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Respiratory Syncytial Virus Infection Among Hospitalized Infants in Four Middle-Income Countries

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Supplementary Data

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Abstract

Background: Understanding respiratory syncytial virus (RSV) global epidemiology is important to inform future prevention strategies.

Methods: Hospitalized infants <1-year-old with acute illness were enrolled prospectively in Albania, Jordan, Nicaragua, and Philippines during respiratory seasons in 2015–2017. Medical chart review, parental interview, and post-discharge follow up were conducted. Respiratory specimens were tested using real-time RT-PCR for RSV. Infant characteristics associated with very severe illness (intensive care unit [ICU] admission or receipt of supplemental oxygen) were assessed using logistic regression to adjust for potential confounders (age, sex, study site, and preterm birth).

Results: Of 3634 enrolled hospitalized infants, 1129 (31%) tested positive for RSV. The median age of RSV-positive infants was 2.7 (IQR: 1.4–6.1) months and 665 (59%) were male. Very severe illness in 583 (52%) RSV-positive infants was associated with younger age (aOR 4.1, 95% CI: 2.6–6.5 for 0–2 compared to 9–11-months; $P < .01$), low weight-for-age z-score (aOR 1.9, 95% CI: 1.2–2.8; $P < .01$), ICU care after birth (aOR 1.6, 95% CI: 1.0–2.5; $P = .048$), and cesarean delivery (aOR 1.4, 95% CI: 1.0–1.8; $P = .03$). RSV subgroups A and B co-circulated at all sites with alternating predominance by year; subgroup was not associated with severity (aOR 1.0, 95% CI: 0.8–1.4). Nine (0.8%) RSV-positive infants died during admission or within ≤30 days of discharge, of which 7 (78%) were <6-months-old.

Conclusions: RSV was associated with nearly a third of infant acute illness hospitalizations in four middle-income countries during the respiratory season, where, in addition to young age, factors including low weight-for-age might be important predictors of severity. RSV prevention strategies targeting young infants could substantially reduce RSV-associated hospitalizations in middle-income countries.

Keywords

Albania; bronchiolitis; global health; infant; Jordan; Nicaragua; Pediatric; Philippines; pneumonia; Respiratory syncytial virus

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infection and hospitalization among infants worldwide [1-3]. Globally, RSV is a leading cause of infant death after the first month of life, with RSV-associated mortality reported disproportionately from low- and middle-income countries (LMICs) [1, 3, 4].

No vaccine is currently licensed to prevent RSV infection in infants, but several candidates are in late stages of development [5, 6]. Immunoprophylaxis with palivizumab is indicated for high-risk children but is unavailable or cost-prohibitive in many LMICs [7, 8]. RSV epidemiology and risk factors for severe illness and death in LMICs may differ compared to high-income countries [9]. Country income classification may impact peak RSV incidence by age group, with LMICs having a higher burden among younger infants compared to high-income countries [3]. Additionally, out-of-hospital deaths may occur more frequently in lower-income countries [3]. Understanding RSV epidemiology and risk factors for severe illness globally is important to inform recommendations as additional RSV prophylactic agents, therapeutics, and vaccine candidates advance through clinical trials.

As part of the *Influenza and Respiratory Syncytial Virus in Infants Study* [10, 11], we prospectively enrolled hospitalized infants with acute illness in four lower- and upper-middle-income countries during respiratory seasons in 2015–2017 and performed systematic testing for RSV among all enrolled infants. We describe RSV epidemiology, factors associated with illness severity, and anti-RSV IgG serum antibodies among RSV-positive infants, with an overall aim of expanding infant RSV data from outside of high-income counties with geographic representation of both temperate and tropical climate zones.

METHODS

Study Design and Data Collection

Hospital enrollment sites were in Albania, Jordan, Nicaragua, and the Philippines. Site characteristics have been previously described and are outlined in Supplementary Table 1 [10, 11]. Nicaragua and the Philippines are classified by the World Bank as lower-middle-income countries and have tropical climates; Albania and Jordan are classified as upper-middle-income and have temperate climates [12]. The study was conducted during two study periods (Year 1 and Year 2) at all sites other than Philippines, where enrollment occurred during a continuous 34-week period. Study periods were selected to coincide with expected influenza circulation in Year 1 and influenza and RSV circulation in Year 2 (Supplementary Table 1). Periods of expected influenza circulation were determined on the basis of previous regional influenza surveillance [11]. Periods of expected RSV circulation for Year 2 were informed by data obtained during the first study year.

Infants <1-year-old and hospitalized with any acute illness regardless of symptoms were screened prospectively and potentially eligible if they had been admitted for <24 hours, lived within the local catchment area, and had an illness onset within 10 days. Infants were ineligible if the reason for admission did not include an acute illness, including admissions exclusively for trauma, elective surgery, repair of a congenital abnormality, or

accidental ingestion.For eligible infants with parent or guardian consent, information was collected by standardized parental interviews and medical record review. Socio-demographic characteristics, medical history, birth history, and symptoms of the acute illness were gathered from parental interviews. Medical records were reviewed to collect data on vital signs, clinical interventions, and level of care. After discharge, study personnel collected data on clinical test results during the hospital course as well as discharge status. Admission and discharge diagnoses, including International Classification of Diseases (ICD) codes, were recorded. Vital status of the infant was documented by study personnel through follow up with the parent/guardian 3–5 weeks after discharge as well as review of medical and administrative records.

