Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Impact of the Withdrawal of Palivizumab Immunoprophylaxis on the Incidence of Respiratory Syncytial Virus (RSV) Hospitalizations Among Infants Born at 33 to 35 Weeks' Gestational Age in the Province of Quebec, Canada: The RSV-Quebec Study

Jesse Papenburg,[1,2,3] Isabelle Defoy,[4] Edith Massé,[5] Georges Caouette,[6] and Marc H. Lebel[7]

[1]Division of Pediatric Infectious Diseases, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada; [2]Division of Microbiology, Department of Clinical Laboratory Medicine, McGill University Health Centre, Montreal, Quebec, Canada; [3]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada; [4]AbbVie Inc., Saint-Laurent, Quebec, Canada; [5]Division of Neonatology, Department of Pediatrics, Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Estrie-CHUS, Sherbrooke, Quebec, Canada; [6]Division of Neonatology, Department of Pediatrics, Centre Hospitalier Universitaire de Québec, Quebec City, Quebec, Canada; [7]Division of Pediatric Infectious Diseases, Department of Pediatrics, Centre hospitalier universitaire (CHU) Sainte-Justine, Université de Montréal, Montreal, Quebec, Canada

Background. Infants born at 33–35 completed weeks' gestational age (wGA) aged <6 months at the start of or born during respiratory syncytial virus (RSV) season and classified as moderate/high risk of severe RSV disease were included in a palivizumab RSV prophylaxis program in the province of Quebec, Canada, until 2014–2015. We assessed the impact of withdrawal of this indication on lower respiratory tract infection (LRTI)/RSV hospitalizations (H) in this population.

Methods. We conducted a 4-year, retrospective, cohort study in 25 Quebec hospitals (2 seasons with and 2 without palivizumab prophylaxis for moderate- to high-risk infants). Our primary outcome was LRTI/RSV-H incidence. We compared LRTI/RSV-H incidence before (2013–2015; seasons 1 + 2 [S1/2]) and after (2015–2017; S3/4) the change in indication.

Results. We identified 6457 33–35 wGA births. LRTI/RSV-H occurred in 105/3353 infants (3.13%) in S1/2 and 130/3104 (4.19%) in S3/4. Among LRTI/RSV-H, 86.4% were laboratory-confirmed RSV-H. Adjusting for sex, wGA, and birth month, S3/4 was significantly associated with increased LRTI/RSV-H incidence (adjusted odds ratio [aOR], 1.36; 95% confidence interval [CI], 1.04–1.76) but not with laboratory-confirmed RSV-H (aOR, 1.19; 95% CI, 0.90–1.58). Mean duration of LRTI/RSV-H was 5.6 days; 22.6% required intensive care unit admission. Comparing S3/4 with S1/2, infant percentage with LRTI/RSV-H classified as moderate/high risk increased from 27.8% to 41.9% ($P = .11$).

Conclusions. In a province-wide study, we observed a significant increase in LRTI/RSV-H incidence among infants born at 33–35 wGA in the 2 years after withdrawal of RSV prophylaxis.

Keywords. hospitalization; palivizumab; premature infant; public health; respiratory syncytial virus.

Respiratory syncytial virus (RSV) is the leading cause of hospitalizations for acute lower respiratory tract infection (LRTI) among infants and young children worldwide [1–4]. In North America, approximately 2% of children aged <12 months are admitted yearly for RSV LRTI, with most hospitalizations occurring in those aged <6 months [4, 5]. Preterm infants, defined as those born at <36 weeks' completed gestational age (wGA), are at higher risk of severe RSV infection requiring hospitalization because of incomplete pulmonary maturation and a relatively immature immune system. In clinical trials, passive immunoprophylaxis with palivizumab (SYNAGIS, AbbVie Inc., Saint-Laurent, Quebec, Canada) has been shown to be safe and effective at preventing RSV-associated hospitalization in the following specific high-risk infant groups: those with bronchopulmonary dysplasia, a history of prematurity (≤35 wGA), or hemodynamically significant congenital heart disease [6–8]. In Canada, palivizumab has been approved for the prevention of severe RSV disease in these high-risk populations since 2002 [9].

In 2015, the Canadian Paediatric Society modified their recommendations to limit palivizumab immunoprophylaxis to infants born at <30 weeks and 0 days unless they have other

Received 19 July 2019; editorial decision 19 April 2020; accepted 28 April 2020; Published online May 29, 2020.

Presented in part: Hot Topics in Neonatology Conference, Washington, DC, 3 December 2018.

Correspondence: Jesse Papenburg, Montreal Children's Hospital, McGill University Health Centre, E05.1905 – 1001 Décarie Blvd, Montréal (Quebec) H4A 3J1 (jesse.papenburg@mcgill.ca).

