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Lower Respiratory Tract Infections in Children in a Well-vaccinated South African Birth Cohort: Spectrum of Disease and Risk Factors

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Background. Childhood lower respiratory tract infections (LRTIs) cause substantial morbidity and under-5 child mortality. The epidemiology of LRTI is changing in low- and middle-income countries with expanding access to conjugate vaccines, yet there are few data on the incidence and risk factors for LRTI in these settings.

Methods. A prospective birth cohort enrolled mother–infant pairs in 2 communities near Cape Town, South Africa. Active surveillance for LRTI was performed for the first 2 years of life over 4 respiratory seasons. Comprehensive data collection of risk factors was done through 2 years of life. World Health Organization definitions were used to classify clinical LRTI and chest radiographs.

Results. From March 2012 to February 2017, 1143 children were enrolled and followed until 2 years of age. Thirty-two percent of children were exposed to antenatal maternal smoking; 15% were born at low birth weights. Seven hundred ninety-five LRTI events occurred in 429 children by February 2017; incidence of LRTI was 0.51 and 0.25 episodes per child-year in the first and second years of life, respectively. Human immunodeficiency virus (HIV)–exposed, uninfected infants (vs HIV-unexposed infants) were at increased risk of hospitalized LRTI in the first 6 months of life. In regression models, male sex, low birth weight, and maternal smoking were independent risk factors for both ambulatory and hospitalized LRTI; delayed or incomplete vaccination was associated with hospitalized LRTI.

Conclusions. LRTI incidence was high in the first year of life, with substantial morbidity. Strategies to ameliorate harmful exposures are needed to reduce LRTI burden in vulnerable populations.

Keywords. Lower respiratory tract infection; pneumonia; child health; incidence.

Childhood lower respiratory tract infections (LRTIs) cause >700 000 deaths in children <5 years of age annually. This is a substantial decrease from 1.7 million LRTI-associated deaths in children <5 years of age in 1990, reflecting decreased LRTI incidence [1]. These improvements in childhood LRTI burden and mortality have largely been due to improved living conditions, childhood nutrition, and expanded access to childhood vaccines, including conjugate vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) [2]. Decreased bacterial LRTI has resulted in proportional increase in viral or mixed infective LRTI [3], which may require different prevention and management strategies. Further reduction of the residual burden of childhood LRTI, especially severe and hospitalized LRTI, requires better understanding of its changing epidemiology and risk factors to strengthen interventions [4].

Young children, especially those <6 months of age, remain at greatest risk for severe LRTI [5, 6]. Prematurity predicts severe viral LRTI [7] and mortality in both low-income and high-income countries (HICs) [8]. However, effects of other risk factors may not be constant across settings: Lack of exclusive breastfeeding has a larger effect in low- and middle-income countries (LMICs; 2.7 times increased risk of severe LRTI) compared to HICs (1.3 times increased risk) [9]. Risk factors such as severe malnutrition are rare in HICs, but common in LMICs. Excess risk associated with human immunodeficiency virus (HIV) exposure may be ameliorated by maternal antiretroviral therapy (ART) and improved breastfeeding [10, 11], or may have an effect only in early infancy, but there are no longitudinal data investigating this.

Accurate measurement of population-based LRTI incidence in young children in LMIC is challenging; birth cohorts with active LRTI surveillance provide unique opportunities for direct measurement of incidence, severity, and risk factors, including variations over seasons. This study aimed to investigate

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incidence, severity, and age-specific risk factors of LRTI among children enrolled in an African birth cohort (the Drakenstein Child Health Study) followed until 24 months of age, over 4 respiratory seasons (2012–2017).

METHODS

Study Design and Population

The Drakenstein Child Health Study is a birth cohort outside Cape Town, South Africa. Detailed description of the cohort is published elsewhere [12]. In brief, pregnant women (20–28 weeks' gestation) attending antenatal care at 1 of 2 clinics were recruited and followed through pregnancy, delivery, and with their children for 2 years. These 2 clinics serve 2 communities with different cultural profiles, reflecting South Africa's political history of racial segregation. One community was historically restricted to individuals of mixed ancestry (Newman); the other to individuals of black African ancestry (Mbekweni). Both communities are of low socioeconomic status (SES) with high unemployment and HIV prevalence. The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC 401/2009; 651/2013) provided ethical approval. Mothers provided written informed consent at enrollment, with annual renewal.

