Do Infants Increase the Risk of Re-emergent Infection in Households after Mass Drug Administration for Trachoma?

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Purpose. Mass treatment with azithromycin for trachoma endemic communities typically excludes infants under age 6 months, whose parents are provided with tubes of tetracycline to administer daily over 4 to 6 weeks. The authors sought to determine whether infants aged <6 months are a source of re-emergent infection in their families after mass treatment in trachoma-endemic communities.

Methods. In a longitudinal study of all children aged less than 10 years in four communities, the authors identified 91 infants aged <6 months living in 86 of 1241 households. All children aged <ten years in all households were examined for trachoma and ocular infection with *C. trachomatis* at baseline, and 6 months after mass drug administration.

Results. The prevalence of infection at baseline in the infants was 5.9%. At 6 months post mass drug administration, the rate of infection among children older than 6 months and less than 10 years who resided in households with infants was 6.0% compared with 11.1% in children in households without infants ($P = 0.18$). After adjustment for age, sex, baseline infection status, and treatment, residing in a household with an infant was not associated with infection at 6 months (odds ratio [95% confidence interval] 0.50 [0.20–1.22]).

Conclusions. This prospective study did not find evidence that living in a household with an infant increased the risk of infection 6 months post mass drug administration in other children residing in the household. (*Invest Ophthalmol Vis Sci.* 2011;52:6040–6042) DOI:10.1167/iovs.11-7372

Trachoma, a chronic conjunctivitis caused by repeated reinfection with *C. trachomatis*, remains the leading infectious cause of blindness worldwide.[1] The World Health Organization (WHO) has endorsed SAFE (Surgery for trichiasis, Antibiotics for active trachoma, Facial hygiene and Environmental improvement to reduce transmission), a multi-faceted strategy for trachoma control in endemic areas. Where the prevalence of follicular trachoma (TF) is greater than 10% in children aged 1 to 9 years, WHO recommends mass drug administration (MDA) for everyone, preferably with azithromycin, a single dose antibiotic given annually and currently donated to countries in need by the manufacturer.

However, the use of azithromycin in children aged <6 months is not approved in many trachoma-endemic countries. Instead, parents of infants are provided with tubes of 1% topical tetracycline to be administered one to two times a day for 4 to 6 weeks. Research suggests that adherence to this protracted regimen of topical tetracycline is less than with a single dose of azithromycin.[2] In a study of a single village, some of the highest loads of infection were found in a few infants before mass treatment.[3] Thus, there is concern that these infants may be a source of re-emergent infection in trachoma-endemic communities after mass treatment.

Conversely, if infants are largely cared for by mothers they may have less exposure to infection from other children, and less opportunity to transmit infection, and thus they may not represent a major source of re-emergent infection. If so, the risk of significant re-emergent infection from the few infants that were infected post MDA could be very low. There are few data on infection and disease in this very young age group of infants, and we sought to investigate the role of infants as a source of re-emergent infection in trachoma-endemic communities after mass treatment.

In the context of a longitudinal cohort study of all children aged under 10 years in four communities undergoing mass treatment in Tanzania, we evaluated the impact of residing in a household with an infant aged <6 months on the risk of re-emergent infection after mass treatment. We hypothesized that children residing in households with infants aged <6 months at baseline would have higher rates of infection with *C. trachomatis* 6 months post MDA compared with children residing in households with no infants.

Methods

All infants and children from four communities located in the Kongwa District of central Tanzania were selected for the study. A household census was conducted in these communities in 2009. Children aged <10 years were identified and their parent or guardian was invited to have their child participate in a longitudinal study of trachoma and infection over a three-year period. When available, maternal and child health cards allowed for the determination of exact birth date. When unavailable, infants' ages were determined in reference to village events in the past year, categorized as likely aged 6 months and older, and likely aged 6 months and younger.

Detailed study methods on the ocular examination and specimen analysis are described elsewhere.[4] In summary, trained trachoma grad-

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Supported by the Bill and Melinda Gates Foundation. Pfizer provided azithromycin to Tanzania as part of their donation program. SKW received a Senior Scientific Investigator award from Research to Prevent Blindness. TCQ was supported by the Division of Intramural Research, NIAID.

Submitted for publication February 10, 2011; revised April 20, 2011; accepted April 21, 2011.

