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ORIGINAL ARTICLE

Performance of Surveillance Case Definitions in Detecting Respiratory Syncytial Virus Infection Among Young Children Hospitalized With Severe Respiratory Illness—South Africa, 2009–2014

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Background. Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infection (ALRTI) in young children, but data on surveillance case definition performance in estimating burdens have been limited.

Methods. We enrolled children aged <5 years hospitalized for ALRTI (or neonatal sepsis in young infants) through active prospective surveillance at 5 sentinel hospitals in South Africa and collected nasopharyngeal aspirates from them for RSV molecular diagnostic testing between 2009 and 2014. Clinical data were used to characterize RSV disease and retrospectively evaluate the performance of respiratory illness case definitions (including the World Health Organization definition for severe acute respiratory infection [SARI]) in identifying hospitalized children with laboratory-confirmed RSV according to age group (<3, 3–5, 6–11, 12–23, and 24–59 months).

Results. Of 9969 hospitalized children, 2723 (27%) tested positive for RSV. Signs and symptoms in RSV-positive children varied according to age; fever was less likely to occur in children aged <3 months (57%; odds ratio [OR], 0.8 [95% CI, 0.7–0.9]) but more likely in those aged ≥12 months (82%; OR, 1.7–1.9) than RSV-negative children. The sensitivity (range, 55%–81%) and specificity (range, 27%–54%) of the SARI case definition to identify hospitalized RSV-positive children varied according to age; the lowest sensitivity was for infants aged <6 months. Using SARI as the case definition would have missed 36% of RSV-positive children aged <5 years and 49% of those aged <3 months; removing the fever requirement from the definition recovered most missed cases.

Conclusion. Including fever in the SARI case definition lowers the sensitivity for RSV case detection among young children hospitalized with an ALRTI and likely underestimates its burden.

Keywords. case definitions; respiratory syncytial virus; respiratory tract infections; South Africa; surveillance.

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory tract infection (ALRTI) and associated death among young children worldwide [1–5]; the highest rates are seen in infants aged <1 year and in developing countries [1, 2, 6]. Better characterization of RSV disease burden in a variety of settings remains a priority, especially as several vaccines and immunoprophylaxis and antiviral agents for RSV are currently in development [7–9].

One of the challenges in assessing RSV burden has been the lack of a uniform case definition for identifying RSV disease in existing surveillance systems, some of which were designed for influenza virus [10, 11]. Clinical presentations of RSV disease can vary according to age and differ from that of influenza [12, 13]; for example, RSV infection can present without fever, which is often a central feature in commonly used case definitions for influenza surveillance. As a result, case definitions designed for influenza may be less sensitive for RSV and have the potential to underestimate RSV burden.

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In this study, we aimed to assess the performance of various case definitions in detecting severe RSV disease among hospitalized children <5 years of age in South Africa.

METHODS

Study Design and Population

Data collected from active prospective hospital-based surveillance for severe acute respiratory illness at 5 sentinel public hospitals in South Africa from February 2009 through December 2014 were analyzed retrospectively to assess the performance of various case definitions in detecting laboratory-confirmed RSV disease [14]. The surveillance hospitals, previously described, were located in rural and urban areas and in temperate and subtropical climates across 4 provinces of South Africa, where RSV is detected year-round; the seasonal peak occurs during the late autumn and early winter months (February/March through May) [11, 14–16]. Case-patients were defined as those aged <5 years and hospitalized within 7 days of illness onset who met age-specific inclusion criteria based on physician-determined admission diagnoses. Children aged 2 days to <3 months were eligible if they were hospitalized with a diagnosis of neonatal sepsis or ALRTI regardless of their signs and symptoms, and children aged 3 months to <5 years were eligible if hospitalized with a physician-diagnosed ALRTI (including bronchiolitis, pneumonia, bronchitis, and pleural effusion). Patients who were transferred from another hospital directly to the intensive care unit (ICU) were excluded from enrollment, as were newborns who had never been discharged after delivery.

After obtaining consent, surveillance staff interviewed the patients' parents, performed medical chart reviews using a standardized case investigation form to collect demographic and clinical information, and collected nasopharyngeal aspirates from each patient.

Laboratory Testing

Nasopharyngeal aspirates were transported on ice to the National Institute for Communicable Diseases in Johannesburg, South Africa, within 72 hours of collection and tested by multiplex real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for respiratory viruses, including RSV; the assay was established as a 2-step rRT-PCR with 5 separate reactions and optimized and validated using external quality-control panels (Quality Control for Molecular Diagnostics, Glasgow, Scotland) [15, 17]. Human immunodeficiency virus (HIV) status was determined on the basis of results of testing performed through standard of care or through anonymized testing of a dried blood spot obtained during surveillance by HIV PCR for children aged <18 months and by enzyme-linked immunosorbent assay for children aged ≥18 months [14, 16, 18–20].

Data Analyses

Retrospective analyses were performed on data from patients enrolled at any of the 5 surveillance hospitals (Chris Hani Baragwanath Hospital [February 2009 to December 2014], Mapulaneng Hospital [January 2010 to December 2014], Matikwana Hospital [January 2010 to December 2014], Edendale Hospital [January 2010 to December 2014], and Klerksdorp Hospital [January 2011 to December 2014]), with analyses restricted to years in which full seasons of data were captured. Only patients tested for RSV were included in the analyses.

