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A Cluster-Randomized Controlled Trial Evaluating the Effects of Mass Azithromycin Treatment on Growth and Nutrition in Niger

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Abstract. Antimicrobials are used primarily to treat infectious disease, but they have other effects. Here, we assess anthropometry measurements in children 6–60 months in 24 communities randomized to one or two mass azithromycin distributions over a 1-year period in Niger. We compared the prevalence of wasting, low mid-upper arm circumference, stunting, and underweight in communities in the two treatment arms. We were unable to prove that there was a difference in the prevalence of wasting in the 12 communities that received one mass azithromycin distribution versus the 12 communities that received two mass azithromycin distributions (odds ratio = 0.75, 95% confidence interval = 0.46–1.23). Likewise, we were unable to detect a difference in the two treatment arms for low mid-upper arm circumference, stunting, and underweight. There may not be an association between antibiotic use and improved growth in humans, or this trial was not powerful enough to detect an association if it exists.

INTRODUCTION

Antimicrobials are used primarily to treat infectious diseases, although their effects are wide-ranging. A relationship between malnutrition and infection has long been recognized.¹ In young children in developing countries, a high proportion of deaths from diarrhea, pneumonia, and malaria are attributable to undernutrition.² In fact, malnutrition is thought to play a role in more than one-half of all childhood deaths worldwide caused by these conditions.³ Periodic treatment or prevention of these common childhood infections could theoretically improve growth and lower mortality in children. If so, this improvement would prove to be an important benefit of mass azithromycin treatments for trachoma.

Azithromycin has some activity against infections that lead to the three main causes of death in the developing world: pneumonia,⁴ diarrhea,^{5,6} and malaria.⁷ A case control⁸ and cluster-randomized clinical trial⁹ showed that mass azithromycin treatments were associated with reduced mortality in children. However, if mass azithromycin treatments affect mortality, the mechanism by which they do so is unknown. We aim to investigate explanatory factors for mortality reduction by measuring anthropometric indices. Mass azithromycin treatments for trachoma provide a unique opportunity to study the effect of these treatments on growth and nutrition. The current investigation is a substudy of the Partnership for the Rapid Elimination of Trachoma (PRET), a cluster-randomized clinical trial (clinicaltrials.gov trial NCT00792922) investigating different treatment strategies for trachoma, an ocular infection with *Chlamydia trachomatis*. The study methods for PRET have been previously described and are summarized briefly below.¹⁰ We hypothesize that children ages 6–60 months in 12 communities randomized to biannual mass azithromycin treatment will have better growth and nutrition compared with children

in 12 communities randomized to annual mass azithromycin in a substudy of a cluster-randomized clinical trial in Niger.

METHODS

Study setting and design. The study took place in the Matameye district of the Zinder region of Niger. The district is divided into grappes (government health units) that are referred to as communities in this manuscript. Communities were selected from six health centers (Center de Santé Intégrée [CSIs]). Inclusion criteria were total population between 250 and 600 persons and prevalence of active trachoma (trachomatous inflammation - follicular [TF] and/or trachomatous inflammation - intense [TI] using the World Health Organization [WHO] system)¹¹ $\geq 10\%$ in children ages 0–60 months. There were 235 eligible communities in the six CSIs, of which 72 (31%) communities satisfied the inclusion criteria for size; 48 communities were randomly selected for the PRET study.

Community and individual randomization. The current substudy took place in May of 2011 in 24 communities randomized to two different mass antibiotic treatment strategies: annual treatment of everyone or biannual treatment of children 0–12 years. Eligible individuals > 6 months were offered their assigned treatment of a single directly observed oral dose of azithromycin (height-based dosing equaling 20 mg/kg) in June or July of 2010. Children < 6 months were offered topical tetracycline to be used two times daily for 6 weeks per the WHO recommendation.¹² A second mass antibiotic treatment was offered to everyone in the biannually treated communities in December of 2010 or January of 2011. All outcome measurements were performed in a random sample of 50 children ages 6–60 months in each of the 24 communities based on the May of 2011 census. If the community did not contain 50 children, all children were included. Randomization of communities to the treatment arms and randomization of individuals within communities were done using RANDOM and SORT functions in Excel (version 2003) or the statistical package R (version 2.12; R Foundation for Statistical Computing, Vienna,

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Austria; www.r-project.org)¹³ by B.N. and T.C.P. as previously described.¹⁴ Study teams monitored antibiotic treatment coverage levels in all communities at both treatments. Analyses were performed at the community level on an intention-to-treat basis, and no adjustments were made for missing or absent individuals.

