

1 Global disease burden of respiratory syncytial virus in  
2 preterm children in 2019: a systematic review and  
3 individual participant data meta-analysis protocol

4 Running title: RSV disease burden in preterm children

5 Xin Wang<sup>1,2\*</sup>, You Li<sup>1,2\*</sup>, Ting Shi<sup>2</sup>, Yiming Ma<sup>3</sup>, Bhanu Wahi-Singh<sup>4</sup>, Richard D. Riley<sup>5</sup>, Harish Nair<sup>2</sup> for  
6 RESCEU investigators

7 1 School of Public Health, Nanjing Medical University, Nanjing, China

8 2 Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK

9 3 Department of Mathematics, Imperial College London, London, UK

10 4 Edinburgh Medical School, University of Edinburgh, Edinburgh, UK

11 5 Centre for Prognosis Research, School of Medicine, Keele University, Keele, UK

12 \*Equal contribution.

## Abstract

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory infection (ALRI) in infants, especially among preterm infants. Existing guidelines on RSV prophylaxis differ greatly by gestational age (GA) and other underlying risk factors, highlighting the data gaps in RSV disease burden among preterm infants. With several novel RSV prophylactic products on the horizon, there is a need for a comprehensive understanding of the global RSV disease burden specifically for children who were born preterm. To this end, we will conduct a systematic review and individual participant data (IPD) meta-analysis. The main objective is to estimate the incidence, hospital admission, and in-hospital mortality for RSV-associated ALRI in preterm infants regionally and globally in 2019, overall and by GA. Secondary objectives are to: estimate RSV disease burden among preterm-born children under two years; identify subgroup(s) of preterm infants who are most vulnerable to RSV-ALRI and severe illnesses (e.g., underlying medical conditions and socio-economic factors); understand the risk profile for RSV disease by finer chronological age groups and GA groups; and understand the severity profile of RSV-associated ALRI in preterm-born children. Three databases, Medline, Embase, and Global Health, will be searched for relevant studies on RSV disease burden for 2019 or before in preterm-born children published between 1 Jan 1995 and 31 Dec 2021. IPD will be sought by contacting the investigators identified from published literature and from existing collaboration networks. Tailored templates are designed for data extraction from published literature and for collection of IPD. One-stage and two-stage random-effects meta-analyses will be used to combine information from IPD and non-IPD studies to produce summary estimates of incidence rate, hospital admission rate, and in-hospital case fatality ratio for RSV-associated ALRI. The framework will be extended to examine subgroup(s) with the most substantial RSV disease burden.

Keywords: RSV; global disease burden; preterm.

Word counts: abstract 296; main text: 2549

## 38 Introduction

39 Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infection (ALRI) in  
40 infants. Globally, RSV-associated ALRI caused approximately 2.2 million hospital admissions and  
41 44,000 in-hospital deaths in infants in 2015 [1]. Infants born preterm are particularly vulnerable to  
42 RSV infection and severe illnesses. Compared to term infants, preterm infants have nearly 2-fold  
43 increased odds of RSV-associated ALRI [2]. Preterm infants who are hospitalised with RSV-associated  
44 ALRI have longer hospital stays and more frequently require intensive care, and are at increased risk  
45 of death than term infants [3]. A global case series study on RSV mortality found children born  
46 preterm accounted for 8–27% of RSV deaths in children under five years old [4]. No estimates have  
47 been made for global RSV disease burden among preterm-born children.

48 Currently, no RSV vaccine is available. As the only licensed RSV prophylactic product, palivizumab (a  
49 monoclonal antibody) is recommended for use among high-risk infants and is used almost  
50 exclusively in high-income countries due to its high cost [5]. A recent review of European clinical  
51 practice guidelines for palivizumab suggests that recommendations vary widely by GA and other  
52 underlying risk factors for preterm infants [Reeves et al. JID. in review]. This highlights the gaps in  
53 knowledge of RSV disease burden by different GA groups. Recently, a new monoclonal antibody  
54 candidate with extended half-life, nirsevimab, showed promising results in phase 2 clinical trial  
55 development; one single-dose of nirsevimab was reported to reduce medically attended RSV-  
56 associated ALRI by 70% and hospital admissions by 78% in preterm infants born at 29-34 weeks'  
57 gestational age (wGA) [6]. Robust estimates of RSV disease burden in preterm infants are necessary  
58 to inform policy decisions on RSV prophylaxis strategy, financing, and prioritisation at global,  
59 regional, and national levels.

