Effectiveness of Palivizumab against Respiratory Syncytial Virus: Cohort and Case Series Analysis

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Objective To measure the real-world effectiveness of palivizumab immunoprophylaxis against respiratory syncytial virus (RSV)-confirmed infection before age 2 years in a population-cohort of high-risk infants.

Study design Palivizumab is funded for high-risk infants in Western Australia. We used probabilistically linked administrative data encompassing RSV laboratory-confirmed infections, hospital admissions, and palivizumab dispensing records for a cohort of 24 329 high-risk infants admitted to neonatal intensive care units, born 2002-2013 with follow-up to 2015. We used a traditional cohort method with Cox proportional hazards regression and a self-controlled case series analysis to assess effectiveness of palivizumab in reducing RSV-confirmed infection by number of doses.

Results From the cohort of 24 329 infants, 271 (1.1%) received at least 1 dose of palivizumab and 1506 (6.2%) had at least 1 RSV-confirmed infection before age 2 years. Using the traditional cohort approach, we found no protective association of palivizumab receipt with RSV detection (adjusted hazard ratio = 0.99 [95% CI 0.5, 1.9] for 1 dose). However, using a self-controlled case series to eliminate confounding by indication, a protective association was seen with a 74% lower RSV incidence (relative incidence = 0.26; 95% CI 0.11, 0.67) following any dose of palivizumab compared with control (nonexposed) periods.

Conclusions After accounting for confounding by indication through a self-controlled analysis, palivizumab appeared effective for reducing virologically confirmed RSV in this high-risk cohort. *(J Pediatr 2019;214:121-7)*.

In 2015, 33.1 million acute lower respiratory infection episodes, 3.2 million hospitalizations, and 59 600 in-hospital deaths in children age <5 years were attributed to respiratory syncytial virus (RSV).[1] Those at highest risk include preterm infants (especially those <28 weeks of gestation) and those with chronic lung disease (CLD) of prematurity or congenital heart disease (CHD).[2] Immuno-prevention of RSV infection is achieved solely through administration of palivizumab, an injectable monoclonal antibody. Two randomized controlled trials established the efficacy of palivizumab monthly intramuscular injections in high-risk populations for preventing RSV-confirmed hospitalization with reductions of 45%-55%.[2,3]

The American Academy of Pediatrics published updated palivizumab guidelines in 2014 with a focus on high-risk infants with CLD.[4] Palivizumab is licensed in Australia for use in high-risk infants, however there is no uniform national guideline or policy governing palivizumab use.[5] Western Australia (WA) is unique among Australian jurisdictions in funding palivizumab for the first RSV season in infants age <12 months with hemodynamically significant or cyanotic CHD or requiring home oxygen for CLD. Following several consequential episodes (including deaths) of nosocomial RSV transmission in 2010, the 2 tertiary neonatal intensive care units (NICUs) in WA have also used palivizumab for in-hospital prophylaxis to prevent nosocomial RSV infection.[6] This high-risk target population includes those with a gestational age of <28 weeks and who are Aboriginal and/or Torres Strait Islander (herein referred to as Aboriginal), or who have CLD. These additional guidelines also allow for palivizumab administration to clinically suitable infants on an

aHR	Adjusted hazard ratio
CHD	Congenital heart disease
CLD	Chronic lung disease
HR	Hazard ratio
ICD	*International Classification of Diseases*
IRR	Incidence rate ratio
NICU	Neonatal intensive care unit
RSV	Respiratory syncytial virus
SCCS	Self-controlled case series
WA	Western Australia

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individual basis.[6] In 2011, the cost of the palivizumab program was estimated to be $AUD 8750 per patient and cost a total of $AUD 300 000 per annum for prophylaxis of 30-35 patients.[6] The use of palivizumab to prevent nosocomial acquisition has not yet been evaluated and nor are there data regarding adherence with dosing guidelines on a population basis. Here, we estimate the effectiveness of a multiple-dose course of palivizumab for preventing RSV detections in infants graduating from NICU over a 12-year period. To mitigate against residual confounding by indication, that is targeting of palivizumab to those at greatest risk of RSV, we supplemented a traditional retrospective cohort-based effectiveness analysis with a self-controlled case series (SCCS) study. This method has previously been used to investigate adverse events following vaccination.[7]