Journal of the Pediatric Infectious Diseases Society 2021;10(3):237–44

DOI: 10.1093/jpids/piaa046

significant comorbidities [10]. Because healthcare is a provincial/territorial jurisdiction in Canada, each province/territory defines their palivizumab immunoprophylaxis eligibility criteria. Before the 2015–2016 RSV season, Quebec infants born at 33–35 wGA (33 weeks and 0 days through 35 weeks and 6 days of GA) without other qualifying comorbidities and aged <6 months at the start of RSV season or born during the RSV season were eligible for palivizumab immunoprophylaxis if they scored moderate to high risk on a Canadian risk scoring tool for RSV hospitalization (RSV-H) (Supplementary Table 1), developed and validated in this population [11, 12]. Effective September 2015, the Quebec Ministry of Health revised the immunoprophylaxis program, and infants born at 33–35 wGA without other qualifying comorbidities were no longer eligible [13, 14].

We assessed the impact of withdrawal of this indication on the incidence of presumed or confirmed RSV-associated LRTI hospitalizations (LRTI/RSV-H; defined as laboratory-confirmed RSV-associated hospitalization or LRTI hospitalization when RSV was circulating in the community and for which no RSV testing was performed) in Quebec infants born at 33–35 wGA without other qualifying comorbidities and aged <6 months at the start of or born during the RSV season. We hypothesized that the change in provincial immunoprophylaxis inclusion criteria would result in an increase in LRTI/RSV-H incidence. Our primary objective was to compare the incidence of LRTI/RSV-H among Quebec infants born at 33–35 wGA and aged <6 months at the start of or born during the RSV season for 2015–2016 (RSV season 3) and 2016–2017 (RSV season 4) vs 2013–2014 (RSV season 1) and 2014–2015 (RSV season 2). Our secondary objectives were to compare the incidence of laboratory-confirmed RSV-H in RSV seasons 3/4 with RSV seasons 1/2 and to describe the clinical course of LRTI/RSV-H.

METHODS

Study Design and Setting

We performed a multicenter, retrospective, cohort study in 25 hospitals from various geographic regions in the province of Quebec, Canada, during 4 RSV seasons, from 2013 to 2017. As per Quebec's Ministry of Health RSV immunoprophylaxis guidelines, the start of RSV season was defined as 1 November of a given year and end-of-season as 30 April of the following year. Thus, season 1 was defined as 1 November 2013 to 30 April 2014, season 2 as 1 November 2014 to 30 April 2015, season 3 as 1 November 2015 to 30 April 2016, and season 4 as 1 November 2016 to 30 April 2017. Seasons 1/2 were jointly considered the period of palivizumab immunoprophylaxis, whereas seasons 3/4 were jointly considered the period without palivizumab immunoprophylaxis.

Five of the 25 study hospitals were "birthing" hospitals, as they perform deliveries but do not readmit infants after birth hospitalization discharge. The 5 birthing hospitals are in the catchment areas of the 20 other study centers that perform deliveries and also admit children outside the newborn period. Infants born at any of the study hospitals are thus reasonably expected to be hospitalized at a study hospital should they require medical admission. All 4 pediatric university-affiliated tertiary/quaternary care centers in Quebec participated in the study.

Study Population

We included all otherwise healthy infants born at 33–35 wGA and aged <6 months at the start of or born during RSV seasons 1, 2, 3, or 4 and hospitalized to 1 of the study centers for LRTI/RSV-H (presumed or confirmed RSV-associated LRTI hospitalization) during study seasons 1 to 4. We defined LRTI/RSV-H as laboratory-confirmed RSV-associated hospitalization or LRTI hospitalization when RSV was circulating in the community and for which no RSV testing was performed. Cases of LRTI/RSV-H were identified by querying hospital discharge abstract databases using LRTI- and RSV-specific *International Classification of Diseases*-10 discharge diagnosis codes for nonspecific bronchiolitis, bronchitis, or pneumonia and for RSV bronchiolitis, RSV acute bronchitis, RSV pneumonia, RSV apnea, or RSV as a cause of disease classified elsewhere. We excluded patients with medical conditions that could otherwise be an indication for palivizumab prophylaxis, such as bronchopulmonary dysplasia, hemodynamically significant congenital heart disease, trisomy 21, cystic fibrosis, immunodeficiency, and neuromuscular disease with difficulty in handling secretions. To estimate the number of late preterm births in our study population, all infants born at 33–35 wGA and aged <6 months at the start of or born during 1 of the 4 RSV seasons (2013–2017) were identified from discharge abstract databases from the 25 participating hospitals.

Outcomes and Exposures

Our primary outcome was the incidence of LRTI/RSV-H. The secondary outcome was laboratory-confirmed RSV-H. Other secondary outcomes relating to LRTI/RSV-H included hospital length of stay (LOS), admission and LOS in a pediatric intensive care unit (PICU) or other special care unit, use of oxygen supplementation, and respiratory support.

Our primary exposure variable was the time period, comparing seasons 1/2 (palivizumab immunoprophylaxis) with seasons 3/4 (absence of immunoprophylaxis). Patient demographic and baseline characteristics (sex, gestational age at birth, birth month, Canadian RSV risk scoring tool classification [low vs moderate/high]) and intensity of the RSV season (defined as the area under the provincial laboratory surveillance epidemic curve of the weekly proportion of positive RSV tests reported to

the Quebec provincial respiratory virus laboratory surveillance program for each season [15]), were considered covariates.

