Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis

Harish Nair, Eric A F Simões, Igor Rudan, Bradford D Gessner, Eduardo Azziz-Baumgartner, Jian Shaoye F Zhang, Daniel R Feikin, Grant A Mackenzie, Jennifer C Moisi, Anna Roca, Henry C Baggett, Syed M A Zaman, Rosalyn J Singleton, Marilla G Lucero, Aruna Chandran, Angela Gentile, Cheryl Cohen, Anand Krishnan, Zulfiquar A Bhutta, Adriano Arguedas, Alexey Wilfrido Clara, Ana Lucia Andrade, Maurice Ope, Raúl Oscar Ruvinisky, Maria Hortal, John P McCracken, Shabir A Madhi, Nigel Bruce, Shamim A Qazi, Saul S Morris, Shams El Arifeen, Martin W Weber, J Anthony G Scott, W Abdullah Brooks, Robert F Breiman, Harry Campbell, for the Severe Acute Lower Respiratory Infections Working Group

Summary

Background The annual number of hospital admissions and in-hospital deaths due to severe acute lower respiratory infections (ALRI) in young children worldwide is unknown. We aimed to estimate the incidence of admissions and deaths for such infections in children younger than 5 years in 2010.

Methods We estimated the incidence of admissions for severe and very severe ALRI in children younger than 5 years, stratified by age and region, with data from a systematic review of studies published between Jan 1, 1990, and March 31, 2012, and from 28 unpublished population-based studies. We applied these incidence estimates to population estimates for 2010, to calculate the global and regional burden in children admitted with severe ALRI in that year. We estimated in-hospital mortality due to severe and very severe ALRI by combining incidence estimates with case fatality ratios from hospital-based studies.

Findings We identified 89 eligible studies and estimated that in 2010, 11.9 million (95% CI 10.3–13.9 million) episodes of severe and 3.0 million (2.1–4.2 million) episodes of very severe ALRI resulted in hospital admissions in young children worldwide. Incidence was higher in boys than in girls, the sex disparity being greatest in South Asian studies. On the basis of data from 37 hospital studies reporting case fatality ratios for severe ALRI, we estimated that roughly 265,000 (95% CI 160,000–450,000) in-hospital deaths took place in young children, with 99% of these deaths in developing countries. Therefore, the data suggest that although 62% of children with severe ALRI are treated in hospitals, 81% of deaths happen outside hospitals.

Interpretation Severe ALRI is a substantial burden on health services worldwide and a major cause of hospital referral and admission in young children. Improved hospital access and reduced inequities, such as those related to sex and rural status, could substantially decrease mortality related to such infection. Community-based management of severe disease could be an important complementary strategy to reduce pneumonia mortality and health inequities.

Funding WHO.

Introduction

Acute lower respiratory infections (ALRI), such as pneumonia and bronchiolitis, are a leading cause of morbidity and mortality in young children. In 2010, 1.4 million children died because of such infections,1 resulting in a substantial burden on the health-care system. No systematically established global estimates have been made of the incidence of hospital admissions for severe ALRI in children younger than 5 years. Rudan estimated that worldwide, 7–13% of 156 million yearly pneumonia cases might progress to severe disease and warrant admission. However, these preliminary estimates were based on findings from only 28 community-based studies of disease incidence, six of which estimated the proportion of severe episodes, and these had variable case ascertainment.

We were aware of additional high-quality data for incidence of and mortality from admissions for severe ALRI. These data were from published and unpublished hospital-based studies with passive case ascertainment—ie, children who reported to the health facility. Therefore, we formed a Severe ALRI Working Group, a consortium of leading researchers in childhood pneumonia working mainly in developing countries, to estimate the incidence of hospital admissions and in-hospital deaths due to severe ALRI in children younger than 5 years in 2010, worldwide and for six WHO regions. Furthermore, we examined how these estimates varied by severity of episode, by sex, by distance from the hospital, and in the period 2008–10 during the influenza A H1N1 pandemic.

Methods

Search strategy and selection criteria We undertook a systematic literature review with various search terms (appendix pp 4–6), hand searched online journals, and scanned the reference lists of identified journals.
citations. We searched Medline (Ovid), Embase, CINAHL, Global Health, Web of Science, WHOLIS, LilACS, IndMed, SIGLE for studies published between Jan 1, 1990, and March 31, 2012. We also searched three Chinese language databases: China National Knowledge Infrastructure, Wanfang Data, and Chongqing VIP for studies published in Chinese.

We included studies reporting data for hospital admission for ALRI and severe ALRI in children younger than 5 years, with data for at least 12 consecutive months, and reporting incidence or mortality for at least the first year of life. Although we assessed studies reporting incidence estimates, we included only those with well defined catchment populations or estimations of the population at risk. We excluded studies in which the case definition was not clearly defined or not consistently applied; description of the methods for estimation of the denominator population was not clear; only cause-specific ALRI incidence or mortality were reported; only incidence or mortality estimates for ALRI confirmed by chest radiograph were reported; those in which incidence or mortality were estimated with modelling techniques; or those reporting data by community-based case ascertainment. We applied no language or publication restrictions. Two investigators (HN and PH) did the search in English language databases and extracted data. Any disagreements were resolved after discussion. One investigator (JSFZ) whose first language was Chinese undertook searches and data abstraction from Chinese language databases and validated identified studies in direct discussion with HN. Unpublished studies were identified in meetings of the Severe ALRI Working Group.

The working group agreed on an approach for data analysis and interpretation and formulated common case definitions. The group either reanalysed data from their already published work with these case definitions or shared hitherto unpublished data from ongoing studies. This method resulted in analysis of substantial unpublished data, which supplemented data from review of published studies (appendix pp 14–16).

Definitions
Most investigators used modified versions of WHO case definitions for severe pneumonia (appendix pp 17–26).

We used the terms severe and very severe ALRI because many young children present with bronchiolitis, which can be clinically indistinguishable from pneumonia. We decided that children with ALRI denoted by cough or difficulty breathing with increased respiratory rate for age, with or without in-drawing of the chest wall who were admitted at the discretion of the attending physician should be referred to as having severe ALRI. We defined very severe ALRI as severe ALRI with hypoxaemia, or WHO Integrated Management of Childhood Illness danger signs, or both. Because data for hypoxaemia were limited to health facilities where pulse oximetry was available, we included studies reporting data for children admitted with severe ALRI and any of the danger signs in the category of very severe ALRI (appendix pp 27–30). We recognised that children admitted with very severe ALRI would have a more life-threatening illness and regarded these patients as a subset of those with severe ALRI. We designated countries as industrialised or developing on the basis of UNICEF’s classification in The State of the World’s Children 2012 report. The child population estimates for 2010 are as in the UN Population Division’s database, World Population Prospects: the 2010 revision.

