

Burden of Severe Respiratory Syncytial Virus Disease Among 33–35 Weeks' Gestational Age Infants Born During Multiple Respiratory Syncytial Virus Seasons

Evan J. Anderson, MD,* Xavier Carbonell-Estrany, MD, PhD,† Maarten Blanken, MD, MSc,‡ Marcello Lanari, MD, PhD,§ Margaret Sheridan-Pereira, FRCPI,¶ Barry Rodgers-Gray, PhD,|| John Fullarton, PhD,|| Elisabeth Rouffiac, MD, Pamela Vo, PharmD, MS, Gerard Notario, MD,** Fiona Campbell, MSc, and Bosco Paes, MD††

Background: Moderate-late preterm infants, 33–35 weeks' gestational age (wGA), are at increased risk for respiratory syncytial virus hospitalization (RSVH). The objective of this study is to quantify the burden of RSVH in moderate-late preterm infants.

Methods: A pooled analysis was conducted on RSVH from 7 prospective, observational studies in the Northern Hemisphere from 2000 to 2014. Infants' 33⁰–35⁶ wGA without comorbidity born during the respiratory syncytial virus season who did not receive respiratory syncytial virus immunoprophylaxis were enrolled. Data for the first confirmed RSVH during the season (+1 month) were analyzed. Incidence and hospitalization rate per 100 patient-seasons, intensive care unit admission and length of stay (LOS), oxygen support, mechanical ventilation and overall hospital LOS were assessed.

Results: The pooled analysis comprised 7,820 infants; 267 experienced a confirmed RSVH at a median age of 8.4 weeks. The crude pooled RSVH incidence rate was 3.41% and the rate per 100 patient-seasons was 4.52. Median hospital LOS was 5.7 days. A total of 22.2% of infants required intensive care unit admission for a median LOS of 8.3 days. A total of 70.4% received supplemental oxygen support for a median of 4.9 days, and 12.7% required mechanical ventilation for a median of 4.8 days.

Conclusions: The burden of RSVH in moderate-late, 33–35 weeks' wGA preterm infants without comorbidities born during the viral season in

Northern Hemisphere countries is substantial. Severe cases required prolonged and invasive supportive therapy.

Key Words: respiratory syncytial virus, lower respiratory tract infections, respiratory syncytial virus hospitalization, moderate-late preterm infants

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Respiratory syncytial virus (RSV) is an important cause of lower respiratory tract infection (LRTI) in infants.^{1,2} In 2005, the estimated global burden of new episodes of RSV LRTIs in children <5 years of age was over 33 million, with at least 3.4 million episodes representing severe RSV LRTI necessitating hospitalization.¹ RSV hospitalizations (RSVHs) have a major impact on healthcare resources^{3–5} and costs,^{6–8} and have been associated with recurrent wheeze and possibly asthma.^{9,10}

Infants born at 33–35 weeks' gestational age (wGA) (moderate-late preterm) are an important risk group for severe RSVH and sequelae.^{3–5,7,11–13} Horn et al.³ found that moderate-late preterm infants had the highest rate of intubation and longest hospital and intensive care unit (ICU) length of stay (LOS) compared with ≤32 or ≥36 wGA infants, potentially linked to critical lung underdevelopment between 32 and 35 wGA and immunologic immaturity. Prophylaxis with palivizumab has been shown to reduce RSVH in moderate-late preterm infants by up to 82%^{14,15}; however, these infants are considered eligible for prophylaxis only under specific circumstances according to different national guidelines from different countries.^{16–20}

Defining and understanding the burden of severe RSV infection can aid judicious use of palivizumab prophylaxis,^{21,22} within the context of limited healthcare resources.²³ Data specific to the epidemiology and disease burden of RSV in Northern Hemisphere moderate-late preterm infants are currently limited by the small number of RSVH available in individual studies. The primary objective was to quantify the epidemiology and burden of severe RSV LRTI in a homogeneous dataset of 33–35 wGA (moderate-late preterm) infants in the Northern Hemisphere born and experiencing first RSVH within the same RSV season (+1 month) as their birth.