Demographic and clinical data were assessed for any association with laboratory-detected RSV, and we adjusted for age and sex when appropriate. Clinical case definitions based on previously established definitions for respiratory illnesses (Table 1) were tested for their performance in detecting RSV [21, 22]. These definitions included World Health Organization (WHO) definitions for pneumonia and severe pneumonia [22] and the WHO severe acute respiratory infection (SARI) definition [21]. Two of the definitions tested were derivations of that for SARI, in which the fever requirement was removed, which yielded case definitions that consisted of patients hospitalized with acute onset of cough and patients hospitalized with acute onset of cough and difficulty breathing (Table 1). Case definition performance characteristics (ie, sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were evaluated according to age group (<3, 3–5, 6–11, 12–23, and 24–59 months) and HIV status. Receiver-operating-characteristic (ROC) curves were generated to assess sensitivity

Table 1. Respiratory Illness Surveillance Case Definitions Tested—Severe Acute Respiratory Illness Sentinel Surveillance, South Africa, 2009–2014

Case Definition	Criteria
SARI[a]	Acute respiratory infection with history of fever or measured fever of ≥38 C° and cough with onset within the last 10 days and requires hospitalization
Acute cough	Acute respiratory infection with cough with onset within the last 10 days and requires hospitalization
Acute cough and difficulty breathing	Acute respiratory infection with cough and difficulty breathing with onset within the last 10 days and requires hospitalization
Pneumonia[b]	Child <5 years old with cough and/or difficult breathing and fast breathing and/or chest-indrawing
Severe pneumonia[b]	Child <5 years old with cough and/or difficult breathing and any 1 of the following danger signs: is not able to drink, has persistent vomiting, has convulsions, is lethargic or unconscious, has stridor (in a calm child), or has severe malnutrition

Abbreviation: SARI, severe acute respiratory infection.
[a]Definition from reference [21].
[b]Based on definitions from reference [22].

and specificity for each case definition stratified according to age. Last, a subset of case definitions were applied to all RSV-positive patients to determine the proportion of those who would have been identified or missed with use of a given case definition.

Frequencies, odds ratios, corresponding 95% confidence intervals (CIs), and *P* values were calculated for all demographic and clinical variables. Two-sided statistical tests were considered significant at a *P* value of <.05. Data analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Demographics and Clinical Characteristics

Between February 2009 and December 2014, 9969 hospitalized children aged <5 years were enrolled and tested for RSV at the 5 surveillance hospitals; 64.1% were aged <1 year, and 25.9% were aged <3 months (Table 2). An underlying cardiac or pulmonary condition was reported for <2% of the patients, and a history of prematurity was reported for 2.7% of patients. Of the 7179 participating patients with a documented HIV status, 793 (11.0%) were HIV positive.

During hospitalization, 37.0% of the patients received oxygen therapy, and 93.0% received antibiotic treatment. Those with a severe hospital course and outcome included 1.3% of patients who had a documented admission to an ICU and 1.0% who required mechanical ventilation; 155 (1.6%) deaths were recorded.

Among all patients, 27.3% tested positive for RSV. Younger patients had a higher likelihood of RSV detection than those in the oldest 24- to 59-month age group; the highest adjusted odds ratio (aOR) was found in the youngest patients (those <3 months of age) (aOR, 2.6 [95% CI, 2.2–3.0]). History of prematurity was reported less commonly in RSV-positive patients (aOR, 0.4 [95% CI, 0.3–0.6]), as was HIV infection (aOR, 0.4 [95% CI, 0.3–0.5]). RSV detection was more likely in patients admitted for bronchiolitis (aOR, 1.6 [95% CI, 1.4–1.8]) but less likely in those diagnosed with neonatal sepsis (aOR, 0.3 [95% CI, 0.2–0.4]). During their hospital course, RSV-positive patients had higher odds of requiring oxygen therapy (aOR, 1.2 [95% CI, 1.1–1.3]) but lower odds of ICU admission (aOR, 0.6 [95% CI, 0.4–0.9), requiring mechanical ventilation (aOR, 0.5 [95% CI, 0.3–0.8), or death (aOR, 0.3 [95% CI, 0.2–0.5]) than did RSV-negative patients. Among RSV-positive patients, rhinovirus/enterovirus (36.4%) and adenovirus (21.3%) were the most frequently occurring viral codetections.

Clinical Predictors of RSV Infection

Among the youngest infants (aged <3 months), several respiratory signs and symptoms were associated with RSV infection (Table 3); cough had the strongest association (OR, 15.5 [95% CI, 9.8–24.4]). Difficulty feeding (ie, unable to drink or breastfeed) was also more likely in RSV-positive than in RSV-negative patients aged <3 months (OR, 1.3 [95% CI, 1.1–1.7]). However, in this youngest age group, fever according to any definition was less likely to occur in RSV-positive children than in RSV-negative children, including history of fever (OR, 0.8 [95% CI, 0.7–0.9]), measured fever of ≥38°C (OR, 0.6 [95% CI, 0.5–0.7]), and any fever (history or measured) (OR, 0.8 [95% CI, 0.7–0.9]).