Specimen Collection and Laboratory Testing

Respiratory specimens, including combined nasal and throat swabs or, for intubated infants, endotracheal aspirates, were collected at the time of enrollment for all infants and tested at site-specific reference laboratories using standardized protocols [10]. All specimens were tested for RSV using a real-time RT-PCR assay, with CDC-supplied protocols, primers, probes, reagents, and proficiency panels. Available RSV-positive specimens were subsequently tested at CDC using a duplex real-time RT-PCR assay to determine RSV A or B subgroup [13].

For infants with an RSV-positive respiratory specimen, available sera from the acute phase of illness were tested using RSV A/B whole virus lysate IgG ELISAs. The presence of anti-RSV antibodies was defined as an optical density (OD) ≥ 0.2 [14].

Study Definitions

All hospitalized infants were considered to have severe illness; very severe illness associated with RSV was defined as having received care in the ICU or supplemental oxygen during hospitalization. Vital signs were recorded by hospital clinicians and abstracted from medical records by study personnel. Tachypnea was defined as ≥60 breaths per minute for infants <2-months-old and ≥50 breaths per minute for infants 2-11 months-old. Fever was a measured temperature ≥38 °C. Hypoxemia was a measured oxygen saturation of <92%. Preterm birth was defined as parent-reported gestational age <37 weeks, very preterm birth as parent-reported gestational age <32 weeks, and low birth weight as parent-reported birth weight of <2.5 kg. A determination of pneumonia on a chest radiograph was made by clinicians (radiologist or other physicians) involved in the infant's care and was not standardized across sites. Low weight-for-age was defined as a weight-for-age *z*-score <−2 using World Health Organization (WHO) growth curves [15]. Weight-for-age *z*-scores were calculated using the CDC Growth Chart Training SAS program based on WHO Growth Charts [16]. Participants with *z*-score outliers (less than −5 or >5) were excluded from *z*-score analysis.

Data Management and Analysis

Data were collected and managed at the study sites using REDCap [17] on computers or mobile devices. Descriptive statistics are presented as proportions, medians, ranges, and interquartile ranges (IQR). The Pearson χ^2 test was used to compare categorical data, and Wilcoxon rank-sum was used to compare categorical and continuous data. A

post-hoc analysis was conducted among RSV-positive infants to identify factors that may be associated with very severe RSV illness. Individual logistic regression models were used to assess associations between very severe RSV and potential risk factor variables. The models were adjusted for possible confounding factors, including study site, categorical age, sex and a history of preterm birth. Odds ratios (OR), adjusted odds ratios (aOR), and 95% confidence intervals (95% CI) are reported. Models were also run to evaluate the association between very severe RSV and categorical age, while considering potential effect modification of this association by study site. Results are presented as percentage of very severe RSV per group, with 95% CI. Data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC) or STATA version 14 (STATACorp, College Station, TX) statistical software.

Ethics

The study protocol and procedures were approved by Institutional Review Boards at each study site and by Abt Associates (the coordinating institution on which CDC relied). Written informed consent was obtained from the parent or guardian in the local languages.

RESULTS

Across study sites, 3897 eligible hospitalized infants were identified during the study period, 3634 (93%) were enrolled, and 1129 (31%) tested RSV-positive (Supplementary Figure 1). RSV-positive infants included 438 (42%) of 1032 enrolled from Albania, 358 (34%) of 1057 in Jordan, 209 (22%) of 937 in Nicaragua, and 124 (20%) of 608 in Philippines. The RSV percent positivity varied by enrollment week at each site (Figure 1). RSV subgroup was assessed for 1103 (98%) available RSV-positive specimens; 433 (39%) were RSV-A, 581 (53%) RSV-B, 14 (1%) both RSV A and B, and 75 (7%) undetermined. RSV A and B co-circulated across sites and study years, with alternating subgroup predominance by year (Figure 1).

Demographic and Clinical Characteristics of RSV-Positive Infants

The median age of RSV-positive infants was 2.7 (IQR: 1.4–6.1) months, 600 (53%) were <3- months-old (Supplementary Figure 2A), and 665 (59%) were male. Among RSV-positive infants, 89 (8%) were born preterm and 154 (14%) had a low birth weight; very preterm birth was uncommon (<1%) (Table 1). Sixty-three (6%) RSV-positive infants had ≥1 parent-reported underlying medical condition. Overall, 80% of RSV-positive infants had no parent-reported history of an underlying condition, preterm birth, or low birth weight. Most infants were currently breast-feeding, including 85% of infants <6-months-old and 73% of infants ≥6-months-old. A low weight-for-age *z*-score was calculated for 170 (16%) infants.

Infants were ill for a median of 3 (IQR: 2–4) days before hospitalization. Cough was the most common parent-reported symptom (90%), followed by difficulty breathing, rhinorrhea, wheezing, and poor feeding (Table 1). Overall, cough or difficulty breathing was reported in 1043 (92%) infants, including 789 (94%) <6-months-old and 254 (88%) ≥6-months-old. Fever or feeling hot was reported by parents for 576 (51%) infants, and 380 (34%) had

a clinician-measured fever on the day of admission; either parent-reported or clinician-measured fever on admission was present in 639 (57%).

