Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis

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Summary

Background Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infection in young children. We previously estimated that in 2015, 33·1 million episodes of RSV-associated acute lower respiratory infection occurred in children aged 0–60 months, resulting in a total of 118 200 deaths worldwide. Since then, several community surveillance studies have been done to obtain a more precise estimation of RSV associated community deaths. We aimed to update RSV-associated acute lower respiratory infection morbidity and mortality at global, regional, and national levels in children aged 0–60 months for 2019, with focus on overall mortality and narrower infant age groups that are targeted by RSV prophylactics in development.

Methods In this systematic analysis, we expanded our global RSV disease burden dataset by obtaining new data from an updated search for papers published between Jan 1, 2017, and Dec 31, 2020, from MEDLINE, Embase, Global Health, CINAHL, Web of Science, LILACS, OpenGrey, CNKI, Wanfang, and ChongqingVIP. We also included unpublished data from RSV GEN collaborators. Eligible studies reported data for children aged 0–60 months with RSV as primary infection with acute lower respiratory infection in community settings, or acute lower respiratory infection necessitating hospital admission; reported data for at least 12 consecutive months, except for in-hospital case fatality ratio (CFR) or for where RSV seasonality is well-defined; and reported incidence rate, hospital admission rate, RSV positive proportion in infection with acute lower respiratory infection in hospital admission, or in-hospital CFR. Studies were excluded if case definition was not clearly defined or not consistently applied, RSV infection was not laboratory confirmed or based on serology alone, or if the report included fewer than 50 cases of acute lower respiratory infection. We applied a generalised linear mixed-effects model (GLMM) to estimate RSV-associated acute lower respiratory infection incidence, hospital admission, and in-hospital mortality both globally and regionally (by country development status and by World Bank Income Classification) in 2019. We estimated country-level RSV-associated acute lower respiratory infection incidence through a risk-factor based model. We developed new models (through GLMM) that incorporated the latest RSV community mortality data for estimating overall RSV mortality. This review was registered in PROSPERO (CRD42021252400).

Findings In addition to 317 studies included in our previous review, we identified and included 113 new eligible studies and unpublished data from 51 studies, for a total of 481 studies. We estimated that globally in 2019, there were 33·0 million RSV-associated acute lower respiratory infection episodes (uncertainty range [UR] 25·4–44·6 million), and unpublished data from 51 studies, for a total of 481 studies. We estimated that globally in 2019, there were 33·1 million episodes of RSV-associated acute lower respiratory infection in children aged 0–60 months, resulting in a total of 118 200 deaths worldwide. Since then, several community surveillance studies have been done to obtain a more precise estimation of RSV associated community deaths. We aimed to update RSV-associated acute lower respiratory infection morbidity and mortality at global, regional, and national levels in children aged 0–60 months for 2019, with focus on overall mortality and narrower infant age groups that are targeted by RSV prophylactics in development.

Interpretation RSV contributes substantially to morbidity and mortality burden globally in children aged 0–60 months, especially during the first 6 months of life and in LMCs. We highlight the striking overall mortality burden of RSV disease worldwide, with one in every 50 deaths in children aged 0–60 months and one in every 28 deaths in children
Introduction

Human respiratory syncytial virus (RSV) is the most common pathogen identified in infants and young children with acute lower respiratory infection.\(^1\) We previously estimated\(^2\) that in 2015, there were 33·1 million episodes of RSV-associated acute lower respiratory infection, 3·2 million hospital admissions for RSV-associated acute lower respiratory infection, and 59 600 in-hospital RSV-associated acute lower respiratory infection deaths in children younger than 5 years.\(^3\) We also estimated that overall RSV-associated deaths from acute lower respiratory infection could be as high as 118 200, based on an indirect approach that inflated in-hospital mortality estimates due to the absence of RSV mortality data in community settings at the time of the analysis.\(^4\) Since 2017, new data on RSV burden in young children have become available, including from several new RSV community surveillance studies initiated to measure RSV mortality in the community (RSV community mortality surveillance studies\(^5\) and child health and mortality prevention surveillance [CHAMPS]\(^6\)) supported by the Bill & Melinda Gates Foundation. Meanwhile, there have been substantial advances in the development of RSV prophylactic products, with several prophylactic candidates in late-phase clinical development.\(^6\) A monoclonal antibody with extended half-life, nirsevimab (AstraZeneca and Sanofi), which demonstrated high

Evidence before this study

Respiratory syncytial virus (RSV) is the main cause of acute lower respiratory infection among young children. We searched PubMed for studies published between Jan 1, 1995, and Oct 31, 2021, that reported global estimates of RSV morbidity and mortality in young children, using the search terms (“Respiratory syncytial virus” OR “RSV”) AND (“incidence” OR “mortality” OR “death” OR “morbidity” OR “burden”) AND (“child” OR “pediatric” OR “paediatric” OR “infant”).\(^7\) We previously estimated that in 2015, there were 33·1 million acute lower respiratory infection episodes, 3·2 million hospital admissions for acute lower respiratory infection and 59 600 acute lower respiratory infection deaths associated with RSV in children aged 0–60 months; we also reported an estimated 118 200 overall deaths (ie, in-hospital and out-of-hospital or community deaths), derived indirectly based on in-hospital deaths. The Global Burden of Disease study by the Institute of Health Metrics and Evaluation estimated that 10·7 million acute lower respiratory infection episodes and over 41 000 acute lower respiratory infection deaths in children aged 0–60 months in 2016 were attributable to RSV. In a separate study, we estimated the national burden of RSV hospitalisation for 58 countries and reported an extrapolated estimate of 2·5–4·1 million RSV-associated hospitalisations globally in children aged 0–60 months in 2019. No robust estimates of RSV overall deaths were available from existing global studies that incorporated RSV community mortality data.

Added value of this study

We substantially expanded our global RSV burden dataset by including 113 new studies from the literature review update and new unpublished data from 51 studies shared through RSV GEN. With these data and improved methods, we have now been able to estimate RSV morbidity and mortality burden for hospital settings and overall, and focus on narrower infant age groups that are targeted by RSV prophylactics in development. With data on RSV community mortality, we estimated the overall RSV mortality burden in different age groups—one death was attributable to RSV in every 50 deaths in children aged 0–60 months and in every 28 deaths in children aged 28 days to 6 months. For every RSV-associated acute lower respiratory infection in-hospital death, there were approximately three more deaths attributable to RSV in the community. RSV passive immunisation programmes targeting protection during the first 6 months of life could have a substantial effect on reducing RSV disease burden, although more data are needed to understand the implications of the potential age-shifts in peak RSV burden to older age when these are implemented.

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efficacy among healthy preterm infants in a phase 2b trial, reduced medically-attended RSV lower respiratory tract infections in healthy late-preterm and term infants in its phase 3 trial (NCT03979313). Moreover, two maternal vaccine candidates aimed to protect infants through transplacental transfer of vaccine-induced maternal antibodies (RSV MAT [GlaxoSmithKline; NCT04605159] and RSVpreF [Pfizer; NCT04424316]), and one monoclonal antibody (MK-1654 [MSD; NCT04767373]) have initiated recruitment for the phase 3 clinical trials, and are expected to complete in the next 3–5 years.