Data collection and intervention and nutritional assessment. Before the trial, field workers attended a 2-day workshop, where the WHO training course on standard growth measurement procedures¹⁵ was administered under the supervision of study coordinators and researchers from the F. I. Proctor Foundation, University of California at San Francisco. We mea-

sured recumbent length in children younger than 24 months or standing height in children older than 24 months when the child was able to stand to the nearest 0.1 cm (Shoreboard; Shorr Productions, LLC, Olney, MD). We subtracted 0.7 cm from the child’s length to derive an estimated height when a child older than 24 months was too sick or weak to stand in accordance with the WHO conversion formula.¹⁶ Children were weighed standing when they were able at all ages or in the arms of a parent or guardian when necessary without clothing or with only light clothing to the nearest 0.1 kg (Seca 874 flat floor scale; Seca GMBH & Co. Kg, Hamburg, Germany). Mid-upper arm

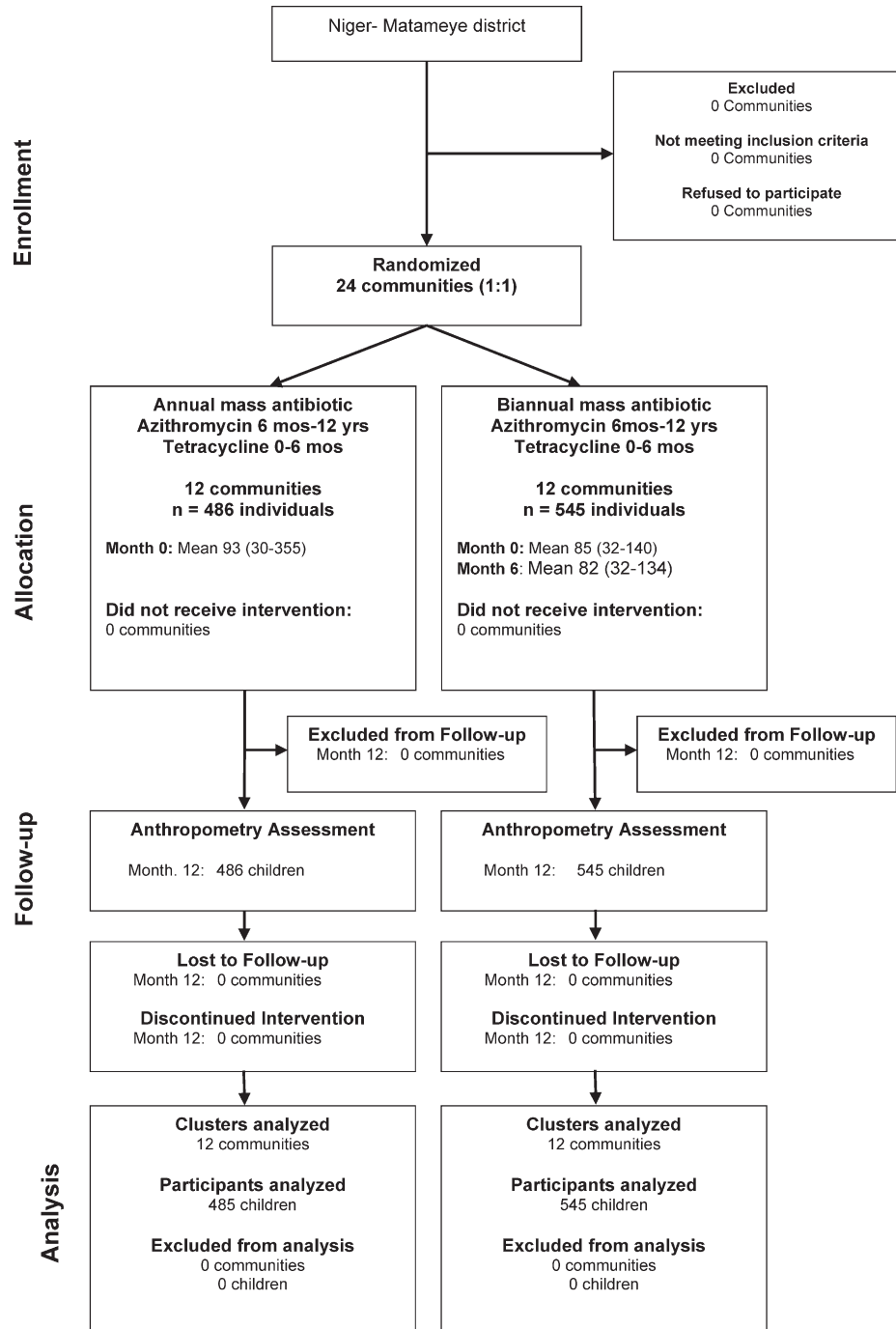


FIGURE 1. Participant flow.