Disclosure: **S.K. West**, None; **D. Stare**, None; **H. Mkocha**, None; **B. Munoz**, None; **C. Gaydos**, None; **T.C. Quinn**, None

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TABLE 1. Prevalence of Trachoma and Infection Prior to Mass Drug Administration and Coverage with Azithromycin, by Age in Children in Kongwa, Tanzania

Age	*n*	% TF Alone	% TI with or without TF	% Infection	% Coverage with Azithromycin
<6 Mo	86	1.2	0.0	5.9	NA*
6–12 Mo	180	6.1	3.9	14.2	91.3
>1–2 Y	246	22.8	4.1	20.1	93.5
>2–3 Y	243	26.7	6.6	22.2	93.7
>3–5 Y	466	33.0	5.2	29.1	94.3
>5–9 Y	931	24.3	2.9	25.3	94.7

* Not applicable, as the children were offered topical tetracycline.

ers performed an ocular examination using 2.5× loupes and a torch to determine active trachoma. The trachoma graders were standardized during a 2 week training exercise before the start of the study. Inter-observer agreement, and agreement with a senior grader had to be above kappa = 0.6 for TF and inflammatory trachoma (TI). Graders are monitored every 6 months by comparison of grades against the senior grader using a series of trachoma images.[4] Active trachoma was graded using the World Health Organization simple grading scheme.[5]

An eyelid-conjunctival swab was obtained to assess infection with *C. trachomatis*. These swabs were taken using strict protocols to avoid contamination. Both the trachoma grader and eyelid flipper used gloves and changed them between each child examined. In addition, "air control" swabs were taken on a random sample of 5% of children. The swabs were waved in the air above the child but do not touch anything, marked as per any other sample, and sent for processing. If positive, further investigations were carried out to determine the source of contamination. The samples were kept at −20°C until they were sent to the International Chlamydia Laboratory at Johns Hopkins University for processing. The samples were analyzed using polymerase chain reaction (Amplicor; Roche Molecular Systems, Indianapolis, IN) according to manufacturer's directions. Optical density was used to identify positive results and defined as >0.7. Optical densities between 0.2 and 0.7 were considered equivocal and were retested. Results of these "air control" swabs showed some evidence of laboratory contamination that affected 34 samples at baseline. These contaminated samples were excluded; all further tests for contamination were negative at baseline and follow-up.

At the time of MDA, parents of infants aged <6 months were provided with tubes of 1% topical tetracycline with instruction to administer 1 to 2 times a day for 6 weeks. Children aged greater than 6 months were given a single dose of azithromycin (20 mg/kg up to 1 g). Community treatment assistants directly observed treatment with azithromycin; however, compliance with topical tetracycline was not monitored. Children and infants were re-evaluated at 6 months for the presence of active trachoma and *C. trachomatis*.

The association between infection in children at 6 months and presence of infants in the house was examined using a logistic model with infection as the outcome and presence of infants in the house as the predictor; the model accounted for the clustering of infection within children residents of the same household. An expanded model of infection was used to examine the independent contribution of age, sex, baseline chlamydial infection, and treatment at baseline, as well as presence of infants in the household. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented where the generalized estimating equation (GEE) approach was used to correct the standard errors to account for the correlation among members of the same house, using the procedure GENMOD in SAS (Cary, NC) with binomial distribution, logit link function, and exchangeable correlation structure.

Written informed consent was obtained at the time of examination from all parents or guardians of children in the study. All procedures for the study were approved by the Johns Hopkins University Institutional Review Board (JHU IRB) and the National Institute of Medical Research (NIMR) in Tanzania and conducted in accordance with the Declaration of Helsinki.

TABLE 2. Prevalence of Active Trachoma by Infection Status, Stratified by Age of Children

Age Group	Infection Status	*n*	% TF and/or TI
<6 Mo	Yes	5	20.0
	No	80	0.0
6–12 Mo	Yes	25	36.0
	No	151	4.6
>1–2 Y	Yes	48	56.3
	No	191	19.4
>2–3 Y	Yes	53	66.0
	No	186	24.7
>3–5 Y	Yes	132	72.0
	No	322	24.5
>5–9 Y	Yes	236	64.0
	No	689	14.4

RESULTS

Of the 1241 households identified in the four communities, a total of 91 infants aged <6 months were found to reside in 86 (7%) of households. Of the total, 81.3% of infants lived with other children aged <10 years. Baseline examinations were conducted on 93% of the infants, and 94% of all children aged >6 months and <10 years. Precise birth date information was available for 80/91 (88%) of the infants.

