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Authors

Amza, Abdou
Kadri, Boubacar
Nassirou, Beido
et al.

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Community-level Association between Clinical Trachoma and Ocular Chlamydia Infection after MASS Azithromycin Distribution in a Mesoendemic Region of Niger

Abdou Amza[a], **Boubacar Kadri**[a], **Beido Nassirou**[a], **Sun Y Cotter**[b], **Nicole E. Stoller**[b], **Sheila K West**[c], **Robin L. Bailey**[d], **Travis C. Porco**[b,e,f], **Jeremy D. Keenan**[b,e,f], **Thomas M. Lietman**[b,e,f], **Catherine E. Oldenburg**[b,e]

[a]Programme FSS/Université Abdou Moumouni de Niamey, Programme Nationale des Soins Oculaire, Niamey, Niger

[b]Francis I. Proctor Foundation, University of California, San Francisco, USA

[c]Dana Center for Preventive Ophthalmology, Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland, USA

[d]Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

[e]Department of Ophthalmology, University of California, San Francisco, USA

[f]Department of Epidemiology & Biostatistics, University of California, San Francisco, USA

Abstract

Purpose: The clinical sign trachomatous inflammation – follicular (TF) is used to monitor indication for and response to mass azithromycin distribution in trachoma-endemic communities. Here, we assess the relationship between TF, trachomatous inflammation – intense (TI), and infection with ocular *Chlamydia trachomatis* over time during annual mass azithromycin distribution.

Methods: We used data from a cluster-randomized trial of mass azithromycin distribution for trachoma control in a mesoendemic region of Niger. This study includes 24 communities that received 3 years of annual mass azithromycin distribution. TF, TI, and ocular chlamydia infection were monitored among children aged 0–5 years. We assessed the correlation between the prevalence of ocular chlamydia infection and 1) TF and 2) TI prevalence over time.

Results: At baseline, ocular chlamydia prevalence was 21.2% (95% CI 14.3–28.1%), TF prevalence was 27.7% (95% CI 21.2–34.2%), and TI prevalence was 8.3% (95% CI 5.2–11.5%). The prevalence of all three measures decreased significantly over time ($P < 0.001$). At baseline, ocular chlamydia infection prevalence was strongly correlated with both TF (rho = 0.78, $P < 0.0001$) and TI (rho = 0.76, $P < 0.0001$). The correlation between ocular chlamydia infection and both TF and TI was weak at months 12 and 24. At 36 months, when TF prevalence had

CONTACT Catherine E. Oldenburg catherine.oldenburg@ucsf.edu Francis I. Proctor Foundation, University of California, San Francisco, 513, Parnassus Ave, Room S334, San Francisco, CA 94143.

dropped below 10%, ocular chlamydia infection and TF were moderately correlated (rho = 0.70, P= 0.0002).

Conclusions: Both TF and TI are good indicators of infection prevalence prior to mass azithromycin distribution. However, this relationship may be affected by repeated rounds of mass azithromycin distribution.

Keywords

Trachoma; azithromycin; mass drug administration

Introduction

Trachoma programs conduct impact assessments to monitor if mass azithromycin distribution is needed or can be stopped in trachoma-endemic districts.[1] These impact assessments consist of measuring trachomatous inflammation – follicular (TF) as the clinical indicator for disease status. Infection with ocular strains of *Chlamydia trachomatis* (henceforth, ocular chlamydia infection) is thought to lead to TF and trachomatous inflammation – intense (TI), collectively referred to as "active trachoma".[2–5] The duration of active trachoma is typically longer than that of active infection.[5,6] As a result, at the individual level, there is substantial discordance between infection and active trachoma.[7–10]

Previous studies have demonstrated high correlation at the community level between TF and ocular chlamydia infection prior to mass azithromycin distribution.[5] However, following azithromycin distribution, previous work has demonstrated that TF overestimates the prevalence of infection.[5,10] A previous study in a region with low prevalence of infection demonstrated a relationship between TI before and after mass azithromycin distribution, and the use of TI as a clinical sign of trachoma likely yields additional information about infection in communities.[5,11,12] Currently, trachoma programs do not measure TI as part of impact assessments. However, if shown to be a more reliable indicator of infection following mass azithromycin distribution, TI could be considered for inclusion in trachoma programs.

Here, we utilize data from a cluster randomized trial of mass azithromycin distribution for trachoma control to evaluate the longitudinal relationship between ocular chlamydia infection and the clinical signs TF and TI at the community level.[13–15] We utilized data from communities receiving annual mass azithromycin distribution in a mesoendemic region of Niger to assess how this relationship changes following multiple rounds of azithromycin distribution.

