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Cost-analysis of Withdrawing Immunoprophylaxis for Respiratory Syncytial Virus in Infants Born at 33–35 Weeks Gestational Age in Quebec

A Multicenter Retrospective Study

Jesse Papenburg, MD, MSc,†‡ Mahwesh Saleem, PhD,§ Johannes Teselink, BSc,§ Abby Li, MSc,§ Georges Caouette, MD, MSc,¶ Édith Massé, MD,‖ and Krista L. Lanctôt, PhD§*

Background: In 2015, the Quebec Ministry of Health limited palivizumab prophylaxis for respiratory syncytial virus (RSV) in premature infants to those born at <33 weeks gestational age (wGA), unless other indications were present. We compared RSV-related costs for 2 seasons before the change (2013–2014, 2014–2015) and 2 seasons after (2015–2016, 2016–2017) in premature infants 33–35 wGA.

Methods: Using payer and societal perspectives, costs associated with hospitalizations for RSV and lower respiratory tract infection (LRTI) in infants born at 33–35 wGA were estimated. Inputs were from a 2013–2017 retrospective cohort study in 25 Quebec hospitals of RSV/LRTI hospitalizations among infants <6 months old at the start of, or born during, the RSV season. Resource utilization data (hospital stay, procedures, visits, transportation, out-of-pocket expenses and work productivity) were collected from charts and parent interviews allowing estimation of direct and indirect costs. Costs, including palivizumab administration, were derived from provincial sources and adjusted to 2018 Canadian dollars. Costs were modeled for preterm infants hospitalized for RSV/LRTI pre- and postrevision of guidelines and with matched term infants hospitalized for RSV/LRTI during 2015–2017 (comparator).

Results: Average total direct and indirect costs for 33–35 wGA infants were higher postrevision of guidelines ($29,208/patient, 2015–2017; n = 130) compared with prerevision ($16,976/patient, 2013–2015; n = 105). Total costs were higher in preterm infants compared with term infants (n = 234) postrevision of guidelines ($29,208/patient vs. $10,291/patient).

Conclusions: Immunoprophylaxis for RSV in infants born at 33–35 wGA held a cost advantage for hospitalizations due to RSV/LRTI.

Key Words: palivizumab, immunoprophylaxis, respiratory syncytial virus, comparison, outcomes, hospitalization, cost

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Respiratory syncytial virus (RSV) is the predominant cause of lower respiratory tract infections (LRTI) in infants and young children.[1,2] RSV-related hospitalizations (RSVH) are associated with a major healthcare burden.[3] Of approximately 2.8 million new episodes of RSV-related infections reported in children less than 5 years of age in high-income countries in 2015, at least 383,000 children required hospital admission.[4] RSV is also estimated to underlie up to 75% of all childhood cases of bronchiolitis and up to 40% of all childhood pneumonias.[5] Furthermore, about 200 infant deaths are reported to be caused by RSV-related lower respiratory tract infection annually in the United States.[6] The risk of RSV and burden of RSVH is greater in premature infants, defined as less than 36 completed weeks of gestational age (wGA), due to incomplete pulmonary development, immature immunologic responses and lower levels of maternally transmitted, RSV-specific antibodies, compared with infants born at term.[7–10] It has previously been shown that preterm infants hospitalized for RSV had significantly higher intensive care unit (ICU) stays and higher intubation rates compared with term infants.[11]

In Canada, passive immunoprophylaxis with palivizumab, a humanized monoclonal antibody, has been approved for high risk infants including those with a history of prematurity (≤35 wGA) since 2002. Palivizumab significantly reduces the incidence of RSVH in infants born at ≤35 wGA, and prophylaxis was associated with shorter length of hospital stay, fewer days with oxygen and lower incidence of ICU admission.[12] In addition, palivizumab was shown to be cost-effective in the 32–35 wGA group in Canadian settings.[13] However, in 2015, the Canadian Pediatric Society modified their position statement to limit the use of palivizumab for prophylaxis in infants <30 weeks (29 completed wGA), unless other comorbidities were also present.[14] Starting in the 2015–2016 RSV season, the Quebec Ministry of Health (Ministère de la Santé et des Services sociaux) also revised their eligibility criteria for palivizumab; late

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From the *Division of Pediatric Infectious Diseases, Department of Pediatrics, Montreal Children's Hospital and †Division of Microbiology, Department of Laboratory Medicine, McGill University Health Centre, Montreal, Quebec, Canada; and ‡Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, §Medical Outcomes and Research in Economics (MORE) Research Group, Sunnybrook Health Sciences Centre, Toronto, Ontario, ¶Division of Neonatology, Department of Pediatrics, Centre Hospitalier Universitaire de Québec, Quebec City, Quebec, and ‖Division of Neonatology, Department of Pediatrics, CIUSSS de l'Estrie-CHUS, Sherbrooke, Quebec, Canada.

