Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study


Summary

Background We have previously estimated that respiratory syncytial virus (RSV) was associated with 22% of all episodes of (severe) acute lower respiratory infection (ALRI) resulting in 55 000 to 199 000 deaths in children younger than 5 years in 2005. In the past 5 years, major research activity on RSV has yielded substantial new data from developing countries. With a considerably expanded dataset from a large international collaboration, we aimed to estimate the global incidence, hospital admission rate, and mortality from RSV-ALRI episodes in young children in 2015.

Methods We estimated the incidence and hospital admission rate of RSV-associated ALRI (RSV-ALRI) in children younger than 5 years stratified by age and World Bank income regions from a systematic review of studies published between Jan 1, 1995, and Dec 31, 2016, and unpublished data from 76 high quality population-based studies. We estimated the RSV-ALRI incidence for 132 developing countries using a risk factor-based model and 2015 population estimates. We estimated the in-hospital RSV-ALRI mortality by combining in-hospital case fatality ratios with hospital admission estimates from hospital-based (published and unpublished) studies. We also estimated overall RSV-ALRI mortality by identifying studies reporting monthly data for ALRI mortality in the community and RSV activity.

Findings We estimated that globally in 2015, 33·1 million (uncertainty range [UR] 21·6–50·3) episodes of RSV-ALRI resulted in about 3·2 million (2·7–3·8) hospital admissions, and 59 600 (48 000–74 500) in-hospital deaths in children younger than 5 years. In children younger than 6 months, 1·4 million (UR 1·1–2·1) hospital admissions, and 27 300 (UR 20 700–36 200) in-hospital deaths were due to RSV-ALRI. We also estimated that the overall RSV-ALRI mortality could be as high as 118 200 (UR 94 600–149 400). Incidence and mortality varied substantially from year to year in any given population.

Interpretation Globally, RSV is a common cause of childhood ALRI and a major cause of hospital admissions in young children, resulting in a substantial burden on health-care services. About 45% of hospital admissions and in-hospital deaths due to RSV-ALRI occur in children younger than 6 months. An effective maternal RSV vaccine or monoclonal antibody could have a substantial effect on disease burden in this age group.

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Introduction

Globally, acute lower respiratory infection (ALRI) remains one of the leading causes of morbidity and mortality in children younger than 5 years.1,2 Human respiratory syncytial virus (RSV) is the most common viral pathogen identified in children with ALRI. We have previously estimated (from few data) that in 2005, about 33.8 million new episodes of RSV-ALRI occurred worldwide in young children, 10% severe enough to necessitate hospital admission.1 We also estimated that 55,000 to 199,000 child deaths could be attributed to RSV. Since then, however, new RSV studies were initiated, collecting new data. Progress in RSV vaccines and therapeutics led WHO’s Product Development for Vaccines Advisory Committee (PDVAC) to highlight RSV as “the most likely big new vaccine area with a vaccine likely to be available in the next 5 to 10 years”.3 Therefore, updated RSV disease burden estimates incorporating latest data are of great relevance for vaccine policy formulation and to prioritise research funding. We established the RSV Global Epidemiology Network (RSV GEN)—a collaboration of more than 70 investigator groups primarily in low-income and middle-income countries to estimate RSV-ALRI disease burden (at global, regional, and national levels) in young children for 2015; and highlight gaps in knowledge for future action.

Methods

Systematic review

We did a systematic literature review (appendix pp 3–6), hand searching of online journals, and scanning reference lists of identified citations to update our previous review.1 The search included MEDLINE (Ovid), Embase, CINAHL, Global Health (1973 onwards), Global Health Library, Web of Science, IndMed, and grey literature (OpenGrey) databases and studies published between June 1, 2009, and Dec 31, 2016. Three authors (TS, EB, and SC) searched the literature (with no language or publication restrictions, and including three Chinese language databases [CNKI, Wanfang and ChongqingVIP for period 1/1/95-31/12/2016 (TS)] and extracted data independently (disagreements arbitrated and abstractions validated by HN). We included studies reporting community incidence, hospital admissions, and in-hospital case fatality ratios (CFRs) for RSV confirmed ALRI in 0–4-year-old children. Studies with data for 12 or more consecutive months (except for mortality-related data), and those reporting RSV-ALRI incidence or mortality for the first year of life were reviewed. We excluded studies where RSV was not a primary outcome, and the case definition was not clear or inconsistently applied, RSV diagnosis was based on serology alone, or with less than 50 ALRI cases admitted to hospital.
RSV GEN formulated common case definitions and agreed on common approaches to data analysis (including re-analysis of already published data) and invited other investigators with relevant data to join RSV GEN. This resulted in analysis of substantial unpublished data to supplement published data (appendix pp 9–12). This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix p 95).1

