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Global disease burden of and risk factors for acute lower respiratory infections caused by respiratory syncytial virus in preterm infants and young children in 2019: a systematic review and meta-analysis of aggregated and individual participant data

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Summary

Background Infants and young children born prematurely are at high risk of severe acute lower respiratory infection (ALRI) caused by respiratory syncytial virus (RSV). In this study, we aimed to assess the global disease burden of and risk factors for RSV-associated ALRI in infants and young children born before 37 weeks of gestation.

Methods We conducted a systematic review and meta-analysis of aggregated data from studies published between Jan 1, 1995, and Dec 31, 2021, identified from MEDLINE, Embase, and Global Health, and individual participant data shared by the Respiratory Virus Global Epidemiology Network on respiratory infectious diseases. We estimated RSV-associated ALRI incidence in community, hospital admission, in-hospital mortality, and overall mortality among children younger than 2 years born prematurely. We conducted two-stage random-effects meta-regression analyses accounting for chronological age groups, gestational age bands (early preterm, <32 weeks gestational age [wGA], and late preterm, 32 to <37 wGA), and changes over 5-year intervals from 2000 to 2019. Using individual participant data, we assessed perinatal, sociodemographic, and household factors, and underlying medical conditions for RSV-associated ALRI incidence, hospital admission, and three severity outcome groups (longer hospital stay [>4 days], use of supplemental oxygen and mechanical ventilation, or intensive care unit admission) by estimating pooled odds ratios (ORs) through a two-stage meta-analysis (multivariate logistic regression and random-effects meta-analysis). This study is registered with PROSPERO, CRD42021269742.

Findings We included 47 studies from the literature and 17 studies with individual participant-level data contributed by the participating investigators. We estimated that, in 2019, 1 650 000 (95% uncertainty range [UR] 1 350 000–1 990 000) RSV-associated ALRI episodes, 533 000 (385 000–730 000) RSV-associated hospital admissions, 3050 (1080–8620) RSV-associated in-hospital deaths, and 26 760 (11 190–46 240) RSV-attributable deaths occurred in preterm infants worldwide. Among early preterm infants, the RSV-associated ALRI incidence rate and hospitalisation rate were significantly higher (rate ratio [RR] ranging from 1·69 to 3·87 across different age groups and outcomes) than for all infants born at any gestational age. In the second year of life, early preterm infants and young children had a similar incidence rate but still a significantly higher hospitalisation rate (RR 2·26 [95% UR 1·27–3·98]) compared with all infants and young children. Although late preterm infants had RSV-associated ALRI incidence rates similar to that of all infants younger than 1 year, they had higher RSV-associated ALRI hospitalisation rate in the first 6 months (RR 1·93 [1·11–3·26]). Overall, preterm infants accounted for 25% (95% UR 16–37) of RSV-associated ALRI hospitalisations in all infants of any gestational age. RSV-associated ALRI in-hospital case fatality ratio in preterm infants was similar to all infants. The factors identified to be associated with RSV-associated ALRI incidence were mainly perinatal and sociodemographic characteristics, and factors associated with severe outcomes from infection were mainly underlying medical conditions including congenital heart disease, tracheostomy, bronchopulmonary dysplasia, chronic lung disease, or Down syndrome (with ORs ranging from 1·40 to 4·23).

Interpretation Preterm infants face a disproportionately high burden of RSV-associated disease, accounting for 25% of RSV hospitalisation burden. Early preterm infants have a substantial RSV hospitalisation burden persisting into the second year of life. Preventive products for RSV can have a substantial public health impact by preventing RSV-associated ALRI and severe outcomes from infection in preterm infants.

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Introduction

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infection (ALRI) in children younger than 5 years.[1] In 2019, 33·0 million episodes of RSV-associated ALRI, 3·6 million RSV-associated ALRI hospital admissions, and 101 400 deaths in children younger than 5 years occurred worldwide; over half of severe episodes occurred in the first year of life.[2] Children born prematurely (ie, with a gestational age of less than 37 weeks), which account for more than one in every ten livebirths globally (ranging from 9–13% across regions),[3] are particularly vulnerable to RSV-associated ALRI and severe disease because they have a less mature immune system, smaller airways, diminished maternal antibody transfer, and higher risk of bronchopulmonary dysplasia than term children.[4,5]

The past 5 years have brought important advances in the development of novel RSV infection prophylaxis products to protect infants during their first RSV season, as exemplified by the regulatory approval of nirsevimab, an anti-RSV monoclonal antibody with an extended half-life, and of a bivalent RSV prefusion F vaccine (known as RSV preF) for maternal immunisation.[6] However, the phase 3 trial results of the maternal RSV vaccine (administered antenatally at 32–36 weeks gestational age [wGA]) were not powered to estimate efficacy for preterm infants (which might be lower because antibody transfer is inversely correlated with gestational age).[7]

As governments begin to consider including RSV vaccines in national immunisation programmes, understanding the global disease burden of (and the risk factors for) RSV-associated ALRI in preterm infants and young children is essential for the design of an optimal RSV prophylaxis strategy. To help inform policy decisions on RSV prophylaxis strategy, financing, and prioritisation, we conducted this study with the aim of understanding the global disease burden and risk factors of RSV-associated ALRI in prematurely born children up to the age of 2 years (henceforth referred to as preterm infants and young children) by systematically analysing aggregated and individual participant data on RSV infection epidemiology.

Methods

Search strategy and selection criteria

The protocol of this systematic review and meta-analysis has been published elsewhere.[8] Definitions used in this

Research in context

Evidence before this study

Preterm children are at higher risk of infection with respiratory syncytial virus (RSV) and of severe outcomes from infection than children born at term. We searched PubMed for studies published between Jan 1, 1995, and Jun 30, 2023, reporting global or regional estimates of RSV-associated morbidity and mortality in preterm infants and 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*") AND ("prematur*" OR "preterm*")". No language restrictions were applied to this search. We identified regional reports on the burden of hospitalisation due to RSV-associated acute lower respiratory infection (ALRI) focusing primarily on Europe and other high-income countries. Global systematic reviews on RSV-associated hospitalisation and mortality burden were identified but they did not collect individual participant-level data and conducted only limited data synthesis to quantify RSV-associated disease burden among preterm infants.

Added value of this study

We collected both aggregated data from published literature and individual participant-level data shared by international collaborators, including 13 studies from low-income and middle-income countries. We found that early preterm infants (ie, those born before 32 weeks of gestation) had higher rates of RSV-associated ALRI incidence and hospitalisation than the general infant population, and that the higher risk of hospitalisation persisted into the second year of life. Late-preterm (ie, those born between 32 weeks and 37 weeks of gestation) infants had a higher RSV-associated ALRI hospitalisation rate than the general infant population in the first 6 months of life. Overall, preterm infants accounted for a quarter of RSV-associated ALRI hospitalisations in all infants. The analysis of individual participant-level data showed little overlap between factors identified to be associated with ALRI caused by RSV (primarily perinatal and sociodemographic characteristics) and factors associated with severe outcomes upon admission (primarily pre-existing medical conditions, such as congenital heart disease, tracheostomy, bronchopulmonary dysplasia, chronic lung disease, and Down syndrome).