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Address for correspondence: Krista L. Lanctôt, PhD, Medical Outcomes and Research in Economics (MORE) Research Group, 2075 Bayview Avenue, Room FG-21, Toronto, Ontario M4N 3M5, Canada. E-mail: krista.lanctot@sunnybrook.ca.

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preterm Quebec infants born 33–35 wGA without qualifying comorbidities were no longer eligible to receive palivizumab for prophylaxis. To study the impact of that change, we evaluated the cost of withdrawing passive RSV immunoprophylaxis in infants born at 33–35 wGA in Quebec using a cost-comparison analysis.

METHODS

Model Design

A cost-comparison model was developed in Microsoft Excel 2013 (Microsoft, Redmond) to estimate the economic impact of withdrawing passive immunoprophylaxis for RSV and applied to a cohort of infants born at 33–35 wGA <6 months of age in Quebec. Guidelines for cost-comparison analysis from the National Institute for Health and Care Excellence were followed.[15] This analysis was performed from both the payer perspective (Quebec Ministry of Health) and the societal perspective and included all direct and indirect costs associated with RSV/LRTI hospitalization. The time horizon in the clinical visits and resource use before hospitalization was 72 hours before hospitalization and 30 days afterward to account for discharge medications. To correct for inflation, all costs were converted to 2018 Canadian Dollars using the inflation rate of 2.16% provided by Bank of Canada.[16] Total costs and average costs per infant rounded to the nearest dollar are presented. A post hoc analysis was also conducted to assess whether costs of prophylaxis offset the cost of RSV/LRTI hospitalization in late preterm infants.

Input Parameters

Data from the RSV-Quebec study (Tables 1 and 2) were used to evaluate the cost of RSV/LRTI hospitalization following withdrawal of immunoprophylaxis over the time horizon of the analysis. RSV-Quebec was a multicenter retrospective cohort study involving 20 hospitals and 5 hospital-based birthing centers across different geographical regions of Quebec.[17,18] All otherwise healthy infants born at 33–35 wGA and <6 months at the start of or born during the RSV season with RSV/LRTI hospitalizations [presumed or confirmed RSV/LRTI) during 4 seasons (2013–2014 (season 1), 2014–2015 (season 2), 2015–2016 (season 3) and 2016–2017 (season 4)] were included. RSV/LRTI hospitalization was 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 and no other etiology found. Eligible participants were identified through the hospital discharge abstract databases using LRTI- and RSV-specific International Classification of Diseases-9 or -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. In addition, for each eligible preterm infant, 2 term infants (≥37 wGA and <6 months at the start of or born during the RSV season) in seasons 3/4 matched for age, gender and month of RSV/LRTI hospitalization were identified for inclusion. This cohort was included to provide a benchmark. Parents/legal guardians of infants hospitalized due to RSV/LRTI in seasons 3/4 were approached to complete questionnaires assessing healthcare resource utilization (HCRU), work productivity and activity impairment during the RSV/LRTI hospitalization of their child to assess burden of illness. Those who agreed to participate gave written consent before completing the questionnaires.

The RSV-Quebec dataset included outcomes from a total of 105 preterm infants who were hospitalized for RSV/LRTI during seasons 1/2 (prerevision of guidelines), 130 preterm in seasons 3/4 (postrevision of guidelines) and 234 term infants hospitalized for RSV/LRTI in seasons 3/4. Of these patients, 97 of 105 (92.4%) tested positive for RSV in seasons 1/2, 106 of 130 (81.5%) in seasons 3/4 and 200 of 234 (85.5%) term infants.

Cost Inputs

Cost inputs were broken down into direct (hospital stay, physician billing, microbiology tests, and hospitalization discharge/medications, HCRU associated with hospitalization, prophylaxis administration) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D940) and indirect costs (missed work and lost productivity, HCRU associated with hospitalization and hospitalization discharge medications) (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/D940). Direct and indirect costs were estimated based on provincial and government sources. Further information regarding unit cost sources, assumptions made for the analysis, and supporting literature[13,17–31] is provided in Supplemental Digital Content 2, http://links.lww.com/INF/D941.