Childhood vaccinations followed national schedules: BCG at birth; 13-valent pneumococcal conjugate vaccine (PCV13) (6 weeks, 14 weeks, 9 months); hexavalent vaccine (including acellular pertussis and Hib) (6, 10, and 14 weeks and 18 months); and measles vaccine (9 and 18 months). Guidelines for prevention of mother-to-child transmission of HIV (PMTCT) changed during the study period. Before 2014, most HIV-infected women received only nevirapine and zidovudine; those with CD4 counts <350 cells/µL initiated triple ART. From 2014, ART was initiated without CD4 restriction. HIV-exposed infants were tested with HIV DNA polymerase chain reaction (Cobas Ampliprep/Cobas TaqMan HIV-1, Roche Diagnostics Systems, Branchburg, New Jersey) between 6 and 10 weeks, and repeated if hospitalized. Repeat testing occurred at 9 and 18 months using age-appropriate tests according to local guidelines. HIV-exposed infants were given co-trimoxazole prophylaxis from 6 weeks until breastfeeding discontinuation.

Study Procedures

The primary outcome was LRTI incidence, with differentiation by severity (World Health Organization [WHO]–severe or hospitalization). Study staff, based at both clinics and the single regional hospital, performed LRTI surveillance using active case finding [13]. LRTI was diagnosed according to revised WHO guidelines when a child had cough or difficulty breathing, with either lower chest wall indrawing (LCWI) or age-appropriate tachypnea (≥50 breaths/minute if 2–12 months of age, ≥40 breaths/minute if ≥12 months of age) [14]. Severe LRTI was diagnosed in children aged <2 months with tachypnea >60 breaths/minute or LCWI; or in children of any age with danger signs (cyanosed, unable to drink, seizures, or decreased level of consciousness) [14]. In children with wheezing, LRTI was not diagnosed if tachypnea and LCWI resolved following administration of an inhaled bronchodilator. LRTI events were diagnosed at the hospital or a clinic; severe cases seen at a clinic were referred to the hospital. Indications for hospitalization included hypoxia (oxygen saturation <92% on room air) or poor social circumstances making ambulatory treatment unfeasible. Decision to hospitalize was made by treating clinicians, not study staff. Events occurring > 14 days following LRTI were considered new-onset LRTI. Chest radiographs were taken when hospitalized for LRTI, and read by 2 independent doctors trained in WHO-standardized chest radiograph reporting [15]. A third reader, blinded to previous readings, resolved discordant results. Risk factors of interest (birth weight and gestation, HIV exposure, SES, exposure to environmental tobacco smoke [ETS]) were recorded for all participants. Trained study staff administered structured interviews regarding symptoms and household/environmental exposures at enrollment, after delivery, at scheduled follow-up visits, and when diagnosed with LRTI. Smoking during pregnancy was classified by antenatal urine cotinine: nonsmoker (<10 ng/mL), passive smoker (10–499 ng/mL), or active smoker (≥500 ng/mL) [16].

Statistical Analysis

Predictors of ambulatory and hospitalized LRTI were explored with Poisson regression using generalized estimating equations clustered on mother–infant pairs [17]. Results are presented as unadjusted and adjusted incidence rate ratios (IRRs). Follow-up was censored at 2 years of age, last visit seen, or 28 February 2017. Analyses were stratified by child age to account for potential effect modification by age, with adjustment for enrollment clinic throughout. Due to markedly increased incidence of LRTI in HIV infection, 2 HIV-infected children were excluded from Poisson regression after sensitivity analysis indicated large changes in IRR estimates of several other risk factors. Final model selection was based on parsimony and lowest Akaike information criterion [18]. Population attributable risks (PARs) [19] of potentially modifiable risk factors for LRTI were calculated, including for maternal smoking. Data were analyzed using Stata version 11 software (StataCorp, College Station, Texas).

