Down Syndrome and the Risk of Severe RSV Infection: A Meta-analysis
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CONTEXT: Down syndrome (DS) is the most common chromosomal condition in live-born infants worldwide, and lower respiratory infection caused by respiratory syncytial virus (RSV) is a leading cause of hospital admissions.

OBJECTIVE: To evaluate RSV-associated morbidity among children with DS compared with a population without DS.

DATA SOURCES: Four electronic databases were searched.

STUDY SELECTION: All cohorts or case-control studies of DS with an assessment of RSV infection and the associated morbidity or mortality were included without language restriction.

DATA EXTRACTION: Two reviewers independently reviewed all studies. The primary outcomes were hospital admission and mortality. Secondary outcomes included length of hospital stay, oxygen requirement, ICU admission, need for respiratory support, and additional medication use.

RESULTS: Twelve studies (n = 1149171) from 10 different countries met the inclusion criteria; 10 studies were cohort studies, 1 study was retrospective, and 1 study had both designs. DS was associated with a higher risk of hospitalization (odds ratio [OR]: 8.69; 95% confidence interval [CI]: 7.33–10.30; I² = 11%) and mortality (OR: 9.4; 95% CI: 2.26–39.15; I² = 38%) compared with what was seen in controls. Children with DS had an increased length of hospital stay (mean difference: 4.73 days; 95% CI: 2.12–7.33; I² = 0%), oxygen requirement (OR: 6.53; 95% CI: 2.22–19.19; I² = 0%), ICU admission (OR: 2.56; 95% CI: 1.17–5.59; I² = 0%), need for mechanical ventilation (OR: 2.56; 95% CI: 1.17–5.59; I² = 0%), and additional medication use (OR: 2.65 [95% CI: 1.38–5.08; I² = 0%] for systemic corticosteroids and OR: 5.82 [95% CI: 2.66–12.69; I² = 0%] for antibiotics) than controls.

LIMITATIONS: DS subgroups with and without other additional risk factors were not reported in all of the included studies.

CONCLUSIONS: Children with DS had a significantly higher risk of severe RSV infection than children without DS.
Acute lower respiratory tract infections (LRTIs) are a leading cause of hospital admissions and pediatric mortality worldwide. Respiratory syncytial virus (RSV) accounts for a great majority of cases, affecting 70% of children <1 year of age and nearly 100% of children <2 years of age. Acute respiratory infections caused by RSV, particularly acute bronchiolitis, create an important economic burden (with a high number of visits to emergency units and outpatient clinics), requiring hospital admissions in up to 3% of cases.

Down syndrome (DS) is the most common chromosomal condition, with a worldwide estimated incidence of 1 in 800 live births. In the United States, the live birth prevalence of DS in recent years (2006–2010) was estimated at 12.6 per 10,000 live births (95% confidence interval [CI]: 12.4–12.8), with ~5300 births annually. Respiratory problems are a frequent cause of morbidity and mortality in this population. Respiratory morbidity includes airway obstruction with consequent sleep-related breathing disorders as well as recurrent respiratory infections with a wide range of severity, including viral upper respiratory tract infections, viral or bacterial LRTIs, and wheezing disorders. Children with DS may suffer from certain anatomic abnormalities, such as macroglossia, pharyngeal hypotonia, adenoid enlargement, and airway malacia, which may be associated with other underlying conditions, such as gastroesophageal reflux, swallowing dysfunction, congenital heart disease (CHD), hypotonia, and immunologic dysfunction.

All these factors contribute to the respiratory morbidity observed in DS. Respiratory infections are the leading cause of hospitalization in children with DS. Most individuals who are affected have at least 1 hospital admission, with multiple hospitalizations being common. A high proportion of these occur during the first year of life and are associated with significant costs.

Therefore, our objective in this systematic review is to evaluate RSV-associated morbidity in children with DS compared with those without DS.

