

Operational Comparison of Single-Dose Azithromycin and Topical Tetracycline for Trachoma

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PURPOSE. World Health Organization guidelines for antibiotic treatment of trachoma currently include a 6-week course of tetracycline eye ointment twice daily or a single dose of oral azithromycin. Previous trials have shown similar efficacy of these two alternatives when administration of the ointment was carefully supervised. It is believed, however, that azithromycin may be a more effective treatment in practice, and the purpose of this study was to test that hypothesis.

METHODS. A masked randomized controlled trial was conducted to compare azithromycin and tetracycline under practical operational conditions—i.e., without supervision of the administration of the ointment. Three hundred fourteen children aged 6 months to 10 years with clinically active trachoma were recruited and individually randomized to receive one of the two treatments. Follow-up visits were conducted at 10 weeks and 6 months. The outcome was resolution of disease (clinical “cure”).

RESULTS. Children allocated to azithromycin were significantly more likely to have resolved disease than those allocated to tetracycline, both at 10 weeks (68% versus 51%; cure rate ratio, 1.31; 95% confidence interval [CI], 1.08–1.59; $P = 0.007$) and at 6 months (88% versus 73%; cure rate ratio, 1.19; 95% CI, 1.06–1.34; $P = 0.004$). Azithromycin was particularly effective for intense inflammation ($P = 0.023$, Fisher’s exact test).

CONCLUSIONS. Single-dose oral azithromycin was a more effective treatment for active trachoma than tetracycline ointment as applied by caregivers. The high cure rate achieved with tetracycline in this study in the absence of supervision and the significantly higher costs of azithromycin, suggest that in the absence of donation programs, switching routine treatment from tetracycline to azithromycin would not be a good use of resources. (*Invest Ophthalmol Vis Sci.* 2000;41:4074–4079)

Trachoma, a chronic follicular conjunctivitis due to *Chlamydia trachomatis*, is the world’s leading cause of preventable blindness. The World Health Organization (WHO) is currently promoting the SAFE strategy (surgery, antibiotic treatment, facial cleanliness, and environmental improvement) for the global elimination of trachoma as a blinding disease by the year 2020 (GET 2020).¹ Clinically, active trachoma is classified as follicular (TF) involving collections of lymphocytes visible on the tarsal conjunctiva or intense inflam-

mation (TI) in which inflammation and edema obscure most of the normal tarsal conjunctival vasculature.² Exposure to repeated reinfections, and the presence of TI have been linked to future conjunctival scarring,³ a necessary precursor for the blinding complications of trichiasis and corneal opacity. Two antibiotic regimens are currently recommended for active trachoma: tetracycline ointment applied topically twice daily for 6 weeks or single-dose oral azithromycin (20 mg/kg).⁴ Azithromycin is a derivative of erythromycin with an extra methyl-substituted nitrogen at position 9a in the lactone ring, a modification that confers improved bioavailability, sustained high tissue concentrations, and concentration at sites of inflammation.⁵

Three randomized controlled trials, in The Gambia, Saudi Arabia, and Egypt, did not find significant differences in efficacy between these alternative treatments.^{6–8} However, in these trials the administration of tetracycline ointment was carefully supervised. In most trachoma-endemic areas the time and resources available to health staff to motivate and monitor a high degree of adherence to a therapeutic regimen are rarely available. Parents of an affected child are given one or two tubes of ointment and told to apply it. For this reason, it was suggested in these studies that single-dose azithromycin might be a superior treatment in practice. If so, it would have important implications for GET 2020. Trachoma generally affects people in poor countries in which there is low expenditure on

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health, and azithromycin is much more expensive than tetracycline. Moreover, the optimum duration of topical treatment with tetracycline ointment has never been empirically investigated, and thus it is possible that the degree of adherence to the regimen achievable under "operational conditions" may be adequate to achieve acceptable cure rates.

The Gambian National Eye Care Program (NECP) has established a network of community ophthalmic nurses trained to recognize and treat trachoma, who reach all districts of the country, together with senior ophthalmic medical assistants in the major health centers who deliver eyelid and cataract surgery. This project was conceived by the NECP to assess whether it should switch its standard treatment from tetracycline to azithromycin. The study was conducted by NECP staff with research support. Studies in which practical clinical effectiveness under program conditions rather than gold standard efficacy is evaluated are needed for this kind of decision making.

