Trachoma: an overview

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Trachoma is the most common infectious cause of blindness worldwide. It afflicts some of the poorest regions of the globe, predominantly in Africa and Asia. The disease is initiated in early childhood by repeated infection of the ocular surface by *Chlamydia trachomatis*. This triggers recurrent chronic inflammatory episodes, leading to the development of conjunctival scarring. This scar tissue contracts, distorting the eyelids (entropion) causing contact between the eyelashes and the surface of the eye (trichiasis). This compromises the cornea and blinding opacification often ensues.

The World Health Organization is leading a global effort to eliminate Blinding Trachoma, through the implementation of the SAFE strategy. This involves surgery for trichiasis, antibiotics for infection, facial cleanliness (hygiene promotion) and environmental improvements to reduce transmission of the organism. Where this programme has been fully implemented, it has met with some success. However, there are significant gaps in the evidence base and optimal management remains uncertain.

Keywords: trachoma/chlamydia trachomatis/pathogenesis/epidemiology/treatment

Clinical features

Clinically, trachoma is sub-divided into active (early) and cicatricial (late-stage) disease. Active disease is more commonly found in children and is characterized by a chronic, recurrent follicular conjunctivitis, most prominently of the upper tarsal conjunctiva. Follicles are collections of lymphoid tissue subjacent to the tarsal conjunctival epithelium. Intense cases are characterized by the presence of papillary hypertrophy—engorgement of small vessels with surrounding oedema. In more severe cases, there is a pronounced inflammatory thickening of the conjunctiva that obscures the normal deep tarsal blood vessels. During an episode of active disease, the cornea can be affected. There may be minimal symptoms of ocular irritation and a slight watery discharge.

The scarring sequelae of trachoma develop in later life, usually from around the third decade, but can present earlier in regions with more

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severe disease. Recurrent chronic conjunctival inflammation promotes conjunctival scarring, which ranges from a few linear or stellate scars to thick distorting bands of fibrosis with fornix shortening and symblepheron (bands between eyelid and globe). The scar tissue contracts causing in-turning of the eyelids (entropion). Contact between the eyelashes and the eye is called trichiasis. In trachoma, trichiasis commonly results from entropion. However, trichiasis may also arise from misdirection of lashes in a normal position (aberrant lashes) or lashes growing from abnormal positions (metaplastic lashes). Ultimately, blinding corneal opacification can develop. Individuals with entropion and trichiasis frequently experience pain as the lashes scratch the cornea.

The clinical features are usually classified using the Simplified WHO Trachoma Grading System (Table 1).[1] This is reliable and easy to use, yielding useful information on the prevalence of active and cicatricial disease. For research purposes, a more detailed system is sometimes used.[2]

Differential diagnosis

Several conditions can produce a chronic follicular conjunctivitis with a similar appearance to active trachoma, including conjunctivitis caused by viruses (e.g. adenovirus) and bacteria (e.g. *Staphylococcus aureus* and *Moraxella*). Adult inclusion conjunctivitis, infection with genital strains of *Chlamydia trachomatis*, is characterized by large opalescent follicles.

There are several causes of entropion and trichiasis that should be considered in the differential diagnosis, although most of these are relatively rare in trachoma endemic regions. Cicatricial conjunctivitis can be caused by mucus membrane pemphigoid, Stevens–Johnson syndrome, systemic sclerosis, chemical injuries and drugs. In non-trachomatous areas, most cases of entropion are due to involutional

Table 1 The simplified WHO system for the assessment of trachoma[1]

Grade	Description
TF	Trachomatous inflammation—Follicular: The presence of five or more follicles (>0.5 mm) in the upper tarsal conjunctiva
TI	Trachomatous inflammation—Intense: Pronounced inflammatory thickening of the tarsal conjunctiva that obscures more than half of the deep normal vessels
TS	Trachomatous scarring: The presence of scarring in the tarsal conjunctiva
TT	Trachomatous trichiasis: At least one lash rubs on the eyeball
CO	Corneal opacity: Easily visible corneal opacity over the pupil

changes. Two rare congenital disorders result in lashes touching the eye: epiblepharon (upward riding of skin and orbicularis over the inferior tarsus) and distichiasis (additional row of lashes arising from the meibomian gland orifices).