Clinical Course and Outcomes of RSV-Positive Infants

The frequency of ICU admission, clinical interventions, and documentation of vital signs varied by site (Table 2). Overall, 306 (27%) of 1129 RSV-positive infants were initially admitted to the ICU, and 358 (32%) required ICU care during hospitalization. During the course of hospitalization, 475 (42%) RSV-positive infants had clinician-measured fever, 329 (34%) of 976 infants with a documented respiratory rate had tachypnea, and 448 (54%) of 837 infants with at least one documented oxygen saturation had hypoxemia. Supplemental oxygen was received by 505 (45%) RSV-positive infants; the highest level of support included mechanical ventilation for 20 (2%) and non-invasive ventilation for 10 (1%). Other interventions included intravenous fluids (n = 650, 57%), tube feeding (n = 77, 7%), and inotropes (n = 40, 4%). Younger RSV-positive infants more commonly received clinical interventions including supplemental oxygen, inotropes, and tube feeding (Supplementary Table 2). Antibiotics were administered to 1083 (96%) RSV-positive infants during hospitalization, and 466 (41%) received inhaled or systemic corticosteroids. Among 1008 (89%) RSV-positive infants with a chest radiograph, 522 (52%) had an interpretation of pneumonia. Use of antibiotics, systemic gluco-corticoids, and radiographic pneumonia was similar across age categories (Supplementary Table 3). RSV-positive infants with very severe illness (received ICU care or supplemental oxygen) were more likely to receive antibiotics (99% compared to 92%, $P < .01$). The median length of hospital stay was 6 days (IQR: 4–7). The primary discharge diagnosis for most RSV-positive infants was either pneumonia (n = 532, 47%) or bronchiolitis (n = 362, 32%).

Nine RSV-positive infants (0.8%) died within ≤30 days of discharge, including six with very severe illness during the enrollment hospitalization. Deaths occurred during the enrollment hospitalization (n = 4), after transfer to another hospital (n = 1), and within 7 days of discharge from the enrollment hospitalization (n = 4, including during re-hospitalization, at home, or in a local health center). Six (67%) infants who died had underlying conditions, including preterm birth or congenital abnormalities. The median age of decedent infants was 2.9 (range: <1 to 7.5) months, and 7 (78%) were male. Seven (78%) deaths were among infants <6-months-old, including three among neonates <1 month-old. RSV subgroups associated with infant deaths included RSV A for 4 (44%), RSV B for 2 (33%), and not determined for 3 (22%).

Factors Associated with Illness Severity among RSV-Positive Infants

A total of 583 (52%) RSV-positive infants received ICU care or supplemental oxygen and were classified as having very severe illness (Table 3). The median age of RSV-positive infants with very severe illness was 2.0 months compared to 4.3 months among infants with severe illness ($P < .001$). The proportion of infants with very severe illness varied significantly by site and by categorical age ($P < .001$) (Figure 2). In Albania and Jordan, the proportion of very severe RSV was higher in infants aged 0–2 months old, compared to infants in other age categories (67% and 79%, respectively). In the Philippines, the proportion of very severe RSV in infants aged 0–2 months and 3–5 months was higher than

the proportion of very severe RSV in infants aged >6 months. In Nicaragua, there were no differences in proportion of very severe RSV infections across infant age categories.

After adjusting for age, sex, study site, and parent-reported preterm birth, RSV-positive infants with very severe illness compared to those with severe illness were more likely to be younger (aOR 4.1, 95%CI: 2.6–6.5 for 0–2 compared to 9–11-months; $P < .01$), have low weight-for-age (aOR 1.9, 95% CI: 1.2–2.8; $P < .01$), had cesarean delivery (aOR 1.4, 95% CI: 1.0–1.8; $P = .03$), or been in the ICU after birth (aOR 1.6, 95% CI: 1.0–2.5; $P = .048$)(Table 3). Severity was not associated with RSV subgroup (aOR 1.0, 95% CI:0.8–1.4, RSV B compared to RSV A, Table 3).

RSV Serum Antibodies

Serum collected during acute illness was tested for 875 (78%) of 1129 RSV-infected hospitalized infants, and 417 (48%) had detectable anti-RSV IgG. Younger infants were more likely to have detectable anti-RSV IgG during acute illness ($P < .001$); 395 (60%) of 663 infants <6-months-old had detectable anti-RSV IgG antibodies during acute illness compared to 22 (10%) of 212 infants ≥6-months-old (OR 12.7, 95% CI 7.9–21.3). Among infants aged <1 month, 89% had detectable acute-phase anti-RSV IgG; this proportion fell to 43% for 3-month-olds and thereafter remained <20% for each age category (Supplementary Figure 3).

DISCUSSION

RSV was associated with nearly a third of acute illness among hospitalized infants <1-year-old in four middle-income countries during the respiratory season, with more than half of hospitalized RSV-positive infants <3-months-old. More severe illness was associated with younger age, low weight-for-age, having been in the ICU after birth, and birth by cesarean section. Nine infants with RSV infection (0.8%) died during or within 30 days of hospitalization, including three otherwise healthy infants. Nearly all RSV hospitalizations were associated with acute respiratory symptoms, though only about half of infants had fever. Most RSV-positive infants (96%) received antibiotics during hospitalization. This study contributes to the descriptive epidemiology of hospitalized infants with RSV illness from middle-income countries in both temperate and tropical climates, where data on infant RSV epidemiology has been limited in comparison to high-income countries.

Younger age was strongly associated with RSV severity in this study and is a well-described risk factor for severe RSV illness [18]. We also observed an association between low weight-for-age and severity, which is consistent with findings of malnutrition or poor infant growth as risk factors for severe RSV infection in studies in Philippines, Kenya, and Argentina [19-21], and might be an important consideration for RSV risk in LMICs. In a retrospective case series that assessed factors associated with RSV mortality in young children (RSV GOLD study), low weight-for-age was present in half of RSV-related deaths in 23 countries; in LMIC countries, in contrast to high-income countries, low weight-for-age was often present in otherwise healthy children, not explained by preterm birth or comorbidities [9]. The association we observed between birth by cesarean section or having received ICU care after birth and severity could indicate birth complications or underlying medical

conditions that were not captured in our dataset; however, cesarean section birth and an increased risk for RSV infection or bronchiolitis hospitalization has been described and may warrant further exploration [22, 23]. Other factors associated with RSV severity in high-income countries, including very premature birth and certain comorbid conditions, were relatively uncommon in our overall study population and among infants with RSV infection [18, 24]. We did not observe a difference in severity between RSV subgroup A and B infections. Co-circulation of both subgroups occurred with an alternating pattern of subgroup predominance by year, as previously recognized [25].