circumference (MUAC) was measured to the nearest 0.1 cm using a non-stretchable tape developed by Johns Hopkins University.¹⁷ All anthropometry measurements were done in triplicate by field workers trained to assess growth in infants and children, and median values were used for analyses. Calibration of height/length and weight measurements was done after every 10th person. Field workers referred severely ill or malnourished children to local health posts for additional evaluation. Field workers were not informed of treatment allocation or antibiotic coverage at all visits. Community members were not masked to their treatment assignment.

Statistical analysis. We calculated age- and sex-adjusted community level nutritional *z* scores for wasting (weight-for-height *z* score [WHZ]), low MUAC (MUAC *z* score [MUACZ]), stunting (height-for-age *z* score [HAZ]), and underweight (weight-for-age *z* score [WAZ]) using the WHO Anthro software program¹⁶ based on the WHO child growth standards.¹⁸ Low anthropometry was defined as < -2.0 *z* scores of the median for the WHO reference population.¹⁹ We determined odds ratios for low anthropometry using mixed effects logistic regression with community as a random effect. We also assessed anthropometry measurements as continuous outcomes using mixed effects linear regression with community as a random effect. We calculated intraclass correlation coefficients (ICCs) using similar models. As an exploratory analysis, we compared community-level WHZ scores after restricting inclusion to participants who took their assigned treatment at baseline in all communities (mixed effects linear regression with community as a random effect). To determine if a dose-response relationship was present, we measured WHZ scores that restricted inclusion to participants who took their assigned treatment one time (baseline) or two times (baseline and 6 months) in the biannually treated communities. Finally, to confirm the presence of any dose response, we measured WHZ scores that restricted inclusion to participants who took their assigned treatment at baseline in the annually treated communities.

Assuming 50 children per village, $\alpha = 0.05$, ICC = 0.015 (from a clinical trial in Niger),²⁰ and 8% prevalence of wasting (from a clinical trial in Niger),²⁰ inclusion of 12 state teams per group would provide 80% power to detect an absolute difference of 6%. We used the statistical package R (version 2.12) or STATA 11 (Stata Corp., College Station, TX) for all analyses.¹³

Human participants and consent procedures. Ethical approval for this study was obtained from the Committee for Human Research of the University of California, San Francisco and le Comité Consultatif National d'Ethique du Ministère de la Santé Publique, Niger (Ethical Committee, Niger Ministry of Health). Oral consent was obtained from the community leaders, and written (thumbprint) consent was obtained from the child's parent or guardian at the time of examination. The study was carried out in accordance with the Declaration of Helsinki.

RESULTS

A total of 48 communities were enrolled in PRET, with 12 communities randomized to annual treatment and 12 communities randomized to biannual treatment according to the study design (Figure 1). All communities received mass treat-

ment in June and July of 2010, and the biannually treated communities received a second treatment in December of 2010 and January of 2011. There were 1,030 individuals (6–60 months) in the 24 communities in this anthropometry study (486 individuals in annually treated communities and 545 individuals in biannually treated communities). The mean antibiotic coverage of children ages 6–60 months was 80.4% (95% confidence interval [CI] = 76.8–84.1) for the single treatment of the annually treated communities and 74.4% (95% CI = 69.4–79.3) and 78.7% (95% CI = 74.6–82.7) for the two treatments in the biannually treated communities. Anthropometry measurements were performed in May of 2011, 10 or 11 months after treatment in the annual arm and 6 months after treatment in the biannual arm as per study design. Baseline characteristics, including average number of children per community, age of children, fraction female, and clinical trachoma prevalence, were similar in the communities randomized to the two treatment arms (Table 1). All communities received their scheduled treatments, and no community was lost to follow-up over the length of the study. There were no serious adverse events attributed to the study medicine reported through a passive surveillance system throughout the entire length of the study.

