Respiratory Syncytial Virus Prophylaxis in Down Syndrome: A Prospective Cohort Study

WHAT'S KNOWN ON THIS SUBJECT: Down syndrome is an independent risk factor for severe respiratory syncytial virus infection and subsequent hospitalization. Immunoprophylaxis may reduce respiratory syncytial virus-related hospitalization by 3.6-fold (95% confidence interval, 1.5–8.7) in children with Down syndrome overall.

BACKGROUND AND OBJECTIVES: Children with Down syndrome (DS) are at significant risk for respiratory syncytial virus (RSV) infection and related hospitalization. We compared hospitalization rates due to respiratory tract infection in children with DS aged <2 years who prospectively received palivizumab during the RSV season with a previously published, similar untreated DS birth cohort.

METHODS: A total of 532 children with DS who prospectively received palivizumab were assembled from the prospective Canadian RSV Evaluation Study of Palivizumab registry between 2005 and 2012. The untreated group included 233 children with DS derived from a nationwide Dutch birth cohort from 2003 to 2005. Events during the RSV seasons were counted. Poisson regression analysis was performed to compare incidence rate ratios (95% confidence intervals [CIs]) between groups while controlling for observation length and known risk factors for severe RSV infection.

RESULTS: In total, 31 (23 untreated, 8 treated) RSV-related hospitalizations were documented. The adjusted risk of RSV-related hospitalizations was higher in untreated subjects than in palivizumab recipients (incidence rate ratio 3.63; 95% CI, 1.52–8.67). The adjusted risk of hospitalization for all respiratory tract infection (147 events; 73 untreated, 74 treated) was similar (incidence rate ratio untreated versus palivizumab 1.11; 95% CI, 0.80–1.55).

CONCLUSIONS: These results suggest that palivizumab is associated with a 3.6-fold reduction in the incidence rate ratio for RSV-related hospitalization in children with DS during the first 2 years of life. A randomized trial is needed to determine the efficacy of RSV immunoprophylaxis in this specific high-risk patient population. Pediatrics 2014;133:1–7

AUTHORS: Hao Yi, BSc,a Krista L. Lanctôt, PhD,a Louis Bont, MD, PhD,b Beatrix L.P. Bloemers, MD, PhD,b Michel Weijerman, MD, PhD,b Chantal Broers, MD,b Abby Li, MSc,a Alexander Kiss, PhD,a Ian Mitchell, MD,d and Bosco Paes, MD,e on behalf of the CARESS investigators

aMedical Outcomes and Research in Economics Research Group, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada. bDivision of Infectious Diseases, Department of Pediatrics, University Medical Centre Utrecht, Utrecht, Netherlands; cDepartment of Pediatrics, VU University Medical Center, Amsterdam, Netherlands; dDivision of Respiratory, Department of Pediatrics, University of Calgary, Calgary, Alberta, Canada, and eDivision of Neonatology, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

KEY WORDS
respiratory syncytial virus, palivizumab, Down syndrome, outcomes

ABBREVIATIONS
CARESS—Canadian RSV Evaluation Study of Palivizumab
CHD—congenital heart disease
CI—confidence interval
CLD—chronic lung disease
DS—Down syndrome
IRR—incidence rate ratio
RSV—respiratory syncytial virus

(Continued on last page)
Down syndrome (DS) is an independent risk factor for respiratory illness and severe respiratory syncytial virus (RSV)-related infection and hospitalization in children. The combined attributes of a compromised innate and adaptive immune system in early infancy with anatomic and physiologic aberrations such as gastroesophageal reflux disease, obstructive sleep apnea, and hemodynamically significant heart disease all lead to significant morbidity and mortality in DS during the first 2 years of life.

