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Comparison of Two Azithromycin Distribution Strategies for Controlling Trachoma in Nepal

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Theme Papers

Comparison of two azithromycin distribution strategies for controlling trachoma in Nepal

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Objective The study compares the effectiveness of two strategies for distributing azithromycin in an area with mild-to-moderate active trachoma in Nepal.
Methods The two strategies investigated were the use of azithromycin for 1) mass treatment of all children, or 2) targeted treatment of only those children who were found to be clinically active, as well as all members of their household.
Findings Mass treatment of children was slightly more effective in terms of decreasing the prevalence of clinically active trachoma (estimated by clinical examination) and of chlamydial infection (estimated by DNA amplification tests), although neither result was statistically significant.
Conclusion Both strategies appeared to be effective in reducing the prevalence of clinically active trachoma and infection six months after the treatment. Antibiotic treatment reduced the prevalence of chlamydial infection more than it did the level of clinically active trachoma.

Keywords: Azithromycin/supply and distribution; Trachoma/drug therapy; Comparative study; Randomized controlled trials; Nepal (*source: MeSH*).

Mots clés: Azithromycine/ressources et distribution; Trachome/chimiothérapie; Etude comparative; Essai clinique randomisé; Népal (*source: INSERM*).

Palabras clave: Azitromicina/provisión y distribución; Tracoma/quimioterapia; Estudio comparativo; Ensayos controlados aleatorios; Nepal (*fuente: BIREME*).

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Voir page 200 le résumé en français. En la página 200 figura un resumen en español.

Introduction

In 1996, WHO initiated the GET 2020 programme (Global Elimination of Trachoma by the year 2020) and declared that high priority should be given to trachoma control in Nepal (*1*). The 1981 Nepal Blindness Survey found trachoma to be the second leading cause of blindness after cataract, with 75% of trachoma cases occurring in the far western region of the country. Blinding trachoma was particularly prevalent among the disadvantaged Tharu ethnic group in this region (*2*).

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For trachoma control in endemic areas, WHO proposed the SAFE strategy — Surgery to correct trichiasis, Antibiotics to treat infectious trachoma, Facial cleanliness to decrease transmission, and Environmental improvements such as access to clean water and control of flies (*1*). Mass distribution of azithromycin, given as a single dose of Zithromax® (Pfizer, New York, NY, USA) by public health workers, prevents the transmission of trachoma before the onset of scarring and blindness. Mass distribution of antibiotics to all members of a community has been found to reduce the prevalence of active trachoma one year after treatment (*3*). However, because of the expense, the risk of side-effects, and the potential for antimicrobial resistance, e.g. streptococcal resistance to macrolides (*4–7*), the amount of antibiotic used should be strictly limited. For example, WHO has suggested that in meso-endemic areas antibiotic treatment could be limited to specific age groups, since children are more likely to be infected than adults, or could be directed towards only those households with active cases (*8*). It was unclear which of these two approaches would be more effective at reducing the prevalence of active disease. The present study was therefore carried out in an area of Nepal with mild-to-moderate active trachoma to compare the efficacy of two azithromycin distribution strategies: mass treatment of all children; and targeted treatment of only children with active disease, as well as all persons in their households.

Methods

The study was a randomized trial that compared the following two groups: 1) *mass treatment* — all children aged 1–10 years in the community were treated; and 2) *targeted treatment* — only children aged 1–10 years who were diagnosed with clinically active trachoma were treated, together with all members of their households.

Several areas of far western Nepal were surveyed to locate a district with an average prevalence of at least 15% active trachoma among the children. Two Village Development Committees (VDCs — politically defined geographical areas), Geta and Sripur, each comprising 9 wards in Kailali District, were chosen as the study site for the following reasons: 1) the moderate-to-high prevalence of trachoma found there in preliminary rapid assessments; 2) the ongoing trachoma control efforts; and 3) the presence of a high concentration of ethnic Tharus. The two strategies for distribution of azithromycin to the study groups were implemented jointly by Helen Keller International, the Nepal Netra Jyoti Sangh (NNJS), and the Francis I. Proctor Foundation as part of the SAFE programme to eradicate blinding trachoma in Kailali District.

