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Authors

Morberg, Daniel P
Alemayehu, Wondu
Melese, Muluken
et al.

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A longitudinal analysis of chlamydial infection and trachomatous inflammation following mass azithromycin distribution

Daniel P Morberg[1], **Wondu Alemayehu**[2], **Muluken Melese**[2], **Takele Lakew**[2], **Alemayehu Sisay**[2], **Zhaoxia Zhou**[1], **Vicky Cevallos**[1], **Catherine E Oldenburg**[1], **Travis C Porco**[1,3,4,5], **Thomas M Lietman**[1,3,4,5], and **Jeremy D Keenan**[1,3]

[1]Francis I. Proctor Foundation, University of California, San Francisco, CA

[2]Orbis International, Addis Ababa, Ethiopia

[3]Department of Ophthalmology

[4]Department of Epidemiology & Biostatistics

[5]Institute for Global Health, University of California, San Francisco, USA

Abstract

Background: Mass azithromycin distributions are effective for clearing ocular strains of *Chlamydia trachomatis*, yet infection frequently returns in areas with hyperendemic trachoma. A better understanding of the factors associated with chlamydial reinfection could be helpful to plan trachoma elimination strategies.

Methods: This was a prospective cohort study conducted in a trachoma-hyperendemic region of Ethiopia in 2003. As part of a larger cluster-randomized trial, 21 villages were treated with a single mass azithromycin distribution and all children 5 years and younger were monitored for ocular chlamydia and clinically active trachoma at baseline and at 2 and 6 months following the treatment.

Results: In 20 villages with available data, azithromycin treatment coverage was 88.7% (95% confidence interval [CI] 85.7 to 91.8%). In total, 1005 children tested negative for ocular chlamydia at the 2-month visit, of whom 41 became infected by 6 months (1.0 incident chlamydia infections per 100 person-months, 95%CI 0.7 to 1.4). The presence of intense trachomatous inflammation (TI) at baseline was associated with incident infection at 6 months (incidence rate ratio 1.91, 95%CI 1.03–3.55). Ocular chlamydia infections clustered more within households than communities: (intraclass correlation coefficient 0.01 for communities and 0.29 for households six months post-treatment). Younger children were more likely to have persistent clinically active trachoma (P=0.03).

Corresponding Author: Jeremy Keenan, 513 Parnassus Avenue, Box 0412, F. I. Proctor Foundation, University of California, San Francisco, Tel: 415-476-6323, Fax: 415-476-0527, jeremy.keenan@ucsf.edu.

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Conclusions: More intensive antibiotic distributions may be warranted for younger children, for children with TI, and for households containing children with ocular chlamydia infections.

Introduction

Trachoma is the most important infectious cause of blindness worldwide, resulting from repeated ocular infection with *Chlamydia trachomatis* and subsequent conjunctival inflammation. In order to eliminate trachoma as a public health concern the World Health Organization (WHO) promotes mass drug administration (MDA) with azithromycin, which has been shown to produce substantial reductions in the prevalence of ocular chlamydia.[1–3] A single mass azithromycin treatment is usually not sufficient to eliminate trachoma, especially in areas with hyperendemic disease.[3,4] Repeated rounds of mass azithromycin distributions reduce the prevalence of ocular chlamydia to low levels, but communities with hyperendemic trachoma often experience return of chlamydial infection after mass treatments have been stopped.[3] Few studies have assessed the epidemiology of chlamydial infection and conjunctival inflammation following a mass azithromycin distribution.[5–8] This information is important, since novel trachoma treatment strategies could be based on targeting those individuals most likely to become re-infected or most likely to have persistent inflammation.

In a series of cluster randomized trials conducted in the Gurage zone of Ethiopia, we collected conjunctival swabs before and after biannual mass azithromycin treatments and investigated pools of swabs for *C. trachomatis* with a polymerase chain reaction (PCR) assay. In previous reports, we performed community-level analyses using pooled PCR results.[3,9–11] We recently tested individually a number of conjunctival samples for a different study, which allowed an individual longitudinal analysis of ocular chlamydial infection and conjunctival inflammation following mass azithromycin treatments. The objective of the present study was to identify populations at risk for re-infection and persistent conjunctival inflammation, with the ultimate goal of being able to design better mass treatment strategies.

Methods

Study design.