Palivizumab, a humanized monoclonal antibody, has been proven safe and efficacious against RSV in randomized, placebo-controlled studies involving preterm infants <35 weeks' gestational age during their first RSV season and children aged <2 years with severe chronic lung disease (CLD) and hemodynamically significant cardiac disease. The Canadian Paediatric Society recommends prophylaxis for children with DS only if they are likely to be exposed to RSV during their first season and are on home oxygen or have experienced prolonged hospitalization for pulmonary disease or are severely immunocompromised. There are no randomized clinical trials of RSV prophylaxis in children with DS and to date no trial has been registered on the US National Institutes of Health Web site. In the absence of trial data, we undertook this prospective analytic cohort study to estimate the effectiveness of RSV prophylaxis in this population. The objective of this study was to compare lower respiratory tract infection hospitalization and RSV-related hospitalization rates between a prospectively followed cohort of children with DS treated with palivizumab and a control group of prospectively followed untreated subjects with DS.

METHODS
Design
The study compared respiratory tract infection hospitalization and RSV-related hospitalization rates between a prospectively followed cohort of children with DS treated with palivizumab and a control group of prospectively followed untreated subjects with DS.

Populations and Inclusion Criteria
Treatment Group
Palivizumab-treated children with DS (n = 532) were selected from the Canadian RSV Evaluation Study of Palivizumab (CARESS). CARESS is a prospective observational registry of palivizumab use and outcomes. Started in 2005, the registry includes a total of 13,310 children assembled from 32 Canadian hospital sites across 7 RSV seasons (2005–2012). Children enrolled in the registry have received ≥1 dose of palivizumab and are followed for the respective annual RSV season. For this analysis, subjects were selected based on the documented presence of DS. In total, 68 of 532 treated subjects were followed for 2 RSV seasons. In Canada, healthy children with DS are uniformly approved for RSV prophylaxis in the provinces of Alberta and Ontario in the first 2 years of life, whereas the rest of the provinces provide palivizumab only to children with DS who have significant underlying medical disorders.

Untreated Group
The untreated group (n = 233) was assembled from the published, prospective national birth cohort registry in the Netherlands of children with DS aged <2 years, including those with respiratory infection hospitalization and RSV-related hospitalization from 2003 to 2005.

Data Collection and Quality Control
Parental or legal guardian informed consent for both groups was obtained before patient enrollment, and approval of the studies was granted by the respective institutional research ethics boards.

Treatment Group
Demographic, medical, and family history data are collected at the time of patient enrollment; hospitalization and palivizumab administration data are obtained monthly. In the event of a hospitalization, relevant hospital records are reviewed by the site's research nurse for detailed information on patient diagnosis, reason for hospitalization, and length of stay.

Untreated Group
The Dutch national birth cohort encompasses 90% to 95% of the total number of children born with DS. Infants were not screened, approached, or excluded. Data on gestational age, presence of CLD, congenital heart disease (CHD), and hospitalization were collected through a telephone questionnaire by one of the investigators and confirmed by patient medical records.

Definitions
CLD was established in both cohorts through medical discharge summaries and conforming to qualifying criteria stipulated by the bronchopulmonary dysplasia proceedings. Hemodynamically significant CHD was similarly defined in both groups as uncorrected or palliated cyanotic or acyanotic CHD with pulmonary hypertension (systolic pulmonary arterial pressure ≥40 mm Hg) or a need for medication to manage congestive heart failure and confirmed by a pediatric cardiologist.

Compliance with treatment was measured by 2 components: the ratio of palivizumab doses received over projected dose number from enrollment to...
the end of the RSV season, and the interdose interval of injections received. Compliance was defined as patients receiving ≥5 injections, or all expected injections if <5 months of the season remained after enrollment. Compliant intervals were 16 to 35 days between the first and second injection and 30 ± 5 days for subsequent injections.

Comparability of Groups
The RSV season duration is very similar in the Netherlands and Canada. In the observed period in the Netherlands, the average duration of the season was 24 weeks.³² The median season onset was the 45th week of the year (first week of November) and offset the 12th week of the next year (last week of March). Similarly, in the observation period in Canada, the average duration of the RSV season was also 24 weeks, with median season onset in November and offset at the end of March.