Materials and methods

Participants and procedures

The Partnership for the Rapid Elimination of Trachoma (PRET) was a series of three cluster-randomized trials in Tanzania[16,17], The Gambia[18], and Niger[13–15] designed to assess the efficacy of azithromycin-based interventions for trachoma control. In Niger, participants were enrolled in Matamèye District, Zinder Region from May 2010 through August 2013. Here, we include data from the 24 grappes (smallest government health unit; henceforth

"community") that were randomized to annual mass azithromycin distribution to all members of the community. Communities from six centres de santé intégré (administrative health unit; CSIs) were eligible for randomization if they had a population between 250 and 600 individuals at the most recent government census and had at least 10% prevalence of active trachoma (TF and/or TI) prior to the first mass azithromycin treatment. In the 6 CSIs, 72 of 235 individual communities met the inclusion criteria for population and TF prevalence, and 48 communities were randomly selected to participate in PRET-Niger, of which 24 were randomized to the annual mass azithromycin distribution arm. Ethical approval was obtained from the Committee on Human Research at the University of California, San Francisco and the Comité d'Ethique du Niger. We obtained verbal consent from each local community chief for the community to participate in the trial prior to randomization. Each individual or guardian provided verbal informed consent for themselves or their child to participate in the study. All study procedures adhered to the tenets of the Declaration of Helsinki.

Azithromycin distribution

All communities received four rounds of mass azithromycin distribution to all members of the community, at months 0, 12, 24, and 36. A single dose of azithromycin (20 mg/kg for children and 1 g for adults) was offered. Children under 6 months of age and those allergic to macrolides were offered topical tetracycline ointment (1%) to be applied to both eyes two times per day for 6 weeks.

Outcome assessments

An annual census was conducted in each community. A random sample of 100 children aged 0–5 years (or all children if the community had fewer than 100 children) was examined biannually over the 36-month course of the study. Clinical examination for clinical signs of trachoma, including TF and TI, was performed according to the WHO simplified grading system by examiners who were trained and certified by experienced graders.[4] All graders underwent standardized training and passed an exam with a kappa>0.6 against a gold standard grader to be certified. To measure ocular chlamydia infection, we swabbed the everted right upper tarsal conjunctiva with a Dacron swab, collected without media. Swabs were placed on ice for <8 h while in the field and then stored in a −20°C freezer until being transported at 4°C to the University of California, San Francisco, and then stored at −80°C until they were processed. Swabs were pooled by community into pools of five plus a remainder pool. The pools were processed with Roche Amplicor PCR testing, and prevalence was estimated from the pools as previously described.[19] The sensitivity and specificity of the Amplicor assay has been shown to be high versus the quantitative Abbott m2000 assay and the Aptima assay in ocular samples.[20,21]

Statistical methods

Mean age and the proportion of female participants were compared across study time points with an analysis of variance (ANOVA) model. Community-level prevalence of TF, TI, and ocular chlamydia was calculated at each biannual data collection time point. Paired t-tests were used to calculate differences in infection, TF, and TI prevalence between baseline and 36 months. We calculated Pearson's correlation coefficients between community-level

ocular chlamydia prevalence and TF and TI separately. A locally estimated scatterplot smoothing (LOESS) curve was fitted to community-level prevalence for ocular chlamydia and TF and TI at each time point to graphically evaluate the relationship between the indicators. As a sensitivity analysis, we included both clinical signs TF and TI in a linear regression model predicting infection prevalence, analyzed at the community level. We considered correlation coefficients of 0.3 to 0.5 to be weakly correlated, 0.5 to 0.7 to be moderately correlated, and above 0.7 to be strongly correlated. All analyses were conducted in R version 3.4.3 (The R Foundation for Statistical Computing).