MATERIALS AND METHODS

Study Selection

An electronic Medline and Embase search was performed using the following search terms: respiratory syncytial virus (RSV), infection, disease, illness, epidemiology, hospitalization, late preterm, premature and gestational age. Filters included the time span of January 1, 1998, to January 1, 2015, English language, and humans. The Cochrane Central Register of Controlled Trials and Database of Systematic Reviews were searched for reviews on RSV infection. All identified reports were checked for references to additional controlled trials or pertinent citations. A pooled analysis was

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From the *Departments of Pediatrics and Medicine, Emory University School of Medicine, Atlanta, GA; †Neonatology Service, Hospital Clinic, Institut d'Investigacions Biomediques August Pi Suñer (IDIBAPS), Barcelona, Spain; ‡Division of Pediatric Immunology and Infectious Diseases, University Medical Center Utrecht, Utrecht, The Netherlands; §Pediatrics and Neonatology Unit, Imola Hospital, Imola, Italy; ¶Department of Paediatrics, Trinity College and Coombe Women and Infants University Hospital, Dublin, Ireland; ||Stratagen Limited, Basingstoke, United Kingdom; **Global Pharmaceutical Research and Development, AbbVie Inc, North Chicago, IL; and ††Department of Pediatrics (Neonatal Division), McMaster University, Hamilton, Ontario, Canada.

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Address for correspondence: Evan J. Anderson, MD, Departments of Pediatrics and Medicine, Emory University School of Medicine, Atlanta, GA. E-mail: evanderson@emory.edu.

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performed on RSVH data from 33 to 35 wGA (defined as 33 weeks and 0 days to 35 weeks and 6 days) moderate-late preterm infants born in the Northern Hemisphere. Gestational age in the selected studies was largely based on standard criteria of ultrasonographic dating in the early phase of pregnancy and/or the number of weeks elapsed between the first day of the last menstrual period and the date of delivery. To avoid potential regional or local biases, studies were only included if they had a multicenter, observational, prospective design; assessed >1000 preterm infants at risk for severe RSV disease; included infants with laboratory-confirmed RSV infection; evaluated data on RSVH morbidity and contained data available for analysis by January 2015. Severe RSV infection was defined as the need for hospitalization. Studies were excluded if >15% of infants received palivizumab prophylaxis to standardize the cohort and avoid the potential confounding effect of prophylaxis. The study did not include more than one dataset from a country (excluding multinational studies) to avoid the perception of bias toward any one country. If more than one dataset met the inclusion criteria for a particular country, then the most recent dataset was selected.

Data Extraction and Infant Selection

All data from studies meeting the inclusion criteria were anonymized before they were transferred to the central database for analysis (Table 1). After receipt of the data from these studies, to ensure homogeneity, infants were excluded from analyses if they had received palivizumab, had a relevant comorbidity, such as congenital heart disease, bronchopulmonary dysplasia, Down syndrome or immunodeficiency, or had incomplete data.

Data Analysis

Descriptive Analyses

Descriptive enumerative analyses were carried out in all datasets including totals, total missing values and range of values by variable. Where appropriate, frequency and dispersive characteristics were investigated, including median and the interquartile range. Reference RSV seasons were taken from each study. Distribution of first RSVH through the RSV season (+1 month) was calculated both as an incidence rate and as the rate per 100 patient-seasons.

Pooled Analysis

A pooled analysis was conducted of homogenous data across the 7 included datasets (Fig. 1). Since the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) database contained only infants born and hospitalized for RSV within the same

RSV season (+1 month),²⁴ to maximize homogeneity, all datasets were standardized to this criterion. Weighted average analyses using inverse variance weighting in a fixed effects model was applied. Missing values within the data were classified as “not recorded” rather than zero and the absence of data was confirmed with the authors of the individual studies. Variances were calculated for each variable across all datasets. Calculated descriptive measurements were weighted by the inverse variance associated with the variables in each dataset. This allowed the calculation of weighted averages.

RSVH rates by gestational age in individual studies and the combined database were compared using the chi square test. The rates of supplemental oxygen use, admission to ICU and mechanical ventilation use in RSVH infants were compared across the individual datasets using the chi square test, while the duration of these outcomes was compared using one-way analysis of variance.

An analysis was undertaken to determine if hospital resource use differed between earlier and more contemporary studies by splitting the combined database into 2 halves and comparing outcomes using *t* tests and Mann-Whitney *U* tests, as appropriate.

