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Performance of novel clinical case definitions for respiratory syncytial virus infections in young infants: a latent class analysis

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Abstract

Performance of novel clinical case definitions for respiratory syncytial virus infections in young infants: a latent class analysis

By Karim Lalani

Background: Respiratory syncytial virus (RSV) is a major cause of pediatric morbidity and mortality worldwide. Appropriate case definitions are needed to accurately assess disease burden and evaluate novel RSV therapeutics and vaccines. Limited data exist on performance of RSV case definitions among young infants or in high-resource settings.

Methods: We used data collected on infants <6 months of age tested for RSV as part of routine clinical care at Children's Healthcare of Atlanta between January 2010-December 2015. We evaluated sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of clinical features, existing case definitions used by the World Health Organization (WHO), and alternative definitions we constructed using latent class analyses (LCA) to detect laboratory-confirmed RSV infection.

Results: Among 565 infants tested for RSV, 161 (28.5%) had laboratory-confirmed RSV infection. Among all case definitions evaluated, WHO-acute respiratory infection (ARI) ("cough or sore throat or shortness of breath or coryza, and a clinician's judgment that illness is due to infection") was the most sensitive [98.1%, 95% confidence interval (CI), 96.1–100.0, NPV 96.3%, 95% CI 92.2–100.0]. The definition developed through LCA (cough and shortness of breath and coryza and wheeze and poor feeding and chest in-drawing) was the most specific (95.8%, 95% CI 93.8–97.8; PPV 51.4%, 95% CI 34.9–68.0).

Conclusions: The WHO ARI definition was the most sensitive for detecting laboratory-confirmed RSV infections among infants aged <6 months. However, alternative case definitions can confer higher specificity. Appropriate case definitions will vary depending on the context and setting in which they are utilized.

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CHAPTER 1: DEFINITION OF TERMS

Acute respiratory infection – an sudden onset illness most often viral caused by viruses that impairs normal breathing function

Case definition – a set of clinical criteria used to identify a positive disease case

Direct immunofluorescence assay – a method in molecular biology to directly visualize presence of fluorescently labeled antibodies

Full-term infant – a baby born at least at 37 weeks of gestation

High-income country – defined by the World Bank in 2016 as one with a gross national income (GNI) per capita of US$12,236 or greater

Latent class analysis – a statistical method that uses likelihood probabilities to identify hidden, or latent, subgroups within a larger sample that share an association

Low-income country – defined by the World Bank in 2016 as one with a GNI per capita of US$1005 or less

Low-middle income country – defined by the World Bank in 2016 as one with a gross national income GNI per capita between US$1006–3955

Pre-term infant – a baby born before 37 weeks of gestation

Prophylaxis – an action or medication taken to prevent occurrence of a specific disease

Real-time reverse transcriptase polymerase chain reaction (rt-PCR) – a procedure used in molecular biology to amplify genetic material (DNA) for many purposes, including identification of microbes and viruses

Respiratory syncytial virus – a common respiratory virus that often causes mild-moderate cold-like symptoms but that can cause more severe disease in certain populations, including young or immunocompromised infants and children

CHAPTER 2: REVIEW OF THE LITERATURE

Respiratory syncytial virus (RSV) is a major cause of pediatric morbidity and mortality worldwide. Consequently, multiple trials are underway to develop potential vaccines for specific target populations. However, evaluating the efficacy and impact of such vaccines requires an accurate case definition for robust and accurate disease surveillance. While numerous studies have assessed potential case definitions among children in low-income settings, very few have focused specifically on infants, who are at greater risk for severe RSV disease, in high-income settings.

2.1 RSV epidemiology, morbidity, and mortality in pediatric populations

In 2009, Nair *et al*. conducted a meta-analysis using a systematic review of 36 community- and hospital-based studies from across the globe from January 1995–June 2009 to estimate the global incidence and mortality rate of RSV-associated acute lower respiratory infections (ALRI) in children <5 years. Inclusion and exclusion criteria and location for studies included in analyses are illustrated in Box 1 and Figure 1, respectively (Nair et al., 2010).

Box 1. Inclusion and exclusion criteria used in systematic review by Nair *et al*. Taken from Nair *et al*., 2010.

Inclusion criteria

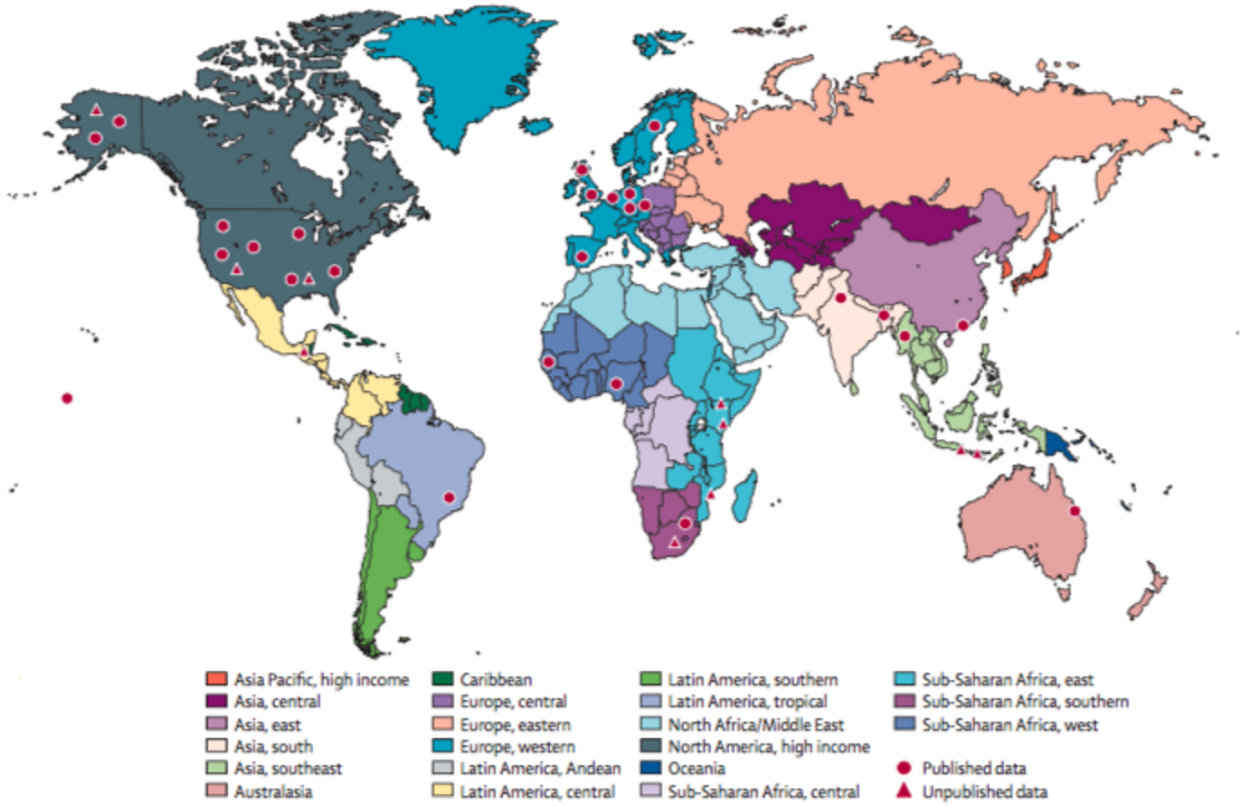
- Reported data for respiratory syncytial virus (RSV)-infected children with acute lower respiratory infection (eg, pneumonia, bronchiolitis) or acute respiratory infection necessitating hospital admission
- Undertook surveillance within a defined population for a minimum of 1 year (apart from studies reporting case fatality ratios)
- Provided data specific to children younger than 5 years
- Reported RSV incidence or mortality for at least the first year of life

Exclusion criteria

- Reported data for children with acute upper respiratory infections not necessitating hospital admission
- Investigated RSV as a co-infection rather than the primary outcome
- Used a case definition of influenza or influenza-like illness
- Used a case definition that was not clearly defined or was not consistently applied

Since incidence data were heterogeneous across the studies, the investigators used pooled estimates using the random effects model and summed estimates from industrialized

Figure 1. Geographic locations of studies included in systematic review by Nair *et al* . Taken from Nair *et al* ., 2010.



and developing countries from 2005. They reported an incidence of 33.8 million (95% confidence interval (CI) 19.3–46.2) RSV ALRIs among children younger than five in 2005, comprising 22% of all ALRI cases that year. Of the 33.8 million, they estimated at least 3.4 million cases (95% CI 2.8–4.3) resulted in hospitalization. Across all the studies, the investigators estimated a range of 66,000–199,000 RSV-associated deaths worldwide among children <5 ranging in 2005. They reported that 99% of these deaths occurred in developing countries (Nair et al., 2010). These findings demonstrate the significant morbidity and mortality associated with RSV in the pediatric population less than 5 years of age and support the urgent need for vaccination in such populations.

A later study by Hall *et al*. in 2013 examined RSV disease burden, morbidity, and mortality specifically among children younger than 2 years of age, as there were limited

data in this age group. They conducted a prospective cohort study of 2149 children in the United States from 2000–2005 who developed an acute respiratory infection (ARI) before 2 years of age and stratified the data by age in months. Of the sample, 559 (26%) had RSV confirmed by reverse-transcriptase polymerase chain reaction (rt-PCR). The average rate of hospitalization among all children <24 months was 5.2 per 1000 (95% CI 4.8–5.7). Rates among infants 6 months, 5 months, 4 months, 3 months, 2 months, 1 month, and <1 month of age were 4.1 per 1000 (95% CI 2.5–6.2), 4.8 per 1000 (95% CI 2.9–7.0), 8.9 per 1000 (95% CI 6.3–11.8), 10.3 per 1000 (95% CI 7.7–13.5), 14.3 per 1000 (95% CI 11.1–17.8), 25.9 per 1000 (95% CI 21.3–30.8), and 13.5 (95% CI 10.3–17.1), respectively. Hall *et al*. demonstrated that younger age, especially below 6 months, was associated with greater severity of RSV disease (Hall et al., 2013). The prospective nature of this study and the identification of RSV via sensitive and specific molecular testing like rt-PCR make the findings robust and help in reducing misclassification bias. However, as the sample was drawn solely from the United States, the specific hospitalization rates may not be generalizable to other populations in low-middle income countries.

2.2 RSV-associated healthcare costs in pediatric populations

There are significant healthcare costs associated with RSV disease in children and infants. In 2014, Zhang and colleagues conducted a retrospective review of children hospitalized at a hospital in China with RSV confirmed via direct immunofluorescence assay from January 2005–December 2009 to study RSV-associated clinical characteristics and direct medical costs. Of the sample, 87% were ≥2 years of age. The median costs of each RSV-associated hospitalization among infants ≤6 months, infants and children 7–24 months, and children >2 years were US$538.55, US$608.39, and US$645.77, respectively.

The median length of hospital stay in each group was 8 days, 8 days, and 7 days, respectively (Zhang et al., 2014).