Fewer significant associations with clinical signs and symptoms were observed among older infants (3–11 months of age). Cough was more likely to be observed among RSV-positive patients in the 3- to 5-month and 6- to 11-month age groups (ORs, 6.8 [95% CI, 2.5–19.0] and 5.0 [95% CI, 1.8–13.9], respectively) than in RSV-negative patients. Hypoxia also was associated with RSV infection in patients in the 6- to 11-month age group (OR, 1.9 [95% CI, 1.1–3.2]). Any fever (history or measured) was not associated with RSV infection in either the 3- to 5-month or 6- to 11-month age groups (ORs, 1.2 [95% CI, 1.0–1.5]) and 1.1 [95% CI, 0.9–1.4], respectively), although among the 3- to 5-month-old patients, measured fever was less likely to be observed with RSV detection (OR, 0.8 [95% CI, 0.6–1.0]).

In contrast with infants, fever was associated with RSV detection in children aged ≥12 months; any fever (history or measured) had increased odds of occurring with RSV infection in the 12- to 23-month (OR, 1.9 [95% CI, 1.4–2.5]) and 24- to 59-month (OR, 1.7 [95% CI, 1.2–2.4]) age groups. Cough also was significantly associated with RSV detection in both the 12- to 23-month (OR, 2.7 [95% CI, 1.2–6.3]) and 24- to 59-month (OR, 3.5 [95% CI, 1.3–9.7]) age groups. To a lesser degree, difficulty breathing (OR, 1.4 [95% CI, 1.01–1.8]) and retractions (OR, 1.4 [95% CI, 1.1–1.9]) were associated with RSV infection in children 24 to 59 months of age, whereas wheezing (OR, 0.4 [95% CI, 0.2–0.9]) was less likely to be observed in this oldest age group. Last, lethargy was less likely to be observed in RSV-positive patients aged ≥12 months (ORs, 0.7–0.8) than in RSV-negative children.

Performance of Case Definitions

The WHO SARI definition had a sensitivity of 55% to 81% across age groups in identifying RSV-positive patients among those aged <5 years (Table 4, Figure 1). The sensitivity of the SARI definition was lowest in the youngest infants aged <3 months (55% [95% CI, 52%–59%]) and 3 to 5 months (68% [95% CI, 64%–72%]). Specificity for the SARI definition ranged 27% to 54% across age groups, and the lowest values were found in those aged ≥6 months.

The case definition of acute cough without the fever requirement yielded higher sensitivity (range, 98%–99%) across all age groups, albeit with poorer specificity (range, 3%–27%). Adding the symptom of difficulty breathing to the acute cough definition resulted in lower sensitivities (range, 66%–80%) and higher specificities (range, 27%–45%) across all age groups. Only in those aged <3 months did this definition have a substantially higher sensitivity than that of the SARI definition.

The WHO case definition for pneumonia had a sensitivity range of 56% to 74% and a specificity range of 33% to 50%

Table 2. Demographic and Clinical Characteristics of Patients According to RSV Detection—Severe Acute Respiratory Illness Sentinel Surveillance, South Africa, 2009–2014