This is an ancillary analysis of a previously reported cluster randomized trial that began in March 2003 in the Gurage zone of Ethiopia. In the trial, 24 communities from a distinct geographical area were randomized in an equal ratio to one of three treatment groups (annual vs. biannual vs. a single mass azithromycin distribution) and 16 communities from a nearby but separate geographic area were randomized to one of two treatment groups (annual versus biannual mass azithromycin distributions).[9–11] Mass azithromycin distributions consisted of a single directly observed dose of oral azithromycin, 20mg/kg, approximated by height-based dosing.[12] We examined and swabbed the upper right tarsal conjunctiva of all children aged 1–5 years in each community at predetermined timepoints; in the present study we include data from study visits before and 2 and 6 months after treatment. As described previously, we used the World Health Organization's simplified grading system for conjunctival examinations, recording the presence of trachomatous

inflammation—follicular (TF) and trachomatous inflammation—intense (TI) for each child.[13] We used Roche AMPLICOR to evaluate swabs for *C. trachomatis*.[9–11] Swabs were pooled after the baseline visit. Individual swabs from positive pools were not tested for the main studies; instead, we estimated the village-level prevalence of ocular chlamydia from the number of positive pools.[14] For a subsequent ancillary study the same chlamydia assay was performed on individual swabs from positive pools of the 2-month and 6-month study visit for 21 communities.[15] This provided individual-level data of ocular chlamydia status for all children aged 1–5 years from these 21 communities at months 0, 2, and 6.

Statistical analyses.

We modeled the incidence of new ocular chlamydia infections after mass azithromycin administration in a Poisson regression model that included the study community as a random effect, and tested for associations with baseline covariates in similarly constructed models. Agreement between three definitions of clinically active trachoma (TF, TI, TF and/or TI) and chlamydial infection was assessed by calculating the positive and negative predictive values of the various definitions as well as Cohen's kappa statistic. We tested for differences in these measures of agreement between study visit by bootstrapping the difference in the estimates (1000 replications, resampled at community level). We investigated the relationship between age at baseline and persistent clinical signs of trachoma in mixed effects logistic regression models with village and household as nested random effects, adjusted for the presence of clinically active trachoma at baseline. Persistent clinically active trachoma was defined as the presence of TF and/or TI according to the WHO simplified grading system at months 2 and 6.[13] We assessed for clustering of chlamydial infection within communities and households by calculating the intraclass correlation coefficient (ICC) from similarly constructed mixed effects linear regression models.

The underlying trial was registered on clinicaltrials.gov (#NCT00221364). We obtained ethical approval from the Committee for Human Research of the University of California, San Francisco and the National Ethical Clearance Committee of the Ethiopian Science and Technology Commission prior to commencing the study. The research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from guardians at the time of conjunctival assessments and antibiotic distributions.

Results

Clearance of chlamydial infection 2 months after MDA.

Each of the 21 communities received a mass azithromycin distribution after the baseline monitoring visit; the average antibiotic coverage in the 20 communities with available coverage data was 88.7% (95%CI 85.7 to 91.8%). 1102 children aged 1–5 years at baseline had conjunctival swabs collected at the baseline, 2-month, and 6-month study visits; 617 (56.0%) of these pre-school children were infected with ocular chlamydia at baseline. Of these, 536 (86.9%) had cleared infection by the 2-month visit. In comparison, of the 485 children not infected at baseline, 469 (96.7%) remained uninfected at the 2-month visit.

Re-infection at 6-month visit.

Of 1005 children not infected at the 2-month visit, 41 converted to a positive chlamydia test at the 6-month visit (incidence: 1.0 new chlamydia infections per 100 person-months, 95%CI 0.7 to 1.4). As shown in Table 1, the rate of incident infections was not associated with baseline infection or the presence of TF at baseline, but was higher in those with TI at baseline (IRR 1.91, 95%CI 1.03–3.55). Re-infection rates did not significantly differ by age or sex (Table 1). Although not statistically significant, the re-infection rate among those who had an infected sibling at month 2 (2.32 new chlamydia infections per 100 person-months, 95%CI 0.73 to 7.28) was higher than the rate among children living in a household without any infected children during the same study visit (0.98 new infections per 100 person-months, 95%CI 0.69 to 1.39); IRR 2.37, 95%CI 0.73–7.73).

Persistent chlamydial infection at 6-month visit.

Of the 81 children infected at both the baseline and 2-month visits, 61 (75.3%) also tested positive for chlamydia at the 6-month visit. Of the 16 children with a negative chlamydia test at baseline but a positive test at the 2-month visit, 14 (87.5%) had a positive chlamydial test at the 6-month visit. Persistent infections were not significantly different between these two groups (IRR 0.86, 95%CI 0.48–1.54).

