for systematic review and meta-analysis (Moher, 2009), and carried out the search independently. According to each research question, a search strategy with key words was developed and the search was performed by two investigators separately. After obtaining all records from the literature search, duplicate articles were removed (same articles identified in different databases or different articles reporting data with overlapped study period from the same study site). Titles and abstracts of non-overlapping articles were read to select studies reporting data of interest. The selection process was based on pre-defined eligibility criteria (inclusion and exclusion criteria). Afterwards, full texts of relevant studies were obtained, reviewed and assessed for qualification. This whole process was displayed in a PRISMA flow diagram (Moher, 2009) showing the number of studies assessed in each step and reasons for any exclusion. The PRISMA contained four major steps: identification, screening, eligibility and inclusion. The list of included articles was compared between two independent investigators and the discrepancies between them were discussed. Any discordance or uncertainties regarding relevance or inclusion were arbitrated by the supervisors for this thesis: Prof Harry Campbell and Dr Harish Nair. The author's first language is Chinese (Mandarin) and second language is English with limited proficiency in Spanish, which makes literature search in databases containing several languages feasible. Google translate was used for articles written in other languages when this was necessary (during full-text review stage).

After the list of included studies was agreed on, relevant data as well as the characteristics of the studies were extracted by each investigator using a standardised data extraction template,

which was designed on Microsoft Excel (Microsoft Office 2007). Similarly, the process was carried out independently. The information and data were compared and cross-verified by two investigators before inclusion in further analysis.

2.2 Unpublished data collection

In order to collect unpublished data across the world, especially from developing countries, my supervisors, Dr Harish Nair and Prof Harry Campbell established RSV Global Estimates Network (RSV GEN). The working group consisted of 45 leading researchers on paediatric pneumonia identified through extensive consultations with subject experts or publication track record. Common case definitions were formulated and a standard approach for data collection, analysis and interpretation was agreed on with collaborators. They either reanalysed data from their already published work with these standardised case definitions or shared hitherto unpublished data from on-going studies.

Two data collection templates designed on Microsoft Excel (Microsoft Office 2007) were sent out by Dr Harish Nair. One included nine sheets covering the main features of the study site and results about RSV positive cases: site description, RSV incidence, gender analysis, RSV proportion, morbidity and mortality (all) by month, morbidity and mortality in children with gestational age 32-36 weeks by month, morbidity and mortality in children with gestational age <32 weeks by month, risk factors for mortality and risk factors for morbidity. The details within each sheet were listed in the Appendices - A1. If the study site had number of RSV associated ALRI cases for at least 12 continuous months as well as a clear and well-defined denominator of the population at risk (in hospital or in community settings), variables necessary to calculate an incidence rate or hospitalisation rate of RSV associated ALRI were provided (in this case, the "RSV proportion" sheet was left empty). If the study site did not have a clear and well-defined catchment area with population number, proportion data were collected instead: proportion of hospitalised ALRI cases with RSV positive ("RSV incidence" sheet was left empty). The data were also required to have a study period of at least 12 continuous months. Overall, the number of RSV associated ALRI cases (including severe and very severe cases) and mortality data were collected as well as other details (proportion of eligible ALRI cases being tested, RSV subtype data, proportion of cases with hypoxemia etc.). If an aetiological study exploring the association between certain risk factors and RSV associated ALRI was also available, the data were collected as well. Another data collection template including site description, verbal autopsy confirmed pneumonia deaths and RSV seasonality data (number of RSV positive cases and number of submitted specimen for laboratory testing) was circulated to collect relevant data to build a

model to estimate RSV mortality in the community. These data were required to cover a minimum continuous period of 36 months. More details were available in Appendices - A2.

Another three documents were also sent out to assist the data collection process: the first contained definitions for a few variables: case definition of ALRI (including severe and very severe cases) in community and hospital settings respectively, definition of hypoxemia, and definition of primary endpoint pneumonia (PEP); the second contained guidelines for populating the RSV data collection template (first excel document); the third one contained guidance notes for populating the mortality data template (second excel document).

Data from unpublished studies provided by RSV GEN collaborators were reviewed for quality and inconsistencies. Data across different sheets were compared and checked. A few Skype meetings were arranged with local researchers or principal investigators if there were a number of queries. Email communications were established with study sites to request missing data in the data collection templates, clarify inconsistencies and double check selected details. Studies were included only after the data were cleaned. Then the data from all included unpublished studies were extracted into a standardised data extraction form (the same as the one used for collecting data from published articles). Afterwards, all information and data from both published articles identified through the systematic search and unpublished studies provided by RSV GEN collaborators were combined and included in a further analysis. This method resulted in a substantial contribution from unpublished studies, especially in finer age bands (infants, children in the first six months of life or neonates), which supplemented the lack of these data from published literature significantly.

Two RSV GEN conferences were arranged to gather all collaborators and stakeholders to discuss the possibility of collecting unpublished data, availability of RSV data from their study sites, ways of collecting unpublished data (standardised case definitions), issues raised in the data collection process, results of interim analysis and suggestions proposed for further analysis. The first conference was held from 4th to 6th November in 2013 in Edinburgh. Over 45 investigators from across the world participated in the meeting and agreed to share their data to contribute to the estimation. The second was on 22nd - 24th June 2015 in Edinburgh. Interim results were presented, feedback from working group was collected and further plans to share data on other common respiratory viruses (PIV and hMPV) were discussed.

Overall, 76 unpublished studies met the selection criteria. The data were collected and included in further assessment and analysis. Another 8 unpublished studies were excluded for the following reasons: less than 50 ALRI cases were enrolled (reporting proportion),

serology was used as the only diagnostic test, proportion data were only provided in outpatients, less than one year of study period, and unclear study design.

2.3 Definitions

2.3.1 Definition of ALRI

RSV associated ALRI was used as the primary outcome of interest (Nair et al., 2010), which includes clinical pneumonia and bronchiolitis. This was to recognise their common manifestations in young children with viral ALRI (Wagner, 2009), and the limitations of the WHO case definition to reliably differentiate bronchiolitis from pneumonia (World Health Organization, 2013a). Data from community-based studies with active ascertainment (health care workers visited house-to-house to identify cases) were included. ALRI was defined as cough or difficulty in breathing with age-related tachypnoea (WHO Integrated Management of Childhood Illness (IMCI) case definition cut-offs: respiratory rate >60 breaths per min in children aged <2 months, >50 breaths per min in children aged 2-11 months, and >40 breaths per min in children aged 12-59 months). Severe ALRI was defined as cough or difficulty in breathing with lower chest wall indrawing for children aged 2-59 months; or an increased respiratory rate (>60 breaths per min) or chest wall indrawing for children aged less than 2 months. Very severe ALRI was defined as a child with cough or difficulty in breathing and with at least one WHO IMCI danger sign (cyanosis, difficulty in breastfeeding or drinking, vomiting everything, convulsions, lethargy, unconsciousness or head nodding) (World Health Organization, 2005). Very severe ALRI was considered as a subgroup of severe ALRI, which was considered to be a subgroup of ALRI. Data from hospital-based studies with passive ascertainment (parents or carers seek help in hospitals) were included. In this case, only children with a physician confirmed diagnosis of ALRI that were hospitalised or recommended hospitalisation were included. Thus, this group comprised children with ALRI or ARI severe enough to require hospital admission. Very severe ALRI was defined as hospitalised ALRI with one danger sign (cyanosis, difficulty in breastfeeding or drinking, vomiting everything, convulsions, lethargy, unconsciousness or head nodding), or hypoxemia (see case definition below; proxies for hypoxemia included – the child receiving mechanical ventilation or ICU admission). Very severe ALRI was considered to be a subgroup of hospitalised ALRI.

2.3.2 Definition of hypoxemia

Hypoxemia was defined variably depending on altitude and age group. For areas at altitude ≤2500m, oxygen saturation (at sea level in room air) lower than 90% (measured by pulse oximetry) in children aged 1-59 months and lower than 88% in neonates was classified as

hypoxemia. For areas with altitude above 2500m, oxygen saturation lower than 87% in children aged 1-59 months and lower than 85% for neonates was classified as hypoxemia.

2.3.3 Definition of regions

Countries were classified into 6 WHO regions or 4 regions according to World Bank income levels (World Bank, 2016, World Health Organization, 2016c). Countries were also categorised as "developing" or "industrialised" according to the "Levels & trends in child mortality - report 2014" by UNICEF (United Nations Children's Fund, 2014). The child population estimates by region for 2015 were provided from the UNICEF report (personal communication). The UNICEF report provided population numbers of children under five years old and of infants. Population number in children of 0-5 months of age was generated by dividing the number of infants evenly; same approach for children in the age group of 6-11 months.

2.4 Statistical analysis

2.4.1 Data standardisation

Relevant data from the included studies (published articles and unpublished studies) were extracted into a standardised template. Data were standardised and reported using a common parameter (in odds ratio or rate) and unit. If summary data were not available, they were calculated from the original input data provided in the studies (or in the supplemental documents) if possible. An odds ratio or rate with 95% confidence intervals were extracted or calculated from included studies. The rate was reported in the unit of per 1000 children per year. When there was a proportion of ALRI cases which were not tested for pathogen, the number of RSV associated ALRI cases was scaled up according to this proportion. This is based on the assumption that ALRI cases which were not tested have a similar rate of RSV detection.

2.4.2 Handling of zero values

Whenever there was no cases or deaths reported in the studies, it led to odds ratio calculation or rate calculation of zero. Combining such data into a subsequent meta-analysis can be problematic. Therefore, a continuity correction of a constant number 0.00005 was applied to replace zero cells. This allowed further calculation not to be zero (but close to zero enough) and enabled inclusion of these studies to subsequent meta-analyses.

2.4.3 Meta-analysis

Using STATA (version 11.2), meta-analyses of outcome of interest (attributable fractions of common respiratory viruses, associations between risk factors and RSV associated ALRI, incidence rate, hospitalisation rate, in-hospital CFR, proportion etc.) were carried out separately, and were reported as pooled estimates with corresponding 95% CIs based on random effects model (DerSimonian-Laird method) (Borenstein et al., 2009). Significant heterogeneity was assumed among included studies (Dersimonian and Laird, 1986) since they differed substantially in study settings, study designs, case ascertainment methods, population under study, socioeconomic status of underlying population, clinical specimens submitted for laboratory testing and diagnostic tests. Subgroup meta-analysis was also carried out to estimate the outcome in different regions (by World Bank income level, by WHO region, developing or industrialised countries), in different age groups (children in the first six months, infants or children aged 0-59 months) and in other categories of interest.

2.4.3.1 Fixed effect and random effects models

Under the fixed effect model, there is only one common effect size for all included studies and all observed dispersion of effects are due to sampling error (within-study variance), which would be zero if the studies had infinitely large sample sizes. Under the random effects model, there is a distribution of true effect sizes for underlying included studies and the differences of observed effects are due to both sampling error (within-study variance) and true variation in effect sizes across studies (between-study variance) (Borenstein et al., 2009). The summary effect under the fixed effect model represents our estimate of this common effect size while under the random effects model it represents the mean of the distribution of true effect sizes.

Study weights are assigned to each study with the goal of minimizing the variance: within-study error in the fixed effect model and both within-study error and between-study variance under the random effects model. They are reflected in the size of box (area) as shown in the forests plots in Appendices. The random-effects will distribute the study weights more evenly (more balanced): a large study has less influence on the summary effect (relatively less weight); a small study has more impact than it would have under the fixed-effect model (relatively more weight). Confidence intervals for the summary effect will tend to be wider under the random effects model since it incorporates both within-study variance and between-study variance (larger variance and standard error) (Borenstein et al., 2009). The power for meta-analysis under the fixed effect model is related to the total number of

subjects across all included studies while under the random effects model, it is driven by both the total number of subjects enrolled and number of studies included in the analysis.

The selection of a computational model should be based on the understanding of the underlying distribution, the context and the characteristics of the included studies, as well as the goal in performing the analysis (Borenstein et al., 2009). Since this series of studies were conducted by different researchers, in different study settings with different methods applied, it suggests that they have differed in certain ways that would have impacted on the outcome. Moreover, the goal of carrying out meta-analyses is mostly to generalise the result to a range of other scenarios. This function is limited under the assumption of fixed effect model. Since studies were identified from the literature review of published articles and unpublished datasets across different settings, the random effects model was selected, and it has been used consistently in the following chapters.

2.4.3.2 Quantify heterogeneity across studies

The observed dispersion in effect sizes across studies includes both random error and true variance (dispersion in true effect sizes). There were three ways to isolate and quantify the heterogeneity of true effects across the included studies: Q statistic (weighted sum of squared deviations on a standardised scale) with a statistical test based on Q (p-value), between-study variance of the true effects (T^2) and between-study standard deviation (T), and the proportion of total observed variation due to true heterogeneity (real differences in effect sizes) (I^2) (Borenstein et al., 2009). The Q method serves as a test of significance and depends on the number of studies and magnitude of effect (just as the significance test in a primary study). Thus, a non-significant p-value result should not be interpreted as that the included studies share a common effect size. There is a possibility that a substantial amount of dispersion exists but it is not successfully identified due to the low statistical power of the test (imprecise studies or small number of studies included). The T^2 and T method measures the absolute value of the true variation of the true effects. The I^2 method indicates the ratio of these true differences to the total observed variance and it ranges from 0% to 100%. It is particularly useful to quantify the heterogeneity across studies using different effect size indexes to measure the outcome (e.g. odds ratio in one study while mean difference in another study). The latter two parameters are calculated based on Q statistic and are independent from number of studies. They each serve to define and quantify the heterogeneity of underlying true effect sizes across included studies from different aspects. I^2 and p-value are selected to display in the forest plots of the following meta-analyses to

indicate the heterogeneity between studies. The 25%, 50% and 75% cut-off values of I^2 are considered to have low, moderate and high heterogeneity respectively (Higgins et al., 2003).

2.4.3.3 Subgroup analysis

Subgroup meta-analysis means a meta-analysis is performed stratified by one (or several) group membership. The analysis is based on groups of studies rather than groups of subjects, but they share the same logic of test and calculation process. Fixed effect model means that all studies within a subgroup share a common effect size while the random effects model indicates that there is a distribution of true effect sizes within each subgroup. Similarly, random effects model has been used in the following chapters due to significant heterogeneity within subgroups were expected. The group membership of interest in this thesis is WHO regions, regions stratified by World Bank income level, developing or industrialised regions.

2.4.3.4 Sensitivity analysis

Sensitivity analyses were used, if necessary, to exclude or include certain studies, to explore how results might have changed if different study inclusion rules had been used: younger age group was focused on, exclusion of studies with less than one-year study period, exclusion of "low quality" studies, exclusion of studies using specific (different) case definitions, inclusion of studies focusing on aboriginal population and exclusion of studies with small sample size. The roles of different study selection criteria were assessed in these sensitivity analyses.

2.4.3.5 Forest plot

The results of each meta-analysis, subgroup analysis and sensitivity analysis were shown in the visual figures (forest plots). In the forest plots, each study as well as the summary effect are depicted as a point estimate (a square or a diamond) bounded by its confidence interval (horizontal line). The location of the squares (or diamonds) indicates the direction and magnitude of the point estimate. A vertical line of x=1 was depicted if the effect size was measured in odds ratios. This is to show whether the confidence interval of odds ratio from each study (and the summary effect) is significant. The test for heterogeneity of true effect sizes cross studies was carried out and reported in the same figure. They were summarised in the parameters of I^2 and p-value. In subgroup analysis, the forest plots showed similar results, except that both summary effect from each subgroup and summary effect for all studies were reported.

2.4.3.6 Commands used in STATA

All meta-analyses were carried out based on the command “metan” in STATA. This program was used to pool statistics of interest into one summary value, such as associations (odds ratio), one-dimensional continuous measures (incidence rate) or binomial measures (proportion), with assumption of approximation to the normal distributions. However, for proportion data, their confidence intervals may contain inadmissible statistics on assumption of normal distribution based on the asymptotic variance, especially when the values are at the margins. “Metaprop” is a newly developed statistical STATA program adapted from “metan” and it is implemented to perform meta-analyses of proportions (Nyaga et al., 2014). “Metaprop” carries out procedures which are specific to binomial data (proportions) and allows computation of exact binomial or score statistic based 95% confidence intervals for the individual studies. It also incorporates Freeman-tukey double arcsine transformation to compute the pooled estimate or uses the binomial distribution to model the within-study variance. The latter one is only available in STATA 13 and later versions. “Metaprop” has two advantages which are the limitations of conducting meta-analyses based on “metan” command: margin values or close to boundary values of proportion are capable to be included (no need for continuity correction); admissible confidence intervals (0-1) are computed for individual studies as well as summary effect. Therefore, by using “metaprop”, no studies with 0% or 100% proportions were excluded from the meta-analysis. On the contrary, a continuity correction of a constant number is applied to the boundary values to retain them in meta-analyses while using the “metan” command, just as what was mentioned previously in terms of handling zero values. Moreover, study specific and pooled confidence intervals are always within admissible values from “metaprop” program. However, when the sample size is large and the proportion is not around the extremes, the meta-analysis results performed relying on “metan” and “metaprop” commands are similar. Considering that in most included studies, the sample size is large and the proportion data (except a few CFR values) are not the extremes, it was considered appropriate to carry out the meta-analyses based on “metan” command. Furthermore, this program requires a lower level of statistical expertise, involves faster computation, and there is statistical software (STATA or R) available to run the analysis.

Chapter 3 Aetiological role of common respiratory viruses in ALRI in children younger than five years old

3.1 Methods

3.1.1 Literature search

3.1.1.1 Search strategy and selection criteria

A systematic review was performed according to the PRISMA guidelines. Tailored search strategies with corresponding search terms were used to search six databases: Medline, Embase, Global Health, LILACS, China National Knowledge Infrastructure (CNKI), Wanfang Data and Chongqing VIP databases (Appendices - A3). The table of contents of specialist journals – the "*Influenza and other Respiratory Viruses*" and "*Pediatric Infectious Diseases Journal*", and the reference lists of relevant papers were further hand searched for eligible articles. All searches were limited to between January 1st, 1990 and April 4th, 2014, and no publication status or language restrictions were applied. Eligible studies were observational studies that reported proportions of at least a specific virus of interest in both children with ALRI and children in control group. Table 2 shows the selection criteria in more detail. Data from included studies were extracted using a standardised data extraction form designed on Microsoft Excel (Microsoft Office 2007).

Table 2: Selection criteria applied in the systematic review of aetiological role of common respiratory viruses in ALRI

Inclusion criteria:
• Published from Jan 1st, 1990 and Apr 4th, 2014 (Mar 19th for three Chinese databases)
• Study design - observational studies (case-control or cohort)
• Provide data for children younger than 5 years
• Case group should be children with a diagnosis of clinical pneumonia or low respiratory infection
• Control group should be children without ALRI (children with upper respiratory infection, children without any respiratory symptoms or healthy children)
• Respiratory specimens were collected and diagnostic tests were conducted using valid laboratory methods
• Report results on virus-specific proportions respectively in case group and control group
Exclusion criteria:
• Definitions used for ALRI or clinical pneumonia, not clearly stated or inconsistently applied

Following PRISMA guidelines, another researcher (Kenneth McLean, BMedSci) conducted an independent search in English language databases (Medline, Embase, Global Health and LILACS) and extracted data using the same standardised data extraction template. Any discordance and/or uncertainties regarding to relevance or inclusion were arbitrated by my supervisor for this thesis (Prof. Harry Campbell and Dr Harish Nair).

3.1.2 Unpublished data collection

For this review, no unpublished data were collected. However, for some studies which didn't provide complete data in the published articles, the first author was contacted and relevant data were requested.

3.1.3 Definition of case group and control group

"ALRI", was used as an equivalent to clinical pneumonia as the case definition, which included both pneumonia and bronchiolitis. This was to recognise this common manifestation in young children with viral ALRI (Wagner, 2009), and the limits of the WHO case definition to reliably differentiate these (World Health Organization, 2013a), as explained and detailed in the Chapter 2 - Methods. The case group was defined as children with ALRI, which was characterized as cough or dyspnoea with age-related tachypnoea, while severe ALRI was defined as those with cough or dyspnoea with indrawing of the lower chest wall (in community-based studies), or an acute respiratory infection severe enough to necessitate hospitalisation (in hospital-based studies). The control group was defined as asymptomatic children (children without any respiratory symptoms), healthy children (children without any respiratory symptoms and any other symptoms) or children with upper respiratory tract infection (URTI) (children with respiratory symptoms).

Study sites were classified as from developing or industrialised regions according to the "Levels & trends in child mortality - report 2014" by UNICEF (United Nations Children's Fund, 2014).

3.1.4 Statistical analysis

Relevant data from all included studies were extracted: proportion of viruses reported in both case group and control group. Data were summarised in a standardised way: crude odds ratios (ORs) with accompanying 95% confidence intervals (95% CIs), to facilitate interpretation and comparison. A continuity correction of a constant 0.0005 was applied if a virus was detected in one group, but not the other arm of the study (Sweeting et al., 2004). This allowed calculation of an OR for these instances, and enabled inclusion of these studies within subsequent meta-analyses. Furthermore, matched (mOR) and adjusted (aOR) odds

ratios were also extracted, where possible. These were used preferentially in subsequent calculations and analyses (than crude ORs).

Using STATA (version 11.2) (StataCorp, 2009), a meta-analysis of virus-specific ORs was performed and pooled estimates with corresponding 95% CIs were reported using the random effects model (DerSimonian-Laird method) since significant heterogeneity between included studies were expected in several aspects: study setting, study population, methodology applied and analysis plan (Borenstein et al., 2009). This was discussed in Chapter 2 - Methods. The virus-specific attributable fraction among the exposed (AFE) was used to explore the etiological role of each virus in ALRI patients. This estimates the percentage of (severe) ALRI cases which can be attributed to each virus, in absolute terms, and was calculated as AFE = 100 * (OR-1)/OR with 95% CIs. Its 95% CIs were generated accordingly from the 95% CIs of the OR. Thus, the percentage of all ALRI cases caused by a given virus can be calculated as overall percentage of ALRI cases positive for that virus multiplied by AFE (adjusted percentage (%a) = crude percentage (%c) * AFE), as used in previous work (Singleton et al., 2010). Analysis of subtypes of virus was carried out in the same way if data were available. Meta-estimate of OR and corresponding AFE would be presented in the same table.

The final estimate was based on studies using hospitalised ALRI as the case group and using asymptomatic or healthy children as the control group. Afterwards, two sensitivity analyses were carried out to include data from studies using a different definition for case group or control group: outpatient ALRI cases and symptomatic controls (URTI) respectively. These data were added to generate an overall meta-estimate and the results were presented in the same table in comparison to the previous estimate (final estimate). A sensitivity analysis excluding studies with less than a one-year study period was carried out. Across studies included for the final estimate, subgroup meta-analysis was performed to explore the outcome of interest in different regions (developing and industrialised).

3.2 Results

Overall, 3,619 records were identified through literature search, of which only 23 studies fulfilled the strict eligibility criteria (Adegbola et al., 1994, Banerji et al., 2009, Berkley et al., 2010, Bigogo et al., 2013, Dare et al., 2007, Fry et al., 2007, Hammitt et al., 2012a, Hasan et al., 2014, Mathisen et al., 2010, Singleton et al., 2010, Xie, 2010, Zhao et al., 2013, Ou et al., 2009a, Edwards et al., 2013, Iwane et al., 2011, Jansen et al., 2011, Longtin et al., 2008, Prill et al., 2012, Rhedin et al., 2014, Yoshida et al., 2013, Wolf et al., 2010, Fry et al., 2011, Feikin et al., 2013). Fifty-six studies were reviewed in full texts but excluded for a variety of reasons including: no data specific from children under 5 years old (n=10), not fulfilling the definitions for cases or controls (n=5), no applicable data reported for cases and controls (n=32) and other reasons (n=9). A list of these fifty-six studies with reasons for exclusion is available in Appendices - A4. This selection process is shown in more details in Figure 7. In the end, 23 studies were included into following analysis and discussion. Among them, two were identified from Chinese databases (Ou et al., 2009a, Xie, 2010). Two articles (Berkley et al., 2010, Mathisen et al., 2010) provided different definitions for case group or control group but didn't report the data separately, thus the first authors were contacted and data stratified by different definitions were provided. Overall eight viruses were reported. They are respiratory syncytial virus (RSV), influenza (IFV), parainfluenza (PIV), human metapneumovirus (hMPV), adenovirus (AdV), rhinovirus (RV), bocavirus (BoV), and coronavirus (CoV). Data regarding to subtypes of RSV (RSV-A and RSV-B), IFV (IFV-A, IFV-B and IFV-C), PIV (PIV-1, PIV-2, PIV-3 and PIV-4) and CoV (HKU1, NL63, 229E and OC43) were also available and meta-analysis result was presented if possible.

All included studies were case-control studies and were primarily conducted within developing countries (n = 14). Most of the studies have been conducted since 2003 (n=20). Among these 23 studies, 4 non-overlapped papers were from one research group in Thailand (Dare et al., 2007, Fry et al., 2007, Hasan et al., 2014, Fry et al., 2011) and provided data for several viruses (RV, CoV, BoV etc.). More features of these 23 studies are available in Table 3.

Definitions of cases and controls were pre-defined to select the qualified studies: the definition for the case group was children identified with ALRI, and the definition for the control group was children without respiratory symptoms or children with URTI; however, some variations of the included studies were still present. Of the case definitions employed, most used ALRI/ARI (n=13), while others used (severe) pneumonia (n=8), SARI (n=1) or bronchiolitis (n=1). Of the case ascertainment used, all articles reported children hospitalised

with ALRI in the case group. Among them, three studies also provided data on children from outpatient settings or community based settings separately (Mathisen et al., 2010, Bigogo et al., 2013, Feikin et al., 2013). Regarding the definitions of the control group, all studies included children who didn't have any respiratory symptoms, among which 10 were considered otherwise "healthy", and 2 studies (Hammitt et al., 2012a, Mathisen et al., 2010) also included children with URTI as another control group and reported the result separately. 20 control groups were ascertained in hospital-based outpatient/clinic sites while 3 were identified in community (Mathisen et al., 2010, Singleton et al., 2010, Banerji et al., 2009).

Regarding sampling methods of clinical specimens and diagnosis tests, most studies used nasopharyngeal swab (NPS) (n=10), nasopharyngeal aspirate (NPA) (n=6) and nasopharyngeal wash (NPW) (n=1) as specimens. Five studies used mixed specimens including NPA, NPS, lung aspirate and oropharyngeal swab (OPS). All studies used polymerase chain reaction (PCR) as the diagnostic testing except one study from Gambia (Adegbola et al., 1994), in which case indirect immunofluorescence (IFA) was applied.

Meta-analyses of virus-specific ORs were reported as well as the corresponding attributable fractions among the exposed (AFE). The final estimate was based on studies using children hospitalised with ALRI as the case group and using children without any respiratory symptoms (or healthy children) as the control group (23 studies totally). Forest plots of the final estimate for each virus (with its subtypes) are available in Appendices - A5. Table 4 presents the final result for eight viruses and their subtypes as well as two sensitivity analyses in which case, data from studies using symptomatic controls (URTI) (Hammitt et al., 2012a, Mathisen et al., 2010) and studies using ALRI cases from outpatients setting (Bigogo et al., 2013, Feikin et al., 2013, Mathisen et al., 2010) were added respectively to carry out another two rounds of meta-analysis. From Table 4, RSV, IFV, PIV, hMPV and RV were significantly more common in children hospitalised with ALRI than asymptomatic controls (significant ORs: 9.79 (4.98-19.27) from 13 studies, 5.10 (3.19-8.14) from 10 studies, 3.37 (1.59-7.15) from 11 studies, 3.76 (2.45-5.78) from 10 studies and 1.43 (1.03-1.97) from 11 studies respectively). Thus, these viruses had statistically significant positive AFEs (90%, 80%, 70%, 73% and 30% respectively), which show clear associations between these viruses and ALRI hospitalisation in children younger than five years old. About subtypes of these viruses, only IFV-A had a significant OR (5.97 (3.29-10.81)) based on 8 studies, which means IFV-A was more commonly identified in hospitalised ALRI cases than children without respiratory symptoms. There was only one study providing data for subtypes of RSV, IFV-C and PIV-4 thus analysis was not carried out. In comparison, the other subtypes didn't have significant associations with hospitalised ALRI. Moreover, AdV, BoV and CoV with

their subtypes were also frequently detected in control children, and so did not have significant ORs or positive AFEs, which means their roles in ALRI hospitalisation remained uncertain.

Two sensitivity analyses were performed to investigate the effect of inclusion of symptomatic (URTI) controls, and of outpatient ALRI cases respectively (Table 4). After data from outpatient cases were included, little impact on the associations was observed. However, this does not necessarily indicate similarity between the associations of inpatient and outpatient ALRI patients. Instead, since only three included articles had ALRI cases from outpatients setting and reported the data separately, the sample size might be too small to detect any significantly different results. In comparison, the inclusion of symptomatic controls had a more substantial influence, which reduced the strength of association with every virus, except AdV and CoV-NL63. Similarly, since only two studies provided data using symptomatic control group (URTI), the result might not be representative due to very small change in sample size (low power).

Table 5 displays the final estimate (hospitalised ALRI in comparison to asymptomatic/healthy children) in the developing country region and industrialised country region respectively. Due to limited data points available for subtypes of each virus, meta-analysis result is missing for all of them (except PIV-3 where there were three studies). For RSV, PIV, hMPV and RV, the magnitude of association between hospitalised ALRI and virus appeared to be stronger in industrialised region than developing countries; while for IFV, the other way around. The strength of associations in both regions is quite similar for viruses of AdV, BoV and CoV. There is no single pattern of virus detection depending on the region classification identified from this review.

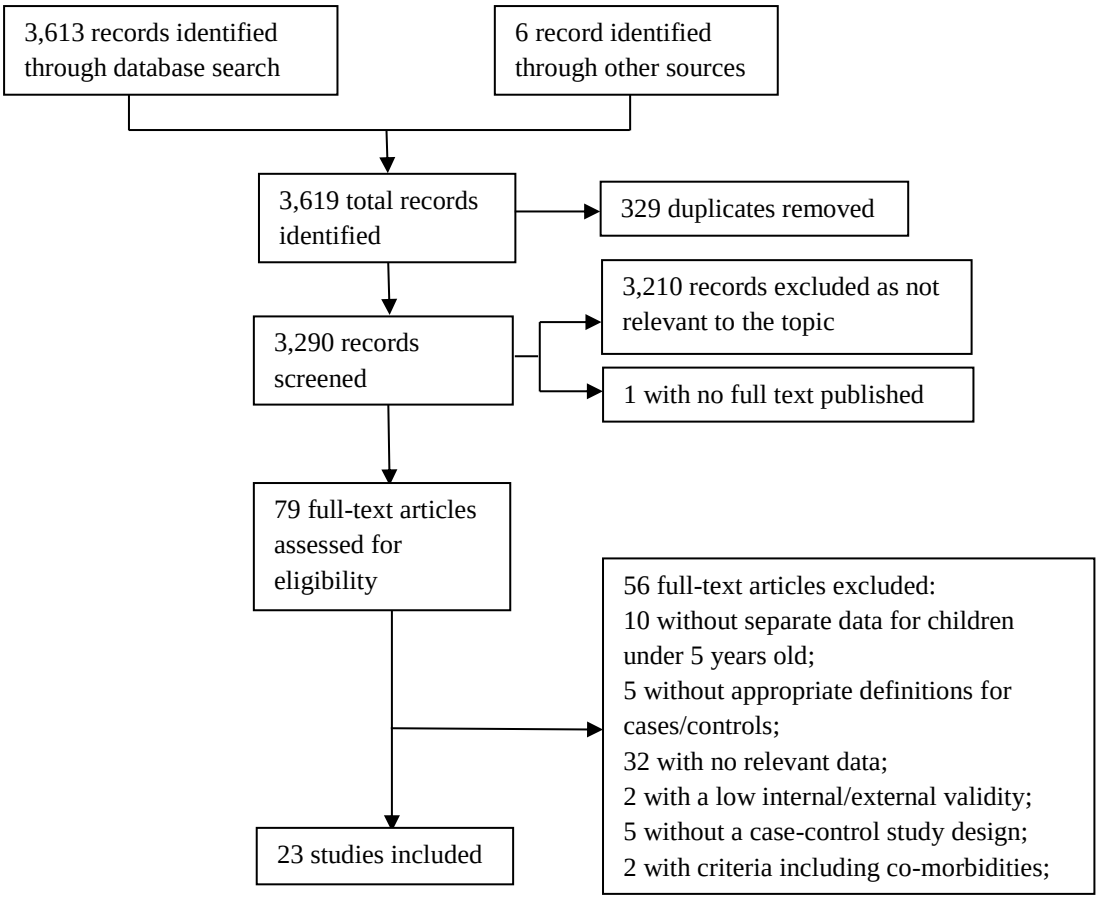

Figure 7: Flow diagram of selection of studies of aetiological role of common respiratory viruses in ALRI

There were eight studies with less than one year of study period (Iwane et al., 2011, Jansen et al., 2011, Longtin et al., 2008, Prill et al., 2012, Rhedin et al., 2014, Wolf et al., 2010, Edwards et al., 2013, Yoshida et al., 2013). Since most viruses have a seasonality pattern (Chan et al., 2015), it might have an effect on the presentation of viruses (detection and virus load), thus these eight studies were excluded in a sensitivity analysis to investigate whether the results would be substantially different (Table 6). Meta-analyses of virus-specific ORs and corresponding AFEs were similar to previous results after studies with less than one-year study period were excluded. Significant associations were also identified for RSV, IFV (inc. IFV-A), PIV, hMPV and RV, which means for studies conducted at least 12 consecutive months, there were similar and clear associations between these five viruses and ALRI hospitalisation in young children.

Table 3: Characteristics of the 23 included studies for aetiological role of common respiratory viruses in ALRI

Study	Age Range	Specimen(s); Diagnostic Test(s)	Bacteria Tested	Case Group		Control Group	
				N; Ascertainment; Pro (%)	Definition (Criteria)	N; Ascertainment; Sampling Method	Definition (Criteria)
Banjul, The Gambia; Periurban; Nov 90 - Oct 92 (Adegbola et al., 1994)	3 - 59 M	NPA, LA; IFA, cell culture	Yes	119; Passive (IP); NS	P (NS)	52; Passive (H) Matched (Age, area)	Healthy (No RS or malnutrition)
Baffin Island, Canada; R; Jan 02 - Mar 03 (Banerji et al., 2009)	0 - 23 M	NPA; ELISA, DFA, m-PCR	No	121; Passive (IP); 91%	ALRI (NS)	119; Active (C); Matched (Age)	Healthy (>2W no RS)
Kenya; R; Jan 07 - Dec 07 (Berkley et al., 2010)	0 - 59 M	NPS; RT-PCR	No	726; Passive (IP); 82%	SP (WHO)	56; Passive (H); Same age group	Healthy (no RS)
Lwak and Kibera, Kenya; R; Mar 07 - Feb 11 (Bigogo et al., 2013)	0 - 59 M	NPS, OPS; qRT-PCR	Yes	538/ 899ŧ; Passive (IP, OP); 36.9%	SARI (WHO)	193/109; Passive (H); Matched (Age)	AS (>2W no RS)
Sa Kaeo, Thailand; R; Sep 04 - Aug 05 (Dare et al., 2007)	0 - 59 M	NPS; RT-PCR	No	365; Passive (IP); 50.5%*	P (CXR)	85; Passive (H); Same number in age/month	AS (>3D no RS)
Multicentre, USA; U; Nov (03 - 09) - May (03 - 09) (Edwards et al., 2013)¶	0 - 59 M	NPS; RT-PCR	No	3490; Passive (IP); NS	ARI (NS)	770; Passive (H); Same age, area, study period	Healthy (>2W no RS)
Asembo, Kenya; R; Jan 09 - Feb 10 (Feikin et al., 2013)	0 - 59 M	NPS, OPS; sq-PCR	Yes	166/33**; Active (C), Passive (IP, OP); NS	SP (WHO)	93; Passive (H); Same age group	AS (>2W no RS)
Sa Kaeo, Thailand; R; Sep 04 - Aug 05 (Fry et al., 2007)	0 - 59 M	NPS; RT-PCR	No	369; Passive (IP); 51%*	P (CXR)	85; Passive (H); Same number in age/month	AS (>3D no RS)
Sa Kaeo, Thailand; R; Sep 04 - Aug 05 (Fry et al., 2011)	0 - 59 M	NPS; RT-PCR	No	379; Passive (IP); 45%*	ALRI (CXR)	85; Passive (H); Same number in age/month	AS (>3D no RS)
Kilifi District, Kenya; R; Jan 10 - Dec 10 (Hammitt et al.,	1 - 59 M	NPS, OPS§, IS§; mRT-PCR	Yes	805; Passive (IP); 84%	SP (WHO)	142/227; Passive (H); Matched (age, month)	AS /URTI (No RS)

Study	Age Range	Specimen(s); Diagnostic Test(s)	Bacteria Tested	Case Group		Control Group	
				N; Ascertainment; Pro (%)	Definition (Criteria)	N; Ascertainment; Sampling Method	Definition (Criteria)
2012a)							
Sa Kaeo and Nakhon Phanom, Thailand; R; Jan 05 - Dec 07 (Hasan et al., 2014)	0 - 59 M	NPS; RT-PCR	No	3809; Passive (IP); NS	ALRI (CXR)	589; Passive (H); Same age group	AS (>3D no RS)
Multicentre, USA; U; Dec 03/Oct 04 - Apr 04/Apr 05 (Iwane et al., 2011)¶	0 - 59 M	NPS; RT-PCR	No	1515; Passive (IP); 83%	ARI (NS)	790; Passive (H); Same age, area, study period	AS (>2W no RS)
Amsterdam, The Netherlands; U; Nov (07-09) - Apr (07-09) (Jansen et al., 2011)¶	0 - 23 M	NPW; mPCR	No	100; Passive (IP); NS	ARI (NS)	59; Passive (H); Same age group	AS (>1W no RS)
Quebec, Canada; U; Dec 02 - Apr 03 (Longtin et al., 2008)¶	0 - 35 M	NPA; qPCR	No	225; Passive (IP); NS	ARI (NS)	100; Passive (H); Same study period	AS (no RS)
Bhaktapur, Nepal; U; Mar 06 - Jul 07 (Mathisen et al., 2010)	2 - 35 M	NPA; mRT-PCR	No	29/671**; Passive (IP, OP); NS	P (WHO)	29/665; Active (C); Matched (age)	AS/URTI (No ab >2D)
Yuedong, China; U; Jan 07 - Dec 07 (Ou et al., 2009a)	0 - 59 M	NPA; mRT-PCR	No	345; Passive (IP); NS	ALRI (NS)	83; Passive (H); Same age group	Healthy (>2W no RS)
Multicentre, USA; U; Dec 03/Oct 04 - Apr 04/Apr 05 (Prill et al., 2012)¶	0 - 59 M	NPS; RT-qPCR	No	1481; Passive (IP); 82%	ARI (NS)	742; Passive (H); Same area, study period	AS (>2W no RS)
Stockholm, Sweden; U; Sep 11 - Jan 12 (Rhedin et al., 2014)¶	0 - 59 M	NPA; qPCR	No	209; Passive (IP); NS	ARI (NS)	209; Passive (H); Matched (Age, Time)	AS (>1W no RS)
YK Delta, Alaska, USA; R; Oct 06 - Sep 07 (Singleton et al., 2010)	0 - 35 M	NPS; sRT-PCR	No	208; Passive (IP); 60%	ALRI (NS)	381; Active (C); Same age group, unmatched	Healthy (>2W no RS)
Beersheba, Israel; U; Nov (01-05) - May (01-05)	0 - 59 M	NPW; RT-PCR, DFA, cell culture	No	1017; Passive (IP); 37%	P (WHO)	136; Passive (H); Same study period	Healthy (no RS)

Study	Age Range	Specimen(s); Diagnostic Test(s)	Bacteria Tested	Case Group		Control Group	
				N; Ascertainment; Pro (%)	Definition (Criteria)	N; Ascertainment; Sampling Method	Definition (Criteria)
(Wolf et al., 2010)¶							
Shantou, China; U; Jun 07 - May 08 (Xie, 2010)	0 - 24 M	NPA; mRT-PCR	No	271; Passive (IP); NS	B (NS)	82; Passive (H); NS	Healthy (no RS)
Nha Trang, Vietnam; U; Jun 08 - Aug 08 (Yoshida et al., 2013)¶	0 - 59 M	NPS; mPCR	No	148; Passive (IP); 97.9%	ARI (WHO)	350; Passive (H); Same age group	Healthy (No RS, No ab >1M)
Shanghai, China; U; Oct 09 - Aug 12 (Zhao et al., 2013)	0 - 59 M	NPA§, NPS‡; qRT-PCR	No	554; Passive (IP); NS	ALRI (CXR)	195; Passive (H); Random	Healthy (SCDC Sample Bank)

U=urban. R=rural. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. OPS=oropharyngeal swab. IS=induced sputum. LA=lung aspirate. IF=immunofluorescence (IFA=indirect; DFA=direct). ELISA=enzyme-linked immunosorbent assay. PCR=polymerase chain reaction (m=multiplex; RT=reverse transcription; s=singleplex; q=quantitative/real time). (S) P=(Severe) Pneumonia. ALRI=acute lower respiratory infection. B=bronchiolitis. NS=not stated. RS=respiratory symptoms. ab=antibiotics. Pro=proportion of eligible cases tested. CXR=chest radiography. SCDC=Shanghai Centre for Disease Control. IP=inpatient. OP=outpatient. H=hospital. C=community. D=days. W=weeks. M=months. AS=asymptomatic. *For whole study (all ages). **Recruitment of IP/OP. §Cases only. ‡Controls only. ǂRecruitment in the respective Lwak/Kibera site. ¶There were 8 studies which were conducted for less than 12 consecutive months.

Table 4: The meta-analyses of the OR and AFE of each virus and its subtypes within the 23 included studies

Virus	Meta Analyses* (hospitalised cases vs. asymptomatic control)			Sensitivity Analyses* Inclusion of symptomatic (URTI) controls			Sensitivity Analyses* Inclusion of outpatient (OP) cases		
	n_s	**OR** (95% CI)	**AFE** (95% CI)	n_s	**OR** (95% CI)	**AFE** (95% CI)	n_s	**OR** (95% CI)	**AFE** (95% CI)
RSV	13	**9.79** (4.98 to 19.27)	**90%** (80 to 95)	13	**8.60** (4.83 to 15.33)	**88%** (79 to 93)	14	**9.59** (5.26 to 17.49)	**90%** (81 to 94)
A	1	-	-	1	-	-	1	-	-
B	1	-	-	1	-	-	1	-	-
IFV	10	**5.10** (3.19 to 8.14)	**80%** (69 to 88)	10	**3.39** (1.64 to 7.02)	**71%** (39 to 86)	10	**5.54** (3.56 to 8.62)	**82%** (72 to 88)
A	8	**5.97** (3.29 to 10.81)	**83%** (70 to 91)	8	**3.99** (1.68 to 9.49)	**75%** (40 to 89)	9	**6.07** (3.35 to 10.98)	**84%** (70 to 91)
B	9	**2.70** (0.97 to 7.53)	**63%** (-3 to 87)	9	**2.70** (0.97 to 7.54)	**63%** (-3 to 87)	9	**3.36** (1.48 to 7.65)	**70%** (32 to 87)
C	1	-	-	1	-	-	1	-	-
PIV	11	**3.37** (1.59 to 7.15)	**70%** (37 to 86)	11	**3.14** (1.25 to 7.85)	**68%** (20 to 87)	11	**4.07** (1.91 to 8.67)	**75%** (48 to 88)
1	6	**2.52** (0.79 to 8.07)	**60%** (-27 to 88)	6	**2.10** (0.64 to 6.88)	**52%** (-56 to 85)	6	**3.10** (1.21 to 7.94)	**68%** (17 to 87)
2	7	**2.22** (0.80 to 6.16)	**55%** (-25 to 84)	7	**1.18** (0.33 to 4.27)	**15%** (-203 to 77)	7	**2.34** (0.94 to 5.83)	**57%** (-6 to 83)
3	8	**2.19** (0.97 to 4.97)	**54%** (-3 to 80)	8	**2.05** (0.77 to 5.43)	**51%** (-30 to 82)	8	**4.14** (1.24 to 13.82)	**76%** (19 to 93)
4	1	-	-	1	-	-	1	-	-
hMPV	10	**3.76** (2.45 to 5.78)	**73%** (59 to 83)	10	**3.61** (2.38 to 5.46)	**72%** (58 to 82)	11	**3.84** (2.51 to 5.88)	**74%** (60 to 83)
AdV	10	**1.13** (0.71 to 1.80)	**12%** (-41 to 44)	10	**1.16** (0.76 to 1.77)	**14%** (-32 to 44)	10	**1.13** (0.71 to 1.80)	**12%** (-41 to 44)
RV	11	**1.43** (1.03 to 1.97) ǂ	**30%** (3 to 49)	11	**1.41** (1.03 to 1.93)	**29%** (3 to 48)	11	**1.43** (1.03 to 1.97)	**30%** (3 to 49)
BoV	8	**1.20** (0.36 to 3.98)	**17%** (-178 to 75)	8	**1.20** (0.36 to 3.98)	**17%** (-178 to 75)	8	**1.20** (0.36 to 3.98)	**17%** (-178 to 75)
CoV	8	**1.03** (0.80 to 1.33)	**3%** (-25 to 25)	8	**0.94** (0.74 to 1.19)	**-6%** (-35 to 16)	8	**1.03** (0.80 to 1.33)	**3%** (-25 to 25)
HKU1	4	**0.61** (0.34 to 1.09)	**-64%** (-194 to 8)	4	**0.61** (0.34 to 1.09)	**-64%** (-194 to 8)	4	**0.61** (0.34 to 1.09)	**-64%** (-194 to 8)
NL63	5	**0.68** (0.38 to 1.24)	**-47%** (-163 to 19)	5	**0.71** (0.41 to 1.25)	**-41%** (-144 to 20)	5	**0.68** (0.38 to 1.24)	**-47%** (-163 to 19)
229E	4	**1.47** (0.58 to 3.72)	**32%** (-72 to 73)	4	**1.42** (0.46 to 4.43)	**30%** (-117 to 77)	4	**1.47** (0.58 to 3.72)	**32%** (-72 to 73)
OC43	5	**0.91** (0.32 to 2.64)	**-10%** (-213 to 62)	5	**0.84** (0.39 to 1.80)	**-19%** (-156 to 44)	5	**0.91** (0.32 to 2.64)	**-10%** (-218 to 62)

n_s=number of studies. 95% CI=95% confidence interval. RSV=respiratory syncytial virus. IFV=influenza. PIV=parainfluenza. hMPV=human metapneumovirus. AdV=adenovirus. RV=rhinovirus. BoV=bocavirus. CoV=coronavirus. OR=odds ratio. AFE=attributable fraction among the exposed. *From the random-effects model. ǂThe OR=1.40 (1.02 to 1.92) and AFE=28% (2 to 48) when studies testing all other enterovirus are excluded.

Table 5: The meta-analyses of the OR and AFE of each virus and its subtypes within the 23 included studies by region

Virus	Meta Analyses globally* (hospitalised cases vs. asymptomatic control)			Meta Analyses stratified by region* Developing region			Industrialised region		
	n_s	**OR** (95% CI)	**AFE** (95% CI)	n_s	**OR** (95% CI)	**AFE** (95% CI)	n_s	**OR** (95% CI)	**AFE** (95% CI)
RSV	13	**9.79** (4.98 to 19.27)	**90%** (80 to 95)	9	**8.72** (3.66 to 20.80)	**89%** (73 to 95)	4	**13.93** (3.38 to 57.47)	**93%** (70 to 98)
A	1	-	-	1	-	-	0	-	-
B	1	-	-	1	-	-	0	-	-
IFV	10	**5.10** (3.19 to 8.14)	**80%** (69 to 88)	7	**5.78** (3.32 to 10.06)	**83%** (70 to 90)	3	**3.50** (1.15 to 10.69)	**71%** (13 to 91)
A	8	**5.97** (3.29 to 10.81)	**83%** (70 to 91)	6	**6.78** (3.46 to 13.27)	**85%** (71 to 92)	2	-	-
B	9	**2.70** (0.97 to 7.53)	**63%** (-3 to 87)	7	**2.70** (0.97 to 7.54)	**63%** (-3 to 87)	2	-	-
C	1	-	-	1	-	-	0	-	-
PIV	11	**3.37** (1.59 to 7.15)	**70%** (37 to 86)	7	**2.41** (0.99 to 5.90)	**59%** (-1 to 83)	4	**6.75** (3.60 to 12.64)	**85%** (72 to 92)
1	6	**2.52** (0.79 to 8.07)	**60%** (-27 to 88)	5	**1.87** (0.50 to 7.01)	**47%** (-100 to 86)	1	-	-
2	7	**2.22** (0.80 to 6.16)	**55%** (-25 to 84)	6	**2.22** (0.80 to 6.15)	**55%** (-25 to 84)	1	-	-
3	8	**2.19** (0.97 to 4.97)	**54%** (-3 to 80)	5	**2.50** (0.87 to 7.21)	**60%** (-15 to 86)	3	**22.9** (0 to 2.19e+23)	**96%** (NA to 100)
4	1	-	-	1	-	-	0	-	-
hMPV	10	**3.76** (2.45 to 5.78)	**73%** (59 to 83)	4	**3.53** (0.52 to 23.83)	**72%** (-92 to 96)	6	**4.15** (2.88 to 5.98)	**76%** (65 to 83)
AdV	10	**1.13** (0.71 to 1.80)	**12%** (-41 to 44)	6	**1.19** (0.66 to 2.16)	**16%** (-52 to 54)	4	**1.09** (0.46 to 2.61)	**8%** (-117 to 62)
RV	11	**1.43** (1.03 to 1.97)	**30%** (3 to 49)	6	**1.15** (0.83 to 1.60)	**13%** (-20 to 38)	5	**1.88** (1.04 to 3.40)	**47%** (4 to 71)
BoV	8	**1.20** (0.36 to 3.98)	**17%** (-178 to 75)	5	**1.25** (0.27 to 5.82)	**20%** (-270 to 83)	3	**1.15** (0.13 to 9.77)	**13%** (-669 to 90)
CoV	8	**1.03** (0.80 to 1.33)	**3%** (-25 to 25)	4	**1.06** (0.59 to 1.88)	**6%** (-69 to 47)	4	**1.03** (0.88 to 1.37)	**3%** (-30 to 27)
HKU1	4	**0.61** (0.34 to 1.09)	**-64%** (-194 to 8)	2	-	-	2	-	-
NL63	5	**0.68** (0.38 to 1.24)	**-47%** (-163 to 19)	3	**0.23** (0.01 to 3.78)	**-335%** (-9900 to 74)	2	-	-
229E	4	**1.47** (0.58 to 3.72)	**32%** (-72 to 73)	3	**1.14** (0.34 to 3.80)	**12%** (-194 to 74)	1	-	-
OC43	5	**0.91** (0.32 to 2.64)	**-10%** (-213 to 62)	3	**0.65** (0.10 to 4.27)	**-54%** (-900 to 77)	2	-	-

n_s=number of studies. NA=not applicable. 95% CI=95% confidence interval. RSV=respiratory syncytial virus. IFV=influenza. PIV=parainfluenza. hMPV=human metapneumovirus. AdV=adenovirus. RV=rhinovirus. BoV=bocavirus. CoV=coronavirus. OR=odds ratio. AFE=attributable fraction among the exposed. *From the random-effects model.

Table 6: The meta-analyses of the OR and AFE of each virus and its subtypes within the 15 included studies (after excluding articles with less than one-year study period)

Virus	Meta Analyses* (hospitalised cases vs. asymptomatic control)			Sensitivity Analyses* Inclusion of symptomatic (URTI) controls			Sensitivity Analyses* Inclusion of outpatient (OP) cases		
	n_s	OR (95% CI)	AFE (95% CI)	n_s	OR (95% CI)	AFE (95% CI)	n_s	OR (95% CI)	AFE (95% CI)
RSV	10	**8.37** (3.92 to 17.91)	**88%** (74 to 94)	10	**7.14** (3.84 to 13.29)	**86%** (74% to 92%)	11	**8.40** (4.34 to 16.25)	**88%** (77 to 94)
A	1	-	-	1	-	-	1	-	-
B	1	-	-	1	-	-	1	-	-
IFV	8	**5.43** (3.14 to 9.38)	**82%** (68 to 89)	8	**3.45** (1.45 to 8.18)	**71%** (31 to 88)	8	**6.00** (3.61 to 9.96)	**83%** (72 to 90)
A	6	**5.88** (2.83 to 12.22)	**83%** (65 to 92)	6	**3.68** (1.16 to 11.68)	**73%** (14 to 91)	7	**6.04** (2.91 to 12.52)	**83%** (66 to 92)
B	7	**2.76** (0.91 to 8.33)	**64%** (-10 to 88)	7	**2.76** (0.91 to 8.34)	**64%** (-10 to 88)	7	**3.48** (1.48 to 8.23)	**71%** (32 to 88)
C	1	-	-	1	-	-	1	-	-
PIV	8	**2.90** (1.30 to 6.45)	**66%** (23 to 84)	8	**2.61** (1.00 to 6.84)	**62%** (0 to 85)	8	**3.61** (1.61 to 8.07)	**72%** (38 to 88)
1	5	**1.87** (0.50 to 7.01)	**47%** (-100 to 86)	5	**1.56** (0.44 to 5.58)	**36%** (-127 to 82)	5	**2.59** (0.91 to 7.36)	**61%** (-10 to 86)
2	5	**2.22** (0.80 to 6.16)	**55%** (-25 to 84)	5	**1.27** (0.27 to 5.86)	**21%** (-270 to 83)	5	**2.34** (0.94 to 5.83)	**57%** (-6 to 83)
3	6	**2.42** (0.90 to 6.49)	**59%** (-11 to 85)	6	**2.18** (0.73 to 6.52)	**54%** (-37 to 85)	6	**4.19** (1.17 to 14.94)	**76%** (15 to 93)
4	1	-	-	1	-	-	1	-	-
hMPV	6	**3.24** (1.18 to 8.88)	**69%** (15 to 89)	6	**2.93** (1.26 to 6.81)	**66%** (21 to 85)	7	**3.69** (1.53 to 8.92)	**73%** (35 to 89)
AdV	7	**0.95** (0.56 to 1.63)	**-5%** (-79 to 39)	7	**1.00** (0.61 to 1.63)	**0%** (-64 to 39)	7	**0.96** (0.56 to 1.64)	**-4%** (-79 to 39)
RV	7	**1.36** (0.92 to 2.02)ł	**26%** (-9 to 50)	7	**1.34** (0.92 to 1.93)	**25%** (-8 to 48)	7	**1.36** (0.92 to 2.01)	**26%** (-9 to 50)
BoV	4	**1.51** (0.24 to 9.63)	**34%** (-317 to 90)	4	**1.51** (0.24 to 9.63)	**34%** (-317 to 90)	4	**1.51** (0.24 to 9.63)	**34%** (-317 to 90)
CoV	4	**1.09** (0.68 to 1.76)	**8%** (-47 to 43)	4	**0.83** (0.57 to 1.22)	**-20%** (-75 to 18)	4	**1.09** (0.68 to 1.76)	**8%** (-47 to 43)
HKU1	2	**0.08** (0.00 to 1.24)	**-1150%** (-EV to 19)	2	**0.08** (0.00 to 1.24)	**-1150%** (-EV to 19)	2	**0.08** (0.00 to 1.24)	**-1150%** (-EV to 19)
NL63	3	**0.23** (0.01 to 3.78)	**-335%** (-9900 to 74)	3	**0.68** (0.17 to 2.83)	**-47%** (-488 to 65)	3	**0.23** (0.01 to 3.78)	**-335%** (-9900 to 74)
229E	3	**1.14** (0.34 to 3.80)	**12%** (-194 to 74)	3	**1.10** (0.26 to 4.67)	**9%** (-285 to 79)	3	**1.14** (0.34 to 3.80)	**12%** (-194 to 74)
OC43	3	**0.65** (0.10 to 4.27)	**-54%** (-900 to 77)	3	**0.54** (0.16 to 1.84)	**-85%** (-525 to 46)	3	**0.65** (0.10 to 4.27)	**-54%** (-900 to 77)

n_s=number of studies. 95% CI=95% confidence interval. EV=extreme value. RSV=respiratory syncytial virus. IFV=influenza. PIV=parainfluenza. hMPV=human metapneumovirus. AdV=adenovirus. RV=rhinovirus. BoV=bocavirus. CoV=coronavirus. OR=odds ratio. AFE=attributable fraction among the exposed. *From the random-effects model. łThe OR=1.26 (0.95 to 1.67) and AFE=21% (-5 to 40) when studies testing all enterovirus are excluded.

3.3 Discussion

This is the first systematic review to evaluate and summarise the published literature on the viral aetiology of ALRI in young children. The aim was to summarise good quality studies with relevant data on the absolute effects of the viral exposure and hence to inform causal inference in ALRI aetiological studies which report viral respiratory data. This review summarises data from 18,592 cases of ALRI in young children reported across 23 studies. Stronger evidence was demonstrated (defined here as a statistically significant OR > 3) for four viruses in support of a causal attribution when a virus is identified in young children presenting with ALRI: RSV (OR 9.79; AFE 90%), IFV (OR 5.10; AFE 80%), PIV (OR 3.37; AFE 70%) and hMPV (OR 3.76; AFE 73%). There was less strong evidence (defined here as a statistically significant OR 1-3) for RV (OR 1.43; AFE 30%). Therefore, this indicates the potential approach for substantive reductions in the number of ALRI cases was young children to be vaccinated against these viruses. There was no statistically significant difference of viral identification for the other respiratory viruses studied: AdV, BoV, CoV as well as subtypes of all viruses (except IFV-A) between ALRI cases and controls. After studies with more than one-year study period were focused on, similar associations were observed. This clarifies the potential problem that the seasonality of viruses has an impact on their presence and the proportion of them being detected in cases.

These findings support the roles of RSV, IFV, PIV and hMPV as important causes of ALRI in young children. They should inform the results of studies which seek to estimate the global / regional / national burden of disease due to these viruses, and disease burden estimates should take into account the AFE estimates that this review reports – thus the true global burden of RSV / IFV / PIV / hMPV associated pneumonia may be 90% / 80% / 70% / 73% of the values reported in recent publications. Applying these estimates to the burden of severe (hospitalised) pneumonia in 2010 (Rudan et al., 2013), we estimate that the likely true burden of RSV and influenza associated ALRI for that year would be about 2.9 (95% CI 1.5-5.5) million and 0.8 (95% CI 0.3-2.2) million respectively. The AFE estimate for RSV (90%) would be applied to the estimation of global burden of RSV associated ALRI in young children which was presented in the Chapter 5. There is considerable international attention on RSV and IFV pneumonia in young children at this time when novel vaccine strategies are under development, being evaluated and prioritised and more accurate disease burden estimates (using these results) would help inform future policies and interventions.

There were several methodological issues affecting the results: ascertainment of case group and control group, definition of cases and controls, clinical specimen and confounding. All

23 studies used passive hospital-based case ascertainment recruiting inpatients which met the selection criteria. Three of them also included cases from outpatients setting or community. Several previous studies have shown that children in developing countries, particularly those residing in rural areas, have in general, limited access to healthcare (Macfarlane, 2000), and health care seeking behaviour is often delayed or absent (Tinuade, 2010). This potentially introduced a selection bias. Children who didn't make it to the hospitals might have a different severity of pneumonia and might have a different presence of viruses (as well as virus load). For control group, only three studies used community based controls (Singleton et al., 2010, Mathisen et al., 2010, Banerji et al., 2009) and the others recruited controls in hospital/clinic. Hospital ascertained controls may not reflect the general population, and may have other health conditions potentially affecting their viral carriage, especially those with URTI. The ideal control group for these studies would be a random sample of an age and sex matched child population from the same area of residence during the same time. Studies, however, recruited controls who were either selected as healthy (asymptomatic) and so biased in favour of those not exposed to the respiratory virus (yielding a falsely high OR) or those who were selected to have respiratory symptoms and so biased in favour of those who had been exposed to the respiratory virus (yielding a falsely low OR). Consistent with this interpretation, odds ratios (of ALRI given viral identification) were found (in Table 4) to be consistently greater where the control group was "healthy" and asymptomatic in comparison to inclusion of symptomatic (URTI) controls except for AdV and CoV-NL63, in which case, their results were slightly higher than ones from asymptomatic control group. Table 6 also showed the same results where studies with less than one year of study period were excluded. We consider that the value of the OR from a population-based control group would lie between these two values as described above.

With regards to case definition, seven of the included studies (Mathisen et al., 2010, Banerji et al., 2009, Dare et al., 2007, Fry et al., 2007, Hammitt et al., 2012a, Wolf et al., 2010, Feikin et al., 2013) employed the WHO case definition for pneumonia (World Health Organization, 2005) and this standardised approach enhanced the comparability of results between these studies. These criteria have high sensitivity for pneumonia (Scott, 2008), but lower specificity when overlapped with other conditions (Graham, 2008), particularly malaria (World Health Organization, 1991) and wheezing disorders. This tends to inflate the number of "cases"/denominator and may contribute to a relatively low level of detection of pathogenic viruses.

All included studies obtained upper respiratory tract specimens (i.e. described as nasopharyngeal secretions, nasopharyngeal wash samples, nasopharyngeal aspirate samples,

oropharyngeal samples). Although their differing sensitivities could result in some heterogeneity, they are broadly comparable and have common flaws. As viruses identified could be from a coincidental upper airways infection, the sole use of these specimens is not sufficient to provide evidence of the cause of ALRI, but can only provide supportive evidence for causality. Lung aspiration is considered the gold-standard sampling technique given it is directly obtained from the infection site (Hammitt et al., 2012b), which would indicate aetiological significance in ALRI cases (high specificity). However, its invasive nature and rate of complications limit its use. All studies used polymerase chain reaction (PCR) to diagnose viruses from these upper respiratory tract specimens (one study used IFA). The high sensitivity of PCR is important for accurate assessment of aetiological contribution.

There were several potential confounding factors which could have distorted the observed associations. Only three studies calculated appropriately adjusted ORs to account for confounding effects from age (Hasan et al., 2014), or age and season (Hammitt et al., 2012a, Feikin et al., 2013). Instead, matching of cases and controls was more commonly used – performed by age (Adegbola et al., 1994, Bigogo et al., 2013, Mathisen et al., 2010, Banerji et al., 2009), or age and month (Hammitt et al., 2012a, Rhedin et al., 2014). Nevertheless, despite the use of matching, no studies maintained this pairing to allow OR calculation. While all studies were conducted on young children under 5 years, six (Banerji et al., 2009, Singleton et al., 2010, Mathisen et al., 2010, Xie, 2010, Jansen et al., 2011, Longtin et al., 2008) were further restricted. As age is an ALRI risk factor (Rudan, 2008), this could potentially affect the viral profile detected, introducing further heterogeneity. However, due to the limited data points obtained in narrower age bands, sensitivity analysis of associations between ALRI and viruses was not carried out.

In addition, multiple aetiological agents may often be identified in young children with ALRI, making the individual contribution of each agent difficult to define. Many of the included studies did not provide virological data that excludes co-infections, so viruses detected in these cases could conceivably fulfil any etiological role. The high rates of viral co-infection detection may overstate the individual contribution (if the rate of co-infection in case group is higher than what is in control group).

Moreover, the small sample size (Adegbola et al., 1994, Mathisen et al., 2010, Jansen et al., 2011), undoubtedly contributed to the imprecise 95% CIs of the outcome. This may have also led to the non-detection of statistically significant associations between ALRI and virus as in some case and/or control groups due to low power of studies. Two studies (Banerji et al., 2009, Singleton et al., 2010) included children from aboriginal community in USA or

Canada and were found to have high ALRI incidence. The viral associations observed in these two studies may not be generalizable to other populations in USA/Canada.

The use of the AFE allows quantification of the excess percentage of ALRI cases due to exposure of a specific virus in absolute terms. However, it assumes that the observed association between the virus (and/or related factors) and ALRI is causal, and, in practice, this will undoubtedly have led to extreme estimations. Furthermore, strict interpretation would entail construal of negative values as indicative of the percentage of ALRI prevented by viral exposure, which is biologically implausible. In these cases, the negative AFE value should be interpreted carefully and the role of this virus in both cases and controls should be explored in-depth to see whether there is an alternative explanation or there are other factors influencing the detection of this virus.

Any viruses detected in asymptomatic children could be from an infection with symptoms but they were not recognised, an infection without any symptoms (persistent or reactivation of latent infection), a nascent infection (symptoms haven't been developed), or they were persistent from a previous infection (remnants of a past infection) (Jartti, 2008). These could explain 'pathogenic' viruses (such as AdV) being identified commonly in asymptomatic children. Therefore, some viruses are detectable for weeks before symptoms of ALRI (during incubation period) and after being infected with ALRI (Lessler, 2009, Jartti, 2008) and so the studies only assessing asymptomatic status without considering past or future history may yield false positive findings (Hammitt et al., 2012a, Adegbola et al., 1994, Longtin et al., 2008, Wolf et al., 2010, Berkley et al., 2010).

A virus (or any pathogen) can be considered to be associated with ALRI when detected with a significantly higher frequency in cases than controls without respiratory symptom (asymptomatic). The following evidence provides support for a causal relationship: the magnitude of the association is strong (significant); the association is consistently observed across studies in various settings, population and study periods; there is a known biologic mechanism underneath the association (Hill, 1965). According to Bradford Hill criteria, this evidence, while necessary, is insufficient for proof of a causal role between a virus and ALRI. Another essential criterion required for the determination of causality is the establishment of a temporal sequence of exposure and outcome (Hennekens et al., 1987). As exposure is investigated after the outcome in case-control studies, these cannot provide this temporal evidence. Therefore, there is a rationale for the conduct of birth cohort studies with routine surveillance of children to track the circulation and course of respiratory viral infections. Moreover, using passive immune-prophylaxis (e.g. palivizumab for RSV) in randomised

controlled trials might be able to provide experimental evidence of the virus as a causal pathogen for ALRI and the strength of the effect. Also, "vaccine-probe studies" could in theory potentially be used (in future, once effective vaccines are available) to test the causal relationship (Feikin, 2014). These would allow conclusive assessment of the burden of ALRI attributable to each virus (consequence of a disease from pathogen infection).

Furthermore, other alternative explanations must first be refuted before causality can be concluded. Firstly, the virus could be an "innocent bystander" which is more prevalent in patients with ALRI, but has no causal role. Such an effect may be observed due to immunocompromised status from the true causal infection, or nosocomial infections. Secondly, the virus may be a risk factor for ALRI development, but not itself the primary cause. It has been well established that viral infections predispose to subsequent bacterial infection, although the exact mechanisms are still debated (Peltola, 2004). Indeed, influenza and RSV epidemics are commonly observed to precede those of bacterial pneumonia (Hament, 1999, Hartshorn, 2010). Furthermore, there has been lethal synergism observed in viral-bacterial super-infections (Bosch, 2013). Viral and bacterial interaction have several possible mechanisms: virus infection might destruct respiratory epithelium via altering the mucosal surfaces, resulting in the epithelium more susceptible to bacterial colonisation; cells with virus infected could present a decreased expression of antimicrobial peptides (beta-defensins) which increases the possibility that bacteria escape the natural defence; viral neuraminidase (NA) activity would remove sialic acids which cover the bacterial receptors and increase the possibility of bacterial adherence; virus could also upregulate the expression of several receptors which are needed for bacterial adherence; virus infection could lead to immunosuppressed status which is favourable for bacterial invasion. Thirdly, the virus may be necessary to cause ALRI, but is not sufficient to do so without the concurrent presence of one or more other causal factors. There are numerous risk factors that have been associated with ALRI, both host and environment (Rudan, 2008). These, singularly or in combination, may provide the opportunity for the respiratory virus to cause ALRI. Fourthly, the virus may be the direct and sole cause of ALRI, with causality yet to be confirmed. Finally, the virus may be the joint cause of ALRI along with other concurrent viral respiratory infections. Considerations of the causal role of these viruses are further complicated by the fact that a recent respiratory virus infection may have caused temporary immuno-suppression leading to a subsequent viral or bacterial infection even though the initial infection can no longer be detected (and other mechanisms through which respiratory viruses predisposed to the following infection). Influenza viral infections leading to subsequent pneumococcal or staphylococcal respiratory infections have been well described (Hament, 1999). This may

result in an under-estimation of the burden of disease associated with respiratory viral infection.

Notwithstanding these limitations, this review provides clear evidence in favour of the causal role of RSV, IFV, PIV, hMPV and to a lesser extent for RV in children with ALRI and presents a first estimate of the proportion of ALRI cases that can be attributed to the viral exposure. Aetiological studies which simply report rates of viral identification as causal should make an attempt to interpret their findings in terms of the proportion of ALRI cases among children that can be attributed to this viral exposure.

Chapter 4 Risk factors for RSV associated ALRI in children younger than five years old

4.1 Methods

4.1.1 Literature search

4.1.1.1 Search strategy and selection criteria

A systematic review was conducted according to the PRISMA guidelines. The search was performed across the following four electronic databases: Medline, Embase, Global Health and LILACS. The search strategy with search terms for each database are listed in Appendices - A6. The reference lists of relevant papers were hand searched for eligible articles. All searches were limited to between January 1995 and July 2015. No restrictions to publication status or language were used. Table 7 provides the selection criteria in details. Eligible studies should be observational studies (or randomised controlled trials with placebo arm only) that assessed the relationship between RSV associated ALRI cases and risk factors of interest. Data were extracted using standardised data extraction template designed on Microsoft Excel (Microsoft Office 2007).

Table 7: Selection criteria applied in the systematic review of risk factors for RSV associated ALRI

Inclusion criteria:
• Published from January 1995 to July 2015
• Study design - observational studies (case-control or cohort) or randomised controlled trials (placebo arm)
• Sample size: at least 50 children under investigation
• Provide data for children younger than 5 years
• Case group should be children with a diagnosis of ALRI and laboratory confirmed RSV illness
• Control group should be children without any respiratory symptoms or healthy children
• Report associations between socio-demographic risk factors and RSV associated ALRI
• Report results of risk factors based on univariable or multivariable analysis
Exclusion criteria:
• Definitions used for ALRI or risk factors, not clearly stated or inconsistently applied
• Focus on risk factors solely among high-risk study population (e.g. preterm babies, children with congenital heart disease, chronic lung disease or immunosuppression etc.)
• Ineligible control group (e.g. RSV negative ALRI cases, children hospitalised for acute infections)

- Methods for analysis not clearly reported

Conforming to the guidelines of PRISMA, another investigator (Evelyn Balsells, MPH) also conducted an independent literature search and extracted the data. Any discordance or uncertainties regarding relevance or inclusion were arbitrated by my supervisors for this thesis (Prof. Harry Campbell and Dr Harish Nair).

The protocol of this review was published in PROSPERO database with registration number: CRD42015017923.

4.1.2 Unpublished data collection

As described in the Chapter 2 - Methods, unpublished studies with relevant data regarding to associations between risk factors and RSV associated ALRI were collected from RSV GEN investigators. Overall, four unpublished studies with data on risk factors met selection criteria. Their data were summarised in the same data extraction form and combined with the data from published articles (Rasmussen, unpublished; Rath, unpublished; Singleton, unpublished; Zar, unpublished).

4.1.3 Definition of risk factor and outcome

RSV associated ALRI was used as the outcome of interest, which was detailed in the Methods Chapter. The case group - ALRI was defined as cough or dyspnoea with age-related tachypnoea, while severe ALRI was defined as cough or dyspnoea with lower chest wall indrawing (community-based) or an acute respiratory infection severe enough to warrant hospital admission (hospital-based). The control group was defined as children without respiratory symptoms or healthy children (without any respiratory symptoms or other symptoms).

The definitions for some of the risk factors varied substantially across the included studies. Where there were several slightly different definitions regarding to one certain risk factor (which may result in differing strengths of association between this risk factor and the outcome), these studies were pooled into one meta-analysis (where possible) and then conducted a sensitivity analysis to focus on the effect of the risk factor with a certain definition. The definitions of risk factors included in the final meta-analysis were listed in Table 8.

Table 8: Definitions of risk factors for RSV associated ALRI included in meta-analysis

Risk factor	Definition
Prematurity	Gestational age <37 weeks Gestational age <33 weeks
Low birth weight	Birth weight <2.5 kg
Gender	Male
Siblings	Mention of siblings or other children living in the household
Maternal smoking	Maternal smoking during pregnancy
History of atopy	Positive family history of asthma or atopy
Low parental education	No parent having bachelor's degree Education of primary caretaker: 1-7 years or no schooling <12 years' maternal education <11 years' maternal education
Passive smoking	Smokers in the household
Daycare centre attendance	Attendance at daycare centre
Indoor air pollution	Use of biomass fuels for cooking or a description of indoor smoke
No breastfeeding	No breastfeeding
Crowding	>7 persons in household
Multiple births	Twins or triplets
HIV	Confirmed presence of HIV infection in child
Lack of plumbed water	Lack of plumbed water in the household

The Alaskan native population in America was considered to share some epidemiological features to populations in developing countries with similar socioeconomic and demographic risk factors for respiratory infections in both populations (Bulkow et al., 2012), thus were classified as in a developing country setting. Other study sites were classified as from developing or industrialised settings according to the "Levels & trends in child mortality - report 2014" by UNICEF (United Nations Children's Fund, 2014).

4.1.4 Quality assessment

The quality of each study was assessed by using a modified GRADE scoring system (Guyatt et al., 2008) focusing on the following seven aspects: study design, quality of control group, sample size, analysis method, bias, confounding factors and geographical spread of studies (Table 9). Each criterion was categorised into three or four groups with an order of scores (from 0 to 2). The overall score for each study was calculated after assigning corresponding score for every criterion as listed in the table. Studies with cumulative score ≤lower quartile

(25th percentile) of all scores were considered to have "low quality" and they were excluded in the final estimate.

Table 9: Modified GRADE scoring system used to assess the quality of included studies of risk factors for RSV associated ALRI

Criteria	Categorisation	Score
Design	Cohort study	+2 point
	Case control study	+1 points
	Cross sectional study	0.5 points
	Randomised control trial (placebo arm)	0 points
Quality of control group	Good (matched to cases)	+2 points
	Average (not matched, but some descriptions about control)	+1 point
	Poor (no further details)	0 point
Sample size	>500 subjects	+2 points
	300-500 subjects	+1 point
	<300 subjects	0 point
Analysis method	Only multivariable	+2 points
	Part of analyses were based on multivariable	+1 point
	Only univariable	0 point
Bias	Good attempt to avoid bias (selection bias etc.)	+2 points
	Some attempt to avoid bias (selection bias)	+1 point
	No attempt to avoid bias	0 point
Confounding factors	All accounted for (analysis of each risk factor has taken into account of the other risk factors investigated in the same study)	+2 points
	Some accounted for (analyses of some risk factors have taken into account of the other risk factors investigated in the same study)	+1 point
	Not accounted for	0 point
Geographical spread of studies	Good geographical distribution	+2 points
	Limited geographical distribution	+1 point
	Studies in one region only (one area)	0 point

4.1.5 Statistical analysis

Data about the risk summary measure (odds ratio and relative risk) with 95% CI for risk factors of interest were extracted as provided (univariable and multivariable analysis), from included studies (published articles and unpublished studies). If such summary data were not reported, data reported in the paper were used (where feasible) to calculate one.

Using STATA (version 11.2) (StataCorp, 2009), a meta-analysis of risk factor specific odds ratios was conducted based on random effects model (DerSimonian-Laird method) since significant heterogeneity was expected (Borenstein et al., 2009), as discussed in the Chapter 2 - Methods. And pooled estimates with corresponding 95% CIs were reported. In the first instance, only results from studies reporting data based on multivariable analysis would be presented since they involved adjustment of other risk factors investigated in the same study and represented a more accurate result for the risk factor of interest. Thereafter, data from studies reporting ORs using univariable analysis were included. Due to limited studies reporting the results based on multivariable analysis and due to the fact that there was no access to original datasets from included studies to run one, the final estimate was based on meta-analysis of both studies using multivariable analysis and studies using univariable analysis. The final estimate didn't include those "low quality" studies according to modified GRADE scoring system. However, a sensitivity analysis including "low quality" studies was run afterwards in comparison to the previous final estimate and to show whether the result from sensitivity analysis would differ substantially when these "low-quality" studies were included. Subgroup analysis was carried out in developing and industrialised countries respectively if possible.

4.2 Overall result

Overall, 2,690 published articles were identified through literature search, of which only 23 studies (Boyce et al., 2000, Bulkow et al., 2002, Choudhuri et al., 2006, Cilla et al., 2006, Gouyon et al., 2013, Grimwood et al., 2008, Houben et al., 2011, Madhi et al., 2006, Nielsen et al., 2003, Okiro et al., 2008, Paynter et al., 2014, Reeve et al., 2006, Rietveld et al., 2006, Rossi et al., 2007, Smith et al., 2011, Stensballe et al., 2006, Von Linstow et al., 2008, Weber et al., 1999, Weigl et al., 2001, Madhi et al., 2000, Moyes et al., 2013, Bruden et al., 2015, Hennessy et al., 2008) fulfilled the strict eligibility criteria. The 165 articles which were reviewed in full texts but then got excluded were listed in Appendices - A7 with corresponding reasons. After including an additional 4 unpublished studies (Rasmussen, unpublished; Rath, unpublished; Singleton, unpublished; Zar, unpublished) provided by RSV GEN collaborators, 27 studies in total were included in the following analysis. The selection process conducted to include studies is shown in Figure 8. Three studies provided data of risk factors for RSV associated ALRI from community-based studies (Okiro et al., 2008) (Rasmussen, unpublished; Zar, unpublished), three studies reported data for RSV associated (hospitalised) ALRI from both outpatient and inpatient settings in hospitals (Houben et al., 2011, Smith et al., 2011) (Rath, unpublished) and 21 studies provided data for RSV associated hospitalised ALRI. Fourteen studies were from industrialised countries and thirteen studies were from developing countries. Map of locations of these 27 study sites was displayed in Figure 9. Table 11 shows main features of the 27 included studies.

According to the modified GRADE scoring system, the quality scores of included studies varied from 2.5 to 11 with 25th percentile score of 6.25 (Table 12). There were 7 studies which had scores ≤6.25 (Bruden et al., 2015, Hennessy et al., 2008, Madhi et al., 2006, Madhi et al., 2000, Okiro et al., 2008, Weigl et al., 2001) (Rath, unpublished). As described in the Methods, these "low quality" with scores ≤6.25 were excluded in the final estimate.

Definitions for each risk factor varied across included studies. Table 10 shows all risk factors with all definitions used in the included studies. Apart from the ones already listed in Table 8, which were included in meta-analysis, there were also several other risk factors in which case there were no enough studies (<3 studies) reporting their roles in RSV associated ALRI thus were not included in the meta-analysis. Moreover, Table 10 also lists other definitions for a certain risk factor which were not displayed in Table 8 because these definitions were substantially different from the others. Therefore, they were not included to the existing meta-analysis of this certain risk factor; and since there were insufficient studies reporting data using these different definitions, thus a separate meta-analysis could not be done. Table

13 presents the final results for 12 risk factors with meta-estimate ORs after excluding “low-quality” studies (20 studies in total). The table displays meta-estimates from studies using multivariable analysis only (if possible) as well as meta-estimates from all studies (using both multivariable analysis and univariable analysis). The final estimate was based on exclusion of “low quality” studies and inclusion of studies using multivariable analysis and univariable analysis (Table 13). The corresponding forest plots of the final estimate were available in Appendices - A8. A sensitivity analysis was run later to include those seven “low-quality” studies to explore whether these studies influenced the overall result substantially and to what extent (Table 14). The comparison was summarised in Table 15.

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Table 10: List of all various definitions of risk factors for RSV associated ALRI among the included studies

Risk factor	Definition
Prematurity	Gestational age <37 weeks (±1 week) Gestational age <33 weeks
Low birth weight	Birth weight <2.5 kg (or <3.0 kg)
No/lack of exclusive breastfeeding	No breastfeeding No or <3 months breastfeeding No breastfeeding for first 14 days Lack of exclusive breastfeeding
Multiple births	Twins or triplets
Gender	Male
History of atopy	Positive family history of asthma or atopy
Low parental education	No parent having bachelor's degree Education of primary caretaker: 1-7 years or no schooling <12 years' maternal education <11 years' maternal education
Siblings	Mention of siblings or other children living in the household
Passive smoking	Smokers in the household
Maternal smoking	Maternal smoking during pregnancy
Daycare centre attendance	Attendance at daycare centre
Crowding	>7 persons in household ≥10 persons in household ≥2 persons per room ≥3 siblings less than 6 years old sleeping in same room >7 persons sleeping per room An increase of 20% of households >1.5 persons/room
Malnutrition	Weight for age ≤2 standard deviations (SD) Growth ≤median measures (weight for age)
Indoor air pollution	Use of biomass fuels for cooking or a description of indoor smoke
HIV	Confirmed presence of HIV infection in child
Previous illness	Previous history of ALRI/RSV
Altitude	High altitude
Lack of plumbed water	Lack of plumbed water in the household, low in-home water service or using other water sources rather than tap in compound

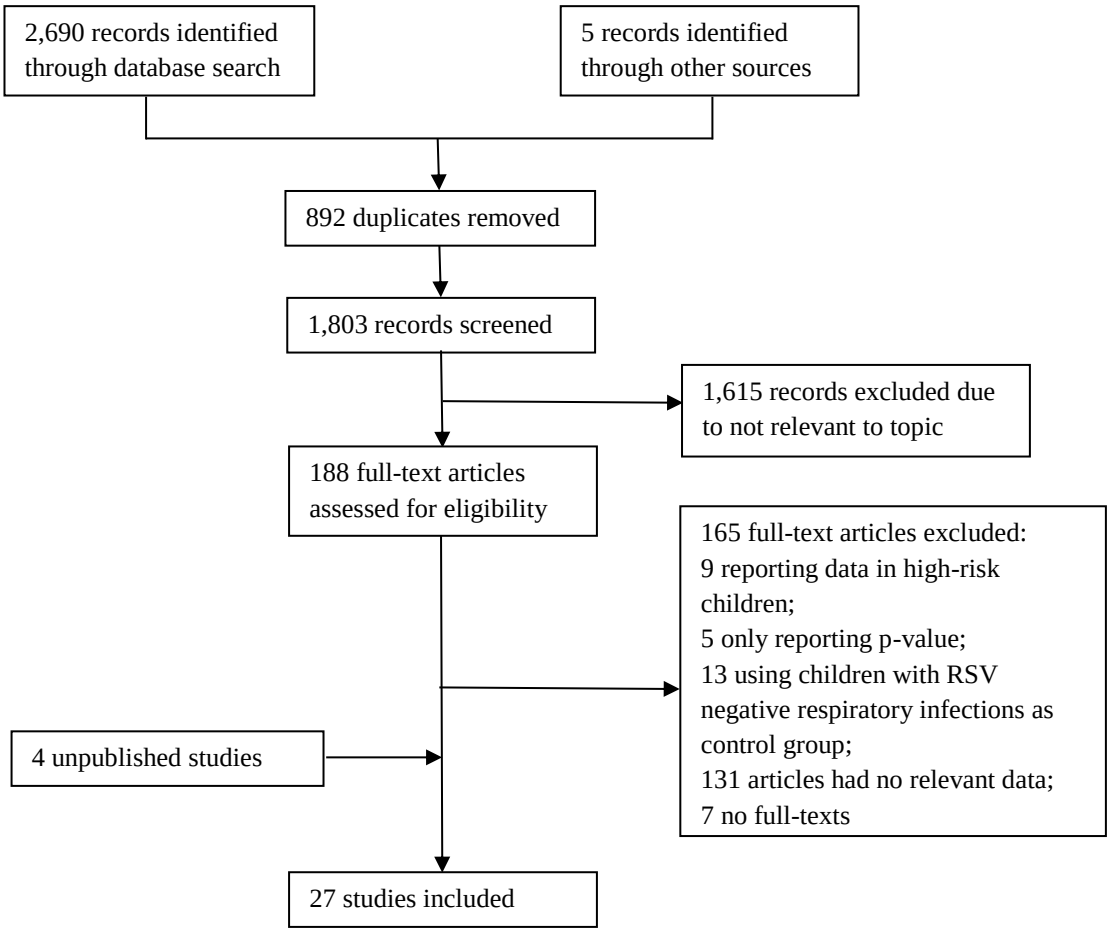


Figure 8: Flow diagram of selection of studies of risk factors for RSV associated ALRI

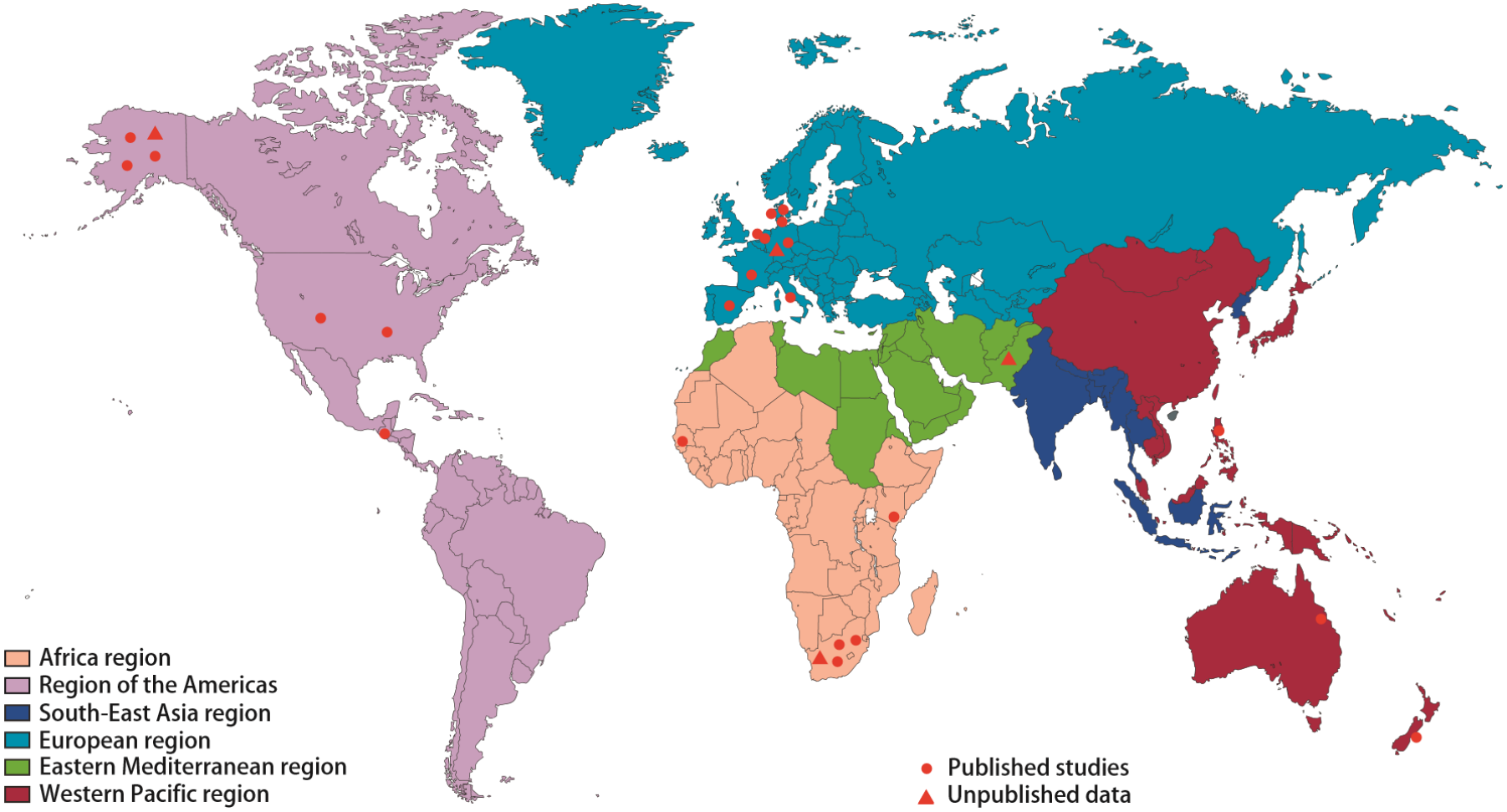


Figure 9: Location of 27 included studies of risk factors for RSV associated ALRI

Table 11: Characteristics of 27 included studies of risk factors for RSV associated ALRI

Study	Study period	Study design	Age	Case ascertainment	Case definition	Sample size	RSV detection	Risk factors included
Hvidovre, Denmark (Von Linstow et al., 2008)	May 2004 - May 2005	Prospective birth cohort	<1y	IP	ARI	217	NPS; PCR	PR, BF, S, PS, MS
Denmark (Stensballe et al., 2006)	1997 - 2003	Case control	<18m	IP	ARI	15380	RSV database	M, HOA, DCA, S, MS
Utrecht, Netherlands (Houben et al., 2011)	Jan 2006 - Dec 2008	Prospective birth cohort	<1y	IP, OP	ALRI	298	Nasal/throat swab; PCR	BF, M, HOA, PE, DCA, MS
Colorado, USA (Choudhuri et al., 2006)	1998 - 2002	Cross sectional	<4y	IP	P, B	4847	ICD-9 RSV codes	Altitude
San Marcos, Guatemala (Smith et al., 2011)	Oct 2002 - Dec 2004	Randomised controlled trial	<18m	IP, OP	ARI	NA	NA; IF	IAP
Kilifi, Kenya (Okiro et al., 2008)	May 2003 - Apr 2007	Birth cohort	<4y	C	ALRI	469	NPW; DFA	MB, PE, MA, C, S, PS
Soweto, South Africa (Madhi et al., 2006)	Mar 1998 - Dec 2004	Prospective cohort	<6y	IP	ALRI	39836	NPA; IF	PR, HIV
South-western Netherlands (Rietveld et al., 2006)	Oct 1996 - Apr 1999	Retrospective cohort	<2y	IP	ARI	NA	NPA; DFA/culture	PR, LBW, M
9 perinatal networks, France (Gouyon et al., 2013)	Mar 2008 to Apr 2009	Retrospective &prospective cohort	<1y	IP	B	498	NPA; IF	PR
Kiel, Germany (Weigl et al., 2001)	Jul 1996 - Jun 1999	Cross sectional	<2y	IP	ARI	NA	NPA; PCR	PR
Bohol, Philippines	Jul 2000 - Dec 2004	Retrospective	<5y	IP	ALRI	10913	NA;	M, PE, MA, S

Study	Study period	Study design	Age	Case ascertainment	Case definition	Sample size	RSV detection	Risk factors included
(Paynter et al., 2014)		cohort					PCR/culture	
Townsville, Australia (Reeve et al., 2006)	Jan 1997 - Jun 2004	Case control	<3y	IP	ALRI	750	NPA; DFA	PR, LBW, M, S
Tennessee, USA (Boyce et al., 2000)	Jul 1989 - Jun 1993	Retrospective cohort	<1y	IP	ARI	3553	NA	PR, M, PE, S, MS
2 Danish counties, Denmark (Nielsen et al., 2003)	1990 - 1994	Case control	<2y	IP	ALRI	7632	NPA; DFA	PR, LBW, S, MS
Basque Country, Spain (Cilla et al., 2006)	Jul 1996 - Jun 2000	Case control	<2y	IP	ALRI	14343	NPA; IF	PR, LBW, MB, M,
Wellington Hospital, New Zealand (Grimwood et al., 2008)	June/July - October, 2003-2005	Case control	<2y	IP	B	11411	NPA; DFA	PR, MB, M, MS
Alaska, USA (Bulkow et al., 2002)	Oct 1993 - Sep 1996	Case control	<3y	IP	ALRI	542	NPA; IF	BF, PE, C, S, S
3 hospitals in western region, Gambia (Weber et al., 1999)	1993 - 1995	Case control	<5y	IP	ALRI	641	NPA; IF	HOA, M, C, S, PS, M, LPW, IAP
Italy (Rossi et al., 2007)	Oct - Apr, 2000 - 2004	Case control	≤4y	IP	ALRI	437	Nasal sample; IF	PR, LBW, BF, M, HOA, PI, S, PS
Alaska, USA (Singleton, unpublished)	Oct 2006 - Sep 2007	Case control	<3y	IP	ALRI	68	NPS; PCR	PR, BF, C, IAP, PS
Oshikhandass, Pakistan (Rasmussen, unpublished)	Apr 2012 - Mar 2014	Case control	<5y	C	ALRI	93	NPS; PCR	C, M, PE, S, IAP, PS

Study	Study period	Study design	Age	Case ascertainment	Case definition	Sample size	RSV detection	Risk factors included
Soweto, South Africa (Madhi et al., 2000)	MAR 1997 - Mar 1998	Cross sectional	2-23m	IP	ALRI	24000	NPA; DFA	HIV
3 sites, South Africa (Moyes et al., 2013)	Jan 2010 - Dec 2011	Cross sectional	<5y	IP	ALRI	835060	NPA; PCR	HIV
Alaska, USA (Bruden et al., 2015)	1995 – 2012	Cross sectional	<1y	IP	ALRI	NA	NPA; DFA/culture	C, IAP, LPW
Alaska, USA (Hennessy et al., 2008)	2000 - 2004	Cross sectional	<1y	IP	ALRI	NA	NPA; DFA/culture	LPW
Paarl, South Africa (Zar, unpublished)	Mar 2012 – Dec 2014	Prospective cohort	<3y	C	ALRI	159	NPS; RT-PCR	PR, LBW, BF, M, HOA, PE, S, PS, MS, DCA, MA, C, IAP, PI
Berlin, Germany (Rath, unpublished)	Apr 2010 – Mar 2014	Prospective cohort	<5y	IP, OP	ALRI	666	NPS/NPA; RT-PCR	PR, LBW, M, C

Case ascertainment: IP=inpatient; OP=outpatient; C=community. Case definition: ALRI=acute lower respiratory infection; ARI=acute respiratory infection; P=pneumonia; B=bronchiolitis. RSV detection: NPA=nasopharyngeal aspirate; NPS=nasopharyngeal swab; NPW=nasopharyngeal wash; PCR=polymerase chain reaction; IF=immunofluorescence; DFA=direct fluorescent antibody test; IFA=indirect fluorescent antibody test. Risk factors included: PR=prematurity; LBW=low birth weight; BF=no/lack of exclusive breastfeeding; MB=multiple births; M=male; HOA=history of atopy; PE=low parental education; S=siblings; PS=passive smoking; MS=maternal smoking; DCA=daycare centre attendance; MA=malnutrition; C=crowding; IAP=indoor air pollution; PI=previous illness; HIV=human immunodeficiency virus; LPW=lack of plumbed water. NA=not available.

