Title

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Can We Stop Mass Drug Administration for Trachoma Prior to 3 Annual Rounds in Hypoendemic Communities? Results from PRET Ziada Trial in Tanzania

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Abstract

Background—The World Health Organization recommends at least 3 annual mass drug administration (MDA)rounds of Azithromycin at 80% coverage to eliminate trachoma in communities where prevalence is greater than 10% in children aged 1 to 9 years. However, stopping MDA prior to 3 rounds, if monitoring indicates absence of infection with *C. trachomatis*, may be more cost effective in low prevalence settings.

Trial design—1:1 community randomized, double blinded trial

Trial Methods—16 communities with estimated trachoma prevalence between 10–20% were randomized into one of two treatment groups: Usual care of 3 rounds of MDA; Cessation Rule group where if the estimated prevalence of infection fell below 5% after one or two rounds of MDA, that community would cease to receive any further MDA. The primary outcome was the prevalence of *C. Trachomatis infection* in children ages under five years at 36 months.

Results—There was no significant difference in baseline characteristics or prevalence of infection or trachoma between the two randomization arms. None of the communities assigned to the cessation arm ever met criteria to stop MDA, so all 16 communities received 2 rounds of MDA and were scheduled to go on for a third round. For this reason, the trial was stopped after the 18 month survey. At 18 months there was no difference in infection prevalence (2.9% versus 4.7%, p=0.25) or trachoma prevalence (6.5% versus 9.4%, p=0.14) between the usual care group and cessation group respectively.

Conclusion—In this trial, communities with low (10–20%) initial prevalence of trachoma could not stop MDA before 3 annual rounds with 80% coverage.

Keywords

trachoma; ocular *Chlamydia trachomatis*; azithromycin; mass treatment; antibiotic coverage; clinical trial; PRET

Introduction

Trachoma is the leading cause of infectious blindness in the world.[1] It is the result of repeated infection with *Chlamydia Trachomatis* (CT) which result in inflammation, scarring of the conjunctiva, entropion and trichiasis, with the blinding sequelae of corneal opacification and visual impairment.[2] Trachoma disproportionately affects the poorest parts of the world and contributes to an ongoing cycle of disability and economic deprivation.

The World Health Organization (WHO) has recommended a 4 pronged approach to trachoma elimination- SAFE: Surgery to repair inturned eyelashes, mass administration of Antibiotics (MDA) to reduce the pool of CT, Face washing to reduce transmission from mucosal secretions and Environmental improvements to interrupt transmission and prevent re-emergence of infection. The Antibiotics portion of these guidelines is an area of ongoing research. In communities where clinical trachoma (follicular trachoma or TF) prevalence is greater than 10% in children aged 1–9 years, the WHO recommends annual community wide mass drug administrations (MDA) for at least three years with coverage of at least 80% of the population.[3] The goal is to achieve a prevalence of trachoma less than 5% in children ages 1 to 9 years. These recommendations were based on expert opinion as there was little clinical data available when the recommendation was made.[4]

There are several issues with these recommendations. The first is how many rounds of annual MDA are needed to achieve the goal. Studies of communities in Tanzania with high prevalence of trachoma prior to the start of a program suggest that multiple rounds, more than seven years, of mass annual treatment may be necessary.[5,6] However, in one hypoendemic (10–20% prevalence) Tanzanian community in a district with very little trachoma, a single round of high antibiotic coverage (>95% coverage) treatment was enough to virtually eliminate infection.[7] Finally, in low prevalence Gambian communities trachoma elimination was feasible with one round of treatment.[8,9]

Such data suggest that in low prevalence communities (e.g., The Gambia) and with delivery of MDA at high coverage, three annual rounds of MDA may be unnecessary. Moreover, relying on clinical signs of trachoma for cessation of treatment may result in unnecessary treatment of communities where infection is virtually eliminated and only residual signs are present. Yet in some communities, even low rates of active trachoma are associated with presence of *Chlamydia Trachomatis* infection.[10] Therefore, using a test for infection might have merit in deciding if MDA can be stopped. But these data also suggest that the expectation that one round of MDA may eliminate trachoma in all low prevalence settings might be unrealistic. The results from hypoendemic Gambian communities[8] that are at the tail end of elimination in that district may not be the same as low prevalence communities that are at the vanguard of elimination efforts in high prevalence districts.

