Breastfeeding is associated with decreased pneumonia incidence among HIV-exposed, uninfected Kenyan infants

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Abstract

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Background: HIV-exposed uninfected (HIV-EU) infants have higher infectious disease morbidity and mortality than their unexposed peers. Pneumonia is a leading cause of infant mortality worldwide, and identifying characteristics that predict pneumonia among HIV-EU infants may enable early identification of those at highest risk. We sought to determine the incidence of pneumonia in a cohort of HIV-EU infants as well as risk factors.

Methods: HIV-EU infants participating in a Kenyan perinatal HIV-1 cohort study enrolled between 1999-2002 were followed monthly from birth to 12 months. Clinician-diagnosed pneumonia episodes were recorded at monthly study visits and at sick-child visits. The incidence of pneumonia was estimated using total person-years of observation and instances of physician-diagnosed pneumonia, with a 14-day window for new episodes. Cox proportional hazards regression was used to identify predictors of first pneumonia occurrence.

Results: Among 365 HIV-EU infants with 323 person-years of follow-up, the incidence of pneumonia was 89.8/100 child-years (95% CI: 80.1-100.8). Crowding in the home [HR=1.4 (95% CI 1.0-2.0)], maternal HIV viral load at 32 weeks' gestation [HR=1.2 (1.0-1.5) per $\log_{10}$ difference] and being underweight (WAZ<-2) at the previous visit [HR=1.9 (1.2-3.0)] were associated with increased risk of pneumonia. Breastfed infants had a 47% lower risk of pneumonia than those who never breastfed [HR=0.53 (0.39-0.73)]. This association was independent of infant growth and maternal viral load.

Conclusions: The incidence of pneumonia in this cohort of HIV EU infants was high. Our observations suggest that maternal viral suppression and breastfeeding may reduce the burden of pneumonia among HIV-EU children.

INTRODUCTION

As increasingly effective measures to prevent infant HIV infection are implemented, addressing morbidity in the growing population of HIV-exposed uninfected (HIV-EU) children becomes a priority. HIV-EU children have higher mortality and morbidity than their unexposed peers[1, 2]. This may be due to a variety of factors related to maternal HIV infection, such as increased exposure to infectious pathogens, impaired maternal caregiving due to illness, reduced breastfeeding[3], impaired placental antibody transfer[4] or compromised immune development[3].

Pneumonia is a leading cause of child mortality worldwide, in both healthy and HIV-infected populations. About 100-150 episodes of severe pneumonia are estimated to occur per 1,000 children born in developing countries during the first 5 years of life[5]. An estimated half of all pneumonias among children in the developing world are caused by vaccine preventable *Haemophilus influenzae* or *Streptococcus pneumoniae*, although the proportion varies by HIV status, nutritional status and region[5]. Viral infections and mixed viral-bacterial infections are also common etiologies of childhood pneumonia in developing countries.[6, 7] HIV-infected children are at high risk for pneumonia due to immune compromise[6, 8] and in a perinatal HIV cohort in Kenya, we previously found pneumonia to be the leading cause of mortality in both HIV infected[9] and HIV-EU infants[10].

Although higher rates of pneumonia have been reported among African HIV-EU than unexposed infants[1], cofactors and mechanisms for this increased risk are not well-defined. Elucidation of cofactors for pneumonia in HIV-EU may inform interventions to prevent pneumonia or identification of mother-infant pairs at highest risk. In this study, we describe the incidence and predictors of pneumonia in a cohort of HIV-EU Kenyan infants.

METHODS

Subject selection: Mother-infant pairs included in this analysis were enrolled in a study of HIV transmission in Nairobi, Kenya between 1999-2002, details of which have been described elsewhere[9, 10]. Briefly, pregnant women over 18 years old who attended Nairobi City Council clinics for antenatal care and were screened and found to be HIV-seropositive before 28 weeks gestation were invited to enroll in the study. Mothers provided written informed consent for their own and their infants' participation until 12 months of age, 24 months if the child became HIV infected. Singleton infants and first-born twins were included in the current analysis if they completed at least one study visit and remained HIV uninfected until study exit or death. Infants were excluded if they became HIV-infected at any time in the first year of life, or if they died or were lost to follow-up without completing a study visit.

