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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

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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and World Bank income regions from a systematic review of studies published between Jan 1, 1995, and Dec 31, 2016, and unpublished data from 76 high quality population-based studies.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by combining in-hospital case fatality ratios with hospital admission estimates from hospital-based (published and unpublished) studies.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] 21–650–3) episodes of RSV-ALRI resulted in about 3·2 million (2·7–3·8) hospital admissions, and 59 000 (48 000–74 500) in-hospital deaths in children younger than 5 years. In children younger than 6 months, 1·4 million (UR 1·2–1·7) 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.3 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”.4 Therefore, updated RSV disease burden estimates incorporating latest data are of great relevance for vaccine policy formulation and to prioritise research funding. We estimated that RSV is associated with about 28% of all ALRI episodes and 13.2–22% of all ALRI mortality in young children. Using historical RSV case fatality data, we show that, in general, there has been a decreasing trend for RSV associated case fatality ratio across all age groups and income regions.

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.5 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 compiles 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 for most hospital-based studies the decision for admission 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 (appendix pp 2, 85). We expanded our definition for hospital for RSV-associated (severe or very severe) ALRI case definitions for hospital-based studies—admission to hospital is based on physician’s overall impression (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 (appendix pp 2, 85). We expanded our definition for influenza seasonality to include RSV.1 Any month in which the virus was detected in more than 5% (at least 4) specimens was considered to be within RSV or influenza season. Industrialised and developing country designations followed UNICEF categories.7 We designated countries as high, upper-middle, lower-middle, and low-income based on the World Bank’s classification. The child population estimates for 2015 are from UNPD World Population Prospects: 2015 revision.

Statistical analysis
For studies not reporting 0–59 month incidence rates, we imputed any missing age group data using median incidence rate ratios (appendix p 7).1.6,9,10 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 proportion of eligible cases and data for all eligible cases were available, we scaled results for proportion sampled. Figure 1 summarises and gives the rationale for our approach.

We did a data meta-analysis (by region and narrow age bands, where possible) for RSV and severe RSV-ALRI incidence, hospital admission rate for RSV-ALRI (studies with well-defined catchment population), proportion of hospital admissions for ALRI that were RSV positive (RSV+ve) and in-hospital RSV-ALRI CFR, and report pooled estimates (with 95% CI).9 Because in-study and between study data heterogeneity was anticipated, we used random effects models.9,10 Incidence and hospital admission rate meta-estimates for RSV-ALRI and severe RSV-ALRI were applied to 0–5 year regional populations estimates to yield new episodes of RSV-ALRI and severe RSV-ALRI in 2015.

We validated hospital admissions for RSV-ALRI estimates with independent data by abstracting the proportion of ALRI hospital admissions that were RSV+ve. We then computed (WHO) regional proportion meta-estimates and applied these to regional estimates of hospital admissions for ALRI updated for 2015.9

We estimated RSV-ALRI episodes in young children in 132 developing countries using a risk-factor based model similar to that described previously.1 We calculated country level RSV-ALRI incidence using odds or rate ratios for six RSV risk factors [prematurity (<37 weeks), low birthweight (<2500 g), siblings, maternal smoking, HIV and crowding] from a meta-analysis of published studies,9,10 country-level risk factor prevalence (from relevant surveys and UN estimates), and estimates of RSV-ALRI incidence in developing countries. This assumes incidence in children without risk factors (unexposed rate) is similar within a region; that rate ratios can be multiplied when two or more are present; and that risk factors were independently 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 10000 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,10,11 therefore, to estimate overall RSV-associated deaths, we used the excess mortality model (as reported previously).9,10 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:

$$\frac{(\text{AvgRSV} - \text{AvgOTHER}) \times \text{MonRSV}}{\text{TOTAL}}$$

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
Figure 1: Approaches for estimation of global RSV associated morbidity and mortality in children aged 0–4 years

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 hospital admissions for RSV-ALRI have been estimated using two independent approaches and datasets (after ensuring all included studies satisfy the common case definition that hospital admission was based on a physician diagnosis of ALRI). Similarly, the in-hospital deaths due to RSV-ALRI are based on studies reporting in-hospital CFR for RSV and RSV-ALRI hospital admissions (again ensuring all included studies satisfy the common case definition). RSV= respiratory syncytial virus. ALRI= acute lower respiratory infection. hCFR= in-hospital case fatality ratio. VA= verbal autopsy.