We hypothesized that, in communities where the starting prevalence of trachoma was hypoendemic (between 10%–20%), that less than three rounds of MDA would be needed to achieve infection less than 5% in children aged less than five years. Furthermore, where communities achieved an estimated prevalence of infection less than 5% (regardless of status of clinical signs), we hypothesized that the community could cease mass treatment without re-emergence of infection. To test this hypothesis, we conducted a community-randomized trial in Kongwa Tanzania, where communities were randomized in a 1:1 design to two different annual MDA strategies: yearly mass treatment for 3 years (usual care) versus yearly mass treatment each year if warranted by *C. Trachomatis* infection prevalence above 5%; otherwise, the MDA would cease for communities in this arm and the community would be monitored for re-emergent infection (cessation rule).

Methods

Overview

The PRET-Ziada trial is a community randomized, double masked, clinical trial nested within the larger Partnership for Rapid Elimination of Trachoma (PRET) trial whose methods have been previously described[11]. Hypoendemic communities in the Kongwa district, Dodoma Region were selected for the study based on preliminary surveys estimating trachoma to be between 10–20% in children 0–5 yrs.

The communities were randomized into two different treatment arms based on treatment frequency as follows:

Usual Care Group: annual community-wide MDAs for 3 years Cessation Group: annual community-wide MDAs for 3 years with the cessation rule that MDA is discontinued if infection rates fall to less than 5% *Communities*

Communities were eligible for the study if they met the following criteria (See Figure 1):

1. Estimated clinical trachoma prevalence between 10–20% in children 0–5yrs based on preliminary surveys
2. Had not been treated in the previous 3 years
3. Were smaller than 5,000 persons
4. Had leadership approval for participation

Prior to participation, community leaders provided consent to overall community involvement in the study. Individual consent was obtained before surveys and administration of annual antibiotic doses. To participate in the study as a sentinel child, the following criteria had to be met:

1. Be aged 5 years or less at the time of census
2. Reside in an eligible community
3. Have no ocular condition that prevents trachoma grading or ocular specimen collection
4. Have an identifiable guardian who can provide consent to participate

Intervention

The intervention was the planned cessation of MDA after 1 or 2 rounds of MDA if infection declined to less than 5% in the community. The working definition of less than 5% was conservative, based on the sample of 100 sentinel children. If zero children had infection in either the 6 month (post one round of MDA) or 18 months survey (post second round of MDA) then the upper bound of the confidence interval on prevalence of infection was less than 5%. We could be relatively certain that the estimate of infection was less than 5%, and stop MDA in those communities randomized to the cessation rule.

Azithromycin was offered to all residents of the community at 20mg/kg up to 1 gram in a single dose. Treatment was directly observed. Children under 6 months of age were offered topical tetracycline, twice per day for 4 to 6 weeks, and treatment was not directly observed. For each MDA, the antibiotics were distributed by two to six trained Community Treatment Assistants in each community over a period of several days. On the first day antibiotics are distributed from a centralized location, followed by household visits on the subsequent day. If antibiotic coverage is below 80% in children under 10 years after 2–3 days, then drug

distribution is prolonged until the 80% coverage mark is reached or all children are accounted for and reasons for non-treatment have been recorded.

The latest census list was used to monitor coverage. Treatment was verified by having a research supervisor re-visit a sample of 5 houses per each community treatment assistant and obtain verbal confirmation of treatment. Community Treatment Assistants received payment of 1,000 TSH per ($0.80) day providing treatment verification showed 80% agreement.

