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The Impact of Human Immunodeficiency Virus Exposure on Respiratory Syncytial Virus–associated Severe Respiratory Illness in South African Infants, 2011–2016

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Abstract

From 2011 through 2016, we conducted surveillance for severe respiratory illness in infants. Human immunodeficiency virus exposure significantly increased the risk of respiratory syncytial

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virus (RSV)–associated hospitalization in infants aged <5 months. More than 60% of RSV-associated hospitalizations occurred in the first 4 months of life and may be preventable through maternal vaccination or birth-dose monoclonal antibody.

Keywords

respiratory syncytial virus; human immunodeficiency virus; incidence; South Africa

Respiratory syncytial virus (RSV) causes an estimated 3.2 million severe acute lower respiratory tract illness (LRTI) hospitalizations and 94 600–149 400 deaths annually in children aged <5 years, with the majority of deaths occurring in developing countries [1, 2]. Few data describe RSV-associated hospitalized illness in infants in high human immunodeficiency virus (HIV)–prevalence areas of sub-Saharan Africa. These data are essential to informing strategies for RSV vaccine introduction and other interventions in low- and middle-income countries (LMICs).

Existing estimates of RSV burden in sub-Saharan Africa have identified high rates of disease in the first year of life [3–6]. However, most estimates were not powered to assess rates of illness by month of life that are necessary to inform policies regarding interventions such as maternal vaccination or birth-dose monoclonal antibody, which may provide passive protection for 3–5 months [7, 8]. In addition, although data have demonstrated that HIV infection and HIV exposure increase the incidence of RSV-associated hospitalization [9], this has not been explored by month of life, and the duration of this increased risk is not known. In South Africa, in utero HIV transmission has dropped below 1%, but HIV prevalence remains high among pregnant women (>30%), making HIV exposure an important public health concern [10, 11]. Given the limited data, we aimed to estimate the rate of RSV-associated hospitalizations by month of life and to evaluate the magnitude and duration of the impact of HIV exposure on RSV-associated hospitalization rates in infants.

METHODS

From 2011 through 2016, we conducted prospective surveillance for severe respiratory illness (SRI) in infants in 3 South African hospitals (two hospitals in Klerksdorp and one hospital in Pietermaritzburg) (two hospitals in Klerksdorp and one hospital in Pietermaritzburg) in 2 provinces [12]. In infants aged 2 days–2 months, SRI was defined as a hospitalized infant with a diagnosis of suspected sepsis or physician-diagnosed acute LRTI. In infants aged 3–11 months, SRI was defined as a hospitalized child with physician-diagnosed LRTI. We tested nasopharyngeal aspirates or swabs for RSV using multiplex polymerase chain reaction (PCR). For 2011–2014, a multiplex PCR assay was used to test for influenza A and B viruses; RSV; parainfluenza virus types 1, 2, and 3; and adenoviruses, rhinoviruses, human metapneumoviruses, and enteroviruses [13]. For 2015–2016, we used a commercial multiplex PCR (FTD Flu/RSV assay, FastTrack Diagnostics, Sliema, Malta) to test for influenza A and B viruses and RSV. We determined HIV-1 exposure status by medical record review, maternal or infant rapid HIV testing, or maternal enzyme-linked immunosorbent assay. We determined HIV-1 infection status in HIV-exposed infants or infants with unknown serostatus by HIV PCR.

We estimated average annual RSV-associated hospitalization rates per 100 000 population using the number of SRI hospitalizations multiplied by the proportion who tested positive for RSV and dividing by the sum of the mid-year population estimate for each catchment area. We adjusted rates for healthcare-seeking behavior, nonenrollment (refusals, weekend admissions), and the attributable fraction of RSV detection to illness [14]. Where published population estimates were unavailable (infants by month of age), we estimated from the relative proportion of infants aged 0–11 months assuming the birth rate was constant throughout the year and adjusting for neonatal and infant mortality [15]. We stratified hospitalization rates by HIV-exposure status. We extrapolated the number of HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infants from national prevalence estimates [16]. We used log binomial regression to estimate age-specific and overall age-adjusted relative risk for RSV-associated SRI among HEU infants compared to HUU infants.

