Investigating Mediators of the Poor Pneumonia Outcomes of Human Immunodeficiency Virus–Exposed but Uninfected Children

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Background. Human immunodeficiency virus–exposed but uninfected (HIV-EU) children have a higher mortality rate than the children of HIV-negative mothers (HIV-unexposed). Causal mediators of the poor health outcomes of HIV-EU children remain poorly defined.

Methods. We conducted a hospital-based prospective cohort study of children aged 1 to 23 months with clinically defined pneumonia. The children were recruited at a referral hospital in Gaborone, Botswana, between April 2012 and June 2016. The primary outcome, treatment failure at 48 hours, was assessed by an investigator blinded to the children's HIV-exposure status. We examined associations between HIV exposure and pneumonia outcomes in HIV-uninfected children. We next determined whether the effect of HIV exposure on outcomes was mediated by low-birth-weight status, nonbreastfeeding, malnutrition, in utero exposure to combination antiretroviral therapy, or pneumonia severity.

Results. A total of 352 HIV-uninfected children were included in these analyses, including 245 (70%) HIV-unexposed and 107 (30%) HIV-EU children. Their median age was 7.4 months, and 57% were male. Treatment failure occurred in 111 (32%) children, and 19 (5.4%) children died. HIV-EU children were more likely to fail treatment (risk ratio [RR], 1.57 [95% confidence interval (CI), 1.19–2.07]; $P = .002$) and had a higher in-hospital mortality rate (RR, 4.50 [95% CI, 1.86–10.85]; $P = .001$) than HIV-unexposed children. Nonbreastfeeding mediated 47% of the effect of HIV exposure on the risk of in-hospital death.

Conclusions. HIV-EU children have worse pneumonia outcomes than HIV-unexposed children. Nonbreastfeeding mediates nearly half of the effect of HIV exposure on pneumonia mortality. Our findings provide additional evidence for a mortality benefit of breastfeeding by HIV-EU children.

Keywords: breastfeeding; children; HIV-exposed uninfected; mortality; pneumonia.

Approximately 1.2 million infants will be born to human immunodeficiency virus (HIV)–infected mothers in sub-Saharan Africa this year, and more than 1 million of these infants will not acquire HIV [1]. Despite the absence of HIV infection, these HIV-exposed but uninfected (HIV-EU) children have a mortality rate that is approximately twice that of the children of HIV-negative mothers (HIV-unexposed) [2–4]. Most of these excess deaths occur during the first 2 years of life and result from a common childhood infections [2–4]. Despite the poor health outcomes of HIV-EU children having been recognized for more than a decade, surprisingly little

is known about the underlying mechanisms [3]. Proposed contributors include replacement feeding, maternal illness or death, exposure to tuberculosis and other infections, reduced access to care, delayed care-seeking behavior, and socioeconomic factors [5]. HIV-EU infants also might be at a higher risk of death resulting from infection because of immune abnormalities that result from in utero exposure to HIV or antiretroviral medications [6–8].

Pneumonia is the leading infectious killer of children; it accounts for 920 000 child deaths each year [9]. More than half (51%) of these deaths occur in sub-Saharan Africa [9]. Several recent studies found that HIV-EU children in sub-Saharan Africa have a higher incidence of pneumonia and worse pneumonia outcomes than HIV-unexposed children [10–12]. We previously reported that in Botswana, HIV-EU children with pneumonia had a higher in-hospital mortality rate than HIV-unexposed children [12]. Within the context of this hospital-based prospective cohort study, we sought to identify causal mediators of the poor pneumonia outcomes of HIV-EU children.

