Nutritional Predictors of Acute Respiratory Infections Among Children Born to HIV-Infected Women in Tanzania

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Summary

We prospectively determined the association between undernutrition and incidence of acute respiratory infections (ARIs) among 711 children born to HIV-infected women. Overall, underweight was associated with a 58% increased risk of ARI. Similarly, wasting (54%), very low birth weight (88%) and child HIV infection (62%) were significantly associated with increased risk of ARI during the first 2 years. Breastfeeding was associated with 52% reduction in risk of ARI only during the first 12 months of life. Among HIV-exposed, but uninfected, children, underweight, wasting and stunting were associated with 73%, 61% and 33% increased risk of ARI, respectively. Very low birthweight and advanced maternal disease stage were also associated with increased risk of ARI. Similar results were observed among HIV-infected children, except for stunting and very low birth weight. Prevention of child undernutrition could have major impact in reducing child ARI morbidity in settings of high HIV prevalence.

Key words: nutrition, pediatrics, respiratory, infections.

Introduction

Acute respiratory infections (ARIs) are major causes of childhood morbidity and mortality worldwide, and they account for a large portion of medically attended illnesses and hospitalizations of children younger than 5 years [1–6]. Similarly, malnutrition is a major contributor to the total global disease burden. It has been estimated that malnutrition is the underlying cause of approximately half of the fatal acute lower respiratory tract infections [7]. Several other factors related to ARI risk, including breastfeeding and low birth weight, have also been investigated. Several studies have shown that breastfeeding, in general, and particularly exclusive breastfeeding for up to 6 months of life, reduces the risk of ARI [8–10]. On the other hand, low birth weight has been recognized as a risk factor for severe respiratory

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infection and death in several studies [7, 10, 11]. However, little is known about the impact of child undernutrition and these other factors on ARI among children exposed to HIV infection *in utero* or after birth through breastfeeding in developing countries with a high burden of HIV infection.

Furthermore, advanced clinical and immunological maternal HIV disease during pregnancy has been shown to be associated with increased risk of mortality in children [12, 13], hence the association between maternal HIV disease stage and ARI among children born to HIV-infected women, whether themselves infected or uninfected, is critical to examine.

We examined the associations between child undernutrition, low birth weight, breastfeeding and maternal HIV disease stage in relation to the incidence of ARI in the first 2 years of life.

Methods

Study design and population

The children in this study were born to HIV-infected women who were part of a randomized, double-blind placebo-controlled trial conducted to examine effects of maternal multivitamin supplementation on maternal and child health outcomes in Dar es Salaam, Tanzania, between April 1995 and July 1997. Details of the trial design have been published elsewhere [14]. Antiretroviral therapy was not yet widely available, and none of the mothers or their children received it during the course of the study.

Measurements

At baseline and during monthly visits to the clinic, women underwent physical examination and provided a detailed medical history and information on socio-demographic characteristics. Measurements of the women's absolute CD4 T cell counts and complete blood cell counts were done at baseline, 6 weeks postpartum and every 6 months thereafter.

Birth weight was measured immediately after birth, and low birth weight and very low birth weight were defined as birth weight <2500 and <2000 g, respectively. During monthly visits to the clinic, children underwent physical examination, including measurement of mid-upper arm circumference, weight and recumbent length. Mothers provided a detailed history of their child's feeding and illnesses, including any occurrence of fever and any respiratory illness in children during the previous month. Child HIV status was assessed at birth, at 6 weeks and at 3-month intervals thereafter. ARI was defined as the occurrence of cough and fever as reported by mothers.

We computed child weight-for-age, height-for-age and weight-for-height standardized Z-scores and defined undernutrition by comparing child anthropometry with the reference WHO Child Growth Standards [15]. A child was considered to be underweight, stunted or wasted when weight-for-age, height-for-age or weight-for-height Z-score, respectively, was below -2 of the reference population.

Data analysis

Of the 939 singletons children born alive, 48 children died by week 6, 94 had no post-birth visit and 86 had no records on ARI outcomes, leaving 711 children available for this analysis. Generalized estimating equations for repeated binary outcomes using SAS software package version 9.1 (SAS Institute Inc., Cary, NC, USA) were used to estimate the relative risks (RRs) for ARI episodes [16]. Child undernutrition indicators were examined as time-varying risk factors for ARI episodes. The binomial distribution with the log link function and a working exchangeable covariance structure was specified. Variables were included in the multivariate models if the estimated RR for their association with ARI was statistically significant at $p \leq 0.20$ in the univariate analyses. For analysis within strata of child HIV status, the variables identified in the models for HIV-uninfected children were applied to the HIV-infected children. The missing indicator method was used for covariates with $>1\%$ of missing data.

