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Efficacy of oral azithromycin versus topical tetracycline in mass treatment of endemic trachoma

Nicole Fraser-Hurt,[1] Robin L. Bailey,[2] Simon Cousens,[3] Denise Mabey,[4] Hannah Faal,[5] & David C.W. Mabey[6]

Objective To compare the impact of mass treatment with oral azithromycin and topical tetracycline on the prevalence of active trachoma.

Methods A total of 1803 inhabitants from 106 households of eight Gambian villages were randomized, in pairs, to receive either three doses of azithromycin at weekly intervals, or daily topical tetracycline over 6 weeks. Ocular examinations were conducted before treatment, and 2, 6 and 12 months after treatment.

Findings Prior to treatment, 16% of the study participants had active trachoma. Two months after treatment, the prevalence of trachoma was 4.6% and 5.1% in the azithromycin and the tetracycline groups, respectively (adjusted odds ratio (OR) = 1.09; 95% confidence interval (CI) = 0.53, 2.02). Subsequently, the prevalence rose to 16% in the tetracycline group, while remaining at 7.7% in the azithromycin group (adjusted OR at 12 months = 0.52; 95% CI = 0.34, 0.80). At 12 months post-treatment, there were fewer new prevalent cases in the azithromycin group, and trachoma resolution was significantly better for this group (adjusted OR = 2.02; 95% CI = 1.42, 3.50).

Conclusion Oral azithromycin therefore appears to offer a means for controlling blinding trachoma. It is easy to administer and higher coverages may be possible than have been achieved hitherto.

Keywords Trachoma/drug therapy; Azithromycin/therapeutic use; Tetracycline/therapeutic use; Clinical trials; Comparative study; Gambia (*source: MeSH*).

Mots clés Trachome/chimiothérapie; Azithromycine/usage thérapeutique; Tétracycline/usage thérapeutique; Drug administration routes; Voies administration médicament; Essai clinique; Etude comparative; Gambie (*source: INSERM*).

Palabras clave Tracoma/quimioterapia; Azitromicina/uso terapéutico; Tetraciclina/uso terapéutico; Vías de administración de medicamentos; Ensayos clínicos; Estudio comparativo; Gambia (*source: BIREME*).

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Voir page 639 le résumé en français. En la página 639 figura un resumen en español.

Introduction

Trachoma is caused by the recurrent, chronic infection of the eye with *Chlamydia trachomatis* serotypes A, B, Ba or C, and progresses from inflammation to conjunctival scarring, lid deformities, corneal abrasion and visual impairment. It is the most common infectious cause of blindness, and is responsible for an estimated 15% of global blindness (*1*). Active trachoma affects an estimated 150 million people (*2*), and about 5.5 million are blind as a consequence of the disease. Blinding trachoma mainly occurs in rural, resource-poor areas of Africa and Asia (for a review of risk factors see Mabey et al. (*3*)). The importance of within-household transmission is supported by epidemiological observations (*4, 5*) and by serotyping and genotyping results (*6–8*).

International efforts to control the disease are based on the SAFE strategy which combines **S**urgery, **A**ntibiotics, **F**acial cleanliness and **E**nvironmental improvement. The <u>G</u>lobal <u>E</u>limination of <u>T</u>rachoma as a disease of public health importance by 2020 (GET 2020) is currently the overall goal in trachoma control efforts (*9*). Active trachoma is routinely treated with tetracycline eye ointment applied daily for 6 weeks. However, topical treatment is not practical for mass treatment since the ointment is difficult and uncomfortable to apply, it blurs the vision, and it must be performed daily over an extended period of time.

Systemic antibiotics tested in randomized controlled trials have shown some efficacy against active trachoma but carried a high risk of adverse side-effects. Treatment with sulfonamides (trisulfa-

pyrimidine (10) and sulfamethoxypyridazine (11) given over 3 weeks, and sulfadimethoxine (12) administered over 5 months), which were evaluated in the 1960s, all have the major drawback of causing systemic complications. The subsequently tested oral tetracyclines, doxycycline (13, 14) and minocycline (15), administered for periods up to 1 year, may cause adverse effects in children and fetuses. Under field conditions the cost of delivery of intensive, supervised topical or multidose oral therapy to rural populations is prohibitive.

Systemic azithromycin is highly effective as a single-dose therapy for genital *C. trachomatis* infection (9, 16), and appears to offer a novel alternative for trachoma control. It has a half-life in tissue of 2–3 days (17) and a good safety profile in all age groups. A trial in the Gambia established that a single dose of azithromycin (20 mg/kg) was as effective as six weeks of twice-daily topical tetracycline (18); but reinfection is common when only individual cases are treated, and 40% of subjects were reinfected 6 months after treatment. In a study on dosage schedules involving Egyptian children with active trachoma, Dawson et al. (19) found that the prevalence of both severe trachoma and *C. trachomatis* infection was similar after 1–6 doses of oral azithromycin or 30 days of topical tetracycline. Tabbara et al. (20) reported comparable efficacy with only a single dose of azithromycin.

