Cohort and Age Effects of Mass Drug Administration on Prevalence of Trachoma: A Longitudinal Study in Rural Tanzania

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PURPOSE. Mass drug administration (MDA) is part of the SAFE strategy for trachoma elimination. This study examined the effect of three annual MDAs on prevalence of trachoma among 13 longitudinal cohorts of Tanzanian children.

METHODS. Children younger than 10 years were assigned to cohorts based on age at baseline and followed annually for 3 years, with newborns assigned to new cohorts over time. Annual MDA consisted of topical tetracycline for children younger than 6 months and oral azithromycin for those 6 months and older. Follicular trachoma (TF) and *Chlamydia trachomatis* infection status were assessed annually before the next MDA. Prevalence and risk factors for TF and infection at each age were compared across cohorts.

RESULTS. At each survey, most age groups and cohorts had MDA coverage of more than 80% and showed decreased TF prevalence after every MDA. One cohort had consistently lower coverage, higher-than-expected TF and infection at ages 6 and 7, and elevated risk of TF at age 7 relative to the preceding cohort in spite of receiving one additional MDA (odds ratio 2.3, 95% confidence interval 1.0–5.2). Cohorts aged 1 or older at baseline generally showed reductions in TF and infection after each MDA, whereas younger cohorts showed decreased infection but increased TF over time. Successive cohorts of never-treated children younger than 1 year showed sequential TF and infection reductions with each MDA ($P < 0.001$).

CONCLUSIONS. Multiple MDAs significantly reduce trachoma prevalence and appear to increasingly protect children born into these communities. The youngest children show declining/stable rates of infection but increasing rates of trachoma, which may reflect longer duration of clinical signs.

Keywords: trachoma, mass drug administration (MDA), Tanzania, cohort study, population-based study

Trachoma is the leading infectious cause of preventable blindness in the world, with an estimated 110 million individuals residing in districts known to be endemic for trachoma. Children are the primary reservoir of infection, and most cases occur among impoverished children in rural sub-Saharan Africa.¹ To eliminate blinding trachoma by 2020, the World Health Organization (WHO) advocates the SAFE strategy, involving surgery for trichiasis, antibiotics to reduce the community pool of *Chlamydia trachomatis*, facial cleanliness, and environmental changes to reduce transmission.² For communities with more than 10% prevalence of follicular trachoma (TF) among children younger than 10 years, WHO recommends mass drug administration (MDA) with azithromycin.

Although it may be possible to eliminate trachoma in villages with low prevalence, other data suggest multiple rounds of MDA over many years are required to achieve WHO

targets of less than 5% prevalence in hyperendemic villages.³ In a study of 71 Tanzanian communities, 3 years of MDA further decreased prevalence of trachoma in a linear fashion. MDA decreased the prevalence of infection with *C. trachomatis* in a nonlinear fashion, with stabilization of infection prevalence after five rounds of MDA. Mathematical models suggest that if coverage is not more than 80%, hyperendemic communities will require more than 7 years of annual MDA to reach trachoma prevalence of less than 5%.⁴ Risk factors for reinfection 6 months after MDA include infection at baseline, age of 2 to 4 years, increased number of baseline-infected children in the household, and increased number of untreated children in the household.⁵

There are well-known age-dependent variations in prevalence of trachoma, with active trachoma declining in teenage and adult years. Constant severe trachoma and constant reinfection with *C. trachomatis* are independently associated

with increased risk of ocular scarring in children. Scarring prevalence increases with age, as do the blinding sequelae of trichiasis and corneal opacity.⁶ Thus, there are variations in risk of trachoma, reinfection, and scarring that are seen across ages and seem to persist among individuals of the same age across time. However, there may be other factors, such as MDA, that affect age cohorts' risks of trachoma over time. More detailed characterization of such cohort effects is needed, especially in the context of repeat MDAs.