RESULTS

Between March 2012 and March 2015, 1137 pregnant women were enrolled, delivering 1143 live-born infants (4 sets of twins, 1 of triplets) (Figure 1). Overall, 849 children (74%) had completed 2 years follow-up by analysis censoring (February 2017), and 153 children (13%) were disenrolled before age 2 years

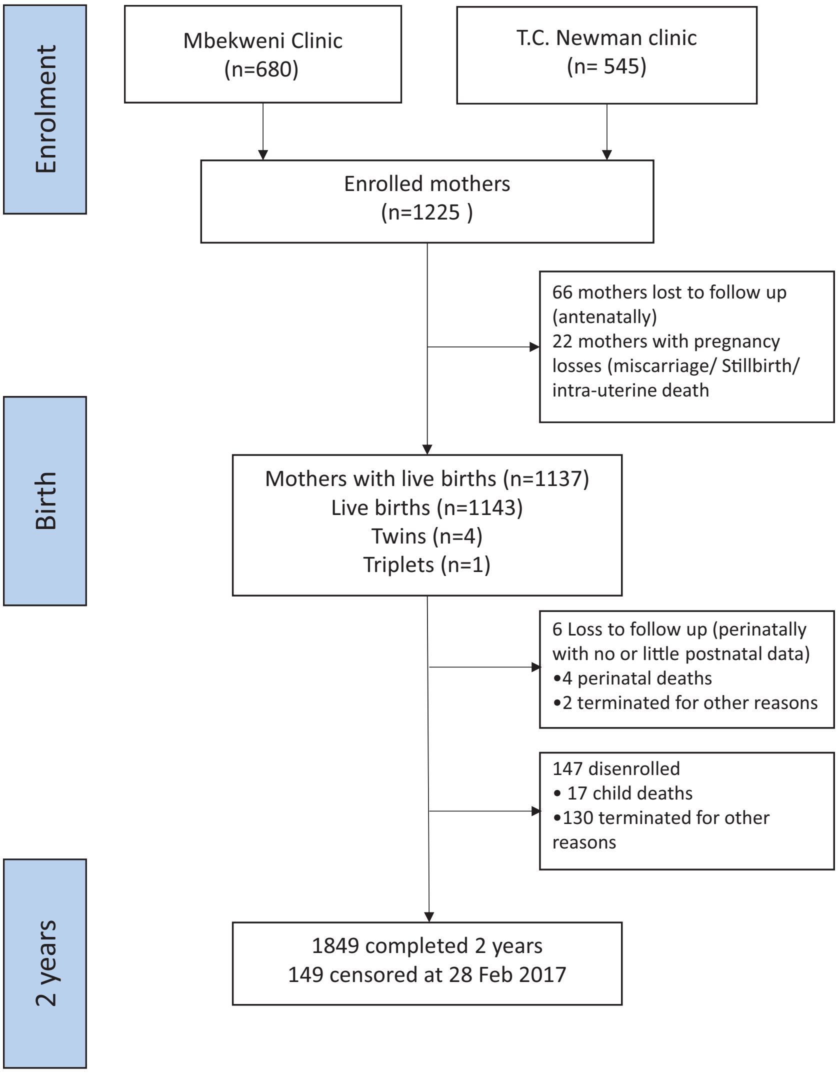

Figure 1. Flowchart of participants through the Drakenstein Child Health Study.

(median disenrollment age, 6 months); reasons were predominantly moving out of area (56 [37%]) and inability to contact mothers (35 [23%]). Median follow-up was 24 (interquartile range [IQR], 23.6–24) months, with 2043 child-years accrued in total.

Table 1 describes mother–child pairs. Household ETS was common: 82% of children were exposed in the first 6 months of life. Antenatal smoking was more common in mixed-ancestry (53%) than in black African households (15%). HIV was more common in African women (36%) than in those of mixed ancestry (3%). Coverage of primary series of PCV13 and hexavalent vaccine was excellent (92%).

There were 247 (22%) HIV-exposed but uninfected (HEU) children; 2 HIV-infected children commenced ART. Most women (1016 [89%]) initiated breastfeeding, but duration of exclusive breastfeeding was short (median, 1.8 [IQR, 0.9–3.7] months). By 6 months, only 86 (8%) babies were exclusively breastfed and 76 (6%) partially breastfed (breast and formula milk). HIV-exposed babies were less likely to initiate any breastfeeding (140/249 [56%]) than HIV-unexposed babies (875/893 [98%]) ($P < .0001$; Supplementary Table 1).

