The SAFE strategy for the elimination of trachoma by 2020: will it work?

Robin Bailey[1] & Tom Lietman[2]

WHO has recently launched a programme (GET 2020) for the elimination of trachoma, the leading cause of preventable blindness. GET 2020 has adopted the SAFE strategy, a comprehensive set of control measures (Surgery for entropion/trichiasis; Antibiotics for infectious trachoma; Facial cleanliness to reduce transmission; Environmental improvements such as control of disease-spreading flies and access to clean water).

The present article reviews the strengths and weaknesses of each component of the strategy. Although significant hurdles remain to be overcome there is every reason to hope that GET 2020 will be successful.

Keywords: Trachoma/surgery/drug therapy/prevention and control; Meibomian glands/surgery; Azithromycin/therapeutic use; Hygiene; Environmental health (*source: MeSH*).

Mots clés: Trachome/chirurgie/chimiothérapie/prévention et contrôle; Glande meibomius/chirurgie; Azithromycine/usage thérapeutique; Hygiène; Hygiène environnement (*source: INSERM*).

Palabras clave: Tracoma/cirurgía/quimioterapia/prevención y control; Glándulas meibomianas/cirugía; Azitromicina/uso terapéutico; Higiene; Salud ambiental (*fuente: BIREME*).

Bulletin of the World Health Organization, 2001, **79**: 233–236.

Voir page 235 le résumé en français. En la página 236 figura un resumen en español.

Introduction

Trachoma is one of the leading causes of blindness worldwide and the leading cause of preventable blindness (*1*). It is endemic in Africa, the Eastern Mediterranean Region, Australia and parts of Southeast Asia (*2*). Ocular serovars of *Chlamydia trachomatis* cause recurrent conjunctivitis in children. In older persons the disease progresses through a cascade of conjunctival scarring, inturned eyelids, trichiasis, and eventually, corneal ulcers and blindness (*3*). The treatment of children with antibiotics can eliminate chlamydia in a high percentage of cases but reinfection is almost inevitable unless there is a comprehensive programme to prevent transmission from the rest of the community (*4*).

WHO, in cooperation with various nongovernmental organizations and national health services, recently began implementing a programme to eliminate blinding trachoma — Global Elimination of Trachoma by 2020 (GET 2020) (*5*). This programme has adopted a strategy (SAFE), consisting of the following control measures: Surgery for entropion/trichiasis; Antibiotics for infectious trachoma; Facial cleanliness to reduce transmission; and Environmental improvements such as control of disease-spreading flies and access to clean water (*6*).

We review the strengths and weaknesses of the components of the SAFE strategy below and consider the opportunities and threats presented by its implementation.

Surgery

Surgery is the most direct and efficient way to prevent blindness from trachoma. Although blindness develops in only a small fraction of persons infected with chlamydial infection, a significant proportion of those with trichiasis become blind. Although a long time elapses between initial chlamydial infection and blindness, persons with trichiasis are at immediate risk of becoming blind (*7*). Bilamellar tarsal rotation can eliminate trichiasis over 1–2 years, and a randomized clinical trial showed that this technique was significantly more effective than several other methods (*8*).

While trichiasis is clearly the greatest risk factor for corneal ulcers and subsequent blindness, other important factors include decreased tear production and dry eye, decreased conjunctival goblet cells, and thus decreased mucin, conjunctival and lid margin keratinization, and poor lid closure. Numerous procedures have been proposed, including tarsal rotations, tarsal grooves, tarsal advances, cautery and cryotherapy, but no single procedure corrects all the risk factors for corneal ulcers and subsequent blindness. Some complications, such as dry eye and

[1] Medical Research Council Laboratories, Banjul, The Gambia; and London School of Hygiene and Tropical Medicine, London, England.

[2] Francis I. Proctor Foundation, University of California, Box 0944, San Francisco, CA 94143-0944, USA (email: tml@itsa.ucsf.edu). Correspondence should be addressed to this author.

Ref. No. **00-1104**

loss of mucin-producing goblet cells, cannot be corrected by surgery. In addition there is a recurrence of trichiasis after all forms of surgery to correct it, and there is some indication that this continues to happen even two years after surgery (*9*).

An excellent opportunity exists for improving the implementation of bilamellar tarsal rotation surgery throughout those regions where trachoma is endemic. Better access to and acceptance of the surgery are necessary in many areas (*10*, *11*). There is interest in the development of procedures that reduce recurrence rates and deal with the more complicated entropion/trichiasis cases. Furthermore, it may be possible to reduce the progression of cicatricial trachoma to trichiasis by reducing reinfection with *Chlamydia*, and perhaps even the recurrence rates of trichiasis after surgery can be reduced also in this way (*7*).