We conducted an individually randomized controlled trial comparing the efficacy of single-dose azithromycin with tetracycline ointment administered twice daily for 6 weeks by caregivers under unsupervised conditions.

METHODS

The study design was in accordance with the World Medical Association Declaration of Helsinki and was approved by the Gambia Government/Medical Research Council (MRC) Joint Ethics Committee. Verbal consent for screening and recruitment to the trial was obtained from the caregiver in charge of the children after explanation in an appropriate local language. After completion of the trial, all subjects with persisting active disease received a supervised course of effective treatment.

Children aged between 6 months and 10 years were recruited by screening in nurseries, schools, and individual households in the Western Division of The Gambia in April and May 1998. Clinical grading was performed using the simplified WHO scale.² Subjects with clinical signs of active trachoma in at least one eye were randomized, using a block design to ensure a reasonable balance between the two treatments in each settlement, to receive either a single dose of oral azithromycin syrup (20 mg/kg) or an unsupervised 6-week course of tetracycline ointment, twice daily.

Assignment

Treatment codes in numbered sealed envelopes were used by the nurse administering treatment to allocate treatment to the subject. The clinical assessors had no knowledge of the randomization sequence or of the treatment received by previous subjects. Similarly, the nurse had no knowledge of the block randomization procedure and did not examine the child but administered treatment according to the allocation in the envelope. The single oral dose of azithromycin syrup was mixed and administered by syringe after the child was weighed on kitchen scales. Alternatively, a single dose of topical tetracycline was administered to both eyes of the child by an ophthalmic community nurse in front of the caregiver. The rest of that tube, plus a second complete tube of ointment, was then given to the caregiver with instruction to apply the ointment in the same way twice daily for 6 weeks.

All subjects were visited 10 weeks and 6 months after treatment was initiated, when both eyes were examined and graded by a clinical assessor blind to the treatment allocation. Subjects were categorized as "cured" if their clinical signs of active disease (in the worst eye at follow-up) had resolved at either follow-up visit.

Validation

Training sessions for those responsible for grading clinical findings were conducted regularly using both slides and patients examined under field conditions. Additionally, both at 10 weeks and 6 months, the worst eye of each subject was photographed using a 35-mm camera, macro lens, and side-mounted flash. Photographic outcomes, assessed by an independent investigator in the UK, were compared with the clinical outcomes, assessed in the field.

Statistical Issues

A previous trial conducted in The Gambia showed cure rates of 78% for azithromycin and 72% for supervised tetracycline. It was judged that a 20% difference in cure rates between the two treatments would be the minimum significant rate for public health planners. For the study to have 90% power to detect a 20% difference between treatments with 95% confidence, assuming a cure rate with azithromycin of 80%, 118 subjects were needed in each arm. Allowing for loss to follow-up, we sought to recruit 300 patients, approximately 150 in each arm.

Analysis was conducted according to treatment received. Comparisons between the resolution rates at 10 weeks and 6 months of follow-up were made with χ^2 methods, the probabilities quoted are those using the Yates correction. In the derivation of cure rates, subjects were regarded as cured if the disease had been observed to resolve at either time point. Thus, subjects who were lost to follow-up at 10 weeks but were found disease free at 6 months were included as cured.

To allow for the joint influences of age, treatment allocation, and disease intensity and to adjust for re-emergent disease, a survival analysis (using the Cox proportional hazards method) was performed with time to observe resolution of disease as the end point, and censoring when patients were cured or lost to follow-up. Agreement between observers and between clinical grading and photographs was examined using Cohen's κ statistic.

Masking

Investigators performing the clinical examinations were unaware of the treatment allocated to each patient. The nurse who administered the drugs took no further part in the subsequent follow-up visits. The treatment code was broken for analysis after the 6-month follow-up visits were completed.