Outcome Measures

The outcome measures were the prevalence of trachoma and infection with C. trachomatis in the communities at 36 months. However, there were no communities in the cessation rule arm that met the cessation criteria at either the 6 months or 18 months survey points, so all communities in both arms proceeded to three rounds of MDA. The Data and Safety Monitoring Committee stopped the trial after viewing the 18 month data on the basis of futility, that all communities in the trial would receive 3 annual MDAs.

Randomization Scheme

The 16 eligible villages were randomized using a constrained randomization scheme to 1:1 to each arm of the trial. The likelihood of unbalanced randomization was reduced by balancing each arm on baseline trachoma prevalence as a co-variate.[12] In each community, 100 children were randomly selected for the surveys, based on the census list and using a simple random number assignment in Access (Microsoft, Redmond, WA).

Sample Size Determination

The null hypothesis for this trial was that the cessation rule arm would be inferior to the usual care arm. We assumed a non-inferiority analysis for the comparison and, the number of communities needed in each group was calculated by solving for n using the following sample size formula for a two sample t-test[13]:

$$\Psi_{2n-2}\left(t_{\alpha/2,2n-2},\frac{|\delta|\sqrt{n}}{\sigma\sqrt{2}}\right)=|\beta$$

Here $\psi_m(x,k)$ is the cumulative distribution function of the t-distribution, α is the significant level, $1-\beta$ is power, δ is the effect size between groups, n is the number of communities necessary in each group and σ is the estimated standard deviation. The null hypothesis is that the cessation group is 8% inferior (δ=0.08) to the control group with a 2-sided α = 0.05, power ($1-\beta$) = 0.8 and estimated standard deviation of 4% (σ=0.04) after 36 months of follow up. Using the formula above we concluded that 8.06 communities were necessary in each arm and therefore 8 communities were assigned to each randomization arm.

Masking

The survey team was masked to the allocation of the communities into the two arms. Team members were not shown allocation schemes and surveys did not occur in order of treatment allocation. It was theoretically possible that survey personnel may have been unmasked once the cessation rule took effect, but this did not occur in the study.

The laboratory at Johns Hopkins University which processed the specimens for infection was also masked to treatment allocation. The specimen labels did not reveal treatment allocation, and all infection data was managed by the study statistician and study data managers who had no access to the study teams. Community members were not told their

laboratory results because all members of the community were eligible to receive the intervention. Therefore, infection outcome in this trial was double masked.

Study Methods

Census Prior to each treatment round, the study team performed a complete census and census-update of all households in the study community. The census allowed for collection of baseline characteristics and was the source for random selection of sentinel children at each survey visit. Each head of household was asked to provide, name, sex and age of all individuals in the household. Additional characteristics collected included: education level of head of household, presence of latrines, distance to sources of water, and access to face washing education programs in the community.

Surveys—At each survey visit, trained graders performed clinical assessment for trachoma by examination of the upper tarsal plate with a 2.5× magnifying loop and grading of the conjunctiva using WHO standards for the presence or absence of follicular trachoma (TF) or intense inflammatory trachoma (TI). To establish the presence or absence of infection with *Chlamydia trachomatis* samples were obtained using Dacron swabs from the conjunctiva of the right eye. The swabs were placed in a tube, kept cold in the field, frozen and sent to The Johns Hopkins International Chlamydia Laboratory for PCR analysis.. Validity of PCR results was confirmed using positive and negative controls in every sample run.

Specimens were analyzed using the Amplicor kit (Roche Molecular systems, Pleasonton, CA) according to manufacturer instructions. Intially, swab elution was performed by vortexing the swab in Amplicor CT/NG lysis buffer. Then, Amplicor dilutent was added. Each batch of specimens was run with two positive and two negative *C. Trachomatis controls*. Positive specimens were defined as those samples whose values in valid runs were >0.8 A_{450}, while negative specimens were defined as samples with <0.2 A_{450}. Samples with equivocal results (between 0.2 and 0.8 A_{450}) were run a second time. If the results were again equivocal, the sample was defined as not positive.