There is some experience in mass or selective mass treatment using topical and oral compounds. Vertical control programmes in Saudi Arabia in the 1960s and late 1980s and in Tunisia in the 1980s combined topical mass treatment with hygiene promotion and eyelid surgery (9). Recent intervention studies in the United Republic of Tanzania assessed topical mass treatment and face washing (21). Tetracycline regimens have been shown to be effective primarily in highly exposed schoolchildren (13). Resnikoff et al. (22) tested oral minocycline in selective mass treatment. Mass treatment has generally, in the absence of improvements in living standards, been accompanied by substantial treatment failures and a short-lived treatment response. The latest recommendation from WHO is that all children should be treated in communities where more than 20% of children show signs of active trachoma. However, in hyperendemic areas the main group responsible for transmission is pre-school children, who are not easily reached through the existing channels.

The ACT (Azithromycin in Control of Trachoma) study was conducted with the objective of comparing the efficacy of mass treatment with oral azithromycin and topical tetracycline in the United Republic of Tanzania, Egypt, and the Gambia. The microbiological findings of the ACT study have been presented in detail by Schachter et al. (23). The present article presents the clinical and selected microbiological results of the ACT trial conducted in the Gambia.

Study design and methods

Study area and participants

The intervention area consisted of eight trachoma-endemic villages in the Sanjal Region of the Upper Baddibu District, located within 10 km of each other and approximately 20 km east of Farafenni town on the north bank of the River Gambia. The main local ethnic groups are Wolof, Fula and Mandinka (24). Most of the population live from subsistence farming, with an average annual per capita income of around US$ 200. The villages are composed of compounds inhabited by the members of one extended family and their livestock ("households"). Water is obtained from deep wells. All residents who were present at the pre-treatment survey were eligible for participation in the trial. The villages were matched in pairs of similar size, and azithromycin and tetracycline were allocated randomly within these pairs.

Diagnosis and case definition

The clinical assessments were performed in the field using a Heine × 2.4 binocular loupe and handheld lights. Diagnosis of trachoma and its sequelae were based on the WHO grading scheme (25, 26). Active trachoma was defined as the presence of either follicular disease (TF) or intense disease (TI). Two experienced tropical ophthalmologists performed all the examinations after careful standardization.

Treatment

In the four villages allocated to azithromycin, women of childbearing age received erythromycin (500 mg) twice daily for 14 days, or amoxycillin (500 mg) three times daily for 14 days in cases of intolerance. All other residents received azithromycin (20 mg/kg to a maximum of 1g) on days 1, 8 and 15. In the tetracycline villages, the entire population received a supervised application of 1% tetracycline ointment to both eyes daily for 6 weeks. Compliance was determined by trained volunteers who recorded the ingestion of tablets or application of ointment.

Follow-up

Three cross-sectional ophthalmic surveys were performed 2, 6 and 12 months after treatment. Census updates were completed at least once per month. Village residents who had not been present at the pre-treatment examination (and therefore did not belong to the intention-to-treat cohort) but moved back to their village of residence during follow-up were also examined during the follow-up period, but were not included in the intention-to-treat analysis. Subjects with active disease were treated at the end of the trial with oral azithromycin or topical tetracycline. All subjects needing surgery were referred to the local health centre, where resources were provided to enable the operations to be conducted free of charge.

Ethical approval

The trial was approved by the joint Medical Research Council/Gambia Government Ethics Committee and the Ethical Committee of the London School of Hygiene and Tropical Medicine. Meetings were held in each village where the aims and methods of the study were explained, and community consent was obtained at this time. Individual verbal informed consent was obtained before clinical examination, after the methods were explained in the appropriate local language.

Statistical methods

Data were entered through a customized system using Paradox 3.5 software, with automatic check and validation features, together with manual checks by a supervisor. Analyses were performed with Stata version 5.0 (http://www.stata.com), based on the intention-to-treat cohort formed by the individuals assessed in the pre-treatment survey. The primary endpoint for the efficacy assessment was active trachoma, i.e. TF or TI. Clinical cure was defined as the resolution of active trachoma, i.e. absence of TF and TI. Outcomes examined for the assessment of treatment efficacy were the point prevalence of active trachoma at 2, 6 and 12 months post-treatment, the occurrence of new prevalent cases at 12 months or any time post-treatment, and disease resolution at 2, 6 or 12 months post-treatment.

The χ^2 test was used to investigate individual-level factors associated with attendance at follow-up surveys. Point estimates of the odds ratio for the comparison of azithromycin with tetracycline, adjusted for age, latrine ownership and, where appropriate, trachoma status at baseline, were obtained using logistic regression with individual records. Confidence intervals around these point estimates were obtained by the bootstrap method (27). To take account of the cluster randomization, re-sampling of clusters rather than individuals was performed. For each analysis 1000 bootstrap samples were drawn and 95% confidence intervals (CI) ascertained using the percentile method.

