Effect of micronutrient supplementation on diarrhoeal disease among stunted children in rural South Africa

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Abstract

Background—The efficacy of zinc combined with vitamin A or multiple micronutrients in preventing diarrhoea is unclear in African countries with high prevalence of HIV-exposed children. Potential modifying factors such as stunting need addressing.

Objective—To determine whether adding zinc, or zinc plus multiple micronutrients, to vitamin A reduces diarrhoea incidence, and whether this differs between strata of stunted or HIV-infected children.

Methods—We analyzed data from a randomized, controlled double-blinded trial (ClinicalTrials.gov NCT00156832) of prophylactic micronutrient supplementation to children aged 6–24 months. Three cohorts of children: 32 HIV-infected children, 154 HIV-uninfected children born to HIV-infected mothers, and 187 uninfected children born to HIV-uninfected mothers, received vitamin A, vitamin A plus zinc, or multiple micronutrients that included vitamin

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A and zinc. The main outcome was incidence of diarrhoea. Poisson regression was used in intent-to-treat analyses. Stratified analyses followed testing for statistical interaction between intervention and stunting.

Results—We observed no significant differences in overall diarrhoea incidence among treatment arms. Stunting modified this effect with stunted HIV-uninfected children having significantly lower diarrhoea incidence if supplemented with zinc or multiple micronutrients compared to vitamin A alone (2.04 and 2.23 vs 3.92 episodes/year respectively, P=0.024). No meaningful sub-group analyses could be done in the cohort of HIV-infected children.

Conclusion—Compared with vitamin A alone, supplementation with zinc, and with zinc and multiple micronutrients, reduced diarrhoea morbidity in stunted rural South African children. Efficacy of zinc supplementation in HIV-infected children needs confirmation in studies that represent the spectrum of disease severity and age groups.

Keywords

Introduction

Despite being a middle-income country, South African children under the age of five years have a relatively high mortality rate and high prevalence of stunting (WHO 2005). HIV and diarrhoeal disease are leading causes of childhood morbidity and death (Garrib et al. 2006). While economic disparities need to be addressed for long-term solutions, shorter-term solutions to the high rates of childhood diarrhoea and mortality need investigation.

One possible means of reducing diarrhoeal incidence is prophylactic micronutrient supplementation. Vitamin A supplementation is currently recommended by the World Health Organization in developing countries to reduce the burden of childhood morbidities. While zinc is part of standard case management for treating diarrhoeal illness, (WHO 2005) the role of zinc and multiple micronutrients in preventing diarrhoeal illness is less certain.

Little is known about micronutrient supplementation as primary prophylaxis in regions where both stunting and HIV disease are highly prevalent. A recent South African trial was unable to detect morbidity reduction in children supplemented with multiple micronutrients for six months (Smuts et al. 2005). Despite concerns about zinc supplementation enhancing HIV virus replication (Bess et al. 1992) preliminary work supports its safety in HIV-infected children (Bobat et al. 2005).

It is therefore important to evaluate utility of zinc combined with vitamin A or multiple micronutrients as primary prophylaxis in regions of sub-Saharan Africa where there is a high prevalence of infants born to HIV-infected mothers. These children may be at high risk of micronutrient deficiencies related to maternal deficiencies, inadequate infant feeding and weaning practices, and a high infectious diseases burden that may limit utilization of some nutrients.

The per-protocol analysis of this study, published previously, showed no effect on prevalent days of diarrhoea (Luabeya et al. 2007). Prevalent days are a combined measure of frequency and duration. In the current analysis we focus on incidence density to better describe diarrhoea frequency. The purpose of this analysis was to assess whether, in a community with a high prevalence of HIV, stunting or HIV modified the effect of micronutrient supplementation on incidence of diarrhoea in children 6–24 months old.

Methods

Study design, site and population

We analyzed data from a randomized, controlled, double-blinded community-based trial of prophylactic zinc and multiple micronutrient supplements in the primary prevention of diarrhoea in three cohorts of children (Luabeya et al. 2007). The trial was performed in rural northern KwaZulu-Natal Province, South Africa during 2003 to 2006. Details of the methodology and characteristics of this community have been previously described (Luabeya et al. 2007; Van den Broeck et al. 2007).

