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# Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infections in Children With Bronchopulmonary Dysplasia: Systematic Review and Meta-Analysis

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**Background.** Respiratory syncytial virus (RSV) is among the most important causes of acute lower respiratory tract infection (ALRI) in young children. We assessed the severity of RSV-ALRI in children less than 5 years old with bronchopulmonary dysplasia (BPD).

**Methods.** We searched for studies using EMBASE, Global Health, and MEDLINE. We assessed hospitalization risk, intensive care unit (ICU) admission, need for oxygen supplementation and mechanical ventilation, and in-hospital case fatality (hCFR) among children with BPD compared with those without (non-BPD). We compared the (1) length of hospital stay (LOS) and (2) duration of oxygen supplementation and mechanical ventilation between the groups.

**Results.** Twenty-nine studies fulfilled our inclusion criteria. The case definition for BPD varied substantially in the included studies. Risks were higher among children with BPD compared with non-BPD: RSV hospitalization (odds ratio [OR], 2.6; 95% confidence interval [CI], 1.7–4.2;  $P < .001$ ), ICU admission (OR, 2.9; 95% CI, 2.3–3.5;  $P < .001$ ), need for oxygen supplementation (OR, 4.2; 95% CI, .5–33.7;  $P = .175$ ) and mechanical ventilation (OR, 8.2; 95% CI, 7.6–8.9;  $P < .001$ ), and hCFR (OR, 12.8; 95% CI, 9.4–17.3;  $P < .001$ ). Median LOS (range) was 7.2 days (4–23) (BPD) compared with 2.5 days (1–30) (non-BPD). Median duration of oxygen supplementation (range) was 5.5 days (0–21) (BPD) compared with 2.0 days (0–26) (non-BPD). The duration of mechanical ventilation was more often longer (>6 days) in those with BPD compared with non-BPD (OR, 11.9; 95% CI, 1.4–100;  $P = .02$ ).

**Conclusions.** The risk of severe RSV disease is considerably higher among children with BPD. There is an urgent need to establish standardized BPD case definitions, review the RSV prophylaxis guidelines, and encourage more specific studies on RSV infection in BPD patients, including vaccine development and RSV-specific treatment.

**Keywords.** acute lower respiratory infections; bronchopulmonary dysplasia; chronic lung disease; respiratory syncytial virus.

Respiratory syncytial virus (RSV) is among the leading causes of acute lower respiratory tract infection (ALRI) in children, with an increased risk of severe RSV-ALRI in children with comorbidities such as bronchopulmonary dysplasia (BPD) [1]. Bronchopulmonary dysplasia is strongly linked with prematurity; with the increase in the viability of premature infants

due to the advancements in neonatal medicine, 15%–50% of these children will be affected by BPD [2]. Approved RSV antiviral treatments are lacking, and prevention of RSV-ALRI is currently limited to infection control measures and postnatal prophylaxis with palivizumab [3]. However, there is promising research progress in the development of an RSV vaccine, with 16 candidate vaccines/monoclonal antibodies currently at various phases of clinical trials [4].

There has been a growing recognition of RSV-ALRI disease burden, for example, Paes et al [1] showed a significant association between BPD and RSV-ALRI hospitalization, an increased risk of prolonged hospitalization, and a greater requirement for medical support. However, a meta-analysis of published data on RSV-ALRI disease severity among infants with BPD is lacking. We performed a systematic review of studies and a meta-analysis on available data regarding RSV-ALRI hospitalization, intensive care unit (ICU) admission, need for oxygen supplementation and mechanical ventilation, and in-hospital

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case fatality ratio (hCFR) among children with BPD compared with those without (non-BPD).

## METHODS

### Study Search and Selection

P.S.C. and L.H. independently conducted a systematic search for studies using EMBASE, Global Health, and MEDLINE (Supplementary Table 1), completed on April 4, 2017. We selected the relevant studies following the PRISMA protocol (<http://www.prisma-statement.org/PRISMAStatement/FlowDiagram>). Where discrepancies existed, the 2 researchers discussed to reach a consensus. Restriction was only based on the language of publication (English and French). The review was registered on PROSPERO, registration number CRD42018090848 (<https://www.crd.york.ac.uk/prospéro/>).