0–4 year ALRI mortality, 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; about 45% of these in children younger than 6 months (appendix pp 17–22). Across all regions, hospital admission rates for RSV-ALRI for young children 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 per 1000 neonates per year in developing countries (appendix pp 42). About 20% of (community) cases in young children had lower chest wall indrawing (severe RSV-ALRI); a third observed in infants (table 1, appendix p 43). We also estimated the incidence and number of RSV-ALRI episodes in young children in 132 LMICs in 2015. Despite a wide range of incidence rates from 65·6 (UR 40·3–105·1) per 1000 children per year in Senegal to 31·0 (18·7–50·8) in China, there was only a limited variation in point estimates with very wide uncertainty ranges for most countries (appendix p 87). Five countries (with about 43% of global 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 (appendix p 42).

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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 (appendix pp 46–47). About 85% of all hospital admission cases had chest wall indrawing (data not shown). 28 (61%) of 46 studies recording SpO2 by pulse oximetry used our hypoxaemia case definition and these reported about 20% of all hospital admissions for RSV-ALRI cases aged 0–4 years (all age groups) had hypoxaemia (appendix pp 45, 83–84). This translates to about 1·0 million (UR 0·6–1·6) episodes of hospital admissions for severe RSV-ALRI with hypoxaemia in young children from developing countries, 58% in infants younger than 6 months. We also estimated 0·6 million (UR 0·4–1·1) hospital admissions for very severe RSV-ALRI in young children in developing countries in 2015, 51% in infants younger than 6 months.

Data were insufficient to provide global incidence or hospital admissions by RSV subtype. RSV-A was the more common circulating subtype and resulted in more severe hospital admissions by RSV subtype. RSV-A was the more common circulating subtype and resulted in more severe hospital admissions by RSV subtype.

Figure 3: Location of studies reporting incidence, hospital admission, and in-hospital case fatality in children with RSV-ALRI.

RSV-ALRI=RSV-associated acute lower respiratory infection.
<table>
<thead>
<tr>
<th></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><strong>RSV-ALRI</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–5 months</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
<td>16 (6)</td>
</tr>
<tr>
<td>Incidence (uncertainty range)</td>
<td>127·2 (108·4–126·6)</td>
<td>63·3 (38·5–104·0)</td>
<td>168·9 (47·9–596·1)</td>
<td>66·1 (33·5–130·4)</td>
<td>82·5 (50·4–135·2)</td>
<td>6·7 (3·3–13·0)</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 (3750–8765)</td>
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<td>6–11 months</td>
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<tr>
<td>Studies</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td></td>
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<tr>
<td>Incidence (uncertainty range)</td>
<td></td>
<td>80·7 (48·135·6)</td>
<td>223 (95·2–522·1)</td>
<td></td>
<td>98·8 (58·8–166·1)</td>
<td></td>
<td></td>
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<tr>
<td>Number of episodes (thousands)</td>
<td>.. (2595)</td>
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<td></td>
<td>.. (3619–10223)</td>
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<td>0–59 months</td>
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<td>3 (2)</td>
<td>2 (1)</td>
<td>14 (8)</td>
<td>2 (1)</td>
<td>16 (9)</td>
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<td>Incidence (uncertainty range)</td>
<td>94 (89·1–99·1)</td>
<td>40·8 (25·7–66·5)</td>
<td>85·5 (33·8–216·7)</td>
<td>35·6 (16·6–76·2)</td>
<td>50·8 (32·4–79·7)</td>
<td>35·6 (16·6–76·2)</td>
<td></td>
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<tr>
<td>Number of episodes (thousands)</td>
<td>9541 (9044–10059)</td>
<td>12864 (8081–20478)</td>
<td>14887 (5876–37711)</td>
<td>2841 (1326–6090)</td>
<td>3516 (19463–47853)</td>
<td>2482 (1158–5220)</td>
<td>33059 (21583–50312)</td>
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<td><strong>RSV-associated severe ALRI</strong></td>
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<td>0–5 months</td>
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<tr>
<td>Studies</td>
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<td>1</td>
<td>1 (1)</td>
<td>8 (2)</td>
<td>1 (1)</td>
<td>9 (3)</td>
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<tr>
<td>Incidence (uncertainty range)</td>
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<td>(316·4–522·7)</td>
<td>(1·8–5·8)</td>
<td>(10·1–129·1)</td>
<td>(1·8–5·8)</td>
<td></td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>.. (808)</td>
<td>7001 (5503–2955)</td>
<td>25 (14–45)</td>
<td>2222 (622–7945)</td>
<td>22 (12–39)</td>
<td>2174</td>
<td></td>
</tr>
<tr>
<td>6–11 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Incidence (uncertainty range)</td>
<td>.. (19·5)</td>
<td>(8·3–45·8)</td>
<td>82·1 (45·5–148·2)</td>
<td>.. (11·5–52·2)</td>
<td>.. (6·9–74·70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>.. (628)</td>
<td>1454 (805–2625)</td>
<td>.. (707–3272)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–59 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>0</td>
<td>7 (4)</td>
<td>1 (1)</td>
<td>1</td>
<td>8 (5)</td>
<td>1</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Incidence (uncertainty range)</td>
<td>.. (7·5)</td>
<td>(3·1–18·9)</td>
<td>(68·4–108·6)</td>
<td>(1·7–5·5)</td>
<td>(3·5–29·9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>.. (2357)</td>
<td>15003 (11909–18902)</td>
<td>243 (133–439)</td>
<td>6145 (2103–7943)</td>
<td>212 (117–383)</td>
<td>6303</td>
<td>(2317–18196)</td>
</tr>
<tr>
<td>Hospital admission for RSV-associated ALRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–5 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>5 (2)</td>
<td>17 (8)</td>
<td>15 (9)</td>
<td>34 (25)</td>
<td>43 (22)</td>
<td>28 (22)</td>
<td>71 (44)</td>
</tr>
<tr>
<td>Hospital admission rate</td>
<td>7·4 (2·4–22·6)</td>
<td>22·9 (17·7–29·7)</td>
<td>23·0 (16·1–32·9)</td>
<td>26·3 (22·8–30·2)</td>
<td>20·2 (16·7–24·5)</td>
<td>27·1</td>
<td>(23·3–31·6)</td>
</tr>
<tr>
<td>Number of episodes (thousands)</td>
<td>79 (26–240)</td>
<td>737 (569–955)</td>
<td>407 (284–582)</td>
<td>205 (178–237)</td>
<td>1243 (1025–1508)</td>
<td>184 (158–214)</td>
<td>1447 (1204–1744)</td>
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<tr>
<td>6–11 months</td>
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<td>9</td>
<td>20</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Hospital admission rate</td>
<td>3·4 (0·6–19·5)</td>
<td>11·3 (6·1–21·0)</td>
<td>18·5 (9·8–34·7)</td>
<td>11·3 (6·1–20·9)</td>
<td>11·0 (7·7–15·7)</td>
<td>9·8</td>
<td>(4·8–19·6)</td>
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<tr>
<td>12–59 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td>3</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>21</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Hospital admission rate</td>
<td>0·4 (0·1–3·7)</td>
<td>1·8 (1·2–2·8)</td>
<td>2·2 (1·3–3·9)</td>
<td>1·4 (0·9–2·0)</td>
<td>1·5 (1·0–2·1)</td>
<td>1·6</td>
<td>(1·0–2·5)</td>
</tr>
</tbody>
</table>
RSV morbidity and mortality vary substantially from year to year. 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 118,200 (UR 94,600–149,400). Available morbidity and mortality data show substantial yearly variation in RSV activity and associated ALRI deaths (appendix pp 89–93), suggesting that national, regional, and global RSV morbidity and mortality vary substantially from year to year.

