The possibility of eliminating blinding trachoma

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Global elimination of blinding trachoma, the world's leading preventable cause of blindness, now seems possible. The disease, which persists most severely in the poorest parts of Africa and Asia, is already eliminated in North America and Europe. On a scientific basis, the case for elimination was outlined at a WHO global scientific meeting in 1996. To facilitate action, WHO founded the Alliance for Global Elimination of Trachoma by 2020 (GET 2020) in 1997. In 1998 a World Health Assembly resolution called for member states to take steps to eliminate blinding trachoma by 2020 using the WHO recommended SAFE strategy (surgery of late stage disease, antibiotics for acute infection, and improved facial hygiene and environmental change—ie, improved access to water and sanitation). These developments contributed to the decision by Pfizer Inc to donate azithromycin in support of national programmes implementing SAFE and, with the Edna McConnell Clark Foundation, to found the International Trachoma Initiative as a charity dedicated to the elimination of blinding trachoma by 2020. Reports of the early programme scope and impact are encouraging. In ten national programmes currently underway (constituting about 50% of the global burden) more than 55 000 lid surgeries have halted further corneal damage and prevented blindness, and more than 6 million treatments with azithromycin have been given with reductions in acute infections of around 50% in children. Morocco, one of the first countries to implement SAFE with azithromycin, has achieved remarkable results and expects to eliminate blinding trachoma by 2005. If political will and public-health support can be mobilised, the goal of eliminating this cause of blindness can become a reality by 2020.

Lancet Infect Dis 2003; **3:** 728–34

Global elimination of the world's leading preventable cause of blindness—trachoma—seems possible as a result of developments over the past 5 years. Recognising that elimination of disease is a central aim of public health, the WHO devoted an entire supplement to its *Bulletin* in 1998 to a detailed discussion of the possibilities for disease elimination or eradication.[1] In this paper we will briefly review the progress made in a number of endemic countries, to support the assertion that elimination of trachoma is possible.

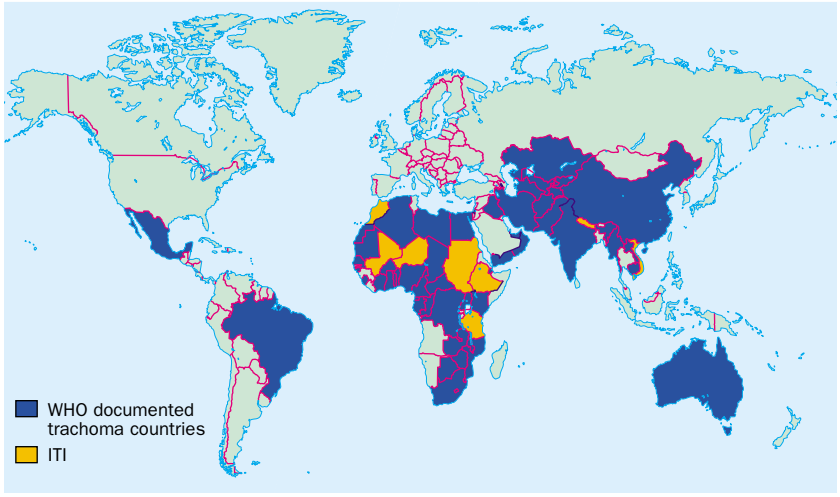

Figure 1. Global distribution of trachoma and ITI supported country programmes. Adapted from http://www.who.int/pbd/trachoma/img/world%20trachoma%202.jpg (accessed Sept 25, 2003).

Trachoma persists most severely in the poorest parts of Africa and Asia (figure 1), although it is already eliminated from North America and Europe probably due in large part to improved socioeconomic conditions, particularly the availability of water and sanitation. Yet, after cataract, trachoma remains the major cause of blindness; WHO estimates that 6 million people are blind based on results of country responses to questionnaires on causes of blindness. It is clear that this visual impairment is most common in the areas of the world with the lowest socioeconomic standards, with rates in women two to three time higher than in men. Worse still, a recent study by Frick and colleagues estimates that this morbidity results in productivity losses of US$2·9 billion per year.[2]

History of trachoma

Descriptions of clinical signs of trachoma, including trichiasis—inturned eyelashes—and surgery for their removal are found in Egyptian papyri. Galen is given credit for the first description of trachoma, the name deriving from the Greek word for rough and describing the lymphoid follicles of the upper lid that are considered pathognomonic of the disease.

