

## PERSPECTIVE

## Eradication of trachoma worldwide

David Mabey, Robin Bailey

Trachoma is an ancient scourge, described in the Egyptian Ebers papyrus in 1900 BC and well known to Hippocrates. The disease was endemic in Europe until well into this century, and would-be immigrants to the USA were screened for trachoma by examination of the everted upper eyelid on arrival at Ellis Island, New York. Those in whom the characteristic follicles were seen were put on the next boat back to Europe so great was the fear of what was clearly recognised to be a contagious condition.<sup>1 2</sup> Many of the eye hospitals in Europe, including Moorfields, were founded specifically to treat trachoma, and in 1937 Duke-Elder stated that “its importance as a source of human suffering, as a cause of blindness, and as a national economic loss over large tracts of the world’s surface, is second to none among diseases of the eye”.<sup>2</sup>

Trachoma has now disappeared from Western Europe and North America as a result of improved living standards, but unfortunately there are many parts of the world where living standards have not improved, and do not seem likely to in the near future. Trachoma remains the third commonest cause of blindness worldwide after cataract and glaucoma; 150 million people are affected, in 48 countries, and 6 million of these are blind.<sup>3</sup>

The treatment for trachoma recommended by Duke-Elder, copper sulphate, was also used by the ancient Egyptians. But there have been several major advances in our understanding of the disease this century, and in 1997 the World Health Organisation announced a new initiative to eliminate trachoma as a cause of blindness by the year 2020. In this paper we review recent advances and the current state of knowledge about trachoma, and critically discuss the prospects for its eradication.

**Aetiology**

The cause of trachoma was identified in 1907, when two members of Dr Neisser’s team described cytoplasmic inclusions in epithelial cells in Giemsa stained scrapings from the conjunctiva of Indonesian children with trachoma.<sup>4</sup> They called them *Chlamydozoa*, or cloaked animals, because of the way in which the inclusions were draped around the nucleus of the cell. It was not until 1957 that Tang *et al*, in Peking, isolated the organism now known as *Chlamydia trachomatis* in fertile hens’ eggs.<sup>5</sup> Koch’s postulates were fulfilled soon after this, at the Institute of Ophthalmology in London, when the characteristic signs of trachoma were induced by the inoculation of a blind volunteer with an isolate of *C trachomatis*.<sup>6</sup>

The isolation of *C trachomatis* in pure culture was a major advance. It became clear that it was a bacterium rather than a virus, as had previously been thought, and therefore susceptible to antibiotics. A number of treatment campaigns were undertaken with oral sulphonamides in North American Indian populations, but although successful in controlling trachoma, these resulted in severe side effects in a few cases, and had to be discontinued.<sup>7</sup> Topical tetracycline ointment was shown to be effective in

individual cases when applied once daily for 6 weeks, or for 5 days a month for 6 months, but attempts to control trachoma through topical treatment were not successful at the community level, owing to poor compliance and rapid reinfection when only individual cases were treated.<sup>8 9</sup>

**Vaccine trials**

The availability of laboratory cultured organisms stimulated the search for a vaccine against trachoma. Following limited success in preventing trachoma in subhuman primates using killed whole organisms given parenterally, several large field trials were undertaken in humans in the 1960s in Taiwan, Saudi Arabia, and Italy, and at the MRC trachoma unit in the Gambia.<sup>10 11</sup> These vaccines were ultimately unsuccessful, but the trials greatly advanced our understanding of the natural history and pathogenesis of trachoma. In particular, the importance of repeated reinfection in the pathogenesis of the scarring (and blinding) sequelae of trachoma became clear, and the fact that vaccination led in some cases to more severe disease on rechallenge highlighted the importance of immunopathology in chlamydial infection.<sup>12</sup>

**Clinical staging**

When it became clear that whole organism vaccines would not prevent trachoma, and might make it worse, attention turned to preventing transmission as a possible strategy for trachoma control. To identify communities at risk of blinding trachoma, and to provide a tool for measuring the impact of control programmes, a new, simplified diagnostic and scoring system for trachoma was developed and validated by the WHO in the 1980s.<sup>13</sup> This new system had the advantage over the old MacCallan classification of being simpler, so that community eye nurses could obtain reproducible and accurate results, and also of enabling the severity of active (inflammatory) trachoma to be recorded: cases in which more than half the subtarsal conjunctival blood vessels were obscured by inflammation were defined as intense trachoma (TI), as opposed to milder cases, which were defined as follicular trachoma (TF). The prevalence of TI is believed to predict the prevalence of conjunctival scarring, trichiasis, and corneal opacity in the future, and hence to be a measure of the public health importance of trachoma in the community.

