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A Meta-analysis Assessing Diarrhea and Pneumonia in HIV-Exposed Uninfected Compared With HIV-Unexposed Uninfected Infants and Children

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Abstract

Objective: Previous studies have demonstrated that HIV-exposed uninfected (HEU) infants and children experience morbidity and mortality at rates exceeding those of their HIV-unexposed uninfected (HUU) counterparts. We sought to summarize the association between HEU vs. HUU infants and children for the outcomes of diarrhea and pneumonia.

Design: Meta-analysis.

Methods: We reviewed studies comparing infants and children in the 2 groups for these infectious disease outcomes, in any setting, from 1993 to 2018 from 6 databases.

Results: We included 12 studies, and 17,955 subjects total [$n = 5074$ (28.3%) HEU and $n = 12,881$ (71.7%) HUU]. Random-effects models showed HEU infants and children had a 20% increase in the relative risk of acute diarrhea and a 30% increase in the relative risk of pneumonia when compared with their HUU counterparts. When stratifying by time since birth, we showed that HEU vs. HUU children had a 50% and 70% increased risk of diarrhea and pneumonia, respectively, in the first 6 months of life.

Conclusions: We show an increased risk of diarrhea and pneumonia for HEU vs. HUU infants and children. Although we acknowledge, and commend, the immense public health success of prevention of mother-to-child transmission, we now have an enlarging population of children that

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seem to be vulnerable to not only death, but increased morbidity. We need to turn our attention to understanding the underlying mechanism and designing effective public health solutions. Further longitudinal research is needed to elucidate possible underlying immunological and/or sociological mechanisms that explain these differences in morbidity.

Keywords

HIV-exposed uninfected; HIV-unexposed uninfected; morbidity; pneumonia; diarrhea meta-analysis

INTRODUCTION

Great progress has been made in efforts to prevent mother-to-child transmission (PMTCT) of HIV. The percentage of pregnant women receiving antiretroviral therapy (ART) for PMTCT increased from 47% in 2010 to 80% in 2016.¹ The global scale-up of PMTCT of HIV through provision of maternal ART is credited with a 70% worldwide decline in new HIV infections among children between 2000 and 2015.² Today, there is substantial evidence that under ideal conditions effective maternal ART use can almost eliminate mother-to-child transmission, and at a programmatic level, it may be possible to decrease transmission to >2% in low- and middle-income countries.^{3,4} Despite this significant progress, the number of children exposed to HIV remains unacceptably high, with an estimated 1.3 million children born (exposed) to HIV-positive mothers in 2015,^{1,5} most of whom reside in sub-Saharan Africa. Assuming continued high uptake of PMTCT under current World Health Organization (WHO) guidelines,⁶ HIV-exposed but uninfected infants and children are now the predominant pediatric population affected by HIV.

Infants and children perinatally infected with HIV experience higher rates of morbidity and mortality than uninfected infants and children.⁷ However, there is a growing body of literature reporting HIV-exposed uninfected (HEU) children also experience increased mortality⁸ and morbidity^{9–20} compared with HIV-unexposed uninfected (HUU) children. This increased mortality for HEU children has been noted in both the pre-PMTCT and post-PMTCT eras and across various study settings.^{21,22} While effective PMTCT programs have sharply reduced rates of HIV transmission, the effects of in utero exposure to an infected mother remain even if the child is not infected. Precise etiology of the disparity between exposed and unexposed infants is likely multifactorial in nature, encompassing immunological, biological, maternal, social, behavioral, and health systems factors.

Given the large numbers of children perinatally exposed to HIV each year, further analysis and examination of these trends in morbidity, in particular, is warranted. In a previous meta-analysis focused specifically on mortality among HEU compared with HUU children, we reported a 60% increase in risk of death.⁸ In this follow-on analysis, we focus on impacts on morbidity due to pneumonia and diarrhea in these 2 populations.

METHODS

Search Strategy and Selection Criteria

We searched the databases PubMed, Web of Science (including Medline), Excerpta Medica Abstract Journals (EMBASE), ProQuest Dissertation & Thesis Outline, International AIDS Society abstract archives, and AIDS Conference abstract archives for articles and abstracts published between January 1, 1993, and August 1, 2018. Our search key words can be found in Table 1, Supplemental Digital Content, <http://links.lww.com/QAI/B341>. We limited the search to human studies published in English. Two reviewers (M.K. and R.B.) screened all titles and abstracts to capture potentially relevant studies and one reviewer (A.T.B.) resolved any discrepancies between them. We reviewed the references in the included articles and added any studies that met our inclusion criterion. We included studies published during those years from any geographic location that compared pneumonia and/or diarrhea among HEU infants or children to HUU infants or children. Because morbidity can be a challenging definition, all studies that reported on any pneumonia and/or diarrhea outcome were included, regardless of follow-up time for each study. We used each study's definition of pneumonia and/or diarrhea (summarized in Table 1). Additional data were not obtained from study authors.