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In the 11th century, the Arab physician Ibn 'Isa identified four stages of trachoma and was the first to mention trichiasis as a sequelae of trachoma infection.[3] Eye disease, called "Egyptian ophthalmia", became known in Europe following the experience of French soldiers who occupied Egypt from 1798 to 1801. A similar disease afflicted the opposing British troops, and it is commonly believed that the disease spread in this way to Europe and later by immigrant populations to North America. Many of the eye hospitals founded in England in the 19th century, including Moorfields in London, were established to deal with trachoma. Although its communicable nature was recognised early and the infectious agent was seen microscopically as early as 1907, the organism was not cultured until 1957.[4] In addition to its ability to spread, trachoma was known to be associated with poverty, crowding, poor hygiene, and lack of adequate water supply. New York newspapers at the beginning of the 20th century often contained public-health warnings about trachoma in schools. As a result, trachoma became an exclusion criterion for immigrants to the USA. Immigrants were examined at Ellis Island and signs of the disease could result in hospitalisation or rejection; 36 035 immigrants were denied entry into the USA between 1897 and 1924. Howard Markel describes the impact of this immigration policy on immigrant families in detail.[5] At the same time that immigrants were being turned away from US shores, the US Public Health Service was engaged in a vigorous campaign to control the trachoma "menace" in what was described as the "trachoma belt".[6] Special public education efforts were carried out and trachoma hospitals were established in many of the southeastern US states. The US Public Health Service programme was turned over to the individual states in 1935, and trachoma had ceased to be a problem in the USA by the 1950s.

Trachoma is a chronic keratoconjunctivitis caused by repeated reinfection with the ocular serovars A, B, Ba, and C of *Chlamydia trachomatis* (the other serovars cause genital tract disease). Repeated infections with the ocular strains result in chronic inflammation of the tarsal conjunctiva of the upper lid. The chronic condition results in scarring, shortening of the upper lid with in-turning of the eyelashes—ie, trichiasis. The painful abrading of the cornea, if not corrected, results in corneal scarring, opacity, and blindness. Women are blinded two to three times as often as men probably due to increased exposure and infection as a result of child rearing.[7]

Trachoma is spread from eye to eye in endemic communities by fingers, shared clothing or towels, and probably by fluid-seeking flies in the poor, dry, and dusty areas where it is so often found. Transmission of the infection seems to require close personal contact and therefore the disease commonly clusters in families and villages.[8] The prevalence of active trachoma is highest in children, peaking between 2 and 5 years of age. Prevalence rates of 20% in children are common in endemic areas and may rise to 90% in severely affected communities. Mabey and colleagues recently reviewed in detail the organism, natural history, pathogenesis, immunology, and strategy for management and control of trachoma.[9]

The WHO estimates that trachoma remains endemic in 48 countries including many of the countries of Africa as well as focal areas in the Middle East, and south and central Asia (figure 1). Only small pockets of disease exist in Latin America and Australia. An estimated 146 million people are thought to have active infections leading to the continuing burden of blindness noted above. The heaviest rates of blindness and visual impairment are found in sub-Saharan Africa.