RESULTS

Base-case Estimate

As shown in Table 3, the observed average direct cost in preterm infants hospitalized due to RSV/LRTI in seasons 3/4 was higher at $28,465 compared with $16,232 for preterm infants in seasons 1/2. In univariate analyses, length of stay in the emergency department during hospitalization was associated with higher direct costs in seasons 3/4 (Table 1). Also, the proportion of infants discharged with medications in seasons 3/4 was lower compared with infants in seasons 1/2. Specifically, the proportion of infants discharged with antibiotics in seasons 3/4 was lower compared with infants in seasons 1/2 (21% vs. 32%; $\chi^2 = 4.08$, $P = 0.044$). As expected, indirect costs were similar between preterm infants in seasons 3/4 and those in seasons 1/2 ($742 vs. $744). This difference reflects differences in numbers of patients because indirect costs in seasons 1/2 were imputed from data collected in seasons 3/4.

Impact of Palivizumab

Based on the Risk Scoring Tool Validation article by Paes et al,[28] which estimated that 19% of infants with 33–35 wGA would have moderate-to-high risk scores, 20 infants were projected to qualify for RSV prophylaxis in the RSV-Quebec study in seasons 1/2. The total cost of prophylaxis for those infants was $93,184 with an average cost of $4659 per infant. The additional cost of prophylaxis among hospitalized infants increased the average direct costs in seasons 1/2 to $20,892, which was still lower than direct costs in seasons 3/4.

Comparison to Term Infants

When comparing preterm infants in seasons 3/4 to term infants who were hospitalized due to RSV/LRTI during that same time period, average direct costs were higher in preterm infants compared with term infants ($28,465 vs. $9509) (Table 4). Determinants of direct costs were longer length of stay in the pediatric unit, higher proportion of infants hospitalized in the PICU and longer length of stay in the PICU, higher proportion of infants hospitalized in the neonatal ICU and a higher proportion of infants hospitalized in the short-stay unit. In addition, compared with term infants, a higher proportion of preterm infants required complex ventilation. Specifically, a higher proportion of preterm infants required high-frequency oscillatory ventilation compared with term infants (2% vs. 0%; $\chi^2 = 5.45$, $P = 0.020$). A higher proportion of preterm infants also required feeding tubes, specifically duodenal feeding tubes, (5% vs. 1%; $\chi^2 = 5.27$, $P = 0.022$) during hospitalization. In terms of HCRU, a higher proportion of preterm infants required clinical visits and transfers to another medical facility before hospitalization.

TABLE 1. Clinical Inputs Used to Model Direct Costs of Withdrawing Immunoprophylaxis in Infants Born at 33–35 Weeks Gestational Age