In 1995 WHO estimated that there were 10.6 million people worldwide with trichiasis attributable to trachoma (*12*). Such people are at high risk for bacterial or fungal corneal ulcer. If trichiasis cases are left untreated, a significant fraction of them develop corneal scarring and blindness. Even if programmes succeeded in reducing or eliminating chlamydial infections there would still be individuals at risk for trichiasis and blindness from cicatricial trachoma, many in urgent need of surgery. Because of the recurrence of trichiasis, there is bound to be a continuing need for reoperation. It is important for surgical trachoma programmes not to lose momentum, even if new incident cases of cicatricial trachoma can be eliminated by reducing chlamydial infection.

Antibiotics

The feasibility of this component of the SAFE strategy has been greatly enhanced by the advent of azithromycin (a macrolide-like antibiotic) for the treatment of active trachoma in one or a few doses, together with Pfizer's Zithromax® donation programme. Several trials have confirmed that azithromycin treatment is at least as good as, if not better than, topical tetracycline for the clinical and microbiological cure of active trachoma (*13*–*16*). Most of these trials have striven to maintain compliance with topical tetracycline treatment. The relative advantage of azithromycin is greatest under practical operational conditions (*17*). Community volunteers can administer azithromycin treatments and can effectively use height-based dosing. A million doses of azithromycin have been administered without apparent serious side-effects and with favourable effects on other common diseases (*18*).

It is assumed that a reduction in active disease by antibiotic treatment will prevent future blindness. However, this may never be rigorously tested because of the long time lapse between initiation of active disease and the development of blindness. Antibiotic treatment alone does not give lasting control because: disease re-emerges in the absence of other control measures; not everyone with infection receives treatment; or migration from untreated areas takes place. The rate and sources of disease re-emergence are poorly understood but knowledge of them is vital when decisions are being taken on whom and how often to treat.

There is an unparalleled opportunity to obtain new knowledge through research within the framework of the donation programme and the implementation of the SAFE strategy. Studies using quantitative molecular diagnostic and typing methods could lead to a better understanding of the relationship between infection and clinical signs and to the identification of likely sources of infectious shedding in affected communities. The public health significance of extraocular reservoirs of infection and subclinical infections in different groups can be evaluated by comparing different treatment strategies. Azithromycin apparently suppresses infection for prolonged periods even in the context of re-emergent disease, perhaps by enhancing functional immunity to chlamydial infection (*16*). This requires further study.

The development of serious resistance of *C. trachomatis* to azithromycin or tetracyclines would seriously compromise the antibiotic component of the SAFE strategy. There are, however, few indications that this is likely to occur. Tetracyclines, for example, have remained effective for many years. The emergence of resistance to common dangerous pathogens such as *Streptococcus pneumoniae* and *Plasmodium falciparum* needs to be to monitored, although macrolide antibiotics are not widely used against these pathogens in areas where trachoma is endemic. The risk of Stevens–Johnson syndrome stopped mass treatments of trachoma with sulfonamides among native Americans in the south-west of the USA (*19*), but there are no reports of such rare serious side-effects associated with azithromycin. Nevertheless, appropriate monitoring should be in place (*18*).

Facial cleanliness

There is considerable evidence that persons with clean faces are less likely than others to have active trachoma. Consequently, there is an assumption that promoting hygiene may reduce trachoma (*20*, *21*). A controlled trial suggested that a vigorous campaign promoting facial cleanliness may reduce the likelihood of persons developing intense trachoma (*22*). Educational activities in the form of skits, school programmes and national radio announcements have been implemented in a variety of cultural conditions, and many groups have long included the distribution of soap and the availability of fresh water as important aspects of trachoma programmes.

Unfortunately, it has been difficult to show that facial cleanliness programmes substantially reduce the prevalence of trachoma in communities. Several studies have attributed changes in the prevalence of active trachoma to such programmes without adequately accounting for chance variation, seasonal

effects, or secular trends (*23*). When villages with intense facial cleanliness campaigns were compared to control villages it was found that face-washing had a minimal effect on the prevalence of active trachoma after a year (*24*). It is hoped that programmes lasting more than a year will have a greater effect.

Any effect of hygiene on trachoma would be extremely important. Antibiotics may well reduce the prevalence of trachoma, but unless mass antibiotic administration is to be continued indefinitely the reintroduction of even a few chlamydial infections may eventually lead to pretreatment levels of infection (*25*). Infection may be delayed or even prevented if a facial cleanliness campaign can reduce transmission.

There is some concern that excessive faith in mass antibiotic distribution could result in diminished enthusiasm for the improvement of hygiene. It should be emphasized, however, that measures to reduce transmission are crucially important unless antibiotics alone can eradicate chlamydial infection locally.