Data Collection

Trained research personnel extracted data from the medical charts pertaining to patient demographics and birth hospitalization characteristics, presenting clinical manifestations, medical management, diagnostic tests, final disposition, and mortality. A letter from the treating physician was sent to the parents or legal guardians of LRTI/RSV-H cases to inform them of the study and to obtain their approval to receive and complete questionnaires about the LRTI/RSV-H and their child's risk factors pertinent to the Canadian RSV risk scoring tool classification.

Sample Size Calculation

Our sample size calculation was predicated on practical and statistical considerations. We anticipated 20 participating study sites. Knowing that approximately 2400 preterm infants are born at 33–35 wGA in Quebec per year [16], we conservatively estimated that during each of the 4 RSV study seasons, there would be approximately 850 eligible 33–35 wGA births identified. Assuming an incidence of LRTI/RSV-H in study participants of 2% in seasons 1/2 and 4% in seasons 3/4, we calculated 91% power for the assessment of the difference in LRTI/RSV-H incidences between study periods using a 2-sided χ^2 test with an α of 0.05.

Statistical Analyses

Statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were performed, including number of observations, mean (with standard deviation), median (with interquartile range) for continuous variables, and absolute and relative frequencies for categorical variables. Data were described separately for each of the 2 time periods (RSV seasons 1/2 and RSV seasons 3/4). In addition, the subgroup of moderate- to high-risk late preterm births as per the Canadian RSV risk scoring tool were analyzed descriptively.

Multivariable logistic regression was performed to evaluate the association between the study period (seasons 1/2 vs seasons 3/4) and the hospitalization outcomes (LRTI/RSV-H and RSV-H) after adjusting for relevant confounders determined a priori (sex, gestational age at birth, birth month). Sensitivity analyses were performed that were adjusted for RSV season intensity using that season's epidemic curve's area under the curve (AUC) (calculated using the logarithmic trapezoidal method applied to weekly provincial RSV surveillance data); restricted to male infants born in November–December–January (these infants are attributed at least 36 of a possible 100 points on the Canadian RSV risk scoring tool); or restricted to calendar weeks where provincial RSV test positivity was ≥10%. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were calculated. The χ^2 test was used to compare proportions where appropriate. A 2-tailed P value < .05 was considered statistically significant.

Ethics

The McGill University Health Centre Research Ethics Board, Montreal, Canada, approved the study; authorization to conduct the research was obtained from each participating institution. The requirement of informed consent was waived for medical records review. Parents or legal guardians needed to provide consent to answer the questionnaire on underlying RSV disease severity risk factors.

RESULTS

Incidence of LRTI/RSV-H and RSV-H

We identified 6457 eligible 33–35 wGA births (Table 1) representing approximately 67% of all 33–35 wGA births in Quebec during the 4-year study period. LRTI/RSV-H occurred in 105 of 3353 infants (3.13%) in seasons 1/2 compared with 130 of 3104 (4.19%) in seasons 3/4 (OR, 1.36; 95% CI, 1.04–1.77). Overall, 86.4% of LRTI/RSV-H were laboratory-confirmed RSV-H (97 of 105 [92.4%] in seasons 1/2 vs 106 of 130 [81.5%] in seasons 3/4; P = .16), representing an RSV-H incidence of 2.89% in seasons 1/2 compared with 3.41% in seasons 3/4 (OR, 1.19; 95% CI, 0.90–1.75).

Patient Demographics and Baseline Characteristics

Patient demographics and birth hospitalization characteristics were similar in seasons 1/2 and seasons 3/4 (Table 2). Overall, 57.4% were male, mean birth weight was 2351 g, 18.5% were born at 33 0/7–33 6/7 wGA, 32.7% were born at 34 0/7–34 6/7 wGA, 48.8% were born at 35 0/7–35 6/7 wGA, and 68.1% were singleton births.

A questionnaire to assess the study patient's risk of RSV-H by the Canadian RSV risk scoring tool was completed by the parent or guardian of 54 of 105 infants (51.4%) in seasons 1/2

Table 1. Incidence of Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations (RSV-H) and Laboratory-Confirmed RSV-H by Season Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age

Characteristic	Season 1	Season 2	Season 3	Season 4
Total LRTI/RSV-H	45	60	58	72
Total births (33–35 wGA)	1697	1656	1633	1471
Incidence by season, %	2.65	3.62	3.55	4.89
Incidence by period, %	3.13		4.19	
Total laboratory-confirmed RSV-H	42	55	41	65
Total births (33–35 wGA)	1697	1656	1633	1471
Incidence by season, %	2.47	3.32	2.51	4.42
Incidence by period, %	2.89		3.41	

Abbreviation: LRTI/RSV-H, lower respiratory tract infection/respiratory syncytial virus hospitalizations; wGA, weeks' gestational age.

