

Can we eliminate trachoma?

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Trachoma is the leading cause of preventable blindness worldwide.¹ Although it disappeared long ago from Western Europe and the United States, trachoma is still as endemic as ever in parts of Africa, the Middle East, Australia, and South East Asia.² Ocular strains of *Chlamydia trachomatis* cause repeated episodes of conjunctivitis in children. In teenagers and adults, the disease progresses through a cascade of conjunctival scarring, entropion, trichiasis, and finally blinding corneal ulceration.³ Most cases of the infectious conjunctivitis are not apparent without flipping a child's lids, so affected children rarely receive appropriate treatment. Treatment with oral or prolonged topical antibiotics can eliminate chlamydia in the majority of cases,^{4,5} but treated children will almost inevitably be reinfected unless infection in the rest of the community is addressed.⁶ Thus, trachoma can only be reduced significantly through an extensive public health campaign that targets whole communities.

The World Health Organization (WHO), in conjunction with non-governmental organisations and national health services, recently began implementing a programme designed to eliminate blinding trachoma.² The WHO's GET 2020 programme (global elimination of trachoma by the year 2020) has adopted a comprehensive set of control measures for trachoma endemic areas summarised as the SAFE strategy (Surgery for entropion/trichiasis, Antibiotics for infectious trachoma, Facial cleanliness to reduce transmission, and Environmental improvements such as access to clean water and control of disease-spreading flies).⁷ Antibiotics are a key component of this programme, and Pfizer Inc has already donated nearly a million doses of azithromycin to Morocco and Tanzania for trachoma control, and has committed at least a million more to Mali, Ghana, and Vietnam. The GET 2020 strategy has been carefully designed by a consortium of scientists and public health experts from around the world. Optimism is high, but the question remains—will it work?

There are many reasons to think that the current elimination efforts will be successful. Theoretically, it is possible to eliminate chlamydial infection from a community with repeat mass antibiotic administrations, even without a 100% effective treatment and without complete coverage.⁸ This is because ocular chlamydial infection progresses so slowly through a community that if antibiotics

are administered frequently enough (that is, annually in most locations), then infection will not be given a chance to return to its previous prevalence before the next treatment. Thus, infection should progressively decrease and eventually disappear stochastically. In fact, determining the proper "dosing regimen" for a community is somewhat analogous to determining the dose frequency of an antibiotic in an individual using pharmacokinetics.⁹ In some studies, infection appears to return to a community after mass antibiotic administration even more slowly than had been anticipated, further validating this approach⁵ (Osaki Holm S, Jha H, Bhatta R, *et al.* Azithromycin distribution strategies for trachoma, submitted for publication).

Another encouraging sign is that in many areas trachoma appears to be disappearing in the absence of any specific control measures.¹⁰ Trachoma is a disease of the rural poor.¹¹ As living conditions have improved over large areas of the world in the last century, trachoma has also disappeared.¹⁰ Also, since urban poor have never been affected to the same degree as rural poor, then current trends of mass urban migrations should reduce trachoma (although perhaps at the expense of an increase in other diseases). Interestingly, studies in Nepal and other areas have suggested that as trachoma disappears, the prevalence of clinical signs (follicular conjunctivitis) may actually overestimate the prevalence of ocular chlamydial infections in a community.^{5,12} Public health programmes that monitor trachoma prevalence are forced to rely on the clinical examination because laboratory tests are prohibitively expensive; thus, many areas which appear to have hypoendemic trachoma by clinical examination may have even less disease than we currently think.

Perhaps most encouraging is that there may very well be a margin of error in eliminating active trachoma—we may not have to completely eradicate disease to prevent blindness due to trachoma. Ophthalmologists know that a single episode of genitally transmitted *C trachomatis* eye infection (adult inclusion conjunctivitis) will not typically lead to scarring.³ Similarly, investigators have long felt that less frequent or less severe episodes of trachoma in children do not typically lead to cicatricial disease—only repeated, severe disease leads to blindness.¹³ Trachoma is a disease where most morbidity can be eliminated even without

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eradicating the causative agent. If we reduce sufficiently the prevalence of *C trachomatis* in communities with antibiotics while also reducing transmission with improved hygiene and environmental conditions, then infection might never return to its pretreatment levels, even were mass antibiotic programmes to be concluded before ocular chlamydia is itself eradicated. In fact, there is some evidence that intense campaigns to promote facial cleanliness¹⁴ and to reduce a village's fly population¹⁵ may help decrease transmission enough to have an effect on the prevalence.