Results

Pre-treatment survey

Participants and group allocations. A total of 1803 individuals were examined in the eight intervention villages between 4 July and 4 October 1994 (Table 1). Of the azithromycin villages, two were inhabited exclusively by members of the Wolof ethnic group, one by members of the Fula group, and one by both ethnic groups. Three tetracycline villages were inhabited exclusively by Wolofs, while the fourth also had a small number of Fulani.

The proportions of males in the azithromycin and tetracycline groups were 56% and 59%, respectively. The mean ages in the two groups were 21.4 years and 20.7 years, respectively, and were similar within pairs, as were the proportions of the

population aged less than 10 years (Table 1). The mean numbers of individuals per household were 17.2 and 15.9 in the azithromycin and tetracycline groups, respectively. Households with, on average, more than two individuals per bedroom were more common in the azithromycin villages (65%) than in the tetracycline villages (53%). The presence of latrines was reported in 25% and 32% of households in azithromycin and tetracycline villages, respectively. Overall, 34% of children up to 10 years of age were observed to have ocular flies present at the time of the baseline examination.

Ocular examination results. TF (26) was diagnosed in 9.4% of individuals allocated to azithromycin and in 14.6% of individuals allocated to tetracycline. The prevalence of TI was 7.4% in the azithromycin group and 7.1% in the tetracycline group. The age distribution of trachoma markers showed the typical pattern for an endemic area, with inflammation in children of pre-school age, and scarring, potentially disabling and disabling lesions in adolescents and adults (Fig. 1). Overall, 16% of all participants had active trachoma (TF or TI) at baseline (Table 1), with similar prevalences in males (15%) and females (18%). The disease prevalence in the azithromycin group was 14.4%, compared with 18.4% in the tetracycline group (Table 2). The greatest difference in prevalence was observed in the 5–9 year-old age group.

Classification of villages. The prevalence of active disease among children up to 10 years of age (assessed in at least 50 individuals) is a key criterion in the choice of control strategy (9). Apart from one village (Sinchu Pallen) with a 17% prevalence of active disease in children, all other villages would be eligible for mass treatment in the current framework of trachoma control strategies based on their disease prevalence exceeding 20% in the indicator group (Table 1).

Treatment and compliance. The median intervals between baseline examination and treatment were 1.2 months and 0.9 months for the azithromycin and tetracycline groups, respectively. Compliance with treatment was defined as at least one dose of azithromycin (or one week of erythromycin), or at least 4 weeks of tetracycline application. Data on compliance were available for 96% of the 1803 participants. A total of 228 individuals received erythromycin instead of azithromycin. The overall treatment compliance was 97%, and was slightly higher in the azithromycin-treated (range, 94–100%) than in the tetracycline-treated villages (range, 89–98%).

Post-treatment surveys

Schedule of surveys and attendance. The three post-treatment surveys were conducted after median periods (post-treatment) of 2.7, 6.1 and 11.9 months (azithromycin group) and 2.8, 6.4 and 12.2 months (tetracycline group). These follow-up surveys were attended by 747 (79%), 487 (51%), and 573 (61%) of the individuals randomized to azithromycin, and by 677 (79%), 383 (45%), and 427 (50%) of those

Table 1. **Baseline characteristics of the eight study villages for treatment with azithromycin (AZ) or tetracycline (TC)**

Pair	Treatment allocation	Village	No. of households	No. of individuals	Mean age (years)	No. (%) of households with a latrine	% Prevalence of active trachoma among	
							All ages	0–9-year-olds
1	AZ	Ndowen	6	158	18.3	4 (67)	20	39
	TC	Checken	10	131	19.1	6 (60)	17	33
2	AZ	Lumen	20	296	21.8	3 (15)	15	33
	TC	Njaien	11	242	19.7	9 (82)	19	38
3	AZ	Sinchu Pallen	12	273	22.2	6 (50)	8	17
	TC	Sambo Sotor	19	257	21.2	3 (16)	18	39
4	AZ	Balo	16	220	22.0	4 (25)	17	41
	TC	Keur Bamba Lowe	12	226	22.0	4 (33)	20	47
Total			**106**	**1803**	**21.0**	**39 (37)**	**16**	**36**

randomized to tetracycline. One azithromycin village, Balo, had very poor post-treatment follow-up, 51% at 2 months, 5% at 6 months, and 0% at 12 months. Individual factors statistically associated with attendance at none or only one of the three post-treatment surveys were increasing age ($P = 0.02$), Wolof ethnicity ($P < 0.001$), absence of active trachoma at baseline ($P = 0.001$), and non-compliance with treatment ($P = 0.06$).

Effect of treatment on active disease in individuals. Table 2 presents the age- and sex-specific prevalences of active disease, by treatment group, at 6 and 12 months post-treatment. Fig. 2 shows the prevalence of follicular and intense disease in the two intervention groups at 2, 6 and 12 months post-treatment. Table 3 presents estimates of the effect on active trachoma of using azithromycin rather than tetracycline at 6 and 12 months post-treatment. Fig. 3 shows the evolution of village prevalences of active disease over time.