The odds of wasting were 25% less (odds ratio [OR] = 0.75, 95% CI = 54% less to 23% more), low MUAC was 7% less (OR = 0.93, 95% CI = 41% less to 46% more), stunting was 11% less (OR = 0.89, 95% CI = 35% less to 22% more), and underweight was 19% less (OR = 0.81, 95% CI = 43% less to 16% more) in the biannually treated communities than the annually treated communities (mixed effects logistic regression with community as a random effect). The mean prevalence of severe wasting (WHZ < -3.0) was not different in annually and biannually treated communities (OR = 1.08, 95% CI = 47% less to 222% more). The ICC was 0.019 (95% CI = 0.000–0.043) for height and 0.022 (95% CI = 0.000–0.050) for weight. In a linear model (mixed effects linear regression with community as a random effect), we were unable to detect a difference in anthropometry between the biannually treated communities and the annually treated communities (Tables 2 and 3).

With the analysis restricting enrollment to individuals who participated in the program and received their assigned antibiotic treatment at baseline, there was no significant change in the results for the association of antibiotic treatment and anthropometry in the logistic regression models for wasting, low MUAC, stunting, and underweight (data not shown). However, WHZ was 50% higher in the biannually treated

TABLE 1

Baseline characteristics of 24 communities randomized (1:1) to annual or biannual mass azithromycin treatment in a cluster-randomized clinical trial for trachoma in Niger

	Annual treatment (12 communities)	Biannual treatment (12 communities)
Children per community < 60 months	124 (42–207)	118 (88–147)
Age of children (months)	30.8 (29.8–31.9)	31.9 (30.7–33.0)
Proportion female	51.3% (48.2–54.4)	50.1% (47.1–53.1)
Prevalence trachoma TF*	26.5% (14.9–38.0)	24.1% (15.9–32.3)
Prevalence trachoma TI*	8.6% (4.4–12.8)	9.4% (4.9–14.0)

All values are community-level means in children < 60 months with 95% CI values.
*Using the WHO simplified grading system.¹¹

TABLE 2

Nutritional assessment of children ages 6–60 months in 24 communities randomized (1:1) to annual or biannual mass azithromycin treatment in a cluster-randomized clinical trial

Measurement	Annual treatment (12 communities)		Biannual treatment (12 communities)		OR (95% CI)	P value
	Percent	Number/total	Percent	Number/total		
Wasting	14.8	72/486	11.6	63/545	0.75 (0.46–1.23)	0.26
Low MUAC	20.2	98/486	18.5	101/545	0.93 (0.59–1.46)	0.74
Stunting	76.5	371/485	74.5	406/545	0.89 (0.65–1.22)	0.48
Underweight	64.1	311/485	59.5	324/545	0.81 (0.57–1.16)	0.26

ORs from mixed effects logistic regression use community as a random effect. All measurements are based on *z* score < -2.0. Numbers may be different because of some loss during field examination.

communities than the annually treated communities in this restricted analysis (mixed effects linear regression, 0.49, 95% CI = 0.29–0.70, $P < 0001$). In the biannually treated communities, individuals who participated in the program and received their assigned treatment at baseline had 35% higher WHZ (0.35, 95% CI = -0.008 to 0.72, $P = 0.056$) than those individuals who did not receive baseline treatment. Note that those individuals who missed their baseline treatment but received treatment at 6 months had a similar increase in their WHZ score (0.34, 95% CI = -0.20 to 0.71), consistent with a dose response for each antibiotic treatment. In these same communities, individuals who received their assigned treatment two times (at baseline and 6 months) had WHZ scores 65% higher (0.65, 95% CI = 0.37–0.93, $P < 0001$) than those individuals who received no treatment.

DISCUSSION

This cluster-randomized clinical trial in Niger of children ages 6–60 months shows that growth and nutrition are not different in communities randomized to a single mass azithromycin treatment versus communities randomized to two mass azithromycin treatments. We were unable to detect a difference in height, weight, and MUAC in the communities that received a single additional mass treatment.

With the analysis restricting inclusion to participants who received their prescribed antibiotics at baseline, we were unable to show a difference in WHZ scores between communities randomized to annual treatment and communities randomized to biannual treatment. Note that this restriction is a deviation from our primary pre-specified intention-to-treat analysis, where participants were not withdrawn after randomization for any reason. We are aware that withdrawing individuals from the study, even because of non-adherence, may offer bias of unknown magnitude and direction.²¹ Nevertheless, these restricted analyses can present an estimate of biological efficacy that intention-to-treat analyses may be unable to provide.²² For example, we detected a dose response

in those individuals who received their assigned treatment, and each additional treatment (from zero treatments to one treatment and from one treatment to two treatments) resulted in a WHZ score that was approximately 30% higher.