Study procedures: Sociodemographic information and maternal health information were collected at enrollment. Mothers provided a blood sample for CD4 and HIV viral load at 32 weeks' gestation. Mothers received short-course zidovudine from 32 weeks' gestation and during delivery. Mothers received counseling regarding infant feeding options and fed their infants according to their own preference. Mothers and infants completed scheduled study visits within 48 hours of delivery, 2 weeks after delivery and monthly thereafter until study completion at 12 months post-delivery.

Clinical data collection: Infant health information was collected in two ways throughout follow-up. At scheduled study visits, infants underwent detailed clinical examination by a study pediatrician. Mothers were interviewed and a history of illness and hospitalization since the last study visit, as well as information on current feeding practices, were collected on a standardized form. At sick-child visits, infants were assessed and treated and a written diagnosis recorded, but examination and history were limited to features related to the infant's reporting complaint. For infants who died, verbal autopsy was conducted to determine most likely cause of death.

Outcome: Pneumonia diagnoses were made according to Integrated Management of Childhood Illness (IMCI) guidelines. Pneumonia diagnoses recorded at the scheduled study visits (via check-box) or at the sick-child visits (written diagnosis) or recorded as most likely cause of death at verbal autopsy were included in this analysis. To avoid counting an unresolved episode more than once, a 14-day window was imposed; a diagnosis was considered to refer to the same episode if 14 days or less had passed since the initial diagnosis.

Statistical analysis: All analyses were conducted using Stata 11.2 (StataCorp, College Station, Texas). Infant growth was assessed using the WHO Child Growth Standards Stata igrowup package.

Overall incidence of pneumonia in the study cohort was calculated using all pneumonia diagnoses made by a study physician, whether recorded at scheduled visits or sick-child visits, or recorded as cause of death at verbal autopsy. We allowed for repeated episodes per child if more than 14 days passed between diagnoses. Infants contributed person-time until death, loss to follow up or study exit at one year of age, but did not contribute person-time during the 14 days when new diagnoses would not have been counted. In a secondary analysis, pneumonia incidence was calculated separately for infants by breastfeeding status (ever / never). Incidence of first pneumonia was calculated with infants contributing person-time until first pneumonia diagnosis, death, loss to follow-up or study exit.

Predictors of first pneumonia diagnosis in the first year of life were identified using Cox proportional hazards regression. Infants were censored at loss to follow-up or death due to causes other than pneumonia. Infants were excluded from each analysis if information on the exposure was missing. Univariate predictors assessed were maternal age, maternal education, living in a one-room house, crowding, maternal CD4 count and viral load at 32 weeks' gestation, breast feeding (ever/never, current), infant gestational age at delivery, birth weight, and weight-for-age Z-score according to the WHO child growth standards (WAZ). All exposures were assessed at baseline with the exception of breastfeeding and WAZ. An infant was considered "ever" breastfed if mother ever reported

breastfeeding at a study visit; current breastfeeding and weight-for-age Z-score were assessed at each study visit and analyzed as time-varying covariates.

In selected instances, multivariate predictors were identified using multivariate Cox proportional hazards regression. In order to address whether any association with current breastfeeding was mediated by its effect on infant growth, current breastfeeding and WAZ at the previous visit were included in the same model. To address confounding by advanced maternal disease of the association between breastfeeding and pneumonia, HIV viral load at 32 weeks' gestation and any breastfeeding were included in an alternative model.

RESULTS

Study population: A total of 365 HIV-EU singleton infants or first-born twins and their mothers met inclusion criteria and were included in this analysis (Table 1). Mothers' mean age at enrollment was 25 years (IQR 22-28). Most were married, lived in one-room houses and lacked an independent income, although nearly all those who provided information had spouses who were employed. The women were moderately immunosuppressed at 32 weeks' gestation with a mean CD4 count of 487 cells/mm^3 (IQR 316-621) and a mean CD4% of 24 (IQR 19-30). Mothers' baseline mean viral load was 4.6 log_{10} copies/ml (IQR 4.1-5.2). The majority of mothers (75%) elected to breastfeed their infants after feeding counseling.