The three micronutrient treatment arms were: daily vitamin A, daily vitamin A and zinc, and daily multiple micronutrients that included both vitamin A and zinc. The three cohorts of children were HIV-infected children, HIV-uninfected children born to HIV-infected mothers, and uninfected children born to HIV-uninfected mothers. Supplementation commenced at six months of age and continued for 18 months. Children were excluded from the study if they received micronutrients other than vitamin A in the past month, had weight below 60% of the median for age by National Center for Health Statistics standards (Hamill et al. 1979), if they had nutritional oedema or diarrhoea exceeding seven days' duration at time of study enrolment, or if participating in other intervention trials.

The study was approved by the Ethics Review Committee of University of KwaZulu-Natal and Institutional Review Board of Tufts-New England Medical Center. There was close consultation with the local Community Advisory Board of the Africa Centre for Health and Population Study, which sponsored the study. A Data Monitoring and Safety Board established by the National Institutes of Health monitored study conduct. Enrolment of children occurred only after mothers provided written informed consent for participation and HIV testing.

Micronutrient supplements

Each of the three supplements was in the form of tablets, which were crushed into food. Each contained 1250 IU of vitamin A. Two of the three supplements contained 10 mg of zinc as zinc gluconate. The multiple micronutrient supplement was similar in content to that used in other international trials. In addition to vitamin A and zinc, it contained 0.5 mg each of vitamins B1, B2 and B6; 0.9 µg vitamin B12; 35 mg vitamin C; 5 µg vitamin D; 6 mg vitamin E; 10 µg vitamin K; 0.6 mg copper; 150 µg folate; 50 µg iodine; 10 mg iron as ferrous fumerate; and 6 mg niacin. Tablets were manufactured by Hersil Ltd. (Lima, Peru) and packaged in blister packs of seven. All supplements had similar taste, form, colour and

texture. Children who were found to have haemoglobin below 10 g/dL during the study were given therapeutic doses of iron supplementation.

Study outcomes

The outcome of interest was diarrhoea incidence. Information on diarrhoea was collected during weekly home visits, as previously described (Luabeya et al. 2007). The incidence rate for each child was calculated as the number of episodes per child year of exposure since commencing study treatments. An episode of diarrhoea was defined as a period of diarrhoea separated by two or more diarrhoea-free days. Persistent diarrhoea was defined as episodes lasting 14 or more days. Severe diarrhoea included episodes with blood in the stool, presence of dehydration, episodes that were persistent or required hospitalization. Diarrhoea episodes and duration were computed from daily records for each individual.

Analysis

Poisson regression was used to calculate incidence rates and 95% confidence intervals. Individual level rates were used in the regression models with correction for over-dispersion through negative binomial regression. The chi-square statistic based on likelihood ratio tests was used to assess differences between treatment arms. Bonferroni adjustment was performed for multiple comparisons. We re-assessed models using robust methods to account for non-independence of events within subjects. We assessed potential confounding by age at enrolment, sex, proportion of observation time spent in the summer months (peak diarrhoea season in South Africa), use of therapeutic iron supplementation and year of enrolment. We examined the association of these variables with treatment and outcome respectively to decide whether to include them in multivariable models. We compared the cumulative incidence of diarrhoea episodes over time graphically using non-parametric Nelson-Aalen estimates.

Stunting was defined as a length-for-age below 2 Z-scores of the median value for age. Anthropometric Z-scores were computed using recently published WHO International Growth References (WHO 2007). We examined statistical interaction between treatment variable and baseline stunting, followed by subgroup analyses stratified by stunting. Comparisons of treatment effect were performed using intent-to-treat analyses with all cohorts combined, as well as separated by HIV status. One-way sensitivity analyses were done to explore whether the unmeasured outcomes in children who were lost to follow-up could have a major influence on our results or interpretations. This was especially important for persistent diarrhea, an outcome with very low incidence; where even a few unmeasured episodes could change the direction of our findings. We assigned zero (representing best case scenario), one, two or three (representing average scenario) episodes of diarrhoea per child for all subjects who had no follow-up observations documented or who were lost to the study before reaching median observation time. We also assigned an observation time equal to the median observation time for study subjects who left the study before reaching median observation time. Data were analysed using SPSS V13.0 (SPSS Inc., Chicago) and SAS V9.1 (SAS Institute, Inc., Cary, North Carolina) statistical software packages.