Table 2. Patient Demographics and Baseline Characteristics Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age With Subsequent Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations

Characteristic	Seasons 1 and 2 (n = 105)	Seasons 3 and 4 (n = 130)
Male sex	62 (59.0)	73 (56.2)
Birth weight, mean (SD), g	2363.5 (424.6)	2341.1 (500.7)
Gestational age at birth, weeks' gestational age		
33 0/7–33 6/7	20 (19.0)	22 (16.9)
34 0/7–34 6/7	34 (32.4)	46 (35.4)
35 0/7–35 6/7	51 (48.6)	62 (47.7)
Singleton birth	75 (71.4)	85 (65.4)
Respiratory support needed during hospitalization[a]	37 (35.2)	47 (36.2)
Length of stay, mean (SD), days	13.5 (10.1)	14.8 (10.7)
Birth month (November, December, January)	30 (28.6)	50 (38.5)
Moderate to high risk of respiratory syncytial virus severe disease[b]	15/54 (27.8)	26/62 (41.9)

Values are presented as n (%) of patients unless otherwise noted.
Abbreviation: SD, standard deviation.
[a]Defined as invasive or noninvasive mechanical ventilation or high-flow air (>2 L/min) by nasal cannula/nasal prongs.
[b]Canadian respiratory syncytial virus risk scoring tool classification [12]. Among patients whose parent/guardian responded to a questionnaire: 54 of 105 infants in seasons 1/2 and 62 of 130 infants in seasons 3/4.

and 62 of 130 infants (47.7%) in seasons 3/4. According to the risk scoring tool [12], in seasons 1/2 and seasons 3/4, respectively, 68.5% and 56.5% were considered low risk, 14.8% and 19.4% moderate risk, 13.0% and 22.6% high risk. The percentage of infants with LRTI/RSV-H classified as moderate to high risk increased from 27.8% to 41.9% ($P = .11$) when comparing seasons 1/2 with seasons 3/4.

LRTI/RSV-H Characteristics

Mean ages at LRTI/RSV-H were 16.9 weeks and 15.3 weeks in seasons 1/2 and 3/4, respectively (Table 3). Mean LOSs were 5.2 days and 6.0 days in seasons 1/2 and 3/4, respectively. Mean PICU admissions were 21.0% and 19.2% in seasons 1/2 and 3/4, respectively. Overall, approximately half of all infants required oxygen supplementation. In seasons 1/2 and seasons 3/4, respectively, 12.4% and 10.0% of infants required invasive mechanical ventilation and 9.5% and 11.5% required noninvasive continuous positive airway pressure (Table 4). No in-hospital deaths were observed.

Among infants known to be moderate to high risk, we found similar hospitalization courses in seasons 1/2 and seasons 3/4, respectively, for total LOS (7.5 and 7.8 days), PICU admission (26.7% and 26.9%), mechanical ventilation (20.0% and 15.4%), and oxygen supplementation (66.7% and 65.4%).

Overall, the primary LRTI/RSV-H discharge diagnosis was pneumonia in 8.1% and bronchiolitis in 87.6%. Additional medical care received during LRTI/RSV-H, including tests, procedures, treatment, and professional consultations, are described in Supplementary Table 2.

Consistent with 3 study hospital laboratories adopting polymerase chain reaction (PCR)–based RSV diagnostic testing during 2015–2017, the proportion of RSV-H cases tested by PCR increased modestly in seasons 3/4 (37.1% vs 48.1%; $P = .11$).

Impact of Withdrawal of Palivizumab Immunoprophylaxis on LRTI/RSV-H and RSV-H

In multivariable logistic regression analyses adjusting for clinically relevant confounders selected a priori (Table 5), infants born at 33–35 wGA were at significantly greater odds of LRTI/RSV-H in seasons 3/4 compared with seasons 1/2 (aOR, 1.36; 95% CI, 1.04–1.76). Birth month of November–December–January was the only other variable significantly associated with LRTI/RSV-H (aOR, 1.62; 95% CI, 1.23–2.14). The odds of RSV-H were greater in seasons 3/4, but this association did not reach statistical significance (aOR, 1.19; 95% CI, 0.90–1.58).

In sensitivity analyses, logistic regression models (Table 5) that additionally adjusted for the intensity of RSV circulation in Quebec during each season (Supplementary Figure 1) showed a significant increase in the odds of LRTI/RSV-H in seasons 3/4 compared with seasons 1/2 (aOR, 1.57; 95% CI, 1.18–2.11). Similarly, after adjusting for seasonal intensity, we found the odds of RSV-H to be significantly greater in seasons 3/4 (aOR, 1.50; 95% CI, 1.11–2.03). Further sensitivity analyses (Supplementary Tables 3–6) all showed similar point estimates consistent with increased risk of LRTI/RSV-H and RSV-H in seasons 3/4 but with wider 95% CIs when restricting to males born in November–December–January due to a much smaller sample size.

DISCUSSION

In this Quebec-wide cohort study, in the 2 seasons following the provincial withdrawal of eligibility for palivizumab immunoprophylaxis among infants born 33–35 wGA aged <6 months at the start of or born during RSV season, we observed an increase of approximately 30% in LRTI/RSV-H incidence (aOR, 1.36; 95% CI, 1.04–1.76), thereby demonstrating a significant impact of the change in recommendations.

A smaller increase in laboratory-confirmed RSV-H that did not reach statistical significance (aOR, 1.19; 95% CI, 0.90–1.58) was seen in multivariable regression analyses adjusting for prespecified confounders. Sensitivity analyses that also adjusted for RSV seasonal intensity in Quebec showed a significant increase in the incidence of LRTI/RSV-H (aOR, 1.57; 95% CI, 1.18–2.11) and of laboratory-confirmed RSV-H (aOR, 1.50; 95% CI, 1.11–2.03) in seasons 3/4.

