

## BLINDING TRACHOMA: PREVENTION WITH THE SAFE STRATEGY

SHEILA K. WEST

*Dana Center for Preventive Ophthalmology Johns Hopkins School of Medicine, Baltimore, Maryland*

**Abstract.** Trachoma, the second leading cause of blindness worldwide, differentially affects the poorest communities, which may have the least access to resources. With the establishment of the Global Elimination of Blinding Trachoma by 2020 (GET 2020) goal, the World Health Organization has set an ambitious target for country programs. The currently recommended surgery for trichiasis/entropion, antibiotics for active disease, facial cleanliness, and environmental change to reduce transmission (SAFE) strategy targets all key elements believed to be necessary for a short- and long-term intervention program. This report reviews the need for a multi-faceted strategy, and the evidence supporting the elements of SAFE. Concerns about the implementation are discussed. Additional research is suggested that will enhance the implementation of the SAFE strategy. In the current climate of significant political and social momentum for trachoma control, the SAFE strategy is a safe bet to accomplish the elimination of blinding trachoma.

### INTRODUCTION

Trachoma, the leading cause of preventable blindness worldwide, continues to be hyperendemic in many of the poorest and most remote areas of Africa, Asia, Australia, and the Middle East. Communities with trachoma are often those with the fewest resources to target health issues, and trachoma affects the most vulnerable members of those communities, women and children. Because of its disappearance from developed countries, trachoma was largely forgotten as a public health issue until recently when a new antibiotic donation program coupled with renewed focus by the World Health Organization (WHO) rekindled interest in eradicating blinding trachoma.

In line with the Vision 2020 initiative, WHO has adopted a resolution to eliminate blinding trachoma by the year 2020.<sup>1</sup> To accomplish this ambitious goal, WHO recommends the use of the SAFE strategy for countries implementing trachoma control programs. This multi-faceted approach includes surgery for trichiasis cases, antibiotics to treat the community pool of infection, facial cleanliness to reduce transmission, and environmental improvement to reduce transmission from sources such as flies. There is epidemiologic evidence to support each component of the SAFE strategy, which must be implemented on a community wide basis. Two critical reviews of the SAFE strategy have concluded there is rationale to support its use.<sup>2,3</sup> The purpose of this paper is to discuss why a multi-pronged approach is necessary, to review the data to support the decision to use SAFE, and to suggest areas where further research is necessary.

### TRACHOMA AND THE NEED FOR A MULTI-FACETED CONTROL STRATEGY

Trachoma is a chronic conjunctivitis, with different manifestations depending on the number, severity, and longevity of bouts of infection experienced. In hyperendemic communities, every member of the community can be affected by trachoma, at different stages. Thus, trachoma control strategies, which have a long-term goal of eliminating blinding trachoma, must address each stage differently.

The community pool of active inflammatory disease, and most of the infection with *Chlamydia trachomatis*, resides in the children, particularly pre-school children. Some children

may have signs of active trachoma for prolonged periods as a result of repeated or persistent infections. In adults, the prevalence of active trachoma is much lower; however, the lower prevalence may reflect a much shorter duration of infection and disease in adults, compared with children.<sup>4</sup> Active trachoma, or infection, by itself is not immediately sight threatening, and many infections are asymptomatic. Control strategies targeted for this stage are meant to prevent the blinding complications of repeated infection that are observed in later life. In communities with trachoma, infection and active disease cluster in households or social groups. Thus, active disease and infection control should consist of community-based efforts to interrupt transmission to other children and adults, by isolating infectious secretions and treatment of infection.

Multiple infections and/or prolonged, severe infection are followed by evidence of scarring of the conjunctiva. Even in scarring without evidence of active disease there can be laboratory evidence of *C. trachomatis* infection.<sup>5–8</sup> This infection is suspected to play an active role in the continued pathogenesis of scarring,<sup>9</sup> and cryptic infection may continue to drive the progression to severe scarring and trichiasis.<sup>7,10,11</sup> Mild scarring alone is not a public health problem, but may indicate an ongoing process that could lead to potentially sight-threatening consequences. To prevent scarring, and possibly progression, the number or duration of episodes of severe trachoma must be decreased through community-based efforts alluded to previously.

