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Infectious disease morbidity and growth among young HIV-exposed uninfected children in Jamaica

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ABSTRACT

Objective. *There is a growing body of data that demonstrates increased infectious disease outcomes for HIV-exposed uninfected (HIV-EU) infants as compared to their HIV-unexposed (HU) counterparts. We hypothesized that these HIV-EU infants are at greater risk for infectious morbidity and mortality when compared to the general childhood population. We therefore aimed to characterize infections and growth outcomes among HIV-EU infants in Jamaica during their first two years of life. By identifying these outcomes, specific interventions could be implemented to mitigate this risk of morbidity and mortality.*

Methods. *HIV-EU infants born between 1 January 2004 and 31 December 2006 in Kingston, Jamaica, were enrolled and followed in multicenter health facilities, using standardized protocols. HIV status was determined by RNA/DNA polymerase chain reaction (PCR) and confirmatory HIV enzyme-linked immunoassay (ELISA). Data were collected on demographic and anthropometric characteristics, infectious morbidity and mortality, and hospitalizations. Outcomes (incidence of infections and hospitalizations; growth (z scores for weight)) were determined, using univariate analyses.*

Results. *Of 195 HIV-EU infants followed for 25.9 months (standard deviation, 10.9 months), 102 (52%) were male, 185 (95%) were non-breast-fed, 161 (83%) experienced at least one infection, and 58 (30%) were hospitalized at least once. Infectious disease incidence per 1 000 child-weeks included upper respiratory tract infection of 7.25 (95% confidence interval (CI): 5.92–8.90), otitis media of 4.12 (3.21–5.20), and acute gastroenteritis (AGE) of 1.92 (1.35–2.65). Hospitalization incidence per 1 000 child-weeks included lower respiratory tract infections (LRTIs) of 0.89 (0.53–1.40), sepsis of 0.48 (0.23–0.89), and AGE of 0.43 (0.20–0.81). These infection incidence rates among the HIV-EU infants were higher than those for published community controls. Among the HIV-EU infants, the low-birthweight ones and those born via cesarean section had significantly higher hospitalization rates from LRTI and sepsis than did published community controls. The mean z score for weight during the infants' first 6 months ranged from -0.06 to 0.78 in this predominantly non-breast-fed population. That score trended upwards to 24 months of age.*

Conclusions. *Infectious disease morbidity was higher but growth was normal in this cohort of HIV-EU non-breast-fed infants, in comparison to published community controls. Specific interventions should be implemented to mitigate the risk in this setting.*

Key words HIV; infant; infection; morbidity; Jamaica.

In Jamaica, which is a middle-developing island nation, effective interventions since 2006 have reduced mother-to-child transmission of HIV from 25% preceding highly active antiretroviral therapy (HAART) to less than 5% in subsequent years. These interventions have resulted in a growing population of HIV-exposed uninfected (HIV-EU) children (1).

Although uninfected, these children appear to be at increased risk for infectious diseases when compared to their unexposed peers, and they also demonstrate

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early growth delay. Filteau (2) has proposed that poor maternal health, reduced breast-feeding, use of replacement feeds, and possible exposure to antiretroviral agents contribute to increased risk for infectious morbidity. Kuhn et al. (3) showed that early infant mortality and severe morbidity among HIV-EU infants doubled when maternal CD4+ T-cell counts were low. The increase was not explained by maternal mortality, separation due to maternal hospitalization, lower birthweight, or any other factors investigated. Infant growth was also slower when the maternal HIV load was higher.

The anti-infective benefits of breast-feeding are well documented. Breast milk provides immune protection when innate and specific host defenses are still developing in the young infant. The benefits include immune protection against diarrheal and respiratory diseases, which are both important causes of childhood mortality (4). The use of breast-milk replacements for postpartum prevention of mother-to-child HIV transmission has resulted in increased infant mortality in underdeveloped settings where safe water sources are inaccessible. The World Health Organization (WHO) has revised recommendations on infant feeding by HIV-positive mothers, and has advocated use of antiretroviral therapy (ART) in mothers and infants, while encouraging exclusive breast-feeding (5). These recommendations were supported by the evidence of lowered risk of postnatal transmission of HIV when maternal viral load is reduced. In fact, with appropriate support services from health care providers, prolonged breast-feeding is encouraged for at least six months, given that early weaning may be associated with acute morbidity and cumulative mortality in HIV-exposed uninfected infants (6). In Jamaica, the national guidelines for prevention of mother-to-child transmission of HIV advocate use of breast-milk replacement (7). This is provided free of cost for up to one year, and appropriate nutritional counseling is provided. For mothers who opt to breast-feed, appropriate antiretroviral drugs and nutritional support are provided.

In larger studies, the outcome of HIV-EU infants has differed in various settings. The Woman and Infant's Transmission Study (WITS), an ongoing multicenter study in the United States of America (including Puerto Rico), determined that HIV-EU infants had poor weight gain and linear growth as compared to the general population. These results were attributed to unstable social conditions (8). In contrast, the European Collaborative Study reported normal growth patterns in their HIV-EU infants, probably because the socially disadvantaged HIV-infected populations are smaller in Europe than they are in the United States. Growth patterns for HIV-infected infants were compared to those for the HIV-EU group. Specific morbidities were not fully explored (9).