Definitions
As previously,1 we adapted WHO Integrated Management of Childhood Illnesses (IMCI) pneumonia case definitions to include RSV laboratory confirmation; and elected to replace “clinical pneumonia” and “severe pneumonia” with the terms “ALRI” and “severe ALRI” (appendix pp 2, 85). We recognised that WHO IMCI case definitions were developed for use by first level health workers, and for most hospital-based studies the decision for admission to hospital is based on physician’s overall impression (and not IMCI signs alone). Therefore, we developed separate case definitions for hospital-based studies—admission to hospital for RSV-associated (severe or very severe) ALRI cases (appendix pp 2, 85). We expanded our definition for hospital-based studies—admission for RSV-associated (severe or very severe) ALRI (appendix pp 2, 85). We defined ALRI cases using median incidence rate ratios (appendix p 7).13,16 We did a sensitivity analysis using un-imputed data and noted final estimates did not differ substantially. When the study was longer than 12 months, but not in multiples of 1 year, we calculated annualised incidence by adjusting for population at risk. If clinical specimens were systematically collected in a distributed within countries (appendix pp 56–57). We estimated in-hospital RSV-ALRI deaths by applying regional RSV-associated in-hospital CFR (hCFR) meta-estimates to regional number of RSV-ALRI hospital admissions (within narrow age bands; figure 1). We estimated in-hospital death uncertainty ranges (UR) using Monte Carlo Simulation (calculating estimates from 10 000 samples from log-normal distributions with 2.5th and 97.5th centiles defining the UR). We previously reported that about 80% of (all-cause) ALRI deaths in young children occur outside hospital.10 Therefore, to estimate overall RSV-associated deaths, we used the excess mortality model (as reported previously).13,14 We identified sites with monthly death records (causes of death based on verbal autopsy, mortality surveys, and medical certification of deaths) with at least 100 ALRI community deaths over 3 consecutive years. We calculated the average number of ALRI community deaths per month during (AvgRSV) and outside (AvgOTHER) the RSV season, and the total number of deaths (TOTAL) during the year. We assumed that all excess ALRI mortality during RSV season was caused by RSV and that there is no RSV mortality outside RSV season. We defined the RSV season duration in months for every study year (MonRSV). The proportion of yearly deaths due to RSV was then estimated as:

\[ \text{RSV-ALRI} = \frac{\text{RSV-ALRI}}{\text{TOTAL}} \]

Because there is often some overlap in RSV and influenza seasonality, we calculated the area under the curve during RSV season and proportionately attributed excess ALRI mortality during RSV season to the two pathogens. Using published national estimates of...
In this study, we report four different sets of estimates—number of episodes of (severe) RSV-ALRI at global and national levels, global RSV-ALRI hospital admissions, and global estimates of RSV-ALRI deaths in hospital and overall (in community). This figure summarises our approach for each of these categories and also shows how they relate to (and feed into each other). Global estimates of RSV-ALRI in 2015 by region

Country-specific estimates of RSV-ALRI incidence

In this study, we estimated RSV attributable ALRI mortality if community based case ascertainment was used. We then calculated the ratio between RSV-ALRI community and in-hospital deaths for each country to yield an “inflation factor”. Because the three inflation factors in these diverse developing country settings were similar, we assumed that these sites, and their inflation factors, are broadly representative of developing countries. We thus applied the mean inflation factor (for developing countries) to the estimated RSV-ALRI in-hospital deaths (in developing countries) to estimate the overall RSV-ALRI mortality for this region, and then...
calculated the “adjusted overall RSV mortality estimate” after accounting for overlap with influenza activity. We report all global and regional morbidity and mortality estimates to the nearest thousands of cases and hundreds of deaths. Country-specific results are reported without rounding.

Data were analysed with Stata version 11.2 and R version 3.0.2.

Results

We identified 326 articles (329 studies) with data for community incidence, hospital admissions, in-hospital CFR, and proportion of hospital admissions for ALRI that are RSV+ve cases (figure 2). 250 were published (83 in Chinese) and 76 were unpublished (figure 3; appendix pp 9–12, 86). 41 studies were in rural, 250 in urban, and 38 in mixed populations. 30 (54%) of 56 developing country studies were either cohort or demographic surveillance site studies; and 26 (46%) were hospital studies with well-defined catchment populations. Only 40 studies (12 published and 28 unpublished) reported disease incidence or hospital admission rate by age group for the full age range; we imputed data in 51 studies (supplementary material pp 6–10). 63 studies (21%) reported the incidence or hospital admission rate or in-hospital CFR by narrow age bands for the first year of life. Only 37 studies (one published and 36 unpublished) reported data for neonates and only 19 studies by RSV sub-type.

Community-based studies with active case ascertainment reported RSV-ALRI incidence (14 studies), severe RSV-ALRI (eight studies) and very severe RSV-ALRI (four studies) in low-income and middle-income countries (LMICs; appendix pp 13–16); and an additional two studies reported incidence of RSV-ALRI outpatient clinic visits in high income countries. All but three studies reported peak RSV-ALRI incidence in children younger than 6 months (table 1; appendix pp 13–14).

