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Strategies to Control Trachoma

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Abstract

Trachoma is a significant public health problem that is endemic in 57 countries, affecting 40.6 million people and contributing to 4% of the global burden of blindness. Repeated episodes of infection from *Chlamydia trachomatis* lead to long-term inflammation, scarring of the tarsal conjunctiva and distortion of the upper eyelid with in-turning of eyelashes that abrade the surface of the globe. This constant abrasion, in turn, can cause irreversible corneal opacity and blindness. The Alliance for the Global Elimination of Trachoma by 2020 (GET2020) has adopted the SAFE (Surgery, Antibiotics, Facial cleanliness and Environmental improvement) strategy as the main action against trachoma. Trichiasis surgery reduces the risk of blindness by reversing the in-turning of eyelashes and also improves the quality of life from non-visual symptoms. However, future efforts need to aim at increasing accessibility to surgery and improving acceptance. Antibacterials are required to reduce the burden of infection. Oral azithromycin is as close to the perfect antibacterial as we will get for mass distribution: it is safe, requires only a single oral dose, treatment is usually repeated every 6–12 months, resistance is not seen as a problem, and cost is not a limiting factor with a large donation programme and newer generic versions of the drug. Future focus should be on the details of antibacterial distribution such as coverage, frequency of distribution and target population. The promotion of facial cleanliness

through education may be the key to trachoma elimination as it will stop the frequent exchange of infected ocular secretions and thus reduce the transmission of infection. However, innovative methods are required to translate health education and promotion activities into sustainable changes in hygiene behaviour. Environmental improvements should focus on the barriers to achieving facial cleanliness and cost-effective means need to be identified. There are a number of countries already eligible for certification of trachoma elimination and if current momentum continues, blinding trachoma can be eliminated by the year 2020.

1. Trachoma

The obligate intracellular Gram-negative bacteria *Chlamydia trachomatis* has existed from the Jurassic period, but probably started to manifest as 'trachoma' after the last Ice Age when humans congregated into the first settlements.[1] The disease was once so widespread that it formed the basis for the development of the major eye hospitals in Europe, North America and Australia. Today, trachoma remains a significant public health problem amongst the worlds' poorest and most disadvantaged. The disease is endemic in 57 countries, with 40.6 million having the active disease and 8.2 million afflicted with trichiasis (in-turning of eyelashes that abrade the surface of the globe) [figure 1].[2]

Children, especially pre-school children, are the major reservoirs of *C. trachomatis*.[4-6] Infection is transmitted by sharing infected eye secretions through close physical contact (e.g. during play or when sharing a bed), indirect spread of fomites (e.g. shared towels) or by eye-seeking flies. A single episode of infection results in a self-limiting episode of chlamydial conjunctivitis ('inclusion conjunctivitis'). Repeated episodes of infection lead to long-term inflammation and, if uninterrupted, severe inflammation will lead to scarring of the tarsal conjunctiva.[7] This scarring will distort the upper eyelid and lead to the insidious progression to trichiasis. The scar tissue can also result in loss of mucus-secreting glands, causing a dry eye and/or blockage of the nasolacrimal duct followed by a watery eye and bacterial conjunctivitis.[8] If untreated, trichiasis leads to irreversible opacity to the cornea and blindness.[9]

Trachoma is a disease that tends to cluster because of socioeconomic, environmental and cultural factors.[10] On a global scale, trachoma is clustered in the most impoverished regions, which tend to be the hot and dry areas.[11] At the village and household level, family hygiene appears to be the final major factor contributing to clustering. Family hygiene, in turn, is dependent on various socioeconomic factors including low family income and socioenvironmental factors such as lack of latrine facilities and difficult access to water.[12] Some have suggested that genetic factors may also play a role, possibly as a modifier of the host response, although more data are required to resolve this. Sociocultural factors are perhaps the most important in determining trachoma risk, as these factors determine a family's knowledge, attitudes and practice of hygiene. Socioeconomic, environmental and cultural factors together determine an individual's ability to carry out hygiene practices and the ability to share infected ocular secretions from unclean faces, a factor that has been repeatedly associated with higher rates of active trachoma.[13,14]

Chlamydiae are characterized by their unique development cycle.[15] The organism usually replicates every 4–7 days.[16] However, the inert 'elementary body' survives in the extracellular environment, and *in vitro*, developing 'reticular bodies' can remain in a suspended, so-called 'latent' state, for several weeks.[17] The elementary body is able to attach itself to an epithelial cell and become internalized. The elementary body then transforms into a metabolically active 'reticulate body' that uses hosts' mechanisms to replicate. The bacterium has also developed

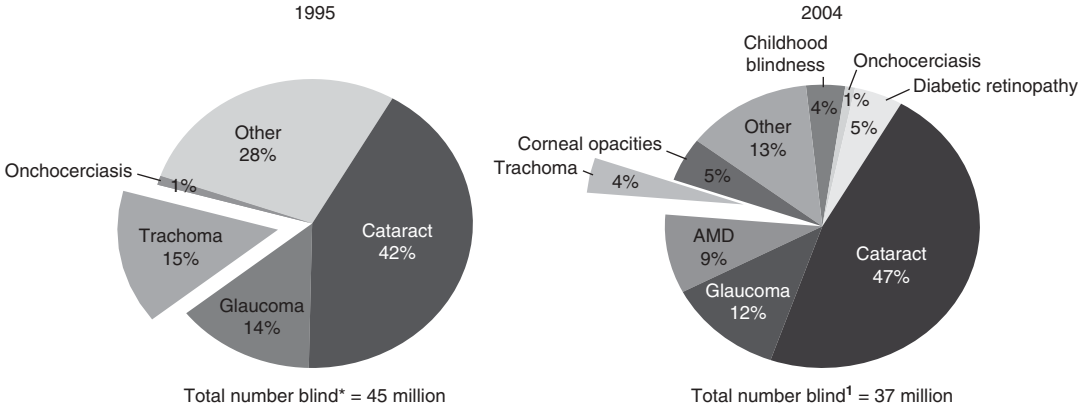

Fig. 1. Causes of blindness.[3] **AMD** = age-related macular degeneration. **1** Refractive error is excluded.

several mechanisms to evade the hosts' immune response. These include its intracellular position inside a phagosome allowing the bacteria to evade antibody and complement attack, inhibition of phagocytosis by host lysosomes, and downregulation of the host cells' major histocompatibility complex class I molecules that restrict the binding and action of cytotoxic T cells.