Incidence of pneumonia among HIV-EU infants: The 365 infants completed a total of 323 person-years of follow-up (mean 10.6 months of observation per infant). Of these infants, 172 (47%) experienced an episode of pneumonia, and 67 of these (39%) experienced more than one episode. A total of 289 pneumonia episodes were recorded during the 323 person-years of follow-up, 128 of which were first diagnosed at a routine visit, 156 at sick-child visits, and 5 were never diagnosed at the study clinic but were recorded as cause of death at verbal autopsy. The total incidence of pneumonia, allowing for repeated episodes, was 89.8/100 child-years (95% CI: 80.1-100.8) (Figure 1A) and the

incidence rate did not differ significantly between three-month intervals of age. Incidence of first pneumonia, with infants exiting from the analysis at the time of their first pneumonia diagnosis or at censoring, was 74.1/100 child-years (95% CI: 63.8-86.0) (Figure 1B). According to maternal report, 28 of the infants in the cohort were hospitalized a total of 35 times for pneumonia (Figure 1C), which corresponds to an incidence of pneumonia hospitalization of 109/1000 child-years (95% CI 78-151), allowing for repeated events. Ten infants were determined to have died of pneumonia (Figure 1D), for a total pneumonia-related mortality rate of 31/1000 child-years (95% CI 17-57).

Risk factors for first pneumonia: Maternal age and education were not associated with pneumonia risk in the infant (Table 2). Crowding in the home (3 or more residents per room) was associated with a 40% increase in risk (HR=1.4, 95% CI 1.0-2.0). There was no association between maternal CD4% at 32 weeks' gestation and pneumonia risk in the infant, whether CD4% was examined as a continuous variable or dichotomized as <20% vs. ≥20%. The same was true when maternal CD4 count at 32 weeks' gestation was considered (data not shown). In contrast, each $\log_{10}$ increase in maternal viral load at 32 weeks' gestation was associated with a 20% increased pneumonia risk [HR=1.2 (1.0-1.5) per $\log_{10}$ difference]. Low birth weight and prematurity were not associated with risk of pneumonia in our study. Being underweight (WAZ < -2) at a study visit was associated with increased risk of pneumonia at the following visit [HR=1.9 (1.2-3.1)]. When treated as a continuous variable, WAZ was associated with a 15% reduced risk of pneumonia at the subsequent visit per standard deviation of infant weight [HR=0.85 (0.74-0.97)].

Breastfeeding is associated with decreased pneumonia incidence and severity: Infants whose mothers reported breastfeeding at one or more visits had a 47% lower risk of pneumonia than those who were never breastfed [Figure 2A, HR=0.53 (0.39-0.73)]. When breastfeeding was considered as a time-varying covariate, current breastfeeding was associated with a 51% reduced risk of pneumonia at that visit [Figure 2B, HR=0.49 (0.36-0.68)]. When current breastfeeding and WAZ at the previous visit

were included in the same model (Table 3), breastfeeding remained associated with reduced risk of pneumonia [aHR=0.50 (0.37-0.70)], suggesting that the association of breastfeeding with reduced risk is not fully mediated by infant growth. The magnitude of the association with weight-for-age Z-score at the previous visit was also unaffected [aHR=0.88 (0.77-1.00)]. Similarly, when adjusting for maternal $\log_{10}$ viral load at 32 weeks' gestation, breastfeeding remained associated with reduced risk [HR=0.51 (0.36-0.72)] and there was a trend toward an association with maternal $\log_{10}$ viral load [HR=1.18 (0.96-1.45)], which suggests that the inverse association of breastfeeding with infant pneumonia is not confounded by maternal disease severity. Infants whose mothers reported breastfeeding at one or more visits had a 78% lower risk of pneumonia-related hospitalization than those never breastfed [Figure 2C, HR=0.22 (0.11-0.43)] and there was a trend toward an association with reduced risk of pneumonia-related mortality [Figure 2D, HR=0.33 (0.10-1.1)].