Epidemiology

Prevalence

Trachoma is probably the third most common cause of blindness worldwide, after cataract and glaucoma.[3] Current estimates indicate that there are 8 million people who are blind or have severe visual impairment from trachoma, 7.6 million unoperated trichiasis cases and 84 million with active trachoma. These figures were a significant reduction from the previous estimates (1995) of 6 million blind, 10 million trichiasis cases and 146 million with active disease.[4]

Distribution

During the last two centuries, trachoma retreated from some formerly endemic regions, such as Europe and North America. This change is attributed to general improvements in living standards, rather than specific interventions against the disease.[5] Today trachoma is prevalent in large parts of Africa, and in some regions of the Middle East, the Indian Subcontinent, South-east Asia and South America.[6] The highest prevalence of trachoma is reported from countries such as Ethiopia and Sudan where the prevalence of active trachoma in children is often greater than 50% and trichiasis is found in up to 5% of adults.[7] For many trachoma endemic countries, the socio-economic developments that might promote the disappearance of the disease are likely to be very slow in arriving, which in the light demographic trends and in the absence of effective control programmes could lead to an increase in the amount of trachoma blindness.[8]

Clustering of trachoma

In common with other infectious diseases, trachoma is frequently found to cluster within endemic regions.[9–12] Clustering has been demonstrated at the village, household and bedroom level. This supports the hypothesis that transmission of *C. trachomatis* generally occurs with prolonged close contact between individuals. From the trachoma control perspective clustering is very significant, as it greatly

increases the sample size required to accurately estimate the prevalence within a region.[12]

Transmission of infection

Chlamydia trachomatis, the causative agent in trachoma, is probably transmitted from infected to uninfected individuals within an endemic community by various mechanisms: direct spread from eye to eye during close contact, spread on fingers, indirect spread on fomites (e.g. face cloths) and transmission by eye-seeking flies.[5] A combination of these and other modes of transmission probably functions in most environments, with their relative importance varying between different communities and between members of a community. Therefore, a combination of interventions will be necessary to interrupt transmission.

Age

The signs of trachoma are strongly related to age. The prevalence of active disease peaks in pre-school children and declines to low levels in adulthood.[11,13–15] However, this maybe in part be due to shorter infection/disease episodes with increasing age.[16] Where tests have been used to confirm the presence of *C. trachomatis*, the findings have generally paralleled the clinical observations with much of the infection occurring in children.[14,17] In contrast to the signs of active disease, the prevalence of trachomatous conjunctival scarring increases with age, reflecting the cumulative nature of the damage.[11,15]

Gender

Clinically active trachoma generally occurs with equal prevalence in male and female children. However, in most areas women are more frequently affected by the blinding complications than men.[11,15] About 75% of trichiasis and corneal blindness cases are women, probably due to their greater lifetime exposure to *C. trachomatis* infection through contact with children.[18]

Risk factors for trachoma

Various individual and environmental risk factors have been identified, which may facilitate the introduction and transmission of *C. trachomatis* in endemic communities. Migration of people between communities

is probably important for maintaining trachoma endemicity through the introduction of new strains of *C. trachomatis*.[19] Transmission is probably promoted by crowded living conditions.[9] Children with active trachoma frequently have infectious ocular and nasal secretions and trachoma is often prevalent in regions where water is scarce, probably because less can be used for face washing.[20]

Eye-seeking flies are a common feature of life in many trachoma endemic communities and are frequently observed feeding on ocular secretions. There is good evidence that they can act as vectors for *C. trachomatis* transmission in some environments.[21] The fly most commonly found in contact with eyes is *Musca sorbens*, which preferentially breeds in human faeces. Lack of latrines has often been associated with increased risk of trachoma, probably due to a larger fly population.[10] No animal reservoir for *C. trachomatis* has been found in trachoma endemic environments, although there is an association with cattle, which may result in an abundance of flies.[22]

Chlamydia trachomatis

Chlamydia trachomatis is an obligate intracellular bacteria, with 19 different serovars. These are sub-divided into two biovars; the trachoma biovar (serovars A–K) and the lymphogranuloma venereum biovar (serovars L1, L2, L2a and L3). Endemic trachoma is caused by serovars A, B, Ba and C.[23] Genital chlamydial infection, which causes pelvic inflammatory disease and infertility, is associated with serovars D–K.