This article aims to outline knowledge supporting the current trachoma control strategy and areas of the strategy that require further investigation. In keeping with the focus of this journal, the emphasis of this article is to review the antibacterial arm of the control strategy. However, to provide a more complete picture, we have also provided a brief review of the other components of the strategy. To research this article, we searched MEDLINE with the terms 'trachoma', 'SAFE strategy', 'antibiotics' and 'azithromycin'. The WHO database and the reference section of key articles and books were also used as a resource for relevant articles. Only resources written in English were included.

2. The SAFE Strategy

The control strategy for trachoma recommended by the WHO is based on a four-pronged approach known as the SAFE (Surgery, Antibiotics, Facial cleanliness and Environmental improvement) strategy [table I].[18] The SAFE strategy is the main action against trachoma recommended by the Alliance for the Global Elimination of Trachoma by 2020 (GET2020).[19] The aim of this strategy is not to eradicate *C. trachomatis* infection in humans because that would be an unrealistic expectation against a bacterium that has stood the test of time. Instead, the aim is to eliminate endemic blinding trachoma by reducing the risk of transmission with improved hygiene, reduction of infection with antibacterials and treatment of trichiasis with surgery to delay the onset of blindness.[20,21] Although the acronym SAFE is convenient, it reverses the order of importance of the four components.

3. Surgery

The aim of trachoma surgery is to correct the inturning of eyelashes. On the basis of the findings of a randomized controlled trial (RCT),[22] the WHO recommends the bilamellar tarsal rotation procedure.[23] However, several other surgical techniques are still used including the Trabut and Cuenod Nataf procedures. There are limited surgical trials published on these latter procedures,[24] although all three are included in the WHO *Manual for the Assessment of Trichiasis Surgeons*.[25]

The major problem with any trichiasis surgery procedure is high recurrence, varying from 5% up to 40% of operated eyelids after 1 year.[22,26-28]

Table I. The SAFE (Surgery, Antibiotics, Facial cleanliness and Environmental improvement) strategy[18]

Component of the strategy	WHO recommendations
Surgery for trichiasis	Bilamellar tarsal rotation procedure for anyone with trichiasis, regardless of the number or position of eyelashes touching the globe
Antibacterials	1% tetracycline eye ointment to both eyes twice daily for 6 wk OR one oral dose of azithromycin (20 mg/kg bodyweight; maximum 1 g)
	Mass community treatment or targeted household treatment depending on prevalence
Facial cleanliness	Health promotion to educate community about trachoma, the importance of hygiene and practical advice on facial cleanliness
Environmental improvement	Improve water and sanitation facilities

Recurrence may be inevitable because of the progressive nature of the disease and ongoing pathological scarring that may be augmented by changes to the tear film and predisposition to bacterial infection. However, a key factor is often poor surgical technique with lack of attention to operative detail.[29] Recurrence has also been attributed to recurrent *C. trachomatis* infection,[27] other bacterial infection,[30] conjunctival inflammation[28,30] and living in high-risk areas.[28] Other modifiable factors that determine recurrence rates include severity of pre-operative trichiasis,[31] variations in surgical technique[29] and the operating surgeon.[31] These factors emphasize the need for surgery to be performed during early stages of trichiasis and for surgery to be of a high standard with strict audit procedures.

Azithromycin at the time of surgery to improve outcomes has been trialled in three well designed RCTs. The results are not clear-cut. In one study, azithromycin was found to be as effective as tetracycline in an area of low-infection prevalence.[31] In another study, azithromycin decreased the risk of recurrence in major trichiasis cases, but increased the risk of recurrence in minor cases,[32] and the third study showed a statistically significant reduction in azithromycin-treated groups.[33] It is not clear whether azithromycin has a non-specific antibacterial effect preventing post-operative bacterial infection, or a specific effect on potential or actual chlamydial infection.

Current estimates are that 8.2 million people require trichiasis surgery with 50% of the burden concentrated in China, Ethiopia and Sudan.[2] Trichiasis surgical programmes have been implemented in a number of endemic areas; however, despite this, up to 90% of people with trichiasis do not seek medical attention.[34] Barriers to surgery include not knowing that trichiasis is a sight-threatening condition, ignorance of availability of surgery, being aware of poor results of trichiasis surgery, fear of surgery, direct costs (e.g. cost of surgery and transport) and indirect costs (e.g. time away from work, needing someone to look after children).[35-37] To overcome these barriers, an increase in community and individual awareness is required, especially regarding the need for and effectiveness of surgery, and to create realistic expectations of surgical outcome. Improved accessibility such as the provision of village-based surgery also needs to be implemented,[38] and provider-level barriers such as shortage of equipment and supplies need to be addressed.[39,40] However, it is important to remember that elderly patients, long blinded by corneal scarring with now insensitive corneas have little to gain from trichiasis surgery, especially when they are aware of many surgical failures.

Nevertheless, trichiasis surgery is an important arm of the SAFE strategy, not only to reduce the risk of blindness, but to improve quality of life from non-visual symptoms such as photophobia and eye pain.[41] Providing surgery to 80% of the current prevailing trichiasis patients over 10 years has been predicted to avert more than 11 million disability-adjusted life years (DALY) per year globally, with cost effectiveness ranging from $13–$78 (2004 International dollars) per DALY averted.[42] This compares favourably to well accepted extra-capsular cataract surgery, which has estimated to cost $57–$2307 (2004 International dollars) per DALY averted.[43] Future

strategies need to aim at increasing accessibility to surgery and improving acceptance.