In this study, we aim to estimate RSV-associated acute lower respiratory infection morbidity and mortality in 2019 at global, regional, and national levels in children aged 0–60 months, with a primary focus on narrower infant age groups that are targeted by RSV prophylactics under development, and on overall mortality.

**Methods**

**Definitions**

As previously described, acute lower respiratory infection was defined by setting. For community-level setting (eg, primary care), we used WHO Integrated Management of Childhood Illnesses pneumonia case definitions and replaced the terms “clinical pneumonia” with “ALRI” for hospital setting; we used physician-confirmed diagnosis of acute lower respiratory infection (pneumonia or bronchiolitis). RSV-associated acute lower respiratory infection was defined as acute lower respiratory infection with laboratory-confirmed RSV infection. RSV-attributable acute lower respiratory infection was defined as acute lower respiratory infection that could be causally attributable to laboratory-confirmed RSV infection. Hypoxaemia was defined as SpO2 less than 90% (or <87% if at altitude >2500 metres) in children aged 1–60 months and less than 88% (or <85% if at altitude >2500 metres) for children younger than 1 month. For more detailed definitions see the appendix (p 8).

**Search strategy and selection criteria**

We conducted a systematic literature review, updating our previous review. We searched MEDLINE, Embase, Global Health, CINAHL, Web of Science, LILACS, OpenGrey, CNKI, Wanfang, and ChongqingVIP for studies published between Jan 1, 2017, and Dec 31, 2020, that reported RSV-associated acute lower respiratory infection morbidity and mortality estimates in children aged 0–60 months in 2019 or before, (ie, before the onset of the COVID-19 pandemic). The literature search used the terms (with synonyms and closely related words) “respiratory syncytial virus”, “pneumonia”, “bronchiolitis”, “respiratory tract infections”, “incidence”, “morbidity”, “mortality”, “burden”, and “epidemiology”. For a detailed search strategy, see the appendix (pp 4–7). References cited in retrieved articles were also examined for eligibility. No language restrictions were applied. Two authors (YL and ABP) conducted quality assessment at the study level independently. Eligible studies reported data for children aged 0–60 months with RSV as primary infection with acute lower respiratory infection in community settings or acute lower respiratory infection necessitating hospital admission; reported data for at least 12 consecutive months, except for in-hospital case fatality ratio (CFR) or where RSV seasonality is well defined (eg, in temperate regions); and reported incidence rate, hospital admission rate, RSV positive proportion in acute lower respiratory infection hospital admission, or in-hospital CFR.

Studies were excluded if case definition was not clearly defined or not consistently applied, RSV infection was not laboratory confirmed or based on serology alone, or if the report included fewer than 50 cases of acute lower respiratory infection.

Data extraction was done independently by two authors (XW and ABP) using a tailored spreadsheet, with any disagreements arbitrated by YL. The data collection spreadsheet collected study-level information, such as location or country, study period, eligibility criteria, case definition, clinical specimen and diagnostic tests, and the reported morbidity and mortality estimates.

**Unpublished RSV data**

Previously, we established the Respiratory Virus Global Epidemiology Network (RSV GEN) to collect unpublished data (including re-analysis of published data), applying common case definitions and approaches to data analysis, yielding unpublished data from over 70 individual study sites. For this study, we continued to encourage existing members of RSV GEN to contribute new RSV data while inviting other investigators with eligible RSV data to join this collaborative network. This resulted in novel unpublished data from 51 study sites to supplement published data and data included in our previous estimates (appendix pp 9–11).

**Quality assessment**

For both published and unpublished RSV data, two authors (YL and XW) conducted quality assessment at the study level independently using an evidence-based quality scoring form (appendix p 18). The quality scoring form assessed the study quality and risk of bias on study design, subjects, case definition, sampling strategy (for RSV testing), and diagnostic tests; for hospital-based studies, adjustment for health-care utilisation and ascertainment for hypoxaemia were also assessed where applicable. Based on the individual assessment questions above, an overall quality score was calculated for each study, ranging between 0 (lowest quality) and 1 (highest quality). Regardless of the scores, all studies were included in main analysis; studies with quality scores <0.6 were excluded in sensitivity analysis.
Data analysis

We estimated RSV-associated acute lower respiratory infection incidence, RSV-associated acute lower respiratory infection hospital admission, RSV-associated acute lower respiratory infection in-hospital deaths, and RSV-associated and RSV-attributable overall deaths for children aged 0–60 months and, where data were available, for narrower age bands (figure 1).

We conducted meta-analysis of RSV-associated acute lower respiratory infection incidence rate and hospital admission rate by regions (UNICEF country development status and World Bank income classification), age band, and severity (ie, acute lower respiratory infection with or without chest wall indrawing, and with or without hypoxaemia), through a generalised linear mixed-effects model (GLMM) of two levels (within-study and between-study).

As we prioritised the geographical representativeness of our study sites, we were flexible in terms of study years considered in the meta-analysis. We adjusted for proportion of acute lower respiratory infection cases not tested for RSV by applying the RSV positive proportion among acute lower respiratory infection cases tested for RSV to the total tested and untested acute lower respiratory infection cases, if it was not already done in the individual studies. Data imputation was done for studies not reporting RSV-associated acute lower respiratory infection incidence rate or hospital admission rate for children aged 0–60 months (appendix p 12). The incidence rate and hospital admission rate meta-estimates were applied to regional population estimates for 2019 to yield the number of RSV-associated acute lower respiratory infection episodes and hospital admission for RSV-associated acute lower respiratory infection or RSV-associated acute lower respiratory infection with hypoxaemia.

For RSV-associated acute lower respiratory infection incidence, we also estimated country-specific RSV-associated acute lower respiratory infection incidence rate and episodes in children aged 0–60 months in 137 LMICs using a risk-factor based model similar to previous work (appendix pp 13–14). For RSV-associated acute lower respiratory infection hospital admission, we validated the estimates with independent data by applying the meta-estimates of RSV positive proportion among acute lower respiratory infection hospital admissions (through GLMM) in our study to the external sources of acute lower respiratory infection hospital admission estimates (appendix p 19 and p 42).

We obtained meta-estimates of in-hospital CFR for RSV-associated acute lower respiratory infection hospital admission by region (UNICEF country development status and World Bank Income classification) and age band using GLMM. Then we applied the in-hospital CFR to the RSV-associated acute lower respiratory infection hospital admission estimates, by region and age band, to calculate RSV-associated acute lower respiratory infection in-hospital deaths.

With RSV community mortality data from 2017–19, we developed a new suite of models for estimating RSV-associated and attributable overall deaths (ie, in-hospital and out-of-hospital or community deaths) for children aged 0–60 months and for narrower age bands, both regionally and globally. Rather than inflating indirectly from in-hospital estimates as previously, we aimed to model the RSV proportion among overall all-cause deaths (as the main model) and among overall acute lower respiratory infection deaths (as secondary model). Both models were based on a GLMM framework that accounted for study setting (ie, community only vs community and in-hospital), method for RSV confirmation, age band (0–27 days, 28 days–6 months, 6–12 months, and 12–60 months), country’s under-5 years all-cause mortality rate, and method for assigning cause of death (ie, whether only verbal autopsy was available for the secondary acute lower respiratory infection model) as model covariates.