A total of 17 of the 18 wards in Geta and Sripur VDCs were included in the study. The risks and benefits of participation were explained to the ward chiefs and members of the community. Verbal consent was obtained from the ward chiefs and members of their communities, and from the guardians of all the children. To reduce mixing of the treatment groups, wards that shared a government elementary school were combined into one randomization unit. Consequently, there were four randomization units composed of 2 or 3 wards and eight units consisting of a single ward. These 12 units were then randomly assigned, without matching, to either mass treatment of children (9 wards, combined into 6 units) or targeted household treatment (8 wards, combined into 6 units). Before the initial treatment, a house-to-house census was performed in five wards to allow estimation of the coverage rates of the programme and to collect information on household composition. The census data of 0–10-year-old children were corrected to estimate the number of children aged 1–10 years (who were eligible for examination) by reducing the census figures proportionally by 9.01%. During the study, the ward chiefs were notified at least one day in advance so that community members could assemble at a designated time and place, where the examination and treatment procedures were carried out.

The measures for assessing the outcome included clinical examination, photographic examination, and ligase chain reaction (LCR) testing. The cross-sectional prevalence of clinically active trachoma (see definitions below) 6 months after treatment was compared to the baseline prevalence. During the baseline and follow-up visits, conjunctival photography, conjunctival swabs for chlamydia testing, and repeat clinical examinations by a second examiner were carried out on a cohort group of approximately 50 randomly chosen 1–7-year-old children from each of the 12 units. Each child had a $55/x$ chance of being selected into this group (where x is the estimated number of children in the unit); recruitment stopped after 55 children had been enrolled in a randomization unit. At the follow-up visit, in an effort to oversample active cases, the first 25 clinically active cases aged 1–7 years from each of the 12 randomization units were photographed and swabbed. LCR testing (LCx probe system, Abbott Laboratories, Abbott Park, IL, USA) was performed on all the sampled clinically active cases (118 at the first visit and 276 at the follow-up visit) and on a randomly chosen 118 of the sampled clinically normal cases at each visit.

Procedures

Clinical examinations. The upper tarsal conjunctiva of the right eye was examined with a binocular loupe (× 2.5) and a hand light. Well-trained ophthalmic technicians and ophthalmologists performed the examinations, utilizing the WHO Simplified Trachoma Grading Scale (*9*), to identify active cases — i.e. follicular trachoma (TF) or intense trachoma (TI) for normal cases.

Clinical photography. Two photographs were taken of the upper right tarsal conjunctiva of each child in the cohort group, using a handheld 35-mm

camera with a macro lens (1:1) at a distance of 12.5 cm. The results were later evaluated by a trained grader at the Proctor Foundation, in San Francisco, according to the WHO Simplified Trachoma Grading Scale, as either active cases (TF or TI) or normal. The photographs were read in a random order; the ward of origin, the clinical grades, and the results of LCR testing were masked and not revealed to the grader.

LCR testing. A conjunctival swab was placed in LCR transport medium and used as a source for the detection of *Chlamydia trachomatis* DNA by LCR. The specimens were placed on ice in the field and then stored and transported at 4 °C until analysed, within 12 weeks, at the University of California, San Francisco Chlamydia Research Laboratory (according to the LCx protocol). The wards of origin and the clinical and photographic grades were masked and not revealed to the laboratory technicians who performed the analyses.

Treatment. Children were weighed and given a single dose of oral azithromycin as a paediatric suspension (20 mg/kg) or 250 mg capsules (20 mg/kg, those aged $\geqslant 8$ years). Adults (i.e. individuals aged $\geqslant 18$ years) were given a single dose (1 g) of azithromycin capsules. Pregnant women were offered an alternative treatment (500 mg erythromycin, twice a day, for 7 days or topical treatment).

Definitions. Clinical activity was assessed by trained personnel using the WHO Simplified Trachoma Grading Scale (*9*), based on clinical examination with a loupe ($\times$ 2–2.5) or by examination of conjunctival slides with loupes, as follows:

- TF (trachomatous inflammation – follicular): presence of five or more follicles in the upper tarsal conjunctiva.
- TI (trachomatous inflammation – intense): pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels.
- Clinically active trachoma: defined as either TF or TI by the examiner.
- Chlamydial infection: defined as a positive LCR test for *C. trachomatis*.

Statistics. All statistical tests were performed using Stata 6.0 software (Stata Statistical Software, Release 6.0, 1999) (*10*). All confidence intervals (95% CI) for proportions were binomial (exact) statistics. Proportions were compared using the χ^2 test or Fisher's exact test, if a cell contained $\leqslant 5$ individuals. The kappa statistic and concordance rates were calculated to evaluate the reproducibility of the clinical and photographic examinations. Logistic regression (cross-sectional, pre-treatment/post-treatment) was used to predict clinical activity with the following covariates: strategy (mass treatment of children or targeted household treatment), time (pre- or post-treatment), and the joint effect of strategy and time (the treatment effect) (*11*). Within-randomization group correlation was accounted for using the robust estimator of variance described by Huber & White (using the "cluster" command in Stata 6.0) (*10, 11*). Since for LCR testing at the follow-up visit we oversampled clinically active cases, the sampling weights were adjusted proportionally without inflating the accuracy (using "p weights" in Stata 6.0) (*10*).