Data Extraction

The primary objective of this study was to compare pneumonia and diarrhea outcomes among HEU children to HUU children in any setting. For each study, when possible, we extracted year published, region, country, dates enrollment started and ended, length of follow-up, and total N in each cohort. For our outcomes (Table 1), we extracted data on the number of pneumonia and/or diarrhea events in the total population and/or simple proportions, ratio, and difference measures, in addition to corresponding 95% confidence intervals (CIs) from individual studies, if available.

Data Analysis

We conducted meta-analyses to estimate proportions of acute (defined as ≥ 3 loose stools in 24–48 hours) and chronic diarrhea (defined as loose stools lasting ≥ 14 days) and pneumonia (defined as chest in-drawing with or without fast breathing) comparing HEU and HUU children. We stratified by duration of follow-up time from birth (0) to 6, 0 to 12, 0 to >24 , and 0 to >24 months and stratified by year enrollment ended in each study: pre 2002 vs. 2002 or after and pre 2004 vs. 2004 or after, when single-dose nevirapine (2002)²¹ and combination therapy (2004)²² for PMTCT commenced in most public-sector clinics in low-income and middle-income countries. We also used metaregression to assess the effect of year study enrollment ended (1993–2018) on diarrhea and pneumonia by regressing the natural log of the ratio measures for our desired outcomes on the year study enrollment ended as a continuous variable. We examined heterogeneity between the studies using Cochran's Q and the I^2 statistic.²³ Random-effects models were used to estimate all infectious disease proportions and corresponding 95% CIs using standard methods because there was evidence of high heterogeneity between studies.²⁴ We performed an analysis of publication bias for diarrhea and pneumonia using a funnel plot and Egger's linear regression test.²⁴ We assessed the quality of each study using the Newcastle-Ottawa scale.²⁵

Those studies that scored above a 7 were defined as high quality, those with a score between 4 and 6 were considered moderate quality, while those <4 were considered low quality.

RESULTS

A total of 2842 potentially relevant citations were identified, and 2451 remained after de-duplication (Fig. 1). Of 2451 articles, 206 appeared relevant and merited full text review, of which 12 studies published between 1993 and 2018 reported on diarrhea and/or pneumonia and were included; all 12 were from sub-Saharan Africa (Table 1).^{9–20} The total population of HEU and HUU in our study was 17,955 subjects [n = 5074 (28.3%) HEU and n = 12,881 (71.7%) HUU]. Cohort size ranged from 17⁹ to 11,868¹⁹ HEU and HUU children combined.

All estimates are summary pooled random-effects estimates of diarrhea (acute or chronic) and pneumonia. Although imprecise, the summary measures of association suggest that HEU children have over a 20% increased risk in acute diarrhea over 5 years [risk ratio (RR): 1.20; 95% CI: 0.90 to 1.60] and close to a 10% increased risk of chronic diarrhea (RR: 1.09; 95% CI: 0.98 to 1.99). In regard to pneumonia, there was a 30% increased risk (RR: 1.30; 95% CI: 1.12 to 1.52) over 5 years of follow-up (Fig. 2) when comparing the 2 groups. When stratifying by time since birth, we found that HEU infants and children had close to a 50% increased risk of diarrhea at 6 months (RR: 1.48; 95% CI: 1.03 to 2.12) and close to 40% increased risk at >24 months (RR: 1.37; 95% CI: 0.75 to 2.51) (Fig. 3) vs. HUU infants and children. For pneumonia, we saw the same trend at 6 (RR: 1.71; 95% CI: 0.78 to 3.72) and >24 months of life (RR: 1.29; 95% CI: 0.99 to 1.69) (Fig. 4).

When comparing HEU children with HUU children after implementation of PMTCT globally (pre 2002 vs. 2002 and after), we saw little difference in the relative risk of diarrhea or pneumonia before and after 2002 (see Figure 1 and 2, Supplemental Digital Content, <http://links.lww.com/QAI/B341>). When shifting the cutoff to 2004, our results remained the same. Metaregression analyses indicated no evidence of any trend from 1993 to 2018 (year study enrollment ended) in diarrhea or pneumonia among the HEU children vs. HIV-unexposed children. We did find evidence of asymmetry using Egger's test for diarrhea suggesting some publication bias, while we found no evidence of asymmetry for pneumonia suggesting little to no publication bias (see Figure 3A and B, Supplemental Digital Content, <http://links.lww.com/QAI/B341>).

The overall quality of the evidence for the association between HIV exposure status and the outcomes of pneumonia, and diarrhea was moderate to high (see Table 2, Supplemental Digital Content, <http://links.lww.com/QAI/B341>). All studies received a score of 7 points or above on the 9-point Newcastle-Ottawa scale²⁵ for quality. Studies in our meta-analysis assessing the association between HIV exposure status, and diarrhea showed either no association or a slight increased risk when comparing HEU with HUU, while all studies included for the outcome of pneumonia showed an increased risk in pneumonia when comparing the 2 groups.

