SENTINEL1: An Observational Study of Respiratory Syncytial Virus Hospitalizations among U.S. Infants Born at 29 to 35 Weeks' Gestational Age Not Receiving Immunoprophylaxis

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Abstract

Objective SENTINEL1 characterized U.S. preterm infants 29 to 35 weeks' gestational age (wGA) $<$ 12 months old hospitalized for laboratory-confirmed respiratory syncytial virus (RSV) disease and not receiving RSV immunoprophylaxis during the 2014 to 2015 RSV season.

Study Design This is a noninterventional, observational, cohort study.

Results A total of 702 infants were hospitalized with community-acquired RSV disease, of whom an estimated 42% were admitted to the intensive care unit (ICU) and 20% required invasive mechanical ventilation (IMV). Earlier gestational age and younger chronologic age were associated with an increased frequency of RSV-confirmed hospitalization (RSVH), ICU admission, and IMV. Among infants 29 to 32 wGA and $<$ 3 months of age, 68% required ICU admission and 44% required IMV. One death occurred of an infant 29 wGA. Among the 212 infants enrolled for in-depth analysis of health care

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resource utilization, mean and median RSVH charges were $55,551 and $27,461, respectively, which varied by intensity of care required. Outpatient visits were common, with 63% and 62% of infants requiring visits before and within 1 month following the RSVH, respectively.

Conclusion Preterm infants 29 to 35 wGA are at high risk for severe RSV disease, which imposes a substantial health burden, particularly in the first months of life.

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract illness in infants and young children, causing annual epidemics.[1] RSV is estimated to cause up to 75% of all infant bronchiolitis and 40% of all pediatric pneumonias.[2,3] Medical conditions in young children associated with an increased risk of severe RSV disease include chronic lung disease of prematurity (CLDP), hemodynamically significant congenital heart disease (HS-CHD), and preterm birth $\leq$ 35 weeks' gestational age (wGA).[4–6] The largest population of these high-risk children is infants who are born preterm.

Current treatment of RSV disease primarily involves supportive care. Despite considerable efforts to develop vaccines and antiviral treatments for RSV, such interventions remain elusive. Although those efforts continue,[7–9] RSV immunoprophylaxis (RSV IP) with palivizumab is the only safe and effective intervention approved for the prevention of severe RSV disease. RSV IP has been shown to reduce hospitalizations for severe RSV disease in preterm infants $\leq$ 35 wGA and children $\leq$ 24 months of age with CLDP or HS-CHD compared with placebo in randomized, placebo-controlled clinical trials.[10–12] The American Academy of Pediatrics Committee on Infectious Diseases (COID) began to publish its recommendations for the use of RSV IP in 1998 with subsequent updates and revisions, the most recent being in 2014.[13–18] The COID guidance has consistently recommended RSV IP for infants with CLDP and HS-CHD. From 1998 through mid-2014, monthly RSV IP was recommended for all preterm infants born at $<$ 32 wGA who were $<$ 6 months of age at the start of RSV season and a high-risk subset of infants born at 32 to 35 wGA. In 2009 and 2012, this high-risk subset was defined as infants born at 32 to 34 wGA who were $<$ 90 days of age and attended daycare or had preschool-aged siblings. In mid-2014, the COID recommended against the use of RSV IP among preterm infants born at 29 to 35 wGA except for those with another qualifying medical condition, such as CLDP or HS-CHD.[14]

Although several recent studies have described the persistent burden of RSV disease in U.S. infants without CLDP or HS-CHD born at 32 to 35 wGA who did not receive RSV IP,[19–21] there are no recent published data regarding the burden of severe RSV disease in U.S. preterm infants $<$ 32 wGA who did not receive RSV IP. Given the 2014 COID guidance change in the recommended use of RSV IP in U.S. preterm infants, the objective of this study is to characterize RSV-confirmed hospitalizations (RSVH) in U.S. preterm infants born at 29 to 35 wGA who were not receiving RSV IP, particularly with regard to the association of gestational age (GA) and chronologic age with severity of RSV disease in this population.

Methods

Study Design

SENTINEL1 is a multicenter, noninterventional, observational cohort study of preterm infants born at 29 to 35 wGA who were not receiving RSV IP and were hospitalized for laboratory-confirmed community-acquired or nosocomial RSV disease (ClinicalTrials.gov identifier: NCT02273882). The study eligibility period for the 2014 to 2015 RSV season was October 1, 2014, through April 30, 2015.

Study Site Characteristics

The study was conducted at 43 geographically diverse U.S. sites that were selected based on the following qualifications: served a large population of preterm infants 29 to 35 wGA, based in a community that was not providing RSV IP to most preterm infants 29 to 35 wGA without CLDP or CHD, had a robust electronic medical records system for patient identification, and tested a high proportion of infants hospitalized with respiratory illness for RSV. To quantify these qualifications, sites completed surveys regarding these factors for the 2013 to 2014 RSV season and at the end of the 2014 to 2015 RSV season.

Infant Eligibility Criteria

Preterm infants born at 29 weeks, 0 days through 35 weeks, 6 days GA were eligible for inclusion in the study if they were hospitalized $\geq$ 24 hours with a principal diagnosis of laboratory-confirmed community-acquired or nosocomial RSV disease and were $<$ 12 months of age at the time of admission (i.e., index RSVH). Tests performed for the current respiratory illness in the outpatient or inpatient settings were used to confirm the RSV diagnosis. Infants were excluded if they received RSV IP within the 35 days before the onset of respiratory symptoms associated with the index RSVH.