Concomitant risk factors for RSV hospitalization were identified in treated and untreated subjects and compared. These were hemodynamically insignificant CHD, hemodynamically significant CHD, CLD, prematurity (≤35 completed weeks’ gestational age), and other relevant multisystem anomalies such as duodenal atresia, Hirschsprung disease, or musculoskeletal malformations.

Outcomes
Hospital admissions for lower respiratory tract infection with a subsequent positive or negative detection of RSV were the primary outcomes measured in this study. To account for possible undetected RSV infections within respiratory infection hospitalizations among children who were not tested for RSV, those subjects were excluded from the RSV hospitalization analysis. Only hospitalizations occurring within the broad time frame of the RSV season, defined as September 1 to May 31 each year, were counted, because RSV events in the treated group beyond the RSV season were not evaluated.

Diagnostic and Laboratory Criteria for RSV Confirmation
Untreated Group
RSV hospitalization was defined as symptomatic admission for deep or wet chest cough, wheezing, hoarseness, stridor, or shortness of breath. RSV positivity was confirmed by enzyme or immunoﬂuorescent assay or a positive viral culture for RSV from nasopharyngeal secretions. All untreated children hospitalized during the RSV season with a symptomatic lower respiratory tract infection as previously described were tested for the presence of RSV infection. Negative RSV results during hospitalization for lower respiratory tract infection were classiﬁed as respiratory infection hospitalizations. RSV infection without hospitalization was not assessed.

Treatment Group
RSV hospitalization was similarly defined symptomatically as in the untreated group. Diagnostically, in addition to the aforementioned assays, cases were also identiﬁed by reverse transcription polymerase chain reaction. RSV infection without hospitalization was not assessed.

Statistical Analysis
Demographics and risk factors were compared between groups by using t test or χ² where appropriate. For the primary analysis, groups (treated versus untreated) were compared on the basis of frequency of admission to hospital for respiratory infections and conﬁrmed RSV hospitalization using Poisson log linear regression analysis with adjustment for possible confounding variables. The model was used to generate an incidence rate ratio (IRR) for hospitalization. Models were adjusted for hemodynamically significant CHD, insignificant CHD, gestational age, birth weight, and RSV prophylaxis with palivizumab.

Secondary Analyses
To evaluate the hospitalization course, secondary analyses compared the respective ages of children at hospital admission and the lengths and frequency of hospitalization groups by t test or χ² where appropriate.

Subgroup Analyses
Because insignificant CHD may or may not contribute to RSV hospitalization, it was analyzed both independently and combined with patients without risk factors across the treated and untreated groups. To speciﬁcally compare outcomes in children with DS who meet current standard indications for RSV prophylaxis in international pediatric guidelines²⁵,³³–³⁷ (namely hemodynamically significant CHD, prematurity, or CLD), a group of children with only these risk factors was identiﬁed, and outcomes were compared between treated and untreated children. Patients with multisystem anomalies were excluded from this analysis. Finally, a subgroup analysis was performed to measure the treatment effect of palivizumab on children with DS speciﬁcally within the ﬁrst RSV season of life. Primary outcomes, that is, RSV hospitalizations between September and May, within 365 days from the child’s date of birth, in treated and untreated groups, were compared by using Poisson log linear regression as described earlier.

RESULTS
There were 324 patient-years of observation in the untreated group and 184 patient-years of observation in the treated, palivizumab group during the designated RSV seasons. The treated group received 4.3 (±1.4) injections on average during a given RSV season; 89% of participants received all expected
palivizumab doses, where the expected number was determined by the number of months remaining in the RSV season after enrollment. Treated and untreated groups differed with respect to prematurity, birth weight, gestational age, race, and the proportions of children with underlying risk factors for RSV hospitalization (Table 1).