In a percentage of cases with scarring, the scarring is significant enough to cause trichiasis, or inturned eyelashes. In affected communities, trichiasis is usually most prominent in those more than 40 years old, but can appear in adolescents in affected areas as well. Trichiasis and entropion eventually requires lid surgery to correct the eyelashes rubbing on the globe and prevent visual loss from corneal opacification. The correction of inturned lashes with appropriate surgery can prevent corneal opacification.

This overview demonstrates the need to use a multi-faceted, public health approach that targets trachoma at all stages in these communities. Surgical intervention is needed immediately to prevent those with trichiasis who are at high risk of visual loss from going blind. Prevention of trichiasis can only occur by prevention of the active disease and scarring. Antibiotic provision treats active infections and decreases the community pool of infection, and may prevent progression of scarring in those with scarring and sub-clinical

infection. Face washing and environmental change are efforts towards accomplishing the long-term goal of interrupting transmission and ultimately reducing the level of trachoma to where it is no longer blinding. The immediacy of the goal for elimination of blinding trachoma by 2020 argues for appropriate use of all components of the strategy.

## REVIEW OF THE SAFE STRATEGY

**Surgery.** Even if current control strategies are immediately effective in reducing active trachoma in children, trichiasis will continue to occur in the adult population as result of previous years of exposure to trachoma, and many will progress to corneal opacification and blindness without surgical intervention.<sup>12,13</sup> There are a number of different surgical techniques that have been used to correct trichiasis.<sup>14,15</sup> In particular, tarsal rotation, when performed by an ophthalmologist, was effective in correcting minor and major trichiasis in 80% of cases studied for up to one year.<sup>15</sup> However, in areas in which trachoma is endemic, patients with trichiasis often have very limited if any access to an ophthalmologist. Alternative surgical personnel can be successfully trained to perform trichiasis surgery.<sup>16</sup> Training manuals and videos for use in training alternative manpower are available from the WHO.<sup>17</sup> The cost of surgery is relatively inexpensive, depending on the background and training requirements of the surgeon and the choice of consumables; in The Gambia, costs were estimated at \$6.13 (1998 US dollars).<sup>18</sup>

Availability of trained personnel does not necessarily ensure that patients will use the services. In Tanzania, even after patients were aware that surgery was available and could prevent vision loss, compliance with surgery was very low: only 18% of individuals with trichiasis to whom surgery was offered opted to have the operation in a two-year period and 27% by seven years. The main barriers were perceived cost and lack of accessibility to the health facilities.<sup>19,20</sup> In this environment, costs include those for transportation, food, and an accompanying person who acts as a caretaker. Similar barriers were reported in a study of trichiasis cases in Nigeria, of whom 9% had had surgery<sup>21</sup> and in The Gambia, where 23% of those with major trichiasis had surgery.<sup>22</sup> The introduction of surgery at the village level, as opposed to requiring patients to present at a hospital or health center, should reduce these barriers somewhat.<sup>23</sup>

Some countries have instituted reforms in the health care system that mandate cost recovery. Before considering recovering costs for trichiasis surgery, country planners must weigh the fact that trichiasis differentially affects women,<sup>12,24</sup> who may not have access to cash to pay for services, nor sufficient power in the family structure to demand allocation of cash resources, particularly if elderly.<sup>25</sup> Surgical acceptance may decrease markedly with the institution of cost-recovery schemes, which increases the cost barrier, regardless of location of the surgery. Inequity by sex in access to trichiasis surgical services may result as well. A study from two national trachoma control programs in Vietnam and Tanzania, where surgical services are provided free of charge, found no evidence that women are less likely to obtain trichiasis surgery compared with men (West SK, Nguyen MP, Mkocho H, Holdsworth G, Ngirwamungu E, Kilima P, and Munoz B, unpub-

lished data). However, in a study from Egypt, women were less likely to have surgery compared with men, although trichiasis was 68% higher in women.<sup>26</sup>