4. Antibacterials

Tetracycline, introduced in 1945, has been one of the mainstays of antibacterial treatment for trachoma over the last 50 years.[1] Although oral tetracycline is contraindicated in young children because of the risk of permanent teeth staining, long bone deposition and photodermatitis,[44,45] its topical form has been used for individual and mass treatment. Various treatment schedules have been used, for example, once daily for 10 consecutive days each month for 6 months or twice daily for 5 days each month for 6 months. These regimens have been found to have generally similar results.[46] However, the main problem with all strategies has been compliance because of the prolonged treatment schedule required and frequent adverse effects of discomfort and blurring of vision.[47,48]

Topical treatments also have limited effect and are usually not curative.[49] This has been explained by a variety of reasons including inadequate drug levels, inadequate treatment periods and auto-infection from extra-ocular sites.[44] A medication that was chlamydicidal, non-toxic and effective as a single-dose was required for effective mass treatment.[49]

Azithromycin, derived from erythromycin, met these requirements for an 'ideal drug' (table II). Azithromycin is the first member of the new class of azalide antimicrobials and contains a methyl-substituted nitrogen in the lactone ring.[50] This expanded ring results in improved bio-availability. Compared with erythromycin, azithromycin binds more effectively to the 50S ribosomal subunit, to prevent translation of RNA, thus more effectively inhibiting bacterial protein synthesis. *In vitro*, it has been shown to prevent the growth of *Chlamydia* spp. at all stages of development and is effective for up to 7 days after infection. This is in contrast to tetracyclines and erythromycin, which only inhibit the growth of *C. trachomatis* in cell cultures effectively when added within the first 6 hours.[16] Azithromycin is also unlike penicillin, which affects only binary fission

Table II. Features of azithromycin[50,51]

Feature	Description
Proprietary name	Zithromax® (Pfizer)
Chemistry	Semi-synthetic derivative of erythromycin: contains methyl-substituted nitrogen in the lactone ring
Mode of action	Inhibits bacterial polypeptide synthesis by binding to the 50S ribosomal subunit
Metabolism	Mainly in the liver with biliary excretion
Distribution	Widely distributed in the body with high tissue concentrations
Microbiology	Broad-spectrum activity against Gram-positive and -negative bacteria
Clinical indications	Upper and lower respiratory tract infections
	Otitis media
	Skin and soft tissue infections
	Sexually transmitted diseases
	Trachoma and Lyme disease
Contraindications	Should not be administered to those with known hypersensitivity to azithromycin or any of the macrolides
Clinical safety and tolerance	Adverse effects: well tolerated with minimal adverse effects, including in the elderly and in those with mild to moderate renal or hepatic impairment. Less than 5% experience diarrhoea, nausea, vomiting or abdominal pain
	Drug interactions: does not induce or inhibit cytochrome P450 enzymes. No significant interactions reported that requires dose adjustment
	Paediatric use: approved for use in children >6 mo of age.[51] First line of treatment in children <1 mo of age for the prophylaxis of pertussis[52]
	Use in pregnancy: no evidence of mutagenicity when used in pregnancy.[53] Recommended first-line antimicrobial for treatment of genital chlamydial infection in pregnancy[54]

and causes a state of persistent infection instead of inhibiting chlamydial growth completely through disruption of protein synthesis.[16]

Azithromycin has a broad spectrum of activity against Gram-positive and -negative bacteria including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella* and *Chlamydia* spp.[50] High tissue selectivity with a long tissue half-life makes it suitable for a once-daily administration regimen. In relation to *C. trachomatis* (lifecycle 48 hours to 4–7 days), levels of azithromycin above the 90% minimal inhibitory concentration have been detected after 4 days in tear samples,[55,56] and after 14 days in conjunctival tissue specimens.[55] In addition, it is well tolerated by the elderly (even with mild to moderate renal or hepatic insufficiency), young children[52] and pregnant women,[54,53] and has little interaction with other drugs.[50,55]

The ability for chlamydial elementary bodies to remain in a suspended state for several weeks (i.e. in a state of 'latent infection'[17]) implies that it may not be possible for an antibacterial to kill all the *Chlamydia* present as the bacteria are only susceptible to antibacterials during active replication. Thus, even though azithromycin remains in tissue for more than a week, a single treatment may not be able to eliminate all infection. This underlines the importance of the 'F' and 'E' components of the SAFE strategy in combination with the 'A' component for the effective elimination of trachoma.

In 2005, the Cochrane collaboration published a review of the antibacterial treatment of trachoma.[57] The review included only 15 RCTs and excluded evidence provided by cohort studies. The review concluded that the evidence for the use of antibacterials for trachoma was inconclusive and that ''oral treatment is neither more nor less effective than topical treatment''. This provoked a number of criticisms related to the rigidity of some of the Cochrane Collaboration conventions.[58] The review did not include evidence from several large cohort studies, most of the studies that were included assessed individual rather than mass treatment strategies (which is the WHO recommendation) and three of the included studies assessed antibacterials that were not currently being used in control programmes (sulfafurazole, trisulfapyrimidines and doxycycline).

Three of the early RCTs included in the Cochrane review trialled a single dose of oral azithromycin compared with a course of topical tetracycline in the treatment of individuals with active trachoma and found both to be efficacious with no differences in treatment effect.[48,55,59] However, in all these studies, the application of tetracycline was supervised, thus compliance was satisfactory, which is not necessarily the case in reality. Bowman and colleagues[60] subsequently published a study randomizing individuals with active trachoma to either one dose of azithromycin or a course of unsupervised tetracycline, thus modelling operational conditions. At 6 months, azithromycin was found to be more effective for treating active trachoma (88% vs 73% cure rate).