The three recorded outcomes were RSV-attributable deaths (primary outcome, defined as RSV being in the causal chain based on CHAMPS, including RSV being the underlying, intermediate [comorbid or antecedent causes], and immediate causes of death), RSV-associated all-cause, and acute lower respiratory infection deaths (secondary outcomes, defined as RSV being tested positive in upper respiratory samples). Detailed methods are presented in the appendix (pp 16–17).

For estimates that were generated from single meta-analysis, the uncertainty range (UR) was derived from the coefficient and its standard error of that meta-analysis. For estimates that were generated through results from multiple meta-analyses, the UR of the estimates were generated using the Monte Carlo simulation to avoid inflation of the UR, based on 1000 samples of each of the meta-estimates from log-normal distributions, with 2.5th percentile and 97.5th percentile defining the lower and upper bounds.

All data analyses were done using R software (version 4.0.5). The study data and R codes for the analysis are available in Edinburgh DataShare (https://doi.org/10.7488/ds/3138). This study was conducted and reported in accordance with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix p 51). The systematic literature review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020 (appendix pp 52–54). This review was registered in PROSPERO (CRD42021252400).

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit.
Results

In addition to the 317 studies included in the previous review, we identified and included 113 new eligible studies from the literature review update and included new unpublished data from 51 studies from RSV GEN collaborators. This brought the total number of studies included in the present analysis to 481. Among the 481 studies, 140 contributed to the estimate of RSV-associated acute lower respiratory infection incidence or hospitalisation rate; 339 contributed to the estimate of RSV-positive proportion among acute lower respiratory infection hospital admission; 147 contributed to the estimate of RSV-associated in-hospital deaths; and 15 studies contributed to the estimate of RSV overall deaths (appendix pp 20–23). Study-level characteristics are presented in the appendix (pp 24–31). Through regional-level meta-analyses, we estimated that 33.0 million (UR 25.4–44.6 million) RSV-associated acute lower respiratory infection episodes occurred globally in children aged 0–60 months in 2019, with one in five episodes occurring in infants aged 0–6 months (6.6 million, 4.6–9.7 million). In low-income and lower-middle-income countries, the RSV-associated acute lower respiratory infection incidence rate peaked in children aged 0–3 months whereas the rate peaked in children aged 3–6 months in upper-middle-income and high-income countries. More than 95% of RSV-associated acute lower respiratory infection episodes...
## RSV-associated acute lower respiratory infection

| Studies | Incidence rate | Number of episodes | Number of episodes | Number of episodes | Number of episodes | Global* |
|---------|----------------|--------------------|--------------------|--------------------|--------------------|---------|
| 0-3 months |
| Studies |
| Incidence rate | 8.0 | (48-136) |
| Number of episodes | 49,000 | (29,000-82,000) |
| 3-6 months |
| Studies |
| Incidence rate | 8.9 | (44.5-154.7) |
| Number of episodes | 50,000 | (270,000-939,000) |
| 0-6 months |
| Studies |
| Incidence rate | 7.9 | (40.7-134.7) |
| Number of episodes | 92,000 | (528,000-1,636,000) |
| 6-12 months |
| Studies |
| Incidence rate | 6.7 | (31.5-159.8) |
| Number of episodes | 835,000 | (383,000-1,821,000) |
| 0-12 months |
| Studies |
| Incidence rate | 7.3 | (48.2-142.2) |
| Number of episodes | 1,902,000 | (1,048,000-3,453,000) |
| 12-60 months |
| Studies |
| Incidence rate | 3.9 | (84.4-154.7) |
| Number of episodes | 3,307,000 | (770,000-14,208,000) |
| 0-60 months |
| Studies |
| Incidence rate | 4.3 | (29.4-82.8) |
| Number of episodes | 573,000 | (341,000-963,000) |

*Table 1 continues on next page*
### Table 1: Incidence and number of episodes of RSV-associated acute lower respiratory infection in children younger than 5 years in 2019, by World Bank income regions and development status

| 0–3 months | Low income | Lower-middle income | Upper-middle income | High income | Developing countries | Industrialised countries | Global* |
|------------|------------|---------------------|---------------------|-------------|---------------------|------------------------|--------|
| Studies    | 2          | 6                   | 5                   | 3           | 13                  | 3                      | 16     |
| Incidence rate | 20         | 45.6                | 75.6                | 4.0         | 30.9                | 4.0                    | 28.3   |
| Number of episodes | 12,000    | 714,000             | 675,000             | 13,000      | 949,000             | 13,000                 | 963,000 |
| 3–6 months |            |                     |                     |             |                     |                        |        |
| Studies    | 2          | 6                   | 5                   | 3           | 13                  | 3                      | 16     |
| Incidence rate | 18.1       | 40.6                | 14.1                | 4.0         | 27.6                | 4.0                    | 25.3   |
| Number of episodes | 110,000   | 626,000             | 126,000             | 13,000      | 848,000             | 12,000                 | 862,000 |
| 6–12 months |            |                     |                     |             |                     |                        |        |
| Studies    | 4          | 6                   | 5                   | 3           | 15                  | 3                      | 18     |
| Incidence rate | 20.7       | 45.8                | 50.8                | 1.4         | 38.2                | 1.4                    | 34.4   |
| Number of episodes | 251,000   | 143,000             | 907,000             | 900         | 234,000             | 900                    | 234,000 |
| 0–6 months† |            |                     |                     |             |                     |                        |        |
| Studies    | 4          | 6                   | 5                   | 3           | 16                  | 3                      | 19     |
| Incidence rate | 13.1       | 27.8                | 9.7                 | 12.6        | 17.4                | 12.6                   | 16.9   |
| Number of episodes | 160,000   | 87,000              | 124,000             | 84,000      | 107,000             | 85,000                 | 115,000 |
| 0–12 months‡ |            |                     |                     |             |                     |                        |        |
| Studies    | 4          | 7                   | 5                   | 3           | 16                  | 4                      | 20     |
| Incidence rate | 19.5       | 36.7                | 31.0                | 9.0         | 30.0                | 9.0                    | 27.9   |
| Number of episodes | 474,000   | 230,000             | 110,000             | 121,000     | 364,000             | 120,000                | 379,000 |
| 12–60 months |            |                     |                     |             |                     |                        |        |
| Studies    | 2          | 3                   | 0                   | 0           | 5                   | 0                      | 0      |
| Incidence rate | 14         | 8.1                 | –                   | –           | 37                  | –                      | –      |
| Number of episodes | 124,000   | 20,000              | –                   | –           | 180,000             | –                      | –      |
| 0–60 months‡ |            |                     |                     |             |                     |                        |        |
| Studies    | 2          | 3                   | 0                   | 1           | 5                   | 1                      | 6      |
| Incidence rate | 48         | 140                 | 3                   | 31          | 88                  | 31                     | 81     |
| Number of episodes | 560,000   | 43,500              | –                   | 208,000     | 534,000             | 207,000                | 548,000 |

Data are n, incidence rate per 1000 children per year (UR), or n (UR). RSV = respiratory syncytial virus. UR = uncertainty range. *Global estimates were obtained by summing the numbers of developing and industrialised countries for each of the 3000 samples in the Monte Carlo simulation. †The positive and uncertainty range estimates are not necessarily equal to the sum of the estimates by finer age bands; this is because the studies that contributed to different age group specific estimates were different. ‡Data in parentheses indicate the number of studies with imputed data; comparisons between estimates using imputed data and not using imputed data are presented in the appendix (p 44).
occurred in low-income and middle-income countries (LMICs) across all age groups; table 1) Country-level estimates from the risk-factor-based model showed substantial variations in RSV-associated acute lower respiratory infection rate among LMICs, ranging from 40·3 per 1000 children per year in China (95% UR 29·7–54·6) to 83·4 per 1000 children per year in Eswatini (61·6–113·1; appendix pp 32–34). Approximately 5·5 million (17%) of 33·0 million RSV-associated acute lower respiratory infection episodes had chest wall indrawing (2·2–15·7 million). Infants aged 0–6 months had the highest incidence of RSV-associated acute lower respiratory infection with chest wall indrawing, with an estimated 2·3 million episodes (1·4–4·3 million), which accounted for 36% of all 6·6 million acute lower respiratory infection episodes in this age group (4·6–9·7 million; table 1).