Data Collection

Participating sites systematically identified, prospectively and/or retrospectively, all eligible infants and collected anonymized data to characterize the entire population of infants 29 to 35 wGA hospitalized for RSV disease, unaffected by parental willingness or ability to consent. The collected data included the infant's wGA, birth month, public versus private insurance, hospital admission date, hospital length of stay

(LOS), intensive care unit (ICU) admission, ICU LOS, need for invasive mechanical ventilation (IMV), and survival status at discharge. IMV was defined as conventional mechanical ventilation with intubation, invasive continuous positive airway pressure, extracorporeal membrane oxygenation, high-frequency oscillatory ventilation, and jet ventilation. In this observational study, the need for ICU admission and/or IMV was based on the clinical assessment of the infant's health care provider.

Parents of these infants were subsequently approached for enrollment to enable in-depth RSV illness characterization. As the 2014 Centers for Disease Control and Prevention (CDC) natality statistics demonstrated that there were approximately three-fold more infants born at 33 to 35 wGA ($n = 151{,}788$) relative to 29 to 32 wGA ($n = 48{,}685$) in the United States[22] and previous studies demonstrated that infants born at earlier GA were at a higher risk of RSV-related hospitalization,[6] a systematic sampling approach was used to better balance the enrolled cohort by GA group. Site staff approached for enrollment all eligible infants born at 29 to 32 wGA and every other eligible infant born at 33 to 35 wGA. Enrollment of these infants required written informed consent from a parent or guardian. Infants could be enrolled during the index RSVH (prospective enrollment) or following hospital discharge via telephone contact (retrospective enrollment). For those enrolled, detailed data were collected regarding their RSV illness before and during the index RSVH and 1 month following hospital discharge. Data were collected on health care resource utilization related to RSV disease, clinical outcomes, and subsequent medically attended wheezing episodes. Hospital charges associated with the index RSVH were reported by the sites based on insurance claim forms (UB04 or UB92) and billing records.

Statistical Analysis

Descriptive analyses were conducted to characterize all identified infants with RSVH by GA group and overall. The frequency of ICU admission and need for IMV were further summarized by GA and chronologic age. As the enrolled population was a subset of the population of all identified infants with RSVH, to identify any potential bias due to parental willingness or ability to consent and enroll these infants, characteristics of the index RSVH that were collected for both populations were compared. Exploratory statistical comparisons between GA groups, and between the enrolled and nonenrolled groups, were performed using the Wilcoxon rank-sum test for continuous variables (age at index RSVH admission, hospital LOS, and ICU LOS) and the Pearson chi-square test for categorical variables (ICU admission and need for IMV). Testing was two-sided and conducted at the 5% level of significance, with no adjustment for multiple comparisons. To provide context for the observed characteristics of the enrolled population with community-acquired RSV disease, the prevalence of various sociodemographic factors and birth hospitalization characteristics among the 2014 U.S. birth cohort of preterm infants born at 29 to 35 wGA was calculated using CDC natality statistics.[22] Stepwise logistic regression was used to identify factors having an impact on the frequency of ICU admission among all identified infants with RSVH. Factors from individual univariate analyses with a p-value < 0.2 were considered candidates for the stepwise analysis. The final multivariate model identified via this process was also used for the analysis of the need for IMV.