In total, 31 subjects were hospitalized for RSV (23 untreated and 8 treated). Comparing groups on RSV hospitalization showed that untreated subjects had a 3.63-fold higher IRR than treated subjects (95% CI, 1.52–8.66) after adjustment for covariates. The Poisson regression model had a reasonable goodness of fit ($P = .257$) and was statistically significant (likelihood ratio $P = .002$).

In the subgroup analysis for RSV-related hospitalization, significant IRR differences were also found between the groups of children who additionally qualified for prophylaxis by standard indications (untreated, $n = 94$; treated, $n = 228$) irrespective of having DS (Table 2). No significant IRR differences were found between treated and untreated children with no risk factors (untreated, $n = 67$; treated, $n = 196$), but combination with the insignificant CHD group (untreated, $n = 117$; treated, $n = 279$) yielded a trend of lower risk for the treated group (Table 2).

A total of 147 respiratory infection hospitalizations were reported (untreated group, $n = 73$; treated, $n = 74$). Analysis and subgroup analyses of respiratory infection hospitalizations found the IRR to be similar between treated and untreated groups (Table 2). Significant contributing factors to respiratory infection hospitalizations were hemodynamically significant CHD (IRR = 2.84; 95% CI, 1.80–4.51), and insignificant CHD (IRR = 2.06; 95% CI, 1.31–3.22).

With regard to the hospitalization course, there were no differences between the groups with respect to the frequency or duration of hospitalization for respiratory infection-related events (Table 3). A higher proportion of children hospitalized with respiratory infection received respiratory support in the treated group. With respect to RSV hospitalization, no differences were found between treated and untreated groups in age at first RSV hospitalization or hospital duration. Four untreated children versus none of the treated group needed intensive care or respiratory support, a significantly higher proportion of untreated RSV hospitalized children needed oxygen, and their mean number of days of oxygen treatment was higher (Table 3).

### Post Hoc Analysis

In total, 83% and 50% of RSV hospitalizations occurred within the first year of the child’s life in untreated and treated groups, respectively. Untreated subjects had an RSV hospitalization IRR of 5.25 (95% CI, 1.46–18.87) compared with treated subjects over the first year; no other covariates were significant.

### DISCUSSION

In the first 2 years of life, children with DS are more prone to respiratory tract infections7,19,20 and develop significant complications after RSV-associated bronchiolitis and pneumonia compared with those without DS.1–6 Across 4 reported studies,1–3,5 which have cumulatively evaluated 1646 children with DS aged <2 years, the risk estimate for RSV hospitalizations ranged from 9.9% to

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**TABLE 1** Demographics and Prevalence of RSV Risk Factor Variables in the Groups of Treated and Untreated Children With Down Syndrome

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Untreated (n = 235)</th>
<th>Treated (n = 532)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>133 (57.1%)</td>
<td>302 (56.8%)</td>
<td>.956</td>
</tr>
<tr>
<td>Caucasian</td>
<td>197 (84.5%)</td>
<td>356 (66.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Have siblings</td>
<td>154 (68.1%)</td>
<td>359 (67.5%)</td>
<td>.71</td>
</tr>
<tr>
<td>Birth wt (g)</td>
<td>3056.6 (±591.3)</td>
<td>2807.6 (±769.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>38.4 (±1.86)</td>
<td>37.44 (±2.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Have no risk factors</td>
<td>67 (28.8%)</td>
<td>196 (36.8%)</td>
<td>.03</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodynamically significant CHD</td>
<td>83 (35.6%)</td>
<td>152 (28.6%)</td>
<td>.05</td>
</tr>
<tr>
<td>CLD</td>
<td>1 (0.4%)</td>
<td>30 (5.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multisystem anomalies</td>
<td>10 (4.3%)</td>
<td>52 (8.5%)</td>
<td>.01</td>
</tr>
<tr>
<td>Premature (&lt;35 wk gestational age)</td>
<td>13 (5.6%)</td>
<td>84 (15.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Insignificant CHD</td>
<td>64 (27.5%)</td>
<td>105 (19.7%)</td>
<td>.02</td>
</tr>
</tbody>
</table>

* Risk factors are not mutually exclusive.

