



Epidemiology of influenza- and respiratory syncytial virus (RSV)-associated hospitalization in children aged less than 5 years in a setting with high HIV prevalence, South Africa, 2011-2016

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Best Practices and Innovations in Paediatric HIV & TB Care and Treatment

3 November 2017

Objectives

- Describe the epidemiology of influenza- and respiratory syncytial virus (RSV)-associated hospitalizations among children aged <5 years
- Estimate the incidence of influenza- and RSV-associated hospitalization among children aged <5 years, by HIV status
- Estimate the incidence of influenza- and RSV-associated hospitalization among children aged <1 year, by HIV exposure status
- Examine differences between hospitalized children who tested positive for influenza versus RSV using multivariable penalized logistic regression

Background

- Influenza and RSV are leading causes of hospitalization and death among children globally
- Limited data on influenza- and RSV-associated hospitalizations in low- and middle-income countries (LMIC)
 - Estimated that 99% of influenza- and RSV-associated deaths in children <5 years occur in developing countries
- Rates of influenza-associated hospitalizations in South African children are largely from the pandemic period and may not reflect seasonal burden
- Rates of RSV-associated hospitalizations in SA children are highly variable
- Few studies have assessed the impact of HIV exposure on hospitalization risk

Methods: Surveillance

- January 2011-December 2016
- Prospective, hospital-based surveillance for severe respiratory illness (SRI)
- SRI case definitions were age-specific:
 - 2 days to <3 months: a hospitalized infant with a diagnosis of suspected sepsis or physician-diagnosed lower respiratory tract infection
 - 3 to 59 months: a hospitalized child with physician-diagnosed lower respiratory tract infection
- Standardized case report form for consenting SRI cases
- Nasopharyngeal aspirates collected for multiplex rRT-PCR
- HIV serostatus determined by rapid HIV, ELISA or HIV-PCR