DISCUSSION

The overall benefits of PMTCT programs in low- and middle-income countries are undeniable: maternal ART in pregnancy has prevented millions of children from acquiring HIV-1 infection.⁵ Nevertheless, there is compelling evidence that uninfected children born to HIV-infected mothers, particularly in the low- and middle-income countries, can experience increased morbidity and mortality, predominantly from infectious diseases.^{8–20} In our meta-analysis of the literature, although imprecise, we found that HEU children had a 30% increase in the risk of pneumonia over 5 years and a 20% increased risk in acute diarrhea over 5 years compared with HUU children. Our results also suggest that HEU vs. HUU children have the highest risk of diarrhea and pneumonia within the first 6 months of life. There is also some suggestion that the risk of these infectious diseases seems to decrease as children aged beyond 24 months.

As we reported in our previous meta-analysis assessing mortality between HEU infants and children compared with their HIV-unexposed counterparts,⁸ we believe the precise reason for this difference in morbidity is likely multifactorial. Factors may include, but are not limited to (1) unrecognized or unreported co-infections in HEU children, (2) the impact of HIV on maternal health status during pregnancy, (3) poorer maternal health or maternal postnatal death impairing the quality of childcare, or (4) corresponding lower socioeconomic status and subsequent threat of food insecurity for children born into households with an HIV-infected mother.⁸ While unrecognized HIV transmission postnatally (either delayed diagnosis or through breastmilk transmission) may also be a contributing factor, the cohorts included in this meta-analysis repeatedly assessed infant/child HIV infection status, and it is unlikely that HIV-infected subjects were misclassified as exposed uninfected.^{9–20}

It is important to note that even when neonates escape HIV infection, HIV exposure in utero may present an altered environment for fetal growth and development. As such, the dysregulation of transplacental antibody transfer could be another contributing factor to our results. Transfer of maternal immunoglobulin G (IgG) is an efficient process in HIV-negative mothers who have healthy pregnancies. Infant cord blood concentrations of maternal IgG can well exceed maternal IgG serum concentrations by delivery in full-term pregnancies.²⁶ However, in HIV-positive mothers, several studies have demonstrated that HIV-exposed uninfected infants have lower levels of maternal antibodies than their unexposed counterparts,^{27–33} specifically to pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, group B *Streptococcus*, pertussis, poliomyelitis, and measles.³⁴ In our study, we saw an increased risk of pneumonia and diarrhea for HEU children persisting up to 2 years postnatally, suggesting that poor antibody transfer cannot be the sole explanation for the difference observed, as passive maternal antibody transfer has most likely waned by 12 months of life.

The potential impact of both HIV exposure and maternal ART on the immune system of an infant without HIV is unclear. Increased immune activation factors have been observed in the infants of HIV-infected mothers, associated with high maternal viral load.^{35–37} Previous research has documented HIV-exposed uninfected infants, exposed to various maternal ART regimens, as having altered cell-mediated immunity. One study reported lower CD4 T-

lymphocyte cell counts in HEU infants born to mothers who had a viral load >1000 copies/mL at the time of delivery compared with HEU infants whose mothers had a viral load <50 copies/mL at the time of delivery.³⁸ Prevacination vaccine-specific antibody levels are lower in HIV-exposed uninfected infants than HIV-unexposed uninfected infants, with some HIV-exposed uninfected infants mounting insufficient humoral immune response after vaccination with diphtheria toxoid, haemophilus influenza type B, pertussis, measles, hepatitis B, tetanus toxoid, and pneumococcal conjugate vaccines.³⁹ However, HIV-specific immune responses have not been thoroughly assessed in HEU infants born to mothers on ART with a suppressed HIV viral load.³⁸ Given the persistence of increased risk for pneumonia beyond 2 years of age, early immunological differences noted in HIV-exposed infants and children, whether due to high maternal viral loads or the presence of maternal ART, likely does not account for our observed difference in morbidity between the 2 groups.

Decreased adaptive immunity to standard childhood immunizations has also been found in HEU children up to 2 years of age,^{40,41} although the data on this is conflicted. Some studies report that HIV-exposed uninfected infants' humoral and cell-mediated responses to vaccines, including to the measles vaccine and bacille Calmette-Guerin, are similar to responses in unexposed infants.^{42–44} One study out of South Africa even demonstrated that HIV-exposed uninfected infants mounted higher increments of antibody responses to pertussis and pneumococcus vaccines.⁴⁴ The same research group also studied the impact of maternal HIV infection and demonstrated that HIV-exposed, uninfected infants have normal responses to bacille Calmette-Guerin vaccination administered at birth.⁴⁴ However, this likely does not account for differences in morbidity described in our study, as *H. influenzae* type B, and pneumococcal vaccines for pneumonia were not widely available in low-income countries before 2000 and 2008, respectively,^{45,46} and rotavirus for diarrhea before 2012.⁴⁷

