# Epidemiology of Pediatric Respiratory Syncytial Virus-Associated Illness in FDA's Sentinel System

## Sentinel Final Report

Amol Purandare, MD[1], Noelle Cocoros, DSc, MPH[2], Ann McMahon, MD, MS[3], Nicole Haug, MPH[2], Michael Nguyen, MD[4], Prabha Viswanathan, MD[1]

1. *Division of Antiviral Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD*
2. *Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA*
3. *Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration, Silver Spring, MD*
4. *Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD*

Version 1.0

November 5, 2019

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

# Epidemiology of Pediatric Respiratory Syncytial Virus-Associated Illness in FDA's Sentinel System

Sentinel Final Report

## Table of Contents

## History of Modifications

| Version | Date | Modification | Author |
|---|---|---|---|
| 1.0 | 11/05/2019 | Original Version | Sentinel Operations Center |

# 1. Background

Respiratory syncytial virus (RSV) is a major cause of morbidity and mortality in young children in the United States (U.S.) and worldwide. [1, 2] RSV-associated illness (RSV-AI) is a primary cause of hospitalization of young children and infants [3], most often presenting as bronchiolitis or other types of lower respiratory tract infection. Approximately 2.1 million children under 5 years of age present for treatment of RSV-AI across all health care settings each year. [4]

Therapies for prevention and treatment of RSV-AI are currently limited. Palivizumab is the only product in the U.S. approved for RSV prophylaxis in high risk children less than 24 months of age; inhaled ribavirin is the only antiviral approved for RSV treatment but is rarely used due to toxicity, among other reasons. There has been increased interest in drug development over the past few years, with numerous products in development for both treatment [5]and prevention [6] of RSV-AI. An assessment of RSV disease burden and natural history could inform clinical trial design of novel RSV products. [7]

FDA's Sentinel System is an active surveillance system that uses electronic healthcare data, comprised primarily of commercial administrative claims, from data partners across the U.S. Although the majority of Sentinel studies to date have concentrated on post-marketing safety for drugs and biologics, the size and scope of Sentinel are suited for broader queries beyond product safety, including disease characterization and risk factor analyses to inform pre-market clinical development programs. [8]

## 1.1. Objective

Our goal was to assess the clinical and demographic factors of RSV-AI cases and explore epidemiologic patterns of RSV-AI in a cohort of young children in the U.S, which may be used to inform RSV drug development.

# 2. Methods

## 2.1. Study Design and Data Source

This retrospective cohort analysis used data obtained from 16 Sentinel Data Partners contributing to the Sentinel distributed database. [9] We conducted our analysis using the Sentinel Cohort Identification and Descriptive Analysis tool, version 4.0.0.

## 2.2. Cohorts and Eligibility

For the main cohort, we examined clinical features of RSV-AI cases in children 1 month to 5 years of age from January 1, 2008 to June 30, 2016. RSV-AI was defined as the documentation of an RSV diagnosis code of interest in the child's claims data during the study period (Table 1) in any care setting (i.e., outpatient and inpatient).

To be included in the analysis, children 7 months and older had to have been continuously enrolled in plans with medical and drug coverage for at least 183 days prior to their RSV-AI diagnosis date, during which gaps in coverage of up to 45 days were allowed. Only one day of enrollment was required for children 1-6 months of age. Incident RSV-AI was defined for children 7 months and older using a 183-day washout; children 1-6 months of age did not have a washout applied. We included only the first incident RSV-AI diagnosis per child, though the age groups were evaluated separately and thus are not mutually exclusive for children with multiple RSV-AI diagnoses at different ages.

For each of the two age groups we created three additional cohorts during the study period: (a) those with an incident diagnostic code for bronchiolitis in any care setting, (b) those with an incident RSV diagnostic assay recorded in any care setting via a procedure code, and (c) those with an incident

dispensing of palivizumab in the outpatient setting (see Table 1 for diagnosis and procedure codes). The same enrollment requirements were applied for these cohorts, based on age, as described above; incidence was defined using a 183-day washout for these cohorts for those 7 months and older.

### 2.3. Analysis

Children with RSV-AI were evaluated for baseline characteristics, care setting of RSV-AI diagnosis code, and three RSV risk factors: prematurity, chronic lung disease (CLD), and congenital heart disease (CHD). Risk factors were defined as occurrence of a relevant diagnosis code in the child's claims history from birth through the RSV-AI index date for prematurity, and through 2 months post RSV-AI index date for CLD and CHD. We used the same criteria used in a published report to identify patients with CLD and CHD.[10, 11] RSV diagnoses were classified by care setting: inpatient, outpatient (emergency department and ambulatory care). We calculated the proportion of these children with diagnosis of bronchiolitis, past dispensing of palivizumab, and a procedure code for an RSV diagnostic assay, separately, in two different time windows depending on age group: for those <7 months of age, we looked in the entire prior history through 60 days after RSV-AI diagnosis, and for those 7 months and older, we looked in the three months before through two months after RSV-AI diagnosis. For all ages, we assessed the documentation of an intensive care unit (ICU) stay in the 15 days before through 15 days after RSV-AI diagnosis via procedure codes.