**Risk factors**

Trachoma is a disease of poverty and within endemic communities cases tend to cluster within the poorest families. The infection is thought to be transmitted from eye to eye, but the relative importance of fingers, clothes, eye make up, flies, or aerosol transmission via infected nasopharyngeal secretions in this process is unknown.

Numerous studies have implicated poverty, distance to water, the amount of water used by the household, the presence of flies, and poor hygiene as risk factors for trachoma.<sup>14 15</sup> The provision of water to all households with

trachoma is not feasible; it would be prohibitively expensive, and the provision of piped water at the household level was noted to be among the least cost effective health interventions in the 1993 World Bank Development Report "Investing in Health".<sup>16</sup>

### Health education

The demonstration, in the 1980s, of an association between trachoma and dirty faces suggested an alternative control strategy: health education to encourage parents to keep their children's faces clean by regular washing.<sup>17</sup> To be successful, interventions based on behaviour change must involve the community and have its full support; the success of community based approaches has been demonstrated in both Africa and Asia.<sup>18, 19</sup>

A community randomised trial was undertaken in Kongwa, an arid district in central Tanzania with a high prevalence of blinding trachoma, to formally evaluate the impact of health education to encourage face washing on the prevalence of active trachoma.<sup>20</sup> Three matched pairs of villages were recruited. The entire populations of all six villages were treated with tetracycline 1% ointment, applied daily for 30 days, and one village in each pair was also selected, at random, to receive an intensive educational intervention to encourage face washing. A total of 1417 randomly selected children aged 1–7 years were examined at baseline and 2, 6, and 12 months after treatment. At 12 months, children in the intervention villages were 60% more likely to have a clean face. There was no difference between the two arms in the overall prevalence of active trachoma (TF and/or TI), but the prevalence of intense disease (TI) was significantly reduced in the intervention villages (odds ratio 0.62, 95% confidence interval 0.40–0.97). This study showed that it was possible to increase facial cleanliness through education, even in an environment where water is scarce, and that this could reduce the prevalence of severe inflammatory trachoma.

### Treatment with azithromycin

The control of onchocerciasis was revolutionised by ivermectin, when it was shown that a single annual dose could reduce the level of infection to such an extent that it reduced transmission, as well as relieving symptoms and reversing pathology in individual cases. In 1993 we published the results of a randomised, single blind trial conducted in two trachoma endemic villages in the Gambia, west Africa, in which we showed that a single oral dose of the long acting azalide antibiotic, azithromycin (20 mg/kg), was as effective as 6 weeks of 1% tetracycline ointment applied twice daily to both eyes under the supervision of local school teachers.<sup>21</sup> It was also found to be safe and well tolerated. In the tetracycline arm of the study, oral erythromycin was also given to subjects with intense inflammatory trachoma (TI according to the simplified WHO criteria). There were 97 subjects with active trachoma (TF or TI) in each arm, compliance was excellent (>98% of treatment witnessed), and all subjects except one child who died were followed up to 6 months after treatment. By 6 months, disease had resolved in 76 of 97 who received azithromycin (78%), and in 70 of 97 who received tetracycline ointment (72%). The fact that more than 20% of subjects failed to resolve clinical signs of disease was due to the high rate of reinfection, rather than treatment failure. Monitoring of ocular chlamydial infection by an antigen detection assay showed that approximately 40% of subjects had been reinfected within 6 months of treatment. Smaller trials in Saudi Arabia and Egypt also found no difference in treatment efficacy between a single dose of oral azithromycin and several weeks of topical tetracycline ointment.<sup>22, 23</sup>

In an attempt to reduce the high rate of reinfection, we undertook a multicentre trial to compare the impact of community based mass treatment, in which whole village populations were treated with either azithromycin or tetracycline ointment, regardless of whether or not clinical signs of trachoma were present. Villages in Egypt, Tanzania, and the Gambia were randomised to receive either three oral doses of azithromycin (20 mg/kg) at weekly intervals (or 2 weeks of oral erythromycin in the case of women of child-bearing age), or 6 weeks of once daily tetracycline 1% ointment. All village residents were followed up for 12 months with clinical examinations and eye swabs for the detection of *C trachomatis* DNA using a sensitive amplification technique, the ligase chain reaction (LCR).<sup>24</sup> This study showed that azithromycin was at least as effective as 6 weeks of supervised tetracycline ointment under trial conditions, implying that under operational conditions, where compliance with daily ointment is expected to be poor, it is likely to be significantly more effective. The prevalences of ocular chlamydial infection, of TF and, in particular, of TI were all reduced in both treatment arms up to 12 months after mass treatment.