### Outcomes of Interest

The population of interest is children less than 5 years old, the exposure is a diagnosis of BPD, and the comparator group are those without (non-BPD). We assumed all children not diagnosed with BPD as “non-BPD”. Where specified, we conducted subgroup analysis based on gestation age and existence of comorbidity. Our outcomes of interest were RSV associated hospitalizations, length of hospital stay (LOS), admissions to and length of stay in the intensive care unit (ICU) (LOS-ICU), need for and duration of oxygen supplementation, need for and duration of mechanical ventilation, and hCFR. We considered all the cases referred to as chronic lung disease as BPD, excluding other conditions such as asthma and cystic fibrosis. For an interventional study, we used the placebo arm to extract the required data.

### Inclusion and Exclusion Criteria

We included the following: any published study that reported data on RSV-associated ALRI hospitalizations among children aged less than 5 years with BPD and non-BPD; studies that assessed ALRIs hospitalizations specifically due to RSV rather than as a coinfection; studies that specifically assessed BPD as an underlying disease rather than as a comorbidity; studies that assessed the use of immunotherapy with specific data on our outcomes of interest in the placebo group; and studies that did not specify use of prophylaxis or regarded prophylaxis as not appropriate. We excluded studies that included children with unspecified age or  $\geq 5$  years old without relevant data for the under-5-year-old subgroup.

### Data Extraction and Synthesis

P.S.C. and L.H. independently extracted all available data on the outcomes of interest using a standard Microsoft Excel 2000 spreadsheet. We modified the GRADE scoring system to evaluate the quality of the included studies [5] (Supplementary Table 2). We used Stata version 12 (Stata Corp., College Station,

TX) to analyze the data and applied odds ratio (OR) to compare risk for RSV-ALRI among BPD group for hospitalization, ICU admission, oxygen supplementation, mechanical ventilation, and hCFR; and rate ratio for hospitalization rate in comparison to non-BPD. We performed a stratified analysis where feasible. We used the most widely accepted definition of BPD as the “requirement for any respiratory support at 36 weeks corrected gestation” [6], and we defined prematurity as gestational age (GA) of  $\leq 36$  weeks, as implied in our BPD definition. When a study provided separate data for different GAs, we extracted data for BPD and non-BPD and conducted the meta-analysis based on GA. When meta-analysis was not feasible, we reported the proportions, mean, median, and the measures of risk as provided by any single study. We calculated the risk from the data in the original articles when the measures of risk were not provided. We used Egger’s test to assess publication bias (<https://www.bmj.com/content/346/bmj.f1342>). Where applicable, we used the 95% confidence interval (CI). We set the statistical significance at  $< 0.05$ .