This was a 3-year longitudinal study of the effects of three repeat MDAs on cross-sectional prevalence of TF and *C. trachomatis* infection among different birth cohorts of children living in four rural Tanzanian villages. This study aimed to compare data from different age and exposure cohorts and determine whether cohorts undergoing MDA starting at younger ages have different prevalence of and risk factors for trachoma and infection than cohorts beginning MDA at older ages. In addition, this study aimed to determine whether different age groups respond similarly to repeated rounds of MDA and whether multiple rounds of MDA can reduce prevalence enough to induce protective herd effects.

METHODS

Study Population

The study was conducted in the context of the Partnership for the Rapid Elimination of Trachoma (PRET) clinical trial, described extensively elsewhere.⁷ Of the 32 communities selected to be part of the trial, we randomly selected 4 communities to enroll all children younger than 10 years. We followed all children, whether enrolled at baseline or newly arrived in the village, over the course of 3 years and three rounds of MDA.

Annual Visits

Annual visits occurred at baseline, and 2, 3, and 4 years. Each annual visit consisted of a census, a trachoma survey, and MDA. The baseline census enrolled all children younger than 10 years, whereas three follow-up censuses enrolled newcomers who were born into or had migrated to the community since the previous census.

The survey methods have been described in detail elsewhere.⁷ The baseline trachoma survey ascertained children's trachoma status, obtained conjunctival swabs for determination of *C. trachomatis* infection status, and collected information on known trachoma risk factors at the individual level (age, sex) and the household level (presence of a household latrine, distance to primary water source, years of education completed by the head of household). Three follow-up trachoma surveys ascertained children's trachoma status and obtained conjunctival swabs. Follow-up trachoma surveys also collected data on newcomers who had been identified in that year's census.

Clinical trachoma status was classified using the WHO simplified grading scheme,⁸ with TF defined as five or more follicles of size 0.5 mm on an everted upper eyelid. Trachoma assessment was monitored over time using field photographs, with at least 50 photographs taken per grader per visit. Photographs were graded after each survey by a senior grader masked to the field grades and to the grades of the images by the field graders. Agreement between senior grader and field graders was always above 0.7 Cohen's κ for active trachoma signs. Conjunctival swabs were collected from the left upper eyelid of each child. A Dacron swab

(Fisher HealthCare, Houston, TX, USA) was rotated and swiped across the upper conjunctiva three times and placed dry in a vial. Vials were placed in a cooler in the field, transferred to a refrigerator at the end of the day, and temporarily stored there until shipped within 30 days of collection to the International Chlamydia Laboratory at Johns Hopkins University. All ocular specimens were processed for detection of *C. trachomatis* in the laboratory using the AMPLICOR CT/NG test (Roche Molecular Diagnostics, Indianapolis, IN, USA) according to the manufacturer's specifications. Each ocular swab was eluted by vortexing in lysis buffer in polypropylene tubes, after which diluent was added. Using a known positive sample, two positive and two negative processing controls were run with each batch of specimens. After the hybridization reaction, the optical density (OD) for each specimen was measured. Samples with ODs of 0.8 or greater were recorded as positive for *C. trachomatis* and evidence for infection, samples with ODs of less than 0.2 were recorded as negative, and samples with ODs between 0.2 and 0.7 were considered equivocal. Samples with equivocal results were retested in duplicate; samples that retested equivocal or repeated as negative on two occasions were considered negative. Fewer than 0.1% of specimens were equivocal.

Within 2 weeks of the trachoma survey, all residents of the community were invited to participate in MDA. Children 6 months of age or older received a single dose of oral azithromycin (20 mg/kg up to 1 g), whereas guardians of children younger than 6 months were offered topical tetracycline ointment to be applied to children's eyelids twice a day for 6 weeks. By the end of the study, children had undergone four censuses, four trachoma surveys, and three rounds of MDA. All procedures and protocols were reviewed and approved by the Johns Hopkins Institutional Review Board and the National Institute for Medical Research in Tanzania. Written, informed consent was obtained from the guardians of all children.