Table 12: Score of each study based on modified GRADE scoring system

Study	Design	Quality of control group	Sample size	Analysis	Bias	Confounding factors	Geographical spread of studies	Total *
(Stensballe et al., 2006)	1	2	2	2	1	1	2	11
(Paynter et al., 2014)	2	1	2	2	1	2	1	11
(Rietveld et al., 2006)	2	1	2	2	0	1	2	10
(Reeve et al., 2006)	1	2	2	1	2	1	1	10
(Nielsen et al., 2003)	1	2	2	1	2	1	1	10
(Choudhuri et al., 2006)	0.5	1	2	2	0	2	2	9.5
(Boyce et al., 2000)	2	1	2	1	0	1	2	9
(Bulkow et al., 2002)	1	2	2	1	1	1	1	9
(Weber et al., 1999)	1	2	2	1	1	1	1	9
(Zar, unpublished)	2	2	0	0	2	1	2	9
(Houben et al., 2011)	2	1	0	1	2	1	1	8
(Smith et al., 2011)	0	1	2	2	1	1	1	8
(Gouyon et al., 2013)	2	1	1	0	1	1	2	8
(Grimwood et al., 2008)	1	1	2	2	1	1	0	8
(Rasmussen, unpublished)	1	2	0	1	2	1	1	8
(Von Linstow et al., 2008)	2	2	0	1	1	1	0	7
(Cilla et al., 2006)	1	1	2	1	1	1	0	7
(Rossi et al., 2007)	1	1	1	1	1	1	1	7

Study	Design	Quality of control group	Sample size	Analysis	Bias	Confounding factors	Geographical spread of studies	Total *
(Singleton, unpublished)	1	2	0	2	0	1	1	7
(Moyes et al., 2013)	0.5	0	2	2	0	1	1	6.5
(Okiro et al., 2008)	2	1	1	1	0	1	0	6
(Rath, unpublished)	2	1	2	0	0	0	1	6
(Bruden et al., 2015)	0.5	0	2	1	0	1	1	5.5
(Madhi et al., 2006)	2	1	2	0	0	0	0	5
(Weigl et al., 2001)	0.5	1	2	0	0	0	1	4.5
(Hennessy et al., 2008)	0.5	0	2	0	0	0	1	3.5
(Madhi et al., 2000)	0.5	0	2	0	0	0	0	2.5

*The list of risk factors is ordered based on total score from high to low.

4.3 Results by each risk factor

For each risk factor, the definitions applied and the characteristics of the included studies (region of study setting, case ascertainment approach, analysis method) as well as the overall meta-estimate are presented in the following section.

Prematurity (gestational age <37 weeks)

Three different definitions were applied among the thirteen included studies. One study (Von Linstow et al., 2008) used gestational age <38 weeks as the definition for prematurity, three studies (Boyce et al., 2000, Madhi et al., 2006, Rossi et al., 2007) used gestational age <36 weeks and nine studies used gestational age <37 weeks (Cilla et al., 2006, Grimwood et al., 2008, Nielsen et al., 2003, Reeve et al., 2006, Rietveld et al., 2006, Weigl et al., 2001) (Rath, unpublished; Singleton, unpublished; Zar, unpublished). Only studies using gestational age <37 weeks to define prematurity were included in meta-analysis. Among these nine studies, two (Cilla et al., 2006) (Singleton unpublished) reported the associations based on multivariable analysis and the others used univariable analysis. Two studies (Singleton, unpublished; Zar, unpublished) were based on settings categorised as developing countries, while the rest were from industrialised countries. One study (Zar, unpublished) was community-based, another (Rath, unpublished) included both outpatients and inpatients in the case group and the other seven studies used hospitalised children as cases. Two studies (Weigl et al., 2001) (Rath, unpublished) were considered to be "low-quality" studies according to GRADE scoring system. After excluding these two studies, the odds ratio meta-estimate was 1.96 (95% CI 1.44-2.67) based on seven studies. Alternatively, if all studies irrespective of quality scores (nine studies) were included the meta-estimate was 1.47 (95% CI 0.98-2.21).

Prematurity (gestational age <33 weeks)

This risk factor was considered as a subgroup (more severe case) of children with prematurity. Eight studies reported relevant data. Three hospital-based studies (Boyce et al., 2000, Nielsen et al., 2003, Rietveld et al., 2006) from industrialised countries reported significant associations between prematurity (gestational age <33 weeks) and RSV associated ALRI using multivariable analysis. The overall odds ratio meta-estimate was 2.68 (95% CI 2.02-3.55). Five additional studies (Gouyon et al., 2013, Madhi et al., 2006, Rossi et al., 2007) (Rath unpublished; Zar, unpublished), two of which were from developing countries (Madhi et al., 2006) (Zar, unpublished), reported odds ratios using univariable analysis. The inclusion of these studies resulted in the odds ratio meta-estimate of 2.74 (95% CI 1.59-4.71) based on eight studies. Two studies (Madhi et al., 2006) (Rath, unpublished)

were considered to have “low quality”. After excluding them, the final odds ratio meta-estimate was 2.79 (95% CI 2.19-3.55) from six studies.

Low birth weight

Seven studies in total were included. Six of them used birth weight <2.5 kg to define low birth weight (Cilla et al., 2006, Reeve et al., 2006, Rietveld et al., 2006, Rossi et al., 2007) (Rath, unpublished; Zar, unpublished). One study (Nielsen et al., 2003) from Denmark used a definition of <3.0 kg, thus it was not included in the meta-analysis. Two hospital-based studies (Cilla et al., 2006, Rietveld et al., 2006) from industrialised countries reported significant associations between low birth weight (<2.5 kg) and RSV associated ALRI using multivariable analysis. Four additional studies (Reeve et al., 2006, Rossi et al., 2007) (Rath, unpublished; Zar, unpublished), one of which (Zar, unpublished) was from a developing country setting, reported odds ratios based on univariable analysis. When studies using univariable analysis were combined with studies using multivariable analysis, the overall meta-estimate of odds ratio was 1.37 (95% CI 0.85-2.21) in these 6 studies. After excluding one study with “low quality” (Rath, unpublished), the final meta-estimate was 1.91 (95% CI 1.45-2.53) based on five studies.

Male sex

There were 13 studies reporting associating between being male and RSV associated ALRI. Five hospital-based studies (Boyce et al., 2000, Grimwood et al., 2008, Paynter et al., 2014, Rietveld et al., 2006, Stensballe et al., 2006) and one community-based study (Rasmussen, unpublished), reported associations using multivariable analysis. Two of them reported non-significant associations (Grimwood et al., 2008) (Rasmussen, unpublished) and in the other four studies significant associations were reported. The overall odds ratio meta-estimate was 1.32 (95% CI 1.24-1.40) for these six studies. Seven additional studies (Cilla et al., 2006, Houben et al., 2011, Reeve et al., 2006, Rossi et al., 2007, Weber et al., 1999) (Rath, unpublished; Zar, unpublished), two of which were from developing countries, reported the odds ratios using univariable analysis. Two studies (Houben et al., 2011) (Rath, unpublished) recruited cases from hospital inpatients and outpatients and another one (Zar, unpublished) identified cases based on active community ascertainment. The inclusion of these seven studies did not alter the odds ratio meta-estimate substantially, which was estimated as 1.21 (95% CI 1.12-1.32) from thirteen studies totally. After excluding one “low-quality” study (Rath, unpublished), the final meta-estimate was 1.23 (95% CI 1.13-1.33) based on twelve studies.

Siblings

Twelve studies were included. Six hospital-based studies (Boyce et al., 2000, Nielsen et al., 2003, Paynter et al., 2014, Reeve et al., 2006, Stensballe et al., 2006, Von Linstow et al., 2008), one of which was from a developing country (Paynter et al., 2014), reported associations between siblings (mention of siblings or other children living in the house) and RSV associated ALRI using multivariable analysis. Only one of them reported a non-significant association (Nielsen et al., 2003). The overall odds ratio meta-estimate was 1.53 (95% CI 1.20-1.95). Six additional studies (Bulkow et al., 2002, Okiro et al., 2008, Rossi et al., 2007, Weber et al., 1999) (Rasmussen, unpublished; Zar, unpublished), one of which was from an industrialised country (Rossi et al., 2007), reported odds ratios for siblings and RSV associated ALRI using univariable analysis. Three studies (Okiro et al., 2008) (Rasmussen, unpublished; Zar, unpublished) were based on active community ascertainment. The inclusion of these six studies did not have any substantial effect on the odds ratio meta-estimate, which was 1.62 (95% CI 1.34-1.95) based on overall twelve studies. One study (Okiro et al., 2008) was denoted as "low quality". Therefore, the final estimate was based on eleven studies after excluding this study and the meta-estimate was 1.60 (95% CI 1.32-1.95).

Maternal smoking

There were seven studies identified from the literature search and unpublished data collection network. Four hospital-based studies (Boyce et al., 2000, Grimwood et al., 2008, Nielsen et al., 2003, Stensballe et al., 2006), all of which were from industrialised countries, reported associations between maternal smoking during pregnancy (active) and hospitalised RSV associated ALRI using multivariable analysis. Only one of them reported a non-significant association (Grimwood et al., 2008). The overall odds ratio meta-estimate was 1.34 (95% CI 1.26-1.42). Three additional studies (Houben et al., 2011, Von Linstow et al., 2008) (Zar, unpublished) reported data using univariable analysis: two community-based studies from the Netherlands and South Africa (Houben et al., 2011) (Zar, unpublished) reporting non-significant odds ratios and one hospital-based study from Denmark (Von Linstow et al., 2008) reporting a significant odds ratio. The inclusion of these three studies resulted in a similar meta-estimate of odds ratio - 1.36 (95% CI 1.24-1.50) based on seven studies totally. There were no studies considered to be of "low quality" thus no sensitivity analysis was carried out for this risk factor. However, there was no studies reporting the association between prenatal passive tobacco smoke exposure and RSV associated ALRI, which required further investigation.

Table 13: Meta-estimate of odds ratio for 12 risk factors after excluding studies with quality score ≤6.25 (i.e. "low-quality")

Risk factor*	Multivariable analysis		Multivariable and univariable analysis	
	No. of studies	Meta-estimate OR (95% CI)	No. of studies	Meta-estimate OR (95% CI)
No breastfeeding	1	-	3	2.24 (1.56-3.20)
Prematurity (gestational age <37 weeks)	2	-	7	1.96 (1.44-2.67)
Crowding (>7 persons in household)	1	-	3	1.94 (1.29-2.93)
Low birth weight	2	-	5	1.91 (1.45-2.53)
Daycare centre attendance	2	-	3	1.61 (0.98-2.64)
Siblings	6	1.53 (1.20-1.95)	11	1.60 (1.32-1.95)
History of atopy	1	-	5	1.47 (1.16-1.87)
Low parental education	4	1.23 (0.73-2.09)	6	1.40 (0.94-2.08)
Maternal smoking	4	1.34 (1.26-1.42)	7	1.36 (1.24-1.50)
Passive smoking	4	1.40 (0.65-3.00)	8	1.29 (0.96-1.73)
Being male	6	1.32 (1.24-1.40)	12	1.23 (1.13-1.33)
Indoor air pollution	4	0.69 (0.35-1.37)	5	0.81 (0.42-1.57)

*Only listing risk factors where meta-estimate is available, and the list of risk factors is ordered based on meta-estimate of studies using multivariable and univariable analysis from high to low.

History of atopy

Overall, five studies were available reporting the association between history of atopy (positive family history of asthma or atopy) and RSV associated ALRI. One hospital-based study (Stensballe et al., 2006) from Denmark reported a significant association between history of atopy and hospitalised RSV associated ALRI using multivariable analysis. Four additional studies (Houben et al., 2011, Rossi et al., 2007, Weber et al., 1999) (Zar, unpublished), two of which were from developing countries (Weber et al., 1999) (Zar, unpublished), reported the odds ratios using univariable analysis. One study (Houben et al., 2011) was based on both inpatient and outpatient settings in hospital and another one (Zar, unpublished) was a community-based study. The overall odds ratio meta-estimate was 1.47 (95% CI 1.16-1.87). All were considered "good quality" studies.

Low parental education

Definitions of low parental education varied among the included studies. Four studies (Boyce et al., 2000, Houben et al., 2011, Paynter et al., 2014) (Rasmussen, unpublished), two of which were from developing countries (Paynter et al., 2014) (Rasmussen, unpublished), reported associations between low parental education (no parent having bachelor's degree in an industrialised country, <11 or <12 years maternal education, primary or no schooling) and RSV associated ALRI using multivariable analysis. Additionally, two studies reported significant associations. One study (Houben et al., 2011) identified cases from both inpatient and outpatient settings in hospital. One study (Rasmussen, unpublished) was a community-based study and used active ascertainment method. The overall odds ratio meta-estimate was 1.23 (95% CI 0.73-2.09). Three additional studies (Bulkow et al., 2002, Okiro et al., 2008) (Zar, unpublished) from developing countries reported odds ratios for low parental education (≤12 grade or primary or no schooling) and RSV associated ALRI based on univariable analysis. Two studies (Okiro et al., 2008) (Zar, unpublished) used active community ascertainment to identify cases. The inclusion of these three studies resulted in a slightly higher odds ratio meta-estimate of 1.77 (95% CI 0.91-3.46) (seven studies in total). After excluding one "low-quality" study (Okiro et al., 2008), the meta-estimate was 1.40 (95% CI 0.94-2.08) based on six studies.

Passive smoking

Nine studies were included and reported relevant data for associations between postnatal passive smoking (smokers in the house) and RSV associated ALRI. Three hospital-based studies and one community-based study reported the associations using multivariable analysis with the meta-estimate 1.40 (95% CI 0.65-3.00) (Von Linstow et al., 2008, Weber et al., 1999) (Rasmussen, unpublished; Singleton, unpublished). Only one study from Denmark (Von Linstow et al., 2008) reported a significant association. Five additional studies (Bulkow et al., 2002, Okiro et al., 2008, Reeve et al., 2006, Rossi et al., 2007) (Zar, unpublished), two of which were from industrialised countries (Reeve et al., 2006, Rossi et al., 2007), reported odds ratios for passive smoking and RSV associated ALRI based on univariable analysis. Two of them reported significant associations (Bulkow et al., 2002, Reeve et al., 2006). Two studies (Okiro et al., 2008) (Zar, unpublished) identified cases based on active community ascertainment. After combining all studies (studies using multivariable and studies using univariable analysis), the meta-estimate of odds ratio was 1.23 (95% CI 0.95-1.60) based on nine studies. One study (Okiro et al., 2008) was "low quality". After excluding this study, the final meta-estimate was 1.29 (95% CI 0.96-1.73) and there were eight studies in total.

Daycare centre attendance

Three studies were identified. One hospital-based study (Stensballe et al., 2006) from Denmark reported a significant association between daycare centre attendance and hospitalised RSV associated ALRI using multivariable analysis (1.40 (95% CI 1.15-1.70)). One study (Houben et al., 2011) from the Netherlands, which had cases from both inpatient and outpatient settings in hospital, reported a non-significant association between daycare centre attendance and RSV associated ALRI using multivariable analysis (5.80 (95% CI 0.76-44.4)). One community-based study (Zar, unpublished) from South Africa also reported a non-significant association using univariable analysis. Overall, the odds ratio meta-estimate was 1.61 (95% CI 0.98-2.64). All studies were of "good quality" and were included in the final analysis.

Indoor air pollution

Overall, six studies were included reporting the associations between indoor air pollution (woodstove in household) and RSV associated ALRI. Three hospital-based studies (Bruden et al., 2015, Weber et al., 1999) (Singleton, unpublished) from Alaska and Gambia reported associations using multivariable or univariable analysis. Another study (Smith et al., 2011) from Guatemala, which was based on both inpatient and outpatient settings in hospital, reported a non-significant association using multivariable analysis (0.76 (95% CI 0.42-1.16)). A further two studies (Rasmussen, unpublished; Zar, unpublished) from Pakistan and South Africa identified cases using active community ascertainment and also reported non-significant associations using univariable analysis. Overall, the meta-estimate of odds ratio was 0.86 (95% CI 0.57-1.31) based on six studies. One study (Bruden et al., 2015) was considered as having "low quality", thus after excluding this study, the final meta-estimate was 0.81 (0.42-1.57) from five studies.

No breastfeeding

Three hospital-based studies (Bulkow et al., 2002) (Singleton, unpublished; Zar, unpublished) from developing countries reported associations between no breastfeeding and RSV associated ALRI. Only one of them (Bulkow et al., 2002) reported a significant association based on univariable analysis. All of these three studies had "good quality" and the overall meta-estimate of odds ratio was 2.24 (95% CI 1.56-3.20). Another four studies (Houben et al., 2011, Rossi et al., 2007, Von Linstow et al., 2008) (Zar, unpublished), three from industrialised countries, reported odds ratios for lack of breastfeeding (no breastfeeding for first 14 days, <3 months breastfeeding or lack of exclusive breastfeeding) and RSV associated ALRI. Only one study (Von Linstow et al., 2008) reported a significant odds ratio

based on multivariable analysis. One study (Houben et al., 2011) was based on both inpatient and outpatient settings in hospital and another one (Zar, unpublished) was community-based. Since these four studies used substantially different definitions for breastfeeding and there were no enough studies for each category of different definitions, meta-analysis was not carried out.

Crowding

Included studies used varied definitions for crowding. Four studies (Bulkow et al., 2002) (Rath, unpublished; Singleton, unpublished; Zar, unpublished) reported associations between crowding (>7 persons in household) and RSV associated ALRI. One study (Rath, unpublished) from Germany only had 5 children with crowding exposed (5 in case group and 0 in control group). The prevalence of crowding is too small to generate a reliable estimate; thus this study was not included in analysis. One of them (Singleton, unpublished) reported the association using multivariate analysis. One study (Zar, unpublished) was community-based and the other two were hospital-based. These three studies all had "good quality". Overall, the meta-estimate of the odds ratios was 1.94 (95% CI 1.29-2.93) for these three studies. Other studies used substantially different case definitions and, for these, they were not included in the meta-analysis. Two studies (Bruden et al., 2015, Bulkow et al., 2002) from Alaska presented significant associations between crowding (defined as ≥2 persons/room in household and an increase of 20% of households >1.5 persons/room) and hospitalised RSV associated ALRI. One hospital-based study (Weber et al., 1999) from Gambia also reported a significant association using the definition of ≥10 people living in the household. Two community-based studies from Kenya (Okiro et al., 2008) and Pakistan (Rasmussen, unpublished) reported non-significant associations with definitions of ≥3 siblings/room or >7 persons/room. These definitions were considerably different from each other and there were no sufficient studies reporting data for each category, thus a separate meta-analysis was not done.

Multiple births

Only one study (Grimwood et al., 2008) from New Zealand reported a non-significant association between multiple births (twins or triplets) and hospitalised RSV associated ALRI using multivariable analysis. Two additional studies reported non-significant odds ratios using univariable analysis. One study from Spain (Cilla et al., 2006) presented the association for multiple births and hospitalised RSV associated ALRI whilst another study from Kenya (Okiro et al., 2008) was based on active community-based case ascertainment. After these three studies were combined, the odds ratio meta-estimate was 1.41 (95% CI

0.98-2.03). However, one study (Okiro et al., 2008) was considered as "low-quality" and thus no meta-estimate was available after excluding this study (no meta-estimates results shown in Table 13).

HIV

Three hospital-based studies (Madhi et al., 2006, Madhi et al., 2000, Moyes et al., 2013) from South Africa reported significant associations between HIV (confirmed presence of HIV infection in child) and RSV associated ALRI. One of them reported an age-adjusted association and provided data for two years separately (Moyes et al., 2013). The overall meta-estimate of odds ratio was 3.74 (95% CI 2.47-5.66) for these three studies. Two of them (Madhi et al., 2006, Madhi et al., 2000) were considered to be of "low quality". Thus no meta-estimate was available after these two "low-quality" studies were excluded (no meta-estimates results shown in Table 13).

Malnutrition

Only three studies were included. Two community-based studies from Kenya (Okiro et al., 2008) and South Africa (Zar, unpublished) reported non-significant associations between malnutrition (weight for age ≤2 standard deviations) and RSV associated ALRI using univariable analysis (1.28 (95% CI 0.75-2.21) and 1 (95% CI 0.4-2.9)). Another hospital-based study (Paynter et al., 2014) from the Philippines reported a significant association between measures less than or equal to median growth (weight for age) and hospitalised RSV associated ALRI using multivariable analysis (1.34 (95% CI 1.02-1.76)). This definition is substantially different from what was used in the previous two studies (weight for age ≤2 standard deviations), thus meta-analysis could not be done (no meta-estimates results shown in Table 13).

Altitude

Only one hospital-based study (Choudhuri et al., 2006), from Colorado, reported a significant association between high altitude and hospitalised RSV associated ALRI using multivariable analysis, stratified by age and control group (no meta-estimates results shown). The odds ratio of RSV associated hospitalised ALRI among infants at high altitude (>2500 m) compared to moderate altitude (1500-2500 m) was 1.30 while it was 1.22 when compared to low altitude (<1500 m). Also, the odds ratio among children aged 1-4 years old in high altitude was 1.80 when compared to moderate altitude and 1.62 when compared to low altitude. Since only one study was identified, no analysis plan was carried out.

Previous respiratory illness

One hospital-based study (Rossi et al., 2007) from Italy reported a significant association between no previous RSV infections and hospitalised RSV associated ALRI using univariable analysis (1.85 (95% CI 1.02-3.36)). Another community-based study from South Africa (Zar, unpublished) reported a significant association between previous history of ALRI and RSV associated ALRI using univariable analysis (3.9 (95% CI 1.2-12.5)). These two studies reported completely different results, although one referred to previous RSV infection and another one to previous ALRI infection (aetiology not specified). No further details were provided from both studies. They were based on hospital and community settings respectively, which might have influenced the result in some unknown way. More investigation about the role of this risk factor was required (no meta-estimates results shown in Table 13).

Lack of plumbed water (available within the household)

Two hospital-based studies (Bruden et al., 2015, Hennessy et al., 2008) from Alaska reported significant associations between lack of plumbed water or low proportion in-home water service (<80%) and hospitalised RSV associated ALRI (1.45 (95% CI 1.19-1.78) and 2.81 (95% CI 2.42-3.26)) respectively. However, both studies were considered to be of "low-quality". Another study from Gambia (Weber et al., 1999) reported "tap in compound" compared to other water sources and the adjusted OR was 1.75 (95% CI 0.85-3.60). This number was converted to be comparable (0.57 (95% CI (0.28-1.18)) to those two studies mentioned above (no meta-estimates results shown in Table 13).

Table 14: Meta-estimate of odds ratio for risk factors including data from all studies (irrespective of quality scores)

Risk factor*	Multivariable analysis		Multivariable and univariable analysis	
	No. of studies	Meta-estimate OR (95% CI)	No. of studies	Meta-estimate OR (95% CI)
HIV	2	-	3	3.74 (2.47-5.66)
No breastfeeding	1	-	3	2.24 (1.56-3.20)
Crowding (>7 persons in household)	1	-	3	1.94 (1.29-2.93)
Low parental education	4	1.23 (0.73-2.09)	7	1.77 (0.91-3.46)
Siblings	6	1.53 (1.20-1.95)	12	1.62 (1.34-1.95)
Daycare centre attendance	2	-	3	1.61 (0.98-2.64)
History of atopy	1	-	5	1.47 (1.16-1.87)
Prematurity (gestational age <37 weeks)	2	-	9	1.47 (0.98-2.21)
Lack of plumbed water	2	-	3	1.46 (0.76-2.79)
Multiple births	1	-	3	1.41 (0.98-2.03)
Low birth weight	2	-	6	1.37 (0.85-2.21)
Maternal smoking	4	1.34 (1.26-1.42)	7	1.36 (1.24-1.50)
Passive smoking	4	1.40 (0.65-3.00)	9	1.23 (0.95-1.60)
Being male	6	1.32 (1.24-1.40)	13	1.21 (1.12-1.32)
Indoor air pollution	4	0.69 (0.35-1.37)	6	0.86 (0.57-1.31)

*Only listing risk factors where meta-estimate is available, and the list of risk factors is ordered based on meta-estimate of studies using multivariable and univariable analysis from high to low.

Table 15: Comparison of meta-estimates after excluding or including "low quality" studies (with quality score ≤6.25)

Risk factor*	Final estimate		Sensitivity analysis (including "low-quality" studies)	
	No. of studies	Meta-estimate OR (95% CI)	No. of studies	Meta-estimate OR (95% CI)
HIV	1	-	3	3.74 (2.47-5.66)
No breastfeeding	3	2.24 (1.56-3.20)	3	2.24 (1.56-3.20)
Crowding (>7 persons in household)	3	1.94 (1.29-2.93)	3	1.94 (1.29-2.93)
Low parental education	6	1.40 (0.94-2.08)	7	1.77 (0.91-3.46)
Siblings	11	1.60 (1.32-1.95)	12	1.62 (1.34-1.95)
Daycare centre attendance	3	1.61 (0.98-2.64)	3	1.61 (0.98-2.64)
History of atopy	5	1.47 (1.16-1.87)	5	1.47 (1.16-1.87)
Prematurity (gestational age <37 weeks)	7	1.96 (1.44-2.67)	9	1.47 (0.98-2.21)
Lack of plumbed water	1	-	3	1.46 (0.76-2.79)
Multiple births	2	-	3	1.41 (0.98-2.03)
Low birth weight	5	1.91 (1.45-2.53)	6	1.37 (0.85-2.21)
Maternal smoking	7	1.36 (1.24-1.50)	7	1.36 (1.24-1.50)
Passive smoking	8	1.29 (0.96-1.73)	9	1.23 (0.95-1.60)
Being male	12	1.23 (1.13-1.33)	13	1.21 (1.12-1.32)
Indoor air pollution	5	0.81 (0.42-1.57)	6	0.86 (0.57-1.31)

*Only listing risk factors where meta-estimate is available, and the list of risk factors is ordered based on meta-estimate of studies including "low-quality" ones from high to low.

Table 16: Meta-estimate of odds ratio for risk factors in developing and industrialised regions (irrespective of quality scores)

Risk factor	Developing region		Industrialised region	
	No. of studies	Meta-estimate OR (95% CI)	No. of studies	Meta-estimate OR (95% CI)
HIV	3	3.74 (2.47-5.66)	0	-
No breastfeeding	3	2.24 (1.56-3.20)	0	-
Crowding (>7 persons in household)	3	1.94 (1.29-2.93)	0	-
Low parental education	5	2.49 (1.12-5.54)	2	-
Siblings	6	1.65 (1.37-1.98)	6	1.56 (1.20-2.01)
Daycare centre attendance	1	-	2	-
History of atopy	2	-	3	1.42 (1.12-1.80)
Prematurity (gestational age <37 weeks)	2	-	7	1.60 (1.04-2.44)
Lack of plumbed water	3	1.46 (0.76-2.79)	0	-
Multiple births	1	-	2	-
Low birth weight	1	-	5	1.52 (0.93-2.49)
Maternal smoking	1	-	6	1.37 (1.24-1.52)
Passive smoking	6	1.16 (0.91-1.46)	3	1.46 (0.74-2.86)
Being male	4	1.20 (0.93-1.55)	9	1.21 (1.11-1.33)
Indoor air pollution	6	0.86 (0.57-1.31)	0	-

4.4 Discussion

This study presents the most up-to-date and comprehensive report of the strength of association between various socio-demographic risk factors and RSV associated ALRI in children younger than five years old. After excluding "low-quality" studies, the final results for a total of 18 putative risk factors were described and the meta-estimates were presented if possible. Among them, eight risk factors (prematurity, low birth weight, being male, siblings, maternal smoking, history of atopy, no breastfeeding and crowding - >7 persons in household) were observed to be significantly associated with RSV associated ALRI. Children born with prematurity of gestational age <37 weeks were estimated to have higher odds (1.96 (1.44-2.67)) of RSV associated ALRI than children born without prematurity. Children with low birth weight (<2.5 kg) were at an increased risk (1.91 (1.45-2.53)). Gender (being males) also played as a risk factor for RSV associated ALRI (1.23 (1.13-1.33)). Having siblings represented an increased risk of outcome (1.60 (1.32-1.95)). Maternal smoking during pregnancy also was observed to have a positive OR with RSV associated ALRI (1.36 (1.24-1.50)). Positive family history of asthma or atopy similarly had significant association with outcome of interest (1.47 (1.16-1.87)). No breastfeeding tended to increase the risk by 1.24 (2.24 (1.56-3.20)). Living in a household with more than 7 persons also increased the association (1.94 (1.29-2.93)). Other risk factors (low parental education, passive smoking, daycare centre attendance, indoor air pollution, HIV, multiple births, malnutrition, higher altitude, previous illness and lack of plumbed water in the household) were also observed to have an association with RSV associated ALRI. Six out of eighteen risk factors did not have meta-estimates available due to insufficient data points (e.g. HIV, multiple births). Moreover, for some of these risk factors, which had several different definitions (e.g. lack of breastfeeding, crowding), meta-analysis could not be performed to generate a separate odds ratio meta-estimate as the case definitions were substantially different and there were no sufficient studies available for this specific different definition. Therefore, the associations between these risk factors (and certain definitions of some risk factors) and RSV associated ALRI require further study.

There was considerable variation regarding to study design among the 27 included studies (including "low-quality" studies). Nine (Boyce et al., 2000, Gouyon et al., 2013, Houben et al., 2011, Madhi et al., 2006, Okiro et al., 2008, Paynter et al., 2014, Rietveld et al., 2006, Von Linstow et al., 2008) (Rath, unpublished) were cohort studies; eleven (Bulkow et al., 2002, Cilla et al., 2006, Grimwood et al., 2008, Nielsen et al., 2003, Reeve et al., 2006, Rossi et al., 2007, Stensballe et al., 2006, Weber et al., 1999) (Rasmussen, unpublished; Singleton, unpublished; Zar, unpublished) were case control studies; six (Choudhuri et al., 2006, Weigl

et al., 2001, Madhi et al., 2000, Moyes et al., 2013, Bruden et al., 2015, Hennessy et al., 2008) were cross sectional studies; and one (Smith et al., 2011) was a randomised controlled trial with placebo arm only. Most studies used questionnaires or interviews (of caretakers or parents) to gather information on various risk factors, which could be a source of several biases, such as response bias (a proportion of participants failed to provide needed information and thus excluded in further analysis), recall bias (participants from both groups might provide information of the past in a non-comparable manner), interviewer bias (investigators might elicit or interpret the information differentially) and misclassification bias (misclassification of cases or controls). Other potential biases also existed. For example, there could be follow-up bias in cohort studies. Among eleven case control studies, only seven (Bulkow et al., 2002, Nielsen et al., 2003, Reeve et al., 2006, Stensballe et al., 2006, Weber et al., 1999) (Rasmussen, unpublished; Zar, unpublished) selected a control group matched by date of birth and/or sex and/or location of residence. For the remaining four studies, which did not use matched control groups, substantial bias in the selection of controls might exist.

Among these 27 studies, 14 were based on settings considered as industrialised regions while the rest 13 were based on developing settings. Meta-estimates for each risk factor by regions were presented in Table 16. For most risk factors, the result was absent for at least one region due to insufficient data points (one or two studies only) or no studies providing relevant data, which remained the comparison of strength of associations between risk factors and RSV associated ALRI in different regions unavailable. Whether the magnitude of reported association varies across regions remains unknown.

Considering the limited data points from multivariable analysis contributed to estimates, estimates from studies using univariable analysis were also considered to produce the final estimate. However, there were substantial differences with regards to the number of confounders adjusted in each study. Seven studies (Grimwood et al., 2008, Paynter et al., 2014, Choudhuri et al., 2006, Rietveld et al., 2006, Smith et al., 2011, Stensballe et al., 2006) (Singleton, unpublished) used multivariable analysis to adjust for all other risk factors investigated in the same study. Some also adjusted for age at third dose of pneumococcal conjugate vaccine, age at risk and weight for age z-score at first vaccination (Paynter et al., 2014), or population distribution of education level, households that were living below poverty level and race (Choudhuri et al., 2006). One study reported age adjusted relative risk (Moyes et al., 2013). Four studies (Madhi et al., 2006, Madhi et al., 2000, Moyes et al., 2013, Von Linstow et al., 2008) also reported concurrent bacteraemia or coinfection with other viruses. Another seven studies used univariable analysis, and twelve studies reported the

results for some risk factors by using multivariable analysis while other studies only used univariable analysis. For those risk factors where meta-estimate was based on univariable analysis, nothing was done to account for potential confounding factors (including those investigated in the same study), which might hide the real association between the risk factors and RSV associated ALRI. Moreover, the exposure of a few risk factors is related to one another (e.g. prematurity and low birth weight, crowding and having sibling in the household). Analysing data only focusing on one single risk factor without taking into consideration other confounders or other related aspects might produce misleading estimate. Inclusion of the results from univariable analysis to those based on multivariable analysis might not be ideal, which requires further investigation.

The quality score of each study obtained from modified GRADE scoring system varied from 2.5 to 11 with a mean of 7.6. There were seven studies with "low quality" (quality score ≤6.25). Most of the studies were not designed as case-control studies, did not avoid/consider biases within the research, did not take into account of potential confounders or reported estimates using univariable analysis. A sensitivity analysis was carried out to include these "low-quality" studies for each risk factor. The meta-estimate OR from sensitivity analysis did not differ substantially from the analysis where only studies with quality scores >6.25 were included (Table 15). Besides, this quality assessment tool did not address all aspects related to quality of study since only seven of them were looked into: study design, quality of control group, sample size, analysis method, bias, confounding factors and geographical spread of studies. More detailed and appropriate quality assessment tools should be applied to evaluate the quality of included studies and studies with higher quality would be needed to generate more reliable results. In this review, selection criteria were not based on the quality of studies, which means, all studies irrelevant of quality scores were included in the analysis and were discussed, but only studies with "good quality" were included to generate the final estimate for each risk factor.

It is noteworthy that there was substantial heterogeneity in the definitions for a specific risk factor across the included studies, which limited the analysis. For example, six studies used a definition of birthweight <2.5 kg to define low birth weight, while one study (Nielsen et al., 2003) used a higher threshold - birthweight <3.0 kg, and was therefore excluded from the meta-analysis. Nine studies defined prematurity as gestational age <37 weeks, while three studies (Boyce et al., 2000, Rossi et al., 2007, Madhi et al., 2006) used gestational age <36 weeks and another one (Von Linstow et al., 2008) used <38 weeks. After excluding "low-quality" studies and these four studies using different definitions of prematurity, the meta-estimate of the association between prematurity (gestational age <37 weeks) and RSV

associated ALRI was 1.96 (95% CI 1.44-2.67), which was slightly higher than the alternative estimate 1.47 (95% CI 0.98-2.21) when all studies irrespective of quality scores were included. Only one study (Zar, unpublished) reported that prematurity was determined using ultrasonography. Seven studies defined low parental education using five different definitions - no parent having bachelor's degree (Houben et al., 2011), 1-7 years of education or no schooling for primary caretaker (Okiro et al., 2008) (Zar, unpublished), 1-5 years of education or no schooling for parents (Rasmussen, unpublished), <12 years maternal education (Boyce et al., 2000, Bulkow et al., 2002) and <10 years maternal education (Paynter et al., 2014). Since there were insufficient studies in each category, a subgroup meta-analysis was not conducted. Similarly crowding was defined using substantially different definitions in the included studies: >7 persons living in household (Bulkow et al., 2002) (Singleton, unpublished; Zar, unpublished), ≥10 persons in household (Weber et al., 1999), ≥2 persons per room (Bulkow et al., 2002) (Zar, unpublished), ≥3 siblings less than 6 years old sleeping in the same room (Okiro et al., 2008), >7 persons sleeping per room (Rasmussen, unpublished), an increase of 20% in number of households >1.5 persons/room (Bruden et al., 2015). Therefore, once again, a subgroup meta-analysis was not carried out in this instance except for the definition of >7 persons living in household (3 studies reported this). The substantial variability in definitions used for the same risk factor require that standardised definitions should be proposed for future studies, which will improve the comparability of these studies. Alternatively, if those standardised definitions are not compatible for different study setting/regions, more studies referring to a specific definition of a risk factor should be carried out and a separate meta-analysis should be conducted.

Moreover, participants with various age groups were included in each study. Only six studies included children younger than five years old (Madhi et al., 2006, Paynter et al., 2014, Weber et al., 1999, Moyes et al., 2013) (Rath, unpublished), and 21 studies included children in younger age bands (eg, 0-11months, 0-18 months, 0-23 months). Fourteen studies focused on children younger than two years old, and among them, six studies included only infants (children aged 0-11 months) (Boyce et al., 2000, Gouyon et al., 2013, Houben et al., 2011, Von Linstow et al., 2008, Bruden et al., 2015, Hennessy et al., 2008). Since data from different age groups were pooled together into one analysis, and RSV is predominantly an infection in children younger than 2 years (Nair et al., 2010), the association between these risk factors and RSV associated ALRI in children aged 0-59 months may have been overestimated, where actually children with a younger age group were (partially) involved.

Another limitation is that we did not have access to individual patient data on risk factors for RSV associated ALRI. Further research should focus on obtaining individual patient data

from previous studies or ongoing studies, such as multi-centre Pneumonia Etiology Research for Child Health (PERCH) project. With these patient level data, we could have a better understanding about the role of each risk factor in RSV associated ALRI (particularly with regard to the lack of independence of prematurity and low birth weight as well as crowding and presence of siblings) and adjust for possible confounders (investigated in the same study) in a pooled analysis.

Table 17 displays results after studies conducted among children younger than two years old (14 studies) were focused on. Meta-estimate results were missing for most risk factors due to insufficient data points available. The magnitude of association between prematurity (gestational age <37 weeks) and RSV associated ALRI was slightly higher in children under two years compared to the association in children under five years (also for being male), while for the rest risk factors the associations were pretty similar.

Furthermore, the sample size of each study varied considerably. Only studies with a sample size greater than 50 were included, as specified in the eligibility criteria. However, among the 27 included studies, the sample size varied from 68 (Singleton, unpublished) to 835060 (Moyes et al., 2013). This is reflected in the wide confidence intervals of the ORs for some studies with small sample size, indicating less precise estimates. Studies with larger sample sizes with more statistical powerful results were required.

Another limitation is that we did not have access to individual patient data on risk factors for RSV associated ALRI. Further research should focus on obtaining individual patient data from previous studies or ongoing studies, such as multi-centre Pneumonia Etiology Research for Child Health (PERCH) project. With these patient level data, we could have a better understanding about the role of each risk factor in RSV associated ALRI (particularly with regard to the lack of independence of prematurity and low birth weight as well as crowding and presence of siblings) and adjust for possible confounders (investigated in the same study) in a pooled analysis.

Table 17: Comparison of associations with risk factors in children younger than five years and children younger than two years respectively (after excluding "low quality" studies)

Risk factor*	Children under five years		Children under two years	
	No. of studies	Meta-estimate OR (95% CI)	No. of studies	Meta-estimate OR (95% CI)
No breastfeeding	3	2.24 (1.56-3.20)	0	-
Prematurity (gestational age <37 weeks)	7	1.96 (1.44-2.67)	4	2.28 (1.64-3.17)

Crowding (>7 persons in household)	3	1.94 (1.29-2.93)	0	-
Low birth weight	5	1.91 (1.45-2.53)	2	-
Daycare centre attendance	3	1.61 (0.98-2.64)	2	-
Siblings	11	1.60 (1.32-1.95)	4	1.51 (1.09-2.08)
History of atopy	5	1.47 (1.16-1.87)	2	-
Low parental education	6	1.40 (0.94-2.08)	2	-
Maternal smoking	7	1.36 (1.24-1.50)	6	1.37 (1.24-1.52)
Passive smoking	8	1.29 (0.96-1.73)	1	-
Being male	12	1.23 (1.13-1.33)	6	1.28 (1.19-1.38)
Indoor air pollution	5	0.81 (0.42-1.57)	1	-

*the list of risk factors is ordered based on meta-estimate of studies in children under five years old from high to low.

Compared to the previous review (Simoes, 2003) conducted over one decade ago, this review presented an overview of a larger number and more recent studies investigating more risk factors associated with RSV and summarised the findings using meta-analysis (rather than descriptive methods). Both reviews shared similar results for some risk factors, such as being male, crowding/siblings and day care attendance. Also, more evidence for some risk factors which had an unclear role with regard to RSV in previous review were provided (passive smoking, low parental education). In addition, more risk factors associated with RSV which were not available in previous review due to insufficient evidence were identified (prematurity, low birth weight, maternal smoking, history of atopy, indoor air pollution, no breastfeeding). However, age of acquisition of RSV as well as birth during the first half of RSV season, race/ethnicity, which were investigated in previous review, were not evaluated in this review because no recent relevant studies were found or they didn't meet the selection criteria (such as, studies were done in children with prematurity). In previous review, the majority of RSV hospitalisation cases occurred within first year of life. This review didn't specifically look into age of acquisition of RSV as a risk factor, however, the following Chapter 5 of disease burden of RSV showed that incidence rate of RSV associated ALRI is high in infants. Birth during the first half of RSV season was also assumed to be a risk factor for RSV associated ALRI (development and hospitalisation) probably due to low maternal antibody level (not exposed to RSV yet). Hospitalisation rate due to RSV was observed higher in Hispanic infants, American Indian/Alaskan Native and Inuit infants, and Japanese infants without further details/explanation. More studies are

needed to update/verify the roles of these risk factors. Moreover, several risk factors which were mentioned in some studies were not included in the search strategy (then in the analysis), such as, sibling's death, parent's nationality, parent's occupation, their roles also remained unknown (Weber et al., 1999). A more comprehensive research of all possible risk factors on RSV associated ALRI should be carried out.

In this systematic review, asymptomatic children (children without respiratory symptoms) or healthy children (children do not have respiratory symptoms or any other symptoms) were chosen as the control group. This is clearly stated in the selection criteria. RSV negative ALRI cases, which means that ALRI cases were positive for other pathogens, were not used as a control group. This is because ALRI cases (RSV negative) might share similar socio-demographic risk factors with RSV associated ALRI cases, which would conceal the real roles of RSV. This is explained in details in the next paragraph.

The definitions of some risk factors were similar or the same as those reported in a review (Jackson et al., 2013) investigating risk factors for severe ALRI (for which aetiology was not further specified), which indicates that pneumonia and RSV associated ALRI do share a few socio-demographic risk factors which are amenable to public health interventions, such as maternal smoking, passive smoking and no breastfeeding. This supported the selection criteria – only children without any respiratory symptoms or healthy children should be included in control group and children with ALRI (RSV negative) should not be used as a control. Table 18 compares the strength of association of risk factors discussed in both reviews. The strength of association between risk factors and severe ALRI was generally slightly stronger than the corresponding ones in RSV associated ALRI. Several risk factors were only investigated for severe ALRI, such as incomplete immunization, vitamin D deficiency, anaemia, zinc deficiency, birth interval, birth order, and vitamin A deficiency (one study), while some risk factors were only explored for RSV associated ALRI (siblings, history of atopy, multiple births, high altitude (one study), and lack of plumbed water in the household (one study)). On the other hand, since pneumonia and RSV associated ALRI share some risk factors and this review is investigating the roles of risk factors in ALRI cases which are positive for RSV, whether the (significant) associations between risk factors and outcome of interest were partially due to ALRI and to what extent remains unknown. Therefore, when interpreting the results, we should state it clearly that the results reflect the association between risk factors and RSV associated ALRI.

The Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea (GAPPD) highlighted several proven effective interventions in order to achieve

maximum benefit of coordinated management of both major preventable causes of child death (UNICEF and Organization, 2013). Some of them were covered by this review: exclusive breastfeeding for 6 months, safe drinking-water and sanitation, reduce household air pollution, HIV prevention. Also several other interventions were proposed: adequate complementary feeding, vitamin A supplementation, handwashing with soap, vaccination etc. Since RSV associated ALRI shared common risk factors with pneumonia. Interventions which are aimed to decrease pneumonia occurrence might also contribute to a reduction of RSV associated ALRI. Moreover, there were several risk factors associated with both RSV associated ALRI and pneumonia which were not covered by GAPPD: maternal smoking during pregnancy, passive smoking, low parental education etc. Their roles should be evaluated with more substantial studies and if verified, should be incorporated into this integrated key intervention framework. This integrated approach should be implemented effectively with priority and slight adjustment in national level (and community level) depending on the circumstances of this area. All sectors including governments, health workers, education professionals, NGOs, financial sponsors should be engaged in this process to maximise the benefit from this strategy.

Table 18: Summary of risk factors for RSV associated ALRI and severe ALRI

Risk factor*	RSV associated ALRI		Severe ALRI (aetiology not specified)	
	No. of studies	Meta-estimate OR (95% CI)	No. of studies	Meta-estimate OR (95% CI)
Vitamin D deficiency	0	-	3	7.3 (2.5-21.5)
HIV	1	-	2	4.6 (2.2-9.7)
Anaemia	0	-	5	3.9 (2.4-6.3)
Daycare centre attendance	3	1.61 (0.98-2.64)	3	3.7 (0.7-20.2)
Malnutrition (weight for age ≤2 standard deviations)	2	-	10	3.2 (1.6-6.4)
Low birth weight	5	1.91 (1.45-2.53)	4	3.2 (1.0-9.9)
Maternal smoking	7	1.36 (1.24-1.50)	3	2.7 (1.0-7.8)
Passive smoking	8	1.29 (0.96-1.73)	4	2.4 (1.0-5.8)
No breastfeeding	3	2.24 (1.56-3.20)	6	2.3 (1.4-3.9)
Lack of exclusive breastfeeding	2	-	10	2.3 (1.4-3.9)
Crowding (≥2 persons/room in household)	2	-	4	2.2 (1.8-2.7)
Birth order	0	-	3	2.1 (1.2-4.4)

Crowding (>7 persons in household)	3	1.94 (1.29-2.93)	3	1.9 (1.5-2.5)
Prematurity (gestational age <37 weeks)	7	1.96 (1.44-2.67)	5	1.9 (1.3-2.8)
Incomplete immunization	0	-	5	1.8 (1.3-2.5)
Previous respiratory illness	2	-	5	1.7 (0.8-3.4)
Low parental education	6	1.40 (0.94-2.08)	6	1.6 (1.0-2.6)
Indoor air pollution	5	0.81 (0.42-1.57)	5	1.6 (1.1-2.3)
Being male	12	1.23 (1.13-1.33)	6	1.5 (1.0-2.3)
Birth interval	0	-	2	1.4 (0.9-2.2)
Zinc deficiency	0	-	2	0.5 (0.3-0.9)
Multiple births	2	-	0	-
Siblings	11	1.60 (1.32-1.95)	0	-
History of atopy	5	1.47 (1.16-1.87)	0	-

*Only listing risk factors where meta-estimate is available. The list of risk factors is ordered based on meta-estimate of severe ALRI from high to low.

Together with estimates for the prevalence of these risk factors across countries, evidence generated from this study examining the strength of association between risk factors and RSV associated ALRI as well as the incidence rate of RSV associated ALRI globally and regionally (from Chapter 5), the national incidence estimates of RSV associated ALRI could be modelled.

Further research on this topic should identify, seek access to, and analyse additional unpublished RSV datasets to further improve the precision of these estimates. Individual patient data should be obtained to explore the role of each risk factor with consideration of potential confounders. Such analysis should include, where possible, investigation of possible association with risk factors which have been reported to show association with (all cause) ALRI: incomplete immunization, vitamin D deficiency, anaemia, zinc deficiency, birth interval, birth order, and vitamin A deficiency. Also, this should involve those risk factors with unclear associations due to limited data available so far. Risk factors with various definitions should also be investigated: either a standard definition should be proposed and used consistently or more studies of each category of the definitions would be needed to generate a separate estimate.

Chapter 5 Global burden of RSV associated ALRI in children younger than five years old

5.1 Methods

5.1.1 Literature search

5.1.1.1 Search strategy and selection criteria

A systematic review was conducted across the following 9 electronic databases: Medline (Ovid), Embase, Global Health, CINAHL, Web of Science, WHOLIS, LILACS, IndMed and grey literature (SIGLE). In order to follow the guidelines from PRISMA for systematic review and meta-analysis, the literature search was also carried out independently by another researcher (Evelyn Balsells, MPH) and data were extracted. Three Chinese databases: China National Knowledge Infrastructure (CNKI), Wanfang data and Chongqing VIP were also searched to identify studies published in Chinese language (Mandarin) because most of them were not searchable in PubMed. This is feasible because the author's first language is Chinese (Mandarin).

The reference lists of identified records were further hand searched for more eligible articles. No publication status or language restrictions were applied. Search strategies including search terms for each database were displayed in Appendices - A9. Table 19 shows selection criteria in detail. Any discordance or uncertainties regarding relevance or inclusion were arbitrated by my supervisors for this thesis (Prof. Harry Campbell and Dr Harish Nair). Data were extracted using a standardised data extraction template designed on Microsoft Excel (Microsoft Office 2007).

5.1.2 Unpublished data collection

As introduced in the Chapter 2 - Methods, RSV GEN research group consists of leading researchers in paediatric pneumonia from all over the world, mainly in developing countries. This network has provided substantial unpublished data contributing to the estimate of global burden of RSV associated ALRI. Overall, 76 unpublished studies were collected and were combined with qualified published papers identified through literature search. All unpublished data were cross-checked with local researchers if there were any inconsistencies or queries.

Table 19: Selection criteria applied in the systematic review of global burden estimate

Inclusion criteria:
• Studies published from Jan 1995 to Aug 2015
• Report data for children younger than 5 years
• Use case definition of ALRI (e.g. pneumonia, bronchiolitis) or ARI/ALRI involving hospitalisation with evidence of RSV infection
• At least 12 consecutive months of study period (except for CFR studies)
• Report data for at least the first year of life
• Provide clear and well-defined catchment denominators or estimates of the population at risk (for studies reporting incidence or hospitalisation rate)
Exclusion criteria:
• Investigate RSV as a co-infection rather than primary outcome
• Case definition not clearly defined or not consistently applied
• Studies using serology as the only diagnosis test
• Number of hospitalised ALRI cases which were tested was less than 50 (for proportion studies)
• Studies providing duplicate data as in unpublished studies

5.1.3 Definitions

5.1.3.1 Definition of ALRI

As described in the Chapter 2 - Methods, ALRI, which includes clinical pneumonia and bronchiolitis, was used as the case definition to recognise the fact that they are common in children with viral ALRI and WHO definitions of cases could not distinguish bronchiolitis from pneumonia reliably. ALRI cases include all severe ALRI cases, which in turn include all very severe ALRI cases. In community-based settings, cases were identified by active ascertainment (health workers visiting house-to-house to diagnose cases). ALRI was defined as cough or difficulty in breathing and fast breathing with age (IMCI cut-offs: respiratory rate >60 breaths per min in children aged <2 months, >50 breaths per min in children aged 2-11 months, >40 breaths per min in children aged 12-59 months), while severe ALRI cases was defined as cough or difficulty in breathing with lower chest wall indrawing for children aged 2-59 months; an increased respiratory rate (>60 breaths/min) or chest wall indrawing for children aged <2 months. Severe ALRI with at least one WHO IMCI danger sign (World Health Organization, 2005) (cyanosis, difficulty in breastfeeding or drinking, vomiting everything, convulsions, lethargy, unconsciousness or head nodding) was defined as very severe ALRI. In hospital-based settings, cases were identified by passive ascertainment

(carers seek help in hospitals), only children hospitalised with ALRI or ARI were included (physician confirmed diagnosis). Among them, there were severe cases, which included hospitalised ALRI cases with chest wall indrawing and very severe hospitalised ALRI cases, which normally had hypoxemia or at least one WHO IMCI danger sign, required mechanical ventilation or ICU admission. The definitions were classified into three categories: WHO definition applied by a health worker (coded as I), physician's assessment (coded as II), severe acute respiratory illness (SARI) definition (coded as III), with or without other features contributing to case definition, such as wheeze (coded as W+/-), crepitation (coded as C+/-), fever (coded as F+/-), tachypnea (coded as T+/-), X-ray confirmation (coded as XR), chest wall indrawing (coded as CWI+/-), hypoxemia (coded as O2+/-), danger signs (coded as DS+/-), mechanical ventilation (coded as MV+/-), intensive care unit (ICU) admission (coded as ICU+/-).

5.1.3.2 Definition of hypoxemia

Hypoxemia was defined by altitude and age group. For areas at altitude ≤2500m, oxygen saturation (at sea level in room air) lower than 90% (measured by pulse oximetry) in children aged 1-59 months and lower than 88% in neonates was regarded as hypoxemic. For areas with altitude above 2500m, if oxygen saturation was lower than 87% in children aged 1-59 months and lower than 85% for neonates, they would be classified as having hypoxemia.

5.1.3.3 Definition of RSV season

A modification of the definition for RSV season was used – at least 10 specimens were analysed and any month of a year with RSV detected in more than 5% of the submitted respiratory specimens were deemed to be within the RSV season.

5.1.3.4 Definition of region category

Countries were separated into 6 WHO regions or 4 regions according to World Bank income levels (World Health Organization, 2016c, World Bank, 2016). Countries were categorised as developing or industrialised region according to the "Levels & trends in child mortality - report 2014" by UNICEF (United Nations Children's Fund, 2014). The child population number in 2015 by region and by age group (0-11m and 0-59m) were provided by UNICEF report (personal communication). Child population in narrower age bands within infants (0-5m and 6-11m) were obtained by dividing the population in infants evenly.

5.1.4 Statistical analysis

5.1.4.1 Data scale-up to estimate number of cases

In studies reporting number of RSV associated ALRI cases (both in community and in hospital) where only a proportion of eligible ALRI cases were tested for pathogen, the number of cases was scaled up according to the proportion of ALRI cases which were tested for RSV, on assumption that among the untested ALRI cases, the proportion of RSV detection would be the same as in those tested ALRI cases: overall RSV cases = reported RSV cases/proportion of ALRI cases tested for virus. This is an exception in very severe cases (in community or in hospital settings).

5.1.4.2 Data imputation across age groups

Few studies reported RSV data for the full age range (0-59 months). Data imputation was used on the basis of the approach adopted by Nair where necessary (Nair et al., 2010). For community-based studies reporting incidence rate, relative to an incidence of 1.0 for RSV associated ALRI in the 0-11 months age group, an incidence rate ratio of 1.01 was calculated for children aged 0-5 months (based on 9 studies), 0.90 for children aged 0-23 months (8 studies), 0.84 for children aged 0-35m (6 studies) and 0.57 for those younger than 5 years (6 studies), by taking the median of the incidence rate ratios of studies reporting incidence for these age ranges; for severe RSV associated ALRI, an incidence rate ratio of 1.26 was calculated for children aged 0-5 months (based on 7 studies), whereas for those younger than 2 years, 3 years and 5 years, the ratios were 0.64 (7 studies), 0.56 (4 studies) and 0.34 (4 studies). For hospital-based studies reporting hospitalisation rate, relative to children younger than 1 year, the median hospitalisation rate ratio for children aged 0-5 months was 1.32 (based on 27 studies), for those younger than 2 years, 3 years and 5 years, the median rate ratios were estimated as 0.63 (38 studies), 0.44 (23 studies) and 0.27 (34 studies); for studies reporting hospitalisation rate in cases with chest wall indrawing, the median rate ratio was 1.33 (6 studies) and 0.27 (6 studies) for children aged 0-5 months and 0-59 months, compared to infants. Figure 10, Figure 11 and Figure 12 summarise the overall approach and the associated rationale for the decisions adopted.

5.1.4.3 Deal with zero data

Whenever there are no hospital deaths, combining such data to meta-analysis of in-hospital CFR can be problematic, so continuity correction of a constant of 0.00005 was used. This allowed calculation of CFR for these instances, and enabled inclusion of these studies within subsequent meta-analyses.

5.1.4.4 Meta-analysis

Using STATA (version 11.2) (StataCorp, 2009), meta-analyses of incidence rate (community-based studies), hospitalisation rate, in-hospital CFR, and proportion data (hospital-based studies) were conducted separately based on random effects model (DerSimonian-Laird method) since significant heterogeneity was assumed among included studies (Dersimonian and Laird, 1986, Borenstein et al., 2009). They differed in various aspects, such as geographical distribution, study setting, ascertainment method, clinical specimen and diagnosis test. The pooled estimates with corresponding 95% CIs were reported. Studies conducted in indigenous populations from industrialised countries (Australia and USA) were excluded in the final estimate because they reported substantially different data (higher) compared to other areas within these two industrialised countries and might not be representative. The studies comprised those in the aboriginal population in Townsville Australia, Alaska and Indian Native populations in America, and Navajo and White Mountain Apache populations in America. These studies were included in a later sensitivity analysis. Studies using criteria of fever, wheeze exclusion or SARI to define the cases were excluded in another sensitivity analysis. Subgroup meta-analysis was carried out in different regions (WHO region, region by World Bank income level or developing/industrialised region) and in different age groups (large age bands such as 0-11m, 0-59m; narrower exclusive age bands such as 0-5m, 6-11m, 12-59m).

5.1.4.5 Estimate of RSV associated ALRI cases

For community-based or outpatient-based (industrialised countries only) studies reporting incidence rate where catchment was well defined and denominator population were available, the meta-estimate of incidence rate of RSV associated ALRI was reported by WHO regions, World Bank income regions as well as for industrialised and developing countries respectively. Age and region specific population number in 2015 was applied to the corresponding meta-estimate of incidence rate to produce the number of new cases of RSV associated ALRI in community. The approach was summarised in Figure 10.

For hospital-based studies reporting hospitalisation rate where denominator population were provided, similarly, the data were analysed in different regions and in different age groups. Then the region and age specific population number in 2015 was applied to the corresponding meta-estimate of hospitalisation rate to generate the number of new episodes of RSV associated hospitalised ALRI in 2015. The global number of cases was summed from regional estimates and the number of cases for children aged 0-59m was summed from estimates in narrower exclusive age bands (0-5m, 6-11m and 12-59m). This represents the

first approach to estimate number of RSV associated ALRI cases admitted in hospitals. In a parallel second approach based on proportion data – the proportion of hospitalised ALRI cases which are RSV positive, extracted from hospital-based studies where population denominator was not available, the number of hospitalised ALRI cases in 2015 was combined with the respective meta-analysis result of proportion data to produce the number of new cases of RSV associated hospitalised ALRI. The number of hospitalised ALRI cases in 2015 was provided by my supervisor, Dr Harish Nair (personal communication), who developed the estimates for 2010, and whose team updated these estimates for 2015 after incorporating novel data. This represents the second approach to obtain the number of new cases of RSV associated ALRI which required hospital admission. These two approaches were summarised in Figure 11. They represent two independent approaches to estimate the same outcome of interest. They used completely different data from different studies as input data and were based on different assumptions. The final estimate was based on the approach which used studies reporting hospitalisation rate (the first approach) since these were population-based studies and were designed to estimate the burden of RSV associated ALRI in hospital settings with well-defined catchment area.

5.1.4.6 Estimate of RSV associated ALRI mortality

This process was shown in Figure 12 where the approach to generate RSV associated ALRI mortality in hospital and in community was summarised respectively. To estimate number of in-hospital deaths from RSV associated ALRI, the age and region specific meta-estimate of hospitalisation rate and meta-estimate of in-hospital case fatality ratio (CFR) with their confidence intervals were used.

For each age-group and region, and summing across regions and age-groups, the number of in-hospital deaths was estimated as the product of the hospitalisation rate, population in 2015 and the in-hospital CFR. Estimates of hospitalisation rates and in-hospital CFR were obtained from meta-analyses (random effects method in STATA) and population data from UNICEF. The CFR analysis was based on studies which reported data for all three exclusive age bands: 0-5m, 6-11m and 12-59m. Uncertainty intervals for the in-hospital deaths were obtained via Monte Carlo simulation. The estimates and standard errors for each meta-estimate of hospitalisation rate and in-hospital CFR were used to define log-normal distributions. 10,000 independent samples were drawn from each of these log-normal distributions. In-hospital deaths (output variable) was calculated as: hospitalisation rate*population in 2015*in-hospital CFR for each of the 10,000 samples to obtain samples from the posterior distribution for this hospital deaths. This analysis was repeated for each

outcome. The median of this distribution was used to obtain the point estimate of in-hospital deaths and the 2.5th and 97.5th centiles were reported as the lower and upper confidence limits for the point estimate (95% uncertainty interval). The simulation process was carried out in R (version 3.0.2). The R codes used to generate these estimates by Monte Carlo simulation were shown in Appendices - A10. The global estimate of in-hospital mortality was generated from samples formulating regional estimates (developing countries and industrialised countries). For children aged 0-59m, the estimate was produced based on samples in narrower age bands: 0-5m, 6-11m and 12-59m.

Access to health services is known to be limited in developing countries, thus RSV associated ALRI mortality in community was calculated for these countries. All excess mortality from ALRI in children younger than 5 years within the RSV season was assumed to be due to RSV and that non-RSV mortality was equal within and between RSV epidemic months. The duration of RSV season for each calendar year of study was defined by months (MonRSV). In each year, the overall number of verbal autopsy confirmed pneumonia deaths (TOTAL), and the mean number of pneumonia deaths that occurred during RSV season per month (AvgRSV) and outside RSV season per month (AvgOTHER) were calculated. The proportion of yearly deaths of pneumonia due to RSV for each year was then calculated as:

[(AvgRSV – AvgOTHER) × MonRSV]/TOTAL

Application of this proportion to the estimated under five child deaths attributable to pneumonia (Liu et al., 2014) in the same year would provide an estimate of child deaths due to RSV in that year. This approach required population-based data for RSV seasonality by month and number of monthly pneumonia deaths (verbal autopsy confirmed) for an at least 3-year period. Then, an average number of RSV deaths if community-based active case ascertainment was used was generated. This was compared to the corresponding in-hospital mortality (meta-estimate of hospitalisation rate and CFR in developing countries and population from this country in the mean study year) and an inflation factor was calculated as follows: inflation factor = number of RSV deaths in community/number of RSV deaths in hospital. The mean inflation factor was calculated and would be used to extrapolate the in-hospital mortality from RSV associated ALRI in developing countries, and generate global mortality in community. Global mortality from RSV associated ALRI in children under five years old in community = in-hospital mortality of RSV associated ALRI from developing countries*mean inflation factor + in-hospital mortality of RSV associated ALRI from industrialised countries.

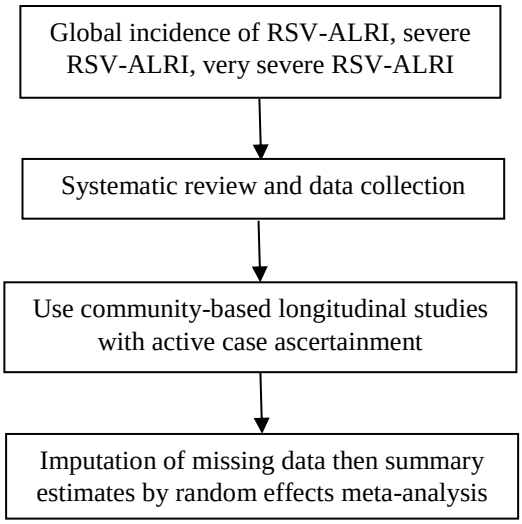


Figure 10: Approach to estimate community-based number of RSV associated ALRI

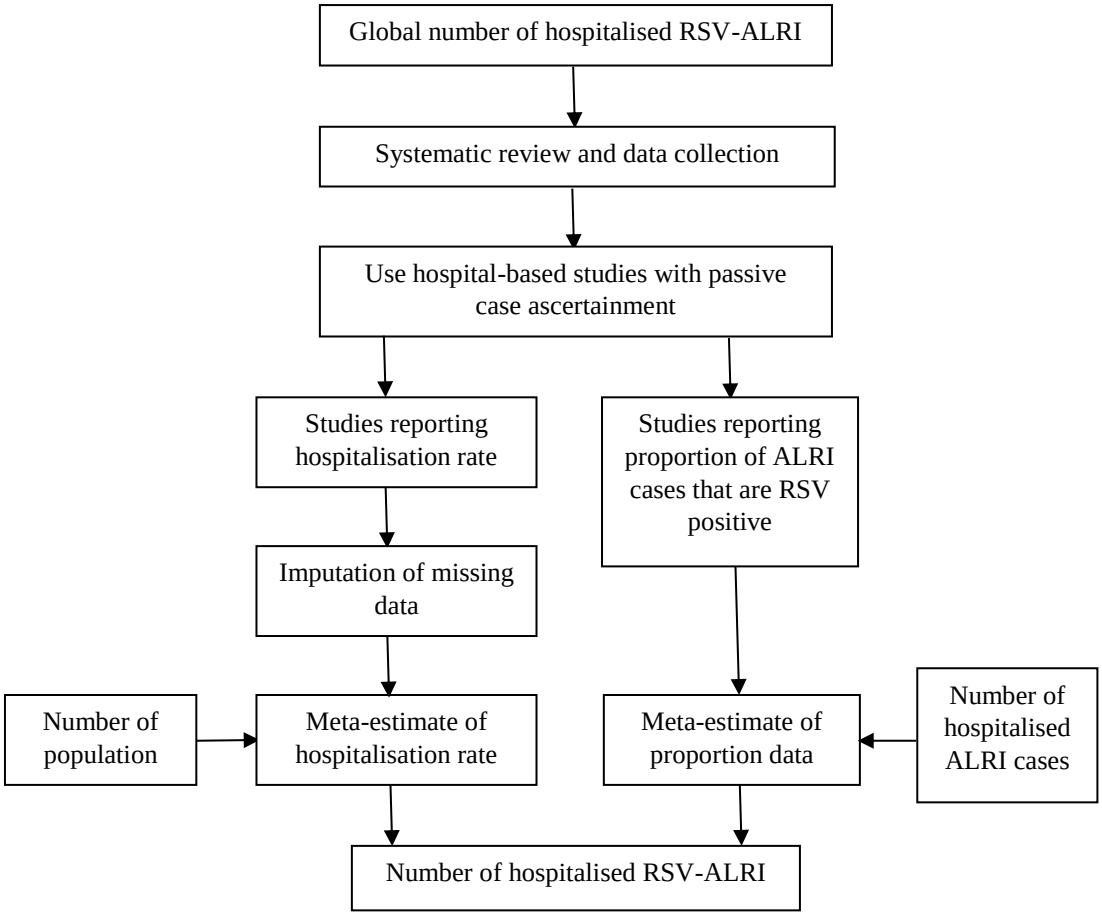


Figure 11: Approach to estimate number of RSV associated hospitalised ALRI cases

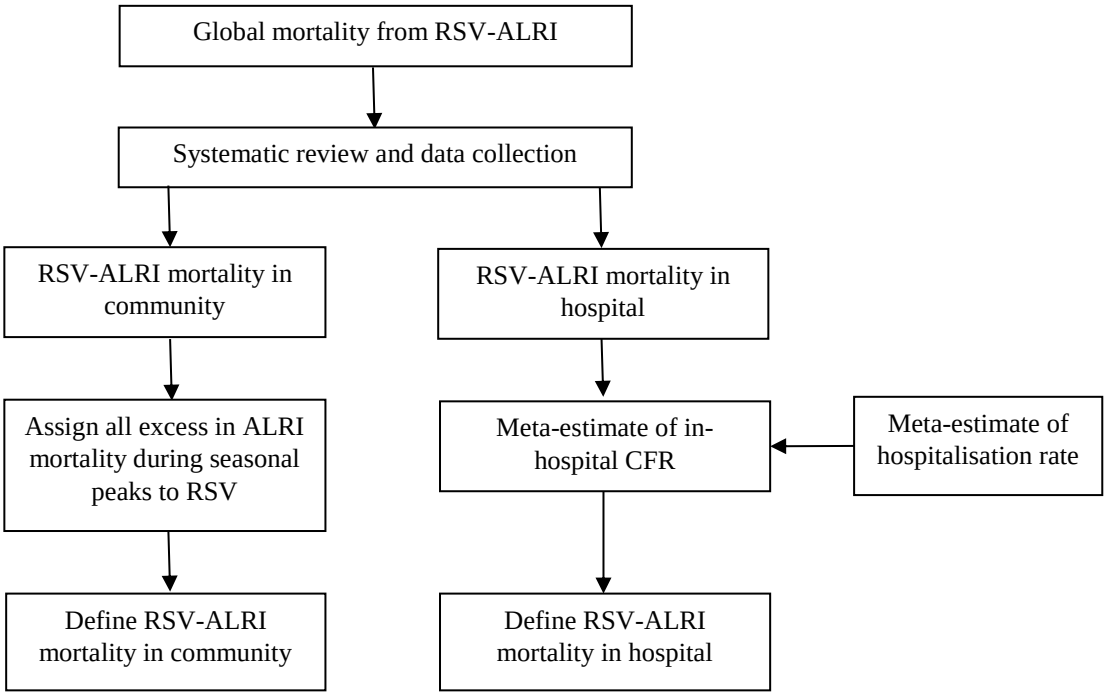


Figure 12: Approach to estimate mortality from RSV associated ALRI

5.2 Results

Overall, 13,387 records were identified through database searching, after removing duplicates and excluding studies not relevant to the topic, 880 records remained for full-text review. After reviewing the full texts, 225 published articles met the selection criteria. There were 3 articles providing 2 data points for different areas in each article, thus in total 228 studies were included in further analysis. The list of excluded articles during full-text review process with corresponding reasons was listed in Appendices – A11. Another 76 unpublished studies[U1-76] with appropriate data were collected from RSV GEN (listed in Table 20). Two of them provided both community-based incidence rate and hospital-based hospitalisation rate[U1, U10]. Therefore, 304 studies in total were included for further assessment and analysis (266 new data points were added compared to previous estimate published in Lancet). The selection process was shown in Figure 13. More than 41 million children with relevant data were reported. Among all of them, 41 studies were in rural populations, 225 studies in urban populations and 38 were in a mixture of both. 225 studies were based in developing countries. Among them, 30 studies were either cohort studies or in the demographic surveillance site; 1 study had a well-defined catchment area for which the population were

estimated with a healthcare utilisation survey; 25 studies were conducted in hospitals with well-defined catchment areas. These 56 studies reported either incidence rate of RSV associated ALRI (community-based setting) or hospitalisation rate (hospital-based setting). Only 40 studies (11 published articles (Robertson et al., 2004, Ahmed et al., 2012, Chiu et al., 2010, Fry et al., 2010, Gil-Prieto et al., 2015, Hall et al., 2009, Iwane et al., 2004, Muller-Pebody et al., 2002, Paramore et al., 2004, Rowlinson et al., 2013, Vicente et al., 2003) with 12 studies and 28 unpublished studies[U3-5, U8, U11, U15-24, U26-29, U32, U34-37, U39-40, U42, U45]) reported disease incidence / hospitalisation rate by age group for the full age range (for 0-59m group); for the remaining studies data were imputed where necessary. There were 18 population-based studies reporting incidence rate of RSV associated (severe) ALRI in populations under surveillance, 73 studies estimating hospitalisation rate on the basis of hospital discharge records or laboratory diagnosis reports and a census-based or defined denominator of children at risk, 99 studies reporting RSV mortality in hospital, 199 studies estimating proportion of hospitalised ALRI cases that are RSV positive (73 were from Chinese language databases). 63 studies reported the incidence rate, hospitalisation rate or in-hospital CFR by narrow age bands for the first year of life. Only 37 studies (1 published and 36 unpublished) reported data specifically for neonates (aged 0-27 days). Not all eligible ALRI cases were tested. The list of studies which didn't have all ALRI cases tested for pathogen were listed in Appendices – A12. In these studies, the number of RSV associated ALRI cases (except for very severe cases) were scaled up according to the proportion of eligible ALRI cases tested for RSV (as described in the Chapter 2 - Methods). Studies reporting rate in community and hospital settings as well as in-hospital mortality were mapped in Figure 14, stratified by WHO region. Studies reporting hospital-based proportion data were mapped in Figure 15.

Table 20: List of 76 unpublished studies with relevant data

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
U1	Kilifi birth cohort, Kenya (Nokes and colleagues)	Jan 2002 - May 2005	rural	Clin Infect Dis 2008; 46:50-7	report both community-based rate and hospital-based rate; data re-analysed using common case definitions
U2	San Marcos, Guatemala (Bruce and colleagues)	Dec 2002 - Dec 2004	rural	Lancet 2011; 378(9804): 1717-26	data re-analysed using common case definitions
U3	Dhaka, Bangladesh (Brooks and colleagues)	Jan 2005 - Feb 2008	urban	Pediatr Infect Dis J 2010; 29(3): 216-21	RSV was tested for the first 4 years of study; 15 ALRI deaths without information about virus
U4	Ballabhgarh, India (Krishnan and colleagues)	Aug 2012 - Aug 2013	rural	BMC Infect Dis 2015; 15: 462	data re-analysed using common case definitions
U5	Bandung, Indonesia (Simoes and colleagues)	1st Feb 1999 - 26th Apr 2001	periurban and rural	Pediatr Infect Dis J 2011; 30(9): 778-84	data re-analysed using common case definitions
U6	Managua, Nicaragua (Gordon and colleagues)	Sep 2011 - Sep 2012	urban	Pediatr Infect Dis J 2016; 35(2): 152-6	data re-analysed using common case definitions
U7	Matiari, Pakistan (Ali and colleagues)	Oct 2011 - Jun 2014	rural	PLoS One 2013; 8(9)	data re-analysed using common case definitions
U8	Gilgit, Pakistan (Rasmussen and colleagues)	1st Apr 2012 - 31st Mar 2014	rural	no	data are not yet published
U9	Puerto Maldonado, Peru (Romero and colleagues)	Jan - Dec 2013	periurban	no	only one very severe case in 12-23m
U10	Paarl, South Africa (Zar and colleagues)	Mar 2012 - Dec 2014	periurban	i. Thorax 2015; 70(6): 592-4 ii. Lancet Glob Health 2015; 3(2): e95-e103	report both community-based rate and hospital-based rate; data re-analysed using common case definitions
U11	Nashville, Tennessee, USA	Jan 1973 - Dec	urban	no	data are not yet published; reporte rate in

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
	(Wright and colleagues)	1993			outpatients in industrialised countries
U12	CEMIC, Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010	urban	i. Arch Argent Pediatr 2011;109(4):296-304 ii. Pediatr Infect Dis J 2013; 32(3): e105-e110 iii. Medicina 2012; 72(1): 28-32	another paper is in preparation; data re-analysed using common case definitions
U13	Buenos Aires, Argentina (Polack and colleagues)	2011 - 2013	urban and rural	Am J Respir Crit Care Med 2013; 187(9): 983-90	data re-analysed using common case definitions
U14	Kishoregonj, Bogra, Comilla and Barisal, Bangladesh (Homaira and colleagues)	2010 - 2013	urban and rural	PLoS One 2016; 11(2): e0147982.	data re-analysed using common case definitions
U15	Belo Horizonte, Brazil (Oliveira and colleagues)	2011 - 2013	urban	no	data are not yet published
U16	Concepcion, Chile (Fasce and colleagues)	Jan 2012 - Dec 2013	urban and rural	no	data are not yet published
U17	Iquique, Chile (Fasce and colleagues)	Jan 2012 - Dec 2013	urban and rural	no	data are not yet published
U18	Jingzhou, China (Yu and colleagues)	Jan 2010 - Dec 2012	urban and rural	J Infect Dis 2013; 208 Suppl 3: S184-8	data re-analysed using common case definitions
U19	Santa Ana, El Salvador (Clara and colleagues)	2008 - 2013	urban	i. Bull World Health Organ 2012; 90(10): 756-63 ii. Influenza Other Respir Viruses 2016	data re-analysed using common case definitions
U20	Gambia Western Region, Gambia (Howie and colleagues)	Jul 2007 - Jun 2008	urban and rural	Clin Infect Dis 2014; 59(5): 682-5	data re-analysed using common case definitions

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
U21	Santa Rosa, Guatemala (McCracken and colleagues)	2008 - 2013	urban and rural	i. Infect Dis 2013; 208 Suppl 3: S197-206 ii. Pediatr Infect Dis J 2013; 32(6): 629-35	data re-analysed using common case definitions
U22	Quetzaltenango, Guatemala (McCracken and colleagues)	2009 - 2013	urban and rural	i. Infect Dis 2013; 208 Suppl 3: S197-206 ii. Pediatr Infect Dis J 2013; 32(6): 629-35	data re-analysed using common case definitions
U23	Ballabhgarh, India (Broor and colleagues)	Jan 2010 - Dec 2012	rural	J Infect 2015; 70(2): 160-70	data re-analysed using common case definitions
U24	Pune, India (Chadha and colleagues)	May 2009 - Apr 2013	rural	J Infect 2015; 70(2): 160-70	data re-analysed using common case definitions
U25	Lombok, Indonesia (Gessner and colleagues)	2000 - 2002	urban and rural	Epidemiol Infect 2008; 136(10): 1319-27	data re-analysed using common case definitions
U26	Kilifi hospital study, Kenya (Nokes and colleagues)	Jan 2002 - Dec 2010	urban and rural	JAMA 2010; 303(20): 2051-7	data re-analysed using common case definitions
U27	Bondo district, Kenya (Feikin and colleagues)	Jan 2007 - Jun 2009	rural	J Med Virol 2013; 85(5): 924-32	data re-analysed using common case definitions
U28	Manhiça, Mozambique (Bassat and colleagues)	20th Sep 2006 - 19th Sep 2007	rural	Pediatr Infect Dis J 2011; 30(1): 39-44	data re-analysed using common case definitions
U29	Manhiça, Mozambique (Bassat and colleagues)	1st Jan 2011 - 30th Jun 2014	rural	Pediatr Infect Dis J 2011; 30(12): 1032-6	data re-analysed using common case definitions
U30	Utrecht, Netherlands (Bont and colleagues)	2001 - 2010	urban	i. Pediatr Infect Dis J 2014; 33(1): 19-23 ii. Pediatrics 2011; 127(1): 35-41	healthy term infants; data re-analysed using common case definitions
U31	41 sites in Netherlands (Bont	2008 - 2013	urban	N Engl J Med 2013; 368(19): 1791-9	late preterm infants; data re-analysed using

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
	and colleagues)		and rural		common case definitions
U32	David City, Panama (Jara and colleagues)	Jan 2011 - Dec 2013	urban	no	data are not yet published
U33	Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	5th Jul 2000 - 31st Dec 2004	urban and rural	i. Pediatr Infect Dis J 2009; 28(6): 455-62 ii. J Clin Microbiol 2013; 51(3): 945-53	data re-analysed using common case definitions
U34	Gauteng province, South Africa (Cohen and colleagues)	2009 - 2012	urban	i. J Infect Dis 2013; 208 Suppl 3: S217-26 ii. J Infect Dis 2012; 206 Suppl 1: S159-65	data re-analysed using common case definitions
U35	KwaZulu-Natal province, South Africa (Cohen and colleagues)	2010 - 2014	periurban	i. J Infect Dis 2013; 208 Suppl 3: S217-26 ii. J Infect Dis 2012; 206 Suppl 1: S159-65	data re-analysed using common case definitions
U36	Klerksdorp site, South Africa (Cohen and colleagues)	Jan 2011 - Dec 2014	periurban	i. J Infect Dis 2013; 208 Suppl 3: S217-26 ii. J Infect Dis 2012; 206 Suppl 1: S159-65	data re-analysed using common case definitions
U37	Soweto, South Africa (Madhi and colleagues)	Mar 1998 - Oct 2005	urban	J Clin Virol 2006; 36(3): 215-21	data re-analysed using common case definitions
U38	Maela Camp, Tak Province, Thailand (Turner and colleagues)	Nov 2007 - Oct 2010	rural	i. PLoS ONE 2012; 7(11): e50100 ii. BMC Infect Dis 2013; 13(1)	data re-analysed using common case definitions
U39	Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	Jan 2008 - Dec 2011	rural	i. Pediatr Infect Dis J 2014; 33(2): e45-e52 ii. J Infect Dis 2013; 208 Suppl 3:	data re-analysed using common case definitions

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
				S238-45	
U40	Tone district, Togo (Gessner and colleagues)	Aug 2011 - Dec 2013	rural	no	data are not yet published
U41	Alaska, USA (Singleton and colleagues)	Jul 1994 - Jun 2012	rural	i. Pediatr Infect Dis J 2007; 26(11(Supplement): S46-S50 ii. J Med Virol 2010; 82(7): 1282-90	reporte very severe cases from 1994 to 2007; hypoxemia data from Oct 2005 to Sep 2007; data re-analysed using common case definitions
U42	Colorado, USA (Simoes and colleagues)	Jan 2008 - Jun 2013	urban and rural	no	ICD-9 codes for hypoxemia
U43	Navajo and WMA, USA - MEDI (O'Brien and colleagues)	Oct 2004 - Dec 2010	rural	submitted to journal	data re-analysed using common case definitions
U44	Navajo and WMA, USA - EPI (O'Brien and colleagues)	Oct 1997 - Mar 2000	rural	Pediatrics 2002; 110(2 Pt 1): e20	data re-analysed using common case definitions
U45	Nha Trang, Vietnam (Yoshida and colleagues)	Feb 2007 - Dec 2012	urban and rural	i. Pediatr Infect Dis J 2010; 29(1): 75-7 ii. Eur Respir J 2013; 42(2): 461-9	subtypes data from 2010 to 2012; another paper is in preparation; data re-analysed using common case definitions
U46	Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010	urban	i. Arch Argent Pediatr 2011;109(4):296-304 ii. Pediatr Infect Dis J 2013; 32(3): e105-e110 iii. Medicina 2012; 72(1): 28-32	another paper is in preparation; data re-analysed using common case definitions
U47	Buenos Aires, Argentina (Gentile and colleagues)	2001 - 2013	urban	Arch Argent Pediatr 2014; 112(5): 397-404	data re-analysed using common case definitions
U48	Takeo and Kampong Cham, Cambodia (Goyet and colleagues)	Apr 2007 - Feb 2010	urban	Pediatr Infect Dis J 2013; 32(1): e8-13	data re-analysed using common case definitions

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
U49	Chillan, Chile (Fasce and colleagues)	2010 - 2013	urban and rural	no	data are not yet published
U50	Osorno, Chile (Fasce and colleagues)	2010 - 2013	urban and rural	no	data are not yet published
U51	Punta Arenas, Chile (Fasce and colleagues)	2010 - 2013	urban and rural	no	data are not yet published
U52	Santiago, Chile (Fasce and colleagues)	2010 - 2013	urban	no	data are not yet published
U53	Valparaiso, Chile (Fasce and colleagues)	2010 - 2013	urban mostly	no	data are not yet published
U54	China (Yu and colleagues)	Jan 2009 - Sep 2013	urban and rural	PLoS One 2014; 9(6): e99419	data re-analysed using common case definitions
U55	Beijing, China (GABRIEL)	Jan 2011 - Dec 2012	urban	no	data are not yet published
U56	Ulaanbaatar, Mongolia (GABRIEL)	Sep 2011 - Oct 2012	urban	no	data are not yet published
U57	Phnom Penh, Cambodia (GABRIEL)	Oct 2010 - Jan 2013	urban	no	data are not yet published
U58	Lucknow, India (GABRIEL)	Jun 2012 - Dec 2013	urban and rural	no	data are not yet published
U59	Antananarivo, Madagascar (GABRIEL)	Dec 2010 - Feb 2013	urban and rural	no	data are not yet published
U60	Asuncion, Paraguay (GABRIEL)	Jul 2010 - May 2013	urban	no	data are not yet published
U61	Bamako, Mali (GABRIEL)	Jul 2011 - Nov	urban	no	data are not yet published

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
		2012			
U62	Berlin, Germany (Rath and colleagues)	1st Apr 2010 - 31st Mar 2014	urban	i. iagn Microbiol Infect Dis 2015; 81(3): 171-6 ii. J Clin Microbiol 2009; 47(6): 1800-10	data re-analysed using common case definitions
U63	Amman, Jordan (Khuri and colleagues)	Mar 2010 - Mar 2013	urban	Vaccine 2015; 33(47): 6479-87	data re-analysed using common case definitions
U64	Lwak, Kenya (Montgomery and colleagues)	2007 - 2011	rural	J Infect Dis 2013; 208 Suppl 3: S207-16	data re-analysed using common case definitions
U65	Rabat, Morocco (Bassat and colleagues)	Nov 2010 - Dec 2011	urban	i. J Trop Pediatr 2014; 60(4): 270-8 ii. Epidemiol Infect 2016; 144(3): 516-26	data re-analysed using common case definitions
U66	Kathmandu, Nepal (Basnet and colleagues)	Jan 2006 - Jun 2008	urban	i. Pediatr Infect Dis J 2011; 30(12): 1032-6 ii. Pediatrics 2012; 129(4): 701-8	data re-analysed using common case definitions
U67	Karachi, Pakistan (Ali and colleagues)	Aug 2009 - Jul 2012	urban	PLoS One 2013; 8(9)	data re-analysed using common case definitions
U68	Basse, Gambia (PERCH)	3rd Nov 2011 - 2nd Nov 2013	rural	no	data are not yet published
U69	Kilifi, Kenya (PERCH)	15th Aug 2011 - 15th Nov 2013	urban	no	data are not yet published
U70	Bamako, Mali (PERCH)	3rd Jan 2012 - 14th Jan 2014	urban	no	data are not yet published
U71	Nakhon Phanom and Sa Kaeo, Thailand (PERCH)	1st Jan 2012 - 31st Jan 2014	rural	no	data are not yet published

Study number	Location (reference)	Study period	Setting	Published reference	Remarks
U72	Lusaka, Zambia (PERCH)	10th Oct 2011 - 31st Oct 2013	urban	no	data are not yet published
U73	Dhaka, Bangladesh (PERCH)	1st Jan 2012 - 31st Dec 2013	urban	no	data are not yet published
U74	Matlab, Bangladesh (PERCH)	1st Jan 2012 - 31st Dec 2013	rural	no	data are not yet published
U75	Tacloban, Philippines (Lupisan and colleagues)	May 2008 - Jul 2012	rural	BMC Infect Dis 2012; 12: 267	data re-analysed using common case definitions
U76	Mpumalanga, South Africa (Cohen and colleagues)	Jan 2010 - Dec 2014	rural	i. J Infect Dis 2013; 208 Suppl 3: S217-26 ii. J Infect Dis 2012; 206 Suppl 1: S159-65	data re-analysed using common case definitions

*Two studies provided data for both incidence rate (community-based) and hospitalisation rate (hospital-based)

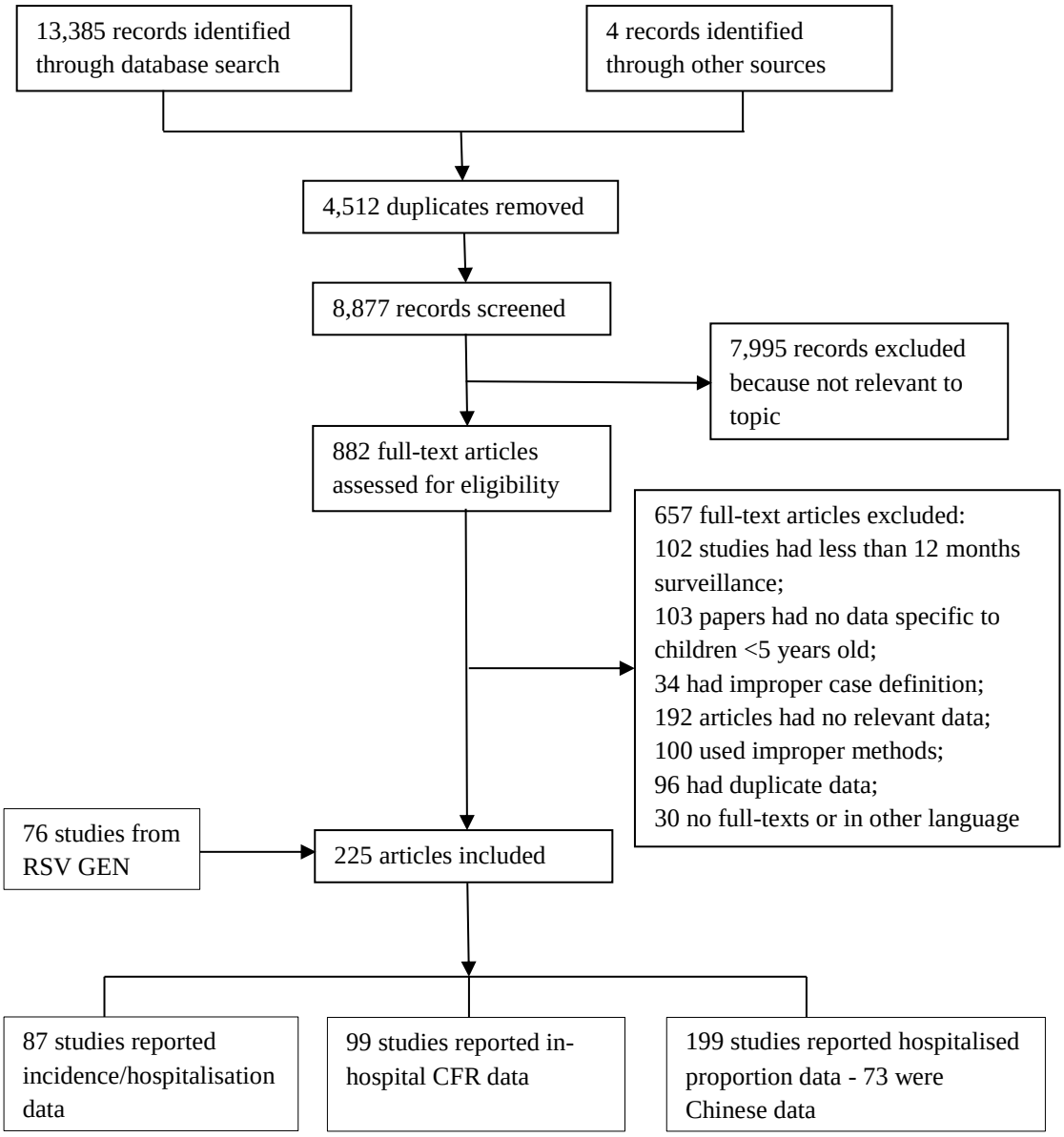


Figure 13: Flow diagram of selection of studies of global burden of RSV associated ALR

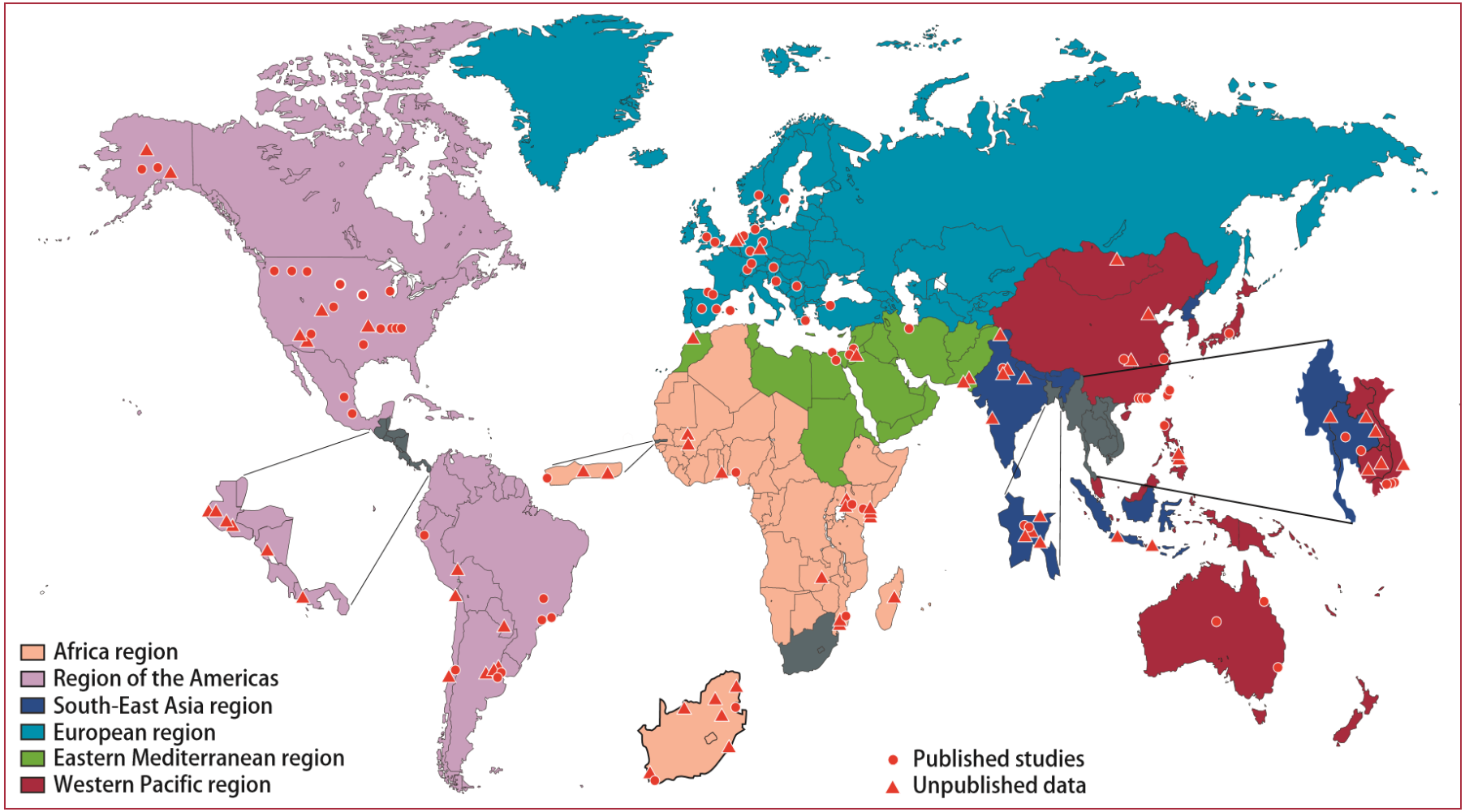


Figure 14: Location of studies reporting incidence, hospitalisation rate and in-hospital CFR by WHO region

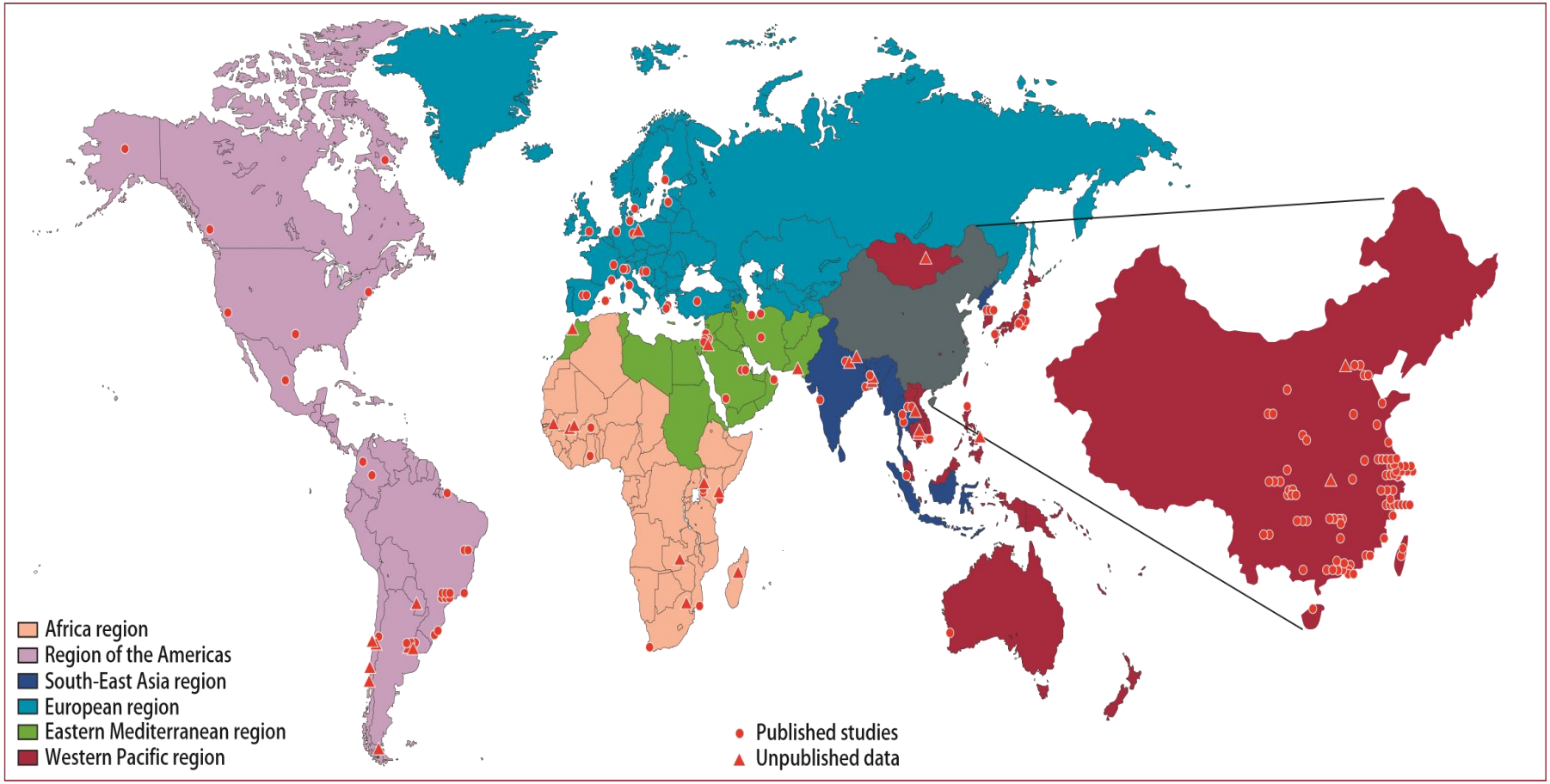


Figure 15: Location of studies reporting proportion data by WHO region

5.2.1 Incidence rate of RSV associated ALRI

In total 18 studies reported community-based or outpatient-based (industrialised countries only) incidence rate of RSV associated (severe) ALRI with a well-defined catchment area with denominator data. Seven were published articles (Homaira et al., 2012, Broor et al., 2007, Hasan et al., 2006, Robertson et al., 2004, Sutmoller et al., 1995, Wu et al., 2015, Forster et al., 2004) and 11 were unpublished studies[U1-U11] (Table 21). Five of them were from urban settings, three from mix areas (both urban and rural) and the rest 10 study sites were based in rural areas. All studies from developing countries (16 studies) adopted community-based active case ascertainment - ALRI cases sought by health workers during regular house-to-house visits. Sixteen of them reported incidence rate of RSV associated ALRI and main characteristics of these included studies (location, study period, case definition, study denominator, specimen and diagnostic test, incidence rate in children aged 0-5m/0-11m/0-59m) were summarised in Table 22. Data computed using median rate ratio from studies providing data for full age range were highlighted with parentheses. Another table containing data in narrower age bands was in Appendices – A13. Similarly, 9 studies reporting RSV associated severe ALRI were presented in Table 23. Four studies provided data of RSV associated very severe ALRI (Table 24). Data regarding meta-estimate of incidence rate as well as number of new cases from different regions were presented in Table 25. Corresponding forest plots were available in Appendices – A14. Overall, the meta-estimate of incidence rate of RSV associated ALRI in infants from developing countries was 88.3 per 1000 children per year, 28.7 for severe cases and 5.8 for very severe cases. For children under five years old from developing countries, the meta-estimate for RSV associated ALRI was 50.8 per 1000 children per year, 10.2 for RSV associated severe ALRI, and 1.4 for RSV associated very severe ALRI. Thus, in 2015, there were 30.5 (95% CI 19.5-47.9) million new episodes of RSV associated ALRI among children younger than 5 years from developing countries (30.0 (95% CI 19.1-47.0) million in low and middle income countries). 20.1% of them were severe cases and 2.7% were very severe cases. The incidence rate for children aged 0-59m in industrialised countries was estimated as 35.6 per 1000 children per year based on two studies, which means that 2.5 (95% CI 1.2-5.3) million of RSV associated ALRI cases occurred in this region in 2015. Globally there were 33.0 (95% CI 20.6-53.2) million of new episodes of RSV associated ALRI among children younger than five years old. Among infants, there were 10.9 million new cases of RSV associated ALRI in developing countries (10.7 million in low and middle income countries); 0.9 million in industrialised countries (1.0 million in high income countries). The meta-estimate result of incidence data from developing countries in exclusive finer age bands was shown in Figure

16. The incidence rate was high in children at the first two years, especially among infants. A sensitivity analysis was carried out to compare the meta-estimate of incidence rate after excluding the imputed data (Appendices – A15). No substantial difference was found.