Following immunological and operational research in trachoma supported by the Edna McConnell Clark Foundation, trachoma control received renewed interest during the late 1980s and early 1990s. These research efforts led to the development and enunciation of a comprehensive strategy that combines treatment and prevention and puts in place the measures of hygiene and water use that can sustain control.[10] In 1987, a simple system for the assessment of trachoma was developed,[11] and in 1993 WHO published this simplified trachoma grading scheme in a manual for health workers making possible a sound epidemiological assessment of trachoma at the community level.[12]

The scientific argument for the feasibility of elimination was first outlined at a WHO global scientific meeting in 1996.[13] To facilitate action, WHO founded the Alliance for Global Elimination of Trachoma by 2020 (GET 2020) the following year. These developments contributed to the decision by Pfizer Inc to donate azithromycin (Zithromax) to support national trachoma-elimination programmes and, with the Edna McConnell Clark Foundation, to found the International Trachoma Initiative (ITI) as a charity dedicated to advancing the elimination of blinding trachoma by 2020. In 1998 the World Health Assembly called on member states to take the necessary steps to eliminate blinding disease trachoma by implementing the SAFE strategy.[14]

SAFE consists of the following four components: surgery to correct trichiasis—the immediate precursor to blindness; antibiotics to treat active disease, particularly azithromycin; facial cleanliness to reduce transmission; and environmental improvement to affect the determinants of vulnerability.

Surgery

People with trichiasis, the late stages of trachoma, require surgical correction to halt corneal damage from the disease. To reach effectively this group of people, a high volume of operations needs to be conducted at the community level. Thus there was a dire need to establish the efficacy of a simple technique that could be applied by eye nurses or others in the community. Reacher and colleagues in Oman established that the bilamellar tarsal rotation procedure (BTRP) is simple, quick, and carries a low risk of over correction and defective lid closure.[15,16] The BTRP is not substantially different from the Trabut procedure, which was the widely practised surgical procedure in the past, and is still the preferred procedure in the French-speaking countries of Africa.[17] In 1993, WHO published a manual that is used in training physicians, eye nurses, or other health personnel to carry out this tertiary approach to prevention of blinding trachoma.[18] The challenge now is to make this

procedure readily available at the community level and motivate people with trichiasis to come forward for surgical correction. Bowman and his colleagues in the Gambia have shown that by making trichiasis surgery available at the community level, acceptance rates increased from 44% in health centres to 66%.[19]

Antibiotics

Oral sulphonamides were initially used extensively against trachoma with good results, but their use was discontinued because of frequent adverse reactions.[20] Tetracyclines and erythromycin derivatives (macrolides) have also been widely used in public-health programmes to control trachoma. After large-scale community trials in many countries, the recommended treatment for active trachoma was topical tetracycline, twice daily for 6 weeks.[21] However, the ointment is irritating and difficult to use, especially for the long period required. Furthermore, ocular chlamydia serovars have also been recovered from rectal and nasopharyngeal tissue in 28% of children in communities with trachoma. Additionally, extraocular reservoirs of infection are not amenable to topical therapy and may have a role in the transmission of the organism even after successful treatment of the conjunctiva.[22] This may lead to autoinoculation of an individual and further transmission to other members of the community.

Given the need to treat extra-ocular reservoirs of infection and for compliance in treatment, a single dose, oral, systemic antibiotic was a priority for disease control and ultimately elimination. Azithromycin is an oral systemic antibiotic that results in high tissue to serum concentrations; its concentration in phagocytes ensures delivery to infected tissues, and it provides high, sustained tissue levels as well as high concentration in tears.[23,24] Studies have shown levels above the 90% minimal inhibitory concentration for *C trachomatis* after 4 days in all tear samples and after 14 days in all conjunctival tissue specimens following oral azithromycin administration.[25] Early clinical trials of azithromycin showed efficacy against the genital serovars of *C trachomatis*. Subsequent field trials for trachoma treatment demonstrated on a clinical level and in community use that a single oral dose was as effective as 1% tetracycline eye ointment applied continuously twice daily for 6–10 weeks, or alternatively intermittent twice daily dosing on 5 consecutive days each month for 6 months.[26–29] The experience in these limited trials has been borne out in the experience of the ITI in ten countries using azithromycin as the antibiotic component of the SAFE strategy.