60 Given the need for RSV disease burden estimates in preterm-born children, we aim to estimate the  
61 global and regional disease burden of RSV-associated ALRI in preterm-born children in 2019, with a  
62 primary focus on the infants that are most relevant to RSV prophylaxis. This will be done through a

systematic literature review and individual participant data (IPD) meta-analysis. We are hereby reporting the study protocol.

## Definitions

For data from community settings, we will use WHO Integrated Management of Childhood Illnesses (IMCI) pneumonia case definitions and replace the terms “clinical pneumonia” with “ALRI”; for data from hospital settings, we will use physician-confirmed diagnosis of ALRI (pneumonia or bronchiolitis) [7-9]. We define RSV-associated ALRI as ALRI with laboratory-confirmed RSV infection. The definition for prematurity is based on WHO classification; preterm is defined as infants born alive before 37 weeks of pregnancy are completed, which includes three subgroups: extremely preterm (<28 wGA), very preterm (28–<32 wGA), and moderate-to-late preterm (32–<37 wGA) [10]; where available, the moderate-to-late preterm group will be further stratified into 32–<35 wGA and 35–<37 wGA.

## Aim and Objectives

We aim to estimate the global and regional disease burden of RSV-associated ALRI in preterm-born children under two years of age, with a primary focus on infants, and to understand the risk of RSV-associated ALRI by different GA groups. The primary objective is to: estimate the incidence (rate and episodes), hospital admission (rate and episodes), and in-hospital mortality (case fatality ratio [CFR] and deaths) of RSV-associated ALRI in preterm infants regionally and globally, overall and by GA. The secondary objectives are to:

1. Estimate incidence, hospital admission, and in-hospital mortality of RSV-associated ALRI in preterm-born children under two years (and for narrower age groups) regionally and globally, overall and by GA.
2. Assess how the incidence, hospital admission, and in-hospital mortality related to RSV-associated ALRI in preterm-born children under two years are influenced by several factors

- (including gender, birth weight, use of palivizumab, underlying medical conditions, and socioeconomic risk factors), and where possible, apply the information to produce RSV disease burden estimates by these subgroups.
3. Explore how the incidence rate, hospital admission rate, and in-hospital CFR change by chronological age (in months) and by wGA.
  4. Understand the severity profile of hospital admission for RSV-associated ALRI in preterm-born children under two years.

## Methods

Overall, we will follow the methods for IPD meta-analysis by Riley et al. for conducting this study [11]. For reporting, we will adapt the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) [12].

### Systematic literature review

The systematic literature review has been registered on the International Prospective Register for Systematic Reviews (PROSPERO CRD42021269742). We will search three databases Medline, Embase, and Global Health for studies published between 1 Jan 1995 and 31 Dec 2021 (provisionally) that reported RSV-associated morbidity and mortality burden estimates among preterm-born children under two 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 will be applied. The detailed proposed search strategy is in the appendix.

### Eligibility criteria

#### Inclusion criteria

- Reporting data for RSV infections in preterm-born children under two years as primary infection with ALRI in community settings or ALRI necessitating hospital admission, with no constraints on study designs; AND
- Reporting data on community incidence, hospital admissions, and in-hospital CFR for RSV-associated ALRI in preterm-born children under two years; AND
- Reporting data for at least 12 consecutive months, except for in-hospital CFR or studies reporting data for the full RSV season where seasonality is well known and documented.

#### **Exclusion criteria**

- RSV-associated ALRI not clearly defined or the case definition not consistently applied; OR
- Incidence rate, hospital admission rate, or mortality estimated by modelling techniques with no actual data on RSV-associated ALRI (e.g., regression models of viral activity with ALRI time series, and mathematical models); OR
- Population denominator is unavailable or cannot be calculated; OR
- RSV diagnosis based on serology alone; OR
- Including fewer than 100 preterm infants; OR
- Only including infants who received RSV prophylaxis; OR
- Only including infants with underlying medical conditions (e.g., congenital heart disease).

