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The SENTINEL 1 Study:
An Observational, Non-Interventional Study in the United States to
Characterize Respiratory Syncytial Virus Hospitalizations among Infants
Born at 29 to 35 Weeks Gestational Age Not Receiving Immunoprophylaxis

Objectives

The objective of this study was to document the burden of illness (BOI) associated with RSVH among preterm infants <12 months of age born at 29 to 35 wGA who had been hospitalized due to nosocomial or community-acquired RSV disease in regards to:

- Clinical severity
- Clinical outcomes deemed by the investigator to be related to the index RSVH
- Parent/Guardian's emotional distress, lost productivity, and assessment of infant's health status
- Healthcare-related and other costs associated with disease
- Factors associated with an increased risk of RSVH or disease severity (e.g., ICU admission, mechanical ventilation, length of stay)

Study design and methods

This observational, non-interventional surveillance study planned to enroll approximately 500 eligible infants from approximately 40 study sites in the US hospitalized for laboratory-confirmed, nosocomial or community-acquired respiratory syncytial virus (RSV) disease during the study eligibility periods of 01 October 2014 through 30 April 2015 (Season 1) and 01 October 2015 through 30 April 2016 (Season 2). During these eligibility periods, infants were enrolled:

- Prospectively at the time of their index respiratory syncytial virus hospitalizations (RSVH) admission or any time prior to their index RSVH discharge, or
- Retrospectively on the basis of electronic medical record (EMR) review following discharge from the index RSVH

The clinical, humanistic, and health economic outcomes associated with the RSV disease were characterized in the outpatient and inpatient settings from the onset of symptoms of RSV disease pre index RSVH to 4 months post index RSVH discharge date (additionally to 12 months post index RSVH discharge date in Season 1 only) on the basis of medical records and Parent/Guardian self-report. Case report forms were specifically designed for the collection of data from this study. Data were collected for the following study outcome variables:

- Frequency of RSVH
- Characteristics of RSVH
 - Prior Hospitalization(s) for the Current RSV Disease
 - Index RSVH
 - Hospitalizations Post Index RSVH Discharge
- Healthcare Resource Utilization
- Humanistic Outcomes
 - Work Productivity and Activity Impairment (WPAI)
 - Parent and Infant Stress and Assessment of Infant Health
- Risk Factor Analysis
- Hospital and Community Characteristics Survey (HCCS)
- RSVH Cost/Charge Data

Summary of results

Frequency of RSVH

The majority of infants had 1 RSVH in Season 1 (89.2%) and Season 2 (92.6%), which included prior hospitalizations for the current RSV disease, the index RSVH, and any RSVH following discharge from the index RSVH. One (0.5%) infant had 5 RSVHs in Season 1.

Characteristics of RSVH

One (0.5%) infant (1 [1.2%] 33 to 34 wGA) in Season 1 had a prior hospitalization for the current RSV disease, and 3 (1.1%) infants in Season 2 (1 [1.2%] 33 to 34 wGA and 2 [3.2%] 35 wGA) had 1 prior hospitalization for the current RSV disease.

During the index RSV hospitalization, most infants received care in the pediatric inpatient unit (187 [88.2%] in Season 1 and 242 [90.0%] in Season 2) and half received care in the ICU (108 [50.9%] in Season 1 and 138 [51.3%] in Season 2). The median (IQR) length of stay in the ICU was 6.0 (8.5) days in Season 1 and 5.0 (9.0) days in Season 2. Median (IQR) hospital length of stay was 5.5 (8.0) days in Season 1 and 5.0 (7.0) days in Season 2.

There were 45 (21.2%) infants in Season 1 and 65 (24.2%) infants in Season 2 who required IMV. The median (IQR) duration of IMV decreased with gestational age in both seasons and was a total of 7.0 (8.0) days in Season 1 and 7.0 (7.0) days in Season 2.

Most infants received medication during the index RSVH (196 [92.5%] in Season 1 and 241 [89.6%] in Season 2). The most common medications received by infants during hospitalization were bronchodilators (113 [53.3%] in Season 1 and 137 [50.9%] in Season 2) and antibiotics (102 [48.1%] in Season 1 and 131 [48.7%] in Season 2); however, the majority were classified as other (141 [66.5%] in Season 1 and 185 [68.8%] in Season 2).

In Season 1, 58 (27.4%) infants were hospitalized at any time post index RSVH discharge and 22 (10.4%) were related to the RSV illness. In Season 2, 40 (14.9%) infants were hospitalized at any time post index RSVH discharge and 18 (6.7%) were related to the RSV illness.