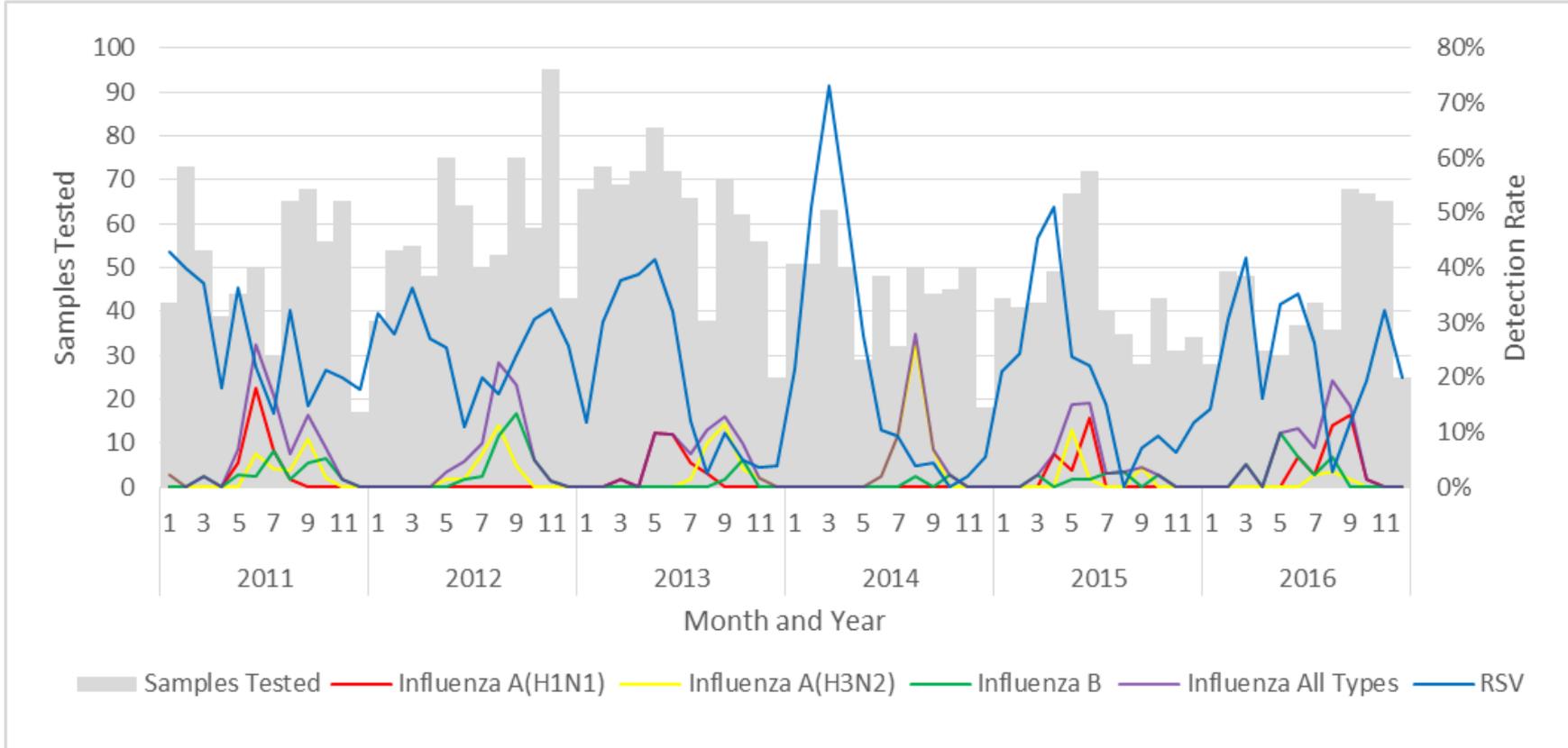
Methods: Rates

- Hospitalization rates per 100,000 population were calculated
- Number of SRI hospitalizations was multiplied by the proportion positive for influenza or RSV and divided by the mid-year population estimate
- Rates were adjusted for the following:
 - Non-enrollment (refusals, weekend admissions)
 - Healthcare seeking behavior
 - Attributable fraction of infection to illness
- Log binomial regression used to estimate relative risk of influenza- or RSV-associated SRI
 - among HIV-infected vs HIV-uninfected 0-59 months
 - HIV-infected, HIV-exposed uninfected (HEU) vs HIV-unexposed uninfected (HUU) infants

Methods: Comparison of influenza- vs RSV-infected

- Pearson's chi-square tests and Wald chi-square tests using logistic regression were used to assess differences in categorical variables
- Wilcoxon rank-sum tests were used to assess differences in median age
- Unconditional multivariable penalized logistic regression was used to determine factors associated with influenza vs RSV infection
 - Variables with p-values <0.2 in univariate analysis were assessed
 - Backwards elimination used to determine the final model
 - p-value <0.05 statistically significant

Figure 1. Influenza and RSV in children aged 0-59 months enrolled in surveillance, South Africa, 2011-2016



Detection rate of influenza and RSV, age distribution

- Among 3647 hospitalized children aged 0-59 months enrolled and tested:
 - 200 (5.5%) tested positive for influenza and 877 (24.1%) for RSV
 - Highest detection rate for influenza in children 24-59 months (8.5%)
 - Highest detection rate for RSV in infants aged 0-2 months (38.6%)

Age Group (months) (n, %)	Total samples tested (N=3647)	Total positive for influenza or RSV (N=1077)	Influenza positive (n=200)	RSV positive (n=877)	Univariate Odds Ratio (95% CI)	Multivariable Odds Ratio (95% CI)
0-2	839 (23.0)	336 (31.2)	11 (5.5)	324 (36.9)	Ref	Ref
3-5	645 (17.7)	225 (20.9)	24 (12.0)	201 (22.9)	3.5 (1.7-7.3)	3.5 (1.7-7.3)
6-11	760 (20.8)	210 (19.5)	55 (27.5)	155 (17.6)	10.5 (5.3-20.5)	10.7 (5.4-21.2)
12-23	730 (20.0)	169 (15.7)	53 (26.5)	116 (13.2)	13.5 (6.8-26.6)	11.2 (5.6-22.3)
24-59	673 (18.5)	138 (12.8)	57 (28.5)	81 (9.2)	20.7 (10.4-41.3)	14.3 (7.1-28.7)
Median age (IQR)^a	8.2 (15.4)	5.6 (11.5)	14.3 (19.5)	4.5 (8.5)	–	–

HIV serostatus and exposure status of influenza- and RSV- positive hospitalized children

- HIV serostatus available for 973 (90.3%) of children who tested positive for influenza or RSV, 10.7% and 5.9% HIV-infected, respectively ($p=0.02$)
- HIV exposure status available for 652 (84.7%) of 770 infants who tested positive for influenza or RSV
 - 78 influenza positive: 8 (10%) HIV-infected, 25 (32%) HEU, 45 (58%) HUU
 - 573 RSV positive: 21 (4%) HIV-infected, 239 (42%) HEU, 313 (55%) HUU