Results

In March 1998, a pre-treatment survey of 1597 children in five arbitrarily chosen wards (G1, G2, G9, S1, S8) in Geta and Sripur VDCs revealed an average prevalence of 28.5% of active trachoma among children aged 1–10 years. The baseline examinations and treatments were performed from 30 November to 15 December 1998. A total of 5262 children were examined in Geta and Sripur — 2598 in the 6 randomization units of the group for mass treatment of children, all of whom were offered treatment, and 2664 children in the 6 units of the group for targeted household treatment, of whom 409 were treated along with all their household members. Treatment refusals were rare and not recorded; we estimated that well over 95% of the children who were offered treatment received it. Between 26 May and 10 June 1999, a 6-month follow-up evaluation of the 17 wards was completed. A total of 5214 children were examined — 2641 in the mass treatment group and 2573 in the targeted treatment group (Table 1). The results of these examinations are presented in Fig. 1.

The census of the 5 wards (G1, G2, G9, S8, S9) indicated a total of 1325 children. Baseline examinations were performed on 1027 of these children, and follow-up examinations on 1071 (Table 2). The estimated average coverage rate of these examinations (relative to the census) was 79%.

Household composition data collected from three of the wards revealed that there were 1.52 (650/427) families per household, where a family was defined by the presence of a father and/or mother and their children, and a household was defined as persons dwelling in the same free-standing structure. Each household had, on average, 8 (3613/427) family members. An average of 91% (387/427; 95% CI = 87–93%) of these households had at least one child aged $\leqslant 10$ years.

The inter-observer reliability was measured by having two examiners independently grade each child in the cohort during the second visit. There was a 94% concordance rate in the diagnosis of the examiners, resulting in a kappa statistic of 0.81 (Table 3). There was an 88% concordance rate between the first clinical examiner and the photographic examiner, resulting in a kappa statistic of 0.71 (Table 4).

To determine if there was any bias in clinical grading between the two treatment groups, a total of 619 children were randomly selected (44–55 from each unit) from the cohort group to receive further evaluation. Of these 619 children, 441 (71%) were later identified at the 6-month follow-up visit. To enrich the follow-up sample with clinically active cases, an additional 212 clinically active cases (not

Table 1. **Results from the pre-study, baseline, and follow-up examinations of children aged 10 years in Geta and Sripur wards, Nepal, 1998–99**

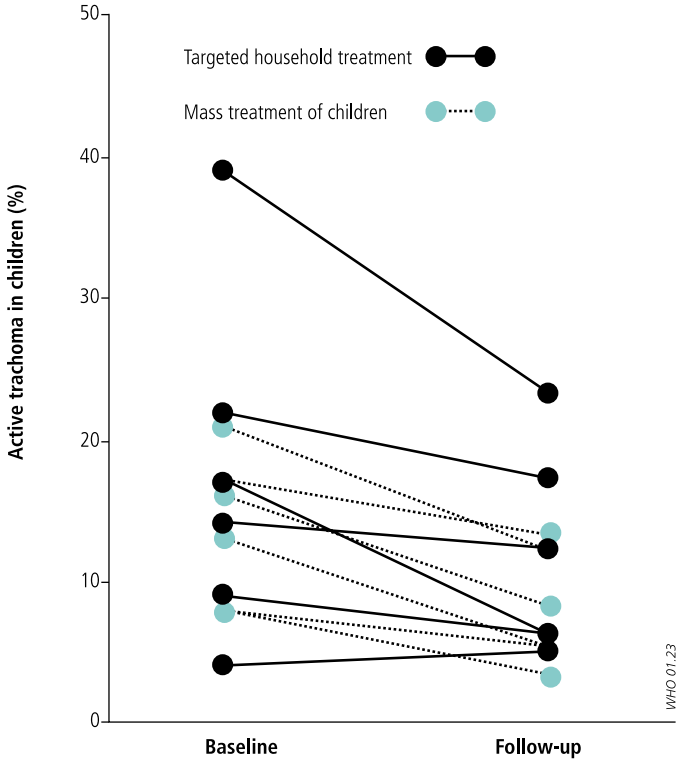
Wards	Type of treatment	No. of children examined in:		% clinically active in:		
		Dec. 1998	June 1999	March 1998	Dec. 1998	June 1999
Geta 4, 5, 7	Mass	786	825	–	17	13
Geta 6	Mass	494	498	–	21	12
Sripur 1, 2	Mass	654	589	27	16	8
Sripur 5	Mass	221	256	–	13	5
Sripur 8	Mass	265	250	20	8	5
Sripur 9	Mass	178	223	–	8	3
Subtotal		**2598**	**2641**		**16**	**9**
Geta 1, 2	Targeted	341	414	31	14	12
Geta 3	Targeted	676	511	–	4	5
Geta 9	Targeted	243	184	36	39	23
Sripur 3, 4	Targeted	673	640	–	22	17
Sripur 6	Targeted	252	394	–	17	6
Sripur 7	Targeted	479	430	–	9	6
Subtotal		**2664**	**2573**	**–**	**15**	**10**
Total		**5262**	**5214**	**–**	**16**	**10**