#### **Study selection and data extraction**

Two reviewers will independently screen the titles and abstracts for eligibility using the pre-specified eligibility criteria above. For potentially eligible studies, the reviewers will read full-text articles for final inclusion, and extract data from eligible studies using a standardised form. The data extraction form is available in the appendix. Briefly, the form consists of four spreadsheets — sheet 1 collects study-level information that includes study location, study period, inclusion criteria, case definition, specimen(s) collected, and diagnostic tests; sheets 2.1 to 2.3 collect detailed data on RSV-associated

ALRI incidence, hospital admission, and in-hospital mortality. Disagreements between the two reviewers will be resolved by discussion within the review team.

## Individual participant data (IPD)

### Identification of IPD

We plan to contact the investigators of eligible studies identified from the literature review as well as the investigators within our Respiratory Virus Global Epidemiology Network [1, 7, 13, 14] who might have RSV data eligible for inclusion in this study and invite them to share their IPD. The extracted data from the literature review described above will not be used for the primary analysis if the underlying IPD in the published papers are shared and included.

### Data collection

We will provide a list of all the variables of interest to investigators to collect both individual participant-level and study-level information in each study (the working data collection form in the appendix). We will collect study-level information similar to the data extraction form used for the literature review. The following information will be requested to be included in the IPD provided: participant ID, date of birth, enrolment date, follow-up end date, RSV infection status, gender, GA, birth weight, underlying medical conditions (e.g., Down syndrome, congenital heart disease, cystic fibrosis, chronic lung disease, bronchopulmonary dysplasia, human immunodeficiency virus- (positive, others), tracheostomy, multiple births, receipt of palivizumab and any other RSV prophylaxis, doses of palivizumab received. Among those with RSV infections, we will collect additional data on the date of RSV diagnosis, diagnostic method/criteria, RSV subtype, hospital admission date, hospital admission type (e.g., ambulatory; inpatient), weight at hospital admission, length of hospital stay, status at discharge, use of supplemental oxygen, duration of supplemental oxygen use, need for mechanical ventilation, duration of mechanical ventilation, admission to the intensive care unit (ICU), length of ICU stay, out-of-hospital death due to RSV (where available). Where possible, we will also attempt to collect data on common RSV risk factors: the number of

other children under 5 years in the household, biomass fuel use, smoking during pregnancy, household smoking, maternal HIV infection status, antiretroviral therapy use during pregnancy, and socioeconomic status.

#### Data management and ethics

We will obtain a signed data sharing agreement with the investigators where needed. The Edinburgh DataSync platform (<https://www.ed.ac.uk/information-services/computing/desktop-personal/datasync>) will be used for the safe transfer and storage of individual participant study data. All documents will be stored securely and only accessible by study staff and authorised personnel.

Ethical approval was obtained for the individual studies by the investigators from relevant local ethics committees. This study will include de-identified data for secondary analysis and the investigators will be asked to check that this is consistent with their existing approvals; Usher Research Ethics Group at University of Edinburgh determined that additional ethics approval for this meta-analysis was not necessary. Study data will not be used for any other purpose without the permission of the collaborators.

#### IPD integrity

Each dataset will be cleaned and checked for completeness by a statistician on the team and cross-validated by a senior member of the team with extensive knowledge on the topic. Any discrepancies and unreasonable values will be flagged out and clarification sought from the investigators. Both the original dataset and cleaned dataset will be maintained.

#### Quality assessment (risk of bias)

Study-level quality assessment will be carried out independently by two members of the team for both studies identified from the literature review and studies providing IPD. We will assess the risk of bias using a modified Newcastle-Ottawa Scale as previously [7], based on study design, subjects, case definition, sampling strategy (for RSV testing), diagnostic test, confirmation of GA, and



adjustment for health-care utilisation (for studies reporting hospital admission rate). Detailed quality assessment criteria are in the appendix. We will conduct sensitivity analyses by excluding studies at moderate and high risk of bias where applicable.