An alternative analysis using a composite endpoint of first pneumonia or all-cause infant mortality was conducted. All predictors identified in the main analysis were consistent in this analysis (data not shown).

Severity of infant pneumonia: All pneumonia diagnoses made at scheduled study visits (n=128) were accompanied by at least one symptom listed in IMCI guidelines. Of these 128 cases, 88% presented with cough, 65% had fever (>37.5°C), 62% had tachypnea, and 13% had wheezing. Severe pneumonia was indicated for 11% of diagnoses by chest in-drawing and 7.6% by difficulty feeding.

DISCUSSION

We found a very high incidence of pneumonia and a substantial burden of pneumonia-related hospitalizations and mortalities in this cohort of HIV-EU infants. Predictors of pneumonia included living in a crowded home, lack of breastfeeding, and low infant weight. Maternal HIV viral load during pregnancy was associated with increased risk of pneumonia.

Overall incidence of pneumonia in this cohort was 89.8/100 child-years (95% CI: 80.1-100.8). Close to half the infants (47%) experienced an episode of pneumonia during the time they were under observation, and 39% of these experienced one or more repeat episodes, which is higher than has been reported in previous studies[5]. The incidence of pneumonia-related hospitalization was 109/1,000 person-years, with 7.7% of infants hospitalized one or more times for pneumonia. This incidence is higher than that reported in population-based Kenyan studies in rural settings, which observed hospitalization rates of 48/1,000 person-years among infants[7] and 7/1,000 person-years among children under five years old[11]. Pneumonia-related mortality risk in our study cohort was 31/1,000 child-years, which is also high compared to reports in the general population in Kenya. A study of children under five years old in Nairobi's informal settlements found a pneumonia mortality risk of 5.2/1,000 child-years[12]. These differences may be partly explained by the age of our cohort – rates of pneumonia are higher in the first year of life than among older children under 5 years of age[7] – and increased hospitalization rates may be partly explained by increased detection and access to clinical care. Active surveillance was conducted monthly by study pediatricians in our study, and infants were referred for hospitalization when necessary, while one of the studies in rural Kenya showed an inverse association between hospitalization and distance of residence from the hospital[11]. However, it is likely that there are true differences between our cohort and the general population of Kenyan infants due to maternal HIV infection. The incidence of hospitalization we observed (109/1000 child-years, 7.7% during an average of 10.6 months of observation) was comparable to that found in a Zambian prospective cohort of HIV-EU infants in which 4.9% of infants were hospitalized by 4 months of age for pneumonia and/or sepsis[13]. Maternal HIV infection may place infants at increased risk of pneumonia through a variety of mechanisms*;* in our cohort, breastfeeding avoidance due to HIV infection was likely a key factor. Incidence of pneumonia-related hospitalization among breastfed infants was 58/1000 child-years (95% CI 34-98), much more comparable to the population-based estimate, while incidence among those who were never breastfed was 262/1000 child-years (95% CI

171-403).

Our finding that breastfeeding was associated with lower risk of pneumonia among HIV-EU infants is consistent with literature supporting the role of breastfeeding in the prevention of respiratory tract infections among children in general[14-16] and in reducing other infectious morbidity among HIV-EU children.[13, 17-19] A variety of possible mechanisms whereby breastfeeding could stimulate the infant immune system or protect against infection have been proposed[16, 20]. Breastfed infants have a larger thymus at four months of age than those not breastfed, show higher titers of neutralizing antibodies post-vaccination, and may mount more effective immune responses[16]. IgA antibodies ingested in breastmilk have been suggested to protect against infection by neutralizing microbes before they reach mucosal membranes[16, 20]. At the time of this study, the PMTCT regimen used did not include ART to mothers during breastfeeding. WHO 2010 guidelines recommend that HIV-infected mothers breastfeed with either extended maternal ART or infant prophylaxis[21]. Our study suggests that in addition to the enhanced prevention of infant HIV afforded by maternal ART, these safe breastfeeding guidelines may lead to decreased pneumonia among HIV-EU infants.