Environmental improvements

There are compelling grounds for believing that trachoma is a disease of poverty and underdevelopment. Much circumstantial evidence suggests that environmental improvement reduces the incidence of trachoma. Evidence from a small intervention trial indicated that the transmission of trachoma could be reduced by fly control and that members of a subpopulation of the fly species *Musca sorbens* were probably mechanical vectors (*23*, *26*). This may be why the use of pit latrines, which reduces the numbers of breeding sites available to *M. sorbens*, has a protective function (*27*).

No single environmental intervention can be recommended for trachoma control since the environmental risk factors are not the same in all settings. Few studies have been free of methodological difficulties, and observational studies typically find that a number of attributes indicative of poverty are correlated (*23*).

The evidence base for the environmental component of the SAFE strategy needs to be strengthened by creative and opportunistic studies. Many of the same issues have been rehearsed in diarrhoeal disease research where considerable experience has been gained in attempts to modify environmental and hygiene factors through participatory health education. Studies of hygiene interventions aimed at diarrhoeal disease should include evaluations of trachoma, which is present in many of the same settings (*28*). Opportunities exist for evaluating sustainable interventions such as the use of latrines and fly traps.

The main threat to the environmental component is that it will be ignored. In many countries there is a separation of education, community development, and water and sanitation from the health ministries, where disease control activities are usually based. Establishing links between agencies and departments in order to underpin action on the environmental component of trachoma control is a formidable challenge on which the ultimate success of SAFE may depend.

Conclusion

We have attempted to review the strengths, weaknesses, opportunities and threats of the SAFE strategy for trachoma control. Pfizer has generously donated over a million doses of oral azithromycin, and is committed to donating millions more. Public health care workers around the world have already begun the difficult task of eliminating blinding trachoma. The early results of GET 2020 have been encouraging but many hazards clearly have to be avoided. There is still severe trachoma in areas where the disease was known to be endemic over 3500 years ago (*29*). Facilitated by WHO and the International Trachoma Initiative, GET 2020 needs to maintain its early success over a very wide area. With adequate support, however, there is every reason to hope that it will achieve results comparable to those of previous mass drug administrations for eye diseases, including Credé's prophylaxis for ophthalmia neonatorum, ivermectin for onchocerciasis, and vitamin A for xerophthalmia. ■

Acknowledgements

T.L. wishes to thank the Alta California Eye Research Foundation, Research to Prevent Blindness, the Edna McConnell Clark Foundation, the International Trachoma Initiative, and the National Institute of Allergy and Infectious Diseases of the USA (Grant K08 AI 01441) for their generous support. *R.B.* acknowledges the generous support of the United Kingdom Medical Research Council, the Edna McConnell Clark Foundation, Sight Savers International, and the United Kingdom Department for International Development.

Résumé

La stratégie CHANCE permettra-t-elle d'éliminer le trachome d'ici 2020 ?

L'OMS a lancé récemment un programme (EMT 2020) visant à éliminer le trachome, cause première de la cécité évitable. EMT 2020 a adopté la stratégie CHANCE intégrant une série complète de mesures de lutte, à savoir : CHirurgie de l'entropion/trichiasis ; Antibiothérapie de l'infection trachomateuse ; Nettoyage du visage pour réduire la transmission de la maladie ; Changements de l'Environnement (lutte contre les mouches qui favorisent la propagation de la maladie et accès à l'eau propre).

Dans le présent article, les auteurs passent en revue les avantages et les faiblesses de chaque composante de la stratégie. Même s'il reste bon nombre d'obstacles à surmonter, tout porte à croire que le programme EMT 2020 sera un succès.

Resumen

Eliminación del tracoma para 2020: ¿funcionará la estrategia SAFE?

La OMS ha iniciado recientemente un programa (GET 2020) para eliminar el tracoma, causa principal de ceguera prevenible. GET 2020 ha adoptado la estrategia SAFE, un conjunto integrado de medidas de control (cirugía para el entropión/triquiasis; antibióticos para el tracoma infeccioso; higiene facial para reducir la transmisión; y mejoras ambientales como la lucha contra las moscas transmisoras de enfermedades y el acceso a agua salubre).

En el presente artículo se analizan los puntos fuertes y débiles de cada componente de la estrategia. Aunque quedan importantes obstáculos por salvar, todo hace confiar en el éxito del programa GET 2020.