### 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 21·6–50·3) RSV-ALRI episodes resulting in about 3·2 (UR 2·7–3·8) million hospital admissions, and 59·600 (48·000–74·500) in-hospital deaths in (670·5 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). If the in-hospital mortality estimates are based on a subset of 22 studies that reported RSV data by narrower age bands (including the neonatal period), then the in-hospital mortality estimates would increase by 36% (appendix pp 70–79). If the in-hospital mortality estimates are based on the maximum number of eligible datapoints. Consistent with this, our hCFR estimates...
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. 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 to begin phase 3) could have a substantial impact in this age group. For example, if a future seasonal cocirculation of other respiratory pathogens. These could have resulted in an overestimate of overall RSV mortality. Peak pneumococcal mortality is closely linked to (and temporally follows) RSV activity. A sensitivity analysis extending the RSV season by 1 month and analysing the in-hospital RSV-ALRI mortality accordingly suggests that this could increase RSV-ALRI mortality by about 60% (appendix p 66). Thus, failure to account for this indirect effect on pneumococcal deaths could result in an underestimate of the contribution of RSV to ALRI deaths.

We have been unable to report estimates of overall RSV-ALRI mortality separately in infants or children younger than 6 months. Further estimates of overall RSV-ALRI mortality from population-based studies with demographic surveillance (which identify child ALRI deaths and conduct RSV and influenza surveillance to define seasonality) could provide more data to allow 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.
Hyponaemia is an important indicator of severity and key predictor of ALRI mortality. About 20% of all children admitted to hospital with RSV-ALRI have hyponaemia. 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 hospital care and conditions that restrict the ability of caregivers to seek hospital care for their children (these studies occurred when WHO recommended hospital admission for all ALRI cases with lower chest wall indrawing). With the wider use of RSV testing 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 two-fold 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.

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 ranges of socioeconomic development.

These updated estimates of 33.1 million (UR 21.6–50.3) RSV-ALRI episodes resulting in about 3.2 million (UR 2.7–3.8) 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,22 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).