METHODS

Search and Selection Criteria

We searched 4 electronic databases (Medline, the Cochrane Central Register of Controlled Trials, Latin American and Caribbean Literature on Health Sciences database, and the Cumulative Index to Nursing and Allied Health Literature) up to May 2017. The search was conducted by using the following keywords: (Down syndrome) AND (respiratory syncytial virus) OR (respiratory infection). We also searched other nonbibliographic data sources, such as through Web searching, references of the included publications, and pharmaceutical industry Web sites. The inclusion criteria were (1) cohorts or case-control (C-C) studies of DS, (2) assessment of RSV infection (by any laboratory diagnosis test) and the associated morbidity, and (3) no language restriction. The exclusion criteria were (1) no specific RSV analysis, (2) a DS morbidity description with an absence of a control group (CG) with which to compare, and (3) reviews, letters, or abstracts because of the lack of full information about the included studies. The primary outcomes in this systematic review were hospital admission and mortality. Secondary outcomes included length of hospital stay (LOS), oxygen requirement, admission to the ICU, need for respiratory support, and additional medication use (ie, in addition to the patient’s baseline). When data from participants with DS without additional risk factors (eg, CHD or prematurity) were reported, the group without any additional risk factors was used for calculations.

Data Abstraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by 2 independent investigators (A.A.B. and J.A.C.R.), and any disagreement was resolved after discussion. From the full texts, the reviewers independently assessed all studies for inclusion on the basis of the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they independently assessed eligibility. If the information was incomplete, they attempted to contact the authors. The risk of bias from including certain studies was assessed according to the Newcastle–Ottawa scale.

Data Analysis

We calculated pooled odds ratios (ORs) with 95% CIs for categorical outcomes and mean differences with 95% CIs for continuous outcomes. Heterogeneity was assessed by using the $I^2$ test (≤25% absence of bias, 26%–39% unimportant, 40%–60% moderate, and 60%–100% substantial bias). For all outcomes measured, a fixed-effects meta-analysis was used when low heterogeneity was present ($I^2 < 40%$), and a random-effects meta-analysis was performed when high heterogeneity was detected ($I^2 \geq 40%$) to address the variation across the included studies. Data from cohort and retrospective studies were pooled together and into separate meta-analyses. The meta-analyses were performed by using Review Manager 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

A total of 36 studies were initially identified in the databases and other
Sources (Fig 1). After excluding 3 duplicates, we reviewed 33 abstracts. Eighteen studies were excluded because they did not meet inclusion criteria. Fifteen full-text articles were evaluated, and after excluding 3 studies, 12 studies fulfilled the inclusion criteria for the qualitative and quantitative synthesis. These 12 studies \((n = 1149171 \text{ children: } 3662 \text{ children with DS and } 1145509 \text{ children without DS})\) were published from 2004 to 2017.\(^{12–23}\) Ten studies were cohort studies,\(^{12–16,18–20,22,23}\) 1 study was a C-C study,\(^{21}\) and 1 study had both designs.\(^{17}\) Most studies included participants up to 2 years of age,\(^{12–14,16,17,22,23}\) whereas some studies included all pediatric ages.\(^{15,18–21}\) Six studies were conducted in Europe,\(^{12–14,16,22,23}\) 3 studies were conducted in Asia,\(^{15,18,21}\) 2 studies were conducted in the United States,\(^{17,19}\) and 1 study was conducted in Latin America.\(^{20}\) A detailed description of these 12 studies is shown in Table 1, and a description of our quality assessment is presented in Table 2.