### Fly control

It is often stated in the literature that flies are important vectors of trachoma, but the evidence for and against this view has been anecdotal. Forsey and Darougar showed in 1981 that it was possible to re-isolate *C trachomatis* from flies 30 minutes after feeding them on heavily infected yolk sac preparations, thus demonstrating that transmission by this route is feasible.<sup>25</sup> In 1999 we published the results of a pilot study in the Gambia in which we measured the prevalence of active trachoma in two pairs of villages over a 3 month period. One member of each pair was randomised to receive fly control measures, consisting of twice weekly followed by once weekly ultra low volume spraying with deltamethrin, and the other served as a control. Fly populations were reduced by 75% in the intervention villages, the number of eye seeking flies on children's faces was reduced by more than 90%, and the prevalence of active trachoma fell by 61% after 3 months.<sup>26</sup> More than 90% of flies identified on the faces of children were *Musca sorbens*, the bazaar fly. *M. sorbens* breeds in exposed human faeces, but not in latrines, suggesting that encouraging the use of latrines could prove a sustainable method of controlling trachoma transmission by flies.

### Surgical treatment

Even if it were possible to stop the transmission of ocular chlamydial infection in trachoma endemic communities tomorrow, a large burden of blindness would persist, owing to the presence of irreversible conjunctival scarring and trichiasis. For demographic reasons, the number of individuals with trichiasis is predicted to increase in the next century, even in communities where the prevalence of active disease is falling.<sup>27</sup> To prevent blindness due to trachoma, it will be necessary to make lid surgery available to people with trichiasis. This will not be easy, since blinding trachoma is found in marginalised communities, who lack access to hospital treatment. Moreover, in Africa overall, there is only one ophthalmologist per million population, and these are usually found in the capital city, where they have busy practices.

The operation of choice for trachomatous trichiasis is bilamellar tarsal rotation, which in good hands can lead to freedom from trichiasis in 80% of operated individuals after 2 years.<sup>28</sup> Fortunately this is a simple and safe operation, and equally good results have been obtained by ophthalmic nurses in Tanzania.<sup>29</sup>

### Global elimination

The identification of feasible and effective methods for trachoma control led the WHO to launch, in collaboration with a number of the larger non-governmental development organisations (NGDOs), a new initiative in 1997 for the global elimination of blinding trachoma by the year 2020, based on the "SAFE" strategy: **S**urgery for trichiasis; **A**ntibiotics for the treatment of active (inflammatory) trachoma and for the elimination of the reservoir of infection; **F**acial cleanliness to reduce transmission between children; and **E**nvironmental improvement to reduce fly populations. A major stumbling block which prevented the widespread use of azithromycin in trachoma control was its cost; this problem was overcome, at least for some countries, in 1998, when a new international trachoma initiative was launched by the Edna McConnell Clark Foundation and Pfizer Inc, in collaboration with the WHO, which includes a donation programme in which the drug is provided free to national trachoma control programmes in selected countries.

For this initiative to succeed, it will be necessary to identify communities at risk from local information and rapid assessments to determine the prevalence of TF, TI, and trichiasis. This will not be easy, as trachoma endemic communities are usually "at the end of the road",<sup>30</sup> in remote and inaccessible areas. It will be essential to mobilise and educate target communities themselves<sup>18 19</sup>; the provision of surgery for trichiasis is often a good starting point, and members of the community who have been successfully operated on can be excellent motivators. This in turn will require that ophthalmic nurses or other paramedical workers are trained to perform lid surgery at an affordable price in accessible locations. The best way to deliver azithromycin will have to be decided for each region, even where it is donated free of charge; much can be learned from the experience with ivermectin delivery for onchocerciasis. The importance of flies as vectors will need to be determined in different geographical areas and, if they are important, it will be necessary to develop and evaluate sustainable methods of fly control.

### Conclusion

Trachoma is a forgotten disease of forgotten people, affecting the poorest rural communities in the developing world. It has received far less attention from national governments and the international community than, for example, onchocerciasis, in spite of being a much greater global public health problem. In part, this has been because of the lack of an effective intervention against trachoma. The availability of effective single dose oral treatment is a major advance, and, combined with fly control, community mobilisation, health education, and the provision of surgical services, it could have a major impact on the prevalence of blinding trachoma. It will not be necessary to eradicate ocular chlamydial infection to prevent blinding trachoma, but only to reduce the frequency of reinfection in endemic populations to such an extent that severe conjunctival

scarring, leading to trichiasis and blindness, is prevented. Given sufficient resources and political will, it should be possible to eliminate blinding trachoma by the year 2020.

DAVID MABEY  
ROBIN BAILEY

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine

Correspondence to: Professor D C W Mabey, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT

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