At 2 months post-treatment there was little indication of any difference in active trachoma prevalence between the two groups (Table 3). By 12 months post-treatment, however, there was evidence that the overall prevalence of active disease was lower in the azithromycin group (adjusted odds ratio (OR) = 0.52; 95% CI = 0.34, 0.80). Similar patterns were observed when separate analyses were performed for those with and without active disease at baseline. At 12 months post-treatment, among individuals without active trachoma at baseline, a smaller number in the azithromycin group than in the tetracycline group had become prevalent cases (adjusted OR = 0.54); however, the 95% CI around this estimate is wide (0.22, 1.15). Among individuals with active disease at baseline, a higher proportion among those receiving azithromycin had resolved at 12 months (adjusted OR = 2.02; 95% CI = 1.42, 3.50).

The relationship between presence of active disease and *C. trachomatis* infection was determined among the participants for whom both clinical and microbiological data were available. In the follow-up survey at one year, there was a strong association between infection and disease in both treatment groups (azithromycin group: χ^2 test = 11.1, $P = 0.001$; tetracycline group: χ^2 test = 22.3, $P < 0.001$). Participants with active trachoma at baseline were significantly more likely to have infection one year after treatment in the tetracycline group (χ^2 test = 9.6, $P = 0.002$), but not in the azithromycin group (χ^2 test = 1.24, $P = 0.27$). Among all those with disease at baseline, the prevalence of infection at one year was 21.4% in the tetracycline group ($n = 103$) and 11.7% in the azithromycin group ($n = 77$).

The reduction in the prevalence of active trachoma at 12 months post-treatment among those receiving azithromycin appears to hold for both sexes and for children up to 14 years of age (Table 2). There is less indication of a difference between the two treatment groups for adults. Interestingly, there was a considerable reduction in the prevalence of TI as compared to TF in both intervention groups (Fig. 2). Prior to treatment, approximately 7% of the participants were positive for TI. After 1 year, 8 (1.4%) of those allocated to azithromycin and 12 (2.8%) of those allocated to tetracycline had TI.

In two of the three azithromycin villages with follow-up at 12 months (Ndowen and Lumen), the prevalence of active disease remained substantially lower than it had been at baseline (Fig. 3). In the third village it remained slightly lower. Among the four tetracycline villages, prevalence at 12 months post-treatment was only substantially lower than at baseline in one village (Sambo Sotor). In two other villages (Checken and Keur Bamba Lowe) the prevalences at 12 months were similar to those at baseline, while in the remaining village (Njaien) the prevalence was substantially higher at 12 months post-treatment.

Discussion

The present trial of community randomized mass treatment with azithromycin complements the experi-

Fig. 1. **Baseline age-specific prevalence rates of trachoma a) follicular disease (TF), b) intense disease (TI) and c) conjunctival scarring, by treatment group**

a) Follicular disease (TF)

b) Intense disease (TI)

c) Conjunctival scarring

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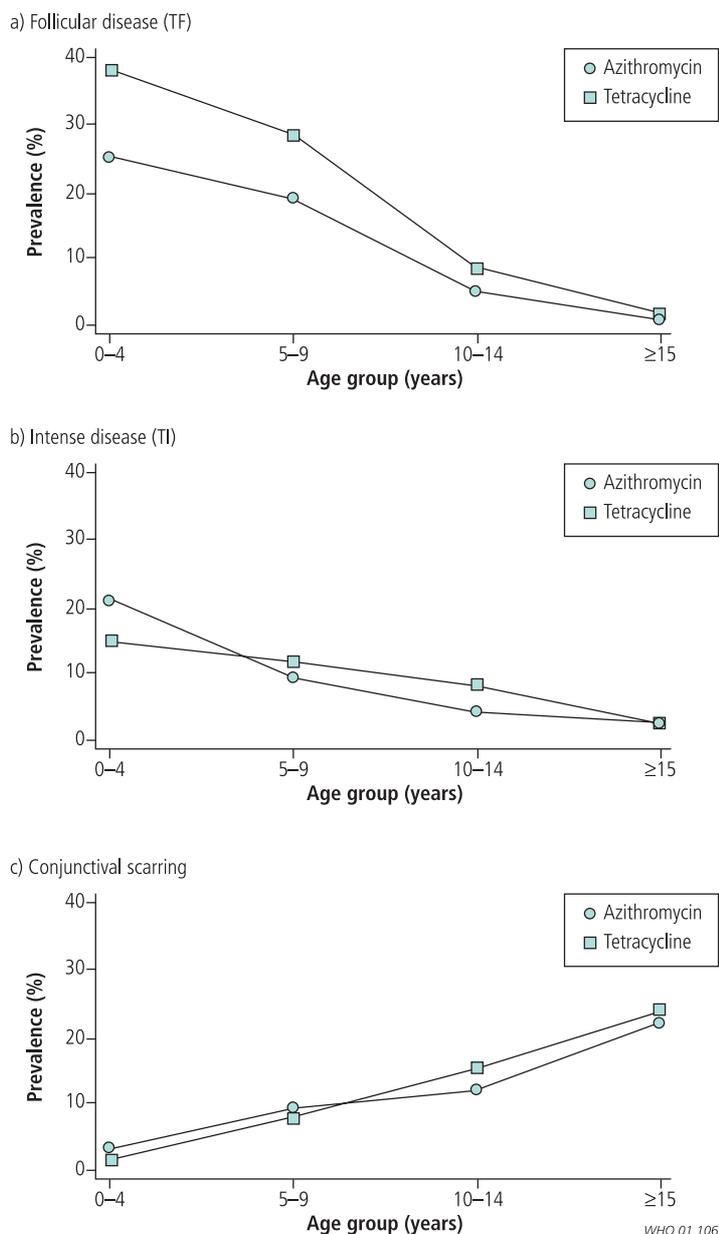
ence gained in individually randomized controlled clinical trials using azithromycin, which have consistently shown the drug's potential to resolve active trachomatous disease (*18–20*). It was the high rate of reinfection in previous azithromycin trials that called for the evaluation of the drug in mass treatment. It is generally accepted that sequelae are more common after repeated reinfection, and that frequent reinfection is associated with severe inflammatory changes (*28*). Bobo et al. (*29*) have documented in children the relationship between infection intensity, dynamics of infection, and disease severity. A high *C. trachomatis* burden is associated with persistent infection and severe disease, whereas a low burden is associated with sporadic infection and milder (follicular) disease. The study by Detels et al. (*30*) of migrants has shown that scarring does not progress in the absence of continued exposure to reinfection.