**Primary Outcomes**

**Hospital Admissions**

The authors of 6 studies reported differences in RSV hospital admissions between children with DS and children without DS.\(^{12,13,16,19,22,23}\) DS was associated with higher odds of admission (pooled OR: 8.69; 95% CI: 7.33–10.30; \(I^2 = 11\%\)) with the absence of bias (Fig 2). Excluding studies with no description of additional risk factors and studies that included a population with DS with known additional risk factors, the same results were obtained (pooled OR: 16.66; 95% CI: 7.23–39.46; \(I^2 = 0\%\)).\(^{13,22}\) The authors of 1 study reported that the age distribution also tended to be different between both groups, with children with DS continuing to have more hospitalizations for RSV during their second year of life than controls.\(^{22}\) Similar results were obtained when only data from prospective studies were analyzed (data not shown).

The authors of 1 study compared children with CHD with children with DS who had CHD or did not have CHD. The study revealed that DS appeared to be associated with a higher risk of hospital admission compared with CHD without DS (OR: 1.82; 95% CI: 1.30–2.74).\(^{14}\)

**Mortality**

The authors of 5 studies reported RSV mortality.\(^{12,20–23}\) Children with DS had a statistically increased risk of mortality than children without DS (pooled OR: 9.4; 95% CI: 2.26–39.15;
**TABLE 1** Summary of Included Studies

<table>
<thead>
<tr>
<th>Author, y</th>
<th>Country</th>
<th>Study Design</th>
<th>Included Participants</th>
<th>Outcomes</th>
<th>No. Participants, n</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fjaerli et al, 2004</td>
<td>Norway</td>
<td>RC</td>
<td>Children &lt;2 y of age hospitalized for RSV bronchiolitis compared with all children &lt;2 y of age living in same area identified from official populations statistics and hospital records (DS: 52; CG: 58/127); DS group included participants with additional risk factors (4 children with CHD)</td>
<td>Hospital admissions, mortality, need of mechanical ventilation, LOS</td>
<td>DS: 52; CG: 58/127</td>
<td>DS median: 9 mo; CG median: 6 mo</td>
</tr>
<tr>
<td>Bloemers et al, 2007</td>
<td>Netherlands</td>
<td>RC and PC</td>
<td>RC: children with DS managed by DS study group, data obtained from medical records; PC: birth prospective cohort of children with DS managed until 2 y of age. DS: without additional risk factors 216 (103 in retrospective study and 113 in prospective study); CG: 276 siblings of the birth cohort. Participants with CHD and prematurity were included in this study, but only the non–high-risk population with DS was included in analysis.</td>
<td>Hospital admissions, mortality, need of mechanical ventilation, need of supplemental oxygen, LOS</td>
<td>DS: 216; CG: 276</td>
<td>DS range: 0–24 mo; CG range: 0–24 mo</td>
</tr>
<tr>
<td>Medrano López et al, 2009</td>
<td>Spain</td>
<td>PC</td>
<td>Multicentric study including individuals with CHD and participants with DS (with and without CHD) &lt;2 y of age with LRTI. DS: 279 (105 without CHD); CG: 805. Individuals with CHD were studied, but the prematurity condition was excluded.</td>
<td>Hospital admissions, need of mechanical ventilation, admission to PICU, LOS</td>
<td>DS: 279; CG: 805</td>
<td>DS median: 10 mo; CG median: 8.5 mo</td>
</tr>
<tr>
<td>Megged and Schlesinger, 2010</td>
<td>Israel</td>
<td>RC</td>
<td>Review of medical records of 222 children with DS hospitalized because of unspecified reasons; CG was the general population with RSV infection (DS: 222; CG: not reported); no description of additional risk factors</td>
<td>Mortality, need of mechanical ventilation, LOS</td>
<td>DS: 222; CG: not reported</td>
<td>—</td>
</tr>
<tr>
<td>Kristensen et al, 2012</td>
<td>Denmark</td>
<td>PC</td>
<td>Population-based cohort study to evaluate risk and severity of RSV hospitalization in children with chronic conditions &lt;2 y of age (DS: 399; CG: 451806); no description of additional risk factors</td>
<td>Hospital admissions, mortality, LOS</td>
<td>DS: 399; CG: 451806</td>
<td>DS range: 0–23 mo; CG range: 0–23 mo</td>
</tr>
<tr>
<td>Zachariah et al, 2012</td>
<td>United States</td>
<td>RC and C-C</td>
<td>RSV hospitalization data and birth data of children with and without DS &lt;2 y of age (2 different databases and state census). Database 1: DS 630; CG not reported. Database 2: DS not reported; CG not reported. C-C study of clinical features of RSV between DS and non-DS admissions: DS 35 (16 without other risk factors); CG 48. Participants with CHD and prematurity were included in this study, but only the non–high-risk population with DS was included in analysis.</td>
<td>Hospital admissions, need of mechanical ventilation, LOS, use of bronchodilators, use of systemic corticosteroids, use of antibiotics</td>
<td>Database 1: DS 630; CG not reported. Database 2: DS not reported; CG not reported. C-C: DS 35 (16 without other risk factors); CG 48</td>
<td>Database 1: DS range: 0–23 mo</td>
</tr>
<tr>
<td>Zhang et al, 2013</td>
<td>China</td>
<td>PC</td>
<td>Children 1 mo to 14 y of age admitted to the PICU for severe RSV LRTI were managed during hospitalization (DS: 13 [9 without other risk factors]; CG 158; individuals with chronic preexisting conditions were excluded in this study.</td>
<td>Need of ventilatory support, LOS in PICU, mortality</td>
<td>DS: 13; CG: 158</td>
<td>Total: median 3 mo (1 mo to 3 y)</td>
</tr>
</tbody>
</table>
When only data from prospective studies were analyzed, results maintained their significance (data not shown). The single study that only included individuals with DS without additional risk factors revealed no mortality in both groups.