Results

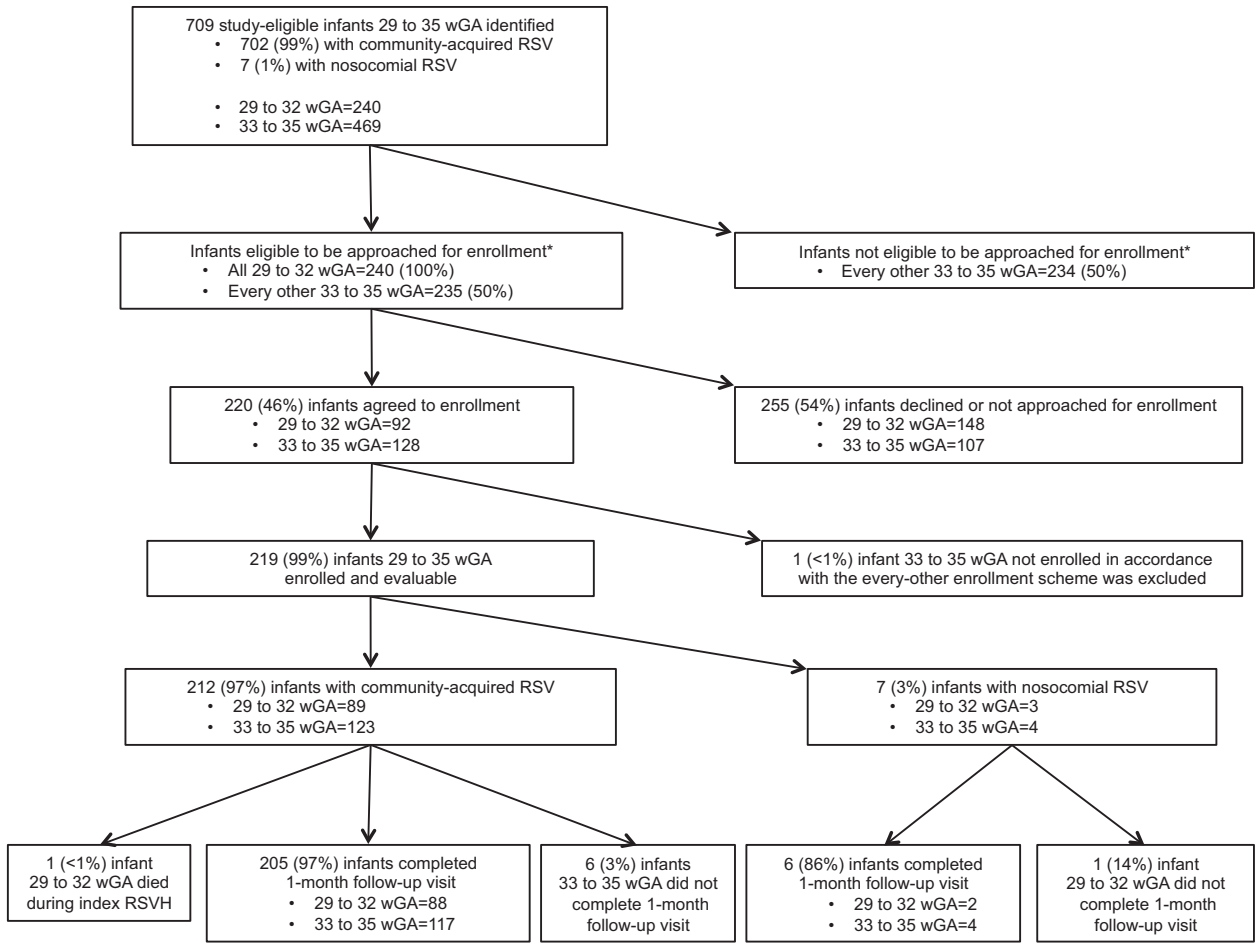
All Identified RSV-Hospitalized Infants

In total, 709 infants with laboratory-confirmed RSV met study eligibility criteria; 702 (99%) had community-acquired RSV disease and 7 (1%) had nosocomial RSV disease **(►Fig. 1)**. All seven infants with nosocomial RSV disease were enrolled and are discussed separately below. Characteristics of the 702 infants hospitalized with community-acquired RSV disease are summarized in **►Table 1**. Among the 680 infants for whom payer information was available, most (70%) infants had public insurance. Hospital LOS, ICU LOS, and proportions admitted to the ICU and requiring IMV were similar for those with public and private insurance. One death attributed to RSV occurred in a 29-wGA male twin hospitalized at 2 months of age with community-acquired RSV disease and no other comorbidities.

RSV-confirmed hospitalizations, ICU admissions, and need for IMV were most frequent at younger chronologic ages **(►Fig. 2)**. Infants < 6 months of age accounted for 78% of RSVHs, 87% of ICU admissions, and 92% of those who required IMV. By birth month, the majority (65%) of the 702 RSVHs occurred among infants born September 2014 through January 2015. As shown in **►Fig. 3**, earlier GA and younger chronologic age were associated with ICU admission and need for IMV. Multivariate logistic regression analyses confirmed that both earlier GA and younger chronologic age were independently associated with ICU admission and need for IMV **(►Table 2)**.

Enrolled RSV-Hospitalized Infants

Among the 709 identified infants, 219 were enrolled in accordance with the enrollment scheme **(►Fig. 1)**. Characteristics of the index RSVH of the 212 enrolled infants with community-acquired RSV disease are presented in **►Table 1**. Among the 209 infants for whom birth hospitalization discharge dates were available, 31% of RSVHs occurred within 30 days after birth hospitalization discharge and 54% occurred within 60 days. Chronologic age at birth hospitalization discharge differed by GA group; however, the interval between birth hospitalization discharge and index RSVH admission was similar among GA groups (**►Table 1**). Thus, at the time of the index RSVH admission, infants 29 to 32 wGA were the oldest and infants 35 wGA were the youngest. For infants 29 to 32 wGA, enrolled and nonenrolled infants were similar with regard to chronologic age at admission, hospital LOS, ICU admission, ICU LOS, and need for IMV. For infants 33 to 35 wGA, enrolled infants were younger (median age of 2 months for both groups; mean age of 2.6 months vs. 3.4 months for nonenrolled; $p = 0.01$), had a longer hospital LOS (median of 6 days vs. 5 days for nonenrolled; $p = 0.02$), and had a



*Per study protocol, all infants 29 to 32 wGA and every other infant 33 to 35 wGA were eligible to be approached for enrollment.

Fig. 1 Populations of infants 29 to 35 wGA with RSV-confirmed hospitalizations. SENTINEL1 included two populations of study-eligible infants 29 to 35 wGA hospitalized with laboratory-confirmed RSV disease during the 2014 to 2015 RSV season. RSV, respiratory syncytial virus; RSVH, RSV-confirmed hospitalization; wGA, weeks' gestational age.

greater proportion admitted to the ICU (50% vs. 35% for nonenrolled, $p < 0.01$).

Sociodemographic and birth hospitalization characteristics of the enrolled infants with community-acquired RSV disease compared with the 2014 U.S. birth cohort of infants born at 29 to 35 wGA based on CDC natality data are presented in ►**Supplementary Table S1** (online only). Within the group of all identified RSV-hospitalized infants as well as the enrolled population, infants 29 to 32 wGA were overrepresented (34% and 42%, respectively) relative to their prevalence (24%) in the corresponding 2014 U.S. birth cohort. Compared with the U.S. birth cohort, a larger proportion of enrolled infants 29 to 35 wGA was covered by public insurance, was of low/very low birth weight, and required care in the neonatal ICU (NICU) during the birth hospitalization (►**Supplementary Table S1** [online only]).