The only randomized mass distribution studies included in the Cochrane review compared azithromycin and tetracycline in Egypt, the Gambia and Tanzania.[47,61] Pairs of villages were matched based on trachoma rates in 1- to 10-year-old children. Laboratory and clinical activity were substantially lower following each treatment, although azithromycin produced a more substantial and sustained decrease after 1 year.

There are ethical difficulties with RCTs comparing treatment versus no treatment groups in regards to trachoma, because there is a widely accepted and effective treatment available.[58] Chidambaram et al.[62] attempted to overcome the ethical obstacle by not measuring baseline prevalence of control villages. The study found a strong treatment effect 24 months after treatment with a single mass distribution of azithromycin. This was seen after accounting for a secular trend demonstrated in the 15 control villages.

Further support for the effectiveness of azithromycin comes from large cohort studies. Solomon and colleagues[63] showed that mass treatment with high coverage in a community in Tanzania, accompanied by tetracycline treatment of all those affected repeated every 6 months, reduced the prevalence of infection as measured by polymerase chain reaction (PCR) from 9.5% at

baseline to 0.1% at 24 months. A further azithromycin mass treatment was administered at 24 months. Follow-up was undertaken at 60 months and chlamydial DNA was not detected.[64] Mass treatment has also shown to be effective in communities with higher baseline prevalence of trachoma, as demonstrated by Melese et al.[65] in Ethiopia (56.3% pre-treatment to 11% 6 months post-treatment) and West et al.[66] in Tanzania (57% pre-treatment to 12% 12 months' post-treatment).

Despite the evidence, the major barrier to the widespread use of azithromycin has been cost, for example the cost of a 250 mg capsule in Kenya is up to $US7.50 (year of costing, 2005).[42] Mass antibacterial treatment of children using azithromycin at prevailing market prices was calculated to avert more than 4 million DALYs per year globally with cost effectiveness ranging between $9000 and $65 000 (2005 International dollars) per DALY, i.e. above the cost-effectiveness threshold. However, large-scale donation programmes by the manufacturer of azithromycin (Pfizer Inc.) has made the elimination of blinding trachoma an achievable goal. In 1998, Pfizer and the McConnell Clark Foundation founded the International Trachoma Initiative (ITI)[67] and in 2003 Pfizer pledged to donate 135 million doses of azithromycin. However, in 2006, the company extended this pledge and generously committed itself to provide an uncapped supply of azithromycin as long as significant progress continues.[68,69] More affordable generic production of azithromycin since patent expiry ($US0.50 in India; year of costing, 2005)[42] has also enabled mass treatment efforts to be cost effective.

Topical azithromycin has been trialled as a targeted option of treating active trachoma. Although an RCT showed it to be as efficacious as oral treatment,[70] compliance may be still an issue as topical azithromycin is required twice a day for 2 or 3 days and re-emergence may be a problem as non-ocular reservoirs of *C. trachomatis* may not be eliminated.[71] Thus, at present, topical azithromycin is not likely to replace oral azithromycin in programmatic activities, although it may well replace topical tetracycline for those not eligible for oral treatment if it can be made available at low enough cost.

Current WHO guidelines for the antibacterial component of the SAFE strategy recommends treatment with a single oral dose of azithromycin 20 mg/kg (maximum 1 g) or tetracycline ointment to both eyes daily for 6 weeks.[18] If the baseline prevalence of active, follicular trachoma in 1- to 9-year-old children is ≥10% in a community, the guidelines recommend that "antibiotic treatment of all residents should be undertaken annually for (at least) 3 years" (coverage of ≥80%) and then a "repeat survey should be carried out". Annual mass treatment should continue until the prevalence at a community level is <5%. When the prevalence of active disease is above 10%, it is logistically easier and more resource efficient to use community-based mass treatment as trained personnel are not required to examine each person.[72] The 3-year time stipulation is suggested as trachoma is unlikely to be eliminated before this time[73] and undertaking costly prevalence surveys before this time is unlikely to show a change and will not be resource efficient. Some important unresolved issues remain regarding azithromycin distribution strategies and the remainder of this section aims to address some of these issues.

4.1 How to Treat?

There has been debate whether antibacterial treatment should be directed at only individuals with active disease, targeted at all members of households that include some with active trachoma, or mass treatment of the whole community.

Treating individuals with clinically active disease has been shown to miss a significant proportion with *C. trachomatis* infection.[74-76] Targeting treatment to the clusters in which trachoma occurs, that is those households positive for the disease,[77-80] is intuitive as treatment will be directed at the individuals most in need and to whom the disease could be transmitted. This method is also appealing because of the expectation that fewer resources will be used, including antibacterials, and fewer people will be treated unnecessarily.[72] Household-based treatment has shown to be effective in low-prevalence settings.[75] However, in high-prevalence settings,

this method is less effective than either the mass treatment of children[72,81] or community based mass treatment,[82] and much less resource efficient as a result of the need for trained personnel to identify households with positive cases,[72] and the presence of numerous subclinical infections.[82]

Schemann et al.[82] estimated from a study in Mali that at a prevalence level of 35% and if the drug was bought at generic prices, the unit cost of treating each person at risk would be $US0.43 (year of costing for study, 2001) for mass treatment of children and women of child-bearing age compared with $US0.56 for targeted household treatment. However, if the prevalence level was 10%, then unit cost per person at risk would be $US1.50 for mass treatment of children and women of child-bearing age compared with $US0.82 for targeted household treatment as fewer individuals at risk would need to be treated. The calculations in this study suggest that the cut-off prevalence level for shifting to a targeted distribution could be between 15–20% instead of 10%. Thus, the choice between mass treatment of all individuals or family-based treatment should be based on prevalence, with very high prevalence favouring community-based mass treatment as there are more people at risk, it is logistically simpler and more cost effective.[64,74,82]