## Statistical analysis

As summarised in **Table 1**, we will report global and regional (by country development status [15] and by World Bank Income group [16]) estimates of RSV disease burden in preterm infants aged <12 months as primary estimates, and in other chronological age groups (including 0–<6 months, 6–<12 months, 12–<24 months, and 0–<24 months) as secondary estimates, based on both IPD and the data extracted from the literature. As an exploratory analysis, we will report RSV disease burden estimates by different subgroups, by finer chronological age bands, by finer GA bands, and by severity, based on IPD alone.

## Primary estimates

We will estimate RSV-associated ALRI incidence rate, hospital admission rate, and in-hospital CFR in preterm infants regionally, by country development status and by World Bank Income group, and for different GA groups including <37 wGA, <28 wGA, 28–<32 wGA, <32 wGA, and 32–<37 wGA (further stratified into 32–<35wGA and 35–<37wGA where available). This will be done through a one-stage or two-stage generalised linear mixed-effects (GLMM) meta-analysis framework [11], which should produce similar findings when they make the same assumptions. The one-stage approach analyses all studies in a single framework (e.g., Poisson random-effects regression), accounting for heterogeneity across studies [11]. The two-stage approach will produce aggregate data (derived directly from IPD studies or extracted from publications of non-IPD studies), including numerators and denominators for calculating incidence rate, hospital admission rate, and in-hospital CFR. In the second stage, this aggregate data (from the IPD studies and the non-IPD studies) will be combined using a GLMM meta-analysis model [17] to produce summary estimates of incidence rate, hospital admission rate, and in-hospital CFR for each age group similar to previously done [7, 13, 14]. As

events may be sparse in many studies, we will pool counts directly (rather than rates), as this is preferred [11]. Heterogeneity will be summarised using the estimate of between-study standard deviation ('tau') and, if the number of studies is seven or above, a 95% prediction interval [18]. Where possible, variation in the estimates over years will be assessed.

To translate the meta-analysis results to population event frequency, the expected number of RSV-associated ALRI episodes and hospital admissions will be calculated by applying the summary rate estimates to estimates of the preterm-born children under two years in 2019 (based on the 2019 population [19] and the latest regional preterm rate estimates [20]). Global estimates will be generated by totalling up each pair of random draws of regional meta-estimates from log-normal distributions using Monte Carlo simulation, with 2.5<sup>th</sup> percentile and 97.5<sup>th</sup> percentile defining the lower and upper bounds of the uncertainty range (UR). In-hospital deaths will be estimated by applying the number of hospital admissions to the in-hospital CFR estimates.

## Secondary estimates

The one-stage and two-stage meta-analysis framework will also be adapted for other age groups of children under two years. To utilise the granularity of data available for the IPD analysis, we will assess how the rate of RSV-associated ALRI and disease severity is associated with several factors, including gender, birth weight, use of palivizumab, underlying medical conditions, and socioeconomic risk factors. We will also attempt to estimate the relative risk (as incidence rate ratio; compared with infants <1 month of age) for RSV-associated ALRI incidence or hospital admission with variation in chronological age (for the first 24 months of life) and different wGA (compared with infants <28 wGA). For studies with available data on the use of supplemental oxygen, need for mechanical ventilation, and ICU admission, we will estimate the proportion of use of these resources among RSV-associated ALRI hospital admissions as proxies for disease severity. If there are missing values for some covariates, then multiple imputation will be used. Imputation will be done separately for each study (to ensure heterogeneity across studies is preserved), and using a fully

conditional specification to predict missing covariate values conditional on other known variables (including the outcome) [21]. Results will then be combined using Rubin's rules [22].

### Assessment of small-study effects

Small-study effects (potential for publication related biases) will be examined using funnel plots and visual examination of asymmetry in a meta-analysis that includes 10 or more studies.

## Discussion

To our knowledge, this will be the first study to estimate the global disease burden of RSV-associated ALRI among preterm-born children. With the comprehensive subgroup analyses, our study will help identify subgroup(s) of preterm infants who are disproportionately affected. This is important for revising existing guidelines on administration of palivizumab as well as for novel RSV prophylactic products. Our estimates will also serve as important baseline data for estimating cost-effectiveness of novel RSV prophylactic products in this specific population at higher risk of RSV disease.