The Research and Publications Committee of Muhimbili University of Health and Allied Sciences and the Institutional Review Board of the Harvard School of Public Health approved the study protocol.

Results

Seven hundred eleven children born to HIV-infected women were followed up for a median of 11 months (interquartile range, 6–17 months). The distribution of general characteristics of children and their mothers at enrollment are given in Table 1. Majority of women had a favorable nutritional and immunological status, 74% were not anemic (hemoglobin ≥ 8.5 g/dl) and 81% were in HIV disease stage I.

We examined the association of child nutritional status as it varied over time in relation to bouts of ARI. The results of the association of the various predictors and subsequent risk of ARI during the first 24-month period are presented in Table 2. Underweight was associated with 58% increased risk of ARI [95% confidence interval (CI), 1.29–1.93], wasting was associated with 54% increased risk of ARI (95% CI, 1.25–1.90) and stunting was associated with 13% non-statistically significant increased risk of ARI (95% CI, 0.93–1.36). HIV infection in the child was associated with 62% increased risk of ARI (95% CI, 1.38–1.89). Similarly, very low birth weight was associated with 88% increased risk of ARI (95% CI, 1.26–2.80) during the first 24 months of life. Maternal HIV disease above stage I was associated with 18%

TABLE 1
Socio-demographic and clinical characteristics among HIV-infected mothers and children born to HIV-infected mothers

Characteristic	Number (%)[a]
Maternal age (years)	
<20	82 (12)
20–24	281 (40)
25–29	231 (32)
≥30	117 (16)
Maternal education	
None or less than high school	633 (89)
High school or above	78 (11)
Marital status	
Single, divorced or widowed	82 (12)
Cohabiting	172 (24)
Married (monogamous and polygamous)	457 (64)
Maternal occupation	
Housewife	514 (72)
Professional, employed, business, public office and other	197 (28)
Paternal education	
None or less than high school	406 (57)
High school or above	305 (43)
Parity	
1	224 (32)
2	197 (28)
3	152 (21)
≥4	138 (19)
Family expenditure for food (TZS/day/person)	
<500	263 (41)
≥500	372 (59)
Maternal BMI at 6 weeks after delivery (kg/m^2)	
<18.5	55 (9)
18.5–24.49	455 (74)
≥25	105 (17)
Maternal baseline hemoglobin level (g/dl)	
<8.5	183 (26)
≥8.5	528 (74)
Maternal MUAC at 6 weeks after delivery (cm)	
<23	299 (42)
≥23	412 (58)
Maternal WHO HIV disease stage	
I	578 (81)
II and above	132 (19)
Maternal baseline CD4+ T-cell count (cells/μl)	
<200	70 (10)
200–499	384 (54)
≥500	257 (36)
Child sex	
Male	360 (51)
Female	349 (49)
Gestational age at birth (weeks)	
<34	50 (7)
34–36	111 (16)
≥37	550 (77)
Birth weight (g)	
<2000	9 (1)
2000–2499	46 (6)
≥2500	656 (92)

[a]Percentages may not total 100 because of rounding.
BMI, body mass index; MUAC, mid-upper arm circumference; TZS, Tanzanian Shillings.

TABLE 2
Associations of undernutrition, birth weight, child HIV infection, maternal HIV disease stage and subsequent risk ARI during the first 24 months of life in the overall group (n = 698 episodes/5918 child-visits)

Characteristic	Univariate RR (95% CI)	Multivariate[a] RR (95% CI)
Underweight		
Yes	1.94 (1.60–2.35)	1.58 (1.29–1.93)
No	1.00	1.00
Wasting		
Yes	1.88 (1.53–2.30)	1.54 (1.25–1.90)
No	1.00	1.00
Stunting		
Yes	1.32 (1.10–1.59)	1.13 (0.93–1.36)
No	1.00	1.00
Birth weight (g)		
<2000	2.09 (1.40–3.11)	1.88 (1.26–2.80)
≥2000	1.00	1.00
HIV infection		
Yes	1.77 (1.52–2.05)	1.62 (1.38–1.89)
No	1.00	1.00
Maternal WHO disease stage		
I	1.00	1.00
II and above	1.25 (0.99–1.58)	1.18 (0.94–1.49)

[a]Adjusted for birthweight, parity, household expenditure for food, time-varying child nutritional status, child HIV status and maternal HIV disease stage.

non-statistically significant increased risk of ARI during this period (95% CI, 0.94–1.49).