The National Institute of Child Health and Human Development International Site Development Initiative (NISDI) Perinatal Study followed the frequency of infectious disease morbidity in HIV-EU infants in Latin America and the Bahamas during the first six months of life (10). The findings indicated a high incidence of neonatal sepsis, mucocutaneous candidiasis, and hospitalizations for acute bronchiolitis. The occurrence of neonatal infections was higher in these HIV-EU infants than it was in mainly outpatient and inpatient neonates in a large study conducted at the Brigham and Women's Hospital (Boston, Massachusetts, United States) (11). Among the HIV-EU infants in the NISDI study, the risk for lower respiratory tract infections, especially acute bronchiolitis, was associated with the severity of maternal HIV infection (lower maternal CD4 + T-cell counts) (11, 12).

Among African HIV-EU children, diarrheal and respiratory illnesses have contributed significantly to morbidity and mortality (2, 13, 14). However, in this setting, discontinuation of breast-feeding is the strongest predictor of mortality, in addition to risk associated with maternal death. A study in Belgium reported a higher incidence of invasive group B streptococcal infections among HIV-EU infants than in their unexposed counterparts (15).

Given the results from those various studies, we considered that the cohort of HIV-EU infants and children might be at risk for increased infectious disease morbidity. We hypothesized that HIV-EU children in Jamaica would have higher morbidity than published controls born to HIV-negative mothers (16), and lower morbidity than published community controls of perinatally infected HIV-positive children before HAART was commenced (17).

We aimed to characterize the morbidity and mortality outcomes of these HIV-EU children during the first two years of life, including their growth pattern and hospitalizations. The larger goal was to identify risks for morbidity and mortality and implement specific interventions that could mitigate these risks.

MATERIALS AND METHODS

Setting and participants

Children were followed up in Kingston, Jamaica, by the Kingston Paediatric and Perinatal HIV/AIDS Programme (KPAIDS) in ambulatory clinics at Bustamante Hospital for Children (BHC), Comprehensive Health Centre (CHC), and University Hospital of the West Indies (UHWI) (17, 18).

The study population consisted of infants born at the UHWI and Victoria Jubilee Hospital between 1 January 2004 and 31 December 2006, who were consecutively enrolled and followed up in the KPAIDS Programme, as part of a larger observational study (19). In 2002 the KPAIDS Programme was established as a multidisciplinary team focused on preventing mother-to-child HIV transmission and improving the quality of life and survival of infected children. The KPAIDS Programme collaborated with 42 feeder antenatal clinics in the parishes of Kingston, Saint Andrew, and Saint Catherine and additionally with the high-risk obstetric clinics at Victoria Jubilee Hospital, Spanish Town Hospital, and the UHWI. With the overall aim of reducing perinatal transmission, the mothers received antiretroviral therapy (for treatment or chemoprophylaxis), and infants received chemoprophylaxis with nevirapine (NVP) and zidovudine (AZT), had breast-milk replacement, and were followed through to confirmation of HIV serological status. The HIV status was established by RNA/DNA polymerase chain reaction (PCR) methodology and with a confirmatory HIV enzyme-linked immunoassay (ELISA) at 12–18 months (if negative PCR) or confirmatory virologic test (if positive PCR).

Inclusion criteria. HIV-1 uninfected children with follow-up data at the UHWI, CHC, and the BHC were included. The HIV status was established by RNA/DNA PCR methodology or with confirmatory HIV ELISA at 12–18 months. In situations where the infant/mother dyad had defaulted from clinic, data were collected if the infant had a negative HIV

RNA/DNA PCR or negative HIV ELISA or rapid HIV test.

Exclusion criteria. Children with undetermined HIV status, children who were HIV-positive, and those born to HIV-negative mothers were excluded.

Procedure

Data were collected through search of the electronic record database and validated by assessment of the medical records of the respective patients. The data included demographics (age, gender, and clinic location), antenatal and perinatal characteristics (antiretrovirals (ARVs) in pregnancy, length of pregnancy, mode of delivery, birthweight, neonatal antiretrovirals, and mode of infant feeding), infant anthropometric measurements from birth to the last visit at clinic sites, interval history of illnesses and hospitalizations, documentation of definitive and presumed infection, and survival.

The database identified 293 HIV-exposed infants born between 1 January 2004 and 31 December 2006. Of these, 59 medical records were not found, and these infants were thus excluded. Another 39 infants were excluded because 21 had no results in the medical records, 9 were followed at other clinic sites, 7 had HIV-negative mothers, and 2 were HIV-positive. Data were therefore collated and analyzed for 195 patients.