Statistical Analysis

Children were assigned to 1 of 13 birth cohorts according to the age at which they were first eligible to receive MDA (Table 1). Migrants were incorporated into preexisting cohorts based on age, whereas newborns were assigned to new birth cohorts every year. Analyses were performed using Stata Version 12 (StataCorp, College Station, TX, USA). Differences in risk factors across cohorts at each visit were assessed using Pearson's chi-squared test for categorical variables and a test of trend for ordinal variables. Cross-sectional prevalence of TF and *C. trachomatis* infection were calculated for each cohort at each visit. Changes in prevalence over time were assessed for significance using a test of trend.

Cohort effect was assessed using multiple logistic regression modeling. Univariate logistic regression was used to identify potential individual- and household-level risk factors for TF or infection at each age. Multivariable logistic regression adjusting for these risk factors and accounting for clustering within households was used to determine independent predictors of TF or infection at each age. To examine cohort effects and rule out age effects, we compared a given cohort at a particular age with an older or younger cohort observed at the same age.

To rule out the effect of differences that might result from using topical tetracycline versus azithromycin in children younger than 1 year, we compared differences in cross-sectional prevalence across these two treatment groups at age 2.

TABLE 1. Cohort Assignments From 1 to 13 Based on Age and Study Visit

	Baseline	Visit 2	Visit 3	Visit 4
Age <1 y	10	11	12	13
Age 1 y	9	10	11	12
Age 2 y	8	9	10	11
Age 3 y	7	8	9	10
Age 4 y	6	7	8	9
Age 5 y	5	6	7	8
Age 6 y	4	5	6	7
Age 7 y	3	4	5	6
Age 8 y	2	3	4	5
Age 9 y	1	2	3	4

RESULTS

Baseline Characteristics

A total of 3823 children were enrolled in the study across four annual surveys, with annual enrollment ranging from a high of 2059 children at the third survey to a low of 2082 children at

the fourth survey (Table 2). There was no significant difference in terms of sex ($P = 0.40$), presence of household latrine ($P = 0.89$), distance to primary water source ($P = 0.76$), or number of years of education of the head of household ($P = 0.79$) across the cohorts. Antibiotic coverage was consistently 85% or more for all rounds of MDA and nearly all cohorts. Birth cohort 5 (aged 5 years old at the baseline visit) had consistently lower antibiotic coverage for all three MDAs (73%, 69%, and 70%, $P < 0.01$ for each MDA) and across all four communities.

Newly immigrated children comprised 7% to 12% of the study population at follow-up surveys (Table 2). Comparing children who were migrants to nonmigrants, there were no significant differences in terms of sex ($P = 0.25$) or presence of household latrine ($P = 0.10$) (Table 3). Among migrants, households were closer to their primary water source ($P < 0.01$), heads of households were more educated ($P < 0.01$), and children were more likely to belong to village 1501 ($P < 0.01$). At each visit, antibiotic coverage was similar between nonmigrants and new migrants, with 89% coverage among nonmigrants and 90% among migrants at the second round of MDA ($P = 0.92$), and 88% coverage among nonmigrants and 86% among migrants at the third round of MDA ($P = 0.41$) (Table 4).