Heterogeneity Tests

Heterogeneity (equality of variance) tests across datasets for key variables were undertaken using nonparametric Levene tests to determine whether data were suitable for pooled analyses. Cox regression analyses were also used to test homogeneity. The variables and outcomes of interest were then assembled into a combined database.

All analyses were performed using SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL), Microsoft Access SQL (Microsoft, Redmond, WA) and Microsoft Access/Excel VBScript (Microsoft, Redmond, WA).

RESULTS

Birth and first confirmed RSVH data on 33⁰–35⁶ wGA (moderate-late preterm) infants born during the period 2000–2014 were collected from 7 separate databases across the Northern Hemisphere. Five studies were identified via the systematic search and a further 2 were found that were awaiting publication (Fig. 1). The datasets included were as follows: second Risk Factors Linked to RSV Infection Requiring Hospitalization in Premature Infants Study (FLIP-2, Spain),¹¹ RISK study (Netherlands),²⁵ PICNIC (Canada),²⁴ RSV Preterm Risk Estimation Measure for RSVH in Ireland (RSV-PREMI, Ireland),¹³ Italian National Birth Cohort (IBC, Italy),²⁶ RSV Respiratory Events among Preterm Infants Outcomes and Risk Tracking (REPORT, US)⁵ and Predictors Associated with RSV hospitalization in Nonprophylaxed, Premature Infants (PONI, multinational).²⁷ Individual study designs and demographics are shown in Tables 2 and 3.

Data from 17,669 moderate-late preterm infants were identified from these 7 datasets. Of these, 4213 (23.8%) did not meet the inclusion criteria and were excluded (Fig. 2), primarily for failure to meet the 33⁰–35⁶ wGA criteria (3268, 18.5%), palivizumab prophylaxis (404, 2.3%), presence of comorbidities (470, 2.7%) or incomplete data (71, 0.4%). Of the 13,456 remaining infants, 474 (3.5%) had clinically confirmed RSVH. However, nonparametric Levene tests showed significant heterogeneity between datasets within this group ($P = 0.001$ for age at admission; $P < 0.001$ for duration of hospitalization).

The PICNIC database contained only infants born within the RSV season (+1 month).²⁴ In the majority of the other datasets, around 50% cases of RSVH were observed in infants born within the RSV season: FLIP-2 (57.7%), RISK (45.2%), REPORT (46.3%), IBC (75.0%), PREMI (47.2%) and PONI (50.0%). To maximize homogeneity across the datasets, all data were standardized to 33⁰–35⁶ wGA infants born during the RSV season and

TABLE 1. Data Extracted From Each Dataset

Demographic	<ul style="list-style-type: none"> • Date of birth • wGA • LRTI hospitalization (yes/no) • Age at hospitalization (wk)
Testing	<ul style="list-style-type: none"> • RSV test performed (yes/no) • RSV status (positive/negative)
Therapy	<ul style="list-style-type: none"> • Need for oxygen therapy (yes/no) • Duration of oxygen therapy (d)
Outcomes	<ul style="list-style-type: none"> • Admission to ICU (yes/no) • ICU LOS (d) • Need for mechanical ventilation, ie, any intervention including intubation plus any modality of ventilation or ECMO for the specific treatment of worsening respiratory distress (yes/no) • Duration of mechanical ventilation (d) • Hospitalization LOS, ie, total LOS including time in ICU (d)

ECMO indicates extracorporeal membrane oxygenation.

FIGURE 1. PRISMA of systematic review process. Stage 1 review: 2 reviewers assessed citations for inclusion/exclusion based on the title and abstract. Stage 2 review: 2 reviewers assessed each citation for inclusion/exclusion based on the full text. Reasons for exclusion were categorized as follows: population (eg, outside 33–35 weeks' gestational age range), intervention (eg, study including >15% of infants receiving prophylaxis), study type (eg, retrospective) or new study available (ie, 2 studies available from the same country whereupon the newer one would be included). For both stages, if a consensus could not be reached, a third experienced reviewer made the decision. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