We estimated that 30.0 million (95% CI 19.1–47.0) RSV-ALRI episodes occurred in 0–4-year-old children in LMIC in 2015, about a third in the first year of life. An estimated 2.8 million (95% CI 1.3–6.1) RSV-ALRI episodes occurred in high-income countries. Therefore, globally, we estimate 33.1 million (UR 21.6–50.3) RSV-ALRI episodes in young children in 2015. Few data from three (of 14) community based studies indicate a high incidence rate, even in the neonatal period—40 (95% CI 2.5–635.7) episodes per 1000 neonates per year (appendix p 42).

About 20% of (community) cases in young children had lower chest wall indrawing (severe RSV-ALRI); a third of hospital admissions for RSV-ALRI occurred globally in under-5 children—India, China, Nigeria, Pakistan, and Indonesia—contributed about half the global RSV-ALRI burden (appendix pp 58–61).

76 hospital-based studies (five in indigenous populations) with passive case ascertainment reported hospital admission rates for RSV-ALRI for young children (appendix pp 17–22). Across all regions, hospital admission rates were highest in infants younger than 6 months. Hospital admission rates were also high in the neonatal period—15.9 (95% CI 8.8–28.9) hospital admissions per 1000 neonates per year—a third in the first year of life. Most children (in upper-middle-income countries) were admitted to hospital in the first year of life (appendix p 44). There were relatively few studies reporting hospital admissions for RSV-ALRI in low-income countries and their hospital admission (across all age groups) were much lower than the highest rates (in upper-middle-income countries). We estimated 3.2 million (UR 2.7–3.8) hospital admissions for RSV-ALRI occurred globally in young children in 2015; about 45% of these in children aged younger than 6 months (table 1).
Of the 218 hospital-based studies (without clear population denominator) that reported proportion of RSV+ve cases among all hospital admissions for ALRI, only 104 studies reported 0–59 month data (appendix pp 23–32). Using this independent dataset we estimated that about 2·9 million (95% CI 2·6–3·3) hospital admissions for RSV-ALRI occurred in young children in 2015, 51% in infants younger than 6 months. Because this estimate only includes children admitted to hospital, it is an underestimate due to limited access to care and poor care seeking in LMICs.10,11

To estimate the overall RSV-ALRI deaths in young children (including those dying outside hospitals), we identified eight LMIC sites that could provide requisite data. However, data from only three sites (multiple villages across rural Bangladesh, urban slums in Buenos Aires, and multiple hamlets in Lombok, Indonesia) met our strict eligibility criteria. Data for both RSV and influenza activity were available from Bangladesh and Buenos Aires. In Bangladesh (after excluding 2010 influenza data which overlapped with second wave of influenza A (H1N1) pdm09 virus pandemic), there was some overlap between RSV and influenza activity during RSV season. We estimated that about 90% (range 86–93) of excess mortality during RSV season can be attributed to RSV (appendix p 64). There was no overlap between RSV and influenza seasons in years studied.16

The “inflation factors” ranged from 1·5 in Argentina to 2·9 in Lombok, Indonesia (appendix p 65). We “adjusted” our estimates for overall RSV-ALRI mortality in developing countries to account for influenza activity during RSV season and estimated that the global RSV-ALRI mortality in young children in 2015 was about 5·6 million (95% CI 4·0–7·4), 58% occurring in infants younger than 6 months.

Figure 3: Location of studies reporting incidence, hospital admission, and in-hospital case fatality in children with RSV-ALRI.
<table>
<thead>
<tr>
<th>RSV-ALRI</th>
<th>Low income</th>
<th>Lower-middle income</th>
<th>Upper-middle income</th>
<th>High income*</th>
<th>Developing countries</th>
<th>Industrialised countries</th>
<th>Global†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5 months</td>
<td>Studies</td>
<td>1 (1)</td>
<td>10 (2)</td>
<td>3 (1)</td>
<td>2 (2)</td>
<td>14 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Incidence‡ (uncertainty range)</td>
<td>117.2 (108.4–126.6)</td>
<td>63.3 (38.5–104)</td>
<td>168.9 (47.9–596.1)</td>
<td>66.1 (33.5–130.4)</td>
<td>82.5 (50.4–145.2)</td>
<td>61.7 (33.5–130.4)</td>
<td>..</td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>1247 (1533–1347)</td>
<td>2034 (1238–3344)</td>
<td>2991 (848–10555)</td>
<td>517 (262–1020)</td>
<td>5077 (3999–8318)</td>
<td>448 (227–884)</td>
<td>5560 (3570–8765)</td>
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<tr>
<td>6–11 months</td>
<td>Studies</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Incidence‡ (uncertainty range)</td>
<td>..</td>
<td>80.7 (48–135.6)</td>
<td>223 (95–522.1)</td>
<td>..</td>
<td>98.8 (58.8–166.1)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>..</td>
<td>2595 (1544–4361)</td>
<td>3948 (2503–7255)</td>
<td>..</td>
<td>6082 (3619–10223)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>0–59 months</td>
<td>Studies</td>
<td>1 (6)</td>
<td>10 (6)</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>14 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Incidence‡ (uncertainty range)</td>
<td>94 (89–100)</td>
<td>40.8 (25.7–65)</td>
<td>85.5 (33.8–216.7)</td>
<td>35.6 (16.6–76.2)</td>
<td>50.8 (22.9–97.1)</td>
<td>36 (16–76.2)</td>
<td>..</td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>9541 (9044–10607)</td>
<td>12864 (8081–20478)</td>
<td>2841 (1576–37711)</td>
<td>5176 (2846–9853)</td>
<td>30516 (19463–81783)</td>
<td>2482 (1558–5220)</td>
<td>33059 (21583–50312)</td>
</tr>
</tbody>
</table>