Compared to the conventional systematic review and meta-analysis, IPD meta-analysis improves the standardisation of methods between studies, e.g., by applying the same GA cut-offs. It also offers an opportunity to assess and account for both patient-level and study-level factors that influence the risk of RSV disease and severity [23]. Additionally, through the exercise of conducting the study, we will be able to identify data gaps and unanswered questions, informing future research.

## Footnote page

### **RESCEU investigators**

You Li and Xin Wang (Nanjing Medical University, Nanjing, China); Harish Nair, Harry Campbell and Ting Shi (University of Edinburgh, Edinburgh, UK); Philippe Beutels (University of Antwerp, Antwerpen, Belgium); Louis Bont (University Medical Centre Utrecht, the Netherlands); Andrew Pollard (University of Oxford, Oxford, UK); Peter Openshaw (Imperial College London, London, UK); Federico Martinon-Torres (Servicio Galego de Saude, Santiago de Compostela, Spain); Terho Heikkinen (University of Turku and Turku University Hospital, Turku, Finland); Adam Meijer (Institute for Public Health and the Environment, Bilthoven, the Netherlands); Thea K Fischer (Statens Serum Institut, Copenhagen, Denmark); Maarten van den Berge (University of Groningen, Groningen, the Netherlands); Carlo Giaquinto (PENTA Foundation, Padua, Italy); Michael Abram (AstraZeneca, Gaithersburg, Maryland, USA); Tin Tin Myint (Pfizer, Paris, France); Bishoy Rizkalla (GlaxoSmithKline, Rockville, Maryland, USA); Charlotte Vernhes and Scott Gallichan (Sanofi Pasteur, Lyon, France); Jeroen Aerssens (Janssen, Beerse, Belgium); Veena Kumar (Novavax, Gaithersburg, Maryland, USA); Eva Molero (TEAM-IT Research S.L, Barcelona, Spain).

### **Financial support**

This work was supported by Innovative Medicines Initiative 2 Joint Undertaking (grant number 116019 to RESCEU). This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation Programme and European Federation of Pharmaceutical Industries and Associations. This work reflects only the authors' view and the Joint Undertaking is not responsible for any use that may be made of the information it contains.

### **Contributors**

273 HN conceptualised the study. XW and YL led the analysis plan with contribution from TS. XW and YL  
274 drafted the first version of the protocol with contribution from RDR and HN. All authors reviewed  
275 the protocol for intellectual contents and approved the final version of the protocol for publication.

#### 276 **Potential conflicts of interest**

277 YL reports grants from Wellcome Trust and WHO, outside the submitted work. HN reports grants  
278 from the Innovative Medicines Initiative related to the submitted work; and consulting fees from  
279 BMGF, Pfizer, and Sanofi, honoraria from Abbvie, support from Sanofi for attending meetings, and  
280 participation on advisory boards from Sanofi, Janssen, Novavax, Reviral, Resvinet, and WHO, outside  
281 the submitted work. All other authors report no conflicts of interest.

#### 282 **Corresponding author contact information**

283 Prof. Harish Nair ([Harish.Nair@ed.ac.uk](mailto:Harish.Nair@ed.ac.uk)), Centre for Global Health, Usher Institute, University of  
284 Edinburgh, Edinburgh EH8 9AG, UK

## References

1. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *The Lancet* **2017**; 390:946-58.
2. Shi T, Balsells E, Wastnedge E, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: Systematic review and meta-analysis. *J Glob Health* **2015**; 5:020416-.
3. Kenmoe S, Kengne-Nde C, Modiyinji AF, La Rosa G, Njouom R. Comparison of health care resource utilization among preterm and term infants hospitalized with Human Respiratory Syncytial Virus infections: A systematic review and meta-analysis of retrospective cohort studies. *PLOS ONE* **2020**; 15:e0229357.
4. Scheltema NM, Gentile A, Lucion F, et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. *The Lancet Global Health* **2017**; 5:e984-e91.
5. DISEASES COI, COMMITTEE BG. Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics* **2014**; 134:415-20.
6. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *New England Journal of Medicine* **2020**; 383:415-25.
7. Wang X, Li Y, Deloria-Knoll M, et al. Global burden of acute lower respiratory infection associated with human parainfluenza virus in children younger than 5 years for 2018: a systematic review and meta-analysis. *The Lancet Global Health* **2021**; 9:e1077-e87.
8. World Health Organization. Handbook : IMCI integrated management of childhood illness. Geneva: World Health Organization, **2005**.
9. World Health Organization. Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. Geneva: World Health Organization, **2014**.