At baseline, the prevalence of chlamydia infection in infants was 5.9% and 1.2% had follicular trachoma (Table 1). The prevalence of infection and active trachoma was lower in infants than in older children. The prevalence of TF in those less than 3 months of age was 1.8% (1/55) compared with 0% (0/31) in those 3 to 6 months (Fisher's exact test $P = 1.0$).

With increasing age, the likelihood of signs of trachoma lingering after infection was gone also increased (Table 2). In children aged <1 year, clinical signs were highly associated with infection.

Of the 91 infants in the census at baseline, seven were not seen during MDA and thus were not provided with topical tetracycline. Of those seven, six infants were found to be not infected at baseline and one had an unknown infection status.

TABLE 3. Prevalence of Infection at Six Months Post Mass Treatment by Residence in a Household with an Infant

Lives in a Household with an Infant Aged <6 Mo	*n*	Six-Month Prevalence of Infection (%)	*P**
Yes	133	6.0	0.18
No	1780	11.1	

Table data excludes the infant.
* Adjusted for household clustering.

Table 4. Risk Factors for Infection at 6 Months Post Mass Treatment among Children Aged <10 Years

Factor	OR	95% CI*
Baseline infection		
No	1.00	
Yes	3.60	2.51–4.93
Lives in house with infant		
No	1.00	
Yes	0.50	0.20–1.22
Treated at baseline		
No	1.00	
Yes	0.44	0.24–0.85

* Adjusted for age, sex, and clustering at household level.

Mass drug administation (MDA) coverage of children older than 6 months with azithromycin was overall very high and averaged 94%.

Six months post mass treatment, 82 of the 91 infants were examined and two (1.2%) were found to be infected (both were negative for infection at baseline). None of the infants with infection at baseline had infection at 6 months (data not shown). The prevalence of infection among children aged <10 years who resided in households with infants was 6.0% compared with 11.1% for children who resided in households without infants ($P = 0.18$; Table 3). In fact, contrary to our hypothesis, when controlling for age, sex, treatment status, and baseline infection status, children residing in a household with an infant had a reduced, but not statistically significant, risk of infection at 6 months [odds ratio [95% confidence interval] 0.50 [0.20–1.22]; Table 4).

Discussion

This prospective study found no evidence to indicate that children living in a household with an infant had an increased risk of infection 6 months post MDA. None of the infants infected at baseline were found to have infection at 6 months post MDA, suggesting that not only had the infection cleared (either with treatment or on its own), but that the infants had largely not become re-infected.

It is possible that compliance with topical tetracycline in the infants was better than expected. We did not monitor compliance with topical treatment to confirm compliance, which we did for azithromycin. Coverage with azithromycin was very high, and was likely instrumental in preventing cross infection of the infants up to 6 months. Other studies have reported topical tetracycline to be equally effective as oral azithromycin in decreasing infection when compliance is high.[6]

We have shown that treatment with azithromycin decreases the load of infection, but if the load of infection pretreatment is high, eliminating infection with a single dose is less likely.[7] We did not measure the load of infection in these infants, but we would not expect the load of infection pre-MDA to be lower than observed elsewhere. Thus, if the infants had high organism loads, as reported in other studies,[3] and topical tetracycline was not as effective in such cases, the infants would be a risk to other children in the households. Our finding of no increased risk suggests that topical tetracycline may have been adequate treatment and/or infants are not a significant source of infection for older children in the family.

Only one infant <6 months old presented at baseline with follicular trachoma. The infection rate was higher, 6%, suggesting most children in this age group still cannot mount a clinical response to infection. Few children aged <1 year had clinical signs of trachoma that were not associated with infection, as contrasted with older children whose follicular response tends to linger. The fact that 6% of infants <6 months old had infection indicates how early in life exposure to *C. trachomatis* may occur. Consequently, researchers working on a chlamydia vaccine ought to give consideration toward the provision of protection at an early age to those in trachoma-endemic communities.

In summary, our data suggest that the topical alternative for infants, in a setting of high compliance with azithromycin during MDA, did not leave a reservoir of infection that resulted in risk of infection in other children in the families. High coverage with MDA in trachoma-endemic areas is critical in reducing the burden of infection and trachoma, and may provide protection against new acquisition of infection in infants.

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