Healthcare resource utilization

A total of 133 (62.7%) infants in Season 1 and 206 (76.6%) infants in Season 2 had at least 1 outpatient visit for RSV illness prior to the index RSVH. Most visits were to a primary care provider/pediatrician (88 [41.5%] in Season 1 and 123 [45.7%] in Season 2) and to the emergency department (74 [34.9%] in Season 1 and 131 [48.7%] in Season 2).

There were 66 (31.1%) infants in Season 1 and 93 (34.6%) infants in Season 2 who were prescribed medication prior to the RSVH. The most common class of prescribed medication was bronchodilators (36 [17.0%]) in Season 1 and 55 [20.4%] in Season 2). There were 63 (29.7%) infants in Season 1 and 111 (41.3%) infants in Season 2 who took over the counter (OTC) medication prior to the RSVH with the most common being antipyretics (38 [17.9%] in Season 1 and 61 [22.7%] Season 2).

A total of 72 (34.0%) infants in Season 1 and 103 (38.3%) in Season 2 had a least 1 caregiver who missed work during the week prior to the RSVH. Total hours of missed work during the week prior to the RSVH for all caregivers was a mean (SD) of 21.8 (\pm 14.57) hours in Season 1 and 26.1 (\pm 21.55) hours in Season 2.

Out-of-pocket expenses for management of respiratory illness for infants prior to the RSVH decreased with gestational age and included travel expenses to the clinic visit (91 [42.9%] in Season 1 and 134 [49.8%] in Season 2), humidifier (44 [20.8%] in Season 1 and 60 [22.3%] in Season 2), other (24 [11.3%] in Season 1 and 49 [18.2%] in Season 2), and babysitting or extra daycare expenses (18 [8.5%] in Season 1 and 33 [12.3%] in Season 2). Out-of-pocket expenses were not incurred for a total of 93 (43.9%) infants in Season 1 and 94 (34.9%) infants in Season 2.

Humanistic outcomes

For Season 1, the total median WPAI scores for the 3 wGA groups at index RSVH discharge for absenteeism, presenteeism, overall work productivity loss, and daily activity impairment were higher for the mother (range: 80.0% to 100.0%) compared with the father (range: 53.3% to 91.3%), grandparents (range: 40.5% to 80.0%), and other caregivers (range: 0.0% to 88.0%). Similar results were seen in Season 2, where the total median WPAI scores for the 3 wGA groups at index RSVH discharge for absenteeism, presenteeism, overall work productivity loss, and daily activity impairment

were also higher for the mother (range: 80.0% to 100.0%) compared with the father (range: 40.0% to 80.0%), grandparents (range: 36.7% to 81.0%), and other caregivers (range: 0.0% to 90.0%).

For Season 1, the mother's median assessment scores for the 3 wGA groups ranged from 5.0 to 7.0 based on a 7 point Likert-type scale from 1 (not stressful at all) to 7 (very stressful) for items related to infant and personal health and stress. This was similar to median scores for the father (range: 5.0 to 6.0), grandparents (range: 6.0 to 7.0), and other caregivers (range: 5.0 to 6.0). For the assessment of infant's current health based on a scale from 0 to 100, where 0 represents the worst imaginable health and 100 represents the best imaginable health, the median score of 70.0 reported by the mother was the same as the median score reported by the father (70.0) and higher compared with grandparents (50.0) and other caregivers (55.0). Similar results were seen in Season 2, with similar median scores for the 3 wGA groups reported by the mother (range: 6.0 to 7.0), father (range: 6.0 to 7.0), grandparents (range: 6.5 to 7.0), and other caregivers (range: 5.0 to 6.0). For the assessment of infant's current health, the median score of 70.0 reported by mothers was the same compared to the median score reported by fathers (70.0) and other caregivers (70.0) and higher than grandparents (62.5).

Risk factor analysis

Overall, for Season 1 and Season 2, multivariate logistic regression analysis showed that earlier gestational age and younger estimated chronological age were associated with ICU admission and the need for IMV.

Hospital and Community Characteristics Survey (HCCS)

There were 43 (100.0%) sites in Season 1 and 40 (95.2%) in Season 2 with pre-screened infants that responded to at least 1 item from the HCCS. Note that the denominator used for calculating these percentages was the number of sites that responded to at least 1 item from the HCCS. For Season 2, there were 2 sites that were sent the survey and responded to at least 1 item, but these sites did not pre-screen any infants (i.e., $40/42=95.2\%$).