Table 2: Mean annual rates of influenza- associated severe respiratory illness hospitalization in children aged 0-59 months by HIV status, South Africa, 2011-2016

Age group (in months)	Severe respiratory illness hospitalization rates ^{a,b} (95% CI)			RR HIV-infected vs HIV-uninfected (95% CI)
	All	HIV-infected	HIV-uninfected	
Influenza-associated				
0-2	214.3 (86.8-358.1)	480.8 (27.3-1575.9)	195.6 (66-335)	2.5 (0.8-7.9)
3-5	403.9 (255.3-583.7)	564 (19.5-1872.9)	261.1 (160.4-377.1)	2.2 (0.6-7.4)
0-5^c	308.5 (170.6-470.3)	515.8 (23.4-1701)	234.7 (122.4-360.1)	2.3 (1.0-5.4)
6-11	524.1 (389.5-676.9)	1092.2 (359-2175.1)	469.3 (346.3-616.2)	2.3 (1.4-3.8)
0-11^d	415.7 (279.5-573)	851 (208.8-1976.8)	338.4 (221.4-473.3)	2.3 (1.5-3.6)
12-23	224.3 (161.6-288.3)	419.9 (83.4-858.8)	194.9 (140.1-260.5)	2.2 (1.3-3.7)
24-59	77.6 (58.4-99.3)	156.9 (36.5-335.3)	71.2 (52-92.9)	2.2 (1.2-4.0)
0-59^e	174.3 (123.1-231.6)	358.3 (81.8-786.6)	154.3 (106.5-209.5)	2.2 (1.7-3.0)

Table 3. Mean annual rates of influenza-associated severe respiratory illness hospitalization in infants aged 0-11 months by HIV exposure status, South Africa, 2011-2016

Age group (in months)	Severe respiratory illness hospitalization rates ^{a,b} (95% CI)				RR HIV-infected vs. HIV- unexposed uninfected (95% CI)	RR HIV-exposed uninfected vs. HIV-unexposed uninfected (95% CI)
	All	HIV-infected	HIV-exposed uninfected	HIV-unexposed uninfected		
Influenza-associated						
0-2	214.3 (86.8-358.1)	480.8 (27.3-1575.9)	260.1 (51.4-519.7)	91.7 (8.7-235.9)	5.2 (1.5-18.2)	2.8 (1.3-6.0)
3-5	403.9 (255.3-583.7)	564 (19.5-1872.9)	272.6 (83-503.6)	144.4 (77.5-223.5)	3.9 (1.1-13.4)	1.9 (1.1-3.3)
0-5^c	308.5 (170.6-470.3)	515.8 (23.4-1701)	267.7 (60.5-460.4)	113.9 (48.8-199.8)	4.5 (1.9-10.7)	2.2 (1.4-3.4)
6-11	524.1 (389.5-676.9)	1092.2 (359-2175.1)	553.5 (249.4-918.8)	404.1 (283.5-553.8)	2.7 (1.6-4.5)	1.4 (0.9-2.0)
0-11^d	415.7 (279.5-573)	851 (208.8-1976.8)	323.3 (113.5-579)	213.1 (131.2-317.9)	3.0 (1.9-4.7)	1.7 (1.2-2.2)

Table 4: Mean annual rates of RSV- associated severe respiratory illness hospitalization in children aged 0-59 months by HIV status, South Africa, 2011-2016

Age group (in months)	Severe respiratory illness hospitalization rates ^{a,b} (95% CI)			RR HIV-infected vs HIV-uninfected (95% CI)
	All	HIV-infected	HIV-uninfected	
RSV-associated				
0-2	6556.9 (5971.7-7260.8)	14,241.5 (27.3-38,046.2)	6297.7 (5708.8-6865.3)	2.3 (1.1-4.6)
3-5	3433.6 (3018.9-3916.1)	7530.9 (19.5-15,922.5)	3383.4 (2985.1-3817.7)	2.2 (1.2-4.0)
0-5^c	5003.4 (4503-5597.2)	9176.3 (1270.9-21,347)	4883.4 (4387.3-5386.7)	2.2 (1.4-3.5)
6-11	1494.8 (1263.3-1731.6)	6068.9 (1978.8-11,963.3)	1426.1 (1205-1662.9)	4.3 (2.7-6.8)
0-11^d	3258.5 (2891.9-3674.8)	7315 (1694.9-15,726.2)	3185.5 (2824.5-3557.9)	2.9 (2.1-4.0)
12-23	403.3 (324.6-486.9)	2015.4 (890.6-3517.9)	382.5 (301.5-463.4)	5.3 (3.5-7.9)
24-59	92.1 (71.1-114.6)	564.1 (219.9-991.8)	84.7 (63.3-106.3)	6.7 (4.2-10.5)
0-59^e	786.7 (685.1-900)	1469.4 (498.1-2821.7)	775.2 (672.9-880.1)	3.9 (3.2-4.9)