Among the cohort defined by bronchiolitis, we calculated the proportion seen in the outpatient versus inpatient setting, the proportion with evidence of an ICU stay in the 15 days before through 15 days after bronchiolitis diagnosis.

Among the cohort defined by documentation of an RSV diagnostic assay, and the cohort defined by incident palivizumab use, we calculated the proportion with bronchiolitis diagnosis and RSV-AI diagnosis using different windows by age group: for those <7 months of age, we looked in the entire prior history through 60 days after diagnostic assay, or palivizumab; for those 7 months and older, we looked in the three months before through two months after diagnostic assay, or palivizumab.

For all cohorts, children 1-6 months of age were analyzed separately from children 7-60 months of age. The exposures were defined with National Drug Codes, Current Procedural Terminology procedure codes, and International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) diagnosis and procedure codes.[10]

## 3. Results

### 3.1. RSV-AI and Bronchiolitis Cohorts

Our analysis identified 138,669 cases of RSV-AI among children 1-6 months of age and 179,259 cases among children 7 to 60 months of age. Table 2 summarizes the RSV-AI cases by demographic variables, RSV risk factors, and setting of care. Trends were similar in both age groups. There were more RSV-AI cases in males than females. Children with documented risk factors for RSV-AI (CHD, CLD, prematurity) comprised a small proportion of total cases. Outpatient visits comprised 81.5% and 83.7% of encounters for the younger and older cohorts, respectively.

We separately identified 349,758 cases of bronchiolitis in children ≤6 months old and 514,532 cases in children 7 to 60 months old. Relative to RSV-AI, a higher proportion of bronchiolitis cases were outpatient, with 93.6% of cases managed in the outpatient setting for both age groups. The need for intensive care was low for both RSV-AI and bronchiolitis cases. Among children 1-6 months of age, 2.0% of RSV-AI cases and 1.0% of bronchiolitis cases had an intensive care unit stay. For the older age group, 1% of RSV-AI cases and 0.5% of bronchiolitis cases required intensive care.

## 3.2. Cohort with Laboratory Testing for RSV

A diagnostic assay for RSV was documented for 226,507 children 1-6 months of age, of whom 31.1% were diagnosed with RSV-AI and 50.2% were diagnosed with bronchiolitis. Among children 7 to 60 months of age, 319,032 children had an RSV assay ordered, of whom 24.4% were diagnosed with RSV-AI and 36.5% were diagnosed with bronchiolitis. For both age cohorts, 93.1% of tests were ordered in the outpatient setting.

## 3.3. Cohort of Palivizumab Users

At least one dose of palivizumab was dispensed for 18,208 children 1-6 months of age and 4, 979 children ≥7 months of age. For the younger group, the mean (SD) age was 0.3 (0.1) years and 52.1% were male; for the older group, the mean (SD) age was 1 (0.4) years and 54.6% were male.

Of the 18,208 children 1-6 months who received palivizumab, 6.9% had an RSV diagnosis code and 13.1% had a bronchiolitis diagnosis code. Among children 7 months and older dispensed palivizumab, 8.4% had an RSV diagnosis and 18.7% had a bronchiolitis diagnosis. A substantial proportion of children who received palivizumab had at least one RSV risk factor. Among children 1-6 months, 4.6% had CLD, 13.1% had CHD, 19.4% were extremely pre-term (<29 weeks), 30.8% were very preterm (29 to <32 weeks), and 26.3% were moderate to late preterm (32 to <37 weeks). Among those ≥7 months, 15.8% had CLD, 30.3% had CHD, 42.9% were extremely pre-term, 16.0% were very preterm, and 10.8% were moderate to late preterm.

# 4. Discussion

Understanding the current epidemiology of RSV-AI and identifying the populations at the greatest risk is essential to inform drug and vaccine development. The results of our analysis using data from the Sentinel System are consistent with other published literature which report that the majority of RSV-AI cases are managed in the outpatient setting and occur in children without recognized RSV risk factors other than young age[3,12]. Even among hospitalized patients, we found that children with CLD, CHD, or prematurity make up a small fraction of the total cases. The proportion of hospitalized children with risk factors is higher in children above 6 months of age; this may be due to the population encountering more than one RSV season, or the decreased cardiopulmonary reserve associated with the comorbid conditions. Our results suggest the burden of disease lies with full-term rather than pre-term children. Given these findings, RSV related studies may benefit from exploring RSV epidemiology in the population as a whole, rather than classically labeled at-risk subsets.