	Seasons 1/2 (n = 105) Mean ± SD or n (%)	Seasons 3/4 (n = 130) Mean ± SD or n (%)	F or χ^2, *P*	Term (n = 234) Mean ± SD or n (%)	F or χ^2, *P*
Hospital stay					
Pediatric unit	96 (91)	120 (92)	0.06, 0.806	213 (91)	0.18, 0.68
Length of stay, d	3.7 ± 2.6	3.6 ± 2.7	0.21, 0.650	3.0 ± 1.8	6.30, 0.013*
PICU	22 (21)	25 (19)	0.11, 0.743	25 (11)	5.15, 0.023*
Length of stay, d	5.9 ± 4.4	7.0 ± 4.1	0.77, 0.385	3.4 ± 2.6	13.53, 0.001*
NICU	1 (1)	5 (4)	1.96, 0.162	2 (1)	3.97, 0.046*
Length of stay, d	4.0	26.6 ± 26.8	0.59, 0.485	3.0 ± 2.8	1.38, 0.294
Short-stay unit	12 (11)	6 (5)	3.81, 0.051	25 (11)	3.95, 0.047*
Length of stay, d	2.1 ± 1.1	1.7 ± 0.5	0.78, 0.390	2.2 ± 1.3	0.80, 0.378
Emergency	26 (25)	21 (16)	2.69, 0.101	51 (22)	1.68, 0.195
Length of stay, d	1.2 ± 0.4	1.5 ± 0.5	6.19, 0.017*	1.4 ± 0.5	1.80, 0.184
Procedures					
Imaging	87 (83)	98 (75)	1.94, 0.164	188 (80)	1.22, 0.269
Complex ventilation	10 (10)	21 (16)	2.23, 0.135	21 (9)	4.22, 0.040*
Microbiology tests	90 (86)	107 (82)	0.50, 0.481	183 (78)	0.87, 0.351
Feeding tube placement	17 (16)	22 (17)	0.02, .881	22 (9)	4.45, 0.035*
Tissue biopsy	1 (1)	0 (0)	1.24, 0.265	0 (0)	—
Lumbar puncture	2 (2)	3 (2)	0.05, 0.831	8 (3)	0.35, 0.553
Lung recruitment	0 (0)	2 (1)	1.63, 0.202	0 (0)	3.62, 0.057
Pleurocentesis	0 (0)	1 (1)	0.81, 0.368	0 (0)	1.81, 0.179
Catheterization	0 (0)	1 (1)	0.81, 0.368	1 (0.4)	0.18, 0.672
Cardiopulmonary resuscitation	0 (0)	1 (1)	0.81, 0.368	0 (0)	1.81, 0.179
Specialist consultations	42 (40)	50 (39)	0.06, 0.810	87 (37)	0.06, 0.809
Hospitalization discharge					
Transfer to home	102 (97)	125 (96)	0.17, 0.678	228 (97)	0.47, 0.494
Transfer to another medical facility	3 (3)	5 (4)	0.17, 0.678	6 (3)	0.47, 0.494
Discharged with medications	44 (42)	34 (26)	6.50, 0.011*	64 (27)	0.06, 0.805
HCRU: before					
Clinical visits	—	41 (67)	—	60 (50)	5.10, 0.024*
Transport in ambulance	—	8 (14)	—	7 (6)	3.14, 0.076
Visit to emergency	—	36 (58)	—	57 (47)	1.97, 0.161
Transfer to another medical facility	—	16 (27)	—	7 (6)	16.39, <0.0005*
Medical consultations	—	38 (60)	—	83 (69)	1.26, 0.262

* indicates statistical significance, i.e. $P < 0.05$.
NICU indicates neonatal intensive care unit.

TABLE 2. Clinical Inputs Used to Model Indirect Costs of Withdrawing Immunoprophylaxis in Infants Born at 33–35 Weeks Gestational Age

	Seasons 1 and 2 (n = 105) Mean ± SD or n (%)	Seasons 3 and 4 (n = 130) Mean ± SD or n (%)	F or χ^2, *P*	Term (n = 234) Mean ± SD or n (%)	F or χ^2, *P*
HCRU: during					
Transport to hospital	—	61 (98)	—	115 (95)	1.25, 0.264
Other expenses	—	59 (97)	—	113 (93)	0.87, 0.352
Paid help	—	0 (0)	—	2 (2)	1.04, 0.309
Out-of-pocket medical expenses	—	15 (24)	—	40 (33)	1.53, 0.216
Reimbursements	—	8 (13)	—	19 (16)	0.26, 0.613
Productivity, hours lost					
Mother	—	4.7 ± 14.9	—	33.9 ± 197.2	0.63, 0.429
Father	—	34.3 ± 43.6	—	20.1 ± 23.0	6.96, 0.009*
Other guardian	—	—	—	66.0 ± 8.5	—

Specifically, a higher proportion of preterm infants visited the local community health center (CLSC) compared with term infants (13% vs. 5%; $\chi^2 = 3.94$, $P = 0.047$). Average indirect costs associated with an RSV/LRTI hospitalization were lower in preterm infants compared with term infants ($742 vs. $782). Paternal loss of productivity ($F = 6.96$, $P = 0.009$) was the only parameter that was significantly different between groups.

Outcomes

As shown in Table 4, there were no differences in outcomes between preterm infants in seasons 1/2 and preterm infants in seasons 3/4. While Parental Stressor scale total scores were not significantly different for both parents between preterm and term infants in seasons 3/4, fathers of preterm infants reported a significantly higher percentage of activity impairment compared with fathers of term infants.