Results

Antibiotic coverage has been previously reported for the study communities and was over 80% at most time points.[14] At baseline, 2,212 children were evaluated for clinical signs of trachoma and ocular chlamydia infection. Approximately 2,000 children were evaluated at each time point (Table 1). There was no difference in age ($P = 0.34$) or sex ($P = 0.58$) distribution across study time points (Table 1). At baseline, among children aged 0–5 years, ocular chlamydia prevalence was 21.2% (95% CI 14.3–28.1%), TF prevalence was 27.7% (95% CI 21.2–34.2%), and TI prevalence was 8.3% (95% CI 5.2–11.5%). The prevalence of infection, TF, and TI decreased significantly from baseline to 36 months (infection: $P = 0.0002$, TF: $P < 0.0001$, TI: $P = 0.0002$; Figure 1). For ocular chlamydia infection, prevalence dropped significantly between the first treatment round and 6 months following treatment, but there was no significant difference in ocular chlamydia prevalence between 6 months and 36 months ($P = 0.44$). TF prevalence continued to reduce more slowly over time. TI prevalence followed a similar pattern to ocular chlamydia infection, with no difference in prevalence between 6 and 36 months ($P = 0.81$).

At baseline, community ocular chlamydia infection prevalence was strongly correlated with both TF prevalence (rho = 0.78, 95% CI 0.54–0.90, P < 0.0001, Figure 2a) and TI prevalence (rho = 0.76, 95% CI 0.52–0.89, P < 0.0001, Figure 3a). At months 12 and 24, after one and two rounds of mass azithromycin distribution, respectively, there was a weak correlation between ocular chlamydia infection prevalence and TF prevalence ($P = 0.006$ and $P = 0.07$, respectively; Figure 2b–c). At 36 months, ocular chlamydia infection and TF were moderately correlated (rho = 0.70, 95% CI 0.41–0.86, $P = 0.0002$; Figure 2d). After mass azithromycin distribution, ocular chlamydia infection prevalence and TI prevalence remained only weakly to moderately correlated at each time point (Figure 3b–d). Including both TF and TI in the same model did not qualitatively affect results.

Discussion

At baseline, both TF and TI were strongly correlated with ocular chlamydia infection prevalence at the community level. Indication for mass azithromycin distribution was based on district-level TF prevalence of 10% or higher at the time of the study. Previous work has demonstrated that TF overestimates ocular chlamydia infection following mass azithromycin distribution[10] and that TI correlates with infection after treatment.[12] Here, TF prevalence decreased more slowly over time than infection prevalence, which is consistent with previous evidence that clinical trachoma disappears more slowly than infection.[22] Infection

decreased substantially after the first distribution, but infection prevalence remained at approximately 5% for the remainder of the study, despite good antibiotic coverage, similar to other settings where infection prevalence has remained relatively stable at low levels despite ongoing treatment.[23] Transmission of ocular chlamydia infection may reach an equilibrium in the presence of annual azithromycin treatment, at which prevalence is decreased but stays at a low level over time. After a single treatment round, the correlation between infection and both TF and TI decreased substantially. At the individual level, active trachoma has been shown to poorly correlate with infection[7,10], presumably because infection clears more rapidly than active trachoma. Similar to previous reports[5], we demonstrate that the community prevalence of both TF and TI correlated well with infection prior to mass azithromycin distribution and that the correlated waned after antibiotic distribution. The correlation between ocular chlamydia and active disease may be better following mass azithromycin distribution in areas with less prevalent trachoma.

There are several reasons why the prevalence of TF and infection may correlate more poorly after mass azithromycin distribution. The prevalence of infection decreased much more quickly and then remained at a stable but low level in the presence of additional antibiotic distributions. TF prevalence decreased more slowly over time, and over this three-year study did not stabilize. Mass azithromycin distribution reduces bacterial load of *C. trachomatis*.[24] Some individuals with low bacterial loads may have an inflammatory response but infection is not detected, or inflammation may not reach the threshold for TF or TI. Previous studies have indicated that TI is associated with higher bacterial loads.[25] TI and infection have been shown to be highly correlated at the zonal level in a region of Ethiopia with similar infection prevalence among 1–5-year-old children.[12] In the present study, if TI was caused by inflammation due to another pathogen, the correlation between TI and infection may decrease over time if bacterial loads are decreasing. If TI is due to ocular chlamydia infection, the prevalence of TI would be expected to decrease as bacterial load decreases. The present study utilized a qualitative PCR assay, and future work with quantitative PCR may provide additional insights into the relationship between bacterial load and clinical signs of trachoma.

The results of this study must be interpreted in the context of several limitations. First, there was no untreated control group in this study. It is therefore difficult to disentangle any temporal trends in trachoma epidemiology from the effects of azithromycin distribution itself. It is possible that infection would reduce on its own in the absence of treatment, which in and of itself could affect the correlation between active trachoma and infection. This study included only children aged 0–5 years. Although young children are the most likely to be infection with ocular chlamydia[26–29], the correlation between active trachoma and infection may differ in other age groups. We did not have individual-level infection data to be able to assess correlations at the individual level or by age group. This study followed communities for three years. The current WHO recommendation includes three to five years of mass azithromycin distribution in districts meeting azithromycin distribution criteria. Longer term follow-up, including follow-up of districts until TF prevalence drops below the 5% threshold for discontinuing treatment, could further elucidate the relationship between ocular chlamydia infection and active trachoma.