We found an inverse association between infant weight-for-age Z score (WAZ) in the first year and risk of pneumonia, consistent with previous studies[22, 23]. Underweight infants were at nearly twice the risk of pneumonia at the following visit compared to those who were not underweight. Several explanations could underlie this association, including increased susceptibility to infection due to malnutrition or increased risk of pneumonia following other acute illness, which is often accompanied by weight loss[23, 24].

Several African studies have noted an association between low maternal CD4 counts or CD4% and rates of infant hospitalization[1, 13] and mortality.[13, 25] A South American study found increased risk of lower respiratory tract infections associated with low maternal CD4 count and CD4% among formula fed HIV-EU infants[26]. We detected no association between maternal CD4% or CD4 count

at 32 weeks' gestation and infant pneumonia in our study, but did find a moderate association between maternal HIV viral load at 32 weeks gestation and infant risk of pneumonia. Our observations are consistent with a study conducted in South Africa, which found that high maternal plasma viral load was predictive of infant hospitalization and death, but maternal CD4 count was not[27]. Maternal viremia has been associated with compromised transplacental transport of antibodies[4], which could put the infant at greater risk for infection, and higher viral set-point may be a better predictor of maternal HIV progression than CD4 count[28], although evidence is inconsistent[29]. It is possible that the association with longer-term CD4 levels was attenuated due to pregnancy-related CD4 changes, and both CD4 and HIV viral load associations may have been attenuated due to their measurement at 32 weeks gestation predating the outcome by several weeks or months.

Our study has several strengths and limitations. Strengths of the study included detailed standardized characterization of serial morbidity, exposure history and maternal HIV status. Limitations include a lack of systematic confirmatory diagnostic studies such as chest X-rays and culture. Previous studies in African settings have found that only 15% of clinical pneumonia diagnoses[30] and 35–40% of severe clinical pneumonia diagnoses[30, 31] are radiologically confirmed when X-rays are available. Our ability to identify predictors of pneumonia would tend to be attenuated by misclassification of the outcome; therefore the associations we report may be underestimated. A second limitation is the potential for non-random loss to follow up and censoring. Low birth weight[32] and prematurity[33] have been consistently found to be associated with increased risk of pneumonia among children in general, but we found no association with these factors. In our cohort, low birth weight and prematurity may have contributed to early mortality before the first study visit and exclusion from the study. Similarly, it is possible that loss to follow up varied by infant health status, and that sicker children were more likely to return to clinic for free care during the study. We do not have an HIV-unexposed comparison cohort and so cannot estimate relative contribution of HIV exposure to high

incidence of pneumonia in the cohort. Finally, the study was conducted prior to addition of Hib and pneumococcal vaccines to the Kenyan EPI schedule. Although these would be expected to decrease incidence of pneumonia, ~50% of pneumonias are estimated to be caused by other pathogens[5, 7] and the cofactors that we identified likely remain relevant to HIV-EU infants.

As access to PMTCT expands, the population of HIV-EU infants will increase, and understanding and addressing the increased vulnerability of this population will be critical for optimizing child health. In our study, we observed an association between maternal viral load during pregnancy and increased pneumonia risk in the infant, while breastfeeding was associated with decreased risk. This suggests that in addition to reducing HIV transmission and improving maternal health, new WHO guidelines calling for maternal HAART may offer the best protection against pneumonia for the HIV-EU infant, both directly through reducing viral load and by allowing safe extended breastfeeding.

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Table 1 Description of the study cohort. 365 HIV-EU infants were included in the analysis.