In our study, anti-RSV serum IgG during the acute phase of illness was most often detectable among the youngest infants, with the proportion positive declining precipitously by age 4 months. This is consistent with findings of Nyiro et al. among a population of hospitalized children in Kenya in which RSV-specific antibody prevalence was 100% among infants <1-month-old, and seroprevalence was lowest at ages 5-11 months [26]. RSV-specific antibodies during acute illness among young infants likely represent maternal antibodies, which are generally estimated to wane by 6 months of age or sooner, with some RSV-specific models showing decay by 3–4 months [27-30]. Additional analysis is warranted to examine specific antibody profiles, including antigen-specific and functional responses, and associations with severity.

Global estimates attribute one in 28 deaths among children aged 28 days to 6 months to RSV, with the vast majority (>97%) of RSV-associated deaths occurring in LMICs [3]. In our study, we observed deaths among 0.8% RSV-positive infants during or soon after hospitalization; most deaths were among infants <6-months-old (78%) or with substantial comorbidities (67%), aligning with findings from the RSV GOLD study [9]. However, three apparently healthy infants also died, including two in the community shortly after discharge (at home and at a local health center). In our study, a total of four deaths among RSV-positive infants occurred within a week of discharge from the enrollment hospitalization and could have been missed if follow-up of study participants after discharge had not occurred. Importantly for RSV mortality and burden estimates in LMICs, community deaths are unlikely to be captured by in-hospital mortality estimates but may comprise a substantial proportion RSV-associated mortality [3, 31, 32]. In one analysis, out-of-hospital deaths comprised three-quarters of childhood RSV deaths in LMICs [3]. Capturing community deaths and deaths after discharge, though challenging, is a critical consideration for accurate burden estimates.

Understanding the performance of RSV case definitions in LMICs is also essential for future global RSV burden estimates. A strength of our study was broad enrollment criteria not restricted to respiratory signs and symptoms, allowing the opportunity to capture infants with less typical RSV presentations. Our findings support other studies that have shown fever is an unreliable indicator of RSV in infants, and that surveillance case definitions including fever would miss a substantial proportion of RSV infections [33, 34]. In our study, only 34% of RSV-positive infants had measured fever on admission, and either parent-reported or measured fever would have captured 57%. Parent-reported cough or shortness of breath was documented for 92% of RSV-positive infants, including 94% of infants <6-months-old and 88% ≥6-months-old, indicating that most RSV-positive infants in our study

would likely be captured by the WHO extended SARI case definition for surveillance for severe RSV infection [35]. Other components of the WHO extended surveillance definition for infants <6-months-old, including apnea, shock, or sepsis criteria, were not systematically collected in our study.

Nearly all RSV-positive infants in our study received antibiotics during hospitalization. This finding may not be unexpected given high rates of antibiotic prescription for children with acute respiratory infections in LMICs observed in other studies, including in outpatient settings [36]. Although we cannot determine the proportion of antibiotic administration that was inappropriate in our study, it is likely that antibiotics were not indicated for many RSV-positive infants. In addition to reducing morbidity and mortality, prevention of RSV infection and hospitalization in LMIC could potentially contribute to reducing the use of antibiotics for viral infection in infants.

Our study is subject to several limitations. Clinician thresholds for hospital and ICU admission and administration of oxygen therapy likely varied by site. This could have influenced our post-hoc definition and analysis of disease severity. Furthermore, differences between sites in resources and capacity, including ICU capacity, existed; for example, in Nicaragua and the Philippines data on oxygen saturation was less commonly available and a smaller proportion of RSV-positive infants received supplemental oxygen compared to Albania and Jordan. Data were incomplete to determine possible bacterial co-infection, and details on antibiotic use were limited. We relied on parental reports of birth history, including preterm birth and low birth weight. Enrollment periods were chosen primarily to capture the influenza season during Year 1 and may not have captured the full RSV season in either study year.