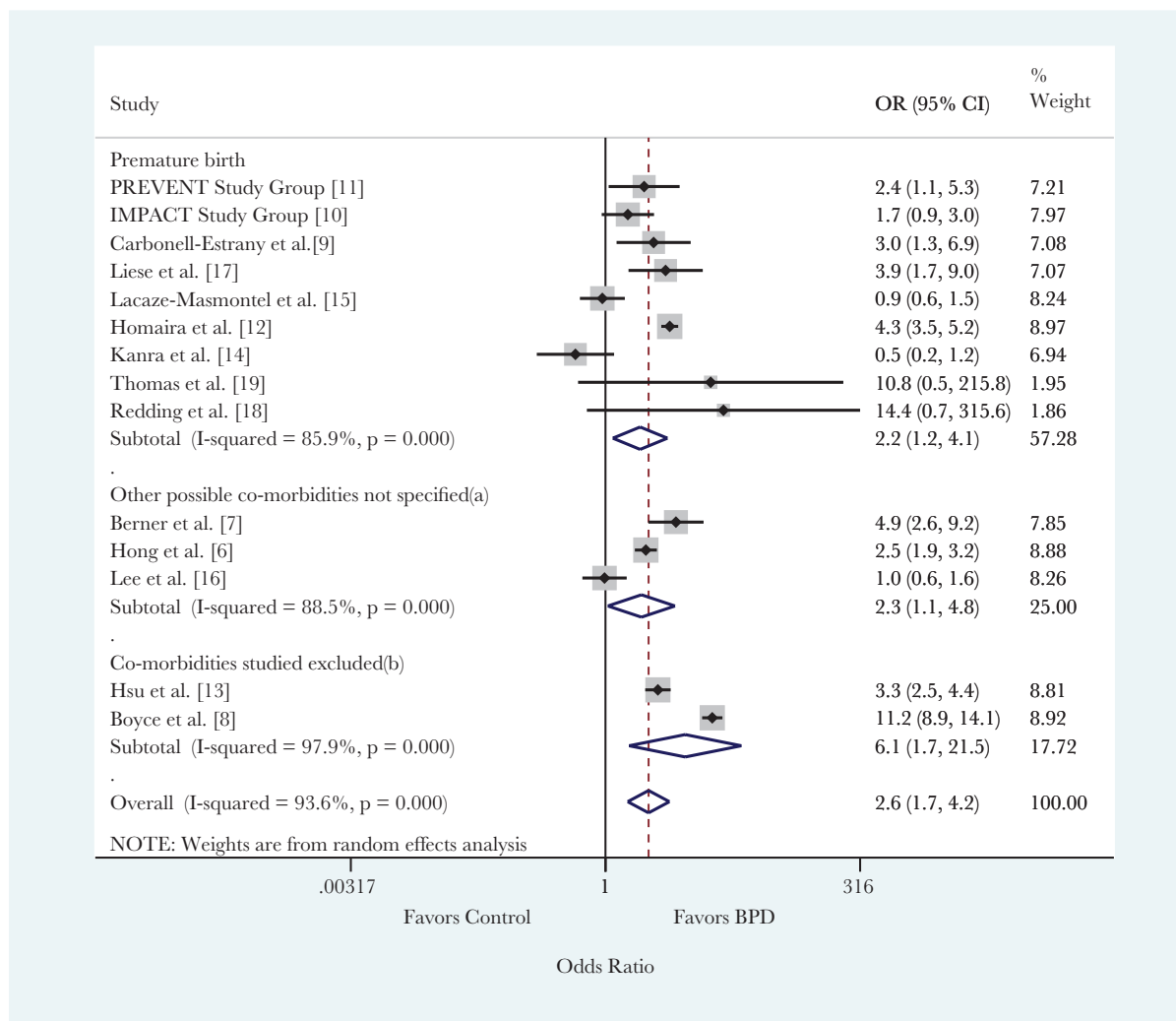
## RESULTS

### Study Characteristics and Population

Twenty-nine studies fulfilled our inclusion criteria (Supplementary Figure 1 and Supplementary Tables 4 and 5). There was substantial heterogeneity in the case definition for BPD among included studies (Supplementary Table 4). The overall quality of the studies was moderate (average score of 3.4): 25 were of moderate quality, and 4 were of low quality (Supplementary Table 3). Outcomes with significant heterogeneity were hospitalization rate ( $I^2 = 97.1\%$ ,  $P < .001$ ) (Figure 2) and proportion of episodes associated with hospitalization ( $I^2 = 93.6\%$ ,  $P < .001$ ) (Figure 1). There was no evidence of publication bias in any of the measured outcomes where the test was feasible: risk of hospitalization ( $P = .200$ ), ICU admission ( $P = .301$ ), mechanical ventilation (0.950), and hCFR ( $P = .836$ ).

### Hospitalization and Length of Hospital Stay

Two studies reported RSV hospitalization rate among children with BPD and non-BPD. Mean hospitalization rate was 186.4/1000 person-years for BPD and 13.3/1000 person-years for non-BPD (incidence rate ratio [IRR]), 20.0; 95% CI, 10.0–39.8;  $P < .001$ ) (Supplementary Figure 2). Respiratory syncytial virus hospitalization rate and IRR were age dependent: 412.9/1000 person-years for BPD, 33.6/1000 person-years for non-BPD (IRR, 9.9; 95% CI, 4.9–20.0;  $P < .001$ ) in children less than 12 months old; 121.8/1000 person-years for BPD, 5.1/1000 person-years for non-BPD (IRR, 24.5; 95% CI, 13.8–43.4;  $P < .001$ ) in children aged 12 to 24 months; and 24.4/1000 person-years for BPD, 1.2/1000 person-years for non-BPD (IRR, 35.8; 95% CI, 4.9–264.0;  $P < .001$ ) in children aged older than 24 months. The difference between the age groups was not significant ( $P = .060$ ).