RESULTS

A total of 2616 children were screened, and 314 children with active trachoma (TF or TI in at least one eye) were recruited into the trial, a prevalence rate of 12%. Twenty-four (0.9%) of those screened had intense disease (TI). The 314 children came from 199 compounds, and 178 children (57%) shared a compound (family residence) with at least one other subject recruited to the trial (range, 1-10 subjects). There were no significant differences in age, sex, prevalence of TI, or propor-

TABLE 1. Comparison of Treatment Groups

	Azithromycin (n = 160)	Tetracycline (n = 154)
Boys	78 (49%)	77 (50%)
Age 5 years or less	100 (62%)	96 (62%)
Intense disease (TI)	15 (9%)	9 (6%)
Number sharing compound with other trial subjects	74 (46%)	62 (40%)

tions sharing compounds with other subjects at baseline between the treatment groups (Table 1). The flow of patients through the 6-month trial period is illustrated in Figure 1. Four treatment errors occurred, three children received azithromycin who were randomized to receive tetracycline, and one child incorrectly received tetracycline. At the 10-week follow-up, 291 (93%) of 314 children were traced and at the 6-month follow-up 288 (92%) were traced.

The prevalence of active disease in the treatment groups found at 10 weeks and 6 months is illustrated in Figure 2, and the disease resolution (cure) and re-emergence rates are presented in Table 2. Subjects who were disease free at 10 weeks were counted as having resolved disease, whether or not they were reinfected at 6 months. Subjects receiving azithromycin were significantly more likely to have resolved disease than those allocated to tetracycline, both at 10 weeks and at 6 months (Table 2). Similar results were obtained when analysis was conducted by intention to treat: Subjects allocated to azithromycin were significantly more likely to have resolved disease after 6 months than those allocated to tetracycline, assuming that all missing subjects were unchanged from their previous examination. An analysis of resolution rates by treatment type, according to whether subjects sharing household units received the same or different treatments, is shown in Table 3, and this did not significantly affect resolution rates for either treatment.

Azithromycin appeared to be more effective than tetracycline in curing intense disease; 12 (80%) of 15 of subjects who had intense disease initially were observed to be cured by 6 months in the azithromycin group, whereas only 2 (25%) of 8 subjects were observed to have cleared disease in the tetracy-

cline group (1 was lost to follow-up; $P = 0.023$, Fisher's exact test). Survival analysis suggested that, independently, both tetracycline treatment allocation (TET versus AZI; hazard ratio 0.48) and the presence of intense disease at baseline (hazard ratio, 0.44) were associated with prolonged disease resolution (reduced cure rates). This effect of intense disease was more marked in subjects who received tetracycline, but formal tests of interaction did not reach significance. There was a trend for older subjects to resolve disease sooner (age 6 years or more versus 5 years or less; hazard ratio, 1.145; 95% confidence interval [CI], 0.77–1.7), but this effect was not significant.

At four training and validation sessions (two in the field and two with projected slides) all observers had κ scores of 0.80 or higher, compared with the principal investigator (RJC/B), representing excellent agreement. There were difficulties with photographic quality, owing to technical problems, but 129 slides from the 10-week follow-up and 130 from the 6-month follow-up were readable. Comparison with the outcomes graded by the field clinical assessors yielded κ scores of 0.59 (moderate agreement) at 10 weeks and 0.76 (very good agreement) at 6 months. When photographic outcome was analyzed by treatment, a similar advantage for azithromycin over tetracycline was seen with cure rate ratios of 1.20 at 10 weeks and 1.19 at 6 months, although, owing to the enforced smaller sample, these differences did not attain statistical significance.

DISCUSSION

This is the first individually randomized controlled trial to show that azithromycin is a more effective treatment than topical tetracycline for clinical cases of trachoma. Previous studies, including one in The Gambia, which adopted measures to supervise the delivery of topical tetracycline did not find a significant difference between the two treatments. In contrast, we examined the effectiveness of the two drugs in normal program practice. The resources to supervise a twice-daily 6-week course of eye ointment are unlikely to be available to the program, and it is likely that the method we adopted in this study of giving tubes of ointment to the caregiver with instructions is closer to reality.