Characteristic	No. of Patients			OR[a] (95% CI)	aOR[c] (95% CI)
	Total Tested (N = 9969) (n [%])	RSV-Positive (N = 2723) (n/total N [%])	RSV-Negative (N = 7246) (n/total N[%])		
Age (mo)					
<3	2586 (25.9)	878/2723 (32.2)	1708/7246 (23.6)	2.6 (2.2–3.0)[b]	2.6 (2.2–3.0)[b]
3–5	1752 (17.6)	582/2723 (21.4)	1170/7246 (16.2)	2.5 (2.1–2.9)[b]	2.5 (2.1–2.9)[b]
6–11	2057 (20.6)	560/2723 (20.6)	1497/7246 (20.7)	1.9 (1.6–2.2)[b]	1.9 (1.6–2.2)[b]
12–23	1995 (20.0)	439/2723 (16.1)	1556/7246 (21.5)	1.4 (1.2–1.7)[b]	1.4 (1.2–1.7)[b]
24–59	1579 (15.8)	264/2723 (9.7)	1315/7246 (18.2)	Ref	Ref
Sex (male vs female)	5761 (57.8)	1535/2723 (56.4)	4226/7245 (58.3)	0.9 (0.8–1.0)	0.9 (0.8–1.0)
Underlying medical condition					
Asthma or reactive airways disease	94 (0.9)	27/2721 (1.0)	67/7237 (0.9)	1.1 (0.7–1.7)	1.6 (1.0–2.5)
Other chronic lung disease	9 (0.1)	2/2721 (0.1)	7/7236 (0.1)	0.8 (0.2–3.7)	1.1 (0.2–5.0)
History of prematurity	271 (2.7)	46/2721 (1.7)	225/7237 (3.1)	0.5 (0.4–0.7)[b]	0.4 (0.3–0.6)[b]
Valvular heart disease	20 (0.2)	2/2721 (0.1)	18/7237 (0.3)	0.3 (0.1–1.3)	0.3 (0.7–1.4)
Heart failure	20 (0.2)	5/2721 (0.2)	15/7237 (0.2)	0.9 (0.3–2.4)	0.8 (0.3–2.3)
Immunosuppression[d]	12 (0.1)	2/2721 (0.1)	10/7237 (0.1)	0.5 (0.1–2.4)	0.6 (0.1–3.1)
HIV infection	793 (11.0)[e]	104/1906 (5.5)	689/5273 (13.1)	0.4 (0.3–0.5)[b]	0.4 (0.3–0.5)[b]
Admission diagnosis					
Neonatal sepsis	755 (7.7)	104/2620 (4.0)	651/7166 (9.1)	0.4 (0.3–0.5)[b]	0.3 (0.2–0.4)[b]
Bronchiolitis	1406 (14.4)	505/2620 (19.3)	901/7165 (12.6)	1.7 (1.5–1.9)[b]	1.6 (1.4–1.8)[b]
Bronchopneumonia, pneumonia, or LRTI	7616 (77.8)	2063/2620 (78.7)	5553/7165 (77.5)	1.1 (1.0–1.2)	1.1 (1.0–1.2)
Bronchitis	47 (0.5)	15/2620 (0.6)	32/7166 (0.5)	1.3 (0.7–2.4)	1.3 (0.7–2.4)
Clinical course and outcomes					
Oxygen therapy	3659 (37.0)	1134/2699 (42.0)	2525/7190 (35.1)	1.3 (1.2–1.5)[b]	1.2 (1.1–1.3)[b]
Antibiotic treatment	9052 (93.0)	2458/2666 (92.2)	6594/7069 (93.3)	0.9 (0.7–1.0)	0.9 (0.7–1.1)
ICU admission	133 (1.3)	28/2697 (1.0)	105/7189 (1.5)	0.7 (0.5–1.1)	0.6 (0.4–0.9)[b]
Mechanical ventilation	104 (1.0)	21/2697 (0.8)	83/7189 (1.2)	0.7 (0.4–1.1)	0.5 (0.3–0.8)[b]
Shock	21 (0.2)	6/2696 (0.2)	15/7179 (0.2)	1.1 (0.4–2.8)	0.9 (0.4–2.4)
Cardiac arrest	21 (0.2)	3/2698 (0.1)	18/7188 (0.3)	0.4 (0.1–1.5)	0.4 (0.1–1.2)
Death	155 (1.6)	18/2677 (0.7)	137/7110 (1.9)	0.3 (0.2–0.6)[b]	0.3 (0.2–0.5)[b]
Detection of other pathogens					
Influenza	657 (6.6)	55/2723 (2.0)	602/7246 (8.3)	0.2 (0.2–0.3)[b]	0.2 (0.2–0.3)[b]
Human metapneumovirus	577 (5.8)	47/2723 (1.7)	530/7246 (7.3)	0.2 (0.2–0.3)[b]	0.2 (0.2–0.3)[b]
Parainfluenza virus 1	206 (2.1)	26/2723 (1.0)	180/7246 (2.5)	0.4 (0.3–0.6)[b]	0.4 (0.3–0.6)[b]
Parainfluenza virus 2	129 (1.3)	24/2723 (0.9)	105/7246 (1.5)	0.6 (0.4–0.9)[b]	0.7 (0.4–1.0)
Parainfluenza virus 3	590 (5.9)	40/2723 (1.5)	550/7246 (7.6)	0.2 (0.1–0.3)[b]	0.2 (0.1–0.2)[b]
Rhinovirus/enterovirus	4651 (46.7)	991/2723 (36.4)	3660/7246 (50.5)	0.6 (0.5–0.6)[b]	0.6 (0.5–0.6)[b]
Adenovirus[f]	2479 (26.0)	576/2702 (21.3)	1903/6838 (27.8)	0.7 (0.6–0.8)[b]	0.8 (0.7–0.9)[b]

Abbreviation: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; ICU, intensive care unit; LRTI, lower respiratory tract infection; OR, odds ratio; Ref, reference; RSV, respiratory syncytial virus.

[a]Odds ratios were calculated comparing RSV-positive and RSV-negative patients according to characteristic.

[b]Significant association ($P < .05$).

[c]Odds ratios were adjusted for age (continuous in months) and sex.

[d]Conditions included chronic renal failure, splenectomy/asplenia, autoimmune disease, systemic lupus erythematosus, malignancy/cancer, organ transplant, any immunosuppressive therapy, nephrotic syndrome, sickle cell disease, and immunoglobulin deficiency.

[e]Percentage calculated out of 7179 total patients with a documented HIV status.

[f]Adenovirus testing was not performed between August and October 2009 because of limited availability of reagents [17].

across all age groups, and a trend toward lower sensitivity in those ≥12 months (56%–58%) was observed. In comparison, the SARI definition had higher sensitivities in these oldest age groups (range, 80%–81%). The WHO case definition for severe pneumonia had the lowest sensitivities (range, 47%–55%) and highest specificities (48%–62%) of the definitions tested, and no appreciable trends with age were found.

All case definitions had a PPV of <45% across all age groups with a trend toward a lower PPV with increasing age, as would be expected with the decreasing prevalence of RSV disease (Supplementary Table 1). NPVs in our population were relatively higher (>65%) across all age groups.