Data imputation
For studies that did not report disease incidence for the full age range (ie, 0–59 months), we used imputation to calculate missing data by use of the median incidence rate ratio (appendix pp 7–8). We did a sensitivity analysis with unimputed data and noted that the final estimates did not differ significantly. If the duration of the study exceeded 12 months, but was not in exact multiples of 1 year, we calculated and reported the annualised incidence by adjusting for the population at risk.

Statistical analysis
We did a meta-analysis of data for disease incidence and case-fatality ratio and reported pooled estimates and 95% CIs. We used the random effects model (DerSimonian-Laird method) because of significant heterogeneity in the data (I²>80%, p<0·0005). Because HIV is a major risk factor for admission for severe ALRI, and the prevalence of HIV in children younger than 5 years has decreased substantially and access to highly active antiretroviral treatment has increased greatly in South Africa since 2002 (median year for the study from Soweto, South Africa), we adjusted the incidence (appendix pp 17–26) taking into consideration both determinants and used the adjusted rates when undertaking the meta-analysis (appendix pp 9–11). We used data for the period Jan 1, 1981, to Dec 31, 2010, and estimated the incidence for industrialised and developing countries and for the six WHO regions, and applied these estimates to children younger than 5 years in 2010. We used two approaches to estimate the probable number of children with episodes of severe ALRI who were not admitted and hence (by combining those estimates with our hospital estimates), the total number of severe cases in developing countries in 2010. First, we used data for health-care use (in children with reported signs of pneumonia) from Demographic Health Survey (DHS) and Multi Indicator Cluster Survey (MICS) databases from 81 surveys from developing countries as a proxy for the proportion of children with severe ALRI who sought hospital care.

For the second approach we used data from four hospital studies that recorded all admissions for severe ALRI within the setting of community-based active surveillance of all episodes of ALRI and severe ALRI
Articles

Secretariat, Arusha, Tanzania (M Ope MBChB); National University of Buenos Aires, Buenos Aires, Argentina (Prof R O Ruvinsky MD); Program for Basic Sciences Development, National University/PNUD, Montevideo, Uruguay (Prof M Hortal MD); Center for Health Studies, Universidad del Valle de Guatemala, Guatemala (J P McCracken ScD); University of Liverpool, Liverpool, UK (Prof N Bruce PhD); Department of Maternal, Neonatal and Child and Adolescent Health, WHO, Geneva, Switzerland (S A Qazi MD); Bill & Melinda Gates Foundation, Seattle, WA, USA (S S Morris PhD); International Centre for

(on the basis of WHO Integrated Management of Childhood Illness case definitions). This approach enabled us to estimate the proportion of children who were actually admitted (appendix p 12). We assessed variation in incidence by case definitions for disease severity and by distance from the hospital. We used incidence ratios to compare the difference in incidence between boys and girls.

To estimate in-hospital deaths due to severe and very severe ALRI, we applied the meta-estimates of the in-hospital case-fatality ratios to incidence data for admissions for severe and very severe ALRI for developing and industrialised regions. We did a sensitivity analysis to assess whether the case fatality ratio was a function of the disease incidence and noted no such relation across the developing world (appendix pp 44–45). This finding supports our decision to use a standard ratio (obtained from the random effects model) for all developing countries. We did all data analysis with Stata (version 11.2).

Role of the funding source
The funding sources supported a meeting of the Severe ALRI Working Group in Edinburgh, UK (Aug 30–31, 2010). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. HN had full access to all the data in the study and HN and HC had final responsibility for the decision to submit for publication.

Results
We identified 89 hospital-based studies with suitable data for incidence (figure 1); 61 were published (of which 14 were in Chinese and two had data for two different populations) and 28 were unpublished (figure 2; appendix pp 17–26). 30 studies were in rural populations, 17 in urban populations, and 42 were in a mixture of both. 25 (40%) of 62 studies from developing countries were either cohort studies or were in a demographic surveillance site; seven (11%) had a well-defined catchment area for which we estimated the population with a health-care utilisation survey, and 30 (49%) were undertaken in hospitals with well defined catchment areas. Only 43 studies (24 published and 19 unpublished; appendix pp 7–8) reported disease incidence by age group for the full age range and we imputed data for the remaining 46 studies. 19 studies (15 unpublished) reported incidence specifically for neonates (infants aged 0–27 days; appendix pp 31–32). The 62 studies from developing countries reported incidence of hospital admissions for severe ALRI in children aged 0–59 months (about 20 episodes per 1000 children per year; table 1).

Disease incidence was highest in neonates aged 0–27 days (68.6 episodes per 1000 per year, 95% CI 47.8–98.4; appendix pp 31–32) and infants aged 0–11 months (51.8 episodes per 1000 per year, 44.8–59.8). With data from 27 studies in industrialised countries, estimates of the incidence of admissions for severe ALRI was about 20 episodes per 1000 children per year in children aged 0–11 months, and about 10 episodes per 1000 children per year in those aged 0–59 months, which translate to about 12 million episodes worldwide in children younger than 5 years in 2010, with disease in neonates contributing to about 6% of this overall burden (table 1). Data from 15 unpublished studies that recorded this information showed that only about 60% of children admitted with ALRI had indrawing of the lower-chest wall (appendix pp 38–39). 36 studies (34 from developing countries) reported the incidence of admissions for very severe ALRI in children aged 0–59 months (appendix pp 27–30). We estimated that the incidence of admissions for very severe ALRI in this age group in developing countries was about five episodes per 1000 children per year, which translates to about 3 million cases worldwide.

Figure 1: Flow diagram for selection of studies

1382

www.thelancet.com Vol 381 April 20, 2013
Figure 2: Location of the 89 studies by WHO region

Table 1: Estimates of incidence (per 1000 children per year) and the number of episodes of severe ALRI and very severe ALRI in children younger than 5 years admitted to hospital in 2010, by WHO regions

| Region            | Severe ALRI | Very severe ALRI |
|-------------------|-------------|------------------|
|                   | Aged <1 year|                  |
|                   | Aged <5 years|               |
|                   | Very severe |                  |
|                   | Aged <1 year|                  |
|                   | Aged <5 years|               |
|                   | Very severe |                  |
| Data in parentheses are imputed number of studies or 95% CI. | | |
| ALRI = acute lower respiratory infection. | Data include American Indian and Alaska native populations in the USA because the socioeconomic and demographic risk factors for ALRI in these populations are similar to those in the developing countries. | For the China National Knowledge Infrastructure see http://www.global.cnki.net | For Wanfang Data see http://www.wanfangdata.com.cn | For Chongqing VIP see http://www.cqvip.com |
in 2010 (table 1). We estimate that about 15% (95% CI 10·2–20·8) of all infants and 11% (7–16·3) of children aged 12–59 months admitted with severe ALRI have hypoxaemia. However, the prevalence of hypoxaemia in these children is highly variable across study sites and regions (appendix pp 42–43).