TABLE 2. Baseline Characteristics of Study Population, Overall and by Cohort

	Cohort*													Overall†	P‡
	1	2	3	4	5	6	7	8	9	10	11	12	13		
<i>n</i>															
Visit 1	141	181	183	188	235	226	231	243	246	265	—	—	—	2139	
Visit 2	—	185	176	180	228	229	234	229	248	277	239	—	—	2225	
Visit 3	—	—	164	177	217	232	229	224	252	291	273	234	—	2059	
Visit 4	—	—	—	158	210	221	227	214	248	279	274	251	197	2082	
Village, %															
0301	22	25	21	20	29	20	24	22	28	19	24	22	26	23	0.52
0501	35	38	32	35	30	35	34	33	33	35	32	36	32	34	
1302	20	18	21	23	17	18	18	21	17	18	16	18	16	18	
1501	23	19	26	22	24	26	23	24	23	28	28	25	25	25	
Sex, %															
Male	47	45	51	52	48	53	46	46	53	46	50	53	53	49	0.40
Female	53	55	49	48	52	47	54	54	47	54	50	47	47	51	
New migrants, %															
Visit 2	—	10	7	10	8	12	11	11	12	15	—	—	—	11	<0.01
Visit 3	—	—	6	9	11	12	10	13	15	12	18	—	—	12	<0.01
Visit 4	—	—	—	3	7	5	7	6	9	5	10	13	—	7	<0.01
Antibiotic coverage, %															
Visit 1	95	95	94	96	73	94	94	93	93	91	—	—	—	91	<0.01
Visit 2	—	89	94	91	69	91	88	89	89	88	91	—	—	88	<0.01
Visit 3	—	—	89	86	70	87	88	85	87	92	86	91	—	87	<0.01
Household latrine, %	65	65	70	62	67	69	67	66	69	66	66	65	64	67	0.89
Distance to water, %															
<60 min	25	27	28	32	33	32	32	32	30	32	33	34	34	31	0.76
>60 min	75	73	72	68	67	68	68	68	70	68	67	66	66	69	
Years of education, %															
0–5	53	58	55	60	58	58	58	59	61	59	56	61	63	59	0.79
5–10	45	37	41	38	40	38	39	38	37	38	41	37	36	39	
>10	3	5	4	2	2	3	3	3	2	3	3	2	1	3	

* Columns may not add up to 100% due to rounding.

† “Overall” refers to row sum (*n*) for number of children per visit and population-weighted row average (%) for all other variables.

‡ *P* values calculated using Pearson's χ^2 test for categorical variables (village, sex, migrant status, antibiotic coverage, household latrine, distance to water) and test of trend for ordinal variables (years of education of head of household).

TABLE 3. Risk Factors Among Nonmigrant Versus Ever-Migrant Children

	Migrant Status		<i>P</i> *
	Never-Migrants, <i>n</i> = 2932	Ever-Migrants, <i>n</i> = 891	
Sex, <i>n</i> , %			
Male	1457, 50	423, 47	0.25
Female	1475, 50	468, 53	
Village, %			
0301	708, 24	183, 22	<0.01
0501	1032, 35	252, 21	
1302	526, 18	180, 27	
1501	666, 23	276, 31	
Household latrine, <i>n</i> , %			
Yes	1961, 67	528, 64	0.10
No	965, 33	294, 36	
Distance to water, min, %			
<60	784, 27	395, 48	<0.01
>60	2141, 73	432, 52	
Years of education, <i>n</i> , %			
0–5	1748, 60	489, 55	<0.01
6–10	1156, 39	327, 37	
>10	28, 1	75, 8	

* *P* values calculated using Pearson's χ^2 test for categorical variables (sex, village, antibiotic coverage, household latrine, distance to water) and test of trend for ordinal variables (years of education of head of household).

Prevalence of TF and Infection

Overall TF prevalence declined after each round of MDA, from 27.3% at baseline to 15.8%, 11.1%, and 9.4% at the second, third, and fourth visits, respectively ($P < 0.01$, test of trend). Age-specific TF prevalence declined with each round, meaning that later cohorts generally had lower age-specific TF prevalence than earlier cohorts at the same age, reflecting the impact of MDA. One exception was children who were 7 years old at the third visit and 8 years old at the fourth visit (cohort 5), who had higher prevalence than children who were that age at the previous visit (cohort 4) (Fig. 1). Another exception was the youngest age cohorts. Although cohort-specific prevalence of TF declined with each round of MDA among cohorts of children aged 1 or older at time of baseline survey (cohorts 1 to 9), it consistently increased among cohorts of children younger than 1 at baseline or born in subsequent years (cohorts 10 to 12).

The differences in cohort 5 relative to other cohorts, as well as the youngest age cohorts relative to older age cohorts, were further explored by examining data on ocular *C. trachomatis* infection. Overall infection prevalence declined after each round of MDA, as was observed for TF. Younger cohorts generally had lower age-specific infection prevalence than older cohorts, likely reflecting MDA, but cohort 5 had higher than expected infection prevalence at age 7 (Fig. 2).