Very few studies included in this analysis reported clearly on breastfeeding practices, maternal ART, or use of cotrimoxazole prophylaxis in children and infants, in addition to social or environmental conditions that might contribute to this difference in infectious disease outcomes. One possibility is that HIV-infected mothers may be sicker or more likely to be deceased (along with their male partner) than non-HIV-infected mothers and therefore may be less able to provide care. Poor socioeconomic status resulting in food insecurity could also be a factor. A review of the literature found data to support food insecurity as a critical barrier to adherence to ART and to other health care recommendations among HIV-infected adults, HIV-infected pregnant women and their HIV-exposed infants, and child and adolescent populations of people living with HIV and AIDS.⁴⁸ Such differences in maternal health status could also account for differences in breastfeeding practices between HIV-positive and HIV-negative mothers. It is well established that breastfeeding is protective against pneumonia and diarrhea for all infants^{49,50} and is the recommended feeding modality for all mothers, including those with HIV, in low- and middle-income countries, when feasible.⁵⁰

In high-income countries, both monotherapy⁵¹ and combination ART⁵² have been used since the mid-1990's in PMTCT efforts and to improve maternal health status, so women could live longer to care for their offspring.^{52,53} ART in the form of single-dose nevirapine

for PMTCT use was introduced in resource-limited settings in 2002²¹ and ART combination therapy in 2004.²² Our results show no difference in the risk of diarrhea or pneumonia before 2002 compared with during and after 2002 (or when we shifted the cutoff to 2004), in HEU vs. HUU children. While the World Health Organization recommended the use of cotrimoxazole prophylaxis for all HIV-exposed infants in 2000,⁵⁴ very few studies included in this analysis clearly reported on cotrimoxazole use, and subanalyses based on a cutoff date of 2000 (cotrimoxazole guidelines) were not possible with these data.

It is important to note that, although imprecise, there has been a substantial, overall decrease in incidence of pneumonia and diarrhea globally since the mid-1990's,⁵³ synchronous with improved treatment guidelines, including Integrated Management of Childhood Illness⁵⁵ and increased access to vaccines.⁵⁶ As such, one may expect to see an overall smaller effect size over calendar time, with the assumption that childhood pneumonia morbidity would similarly decline in both HEU and HUU populations over the same period. Alternatively, if overall risk in the population is declining, then the relative effect may be increasing because the baseline risk is decreasing, potentially explaining why we do not see a decline in effect sizes over time in our study.

Our results should be considered alongside their limitations. First, as with any meta-analysis, there is the possibility of incomplete retrieval or abstraction of data, due to either human error, or that the primary outcomes of the studies were not infectious disease morbidity. However, we used the most comprehensive publicly available literature in which most major and well-conducted studies should be reported. Second, we did not obtain raw data from study investigators for pooled estimation of infectious disease outcomes. While all studies included happened to be from sub-Saharan Africa, there are a small number of studies reporting on other clinical outcomes than pneumonia and diarrhea in higher income countries, such as neonatal sepsis, with higher incidence in HIV-exposed infants and children compared with unexposed infants.⁵⁷ Third, there was also substantial heterogeneity among the studies. With respect to the specific infectious disease morbidities, we did not have further specific data on etiology of illness (eg, pneumonia due to pneumocystis as opposed to *S. pneumoniae*). Despite this heterogeneity, we felt it was important to pool the existing data to estimate infectious disease probability as these data provide a more robust estimate than any single study alone. Fourth, as no studies included in our analysis controlled for nonbiological risk factors, we may have unmeasured confounding, potentially resulting in bias in our summary estimates. Fifth, time-varying rates of disease incidence were lacking in most of these studies. As discussed previously, whether in the presence of HIV exposure or not, infant mortality from these infectious diseases is greatest in the first month of life, and meta-analysis itself risks obscuring those events by averaging them out. Finally, given the smaller number of studies in the pre- and post-ART PMTCT eras, it is not possible for us to know how much of this effect on child morbidity is mediated by maternal ART (and, subsequently, improved maternal or paternal health status).

CONCLUSIONS

Our results suggest an increased risk of diarrhea and pneumonia for HIV-exposed, uninfected vs. HIV-unexposed, uninfected infants, and children. Our results may be