Interpretation

Overall, preterm infants hospitalized for RSV/LRTI postrevision of guidelines incurred higher average direct costs than preterm infants hospitalized prerevision of guidelines. In addition, direct costs associated with hospitalization in preterm infants postrevision of guidelines were higher compared with term infants

TABLE 3. Cost-Comparison Analysis (Societal Perspective)

	Seasons 1/2 (n = 105)	Seasons 1/2 (Average)	Seasons 3/4 (n = 130)	Seasons 3/4 (Average)	Term Seasons 3/4 (n = 234)	Term Seasons 3/4 (Average)
Hospital stay						
Pediatric unit	$815,908	$7771	$993,807	$7645	$1486,280	$6352
PICU	$728,853	$6941	$980,117	$7539	$483,073	$2064
NICU	$49,227	$469	$1,622,470	$12,481	$74,094	$317
Short-stay unit	$26,792	$255	$11,368	$87	$57,929	$248
Emergency	$14,207	$135	$11,937	$92	$28,615	$122
Procedures						
Imaging	$3770	$36	$5133	$39	$7050	$30
Complex ventilation	$2302	$22	$5847	$45	$4351	$19
Microbiology tests	$9067	$86	$8081	$62	$15,257	$65
Feeding tube placement	$451	$4	$481	$4	$593	$3
Lumbar puncture	$310	$$3	$465	$4	$1241	$5
Lung recruitment	—	—	$277	$2	—	—
Pleurocentesis	—	—	$260	$2	—	—
Tissue biopsy	$158	$2	—	—	—	—
Catheterization	—	—	$190	$1	$810	$3
CPR	—	—	$82	$1	—	—
Specialist consultations	$10,490	$100	$14,040	$108	$21,944	$94
Hospitalization discharge						
Transfer to home	$466	$4	$571	$4	$1042	$4
Transfer to another medical facility	$868	$8	$1447	$11	$1736	$7
Medications	$6110	$58	$259	$2	$564	$2
HCRU: before						
Clinical visits	$14,480	$138	$17,794	$137	$23,994	$103
Transport in ambulance	$1995	$19	$2423	$19	$1995	$9
Visit to ER	$ 10,631	$101	$13,245	$102	$9212	$39
Transfer to another medical facility	$7543	$72	$9159	$70	$3771	$16
Medical consultations	$867	$8	$1055	$8	$1506	$6
Total direct costs	$1,704,337	$16,232	$3,700,506	$28,465	$2,225,056	$9509
HCRU: –during						
Transportation	$11,946	$114	$14,804	$114	$24,615	$105
Meals	$11,922	$114	$14,837	$114	$27,686	$118
Accommodations	$765	$7	$984	$8	$437	$2
Paid help	$1596	$15	$1995	$15	$4389	$19
Out-of-pocket medical expenses	$1502	$14	$1846	$14	$4129	$18
Other expenses	$88	$1	$131	$1	$701	$3
Reimbursements	$2985	$28	$3489	$27	$8374	$36
Productivity						
Mother	$3045	$29	$3748	$29	$7963	$34
Father	$44,311	$422	$54,682	$421	$98,050	$419
Other	—	—	—	—	$6,711	$29
Total indirect costs	$78,160	$744	$96,515	$742	$183,055	$782
Total direct and indirect costs	$1,782,497	$16,976	$3,797,022	$29,208	$2,408,111	$10,291

CPR indicates cardiopulmonary resuscitation; ER, emergency room; NICU, neonatal intensive care unit.

TABLE 4. Health Outcomes in the RSV-Quebec Study

	Seasons 1/2 (n = 105)	Seasons 3/4 (n = 130)	F or χ^2, *P*	Term (n = 234)	F or χ^2, *P*
Length of stay PICU, d	5.9 ± 4.4	7.0 ± 4.1	0.77, 0.385	3.4 ± 2.6	13.53, 0.001*
Mechanical ventilation, d	4.8 ± 2.5	6.1 ± 3.9	1.03, 0.320	2.3 ± 2.3	2.45, 0.140
Supplemental oxygen, d	4.0 ± 3.3	4.4 ± 3.7	0.42, 0.518	2.5 ± 1.9	19.98, <0.0005*
Visit to emergency	—	36 (58)	—	57 (47)	1.97, 0.161
Parental stressor scale, mother	—	66.6 ± 20.7	—	62.7 ± 17.9	1.70, 0.194
Parental stressor scale, father	—	60.0 ± 19.1	—	61.1 ± 16.7	0.14, 0.705
Activity impairment, mother	—	89%	—	84%	1.66, 0.199
Activity impairment, father	—	78%	—	67%	7.14, 0.008*

hospitalized in the same time period. Indirect costs were similar between preterm infants pre- and postrevision of guidelines but were slightly higher in term infants. Compared with term infants, fathers of preterm infants in seasons 3/4 reported significantly higher absenteeism from work and higher activity impairment.