Table 5. Mean annual rates of RSV-associated severe respiratory illness hospitalization in infants aged 0-11 months by HIV exposure status, South Africa, 2011-2016

Age group (in months)	Severe respiratory illness hospitalization rates ^{a,b} (95% CI)				RR HIV- infected vs. HIV-unexposed uninfected (95% CI)	RR HIV- exposed uninfected vs. HIV-unexposed uninfected (95% CI)
	All	HIV-infected	HIV-exposed uninfected	HIV-unexposed uninfected		
RSV-associated						
0-2	6556.9 (5971.7-7260.8)	14,241.5 (27.3-38,046.2)	9661.5 (8197.5- 11,211.6)	6197.7 (8.7-6938)	2.3 (1.1-4.7)	1.6 (1.4-1.8)
3-5	3433.6 (3018.9-3916.1)	7530.9 (19.5-15,922.5)	4727.6 (3715.4-5818.1)	3337 (2817.8-3901.5)	2.3 (1.3-4.0)	1.4 (1.2-1.7)
0-5^c	5003.4 (4503-5597.2)	9176.3 (1270.9-21,347)	6474.8 (5360.5-7663)	4234.5 (3697.9-4811)	2.3 (1.4-3.6)	1.5 (1.4-1.7)
6-11	1494.8 (1263.3-1731.6)	6068.9 (1978.8- 11,963.3)	1278.9 (987.7-1603.7)	1107.9 (894.4-1340.3)	5.5 (3.4-8.8)	1.1 (1.0-1.4)
0-11^d	3258.5 (2891.9-3674.8)	7315 (1694.9- 15,726.2)	2920.3 (2375-3510.3)	2526.1 (2172.3-2907.7)	3.1 (2.3-4.3)	1.4 (1.3-1.5)

Table 6. Comparison of influenza- vs RSV-associated hospitalizations in children, South Africa, 2011-2016

	Total positive for influenza or RSV (N=1077)	Influenza positive (n=200)	RSV positive (n=877)	Univariate Odds Ratio (95% CI)	Multivariable Odds Ratio (95% CI)
Non-HIV chronic illness ^b	108/1077 (10.0)	37/200 (18.5)	71/877 (8.1)	2.6 (1.7-4.0)	2.2 (1.4-3.6)
Tachypnea ^e	636/1074 (59.2)	96/200 (48.0)	540/874 (61.8)	0.6 (0.4-0.8)	0.6 (0.4-0.9)
Given supplemental oxygen	711/1064 (66.8)	93/197 (47.2)	618/867 (71.3)	0.4 (0.3-0.5)	0.5 (0.4-0.8)
Mechanical ventilation	24/1061 (2.3)	7/197 (3.6)	17/864 (2.0)	1.8 (0.7-4.5)	3.0 (1.1-7.7)
Non-respiratory admission diagnosis (e.g. sepsis, diarrhea, etc.)	64/1066 (6.0)	23/197 (11.7)	41/869 (4.7)	2.7 (1.6-4.6)	2.1 (1.1-4.1)
Deaths, case fatality ratio (%)	10/1059 (0.9)	2/197 (1.0)	8/862 (0.9)	1.1 (0.2-5.2)	-

Influenza vs RSV in hospitalized children

- Differences in seasonality
- Differences in burden by age group
 - RSV burden 8x's that of influenza in infants
 - Similar burden among children aged 24-59 months
- Differences in relative risk by HIV serostatus, HIV exposure status
 - Highest RR for influenza in infants 0-2 months
 - RSV RR increased with increasing age
- No difference in case-fatality ratio in this study
 - Prior studies reported higher CFR for influenza

Clinical/programmatic implications

- HIV-infected and HEU infants have increased risk of influenza- and RSV-associated hospitalizations
- Maternal influenza vaccination should be encouraged to protect both mother and child
- Vaccination of HIV-infected infants from 6 months should also be considered
- Vaccines or long-life monoclonal antibodies to prevent RSV-infection may be available in 3-5 years
 - 1 new vaccine in Phase 3, 5 products in Phase 2 trials
 - HIV-infected and HEU infants should be prioritized for these interventions

For more information, contact CDC
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