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Unit</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated (severe) RSV-ALRI deaths in children in developing countries</td>
<td></td>
<td>3.2 million</td>
</tr>
<tr>
<td>P95:2.1 – 5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number of episodes of RSV-severe ALRI in LMIC children in 2015</td>
<td></td>
<td>6.0 million</td>
</tr>
<tr>
<td>P95:4.2 – 9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFR in hospital admitted cases</td>
<td></td>
<td>2.1% (1.9–2.3)</td>
</tr>
<tr>
<td>CFR in communities 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51% of deaths were in hospital</td>
<td></td>
<td>59,600 (UR 47,800–74,300)</td>
</tr>
<tr>
<td>49% of deaths occur outside hospital</td>
<td></td>
<td>59,600 (UR 46,700–72,900)</td>
</tr>
</tbody>
</table>

RSV = respiratory syncytial virus. ALRI = acute lower respiratory infection. 23 Our estimates of RSV-ALRI hospital admissions suggests 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 hospital care and conditions that restrict the ability of caregivers to seek hospital care for their children (these studies occurred when WHO recommended hospital admission for all ALRI cases with lower chest wall indrawing). 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 hospital care and conditions that restrict the ability of caregivers to seek hospital care for their children (these studies occurred when WHO recommended hospital admission for all ALRI cases with lower chest wall indrawing). 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 hospital care and conditions that restrict the ability of caregivers to seek hospital care for their children (these studies occurred when WHO recommended hospital admission for all ALRI cases with lower chest wall indrawing).
(intracountry) variations in socioeconomic conditions and associated risk factor prevalence in populations residing in middle-income countries.

RSV PCR-based assays were used in 127 of 329 studies; immunofluorescence was in 30 studies, direct immunofluorescence test in 74 studies, indirect immunofluorescent antibody test in 18 studies, ELISA in 12 studies, a mixture in 48 studies, and no details were given in 20 studies. Immunofluorescence assays have variable and lower sensitivity (69.4%) compared with PCR.11 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 respiratory carriage of potential pathogens and common presence of multiple agents and is best assessed in case-control studies. Our recent meta-analysis suggests that in about 90% of cases RSV in a nasopharyngeal specimen can be causally attributed to ALRI.12

Our 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, BDG, and FPP led data interpretation. HN wrote the first draft of the report with inputs from DAM and HC. KLOB, EAFS, SAM, BDG, and FPP 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.

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For the UNDP Population Prospects see [http://esa.un.org/unpd/wpp/Download/Standard/Population/]
See Online for appendix For the Child Health and Mortality Prevention Surveillance see [https://champshealth.org/]

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Declaration of interests

DAM reports personal fees from Roche and grants from Galexto outside the submitted work. EAFS reports grants from AstraZeneca, Regeneron, Ablivie, Pfizer, and Novavax outside of the submitted work. SAM reports grants and personal fees from BMDG and Pfizer; grants from GSK, Novartis, and personal fees and travel expenses from the submitted work. BDG reports grants from Pfizer, Sanofi Pasteur, Merck, Novartis, Crucell, and GSK outside of the submitted work. FPP reports consulting from Novavax, Bavarian Nordic, Janssen, Ablynx, GSK, Sanofi Pasteur, and Maluoxience, and grants from Janssen. LB reports grants from MedImmune, Ablivie, Janssen, Meded, and BMDG outside of the submitted work. PB reports that he is currently an employee of GSK vaccines. PC-L reports that her institution received payments for running a clinical study on RSV in hospitalised infants from AstraZeneca, that her institution received payments for running a clinical study on maternal antibody transfer of RSV immunoglobulins in newborn infants from Pfizer, and that her institution received payments for locally running a clinical trial for REGN2222 (drug) on prevention of RSV in infants from Regeneron outside of the submitted work. CC reports grants from Sanofi Pasteur outside of the submitted work. MD-K reports grants from BMGF during the conduct of the study. NH reports grants from AstraZeneca, Biocyst, and Sanofi Pasteur outside of the submitted work. MPN reports grants from BMGF during the conduct of the study. DJN reports grants from GSK outside of the submitted work. HO reports grants from Janssen Sciences Ireland UC outside of the submitted work. PS reports grants from BMGF during the conduct of the study. HJZ reports grants from BMGF during the conduct of the study. KCS reports grants and personal fees from BMGF and WHO during the conduct of the study; and grants and personal fees from Sanofi outside of the submitted work. HN reports grants from BMGF during the conduct of the study; grants and personal fees from Sanofi-Pasteur, grants from WHO, and personal fees from Medimmune outside of the submitted work. All other authors declare no competing interests.

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References