Among the enrolled infants with community-acquired RSV disease, 3 (1%) infants had CLDP, only 1 of whom was < 32 wGA, and 18 (8%) infants had CHD. Among those with CHD, 2 (11%) infants were reported to have HS-CHD (1 infant had coarctation of the aorta [acyanotic] and the other had complete atrioventricular canal [cyanotic]), and 16 (89%) had acyanotic CHD (diagnoses included atrial septal defect, patent ductus arteriosus, and patent foramen ovale) that was not considered hemodynamically significant.

Among the 45 enrolled infants who required IMV (►**Table 1**), conventional mechanical ventilation was used for 43 (96%) infants for a median (interquartile range) duration of 7 (4–12) days. The other types of IMV used included invasive continuous positive airway pressure ($n = 5$) and high-frequency oscillatory ventilation ($n = 3$). Of the 212 enrolled infants, 27 (13%) required noninvasive mechanical ventilation (i.e., nasal continuous positive airway pressure). Among the 200 (94%) infants who had procedures performed, 86% had pulse oximetry, 81% had a chest radiograph, 56% had a complete blood count analysis, 62% had additional blood laboratory analyses, and 59% received care by a respiratory therapist. Among the 196 (93%) infants who received medications during the index RSVH, 58% received bronchodilators, 52% received antibiotics, 13% received inhaled steroids, and 29% received systemic steroids. In total, 124 (59%) infants were discharged home on medication; 31% were prescribed a

Table 1 Characteristics of community-acquired RSV-confirmed hospitalizations among all identified infants and enrolled infants by gestational age group

	All identified infants by GA group, wk[a]				Enrolled infants by GA group, wk[a]			
Variable	**29–32 ($n = 237$)**	**33–34 ($n = 283$)**	**35 ($n = 182$)**	**29–35 ($n = 702$)**	**29–32 ($n = 89$)**	**33–34 ($n = 81$)**	**35 ($n = 42$)**	**29–35 ($n = 212$)**
Interval between birth hospitalization discharge and index RSVH admission, d[b]								
Median (IQR)	–	–	–	–	54 (26–155)	54 (23–138)	49 (22–67)	53 (25–130)
Mean (SD)	–	–	–	–	100 (90)	88 (80)	57 (48)	87 (81)
Minimum; maximum	–	–	–	–	7; 308	3; 345	4; 240	3; 345
Age at admission, mo								
Median (IQR)	**3 (2–5)**[c]	**2 (1–4)**[c]	2 (1–5)	2 (1–5)	3 (2–6)	2 (1–4)	1 (1–2)	2 (1–5)
Mean (SD)	4 (3)	3 (3)	3 (3)	3 (3)	4 (3)	3 (3)	2 (2)	3 (3)
Minimum; maximum	0; 11	0; 11	0; 11	0; 11	1; 11	0; 11	0; 7	0; 11
Confirmatory RSV test type, *n* (%)								
Rapid antigen	–	–	–	–	37 (42)	31 (38)	22 (52)	90 (42)
RT-PCR	–	–	–	–	52 (58)	49 (60)	20 (48)	121 (57)
Virus culture	–	–	–	–	0	1 (1)	0	1 (< 1)
Hospital LOS, d[d]								
Median (IQR)	**6 (3–12)**[e]	**6 (3–10)**[e]	5 (3–7)	5 (3–10)	6 (3–12)	6 (3–11)	5 (3–9)	6 (3–11)
Mean (SD)	10 (10)	9 (12)	7 (11)	9 (11)	10 (11)	8 (6)	7 (7)	8 (9)
Minimum; maximum	1; 67	1; 101	1; 135	1; 135	1; 67	1; 31	1; 38	1; 67
ICU admission, *n* (%)[fg]	**115 (49)**[h]	**117 (43)**[h]	56 (31)	288 (42)	46 (52)	45 (56)	17 (40)	108 (51)
ICU LOS, d[ij]								
Median (IQR)	8 (3–14)	6 (3–12)	5 (3–9)	6 (3–12)	8 (3–14)	6 (2–9)	6 (2–9)	6 (3–11)
Mean (SD)	9 (8)	9 (12)	8 (9)	9 (10)	9 (7)	7 (6)	7 (6)	8 (6)
Minimum; maximum	1; 61	1; 91	1; 59	1; 91	1; 27	1; 23	1; 24	1; 27
IMV among all admissions, *n* (%)[g]	**58 (24)**[k]	53 (20)[k]	23 (13)	134 (20)	24 (27)	13 (16)	8 (19)	45 (21)
Duration of IMV, d[l]								
Median (IQR)	–	–	–	–	8 (5–14)	7 (4–11)	7 (4–11)	7 (4–12)
Mean (SD)	–	–	–	–	10 (6)	8 (4)	8 (6)	9 (5)
Minimum; maximum	–	–	–	–	3; 24	3; 15	1; 19	1; 24

Abbreviations: GA, gestational age; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; LOS, length of stay; NS, not significant; RSV, respiratory syncytial virus; RSVH, RSV-confirmed hospitalization; RT-PCR, reverse transcriptase polymerase chain reaction; SD, standard deviation; wGA, weeks' gestational age.

Note: Bold values represent statistically significant differences between GA groups.

[a]Exploratory statistical comparisons among the GA groups in the all-identified population were performed using the Wilcoxon rank-sum test or the Pearson chi-square test. No statistical analyses were performed for the enrolled population. Proportions were calculated using the total number of infants with nonmissing data as the denominator; *n* values are provided in footnotes.

[b]Birth hospitalization discharge date was available for 209 enrolled infants 29 to 35 wGA; $n = 78$ for 33 to 34 wGA. Birth hospitalization data were not collected for the all-identified population.