We next examined the association between the nutritional predictors and ARI during the 1.5–12-month and 13–24-month periods of life (Tables 3 and 4). Being underweight was associated with 69% increased risk of ARI (95% CI, 1.30–2.20), and wasting was associated with 65% increased risk of ARI (95% CI, 1.26–2.16), whereas stunting was not associated with the risk of ARI; very low birth weight was associated with 77% increased risk of ARI (95% CI, 1.16–2.71) during the first 12 months of life. Breastfeeding, on the other hand, was associated with 52% reduction in risk of ARI (95% CI, 0.35–0.64) in the first 12 months of life. Child HIV infection and maternal WHO HIV disease stage above I were also associated with increased risk of ARI during this period of life. Results for the 13–24-month period were similar to those seen in the 1.5–12-month period (Table 4). The major difference was that breastfeeding and maternal HIV disease stage were not associated with risk of ARI during this period of life. Similarly, low birth weight was not associated with statistically significant increase in risk of ARI during this period of life.

Finally, we examined the association between the various predictors and the risk of ARI in the first

TABLE 3
Associations of undernutrition, birthweight, child HIV infection, maternal HIV disease stage and subsequent risk of ARI during 6 weeks – 12 months of life (n = 403 episodes/3184 child-visits)

Characteristic	Univariate RR (95% CI)	Multivariate RR (95% CI)
Underweight		
Yes	2.24 (1.74–2.89)	1.69 (1.30–2.20)[a]
No	1.00	1.00
Wasting		
Yes	2.19 (1.67–2.86)	1.65 (1.26–2.16)[a]
No	1.00	1.00
Stunting		
Yes	1.50 (1.14–1.98)	1.28 (0.98–1.67)[b]
No	1.00	1.00
Birth weight (g)		
<2000	2.44 (1.56–3.81)	1.77 (1.16–2.71)[a]
≥2000	1.00	1.00
Breastfeeding		
Yes	0.40 (0.29–0.56)	0.48 (0.35–0.64)[a]
No	1.00	1.00
HIV infection		
Yes	1.77 (1.46–2.16)	1.57 (1.28–1.92)[a]
No	1.00	1.00
Maternal WHO disease stage		
I	1.00	1.00
II and above	1.36 (1.04–1.79)	1.34 (1.02–1.74)[a]

[a]Adjusted for birthweight, maternal education, partner education, time-varying nutritional status, breastfeeding status, child HIV status and maternal HIV disease stage.
[b]Adjusted for birthweight, household expenditure for food, parity, maternal education, partner education, time-varying nutritional status, breastfeeding status, child HIV status and maternal HIV disease stage.

24 months of life separately among HIV-infected versus un-infected children (Table 5). Among HIV-exposed, but uninfected, children, being underweight was associated with a 73% increased risk of ARI (95% CI, 1.32–2.27). Similarly, wasting (61%; 95% CI, 1.21–2.15), stunting (33%; 95% CI, 1.05–1.68) and maternal WHO HIV disease stage above I (81%; 95% CI, 1.30–2.53) were associated with increased risk of ARI. Very low birth weight was associated with >2-fold increased risk of ARI in these children (RR, 2.25; 95% CI, 1.43–3.53) during the first 2 years of life. Similar results were observed among HIV-infected children for underweight and wasting, whereas stunting and very low birth weight were not associated with increased risk of ARI in these children.

Discussion

We have shown in this cohort of children that child undernutrition was significantly associated with

TABLE 4
Associations of undernutrition, birthweight, child HIV infection and subsequent risk of ARI during 13–24 months of life (n = 294 episodes/2721 child-visits)

Characteristic	Univariate RR (95% CI)	Multivariate[a] RR (95% CI)
Underweight		
Yes	1.75 (1.32–2.34)	1.64 (1.22–2.20)
No	1.00	1.00
Wasting		
Yes	1.69 (1.25–2.28)	1.60 (1.18–2.17)
No	1.00	1.00
Stunting		
Yes	1.30 (1.00–1.68)	1.15 (0.89–1.51)
No	1.00	1.00
Birth weight (g)		
<2500	0.57 (0.31–1.04)	0.55 (0.30–1.00)
≥2500	1.00	1.00
HIV infection		
Yes	1.75 (1.38–2.21)	1.61 (1.26–2.06)
No	1.00	1.00

[a]Adjusted for birthweight, child sex, partner education, household expenditure for food, time-varying child nutritional status and child HIV status.