During the course of its developmental cycle, *C. trachomatis* exists in two principle forms: reticulate bodies (RB) and elementary bodies (EB).[24] The reticulate body is the larger, metabolically active, intracellular stage. EB are the small, hardy, metabolically inactive extracellular form of the organism in which it transfers between host cells and organisms. The chlamydial developmental cycle commences with the attachment of the EB to the surface of epithelial cells which triggers endocytosis of the bacteria. Inside the host cell, the EB transforms into the RB form which replicates by binary fission. Cells infected with chlamydia are characterized by the presence of a chlamydial inclusion in the peri-nuclear region of the host cell. Eventually, the newly formed RB transform into EB, with condensation of nuclear material and an overall reduction in size. The newly formed EB are released either by lysis of the host cell or by the fusion of the inclusion body with the plasma membrane. *In vitro*, the chlamydial development cycle takes between 36 and 70 h to complete.

The major outer membrane protein (MOMP) accounts for 60% of the surface protein. Variations in MOMP epitopes define serovar specificity and may be an important target for the immune response to *C. trachomatis*. The organism has a single chromosome coding 875 genes and a variable numbers of small plasmids.[25] Although originally believed to lack the ability to generate energy-rich compounds, the chlamydial genome was found to contain a surprising number of genes related to energy metabolism and may be able to perform some limited ATP synthesis for at least part of its life cycle.[25]

Detection of *Chlamydia trachomatis* infection

The detection of *C. trachomatis* infection is problematic. Operationally, trachoma control programmes rely on the clinical signs of disease for diagnosis. However, for research studies, it is often important to know the individual infection status. Various diagnostic tests have been used to detect *C. trachomatis*, but there is no 'Gold Standard' test.[26,27] The earliest method was Giemsa staining of smears of conjunctival cells to demonstrate the chlamydial inclusion body. This allows assessment of the adequacy of the specimen, it is specific but lacks sensitivity.[26,27] The sensitivity of microscopy can be increased by direct immunofluorescence with monoclonal antibodies to *C. trachomatis* antigens.[26,27] *Chlamydia trachomatis* can be grown in cell culture from clinical specimens and then detected by microscopy. This approach confirms the viability of the organism; however, it requires stringent conditions and also lacks sensitivity.[26,27] Enzyme-linked immunoassays are commercially produced which detect chlamydial antigens; however, these have moderate sensitivity and cross-reaction with other bacteria is reported, reducing specificity.[27]

Nucleic acid amplification tests, such as polymerase chain reaction (PCR), are the current favoured modality for *C. trachomatis* detection.[27] These tests are both highly specific and sensitive, identifying significantly more individuals harbouring *C. trachomatis* in endemic populations than previously recognized. However, they are not appropriate for non-research use due to expense and complexity. Considerable care needs to be taken in the collection and processing of conjunctival swab specimens to avoid contamination leading to false positive results. Recently quantitative real-time PCR has been used to measure the load of *C. trachomatis* infection in members of trachoma endemic communities to better define the major reservoirs of infection and monitor response to treatment.[10,17,19,28] Currently, a point-of-care

rapid diagnostic test is being developed which may be of use to trachoma control programmes in the future.[29]

Relationship between clinical signs and infection

Chlamydia trachomatis is thought to be the major stimulant triggering conjunctival inflammation in trachoma, although other bacterial infections have more recently been implicated in individuals with established scarring and trichiasis.[30,31] Corneal opacification and blindness probably develop as a result of traumatic damage by trichiasis and secondary bacterial infection.[30,31]