Findings from 28 unpublished studies show that the incidence of admissions for severe ALRI was higher in boys than in girls for all age groups and regions; this sex difference was greatest in studies from South Asia (figure 3). We identified two studies that reported data for residence of children with the Geographic Information System, which showed that disease incidence generally decreased with increasing distance from hospital, except at one site in which admission rates were low for children living within 2 km of hospital (appendix p 46).

We identified four unpublished studies that used both active community-based case ascertainment and had a hospital group for passive case ascertainment (appendix p 33). The proportion of children with chest wall in-drawing identified in the community that were treated in hospital varied greatly between these studies (median proportion 0·5, IQR 0·4–0·6). We used this proportion and data for health-care use for ALRI from DHS and MICS databases to estimate that about 19 million episodes of severe ALRI occurred in children aged 0–59 months globally in 2010 (figure 4). This preliminary estimate is consistent with published and well accepted incidence and mortality estimates and is within the confidence intervals of the previous global estimate (figure 4).1,2

We sought to describe the variation in incidence of admissions for severe ALRI in children aged younger than 5 years between 2008 and 2010, mainly during the influenza A H1N1 pandemic in 2009–10. Eight studies (see appendix pp 14–15 for study numbers U7, U9, U11, U17, U18, U22, U25, U26) had data for 2007–08 and 2009–10. Overall, a 32·5% (95% CI 31–33·9; p<0·0005) increase was recorded in the incidence of admissions for severe ALRI between 2007–08 and 2009–10. However, the reported individual rates varied substantially and did not differ in neonates. Similarly, with data from eight studies we noted a 40% (33–47) increase in incidence of admissions for very severe ALRI, again restricted to the post-neonatal population.

We identified ten published11,14,21,24,35,40,41,63,64,66 and 27 unpublished studies (appendix pp 34–35) providing data for in-hospital case fatality in children aged younger than 5 years admitted with severe ALRI, and 16 unpublished studies (appendix p 36) reporting case fatality for very severe ALRI. We estimated that the hospital-based case-fatality ratio was 2·3% (95% CI 1·6–3·4; table 2) in children aged 0–59 months admitted with severe, and 6·1% (4·6–8·1) for those with very severe ALRI in developing countries in 2010, with the highest rates reported in studies from Africa; by contrast, estimated case-fatality ratios in industrialised countries were 0·6% (0·4–0·8; table 2) and 3·9% (3·1–4·8), respectively.

We applied the in-hospital meta-estimates of case fatality for the developing and industrialised regions to the incidence meta-estimates for those regions and

![Figure 3: Incidence of admissions for severe acute lower respiratory infection in boys versus girls aged 0–59 months](http://www.thelancet.com)

Error bars show 95% CIs. Appendix pp 14–16 show details of the unpublished studies and study numbers.
estimated that worldwide in 2010, severe ALRI resulted in about 0.3 million in-hospital deaths in children aged 0–4 years, and 67% of these deaths were in young children who presented with signs of very severe ALRI on admission (panel). The case-fatality ratio was 9% (95% CI 1–18) higher in girls (p=0.01) aged 0–11 months than in boys of this age, but did not differ significantly (p=0.49) by gender in children aged 12–59 months, in whom the ratio was 6% (−13 to 22) higher in boys (p=0.49).

**Discussion**

We estimated that in 2010, there were about 12 million episodes of hospital admissions for severe and 3 million for very severe ALRI. We further estimated that severe or very severe ALRI resulted in about 0.3 million deaths in hospitals in young children. 99% of these deaths were in developing countries, and in-hospital deaths were about 19% (uncertainty range 12–41%, based on extreme combinations of numerator and denominator 95% CI values) of the estimated total number of ALRI deaths in young children in 2010. The incidence of admissions for severe ALRI were more than three times higher in neonates and about 1.3 times higher in infants aged 0–11 months than the overall rate in young children aged 0–59 months. Estimates are very variable within and between countries and regions and across different study periods (table 1, table 2, appendix pp 17–30).

Several factors affect these estimates: method of case ascertainment, precise case definitions for the various categories of admission, geographical location of the study sites, cultural factors, and health-care seeking behaviour of the population. Hence, the true uncertainties around these estimates are larger than those expressed in a standard 95% CI that we report. We have attempted to reduce these biases by using strict case definitions and minimum quality criteria for included studies. Estimates from developing and industrialised countries are not strictly comparable because case definitions in developing countries tend to be based on simple clinical syndromic criteria, with no requirement for results of investigations. Health information systems in developing countries do not typically provide accurate information about the regional and national burden of severe ALRI on hospital services, despite this information being of key importance for the planning of these services. Therefore, such estimates could be useful in the many settings where data are scarce. The incidence metaestimate for admissions of severe ALRI in developing countries derives largely from studies in which the catchment population had fairly good access to care, and where study interventions might have changed health-care seeking behaviour of participants. We recognise that many children with severe ALRI in developing countries do not receive hospital care. Therefore, our global and regional estimates are likely to underestimate the true burden of severe ALRI, but rather show the burden of such infection on hospital services, with the assumption that the level of health-care access and use is similar to that in the included 89 studies.

We estimated the extent to which these hospital-based data underestimate the true incidence of severe ALRI in developing countries with poor access to and use of hospital care (figure 4). Although based on indicator data from DHS and MICS for seeking of appropriate health care for children with reported signs of ALRI (rather than care sought for severe ALRI), our estimate of severe ALRI in young children receiving hospital care is broadly consistent with that (49%, IQR 36–62%) from the four hospital studies used in the second of our two analytical approaches. Furthermore, our estimates are consistent with those reported elsewhere (figure 4).
Table 2: Case-fatality ratio due to severe acute lower respiratory infections in children younger than 5 years who were admitted, by region