Microbiological data (*23*) demonstrate that azithromycin and tetracycline therapy lowered the village-wide prevalence of conjunctival infection within one year by 78% and 66%, respectively. Variables predicting infection status in the study cohort at the 1-year follow-up were the infection at baseline, age, and treatment compliance. Those participants found infected prior to treatment were significantly less likely to be infected at one year if they were in the azithromycin treatment group. In addition, resolution of infection in participants with disease at baseline was better after azithromycin than tetracycline treatment.

Our analysis of the clinical trial data suggests that, over a period of 12 months, oral azithromycin has a greater impact than topical tetracycline on the prevalence of active disease and resolution of active trachoma. The data are also consistent with a greater impact of azithromycin on the occurrence of new prevalent cases. Both compounds tested were given under optimal conditions, i.e. azithromycin was given in three doses at weekly intervals to maximize the coverage, and tetracycline ointment was applied by health workers on a daily basis over 6 weeks. The effect of different numbers of azithromycin doses was not evaluated.

Table 2. **Sex- and age-specific prevalences of active trachoma at baseline and 6 and 12 months after treatment with azithromycin (AZ) or tetracycline (TC), by treatment group**

	% prevalence at baseline		% prevalence 6 months after treatment		% prevalence 12 months after treatment	
	AZ	TC	AZ	TC	AZ	TC
Males	13.4	17.6	4.2	8.4	5.9	14.9
Females	15.7	19.6	6.3	9.1	10.1	17.7
Age group (years)						
0–4	40.7	47.2	10.2	22.5	18.9	41.1
5–9	22.7	32.1	7.9	12.7	9.9	18.8
10–14	7.9	12.8	3.2	3.0	2.9	12.5
⩾15	2.9	3.2	1.9	3.1	3.2	4.2
All	**14.4**	**18.4**	**5.1**	**8.7**	**7.7**	**16.1**

One year after treatment, the prevalence of active trachoma was reduced by 47% (from 14.4% to 7.7%) and by 13% (from 18.4% to 16.1%) in the azithromycin and tetracycline groups, respectively. In children aged 0–4 years, the prevalence of the disease one year after tetracycline treatment was close to the pre-treatment level, while it was only half of the pre-treatment level in those allocated to azithromycin. Young children are notoriously difficult to treat with ointment, and the safe and efficacious azithromycin regimen may be an important advance in treatment of childhood trachoma. In school-age children, both treatments appeared to work equally well within the first half of the follow-up period, but disease prevalence rose steeply in the second half among those allocated to tetracycline. The greater efficacy of azithromycin may have become more evident in the longer term, through a greater reduction in the reservoir of infection, with systemic treatment being more likely to have a greater impact than topical treatment on extra-ocular infection.

Oral azithromycin may have a more marked effect than topical tetracycline on reducing *C. trachomatis* transmission, as suggested by the higher likelihood for participants allocated to tetracycline to be diagnosed as new prevalent cases during follow-up. The efficacy of azithromycin versus tetracycline against not being identified as a new prevalent case was 46% at 1 year. In terms of disease resolution, tetracycline appeared to perform as well, if not better than azithromycin during the early follow-up period, which might be explained by the extended treatment period of tetracycline over 6 weeks. In the subsequent follow-up examinations, azithromycin appeared superior in resolving active disease, presumably because it reduced the likelihood of reinfection.