confounded by a number of other factors not reported in the main studies, such as maternal health and functional care-taking status, duration of maternal antiretroviral treatment, infant feeding modality and nutritional status. Although we acknowledge, and commend, the immense public health success of prevention of mother-to-child transmission, we now have an enlarging population of children that seem to be vulnerable to not only death, but increased morbidity. We need to turn our attention to understanding the underlying mechanism and designing effective public health solutions. Further longitudinal research is needed to elucidate possible underlying immunological and/or sociological mechanisms that explain these differences in morbidity and mortality between these 2 groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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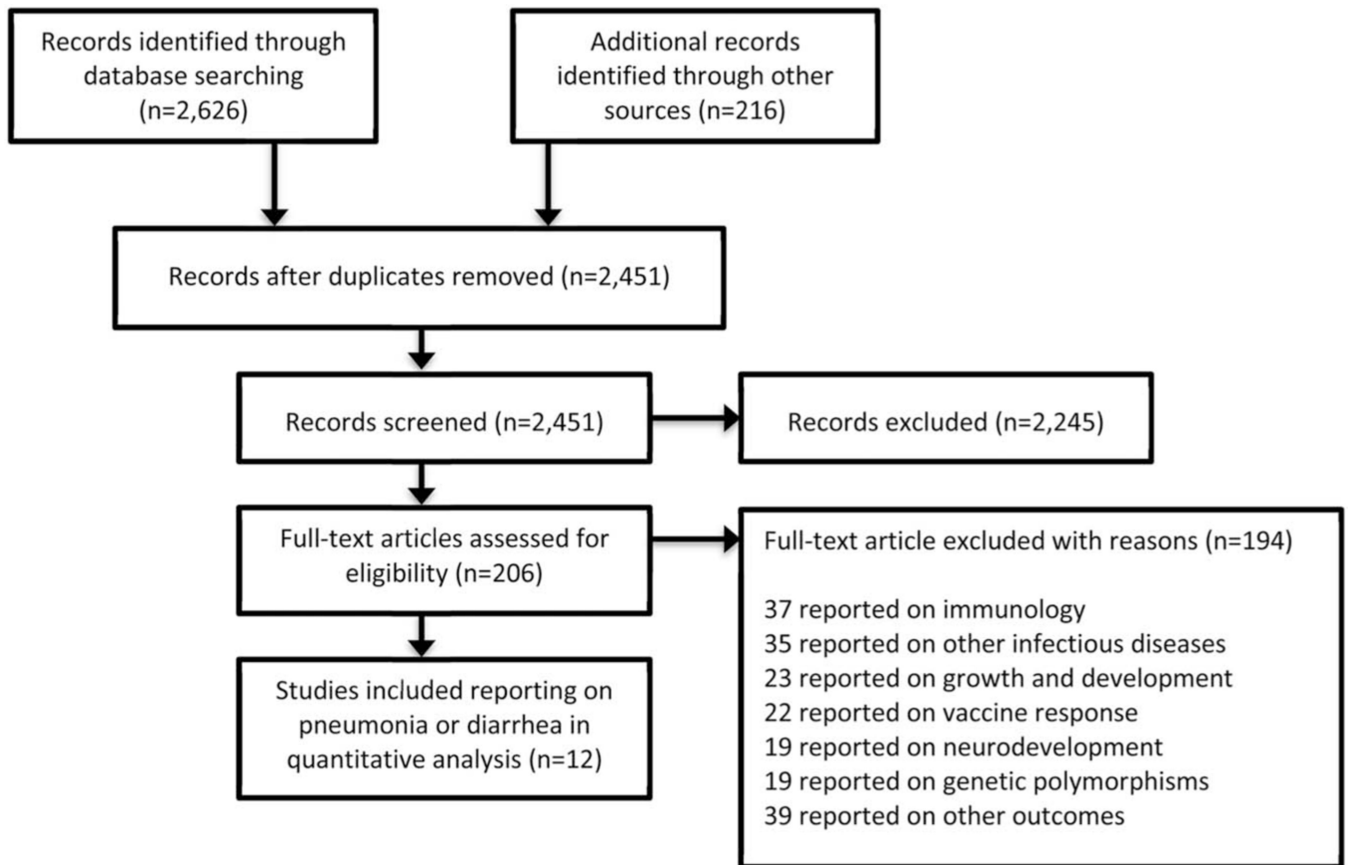


FIGURE 1.
Study selection process and reasons for exclusion of studies.