| Region         | Aged 0-11 months | Aged 12-59 months | Aged 0-59 months |
|----------------|------------------|------------------|------------------|
|                | Studies CFR (%)  | Studies CFR (%)  | Studies CFR (%)  |
| Africa         | 9                | 3.8% (2.4-5.9)   | 8                | 1.9% (1.2-3.2)   | 11                | 3.9% (2.7-5.5)   |
| America        | 10               | 1.6% (1.1-2.4)   | 10               | 0.6% (0.2-1.3)   | 11                | 1.3% (0.8-1.9)   |
| Eastern Mediter| 1                | 9.9% (8.6-11.5)  | -                | -                | 2                 | 7.6% (4.1-13.9)  |
| Europe         | -                | -                | -                | -                | 1                 | 0.4% (0.3-0.5)   |
| Southeast Asia | 6                | 2.6% (1.4-4.7)   | 4                | 0.3% (0.1-0.9)   | 9                 | 2.1% (1.1-4)     |
| West Pacific   | 1                | 2.4% (1.3-4.3)   | -                | -                | 3                 | 2.3% (1.7-3.2)   |
| Developing     | 26               | 2.4% (1.7-3.6)   | 21               | 0.8% (0.4-1.3)   | 34                | 2.3% (1.6-3.4)   |
| Industrialised | 1                | 0.8% (0.7-0.9)   | 1                | 0.3% (0.2-0.5)   | 3                 | 0.6% (0.4-0.8)   |
| Global         | 27               | 2.3% (1.5-3.4)   | 22               | 0.7% (0.4-1.2)   | 37                | 2.1% (1.4-3.1)   |

Data in parentheses are 95% CI. CFR=case-fatality ratio.

Panel: Estimated new cases per year, case-fatality ratio, and mortality in children younger than 5 years admitted to hospital for severe acute lower respiratory infections (ALRI)

Children admitted for severe ALRI

- Estimated new cases per year in developing countries: 11 372 600 (95% CI 9 871 650-13 104 470)
- Estimated case-fatality ratio in developing countries: 2.3% (1.6-3.4)
- Estimated mortality in hospitals in developing countries: 261 570 (1 980 100–3 983 300)

Children admitted for very severe ALRI

- Estimated new cases per year in developing countries: 2 794 080 (1 980 100-3 983 300)
- Estimated case-fatality ratio in developing countries: 6.1% (4.6-8.1)
- Estimated mortality in hospitals in developing countries: 172 430 (166 680-178 180)

The high number of severe ALRI episodes mostly shows inadequate care-seeking behaviour or poor access to hospital care, or both, in some settings. For example, many children referred for hospital care do not attend because of cost or cultural factors. This estimate also shows the extent of the large referral burden on hospital services in developing countries, which suggests a need for substantially increased investment in hospital capacity for inpatient and outpatient services, both in terms of human resources and for provision of relevant drugs and supplies for paediatric care. New approaches to increasing of treatment coverage for severe pneumonia, as defined by WHO, in communities that are underserved by hospitals have been effective in Asian settings. WHO recommendations, based on findings from these controlled trials in Asia for management of cases of severe pneumonia with oral antibiotics at home is one strategy that could be effective in some settings.

The analysis in figure 4 shows a general consistency in estimates and has important policy implications: although 62% of children manage to reach hospitals, most deaths still take place outside hospitals. This result is attributable to the large difference in case fatality between hospital-treated and non-hospital-treated severe ALRI. Furthermore, the findings suggest that even if very high rates of access and care seeking were achieved, the number of deaths might still be high. In addition to strategies to increase coverage of pneumococcal vaccination in young children, scaling up of community case management of childhood ALRI (including management of severe pneumonia when appropriate) should be regarded as an effective strategy that could help to reduce the remaining burden of mortality, remove the burden on hospital services, and improve equity in reduction of child mortality.

Findings from two studies (appendix p 46) showing that incidence of admissions for severe ALRI decreased with increasing distance from the hospital were consistent with previous reports and emphasise that access to hospital care is an important determinant of deaths from pneumonia in children in developing countries. We noted a consistently higher incidence of admissions for severe ALRI in boys than in girls. Although this increased risk could be attributable to the smaller airway size in young boys than in young girls, the substantially heightened sex differences in South Asian studies (India, Pakistan, and Bangladesh) probably shows the importance of cultural factors, such as preference in seeking medical care for boys. Global burden of disease estimates tend not to include estimates by sex for child mortality from pneumonia; therefore, to what extent sex differences affect pneumonia mortality is uncertain. These differences, especially those in South Asia, merit further study and programmatic attention because they could represent substantial health inequity. Investigators of future epidemiological studies should make increased efforts to gather, analyse, and report gender-specific data to increase the attention given to this important issue.

Hypoxaemia is a key predictor of ALRI mortality and an important indicator of severity. Hypoxaemia prevalence estimates were variable across study sites and defined by factors such as altitude of the study site. 12.6% of severe cases had hypoxaemia, which is consistent with findings from a systematic review and meta-analysis. Our estimates suggest that every year about 1.5 million children admitted with severe ALRI need oxygen treatment. The estimates further emphasise and quantify the need for pulse oximetry equipment and related staff training for identification of children with
hypoxaemia, because clinical signs are poor indicators of this complication.3

We estimate that about a third of all admissions for severe ALRI meet clinical criteria for very severe ALRI and need second-line parenteral treatment with antibiotics; however, substantial heterogeneity exists. In general, the incidence estimates for African countries are about five times higher than those for other developing regions. This finding could show poor access to care in these regions, leading to delays in antibiotics and frequent progression to more severe disease. Furthermore, the estimates are consistent with severe falciparum malaria in endemic areas being misclassified as severe ALRI in settings with few diagnostic facilities.7

In 2010, during the influenza A H1N1 pandemic, our estimates showed an increase in the incidence of admissions for severe and very severe ALRI compared with estimates from the same sites for 2008. This finding could result from increased community awareness about respiratory illness during the pandemic period, leading to increased care seeking and hospital admission or because of an annual variation in the incidence of severe ALRI. However, the increase in admission could be partly explained by disease due to the pandemic predisposing to subsequent bacterial pneumonias.7 This relation needs to be investigated because the ability of health services to respond to a substantial increase in childhood severe ALRI could be an important component of pandemic influenza preparedness and for reducing of influenza-related childhood mortality.

No data are available for several regions worldwide with large high-burden populations—eg, WHO’s Eastern Mediterranean region and much of sub-Saharan Africa. Our estimates of the incidence of admissions for severe ALRI could be used to assess the needs for equipment, such as pulse oximeters and oxygen concentrators, and for drugs in hospitals in developing countries where health information systems cannot supply these data. The fairly low estimated percentage of overall deaths that take place in hospital emphasises that access to hospital care is inadequate in many developing countries. Investment should be made to improve such access and to introduce new strategies, such as community case management for cases presently classified as WHO severe pneumonia. Access to care, sex inequities in care seeking, and appropriate case management of children with severe and very severe pneumonia needs urgent assessment if further reductions in childhood deaths from pneumonia are to be achieved.