Statistical considerations

The sample size calculations for the primary analysis were based on detecting differences in prevalent days of diarrhoea. From the numbers eventually recruited, we estimated that we would have 80% power to detect a 40% reduction in diarrhoea incidence in HIV-infected children. For each cohort of HIV-uninfected children, we would have at least 90% power to detect a 33% reduction in diarrhoea incidence. These were based on previously published background estimates of diarrhoea incidence (Sazawal et al. 1997; Sempertegui et al. 1999; Gupta et al. 2003). Analyses are presented using 95% confidence intervals for main outcomes and Bonferroni adjusted P-values for multiple comparisons, with two-sided significance level of 0.05.

Results

The full CONSORT statement has been previously presented (Luabeya et al. 2007). A total of 373 infants were enrolled between June 2003 and October 2004. Follow-up was completed in January 2006. Of 373 enrolled infants, 32 were HIV-infected, 154 were HIV-uninfected infants born to HIV-infected mothers, and 187 were HIV-uninfected infants born to HIV-uninfected mothers. Thirty-six infants withdrew without taking any of the supplements and before any observations. Information on outcomes was available for 337 subjects, ten of whom never took any supplement. One child in the vitamin A arm and one in the vitamin A plus zinc arm received megadose vitamin A supplementation two months before randomization to study interventions. One child in the multiple micronutrient arm received vitamin A one month before randomization. One child each in the zinc plus vitamin A and multiple micronutrient arms received a multivitamin supplement more than one month prior to randomization.

The treatment arms were similar in the distribution of subjects in each of the three cohorts defined by HIV status above, and in other baseline characteristics (Table 1). Despite exclusion of children who were severely underweight for age, 69/373 (18%) were stunted at baseline. Of those with at least one observation 88/337 (26%) withdrew or did not complete the study. Treatment arms were similar in duration of follow-up (Table 1) and compliance with study interventions. Children who were HIV-infected, younger at enrolment, spent a larger proportion of observation time in summer months, or who were prescribed iron therapy, had a higher incidence of diarrhoea. The distribution of these characteristics however did not differ significantly across treatment arms (Table 1). Twelve children died of whom eight were HIV-infected. Six deaths occurred in the vitamin A plus zinc arm and three deaths in each of the other arms.

With all cohorts (as defined by HIV status) combined, there were no differences among treatment groups in the incidence of diarrhoea over the total study period. HIV-uninfected children born to HIV-infected or to uninfected mothers were similar in terms of diarrhoeal outcomes; these cohorts were therefore collapsed into a single group of HIV-uninfected children for all analyses. HIV-infected children had a higher incidence of diarrhoea than uninfected children (Table 2). Among HIV-infected children, zinc or multiple micronutrient supplemented groups had higher incidence of persistent and severe diarrhoea than those

supplemented with vitamin A alone (Table 2). Among HIV-uninfected children there were no detectable differences in persistent or severe diarrhoea across treatment arms (Table 2).

We found a significant interaction between treatment and stunting at baseline. In stratified analyses, HIV-uninfected children who were stunted at baseline had a lower incidence of diarrhoea if supplemented with vitamin A plus zinc (RR 0.52, 95% CI 0.45 to 0.60), or with multiple micronutrients (RR 0.57, 95% CI 0.49 to 0.67) than those receiving vitamin A alone. Graphical comparison of the cumulative mean function of diarrhoea frequency showed these protective effects in stunted children became apparent after six months of supplementation (Figure 1). These treatment effects were not apparent in HIV-infected children (Table 3). There were no detectable treatment effects in children who were not stunted at baseline, irrespective of HIV status (Table 3). In sensitivity analyses, we imputed the overall median follow-up time of 1.35 years for each subject lost to follow-up before reaching median follow-up time; and varied assumptions around number of diarrhoea episodes. The pattern of differences between treatment groups was consistent in those who were stunted at baseline (Table 4).

The incidence of persistent diarrhoea in children who were not stunted at baseline was significantly higher in those receiving vitamin A plus zinc or multiple micronutrients than those supplemented with vitamin A alone (Table 2). In sensitivity analyses these differences were unstable to varying assumptions (Table 5). Small sample size in HIV-infected children did not allow us to obtain estimates for incidence of persistent/severe diarrhoea stratified by presence of stunting.