Other benefits of azithromycin treatment must also be considered, such as the favourable effects on common infectious causes of morbidity such as skin infections and diarrhoea.[83,84] Another argument for mass treatment is the indirect protective effect among untreated individuals (excluded because of age, contraindication to azithromycin or absence during the treatment period), similar to the 'herd protection' described in vaccination programmes.[85,86]

4.2 Who to Treat?

The main burden of *C. trachomatis* is known to be in very young children.[4,87,88] Some have suggested this finding may be less striking in areas of low prevalence and a small number of adults without signs of inflammation have been shown to be positive for *C. trachomatis*.[87] The implications of latent infection as a potential source of infection transmission[74] or as a cause of ongoing scarring[87] is not completely understood, and thus limiting treatment to children may exclude an important reservoir of infection.

Infants <6 months of age have not been included in most mass treatment strategies and children <1 year of age are often excluded from studies[15] on the basis that azithromycin is not widely approved for use in this age group. There are three reasons why this age group should be included in mass azithromycin treatment strategies. First, infants are a significant source of infection and in extreme cases, >50% of the community bacterial load may be harboured in children under 1 year of age.[87] Secondly, the alternative treatment prescribed, such as tetracycline ointment or oral erythromycin, is not without its compliance and complication issues.[47,48,89] Thirdly, azithromycin is recognized as safe in young children and has been approved for use in children over 6 months of age.[51] Azithromycin is also recommended by the US Centers for Disease Control and Prevention as the treatment of choice in infants aged <1 month for the prophylaxis of pertussis as it is better tolerated and is associated with improved compliance compared with erythromycin.[90] Thus, safety issues need not be grounds to exclude azithromycin for the treatment of children aged <1 year. It is noteworthy that infants <6 months of age have recently been included in azithromycin mass drug administration protocols for the Northern Territory in Australia and documentation of safety should be available shortly.[91]

Pregnant women are also often excluded from azithromycin treatment strategies and treated with alternatives such as tetracycline. These women are often the primary care-takers for other young children who are reservoirs of *C. trachomatis*.[87] Thus, pregnant women are also likely to harbour active disease and be potential sources of transmission.[92] Azithromycin is recommended as a first-line antimicrobial for the treatment of genital chlamydial infection in pregnancy[54] and in an RCT of presumptive treatment of mothers for sexually transmitted diseases (STDs), it was shown that mothers treated with antibacterials

(including azithromycin) had better outcomes in terms of neonatal health when compared with the group who did not receive treatment.[53] Thus, azithromycin should be appropriate treatment for pregnant women in mass treatment strategies.

4.3 How Often to Treat?

Solomon et al.[63] suggest that one round of mass drug administration with high coverage (>95%) may be sufficient to eliminate infection, as PCR-detected infection reduced from 9.5% to 0.1% 24 months after treatment. Repeat community-based mass treatment was administered at 24 months and a follow-up study at 60 months after initial treatment showed no evidence of infection.[64] However, in this study, everyone with active disease at each follow-up (at 6, 12, 18 and 42 months) was treated with a 6-week course of topical tetracycline. Therefore, despite the misleading title of the original article and the follow-up article, this study did not actually show the impact of a single dose of azithromycin, but rather the combined effect of 6-monthly treatment with azithromycin and tetracycline.[93]

Other evidence suggests that trachoma will re-emerge if treatment is only given once[65,66] and frequency of treatment depends on initial prevalence.[65,94] Melese et al.[65] found prevalence of infection to drop from 56.3% to 6.7% after mass treatment of a community with 92% coverage; however, infection levels rose again to 11% 6 months post-treatment. West et al.[66] also found re-emergence of infection after mass treatment of a community with a baseline prevalence of infection of 57%. Thus, biannual treatment maybe preferable for areas of high endemicity (>50%). This is strongly supported by mathematical modelling (figure 2)[95] and an RCT of annual versus biannual treatment in communities with high endemicity of infection (mean of 42.6% and 31.6%, respectively).[96] In the study by Melese et al.,[65] the prevalence of infection was tested mainly in pre-school children (a random sample of 25 individuals aged >5 years was also selected from each community) and the results were extrapolated to the rest of the community. However, after adjusting for differences in baseline prevalence, biannual treatment was associated with lower prevalence of infection at 24 months.

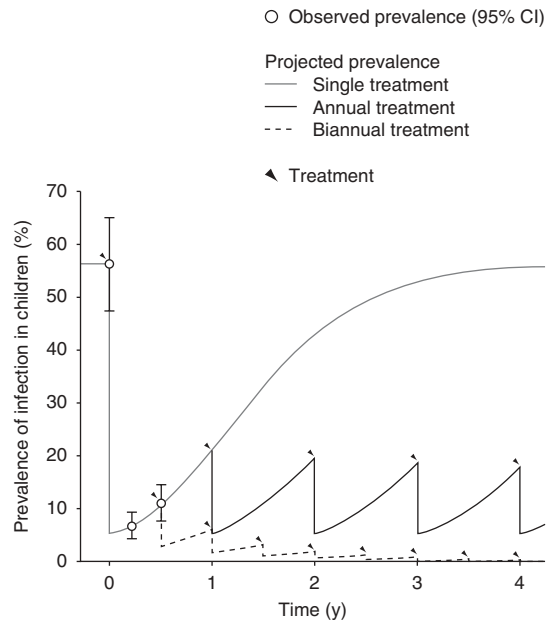

Fig. 2. Mathematical projections of trachoma prevalence derived from empirical pre-treatment, 2- and 6-month post-treatment results (reproduced from Melese et al.,[65] with permission. Copyright © 2004, American Medical Association. All rights reserved).