TABLE 5
Associations of undernutrition, low birthweight, maternal HIV stage and subsequent risk of ARI during the first 24 months of life among HIV-infected and un-infected children[a]

Characteristic	HIV-uninfected RR (95% CI)	HIV-infected RR (95% CI)
Underweight		
Yes	1.73 (1.32–2.27)	1.54 (1.15–2.07)
No	1.00	1.00
Wasting		
Yes	1.61 (1.21–2.15)	1.56 (1.15–2.11)
No	1.00	1.00
Stunting		
Yes	1.33 (1.05–1.68)	0.89 (0.65–1.22)
No	1.00	1.00
Birth weight (g)		
<2000	2.25 (1.43–3.53)	0.72 (0.11–4.75)
≥2000	1.00	1.00
Maternal WHO disease stage		
I	1.00	1.00
II and above	1.81 (1.30–2.53)	0.66 (0.49–0.90)

[a]Adjusted for birthweight, maternal age, maternal occupation, household expenditure for food, partner education, parity, gestational age at birth, time-varying child nutritional status and maternal HIV disease stage.

increased risk of ARI during the first 2 years of life. The effect was more pronounced for underweight and wasting in all the periods examined and among both HIV-infected and un-infected children. Stunting, however, was an independent risk factor only among HIV un-infected children. Our findings are consistent with studies conducted in other populations [10, 17–21]. A study in India showed that severe malnutrition was associated with 85% increased risk of lower respiratory tract infections [17]. Victora *et al*. (20) in their review showed that many studies that have examined the relation between malnutrition, particularly underweight, and the incidence of pneumonia or acute lower respiratory infections demonstrated a positive association.

A causal effect of undernutrition is plausible, given the previous literature that has established strong links between malnutrition, immune dysfunction and infectious diseases [11, 22, 23]. Child undernutrition leads to a spectrum of immune dysfunction, including impairment of cell-mediated immunity, immunoglobulin and cytokine production [7, 20].

We found that low birth weight was associated with increased risk of ARI. Low birth weight has been recognized as a risk factor for severe respiratory infection and death in several other studies [7, 10, 20]. Possible mechanisms by which low birth weight may affect the risk of ARI include abnormality of lung structure and function, and impaired immunocompetence as a result of intra-uterine growth restriction [24, 25].

We also found that breastfeeding was associated with 51% reduction in risk of ARI during the first 12 months of life. Other studies have reported similar findings in both developed [8, 9] and developing [26, 27] countries. The mechanism by which breastfeeding can lower the risk of ARI is through maternal-infant transfer of innate immune components such as lactoferrin, lysozyme and secretory IgA; influences of breast milk on immune-system maturation, and enhancement of the antibody response to pathogens [28, 29].

Child HIV infection was consistently associated with increased risk of ARI in this study. HIV infects cells of the immune system, destroying or impairing their function—as the infection progresses, the immune system becomes weaker, and the person becomes more susceptible to infections, including ARI.

We found a positive association between advanced maternal HIV disease stage and the development of ARI in the first 12 months of life (all children combined) and in the first 2 years of life among HIV-uninfected children. Advanced maternal HIV disease could interfere with the transfer of antibodies that occurs from the mother to the fetus, but also sick women could have reduced capacity to care for their children. Advanced clinical and immunological maternal HIV disease during pregnancy has been shown to be associated with increased risk of mortality in both HIV-infected [12, 13] and un-infected [30] children. The reduction in risk of ARI among HIV-infected children born to mothers with advanced HIV disease stage is difficult to explain, given the probable mechanism of action described previously, and could be due to some methodological limitations such as confounding; for instance, these children might have received more care from relatives because their mothers could not provide adequate care due to illness. We looked at whether HIV-infected children born to mothers with advanced HIV disease stage had greater interactions with the health care system but it was not the case.

The major strength of this study is that we limited information bias through prospective data collection and updating the exposure measurements over time and its large sample size. However, misclassification of outcome could be one of the limitations of this study, as information on cough and fever was reported by the women. Such misclassification would result in an overestimation of the association between undernutrition and ARI. We examined how ARI as defined by occurrence of cough and fever related to mortality as a way to validate the definition, and found that cough and fever was associated with 37% risk of death—slightly lower than other studies [20], nonetheless statistically significant.

In conclusion, we observed a strong association between child undernutrition and ARI in the first 2 years of life among children born to HIV-infected women. Programs such as nutrition interventions, health education, and income growth, aimed at preventing or reducing the prevalence of child undernutrition and low birth weight, and at promoting breastfeeding could have major impact in reducing child ARI morbidity in settings of high HIV prevalence, and achieving the Millennium Development Goal 4 of reducing child mortality.

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