Association of clinically active trachoma and chlamydial infection.

Table 1 shows the predictive value of the clinical signs of trachoma for ocular chlamydia infection at months 0, 2, and 6. Before mass azithromycin treatments, 60.4% of children with the clinical signs of trachoma (TF and/or TI) were infected with ocular chlamydia. In contrast, 10.6% of children with clinically active trachoma at the 2-month visit were infected with ocular chlamydia (49.9% lower than month 0, 95%CI 43.8–56.0%, $P<0.001$) and 14.3% of children with clinically active trachoma at the 6-month visit were infected (3.9% higher than month 2, 95%CI 2.1–5.6%, $P<0.001$). Analyzed a different way, the agreement between clinical activity and infection, while fairly poor at baseline (Cohen's $\kappa=0.17$, 95%CI 0.11–0.23), was even lower 2 months after mass azithromycin treatment ($\kappa=0.03$, 95%CI 0.02–0.07; 0.14 less than baseline, 95%CI 0.08–0.20, $P<0.001$) and then increased slightly at the 6-month visit ($\kappa=0.08$, 95%CI 0.06–0.11; 0.05 higher than month 2, 95%CI 0.02–0.07, $P<0.001$).

Clustering of ocular chlamydial infections.

Estimates of community and household clustering of chlamydial infection at each time point are shown in Table 2. The ICC was higher for households than communities, suggesting that individuals in the same household were more likely to have the same infection status compared with individuals in different households of the same community. The ICC for both the community level and household level decreased after the mass azithromycin distribution, indicating less similarity of infection status within each class after treatment.

Resolution of clinical signs of trachoma after mass azithromycin.

After the baseline mass azithromycin distribution, 964 children had consecutive negative tests for chlamydia at months 2 and 6, representing a cohort of children with cleared

infection. Figure 1 depicts the progression of clinical signs in this group of children, with each row symbolizing the clinical signs of a unique child, stratified by age at entry into the cohort and baseline infection status. Persistent clinically active trachoma, defined as TF and/or TI both at month 2 and 6, was more common in younger children and in those infected at baseline in a mixed effects logistic regression adjusted for the presence of clinically active trachoma at baseline (Table 4).

Discussion

We made several observations regarding ocular chlamydia infection and clinically active trachoma by analyzing the outcomes of individual children residing in trachoma-hyperendemic communities treated with mass azithromycin distributions. In these communities, 87% of children with ocular chlamydia infection before treatment tested negative for infection at month 2. From months 2 to 6, the re-infection rate was 1% per month among the pre-school children who would be expected to be most at risk, with increased risk among children who had TI at baseline. Ocular chlamydial infection clustered by community and household, with more similar infection status within households than within communities. Resolution of the clinical signs of trachoma was associated with age, with younger children more likely to have persistent clinically active trachoma even after documented clearance of infection.

Previous studies have estimated incident ocular chlamydial infections following mass distribution of antibiotics. In a 1993 study of a Tanzanian village in which all villagers were treated with a 30-day course of topical tetracycline, 20% of individuals not infected with ocular chlamydia at the conclusion of the course of antibiotics had developed a new infection 1 month later.[16] A study of a different Tanzanian village completed in 2002 found that 15% of uninfected children under 8 years of age became infected with ocular chlamydia during the period of time from 2 to 6 months following a mass azithromycin distribution.[4] The re-infection rate in the present study, at approximately 1% per month, was more similar to the latter Tanzanian study, suggesting that mass administration of azithromycin is likely more effective at preventing incident infections than topical tetracycline. The reasons for a reduced rate of re-infection following azithromycin are not clear, but could be related to the longer half-life of oral azithromycin as well as the ability of systemic treatment to clear non-ocular reservoirs such as the nares. It is important to note that the incidence would be expected to vary between different geographic locations so the results could also be explained by chance or a secular trend.

In the present study, children not infected at the 2-month visit were more likely to test positive for infection at the 6-month visit if they had been diagnosed with TI at baseline. Although we do not have quantitative PCR data from this population, previous studies have shown that the load of ocular chlamydia is highest among children with TI.[2,5,17,18] This suggests that children with high loads of ocular chlamydia at baseline are at greater risk of incident infection after a mass azithromycin distribution. Children with TI at baseline are likely to have greater exposure to the underlying risk factors for trachoma (e.g., poor access to water, sanitation, and health services) and therefore are more likely to be re-infected. Thus, although the magnitude of the association between baseline TI and incident infection

was somewhat low in this study, it might nonetheless be reasonable to consider testing the effectiveness of a strategy of targeting these children with TI for more frequent antibiotic distributions.