Growth measurements. The weight was recorded at each visit by the research nurses who coordinated their care at each site. The weight was measured in kilograms (kg) using a Tanita BD-585 pediatric digital scale. All the sites had the same model of digital infant scale. At the beginning of the program, the research nurses were specifically trained in the method of anthropometric measurements by an expert in infant and child nutrition. The *z* scores represent the distance in standard deviations (SDs) from the National Center for Health Statistics/World Health Organization normative reference for age and sex. Standardized weight-for-age z-score indices were calculated. A *z* score (standard deviation from the mean of a standard population) for each measurement of weight was calculated according to age and gender using the LMS method (20). The LMS parameters are the median (M), the generalized coefficient of variation (S), and the power in the Box-Cox transformation (L). The LMS method summarizes the changing distribution of a measurement, such as weight over age, by curves that represent the median, coefficient of variation, and skewness. The use of *z* scores means that measurements are no longer age dependent and thus maximizes the data available for analysis. A *z* score of 0 means the child has the mean measurement for that age and gender as compared with the standard population.

Laboratory. HIV RNA and DNA polymerase chain reaction (PCR) was the virologic test used for diagnosis of HIV status, which was assessed at 6 weeks and approximately 3–4 months of age. HIV ELISA was used to confirm HIV serological status after 12 months of age.

Morbidity. An illness was defined as having occurred when a definitive or presumptive diagnosis of infection was recorded by the pediatrician treating the child at each scheduled visit. If an interval illness occurred before the scheduled visit, the medical records were reviewed for validation even when medical attention was sought at another institution. All hospitalizations were documented, including with length of hospital stay and discharge diagnosis. Outcomes (discharge from the clinic, default from follow-up, death) were determined.

Analysis

Data were summarized and analyzed using STATA Version 11.1 and Microsoft Excel 2007. Incidence rates were calculated, using person-weeks as the denominator. The 95% confidence intervals were also calculated, using the exact binomial method. Statistical significance was assigned by a two-sided alpha level of 0.05. All *P* values were two-tailed.

Ethical statement

Ethical approval was received from the University Hospital of the West indies/University of the West Indies/Faculty of Medical Sciences (UHWI/UWI/FMS) Ethics Committee.

RESULTS

Demographics

Of the 195 records reviewed, 35 (17.9%) were followed up at BHC, 56 (28.7%) at the University Hospital of the West Indies, and 104 (53.3%) at Comprehensive Health Centre. Fifty-two percent of the cohort was male (Table 1).

Of the 195 mothers, 125 of them (64%) were diagnosed as HIV-positive during their pregnancy, and only 4 (2%) after the birth of the infant. The majority of the mothers received antiretroviral therapy during pregnancy: AZT (zidovudine), 107 mothers (55%); highly active antiretroviral therapy, 66 mothers (34%). Among the deliveries, 140 of them (72%) were vaginal, and 170 of them (87%) were at term.

Antiretroviral prophylaxis was provided to 127 of the infants (65%) using AZT and to 54 of them (28%) using nevirapine/AZT. Among the infants, 185 of them (95%) received breast-milk replacement, and 8 of them (4%) were breast-fed.

All infants received at least one clinic visit, with one having 14 visits. Mean age at first clinic visit was 3.61 months (SD, 5.32 months). The mean follow-up time was 25.9 months (SD, 10.9 months). Delayed initiation of infant clinic follow-up was due to postpartum HIV maternal diagnosis, maternal delay in accessing the clinic, and delayed identification of HIV-exposed uninfected infants.

Eighty-eight of the infants (45%) defaulted from follow-up. However, among these 88, 84 of them (95%) received at least two clinic visits.

Illnesses

Of the 195 children, 161 of them (83%) experienced at least one infection. The most common infections, in order of frequency, were upper respiratory tract infection (URTI), otitis media, acute gastroenteritis, candidiasis (oral, groin), and lower respiratory tract infection (LRTI) pneumonia (Table 2). Thirty-four infants (17%) were illness-free during the period of follow-up.

Infants delivered by cesarean section had about twice the incidence of candidiasis (oral, groin) (Table 3). No difference in infection incidence rate was observed by birthweight, exposure to maternal ARVs, or mode of infant feeding (Table 3).

Hospitalizations

Of the 195 children, 58 (30%) were hospitalized, together accounting for 72 hospitalizations and 512 days of

TABLE 1. Characteristics of study population (*n* = 195) in study of infectious disease morbidity and growth among young HIV-exposed uninfected children in Jamaica, 2004–2006