Case Definition Performance According to HIV Status

Testing case definitions on the subset of patients with a documented HIV status revealed similar trends in test performance regardless of HIV status (Table 5). No observable difference between HIV-infected and HIV-uninfected patients in

Table 3. Clinical Predictor Frequency and Associations in RSV-Positive Patients According to Age Group—Severe Acute Respiratory Illness Sentinel Surveillance, South Africa, 2009–2014

	Age									
	<3 mo (N = 878)		3–5 mo (N = 582)		6–11 mo (N = 560)		12–23 mo (N = 439)		24–59 mo (N = 264)	
Clinical Predictor	n/N RSV+ (%)	OR (95% CI)	n/N RSV+ (%)	OR (95% CI)	n/N RSV+ (%)	OR (95% CI)	n/N RSV+ (%)	OR (95% CI)	n/N RSV+ (%)	OR (95% CI)
Any fever	460/808 (56.9)	0.8 (0.7–0.9)[a]	374/542 (69.0)	1.2 (1.0–1.5)	401/518 (77.4)	1.1 (0.9–1.4)	341/415 (82.2)	1.9 (1.4–2.5)[a]	189/230 (82.2)	1.7 (1.2–2.4)[a]
History of fever	451/864 (52.2)	0.8 (0.7–0.9)[a]	365/573 (63.7)	1.1 (0.9–1.4)	391/553 (70.7)	1.0 (0.8–1.3)	331/434 (76.3)	1.6 (1.2–2.0)[a]	180/257 (70.0)	1.1 (0.8–1.4)
Measured fever (≥38.0°C)	118/772 (15.3)	0.6 (0.5–0.7)[a]	121/522 (23.2)	0.8 (0.6–1.0)[a]	168/503 (33.4)	0.8 (0.7–1.0)	169/396 (42.7)	1.3 (1.1–1.7)[a]	103/218 (47.3)	1.4 (1.1–1.9)[a]
Tachypnea[b]	539/875 (61.6)	1.3 (1.1–1.5)[a]	366/579 (63.2)	1.1 (0.9–1.4)	323/559 (57.8)	1.1 (0.9–1.4)	235/438 (53.7)	1.1 (0.9–1.4)	127/262 (48.5)	1.1 (0.9–1.5)
Hypoxia[c,d]	55/245 (22.5)	1.8 (1.2–2.6)[a]	24/148 (16.2)	1.4 (0.8–2.3)	26/149 (17.5)	1.9 (1.1–3.2)[a]	13/97 (13.4)	1.9 (1.0–3.9)	3/41 (7.3)	0.8 (0.2–2.7)
Cough	855/875 (97.7)	15.5 (9.8–24.4)[a]	575/579 (99.3)	6.8 (2.5–19.0)[a]	555/559 (99.3)	5.0 (1.8–13.9)[a]	432/438 (98.6)	2.7 (1.2–6.3)[a]	259/263 (98.5)	3.5 (1.3–9.7)[a]
Difficulty breathing	711/875 (81.3)	2.1 (1.7–2.6)[a]	433/579 (74.8)	1.0 (0.8–1.2)	407/559 (72.8)	1.0 (0.8–1.3)	293/438 (66.9)	1.0 (0.8–1.2)	193/263 (73.4)	1.4 (1.0–1.8)[a]
Retractions (chest-indrawing)	527/875 (60.2)	2.0 (1.7–2.4)[a]	302/579 (52.2)	1.0 (0.9–1.3)	292/559 (52.2)	1.2 (1.0–1.4)	197/438 (45.0)	1.1 (0.9–1.4)	126/262 (48.1)	1.4 (1.1–1.9)[a]
Wheezing[d]	77/273 (28.2)	1.5 (1.0–2.0)[a]	54/177 (30.5)	0.9 (0.6–1.3)	61/173 (35.3)	1.2 (0.8–1.7)	32/117 (27.4)	0.9 (0.6–1.5)	8/56 (14.3)	0.4 (0.2–0.9)[a]
Stridor	184/875 (21.0)	1.7 (1.4–2.1)[a]	108/579 (18.7)	1.2 (0.9–1.6)	102/559 (18.3)	1.0 (0.7–1.2)	71/438 (16.2)	0.9 (0.7–1.2)	47/262 (17.9)	1.2 (0.8–1.7)
Unable to drink or breastfeed	169/875 (19.3)	1.3 (1.1–1.7)[a]	110/579 (19.0)	1.1 (0.8–1.4)	129/559 (23.1)	1.0 (0.8–1.3)	96/438 (21.9)	0.9 (0.7–1.2)	66/262 (25.2)	1.3 (0.9–1.7)
Vomiting everything	121/875 (13.8)	1.1 (0.8–1.4)	105/579 (18.1)	1.1 (0.9–1.5)	139/559 (24.9)	1.2 (1.0–1.5)	91/438 (20.8)	1.1 (0.9–1.5)	42/262 (16.0)	1.1 (0.7–1.5)
Lethargy	192/874 (22.0)	1.1 (0.9–1.3)	105/579 (18.1)	0.8 (0.7–1.1)	121/559 (21.7)	0.9 (0.7–1.1)	72/438 (16.4)	0.8 (0.6–1.0)[a]	44/262 (16.8)	0.7 (0.5–1.0)[a]
Unconsciousness	3/875 (0.3)	0.6 (0.2–2.4)	3/579 (0.5)	0.7 (0.2–2.5)	1/559 (0.2)	0.5 (0.1–4.6)	6/438 (1.4)	2.4 (0.8–6.7)	0/262 (0.0)	NA
Convulsions	6/875 (0.7)	0.5 (0.2–1.2)	1/579 (0.2)	0.3 (0–2.3)	4/559 (0.7)	0.4 (0.2–1.3)	8/438 (1.8)	0.5 (0.2–1.1)	10/262 (3.8)	0.7 (0.4–1.4)
Severe malnutrition[e]	0/877 (0.0)	NA	0/582 (0.0)	NA	2/559 (0.4)	0.4 (0.1–1.6)	1/439 (0.2)	0.2 (0–1.5)	0/264 (0.0)	NA