Implications of all the available evidence

Preterm infants face a disproportionally high burden of RSV-associated ALRI in the first year of life and account for a quarter of RSV-associated hospitalisations in all infants. Early preterm infants have a particularly high burden of hospitalisation due to RSV-associated ALRI that can persist into the second year of life. These estimates, together with the identified risk factors for severe outcomes from RSV infection, provide important evidence for the optimisation of strategies for prevention and clinical management of RSV-associated ALRI in preterm infants and young children.

report were consistent with those in the protocol. Briefly, we used the 2014 revised WHO Integrated Management of Childhood Illnesses definitions to define ALRI in community settings, and a physician-confirmed diagnosis of ALRI (pneumonia or bronchiolitis) in hospital settings. We defined RSV-associated ALRI as ALRI with laboratory-confirmed RSV infection. We categorised preterm births as early preterm (less than 32 wGA) or late preterm (32 to less than 37 wGA) on the basis of the WHO definition[9] (although we were not able to analyse births at less than 28 wGA and from 28 wGA to less than 32 wGA as per WHO definition due to data scarcity). The overall methodology flowchart of the study is shown in the appendix (p 3).

We searched MEDLINE, Embase, and the Global Health database for studies published between Jan 1, 1995, and Dec 31, 2021, that reported RSV-associated morbidity and mortality burden estimates among prematurely born children younger than 2 years for the year of 2019 or before, using a combination of search terms and related words: "RSV" AND "acute lower respiratory infections" AND "burden" AND "children with prematurity". No constraints on language were applied. Details of the search strategy, eligibility criteria, and data extraction template can be found in the appendix (pp 4–7) and the published protocol.[8] The literature screening and extraction was conducted independently by two groups of reviewers (group 1 BW-S; group 2 ES and XW), with disagreements resolved through discussion within the review team members (XW, YL, TS, BW-S, ES, and HN).

We invited the lead investigators of eligible studies identified from the literature review and investigators within the Respiratory Virus Global Epidemiology Network[2,10–12] to contribute with individual participant data to this work. Details of individual participant datasets included in the study can be found in the appendix (p 8). We collected general information regarding the participants, common risk factors for RSV infection if available (ie, number of other children younger than 5 years in the household, biomass fuel use, maternal smoking during pregnancy, household smoking, maternal HIV infection status, antiretroviral therapy use during pregnancy, and socioeconomic status), health-care resource use for hospital-based studies (ie, duration of hospital stay, use of supplemental oxygen, and use of mechanical ventilation or admission to an intensive care unit), and underlying medical conditions (appendix pp 9–10). Each dataset was cleaned and checked for completeness by YM and BC. Any discrepancies and unreasonable values were flagged and clarifications were sought from the responsible investigators.

All included studies were individually assessed for quality using a predesigned assessment form by two groups of reviewers independently (group 1: BW-S; group 2: XW and YL). An overall quality assessment score was calculated from the mean scores of the seven questions on study design, participants, case definition, sampling strategy for RSV testing, diagnostic test for RSV, confirmation of gestational age, and adjustment for health-care use (for studies reporting hospital admission rate). The overall score ranged between 0 (lowest quality) and 1 (highest quality). More details on quality assessment can be found in the appendix (p 11).

Data analysis

As predefined in the published protocol,[8] we estimated RSV-associated ALRI incidence rate (in community), hospital admission rate, and in-hospital case fatality ratio in preterm infants by region, country development status,[13] World Bank Income group[14] where possible, and globally. The primary age group for reporting was 0 months to less than 12 months. Other age groups, namely, 0 months to less than 6 months, 6 months to less than 12 months, and 12 months to less than 24 months were considered as secondary age groups. For each age group, we considered less than 37 wGA as the primary gestational age band, and less than 32 wGA and 32 to less than 37 wGA were classified as secondary gestational age bands.

The data from individual studies were synthesised through a two-stage meta-analysis framework.[15] In the first stage, data were aggregated in each of the individual participant datasets, including numerators and denominators for calculation of incidence rate, hospital admission rate, and in-hospital case fatality ratio. In the second stage, the aggregated data from individual participant data were combined with the data extracted from the published literature; a generalised linear mixed-effects model meta-regression[16] was then conducted to produce summary estimates of RSV-associated ALRI incidence rate, hospital admission rate, and in-hospital case fatality ratio separately for each region; covariates used in the meta-regression included age group, gestational age band, and changes over 5-year intervals (ie, 2000–04, 2005–09, 2010–14, and 2015–19). The predictive values of the meta-regression models conditioning on age group, gestational age band, and time interval were used as estimates for the corresponding age group, gestational age band, and time period. The number of RSV-associated ALRI community episodes and hospital admissions was calculated through application of the rate estimate for 2015–19 to the population estimates of preterm infants and young children in 2019 (based on the 2019 total population[17] and the proportion of preterm live births[3]). The number of RSV-associated ALRI in-hospital deaths was calculated through application of the in-hospital case fatality ratio estimates to the estimated number of hospital admissions obtained above.

For exploratory analyses, we selected studies that reported preterm children from 32 wGA to less than 35 wGA and from 35 wGA to less than 37 wGA separately

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See Online for appendix

and estimated the incidence rate ratio (RR) and hospital admission RR between these two gestational age bands. An ad-hoc exploratory analysis was also conducted to compare the prevalence of comorbidities between different age groups and gestational age bands separately by country development status. We conducted three sets of sensitivity analyses: the first set included only studies that reported the exact gestational age bands as applied in this study (eg, studies reporting preterm children from 32 wGA to less than 36 wGA were not included); the second set excluded studies with low quality assessment scores (overall score of less than 0·6); and the third set removed data imputation by conducting simple random-effects meta-analysis using only studies that contributed data to the specific age group, gestational age band, and the time period.

Furthermore, we compared the global RSV-associated morbidity and mortality burden in 2019 between preterm children estimated from this study and all children (ie, preterm and term children) from our previously published study.[2] We calculated the proportion of RSV-associated ALRI episodes, hospitalisations, and in-hospital deaths in preterm children compared with all children. We also calculated the ratio of RSV-associated ALRI incidence rate, ratio of RSV-associated ALRI hospitalisation rate, and ratio of RSV-associated ALRI in-hospital case fatality ratio between preterm children and all children. As an ad-hoc exploratory analysis, we also estimated the overall (ie, in-hospital and out-of-hospital) RSV-attributable mortality in preterm infants by multiplying the proportion of preterm infants in RSV-attributable infant mortality from the Child Health and Mortality Prevention Surveillance (CHAMPS) Network[18] with the previously published estimated RSV-attributable deaths in the general infant population.[2]

As in our previously published study,[2] for estimates derived from multiple meta-regression models (eg, when estimating the global number of RSV-associated ALRI episodes and hospitalisations and the number of RSV-associated ALRI in-hospital deaths), the uncertainty range (UR) for the estimates was based on 1000 Monte Carlo samples of each of the model estimates from log-normal distributions, with 2·5th percentile and 97·5th percentile defining the lower and upper bounds. When comparisons of estimates were made between preterm children and all children (as previously reported[2]), all calculations were conducted for each of the 1000 samples to avoid artificially inflating the uncertainty.

We assessed factors associated with risk of RSV-associated ALRI episodes (in community) and hospital admission in the first year of life, separately, using individual participant datasets through a two-stage meta-analysis framework. In the first stage, a multivariate logistic regression model was conducted within each individual participant dataset to assess the association between different factors of interest and the occurrence of RSV-associated ALRI community episodes and hospital admission. We followed a so-called base-model approach for selection of variables to be included in the regression model: first, a list of base factors known to be associated with the outcome of interest were selected a priori; second, a base model was fitted using all base factors as covariates to evaluate the preselected base factors; and third, exploratory models that added one of the additional factors (referred to as exploratory factors) to the base model at each time were fitted to evaluate other available factors (other than based factors). For base factors known to be associated with ALRI caused by RSV, we selected the following on the basis of existing literature: sex, gestational age (less than 32 wGA, and 32 wGA to less than 37 wGA), birth month relative to the local RSV season (within 3 months before the peak, within 3 months after the peak, and other interseasonal months), maternal smoking during pregnancy, and the number of other children younger than 5 years in the household (one, two, or more).[19,20] In the second stage, the regression coefficient for each factor (including base and exploratory factors) was pooled through random-effects meta-analysis across datasets. In the exploratory analysis, we assessed the risk of RSV-associated ALRI community episodes and hospital admission for each week of gestational age, from 28 wGA to 36 wGA.