Contributors
HN, HC, and MWW conceptualised the study. HN led the literature search, data collection, data analysis, data interpretation, and writing of the report. JSFZ did the literature search and data extraction from Chinese language databases. EAFS, EA-B, DRF, GAM, BDG, ICM, ZAB, AR, HCB, SMAZ, RJS, MGL, AC, AG, CC, AK, AA, AWC, ALA, MO, ROR, MH, JPM, SAM, SAM, NB, SEA, WAB, and RFB contributed to data collection and analysis of primary data, data interpretation, and critically reviewed the manuscript. PH did the literature search and data extraction from English language databases. SAQ, JAGS, and MWW contributed to data interpretation and critically reviewed the manuscript. IR and HC participated in data interpretation, contributed to report writing, and critically reviewed the manuscript. All other members of the Severe ALRI Working Group contributed to data collection, data analysis, and critically reviewed the manuscript. All authors read and approved the final draft of the manuscript.

Severe ALRI Working Group
Harish Nair, Harry Campbell, Igor Rudan, Evropi Theodoratou, David A McAllister, Peter Hanlon, Peter Sammon (The University of Edinburgh); Eric AF Simões and Phyllis Carosone-Link (University of Colorado Denver and Children’s Hospital, Denver, CO, USA); Eduardo Azziz-Baumgartner, Sonja J Olsen (Centers for Disease Control and Prevention, Atlanta, GA, USA); Jian Shayne F Zhang (The University of Melbourne, Australia); Daniel R Feikin, Allan Audi, Gideon Emunule, Mark Katz, Robert F Breiman (Centers for Disease Control and Prevention-Kenya, Nairobi, Kenya); Grant A Mackenzie, Syed MA Zaman, Stephen RC Howie (Medical Research Council, The Gambia); Bradford D Gessner (Agence de Médecine Préventive, Paris, France); Jennifer C Moisi, Patrick K Munywoki, J Anthony G Scott (Kenya Medical Research Institute–Wellcome Trust Research Programme, Kilifi, Kenya); Zulfiaq A Bhutta, Saajid Soofi (Aga Khan University, Karachi, Pakistan); Anna Roca, Betuel Lázaro Siguñé (Universitat de Barcelona, Barcelona, Spain); Henry C Baggett, Julio Alberto Armero Guardado (Ministry of Health of El Salvador); Susan A Maloney (Thailand MOPH–US CDC Collaboration, Thailand); Kummuun Ungchusak (Thailand MOPH, Thailand); Doli Goswami, Tanvir Mahmudul Huda, Aliya Naheed, Nusrat Homaira, Shams El Afireen, W Abdullah Brooks (International Centre for Diarrhoeal Disease Research, Bangladesh); Rosalyn J Singleton, Dana Braden (Arctic Investigations Program, CDC, Anchorage, AK, USA); Marília G Lucero (Research Institute for Tropical Medicine, Philippines); Aruna Chandran, Geoffrey Kahn, Katherine L O’Brien (Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA); Angela Gentile, Julia Bakir (Ricardo Gutierrez Children’s Hospital, Buenos Aires, Argentina); Cheryl Cohen, Marietje Venter, Shabir A Madhi (National Institute for Communicable Diseases, South Africa); Anand Krishnan, Shobha Broor (All India Institute of Medical Sciences, New Delhi, India); Arturo Abdelnour, Adriano Arguedas (Universidad de Ciencias Médicas de Centro América, San José, Costa Rica); Alexey Wilfrido Clara (CDC-Central American Region, Guatemala); Ana Lucia Andrade, Ruth Minamisawa (Federal University of Goiás, Goiânia, Brazil); Cissy B Kartassmita, Kuswandewi Mutya (The University of Padjadjaran, Bandung, Indonesia); Maurice Ope (East African Community Secretariat, Arusha, Tanzania); Raúl Oscar Ruvinsky (National University of Buenos Aires, Argentina); María Hortal (Program for Basic Sciences Development, National University/PNUD, Uruguay); Abdul Bari (Save the Children US, Pakistan Country Office, Islamabad, Pakistan); John P McCracken, María Renée López (Universidad del Valle de Guatemala, Guatemala); Mukesh Dherani, Nigel Bruce (University of Liverpool, UK); Shama Parveen (Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, New Delhi); Miguel Tregnaghi (CEDEPAP, Cordoba, Argentina); Hanna Nokynek (National Institute for Health and Welfare, Finland); Vivek Gupta (The INCLEN Trust International, New Delhi); Mahmudur Rahman (Institute of Epidemiology, Disease Control and Research, Dhaka, Bangladesh); Endang R Sedyaningistih (Indonesian Ministry of Health, Jakarta, Indonesia); Julio Alberto Armero Guardado (Ministry of Health of El Salvador); Anthony W Mounts, Shamim A Qazi (WHO Geneva, Switzerland); Martin W Weber (WHO, Indonesia Country Office); Sajid S Morris (Bill & Melinda Gates Foundation, Seattle, WA, USA).

Conflicts of interest
AA has received research grants, honoraria for participation in advisory boards, and travel grants from GlaxoSmithKline (GSK), Wyeth, and Pfizer. BDG works for Agence de Médecine Préventive, which receives unrestricted funding from Sanofi Pasteur, and has received grant support from Crucell, GSK, Merck, Pfizer, and Sanofi Pasteur. JAGS has received research funding from GSK and a travel grant from Merck. SAM has been a clinical trialist in studies of vaccines against pneumonia-causing pathogens from GSK, Pfizer, Sanofi-Aventis, Novartis, and Medimmune; his institution has received research grants from GSK, Pfizer, and
Novartis; and he has been on the speaker’s bureau of GSK, Pfizer, and Sanofi-Aventis, has received travel support and honoraria, and has acted on advisory boards of GSK, Pfizer, and Novartis. HNO is part of ARIVAC consortium that includes Sanofi Pasteur, undertook a phase 3 trial of an 11-valent pneumococcal conjugate vaccine (Sanofi Pasteur; Lyon, France) in the Philippines in 2002–04, and has received research funding from Pfizer. G. A. L. A. has received research grant from GSK, financial support from Pfizer and GSK to attend meetings, and has served as an advisor to Pfizer. WAB has received funding from the Bill & Melinda Gates Foundation for vaccine-related work related to childhood pneumonia: donation of vaccine from Sanofi Pasteur for a vaccine trial against early childhood pneumonia; project funding from Sanofi Pasteur for pneumococcal vaccine trials and a study in pneumococcal pneumonia disease burden in young children; and has been on the speakers bureau for Sanofi Pasteur. SSM is an employee of the Bill & Melinda Gates Foundation. SAQ, AWM, and MWW are WHO staff members. All other authors declare that they have no conflicts of interest.