| RSV-associated severe ALRI** | 0–5 months | Studies | 0 (1) | 7 (2) | 1 (1) | 1 (1) | 8 (2) | 1 (3) | 9 (3) |
| Incidence‡ (uncertainty range) | .. | 25.1 (10–59.3) | 406.7 (316.4–522.7) | 3.2 (1.8–5.8) | 36.1 (10–129.1) | 3 (1.8–5.8) | .. |
| Number of episodes (thousands) | .. | 808 (243–1906) | 7001 (5003–1255) | 25 (14–45) | 2222 (622–7945) | 22 (12–39) | 2574 (659–7470) |
| 6–11 months | Studies | 0 | 6 | 1 | 0 | 7 | 0 | .. |
| Incidence‡ (uncertainty range) | .. | 19.5 (8–34.5) | 82.1 (45.5–148.2) | .. | 24.7 (11.5–52.2) | .. | .. |
| Number of episodes (thousands) | .. | 628 (268–1423) | 1454 (805–2625) | .. | 1521 (707–3272) | .. | .. |
| 0–59 months | Studies | 0 (1) | 7 (4) | 1 (1) | 1 | 8 (5) | 1 | 9 (5) |
| Incidence‡ (uncertainty range) | .. | 7.5 (3–18) | 86.2 (68–108.6) | 3 (17–55) | 10.2 (3.5–29.9) | 3 (1.7–5.5) | .. |
| Number of episodes (thousands) | .. | 2357 (590–5655) | 2007 (1190–18902) | 483 (133–439) | 243 (1023–7943) | 212 (117–383) | 6303 (2317–18196) |

| Hospital admission for RSV-associated ALRI | 0–5 months | Studies | 5 (2) | 17 (8) | 15 (9) | 34 (25) | 43 (22) | 28 (22) | 71 (44) |
| Hospital admission rate | 7.4 (2.4–22.6) | 22.9 (12.7–29.7) | 23.0 (16.1–32.9) | 26.3 (18.8–30.2) | 20.2 (16.7–24.5) | 27.1 (23.3–31.6) | .. |
| Number of episodes (thousands) | 79 (26–240) | 737 (569–955) | 407 (284–582) | 205 (178–237) | 1243 (1025–1508) | 184 (158–214) | 1447 (1204–1744) |
| 6–11 months | Studies | 4 | 9 | 5 | 9 | 20 | 7 | 27 |
| Hospital admission rate | 3.4 (0.6–19.5) | 11.3 (6.1–21.0) | 18.5 (9.8–34.7) | 11.3 (6.1–20.9) | 11.0 (7.7–15.7) | 9.8 (4.8–19.6) | .. |
| 12–59 months | Studies | 3 | 9 | 7 | 7 | 21 | 5 | 26 |
| Hospital admission rate | 0.4 (0.1–3.7) | 1.8 (1.2–2.8) | 2.2 (1.3–3.5) | 1.4 (0.9–2.0) | 1.5 (1.0–2.3) | 1.6 (1.0–2.5) | .. |

(Table 1 continues on next page)
Discussion
Our revised RSV burden estimates are based on 329 studies (291 of which were not included in our 2005 estimates). We estimate that globally in 2015 there were about 33·1 million (UR 32·9–33·3) RSV-ALRI hospital admissions, and 59·6 million (48·0–74·5) in-hospital deaths in (670·5–718·5) million children younger than 5 years. A plausible check using an independent approach with non-overlapping data from 218 different studies was in good agreement and supports the validity of the hospital admission estimates. The proportion of eligible cases that were tested for RSV varied substantially (appendix pp 49–53). Because the most common reasons for not collecting specimens for testing were death, discharge, absence of parental consent or the child being too ill, studies might have underestimated in-hospital mortality estimates. Consistent with this, hCFR among those not tested was substantially higher than those tested for RSV (appendix pp 67–69). We did several sensitivity analyses considering various scenarios (if RSV positivity in the untested were the same as that in those tested; and if none or all of the deaths in untested cases are RSV positive), suggesting that the overall in-hospital RSV-ALRI mortality estimates could increase by 7–40% (appendix pp 70–79).
for RSV-ALRI are substantially lower than those estimated for all-cause hospital admissions for ALRI as would be expected since the hCFR for RSV-associated ALRI is much lower than that for bacterial ALRI.26 However, the above sensitivity analyses suggest that the RSV-ALRI in-hospital mortality estimates might represent an underestimate of the true value.