Characteristic	Total no. (%)	BHC[a] No. (%)	CHC[b] No. (%)	UHWI[c] No. (%)
Sex				
Male	102 (52%)	19 (54%)	57 (55%)	26 (46%)
Female	93 (48%)	16 (46%)	47 (45%)	30 (54%)
Mother HIV test positive				
Prepregnancy	62 (32%)	13 (37%)	28 (28%)	21 (37%)
In pregnancy	125 (64%)	18 (51%)	75 (72%)	32 (57%)
Postpregnancy	4 (2%)	2 (6%)	0 (0%)	2 (4%)
Missing	4 (2%)	2 (6%)	1 (1%)	1 (2%)
Mother ARV[d] type				
None	16 (18%)	2 (6%)	8 (8%)	6 (11%)
AZT[e]	107 (55%)	20 (57%)	57 (55%)	30 (53%)
Nevirapine	1 (0%)	1 (3%)	0 (0%)	0 (0%)
HAART[f]	66 (34%)	7 (20%)	39 (37%)	20 (36%)
Missing	5 (3%)	5 (14%)	0 (0%)	0 (0%)
CD4 count				
< 200	6 (3%)	0 (0%)	2 (2%)	4 (7%)
200 to < 500	42 (21%)	2 (6%)	21 (20%)	19 (34%)
≥ 500	25 (13%)	0 (0%)	19 (18%)	6 (11%)
Missing	122 (63%)	33 (94%)	62 (60%)	27 (48%)
Mode of delivery				
Vaginal	140 (72%)	25 (71%)	84 (81%)	31 (55%)
C-section	52 (27%)	8 (23%)	19 (18%)	25 (45%)
Missing	3 (1%)	2 (6%)	1 (1%)	0 (0%)
Gestational age				
≥ 37 weeks	170 (87%)	28 (80%)	94 (90%)	48 (86%)
< 37 weeks	18 (9%)	3 (9%)	8 (8%)	7 (12%)
Missing	7 (4%)	4 (11%)	2 (2%)	1 (2%)
Birthweight				
≥ 2.5 kg	161 (82%)	24 (69%)	91 (87%)	46 (82%)
< 2.5 kg	23 (12%)	6 (17%)	9 (9%)	8 (14%)
Missing	11 (6%)	5 (14%)	4 (4%)	2 (4%)
Neonatal ARVs				
AZT	127 (65%)	22 (63%)	68 (65%)	37 (66%)
Nevirapine/AZT	54 (28%)	6 (17%)	34 (33%)	14 (25%)
NVP stat[g]	2 (1%)	1 (3%)	0 (0%)	1 (2%)
None	8 (4%)	2 (6%)	2 (2%)	4 (7%)
Missing	4(2%)	4 (11%)	0 (0%)	0 (0%)
Breast-feeding				
No	185 (95%)	32 (91%)	100 (96%)	53 (95%)
Yes	8 (4%)	1 (3%)	4 (4%)	3 (5%)
Missing	2 (1%)	2(6%)	0 (0%)	0 (0%)
Outcomes				
Discharged	107 (55%)	15 (43%)	59 (57%)	33 (59%)
Defaulted	88 (45%)	20 (57%)	45 (43%)	23 (41%)

[a] BHC = Bustamante Hospital for Children.
[b] CHC = Comprehensive Health Centre.
[c] UHWI = University Hospital of the West Indies.
[d] ARV = antiretroviral.
[e] AZT = zidovudine.
[f] HAART = highly active antiretroviral therapy.
[g] NVP stat = single dose nevirapine.

hospitalization (mean, 7.1 days; SD, 6.3 days; range, 1 to 30 days). The greatest mean length of stay was due, in descending order, to prematurity, meningitis, sepsis, lower respiratory tract infections, bronchiolitis, and acute gastroenteritis.

Incidence rates for hospitalizations (per 1 000 child-weeks at risk) were greatest for lower respiratory tract infections [0.89 (95% CI: 0.53–1.40)], sepsis [0.48 (0.23–0.89)], acute gastroenteritis [0.43 (0.20–0.81)], prematurity [0.29 (0.10–0.62)], meningitis [0.14 (0.003–0.41)], and bronchiolitis [0.09 (0.001–0.34)]. Low-birthweight infants (< 2.5 kg) and those born via cesarean section had significantly higher incidence rates for hospitalizations due to LRTI and sepsis (Table 4).

Growth

The mean *z* scores for weight in the first 24 months of life ranged from -0.06 to 0.78. The scores generally showed an increasing trend after 10 months of age (Table 5).

Of note is the fact that the mean *z* score was particularly stable during 2–6 months of age in this population, which was predominantly non-breast-fed. The outliers (*z* scores < -2.0) consisted of infants who were born prematurely and/or with birthweight < 2.5 kg.

DISCUSSION

In this Jamaican cohort of HIV-exposed uninfected (HIV-EU) children, the majority experienced at least one infection during the follow-up period. Upper respiratory tract infections, including otitis media, were the most frequent infections, followed by acute gastroenteritis, mucocutaneous candidiasis, and lower respiratory tract infections. Incidence rates for hospitalization were greatest for lower respiratory tract infections, followed by sepsis and acute gastroenteritis.

These observations are consistent with a growing body of data that demonstrates increased infectious disease outcomes of HIV-EU infants as compared to their HIV-unexposed (HU) counterparts. The trends for HIV-EU infants include increased severity of common childhood infections (e.g., diarrheal disease, severe respiratory tract infections, and sepsis), increased mortality, and more frequent hospitalizations (21). Studies in Europe, the United States, Latin America, and the Caribbean have reported increased rates of morbidity and hospitalizations in HIV-EU infants (22, 23, 24, 10). However, in these observational studies, there was no comparison

TABLE 2. Frequency and incidence rates of infections among young HIV-exposed uninfected children (*n* = 195) in Jamaica, 2004–2006