Table 21: List of 11 unpublished studies reporting incidence rate

Study number	Location (reference)	Study period
U1	Kilifi birth cohort, Kenya (Nokes and colleagues)	Jan 2002 - May 2005
U2	San Marcos, Guatemala (Bruce and colleagues)	Dec 2002 - Dec 2004
U3	Dhaka, Bangladesh (Brooks and colleagues)	Jan 2005 - Feb 2008
U4	Ballabhgarh, India (Krishnan and colleagues)	Aug 2012 - Aug 2013
U5	Bandung, Indonesia (Simoes and colleagues)	1st Feb 1999 - 26th Apr 2001
U6	Managua, Nicaragua (Gordon and colleagues)	Sep 2011 - Sep 2012
U7	Matiari, Pakistan (Ali and colleagues)	Oct 2011 - Jun 2014
U8	Gilgit, Pakistan (Rasmussen and colleagues)	1st Apr 2012 - 31st Mar 2014
U9	Puerto Maldonado, Peru (Romero and colleagues)	Jan - Dec 2013
U10	Paarl, South Africa (Zar and colleagues)	Mar 2012 - Dec 2014
U11	Nashville, Tennessee, USA (Wright and colleagues)	Jan 1973 - Dec 1993

Table 22: List of 16 studies reporting incidence rate of RSV associated ALRI

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Incidence of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
San Marcos, Peru (rural, Mar 2009 - Sep 2011) (Wu et al., 2015)	I	Defined population base	nasal swab; RT-PCR	343.8	338.1	340.8	304.3		(194.3)
Dhaka, Bangladesh (urban, Apr 2009 - Mar 2011) (Homaira et al., 2012)	I	Defined population base	NPW; RT-PCR	150.0	110.0	(148.5)	120.0		(84.7)
Kilifi birth cohort, Kenya (rural, Jan 2002 - May 2005) (Nokes and colleagues)	I, O2+/-	Defined population base	NPA, nasal wash; DFA	147.0	63.0	105.1	71.0		(59.9)
Mirzapur, Bangladesh (rural, Oct 1993 - Aug 1996) (Hasan et al., 2006)	I	Defined population base	NPA; ELISA	(46.8)		(46.3)			(26.4)
Ballabhgarh, India (rural, Oct 2001 - Mar 2005) (Broor et al., 2007)	I	Defined population base	NPA; DFA	60.2	18.0	38.0	52.0		(21.7)
Ibadan, Nigeria (rural, Jun 1999 - May 2001) (Robertson et al., 2004)	I	Defined population base	NPA, NPW; ELISA	(117.2)		116.0			94.0
San Marcos, Guatemala (rural, Dec 2002 - Dec 2004) (Bruce and colleagues)	I, II, DS+/-	Defined population base	NPA; DFA	107.7	172.4	147.5	124.5		(84.1)
Rio de Janeiro, Brazil (rural, Jan 1987 - Dec 1989) (Sutmoller et al., 1995)	II, T+/-, W+/-	Defined population base	NPA; IFA, culture	(24.8)		(24.6)			14.0
Dhaka, Bangladesh (urban, Jan 2005 - Feb 2008) (Brooks and colleagues)	I, W+/C+, DS+/-	Defined population base	NPW, serum; serology, RT-PCR	28.3	36.7	32.2	21.8	9.5	17.5
Ballabhgarh, India (rural, Aug 2012 - Aug 2013) (Krishnan and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	97.3	76.9	85.5	54.6	10.1	33.4
Bandung, Indonesia (periurban and rural, 1st Feb 1999 - 26th Apr 2001) (Simoes and colleagues)	I, DS+/-	Defined population base	nasal wash; RT-PCR	26.6	141.5	87.9	97.3	21.1	65.4
Managua, Nicaragua (urban, Sep 2011 - Sep 2012) (Gordon and colleagues)	I, DS+/-	Defined population base	nasal and throat swab; RT-PCR	(61.4)		60.8			(34.7)
Gilgit, Pakistan (rural, 1st Apr 2012 - 31st Mar 2014) (Rasmussen and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	30.8	101.9	62.5	58.6	15.9	35.9

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Incidence of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	506.7	141.8	331.0	78.6		(188.7)
Nashville, Tennessee, USA (urban, Jan 1973 - Dec 1993) (Wright and colleagues)#	II	Defined population base	NA; culture	(46.3)		45.8			24.0
Multicentric, Germany (urban, Nov 1999 - Oct 2001)# (Forster et al., 2004)	II	Census-derived estimate	NPS; PCR	(92.6)		(91.7)			(52.3)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. RT-PCR=reverse transcriptase polymerase chain reaction. IFA=indirect immunofluorescent antibody test. DFA=direct immunofluorescent antibody test. ELISA=enzyme-linked immunosorbent assay. I=WHO definition applied by a health worker. II=physician's assessment. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. C+/-=crepitation part of case definition or not. NA=not applicable. #Except for these two studies from hospital outpatient settings (high-income countries), the others were active community based. *Data in parentheses are computed incidence estimates.

Table 23: List of 9 studies reporting incidence rate of RSV associated severe ALRI

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Incidence of RSV associated severe ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Kilifi birth cohort, Kenya (rural, Jan 2002 - May 2005) (Nokes and colleagues)	I, O2+/-	Defined population base	NPA, nasal wash; DFA	86.0	47.0	68.5	17.0		(23.3)
Ballabhgarh, India (rural, Oct 2001 - Mar 2005) (Broor et al., 2007)	I	Defined population base	NPA; DFA	20.1	9.0	14.3	6.5		(4.8)
Dhaka, Bangladesh (urban, Jan 2005 - Feb 2008) (Brooks and colleagues)	I, W+/C+, DS+/-	Defined population base	NPW, serum; serology, RT-PCR	5.1	1.4	3.4	0.5		1.0
Ballabhgarh, India (rural, Aug 2012 - Aug 2013) (Krishnan and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	53.1	51.3	52.0	32.1	2.3	17.7
Bandung, Indonesia (periurban and rural, 1st Feb 1999 - 26th Apr 2001) (Simoes and colleagues)	I, DS+/-	Defined population base	nasal wash; RT-PCR	(24.1)	35.8	19.1	13.0	3.1	11.2
Managua, Nicaragua (urban, Sep 2011 - Sep 2012) (Gordon and colleagues)	I, DS+/-	Defined population base	nasal and throat swab; RT-PCR	(28.9)		22.9			(7.8)
Matiari, Pakistan (rural, Oct 2011 - Jun 2014) (Ali and colleagues)	I, F+/-	Census-derived estimate	NPS; RT-PCR	19.0	22.2	20.6	3.1		(7.0)
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	406.7	82.1	253.5	36.9		(86.2)
Nashville, Tennessee, USA (urban, Jan 1973 - Dec 1993) (Wright and colleagues)#	II	Defined population base	NA; culture	(3.2)		9.5			3.0

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. OP=outpatient. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. RT-PCR=reverse transcriptase polymerase chain reaction. DFA=direct immunofluorescent antibody test. I=WHO definition applied by a health worker. II=physician's assessment. W+/-=wheeze part of case definition or not. DS+/-=danger signs part of case definition or not. F+/-=fever part of case definition or not. O2+/-=hypoxemia part of case definition or not. C+/-=crepitation part of case definition or not. NA=not applicable. #Except for this study from hospital outpatient settings (high-income countries), the others were active community based. *Data in parentheses are computed incidence estimates.

Table 24: List of 4 studies reporting incidence rate of RSV associated very severe ALRI

Location (reference)#	Case definition (codes)	Denominator source	Specimen and diagnostic test	Incidence rate of RSV associated very severe ALRI (per 1000 children per year)					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Puerto Maldonado, Peru (periurban, Jan - Dec 2013) (Romero and colleagues)	I, W+/C+, DS+/-	Defined population base	NPW, serum; serology, RT-PCR				18.2		4.4
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	26.7	14.9	21.1	2.5		
Dhaka, Bangladesh (urban, Jan 2005 - Feb 2008) (Brooks and colleagues)	I, DS+/-	Defined population base	OPS; RT-PCR	1.1	0.5	0.8			0.2
Ballabhgarh, India (rural, Aug 2012 - Aug 2013) (Krishnan and colleagues)	I, DS+/-	Defined population base	NPS; RT-PCR	17.7	6.4	11.1	6.4		3.4

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. OPS=oropharyngeal swab. RT-PCR=reverse transcriptase polymerase chain reaction. I=WHO definition applied by a health worker. W+/-=wheeze part of case definition or not. DS+/-=danger signs part of case definition or not. C+/-=crepitation part of case definition or not. #All studies were active community-based.

Table 25: Summary of incidence rate and number of new cases of RSV associated ALRI

Region	Severity	No.	0-5m		0-11m		0-59m	
			Incidence rate (per 1000 children per year)	Number of new cases (*10^3)	Incidence rate (per 1000 children per year)	Number of new cases (*10^3)	Incidence rate (per 1000 children per year)	Number of new cases (*10^3)
Developing and industrialised regions								
Developing countries	RSV-ALRI	14	82.5 (50.4-135.2)	5077 (3099-8318)	88.3 (58.6-133)	10863 (7209-16366)	50.8 (32.4-79.7)	30516 (19463-47853)
	RSV-severe ALRI	8	36.1 (10.1-129.1)	2222 (622-7945)	28.7 (9.1-90.3)	3529 (1120-11114)	10.2 (3.5-29.9)	6145 (2103-17943)
	RSV-very severe ALRI	3	8.0 (1.0-62.3)	492 (63-3834)	5.8 (0.8-43.9)	713 (95-5400)	1.4 (0.2-11.3)	817 (96-6782)
Industrialised countries	RSV-ALRI	2	66.1 (33.5-130.4)	448 (227-884)	65.4 (33.2-129.1)	887 (450-1751)	35.6 (16.6-76.2)	2482 (1158-5320)
Globally	RSV-ALRI	16		5525 (3326-9202)		11750 (7659-18117)		32999 (20622-53173)
World Bank income regions								
Low and middle income countries	RSV-ALRI	14	82.5 (50.4-135.2)	4991 (3046-8177)	88.3 (58.6-133)	10678 (7087-16088)	50.8 (32.4-79.7)	30003 (19136-47048)
	RSV-severe ALRI	8	36.1 (10.1-129.1)	2184 (611-7811)	28.7 (9.1-90.3)	3469 (1101-10925)	10.2 (3.5-29.9)	6042 (2067-17642)
	RSV-very severe ALRI	3	8.0 (1.0-62.3)	483 (62-3769)	5.8 (0.8-43.9)	713 (95-5400)	1.4 (0.2-11.3)	803 (94-6668)
High income countries	RSV-ALRI	2	66.1 (33.5-130.4)	517 (262-1020)	65.4 (33.2-129.1)	1024 (519-2020)	35.6 (16.6-76.2)	2841 (1326-6090)

Globally	RSV-ALRI	16		5508 (3308-9197)		11702 (7606-18109)		32844 (20462-53138)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. No.=number of studies

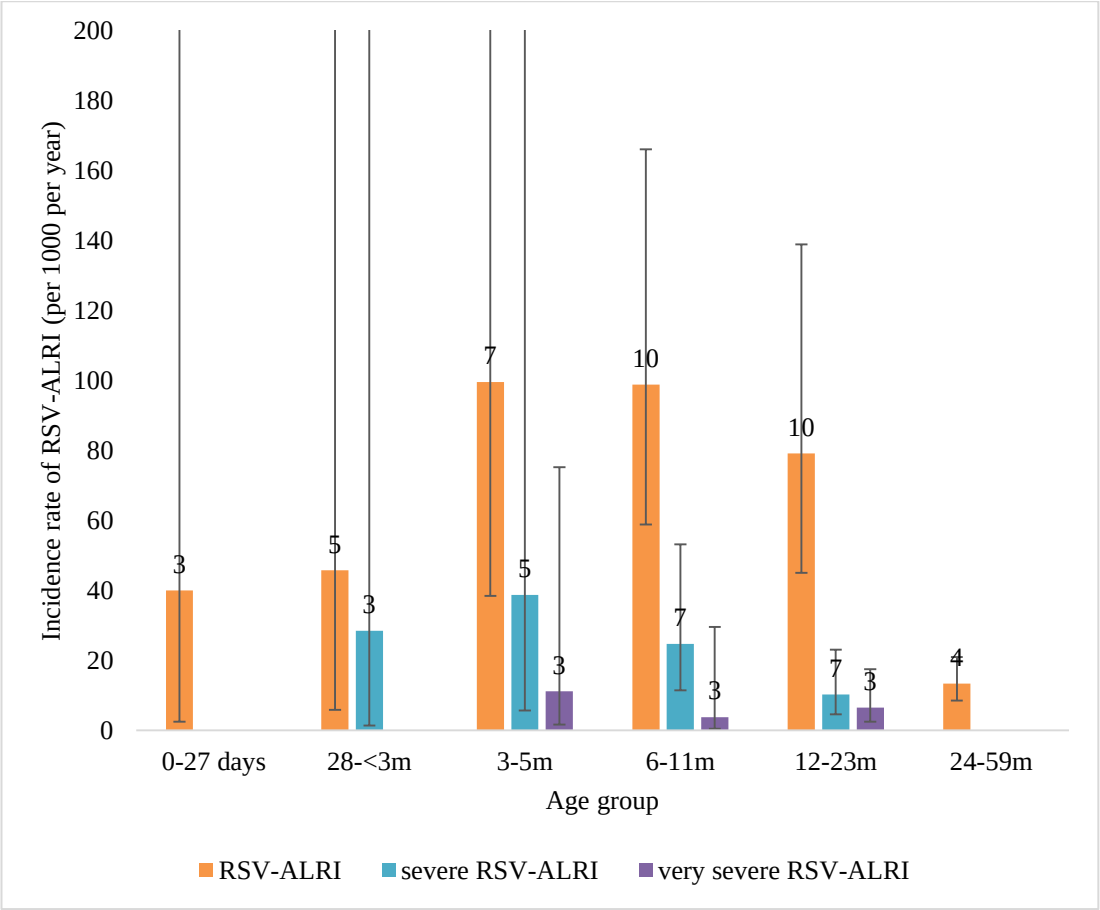


Figure 16: Meta-estimate of incidence rate of RSV associated ALRI by finer age bands

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. Numbers above each bar are number of studies included in meta-analysis for that category. Error bars are 95% confidence intervals of the point estimate.

5.2.2 Hospitalisation rate of RSV associated ALRI

In total, 37 published studies (Ahmed et al., 2012, Anders et al., 2015, Boyce et al., 2000, Chan et al., 1999a, Chiu et al., 2010, Cilla et al., 2009, Dede et al., 2010, Deshpande and Northern, 2003, Diez Domingo et al., 2006, Emukule et al., 2014, Eriksson et al., 2002, Fjaerli et al., 2004, Forster et al., 2004, Fry et al., 2010, Gil-Prieto et al., 2015, Hacimustafaoglu et al., 2013, Hall et al., 2009, Henrickson et al., 2004, Holman et al., 2004, Iwane et al., 2004, Jain et al., 2015, Jansen et al., 2007, Ji et al., 2010, Muller-Pebody et al., 2002, Resch et al., 2002, Robertson et al., 2004, Rowlinson et al., 2013, Stockman et al., 2012, Suwanjutha et al., 2002, Vicente et al., 2003, Weber et al., 2002, Weigl et al., 2002a, Whitehall et al., 2001, Leader and Kohlhase, 2003, Paramore et al., 2004) were identified to report hospitalisation rate (two articles provided four studies). 36 unpublished studies from RSV GEN were provided[U1, U10, U12-45] (Table 26). Overall, 73 studies were included in the meta-analysis of hospitalisation rate (Table 27). Data computed using median rate ratios from studies providing data for full age range were highlighted with parentheses. A sensitivity analysis was carried out to compare the meta-estimate of hospitalisation rate after excluding the imputed data (Appendices – A15). All studies adopted passive hospital-based or clinic-based case ascertainment (inpatients only) – children with ALRI who have sought treatment in hospitals or clinics are enrolled. There were 43 studies from developing countries and 30 from industrialised countries. Regarding the study setting, 30 studies were based on urban areas, another 25 studies were from study sites with a mix of population (both urban and rural) while the remaining 18 studies were from rural areas. The table containing data in narrower age bands was in Appendices – A16. Two published articles (Holman et al., 2004, Whitehall et al., 2001) and 3 unpublished studies[U41, U43, U44] reported data in study sites with aboriginal population (Townsville in Australia, Alaska, Navajo and White Mountain Apache in United States). They were from a special group of population, and reported relevantly higher rates than other areas from the same country. Thus, they were excluded in the final estimate. Three published studies (Ahmed et al., 2012, Chiu et al., 2010, Emukule et al., 2014) and four unpublished studies[U15, U18, U19, U20] used different case definitions: 2 studies including fever as part of the case definitions, 4 studies using SARI as the case definition, 1 study excluding children with wheeze condition. These studies were excluded in a sensitivity analysis in order to explore the effects of studies using different case definitions on the outcome. The summary of meta-estimate of hospitalisation rate in different age groups and in different regions (regions by World Bank income, developing and industrialised) was presented in Figure 17 and Table 28, and corresponding number of hospitalised cases was shown in Table 29. The forest plots were available in Appendices -

A17. Hospitalisation rate was high among children in first year of life and high in upper middle income countries. It was estimated that 3.0 (95% CI 2.2-4.0) million new cases of RSV associated hospitalised ALRI occurred in children younger than 5 years old in the worldwide in 2015, of which 87% were in developing countries. The overall number was added up from estimates of exclusive finer age bands in different regions. There were 21 countries in sub-Saharan Africa with high HIV burden according to UNAIDS Global Plan (UNAIDS, 2013). Thirteen studies identified in this review reported hospitalisation rate in young children from these African countries, and the number of new episodes of RSV associated hospitalised ALRI in children under five was around 0.7 (95% CI 0.6-0.9) million. Among 73 studies, 9 also reported hospitalisation rate in RSV associated hospitalised ALRI cases with chest wall indrawing. All of them were unpublished studies from developing countries (Table 30). The meta-estimate in children younger than 5 years was 4.6 (95% CI 2.8-7.4) per 1000 children per year in developing countries (no estimate available for industrialised countries). This is translated to 2.6 (95% CI 1.6-4.5) million new cases of RSV associated hospitalised ALRI which had chest wall indrawing in developing countries (sum of estimates from exclusive narrower age bands). Regarding very severe cases in hospital settings, 18 studies were available to provide the estimates (Table 31). All of them were unpublished studies. Three studies were from industrialised countries while the other 15 studies were based in developing countries. One study was carried out in an aboriginal population and thus excluded in final estimate[U41]. Adjustment of number of cases according to proportion of ALRI cases which were tested and imputation of missing data across age groups was not performed among very severe cases since the underlying assumptions might not be valid. Among these 18 studies, 8 also provided hospitalisation rate of very severe cases which were ICU admitted (Table 32); 4 reported hospitalisation rate in very severe cases requiring mechanical ventilation (Table 33). The hospitalisation rates of RSV associated very severe ALRI in children aged 0-5m, 6-11m and 12-59m from developing countries were estimated as 5.2 (95% CI 2.4-11.0), 3.0 (95% CI 1.2-7.7) and 0.2 (95% CI 0.1-0.4) per 1000 children per year respectively (Table 34). Therefore, it was estimated that in 2015, around 598,000 (95% CI 265,000-1,359,000) new episodes of RSV associated very severe ALRI occurred in children under five years old in developing countries (Table 35). Among them, about 212,000 (95% CI 102,000-215,000) cases were estimated with ICU admission (no estimate for mechanical ventilation). There were no enough studies to produce the estimate in industrialised countries.

Two sensitivity analyses were carried out to include studies with indigenous populations in industrialised countries and to exclude studies using different case definitions (fever, wheeze

negative or SARI) respectively. From Table 36, after five studies with indigenous populations were included, the meta-estimate of RSV associated hospitalised ALRI in 0-59m in high income countries was increased from 5.5 to 6.7 per 1000 children per year. Four studies were from America, which increased the meta-estimate in Americas region substantially (5.1 vs. 7.2). This supports the decision to report the regional/global meta-estimate after excluding studies with aboriginal population. When 7 studies using different case definitions for ALRI were excluded, the meta-estimate stratified by different regions was slightly lower than the previous estimate except in upper middle income region.

Table 26: List of 36 unpublished studies reporting hospitalisation rate

Study number	Location (reference)	Study period
U1	Kilifi birth cohort, Kenya (Nokes and colleagues)	Jan 2002 - May 2005
U10	Paarl, South Africa (Zar and colleagues)	Mar 2012 - Dec 2014
U12	CEMIC, Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010
U13	Buenos Aires, Argentina (Polack and colleagues)	2011 - 2013
U14	Kishoregonj, Bogra, Comilla and Barisal, Bangladesh (Homaira and colleagues)	2010 - 2013
U15	Belo Horizonte, Brazil (Oliveira and colleagues)	2011 - 2013
U16	Concepcion, Chile (Fasce and colleagues)	Jan 2012 - Dec 2013
U17	Iquique, Chile (Fasce and colleagues)	Jan 2012 - Dec 2013
U18	Jingzhou, China (Yu and colleagues)	Jan 2010 - Dec 2012
U19	Santa Ana, El Salvador (Clara and colleagues)	2008 - 2013
U20	Gambia Western Region, Gambia (Howie and colleagues)	Jul 2007 - Jun 2008
U21	Santa Rosa, Guatemala (McCracken and colleagues)	2008 - 2013
U22	Quetzaltenango, Guatemala (McCracken and colleagues)	2009 - 2013
U23	Ballabhgarh, India (Broor and colleagues)	Jan 2010 - Dec 2012
U24	Pune, India (Chadha and colleagues)	May 2009 - Apr 2013
U25	Lombok, Indonesia (Gessner and colleagues)	2000 - 2002
U26	Kilifi hospital study, Kenya (Nokes and colleagues)	Jan 2002 - Dec 2010
U27	Bondo district, Kenya (Feikin and colleagues)	Jan 2007 - Jun 2009
U28	Manhiça, Mozambique (Bassat and colleagues)	20th Sep 2006 - 19th Sep 2007
U29	Manhiça, Mozambique (Bassat and colleagues)	1st Jan 2011 - 30th Jun 2014
U30	Utrecht, Netherlands (Bont and colleagues)	2001 - 2010
U31	41 sites in Netherlands (Bont and colleagues)	2008 - 2013
U32	David City, Panama (Jara and colleagues)	Jan 2011 - Dec 2013
U33	Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	5th Jul 2000 - 31st Dec 2004
U34	Gauteng province, South Africa (Cohen and colleagues)	2009 - 2012
U35	KwaZulu-Natal province, South Africa (Cohen and colleagues)	2010 - 2014
U36	Klerksdorp site, South Africa (Cohen and colleagues)	Jan 2011 - Dec 2014
U37	Soweto, South Africa (Madhi and colleagues)	Mar 1998 - Oct 2005
U38	Maela Camp, Tak Province, Thailand (Turner and colleagues)	Nov 2007 - Oct 2010

Study number	Location (reference)	Study period
U39	Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	Jan 2008 - Dec 2011
U40	Tone district, Togo (Gessner and colleagues)	Aug 2011 - Dec 2013
U41	Alaska, USA (Singleton and colleagues)	Jul 1994 - Jun 2012
U42	Colorado, USA (Simoes and colleagues)	Jan 2008 - Jun 2013
U43	Navajo and WMA, USA - MEDI (O'Brien and colleagues)	Oct 2004 - Dec 2010
U44	Navajo and WMA, USA - EPI (O'Brien and colleagues)	Oct 1997 - Mar 2000
U45	Nha Trang, Vietnam (Yoshida and colleagues)	Feb 2007 - Dec 2012

Table 27: List of 73 studies reporting hospitalisation rate of RSV associated ALRI

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Alice Springs, Australia (urban, 1st Jan 2000 - 31st Dec 2004) (Dede et al., 2010)	II	Census-derived estimate	NPA; DFA	(42.7)		(32.4)			(8.7)
Suzhou, China (urban, Jan 2007 - Dec 2008) (Ji et al., 2010)	II	Census-derived estimate	nasal aspirate; DFA	(14.1)		(10.7)			2.9
Hong Kong, China (urban, 2003 - 2006) (Chiu et al., 2010)	II, F+	Census-derived estimate	NPA; DFA, culture	26.8	10.4	18.7	10.1	4.4	13.0
Sa Kaeo and Nakhom Phanom, Thailand (rural, 1st Jan 2004 - 31st Dec 2007) (Fry et al., 2010)	II, XR	Census-derived estimate	NPS, serum; RT-PCR, IFA	(14.3)		10.9			5.4
Damanhour, Egypt (urban and rural, Jun 2009 - Jun 2012) (Rowlinson et al., 2013)	II	Census-derived estimate	NPS, OPS; RT-PCR	(23.0)		17.5			2.4
Lørenskog, Norway (periurban, 1993 - 2000) (Fjaerli et al., 2004)	II	Census-derived estimate	NPA; ELISA	(28.6)		21.7	6.8		(5.9)
Valencia, Spain (urban, 2001 - 2002) (Diez Domingo et al., 2006)	II	Census-derived estimate	NA	(37.2)		(28.2)	9.8		(7.6)
Gipuzkoa, Spain (urban, Jul 2004 - Jun 2007) (Cilla et al., 2009)	II	Census-derived estimate	NPA; RT-PCR	39.4	10.8	25.1	3.0		(6.8)
Bursa, Turkey (urban, 1st Mar 2010 - 28th Feb 2011) (Hacimustafaoglu et al., 2013)	II	Census-derived estimate	nasal swab; IF	(16.1)		(12.2)			(3.3)
USA (urban and rural, 1997 - 2006) (Stockman et al., 2012)	II	Census-derived estimate	NA	(32.8)	13.4	(24.8)	5.0	0.8	6.7
Dadaab and Kakuma, Kenya (rural, Sep 2007 - Aug 2010)§ (Ahmed et al., 2012)	III, T+/-, CWI+/-, O2+/-	Census-derived estimate	NPS, OPS; RT-PCR	(38.3)		29.0			9.3
Gipuzoka, Spain (urban, Jul 1996 - Jun 2000) (Vicente et al., 2003)	II	Census-derived estimate	NPA; ELISA	36.8	14.2	25.5	3.6	0.5	6.2
Kiel, Germany (urban, 1996 - 97 to 2000 - 2001) (Weigl et al., 2002a)	II, XR, W+/-	Defined population base	NPA; RT-PCR	(21.5)		16.3			(4.4)
Multicentric, Germany (urban, Nov 1999 -	II	Census-derived	NPS; PCR	(33.5)		(25.4)			(6.9)

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Oct 2001) (Forster et al., 2004)		estimate							
Shropshire, United Kingdom (urban, 1996 - 1999) (Deshpande and Northern, 2003)	II	Census-derived estimate	NA; IF	(34.2)		(25.9)			(7.0)
Stockholm, Sweden (urban, 1987 - 1998) (Eriksson et al., 2002)	II	Census-derived estimate	NPW; IFA	(18.5)		14.0			(3.8)
Graz, Austria (urban, 1999 - 2000) (Resch et al., 2002)	II	Census-derived estimate	NPA; ELISA	(14.7)		(11.1)			(3.0)
England, United Kingdom (urban, Apr 1995 - Mar 1998) (Muller-Pebody et al., 2002)	II	Census-derived estimate	NA	(37.4)		28.3			10.1
Netherlands (urban, 1997 - 2003) (Jansen et al., 2007)	II	Census-derived estimate	NA; cell culture, IF	(12.5)		9.5			(2.6)
Banjul, Fajara and Sibanor, Gambia (urban and rural, Jan 1994 - Dec 1996) (Weber et al., 2002)	II	Census-derived estimate	NPA; IF	(23.4)		17.7			(4.8)
Mpumalanga, South Africa (rural, Apr 2000 - Mar 2001)§ (Robertson et al., 2004)	II, CWI+/-, W+/-, T+/-	Census-derived estimate	NPA, NPW; ELISA	17.1		15.0			9.0
Takhli, Thailand (rural, 1999 - 2000) (Suwanjutha et al., 2002)	II, T+, CWI+, XR	Defined population base	NPA; IF	(43.0)		(32.6)			8.8
Hong Kong, China (urban, 1993 - 1997) (Chan et al., 1999a)	II	Census-derived estimate	NPA, throat swab; DFA, virus isolation	(12.2)		(9.3)			2.5
Townsville (Queensland), Australia (urban and rural, Jan 1997 - Oct 1999)# (Whitehall et al., 2001)	II	Census-derived estimate	NA; IF, culture	(23.8)		18.0			(4.9)
Monroe and Davidson Counties in Tennessee, USA (urban and rural, Oct 2000 - Sep 2001) (Iwane et al., 2004)	II	Census-derived estimate	nasal and throat swab; viral culture, RT-PCR	18.5	7.4	12.9	3.3	0.4	3.5
Milwaukee, USA (urban, Nov 1996 - Oct 1998) (Henrickson et al., 2004)	II	Census-derived estimate	NPS, throat swab; culture, ELISA	(28.4)		(21.5)			5.8

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Tennessee, USA (urban, Jul 1989 - Jun 1993) (Boyce et al., 2000)	II	Census-derived estimate	NA	88.2	30.1	63.0	7.3		(17.0)
Alaska, USA (rural, Jan 2000 - Dec 2001)# (Holman et al., 2004)	II	Census-derived estimate	NA	(45.4)		34.4			(9.3)
USA (urban and rural, Jan 2000 - Dec 2001) (Holman et al., 2004)	II	Census-derived estimate	NA	(36.2)		27.4			(7.4)
Nashville, Rochester and Cincinnati, USA (urban, Oct 2000 - Sep 2004) (Hall et al., 2009)	II, F+/-, W+/-	Census-derived estimate	nasal and throat swab; RT-PCR, culture	16.9	5.1	11.1	2.7	0.4	3.0
Kilifi birth cohort, Kenya (rural, Jan 2002 - May 2005) (Nokes and colleagues)§	II, T+, CWI+/DS+/O2+	Defined population base	NPA, nasal wash; DFA	20.0	6.0	11.6	5.4		(3.1)
CEMIC, Buenos Aires, Argentina (urban, 1st Jun 2008 - 31st Dec 2010) (Echavarria and colleagues)	II, ICU+/-, MV+/-	Defined population base	NPA; IFA	14.3		(16.8)		0.7	4.5
Buenos Aires, Argentina (urban and rural, 2011 - 2013) (Polack and colleagues)	II, O2+, W+, F+/-, ICU+/-, MV+/-	Census-derived estimate	NPA; PCR	64.5	33.4	48.9	9.1		(13.2)
Kishoregonj, Bogra, Comilla and Barisal, Bangladesh (urban and rural, 2010 - 2013) (Homaira and colleagues)	II, F+/-	Census-derived estimate	nasal and throat swab; RT-PCR	(18.7)		(14.1)			3.8
Belo Horizonte, Brazil (urban, 2011 - 2013) (Oliveira and colleagues)	II, F+, O2+/-, ICU+/-	Census-derived estimate	nasal swab; RT-PCR	(10.4)		7.9	1.3	0.9	2.2
Concepcion, Chile (urban and rural, Jan 2012 - Dec 2013) (Fasce and colleagues)	II, F+/-, ICU+/-	Census-derived estimate	NPA; IF	(11.0)		8.3	1.9	0.3	2.2
Iquique, Chile (urban and rural, Jan 2012 - Dec 2013) (Fasce and colleagues)	II, F+/-, ICU+/-	Census-derived estimate	NPA; IF	(30.4)		23.0	3.2	0.5	4.9
Jingzhou, China (urban and rural, Jan 2010 - Dec 2012) (Yu and colleagues)	III, T+/-, XR	Census-derived estimate	NPS; RT-PCR	3.5	6.6	5.2	11.2	3.4	5.4

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Santa Ana, El Salvador (urban, 2008 - 2013) (Clara and colleagues)	III	Census-derived estimate	NPS; IFA	(52.5)		39.8	16.2	2.0	12.2
Gambia Western Region, Gambia (urban and rural, Jul 2007 - Jun 2008) (Howie and colleagues)	II, CWI+/-, W-, O2+/-	Defined population base	NPA; PCR	(32.2)	17.4	24.4	6.3	1.6	5.7
Santa Rosa, Guatemala (urban and rural, 2008 - 2013) (McCracken and colleagues)	II, CWI+/-, DS+/-	Census-derived estimate	NPS, OPS; RT-PCR	(34.9)		26.4	5.6	0.8	7.1
Quetzaltenango, Guatemala (urban and rural, 2009 - 2013) (McCracken and colleagues)	II, CWI+/-, DS+/-	Census-derived estimate	NPS, OPS; RT-PCR	(19.1)		14.4	3.3	0.4	3.8
Ballabhgarh, India (rural, Jan 2010 - Dec 2012) (Broor and colleagues)	II, DS+/-	Defined population base	NPS; RT-PCR	6.3	2.0	3.8	1.0	0.1	1.0
Pune, India (rural, May 2009 - Apr 2013) (Chadha and colleagues)	II	Census-derived estimate	NPS; RT-PCR	12.2	22.1	18.5	11.1	2.2	5.3
Lombok, Indonesia (urban and rural, 2000 - 2002) (Gessner and colleagues)	II, CWI+	Defined population base	nasal wash; ELISA	14.0	12.3	13.1	2.6		(3.5)
Kilifi hospital study, Kenya (urban and rural, Jan 2002 - Dec 2010) (Nokes and colleagues)§	II, CWI+, O2+/DS+	Census-derived estimate	OPS, NPS, nasal wash; DFA	27.2	11.1	19.3	3.4	0.6	4.9
Bondo district, Kenya (rural, Jan 2007 - Jun 2009) (Feikin and colleagues)§	II, O2+/DS+	Census-derived estimate	NPS, OPS; RT-PCR	52.6	25.0	32.0	6.3	7.1	16.5
Manhiça, Mozambique (rural, 20th Sep 2006 - 19th Sep 2007) (Bassat and colleagues)§	II, T+	Census-derived estimate	NPA; RT-PCR	14.5	6.6	11.0	2.8	0.6	3.2
Manhiça, Mozambique (rural, 1st Jan 2011 - 30th Jun 2014) (Bassat and colleagues)§	II, T+, O2+/-	Defined population base	NPA; RT-PCR	4.4	1.9	3.2	1.2	0.4	1.1
Utrecht, Netherlands (urban, 2001 - 2010) (Bont and colleagues)	II	Defined population base	NPS, NPW; PCR, IF	(11.1)		8.4			(2.3)
41 sites in Netherlands (urban and rural, 2008 - 2013) (Bont and colleagues)	II, ICU+/-	Defined population base	NPS, NPW; PCR, IF	(53.5)		40.5			(10.9)
David City, Panama (urban, Jan 2011 - Dec	II	Defined	NPS, OPS; IFA,	(24.3)		18.4			5.6

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
2013) (Jara and colleagues)		population base	RT-PCR						
Tagbilaran and 6 rural sites, Philippines (urban and rural, 5th Jul 2000 - 31st Dec 2004) (Lucero and colleagues)	II, CWI+, DS+/-	Defined population base	NPA, nasal swab; culture, PCR	73.1	54.8	62.4	23.1		(16.8)
Gauteng province, South Africa (urban, 2009 - 2012) (Cohen and colleagues)§	II	Defined population base	NPA; PCR	(38.9)		29.4	6.8	1.3	7.8
KwaZulu-Natal province, South Africa (periurban, 2010 - 2014) (Cohen and colleagues)§	II	Defined population base	NPA; PCR	(27.5)		20.8	2.6	0.7	5.1
Klerksdorp site, South Africa (periurban, Jan 2011 - Dec 2014) (Cohen and colleagues)§	II	Defined population base	NPA; PCR	(16.3)		12.3			3.3
Soweto, South Africa (urban, Mar 1998 - Oct 2005) (Madhi and colleagues)§	II, CWI+, O2+/-	Defined population base	NPA; IF	33.1	10.2	20.0	4.0	0.5	4.7
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)§	II, CWI+, T+, DS+/-	Defined population base	NPS; RT-PCR	146.7	29.9	91.5	4.9		(24.7)
Maela Camp, Tak Province, Thailand (rural, Nov 2007 - Oct 2010) (Turner and colleagues)	II, CWI+, T+	Defined population base	NPA; RT-PCR	135.7	73.1	105.0	61.9		(28.4)
Sa Kaeo and Nakhon Phanom, Thailand (rural, Jan 2008 - Dec 2011) (Thamthitiwat and colleagues)	II, F+/-, T+/-, CWI+, O2+/-	Census-derived estimate	NPS; PCR	12.2	18.6	15.4	15.3	6.3	9.8
Tone district, Togo (rural, Aug 2011 - Dec 2013) (Gessner and colleagues)	II, CWI+	Census-derived estimate	nasal wash; RT-PCR	0.4	0.3	0.4	0.2	0.0	0.1
Alaska, USA (rural, Jul 1994 - Jun 2012) (Singleton and colleagues)#	II, MV+/-	Census-derived estimate	NPS; ELISA, DFA, culture	202.0	121.1	161.6	39.8		(43.6)
Colorado, USA (urban and rural, Jan 2008 - Jun 2013) (Simoes and colleagues)	II	Census-derived estimate	nasal wash; PCR	(23.8)		18.1	5.8	1.6	5.7
Navajo and WMA, USA - MEDI (rural, Oct 2004 - Dec 2010) (O'Brien and colleagues)#	II, O2+/-	Defined population base	NPS; RT-PCR	314.4	236.3	292.3			(78.9)

Location (reference)	Case definition (codes)	Denominator source	Specimen and diagnostic test	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)*					
				0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Navajo and WMA, USA - EPI (rural, Oct 1997 - Mar 2000) (O'Brien and colleagues)#	II, O2+/-	Defined population base	NPA; ELISA	230.2	158.9	194.4	81.7		(52.5)
Nha Trang, Vietnam (urban and rural, Feb 2007 - Dec 2012) (Yoshida and colleagues)	II, CWI+/DS+	Census-derived estimate	NPS; RT-PCR	9.3	3.8	7.5	4.1	0.8	2.8
Memphis, Nashville and Salt Lake City, USA (urban, Jul 2010 - Jun 2012) (Jain et al., 2015)	II, XR	Census-derived estimate	NPS, OPS; RT-PCR	(5.8)		(4.4)		0.7	(1.2)
Spain (urban, Jan 1997 - Dec 2011) (Gil-Prieto et al., 2015)	II	Census-derived estimate	NA	(54.6)		41.4	8.0	2.2	10.7
Karemo, Kenya (rural, Aug 2009 - Jul 2012)§ (Emukule et al., 2014)	III	Census-derived estimate	NPS, OPS; RT-PCR	13.4	14.0	(19.3)	8.1	2.0	5.2
Ho Chi Minh, Vietnam (urban, Jul 2009 - Dec 2013) (Anders et al., 2015)	II	Defined population base	NPS; RT-PCR	(10.6)		8.0			(2.2)
Dong Thap, Vietnam (urban and rural, Aug 2009 - Dec 2012) (Anders et al., 2015)	II	Defined population base	NPS; RT-PCR	(40.8)		30.9			(8.3)
USA (urban, 1997 - 2000) (Leader and Kohlhase, 2003)	II	Census-derived estimate	NA	(30.0)		22.7			(6.1)
USA (urban, 2000) (Paramore et al., 2004)	II	Census-derived estimate	NA	(22.9)		17.4			4.5

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. OPS=oropharyngeal swab. RT-PCR=reverse transcriptase polymerase chain reaction. IFA=indirect immunofluorescent antibody test. DFA=direct immunofluorescent antibody test. ELISA=enzyme-linked immunosorbent assay. IF=immunofluorescence. II=physician's assessment. III=SARI definition. F+/-=fever as part of case definition or not. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. C+/-=crepitation part of case definition or not. XR=X-ray confirmed (radiologically confirmed pneumonia). CWI+/-=chest wall indrawing part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation. NA=not applicable. *Data in parentheses are computed hospitalisation rate estimates. #Studies reporting hospitalisation rate in an aboriginal population from a high-income country. §Studies sites in sub-Saharan Africa which had high-HIV burden.

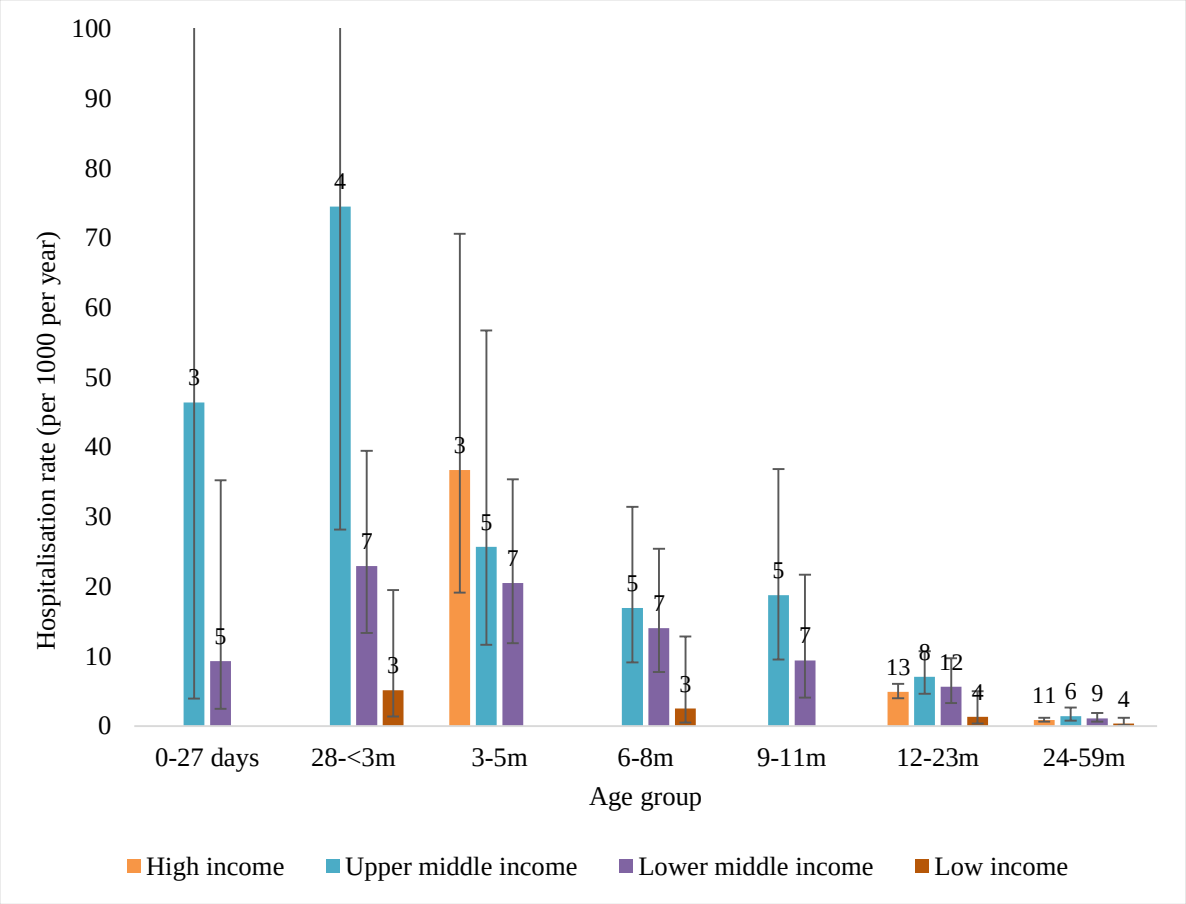


Figure 17: Meta-estimate of hospitalisation rate of RSV associated ALRI in finer age bands

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. Numbers above each bar are number of studies included in meta-analysis for that category. Error bars are 95% confidence intervals of the point estimate.

Table 28: Meta-estimate of hospitalisation rate of RSV associated ALRI

Region	0-5m		6-11m		12-59m	
	No. of studies	Hospitalisation rate (per 1000 children per year)	No. of studies	Hospitalisation rate (per 1000 children per year)	No. of studies	Hospitalisation rate (per 1000 children per year)
Low income	5	7.4 (2.4-22.6)	4	3.4 (0.6-19.5)	3	0.4 (0.1-1.7)
Lower middle income	17	22.9 (17.7-29.7)	9	11.3 (6.1-21.0)	9	1.8 (1.2-2.8)
Upper middle income	15	23.0 (16.1-32.9)	5	18.5 (9.8-34.7)	7	2.2 (1.3-3.9)
High income	31	26.3 (22.6-30.5)	8	13.0 (7.2-23.7)	6	1.6 (1.1-2.3)
Developing	43	20.2 (16.7-24.5)	20	11.0 (7.7-15.7)	21	1.5 (1.0-2.1)
Industrialised	25	27.3 (23.1-32.1)	6	11.5 (5.5-24.2)	4	2.0 (1.3-3.1)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection.

Table 29: Number of new cases of RSV associated hospitalised ALRI from studies reporting hospitalisation rate

Region	0-5m	6-11m	12-59m	0-59m*
	Hospitalised cases ($*10^3$)	Hospitalised cases ($*10^3$)	Hospitalised cases ($*10^3$)	Hospitalised cases ($*10^3$)
Low income	79 (26-240)	36 (6-207)	30 (7-132)	145 (39-580)
Lower middle income	737 (569-955)	362 (195-674)	451 (288-702)	1551 (1052-2331)
Upper middle income	407 (284-582)	327 (174-615)	305 (173-538)	1039 (632-1735)
High income	206 (177-239)	102 (56-185)	100 (69-145)	407 (302-569)
Developing	1243 (1025-1508)	674 (471-963)	693 (482-1003)	2610 (1979-3474)
Industrialised	185 (157-218)	78 (37-164)	113 (73-176)	376 (267-557)
Global#	1428 (1182-1726)	752 (509-1127)	806 (556-1179)	2986 (2246-4032)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. *number of hospitalised cases in 0-59m is sum of estimates from exclusive finer age bands (0-5m, 6-11m and 12-59m). #Global estimate is sum of regional estimates in developing countries and industrialised countries.

Table 30: List of 9 studies reporting hospitalisation rate of RSV associated ALRI with chest wall indrawing

Location (reference)	Case definition (codes)	Hospitalisation rate of RSV associated ALRI cases with chest wall indrawing (per 1000 children per year)*					
		0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Gambia Western Region, Gambia (Howie and colleagues)	II, CWI+/-, W-, O2+/-	(16.4)	17.4	12.4	3.4	1.0	3.4
Santa Rosa, Guatemala (McCracken and colleagues)	II, CWI+/-, DS+/-	(34.3)		25.8	5.2	0.8	6.9
Quetzaltenango, Guatemala (McCracken and colleagues)	II, CWI+/-, DS+/-	(18.7)		14.1	3.1	0.4	3.7
Lombok, Indonesia (Gessner and colleagues)	II, CWI+	13.9	12.1	13.0	2.6		(3.5)
Kilifi hospital study, Kenya (Nokes and colleagues)	II, CWI+, O2+/DS+	22.8	10.3	16.6	3.2	0.5	4.3
Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	II, CWI+, DS+/-	69.5	52.1	59.3	20.5		(16.0)
Soweto, South Africa (Madhi and colleagues)	II, CWI+, O2+/-	9.2	3.3	5.8	0.9	0.2	1.3
Maela Camp, Tak Province, Thailand (Turner and colleagues)	II, CWI+, T+	128.7	70.6	100.3	58.9		(27.1)
Nha Trang, Vietnam (Yoshida and colleagues)	II, CWI+/DS+	5.4	1.4	3.8	1.1	0.3	1.1

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. II=physician's assessment. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. CWI+/-=chest wall indrawing part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. *Data in parentheses are computed hospitalisation rate estimates.

Table 31: List of 18 studies reporting hospitalisation rate of RSV associated very severe ALRI

Location (reference)	Case definition (codes)	Hospitalisation rate of RSV associated very severe ALRI cases (per 1000 children per year)					
		0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Buenos Aires, Argentina (Polack and colleagues)	II, O2+, W+, F+/-, ICU+, MV+	28.8	12.4	20.6	3.8		
Belo Horizonte, Brazil (Oliveira and colleagues)	II, F+, O2+, ICU+			0.6	0.1	0.0	0.1
Concepcion, Chile (Fasce and colleagues)	II, F+/-, ICU+			0.3	0.2	0.1	0.2
Iquique, Chile (Fasce and colleagues)	II, F+/-, ICU+			3.4	0.2	0.1	0.7
Santa Rosa, Guatemala (McCracken and colleagues)	II, CWI+/-, DS+			18.7	4.5	0.7	5.1
Quetzaltenango, Guatemala (McCracken and colleagues)	II, CWI+/-, DS+			11.1	2.6	0.3	3.0
Ballabhgarh, India (Broor and colleagues)	II, DS+	3.2	1.1	2.0	0.3	0.1	0.6
Kilifi hospital study, Kenya (Nokes and colleagues)	II, CWI+, O2+/DS+	3.2	0.6	2.0	0.2	0.1	0.5
Bondo district, Kenya (Feikin and colleagues)	II, O2+/DS+	14.7	5.9	9.5	5.0	3.9	6.4
Manhiça, Mozambique (Bassat and colleagues)	II, T+	6.0	3.3	4.7	0.6	0.0	1.1
Manhiça, Mozambique (Bassat and colleagues)	II, T+, O2+	1.0	0.5	0.7	0.2	0.1	0.2
41 sites in Netherlands (Bont and colleagues)	II, ICU+			2.8			
Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	II, CWI+, DS+	5.5	4.2	4.8	1.8		
Soweto, South Africa (Madhi and colleagues)	II, CWI+, O2+	9.9	1.6	5.2	0.6	0.0	1.1
Maela Camp, Tak Province, Thailand (Turner and colleagues)	II, CWI+, T+	44.5	26.8	35.8	24.1		
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	II, F+/-, T+/-, CWI+, O2+	0.1	0.0	0.0	0.0	0.0	0.0
Colorado, USA (Simoes and colleagues)	II			2.1	0.4	0.2	0.6
Alaska, USA (Singleton and colleagues)#	II, MV+	9.1	3.1	6.1	0.1		

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. II=physician's assessment. F+/-=fever as part of case definition or not. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. CWI+/-=chest wall indrawing part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation. #Studies reporting hospitalisation rate in an aboriginal population from a high-income country.

Table 32: List of 8 studies reporting hospitalisation rate of RSV associated ALRI with ICU admission

Location (reference)	Case definition (codes)	Hospitalisation rate of RSV associated ALRI cases with ICU admission (per 1000 children per year)					
		0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Buenos Aires, Argentina (Polack and colleagues)	II, O2+, W+, F+/-, ICU+, MV+	5.6	1.4	3.5	0.2		
Belo Horizonte, Brazil (Oliveira and colleagues)	II, F+, O2+, ICU+			0.5	0.1	0.0	0.1
Concepcion, Chile (Fasce and colleagues)	II, F+/-, ICU+			0.3	0.2	0.1	0.2
Iquique, Chile (Fasce and colleagues)	II, F+/-, ICU+			3.4	0.2	0.1	0.7
Kilifi hospital study, Kenya (Nokes and colleagues)	II, CWI+, O2+/DS+	2.2	0.4	1.3	0.2	0.1	0.4
41 sites in Netherlands (Bont and colleagues)	II, ICU+			2.8			
Soweto, South Africa (Madhi and colleagues)	II, CWI+, O2+	0.8	0.1	0.4	0.0	0.0	0.1
Colorado, USA (Simoes and colleagues)	II			2.1	0.4	0.2	0.6

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. II=physician's assessment. F+/-=fever as part of case definition or not. W+/-=wheeze part of case definition or not. CWI+/-=chest wall indrawing part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation.

Table 33: List of 4 studies reporting hospitalisation rate of RSV associated ALRI with mechanical ventilation

Location (reference)	Case definition (codes)	Hospitalisation rate of RSV associated ALRI cases with mechanical ventilation (per 1000 children per year)					
		0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Buenos Aires, Argentina (Polack and colleagues)	II, O2+, W+, F+/-, ICU+, MV+	2.1	1.6	1.8	0.6		
41 sites in Netherlands (Bont and colleagues)	II, ICU+			2.3			
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	II, F+/-, T+/-, CWI+, O2+	0.1	0.0	0.0	0.0	0.0	0.0
Colorado, USA (Simoes and colleagues)	II			0.8	0.1	0.0	0.2

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. II=physician's assessment. F+/-=fever as part of case definition or not. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. CWI+/-=chest wall indrawing part of case definition or not. O2+/-=hypoxemia part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation.

Table 34: Meta-estimate of hospitalisation rate of RSV associated very severe ALRI

Region	0-5m		6-11m		12-59m	
	No. of studies	Hospitalisation rate (per 1000 children per year)	No. of studies	Hospitalisation rate (per 1000 children per year)	No. of studies	Hospitalisation rate (per 1000 children per year)
Low income	3	4.5 (1.1-19.0)	3	2.2 (0.6-8.6)	3	0.4 (0.0-6.4)
Lower middle income	3	3.8 (2.7-5.6)	3	1.5 (0.4-5.9)	4	0.4 (0.1-1.3)
Upper middle income	4	8.4 (3.4-21.1)	4	8.0 (1.8-35.2)	3	0.1 (0.0-0.2)
High income	0	-	0	-	3	0.2 (0.1-0.3)
Developing	10	5.2 (2.4-11.0)	10	3.0 (1.2-7.7)	12	0.2 (0.1-0.4)
Industrialised	0	-	0	-	1	-

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection.

Table 35: Number of new cases of RSV associated very severe hospitalised ALRI

Region	0-5m	6-11m	12-59m	0-59m*
	Hospitalised cases	Hospitalised cases	Hospitalised cases	Hospitalised cases
Low income	47774 (11279-202481)	23089 (5852-90973)	33694 (2407-512628)	104557 (19537-806083)
Lower middle income	123468 (85205-179092)	47265 (11897-189060)	107821 (35104-318448)	278553 (132207-686600)
Upper middle income	149448 (59850-373090)	142366 (32404-624001)	6932 (1386-29115)	298746 (93641-1026206)
High income	-	-	10927 (5785-19926)	-
Developing	318188 (149554-677611)	184020 (72008-471435)	95526 (42987-210156)	597733 (264549-1359202)#
Industrialised	-	-	-	-

*number of hospitalised cases in 0-59m is sum of estimates from exclusive finer age bands (0-5m, 6-11m and 12-59m). #212088 (101602-214723) were estimated to be admitted to ICU among very severe cases.

Table 36: Sensitivity analyses of hospitalisation rate to include studies with aboriginal population and exclude studies with different case definitions respectively

Region	Final estimate in 0-59m		Sensitivity analysis to include studies with aboriginal population		Sensitivity analysis to exclude studies with different case definitions	
	No. of studies	Hospitalisation rate (per 1000 children per year)	No. of studies	Hospitalisation rate (per 1000 children per year)	No. of studies	Hospitalisation rate (per 1000 children per year)
Low income	5	1.7 (0.6-5.1)	5	1.7 (0.6-5.1)	4	1.2 (0.3-4.5)
Lower middle income	17	5.1 (3.7-6.9)	17	5.1 (3.7-6.9)	14	4.5 (3.4-6.1)
Upper middle income	15	6.2 (5.0-7.8)	15	6.2 (5.0-7.8)	13	6.9 (5.3-8.9)
High income	31	5.5 (4.7-6.3)	36	6.7 (5.9-7.8)	30	5.3 (4.6-6.2)
Developing	43	4.9 (4.1-5.8)	43	4.9 (4.1-5.8)	36	4.6 (3.8-5.6)
Industrialised	25	5.5 (4.7-6.5)	30	7.1 (6.1-8.2)	25	5.5 (4.7-6.5)

5.2.3 Proportion of RSV associated hospitalised ALRI

Overall, 168 articles (Al-Shehri et al., 2005, Al-Toum et al., 2006, Assaf-Casals et al., 2015, Avendano et al., 2003, Bakir et al., 1998, Balmaks et al., 2014, Banerji et al., 2009, Bdour, 2001, Bedoya et al., 1996, Bukhari and Elhazmi, 2013, Calvo et al., 2010, Canducci et al., 2008, Carballal et al., 2000, Cevey-Macherel et al., 2009, Chan et al., 2007, Chan et al., 1999b, Chen et al., 2005, Chen et al., 2014b, Chung et al., 2007, Do et al., 2011, Ekalaksananan et al., 2001, Farzin et al., 2015, Feikin et al., 2013, Ferone et al., 2014, Ferronato et al., 2012, Flaherman et al., 2010, Foulongne et al., 2006, Fuller et al., 2013, Garcia et al., 2010, Garcia-Garcia et al., 2006, Hamada et al., 2014, Hammitt et al., 2012a, Harada et al., 2013, He et al., 2014, Hervas et al., 2012, Huang et al., 2013a, Hussey et al., 2000, Jansson et al., 2002, Juven et al., 2000, Kaneko et al., 2002, Khamis et al., 2012, Kwofie et al., 2012, Lamarao et al., 2012, Loscertales et al., 2002, Macedo et al., 2002, Maggi et al., 2007, Mazumdar et al., 2013, Min et al., 2011, Mlinaric-Galinovic et al., 2009a, Mlinaric-Galinovic et al., 2009b, Moore et al., 2012, Moriyama et al., 2010, Moura et al., 2002, Murray et al., 2014, Nascimento-Carvalho et al., 2010, Noyola et al., 2007, Okada et al., 2012, Oliveira et al., 2009, Ouedraogo et al., 2014, Pecchini et al., 2008, Pineros et al., 2013, Pourakbari et al., 2014, Salomao Jr et al., 2011, Santibanez et al., 2012, Singh et al., 2014, Singleton et al., 1995, Siritantikorn et al., 2002, Sparremberger et al., 2011, Sung et al., 2009, Suryadevara et al., 2011, Sutmoller et al., 1995, Takeyama et al., 2014, Tallo et al., 2014, Tang et al., 2008, Teeratakulpisarn et al., 2007, Tran et al., 2013, Tsolia et al., 2003, Turkish Neonatal, 2012, Turner et al., 2013, Vagia et al., 2010, Van Leeuwen et al., 2012, Videla et al., 1998, Viegas, 2011, Vieira et al., 2007, Wasem et al., 2008, Weigl et al., 2002b, Wolf et al., 2006, Wolf et al., 2010, Yeolekar et al., 2008, Yoo et al., 2007, Zhang et al., 2012b, Zhang et al., 2011, Zuccotti et al., 2011, Cao et al., 2004, Cao et al., 2007, Cao et al., 2015, Cao et al., 2013, Chang et al., 2010, Che et al., 2004, Chen, 2012, Chen and Chen, 2009, Chen et al., 2010, Chen et al., 2014a, Ding and Tian, 2014, Ding et al., 2012, Du, 2012, Fan et al., 2007, He, 2015, Hu and Wang, 2014, Huang et al., 2013b, Ji et al., 2013, Jiang and Lan, 2007, Jiang et al., 2013a, Jiang et al., 2013b, Ju et al., 2012, Lei, 2012, Li et al., 2013, Liang and Ge, 2014, Liang et al., 2012, Lin et al., 2015, Liu et al., 2013a, Liu et al., 2015b, Liu et al., 2013b, Lu et al., 2005, Lu et al., 2012, Ma et al., 2005, Miao et al., 2010, Ou et al., 2009b, Peng et al., 2009b, Qin et al., 2008, Ru et al., 2013, Sheng et al., 2014, Shi et al., 2012, Sun et al., 2004, Tan et al., 2009, Wan et al., 2006, Wang et al., 2015, Wang et al., 2011, Wang, 2011, Wang et al., 2012, Xiang et al., 2005, Xiao et al., 2012, Xie et al., 2013, Xie and Deng, 2011, Xu et al., 2014, Xue et al., 2014, Yang et al., 2009, Yao et al., 2015, Ye and Yuan, 2004, Ye et al., 2014, Yin, 2014, Yin et al., 2012, Zeng et al., 2008,

Zhang et al., 2013a, Zhang et al., 2012a, Zhang et al., 2014a, Zhang and Yu, 2015, Zhang, 2008, Zhang et al., 2014b, Zhang et al., 2013b, Zhang et al., 2014c, Zhang et al., 2002, Zhao et al., 2011, Zhao et al., 2003, Zheng, 2011, Zhu and Hua, 2011, Malekshahi et al., 2010, Faghihloo et al., 2014) were identified providing proportion data (proportion of hospitalised ALRI cases which are RSV positive) and 73 of them were identified in Chinese language based databases. An additional 31 unpublished studies from RSV GEN were provided[U46-76] (Table 37). Overall, 199 studies were included in the meta-analysis (Table 38). All of these studies adopted passive hospital-based or clinic-based case ascertainment, and recruited only inpatients. Among them, 36 were from industrialised countries while 163 were from developing countries. Most studies (178 studies) were based in urban settings, 13 were from rural areas and 8 were from districts with mixed populations. Five studies provided proportion data in only neonates. One study reported proportion data in Alaska among an aboriginal population and therefore was excluded from the final estimate (Singleton et al., 1995). There were 15 published studies (Avendano et al., 2003, Bakir et al., 1998, Calvo et al., 2010, Cevey-Macherel et al., 2009, Feikin et al., 2013, Ferronato et al., 2012, He et al., 2014, Juven et al., 2000, Mazumdar et al., 2013, Okada et al., 2012, Sparremberger et al., 2011, Suryadevara et al., 2011, Tallo et al., 2014, Zhang et al., 2012b, Ding et al., 2012) and 9 unpublished studies[U48, U55-62] which used different definitions (SARI, wheeze exclusion or fever inclusion) to define ALRI and thus they were excluded in a further sensitivity analysis to explore the influence of these studies. The meta-analysis result was presented by six WHO regions because the updated estimate of hospitalisation rate of pneumonia is only available by WHO region. After application of the population number in 2015, the number of new cases of pneumonia was generated, which was then combined with the corresponding meta-estimate of the proportion data. The summary of the meta-estimate of the proportion data in each region as well as number of hospitalised cases were shown in Table 39. The relevant forest plots were available in Appendices – A18. In Africa, 21.3% of hospitalised ALRI cases were estimated to be positive with RSV among children younger than 5 years, the proportion was 28.6% in Americas, 23.9% in Eastern Mediterranean, 28.3% in Europe, 24.2% in South-East Asia, and 22.1% in Western Pacific. After applying the number of hospitalised ALRI cases in each WHO region to the corresponding meta-estimate of the proportion data respectively, the global number of new episodes of RSV associated hospitalised ALRI in children younger than five years was around 2.8 (95% CI 2.3-3.4) million. Compared to the estimate of hospitalised cases from studies reporting hospitalisation rate, which is 3.0 (95% CI 2.2-4.0) million, both estimates are quite similar and their confidence intervals overlap. These two approaches represent two independent methods to estimate number of new cases

of RSV associated hospitalised ALRI based on completely different studies (different study sites, different underlying population enrolled, different methodologies used etc.). However, the substantial similarity between estimates from these two approaches cross check and act to broadly replicate the estimate of the number of hospitalised cases. The estimate from the first approach which used studies reporting hospitalisation rate will be used in the following analysis.

A sensitivity analysis was carried out to exclude studies with different case definitions which were mentioned above. The result was compared to previous estimate and was shown in Table 40. In general, the proportion from sensitivity analysis where studies using different case definitions were excluded was consistently lower than the meta-estimate where these studies were included, however, no substantial difference was identified across regions. Another sensitivity analysis to include studies reporting data in aboriginal population was not carried out due to the reason that there was only one study conducted in aboriginal population.

Table 37: List of 33 unpublished studies reporting hospital based proportion data

Study number	Location (reference)	Study period
U46	Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010
U47	Buenos Aires, Argentina (Gentile and colleagues)	2001 - 2013
U48	Takeo and Kampong Cham, Cambodia (Goyet and colleagues)	Apr 2007 - Feb 2010
U49	Chillan, Chile (Fasce and colleagues)	2010 - 2013
U50	Osorno, Chile (Fasce and colleagues)	2010 - 2013
U51	Punta Arenas, Chile (Fasce and colleagues)	2010 - 2013
U52	Santiago, Chile (Fasce and colleagues)	2010 - 2013
U53	Valparaiso, Chile (Fasce and colleagues)	2010 - 2013
U54	China (Yu and colleagues)	Jan 2009 - Sep 2013
U55	Beijing, China (GABRIEL)	Jan 2011 - Dec 2012
U56	Ulaanbaatar, Mongolia (GABRIEL)	Sep 2011 - Oct 2012
U57	Phnom Penh, Cambodia (GABRIEL)	Oct 2010 - Jan 2013
U58	Lucknow, India (GABRIEL)	Jun 2012 - Dec 2013
U59	Antananarivo, Madagascar (GABRIEL)	Dec 2010 - Feb 2013
U60	Asuncion, Paraguay (GABRIEL)	Jul 2010 - May 2013
U61	Bamako, Mali (GABRIEL)	Jul 2011 - Nov 2012
U62	Berlin, Germany (Rath and colleagues)	1st Apr 2010 - 31st Mar 2014
U63	Amman, Jordan (Khuri and colleagues)	Mar 2010 - Mar 2013
U64	Lwak, Kenya (Montgomery and colleagues)	2007 - 2011
U65	Rabat, Morocco (Bassat and colleagues)	Nov 2010 - Dec 2011
U66	Kathmandu, Nepal (Basnet and colleagues)	Jan 2006 - Jun 2008
U67	Karachi, Pakistan (Ali and colleagues)	Aug 2009 - Jul 2012
U68	Basse, Gambia (PERCH)	3rd Nov 2011 - 2nd Nov 2013
U69	Kilifi, Kenya (PERCH)	15th Aug 2011 - 15th Nov 2013
U70	Bamako, Mali (PERCH)	3rd Jan 2012 - 14th Jan 2014
U71	Nakhon Phanom and Sa Kaeo, Thailand (PERCH)	1st Jan 2012 - 31st Jan 2014
U72	Lusaka, Zambia (PERCH)	10th Oct 2011 - 31st Oct 2013
U73	Dhaka, Bangladesh (PERCH)	1st Jan 2012 - 31st Dec 2013

Study number	Location (reference)	Study period
U74	Matlab, Bangladesh (PERCH)	1st Jan 2012 - 31st Dec 2013
U75	Tacloban, Philippines (Lupisan and colleagues)	May 2008 - Jul 2012
U76	Mpumalanga, South Africa (Cohen and colleagues)	Jan 2010 - Dec 2014

Table 38: List of 199 studies reporting proportion of hospitalised ALRI cases which were RSV positive

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Subiaco, Australia (urban, Jan 2000 - Dec 2005) (Moore et al., 2012)	II	NPA; DFA, RT-PCR, viral culture	54.4	51.4		
Hangzhou, China (urban, Jan 2001 - Dec 2006) (Tang et al., 2008)	II	NPA; DFA	30.1		27.1	
Lanzhou, China (urban, 1st Jan - 31st Dec 2011) (Huang et al., 2013a)	II, F+/-, W+/-, XR	throat swab; RT-PCR	19.3			
Lanzhou, China (urban, Oct 2004 - Oct 2005) (Zhang et al., 2011)	II, F+/-, XR	NPA, serum; DFA, ELISA	23.4		20.3	19.2
Shanghai, China (urban, May 2009 - Jul 2010) (Zhang et al., 2012b)	II, F+	NPS; RT-PCR			11.6	
Hong Kong, China (urban, 1st Jan 2004 - 31st Dec 2004) (Chan et al., 2007)	II	NPA; DFA			11.6	
Hong Kong, China (urban, Nov 2005 - Oct 2006) (Sung et al., 2009)	II, W+/-, F+/-	NPA, nasal swab; DFA, RT-PCR, viral culture				8.4
Taiwan, China (urban, Jan 2001 - Dec 2003) (Chen et al., 2005)	II	NPA; virus culture, IF	26.1	24.3		23.5
Shizuoka, Japan (urban, 1st Jul 1997 - 30th Jun 2000) (Kaneko et al., 2002)	II, W+/-, XR	NPA; ELISA			31.4	
Tokyo, Japan (urban, Mar 2007 - Jul 2009) (Moriyama et al., 2010)	II, W+/-, F+/-, XR	NPS; RT-PCR		27.6		
Japan (urban, Apr 2008 - Apr 2009) (Okada et al., 2012)	II, F+, XR	NPS; RT-PCR	26.9	28.7		26.1
Nagasaki, Japan (urban, Apr 2009 - Mar 2010) (Harada et al., 2013)	II, XR	NPS; IF, RT-PCR				55.9
Seoul, Korea (urban, Jan - Dec 2004) (Yoo et al., 2007)	II, W+, XR	NPA; RT-PCR				29.5
Seoul, Korea (urban, Jul 2004 - Jan 2006) (Chung et al., 2007)	II, XR, W+	NPA; DFA				20.6
Seoul, Korea (urban, Jan 2007 - Feb 2011) (Min et al., 2011)	II	NPA; RT-PCR			67.7	
Kuala Lumpur, Malaysia (urban, Jan 1982 - Dec 1997) (Chan et al., 1999b)	II	NPA; IFA, culture	19.2	18.4		

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Ho Chi Minh City, Vietnam (urban, Nov 2004 - Jan 2008) (Do et al., 2011)	II, T+, CWI+/-, ICU+/-	nasal swab, throat swab, NPA; RT-PCR	21.4			24.4
Ho Chi Minh City, Vietnam (urban, Apr 2010 - May 2011) (Tran et al., 2013)	II, XR	NPS; RT-PCR		24.7		
Pune, India (urban, Feb 2002 - Dec 2004) (Yeolekar et al., 2008)	II	NPA; IF	46.0		42.5	
Kolkata, India (urban, Apr 2010 - Mar 2011) (Mazumdar et al., 2013)	III, CWI+, W+, C+, T+	nasal and throat swabs; RT-PCR	21.0			16.7
Lucknow, India (urban, Jun 2011 - May 2012) (Singh et al., 2014)	II, CWI+	NPA; RT-PCR	34.3			25.2
Khon Kaen, Thailand (urban, Aug 1992 - Nov 1994) (Ekalaksananan et al., 2001)	II, CWI+, XR	NPA; virus culture, IF, ELISA				29.0
Nakhon Sawan, Thailand (rural, Nov 1998 - Feb 2001) (Siritantikorn et al., 2002)	II, CWI+	NPA; IFA				34.2
Khon Kaen, Thailand (urban, Apr 2002 - Aug 2004) (Teeratakulpisarn et al., 2007)	II, W+, T+	NPA; RT-PCR	67.6	64.7		
Tak Province, Thailand (rural, Apr 2009 - Sep 2011) (Turner et al., 2013)	II, CWI+/-, DS+/-	NPA; RT-PCR	39.1			
Seeb, Oman (urban, Dec 2007 - Dec 2008) (Khamis et al., 2012)	II	NPA; IF, RT-PCR				21.6
Zarqa, Jordan (urban, Jan 1997 - May 1999) (Bdour, 2001)	II	NPW; DFA, RT-PCR		25.5		
Amman, Jordan (urban, Sep 2002 - Mar 2004) (Al-Toum et al., 2006)	II	NPA; DFA	15.6	12.5		
Riyadh, Saudi Arabia (urban, Apr 1993 - Mar 1996) (Bakir et al., 1998)	II, F+, W+/-, XR	NPA; IFA				28.9
Riyadh, Saudi Arabia (urban, Jan 2005 - Dec 2010) (Bukhari and Elhazmi, 2013)	II	NPA; DFA	48.8		48.4	47.4
Abha, Saudi Arabia (urban, Oct 1997 - Sep 2001) (Al-Shehri et al., 2005)	II	NPA; ELISA, IFA				35.3
Zagreb County, Croatia (urban, 1994 - 2005) (Mlinaric-Galinovic et al., 2009b)	II	NPA; DFA, virus isolation	50.9	47.4		45.8
Zagreb County, Croatia (urban, Aug 2006 - Aug 2007)	II	NPA; DFA	48.1	47.0		46.5

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
(Mlinaric-Galinovic et al., 2009a)						
Turku, Finland (urban, Jan 1993 - Dec 1995) (Juven et al., 2000)	II, F+, XR	NPA; ELISA, culture		46.3		
Montpellier, France (urban, 1st Nov 2003 - 31st Oct 2004) (Foulongne et al., 2006)	II	NPA; DFA, virus culture	33.8	30.5	29.4	
Kiel, Germany (urban, Jul 1996 - Jun 2001) (Weigl et al., 2002b)	II	NPA; ELISA, RT-PCR	28.2	23.6		19.8
Germany (urban, Nov 1999 - Oct 2001 and Oct 2002 - Jun 2005) (Wasem et al., 2008)	II	NPA; RT-PCR, ELISA	42.8	36.2	34.1	
Athens, Greece (urban, 2008 - 2009) (Vagia et al., 2010)	II	NPA; IF				28.5
Be'er Sheva, Israel (urban, Nov 2001 - Oct 2002) (Wolf et al., 2006)	II	nasal wash; DFA				19.6
Be'er Sheva, Israel (urban, Nov 2001 - Oct 2005) (Wolf et al., 2010)	II, XR	NPW; DFA, culture				28.0
Pisa, Italy (urban, Jan 2000 - May 2006) (Maggi et al., 2007)	II	nasal swab; DFA		31.1		
Milan, Italy (urban, Oct 2004 - Sep 2006) (Canducci et al., 2008)	II, W+/-	NPA; RT-PCR		28.0		
Milan, Italy (urban, 1st Dec 2008 - 31st Dec 2009) (Zuccotti et al., 2011)	II, W+/-	OPS; RT-PCR	52.0	42.6		37.0
Enschede, Netherlands (urban, 2006 - 2007) (Van Leeuwen et al., 2012)	II, W+/-, F+/-	NPW; RT-PCR		48.3		
Palma, Spain (urban, Jan 1995 - Dec 2006) (Hervas et al., 2012)	II	NPA, NPW; ELISA, culture		62.7		
Madrid, Spain (urban, Oct 2000 - Jun 2005) (Garcia-Garcia et al., 2006)	II	NPA; IFA, RT-PCR		45.3		
Madrid, Spain (urban, Sep 2005 - Aug 2008) (Calvo et al., 2010)	II, W-, ICU+/-	NPA; RT-PCR		61.3		
Malmo, Sweden (urban, 1998 - 1999) (Jansson et al., 2002)	II	NPA; IF	54.5			
Lausanne and Geneva, Switzerland (urban, Mar 2003 - Dec 2005) (Cevey-Macherel et al., 2009)	II, CWI+, W-	NPA, serum; RT-PCR, IFA, ELISA, serology				13.1
Turkey (urban, May 2008 - Sep 2010) (Turkish Neonatal, 2012)	II	NPA, NPS, nasal wash, nasal swab; IF		16.9		
Buenos Aires and Santa Fe, Argentina (urban, 1990 - 1996)	II, T+/-, W+/-, XR	NPA; IFA		27.0		

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
(Carballal et al., 2000)						
Buenos Aires, Argentina (urban, 1999 - 2004) (Viegas, 2011)	II	NPA; RT-PCR, DFA				31.6
Pelotas, Brazil (urban, 1st Aug 1997 - 31st Jul 1998) (Macedo et al., 2002)	II, CWI+	NPA; DFA	30.8			
Bahia, Brazil (urban, Jan - Dec 1998) (Moura et al., 2002)	II	NPA; IFA				23.8
Sao Paulo, Brazil (urban, Mar 1999 - Jun 2000) (Vieira et al., 2007)	II, W+, XR	NPA, nasal swab; IFA, virus culture, RT-PCR	60.9			
Sao Paulo, Brazil (urban, Jan 2003 - Dec 2006) (Oliveira et al., 2009)	II	NPA, nasal swab; RT-PCR	45.4			42.0
Sao Paulo, Brazil (urban, Jan 2006 - Dec 2007) (Ferronato et al., 2012)	II, W-	NPA; IFA	63.5			
Bahia, Brazil (urban, Sep 2003 - May 2005) (Nascimento-Carvalho et al., 2010)	II, XR	NPA, serum; IF, ELISA				15.2
Sao Paulo, Brazil (urban, May 2004 - Sep 2005) (Salomao Jr et al., 2011)	II, T+/-, W+/-	NPA; RT-PCR	40.4	34.1		
Sao Paulo, Brazil (urban, Feb 2005 - Sep 2006) (Pecchini et al., 2008)	II, W+/-	NPA; IFA	30.1			28.6
Sao Paulo, Brazil (urban, Mar 2008 - Aug 2011) (Ferone et al., 2014)	II, CWI+	NPA; RT-PCR		27.3		
Belem, Brazil (urban, Nov 2006 - Oct 2007) (Lamarao et al., 2012)	II, F+/-, XR	NPA; DFA, RT-PCR			23.1	
Porto Alegre, Brazil (urban, Sep 2009 - Sep 2010) (Sparremberger et al., 2011)	II, W-	NPA; DFA	53.5			
Iqaluit, Canada (urban, 28th Jan 2002 - 27th Mar 2003) (Banerji et al., 2009)	II	NPA; ELISA		51.2		
British Columbia, Canada (urban, Apr 2008 - Mar 2010) (Santibanez et al., 2012)	II	NA	48.1			
Medellin, Colombia (urban and rural, Apr 1994 - Apr 1995) (Bedoya et al., 1996)	II	NPW; DFA	41.7			
Colombia (urban, Apr 2005 - Apr 2006) (Pineros et al., 2013)	II	NPA; IF	30.1			

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
San Luis Potosi, Mexico (urban, 1st May 2003 - 30th Apr 2005) (Noyola et al., 2007)	II	NPW; DFA	26.9	25.9	24.8	
Alaska, USA (rural, 1st Oct 1991 - 30th Sep 1993)# (Singleton et al., 1995)	II	NA; ELISA, IF, culture		38.4		
California, USA (urban, 1996 - 2004) (Flaherman et al., 2010)	II	NA; DFA		56.2		
Dallas, Texas, USA (urban, Jan 2002 - Dec 2007) (Garcia et al., 2010)	II	NPA; IF, DFA, virus culture		66.3		
New York, USA (urban, Oct 2007 - May 2010) (Suryadevara et al., 2011)	II, F+	NPS; RT-PCR, ELISA, virus culture		53.7		
Kumasi, Ghana (urban, Jan 2008 - Dec 2008) (Kwofie et al., 2012)	II, CWI+, DS+/-	NPS; RT-PCR		14.6		14.1
Rarieda, Kenya (rural, 1st Mar 2007 - 28th Feb 2010) (Feikin et al., 2013)	III, DS+/CWI+	NPS, OPS; RT-PCR				22.6
Kilifi, Kenya (rural, Jan - Dec 2010) (Hammitt et al., 2012a)	II, CWI+	NPA, OPS, sputum; RT-PCR				26.5
Bondo district, Kenya (rural, Aug 2008 - Dec 2010) (Fuller et al., 2013)	II, CWI+/DS+/O2+	NPS, OPS; RT-PCR				17.1
Santiago, Chile (urban, Jan 1989 - Dec 2000) (Avendano et al., 2003)	II, W-	NPA; IFA		29.0		
Cape Town, South Africa (urban, Jun 1995 - Aug 1996) (Hussey et al., 2000)	II, W+/-	NPA; ELISA		15.8		
Manhica District, Mozambique (rural, Oct 1998 - May 2000) (Loscertales et al., 2002)	II, CWI+/-, W+/-, T+/-	NPA; ELISA	10.7			
Athens, Greece (urban, Feb 1997 - Jun 2000) (Tsolia et al., 2003)	II, XR, W+/-, T+/-	NPW; DFA	61.5			
Buenos Aires, Argentina (urban, May 1991 - Dec 1992) (Videla et al., 1998)	II, CWI+/-, XR, W+/-, T+/-	NPA; IFA		38.6		
Rio de Janeiro, Brazil (rural, Jan 1987 - Dec 1989) (Sutmoller et al., 1995)	II, T+/-, W+/-	NPA; IFA, culture				40.5
Beijing, China (urban, Feb 2001 - Mar 2003) (Cao et al., 2004)	II	NPA; virus culture, IFA	44.9		39.0	36.5
Beijing, China (urban, Mar 2010 - Feb 2012) (Liu et al., 2013a)	II	NPA, throat swab; RT-PCR	56.3		49.1	41.8