We estimate that in the first 6 months of life there were 1·4 million (UR 1·2–1·7) RSV-ALRI hospital admissions, and 27 300 (20 700–36 200) in-hospital deaths, a substantial number of these being in the neonatal period when RSV often presents as apnoea or sepsis. Thus, an effective RSV vaccine for maternal immunisation (with a candidate in phase 3)17 or extended half-life monoclonal antibody (candidate to begin phase 3)18 could have a substantial potential to directly prevent up to 1·1 million hospital deaths globally due to RSV-ALRI hospital admissions, consistent with RSV being associated with 13–22% of this age group.21 Our data-derived estimates are more robust estimates. In some settings, it might be possible to take respiratory samples soon after death to directly identify RSV-ALRI deaths. Because the current data are consistent with most RSV-ALRI deaths occurring outside of hospital (figure 4), investment in these approaches is warranted to improve estimates of overall RSV-ALRI mortality.

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. hCFR=in-hospital CFR. hCFR and number of deaths are presented with 95% CI. *Global total for a given age band is sum of the deaths in developing and industrialised countries. We have taken this more conservative approach because there are only a small number of studies contributing to deaths by World Bank income region in narrow age bands leading to large uncertainties in some of these estimates. †Although the overall number of deaths was obtained by summing the age and region-specific numbers for each of the 10 000 samples in the Monte Carlo simulation, the point estimates and uncertainty interval limits for the overall deaths are not equal to the sum of the age and region-specific results. This reflects the fact that the overall estimates are determined by the full uncertainty distributions for each age and region-specific estimates, and not simply the point estimates. ‡Data in parentheses are 95% CI. §The number of deaths has been rounded to the nearest hundreds.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Low income</th>
<th>Lower-middle income</th>
<th>Upper-middle income</th>
<th>High income</th>
<th>Developing countries</th>
<th>Industrialised countries</th>
<th>Global‡§</th>
</tr>
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<tr>
<td>0–5 months</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>hCFR (%)</td>
<td>1·7 (0·4–6·8)</td>
<td>2·7 (2·0–3·6)</td>
<td>1·8 (1·2–2·6)</td>
<td>0·2 (0·0–12·8)</td>
<td>2·2 (1·8–2·7)</td>
<td>0·0 (0·0–0·0)</td>
<td>...</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>12 000 (200–7900)</td>
<td>20 000 (12 500–29 500)</td>
<td>7 200 (4 200–12 300)</td>
<td>400 (1 128 200)</td>
<td>27 100 (20 700–35 500)</td>
<td>&lt;50 (0–2000)</td>
<td>27 300 (20 700–36 200)</td>
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<tr>
<td>6–11 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>hCFR (%)</td>
<td>9·3 (3·0–28·7)</td>
<td>2·8 (1·8–4·4)</td>
<td>2·4 (1·1–5·4)</td>
<td>0·9 (0·2–4·0)</td>
<td>2·4 (1·9–3·2)</td>
<td>0·1 (0·0–0·4)</td>
<td>...</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>3 400 (400–26 600)</td>
<td>10 300 (4 800–21 600)</td>
<td>8 000 (2 800–22 100)</td>
<td>900 (200–4600)</td>
<td>16 500 (10 400–25 800)</td>
<td>&lt;50 (0–300)</td>
<td>16 500 (10 500–26 100)</td>
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<tr>
<td>12–59 months</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>hCFR (%)</td>
<td>4·7 (0·7–33·7)</td>
<td>2·7 (1·7–4·3)</td>
<td>0·5 (0·1–3·5)</td>
<td>0·7 (0·1–5·2)</td>
<td>2·2 (1·6–3·0)</td>
<td>0·1 (0·0–0·3)</td>
<td>...</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>1 400 (100–16 100)</td>
<td>12 300 (6 500–23 100)</td>
<td>1 500 (200–11 700)</td>
<td>700 (100–5 600)</td>
<td>15 300 (9 500–25 000)</td>
<td>100 (0–300)</td>
<td>15 400 (9 500–24 900)</td>
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<td>0–59 months</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>8 200 (2 200–36 900)</td>
<td>43 600 (31 400–60 400)</td>
<td>17 900 (10 300–34 500)</td>
<td>3 300 (700–23 100)</td>
<td>59 600 (47 800–74 300)</td>
<td>200 (100–2200)</td>
<td>59 600 (48 000–74 500)</td>
</tr>
</tbody>
</table>

Table 2: CFR meta-estimates and number of in-hospital deaths in children with RSV-ALRI younger than 5 years in 2015, by World Bank Income regions