Discussion

The important finding of this analysis was that zinc or multiple micronutrients were protective against diarrhoea in stunted children. This concurs with other trials where nutritional status modified response to zinc supplementation: in Bangladesh, morbidity benefits were restricted to infants who were zinc deficient (Osendarp et al. 2002); in Ethiopia diarrhoea and respiratory morbidity was reduced in a subgroup of stunted infants (Umeta et al. 2000). Similarly, nutritional status modified responses in vitamin A supplementation trials: well nourished children showed a paradoxical increase in lower respiratory infection in Ecuador (Sempertegui et al. 1999), and an increase in diarrhoea incidence in Tanzania. (Fawzi et al. 2000). In Mexican children receiving vitamin A and/or zinc supplements the intervention effect was pathogen-specific.(Long et al. 2007) In our study, stunted children receiving zinc or multiple micronutrients experienced similar diarrhoea incidence, suggesting that the effect of the multiple micronutrients is attributable to the zinc content rather than to the additional micronutrients.

While the micronutrient status of children in this trial was not measured, other studies found South African children to be zinc deficient, (Labadarios et al. 2005; Smuts et al. 2005) thus providing biologic plausibility for the findings of this study. Previous research at our study site found zinc deficiency in 25% of HIV-uninfected, and 45% of HIV-infected mothers, 24 weeks post-partum, while only 5.0% and 7.9% respectively had marginal retinol deficiency (Papathakis et al. 2007). The prevalence of maternal zinc deficiency approximates

prevalence of stunting in this trial. We therefore postulate that deficiency in these children might be attributable to maternal zinc deficiency (Dijkhuizen et al. 2001). While this study was not designed to detect synergy between supplements, it is probable that zinc deficiency limited response to vitamin A supplementation (Rahman et al. 2001). Despite the limitations posed by subgroup analyses, the results of this study are supported by biologic plausibility and consistency across trials (Umeta et al. 2000).

The varying efficacy across trials of zinc supplementation in children may be partially explained by the varying prevalence of stunting and wasting in study populations. Prevalence of stunting in children below the age of five years is a simple indicator of population zinc deficiency (Brown et al. 2004). Zinc trials in regions such as India and Bangladesh, with high prevalence of stunting and/or wasting, are more likely to show benefits to entire study populations (Bhutta et al. 2000; Rahman et al. 2001). Trials in regions with lower prevalence of stunting and wasting tend to report benefits restricted to malnourished subgroups. Children with severe wasting were not included in this trial because local standard-of-care required administration of multiple micronutrients including zinc. The effect size observed in this trial might have been larger if severely wasted children were also included.

The lower than targeted enrolment in the HIV-infected cohort limited our ability to make inferences on efficacy in that cohort. The higher incidence of persistent and severe diarrhoea in HIV-infected children receiving zinc or multiple micronutrients is of concern. This contrasts with an earlier trial that found zinc supplementation to be safe in HIV-infected children (Bobat et al. 2005). Only a small proportion of children in that trial, however, were below 18 months of age. Differences in findings may be related to differences in age profiles, HIV disease stage or interaction with specific enteric pathogens (Long et al. 2007). Neither this study, nor that by Bobat et al (Bobat et al. 2005) had a sufficiently varied age range or HIV disease stage to allow broad conclusions to be drawn about routine zinc supplementation in HIV-infected children.

Subject drop-out and missing data are challenges in a study with such a lengthy follow-up. While lack of differences in drop-out rates and similar durations of observation across treatment arms are reassuring, we performed sensitivity analyses to explore the stability of our estimates in sub-group analyses. The sensitivity analyses support our findings that adding zinc to vitamin A reduces diarrhoea incidence in stunted children. The lack of agreement on sensitivity analyses for the effect on persistent diarrhoea suggest that we need to interpret with caution the finding of greater incidence of persistent diarrhoea in non-stunted children given zinc or multiple micronutrients.