Methods

We conducted a retrospective birth cohort study using WA administrative data. WA covers the western one-third of Australia, an area of 2.5 million square kilometres with a population of nearly 2.6 million; 76.9% of whom reside in the Perth metropolitan region.[8] The study cohort was defined as all infants admitted to either of the 2 tertiary NICUs at King Edward Memorial Hospital and Princess Margaret Hospital immediately after birth from January 1, 2002-December 31, 2013. The WA NICU database was used to identify the study cohort. The Midwives' Notifications System was used as a source of additional maternal and infant demographic information. Death registrations identified any deaths in the cohort 2002-2015. The exposure of interest, palivizumab doses administered 2002-2015, were identified from a collection of historical and current hospital-based and state-based pharmacy dispensing datasets. Hospitalizations were identified from the Hospital Morbidity Data Collection January 2002-June 2015, and RSV detections were identified from the PathWest Laboratory Database of routine pathology testing January 2002-December 2015. PathWest Laboratory Medicine WA is the sole public pathology provider in WA and services King Edward Memorial Hospital and Princess Margaret Hospital, and all but 3 hospitals admitting pediatric patients in the state as well as referred samples from private pathology laboratories in WA.[9,10] Data were extracted and probabilistically linked by the Western Australian Data Linkage Branch using a series of demographic identifiers.[11]

The primary outcome of interest was a positive laboratory test result for RSV before age 2 years. We included positive RSV tests from respiratory specimens with standard detection methods as per our established protocols[10] using date of specimen collection to determine patient age at the time of RSV detection. The vast majority of RSV detections (90%) were identified within hospital and therefore represent RSV-confirmed hospitalizations. The primary exposure was palivizumab administration stratified by the number of doses and included both inpatients and outpatients. Date of palivizumab dispensing was used in the absence of an actual administration date. Following intramuscular administration, palivizumab levels have a mean-half-life of 20 days, and doses are given 28 days apart usually during the duration of the RSV season (April/May-October).[12] However, because our primary interest was the real-world effectiveness of palivizumab, we did not omit nor censor subsequent doses that were given less than 28 days apart.

Statistical Analyses

Cohort Study. We used a time-to-first-event analysis to measure the effectiveness of the number of palivizumab doses on the first RSV detection before age 2 years. Person-time for each child started at birth and was censored at first RSV detection, death, age 2 years or the end date of the study period (December 31, 2015), whichever occurred first. Cox proportional hazards regression with RSV detection as the outcome was used to calculate hazard ratios (HRs) and their associated 95% CIs for each dose of palivizumab compared with no vaccine dose, with palivizumab status as a time-dependant explanatory variable and age of the child (in days) as the time-scale. Models were run for the full cohort of births (2002-2013) and a restricted cohort with birth year 2010 onwards to reflect the period of increased palivizumab use in WA NICUs. We also examined the effectiveness of palivizumab only in those high-risk infants targeted in the extended NICU RSV prophylaxis guidelines.

We conducted univariate and multivariable analyses including a priori covariates that were expected to be related to both palivizumab use and RSV detection to mitigate against confounding. These covariates included gestational age, Aboriginal identification, sex, and presence of CLD and CHD. For the restricted cohort and for high-risk infants targeted in the NICU guidelines (<28 weeks of gestation and either Aboriginal or with CLD), effectiveness estimates were only adjusted for sex, CHD and Aboriginality, and CLD where appropriate. CLD was defined using an indicator variable on the NICU dataset (for oxygen requirement after 36 weeks of postmenstrual age), as well as *all International Classification of Diseases* (ICD), version 10, Australian Modification diagnosis fields in the hospitalization dataset (P27.1). CHD was defined using all ICD, version 10, Australian Modification diagnosis fields in the hospitalization dataset (Q20-26). Aboriginal identification was defined using a validated algorithm.[13] Sensitivity analyses were conducted by further restricting palivizumab doses to those given before the end of the child's first RSV season, defined as October 31 in any given year.