Forty-three sites used a median (IQR) of 1.0 (0.0) hospital to recruit/enroll for Season 1; 40 sites used 1.0 (0.0) for Season 2. For Season 1, the mean (SD) number of hospital admissions (non-birth, <12 month infant) was 5389.6 (± 5338.99). For Season 2, the mean (SD) number of hospital admissions (non-birth, <12 month infant) was 2286.6 (± 1789.75).

Most hospitals reported they did not have any minimum criteria for a hospital admission to be entered into their EMR system (34 [79.1%] in Season 1 and 34 [85.0%] in Season 2). Most hospitals also reported they did not have any formal policies regarding when an infant with bronchiolitis or pneumonia should be charged (35 [81.4%] in Season 1 and 24 [60.0%] in Season 2), although a majority had policies regarding routine testing for RSV in infants with lower respiratory illness (e.g., bronchiolitis, pneumonia) (26 [60.5%] in Season 1 and 23 [57.5%] in Season 2) and in all preterm infants admitted with lower respiratory illness (e.g., bronchiolitis, pneumonia) (27 [62.8%] in Season 1 and 26 [65.0%] in Season 2).

Based on the EMR at hospitals, the median (IQR) number of infants admitted with bronchiolitis was 184.0 (447.0) in Season 1 and 178.5 (390.5) in Season 2. The median (IQR) number of infants admitted with bronchiolitis who were tested for RSV was 103.0 (260.0) in Season 1 and 154.0 (290.0) in Season 2.

The customary method used for determining infant 'hospitalization start time' was based on the time the decision to admit was made (22, 51.2%) followed by the time the patient arrived on the inpatient floor or the ICU (14, 32.6%). Most (39, 90.7%) sites captured data for all 29 to 35 wGA infants <12 months of age hospitalized with RSV at their institution on the pre-screening log.

For Season 1, there was a median (IQR) of 2139.0 (3450.0) birth admissions, 2164.5 (4676.0) infant admissions, 535.5 (555.0) NICU admissions, 740.0 (873.0) PICU admissions, and 18.0 (13.0) beds in the PICU.

The median (IQR) number of infants admitted with bronchiolitis was 182.0 (429.0) and those admitted with bronchiolitis who were tested for RSV was 122.0 (252.0).

In Season 1, most sites provided pre-discharge palivizumab doses to all preterm infants with evidence of chronic lung disease for the 29 to 31 wGA group (36 [83.7%]), but fewer did for the 32 to 34 wGA group (12 [27.9%]) and 35 wGA group (10 [23.3%]). Pre-discharge palivizumab doses were also provided to preterm infants without evidence of chronic lung disease for the 29 to 31 wGA group (17 [39.5%]), 32 to 34 wGA group (9 [20.9%]), and the 35 wGA group (5 [11.6%]).

Data were not collected in Season 2 on whether sites provided pre-discharge palivizumab doses to all preterm infants with evidence of chronic lung disease; however, similar to Season 1, a low percentage of sites provided pre-discharge palivizumab doses to preterm infants without evidence of chronic lung disease for the 29 to 31 wGA group (7 [17.5%]) as well as the 32 to 34 wGA group (4 [10.0%]) and 35 wGA group (1 [2.5%]).

Most sites responded to survey items 11 and 12 for Season 1 and items 15 and 16 for Season 2 on the HCCS (35 [81.4%] in Season 1 and 34 [85.0%] in Season 2). The total number of infants (across sites) admitted with bronchiolitis who were tested for RSV was 10600 (73.6%) in Season 1 and 6842 (62.9%) in Season 2.

Total costs/charges

In Season 1, median (IQR) total costs/charges associated with the index RSVH were highest for infants in the 35 wGA group (\$32234.0 [58346.4]) compared with the 29 to 32 wGA group (\$28207.0 [94120.7]) and the 33 to 34 wGA (\$27326.9 [48902.9]). In Season 2, median (IQR) total costs/charges associated with the RSVH were highest for the 33 to 34 wGA group (\$36568.5 [94129.5]) compared with the 35 wGA group (\$31984.0 [46480.0]) and 29 to 33 wGA group (\$27131.5 [81314.0]). Season 2 overall median (IQR) total costs (\$31984.0 [75543.0]) were higher than Season 1 (\$28351.6 [67835.0]).

In Season 2, median (IQR) total payments associated with the RSVH were highest for the 33 to 34 wGA group (\$21859.0 [81485.0]) compared with the 35 wGA group (\$13696.0 [31912.0]) and 29 to 33 wGA group (\$12056.0 [40437.0]). Total median (IQR) payments for Season 2 were \$13773.0 (39772.5). Total payment data were not collected for Season 1.