Although we did not detect a difference between annual and biannual mass antibiotic treatments on anthropometry, this finding may be because of the following reasons. First, a single extra mass azithromycin treatment over the course of 1 year may not be sufficient to have an effect on growth. Second, this study was a cross-sectional study and did not follow communities longitudinally; a longitudinal study might be better able to detect a smaller effect size. Third, there is a seasonal component to wasting in Niger, with high prevalence from December to February (after the rainy season) and lower prevalence in October (in the dry season when our study took place).²⁰ Performing a study when wasting is at its lowest might make it more difficult to detect an effect of mass antibiotic treatment.

The outcome measures were performed 1 year after treatment in the annually treated communities and 6 months after treatment in the biannually treated communities by study design. In future studies, we plan to perform outcome measurements at the same time after treatment in compared communities to help with interpretation.

In conventional livestock production, antibiotics have been used to enhance weight gain and promote growth since the early 1950s.²³ The use of antibiotics in food-producing animal agriculture results in healthier, more productive animals, lower disease incidence, and reduced morbidity and mortality, although this practice is controversial.²⁴ The biological basis for the growth-promoting effects of oral antibiotics could be a reduction in intestinal microflora, which compete for nutrients,²⁵ or treatment of subclinical infection.^{26,27} The Animal Health Institute (AHI) estimates that between 9% and 17% of all antibiotics sold in the United States for animals are for growth promotion or improved feed efficiency.²³ Antibiotics are not currently prescribed for growth promotion in humans, although treatment of children with deworming drugs has been shown to increase weight in some studies.²⁸ The mechanism

TABLE 3

Nutritional *z* scores in children ages 6–60 months in 24 communities randomized (1:1) to annual or biannual mass azithromycin treatment in a cluster-randomized clinical trial

Metric	Annual treatment (12 communities)		Biannual treatment (12 communities)		Coefficient (95% CI)*	P value
	N	Mean	N	Mean		
WHZ	481	-0.89 ± 1.30	538	-0.78 ± 1.08	0.09 (-0.16 to 0.34)	0.48
MUACZ	483	-1.25 ± 1.01	541	-1.20 ± 0.93	0.03 (-0.18 to 0.23)	0.81
HAZ	482	-3.13 ± 2.24	541	-3.07 ± 1.71	0.07 (-0.31 to 0.45)	0.71
WAZ	483	-2.44 ± 1.45	541	-2.23 ± 1.24	0.12 (-0.15 to 0.39)	0.38

Numbers may be different because of some loss during field examination, and *z* scores could not be calculated for children age 5 years at the time of anthropometry.

*Mixed effects linear regression was used with community as a random effect; coefficient reflects the change in *z* score in the biannually treated arm relative to the annually treated arm.

for the observed reduction in childhood mortality associated with mass azithromycin treatments is unknown, and it may be, in part, because of improved growth and nutrition.

Antibiotics do not provide a benefit for the treatment of undernutrition based on our study. Mass azithromycin treatments have proven to be very effective in programs for trachoma control, and the treatments are well-tolerated.²⁹ Since 1999, over 225 million treatments of azithromycin have been donated through the International Trachoma Initiative for distribution by local partners in 19 countries.³⁰ Investigation of positive and negative secondary effects associated with these treatments should be part of any mass treatment trial or program, particularly a study of emerging antibiotic resistance. Although there is a large increase in the prevalence of resistance in nasopharyngeal pneumococcus after mass antibiotic use,³¹ this resistance drops quickly when mass distributions are discontinued.³² Nevertheless, a strategy that provides antibiotics to large numbers of children to prevent non-specific infectious diseases to improve growth parameters is currently not advised based on our study.

In summary, we were unable to detect differences in anthropometry measurements in communities randomized to receive an extra mass azithromycin distribution; there were fewer cases of stunting and wasting with the extra treatment, but the result was not significant. There may not be an association between antibiotics and enhanced growth, or this trial may not have been powerful enough to detect an association. Larger studies, longer studies, or longitudinal measurements of growth may be able to find a beneficial effect of antibiotics on growth if it exists.

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