We estimated that there were 3·6 million RSV-associated acute lower respiratory infection hospital admissions globally in children aged 0–60 months in 2019 (UR 2·9–4·6 million), approximately 1·4 million (39%) of which occurred in infants aged 0–6 months.

| RSV-associated acute lower respiratory infection hospital admission | Low income | Lower-middle income | Upper-middle income | High income | Developing countries | Industrialised countries | Global* |
|---|---|---|---|---|---|---|---|
| **0–3 months** | | | | | | | |
| Studies | 6 | 11 | 16 | 19 | 36 | 16 | 52 |
| Hospital admission rate | 10·6 | 11·0 | 26·4 | 34·7 | 23·5 | 36·9 | 24·7 |
| Number of episodes | 36 000 | 36 000 | 226 000 | 116 000 | 721 000 | 122 000 | 841 000 |
| (20 000–204 000) | (267 000–884 000) | (114 000–486 000) | (72 000–188 000) | (466 000–115 000) | (69 000–215 000) | (597 000–1261 000) | |
| **3–6 months** | | | | | | | |
| Studies | 6 | 13 | 16 | 21 | 38 | 18 | 56 |
| Hospital admission rate | 6·0 | 9·2 | 20·6 | 20·7 | 16·7 | 20·6 | 17·0 |
| Number of episodes | 36 000 | 30 000 | 184 000 | 69 000 | 513 000 | 68 000 | 579 000 |
| (50 000–242 000) | (180 000–503 000) | (106 000–321 000) | (45 000–106 000) | (345 000–765 000) | (41 000–113 000) | (422 000–846 000) | |
| **0–6 months†** | | | | | | | |
| Studies | 10 | 12 | 16 | 27 | 41 | 24 | 65 |
| Hospital admission rate | 7·9 | 12·7 | 24·3 | 28·4 | 19·3 | 29·3 | 20·2 |
| Number of episodes | 96 000 | 87 000 | 434 000 | 190 000 | 1 188 000 | 194 000 | 1 376 000 |
| (34 000–266 000) | (523 000–1 460 000) | (236 000–798 000) | (135 000–267 000) | (802 000–1 759 000) | (133 000–283 000) | (1 017 000–1 982 000) | |
| **6–12 months** | | | | | | | |
| Studies | 10 | 13 | 15 | 27 | 41 | 24 | 65 |
| Hospital admission rate | 5·7 | 12·1 | 12·1 | 11·2 | 10·0 | 11·1 | 10·0 |
| Number of episodes | 69 000 | 381 000 | 215 000 | 75 000 | 612 000 | 74 000 | 683 000 |
| (22 000–150 000) | (203 000–715 000) | (117 000–394 000) | (50 000–112 000) | (422 000–886 000) | (47 000–216 000) | (50 000–973 000) | |
| **0–12 months†** | | | | | | | |
| Studies | 13 | 20 | 15 | 41 | 51 | 38 | 89 |
| Incidence rate | 9·6 | 17·5 | 18·7 | 22·3 | 15·3 | 22·5 | 15·9 |
| Number of episodes | 234 000 | 1 095 000 | 669 000 | 294 000 | 1 881 000 | 298 000 | 2 170 000 |
| (120 000–455 000) | (722 000–1 661 000) | (363 000–1 232 000) | (228 000–380 000) | (1 386 000–2 552 000) | (227 000–391 000) | (1 713 000–2 882 000) | |
| **12–60 months** | | | | | | | |
| Studies | 9 | 12 | 8 | 17 | 31 | 15 | 46 |
| Hospital admission rate | 1·6 | 1·6 | 1·5 | 1·6 | 1·5 | 1·7 | 1·5 |
| Number of episodes | 145 000 | 396 000 | 220 000 | 88 000 | 735 000 | 95 000 | 827 000 |
| (50 000–421 000) | (235 000–667 000) | (117 000–435 000) | (67 000–116 000) | (491 000–1 101 000) | (72 000–125 000) | (600 000–1 207 000) | |
| **0–60 months†** | | | | | | | |
| Studies | 16 (4) | 22 (6) | 16 (8) | 51 (28) | 57 (19) | 48 (27) | 105 (46) |
| Hospital admission rate | 3·5 | 6·2 | 6·2 | 6·0 | 5·2 | 6·1 | 5·3 |
| Number of episodes | 411 000 | 1 908 000 | 1 139 000 | 409 000 | 3 163 000 | 413 000 | 3 567 000 |
| (231 000–731 000) | (1 251 000–2 909 000) | (693 000–1 872 000) | (1 019 000–5 240 000) | (2 395 000–4 179 000) | (3 188 000–5 373 000) | (2 856 000–4 634 000) | |

(Table 2 continues on next page)
| Low income | Lower-middle income | Upper-middle income | High income | Developing countries | Industrialised countries | Global* |
|------------|---------------------|--------------------|-------------|----------------------|------------------------|---------|
| 0-3 months |                     |                    |             |                      |                        |         |
| Studies    | 9                   | 7                  | 15          | 9                    | 32                     | 8       | 40       |
| Admission rate | (0.4–14.9) | (1.5–18.0) | (2.4–29.9) | (2.7–40.7) | (3.1–15.4) | (1.4–41.3) | (3.6–15.5) |
| Number of episodes | 15 000 | 90 000 | 82 000 | 42 000 | 211 000 | 31 000 | 252 000 |
| 3-6 months |                     |                    |             |                      |                        |         |
| Studies    | 9                   | 10                 | 15          | 10                   | 35                     | 9       | 44       |
| Admission rate | (0.1–12.4) | (1.1–7.9) | (2.0–17.4) | (1.9–22.9) | (1.9–8.6) | (1.0–21.3) | (2.1–8.6) |
| Number of episodes | 6000 | 50 000 | 56 000 | 26 000 | 122 000 | 18 000 | 144 000 |
| 0-6 months |                     |                    |             |                      |                        |         |
| Studies    | 9                   | 7                  | 15          | 10                   | 32                     | 9       | 41       |
| Admission rate | (0.3–7.8) | (1.5–11.9) | (2.5–23.7) | (3.0–28.6) | (2.5–11.2) | (1.7–26.6) | (2.9–13.3) |
| Number of episodes | 19 000 | 142 000 | 149 000 | 73 000 | 322 000 | 54 000 | 385 000 |
| 6-12 months |                     |                    |             |                      |                        |         |
| Studies    | 9                   | 10                 | 15          | 10                   | 35                     | 9       | 44       |
| Admission rate | (0.2–3.7) | (0.7–5.3) | (0.6–10.8) | (1.4–12.8) | (1.0–4.9) | (0.8–11.1) | (1.2–4.9) |
| Number of episodes | 11 000 | 62 000 | 53 000 | 33 000 | 133 000 | 23 000 | 159 000 |
| 0-12 months |                     |                    |             |                      |                        |         |
| Studies    | 9                   | 11                 | 15          | 10                   | 36                     | 9       | 45       |
| Admission rate | (0.4–6.2) | (1.6–8.7) | (1.7–17.9) | (2.8–20.8) | (2.2–7.9) | (1.7–18.5) | (2.5–8.0) |
| Number of episodes | 42 000 | 245 000 | 214 000 | 120 000 | 509 000 | 88 000 | 606 000 |
| 12-60 months |                     |                    |             |                      |                        |         |
| Studies    | 8                   | 8                  | 9           | 8                    | 26                     | 7       | 33       |
| Admission rate | (<0.05–1.0) | (<0.05–8.0) | (<0.05–19) | (0.1–1.16) | (0.1–0.7) | (0.1–1.4) | (0.1–0.7) |
| Number of episodes | 13 000 | 52 000 | 50 000 | 34 000 | 106 000 | 24 000 | 134 000 |
| 0-60 months |                     |                    |             |                      |                        |         |
| Studies    | 8                   | 8                  | 9           | 8                    | 26                     | 7       | 33       |
| Admission rate | (0.1–1.7) | (0.4–3.3) | (0.4–7.2) | (0.6–1.9) | (0.6–5.9) | (0.6–2.8) | (0.3–4.8) |
| Number of episodes | 56 000 | 406 000 | 385 000 | 159 000 | 395 000 | 102 000 | 911 000 |