Sociodemographic characteristics	**n**	**Mean (IQR) or n (%)**	
Mother's age	365	25	(22-28)
Mother's education > primary school	361	148	(40%)
Mother married	365	328	(90%))
Mother employed	365	108	(30%)
Spouse employed	219	213	(97%)
One room in house	365	285	(78%)
Crowding (>3 people/room in house)	362	78	(22%)
Maternal health			
CD4 count at 32 weeks gestation	357	487	(316-621)
CD4 % at 32 weeks gestation	357	24	(19-30)
CD4% < 20 at 32 weeks gestation	357	107	(30%)
$\log_{10}$ HIV viral load at 32 weeks gestation	326	4.6	(4.1-5.2)
$\log_{10}$ HIV viral load at delivery	180	3.9	(3.4-4.6)
Mother died during study	365	9	(2.5%)
Infant health			
Estimated gestational age at delivery	324	39	(39-40)
Premature (estimated GA<37 weeks)	324	21	(6.5%)
Birthweight (kg)	356	3.1	(2.9-3.4)
Low birthweight (<2500g)	356	31	(8.5%)
Infant breastfed (ever)	365	273	(75%)
Infant died during study	365	21	(7.1%)

Table 2 Univariate predictors of first pneumonia diagnosis identified using Cox proportional hazards regression. Pneumonia incidence reported is per 100 infant-years.

	n	Pneumonia (ever)	Incidence (95% CI)		HR	95% CI	p-value
Sociodemographic factors							
Maternal age ≤ 20 years	45	20	73	(46-113)	1.0	Ref,	
Maternal age 21-25 years	170	79	75	(60-94)	1.1	0.65-1.7	0.8
Maternal age 26-30 years	109	54	75	(57-98)	1.1	0.63-1.8	0.8
Maternal age >30 years	41	19	68	(44-107)	1.0	0.53-1.9	>0.9
Maternal education ≤ primary school	148	76	72	(59-87)	1.0	Ref.	
Maternal education >primary school	213	96	80	(64-100)	1.1	0.82-1.5	0.5
>One room house	80	37	70	(51-98)	1.0	Ref.	
One room house	285	135	75	(63-89)	1.1	0.74-1.5	0.8
≤3 people/room of house	284	128	69	(58-82)	1.0	Ref.	
>3 people/room of house	78	43	98	(72-130)	1.4	1.0-2.0	0.05
Maternal characteristics							
CD4% at 32 weeks' gestation (continuous)	357	165	72	(62-84)	1.0	0.99-1.0	0.9
CD4%≥20 at 32 weeks gestation	250	113	70	(58-84)	1.0	Ref	
CD4%<20 at 32 weeks gestation	107	52	77	(59-100)	1.1	0.78-1.5	0.6
HIV viral load at 32 weeks gestation (per $\log_{10}$)	326	145	68	(58-80)	1.2	1.0-1.5	0.06
HIV viral load <4.1 $\log_{10}$ at 32 weeks gestation	82	30	52	(36-74)	1.0	Ref.	
HIV viral load 4.1-5.2 $\log_{10}$ at 32 weeks gestation	164	75	67	(54-84)	1.3	0.85-2.0	0.2
HIV viral load >5.2 $\log_{10}$ at 32 weeks gestation	80	40	91	(67-124)	1.7	1.1-2.8	0.02
Infant characteristics							
Birth weight ≥2.5 kg	325	157	76	(65-89)	1.0	Ref.	
Birth weight <2.5 kg	31	12	60	(34-106)	0.78	0.43-1.4	0.4
Infant born at term	303	148	76	(64-89)	1.0	Ref.	
Infant born pre-term	21	9	92	(48-177)	1.2	0.59-2.3	0.7
Never breastfed	91	57	118	(91-153)	1.0	Ref.	
Ever breastfed	273	114	62	(52-75)	0.53	0.39-0.73	<0.001
TIME-VARYING COVARIATES	**Infant-years**	**Pneumonia (ever)**	**Incidence (95% CI)**		**HR**	**95% CI**	**p-value**
Not currently breastfeeding	88	87	99	(80-122)	1.0	Ref.	
Currently breastfeeding	142	75	52	(42-66)	0.49	0.36-0.68	<0.001
WAZ –score at previous visit (continuous)	215	162	75	(65-88)	0.85	0.74-0.97	0.02
Not underweight (WAZ≥ -2) at previous visit	201	142	70	(60-83)	1.0	Ref.	
Underweight (WAZ <-2) at previous visit	14	20	146	(94-226)	1.9	1.2-3.1	0.007

Table 3 Multivariate predictors of first pneumonia diagnosis identified using Cox proportional hazards regression.