[c]$p < 0.001$ for 29 to 32 versus 33 to 34 wGA; $p < 0.01$ for 29 to 32 versus 35 wGA; and $p < 0.001$ for 33 to 34 versus 35 wGA (Wilcoxon rank-sum test).

[d]Hospital LOS was available for 678 of the 702 infants 29 to 35 wGA in the all-identified population; $n = 236$ for 29 to 32 wGA, $n = 268$ for 33 to 34 wGA, and $n = 174$ for 35 wGA.

[e]$p =$ NS for 29 to 32 versus 33 to 34 wGA; $p = 0.001$ for 29 to 32 versus 35 wGA; and $p < 0.05$ for 33 to 34 versus 35 wGA (Wilcoxon rank-sum test).

[f]ICU represents the pediatric and neonatal ICUs. Infants admitted to both units during the index RSVH were counted only once.

[g]Data pertaining to ICU admission status and need for IMV were available for 684 of the 702 infants 29 to 35 wGA in the all-identified population; $n = 237$ for 29 to 32 wGA, $n = 269$ for 33 to 34 wGA, and $n = 178$ for 35 wGA.

[h]$p =$ NS for 29 to 32 versus 33 to 34 wGA; $p < 0.001$ for 29 to 32 versus 35 wGA; and $p = 0.01$ for 33 to 34 versus 35 wGA (Pearson chi-square test).

[i]ICU LOS was available for 284 of the 288 infants 29 to 35 wGA in the all-identified population who were admitted to the ICU; $n = 114$ for 29 to 32 wGA, $n = 115$ for 33 to 34 wGA, and $n = 55$ for 35 wGA.

[j]Differences among the GA groups in the all-identified population were not statistically significant (Wilcoxon rank-sum test).

[k]$p =$ NS for 29 to 32 versus 33 to 34 wGA; $p < 0.01$ for 29 to 32 versus 35 wGA; and $p =$ NS for 33 to 34 versus 35 wGA (Pearson chi-square test).

[l]Duration of IMV was available for all 45 infants 29 to 35 wGA in the enrolled population who required IMV; $n = 24$ for 29 to 32 wGA, $n = 13$ for 33 to 34 wGA, and $n = 8$ for 35 wGA.

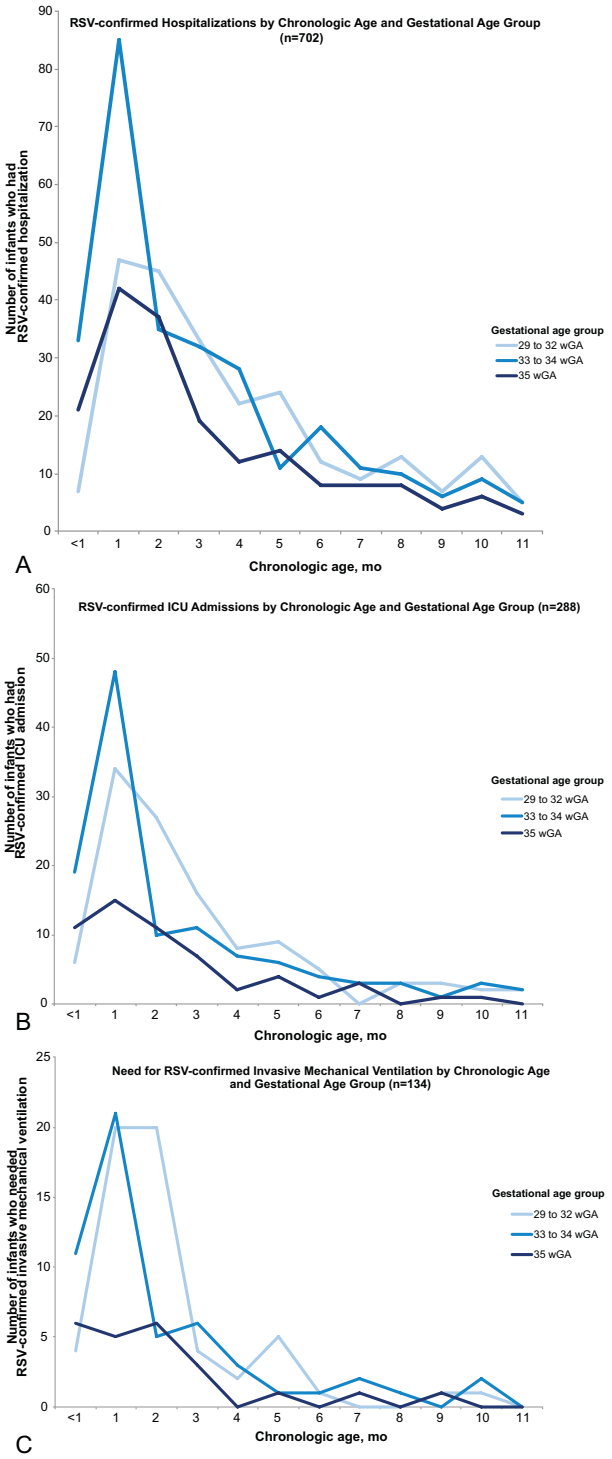


Fig. 2 (A) Distribution of community-acquired RSV-confirmed hospitalizations, (B) ICU admissions, and (C) need for IMV by chronologic age and gestational age group among all identified infants 29 to 35 wGA. The distribution of community-acquired RSV-confirmed disease outcomes by chronologic age and gestational age group for infants 29 to 35 wGA during the 2014 to 2015 RSV season. ICU, intensive care unit; RSV, respiratory syncytial virus; wGA, weeks' gestational age.

bronchodilator, 15% were prescribed inhaled steroids, and 10% were prescribed systemic steroids.