Successive cohorts of children younger than 1 year old had progressively lower rates of TF ($P < 0.01$) and infection ($P < 0.01$). At the baseline visit, cohort 10 had TF prevalence of 6.4% and infection prevalence of 11.5%. After three rounds of MDA in the community, cohort 13 had no evidence of TF or infection.

TABLE 4. Antibiotic Coverage Among Nonmigrants Versus Newly Migrated Children at Each Visit

Antibiotic Coverage,† <i>n</i> , %	Nonmigrants	New Migrants	<i>P</i> *
Visit 1	2056, 93	—	—
Visit 2	2021, 89	234, 90	0.92
Visit 3	2040, 88	252, 86	0.41

* *P* values calculated using Pearson's χ^2 test.

† Visit 1 (baseline) had 2204 nonmigrants and no new migrants. Visit 2 had 2259 nonmigrants and 261 new migrants. Visit 3 had 2319 nonmigrants and 292 new migrants.

Risk Factor Analysis

Risk factors for TF and infection at each of nine ages were investigated. Univariate logistic regression showed that the child's cohort identity, antibiotic coverage at the previous annual visit, and presence of TF or infection at the previous annual visit were significant risk factors for TF or infection at each age. Multivariable logistic regression incorporating the above risk factors was performed for each of nine ages. Because analysis for each age involved data from three cohorts, the comparison group used was the cohort that had received the most rounds of MDA by that age (i.e., the youngest cohort). Separate analyses were conducted for outcomes of TF at each age (Table 5) and infection at each age (Table 6).

Belonging to a cohort exposed to fewer rounds of MDA (i.e., an older cohort) was a significant, independent predictor of infection at age 3 (odds ratio [OR] 3.4, 95% confidence interval [CI] 1.7–6.8), age 4 (OR 2.1, 95% CI 1.1–4.2), and age 6 (OR 2.8, 95% CI 1.3–6.2), as well as a nonsignificant predictor of infection at age 5 (OR 1.5, 95% CI 0.8–3.1) and age 8 (OR 2.4, 95% CI 0.9–6.0) (Table 6). Age 7 had a different pattern due to cohort 5. At age 7, belonging to cohort 5 was a greater risk factor for infection (OR 1.8, 95% CI 0.9–3.6) than belonging to cohort 4 (OR 1.1, 95% CI 0.5–2.6), even though cohort 4 had received fewer rounds of MDA by the same age. A similar result was obtained for TF at age 7 (Table 5).

To directly compare cohort 4 against cohort 5, risk factors for TF and infection at age 7 were reexamined using cohort 4 (i.e., the oldest cohort) as the comparison group (Table 7). Relative to cohort 4, belonging to cohort 5 was a significant risk factor for TF at age 7 (OR 2.3, 95% CI 1.0–5.2, $P = 0.05$) and was associated with a nonsignificant but elevated risk for infection at age 7 (OR 1.6, 95% CI 0.8–3.2, $P = 0.22$) even though cohort 5 had received one more round of MDA than cohort 4 by that age.

Among cohorts 10, 11, and 12, belonging to the oldest cohort (cohort 10) was a significant, independent risk factor for TF at age 1 year, even after adjusting for antibiotic coverage at younger than 1 year and diagnosis of TF at younger than 1 year (OR 2.1, 95% CI 1.1–3.9) (Table 5).

Azithromycin Versus Tetracycline

Cohorts 10, 11, and 12 comprised children who were younger than 1 year at the time of their first MDA, meaning they were eligible to receive either azithromycin if they were 6 months of age or older or tetracycline if they were younger than 6 months. These children's initial infection and trachoma data were collected before their first MDA, reflecting their pretreatment prevalence. Data from cohorts 10, 11, and 12 showed that children receiving azithromycin had higher pretreatment TF prevalence than those receiving tetracycline (26/449 [5.8%] azithromycin versus 2/228 [0.9%] tetracycline,

FIGURE 1. Cohort-specific prevalence of TF.

$P < 0.01$), an expected finding, as children receiving azithromycin (age 6 to < 12 months) were older than children receiving tetracycline (age < 6 months).