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PATIENTS AND METHODS

Setting

This study was conducted between April 2012 and June 2016 at Princess Marina Hospital, a referral medical center in Gaborone, Botswana. The country's HIV prevalence among adults aged 15 to 49 years was 22.2% in 2015 [13]. HIV-infected women in Botswana are counseled to exclusively breastfeed their children until they are at least 6 months of age unless replacement feeding is deemed to be acceptable, feasible, affordable, sustainable, and safe (AFASS); free infant formula is provided to HIV-infected women who meet these criteria, including mothers who are on combination antiretroviral therapy. *Haemophilus influenzae* type B (Hib) and 13-valent pneumococcal conjugate (PCV-13) vaccinations were introduced in Botswana in November 2010 and July 2012, respectively. These vaccines are administered routinely to infants in Botswana at 2, 3, and 4 months of age. Coverage estimates in 2014 for 3 doses of Hib vaccine and 3 doses of PCV-13 vaccine were 95% and 81%, respectively [14].

Study Population

Children aged 1 to 23 months with pneumonia, defined by the World Health Organization (WHO) as "cough or difficulty in breathing with lower chest wall indrawing" [15], were eligible for inclusion. The presence of 1 or more danger signs (central cyanosis, convulsions, inability to drink, and abnormal sleepiness) at enrollment classified children as having WHO-defined severe pneumonia [15]. We excluded children with a chronic medical condition (other than HIV infection) that predisposed them to pneumonia, hospitalization in the previous 14 days, asthma, wheezing with resolution of lower chest wall indrawing after 2 or fewer bronchodilator treatments, or previous enrollment in this study. All children were recruited within 6 hours of triage in the emergency department. Recruitment occurred between Monday and Friday from 7:30 AM to 4:30 PM and, when staffing was available, during evenings and weekends.

Clinical care was provided on a pediatric ward staffed by medical officers and pediatric residents and supervised by pediatricians. Supplemental oxygen and continuous positive airway pressure (CPAP) were routinely available on the ward, but access to mechanical ventilation in the hospital's 6-bed intensive care unit was limited. Antibiotic treatment decisions were made by the supervising pediatrician.

Data Collection

Sociodemographic and clinical data were collected at enrollment from the initial physical examination, review of infant and maternal medical records, and a face-to-face questionnaire completed with the child's caregivers. Severe acute malnutrition was defined as weight for length of less than

−3 standard deviations from the median on standard WHO growth curves, a mid-upper arm circumference of less than 115 mm (for children aged 6 months or older), or bilateral edema of nutritional origin [16]. Hypoxia was defined as an oxygen saturation of <90% while breathing room air. Proximity to health care services was categorized as travel of <1 or ≥1 hour before first contact with the health system (at a clinic or hospital) on the enrollment date. To assess for current breastfeeding, caregivers were asked, "When this illness started, was the child breastfeeding?" Research staff assessed the children, reviewed their hospital charts daily until hospital discharge (or death), and recorded additional clinical information, including level of respiratory support and the dates and times of antibiotic doses. Study data were managed using REDCap electronic data-capture tools hosted at the Children's Hospital of Philadelphia in Pennsylvania [17].

Classification of HIV-Exposure Status

Women in Botswana are tested routinely for HIV during pregnancy using dual parallel rapid testing. Children of a mother with documented negative HIV testing results during pregnancy, at delivery, or at enrollment were classified as HIV-unexposed. Children whose mother tested positive for HIV before or at delivery were considered HIV-exposed. HIV-exposed children were classified as HIV-EU if they tested negative for HIV after the age of 6 weeks if they were exclusively formula fed, at least 6 weeks after breastfeeding cessation, or at enrollment. HIV testing of infants less than 18 months of age was performed using the Amplicor 1.5 HIV-1 DNA polymerase chain reaction (PCR) assay (Roche, Alameda, California). Testing of infants aged 18 months or older was performed using dual parallel rapid testing and, for children with positive or discordant results, a confirmatory HIV DNA PCR assay. Before April 2014, infant HIV testing was performed at the discretion of the clinical team. Thereafter, we collected a dried blood spot from all HIV-exposed infants and performed HIV testing using the Amplicor 1.5 HIV-1 DNA PCR assay.