Recurrence of trichiasis following surgery is a major problem. Recurrence undermines the confidence of patients in the surgery, and is frustrating for the surgical team. Data from different settings suggest trichiasis recurs following surgery at a rate of approximately 17% per year,<sup>14,16,27,28</sup> although this can vary greatly and has been reported as high as 43% at two years (West E, unpublished data). Recurrence is higher in those for whom repeat surgery is attempted because these are more difficult cases to correct.<sup>15</sup> Incident recurrence following surgery in some studies increases in the years following surgery, suggesting other factors are also important. A study of risk factors in Oman found that surgical patients residing in areas with high trachoma rates were more likely to have recurrence, providing some support to the hypothesis that ongoing exposure to infection is a factor in both the development of trichiasis and recurrence following surgery.<sup>27</sup>

Some of the recurrence is surgery related, which is apparent within a short time following surgery.<sup>23</sup> Several steps can be undertaken to keep surgical failure as low as possible. One is to be certain the training program has a certification component by a surgeon not involved in the training, and preferably a senior surgeon. Trichiasis training programs are often under some pressure to “graduate” trichiasis surgeons who are sent from their districts or regions, and some should probably not be permitted to operate. A manual for certification of trichiasis surgeons is currently in preparation by the WHO, and has been tested in Ethiopia. Such a manual will provide guidelines to programs considering the implementation of certification procedures. Regular review of surgical results, with refresher courses as needed, is another way to lower surgical failures.<sup>22</sup>

There is significant disability associated with trichiasis, which is not confined to those with visual loss. Limitations in the daily activities of village life were found, for women especially, in those with trichiasis but no visual loss.<sup>29</sup> For men and women, having trichiasis and visual loss were associated with more disability than having visual loss from other causes. Such data suggest that the burden of trichiasis is greater than that traditionally expressed as the result of visual loss from trichiasis. Moreover, it points to the necessity of targeting surgery for trichiasis well in advance of visual loss to restore function.

**Antibiotics.** Active trachoma is treated primarily by the use of 1% topical tetracycline eye ointment, using a daily regimen of once or twice a day for 4–6 weeks, or an intermittent regimen. For countries in a special donation program, a single dose of azithromycin, 20 mg/kg up to 1 gm is used, with pregnant women receiving topical tetracycline. Either topical tetracycline or azithromycin is effective in curing cases of ocular *C. trachomatis* infection, although the follicles may not resolve for months following treatment.<sup>30</sup> However, trachoma is a community disease and reinfection is very likely to occur if only isolated cases are treated. A clinical trial of treating the entire community with azithromycin versus tetracycline demonstrated the value of mass treatment in reducing the community burden of infection.<sup>30</sup> Country trachoma control programs currently involve antibiotic treatment of either whole communities or selected groups considered at high risk, usu-

ally at one-year intervals, with the aim of reducing the pool of infection. The effectiveness of this approach, and the length of time it reduces infection in the community is in large part dependent on coverage. Research projects that report coverage of 80% or higher have significantly less recurrence than projects where compliance was less than 80%.<sup>30,31</sup> More frequent treatment has been suggested to be more effective in reducing infection over time in hyperendemic countries, based on mathematical modeling.<sup>32</sup> While all these approaches are effective in the short term, a long-lasting effect has not been attained when antibiotics are used as the only mode of control of active disease.<sup>33-35</sup>