**TABLE 2** IRRs for RSV-Related Hospitalization and Respiratory Illness–Related Hospitalization for Groups of Untreated Compared With Treated Children With Down Syndrome

<table>
<thead>
<tr>
<th>RSV-related hospitalizations</th>
<th>Adjusted IRR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall group</td>
<td>3.63 (1.52–8.67)</td>
</tr>
<tr>
<td>No risk factors</td>
<td>6.57 (0.70–82.16)</td>
</tr>
<tr>
<td>No risk factors or insignificant CHD only</td>
<td>4.46 (0.94–21.29)</td>
</tr>
<tr>
<td>Standard indication risk factors</td>
<td>3.39 (1.02–11.25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory infection–related hospitalizations</th>
<th>Adjusted IRR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall group</td>
<td>1.11 (0.80–1.55)</td>
</tr>
<tr>
<td>No risk factors</td>
<td>0.80 (0.34–1.88)</td>
</tr>
<tr>
<td>No risk factors or insignificant CHD only</td>
<td>0.64 (0.35–1.19)</td>
</tr>
<tr>
<td>Standard indication risk factors</td>
<td>1.10 (0.70–1.74)</td>
</tr>
</tbody>
</table>

* Adjusted for hemodynamically significant CHD, insignificant CHD, gestational age, and birth weight. Ratios >1 indicate higher risk in the untreated group.

* Risk factors that involve standard indications for RSV prophylaxis, namely any combination of hemodynamically significant CHD, CLD, or prematurity <35 wk gestational age.
TABLE 3 Frequencies, Duration, and Course of Hospitalizations in the Treated and Untreated Groups of Children with Down Syndrome

<table>
<thead>
<tr>
<th>RSV-related hospitalization course</th>
<th>Untreated</th>
<th>Treated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitalizations</td>
<td>23</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age at first RSV hospitalization (mean ± SD)</td>
<td>255.58 ± 174</td>
<td>314.13 ± 224.0</td>
<td>.45</td>
</tr>
<tr>
<td>RSV hospital duration (mean ± SD)</td>
<td>12.43 ± 16.2</td>
<td>6.4 ± 4.5</td>
<td>.48</td>
</tr>
<tr>
<td>Admissions to intensive care, count (mean ± SD)</td>
<td>4 (10.3 ± 8.9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Oxygen use, count (mean ± SD)</td>
<td>19 (13.7 ± 19.2)</td>
<td>2 (4.0 ± 0)</td>
<td>&lt;.001; .046</td>
</tr>
<tr>
<td>Respiratory support, count (mean ± SD)</td>
<td>4 (10.3 ± 8.9)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Respiratory support is the use of mechanical ventilation during hospitalization.

19.5%. However, time frames for evaluation differed in the studies, making comparison across studies difficult, and the impact of treatment was not evaluated.

In this study, conducted between 2003 to 2012, which evaluated 2 DS cohorts prospectively during the first two years of life, palivizumab was associated with a 3.6-fold reduction in the incidence rate of RSV hospitalization. This corresponds to an overall 72% reduction (1-1/3.6). The documented reduction in RSV hospitalizations in this study aligns with the projected probability of an 80% reduction in RSV hospitalizations in children with DS, as estimated in our recent publication.38 While, the treated group were hospitalized for a RSV-positive infection at a similar mean age of 10.5 months versus 8.5 months (untreated), a smaller proportion of treated children required oxygen and for shorter periods of time during hospitalization. There was a non-significant tendency toward shorter hospitalizations, need for intensive care, and respiratory support, which may indicate a decrease in the severity of RSV-related illness after prophylaxis.