**Figure 1.** Risk of respiratory syncytial virus (RSV)-associated hospitalization in children with bronchopulmonary dysplasia (BPD) versus those without BPD (odds ratios [ORs] and corresponding confidence intervals based on proportions of RSV hospitalization among BPD and non-BPD). Comorbidities studied: BPD; congenital heart disease, other than patent ductus arteriosus or a septal defect. <sup>a</sup>Other possible comorbidities not specified: these studies provided data for children without BPD as comparison group, other possible underlying diseases other than BPD were not specifically excluded. <sup>b</sup>Comorbidities studied excluded: these studies provided specific data for children without BPD and other underlying diseases other than BPD as comparison group (Hsu et al [13] reported this as children born at 37 weeks gestational age (GA) without BPD; congenital heart disease, other than patent ductus arteriosus, or a septal defect that was hemodynamically insignificant; or any congenital anomaly. Boyce et al [8] reported this as “low risk” children). I-squared: the variation in OR due to heterogeneity. Subgroup analysis for the prematurity subgroup based on GA was excluded from the figure due to space limitation, details are provided in text.

Fourteen studies reported the risk of RSV hospitalizations [6–19]: 16.8% in BPD and 9.1% in non-BPD (OR, 2.6; 95% CI, 1.7–4.2;  $P < .001$ ) (Figure 1). Within the prematurity subgroup, BPD was 15.2% versus non-BPD at 9.2%: OR = 2.2 (95% CI, 1.2–4.1;  $P = .013$ ) (in overall premature group), OR = 1.9 (95% CI, .9–4.0;  $P = .104$ ) ( $\leq 35$  weeks GA), and OR = 2.6 (95% CI, 1.0–7.2;  $P = .062$ ) ( $\leq 33$  weeks GA).

By World Bank income regions, RSV hospitalization was 17.8% for BPD and 6.7% for non-BPD from high-income countries [6, 8–12, 15, 17–20] (OR, 3.3; 95% CI, 2.0–5.7;  $P < .001$ ) and 13.7% for BPD and 13.6% for non-BPD from upper-middle-income countries (OR, 1.2; 95% CI, .4–3.8;  $P = .710$ )

(Supplementary Figure 3). The difference between the 2 groups was not significant ( $P = .100$ ).

In addition, in adjusted multivariable analyses, studies reported higher odds for risk of RSV hospitalization for BPD versus non-BPD (Supplementary Figure 4). Two studies only provided data on the risk during a specific period: Rietveld et al [21] reported a 10.4% hospitalization risk in the first year of life for BPD and 7.5% for non-BPD (OR, 1.4; 95% CI, 1.0–2.0;  $P = .047$ ; GA unspecified). Weigl et al [22] reported a 17.8-fold increased risk of hospitalization for RSV in children less than 2 years old with BPD (95% CI, 1.7–188.0) compared with non-BPD (GA of  $< 32$  weeks for both groups).

### Intensive Care Unit (ICU) Admission and Length of ICU Stay

We obtained the proportion of ICU admissions due to RSV among BPD (17.2%) versus non-BPD (6.8%) (OR, 2.9; 95% CI, 2.3–3.5;  $P < .001$ ) from 4 studies (Supplementary Figure 5). Two studies reported the proportion of RSV-associated hospitalizations that required ICU admission as 12.0% (BPD-RSV) and 4.0% (non-BPD-RSV with comorbidities excluded) (OR, 3.0; 95% CI, .4–20.7;  $P < .258$ ; GA unspecified) [23, 24].