An RSV-specific International Classification of Diseases (ICD), Ninth Revision (ICD-9; 466.11, 480.1, or 079.6) and ICD-10 (J21.0 or B97.4) code was recorded as a primary or secondary discharge code for 70% and 16% of infants, respectively. Of the 29 infants who did not have an RSV-specific ICD discharge code despite their positive RSV test, 90% had a discharge code of acute bronchiolitis (466.1, 466.19, or J21.9). At the time of discharge from the index RSVH, 19 (9%) of the 212 infants hospitalized with community-acquired RSV disease were noted to have serious clinical outcomes that substantially diminished their overall health and/or would require long-term medical care: wheezing/reactive airways disease/chronic lung disease ($n = 10$), deep vein thrombosis ($n = 3$), laryngomalacia ($n = 2$), tracheal aspiration and difficulty feeding requiring physical therapy ($n = 1$), difficulty feeding and muscle atrophy requiring physical and occupational therapy ($n = 1$), difficulty gaining weight ($n = 1$), and death ($n = 1$).

Reported hospital charges associated with the index RSVH, based on insurance claims forms and billing records, were available for 183 of the 212 infants **(►Table 3)**. Hospital charges were substantially higher for infants who required greater intensity of care, as reflected by ICU admission and need for IMV, regardless of GA and chronologic age. Among infants 29 to 35 wGA, overall median (interquartile range) charges were $38,998 ($17,809–$113,395), $21,406 ($13,330–$46,951), and $16,137 ($8,900–$35,707) for infants < 3, 3 to < 6, and 6 to < 12 months of age, respectively. These charges were similar across the 29 to 32, 33 to 34, and 35 wGA groups.

RSV-Related Health Care Resource Utilization before the Index RSVH

Health care resource utilization for the current RSV illness before the index RSVH was available and collected for 211 of the 212 enrolled infants with community-acquired RSV disease. In total, 132 (63%) infants had at least one outpatient visit before the index RSVH: 88 infants had primary care provider visits, 73 infants had emergency department visits, and 7 infants had urgent care visits. Sixty-six infants received prescription medication, which included bronchodilators ($n = 36$), inhaled steroids ($n = 8$), systemic steroids ($n = 12$), and antibiotics ($n = 14$). One infant 33 wGA had a prior hospitalization for the index RSV illness that lasted 1 day and did not require ICU admission. The infant was discharged home but was rehospitalized the following day.

RSV-Related Health Care Resource Utilization during the 1-Month Period after Discharge from the Index RSVH

Follow-up information pertaining to outpatient medical care during the first month after discharge was available and collected for 191 of the 211 enrolled infants who were discharged home. Among them, 118 (62%) infants had at least 1 outpatient visit related to their RSV illness: 104 infants had visits to the primary care provider, 15 infants had visits to a specialist physician, and 14 infants had emergency department visits. Thirty-five infants received prescription medication for wheezing, which included bronchodilators ($n = 27$), inhaled steroids ($n = 17$), and systemic steroids ($n = 4$).

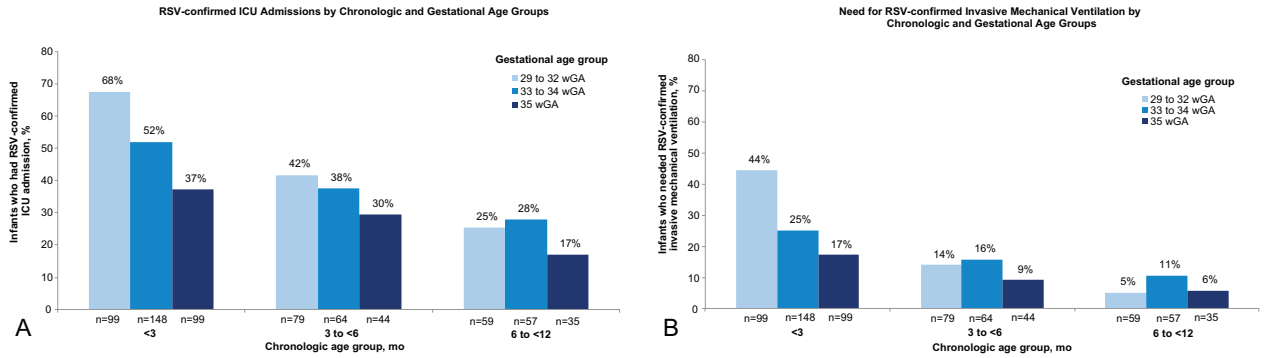


Fig. 3 (A) Proportion of ICU admissions and (B) need for IMV by chronologic and gestational age groups among all identified infants 29 to 35 wGA hospitalized with community-acquired laboratory-confirmed RSV disease during the 2014 to 2015 RSV season. The denominator for each proportion calculation was the number of infants within each chronologic age group categorized by GA group (*n* values shown in the graph). ICU, intensive care unit; IMV, invasive mechanical ventilation; RSV, respiratory syncytial virus; wGA, weeks' gestational age.