from the original cohort) were also tested during the follow-up examination. We were unable to detect a significant difference in the ratio of misgraded clinical examination between the two treatment groups ($P = 0.73$) (false positives versus false negatives, taking the photographic grade as the gold standard).

A multivariate logistic model was used to predict the results of the clinical examination, accounting for within-randomization unit correlation. For both groups, the follow-up examination was significantly less likely (41% less likely; 95% CI = 29–51%) to reveal active trachoma compared to the baseline examination. There was no significant difference in the baseline clinical activity between the two treatment groups (odds ratio (OR) for being clinically active if in the targeted group = 0.97; 95% CI = 0.49–1.91, $P = 0.93$). Nor was there a significant difference in the treatment effect of the two strategies; OR = 1.29 (95% CI, 0.8–1.8, $P = 0.33$) for being clinically active at 6 months in the targeted group compared to the group for mass treatment of children, after treatment.

LCR tests were performed on conjunctival specimens from all clinically active cases in the cohort from both villages and on 118 normal persons at each visit. Of the clinically active cases, 29 out of 117 (25%; 95% CI = 17–34%) were LCR positive at baseline, and 31 out of 263 (12%; 95% CI = 8–16%) were positive at follow-up (there were more clinically active cases at follow-up because of the additional sampling of up to 25 clinically active cases per village). The proportion of clinically active cases that were LCR positive was significantly lower at follow-up (χ^2 test, $P < 0.01$). Of the clinically normal cases, 5 out of 118 (4%; 95% CI = 1–10%) were LCR positive at baseline and 6 out of 118 (5%; 95% CI = 2–11%) were positive at follow-up. The proportion of clinically normal cases that were LCR positive was not significantly different between baseline and follow-up (χ^2 test, $P = 0.76$).

Fig. 1. **Prevalence of clinically active disease among 1–10-year-old children at baseline examination and 6 months after treatment**



A multivariate logistic model was also used to predict the effect of the two treatment strategies on infection (accounting for within-ward correlation as above, and adjusting for sampling weights). Children in communities receiving targeted household treatment were more likely to be infected with *C. trachomatis*

Table 2. **Results of attendance for examination and census of 1–10-year-old children in 5 study wards, Nepal, 1998–99**

Ward	No. of children examined in:		Census in 1998
	1998	1999	
G1, 2	341	414	489
G 9	243	184	201
S 8	265	250	301
S 9	178	223	334
Total	**1027**	**1071**	**1325**

Table 3. **Comparison of findings by two clinical graders at follow-up examination**[a]

Clinical grader 1	Clinical grader 2:	
	Active	Normal
Active	61	18
Normal	6	341

[a] Kappa statistic measure of agreement: 0.80.

Table 4. **Comparison of findings by the clinical examiner and conjunctival photograph grader**[a]

Clinical examiner	Photographic grader:	
	Active	Normal
Active	275	76
Normal	62	741

[a] Kappa statistic measure of agreement: 0.71.

(LCR positive) than those in communities receiving mass treatment (OR = 2.9; 95% CI = 0.8–10.9), although this odds ratio was not significant ($P = 0.11$).

Antibiotic usage for each randomization unit is shown in Fig. 2 according to the prevalence of active disease in children. As expected, the amount of antibiotic used increased dramatically with the prevalence of active disease in the group for targeted household treatment (306 g of azithromycin per 10% increase in prevalence; 95% CI = 151–460 g per 10% increase), but was not dependent on the prevalence of active disease in the group for mass treatment of children ($P = 0.86$).