Among HIV-uninfected stunted children, the multiple micronutrient arm had similar diarrhoea incidence to the zinc arm despite inclusion of 10 mg iron in the former. Micronutrient trials have reported mixed results for the effect of including iron on incidence of diarrhoea (Baqui et al. 2003; Penny et al. 2004; Untoro et al. 2005). The apparent lack of adverse consequences in this trial may be due to the equal ratio of iron-to-zinc in the supplement used here compared to trials that used higher iron doses and ratios. A total dose of iron greater than 25 mg may interfere with zinc absorption or increase intestinal

permeability (Nchito et al. 2006). The finding that children in this trial who received therapeutic iron in addition to trial supplements experienced more diarrhoea than those who never received iron treatment further supports this.

Interpretation and recommendations

This analysis supports the use of stunting as an indicator for identifying children or populations who will benefit from zinc supplementation. This adds to existing guidelines for management of malnourished children that rely on measures of wasting to identify individual children for supplementation. This study further suggests that even in the absence of wasting, stunting is useful for identifying children who may benefit from zinc supplementation in addition to vitamin A. This is important because, the prevalence of stunting in many regions is higher than prevalence of wasting(WHO 2005), and remains unchanged despite declines in wasting (WHO 2007). Multiple micronutrient interventions that include zinc and iron do not appear to increase risk of diarrhoea, and this is important for concurrent iron prevention programs. Addition of therapeutic iron however, is associated with higher risk of diarrhoea. The safety of zinc supplementation in HIV-infected children needs confirmation in studies that represent the spectrum of disease stage and age groups, as well as the co-morbidities present in African settings.

Acknowledgements

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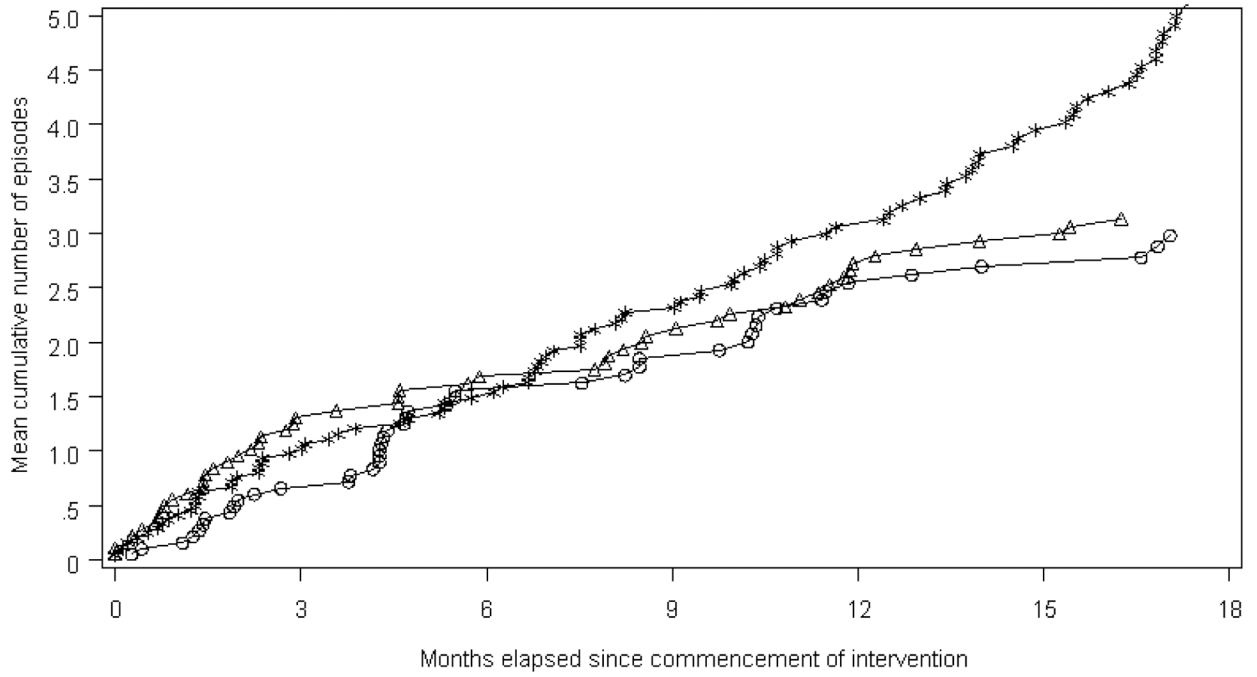
Figure 1.
Mean cumulative function for the number of diarrhoea episodes by treatment arm for all
cohorts combined
* vitamin A
   vitamin A plus zinc
○ multiple micronutrients