Acknowledgments

Financial support for this work was provided by WHO Global Influenza Program (Grant number HQGIP0820096). The findings and conclusions in this report are those of the authors and do not necessarily represent the policies of the United States Centers for Disease Control and Prevention or WHO. This work was done as part of the wider programme of the Child Health Epidemiology Working Group (CHERG) and Global Health Epidemiology Reference Group (GHERG) to establish the major causes of global childhood disease burden. Endang Sedyanginis had died suddenly and unexpectedly while this paper was being prepared for publication. We would like to acknowledge her important contribution to this study and her role as a promoter of child health in Indonesia. We thank Johannes Forster (Department of Paediatrics, St Josef Krankenhaus Freiburg and University of Freiburg, Freiburg, Germany); Gabriele Ihorst (Clinical Trials Center, University Medical Center Freiburg, Freiburg, Germany); and Carlos G Grijalva (Vanderbilt University, US) for providing additional data from their published papers. We are grateful to Felicity Cutts (London School of Hygiene and Tropical Medicine, London, UK); Fatema Khatun, Peter Kim Streifel, Sajaj Kumar Saha, Kamrun Nahar, Amina Tahia Sharmeen, Anjali Bilkis Ara, Sultana Yeasmin (International Centre for Diarrhoeal Disease Research, Bangladesh); Leilani T Nilos (Research Institute for Tropical Medicine, Philippines); Elias Jimenez, Ana Laura Jimenez, Carolina Soley (Instituto de Atención Pediátrica, Costa Rica); Ron Dagan, Nuntich Porat (Pediatric Infectious Disease Unit, Sorka University Medical Center and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel); Gail Rodgers, Sharon Gray, Darmsendra Ramcharran (Pfizer Inc. Collegeville, PA, USA); Uchendu Uchendu, David Ameh, Bolane Akinvola, Reade Idhe, Bernard Ehrask, Deborah Saha, Momodou Jasseh (MRC Unit, The Gambia); Pedro L. Alonso, Llorenç Quinto (Barcelona Centre for International Health Research (CRESIB, Hospital Clinic–Universitat de Barcelona) and Centro de Investigación en Saúde de Manhiça, Mozambique); Maria Aparecida da Silva Vieira (Pontifical Catholic University of Goiás, Goiânia, Brazil); Renato Mauricio Oliveira (Federal University of Goiás, Goiânia, Brazil); Vicente Puriforio Pessoa-Jr (Secretariat of Health of Municipality of Goiânia, Brazil); Simonne Nour (UTHSC–Department of Preventive Medicine, Memphis, TN, USA); Licia Kamilla Assis Melo Thorn (Karolinska Institutet, Stockholmen); Luzia Helena Ribeiro (Samartiano Hospital, Goiânia, Brazil); José Cássio de Moraes (Santa Casa School of Medical Sciences, São Paulo, Brazil); David Rodriguez (Ministry of Health of El Salvador); Celina de Lozano (National Influenza Center of El Salvador); Kim A Lindblade, Jennifer Verani (US Centers for Disease Control and Prevention Regional Office for Central America and Panama, International Emerging Infections Program, Guatemala); Somasak Thammasitwat, Sununta Henchaichon, Prabda Prapasiri, Sathapana Naorat (International Emerging Infections Program, Global Disease Detection Regional Center, Thailand Ministry of Public Health - U.S. Centers for Disease Control and Prevention Collaboration, Nonthalawan, Thailand); Peeraveerach (Nakhon Phanom Provincial Health Office, Nakhon Phanom, Thailand); Assang Buayajin (Sa Kaeo Provincial Health Office, Sa Kaeo, Thailand) for their assistance. The Indian Council for Medical Research (ICMR) led a multisite study with funding provided by the Hih Initiative; we thank the investigators at ICMR and the study sites of Christian Medical College, Vellore; Post Graduate Institute of Medical Education and Research, Chandigarh; and the National Institute of Cholera and Enteric Diseases, Kolkata. Costa Rica’s LEAP study team thank all the physicians within the study area, in particular the key private practice, and from the Caja Costarricense de Seguro Social for referring their patients to participate in the active epidemiological surveillance. We thank the South African Severe Acute Respiratory Infections Surveillance Group, Wyeth-Pfizer, CNPq/Brazilian Council for Scientific Development and Technology, MRC Gambia Pneumococcal Surveillance Project and Severe Pneumonia Studies team, MRC Gambia Basse Health and Demographic Surveillance System, Gambia Government, Basse Health Centre staff, the MRC Gambia Pneumococcal Vaccine Trial team for their assistance; Ana Ceballos, (CEDEPAP, Cordoba, Argentina), Jane Crawley (University of Oxford), and Olaf Muller (Ruprecht-Karls-University Heidelberg, Germany) for participating in the Working Group Meeting and providing valuable inputs; and Arti Nair (University of Edinburgh) for assistance with extracting data from the DHS and MICS databases.

References

1 Liu I, Johnson HL, Couzens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012; 379: 2151–61.

2 Rudan I, Boschi-Pinto C, Biloglav Z, et al. Global burden of lower respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet 2008; 367: 1455–55.

3 Department of Child and Adolescent Health. Handbook: IMCI integrated management of childhood illness. Geneva: World Health Organization, 2005.

4 Nair H, Nokes D, Gessner B, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010; 375: 1917–30.

5 Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet 2011; 378: 1917–30.

6 DerSimorian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 77–88.

7 Madhi SA, Kuvanda I, Cutland C, Klugman KP. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. Clin Infect Dis 2005; 40: 1511–18.

8 Mulholland K, Hilton S, Adegbola R, et al. Randomised trial of Haemophilus influenzae type b tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants. Lancet 1997; 349: 1191–97.

9 Robertson SE, Roca A, Alonso P, et al. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ 2004; 82: 914–22.

10 Campbell JD, Sow SO, Levine MM, Kotloff KL. The causes of hospital admission and death among children in Bamako, Mali. J Trop Pediatr 2004; 50: 158–63.

11 Tornheim JA, Manya AS, Oyando N, Kabakka S, Breiman RF. The causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012; 379: 2151–61.

12 Lowther SA, Shay DK, Holman RC, Clarke MJ, Kaufman SF, Anderson LJ. Bronchiolitis-associated hospitalizations among American Indian and Alaska Native children. Pediatr Infect Dis J 2000; 19: 11–17.

13 Carroll RN, Gebretsadik T, Griffin MR, et al. Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state health care insurance plan. Pediatrics 2008; 122: 58–64.