In 2016 McLaurin *et al*. examined similar variables more specifically among infants <1 year of age in the United States sampled through online databases. They conducted a retrospective review of 3,018,188 full-term and 328,832 preterm infants born between July 2003–June 2013 to study clinical outcomes and costs from RSV-associated hospitalization in 2014. All infants were without high-risk comorbid conditions (chronic lung disease, hemodynamically significant congenital heart disease, cystic fibrosis, trisomy 21, immunodeficiencies, or organ transplants). Mean hospitalization costs for full-term infants, preterm infants born at 33-34 weeks of gestation (wGA), and preterm infants born <29 wGA in their first year of life ranged from US$8324–$10,570, US$15,839–$19,931, and US$39,354–$40,813, respectively. Additionally, the investigators found that among Medicaid-insured infants, the mean length of hospital stay was 4.3 days for full-term infants compared to 9.2 days for preterm infants born <29 wGA. Among commercially insured infants, mean length of stay was 4.1 days for full-term infants and 7.7 days for preterm infants born <29 wGA (McLaurin et al., 2016).

The data from the previous two studies are specific to China and the United States, respectively, each of which may have different treatment protocols for various clinical presentation and various healthcare resources allocated to management of respiratory infections in infants and children. However, both studies still demonstrate the significant healthcare costs and resource utilization–through length of hospital stay–associated with RSV disease among children and infants. They additionally highlight increasing cost burden and healthcare utilization with younger age at time of RSV-associated hospitalization.

2.3 Development of an RSV vaccine

The significant morbidity, mortality, and healthcare cost burden of RSV has led to extensive work over recent decades in testing and developing potential vaccinations against RSV. While a targeted monoclonal antibody, palivizumab, has been developed and is recommended for RSV prophylaxis for certain high-risk infants and children (American Academy of Pediatrics, 2014), no vaccine currently exists that is recommended for the larger general infant or childhood population. This is the result of many challenges in vaccinology, including inducing robust immunogenicity while demonstrating a relatively benign safety profile (Collins & Melero, 2011; Higgins et al., 2016; Kapikian, 1969). However, the rise of such vaccines in the future will subsequently require the need for sensitive and specific RSV case definitions, potentially in specific vaccine target populations. Such definitions will be instrumental in informing global RSV disease surveillance and in accurately assessing treatment outcomes in future vaccine efficacy and impact trials.

2.4 Evaluation of potential RSV case definitions

Multiple recent studies have used clinical features associated with RSV to test the ability of various potential case definitions to capture RSV infection. In 2015, Saha *et al*. published the results of a prospective cohort study of 505 children <5 years of age admitted to a hospital in India for acute medical conditions from July 2009–December 2012. They tested all children for RSV using real-time polymerase chain reaction (RT-PCR) from nasal and throat swab samples. The investigators used bivariate analysis to identify signs and symptoms associated with RSV and stepwise logistic regression to identify those that predict RSV-associated hospitalization. The investigators then evaluated various case

definitions and clinical syndromes used by the World Health Organization (WHO) for surveillance of respiratory pathogens to assess how well they capture RSV infection (see Box 2) (Saha et al., 2015; World Health Organization, 2011). Finally, Saha *et al*. calculated incidence rates for RSV using each case definition to observe the impact of varying screening definitions on estimating RSV disease burden (Saha et al., 2015).

Saha and colleagues detected RSV in 82 (16%) children, with 73 (89%) cases among those <2 years of age (p<.001). Among all children tested, they found symptoms of cough (OR 5.3, 95% CI 2.8–10.1) and fast breathing (OR 3.9, 95% CI 2.4–6.3), and signs of stridor (OR 5.7, 95% CI 2.2–14.8), nasal flaring (OR 5.1, 95% CI 2.0–12.9), chest in-drawing (OR 5.7, 95% CI 2.9–11.3), grunting (OR 5.6, 95% CI 2.2–14.7), crepitation (OR 5.0, 95% CI 3.0–8.2), wheeze (OR 4.5, 95% CI 2.7–7.5), tachypnea (OR 2.2, 95% CI 1.4–3.5), and hypoxia (OR 2.5, 95% CI 1.3–4.8) to be significantly associated with positive RSV status. Among

Box 2. Case definitions and clinical syndromes used by the World Health Organization for surveillance of respiratory illness. Taken from Saha *et al*., 2015.

ARI – acute respiratory infection (WHO, 2011):

Acute onset of at least one of the following four respiratory symptoms: cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection.

ILI – influenza–like illness (WHO, 2011):

An acute respiratory illness with onset during the last 7 days with measured temperature ≥38°C, AND cough. (Dropped sore throat).

ILI (old):

Sudden onset of fever (>38°C) with cough or sore throat, in absence of other diagnoses.

SARI – severe ARI (WHO, 2011):

An acute respiratory illness with onset during the previous 7 days requiring overnight hospitalization that includes history of fever or measured fever of ≥38°C, AND cough, AND shortness of breath or difficulty breathing.

SARI (old):

Meets ILI (old) definition (sudden onset of fever (>38°C) with cough or sore throat) and has shortness of breath or difficulty breathing and requires overnight hospitalization.

Pneumonia (IMCI):

Fast breathing or chest indrawing

Severe pneumonia (IMCI):

General danger signs – Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor, or severe malnutrition

infants 0–5 months of age, symptoms of cough (OR 4.4, 95% CI 1.2–15.7), breathing difficulty (OR 3.5, 95% CI 1.5–7.9), and fast breathing (OR 2.9, 95% CI 1.3–6.7), and signs of chest in-drawing (OR 5.1, 95% CI 1.2–13.9), crepitation (OR 2.9, 95% CI 1.3–6.6), and wheeze (OR 5.0, 95% CI 2.1–11.8) were significantly associated with RSV. Adjusting for age, the investigators identified presence of cough (OR 1.85, p=.013), history of fast breathing (OR 3.44, p<.001), crepitation (OR 2.79, p<.001), and hypoxia (OR 2.71, p<.001) as significant predictors of hospitalization among RSV-positive infants and children (Saha et al., 2015).

Among the WHO case definitions and clinical syndromes tested, the ARI definition showed the greatest sensitivity (87.8%) and specificity (40%) for RSV. Among any combination of clinical features, history of cough or crepitation with presence of history of fast breathing, breathing difficulty, nasal discharge, sore throat, chest in-drawing, wheeze, or hypoxia showed a sensitivity of 81.7% and specificity of 60% for RSV (Saha et al., 2015).

The investigators found an average annual incidence of RSV-associated hospitalization to be 7.4 (95% CI 4.9–10.5) per 1000 child-years among children <2 years old and 0.5 (95% CI 0.1–1.5) per 1000 child-years among those 2–5 years of age. In those <2 years, the highest incidence was in infants <6 months at 15.2 (95% CI 8.3–26.8) per 1000 child-years. Additionally, they found the ARI definition to be the best estimator of RSV disease burden, capturing 90% and 86% of RSV-associated hospitalization incident cases among children <2 years and <5 years, respectively (Saha et al., 2015).

Saha *et al.*'s findings corroborated previous research indicating RSV as a major cause of hospitalization among children <2 years old, especially those <6 months. They concluded that the WHO ARI case definition the most appropriate screening definition for

capturing RSV disease burden. However, there exist multiple limitations to this study. As the investigators only tested hospitalized infants and children, they may have missed cases of RSV among those not hospitalized. Thus, the true incidence of RSV may have been higher than what they observed. The use of only hospitalized cases also introduces selection bias into the odds ratio estimates of the clinical features and into the sensitivities and specificities of the case definitions tested, as non-hospitalized children with respiratory syndromes may present with varying signs and symptoms compared with those who are hospitalized. Finally, as this study was conducted using a rural population in Northern India, the findings may not be generalizable to the larger pediatric population in other low- and high-income countries, where differences in RSV genotypes may produce slight differences in clinical presentation (Vandini, Biagi, & Lanari, 2017).

In 2016, Nyawanda and colleagues added to the findings by Saha *et al*. through their prospective cohort study of children <5 years of age in rural Western Kenya. They tested 3810 children for RSV hospitalized from September 2009–August 2013 to evaluate the association of various clinical features and WHO case definitions or clinical syndromes (see Figure 2) with RSV using risk ratios, sensitivities, and specificities. In addition to Saha *et al*., however, they also test the positive (PPV) and negative predictive values (NPV) of clinical features, case definitions, and clinical syndromes for RSV. Finally, they test an alternative case definition constructed using a logistic regression including all signs and symptoms in the model. All cases of RSV were identified using RT-PCR from nasopharyngeal and oropharyngeal swab samples (Nyawanda et al., 2016).

Of the tested cohort, 470 (12%) children were positive for RSV. Among all signs and symptoms, the investigators found a significant association between RSV and cough (RR

Figure 2. Case definitions and clinical syndromes used by the World Health Organization for surveillance of respiratory illness tested by Nyawanda *et al*. Taken from Nyawanda *et al*., 2016.

Case definition	All age groups
SARI	An Acute Respiratory Infection with: • History of fever or Measured fever of ≥38 °C • And cough • With an onset within the last 10 days • And requires hospitalization
IMCI non-severe pneumonia[a]	Cough or difficulty breathing with fast breathing. - Fast breathing • <2 months ≥ 60 breaths/minute • 2- > 12 months- ≥ 50breaths/min • 12–59 months- ≥ 40 breaths/min
IMCI severe pneumonia[b]	Cough or difficulty breathing with chest in-drawing when calm
IMCI very severe pneumonia	Cough or difficulty breathing with any one of: - Stridor when calm - Not able to breastfeed/drink - Convulsions - Lethargy - Unconscious - Vomit everything
Hospitalized ILI	A hospitalized Acute Respiratory Infection with: • Measured fever of ≥38 °C • And cough • With an onset within the last 10 days

[a]Excludes those with chest in-drawing and those with danger signs (stridor, unable to drink/breastfeed, convulsions, lethargy, unconsciousness and vomit everything)
[b]Excludes those with danger signs

2.56, 95% CI 1.60–4.10), difficulty breathing (RR 1.46, 95% CI 1.23–1.74), hypoxia (RR 1.76, 95% CI 1.46–2.12), wheeze (RR 1.63, 95% CI 1.35–1.96), nasal flaring (RR 1.49, 95% CI 1.24–1.78), and chest in-drawing (RR 1.57, 95% CI 1.31–1.88). Of these features, cough displayed the greatest sensitivity (96.4%, 95% CI 94.7–98.1), and hypoxia the greatest specificity (84.8%, 95% CI 83.5–86.0) for RSV infection. Among the WHO case definitions and clinical syndromes tested in all children, the SARI definition showed the greatest sensitivity (82.8%, 95% CI 79.4–86.2) and NPV (90.4%, 95% CI 88.4–92.4) for RSV. The clinical syndrome of severe pneumonia displayed the greatest specificity (90.7%, 95% CI 89.7–91.7) and PPV (18.6%, 95% CI 14.7–22.6). Specifically among infants <1 year of age, the constructed case definition of cough or difficulty breathing with hypoxia, chest in-drawing, or wheeze demonstrated a sensitivity of 66.0% (95% CI 60.0–72.0), specificity of 54.0% (95% CI 51.5–56.5), PPV of 18.4% (95% CI 15.8–21.0), and NPV of 91.0% (95% CI 89.1–92.9). Nyawanda *et al*. concluded that determining the appropriate definition(s) to use, such as a more sensitive versus a more specific one, must be based on the context and purpose for which a study is being

conducted (Nyawanda et al., 2016). Similar to Saha *et al.*'s study, however, selection bias is present here, as only hospitalized children are included in this cohort from rural Kenya. Thus, the predictive values of the clinical features and case definitions for RSV may not be generalizable to infants and children living in more urban environments or who are not hospitalized for their respiratory illness.