After receiving their first MDA with either azithromycin or tetracycline at age younger than 1 year, children from cohorts 10, 11, and 12 were reassessed 1 year later for TF and infection at age 1 year. After receiving their second MDA with azithromycin at age 1 year, they were reassessed 1 year later for TF and infection at age 2 years. Therefore by age 2 years, these children had received their first MDA with either tetracycline or azithromycin, as well as a second MDA with azithromycin alone. Data from cohorts 10 and 11 showed that by age 2 years, when all children had received azithromycin as part of their second MDA, the TF prevalence among children who had initially received azithromycin was nearly equal to TF

prevalence among children who had initially received tetracycline (38/263 [14.5%] azithromycin versus 24/151 [15.9%] tetracycline, $P = 0.34$). Infection prevalence at age 2 was also similar (17/263 [6.5%] azithromycin versus 10/151 [6.6%] tetracycline, $P = 0.95$).

DISCUSSION

Overall

MDA reduced prevalence of TF in all four communities ($P < 0.01$), with dramatic reductions after the initial round of MDA and smaller reductions with subsequent rounds of MDA. However, after three rounds of MDA, only 3 of 13 cohorts had achieved TF prevalence below 5% and only 3 of 13 cohorts had

FIGURE 2. Cohort-specific prevalence of *C. trachomatis* infection.

TABLE 5. Risk Factors for Follicular Trachoma at Each Age

	Age 1	Age 2	Age 3	Age 4	Age 5	Age 6	Age 7	Age 8	Age 9
Antibiotic	0.9, 0.3–2.4	1.1, 0.5–2.5	4.4, 1.0–20.0	2.4, 0.5–10.4	0.6, 0.2–1.9	0.7, 0.2–2.5	4.6, 0.6–34.0	0.6, 0.2–1.9	0.2, 0.0–1.6
Prior TF	7.7, 3.1–18.9	5.5, 3.4–9.0	8.8, 5.4–14.3	10.4, 6.5–16.7	9.3, 5.4–16.0	13.7, 7.0–26.5	9.3, 4.7–18.2	3.9, 1.9–8.1	13.0, 4.3–39.0
Cohort 2	—	—	—	—	—	—	—	—	3.0, 0.7–12.2
Cohort 3	—	—	—	—	—	—	—	1.5, 0.7–3.1	0.6, 0.1–3.7
Cohort 4	—	—	—	—	—	—	0.8, 0.3–2.0	0.7, 0.3–1.8	REF
Cohort 5	—	—	—	—	—	1.1, 0.5–2.2	1.8, 0.9–3.8	REF	—
Cohort 6	—	—	—	—	1.3, 0.7–2.5	0.7, 0.3–1.6	REF	—	—
Cohort 7	—	—	—	1.2, 0.7–2.2	1.4, 0.7–2.6	REF	—	—	—
Cohort 8	—	—	1.3, 0.7–2.3	1.4, 0.8–2.6	REF	—	—	—	—
Cohort 9	—	1.0, 0.6–1.7	0.9, 0.5–1.5	REF	—	—	—	—	—
Cohort 10	2.1, 1.1–3.9	1.0, 0.6–1.7	REF	—	—	—	—	—	—
Cohort 11	1.7, 0.8–3.7	REF	—	—	—	—	—	—	—
Cohort 12	REF	—	—	—	—	—	—	—	—

C. trachomatis infection prevalence below 5%. For these four communities, it seems that more than three rounds of MDA will be needed to reduce trachoma prevalence to below 5%.