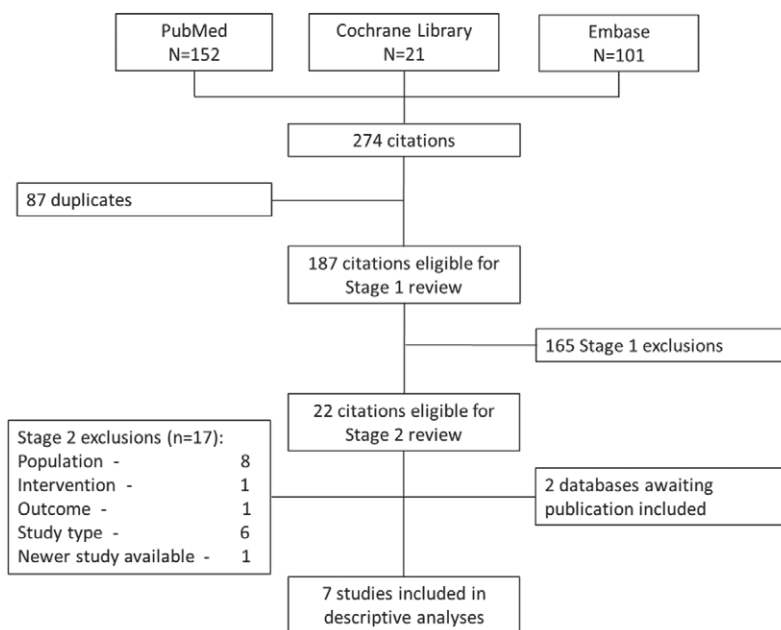


TABLE 2. Data Derivation

Database	Total N	wGA (<33 or >35)	Exclusions					Born Outside RSV Season	N in Analysis	RSVH
			Comorbidities	Prophylaxed	Other					
PICNIC	1758	0	232	0	9*	0	1517	46		
FLIP-2	5441	844	165	404	0	1689	2339	86		
RISK	2421	238	0	0	11†	992	1180	52		
REPORT	1642	142	0	0	0	950	550	25		
IBC	2210	1184	0	0	51‡	539	436	12		
PREMI	1807	860	8	0	0	396	543	17		
PONI	2390	0	65	0	0	1070	1255	29		
Total	17,669	3268	470	404	71	5636	7820	267		

*Nine RSV cases not confirmed in hospital.

†Infants with no recorded wGA.

‡Fifty infants lost to follow-up; 1 infant with unknown RSV status.

who experienced their first RSVH during the same RSV season (+1 month). This excluded an additional 5636 infants (41.9%) and resulted in a core database of 7820 infants (58.1%) for analysis (Table 2). Nonparametric Levene tests showed no significant heterogeneity between datasets within this group ($P = 0.129$ for age at admission; $P = 0.150$ for duration of hospitalization). A Cox regression analysis confirmed similarity of the datasets with a non-significant source covariate ($P = 0.609$). This approach captured 56% of the total RSVH (267/474).

RSV-positive Hospitalization Rates

The incidence of RSVH in the homogeneous population varied among the datasets, from 2.31% to 4.55% (Table 4). The individual incidence rates ranged from 3.15 to 5.92 per 100 patient-seasons. In the pooled analysis, 33–35 wGA preterm infants born and hospitalized within the same RSV season showed a crude RSVH incidence rate of 3.41% and a rate per 100 patient-seasons of 4.52, 95% confidence interval (3.83–5.21).

Incidence Rate of RSVH Stratified by Gestational Age

The pooled incidence rate was similar across gestational age groups: 3.63% for 33 wGA; 3.25% for 34 wGA and 3.45% for 35 wGA (Table 5). No consistent trend in RSV incidence by wGA was evident among the different datasets.

Seasonality of RSV-positive Hospitalizations

The rates of RSVH during the RSV season (+1 month) for infants born in that season show a degree of variation between the datasets in terms of the calendar month (Fig. 3). There are fewer hospitalizations during the first month of the season with a peak in December–March and then a steep decline. There was a difference in the peak of the RSV season with time. Taking the midpoint in terms of number of seasons for which data were available, before 2010, 27.3% of cases occurred in December, whereas 27.1% of cases occurred in January after 2010.