In conclusion, we confirmed a substantial proportion of acute-illness hospitalizations among infants at our study sites in middle-income countries were associated with RSV. Young infants hospitalized with RSV frequently received ICU care or oxygen therapy and were admitted for an average of 6 days, likely resulting in a substantial healthcare burden in areas with limited resources. In addition to younger age, other risk factors including low weight-for-age might be important in middle-income countries. Consideration of RSV epidemiology in LMICs compared to high-income countries will be important as vaccine and therapeutic strategies continue to advance. Prevention of RSV could have a substantial impact on infant hospitalizations in middle-income countries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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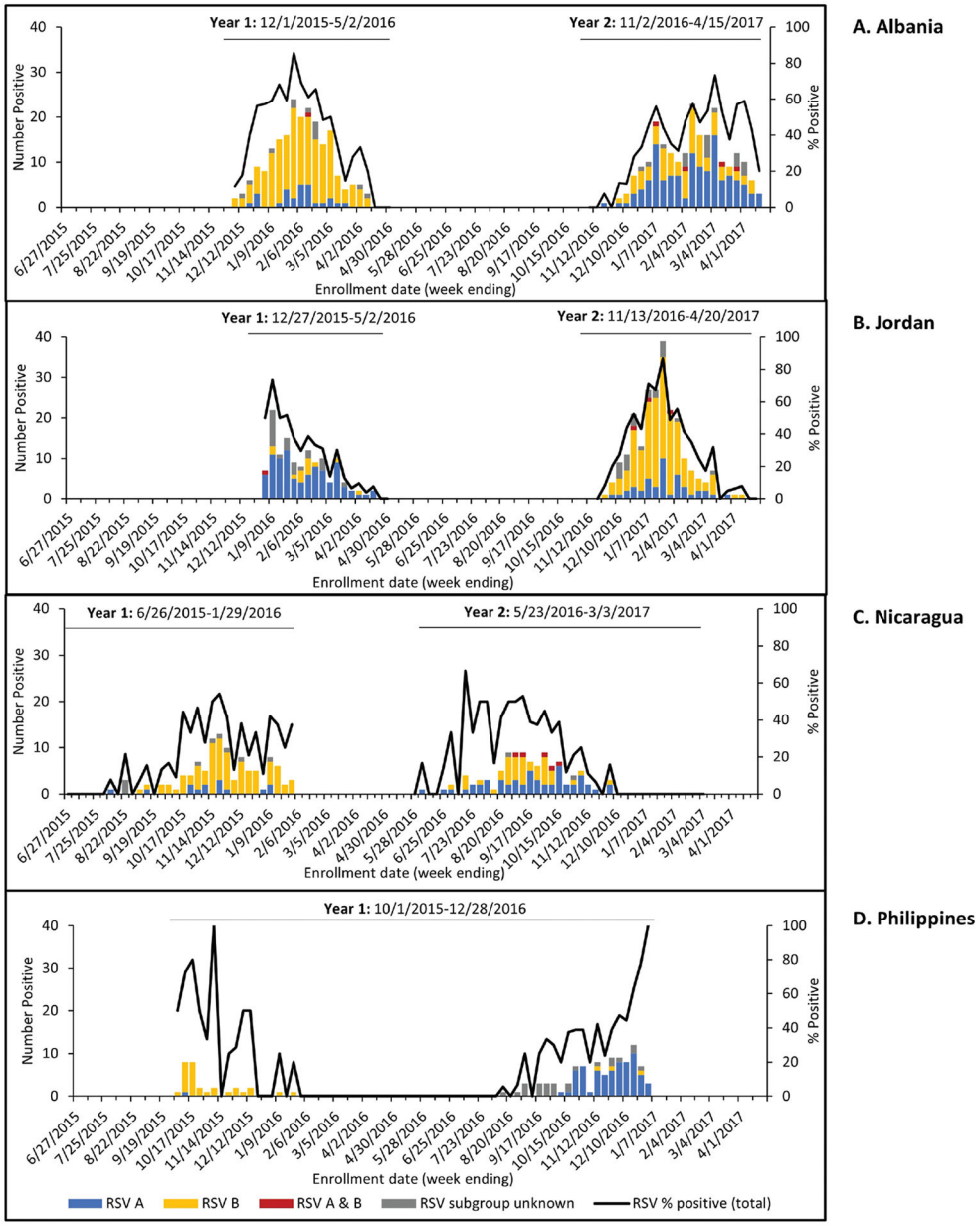

Figure 1.

Respiratory syncytial virus (RSV) subgroups, weekly number and overall percent positive by site and year, hospitalized infants, Albania (A), Jordan (B), Nicaragua (C), Philippines (D). Enrollment dates by site: Albania, Year 1: 12/1/2015–5/2/2016, Year 2: 11/2/2016–4/15/2017; Jordan, Year 1: 12/27/2015–5/2/2016, Year 2: 11/13/2016–4/20/2017; Nicaragua, Year 1: 6/26/2015–1/29/2016, Year 2: 5/23/2016–3/3/2017); Philippines, 10/1/2015–12/28/2016.