We applied the same two-stage meta-analysis framework to assess factors associated with severe outcomes from RSV-associated ALRI requiring hospital admission. Three different outcomes were assessed separately: long hospital stay (defined as a length of hospital stay of more than 4 days, on the basis of the reported median length of stay in a global systematic review[21]), supplemental oxygen administration during hospital stay, and a composite endpoint of receipt of mechanical ventilation or admission to the intensive care unit. Of note, mortality could not be considered as an outcome as predefined in the published protocol[8] due to sparse mortality data in the individual participant datasets. Because most of the datasets had data available for children older than 1 year (in addition to the predefined infant age groups), we decided to extend the analysis to children younger than 5 years with appropriate adjustment for age-specific effects in the model.

We followed the same so-called base-model approach for selection of variables to include in the regression model. The base factors (identified from published systematic review[22]) included gestational age (less than 32 wGA and 32 wGA to less than 37 wGA), chronological age (less than 6 months, 6 months to less than 12 months, 12 months to less than 24 months, and 24 months to less than 59 months), and congenital heart disease. We conducted subgroup analysis to evaluate these variables separately in the less than 32 wGA and 32 wGA to less than 37 wGA groups. In exploratory analyses, we assessed the risk of severe outcomes from RSV-associated ALRI requiring hospital admission for each week of gestational age, from 28 wGA to 36 wGA;

we also assessed the risk at each month of chronological age for the first year of life.

All data analyses were conducted using R (version 4.1.2). Package metafor (version 3.0.2) was used for the meta-analysis and package ggplot2 (version 3.3.5) was used for the production of figures.

Ethics approval for individual studies was obtained from local ethics committees by the respective lead investigators. The present study used de-identified data for secondary analysis. The need for additional ethics approval for this analysis was dispensed with by Usher Research Ethics Group at the University of Edinburgh and the Nanjing Medical University Research Ethics Committee. This systematic review and meta-analysis was registered with PROSPERO, CRD42021269742.

Role of the funding source

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

Results

3302 records were identified through the systematic review of the literature, of which 177 records were considered for full-text review; of these, 47 studies met our eligibility criteria and were included in the analysis. With the addition of 17 studies with individual participant data shared by collaborators, ranging from 111 participants to 19 336 participants per individual dataset (providing data from a total of 42 374 participants), the total number of included studies was 64 (figure 1; appendix p 12). Of the 64 studies, three studies (5%) reported data from low-income and lower-middle-income countries (two studies with individual participant data); ten studies (17%) reported data from upper-middle-income countries (five studies with individual participant data); and 52 studies (81%) reported data from high-income countries (ten studies with individual participant data). Detailed study-level information and quality assessment results are in the appendix (pp 13–21).

Decreasing incidence rates of RSV-associated ALRI in preterm infants between 2000 and 2019 were observed in both developing and industrialised[13] countries (appendix p 22). In 2019, there were 1650000 (95% UR 1350000–1990000) episodes of RSV-associated ALRI episodes in the community in preterm infants aged 0 months to less than 12 months, with about 1540000 (93%) occurring in developing countries (table 1). The incidence rate was consistently higher in infants born before 32 wGA than in infants born between 32 wGA and less than 37 wGA (table 1); in infants born between 32 wGA and less than 37 wGA, the incidence rate was lower in those born between 35 wGA and less than 37 wGA than in those born between 32 wGA and less than 35 wGA, but the difference was not significant (appendix p 26). Sensitivity analyses yielded generally similar estimates (appendix pp 47, 50).

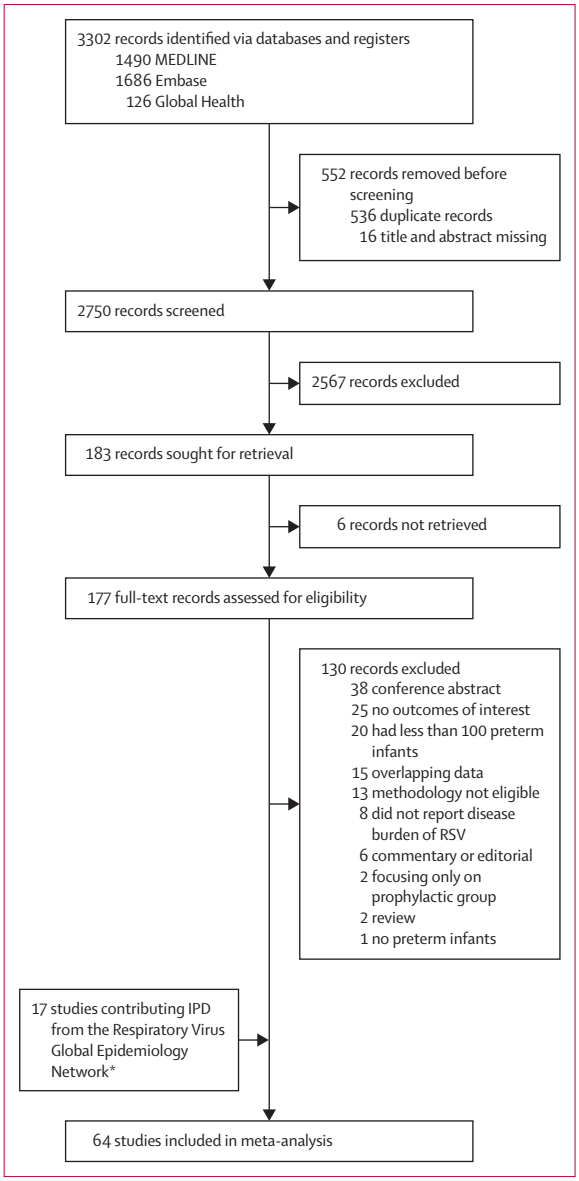


Figure 1: **PRISMA flow diagram of included studies**
IPD=individual participant data. RSV=respiratory syncytial virus. *Details of the IPD are available in the appendix (p 8).

Decreasing hospitalisation rates due to RSV-associated ALRI between 2000 and 2019 were also observed, particularly in developing countries (appendix p 23). Globally, in 2019, there were 533000 (95% UR 385000–730000) RSV-associated ALRI hospital admissions of preterm infants aged 0 months to less than 12 months, with about 92% (493000) occurring in developing countries (table 2). Across all regions, hospitalisation rates over age decreased consistently in the period of 2000–19; hospitalisation rates were also consistently higher in infants born before 32 wGA than in infants born between 32 wGA and less than 37 wGA