Although the precise reasons for re-emergent trachoma following community-based treatment are unknown, several likely sources exist: first, compliance with treatment is never 100% in the community, especially with topical tetracycline. In studies of community-based treatment, compliance with treatment was a main predictor of no infection and resolution of disease at follow up.<sup>30</sup> Theoretically, infection should continue to decrease with 100% compliance,<sup>32</sup> but in practice that level is never achieved in programs, which strive to cover 75% of target persons each year.<sup>36</sup> Second, populations in these communities are very mobile, with migration of individuals who can bring in new disease, and returning community members who acquire infection outside. Third, the use of topical antibiotics for active disease does not address the problem of extra-ocular reservoirs of *C. trachomatis*, which may result in auto-reinfection in children. However, one study in Tanzania failed to find evidence that nasopharyngeal carriage was an important source of re-emergent infection following treatment.<sup>35</sup> The use of a systemic antibiotic compared with a topical treatment of trachoma in children in a study in The Gambia did not lower the re-emergent rates of infection at follow-up.<sup>37</sup> These two studies suggest that the source of *Chlamydia* reinfection following treatment is not likely to be extra-ocular sources.

Different strategies to distribute azithromycin in trachoma-endemic communities, and different populations to target, provide information on the effectiveness and cost-effectiveness of various alternatives for improving coverage and decreasing disease, although the results may be specific to the country situation.<sup>31,38,39</sup> The decision of whom to treat is a significant issue facing the managers of trachoma control programs. On the one hand, mass treatment programs involve treating non-symptomatic persons with systemic antibiotics. On the other hand, research has shown a significant rate of sub-clinical infection in these communities, and such persons will escape treatment targeted at cases of clinically apparent disease. Left untreated, these sub-clinical cases may be the source of re-emergent disease and are likely to be at increased risk of progression of their own trachoma. Mass treatment of whole communities has been shown to be effective at reducing infection, depending on the coverage rate, for up to one year post-treatment.<sup>30</sup>

Program managers are increasingly looking to devolve control of the trachoma control program to the communities, and one way is to involve the community members in distributing azithromycin. A pilot study in Ghana demonstrated the competency of trained community volunteers at diagnosing trachoma, and properly treating cases with azithromycin.<sup>39</sup> A comparison of using community volunteers versus village government leaders to recruit families for mass treatment in com-

munities in Tanzania showed higher coverage rates for women and children in villages under the community volunteer program.<sup>31</sup> Research showing that for children more than two years old height can be used as a proxy for weight in dosing azithromycin also simplifies the logistics of providing treatment.<sup>40,41</sup>

**Face washing.** In general, poor hygienic conditions favor the transmission of *C. trachomatis* through contact with infectious secretions,<sup>42</sup> with exposure to the ocular and nasal secretions of pre-school children clearly a potential source of infection.<sup>35,43</sup> Several investigations have been carried out on the impact of unclean faces in children, and the value of face washing, on trachoma.

Improving facial cleanliness may decrease the likelihood of transmission. However, ascertaining the frequency of face washing among children is difficult and prone to reporting bias, since in most cultures, mothers are aware that face washing is a desirable activity, regardless of their actual practices. Thus, studies that rely on self-report of face washing may have significant misclassification. In a Tanzanian study, children observed in the home to have clean faces were less likely to have trachoma or severe trachoma compared with children with unclean faces.<sup>44</sup> A longitudinal study of children at two time points six years apart found that children with unclean faces who had clean faces at follow up were less likely to have severe trachoma at follow up (odds ratio = 0.21) compared with children who had unclean faces at both time points, even adjusting for baseline trachoma status.<sup>45</sup> Further research in Tanzania determined the specific elements of an unclean face that were related to the risk of trachoma in children. Four elements were studied: flies, nasal discharge, food on the face, and dust. Children having simultaneously flies on the face and nasal discharge had a two-fold increased risk of active trachoma compared with children without these signs.<sup>46</sup>

The actual mechanism by which face washing or having a clean face may be protective against trachoma has not been identified, but several are likely. Face washing obviously has no effect the course of an episode of infection, but may reduce the likelihood of auto-reinfection or transmission of infection to others. Several studies have found that mothers of children with trachoma are more likely themselves to have active disease, compared with women who either did not take care of children or whose children did not have trachoma.<sup>47-49</sup> Flies seeking moisture and protein, which may be physical vectors of infection, are liable to be less attracted to clean faces than to faces with ocular and nasal secretions (Emerson P, unpublished data).