Infections	No. of infants (%)	No. of illnesses (%) (*n* = 553)	Incidence rates, infections per 1 000 child-weeks at risk (95% CI)
Upper respiratory tract	…[a]	318 (57.5%)	…
URTI[b]	104 (53.3%)	177 (32%)	7.25 (5.92–8.79)
Otitis media	70 (35.9%)	115 (20.8%)	4.12 (3.21–5.20)
Tonsillitis	17 (8.7%)	19 (3.4%)	0.81 (0.47–1.30)
Sinusitis	7 (3.6%)	7 (1.3%)	0.33 (0.13–0.67)
Lower respiratory tract	…	44 (7.9%)	…
LRTI[c] pneumonia	24 (12.3%)	27 (4.9%)	1.18 (0.76–1.75)
Bronchiolitis	16 (8.2%)	17 (3.1%)	0.78 (0.45–1.27)
Skin and mucus membranes	…	144 (25.5%)	…
Oral candidiasis	33 (16.9%)	36 (6.5%)	1.79 (1.23–2.52)
Groin candidiasis	26 (13.3%)	31 (5.6%)	1.33(0.87–1.95)
Skin candidiasis	6 (3.1%)	6 (1.1%)	0.28 (0.10–0.61)
Conjunctivitis	14 (7.2%)	14 (2.5%)	0.68 (0.37–1.14)
Impetigo	13 (6.7%)	13 (2.4%)	0.62 (0.33–1.05)
Scabies	11 (5.6%)	13 (2.4%)	0.53 (0.26–0.94)
Tinea corporis	12 (6.2%)	12 (2.2%)	0.57 (0.30–0.99)
Tinea capitis	9 (4.6%)	9 (1.6%)	0.42 (0.19–0.80)
Gingivostomatitis	7 (3.6%)	7 (1.3%)	0.33 (0.13–0.68)
Gastrointestinal	…	42 (7.6%)	…
Acute gastroenteritis	37 (19.0%)	42 (7.6%)	1.92 (1.35–2.65)
Miscellaneous[d]	8 (4.1%)	8 (1.4%)	…[d]

[a] … = no observations were made.
[b] URTI = upper respiratory tract infection.
[c] LRTI = lower respiratory tract infection.
[d] The 8 miscellaneous were: helminthiasis, 2; apthous ulcers, 2; otitis externa, 2; varicella, 1; and croup, 1.

with HU counterparts. Despite this, the evidence is compelling that HIV-EU infants have increased risk. Evidence from studies in Mozambique and South Africa indicate that HIV-EU infants have a 1.5-fold increased risk for infectious morbidity when compared to their HU counterparts (25, 26).

The frequency of respiratory tract infections and gastroenteritis might be expected in our non-breast-fed group of infants. The protection that breastfeeding offers against respiratory and gastrointestinal infections is well recognized. Furthermore, both of those infections are globally the most common ones among infants and young children, whose susceptibility is increased due to the fact that their immune system is still developing. The socioeconomic and sociocultural conditions of the mother-infant dyad may also contribute to the occurrence of mucocutaneous infections. However, a South African study showed an increased risk for LRTI (especially severe pneumonia) among breast-fed HIV-EU infants as compared to HU infants (27).

The outcome for gastrointestinal infections differs among studies. Among formula-fed infants in South Africa, there was an increased incidence of diarrhea in HIV-EU infants as compared to HU infants (25). However, other studies from South Africa and Kenya showed no difference in the incidence of diarrhea between infant groups when adjustments were made in the analyses for varied feeding patterns (formula-fed, breastfed, and mixed) (28, 29).

There are no large-scale community-based studies in Jamaica with incidence rates of common infections to allow comparison with the study population. However, one large multicenter clinical trial conducted internationally, the Rotavirus Efficacy and Safety Trial (REST) study, does provide some relevant information on Jamaica (30). In Jamaica, between 25 February 2002 and 4 October 2005, at the University Hospital of the West Indies, researchers investigated the frequencies of adverse clinical events that occurred within 42 days after each dose of the rotavirus vaccine, which was given as three doses. The Jamaica REST placebo group of 888 normal infants provides some limited comparison of infectious conditions with the cohort of HIV-EU infants and children in our study. In the REST study, 88% of the placebo group was sometimes breast-fed, and 9% were always breast-fed. In that REST placebo group, there were was no upper respiratory tract infections during the period of observation, and only three of the infants (0.3%) developed otitis media. That is a sharp contrast with our study population of HIV-EU infants, where 53.3% of the infants developed URTI and 35.9% experienced otitis media.

In our study, 19.0% of the children developed acute gastroenteritis, compared to 0.3% of the infants in the placebo group of the REST study. This substantial difference is against the background occurrence of a rotavirus gastroenteritis outbreak in Jamaica in 2003, during the conduct of the REST study. Similar differences were noted in the frequency of lower respiratory tract infections in our HIV-EU infants (12.3%), as compared to the placebo group (0%) in the REST study. Similarly, the frequency of bronchiolitis was 8.2% in our HIV-EU infants versus 1.2% among the REST placebo group.