Self-Controlled Case Series Study. To complement the cohort analysis and because of the high likelihood of confounding by indication between the relationship of palivizumab use and RSV detection as previously demonstrated,[14, 15] we also conducted a SCCS. This analytic method only uses data on cases (those with the outcome of interest) over a defined observation or exposure period.[16] The time within the exposure period is classified as a risk or as a control

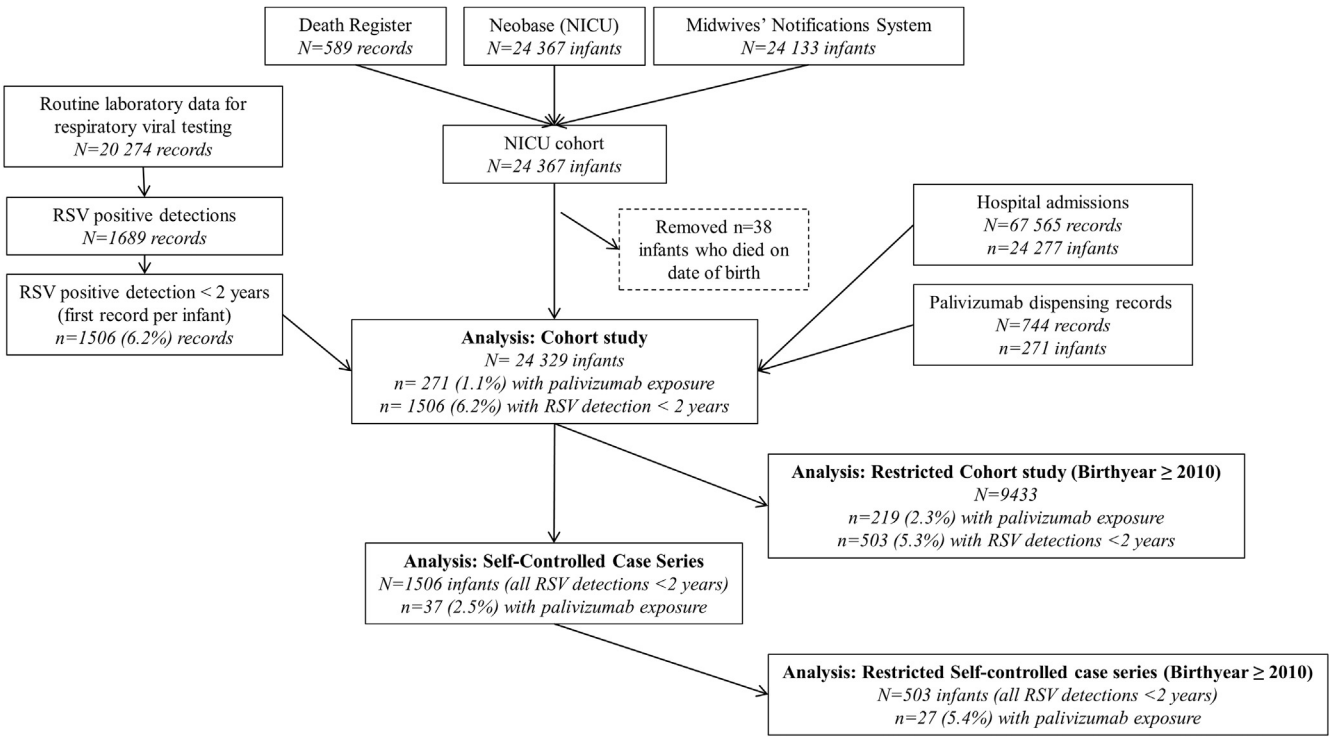

Figure 1. Flow of study datasets.