2.5 Summary, problem, and purpose statement

In summary, RSV is a significant contributor to pediatric morbidity and mortality worldwide, as well as healthcare costs worldwide. This is especially true among infants <1 year of age. Potential RSV vaccines are currently in development or clinical trials to help mitigate its substantial global health and economic burden. Such vaccines, however, will require use of both, sensitive and specific, case definitions to accurately monitor disease surveillance and inform vaccine efficacy and impact trials. Alternate case definitions may be needed for different vaccine target populations, such as children >2 years of age, those 1-2 years of age, infants 6-12 months of age, and infants <6 months of age. Multiple studies have examined various potential definitions; however, most were conducted with hospitalized pediatric populations >1 year old or in low-medium income settings. Additionally, no studies exist that evaluate a comprehensive list of case definitions tested in previous research, thereby, preventing reliable assessments of case definitions in differing populations and environmental settings. We aim to help bridge this knowledge gap by testing case definitions used in previous research in infants <6 months, who are at greatest risk of severe RSV disease, sampled from a large, quaternary healthcare system in a high-income country, including both, hospitalized and non-hospitalized, infants.

CHAPTER 3: MANUSCRIPT

Prepared for submission to Journal of Clinical Infectious Diseases, peer-reviewed journal of the Infectious Diseases Society of America.

ABSTRACT

Background.

Respiratory syncytial virus (RSV) is a major cause of pediatric morbidity and mortality worldwide. Appropriate case definitions are needed to accurately assess disease burden and evaluate novel RSV therapeutics and vaccines. Limited data exist on performance of RSV case definitions among young infants or in high-resource settings.

Methods.

We used data collected on infants <6 months of age tested for RSV as part of routine clinical care at Children's Healthcare of Atlanta between January 2010-December 2015. We evaluated sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of clinical features, existing case definitions used by the World Health Organization (WHO), and alternative definitions we constructed using latent class analyses (LCA) to detect laboratory-confirmed RSV infection.

Results.

Among 565 infants tested for RSV, 161 (28.5%) had laboratory-confirmed RSV infection. Among all case definitions evaluated, WHO-acute respiratory infection (ARI) ("cough or sore throat or shortness of breath or coryza, and a clinician's judgment that illness is due to infection") was the most sensitive [98.1%, 95% confidence interval (CI), 96.1–100.0, NPV 96.3%, 95% CI 92.2–100.0]. The definition developed through LCA (cough

and shortness of breath and coryza and wheeze and poor feeding and chest in-drawing) was the most specific (95.8%, 95% CI 93.8–97.8; PPV 51.4%, 95% CI 34.9–68.0).

Conclusions.

The WHO ARI definition was the most sensitive for detecting laboratory-confirmed RSV infections among infants aged <6 months. However, alternative case definitions can confer higher specificity. Appropriate case definitions will vary depending on the context and setting in which they are utilized.

Keywords.

Respiratory syncytial virus; case definitions; infants; latent class analysis; high-income setting.

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INTRODUCTION

Respiratory syncytial virus (RSV) is a leading cause of morbidity and mortality in young children worldwide. Up to 33 million cases of RSV infection occur each year among children younger than five, resulting in 3.4 million hospital admissions and roughly 200,000 deaths (Nair et al., 2010). Those younger than six months are at greatest risk for severe RSV disease and RSV-associated hospitalization, which contributes to significant resource utilization and healthcare costs (Hall et al., 2013; McLaurin, Farr, Wade, Diakun, & Stewart, 2016; Simoes, 2003; Zhang et al., 2014).

Though the significant cost and mortality burden of RSV has made vaccine development a top priority for the past several decades, no safe and efficacious vaccine currently exists (Collins & Melero, 2011; Higgins, Trujillo, & Keech, 2016; Kapikian, 1969). However, multiple trials are ongoing that may yield a promising vaccine in the near future (Higgins et al., 2016). Subsequently, the need for sensitive and specific RSV case definitions in different vaccine target populations will be vital to better inform global disease surveillance and accurately assess disease burden and treatment outcomes in future vaccine efficacy and impact trials. There already exists abundant literature describing the clinical features associated with RSV-hospitalization among different populations, including a few recent studies evaluating specific case definitions (Atwell, Geoghegan, Karron, & Polack, 2016; Bont et al., 2016; Nyawanda et al., 2016; Saha et al., 2015). However, these studies are largely from low-resource settings and have focused predominantly on children older than six months of age. Furthermore, no studies have yet yielded a promising case definition with robust sensitivity and specificity for RSV in the context of other respiratory infections.

The purpose of this study is to evaluate different case definitions for detection of RSV infections using data from one of the largest pediatric clinical registries in the United States with greater than 390,000 unique patient encounters and more than 220,000 emergency department patient visits annually (Children's Healthcare of Atlanta, 2017).

We used data collected exclusively on infants 0–6 months of age from a large quaternary hospital in an urban, high-income setting and constructed alternative case definitions using latent class analyses (LCA) to detect laboratory-confirmed RSV infection. We evaluated sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of clinical features, existing case definitions used by the World Health Organization (WHO), and alternative case definitions we constructed using latent class analyses (LCA) to detect laboratory-confirmed RSV infection.

METHODS

Study sample and design

This study was conducted at Children's Healthcare of Atlanta, the largest health care system that provides comprehensive tertiary care to most young children in Atlanta, Georgia (Children's Healthcare of Atlanta, 2017). Subjects included all infants <6 months of age who were tested for RSV by at least one of the following: serological antibody testing, enzyme immunoassay antigen testing, or nucleic acid detection by polymerase chain reaction (PCR), as part of routine clinical care at Children's Healthcare of Atlanta in Atlanta, Georgia between January 1, 2010 and December 31, 2015. We randomly selected 100 patients for each year to represent all children who were tested for RSV during the study period. We retrospectively reviewed medical records for collecting data on patient

demography, clinical symptoms, complications, underlying diseases and laboratory findings.

Definitions

We defined history of prematurity as gestational age <37 weeks. Duration of symptoms before presentation was defined as duration of cough, as this was the only variable common to all reviewed charts that measured a time interval of any symptom. Fever was defined as a history of or initial measured temperature in the hospital of ≥38.0°C. A history of "fever" was not counted as fever to reduce misclassification bias, as oftentimes guardians had classified temperatures <38°C as a fever. Tachypnea was defined using World Health Organization criteria (WHO): ≥60 breaths/min for infants <2 months of age, and ≥50 breaths/min for infants 2–6 months of age (World Health Organization, 2011). Hypoxia was defined as initial or lowest measured oxygen saturation <90% (whichever was lower). Breathing difficulty (shortness of breath) on exam was defined as presence of grunting, nasal flaring, or stridor. Hospitalization was defined as admission to the pediatrics floor or intensive care unit from the emergency department. "Poor feeding" was defined as any history of refusal to eat (confirmed by poor sucking) or vomiting. The following remaining symptom variables were defined as identified in electronic medical records per guardian reports: cough, breathing difficulty (shortness of breath), cyanosis, apnea, productive cough, nasal discharge (coryza), wheezing, whooping, lethargy (altered mental status), seizure, conjunctival injection, and post-tussive emesis. Case definitions for acute respiratory infection (ARI), influenza-like illness (ILI), pneumonia (PNA), and severe acute respiratory infection (SARI) were defined according to WHO criteria (see Box 1).

Statistical analyses

Categorical variables were described as counts and percentages. Quantitative variables were described as medians and ranges. We assessed different clinical signs and symptoms associated with RSV positivity using bivariate analysis where discrete data were compared using Chi-square, and continuous data using T-tests or one-way analysis of variance, as applicable. We used logistic regression to evaluate the ability of clinical features to capture positive RSV diagnoses and predict RSV-associated hospitalizations by calculating odds ratios and 95% confidence intervals adjusted for age groups.

To determine which set of clinical predictors to use in constructing RSV case definitions, we conducted latent class analyses to compare probabilities of clinical features between groups likely and unlikely to be RSV-positive. We conducted the analyses with 2–5 different classes using the SAS code outlined by Lanza *et al.* (Lanza, Collins, Lemmon, & Schafer, 2007) Model development and selection was performed using a minimum Akaike information criteria. Signs or symptoms with a >50% chance of being present in a given class were used to test new RSV case definitions. Thus, we constructed five new case definitions, each using a set of clinical features within each class with high probabilities of occurrence.

Finally, we calculated the sensitivities, specificities, PPVs, and NPVs for each case definition, plotted them on a receiver operator characteristic (ROC) curve, and compared them with the standard definitions established by the World Health Organization: ARI, ILI, PNA, SARI (Gove, 1997). We additionally compared the results to those obtained from a secondary analysis of data from our community-based prospective surveillance study of pertussis in Pakistan (unpublished data), in which three syndromic surveillance screening

definitions were tested: (a) presence of wheeze or apnea or cyanosis; (b) presence of chest in-drawing with either cough or tachypnea; and (c) presence of fever or any Integrated Management of Childhood Illness (IMCI) danger sign (i.e. lethargy, or poor feeding confirmed by poor suck, or seizure) (Gove, 1997). All tests were 2-sided at an alpha level of 0.05. The data analysis was performed with the SAS statistical package (9.4 Edition, SAS Institute, Cary, NC) and the SAS LCA code described by Lanza *et al.* (Lanza et al., 2007). This study was approved by the Children's Healthcare of Atlanta institutional review board.

RESULTS

Of the 600 patient charts reviewed, 35 were excluded due to missing patient data, yielding 565 patients included in the analyses. Of the 565 infants, 214 (37.9%) were female, 281 (49.8%) were aged <2 months, and 118 (20.9%) had a positive history of prematurity. RSV was detected in 161 (28.5%) patients (i.e. RSV-positives), of which 102 (63.0%) were positive by PCR, 51 (31.7%) by antigen testing, and 8 (5.0%) by serology. Among those born premature, 28 (23.7%) were RSV-positive; among those born term, 107 (31.7%) were RSV-positive. Among RSV-positive cases, 20 (12.4%) infants had coinfections with other respiratory pathogens in addition to RSV (2 influenza, 1 parainfluenza, 11 rhinovirus, 3 coronavirus, 2 human metapneumovirus, 1 adenovirus, and 2 *Mycoplasma pneumoniae*). Of 404 RSV-negative infants, 131 (32.4%) had at least one non-RSV respiratory pathogen identified (3 *Bordetella pertussis*, 1 *B. parapertussis*, 9 influenza, 26 parainfluenza, 75 rhinovirus, 7 coronavirus, 14 human metapneumovirus, and 7 adenovirus) (Supplemental Table 1). A total of 50 (31.0%) RSV-positive infants were admitted to the intensive care unit. No significant differences were found in demographic characteristics (age, sex, race,

history of prematurity), duration of symptoms, hospitalization, ICU admission, or mortality rates between RSV-positive and RSV-negative patients (Table 1).