In an observational cohort study of 462 HIV-EU infants in Latin America and the Caribbean (LAC) who were enrolled in October 2004 and completed the six-month follow-up protocol (10), frequencies of mucocutaneous and lower respiratory tract infections were 44.4% and 20.7%, as compared to 25.5% and 7.9%, respectively, among the Jamaican HIV-EU infants in our study. The relatively high frequency of mucocutaneous infections in both groups occurred despite ensuring nutritional counseling and replacement feeds. This could be a result of inadequate formula preparation, storage, and hygiene. The differences in frequency of lower respiratory tract infections between the LAC group and our group of infants may be explained by a combination of factors, including immune dysfunction, severity of maternal disease, and socioeconomic conditions.

Although few cases of invasive bacterial infection were noted in our cohort, data from studies in South Africa and Belgium indicate a significantly greater risk for invasive pneumococcal disease among HIV-EU infants as compared to HU infants, especially in the first six months of life (23, 31, 32).

Among our cohort of predominantly non-breast-fed infants, the mean *z* score for weight was normal, and it increased

TABLE 3. Incidence rates of illnesses by key demographic features among young HIV-exposed uninfected children (*n* = 195) in Jamaica, 2004–2006

Illnesses	No. of infants	Incidence rate (95% CI) Infections per 1 000 child-weeks at risk	No. of infants	Incidence rate (95% CI) Infections per 1 000 child-weeks at risk	Incidence rate ratios (95% CI)	*P* value
		Birthweight < 2.5kg		Birthweight ≥ 2.5 kg		
OC[a]	5	3.32 (1.08–7.74)	26	1.64(1.07–2.41)	2.02 (0.61–5.34)	0.176
GC[b]	4	2.14 (0.58–5.49)	21	1.26 (0.78–1.93)	1.70 (0.42–5.03)	0.343
URTI	8	4.95 (2.14–9.75)	89	7.55 (6.06–9.29)	0.65 (0.27–1.35)	0.248
OM[c]	5	2.89 (0.94– 6.75)	62	4.35 (3.34–5.58)	0.66 (0.21–1.63)	0.391
LRTI	4	2.29 (0.63–5.87)	20	1.15 (0.70–1.77)	2.00 (0.50–5.97)	0.230
AGE[d]	4	2.07 (0.56–5.29)	31	1.90 (1.29–2.69)	1.09 (0.28–3.08)	0.826
		C-section		Vaginal delivery		
OC	12	2.74 (1.42–4.79)	20	1.45 (0.89–2.25)	1.89 (0.84–4.05)	0.093[e]
GC	11	2.49 (1.24–4.45)	15	1.01 (0.57–1.67)	2.45 (1.02–5.72)	0.030[f]
URTI	31	9.46 (6.43–13.43)	71	6.51 (5.08–8.21)	1.45 (0.92–2.25)	0.089[e]
OM	19	4.41 (2.66–6.88)	50	4.04 (3.00–5.33)	1.09 (0.61–1.88)	0.736
LRTI	9	1.78 (0.81–3.38)	15	1.00 (0.56–1.65)	1.78 (0.69–4.34)	0.184
AGE	11	2.42 (1.21–4.33)	25	1.73 (1.12–2.55)	1.40 (0.62–2.95)	0.358
		No maternal ARVs		Maternal ARVs		
OC	2	1.32 (0.16–4.77)	30	1.85 (1.25–2.65)	0.71 (0.08–2.81)	0.704
GC	4	2.79 (0.76–7.14)	22	1.27 (0.79–1.92)	2.20 (0.55–6.49)	0.176
URTI	8	6.57 (2.84–12.93)	94	7.52 (6.08–9.21)	0.87 (0.37–1.79)	0.747
OM	4	2.69 (0.73–6.89)	65	4.40 (3.40–5.61)	0.61 (0.16–1.64)	0.345
LRTI	1	0.60 (0.02–3.32)	23	1.28 (0.81–1.93)	0.47 (0.01–2.86)	0.497
AGE	4	2.81 (0.77–7.20)	31	1.80 (1.23–2.56)	1.56 (0.40–4.41)	0.404
		Non-breast-fed infant		Breast-fed infant		
GC	25	1.35 (0.87–1.99)	1	1.24 (0.03–6.88)	1.09 (0.18–44.79)	0.516
URTI	101	7.47 (6.09–9.08)	2	2.84 (0.34–10.24)	2.63 (0.71–22.06)	0.143
OM	69	4.28 (3.33–5.42)	1	1.51 (0.04–8.41)	2.84 (0.49–113.65)	0.291
LRTI	23	1.18 (0.75–1.77)	1	1.49 (0.04–8.30)	0.79 (0.13–32.65)	0.746
AGE	34	1.86 (1.29–2.59)	2	2.50 (0.30–9.03)	0.74 (0.19–6.38)	0.638

[a] Oral candidiasis.
[b] Groin candidiasis.
[c] Otitis media.
[d] Acute gastroenteritis.
[e] Borderline significance ($.05 \leq P < .10$).
[f] Significant ($P < .05$).

after 10 months of age. The finding of normal mean *z* score for the weight of the infants within the first two years of life is evidence of the efficacy of nutrition interventions in Jamaica. The Ministry of Health of Jamaica provides replacement infant formula free of cost to HIV-exposed infants for up to 12 months of age. Additionally, nutrition counseling, surveillance, and infant growth monitoring are essential components of the national guidelines.