References

1. **Thylefors B.** The World Health Organization's programme for the prevention of blindness. *International Ophthalmology*, 1990, **14**: 211–219.
2. **Muñoz B, West S.** Trachoma: the forgotten cause of blindness. *Epidemiologic Reviews*, 1997, **19**: 205–217.
3. **Lietman T, Whitcher J.** Chlamydial conjunctivitis. *Ophthalmology Clinics of North America*, 1999, **12**: 21–32.
4. **West S et al.** Nonocular chlamydia infection and risk of ocular reinfection after mass treatment in a trachoma hyperendemic area. *Investigative Ophthalmology and Visual Science*,1993, **34**: 3194–3198.
5. *Report of the First Meeting of the WHO Alliance for the Global Elimination of Trachoma, Geneva, Switzerland, 30 June–1 July 1997* (unpublished document WHO/PBL/GET/ 97.1) Geneva, World Health Organization, 1997 (available at: http://wholibdoc.who.int/hq/1997/WHO PBL GET 97.1pdf).
6. *Report of the Third Meeting of the WHO Alliance for the Global Elimination of Trachoma, Ouarzazate, Morocco, 19–20 October 1998* (unpublished document WHO/PBL/GET/99.3) Geneva, World Health Organization, 1999 (available at: http://wholibdoc.who.int/hq/1999/WHO PBL GET 99.3pdf).
7. **Muñoz B et al.** Incidence of estimates of late stages of trachoma among women in a hyperendemic area of central Tanzania. *Tropical Medicine and International Health*, 1997, **2**: 1030–1038.
8. **Reacher M et al.** A controlled trial of surgery for trachomatous trichiasis of the upper lid. *Archives of Ophthalmology*, 1992, **110**: 667–674.
9. *Report of the Fourth Meeting of the WHO Alliance for the Global Elimination of Trachoma.* Geneva, World Health Organization, 2000 (in preparation).
10. **Courtright P.** Acceptance of surgery for trichiasis among rural Malawian women. *East African Medical Journal*, 1994, **71**: 803–804.
11. **Bowman R et al.** Should trichiasis surgery be offered in the village? A community randomised trial of village vs. health centre-based surgery. *Tropical Medicine and International Health*, 2000, **5**: 528–533.
12. *Global Initiative for the Elimination of Avoidable Blindness.* Geneva, World Health Organization, 1997 (unpublished document WHO/PBL/97.61).
13. **Bailey RL et al.** Randomised controlled trial of single-dose azithromycin in treatment of trachoma. *Lancet*, 1993, **342**: 453–456.
14. **Tabbara KF et al.** Single-dose azithromycin in the treatment of trachoma. A randomized, controlled study. *Ophthalmology*, 1996, **103**: 842–846.
15. **Dawson CR et al.** A comparison of oral azithromycin with topical oxytetracycline/polymyxin for the treatment of trachoma in children. *Clinical Infectious Diseases*, 1997, **24**: 363–368.
16. **Schachter J et al.** Azithromycin in control of trachoma. *Lancet*, 1999, **354**: 630–635.
17. **Bowman R et al.** Operational comparison of single-dose azithromycin and topical tetracycline for trachoma. *Investigative Ophthalmology and Visual Science,* 2000, **41**: 4074–4079.
18. *Report of the Trachoma Technical Meeting.* New York, NY, Columbia University, 2000.
19. **Dawson C.** Personal communication, 2000.
20. **West S, Congdon NS, Mele L.** Facial cleanliness and risk of trachoma in families. *Archives of Ophthalmology*, 1991, **109**: 855–857.
21. **Taylor HR, Sommer A.** Risk-factor studies as an epidemiological tool. *Reviews of Infectious Diseases*, 1985, **7**: 765–767.
22. **West S et al.** Impact of face-washing on trachoma in Kongwa, Tanzania. *Lancet*, 1995, **345**: 155–158.
23. **Emerson P et al.** Review of the evidence base for the 'F' and 'E' components of the SAFE strategy for trachoma control. *Tropical Medicine and International Health*, 2000, **5**: 515–527.
24. **West S et al.** Impact of face-washing on trachoma in Kongwa, Tanzania. *Lancet*, 1995, **345**: 155–158.
25. **Lietman T et al.** Global elimination of trachoma: how frequently should we administer mass chemotherapy? *Nature Medicine*, 1999, **5**: 572–576.
26. **Emerson P et al.** Effect of fly control on trachoma and diarrhoea. *Lancet*, 1999, **353**: 1401–1403.
27. **Courtright P et al.** Latrine ownership as a protective factor in inflammatory trachoma in Egypt. *British Journal of Ophthalmology*, 1991, **75**: 322–325.
28. **Curtis C, Hawkins P.** Entomological studies of on-site sanitation systems in Botswana and Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1982, **76**: 99–108.
29. **Estes J.** *The medical skills of ancient Egypt.* Canton, MA, Science History Publications, 1989.