310 10. World Health Organisation. Preterm birth. Available at: [https://www.who.int/news-room/fact-](https://www.who.int/news-room/fact-sheets/detail/preterm-birth)  
311 [sheets/detail/preterm-birth](https://www.who.int/news-room/fact-sheets/detail/preterm-birth). Accessed 6-Oct 2021.

312 11. Riley RD, Tierney JF, Stewart LA. Individual Participant Data Meta-Analysis: A Handbook for  
313 Healthcare Research. Chichester: Wiley, **2021**.

314 12. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and  
315 Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *Jama* **2015**; 313:1657-65.

316 13. Wang X, Li Y, Deloria-Knoll M, et al. Global burden of acute lower respiratory infection associated  
317 with human metapneumovirus in children under 5 years in 2018: a systematic review and modelling  
318 study. *The Lancet Global Health* **2021**; 9:e33-e43.

319 14. Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal  
320 influenza in children under 5 years in 2018: a systematic review and modelling study. *The Lancet*  
321 *Global Health* **2020**; 8:e497-e510.

322 15. United Nations Inter-agency group for child mortality estimation. Levels and trends in child  
323 mortality report 2015. New York, **2015**.

324 16. The World Bank. World Bank Country and Lending Groups. Available at:  
325 [https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-](https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups)  
326 [lending-groups](https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups). Accessed 12th May 2021.

327 17. Stijnen T, Hamza TH, Özdemir P. Random effects meta-analysis of event outcome in the  
328 framework of the generalized linear mixed model with applications in sparse data. *Statistics in*  
329 *Medicine* **2010**; 29:3046-67.

330 18. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* **2011**;  
331 342:d549.

332 19. United Nations. World Population Prospects 2019. Available at:  
333 <https://population.un.org/wpp/Download/Standard/Population/>. Accessed 5-March 2021.

334 20. Chawanpaiboon S, Vogel JP, Moller A-B, et al. Global, regional, and national estimates of levels of  
335 preterm birth in 2014: a systematic review and modelling analysis. *The Lancet Global Health* **2019**;  
336 7:e37-e46.

337 21. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, Rubin DB. Fully conditional specification in  
338 multivariate imputation. *Journal of Statistical Computation and Simulation* **2006**; 76:1049-64.

339 22. Rubin DB. Multiple imputation for nonresponse in surveys. Vol. 81. John Wiley & Sons, **2004**.

340 23. Riley RD, Lambert PC, Staessen JA, et al. Meta-analysis of continuous outcomes combining  
341 individual patient data and aggregate data. *Statistics in Medicine* **2008**; 27:1870-93.