Studies among formula-fed HIV-EU infants in developed-world settings have shown no or negligible difference in growth patterns as compared to their HU counterparts (33, 34, 35). In resource-limited settings where breast-feeding practices are prevalent, the growth outcomes have been heterogeneous (36).

There is growing evidence that the immune system of HIV-EU infants is primed by the exposure to maternal HIV infection. It is well established that chronic immune activation is a hallmark of HIV infection. It is proposed by Afran et al. (37) that the primed immune system of HIV-EU infants increases their susceptibility to infectious morbidity.

Our findings suggest higher morbidity among the HIV-EU infants in our study group than among the large placebo group of uninfected children in the REST clinical trial. The NISDI study, which was observational and did not have a community-based control group of uninfected children, also showed increased occurrence of infectious disease morbidity among HIV-EU infants compared to the unexposed children in the REST study.

This apparent increased morbidity among HIV-EU infants may be related to poor infant and child health that is secondary to declining maternal health. It may also be associated with maternal death and the resulting shift in caregiving responsibilities to the extended family or community aides (3). Low birthweight may be a consequence of poor maternal health. A high incidence rate for hospitalizations secondary to LRTI and sepsis was observed among low-birthweight infants as compared to their peers. In a majority of the cases in our study, the data were missing on the maternal CD4+ T-cell count. Therefore, we were unable to determine if there was any association between hospitalization outcomes and maternal immune status. Although the observational nature of our study may limit the generalizability of the reported outcomes, those outcomes occurred in the natural community outpatient setting,

TABLE 4. Incidence rates of hospitalizations by key demographic features among young HIV-exposed uninfected children (*n* = 195) in Jamaica, 2004–2006

Diagnosis	No. of events	Incidence rate (95% CI) of hospitalizations per 1 000 child-weeks at risk	No. of events	Incidence rate (95% CI) of hospitalizations per 1 000 child-weeks at risk	Incidence rate ratios (95% CI)	*P* value
		Birthweight < 2.5kg		Birthweight ≥2.5 kg		
LRTI[a]	4	2.22 (0.60–5.67)	11	0.62 (0.31–1.12)	3.55 (0.82–11.98)	0.053[c]
Sepsis	3	1.68 (0.35–4.91)	6	0.33 (0.12–0.73)	5.02 (0.81–23.50)	0.047[c]
AGE[b]	1	0.50 (0.01–2.80)	8	0.45 (0.19–0.88)	1.12 (0.03–8.39)	0.838
Meningitis	1	0.50 (0.01–2.78)	2	0.11 (0.01–0.39)	4.57 (0.08 – 87.81)	0.295
		C-section		Vaginal delivery		
LRTI	10	2.11 (1.01–3.87)	7	0.45 (0.18–0.94)	4.64 (1.59–14.36)	0.002[d]
Sepsis	5	0.98 (0.32–2.29)	5	0.32 (0.11–0.76)	3.03 (0.70–13.16)	0.095[c]
AGE	2	0.37 (0.05–1.34)	7	0.45 (0.18–0.94)	0.82 (0.08–4.30)	0.856
Meningitis	1	0.18 (0.00–1.02)	2	0.13 (0.02–0.46)	1.44 (0.02 –27.73)	0.755
		No maternal ARVs		Maternal ARVs		
LRTI	2	1.25 (0.15–4.53)	15	0.83 (0.46–1.36)	1.51 (0.17–6.51)	0.559
Sepsis	2	1.32 (0.16–4.75)	8	0.43 (0.19–0.85)	3.05 (0.32–15.29)	0.207
		Non-breast-fed infants		Breast-fed infants		
LRTI	16	0.82 (0.47–1.33)	1	1.28 (0.03–7.14)	0.64 (0.10–26.85)	0.624

[a] LRTI = lower respiratory tract infection.
[b] AGE = acute gastroenteritis.
[c] Borderline significance (.05 ≤ *P* < .10).
[d] Significant (*P* < .05).

TABLE 5. *Z* score for weight for the first 24 months of life among young HIV-exposed uninfected children (*n* = 195) in Jamaica, 2004–2006