	Developing countries	Industrialised countries	Global*
Data source†	4 studies (28 data points‡)	6 studies (17 data points‡)	10 studies (45 data points‡)
I^2	0·0	0·0	..
Infants born before 37 wGA			
Aged 0 months to <6 months			
Incidence rate	128·8 (105·5–157·3)	74·0 (18·3–298·8)	126·1 (101·8–157·7)
Number of episodes	863 000 (706 000–1053 000)	42 000 (10 000–168 000)	915 000 (739 000–1 145 000)
Aged 6 months to <12 months			
Incidence rate	86·3 (65·5–113·7)	261·8 (137·9–497·0)	100·8 (76·2–131·2)
Number of episodes	578 000 (438 000–761 000)	147 000 (78 000–280 000)	732 000 (553 000–952 000)
Aged 0 months to <12 months			
Incidence rate	115·3 (94·1–141·3)	88·5 (68·7–113·8)	113·4 (93·2–136·9)
Number of episodes	1 544 000 (1 260 000–1 892 000)	100 000 (77 000–128 000)	1 646 000 (1 352 000–1 987 000)
Aged 12 months to <24 months			
Incidence rate	47·2 (31·7–70·3)	61·2 (15·1–247·7)	49·5 (32·8–75·8)
Number of episodes	630 000 (423 000–937 000)	70 000 (17 000–282 000)	717 000 (474 000–1 096 000)
Infants born between 32 wGA and <37 wGA, aged 0 months to <12 months			
Incidence rate	99·6 (78·9–125·9)	71·4 (48·9–104·0)	97·7 (77·7–121·4)
Number of episodes	1 130 000 (895 000–1 428 000)	68 000 (47 000–99 000)	1 201 000 (955 000–1 493 000)
Infants born before 32 wGA, aged 0 months to <12 months			
Incidence rate	150·1 (114·4–197·0)	140·8 (55·3–358·3)	150·9 (114·3–195·1)
Number of episodes	310 000 (236 000–406 000)	24 000 (10 000–62 000)	337 000 (255 000–436 000)

Data are rate per 1000 people per annum (95% CI) for incidence rates and n (95% uncertainty range) for number of episodes. Incidence rates are per 1000 infants and young children per year. Point estimates and uncertainty range estimates are not necessarily equal to the sum of the estimates by finer age groups or by finer gestational age bands because the studies contributing to these estimates were different. wGA=weeks gestational age. *Global estimates were obtained by summing the numbers of developing and industrialised countries[33] for each of the 1000 samples in the Monte Carlo simulation. †Detailed information on individual studies that contributed to the analysis can be found in the appendix (p 6). ‡A study could contribute data to more than one gestational band and more than age group. Each combination of gestational band and age group is considered a data point.

Table 1: **Incidence rates and number of episodes of respiratory syncytial virus-associated acute lower respiratory infection in preterm infants and young children younger than 2 years in 2019, by country development status**

(table 2). Within those born between 32 wGA and less than 37 wGA, hospitalisation rates were significantly lower in infants born between 35 wGA and less than 37 wGA than in infants born between 32 wGA and less than 35 wGA for children aged 0 months to less than 6 months and 6 months to less than 12 months, but not for children aged 12 months to less than 24 months (appendix p 26). Estimates from sensitivity analyses were generally similar to those from the main analysis, with a few exceptions: lower estimates were observed in studies from low-income or lower-middle income countries that reported the exact gestational age bands (appendix p 48); higher estimates were observed in studies from high-income and industrialised countries with lower quality assessment scores (<0·6; appendix p 51).

The in-hospital case fatality ratio of RSV-associated ALRI among preterm infants decreased substantially in developing countries over time (appendix p 25), from 5·4% (95% UR 2·6–10·1%) in 1995–99 to 0·6% (0·2–1·2%) in 2015–19, whereas the case fatality ratio in industrialised countries remained low over the past 20 years (0·1% [0·02–0·5] in 1995–99 and 0·7% [0·3–1·6%] in 2015–19). Globally, in 2019, there were 3050 (95% UR 1080–8620) in-hospital deaths associated with RSV-associated ALRI, with 2700 (88·5%) occurring in developing countries. The case fatality ratio was higher in younger infants (aged 0 months to less than 6 months) and early preterm infants. The sensitivity analysis including only studies that reported the exact gestational age bands yielded higher case fatality ratio estimates in industrialised countries, whereas the sensitivity analysis excluding studies with lower quality scores had generally lower case fatality ratio estimates in both developing and industrialised countries (appendix pp 49, 52). By analysing the CHAMPS data on overall mortality, we found that infants born prematurely accounted for 40% (17–65%) of RSV-attributable infant mortality, which equates to 26 760 (11 190–46 240) overall RSV-attributable deaths globally in 2019.

We further compared the estimates for preterm infants and young children with those for all children[2] (table 3; appendix pp 27–28). Although preterm infants overall had similar incidence rates of RSV-associated ALRI when compared with all infants, the incidence rate for early preterm infants was significantly higher than that in all infants (incidence RR 1·74 [95% UR 1·08–2·86] in infants aged 0 months to less than 6 months; 1·69 [1·01–3·03] in infants aged 6 months to less than 12 months). Early preterm infants and young children also had significantly higher hospitalisation rates for

	Low income or lower-middle income	Upper-middle income	High income	Developing country	Industrialised country	Global*
Data source†	2 studies (24 data points‡)	5 studies (40 data points‡)	32 studies (88 data points‡)	10 studies (72 data points‡)	31 studies (82 data points‡)	41 studies (154 data points‡)
I^2	0·0	38·2	98·8	82·4	98·9	..
Infants born before 37 wGA						
Aged 0 months to <6 months						
Hospital admission rate	21·2 (15·9–28·2)	116·6 (83·2–163·4)	40·9 (30·3–55·1)	51·1 (33·9–77·2)	42·5 (31·2–57·9)	50·5 (34·3–73·8)
Number of episodes	106 000 (80 000–141 000)	200 000 (143 000–281 000)	22 000 (16 000–29 000)	342 000 (227 000–517 000)	24 000 (18 000–33 000)	366 000 (249 000–536 000)
Aged 6 months <12 months						
Hospital admission rate	8·8 (6·3–12·2)	28·5 (18·4–44·3)	24·9 (17·4–35·5)	18·9 (12·1–29·5)	23·3 (16·0–33·9)	19·3 (12·8–28·8)
Number of episodes	44 000 (32 000–61 000)	49 000 (32 000–76 000)	13 000 (9000–19 000)	126 000 (81 000–197 000)	13 000 (9000–19 000)	140 000 (93 000–209 000)
Aged 0 months to <12 months						
Hospital admission rate	14·1 (10·7–18·6)	68·0 (51·2–90·2)	33·6 (25·3–44·7)	36·8 (26·1–51·9)	34·3 (25·7–45·7)	36·7 (26·5–50·3)
Number of episodes	142 000 (108 000–187 000)	233 000 (176 000–310 000)	36 000 (27 000–47 000)	493 000 (350 000–695 000)	39 000 (29 000–51 000)	533 000 (385 000–730 000)
Aged 12 months to <24 months						
Hospital admission rate	2·8 (1·9–4·0)	7·4 (4·3–12·7)	13·9 (10·0–19·3)	6·4 (3·9–10·4)	13·7 (9·7–19·2)	7·0 (4·6–10·6)
Number of episodes	28 000 (19 000–40 000)	26 000 (15 000–44 000)	15 000 (11 000–21 000)	85 000 (52 000–138 000)	16 000 (11 000–22 000)	101 000 (66 000–153 000)
Infants born between 32 wGA and <37 wGA, aged 0 months to <12 months						
Hospital admission rate	12·7 (9·5–16·8)	51·5 (37·5–70·8)	29·3 (22·7–37·8)	28·1 (19·3–40·8)	29·8 (22·9–38·8)	28·3 (20·0–39·7)
Number of episodes	108 000 (81 000–143 000)	150 000 (109 000–206 000)	26 000 (20 000–34 000)	319 000 (219 000–463 000)	28 000 (22 000–37 000)	348 000 (246 000–488 000)
Infants born before 32 wGA, aged 0 months to <12 months						
Hospital admission rate	18·9 (13·5–26·6)	114·8 (82·0–160·9)	51·6 (38·4–69·4)	57·2 (39·5–82·8)	50·5 (36·8–69·3)	56·8 (40·0–79·7)
Number of episodes	29 000 (21 000–41 000)	61 000 (43 000–85 000)	8000 (6000–11 000)	118 000 (82 000–171 000)	9000 (6000–12 000)	127 000 (90 000–178 000)

Data are rate per 1000 people per annum (95% CI) for hospital admission rate and n (95% uncertainty range) for number of episodes. Point estimates and uncertainty range estimates are not necessarily equal to the sum of the estimates by finer age groups or by finer gestational age bands because the studies contributing to these estimates were different. wGA=weeks gestational age. *Global estimates were obtained by summing the numbers of developing and industrialised countries for each of the 1000 samples in the Monte Carlo simulation. †Detailed information on individual studies that contributed to the analysis is in the appendix (pp 7–9). ‡A study could contribute data to more than one gestational band and more than age group. Each combination of gestational band and age group is considered a data point.