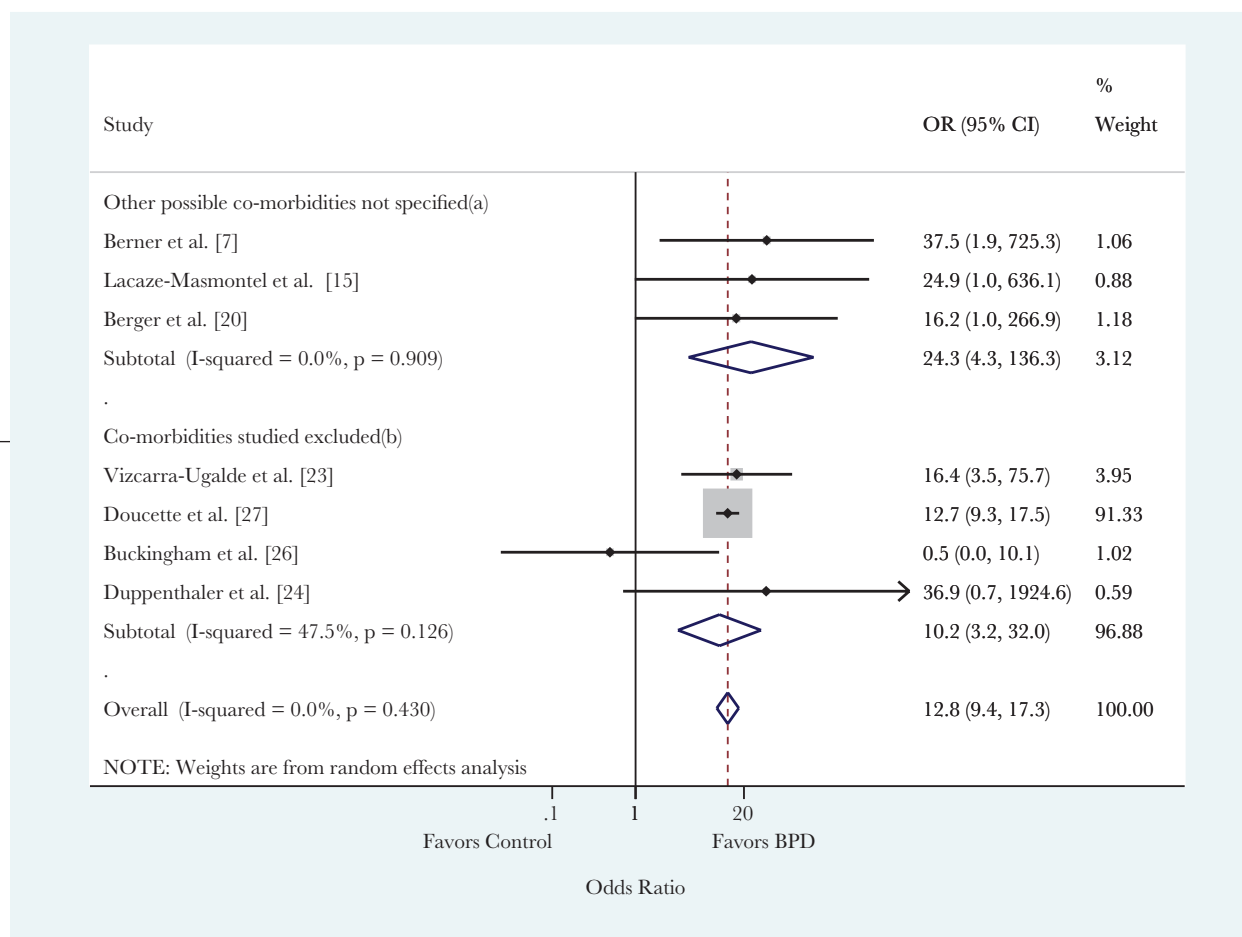
### Oxygen Supplementation and Mechanical Ventilation

Two studies provided data on BPD versus non-BPD that needed oxygen supplementation. Oxygen supplementation was required by 80% of BPD and 65% of non-BPD (OR, 4.2; 95% CI, .5–33.7;  $P = .175$ ) [24, 25].

Four studies provided the proportion of BPD versus non-BPD that required mechanical ventilation (GA unspecified): 2

reported 24.0% for BPD versus 19.0% for non-BPD (OR, 1.1; 95% CI, .5–2.4;  $P = .874$ ) [26, 27]; 2 reported 24.0% for BPD versus 4.0% for non-BPD and other underlying diseases excluded (OR, 8.2; 95% CI, 7.6–8.9;  $P < .001$ ) [24, 27]. Borckink et al [28] reported that BPD children had an increased probability of needing mechanical ventilation (hazard ratio, 3.5; 95% CI, 1.1–11.9;  $P = .04$ ).

The reported LOS, LOS-ICU, and duration of oxygen supplementation and mechanical ventilation in the 2 groups are heterogeneous (Supplementary Table 7). In addition, Zhang et al [29] provided data on severe RSV-ALRI based on clinical signs, defined as children with RSV-ALRI with apnea in the hospital,  $\text{pH} < 7.35$ ,  $\text{pCO}_2 > 45$  mmHg, arterial  $\text{sO}_2 < 87\%$ , LOS  $> 5$  days, and if mechanical ventilation was required. In their study, the BPD group had a 12.4-fold higher risk of severe disease (95% CI, 2.7–56.2;  $P = .001$ ) compared with non-BPD.