The percentage of LRTI/RSV-H that were laboratory-confirmed RSV-H declined from 92.4% in seasons 1/2 to 81.5% in seasons 3/4. We hypothesize that this increase in the proportion of untested and unconfirmed LRTI cases coincides with

Table 3. Level and Duration of Hospital Care of Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age

Characteristic	All Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations		Known Moderate/High Risk[a]	
	Seasons 1 and 2 (n = 105)	Seasons 3 and 4 (n = 130)	Seasons 1 and 2 (n = 15)	Seasons 3 and 4 (n = 26)
Age at index hospitalization, mean, wk	16.9	15.3	10.8	12.9
Age at index hospitalization, median (IQR), wk	16 (7–24)	13 (8–23)	8.5 (4–15.5)	10 (7–12)
Total LOS, mean, days	5.2	6.0	7.5	7.8
Total LOS, median (IQR), days	4.0 (2–7)	4.0 (2–7)	7 (4–11)	5.5 (3–12)
Pediatric unit	96 (91.4)	120 (92.3)	15 (100)	23 (88.5)
Median (IQR) number of days	3 (2–5)	3 (2–5)	5 (4–7)	3 (2–7)
Pediatric intensive care unit	22 (21.0)	25 (19.2)	4 (26.7)	7 (26.9)
Median (IQR) number of days	4.5 (2–9)	6 (4–9)	5 (3.5–8)	6 (4–10)
Neonatal intensive care unit	1 (1.0)	5 (3.8)	1 (6.7)	1 (3.8)
Median (IQR) number of days	4 (4–4)	19 (3–55)	4 (4–4)	19 (19–19)
Short stay unit	12 (11.4)	6 (4.6)	2 (13.3)	1 (3.8)
Median (IQR) number of days	2 (1.5–2)	2 (1–2)	2 (2–2)	1 (1–1)
Other (emergency)	26 (24.8)	21 (16.2)	7 (46.7)	10 (38.5)
Median (IQR) number of days	1 (1–1)	2 (1–2)	1 (1–2)	2 (2–2)

Values are presented as n (%) of patients unless otherwise noted.

Abbreviations: IQR, interquartile range; LOS, length of stay.

[a]Canadian respiratory syncytial virus risk scoring tool classification [12]. Classification performed among patients whose parent/guardian responded to a questionnaire: 54 of 105 infants in seasons 1/2 and 62 of 130 infants in seasons 3/4. All other data are from the patients' hospitalization records.

a directive from the Quebec College of Physicians issued in November 2015 to stop routine screening for RSV in cases of hospitalized bronchiolitis [17], as recommended by bronchiolitis clinical practice guidelines [18]. This directive regarding diagnostic testing in bronchiolitis was also evidenced in our population by a decrease in ordering of tests for other respiratory viruses from 58% in seasons 1/2 to 42% in seasons 3/4. These recommendations likely decreased our ability to detect RSV-H in seasons 3/4, as laboratory confirmation was dependent on clinician testing. On the other hand, RSV-H detection may have been enhanced in seasons 3/4 because 3 hospital laboratories changed RSV diagnostics from rapid antigen testing to

Table 4. Use of Respiratory Support in Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age

Characteristic	All Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations		Known Moderate/High Risk[a]	
	Seasons 1 and 2 (n = 105)	Seasons 3 and 4 (n = 130)	Seasons 1 and 2 (n = 15)	Seasons 3 and 4 (n = 26)
Respiratory support needed[b]	43 (41.0)	46 (35.4)	9 (60.0)	14 (53.8)
Conventional mechanical ventilation	13 (12.4)	13 (10.0)	3 (20.0)	4 (15.4)
Mean number of days	4.8	6.1	2.7	7.0
CPAP (invasive)	3 (2.9)	3 (2.3)	1 (6.7)	–
Mean number of days	1.7	1.3	2.0	…
CPAP (noninvasive)	10 (9.5)	15 (11.5)	6 (23.1)	8 (19.5)
Mean number of days	3.1	5.3	8.0	3.5
High-frequency oscillatory ventilation	0	3 (2.3)	0	1 (3.8)
Mean number of days	…	3.0	…	2.0
High-flow air	10 (9.5)	19 (14.6)	0	4 (15.4)
Mean number of days	2.0	2.2	…	1.8
Other (not intubated)	24 (22.9)	24 (18.5)	7 (46.7)	12 (46.2)
Mean number of days	3.3	3.6	3.0	4.7
Oxygen supplementation needed	52 (49.5)	69 (53.1)	10 (66.7)	17 (65.4)
Mean number of days	4.0	4.4	4.4	6.4

All values are presented as n (%) of patients unless otherwise noted.

Abbreviation: CPAP, continuous positive airway pressure.

[a]Canadian respiratory syncytial virus risk scoring tool classification [12]. Classification performed among patients whose parent/guardian responded to a questionnaire: 54 of 105 infants in seasons 1/2 and 62 of 130 infants in seasons 3/4. All other data are from the patients' hospitalization records.