The results of this study indicate that community prevalence of both TF and TI are good correlates of ocular chlamydia infection prior to mass azithromycin distribution. Thus, in similar mesoendemic settings, monitoring communities for indication for treatment via measurement of TF prevalence appears warranted. However, in this setting, the relationship between ocular chlamydia and active trachoma became more complicated after treatment, with community correlations generally decreasing over time. After up to two rounds of mass azithromycin distribution, both of the indicators TF and TI were weakly correlated with ocular chlamydia infection. Although previous studies have demonstrated strong correlations between TI and infection after mass azithromycin distribution, in this study TI did not appear to be a better indicator than TF at the community level in the presence of annual azithromycin distribution.

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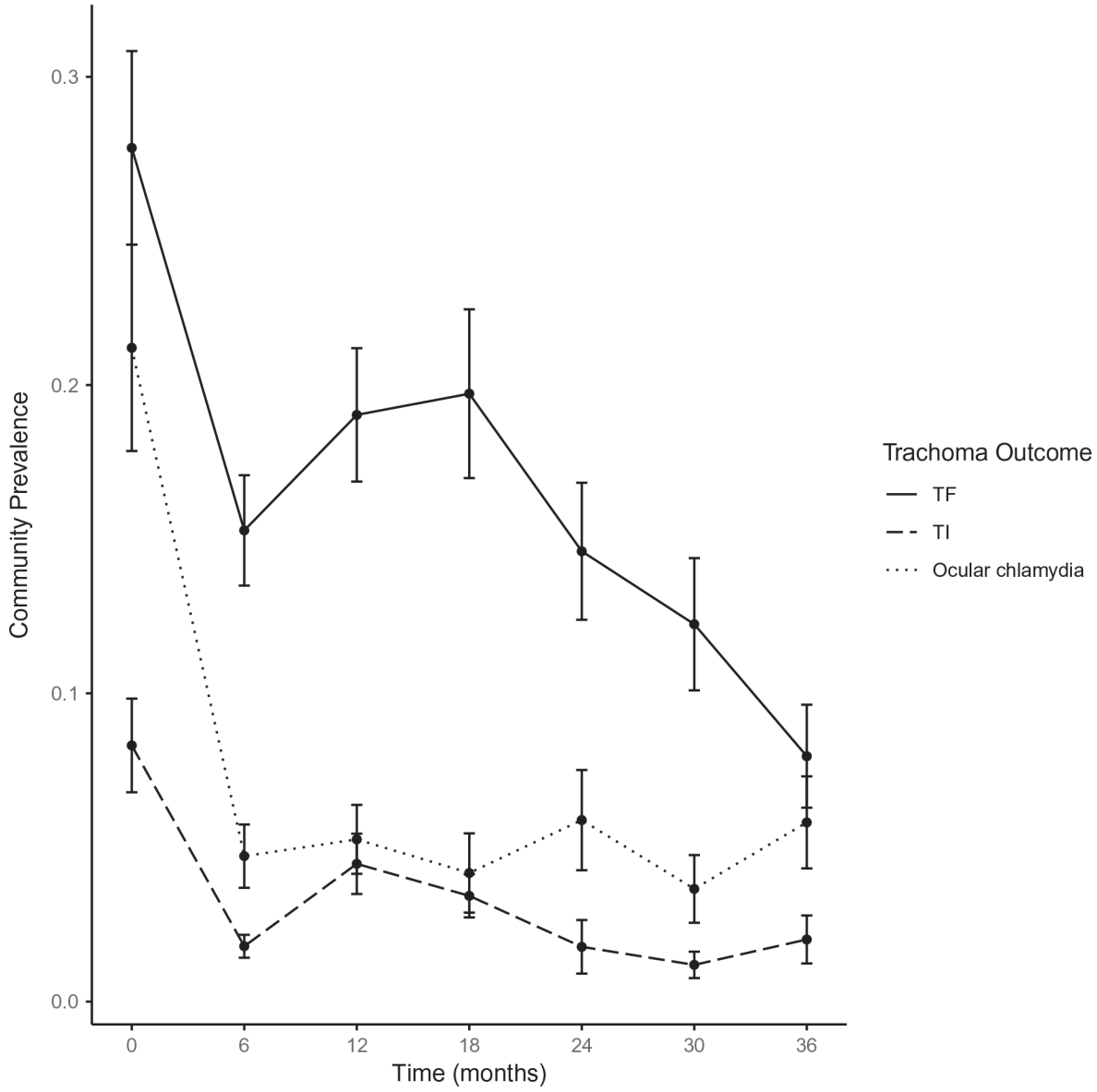

Figure 1.