	n	Pneumonia (ever)	Adjusted hazard ratio	95% CI	p-value
Model 1:					
Infant currently breastfeeding	349	155	0.50	0.37-0.70	<0.001
WAZ at previous visit (continuous)			0.88	0.77-1.00	0.06
Model 2:					
Infant ever breastfed	326	145	0.51	0.36-0.72	<0.001
Maternal $\log_{10}$ viral load at 32 weeks gestation (per $\log_{10}$)			1.18	0.96-1.45	0.1

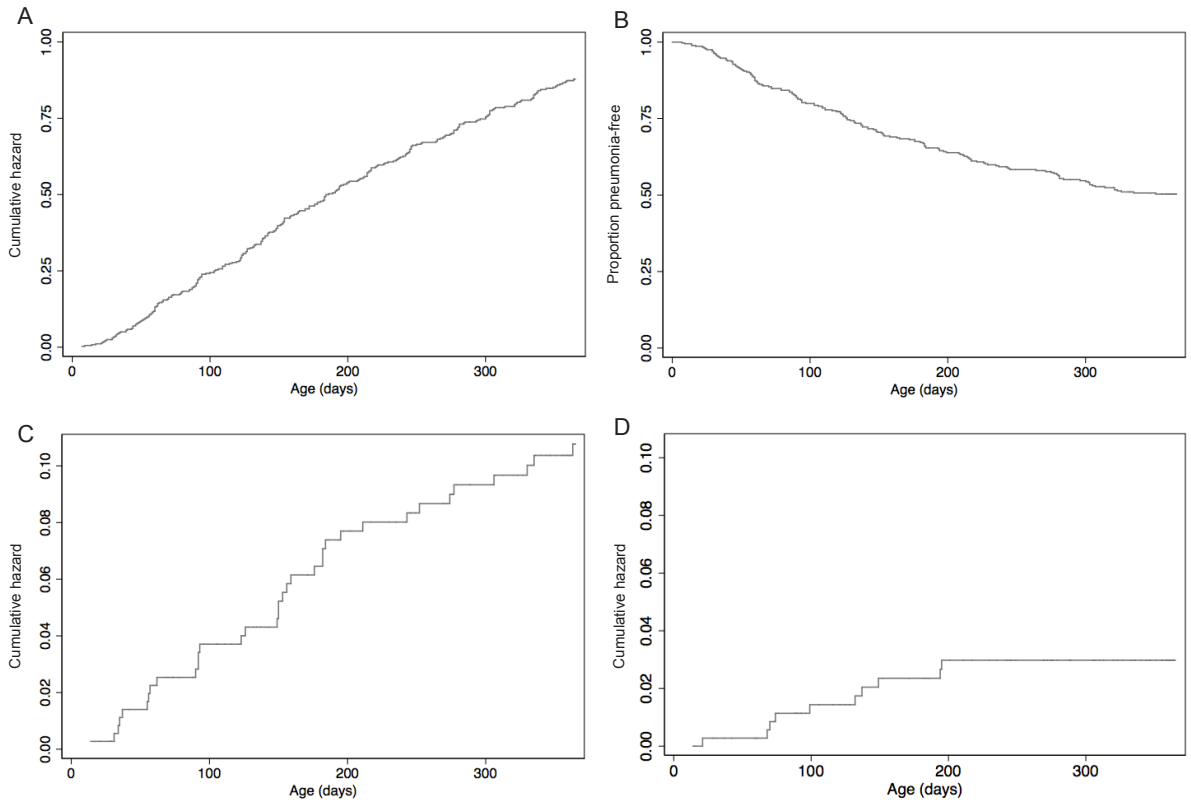

Figure 1 Panel A shows cumulative hazard of pneumonia, allowing for repeat episodes per infant. A total of 289 episodes were recorded among 172 infants, and total pneumonia incidence was 89.8/100 infant-years (95% CI 80.1-100.8). Panel B shows time to first pneumonia diagnosis; incidence of first pneumonia was 74.1/100 infant-years (63.8-86.0). Panel C shows cumulative hazard of pneumonia-related hospitalization; incidence of hospitalization was 109/1,000 infant-years (78-151), with 35 hospitalizations reported among 28 infants. Panel D shows cumulative hazard of pneumonia-related mortality; ten infants died of pneumonia during the study and pneumonia-related mortality rate was 31/1,000 infant-years (17-57).