**Figure 2.** Risk of respiratory syncytial virus (RSV)-associated deaths in children with bronchopulmonary dysplasia (BPD) versus those without BPD and with or without other comorbidities (odds ratios [ORs] and corresponding confidence intervals based on proportion of children with BPD and non-BPD who died during hospitalization). <sup>a</sup>Other possible comorbidities not specified: these studies provided data for children without BPD as comparison group, other possible underlying diseases other than BPD were not specifically excluded. <sup>b</sup>Comorbidities studied excluded: these studies provided specific data for children without BPD and other underlying diseases other than BPD as comparison group (Vizcarra-Ugalde et al [23] reported this as “children without underlying medical conditions.” Doucette et al reported this as “non-high risk” children. Buckingham et al [26] reported this as “non-CLD, non-CHD, non-Upper airway abnormalities, and no other non-cardiac congenital malformations” children. Duppenthaler et al [24] reported this as children with “no risk factor”). I-squared: the variation in OR due to for heterogeneity.



### In-Hospital Case Fatality Ratio

We obtained the hCFR for RSV-ALRI among BPD and non-BPD from 7 studies, with a proportion of 4.4% and 0.2%, respectively (OR, 12.8; 95% CI, 9.4–17.3;  $P < .001$ ) (Figure 2). Prill et al [30] reported a total registered RSV-associated mortalities of 26 (RSV positive) among children <2 years old, 6 (23.1%) with BPD, 5 (19.2%) with low risk (GA unspecified), and the rest had other risk factors.

### DISCUSSION

We have demonstrated that the risk of severe RSV-ALRI, defined by the measured outcomes, was higher among BPD compared with non-BPD. The LOS, LOS-ICU, and duration of oxygen supplementation and mechanical ventilation were longer among BPD compared with non-BPD, also suggesting a more severe disease among the former.

Overall hospitalization rate was approximately 20-fold higher among the BPD than the non-BPD. Our results show that the RSV-associated hospitalization rates tend to decrease with age, especially after 24 months of the age as reported previously [22]. However, the rate of decline was higher among non-BPD than BPD, thus leading to the wider difference in rates and higher odds as the children got older. The ORs for RSV hospitalization among BPD compared with non-BPD were higher in high-income countries compared with upper-middle-income countries. This may have been partly due to the higher disease burden and therefore a higher proportion of hospitalizations among the non-BPD group in upper-middle-income countries. However, the proportion of hospitalizations for BPD remained high in high-income countries, even higher than in the upper-middle-income countries. This suggests the need for control measures even in developed countries where a cost effectiveness of immunotherapy prophylaxis compared with treatment of severe RSV disease for children with BPD has already been shown [31]. Hospitalization risks were inversely proportional to GA of the children, suggesting a more severe disease outcome the lower the GA.

Both LOS and LOS-ICU were longer among BPD compared with non-BPD. Hong et al [6] reported a slightly longer LOS for BPD without use of home oxygen (7.2; interquartile range [IQR], 3.2–11.2) compared with BPD using home oxygen (7.0; IQR, 4.2–12.8), probably due to longer waiting time for doctors to discharge patients who may have needed oxygen during admission until when they no longer need it, compared with those who can continue on their oxygen need at home upon discharge. The high odds of need for oxygen supplementation in BPD demonstrate the increase in the dependency of the BPD cases on oxygen following RSV-ALRI. Respiratory syncytial virus-ALRI worsens the already underfunctioning lung in BPD, increasing the need for ventilation support [32], thus many of the hospitalized children may have ended up in an ICU where additional ventilation support can be accessed. There is

also an increased risk of long-term disease complications and disabilities further affecting child wellbeing including a decline in lung function with age [32]. Therefore, severe RSV disease in children with risk factors such as BPD will not only lead to a longer hospital stay, but also to a higher need for long-term follow up and management, and thus incur significantly higher costs of treatment. Therefore, interventional measures to prevent RSV infections are useful and should be made available and affordable.