Table 2 Stepwise multivariate regression to evaluate the effect of gestational age and chronologic age on ICU admission and need for IMV among all identified infants 29 to 35 wGA with community-acquired RSV-confirmed hospitalization

RSV-confirmed event	Odds ratio (95% CI)	*p*-Value
RSV-confirmed ICU admission by gestational age, wk		
29	2.21 (1.04, 4.72)	0.04
30	2.97 (1.50, 5.91)	< 0.01
31	2.11 (1.10, 4.08)	0.03
32	2.49 (1.48, 4.17)	< 0.001
33	2.01 (1.19, 3.39)	< 0.01
34	1.62 (1.03, 2.54)	0.04
35	Reference level	–
RSV-confirmed ICU admission by chronologic age group, mo		
< 3	3.28 (1.73, 6.23)	< 0.001
3 to < 6	1.62 (0.83, 3.17)	0.16
6 to < 9	0.84 (0.39, 1.81)	0.65
9 to < 12	Reference level	–
Need for RSV-confirmed IMV by gestational age, wk		
29	3.72 (1.52, 9.12)	< 0.01
30	3.70 (1.63, 8.39)	< 0.01
31	2.04 (0.87, 4.76)	0.10
32	2.47 (1.29, 4.72)	< 0.01
33	1.58 (0.80, 3.12)	0.19
34	1.81 (1.00, 3.27)	0.05
35	Reference level	–
Need for RSV-confirmed IMV by chronologic age group, mo		
< 3	4.58 (1.75, 11.99)	< 0.01
3 to < 6	1.54 (0.55, 4.27)	0.41
6 to < 9	0.69 (0.20, 2.40)	0.56
9 to < 12	Reference level	–

Abbreviations: CI, confidence interval; ICU, intensive care unit; IMV, invasive mechanical ventilation; RSV, respiratory syncytial virus; wGA, weeks' gestational age.

Table 3 Hospital charges of enrolled infants with community-acquired RSV-confirmed hospitalizations by intensity of care required and gestational age group

Hospital charges, $	29–32 wGA	33–34 wGA	35 wGA	29–35 wGA
Overall				
Number of infants	78	71	34	183
Median (IQR)	27,258 (13,330–103,571)	26,158 (13,079–58,409)	33,203 (10,598–68,944)	27,461 (12,858–74,419)
Mean (SD)	60,441 (71,488)	49,382 (53,991)	57,218 (66,313)	55,551 (64,080)
Minimum; maximum	1,302; 311,243	1,169; 230,555	2,139; 258,655	1,169; 311,243
ICU = no and IMV = no				
Number of infants	37	35	19	91
Median (IQR)	13,364 (6,638–20,000)	13,079 (8,347–19,523)	11,508 (8,519–32,234)	13,093 (8,347–20,055)
Mean (SD)	16,190 (11,053)	17,968 (17,551)	19,085 (15,327)	17,478 (14,613)
Minimum; maximum	1,302; 49,450	1,169; 95,953	2,139; 48,406	1,169; 95,953
ICU = yes and IMV = no				
Number of infants	21	26	8	55
Median (IQR)	31,800 (22,574–51,216)	46,031 (28,496–58,409)	51,577 (35,808–82,739)	41,911 (26,137–58,409)
Mean (SD)	47,368 (40,218)	50,705 (28,047)	62,290 (38,891)	51,116 (34,400)
Minimum; maximum	5,793; 152,061	20,000; 116,426	18,429; 139,643	5,793; 152,061
ICU = yes and IMV = yes				
Number of infants	20	10	7	37
Median (IQR)	144,188 (114,350–175,944)	133,391 (113,395–212,661)	158,737 (68,944–236,392)	140,535 (113,395–194,765)
Mean (SD)	156,030 (71,808)	155,894 (53,628)	154,924 (77,070)	155,784 (66,563)
Minimum; maximum	45,852; 311,243	92,161; 230,555	52,729; 258,655	45,852; 311,243

Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; RSV, respiratory syncytial virus; SD, standard deviation; wGA, weeks' gestational age.

Nine (5%) infants (three infants in each GA group) were rehospitalized for RSV-related disease during the 1-month follow-up interval; seven rehospitalizations occurred within 2 weeks of discharge. Primary admission diagnoses were RSV bronchiolitis (7), respiratory failure (1), and hypothermia (1). Four of the nine rehospitalized infants were admitted to the ICU, and two infants required IMV.

Nosocomial RSV Disease

Among the seven infants who had nosocomial RSV disease at seven different sites, three were 29 to 32 wGA, three were 33 to 34 wGA, and one was 35 wGA. All were $\leq$ 6 months of age at the time of the RSV diagnosis. Six acquired RSV in the NICU during the birth hospitalization; according to the site principal investigator, nosocomial RSV disease resulted in additional NICU LOS (median of 11 days) for four of these infants. Among these six infants, two newly required IMV, two required ongoing IMV, and one required ongoing noninvasive mechanical ventilation. The seventh infant who was reported to have possible nosocomial RSV disease was rehospitalized for apnea and hypothermia 11 days after his birth hospitalization discharge. He was admitted to the ICU and required IMV. No RSV test was performed at the time of rehospitalization. On the fourth day of the hospitalization, he was diagnosed with nosocomial RSV disease, which reportedly prolonged his ICU stay by 13 days. He developed vocal cord paresis and dysphagia that required gastrostomy tube feeding.

Study Site Characteristics Regarding RSV IP Use and RSV Testing Policies

Thirty-seven (86%) of the 43 U.S. sites that participated in the study were children's hospitals and/or academic medical centers (►**Supplementary Fig. S1** [online only]). According to the institutional policy for inpatient RSV IP administration to preterm infants without CLDP before birth hospitalization discharge, 60%, 79%, and 88% of sites reported that preterm infants 29 to 31, 32 to 34, and 35 wGA, respectively, were not routinely receiving RSV IP. At study initiation, 27 (63%) sites reported that they routinely tested all preterm infants hospitalized with lower respiratory illness for RSV. Among sites that did and did not routinely test for RSV, similar proportions of infants 29 to 35 wGA were admitted to the ICU (41% vs. 43%) and required IMV (21% vs. 19%). For the 2014 to 2015 RSV

season, 38 sites were able to quantitatively describe the proportion of infants hospitalized with bronchiolitis who were tested for RSV. Among these sites, the average RSV testing frequency was 61%.