Some authors have suggested that a potential complication of antibacterial treatment and the need for repeated treatment may result from a decrease in development of protective immunity, leaving the person more susceptible to subsequent reinfection. This theory gains some support from animal experiments,[97] and the observation of an apparent increase in infection and reinfection after a control programme for chlamydial STDs had been introduced in British Columbia, Canada.[98] However, others have reported a significant change in the frequency of positive reports following a change in chlamydial testing and have cautioned about the over-interpretation of these trends.[99] It should be noted that such an effect has not been observed in any of the areas where trachoma has been eliminated with the help of antimicrobials over the last 70 years.

Success of mass drug administration also depends on adequate treatment coverage,[100] and

the interaction with untreated communities or migration.[94] Mathematical modelling suggests that annual mass treatment of 80% of the population in a hyperendemic area will eliminate infection in 95% of villages within 12 years.[100] Modelling also suggests that increasing coverage to 90% and frequency of treatment to 6-monthly, can lead to elimination of infection in 95% of hyperendemic villages within 5 years. However, most studies assess antibacterial treatment in isolation and have not included other components of the SAFE strategy. Instituting the facial cleanliness and environmental components will reduce the likelihood of ongoing reinfection, most probably reduce the number of antibacterial treatments required and give sustainable reductions in trachoma.

4.4 What should be the Indicators for Treatment?

There has been debate on the use of clinical grading (as the WHO guidelines suggest) or more specific laboratory detection of trachoma for implementing and monitoring trachoma control strategies.

The laboratory tests of highest sensitivity and specificity for the detection of trachoma at present are nucleic acid amplification tests such as PCR.[101,102] Resolution of clinical active trachoma has been shown to resolve more slowly than PCR positivity;[59,64,76,80,81,103] however, the correlation between nucleic acid amplification tests and clinical grading increases with prevalence and increasing severity of the disease.[75,101] The implication is that clinical grading may underestimate the effect of trachoma control strategies and overestimate the number of people who require antibacterial treatment.[64,76] The discrepancy between clinical and laboratory diagnosis is most likely due to the natural history of trachoma. Other infectious diseases such as measles or chicken pox have distinct stages: an incubation period with infection in the absence of clinical signs is followed by frank disease and finally a recovery phase, where the micro-organism has been cleared and the clinical signs slowly resolve (figure 3a).[101] However, trachoma can be characterized by a delayed-type hypersensitivity reaction to chlamydial antigens, where the disease process is complicated by repeated episodes of infection that maintain this destructive immune response, recognized clinically as active trachoma (figure 3b). This progression of trachoma disease is supported by evidence from human studies[88,103] and from controlled animal models, especially the cynomolgus monkey model, which is most similar to human beings.[104] Thus, the argument to use laboratory methods that are often expensive and difficult to access in trachoma-endemic areas,[101] becomes less justifiable when reliable, user-friendly clinical methods exist.

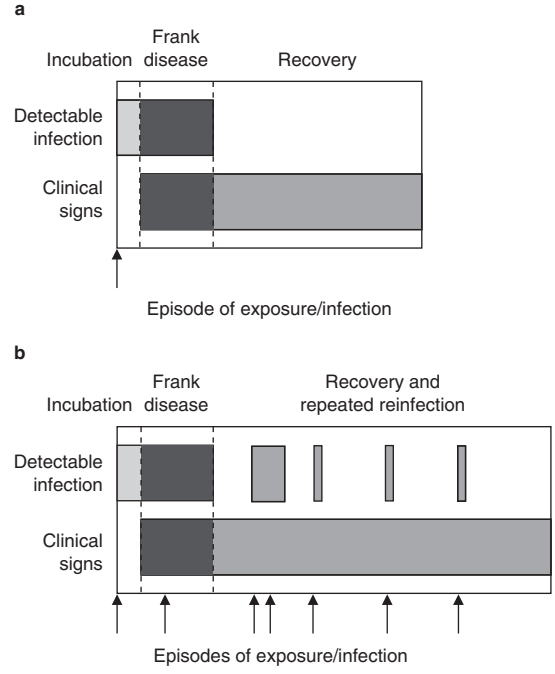

Fig. 3. Relationship between infection and clinical signs in a standard infectious disease (**a**) and trachoma (**b**). A standard infectious disease (**a**) has distinct stages: an incubation period with detectable infection in the absence of clinical signs is followed by frank disease and finally a recovery phase, where the organism has been cleared and the clinical signs slowly resolve.[101] The disease process in trachoma (**b**) is complicated by repeated episodes of infection that may be detectable with laboratory methods in the initial stages of each episode. Evidence suggests that active trachoma is a delayed-type hypersensitivity reaction to chlamydial antigens.

An inexpensive, rapid, field-based assay would be useful, and a dipstick test showed some initial promise in 2006[105] but has been less useful in

further field trials (unpublished observation). Until a reliable, cost-effective test can be found, clinical grading appears to be the best diagnostic tool available for field work in operational conditions at present.

Other possible reasons for the discrepancy between nucleic acid amplification tests and clinical grading that needs to be kept in mind during fieldwork include incorrect clinical grading, other infectious stimuli producing conjunctival inflammation, contamination of laboratory tests, asymptomatic carriage or persistent infection.[101,106]

4.5 When to Stop Treatment?

The WHO guidelines suggesting that treatment should continue annually for at least 3 years[18] does not imply that treatment should automatically stop after this period. Repeat surveys need to be performed and mass treatment should only stop once the prevalence of active follicular trachoma in children aged 1–9 years is <5%.[18] Recent studies suggest that the initial 3 years of annual antibacterial treatment will not be sufficient to decrease trachoma prevalence to <5% in hyperendemic areas[73,100] and that 5–7 years may be required. The level of implementation of other components of the SAFE strategy may alter this timeframe.