The University of the Witwatersrand Human Research Ethics Committee and the University of KwaZulu-Natal Human Biomedical Research Ethics Committee approved SRI surveillance (protocols M140824 and BF157/08 [updated protocol BE496/14]). The US Centers for Disease Control and Prevention determined that this did not constitute human subjects research (NRD ID2012–6197 [updated protocol NRD CGH2015–210]).

RESULTS

During the study period, 5216 hospitalized infants met our surveillance case definition, and 2363 (45.3%) were enrolled (Figure 1). Among the 2243 (94.9%) enrolled infants with RSV results, 680 (30.3%) tested positive for RSV. Among the 680 RSV-positive infants, 578 (85.1%) were admitted with a diagnosis of LRTI, 106 (15.6%) with bronchiolitis, and 3 (0.4%) with suspected sepsis. The median age of hospitalized infants with RSV was 3.2 months compared to 4.7 months for infants who tested RSV negative ($P < .001$). Estimated mean RSV-associated hospitalization rates were highest in infants aged <1 month—7910 (95% confidence interval [CI], 6155–9665) per 100 000 population, and rapidly declined thereafter: 6 months, 2609 (95% CI, 1971–3398) and 11 months, 927 (95% CI, 531–1404) per 100 000 population (Table 1). More than 60% of RSV-associated hospitalizations occurred in the first 4 months of life.

Among the 581 (85.4%) RSV-positive infants with HIV results, 21 (3.6%) were HIV infected and 243 (41.8%) were HEU. HIV exposure statistically significantly increased the risk of RSV-associated hospitalization in infants aged <5 months (Table 1). There was no statistically significant difference in risk by month after the fifth month of life.

DISCUSSION

In South Africa, the burden of RSV-associated hospitalizations is highest in the youngest infants, suggesting maternal antenatal vaccination or birth-dose monoclonal antibody might be effective strategies for reducing severe disease in infants. HIV-exposed infants aged <5 months are at increased risk of RSV-associated hospitalization compared to HUU infants and could be prioritized for such interventions, when available.

We identified rates of RSV-associated SRI hospitalization in infants aged <6 months that were higher than those reported from Kenya [3, 4]. Studies that report child-years of observation (cyo) are typically cohort studies where the population is well defined and followed at regular intervals. Assuming population denominators and adjustments for seeking care are accurate, reports of cyo- and population-based estimates should be comparable. In Kilifi, Kenya, RSV-associated hospitalizations in infancy occurred at a much lower rate (13/1000 cyo) than RSV-associated severe LRTI (121/1000 cyo), which may indicate differences in hospitalization practices, differences in diagnostic practices, or possible barriers to accessing care [3]. Another study estimated rates of RSV-associated severe acute respiratory illness hospitalization for infants aged <6 months from Western Kenya to be 13.4 (95% CI, 7.5–23.8) per 1000 persons, which is considerably lower than our estimate of 5010 per 100 000 (ie, 50.1 per 1000) [4]. In South Africa, a prior study reported incidence of RSV-associated acute LRTI hospitalization among infants aged <6 months as 24–32/1000 persons, which is also lower than our estimates [5]. We used adjustment factors for healthcare seeking (1.33 for Klerksdorp and 1.46 for Pietermaritzburg) that may have contributed to these differences. A private hospital network in South Africa estimated the mean annual RSV-associated hospitalization rate in children aged <1 year from 2007 through 2012 to be 7601 (95% CI, 4312–10 817) per 100 000 infants using an ecologic model; this is more than double our estimate of 3262 per 100 000 [6]. The higher rate in the private sector hospitals could reflect differences in methodology or differing criteria for hospital admission at private vs public hospitals.