Table 2: **Estimates of respiratory syncytial virus-associated acute lower respiratory infection hospital admissions in preterm infants and young children younger than 2 years in 2019 by World Bank income regions and country development status**

RSV-associated ALRI than did all children in both the first year and second year of life (hospitalisation RR 3·87 [95% UR 2·23–6·55] in infants aged 0 months to less than 6 months; 2·95 [1·69–5·14] in infants aged 6 months to less than 12 months; and 2·26 [1·27–3·98] in children aged 12 months to less than 24 months). Late preterm infants had significantly higher hospitalisation rates for RSV-associated ALRI than did all infants in the first 6 months of life (hospitalisation RR 1·93 [95% UR 1·11–3·26]). Overall, preterm infants accounted for 25% (95% UR 16–37) of hospitalisations due to RSV-associated ALRI in all infants of any gestational age (appendix p 27).

Maternal smoking during pregnancy (odds ratio [OR] 1·68 [95% CI 1·03–2·73]), having two or more children younger than 5 years in the household (1·80 [1·06–3·04]), and multiple births (1·71 [1·00–2·93]) were independent risk factors for RSV-associated ALRI in the community; these factors had similar, non-significant OR estimates for RSV-associated ALRI hospitalisation (ranging from 1·26 to 6·55). Compared with infants born before 32 wGA, infants born between 32 wGA and less than 37 wGA had a lower risk of RSV-associated ALRI in the community (OR 0·57 [0·40–0·81]; figure 2). Compared with birth during interseasonal months, infants born within 3 months before the RSV peak had a higher risk of RSV-associated ALRI episodes in community and hospitalisation; infants born within 3 months after the RSV peak had a lower risk (figure 2). Based on two studies

	Preterm infants		All infants[2]
	Born before 32 wGA	Born between 32 wGA and <37 wGA	
Respiratory syncytial virus-associated acute lower respiratory infection in the community			
Infants aged 0 months to <6 months			
Incidence rate	167·0 (124·6–232·8)	108·7 (86·0–138·1)	96·3 (67·9–142·6)
Incidence rate ratio	1·74 (1·08–2·86)	1·14 (0·72–1·79)	Ref
Number of episodes	187 000 (139 000–260 000)	668 000 (529 000–849 000)	6 554 000 (4 620 000–9 702 000)
Proportion of episodes	3% (2–5)	10% (7–16)	Ref
Infants aged 6 months to <12 months			
Incidence rate	138·9 (95·0–218·9)	86·2 (63·3–114·8)	82·6 (60·8–116·9)
Incidence rate ratio	1·69 (1·01–3·03)	1·05 (0·68–1·67)	Ref
Number of episodes	155 000 (106 000–245 000)	530 000 (389 000–706 000)	5 619 000 (4 135 000–7 953 000)
Proportion of episodes	3% (2–5)	9% (6–15)	Ref
Infants aged 12 months to <24 months			
Incidence rate	66·6 (41·7–111·9)	42·6 (27·8–66·0)	59·4 (43·4–84·6)
Incidence rate ratio	1·13 (0·63–2·12)	0·72 (0·41–1·26)	Ref
Number of episodes	148 000 (93 000–249 000)	522 000 (340 000–808 000)	8 077 000 (5 891 000–11 491 000)
Proportion of episodes	2% (1–3)	6% (4–11)	Ref
Respiratory syncytial virus-associated acute lower respiratory infection hospitalisations			
Infants aged 0 months to <6 months			
Hospital admission rate	78·1 (52·4–115·5)	38·9 (26·1–57·5)	20·2 (14·9–29·1)
Hospital admission rate ratio	3·87 (2·23–6·55)	1·93 (1·11–3·26)	Ref
Number of episodes	87 000 (59 000–129 000)	239 000 (160 000–353 000)	1 376 000 (1 017 000–1 982 000)
Proportion of episodes	6% (4–11)	17% (10–29)	Ref
Infants aged 6 months to <12 months			
Hospital admission rate	29·8 (19·6–45·0)	14·9 (9·8–22·5)	10·0 (7·4–14·3)
Hospital admission rate ratio	2·95 (1·69–5·14)	1·48 (0·84–2·56)	Ref
Number of episodes	33 000 (22 000–50 000)	92 000 (60 000–138 000)	683 000 (507 000–973 000)
Proportion of episodes	5% (3–8)	13% (8–23)	Ref
Infants aged 12 months to <24 months			
Hospital admission rate	10·7 (7·0–16·5)	5·4 (3·6–8·3)	4·7 (3·4–6·9)
Hospital admission rate ratio	2·26 (1·27–3·98)	1·14 (0·65–2·00)	Ref
Number of episodes	24 000 (16 000–37 000)	67 000 (44 000–102 000)	645 000 (468 000–937 000)
Proportion of episodes	4% (2–7)	10% (6–18)	Ref

Data are rate ratio (95% CI) for incidence rate ratio and hospital admission rate ratio, n (95% uncertainty range) for number of episodes, rate per 1000 people per annum (95% CI) for incidence rate and hospital admission, and % (95% uncertainty range). Incidence rate and hospital admission rate are per 1000 infants and young children per year. The uncertainty range f rate ratio and proportion of episodes was calculated based on the underlying individual 1000 Monte Carlo samples of the original rate and episode estimates. Ref=reference. wGA=weeks gestational age.

Table 3: **Global burden of infections in community and hospitalisations due to respiratory syncytial virus-associated acute lower respiratory in preterm infants and all infants younger than 2 years**

(from Singapore [Yung C F, unpublished] and Spain [Figueras-Aloy J, unpublished]), passive immunisation of infants with palivizumab for RSV prophylaxis reduced the risk of hospitalisation due to RSV-associated ALRI (OR 0·25 [0·11–0·59]; figure 2). Male sex, living with smokers in the household, and bronchopulmonary dysplasia were not found to be associated with RSV-associated ALRI community episodes or hospitalisation (figure 2).