Limitations of the study

This study has a number of limitations. First, the number of clusters randomized was very small, leading to a small effective sample size and wide confidence intervals. Data analysis was conducted without taking the paired design into account, in order to optimize what power there was (*31*). A further limitation associated with randomizing only a small number of clusters is that the two treatment groups may have remained unbalanced with respect to important risk factors for the outcome. In our analyses we controlled for age, latrine ownership and, where appropriate, the presence of active trachoma at baseline. We cannot exclude the possibility that other unmeasured or uncontrolled risk factors may have confounded our comparison of azithromycin and tetracycline. Second, we measured the prevalence rather than the incidence of disease. It is possible that some individuals who were not considered to have active trachoma at any of the cross-sectional surveys may have experienced episodes of active disease between the surveys. This may be particularly true for older participants. Bailey et al. (*32*) reported that in the Gambia adults tended to experience short bursts of the intense form of trachoma, while children

Fig. 2. **Changes in the prevalence of active trachoma over time, by treatment group, a) azithromycin group, b) tetracycline group**
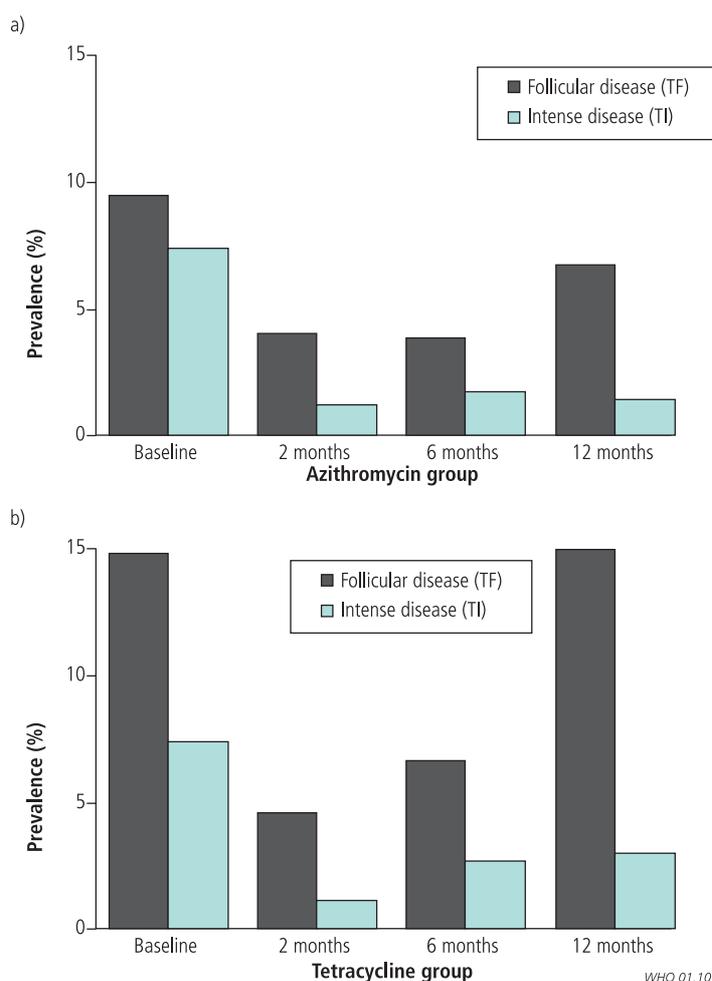

Table 3. **Comparison of the impact of azithromycin versus topical tetracycline on the prevalence of active trachoma, on newly prevalent cases, and on the resolution of prevalent cases at baseline**

	Azithromycin group	Tetracycline group	Odds ratio[a]
Prevalence			
At 2 months	34/740 (4.6)[b]	34/672 (5.1)	1.09[c]; *0.53, 2.0*[d]
At 6 months	24/470 (5.1)	33/380 (8.7)	0.62[c]; *0.28, 1.62*
At 12 months	44/571 (7.7)	68/422 (16)	0.52[c]; *0.34, 0.80*
New prevalent cases			
At 12 months	18/488 (3.7)	19/316 (6.0)	0.54[e]; *0.22, 1.15*
At any time	22/597 (3.7)	27/597 (4.5)	0.74[e]; *0.39, 1.28*
Resolution[f]			
At 2 months	86/115 (75)	98/127 (73)	0.84[f]; *0.51, 1.42*
At 6 months	56/77 (73)	54/80 (67)	1.30[f]; *0.59, 2.89*
At 12 months	55/81 (68)	56/105 (53)	2.02[f]; *1.42, 3.50*