Thus, a prevalence of 5% has been taken as an indicator under which mass treatment may not be necessary. This threshold is based on a denominator of a community with a base population of <5000 (a community is typically 1000–5000 individuals in Africa).[1] A larger denominator, such as the population in a district or region, may dilute the actual prevalence of trachoma. If the prevalence of trachoma in a community has remained <5% for 3 years after mass treatment was stopped, then trachoma is considered unlikely to lead to blinding complications and therefore is no longer a public health problem. Although it may not be appropriate to continue mass treatment with antibacterials when prevalence is <5%, family-based treatment should be instituted for each positive case found. The move from community-based to family-based treatment may be logistically difficult, as trained personnel are required to examine every person, identify those households with residual positive cases and be able to treat all relevant household members instead of everyone in the community.[72]

Some have suggested that complete elimination of evidence of ocular infection may be an important endpoint for mass treatment because of the concern that infection will return to communities that have lost immunity to *C. trachomatis* after antibacterials are discontinued.[96] This argument is primarily based on one study with poor treatment coverage and no measures of immune response,[107] and another study of apparent increase in reinfection of chlamydial STD after an infection control programme.[98] Others have noted that elimination of infection may be an important goal as infection may re-emerge from low residual levels.[66] Mathematical modelling[100] and a study in Ethiopia[96] have shown that elimination of infection is an achievable goal even in hyperendemic settings. However, the total elimination of chlamydial infection may neither be necessary nor desirable in the quest to eliminate blinding trachoma. On the one hand, the ongoing cost of treatment and the potential for macrolide resistance in other bacteria need to be considered. On the other hand, the simple presence of ocular chlamydial infection does not lead to blinding trachoma. This is seen in the developed world where outbreaks of blinding trachoma do not occur despite the continuing presence of ocular chlamydial infection that occurs with chlamydial STDs.[21,108]

4.6 Issues with Resistance

To date, *C. trachomatis* has not developed resistance to any antibacterial that has been used on a large scale to treat trachoma.[15] This includes sulfonamides, tetracycline, erythromycin and azithromycin, all of which have been used at difference stages in the fight against trachoma over the last 70 years.[1] The horizontal exchange of antimicrobial resistance factors is not seen as an issue because of the unique replication cycle of *Chlamydia* spp.[109]

However, azithromycin is a potent drug for potential use in a number of other medical

conditions including community-acquired pneumonia, skin infections and genital ulcers,[50] and the concern is that large-scale distribution of azithromycin may induce resistance in other bacterial species.[110] Azithromycin-resistant *S. pneumoniae* strains have been shown to increase immediately after treatment but wane 6–12 months after treatment.[111,112] Even taking into account this transient increase in resistance, elimination strategies are likely to be carried out in locations where macrolides are seldom used and where macrolide resistance even after treatment is less than levels found in Western countries.[113,114] In addition, an infection resulting from a macrolide-resistant *S. pneumonia* in these community-based mass treatment locations, is unlikely to be treated with a macrolide but instead with antibacterials to which *S. pneumoniae* will presumably remain sensitive.[110] Another promising fact is that >65 million doses of azithromycin have been distributed to date by the mass donation programmes of Pfizer[69] with no reported problems of bacterial resistance. Nevertheless, ongoing surveillance of resistance in areas receiving repeated mass administrations of azithromycin is required.

5. Facial Cleanliness

Facial hygiene may be the most important component of the SAFE strategy as lack of facial cleanliness may be ''the final common pathway for all the environmental risk factors'' of trachoma.[1] Crowding leads to the increased likelihood of transmission of trachoma through close proximity and the transference of bacteria from the infected ocular secretions on a dirty face; poor access to water or more importantly the failure to use water appropriately leads to a dirty face; and finally, improper or absent latrines, garbage disposal and close proximity of livestock leads to an increased density of flies that are more likely to land on a dirty face than a clean face and may carry infected ocular secretions to the next child (figure 4).

There are multiple risk factor studies that show an association between poor facial hygiene and rates of trachoma.[4,13,14,115-118] West and colleagues[119] demonstrated that facial hygiene promotion combined with mass drug administration had a larger effect in reducing rates of active trachoma than mass drug administration alone. This effect was statistically significant for

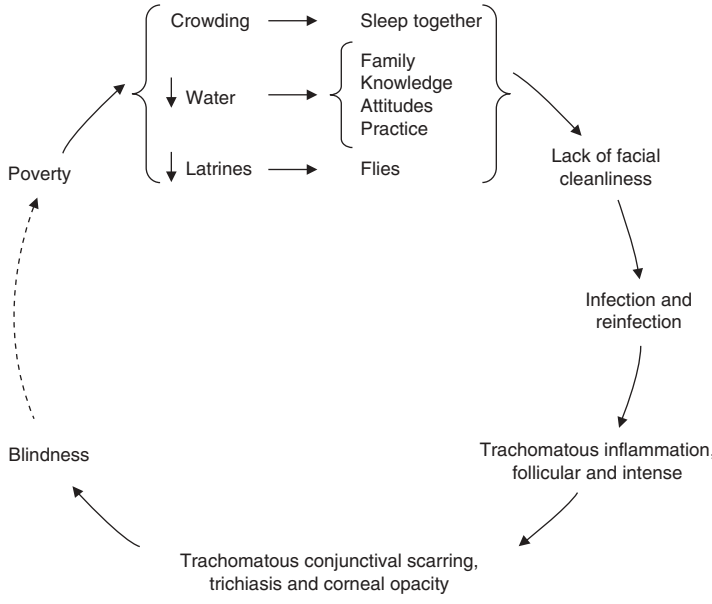

Fig. 4. Interaction of trachoma risk factors (reproduced from Wright et al.,[15] with permission. © 2008, Elsevier Limited. All rights reserved).

the children with the most severe disease and showed a similar trend in those with milder disease.[119] The significance of decreasing the severity of disease is often overlooked; however, this is of prime importance as the severe blinding consequences follow severe active trachoma. When the same cohort was followed-up 6 years later, facial cleanliness still remained marginally protective for persistent trachoma.[13] Sustainable changes in hygiene behaviour can be difficult to achieve and benefits may be gained from integration with general hygiene promotion.