[b]Defined as invasive or noninvasive mechanical ventilation or high-flow air (>2 L/min) by nasal cannula/nasal prongs.

Table 5. Multivariable Logistic Regression Models for Lower Respiratory Tract Infection/Respiratory Syncytial Virus Hospitalizations (RSV-H) and for Laboratory-Confirmed RSV-H Among Preterm Infants Born at 33 to 35 Completed Weeks' Gestational Age

Covariate	LRTI/RSV-H Primary Model	LRTI/RSV-H Adjustment for Season Intensity	RSV-H	RSV-H Adjustment for Season Intensity
Season intensity in Quebec[a]	NA	4.42 (1.07–18.23)	NA	12.15 (2.47–59.82)
Season group				
Seasons 3 and 4 vs. seasons 1 and 2	1.36 (1.04–1.76)	1.57 (1.18–2.11)	1.19 (0.9–1.58)	1.50 (1.11–2.03)
wGA: 33 vs 35	0.99 (0.69–1.42)	0.98 (0.68–1.41)	0.98 (0.68–1.47)	0.98 (0.67–1.45)
wGA: 34 vs 35	1.05 (0.79–1.41)	1.06 (0.79–1.42)	1.10 (0.81–1.50)	1.11 (0.81–1.52)
Male sex	1.17 (0.90–1.54)	1.18 (0.91–1.54)	1.16 (0.87–1.54)	1.17 (0.88–1.55)
Birth month group of November, December, January vs other months	1.62 (1.23–2.14)	1.62 (1.23–2.14)	1.69 (1.26–2.26)	1.69 (1.26–2.27)

Values are presented as adjusted odds ratio (95% confidence interval).
Abbreviations: LRTI/RSV-H, lower respiratory tract infection/respiratory syncytial virus hospitalizations; NA, not applicable; wGA, weeks' gestational age.
[a]Defined as the area under the provincial laboratory surveillance epidemic curve of the weekly proportion of positive RSV tests reported to the Quebec provincial respiratory virus laboratory surveillance program for each season. [https://www.canada.ca/en/public-health/services/surveillance/respiratory-virus-detections-canada.html]

more sensitive PCR-based methods during 2015–2017 [19, 20], resulting in an increase in PCR-confirmed RSV-H (from 37.1% to 48.1%). It is unclear if the net result of these temporal changes in S3/S4 (decreased number of children tested, implementation of molecular testing for RSV) led to a net increase or a net decrease in the ability to detect laboratory-confirmed RSV-H compared with the first 2 seasons of our study. However, the primary study outcome of LRTI/RSV-H should not be biased by temporal changes in RSV test ordering or by laboratory methods used.

In the absence of immunoprophylaxis in seasons 3 and 4, we observed incidences of LRTI/RSV-H of 3.6% and 4.9%, respectively, for a weighted average of 4.2%. Incidences reported for infants born at 33–35 wGA not receiving palivizumab from studies performed in Europe and North America have ranged from 2.1% to 14.7% [8, 11, 21–28], with several recent estimates centered around 4% [29–31]. Taken together, these findings show that despite significant advances in the neonatal care of premature infants, LRTI/RSV-H remains an important burden during the first year of life among 33–35 wGA infants. Moreover, LRTI/RSV-H presented substantial morbidity in our population, with 1 in 5 cases requiring PICU admission and approximately 10% requiring mechanical ventilation.

Given that the reported efficacy of palivizumab in premature infants without significant comorbidities is approximately 80% [6, 8], we had conservatively anticipated an LRTI/RSV-H incidence of 2% in seasons 1/2, or approximately 50% of our expected incidence without prophylaxis. This would also be in line with 2006–2011 data from the Canadian Registry of Palivizumab (CARESS), which reported an RSV-H incidence of 1.4% in healthy infants born at 33–35 wGA receiving palivizumab prophylaxis [32]. Our observed LRTI/RSV-H incidences were 2.7% and 3.6% for seasons 1 and 2, respectively (weighted average of 3.1%). In our study, only a minority of infants in seasons 1/2 would have received palivizumab as indicated by the Canadian risk scoring tool [12]. Unfortunately, we had no means by which to reliably collect individual patient data on palivizumab immunoprophylaxis in our cohort of 6457 births at 33–35 wGA. However, province-wide among the estimated 2400 births at 33–35 wGA yearly in Quebec, an average of only 305 infants without other qualifying comorbidities received palivizumab yearly during 2013–2014 to 2014–2015 [14]. Among these 2400 births, in the absence of other qualifying comorbidities, only those aged <6 months at the start of or born during the RSV season would have been evaluated for palivizumab eligibility. Using the Canadian risk scoring tool, Canadian studies of infants born at 33–35 wGA have reported that 19%–30% were classified as moderate to high risk [11, 33]. Because the data required for risk scoring are not available in a patient's birth hospitalization or LRTI/RSV-H medical chart, we do not know the distribution of risk categories in our base population or among all of our hospitalized cases. Nonetheless, data collected by parental questionnaire were available for approximately half of our LRTI/RSV-H. Among respondents, the percentage classified as moderate to high risk increased from 28% to 42% in the latter 2 seasons. Healthcare utilization was particularly high among this subgroup in terms of hospital LOS (7.7 days) and percentage requiring PICU admission (27%) or mechanical ventilation (17%), suggesting that these infants are at risk of a more complicated hospital course.