Only 1 published study from South Africa has assessed the incidence of RSV-associated LRTI hospitalizations among HUU, HEU, and HIV-infected infants. This study found similar rates RSV-associated hospitalization among HUU (3074 [95% CI, 2827–3357]), HEU (5003 [95% CI, 4505–5541]), and HIV-infected infants aged <6 months (6709 [95% CI, 4589–9471]) per 100 000 population, with incidence rate ratios of 1.4 (95% CI, 1.3–1.6) and 1.9 (95% CI, 1.3–2.7) compared to HUU infants, respectively [9]. We found the same relative risk of RSV-associated hospitalization in HEU compared to HUU infants aged <6 months, 1.4 (95% CI, 1.3–1.6).

There were several limitations to this analysis. First, there were no estimates of the population by month of age. Second, we applied the same attributable fraction of RSV detection to illness to infants of all age groups as our estimates were not available by month of age. However, because the attributable fraction was very high in this age group (94%), month-to-month variations are likely small. Furthermore, persistence of RSV in the nasopharynx after acute illness [17] may have led us to overestimate rates of disease in this population. Third, we assumed the same proportion of RSV positivity among children enrolled and not enrolled in our surveillance system. There may have been biases in enrollment procedures that could have either increased or decreased the proportion of RSV-infected infants enrolled in our surveillance platform. Finally, we relied on medical record review or testing when consent was provided to determine HIV-exposure status. Therefore, data on HIV-infection and HIV-exposure status were missing for 99 (14.6%) RSV-positive infants.

Our data demonstrate a considerable burden of RSV-associated severe disease in young infants. While currently there is only one product licensed in high-income countries for the prevention of RSV, that is, palivizumab, there are at least 4 other maternal or pediatric vaccines or monoclonal antibody products in phase 2 or phase 3 clinical trials that may be considered for implementation in LMICs [18]. Data on the burden of RSV-associated illness by month of age are essential to inform country-specific policies for the evaluation and use of these interventions.

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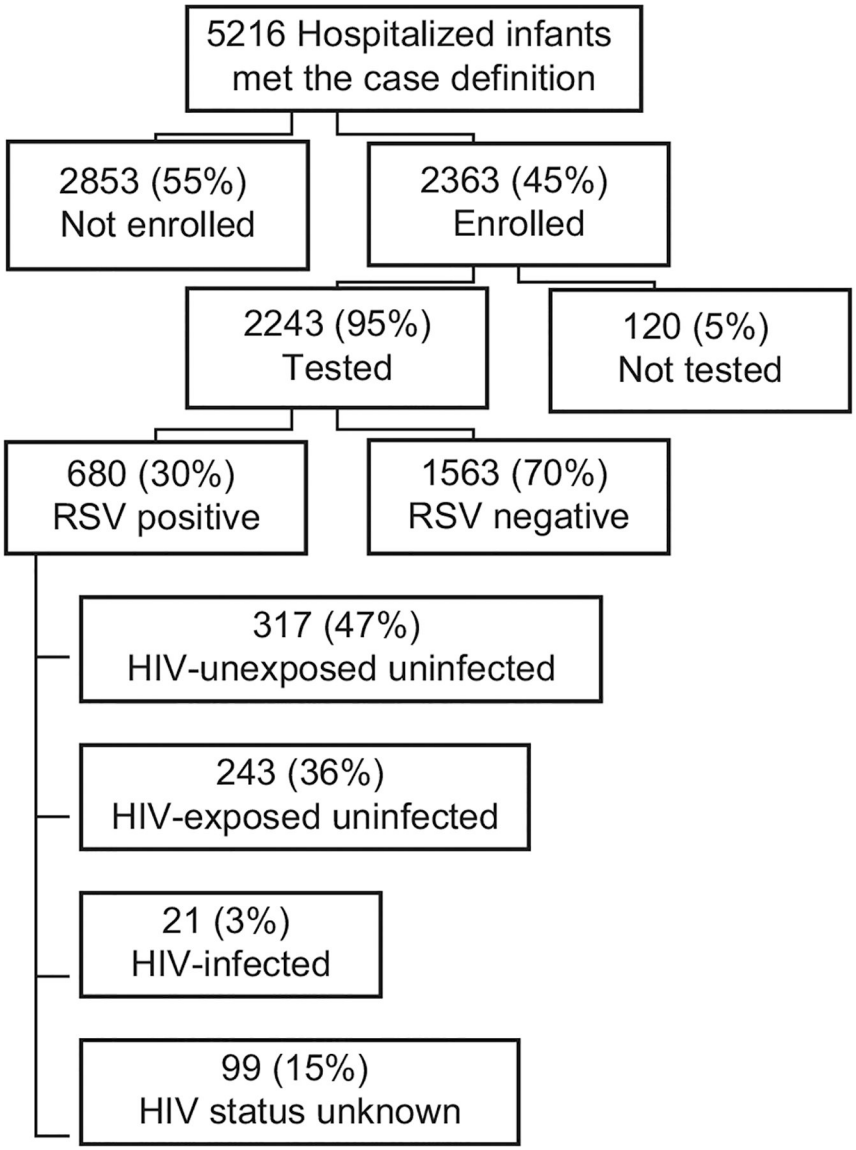