Clinical Characteristics of LRTI Events

There were 795 LRTIs in 429 children in the first 2 years of life. Some children had multiple LRTIs; by 2 years, 38% of the cohort had had at least 1 LRTI. Young children had the highest burden: 96 (55%) hospitalizations and 116 (66%) WHO-severe LRTIs occurred in children <6 months of age. Of all LRTIs, 176 (22%) were WHO-severe, of which 92 of 176 (52%) required hospitalization. Associated comorbidities and non-LRTI reasons for hospitalization are shown in Supplementary Table 2. Median age at hospitalized LRTI was 4.4 (IQR, 1.8–11.0) months, compared to 7.3 (IQR, 4.0–14.2) months for ambulatory LRTI ($P < .0001$; Table 2). There were no significant

Table 1. Baseline Characteristics of 1143 Mother–Infant Pairs Enrolled Into the Birth Cohort at 2 Sites

Characteristic	Mbekweni (n = 626)	T.C. Newman (n = 511)	Total (N = 1137)	*P* Value
Maternal characteristics				
Formal housing	353 (56)	362 (71)	715 (63)	<.0001
Household crowding				
≤4 people	263 (42)	118 (23)	381 (34)	<.0001
≥5 people	362 (58)	391 (77)	753 (66)	
Maternal smoking (by antenatal urine cotinine)				
Nonsmoker (cotinine <10 ng/mL)	195 (34)	56 (12)	251 (24)	
Passive smoker (cotinine 10–500 ng/mL)	291 (51)	173 (36)	464 (44)	<.0001
Active smoker (cotinine >500 ng/mL)	89 (15)	254 (53)	343 (32)	
Infant characteristics	(n = 632)	(n = 511)	1143	
Male sex	312 (49)	278 (54)	590 (52)	.09
Preterm (<37 wk)	108 (17)	82 (16)	190 (17)	.60
Low birth weight (<2500 g)	78 (12)	96 (19)	174 (15)	.003
HIV status				
HIV unexposed	400 (63)	494 (97)	894 (78)	<.0001
HIV exposed but uninfected	230 (36)	17 (3)	247 (22)	
HIV infected	2 (0.3)	0	2 (0.2)	
Breastfeeding				
Never breastfed	99 (16)	11 (2)	110 (10)	<.0001
Breastfed <6 mo	421 (67)	433 (85)	854 (75)	
Breastfed at least 6 mo	97 (15)	65 (13)	162 (14)	
Unknown	15 (2)	2 (0.4)	17 (1.5)	
EPI vaccine coverage (n = 871)				
All doses given, on time	437 (92)	360 (91)	797 (92)	.43
All doses given, some doses late	34 (7)	36 (9)	70 (8)	
At least 1 missing dose	3 (0.6)	1 (0.25)	4 (0.5)	

Data are presented as n (%) unless otherwise indicated.

Abbreviations: EPI, Expanded program on Immunization; HIV, human immunodeficiency virus.

differences between ambulatory and hospitalized events by enrollment clinic, SES, or season. Preceding coryza and upper respiratory tract symptoms (82%), history of fever (66%), and wheezing (45%) were common.

Of 174 hospitalized LRTI events, 162 (93%) had interpretable chest radiographs. Radiological abnormality was reported in 124 (78%); 64 (40%) had primary end-point consolidation and 62 (38%) had other infiltrates. Children with radiological abnormality were equally likely to be hypoxic (32/126 [25%]) as children without radiological changes (10/36 [28%]; $P = .77$). Continuous positive airway pressure or intubation and mechanical ventilation was needed in 14 children (8%). There were 3 deaths (case fatality rate, 1.7% of hospitalized, 0.4% overall).

Incidence of LRTI

Incidence of LRTI in the first year of life was 0.51 episodes per child-year (e/cy), decreasing to 0.25 e/cy in the second year. Incidence of hospitalized LRTI in the first year of life was 0.13 e/cy and in the second year, 0.04 e/cy (Table 3). There were more LRTI cases in 2014–2015 than in 2012–2013; the incidence of hospitalized LRTI <1 year was 0.10 e/cy (95% confidence interval [CI], .08–.14) in the early time period, and 0.15 e/cy (95% CI, .12–.18) in the later period.

Risk Factors for LRTI

In unadjusted Poisson regression, hospitalized LRTI in the first 6 months of life was associated with maternal smoking, male sex, delayed or missed vaccinations, preterm delivery (PTD), and low birth weight (LBW; <2500 g) as well as maternal HIV infection and household crowding. Maternal smoking, delayed or missed vaccinations, LBW, or PTD remained significant risk factors between 6 and 12 months, but not after 12 months (Table 4).