A 3-year follow-up of various components of the SAFE strategy in Ethiopia was recently published.[120] The results are difficult to interpret as the experimental design was not strictly followed and communities received varying interventions than those originally planned. However, regression analysis showed that the odds of active trachoma and PCR positive infection were lower in communities receiving antibacterials in combination with one or two health education components. Knowledge of trachoma control increased in all communities, but there was little change in behaviour related to personal hygiene. A 3-year intervention study of the SAFE strategy in Sudan showed greater decline in prevalence of active trachoma in communities where more 'F' and 'E' activities had been implemented, and also showed independent protective effects against active trachoma of facial cleanliness and face washing more than three times per day.[121,122] Finally, behaviour change was also found difficult to achieve in a study in Vietnam, where health education was implemented in combination with the E, S and A components.[123] There was a significant additional reduction in active trachoma in villages with all components of the SAFE strategy implemented compared with implementation of the 'S' and 'A' components alone. The study also showed that the knowledge of trachoma prevention had increased, but attitudes towards trachoma control and behaviour change were not significantly different between the two villages.

Thus, facial hygiene promotion is an important component of the SAFE strategy even though it may be more difficult to implement and to achieve sustainable change. Innovative methods are required to overcome these challenges.

6. Environmental Improvement

Recommended environmental sanitary interventions undertaken to reduce trachoma have been broad and have included provision of water, latrines, refuse dumps, insecticide spray to control flies, animal pens away from human households, and health education to improve personal and environmental hygiene.[124] These activities are based on a number of epidemiological studies that support these potentially modifiable risk factors as targets for intervention.[6,12,14,77,115,116,125] However, there are few data supporting the effectiveness of interventions targeting these factors. Intensive insecticide spraying has been shown to reduce the population of flies and prevalence of active trachoma in a hypoendemic area in the Gambia.[126,127] However, it is an expensive solution that is not sustainable and was not found to be effective in a hyperendemic area in central Tanzania when it was added to mass antibacterial treatment.[128] Latrine provision was found to not have a statistically significant reduction in active trachoma in the Gambia.[126] However, latrine provision in combination with provision of clean water and health education was found to further reduce active trachoma compared with implementation of the surgery and antibacterial components alone in Vietnam.[123] Independent protective effects of latrine use were also seen in Sudan where the SAFE strategy was implemented in real world conditions and not under stringent clinical trial criteria.[122] These efforts required significant funding and provision of the 'E' component in Vietnam cost $US30–40 per household, made possible only from overseas contributions (years of costings 2002-5).

It is clear that many routes of transmission for trachoma are possible and the relative importance of each may vary in different environments. With lack of strong evidence for cost-effective strategies, the emphasis should be placed on health education and on situation-specific barriers to achieving facial cleanliness, such as access to water and appropriate use of water for

hygiene purposes. The significance of improved hygiene and environmental improvements should not be diminished by the difficulties in achieving this, as the benefits also include reduced morbidity from other diseases, such as infectious diarrhoea, that share similar risk factors.[127,129] Recently, the common features of trachoma and other diseases of poverty have lead to an integrated approach to the control of neglected tropical diseases supported by WHO and major funding bodies such as the Bill and Melinda Gates Foundation.[69] This integrated approach shows promise for combining health promotion messages into an holistic programme and may reduce cost by resource pooling. However, the goal of improving facial cleanliness to decrease trachoma transmission must not be lost in this integrated approach.

7. Conclusion

The elimination of *C. trachomatis* is an unrealistic goal as the organism has coexisted with humans and our ancestors for more than 150 million years. However, one can aim to eliminate blinding trachoma as this goal has clearly been achieved in nearly every developed country. The WHO SAFE strategy is a four-pronged approach that is evidence-based and brings together the behavioural, medical and surgical elements required to address trachoma. The strategy embodies the tenets of the Alma-Ata Declaration of 1978 by attempting to decrease ''gross inequities in health status'',[130] and is closely linked with the Millennium Development Goals[131] and the recent WHO restatement of the importance of comprehensive primary healthcare.[132]

One could recast the SAFE strategy as the FASE strategy to emphasize the appropriate public health importance on each component. To eliminate blinding trachoma we need to ultimately stop the frequent exchange of infected ocular secretions. Thus, the emphasis should be on facial cleanliness (F) through general hygiene education and reducing environmental barriers to clean faces such as access to water, and antibacterial distribution (A) to decrease the reservoir of infection. Surgery (S) is important to address the increasing burden of trichiasis and environmental improvement (E) is important to address hygiene conditions and decrease transmission of infection. However, surgery does not deal with the root cause and non-specific environmental changes are not cost effective if the appropriate risk factors for trachoma in each situation are not targeted.

Oral azithromycin is as close to the perfect antibacterial as we will get for mass distribution: it is safe, requires only a single oral dose, treatment is usually repeated every 6–12 months, resistance is not seen as a problem, and cost is reduced by the large donation programme and newer generic versions of the drug.

There has been a progressive decrease in the estimate of the number cases of trachoma worldwide over time to 40.6 million with active trachoma in 2008.[2] This can be attributed both to socioeconomic development and to the successes of the SAFE strategy. The International Trachoma Initiative is working in 16 countries, and 35 of 38 endemic countries with recorded data have reported some activity towards trachoma control.[69] However, the most recent estimates suggest that antibacterial treatment is still required for some 340 million people and trichiasis surgeries for at least 8.2 million people in 57 endemic countries.[2] Thus, there is still significant work to be done. Future focus should be on the details of antibacterial distribution and the most cost-effective and innovative ways of implementing other components of the SAFE strategy.

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