Outcome Assessment

The primary outcome, treatment failure, was assessed at 48 (±2) hours by a study physician or nurse blinded to enrollment data, including the child's HIV-exposure status. Treatment failure was defined as persistent lower chest wall indrawing, the development of new WHO danger signs, an oxygen saturation of <80% while breathing room air, need for CPAP or mechanical ventilation, and/or death. This definition was adapted for our setting from criteria used in previous studies of childhood pneumonia [18–20]. Training sessions were held every 3 months for study physicians and nurses throughout the study to standardize the assessment process. Children who were discharged from the

hospital before 48 hours were considered treatment responders, but we attempted to contact their caregivers by telephone to confirm treatment response.

Secondary outcomes included days of respiratory support (supplemental oxygen, CPAP, or mechanical ventilation), length of stay, and in-hospital death. For each day, only the highest level of respiratory support required by a child was recorded. The length of stay was calculated from time of triage in the emergency department to the time of hospital discharge or death.

Statistical Analysis

The analyses presented herein included only children who were classified as HIV-unexposed or HIV-EU. We documented baseline characteristics of the study population according to HIV-exposure status by using frequencies and percentages for categorical variables and medians and 25th and 75th percentiles for continuous variables. To assess for differences in these characteristics according to HIV-exposure status, we used the χ^2 or Fisher exact test for categorical variables and 2-sample *t* tests for continuous variables. We used Cox proportional hazards to estimate risk ratios (RRs) for treatment failure and in-hospital mortality according to HIV-exposure status [21]. Given the right-skewed distribution of days of respiratory support and lengths of stay, we used negative binomial regression models to estimate incidence rate ratios (IRRs) for these outcomes according to HIV-exposure status. The analyses were adjusted for age and proximity to health care services (travel of <1 or ≥ 1 hour to a clinic or hospital for the current illness), which were potential confounding variables identified on the basis of subject matter knowledge and construction of a causal diagram (Figure 1) [12].

We next sought to determine whether the following clinical variables were mediators of the effect of HIV exposure on pneumonia outcomes: (1) low-birth-weight status, (2) current nonbreastfeeding, (3) severe malnutrition, (4) in utero exposure to combination antiretroviral therapy (compared with zidovudine monotherapy or no antiretroviral therapy), and (5) WHO-defined severe pneumonia. We first included HIV exposure, the candidate mediator, and the potential confounders of age and

proximity to healthcare services in log binomial regression models for the outcomes of interest (treatment failure at 48 hours and in-hospital death). We next used logistic regression to evaluate whether HIV exposure was associated with each candidate mediator by adjusting for the same potential confounders. We considered a variable to be a significant mediator of the effect of in utero HIV exposure if we found evidence of associations with both the outcome and the exposure ($P < .20$). For candidate mediators that met these criteria, we calculated the ratio of the natural indirect effect to the total effect on the risk-difference scale, which can be interpreted as the proportion of the total effect of HIV exposure on the outcome that is mediated by that variable [22].

All statistical analyses were conducted using SAS 9.4 software (SAS Institute, Cary, North Carolina). This study was approved by the Health Research and Development Committee (Botswana Ministry of Health), the Princess Marina Hospital Ethics Committee, and the University of Pennsylvania, Children's Hospital of Philadelphia, and Duke University institutional review boards. A legal guardian provided written informed consent for each child included in this study.