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Changsha, China (urban, Sep 2007 - Aug 2008) (Ding et al., 2012)	II, F+, T+	NPA; RT-PCR	42.0		37.1	37.0
Changsha, China (urban, Sep 2007 - Aug 2008) (Xiao et al., 2012)	II	NPA; RT-PCR	30.1		27.6	27.6
Changsha, China (urban, Jun 2011 - Jun 2012) (Li et al., 2013)	II	NPA; DFA	55.1		53.7	53.9
Chaozhou, China (urban, Jun 2011 - Oct 2012) (Xie et al., 2013)	II	NPA; IFA	9.3		6.9	
Chengdu, China (urban, Jan - Dec 2007) (Zhang, 2008)	II	NPA; DFA	29.8		26.4	
Chengdu, China (urban, Mar 2010 - Feb 2011) (Cao et al., 2013)	II	NPA; RT-PCR		30.6		
Chenzhou, China (urban, Jan - Dec 2010) (Shi et al., 2012)	II	NPA; PCR	21.5		18.2	
Chongqing, China (urban, Apr 2003 - Oct 2007) (Peng et al., 2009b)	II	NPA; DFA	36.4		29.6	
Chongqing, China (urban, Apr 2008 - Mar 2009) (Du, 2012)	II	NPA; RT-PCR	31.7	29.3	28.7	
Chongqing, China (urban, Feb 2009 - Mar 2011)* (Zhu and Hua, 2011)	II	NPA; DFA				
Chongqing, China (urban, Jan 2009 - Dec 2011) (Lei, 2012)	II	NPA; DFA	34.5		31.9	
Dongguan, China (urban, Mar 2011 - May 2012) (Lu et al., 2012)	II	NPA; DFA	32.1		23.2	
Chengdu, China (urban, Jan 2007 - Dec 2009) (Wang, 2011)	II	NPA; IF	25.5		27.5	
Fuyang, China (urban, Jan 2003 - Dec 2004)* (Jiang and Lan, 2007)	II	NPA; DFA				
Guangzhou, China (urban, Oct 2009 - Sep 2010) (Xie and Deng, 2011)	II	NPS; RT-PCR	10.7		8.5	7.5
Guiyang, China (urban, Jan 2010 - May 2011) (Yin et al., 2012)	II	NPA; IF			21.0	
Guiyang, China (urban, Jun 2006 - Apr 2011) (Huang et al., 2013b)	II	NPA; DFA	27.1		24.1	
Haikou, China (urban, Jan 2007 - Oct 2008) (Tan et al., 2009)	II	NPA; RT-PCR	41.7		39.7	
Hangzhou, China (urban, 2000 - 2001) (Ye and Yuan, 2004)	II	NPA; IF	34.9		29.5	
Hangzhou, Chin (urban, 2001 - 2003)* (Ma et al., 2005)	II	NPA; DFA				

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Jiaxing, China (urban, Dec 2008 - Dec 2009) (Miao et al., 2010)	II	NPA; RT-PCR, DFA	16.8	15.8		
Jiaxing, China (urban, Aug 2010 - Aug 2012) (Zhang et al., 2013a)	II	NPA; DFA	18.6		14.6	
Kunming, China (urban, Oct 2005 - Oct 2007) (Fan et al., 2007)	II	NPA; DFA	28.5		25.9	
Kunming, China (urban, Sep 2009 - Sep 2010) (Zheng, 2011)	II	NPA; RT-PCR	46.2	42.9	40.8	40.2
Yueqing, China (urban, Jan 2006 - Dec 2010) (Zhang et al., 2012a)	II	NPA; DFA	32.0		23.2	19.3
Liaocheng, China (urban, Oct 2007 - Oct 2008) (Chen and Chen, 2009)	II	NPA; DFA	43.1		38.9	
Linyi, China (urban, Dec 2010 - Dec 2011) (Chen, 2012)	II	NPA; RT-PCR	33.2	31.5		
Nanjing, China (urban, Apr 2006 - Mar 2007) (Qin et al., 2008)	II	NPA; DFA	28.3	20.9		17.1
Nanjing, China (urban, Sep 2008 - Aug 2009) (Chen et al., 2010)	II	NPA; DFA	33.1		29.0	
Nanjing, China (urban, Jan 2009 - Dec 2011) (Jiang et al., 2013a)	II	NPA; DFA	36.8		34.1	
Shanghai, China (urban, May 2001 - Apr 2002) (Zhao et al., 2003)	II	NPA; IF	25.3		21.1	
Shanghai, China (urban, Jan - Dec 2000) (Che et al., 2004)	II	NPA; IF	21.1		19.1	18.6
Shanghai, China (urban, Oct 2002 - Apr 2004) (Lu et al., 2005)	II	NPA; DFA	29.8		20.4	19.0
Shanghai, China (urban, 2003 - 2006) (Zeng et al., 2008)	II	NPA; DFA	21.4		23.0	21.6
Shanghai, China (urban, Jan 2009 - Mar 2010) (Zhao et al., 2011)	II	NPA, throat swab; RT-PCR	28.1		25.6	
Shanghai, China (urban, Mar 2011 - Feb 2012) (Zhang et al., 2013b)	II	NPA; DFA			10.1	
Shangluo, China (urban, May 2011 - May 2012) (Ru et al., 2013)	II	NPA; IF	43.3		40.6	39.7
Shantou, China (urban, Jan 2007 - Dec 2007) (Ou et al., 2009b)	II	NPA; RT-PCR				19.1
Suzhou, China (urban, Sep 2005 - Oct 2011) (Ji et al., 2013)	II	NPA; DFA	22.4		18.9	17.1
Tianjin, China (urban, Jan 2002 - Mar 2004) (Sun et al., 2004)	II	NPA; IFA	9.8		9.4	

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Tianjin, China (urban, Jan 2010 - Jun 2011) (Wang et al., 2012)	II	NPA; DFA	7.5		6.5	
Weifang, China (urban, Nov 2007 - Nov 2008) (Yang et al., 2009)	II	NPA, NPS; DFA	31.0		25.8	
Wenzhou, China (urban, Jan 2003 - Jan 2005) (Xiang et al., 2005)	II	NPA; DFA	42.8		39.5	
Wenzhou, China (urban, Nov 2003 - Feb 2005) (Wan et al., 2006)	II	NPS; IFA			27.5	
Wenzhou, China (urban, Nov 2004 - Nov 2006) (Cao et al., 2007)	II	NPA; DFA	39.5		39.6	
Wenzhou, China (urban, Jan 2007 - Dec 2008) (Chang et al., 2010)	II	NPA; DFA	38.1		35.6	
Wenzhou, China (urban, Feb 2009 - Jan 2010) (Wang et al., 2011)	II	NPA; DFA	34.1		30.4	28.2
Wenzhou, China (urban, Jan - Dec 2010)* (Liang et al., 2012)	II	NPA; IF				
Xian, China (urban, 1994 - 1997) (Zhang et al., 2002)	II	NPA; IF	27.4		25.8	
Yancheng, China (urban, Jun 2011 - Jul 2012) (Ju et al., 2012)	II	NPA; DFA	22.1		20.0	
Zhongshan, China (urban, Apr 2011 - Mar 2012) (Liu et al., 2013b)	II	NPS; IF	17.8			
Zhuzhou, China (urban, Jan - Dec 2011) (Jiang et al., 2013b)	II	NPA; DFA	26.7		25.3	22.5
Buenos Aires, Argentina (urban, 1st Jun 2008 - 31st Dec 2010) (Echavarria and colleagues)	II, ICU+/-, MV+/-	NPA; IFA	43.0	36.8	34.8	33.3
Buenos Aires, Argentina (urban, 2001 - 2013) (Gentile and colleagues)	II, MV+/-	NPA; IFA	42.7	40.4	39.8	38.9
Takeo and Kampong Cham, Cambodia (urban, Apr 2007 - Feb 2010) (Goyet and colleagues)	II, F+, T+	NPS, throat swab; RT-PCR	22.6	20.5	20.2	18.8
Chillan, Chile (urban and rural, 2010 - 2013) (Fasce and colleagues)	II	NPA; IF	27.2			23.7
Osorno, Chile (urban and rural, 2010 - 2013) (Fasce and colleagues)	II	NPA; IF	25.4			22.3
Punta Arenas, Chile (urban and rural, 2010 - 2013) (Fasce and colleagues)	II	NPA; IF	60.8			56.4

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Santiago, Chile (urban, 2010 - 2013) (Fasce and colleagues)	II	NPA; IF	33.5			28.2
Valparaiso, Chile (urban mostly, 2010 - 2013) (Fasce and colleagues)	II	NPA; IF	20.1			16.0
China (urban and rural, Jan 2009 - Sep 2013) (Yu and colleagues)	II, XR, W+/-, F+/-	NPA, NPS; PCR	27.0	24.9	23.5	21.6
Beijing, China (urban, Jan 2011 - Dec 2012) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	73.8	53.8	42.2	33.1
Ulaanbaatar, Mongolia (urban, Sep 2011 - Oct 2012) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	21.4	21.5	24.7	22.8
Phnom Penh, Cambodia (urban, Oct 2010 - Jan 2013) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	21.8	22.6	22.8	21.7
Lucknow, India (urban and rural, Jun 2012 - Dec 2013) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	9.1	6.4	6.2	5.7
Antananarivo, Madagascar (urban and rural, Dec 2010 - Feb 2013) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	10.9	15.9	15.0	13.2
Asuncion, Paraguay (urban, Jul 2010 - May 2013) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	25.6	16.9	14.9	14.3
Bamako, Mali (urban, Jul 2011 - Nov 2012) (GABRIEL and colleagues)	II, T+, W-, XR	NPA, NPS; RT-PCR	43.6	36.4	30.9	26.5
Berlin, Germany (urban, 1st Apr 2010 - 31st Mar 2014) (Rath and colleagues)	II, F+, ICU+/-	NPS, NPA; RT-PCR	38.8	31.2	29.5	27.7
Tehran, Iran (urban, Mar 2008 - May 2009) (Malekshahi et al., 2010)	II	throat swab and wash; PCR	20.5	18.9	17.6	17.6
Iran (urban, Nov 2007 - Apr 2013) (Faghihloo et al., 2014)	II	throat swab; RT-PCR	24.6	24.7		
Amman, Jordan (urban, Mar 2010 - Mar 2013) (Khuri and colleagues)	II, T+, O2+/ICU/MV	nasal and throat swab; PCR	55.7	52.5		
Lwak, Kenya (rural, 2007 - 2011) (Montgomery and colleagues)	II, CWI+/DS+/O2+	NPS, OPS; RT-PCR	32.9	25.9	23.3	21.5
Rabat, Morocco (urban, Nov 2010 - Dec 2011) (Bassat and colleagues)	II, CWI+, T+	NPA; RT-PCR	29.3	22.3	19.9	17.3
Kathmandu, Nepal (urban, Jan 2006 - Jun 2008) (Basnet and	II, CWI+	NPA; RT-PCR	15.2	14.1	13.8	

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
colleagues)						
Karachi, Pakistan (urban, Aug 2009 - Jul 2012) (Ali and colleagues)	II	throat swab; RT-PCR	22.1	21.2	20.5	19.4
Basse, Gambia (rural, 3rd Nov 2011 - 2nd Nov 2013) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	25.5	21.9	20.3	19.3
Kilifi, Kenya (urban, 15th Aug 2011 - 15th Nov 2013) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	33.7	27.0	25.2	23.7
Bamako, Mali (urban, 3rd Jan 2012 - 14th Jan 2014) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	32.0	27.5	26.4	25.4
Nakhon Phanom and Sa Kaeo, Thailand (rural, 1st Jan 2012 - 31st Jan 2014) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	26.4	26.2	29.1	27.3
Lusaka, Zambia (urban, 10th Oct 2011 - 31st Oct 2013) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	20.4	19.6	18.9	18.7
Dhaka, Bangladesh (urban, 1st Jan 2012 - 31st Dec 2013) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	21.3	19.9	19.6	18.7
Matlab, Bangladesh (rural, 1st Jan 2012 - 31st Dec 2013) (PERCH and colleagues)	II, CWI+, DS+/-	NPS, OPS; PCR	53.6	39.0	35.8	33.3
Tacloban, Philippines (rural, May 2008 - Jul 2012) (Lupisan and colleagues)	II, CWI+, DS+/-	NPS, serum; PCR, virus isolation, culture, serology	21.6	18.9	17.9	17.0
Mpumalanga, South Africa (rural, Jan 2010 - Dec 2014) (Cohen and colleagues)	II	NPA; PCR	25.9	23.2	22.4	21.3
Nanjing, China (urban, Jan 2013 - Dec 2013) (Zhang et al., 2014a)	II	NPA; DFA	26.5		11.5	
Guangdong, China (urban, Jul 2010 - Jul 2012) (Xu et al., 2014)	II	NPA; RT-PCR	6.1		8.8	7.5
Yanting, China (urban, Jan 2011 - Dec 2012) (He, 2015)	II	NPA; RT-PCR	56.3		49.0	41.7
Guiyang, China (urban, Jan 2012 - Dec 2013) (Liang and Ge, 2014)	II	NPA; DFA	40.6		32.4	
Qingyuan, China (urban, Aug 2012 - Apr 2014) (Cao et al., 2015)	II	NPA; RT-PCR	7.9		7.4	
Guangzhou, China (urban, Jun 2012 - Jun 2013) (Chen et al., 2014a)	II	NPA; RT-PCR	7.2		7.2	6.8

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
Guangxi, China (urban, Jan 2013 - Dec 2013) (Zhang and Yu, 2015)	II	NPA; DFA	13.9		13.0	12.5
Huzhou, China (urban, Jan 2011 - Dec 2013) (Yao et al., 2015)	II	NPA; DFA	18.4		17.2	16.8
Foshan, China (urban, Feb 2012 - Jan 2014) (Zhang et al., 2014b)	II	NPA; DFA	16.6	15.4		13.0
Wuhan, China (urban, Jan 2011 - Dec 2012) (Hu and Wang, 2014)	II	NPA; DFA	20.2			
Wenzhou, China (urban, Jan 2013 - Dec 2013) (Ye et al., 2014)	II	NPA; RT-PCR	42.6			42.4
Wenzhou, China (urban, Dec 2012 - Nov 2013) (Xue et al., 2014)	II	NPA; DFA	20.0		16.3	13.0
Chongqing, China (urban, Feb 2013 - Apr 2014) (Wang et al., 2015)	II	NPA; DFA	11.7		10.4	9.3
Ningxia, China (urban, Jan 2010 - Dec 2013) (Ding and Tian, 2014)	II	NPA; DFA	91.8	82.5	76.8	
Lishui, China (urban, Jan 2010 - Mar 2013) (Zhang et al., 2014c)	II	NPA; DFA	24.3		21.7	
Nantong, China (urban, Jan 2012 - Mar 2013) (Sheng et al., 2014)	II	NPA; DFA	39.7		30.8	28.5
Quanzhou, China (urban, Jan 2012 - Jan 2013) (Lin et al., 2015)	II	NPS; DFA	37.7		31.0	25.6
Suzhou, China (urban, Jan 2009 - Dec 2013) (Yin, 2014)	II	NPS; DFA	18.9	17.6	17.1	15.8
Changsha, China (urban, Apr 2013 - Mar 2014) (Liu et al., 2015b)	II	NPA; DFA	50.7		46.4	45.0
Shenzhen, China (urban, Jul 2007 - Jun 2010) (He et al., 2014)	II, F+	NPA; RT-PCR	16.3	15.6		
Soma, Japan (urban, Feb 2008 - Aug 2009) (Takeyama et al., 2014)	II	NPA; RT-PCR			34.2	
Tokyo, Japan (urban, Apr 2007 - Mar 2012) (Hamada et al., 2014)	II	nasal swab; RT-PCR		30.8		
Baguio, Philippines (urban, Apr 2009 - Dec 2011) (Tallo et al., 2014)	III	NPS, OPS; RT-PCR		31.7		28.4
Riga, Latvia (urban, Jul 2009 - Jun 2012) (Balmaks et al., 2014)	II	NPA; RT-PCR		42.5		
Mirzapur, Bangladesh (both, Jun 2006 - Sep 2007)* (Farzin et	II	nasal wash; RT-PCR				

Location (reference)	Case definition (codes)	Specimen and diagnostic test	Proportion of RSV associated hospitalised ALRI (%)			
			0-11m	0-23m	0-35m	0-59m
al., 2015)						
Beirut, Lebanon (urban, Oct 2012 - Mar 2014) (Assaf-Casals et al., 2015)	II	NPW; IF		25.8		
England, UK (urban, Apr 2007 - Mar 2008) (Murray et al., 2014)	II	NA	28.0			
Tehran, Iran (urban, Jan 2012 - Dec 2012) (Pourakbari et al., 2014)	II	NPA; RT-PCR				17.2
Taiwan, China (urban, Jan 2009 - Mar 2011) (Chen et al., 2014b)	II	NPA; culture, IF		43.4		
Ouagadougou, Burkina Faso (urban, Jul 2010 - Jul 2011) (Ouedraogo et al., 2014)	II	NPA; DFA			14.0	

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. OPS=oropharyngeal swab. RT-PCR=reverse transcriptase polymerase chain reaction. IFA=indirect immunofluorescent antibody test. DFA=direct immunofluorescent antibody test. ELISA=enzyme-linked immunosorbent assay. IF=immunofluorescence. II=physician's assessment. III=SARI definition. F+/-=fever as part of case definition or not. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. C+/-=crepitation part of case definition or not. XR=X-ray confirmed (radiologically confirmed pneumonia). CWI+/-=chest wall indrawing part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation. NA=not applicable. #Studies reporting proportion rate in an aboriginal population from a high-income country. *Five studies reported data in neonates only.

Table 39: Meta-estimate of proportion data and number of new hospitalised cases

Region	0-11m		0-59m		0-59m*
	No. of studies	Prop (%)	No. of studies	Prop (%)	Hospitalised cases (*10^3)
Africa	9	24.7 (18.7-32.5)	12	21.3 (19.3-23.5)	945 (856-1043)
Americas	19	37.5 (32.6-43.3)	14	28.6 (24.6-33.2)	176 (152-204)
Eastern Mediterranean	7	28.9 (20.1-41.5)	8	23.9 (17.8-32.1)	429 (319-577)
Europe	10	42.3 (34.1-52.5)	9	28.3 (22.3-35.9)	529 (417-671)
South-East Asia	10	30.8 (21.8-43.7)	8	24.2 (19.0-30.6)	635 (500-805)
Western Pacific	79	26.9 (24.7-29.4)	45	22.1 (19.5-25.0)	109 (96-123)
Global#					2823 (2340-3423)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. *number of hospitalised cases in 0-59m is generated from meta-estimate of proportion in 0-59m and number of hospitalised ALRI cases in 0-59m. #Global estimate is sum of WHO regional estimates.

Table 40: Sensitivity analysis of proportion data to exclude studies with different case definitions

Region	Final estimate in 0-59m		Sensitivity analysis to exclude studies with different case definitions	
	No. of studies	Prop (%)	No. of studies	Prop (%)
Africa	12	24.7 (18.7-32.5)	9	21.2 (19.1-23.7)
Americas	14	37.5 (32.6-43.3)	13	29.4 (25.3-34.3)
Eastern Mediterranean	8	28.9 (20.1-41.5)	7	23.2 (15.7-34.3)
Europe	9	42.3 (34.1-52.5)	7	30.5 (23.0-40.4)
South-East Asia	8	30.8 (21.8-43.7)	6	28.1 (23.5-33.5)
Western Pacific	45	26.9 (24.7-29.4)	38	21.4 (18.7-24.6)

5.2.4 In-hospital CFR from RSV associated ALRI

There were 44 studies reporting in-hospital CFR from systematic review (one article provided two studies) (Avendano et al., 2003, Berner et al., 2001, Bockova et al., 2002, Byington et al., 2015, Carballal et al., 2001, Chan et al., 2007, Chan et al., 1999a, Chen et al., 2005, Chi et al., 2011, Deshpande and Northern, 2003, Do et al., 2011, Duppenthaler et al., 2003, El Kholy et al., 2013, Eriksson et al., 2002, Fjaerli et al., 2004, Forster et al., 2004, Fry et al., 2010, Garcia et al., 2010, Gil-Prieto et al., 2015, Greenberg et al., 2014, Hervas et al., 2012, Huo et al., 2013, Hussey et al., 2000, Khuri-Bulos et al., 2010, Loscertales et al., 2002, Miranda-Novales et al., 1999, Mori et al., 2011, Noyola et al., 2007, Numa, 2000, Pourakbari et al., 2014, Resch et al., 2002, Roglic et al., 2009, Rowlinson et al., 2013, Savic et al., 2011, Simon et al., 2007, Singleton et al., 2010, Tallo et al., 2014, Tsolia et al., 2003, Videla et al., 1998, Vieira et al., 2001, Weber et al., 2002, Whitehall et al., 2001, Paramore et al., 2004). An additional 55 unpublished studies were also included[U10, U12-13, U15-17, U19-37, U39-45, U47-48, U55-65, U67-76] (Table 41). In total, 99 studies contributed to the meta-analysis of in-hospital CFR due to RSV associated hospitalised ALRI (Table 42). Similar to studies reporting hospitalisation rate, all studies adopted passive hospital-based or clinic-based case ascertainment (inpatients only). 69 studies came from developing countries and 30 were from industrialised countries. There were 54 studies from urban areas, 25 studies from mixed study settings (urban and rural) while 20 studies were based on rural settings. The table containing data in narrower age bands was in Appendices – A19. Three published studies (Bockova et al., 2002, Singleton et al., 2010, Whitehall et al., 2001) and another three unpublished studies[U41, U43-44] reported in-hospital mortality among indigenous population in Australia (Townsville) and America (Alaska, Navajo and White Mountain Apache). They were excluded in the following estimate. There were 4 published studies (Avendano et al., 2003, El Kholy et al., 2013, Huo et al., 2013, Tallo et al., 2014) and 12 unpublished studies[U15, U19-20, U48, U55-62] using SARI, wheeze negative or fever positive as part of the case definitions and these studies were excluded in a sensitivity analysis. In order to increase the comparability of in-hospital mortality across age groups, studies which provided complete dataset for three exclusive non-overlapping age bands (0-5m, 6-11m and 12-59m) were included to carry out the meta-analysis. There were 43 studies in total which had CFR data in these three age groups. Among them, there were no studies carried out among aboriginal population and 10 studies used different definitions (as mentioned above). The number of RSV mortality in hospital in 2015 was based on the Monte Carlo simulation incorporating the meta-estimate of hospitalisation rate (Table 28) and the corresponding meta-estimate of in-hospital CFR (Table 43) from the same age group and region (as explained in Chapter 2 – Methods). The

global estimate was generated from regional samples while the estimate in children aged 0-59m was produced from samples in three exclusive age groups (0-5m, 6-11m, 12-59m). The results were shown in Table 44. Overall, around 60,000 (95% CI 48,000-75,000) children younger than 5 years were estimated to die from RSV associated ALRI in hospital in 2015, with 99% of these deaths occurring in developing countries (where 89% of the world's population aged younger than 5 years reside). For children in the first six months, the number of in-hospital deaths was around 27,000 (95% CI 21,000-36,000), for children aged 6-11m, the number was about 17,000 (95% CI 11,000-26,000), while for children aged 12-59m the number of deaths was 15,000 (95% CI 10,000-25,000).

When considering all studies reporting in-hospital CFR regardless whether or not they provided data for the full age range, there were 93 studies totally (exclusion of 6 studies in aboriginal population). Another round of meta-analysis was carried out in three age groups: 0-5m, 6-11m and 12-59m. The results were compared to the previous estimates from 43 studies which had data for the full age range (Table 45). Meta-estimates in several age groups/regions were different substantially (such as in 0-5m from high income countries). A different (higher or lower) result would be expected since studies with different study settings, population and methodologies were included in each age group analysis, which compromised the comparability of estimates across age groups. Thirteen studies reported in-hospital CFR in young children aged 0-59m from African countries with high HIV burden, and the total RSV mortality in hospital was estimated as 15,000 in these countries. Only two unpublished studies provided in-hospital CFR stratified by HIV status. In South Africa[U37], in-hospital CFR for RSV associated ALRI in young children (0-59m) with HIV positive was 6.5% compared to 0.6% in children without HIV. For infants, the CFR for RSV associated hospitalised ALRI was 7.5% if the infants were HIV positive, while it was 0.8% if infants did not have HIV. Similarly, in Zambia[U72], one of the PERCH studies, the RSV mortality in hospital was much higher in children with positive HIV than children with negative HIV (28.6% vs. 4.2%). These two studies showed consistently that in-hospital CFR of RSV associated hospitalised ALRI was much higher in HIV positive children compared to HIV negative children. However, the hospitalisation rate is not available stratified by HIV status, thus the number of cases or deaths is not available.

Similar to previous analyses, two sensitivity analyses to include studies reporting data in aboriginal population and exclude studies using different case definitions were performed in infants and the results were compared (Table 46). In general, the results were similar. The meta-estimate after excluding those studies with different definitions of cases was slightly lower than the previous estimate where these studies were included. Fifteen studies didn't

include neonates and therefore reported data in children aged 1-59m rather than 0-59m. A meta-analysis was run after excluding these 15 studies. The meta-estimate was 1.26% (95% CI 0.77-2.09) in developing countries compared to 1.47% (95% CI 0.94-2.30) where these studies were included. For those 43 studies which provided data for full age range, there were 11 studies with less than 50 RSV positive cases. These studies were excluded in another sensitivity analysis. The results were shown in Table 47. After excluding studies with small sample size, meta-estimate of in-hospital CFR was similar to previous estimate except in the age group of 6-11m from low income region. This is because there were two studies[U28, U61] with small sample sizes reporting high in-hospital CFR and they were excluded in the sensitivity analysis. The in-hospital mortality data were generated from the estimates of developing countries and industrialised countries; thus this didn't affect the global mortality estimate substantially.

The case definitions applied in studies reporting in-hospital CFR were compared to those used in studies providing hospitalisation rate data (Table 48). The percentage of each definition as well as each clinical feature in these two groups of studies were measured and summarised. Most studies used physician's assessment as the case definition (around 97%). X-ray confirmation, tachypnea, chest wall indrawing, hypoxemia and WHO IMCI danger signs were also widely used to define ALRI (around 10%). In general, the percentage of each definition code was similar between those two groups of studies. This made combination of data of hospitalisation rate and in-hospital CFR in order to generate in-hospital deaths reasonable.

Table 41: List of 55 unpublished studies reporting in-hospital case fatality ratio

Study number	Location (reference)	Study period
U10	Paarl, South Africa (Zar and colleagues)	Mar 2012 – Dec 2014
U12	CEMIC, Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 – 31st Dec 2010
U13	Buenos Aires, Argentina (Polack and colleagues)	2011 – 2013
U15	Belo Horizonte, Brazil (Oliveira and colleagues)	2011 – 2013
U16	Concepcion, Chile (Fasce and colleagues)	Jan 2012 – Dec 2013
U17	Iquique, Chile (Fasce and colleagues)	Jan 2012 – Dec 2013
U19	Santa Ana, El Salvador (Clara and colleagues)	2008 – 2013
U20	Western Gambia (Howie and colleagues)	Jul 2007 – Jun 2008
U21	Santa Rosa, Guatemala (McCracken and colleagues)	2008 – 2013
U22	Quetzaltenango, Guatemala (McCracken and colleagues)	2009 – 2013
U23	Ballabhgarh, India (Broor and colleagues)	2010 – 2012
U24	Pune, India (Chadha and colleagues)	May 2009 – Apr 2013
U25	Lombok, Indonesia (Gessner and colleagues)	2000 – 2002
U26	Kilifi hospital study, Kenya (Nokes and colleagues)	Jan 2002 – Dec 2010
U27	Bondo district, Kenya (Feikin and colleagues)	Jan 2007 – Jun 2009
U28	Manhiça, Mozambique (Bassat and colleagues)	20th Sep 2006 – 19th Sep 2007
U29	Manhiça, Mozambique (Bassat and colleagues)	1st Jan 2011 – 30th Jun 2014
U30	Utrecht, Netherlands (Bont and colleagues)	2001 – 2010
U31	41 sites in Netherlands (Bont and colleagues)	2008 – 2013
U32	David City, Panama (Jara and colleagues)	Jan 2011 – Dec 2013
U33	Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	5th Jul 2000 – 31st Dec 2004
U34	Gauteng province, South Africa (Cohen and colleagues)	2009 – 2012
U35	KwaZulu-Natal province, South Africa (Cohen and colleagues)	2010 – 2014
U36	Klerksdorp site, South Africa (Cohen and colleagues)	Jan 2011 – Dec 2014
U37	Soweto, South Africa (Madhi and colleagues)	Mar 1998 – Oct 2005
U39	Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	Jan 2008 – Dec 2011
U40	Tone District, Togo (Gessner and colleagues)	Aug 2011 – Dec 2013
U41	Alaska, USA (Singleton and colleagues)	Jul 2001 – Jun 2004
U42	Colorado, USA (Simoes and colleagues)	Jan 2008 – Jun 2013
U43	Navajo and WMA, USA – MEDI (O'Brien and	Oct 2004 – Dec 2010

Study number	Location (reference)	Study period
	colleagues)	
U44	Navajo and WMA, USA – EPI (O'Brien and colleagues)	Oct 1997 – Mar 2000
U45	Nha Trang, Vietnam (Yoshida and colleagues)	Feb 2007 – Dec 2012
U47	Buenos Aires, Argentina (Gentile and colleagues)	2001 – 2013
U48	Takeo ad Kampong Cham, Cambodia (Goyet and colleagues)	Apr 2007 – Feb 2010
U55	Beijing, China (GABRIEL and colleagues)	Jan 2011 – Dec 2012
U56	Ulaanbaatar, Mongolia (GABRIEL and colleagues)	Sep 2011 – Oct 2012
U57	Phnom Penh, Cambodia (GABRIEL and colleagues)	Oct 2010 – Jan 2013
U58	Lucknow, India (GABRIEL and colleagues)	Jun 2012 – Dec 2013
U59	Antananarivo, Madagascar (GABRIEL and colleagues)	Dec 2010 – Feb 2013
U60	Asuncion, Paraguay (GABRIEL and colleagues)	Jul 2010 – May 2013
U61	Bamako, Mali (GABRIEL and colleagues)	Jul 2011 – Nov 2012
U62	Berlin, Germany (Rath and colleagues)	1st Apr 2010 – 31st Mar 2014
U63	Amman, Jordan (Khuri and colleagues)	Mar 2010 – Mar 2013
U64	Lwak, Kenya (Montgomery and colleagues)	2007 – 2011
U65	Rabat, Morocco (Bassat and colleagues)	Nov 2010 – Dec 2011
U67	Karachi, Pakistan (Ali and colleagues)	Aug 2009 – Jul 2012
U68	Basse Santa Su, Gambia (PERCH and colleagues)	3rd Nov 2011 – 2nd Nov 2013
U69	Kilifi, Kenya (PERCH and colleagues)	15th Aug 2011 – 15th Nov 2013
U70	Bamako, Mali (PERCH and colleagues)	3rd Jan 2012 – 14th Jan 2014
U71	Nakhon Phanom and Sa Kaeo, Thailand (PERCH and colleagues)	1st Jan 2012 – 31st Jan 2014
U72	Lusaka, Zambia (PERCH and colleagues)	10th Oct 2011 – 31st Oct 2013
U73	Dhaka, Bangladesh (PERCH and colleagues)	1st Jan 2012 – 31st Dec 2013
U74	Matlab, Bangladesh (PERCH and colleagues)	1st Jan 2012 – 31st Dec 2013
U75	Tacloban City, Philippines (Lupisan and colleagues)	May 2008 – Jul 2012
U76	Mpumalanga, South Africa (Cohen and colleagues)	Jan 2010 – Dec 2014

Table 42: List of 99 studies providing in-hospital CFR for RSV associated hospitalised ALRI

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
Hong Kong, China (urban, 1st Jan 2004 – 31st Dec 2004) (Chan et al., 2007)	II	NPA; DFA					0.0	
Taiwan, China (urban, Jan 2001 – Dec 2003) (Chen et al., 2005)	II	NPA; virus culture, IF						0.0
Ho Chi Minh, Vietnam (urban, Nov 2004 – Jan 2008) (Do et al., 2011)	II, T+, CWI+/-, ICU+/-	nasal swab, throat swab, NPA; RT-PCR						0.0
Palma, Spain (urban, Jan 1995 – Dec 2006) (Hervas et al., 2012)	II	NPA, NPW; ELISA, culture				0.1		
San Luis Potosi, Mexico (urban, 1st May 2003 – 30th Apr 2005) (Noyola et al., 2007)	II	NPW; DFA					0.0	
Alaska, USA (rural, 4th Oct 2005 – 30th Sep 2007)# (Singleton et al., 2010)	II	NPS, NPW; RT-PCR					0.0	
Dallas, Texas, USA (urban, Jan 2002 – Dec 2007) (Garcia et al., 2010)	II	NPA; IF, DFA, virus culture				0.1		
Jingzhou, China (urban, Jan – Dec 2011) (Huo et al., 2013)	III, W+/-, T+/-, XR	NPS, OPS; RT-PCR						0.0
Taiwan, China (urban, 2004 – 2007) (Chi et al., 2011)	II	NA						0.1
Sa Kaeo and Nakhom Phanom, Thailand (rural, 1st Jan 2004 – 31st Dec 2007) (Fry et al., 2010)	II, XR	NPS, serum; RT-PCR, IFA						0.1
Damanhour, Egypt (urban and rural, Jun 2009 – Jun 2012) (Rowlinson et al., 2013)	II	NPS, OPS; RT-PCR						0.0
Lørenskog, Norway (periurban, Feb 1993 – Jan 2000) (Fjaerli et al., 2004)	II	NPA; ELISA				0.2		
272 institutions, Japan (urban, Aug 2006 – Jul 2008) (Mori et al., 2011)	II	NA					1.4	
Cairo, Egypt (urban, Feb 2010 – May 2011) (El Kholy et al., 2013)	III	NPS and OPS; RT-PCR			5.0			
Amman, Jordan (urban, 18th Jan – 29th Mar 2007) (Khuri-	II, F+/-	nasal and throat						0.9

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
Bulos et al., 2010)		swab; RT-PCR						
Croatia (urban, Sep 2003 – Oct 2009) (Roglic et al., 2009)	II	NPA; DFA						0.2
Beer-Sheva, Israel (urban, Nov to Mar, 2004 – 2011) (Greenberg et al., 2014)	II, CWI+, XR	NPW; DFA and culture				0.2		
Belgrade, Serbia (urban, Nov 2008 – Mar 2009) (Savic et al., 2011)	II	NPA; EIA			2.2			
Athens, Greece (urban, Feb 1997 – Jun 2000) (Tsolia et al., 2003)	II, XR, W+/-, T+/-	NPW; DFA			0.7			
Stockholm, Sweden (urban, 1987 – 1998) (Eriksson et al., 2002)	II	NPW; IFA			0.3			
Multicentric, Germany (urban, Nov 1999 – Oct 2001) (Forster et al., 2004)	II	NPS; PCR					0.7	
Shropshire, United Kingdom (urban, Apr 1996 – Mar 1999) (Deshpande and Northern, 2003)	II	NA; IF				0.2		
Berne, Switzerland (urban, Jul 1997 – Jun 2001) (Duppenthaler et al., 2003)	II	NPS; DFA						0.2
Freiburg, Germany (urban and rural, Apr 1997 – Mar 1999) (Berner et al., 2001)	II	NPS; IF						0.7
Germany (urban, 1999 – 2005) (Simon et al., 2007)	II	NPA; ELISA, culture, PCR			0.5			
Manhica, Mozambique (rural, Oct 1998 – May 2000)§ (Loscertales et al., 2002)	II, CWI+/-, W+/-, T+/-	NPA; ELISA						3.4
Banjul, Fajara and Sibanor, Gambia (urban and rural, Oct 1993 – Dec 1996) (Weber et al., 2002)	II	NPA; IF				2.0		
Hong Kong, China (urban, Jan 1993 – Dec 1997) (Chan et al., 1999a)	II	NPA, throat swab; DFA, virus isolation						0.1
Sydney, Australia (urban, May 1997 – Oct 1999) (Numa, 2000)	II	NA				0.3		
Townsville, Australia (urban and rural, Jan 1997 – Oct	II	NA; IF, culture			1.1			

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
1999)# (Whitehall et al., 2001)								
Navajo and WMA, USA (rural, Oct 1997 – Mar 2000)# (Bockova et al., 2002)	II	NPA; ELISA				0.1		
Buenos Aires, Argentina (urban, Apr 1993 – Dec 1994) (Carballal et al., 2001)	II	NPA; DFA						1.3
Santiago, Chile (urban, Jan 1989 – Dec 2000) (Avendano et al., 2003)	II, W-	NPA; IFA				0.1		
Graz, Austria (urban, Nov 1999 – Oct 2000) (Resch et al., 2002)	II	NPA; ELISA			0.0			
Cape Town, South Africa (urban, Jun 1995 – Aug 1996) (Hussey et al., 2000)	II, W+/-	NPA; ELISA				2.1		
Buenos Aires, Argentina (urban, May 1991 – Dec 1992) (Videla et al., 1998)	II, CWI+/-, XR, W+/-, T+/-	NPA; IFA				0.0		
Sao Paulo, Brazil (urban and rural, Mar 1995 – Aug 1996) (Vieira et al., 2001)	II	NPA, NPS; IFA						0.0
Tlaxcala, Mexico (urban and rural, Oct 1994 – Jun 1995) (Miranda-Novales et al., 1999)	II	NPS; IFA						0.0
Alaska, USA (rural, Jul 2001 – Jun 2004) (Singleton and colleagues)#	II	NPS, NPW; RT-PCR					0.4	
Buenos Aires, Argentina (urban, 2001 – 2013) (Gentile and colleagues)*	II, MV+/-	NPA; IFA	1.9	1.7	1.8	1.8	1.8	1.8
Takeo ad Kampong Cham, Cambodia (urban, Apr 2007 – Feb 2010) (Goyet and colleagues)*	II, F+, T+	NPS, throat swab; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Beijing, China (urban, Jan 2011 – Dec 2012) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Ulaanbaatar, Mongolia (urban, Sep 2011 – Oct 2012) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Phnom Penh, Cambodia (urban, Oct 2010 – Jan 2013) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Lucknow, India (urban and rural, Jun 2012 – Dec 2013) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
Antananarivo, Madagascar (urban and rural, Dec 2010 – Feb 2013) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Asuncion, Paraguay (urban, Jul 2010 – May 2013) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Bamako, Mali (urban, Jul 2011 – Nov 2012) (GABRIEL and colleagues)*	II, T+, W-, XR	NPA, NPS; RT-PCR	0.0	14.3	4.2	3.6	3.3	3.2
Berlin, Germany (urban, 1st Apr 2010 – 31st Mar 2014) (Rath and colleagues)*	II, F+, ICU+/-	NPS, NPA; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Amman, Jordan (urban, Mar 2010 – Mar 2013) (Khuri and colleagues)	II, T+, O2+/ICU/MV	nasal and throat swab; PCR	0.4	0.4	0.4	0.4		
Lwak, Kenya (rural, 2007 – 2011) (Montgomery and colleagues)*§	II, CWI+/DS+/O2+	NPS, OPS; RT-PCR	8.3	0.0	4.2	3.8	4.6	4.0
Rabat, Morocco (urban, Nov 2010 – Dec 2011) (Bassat and colleagues)*	II, CWI+, T+	NPA; RT-PCR	4.5	6.1	5.2	3.8	3.2	2.9
Karachi, Pakistan (urban, Aug 2009 – Jul 2012) (Ali and colleagues)*	II	throat swab; RT-PCR	1.1	0.0	0.7	0.5	0.5	0.9
Basse Santa Su, Gambia (rural, 3rd Nov 2011 – 2nd Nov 2013) (PERCH and colleagues)*	II, CWI+, DS+/-	NPS, OPS; PCR	0.0	0.0	0.0	0.0	0.0	0.0
Kilifi, Kenya (urban, 15th Aug 2011 – 15th Nov 2013) (PERCH and colleagues)*§	II, CWI+, DS+/-	NPS, OPS; PCR	3.4	3.7	3.5	3.6	3.5	4.0
Bamako, Mali (urban, 3rd Jan 2012 – 14th Jan 2014) (PERCH and colleagues)*	II, CWI+, DS+/-	NPS, OPS; PCR	1.7	5.6	2.2	2.7	2.6	2.6
Nakhon Phanom and Sa Kaeo, Thailand (rural, 1st Jan 2012 – 31st Jan 2014) (PERCH and colleagues)*	II, CWI+, DS+/-	NPS, OPS; PCR	0.0	0.0	0.0	0.0	0.0	0.0
Lusaka, Zambia (urban, 10th Oct 2011 – 31st Oct 2013) (PERCH and colleagues)*§	II, CWI+, DS+/-	NPS, OPS; PCR	4.8	8.0	5.7	6.1	5.9	5.8
Dhaka, Bangladesh (urban, 1st Jan 2012 – 31st Dec 2013) (PERCH and colleagues)*	II, CWI+, DS+/-	NPS, OPS; PCR	0.0	0.0	0.0	0.0	0.0	0.0
Matlab, Bangladesh (rural, 1st Jan 2012 – 31st Dec 2013) (PERCH and colleagues)*	II, CWI+, DS+/-	NPS, OPS; PCR	0.0	0.0	0.0	0.0	0.0	0.0
Tacloban City, Philippines (rural, May 2008 – Jul 2012)	II, CWI+, DS+/-	NPS, serum;	2.5	2.0	2.3	1.8	1.7	1.7

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
(Lupisan and colleagues)*		PCR, virus isolation, culture, serology						
Mpumalanga, South Africa (rural, Jan 2010 – Dec 2014) (Cohen and colleagues)*§	II	NPA; PCR	2.4	4.6	3.2	2.6	2.4	2.2
CEMIC, Buenos Aires, Argentina (urban, 1st Jun 2008 – 31st Dec 2010) (Echavarria and colleagues)*	II, ICU+/-, MV+/-	NPA; IFA	0.0	0.0	0.0	0.0	0.0	0.0
Buenos Aires, Argentina (urban and rural, 2011 – 2013) (Polack and colleagues)	II, O2+, W+, F+/-, ICU+/-, MV+/-	NPA; PCR	1.4	1.1	1.3	1.1		
Belo Horizonte, Brazil (urban, 2011 – 2013) (Oliveira and colleagues)*	II, F+, O2+/-, ICU+/-	nasal swab; RT-PCR	1.8	2.0	1.9	1.6	1.4	1.3
Concepcion, Chile (urban and rural, Jan 2012 – Dec 2013) (Fasce and colleagues)*	II, F+/-, ICU+/-	NPA; IF	0.0	0.0	0.0	0.0	0.0	0.5
Iquique, Chile (urban and rural, Jan 2012 – Dec 2013) (Fasce and colleagues)*	II, F+/-, ICU+/-	NPA; IF	0.0	3.3	1.0	0.9	0.9	0.8
Santa Ana, El Salvador (urban, 2008 – 2013) (Clara and colleagues)	III, T+/-, XR	NPS; IFA			23.3	17.6		15.9
Western Gambia (urban and rural, Jul 2007 – Jun 2008) (Howie and colleagues)	II, CWI+/-, W-, O2+/-	NPA; PCR		0.0	0.0	0.0	0.0	0.0
Santa Rosa, Guatemala (urban and rural, 2008 – 2013) (McCracken and colleagues)*	II, CWI+/-, DS+/-	NPS, OPS; RT-PCR	3.7	1.7	3.1	2.8	2.6	3.0
Quetzaltenango, Guatemala (urban and rural, 2009 – 2013) (McCracken and colleagues)*	II, CWI+/-, DS+/-	NPS, OPS; RT-PCR	0.9	1.4	1.0	1.4	1.3	1.3
Ballabhgarh, India (rural, 2010 – 2012) (Broor and colleagues)*	II, DS+/-	NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Pune, India (rural, May 2009 – Apr 2013) (Chadha and colleagues)*	II	NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Lombok, Indonesia (urban and rural, 2000 – 2002) (Gessner and colleagues)	II, CWI+	nasal wash; ELISA	3.3	0.7	2.1	1.8		
Kilifi hospital study, Kenya (urban and rural, Jan 2002 –	II, CWI+,	OPS, NPS, nasal	2.1	2.2	2.1	1.9	2.2	2.2

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
Dec 2010) (Nokes and colleagues)*§	O2+/DS+	wash; DFA						
Bondo district, Kenya (rural, Jan 2007 – Jun 2009) (Feikin and colleagues)*§	II, O2+/DS+	NPS, OPS; RT-PCR	0.0	7.7	2.6	1.8	1.6	1.5
Manhiça, Mozambique (rural, 20th Sep 2006 – 19th Sep 2007) (Bassat and colleagues)*§	II, T+	NPA; RT-PCR	0.0	10.0	2.9	2.3	2.2	2.0
Manhiça, Mozambique (rural, 1st Jan 2011 – 30th Jun 2014) (Bassat and colleagues)*§	II, T+, O2+/-	NPA; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Utrecht, Netherlands (urban, 2001 – 2010) (Bont and colleagues)	II	NPS, NPW; PCR, IF	0.0	0.0	0.0			
41 sites in Netherlands (urban and rural, 2008 – 2013) (Bont and colleagues)	II, ICU+/-	NPS, NPW; PCR, IF	0.0	0.0	0.0			
David City, Panama (urban, Jan 2011 – Dec 2013) (Jara and colleagues)*	II	NPS, OPS; IFA, RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Tagbilaran and 6 rural sites, Philippines (urban and rural, 5th Jul 2000 – 31st Dec 2004) (Lucero and colleagues)	II, CWI+, DS+/-	NPA, nasal swab; culture, PCR	0.8	0.8	0.8	0.6		
Gauteng province, South Africa (urban, 2009 – 2012) (Cohen and colleagues)*§	II	NPA; PCR	0.9	0.0	0.6	0.5	0.5	0.5
KwaZulu-Natal province, South Africa (periurban, 2010 – 2014) (Cohen and colleagues)*§	II	NPA; PCR	0.0	0.0	0.0	0.0	0.0	0.0
Klerksdorp site, South Africa (periurban, Jan 2011 – Dec 2014) (Cohen and colleagues)*§	II	NPA; PCR	2.6	0.0	2.0	1.6	1.5	1.5
Soweto, South Africa (urban, Mar 1998 – Oct 2005) (Madhi and colleagues)*§	II, CWI+, O2+/-	NPA; IF	2.4	1.0	2.0	1.7	1.7	1.6
Paarl, South Africa (periurban, Mar 2012 – Dec 2014) (Zar and colleagues)	II, CWI+, T+, DS+/-	NPS; RT-PCR	0.0	0.0	0.0	0.0		
Sa Kaeo and Nakhon Phanom, Thailand (rural, Jan 2008 – Dec 2011) (Thamthitiwat and colleagues)*	II, F+/-, T+/-, CWI+, O2+/-	NPS; PCR	0.0	0.0	0.0	0.0	0.0	0.0
Tone District, Togo (rural, Aug 2011 – Dec 2013) (Gessner and colleagues)*	II, CWI+	nasal wash; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Colorado, USA (urban and rural, Jan 2008 – Jun 2013) (Simoes and colleagues)*	II	nasal wash; PCR	0.0	0.1	0.0	0.0	0.1	0.1

Location (reference)	Case definition (coding)	Specimen and diagnostic test	In-hospital CFR of RSV associated hospitalised ALRI (%)					
			0-5m	6-11m	0-11m	0-23m	0-35m	0-59m
Navajo and WMA, USA – MEDI (rural, Oct 2004 – Dec 2010) (O'Brien and colleagues)#	II, O2+/-	NPS; RT-PCR	0.0	0.0	0.0			
Navajo and WMA, USA – EPI (rural, Oct 1997 – Mar 2000) (O'Brien and colleagues)#	II, O2+/-	NPA; EIA	0.3	0.0	0.2	0.1		
Nha Trang, Vietnam (urban and rural, Feb 2007 – Dec 2012) (Yoshida and colleagues)*	II, CWI+/DS+	NPS; RT-PCR	0.0	0.0	0.0	0.0	0.0	0.0
Spain (urban, Jan 1997 – Dec 2011) (Gil-Prieto et al., 2015)	II				0.1	0.1	0.1	0.1
Baguio, Philippines (urban, Apr 2009 – Dec 2011) (Tallo et al., 2014)	III	NPS, OPS; RT-PCR				0.5		0.4
Tehran, Iran (urban, Jan 2012 – Dec 2012) (Pourakbari et al., 2014)	II	NPA; RT-PCR						0.0
USA (urban, 2000, 2003, 2006 and 2009) (Byington et al., 2015)	II	NA				0.1		
USA (urban, 2000 – 2011) (Byington et al., 2015)	II	NA				0.3		
USA (urban, 2000) (Paramore et al., 2004)	II	NA						0.1

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. CFR=case fatality ratio. NPA=nasopharyngeal aspirate. NPS=nasopharyngeal swab. NPW=nasopharyngeal wash. OPS=oropharyngeal swab. RT-PCR=reverse transcriptase polymerase chain reaction. IFA=indirect immunofluorescent antibody test. DFA=direct immunofluorescent antibody test. ELISA=enzyme-linked immunosorbent assay. IF=immunofluorescence. II=physician's assessment. III=SARI definition. F+/-=fever as part of case definition or not. T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. C+/-=crepitation part of case definition or not. XR=X-ray confirmed (radiologically confirmed pneumonia). CWI+/-=chest wall indrawing part of case definition or not. DS+/-=danger signs part of case definition or not. O2+/-=hypoxemia part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation. NA=not applicable. *Studies providing in-hospital CFR for full age range (0-5m, 6-11m and 12-59m). #Studies reporting in-hospital CFR in an aboriginal population from a high-income country. §Studies sites in sub-Saharan Africa which had high-HIV burden and reported data in 0-59m.

Table 43: Meta-estimate of in-hospital CFR of RSV associated ALRI from 43 studies reporting full data in finer age bands

Region	No. of studies	Meta-estimate of in-hospital CFR (%)		
		0-5m	6-11m	12-59m
Low income	9	1.7 (0.4-6.8)	9.3 (3.0-28.7)	4.7 (0.7-33.7)
Lower middle income	16	2.7 (2.0-3.6)	2.8 (1.8-4.4)	2.7 (1.7-4.3)
Upper middle income	12	1.8 (1.2-2.6)	2.4 (1.1-5.4)	0.5 (0.1-3.5)
High income	6	0.2 (0.0-12.8)	0.9 (0.2-4.0)	0.7 (0.1-5.2)
Developing	41	2.2 (1.8-2.7)	2.4 (1.9-3.2)	2.2 (1.6-3.0)
Industrialised	2	0.0 (0.0-0.1)	0.1 (0.0-0.4)	0.1 (0.0-0.3)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. CFR=case fatality ratio.

Table 44: Number of in-hospital deaths of RSV associated ALRI from 43 studies reporting full data in finer age bands

Region	No. of studies	In-hospital mortality			
		0-5m	6-11m	12-59m	0-59m*
Low income	9	1335 (234-7917)	3376 (413-26619)	1418 (129-16085)	8169 (2225-36928)
Lower middle income	16	19991 (13499-29474)	10260 (4752-21643)	12268 (6515-23132)	43638 (31446-60431)
Upper middle income	12	7170 (4227-12259)	7962 (2802-22140)	1487 (186-11709)	17928 (10265-34485)
High income	6	440 (1-228220)	887 (172-4568)	666 (81-5646)	3280 (673-231067)
Developing	41	27141 (20679-35494)	16460 (10443-25814)	15265 (9456-24967)	59578 (47750-74325)
Industrialised	2	38 (1-2029)	38 (6-277)	102 (33-322)	237 (78-2202)
Global#	43	27271 (20744-36178)	16513 (10533-26094)	15445 (9547-24902)	59581 (47959-74542)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. CFR=case fatality ratio. *number of in-hospital deaths in 0-59m is sum of estimates from exclusive finer age bands (0-5m, 6-11m and 12-59m) based on Monte Carlo Simulation. #Global estimate is sum of regional estimates in developing countries and industrialised countries.

Table 45: Comparison of meta-estimates of in-hospital CFR from 43 studies and all studies

Region	0-5m				6-11m				12-59m			
	43 studies		All studies*		43 studies		All studies*		43 studies		All studies*	
	No.	CFR (%)	No.	CFR (%)	No.	CFR (%)	No.	CFR (%)	No.	CFR (%)	No.	CFR (%)
Low income	9	1.7 (0.4-6.8)	9	1.7 (0.4-6.8)	9	9.3 (3.0-28.7)	10	9.3 (3.0-28.7)	9	4.7 (0.7-33.7)	10	4.7 (0.7-33.6)
Lower middle income	16	2.7 (2.0-3.6)	18	2.8 (2.1-3.6)	16	2.8 (1.8-4.4)	18	2.3 (1.5-3.5)	16	2.7 (1.7-4.3)	16	2.7 (1.7-4.3)
Upper middle income	12	1.8 (1.2-2.6)	14	1.5 (1.0-2.1)	12	2.4 (1.1-5.4)	14	1.9 (0.9-3.9)	12	0.5 (0.1-3.5)	12	0.5 (0.1-3.5)
High income	6	0.2 (0.0-12.8)	9	0.8 (0.3-2.1)	6	0.9 (0.2-4.0)	9	1.1 (0.5-2.4)	6	0.7 (0.1-5.2)	7	0.4 (0.1-2.5)
Developing	41	2.2 (1.8-2.7)	46	2.0 (1.7-2.4)	41	2.4 (1.9-3.2)	47	2.0 (1.6-2.6)	41	2.2 (1.6-3.0)	42	2.2 (1.6-3.0)
Industrialised	2	0.0 (0.0-0.1)	4	0.0 (0.0-0.1)	2	0.1 (0.0-0.4)	4	0.1 (0.0-0.4)	2	0.1 (0.0-0.3)	3	0.1 (0.1-0.1)

CFR=case fatality ratio. No.=number of studies. *all studies irrespective of whether or not they reported data for full age range (0-5m, 6-11m and 12-59m).

Table 46: Sensitivity analyses of in-hospital CFR to include studies with aboriginal population and exclude studies with different case definitions respectively

Region	Meta estimate in 0-11m*		Sensitivity analysis to include studies with aboriginal population		Sensitivity analysis to exclude studies with different case definitions	
	No. of studies	CFR (%)	No. of studies	CFR (%)	No. of studies	CFR (%)
Low income	10	2.7 (1.1-6.4)	10	2.7 (1.1-6.4)	5	2.4 (0.9-6.4)
Lower middle income	20	3.1 (1.7-5.7)	20	3.1 (1.7-5.7)	17	2.4 (1.9-3.0)
Upper middle income	15	1.4 (0.9-2.2)	15	1.4 (0.9-2.2)	11	1.4 (0.8-2.4)
High income	14	0.5 (0.2-1.3)	17	0.4 (0.2-1.2)	13	0.5 (0.2-1.3)
Developing	49	2.3 (1.5-3.4)	49	2.3 (1.5-3.4)	37	2.3 (1.5-3.4)
Industrialised	10	0.3 (0.1-0.7)	13	0.3 (0.2-0.7)	9	0.3 (0.2-0.7)

CFR=case fatality ratio. *all studies irrespective of whether or not they reported data for full age range (0-5m, 6-11m and 12-59m).

Table 47: Sensitivity analysis of in-hospital CFR to exclude studies with small sample size

Region	In-hospital CFR based on 43 studies				Sensitivity analysis excluding studies with small sample size			
	No.	0-5m	6-11m	12-59m	No.	0-5m	6-11m	12-59m
Low income	9	1.71 (0.43-6.82)	9.25 (2.98-28.68)	4.74 (0.67-33.66)	4	1.71 (0.43-6.83)	5.55 (0.78-39.37)	4.75 (0.67-33.75)
Lower middle income	16	2.71 (2.02-3.63)	2.81 (1.79-4.41)	2.73 (1.74-4.28)	14	2.71 (2.02-3.63)	2.81 (1.79-4.41)	2.73 (1.74-4.28)
Upper middle income	12	1.76 (1.20-2.59)	2.43 (1.09-5.41)	0.49 (0.07-3.48)	9	1.76 (1.20-2.59)	2.43 (1.09-5.41)	0.49 (0.07-3.48)
High income	6	0.21 (0.00-12.79)	0.87 (0.19-4.03)	0.66 (0.08-5.18)	5	0.21 (0.00-14.33)	0.85 (0.17-4.27)	0.66 (0.08-5.40)
Developing	41	2.18 (1.80-2.65)	2.44 (1.85-3.23)	2.20 (1.60-3.02)	30	2.18 (1.80-2.65)	2.28 (1.71-3.04)	2.20 (1.60-3.02)
Industrialised	2	0.02 (0.00-0.13)	0.05 (0.01-0.38)	0.09 (0.03-0.25)	2	0.02 (0.00-0.13)	0.05 (0.01-0.38)	0.09 (0.03-0.25)

CFR=case fatality ratio.

Table 48: Comparison of case definitions applied in studies reporting hospitalisation rate and in-hospital CFR

Case definition codes	Percentage among 73 studies reporting hospitalisation rate (%)	Percentage among 99 studies reporting in-hospital CFR (%)
II	97.18	96.94
III	5.63	4.08
F+	2.82	3.06
F+/-	8.45	5.10
XR	7.04	13.27
T+	8.45	14.29
T+/-	5.63	6.12
W+	1.41	1.02
W+/-	4.23	5.10
W-	1.41	9.18
CWI+	12.68	17.35
CWI+/-	9.86	8.16
O2+	1.41	1.02
O2+/-	15.49	11.22
DS+/-	12.68	17.35
ICU+/-	8.45	9.18
MV+/-	4.23	4.08

CFR=case fatality ratio. II=physician's assessment. III=SARI definition. F+/-=fever as part of case definition or not. XR=X-ray confirmed (radiologically confirmed pneumonia). T+/-=tachypnea part of case definition or not. W+/-=wheeze part of case definition or not. CWI+/-=chest wall indrawing part of case definition or not. O2+/-=hypoxemia part of case definition or not. DS+/-=danger signs part of case definition or not. ICU=intensive care unit. MV=mechanical ventilation.

5.2.5 Burden of RSV associated ALRI in neonates (0-27 days)

Overall 37 studies reported relevant data for RSV associated ALRI in neonates aged 0-27 days, including incidence rate in community, hospitalisation rate and in-hospital mortality. One was a published article (Vicente et al., 2003) and the other 36 unpublished studies[U2-3, U10, U13, U15-17, U21-29, U31-32, U34-36, U38-39, U41-44, U47, U62-65, U67, U75-76] (two studies from U10) were provided by RSV GEN. The unavailability of neonatal data from most published articles is probably due to insufficient surveillance in narrower age bands (as excluded in the selection criteria) or the difficulty of defining RSV cases within this special age group (sepsis like episodes). There were 3 studies providing community-based incidence rate of RSV associated ALRI for neonates and the meta-estimate was around 40.0 (2.5-635.7) per 1000 children per year in developing countries (or low and middle income countries). The confidence interval of this estimate is wide and it is only based on 3 studies (with small sample size). More studies from community based studies are needed to verify the high incidence of RSV infection in neonates. Fifteen studies reported hospitalisation rate of RSV associated ALRI in neonates from hospital-based studies. One was from industrialised countries (another 3 were from aboriginal population and thus excluded in analysis) and the remaining 11 studies were from developing countries. Meta-estimate was 15.9 (95% CI 8.8-28.9) per 1000 children per year in developing countries, 46.4 (95% CI 3.9-549.5) in upper middle income countries, 9.3 (95% CI 2.5-35.3) in lower middle income countries. There were 29 studies (another 2 studies with data in aboriginal population were excluded) reporting in-hospital CFR for neonates. 26 of them were in developing countries and 3 of them were from industrialised countries. It was estimated that 5.3% (95% CI 2.8-9.8) of RSV associated hospitalised ALRI cases died in hospitals from developing countries, 1.0% (95% CI 0.1-7.2) in upper middle income countries, 6.3% (95% CI 3.3-12.1) in lower middle income countries, 0 in industrialised countries (and high income countries). If only studies which provided data for the full age range were considered, 22 studies from developing countries reported the same meta-estimate. The results for narrower age bands including neonates are available in Appendices – A13, A16, A19.

5.2.6 RSV associated ALRI mortality in community

Three studies from developing countries (Argentina, Bangladesh and Indonesia) reported number of childhood verbal autopsy confirmed pneumonia deaths in community as well as RSV seasonality data for at least 3 continuous years. The number of months of the RSV season, average number of pneumonia deaths outside and within RSV season as well as proportion of ALRI which were positive for RSV on assumption that any excess deaths within RSV season was attributed to RSV, and community-based mortality due to RSV were summarised in Table 49 for each site. The inflation factor for each site was calculated by comparing community-based RSV mortality to its respective in-hospital mortality (Table 50). In-hospital mortality for each site was generated by combining the meta-estimate of hospitalisation rate, meta-estimate of in-hospital CFR in the region where this study came from (developing region) and population number from mean study year. The mean inflation factor was applied to the overall in-hospital mortality in developing countries in order to get the community-based mortality for developing countries. Therefore, global mortality due to RSV associated ALRI was calculated as: in-hospital mortality in developing countries*inflation factor + in-hospital mortality in industrialised countries. For Argentina, the number of deaths due to RSV in community was estimated as 1.5 times higher than what was estimated in hospital. The adjustment factors for RSV mortality in community compared to in-hospital mortality was 2.1 and 2.9 in Bangladesh and Indonesia respectively. The mean inflation factor was 2.2. When extrapolated to other developing countries, it yielded a crude estimate (for developing countries) of roughly 131043 (95% CI 105539-162720) deaths attributable to RSV associated ALRI in young children in 2015. Although data from Argentina and Indonesia were for children younger than 2 years only, this limitation was not likely to be important since most pneumonia deaths in children occur during the first 2 years of life. Overall, the global mortality due to RSV associated ALRI in children younger than 5 years if active community-based case ascertainment was applied was 131482 (95% CI 105937-163370) (Table 51). Another 2 scenarios were assumed and corresponding analyses were also carried out but the results turned out to be implausible (Appendices – A21).

Table 49: RSV associated ALRI deaths in community from three studies in developing countries

Site	Study year	Months of RSV season (a)	Average ALRI deaths per month during RSV season (b)	Average ALRI deaths per month outside RSV season (c)	Total ALRI deaths in community per year (d)	Proportion of ALRI deaths due to RSV (%) (e)*	ALRI deaths overall in this country (f) (Liu et al., 2015a)	RSV deaths overall in this country (g)#
Buenos Aires, Argentina	2011	4	6.3	1.8	39	46.2	887	409
	2012	4	8.5	0.9	41	74.4	878	653
	2013	4	3.3	0.9	20	47.5	844	401
	Mean							488
Multicentre, Bangladesh	2010	9	3.0	2.7	35	8.6	21917	1879
	2011	4	8.8	5.4	78	17.3	20028	3466
	2012	6	9.5	6.3	95	20.0	18759	3752
	Mean							3032
Lombok, Indonesia	2000	6	73.3	62.3	814	8.1	39257	3183
	2001	6	84.8	48.8	802	26.9	37584	10122
	2002	7	45.0	36.8	499	11.5	36020	4143
	Mean							5816

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. *e=[(b-c)*a]/d. #g=e*f*0.01.

Table 50: Calculation of inflation factors - RSV mortality in community compared to RSV mortality in hospital

Site	Meta-estimate of hospitalisation rate (per 1000 per year) (h)§	Meta-estimate of in-hospital CFR (%) (i)§	Population in mean study period (j)	RSV deaths in hospital overall (k)*	Mean of RSV deaths in community (g)	Adjustment factor (l)#
Argentina	4.9	1.9	3407649	320	488	1.5
Bangladesh	4.9	1.9	15197631	1426	3032	2.1
Indonesia	4.9	1.9	21639000	2030	5816	2.9
Mean						2.2

RSV=respiratory syncytial virus. CFR=case fatality ratio. §Meta-estimate in the developing region (where this country comes from) was used. *k=h*j*0.001*i*0.01. #l=g/k.

Table 51: RSV associated ALRI mortality in children younger than five years old in hospital and in community respectively

	In-hospital mortality	Inflation factor	In-community mortality
Developing	59578 (47750-74325)	2.2	131043 (105539-162720)
Industrialised	237 (78-2202)	1	237 (78-2202)
Global*	59581 (47959-74542)		131482 (105937-163370)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. *Global number of RSV associated ALRI mortality is sum of estimates from developing countries and industrialised countries.

5.2.7 RSV subtypes

There were 19 studies providing data on RSV-A and RSV-B subtypes. Seven were published articles (Bdour, 2001, Carballal et al., 2000, Lamarao et al., 2012, Suryadevara et al., 2011, Tran et al., 2013, Vieira et al., 2007, Balmaks et al., 2014) identified from the systematic review and 12 unpublished studies[U5, U8, U12, U20, U24, U26, U28-29, U45-46, U65, U75] were provided by RSV GEN (Table 52). Two of them were community-based studies and the remaining 17 studies were from hospital settings. Two studies came from industrialised countries and the others were from developing countries. The numbers of cases of each subtype were summarised in Table 53. In most cases, RSV-A was substantially more commonly identified than RSV-B. Subtype data were also presented in several non-overlapping narrower age bands (Table 53). There were 14 studies providing these data. From the table, most RSV cases occurred during the first year. Across all age groups, the number of RSV-A cases was higher than the number of RSV-B. Two studies reported incidence rate of RSV subtypes and another six studies reported hospitalisation rate (all from developing countries). For the latter one where meta-analyses were carried out, the hospitalisation rate of RSV-A associated ALRI was estimated as 2.4 per 1000 children per year in children aged 0-59m, while it was 0.7 for RSV-B associated ALRI and 1.4 for RSV unknown subtype associated ALRI. Regarding the in-hospital case fatality ratio, nine of the studies provided data for both RSV-A and RSV-B (Table 54). All of them were from developing countries. In three sites, where there was at least one death for each subtype, the in-hospital CFR for RSV-A was higher than the one in RSV-B. When meta-analyses were carried out among these studies, in-hospital CFR from RSV-A associated hospitalised ALRI in children younger than 5 years from developing countries was 2.32% (95% CI 1.74-3.10) while it was 1.45% (95% CI 0.76-2.79) for RSV-B associated hospitalised ALRI.

Table 52: List of 12 unpublished studies reporting data of RSV subtypes

Study number	Location (reference)	Study period
U5	Bandung, Indonesia (Simoes and colleagues)	1st Feb 1999 - 26th Apr 2001
U8	Gilgit, Pakistan (Rasmussen and colleagues)	1st Apr 2012 - 31st Mar 2014
U12	CEMIC, Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010
U20	Gambia Western Region, Gambia (Howie and colleagues)	Jul 2007 - Jun 2008
U24	Pune, India (Chadha and colleagues)	May 2009 - Apr 2013
U26	Kilifi hospital study, Kenya (Nokes and colleagues)	Jan 2002 - Dec 2010
U28	Manhiça, Mozambique (Bassat and colleagues)	20th Sep 2006 - 19th Sep 2007
U29	Manhiça, Mozambique (Bassat and colleagues)	1st Jan 2011 - 30th Jun 2014
U45	Nha Trang, Vietnam (Yoshida and colleagues)	Feb 2007 - Dec 2012
U46	Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010
U65	Rabat, Morocco (Bassat and colleagues)	Nov 2010 - Dec 2011
U75	Tacloban, Philippines (Lupisan and colleagues)	May 2008 – Jul 2012

Table 53: List of 19 studies reporting subtypes data for RSV associated ALRI

Location (reference)	Full age group			0-11m			12-23m			24-59m		
	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B
Bandung, Indonesia (Simoes and colleagues)#	163	78	15	74	38	5	69	30	8	20	10	2
Gilgit, Pakistan (Rasmussen and colleagues)#	48	14	0	19	5	0	16	5	0	12	5	0
Buenos Aires, Argentina (Echavarria and colleagues)#	21	1	0	15	1	0	4	0	0	2	0	0
Gambia Western Region, Gambia (Howie and colleagues)#	16	16	1	8	8	1	5	5	0	3	3	0
Pune, India (Chadha and colleagues)#	61	44	22	21	16	7	22	14	9	18	14	6
Kilifi hospital study, Kenya (Nokes and colleagues)#	1428	853	445	1121	666	361	203	122	57	104	65	27
Manhiça, Mozambique (Bassat and colleagues)#	49	49	0	34	34	0	9	9	0	6	6	0
Manhiça, Mozambique (Bassat	68	59	9	39	34	5	15	14	1	14	11	3

Location (reference)	Full age group			0-11m			12-23m			24-59m		
	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B
and colleagues)#												
Nha Trang, Vietnam (Yoshida and colleagues)#	89	61	11	49	37	3	25	16	5	15	8	3
Ho Chi Minh City, Vietnam (Tran et al., 2013)	230	165	21									
Zarqa, Jordan (Bdour, 2001)	69	69	0	67	67	0	2	2	0			
Buenos Aires and Santa Fe, Argentina (Carballal et al., 2000)	352	174	21									
Sao Paulo, Brazil (Vieira et al., 2007)	117	86	24	117	86	24						
Belem, Brazil (Lamarao et al., 2012)	243	18	207									
New York, USA (Suryadevara et al., 2011)	76	38	37									
Buenos Aires, Argentina (Echavarria and colleagues)	128	30	2	102	23	1	19	7	0	7	0	1

Location (reference)	Full age group			0-11m			12-23m			24-59m		
	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B	Number of all RSV*	Number of RSV-A	Number of RSV-B
Rabat, Morocco (Bassat and colleagues)	136	127	61	77	70	42	28	28	11	59	57	19
Tacloban, Philippines (Lupisan and colleagues)	358	165	135	262	121	99	63	28	24	33	16	12
Riga, Latvia (Balmaks et al., 2014)	88	53	33									

RSV=respiratory syncytial virus. ALRI=respiratory syncytial virus. *All RSV included unknown subtypes. #Studies reported incidence rate or hospitalisation rate of RSV subtypes associated ALRI.

Table 54: List of 9 studies reporting in-hospital ratio for RSV associated ALRI subtypes

Location	0-59m			0-59m		
	Deaths of RSV-A	Cases of RSV-A	CFR of RSV-A (%)	Deaths of RSV-B	Cases of RSV-B	CFR of RSV-B (%)
Buenos Aires, Argentina (Echavarria and colleagues)	0	1	0.0	0	0	NA
Gambia Western Region, Gambia (Howie and colleagues)	0	16	0.0	0	1	0.0
Pune, India (Chadha and colleagues)	0	44	0.0	0	22	0.0
Kilifi hospital study, Kenya (Nokes and colleagues)	23	853	2.7	7	445	1.6
Manhiça, Mozambique (Bassat and colleagues)	1	49	2.0	0	0	NA
Manhiça, Mozambique (Bassat and colleagues)	0	59	0.0	0	9	0.0
Nha Trang, Vietnam (Yoshida and colleagues)	0	61	0.0	0	11	0.0
Rabat, Morocco (Bassat and colleagues)	4	127	3.1	1	61	1.6
Tacloban, Philippines (Lupisan and colleagues)	3	165	1.8	1	135	0.7

RSV=respiratory syncytial virus. CFR=case fatality ratio. NA=not applicable.

5.2.8 RSV cases with hypoxemia

Twenty-eight studies provided full details of hypoxemia among RSV positive cases according to a predefined definition. One was a published article (Rowlinson et al., 2013) and the other were unpublished studies[U10, U13, U21, U25, U26-28, U32-33, U37-39, U41-42, U44, U47, U62-63, U65, U68-75] (Table 55). Another 18 studies with hypoxemia data were excluded in the further analysis for several reasons (Table 56): unknown or unclear definition of hypoxemia, impropriate study design, substantially different definitions for hypoxemia, small sample size (less than 20 RSV cases). The detailed definitions of hypoxemia applied in each included study as well as its data were summarised in Table 57. They were all from hospital-based settings and reported hospitalisation rate (when catchment area was well defined and denominator population was available) or proportion of hospitalised ALRI cases with RSV positive (when denominator number was not available). Two unpublished studies[U41, U44] reported data from aboriginal populations and were excluded in the final meta-analysis (being consistent with previous epidemiological analyses). The proportion of RSV cases with recorded oxygen saturation data ranged from 27.4% to 100%. Since there were 0-72.6% of RSV cases with missing data of oxygen saturation, the estimate of hypoxemia (number of cases with hypoxemia, rate of cases with hypoxemia) was substantially underestimated. Overall, 21.2% (95% CI 16.7-27.0) of all hospitalised RSV positive cases in children younger than 5 years were identified with hypoxemia (Table 58). The proportion was similar in children with younger age: 21.6% (95% CI 17.1-27.2) in infants and 20.3% (95% CI 16.1-25.5) in children younger than two years. There were 13 studies with a well-defined denominator population available, thus hospitalisation rate of RSV associated ALRI cases with hypoxemia was summarised in Table 59. One study[U44] was conducted in an aboriginal population and similarly it was excluded in the final analysis. In developing countries, the hospitalisation rate of RSV associated ALRI with hypoxemia for children aged 0-5m was estimated as 8.9 (95% CI 4.4-18.0) per 1000 children per year, 3.8 (95% CI 1.9-7.6) for children aged 6-11m, and 0.3 (95% CI 0.1-0.8) for children aged 12-59m (Table 60). Therefore, 0.9 (95% CI 0.4-1.9) million new cases of RSV associated ALRI with hypoxemia were estimated occurring in hospitals from developing countries in 2015 (Table 61). Among 28 studies with hypoxemia data which met the pre-defined definitions, 25 of them also provided in-hospital mortality for RSV cases with hypoxemia. Their in-hospital CFRs were compared to the corresponding in-hospital CFR in all RSV cases (irrespective of oxygen saturation status) (Table 62). For most study sites, in-hospital mortality in RSV cases which had hypoxemia was higher than the mortality in all RSV cases (with or without hypoxemia).

Two sensitivity analyses of proportion of hospitalised RSV cases with hypoxemia in infants were carried out to exclude studies which did not report mortality data and studies which did not provide in-hospital CFR data for full age range respectively. Only three studies (two were in aboriginal population) did not report in-hospital CFR and the result did not differ much from previous estimate in infants: 21.6% (95% CI 17.1-27.2) vs. 22.1 (95% CI 17.5-28.0). Similar result was observed after excluding studies that did not report in-hospital mortality data for the full age range: 21.6% (95% CI 17.1-27.2) vs. 22.0 (95% CI 17.0-28.4).

Table 55: List of 27 unpublished studies reporting data of RSV cases with hypoxemia

Study number	Location (reference)	Study period
U10	Paarl, South Africa (Zar and colleagues)	Mar 2012 - Dec 2014
U13	Buenos Aires, Argentina (Polack and colleagues)	2011 - 2013
U21	Santa Rosa, Guatemala (McCracken and colleagues)	Jan 2008 to Dec 2013
U25	Lombok, Indonesia (Gessner and colleagues)	2000 - 2002
U26	Kilifi hospital study, Kenya (Nokes and colleagues)	Jan 2002 - Dec 2010
U27	Bondo district, Kenya (Feikin and colleagues)	Jan 2007 - Jun 2009
U28	Manhiça, Mozambique (Bassat and colleagues)	20th Sep 2006 - 19th Sep 2007
U32	David City, Panama (Jara and colleagues)	Jan 2011 - Dec 2013
U33	Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	5th Jul 2000 - 31st Dec 2004
U37	Soweto, South Africa (Madhi and colleagues)	Mar 1998 - Oct 2005
U38	Maela Camp, Tak Province, Thailand (Turner and colleagues)	Nov 2007 - Oct 2010
U39	Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	Jan 2008 - Dec 2011
U41	Alaska, USA (Singleton and colleagues)	Oct 2005 - Sep 2007
U42	Colorado, USA (Simoes and colleagues)	Jan 2008 - Jun 2013
U44	Navajo and WMA, USA - EPI (O'Brien and colleagues)	Oct 1997 - Mar 2000
U47	Buenos Aires, Argentina (Gentile and colleagues)	2001 - 2013
U62	Berlin, Germany (Rath and colleagues)	1st Apr 2010 - 31st Mar 2014
U63	Amman, Jordan (Khuri and colleagues)	Mar 2010 - Mar 2013
U65	Rabat, Morocco (Bassat and colleagues)	Nov 2010 - Dec 2011
U68	Basse, Gambia (PERCH)	3rd Nov 2011 - 2nd Nov 2013
U69	Kilifi, Kenya (PERCH)	15th Aug 2011 - 15th Nov 2013
U70	Bamako, Mali (PERCH)	3rd Jan 2012 - 14th Jan 2014
U71	Nakhon Phanom and Sa Kaeo, Thailand (PERCH)	1st Jan 2012 - 31st Jan 2014
U72	Lusaka, Zambia (PERCH)	10th Oct 2011 - 31st Oct 2013
U73	Dhaka, Bangladesh (PERCH)	1st Jan 2012 - 31st Dec 2013
U74	Matlab, Bangladesh (PERCH)	1st Jan 2012 - 31st Dec 2013
U75	Tacloban, Philippines (Lupisan and colleagues)	May 2008 - Jul 2012

Table 56: List of 18 studies with hypoxemia data which were excluded

Location (reference)	Study Period	Reason for exclusion
Banjul, Fajara and Sibanor, Gambia (Weber et al., 2002)	Jan 1994 - Dec 1996	unclear or unknown definitions for hypoxemia
Freiburg, Germany (Berner et al., 2001)	Apr 1997 - Mar 1999	unclear or unknown definitions for hypoxemia
Hong Kong, China (Chan et al., 2007)	1st Jan 2004 - 31st Dec 2004	unclear or unknown definitions for hypoxemia
Athens, Greece (Vagia et al., 2010)	2008 - 2009	unclear or unknown definitions for hypoxemia
Palma, Spain (Hervas et al., 2012)	Jan 1995 - Dec 2006	unclear or unknown definitions for hypoxemia
Dallas, Texas, USA (Garcia et al., 2010)	Jan 2002 - Dec 2007	unclear or unknown definitions for hypoxemia
Manhiça, Mozambique (Bassat and colleagues)	1st Jan 2011 - 30th Jun 2014	study design: children with oxygen saturation <85% were excluded
Nha Trang, Vietnam (Yoshida and colleagues)	Feb 2007 - Dec 2012	study design: the onset of illness to hospitalisation was short - threshold of hospitalisation is low
Athens, Greece (Tsolia et al., 2003)	Feb 1997 - Jun 2000	different definition: SpO2 <95%
Amman, Jordan (Al-Toum et al., 2006)	Sep 2002 - Mar 2004	different definition: SpO2 <95%
Madrid, Spain (Garcia-Garcia et al., 2006)	Oct 2000 - Jun 2005	different definition: SpO2 <95%
Madrid, Spain (Calvo et al., 2010)	Sep 2005 - Aug 2008	different definition: SpO2 <95%
Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010	different definition: SpO2 <92%
Milan, Italy (Canducci et al., 2008)	Oct 2004 - Sep 2006	different definition: SpO2 <92%
Quetzaltenango, Guatemala (McCracken and colleagues)	Feb 2009 - Dec 2013	different definition: SpO2 <87% for 1-59 months and <85% for neonates at altitude >2500 m
CEMIC, Buenos Aires, Argentina (Echavarria and colleagues)	1st Jun 2008 - 31st Dec 2010	different definition: SpO2 <94%
Gambia Western Region, Gambia (Howie and colleagues)	Jul 2007 - Jun 2008	small number of RSV cases (16)
Tone district, Togo (Gessner and colleagues)	Aug 2011 - Dec 2013	small number of RSV cases (15)

Table 57: List of 28 studies reporting proportion of RSV associated hospitalised ALRI cases with hypoxemia

Location (reference)	Prop of RSV cases with recorded SpO2 (%)	Definition of hypoxemia	Proportion of RSV positive cases with hypoxemia (%)				
			0-11m	12-23m	0-23m	24-59m	0-59m
Matlab, Bangladesh (PERCH)	100.00	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	2.2	0.0	1.9	0.0	1.8
Basse, Gambia (PERCH)	100.00	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	7.4	7.1	7.3	0.0	7.0
Santa Rosa, Guatemala (McCracken and colleagues)	93.00	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m	7.5	5.0	7.1	11.1	7.4
Dhaka, Bangladesh (PERCH)	100.00	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	10.5	0.0	5.9	33.3	8.1
Tacloban, Philippines (Lupisan and colleagues)	100.00	SpO2 <90% (at altitude ≤2500 m) in children aged 1-59 months and <88% for neonates	9.2	12.7	9.8	12.1	10.1
Kilifi hospital study, Kenya (Nokes and colleagues)	99.93	SpO2 <90% for all at altitude ≤2500 m	11.1	5.4	10.2	8.7	10.1
Bondo district, Kenya (Feikin and colleagues)	100.00	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	15.8	5.9	12.7	0.0	10.6
Rabat, Morocco (Bassat and colleagues)	93.38	SpO2 <90% for all at altitude ≤2500 m	12.9	14.8	13.4	6.7	11.8
Nakhon Phanom and Sa Kaeo, Thailand (PERCH)	100.00	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	15.8	6.7	11.8	12.5	12.0
David City, Panama (Jara and colleagues)	71.86	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	17.1	10.3	15.3	33.3	16.7
Berlin, Germany (Rath and colleagues)	78.11	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤0.942500 m	15.9	36.6	20.3	37.5	23.3

Location (reference)	Prop of RSV cases with recorded SpO2 (%)	Definition of hypoxemia	Proportion of RSV positive cases with hypoxemia (%)				
			0-11m	12-23m	0-23m	24-59m	0-59m
Soweto, South Africa (Madhi and colleagues)	99.65	SpO2 <90% for 1-59 months	27.2	15.3	25.0	5.7	23.8
Kilifi, Kenya (PERCH)	100.00	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	26.3	17.4	24.8	15.4	24.0
Lusaka, Zambia (PERCH)	97.09	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	42.5	40.0	36.1	66.7	37.0
Bamako, Mali (PERCH)	100.00	SpO2 <90% or based on supplemental oxygen at altitude ≤2500 m	37.8	393.3	39.3	0.0	37.8
Manhiça, Mozambique (Bassat and colleagues)	100.00	SpO2 <90% for all at altitude ≤2500 m	55.9	22.2	48.8	0.0	42.9
Damanhour, Egypt (Rowlinson et al., 2013)	27.41	SpO2 <90% for all at altitude ≤2500 m					46.9
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	51.95	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	61.6	8.1	54.6	3.9	51.9
Buenos Aires, Argentina (Gentile and colleagues)	99.94	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	60.6	60.7	60.6	62.5	60.8
Colorado, USA (Simoes and colleagues)	100.00	ICD-9 codes	64.2	71.6	66.0	67.8	66.3
Maela Camp, Tak Province, Thailand (Turner and colleagues)	93.02	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	11.3	2.5	8.3		
Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	NA	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	15.2	18.0	16.0		

Location (reference)	Prop of RSV cases with recorded SpO2 (%)	Definition of hypoxemia	Proportion of RSV positive cases with hypoxemia (%)				
			0-11m	12-23m	0-23m	24-59m	0-59m
Alaska, USA (Singleton and colleagues)#	100.00	SpO2 <90% for all at altitude ≤2500 m	16.4	36.4	21.1		
Lombok, Indonesia (Gessner and colleagues)	99.19	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	33.0	36.6	33.6		
Amman, Jordan (Khuri and colleagues)	100.00	SpO2 <90% for all at altitude ≤2500 m	9.4	7.3	9.1		
Paarl, South Africa (Zar and colleagues)	92.86	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m	36.0	0.0	34.6		
Buenos Aires, Argentina (Polack and colleagues)	98.71	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m	41.5	41.6	41.5		
Navajo and WMA, USA - EPI (O'Brien and colleagues)#	92.05	SpO2 <90% for 1-59 months and <88% for neonates at altitude ≤2500 m (at sea level)	82.0	84.4	82.7		

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. ICD=international classification of diseases. NA=not applicable. #Studies reporting hypoxemia data in an aboriginal population from a high-income country.

Table 58: Meta-estimate of proportion of RSV associated hospitalised ALRI cases with hypoxemia

Region	0-11m		12-23m		0-23m		24-59m		0-59m	
	No.	Prop (%)	No.	Prop (%)	No.	Prop (%)	No.	Prop (%)	No.	Prop (%)
Low income	8	16.4 (9.1-29.6)	8	18.9 (2.2-162.7)	8	14.4 (7.8-26.5)	8	10.7 (6.1-18.8)	8	13.9 (7.7-24.9)
Lower middle income	6	16.5 (9.1-30.0)	6	17.7 (9.9-31.8)	6	16.3 (9.2-29.1)	4	14.7 (6.5-33.3)	5	17.3 (7.8-38.6)
Upper middle income	9	26.9 (18.3-39.5)	9	23.0 (14.9-35.3)	9	24.3 (16.7-35.5)	5	36.6 (23.7-56.5)	5	30.5 (20.1-46.1)
High income	2	32.4 (8.3-127.3)	2	53.8 (28.1-103.0)	2	37.0 (11.7-117.4)	2	53.2 (29.9-94.9)	2	39.6 (14.2-110.5)
Developing	23	20.2 (15.1-26.9)	23	19.7 (12.8-30.4)	23	18.6 (14.0-24.8)	17	20.6 (13.3-31.9)	18	18.4(12.8-26.4)
Industrialised	2	32.4 (8.3-127.3)	2	53.8 (28.1-103.0)	2	37.0 (11.7-117.4)	2	53.2 (29.9-94.9)	2	39.6 (14.2-110.5)
Global	25	21.6 (17.1-27.2)	25	23.8 (17.4-32.6)	25	20.3 (16.1-25.5)	19	27.8 (20.4-37.8)	20	21.2 (16.7-27.0)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. No.=number of studies.

Table 59: List of 13 studies reporting hospitalisation rate of RSV associated ALRI cases with hypoxemia

Location (reference)	Hospitalisation rate of RSV associated ALRI cases with hypoxaemia (per 1000 children per year)					
	0-5m	6-11m	0-11m	12-23m	24-59m	0-59m
Kilifi hospital study, Kenya (Nokes and colleagues)	3.5	0.7	2.1	0.2	0.1	0.5
Bondo district, Kenya (Feikin and colleagues)	10.5	4.4	6.9	1.3	0.0	3.0
Manhiça, Mozambique (Bassat and colleagues)	7.9	3.9	6.0	0.6	0.0	1.3
David City, Panama (Jara and colleagues)			12.5	4.5	0.5	3.8
Soweto, South Africa (Madhi and colleagues)	10.4	1.7	5.4	0.6	0.0	1.1
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	1.7	1.3	1.5	0.6	0.1	0.5
Lombok, Indonesia (Gessner and colleagues)	4.4	4.2	4.3	1.0		
Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	11.5	8.1	9.5	4.2		
Paarl, South Africa (Zar and colleagues)	53.3	7.5	31.7	0.0		
Maela Camp, Tak Province, Thailand (Turner and colleagues)	9.4	12.2	10.7	1.5		
Navajo and WMA, USA (O'Brien and colleagues)#	170.3	123.8	147.0	63.3		
Buenos Aires, Argentina (Polack and colleagues)	27.9	12.1	20.0	3.8		
Colorado, USA (Simoes and colleagues)			11.6	4.1	1.1	3.8

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. #Studies reporting hypoxemia data in an aboriginal population from a high-income country.

Table 60: Meta-estimate of hospitalisation rate of RSV associated ALRI cases with hypoxemia

Region	0-5m		6-11m		12-59m	
	Number of studies	Hospitalisation rate (per 1000 children per year)	Number of studies	Hospitalisation rate (per 1000 children per year)	Number of studies	Hospitalisation rate (per 1000 children per year)
Low income	3	6.1 (3.0-12.6)	3	2.1 (0.5-8.7)	3	0.1 (0.1-0.3)
Lower middle income	2	7.1 (2.8-18.1)	2	5.8 (3.1-11.0)	0	NA
Upper middle income	5	11.9 (4.3-33.3)	5	4.6 (1.3-16.1)	3	0.4 (0.1-1.5)
High income	0	NA	0	NA	1	1.8 (1.8-1.9)
Developing	10	8.9 (4.4-18.0)	10	3.8 (1.9-7.6)	6	0.3 (0.1-0.8)
Industrialised	0	NA	0	NA	1	1.8 (1.8-1.9)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NA=not applicable.

Table 61: Number of new cases of RSV associated hospitalised ALRI with hypoxemia

Region	0-5m	6-11m	12-59m	0-59m*
	Hospitalised cases ($*10^3$)	Hospitalised cases ($*10^3$)	Hospitalised cases ($*10^3$)	Hospitalised cases ($*10^3$)
Low income	65 (32-134)	23 (6-93)	11 (5-27)	99 (42-254)
Lower middle income	227 (88-581)	186 (98-355)	NA	NA
Upper middle income	210 (75-589)	81 (23-285)	55 (14-211)	347 (112-1084)
High income	NA	NA	118 (113-121)	NA
Developing	548 (272-1107)	234 (118-469)	129 (48-363)	912 (437-1939)
Industrialised	NA	NA	103 (99-106)	NA

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NA=not applicable. *number of hospitalised cases in 0-59m is sum of estimates from exclusive finer age bands (0-5m, 6-11m and 12-59m).

Table 62: List of 25 studies reporting in-hospital CFR among RSV cases with hypoxemia

Location (reference)	RSV with hypoxemia			All RSV cases		
	Deaths	Cases	CFR (%)	Deaths	Cases	CFR (%)
Damanhour, Egypt (Rowlinson et al., 2013)	0	60	0.0	0	467	0.0
Berlin, Germany (Rath and colleagues)	0	54	0.0	0	297	0.0
Rabat, Morocco (Bassat and colleagues)	1	15	6.7	4	136	2.9
Basse, Gambia (PERCH)	0	8	0.0	0	114	0.0
Kilifi, Kenya (PERCH)	3	36	8.3	6	150	4.0
Bamako, Mali (PERCH)	4	59	6.8	4	156	2.6
Nakhon Phanom and Sa Kaeo, Thailand (PERCH)	0	6	0.0	0	50	0.0
Lusaka, Zambia (PERCH)	4	37	10.8	6	103	5.8
Dhaka, Bangladesh (PERCH)	0	3	0.0	0	37	0.0
Tacloban, Philippines (Lupisan and colleagues)	1	36	2.8	6	358	1.7
Santa Rosa, Guatemala (McCracken and colleagues)	4	47	8.5	15	505	3.0
Kilifi hospital study, Kenya (Nokes and colleagues)	31	144	21.5	31	1428	2.2
Bondo district, Kenya (Feikin and colleagues)	0	7	0.0	1	66	1.5
Manhiça, Mozambique (Bassat and colleagues)	1	21	4.8	1	49	2.0
David City, Panama (Jara and colleagues)	0	20	0.0	0	167	0.0
Soweto, South Africa (Madhi and colleagues)	12	205	5.9	14	863	1.6
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat and colleagues)	0	37	0.0	0	795	0.0
Lombok, Indonesia (Gessner and colleagues)	4	247	1.6	13	741	1.8
Tagbilaran and 6 rural sites, Philippines (Lucero and colleagues)	0	56	0.0	2	357	0.6

Location (reference)	RSV with hypoxemia			All RSV cases		
	Deaths	Cases	CFR (%)	Deaths	Cases	CFR (%)
Paarl, South Africa (Zar and colleagues)	0	9	0.0	0	28	0.0
Amman, Jordan (Khuri and colleagues)	5	123	4.1	6	1352	0.4
Buenos Aires, Argentina (Polack and colleagues)	24	888	2.7	24	2167	1.1
Buenos Aires, Argentina (Gentile and colleagues)	63	2180	2.9	65	3590	1.8
Matlab, Bangladesh (PERCH)	0	2	0.0	0	109	0.0
Colorado, USA (Simoes and colleagues)	0	7686	0.0	6	11592	0.1

RSV=respiratory syncytial virus. CFR=case fatality ratio.