[a] Odds ratios estimated by logistic regression.
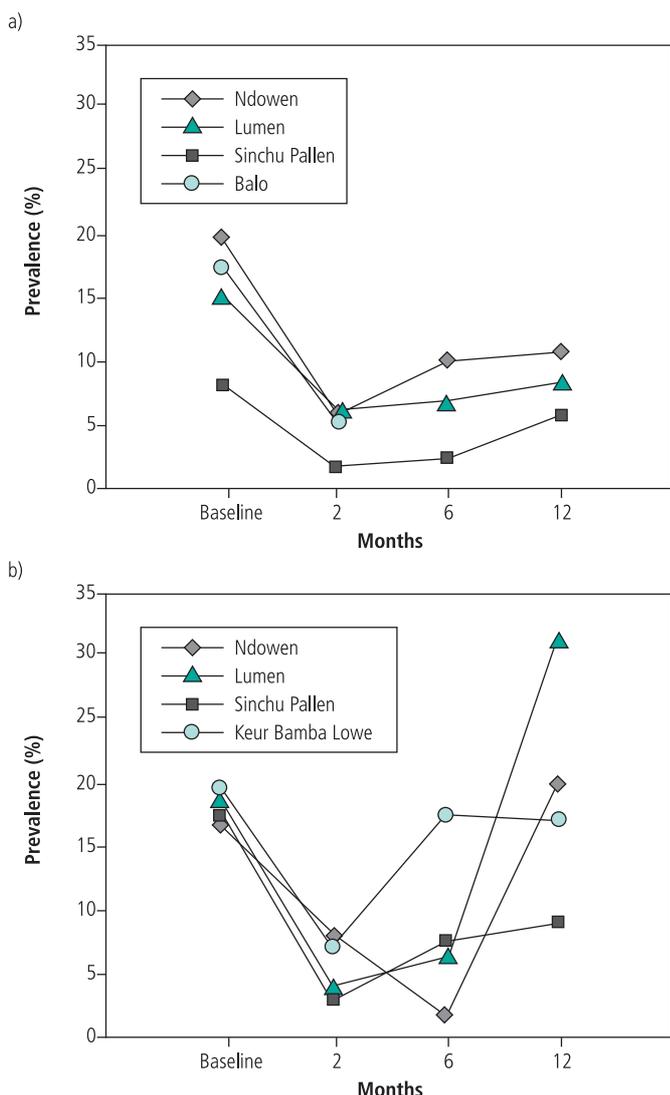
[b] Figures in parentheses are percentages.

[c] Estimated odds ratios adjusted for age, latrine ownership, and active trachoma status at baseline.

[d] Figures in italics are 95% CI obtained by bootstrapping, using the percentile method and taking account of the cluster randomization.

[e] Estimated odds ratios adjusted for age and latrine ownership. Excludes individuals with active trachoma at baseline.

[f] Estimated odds ratios adjusted for age and latrine ownership. Includes only individuals with active trachoma at baseline.

Fig. 3. **Village-specific prevalences of active trachoma over time, by treatment group, a) azithromycin villages, b) tetracycline villages**

a)

b)

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Antibiotics and trachoma control

There is a consensus that antibiotics are a cornerstone in trachoma control, and that oral treatments are more desirable than topical formulations. Oral treatment usually requires less frequent administration, resulting in improved compliance and greater efficiency of control programmes, and thus in cost-savings that may well compensate for the higher drug costs. Furthermore, oral treatment may accelerate the elimination of the infection, because such treatment is more likely to clear *C. trachomatis* in extraocular reservoirs than if treatment is confined to the conjunctiva. However, the applicability of systemic drugs can be hampered by adverse effects, which are of greatest concern when mass treatment is used. Azithromycin has a better safety profile than the oral drugs used previously (*18, 33, 34*), but its safety for pregnant and lactating women is not currently known.

There is reason for concern that azithromycin-resistant pathogens may emerge if the drug is used on a large scale, underlining the importance of both its well-targeted use (*35*), and of monitoring the development of resistance in areas where azithromycin is routinely used (currently among Aborigine children in Australia). Rapid assessment procedures for trachoma and mapping by Geographic Information Systems are now being introduced in order to facilitate rational targeting of antibiotic treatment (*33*). Lietman et al. (*36*) recently presented a trachoma transmission model and its implications for targeting of treatment, mass treatment intervals, and resulting shifts in disease patterns and immunity. The results predict that in areas where the prevalence of trachoma in children is below 35%, annual or biennial mass treatment (i.e. every one or two years) would be sufficient eventually to eliminate the disease, but that prevalences above 35% would require biannual mass treatment (i.e. every 6 months) — assuming universal coverage, no immigration of infected individuals, and absence of clustering of infection within households (*37*). Selective mass treatment of children up to 10 years of age would generally shorten the recommended treatment intervals.

tended to suffer prolonged episodes of TF. Nevertheless, we believe that this trial indicates the higher and more sustained potential of azithromycin compared with tetracycline to reduce the burden of trachoma at community level in settings where the condition is highly prevalent. Third, although compliance with treatment was very high, there were substantial losses to follow-up during the trial. Follow-up was slightly better in the azithromycin than in the tetracycline group. Follow-up was also better in the younger age groups at highest risk of active disease and in those with active disease at baseline. These phenomena combined might bias the comparison in favour of azithromycin. However, even if we assume that all individuals who were not seen at 12 months did not have active trachoma, the prevalence of active disease would be lower in the azithromycin group (4.6%) than in the tetracycline group (7.9%). It seems unlikely, therefore, that losses to follow-up are responsible for the differences observed between the two groups.