The effect of antibiotic use on resistance is of considerable public-health importance, particularly with respect to the management of acute respiratory infections in children. Surveillance studies of *Streptococcus pneumoniae* have demonstrated short-term changes in susceptibility patterns in the nasopharynx of children.[30] Yet, when clinical syndromes are evaluated, short-term benefit in reducing diarrhoea and fever is reported.[31,32] The largest surveillance study done to date in a hyperendemic trachoma region did not show an effect of mass treatment with azithromycin on the prevalence of antibiotic resistant *S pneumoniae*.[33] Additional studies are in progress to evaluate the microbiologic and clinical impact of azithromycin mass treatment.

Facial hygiene and environmental change

The facial hygiene and environmental change elements of the SAFE strategy are presented together here because they are intimately related. A complete review of the importance of these components of the SAFE strategy was published as part of the Cochrane Collaboration in 2000.[34] Risk factor studies have shown trachoma's relation to environmental conditions—ie, water and water use,[35,36] flies,[37] latrines and latrine use,[38] and facial cleanliness.[39,40] The presence of water alone, without sustained behavioural change that leads to use of water to improve facial hygiene, will not be sufficient to reduce transmission. West and colleagues[41] in Tanzania have shown that even in an area of scarce water, behavioural change leading to improved facial cleanliness can be introduced successfully to children in a community resulting in reduced rates of trachoma. Flies have been associated with trachoma for more than 400 years. *Musca sorbens*, the fly implicated in trachoma transmission, prefers human faeces in the environment (not in latrines) as a larval medium, hence strengthening the argument for both fly control and latrine construction and use.[42] Paul Emerson has recently shown that reducing the population of this fly by 75%

Figure 2. A public-health poster on facial hygiene created by BBC World Service Trust and Africa Vision for the Ministry of Health, Tanzania.

decreased child eye–fly contact by 96%, and, consequently, incidence of trachoma was 75% lesser than a comparison group at 3 months.[43]

The studies described above verify what we have known for years: that with improved hygiene and access to water and sanitation, trachoma will disappear as it has from Europe and North America. Coupling primary prevention, facial hygiene and environmental change with the tertiary and secondary prevention interventions of surgery and antibiotics will be the only way to sustain trachoma control. Hence, the WHO endorsed and recommended the strategy combining these four essential components (or interventions) into the rallying cry of SAFE (in English), SAFI (in Swahili; figure 2), CHANCE (in French), or Najat (in Arabic).

Kuper and colleagues in their detailed critical review of the SAFE strategy[44] found strong support for the efficacy of the surgery and antibiotics components in decreasing the backlog of trichiasis and rapidly reducing the prevalence of active trachoma in children. The evidence for the effects of health education and environmental improvement leading to sustained behaviour change and contributing to trachoma elimination is not as strong. However, experience over the past 100 years, despite lack of a rigorous study with statistical support, argues that these must be included in the strategy for trachoma control and sustained development of communities. Implementing the SAFE strategy is in consonance with other disease-control measures and poverty-alleviation strategies leading to general improvement in quality of life.

Table 1. Output of ITI supported national trachoma programmes by year

	1999	2000	2001	2002
Morocco				
Trichiasis surgery	4905	5003	1432	2606
Antibiotic treatments	634 846	673 649	593 310	816 143
Tanzania				
Trichiasis surgery	671	1072	1940	1545
Antibiotic treatment	70 839	209 578	310 671	517 640
Mali				
Trichiasis surgery		400	2000	4887
Antibiotic treatment		0	275 274	700 000
Sudan				
Trichiasis surgery		118	4	2210
Antibiotic treatment		12 000	97 000	189 233
Ghana				
Trichiasis surgery			293	374
Antibiotic treatment			77 730	100 189
Egypt				
Trichiasis surgery			31	0
Antibiotic treatment			15 000	22 000
Vietnam				
Trichiasis surgery			8458	8243
Antibiotic treatment			141 375	286 692
Niger				
Trichiasis surgery				7123
Antibiotic treatment				90 161
Ethiopia				
Trichiasis surgery				736
Antibiotic treatment				0
Nepal				
Trichiasis surgery				2278
Antibiotic treatment				142 909
Total trichiasis surgery	5576	6593	14 158	30 002
Total antibiotic treatment	705 685	895 227	1 510 360	2 864 967