There is a complex relationship between disease and infection in trachoma, with a mismatch between clinical signs and detection of *C. trachomatis*: active trachoma without detectable *C. trachomatis* and conversely *C. trachomatis* detected in clinically normal individuals.[32] This is a significant problem for trachoma control programmes, which rely on signs to guide antibiotic treatment. It also indicates the importance of the host response in the disease process. There are several contributory reasons for this mismatch. First, there may be an 'incubation period' during which infection is present but disease has not yet developed. Secondly, the resolution of signs of disease lags behind the resolution of infection, often by many weeks.[16] The duration of both disease and infection episodes are modified by age, lasting longer in children. Thirdly, it is possible that a sub-clinical persistent form of infection may develop under certain conditions in which the organism is not replicating but lies dormant and may not provoke the disease phenotype [26]. Fourthly, the signs of conjunctival inflammation are not exclusive to trachoma and could be initiated by other pathogens. Finally, the presence of detectable chlamydial antigen or DNA does not necessarily equate to an established, replicating infection. Tests may be positive as a result of a transient inoculation of the conjunctiva with *C. trachomatis* following close contact with a heavily infected individual or the activities of eye-seeking flies.

Quantitative PCR for *omp1* (a single copy gene on the *C. trachomatis* chromosome) has been used to determine the relative load of infection in members of trachoma endemic communities.[10,17,19,28] The distribution of infection load is skewed; the majority of infected individuals have relatively low infection loads, whereas a smaller number have high loads. The highest infection loads are generally found in children, especially those with intense conjunctival inflammation. Clinically normal individuals with detectable *C. trachomatis* tend to have lower infection loads and do not have detectable expression of chlamydial 16S rRNA, a marker for a metabolically active replicating infection.[33]

In contrast, the presence of 16S rRNA expression was associated with high infection loads and clinical disease.

Histopathology

Active trachoma in children is characterized by hyperplastic conjunctival epithelium and a widespread inflammatory infiltrate of T and B lymphocytes, macrophages, plasma cells and neutrophils.[34] In places this is organized into B-cell follicles. Staining for collagen sub-types reveals a generalized increase in the amounts of types I, III and IV (normally found in the stroma) and deposition of new type V.[35] In adults with trachomatous scarring, the conjunctival epithelium is atrophic and goblet cells are lost.[36] The loose sub-epithelial stroma is replaced with a thick scar of type V collagen. These new vertically orientated fibres are firmly attached to the tarsal plate, causing distortion.[36] Conjunctival inflammation in the presence of scarring and trichiasis is often observed and is associated with a T-cell infiltrate.

Immunity and immunopathology in trachoma

The human immune response to *C. trachomatis* is poorly understood. The resolution of infection is probably dependent on a cell-mediated response; however, this may also play a major role in the pathogenesis of trachomatous scarring. Chlamydial infection is usually confined to a minority of epithelial cells, whereas the inflammatory cell infiltrate extends deep into the substantia propria. It is likely that the scarring and blinding complications of trachoma arise from persistent or repeated inflammatory reactions to the infection.

Innate immune response

The initial response to *C. trachomatis* infection at the epithelial surface is probably made by the innate immune system, with the release of pro-inflammatory cytokines (IL-1, TNF-α) by epithelial cells. This promotes rapid influx of neutrophils and macrophages, which may help to limit the initial infection through phagocytosis.[34] Ongoing activation of these cells, even after infection has resolved, probably plays an important part in the development of scarring.

Adaptive immune response

The initial innate immune response to *C. trachomatis* infection is followed by the development of adaptive immune responses with both antibody-meditated (humoral) and cell-mediated components.

Humoral immunity

The role of the humoral immune response appears to be limited in trachoma. Anti-chlamydial antibodies have been found in the tears and serum of patients with clinically active trachoma. Longitudinal studies of tear anti-chlamydial IgG suggest that this is associated with increased risk of active disease, possibly through facilitating the entry of *C. trachomatis* into host cells and may reflect a T_H2 weighted response.[37] An opposite trend was found with anti-chlamydial IgA, which may interfere with attachment to host cells.