The most common clinical symptoms among all infants enrolled in the study included fever (n=191, 33.8%), cough (n=373, 66.0%), breathing difficulty (n=219, 38.8%), nasal discharge (n=381, 67.4%), and history of poor feeding (n=236, 41.8%). The most common physical exam signs were fever (n=128, 22.7%), nasal discharge (n=184, 32.6%), chest in-drawing (n=126, 22.3%), increased work of breathing (n=155, 27.4%), wheezing (n=112, 19.8%), and tachypnea (n=105, 18.5%) (Supplemental Table 2).

Symptoms significantly associated with RSV-positive diagnosis from all infants tested included history of cough (OR 7.0, 95% confidence interval (CI) 4.0–12.2), breathing difficulty (OR 2.0, 95% CI 1.3–2.8), nasal discharge (OR 3.5, 95% CI 2.2–5.7), and wheezing (OR 4.4, 95% CI 2.8–6.8). Signs of nasal discharge (OR 1.6, 95% CI 1.1–2.4), chest in-drawing (OR 2.9, 95% CI 1.1–7.2), increased work of breathing (OR 2.6, 95% CI 1.7–3.8), and wheezing (OR 2.2, 95% CI 1.2–4.1) on physical exam were also significantly associated with RSV-positive diagnosis (Supplemental Table 3).

Among infants who were hospitalized, those with history of cough (OR 9.9, 95% CI 5.3– 18.4), breathing difficulty (OR 2.7, 95% CI 1.7–4.2), nasal discharge (OR 4.8, 95% CI 2.8–8.3), or wheeze (OR 4.5, 95% CI 2.6–7.6) had greater likelihood of being RSV-positive than negative (Table 2). In addition, infants with signs of nasal discharge (OR 1.9, 95% CI 1.2–3.1) or increased work of breathing (OR 2.9, 95% CI 1.8–4.5) on initial exam demonstrated greater odds of being RSV-positive than negative. These findings were largely consistent for infants 1–2 but not 3–6 months of age (Table 2). Among infants who tested positive for RSV, after adjusting for age, history of breathing difficulty (OR 8.2, 95%

CI 3.5–19.3) or increased work of breathing on exam (OR 6.8, 95% CI 2.7–17.2) was more likely to lead to hospitalization (Table 3).

Using latent class analyses, we divided our cohort into five unique classes. There was a 15.3%, 28.7%, 25.9%, 16.3%, and 13.8% chance of infants falling into Class 1, 2, 3, 4, and 5, respectively. Within these classes, there was a 2.8%, 32.2%, 50.8%, 6.2%, and 33.7% chance of RSV-positive status, respectively. In Class 1, fever (70.3%) showed high a high likelihood of occurrence. In Class 2, cough (96.5%), fever (55.5%), and nasal discharge (92.8%) demonstrated significant probabilities of occurrence. Infants in Class 3 were more likely to have cough (94.6%), shortness of breath (100.0%), nasal discharge (85.6%), wheeze (59.6%), poor feeding (57.6%), and chest in-drawing (79.6%). Those in Class 4 were more likely to show apnea (54.0%) and shortness of breath (59.4%). Finally, in Class 5, cough (92.4%), nasal discharge (87.6%), and poor feeding (56.1%) demonstrated significant likelihood of occurrence (Table 4).

We constructed five case definitions from our five classes and compared them to WHO standard definitions (ARI, ILI, PNA, SARI) and the three RSV syndromic surveillance screening definitions recently tested in Pakistan (see Box 1 for descriptions) (Table 5) (Saha et al., 2015). Among the WHO standard definitions, ARI demonstrated the greatest sensitivity (98.1%), followed by PNA (47.2%), ILI (36.7%), and SARI (16.8%). Severe acute respiratory infection showed the greatest specificity (92.3%), followed by ILI (73.5%), PNA (73.3%), and ARI (19.3%). Among the RSV clinical case definitions tested in Pakistan, the Case 1 definition yielded the greatest sensitivity (60.9%), followed by Case 2 (35.4%), and Case 3 (19.3%). Among the definitions constructed using latent class analyses, Class 1 and 5 definitions were the most sensitive (41.0%), followed by Class 2 (32.3%), Class 3

(11.2%), and Class 4 (8.1%). The Class 3 definition was most specific (95.8%), followed by Class 4 (91.3%), Class 5 (77.5%), Class 2 (76.2%), and Class 1 (56.9%). The Class 3 LCA definition was the most specific from all tested definitions and demonstrated the greatest positive predictive value (51.4%) but a lower negative predictive value (73.0%). Meanwhile, the most sensitive definition (ARI) showed the greatest negative predictive value (96.3%) and a lower positive predictive value (32.5%) (Table 5).

DISCUSSION

As work continues on development of safe and effective RSV vaccines, accurately assessing disease burden among various vaccine target populations becomes increasingly important for future vaccine efficacy and impact trials. While numerous studies have examined clinical characteristics and tested potential case definitions among RSV-positive children and adults, to our knowledge, ours is the first to focus solely on a large population of infants <6 months of age in a high-resource setting like the United States.

Among the tested case definitions, we found the standard WHO ARI definition to be the most sensitive (98.1%), similar to findings by Saha *et al*. In contrast to their results, however, we found its specificity (19.3%) to be the lowest among the group (Saha et al., 2015). The differences between our findings may be attributable to differences in age between our cohorts or in RSV genotypes captured by the populations tested, as RSV may demonstrate clinical variation depending on such factors (Vandini et al., 2017). Additionally, we derived our results using both hospitalized and non-hospitalized infants, whereas Saha *et al.* exclusively examined hospitalized children. Therefore, our findings may be more representative of the true RSV disease burden in infants <6 months of age compared to prior studies, which focus only on hospitalized patients.

Among the tested definitions, we found our latent class analysis definition of cough and shortness of breath and nasal discharge and wheeze and poor feeding and chest in-drawing to be the most specific (95.8%) with somewhat useful predictive value for RSV (PPV 51.4%, NPV 73.0%). To our knowledge, this is the greatest specificity achieved thus far for an RSV case definition (Durani, Friedman, & Attia, 2008; Nyawanda et al., 2016; Saha et al., 2015). However, these results were based off only 25% of our sample, of which only 50% were RSV–positive. Additionally, these findings apply solely to infants <6 months of age and may not be generalizable to other vaccine target populations. Based off these findings, the WHO ARI definition may serve as the strongest RSV screening definition among infants <6 months, whereas our latent class analysis definition may serve as the strongest confirmatory definition in the same population.

In this study we also evaluated the association of various clinical features with RSV-positive diagnosis. Most recent studies have examined a weak association between nasal discharge and RSV in young children, with most rates ranging from 3%–52% among RSV-positive children (Cui et al., 2016; Halasa et al., 2015; Saha et al., 2015). One exception has been a cohort of RSV-positive Malaysian children largely <5 years old in which 83.6% demonstrated rhinorrhea (Ng, Tan, Sam, Ting, & Gan, 2017). We observe this relationship to be strong particularly among infants younger than three months of age. One possible explanation is that we studied a much larger sample of infants <6 months of age compared to previous studies, allowing us to detect an association that may have been missed in prior studies. In other ways, however, our findings support the current literature on RSV clinical epidemiology. Among hospitalized infants, cough, breathing difficulty, and wheezing were

all significantly associated with RSV-positive diagnosis in accordance with prior findings (Cui et al., 2016; Durani et al., 2008; Halasa et al., 2015; Ng et al., 2017; Saha et al., 2015).

In RSV-positive infants, we found breathing difficulty and wheezing to be positively associated with hospitalization. Unlike prior studies, we did not observe a significant association between hypoxia and hospitalization (Lucion et al., 2014; Saha et al., 2015). One reason may be that our study was underpowered to detect the association, as only 11 RSV-positive infants were hypoxic in our cohort. Furthermore, we defined hypoxia as initial or lowest measured oxygen saturation <90% during a child's clinical encounter. However, such criteria may under- or overestimate the true incidence of hypoxia in our study, as oxygen saturation is a highly dynamic clinical parameter with varying levels–even if only slightly–over a given period of time. A more longitudinal measure of the variable may better capture the true incidence of hypoxia in future studies to more robustly measure its association with hospitalization and other clinical outcomes.

There are several limitations to this study. Given the retrospective nature of our data collection, there may be significant misclassification bias inherent in the data used, as different clinical providers exercise unique methods of abstracting clinical history and in assessing physical exam findings. Misclassification bias may also result from the heterogeneity in the diagnostic tests used, all of which have varying sensitivity and specificity. Standardized methods in prospective cohort studies in high-resource settings may address this limitation. Furthermore, our findings are also specific to only one potential RSV vaccine target population (0–6 months of age) and should not be extrapolated to older age groups. Additional studies examining other vaccine target populations in high-income countries are needed to address this knowledge gap.

Coinfections were also prevalent in this study. Among RSV-positive infants, 12.4% were positive with one or more respiratory coinfections, which may differentially affect patterns of clinical signs and symptoms and further introduce misclassification bias. Finally, due to the retrospective nature of our study and limitations in patient records, we were able to assess duration of symptoms only as duration of cough, which may not be representative of the true time course of an infant's clinical presentation. Since RSV classically presents as a biphasic illness with upper respiratory infection symptoms preceding lower respiratory infection ones days later, duration of symptoms may be confounding the clinical presentation between RSV-positive and RSV-negative infants (Cherry, Demmler-Harrison, Kaplan, Steinbach, & Hotez, 2014).

CONCLUSION

Even though extensive work has been done to study the epidemiology of RSV infections among pediatric populations globally, no established accurate clinical RSV case definition currently exists. Furthermore, much of the existing data describe children 1–5 years of age, with little focus on those younger than 6 months, particularly from high-income countries. We offer insight into the clinical pattern of RSV in such a population. Additionally, we describe what may be promising case definitions to identify RSV, at least among infants <6 months of age, who are at greater risk for severe disease. While the WHO acute respiratory infection definition demonstrates robust sensitivity and NPV useful for screening purposes, our latent class analysis definition shows high specificity and PPV and may be optimal for confirming RSV cases. Such definitions with high sensitivity or specificity are critical to accurately assess disease burden in future RSV vaccine efficacy and impact trials.

Table 1. Characteristics and clinical outcomes of infants younger than 6 months of age who were tested for respiratory syncytial virus infection in Georgia, Atlanta, USA from January 2010–December 2015.