5.2.9 Year by year variation in individual study site

Several studies reported incidence rate or hospitalisation rate for several years. Therefore, when studies reported data in infants for at least three years and provided the data by year, these studies were selected to display year to year variation of incidence rate or hospitalisation rate for this study site. Two studies[U3, U5] reporting incidence rate of infants for at least three years were selected. Incidence rate in Bangladesh was highest in 2006 while there was little variation in the other three years under investigation (from 13.1 to 84.6 per 1000 children per year). In Indonesia, the incidence rate was highest in 2001 and it was almost the same in years 1999 and 2000 (from 151.7 to 364.4 per 1000 children per year). The figures showing incidence rate year by year from these two sites were available in Appendices - A22. Regarding studies reporting hospitalisation rate, stricter selection criteria were applied. Seven studies[U19, U21-22, U26, U33, U35, U42] reporting hospitalisation rate for at least five years and recording more than 100 RSV associated hospitalised ALRI cases in infants were chosen. There were substantial variations in hospitalisation rate across different study years in several sites, such as El Salvador, Guatemala (2 sites), and South Africa. In Kenya, Philippines and Colorado, however, the hospitalisation rate was similar in each study year with slight variations. The figures displaying their hospitalisation rates by year were available in Appendices – A23.

5.3 Discussion

5.3.1 Main results

In 2015, 30.5 (95% CI 19.5-47.9) million episodes of RSV associated ALRI were estimated to occur in children younger than 5 years in developing countries (30.0 (95% CI 19.1-47.0) million in low and middle income countries). A substantial proportion of RSV associated ALRI - 10.9 (95% CI 7.2-16.4) million occurred in the first year of life, with incidence rate in infants 1.7 times greater than what was reported for children younger than 5 years. The global estimate in children under five was around 33.0 (95% CI 20.6-53.2) million RSV associated ALRI. Also, in 2015, 3.0 (95% CI 2.2-4.0) million young children worldwide were estimated to develop RSV associated ALRI necessitating hospital admission, and around 60,000 (95% CI 48,000-75,000) children younger than 5 years died from RSV associated hospitalised ALRI, with 99% of these deaths occurring in developing countries. An inflation factor was calculated based on three community-based studies from developing countries, considering that access to healthcare in developing countries is limited. This inflation factor was estimated as 2.2. Overall, the global number of RSV associated ALRI deaths if active community based case ascertainment was applied in the developing country settings, was around 131,000 (95% CI 106,000-163,000).

Two independent approaches with differing data sources and assumptions were adopted to obtain a data-derived estimate of the plausible number of RSV associated hospitalised ALRI: hospitalisation rate approach which used meta-estimate of hospitalisation rate and corresponding demographic data of population of interest; proportion approach which combined the proportion of hospitalised ALRI cases that are RSV positive with corresponding number of hospitalised ALRI cases. The two approaches generated estimates of the global number of new episodes of RSV associated hospitalised ALRI with overlapping 95% confidence intervals: 3.0 (95% CI 2.2-4.0) million and 2.8 (95% CI 2.3-3.4) million respectively. This was considered to represent a broad replication of the estimate, which supports the general validity of the estimate.

5.3.2 Variation of estimates

Estimates of RSV associated ALRI are highly variable within countries or regions and across regions. It is impossible to deduce how much of this variation is due to methodological differences and how much is due to variation in RSV epidemiology between study populations or region-specific differences. Thus, the true uncertainty is wider than that expressed in a standard 95% CI. Four methodological factors might have affected the estimates: method of case ascertainment; case definition used in included studies

(community-based and hospital-based); accuracy of diagnostic assays to identify RSV infection, and the fact that a proportion of eligible ALRI cases were not tested.

5.3.2.1 Case ascertainment

All studies reporting incidence rate of RSV associated ALRI used active community-based case ascertainment, which means health-care workers visit house-to-house to identify cases. Even though active case ascertainment was used to identify cases, the RSV associated ALRI incidence estimate in developing countries is still likely to be underestimated because there will be an unknown proportion of cases missed. For studies reporting hospitalisation rate of RSV associated ALRI, in-hospital CFR as well as proportion data, they all used passive case ascertainment including only inpatients. The estimates generated from these hospital-based studies can only indicate the morbidity and mortality of RSV associated ALRI in hospital settings. This is because the health-care access in some developing countries, especially in rural areas, is poor and not all infected children manage to visit clinics or hospitals and receive required treatments (Macfarlane, 2000). Delays in transferring children to health facilities from presentation can affect the disease progression, increase morbidity and mortality of the illness, and also affect RSV titres and test sensitivity. There were 41 studies conducted in rural populations and 38 were in a mixture of urban and rural areas across the included studies. An emergency room based study from a Nigerian tertiary hospital showed that most children received care within homes and after 24 hours of onset of illness (Tinuade, 2010). The duration between onset of illness and presentation at hospital was long, with the majority being after 48 hours. Therefore, an inflation factor was calculated and used to extrapolate the overall mortality from RSV associated ALRI if active community-based ascertainment was applied. Since mothers were involved in most decisions where health-care seeking was approached for their ill children (Tinuade, 2010), empowerment of women and improvement of maternal education is important. This is not only to increase their awareness of prompt health-care seeking behaviour, but also to help them recognise the danger signs or symptoms young children might have. Improving accessibility to health facilities in terms of distance and expenditures will also encourage carers to take sick children to hospitals. The association of parental education and RSV associated ALRI was investigated in Chapter 4.

5.3.2.2 Case definition

Case definitions used among included studies varied from the WHO definition to physician-diagnosed ALRI (with or without chest radiographic confirmation) and unspecified acute respiratory illness that was severe enough to necessitate hospital admission. For community-based studies, healthcare workers used WHO definition to define the cases (cough or

difficulty in breathing with fast breathing for age, with or without chest wall indrawing and general danger signs). For hospital-based studies, the majority of studies defined the cases based on physician's assessment (with or without chest wall indrawing, hypoxemia, general danger signs, mechanical ventilation and intensive care unit admission). Several studies used other case definitions, such as SARI, which was defined as an acute respiratory infection with history of fever or measured fever ≥38°C and cough, with onset within the last ten days and requires hospitalisation. Some studies excluded cases with wheeze or included fever as part of the case definitions. Therefore, these studies were excluded to run a sensitivity analysis. The result did not differ substantially to the estimate where these studies were included. It was slightly lower and the underlying mechanism required further investigation. In Table 48, codes corresponding to different definitions or clinical features used to define ALRI were compared between studies reporting hospitalisation rate and studies providing in-hospital CFR data. A variety of case definition codes was observed. The percentage of each code used in included studies differed from each other but was consistently similar between these two groups of studies.

Ability to recognise and diagnose clinical symptoms and signs accurately is important. For example, fast breathing is diagnosed at different thresholds for children at different ages (WHO IMCI cut-offs). It is best to count the respiratory rate using a timing device when the child is in a quiet but in an alert state. Chest wall indrawing refers to lower chest wall indrawing (subcostal indrawing or subcostal retraction) when the child breaths in, which occurs below the costal margin and indicates that more effort is needed to breath in since the lung becomes stiff due to infection. This must be present clearly and visible all the time.

Despite there being a large number of clinical symptoms and signs that could be assessed in children, none of the clinical features mentioned above has sufficient validity to diagnose pneumonia on its own. The WHO definition of clinical pneumonia has high sensitivity but was claimed to have low specificity (Cardoso et al., 2011). A prospective study involving 390 children aged 2-59 months from Sao Paulo (Brazil) showed that WHO criteria to identify children with pneumonia had a high sensitivity of 84% and a low specificity of 19% (Cardoso et al., 2011). The sensitivity was higher in younger age group (94% in children <24 months compared to 62% in children ≥24 months). A pragmatic perspective led to the WHO clinical case definition emphasising sensitivity over specificity. This is of public health significance because the WHO case definition is aimed to capture the majority of children with pneumonia for timely management, mitigating the progress of illness and decreasing the severity and mortality of the disease. Nevertheless, low specificity may lead to over-use of antibiotics, incur multiple clinic or hospital visits and unnecessary medical expenditure

which increases family financial burden, and also impose more burden on paediatric healthcare system.

5.3.2.3 Clinical specimen and diagnostic test

The 304 included studies also differed in the method of nasal sampling and in the specific diagnostic assays applied, which will also have contributed to some of the variations in reported estimates. Most studies took nasopharyngeal aspirate (NPA), nasopharyngeal wash (NPW), nasopharyngeal swab (NPS), or oropharyngeal swab (OPS) clinical specimens. Children have a higher concentration of RSV secretion compared to adults. The concentration is also lower in elderly people and immune-compromised persons.

A timely diagnosis of respiratory infections which are RSV positive is important for infection control measures, which can limit the transmission and progress of the virus. It can also limit unnecessary antibiotic utilisation and allow early implementation of antiviral treatment. The main diagnostic techniques used in included studies were polymerase chain reaction (PCR), immunofluorescence (IF), direct immunofluorescence (DFA), indirect immunofluorescence (IFA), and enzyme-linked immunosorbent assay (ELISA). Among 304 studies, 117 studies used PCR-based assays; the remaining studies used IF (28 studies), DFA (66 studies), IFA (18 studies), ELISA (12 studies) and a mixture of diagnosis tests (46 studies). Another 17 studies did not provide clear information about diagnosis test.

The effect of these diagnostic methods on the estimates depends on their sensitivity and specificity and factors which affect their performance: quality of specimen (collection and handling), transport conditions of specimen, adequacy of specimen (virus load), manufacturer, quality of reagent, laboratory technician skills and features of population under diagnosis.

As described in the Chapter 1 - Introduction, antigen-based assays (IF, DFA, IFA, ELISA and rapid antigen-detection tests) are widely available, easy to perform, inexpensive and provide results rapidly while they have a relatively low sensitivity and specificity (compared to nucleic acid amplification), especially outside the disease season (low prevalence of virus) and among special populations (immunocompromised individuals and elderly people) (Henrickson and Hall, 2007). They also lack adequate sensitivity in testing adults with RSV infection due to small virus load. They require a high level of laboratory microscope handling experience and a rich sample with cells. The immunofluorescence assays have variable and lower sensitivity (69.4%) and specificity (99.7%) compared to RT-PCR according to a prospective cohort study consisting of 173 healthy new-borns who were followed up until two years old (Reis et al., 2008). During the high season of RSV, rapid

antigen tests could be applied to facilitate viral diagnosis because of their availability and practicality. They have relatively good sensitivity and specificity when the test is carried out during peak season of virus among healthy children (not immunocompromised).

Molecular assays have fulfilled the requirements of rapid diagnosis and high sensitivity and specificity for respiratory viruses testing. However, they are expensive and are not available in most clinical laboratories. They also have the potential to detect viruses for a longer time due to their high sensitivity. During this extended shedding period being detected by PCR, it is possible that the child gets another viral infection. It is difficult to decide which pathogen is the cause of illness. Real time PCR involves fewer steps and decreases risk of contamination. However, its costs are higher and the reagent is unstable and more expensive (Henrickson, 2004). Multiplex virus testing is available and makes it efficient to have several viruses tested at the same time. There are several important issues of molecular diagnostic test remaining to be considered, such as expense of reagents, the requirement for reliable commercial reagents, and the necessity for building up capability and providing platforms that are able to respond to new emerging and "re-emerging" agents (Henrickson, 2004).

Cell culture, which was previously considered as the gold standard to diagnose respiratory viruses, has been replaced by molecular assays (PCR) in many settings due to its long processing time, special requirement of specimen handling procedure, large financial cost and lower sensitivity in comparison to PCR (Henrickson and Hall, 2007, Reis et al., 2008). There were 27 studies using cell culture as part of the diagnostic tests (all of them were combined with other methods). Studies using serology as the only diagnostic test were excluded (listed in Table 19) because it is not useful for diagnosing ALRI and the rate of false negative results is high (Henrickson, 2004).

A prospective study including 378 children aged 2-35 months proposed point-of-care ultrasound for the diagnosis of childhood pneumonia as an alternative imaging approach in resource-limited settings (Chavez et al., 2015). It takes around 6.4 minutes to perform one. A systematic review was carried out to investigate the performance of the lung ultrasound (Pereda et al., 2015). It has a pooled sensitivity of 96% (94%-97%) and a pooled specificity of 93% (90%-96%) using chest radiographs and/or clinical criteria as the reference standard. Also, considering that it is quick to perform and it does not involve ionizing radiation, it is recommended as an alternative approach to diagnose pneumonia, especially when chest radiographs are not available. However, the number of included studies is small (only 8 studies), the sample size from each study is small, and there is a possibility of missing small

consolidations (< 1 cam) that do not reach the pleura. Lung ultrasound, therefore, still needs further research and assessment.

All these diagnosis tests need trained laboratory technicians (except for rapid antigen-detection test) and specialised equipment. With the emergence of these various diagnostic methodologies, it is necessary to develop guidelines to direct their appropriate use in the laboratory. Clinicians should also recognise the benefits and limitations of these diagnostic tests while making clinical decisions about their use.

5.3.2.4 ALRI cases which were not tested

In some studies, a substantial proportion of children with ALRI were not tested for RSV for various reasons: samples were selected randomly and tested; patients were very ill; no informed consent from parents; patients died or got discharged before samples were taken; samples were lost; and poor quality of samples. During the process of extracting data from included studies, the number of RSV associated ALRI cases was scaled up accordingly (if possible) to account for ALRI cases which were not tested, on the assumption that the proportion of ALRI cases which were RSV positive in untested ALRI was the same as in tested ALRI. However, for hospital-based studies reporting CFR, this such adjustment for those untested ALRI cases was not available. Table 63 shows 30 unpublished studies with complete information about proportion of hospitalised ALRI cases not tested for RSV, reasons for not being tested, in-hospital CFR among hospitalised ALRI tested for RSV and untested ALRI cases respectively in their overall age groups. Accordingly, 0.3-75.0% of all eligible ALRI cases were not tested for RSV for various reasons. In most cases, the in-hospital mortality was higher among hospitalised ALRI cases which were not tested for RSV compared to those cases which were tested. This is possible because children who were not tested with RSV probably had a severe illness and clinical specimen was not taken while the children were receiving urgent treatment. Among all deaths due to ALRI, the proportion of these deaths being untested (with unknown pathogen) ranged from 0 to 100% (in this case, there were two deaths of ALRI and both of them were not tested for pathogen). A sensitivity analysis was carried out to estimate in-hospital CFR taking into account of untested ALRI, on the assumptions that the proportion of RSV detection in untested ALRI was the same as in the tested ALRI and the in-hospital CFR of these RSV cases (from untested ALRI) was the same as the CFR of the overall untested ALRI. Under these assumptions, the adjusted in-hospital CFR in children aged 0-59m from the developing countries was 1.57 (95% CI 0.99-2.49). It was slightly higher than the estimate 1.47 (95% CI 0.94-2.30) when no adjustment was made. This result is consistent with the previous observation that in-hospital CFR was

higher among untested ALRI cases than ALRI which were tested for RSV. Therefore, the adjustment factor was 1.07 (1.57/1.47) and if it was applied to the in-hospital deaths estimated above - 59578 (47750-74325), the adjusted in-hospital deaths was 63748 (51093-79528) in children under five from developing countries. More details of calculation process are available in Appendices – A24.

Furthermore, 13 unpublished studies with more than 2 deaths of untested ALRI in infants and with available data regarding seasonality of RSV and number of deaths from untested ALRI in infants by month were selected. They were used to explore whether these deaths of untested ALRI occurred within RSV season or outside RSV season. Seasonality of RSV (proportion of hospitalised ALRI cases which are RSV positive) and number of deaths of untested ALRI in infants by each study month were plotted for each study site. In Figure 18, there were several deaths of untested ALRI occurring during RSV season (overlapped of two lines). This might result in an underestimation of in-hospital deaths of RSV cases.

5.3.3 Mortality estimate

In-hospital mortality estimates were generated by using Monte Carlos simulation on the assumption that meta-estimates of hospitalisation rate and in-hospital CFR followed log-normal distributions. Repeatedly every 10,000 sample from each age band and region specific group were drawn. Output data for each outcome were produced independently from run to run. The median value of the resultant calculation was reported as the point estimate, while the 2.5^{th} and 97.5^{th} percentiles from the resultant calculation were reported as the 95% confidence interval. This Monte Carlos simulation method took the point estimate and its bounding confidence intervals from both variables (hospitalisation rate and in-hospital CFR) into account to create samples of the in-hospital deaths (compound effect measure). Since it considered the uncertainty from both parameters, the confidence intervals for the compound effect measure were wide (Greenland, 2004). The difference between global point estimate and the sum of respective regional point estimates is a result of the sampling from the simulation process.

In-hospital CFR decreased with age. Studies with more than 10 deaths due to RSV associated hospitalised ALRI in the age group of 0-23m were selected considering that most deaths happen within first two years of life. Six studies were included and displayed in the spaghetti plot demonstrating in-hospital CFR by narrower age bands (Figure 19). Each colour represents a different study. Clearly, in each study, the in-hospital CFR is higher in infants compared to the older age group.

The estimate of RSV mortality in the community was generated based on the assumption that all excess ALRI mortality during RSV season is due to RSV, which is unlikely to be true considering that other respiratory pathogens may circulate during RSV season and the likelihood of RSV deaths occurring outside the defined RSV season.

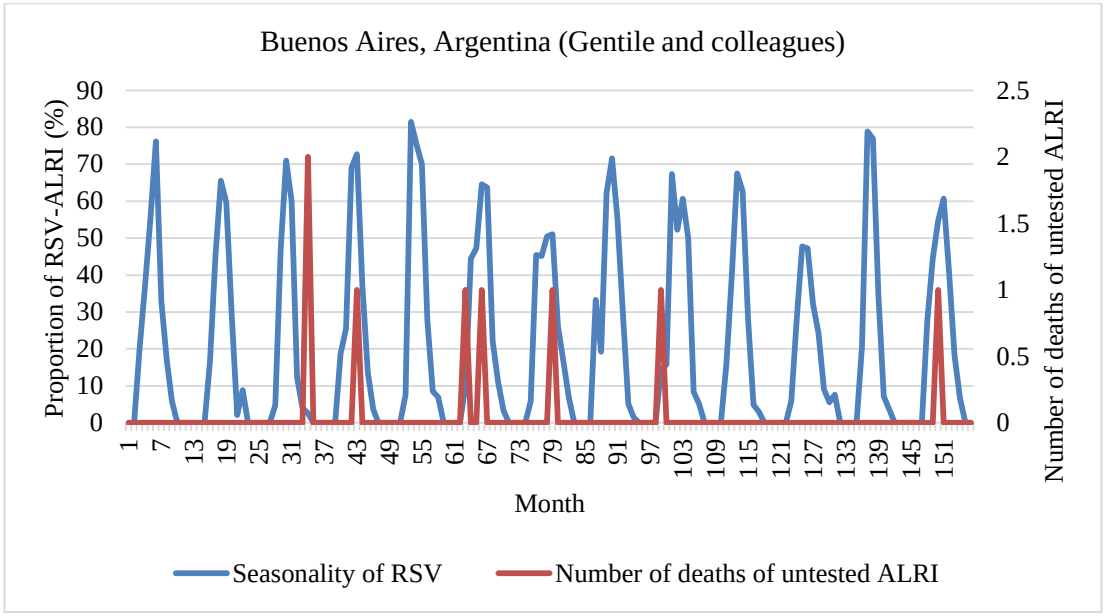
Table 63: List of 30 studies reporting eligible ALRI cases not tested for RSV as well as CFR among tested ALRI and untested ALRI cases

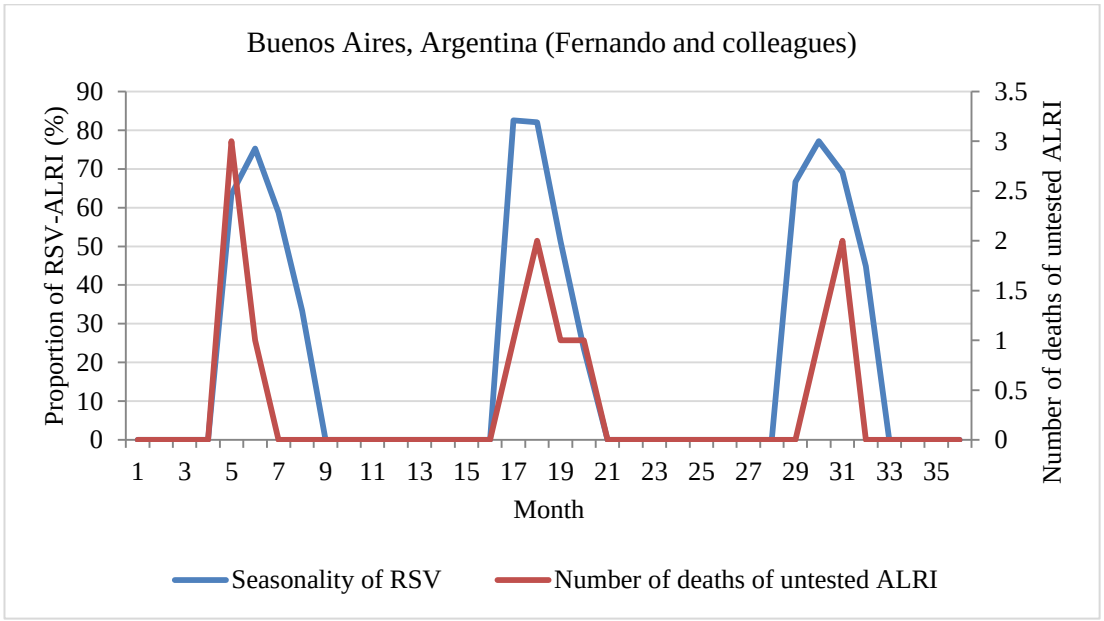
Location (reference)	% of eligible cases not tested for RSV	Reasons for not testing	CFR among hospitalised ALRI tested for RSV (%)	CFR among hospitalised ALRI not tested for RSV (%)	Prop of ALRI deaths being untested (%)
Kilifi, Kenya (PERCH, unpublished)	0.3 (2/634)	specimen not collected	4.9	100.0	6.1
Iquique, Chile (Fasce, unpublished)	0.6 (4/683)	cases were not notified in time so as to collect sample	0.4	0.0	0.0
Buenos Aires, Argentina (Polack, unpublished)	0.9 (30/3371)	sample inadequate	1.3	43.3	23.6
Gauteng province, South Africa (Cohen, unpublished)	2.0 (122/6016)	child too ill to take sample from; specimens not reaching laboratory within 72 hours	0.8	2.5	5.7
Manhiça, Mozambique (Bassat, unpublished)	3.1 (15/491)	NPA not collected or processed without results	2.5	13.3	14.3
Klerksdorp site, South Africa (Cohen, unpublished)	3.2 (30/932)	patient very ill; parents refuse consent, specimen not at lab within 72 hours	2.1	0.0	0.0
Tone District, Togo (Gessner, unpublished)	3.2 (4/124)	testing just started	0.0	66.7	100.0
Concepcion, Chile (Fasce, unpublished)	3.3 (16/481)	cases were not notified in time so as to collect sample	0.4	0.0	0.0
Manhiça, Mozambique (Bassat, unpublished)	3.4 (28/835)	NPA not collected or processed without results	9.3	25.0	8.5
Mpumalanga, South Africa (Cohen, unpublished)	4.0 (52/1310)	patient very ill; parents refuse consent; specimen not at lab within 72 hours	6.1	21.2	12.5
Western Gambia (Howie, unpublished)	4.2 (4/95)	technical problem with specimen	3.3	0.0	0.0
KwaZulu-Natal province, South Africa (Cohen, unpublished)	4.5 (72/1607)	patient very ill; parents refuse consent, specimen not at lab within 72 hours	0.7	1.4	9.1

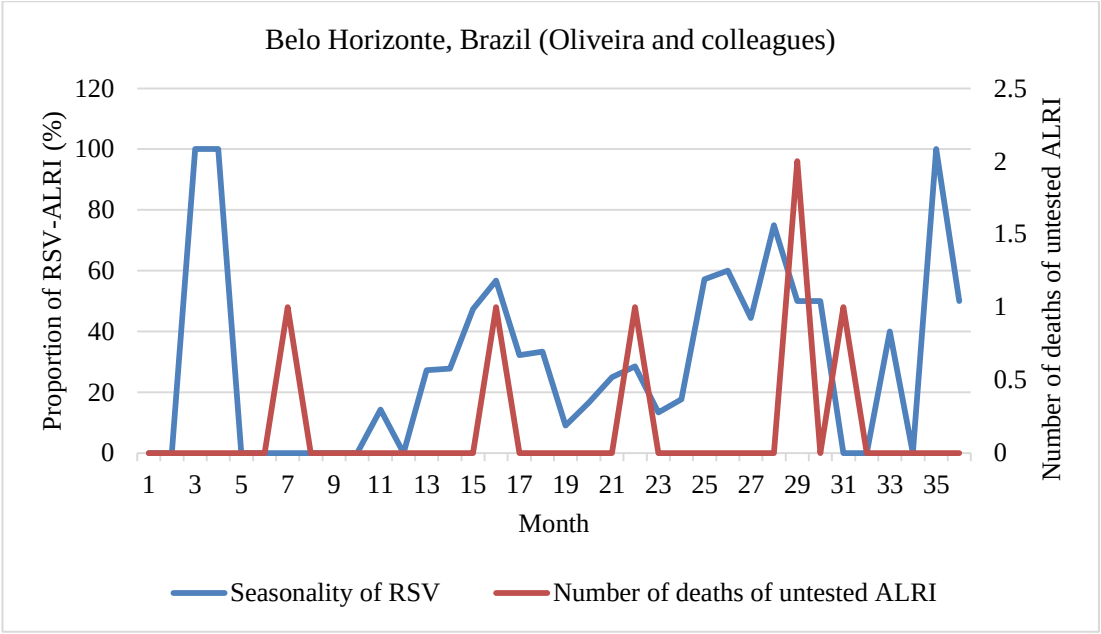
Location (reference)	% of eligible cases not tested for RSV	Reasons for not testing	CFR among hospitalised ALRI tested for RSV (%)	CFR among hospitalised ALRI not tested for RSV (%)	Prop of ALRI deaths being untested (%)
Soweto, South Africa (Madhi, unpublished)	4.6 (240/5231)	missed as part of surveillance	5.5	22.5	16.3
CEMIC, Buenos Aires, Argentina (Echavarria, unpublished)	5.3 (3/57)	insufficient sample	0.0	0.0	NA
Santa Rosa, Guatemala (McCracken, unpublished)	5.8 (104/1810)	no consent or no specimen	5.2	1.9	2.2
Basse Santa Su, Gambia (PERCH, unpublished)	7.2 (46/638)	quality control not yet complete	2.9	10.9	22.7
Bamako, Mali (PERCH, unpublished)	9.1 (61/674)	quality control not yet complete	14.5	21.3	12.7
41 sites in Netherlands (Bont, unpublished)	10.0 (24/241)	reasons for not testing are unknown, as the decisions for testing are made by independent physicians at hospital of presentation	0.0	0.0	NA
Lusaka, Zambia (PERCH, unpublished)	10.5 (65/617)	quality control not yet complete	18.1	26.2	14.5
Quetzaltenango, Guatemala (McCracken, unpublished)	10.9 (207/1893)	no consent or no specimen	2.7	0.0	0.0
Buenos Aires, Argentina (Gentile, unpublished)	12.9 (1361/10581)	NA	2.0	1.6	10.8
Paarl, South Africa (Zar, unpublished)	16.4 (21/128)	specimens were not obtained	0.9	4.8	50.0
Nakhon Phanom and Sa Kaeo, Thailand (PERCH, unpublished)	18.3 (41/224)	quality control not yet complete	1.1	2.4	33.3
Kilifi hospital study, Kenya (Nokes, unpublished)	24.4 (2817/11544)	died; discharged; refusal	5.2	32.7	67.0
Bondo district, Kenya (Feikin,	28.7 (208/726)	NA	5.2	10.1	43.8

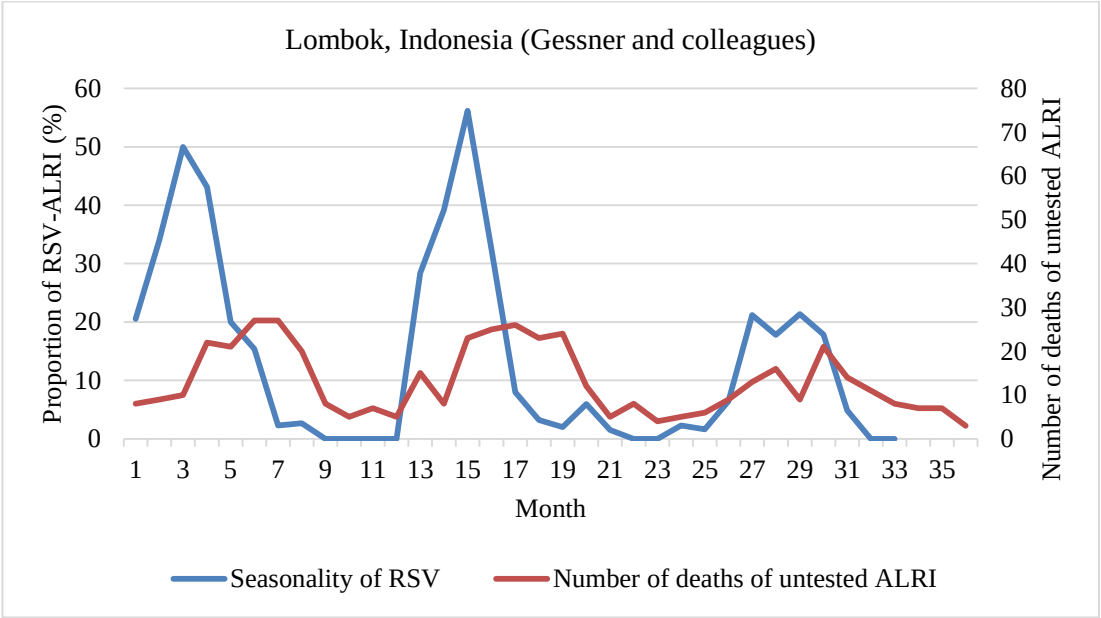
Location (reference)	% of eligible cases not tested for RSV	Reasons for not testing	CFR among hospitalised ALRI tested for RSV (%)	CFR among hospitalised ALRI not tested for RSV (%)	Prop of ALRI deaths being untested (%)
unpublished)					
Lombok, Indonesia (Gessner, unpublished)	28.9 (1500/5198)	primarily age <3 months and critical illness on presentation; specimens collected 4 days a week so if patients who had rapid admission, would not have been done	2.2	33.1	86.1
Tagbilaran and 6 rural sites, Philippines (Lucero, unpublished)	36.0 (537/1491)	no specimen collected for those cases not tested for RSV	0.5	2.2	70.6
Belo Horizonte, Brazil (Oliveira, unpublished)	59.4 (757/1275)	frozen samples at weekends; laboratory refused	1.2	1.3	62.5
Lwak, Kenya (Montgomery, unpublished)	72.4 (1231/1701)	refusal to consent; unavailability of transport from field site to lab; high patient volumes; inadequate staffing levels	3.4	2.5	66.0
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat, unpublished)	75.0 (14334/19103)	patients refused to take part in it	0.0	0.0	NA

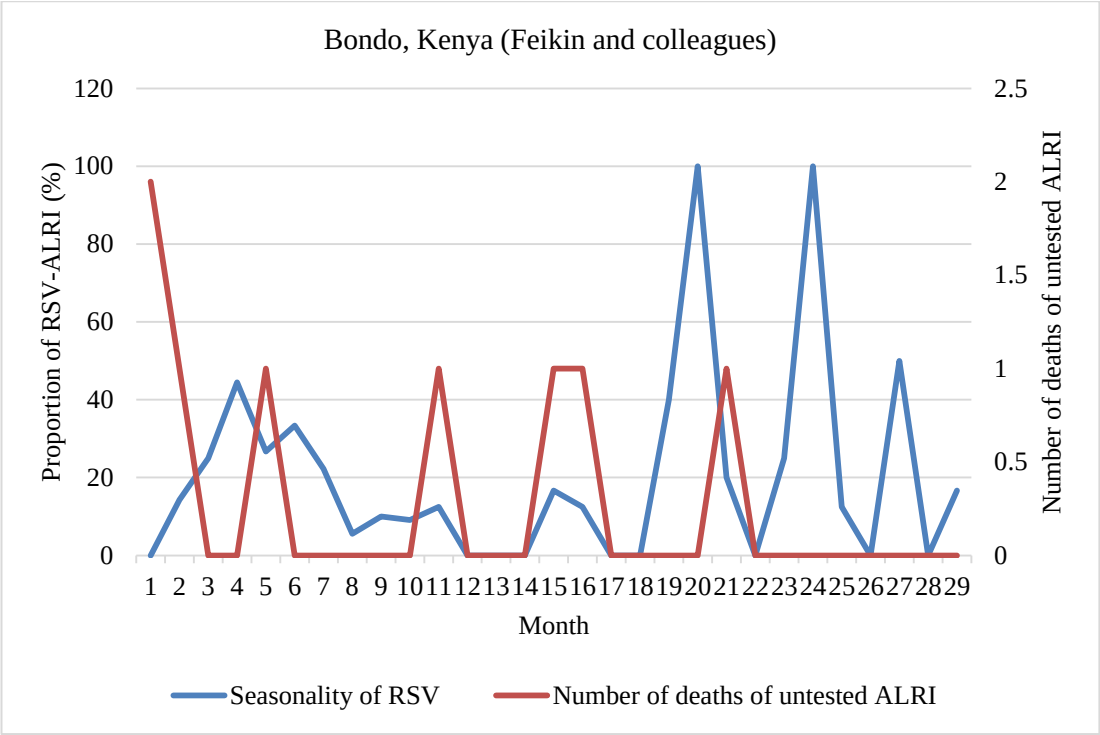
RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. CFR=case fatality ratio. NPA=nasopharyngeal aspirate. NA=not applicable.

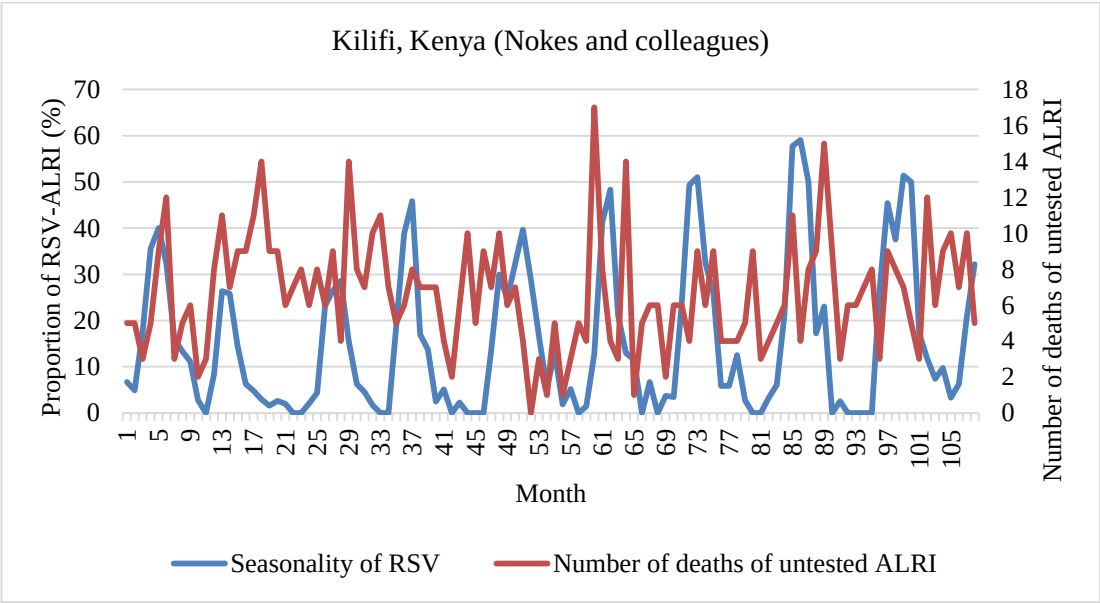

Buenos Aires, Argentina (Gentile and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

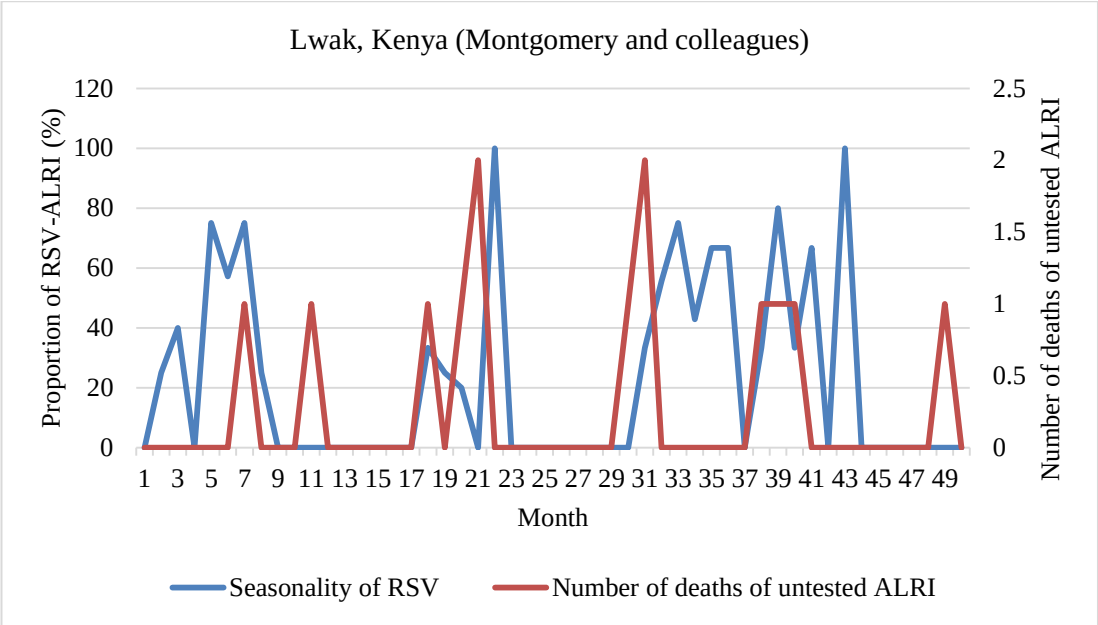

Buenos Aires, Argentina (Fernando and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

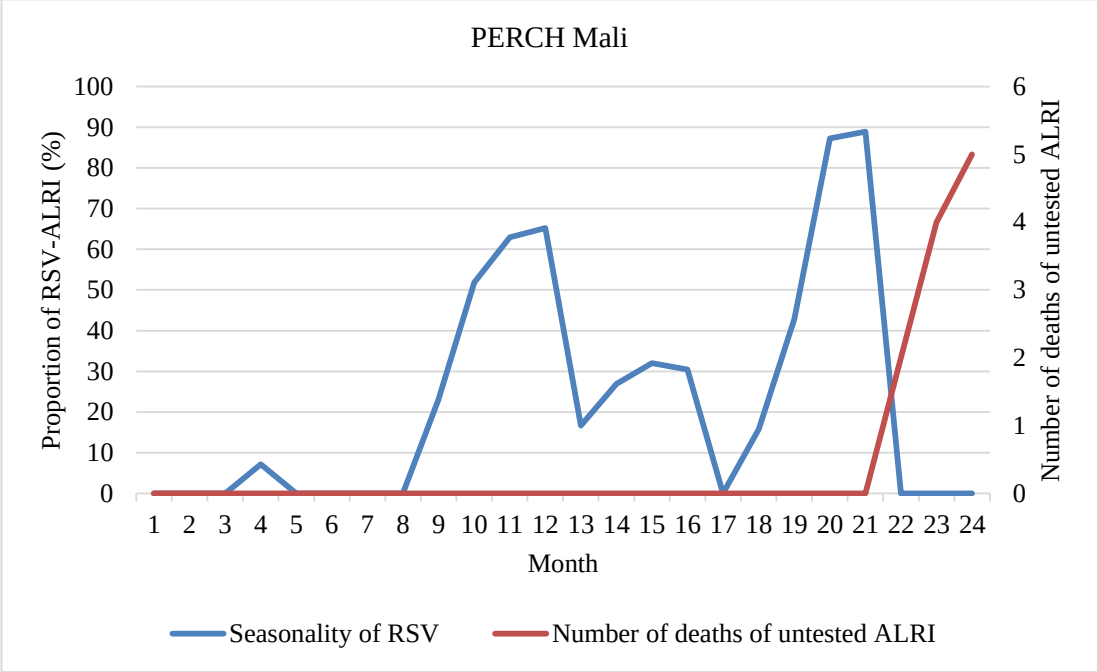

Belo Horizonte, Brazil (Oliveira and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

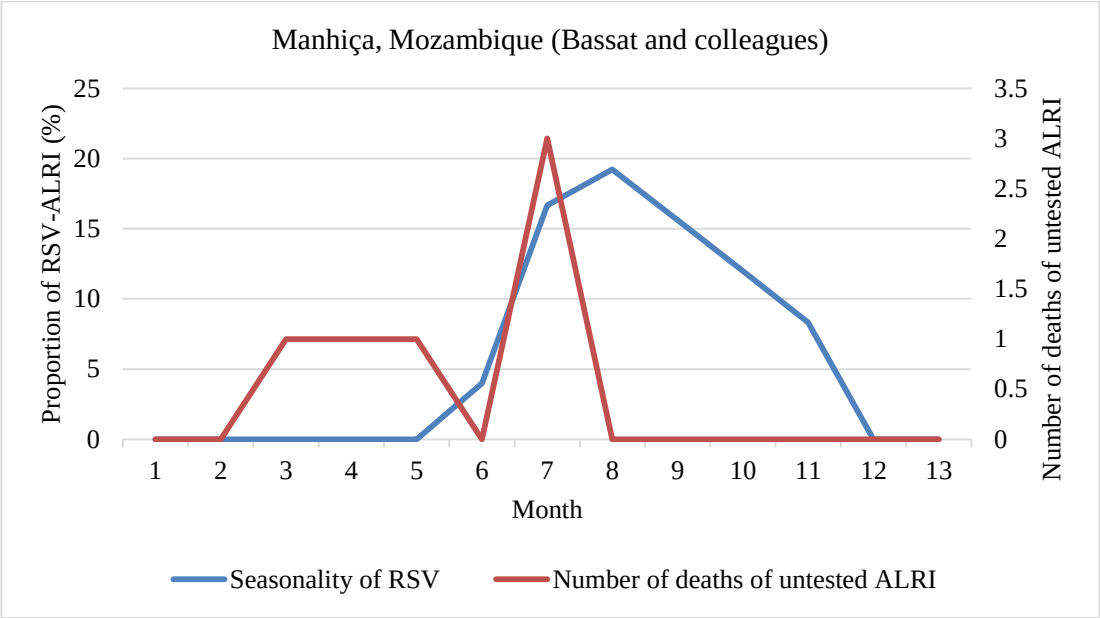

Lombok, Indonesia (Gessner and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

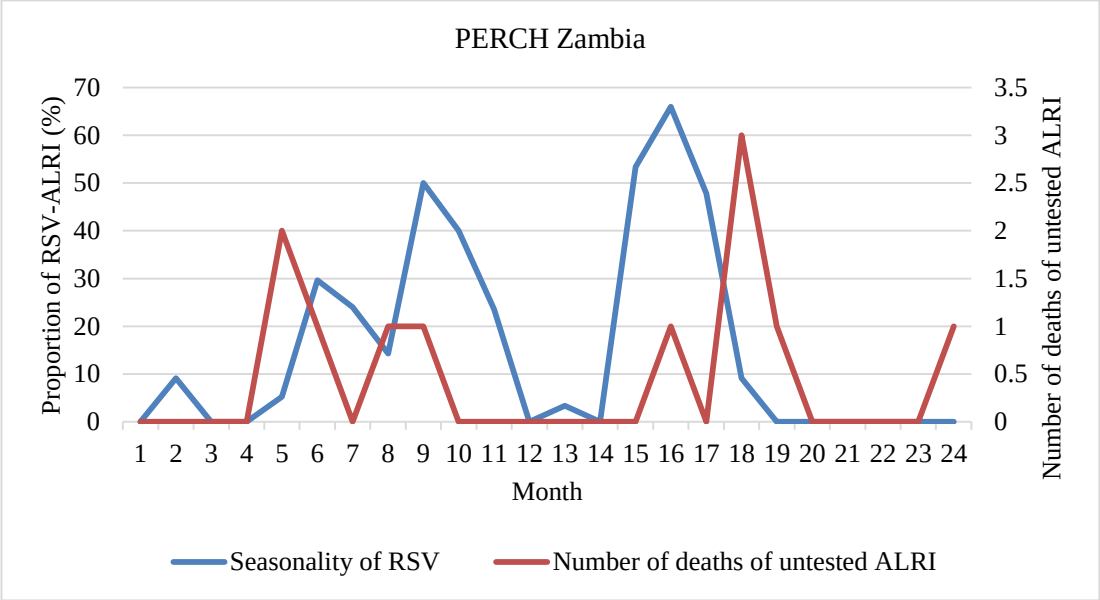

Bondo, Kenya (Feikin and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

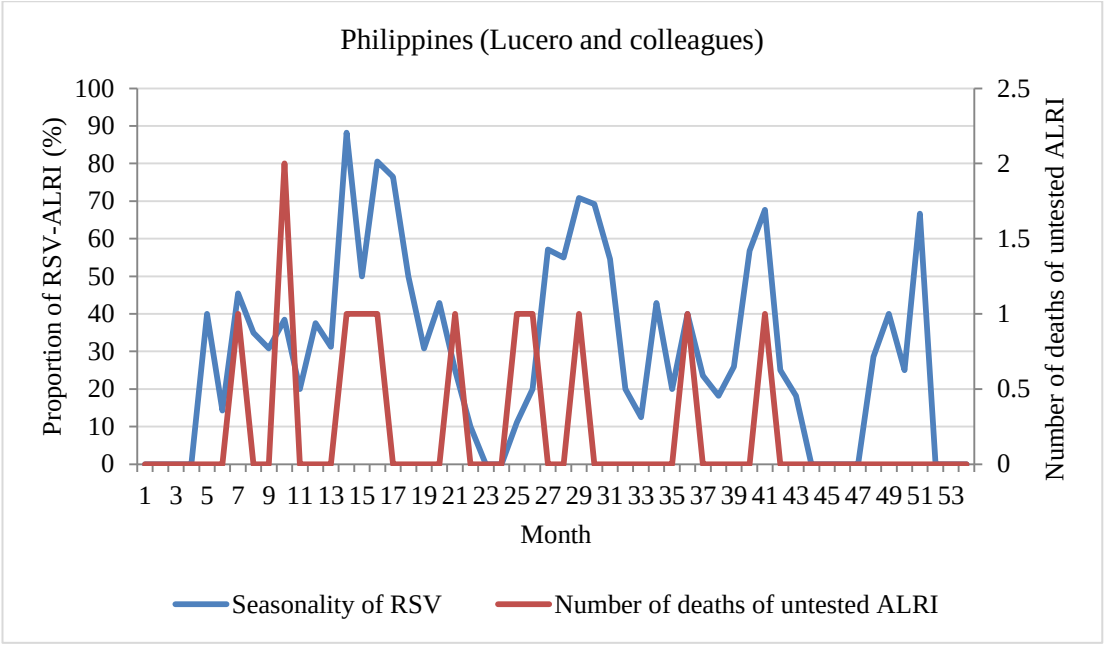

Kilifi, Kenya (Nokes and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

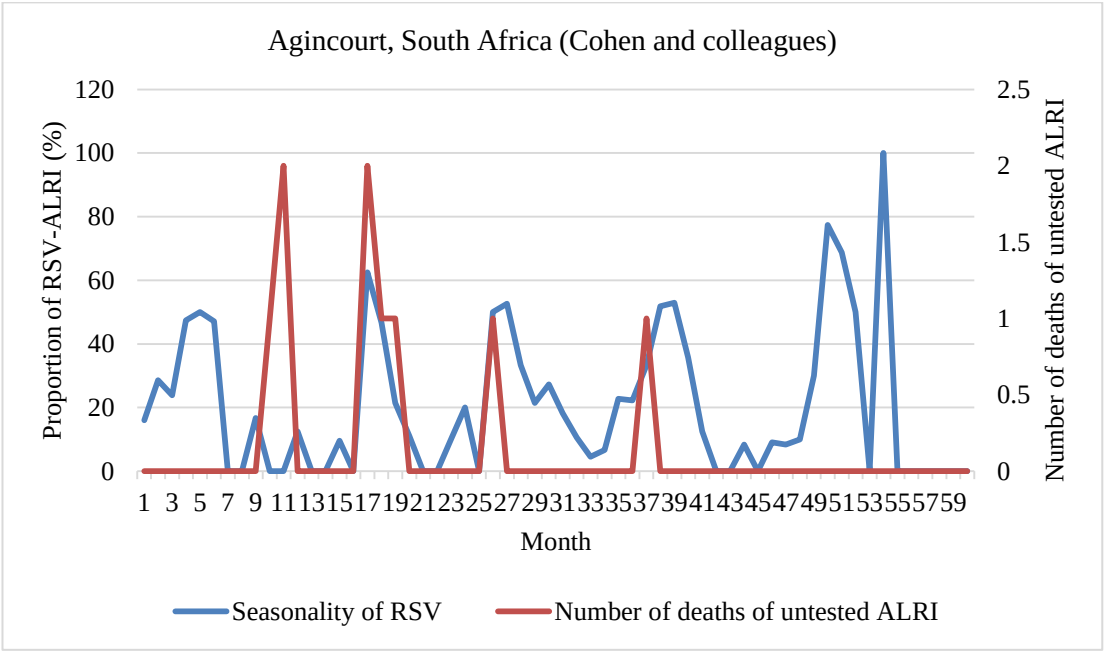

Lwak, Kenya (Montgomery and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI


PERCH Mali
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI


Manhiça, Mozambique (Bassat and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI


PERCH Zambia
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI


Philippines (Lucero and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI


Agincourt, South Africa (Cohen and colleagues)
Proportion of RSV-ALRI (%)
Number of deaths of untested ALRI
Month
Seasonality of RSV
Number of deaths of untested ALRI

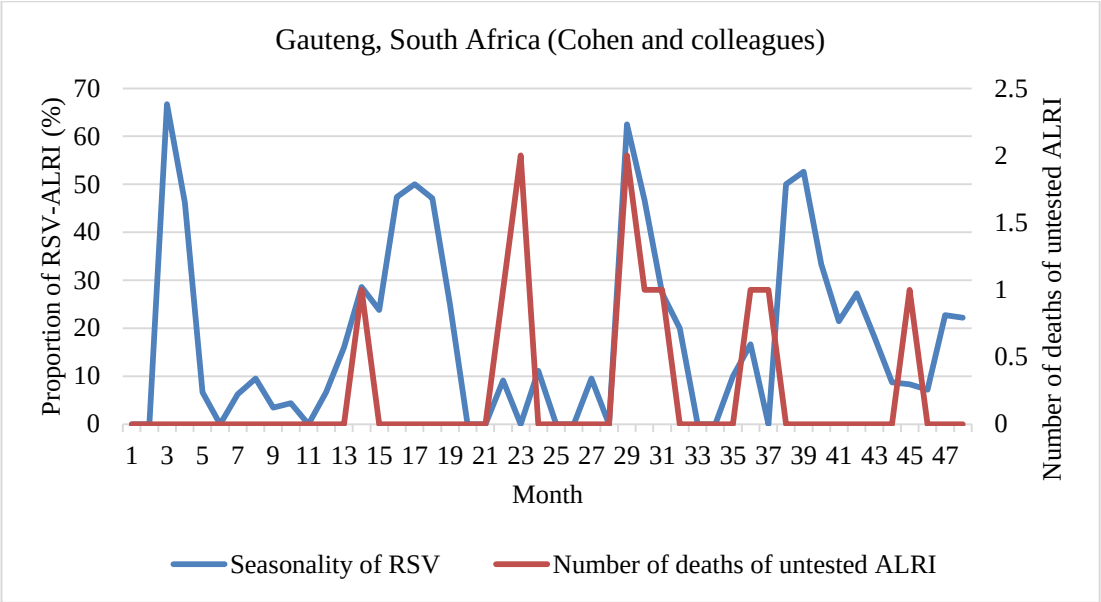


Figure 18: RSV seasonality and number of deaths of ALRI cases which were not tested for RSV among infants in several locations

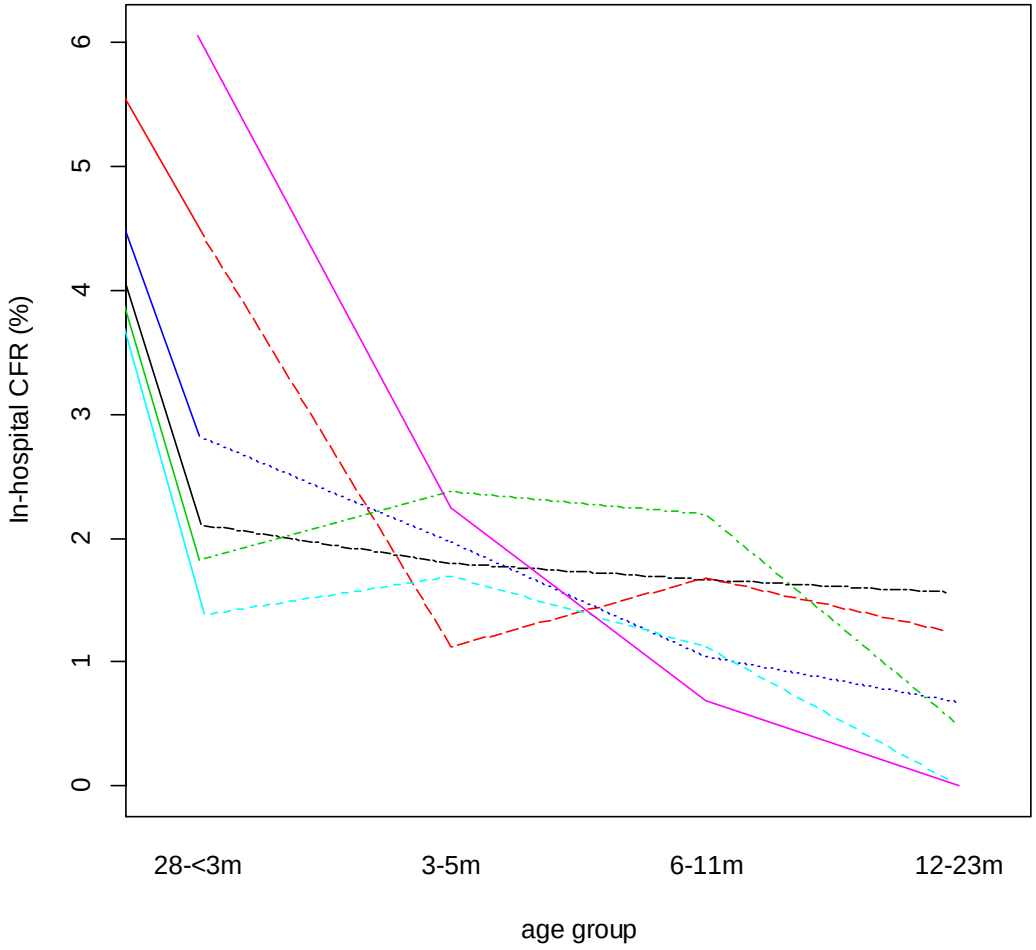


Figure 19: Spaghetti plot of in-hospital CFR by narrower age bands

Black line – Buenos Aires, Argentina (Gentile and colleagues); light green line – Buenos Aires, Argentina (Polack and colleagues); red line – Santa Rosa, Guatemala (McCracken and colleagues); rose line – Lombok, Indonesia (Gessner and colleagues); green line – Kilifi hospital study, Kenya (Nokes and colleagues); blue line – Soweto, South Africa (Madhi and colleagues).

Chapter 6 Discussion

This thesis provides a comprehensive review of the aetiological roles, risk factors, morbidity and mortality of RSV associated ALRI. It assembles epidemiological data on RSV through systematic review of literatures, national or large scale surveillance sites and cohort studies.

Aetiological role of RSV in ALRI

There were 23 studies in total identified through the literature search to investigate the viral aetiology of ALRI in young children. Strong evidence was observed for RSV in support of its causal contribution in children presenting with ALRI and the association was significant measured in the odds ratio: 9.79 (4.98-19.27). Thus, the corresponding attributable fraction among the exposed was estimated as 90% (80%-95%), which means 90% of RSV associated ALRI cases were in fact attributed to RSV in a causal path. This review has been published in Journal of Global Health (Shi et al., 2015b). This was presented in an expanded description of methods, results and critical discussion in Chapter 3.

Risk factors for RSV associated ALRI

In order to assess the roles of various risk factors for RSV associated ALRI, 27 studies (including 4 unpublished studies) were identified and contributed to the analysis. In total 18 risk factors were described and 8 were observed to have significant associations with RSV infection: prematurity - gestational age <37 weeks, low birth weight (<2.5 kg), being male, having siblings, maternal smoking, history of atopy, no breastfeeding and crowding - >7 persons in household. This review has been published in Journal of Global Health (Shi et al., 2015a). This was presented in a detailed and critical description of methods and results in Chapter 4.

Burden of RSV associated ALRI

Overall, 304 studies were included to estimate the global and regional burden of RSV associated ALRI in young children. Among them, 76 were unpublished studies provided by the RSV GEN working group, mainly from developing countries. It is estimated that in 2015, there were 33.0 (95% CI 20.6-53.2) million episodes of RSV associated ALRI occurring in children younger than 5 years old across the world. Among them, 30.5 (95% CI 19.5-47.9) million were in developing countries. 3.0 (95% CI 2.2-4.0) million cases were severe enough and warranted hospitalisation. Around 60,000 children died in hospital settings with 99% of these deaths occurring in developing countries. The overall mortality from RSV associated ALRI was estimated to be about 131,000. More details were presented in Chapter 5.

This thesis aims not only to enhance the epidemiological understanding of RSV in young children, but also to provide important information for public health decision makers. It incorporates both data through systematic reviews of published articles in the past 20 years and more than 70 unpublished data sets shared by RSV GEN working group. The population based incidence, hospitalisation, mortality and risk factor data give a good basis from which to assess the various severity of illness in a specific age group and region and inform local public health professionals regarding appropriate and prompt cases management, treatment and prevention strategies. The disproportionate age distribution in disease burden requires a long-term planning according to the change in population composition.

6.1 Strengths

6.1.1 Incorporation of unpublished data

The RSV GEN research group was formed and data from developing countries were collected, which supplemented the lack of published data in developing region. This research group involves 45 leading researchers on paediatric pneumonia from worldwide. Within the RSV GEN research group, common case definitions were formulated and a standard approach for data collection, analysis and interpretation was agreed on before data collection and the process was consistently carried out. This facilitated comparison across studies to be made. Data were verified and cross checked before being included in the analysis. Substantial data in finer age bands (neonates, children in their first six months of life, infants) were provided which made estimates in these age bands available. Most data obtained from RSV GEN had been fully or partially published recently, or related data within the same context had been previously published. This peer review process helped assure the quality of data from unpublished studies. The meta-estimate generated from unpublished studies was similar to the result from published studies: e.g. incidence rate in children aged 0-59m from developing countries is 51.2 (26.9-97.3) per 1000 children per year based on 8 unpublished studies vs. 51.2 (28.7-91.2) from 6 published studies.

6.1.2 Comprehensive approach to global and regional estimates of RSV infection in young children was adopted

This thesis represents a comprehensive study to estimate the global and regional burden of RSV associated ALRI in children younger than five years old. The following estimates are presented: the incidence rate and number of RSV associated ALRI cases in community-based settings (where active case ascertainment was applied); the rate of children admitted to hospitals and corresponding number of hospitalised cases, the proportion of deaths among hospitalised RSV associated ALRI cases, the proportion of hospitalised ALRI cases which

are RSV positive; and the community-based mortality due to RSV associated ALRI. Global burden of disease was generated from regional estimates and estimates across the full age range was summed from estimates in narrower age bands. The aetiological role of RSV (as well as several other common respiratory viruses) in ALRI was explored and its attributable fraction was reported, and this could be used to adjust estimates of ALRI cases truly attributable to RSV. According to the result, RSV was significantly more identified in young children presenting with ALRI compared to children without any respiratory symptoms (or healthy children). The meta-estimate of odds ratios was 9.8 (5.0-19.3). This means 90% of children infected with RSV associated ALRI were attributed to RSV in a causal pathway. Thus, the likely true burden of RSV associated ALRI in young children in 2015 would be about 29.7 (95% CI 18.5-47.9) million (adjusted from 33.0 (95% CI 20.6-53.2)). Risk factors of RSV associated ALRI were reported and this could be used to inform prevention strategies if the risk factors were modifiable and select interventions targeting at children who are at high risk of developing illness. While the main focus was on children under five years old, analyses limited to children in younger age groups (neonates, infants, children aged 0-5m, children aged 6-11m, and children aged 12-59m) were also presented where possible. The analysis was also carried out in different regions, such as by World Bank income level, WHO region, developing or industrialised countries.

6.2 Limitations

6.2.1 Variable quality of RSV epidemiology data

RSV GEN collaborators either reanalysed data from their already published work with standardised case definitions or shared hitherto unpublished data from ongoing studies. Therefore, a proportion of the unpublished studies were not previously subject to the peer review, which cannot ensure the quality of these unpublished data. Even though the same case definition was required during the data collection process, some variations based on specific study designs or enrolment criteria still occurred, which to some extent compromised the comparison across studies. This concern also applies to data from published articles identified through the literature search. There were several other issues which limited the quality of reported data: quality of surveillance system, scarcity of surveillance outside the hospital setting, insufficiency of diagnostic confirmation of RSV infection (not all ALRI cases were tested for RSV), and a lack of a universal definition used to define the ALRI cases. Therefore, sensitivity analyses were carried out whenever there were studies using substantially different case definitions. This was performed consistently and discussed in Chapter 5. Moreover, for study sites with pulse oximeter data reported

appropriate equipment and standardised methods to obtain pulse oximetry readings are crucial to their proper interpretation. It is also important that healthcare professionals are well trained to conduct the pulse oximetry, especially in infants and young children. Details of these aspects were not always available from studies included in this thesis. In addition, although studies reporting data for nosocomial infection (hospital acquired illness) were excluded consistently across all systematic reviews, there is still an unknown proportion of hospital associated pneumonia involved in studies to the extent that our estimates may overestimate the burden of community acquired pneumonia associated with RSV. The issues discussed above resulted in variable quality of RSV epidemiology data. Most of them existed in both unpublished studies and published articles. A standard and comprehensive quality assessment tool is needed to assess and compare the quality of data from these two sources and measure the direction and strength of the effect. However, this is expected to be very difficult since many clinical/laboratory/technical details are not always available, even in the unpublished studies. Even though the inclusion of unpublished studies and articles in other languages (Chinese and Spanish) might decrease the possibility of publication bias, there is still an unknown proportion of publication bias which might affect the representativeness and validity of this study.

6.2.2 Variation in RSV disease severity

In some developing countries, especially in rural areas, due to long distance (in length or time) from the children's home to the healthcare facility, the threshold for admission to hospitals is lower. Thus, although some of these children present with a non-severe infection, they may be hospitalised. This may mean that the severity of RSV associated ALRI admitted to hospital varies across settings and so are not completely comparable. In some settings, accessibility to healthcare facilities may be poor leading to a delay in seeking care: e.g. due to financial burden to the family, long distance and long travel time to hospital, due to poor road condition, or other cultural and social issues (Tinuade, 2010). In these settings, children may be in a more severe condition when presenting to the clinics/hospitals. Moreover, in some underprivileged areas, sometimes caregivers seek care from a non-medical provider. In these cases, there is an unknown proportion of children with severe infection which are not identified in hospitals and do not receive prompt treatment. This will tend to underestimate the burden of RSV associated ALRI cases in hospital settings.

In addition, hospitals or clinics (or even different personnel) may have different criteria to admit children which leads to a variety of severity of illness among children hospitalised with RSV. This might limit the validity of comparison between different study sites.

Variations in risk factors in the underlying population might affect the severity of RSV disease. A prospective surveillance study was carried out among children less than 2 years old admitted to hospital with respiratory infection in Amman (Halasa et al., 2015). In this study, risk factors for oxygen requirement in children with RSV positive were identified as underlying medical conditions, lack of breastfeeding, younger age, and higher viral load via a multivariable analysis. Younger age was also associated with ICU admission. Mechanical ventilation was related to younger age and higher vitamin D level. Children having underlying medical condition, lack of breastfeeding, at younger age, with lower virus load, or having a low birth weight were associated with longer length of stay in the hospital based on a multivariable analysis.

6.2.3 Variable levels of co-infection among RSV cases

Co-infection with other viruses or bacteria were mentioned in several studies reporting epidemiological data on RSV. This might tend to overestimate the individual role of RSV in ALRI. Around 6% to 30% of young children hospitalised with pneumonia or bronchiolitis with RSV positive were identified with multiple pathogens (Sparremberger et al., 2011, Jain et al., 2015, Canducci et al., 2008, Harada et al., 2013). Respiratory virus could interact with other viruses directly or indirectly, affecting the clinical presentation or the disease outcome. Children with RSV disease co-infected with other respiratory viruses might increase the risk of developing a more severe disease (Harada et al., 2013). An adjusted odds ratio of 1.3 (1.0-1.7) was detected for longer stay in hospital (3 or more days) in young children infected with both RSV and RV, compared to children only infected with RSV (Mansbach et al., 2012). Infants hospitalised with bronchiolitis with RSV and BoV positive had a higher clinical severity score and more days of hospital stay than infants infected with RSV only (Midulla et al., 2010). However, both studies were carried out for less than one year, the co-infection rate from which might be affected by seasonal variations in circulating respiratory viruses. Moreover, greater disease severity in RSV cases with multiple pathogens was not observed in other studies (Peng et al., 2009a, Martin et al., 2012). The rate of co-infection with RSV associated ALRI should be monitored and the severity of RSV disease in these cases should be evaluated in order to elucidate the association between co-infection and severity of outcome. RSV was reported to be significantly associated with an increase of hospitalisation due to pneumococcal pneumonia in infants. After the implementation of pneumococcal conjugate vaccine (PCV7), RSV hospitalisation rate has been reported to decline substantially (Weinberger et al., 2015). Further investigation is needed to clarify the role of bacterial-viral and viral-viral interactions in the pathogenesis of RSV infection.

6.3 RSV illness in adults and elderly

RSV also causes a substantial disease burden in adults and the elderly. Advances in molecular assays using nucleic acid amplification, which has high sensitivity and specificity, makes it possible to detect viruses in adults and elderly people with relatively low titres of virus load more accurately. A 15-year population based study in United Kingdom indicated that during each RSV season, there were around 500,000 general practice visits, 18,000 episodes of hospitalisation and 8,000 deaths attributable to RSV in adults aged more than 18 years (Fleming et al., 2015). Among them, 36% of GP visits, 79% of hospitalisation episodes and 93% of deaths occurred in elderly people aged more than 65 years old. This suggests that RSV also represents a substantial disease burden in adults, especially among the elderly. Another surveillance study in Tennessee also reported a substantial RSV disease in adults in terms of emergency department visits and hospital stays (Widmer et al., 2014). Both of these were higher in adults more than 50 years old, compared to adults aged 18-49 years. Moreover, adults hospitalised with RSV disease can develop severe respiratory complications, such as respiratory failure, requirement of supplemental oxygen and mechanical ventilation, prolonged hospitalisation and high mortality, similar to adults infected with influenza (Lee et al., 2013). This evidence basis requires that RSV prevention and management strategies as well as clinical trials of antivirals and vaccines should take this underlying population into consideration.

6.4 Issues in conducting meta-analysis of data

Conducting meta-analysis based on a fixed effect model at first and then moving to a random effects model if statistically significant heterogeneity is identified across the included studies is technically incorrect. The selection of a computational model should not be based on the statistical test for heterogeneity, but it should focus on the nature of underlying data. If these studies are not functionally identical and differ in several aspects that might have an influence on the results, the effect size is likely to vary from one study to another (within the full set of studies, within subgroups, or for studies with a common set of covariate values), then the random effects model which takes study level variance into consideration should be used even if the test for heterogeneity fails to yield a significant p-value. This lack of significance means only that a certain threshold of proof is failed to meet. It is possibly because of low statistical power and does not prove that the studies share a common effect size.

In the previous three Chapters where systematic reviews were carried out to identify relevant published articles reporting data of interest, differences in methodology and population at

risk were expected and found. Thus, different effect sizes were assumed across these studies and so, random effects model was applied consistently in these three systematic reviews to synthesise results from different studies. The meta-analyses results based on random effects model can then in principle be generalised to a wider population.

When there is a small number of studies included in a meta-analysis and the underlying effects differ across studies, the random effects model is still the proper model to use but the estimate of between-study variance will have poor precision (Borenstein et al., 2009). In this case, there are several other approaches available: an individual effect from each study can be reported instead; a fixed-effect analysis can be used to generate a descriptive result of included studies but it cannot be generalisable to other populations; or a Bayesian approach to estimate the between-study variation from outside data can be used. The third option is in theory the best approach but it is a complex statistical method requiring a special expertise in Bayesian meta-analysis. Therefore, it was decided meta-analyses were conducted only if there were at least three studies and this approach was applied consistently throughout this thesis.

6.5 Implications for the management of RSV disease in young children

Protecting infants from RSV infections is a high public health priority based on the evidence generated from this thesis. Understanding RSV incidence and mortality across different regions and children at different age bands could place a rational basis for health care providers to implement prompt and proper prevention strategies in order to minimise transmission, and also to introduce prophylactic options or supportive treatments (hydration and oxygenation) to high-risk patients as early as possible. There is no effective specific antiviral treatment available to manage RSV infection at present. Therefore, RSV prevention strategy remains the only option.

A few antivirals for RSV are being investigated in clinical trials. Passive immune-prophylaxis with RSV specific monoclonal antibody can be administered to high-risk infants to prevent severe disease outcome during RSV season. Palivizumab, a humanised monoclonal antibody targeting at the RSV fusion F protein, was licensed in 1998 by Food and Drug Administration (FDA) for immune-prophylaxis in high-risk infants. A phase 3 clinical trial involving multiple centres and countries was conducted to evaluate the safety and effectiveness of palivizumab to prevent RSV infection in children at high risk. This RSV trial indicated that a reduction of 55% hospitalisation with confirmed RSV infection was observed in children with prematurity (≤35 weeks) or bronchopulmonary dysplasia (BPD)

after receiving palivizumab prophylaxis, in comparison to children in the placebo arm (The IMpact-RSV Study Group, 1998). It was well tolerated without any significantly different adverse events compared to the placebo group. Since then, the guidance to use palivizumab has been updated periodically based on the emerging new evidence. However, it is expensive and limited in a few high-resource country settings. Another variant of palivizumab, motavizumab, has been discontinued in spite of its higher neutralising activity, possibly because the incidence of cutaneous adverse events was observed higher in the recipients and RSV viral load or severity of illness were not decreased in the previously healthy term infants with motavizumab treatment (Carbonell-Estrany et al., 2010, Ramilo et al., 2014). However, another randomised double-blind phase 3 study in healthy term Native American infants showed a relative 87% of reduction in the proportion of infants admitted to hospital with RSV positive who received motavizumab, compared to the participants in the placebo group (O'Brien et al., 2015). Serious adverse events were also reduced. The safety and efficacy of motavizumab need to be confirmed with further investigations.

The UK National Institute for Health and Care Excellence (NICE) recommends a few new guidelines to manage bronchiolitis in children based on the best available evidence (Ricci et al., 2015). Since RSV is the most common virus associated with bronchiolitis (Meissner, 2016), these guidelines also apply in managing RSV cases. When children present with apnoea, severe respiratory distress, central cyanosis, are hypoxemic (SaO_2 <92%), or appear seriously unwell to a healthcare professional, they should be referred for emergency hospital care immediately; if children have tachypnea (respiratory rate >60 breaths/min), difficulty in breastfeeding, <75% of usual volume of oral fluid intake, or clinical dehydration, they should be referred to secondary care (Ricci et al., 2015). Apart from these clinical features, a few issues should be taken into account for more severe bronchiolitis: children with underlying risk factors (such as chronic lung disease, young age, prematurity, immunodeficiency etc.) and the ability of care-givers to look after the children (such as social economic situation, capability to recognise key symptoms showing disease deterioration, distance from home to nearest health facility etc.). Chest radiography should not be conducted as a routine. Oxygen supplementation should be provided if the children presents with hypoxemia consistently (SaO_2 <92%). Fluids via nasogastric or orogastric tube should be supplied to children if taking fluid orally is not enough for them. Upper airway suctioning might be needed if there are signs of upper airway secretions or if children present with apnoea. There are slight variations in the guidelines to manage bronchiolitis developed in different institution bodies. The differences were summarised in an article and presented in Table 64 (Mazur et al., 2015).

According to the result of this thesis, RSV disease burden is substantial in children in their early months of life, such as infants aged 0-5 months, therefore, a considerable attention should be given to this age group to identify key features indicating varied disease severity and refer them to relevant settings for appropriate treatment. Proper and prompt management of RSV disease in young children could mitigate the progress of RSV associated ALRI in children, and decrease the childhood morbidity and mortality related to this illness. They also enable current available medical resources to be used efficiently, especially in resource-limited areas.

Table 64: Evidence-based global guidelines for bronchiolitis management in children (Mazur et al., 2015)

	Recommended	**Not recommended**
American Academy of Pediatrics, 2014 (Ralston et al., 2014)	Supplemental oxygen optional if SpO2 is greater than 90%, nebulised hypertonic saline optional for hospitalised children with expected length of stay longer than 72 h, nasogastric or intravenous fluids if oral hydration cannot be maintained	Albuterol, epinephrine, nebulised hypertonic saline in emergency department, systemic corticosteroids, antibacterial medicine (unless concomitant bacterial infection), chest physiotherapy, continuous pulse oximetry
Royal Australian College of General Practitioners, 2008 (Turner et al., 2008)	Supplemental oxygen, saline nasal drops, nasal suctioning, comfortable positioning (prone or supine if unable to position self), continuous pulse oximetry monitoring if in prone position, oral feeding can continue unless respiratory distress increases, trial of β2 agonist bronchodilators for children older than 9 months (discontinue if no response), antibiotics if clinical signs or symptoms of bacterial infection, paracetamol or ibuprofen can be used if pyrexia is present	Chest physiotherapy, routine mist, routine steam, routine nebulised saline, routine nebulised adrenaline, routine β2 agonist bronchodilators, routine ipratropium bromide, routine antibiotics, routine corticosteroids, routine ribavirin, routine immunoglobulin, routine oral antitussives, oral expectorants or oral decongestants
Scottish Intercollegiate Guidelines Network, 2006 (Scottish Intercollegiate Guidelines Network, 2006)	Supplemental oxygen if SpO2 is less than 92% or if severe respiratory distress or cyanosis, nasogastric feeding if child cannot maintain hydration or oral intake, nasal suction for hospitalised infants showing respiratory distress, pulse oximetry 8 to 12 h after supplementary oxygen is discontinued	Nebulised ribavirin, antibiotic therapy, inhaled β2 agonist bronchodilators, nebulised ipratropium or epinephrine, inhaled or oral corticosteroids, chest physiotherapy
NICE, 2015 (National Institute for Health and Care Excellence, 2015)	Supplemental oxygen if SpO2 is less than 92%, continuous positive airway pressure if impending respiratory failure, upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions or children who present with apnoea, fluids by nasogastric or orogastric tube if children cannot take fluid	Chest physiotherapy for children who do not have relevant comorbidities, antibiotics, hypertonic saline, nebulised adrenaline, salbutamol, montelukast, ipratropium bromide, systemic or inhaled corticosteroids and nebulised adrenaline, routine upper airway suctioning, routine

	orally, intravenous isotonic fluids to children who do not tolerate nasogastric or orogastric fluids or have impending respiratory failure, consider capillary blood case testing in children with severe worsening respiratory distress or impending respiratory failure	blood gas testing gas testing

Footnote: Peripheral capillary oxygen saturation=SpO_2. Guidelines included are either accepted on a national level (not hospital based) and apply a clearly defined evidence-based framework to recommendations.

6.6 Implications for vaccination policies and allocation strategies

Despite the high disease burden of RSV among young children, currently there is no licensed RSV vaccine available. This leaves children at risk of getting infected and causes a huge burden to caregivers and healthcare systems, especially in developing areas where there are limited resources and a disproportionately high burden of disease. Prophylactic treatment with RSV specific monoclonal antibody is effective in reducing RSV infection in children at high-risk, such as premature children, children with congenital heart illness or chronic lung disease. However, this is only available in selected populations in a few countries due to its high expense and challenges in delivery. Developing a vaccine against RSV becomes critical to mitigate this situation. A disproportionately high burden of RSV disease in young infants has been reported in this thesis: around 5.5 million infants aged 0-5 months of RSV associated ALRI were estimated in the worldwide in 2015 (about 17% of all under five cases). Among them, nearly 1.4 million were severe enough requiring hospital admission (about 48% of all under five cases admitted to hospital), and around 27,000 of them died in hospital (46% of all under five deaths due to RSV associated ALRI). Since RSV incidence is highest in children in the earliest months of life, the development of RSV vaccine has been advanced to focus on this age group, aiming to prevent serious outcome after RSV infection as early as possible in childhood.

Laboratory experiments are instrumental in discovering new potential vaccines. They are helpful in interpreting the immune response in recipients and mechanisms of how new vaccine candidates function as well as identifying their potential adverse events. However, the in vitro and animal models cannot fully mimic the reaction in humans.

There are a variety of vaccine constructs in development currently, such as live-attenuated vaccines, whole-inactivated, particle-based, subunit-based, gene-based vectors and nuclei acid-based vaccines (Figure 20). Several vaccine candidates are being tested in humans at different phases. Different types of vaccine have their specific advantages and target on different populations (infants less than 6 months, older children older than 6 months, pregnant women and elderly people aged 65 years or more). Live vaccines could be used in

older siblings to protect them from RSV infection and to reduce the transmission of RSV to the youngest and most vulnerable infants. This approach is supported by an individual-based transmission model carried out in rural Kenya. This study indicates that 39% of infant infections was attributed to household transmission and children at school-age were the main agents in introducing the infection into the family units and led to around 55% of cases within household (Poletti et al., 2015). Moreover, the decreased level of maternally derived antibodies and the more mature immune system make older children more likely to respond well to the vaccine.

Active immunisation of young infants would be an ideal option to prevent RSV infection in young children but it poses a few challenges to implement. This is because the youngest age groups have the highest susceptibility to RSV infection. However, there is a history of vaccine-enhanced illness with RSV infection leading to more severe outcomes including two deaths in infants after receiving a formalin-inactivated RSV (FI-RSV) vaccine in the 1966-1969 (Kim et al., 1969). This tragedy slowed down efforts to produce RSV vaccines over the past 5 decades. Directly vaccinating infants requires RSV vaccine constructs with an optimal balance of safety and efficacy. Live-attenuated vaccines are mainly targeted to the paediatric population with the aim of safely attenuating RSV virus and inducing maximum immunogenicity. A number of such vaccines are in early clinical testing. Subunit vaccines are an alternative option without possibility of reversing to wild-type but they result in lower immunogenicity in young children. They are more widely designed for maternal immunisation. Paediatric immunisation has several limitations: potential risk of enhanced illness; poor immunogenicity due to immature infant immune system; reduced immunogenicity induced by subunit vaccines; and decreased effectiveness due to interfered by maternally derived antibodies (Mazur et al., 2015, Anderson et al., 2013).

Maternal immunization is an alternative approach which can provide immediate protection for infants at the early stage, approximately for the first six months. This is a promising approach to protect those vulnerable children promptly from birth. RSV specific neutralising monoclonal antibody delivered prophylactically to children has been observed to reduce the incidence of severe RSV disease. The preventive impact of antibody to RSV infection has been confirmed. It has been reported that administering vaccines to pregnant women and boosting the RSV antibody concentrations to a sufficiently protective level facilitates mother-to-child transmission of antibodies, which is critical for newborns since they are unlikely to benefit from active immunization. In a mother-infant pairs study in Bangladesh, RSV-specific IgG placental transfer from pregnant women to infants was shown to be an efficient process resulting in lower risk of serologic infection (Chu et al., 2014). A hospital-

based case-control study among Navajo and White Mountain Apache infants has shown a 30% reduction of hospitalisation with RSV infection with an increase of 1 $\log_2$ in the concentration of cord blood maternally derived RSV neutralising antibodies (Eick et al., 2008), but no association was observed for the severity of illness. Moreover, prevention of RSV infection in the pregnant women also reduces the chance of transmitting the infection from mothers to vulnerable young children. Maternal vaccine should meet high standards of tolerability and safety. Such vaccines that are currently in late stages of clinical trials are particle-based or subunit-based (Neuzil, 2016). One candidate is going through phase 3 testing in third-trimester pregnant women: a RSV recombinant fusion (F) nanoparticle vaccine (National Institutes of Health, 2016). It was previously tested in phase 2 for safety and immunogenicity in healthy women of childbearing age (18-35 years) (Glenn et al., 2016). The result showed that this vaccine was well and immunogenic, and no vaccine-related adverse events were observed. Therefore, it is anticipated that immunogenicity will be reproduced in third trimester pregnant women after receiving this vaccine and these women can confer protective high levels of antibodies to their infants through placental transfer. Furthermore, platform to deliver a maternal tolerated vaccine has been established worldwide. In the majority of countries including those underprivileged areas, women have access to some antenatal health care. Maternal immunisation to protect infants has been successful in the cases of tetanus, pertussis and influenza, which suggests that maternal vaccine in against of RSV infection in infants might be a feasible approach. However, there also remains a few challenges: limitation of placental transfer, need of high titre of neutralising antibody level, limited half-life of antibody, safety in pregnant women, and the fact that having previously experienced several episodes of infection might compromise the response to vaccines (Mazur et al., 2015).

The first WHO RSV vaccine consultation agreed on two strategic goals for developing global-use RSV preventive vaccines: maternal immunisation (passive) to prevent RSV infection in infants in their first 6 months of life; and paediatric immunisation to prevent RSV illness in infants and young children after the maternal immunisation stops protecting them (Modjarrad et al., 2016). Some data from this thesis (global and regional burden of RSV associated ALRI) were made available to WHO at this meeting and helped inform discussions. In order to guarantee the quality, safety and efficacy of vaccines, several other issues need to be taken into account in the clinical trials: a well-defined targeted population; agreement on the most relevant clinical outcomes; standard and precise measures of disease severity; applicable and relevant endpoints of vaccine efficacy depending on the culture context; and objective case definition. In addition, the following aspects are also important:

paediatric vaccine testing first in healthy adults for safety and immunogenicity; phase 1 trials which involve RSV-seronegative infants in settings with good resources and facilities in case of any adverse events; monitoring of safety and immunogenicity when the novel vaccine is administered with routine vaccines in infants; follow up of infants for the first 6 months as long as the antibody persists or to an extended period (second RSV season) to detect unexpected adverse events occurred in later life or assess long-term wheezing; post-trial availability of vaccines is required before the onset of the trial; clinical vaccine development should consider the context of low and middle income countries where there is a disproportionately high burden of RSV disease (Modjarrad et al., 2016).

There are many pharmaceutical companies and academic institutions working on developing and testing RSV vaccine candidates. Local governments should work with them in improving safety, efficacy and feasibility of vaccines based on population specific information. The WHO Product Development for Vaccines Advisory Committee (PDVAC) has reported that it expects that safe and effective RSV vaccine will be available for global use in the short to medium term. The data presented in this thesis should be evidence basis for future vaccine allocation and prioritisation.

RSV Vaccine Snapshot

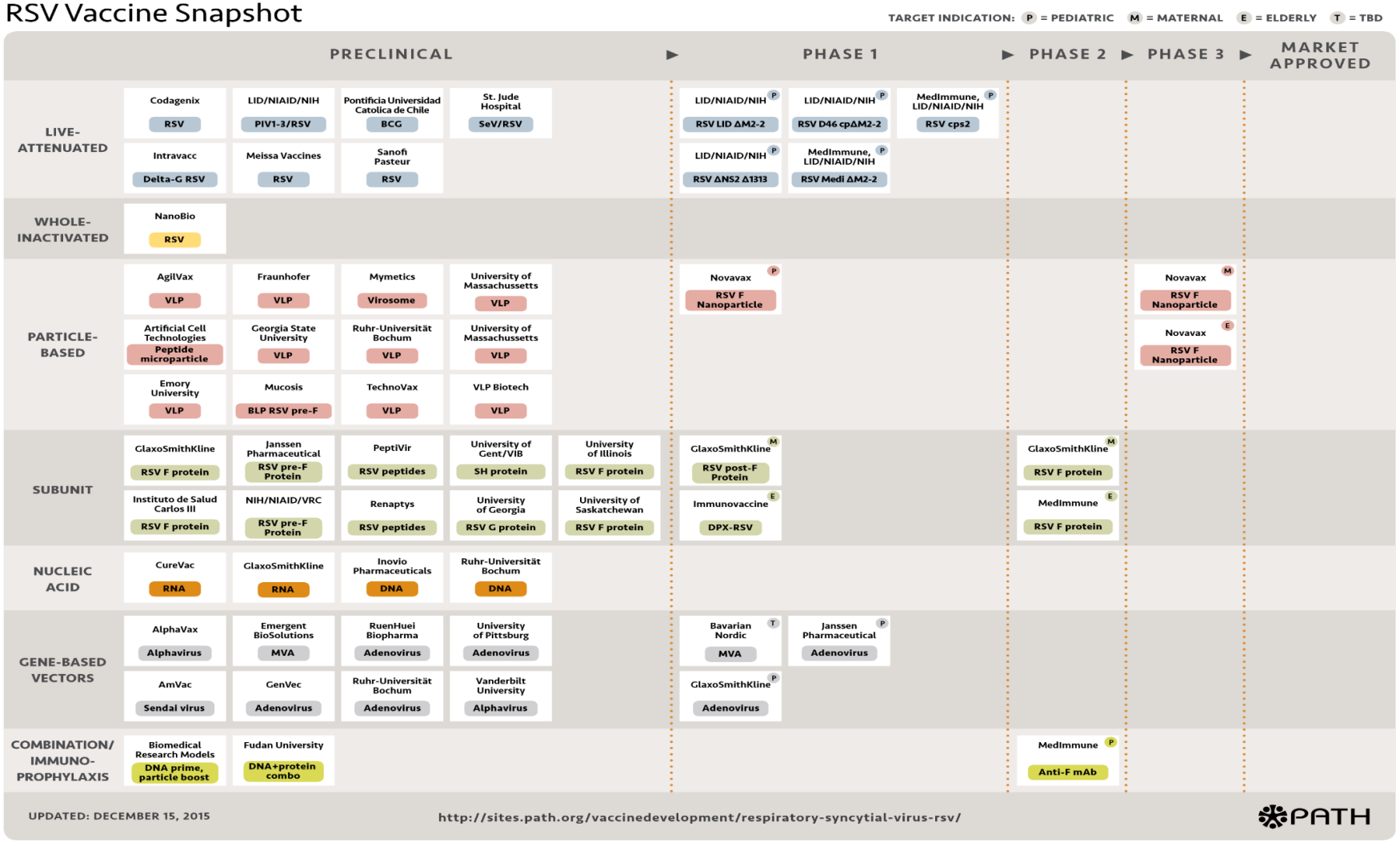


Figure 20: RSV vaccine snapshot (PATH, 2016)

6.7 Proposals for improving future RSV disease estimates in young children

National sentinel systems of RSV surveillance gathering structured and reasonably representative data is needed, especially in some developing countries where there is still a lack of population based data (e.g. Eastern Mediterranean). These data are essential for clinical workers to optimise the management and prevention of RSV disease. They also provide principles for national policy makers and immunisation advisory groups to guide future priority setting of immunisation. There are several approaches available to establish an ongoing surveillance system for RSV (Campbell et al., 2015). Global Influenza Surveillance and Reporting System (GISRS) has been established to collect complete data on influenza from over 140 National Influenza Centres (NICs) worldwide with quality and timeliness, in order to inform the composition of the annual influenza vaccine and prepare for pandemics. More than 1 million respiratory samples each year are shared within GISRS to detect influenza. This system might be adapted to conduct RSV surveillance without compromising its original purpose. However, considering the different seasonal pattern of RSV, different age structure of illness (mainly in the first two years of life) and different clinical features of RSV cases, separate case definitions and sampling procedures should be modified to identify episodes of ALRI cases due to RSV. These pose challenges to set up RSV surveillance within GISRS in parallel to influenza surveillance. Therefore, it is better to assess the validity and feasibility of this approach in a few pilot projects in each global region. The Flu Informed Decisions (FLuID) is a global web-based platform for national focal points to share the epidemiological data of influenza (World Health Organization, 2016a). It combines these data into one single global database and keeps tracking data on the evolution and trend of influenza in order to make informed decisions. A related tool, FluNet, is used to collect influenza virological data globally and monitors the movement of influenza (World Health Organization, 2016b). These two platforms could in principle be used as a basis to build the RSV surveillance system. It will need support from RSV reference laboratories to assure the quality of the data from participating laboratories. In high-resource countries, a new surveillance system can be set up. However, it requires very substantial additional financial and technical support which would need to be introduced in a stepwise manner. An RSV Task Force conducted a five-season surveillance of RSV in 6 countries within European Influenza Surveillance Scheme (EISS) and concluded that a comprehensive RSV surveillance scheme within the EISS framework was feasible (Meerhoff et al., 2009a). All of the approaches mentioned above need to be accompanied by further new large-scale cohort studies which could help to better understand the epidemiology of RSV.

There were several limitations of current studies estimating RSV disease burden as discussed previously: a lack of universal case definition, various diagnostic tests with varied sensitivity and specificity, differed quality of surveillance system, a shortage of surveillance outside hospitals etc. Therefore, establishing an active surveillance or facilitated passive surveillance of RSV activity and its long-term consequences are essential to understand the trend, magnitude and impact of RSV. Within the surveillance system, a universal definition regarding various settings and disease severity should be developed, and diagnostic methods with higher sensitivity and specificity should be applied. This is instrumental for defining target population for RSV prevention and therapeutics.

Chapter 7 Conclusion

This thesis presents an overall picture of epidemiology of RSV associated ALRI in young children from the following aspects: aetiological roles of RSV and other common viruses in ALRI, risk factors of RSV associated ALRI, incidence and mortality of RSV associated ALRI in community and hospital settings. It incorporates data from systematic literature search of publications in the last 20 years and 76 unpublished datasets from RSV GEN working group.

It supports RSV (as well as IFV, PIV, MPV and RV) as important causes of ALRI in young children, and provides quantitative estimates of the absolute proportion of virus-associated ALRI cases to which a viral cause can be attributed. This is used to adjust for global and regional burden of RSV associated ALRI in young children.