Data are n, hospital admission rate per 1000 children per year (UR), or n (UR). Number of studies were rounded to the nearest 1000. RSV=respiratory syncytial virus. UR=uncertainty range. *Global estimates were obtained by summing the numbers of developing and industrialised countries for each of the 1000 samples in the Monte Carlo simulation. †The point estimates and uncertainty range estimates are not necessarily equal to the sum of the estimates by finer age bands, this is because the studies that contributed to different age-group specific estimates were different. ‡Data in parentheses indicate the number of studies with imputed data; comparisons between estimates using imputed data and not using imputed data are presented in the appendix (p 44).

Table 2: Estimates of RSV-associated acute lower respiratory infection hospital admissions in children younger than 5 years by World Bank income regions and development status, 2019

(1–0.2–0.0 million). There was little variation in admission to hospital for RSV-associated acute lower respiratory infection among different income regions, although this rate was lower in low-income countries. The rate of hospital admission for RSV-associated acute lower respiratory infection peaked in children aged 0–3 months across all regions (more specifically at 28 days to 3 months; appendix pp 36–37). Approximately 0.9 million (26%) of 3.6 million hospital admissions for RSV-associated acute lower respiratory infection had hypoxaemia (UR 0.5–1.9 million). In infants aged 0–6 months, we estimated that there were 0.4 million hospital admissions for RSV-associated acute lower respiratory infection with hypoxaemia (0.2–0.8 million).
Within the first six months of life, more than 60% of the RSV-associated acute lower respiratory infection hospital admissions were during the first three months of life (table 2).

The proportion of patients admitted to hospital for acute lower respiratory infection who were positive for RSV was highest in high-income countries for both children aged 0–60 months (29% in high-income countries vs 23–26% in LMICs) and those aged 0–6 months (50% for high-income countries vs 32–33% in LMICs). Among narrower age bands, the proportion of admitted patients with acute lower respiratory infection peaked in children aged 0–3 months (32–51% across different income levels) and then decreased with increasing age (15–24% in children aged 12–60 months across different income levels; appendix p 38). As a sensitivity analysis, we applied these proportion results by age, sex, and development status to external estimates of hospital admissions for acute lower respiratory infection to cross-validate our estimate for hospital admission for RSV-associated acute lower respiratory infection, which yielded an estimated 1.3–4.1 million hospital admissions for RSV-associated acute lower respiratory infection, consistent with our primary point estimate of 3.6 million (appendix p 39).

We estimated that the in-hospital CFR of RSV-associated acute lower respiratory infection ranged from 0.1% (UR 0.1–0.2) in high-income countries to 1.4% (0.6–2.8) in low-income countries among children aged 0–60 months. The regional variation in in-hospital CFR was even more pronounced in children aged 0–6 months. Although the in-hospital CFR remained consistently low in high-income countries across all age groups, there were substantial variations in in-hospital CFR across age groups in developing countries; for example, CFR was highest in children aged 0–3 months (1.1%, UR 0.7–1.8) and lowest in children aged 12–60 months (0.5%, 0.3–1.0) in developing countries. Our stratified analysis by the median study year (which was 2012) suggests that...
## RSV-attributable† deaths (primary measure)

|                      | Low income | Lower-middle income | Upper-middle income | High income | Developing countries | Industrialised countries | Global* |
|----------------------|------------|---------------------|---------------------|-------------|----------------------|--------------------------|---------|
| **0–27 days**        |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 0.8        | 0.7                 | 0.6                 | 0.6         | 0.7                  | 0.6                      | 0.7     |
| Number of deaths     | 2600       | 4700                | 1000                | 200         | 8300                 | 200                      | 8500    |
| **28 days to 6 months** |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 3.8        | 3.6                 | 3.2                 | 2.9         | 3.6                  | 2.8                      | 3.6     |
| Number of deaths     | 10,000     | 22,300              | 4100                | 500         | 36,700               | 500                      | 37,200  |
| **0–6 months**       |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 2.1        | 2.2                 | 1.8                 | 1.3         | 2.1                  | 1.2                      | 2.1     |
| Number of deaths     | 12,600     | 27,000              | 5100                | 700         | 45,000               | 700                      | 45,700  |
| **6–12 months**      |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 2.6        | 2.4                 | 2.1                 | 2.0         | 2.5                  | 1.9                      | 2.5     |
| Number of deaths     | 6300       | 12,500              | 1600                | 100         | 20,500               | 100                      | 20,600  |
| **12–60 months**     |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 1.7        | 1.6                 | 1.4                 | 1.3         | 1.6                  | 1.2                      | 1.6     |
| Number of deaths     | 11,200     | 21,200              | 2400                | 200         | 35,000               | 100                      | 35,100  |
| **0–60 months**      |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 2.0        | 2.0                 | 1.7                 | 1.4         | 2.0                  | 1.3                      | 2.0     |
| Number of deaths     | 30,100     | 60,900              | 9100                | 1000        | 100,500              | 900                      | 101,400 |