Abbreviations: CI, confidence interval; NA, not available (because of insufficient numbers); OR, odds ratio; RSV, respiratory syncytial virus; RSV+, tested positive for RSV.

[a]Significant association ($P < .05$).

[b]Respiratory rates were >50 for children aged 2 months to 1 year and >40 for those aged 1 to 5 years.

[c]Oxygen saturation was <90% on room air.

[d]Variable not collected throughout the entire study period (it was introduced in the questionnaire in June 2012).

[e]Defined as reporting kwashiorkor/marasmus malnutrition.

Table 4. Sensitivity and Specificity of Case Definitions for Detecting RSV Cases According to Age Group—Severe Acute Respiratory Illness Sentinel Surveillance, South Africa, 2009–2014

Age Group	Case Definition	n (%)	Sensitivity (% [95% CI])	Specificity (% [95% CI])
<3 mo (N = 2586)	SARI	1205 (47)	55 (52–59)	54 (52–56)
	Acute cough	2108 (82)	98 (97–99)	27 (24–29)
	Acute cough and difficulty breathing	1639 (63)	80 (77–83)	45 (43–47)
	Pneumonia	911 (35)	73 (69–77)	45 (42–48)
	Severe pneumonia	1063 (41)	47 (44–51)	62 (60–64)
3–5 mo (N = 1752)	SARI	1065 (61)	68 (64–72)	38 (35–41)
	Acute cough	1690 (96)	99 (99–100)	5 (3–6)
	Acute cough and difficulty breathing	1281 (73)	75 (71–78)	27 (25–30)
	Pneumonia	652 (37)	74 (69–79)	33 (29–37)
	Severe pneumonia	801 (46)	48 (44–52)	55 (52–58)
6–11 mo (N = 2057)	SARI	1439 (70)	77 (73–80)	27 (25–29)
	Acute cough	1998 (97)	99 (99–100)	3 (3–4)
	Acute cough and difficulty breathing	1447 (70)	72 (69–76)	30 (28–33)
	Pneumonia	604 (29)	66 (60–72)	38 (35–42)
	Severe pneumonia	1091 (53)	55 (51–59)	48 (45–50)
12–23 mo (N = 1995)	SARI	1354 (68)	81 (77–84)	32 (29–34)
	Acute cough	1927 (97)	99 (98–100)	4 (3–5)
	Acute cough and difficulty breathing	1313 (66)	66 (62–71)	34 (32–36)
	Pneumonia	552 (28)	56 (49–62)	44 (40–47)
	Severe pneumonia	1006 (50)	49 (44–54)	49 (47–51)
24–59 mo (N = 1579)	SARI	1041 (66)	80 (75–86)	32 (29–34)
	Acute cough	1500 (95)	98 (97–100)	5 (4–6)
	Acute cough and difficulty breathing	1036 (66)	73 (67–78)	35 (33–38)
	Pneumonia	412 (26)	58 (49–66)	50 (47–54)
	Severe pneumonia	758 (48)	49 (43–55)	52 (49–55)