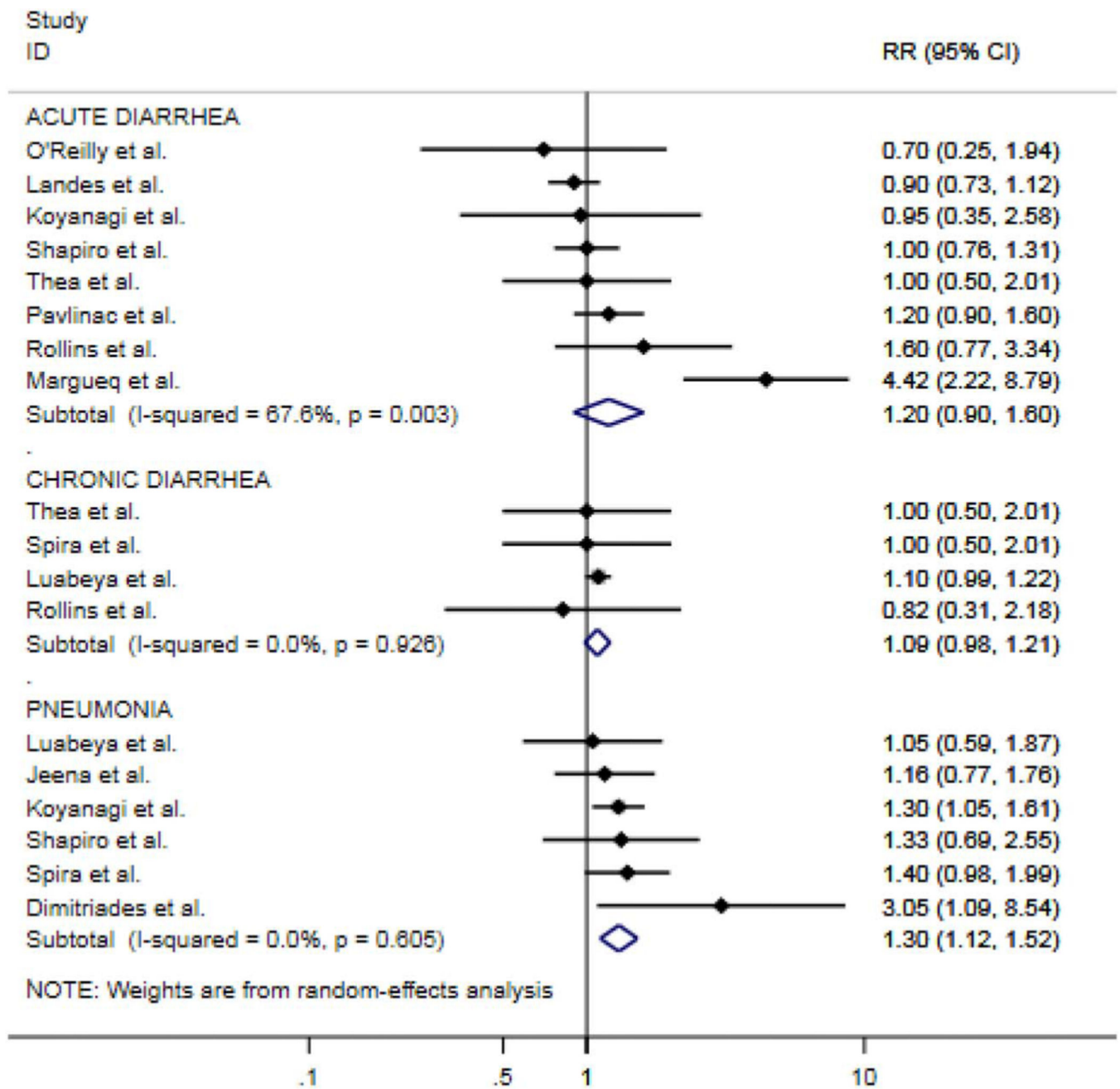


FIGURE 2. Forest plot of RRs for acute and chronic diarrhea and pneumonia comparing HEU with HUU children for all studies stratified by outcome (n = 12).