TABLE 3. Study Designs

Study	Country	Study Years	Duration of Follow-up	Subject wGA	Sample Size	RSV Season
PICNIC	Canada	2000–2002	1-mo post-RSV season	33 wk 0 d to 35 wk 6 d	1832	November 1 to April 30
FLIP-2	Spain	2005–2007	End of May	32 wk 1 d to 35 wk 0 d	5441	October 1 to April 30
RISK	Netherlands	2008–2012	1 year of age	32 wk 1 d to 35 wk 6 d	2421	October 1 to March 31
REPORT	US	2009–2011	End of May	32 wk 0 d to 35 wk 6 d	1642	November 1 to March 31
IBC	Italy	2009–2013	1 year of age	33 wk 0 d+	2210	November 1 to March 31
PREMI	Ireland	2011–2014	1 year of age	32 wk 0 d to 36 wk 6 d	1807	October 1 to March 31
PONI*	Europe, Middle East, North America, Asia	2013–2014	End of April	33 wk 0 d to 35 wk 6 d	2390	October 1 to April 30

*PONI included the following countries: France, Norway, Sweden, Austria, Portugal, Mexico, Korea, Czech Republic, Slovakia, Slovenia, Latvia, Lithuania, Estonia, Russia, Egypt, Bahrain, Oman, Jordan, Lebanon and Saudi Arabia.

Age at First Confirmed RSV LRTI Hospitalization for Infants Born and Hospitalized in the Same RSV Season

The median age for infants born and hospitalized for their first confirmed RSV LRTI in the same RSV season ranged from 7.1 (RISK) to 11.0 (REPORT) weeks (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C555>). The weighted median age at first confirmed RSVH within the pooled analysis was 8.4 weeks.

Healthcare Resource Use During Hospitalization

There was significant variation in the proportion of infants who received supplemental oxygen across the 5 datasets, ranging from 32.0 (REPORT) to 88.2% (PREMI). The median duration of supplemental oxygen showed consistency across datasets at 4–5 days (see Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C555>). In the pooled analysis, a total of 70.4% of infants received supplemental oxygen for a median of 4.9 days.

The percentage of RSV-positive infants admitted to ICU ranged from 15.4% to 41.4%, with a median ICU LOS across the datasets of 3.5–7.0 days. The pooled analyses showed that 22.2% of moderate-late preterm infants were admitted to the ICU as part of their total RSVH, for a median duration of 8.3 days.

The requirement for mechanical ventilation while in hospital varied from 6.5% to 35.3%, with a median duration of 3–8 days. In the pooled analysis, a total of 12.7% of infants received mechanical ventilation for a median of 4.8 days. Five studies documented overall hospital LOS. The median ranged from 3 to 9 days ($P = 0.005$ across datasets), with the pooled LOS being 5.7 days.

When split into studies conducted from 2000 to 2007 ($N = 132$ RSVH) and from 2008 to 2014 ($N = 135$ RSVH), there were no significant differences in terms of hospital resource use ($P = 0.500$ for duration of respiratory support; $P = 0.958$ for duration of mechanical ventilation; $P = 0.659$ for ICU LOS; $P > 0.999$ for total LOS).