Conclusions

In the present trial with highly controlled treatment conditions, the overall prevalence of active trachoma was reduced by 47% in the villages that had received azithromycin treatment 12 months before. This is a promising start in the control of trachoma in these communities. The marked reduction in intense disease, which is thought to be an indicator for future blindness, especially among the azithromycin group, may indicate that annual mass treatment can indeed prevent trachoma-attributable blindness. Application of the trachoma transmission model to aid in the design of cost-effective control programmes might prove valuable. The SAFE strategy foresees the use of antibiotics and surgery as short-

term interventions delivered through the health service, and health promotion and environmental improvements as the consolidating long-term interventions. Improvements in primary health care services and sanitation will undoubtedly be followed by a decline in trachoma (*38*). However, it is hoped that community-based antibiotic treatment will make the global elimination of trachoma by 2020 an achievable target even in very poor areas where development progress is slow. The recent announcement of an azithromycin donation programme for selected trachoma endemic countries could lead to a major advance in the control of blinding trachoma. ■

Résumé

Efficacité comparée de l'azithromycine par voie orale et de la tétracycline en application locale dans le traitement de masse du trachome endémique

Objectif Comparer l'impact d'un traitement de masse par l'azithromycine orale et la tétracycline en application locale sur la prévalence du trachome actif.

Méthodes Dans huit villages de Gambie, 1803 habitants appartenant à 106 ménages ont été répartis par tirage au sort dans deux groupes de traitement, l'un consistant en trois doses orales d'azithromycine à une semaine d'intervalle et l'autre en une application quotidienne de pommade à la tétracycline pendant six semaines. Des examens ophtalmologiques ont été réalisés avant le traitement et 2, 6 et 12 mois après celui-ci.

Résultats Avant le traitement, 16 % des participants présentaient un trachome actif. Deux mois après le traitement, la prévalence du trachome était de 4,6 % dans le groupe traité par l'azithromycine et de 5,1 % dans le groupe traité par la tétracycline (odds ratio ajusté (OR) = 1,09 ; intervalle de confiance (IC) à 95 % : 0,53-2,02). Elle remontait ensuite à 16 % dans le groupe tétracycline mais restait à 7,7 % dans le groupe azithromycine (OR ajusté à 12 mois = 0,52 ; IC 95 % : 0,34-0,80). Au bout de 12 mois, on observait moins de nouveaux cas dans le groupe azithromycine et le taux de résolution du trachome y était significativement plus élevé (OR ajusté = 2,02 ; IC 95 % : 1,42-3,50).

Conclusion L'azithromycine par voie orale semble donc pouvoir offrir un moyen de lutte contre le trachome cécitant. Elle est facile à administrer et devrait permettre d'obtenir une meilleure couverture que ce qui a pu être réalisé jusqu'à maintenant.

Resumen

Eficacia de la azitromicina oral frente a la tetraciclina tópica en el tratamiento masivo del tracoma endémico

Objetivo Comparar los efectos del tratamiento masivo con azitromicina oral y con tetraciclina tópica en la prevalencia del tracoma activo.

Métodos Un total de 1803 habitantes de 106 hogares de ocho aldeas de Gambia fueron distribuidos al azar por pares para que recibieran ya fuera tres dosis de azitromicina a intervalos semanales o tetraciclina tópica diaria a lo largo de seis semanas. Se realizaron exámenes oftalmológicos antes del tratamiento y a los 2, 6 y 12 meses del tratamiento.

Resultados Antes del tratamiento, el 16% de los participantes en el estudio presentaban tracoma activo. Dos meses después del tratamiento la prevalencia de tracoma era del 4,6% y del 5,1% en los grupos tratados con azitromicina y tetraciclina, respectivamente (razón de posibilidades (OR) ajustada = 1,09; intervalo de confianza (IC) del 95% = 0,53, 2,02). Posteriormente la prevalencia aumentó al 16% en el grupo tratado con tetraciclina, mientras que permaneció en el 7,7% en el grupo tratado con azitromicina (OR ajustada a los 12 meses = 0,52; IC95% = 0,34, 0,80). A los 12 meses de acabado el tratamiento, la prevalencia de casos nuevos en el grupo tratado con azitromicina fue menor, y la resolución del tracoma fue significativamente mejor en este grupo (OR ajustada = 2,02; IC95% = 1,42, 3,50).

Conclusión La azitromicina oral constituye una alternativa para combatir el tracoma causante de ceguera. Es fácil de administrar, y se pueden conseguir coberturas más altas que las logradas hasta ahora.

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