This study is limited by its retrospective nature; the validity of our estimates relies on the accuracy of discharge diagnosis coding and on physician testing for RSV. Expected year-to-year variation in RSV burden may also confound results of before and after studies such as ours; however, sensitivity analyses adjusting for RSV season intensity confirmed our primary findings. Also, movement of children either into or out of the catchment areas of the 25 study hospitals could potentially affect calculated hospitalization rates. However, there is no reason to believe that such movement would have been differential between S1/S2 and S3/4; consequently, it would not affect the observed impact of the change in recommendations. Finally, we could not ascertain from medical records the actual numbers of 33–35 wGA eligible births that received palivizumab

prophylaxis during seasons 1/2, nor their adherence to the dosing regimen. During that time, RSV immunoprophylaxis nurse coordinators working in centers that deliver and care for late preterm newborns were charged with identifying, enrolling, ordering, and sometimes providing injections for eligible infants in Quebec. Because of this active program within Quebec's publicly funded healthcare system, we expect that adherence to the palivizumab immunoprophylaxis program would have been high during seasons 1/2. In the CARESS registry, 83.8%–92.7% of Canadian infants receiving palivizumab were adherent to the recommended 5 injection intervals [34]. During seasons 3/4, no infants in the province of Quebec received palivizumab for the sole indication of 33–35 wGA birth (AbbVie, internal data).

In summary, in a province-wide study of more than 6000 births and 235 LRTI/RSV-H among healthy infants born at 33–35 wGA and aged <6 months at the start of or born during 4 consecutive RSV seasons in Quebec, we observed a significant increase in LRTI/RSV-H incidence that correlated with the timing of changes in provincial RSV immunoprophylaxis guidelines. The substantial burden of disease in this population warrants consideration for public health preventive strategies.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

Acknowledgments. We thank all of the participating families. We acknowledge the diligent work of all of the site investigators and their study teams (see Supplementary Table 3 for a list of RSV [respiratory syncytial virus]-Quebec investigators and their affiliations). We thank Fernando Camacho, from Damos Inc, for statistical support (funded by AbbVie Inc.) and Colleen Wegzyn, from AbbVie Inc., for her help with study design.

Financial support. This work was supported by AbbVie Inc. The funder participated in the study design, research, analysis, data collection, interpretation of data, and review and approval of the publication. J. P. wrote the first draft of the manuscript.

Potential conflicts of interest. J. P. has received consulting/speaker fees/honoraria from AbbVie, BD Diagnostics, and Cepheid; research grant funding outside of the current work from AbbVie, BD Diagnostics, MedImmune, Seegene, Sanofi Pasteur, Hoffmann-La Roche, and Janssen Pharmaceutical; and research funding from AbbVie for this study. J. P. is supported by a Chercheur-boursier clinicien career award from the Fonds de recherche Québec santé. I. D. is an AbbVie employee and holds stock or stock options. E. M. received a consulting honorarium from AbbVie and received research funding from AbbVie for this study. G. C. received a consulting honorarium from AbbVie, an educational grant from AbbVie, and research funding from AbbVie for this study. M. H. L. received a consulting honorarium from AbbVie and research funding from AbbVie for 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.