Throughout the first 2 years, ambulatory LRTI was strongly associated with maternal smoking; male sex and lower SES were significant risk factors in the first year of life. PTD and LBW were significant only after 6 months of age; HIV exposure or delayed or missed vaccinations were not associated with ambulatory LRTI (Table 4).

HIV and Breastfeeding

HEU infants aged <6 months had increased incidence of hospitalized LRTI (IRR, 1.99 [95% CI, 1.11–3.54]) compared with HIV-unexposed (HU) infants; there was no effect of HIV exposure beyond 6 months of age (Table 4). In addition, HEU infants born to mothers who received triple ART in pregnancy had lower incidence of LRTI requiring hospitalization in the

Table 2. Comparison of Ambulatory and Hospitalized Lower Respiratory Tract Infection Events

Characteristic	Ambulatory (621 Events)	Hospitalized (174 Events)	*P* Value
No. of children	369	133	
Enrollment clinic			
Mbekweni	366 (59)	95 (53)	
T.C. Newman	255 (41)	79 (47)	.31
Year of study			
2012	36 (6)	16 (9)	< .0001
2013	83 (13)	47 (16)	
2014	238 (38)	62 (37)	
2015	213 (34)	43 25)	
2016	51 (8)	6 (3)	
Season			
Autumn	173 (28)	46 (26)	.35
Winter	205 (33)	69 (40)	
Spring	164 (26)	37 (21)	
Summer	79 (13)	22 (13)	
Mother active smoker in pregnancy[a]	231 (39)	69 (43)	.42
Male sex	376 (61)	116 (67)	.14
Age, mo			
Median (IQR)	7.3 (4.0–14.2)	4.4 (1.8–11.0)	< .0001
<6	266 (43)	96 (55)	< .0001
6–12	134 (22)	42 (24)	
>12	221 (36)	36 (21)	
Preterm: <37 wk	126 (20)	52 (30)	.008
Low birth weight: <2500 g	130 (21)	49 (28)	.046
HIV status			
HIV unexposed	469 (76)	125 (72)	.03
HIV exposed but uninfected	151 (24)	46 (26)	
HIV infected	1 (0.2)	3 (2)	
Weight-for-length *z* score, at time of LRTI, median (IQR)	0.65 (–0.22 to 1.7)	0.6 (–0.84 to 1.72)	.13
Duration of exclusive breastfeeding, mo, median (IQR)	1.84 (0.92–3.22)	1.84 (0.92–4.0)	.81
Preceding diarrhea	66 (11)	37 (21)	< .0001
Respiratory rate, breaths/min, median (IQR)	53 (46–59)	62 (56–69)	< .0001
Lower chest indrawing	383 (63)	150 (86)	< .0001
Wheeze at the time of LRTI	266 (43)	92 (53)	.02
Oxygen saturation, %, median (IQR)	98 (96–99)	94 (89–96)	< .0001
Hypoxia (oxygen saturation <92%)	6 (1)	43 (25)	< .0001
Chest radiographic findings (WHO classification)			
No consolidation/infiltrate		36 (22)	
Other consolidation/infiltrate		62 (38)	
Primary end-point consolidation or pleural effusion		64 (40)	
Ventilation received			
Continuous positive airway pressure		6 (3)	
Mechanical ventilation		8 (5)	

Data are presented as n (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; LRTI, lower respiratory tract infection; WHO, World Health Organization.

[a]Urine cotinine >500 ng/mL.

Table 3. Incidence Rates of Ambulatory, Hospitalized, and World Health Organization–severe Lower Respiratory Tract Infection in the First 2 Years of Life

Age	Ambulatory LRTI	Hospitalized LRTI	WHO-severe LRTI	All Clinical LRTI
<1 y	0.38 (.24–.42) e/cy	0.13 (.11–.15) e/cy	0.13 (.11–.15) e/cy	0.51 (.47–.55) e/cy
1–2 y	0.22 (.19–.25) e/cy	0.04 (.03–.05) e/cy	0.04 (.03–.06) e/cy	0.25 (.22–.29) e/cy
Total	0.30 (.28–.33) e/cy	0.09 (.07–.10) e/cy	0.09 (.07–.10) e/cy	0.39 (.36–.42) e/cy

Data are presented as incidence rate (95% confidence interval).

Abbreviations: e/cy, episodes per child-year; LRTI, lower respiratory tract infection; WHO, World Health Organization.