The global effort to eliminate blinding trachoma

The actions of numerous agencies and individuals support the global elimination effort. WHO guidelines substantiating the major components for control in clinical and field studies provide standardised methods for national programmes, "packaging" these components into the SAFE strategy. Resulting activities in the USA mobilised many of the resources necessary to bring elimination in sight. Pfizer's donation of azithromycin to support national trachoma control programmes was critical. These developments lay the ground for not only the founding of the ITI but also a significant infusion of resources to partner agencies such as the Carter Center, Helen Keller WorldWide, and World Vision from groups like the Conrad N Hilton Foundation, Bill and Melinda Gates Foundation, and the Lions Clubs International Foundation.

As the only entity dedicated solely to the global elimination of blinding trachoma, the ITI has played a significant part in the trachoma effort. Dedicated to attaining the WHO elimination goal by 2020, ITI's activities are organised around three parts: implementation, innovation, and documentation.[45] First, support for country programmes, focusing initially on the countries designated by the WHO as "first priority" for intervention. Second, applied research to improve how the SAFE strategy can best be used in differing economic, social, and epidemiological settings. Third, communication and advocacy to educate both the public and decision-makers of the programme's impact and convince key constituencies to support the elimination effort. Currently, neither trachoma as a cause of blindness nor SAFE as a cost-effective strategy for its control is widely recognised, especially among those whose political will and support is crucial.

As illustrated in figure 1, programmes supported by ITI are underway in ten countries. During its first 2 years, the ITI supported implementation of the SAFE strategy in Ghana, Mali, Morocco, Tanzania, and Vietnam. Based on successful results, the programme was extended to Egypt,

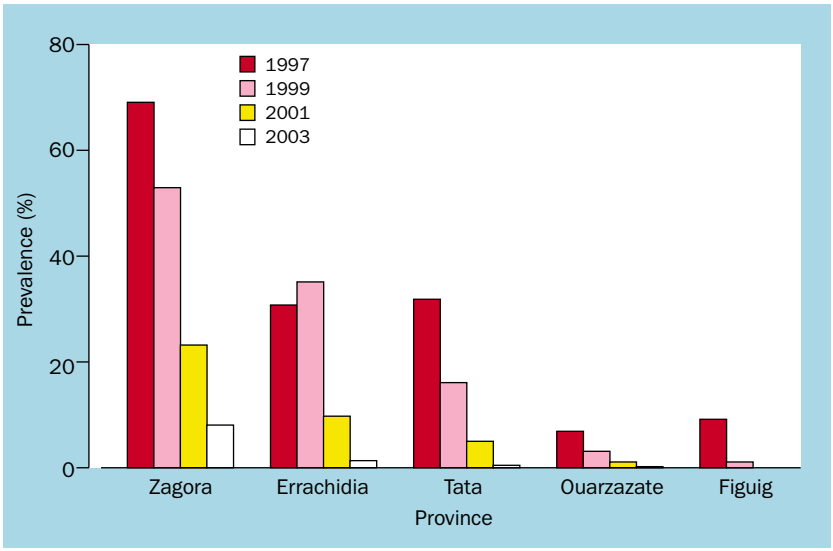

Figure 3. Reduction in the prevalence of active disease in Morocco, 1997–2003.

Ethiopia, Nepal, Niger, and Sudan. These ten countries constitute close to one half of the global burden of active disease and one quarter of the backlog of trichiasis. Additional programme expansion is anticipated later this year.

Progress toward elimination

The early results of national programmes are promising. Ongoing challenges relate to scaling up SAFE to achieve full national coverage and ensuring sustainability of intervention until elimination goals are reached. Table 1 illustrates growth in the output of the national programmes receiving support from ITI. Between 1999 and 2002 the number of people who received trichiasis surgery increased more than five-fold from 5576 to 30 002, and those given antibiotic treatment more than four-fold from 705 685 to 2 864 967. These increases are due both to growth in programme scope and increases in the number of programmes underway. These data provide an indication of programme scope, although they do not provide information on programme impact.