Several previous studies have found evidence that trachoma clusters by household.[19–25] We assessed for household clustering in the present study by calculating the ICC, which can be interpreted in terms of the likelihood that any two household members have the same infection status. An ICC of zero would indicate that all people in the household have a different status, and an ICC of one that all people in the household have the same status. We found a pre-treatment household ICC of 0.37 and community ICC of 0.07, indicating a considerable degree of household clustering before mass treatments. The ICC for both communities and households decreased after mass treatment, though household clustering was still greater than community clustering, suggesting the household may serve as a reservoir for re-infection. The importance of household-transmitted infections is supported by a previous study in Tanzania that found high-load chlamydial infection in one household member to be associated with subsequent chlamydial infection in another, and also with the present study, which found a similar but nonsignificant association.[4] Targeting treatments to households with an infected child may be an appropriate strategy for trachoma programs wishing to limit their use of antibiotics.

Similar to previous studies, we found that the agreement between the clinical signs of trachoma and ocular chlamydia infection was generally poor in this population with hyperendemic trachoma.[2,18,26,27] The agreement between clinically active trachoma and ocular chlamydia infection became even worse after the mass azithromycin distribution, although improved significantly between the 2-month and 6-month study visits. This pattern likely occurs because antibiotics rapidly clear infection, but the clinical signs take months to resolve. Although clinical signs of inflammation are extremely important in terms of the causal pathway for blindness, mass azithromycin distributions are not specifically directed at quieting inflammation, but rather at clearing infection. Thus, impact assessments relying solely on the clinical signs of trachoma, especially when done relatively soon after a mass azithromycin distribution, do not necessarily reflect the true prevalence of ocular chlamydia infection in the community. Diagnostic tests that give more accurate information about ocular chlamydia infection would be helpful for post-treatment surveillance.

Our results are consistent with previous studies in showing that the duration of the clinical signs of trachoma depends on the age of the child, with longer clinical courses in younger children. For example, a study from two villages in the Gambia found that children aged 0–4 years had a longer duration of TF than did older cohorts.[28] A study of 4 communities in Tanzania found that the annual decline in the prevalence of TF after mass azithromycin treatments was generally slower in younger age cohorts.[29] In each of these studies, the longer duration of TF could have been attributable to more re-infection among younger children. In contrast, the present study excluded from the analysis any children with a positive chlamydial test after baseline, so re-infection should play much less of role in explaining the long duration of trachomatous signs. We acknowledge the possibility of short-term ocular chlamydial infections that began and ended within our testing interval, though previous studies have estimated ocular chlamydial infections to last many months, especially

in young children.[30] Our results suggest that independent of re-infection, the clinical signs of trachoma take longer to resolve in younger children than in older children. The reasons for this observation are unclear, but it has been shown in previous studies that the youngest children have the highest loads of ocular chlamydia, which may in turn incite a more vigorous immune response and subsequently result in a longer duration of inflammatory signs.[2,5,17,18]

The most important limitation of this study is the lack of individual-level antibiotic coverage data, which prevented us from conducting several longitudinal analyses in which antibiotic coverage would have been an important predictor. As a result, we were able to perform longitudinal analyses only on periods of time for which no one was eligible for treatment (e.g., incidence of infection from month 2 to month 6) or in cohorts of children that exhibited similar patterns of chlamydial infection (e.g., children with negative chlamydial tests at post-treatment visits). Another limitation is the subjective nature of trachoma grading, which although standardized for the trial, could have resulted in some false negative and false positive tests.[31] Finally, the data come from a trial conducted some years ago, so it is possible that these results do not reflect the trachoma situation today. However, given the persistently high prevalence of trachoma throughout much of Ethiopia and the lack of change in the underlying public health conditions in much of rural Ethiopia, we think it likely that the study's results are still relevant.

In conclusion, we performed several analyses on individual-level data from a previously reported clinical trial. We found that the rate of new ocular chlamydial infections after a mass azithromycin distribution was approximately 1% per month in an area of Ethiopia with hyperendemic trachoma, and that the presence of TI at baseline increased the risk of a new infection. Chlamydial infection clustered in households more so than communities, both before and after mass azithromycin distributions. The clinical signs of trachoma, while generally a poor indicator of ocular chlamydial infection, took longer to resolve in younger children compared with older children after successful azithromycin therapy. A strategy of targeting antibiotic treatments to households containing children with TI may be a reasonable approach after one or several rounds of mass azithromycin distributions, although further studies are needed to test this hypothesis.