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

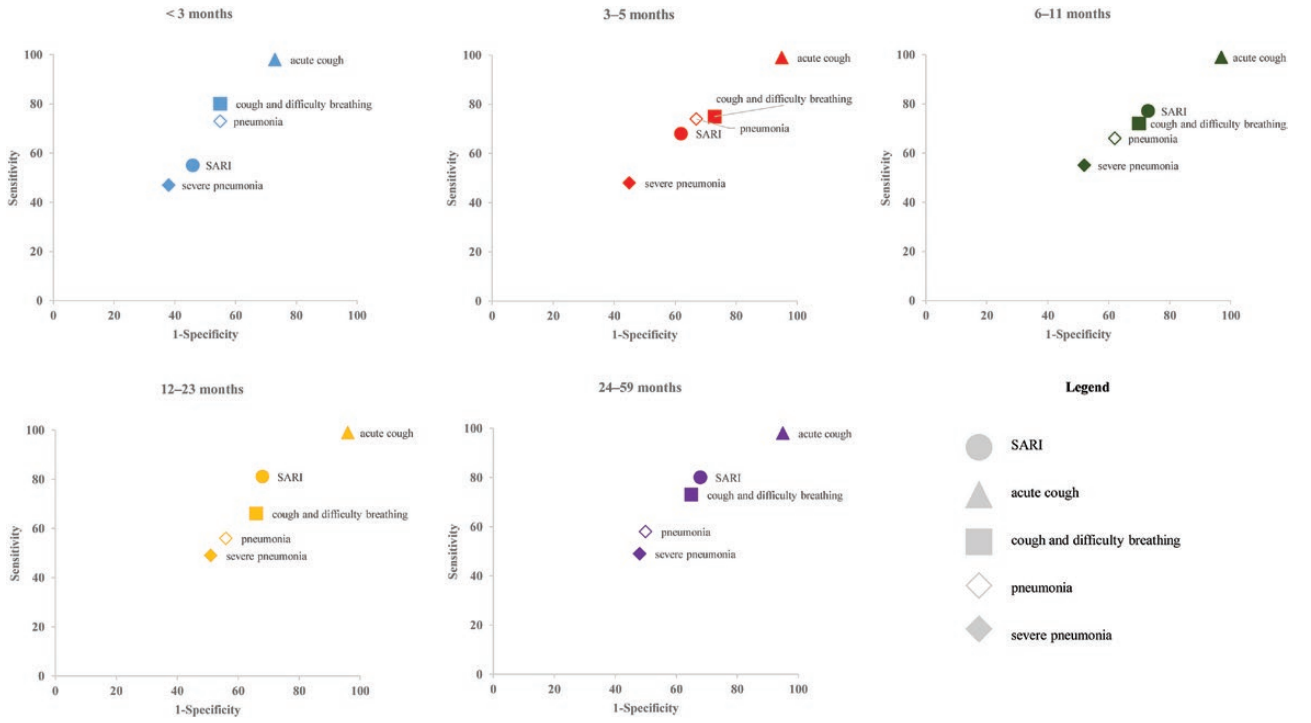

Figure 1. Receiver operator characteristic charts for case definitions according to age group—severe acute respiratory illness sentinel surveillance, South Africa, 2009–2014. See Table 1 for details of the respiratory illness surveillance case definitions tested.

sensitivities of the SARI definition was detected (70% [95% CI, 61%–79%] and 67% [95% CI, 65%–69%], respectively); specificity was low regardless of HIV status, but it was lower in the HIV-infected group (26% [95% CI, 23%–30%] vs 38% [95% CI, 37%–40%], respectively). In both of these groups, removing fever from the SARI definition increased sensitivity in the identification of RSV-positive patients substantially while lowering the specificity.

Effect of Case Definitions on Missed Cases

Given its low sensitivity for RSV, use of the SARI case definition would have missed detection of RSV cases, particularly among the youngest patients (Supplementary Table 2). Of the 2723 RSV-positive children enrolled, 990 (36%) did not meet the SARI case definition and would not have been identified. Among the 990 missed cases, 805 (81%) would have been in infants aged <1 year, with 643 (65%) in patients aged <6 months and 431 (44%) missed cases in those aged <3 months. Therefore, the SARI definition would have missed 49% (431 of 878) of RSV-positive cases in the <3-month age group.

In contrast, removing fever from the SARI definition would have identified 2676 (98%) RSV-positive children, yielding 47 total missed cases among children aged <5 years, of which 23 would have occurred in those aged <3 months.

DISCUSSION

The prevalence and characteristics of the 2723 (27%) RSV-positive hospitalized children enrolled, the majority of whom were infants aged <1 year, are generally consistent with those in previous reports from South Africa [15–17, 20]. Among these children, the association of RSV infection with fever varied substantially with age; fever was less likely to occur with RSV in infants aged <3 months but more likely to present with RSV in children aged ≥12 months. Consequently, it was not unexpected that the sensitivity of a fever-based case definition such as SARI for RSV detection was lowest in younger infants aged <6 months (range, 55%–68%) but higher in older age groups, reaching 80% in children ≥12 months. Compared to the SARI case definition, the sensitivity of case definitions without fever varied less across age groups. Although the risk of hospitalization with an RSV-associated ALRTI in HIV-infected children has been shown to be higher than that in HIV-negative children [16], case definition sensitivities were similar in both groups. Our findings suggest that including fever in case definitions for RSV surveillance would result in missed cases, particularly among the youngest infants, as nearly half of RSV cases among patients aged <3 months were estimated to have been missed with the SARI definition; removing the fever requirement would have recovered most missed cases.

These findings provide further evidence that clinical presentations of RSV can vary according to age, most notably in the youngest infants, who might not present with such classic manifestations as wheezing but instead can present initially with other symptoms such as apnea [12, 23]. Furthermore, our findings are consistent with previous observations that fever can be absent in children with RSV disease [13, 24], in contrast to influenza infection, which is more likely to present with fever [13, 25, 26]. Despite this difference, it is interesting to note that in similar recent analyses of children aged <5 years at 2 of our 5 hospital sites, the sensitivities of the SARI case definition for identifying influenza (69% [95% CI, 59%–77%] in documented HIV-uninfected and 64% [95% CI, 41%–83%] in HIV-infected children) were similar to our estimates for RSV, although there was evidence of slightly higher specificities for identifying influenza (46% [95% CI, 43%–49%] in HIV-uninfected and 43% [95% CI, 37%–48%] in HIV-infected children) than RSV (Ngobeni H, Cohen AL, Walaza S, Kuonza L, Musekiwa A, Tempia S, Cohen C, unpublished data). Further comparison of the performance of the SARI case definition among younger infants was not possible because the influenza analyses were not stratified for children younger than 5 years.