Additionally, at each survey visit sentinel children were assessed for facial cleanliness using the following three factor approach:

- presence of ocular discharge on the eyelashes or lids
- presence of nasal discharge on the nares, cheeks or lips
- whether any flies landed on the face during a three second observation

Quality Control Prior to study initiation in the spring of 2008, a weeklong workshop was conducted with study fieldworkers to standardize methods of data collection and entry. Fieldwork methods reviewed in this workshop included clinical trachoma grading, assessment of clean face status, ocular sample collection and handling and data entry. Trachoma grading of each field worker was assessed daily against a senior grader. A kappa >0.6 was required between the fieldworkers and a senior grader on final examination. All other field methods were performed 5 times under the supervision of a senior grader before certification was granted. Fieldworkers were assessed for adherence to standardized grading criteria every 6 months. Over the course of the study, field “air” controls at the rate of 5% were taken to monitor for contamination. None of the air controls was positive over the study. We also monitored for drift in trachoma grading over time by comparing field grader assessment of photographs to a gold standard grader, and assessing agreement., Throughout the study, agreement on grading TF and TI was greater than kappa=0.6. Data was collected in the field using paper forms and then entered into a customized Microsoft Access 2007 (Microsoft, Redmond, WA) database developed the Dana Center, Johns Hopkins University.

Different data entry personnel were required to duplicate data input into important fields. Real-time reports of missing and discrepant entries were generated and study personnel resolved these entry errors by referencing paper study forms or returning to the field if necessary. Further analysis of inconsistent data entry was performed using the SAS v.9.2 (SAS Institute Inc., Cary, NC, USA). Any inconsistencies that were discovered were investigated by referencing the original field data collection forms.

Statistical Analyses

This study was analyzed on an intention to treat (ITT) basis. As noted, none of the communities in the cessation rule arm stopped treatment, so the outcome was assessed as of the 18 month survey. The communities were analyzed according to their randomization assignment regardless of the fact they were not stopped.

Baseline characteristics of communities analyzed by randomization arm included total population, years of education of head of household, distance to water sources and access to latrines and baseline prevalence of TF and *C. Trachomatis* infection. Proportion of children under 10 in each village receiving antibiotics was calculated at baseline and 12 months. Means values for all characteristics were obtained for each arm by calculating the mean of the village level means. In order to test for significant differences between arms, P-values were calculated using the Wilcox rank-sum test.

Plots were made showing changes in TF and *C. Trachomatis* infection over time in each village and for the mean of the villages in each arm. P-values were calculated using the Wilcox rank-sum test to test for significant difference in TF or *C. Trachomatis* infection between arms at 18 months.

We modeled community-level prevalence of trachoma and *C. trachomatis* infection on a square root transformed scale to stabilize the variance. Multiple linear regression fitted with the ordinal least squares method was used to model the outcome of square root of 18 month prevalence against randomization arm and baseline prevalence. The following equation shows the model parameters that were used

$$\sqrt{p_i}=\beta_0+\beta_1 X_{1i}+\beta_2 X_{2i}+\varepsilon_i \quad (1)$$

Symbol/Term	Meaning
p_i	Prevalence of outcome in village i at 18 months
X_{1i}	Indicator of randomization arm i (0=usual care, 1=cessation rule))
X_{2i}	Square Root of Baseline prevalence of village i
β_0	Intercept term
β_1	Effect of cessation rule
β_2	Regression coefficient for square root of baseline prevalence

The statistical analysis was conducted using R version 2.14.0 (The R Foundation for Statistical Computing).

Results

There were no significant differences in baseline characteristics between the two randomization arms. A comparison of baseline household characteristics for each arm, including average prevalence of trachoma and infection, years of education of head of households, percent of houses located greater than 30 minutes to a water source and percent of houses with latrines, is described in Table 1.