Cohort Effects

A cohort effect was most apparent in cohort 5, which had consistently low antibiotic coverage and exhibited TF and *C. trachomatis* infection prevalence higher than that of the preceding cohort at the same age, even though the preceding cohort had received fewer rounds of MDA at that age. Even after adjusting for treatment status and prior diagnosis, members of cohort 5 were more than twice as likely to have TF at age 7 relative to members of cohort 4 (adjusted OR 2.3, 95% CI 1.0–5.2, $P = 0.05$) even though cohort 4 had received one fewer round of MDA by age 7. Similar but nonsignificant results were obtained for infection at age 7 (adjusted OR 1.6, 95% CI 0.8–3.2, $P = 0.22$). The reasons for this cohort effect are not obvious and not entirely explained by the lower percentage of those treated. The fact that this pattern was consistent for this cohort in each village suggests it is not an artifact. Further detailed investigation of the likely explanations for this cohort effect would be instructive.

Age Effects

The youngest cohorts, who were born approximately at or after the first MDA and were younger than 1 year at the baseline survey, had a different relationship among treatment, infection, and TF than the older cohorts, who were born before the first MDA and were 1 year or older at the baseline

survey. Older cohorts showed overall reductions in TF and parallel reductions in *C. trachomatis* infection from baseline after each round of MDA. This synchronous reduction in both TF and infection did not occur among the youngest cohorts, who showed some reductions in *C. trachomatis* infection but no corresponding reductions in TF. One possible explanation for this altered relationship is that reduced exposure to *C. trachomatis* at or near birth leads to an altered, more robust immunological response to infection, leading to higher TF among these youngest cohorts than would be expected given the low prevalence of actual bacterial infection. This is unlikely given that follicles are not even observed until approximately age 3 months in young children with infection. Another possibility is that although incident *C. trachomatis* infection rates are lower in younger age groups, children at this age take longer to clear follicles due to their immature immune systems, thus leading to an accumulation of follicles and increased cross-sectional prevalence of TF after each new episode of chlamydial infection in spite of overall reductions in the actual number of episodes of infection. Differences in TF by age are consistent with reports by Bailey et al.,⁹ who found that children 4 years or younger had longer duration of clinical active disease than children 5 to 14 years of age, who in turn had longer duration than individuals 15 years or older.

Period Effects (Herd Effects)

Although each cohort usually had lower age-specific TF and infection prevalence than older cohorts at the same age, it is difficult to determine how much of this reduction was due to that cohort directly receiving more rounds of MDA and how

TABLE 6. Risk Factors for *C. trachomatis* Infection at Each Age

	Age 1	Age 2	Age 3	Age 4	Age 5	Age 6	Age 7	Age 8	Age 9
Antibiotic	0.8, 0.3–2.5	0.9, 0.3–2.6	0.4, 0.1–1.0	1.0, 0.3–3.1	1.0, 0.4–2.6	0.4, 0.1–1.4	0.6, 0.2–1.6	0.5, 0.1–1.8	0.8, 0.2–3.3
Prior infection	4.7, 2.1–10.3	2.1, 1.0–4.3	4.1, 2.2–7.8	3.8, 2.1–6.7	1.8, 1.0–3.2	2.7, 1.4–5.0	1.8, 0.9–3.6	1.5, 0.6–3.7	2.9, 1.0–8.2
Cohort 2	—	—	—	—	—	—	—	—	2.0, 0.7–5.6
Cohort 3	—	—	—	—	—	—	—	2.4, 0.9–6.0	0.4, 0.1–1.9
Cohort 4	—	—	—	—	—	—	1.1, 0.5–2.6	1.9, 0.7–5.3	REF
Cohort 5	—	—	—	—	—	2.8, 1.3–6.2	1.8, 0.9–3.6	REF	—
Cohort 6	—	—	—	—	1.5, 0.8–3.1	1.1, 0.5–2.7	REF	—	—
Cohort 7	—	—	—	2.1, 1.1–4.2	1.3, 0.7–2.6	REF	—	—	—
Cohort 8	—	—	3.4, 1.7–6.8	1.2, 0.6–2.5	REF	—	—	—	—
Cohort 9	—	1.2, 0.7–2.3	0.9, 0.4–1.9	REF	—	—	—	—	—
Cohort 10	1.9, 0.8–4.7	0.5, 0.2–1.0	REF	—	—	—	—	—	—
Cohort 11	2.0, 0.9–4.9	REF	—	—	—	—	—	—	—
Cohort 12	REF	—	—	—	—	—	—	—	—