Longitudinal prevalence of trachomatous inflammation-follicular, trachomatous inflammation-intense, and ocular chlamydia infection in 24 trachoma mesoendemic communities in Niger.

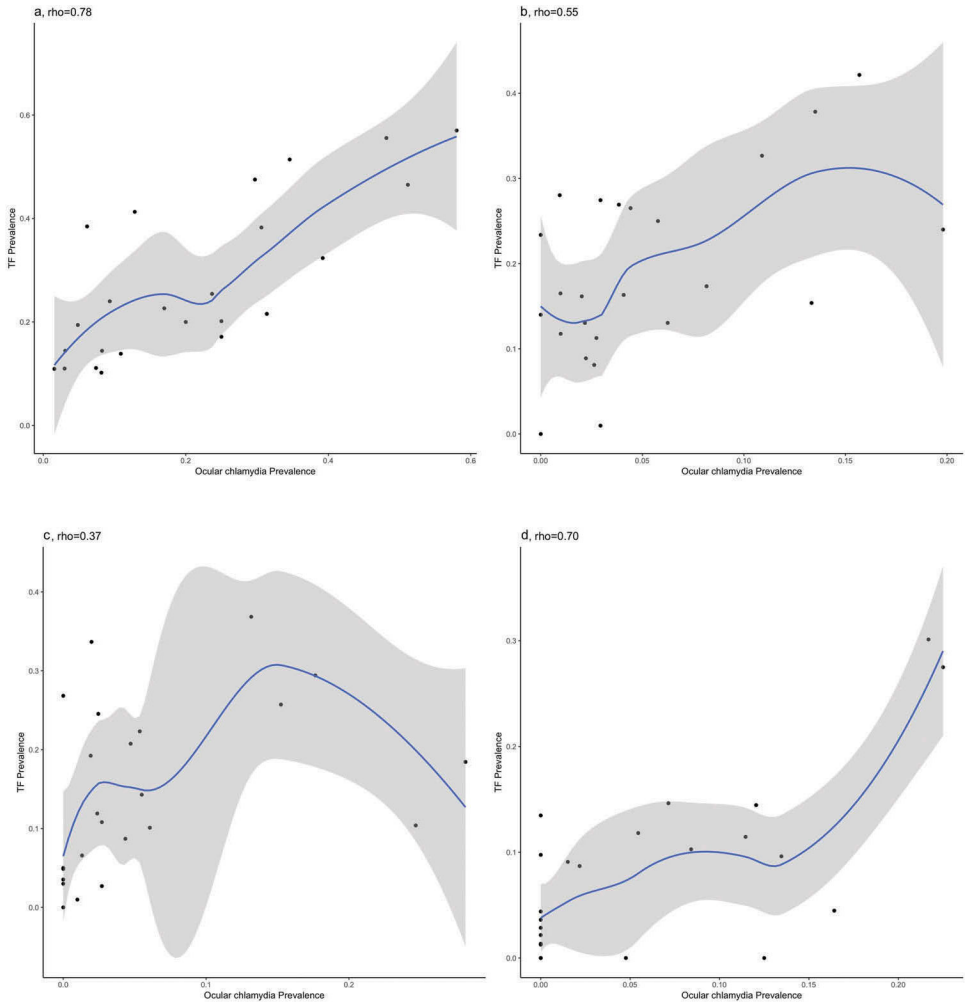

Figure 2.

Relationship between trachomatous inflammation-follicular (TF) and ocular chlamydia infection at Months 0 (a), 12 (b), 24 (c), and 36 (d). Blue lines indicate loess curves for relationship between TF and ocular chlamydia, and grey shading indicates 95% confidence intervals.