Underlying medical conditions, namely congenital heart disease, tracheostomy, bronchopulmonary dysplasia, chronic lung disease, and Down syndrome, were all consistently associated with higher risks of all three severe outcomes from RSV-associated ALRI requiring hospital admission (longer hospital stay, supplemental oxygen administration, and mechanical ventilation or intensive care unit admission), although not all estimates were significant (figure 3). Among these underlying medical conditions, the OR point estimates for longer hospital stay ranged from 1·64 (95% CI 1·03–2·61) for chronic lung disease to 2·75 (1·87–4·05) for congenital heart disease; the OR point estimates for use of supplemental oxygen ranged from 1·45 (1·03–2·05) for bronchopulmonary dysplasia to 2·14 (1·59–2·87) for chronic lung disease; and the OR point estimates for mechanical ventilation or intensive care unit admission

ranged from 1·40 (0·90–2·17) for Down syndrome to 4·23 (1·22–14·61) for paediatric tracheostomy (figure 3). Higher chronological age and gestational age were associated with lower risks for severe outcomes from infection (figure 3), which were also confirmed in exploratory analyses using a deeper granular grouping (appendix p 32). Being male was associated with lower risks for longer hospital stay (OR 0·89 [0·81–0·98]). Other factors, including RSV subtype A, use of palivizumab prophylaxis, multiple births, having two or more children younger than 5 years in the household, maternal smoking during pregnancy, and smokers in the household, were not found to be associated with any severe outcomes (figure 3). Ad-hoc exploratory analyses showed that, among infants and young children who were hospitalised with RSV, early preterm infants and young children had a higher prevalence of comorbidities than did late-preterm infants and young children, and the prevalence was highest in the second year of life (appendix p 29). Among early preterm infants and young children who were hospitalised with RSV, the prevalence of any comorbidities was 32% (95% CI 20–46%) in developing countries and 48% (34–63%) in industrialised countries in the first year of life, and 39% (22–58%) in developing countries and 63% (45–78%) in industrialised countries in the second year of life.

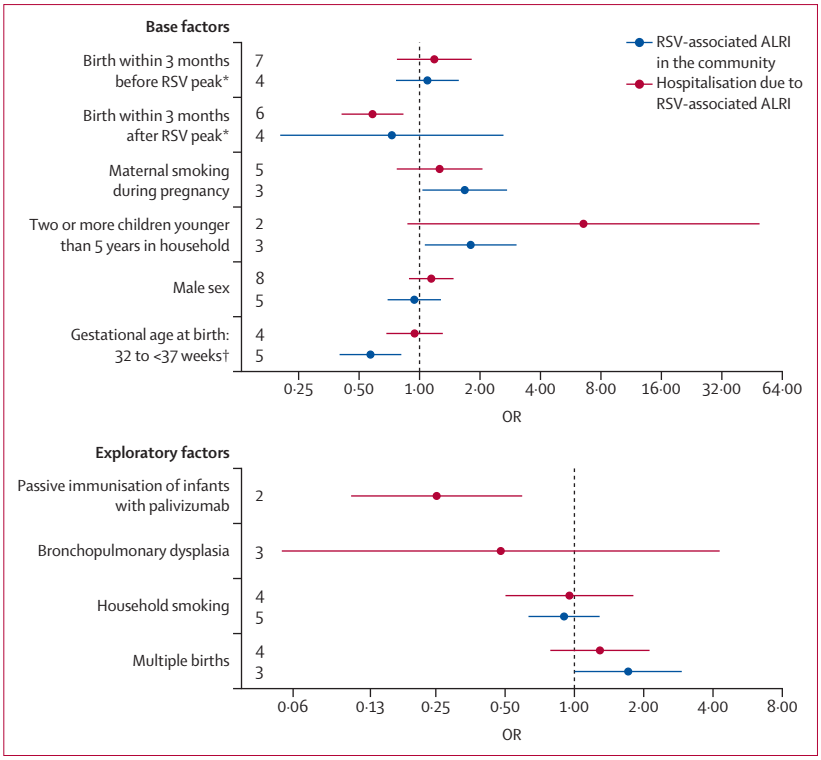


Figure 2: **Risk factors for RSV-associated ALRI community episodes and hospital admissions**
ORs calculated from meta-analysis results. Dots indicate ORs and whiskers indicate 95% CIs. Base factors refer to factors that were fixed in individual regression models, determined a priori; exploratory factors refer to factors that were assessed individually in models with all base factors. Numbers on the left denote the number of studies contributing to the meta-estimates. Note that scales on the x axes differ between plots. ALRI=acute lower respiratory infection. RSV=respiratory syncytial virus. OR=odds ratio. *With births in interseasonal months as reference. †With gestational age at birth of less than 32 weeks as reference.

Discussion

This systematic review and meta-analysis of the global and regional burden of RSV-associated ALRI and risk factors for negative outcomes from RSV infection shows that, in the included studies, preterm infants had higher RSV-associated ALRI incidence and hospitalisation rates compared with all infants. We estimated that, in 2019, 1 650 000 (95% UR 1 350 000–1 990 000) RSV-associated ALRI episodes and 533 000 (95% UR 385 000–730 000) hospital admissions of preterm infants in the first year of life occurred worldwide. Both early and late preterm infants had higher RSV-associated ALRI incidence and hospitalisation rates than all infants of any gestational weeks, and the increased risk of hospitalisation among early preterm infants persisted into the second year of life. Regarding mortality, we estimated that, globally, 3050 in-hospital deaths associated with RSV (95% UR 1080–8620) and 26 760 overall deaths attributable to RSV (11 190–46 240) occurred in preterm infants in 2019, reinforcing the previously highlighted striking gaps between in-hospital and out-of-hospital mortality.[2] Our analysis of individual participant data showed little overlap between factors identified to be associated with ALRI caused by RSV and factors associated with severe outcomes after admission, although most factors associated with ALRI caused by RSV were perinatal and sociodemographic characteristics, and factors associated with severe outcomes upon admission were primarily underlying medical conditions, namely congenital heart disease, tracheostomy, bronchopulmonary dysplasia, chronic lung disease, and Down syndrome (with ORs ranging between 1·40 and 4·23). These findings provide important evidence on RSV morbidity and mortality burden, as well as on risk factors for severe RSV infections in preterm infants and young children, which can help to inform prevention, clinical management, and health service planning strategies.

Although preterm infants are well recognised as a group at high risk of RSV infection and severe outcomes from infection, to our knowledge, no global-level systematic analyses on the disease burden and risk factors for this population have been previously conducted. As expected, our study confirmed that preterm infants, particularly early preterm infants and during the first 6 months of life, had higher risks for RSV-associated ALRI incidence and hospital admission. We highlight the persistently higher hospitalisation rate in the second year of life for early preterm children compared with all children up to the age of 2 years. One explanation is that early preterm children are at higher risk of underlying medical conditions with long-term impact, such as chronic lung diseases and bronchopulmonary dysplasia, as shown by the ad-hoc