Articles

University Graduate School of Medicine, Department of Virology, Miyagi Prefecture, Japan (H Oshita MD); Emerging Pathogens Laboratory, Fondation Mérieux, Centre International de Recherche en Infectiologie (CIRI), Inserm U1111, CNRS UMR5208, ENS de Lyon, UCB11, Lyon, France (G Paranhos-Bacalá PhD, V Sanchez Picot DVM); Emory University, Rollins School of Public Health, AT, USA (I N Phillips MD); Centre d’Infectiologie Charles Mérieux (CICM), Antarananivo, Madagascar (M Kaloto-Andranarivo MD); Fogarty International Center Division of International Epidemiology and Population Studies, NIH, Bethesda, MD, USA (Z A Rasmussen MD, E D Thomas MPH); Department of Pediatrics, Charité University Medicine Center, Berlin, Germany (Prof B A Rath PhD); Hôpital Femme-Mère-Enfant, Antananarivo, Madagascar (Prof A Robinson MD); United States Naval Medical Research Unit No. 6, Callao, Peru (C Romero MD); Departamento de Biología Molecular y Genética, Instituto de Investigaciones en Ciencias de la Salud, Universidad Nacional de Asunción, Paraguay

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Hypoxaemia is an important indicator of severity and key predictor of ALRI mortality. About 20% of all children admitted to hospital with RSV-ALRI have hypoxaemia. Our estimates of RSV-ALRI hospital admissions suggest that about half of the severe RSV-ALRI episodes are being admitted to hospital globally and a similar proportion of all RSV deaths occur in hospitals (figure 4). The high proportion of children with severe ALRI who are not admitted to hospital probably reflects limited access to health-care seeking behaviour of the population, proportion of eligible patients tested for RSV (appendix pp 88). The variation in estimates within countries or regions, and between regions is due to study methodological differences, annual variations in RSV activity (6–75% variation in RSV-ALRI hospital admission rates by year across sites) and variation in RSV epidemiology between study populations. The true uncertainty is wider than that expressed in a standard 95% CI. Data were insufficient to provide regional incidence or hospital admissions rate estimates by RSV subtype.

Several factors affect our estimates, including exact case definitions for (severe) ALRI, case ascertainment method, health-care seeking behaviour of the population, proportion of eligible patients tested for RSV (appendix pp 49–53), geographical location of and environmental conditions at study sites, sample sizes of included studies and differences in sensitivity and specificity of RSV diagnostic assays. Although we used non-specific case definitions in our analyses, several studies used a more restrictive case definition (eg, including wheeze, fever, crepitations, chest wall indrawing, or chest x-ray confirmation). RSV-ALRI hospital admission rates show a clear gradient across World Bank income regions with lower access to care (including longer distance to hospital) and poorer care seeking behaviour in low-income countries. We have also been unable to account for wide

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**Figure 4: Global burden of RSV-associated severe ALRI including burden on hospital services**

- **RSV**=respiratory syncytial virus. ALRI=acute lower respiratory infection.
- Understanding the contribution of RSV to burden on hospital services and the proportion of “severe” cases not accessing hospital care or deaths outside of hospital is relevant for development of health policies to reduce global (RSV-associated) ALRI mortality. The orange boxes show the estimated number of “severe cases” and overall RSV-related deaths in LMICs that are based on care-seeking studies. The blue boxes reflect the proportion of “severe” cases not accessing hospital care or deaths outside of hospital (appendix p 88).
- CFIR in hospital admitted cases 2·1% (1·9–2·3).
- CFIR in communities 1·8% (1·8–1·9).
- CFR in hospitals 47% (46–48).
- CFR in communities 3·2% (3–3·5).
- **Estimated (severe)** RSV-ALRI deaths in children in developing countries 11·8 million (UR 9·5–14·7 million).
- **Estimated number of episodes of RSV-severe ALRI in LMIC children in 2015**
  - 6·0 million (UR 2·1–12·6 million).
  - 47% of cases reach hospital.
  - 2·8 million (UR 2·1–3·9 million).
  - 53% of cases do not reach hospital.
  - 3·2 million.
  - CFR in hospital admitted cases 2·1% (1·9–2·3).
  - CFR in communities 1·8%.
  - 51% of deaths were in hospital.
  - 59·6 million (UR 47·8–74·3 million).
  - 49% of deaths occur outside hospital.
  - 59·6 million (UR 46·7–72·9 million).

This updated estimates of 33·1 million (UR 21·6–50·3 million) RSV-ALRI episodes resulting in about 3·2 million (UR 2·7–3·8 million) hospital admissions show that RSV in children presents a substantial economic burden on health-care services in view that the direct medical costs associated with hospital care for childhood ALRI has been estimated to range from US$243 (95% CI 154–341) to US$559 (269–887) at secondary and tertiary care facilities, respectively, in LMICs; and $2804 (2001–3683) to $7037 (4286–11311) at secondary and tertiary care facilities, respectively, in high-income countries. With an average length of hospital stay for uncomplicated RSV-ALRI in children of about 3 days, this also represents a major challenge for hospital services, requiring substantial investment and seasonal planning both in terms of human resources and provision of relevant medicines and supplies for paediatric care. Simple measures like timely and regular provision of oxygen supplies can substantially decrease RSV-ALRI mortality. The general improvement in diagnosis (particularly availability of pulse oximetry) and improved case management for ALRI is reflected in a decreasing hCFR trend for RSV-ALRI across all age groups and regions (appendix p 94).