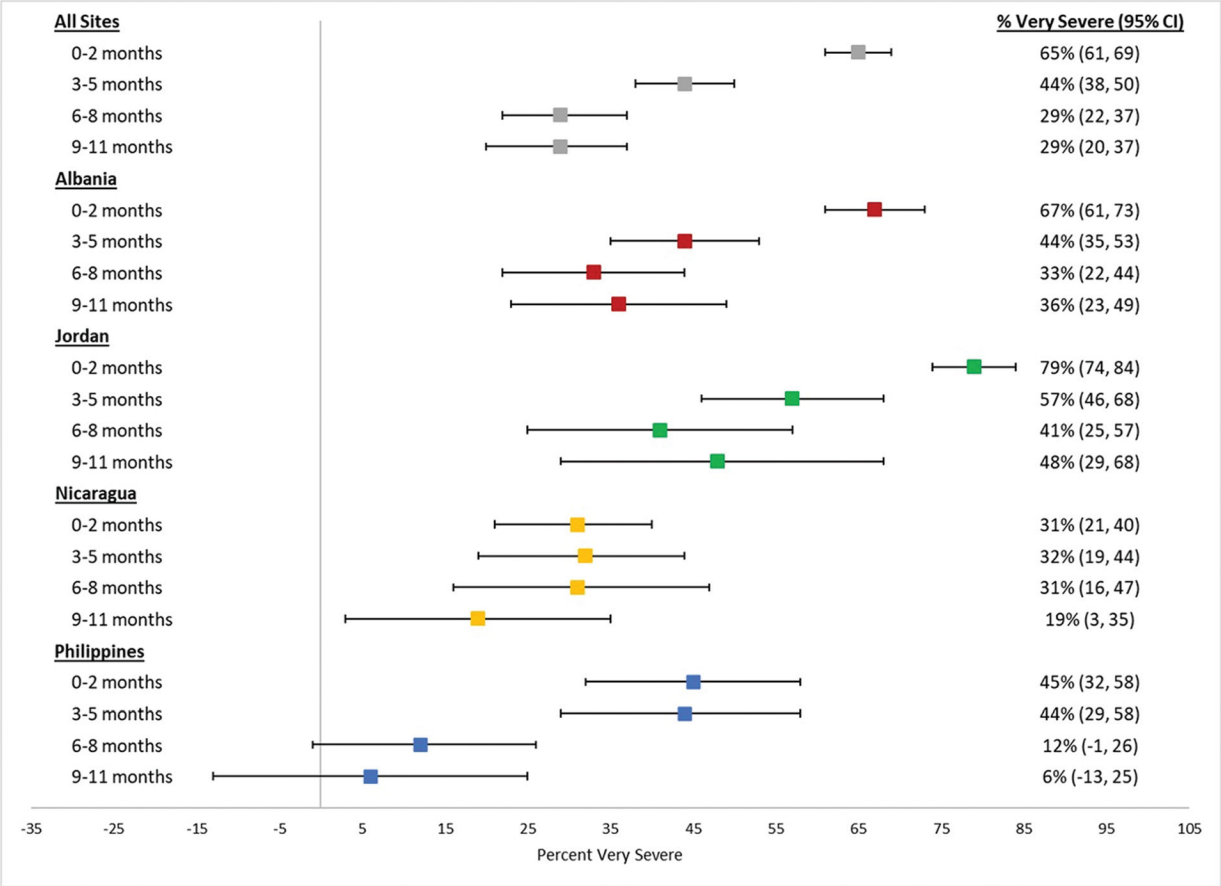

Figure 2.

Percent of respiratory syncytial virus (RSV)-positive infants with very severe illness, by age category and site.

Table 1.

Demographic and Clinical Characteristics of Respiratory Syncytial Virus (RSV)-Positive Hospitalized Infants in Albania, Jordan, Nicaragua, and the Philippines

	Overall ***N*** **= 1129** **No. (%)**	**Albania** ***N*** **= 438** **No. (%)**	**Jordan** ***N*** **= 358** **No. (%)**	**Nicaragua** ***N*** **= 209** **No. (%)**	**Philippines** ***N*** **= 124** **No. (%)**
Age, mo.					
Median (IQR)	2.7 (1.4–6.1)	3.1 (1.7–6.9)	1.9 (1.0–3.3)	3.4 (1.4–6.5)	4.9 (2.4–7.3)
Age group, mo.					
<1	191 (17)	55 (13)	90 (25)	37 (18)	9 (7)
1	233 (21)	78 (18)	103 (29)	37 (18)	15 (12)
2	176 (16)	78 (18)	61 (17)	21 (10)	16 (13)
3	103 (9)	47 (11)	27 (8)	21 (10)	8 (6)
4	78 (7)	26 (6)	18 (5)	18 (9)	16 (13)
5	60 (5)	30 (7)	12 (3)	11 (5)	7 (6)
6 to 8	167 (15)	72 (16)	28 (8)	32 (15)	35 (28)
9 to 11	121 (11)	52 (12)	19 (5)	32 (15)	18 (15)
Sex					
Male	665 (59)	260 (59)	206 (57)	112 (54)	87 (70)
Female	464 (41)	178 (41)	152 (42)	97 (46)	37 (30)
Infant medical and birth history (parent report)					
Preterm birth[a]	89/1085 (8)	30/425 (7)	37/353 (10)	17/186 (8)	5/121 (4)
Very preterm birth[b]	9/1085 (1)	2/425 (<1)	4/353 (1)	2/186 (1)	1/121 (1)
Low birth weight[c]	154/1066 (14)	34/424 (8)	80/347 (22)	19/181 (9)	21/114 (17)
Vaginal delivery	724/1102 (66)	264/428 (62)	234/353 (66)	118/199 (59)	108/122 (89)
Cesarean delivery	378/1102 (34)	164/428 (38)	119/353 (34)	81/199 (41)	14/122 (11)
Underlying medical condition[d]	63 (6)	21 (5)	25 (7)	9 (4)	8 (7)
Low weight-for-age *z*-score[e]	170/1093 (16)	33/419 (8)	81/346 (23)	27/205 (13)	29/123 (24)
Sociodemographic factors					
Maternal age, yr.					
≤ 19	126 (11)	14 (3)	37 (10)	61 (29)	14 (11)