Immunoprophylaxis (using palivizumab) has been shown to have a high efficacy for preventing severe RSV disease and a lower cost compared with treatment of the acute condition [31]. However, their availability and application remains a problem and maybe one of the reasons why RSV disease still remains severe in certain settings. Although current guidelines recommend its use for BPD, it is mainly limited for children under 24 months old, probably due to the higher incidence of RSV infections in this age group. A group of experts, mainly in pediatric cardiology, provided an updated guideline for immunoprophylaxis use [33]. Among the countries included, only Canada and the United States indicated BPD on the list of underlying diseases requiring immunoprophylaxis, and only Canada provided precise indications as “children aged <12 months with BPD, requiring ongoing diuretics, bronchodilators, steroids, or supplemental oxygen, at the start of RSV season” and “children aged <24 months who are on home oxygen, with prolonged hospitalization for pulmonary disease or severely immunocompromised”. The RSV-associated hospitalization rates tend to decrease with age, especially after 24 months of the age, as reported previously [22]. However, although there were limited data from only 2 studies to make any definitive conclusion, our study has shown that despite a lower hospitalization rate in the older group (with a higher rate of decline among non-BPD than BPD as highlighted above), the odds for RSV hospitalization tend to be higher as the child grows older, suggesting a more severe disease among the BPD cases, possibly explained by the persistent pulmonary dysfunction and the worsening ventilation perfusion mismatch [34] in the presence of an increasing body activity and requirement for oxygen use as the child grows older. Therefore, immunoprophylaxis could have a great impact on older children despite the lower hospitalization rates. Considering that the current definition of BPD is a spectrum, defining BPD as mild, moderate, or severe and assessing the oxygen requirement with time for those on home oxygen maybe useful.

The high cost of palivizumab or biosimilars in development and the high number needed to treat to prevent hospitalization could be reasons that limit their use. Because the cost limitation may more seriously affect low-income countries, where RSV disease incidence is reported to be higher compared with higher income countries [35], a success in the current progress on the development of RSV vaccines [4] could be especially useful for

preventing severe RSV disease among high-risk groups when made affordable. Our results show a consistency and a strong positive association between BPD and all outcomes included in the meta-analysis, suggesting a strong positive association between BPD and severe RSV-ALRI disease.

### Strengths and Limitations

The review provides up-to-date data on the association between BPD and RSV-ALRI disease severity. It provides useful information from individual studies and combined effects from different studies through meta-analysis. Sensitivity analysis provides additional information where differences may exist and where focus for interventional measures will be useful. However, there are limitations worth highlighting. There was inconsistency in the case definition for BPD (Supplementary Table 4), and only 11 studies specified GA for infants included in the BPD and non-BPD groups. These could contribute to bias in any effectiveness assessment. The overall quality of the studies was only moderate, affected mainly by the presence of confounding factors, and most of the studies being retrospective and with low sample sizes. The effect of prematurity was not readily assessed for all the included outcomes in the meta-analysis due to limited data with specified GA. We used the random-effects model for meta-analysis due to the assumed variation of the study parameters, and adjustments for zero-events could affect the robustness of our model. Furthermore, there are limited data especially for population-level RSV hospitalization rates, and, in addition, the data for the hospitalization outcomes had significant heterogeneity ( $I^2$  of 97.1% and 93.6%, respectively). The lack of data from lower income countries may also affect the generalizability of our results because these countries may have additional risk factors, which could have an impact on RSV disease burden.

### CONCLUSIONS

Our results highlight a higher risk of severe RSV disease among infants with BPD compared with those without. The lack of standardized indication for prophylactic measures against severe RSV disease in BPD and variations in the treatment and cost effectiveness of immunoprophylaxis may be due to the lack of standardized guidelines and BPD case definition, thus making their assessment difficult. Therefore, there is an urgent need to establish standardized BPD case definitions (and its subtypes), review and assess the guidelines for RSV prophylaxis and their indication, reconsider the recommendations for RSV immunoprophylaxis for BPD with possibility of including older children, and support the development of affordable vaccines and RSV-specific treatments.

### Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to

benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Note

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**Potential conflicts of interest.** S. C. has other financial relationships with Ablynx Pharmaceuticals, Janssen Pharmaceuticals, and Pulmocide Pharmaceuticals outside this study. H. C. received grants from the European Union Innovative Medicines Initiative during the study and grants from the Bill & Melinda Gates Foundation, World Health Organization, United Kingdom National Institute for Health Research, and Sanofi outside this study. H. N. received grants from Innovative Medicines Initiative during the conduct of the study and grants from World Health Organization, Bill & Melinda Gates Foundation, Sanofi, and National Institute of Health Research outside this study. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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