period relative to when the exposure (palivizumab administration) occurred. Three key assumptions of the SCCS are the occurrence of the event does not affect subsequent exposure, event rates are constant within intervals, and events are independently recurrent or rare.[17] To address the first, we included a pre-exposure control period and commenced follow-up for each case from their date of birth. The end of follow-up for each case was day 730 equating to their second birthday. As RSV rates are not constant over intervals, we controlled for age group in 4 discrete categories (0-2 months, 3-5 months, 6-11 months, and 12-23 months) and RSV seasonal period, defined as April-October in any given year. Given that the follow-up was up to age 2 years, some infants experienced up to 3 RSV seasons. As in the cohort study, we limited RSV events to the first detection only, as it is likely that recurrent RSV detections are not independent. Age in days was used as the underlying time scale. We followed the methodology outlined in Whitaker et al using repeat exposures that allowed for a dose effect.[18] The exposure periods following each palivizumab dose were 28 days and adjusted accordingly where exposure periods overlapped (eg, where subsequent doses were given <28 days apart). All other periods were defined as control periods. We used conditional fixed-effects Poisson regression to report the relative incidence with 95% CIs of RSV detection following each palivizumab dose. Because of limited sample size, we also grouped palivizumab doses together to assess the effect of any dose. We conducted the SCCS analysis in the overall cohort as well as the restricted cohort of infants born from 2010. All data cleaning and analyses for both methods were completed in Stata v 15.1 (StataCorp, College Station, Texas).

Ethics approvals were granted by the Western Australian Department of Health, Western Australian Aboriginal Health and Child and Adolescent Health Service. Data access was approved by the Western Australian Data Linkage Branch and relevant Data Custodians. In accordance with requirements from data custodians, cell sizes with numbers <5 were suppressed from the results tables.

Results

The cohort consisted of 24 367 infants born January 2002-December 2013. Thirty-eight infants died on their day of birth and were removed from the analysis, leaving 24 329 infants as the cohort for analysis (Figure 1). Overall, 271 (1.1%) infants received at least one dose of palivizumab. Palivizumab use increased over time with the greatest use in infants born from 2010 onwards, where 2.3% (n = 219) of the cohort received at least one dose (Figure 1). As shown from the cohort characteristics in Table I, palivizumab use was also evident in term infants (12.9% with palivizumab exposure), those without chronic lung disease (29.2% with palivizumab exposure), and without CHD (16.6% with palivizumab exposure). The number of palivizumab doses administered to each infant ranged from 1 to 15, with 89.3% receiving 1-5 doses. For those born from 2010, the range of doses was 1-6, with 89.0%

Table I. Descriptive characteristics of the study cohort, those with palivizumab exposure and those with a positive detection of RSV before age 2 years, 2002-2013