Table 4. Risk Factors as Incidence Rate Ratios for Ambulatory and Hospitalized Lower Respiratory Tract Infection for 1141 Human Immunodeficiency Virus–uninfected Children in the First 2 Years of Life, From Poisson Regression

	Ambulatory			Hospitalized		
Risk Factor	<6 mo	6–12 mo	>12 mo	<6 mo	6–12 mo	>12 mo
Mother active smoker in pregnancy[a]	1.14 (.98–1.34)	1.50 (1.24–1.81)	1.21 (1.01–1.44)	1.35 (1.07–1.72)	1.67 (1.15–2.42)	0.80 (.51–1.24)
SES quartile						
Highest	1	1	1	1	1	1
Moderate-high	1.41 (.92–2.18)	1.14 (.64–2.03)	0.93 (.57–1.51)	1.36 (.72–2.57)	1.33 (.51–3.73)	2.77 (.89–8.64)
Moderate-low	1.71 (1.15–2.55)	2.07 (1.26–3.42)	1.54 (.98–2.42)	1.36 (.72–2.57)	1.53 (.58–4.08)	1.53 (.44–5.33)
Lowest	1.25 (.81–1.93)	1.66 (.96–2.87)	1.69 (1.07–2.66)	1.43 (.75–2.73)	1.70 (.60–4.80)	2.25 (.63–8.09)
Household size						
≤4 people	1	1	1	1	1	1
≥5 people	0.87 (.65–1.17)	0.85 (.59–1.24)	1.10 (.79–1.55)	2.36 (1.34–4.13)	1.34 (.69–2.60)	1.22 (.55–2.73)
Male (compared to female)	1.65 (1.25–2.18)	1.54 (1.07–2.20)	1.22 (.89–1.67)	1.82 (1.15–2.87)	1.77 (.93–3.36)	2.10 (.99–4.48)
Low birth weight	1.10 (.76–1.60)	2.01 (1.35–3.01)	1.88 (1.27–2.77)	2.03 (1.24–3.33)	2.52 (1.13–5.63)	2.03 (.80–5.15)
Preterm	1.00 (.71–1.42)	1.63 (1.09–2.43)	1.57 (1.07–2.30)	2.48 (1.55–3.94)	2.35 (1.08–5.08)	1.09 (.40–2.95)
HIV exposed	1.32 (.95–1.84)	0.98 (.61–1.57)	0.91 (.60–1.38)	1.99 (1.11–3.54)	1.26 (.44–3.60)	0.83 (.21–2.20)
Wasting[b]	0.94 (.70–1.27)	1.20 (.53–2.69)	1.23 (.52–3.42)	0.75 (.45–1.25)	1.76 (.45–6.85)	Unable to calculate
All vaccine doses						
On time	1	1	1	1	1	1
Some doses late or missed	1.08 (.63–1.84)	1.23 (.71–2.15)	1.41 (.77–2.57)	2.31 (1.21–4.41)	3.44 (1.34–8.86)	1.56 (.48–5.04)
Season						
Summer	1	1	1	1	1	1
Spring	1.60 (1.08–2.37)	1.56 (.91–2.66)	1.08 (.68–1.73)	1.48 (.68–3.21)	1.33 (.57–3.14)	1.93 (.64–5.85)
Autumn	1.72 (1.16–2.55)	2.31 (1.37–3.87)	2.09 (1.41–3.09)	2.61 (1.31–5.18)	1.71 (.67–4.32)	2.30 (.77–6.82)
Winter	2.05 (1.37–3.06)	2.04 (1.20–3.44)	2.05 (1.37–3.07)	3.14 (1.61–6.12)	2.23 (.90–5.53)	1.74 (.56–5.43)

Data are presented as incidence rate (95% confidence interval).

Abbreviations: HIV, human immunodeficiency virus; SES, socioeconomic status.

[a]Urine cotinine >500 ng/mL.

[b]Weight-for-length *z* score <–2.

first year of life (0.14 e/cy) compared with HEU infants whose mothers only received dual prophylaxis (nevirapine plus zidovudine) PMTCT (0.28 e/cy; IRR, 0.49 [95% CI, .26–.96]). Effects of breastfeeding varied by HIV exposure status: the 11 of 886 (1.2%) HU infants who never breastfed had higher incidence of hospitalized LRTI <6 months compared with HU infants who ever breastfed (IRR, 7.46 [95% CI, 2.83–19.7]). However, among HEU infants <6 months of age, the 99 of 239 (41%) who never breastfed had similar incidence of hospitalized LRTI compared with breastfed HEU infants (IRR, 1.19 [95% CI, .51–2.74]).