Discussion

The 2014 COID guidance recommends against the use of RSV IP for preterm infants who are otherwise healthy if born at 29 to 35 wGA.[14] SENTINEL1 is the first study to investigate the burden of severe RSV disease in previously eligible infants 29 to 35 wGA who were not receiving RSV IP in accordance with the 2014 COID guidance and also represents the largest study ever conducted of U.S. preterm infants hospitalized with laboratory-confirmed RSV disease. The present analysis demonstrated that the highest risk of severe RSV disease, as indicated by RSVH, ICU admission, and the need for IMV, was associated with earlier GA and younger chronologic age. The cost of the index RSVH increased dramatically with increasing intensity of care, and in addition to hospital care, the majority of infants required outpatient care for the current RSV disease both before and within 1 month following the index RSVH discharge. The enrolled population with community-acquired RSV disease included only three (1.4%) infants who were not receiving RSV IP but could have been eligible under the 2014 COID guidance; they included two infants with HS-CHD and one infant born at < 32 wGA with CLDP. In addition, very few infants had other significant underlying medical conditions (►**Supplementary Table S1** [online only]). As a result, the SENTINEL1 results are applicable to the general population of otherwise healthy preterm infants 29 to 35 wGA who are not currently eligible for RSV IP.

The identification of 702 infants requiring laboratory-confirmed RSV hospitalization at 43 centers demonstrates that community-acquired RSV disease remains a considerable public health concern among infants 29 to 35 wGA. Further, the average RSV testing frequency of 61% indicates that the number of RSVHs documented significantly underestimates the total burden of RSV disease at these 43 centers. In addition, the sites' reported use of RSV IP in infants 29 to 35 wGA before their discharge from the birth hospitalization would be expected to further reduce the observed number of RSVHs, particularly among infants 29 to 31 wGA, in whom its use was highest.

Regarding incidence of RSVH, infants in the earlier GA groups were overrepresented in the all-identified population. Adjusting for their prevalence in the U.S. birth cohort, infants 29 to 32 and 33 to 34 wGA were 2.0-fold and 1.5-fold overrepresented, respectively, relative to infants 35 wGA. This finding suggests that infants 29 to 32 and 33 to 34 wGA not receiving RSV IP are at a higher risk of severe RSV disease than those born at 35 wGA and is consistent with earlier reports of higher risk of RSV-related hospitalization in infants 29 to 32 or 33 wGA.[4,6,23] Two recently published studies using data from 1999 to 2004 and 2005 to 2011 demonstrated a two- to three-fold higher risk of RSV-related hospitalization among infants 32 to 34 wGA relative to full-term infants.[20,21] A third recent study demonstrated that 1 in 20 U.S. infants 32 to 35 wGA < 6 months of age who were not receiving RSV IP were hospitalized for RSV disease, which increased to an incidence of 9 per 100 infant-seasons among infants < 6 months of age with the risk factors of daycare attendance or preschool-aged siblings.[19] In each of these three studies, and consistent with the SENTINEL1 results, the greatest RSV-related hospitalization risk occurred among younger infants[19–21] and among those with risk factors.

As this was an observational study, there was no systematic testing for RSV. When testing was performed, molecular methods of RSV detection, known to be more sensitive than other methods, amounted to only 57% of diagnostic tests. However, during the study period, the majority of sites were routinely testing all preterm infants admitted with lower respiratory illness for RSV. Among the sites that did not routinely conduct RSV testing, there was no evidence of a testing bias based on illness severity. However, other differences between those routinely tested and not tested cannot be ruled out.

To increase the generalizability of the study results, a large number of sites from across the United States were enlisted. The robustness of the sample is supported by the fact that the sociodemographic characteristics of the enrolled population were generally similar to the U.S. preterm birth cohort; the primary differences are consistent with an overrepresentation of infants at increased risk for RSV-related hospitalization, namely, those born at earlier gestation and other risk factors (e.g., public insurance, low birth weight, and tobacco smoke exposure).[4,24–29] A limitation of the reported hospital charges is that they did not include physician fees and likely do not accurately reflect reimbursements negotiated between insurance companies and hospitals. Due to feasibility constraints, data were not collected for infants ≥ 36 wGA with RSVH, which prevented comparisons between high-risk preterm infants 29 to 35 wGA and lower-risk full-term infants.

In conclusion, SENTINEL1 is the largest multicenter surveillance study to examine RSVH among U.S. preterm infants 29 to 35 wGA who were not receiving RSV IP. Substantial morbidity and costs were identified among preterm infants 29 to 34 wGA not receiving RSV IP based on the 2014 COID guidance but who would have previously been recommended for RSV IP according to the 2009 and 2012 COID guidances. Preventing severe RSV disease in this population would provide substantial health benefits, particularly during the first months of life when RSV disease incidence and severity are highest.

Conflict of Interest

E.J.A., L.R.K., J.P.D., P.A.C., N.H., E.A.F.S., J.B.D., M.L.F., and P.S.P. are independent investigators who have received research support from AstraZeneca/MedImmune. J.P.D., E.A.F.S., and M.L.F. also received travel support from AstraZeneca/MedImmune to present the results of this or other research studies at scientific meetings. J.P.D. has served as a consultant to and M.L.F. has served on the speakers' bureau for AstraZeneca/MedImmune. E.J.A.

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