It also assesses the role of putative socio-demographic risk factors for RSV associated ALRI. Many of these risk factors are similar to those that have been identified for (all cause) ALRI and thus, in addition to the potential future impact of novel RSV vaccines currently under development and evaluation, national action against ALRI risk factors as part of national control programmes can be expected to reduce burden of disease from RSV. Since some risk factors are preventable, policy makers and public health practitioners could develop targeted interventions to decrease the prevalence of these risk factors in order to reduce RSV associated ALRI disease burden. However, this evidence base is limited by paucity of data. Therefore, large scale, high quality studies using multivariable analysis should be conducted on a priority basis to better understand the role of each individual risk factor for RSV associated ALRI in diverse settings.

Moreover, this thesis provides comprehensive revised global and regional estimates of RSV associated ALRI in both community and hospital settings. More studies than in previous published estimates were identified for younger age group, especially in infants and neonates. It reports that RSV is a major cause of childhood ALRI, resulting in substantial hospital admission and mortality among young children, especially in developing countries and in children's early months of life. This study will provide important baseline estimates to inform RSV prevention and treatment strategies as well as future vaccine priorities and plans. Objective and clear clinical and laboratory endpoints should be well-defined, established and applied consistently. More active and facilitated passive RSV surveillance sites with good quality data informing RSV incidence and mortality are required to obtain a more accurate estimate of RSV disease burden to better inform policymaking.

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Appendices

A1. RSV data collection template

Sheet 1 – site description

S. No	
Location of study site (including district, state, and country)	
Site characteristics (rural, urban etc.)	
Study period	
Age group under study	
Case ascertainment (Active community based / Passive Hospital based)	
Case definition used for ALRI	
Case definition used for SEVERE ALRI	
Case definition used for VERY SEVERE ALRI	
Case definition for hypoxemia (in case you used this as a criterion to define severe ALRI)	
Clinical specimens	
Diagnostic test	
Manufacturer	
Sensitivity	
Specificity	
Diagnostic testing done onsite or off site?	
Average time lag between specimen collection and diagnostic testing	
Population denominator - midyear catchment population / child years at risk	Source of data
	Year
	0-27 days
	28 days-<3 months
	3-5 months
	6-8 months
	9-11 months
	0-11 months
	12-23 months
	24-35 months
	36-59 months
	12-59 months
	24-59 months
	0-59 months
Scaling- denominator	Whether population has been scaled to adjust for health

	care utilization?
	If yes, what is the scaling factor used. Please provide detailed calculations separately
Malaria	Is the location endemic for malaria
	Which months of the year are malaria season
Paediatric HIV prevalence (0-4 years)	
Any special groups excluded (premature babies / those with co-morbidities)	
Month and year when HiB vaccine introduced	
Hib coverage	
Month and year when PCV introduced	
PCV coverage	
Results from reported study previously published? Please provide reference	

Sheet 2 – RSV incidence

Year			
Number & % of cases not tested for RSV			
Reason for not testing (please provide in text below table if space is inadequate)			
Number of laboratory confirmed cases (unscaled)	RSV associated ALRI	RSV A	0-27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			11-59 months
			24-59 months
			0-59 months
		RSV B	0-27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months

			36-59 months
			11-59 months
			24-59 months
			0-59 months
		All RSV (including un-subtyped RSV)	0-27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			11-59 months
			24-59 months
			0-59 months
	RSV associated severe ALRI	RSV A	0-<27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			12-59 months
			24-59 months
			0-59 months
		RSV B	0-<27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months

			12-59 months
			24-59 months
			0-59 months
		All RSV (including un-subtyped RSV)	0-<27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			12-59 months
			24-59 months
			0-59 months
	RSV associated very severe ALRI	RSV A	0-<27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			12-59 months
			24-59 months
			0-59 months
		RSV B	0-<27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			12-59 months

			24-59 months
			0-59 months
		All RSV (including un-subtyped RSV)	0-<27 days
			28 days-<3 months
			3-5 months
			6-8 months
			9-11 months
			0-11 months
			12-23 months
			24-35 months
			36-59 months
			12-59 months
			24-59 months
			0-59 months

Sheet 3 – gender analysis

Year	Age group	Midyear population / period at risk (males)	Midyear population / period at risk (females)	Whether population has been scaled to adjust for health care utilization?	If yes, what is the scaling factor used. Please provide detailed calculations separately	No. of ALRI admissions (males)	No. of ALRI admissions (females)	No. of RSV-associated ALRI admissions (males)	No. of RSV-associated ALRI admissions (females)	No. of ALRI admissions where clinical specimens were tested for RSV (males)	No. of ALRI admissions where clinical specimens were tested for RSV (females)	No. of in-hospital deaths in RSV-associated ALRI cases (males)	No. of in-hospital deaths in RSV-associated ALRI cases (females)
	0-27 days												
	28 days-<3 months												
	3-5 months												
	6-8 months												
	9-11 months												
	0-11 mont												

	hs												
	12-23 months												
	24-35 months												
	36-59 months												
	12-59 months												
	24-59 months												
	0-59 months												

Sheet 4 – RSV proportion

Year	
Number & % of cases not tested for RSV	
Reason for not testing (please provide in text below table if space is inadequate)	
Number of hospitalised ALRI cases that were tested for RSV	0-27 days
	28 days-<3 months
	3-5 months
	6-8 months
	9-11 months
	0-11 months
	12-23 months
	24-35 months
	36-59 months
	24-59 months
	0-59 months
Number of hospitalised ALRI cases that are positive for RSV A	0-27 days
	28 days-<3 months
	3-5 months
	6-8 months
	9-11 months
	0-11 months
	12-23 months
	24-35 months
	36-59 months
	24-59 months
	0-59 months
Number of hospitalised ALRI cases that are positive for RSV B	0-27 days
	28 days-<3 months
	3-5 months
	6-8 months
	9-11 months
	0-11 months
	12-23 months
	24-35 months
	36-59 months
	24-59 months
	0-59 months

Number of hospitalised ALRI cases that are positive for all RSV (including un-subtyped RSV)	0-27 days
	28 days-<3 months
	3-5 months
	6-8 months
	9-11 months
	0-11 months
	12-23 months
	24-35 months
	36-59 months
	24-59 months
	0-59 months

Sheet 5 – RSV morbidity and mortality by month for children with all gestational ages

S. No	Characteristic	Age group	Month n
1	Total hospitalised ALRI cases	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
2	Total cases of hospitalised ALRI tested for RSV	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
3a	Total cases of hospitalised ALRI positive for RSV A	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	

		12-23 months	
		24-35 months	
		36-59 months	
3b	Total cases of hospitalised ALRI positive for RSV B	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
3c	Total cases of hospitalised ALRI positive for all RSV / un-subtyped RSV	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
4a	Number of RSV positive ALRI cases where SpO2 was recorded	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
4b	Number of RSV positive ALRI cases with hypoxemia (SpO2<90% for 1-59 months and 88% for neonates at altitude<=2500 m; and <87% and 85% for post-neonatal age groups and neonates at altitude above 2500 m)	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
5	Number of RSV positive ALRI cases requiring admission into Intensive Care Units	0-27 days	
		28 days- <3 months	

		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
6	Number of RSV positive ALRI cases requiring mechanical ventilation	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
7	No. of RSV positive ALRI cases with co-morbidities (congenital heart disease, renal disease, cancer, on immunosuppressant, chronic lung disease etc.)	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
8a	Number of ALRI cases where chest X ray was conducted	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
8b	Number of ALRI cases with WHO Primary End-point Pneumonia	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	

		36-59 months	
8c	Number of WHO-PEP cases that are positive for RSV	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
9a	Number of ALRI deaths in hospital	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
9b	Number of ALRI cases tested for RSV and who died in-hospital	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
9c	Number of ALRI cases NOT tested for RSV and who died in-hospital	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
9d	No. of in-hospital deaths in RSV A positive ALRI cases	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	

		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
9e	No. of in-hospital deaths in RSV B positive ALRI cases	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
9f	No. of in-hospital deaths in all RSV positive ALRI cases	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
10	No. of in-hospital deaths in RSV positive ALRI cases with co-morbidities (congenital heart disease, renal disease, cancer, on immunosuppressant, chronic lung disease etc.)	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	
11	Number of in-hospital deaths in RSV positive ALRI cases with hypoxemia (SpO2<90% for 1-59 months and 88% for neonates at altitude <= 2500 m; and <87% and 85% for post-neonatal age groups and neonates at altitude above 2500 m)	0-27 days	
		28 days- <3 months	
		3-5 months	
		6-8 months	
		9-11 months	
		12-23 months	
		24-35 months	
		36-59 months	

Sheet 6 – RSV morbidity and mortality by month for children with gestational age 32-36 weeks

Same table as above

Sheet 7 – RSV morbidity and mortality by month for children with gestational age <32 weeks

Same table as above

Sheet 8 – risk factors for RSV mortality

		0-27 days	28 days-<3 months	3-5 months	6-8 months	9-11 months	12-23 months	24-35 months	36-59 months
1	No. of hospitalised ALRI cases								
2	No. of hospitalised ALRI cases positive for RSV								
3	No. of in-hospital deaths in RSV positive ALRI cases								
3	Prematurity								
a	No. of RSV positive hospitalised ALRI cases where gestational age has been recorded								
b	No. of RSV positive hospitalised ALRI with history of prematurity								
c	No. of in-hospital deaths in RSV positive ALRI cases with history of prematurity								
d	No. of RSV positive hospitalised ALRI with gestational age 32-36 weeks at birth								
e	No. of in-hospital deaths in RSV positive ALRI cases with gestational age 32-36 weeks at birth								
f	No. of RSV positive hospitalised ALRI with gestational age <32 weeks at birth								

g	No. of in-hospital deaths in RSV positive ALRI cases with gestational age <32 weeks at birth								
4	Malnutrition								
a	No. of RSV positive hospitalised ALRI cases where nutritional status (W/A) has been recorded								
b	No. of RSV positive hospitalised ALRI cases with z-score between (-)1 and (-) 1.99 SD								
c	No. of RSV positive hospitalised ALRI cases with z-score between (-)2 and (-)2.99 SD								
d	No. of RSV positive hospitalised ALRI cases with z-score > (-) 3SD								
e	No. of in-hospital deaths in RSV positive ALRI cases with z-score between (-)1 and (-) 1.99 SD								
f	No. of in-hospital deaths in RSV positive ALRI cases with z-score between (-)2 and (-)2.99 SD								
g	No. of in-hospital deaths in RSV positive ALRI cases with z-score > (-) 3SD								
5	Low birth weight								
a	No. of RSV positive hospitalised ALRI cases where birth weight has been recorded								
b	No. of RSV positive hospitalised ALRI cases with birth weight <2500 g								
c	No. of in-hospital deaths in RSV positive ALRI cases with birth weight <2500g								
6	Breast feeding								
a	No. of RSV positive hospitalised ALRI cases where breast feeding history has been recorded								
b	No. of RSV positive hospitalised ALRI cases								

	with exclusive breast feeding (only breast milk in first 4 months of life)								
c	No. of RSV positive hospitalised ALRI cases with partial breast feeding (less than 4 months' exclusive breast feeding)								
d	No. of RSV positive hospitalised ALRI cases not breast fed								
e	No. of in-hospital deaths in RSV positive ALRI cases with exclusive breast feeding								
f	No. of in-hospital deaths in RSV positive ALRI cases with partial breast feeding								
g	No. of in-hospital deaths in RSV positive ALRI cases who were not breast fed								
7	HIV								
a	No. of RSV positive hospitalised ALRI cases with HIV test conducted								
b	No. of RSV positive hospitalised ALRI cases who are HIV positive								
c	No. of in-hospital deaths in RSV positive ALRI cases who are HIV positive								
8	Crowding								
a	No. of RSV positive hospitalised ALRI cases where history of crowding has been recorded								
b	No. of RSV positive hospitalised ALRI cases in households with crowding (> 7 people per household)								
c	No. of RSV positive hospitalised ALRI cases in households with crowding (>2 people sharing child's bedroom)								
d	No. of in-hospital deaths in RSV positive ALRI cases in households with crowding (> 7 people per								

	household)								
e	No. of in-hospital deaths in RSV positive ALRI cases in households with crowding (>2 people sharing child's bedroom)								

Sheet 9 – risk factors for RSV morbidity

Location	
Study period	
Risk factor	
Definition of risk factor if different from that in box below	
Age group	
Study design (case-control, prospective cohort, retrospective cohort, RCT)	
Cases (hospital or community based)	
Controls (hospital or community based)	
Main outcome measure	
Confounding factors	
Confounders adjusted for	
Analysis type (multivariate / univariate)	
Sample size	
Total number of laboratory confirmed RSV cases	
OR (univariate analysis)	
95% CI	
OR (multivariate analysis)	
95% CI	
RSV cases with risk factor	
RSV cases without risk factor	
Controls / reference group with risk factor	
Controls / reference group without risk factor	
Limitations	

A2. Verbal autopsy and RSV seasonality data collection template

Sheet 1 – site description

S. No	Location of study site (including district, state, and country)	Site characteristics (rural, urban etc.)	Study period	VA instrument used	Method to interpret VA data (Physician confirmed VA/algorithm/ probabilistic approach)

Sheet 2 – VA mortality data

Year	Month	VA confirmed pneumonia deaths in children	
		28 days- 11 months	12-59 months

Sheet 3 – RSV and flu seasonality

Year	Month	Number of specimens		
		Submitted for laboratory testing	RSV positive	Influenza positive (all types and sub-types)

A3. Search strategy of aetiological roles of common respiratory viruses in ALRI

Medline

1. Prospective study.mp. or exp Prospective Studies/

2. control*.mp.

3. exp Case-Control Studies/ or case control.mp.

4. (case* adj2 control*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. virus.mp. or exp Viruses/

6. exp Virus Diseases/ or virus disease*.mp.

7. pneumonia.mp. or exp Pneumonia/ or exp Pneumonia, Viral/

8. bronchiolitis.mp. or exp Bronchiolitis/ or exp Bronchiolitis, Viral/

9. exp Respiratory Tract Infections/ or respiratory infection*.mp.

10. exp Respiratory Tract Diseases/ or respiratory disease*.mp.

11. 1 and 2

12. 3 or 4 or 11

13. 5 or 6

14. 7 or 8 or 9 or 10

15. 12 and 13 and 14

16. limit 15 to (yr="1990 -Current" and ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") and (female or humans or male))

Embase

1. virus*.mp. or exp virus/

2. exp virus infection/ or virus disease*.mp.

3. exp community acquired pneumonia/ or exp pneumonia/ or exp virus pneumonia/ or exp infectious pneumonia/ or pneumonia.mp.

4. bronchiolitis.mp. or exp bronchiolitis/ or exp viral bronchiolitis/

5. exp respiratory tract infection/ or exp lower respiratory tract infection/ or respiratory infection*.mp.

6. exp respiratory tract disease/ or respiratory disease*.mp.

7. exp case control study/ or case control.mp.

8. (case* adj2 control*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

9. prospective study.mp. or exp prospective study/

10. control*.mp. or exp control group/ or exp control/

11. 1 or 2

12. 3 or 4 or 5 or 6

13. 9 and 10

14. 7 or 8 or 13

15. 11 and 12 and 14

16. limit 15 to (yr="1990 -Current" and (infant or child or preschool child <1 to 6 years>))

Global Health

1. virus.mp. or exp viruses/

2. viral disease*.mp. or viral diseases.sh.

3. exp community acquired pneumonia/ or pneumonia.mp. or exp pneumonia/

4. bronchiolitis.mp. or exp bronchiolitis/

5. respiratory infection*.mp.

6. respiratory disease*.mp. or respiratory diseases.sh.

7. case control.mp.

8. exp case-control studies/

9. (case* adj2 control*).mp. [mp=abstract, title, original title, broad terms, heading words]

10. prospective study.mp.

11. exp control/ or control*.mp.

12. 1 or 2

13. 3 or 4 or 5 or 6

14. 10 and 11

15. 7 or 8 or 9 or 14

16. 12 and 13 and 15

17. limit 16 to yr="1990 -Current"

LILACS (AMRO/PAHO)

tw:(virus OR viral) AND tw:(pneumonia OR bronchiolitis OR alri OR lrti OR "lower respiratory" OR "respiratory infection") AND tw:(control)

CNKI

Topic: respiratory infection or pneumonia (vague)

Or Topic: bronchiolitis (vague)

And Topic: virus (vague)

And Topic: case control (vague)

And Topic: child (vague)

Publication time: 1st Jan 1990 – 19th Mar 2014

Wanfang Data

All (vague): respiratory infection or

All (vague): pneumonia or

All (vague): bronchiolitis and

All (vague): virus and

All (vague): case control and

All (vague): child

Time: 1990 – 2014

Chongqing VIP

Title/key word: respiratory infection

Or Title/key word: pneumonia

And Title/key word: virus

And Title/key word: case control

And Title/key word: child

Time: 1990 – 2014

A4. List of excluded articles during full-text review in the study of the aetiological roles of common respiratory viruses in ALRI

No separate data for children <5y (10 articles)

1. Calvo C, Casas I, Garcia-Garcia ML, et al. Role of rhinovirus C respiratory infections in sick and healthy children in Spain. *Pediatr Infect Dis J* 2010; **29**(8): 717-20.

2. Feikin DR, Njenga MK, Bigogo G, et al. Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007-2010. *PLoS ONE [Electronic Resource]* 2012; **7**(8): e43656.

3. Mermond S, Zurawski V, D'Ortenzio E, et al. Lower respiratory infections among hospitalized children in New Caledonia: a pilot study for the Pneumonia Etiology Research for Child Health project. *Clin Infect Dis* 2012; **54 Suppl 2**: S180-9.

4. Self WH, Williams DJ, Edwards KM, et al. Viral respiratory detections in children adults with community-acquired pneumonia compared with asymptomatic controls: Evaluating the role of viral pathogens in pneumonia. *Acad Emerg Med* 2013; **1)**: S284-S5.

5. Van Gageldonk-Lafeber AB, Heijnen MLA, Bartelds AIM, Peters MF, Van Der Plas SM, Wilbrink B. A case-control study of acute respiratory tract infection in general practice patients in the Netherlands. *Clin Infect Dis* 2005; **41**(4): 490-7.

6. Phillips PA, Lehmann D, Spooner V, et al. Viruses associated with acute lower respiratory tract infections in children from the eastern highlands of Papua New Guinea (1983-1985). *Southeast Asian J Trop Med Public Health* 1990; **21**(3): 373-82.

7. 沈照波, 曲文华, 吴惠. 郑州地区儿童急性呼吸道感染的病毒血清学研究. *临床儿科杂志* 2000; (05): 292-4.

8. 赵扬. 2008-2009 年兰州地区儿童急性呼吸道感染病毒病原学研究 [硕士]: 兰州大学; 2010.

9. 陈良, 舒蕾, 张媛春, et al. 小儿肺炎支原体检测临床流行病学分析. *中国公共卫生* 1999; (10): 22-3.

10. 庄婉莉. WU 多瘤病毒在儿童急性呼吸道感染的检出及其致病性研究 [硕士]: 汕头大学; 2010.

Inappropriate case / control definition (5 articles)

11. Albargish KA, Hasony HJ. Respiratory syncytial virus infection among young children with acute respiratory tract infection in Iraq. *Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-ihhiyah li-sharq al-mutawassi* 1999; **5**(5): 941-8.

12. Forgie IM, O'Neill KP, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital. *Pediatr Infect Dis J* 1991; **10**(1): 33-41.

13. Onyango D, Kikuvi G, Amukoye E, Omolo J. Risk factors of severe pneumonia among children aged 2-59 months in western Kenya: A case control study. *Pan Afr Med J* 2012; **13**.

14. 蔡晓莹, 林广裕. 儿科重症监护室患儿的病毒病原监测及其临床意义. 中华医学会第十七次全国儿科学术大会; 2012; 中国河南郑州; 2012. p. 1.

15. 曾玫, 王晓红, 俞蕙, 朱启镕. 人博卡病毒与儿童呼吸道感染和腹泻病临床相关性的前瞻性病例对照研究. *中华儿科杂志* 2010; **48**(8): 580-4.

Low internal / external validity (2 article)

16. Guerrier G, Goyet S, Chheng ET, et al. Acute viral lower respiratory tract infections in cambodian children: Clinical and epidemiologic characteristics. *Pediatr Infect Dis J* 2013; **32**(1): e8-e13.

17. Venter M, Lassauniere R, Kresfelder TL, Westerberg Y, Visser A. Contribution of Common and Recently Described Respiratory Viruses to Annual Hospitalizations in Children in South Africa; 2011.

No relevent data (32 articles)

18. Abels S, Nadal D, Stroehle A, Bossart W. Reliable detection of respiratory syncytial virus infection in children for adequate hospital infection control management. *J Clin Microbiol* 2001; **39**(9): 3135-9.

19. Suzuki M, Yoshida LM, Ariyoshi K. Severe pneumonia among Kenyan infants and children. *JAMA* 2010; **304**(9): 964; author reply -5.

20. Foulongne V, Rodiere M, Segondy M. Human Bocavirus in children. *Emerg Infect Dis* 2006; **12**(5): 862-3.

21. Jaimes MB, Caceres DC, de la Hoz F, et al. Risk factors for severe acute lower respiratory tract infection in Bogota, 2001. [Spanish]

Factores de riesgo para infeccion respiratoria aguda baja grave en Bogota, 2001. *Biomedica : revista del Instituto Nacional de Salud* 2003; **23**(3): 283-92.

22. Jansen R, Pajkrt D, Wieringa J, et al. Correlation between (semi-)quantity of respiratory viruses and the presence of clinical respiratory symptoms in children under 7 years. *Antonie van Leeuwenhoek, International Journal of General and Molecular Microbiology* 2009; **95**: 129-30.

23. Hamelin ME, Abed Y, Boivin G. Human metapneumovirus: a new player among respiratory viruses. *Clin Infect Dis* 2004; **38**(7): 983-90.

24. Bulkow LR, Singleton RJ, Karron RA, Harrison LH, Alaska RSVSG. Risk factors for severe respiratory syncytial virus infection among Alaska native children. *Pediatrics* 2002; **109**(2): 210-6.

25. Cheraghi Z, Irani AD, Rezaiean S, et al. Influenza A (H1N1) in Hamedan province, Western Iran in 2009: a case-control study. *Journal of Research in Health Sciences* 2010; **10**(1): 15-21.

26. Spaeder MC. Severe adenoviral respiratory infection in children. *Intensive Care Med* 2013; **39**(6): 1157-8.

27. Weber MW, Milligan P, Hilton S, et al. Risk factors for severe respiratory syncytial virus infection leading to hospital admission in children in the Western Region of The Gambia. *Int J Epidemiol* 1999; **28**(1): 157-62.

28. Bulkow LR, Singleton RJ, DeByle C, et al. Risk factors for hospitalization with lower respiratory tract infections in children in rural Alaska. *Pediatrics* 2012; **129**(5): e1220-e7.

29. Anita C, Bineeta K. Respiratory syncytial virus in lower respiratory tract infections. *Iranian Journal of Pediatrics* 2007; **17**(2): 123-8.

30. Hu YY, Lu XD, Lin GY, et al. [Analysis of human coronavirus NL63 in 690 children with acute respiratory infection in Shanton]. *Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology* 2010; **31**(1): 108-9.

31. 汪小蓉, 赵霞, 杨学文, 汪受传. 直接免疫荧光检测技术在中医药治疗小儿呼吸道合胞病毒肺炎疗效评价中的应用. *中华中医药杂志* 2008; (12): 1128-31.

32. 陈能. 从化市小儿呼吸道人类偏肺病毒感染的临床与分子流行病学特征 [硕士]: 广州医学院; 2010.

33. 周云连. 肺炎支原体耐药基因分析及其临床意义 [硕士]: 浙江大学; 2011.

34. 罗灿. 广州市白云区某社区轮状病毒、诺如病毒腹泻的监测 [硕士]: 南方医科大学; 2011.

35. 陈显琴. 小儿支气管肺炎与 HLA 的相关性研究 [硕士]: 吉林大学; 2004.

36. 李海超. 河南省农村法定传染病报告社会干预试验效果评价 [硕士]: 郑州大学; 2008.

37. 王雪峰, 董丹, 虞坚尔, et al. 儿童肺炎常见病原学分析及中医证候演变规律的多中心随机双盲安慰剂对照试验研究. *中国循证儿科杂志* 2006; (03): 170-6.

38. 叶颖子, 沈军, 曾玫, 王晓红, 俞蕙, 朱启镕. 人博卡病毒在上海地区儿童下呼吸道感染的流行病学. *中华传染病杂志* 2012; **30**(4): 246-9.

39. 占扬清. 成人社区获得性肺炎的病毒病原学及临床特征分析 [硕士]: 广州医学院; 2010.

40. 孙昼. 杭州地区腹泻婴幼儿诺如病毒感染状况及危险因素研究 [硕士]: 浙江大学; 2010.

41. 谷晓阳. 喘息性疾病患儿人类博卡病毒感染临床特征分析 [硕士]: 重庆医科大学; 2010.

42. 林创兴. 粤东地区喘息性疾病患儿中人偏肺病毒的检出及其 N 蛋白编码基因的序列分析 [硕士]: 汕头大学; 2008.

43. 何华. 乌鲁木齐市流行性感冒预防控制研究 [博士]: 新疆医科大学; 2008.

44. 邹映雪, 鲁继荣, 成焕吉, 刘丽. 呼吸道合胞病毒感染与儿童哮喘发病关系的研究. *天津医药* 2003; (08): 512-3.

45. 孙立新. 儿童专科医院重症监护病房住院患儿医院感染危险因素的研究 [硕士]: 河北医科大学; 2010.

46. 谭立明, 段风英, 彭卫华, et al. 病毒性肺炎婴幼儿呼吸道合胞病毒免疫球蛋白 M 抗体检测的意义. *实用儿科临床杂志* 2007; (16): 1249-50.

47. 陈焕辉, 陈翊, 林涛, 朱冰. 广州地区儿童病毒性脑炎病原构成和流行特点. *广州医药* 2012; (01): 18-21.

48. 袁斌. 小儿呼吸道合胞病毒肺炎痰热闭肺证的中医治法及其机理研究 [博士]: 南京中医药大学; 2007.

49. 程卫霞. 博卡病毒流行病学、致病性及基因进化研究 [博士]: 兰州大学; 2011.

Not a case-control study (5 articles)

50. Bezerra PGM, Britto MCA, Correia JB, et al. Viral and atypical bacterial detection in acute respiratory infection in children under five years. *PLoS One* 2011; **6**(4).

51. Advani S, Sengupta A, Forman M, Valsamakis A, Milstone AM. Detecting respiratory viruses in asymptomatic children. *Pediatr Infect Dis J* 2012; **31**(12): 1221-6.

52. Chidlow GR, Laing IA, Harnett GB, et al. Respiratory viral pathogens associated with lower respiratory tract disease among young children in the highlands of Papua New Guinea. *Journal Of Clinical Virology: The Official Publication Of The Pan American Society For Clinical Virology* 2012; **54**(3): 235-9.

53. Hatipoglu N, Somer A, Badur S, et al. Viral etiology in hospitalized children with acute lower respiratory tract infection. *Turk J Pediatr* 2011; **53**(5): 508-16.

54. Peltola V, Jartti T, Putto-Laurila A, et al. Rhinovirus infections in children: A retrospective and prospective hospital-based study. *J Med Virol* 2009; **81**(10): 1831-8.

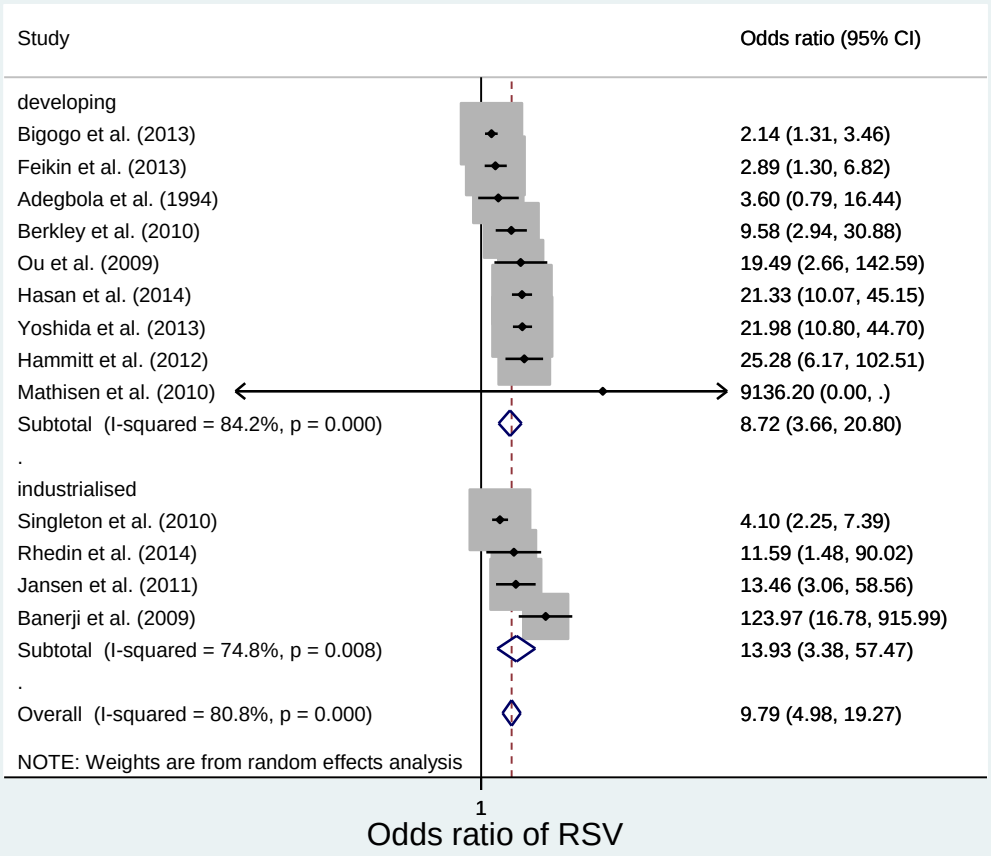
Comorbidities (2 studies)

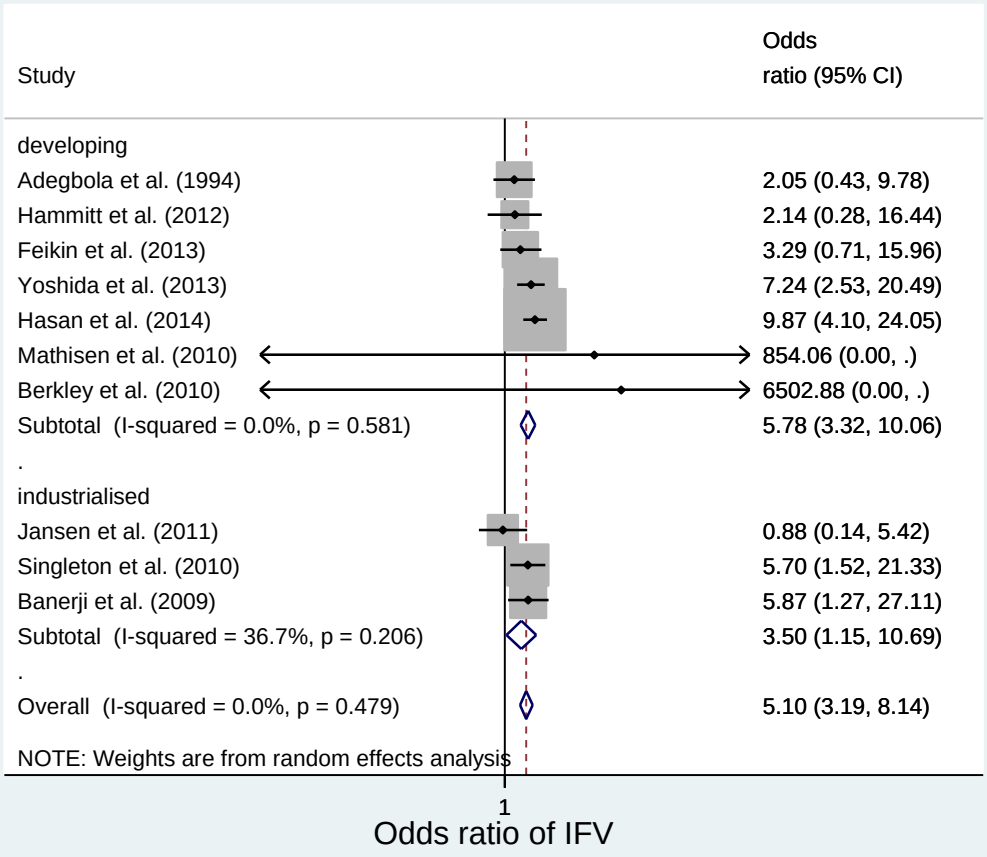
55. Rahman M, Huq F, Sack DA, et al. Acute lower respiratory tract infections in hospitalized patients with diarrhea in Dhaka, Bangladesh. *Rev Infect Dis* 1990; **12 Suppl 8**: S899-906.

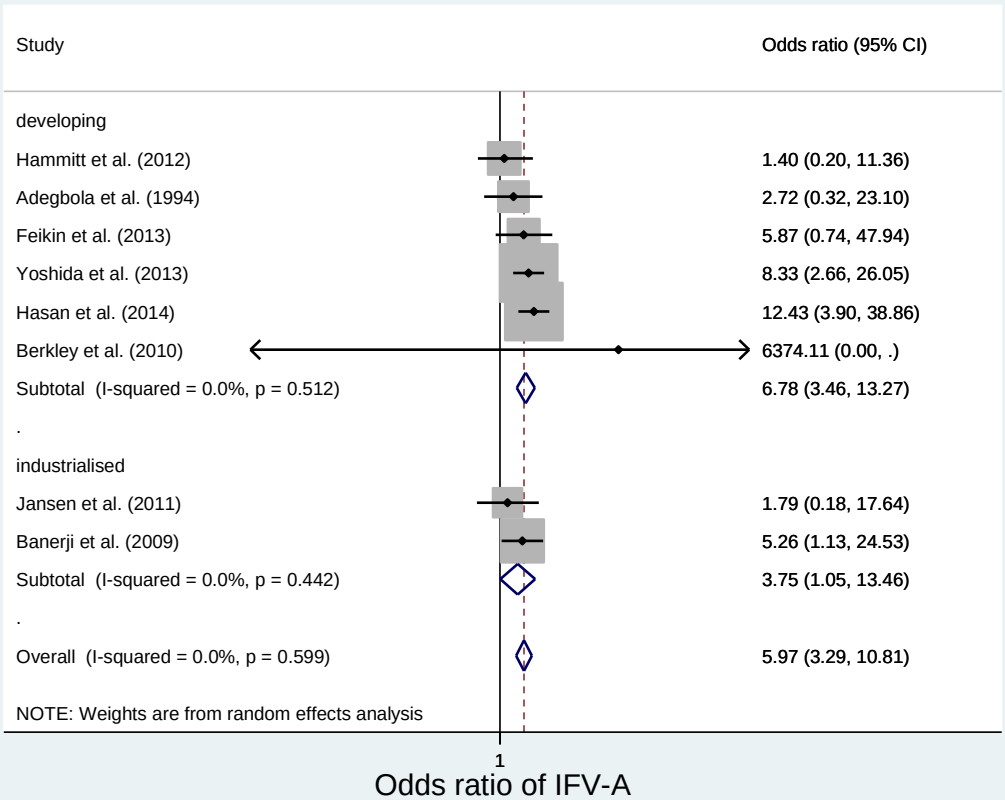
56. Brieu N, Guyon G, Rodiere M, Segondy M, Foulongne V. Human bocavirus infection in children with respiratory tract disease. *Pediatr Infect Dis J* 2008; **27**(11): 969-73.

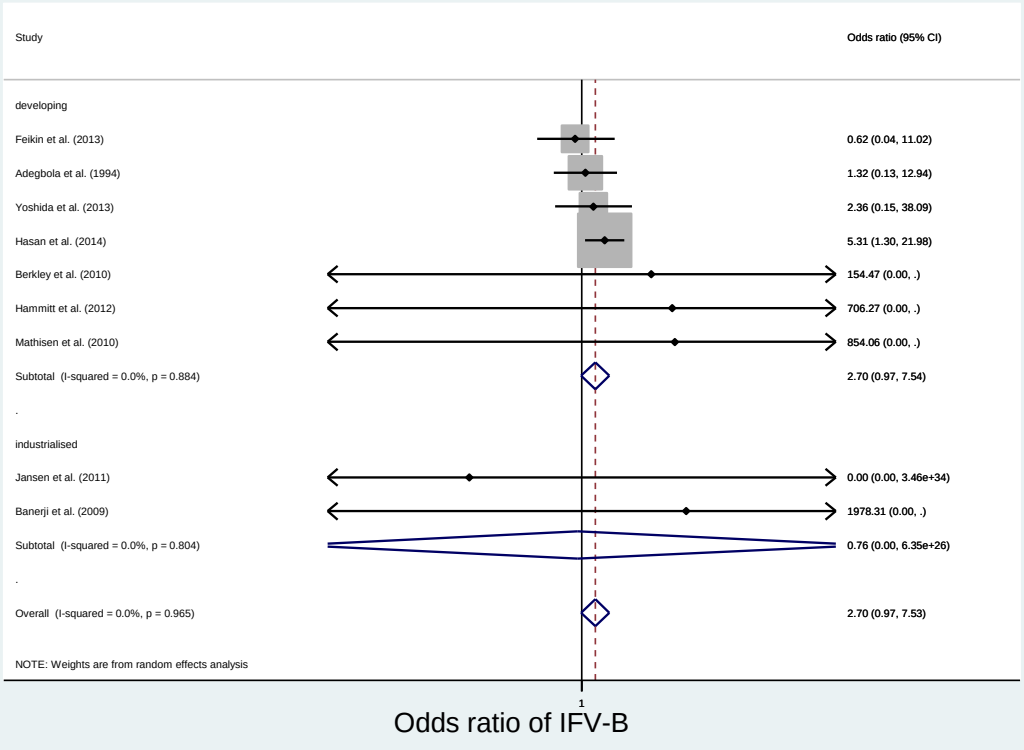
A5. Forest plots for meta-analysis results of the aetiological roles of common respiratory viruses in ALRI

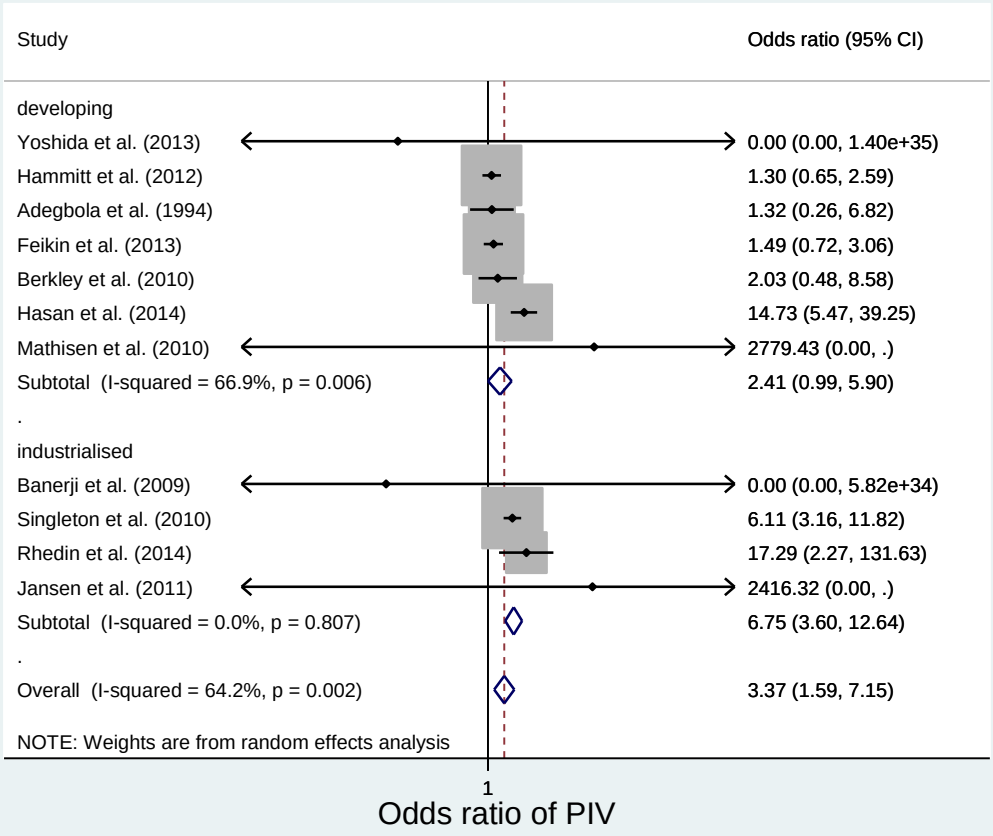
Hospitalised cases vs. asymptomatic controls

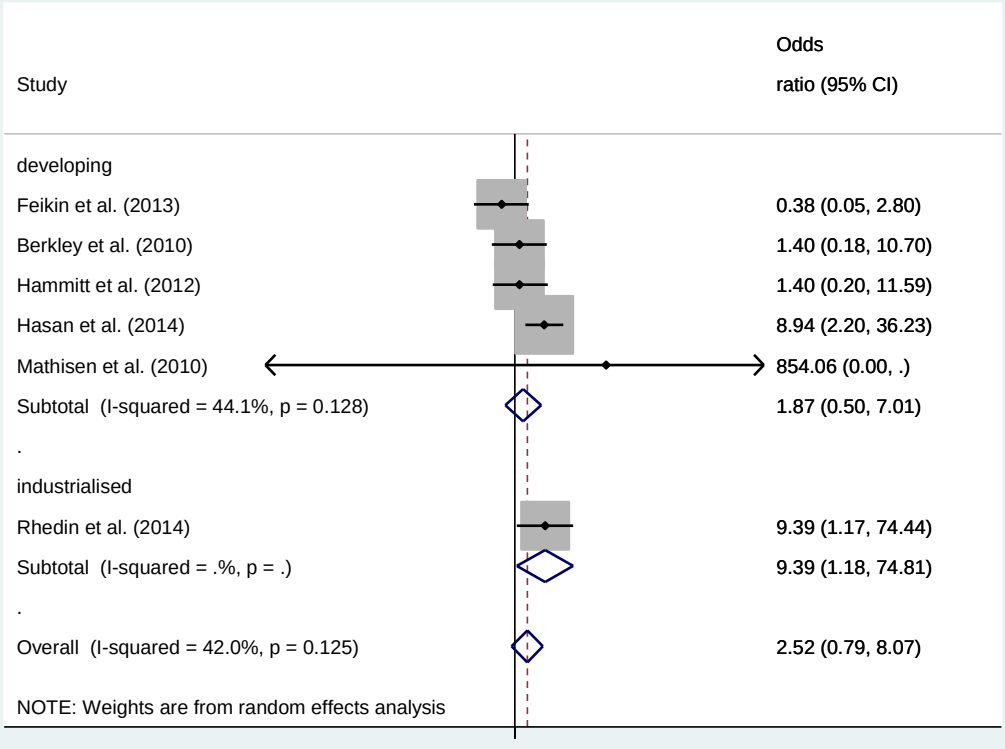



Study
Odds ratio (95% CI)
developing
Adegbola et al. (1994) 2.05 (0.43, 9.78)
Hammitt et al. (2012) 2.14 (0.28, 16.44)
Feikin et al. (2013) 3.29 (0.71, 15.96)
Yoshida et al. (2013) 7.24 (2.53, 20.49)
Hasan et al. (2014) 9.87 (4.10, 24.05)
Mathisen et al. (2010) 854.06 (0.00, .)
Berkley et al. (2010) 6502.88 (0.00, .)
Subtotal (I-squared = 0.0%, p = 0.581) 5.78 (3.32, 10.06)
.
industrialised
Jansen et al. (2011) 0.88 (0.14, 5.42)
Singleton et al. (2010) 5.70 (1.52, 21.33)
Banerji et al. (2009) 5.87 (1.27, 27.11)
Subtotal (I-squared = 36.7%, p = 0.206) 3.50 (1.15, 10.69)
.
Overall (I-squared = 0.0%, p = 0.479) 5.10 (3.19, 8.14)
NOTE: Weights are from random effects analysis
1
Odds ratio of IFV

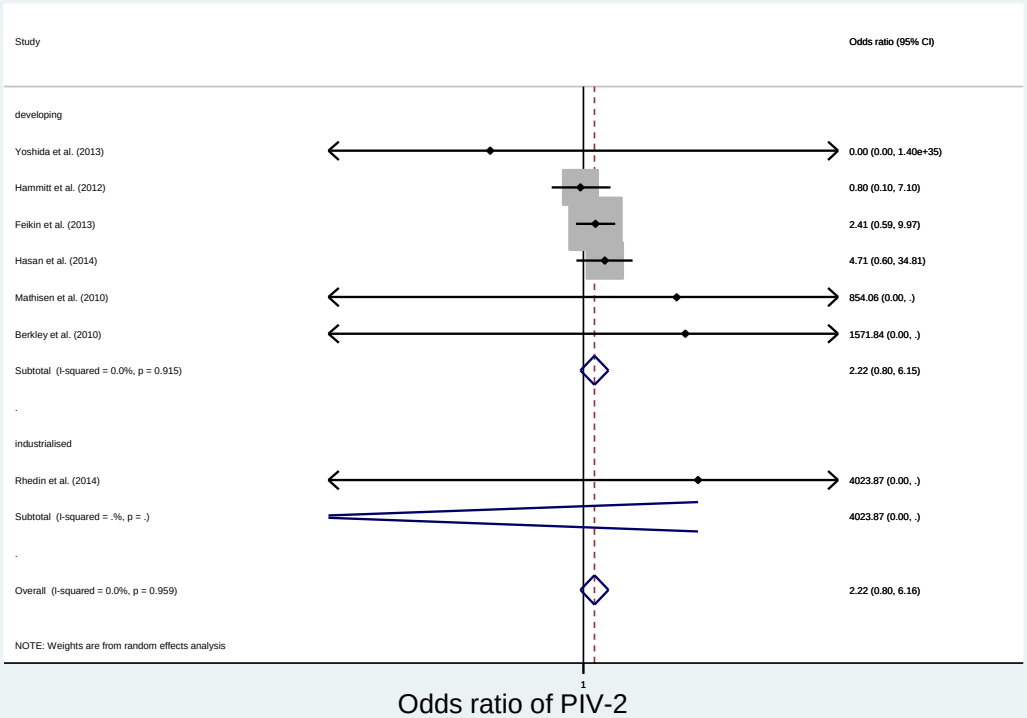

Study
Odds ratio (95% CI)
developing
Hammitt et al. (2012)
1.40 (0.20, 11.36)
Adegbola et al. (1994)
2.72 (0.32, 23.10)
Feikin et al. (2013)
5.87 (0.74, 47.94)
Yoshida et al. (2013)
8.33 (2.66, 26.05)
Hasan et al. (2014)
12.43 (3.90, 38.86)
Berkley et al. (2010)
6374.11 (0.00, .)
Subtotal (I-squared = 0.0%, p = 0.512)
6.78 (3.46, 13.27)
.
industrialised
Jansen et al. (2011)
1.79 (0.18, 17.64)
Banerji et al. (2009)
5.26 (1.13, 24.53)
Subtotal (I-squared = 0.0%, p = 0.442)
3.75 (1.05, 13.46)
.
Overall (I-squared = 0.0%, p = 0.599)
5.97 (3.29, 10.81)
NOTE: Weights are from random effects analysis
1
Odds ratio of IFV-A


Study
Odds ratio (95% CI)
developing
Feikin et al. (2013)
0.62 (0.04, 11.02)
Adegbola et al. (1994)
1.32 (0.13, 12.94)
Yoshida et al. (2013)
2.36 (0.15, 38.09)
Hasan et al. (2014)
5.31 (1.30, 21.98)
Berkley et al. (2010)
154.47 (0.00, .)
Hammitt et al. (2012)
706.27 (0.00, .)
Mathisen et al. (2010)
854.06 (0.00, .)
Subtotal (I-squared = 0.0%, p = 0.884)
2.70 (0.97, 7.54)
.
industrialised
Jansen et al. (2011)
0.00 (0.00, 3.46e+34)
Banerji et al. (2009)
1978.31 (0.00, .)
Subtotal (I-squared = 0.0%, p = 0.804)
0.76 (0.00, 6.35e+26)
.
Overall (I-squared = 0.0%, p = 0.965)
2.70 (0.97, 7.53)
NOTE: Weights are from random effects analysis
1
Odds ratio of IFV-B

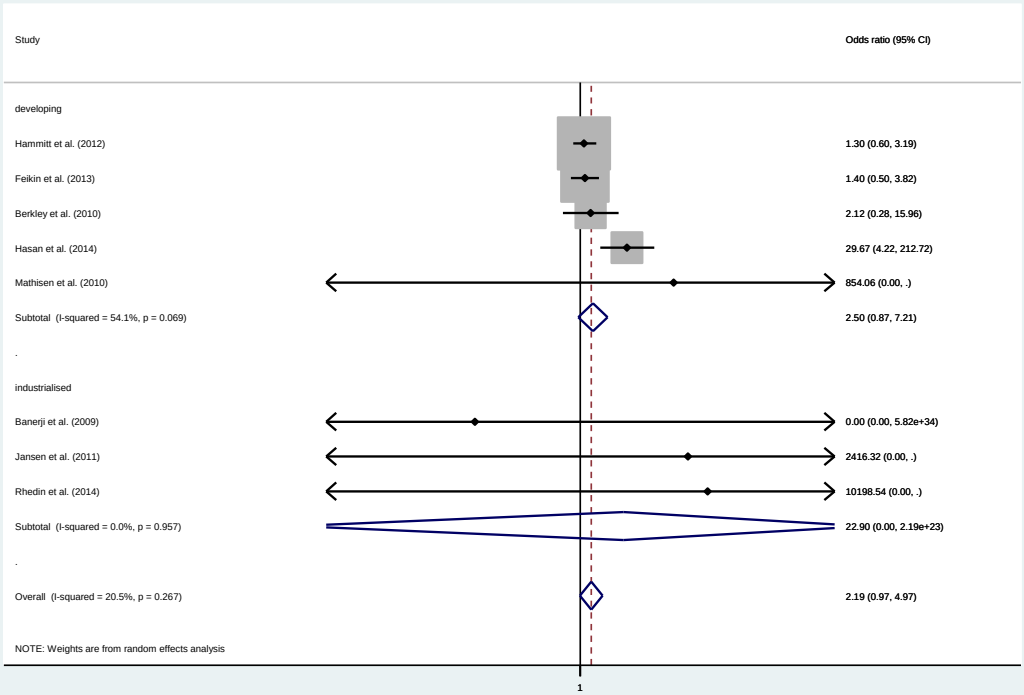

Study
Odds ratio (95% CI)
developing
Yoshida et al. (2013)
0.00 (0.00, 1.40e+35)
Hammitt et al. (2012)
1.30 (0.65, 2.59)
Adegbola et al. (1994)
1.32 (0.26, 6.82)
Feikin et al. (2013)
1.49 (0.72, 3.06)
Berkley et al. (2010)
2.03 (0.48, 8.58)
Hasan et al. (2014)
14.73 (5.47, 39.25)
Mathisen et al. (2010)
2779.43 (0.00, .)
Subtotal (I-squared = 66.9%, p = 0.006)
2.41 (0.99, 5.90)
.
industrialised
Banerji et al. (2009)
0.00 (0.00, 5.82e+34)
Singleton et al. (2010)
6.11 (3.16, 11.82)
Rhedin et al. (2014)
17.29 (2.27, 131.63)
Jansen et al. (2011)
2416.32 (0.00, .)
Subtotal (I-squared = 0.0%, p = 0.807)
6.75 (3.60, 12.64)
.
Overall (I-squared = 64.2%, p = 0.002)
3.37 (1.59, 7.15)
NOTE: Weights are from random effects analysis
1
Odds ratio of PIV



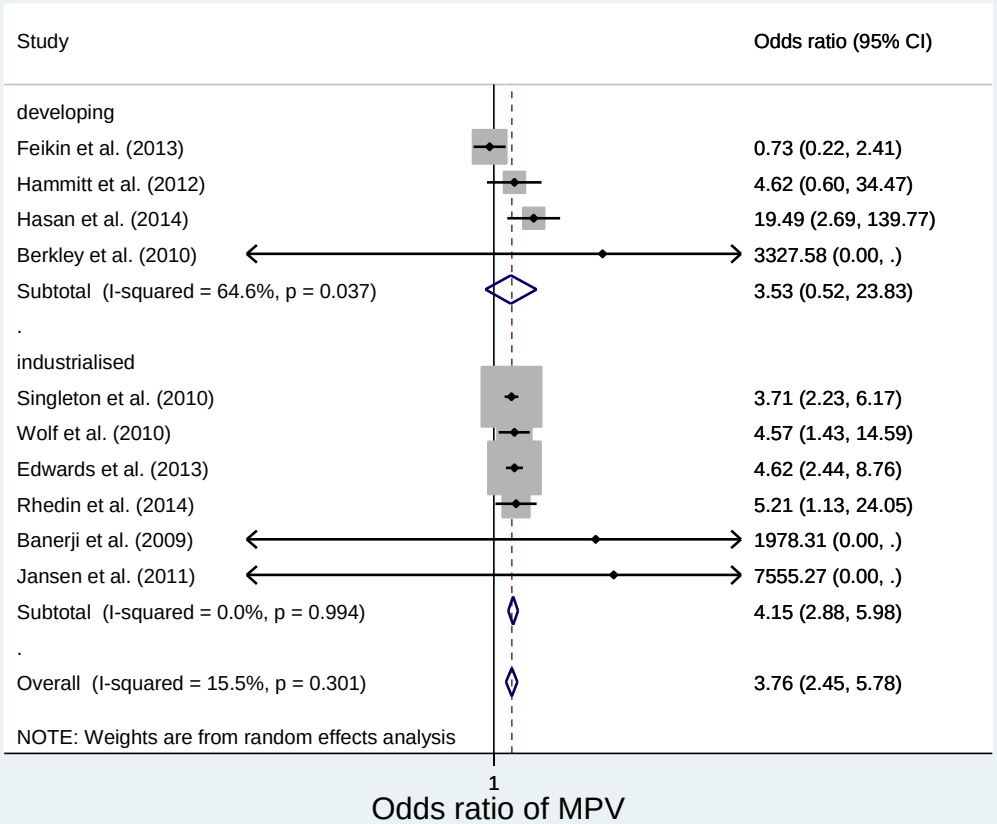
Odds ratio of PIV-1



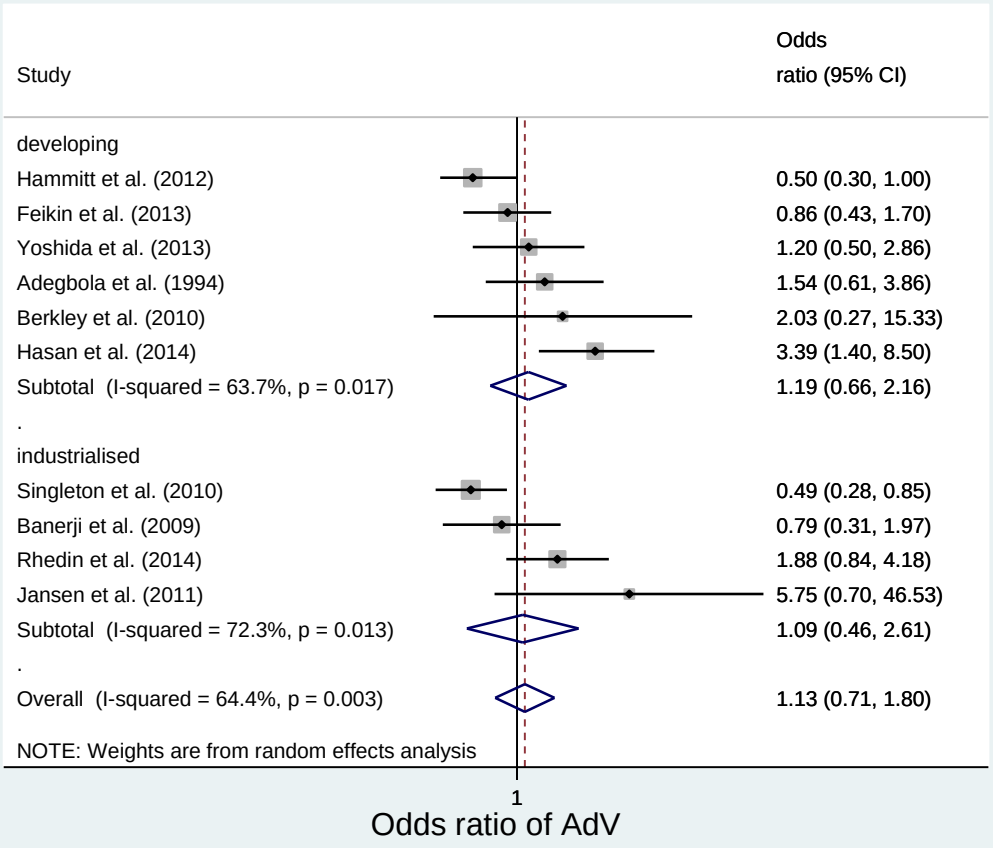
Odds ratio of PIV-2

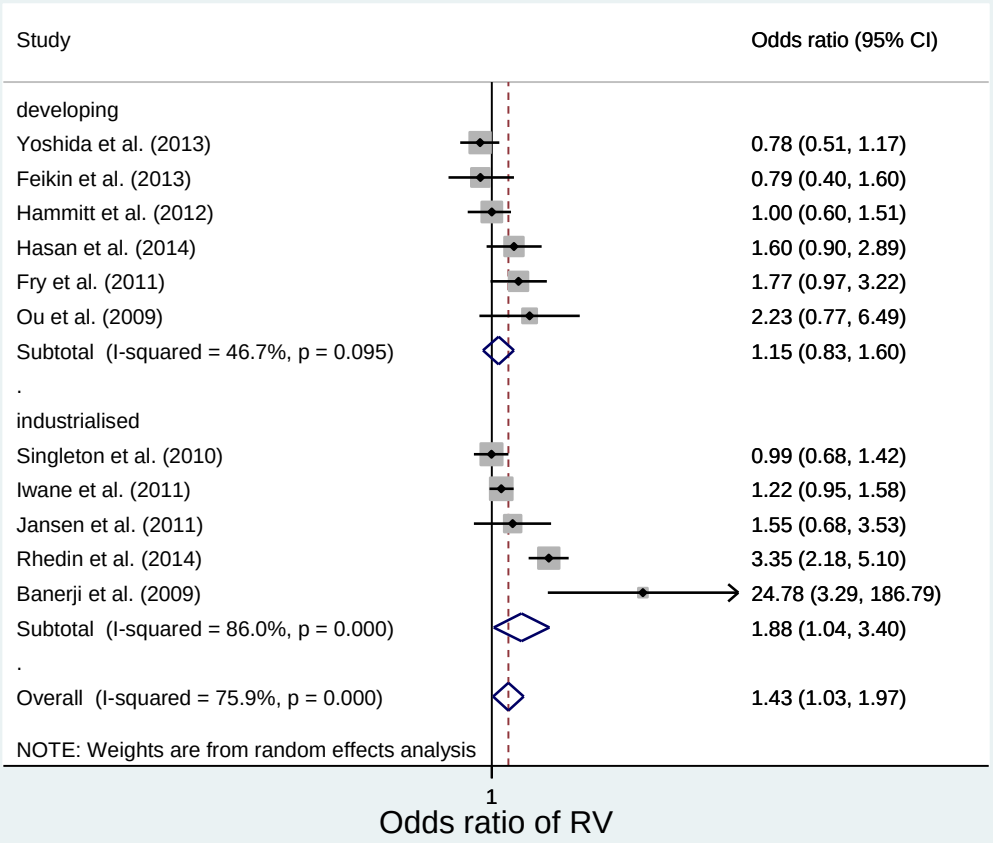


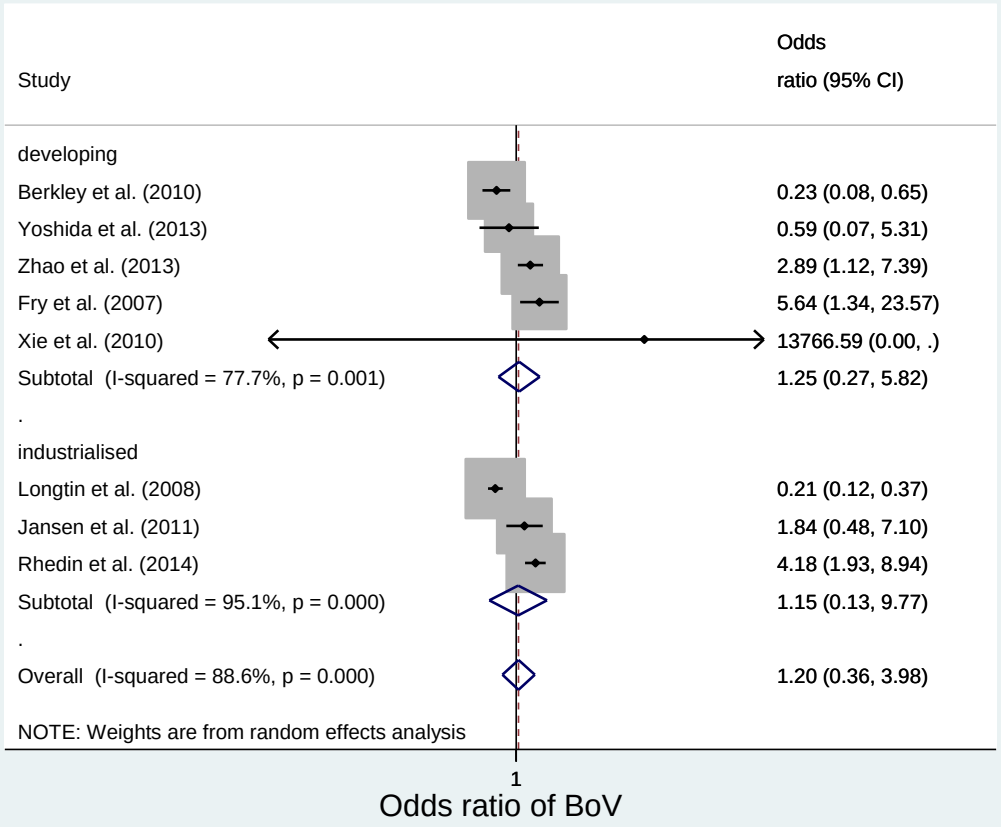
Odds ratio of PIV-3



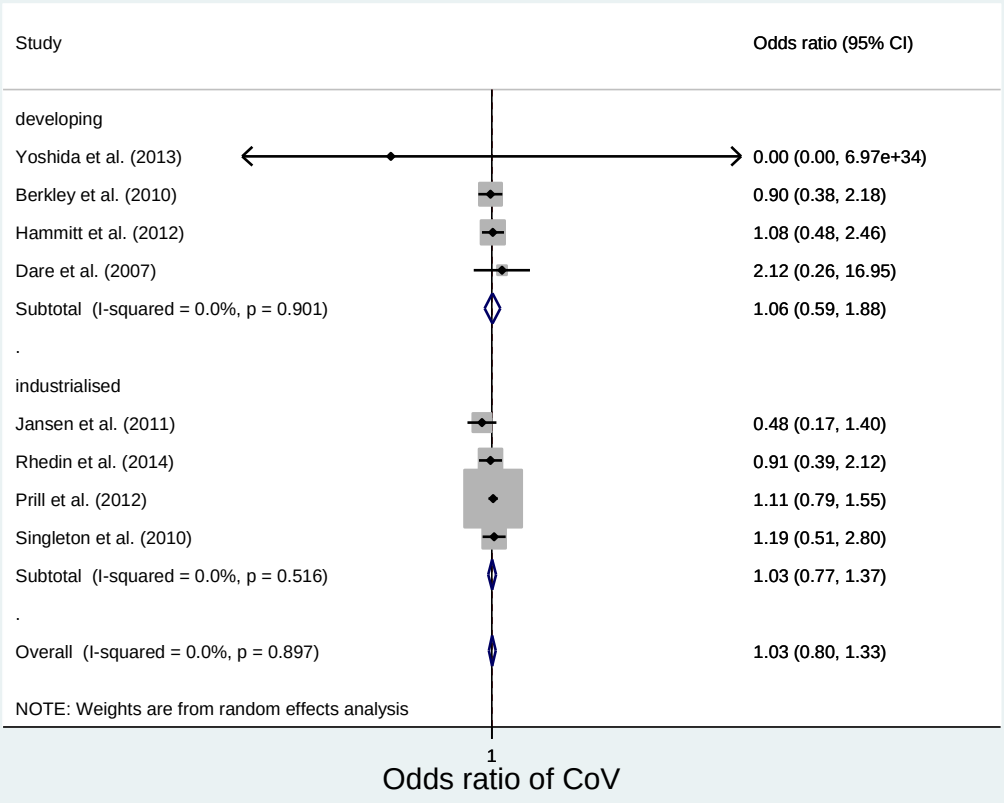
Odds ratio of MPV


Study
Odds ratio (95% CI)
developing
Hammitt et al. (2012)
0.50 (0.30, 1.00)
Feikin et al. (2013)
0.86 (0.43, 1.70)
Yoshida et al. (2013)
1.20 (0.50, 2.86)
Adegbola et al. (1994)
1.54 (0.61, 3.86)
Berkley et al. (2010)
2.03 (0.27, 15.33)
Hasan et al. (2014)
3.39 (1.40, 8.50)
Subtotal (I-squared = 63.7%, p = 0.017)
1.19 (0.66, 2.16)
.
industrialised
Singleton et al. (2010)
0.49 (0.28, 0.85)
Banerji et al. (2009)
0.79 (0.31, 1.97)
Rhedin et al. (2014)
1.88 (0.84, 4.18)
Jansen et al. (2011)
5.75 (0.70, 46.53)
Subtotal (I-squared = 72.3%, p = 0.013)
1.09 (0.46, 2.61)
.
Overall (I-squared = 64.4%, p = 0.003)
1.13 (0.71, 1.80)
NOTE: Weights are from random effects analysis
1
Odds ratio of AdV

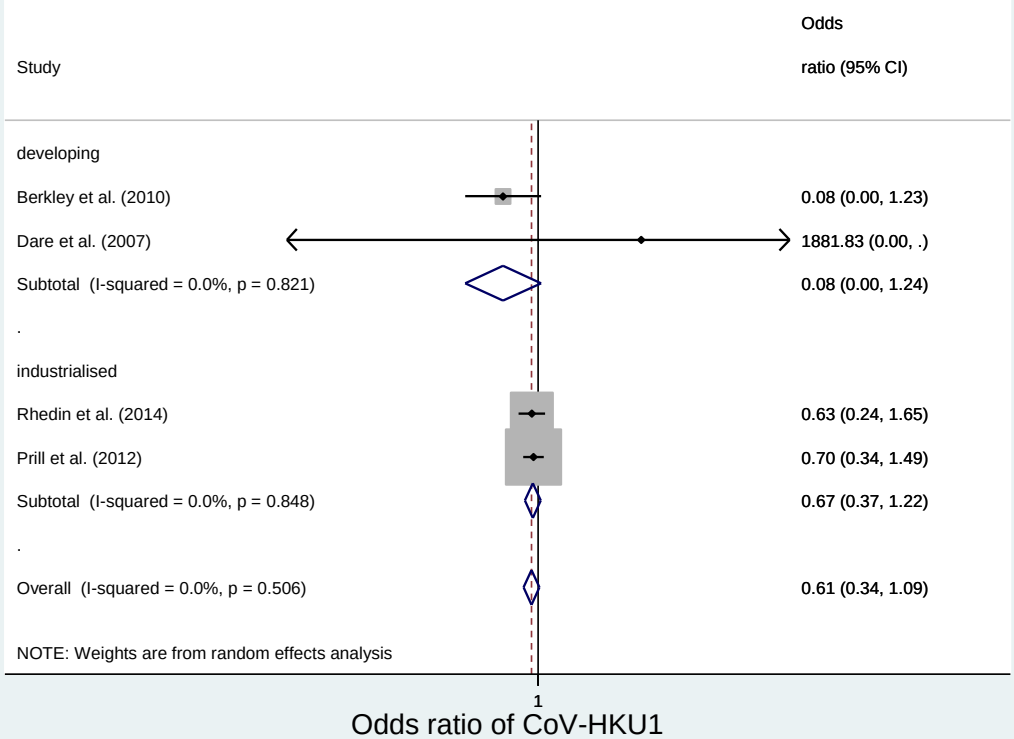

Study
Odds ratio (95% CI)
developing
Yoshida et al. (2013)
0.78 (0.51, 1.17)
Feikin et al. (2013)
0.79 (0.40, 1.60)
Hammitt et al. (2012)
1.00 (0.60, 1.51)
Hasan et al. (2014)
1.60 (0.90, 2.89)
Fry et al. (2011)
1.77 (0.97, 3.22)
Ou et al. (2009)
2.23 (0.77, 6.49)
Subtotal (I-squared = 46.7%, p = 0.095)
1.15 (0.83, 1.60)
.
industrialised
Singleton et al. (2010)
0.99 (0.68, 1.42)
Iwane et al. (2011)
1.22 (0.95, 1.58)
Jansen et al. (2011)
1.55 (0.68, 3.53)
Rhedin et al. (2014)
3.35 (2.18, 5.10)
Banerji et al. (2009)
24.78 (3.29, 186.79)
Subtotal (I-squared = 86.0%, p = 0.000)
1.88 (1.04, 3.40)
.
Overall (I-squared = 75.9%, p = 0.000)
1.43 (1.03, 1.97)
NOTE: Weights are from random effects analysis
1
Odds ratio of RV



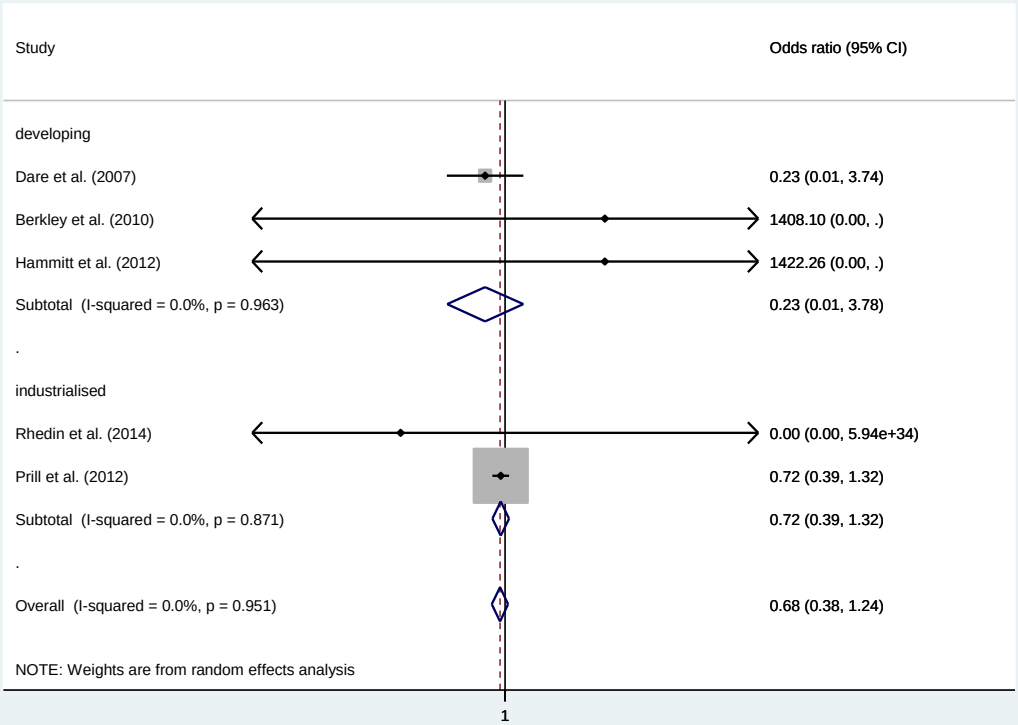
Odds ratio of BoV



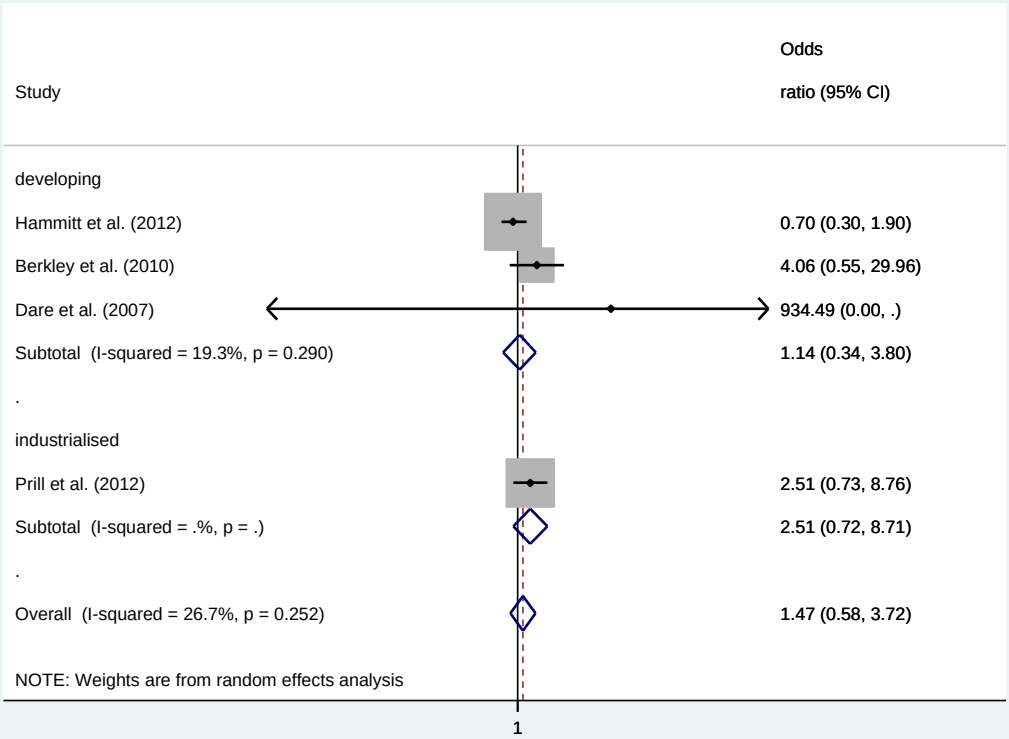
Odds ratio of CoV



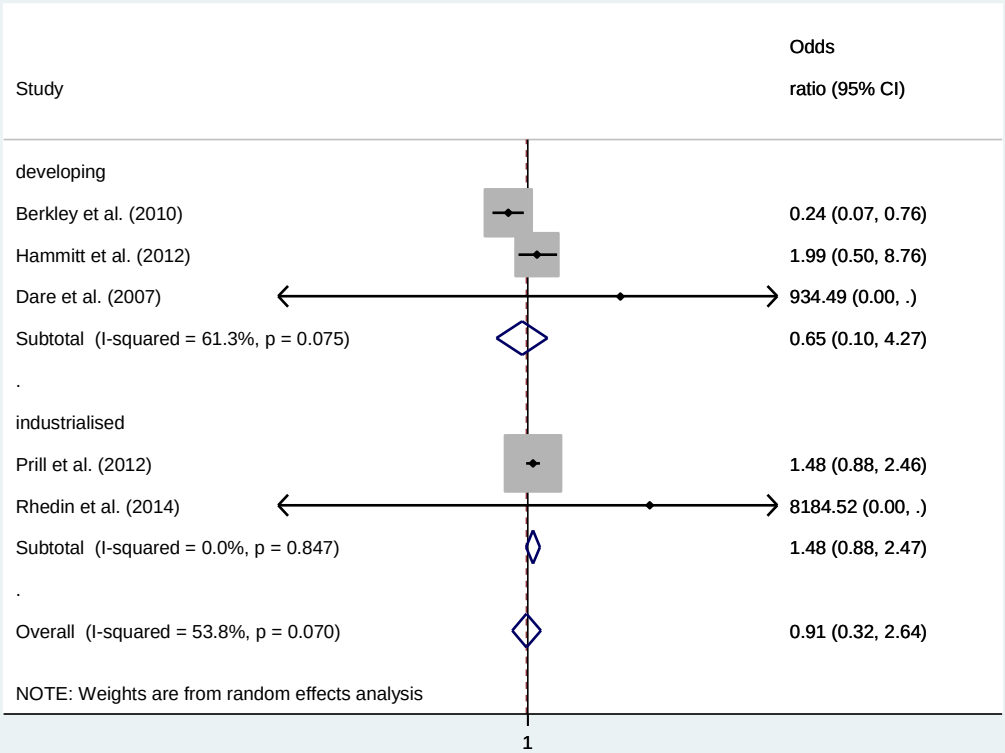
Odds ratio of CoV-HKU1



Odds ratio of CoV-NL63



Odds ratio of CoV-229E



Odds ratio of CoV-OC43

A6. Search strategy of risk factors for RSV associated ALRI

Medline

1. exp Respiratory Syncytial Viruses/ or exp Respiratory Syncytial Virus Infections/ or RSV.mp. or exp Respiratory Syncytial Virus, Human/

2. respiratory syncytial virus*.mp.

3. 1 or 2

4. pneumonia.mp. or exp Pneumonia/ or exp Pneumonia, Viral/

5. bronchiolitis.mp. or exp Bronchiolitis/ or exp Bronchiolitis, Viral/

6. exp Respiratory Tract Infections/ or respiratory infection*.mp.

7. exp Respiratory Tract Diseases/ or respiratory disease*.mp.

8. 4 or 5 or 6 or 7

9. risk factor*.mp. or exp Risk Factors/

10. low birth weight.mp. or exp Infant, Low Birth Weight/

11. breast feeding.mp. or exp Breast Feeding/

12. exp Crowding/ or crowd*.mp.

13. indoor air pollution.mp. or exp Air Pollution, Indoor/

14. exp Malnutrition/ or malnutrition.mp.

15. exp Measles Vaccine/ or measles vaccin*.mp.

16. exp HIV/ or HIV.mp.

17. exp Infant, Premature/ or prematur*.mp.

18. asthma.mp. or exp Asthma/

19. exp Education/ or education.mp.

20. exp Altitude/ or altitude.mp.

21. child care.mp. or exp Child Care/

22. day care.mp. or exp Day Care/

23. atop*.mp.

24. exp Tobacco Smoke Pollution/ or tobacco smok*.mp.

25. hygiene.mp. or Hygiene/

26. water.mp. or Water/ or Water Supply/

27. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. 3 and 8

29. 27 and 28

30. limit 29 to (humans and yr="1995 -Current" and ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)"))

Embase

1. exp respiratory syncytial virus infection/ or RSV.mp. or exp Respiratory syncytial pneumovirus/

2. respiratory syncytial virus*.mp.

3. exp community acquired pneumonia/ or exp pneumonia/ or exp virus pneumonia/ or exp infectious pneumonia/ or pneumonia.mp.

4. bronchiolitis.mp. or exp bronchiolitis/ or exp viral bronchiolitis/

5. exp lower respiratory tract infection/ or exp respiratory tract infection/ or respiratory infection*.mp.

6. exp respiratory tract disease/ or respiratory disease*.mp.

7. 1 or 2

8. 3 or 4 or 5 or 6

9. exp risk factor/ or risk factor*.mp.

10. low birth weight.mp. or exp low birth weight/

11. breast feeding.mp. or exp breast feeding/

12. exp crowding/ or crowd*.mp.

13. indoor air pollution.mp. or exp indoor air pollution/

14. exp malnutrition/ or malnutrition.mp.

15. exp measles vaccine/ or measles vaccin*.mp.

16. HIV.mp. or exp Human immunodeficiency virus/

17. exp prematurity/ or prematur*.mp.

18. exp asthma/ or asthma.mp.

19. education.mp. or exp education/

20. altitude.mp. or exp altitude/

21. child care.mp. or exp child care/

22. day care.mp. or exp day care/

23. atop*.mp.

24. exp smoking/ or exp tobacco smoke/ or exp passive smoking/ or tobacco smok*.mp.

25. water.mp. or water/ or water supply/

26. hygiene/ or hygiene.mp.

27. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. 7 and 8 and 27

29. limit 28 to (human and yr="1995 -Current" and (infant or preschool child <1 to 6 years>))

Global Health

1. exp human respiratory syncytial virus/ or rsv.mp.

2. respiratory syncytial virus*.mp.

3. 1 or 2

4. exp community acquired pneumonia/ or pneumonia*.mp. or exp pneumonia/

5. bronchiolitis.mp. or exp bronchiolitis/

6. respiratory infection*.mp.

7. exp respiratory diseases/ or respiratory disease*.mp.

8. 4 or 5 or 6 or 7

9. exp risk factors/ or risk factor*.mp.

10. low birth weight.mp. or exp low birth weight infants/

11. exp premature infants/ or exp prematurity/ or prematur*.mp.

12. exp asthma/ or asthma.mp.

13. exp atopy/ or atop*.mp.

14. exp education/ or education.mp.

15. exp breast feeding/ or breast feeding.mp.

16. exp altitude/ or altitude.mp.

17. exp malnutrition/ or malnutrition.mp.

18. exp child care/ or child care.mp.

19. exp day care/ or day care.mp.

20. exp Crowding/ or crowd*.mp.

21. exp indoor air pollution/ or indoor air pollution.mp.

22. exp passive smoking/ or exp tobacco smoking/ or tobacco smok*.mp.

23. HIV.mp. or exp human immunodeficiency viruses/

24. measles vaccin*.mp.

25. exp water supply/ or water.mp. or exp water/

26. exp hygiene/ or hygiene.mp.

27. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. 3 and 8 and 27

29. limit 28 to yr="1995 -Current"

LILACS (AMRO/PAHO)

Respiratory syncytial virus and risk factor* in All Indexes

A7. List of excluded articles during full-text review in the study of risk factors for RSV associated ALRI

Data in high-risk children only (9 articles)

1. Blanken MO, Koffijberg H, Nibbelke EE, Rovers MM, Bont L, Dutch RSVNN. Prospective validation of a prognostic model for respiratory syncytial virus bronchiolitis in late preterm infants: a multicenter birth cohort study. *PLoS ONE [Electronic Resource]* 2013; 8(3): e59161.

2. Carbonell-Estrany X, Quero J, Bustos G, et al. Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. *Pediatr Infect Dis J* 2000; 19(7): 592-7.

3. Doering G, Gusenleitner W, Belohradsky BH, Burdach S, Resch B, Liese JG. The risk of respiratory syncytial virus-related hospitalizations in preterm infants of 29 to 35 weeks' gestational age. *Pediatr Infect Dis J* 2006; 25(12): 1188-90.

4. Figueras-Aloy J, Carbonell-Estrany X, Quero J, Group IS. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33-35 weeks in Spain. *Pediatr Infect Dis J* 2004; 23(9): 815-20.

5. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jimenez J, et al. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. *Pediatr Infect Dis J* 2008; 27(9): 788-93.

6. Kanra G, Tezcan S, Yilmaz G, et al. Respiratory syncytial virus epidemiology in Turkey. *Turk J Pediatr* 2005; 47(4): 303-8.

7. Liese JG, Grill E, Fischer B, et al. Incidence and risk factors of respiratory syncytial virus-related hospitalizations in premature infants in Germany. *Eur J Pediatr* 2003; 162(4): 230-6.

8. Resch B, Gusenleitner W, Muller WD, Haas J. Observational study of respiratory syncytial virus-associated hospitalizations and use of palivizumab in premature infants aged 29-32 weeks. *Eur J Clin Microbiol Infect Dis* 2006; 25(2): 120-2.

9. Simoes EAF, Carbonell-Estrany X, Fullarton JR, et al. A predictive model for respiratory syncytial virus (RSV) hospitalisation of premature infants born at 33-35 weeks of gestational age, based on data from the Spanish FLIP study. *Respir Res* 2008; 9(78).

Only report p-value (5 articles)

10. Andres S, Bauer G, Rodriguez S, Novali L, Micheli D, Farina D. Hospitalization due to respiratory syncytial virus infection in patients under 2 years of age with hemodynamically significant congenital heart disease. *J Pediatr (Rio J)* 2012; 88(3): 246-52.

11. Bradley JP, Bacharier LB, Bonfiglio J, et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. *Pediatrics* 2005; 115(1): e7-14.

12. Medici MC, Arcangeletti MC, Merolla R, Chezzi C, Osservatorio VRSSG. Incidence of respiratory syncytial virus infection in infants and young children referred to the emergency departments for lower respiratory tract diseases in Italy. *Acta Bio-Medica de l Ateneo Parmense* 2004; 75(1): 26-33.

13. Piñeros JG, Baquero H, Bastidas J, et al. Infecção por vírus sincicial respiratório como causa de internação na população com menos de 1 ano na Colômbia. Respiratory syncytial virus infection as a cause of hospitalization in population under 1 year in Colombia. *J Pediatr (Rio J)* 2013; 89(6): 544-8.

14. Purcell K, Fergie J. Driscoll Children's Hospital respiratory syncytial virus database: risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatr Infect Dis J* 2004; 23(5): 418-23.

Use children with respiratory infection but RSV negative as control group (13 articles)

15. Dotan M, Ashkenazi-Hoffnung L, Samra Z, et al. Hospitalization for respiratory syncytial virus bronchiolitis and disease severity in twins. *Israel Medical Association Journal: Imaj* 2013; 15(11): 701-4.

16. Flores P, Rebelo-de-Andrade H, Goncalves P, et al. Bronchiolitis caused by respiratory syncytial virus in an area of portugal: epidemiology, clinical features, and risk factors. *Eur J Clin Microbiol Infect Dis* 2004; 23(1): 39-45.

17. Greenberg D, Dagan R, Shany E, Bar-Ziv J, Givon-Lavi N. Increased risk for respiratory syncytial virus-associated, community-acquired alveolar pneumonia in infants born at 31-36 weeks of gestation. *Pediatr Infect Dis J* 2014; 33(4): 381-6.

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19. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009; 360(6): 588-98.

20. Hervas D, Reina J, Yanez A, del Valle JM, Figuerola J, Hervas JA. Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis. *Eur J Clin Microbiol Infect Dis* 2012; 31(8): 1975-81.

21. Hussey GD, Apolles P, Arendse Z, et al. Respiratory syncytial virus infection in children hospitalised with acute lower respiratory tract infection. *S Afr Med J* 2000; 90(5): 509-12.

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

23. Moyes J, Cohen C, Pretorius M, et al. 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* 2013; 208 Suppl 3: S217-26.

24. Riccetto AG, Ribeiro JD, Silva MT, Almeida RS, Arns CW, Baracat EC. Respiratory syncytial virus (RSV) in infants hospitalized for acute lower respiratory tract disease: incidence and associated risks. *Brazilian Journal of Infectious Diseases* 2006; 10(5): 357-61.

25. Suwanjutha S, Sunakorn P, Chantarojanasiri T, et al. Respiratory syncytial virus-associated lower respiratory tract infection in under-5-year-old children in a rural community of central Thailand, a population-based study. *J Med Assoc Thai* 2002; 85(SUPPL. 4): S1111-S9.

26. Tsolia MN, Kafetzis D, Danelatou K, et al. Epidemiology of respiratory syncytial virus bronchiolitis in hospitalized infants in Greece. *Eur J Epidemiol* 2003; 18(1): 55-61.

27. Sritippayawan S, Prapphal N, Wong P, Tosukhowong P, Samransamruajkit R, Deerojanawong J. Environmental tobacco smoke exposure and respiratory syncytial virus infection in young children hospitalized with acute lower respiratory tract infection. *J Med Assoc Thai* 2006; 89(12): 2097-103.

Report risk factor for severity of RSV-ALRI (13 articles)

28. Al-Sonboli N, Hart CA, Al-Aghbari N, Al-Ansi A, Ashoor O, Cuevas LE. Human metapneumovirus and respiratory syncytial virus disease in children, Yemen. *Emerg Infect Dis* 2006; 12(9): 1437-9.

29. Chan PW, Lok FY, Khatijah SB. Risk factors for hypoxemia and respiratory failure in respiratory syncytial virus bronchiolitis. *Southeast Asian Journal of Tropical Medicine & Public Health* 2002; 33(4): 806-10.

30. Chi H, Chang IS, Tsai FY, et al. Epidemiological study of hospitalization associated with respiratory syncytial virus infection in taiwanese children between 2004 and 2007. *Journal of the Formosan Medical Association* 2011; 110(6): 388-96.

31. García G, Schvartzman S, Pérez M. Risk factors for complicated hospitalization in children with respiratory syncitial virus associated lower respiratory tract infection (Factores de riesgo para mala evolución en niños hospitalizados por infección respiratoria baja causada por viris sindical respiratorio). *Arch Argent Pediatr* 2006; 104(1): 23-9.

32. Grimaldi M, Cornet B, Milou C, Gouyon JB. Prospective regional study of an epidemic of respiratory syncytial virus (RSV) bronchiolitis. *Arch Pediatr* 2002; 9(6): 572-80.

33. Hon KL, Leung TF, Cheng WY, et al. Respiratory syncytial virus morbidity, premorbid factors, seasonality, and implications for prophylaxis. *J Crit Care* 2012; 27(5): 464-8.

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36. Langley GF, McCracken J, Arvelo W, et al. The epidemiology and clinical characteristics of young children hospitalized with respiratory syncytial virus infections in Guatemala (2007-2010). *Pediatric Infectious Disease Journal* 2013; 32(6): 629-35.

37. Nishimura T, Suzue J, Kaji H. Breastfeeding reduces the severity of respiratory syncytial virus infection among young infants: a multi-center prospective study. *Pediatr Int* 2009; 51(6): 812-6.

38. Rodriguez DA, Rodriguez-Martinez CE, Cardenas AC, et al. Predictors of severity and mortality in children hospitalized with respiratory syncytial virus infection in a tropical region. *Pediatr Pulmonol* 2014; 49(3): 269-76.

39. Simon A, Ammann RA, Wilkesmann A, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. *Eur J Pediatr* 2007; 166(12): 1273-83.

40. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1995; 126(2): 212-9.

Report risk factor for mortality of RSV-ALRI (1 article)

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Improper study design – small sample size, unclear definition (4 articles)

42. Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics* 2011; 127(6): e1513-20.

43. Broughton S, Roberts A, Fox G, et al. Prospective study of healthcare utilisation and respiratory morbidity due to RSV infection in prematurely born infants. *Thorax* 2005; 60(12): 1039-44.

44. Pedraz C, Carbonell-Estrany X, Figueras-Aloy J, Quero J. Effect of palivizumab prophylaxis in decreasing respiratory syncytial virus hospitalizations in premature infants. *Pediatr Infect Dis J* 2003; 22(9): 823-7.

45. Prinelli F, Musico M, Adorni F, et al. Breastfeeding protects infants against lower respiratory tract infections caused by respiratory syncytial virus. Results from the Italian Cohort Study Group on RSV. *Early Hum Dev* 2012; 88: S115.

Focus on children with co-morbidity (14 articles)

46. Kristensen K, Hjuler T, Ravn H, Simoes EA, Stensballe LG. Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. *Clin Infect Dis* 2012; 54(6): 810-7.

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49. Resch B, Eibisberger M, Morris N, Muller W. Respiratory syncytial virus- and influenza virus-associated hospitalizations in infants less than 12 months of age. *Pediatr Infect Dis J* 2011; 30(9): 797-9.

50. Mori M, Morio T, Ito S, et al. Risks and prevention of severe RS virus infection among children with immunodeficiency and Down's syndrome. *Journal of Infection and Chemotherapy* 2014; 20(8): 455-9.

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57. El Kholy AA, Mostafa NA, El-Sherbini SA, et al. Morbidity and outcome of severe respiratory syncytial virus infection. *Pediatr Int* 2013; 55(3): 283-8.

58. Bloemers BL, van Furth AM, Weijerman ME, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. *Pediatrics* 2007; 120(4): e1076-81.

