COMMENTARY

Elimination of trachoma: are we in danger of being blinded by the randomised controlled trial?

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Implementing SAFE (Surgery for trichiasis, Antibiotics for active trachoma, Facial cleanliness and Environmental improvements) strategy and mass antibiotic treatment and prevent blinding trachoma at low cost.

The past decade has seen a major reduction in the burden of infectious blindness, of which trachoma is the leading cause. Repeated infection with the obligate intracellular bacteria *Chlamydia trachomatis* results in the clinical syndrome of blinding trachoma. Trachoma progresses from inflammation of the upper tarsal conjunctiva to scarring; distortion of the eyelid causes trichiasis and eventual loss of vision secondary to corneal opacity. Accounting for about 7 million cases, or 15% of world blindness a decade ago,¹ trachoma now accounts for approximately 2 million cases or around 4% of the total.² Trachoma is a disease usually associated with poor personal and community hygiene and poverty, now largely confined to the developing world. The gradual improvement in socioeconomic conditions in these nations has contributed to the decrease in the prevalence of this terrible blinding disease. However, the widespread implementation of the SAFE strategy (Surgery for trichiasis, Antibiotics for active trachoma, Facial cleanliness and Environmental improvements) has been important also.

The SAFE strategy was developed by the World Health Organization (WHO) in the 1990s and the mass distribution of antibiotics, particularly azithromycin, in communities where trachoma is endemic is an important component of this strategy. In 1999, the results of the first randomised controlled trial (RCT) that randomised at community level were published and supported community-wide treatment with oral azithromycin as being superior to community-wide treatment with topical tetracycline.³ Since then, at least four large cohort studies carried out in Tanzania,^{4,5} Ethiopia⁶ and The Gambia⁷ have shown reduced prevalence of chlamydial infection or clinical signs of active trachoma after community-wide treatment with

oral azithromycin. The results of a single mass treatment in a village hyperendemic to trachoma in the Kongwa district, Tanzania, showed a reduction in the prevalence of chlamydial infection from 57% to 12% 2 months after treatment.⁴ Similarly, in Rombo district, Tanzania, where trachoma is endemic a sustained reduction in the prevalence of chlamydial infection was achieved after a single mass distribution of azithromycin; however, in Rombo, all children with active disease at 6, 12 and 18 months were offered topical tetracycline treatment.⁵ In addition both studies reported considerable reductions in the prevalence of clinical disease. In Ethiopia, children in 24 randomly selected villages were monitored for chlamydial infection after community-wide mass treatment with oral azithromycin. The prevalence of infection dropped from >50% at baseline to <10% at 2 months.⁶ However, in this community, where trachoma is hyperendemic the prevalence of infection rapidly increased after treatment, suggesting a need for bi-annual treatment to eradicate the disease in such areas. In a region of The Gambia where trachoma is hypoendemic a sustained reduction in the prevalence of chlamydial infection was achieved in 12 of 14 villages that received mass antibiotic treatment with oral azithromycin.⁷

The evidence from cohort studies clearly shows the effectiveness of mass azithromycin distribution programmes and emphasises the need for further research to determine the optimal interval between mass treatments: single, annual or bi-annual. Further support for the efficacy of mass antibiotic treatment comes from a recent RCT in Ethiopia; however, this study will probably not meet the criteria for inclusion in the Cochrane Review.⁸ Intervention and control villages were randomly selected before assigning treatment and control

villages were not assessed at baseline, because it was considered unethical to examine control villages and not provide treatment. Control villages were assessed during a 12-month follow-up, after which treatment was provided. The importance of antibiotics in the race towards the global elimination of trachoma by 2020 should not be underestimated.

A Cochrane Collaboration review, Antibiotics for trachoma,⁹ assessed

... the evidence supporting the antibiotic arm of the SAFE strategy ...

Fifteen randomised trials, from 13 published papers, were included. They compared different antibiotics or compared antibiotics to placebo or no treatment. The main findings were that

For the comparison of oral or topical antibiotics against placebo/no treatment, the data are consistent with there being no effect of antibiotics ...

and

For the comparison of oral against topical antibiotics the results suggest that oral treatment is neither more nor less effective than topical treatment.

We believe the review is inconsistent on three counts. Firstly, it does not assess the question that it asks. The antibiotic arm of the SAFE strategy calls for mass antibiotic distribution, not treatment of individuals with disease. The WHO recommends that if the prevalence of active trachoma is >10% in children aged 1–9 years then the entire community should be treated with antibiotics for 3 years and then reassess the prevalence. In all, 10 of the 13 papers that were reviewed only considered the treatment of individuals, not mass community-wide treatment, and thus should have been excluded from analysis as they did not deal with the question asked.^{10–19} Secondly, three of the reviewed studies assessed antibiotics that are no longer used in trachoma-control programmes.^{11,13,15} Thirdly, the strict inclusion criteria used by the Cochrane Database limited the review to RCTs and meant that good evidence from cohort studies, such as those mentioned above, was not considered.

Owing to the nature of the intervention—mass community-wide antibiotic distribution—randomisation would need to be at the community level. Two of the included RCTs did examine

community-wide antibiotic distribution and randomised at the community level.³⁻²⁰ The results from these two publications were viewed as three separate studies in the Cochrane Review. The study in The Gambia assessed four village pairs, and the studies in Tanzania and Egypt each had only a single village pair. In each pair, one village was randomised to receive mass treatment with azithromycin and the other village received mass treatment with tetracycline. The number of clusters randomised was therefore very small, leading to large confidence intervals, and community level clustering was not analysed. However, the authors of both papers supported the use of azithromycin as being superior to tetracycline.

Owing to the need to randomise at the community level, an RCT designed to provide definitive evidence for the antibiotic arm of the SAFE strategy would need to be large and would be very expensive, an important consideration in a resource-scarce discipline. Furthermore, because of the widely accepted efficacy of the intervention it may not be ethical to incorporate a control arm, as was the case in the recent study in Ethiopia.⁸ For the above reasons, the antibiotic arm of the SAFE strategy will probably never be supported by evidence from RCTs, but this does not mean that community-wide antibiotic distribution is not an effective intervention.

What level of evidence is required before policy makers can initiate public health responses? Certainly no one would advocate acting without evidence, but delaying interventions owing to overly strict evidence requirements may be equally undesirable, nor should evidence requirements be uniform across all areas of health policy. The effectiveness of the treatment is not the only measure that needs to be assessed; cost, quality of life and other factors are also important. The Cochrane Collaboration is given substantial weight in public health and in medicine more generally owing to the thoroughness of reviews. By applying the same rigorous standards, but with an increased flexibility to take alternative research methodologies into account, the

Cochrane Collaboration can only increase its value to health policy makers.

The cost effectiveness of mass antibiotic treatment is partly dependent on the continuation of donated azithromycin,²¹ and the implementation of the SAFE strategy requires a definite commitment from the government. For these reasons, it is important that the SAFE strategy, particularly the antibiotic arm, has the backing of good scientific evidence, and despite the findings of the Cochrane Review we believe that it does. Recently, there have been calls for increased flexibility in the Cochrane Library, particularly to allow the inclusion of different research designs.²² Mass antibiotic distribution for trachoma would seem to be a worthy candidate for such allowances. It will be a tragedy if this effective intervention does not continue to be widely implemented and unnecessary blindness is allowed to occur because we cannot see beyond the RCT.

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