A key challenge to assessing programme impact is defining standards for its assessment with respect to each element of the SAFE strategy. The definition of these standards is complicated for the facial cleanliness and environmental improvement components of the strategy due to a dearth of information on how these interventions relate to reduction in the prevalence of either active disease or trichiasis.[41] The challenge with respect to impact assessment of surgery relates to the relatively low and late occurrence of trichiasis, which rarely exceeds 5% in women over age 40, and the difficulty of assessing changes in the incidence of trachomatous corneal opacities in a programme context. In spite of this difficulty, the surgical output figures reported in table 1 do give a sense of cases of blindness averted. Sustained reduction in the prevalence of active disease is the measure in longer-term progress toward elimination. Despite an absence of consensus on exact age cohort of children to be sampled, reduction in prevalence of active disease in children is a meaningful measure of programme performance and impact.[12]

Morocco will likely be the first country using the SAFE strategy to eliminate blinding trachoma. Progress in the reduction of active disease in Morocco is dramatic. The programme covers the entire endemic area of the five provinces between the Haute Atlas mountains and the Sahara desert. In Zagora province, which remains hardest hit, the prevalence of trachoma is currently estimated at 8·4%, down from 69% in 1997. As illustrated in figure 3, the programme has achieved a 90% reduction in the prevalence of active disease since 1997. Based on these data, there is strong evidence that Morocco will succeed in its effort to eliminate blinding trachoma as a public-health problem by 2005.

While other country programmes are less advanced, operational evaluation conducted under normal public-health operating conditions suggests that the SAFE programme is having an impact. Between 2001 and 2002, inflammatory trachoma in children was reduced by 46·6% in Tanzania. In Ghana, assessment focusing on villages that had a greater than 20% prevalence at baseline found reductions in active disease ranging from 45% to 48·8%. And in a mesoendemic area of Vietnam there was an impressive 91% reduction in active disease over 24 months. Although each country is different, these ministry of health results from national programmes present a consistent pattern of disease reduction.

The possibility of elimination

The progress against blinding trachoma attained by a number of countries highlights the feasibility of the SAFE strategy and the possibility of the global elimination of the

Figure 4. Height as a proxy for weight in calculating dose of azithromycin in Tanzania.

Table 2. ITI programme partners

Programme implementation	Applied research and evaluation	Communications and advocacy
Christofel Blindenmission	Johns Hopkins University	Global Health Council
Helen Keller Worldwide	Worldwide Medical Research Council (UK)	Vision 2020
Ministries of health and other government sectors	Children's Hospital Oakland Research Institute	International Development Enterprises
ORBIS International Sight Savers International	London School of Hygiene and Tropical Medicine Center for Educational Development in Health (Tanzania)	BBC World Service Trust
The Carter Center	University of California, San Francisco	
UNICEF	Health Research Unit (Ghana)	
WaterAid		
WHO		
World Vision		

disease. In less than 5 years, some of the world's poorest countries have planned and implemented successful programmes and demonstrated measurable short-term impact. These successes point to the viability of implementing SAFE in a wide variety of conditions. Thus the prospects for elimination of this disease as a public-health priority are promising and will become a reality in Morocco by 2005. These accomplishments, in conjunction with ongoing innovation for making SAFE implementation easier in the field, such as the validation of height-based antibiotic treatment (figure 4), provide a solid basis for the national and international scale-up necessary to attain further success.[46,47]

Critical to the possibility of elimination is Pfizer's ongoing support of the global trachoma effort. Based on early results, in 2000 Pfizer agreed to continue azithromycin donation for as long as the ITI programmes made progress toward the WHO goal of the global elimination of blinding trachoma. This commitment is necessary, but alone is by no means sufficient to assure elimination.

The recent experience of the Programme to Eliminate Lymphatic Filariasis points to benchmarks, models, and perhaps opportunity for partnerships to expand trachoma control. The use of azithromycin in trachoma control has doubled each year since 2001, and is targeted to treat more than 5 million people in 2003. By comparison, the lymphatic filariasis programme, which was launched in 1999, reached 55 million in 2002 and expects to reach 65 million this year. This contrast points to the possibility of significantly increasing the scope of antibiotic treatment relatively quickly. Similar analysis is required for each component to assess how to improve its efficiency and effectiveness.