This is the first study to suggest that palivizumab may provide a substantial benefit in the reduction of RSV-related hospitalizations in children with DS, which affects potential disease complications, incurred morbidities, and hospital costs. Although the findings have been derived from a less rigorous study design, a randomized, double-blind, placebo-controlled clinical trial would require a substantial sample size, dependent on the RSV hospitalization rate in the control group. Assuming a ≥50% difference in RSV hospitalization rates between the palivizumab and placebo groups, a 9.9% RSV hospitalization rate in the control group, a type I error of 0.05, power = 80%, and 1:1 allocation with full recruitment and no dropouts, a sample size of 896 subjects (448 in each arm) would be needed. This is prohibitively large for the DS population, given that birth rates differ widely between countries.

Several limitations of this study merit consideration. First, the groups were assembled in 2 different countries over different time frames with varying baseline characteristics and environmental risk factors that could influence the severity of RSV infection and hospitalization in the respective DS populations.39–42 However, studies on children with DS from the Netherlands,3 Denmark,2 Israel,5 and the United States1,6 have reported similar RSV hospitalization rates, as previously reported in this untreated cohort.3 Moreover, the greater prevalence of risk factors in the treated group suggests possible underestimation of the treatment effect of RSV prophylaxis. Second, the cohorts were not standardized at study inception. Because the untreated children were enrolled at birth, whereas the prophylaxis subjects were recruited after the first palivizumab dose, this may explain the younger age at first hospitalization in the untreated group compared with the prophylaxis group. Third, the indications for hospitalization may vary between institutions, although the need for oxygen and respiratory support confirms a similar severity of RSV-related lower respiratory tract infections in the subjects in both arms of the study. Fourth, the treatment effect may be underestimated because not all children with DS who received prophylaxis were enrolled in the CARESS registry, and not all were tested for RSV. Lastly, the power of the study to show differences in each of the risk factors and some of the events (intensive care admission, respiratory support) was limited. It should also be noted that this is an observational study, and treatment efficacy cannot be ascertained.

The strengths of our study are that both groups were assembled prospectively and compared based on established and well-defined risk factors for RSV hospitalization such as prematurity, CLD, and hemodynamically significant cardiac disorders. Additional assets of the study include the lengths of observations, which were normalized in both groups to more accurately predict the hazard for RSV hospitalization, and pertinent prognostic factors for RSV.
hospitalization were adjusted for in the analysis.

CONCLUSIONS

In this observational prospective study in children with DS, aged <2 years, RSV immunoprophylaxis with palivizumab was associated with a 3.6-fold (72%) decrease in RSV-related hospitalizations. The findings of this study merit additional confirmation through future clinical trials because the groups of treated and untreated infants may not be entirely comparable. Our results warrant a multicenter, randomized trial to establish the efficacy and cost-effectiveness of RSV prophylaxis in children with DS.

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(Continued from first page)

Ms Yi collated the data from the Netherlands and Canada, conducted the initial analyses, and summarized the information into a preliminary draft with appropriate tables and figures. Dr Lanctôt oversaw the patient data and processing, approved the analyses, and reviewed the manuscript; Dr Bont supervised the data collection and analyses of the Dutch cohort, reviewed the manuscript, and provided critical comments on the final version of the manuscript; Dr Bloemers was instrumental in data collection and entry of patient information into the Dutch database, approved the criteria that were merged with the Canadian registry, and performed an in-depth analysis of the outcomes of interest in the Dutch population, Dr Weijerman was instrumental in the construction, data collection, and entry of patient information into the Dutch National Down Syndrome registry and provided intellectual contributions to the article; Dr Broers was involved in data processing, and generating statistical analyses; Dr Kiss approved the analytical plan and reviewed the final analyses; Dr Mitchell critically reviewed the drafts and final manuscript and provided pertinent amendments where applicable; Dr Paes drafted the initial manuscript and incorporated comments from the investigators; and all authors approved the final manuscript as submitted.

The CARESS registry is registered under ClinicalTrials.gov (identifier NCT00420966).


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Address correspondence to Bosco Paes, MD, McMaster University, Department of Pediatrics, HSC-3A, 1280 Main Street West, Hamilton, Ontario, L8S 4K1, Canada. E-mail: paes@mcmaster.ca

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