	Overall (N = 24 329)		Palivizumab exposure (n = 271)		RSV detection (n = 1506)	
Characteristics	n	%*	n	%*	n	%*
Infant factors						
Sex						
Male	13 437	55.23	157	57.93	817	54.25
Female	10 890	44.76	114	42.07	689	45.75
Indigenous status						
Aboriginal	3005	12.35	33	12.18	256	17.00
Non-Aboriginal	21 324	87.65	238	87.82	1250	83.00
Gestational age						
<28 wk	1215	4.99	208	76.75	138	9.16
28-32 wk	3703	15.22	15	5.54	325	21.58
33-36 wk	8120	33.38	13	4.80	503	33.40
≥37 wk	11 291	46.41	35	12.92	540	35.86
Birth weight						
<1500 g	3147	12.94	221	81.55	335	22.24
1500-2499 g	7800	32.06	14	5.17	500	33.20
2500-2999 g	4146	17.04	14	5.17	233	15.47
3000-3499 g	4354	17.90	13	4.80	231	15.34
≥ 3500 g	4882	20.07	9	3.32	207	13.75
CHD						
Yes	2485	10.21	226	83.39	289	19.19
No	21 754	89.42	45	16.61	1217	80.81
CLD						
Yes	1139	4.68	192	70.85	166	11.02
No	23 190	95.32	79	29.15	1340	88.98
Region of birth						
Metropolitan	19 206	78.94	196	72.32	1203	79.88
Rural	3317	13.63	55	20.30	191	12.68
Remote	1720	7.07	19	7.01	105	6.97
Season of birth						
Summer	6048	24.86	43	15.87	332	22.05
Autumn	6274	25.79	104	38.38	459	30.48
Winter	6051	24.87	86	31.73	448	29.75
Spring	5956	24.48	38	14.02	267	17.73
Year of birth						
2002-2009	14 896	61.23	52	19.19	1003	66.60
2010-2013	9433	38.77	219	80.81	503	33.40
Maternal factors						
Number of previous pregnancies						
0	7685	31.59	90	33.21	280	18.64
1	6342	26.07	70	25.83	430	28.63
2	4077	16.76	33	12.18	283	18.84
≥3	6189	25.44	78	28.78	509	33.89
Smoking during pregnancy						
Yes	5208	21.41	47	17.34	396	26.29
No	19 085	78.45	224	82.66	1106	73.44

*Percentages may not add up to 100% because of missing data.

receiving 1-3 doses. More than 90% of palivizumab doses were administered to infants aged <12 months.

Overall, there were 1689 positive RSV tests before age 2 years with 97.9% detected by antigen detection and/or polymerase chain reaction. This represented 1506 infants (6.2%) with at least 1 RSV detection before age 2 years (Figure 1), and 183 (10.8%) of these infants also had a further episode of RSV detection before age 2 years. The age distribution of a child's first RSV detection (Figure 2; available at www.jpeds.com) ranged from 2 to 730 days (median 165 days) with 52.1% occurring before age 179 days (6 months old) and 78.6% occurring before 12 months of age.

Cohort Study

Among the cohort of 24 329 infants, there were 45 670.3 child-years at risk. Overall, there was no association of palivizumab receipt with lower risk of RSV detection before age 2 years (Table II). In the unadjusted analysis, infants who had received 1, 3, or 4 doses of palivizumab had a higher risk of RSV detection compared with those who received none, with an unadjusted HR of 2.17 (95% CI 1.2, 4.0) for 1 dose, increasing to 5.67 (95% CI 1.83, 17.63) for 4 doses. However, adjusting for the presence of CLD, CHD, Aboriginality, sex, and gestational age accounted for part of the apparent excess in risk among palivizumab recipients, with an adjusted hazard ratio (aHR) of 0.99 (95% CI 0.5, 1.9) for 1 dose vs none (Table II).

In the restricted cohort born from 2010 (n = 9 433), there were 503 (5.3%) children with RSV detection before age 2 years (Figure 1). Despite increased palivizumab use, the risk of RSV detection was greater among palivizumab recipients for all doses (eg, unadjusted HR for dose 1 was 2.65 [95% CI 1.4, 5.0]; Table II). After risk adjustment, the aHR for dose 1 vs none was 1.69 (95% CI 0.8, 3.5; Table II). Two hundred ninety-nine infants were born <28 weeks of gestation, had CLD, and were therefore recommended to receive palivizumab under the extended guidelines. In this targeted group, despite the high use of palivizumab (52.8% with at least 1 dose), there was still no evidence of a protective association after adjusting for infant sex, CHD, and Aboriginal status (Table II). A further 51 infants were Aboriginal and <28 weeks of gestation, with 22 (43.1%) having at least 1 dose of palivizumab and 6 (11.8%) with an RSV detection. The risk of RSV detection was numerically higher among palivizumab recipients, and there was no evidence of a protective association after adjusting for infant sex, CLD, and CHD (aHR for 1 dose: 1.41, 95% CI: 0.19, 10.57), although data were too sparse to draw any conclusion. When the analysis was restricted to palivizumab doses administered in the child's first RSV season (76% of all doses), the univariate and adjusted HRs did not significantly change.