Characteristics		Total n=565		RSV-positive n=161 (28.5%)		RSV-negative n=404 (71.5%)		P-value
Age groups		n	%	n	%	n	%	
	<1 month	127	22.5	41	32.3	86	67.7	
	1–2 months	154	27.3	42	27.3	112	72.7	
	2–3 months	102	18.1	31	30.4	71	69.6	
	3–4 months	84	14.9	22	26.2	62	73.8	0.6
	4–5 months	65	11.5	14	21.5	51	78.5	
	5–6 months	33	5.8	11	33.3	22	66.7	
	Total	565	100.0	161	28.5	404	71.5	
Sex:								
	Female	214	37.9	64	29.9	150	70.1	0.6
	Male	351	62.1	97	27.6	254	72.4	
Race								
	Black	181	32.0	60	33.1	121	66.9	
	Caucasian	297	52.6	74	24.9	223	75.1	
	Asian	20	3.5	4	20.0	16	80.0	0.3
	American Indian/Alaska Native	7	1.2	3	42.9	4	57.1	
	Native Hawaiian/Pacific Islander	4	0.7	2	50.0	2	50.0	
	Other	56	9.9	18	32.1	38	67.9	
Born premature[a]								
	Yes	118	20.9	28	23.7	90	76.3	0.1
	No	338	59.8	107	31.7	231	68.3	
Mean duration of symptoms (days) (SD[b])		4.8 (6.8)		4.0 (4.7)		5.4 (7.9)		0.1
Hospitalization rate		401	71	116	72.0	285	70.5	0.7
Intensive care unit admission rate		158	28	50	31.0	108	26.7	0.3
Mortality rate		9	1.6	0	0.0	9	2.2	0.1

[a]Gestational age <37 weeks. No data reported on 109 infants. [b]Standard deviation.

Table 2. Age–specific clinical signs and symptoms among hospitalized infants <6 months of age tested for RSV.

	Overall		Age groups											
			<1 month		1–2 months		2–3 months		3–4 months		4–5 months		5–6 months	
	RSV+ (n=116)	OR (95% CI)	RSV+ (n=36)	OR (95% CI)	RSV+ (n=26)	OR (95% CI)	RSV+ (n=20)	OR (95% CI)	RSV+ (n=15)	OR (95% CI)	RSV+ (n=9)	OR (95% CI)	RSV+ (n=10)	OR (95% CI)
Symptoms														
Fever[a]	28 (24.1)	0.7 (0.4, 1.2)	10 (27.8)	1.1 (0.4, 2.6)	2 (7.7)	0.1 (0.0, 0.6)	3 (15.0)	0.3 (0.1, 1.1)	5 (33.3)	1.5 (0.4, 5.6)	3 (33.3)	1.9 (0.4, 9.2)	5 (50.0)	3.0 (0.6, 14.9)
Cough	103 (88.8)	9.9 (5.3, 18.4)	29 (80.6)	9.5 (3.7, 24.9)	23 (88.5)	10.3 (2.8, 37.3)	19 (95.0)	21.0 (2.6, 172.3)	13 (86.7)	7.3 (1.4, 36.9)	9 (100.0)	–	10 (100.0)	–
Breathing difficulty	73 (62.9)	2.7 (1.7, 4.2)	19 (52.8)	2.6 (1.1, 5.8)	19 (73.1)	5.1 (1.9, 13.7)	14 (70.0)	4.3 (1.4, 13.8)	8 (53.3)	1.1 (0.3, 3.8)	6 (66.7)	1.8 (0.4, 8.3)	7 (70.0)	2.3 (0.5, 11.7)
Cyanosis	16 (13.8)	0.5 (0.3, 0.9)	8 (22.2)	1.1 (0.4, 2.8)	4 (15.4)	0.5 (0.2, 1.6)	0 (0.0)	–	2 (13.3)	0.5 (0.1, 2.4)	1 (11.1)	0.3 (0.0, 2.8)	1 (10.0)	1.0 (0.1, 12.6)
Apnea	25 (21.6)	0.5 (0.3, 0.9)	5 (13.9)	0.6 (0.2, 1.8)	7 (26.9)	1.3 (0.5, 3.5)	1 (5.0)	0.1 (0.0, 1.0)	2 (13.3)	0.5 (0.1, 2.9)	0 (0.0)	–	1 (10.0)	1.0 (0.1, 12.6)
Productive cough	8 (6.9)	1.0 (0.4, 2.6)	1 (2.7)	0.4 (0.0, 4.4)	1 (3.8)	0.4 (0.0, 4.5)	3 (15.0)	1.6 (0.2, 10.8)	1 (6.7)	–	0 (0.0)	–	2 (20.0)	–
Nasal discharge/coryza	97 (83.6)	4.8 (2.8, 8.3)	29 (80.6)	5.4 (2.1, 13.8)	19 (73.1)	2.5 (0.9, 6.7)	19 (95.0)	19.0 (2.3, 155.8)	15 (100.0)	–	7 (77.8)	2.5 (0.5, 15.5)	8 (80.0)	1.7 (0.3, 10.6)
Wheeze	41 (35.3)	4.5 (2.6, 7.6)	5 (13.9)	3.9 (0.9, 17.4)	8 (30.8)	7.9 (2.1, 29.1)	7 (35.0)	2.5 (0.7, 8.7)	9 (60.0)	12.0 (2.8, 52.0)	7 (77.8)	11.3 (2.0, 64.3)	5 (50.0)	4.0 (0.8, 20.9)
Whooping	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Lethargy/altered mental status	19 (16.4)	0.8 (0.4, 1.4)	7 (19.4)	0.9 (0.3, 2.4)	5 (19.2)	0.9 (0.3, 2.7)	2 (10.0)	0.4 (0.1, 2.3)	4 (26.7)	1.3 (0.3, 5.1)	1 (11.1)	0.5 (0.1, 4.3)	0 (0.0)	–
Refusal to eat/vomiting	62 (53.4)	1.6 (1.0, 2.4)	15 (41.7)	1.6 (0.7, 3.8)	16 (61.5)	2.4 (1.0, 6.0)	14 (70.0)	1.7 (0.6, 5.4)	10 (66.7)	2.2 (0.6, 7.9)	3 (33.3)	0.6 (0.1, 2.6)	4 (40.0)	0.8 (0.2, 3.8)
Seizure	1 (0.9)	0.6 (0.1, 5.5)	0 (0.0)	–	1 (3.8)	3.0 (0.2, 49.9)	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Conjunctival injection	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Post-tussive emesis	16 (13.8)	1.3 (0.6, 2.7)	2 (5.6)	1.6 (0.1, 19.2)	2 (7.7)	0.7 (0.1, 4.0)	6 (30.0)	8.3 (0.9, 77.6)	4 (26.7)	1.1 (0.2, 5.1)	1 (11.1)	0.6 (0.1, 6.2)	1 (10.0)	1.3 (0.1, 24.3)
Signs														
Fever[b]	24 (20.7)	1.0 (0.6, 1.6)	3 (8.3)	0.4 (0.1, 1.7)	2 (7.7)	0.4 (0.1, 2.1)	4 (20.0)	0.4 (0.1, 1.5)	4 (26.7)	0.8 (0.2, 3.2)	6 (66.7)	8.9 (1.8, 44.3)	5 (50.0)	5.7 (1.0, 32.4)
Cough	9 (7.8)	2.1 (0.8, 5.2)	1 (2.7)	–	4 (15.4)	2.5 (0.6, 10.3)	2 (10.0)	4.3 (0.4, 51.0)	1 (6.7)	–	0 (0.0)	–	1 (10.0)	0.4 (0.0, 4.6)
Nasal discharge/coryza	40 (34.5)	1.9 (1.2, 3.1)	9 (25.0)	1.8 (0.7, 4.7)	9 (34.6)	2.1 (0.8, 5.7)	10 (50.0)	4.0 (1.2, 12.9)	5 (33.3)	1.0 (0.3, 3.6)	2 (22.2)	0.9 (0.2, 5.2)	5 (50.0)	3.0 (0.6, 14.9)
Nasal flaring	14 (12.1)	0.8 (0.4, 1.8)	0 (0.0)	–	4 (15.4)	1.4 (0.3, 7.3)	4 (20.0)	1.5 (0.3, 8.5)	2 (13.3)	1.0 (0.1, 7.3)	1 (11.1)	0.5 (0.0, 5.7)	3 (30.0)	1.3 (0.2, 9.9)
Chest in-drawing	53 (45.7)	2.5 (1.0, 6.4)	13 (36.1)	–	12 (46.2)	5.0 (0.5, 49.4)	11 (55.0)	1.7 (0.2, 12.0)	7 (46.7)	1.1 (0.1, 8.0)	5 (55.6)	2.0 (0.2, 22.9)	5 (50.0)	–
Grunting	60 (51.7)	2.9 (1.8, 4.5)	13 (36.1)	3.4 (1.3, 8.5)	13 (50.0)	3.4 (1.3, 8.7)	13 (65.0)	3.9 (1.2, 12.0)	9 (60.0)	2.7 (0.8, 9.1)	6 (66.7)	3.4 (0.7, 15.9)	6 (60.0)	1.8 (0.4, 8.6)
Crepitation	18 (15.5)	1.4 (0.6, 3.0)	7 (19.4)	1.7 (0.3, 9.8)	2 (7.7)	0.6 (0.1, 5.4)	5 (25.0)	5.6 (0.5, 57.0)	1 (6.7)	0.4 (0.0, 4.6)	1 (11.1)	0.5 (0.0, 5.6)	2 (20.0)	3.5 (0.2, 51.9)
Wheeze	39 (33.6)	1.7 (0.9, 3.4)	6 (16.7)	1.3 (0.2, 7.4)	8 (30.8)	2.7 (0.5, 13.9)	10 (50.0)	1.4 (0.3, 7.7)	6 (40.0)	5.3 (0.7, 39.5)	5 (55.6)	5.0 (0.5, 51.8)	4 (40.0)	0.7 (0.1, 6.9)
Tachypnea[c]	23 (19.8)	1.0 (0.6, 1.7)	4 (11.1)	1.5 (0.4, 5.5)	2 (7.7)	0.8 (0.2, 4.2)	8 (40.0)	1.1 (0.4, 3.3)	3 (20.0)	0.6 (0.1, 2.4)	2 (22.2)	0.7 (0.1, 3.9)	4 (40.0)	1.6 (0.3, 7.6)
Apnea	5 (4.3)	1.8 (0.6, 5.7)	3 (8.3)	1.3 (0.3, 5.7)	0 (0.0)	–	1 (5.0)	–	0 (0.0)	–	0 (0.0)	–	1 (10.0)	–
Cyanosis	4 (3.4)	1.7 (0.5, 6.0)	2 (5.6)	2.2 (0.3, 16.1)	0 (0.0)	–	0 (0.0)	–	2 (13.3)	2.6 (0.3, 20.5)	0 (0.0)	–	0 (0.0)	–
Otitis media/abnormal tympanic membrane	6 (5.2)	2.2 (0.7, 6.6)	0 (0.0)	–	2 (7.7)	–	1 (5.0)	2.1 (0.1, 34.6)	1 (6.7)	1.2 (0.1, 14.5)	1 (11.1)	2.3 (0.2, 28.0)	1 (10.0)	1.0 (0.1, 12.6)
Pharyngitis	2 (1.7)	2.5 (0.3, 17.8)	0 (0.0)	–	0 (0.0)	–	1 (5.0)	–	1 (6.7)	2.5 (0.1, 42.8)	0 (0.0)	–	0 (0.0)	–
Lethargy/altered mental status	6 (5.2)	0.7 (0.3, 1.8)	2 (5.6)	1.4 (0.2, 9.0)	2 (7.7)	1.0 (0.2, 5.1)	1 (5.0)	0.6 (0.1, 6.7)	0 (0.0)	–	0 (0.0)	–	1 (10.0)	2.1 (0.1, 37.7)
Dehydration	5 (4.3)	0.6 (0.2, 1.5)	0 (0.0)	–	2 (7.7)	0.8 (0.2, 4.2)	2 (10.0)	0.8 (0.1, 4.4)	1 (6.7)	0.6 (0.1, 5.6)	0 (0.0)	–	0 (0.0)	–
Conjunctival injection	3 (2.6)	0.9 (0.2, 3.5)	2 (5.6)	0.8 (0.2, 4.5)	0 (0.0)	–	1 (5.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Bradycardia	1 (0.9)	0.8 (0.1, 7.9)	1 (2.7)	0.7 (0.1, 6.9)	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Hypoxia[d]	11 (9.5)	0.6 (0.3, 1.3)	3 (8.3)	0.5 (0.1, 2.1)	3 (11.5)	1.3 (0.3, 5.3)	3 (15.0)	1.2 (0.3, 5.8)	0 (0.0)	–	0 (0.0)	–	2 (20.0)	1.0 (0.2, 6.7)