### Secondary Outcomes

#### LOS

The authors of 9 studies evaluated LOS (although data for meta-analysis were not available to perform a meta-analysis). The authors of 3 studies reported oxygen use during RSV infection (Fig 4A). When only data of prospective studies were analyzed (not shown), similar findings with a longer LOS were seen in children with DS than in controls, but not enough data were available to perform a meta-analysis.

### Table 1

<table>
<thead>
<tr>
<th>Author(s), Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Included Participants</th>
<th>Outcomes</th>
<th>No. Participants, n</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stagliano et al, 2015</td>
<td>United States</td>
<td>RC</td>
<td>RSV hospitalization data of children with and without DS within Tricarea &lt;3 y of age (DS: 842; CG: 632, 358); participants with additional risk factors were included (23% hemodynamically significant CHD, 28% prematurity, and 2% chronic lung disease)</td>
<td>Hospital admissions, need of respiratory support, LOS</td>
<td>DS: 842; CG: 632, 358</td>
<td>—</td>
</tr>
<tr>
<td>Galleguillos et al, 2016</td>
<td>Chile</td>
<td>RC</td>
<td>RSV hospitalization data of children &lt;14 y of age with and without DS (DS: 58; CG: 58); participants with additional risk factors were included (15% hemodynamically significant CHD and 10% chronic lung disease)</td>
<td>Mortality, need of respiratory support, need of supplemental oxygen, admission to PICU, LOS, use of systemic corticosteroids, use of antibiotics</td>
<td>DS: 58; CG: 58</td>
<td>DS median: 26.4 mo; CG median: 11.8 mo</td>
</tr>
<tr>
<td>Lee et al, 2016</td>
<td>Taiwan</td>
<td>CC</td>
<td>Children &lt;18 y of age admitted to the PICU for severe RSV LRTI (DS: 9; CG: 177); no description of additional risk factors</td>
<td>Mortality, need of respiratory support, LOS in PICU</td>
<td>DS: 9; CG: 177</td>
<td>Total median: 5.3 mo</td>
</tr>
<tr>
<td>Sánchez-Luna et al, 2017</td>
<td>Spain</td>
<td>PC</td>
<td>Individuals with DS recruited after birth and matched with 1 control (exclusion of individuals with other risk factors); RSV hospitalization for children with DS &lt;1 y of age and assessment of disease severity (DS: 93; CG: 88); individuals with chronic preexisting conditions were excluded in this study.</td>
<td>Hospital admissions, mortality, need of respiratory support, need of supplemental oxygen, admission to PICU, LOS in PICU</td>
<td>DS: 93; CG: 68</td>
<td>DS mean ± SD: 7.4 ± 5.4 mo; CG mean ± SD: 8.4 ± 6.1 mo</td>
</tr>
<tr>
<td>Grut et al, 2017</td>
<td>Sweden</td>
<td>RC</td>
<td>RSV hospitalization and birth data for children with DS, matched with 2 controls each, &lt;2 y of age, 3 different databases (DS: 814; CG: 1628); no description of additional risk factors</td>
<td>Hospital admissions, mortality</td>
<td>DS: 814; CG: 1628</td>
<td>—</td>
</tr>
</tbody>
</table>