Self-Controlled Case Series

The SCCS analysis focused on the 1506 infants with one or more RSV detections ("cases") of whom 37 (2.5%) had at least 1 dose of palivizumab (Figure 1). In the overall cohort, the incidence of confirmed RSV detection before age 2 years was 70% lower (incidence rate ratio [IRR] 0.30; 95% CI 0.10, 0.88) in the 28 days after the first dose of palivizumab compared with control periods (Table III). Subsequent doses were not associated with a significant reduction in the rate of RSV detection, although the point estimate of the rate of RSV detection after one-third dose was nonetheless consistent with a protective effect (IRR 0.44). Because of small numbers, we grouped palivizumab

Table II. Unadjusted and adjusted effectiveness of palivizumab against RSV detection before age 2 years by number of doses in a high-risk cohort

Cohorts	Palivizumab dose number	Population at risk	RSV cases	HR	95% CI	aHR*	95% CI
Overall cohort (N = 24 329)							
	0	23 329	1477	Ref	-	Ref	-
	1	262	10	2.17	1.16, 4.04	0.99	0.52, 1.88
	2	182	5	1.22	0.50, 2.93	0.56	0.23, 1.37
	3	99	7	3.48	1.66, 7.32	1.41	0.66, 3.03
	4	53	<5†	5.67	1.83, 17.63	2.19	0.70, 6.88
	5	39	<5†	2.00	0.23, 14.20	0.94	0.13, 6.70
	6	22	<5†	7.71	1.09, 54.85	4.34	0.61, 30.95
	7+	24	<5†	12.24	3.05, 49.09	6.61	1.64, 26.64
Born ≥2010 (N = 9433)							
	0	9433	480	Ref	-	Ref	-
	1	215	10	2.65	1.42, 4.97	1.69	0.82, 3.50
	2	139	5	1.60	0.67, 3.86	1.02	0.39, 2.66
	3	64	5	3.22	1.33, 7.78	1.93	0.72, 5.20
	4	21	<5†	5.70	1.42, 22.91	3.21	0.74, 13.83
	5	10	<5†	4.18	0.58, 29.74	2.78	0.37, 20.67
	6	<5†	0	-	-	-	-
Recommended for palivizumab under extended guidelines (<28 weeks of gestation and CLD; n = 299)							
	0	299	15	Ref	-	Ref	-
	1	157	7	1.23	0.50, 3.00	1.16	0.47, 2.87
	2	108	<5†	0.52	0.15, 1.79	0.53	0.15, 1.82
	3	59	5	1.04	0.38, 2.87	0.99	0.36, 2.73
	4	19	<5†	1.67	0.38, 7.33	1.46	0.32, 6.61
	5	8	<5†	1.28	0.17, 9.73	1.41	0.18, 10.85
	6	<5†	0	-	-	-	-

Ref, reference level.
*Overall cohort adjusted for CLD, CHD, Aboriginal status, gestational age (categorical), and sex. Those recommended for palivizumab adjusted for CHD, Aboriginal status, and sex.
†Cell sizes with less than 5 counts have been suppressed as per requirements from data custodians. These cases were still used in the models.

doses together for subsequent analyses. The incidence of RSV detection in infants was 74% lower (IRR 0.26; 95% CI 0.11, 0.67; Table III) following any dose of palivizumab compared with control periods.

There were 503 infants born from 2010 with RSV detected before age 2 years, of whom 27 (5.4%) had at least 1 dose of palivizumab (**Figure 1**). The incidence of RSV was 81% lower (IRR 0.19; 95% CI 0.06, 0.66; **Table III**) in the 28 days following any dose of palivizumab compared with control periods (no doses). Of this cohort, 33 cases occurred in infants fulfilling the recommended criteria for palivizumab, being <28 weeks of gestation and having CLD, with 19 (57.5%) of these receiving at least 1 dose of palivizumab. Evidence of a reduction in RSV detection following palivizumab could not be detected in this restricted group.