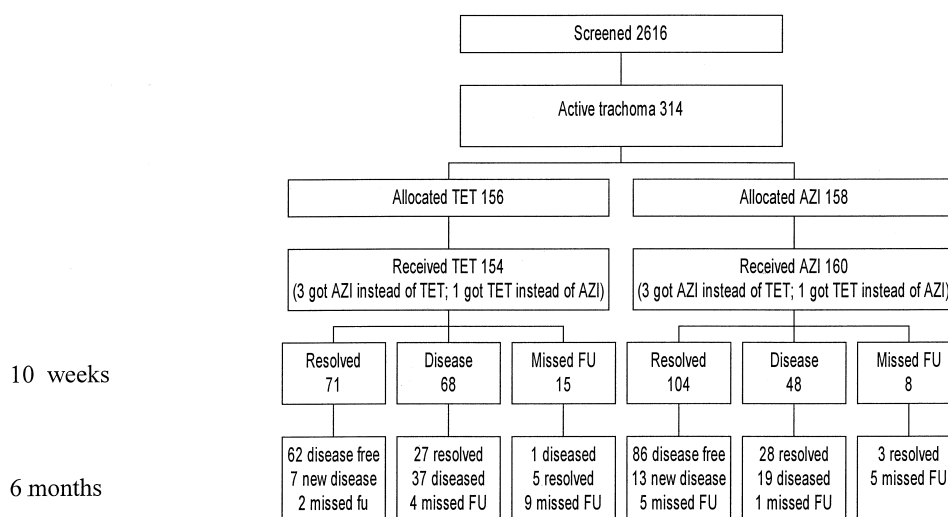


FIGURE 1. Flow of patients through the trial.

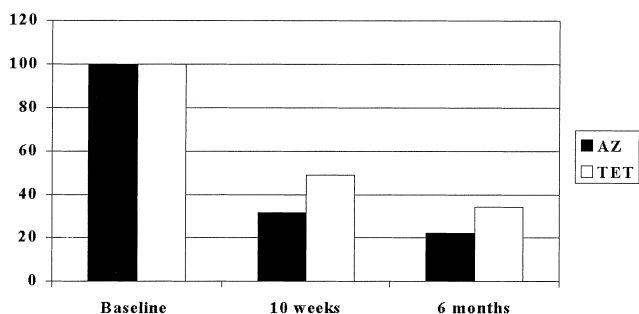


FIGURE 2. Prevalence of active trachoma at baseline and follow-up.

The most likely explanation of the superior effectiveness of azithromycin in this study is that compliance with and duration of treatment with tetracycline under routine unsupervised conditions is suboptimal, but even so, the 73% cure rate seen here with unsupervised treatment is higher than anticipated from results in other studies. The previous randomized trial in The Gambia, which was conducted in a higher prevalence setting found cure rates of 78% for azithromycin and 72% for supervised tetracycline at 6 months.⁶ It is likely that greater transmission and reinfection rates operate where disease prevalence is higher. If reinfection occurs sufficiently rapidly, it will not be clinically distinguishable from treatment failure. Therefore, studies in lower prevalence settings are likely to report better cure rates than those conducted where prevalence is high. This we think explains both the difference in cure rates with azithromycin in the two studies and the apparent small improvement in resolution rate seen here when tetracycline treatment was unsupervised compared with the extensively supervised tetracycline treatments in the first study.⁶ A comparison of the observed re-emergent disease rates, which were higher in the first study further supports this conclusion.

We did not assess compliance with the ointment regimen, because of concerns about difficulties interpreting verbal responses (where compliance tends to be overreported), and about ensuring that ongoing assessment (such as tube inspection) would not influence or alter compliance. Our purpose was to study routine clinical practice, a setting in which monitoring compliance is rarely possible, and we were not able to determine precisely what actual practice meant in this setting. It seems likely that at least initially most of the recommended doses were administered, and this led to acceptable cure rates.

The unit of analysis in this study is the individual, because it is the practice of NECP staff in The Gambia to treat only active disease cases. We did, however, attempt to treat all children with clinical trachoma in each household. All available children sharing compounds with people with known disease

were screened, and all children with active trachoma thus found were recruited. Although children sharing a household with others with active disease might be considered at more risk of reinfection, we found no significant difference between the two treatment groups in proportions of those with disease who shared a household with others who had disease. Furthermore, sharing a household with another case did not significantly affect likelihood of disease resolution at 10 weeks or 6 months. Thus, there is no suggestion that aggregation of active disease in families and households affected our results. Children who received azithromycin could also have been treated with tetracycline ointment, perhaps by the caregiver of a child receiving tetracycline in the same household. We are not in a position to totally exclude this possibility; however, the cure rate ratio advantage for azithromycin was similar in households where treatments were "mixed" as in those where there was no sharing or treatments were the same ("pure" households: Table 3).