PC, prospective cohort; RC, retrospective cohort; —, not applicable.

a US Department of Defense's health care program.
ICU admission than controls (pooled OR: 2.56; 95% CI: 1.17–5.59; \( I^2 = 0\% \)) without bias. Additionally, 1 study revealed that in children with CHD, having DS was not associated with a higher risk of ICU admission (OR: 1.42; 95% CI: 0.77–2.63).\(^{14}\) The single study that only included individuals with DS without additional risk factors revealed no difference between both groups.\(^{22}\)

**Need for Respiratory Support**

The authors of 6 studies reported the necessity for respiratory support during RSV infection.\(^{12,13,17,19,20,22}\) DS was associated with a higher risk of needing mechanical ventilation compared with what was seen in controls (pooled OR: 4.56; 95% CI: 2.17–9.58; \( I^2 = 57\% \)) although with moderate bias (Fig 4B). When only data of prospective studies or studies that only included individuals with DS without additional risk factors were analyzed, similar results were obtained (data not shown). When data from prospective studies were analyzed, similar results were obtained (data not shown). Additionally, the authors of 1 study reported that in children with CHD, having DS was not associated with a higher need for mechanical ventilation (OR: 1.34; 95% CI: 0.90–1.98).\(^{14}\)

**Additional Medication Use**

The authors of 1 study\(^ {17}\) reported a higher chance of prescription of bronchodilators in patients with DS with no additional risk factors than in controls (OR: 5.16; 95% CI: 1.31–20.34). The authors of 2 studies\(^ {17,20}\) reported a higher use of antibiotics and a higher use of systemic corticosteroids in children with DS compared with controls (pooled OR: 2.65 [95% CI: 1.38–5.08; \( F = 0\% \)] and pooled OR: 5.82 [95% CI: 2.66–12.69; \( F = 0\% \)], respectively). The single study that only included individuals with DS without additional risk factors revealed similar results.\(^ {17}\)
FIGURE 2
Pooled ORs and 95% CIs for the number of hospital admissions because of RSV infection between children with DS and children without DS. df, degrees of freedom; M-H, Mantel-Haenszel test.

FIGURE 3
Pooled ORs and 95% CIs for mortality because of RSV infection between children with DS and children without DS. df, degrees of freedom; M-H, Mantel-Haenszel test.

FIGURE 4
A, Pooled ORs and 95% CIs for oxygen requirement because of RSV infection between children with DS and children without DS. B, Pooled ORs and 95% CIs for mechanical ventilation support because of RSV infection between children with DS and children without DS. df, degrees of freedom; M-H, Mantel-Haenszel test.
DISCUSSION

This systematic review with a meta-analysis of 12 studies that were conducted in 10 different countries around the world revealed that children with DS are at a significantly higher risk of having severe RSV infection (higher hospital admission, mortality, LOS, oxygen requirement, ICU admission, need for ventilator support, and additional medication use) than children without DS with the absence of bias in the vast majority these outcomes.