There are important limitations of the Sentinel System and claims data in general. Misclassification is a primary concern. For example, an RSV diagnosis code does not certify the child had RSV infection; we did not have access to laboratory test results, so we could not differentiate laboratory-confirmed cases from those diagnosed empirically based on clinical presentation. Similarly, the lack of a code for a risk factor of interest does not necessarily mean the child does not have that risk factor. In addition, race and ethnicity data are not complete in the data, preventing assessment of those demographic factors, which may be important in RSV-AI epidemiology.

In conclusion, while it is well understood that RSV-AI is a significant concern in children with CLD, CHD, or prematurity, using the Sentinel System we found that the majority of children who experience RSV infection did not have documentation of these risk factors. Future development of new RSV prophylactics and therapeutics should consider the needs of children with and without the traditional risk factors for RSV-AI.

# 5. Acknowledgements

Many thanks are due to the Data Partners who provided data used in the analysis: Aetna, Blue Bell, PA; Blue Cross Blue Shield of Massachusetts, Boston, MA; Harvard Pilgrim Health Care Institute, Boston, MA; HealthCore, Inc., Translational Research for Affordability and Quality, Alexandria, VA; HealthPartners Institute, Minneapolis, MN; Humana, Inc., Comprehensive Health Insights, Miramar, FL; Kaiser Permanente Colorado Institute for Health Research, Denver, CO; Kaiser Permanente Center for Health Research Hawai'i, Honolulu, HI; Kaiser Permanente Mid-Atlantic States, Mid-Atlantic Permanente Research Institute, Rockville, MD; Kaiser Permanente Northern California, Division of Research, Oakland, CA; Kaiser Permanente Northwest Center for Health Research, Portland, OR; Kaiser Permanente Washington Health Research Institute, Seattle, WA; Marshfield Clinic Research Institute, Marshfield, WI; Meyers Primary Care Institute, Worcester, MA; OptumInsight Life Sciences Inc., Boston, MA; Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN, through the Tennessee Division of TennCare of the Department of Finance and Administration which provided data.

*Table 1. Codes Used to Define Respiratory Syncytial Virus Associated Illness (RSV-AI), Bronchiolitis, and Diagnostic Assays*

| Condition | Code | Code Category | Code Type | Description |
|---|---|---|---|---|
| RSV-AI | 079.6 | Diagnosis | ICD-9-CM | Respiratory syncytial virus (RSV) |
| RSV-AI | 466.11 | Diagnosis | ICD-9-CM | Acute bronchiolitis due to respiratory syncytial virus (RSV) |
| RSV-AI | 480.1 | Diagnosis | ICD-9-CM | Pneumonia due to respiratory syncytial virus |
| RSV-AI | B974 | Diagnosis | ICD-10-CM | Respiratory syncytial virus as the cause of diseases classified elsewhere |
| RSV-AI | J121 | Diagnosis | ICD-10-CM | Respiratory syncytial virus pneumonia |
| RSV-AI | J205 | Diagnosis | ICD-10-CM | Acute bronchitis due to respiratory syncytial virus |
| RSV-AI | J210 | Diagnosis | ICD-10-CM | Acute bronchiolitis due to respiratory syncytial virus |
| Bronchiolitis | 466 | Diagnosis | ICD-9-CM | Acute bronchitis and bronchiolitis |
| Bronchiolitis | 466.1 | Diagnosis | ICD-9-CM | Acute bronchiolitis |
| Bronchiolitis | 466.11 | Diagnosis | ICD-9-CM | Acute bronchiolitis due to respiratory syncytial virus (RSV) |
| Bronchiolitis | 466.19 | Diagnosis | ICD-9-CM | Acute bronchiolitis due to other infectious organisms |
| Bronchiolitis | 516.34 | Diagnosis | ICD-9-CM | Respiratory bronchiolitis interstitial lung disease |
| Bronchiolitis | J210 | Diagnosis | ICD-10-CM | Acute bronchiolitis due to respiratory syncytial virus |
| Bronchiolitis | J219 | Diagnosis | ICD-10-CM | Acute bronchiolitis, unspecified |
| Bronchiolitis | J218 | Diagnosis | ICD-10-CM | Acute bronchiolitis due to other specified organisms |
| Bronchiolitis | J84115 | Diagnosis | ICD-10-CM | Respiratory bronchiolitis interstitial lung disease |
| Diagnostic Assay | 87280 | Procedure | CPT | Infectious agent antigen detection by immunofluorescent technique; respiratory syncytial virus |
| Diagnostic Assay | 87420 | Procedure | CPT | Infectious agent antigen detection by immunoassay technique, (eg, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; respiratory syncytial virus |
| Diagnostic Assay | 87807 | Procedure | CPT | Infectious agent antigen detection by immunoassay with direct optical observation; respiratory syncytial virus |
| Diagnostic Assay | 87631 | Procedure | CPT | Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 3-5 targets |