## RSV-associated all-cause deaths (secondary measure)

|                      | Low income | Lower-middle income | Upper-middle income | High income | Developing countries | Industrialised countries | Global* |
|----------------------|------------|---------------------|---------------------|-------------|----------------------|--------------------------|---------|
| **0–27 days**        |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 1.8        | 1.7                 | 1.4                 | 1.3         | 1.7                  | 1.3                      | 1.7     |
| Number of deaths     | 5900       | 10,800              | 2300                | 500         | 19,100               | 500                      | 19,600  |
| **28 days to 6 months** |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 8.4        | 8.1                 | 7.0                 | 6.4         | 8.0                  | 6.3                      | 8.0     |
| Number of deaths     | 22,200     | 49,800              | 9200                | 1200        | 81,400               | 1000                     | 82,500  |
| **0–6 months**       |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 4.7        | 4.8                 | 3.9                 | 3.0         | 4.7                  | 2.8                      | 4.6     |
| Number of deaths     | 28,100     | 60,700              | 11,600              | 1700        | 100,500              | 1600                     | 102,000 |
| **6–12 months**      |            |                     |                     |             |                      |                          |         |
| Proportion (%), in all-cause deaths | 5.7        | 5.5                 | 4.8                 | 4.5         | 5.5                  | 4.2                      | 5.5     |
| Number of deaths     | 14,300     | 28,300              | 3500                | 300         | 46,200               | 200                      | 46,400  |

(Table 4 continues on next page)
### Table 4: Estimates (with 95% uncertainty range) of RSV-attributable deaths, and RSV-associated all-cause and acute lower respiratory infection deaths in children younger than 5 years in 2019, by World Bank income regions and development status

| Time Period | Low income | Lower-middle income | Upper-middle income | High income | Developing countries | Industrialised countries | Global* |
|-------------|------------|---------------------|---------------------|-------------|---------------------|------------------------|---------|
| 0–12 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) in all-cause deaths | 5.0        | 5.0                 | 4.1                 | 3.1         | 4.9                 | 2.9                     | 4.9     |
| Number of deaths | 42,300     | 89,000              | 15,000              | 1900        | 146,600             | 1700                    | 148,500 |
| (36,300–50,100) | (69,900–114,600) | (12,300–18,700) | (15,000–2500)       | (126,200–173,400) | (1300–2400) | (128,000–174,900)     |         |
| 12–60 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) in all-cause deaths | 3.9        | 3.7                 | 3.2                 | 3.0         | 3.7                 | 2.8                     | 3.7     |
| Number of deaths | 25,600     | 48,800              | 5400                | 400         | 80,300              | 200                     | 80,600  |
| (21,700–30,800) | (37,800–64,600) | (4400–6800)         | (300–500)           | (67,700–96,400) | (200–300) | (68,000–96,600)       |         |
| 0–60 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) in all-cause deaths | 4.5        | 4.5                 | 3.8                 | 3.1         | 4.4                 | 2.9                     | 4.4     |
| Number of deaths | 6,700      | 137,800             | 20,500              | 2,200       | 226,800             | 200,000                 | 229,000 |
| (58,000–80,900) | (107,600–178,800) | (16,700–25,500)     | (18,500–3000)       | (194,000–269,400) | (15,000–28,000) | (159,000–271,200)     |         |
| RSV-associated acute lower respiratory infection deaths (secondary measure) | | | | |
| 0–27 days |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 7.4        | 7.4                 | 8.3                 | 8.8         | 7.4                 | 8.9                     | 7.4     |
| Number of deaths | 1500       | 2000                | 2000                | <50         | 3800                | <50                     | 3800    |
| (1300–1800) | (1600–2600) | (200–300)           | (<50–<50)           | (3300–4400) | (<50–<50) | (3400–4400)            |         |
| 28 days to 6 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 16.6       | 17.1                | 18.1                | 18.4        | 17.0                | 19.5                    | 17.1    |
| Number of deaths | 15,100     | 36,100              | 6000                | 300         | 57,300              | 200                     | 57,500  |
| (13,500–17,000) | (30,300–43,700) | (5100–7000)         | (300–400)           | (51,100–65,300) | (100–200) | (51,200–65,400)       |         |
| 0–6 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 14.9       | 16.0                | 17.3                | 17.6        | 15.8                | 17.7                    | 15.8    |
| Number of deaths | 16,700     | 38,000              | 6200                | 300         | 61,100              | 200                     | 61,300  |
| (14,800–18,700) | (32,000–46,100) | (5300–7300)         | (300–400)           | (54,500–69,200) | (200–200) | (54,700–69,400)       |         |
| 6–12 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 10.5       | 10.8                | 11.6                | 12.0        | 10.7                | 12.5                    | 10.7    |
| Number of deaths | 9,000      | 17,200              | 2,200               | 100         | 28,500              | 100                     | 28,700  |
| (7800–10,500) | (14,000–21,600) | (1900–2800)         | (100–200)           | (25,000–33,100) | (100–100) | (25,100–33,200)       |         |
| 0–12 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 13.0       | 13.9                | 15.3                | 15.4        | 13.7                | 15.4                    | 13.7    |
| Number of deaths | 25,700     | 55,300              | 8500                | 500         | 89,700              | 300                     | 89,900  |
| (22,500–29,200) | (46,000–67,500) | (7200–10,200)       | (400–600)           | (79,600–102,200) | (200–400) | (79,800–102,400)      |         |
| 12–60 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 7.3        | 7.5                 | 8.2                 | 8.7         | 7.5                 | 8.8                     | 7.5     |
| Number of deaths | 6,300      | 11,200              | 2,000               | 200         | 19,500              | 200                     | 19,700  |
| (5,400–7200) | (9,200–13,900) | (17,000–25,000)     | (200–200)           | (17,200–23,200) | (200–300) | (17,400–22,500)       |         |
| 0–60 months |            |                     |                     |             |                     |                        |         |
| Proportion (%) | 11.3       | 12.2                | 12.6                | 12.6        | 11.7                | 12.0                    | 11.7    |
| Number of deaths | 33,000     | 66,600              | 10,000              | 700         | 109,100             | 500                     | 109,600 |
| (27,900–36,500) | (55,300–81,600) | (8900–12,700)       | (600–800)           | (96,700–124,400) | (400–600) | (97,200–124,900)      |         |

Data are n, proportion (%) in acute lower respiratory infection deaths (UR), or n (UR). Number of deaths were rounded to the nearest 100, except when the estimate was <50. RSV=respiratory syncytial virus. UR-uncertainty range: *Global estimates were obtained by summing the numbers of developing and industrialised countries for each of the 1000 samples in the Monte Carlo simulation. RSV-attributable death is defined as RSV being anywhere in the causal chain of death.*
there was substantial decrease in in-hospital CFR over time among developing countries (0·99%, 0·69–1·45 before 2012 vs 0·54%, 0·31–0·98 after 2012 in children aged 0–60 months) but limited decrease was observed in industrialised countries (0·11%, 0·07–0·16 vs 0·08%, 0·02–0·31 in children aged 0–60 months; appendix p 41).

At the global level, in 2019, we estimated that there were 26 300 (UR 15 100–49 100) RSV-associated acute lower respiratory infection in-hospital deaths in children aged 0–60 months; 13 300 (51%, 6800–28 100) of which occurred in children aged 0–6 months. LMICs accounted for more than 97% of RSV-associated acute lower respiratory infection in-hospital deaths across all age groups in children younger than 60 months (table 3).

To further supplement these RSV-associated morbidty and in-hospital mortality estimates, we also estimated the acute lower respiratory infection morbidity and in-hospital mortality that could be attributable to RSV (appendix p 15). We estimated that in 2019, there were 29·7 million (22·8–40·2 million) acute lower respiratory infection episodes, 3·2 million (2·6–4·2 million) hospital admissions for acute lower respiratory infection, and 21 100 (12 100–39 300) in-hospital deaths for acute lower respiratory infection that could be attributable to RSV in children aged 0–60 months.