Table III. Relative incidences for RSV detection before age 2 years and palivizumab exposure using a self-controlled case series

Cohorts	Palivizumab dose*	Relative incidence	95% CI
Overall (1506 cases)			
	By dose number		
	1	0.30	0.10, 0.88
	2	-†	-
	3	0.44	0.06, 3.39
	4	-†	-
	5 or more	0.59	0.06, 5.29
Overall (1506 cases)			
	Any dose		
	1 or more	0.26	0.11, 0.67
Born ≥2010 (503 cases)			
	Any dose		
	1 or more	0.19	0.06, 0.66

SCCS is adjusted for age group and RSV season.
*Benefit period is 0-28 days from date of administration of each dose.
†Not enough cases to calculate.

Discussion

This study assessed the effectiveness of immunoprophylaxis on RSV infection in a population-based high-risk cohort of infants under programatic conditions. Here we used 2 analytical methods to address confounding by indication as the children who have the greatest risk of hospitalization because of RSV are also those most likely to receive palivizumab. Using a traditional cohort approach, there was no association observed between palivizumab receipt and RSV detection before age 2 years. Using the SCCS method, however, which inherently removes bias from any time-invariant confounders, a protective effect of palivizumab was detected - a point estimate of a 74% rate reduction in RSV detection in the 28 days after any dose compared with control periods remote from palivizumab doses.

There is considerable debate regarding the use of palivizumab to prevent RSV, especially around cost effectiveness even in high-income countries.[19-21] Population-based studies are needed to evaluate the real-world effectiveness and resulting cost effectiveness under programatic conditions to assist in policy. A recent case control study reported a palivizumab

effectiveness estimate of 43% for RSV-confirmed hospitalization before age 2 years that increased to 58% with a propensity score weighted regression to minimise bias by indication, although effectiveness by number of palivizumab doses was not assessed.[22] Further, in that setting, palivizumab use was much higher (51% in the overall cohort). A recent US study of >211 000 infants with a similar low level of palivizumab use (1.5%), reported a 32% reduced risk of bronchiolitis using similar methodology to our cohort analysis[14]; although their outcome was bronchiolitis ICD coded-hospitalizations rather than the more specific virologically confirmed RSV outcome used in our study, where 90% were hospitalized cases. Additionally in that study, no evidence of a protective effect could be identified in a subgroup of extremely preterm infants.[14]

Palivizumab guidelines vary internationally, and there are no national guidelines in Australia. In WA, tertiary NICUs developed guidelines for the in-hospital use of palivizumab among high-risk infants including those <28 weeks of gestation with CLD or of Aboriginal identification, in-hospital prophylaxis within NICU, and outpatient use for infants with severe CLD and CHD.[6] In our cohort and SCCS analysis, we did not find any evidence of a protective association between palivizumab receipt and subsequent RSV risk in those <28 weeks with CLD. Despite the risk of RSV being higher in Aboriginal infants,[10] we did not find evidence of a protective effect of palivizumab in Aboriginal infants born extremely preterm; however, small numbers reduced our analytical power to detect a statistical association. Palivizumab has been used outside standard recommendations elsewhere,[14, 23] including in our own setting as shown here; thus, it is important to assess the effectiveness on a total population basis and not restricted to those meeting the recommended guidelines.