Previous reports suggest that infants born at 33–35 wGA have the highest RSVH-associated resource use compared with other gestational ages.[11] Lower hospitalization-related costs in seasons 1/2 before guideline revisions imply that immunoprophylaxis in infants born at 33–35 wGA may have a favorable economic impact from the payer perspective despite higher acquisition costs of palivizumab. These findings are supported by previous findings showing cost-effectiveness of palivizumab in late preterm infants based on the presence of risk factors,[32–39] especially in Canada.[13,40] Similarly, late

preterm infant hospitalizations for RSV/LRTI postguideline revisions were associated with higher costs from the payer perspective compared with term infant hospitalizations. These differences were mainly due to the increased morbidity in preterm infants consistent with prior research showing a higher likelihood of being admitted to the ICU and higher frequencies of respiratory distress and feeding difficulties among other complications in late preterm infants compared with term infants.[41] In addition, LRTI/RSVH of preterm infants postrevision of guidelines were associated with significantly higher caregiver burden represented by significant paternal loss of wages during hospitalization and impairment of the ability to conduct activities of daily living, compared with term infants. These findings are consistent with previous reports of paternal burden in Canadian infants hospitalized for RSV[42] and further recognize the societal burden associated with RSV/LRTI.

The Quebec-RSV study provided a unique opportunity to demonstrate the economic impact of a change in guidelines that removed RSV prophylaxis for infants of 33–35 wGA. Furthermore, study findings extend the current literature by analyzing the indirect costs and caregiver burden associated with RSV/LRTI hospitalizations. However, the present study had several limitations. First, average cost of hospital stays in different wards were obtained from the, which may not be reflective of costs in Quebec. However, we have adjusted these costs by including physician billing costs based on data from McGill University Health Centre. Testing for RSV was not systematically conducted in all infants which may create a nonrandom bias; however, the study provided real-world evidence of the economic consequences of removing immunoprophylaxis in an at-risk group. The lack of consistent RSV testing also limited the assessment of RSVH as the primary outcome. However, because RSV is the leading cause of LRTI, the present study assessed RSV/LRTI as the primary outcome. Moreover, >85% of preterm and term RSV/LRTI hospitalizations had laboratory-confirmed RSV infection. Second, RSV prophylaxis of infants of 33–35 wGA in seasons 1/2 (preguideline change) was unavailable to researchers as it was generally not documented in patients' hospitalization records, leading to a mixed group of prophylaxed and nonprophylaxed infants. The mixed group of prophylaxed and nonprophylaxed infants in seasons 1/2 means that the incidence of RSV/LRTI hospitalization in prophylaxed infants only is unknown, which may also subsequently affect the results of the cost-comparison analysis. However, it does represent total costs of hospitalization in that patient population, consistent with the perspective. The Health Resource Utilization Questionnaire was not completed in seasons 1/2. Future studies should extend the present findings by assessing the economic impact of long-term consequences associated with withdrawal of immunoprophylaxis in infants born at 33–35 wGA. For example, severe RSV/LRTI in infancy has been associated with long-term respiratory problems, including recurrent wheezing, asthma and possibly allergic sensitization later in life,[43] which may contribute to increased healthcare costs later in childhood. Because palivizumab has been shown to be effective in reducing recurrent wheezing following RSVH,[43] immunoprophylaxis may have a long-term advantage that should be considered in economic models.

Late preterm infants constitute a group at greater risk of RSVH compared with full-term infants, resulting in substantial morbidity following hospital admission. As simulated in a model by McLaurin et al,[44] the annual number of RSVH in late preterm infants is expected to increase following the change in guidelines based on moderate rates. This increase in RSVH would lead to an increase in hospitalization days, ICU admissions and mechanical ventilation events.[44] This cost-comparison analysis showed that the time period before guideline changes held a cost advantage for hospitalizations due to RSV/LRTI, compared with the time period postguideline change from the payer perspective in infants born at 33–35 wGA. Direct costs were also higher in 33–35 wGA infants hospitalized for RSV/LRTI postrevision of guidelines compared with term infants. These findings suggest that immunoprophylaxis may be cost-saving in this at-risk group and may reduce burden of illness.

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