Adjusted Poisson Model and Population Attributable Risk

In adjusted Poisson regression (controlling for age and enrollment clinic), male sex, LBW, delayed or missed vaccinations, and maternal smoking remained significant predictors of both ambulatory and hospitalized LRTI (Table 5). The PAR of antenatal maternal smoking for LRTI (tobacco-unexposed children vs children of active or passive smokers) was 13.8% (95% CI, –.01% to 27.3%); the PAR for LBW was 9.2% (95% CI, 1.5%–16.1%).

DISCUSSION

This unique birth cohort provides important longitudinal data on incidence, severity, and risk factors for LRTI in a well-vaccinated population, with almost no HIV-infected children, through the first 2 years of life and extending across 4 respiratory seasons. We describe LRTI incidence in the second year of life, with lower overall incidence and increased proportion of ambulatory cases compared to infants aged <1 year. This represents an appreciable burden of LRTI in South Africa, with an annual birth cohort of 1.2 million [20], translating to 48 000 LRTI hospitalizations in the second year of life, adding substantial burden and costs to health systems.

Incidence of LRTI in infants <1 year of age was much higher than previously described [21]. As case detection methods remained constant through the study period, the observed increased incidence is most likely due to severe pneumonia seasons in 2014 and 2015. This interyear variation in seasonal pneumonia severity underscores the importance of multiyear birth cohorts with extended recruitment and follow-up. In addition to high LRTI incidence in infancy, our study highlights vulnerability of infants and young children to LRTI; high prevalence of risk factors such as ETS, LBW, and maternal HIV; and persistence of LRTI burden into the second year of life.

The in-hospital case fatality rate was low (<2%) despite severity of disease, prevalence of radiological abnormality in 78% of hospitalized cases, and hypoxia in 25%. This is lower than

Table 5. Risk Factors for Ambulatory and Hospitalized Lower Respiratory Tract Infection for 1141 Human Immunodeficiency Virus–uninfected Children in the First 2 Years of Life: Adjusted Multivariable Model

	Ambulatory LRTI	Hospitalized LRTI
Risk Factor	Adjusted IRR (95% CI)[a]	Adjusted IRR (95% CI)[a]
Age category		
<6 mo	2.17 (1.75–2.68)	4.87 (3.12–7.63)
6–12 mo	1.34 (1.06–1.69)	2.12 (1.29–2.87)
>12 mo	1	1
Male sex	1.53 (1.20–1.96)	1.88 (1.23–2.87)
Low birth weight	1.53 (1.12–2.08)	1.79 (1.09 –2.94)
Mother active smoker in pregnancy[b]	1.53 (1.20–1.97)	1.63 (1.05–2.94)
Delayed or missing vaccinations	1.03 (.91–1.17)	1.31 (1.09–1.58)

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; LRTI, lower respiratory tract infection.

[a]Adjusted for enrollment clinic, age, sex, low birth weight, maternal smoking, and delayed or missing vaccinations.

[b]Urine cotinine >500 ng/mL.

in the multisite Pneumonia Etiology Research for Child Health (PERCH) study: Of 3587 children admitted with severe LRTI, 54% had radiological abnormality, 36% were hypoxic, and 6% died [22]. Our estimates are also lower than a report of children with severe LRTI in Botswana, where 79% had radiological abnormality, 38% were hypoxic, and 5% died [23]. Our low case fatality rate may reflect good access to care, including access to intensive care and mechanical ventilation. Our cohort also achieved high vaccine coverage, including PCV and Hib; had good nutritional status; and showed a low prevalence of HIV infection in children, factors that may have contributed to low case fatality.

Antenatal maternal smoking was a consistent modifiable risk factor for both ambulatory and hospitalized LRTI throughout the first 2 years. The PAR for LRTI implies that 13.8% of LRTI was due to antenatal maternal smoking. Although higher than reported globally [1], this may still be an underestimate, as measurement of the intensity of postnatal ETS exposure from self-reported questionnaires was difficult; accurate antenatal biomarkers such as maternal urine cotinine may not capture the additive impact of postnatal ETS exposure.