Our study highlights the challenges of assessing palivizumab effectiveness because of confounding by indication, a widely recognized problem of retrospective observational studies, which evaluate targeted interventions.[15] Despite adjusting for known risk factors for severe RSV infection, residual confounding is still likely to have affected our cohort analysis. The strength of our study is supplementation of the cohort analysis with a SCCS. Using this method, we estimated that palivizumab administration afforded a 74% rate reduction in first detection of RSV in high-risk children up to 2 years of age. Although this protective effect was only seen with 1 palivizumab dose, we acknowledge that the small number of cases in our study limited our analysis of subsequent doses. The current guidelines call for 5 consecutive doses of palivizumab over the RSV season, significantly contributing to its high cost.[20] We were not able to conclude that subsequent palivizumab doses confer additional benefit over the first dose, although our analysis was limited by small numbers. It will be important to confirm the incremental benefit of subsequent doses, especially in light of new monoclonal antibody formulations designed to be administered as a single dose.[24] A further strength of our study is the integration of numerous administrative datasets that enabled the outcome measure of virologically confirmed RSV infection as opposed to ICD-coded bronchiolitis hospitalizations, which we have previously shown to be poorly correlated with RSV-confirmed infection.[10]

Although one of the recommended uses of palivizumab in our setting was to prevent nosocomially acquired RSV, we were unable to evaluate this specifically due to the difficulty in distinguishing nosocomially-acquired RSV compared with community-acquired RSV. We have, however, shown an overall protective effect of 1 dose of palivizumab in the high-risk cohort through our SCCS analysis. The decision to continue the recommendation of palivizumab use to prevent nosocomial infections needs to take into consideration the overall cost of the program, which as we highlighted, is considerable in our setting.

Our study does have some unavoidable limitations. Despite broadening of the recommendations for palivizumab use in the guidelines for high-risk infants, the use of palivizumab was lower than expected, which limited statistical power. We used pharmacy dispensing data and therefore assumed that the date of dispensing corresponded to the date of administration. There are no sources of data to verify the palivizumab administration date so there is the potential for bias from exposure misclassification. As not all hospitalized infants with bronchiolitis are tested for RSV (approximately 55% from our previous work[25] with some yearly fluctuations[26]), we might be underestimating the number of RSV infections. However, we chose to restrict our analyses to the highly sensitive outcome of RSV-confirmed infections and testing for RSV would be more routine in this high-risk cohort. We may have underestimated the number of patients with CHD as we relied only on hospitalizations with a CHD diagnosis, rather than verifying this diagnosis from the Western Australian Register of Developmental Anomalies. However, our study cohort consisted of those children who were admitted to NICU, and not necessarily all those with CHD. Guidelines recommend palivizumab doses are given 28 days apart. Approximately 40% of palivizumab doses had a dispensing date <28 days from a subsequent dose with most of these falling in the window of 21-27 days. We did not adjust for this nor censor these potentially invalid doses as our intention was to measure the real-world effectiveness rather than strict dosing regimens as in the randomized clinical trials.[2,3]

RSV causes significant morbidity and mortality worldwide and the World Health Organization now lists RSV prevention through vaccination as a top global priority.[27] However, palivizumab remains the only licensed product for preventing RSV morbidity in high-risk infants. The real-world effectiveness of immunoprophylaxis using integrated population-based datasets is essential to evaluate ongoing RSV prevention efforts. ■

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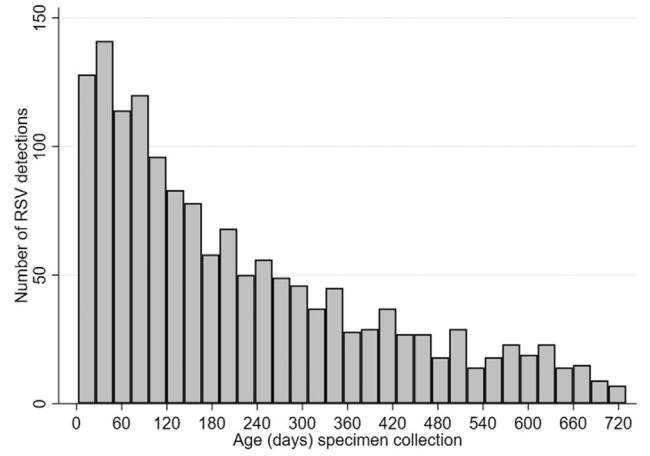

Figure 2. Age distribution of RSV cases (first event only).