There are many hurdles to overcome for a trachoma elimination programme to be successful. Even though infection can theoretically be reduced by repeated mass antibiotic administrations, success depends on attaining adequate coverage in a community.⁸ Under study conditions, it has been possible to reach over 90% of individuals in a village.⁵ Under more realistic programme conditions, treatment coverage has been estimated to be closer to 75–80% (Osaki Holm S, Jha H, Bhatta R, *et al.* Azithromycin distribution strategies for trachoma, submitted for publication). It remains to be seen what coverage level is necessary to achieve the desired reduction or elimination of chlamydia from a community.⁸ Just as smallpox programmes had to step up efforts in the most severely affected areas, trachoma programmes may too have to go to exceptional lengths in the hyperendemic areas—perhaps striving for the levels of coverage achieved in study conditions or perhaps treating even more frequently than once per year.

Although infection can definitely be eradicated from households, and possibly even from entire communities, there is probably little hope of actually eradicating ocular strains of chlamydia from an entire country without an effective vaccine. There are clearly areas that are not developing rapidly enough to stave off reinfection. In some of these areas it may be difficult to sustain mass antibiotic programmes even if they are effective. If mass drug administrations are to be limited in time, it will be important to demonstrate conclusively that other measures can reduce transmission sufficiently to prevent infection from returning to pretreatment levels.

Any campaign that includes mass distribution of antimicrobial agents must be concerned with adverse effects of the medicine, including the emergence of drug resistant organisms. Mass distribution of oral sulphonamides to combat trachoma in northern Africa and the southwest United States in the 1940s, 1950s, and early 1960s was eventually halted, in part because of an unacceptable rate of side effects (most notably Stevens-Johnson syndrome) (Dawson C, personal communication, 2000). The worldwide antimalarial campaigns of the 1960s and 1970s never achieved their most optimistic goals at least partly because of emerging resistance. Fortunately, few side effects of azithromycin have been reported so far (mostly transient gastrointestinal complaints). Although it is difficult to monitor for side effects in the developing world, the need to

attempt to monitor for rare but serious side effects during mass treatment campaigns has been recognised. Chlamydial resistance to macrolides (or to azithromycin, which is a closely related azalide) has not been reported, although antibiotic susceptibility is difficult to measure in chlamydia. However, *Streptococcus pneumoniae*, a common respiratory pathogen, colonises 60–90% of children that are targeted for treatment in some trachoma endemic areas, and this organism is known to acquire resistance to macrolides.^{16 17} As it is possible that in some communities the per capita amount of azithromycin distributed in a trachoma programme may exceed that given in western populations, it will be important to monitor antimicrobial resistant pneumococci in treated communities. A few studies, in Australia¹⁶ and Nepal,^{17 18} have already begun to address this issue; additional programmes to monitor the emergence of macrolide resistant organisms are planned in Africa (Flouty G, personal communication, 2000). Although investigators agree that no current data suggest mass azithromycin treatment has detrimental effects on the community, it will be important to monitor adverse effects.

Even if the A, F, and E components of the SAFE programme succeed in reducing infectious trachoma, many communities will be left with a large backlog of trichiasis cases. Unfortunately, recent studies indicate that trichiasis appears to recur even after surgery. In fact, the longer post-surgical cases are followed, the more recurrence there appears to be.¹⁹ While there is some hope that eliminating chlamydia from a community may help prevent existing scarring from progressing and help reduce trichiasis recurrence rates, this has yet to be proved.²⁰ Also, more could be done to prevent the infectious corneal ulcers that are the major cause of blindness from trachoma.²¹ In our excitement to eliminate infectious trachoma, we shouldn't forget that at best an entire generation of individuals will be left with cicatricial trachoma from previous infections.

Public healthcare workers have begun the difficult task of eliminating blinding trachoma. There is still severe disease in some areas that were known to be endemic from the earliest historical times.²² Even so, early results of the GET 2020 programme have been encouraging. There has been overwhelming support from governments, non-governmental organisations, and foundations. With the facilitation of the WHO and the International Trachoma Initiative, the programme has already penetrated to a remarkably large area.¹⁹ With the proper support, there is every reason to hope that the WHO's GET 2020 programme will achieve the same success seen in the previous mass drug administrations for ocular disease, including Credé prophylaxis for ophthalmia neonatorum, vitamin A for xerophthalmia, and ivermectin for onchocerciasis.

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