| Condition | Code | Code Category | Code Type | Description |
|---|---|---|---|---|
| Diagnostic Assay | 87632 | Procedure | CPT | Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 6-11 targets |
| Diagnostic Assay | 87633 | Procedure | CPT | Infectious agent detection by nucleic acid (DNA or RNA); respiratory virus (eg, adenovirus, influenza virus, coronavirus, metapneumovirus, parainfluenza virus, respiratory syncytial virus, rhinovirus), includes multiplex reverse transcription, when performed, and multiplex amplified probe technique, multiple types or subtypes, 12-25 targets |

CPT: Current Procedural Terminology procedure codes; ICD-9 and ICD-10: International Classification of Diseases, Ninth Revision and Tenth Revision diagnosis and procedure codes

*Table 2. Characteristics of RSV-AI Cases, January 1, 2008 – June 30, 2016, Sentinel System*

| | Inpatient Care Setting | | Outpatient Care Setting | |
|---|---|---|---|---|
| | Age 1-6 months N=24,192 | Age 7-60 months N=20,002 | Age 1-6 months N=119,363 | Age 7-60 months N=156,019 |
| **Mean Age in Years (SD)** | 0.3 (0.1) | 1.7 (1.0) | 0.3 (0.1) | 1.6 (1.0) |
| **Male Sex** | 14,000 (57.9%) | 11,106 (55.5%) | 67, 805 (56.8%) | 85,589 (54.9%) |
| **Chronic Lung Disease (CLD)** | 135 (0.6%) | 547 (2.7%) | 194 (0.2%) | 687 (0.4%) |
| **Congenital Heart Disease (CHD)** | 613 (2.5%) | 1,082 (5.4%) | 1,101 (0.9%) | 2,110 (1.4%) |
| **Extremely Preterm (<29 weeks)** | 261 (1.1%) | 882 (4.4%) | 605 (0.5%) | 1,797 (1.2%) |
| **Very Preterm (29 to <32 weeks)** | 562 (2.3%) | 811 (4.1%) | 1,666 (1.4%) | 2,697 (1.7%) |
| **Moderate to Late Preterm (32 to <37 weeks)** | 2,326 (9.6%) | 1,644 (8.2%) | 7,324 (6.1%) | 8,127 (5.2%) |

# 6. References


1. Nair H, Nokes DJ, Gessner BD, *et al.* Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet, 2010; 375: 1545-1555

2. Shi T, McAllister D, O'Brien K, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet. 2017; 390: 946-958

3. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med. 2009;360:588–598.

4. Stockman L, Curns A, Anderson L, Fischer-Langley G. Respiratory Syncytial Virus-associated Hospitalizations Among Infants and Young Children in the United States, 1997-2006. Pediatr Infect Dis J 2012; 31:5-9.

5. Nicholson EG, Munoz FM. A Review of Therapeutics in Clinical Development for Respiratory Syncytial Virus and Influenza in Children. Clin Ther 2018 Aug; 40: 1268-1281

6. Vaccine Resources. PATH RSV Vaccine and mAb Snapshot. Available at https://vaccineresources.org/files/RSV-snapshot-2018Oct_High%20Resolution%20V3.pdf Accessed November 27, 2018.

7. Simoes EA, DeVincenzo JP, Boeckh M, et al. Challenges and Opportunities in Developing Respiratory Syncytial Virus Therapeutics. J Infect Dis 2015; 211:S1-20.

8. US Food and Drug Administration. FDA's Sentinel Initiative. Available at www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm

9. Sentinel Initiative. Sentinel Data Partners. Available at https://www.sentinelinitiative.org/sentinel/data/data-partners. Accessed 18 November 2018

10. Sentinel Initiative. Sentinel Final Report CDER RSV. Available at Sentinel Initiative Assessments, https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Sentinel_Final_Report_cder_mpl1r_wp052.pdf. Accessed 18 November 2018

11. Winterstein AG, Hampp C, Saidi A. Effectiveness of palivizumab prophylaxis in Infants and Children in Florida. Pharmacoepidemiol Drug Saf 2012; 21:53-60.

12. Centers for Disease Control and Prevention. The National Respiratory and Enteric Virus Surveillance System (NREVSS). Available at www.cdc.gov/surveillance/nrevss/rsv/index.html. Accessed 18 November 2018