[a]Defined as history of temperature ≥38.0°C. [b]Defined as physical exam temperature ≥38.0°C. [c]Defined per WHO criteria. [d]Defined as oxygen saturation <90%.

Table 3. Age-adjusted clinical predictors of respiratory syncytial virus-associated hospitalization among infants aged <6 months of age.

Symptoms	OR	95% CI	P-value
Fever[a]	0.3	(0.2, 0.7)	0.0037
Cough	0.6	(0.2, 2.3)	0.5
Breathing difficulty	8.2	(3.5, 19.3)	<.0001
Cyanosis	6.8	(0.9, 53.1)	0.1
Apnea	–	–	–
Productive cough	1.1	(0.3, 4.5)	0.9
Nasal discharge/coryza	0.8	(0.3, 2.2)	0.7
Wheeze	0.9	(0.4, 2.0)	0.8
Whooping	–	–	–
Lethargy/altered mental status	1.5	(0.5, 4.4)	0.4
Refusal to eat/vomiting	2.1	(1.0, 4.3)	0.0433
Seizure	–	–	–
Conjunctival injection	–	–	–
Post-tussive emesis	1.8	(0.6, 5.6)	0.3
Signs			
Fever[b]	0.7	(0.3, 1.6)	0.4
Cough	–	–	–
Nasal discharge/coryza	0.4	(0.2, 0.9)	0.0174
Nasal flaring	–	–	–
Chest in-drawing	–	–	–
Grunting	6.8	(2.7, 17.2)	<.0001
Crepitation	1.6	(0.5, 5.6)	0.4
Wheeze	0.1	(0.0, 0.6)	0.016
Tachypnea[c]	0.7	(0.3, 1.6)	0.4
Apnea	–	–	–
Cyanosis	–	–	–
Otitis media/abnormal tympanic membrane	0.8	(0.2, 3.6)	0.8
Pharyngitis	0.9	(0.1, 9.8)	0.9
Lethargy/altered mental status	–	–	–
Dehydration	–	–	–
Conjunctival injection	–	–	–
Bradycardia	–	–	–
Hypoxia[d]	2.2	(0.5, 10.5)	0.3

[a]Defined as history of temperature ≥38.0°C. [b]Defined as physical exam temperature ≥38.0°C. [c]Defined per WHO criteria. [d]Defined as oxygen saturation <90%.

Table 4. Likelihood probabilities of sex, clinical features, and outcomes in five classes of 565 infants <6 months of age tested for RSV.

			Class 1 (15.3%)		Class 2 (28.7%)		Class 3 (25.9%)		Class 4 (16.3%)		Class 5 (13.8%)	
Variable	N	N (+)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)	Yes (%)	No (%)
RSV Status	565	161	2.8	97.2	32.2	67.8	50.8	49.2	6.2	93.8	33.7	66.3
Sex*	565		43.2	56.8	40.1	59.9	31.8	68.2	35.3	64.7	42.0	58.0
Cough	384	374	5.1	94.9	96.5	3.5	94.6	5.4	2.8	97.2	92.4	7.6
Apnea	249	92	0.0	100.0	0.0	100.0	5.7	94.3	54.0	46.0	43.6	56.4
Shortness of breath	372	262	0.0	100.0	19.6	80.4	100.0	0.0	59.4	40.6	37.2	62.8
Lethargy/altered mental status	404	95	18.7	81.3	3.2	96.8	12.6	87.4	33.7	66.3	30.9	69.1
Cyanosis	186	94	1.3	98.7	0.7	99.3	13.0	87.0	41.7	58.3	44.2	55.8
Fever	565	240	70.3	29.7	55.1	44.9	37.3	62.7	9.8	90.2	33.8	66.2
Nasal discharge/coryza	475	400	37.1	62.9	92.8	7.2	85.6	14.4	25.9	74.1	87.6	12.4
Wheeze	162	149	1.3	98.7	25.5	74.5	59.6	40.4	4.6	95.4	19.2	80.8
Conjunctival injection	367	15	4.4	95.6	2.5	97.5	2.7	97.3	1.7	98.3	2.1	97.9
Seizure	419	5	0.0	100.0	0.0	100.0	0.7	99.3	2.2	97.8	2.6	97.4
Refusal to eat/vomiting	509	236	45.3	54.7	31.4	68.6	57.6	42.4	19.4	80.6	56.1	43.9
Post-tussive emesis	150	46	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0
Nasal flaring	65	35	0.0	100.0	0.0	100.0	23.5	76.5	0.7	99.3	0.0	100.0
Chest in-drawing/accessory muscle use	136	126	0.0	100.0	0.0	100.0	79.6	20.4	10.1	89.9	0.0	100.0
Crepitation	64	44	0.0	100.0	6.8	93.2	16.3	83.7	4.3	95.7	6.6	93.4
Otitis media/abnormal tympanic membrane	430	18	0.0	100.0	4.3	95.7	5.7	94.3	0.0	100.0	3.4	96.6
Pharyngitis	468	7	1.2	98.8	1.6	98.4	2.3	97.7	0.0	100.0	0.0	100.0
Dehydration	521	27	4.3	95.7	0.0	100.0	6.1	93.9	9.7	90.3	6.8	93.2
Bradycardia	535	4	0.0	100.0	0.0	100.0	0.0	100.0	4.4	95.6	0.0	100.0
Hypoxia	565	59	18.4	81.6	3.4	96.6	12.3	87.7	14.0	86.0	8.6	91.4
Tachypnea	565	105	6.8	93.2	16.0	84.0	36.8	63.2	15.1	84.9	7.0	93.0
Hospitalization	565	401	82.1	17.9	23.8	76.2	87.8	12.2	98.3	1.7	92.7	7.3
Mortality	401	9	0.0	100.0	0.0	100.0	0.5	99.5	8.9	91.1	0.0	100.0

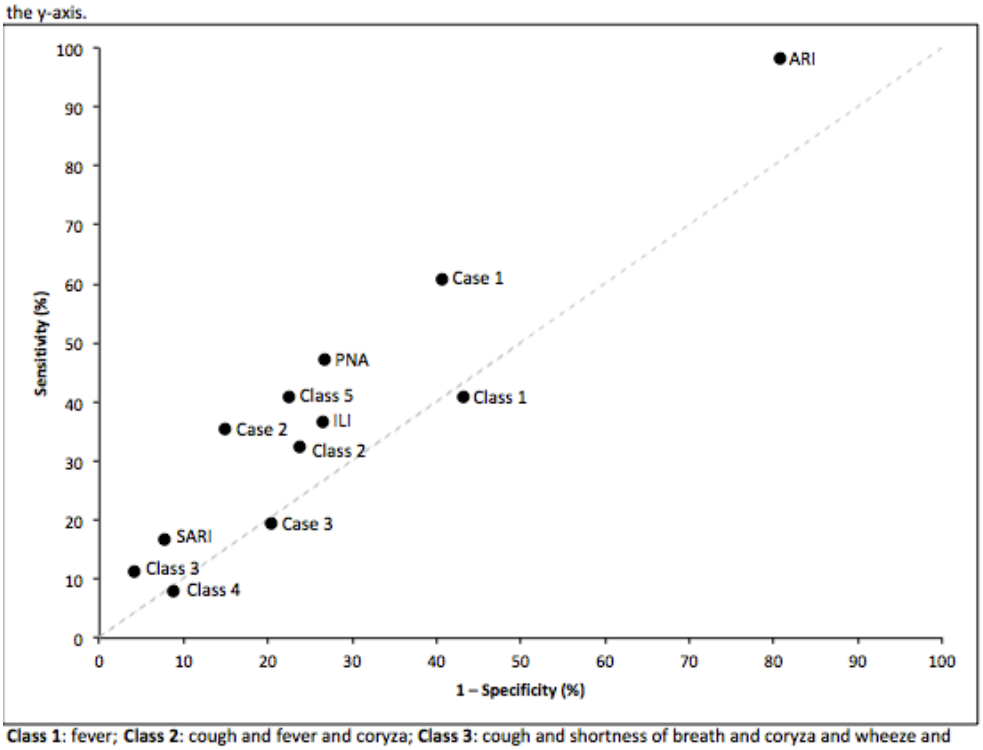
*Yes=female.

Table 5. Sensitivity, specificity, positive predictive value, and negative predictive value of RSV and respiratory syndromic surveillance case definitions. See Box 1 for descriptions of definitions.