Age (months)	Number of observations	Mean *z* score	Standard deviation	Minimum *z* score	Maximum *z* score	95% reference range
Birth	184	-0.54	1.32	-5.06	3.01	-3.12–2.04
1	79	0.78	1.45	-4.90	3.45	-2.07–3.62
2	80	-0.03	1.27	-4.27	2.45	-2.52–2.47
3	82	0.14	1.22	-3.62	2.89	-2.25–2.52
4	74	0.12	1.34	-3.24	3.78	-2.50–2.75
5	53	0.11	1.34	-2.98	2.54	-2.51–2.74
6	65	-0.06	1.24	-3.01	3.04	-2.49–2.36
7	48	0.22	1.41	-3.68	4.23	-2.54–2.99
8	52	0.08	1.20	-3.25	2.69	-2.29–2.45
9	56	0.05	1.17	-3.27	3.12	-2.23–2.34
10	39	0.06	1.17	-1.84	3.26	-2.22–2.35
11	39	0.41	1.17	-2.02	3.43	-1.89–2.71
12	80	0.15	1.19	-2.84	3.49	-2.19–2.49
13	47	0.12	1.13	-3.11	2.13	-2.09–2.33
14	37	0.62	1.15	-1.76	3.32	-1.64–2.87
15	52	0.03	1.13	-2.99	3.34	-2.19–2.55
16	43	0.42	1.11	-1.71	2.92	-1.76–2.60
17	27	0.24	1.11	-2.10	2.96	-1.94–2.42
18	51	0.35	1.05	-2.37	2.43	-1.70–2.41
19	28	0.22	0.89	-2.24	1.73	-1.52–1.95
20	26	0.36	1.48	-3.05	3.85	-2.54–3.25
21	45	0.36	1.08	-1.46	2.80	-1.76–2.49
22	20	-0.08	1.19	-2.32	1.68	-2.41–2.25
23	25	0.35	1.55	-2.80	3.92	-2.69–3.40
24	20	0.42	1.16	-2.63	2.27	-1.85–2.68

and the electronic data were validated through a comprehensive review of the source document medical records.

From our results, we conclude that, in our cohort of HIV-EU non-breast-fed infants in Jamaica, infectious morbidity (particularly respiratory infections, gastroenteritis, and mucocutaneous candidiasis) is increased, and the growth trend is normal. Health care providers should be cognizant of these observations and intensify efforts to optimize appropriate interventions to reduce these morbidities.

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RESUMEN

Morbilidad por enfermedades infecciosas y crecimiento en niños pequeños no infectados pero expuestos al VIH en Jamaica

Objetivo. Existe un volumen cada vez mayor de datos que muestran un aumento de casos de enfermedades infecciosas en lactantes no infectados pero expuestos al VIH en comparación con lactantes no expuestos al virus. Formulamos la hipótesis de que los lactantes no infectados pero expuestos presentan mayor riesgo de morbilidad y mortalidad por enfermedades infecciosas comparados con la población general de niños. Por consiguiente, nos propusimos caracterizar las infecciones y los resultados de crecimiento en lactantes no infectados pero expuestos al VIH en Jamaica durante sus dos primeros años de vida. Al determinarse estos resultados, podrían ejecutarse intervenciones específicas para mitigar este riesgo de morbilidad y mortalidad.

Métodos. Se inscribieron lactantes no infectados pero expuestos al HIV nacidos entre el 1 de enero del 2004 y el 31 de diciembre del 2006 en Kingston (Jamaica), y se les hizo seguimiento en establecimientos multicéntricos de salud, con protocolos estandarizados. El estado con respecto a la infección por el VIH se determinó mediante la reacción en cadena de la polimerasa (PCR) para ARN/ADN y prueba confirmatoria de inmunoadsorción enzimática (ELISA). Se recopilaron datos sobre características demográficas y antropométricas, morbilidad y mortalidad por infecciones y hospitalizaciones. Los resultados (incidencia de infecciones y hospitalizaciones; crecimiento [puntuaciones z para el peso]) se determinaron usando un análisis de una sola variable.

Resultados. De 195 lactantes no infectados pero expuestos a los que se les dio seguimiento durante 25,9 meses (desviación estándar, 10,9 meses), 102 (52%) eran de sexo masculino, 185 (95%) no fueron amamantados, 161 (83%) presentaron al menos una infección y 58 (30%) fueron hospitalizados por lo menos una vez. La incidencia de enfermedades infecciosas por 1 000 niño-semanas incluyó infecciones de las vías respiratorias superiores de 7,25 (intervalo de confianza [IC] de 95%: 5,92–8,90), otitis media de 4,12 (3,21–5,20) y gastroenteritis aguda (AGE) de 1,92 (1,35–2,65). La incidencia de hospitalización por 1 000 niño-semanas incluyó infecciones de las vías respiratorias inferiores de 0,89 (0,53–1,40), septicemia de 0,48 (0,23–0,89) y gastroenteritis aguda de 0,43 (0,20–0,81). Estas tasas de incidencia de infecciones en los lactantes no infectados pero expuestos fueron más altas que las de los controles comunitarios publicados. En los lactantes no infectados pero expuestos, aquellos con peso bajo al nacer y aquellos nacidos por cesárea registraron tasas de hospitalización significativamente más altas por infecciones de las vías respiratorias inferiores y septicemia que los controles comunitarios publicados. La media de la puntuación z para el peso durante los 6 primeros meses de los lactantes se ubicó entre -0,06 y 0,78 en esta población que en su mayoría no fue amamantada. Esa puntuación mostró una tendencia ascendente a los 24 meses de edad.

Conclusiones. La morbilidad por enfermedades infecciosas fue mayor, pero el crecimiento fue normal en esta cohorte de lactantes no infectados pero expuestos al VIH y no amamantados, en comparación con los controles comunitarios publicados. Deben realizarse intervenciones específicas para mitigar el riesgo en este entorno.

Palabras clave VIH; lactante; infección, morbilidad, Jamaica.