RESULTS

Patient Characteristics

A total of 869 children were screened by the study team, and 412 children were eligible (Figure 2). The legal guardians of 22 (5%) children declined consent, and 390 children were enrolled. Our analyses included only the 352 HIV-uninfected children for whom HIV-exposure status could be determined. Table 1 lists baseline characteristics of the study population. The median age was 7.4 months, and 57% were male. A total of 245 (70%) children were HIV-unexposed, and 107 (30%) were HIV-EU. Of the children classified as HIV-EU, 85 (79%) tested negative for HIV at or after enrollment; the remainder of the children had been confirmed uninfected on the basis of previous HIV testing. The HIV-infected mothers of these HIV-EU children received combination antiretroviral therapy ($n = 74$ [69%]), zidovudine monotherapy ($n = 24$ [22%]), or no antiretroviral medication ($n = 9$ [8%]) during pregnancy. One hundred fifteen (33%) children had severe pneumonia, and 125 (36%) children were hypoxic. We observed differences in age, low-birth-weight status, infant feeding practices, and maternal educational level

Figure 1. Causal diagram depicting the relationship between child HIV-exposure status and pneumonia outcome.

Figure 2. Flowchart of study recruitment.

according to HIV-exposure status. However, we found no significant differences in nutritional status, receipt of immunizations, or measures of illness severity between the HIV-EU and HIV-unexposed children.

Outcomes

Two hundred fifteen (61%) children received supplemental oxygen, 28 (8%) required CPAP, and 10 (3%) were mechanically ventilated during the hospitalization. Treatment failure at 48 hours occurred in 111 (32%) children, including 62 (26%) HIV-unexposed and 49 (46%) HIV-EU children. Ninety-two (26%) children were discharged before the treatment-failure assessment; the caregivers of 88 (96%) of these children were contacted by telephone, and only 1 child was reported to have required further medical care after hospital discharge. Nineteen (5.4%) children died, including 6 (2.5%) HIV-unexposed and 13 (12.2%) HIV-EU children. The median length of stay for the 333 children who survived to hospital discharge was 3.2 days (25th percentile, 75th percentile: 1.6, 6.8 days).

Table 2 presents multivariable analyses of outcomes according to HIV-exposure status. Compared with HIV-unexposed children, HIV-EU children were more likely to fail treatment at 48 hours (RR, 1.57 [95% confidence interval (CI), 1.19–2.07]), required more days of respiratory support (IRR, 1.44 [95% CI, 1.06–1.97]), had longer lengths of stay (IRR, 1.25 [95% CI,

1.01–1.55]), and had a higher rate of in-hospital death (RR, 4.50 [95% CI, 1.86–10.85]).

Mediators of the Effect of HIV Exposure

Results of our analyses of candidate mediators of the association between HIV exposure and pneumonia outcomes are listed in Table 3. Low-birth-weight status was the only variable that was a mediator of the effect of HIV exposure on the risk of treatment failure in HIV-uninfected children; it accounted for 10% of the total effect. Current nonbreastfeeding was identified as a mediator of the effect of HIV exposure on the risk of in-hospital death; it accounted for 47% of the total effect. Severe malnutrition, in utero exposure to combination antiretroviral therapy, and pneumonia disease severity were not significant mediators of the effect of HIV exposure on either the risk of treatment failure or in-hospital death.

DISCUSSION

In this study of HIV-uninfected children with pneumonia in Botswana, in utero exposure to HIV was associated with a more than 4-fold-higher risk of in-hospital death. Nearly half (47%) of this effect of HIV exposure on the risk of death resulting from pneumonia was mediated through nonbreastfeeding.

Globally, the number of annual deaths resulting from childhood pneumonia decreased 47% between 2000 and 2015,

Table 1. Baseline Characteristics of the Study Population According to HIV-Exposure Status