A notable difference to our previous estimates is the twofold increase in the number of severe RSV-ALRI episodes. The current estimate is improved because it is based on many more datapoints and only data from community-based studies employing active case ascertainment (unlike previous estimates based partly on passive case ascertainment studies). However, despite this expanded evidence base, there are still wide uncertainty ranges (appendix p 88). The variation in estimates within countries or regions, and between regions is due to study methodological differences, annual variations in RSV activity (6–75% variation in RSV-ALRI hospital admission rates by year across sites) and variation in RSV epidemiology between study populations. The true uncertainty is wider than that expressed in a standard 95% CI. Data were insufficient to provide regional incidence or hospital admissions rate estimates by RSV subtype.
Articles

RSV PCR-based assays were used in 127 of 329 studies; immunofluorescence in 30 studies, direct immunofluorescence test in 74 studies, indirect immunofluorescence test in 30 studies, direct immunofluorescence in 30 studies, direct immunoassay in 30 studies, and indirect immunoassay in 30 studies. Immunofluorescence assays have variable and lower sensitivity (69.4%) compared with PCR. A sensitivity analysis, including only PCR studies, gave similar hospital admission rate in developing countries (4-6 [95% CI 3.6–5.7] vs 4-9 [4.1–5.8]). We observed a slightly higher incidence rate for community-based studies in developing countries using PCR (59.3 [28.5–123.7] vs 50.8 [32.4–79.6]). Causal attribution of pathogens in childhood ALRI is complex due to healthy pathogen pruning or lack of immunity in populations residing in middle-income countries. The revised estimates are based on a substantially larger number of data points from low-income and middle-income countries. However, no data are available from several high burden populations (eg, in the WHO Eastern Mediterranean region and parts of sub-Saharan Africa). Additionally, most studies do not report RSV hospital admission and in-hospital mortality data by narrow age strata in the first year of life, which leads to substantial uncertainty and possible under-estimation of RSV burden in very young children. Unlike in our previous estimate, we have now been able to provide a point estimate with uncertainty ranges for overall RSV-ALRI mortality. However, these are based on very little data and cannot at present support regional mortality estimates. National and regional estimates of burden on health-care systems, long-term sequelae and mortality are required to inform policy for introduction of RSV vaccines and also to assess the effect of these vaccines on morbidity and mortality in young children. Therefore, further research investment to identify RSV-ALRI mortality (in community and in hospitals) in low-income and middle-income countries is warranted.

Contributors

HN and HC conceptualized the study. TS led the literature review with contributions from EB and SC. TS and DAM led the data analysis. HN, HC, KLOB, EAFS, SAM, and BFG led data interpretation. HN wrote the first draft of the report with inputs from DAM and HC. KLOB, EAFS, SAM, and BFG critically reviewed and revised the initial draft. All other named authors contributed to development of analysis plan, collection and analysis of primary data, data interpretation, and critically reviewed the revised initial report. All other members of the RSV Global Epidemiology Network contributed to data collection, data analysis, and critically reviewed the report. All authors read and approved the final draft of the report.

RSV Global Epidemiology Network

Harish Nair, Harry Campbell, Ting Shi, Evelyn Balsells, Stuart Campbell (University of Edinburgh, Scotland, UK); David A McAllister (University of Glasgow, Scotland, UK); Asad Ali (Aga Khan University, Pakistan); Bradford D Gessner, Berthie-Marie Njanpop-Lobourde, Jennifer C Mossi (Agence de Médecine Préventive, Paris, France); Anzal Krishnan, Shiloh Broor (All India Institute of Medical Sciences, New Delhi, India); Dana Bruden, Rosalyn Singleton (Artic Investigations Program, Centers for Disease Control and Prevention, Anchorage, AK, USA); Angela Gentile, Florence Iacono (Austral University and Ricardo Güirreter Children Hospital, Argentina); Budragchiagin Dash-yandag (Bayanzurkh District General Hospital, Ulanbatar, Mongolia); Kunjing Shen (Beijing Pediatric Research Institute, Beijing, China); Donald M Thea (Boston University School of Public Health, Boston, MA, USA); Hongjie Yu, Hui Jiang, Jiaodong Zheng, Luzhao Feng (Center for Disease Control and Prevention, Beijing, China); Mariette Venter (Centre for Viral Zoonoses, Department of Medical Virology, University of Pretoria, Pretoria, South Africa); Kim A Lindbladte, Daniel R Feikin, Maurice O Ope, Deron C Burton (Centers for Disease Control and Prevention, Atlanta, GA, USA); Wilfrido Clara (Centers for Disease Control and Prevention, Central American Region, Guatemala City, Guatemala); Joel M Montgomery (Centers for Disease Control and Prevention, Nairobi, Kenya); Malak Rakoto-Anandianarivo (Centre d’Infectiologie Charles Merieux (CICIM), Antananarivo, Madagascar); Chafiq Mahraoui (Centre Hospitalier Universitaire Ibn Sinan Rabat, Morocco); Mamadou Sylla, Samba O Sow (Centre pour le Développement des Vaccins [CVD-Mali], Bamako, Mali); Basha S, Maiti (Indian Council of Medical Research Unit on Child Health, New Delhi, India); and MRC Unit on Child & Adolescent Health, University of Cape Town, South Africa (Prof H J Zar PhD); and Public Health Foundation of India, New Delhi, India (H Nair). Correspondence to: Prof Harish Nair, Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, Edinburgh Medical School, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK harish.nair@ed.ac.uk