	Overall *N* = 1129 No. (%)	Albania *N* = 438 No. (%)	Jordan *N* = 358 No. (%)	Nicaragua *N* = 209 No. (%)	Philippines *N* = 124 No. (%)
20 to 24	315 (28)	102 (23)	107 (30)	70 (33)	36 (29)
25 to 29	354 (31)	164 (37)	107 (30)	48 (23)	35 (28)
30 to 34	214 (19)	106 (24)	71 (20)	21 (10)	16 (13)
35 to 39	103 (9)	47 (11)	32 (9)	7 (3)	17 (14)
≥40	17 (2)	5 (1)	4 (1)	2 (1)	6 (5)
Attends daycare	20 (2)	13 (3)	6 (2)	1 (<1)	0
Other children <5 years old in home	583 (52)	186 (42)	233 (65)	93 (45)	71 (57)
Household crowding[f]	271 (24)	62 (14)	48 (13)	107 (51)	54 (44)
≥1 indictor of deprivation[g]	204 (18)	12 (3)	26 (7)	48 (23)	118 (95)
Smoking in home[h]	574 (51)	160 (37)	252 (70)	75 (36)	87 (71)
Currently breastfeeding	921 (82)	378 (86)	267 (75)	175 (84)	101 (81)
Sought care for current illness before hospitalization	310 (27)	143 (33)	106 (30)	38 (18)	23 (19)
Symptoms (parent report)					
Fever or felt hot	576 (51)	237 (54)	118 (33)	137 (66)	84 (68)
Chills	110 (10)	32 (7)	61 (17)	14 (7)	3 (2)
Cough	1016 (90)	388 (89)	318 (89)	196 (94)	114 (92)
Difficulty breathing	880 (78)	335 (76)	284 (79)	182 (87)	79 (64)
Wheezing	563 (50)	89 (20)	256 (72)	153 (73)	65 (52)
Rhinorrhea	705 (63)	268 (61)	157 (44)	190 (92)	90 (73)
Lethargy	214 (19)	30 (7)	126 (35)	55 (26)	3 (2)
Excessive crying	325 (29)	71 (16)	120 (34)	117 (57)	17 (14)
Poor feeding	526 (47)	179 (41)	220 (61)	104 (50)	23 (19)
Vomiting	335 (30)	102 (23)	147 (41)	66 (32)	20 (16)
Diarrhea	194 (17)	38 (9)	94 (26)	53 (25)	9 (7)

[a] Parent-reported gestational age <37 weeks (reported gestational age available for 1085).

[b] Parent-reported gestational age <32 weeks (reported gestational age available for 1085).

[c] Parent-reported birth weight <2.5 kg (reported birth weight available for 1066).

[d] Parent report of any ongoing medical problem diagnosed by a healthcare provider that started at birth or lasted at least 2 weeks.

[e] Weight-for-age *z*-score <−2; denominators reflect missing data for weight for some infants or exclusions for outlier values (*z*-score less than −5 or >5).

[f] ≥5 persons in household, including infant.

[g] Indicators of deprivation include: lack of electricity, presence of an earth floor, or lack of an indoor private flush toilet (or water-sealed toilet for the Philippines).

[h] Daily, weekly, or monthly smoking in home.

Table 2.

Clinical Course and Treatment during Hospitalization of Infants with Respiratory Syncytial Virus (RSV) Infection in Albania, Jordan, Nicaragua, and the Philippines

	All Sites ***N*** **= 1129** **No. (%)**	**Albania** ***N*** **= 438** **No. (%)**	**Jordan** ***N*** **= 358** **No. (%)**	**Nicaragua** ***N*** **= 209** **No. (%)**	**Philippines** ***N*** **= 124** **No. (%)**
Duration of illness before admission-median (IQR) days	3 (2–4)	3 (2–4)	3 (1–4)	3 (2–50)	2 (1–3)
Highest level of care					
ICU[a]	358 (32)	201 (46)	111 (31)	31 (15)	15 (12)
General ward	771 (68)	237 (54)	247 (69)	178 (85)	109 (88)
Vital signs					
Fever (≥38°C) [b]	475 (42)	172 (39)	168 (47)	59 (28)	76 (61)
Respiratory rate recorded[c]	976 (86)	426 (97)	217 (61)	209 (100)	124 (100)
Tachypnea[b,d]	329 (34)	113 (27)	28 (13)	86 (41)	102 (82)
Oxygen saturation (SpO_2) recorded [c]	837 (74)	423 (97)	305 (85)	67 (32)	42 (34)
Hypoxemia (SpO_2 <92%) [b]	448 (54)	194 (46)	229 (75)	15 (22)	10 (24)
Clinical interventions and treatment					
Supplemental oxygen (O_2)	505 (45)	186 (42)	226 (63)	56 (27)	37 (30)
Highest level of O_2 support					
Non-invasive ventilation [e]	10 (1)	1 (<1)	4 (1)	0 (0)	5 (4)
Mechanical ventilation	20 (2)	2 (<1)	7 (2)	8 (4)	3 (2)
IV Fluids	650 (58)	122 (28)	329 (92)	95 (45)	104 (84)
Tube feeding	77 (7)	49 (11)	9 (3)	9 (4)	10 (8)
Inotropes	40 (4)	5 (1)	16 (4)	11 (5)	8 (6)
Antibiotics	1083 (96)	431 (98)	347 (97)	184 (88)	121 (98)
Corticosteroids					
Inhaled	29 (3)	16 (4)	3 (1)	8 (4)	2 (2)
Systemic	390 (35)	252 (58)	69 (20)	40 (19)	29 (23)
Both	47 (4)	15 (3)	6 (2)	22 (11)	4 (3)
Chest radiograph (CXR) performed	1008 (89)	403 (92)	309 (87)	179 (86)	117 (94)
CXR interpretation of pneumonia [f]	522 (52)	114 (28)	175 (57)	126 (70)	107 (91)