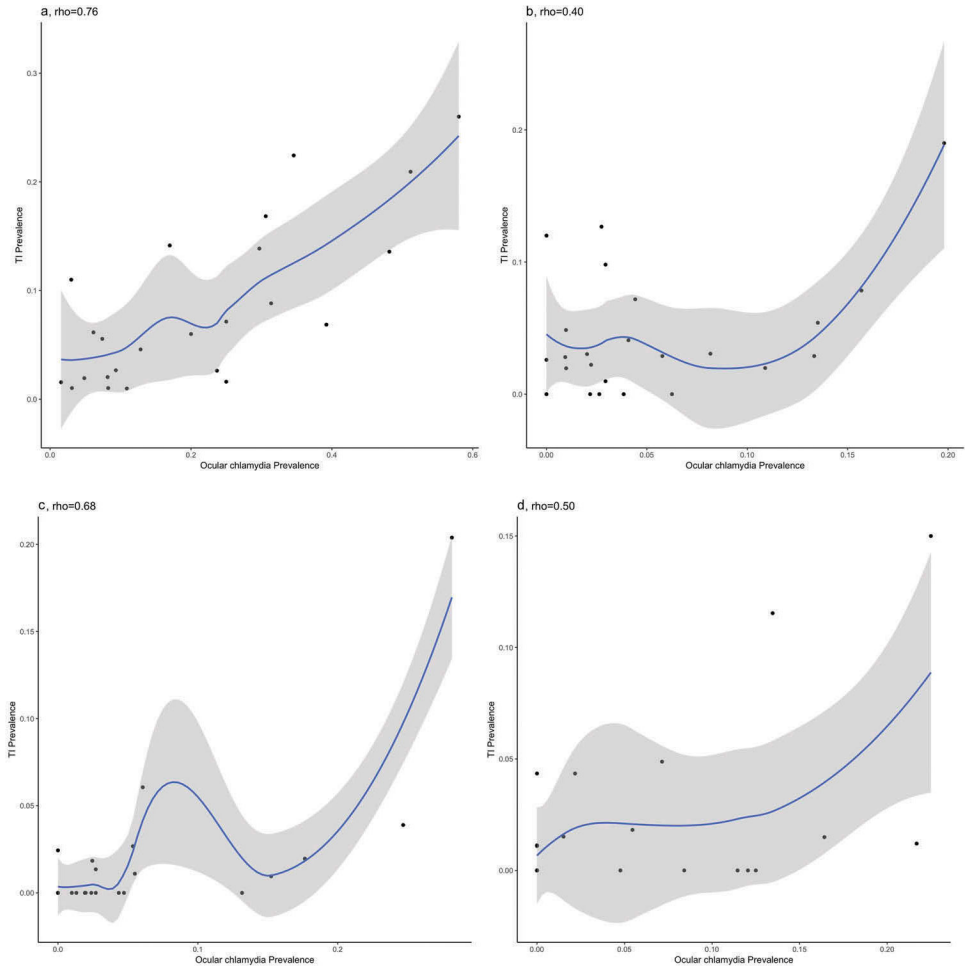

Figure 3.

Relationship between trachomatous inflammation-intense (TI) and ocular chlamydia infection at Months 0 (a), 12 (b), 24 (c), and 36 (d). Blue lines indicate loess curves for relationship between TI and ocular chlamydia, and grey shading indicates 95% confidence intervals.

Table 1.

Age and sex characteristics and longitudinal prevalence of trachomatous inflammation – follicular (TF), trachomatous inflammation – intense (TI) and ocular chlamydia infection in 24 communities in Niger receiving annual mass azithromycin distribution.

	Month 0	Month 12	Month 24	Month 36
No. children monitored	2212	2024	1973	1678
Age, years, mean (95% CI)	2.73 (2.66 to 2.80)	2.74 (2.68 to 2.81)	2.71 (2.62 to 2.80)	2.68 (2.54 to 2.81)
Proportion female (95% CI)	50.3% (48.6 to 52.0)	50.9% (48.5 to 53.4)	49.4% (47.4 to 51.4)	50.0% (47.7 to 52.2)
TF prevalence (95% CI)	27.7% (21.1 to 34.2)	19.0% (14.6 to 23.5)	14.6% (10.0 to 19.2)	8.0% (4.5 to 11.4)
TI prevalence (95% CI)	8.3% (5.2 to 11.5)	4.5% (2.4 to 6.5)	1.8% (0 to 3.6%)	2.0% (0.4 to 3.6%)
Ocular chlamydia prevalence (95% CI)	21.2% (14.3 to 28.1)	5.3% (2.9 to 7.6)	5.9% (2.5 to 9.3)	5.8% (2.7 to 8.9)