Discussion

Treatment of all individuals in a community with systemic oral azithromycin significantly reduced the prevalence of ocular chlamydia infection (*3*). However, for several reasons — such as the expense of treatment, the risk of side-effects, and the potential for emergence of antimicrobial resistance (*4–7*) — the use of antibiotics should be limited. It is known that periodic treatments aimed at those who are at greatest risk for infection may result in the eventual elimination of blinding trachoma (*12, 13*). Effective ways to target treatment within a community are not yet available, although strategies have been suggested. Since a young age is clearly the largest risk factor for infection (*14, 15*), and clinical examinations do not reveal all infectious cases (*16–18*), mass treatment of all children may be appropriate. On the other hand, since many cases of infectious trachoma can be identified by clinical examination and cases of active trachoma are known to cluster within households, it may be more effective to target the treatment at entire households where a child is known to have active clinical disease.

We have demonstrated that, in such a setting, both the treatment strategies examined are capable of reducing the prevalence of active trachoma. The prevalence of clinically active disease six months after treatment with both strategies was reduced by approximately one-third. Individuals in the group for mass treatment of children were about 20% less likely to have clinically active trachoma at the follow-up examination than were those in the targeted household group, but this difference was not statistically significant ($P = 0.33$). Although those in the group for mass treatment of children were less likely to be LCR positive 6 months after treatment, this result was also not clinically significant ($P = 0.11$). Grading of conjunctival photographs by an individual masked from identifying the data found no evidence that the results were due to bias on the part of the clinical graders. In fact, as with the clinical examination assessments, more photographs were graded as clinically active and more LCR tests were positive in the targeted household group than in the mass treatment group.

The Azithromycin in the Control of Trachoma Study revealed that, after treatment, the decline in the prevalence of infection was greater than that of clinical activity (*3*). In the present study, we also found that the percentage of clinically active cases infected with chlamydia (estimated by LCR) was significantly lower after than before treatment. Possible explanations for this are: persistence of conjunctival follicles long after the treatment has eliminated chlamydia (*19*); and the clinical examination appears to be less indicative of infection as the prevalence decreases (*20–22)*. This is encouraging since community antibiotic treatment may be even more successful than that indicated by the clinical results alone.

The degree to which such programmes are able to provide coverage of the intended population with antibiotics will almost certainly be an important factor affecting the efficacy of both strategies — targeted treatment and mass treatment (*12*). The present study was intentionally performed under field programme conditions and achieved only a modest coverage level, estimated at 79%. This is lower, for example, than the 88% level achieved under the more intensive study conditions of the Azithromycin in the Control of Trachoma Study (*3*). The fact that coverage was not complete at either visit in our study implies that children who did not participate in the baseline

examinations and treatment may have participated in the follow-up examination, diluting the treatment effect. It was difficult to estimate the coverage level precisely in Nepal. The available resources limited the performance of the census to only 5 wards; thus, different coverage levels between the two treatment strategies cannot be eliminated as a possible source of bias. It can be seen (Table 2) that while coverage in the 5 sample wards averaged 79%, it varied considerably when using the house-to-house census of all households in a ward as the gold standard. We were unable to determine why more children were examined in the baseline visit of ward G9 than had been estimated in the census. Possible explanations include an incomplete census of the known ward households, fluctuating populations, and visits by children from a neighbouring ward to the examination site (despite efforts to ensure against this).

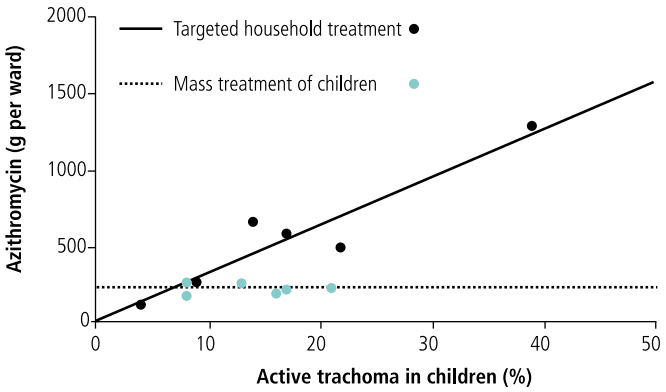
Health care workers in this area of Nepal report anecdotally that the prevalence of active trachoma in children exhibits large seasonal effects. In four wards in the present study, the prevalence fell from 28.5% in late March 1998 to 19.3% in early December 1998, resulting in an average decrease in prevalence of 32%, even before any treatments were instituted. If treatment had not been initiated, the prevalence of active disease may have followed the seasonal fluctuation and been even higher at the time of the early June follow-up examination than it was in the baseline examinations. If this should be the case, the effect of treatment on both groups of the study would be more pronounced than indicated by a simple comparison between baseline and follow-up prevalences.