There was no difference in antibiotic coverage as measured in children less than ten years of age in either arm, at baseline or at 12 months (Table 2). Average coverage was above 80% in both rounds, although lower in the second round.

Overall all, the prevalence of TF and infection declined over the 18 month study period in both groups (Figure 2 A and B). At baseline, *C. Trachomatis* infection was 5% and 6% in the usual care and cessation arms respectively. After baseline antibiotic treatment, infection declined to 3 % at 6 months in both groups; none of the communities in the Cessation rule arm had zero infection so all proceeded to the second round of MDA. By 18 months infection was 3% and 5% in the usual care and cessation groups respectively. No community in the cessation rule arm had 0% infection at 18 months, so all would proceed on to 3 rounds of MDA. There were no statistically significant differences in infection between the groups at any time point.

The prevalence of TF at baseline was 12% and 13% in the usual care arm and cessation rule arm, respectively, then after antibiotic treatment, declined to approximately 8% in both groups at 6 months. At six months, 13 communities of the 16 had a prevalence of TF below 10%. By 18 months, the prevalence of TF was 7% in the Usual Care Arm and 9% in the Cessation rule arm. There were no significant differences in TF prevalence between the groups at any time during the study.

Table 3 presents the intent- to- treat model adjusted for baseline prevalence. There were no significant differences at 18 months in either infection or in trachoma. Treatment arm or baseline infection and TF prevalence were not significant predictors of 18 month prevalence.

We then analyzed any effect of treatment coverage using average of baseline and 12 month coverage. There was no effect of increasing coverage and again, baseline infection or trachoma did not predict 18 month infection or trachoma prevalence (Table 4).

Discussion

The results of this study demonstrate that in Kongwa district, where the overall prevalence of trachoma was greater than 20% at baseline, communities with starting prevalence of trachoma close to 10% still needed at least 3 rounds of MDA and none could be stopped early based on a conservative stopping rule of infection less than 5%.

We note that after one round of MDA, the average trachoma prevalence in both sets of villages had fallen below the WHO 10% TF cut-off where MDA could be stopped. However, all but two of the communities still had at least 1% and up to 8% infection at 6 months. Three of the 16 communities were also still above 10% trachoma. At 18 months, after the second round of MDA, five of the 16 communities were above 10% trachoma, even though the average prevalence of TF was less than 10%. We proceeded to the third round of MDA based on the presence of infection in all the communities randomized to the cessation rule. We believe our data shows the importance of the wider geographic construct to be considered when evaluating even sub districts for potential cessation of antibiotic.

Unlike the experience with low prevalence villages in The Gambia[8,9], two rounds of MDA with high coverage was not sufficient to be able to stop MDA based on our cessation rule. The entire Kongwa district, where trachoma is above 10%, is being treated along with these communities, so it is unlikely that migration in from neighboring communities is a major cause of maintaining infection in this setting, although we cannot rule out migration in from communities outside the district. There were some villages where, even after a second round of MDA, infection appeared to increase at 18 months. Notably, one village in the Cessation rule arm was an outlier with 13% infection at 18 months, where the rest of the 15 villages were at 7% or lower. We have no explanation for this spike and the nearest neighboring communities enrolled in the trial had 18 months infections at 1% and 4%. Antibiotic coverage at 12 months was 80% in this particular village, so low coverage is an unlikely explanation.

We do not feel that the antibiotic coverage would explain the disappointing slow decline in infection, as all communities had coverage above 80% in children at baseline, and only 1 community had less than 80% (71%) for the second round. Treatment verification showed high concordance with observed treatment as well. In a model of infection at 18 months, we examined the relationship of infection to average treatment coverage, and it was not significantly related, suggesting within the range of coverage we observed, there was no difference. Of note, mean antibiotic coverage was non-significantly associated with a lower 18 month infection prevalence suggesting that coverage may be an important factor in eliminating infection. However, our study was not powered to answer this question. Moreover, while there is evidence that missing MDA does not occur at random[14], there is no evidence that missing MDA is related to infection status, suggesting that children with infection were preferentially missed by treatment. We also note data that suggest it takes over 6 months for infection to spread outside the household[15] so even if there were any differential coverage, it is unlikely to explain how infection increased in some communities within 6 months after MDA. Our coverage was similar to that of Burton et al, in the Gambia villages where one round was sufficient to stop infection and re-emergence did not occur[8,9].