For the UNDP Population Prospects see http://esa.un.org/unpd/wpp/Download/Standard/Population/
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For the Child Health and Mortality Prevention Surveillance see https://champshealth.org/
Sahul Pública y Bienestar Social, San Lorenzo, Paraguay;
Samit Faouti (Ministry of Health, Amman, Jordan); Viviana Sotomayor (Ministry of Health, Chile); Elizabeth de Cuellar, Hector Ramos, Ivan Aparicio (Ministry of Health, El Salvador); Agustín Satutno (Ministry of Health, Indonesia); Angel Balmaseda, Guilleminda Kuan (Ministry of Health, Managua, Nicaragua); Ericka Ferguson (Ministry of Health, Panama City, Panama); Issifou Alassani (Ministry of Health, Lome, Togo); Marie Mejia (Ministry of Public Health and Social Welfare, Guatemala City, Guatemala); Sirapiporn Phiyung,
Sunthaveeja Watkinsorn (Ministry of Public Health, Bangkok, Thailand); Pagbiajbyn Nynadawa (Mongolian Academy of Medical Sciences, Ulaanbaatar, Mongolia); Cheryll Cohen, Jocelyn Moyes, Fiorette Teurmrinch (National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa); Duc-Anh Dang, Nhat-Minh Le (National Institute of Hygiene and Epidemiology, Hanoi, Vietnam); Mandeed Chadha, Varsha A Potdar (National Institute of Virology, Pune, India); Tekchheng Eap (National Pediatric Hospital, Phnom Penh, Cambodia); Rodríguez A Fase (Public Health Institute, Chile); Leilani T Nilos, Marilia G Lucero, Socoró P Lupisan (Research Institute for Tropical Medicine, Muntinlupá, Philippines); Brunhilde Schweger (Robert Koch Institute [RKI], Berlin, Germany); Nathaly Gonzalez (Seremi de Salud del Tarapacá, Tarapacá, Chile); Andrea Gutierrez (Seremi de Salud Región del Bio Bio, Bio Bio, Chile); Vahid Salimi (Tehran University of Medical Sciences, Tehran, Iran); Charalada Buntih, Henry C Baggett, Pathanich Sapchokkung, Pongpanw Sangwatn, Sathapana Naorat, Somsak Thamthitiwat (Thailand Ministry of Public Health—US Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand); Hiroshi Oshitani (Tokyo University Graduate School of Medicine, Miyagi Prefecture, Japan); Candice Romero, Yeoy O Tinoco (US Naval Medical Research Unit No 6, Callao, Peru); Carmen Lucia Contreras, John P McCracken, Jorge Jara (Universidad del Valle de Guatemala, Guatemala City, Guatemala); Maria Mathiesen (University Hospital of North Norway, Tromso, Norway); Louis Bont, Wencie Chetelama (University Medical Center Utrecht, Netherlands); Sudha Banerji, Tor A Strand (University of Bergen, Bergen, Norway); Eva Harris (University of California, Berkeley, CA, USA); Mark P Nicol (University of Cape Town and National Health Laboratory Services, Cape Town, South Africa); Heather J Zar (University of Cape Town, Cape Town, South Africa); Phyllis Cantrav-Link, Erica F A Simoes (University of Colorado, Aurora, CO, USA); Monuarm Choe (University of Health Sciences, Phnom Penh, Cambodia); Najwa Khuri-Bulos (University of Jordan, Amman, Jordan); Nigel Bruce, Mukesh Dherani (University of Liverpool, Liverpool, UK); Karen L Rotlof, Milagritos D Tapia (University of Maryland School of Medicine, Baltimore, MD, USA); Audreor Gordon (University of Michigan, Ann Arbor, MI, USA); Phil Seidenberg (University of New Mexico, Albuquerque, NM, USA); Nusrat Homaia (University of New South Wales, Sydney, NSW, Australia); David Murdoch (University of Otago, Dunedin, New Zealand); Cissy B Kartzasmita, Kuswadewi Mutya (University of Padjadjaran, Bandung, Indonesia); John Williams (University of Pittsburgh, Pittsburgh, PA, USA); Michelle Groome, Shahrzad Madihi, Susan Nzerue, Aziwafuri Mudau, David P Moore, Peter V Adrian, Vicky L Baillie (University of the Witwatersrand, Johannesburg, South Africa); James Chipeta, Lawrence Mwanyamunda (University Teaching Hospital, Lusaka, Zambia); Natasha Halasa (Vanderbilt University, Nashville, TN, USA); Christian Hoppe (Vaccine Safety Initiative [VVI], Berlin, Germany); Peter F Wright (Dartmouth Medical School, Lebanon, NH, USA)

Declaration of interests

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