Although the effectiveness of the two strategies was not significantly different, other distinguishing factors may be important for trachoma control programmes. We expect the efficacy of the targeted household treatment group to be more dependent on having well-trained clinical graders. On the other hand, with the strategy for mass treatment of children, a preliminary screening must be performed before it is known whether treatment is even necessary; targeted household treatment can be performed on the very first visit to a village. The costs of the two strategies may differ substantially, depending on the manner and location in which the strategies are implemented. For example, the results in Fig. 2 demonstrate that antibiotic use with targeted household treatment depends strongly on the prevalence of trachoma. An in-depth analysis of the cost-effectiveness of the two treatment strategies has been performed and is described elsewhere (*23*). An analysis of the costs for treating all individuals in a community (children and adults) would also be useful, since neither targeted household treatment nor mass treatment of children can be as effective as treating everyone.

Conclusion

Both the targeted and mass treatment strategies for distributing azithromycin significantly reduced the levels of trachoma in children six months after treatment. The prevalences of both clinical activity and infection tended to decrease more as a result of mass treatment of children than targeted household treatment, but the differences were not statistically significant ($P = 0.33$ and $P = 0.11$, respectively). It appears that both strategies are acceptable for trachoma control programmes over a period of 6 months, but it will be instructive to compare these results with the treatment of all members of a community in the long term. ■

Fig. 2. **Antibiotic usage by type of treatment and ward according to prevalence of active disease**



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The research was conducted in full accord with ethical principles, including the provisions of the World Medical Association's Declaration of Helsinki (as revised at the 48th General Assembly, Somerset West, Republic of South Africa, October 1996) and of the Nepal Netra Jyoti Sangh and the Committee on Human Research at the University of California, San Francisco, USA.

Résumé

Comparaison de deux stratégies de distribution d'azithromycine dans le cadre de la lutte contre le trachome au Népal

Objectif L'étude compare l'efficacité de deux stratégies de distribution de l'azithromycine dans une région du Népal où le trachome actif est relativement bénin à modéré.

Méthodes Les deux stratégies étudiées consistaient à utiliser l'azithromycine pour 1) le traitement de masse de tous les enfants, ou 2) le traitement ciblé sur les enfants trouvés porteurs d'un trachome cliniquement actif et toutes les personnes vivant dans le même ménage.

Résultats Le traitement de masse des enfants était légèrement plus efficace pour réduire la prévalence du trachome cliniquement actif (d'après l'examen clinique) et de l'infection à Chlamydia (d'après les tests d'amplification de l'ADN), bien qu'aucun de ces résultats ne soit statistiquement significatif.

Conclusion Les deux stratégies semblent efficaces pour réduire la prévalence du trachome cliniquement actif et de l'infection six mois après le traitement. Le traitement antibiotique réduisait davantage la prévalence de l'infection à Chlamydia que celle du trachome cliniquement actif.

Resumen

Comparación de dos estrategias de distribución de azitromicina para combatir el tracoma en Nepal

Objetivos En este estudio se compara la eficacia de dos estrategias de distribución de azitromicina en una zona con tracoma activo de carácter leve-moderado en Nepal.

Métodos Las dos estrategias investigadas fueron el uso de azitromicina para 1) el tratamiento masivo de todos los niños, y 2) el tratamiento exclusivo de los niños con signos clínicos de actividad de la enfermedad, así como de todos los miembros de su hogar.

Resultados El tratamiento masivo de los niños fue ligeramente más eficaz en lo que respecta a disminuir la prevalencia del tracoma clínicamente activo (determinado mediante examen clínico) y de la infección clamidiana (determinada mediante pruebas de amplificación del ADN), pero ningún resultado fue estadísticamente significativo.

Conclusión Las dos estrategias parecen reducir eficazmente la prevalencia del tracoma clínicamente activo y de la infección seis meses después del tratamiento. La antibioticoterapia redujo la prevalencia de la infección clamidiana en mayor medida que la del tracoma clínicamente activo.

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