Table 1

Characteristics of 373 children by treatment arm

	Vitamin A (n=124)	Vitamin A + zinc (n=123)	Multiple micronutrients (n=126)	Subjects with at least one follow-up observation (n=337/373)	Subjects missing all follow-up observations because of withdrawal (n=36/373)
HIV status, n (% of total per treatment arm)					
HIV-infected child	9 (7.3)	11 (8.9)	12 (9.5)	28 (8.3)	4 (11.1)
HIV-uninfected child, HIV-infected mother	52 (41.9)	52 (42.3)	50 (39.7)	142 (42.1)	12 (33.3)
HIV-uninfected child, HIV-uninfected mother	63 (50.8)	60 (48.8)	64 (50.8)	167 (49.6)	20 (55.6)
Male	72 (58.1)	61 (49.6)	60 (47.6)	174 (51.6)	19 (52.8)
Age at commencing study treatments (months)	7.5 (1.4)	7.4 (1.1)	7.2 (1.3)	7.3 (1.3)	N/A
Length-for-age Z score[1]	−0.65 (1.11)	−0.64 (1.27)	−0.71 (1.19)	−0.67 (1.20)	−0.60 (1.32)
Weight-for-age Z score[1]	−0.05 (1.37)	0.006 (1.32)	0.05 (1.34)	0.002 (1.35)	0.08 (1.40)
Weight-for-length Z score[1]	0.51 (1.38)	0.58 (1.30)	0.63 (1.38)	0.67 (1.28)	0.63 (1.38)
Children with stunting at baseline	26 (21.0)	20 (16.3)	23 (18.3)	62 (18.4)	7 (19.4)
Months of observation, median (25th–75th centile)	16.6 (9.3–17.9)	16.5 (8.2–17.7)	15.7 (5.8–17.5)	16.6 (11.2–17.7)	N/A[§]
Percent time spent in peak diarrhoea season[2] median (25th–75th centile)	0.31 (0.24–0.39)	0.30 (0.23–0.40)	0.31 (0.23–0.39)	0.31 (0.24–0.40)	N/A[3]
Received iron therapy during study period	28 (22.8)	26 (21.1)	29 (23.2)	82 (24.4)	N/A[3]

Values are mean (standard deviation) or n (%) unless otherwise noted.

[1] As a Z-score of WHO International Growth References (Hoffman and Lee 2005; WHO 2007)

[2] Peak diarrhoea season was defined as January to April

[3] Not applicable to those with no follow-up

Table 2

Diarrhoea incidence in children with at least one follow-up visit[1]

Characteristic	HIV-infected children				HIV-uninfected children			
	Treatment Group			p^2	Treatment Group			p^2
	VA (n = 8)	VAZ (n = 9)	MM (n = 11)		VA (n = 105)	VAZ (n = 104)	MM (n = 98)	
Any diarrhoea	4.16 (2.40, 7.25)	5.15 (3.05, 8.71)	3.93 (2.36, 6.56)	0.76	2.92 (2.50, 3.42)	2.78 (2.37, 3.26)	2.64 (2.22, 3.14)	0.69
Persistent diarrhoea	0.05[a]	0.27[b] (0.10, 0.71)	0.39[b] (0.19, 0.78)	0.02	0.04 (0.02, 0.07)	0.07 (0.05, 0.11)	0.08 (0.05, 0.12)	0.30
Severe diarrhoea	0.05[a]	0.27[b] (0.11, 0.66)	0.39[b] (0.21, 0.74)	0.01	0.06 (0.03, 0.09)	0.10 (0.07, 0.15)	0.09 (0.06, 0.14)	0.27

[1] Incidence is per child observation year with 95% confidence intervals

[2] P values are for the overall group comparison based on the chi-square statistic

Values in the same row with different superscripts are significantly different from each other (*P < 0.05*)

Abbreviations: VA=vitamin A, VAZ=vitamin A plus zinc, MM=multiple micronutrients

Table 3

Incidence of diarrhoea in children stratified by presence of stunting at baseline[1]