TABLE 7. Risk factors for TF and *C. trachomatis* Infection at Ages 7 and 8

	Age 7		Age 8	
	TF	Infection	TF	Infection
Antibiotic	4.6, 0.6–34.0	0.6, 0.2–1.6	0.6, 0.2–1.9	0.5, 0.1–1.8
Prior diagnosis	9.3, 4.7–18.2	1.8, 0.9–3.6	3.9, 1.9–8.0	1.5, 0.6–3.7
Cohort 3	—	—	REF	REF
Cohort 4	REF	REF	0.5, 0.2–1.3	0.8, 0.3–2.0
Cohort 5	2.3, 1.0–5.2	1.6, 0.8–3.2	0.7, 0.3–1.4	0.4, 0.2–1.1
Cohort 6	1.3, 0.5–3.1	0.9, 0.4–2.0	—	—

much was due to reduced *C. trachomatis* transmission within the community. The only way to tease apart these two effects would be to assess prevalence within individuals who had never directly received MDA. At the baseline visit, all children had their pretreatment trachoma status recorded. In our study, there were also three successive birth cohorts of children who were born after an annual community-wide MDA had already occurred (meaning they did not receive that year's MDA) and had their trachoma status assessed for the first time just before receiving the next annual community-wide MDA. Therefore, we have pretreatment prevalence data for four successive birth cohorts of children younger than 1 year old. Each of these cohorts showed sequential reductions in pretreatment prevalence of TF and infection with successive rounds of MDA (Figs. 1, 2: cohorts 10–13 at age < 1). By the last study visit, children younger than 1 year (cohort 13) had a TF and *C. trachomatis* prevalence of 0%. This provides evidence of protective herd effects within these communities.

Herd effect may be defined as “the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population.”¹⁰ Often used in the context of vaccination, the term also describes the indirect benefits of reduced infection transmission secondary to any mass antibiotic treatment program. Herd effect can be quantified as the decline in infection or disease among the untreated segment of a population.¹⁰ Herd effect due to repeat MDA has been described by House et al.,¹¹ who showed that adults living in communities in which children aged 1 to 10 were treated with azithromycin four times over 12 months had 35% lower prevalence of *C. trachomatis* infection compared with adults in untreated communities. However, this study reported prevalence of infection, not clinical trachoma, and did not report prevalence of either outcome among recently born children younger than 1 year old who had never received antibiotics. To our knowledge, our study is the first to provide evidence consistent with a protective herd effect from repeated rounds of MDA in untreated children in the community, in terms of both clinical trachoma and *C. trachomatis* infection.

Our study does have limitations. As with any longitudinal study, the more years of follow-up the more concrete the evidence of trends. We would have liked to have additional follow-up visits for the youngest cohorts to be certain that the trend of increasing TF during younger ages of life, up to approximately age 3, remained consistent and was followed by the expected reduction in TF with increasing rounds of MDA during older ages. The number of children within each cohort, typically approximately 200, was small for conducting detailed risk factor analyses and some of the nonsignificant results may be due to insufficient power to detect differences. However, the overall trends are still apparent. Finally, the presence of migrants may have mitigated the effect of MDA within cohorts, as migrants did not have the same number of rounds of MDA as

their nonmigrant counterparts. Fortunately, migrants comprised approximately 20% cumulatively of all children in the study and were not disproportionately high in one cohort versus another, so they should not have affected the findings between cohorts or ages.

CONCLUSIONS

In summary, this study showed that three rounds of MDA are associated with significant reductions of trachoma and infection, with evidence for a protective herd effect among children born into communities after successive rounds of MDA. Nevertheless, three rounds of MDA with high coverage were not enough to reduce prevalence of trachoma to less than 5% among children younger than 10 years. Cohort effects highlight how the effects of low coverage can persist across multiple treatments among children of a shared age, and also suggest differential responses to treatment and infection among the youngest children born under different pressures of infection from the rest of the community. The need for continuing annual MDA to push infection and trachoma prevalence lower is still evident.

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