We chose a very conservative Cessation rule, with infection estimated at less than 5% but our working rule was no infection in the sentinel sample of 100 children. If we had chosen a less strict guideline, we may have been able to stop MDA earlier. However, there are not data to guide the selection of a stopping rule based on infection, and we reasoned that if The Gambian villages could drop infection below 5% and have no re-emergence, then our guideline was reasonable. Others have shown that even with almost no infection in communities, once antibiotic pressure is removed, re mergence does occur[16]. We suggest that these data support a wider viewpoint than community when considering trachoma status and stopping MDA, in line with WHO guidelines on assessment at district level. In The Gambia, when the last few remaining villages are being treated, then possible acceleration to zero infection with one round of MDA may be reasonable. However, low prevalence communities in a district like Kongwa, which on average has trachoma estimated at above 20%, cannot be singled out and will need at least the full 3 rounds of MDA even with high coverage.

In conclusion, we have found that in low prevalence communities in Kongwa, Tanzania, two rounds of MDA was not sufficient to reduce infection to zero. The fact that these communities were at the low end of baseline prevalence in a district with overall higher rates of trachoma suggests the wisdom of treating a wide geographic area for at least three rounds before impact surveys, and not presuming that sub districts on their own can be stopped if the wider district level prevalence supports mass treatment.