Patients were aware of their treatments, and therefore inadvertent unmasking of the clinical assessors at follow-up by the patients was possible. There were no reports of this occurring, however, and the similar cure rate ratios for both clinical and photographic outcome suggest that unmasking and bias were not a significant problem. The photographs were of variable quality with less than half the pictures being readable. This, and the genuine difficulty of grading disease as it resolves may have contributed to the moderate κ score between clinical and photographic outcomes at 10 weeks.

The methods used for analyzing the results of this study are similar to those used in previous comparisons between the two drugs conducted under research conditions. The cure rates derived here attribute all disease resolution to the treatment. It is known that the signs of active trachoma can remit in the absence of any treatment, and studies elsewhere in the Gambia have found 6-month resolution rates of 30% to 45% in patients in whom treatment was deferred.⁹⁻¹⁰ Serial observations of disease reflect dynamic processes including disease resolution (which may be modified or accelerated by treatment) and re-emergent disease due to treatment failure or reinfection. With few time points the effects of these processes can only partly be addressed by survival analysis, and caution is needed in the interpretation. However if a notional resolution rate without treatment were postulated in both groups, this would act to increase the relative benefit of azithromycin treatment. For example, with a postulated spontaneous resolution rate of 40%, disease resolved in an additional 48% of subjects in this group relative to an additional 33% with tetracycline, for an "additional cure rate ratio" of 1.46, rather than the 1.20 indicated in Table 2.

TABLE 2. Disease Resolution and Re-Emergence Rates at 10 Weeks and 6 Months

	Azithromycin (n = 160)	Tetracycline (n = 154)	Crude Rate Ratio (95% CI) and P
Subjects with disease resolved by 10 weeks	104/152 (68%)	71/139 (51%)	1.34 (1.10-1.63) 0.004
Subjects with disease resolved by 6 months	135/154 (88%)	103/141 (73%)	1.20 (1.07-1.35) 0.002
Subjects with disease remaining at 10 weeks but resolved at 6 months	28/47 (60%)	27/64 (42%)	1.4 (0.97-2.1) 0.07
Re-emergent disease rate at 6 months in those with diseases resolved at 10 weeks	13/104 (12%)	7/71 (10%)	1.27 (0.53-3.02) 0.77

TABLE 3. Cure Rates at 10 Weeks and 6 Months According to Treatments

	Pure*	Mixed†	Rate Ratio (95% CI) and P
Cure rate at 10 weeks—AZI	52/78 (67%)	52/74 (70%)	1.05 (0.85-1.31) 0.762
Cure rate at 6 months—AZI	70/80 (88%)	65/74 (88%)	1.0 (0.89-1.12) 1.00
Cure rate at 10 weeks—TET	41/72 (57%)	30/67 (45%)	1.27 (0.91-1.770) 0.206
Cure rate at 6 months—TET	57/64 (77%)	46/67 (69%)	1.122 (0.92-1.38) 0.353

AZI, azithromycin; TET, tetracycline.

* Households in which all received the same treatment.

† Households in which subjects received different treatments.

The finding that azithromycin is particularly effective for TI may be an important observation. Because the scarring sequelae that lead to trachomatous blindness develop over decades, it is unlikely that an impact of antibiotic treatment on future trachomatous blindness can be conclusively demonstrated. However, data suggest that individuals with TI are at increased risk for future scarring and the subsequent development of blinding complications,³ and thus it is plausible that effective treatment of TI may reduce this risk. Furthermore, because patients with TI are more likely to be positive for *Chlamydia*, detected by polymerase chain reaction (PCR) and other laboratory tests,¹¹ and to have more ocular discharge, it is likely that they are more potent sources of transmission in the community. Azithromycin may be a better treatment for TI than tetracycline, because the vascular dilation and edema associated with TI probably increase the discomfort provoked by topical treatment, and because the concentration of azithromycin at sites of inflammation¹² may increase its availability in the inflamed conjunctiva.

In making decisions about when to switch drugs, national programs should take into account not only the relative effectiveness of the two drugs, but also the ease of switching and the costs. Both treatments, in a low-prevalence setting such as the Western Division of The Gambia, involve screening children and contact with a health care worker. Switching drugs necessitates some retraining of health workers and also requires some research to see how caregivers will respond. Treatment of eye problems with ointment is a well-accepted procedure in The Gambia.

