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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 ≥ 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, Austria).
Austria; www.r-project.org) by B.N. and T.C.P. as previously described. 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 procedures was administered under the supervision of study coordinators and researchers from the F. I. Proctor Foundation, University of California at San Francisco. We measured 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. 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 circumference was measured at mid-forearm with a non-stretchable caliper (Seca no. 202; Seca GMBH & Co. Kg, Hamburg, Germany). The percentage of underweight children was calculated as the number of children who had a weight-for-age z-score (WAZ) below −2 standard deviations (SD) compared with the WHO growth standards.

NUTRITION IN A MASS ANTIBIOTIC TREATMENT TRIAL

FIGURE 1. Participant flow.
circumference (MUAC) was measured to the nearest 0.1 cm using a non-stretchable tape developed by Johns Hopkins University. All anthropometry measurements were done in tripli-
cate by field workers trained to assess growth in infants and
toddlers, and median values were used for analyses. Calibration
of height/length and weight measurements was done after every
tenth person. Field workers referred severely ill or malnourished
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 program based on the WHO child growth
standards. Low anthropometry was defined as < −2.0 z
scores of the median for the WHO reference population. 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, α = 0.05, ICC = 0.015
(from a clinical trial in Niger), and 8% prevalence of
wasting (from a clinical trial in Niger), 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.

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 Sante 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
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 treat-
ments, 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 pas-
sive 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 regres-
sion with community as a random effect). The mean preva-
ence 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 anti-
biotic 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>
<thead>
<tr>
<th>Table 1</th>
</tr>
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<tbody>
<tr>
<td>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</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Children per community</td>
</tr>
<tr>
<td>&lt; 60 months</td>
</tr>
<tr>
<td>Age of children (months)</td>
</tr>
<tr>
<td>Proportion female</td>
</tr>
<tr>
<td>Prevalence trachoma TF*</td>
</tr>
<tr>
<td>Prevalence trachoma TI*</td>
</tr>
<tr>
<td>All values are community-level means in children &lt; 60 months with 95% CI values.</td>
</tr>
<tr>
<td>*Using the WHO simplified grading system.</td>
</tr>
</tbody>
</table>
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

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

*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.

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. Nevertheless, these restricted analyses can present an estimate of biological efficacy that intention-to-treat analyses may be unable to provide. 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). 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. 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. The biological basis for the growth-promoting effects of oral antibiotics could be a reduction in intestinal microflora, which compete for nutrients or treatment of subclinical infection. 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. 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. The mechanism...
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. Since 1999, over 225 million treatments of azithromycin have been donated through the International Trachoma Initiative for 1999, over 225 million treatments of azithromycin have been donated through the International Trachoma Initiative for

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