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	All Sites *N* = 1129 No. (%)	Albania *N* = 438 No. (%)	Jordan *N* = 358 No. (%)	Nicaragua *N* = 209 No. (%)	Philippines *N* = 124 No. (%)
Length of stay-median (IQR) days	6 (4–7)	6 (4–7)	6 (4–8)	5 (3–7)	5 (4–8)
Primary discharge diagnosis					
Bronchiolitis	362 (32)	279 (64)	33 (9)	48 (23)	2 (2)
Pneumonia [g]	532 (47)	97 (22)	198 (55)	126 (61)	111 (90)
Pertussis-like syndrome	46 (4)	1 (<1)	42 (12)	3 (1)	0
Sepsis	45 (4)	1 (<1)	39 (14)	2 (1)	3 (2)
Other respiratory diagnosis [h]	44 (4)	27 (6)	10 (3)	6 (3)	1 (<1)
Other non-respiratory diagnosis [h]	91 (8)	33 (8)	28 (8)	23 (11)	7 (6)
Not documented	9 (1)	0	8 (2)	1 (<1)	0
Outcome					
Died	9 (1)	1 (<1)	4 (1)	1 (<1)	3 (2)
During hospitalization	4 (<1)	0	3 (1)	1 (<1)	0
After hospital transfer	1 (<1)	0	0	0	1 (1)
After discharge (within 30 days)	4 (<1)	1 (<1)	1 (<1)	0	2 (2)
Readmitted within 30 days	21 (2)	4 (1)	13 (4)	1 (<1)	3 (2)

[a] Includes nine for which a determination was made that the infant needed ICU care but was not available.

[b] Any instance recorded during hospitalization.

[c] ≥1 measurement recorded during hospitalization.

[d] Defined as ≥60 breaths per minute for infants <2 months old and ≥50 breaths per minute for infants 2–12 months old.

[e] Includes CPAP or BiPAP.

[f] Radiologist or physician interpretation of pneumonia.

[g] Includes unspecified pneumonia, bacterial pneumonia, viral pneumonia, bronchial pneumonia, and consolidated pneumonia.

[h] Respiratory diagnoses include reactive airway disease, viral respiratory illness, upper respiratory illness, otitis media, bronchitis, transient tachypnea of the newborn; non-respiratory diagnoses include bacteremia, dehydration, seizure, meningitis, urinary tract infection, non-respiratory viral illness, and diarrhea/gastroenteritis.

Table 3.

Factors Associated with Illness Severity among Hospitalized Respiratory Syncytial Virus (RSV)-Positive Infants, All Sites

	Severe Illness *N* = 546 No. (%)	Very Severe Illness *N*=583 No. (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Age group, months				
0–2	208 (38)	392 (67)	4.6 (3.0-7.1) [b]	4.1 (2.6–6.5) [b]
3—5	134 (25)	107 (18)	2.0 (1.2–3.1) [b]	1.9 (1.1–3.1) [b]
6—8	118 (22)	49 (8)	1.0 (0.61–1.7)	0.96 (0.55–1.7)
9—11	86 (16)	35 (6)	Ref	Ref
Sex				
Male	321 (59)	344 (59)	Ref	Ref
Female	225 (41)	239 (41)	1.0 (0.78–1.3)	0.92 (0.71–1.2)
Site				
Albania	207 (38)	231 (40)	2.7 (1.9–3.9) [b]	2.8 (1.9–4.1) [b]
Jordan	104 (19)	254 (44)	5.9 (4.1–8.6) [b]	4.8 (3.2–7.1) [b]
Nicaragua	148 (27)	61 (10)	Ref	Ref
Philippines	87 (16)	37 (6)	1.0 (0.63–1.7)	1.2 (0.70–2.0)
Infant medical and birth history				
Preterm birth	34/521 (7)	55/564 (10)	1.5 (1.0–2.4)	1.5 (0.91–2.4)
Low birth weight	67/511 (13)	87/555 (16)	1.2 (0.86–1.8)	0.83 (0.52–1.3)
Type of delivery				
Vaginal	370/534 (69)	354/568 (62)	Ref	Ref
Cesarean section	164/534 (30)	214/568 (38)	1.4 (1.1–1.8) [b]	1.4 (1.03–1.8) [b]
In ICU after birth	45/529 (9)	107/568 (19)	2.5 (1.7–3.6) [b]	1.6 (1.0–2.5) [b]
Required ventilator after birth	23/533 (4)	42/563 (7)	1.8 (1.1–3.2) [b]	1.2 (0.66–2.2)
Prior hospitalization	94 (17)	79 (14)	0.75 (0.54–1.1)	1.4 (0.94–1.9)
Parent-reported underlying condition	29 (5)	34 (6)	1.1 (0.64–1.9)	1.2 (0.66–2.1)
Chronic heart or respiratory tract disease[c]	21 (4)	34 (6)	1.5 (0.86–2.8)	1.8 (0.95–3.3)
Low weight-for-age *z*-score	60/540 (11)	110/553 (20)	2.0 (1.4–2.8) [b]	1.9 (1.2–2.8) [b]
Breast feeding				

	Severe Illness *N* = 546 No. (%)	Very Severe Illness *N*=583 No. (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Not initiated	28 (5)	44 (8)	Ref	Ref
Initiated but not currently	78 (15)	56 (10)	0.44 (0.28–0.80) [a]	0.59 (0.29–1.2)
Currently, partial	279 (51)	276 (47)	0.63 (0.38–1.0)	0.84 (0.46–1.5)
Currently, exclusive	158 (29)	207 (35)	0.83 (0.50–1.40)	0.65 (0.35–1.2)
RSV subgroup				
RSV A	213/486 (44)	220/528 (42)	Ref	Ref
RSV B	273/486 (56)	308/528 (58)	1.1 (0.85–1.4)	1.0 (0.78–1.4)

[a] Individual variables adjusted for categorical age, sex, site, and preterm birth.

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

[c] Chronic heart or respiratory tract disease: (1) parent report of chronic respiratory disease or heart condition ($n = 37$), or (2) discharge diagnosis or discharge code indicating congenital/chronic heart or lung disease ($n = 18$, in addition to those identified by parent report).