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No relevant data (99 articles)

60. Albargish KA, Hasony HJ. Respiratory syncytial virus infection among young children with acute respiratory tract infection in Iraq. *Eastern Mediterranean Health Journal* 1999; 5(5): 941-8.

61. Lanari M, Adorni F, Silvestri M, Coscia A, Musicco M, Italian Study Group on Risk Factors for RSVrH. The multicenter Italian birth cohort study on incidence and determinants of lower

respiratory tract infection hospitalization in infants at 33 weeks GA or more: preliminary results. *Early Human Development* 2011; 87 Suppl 1: S43-6.

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74. Heikkinen T, Valkonen H, Lehtonen L, Vainionpaa R, Ruuskanen O. Hospital admission of high risk infants for respiratory syncytial virus infection: implications for palivizumab prophylaxis. *Archives of Disease in Childhood* 2005; 90(1): F64-F8.

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81. Madhi SA, Kuwanda L, Cutland C, Klugman KP. Five-year cohort study of hospitalization for respiratory syncytial virus associated lower respiratory tract infection in African children. *Journal of Clinical Virology* 2006; 36(3): 215-21.

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No full texts (7 articles)

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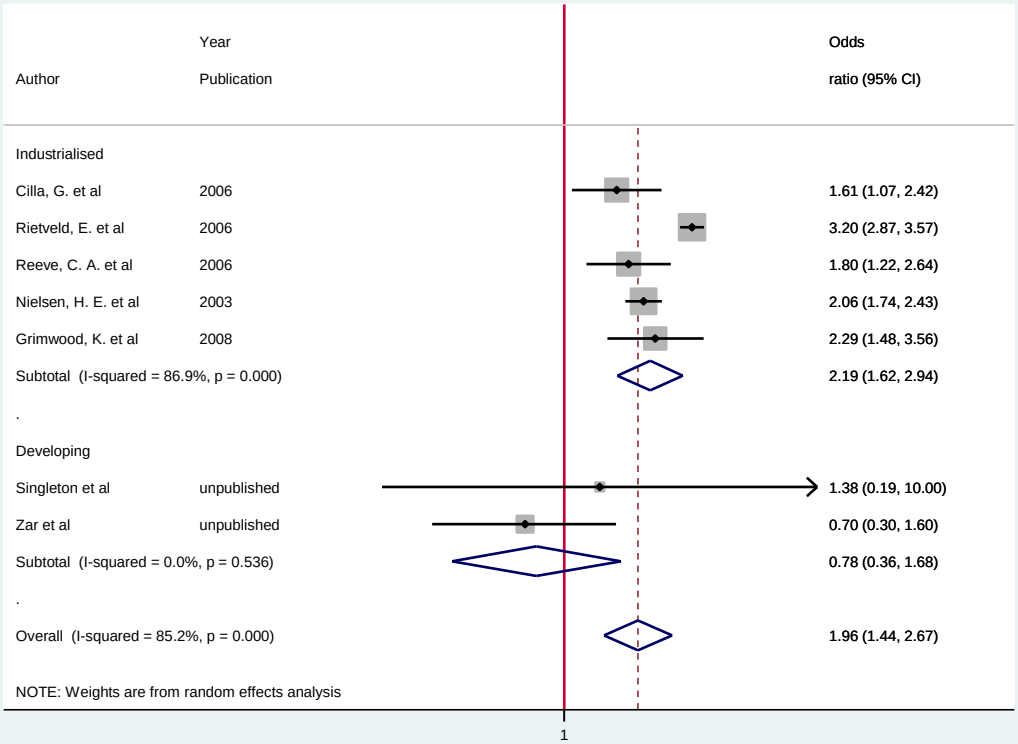
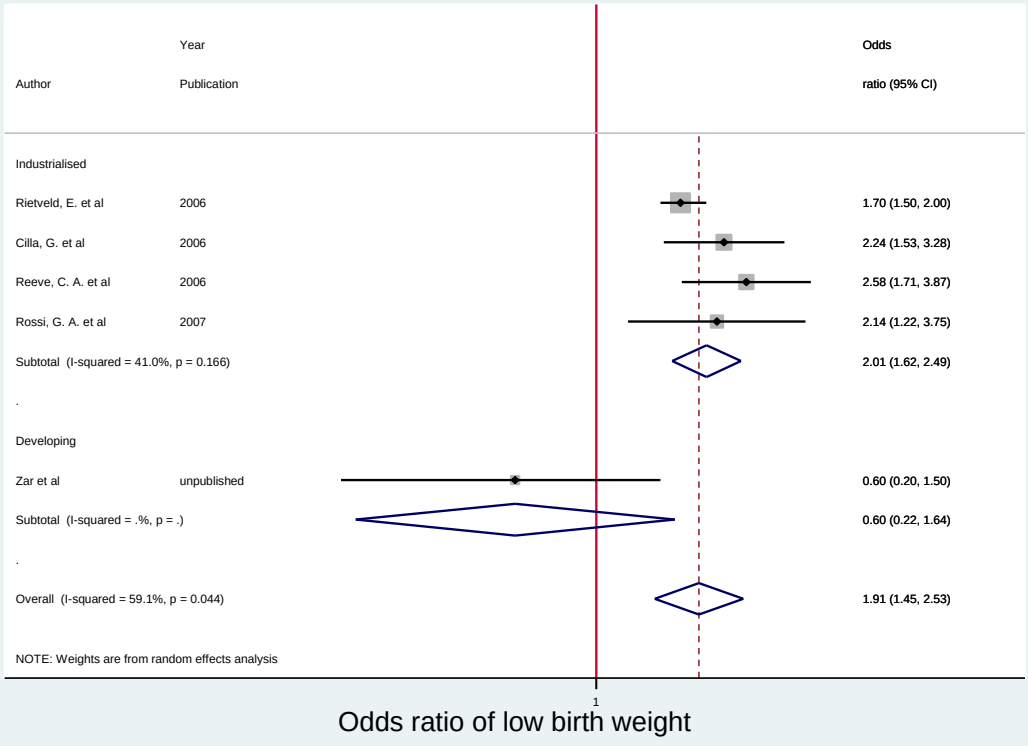
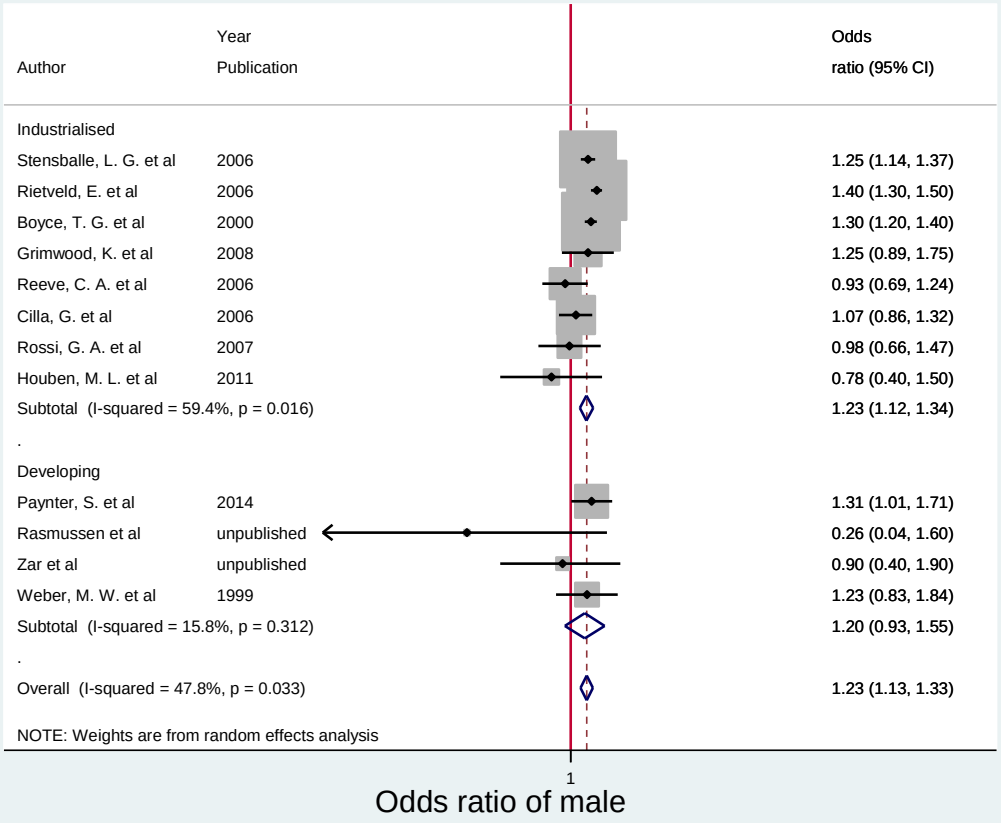
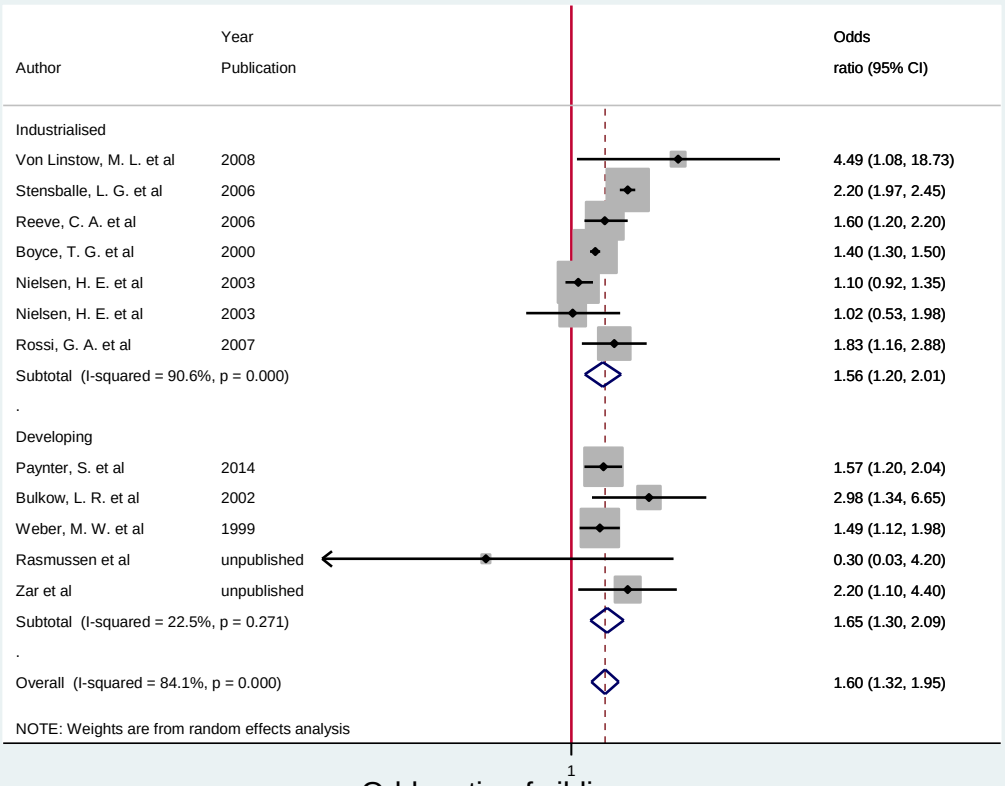
A8. Forest plots for meta-analysis results of 12 risk factors

After excluding "low-quality" studies

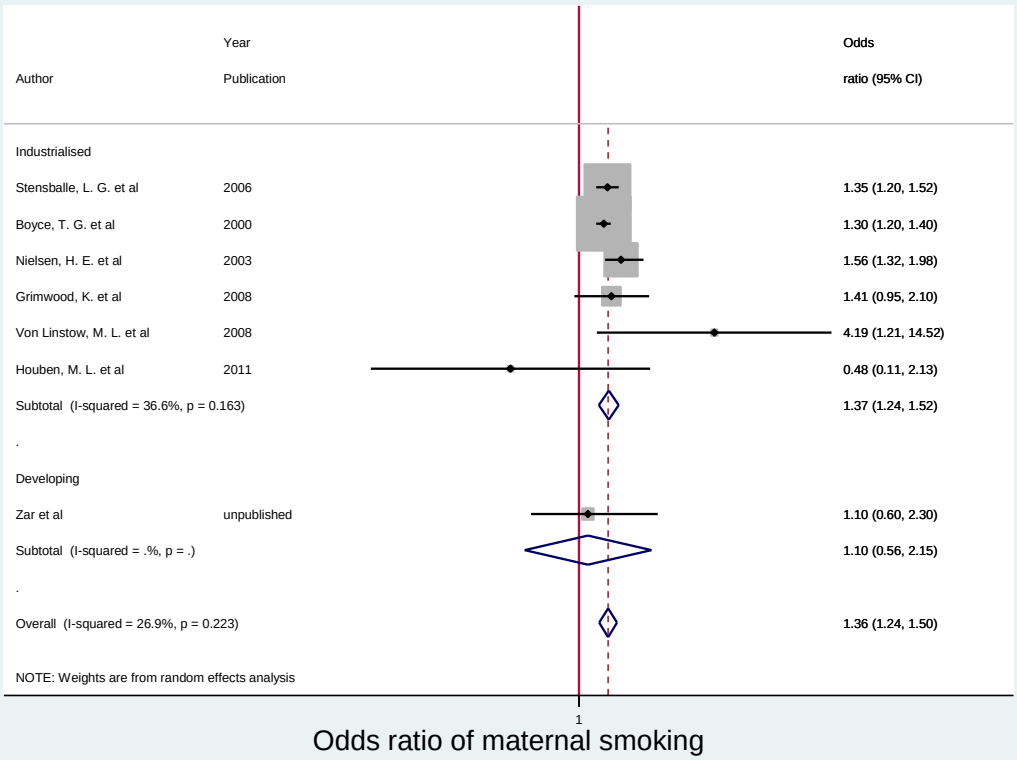




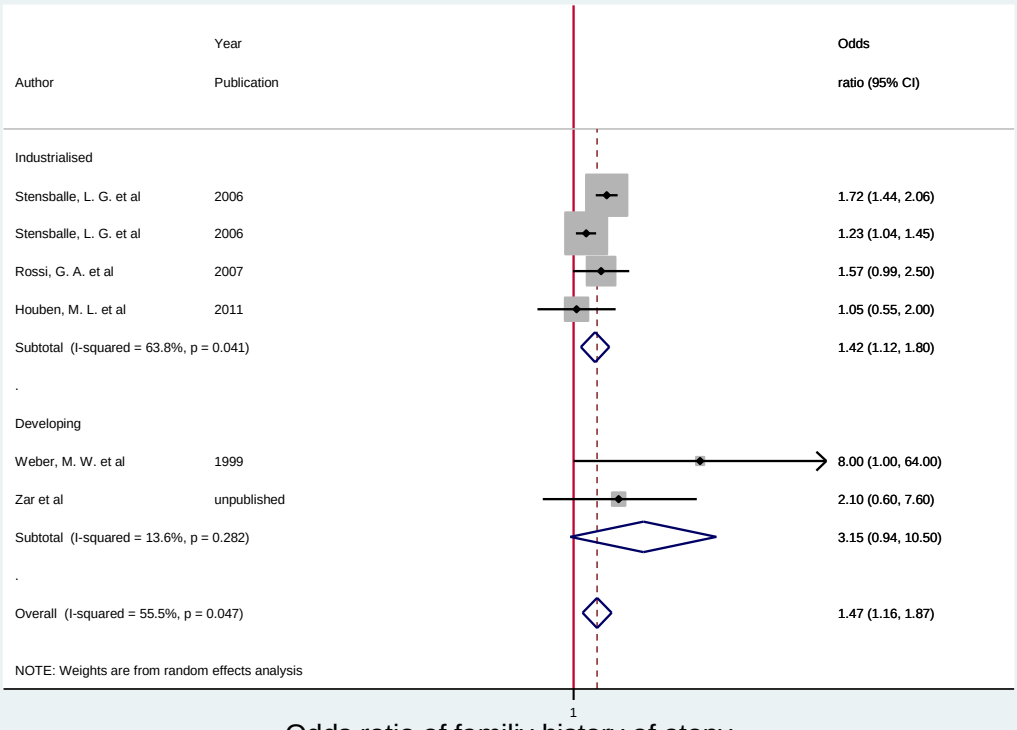

Author
Year
Publication
Odds
ratio (95% CI)
Industrialised
Stensballe, L. G. et al 2006 1.25 (1.14, 1.37)
Rietveld, E. et al 2006 1.40 (1.30, 1.50)
Boyce, T. G. et al 2000 1.30 (1.20, 1.40)
Grimwood, K. et al 2008 1.25 (0.89, 1.75)
Reeve, C. A. et al 2006 0.93 (0.69, 1.24)
Cilla, G. et al 2006 1.07 (0.86, 1.32)
Rossi, G. A. et al 2007 0.98 (0.66, 1.47)
Houben, M. L. et al 2011 0.78 (0.40, 1.50)
Subtotal (I-squared = 59.4%, p = 0.016) 1.23 (1.12, 1.34)
.
Developing
Paynter, S. et al 2014 1.31 (1.01, 1.71)
Rasmussen et al unpublished 0.26 (0.04, 1.60)
Zar et al unpublished 0.90 (0.40, 1.90)
Weber, M. W. et al 1999 1.23 (0.83, 1.84)
Subtotal (I-squared = 15.8%, p = 0.312) 1.20 (0.93, 1.55)
.
Overall (I-squared = 47.8%, p = 0.033) 1.23 (1.13, 1.33)
NOTE: Weights are from random effects analysis
1
Odds ratio of male



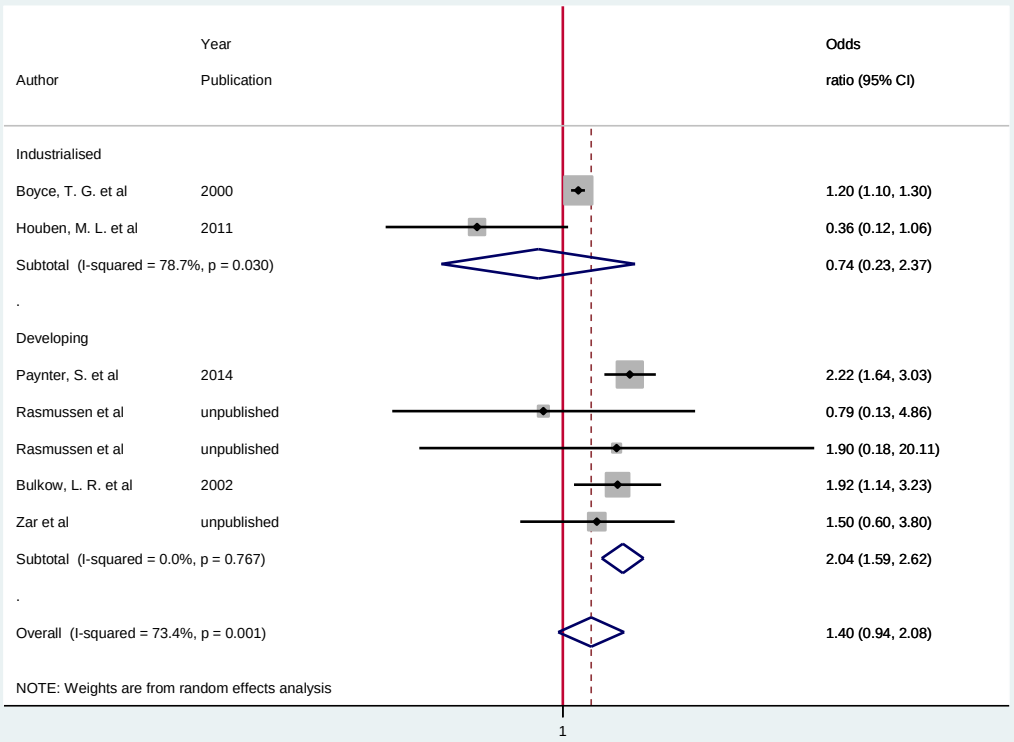
Odds ratio of siblings



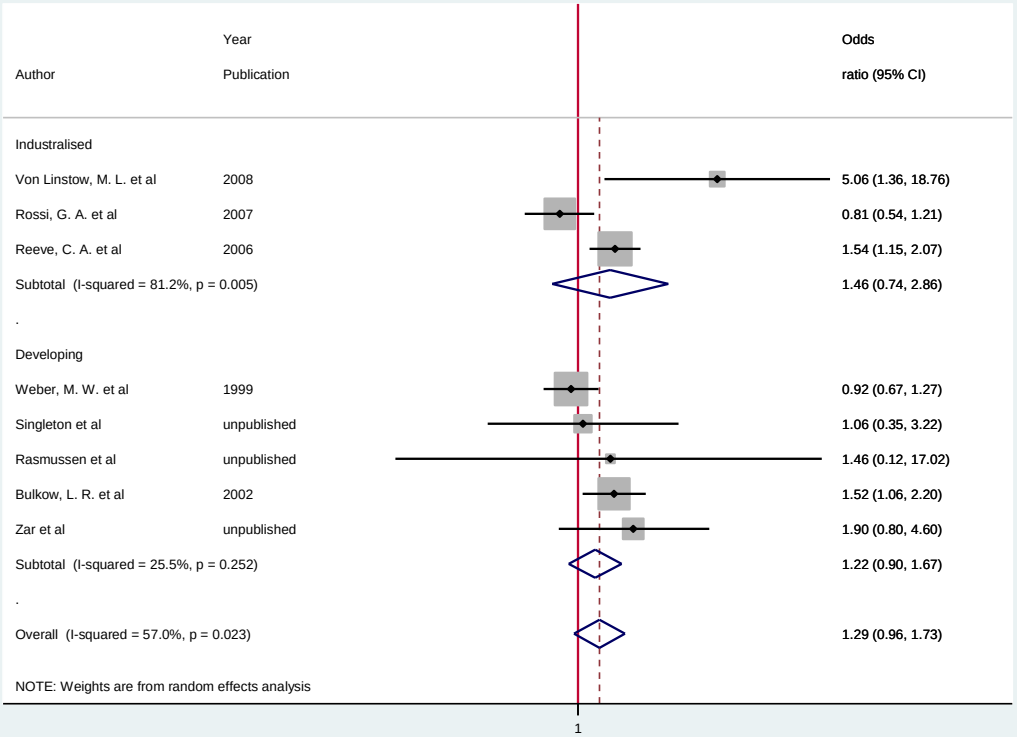
Odds ratio of maternal smoking



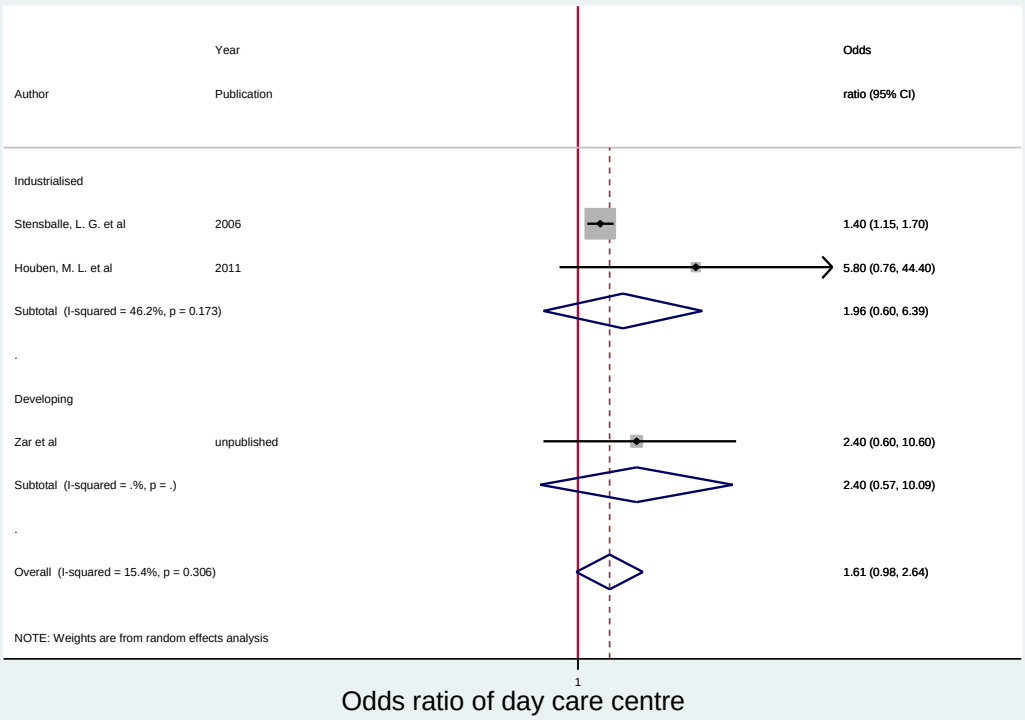
Odds ratio of familiy history of atopy



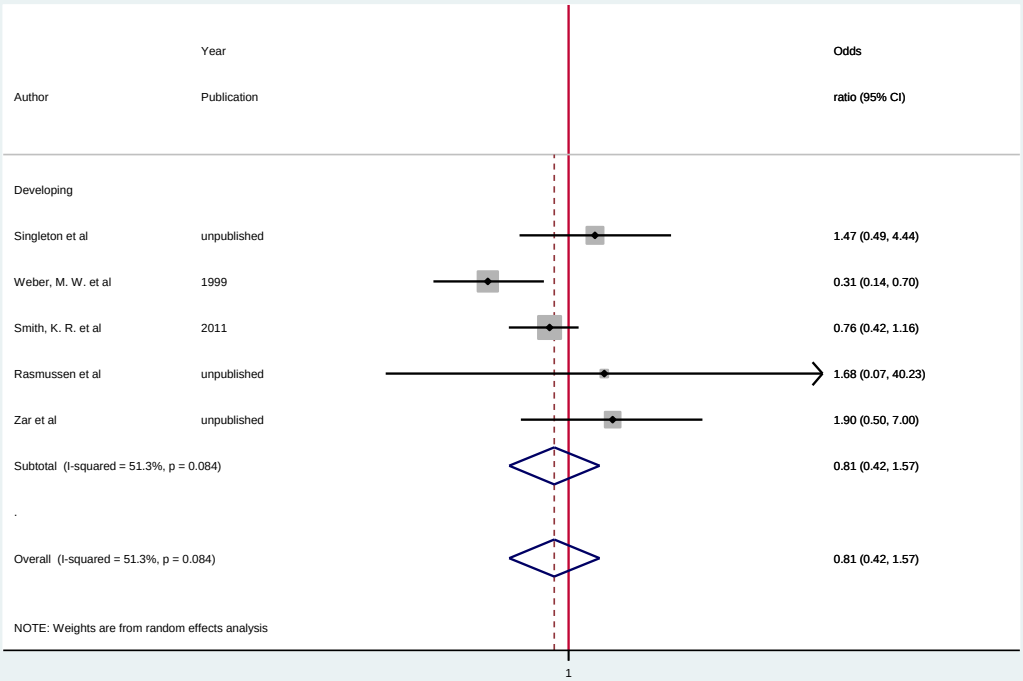
Odds ratio of low parental education



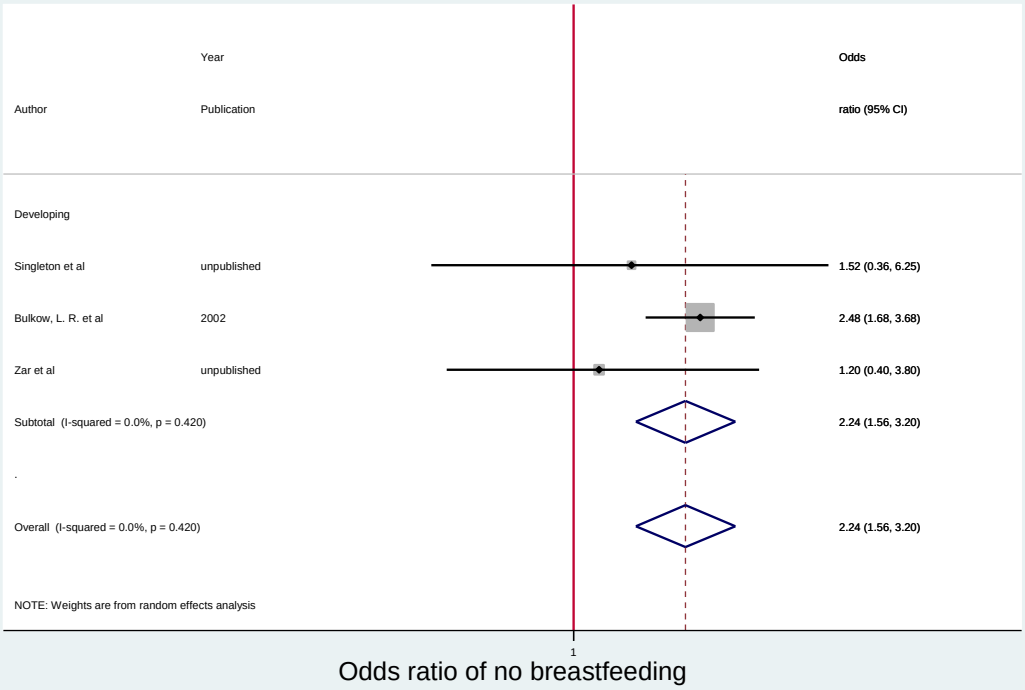
Odds ratio of passive smoking



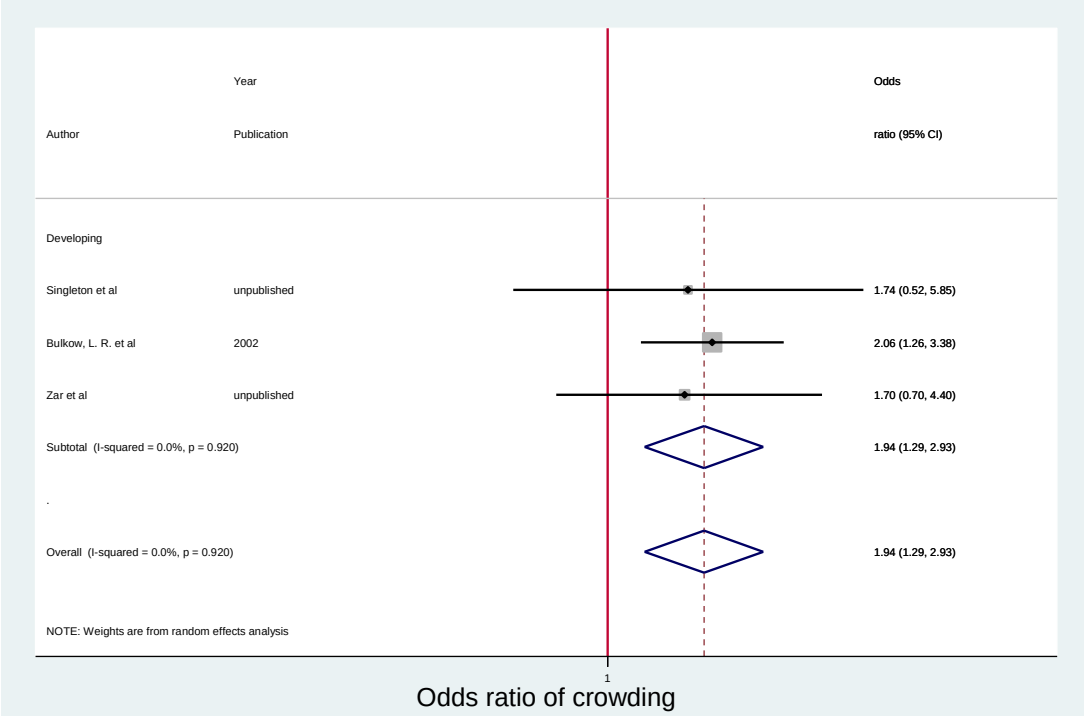
Odds ratio of day care centre



Odds ratio of indoor air pollution



Odds ratio of no breastfeeding


Year
Odds
Author
Publication
ratio (95% CI)
Developing
Singleton et al
unpublished
1.74 (0.52, 5.85)
Bulkow, L. R. et al
2002
2.06 (1.26, 3.38)
Zar et al
unpublished
1.70 (0.70, 4.40)
Subtotal (I-squared = 0.0%, p = 0.920)
1.94 (1.29, 2.93)
.
Overall (I-squared = 0.0%, p = 0.920)
1.94 (1.29, 2.93)
NOTE: Weights are from random effects analysis
1
Odds ratio of crowding

A9. Search strategy of global burden of RSV associated ALRI

Medline

1. exp Respiratory Syncytial Viruses/ or exp Respiratory Syncytial Virus, Human/ or exp Respiratory Syncytial Virus Infections/ or RSV.mp.

2. respiratory syncytial virus*.mp.

3. pneumonia.mp. or exp Pneumonia/ or exp Pneumonia, Viral/

4. bronchiolitis.mp. or exp Bronchiolitis/ or exp Bronchiolitis, Viral/

5. exp Respiratory Tract Infections/ or respiratory infection*.mp.

6. exp Respiratory Tract Diseases/ or respiratory disease*.mp.

7. incidence.mp. or exp Incidence/

8. prevalence.mp. or exp Prevalence/

9. exp Child Mortality/ or exp Infant Mortality/ or mortality.mp. or exp Hospital Mortality/ or exp Mortality/

10. death*.mp. or exp Death/ or exp "Cause of Death"/

11. morbidity.mp. or exp Morbidity/

12. burden.mp.

13. epidemiology.mp. or exp Epidemiology/

14. 1 or 2

15. 3 or 4 or 5 or 6

16. 7 or 8 or 9 or 10 or 11 or 12 or 13

17. 15 or 16

18. 14 and 17

19. limit 18 to (yr="1995 -Current" and ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") and (female or humans or male))

EMBASE

1. RSV.mp. or exp Respiratory syncytial pneumovirus/ or exp respiratory syncytial virus infection/

2. respiratory syncytial virus*.mp.

3. exp community acquired pneumonia/ or exp pneumonia/ or exp virus pneumonia/ or exp infectious pneumonia/ or pneumonia.mp.

4. bronchiolitis.mp. or exp bronchiolitis/ or exp viral bronchiolitis/

5. exp respiratory tract infection/ or exp lower respiratory tract infection/ or respiratory infection*.mp.

6. exp respiratory tract disease/ or respiratory disease*.mp.

7. exp incidence/ or incidence.mp.

8. prevalence.mp. or exp prevalence/

9. exp newborn mortality/ or exp mortality/ or exp childhood mortality/ or mortality.mp. or exp infant mortality/

10. exp death/ or death*.mp. or exp "cause of death"/ or exp child death/

11. morbidity.mp. or exp morbidity/ or exp newborn morbidity/

12. burden.mp.

13. exp epidemiology/ or epidemiology.mp.

14. 1 or 2

15. 3 or 4 or 5 or 6

16. 7 or 8 or 9 or 10 or 11 or 12 or 13

17. 15 or 16

18. 14 and 17

19. limit 18 to (yr="1995 -Current" and (infant or preschool child <1 to 6 years>))

Global Health

1. RSV.mp.

2. exp human respiratory syncytial virus/

3. respiratory syncytial virus*.mp.

4. exp community acquired pneumonia/ or pneumonia*.mp. or exp pneumonia/

5. bronchiolitis.mp. or exp bronchiolitis/

6. respiratory infection*.mp.

7. exp respiratory diseases/

8. respiratory disease*.mp.

9. incidence.mp. or exp disease incidence/ or exp incidence/

10. prevalence*.mp. or exp disease prevalence/

11. mortality.mp. or exp infant mortality/ or exp neonatal mortality/ or exp mortality/

12. death*.mp. or exp death/ or exp "causes of death"/

13. morbidity.mp. or exp morbidity/

14. exp epidemiology/ or epidemiology.mp.

15. burden.mp.

16. 1 or 2 or 3

17. 4 or 5 or 6 or 7 or 8

18. 9 or 10 or 11 or 12 or 13 or 14 or 15

19. 17 or 18

20. 16 and 19

21. limit 20 to yr="1995 -Current"

CINAHL

S1= (MH “respiratory syncytial virus infections”) OR (MH “respiratory syncytial viruses”) OR “respiratory syncytial virus”

S2= “RSV”

S3= (MH “pneumonia+”) OR “pneumonia” OR (MH “pneumonia, viral”) OR (MH “community-acquired pneumonia”)

S4= (MH “bronchiolitis+”) OR “bronchiolitis”

S5= (MH “respiratory tract infections+”) OR “respiratory infection”

S6= (MH “respiratory tract diseases+”) OR “respiratory disease”

S7= (MH “incidence”) OR “incidence”

S8= (MH “prevalence”) OR “prevalence”

S9= (MH “mortality+”) OR “mortality” OR (MH “infant mortality”) OR (MH “child mortality”) OR (MH “hospital mortality”)

S10= (MH “death+”) OR “death” OR (MH “cause of death”) OR (MH “infant death+”)

S11= (MH “morbidity+”) OR “morbidity”

S12= “burden”

S13= (MH “epidemiology+”) OR “epidemiology”

S14= S1 OR S2

S15= S3 OR S4 OR S5 OR S6

S16= S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S17= S15 OR S16

S18= S14 AND S17

Limiters: Published date: 19950101 – 20150804; Age groups: infant, newborn: birth-1 month, infant: 1-23 months, child, preschool: 2-5 years

Web of Science

Topic= (respiratory syncytial virus) AND Topic= (epidemiology) AND Topic= (children)

From 1995 to 2015

WHOLIS (KMS)

Respiratory syncytial virus in All Indexes

LILACS (AMRO/PAHO)

Respiratory syncytial virus in All Indexes

IndMed

RSV in anywhere

SIGLE

Respiratory syncytial virus

CNKI

Topic: respiratory infection or pneumonia (vague)

Or Topic: bronchiolitis (vague)

And Topic: respiratory syncytial virus (vague)

And Topic: children (vague)

Publication time: 1st Jan 1995 – 30th Aug 2015

Wanfang Data

All (vague): respiratory infection or

All (vague): pneumonia or

All (vague): bronchiolitis and

All (vague): respiratory syncytial virus and

All (vague): children

Time: 1995 – 2015

ChongQing VIP

Title/key word: respiratory tract infection

Or Title/key word: pneumonia

Or Title/key word: bronchiolitis

And Title/key word: respiratory syncytial virus

And Title/key word: children

Time: 1995 – 2015

A10. R codes to estimate in-hospital mortality from RSV associated ALRI

In-hospital deaths from RSV associated ALRI in developing countries

```
#Developing in 0-5m
# The population
pop0to5 <- 61545050

# The hospitalisation rate
# Log transform and calculate standard deviation
de0to5 <- c(est = 20.20, lci = 16.66, uci = 24.50)
de0to5_log <- log(de0to5)
de0to5_se <- (de0to5_log["uci"] - de0to5_log["lci"]) / (2*1.96)

# Sample 10,000 from a normal distribution
de0to5_sample <- rnorm(10000, de0to5_log["est"], de0to5_se)
de0to5_sample <- exp(de0to5_sample)

# Summarise and plot the hospitalisation rate
hist(de0to5_sample)
mean(de0to5_sample)
quantile(de0to5_sample, probs = c(0.025, 0.975))

# Case fatality
# Log transform and calculate standard deviation
de0to5_cfr <- c(est = 2.18, lci = 1.80, uci = 2.65)
de0to5_cfr_log <- log(de0to5_cfr)
de0to5_se_cfr <- (de0to5_cfr_log["uci"] - de0to5_cfr_log["lci"]) / (2*1.96)

# sample 10,000 from a normal distribution
de0to5_cfr_sample <-  rnorm(10000, de0to5_cfr_log["est"], de0to5_se_cfr)
de0to5_cfr_sample <- exp(de0to5_cfr_sample)

# Summarise and plot cfr
plot(density((de0to5_cfr_sample)), xlim = c(0,10))
median((de0to5_cfr_sample))
quantile((de0to5_cfr_sample), probs = c(0.025, 0.975))
```

```
## Combine two samples to make estimate for number of deaths
de0to5_num_deaths_sample <-(de0to5_sample) * 0.001 * pop0to5 * 0.01 * (de0to5_cfr_sample)

## Examine combined results
plot(density((de0to5_num_deaths_sample)), xlim= c(0,40000))
quantile((de0to5_num_deaths_sample), probs = c(0.025, 0.975))
median(de0to5_num_deaths_sample)

####### Developing 0-5m deaths



#Developing in 6-11m
# The population
pop6to11 <- 61545050

# The hospitalisation rate
# Log transform and calculate standard deviation
de6to11 <- c(est = 10.95, lci = 7.66, uci = 15.65)
de6to11_log <- log(de6to11)
de6to11_se <- (de6to11_log["uci"] - de6to11_log["lci"]) / (2*1.96)

# Sample 10,000 from a normal distribution
de6to11_sample <- rnorm(10000, de6to11_log["est"], de6to11_se)
de6to11_sample <- exp(de6to11_sample)

# Summarise and plot the hospitalisation rate
hist(de6to11_sample)
mean(de6to11_sample)
quantile(de6to11_sample, probs = c(0.025, 0.975))

# Case fatality
# Log transform and calculate standard deviation
de6to11_cfr <- c(est = 2.44, lci = 1.85, uci = 3.23)
de6to11_cfr_log <- log(de6to11_cfr)
de6to11_se_cfr <- (de6to11_cfr_log["uci"] - de6to11_cfr_log["lci"]) / (2*1.96)

# sample 10,000 from a normal distribution
de6to11_cfr_sample <-  rnorm(10000, de6to11_cfr_log["est"], de6to11_se_cfr)
```

```
de6to11_cfr_sample <- exp(de6to11_cfr_sample)

# Summarise and plot cfr
plot(density((de6to11_cfr_sample)), xlim = c(0,10))
median((de6to11_cfr_sample))
quantile((de6to11_cfr_sample), probs = c(0.025, 0.975))

## Combine two samples to make estimate for number of deaths
de6to11_num_deaths_sample <-(de6to11_sample) * 0.001 * pop6to11 * 0.01 * (de6to11_cfr_sample)

## Examine combined results
plot(density((de6to11_num_deaths_sample)), xlim= c(0,25000))
quantile((de6to11_num_deaths_sample), probs = c(0.025, 0.975))
median(de6to11_num_deaths_sample)

####### Developing 6-11m deaths



#Developing in 12-59m
# The population
pop12to59 <- 477627786

# The hospitalisation rate
# Log transform and calculate standard deviation
de12to59 <- c(est = 1.45, lci = 1.01, uci = 2.10)
de12to59_log <- log(de12to59)
de12to59_se <- (de12to59_log["uci"] - de12to59_log["lci"]) / (2*1.96)

# Sample 10,000 from a normal distribution
de12to59_sample <- rnorm(10000, de12to59_log["est"], de12to59_se)
de12to59_sample <- exp(de12to59_sample)

# Summarise and plot the hospitalisation rate
hist(de12to59_sample)
mean(de12to59_sample)
quantile(de12to59_sample, probs = c(0.025, 0.975))

# Case fatality
```

```
# Log transform and calculate standard deviation
de12to59_cfr <- c(est = 2.20, lci = 1.60, uci = 3.02)
de12to59_cfr_log <- log(de12to59_cfr)
de12to59_se_cfr <- (de12to59_cfr_log["uci"] - de12to59_cfr_log["lci"]) / (2*1.96)

# sample 10,000 from a normal distribution
de12to59_cfr_sample <-  rnorm(10000, de12to59_cfr_log["est"], de12to59_se_cfr)
de12to59_cfr_sample <- exp(de12to59_cfr_sample)

# Summarise and plot cfr
plot(density((de12to59_cfr_sample)), xlim = c(0,10))
median((de12to59_cfr_sample))
quantile((de12to59_cfr_sample), probs = c(0.025, 0.975))

## Combine samples to make estimate for number of deaths
de12to59_num_deaths_sample <-(de12to59_sample) * 0.001 * pop12to59 * 0.01 * (de12to59_cfr_sample)

## Examine combined results
plot(density((de12to59_num_deaths_sample)), xlim= c(0,30000))
quantile((de12to59_num_deaths_sample), probs = c(0.025, 0.975))
median(de12to59_num_deaths_sample)

####### Developing 12-59m deaths


####### deaths in 0-59m in developing countries (sum of estimates in 0-5m, 6-11m, 12-59m)
de0to59_num_deaths_sample <- (de0to5_num_deaths_sample)+(de6to11_num_deaths_sample)+(de12to59_num_deaths_sample)
plot(density((de0to59_num_deaths_sample)), xlim=c(0,80000))
quantile((de0to59_num_deaths_sample), probs = c(0.025, 0.975))
median(de0to59_num_deaths_sample)
```

In-hospital deaths from RSV associated ALRI in industrialised countries

```
#Industrialised in 0-5m
# The population
pop0to5 <- 6778914
```

```
# The hospitalisation rate
# Log transform and calculate standard deviation
ind0to5 <- c(est = 27.26, lci = 23.14, uci = 32.11)
ind0to5_log <- log(ind0to5)
ind0to5_se <- (ind0to5_log["uci"] - ind0to5_log["lci"]) / (2*1.96)

# Sample 10,000 from a normal distribution
ind0to5_sample <- rnorm(10000, ind0to5_log["est"], ind0to5_se)
ind0to5_sample <- exp(ind0to5_sample)

# Summarise and plot the hospitalisation rate
hist(ind0to5_sample)
mean(ind0to5_sample)
quantile(ind0to5_sample, probs = c(0.025, 0.975))

# Case fatality
# Log transform and calculate standard deviation
ind0to5_cfr <- c(est = 0.02, lci = 0+0.00005, uci = 0.13)
ind0to5_cfr_log <- log(ind0to5_cfr)
ind0to5_se_cfr <- (ind0to5_cfr_log["uci"] - ind0to5_cfr_log["lci"]) / (2*1.96)

# sample 10,000 from a normal distribution
ind0to5_cfr_sample <-  rnorm(10000, ind0to5_cfr_log["est"], ind0to5_se_cfr)
ind0to5_cfr_sample <- exp(ind0to5_cfr_sample)

# Summarise and plot cfr
plot(density((ind0to5_cfr_sample)), xlim = c(0,10))
median((ind0to5_cfr_sample))
quantile((ind0to5_cfr_sample), probs = c(0.025, 0.975))

## Combine two samples to make estimate for number of deaths
ind0to5_num_deaths_sample <-(ind0to5_sample) * 0.001 * pop0to5 * 0.01 * (ind0to5_cfr_sample)

## Examine combined results
plot(density((ind0to5_num_deaths_sample)), xlim= c(0,40000))
quantile((ind0to5_num_deaths_sample), probs = c(0.025, 0.975))
median(ind0to5_num_deaths_sample)
```

```
####### Industrialised 0-5m deaths


#Industrialised in 6-11m
# The population
pop6to11 <- 6778914

# The hospitalisation rate
# Log transform and calculate standard deviation
ind6to11 <- c(est = 11.53, lci = 5.49, uci = 24.23)
ind6to11_log <- log(ind6to11)
ind6to11_se <- (ind6to11_log["uci"] - ind6to11_log["lci"]) / (2*1.96)

# Sample 10,000 from a normal distribution
ind6to11_sample <- rnorm(10000, ind6to11_log["est"], ind6to11_se)
ind6to11_sample <- exp(ind6to11_sample)

# Summarise and plot the hospitalisation rate
hist(ind6to11_sample)
mean(ind6to11_sample)
quantile(ind6to11_sample, probs = c(0.025, 0.975))

# Case fatality
# Log transform and calculate standard deviation
ind6to11_cfr <- c(est = 0.05, lci = 0.01, uci = 0.38)
ind6to11_cfr_log <- log(ind6to11_cfr)
ind6to11_se_cfr <- (ind6to11_cfr_log["uci"] - ind6to11_cfr_log["lci"]) / (2*1.96)

# sample 10,000 from a normal distribution
ind6to11_cfr_sample <-  rnorm(10000, ind6to11_cfr_log["est"], ind6to11_se_cfr)
ind6to11_cfr_sample <- exp(ind6to11_cfr_sample)

# Summarise and plot cfr
plot(density((ind6to11_cfr_sample)), xlim = c(0,10))
median((ind6to11_cfr_sample))
quantile((ind6to11_cfr_sample), probs = c(0.025, 0.975))
```

```
## Combine two samples to make estimate for number of deaths
ind6to11_num_deaths_sample <-(ind6to11_sample) * 0.001 * pop6to11 * 0.01 * (ind6to11_cfr_sample)

## Examine combined results
plot(density((ind6to11_num_deaths_sample)), xlim= c(0,25000))
quantile((ind6to11_num_deaths_sample), probs = c(0.025, 0.975))
median(ind6to11_num_deaths_sample)

####### Industrialised 6-11m deaths



#Industrialised in 12-59m
# The population
pop12to59 <- 56260723

# The hospitalisation rate
# Log transform and calculate standard deviation
ind12to59 <- c(est = 2.01, lci = 1.30, uci = 3.12)
ind12to59_log <- log(ind12to59)
ind12to59_se <- (ind12to59_log["uci"] - ind12to59_log["lci"]) / (2*1.96)

# Sample 10,000 from a normal distribution
ind12to59_sample <- rnorm(10000, ind12to59_log["est"], ind12to59_se)
ind12to59_sample <- exp(ind12to59_sample)

# Summarise and plot the hospitalisation rate
hist(ind12to59_sample)
mean(ind12to59_sample)
quantile(ind12to59_sample, probs = c(0.025, 0.975))

# Case fatality
# Log transform and calculate standard deviation
ind12to59_cfr <- c(est = 0.09, lci = 0.03, uci = 0.25)
ind12to59_cfr_log <- log(ind12to59_cfr)
ind12to59_se_cfr <- (ind12to59_cfr_log["uci"] - ind12to59_cfr_log["lci"]) / (2*1.96)

# sample 10,000 from a normal distribution
ind12to59_cfr_sample <-  rnorm(10000, ind12to59_cfr_log["est"], ind12to59_se_cfr)
```

```
ind12to59_cfr_sample <- exp(ind12to59_cfr_sample)

# Summarise and plot cfr
plot(density((ind12to59_cfr_sample)), xlim = c(0,10))
median((ind12to59_cfr_sample))
quantile((ind12to59_cfr_sample), probs = c(0.025, 0.975))

## Combine samples to make estimate for number of deaths
ind12to59_num_deaths_sample <-(ind12to59_sample) * 0.001 * pop12to59 * 0.01 * (ind12to59_cfr_sample)

## Examine combined results
plot(density((ind12to59_num_deaths_sample)), xlim= c(0,30000))
quantile((ind12to59_num_deaths_sample), probs = c(0.025, 0.975))
median(ind12to59_num_deaths_sample)

####### Developing 12-59m deaths


####### deaths in 0-59m in industrialised countries (sum of estimates in 0-5m, 6-11m, 12-59m)
ind0to59_num_deaths_sample <- (ind0to5_num_deaths_sample)+(ind6to11_num_deaths_sample)+(ind12to59_num_deaths_sample)
plot(density((ind0to59_num_deaths_sample)), xlim=c(0,80000))
quantile((ind0to59_num_deaths_sample), probs = c(0.025, 0.975))
median(ind0to59_num_deaths_sample)
```

In-hospital deaths from RSV associated ALRI in children aged 0-59m

```
####### global deaths in 0-59m

num0to59_deaths_sample <-(de0to59_num_deaths_sample)+(ind0to59_num_deaths_sample)
plot(density((num0to59_deaths_sample)), xlim=c(0,300000))
quantile((num0to59_deaths_sample), probs = c(0.025, 0.975))
median(num0to59_deaths_sample)


####### global deaths in 0-59m after adjustment
num0to59_deaths_sample_adjust <- (de0to59_num_deaths_sample)*2.2+(ind0to59_num_deaths_sample)
```

```
plot(density((num0to59_deaths_sample_adjust)), xlim=c(0,300000))
quantile((num0to59_deaths_sample_adjust), probs = c(0.025, 0.975))
median(num0to59_deaths_sample_adjust)
```

A11. List of excluded articles during full-text review in the study of the global burden of RSV associated ALRI

Less than 12-months surveillance (102 articles)

1. Bennett BL, Garofalo RP, Cron SG, et al. Immunopathogenesis of respiratory syncytial virus bronchiolitis. *J Infect Dis* 2007; **195**(10): 1532-40.

2. Jennings LC, Anderson TP, Werno AM, Beynon KA, Murdoch DR. Viral etiology of acute respiratory tract infections in children presenting to hospital: role of polymerase chain reaction and demonstration of multiple infections. *Pediatr Infect Dis J* 2004; **23**(11): 1003-7.

3. Jacques J, Moret H, Renois F, Leveque N, Motte J, Andreoletti L. Human Bocavirus quantitative DNA detection in French children hospitalized for acute bronchiolitis. *J Clin Virol* 2008; **43**(2): 142-7.

4. Ciervo A, Mancini F, Puzelli S, et al. Detection and correlates of Chlamydophila pneumoniae among children with acute respiratory infections. *Journal of Pediatric Infectious Diseases* 2010; **5**(3): 249-54.

5. Wu H, Deng J, Qian Y, et al. [Viruses and clinical features associated with hospitalized children with acute respiratory infections in Lhasa, Tibet]. [Chinese]. *Zhonghua Er Ke Za Zhi* 2012; Chinese journal of pediatrics. **50**(10): 740-2.

6. Hamze M, Hlais S, Rachkidi J, Mallat H, Lichaa E, Zahab N. Infections with respiratory syncytial virus in North Lebanon - prevalence during winter 2008. [French]. *Eastern Mediterranean Health Journal* 2010; **16**(5): 539-45.

7. Mammas IN, Koutsaftiki C, Nika E, et al. Detection of human metapneumovirus in infants with acute respiratory tract infection. *Mol Med Report* 2011; **4**(2): 267-71.

8. Lopez Guinea A, Casado Flores J, Martin Sobrino Ma A, et al. Severe bronchiolitis. Epidemiology and clinical course of 284 patients. [Spanish]

Bronquiolitis grave. Epidemiologia y evolucion de 284 pacientes. *Anales de Pediatria* 2007; **67**(2): 116-22.

9. Mansbach JM, Piedra PA, Teach SJ, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med* 2012; **166**(8): 700-6.

10. Alavi SM, Makvandi M, Fard SN, Alavi L. Human respiratory syncytial virus infection and its subgroups among the hospitalized young children with acute respiratory infection. *Jundishapur Journal of Microbiology* 2013; **6**(8).

11. Ding G, Wang L, Wang Z. Viral etiological analysis on hospitalized children with acute lower respiratory tract infection in Jiujiang area in winter and spring from 2008 to 2012. [Chinese]. *Matern Child Health Care China* 2013; **28**(35): 5828-9.

12. Faghihloo E, Rezaie F, Salimi V, et al. Molecular epidemiology of human respiratory syncytial virus in Iran. *Acta Virol* 2011; **55**(1): 81-3.

13. Boyce TG, Weaver AL, St Sauver JL, Stancl JK, Woodward-Lee AE. Incidence of bronchiolitis-associated hospitalization among children in Olmsted County, Minnesota. *Mayo Clin Proc* 2004; **79**(6): 832-3.

14. Winterstein AG, Hampp C, Saidi A. Effectiveness of palivizumab prophylaxis in infants and children in Florida. *Pharmacoepidemiol Drug Saf* 2012; **21**(1): 53-60.

15. Midulla F, Scagnolari C, Bonci E, et al. Respiratory syncytial virus, human bocavirus and rhinovirus bronchiolitis in infants. *Arch Dis Child* 2010; **95**(1): 35-41.

16. Farshad N, Saffar MJ, Khalilian AR, Saffar H. Respiratory viruses in hospitalized children with acute lower respiratory tract infections, Mazandaran Province, Iran. *Indian Pediatr* 2008; **45**(7): 590-2.

17. Kayiran SM, Paloglu E, Gurakan B. The frequency, clinical and laboratory features of RSV in small children with bronchiolitis [Turkish]. *Turkish Pediatrics Archive / Turk Pediatri Arsivi* 2010; **45**(3): 252-6.

18. Navarro-Mari JM, Palacios Del Valle E, Perez-Ruiz M, De La Rosa M. The impact of influenza viruses on hospitalizations in infants younger than two years old during epidemics of respiratory syncytial virus infection. *Clin Microbiol Infect* 2003; **9**(9): 959-63.

19. Ajayi-Obe EK, Coen PG, Handa R, et al. Influenza A and respiratory syncytial virus hospital burden in young children in East London. *Epidemiol Infect* 2008; **136**(8): 1046-58.

20. Hatipoglu S, Arica S, Çelik Y, Öztora S, Sevketoglu E, Erkum T. The frequency and clinical features of RSV infection among babies hospitalized with the diagnosis of lower respiratory tract infection [Turkish]. *Duzce Medical Journal* 2009; **11**(1): 38-44.

21. Bilavsky E, Yarden-Bilavsky H, Shouval DS, et al. Respiratory syncytial virus-positive bronchiolitis in hospitalized infants is associated with thrombocytosis. *Israel Medical Association Journal: Imaj* 2010; **12**(1): 39-41.

22. Laurent C, Dugue AE, Brouard J, et al. Viral epidemiology and severity of respiratory infections in infants in 2009: a prospective study. *Pediatr Infect Dis J* 2012; **31**(8): 827-31.

23. Bicer S, Giray T, Col D, et al. Virological and clinical characterizations of respiratory infections in hospitalized children. *Ital J Pediatr* 2013; **39**: 22.

24. Jansen RR, Schinkel J, Dek I, et al. Quantitation of respiratory viruses in relation to clinical course in children with acute respiratory tract infections. *Pediatr Infect Dis J* 2010; **29**(1): 82-4.

25. Brouard J, Freymuth F, Vabret A, Jokic M, Guillois B, Duhamel JF. [Viral co-infections in immunocompetent infants with bronchiolitis: prospective epidemiologic study]. *Arch Pediatr* 2000; **7 Suppl 3**: 531s-5s.

26. Beneri C, Ginocchio CC, Manji R, Sood S. Comparison of clinical features of pediatric respiratory syncytial virus and human metapneumovirus infections. *Infect Control Hosp Epidemiol* 2009; **30**(12): 1240-1.

27. Culebras E, Betriu C, Vazquez-Cid E, Lopez-Varela E, Rueda S, Picazo JJ. Detection and genotyping of human respiratory viruses in clinical specimens from children with acute respiratory tract infections

Deteccion y genotipado de virus respiratorios humanos en muestras clinicas de ninos con infeccion respiratoria aguda. *Rev Esp Quimioter* 2013; **26**(1): 47-50.

28. Hatipoglu N, Somer A, Badur S, et al. Viral etiology in hospitalized children with acute lower respiratory tract infection. *Turk J Pediatr* 2011; **53**(5): 508-16.

29. Gupta S, Shamsundar R, Shet A, Chawan R, Srinivasa H. Prevalence of respiratory syncytial virus infection among hospitalized children presenting with acute lower respiratory tract infections. *Indian J Pediatr* 2011; **78**(12): 1495-7.

30. Baumeister EG, Hunicken DS, Savy VL. RSV molecular characterization and specific antibody response in young children with acute lower respiratory infection. *J Clin Virol* 2003; **27**(1): 44-51.

31. Anita C, Bineeta K. Respiratory syncytial virus in lower respiratory tract infections. *Iranian Journal of Pediatrics* 2007; **17**(2): 123-8.

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A12. List of studies reporting untested ALRI and corresponding reasons

Reference	% of eligible cases not tested for RSV	Reasons for not testing
Dhaka, Bangladesh (Jan 2005 - Feb 2008) (Brooks, unpublished)	19.3 (290/1500)	NA
Bandung, Indonesia (1st Feb 1999 - 26th Apr 2001) (Simoes, unpublished)	65.6 (1535/2339)	subjects did not meet case definition (LRI)
Gilgit, Pakistan (1st Apr 2012 - 31st Mar 2014) (Rasmussen, unpublished)	14.3 (34/238)	child absent when collecting samples, samples were not valid by the time it reached the testing center, mother refusal
Paarl, South Africa (Mar 2012 - Dec 2014) (Zar, unpublished)	36.1 (116/321)	specimen not collected, PCR results not available
Sa Kaeo and Nakhom Phanom, Thailand (1st Jan 2004 - 31st Dec 2007) (Fry et al., 2010)	51.5 (11760/22857)	NA
Damanhour, Egypt (Jun 2009 - Jun 2012) (Rowlinson et al., 2013)	12.4 (659/5324)	no informed consent or samples
Multicentric, Germany (Nov 1999 - Oct 2001) (Forster et al., 2004)	36.9 (1078/2924)	no informed consent, unavailable clinical specimens or specimens were not tested
Banjul, Fajara and Sibanor, Gambia (Jan 1994 - Dec 1996) (Weber et al., 2002)	59.5 (3305/5557)	no village of origin documented, from outside the western region, no sex documented, samples not being taken because children admitted during weekends/holidays, absence of the patient from the ward for investigations and lack of documentation of an admission diagnosis on the patient's chart
Nashville, Rochester and Cincinnati, USA (Oct 2000 - Sep 2004) (Hall et al., 2009)	18.6 (1158/6225)	a lack of parental consent or unavailability of parents
CEMIC, Buenos Aires, Argentina (1st Jun 2008 - 31st Dec 2010) (Echavarria, unpublished)	5.3 (3/57)	insufficient sample
Buenos Aires, Argentina (2011 - 2013) (Polack, unpublished)	0.9 (30/3371)	sample inadequate
Belo Horizonte, Brazil (2011 - 2013) (Oliveira, unpublished)	59.4 (757/1275)	frozen samples at weekends; laboratory refused
Concepcion, Chile (Jan	3.3 (16/481)	cases were not notified in time so as to collect

Reference	% of eligible cases not tested for RSV	Reasons for not testing
2012 - Dec 2013) (Fasce, unpublished)		sample
Iquique, Chile (Jan 2012 - Dec 2013) (Fasce, unpublished)	0.6 (4/683)	cases were not notified in time so as to collect sample
Jingzhou, China (Jan 2010 - Dec 2012) (Yu, unpublished)	97.1 (19092/19660)	sample selection
Santa Ana, El Salvador (2008 - 2013) (Clara, unpublished)	78.8 (4388/5570)	NA
Gambia Western Region, Gambia (Jul 2007 - Jun 2008) (Howie, unpublished)	4.2 (4/95)	technical problem with specimen
Santa Rosa, Guatemala (2008 - 2013) (McCracken, unpublished)	5.7 (104/1810)	no consent or no specimen
Quetzaltenango, Guatemala (2009 - 2013) (McCracken, unpublished)	10.9 (207/1893)	no consent or no specimen
Pune, India (May 2009 - Apr 2013) (Chadha, unpublished)	12.7 (78/612)	poor quality swab; inadequate specimen; sample lost
Lombok, Indonesia (2000 - 2002) (Gessner, unpublished)	28.9 (1500/5198)	primarily age <3 months and critical illness on presentation; specimens collected 4 days a week so if patients who had rapid admission, would not have been done
Kilifi hospital study, Kenya (Jan 2002 - Dec 2010) (Nokes, unpublished)	24.4 (2817/11544)	died; discharged; refusal
Bondo district, Kenya (Jan 2007 - Jun 2009) (Feikin, unpublished)	28.7 (208/726)	low swab quality
Manhiça, Mozambique (20th Sep 2006 - 19th Sep 2007) (Bassat, unpublished)	3.4 (28/835)	NPA not collected or processed without results
Manhiça, Mozambique (1st Jan 2011 - 30th Jun 2014) (Bassat, unpublished)	3.1 (15/491)	NPA not collected or processed without results
41 sites in Netherlands (2008 - 2013) (Bont, unpublished)	10.0 (24/241)	reasons for not testing are unknown, as the decisions for testing are made by independent physicians at hospital of presentation

Reference	% of eligible cases not tested for RSV	Reasons for not testing
David City, Panama (Jan 2011 - Dec 2013) (Jara, unpublished)	81.8 (2152/2631)	lack of resources at the lab to test
Tagbilaran and 6 rural sites, Philippines (5th Jul 2000 - 31st Dec 2004) (Lucero, unpublished)	36.0 (537/1491)	no specimen collected for those cases not tested for RSV
Gauteng province, South Africa (2009 - 2012) (Cohen, unpublished)	2.0 (122/6016)	child too ill to take sample from; specimens not reaching laboratory within 72 hours
KwaZulu-Natal province, South Africa (2010 - 2014) (Cohen, unpublished)	4.5 (72/1607)	patient very ill; parents refuse consent, specimen not at lab within 72 hours
Klerksdorp site, South Africa (Jan 2011 - Dec 2014) (Cohen, unpublished)	3.2 (30/932)	patient very ill; parents refuse consent, specimen not at lab within 72 hours
Soweto, South Africa (Mar 1998 - Oct 2005) (Madhi, unpublished)	4.6 (240/5231)	missed as part of surveillance
Male Camp, Tak Province, Thailand (Nov 2007 - Oct 2010) (Turner, unpublished)	2.3 (8/354)	parents refused NPA taken
Sa Kaeo and Nakhon Phanom, Thailand (Jan 2008 - Dec 2011) (Thamthitiwat, unpublished)	75.0 (14334/19103)	NA
Tone district, Togo (Aug 2011 - Dec 2013) (Gessner, unpublished)	3.2 (4/124)	testing just started
Alaska, USA (Jul 1994 - Jun 2012) (Singleton, unpublished)	20.5 (1222/5965)	at provider discretion
Navajo and WMA, USA - MEDI (Oct 2004 - Dec 2010) (O'Brien, unpublished)	3.8 (5/132)	specimen not collected, most probably due to short hospitalisation stay (<2 days)
Nha Trang, Vietnam (Feb 2007 - Dec 2012) (Yoshida, unpublished)	3.1 (25/795)	some sample being lost
Subiaco, Australia (Jan 2000 - Dec 2005) (Moore et al., 2012)	54.8 (10877/19849)	NA
Lanzhou, China (Oct 2004 - Oct 2005) (Zhang et al.,	7.1 (63/884)	lack of consent and convalescent serum sample

Reference	% of eligible cases not tested for RSV	Reasons for not testing
2011)		was not obtained
Hong Kong, China (Nov 2005 - Oct 2006) (Sung et al., 2009)	80	sampling
Nagasaki, Japan (Apr 2009 - Mar 2010) (Harada et al., 2013)	3.0 (13/433)	NA
Seoul, Korea (Jan - Dec 2004) (Yoo et al., 2007)	71.8 (509/709)	excluded during sampling process and small quantities not enough for RNA extraction
Khon Kaen, Thailand (Apr 2002 - Aug 2004) (Teeratakulpisarn et al., 2007)	35.0 (91/260)	parents didn't give consent for collection of NPA from their children; inappropriately stored for viral detection
Tak Province, Thailand (Apr 2009 - Sep 2011) (Turner et al., 2013)	14.0 (117/836)	failure to meet the case definition; presented twice within 14 days; inadequate specimens
Turku, Finland (Jan 1993 - Dec 1995) (Juven et al., 2000)	14.2 (42/296)	a convalescent serum sample was not obtained, chest radiographs did not have infiltrates compatible with pneumonia at the reevaluation done by 3 pediatric radiologists, or the radiographs were not available for the reevaluation
Kiel, Germany (Jul 1996 - Jun 2001) (Weigl et al., 2002b)	37.3 (1015/2721)	NA
Pisa, Italy (Jan 2000 - May 2006) (Maggi et al., 2007)	19.5 (39/200)	some specimens were frozen immediately after collection and unsuitable for virus detection by DFA or rapid culture in shell vials
Milan, Italy (1st Dec 2008 - 31st Dec 2009) (Zuccotti et al., 2011)	4.0 (24/600)	no guardian consent
Palma, Spain (Jan 1995 - Dec 2006) (Hervas et al., 2012)	17.5 (505/2889)	no info about RSV microbiology; erroneously codified; >2y; had a previous episode of obstructive lower airway infection
Madrid, Spain (Sep 2005 - Aug 2008) (Calvo et al., 2010)	14.1 (52/370)	lack of NPA samples or they refused to participate
Lausanne and Geneva, Switzerland (Mar 2003 - Dec 2005) (Cevey-Macherel et al., 2009)	10.8 (12/111)	impossibility to obtain samples or interrupt the study
Pelotas, Brazil (1st Aug 1997 - 31st Jul 1998) (Macedo et al., 2002)	30.4 (266/874)	refusals and losses; insufficient available data to generate adequate diagnostic by the judge or the judge did not give a diagnostic of ARD; readmission; not tested for RSV
Sao Paulo, Brazil (Jan 2006 - Dec 2007)	17.7 (53/299)	didn't meet criteria; incomplete data in their medical records

Reference	% of eligible cases not tested for RSV	Reasons for not testing
(Ferronato et al., 2012)		
Sao Paulo, Brazil (May 2004 - Sep 2005) (Salomao Jr et al., 2011)	4.3 (13/303)	loss of specimen
Sao Paulo, Brazil (Mar 2008 - Aug 2011) (Ferone et al., 2014)	27.5 (308/1121)	repeated or inadequate samples
Belem, Brazil (Nov 2006 - Oct 2007) (Lamarao et al., 2012)	13.5 (164/1214)	no consent from parents or legal guardians
Porto Alegre, Brazil (Sep 2009 - Sep 2010) (Sparremberger et al., 2011)	3.0 (2/67)	no samples collected
Iqaluit, Canada (28th Jan 2002 - 27th Mar 2003) (Banerji et al., 2009)	7.3 (9/124)	NA
San Luis Potosi, Mexico (1st May 2003 - 30th Apr 2005) (Noyola et al., 2007)	16.1 (118/734)	no respiratory samples
California, USA (1996 - 2004) (Flaherman et al., 2010)	15.0 (309/2060)	NA
Dallas, Texas, USA (Jan 2002 - Dec 2007) (Garcia et al., 2010)	4.4 (211/4800)	not tested
Rarieda, Kenya (1st Mar 2007 - 28th Feb 2010) (Feikin et al., 2013)	78.1 (1250/1600)	NA
Kilifi, Kenya (Jan - Dec 2010) (Hammitt et al., 2012a)	16.0 (154/963)	refused; died during the admission process; failure of the computerized flagging system; other reasons
Bondo district, Kenya (Aug 2008 - Dec 2010) (Fuller et al., 2013)	58.9 (974/1654)	not tested
Santiago, Chile (Jan 1989 - Dec 2000) (Avendano et al., 2003)	NA	poor sample quality or quantity
Cape Town, South Africa (Jun 1995 - Aug 1996) (Hussey et al., 2000)	68.3 (2776/4064)	NA
Manhica District, Mozambique (Oct 1998 - May 2000) (Loscertales et al., 2002)	44.2 (793/1794)	no NPA or complete information or valid NPA result

Reference	% of eligible cases not tested for RSV	Reasons for not testing
Athens, Greece (Feb 1997 - Jun 2000) (Tsolia et al., 2003)	25.6 (163/636)	NA
Buenos Aires, Argentina (2001 - 2013) (Gentile, unpublished)	12.9 (1361/10581)	NA
Lwak, Kenya (2007 - 2011) (Montgomery, unpublished)	72.4 (1231/1701)	refusal to consent; unavailability of transport from field site to lab; high patient volumes; inadequate staffing levels
Kathmandu, Nepal (Jan 2006 - Jun 2008) (Basnet, unpublished)	71.8 (1630/2271)	other severe illness, history of documented TB, severe malnutrition, heart disease, diarrhoea with dehydration, disappearance of indrawing after salbutamol, recurrent wheezing, effusion/pneumothorax on chest X-ray, Hb% < 7 gm/dl, chronic cough, already enrolled in study once
Basse, Gambia (3rd Nov 2011 - 2nd Nov 2013) (PERCH, unpublished)	7.2 (46/638)	quality control not yet complete
Kilifi, Kenya (15th Aug 2011 - 15th Nov 2013) (PERCH, unpublished)	0.3 (2/634)	specimen not collected
Bamako, Mali (3rd Jan 2012 - 14th Jan 2014) (PERCH, unpublished)	9.1 (61/674)	quality control not yet complete
Nakhon Phanom and Sa Kaeo, Thailand (1st Jan 2012 - 31st Jan 2014) (PERCH, unpublished)	18.3 (41/224)	quality control not yet complete
Lusaka, Zambia (10th Oct 2011 - 31st Oct 2013) (PERCH, unpublished)	10.5 (65/617)	quality control not yet complete
Mpumalanga, South Africa (Jan 2010 - Dec 2014) (Cohen, unpublished)	4.0 (52/1310)	patient very ill; parents refuse consent; specimen not at lab within 72 hours
Beirut, Lebanon (Oct 2012 - Mar 2014) (Assaf-Casals et al., 2015)	18.3 (99/542)	no specimens collected or had onset of respiratory symptoms for more than 7 days
Buenos Aires, Argentina (Apr 1993 - Dec 1994) (Carballal et al., 2001)	3.4 (44/1278)	NA
Beer-Sheva, Israel (Nov to Mar, 2004 - 2011) (Greenberg et al., 2014)	52.8 (1182/2240)	specimens were not obtained
Jingzhou, China (Jan - Dec 2011) (Huo et al.,	93.0	random samples

Reference	% of eligible cases not tested for RSV	Reasons for not testing
2013)	(6803/7314)	
Amman, Jordan (18th Jan - 29th Mar 2007) (Khuri-Bulos et al., 2010)	2.0 (15/743)	clinical or laboratory data were not available

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. NPA=nasopharyngeal aspirate. NA=not applicable.

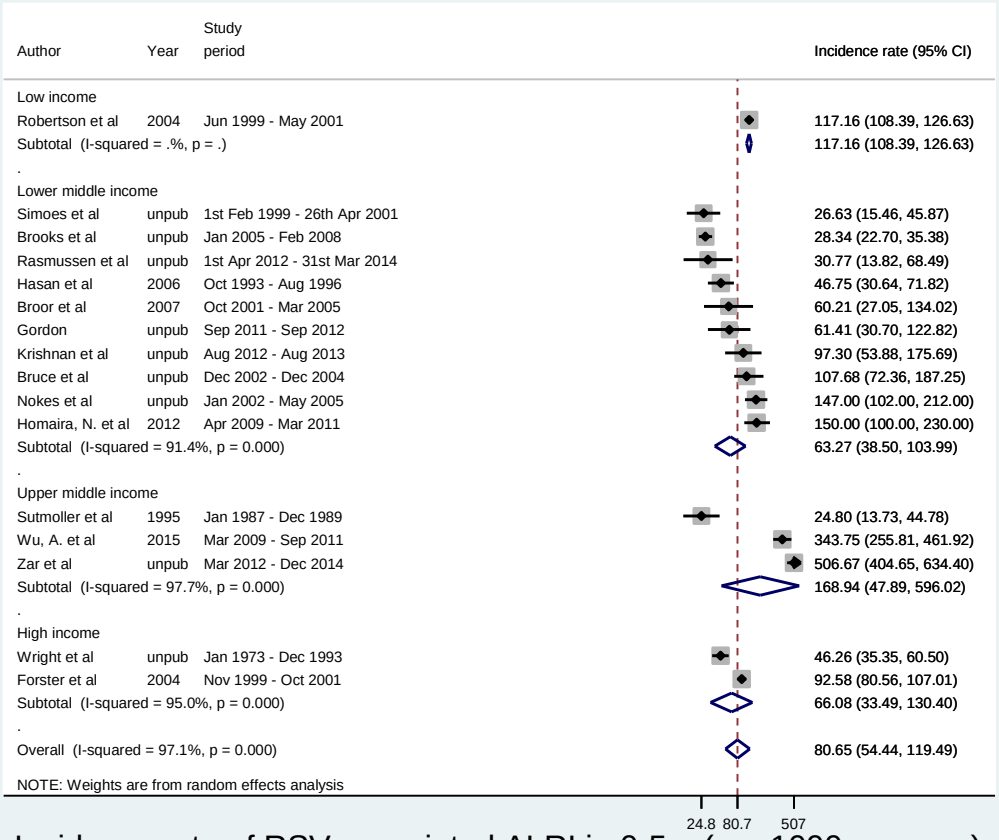
A13. List of studies reporting the incidence rate of RSV associated ALRI in narrower age bands

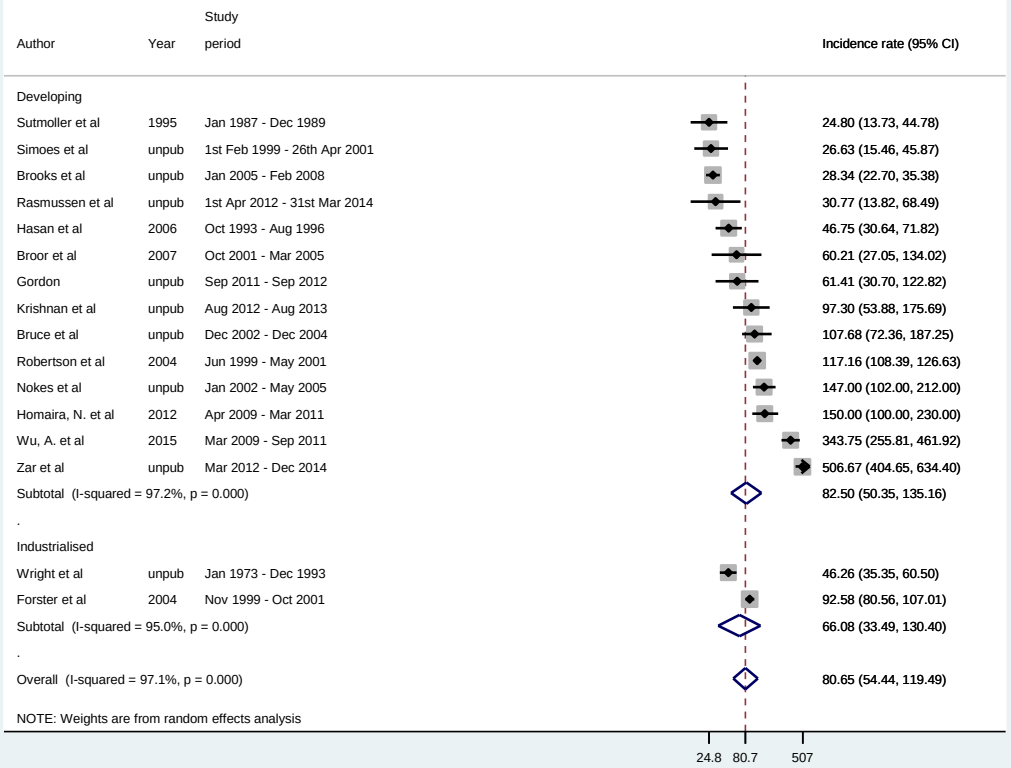
Location (reference)	Incidence of RSV associated ALRI (per 1000 children per year)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
San Marcos, Guatemala (rural, Dec 2002 - Dec 2004) (Bruce and colleagues)	97.2	67.8	127.6	149.8	195.4	
Dhaka, Bangladesh (urban, Jan 2005 - Feb 2008) (Brooks and colleagues)	2.1	8.7	54.3	31.6	42.4	12.6
Ballabhgarh, India (rural, Aug 2012 - Aug 2013) (Krishnan and colleagues)		55.0	123.5	77.2	76.6	21.7
Bandung, Indonesia (periurban and rural, 1st Feb 1999 - 26th Apr 2001) (Simoes and colleagues)		11.8	44.7	189.7	96.7	55.5
Managua, Nicaragua (urban, Sep 2011 - Sep 2012) (Gordon and colleagues)			47.5	142.9		
Gilgit, Pakistan (rural, 1st Apr 2012 - 31st Mar 2014) (Rasmussen and colleagues)			69.8	107.1	95.9	27.3
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)	235.3	471.4	619.0	144.7	137.9	

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection.

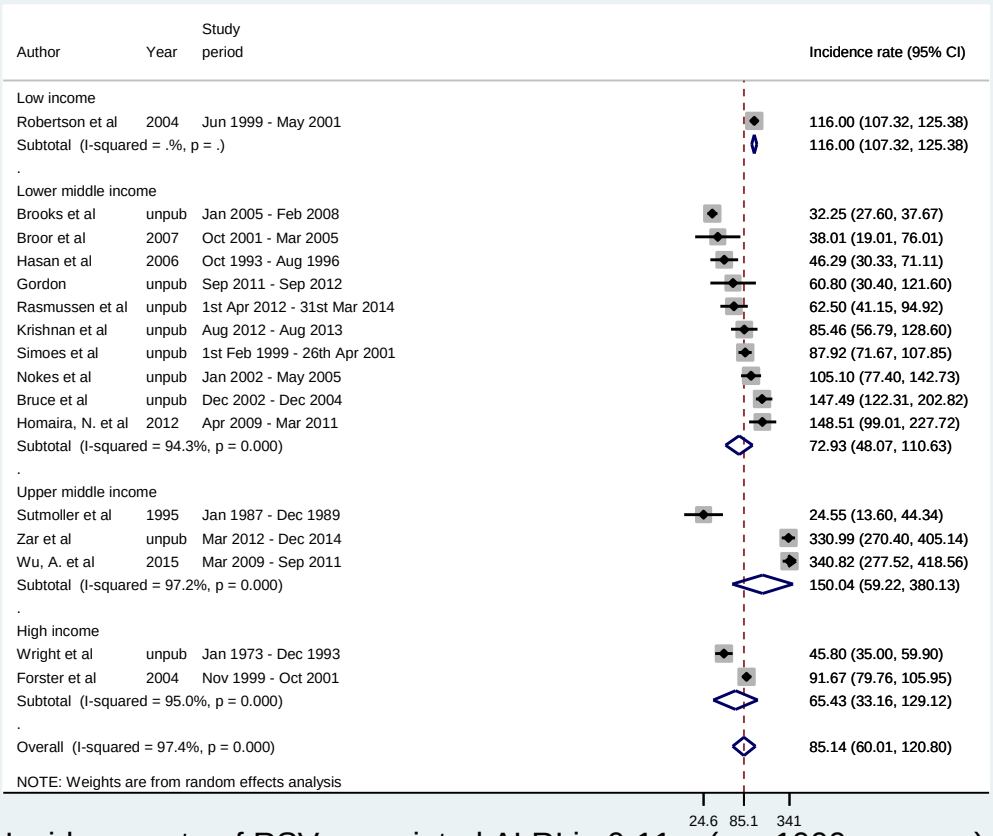
A14. Forest plots for meta-analysis results of incidence rate of RSV associated ALRI

By regions (world bank income level and developing/industrialised)

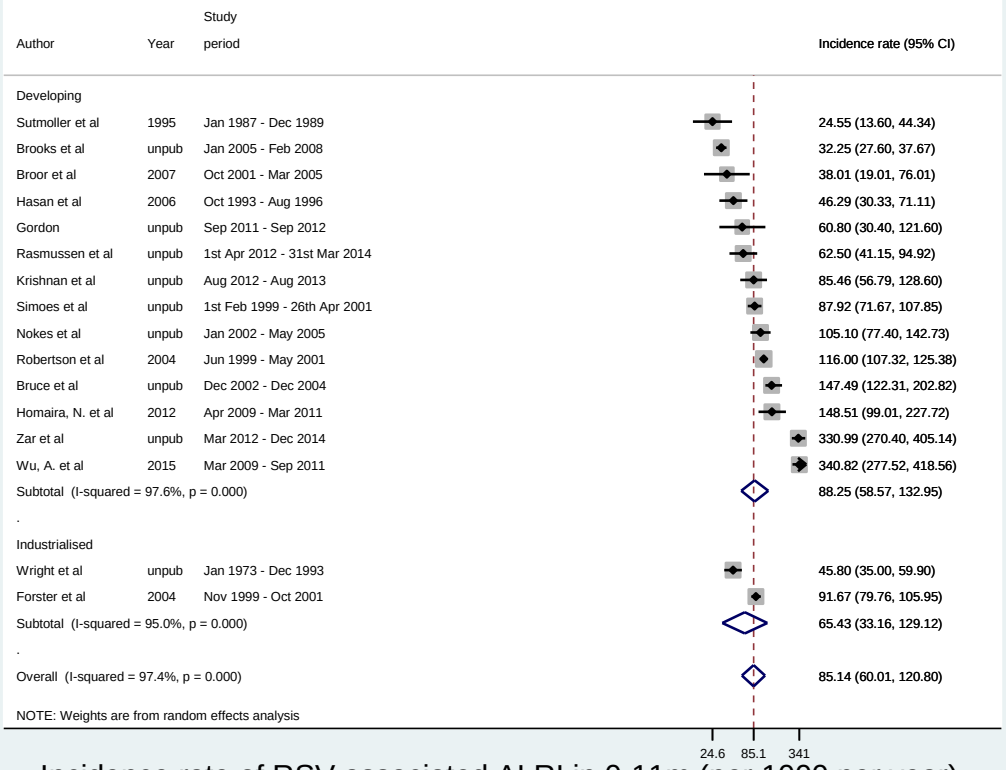




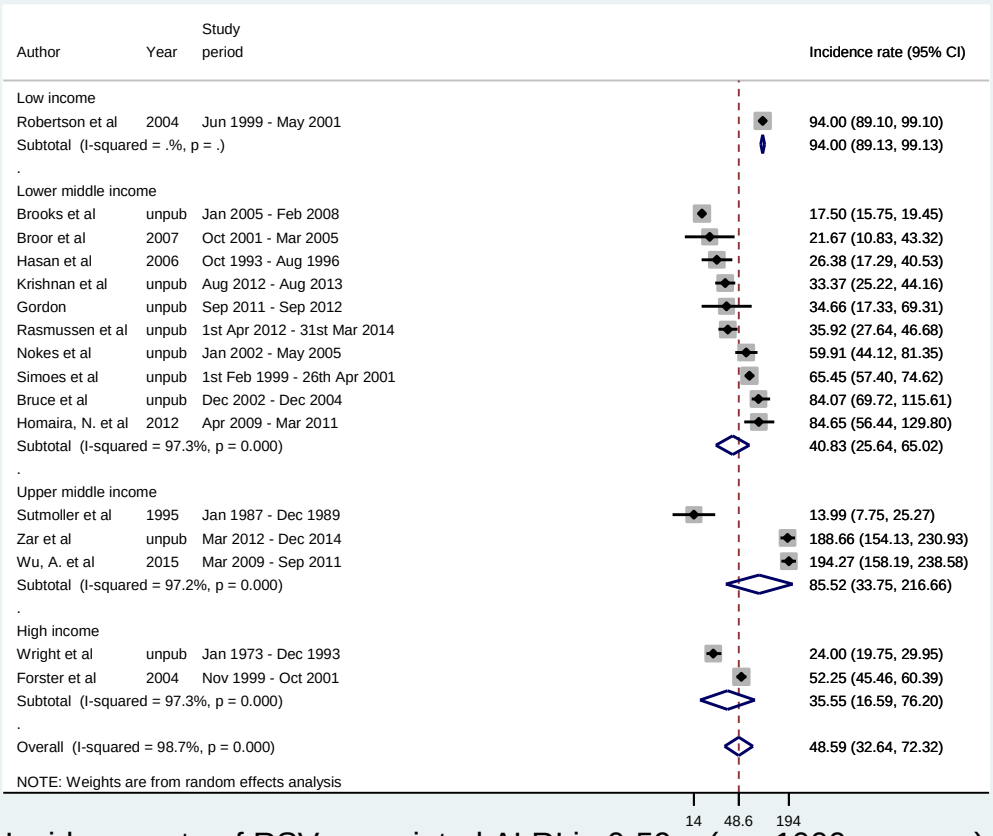
Incidence rate of RSV associated ALRI in 0-5m (per 1000 per year)



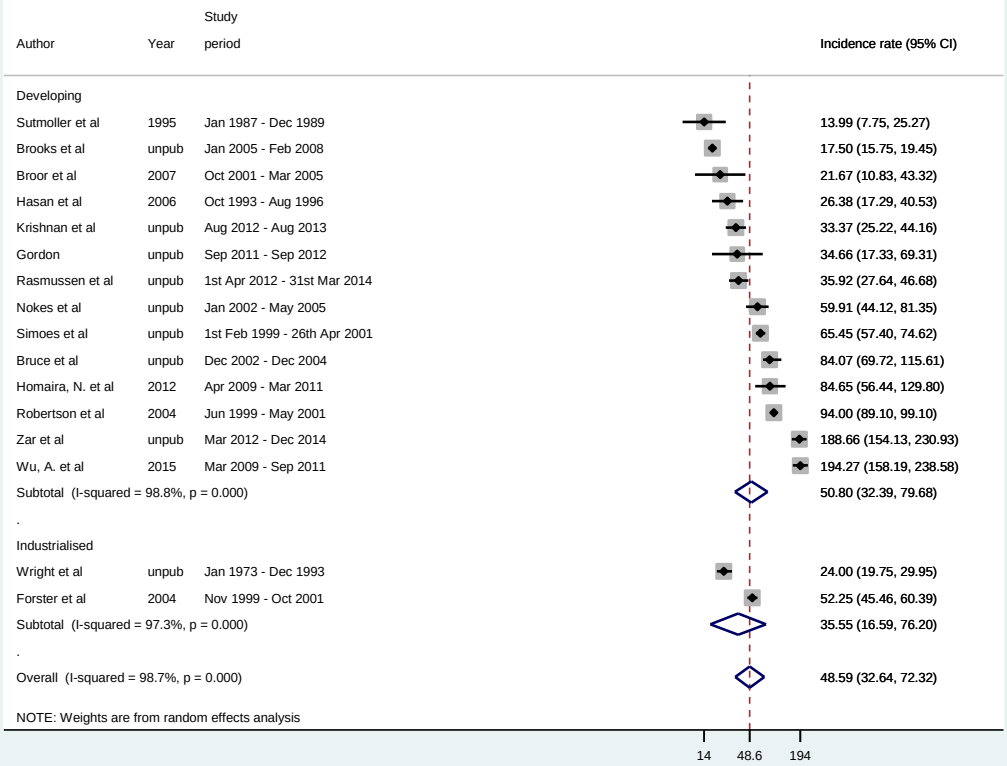
Incidence rate of RSV associated ALRI in 0-11m (per 1000 per year)



Incidence rate of RSV associated ALRI in 0-11m (per 1000 per year)



Incidence rate of RSV associated ALRI in 0-59m (per 1000 per year)



Incidence rate of RSV associated ALRI in 0-59m (per 1000 per year)

A15. Comparison of meta-estimate after excluding imputed data

Table 65: Comparison of incidence rate meta-estimate after excluding imputed data

Region	0-11m				0-59m			
	Excluding imputed data		Including imputed data		Excluding imputed data		Including imputed data	
	No.	Incidence rate	No.	Incidence rate	No.	Incidence rate	No.	Incidence rate
Developing	11	99.3 (62.6-157.3)	14	88.3 (58.6-133)	6	35.5 (17.2-73.1)	14	50.8 (32.4-79.7)

No.=number of studies

Table 66: Comparison of hospitalisation rate meta-estimate after excluding imputed data

Region	0-11m				0-59m			
	Excluding imputed data		Including imputed data		Excluding imputed data		Including imputed data	
	No.	Hospitalisation rate	No.	Hospitalisation rate	No.	Hospitalisation rate	No.	Hospitalisation rate
Low income	5	5.6 (1.7-18.1)	5	5.6 (1.7-18.1)	4	1.3 (0.3-5.1)	5	1.7 (0.6-5.1)
Lower middle income	15	18.4 (13.7-24.8)	17	18.2 (13.9-23.8)	12	4.9 (3.5-6.9)	17	5.1 (3.7-6.9)
Upper middle income	12	19.2 (12.8-28.7)	15	18.5 (13.3-25.8)	12	5.3 (4.2-6.7)	15	6.2 (5.0-7.8)
High income	21	20.8 (17.4-24.9)	31	19.6 (16.9-22.8)	14	5.3 (4.0-7.0)	31	5.5 (4.7-6.3)
Developing	36	16.2 (13.0-20.1)	43	16.0 (13.2-19.4)	33	4.3 (3.5-5.1)	43	4.9 (4.1-5.8)
Industrialised	17	20.9 (17.1-25.4)	25	20.2 (17.2-23.8)	9	5.8 (4.1-8.2)	25	5.5 (4.7-6.5)

No.=number of studies

A16. List of studies reporting hospitalisation rate of RSV associated hospitalised ALRI in narrower age bands

Location (reference)	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
Sa Kaeo and Nakhom Phanom, Thailand (rural, 1st Jan 2004 - 31st Dec 2007) (Fry et al., 2010)						4.1
Damanhour, Egypt (urban and rural, Jun 2009 - Jun 2012) (Rowlinson et al., 2013)						0.7
USA (urban and rural, 1997 - 2006) (Stockman et al., 2012)			28.4			
Dadaab and Kakuma, Kenya (rural, Sep 2007 - Aug 2010)§ (Ahmed et al., 2012)						5.2
Gipuzoka, Spain (urban, Jul 1996 - Jun 2000) (Vicente et al., 2003)	31.0	54.6	26.9			1.3
England, United Kingdom (urban, Apr 1995 - Mar 1998) (Muller-Pebody et al., 2002)						1.3
Buenos Aires, Argentina (urban and rural, 2011 - 2013) (Polack and colleagues)	32.1	82.0	63.5	40.8	25.9	
Belo Horizonte, Brazil (urban, 2011 - 2013) (Oliveira and colleagues)						0.7
Concepcion, Chile (urban and rural, Jan 2012 - Dec 2013) (Fasce and colleagues)						0.7
Iquique, Chile (urban and rural, Jan 2012 - Dec 2013) (Fasce and colleagues)						1.1
Jingzhou, China (urban and rural, Jan 2010 - Dec 2012) (Yu and colleagues)			6.1	6.5	6.7	2.5
Gambia Western Region, Gambia (urban and rural, Jul 2007 - Jun 2008) (Howie and colleagues)						1.6
Santa Rosa, Guatemala (urban and rural, 2008 - 2013) (McCracken and colleagues)						2.0
Quetzaltenango, Guatemala (urban and rural, 2009 - 2013) (McCracken and colleagues)						1.1

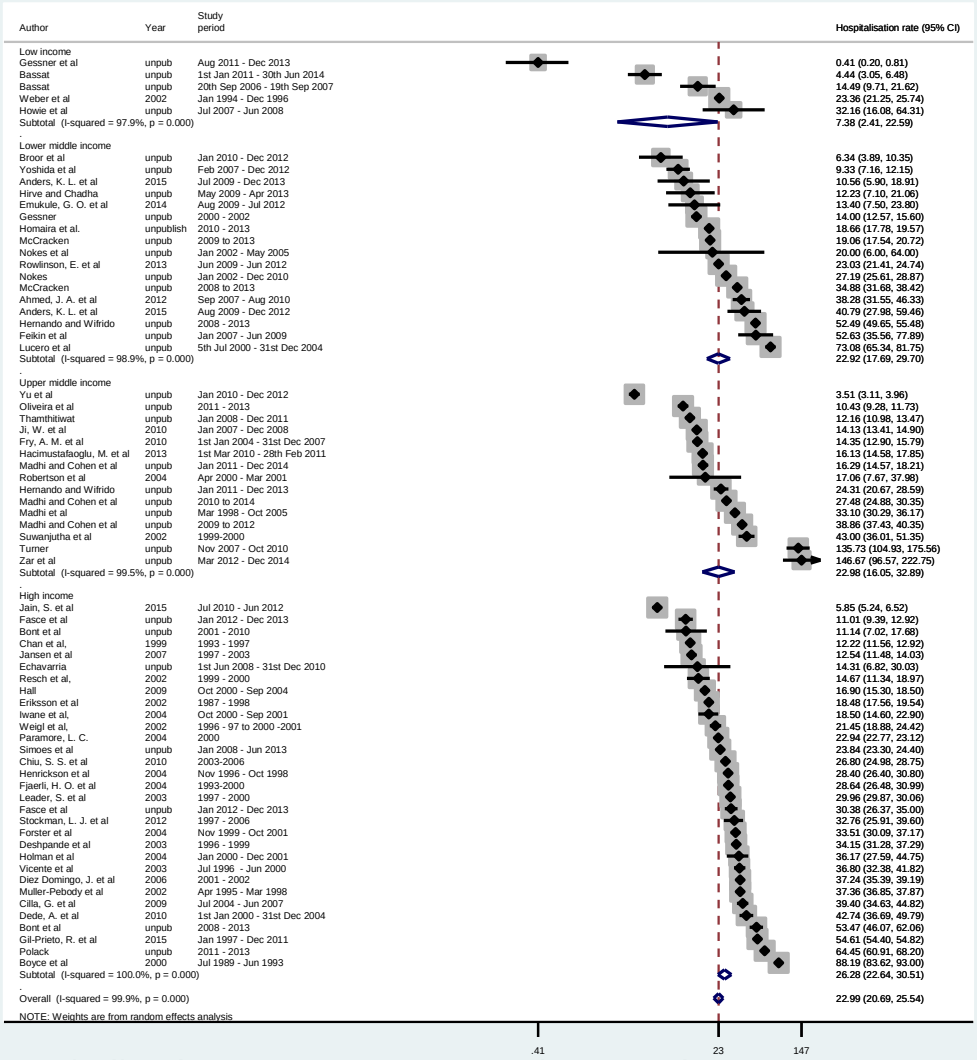
Location (reference)	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
Ballabhgarh, India (rural, Jan 2010 - Dec 2012) (Broor and colleagues)	4.5	10.5	4.5	2.9	1.1	0.3
Pune, India (rural, May 2009 - Apr 2013) (Chadha and colleagues)	12.6	5.1	17.5	20.5	23.4	3.9
Lombok, Indonesia (urban and rural, 2000 - 2002) (Gessner and colleagues)	2.0	12.6	18.9	14.6	10.0	
Kilifi hospital study, Kenya (urban and rural, Jan 2002 - Dec 2010) (Nokes and colleagues)§	23.9	25.5	31.7	14.8	7.9	1.3
Bondo district, Kenya (rural, Jan 2007 - Jun 2009) (Feikin and colleagues)§	32.3	108.5	31.7	16.8	15.5	19.3
Manhiça, Mozambique (rural, 20th Sep 2006 - 19th Sep 2007) (Bassat and colleagues)§	16.7	13.7	14.0	10.9	2.5	1.3
Manhiça, Mozambique (rural, 1st Jan 2011 - 30th Jun 2014) (Bassat and colleagues)§	1.1	8.1	3.3	2.3	1.6	0.6
Tagbilaran and 6 rural sites, Philippines (urban and rural, 5th Jul 2000 - 31st Dec 2004) (Lucero and colleagues)		65.5	76.1	56.2	53.5	
Gauteng province, South Africa (urban, 2009 - 2012) (Cohen and colleagues)§						2.6
Klerksdorp site, South Africa (periurban, Jan 2011 - Dec 2014) (Cohen and colleagues)§						1.1
Soweto, South Africa (urban, Mar 1998 - Oct 2005) (Madhi and colleagues)§		45.6	26.9	10.1	10.4	1.4
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)§	176.5	171.4	111.1	26.3	34.5	
Maela Camp, Tak Province, Thailand (rural, Nov 2007 - Oct 2010) (Turner and colleagues)	117.5	246.0	77.0	71.5	74.7	
Sa Kaeo and Nakhon Phanom, Thailand (rural, Jan 2008 - Dec 2011) (Thamthitiwat and colleagues)	5.3	17.6	10.5	17.1	20.1	8.5
Tone district, Togo (rural, Aug 2011 - Dec 2013) (Gessner and		1.2		0.6		0.1

Location (reference)	Hospitalisation rate of RSV associated ALRI (per 1000 children per year)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
colleagues)						
Alaska, USA (rural, Jul 1994 - Jun 2012) (Singleton and colleagues)#	264.8	240.7	156.2	138.1	104.2	
Colorado, USA (urban and rural, Jan 2008 - Jun 2013) (Simoes and colleagues)						2.6
Navajo and WMA, USA - MEDI (rural, Oct 2004 - Dec 2010) (O'Brien and colleagues)#	65.9	601.6	199.6	278.7		
Navajo and WMA, USA - EPI (rural, Oct 1997 - Mar 2000) (O'Brien and colleagues)#	209.5	284.5	198.6	162.4	155.4	
Nha Trang, Vietnam (urban and rural, Feb 2007 - Dec 2012) (Yoshida and colleagues)		12.6	9.0	6.2	2.1	1.8
Spain (urban, Jan 1997 - Dec 2011) (Gil-Prieto et al., 2015)						3.6

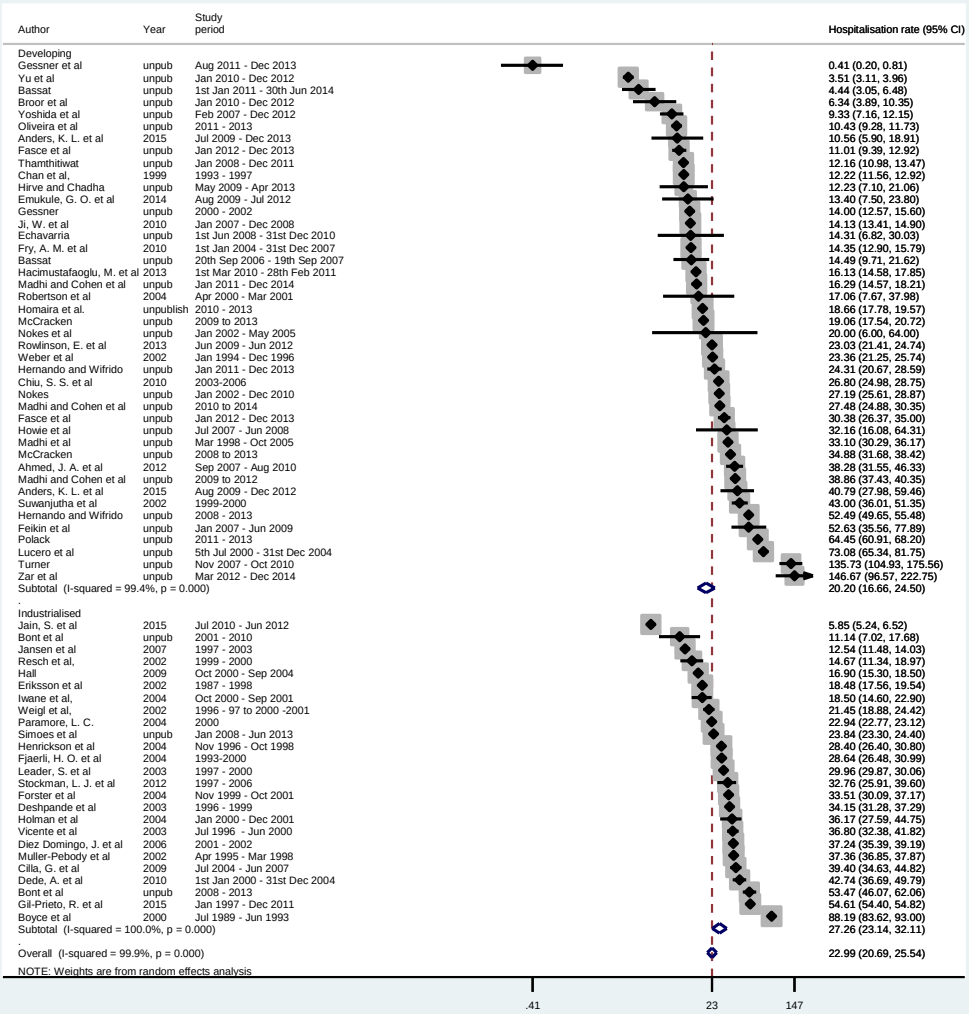
RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. #Studies reporting hospitalisation rate in an aboriginal population from a high-income country. §Studies sites in sub-Saharan Africa which had high-HIV burden.