Tetracycline eye ointment is relatively inexpensive (£0.21 for two tubes, ECHO, Coulsdon, UK, 1999) and readily available. Azithromycin pediatric suspension (Zithromax), which was donated by Pfizer in this study but is considerably more expensive, costing £5.08 for 600 mg/15 ml (basic National Health Service cost, British National Formulary, UK, 1999) equating to an average cost of £3.20 or so per child treated in the study. Cheaper formulations of azithromycin are becoming available; tablets can be found in local pharmacies in some West African urban centers at a cost of £2.50 for six 250-mg tablets (Aziwok; Mumbai Pharmaceuticals, Bombay, India), which would equate to £0.80 per child treated for active trachoma in our study. However, a pediatric suspension is not available at present from this source, and no studies have assessed the tablet formulation as treatment for active trachoma.

For The Gambian NECP, the costs of the drugs to treat 1000 children with active disease would increase 15 fold from £210 to £3200 if the authorities decided to switch from tetracycline to azithromycin suspension (Zithromax; Pfizer, Sand-

wich, UK) and had to buy both drugs on the commercial market. Based on the results of our study this would result in 875 rather than 730 children being cured, an extra £20.62 for each of the 145 extra children cured. Switching to a tablet formulation instead, and assuming it is as effective as the pediatric suspension, would increase total costs fourfold and equate to a total of £4.06 for each extra patient cured. Also based on our study, in situations in which 8% of the subjects had TI, the 1000 cases would include 80 patients with TI, 64 of which could be cured with azithromycin, compared with 20 with tetracycline. If the authorities decided to switch to azithromycin suspension (Zithromax) only for patients with TI, for an additional cost of £240 (approximate doubling of the total cost), an additional 44 cases of TI could be cured, equating to £5.45 per extra TI case cured. However if the tablet formulation were equally effective, switching to it for patients with TI alone would only involve a more modest 25% increase in total drug costs, and equate to £1.07 per extra TI case cured. This analysis only considers drug as a marginal cost. The costs of screening would be the same for the two treatment strategies but are likely to vary greatly in other environments, depending on the approach and personnel used.

Through the International Trachoma Initiative,¹³ azithromycin donation projects are under way in some countries. For a country such as The Gambia, which has not been included in the first phase of the International Trachoma Initiative, the results of this trial suggest that in the absence of a donation program or a major reduction in the price of azithromycin, the cost implications of switching drugs are significant. The national program may have to continue to use tetracycline as standard treatment for active trachoma. However overseers of programs without donation schemes at present might consider using azithromycin only for patients with TI.

Some caution is necessary in generalizing these findings: This study was conducted in a setting of relatively low prevalence (12% of screened children), and the comparative advantage of azithromycin may be greater where active trachoma, and intense disease particularly, is more prevalent. Furthermore, it is unclear whether, or to what extent, the clinical cure of active disease can be assumed to predict the future impact of any antibiotic treatment program on trachomatous blindness.

The reason that antibiotic therapy has not led to the eradication of trachoma (and that environmental and behavioral interventions designed to reduce transmission are so important) is that it is impossible to treat all cases in a community, and therefore reinfection occurs. Although re-emergent disease rates were rather lower in this study than in other parts of The Gambia where prevalence is higher,^{6,14} strategies of mass or

family treatment and of determining how often retreatment is needed to effectively suppress the infectious reservoir require further investigation. A recent model constructed by Lietman et al.,¹⁵ using Gambian data implied that annual treatment would result in the eventual suppression of active disease, but assumed complete coverage of the population at risk, which is likely to be overoptimistic in practice.

This study was conceived by the Gambian NECP to help decide whether they should be switching their standard drug for treating trachoma from tetracycline ointment to azithromycin. Results from the study show that although azithromycin was a more effective treatment of active trachoma (and of intense cases, especially) than topical tetracycline applied by unsupervised caregivers, both treatments had high cure rates. Given the differences in price between the two drugs, the Gambian NECP decided not to switch its first-line treatment for active trachoma. They are, however, considering the possibility of a change in first-line treatment for children with TI and are monitoring the price of azithromycin. This study was conducted with a low budget, largely within the resources of a national program, and is an example of the kind of practical operational research that can be performed within such programs. Effectiveness studies such as this are needed to help translate research findings into policy and practice, especially in developing countries where they are needed in other areas.

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