Whatever the mechanism(s), the results of a randomized, community-based intervention trial in Tanzania suggested that children who had clean faces, following a face washing campaign, had less severe trachoma. Six villages were randomly assigned to either mass treatment alone or mass treatment plus an intensive participatory face-washing campaign that involved the entire community.<sup>50</sup> After mass treatment, children who kept their faces clean were about half as likely to have trachoma at the end of the one-year follow-up, and one-third as likely to have severe trachoma compared with children who did not have clean faces.<sup>51</sup> The difficulties of carrying out a behavioral intervention were evident, but such an approach is likely to be more sustainable for communities with trachoma than the constant provision of antibiotic treatment.

## ENVIRONMENTAL FACTORS

**Provision of water.** Several studies have found a positive association between the distance from the household to the water source and the prevalence of active trachoma.<sup>44,52–54</sup> Clearly the distance to water can place constraints on the amount of water brought to the house, and water becomes a scarce resource whose use for hygiene purposes may be limited. However, the availability of water affects household decisions on how water is to be used, which must also be a factor. In one study in Tanzania, distance to water was related to trachoma, but there was no relationship with the observed amount of water available for use in the household, nor was there a relationship between a functional water supply in the village and the prevalence of trachoma.<sup>24,55</sup> In The Gambia, after controlling for family size, distance to water, and other socioeconomic factors, families with trachoma appeared to use less water for washing children than did the control families without trachoma, regardless of the amount of water available for consumption.<sup>56</sup> These findings suggest that behavioral factors around water use may be more important for trachoma than the total amount of water available.

In general, in areas in which trachoma is endemic, communities with a poor water supply are more likely to have a higher prevalence of trachoma,<sup>54,57,58</sup> but the provision of adequate water does not necessarily ensure that trachoma rates will decrease. The decision to use water to improve hygienic conditions is very complex in these communities, and is clearly an important factor as well.<sup>59</sup> Provision of adequate water for communities is a large infrastructure development issue, with justification based on benefits more extensive than just trachoma. Therefore, trachoma control programs should create partnerships with ministries and donors who are involved in water programs for maximal efficiency.

**Control of flies.** One of the earliest risk factors noted for trachoma was the presence of flies.<sup>42,44,46,60–62</sup> In trachoma-endemic areas, epidemics of bacterial conjunctivitis and increases in the prevalence of active trachoma have been observed following peaks in the fly population.<sup>33,63</sup> Flies are suspected to act as physical vectors for transmission of *C. trachomatis*, and their ability to carry *Chlamydia* that may transmit ocular infection has been demonstrated in laboratory settings.<sup>64</sup>

In a pilot study in The Gambia to investigate the role of flies in trachoma, Emerson and others conducted a trial in which one member of each pair of villages received three months of spraying with deltamethrin to control flies.<sup>65</sup> Muscid flies were the targets of the intervention, especially *Musca sorbens*, the fly most commonly found in contact with eyes. After three months, the continual spraying resulted in significantly fewer flies in the intervention villages, and 61% less active trachoma. There were significantly fewer new active cases in the intervention villages as well, which was attributed to the lower fly population as a result of spraying. While spraying whole villages is not a sustainable approach to fly control, these data do provide impetus to design fly control measures that can be tested and implemented at the community level.