Because DS is the most common chromosomal disorder worldwide and given that RSV is associated with ~28% of all acute LRTI episodes and 13% to 22% of all acute LRTI mortality in young children,24 the results of the current study carry high importance and consequences for public health. Therefore, any potential strategy to reduce RSV infection (eg, prophylaxis with monoclonal antibodies or new vaccines25) in children with DS could decrease their morbidity and mortality.

Palivizumab, a humanized monoclonal antibody, is used for prophylaxis against RSV and reduces hospitalizations in children at high risk (eg, those with chronic lung disease, hemodynamically significant CHD, neuromuscular disease, immunodeficiency, and/or prematurity) <2 years of age.26–30 Currently, the American Academy of Pediatrics does not recommend the routine use of palivizumab to prevent RSV infection in patients with DS who do not qualify for other reasons (eg, CHD, chronic lung disease, airway clearance issues, or prematurity) because insufficient data are available to recommend palivizumab prophylaxis routinely for children with Down syndrome.31,32 However, according to the present systematic review and the results of our meta-analysis, children with DS have a 9 times higher mortality risk and an 8.7 times higher risk of hospitalization because of RSV than children without DS. There is also a high economic burden on families and health care systems. They have a 6.5-fold higher risk of a supplemental oxygen requirement, a 2.7-fold increased risk of ICU admission, and a 4.7-fold higher risk of need for ventilator support and on average spend 4.7 days longer in the hospital. Our analysis also revealed that even in children with DS without additional risk factors (eg, CHD or prematurity), they had significantly more risk.

A recent report revealed a decrease in hospitalization rates because of RSV in the United States (between 1997 and 2012) in non–high-risk infants as well as among those with chronic lung disease and high-risk CHD but not among those with DS without CHD.33 Indeed, this latter group had the highest hospitalization rate trend in this period.33 In 2015, the total charges for infants with DS who were hospitalized for RSV increased from $10141 (US dollars) to $18217 (from 1997 to 2012, respectively); in contrast, charges for non–high-risk infants increased from $6983 to $11273.33 The authors of a recent prospective study of 532 Canadian children with DS who received palivizumab reported a 3.6-fold reduction in the incidence rate ratio of RSV-related hospitalizations during the first 2 years of life.34 A recent Japanese multicenter postmarketing surveillance study about palivizumab prophylaxis against RSV infection in 138 children with DS without hemodynamically significant CHD revealed palivizumab prophylaxis to be safe and effective for the prevention of LRTI caused by RSV. Only 2 (0.7%) children were hospitalized.35 However, it is important to note that hospitalization might be a weak proxy outcome because the threshold to admit a patient with DS might be lower. More cost-utility studies used to determine the efficacy of RSV immunoprophylaxis in this specific high-risk patient population need to be done.

A limitation of the present systematic review is that not all of the studies had a subgroup of participants with DS with CHD and without CHD or other additional risk factors, but almost all results were similar when only studies with data of participants with DS without other risk factors were considered. However, the present review had strengths. In regard to methodology, according to the Newcastle–Ottawa scale, the risk of bias of the 12 included studies was reasonably low, the total number of participants was considerably high (n = 3662 children with DS and 1 145 509 children without DS; 1 149 171 children in total), and the outcomes selected had importance for the patients and also public health implications. It is important to remark that the vast majority of the outcomes that were analyzed had no or unimportant bias.

CONCLUSIONS

This systematic review reveals that children with DS are at a significantly higher risk of having severe RSV infections (higher hospital admission, mortality, LOS, oxygen requirement, ICU admission, need for respiratory support, and additional medication use) than children without DS.

ABBREVIATIONS

C-C: case-control
gg: control group
CHD: congenital heart disease
CI: confidence interval
DS: Down syndrome
LOS: length of hospital stay
LRTI: lower respiratory tract infection
OR: odds ratio
RSV: respiratory syncytial virus
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