As previously noted, WHO estimates that 11 million individuals have trichiasis, with 150 million more having active disease. An updated estimate of the global burden of trachoma, which is under revision by WHO, supports the scale of these figures. This burden of disease translates into providing surgical services to the 11 million with trichiasis. Lowest cost estimates from The Gambia suggest that such surgery could be delivered for about US$6 per person.[48] More recent, as yet unpublished, estimates by ITI suggest that the total cost of surgery would likely approach $15–25 per person. Even with donated medicines, the cost of treatment is not insignificant. Review of ITI data reveals that some programmes have already brought their costs down to below $0·30 per treatment. This figure would bring the cost of delivery of azithromycin treatment in line with the delivery cost of $0·21–0·54 per person reported in other treatment programmes.[49] Taken in light of the burden of trachoma, these figures are not paltry. Estimates—again conducted by ITI—suggest, based on currently recommended treatment strategies,[50] close to 400 million people are in need of antibiotic treatment. This scale of programme will entail a major increase in the pace of expansion. It will also entail a significant infusion of addition political, technical, and financial support. The campaign to eliminate blinding trachoma should learn from the worldwide effort to eradicate poliomyelitis.[51] However, without the need to eradicate an organism, threats to the success of elimination of blinding trachoma are more modest.

The progress achieved over the past 5 years supports the contention that eliminating blinding trachoma is possible. Progress against trachoma to date is a result of cooperation among UN agencies, bilateral donors, non-governmental organisations, and the commitment of countries to integrate the SAFE strategy into their health systems. ITI involves many partners: public, private, national, and non-governmental organisations as well as the bilateral and multilateral agencies. Table 2 provides an example of the agencies actively cooperating on trachoma control. Success in this mission will require many partners and a partnership that adheres to the principles of successful global health alliances described in a recent study conducted by the Bill and Melinda Gates Foundation: sound science, transparency, accountability, and shared responsibility.[52]

Conclusions

While some might suggest that elimination of blinding trachoma is unlikely to be achieved, other experts contend that it is possible.[53] Key to consideration of feasibility is an appreciation that the elimination of blinding trachoma does not involve eradication of the infectious agent; rather it entails suppression of infection and disease and the elimination of its severe, blinding sequelae.

It is the promise of elimination that provides the argument for investing in trachoma control. SAFE is a research-based, field-proven strategy for trachoma control, with components that are part of primary health care, maternal, and child-health programmes, and water, sanitation, and community development. Encouraging reports are coming out on early programme scope and impact. In ten national programmes currently underway, more than 55 000 lid surgeries have halted further corneal damage preventing blindness, and more than 6 million treatments with azithromycin have been given, with reductions in acute infections of around 50% in children. Morocco, one of the first countries to implement SAFE with azithromycin, has achieved remarkable results and expects to eliminate blinding trachoma by 2005. If political will and public-health support can be mobilised, the goal of eliminating this cause of blindness can become a reality by 2020, and in so doing improve the standard of living for some of society's most vulnerable populations.

Acknowledgments

The ITI receives support from the Edna McConnell Clark Foundation, Pfizer Inc, the Bill and Melinda Gates Foundation, the UK Department of International Development, the Rockefeller Foundation, the Dibner Fund, the Izumi Foundation, the Lavelle Fund for the Blind, and private donors. We are indebted to many partners who have carried out the work of trachoma control in many countries. In addition to the ministries of health in the countries described in this paper, we collaborate with Helen Keller Worldwide, Christoffel Blindenmission, the Carter Center, Water Aid, and numerous other partners.

Conflicts of interest

The authors are all associated with the work of the ITI. As noted above, the ITI receives financial support from many sources including Pfizer and serves as the executing agency for Pfizer's donation of azithromycin to national control programmes to eliminate blinding trachoma.

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