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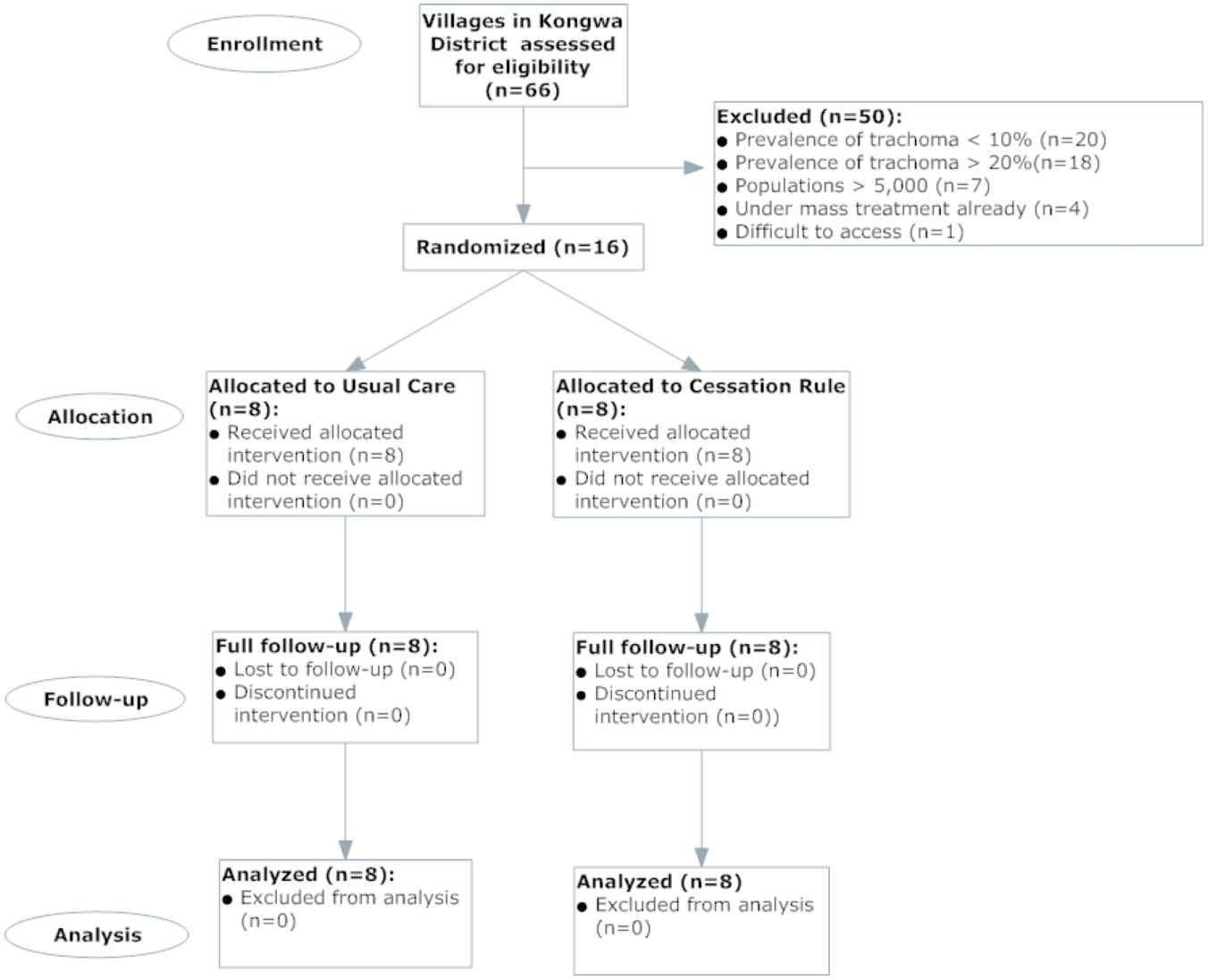
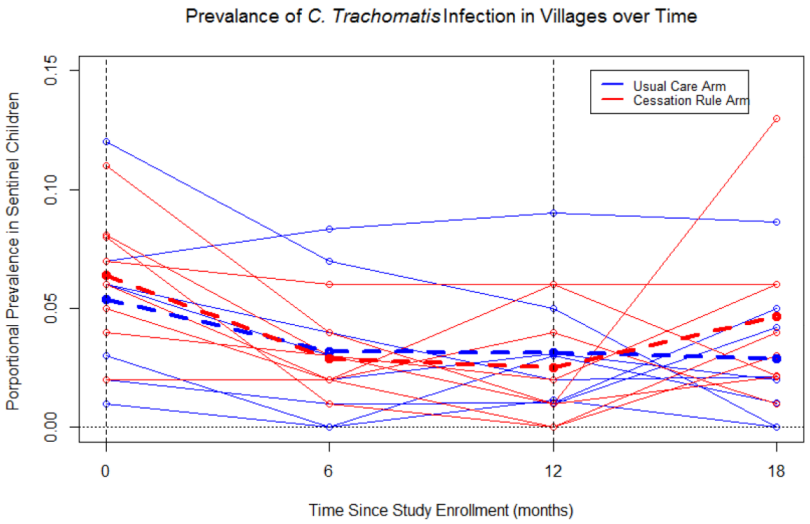


Figure 1.

Consort diagram of design and characteristics of PRET-Ziada Trial. The usual care group received MDA at baseline and 12 months while the graduation group received antibiotics at baseline but only to received antibiotics at 12 months if infection prevalence was >0% at the 6 month follow-up visit.