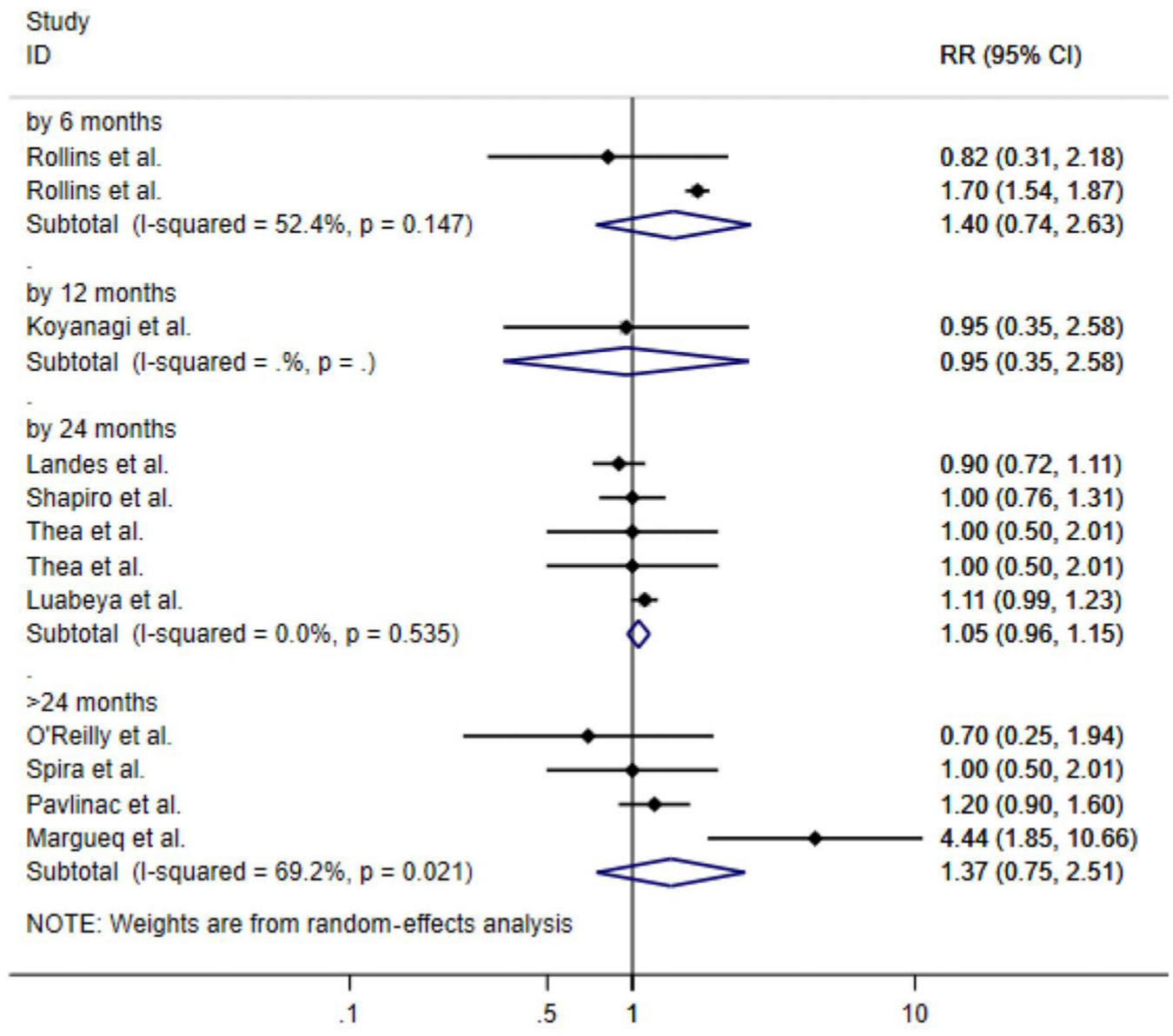


FIGURE 3. Forest plot of RRs for diarrhea (acute and chronic combined) comparing HEU children with HUU children for all studies stratified by follow-up time from birth (0) to 6, 0 to 12, 0 to 24, and 0 to >24 months.

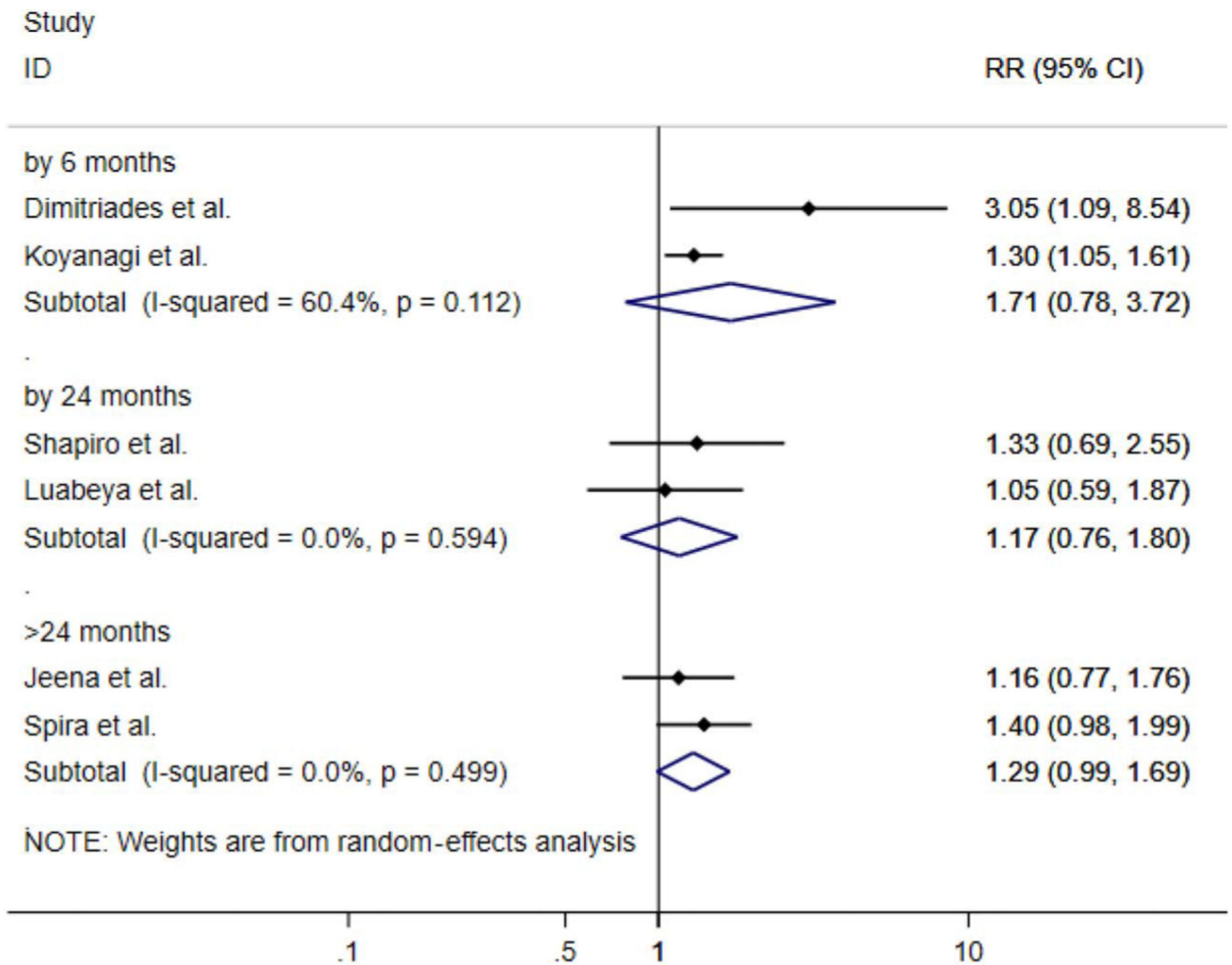


FIGURE 4. Forest plot of RRs for pneumonia comparing HEU children with HUU children for all studies stratified by follow-up time from birth (0) to 6, 0 to 24, and 0 to >24 months.