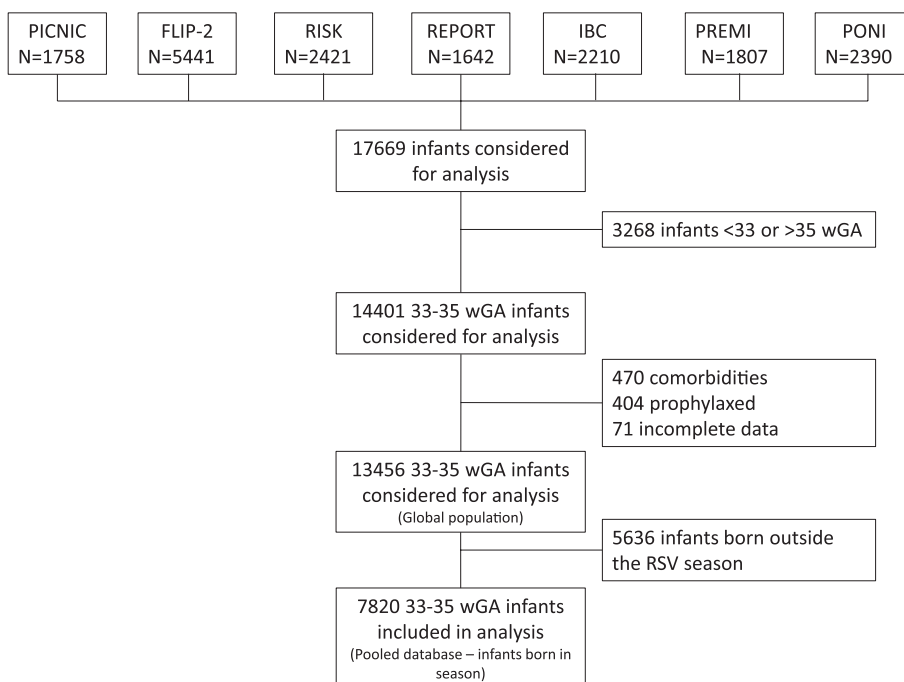


FIGURE 2. Diagram of derivation of analytical dataset.

wGA: weeks' gestational age; RSV: respiratory syncytial virus

TABLE 4. Number and Incidence of RSVH in 33–35 wGA Moderate-Late Preterm Infants in Each Dataset

Dataset/Years Studied	Global Population			Born in the RSV Season Population		
	Number of RSVH	RSVH Incidence Rate (%)	Rate/100 Patient-Season	Number of RSVH, n (%)	RSVH Incidence Rate (%)	Rate/100 Patient-Season
PICNIC (2000–2002)	46	3.03	4.27	46 (100)	3.03	4.27
FLIP-2 (2005–2007)	149	3.8	4.33	86 (57.7)	3.68	4.76
RISK (2008–2012)	115	2.3	6.30	52 (45.2)	4.41	5.54
REPORT (2009–2011)	54	3.6	3.72	25 (46.3)	4.55	5.92
IBC (2009–2013)	16	1.6	2.27	12 (75.0)	2.75	4.36
PREMI (2011–2014)	36	3.9	4.86	17 (47.2)	3.13	4.04
PONI* (2013–2014)	58	2.6	2.96	29 (50.0)	2.31	3.15
Total	474	3.52; 95% CI (2.67–4.38)	4.18; 95% CI (3.23–5.13)	267 (56.3)	3.41; 95% CI (2.79–4.04)	4.52; 95% CI (3.83–5.21)

The rate per 100 patient-seasons reports the number of infants with RSVH per 100 infants in an RSV season. This is calculated by (incident rate/% complete season exposure) × 100.

*PONI has an approximate incidence rate. Day of birth was not recorded; duration of exposure was calculated from an estimated birth date using the 1st day of the month of birth.

CI indicates confidence interval.

TABLE 5. Incidence Rate of RSVH Stratified by Gestational Age at Birth in 33–35 wGA Infants Born and Hospitalized in the Same RSV Season

	Gestational Age in Weeks*, %		
	33	34	35
PICNIC	3.58	3.26	2.57
FLIP-2	3.90	3.33	4.38
RISK	5.32	5.28	3.03
REPORT†	1.69	2.92	5.65
IBC	4.55	1.10	3.25
PREMI	5.79	1.64	2.93
PONI	0.89	2.64	3.02
TOTAL	3.63	3.25	3.45

*Chi square tests showed no significant differences between the gestational age groups within each study.

†The incidence rates of REPORT may be related to palivizumab prophylaxis and subsequent enrolment exclusion of 32–34 wGA infants <3 months, consistent with the American Academy of Pediatrics policy at the time of study.

DISCUSSION

The results of this analysis illustrated that the burden of RSV LRTI in 33–35 wGA (moderate-late preterm) infants born during the RSV season in Northern Hemisphere countries is substantial, although RSVH rates varied between studies. Overall, the incidence rates of RSVH per 100 patient-seasons ranged from 3.15 (PONI) to 5.92 (REPORT), with a pooled rate of 4.52.