References

1. Jain S, Williams DJ, Arnold SR, et al.; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med **2015**; 372:835–45.
2. Meissner HC. Viral bronchiolitis in children. N Engl J Med **2016**; 374:62–72.
3. Papenburg J, Hamelin MÈ, Ouhoummane N, et al. Comparison of risk factors for human metapneumovirus and respiratory syncytial virus disease severity in young children. J Infect Dis **2012**; 206:178–89.
4. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med **2009**; 360:588–98.
5. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis **2012**; 54:1427–36.
6. IMPACT-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics **1998**; 102(3 Pt 1):531–7.
7. Feltes TF, Cabalka AK, Meissner HC, et al.; Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr **2003**; 143:532–40.
8. Blanken MO, Rovers MM, Molenaar JM, et al.; Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med **2013**; 368:1791–9.
9. AbbVie Inc. SYNAGIS (palivizumab) Product Monograph. Saint-Laurent, Quebec, Canada: AbbVie Inc; **2018**.
10. Robinson JL, Le Saux N; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Preventing hospitalizations for respiratory syncytial virus infection. Paediatr Child Health **2015**; 20:321–33.
11. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. Pediatr Infect Dis J **2004**; 23:806–14.
12. Sampalis JS, Langley J, Carbonell-Estrany X, et al. Development and validation of a risk scoring tool to predict respiratory syncytial virus hospitalization in premature infants born at 33 through 35 completed weeks of gestation. Med Decis Making **2008**; 28:471–80.
13. Héma-Québec. Circulaire HQ-15–025. Information sur la disponibilité du Synagis® pour la saison 2015–2016. Available at: https://www.hema-quebec.qc.ca/userfiles/file/HQ-15-025%20Disponibilit%C3%A9%20du%20Synagis%20Saison%202015-2016.pdf Accessed May 7, 2019.
14. Institut national d'excellence en santé et services sociaux (INESSS). Final Report. Reevaluation of eligibility criteria for palivizumab (Synagis) for the prevention of severe syncytial respiratory virus infections in children. Available at: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Medicaments/INESSS_Report_Synagis_EN.pdf?sword_list%5B0%5D=domicile&no_cache=1. Accessed March 3, 2019.
15. Public Health Agency of Canada. Respiratory Virus Detections in Canada. Available at: https://www.canada.ca/en/public-health/services/surveillance/respiratory-virus-detections-canada.html. Accessed February 20, 2019.
16. Statistics Canada. Live Births by Sex and Gestational Period, Canada, provinces and territories, 2001 to 2011. Ottawa, Canada: Statistics Canada.
17. Collège de médecins du Québec. *Bronchiolite chez les enfants hospitalisés âgés de 0 à 12 mois.* Available at: http://www.cmq.org/nouvelle/en/saison-des-bronchiolites-debute-prochainement.aspx. Accessed February 20, 2019.
18. Friedman JN, Rieder MJ, Walton JM; Canadian Paediatric Society, Acute Care Committee, Drug Therapy and Hazardous Substances Committee. Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. Paediatr Child Health **2014**; 19: 485–98.
19. Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: systematic review and meta-analysis. J Clin Microbiol **2015**; 53:3738–49.
20. Papenburg J, Buckeridge DL, De Serres G, Boivin G. Host and viral factors affecting clinical performance of a rapid diagnostic test for respiratory syncytial virus in hospitalized children. J Pediatr **2013**; 163:911–3.
21. Figueras-Aloy J, Carbonell-Estrany X, Quero-Jiménez J, et al.; IRIS Study Group. FLIP-2 Study: risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born in Spain at a gestational age of 32 to 35 weeks. Pediatr Infect Dis J **2008**; 27:788–93.
22. Mitchell I, Tough S, Gillis L, Majaesic C. Beyond randomized controlled trials: a "real life" experience of respiratory syncytial virus infection prevention in infancy with and without palivizumab. Pediatr Pulmonol **2006**; 41:1167–74.
23. Notario G, Vo P, Gooch K, et al. Respiratory syncytial virus-related hospitalization in premature infants without bronchopulmonary dysplasia: subgroup efficacy analysis of the IMpact-RSV trial by gestational age group. Pediatric Health, Medicine and Therapeutics **2014**; 5:43–8.
24. Haerskjold A, Kristensen K, Kamper-Jørgensen M, et al. Risk factors for hospitalization for respiratory syncytial virus infection: a population-based cohort study of Danish children. Pediatr Infect Dis J **2016**; 35:61–5.

25. Ambrose CS, Anderson EJ, Simões EA, et al. Respiratory syncytial virus disease in preterm infants in the U.S. born at 32-35 weeks gestation not receiving immunoprophylaxis. Pediatr Infect Dis J **2014**; 33:576–82.
26. Olabarrieta I, Gonzalez-Carrasco E, Calvo C, et al. Hospital admission due to respiratory viral infections in moderate preterm, late preterm and term infants during their first year of life. Allergol Immunopathol (Madr) **2015**; 43:469–73.
27. Ryan VM, Langley JM, Dodds L, Andreou P. Estimating respiratory syncytial virus-associated hospitalization in the first year of life among infants born at 32-35 weeks of gestation. Pediatr Infect Dis J **2016**; 35:851–5.
28. Capizzi A, Silvestri M, Orsi A, et al. The impact of the recent AAP changes in palivizumab authorization on RSV-induced bronchiolitis severity and incidence. Italian Journal of Pediatrics **2017**; 43:71.
29. Farber HJ, Buckwold FJ, Lachman B, et al. Observed effectiveness of palivizumab for 29-36-week gestation infants. Pediatrics **2016**; 138: e20160627.
30. Sheridan-Pereira M, Murphy J, Sloan J, et al. Respiratory syncytial virus preterm (32–36 completed weeks of gestation) risk estimation measure for RSV hospitalization in Ireland: a prospective study. Pediatr Infect Dis J **2016**; 35:19–24.
31. Lanari M, Prinelli F, Adorni F, et al.; Study Group of the Italian Society of Neonatology on Risk Factors for RSV Hospitalization. Risk factors for bronchiolitis hospitalization during the first year of life in a multicenter Italian birth cohort. Ital J Pediatr **2015**; 41:40.
32. Paes B, Mitchell I, Li A, Lanctôt KL; CARESS Investigators. A comparative study of respiratory syncytial virus (RSV) prophylaxis in premature infants within the Canadian Registry of Palivizumab (CARESS). Eur J Clin Microbiol Infect Dis **2012**; 31:2703–11.
33. Paes B, Steele S, Janes M, Pinelli J. Risk-scoring tool for respiratory syncytial virus prophylaxis in premature infants born at 33-35 completed weeks' gestational age in Canada. Curr Med Res Opin **2009**; 25:1585–91.
34. Chan P, Li A, Paes B, et al.; CARESS investigators. Adherence to palivizumab for respiratory syncytial virus prevention in the Canadian registry of palivizumab. Pediatr Infect Dis J **2015**; 34:e290–7.