TABLE 1.

Characteristics of Included Studies and Overall Risk of Acute or Chronic Diarrhea and Pneumonia and Risk Ratios Comparing HEU and HUU for Each Study (n = 12)

Author	Year Published	Region	Country	Followup Period (mo)	Overall Loss to Follow-up (%)	Outcome Definition	HEU Total, N	HEU events, n	HUU Total, N	HUU events, n	Crude RR % (95% CI)	Study Quality
Acute diarrhea												
O'Reilly et al ¹⁰	2011	SSA	Kenya	0–60 mo	10.0	3 loose stools in 24–48 h	45	4	152	20	0.70 (0.25 to 1.94)	High
Landes et al ¹¹	2012	SSA	Malawi	0–20 mo	53.8	3 loose stools in 24–48 h	128	63	200	114	0.90 (0.73 to 1.12)	High
Koyanagi et al ¹²	2011	SSA	Zimbabwe	0–12 mo	0.4	3 loose stools in 24–48 h	2661	—	9207	—	0.95 (0.35 to 2.58)*	High
Shapiro et al ¹³	2007	SSA	Botswana	0–24 mo	1.8	3 loose stools in 24–48 h	534	171	137	46	1.00 (0.76 to 1.31)	High
Thea et al ¹⁵	1993	SSA	DRC	0–24 mo	20.0	3 loose stools in 24–48 h	139	—	191	—	1.00 (0.50 to 2.01)*	High
Pavlinac et al ¹⁸	2014	SSA	Kenya	6–60 mo	17.0	3 loose stools in 24–48 h	105	35	821	224	1.20 (0.90 to 1.60)	High
Rollins et al ¹⁹	2013	SSA	South Africa	0–6 mo	19.8	3 loose stools in 24–48 h	936	—	1155	—	1.60 (0.77 to 3.34)*	High
Marquez et al ²⁰	2014	SSA	Uganda	6–36 mo	13.8	3 loose stools in 24–48 h	200	25	389	11	4.42 (2.22 to 8.79)	High
Chronic diarrhea												
Spira et al ¹⁴	1999	SSA	Rwanda	0–60 mo	11.0	Chronic diarrhea (14 days)	138	—	209	—	1.00 (0.50 to 2.01)*	High
Thea et al ¹⁵	1993	SSA	DRC	0–24 mo	20.0	Chronic diarrhea (14 days)	139	—	191	—	1.00 (0.50 to 2.01)*	High
Luabeya et al ¹⁶	2007	SSA	South Africa	6–24 mo	26.3	Chronic diarrhea (14 days)	142	123	165	132	1.08 (0.99 to 1.22)	High
Rollins et al ¹⁸	2013	SSA	South Africa	0–6 mo	19.8	Chronic diarrhea (14 days)	936	—	1155	—	0.82 (0.31 to 2.18)*	High
Pneumonia												

Author	Year Published	Region	Country	Followup Period (mo)	Overall Loss to Follow-up (%)	Outcome Definition	HU Total, N	HEU events, n	HU Total, N	HUU events, n	Crude RR % (95% CI)	Study Quality
Luabeya et al ¹⁶	2007	SSA	South Africa	6–24 mo	26.3	Children who had chest in-drawing with or without fast breathing	142	19	165	21	1.05 (0.59 to 1.87)	High
Jeena et al ¹⁷	2007	SSA	South Africa	3–59 mo	13.9	Children who had chest in-drawing with or without fast breathing	40	16	244	84	1.16 (0.77 to 1.76)	High
Koyanagi et al ¹²	2011	SSA	Zimbabwe	0–6 mo	0.4	Children who had chest in-drawing with or without fast breathing	2661	—	9207	—	1.30 (1.05 to 1.61)*	High
Shapiro et al ¹³	2007	SSA	Botswana	0–24 mo	1.8	Children who had chest in-drawing with or without fast breathing	534	52	137	10	1.33 (0.69 to 2.55)	High
Spira et al ¹⁴	1999	SSA	Rwanda	0–60 mo	11.0	Children who had chest in-drawing with or without fast breathing	138	—	209	—	1.40 (0.98 to 1.99)*	High
Dimi triades et al ⁹	2014	SSA	South Africa	0–6 mo	NR	Children who had chest in-drawing with or without fast breathing, with or without isolation of multidrug-resistant bacteria	6	5	11	3	3.05 (1.09 to 8.54)	Moderate

Note that each study can contribute to all outcomes.

* Studies only reported ratio measures and not the number of morbidity events.