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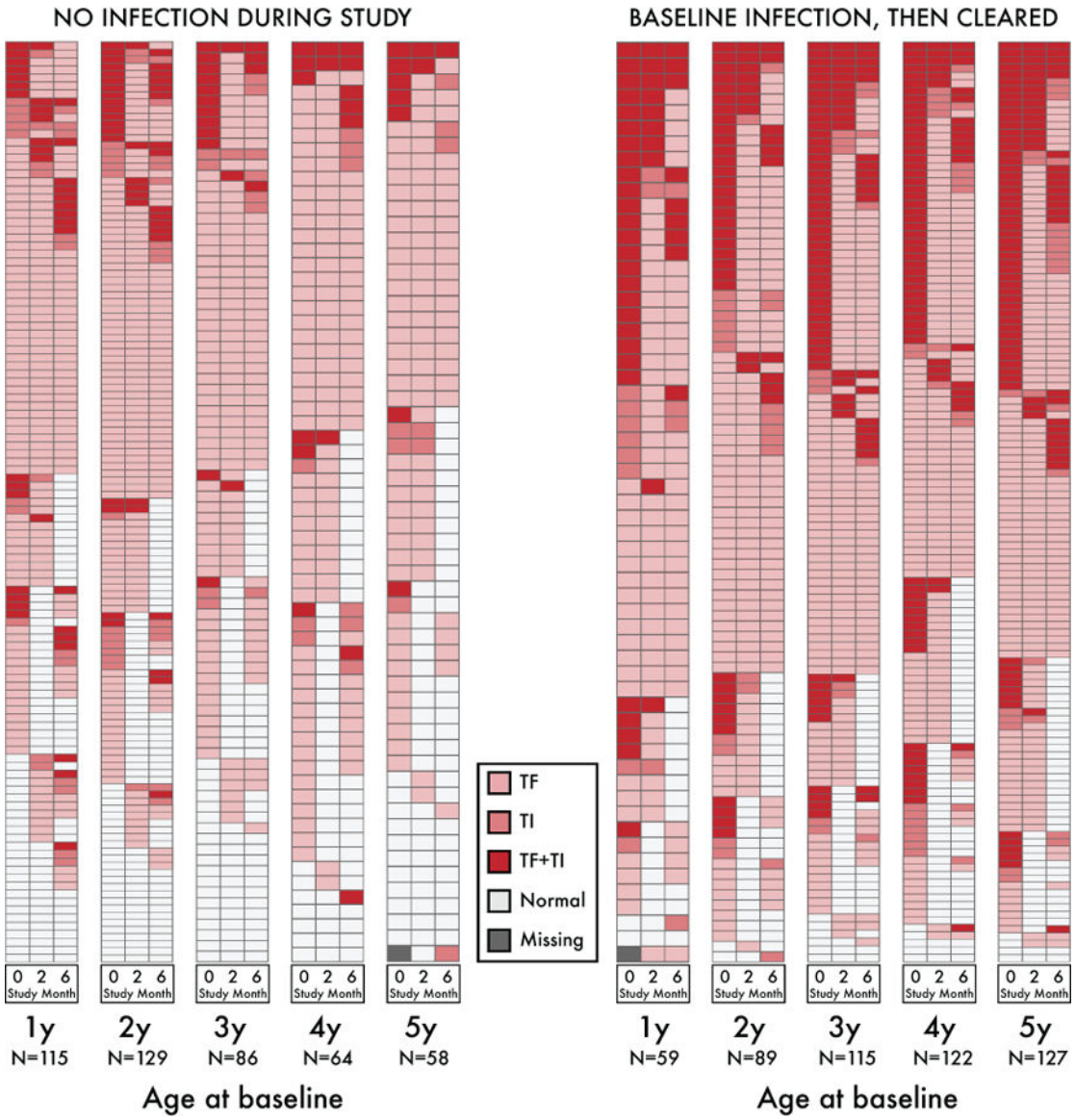

Figure 1. Clinical signs of trachoma over time for 964 children cleared of chlamydia infection after a mass azithromycin distribution.

All children tested negative for ocular chlamydia at months 2 and 6. Results are stratified by baseline infection status (left panel shows children uninfected at baseline and right panel shows children infected at baseline) and age at entry into the cohort. Each row represents a single child, with the results from the clinical examination shown for each study visit.

Table 1.

Risk factors for incident chlamydial infection after a single mass azithromycin treatment.