For overall RSV deaths, we estimated that 101 400 (2·0%, UR 84 500–125 200) of 52 million all-cause deaths were attributable to RSV in children aged 0–60 months and this proportion was highest in children aged 28 days–6 months (3·6%, 3·0–4·4). Although only 0·7% of all-cause deaths during the neonatal period (age 0–27 days) were attributable to RSV, RSV deaths in neonates still accounted for 19% of the RSV-attributable deaths in the first six months of life. LMICs accounted for more than 97% of the RSV-attributable deaths across all age groups. As a secondary estimate, we computed that there were 229 000 (UR 196 000–271 200) RSV-associated all-cause deaths and 109 600 (97 200–124 900) RSV-associated acute lower respiratory infection deaths in children aged 0–60 months in 2019 (table 4). Taken with the estimated RSV-associated acute lower respiratory infection in-hospital deaths, only 26 300 (26%) of 101 400 RSV-attributable deaths occurred in hospitals in patients aged 0–60 months and 13 300 (29%) of 45 700 RSV-attributable deaths occurred in hospitals in children aged 0–6 months. Only 2300 (18%) of 12 500 RSV-attributable deaths occurred in hospitals in infants aged 0–6 months in low-income countries, and CFR was as high as 6·6% in communities (figure 2).

**Discussion**

In this study, we expanded our existing global RSV disease burden dataset by including 113 new eligible studies from the literature review update and new unpublished data from 51 studies shared through RSV GEN. We estimated that globally in 2019, there were 33·0 million RSV-associated acute lower respiratory infection episodes, 3·6 million RSV-associated acute lower respiratory infection hospital admissions, and 26 300 RSV-associated acute lower respiratory infection in-hospital deaths in children aged 0–60 months. In infants aged 0–6 months, there were 6·6 million RSV-associated acute lower respiratory infection episodes, 1·4 million RSV-associated acute lower respiratory infection hospital admissions, and 26 300 RSV-associated acute lower respiratory infection in-hospital deaths in children aged 0–6 months.
infection hospital admissions, and 13 300 RSV-associated acute lower respiratory infection in-hospital deaths. We highlighted the substantial unmeasured burden of RSV mortality, with one in every 50 deaths in children aged 0–60 months and one in every 28 deaths in children aged 28 days–6 months attributable to RSV. These findings suggest that RSV passive immunisation programmes targeting the first 6 months of life could have a substantial effect on reducing RSV morbidity and mortality burden.

Our estimates of RSV morbidity (including disease burden in the community and hospital) were broadly consistent with our previous estimates for the year 2015.1 The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 201615 reported 10·7 million acute lower respiratory infection hospital admission rates in LMICs, and for children aged 0–6 months, and for children aged 0–6 months, reflecting the fact that access and availability to hospital care is still limited in LMICs. Despite higher incidence in LMICs, a broader definition than that used in GBD 2016 (a narrower definition than that used in GBD 2016), and 33·0 million RSV-associated acute lower respiratory infection episodes (attending or not attending health care, a broader definition than that used in GBD 2016). The estimate of 3·6 million hospital admissions for RSV-associated acute lower respiratory infection in the present study is also broadly consistent with extrapolated global estimates (2·5–4·1 million) from the national estimates for 58 countries.21

In our previous estimates for 2015,1 we had to use imputed rates for children aged 0–6 months due to paucity of data. For example, our previous estimates of RSV-associated acute lower respiratory infection incidence in children aged 0–6 months for low-income and high-income countries were exclusively based on imputed rates from older age groups. Because infant age groups are crucial for RSV immunisation strategy, we made extensive efforts to identify and collect unpublished data on these age groups in this study. For children aged 0–6 months, we included 12 more community-based studies with RSV incidence data, more than double the number of studies in the previous study (22 vs ten); each of the income regions had available RSV data so imputation was not required in this study. Because of the expanded dataset, we could observe a larger gap in RSV disease burden between LMICs and high-income countries in children aged 0–6 months than in children aged 0–60 months. The disproportionately high RSV burden in the younger age groups in LMICs warrants more extensive community case management and effective and affordable immunisation programmes. The gap is even larger when it comes to hospital admission, reflecting the fact that access and availability to hospital care is still limited in LMICs. Despite higher incidence in the community, the RSV-associated acute lower respiratory infection hospital admission rate in LMICs was similar to that in high-income countries for children aged 0–60 months, and for children aged 0–6 months, astonishingly, the hospital admission rate in LMICs was consistently lower than that in high-income countries.

Since our previous estimates for 2015,1 we have improved our methods to develop more robust estimates in our subsequent global disease burden studies for other viral infections.8,10,22 One important change is the use of GLMM framework in place of the conventional random-effects model (REM); compared with REM, GLMM has advantages when handling sparse data (ie, when case or denominator counts are small).23 This helps explain the differences in the RSV-associated acute lower respiratory infection in-hospital deaths between our present and previous estimates, as REM tends to bias CFR estimates upwards, towards 0·5,23 which inflated the CFR estimate for older children in particular. When applying the same model to our present and previous data, there was only moderate difference in the estimates. Nevertheless, the decrease in the in-hospital mortality estimates from previous estimates cannot be attributed entirely to the use of different models. Our stratified analysis (by the study median year, 2012) identified a decrease in in-hospital CFR over time, especially among LMICs, highlighting the overall improvement in quality of care in recent years. We observed some interesting trends for RSV-associated acute lower respiratory infection in-hospital CFR when stratified by age and income regions. Overall, in-hospital CFR of RSV-associated acute lower respiratory infection decreased with increase in income level. This could be due to several reasons. First, the paucity of appropriate care in the form of supportive management (eg, oxygen supplementation and suction of respiratory secretions) in LMICs. Second, differences in health-care accessibility and affordability in LMICs where children are likely to be more severely ill when brought to hospitals. In addition, CFR decreased with age in LMICs but did not change substantially over age in high-income countries; we were unable to observe such trends over age in our previous analysis,3 largely because of REM inflating the CFR estimates in older children. Results from our sensitivity analysis suggest that the gap in in-hospital CFR between LMICs and high-income countries has reduced but is still substantial.

We previously estimated that there were 118200 RSV-associated deaths from acute lower respiratory infection in children aged 0–60 months in 2015, but this was based on limited data, through an indirect excess mortality approach that relied on the statistical correlation between RSV morbidity and crude lower respiratory infection mortality.1 In the present study, we developed new models that could incorporate all the RSV community mortality data that became available in the last 3 years. This has been a major advancement in understanding the previously unrecognised burden of overall RSV mortality in infants. For the first time, we were able to estimate RSV overall mortality burden by narrower age bands and by region. We decided to report RSV-attributable all-cause deaths as the primary estimate and RSV-associated all-cause and
acute lower respiratory infection deaths as secondary estimates in this study, with several considerations. Compared with all-cause death, determination of acute lower respiratory infection as cause of death relied mostly on verbal autopsy; misclassification and recall bias related to verbal autopsy could affect the estimate.\(^\text{14}\) which was also reflected by our finding that RSV-associated acute lower respiratory infection deaths only accounted for 48% of RSV-associated all-cause deaths. Compared with RSV-associated death where RSV was identified in the upper respiratory tract, but not necessarily in the causal chain, using RSV-attributable death is more relevant for understanding the impact of RSV prophylactics on RSV mortality. As the primary measure, we estimated that there were RSV-attributable deaths accounted for 2% of all-cause deaths in children aged 0–60 months. Approximately 45% of these RSV-attributable deaths occurred in the first 6 months of life, with RSV being in the causal chain in about 4% of all-cause deaths for post-neonatal infants. Although not being a common cause of deaths in the neonatal period, RSV was in the causal chain for about 19% of RSV-attributable deaths in children aged 0–6 months. Approximately 45% of these RSV-attributable deaths occurred in the first 6 months of life, with RSV being in the causal chain in about 4% of all-cause deaths for post-neonatal infants. Although not being a common cause of deaths in the neonatal period, RSV was in the causal chain for about 19% of RSV-attributable deaths in children aged 0–6 months. A study\(^\text{15}\) based on global case series of RSV mortality reported a greater proportion of RSV neonatal deaths in community than in hospitals. These findings highlight the need for RSV maternal vaccine or a birth-dose of RSV monoclonal antibody.