		Stunted[2]				Not stunted[2]			
		Treatment group				Treatment group			
		VA	VAZ	MM	P	VA	VAZ	MM	P
Any diarrhoea	HIV-infected (n=28)	3.05 (0.77, 12.09)	4.47 (1.22, 16.38)	3.78 (1.33, 10.72)	0.92	4.69 (2.53, 8.71)	5.41 (3.02, 9.71)	4.02 (2.17, 7.46)	0.79
	HIV uninfected (n=309)	3.92 (3.02, 5.09)[b]	2.04 (1.37, 3.05)[a]	2.23 (1.48, 3.35)[a]	0.023	2.68 (2.23, 3.22)	2.92 (2.46, 3.48)	2.72 (2.25, 3.28)	0.77
	All cohorts (n=337)	3.83 (2.92, 5.03)	2.26 (1.53, 3.34)	2.49 (1.70, 3.65)	0.14[3]	2.78 (2.33, 3.33)	3.04 (2.57, 3.60)	2.78 (2.33, 3.33)	0.72
Persistent diarrhoea	HIV uninfected	0.08 (0.03, 0.22)	0.05 (0.01, 0.20)	0.11 (0.04, 0.31)	0.63	0.03 (0.02, 0.06)[a]	0.08 (0.05, 0.12)[b]	0.07 (0.05, 0.12)[b]	0.09[3]
	All cohorts	0.06 (0.02, 0.18)	0.19 (0.09, 0.41)	0.22 (0.09, 0.54)	0.29	0.03 (0.01, 0.06)[a]	0.06 (0.04, 0.10)[b]	0.09 (0.06, 0.14)[b]	0.05[3]
Severe diarrhoea	HIV uninfected	0.07 (0.02, 0.21)	0.24 (0.11, 0.54)	0.16 (0.05, 0.50)	0.51	0.05 (0.03, 0.09)	0.08 (0.06, 0.13)	0.09 (0.06, 0.14)	0.78
	All cohorts	0.06 (0.02, 0.20)	0.29 (0.15, 0.57)	0.22 (0.08, 0.58)	0.11	0.05 (0.03, 0.09)	0.08 (0.05, 0.13)	0.11 (0.08, 0.17)	0.24

[1] Incidence is per child observation year with 95% confidence intervals

[2] Stunting was defined as length-for-age Z-score below -2 based on WHO International Growth References

[3] Bonferroni adjustment used for three pair-wise comparisons

Values in the same row with different superscripts are significantly different from each other (*P < 0.05*)

Abbreviations: VA=vitamin A, VAZ=vitamin A plus zinc, MM=multiple micronutrients

Table 4

Incidence of all diarrhoea episodes: Sensitivity analysis for children who were stunted at baseline assuming an observation period of 1.35 years for each subject who did not stay in study for that long

	Treatment group		
Assumption	**Vitamin A**	**Vitamin A + zinc**	**Multiple micronutrients**
No diarrhoea episodes experienced during rest of follow-up	2.90 (2.14, 3.93)[a]	1.81 (1.17, 2.81)[ab]	1.66 (1.08, 2.54)[b]
One diarrhoea episode experienced during rest of follow-up	3.17 (2.49, 4.04)[a]	1.99 (1.40, 2.82)[b]	1.97 (1.42, 2.72)[b]
Three diarrhoea episodes experienced during rest of follow-up	3.72 (3.03, 4.55)[a]	2.35 (1.75, 3.14)[b]	2.58 (1.99, 3.34)[b]

Values in the same row with different superscripts are significantly different from each other ($P < 0.05$)

Table 5

Incidence of persistent diarrhoea: Sensitivity analysis for all children assuming an observation period of 1.35 years

	Treatment group		
Assumption	**Vitamin A**	**Vitamin A + zinc**	**Multiple micronutrients**
No persistent diarrhea episodes experienced during rest of follow-up	0.03 (0.02, 0.05)[a]	0.06 (0.04, 0.09)[b]	0.07 (0.05, 0.10)[b]
One persistent diarrhea episode experienced during rest of follow-up	0.35 (0.28, 0.44)[a]	0.39 (0.31, 0.48)[a]	0.48 (0.39, 0.)[b]
Two persistent diarrhea episodes experienced during rest of follow-up	0.68 (0.55, 0.84)	0.71 (0.57, 0.88)	0.88 (0.73, 1.06)

Values in the same row with different superscripts are significantly different from each other ($P < 0.05$)