14 Grijalva CG, Nuorti JP, Zhu Y, Griffin MR. Increasing incidence of influenza activity and risk of hospitalization in American Indian and Alaska Native children. J Pediatr 2010; 156: 376–83.
Peck AJ, Holman RC, Curns AT, et al. Lower respiratory tract infections among American Indian and Alaska Native children and the general population of US Children. Pediatr Infect Dis J 2005; 24: 142–51.

Weinkgberg GA, Hall CB, Iwane MK, et al. Pneumonia virus infection of young children: estimates of the population-based burden of hospitalization. J Pediatr 2009; 154: 694–99.

Yortia KL, Holman RC, Seiyar J, Steiner CA, Schonberger LB. Infections disease hospitalizations among infants in the United States. Pediatrics 2008; 12: 246–52.

Nizami SQ, Bhatta ZA, Hasan R. Incidence of acute respiratory infections in children 2 months to 5 years of age in periurban communities in Karachi, Pakistan. JAPA J Pak Med Assoc 2006; 56: 163–67.

Owais A, Tirkmani SS, Sultana S, et al. Incidence of pneumonia, bacteremia, and invasive pneumococcal disease in Pakistani children. Trop Med Int Health 2010; 15: 1029–36.

Boxburgh CSD, Youngoon GG, Towner JA, Turner SD. Trends in pneumonia and empyema in Scottish children in the past 25 years. Arch Dis Child 2008; 93: 316–18.

Jokinen C, Heiskanen L, Juvonen H, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol 1993; 137: 977–88.

Monge V, Gonzalez A. Hospital admissions for pneumonia in Spain. Infection 2001; 29: 3–6.

Gil A, San-Martin M, Carrasco P, Gonzalez A. Epidemiology of pneumonia hospitalizations in Spain, 1995–1998. J Infect 2002; 44: 84–87.

Garcés-Sanchez MD, Diez-Domingo J, Ballester Sanz A, et al. Epidemiology of community-acquired pneumonia in children aged less than 5 years old in the Autonomous Community of Valencia. An Pediatr 2005; 63: 123–20 (in Spanish).

Cornez Castellano AM, Lluch Rodrigo JA, Portero Alonso A, Pastor Vilche E, Sanz Valero M. Development of the incidence of pneumonia in the autonomous community of Valencia throughout the 1995-2001 period. A retrospective study. An Med Interna 2005; 22: 118–23 (in Spanish).

Vicente D, Montes M, Cilla G, Perez-Yarza EG, Perez-Trailero E. Hospitalization for respiratory syncytial virus in the paediatric population in Spain. Epidemiol Infect 2003; 131: 867–72.

Weigl JA, Pupe W, Lluch Rodrigo JA, Portero Alonso A. Population-based incidence of severe pneumonia in children in Kiel, Germany. Klin Padiatr 2005; 217: 211–19.

van Gageldonk-Lafeber AB, Bogaerts MA H, Verheij RA, Weigl JA, Puppe W, Belke O, Neus J, Bagci F, Schmitt HJ. Time trends in primary-care morbidity, and hospitalization and mortality due to pneumonia. Epidemiol Infect 2009; 137: 472–78.

Forster I, Illeost R, Gieger CHL, et al. Prospective population-based study of viral lower respiratory tract infections in children under 3 years of age (the PRL.DE study). Eur J Pediatr 2004; 163: 709–16.

Ansaldi F, Sticchi L, Durando P, et al. Decline in pneumonia and acute otitis media after the introduction of childhood pneumococcal vaccination in Liguria, Italy. J Int Med Res 2008; 36: 1255–60.

Cilla G, Oxente E, Perez-Yarza EG, Montes M, Vicente D, Perez-Trailero E. Hospitalization rates for human metapneumovirus infection among 0- to 3-year-olds in Gipuzkoa (Basque Country). Spain. Epidemiol Infect 2009; 137: 66–72.

Che D, Caillere N, Brossot P, Vallojo C, Josseran L. Burden of infant bronchiolitis: data from a hospital network. Epidemiol Infect 2010; 138: 573–75.

Zaman K, Baqui AH, Yunus M, et al. Acute respiratory infections in children: a community-based longitudinal study in rural Bangladesh. J Trop Pediatr 1997; 43: 133–37.

Brooks WA, Santoshmam NA, Hehder A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. Lancet 2005; 366: 1000–04.

Baqui AH, Rahman M, Zaman K, et al. A population-based study of hospital admission incidence rate and bacterial aetiology of acute lower respiratory infections in children aged less than five years in Bangladesh. J Health Popul Nutr 2007; 25: 179–88.

Chandyo RK, Shrestha PS, Valenter-Branth P, et al. Two weeks of zinc administration to Nepalese children with pneumonia does not reduce the incidence of pneumonia or diarrhea during the next six months. J Nutr 2000; 130: 1677–82.

Shah AS, Knell MD, Sharma PR, et al. Invasive pneumococcal disease in Kanti Children’s Hospital, Nepal, as observed by the South Asian Pneumococcal Alliance network. Clin Infect Dis 2009; 48 (suppl 2): S123–28.

Williams EF, Thornson S, Maskey M, et al. Hospital-based surveillance of invasive pneumococcal disease among young children in urban Nepal. Clin Infect Dis 2009; 48 (suppl 2): S114–22.

Shah AS, Nisarga R, Ravi Kumar KL, Hubler R, Herrera G, Kilgore PE. Establishment of population-based surveillance for invasive pneumococcal disease in Bangladesh, India. Indian J Med Sci 2009; 63: 498–507.

Tupasi TE, de Leon LE, Lupisan S, et al. Patterns of acute respiratory tract infection in children: a longitudinal study in a depressed community in Metro Manila. Rev Infect Dis 2000; 12 (suppl 8): S940–49.

Williams P, Graezy M, Smith P. Hospitalization of aboriginal and non-aboriginal patients for respiratory tract diseases in Western Australia, 1988–1993. Int J Epidemiol 1997; 26: 797–805.

Sun YF, Fang XQ, He HX, Zhuo QZ, Wang Q, Chen HY. Analysis of acute respiratory infections surveillance in children aged 0–4 years old. Chinese Maternal and Child Health 2009; 17: 42–45 (in Chinese).

Huc YC, Lu WY. Effect of acute respiratory infections management in children. Shanghai J Prev Med 1996; 8: 94–95 (in Chinese).

Wang L, Dong SP, Zhao GZ, Li JS. Promoting standard case management of acute respiratory infections to reduce mortality in children aged 0–4 years old. Chinese J Primary Health Care 1997; 11: 28–29 (in Chinese).