Based on the estimates for in-hospital and overall mortality above, we further showed that globally, only 26% of RSV-attributable deaths occurred in hospitals in children aged 0–60 months; that is three deaths in the community for every RSV-associated acute lower respiratory infection death. This proportion is lower than the 50% that we estimated previously with limited data.\(^\text{1}\) The gap between in-hospital and community deaths is even more pronounced in low-income countries, with 19% of the RSV-attributable deaths occurring in hospitals (ie, four deaths in community for every in-hospital death). A study conducted in a remote rural area with poor access to care in India reported that for every RSV in-hospital death, there could be as many as 13 RSV community deaths.\(^\text{2}\) Most of the striking gap between in-hospital and community deaths in low-income settings can be explained by the poor access to care, cost of care, and limited beds in hospitals during an RSV epidemic.\(^\text{3}\) Another explanation is that some of the RSV deaths might be in children with rapidly progressive illness who, initially, do not appear to be severely ill. An RSV community mortality study in urban slums in Buenos Aires, Argentina, showed that home deaths could occur during sleep, with mild bronchiolitis or even without any apparent lung disease.\(^\text{4}\) This justifies our reporting of all-cause deaths over acute lower respiratory infection death for overall deaths estimation.

One of the major differences between in-hospital mortality data and community mortality data included in our study is the time of testing. RSV was often tested upon admission in hospital-based studies, whereas in community mortality studies, only post-mortem samples were tested. It is widely acknowledged that RSV could predispose individuals to secondary bacterial infection,\(^\text{5–10}\) the latter of which could be lethal. Therefore, it is likely that some of the RSV-attributable deaths could not be captured by post-mortem testing alone as RSV would probably be undetectable by the time of testing. An analysis of the Scottish health-care data\(^\text{11}\) suggests that deaths occurring up to 1 month following the initial RSV diagnosis could be attributable to RSV. This suggests that the estimated overall RSV mortality burden in our study could still be an underestimate of the true burden, which might only be quantified by vaccine probe studies. Moreover, some of the community mortality studies were done in under-resourced settings and therefore might not be fully representative of the country. This could affect our estimates if the proportion of RSV in all-cause and acute lower respiratory infection deaths differed by level of deprivation within that country.

Given the disproportionally high burden of RSV morbidity and mortality in children aged 0–6 months, passive immunisation programmes targeting the first 6 months of life could have a substantial effect on reducing RSV disease burden. For example, assuming that RSV passive immunisation could confer 70% protection to infants aged up to 5 months, then this could directly avert up to 864000 RSV-associated acute lower respiratory infection hospital admissions and 26800 RSV-attributable deaths globally per year. Within the first 6 months of life, 60% of the RSV-associated acute lower respiratory infection hospital admissions were during the first 3 months of life. This suggests that RSV immunisation products could still be impactful even with a shorter duration of protection, although they would probably miss the substantial RSV-associated acute lower respiratory infection incidence that only peaked during 3–6 months of age in low-income and lower-middle-income countries. Compared with children aged 0–6 months, the disease burden in children aged 6–12 months was smaller but still substantial, especially for morbidity burden. This suggests that further investment is warranted for RSV prophylactic products targeting this age group.

Our study had several limitations, as discussed previously.\(^\text{1}\) First, heterogeneities in factors such as study setting, exact case definition for acute lower respiratory infection, health-care access and seeking behaviour, eligibility for RSV testing and proportion of specimens tested, and RSV testing assay could affect our estimates, although sensitivity analyses based on the factors above that removed studies with high risks of bias showed broadly consistent estimates (appendix pp 44–48). Second, for both morbidity and mortality estimates, we were constrained by the data to break down the age bands any further or to model the year-on-year changes in the RSV
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...disease burden; for which more data on multi-year changes in RSV morbidity and mortality are warranted. Third, we did not specifically report the burden of RSV-associated acute lower respiratory infection in primary care, such as general practice and outpatient. Fourth, we applied data imputation for estimating the RSV-associated acute lower respiratory infection incidence and hospital admission rates for children aged 0–60 months among studies that did not report data in specific age bands but reported data either overall for children aged 0–60 months or some of the narrower age bands; nonetheless, sensitivity analyses that excluded imputed rates did not yield substantial differences in the estimates. Fifth, the data for RSV overall mortality estimates were still scarce (15 studies) and mostly represented under-resourced settings. Finally, all of our included data were collected before the coronavirus disease 2019 (COVID-19) pandemic; reports from France, Iceland, and Australia showed that children hospitalised for RSV disease in the first wave of RSV epidemics following the onset of the COVID-19 pandemic were older than those in the pre-pandemic period. It is unknown how the COVID-19 pandemic could affect RSV disease burden in the long term. Our estimates could serve as a reference for understanding RSV epidemiology in the context of the ongoing COVID-19 pandemic.

Despite these limitations, our revised estimates are based on a substantially expanded dataset (including the community mortality data) and improved methodology. For the first time, we managed to break down the population of children aged 0–6 months into narrower age bands for both morbidity and mortality estimates that are essential for estimating the impact of RSV prophylactics. These estimates should provide a comprehensive global overview of RSV morbidity and mortality burden in infants and young children. With the numerous RSV prophylactic products in the pipeline, our estimates provide an important baseline profile of RSV disease burden for evaluating their potential clinical impact and cost-effectiveness of public health programmes.

Contributors
YL and HN conceptualised the study. YL led the literature review with contributions from XW and ABP. YL led the data analysis with substantial contributions from XW, YL, HN, and XW led the data interpretation. DMB, MTC, DRF, CJG, SAM, SBO, and EAFS were members of a mortality subgroup that provided critical inputs to the mortality estimates. YL wrote the first draft of the manuscript with inputs from XW and HN. All other authors contributed to collection and analysis of the primary data and data interpretation, and critically reviewed the manuscript. All authors read and approved the final draft of the manuscript. All authors who contributed to primary data analysis accessed and verified the disaggregated data from their local studies, and provided aggregated data for the analysis of this study. YL and HN have full access to and have verified all the aggregated study data provided for the analysis. YL and HN were responsible for the decision to submit the manuscript.

Declaration of interests
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Data sharing
The study data and R codes for the analysis are freely available in Edinburgh DataShare (https://doi.org/10.7488/ds/3138).

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