The pooled median hospital LOS was 5.7 days, with 22.2% of infants requiring admission to ICU for a median of 8.3 days. Among those infants with RSVH, up to 88% required supplemental oxygen (PREMI) and up to 35% required mechanical ventilation (PREMI), with the pooled analysis showing that 70.4% of all RSVH infants received oxygen and 12.7% received mechanical ventilation. In the 6 datasets reporting on mortality (PONI excluded mortality data from their analyses), there were no RSV-associated deaths.

Our findings on the effect of prematurity on hospital resource use and outcomes are consistent with previous observations.^{3,28} Diez-Domingo et al²⁸ recently, systematically searched the literature and found that between 17.8% and 48.4% of 33–35 wGA infants with RSVH are admitted to the ICU, and a substantial proportion of all infants with RSVH required assisted ventilation for recurrent apnea, labored breathing, hypoxemia and respiratory

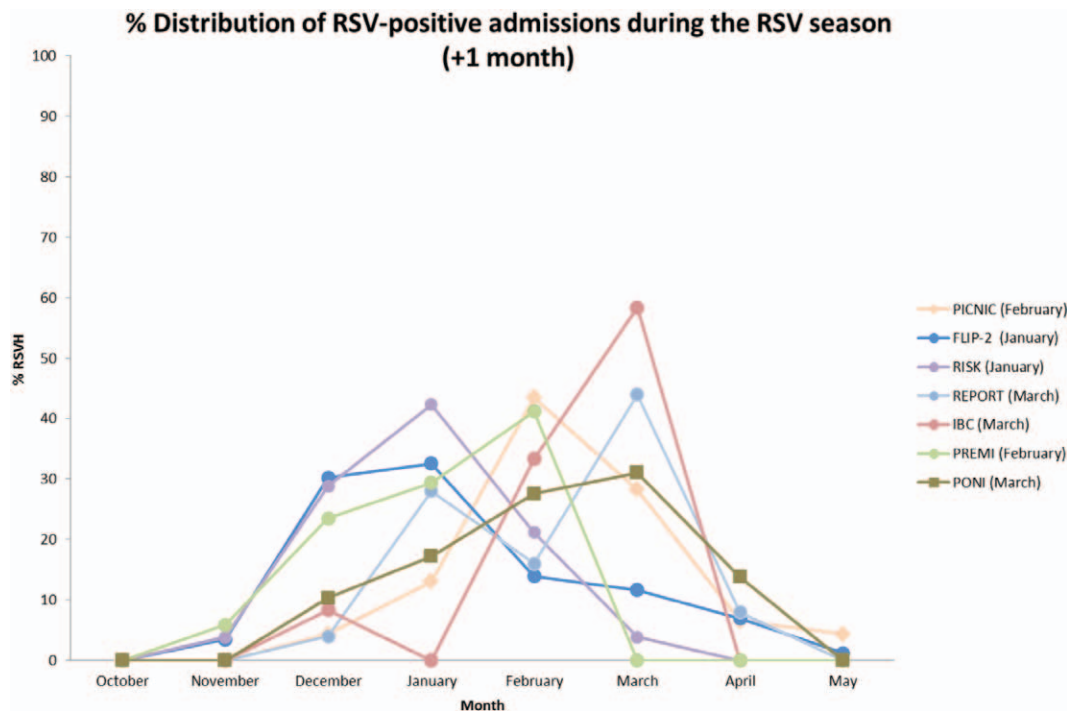
failure (~10%), but this figure doubled in preterm infants (20% in 32 wGA RSVH infants).

Moderate-late preterm infants, 33–36 wGA, with a history of RSV cost the US healthcare system almost 5 times more over the first year of life than premature infants with no history of RSV.²⁹ The use of palivizumab to prevent RSVH has been shown to be highly cost-effective in some studies and not cost-effective in others, depending on the modeling approaches, type of analyses performed, assumptions used and cost-effectiveness thresholds applied.³⁰ In moderate-late preterm infants, the cost-effectiveness of palivizumab has been shown to be improved with the inclusion of risk factors for RSVH.^{31,32} In addition to increasing healthcare utilization and causing considerable distress for infants and children, hospitalization can significantly disrupt the lives of the families of affected infants, leading to increased emotional and financial burdens.^{33–36}

The pooled analysis of data from 33 to 35 wGA preterm infants born and hospitalized for RSV within the same season highlight the risk for early burden of RSVH, which is linked to longer term respiratory morbidity in this gestational age group.⁹ The data suggest that moderate-late preterm infants are a potential target group for intervention: 32–35 wGA infants have smaller airways and greater lung immaturity than full-term infants,^{37,38} although they are often considered physiologically and functionally close to full-term infants.