	Sensitivity	95% CI	Specificity	95% CI	PPV[a]	95% CI	NPV[b]	95% CI
Case1	60.9	(53.3, 68.4)	59.4	(54.6, 64.2)	37.4	(31.6, 43.3)	79.2	(74.6, 83.8)
Case2	35.4	(28.0, 42.8)	85.2	(81.7, 88.6)	48.7	(39.7, 57.8)	76.8	(72.9, 80.7)
Case3	19.3	(13.2, 25.4)	79.7	(75.8, 83.6)	27.4	(19.2, 35.7)	71.2	(67.1, 75.4)
Class 1	41.0	(33.4, 48.6)	56.9	(52.1, 61.8)	27.5	(21.9, 33.2)	70.8	(65.8, 75.7)
Class 2	32.3	(25.1, 39.5)	76.2	(72.1, 80.4)	35.1	(27.4, 42.8)	73.9	(69.6, 78.1)
Class 3	11.2	(6.3, 16.1)	95.8	(93.8, 97.8)	51.4	(34.9, 68.0)	73.0	(69.2, 76.8)
Class 4	8.1	(3.9, 12.3)	91.3	(88.6, 94.1)	27.1	(14.5, 39.7)	71.4	(67.5, 75.3)
Class 5	41.0	(33.4, 48.6)	77.5	(73.4, 81.6)	42.0	(34.3, 49.8)	76.7	(72.6, 80.8)
ARI	98.1	(96.1, 100.0)	19.3	(15.5, 23.2)	32.5	(28.5, 36.8)	96.3	(92.2, 100.0)
ILI	36.7	(29.2, 44.1)	73.5	(69.2, 77.8)	35.5	(28.3, 42.8)	74.4	(70.2, 78.7)
SARI	16.8	(11.0, 22.5)	92.3	(89.7, 94.9)	46.6	(33.7, 59.4)	73.6	(69.7, 77.4)
PNA	47.2	(39.5, 54.9)	73.3	(69.0, 77.6)	41.3	(34.2, 48.4)	77.7	(73.5, 81.9)

[a]Positive predictive value. [b]Negative predictive value.

Figure 1. Receiver operator characteristic curve for RSV case definitions with 1-specificity on the x-axis and sensitivity on the y-axis.



Class 1: fever; **Class 2**: cough and fever and coryza; **Class 3**: cough and shortness of breath and coryza and wheeze and poor feeding and chest retractions; Class 4: apnea and shortness of breath; Class 5: cough and nasal discharge and poor feeding.

Case 1: wheeze or apnea or cyanosis; **Case 2**: chest in-drawing AND cough or tachypnea; **Case 3**: fever and any IMCI danger sign (lethargy or poor feeding confirmed by poor sucking/vomiting or seizure).

ARI (acute respiratory infection): cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection; **ILI** (influenza-like illness): acute respiratory illness with onset during last 7 days with temperature ≥38.0°C and cough; **PNA** (pneumonia): fast breathing or chest in-drawing; **SARI** (severe ARI): acute respiratory illness with onset during previous 7 days requiring overnight hospitalization that includes history of fever or measured fever of ≥38.0°C and cough and shortness of breath or difficulty breathing.

Box 1. Case definitions for respiratory syncytial virus developed through latent class analysis, a Pakistani syndromic surveillance study, and by the World Health Organization.

Latent class analysis

Class 1: fever

Class 2: cough and fever and coryza

Class 3: cough and shortness of breath and coryza and wheeze and poor feeding and chest in-drawing

Class 4: apnea and shortness of breath

Class 5: cough and nasal discharge and poor feeding

Pakistan syndromic surveillance study (unpublished data)

Case 1: wheeze or apnea or cyanosis

Case 2: chest in-drawing and: cough or tachypnea

Case 3: fever and any IMCI danger sign (lethargy or poor feeding confirmed by poor sucking/vomiting or seizure)

WHO standard definitions (WHO, 2011)

Acute respiratory infection (ARI): cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection

Influenza-like illness (ILI): acute respiratory illness with onset during last 7 days with temperature ≥38.0°C and cough

Severe acute respiratory infection (SARI): acute respiratory illness with onset during previous 7 days requiring overnight hospitalization that includes history of fever or measured fever of ≥38.0°C and cough and shortness of breath or difficulty breathing

Pneumonia (PNA): fast breathing or chest in-drawing

Supplemental Table 1. Coinfections among RSV-positive infants <6 months of age in Atlanta, Georgia, USA from January 2010–December 2015.

	RSV-positive n=161 (28.5%)		RSV-negative n=404 (71.5%)		P-value
	n	%	n	%	
Bordatella pertussis	0	0	3	0.7	0.8
Bordatella parapertussis	0	0	1	0.2	0.8
Influenza	2	1.2	9	2.2	0.3
Parainfluenza	1	0.6	26	6.4	0.1
Rhinovirus	11	6.8	75	18.6	0.1
Coronavirus	3	1.9	7	1.7	0.8
Human metapneumovirus	2	1.2	14	3.5	0.5
Adenovirus	1	0.6	7	1.7	0.3
Mycoplasma pneumoniae	2	1.2	0	0	0.7
Chlamydophila pneumoniae	0	0	0	0	0.6

Supplemental Table 2. Age–specific clinical signs and symptoms among all infants <6 months of age who were tested for respiratory syncytial virus infection.

	Overall		Age groups											
			1 month		2 months		3 months		4 months		5 months		6 months	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Symptoms														
Fever[a]	191	33.8	32	25.2	57	37.0	38	37.3	33	39.3	21	32.3	10	30.3
Cough	373	66.0	66	52.0	95	61.7	75	73.5	62	73.8	49	75.4	26	78.8
Breathing difficulty	219	38.8	47	37.0	51	33.1	39	38.2	33	39.3	30	46.2	19	57.6
Cyanosis	89	15.8	24	18.9	25	16.2	10	9.8	14	16.7	13	20.0	3	9.1
Apnea	87	15.4	22	17.3	25	16.2	13	12.7	11	13.1	13	20.0	3	9.1
Productive cough	32	5.7	4	3.1	6	3.9	11	10.8	3	3.6	6	9.2	2	6.1
Nasal discharge/coryza	381	67.4	72	56.7	102	66.2	73	71.6	63	75.0	46	70.8	25	75.8
Wheeze	106	18.8	11	8.7	14	9.1	24	23.5	22	26.2	23	35.4	12	36.4
Whooping	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lethargy/altered mental status	86	15.2	23	18.1	25	16.2	13	12.7	13	15.5	10	15.4	2	6.1
Refusal to eat/vomiting	236	41.8	45	35.4	65	42.2	48	47.1	35	41.7	27	41.5	16	48.5
Seizure	5	0.9	1	0.8	2	1.3	1	1.0	1	1.2	0	0.0	0	0.0
Conjunctival injection	5	0.9	1	0.8	1	0.6	0	0.0	3	3.6	0	0.0	0	0.0
Post-tussive emesis	46	8.1	4	3.1	11	7.1	12	11.8	12	14.3	5	7.7	2	6.1
Signs														
Fever[b]	128	22.7	16	12.6	30	19.5	35	34.3	19	22.6	20	30.8	8	24.2
Cough	28	5.0	1	0.8	12	7.8	6	5.9	3	3.6	1	1.5	5	15.2
Nasal discharge/coryza	184	32.6	26	20.5	50	32.5	41	40.2	33	39.3	24	36.9	10	30.3
Nasal flaring	35	6.2	3	2.4	8	5.2	7	6.9	5	6.0	5	7.7	7	21.2
Chest in-drawing	126	22.3	22	17.3	26	16.9	24	23.5	19	22.6	18	27.7	17	51.5
Grunting	155	27.4	27	21.3	33	21.4	30	29.4	24	28.6	23	35.4	18	54.5
Crepitation	44	7.8	11	8.7	6	3.9	8	7.8	7	8.3	9	13.8	3	9.1
Wheeze	112	19.8	12	9.4	17	11.0	30	29.4	22	26.2	18	27.7	13	39.4
Tachypnea[c]	105	18.6	13	10.2	13	8.4	30	29.4	23	27.4	16	24.6	10	30.3
Apnea	12	2.1	8	6.3	2	1.3	1	1.0	0	0.0	0	0.0	1	3.0
Cyanosis	10	1.8	4	3.1	1	0.6	0	0.0	4	4.8	0	0.0	1	3.0
Otitis media/abnormal tympanic membrane	18	3.2	0	0.0	2	1.3	6	5.9	3	3.6	4	6.2	3	9.1
Pharyngitis	7	1.2	0	0.0	1	0.6	1	1.0	4	4.8	0	0.0	1	3.0
Lethargy/altered mental status	27	4.8	5	3.9	9	5.8	4	3.9	4	4.8	3	4.6	2	6.1
Dehydration	27	4.8	2	1.6	9	5.8	8	7.8	5	6.0	1	1.5	2	6.1
Conjunctival injection	15	2.7	7	5.5	2	1.3	1	1.0	5	6.0	0	0.0	0	0.0
Bradycardia	4	0.7	4	3.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Hypoxia[d]	59	10.4	15	11.8	14	9.1	11	10.8	9	10.7	4	6.2	6	18.2

[a]Defined as history of temperature ≥38.0°C. [b]Defined as physical exam temperature ≥38.0°C. [c]Defined per WHO criteria. [d]Defined as oxygen saturation <90%.

Supplemental Table 3. Age–specific clinical signs and symptoms among all infants <6 months of age tested for RSV.