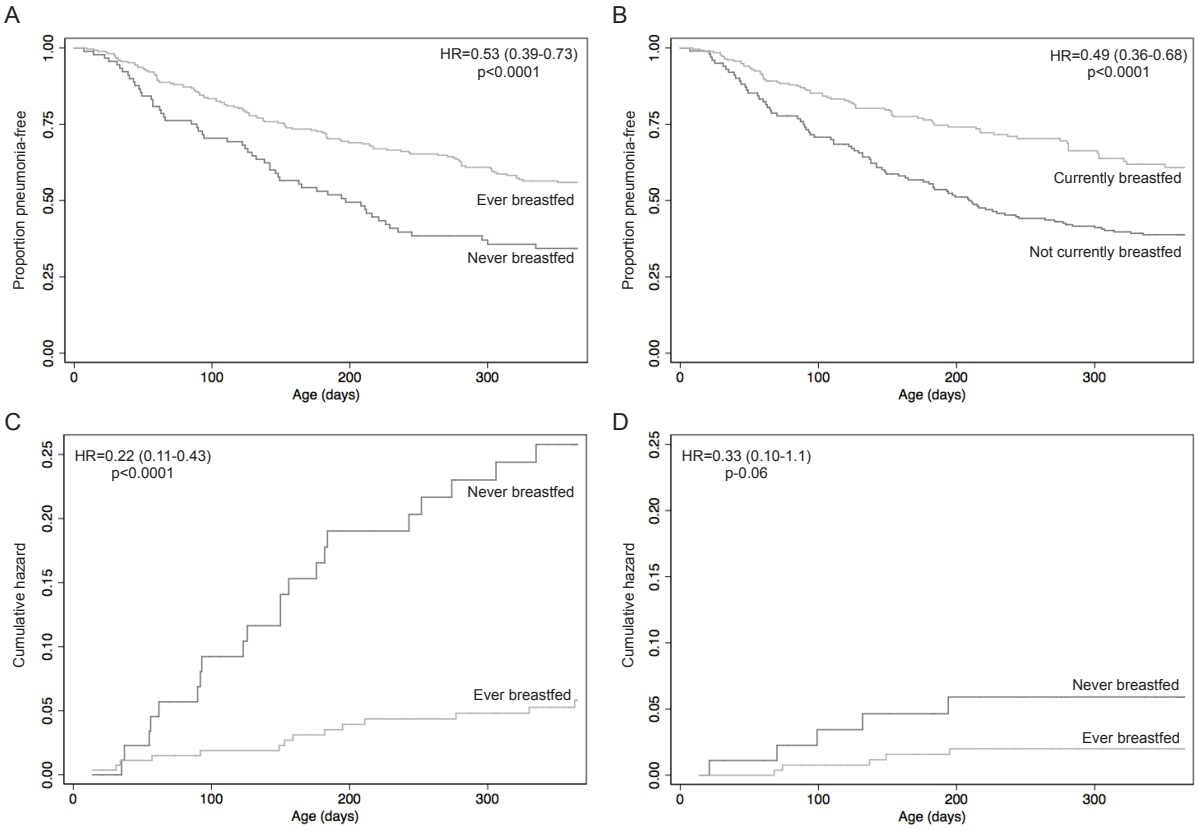

Figure 2 Panel A shows time to first pneumonia by breastfeeding history, ever breastfed / never breastfed. Panel B shows time to first pneumonia by current breastfeeding status, breastfeeding / not breastfeeding. Panel C shows cumulative hazard of pneumonia-related hospitalization by breastfeeding history, ever breastfed / never breastfed. Panel D shows cumulative hazard of pneumonia-related mortality by breastfeeding history, ever breastfed / never breastfed. All p-values refer to comparisons of curves using the log-rank test.