Figure 1.

Screening and enrollment of infants aged 0–11 months with severe respiratory illness, Klerksdorp and Pietermaritzburg, South Africa, 2011–2016. Abbreviations: HIV, human immunodeficiency virus; RSV, respiratory syncytial virus.

Table 1.

Estimated Mean Annual Rates of and Relative Risk Associated With Human Immunodeficiency Virus Exposure for Respiratory Syncytial Virus–associated Severe Respiratory Illness Hospitalization in Infants Aged 0–11 Months, Klerksdorp and Pietermaritzburg, South Africa, 2011–2016

Age, mo	Severe Respiratory Illness Hospitalization Rates[a,b] (95% Confidence Interval)			Relative Risk HIV-exposed Uninfected vs HIV-unexposed Uninfected	Cumulative Percent of Respiratory Syncytial Virus-associated Hospitalizations in Infants
	All	HIV-exposed Uninfected	HIV-unexposed Uninfected		
<1	7910 (6155–9665)	10 228 (6871–13 825)	6571 (4209–9135)	**1.6 (1.3–1.9)**	20.0
1	6808 (5900–7752)	9524 (7413–12 163)	6511 (5358–7679)	**1.5 (1.2–1.8)**	37.1
2	4913 (4109–5811)	6591 (4714–8580)	4462 (3431–5593)	**1.5 (1.1–1.9)**	49.5
3	4233 (3423–5087)	5563 (3838–7552)	3979 (2850–5139)	**1.4 (1.0–1.9)**	60.2
4	4103 (3274–5108)	5301 (3023–7898)	3853 (2972–4787)	**1.4 (1.0–1.9)**	70.6
5	2795 (2042–3594)	3585 (2323–5104)	2602 (1796–3540)	1.4 (1.0–2.0)	77.6
6	2609 (1971–3398)	3024 (1712–4672)	2399 (1499–3455)	1.3 (0.8–1.9)	84.2
7	1920 (1345–2646)	2005 (1138–3027)	1757 (694–3106)	1.1 (0.7–1.8)	89.0
8	1164 (720–1641)	1214 (543–2137)	1132 (625–1702)	1.1 (0.6–2.0)	92.0
9	1141 (637–1739)	1187 (406–2408)	1082 (425–1915)	1.1 (0.6–2.0)	94.9
10	1109 (657–1601)	1185 (456–2148)	1053 (431–1839)	1.1 (0.6–2.1)	97.7
11	927 (531–1404)	954 (301–1935)	871 (341–1508)	1.1 (0.5–2.2)	100
<6 months	5010 (4468–5550)	6419 (5335–7604)	4488 (3852–5148)	**1.4 (1.3–1.6)**	77.6
<12 months	3262 (2878–3655)	2933 (2403–3521)	2687 (2272–3129)	**1.3 (1.2–1.5)**	100

Bolded numbers are statistically significant.

[a]Rates expressed per 100 000 population.

[b]Estimated rates adjusted for the attributable fraction of respiratory syncytial virus, the proportion positive among those enrolled, and healthcare seeking.