		n (Column %) or Median (25th, 75th percentiles)						
Characteristic	N	Total (n = 352)		HIV-Unexposed Children (n = 245)		HIV-EU Children (n = 107)		P
Demographics								
Age (mo)	352	7.4	(2.9, 13.9)	8.3	(3.4, 14.4)	4.9	(2.3, 12.2)	.01
Sex	352							.96
Female		152	(43)	106	(43)	46	(43)	
Male		200	(57)	139	(57)	61	(57)	
Low birth weight (<2500 g)	347	64	(18)	38	(16)	26	(25)	.046
Deceased mother	352	0	(0)	0	(0)	0	(0)	>.99
Nutritional factors								
Severe malnutrition ^b	334	16	(5)	12	(5)	4	(4)	.68
Currently breastfed	352	141	(40)	134	(55)	7	(7)	<.0001
Ever breastfed	352	259	(74)	243	(99)	16	(15)	<.0001
Socioeconomic factors								
Maternal educational level	352							.001
None or primary		34	(10)	18	(7)	16	(15)	
Secondary		239	(68)	160	(65)	79	(74)	
Tertiary		79	(22)	67	(27)	12	(11)	
Electricity in home	352	232	(66)	169	(69)	63	(59)	.07
Municipal or private water source	352	308	(88)	219	(89)	89	(83)	.11
Refrigerator in home	352	220	(63)	161	(66)	59	(55)	.06
Use of wood as a cooking fuel	352	139	(39)	94	(38)	45	(42)	.51
Household contact with tuberculosis, past 12 mo	351	27	(8)	18	(7)	9	(8)	.74
Immunization status								
Hib vaccine status up to date	350	299	(85)	211	(86)	88	(83)	.40
PCV-13 status up to date	350	195	(56)	133	(55)	62	(58)	.49
Current illness factors								
Days of cough	351	3	(2, 5)	3	(2, 5)	3	(2, 5)	.90
Days of fever	350	2	(0, 3)	2	(1, 3)	1	(0, 2)	.06
Respiratory rate (breaths per min)	352	64	(57, 72)	64	(56, 72)	64	(58, 76)	.08
WHO-defined severe pneumonia ^a	352	115	(33)	74	(30)	41	(38)	.14
Hypoxia (oxygen saturation < 90%, room air)	350	125	(36)	82	(34)	43	(41)	.21
White blood cell count (cells/ μ L)	306	11.6	(8.9, 16.2)	11.6	(8.7, 16.2)	12.1	(9.4, 15.8)	.50
Hemoglobin (g/dL)	306	10.7	(9.7, 11.7)	10.8	(9.7, 11.8)	10.6	(9.6, 11.5)	.61
Travel of ≥ 1 hour to clinic or hospital	351	32	(9)	18	(7)	14	(13)	.09
Received antibiotics before presentation	351	215	(61)	149	(61)	66	(62)	.91

Abbreviations: HIV-EU, human immunodeficiency virus exposed but uninfected; Hib, *Haemophilus influenzae* type B; PCV-13, 13-valent pneumococcal conjugate vaccine; WHO, World Health Organization.

^aP values were calculated using χ^2 or Fisher's exact tests for categorical variables and 2-sample t tests for continuous variables.

^bDefined as weight for length ≤ 3 standard deviations from the median on standard WHO growth curves, mid-upper arm circumference <115 mm (for children ≥ 6 months old), or the presence of bilateral edema of nutritional origin.

^cPneumonia accompanied by WHO danger signs (central cyanosis, convulsions, inability to drink, or abnormal sleepiness).

largely as a result of the increasingly widespread use of Hib and pneumococcal conjugate vaccines and improved pneumonia case management [9]. However, implementation of these interventions in sub-Saharan Africa has lagged behind other regions, and pneumonia deaths have become increasingly concentrated in sub-Saharan Africa [9]. In many sub-Saharan African countries, the prevalence of HIV among pregnant women remains high, and HIV infection or exposure continues to contribute substantially to the child mortality rate. In Botswana, more than half of all deaths among children occur in those who have been exposed to HIV, despite the country having the African continent's lowest rate (2.6%) of mother-to-child HIV transmission [23, 24]. Indeed, although only 30% of the HIV-uninfected

children in our study were HIV-EU, these children accounted for more than two-thirds (68%) of the pneumonia-related deaths. This finding highlights the importance of improving pneumonia outcomes of HIV-EU children to further reduce child pneumonia mortality rates in sub-Saharan Africa.