A



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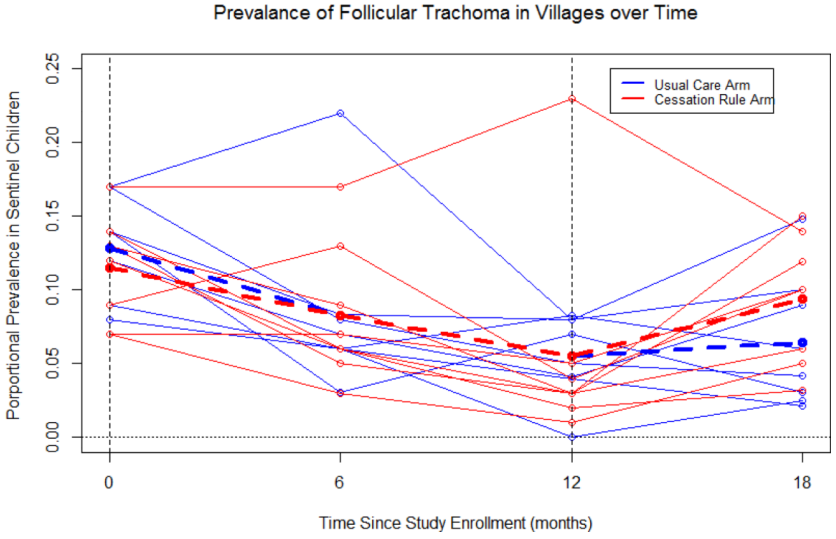

Figure 2.

A: Prevalence of *C. Trachomatis* infection over time in Usual Care and Cessation Rule Arms. Thick dashed line indicate mean prevalence in each arm and thin lines indicate village level prevalence

b: Prevalence of TF over time in Usual Care and Cessation Rule Arms. Thick dashed lines indicate mean prevalence in each arm and thin lines indicate village level prevalence

Table 1

Baseline characteristics of communities in the two study arms.

Characteristic	Statistic	Usual Care Group	Cessation Rule Group	P-value*
Population size	Mean (SD)	1140 (390)	1121 (255)	0.96
Average Years of Education of Household Head	Mean (SD)	4.0 (0.7)	3.9 (0.4)	0.51
% houses > 30 minutes from water	Mean (SD)	61.6 (17.9)	58.4 (22.7)	0.80
% houses with latrine	Mean (SD)	68.3 (9.5)	67.5 (14.6)	0.88
Prevalence of TF	Mean (SD)	12.9 (3.3)	11.5 (3.5)	0.46
Prevalence of *C. trachomatis*	Mean (SD)	5.4 (3.5)	6.4 (2.8)	0.46

* P-values were calculated using the Wilcoxon rank-sum test for non-parametric data.

Table 2

Proportion of children under 10 in communities in each study arm treated at baseline and 12 months.

Characteristic	Statistic	Usual Care Group	Cessation Rule Group	P-value*
Baseline Antibiotic Coverage	Mean (SD)	89.6 (5.9)	94.2 (5.0)	0.13
12 Month Antibiotic Coverage	Mean (SD)	82.7 (7.4)	88.9 (5.4)	0.13

* P-values were calculated using the Wilcoxon rank-sum test for non-parametric data.

Table 3

Multivariate Linear model of square root of infection of TF prevalence at 18 months predicted by randomization group and square root of baseline infection or trachoma

Characteristic	β Coefficient	95% CI	P value
Predicting Infection			
Cessation Rule Arm	0.064	−0.033 to 0.161	0.219
Baseline Infection (square root)	−0.020	−0.755 to 0.715	0.958
Predicting Follicular Trachoma			
Cessation Rule Arm	0.071	−0.005 to .147	0.092
Baseline Trachoma (square root)	0.662	−0.125 to 1.450	0.123

Table 4

Multivariate Linear model of square root of infection of TF prevalence at 18 months predicted by 12 month antibiotic coverage and square root of baseline infection or trachoma

Characteristic	β Coefficient	95% CI	P value
Predicting Infection			
Mean Antibiotic coverage	−0.340	−1.42 to 0.745	0.550
Baseline Infection (square root)	−0.211	−0.655 to 1.08	0.641
Predicting Follicular Trachoma			
Mean Antibiotic coverage	0.289	−0.498 to 1.08	0.485
Baseline Trachoma (square root)	0.458	−0.397 to 1.313	0.312