Table 5. Sensitivities and Specificities of Case Definitions for Detecting RSV Cases in Patients <5 Years of Age According to HIV Status (N = 7179)—Severe Acute Respiratory Illness Sentinel Surveillance, South Africa, 2009–2014

	HIV^+ (N = 793)			HIV^- (N = 6386)			*P*	
Case Definition	n (%)	Sensitivity (% [95% CI])	Specificity (% [95% CI])	n (%)	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Sensitivity	Specificity
SARI	566 (71)	70 (61–79)	26 (23–30)	3927 (61)	67 (65–69)	38 (37–40)	.155	<.001
Acute cough	763 (96)	99 (97–100)	4 (2–5)	5918 (93)	98 (98–99)	9 (8–10)	.101	.001
Acute cough and difficulty breathing	572 (72)	75 (67–84)	28 (25–31)	4277 (67)	72 (70–74)	35 (33–36)	.136	.001
Pneumonia	227 (29)	68 (55–81)	38 (33–43)	2012 (32)	66 (63–69)	42 (40–44)	.347	.071
Severe pneumonia	425 (54)	54 (44–64)	46 (42–50)	3021 (47)	50 (48–52)	54 (52–55)	.075	001

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HIV^+ and HIV^-, HIV positive and negative, respectively; RSV, respiratory syncytial virus.

Our findings add to those of 2 previous similar studies of smaller cohorts enrolled in a population-based surveillance system. Analyses of 505 children aged <5 years hospitalized in rural northern India for any acute medical condition in 2009 to 2012 found that a history of fever was significantly less likely to occur in RSV-positive than in RSV-negative patients after the authors adjusted for age [27]. Similar to our findings, they found that fever-based case definitions such as previously recommended SARI and influenza-like illness definitions had a lower sensitivity (<60%) than non–fever-based definitions, and the fever-based case definitions were found to underestimate RSV-hospitalization incidence rates by 50% to 85% [27].

In contrast, analyses of 3810 children aged <5 years hospitalized with acute respiratory illness in Kenya in 2009 to 2013 found no difference between RSV-positive and RSV-negative children in the likelihood of fever [28]. The sensitivity of the SARI case definition in the Kenyan study ranged from 79% in children aged <1 year to 86% in the older 1- to 5-year age group, which was higher than that in the Indian study. Detailed comparisons with our study are limited because analyses of data in the Kenyan cohort were not stratified for children younger than 1 year. However, the sensitivities of the SARI case definition for children aged ≥6 months in our population (range, 77%–81%) were comparable to the overall Kenyan study estimates, whereas the substantially lower sensitivities among our children <6 months of age more closely match overall Indian study estimates. It is possible that differences between the Indian and Kenyan cohorts in age distribution could help account for the observed differences in sensitivity, particularly if the smaller Indian cohort had a greater proportion of RSV-positive patients <6 months of age (43%) relative to that in the Kenyan cohort.

Our study included some limitations. Inclusion criteria were based on physician diagnoses and admitting practices, which may vary by physician and hospital site. Clinical factors that comprise case definitions were obtained by history from each patient's parent/caregiver and could be subject to recall bias, although we would not expect recall bias to be related to RSV status. We were unable to evaluate the ≤10-day duration component of the SARI definition because surveillance enrollment criteria excluded patients with symptom onset >7 days before hospitalization, and we were unable to address less severe cases of RSV disease that did not necessitate hospitalization. In addition, subanalyses based on HIV status were limited to documented HIV results, which were not available for all the patients. The relatively lower specificities of certain case definitions observed among HIV-infected patients might be a result of other factors and conditions in that population and requires further investigation. Last, determinations of the PPV and NPV were performed in aggregate over the entire study period such that we could not account for relative peaks of RSV activity that might affect estimates influenced by prevalence. Despite these limitations, our surveillance system provided a broad platform on which to identify a large number of severe presentations of RSV disease regardless of the presence of fever, which has yielded robust data from a setting in which this type of evaluation had not been represented previously in the published literature.

Our findings demonstrate that the SARI case definition has a relatively low sensitivity for RSV disease, particularly in the youngest infants, in whom fever can be absent and the burden of severe disease is highest. As such, estimates of RSV burden generated by data from surveillance systems designed for influenza should be interpreted with consideration of the case definition used. Developing surveillance case definitions optimized for detecting RSV could help further the development of surveillance platforms that would yield improved estimates of RSV morbidity and deaths, along with associated health costs. In general, the goals of surveillance should inform case definition development and include considerations of sensitivity and specificity. Emphasizing improved sensitivity of case definitions for RSV in surveillance systems should lead to better characterization of its burden, particularly in young infants, which in turn should aid in evaluation of the impact of vaccines, immunoprophylaxis products, and antiviral agents currently in development and help guide recommendations for their use worldwide.

Supplementary Data

Supplementary materials are available at *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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