Several previous studies found a mortality benefit to breastfeeding for HIV-exposed infants in sub-Saharan Africa. In a study conducted in 3 African countries (Burkina Faso, Kenya, and South Africa), HIV-exposed infants who had weaned or were never breastfed had a 7-fold-higher risk of death during their first 6 months of life than HIV-exposed infants who were still breastfed [25]. Similarly, the 15-month cumulative mortality rate in nonbreastfed HIV-EU children (6.4%) was higher

Table 2. Multivariable Analyses of Pneumonia Outcomes Among HIV-Uninfected Children According to HIV-Exposure Status

HIV-EU vs HIV-Unexposed Children	RR or IRR (95% CI)	P
Treatment failure at 48 hours	1.57 (1.19–2.07)	.002
Days of respiratory support	1.44 (1.06–1.97)	.02
Length of stay (days)	1.25 (1.01–1.55)	.04
In-hospital death	4.50 (1.86–10.85)	.001

Abbreviations: CI, confidence interval; HIV-EU, human immunodeficiency virus–exposed but uninfected; IRR, incidence rate ratio; RR, risk ratio.

Risk ratios (or incidence rate ratios) estimated from Cox proportional hazards models (or negative binomial regression models) adjusted for age and proximity to health care services.

than that in breastfed HIV-EU children (3.5%) in Malawi [26]. In a study conducted in Zambia, the benefits of breastfeeding to HIV-EU children were shown to extend beyond the first year of life; weaning at 12 to 18 months of age was associated with a more than 4-fold-higher risk of death than continued breastfeeding [27]. The WHO currently recommends that HIV-infected mothers breastfeed their infants for at least 12 months, and for up to 24 months or longer, while receiving combination antiretroviral therapy [28]. Such a strategy confers the nutritive and immunological benefits of breastfeeding to HIV-exposed infants and is associated with a low rate of mother-to-child HIV transmission, which maximizes HIV-free survival [29]. Our findings suggest that adoption of this recommendation in Botswana would result in substantially lower pneumonia mortality rates among HIV-EU children.

Although data in the available literature indicate that breastfeeding offers substantial health benefits to HIV-EU children, several studies found that breastfed HIV-EU children still have worse health outcomes than breastfed HIV-unexposed children [3, 30]. Thus, we investigated several other potential contributors to the poor pneumonia outcomes of HIV-EU children. It is notable that in utero exposure to combination antiretroviral therapy, which contributes to the immunological abnormalities observed among HIV-EU children, was not a causal mediator of the effect of HIV exposure on pneumonia outcomes [7, 8]. Although further work is needed to fully understand the effects of antiretroviral medications on the fetal immune system, our findings suggest that in utero exposure to these medications does not account for the poor infectious outcomes of HIV-EU children. Severe malnutrition and pneumonia disease severity also were not causal mediators of the associations between HIV exposure and outcomes. Finally, low-birth-weight status was a weak causal mediator of the effect of HIV exposure on the risk of treatment failure, but it did not mediate the association between HIV exposure and in-hospital death.

Although we did not assess for mediation by other variables formally, our results indicate that several other potential contributing factors are unlikely to have accounted for the poor pneumonia outcomes of HIV-EU children. First, no child in our cohort had a deceased mother, which suggests that severe

Table 3. Candidate Mediators of the Effect of HIV Exposure on Pneumonia Outcomes

Mediator	Association With Outcome ^a (P)	Association With HIV Exposure ^b (P)	Proportion (%) Mediated ^c
Treatment failure at 48 hours			
Low-birth-weight status	.001	.06	10.0
Current nonbreastfeeding	.38	—	—
Severe malnutrition	.09	.68	—
In utero exposure to cART	.49	—	—
WHO-defined severe pneumonia	<.0001	.23	—
In-hospital death			
Low-birth-weight status	.37	—	—
Current nonbreastfeeding	.17	<.0001	46.9
Severe malnutrition	.01	.68	—
In utero exposure to cART	.65	—	—
WHO-defined severe pneumonia	.003	.23	—

Abbreviations: cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; WHO, World Health Organization.