342



343 **Table 1. Summary of proposed estimates.**

Estimates	Geographical coverage	Chronological age group	Gestational age group	Other subgroup(s)	Data sources
<b>Primary</b>					
<ul style="list-style-type: none"> <li>• RSV-associated ALRI rate/episodes</li> <li>• RSV-associated ALRI hospital admission rate/episodes</li> <li>• RSV-associated ALRI in-hospital CFR/deaths</li> </ul>	<ul style="list-style-type: none"> <li>• Global</li> <li>• Developing / industrialised</li> <li>• By World Bank Income group</li> </ul>	<ul style="list-style-type: none"> <li>• 0–&lt;12m</li> </ul>	<ul style="list-style-type: none"> <li>• &lt;37 wGA</li> <li>• &lt;28 wGA</li> <li>• 28–&lt;32 wGA</li> <li>• &lt;32 wGA</li> <li>• 32–&lt;37 wGA (further stratified to 32–&lt;35 wGA and 35–&lt;37 wGA where possible)</li> </ul>	—	IPD + data from literature
<b>Secondary</b>					
<ul style="list-style-type: none"> <li>• RSV-associated ALRI rate/episodes</li> <li>• RSV-associated ALRI hospital admission rate/episodes</li> <li>• RSV-associated ALRI in-hospital CFR/deaths</li> </ul>	<ul style="list-style-type: none"> <li>• Global</li> <li>• Developing / industrialised</li> <li>• By World Bank Income group</li> </ul>	<ul style="list-style-type: none"> <li>• 0–&lt;6m</li> <li>• 6–&lt;12m</li> <li>• 12–&lt;24m</li> <li>• 0–&lt;24m</li> </ul>	<ul style="list-style-type: none"> <li>• &lt;37 wGA</li> <li>• &lt;28 wGA</li> <li>• 28–&lt;32 wGA</li> <li>• &lt;32 wGA</li> <li>• 32–&lt;37 wGA (further stratified to 32–&lt;35 wGA and</li> </ul>	—	IPD + data from literature

Estimates	Geographical coverage	Chronological age group	Gestational age group	Other subgroup(s)	Data sources
			35–<37 wGA where possible)		
<b>Additional (where applicable)</b>					
<ul style="list-style-type: none"> <li>• RSV-associated ALRI rate/episodes</li> <li>• RSV-associated ALRI hospital admission rate/episodes</li> <li>• RSV-associated ALRI in-hospital CFR/deaths</li> </ul>	<ul style="list-style-type: none"> <li>• Global</li> <li>• Developing / industrialised</li> </ul>	<ul style="list-style-type: none"> <li>• 0–&lt;12m</li> </ul>	<ul style="list-style-type: none"> <li>• &lt;37 wGA</li> </ul>	<ul style="list-style-type: none"> <li>• Gender</li> <li>• Birth weight</li> <li>• Use of palivizumab</li> <li>• Underlying medical conditions*</li> <li>• Socioeconomic risk factors</li> </ul>	IPD
<ul style="list-style-type: none"> <li>• RSV-associated ALRI rate ratio</li> <li>• RSV-associated ALRI hospital admission rate ratio</li> <li>• RSV-associated ALRI in-hospital CFR ratio</li> </ul>	<ul style="list-style-type: none"> <li>• Global</li> </ul>	By incremental month of age for 0–<24m (ref: 0–<1m)	<ul style="list-style-type: none"> <li>• &lt;37 wGA</li> </ul>	—	IPD
<ul style="list-style-type: none"> <li>• RSV-associated ALRI rate ratio</li> <li>• RSV-associated ALRI hospital admission rate ratio</li> <li>• RSV-associated ALRI in-hospital CFR ratio</li> </ul>	<ul style="list-style-type: none"> <li>• Global</li> </ul>	<ul style="list-style-type: none"> <li>• 0–&lt;12m</li> </ul>	By incremental gestational week, between 28–36 wGA (ref: <28 wGA)	—	IPD
<ul style="list-style-type: none"> <li>• % of RSV-associated ALRI hospital admission receiving supplemental oxygen</li> <li>• % of RSV-associated ALRI hospital admission receiving mechanical ventilations</li> </ul>	<ul style="list-style-type: none"> <li>• Global</li> <li>• Developing / industrialised</li> </ul>	<ul style="list-style-type: none"> <li>• 0–&lt;12m</li> </ul>	<ul style="list-style-type: none"> <li>• &lt;37 wGA</li> </ul>	—	IPD

Estimates	Geographical coverage	Chronological age group	Gestational age group	Other subgroup(s)	Data sources
<ul style="list-style-type: none"> <li>% of RSV-associated ALRI hospital admission admitted to ICU</li> </ul>					

344 Abbreviation: RSV = respiratory syncytial virus; ALRI = acute lower respiratory infection; CFR = case fatality ratio; IPD = individual participant data; ICU = intensive care unit;

345 m = month; wGA = weeks' gestational age.

346 \*Includes Down syndrome, congenital heart disease, cystic fibrosis, chronic lung disease, bronchopulmonary dysplasia, HIV-positive, and others.

347