Preterm and LBW children were at high risk for LRTI throughout early childhood, with younger infants more likely to require hospitalization, consistent with previous studies [2]. PTD and LBW were significant risk factors for ambulatory LRTI after 6 months of age, and through the second year of life. Children with delayed or missed vaccinations had increased incidence of LRTI, even after adjusting for other risk factors. This may reflect immunological susceptibility; however, delayed vaccinations may also indicate social vulnerability, or be a marker of other unmeasured risk factors [24, 25].

HEU infants had 2-fold increased incidence of hospitalized LRTI compared to HU infants, as previously described [11, 26]. A novel finding was that this was limited to the first 6 months of life, possibly due to impaired maternal transplacental antibody [27] or transient innate or adaptive immune effects in HEU [28, 29]. This raises questions about optimal prevention strategies, including possible co-trimoxazole prophylaxis in HEU for 6 months. HEU born to mothers using simple PMTCT regimens had a higher incidence of hospitalized LRTI than infants born to mothers using triple ART in pregnancy. This is consistent with evidence that maternal triple ART is associated with decreased all-cause child mortality at 24 months [30]. Future estimates of population effects of HIV exposure on childhood LRTI should adjust for maternal ART regimens.

Globally, breastfeeding is associated with decreased LRTI hospitalization for 2 years [31]. We observed lower hospitalized LRTI incidence among the 99% of HU infants aged <6 months who were breastfed compared with 1% of HU infants who never breastfed; however, there is possibility of unmeasured confounding among those who never breastfed. Short duration of protective effect is likely due to overall short duration of breastfeeding. Differential effect of breastfeeding on LRTI incidence by HIV exposure status has been described in 2 previous South African cohorts. In a case-control study in Soweto, breastfeeding was protective against "presumed bacterial pneumonia" among HU, but not HEU, children [32]; in a Cape Town cohort, breastfeeding among HEU infants was not protective against hospitalization [33]. By contrast, a cohort of breastfed Kenyan HEU infants had a 47% decreased risk of LRTI compared with nonbreastfed HEU infants [34]. It is possible that in South African cohorts (well-vaccinated, receiving co-trimoxazole prophylaxis, well-nourished, with good access to care), breastfeeding among HEU did not confer the same protection against LRTI as in Kenya.

A major strength of this study is the long follow-up, including several respiratory seasons. Longitudinal birth cohorts are rare in LMICs; cross-sectional analyses of LRTI do not have accurate measurement of preexisting risk factors, but rely on recall [35, 36]. With this study design, we could prospectively measure risk factors for LRTI at different time points while allowing for interyear variation in background risk. Limitations include low specificity of WHO clinical case definitions, alongside possibility of LRTI overdiagnosis due to heightened awareness of staff and mothers about respiratory symptoms. Nonetheless, LRTI signs were verified by study staff and a high proportion required hospitalization, of which most had radiological changes. Some cases of LRTI may have been missed; however, this is unlikely given strong surveillance systems and high cohort retention. Another limitation is lack of etiology data. Although microbiologic data have been reported [37], ascribing etiology can be complex and is beyond the scope of this report. A further limitation is potential for interobserver variability in radiological interpretation of LRTI; however, we used the same 3 readers and a standardized WHO reporting form. Moreover, interobserver variability has been reported to be high for end-point consolidation [38].

In conclusion, we report high incidence of clinical and radiological LRTI in the first 2 years of life, with low case fatality. There remains an appreciable burden, especially of ambulatory disease, in the second year. Low birth weight, delayed or missed vaccinations, and maternal smoking were strong risk factors for LRTI. HIV-exposed but uninfected infants were at higher risk of hospitalized LRTI only in the first 6 months of life. Strategies to identify incompletely vaccinated children and prevent harmful exposures including ETS must be strengthened, and new strategies for protecting vulnerable children are needed to reduce the burden of LRTI.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. H. J. Z. is the principal investigator, conceived and designed the study, and obtained funding, together with M. P. N., the lead microbiologist, and L. M., who led the epidemiological analyses. H. J. Z., M. P. N., and L. M. provided operational oversight. D. M. l. R. was the study clinician and coordinator, analyzed data with supervision from L. M., and was the main investigator responsible for interpretation of results and drafting of the manuscript. A. V. obtained funding for and led analysis of environmental tobacco smoke. J. A. M. S. was study clinician and coordinator and read and reviewed radiographs. E. v. D. read and reviewed radiographs and advised on clinical assessments. All authors reviewed, contributed to, and approved the final manuscript.

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