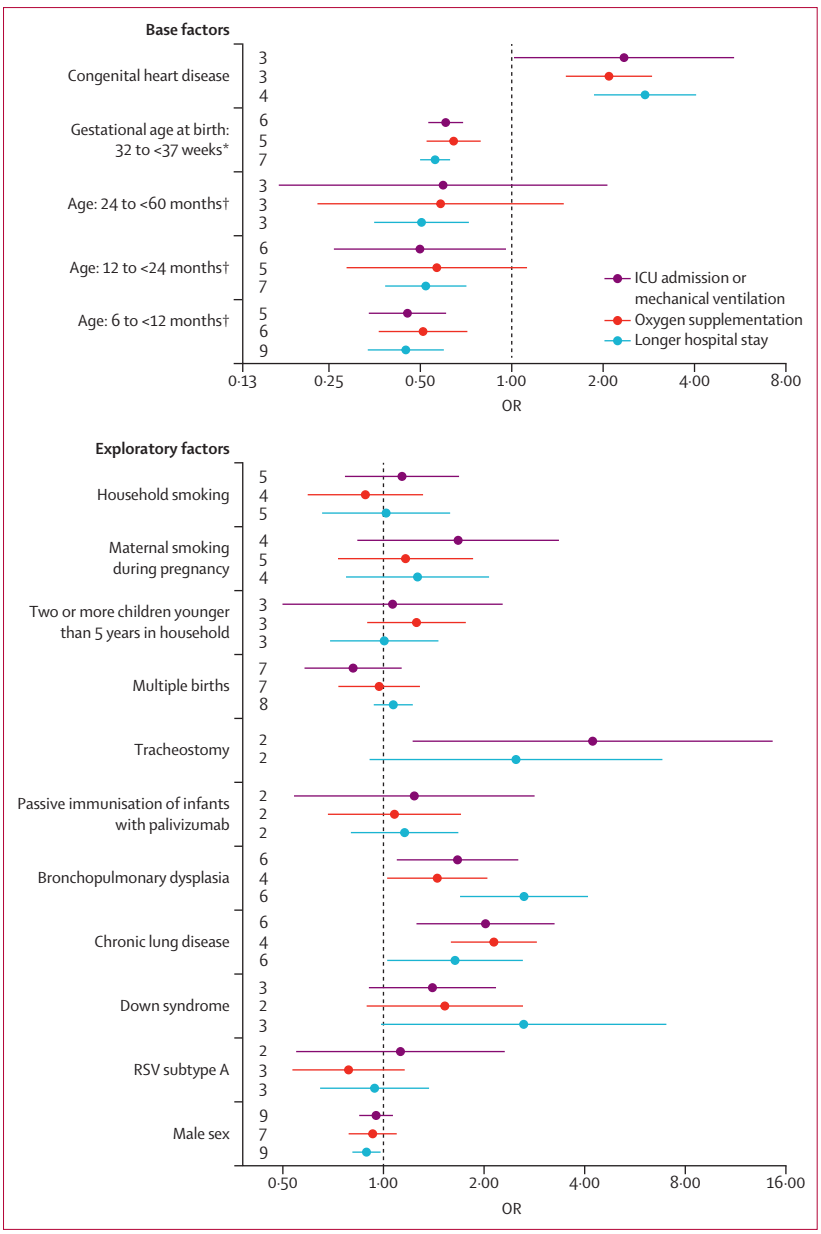


***Figure 3*: Risk factors for severe outcomes from RSV-associated ALRI requiring hospital admission**
ORs calculated from meta-analysis results. Points indicate ORs and whiskers indicate 95% CIs. Base factors refer to factors that were fixed in individual regression models, determined a priori; exploratory factors refer to factors that were assessed individually in models with all base factors. Numbers on the left denote the number of studies contributing to the meta-estimates. Note that scales on the x axes differ between plots. ALRI=acute lower respiratory infection. ICU=intensive care unit. RSV=respiratory syncytial virus. OR=odds ratio. *With gestational age at birth of less than 32 weeks as reference. †With age between 0 months and less than 6 months as reference.

exploratory analysis of prevalence of comorbidities. This finding suggests that prevention and clinical management efforts against RSV might need to be extended to early preterm children in their second year of life, particularly for those with comorbidities that accounted for 39% (95% UR 22–58) of early preterm children hospitalised with RSV in developing and countries and for 63% (45–78) in industrialised countries.

In our previously published global analysis of RSV disease burden in the general population of children younger than 5 years,[2] we observed the poor access to health care in developing countries, where RSV-associated ALRI incidence rates were twice as high as that in industrialised countries, although the hospitalisation rate was similar across the two groups. However, in this study, we observed broadly similar RSV-associated ALRI incidence and hospitalisation rates between developing and industrialised countries; this suggests that preterm infants might have better access to the inpatient health-care services than the general population of infants in low-income and middle-income countries, and possibly higher priority for admission, as judged by clinicians, compared with term infants. Nonetheless, our analysis by income region showed that low-income and lower-middle-income countries had a much lower rate of hospitalisation due to RSV-associated ALRI than did upper-middle-income and high-income countries, suggesting that overall access to inpatient health-care services for preterm infants in LMICs might be still insufficient. The insufficient access to inpatient health-care services for preterm infants in LMICs was also reflected by the striking differences in the number of estimated in-hospital deaths associated with RSV (3050 [95% UR 1080–8620]), and overall deaths (26 760 [11 190–46 240]) in preterm infants globally, suggesting that a substantial proportion of preterm infants with severe RSV illnesses did not receive medical care and died outside of health-care settings.

When comparing the morbidity and mortality estimates between developing and industrialised countries, the role of survivor bias needs to be considered. Mortality rates due to preterm birth complications are much higher in developing countries than in industrialised countries.[23] Preterm infants who died with particular comorbidities early in life (ie, during the neonatal period) in developing countries might have survived if they had been in industrialised countries with better access to and quality of health care. Therefore, in the preterm population who survived the neonatal period, the proportion of comorbidities is expected to be higher in industrialised countries than in developing countries, which was supported by the finding in our exploratory analysis that the prevalence of any comorbidities in early-preterm infants hospitalised with RSV in industrialised countries was substantially higher (roughly 1·5 fold) than that in developing countries. This finding could help to explain the generally similar estimates between developing and industrialised countries, particularly for the similar in-hospital case fatality ratio. Rather than indicating similar quality of health-care provision, the similar case fatality ratio was probably a result of survivor bias between the two regions.

In this study, we noted decreasing incidence rates of RSV-associated ALRI among preterm infants, especially in developing countries. Consistent with previous estimates of all-cause pneumonia in the general population of

children younger than 5 years, such decreases are likely to result from reductions in community-level and household-level exposures to risk factors such as air pollution (indoors and outdoors), second-hand smoking, and lack of hand hygiene.[24,25] We observed a similar decrease in the hospitalisation rate of preterm infants with RSV-associated ALRI, which contrasts with the a reported increase in the hospitalisation rate for all-cause pneumonia in the general population of children younger than 5 years.[24] We hypothesise that, compared with term infants, preterm infants generally had good access to care and that it was the overall decrease in the incidence rate over years that translated to a decreased hospitalisation rate. Our speculation is consistent with the results from a study in California, USA, which showed a decreasing rate of hospitalisation due to RSV among preterm infants from 1997–2011 (and a less pronounced decrease among term infants).[26] Furthermore, we observed a decrease in the in-hospital case fatality ratio of RSV-associated ALRI, reflecting the overall improved quality of care.

Because RSV has clear seasonality in most parts of the world (with the exception of tropical sites),[27] birth month can significantly affect the risk of RSV infection in the first year of life. Consistently with previous studies on the general population of infants (ie, aged <1 year)[28–30] we found that birth month relative to the local RSV season was an independent risk factor for RSV-associated ALRI episodes and hospitalisation; in particular, those born less than 3 months before an RSV epidemic peak had higher risks than those born after an RSV epidemic peak. In addition to birth month, risk factors for RSV-associated ALRI episode and hospitalisation among preterm infants were mainly perinatal and sociodemographic factors, including maternal smoking during pregnancy, having two or more children younger than 5 years in household, and multiple births, but not underlying medical conditions such as bronchopulmonary dysplasia; this finding was generally consistent with reported risk factors for the general paediatric population,[19] although sex was not found to be a risk factor in premature infants. By contrast, risk factors for poor outcomes associated with RSV requiring hospital admission were primarily underlying medical conditions including congenital heart disease, tracheostomy, bronchopulmonary dysplasia, chronic lung disease, and Down syndrome, but not perinatal or sociodemographic factors. A previous systematic review[22] in the general child population reported similar findings, although only congenital heart disease was identified as an individual risk factor in that analysis. The differentiation between risk factors for RSV infection and those for severe outcomes from infection has important implications for targeted prevention and clinical management efforts.