	Age groups													
	Overall		1 month		2 months		3 months		4 months		5 months		6 months	
	RSV+ (n=161)	OR (95% CI)	RSV+ (n=41)	OR (95% CI)	RSV+ (n=42)	OR (95% CI)	RSV+ (n=31)	OR (95% CI)	RSV+ (n=22)	OR (95% CI)	RSV+ (n=14)	OR (95% CI)	RSV+ (n=11)	OR (95% CI)
Symptoms														
Fever[a]	50 (31.1)	0.8 (0.6, 1.2)	12 (29.3)	1.4 (0.6, 3.2)	9 (21.4)	0.4 (0.2, 0.8)	10 (32.3)	0.7 (0.3, 1.8)	7 (31.8)	0.6 (0.2, 1.8)	7 (50.0)	2.6 (0.8, 8.9)	5 (45.5)	2.8 (0.6, 13.3)
Cough	145 (90.1)	7.0 (4.0, 12.2)	34 (82.9)	8.2 (3.3, 20.6)	36 (85.7)	5.4 (2.1, 13.8)	30 (96.7)	7.3 (2.2, 134.6	20 (90.9)	4.8 (1.0, 22.4)	14 (100.0)	–	11 (100.0)	–
Breathing difficulty	81 (50.3)	2.0 (1.3, 2.8)	20 (48.8)	2.1 (1.0, 4.5)	20 (47.6)	2.4 (1.1, 4.9)	17 (54.8)	2.7 (1.1, 6.4)	10 (45.5)	1.4 (0.5, 3.8)	7 (50.0)	1.2 (0.4, 4.0)	7 (63.6)	1.5 (0.3, 6.5)
Cyanosis	17 (10.6)	0.5 (0.3, 1.0)	8 (19.5)	1.1 (0.4, 2.7)	4 (9.5)	0.5 (0.1, 1.4)	0 (0.0)	–	3 (13.6)	0.7 (0.2, 2.9)	1 (7.1)	0.3 (0.0, 2.1)	1 (9.1)	1.0 (0.1, 12.4)
Apnea	16 (9.9)	0.5 (0.3, 0.9)	5 (12.2)	0.6 (0.2, 1.7)	7 (16.7)	1.0 (0.4, 2.7)	1 (3.2)	0.2 (0.0, 1.3)	2 (9.1)	0.6 (0.1, 3.0)	0 (0.0)	–	1 (9.1)	1.0 (0.1, 12.4)
Productive cough	11 (6.8)	0.8 (0.4, 1.7)	1 (2.4)	0.3 (0.0, 3.0)	1 (2.4)	0.3 (0.0, 2.8)	5 (16.1)	1.3 (0.4, 4.7)	2 (9.1)	4.6 (0.4, 53.5)	0 (0.0)	–	2 (18.2)	–
Nasal discharge/coryza	136 (84.5)	3.5 (2.2, 5.7)	32 (78.0)	4.1 (1.7, 9.6)	34 (81.0)	2.8 (1.2, 6.5)	29 (93.5)	8.9 (2.0, 40.3)	20 (90.9)	4.4 (0.9, 20.8)	12 (85.7)	3.0 (0.6, 14.9)	9 (81.8)	1.7 (0.3, 10.2)
Wheeze	59 (36.6)	4.4 (2.8, 6.8)	6 (14.6)	2.8 (0.8, 9.7)	9 (21.4)	5.8 (1.8, 18.6)	15 (48.4)	6.5 (2.4, 17.4)	13 (59.1)	8.5 (2.8, 25.7)	10 (71.4)	7.3 (2.0, 27.3)	6 (54.5)	3.2 (0.7, 14.5)
Whooping	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Lethargy/altered mental status	24 (14.9)	1.0 (0.6, 1.6)	7 (17.1)	0.9 (0.3, 2.4)	7 (16.7)	1.0 (0.4, 2.7)	3 (9.7)	0.7 (0.2, 2.6)	5 (22.7)	2.0 (0.6, 6.9)	1 (7.1)	0.4 (0.0, 3.1)	1 (9.1)	2.1 (0.1, 37.1)
Refusal to eat/vomiting	78 (48.4)	1.5 (1.0, 2.1)	19 (46.3)	2.0 (0.9, 4.3)	20 (47.6)	1.4 (0.7, 2.8)	16 (51.6)	1.3 (0.6, 3.0)	13 (59.1)	2.6 (1.0, 7.1)	5 (35.7)	0.7 (0.2, 2.5)	5 (45.5)	0.8 (0.2, 3.6)
Seizure	1 (0.6)	0.6 (0.1, 5.6)	0 (0.0)	–	1 (2.4)	2.7 (0.2, 44.3)	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Conjunctival injection	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Post-tussive emesis	20 (12.4)	1.2 (0.7, 2.3)	2 (4.9)	0.9 (0.1, 7.1)	5 (11.9)	1.4 (0.4, 5.1)	7 (22.6)	2.4 (0.7, 8.6)	4 (18.2)	1.1 (0.3, 4.1)	1 (7.1)	0.6 (0.1, 5.9)	1 (9.1)	1.4 (0.1, 25.1)
Signs														
Fever[b]	37 (23.0)	1.0 (0.7, 1.6)	3 (7.3)	0.4 (0.1, 1.7)	7 (16.7)	0.8 (0.3, 2.0)	9 (29.0)	0.7 (0.3, 1.8)	4 (18.2)	0.7 (0.2, 2.4)	9 (64.3)	6.5 (1.8, 23.6)	5 (45.5)	5.3 (1.0, 28.9)
Cough	9 (5.6)	1.2 (0.5, 2.7)	1 (2.4)	–	4 (9.5)	1.4 (0.4, 4.8)	2 (6.4)	1.2 (0.2, 6.7)	1 (4.5)	1.4 (0.1, 16.6)	0 (0.0)	–	1 (9.1)	0.5 (0.0, 4.6)
Nasal discharge/coryza	65 (40.4)	1.6 (1.1, 2.4)	11 (26.8)	1.7 (0.7. 4.2)	20 (47.6)	2.5 (1.2, 5.2)	17 (54.8)	2.4 (1.0, 5.6)	7 (31.8)	0.6 (0.2, 1.8)	5 (35.7)	0.9 (0.3, 3.2)	5 (45.5)	2.8 (0.6, 13.3)
Nasal flaring	14 (8.7)	0.8 (0.4, 1.8)	0 (0.0)	–	4 (9.5)	1.5 (0.3, 7.4)	4 (12.9)	1.7 (0.3, 9.6)	2 (9.1)	0.7 (0.1, 5.5)	1 (7.1)	0.5 (0.0, 5.5)	3 (27.3)	1.3 (0.2, 9.1)
Chest in-drawing	60 (37.3)	2.9 (1.1, 7.2)	14 (34.1)	–	13 (31.0)	6.0 (0.6, 57.0)	12 (38.7)	2.0 (0.3, 13.1)	9 (40.9)	1.4 (0.2, 10.0)	6 (42.9)	2.0 (0.2, 22.1)	6 (54.5)	–
Grunting	67 (41.6)	2.6 (1.7, 3.8)	14 (34.1)	2.9 (1.2, 7.0)	14 (33.3)	2.4 (1.1, 5.5)	14 (45.2)	2.8 (1.2, 7.0)	11 (50.0)	3.8 (1.3, 10.6)	7 (50.0)	2.2 (0.7, 7.3)	7 (63.6)	1.8 (0.4, 7.7)
Crepitation	22 (13.7)	1.3 (0.6, 2.5)	8 (19.5)	3.0 (0.6, 16.2)	4 (9.5)	1.5 (0.2, 9.7)	5 (16.1)	1.9 (0.4, 9.0)	1 (4.5)	0.2 (0.0, 2.0)	2 (14.3)	0.8 (0.1, 4.8)	2 (18.2)	3.6 (0.3, 50.3)
Wheeze	60 (37.3)	2.2 (1.2, 4.1)	7 (17.1)	1.1 (0.2, 5.0)	12 (28.6)	2.7 (0.7, 10.6)	18 (58.1)	3.8 (1.0, 14.8)	11 (50.0)	5.0 (0.9, 28.3)	7 (50.0)	7.6 (0.8, 72.4)	5 (45.5)	0.6 (0.1, 6.0)
Tachypnea[c]	35 (21.7)	1.3 (0.8, 2.1)	5 (12.2)	1.4 (0.4, 4.4)	4 (9.5)	1.2 (0.4, 4.1)	11 (35.5)	1.5 (0.6, 3.7)	7 (31.8)	1.3 (0.5, 3.9)	4 (28.6)	1.3 (0.3, 4.9)	4 (36.4)	1.5 (0.3, 7.1)
Apnea	5 (3.1)	1.8 (0.6, 5.8)	3 (7.3)	1.3 (0.3, 5.6)	0 (0.0)	–	1 (3.2)	–	0 (0.0)	–	0 (0.0)	–	1 (9.1)	–
Cyanosis	4 (2.5)	1.7 (0.5, 6.1)	2 (4.9)	2.2 (0.3, 15.9)	0 (0.0)	–	0 (0.0)	–	2 (9.1)	3.0 (0.4, 22.7)	0 (0.0)	–	0 (0.0)	–
Otitis media/abnormal tympanic membrane	9 (5.6)	2.6 (1.0, 6.7)	0 (0.0)	–	2 (4.8)	–	3 (9.7)	2.4 (0.5, 12.8)	1 (4.5)	1.4 (0.1, 16.6)	2 (14.3)	4.1 (0.5, 32.0)	1 (9.1)	1.0 (0.1, 12.4)
Pharyngitis	3 (1.9)	1.9 (0.4, 8.6)	0 (0.0)	–	0 (0.0)	–	1 (3.2)	–	2 (9.1)	3.0 (0.4, 22.7)	0 (0.0)	–	0 (0.0)	–
Lethargy/altered mental status	6 (3.7)	0.7 (0.3, 1.8)	2 (4.9)	1.4 (0.2, 8.8)	2 (4.8)	0.8 (0.1, 3.8)	1 (3.2)	0.8 (0.1, 7.6)	0 (0.0)	–	0 (0.0)	–	1 (9.1)	2.1 (0.1, 37.1)
Dehydration	5 (3.1)	0.6 (0.2, 1.5)	0 (0.0)	–	2 (4.8)	0.8 (0.1, 3.8)	2 (6.4)	0.7 (0.1, 3.9)	1 (4.5)	0.7 (0.1, 6.5)	0 (0.0)	–	0 (0.0)	–
Conjunctival injection	3 (1.9)	0.6 (0.2, 2.2)	2 (4.9)	0.8 (0.2, 4.5)	0 (0.0)	–	1 (3.2)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Bradycardia	1 (0.6)	0.8 (0.1, 8.1)	1 (2.4)	0.7 (0.1, 6.9)	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–	0 (0.0)	–
Hypoxia[d]	13 (8.1)	0.7 (0.4, 1.3)	4 (9.8)	0.7 (0.2, 2.5)	3 (7.1)	0.7 (0.2, 2.7)	4 (12.9)	1.4 (0.4, 5.0)	0 (0.0)	–	0 (0.0)	–	2 (18.2)	1.0 (0.2, 6.5)

[a]Defined as history of temperature ≥38.0°C. [b]Defined as physical exam temperature ≥38.0°C. [c]Defined per WHO criteria. [d]Defined as oxygen saturation <90%.

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CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

Respiratory syncytial virus has a profound impact on pediatric morbidity, mortality, and their associated healthcare costs worldwide. Development and clinical trials of potential RSV vaccines are underway. This will require sensitive and specific case definitions to accurately gauge their efficacy and impact in large-scale trials before vaccinations become implemented as public health policy. Such case definitions, however, must be carefully selected or constructed for various potential vaccine target populations and be globally representative of said populations, as this would maximize the public health impact of immunization. To this end, the findings and challenges we faced through our research support the following recommendations:

1. **Evaluate potential RSV case definitions in both, hospitalized and non-hospitalized, pediatric populations.** Most studies that have examined case definitions have exclusively sampled infants or children that were hospitalized. However, many patients may present to a healthcare facility with ARI symptoms that may not require hospitalization. Such patients may be infected with RSV but would not be diagnosed, consequently yielding a falsely low RSV disease burden in epidemiological studies. Additionally, restricting the sample to only hospitalized patients may undermine the sensitivities, specificities, and predictive values of tested case definitions, as they would not be representative of the larger population that includes both, hospitalized and non-hospitalized, infants and children.

2. **Evaluate potential RSV case definitions in high-income settings.** Most published literature examining case definitions in pediatric populations have done so in low-medium income countries, such as India and Kenya. This severely limits the generalizability of RSV epidemiological data, which are instrumental in informing development and testing of potential case definitions. We recommend use of prospective cohort studies in high-income countries using standardized history and physical exam coding to help strengthen the generalizability of RSV epidemiological data and to help limit many of the challenges we faced in our retrospective study, such as misclassficiation bias in sign and symptom variables.

3. **Evaluate novel but also existing standard and alternative case definitions tested in previous research.** Through our research, we found many investigations testing a range of potential case definitions, including standard definitions or clinical syndromes used by the WHO, alternate definitions constructed using logistic regression, and even single sign or symptom variables, such as presence of cough. We suggest a thorough review of the literature by future investigators so they may assess not only their own definitions, but also those tested by their colleagues. This would aid in providing a more robust assessment of the sensitivities, specificities, and predicitive values of case definitions and informing their reliability and generaliability to various pediatric populations in multiple clinical and environmental settings.