Baseline covariate	Number	Infections per 100 person-months	Incidence rate ratio
Sex			
Male	477	1.15 (0.74–1.79)	1.28 (0.69–2.36)
Female	528	0.90 (0.56–1.45)	Reference
Age			
1y	181	0.97 (0.46–2.06)	1.07 (0.37–3.05)
2y	223	0.56 (0.23–1.37)	0.62 (0.20–1.96)
3y	212	1.30 (0.71–2.37)	1.43 (0.55–3.68)
4y	197	1.39 (0.76–2.54)	1.52 (0.59–3.94)
5y	192	0.91 (0.43–1.93)	Reference
Infection			
Infected	536	1.11 (0.72–1.69)	1.21 (0.64–2.27)
Not infected	469	0.92 (0.56–1.51)	Reference
TF			
TF present	822	1.06 (0.74–1.52)	1.27 (0.53–3.03)
TF absent	183	0.84 (0.37–1.90)	Reference
TI			
TI present	377	1.45 (0.94–2.24)	1.91 (1.03–3.56)
TI absent	628	0.76 (0.48–1.21)	Reference

Table 2.

Clinical signs of trachoma as a predictor for concomitant chlamydial infection before and after a single mass azithromycin distribution in 21 Ethiopian villages with hyperendemic trachoma.

	Baseline[a]		Month 2[b]		Month 6	
	n/N	Estimate (95% CI)	n/N	Estimate (95% CI)	n/N	Estimate (95% CI)
PPV						
TF	546/903	60.5% (54.6–66.3%)	86/810	10.6% (8.0–13.8%)	102/703	14.5% (11.3–17.8%)
TI	321/419	76.6% (70.2–82.1%)	39/171	22.8% (15.8–31.6%)	73/291	25.1% (20.0–31.5%)
TF±TI	594/984	60.4% (54.4–67.1%)	89/851	10.5% (7.7–13.4%)	115/803	14.3% (11.5–17.7%)
NPV						
TF	127/197	64.5% (53.2–73.6%)	277/288	96.2% (94.2–98.0%)	385/399	96.5% (94.6–98.5%)
TI	386/681	56.7% (50.6–61.7%)	869/927	93.7% (92.1–95.2%)	768/811	94.7% (92.5–96.5%)
TF±TI	94/116	81.0% (71.0–87.4%)	239/247	96.8% (94.8–98.6%)	298/299	99.7% (98.8–100%)

PPV=positive predictive value; NPV=negative predictive value; TF=follicular trachoma; TI=intense inflammatory trachoma

[a]Missing conjunctival examination data for 2 children

[b]Missing conjunctival examination data for 4 children

Table 3.

Community- and household-level clustering of ocular chlamydial infections before and after mass azithromycin distributions.

	Intraclass correlation coefficient (95% CI)		
Class	**Baseline**	**Month 2**	**Month 6**
Community-level	0.07 (0.03–0.14)	0.002 (<0.001–0.29)	0.01 (0.002–0.06)
Household-level	0.37 (0.28–0.48)	0.27 (0.18–0.40)	0.29 (0.19–0.41)

Table 4.

Persistent clinically active trachoma stratified by baseline age and infection.

	Persistent trachoma*		
Baseline characteristic	**Persistent trachoma/ Total**	**Predicted probability (95%CI)†**	**OR (95%CI)†**
Age group			
1y	104/174	71% (60–83%)	1.80 (1.00–3.24)
2y	130/218	66% (55–77%)	1.41 (0.83–2.42)
3y	124/201	67% (56–79%)	1.50 (0.87–2.58)
4y	100/186	51% (39–64%)	0.76 (0.44–1.31)
5y	110/185	58% (46–70%)	Ref
Chlamydia infection			
Infected	345/512	54% (44–64%)	2.04 (1.39 to 3.01)
Not infected	223/452	71% (61–80%)	Ref
Clinically active trachoma			
TF and/or TI	546/855	69% (60–77%)	9.56 (4.52 to 20.2)
Neither TF nor TI	21/107	19% (8–30%)	Ref

*Persistent clinically active trachoma was defined as trachomatous inflammation – follicular (TF) and/or trachomatous inflammation – intense (TI) at months 2 and 6.

†Predicted probabilities and odds ratios from a mixed effects logistic regression adjusted for baseline age as a categorical variable (P=0.03), baseline clinically active trachoma (P<0.001), and baseline chlamydial infection (P<0.001), with random effects for village and household. Predicted probabilities assume the means of other covariates.