As a global systematic analysis of data from multiple sources, our study shared some of the limitations with studies of this type.[2,10–12] First, despite the use of meta-regression that accounted for differences in chronological age groups, gestational age bands, and changes over 5-year intervals, we were unable to fully reconcile heterogeneities in factors including study setting, exact case definition for ALRI, method for estimation of gestational age, health-care access and seeking behaviour, local criteria for RSV testing, and RSV diagnostics. Only six (9%) of the 67 studies confirmed gestational age through ultrasound, which could additionally result in misclassification bias. Second, although substantial efforts were made to collect RSV epidemiological data across the globe, geographically, the included data had no representation from several regions in Africa, eastern Mediterranean, eastern Europe, and central Asia, and we were unable to provide regional estimates for RSV-associated ALRI incidence or mortality by country income group. Most of the included data were collected in hospital settings, rather than from the community; a knowledge gap around RSV morbidity and mortality burden in preterm infants in the community persists. Moreover, we had to exclude numerous studies because lacking information on gestational age, which might have introduced a selection bias. We also did not have sufficient data to explore all combinations of chronological age groups and gestational age bands.[8] Third, the uncertainty range of mortality estimates was wide due to sparse data that contributed to the estimates in preterm infants; in addition, over 40% of the individuals in the CHAMPS dataset had no information on gestational age and selection bias could be present if information on gestational age was not missing at random.

There are a few additional points of caution when interpreting the findings. First, we followed the WHO gestational age cutoffs for reporting although the reported gestational age bands varied across the published literatures; for example, some studies reported estimates for 32 wGA to less than 36 (or 32–35) wGA rather than from 32 wGA to less than 37 wGA. However, we expect that this inconsistency had a minimal effect on the robustness of our estimates, given that our sensitivity analysis restricted to studies reporting the exact gestational age bands returned generally similar estimates to that of the main analysis. Nonetheless, our estimates for any of the gestational age bands should only be interpreted as the estimates for the corresponding broad gestational age band. Second, we could not rule out residual confounding when assessing the association of different factors and RSV-associated ALRI outcomes. For example, we were unable to assess individual-level socioeconomic status on the risk of RSV-associated ALRI due to absence of data. Moreover, any association reported in this study should not be interpreted as a causal relationship. Third, the focus of our analysis was on the period before the onset of the COVID-19 pandemic; as a result, the potential effect of the COVID-19 pandemic on RSV epidemiology should be considered when interpreting our findings.

Despite these limitations, this study leveraged both population-level aggregated data and individual

patient-level data to provide a comprehensive overview of RSV morbidity and mortality burden and risk factors for infection and negative outcomes for infection for preterm infants and young children, who face a disproportionately high RSV disease burden, particularly in the first 6 months. Moreover, early preterm infants have a noteworthy RSV hospitalisation burden persisting into the second year of life. These findings, together with the identified risk factors for RSV infections and severe outcomes, provide important evidence to optimise strategies for RSV prevention and clinical management in preterm infants and young children.

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HN conceptualised the study with input from XW, YL, and TS. XW, YL, TS, LJB, HYC, HJZ, EAFS, BW-S, YM, BC, ES, JD, JF-A, TH, MHJ, JGL, JM, AM, MCN, BR, AS, and KTY contributed to data collection. XW and YL co-led data analysis with input from RDR. XW, YL, and HN led the data interpretation. EAFS, LJB, HYC, and HJZ were members of the study advisory subgroup that provided critical input to the study. YL wrote the first draft of the manuscript with input from XW and HN. All members in the Respiratory Virus Global Epidemiology Network group contributed to data collection and interpretation, and critically revised the manuscript. All authors read and approved the final draft of the manuscript. XW, LJB, HYC, HJZ, JD, JF-A, TH, MHJ, JGL, JM, AM, MCN, BR, AS, KTY, and EAFS contributed individual participant-level data and accessed and verified the data from their local studies. XW, YL, and HN had full access to and verified all the study data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests
YM and ES were affiliated with the University of Edinburgh when this work was conducted. YM is currently affiliated to the School of Public Health, Wuhan University, Wuhan, China and ES is employed by University College Hospital, University College Hospitals NHS Foundation Trust, London, UK. XW reports grants from GSK to their institution and personal fees from Pfizer, outside the submitted work. YL reports grants from Wellcome Trust, WHO, and GSK paid to their institution, and personal fees from Pfizer, outside the submitted work. TS reports grants from Royal Society of Edinburgh outside the submitted work. LJB reports regular interactions with AbbVie, MedImmune, Ablynx, Bavaria Nordic, MabXience, GSK, Novavax, Pfizer, Moderna, AstraZeneca, MSD, Sanofi, Genzyme, MeMed Diagnostics, and Janssen but has not received personal fees or other personal benefits; being the founding chairman of the ReSViNET Foundation; their affiliation (University Medical Centre Utrecht) has received major funding (>€100 000 per industrial partner) for investigator-initiated studies from AbbVie, MedImmune, AstraZeneca, Sanofi, Janssen, Pfizer, MSD, and MeMed Diagnostics; major funding for the RSV GOLD study from the Bill & Melinda Gates Foundation; major funding as part of the public private partnership IMI-funded RESCEU and PROMISE projects with partners GSK, Novavax, Janssen, AstraZeneca, Pfizer, and Sanofi; major funding by Julius Clinical for participating in clinical studies sponsored by MedImmune and Pfizer; and minor funding (€1000–€25 000 per industrial partner) for consultation and invited lectures by AbbVie, MedImmune, Ablynx, Bavaria Nordic, MabXience, GSK, Novavax, Pfizer, Moderna, AstraZeneca, MSD, Sanofi, and Janssen. HYC reports consulting for Ellume, Pfizer, and the Gates Foundation; serving on advisory boards for Vir, Merck, and AbbVie; conducting continuing medical education teaching with Medscape, Vindico, Cataylst CME, and Clinical Care Options; research funding from Gates Ventures; and receiving support and reagents from Ellume and Cepheid, all outside of the submitted work. HJZ reports grants from the Gates Foundation, AstraZeneca, MSD, and Pfizer paid to their institution outside the submitted work, and serving on advisory boards for MSD. TH reports personal fees from Janssen, Sanofi, Enanta, MSD, and Moderna, all outside of the submitted work. MHJ reports personal fees from AstraZeneca, OM-Pharma, Chiesi, GSK, and Boehringer Ingelheim, outside the submitted work. MCN reports grants from the Gates Foundation, European & Developing Countries Clinical Trials Partnership, Pfizer, AstraZeneca, and Sanofi; and serving on advisory boards for Sanofi, all outside the submitted work. BR received honoraria due to lectures from AbbVie, Germania, Sanofi, AstraZeneca, Milupa, Nestle, and Fresenius, outside the submitted work; and travel support from AbbVie, Chiesi, AstraZeneca, Sanofi, and Nestle. HN reports grants from the Innovative Medicines Initiative related to the submitted work; grants from WHO, the National Institute for Health Research, Pfizer, and Icosavax; and personal fees from the Gates Foundation, Pfizer, ReViral, GSK, Merck, Icosavax, Sanofi, Novavax, and AbbVie, outside the submitted work. CFY reports grants from National Medical Research Council Singapore and Wellcome Trust, and funding to attend conferences and honorarium from Sanofi, Pfizer, and Takeda, outside the submitted work. All other authors declare no competing interests.

Data sharing
Aggregated study data on RSV disease burden are freely accessible at https://github.com/leoly2017/rsvGBDpreterm.

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