^aHIV exposure, the candidate mediator, and the potential confounders of age and proximity to healthcare services were included in a log binomial regression model for the outcome of interest; the P value for the association of the candidate mediator with the outcome is shown.

^bAssociations of candidate mediators with HIV exposure were calculated only for potential mediators that were associated with the outcome of interest (P < .20). For these candidate mediators, HIV exposure and the potential confounders of age and proximity to healthcare services were included in a logistic regression model with the candidate mediator; the P value for the association of HIV exposure with the candidate mediator is shown.

^cWe calculated the ratio of the natural indirect effect to the total effect on the risk difference scale for candidate mediators that were associated with both the outcome of interest and HIV exposure (P < .20), which can be interpreted as the proportion of the total effect of HIV exposure on that outcome that is mediated by that variable.

maternal illness or death was not a major contributor to the observed differences in pneumonia outcomes according to HIV-exposure status. Although maternal educational levels differed in HIV-EU and HIV-unexposed children, other measures of socioeconomic status, including use of wood as a cooking fuel and a recent household contact with tuberculosis, did not differ in these groups. Duration of cough or fever, receipt of immunizations, proximity to healthcare services, and antibiotic treatment before hospital presentation also did not differ between HIV-EU and HIV-unexposed children, which provides an argument against systematic differences in either access to care or care-seeking behavior by HIV-infected mothers in Botswana. Last, other measures of illness severity, such as respiratory rate and the presence of hypoxia on presentation, were similar in HIV-EU and HIV-unexposed children. It should be noted that the HIV-EU children in our cohort were significantly younger than the HIV-unexposed children, and young age is an established risk factor for poor pneumonia outcomes [12, 20, 31]. It is possible that we observed this age difference according to HIV-exposure status because the immune abnormalities of HIV-EU children are most prominent during early infancy and tend to resolve with age [7, 8]. Alternatively, HIV-EU children were less likely to be breastfed than HIV-unexposed children, and the protective effect of breastfeeding on death resulting from infectious diseases declines with age [32].

Our study had several limitations. First, this research was conducted at a tertiary hospital staffed by pediatricians with access to diagnostic radiology services and advanced respiratory-support modalities. Thus, our findings might not be generalizable to facilities with more limited diagnostic and treatment capabilities. Second, the study population represented a convenience sample of children with pneumonia, most of whom were recruited during regular hours on weekdays. We excluded children with a chronic medical condition that predisposed them to pneumonia. Although they were excluded to more precisely define the effect of HIV exposure on pneumonia outcomes, it is possible that chronic conditions are an additional mechanism by which HIV exposure affects clinical outcomes. In addition, 21% of HIV-EU children were not retested for HIV during the enrollment hospitalization, and it is possible that a child classified as HIV-EU was infected through undisclosed breastfeeding. However, the associations between HIV exposure and pneumonia outcomes were substantively unchanged when these children were excluded from the analyses (data not shown). Moreover, false-negative HIV testing is unlikely given the high sensitivity (>98%–99%) of the tests that were used for HIV diagnosis in this study [33, 34]. Last, this was an observational study, and because causal mediators such as breastfeeding were not assigned to study participants systematically, the potential for bias by unmeasured confounding existed.

In conclusion, we found that HIV-EU children accounted for the majority of HIV-uninfected children who died of pneumonia in this cohort from Botswana. Among HIV-uninfected children, not being breastfed mediated nearly half of the effect of HIV exposure on the risk of in-hospital death from pneumonia. Our findings provide further evidence for a survival benefit of breastfeeding in HIV-exposed infants and suggest that the adoption of current WHO recommendations for infant feeding by HIV-infected mothers would reduce pneumonia mortality rates among children in Botswana.

Notes

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