No trends were reported in comparison of relative RSVH incidence by wGA, and the pooled data shown in Table 5 illustrated similar overall means of between 3.25% and 3.63%. A bias against the most preterm infants might be expected in the data: those born at 33 wGA would receive extended neonatal hospitalization compared with 35 wGA infants and therefore experience a shorter duration of RSV seasonal exposure. However, the data reported here did not reflect any bias in this direction. In terms of seasonality, there appeared to be a trend for the majority of cases of RSVH to peak during December/January but it is difficult to draw any generalizations as the start date and length of the RSV season, as well as RSVH rates in developed countries, can vary from year-to-year.^{39–43}

A key strength of our study is that data were collected from 7 large, methodologically similar but independent multicenter, observational, prospective studies that enrolled moderate-late preterm infants from several countries across the Northern Hemisphere. The combined analysis lends more robust credence that the burden of RSV illness in this population is substantial and similar to the morbidities experienced by preterm infants <32 wGA.³



wGA: weeks' gestational age; RSV: respiratory syncytial virus; RSVH: RSV hospitalization

FIGURE 3. RSVH distribution in 33–35 wGA preterm infants during the RSV season (+1 month). Peak month shown in parentheses.

There were several important limitations in this study. The combined dataset was affected by the focus of each individual study. FLIP-2, RISK and PICNIC concentrated exclusively on RSV-positive hospitalizations, whereas PONI, REPORT and IBC evaluated all LRTI admissions. FLIP-2, RISK and RSV-PREMI collated hospitalizations over a calendar year, whereas PICNIC focused on births during the RSV season. PONI, RSV-PREMI and IBC used a wider span of gestational age ranges than the other studies. Consequently, studies that were large in terms of initial patient numbers had reduced numbers of RSVH for 33–35 infants, particularly those born within the RSV season. RSV testing was not standardized in many hospitals involved in these studies. Furthermore, rapid antigen testing, shell vial culture and viral culture predominated in earlier studies, which are typically less sensitive than currently available polymerase chain reaction–based assays. This may have resulted in an underestimate of the true burden of RSV LRTI, and may also explain the variation in RSVH rates between the datasets. Variations in the frequency of recognized biologic/medical (eg, male sex) and social/environmental (eg, day care attendance) risk factors for RSVH could also have influenced the respective rates of RSVH across the datasets.^{5,11,13,24–27} Coinfections are another factor that could have influenced the severity of disease, but such data were not available for most of the datasets and were not analyzed.

The studies were multinational, with variance in hospitalization practices (including admission criteria, criteria for oxygen use, admission to ICU and type of respiratory support used) and data extending over >10 years, which could be affected by time-related changes in medical practice. However, this practice variation may still be prevalent, because the use of oxygen in the management of bronchiolitis relative to accepted criteria for hospitalization vary

significantly, inclusive of the criteria for ICU admission.^{44–46} An additional limitation in these analyses is that the data were restricted to those infants born and/or hospitalized in the same RSV season. Also, infants who received palivizumab prophylaxis and those with significant comorbidities (eg, chronic lung disease and congenital heart disease) were excluded and only infants with laboratory-confirmed RSV infection were included in the analyses. Thus, although this resulted in a homogeneous subset of 7820 infants, important at risk infants were excluded from the analysis of these 7 multinational studies. Data from a broader study covering the entire first year of life would provide a complementary understanding of the “real life” clinical situation. Additional analyses could also further investigate the effect of chronologic age and chronologic versus developmental age on the incidence and severity of RSV illness in these infants.

This study contributes important data on the burden of RSV LRTI in 33–35 wGA (moderate-late preterm) infants in Northern Hemisphere countries. Knowledge of the health risk and burden of RSVHs in high-risk infants could guide the cost-effective use of prophylaxis with palivizumab or future RSV vaccines. Identification of higher risk moderate-late preterm infants for prophylaxis could reduce the substantial clinical and economic burden of RSV in these infants.

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