Liu Q, Fu P, Zhao S, Zou SH. Analysis of acute respiratory infections surveillance in children aged 0–4 years old in Qingdao. Acta Academiae Medicinae Qingdao 1994; 1: 232–35 (in Chinese).

Xie SM, Chen I, Hou YJ, Zhen SY, Yu Q. Analysis of acute respiratory infections surveillance in 3097 children aged 0–4 years old. Chongqing Med J 1993; 22: 375–76 (in Chinese).

Lou LY, Cong GQ, Sun SX, Song YH, Li GL, Yang S. Analysis of acute respiratory infections surveillance in children aged under 5 years in Heilongjiang. Chinese J Primary Health Care 1995; 9: 39 (in Chinese).

Grant CC, Schreg R, Tan D, Pati A, Ackin R, Yee RL. Hospitalization for pneumonia in children in Auckland, New Zealand. J Paediatr Child Health 1999; 34: 155–59 (in Chinese).

Chi XX, Chen X, Ouyang Y, Xue XL. Preliminary analysis of acute respiratory infections surveillance in children under 5 years in Fujian. Strait J Prev Med 1996; 2: 1–2 (in Chinese).

Chen W, Zhao MR, Zhao YY, Ma BJ. Analysis of acute respiratory infections surveillance in children in rural Henan. Chinese J Rural Med 1997; 25: 25–26 (in Chinese).

Chen P. Effect of acute respiratory infections management to reduce mortality in children with pneumonia. Jiangsu J Prev Med 1996; 2: 48–49 (in Chinese).

Mo JZ. Analysis of acute respiratory infections surveillance in 20867 children aged 0–4 years old in Southern Jiangsu. Chinese J Primary Health Care 1998; 12: 26 (in Chinese).

Huang WH, Chen LN, Shi LB. Analysis of acute respiratory infections surveillance in children aged 0–4 years old in Licheng. Strait J Prev Med 1999; 5: 21 (in Chinese).

Xu GL, Zheng JY, Li LX, Wei YH, Cai ZL. Analysis of acute respiratory infections surveillance in children aged 0–4 years old in Fujian. J Pediatr 2004; 163: 709–16.

Che D, Caillere N, Brossot P, Vallojo C, Josseran L. Burden of infant bronchiolitis: data from a hospital network. Epidemiol Infect 2010; 138: 573–75.

Zaman K, Baqui AH, Yunus M, et al. Acute respiratory infections in children: a community-based longitudinal study in rural Bangladesh. J Trop Pediatr 1997; 43: 133–37.

Brooks WA, Santoshmam NA, Hehder A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. Lancet 2005; 366: 1000–04.

Baqui AH, Rahman M, Zaman K, et al. A population-based study of hospital admission incidence rate and bacterial aetiology of acute lower respiratory infections in children aged less than five years in Bangladesh. J Health Popul Nutr 2007; 25: 179–88.
61 Russell FM, Fakakovi T, Paasi S, Ika A, Mulholland EK. Reduction of meningitis and impact on under-5 pneumonia after introducing the Hib vaccine in the Kingdom of Tonga. *Ann Trop Paediatr* 2009; 29: 111–17.

62 Ho P-L, Chiu SS, Chow FH, Mak GC, Lau YL. Pediatric hospitalization for pneumococcal diseases preventable by 7-valent pneumococcal conjugate vaccine in Hong Kong. *Vaccine* 2007; 25: 6837–41.

63 Magree HC, Russell FM, Sa’aga R, et al. Chest X-ray-confirmed pneumonia in children in Fiji. *Bull World Health Organ* 2005; 83: 427–33.

64 Anh DD, Kilgore PE, Slack MP, et al. Surveillance of pneumococcal-associated disease among hospitalized children in Khanh Hoa Province, Vietnam. *Clin Infect Dis* 2009; 48 (suppl 2): S57–64.

65 Yoshida LM, Suzuki M, Yamamoto T, et al. Viral pathogens associated with acute respiratory infections in central Vietnamese children. *Pediatr Infect Dis J* 2010; 29: 75–77.

66 Banajeh SM. Outcome for children under 5 years hospitalized with severe acute lower respiratory tract infections in Yemen: a 5 year experience. *J Trop Pediatr* 1998; 44: 343–46.

67 Chowdhury EK, El Arifeen S, Rahman M, et al. Care at first-level facilities for children with severe pneumonia in Bangladesh: a cohort study. *Lancet* 2008; 372: 822–30.

68 Bari A, Sadruddin S, Khan A, et al. Community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Haripur district, Pakistan: a cluster randomised trial. *Lancet* 2011; 378: 1796–803.

69 Soofi S, Ahmed S, Fox MP, et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Matari district, rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2012; 379: 729–37.

70 WHO. Recommendations for management of common childhood conditions: evidence for technical update of pocket book recommendations: newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. Geneva: World Health Organization, 2012.

71 Sutanto A, Gessner BD, Djelantik I, et al. Acute respiratory illness incidence and death among children under two years of age on Lombok Island, Indonesia. *Am J Trop Med Hyg* 2002; 66: 175–79.

72 Weber MW, Milligan P, Sanneh M, et al. An epidemiological study of RSV infection in the Gambia. *Bull World Health Organ* 2002; 80: 562–68.

73 Hoo AF, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for Vmax[FRC] in infancy: a multicenter collaborative study. *Am J Respir Crit Care Med* 2002; 165: 1084–92.

74 Alam N, van Ginneken JK, Timaeus I. Determinants of perceived morbidity and use of health services by children less than 15 years old in rural Bangladesh. *Matern Child Health J* 2009; 13: 119–29.

75 Pandey A, Sengupta PG, Mondal SK, et al. Gender differences in healthcare-seeking during common illnesses in a rural community of West Bengal, India. *J Health Popul Nutr* 2002; 20: 306–11.

76 Subhi R, Adamson M, Campbell H, et al. The prevalence of hypoaxemia among ill children in developing countries: a systematic review. *Lancet Infect Dis* 2009; 9: 219–27.

77 Byass P, Campbell H, O’Dempsey TJ, Greenwood BM. Coincidence of malaria parasitaemia and abnormal chest X-ray findings in young Gambian children. *J Trop Med Hyg* 1991; 94: 22–23.

78 Palacios G, Hornig M, Cisterna D, et al. *Streptococcus pneumoniae* coinfection is correlated with the severity of H1N1 pandemic influenza. *PLoS One* 2009; 4: e8540.

79 Rudan I, Lawn J, Cousens S, et al. Gaps in policy-relevant information on burden of disease in children: a systematic review. *Lancet* 2005; 365: 2031–40.