However, flies are not the only source of transmission, as others have found trachoma where the fly populations are absent<sup>49</sup> or less intense.<sup>66</sup> Flies are associated with trachoma based on studies in areas with moderate-to-high prevalence of

disease, suggesting they contribute to ongoing transmission with efficiency related to the likelihood of landing on an infectious eye.

*Musca sorbens*, the eye-seeking fly, breeds preferentially in solid human feces on the ground.<sup>67</sup> Feces within a latrine do not support the breeding of *M. sorbens*. Thus, removal of human feces through appropriate construction and use of latrines may decrease the fly population, leading to less trachoma.<sup>67</sup> The presence of a functional latrine near the house has been associated with lower trachoma prevalence in several different countries.<sup>44,54,68</sup> The hypothesis that construction and use of sanitary latrines may reduce the risk of trachoma is being tested in a community-based clinical trial. The latrine may also be a marker for families who have better hygiene practices overall.<sup>68</sup>

## FUTURE RESEARCH

The summary of research supporting the SAFE strategy suggests that a multi-faceted approach is necessary, and that the components are justified. The evaluation of the Tanzanian National Program at two years suggests that districts that implement the full strategy show the largest decrease in active trachoma.<sup>36</sup> However, some components have stronger evidence than others, and there is ample need for further research to enhance the effectiveness of the basic SAFE approach. The following research questions and areas deserve immediate attention to maximize the benefits of resources directed towards trachoma control.

1) What are the risk factors for recurrence after trichiasis surgery, and how can we improve the surgical technique? These issues are critical for the performance of trachoma control programs. Operational research on reasons for reluctance to have surgery and barriers to surgery may benefit programs where uptake is low.

2) Why does trachoma re-emerge after treatment in communities? The sources of re-infection have not been clarified. Adults appear to have high rates of sub-clinical infection, but it is not known if such infection is capable of infecting others. Of particular interest is the role of pregnant women and children less than six months old, who must now be treated with topical tetracycline in many areas and could serve as a continued source of infection. As the trachoma rates and infection rates hopefully decrease over time, further research clarifying the targets for treatment, and for how long, are indicated. While models would indicate that trachoma might re-emerge over time, perhaps there is a threshold within the community below which re-emergence as a blinding disease is unlikely.

3) Operational research on alternative strategies for implementation of the antibiotic, face washing, and environmental components of SAFE, with appropriate evaluation, is critically important for determining the most cost-effective implementation of trachoma control programs. The “value added” of face washing and environmental improvements to a program of antibiotic provision over a long period of time has not been demonstrated, and may be different depending on the endemicity of trachoma.

Trachoma has disappeared in many countries without benefit of antibiotics, and this disappearance is attributed to improvements in socioeconomic conditions, better hygiene, and

environmental sanitation. Without the inclusion of hygiene and environmental behavior changes as part of trachoma control, it is unlikely that antibiotics alone will create a long-term reduction in disease. The challenge for trachoma control program managers will be the integration of persons skilled in community development and water and sanitation projects into the country strategy. Another major challenge lies in motivating community participation, a daunting task for these resource-poor areas. A program developed in South Africa using women's groups and the idea of self help in the prevention of disease was very effective in mobilizing community members.<sup>69,70</sup> The local groups were able to identify and treat the clinical signs of active trachoma and took charge of improving personal hygiene in their communities; these groups took a relatively long time to grow but were the key element of the success of the program. The implementation of the SAFE strategy at the local level is critically important, since the strong temptation is to concentrate on provision of surgery and antibiotics and pay less attention to the hygiene and environmental components. The part of the strategy involving motivating significant behavior change on a community level is not easy and involves training and experience that is not traditionally part of an eye care worker's job. Much work remains to be done on the implementation of the strategy and the length of time each component must be placed to reduce blinding trachoma so that it is no longer a public health problem.

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**Author's address:** Sheila K. West, Wilmer Eye Institute, Room 129, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287, Telephone: 410-955-2606, Fax: 410-955-0096, E-mail: shwest@jhmi.edu.

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