A17. Forest plots for meta-analysis results of hospitalisation rate of RSV associated hospitalised ALRI

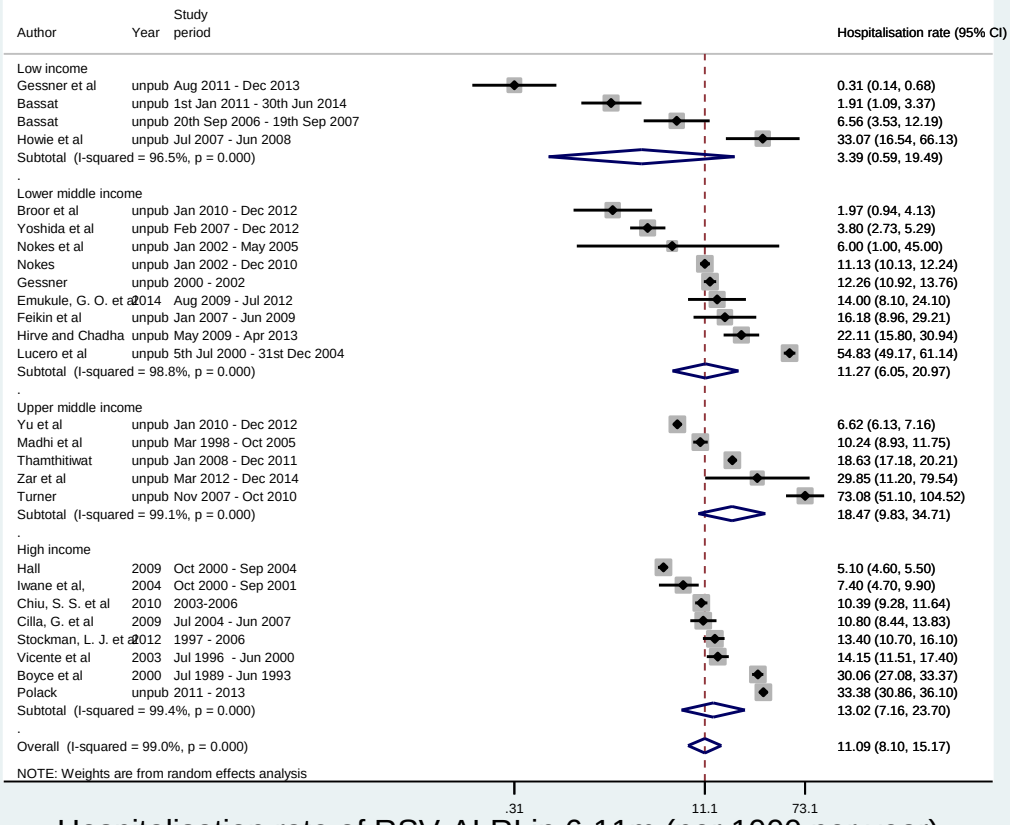
By regions (world bank income level and developing/industrialised)



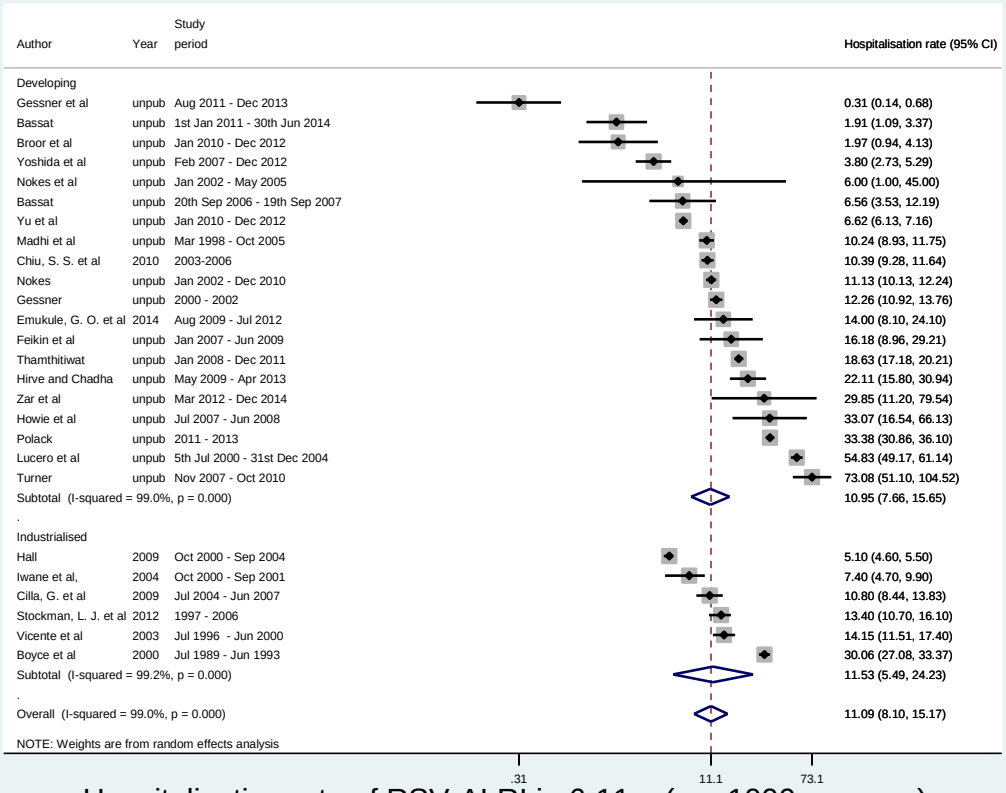
Hospitalisation rate of RSV-ALRI in 0-5m (per 1000 per year)



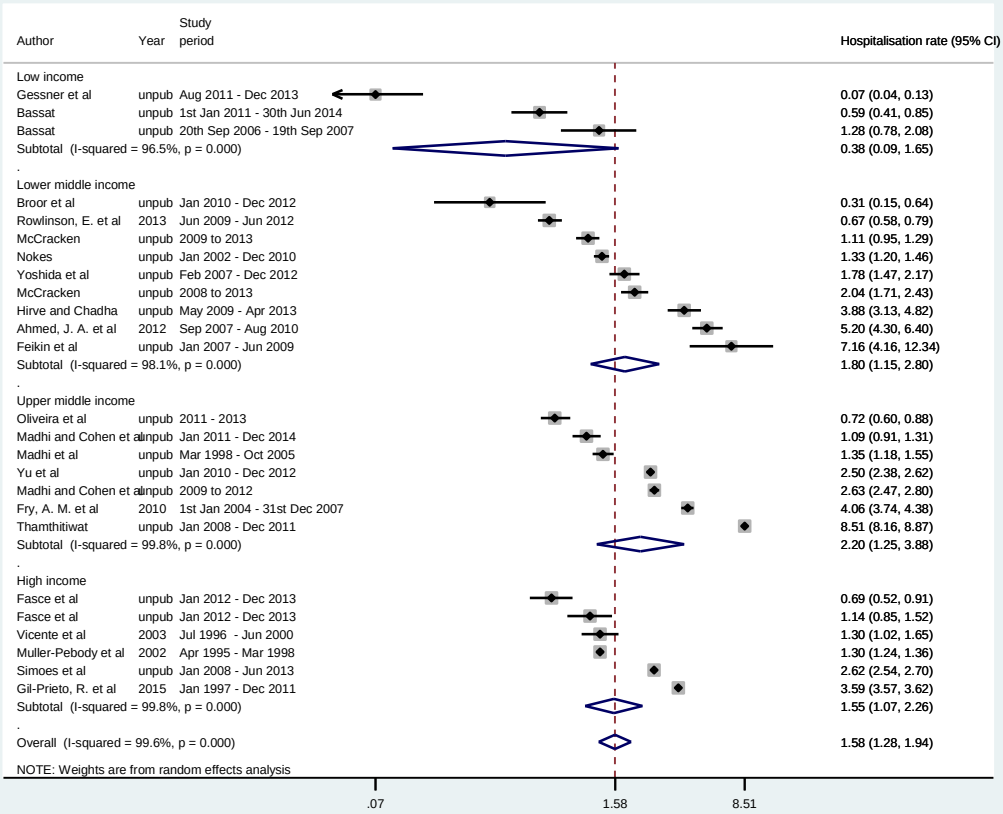
Hospitalisation rate of RSV-ALRI in 0-5m (per 1000 per year)



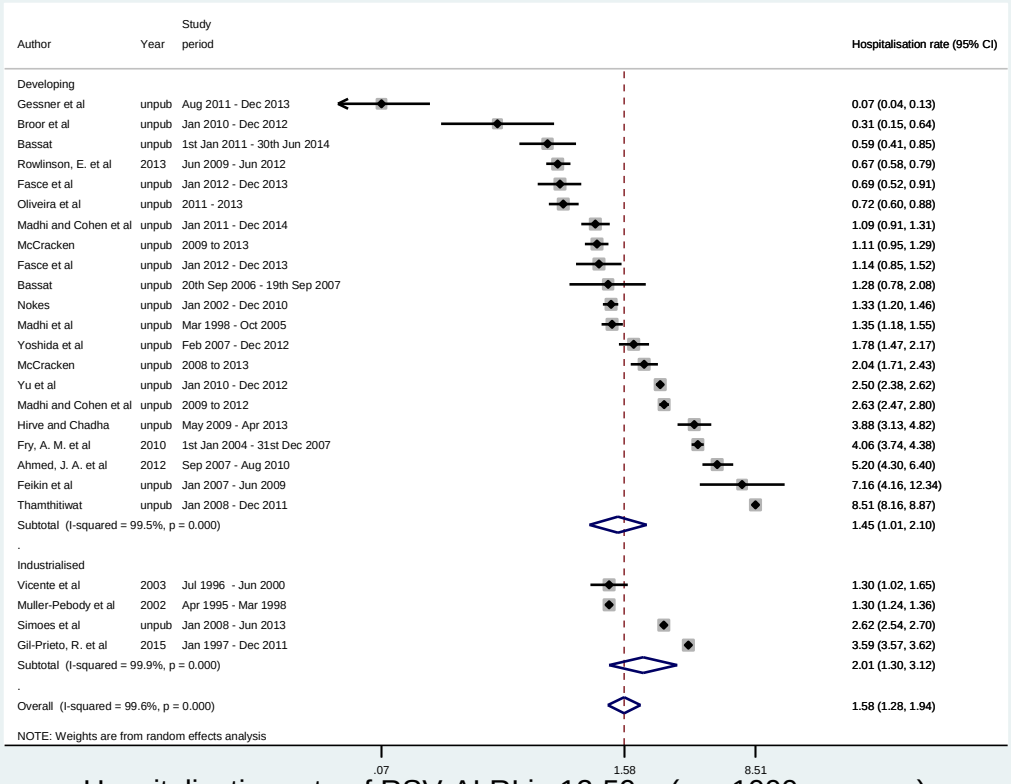
Hospitalisation rate of RSV-ALRI in 6-11m (per 1000 per year)



Hospitalisation rate of RSV-ALRI in 6-11m (per 1000 per year)



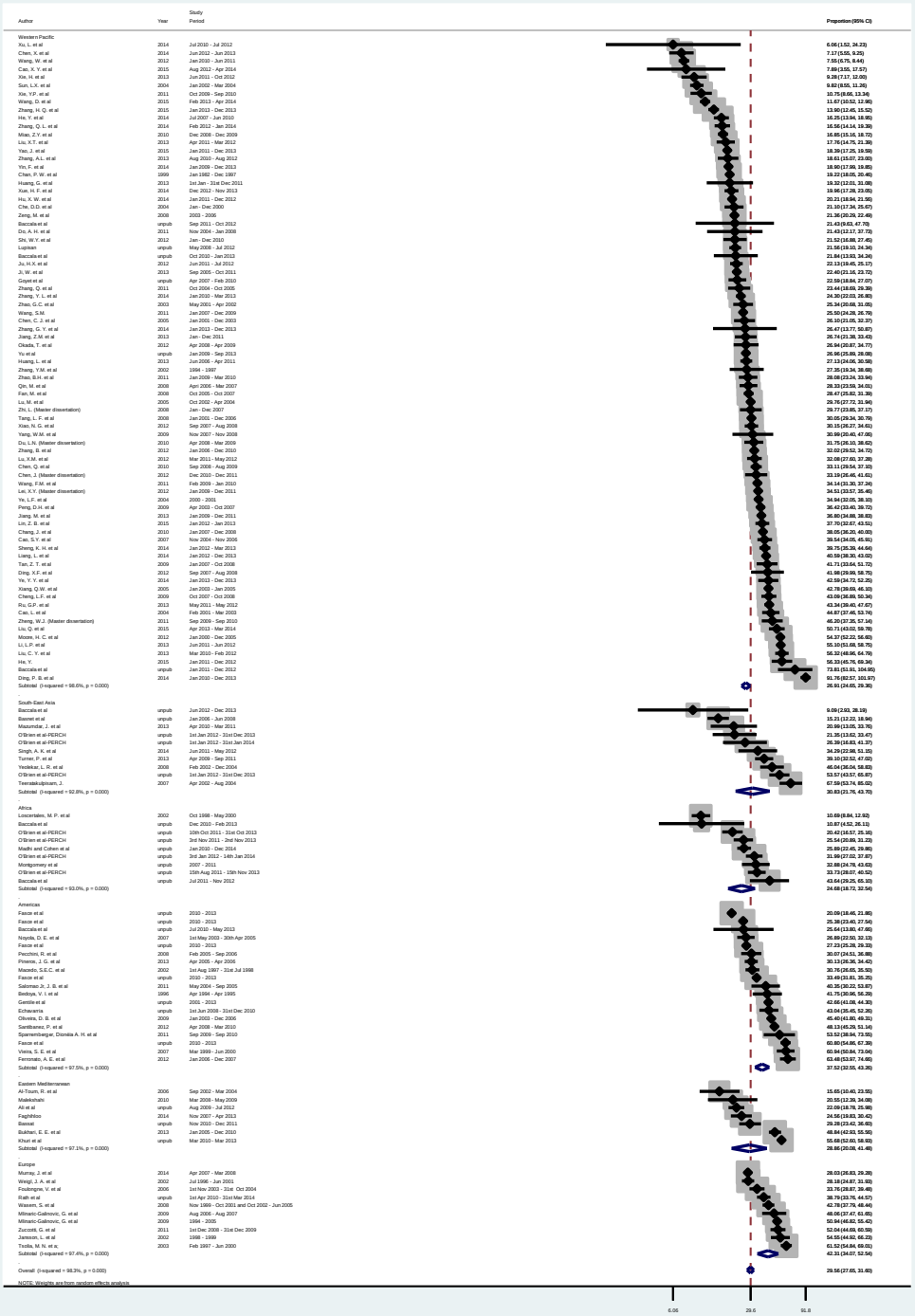
Hospitalisation rate of RSV-ALRI in 12-59m (per 1000 per year)



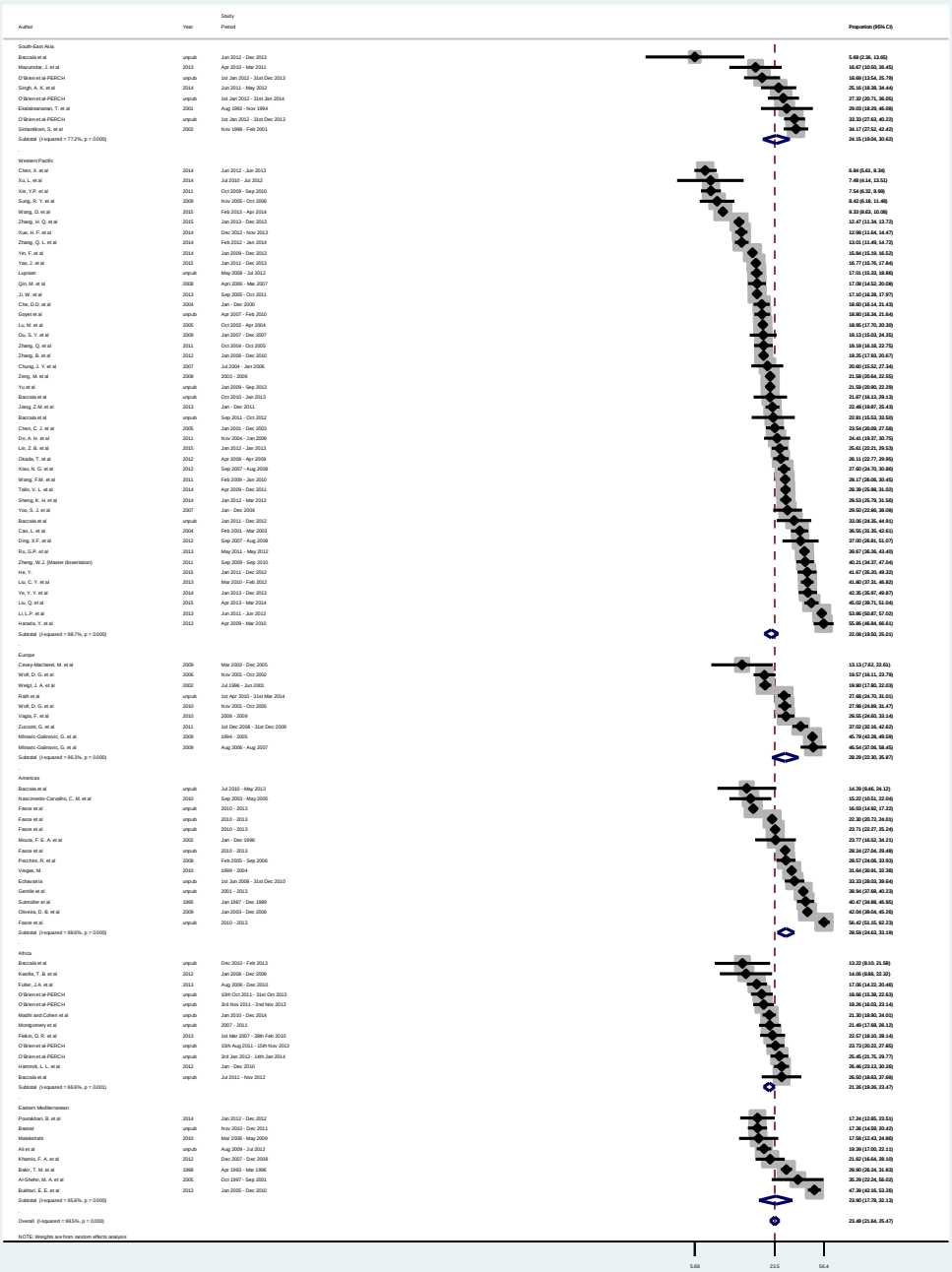
Hospitalisation rate of RSV-ALRI in 12-59m (per 1000 per year)

A18. Forest plots for meta-analysis results of proportion of hospitalised ALRI cases which are RSV positive

By WHO regions



Proportion of hospitalised ALRI positive with RSV in 0-11m (%)



Proportion of hospitalised ALRI positive with RSV in 0-59m (%)

A19. List of studies reporting in-hospital CFR for RSV associated hospitalised ALRI in narrower age bands

Location (reference)	In-hospital CFR of RSV associated hospitalised ALRI (%)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
Buenos Aires, Argentina (urban, 2001 - 2013) (Gentile and colleagues)*	0.0	2.1	1.8	2.1	1.1	1.8
Takeo ad Kampong Cham, Cambodia (urban, Apr 2007 - Feb 2010) (Goyet and colleagues)*		0.0	0.0	0.0	0.0	0.0
Beijing, China (urban, Jan 2011 - Dec 2012) (GABRIEL and colleagues)*		0.0	0.0	0.0	0.0	0.0
Ulaanbaatar, Mongolia (urban, Sep 2011 - Oct 2012) (GABRIEL and colleagues)*			0.0	0.0	0.0	0.0
Phnom Penh, Cambodia (urban, Oct 2010 - Jan 2013) (GABRIEL and colleagues)*			0.0	0.0	0.0	0.0
Lucknow, India (urban and rural, Jun 2012 - Dec 2013) (GABRIEL and colleagues)*			0.0	0.0		0.0
Antananarivo, Madagascar (urban and rural, Dec 2010 - Feb 2013) (GABRIEL and colleagues)*		0.0	0.0		0.0	0.0
Asuncion, Paraguay (urban, Jul 2010 - May 2013) (GABRIEL and colleagues)*		0.0	0.0	0.0	0.0	0.0
Bamako, Mali (urban, Jul 2011 - Nov 2012) (GABRIEL and colleagues)*		0.0	0.0	33.3	0.0	0.0
Berlin, Germany (urban, 1st Apr 2010 - 31st Mar 2014) (Rath and colleagues)*	0.0	0.0	0.0	0.0	0.0	0.0
Amman, Jordan (urban, Mar 2010 - Mar 2013) (Khuri and colleagues)	0.0	0.8	0.0	0.5	0.0	
Lwak, Kenya (rural, 2007 - 2011) (Montgomery and colleagues)*§	33.3	0.0	12.5	0.0	0.0	3.8
Rabat, Morocco (urban, Nov 2010 - Dec 2011) (Bassat and colleagues)*	0.0	0.0	6.5	0.0	11.8	0.0
Karachi, Pakistan (urban, Aug 2009 - Jul 2012) (Ali and colleagues)*	25.0	0.0	0.0	0.0	0.0	1.3

Location (reference)	In-hospital CFR of RSV associated hospitalised ALRI (%)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
Basse Santa Su, Gambia (rural, 3rd Nov 2011 - 2nd Nov 2013) (PERCH and colleagues)*		0.0	0.0	0.0	0.0	0.0
Kilifi, Kenya (urban, 15th Aug 2011 - 15th Nov 2013) (PERCH and colleagues)*§		4.3	2.4	0.0	14.3	5.6
Bamako, Mali (urban, 3rd Jan 2012 - 14th Jan 2014) (PERCH and colleagues)*		0.0	3.8	10.0	0.0	4.8
Nakhon Phanom and Sa Kaeo, Thailand (rural, 1st Jan 2012 - 31st Jan 2014) (PERCH and colleagues)*		0.0	0.0	0.0	0.0	0.0
Lusaka, Zambia (urban, 10th Oct 2011 - 31st Oct 2013) (PERCH and colleagues)*§		0.0	10.0	0.0	16.7	6.7
Dhaka, Bangladesh (urban, 1st Jan 2012 - 31st Dec 2013) (PERCH and colleagues)*		0.0	0.0	0.0	0.0	0.0
Matlab, Bangladesh (rural, 1st Jan 2012 - 31st Dec 2013) (PERCH and colleagues)*		0.0	0.0	0.0	0.0	0.0
Tacloban City, Philippines (rural, May 2008 - Jul 2012) (Lupisan and colleagues)*	5.3	2.5	1.6	3.0	0.0	0.0
Mpumalanga, South Africa (rural, Jan 2010 - Dec 2014) (Cohen and colleagues)*§	0.0	1.6	3.9	4.7	4.5	0.0
CEMIC, Buenos Aires, Argentina (urban, 1st Jun 2008 - 31st Dec 2010) (Echavarria and colleagues)*		0.0	0.0			0.0
Buenos Aires, Argentina (urban and rural, 2011 - 2013) (Polack and colleagues)	0.0	1.4	1.7	1.0	1.2	
Belo Horizonte, Brazil (urban, 2011 - 2013) (Oliveira and colleagues)*	0.0	0.0	4.3	3.8	0.0	0.0
Concepcion, Chile (urban and rural, Jan 2012 - Dec 2013) (Fasce and colleagues)*	0.0	0.0	0.0	0.0	0.0	2.0
Iquique, Chile (urban and rural, Jan 2012 - Dec 2013) (Fasce and colleagues)*	0.0	0.0	0.0	4.7	0.0	0.0
Western Gambia (urban and rural, Jul 2007 - Jun 2008) (Howie				0.0	0.0	0.0

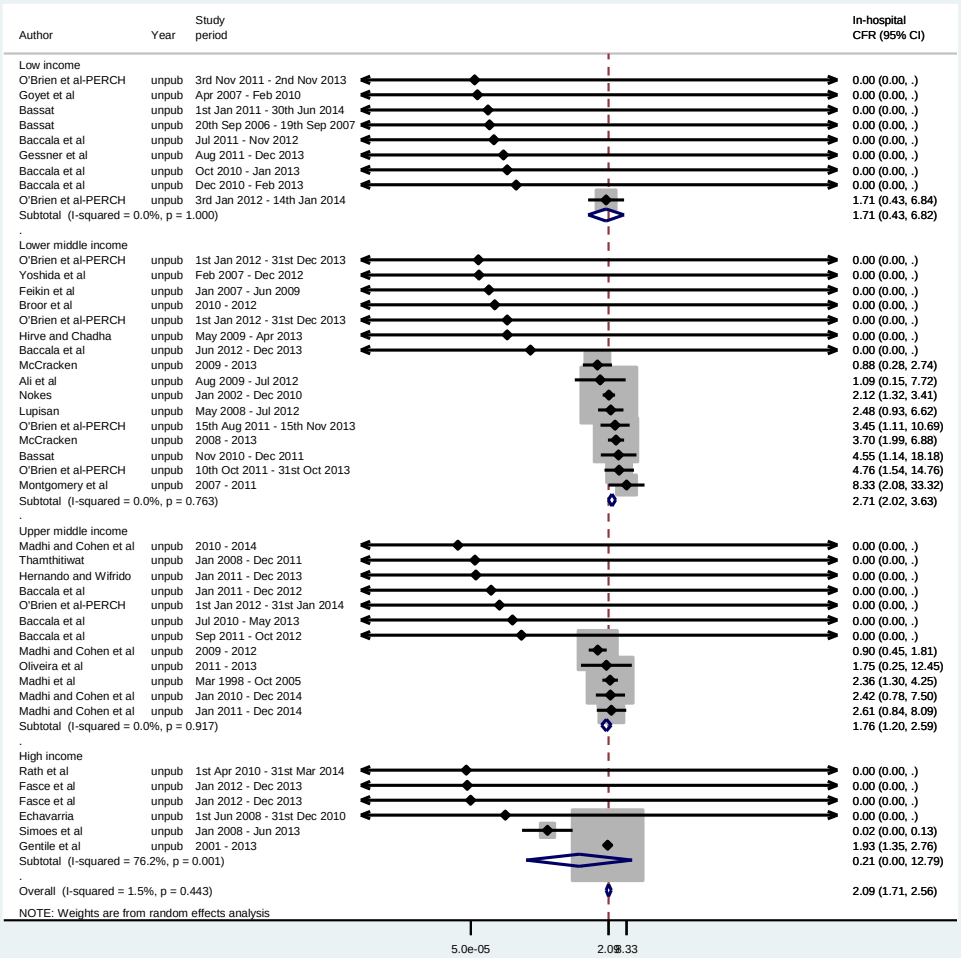
Location (reference)	In-hospital CFR of RSV associated hospitalised ALRI (%)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
and colleagues)						
Santa Rosa, Guatemala (urban and rural, 2008 - 2013) (McCracken and colleagues)*	6.3	4.5	1.1	0.0	4.5	2.6
Quetzaltenango, Guatemala (urban and rural, 2009 - 2013) (McCracken and colleagues)*	0.0	1.7	0.0	2.4	0.0	2.1
Ballabhgarh, India (rural, 2010 - 2012) (Broor and colleagues)*	0.0	0.0	0.0	0.0	0.0	0.0
Pune, India (rural, May 2009 - Apr 2013) (Chadha and colleagues)*	0.0	0.0	0.0	0.0	0.0	0.0
Lombok, Indonesia (urban and rural, 2000 - 2002) (Gessner and colleagues)	0.0	6.1	2.3	0.6	0.9	
Kilifi hospital study, Kenya (urban and rural, Jan 2002 - Dec 2010) (Nokes and colleagues)*§	2.5	1.8	2.4	1.0	4.2	2.3
Bondo district, Kenya (rural, Jan 2007 - Jun 2009) (Feikin and colleagues)*§	0.0	0.0	0.0	14.3	0.0	0.0
Manhiça, Mozambique (rural, 20th Sep 2006 - 19th Sep 2007) (Bassat and colleagues)*§	0.0	0.0	0.0	12.5	0.0	0.0
Manhiça, Mozambique (rural, 1st Jan 2011 - 30th Jun 2014) (Bassat and colleagues)*§	0.0	0.0	0.0	0.0	0.0	0.0
Utrecht, Netherlands (urban, 2001 - 2010) (Bont and colleagues)		0.0	0.0	0.0	0.0	
41 sites in Netherlands (urban and rural, 2008 - 2013) (Bont and colleagues)	0.0	0.0	0.0	0.0	0.0	
David City, Panama (urban, Jan 2011 - Dec 2013) (Jara and colleagues)*	0.0	0.0	0.0	0.0	0.0	0.0
Tagbilaran and 6 rural sites, Philippines (urban and rural, 5th Jul 2000 - 31st Dec 2004) (Lucero and colleagues)		0.0	1.1	1.5	0.0	
Gauteng province, South Africa (urban, 2009 - 2012) (Cohen and colleagues)*§	1.0	0.7	1.1	0.0	0.0	0.0
KwaZulu-Natal province, South Africa (periurban, 2010 - 2014) (Cohen and colleagues)*§	0.0	0.0	0.0	0.0	0.0	0.0

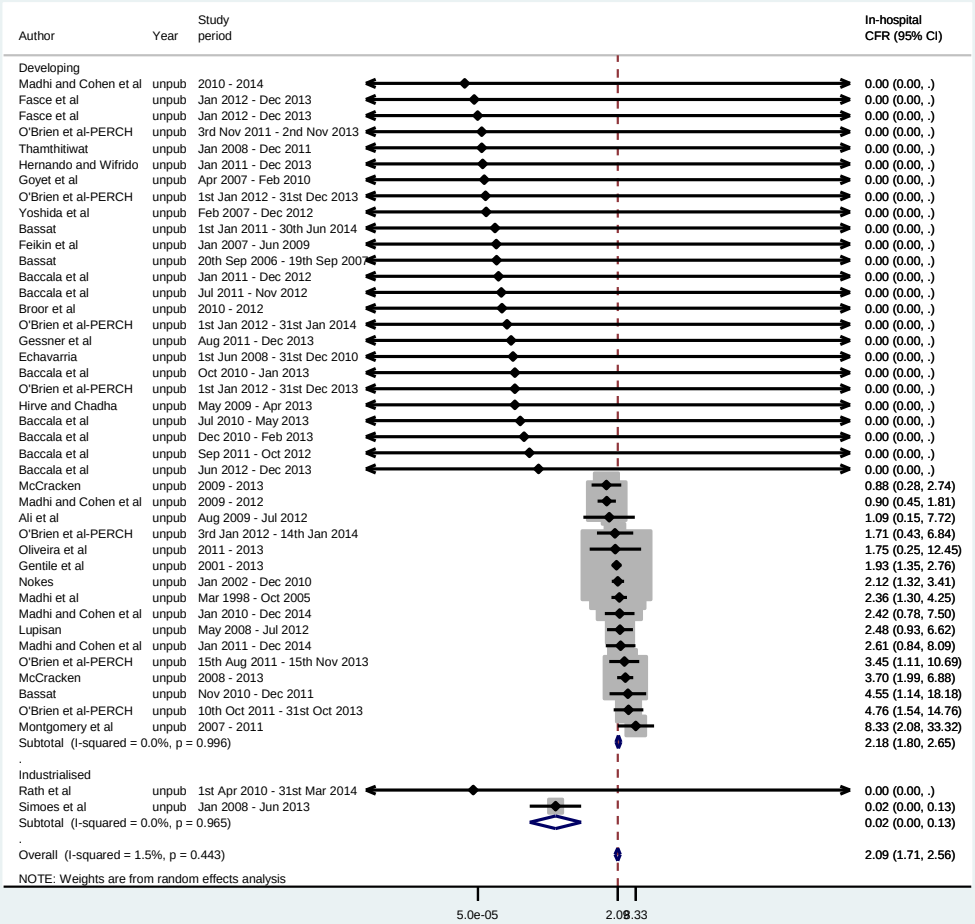
Location (reference)	In-hospital CFR of RSV associated hospitalised ALRI (%)					
	0-27 days	28 days-<3m	3-5m	6-8m	9-11m	12-59m
Klerksdorp site, South Africa (periurban, Jan 2011 - Dec 2014) (Cohen and colleagues)*§	0.0	3.1	2.0			0.0
Soweto, South Africa (urban, Mar 1998 - Oct 2005) (Madhi and colleagues)*§		2.8	2.0	1.0	1.0	0.5
Paarl, South Africa (periurban, Mar 2012 - Dec 2014) (Zar and colleagues)	0.0	0.0	0.0	0.0	0.0	
Sa Kaeo and Nakhon Phanom, Thailand (rural, Jan 2008 - Dec 2011) (Thamthitiwat and colleagues)*	0.0	0.0	0.0	0.0	0.0	0.0
Tone District, Togo (rural, Aug 2011 - Dec 2013) (Gessner and colleagues)*		0.0		0.0		0.0
Colorado, USA (urban and rural, Jan 2008 - Jun 2013) (Simoes and colleagues)*	0.0	0.0	0.1	0.1	0.0	0.1
Navajo and WMA, USA - MEDI (rural, Oct 2004 - Dec 2010) (O'Brien and colleagues)#	0.0	0.0	0.0	0.0		
Navajo and WMA, USA - EPI (rural, Oct 1997 - Mar 2000) (O'Brien and colleagues)#	0.0	0.6	0.0	0.0	0.0	
Nha Trang, Vietnam (urban and rural, Feb 2007 - Dec 2012) (Yoshida and colleagues)*		0.0	0.0	0.0	0.0	0.0
Spain (urban, Jan 1997 - Dec 2011) (Gil-Prieto et al., 2015)						0.1

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. CFR=case fatality ratio. *Studies providing in-hospital CFR for full age range (0-5m, 6-11m and 12-59m). #Studies reporting in-hospital CFR in an aboriginal population from a high-income country. §Studies sites in sub-Saharan Africa which had high-HIV burden and reported data in 0-59m.

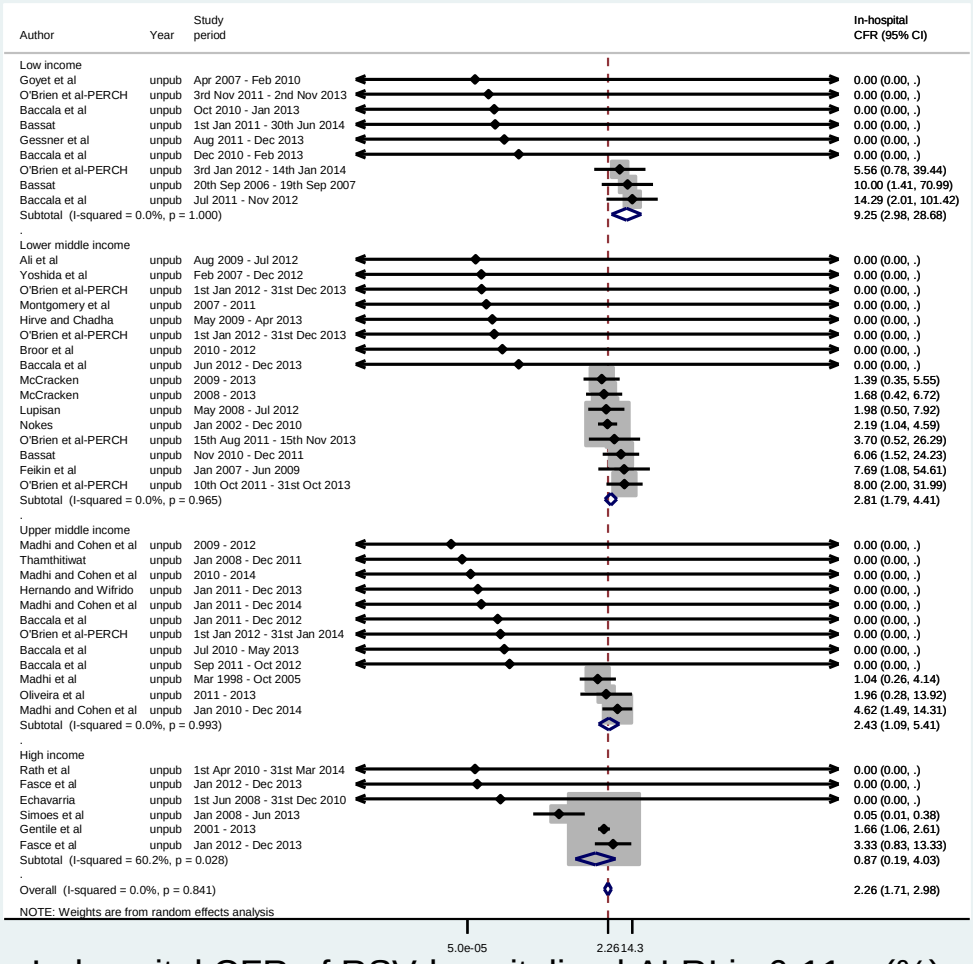
A20. Forest plots for meta-analysis results of in-hospital CFR of RSV associated hospitalised ALRI

43 studies reporting data in full age range – stratified by regions (world bank income level and developing/industrialised)

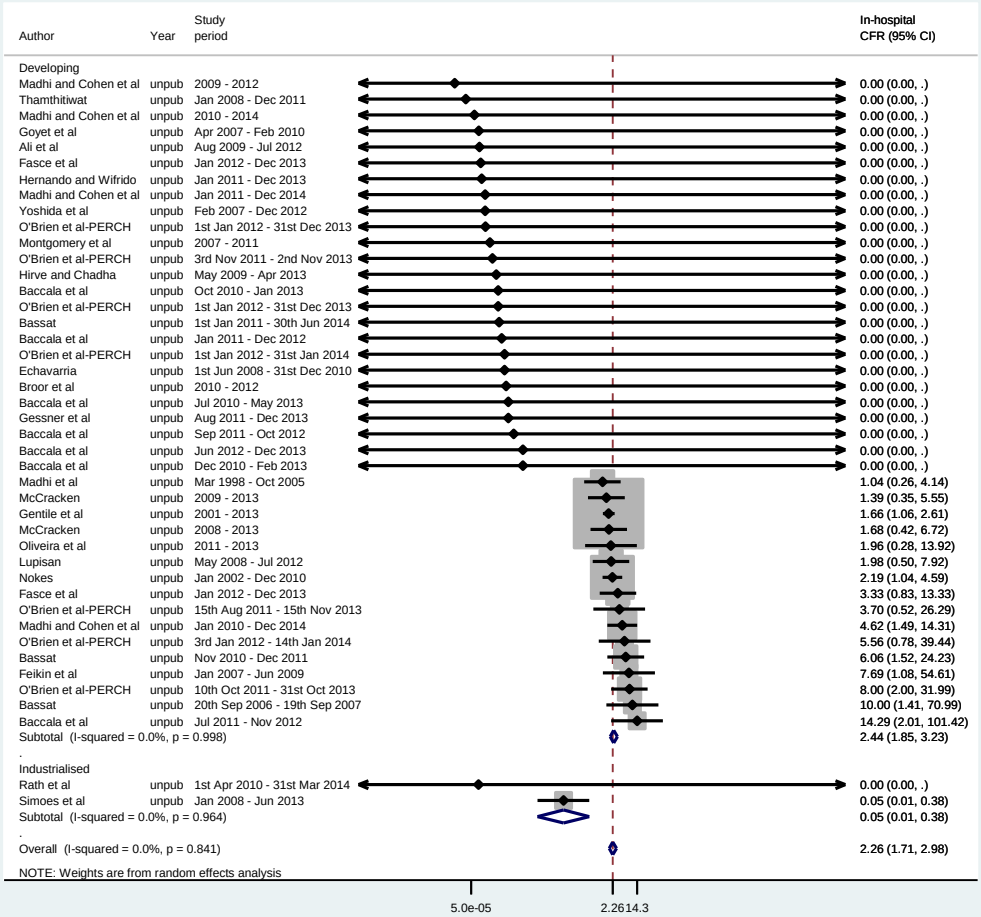




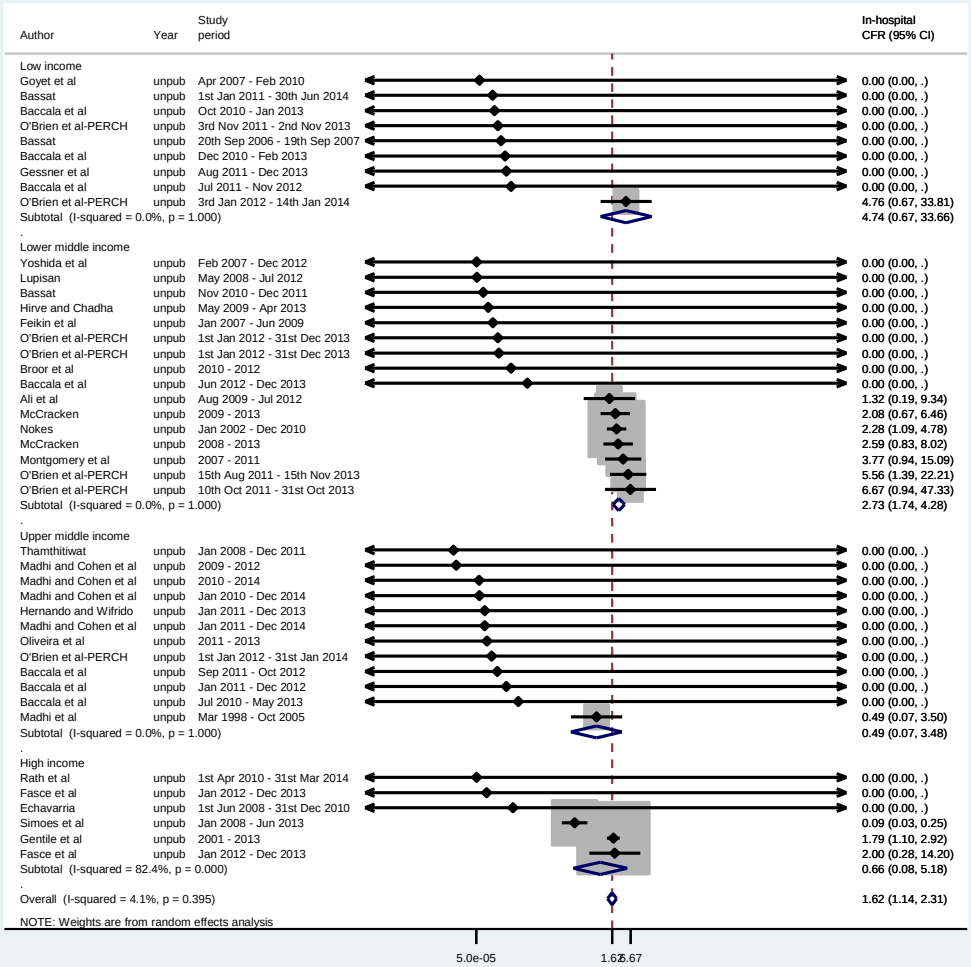
In-hospital CFR of RSV-hospitalised ALRI in 0-5m (%)



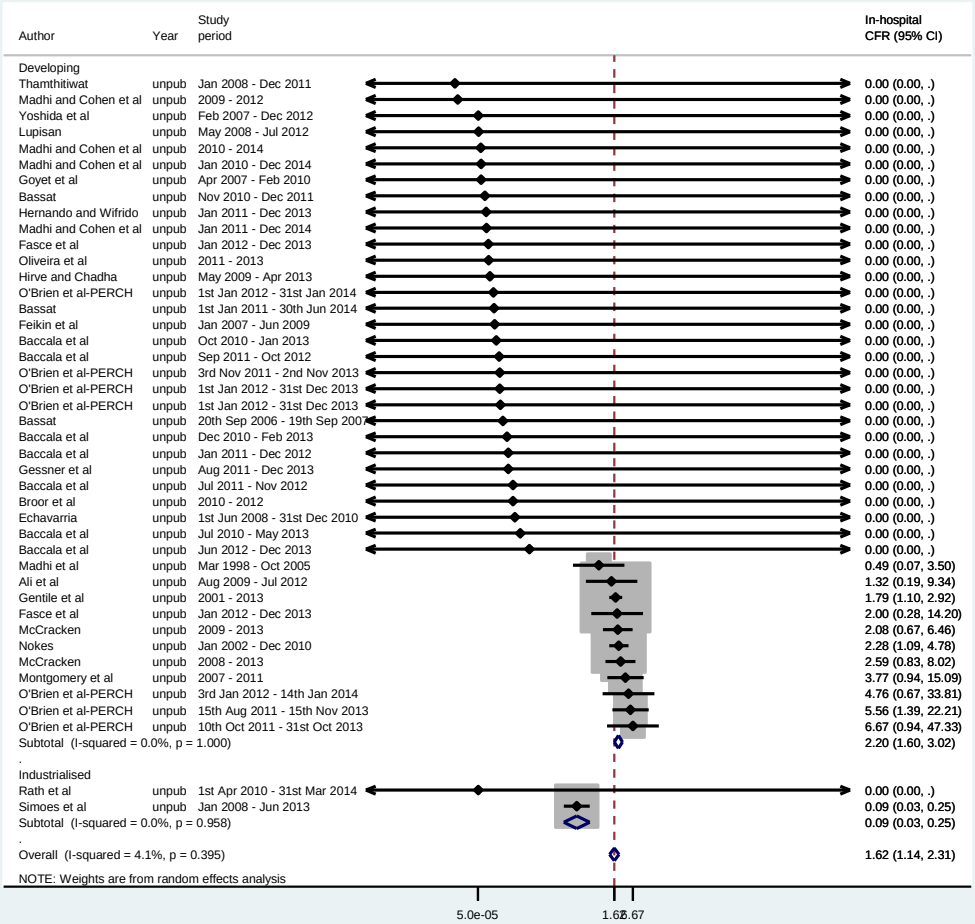
In-hospital CFR of RSV-hospitalised ALRI in 6-11m (%)



In-hospital CFR of RSV-hospitalised ALRI in 6-11m (%)



In-hospital CFR of RSV-hospitalised ALRI in 12-59m (%)



In-hospital CFR of RSV-hospitalised ALRI in 12-59m (%)

A21. Sensitivity analyses to compute inflation factors for RSV in community mortality from developing countries

Use "at least 4 (5%) of the submitted specimen were RSV positive" to define RSV seasonality – same result

Site	Study year	Months of RSV season (a)	Average ALRI deaths per month during RSV season (b)	Average ALRI deaths per month outside RSV season (c)	Total ALRI deaths in community per year (d)	Proportion of ALRI deaths due to RSV (%) (e)*	ALRI deaths overall in this country (f) (Liu et al., 2015a)	RSV deaths overall in this country (g)#
Buenos Aires, Argentina	2011	4	6.3	1.8	39	46.2	887	409
	2012	4	8.5	0.9	41	74.4	878	653
	2013	11	3.3	0.9	20	47.5	844	401
	Mean							488
Multicentre, Bangladesh	2010	9	3.0	2.7	35	8.6	21917	1879
	2011	4	8.8	5.4	78	17.3	20028	3466
	2012	6	9.5	6.3	95	20.0	18759	3752
	Mean							3032
Lombok, Indonesia	2000	6	73.3	62.3	814	8.1	39257	3183
	2001	6	84.8	48.8	802	26.9	37584	10122
	2002	7	45.0	36.8	499	11.5	36020	4143
	Mean							5816

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. *e=[(b-c)*a]/d. #g=e*f*0.01.

Site	Meta-estimate of hospitalisation rate (per 1000 per year) (h)§	Meta-estimate of in-hospital CFR (%) (i)§	Population in mean study period (j)	RSV deaths in hospital overall (k)*	Mean of RSV deaths in community (g)	Adjustment factor (l)#
Argentina	4.9	1.9	3407649	320	488	1.5
Bangladesh	4.9	1.9	15197631	1426	3032	2.1
Indonesia	4.9	1.9	21639000	2030	5816	2.9
Mean						2.2

RSV=respiratory syncytial virus. CFR=case fatality ratio. §Meta-estimate in the developing region (where this country comes from) was used. *k=h*j*0.001*i*0.01. #l=g/k.

Add one more month as RSV season (based on "at least 10 specimens were analysed and 5% of the submitted specimens were RSV positive") – increase inflation factor

Site	Study year	Months of RSV season (a)	Average ALRI deaths per month during RSV season (b)	Average ALRI deaths per month outside RSV season (c)	Total ALRI deaths in community per year (d)	Proportion of ALRI deaths due to RSV (%) (e)*	ALRI deaths overall in this country (f) (Liu et al., 2015a)	RSV deaths overall in this country (g)#
Buenos Aires, Argentina	2011	5	5.6	1.6	39	51.6	887	458
	2012	5	7.4	0.6	41	83.3	878	731
	2013	5	3.0	0.7	20	57.1	844	482
	Mean							557
Multicentre, Bangladesh	2010	11	3.0	2.0	35	31.4	21917	6888
	2011	4	8.8	5.4	78	17.3	20028	3466
	2012	8	9.5	4.8	95	40.0	18759	7504
	Mean							5953
Lombok, Indonesia	2000	7	78.7	52.6	814	22.5	39257	8816
	2001	7	86.3	39.6	802	40.7	37584	15315
	2002	9	43.2	36.7	499	11.8	36020	4259
	Mean							9463

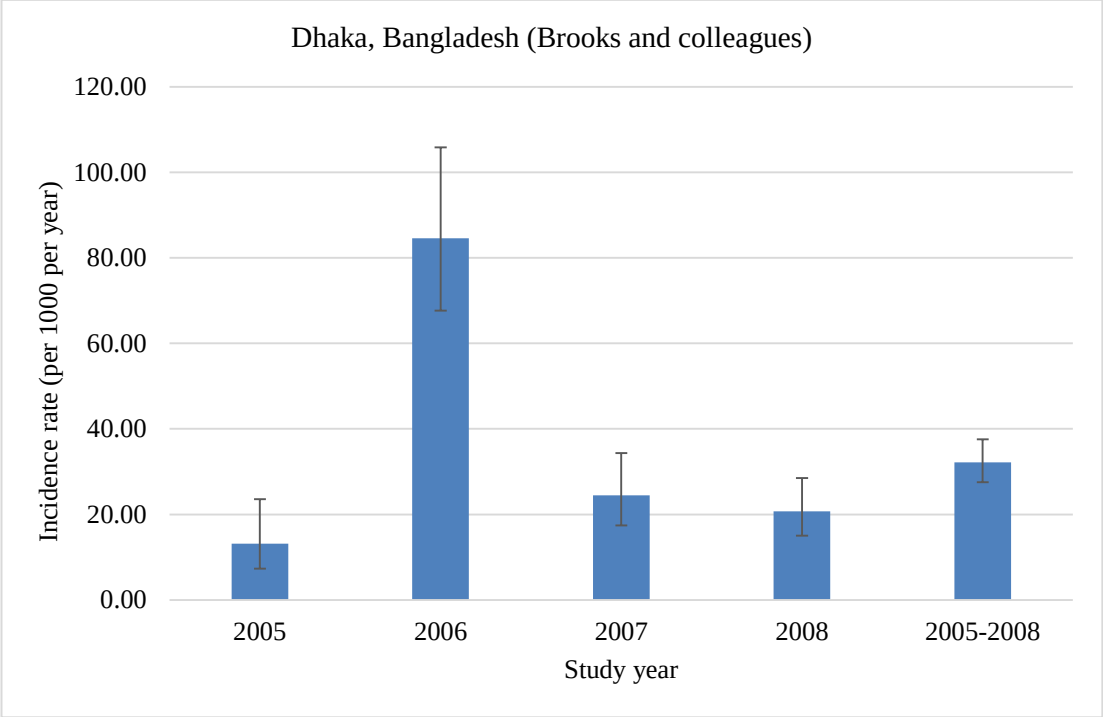
RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. *e=[(b-c)*a]/d. #g=e*f*0.01.

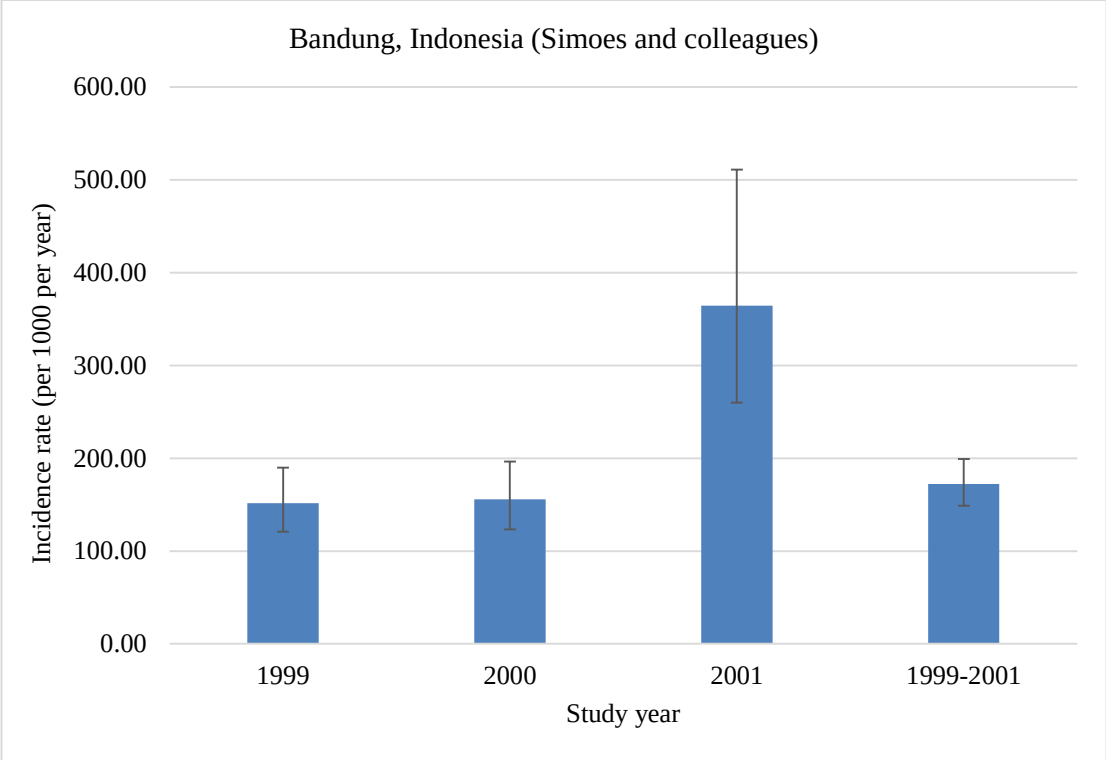
Site	Meta-estimate of hospitalisation rate (per 1000 per year) (h)§	Meta-estimate of in-hospital CFR (%) (i)§	Population in mean study period (j)	RSV deaths in hospital overall (k)*	Mean of RSV deaths in community (g)	Adjustment factor (l)#
Argentina	4.9	1.9	3407649	320	557	1.7
Bangladesh	4.9	1.9	15197631	1426	5953	4.2
Indonesia	4.9	1.9	21639000	2030	9463	4.7
Mean						3.5

RSV=respiratory syncytial virus. CFR=case fatality ratio. §Meta-estimate in the developing region (where this country comes from) was used. *k=h*j*0.001*i*0.01. #l=g/k.

A22. Incidence rate of RSV associated ALRI in infants by year

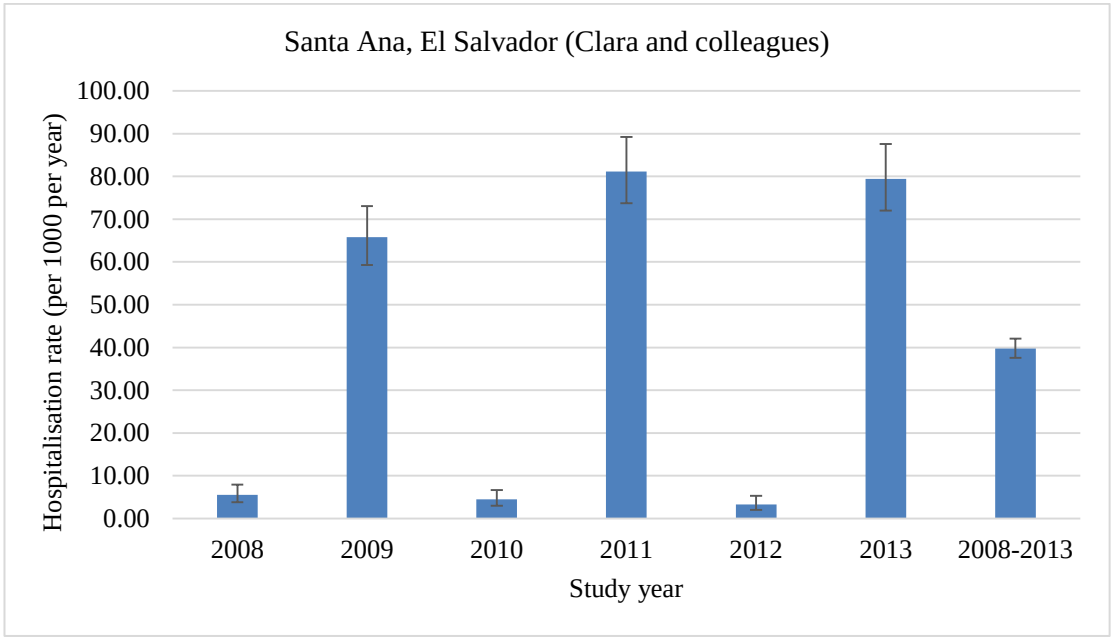
Error bars are 95% confidence intervals of the point estimate.

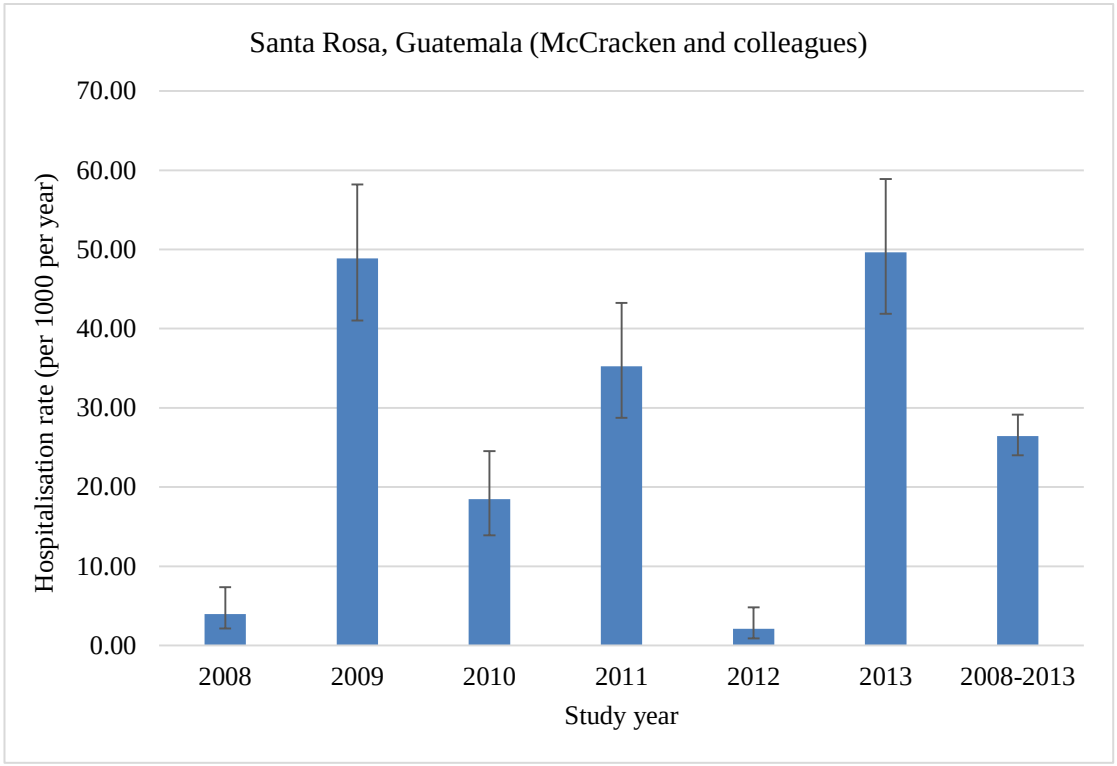


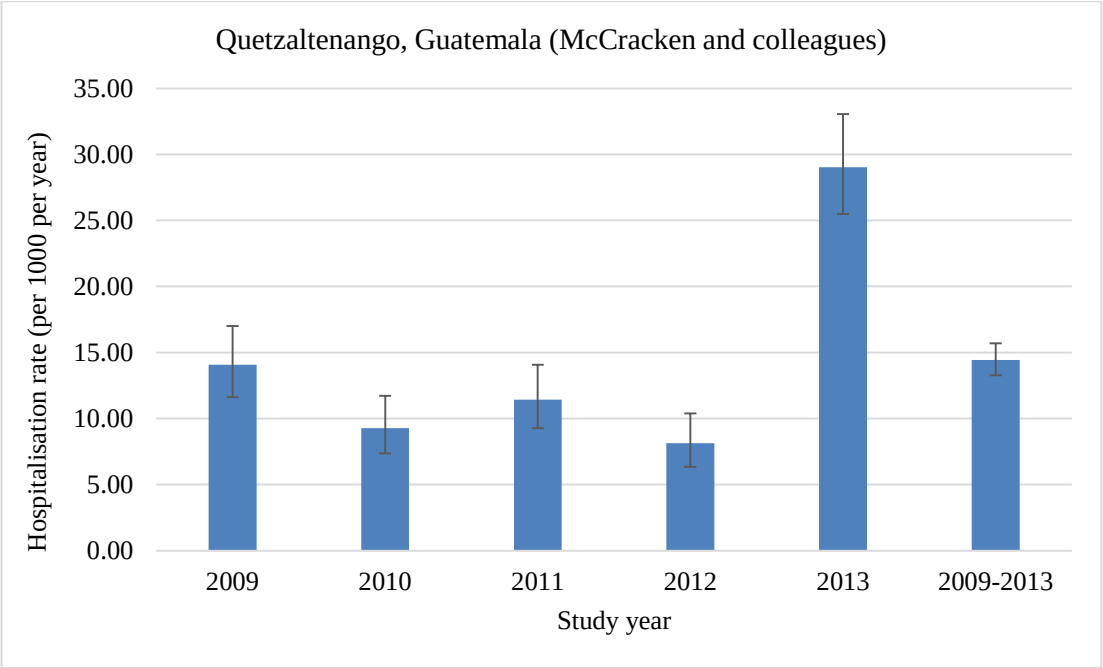


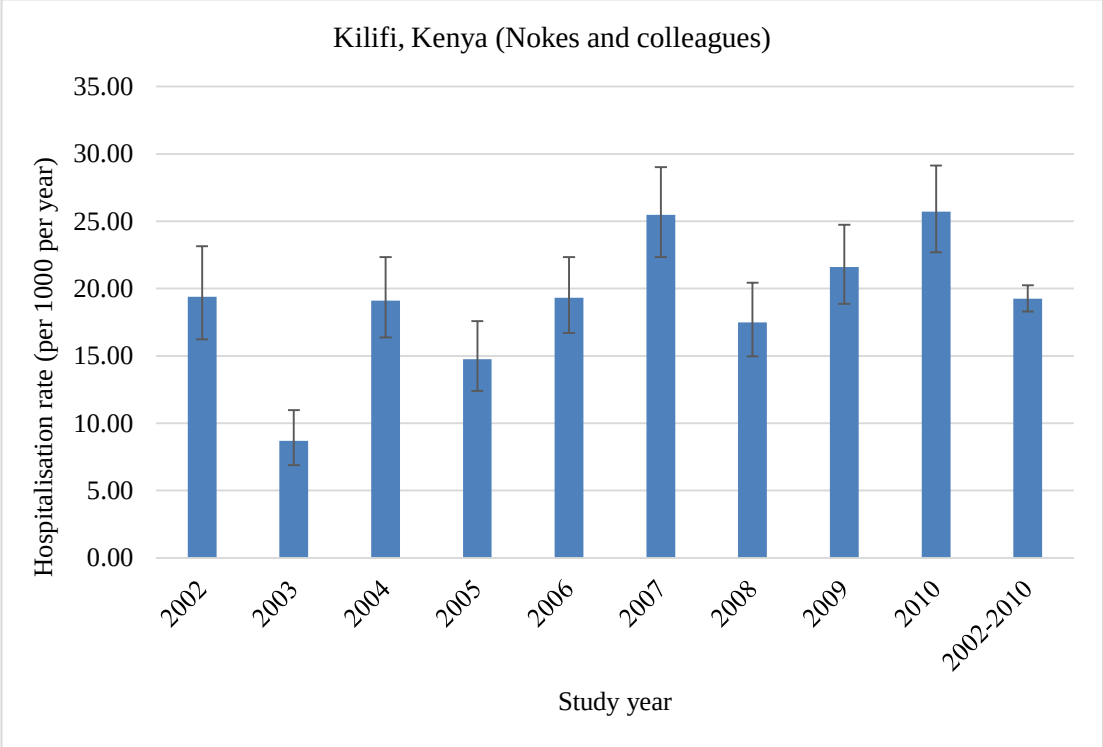
A23. Hospitalisation rate of RSV associated ALRI in infants by year

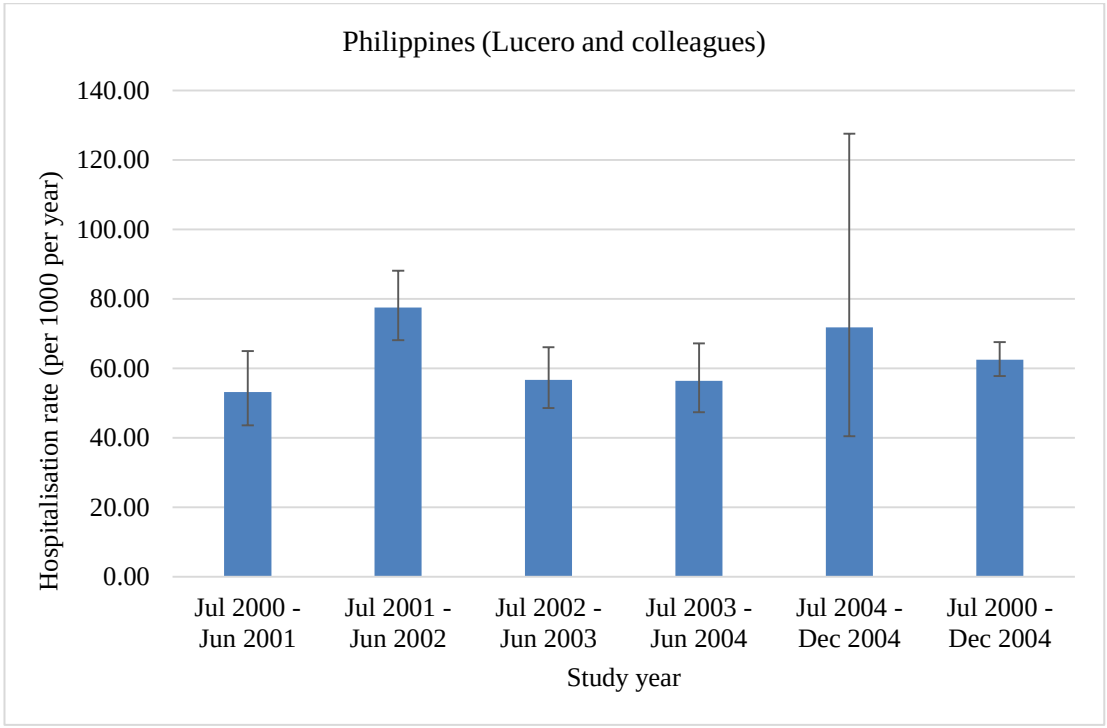
Error bars are 95% confidence intervals of the point estimate.

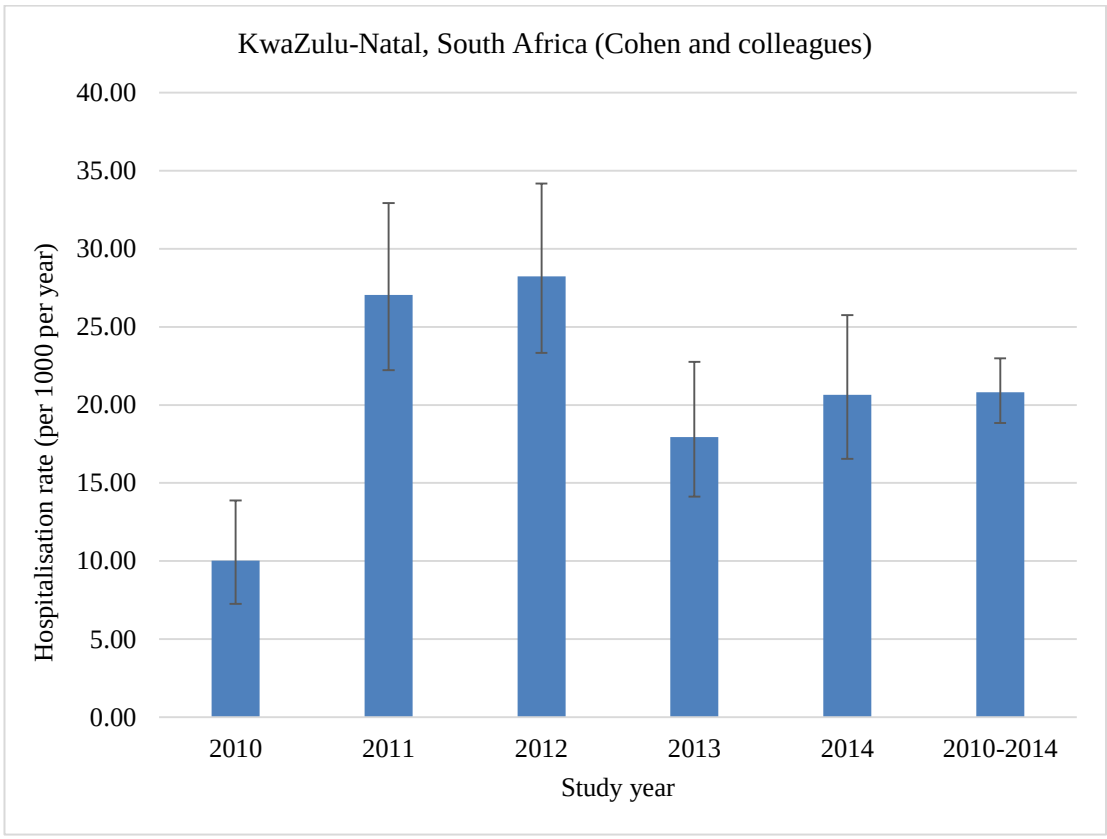


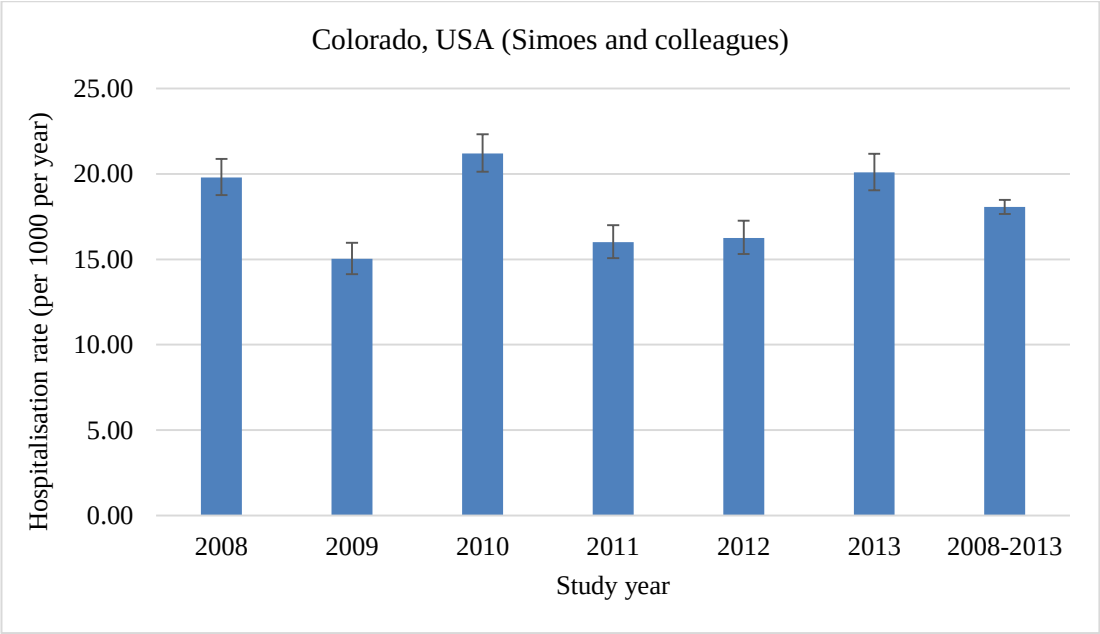



Quetzaltenango, Guatemala (McCracken and colleagues)
Hospitalisation rate (per 1000 per year)
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
2009
2010
2011
2012
2013
2009-2013
Study year


Kilifi, Kenya (Nokes and colleagues)
Hospitalisation rate (per 1000 per year)
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
2002
2003
2004
2005
2006
2007
2008
2009
2010
2002-2010
Study year


Philippines (Lucero and colleagues)
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Hospitalisation rate (per 1000 per year)
Jul 2000 - Jun 2001
Jul 2001 - Jun 2002
Jul 2002 - Jun 2003
Jul 2003 - Jun 2004
Jul 2004 - Dec 2004
Jul 2000 - Dec 2004
Study year


KwaZulu-Natal, South Africa (Cohen and colleagues)
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Hospitalisation rate (per 1000 per year)
2010
2011
2012
2013
2014
2010-2014
Study year


Colorado, USA (Simoes and colleagues)
Hospitalisation rate (per 1000 per year)
25.00
20.00
15.00
10.00
5.00
0.00
2008
2009
2010
2011
2012
2013
2008-2013
Study year

A24. Adjustment of in-hospital CFR accounting for untested ALRI cases

Location (reference)	CFR of untested ALRI (%) (a)	No. of untested ALRI (b)	Prop of ALRI with RSV positive (c)	No. of RSV+ from untested ALRI (d)§	RSV deaths from untested ALRI (e)*	Deaths of RSV-tested ALRI (f)	Cases of RSV-tested ALRI (g)	CFR of RSV-tested ALRI (h)#	Adjusted CFR of RSV-ALRI (i)$
Kilifi, Kenya (PERCH, unpublished)	100.0	2	0.24	0.47	0.47	6	150	4.00	4.30
Iquique, Chile (Fasce, unpublished)	0.0	4	0.35	1.40	0.00	2	237	0.84	0.84
Buenos Aires, Argentina (Polack, unpublished)	43.3	30	0.65	19.46	8.43	24	2167	1.11	1.48
Gauteng province, South Africa (Cohen, unpublished)	2.5	122	0.29	35.04	0.86	8	1693	0.47	0.51
Manhiça, Mozambique (Bassat, unpublished)	13.3	15	0.14	2.14	0.29	0	68	0.00	0.41
Klerksdorp site, South Africa (Cohen, unpublished)	0.0	30	0.22	6.72	0.00	3	202	1.49	1.44
Tone District, Togo (Gessner,	66.7	3	0.12	0.37	0.25	0	15	0.00	1.61

Location (reference)	CFR of untested ALRI (%) (a)	No. of untested ALRI (b)	Prop of ALRI with RSV positive (c)	No. of RSV+ from untested ALRI (d)§	RSV deaths from untested ALRI (e)*	Deaths of RSV-tested ALRI (f)	Cases of RSV-tested ALRI (g)	CFR of RSV-tested ALRI (h)#	Adjusted CFR of RSV-ALRI (i)$
unpublished)									
Concepcion, Chile (Fasce, unpublished)	0.0	16	0.43	6.92	0.00	1	201	0.50	0.48
Manhiça, Mozambique (Bassat, unpublished)	25.0	28	0.06	1.70	0.43	1	49	2.04	2.81
Mpumalanga, South Africa (Cohen, unpublished)	21.2	52	0.21	11.08	2.34	6	268	2.24	2.99
Western Gambia (Howie, unpublished)	0.0	100	0.18	17.58	0.00	0	16	0.00	0.00
KwaZulu-Natal province, South Africa (Cohen, unpublished)	1.4	72	0.28	20.22	0.28	0	431	0.00	0.06
Soweto, South Africa (Madhi, unpublished)	22.5	240	0.17	41.50	9.34	14	863	1.62	2.58
CEMIC, Buenos Aires, Argentina (Echavarria, unpublished)	0.0	3	0.39	1.17	0.00	0	21	0.00	0.00

Location (reference)	CFR of untested ALRI (%) (a)	No. of untested ALRI (b)	Prop of ALRI with RSV positive (c)	No. of RSV+ from untested ALRI (d)§	RSV deaths from untested ALRI (e)*	Deaths of RSV-tested ALRI (f)	Cases of RSV-tested ALRI (g)	CFR of RSV-tested ALRI (h)#	Adjusted CFR of RSV-ALRI (i)$
Santa Rosa, Guatemala (McCracken, unpublished)	1.9	104	0.41	34.10	0.66	15	505	2.97	2.90
Basse Santa Su, Gambia (PERCH, unpublished)	10.9	46	0.19	8.86	0.96	0	114	0.00	0.78
Bamako, Mali (PERCH, unpublished)	21.3	61	0.25	15.52	3.31	4	156	2.56	4.26
41 sites in Netherlands (Bont, unpublished)	0.0	24	0.72	17.25	0.00	0	156	0.00	0.00
Lusaka, Zambia (PERCH, unpublished)	26.2	65	0.19	12.13	3.17	6	103	5.83	7.97
Quetzaltenango, Guatemala (McCracken, unpublished)	0.0	207	0.37	69.28	0.00	8	628	1.27	1.15
Buenos Aires, Argentina (Gentile, unpublished)	1.6	1361	0.39	529.93	8.57	65	3590	1.81	1.79

Location (reference)	CFR of untested ALRI (%) (a)	No. of untested ALRI (b)	Prop of ALRI with RSV positive (c)	No. of RSV+ from untested ALRI (d)§	RSV deaths from untested ALRI (e)*	Deaths of RSV-tested ALRI (f)	Cases of RSV-tested ALRI (g)	CFR of RSV-tested ALRI (h)#	Adjusted CFR of RSV-ALRI (i)$
Paarl, South Africa (Zar, unpublished)	4.8	21	0.26	5.50	0.26	0	28	0.00	0.78
Nakhon Phanom and Sa Kaeo, Thailand (PERCH, unpublished)	2.4	41	0.27	11.20	0.27	0	50	0.00	0.45
Kilifi hospital study, Kenya (Nokes, unpublished)	32.7	2817	0.16	460.95	150.87	31	1428	2.17	9.63
Bondo district, Kenya (Feikin, unpublished)	10.1	208	0.13	26.50	2.68	1	66	1.52	3.97
Lombok, Indonesia (Gessner, unpublished)	33.1	1500	0.20	300.57	99.59	13	741	1.75	10.81
Tagbilaran and 6 rural sites, Philippines (Lucero, unpublished)	2.2	537	0.37	200.95	4.49	2	357	0.56	1.16
Belo Horizonte, Brazil (Oliveira, unpublished)	1.3	757	0.29	222.13	2.93	2	152	1.32	1.32

Location (reference)	CFR of untested ALRI (%) (a)	No. of untested ALRI (b)	Prop of ALRI with RSV positive (c)	No. of RSV+ from untested ALRI (d)§	RSV deaths from untested ALRI (e)*	Deaths of RSV-tested ALRI (f)	Cases of RSV-tested ALRI (g)	CFR of RSV-tested ALRI (h)#	Adjusted CFR of RSV-ALRI (i)$
Lwak, Kenya (Montgomery, unpublished)	2.5	1231	0.21	264.53	6.66	4	101	3.96	2.92
Sa Kaeo and Nakhon Phanom, Thailand (Thamthitiwat, unpublished)	0.0	14334	0.17	2389.50	0.00	0	795	0.00	0.00

§d=b*c. *e=d*a*0.01. #h=f/g*100. $i=(f+e)/(g+d)*100.