Cell-mediated immunity

Animal models of chlamydial infections suggest that effective cell-mediated immune (CMI) responses are necessary for the resolution of chlamydial infection.[38] Individuals who resolve clinically active trachoma have greater lymphoproliferative responses to chlamydial antigens compared with those who had persistent clinical disease.[39] In contrast, individuals with trachomatous conjunctival scarring had weaker peripheral blood lymphocyte proliferation responses compared with normal controls.[40] Interferon-γ (IFN-γ) appears to be the pivotal cytokine in the resolution of infection through a variety of anti-chlamydial actions.[41] It is primarily released by T_H1 lymphocytes. Individuals with chlamydial infection have increased expression of IFN-γ, IL-2 and IL-12 within the conjunctiva, consistent with this.[42] $CD8^+$ cytotoxic lymphocytes (CTL) are found in the conjunctiva of individuals with active trachoma, but their importance is uncertain.[34]

Inflammation and immunopathology

Clinically active trachoma often persists long after chlamydial infection becomes undetectable. Chronic severe conjunctival inflammation is associated with progression to scarring complications probably through the activation of fibrogenic pathways.[43] Clinically active trachoma, irrespective of the presence of infection, is associated with increased expression of pro-inflammatory cytokines (IL-1β, TNF-α), particularly by macrophages.[34,42] TNF-α has been found more frequently in the tears of individuals with trachomatous scarring.[44] A single nucleotide polymorphism (SNP) in the *TNF*-α promoter region, TNFA-308A,

which leads to increased levels of TNF-α has been associated with increased risk of trachomatous scarring and trichiasis.[45] The anti-inflammatory cytokine IL-10 also appears to influence the outcome of trachoma. It is produced by various cells including Regulatory T-cells and type 2 T-helper cells. It counteracts pro-inflammatory responses. However, IL-10 also opposes the action of the T_H1 response mediated through IFN-γ, so may impede the resolution of infection. IL-10 is expressed at increased levels in the conjunctiva of individuals with active trachoma and certain genetic polymorphisms have been associated with increased scarring, although their functional significance is uncertain.[42,46]

The fibrogenic processes leading to trachomatous scarring remain to be elucidated. As with other fibrotic diseases, it is likely that TGF-β is important. Other fibrogenic cytokines associated with a T_H2 response, such as IL-13, may also be important.[47] Matrix metalloproteinases (MMP) are a family of proteolytic enzymes which are central to the regulation of the extracellular matrix (ECM) and have been implicated in many scarring disorders. They degrade the ECM and facilitate scar contraction. The expression of MMP-9 is elevated in the conjunctiva with active trachoma, becoming more marked with increasing severity of inflammatory disease.[42] A SNP in the catalytic domain of *MMP-9*, possibly resulting in reduced function, is associated with a reduced risk of scarring complications in trachoma.[48]

Trachoma control

The World Health Assembly has resolved to eliminate blinding trachoma by the year 2020.[49] To this end, the Global Alliance for the Elimination of Blinding Trachoma (GET2020) was formed in 1998, including the WHO, trachoma endemic countries and organizations working in the field. Control activities focus on the implementation of the SAFE strategy, surgery for trichiasis, antibiotics for infection, facial cleanliness (hygiene promotion) and environmental improvements, to reduce transmission of the organism. Each of these components tackles the pathway to blindness at different stages. In this section, the major issues around the implementation of this strategy and some of the supporting evidence will be reviewed.

Trichiasis surgery

There are about 10 million people with trachomatous trichiasis (TT) worldwide who are at increased risk of developing irreversible blinding

corneal opacification (CO). Surgical correction of TT probably reduces the risk of progressive CO and blindness. The indications for TT surgery vary between control programmes. Some advocate early surgery when one or more lashes touch the eye, whereas others practice epilation until more severe TT develops. As the progression of TT can be quite swift in some people, where access to ophthalmic services is limited, surgery for mild disease is a logical approach.

Various surgical procedures are in use. Several of these were compared, of which the bilamellar tarsal rotation (BLTR) was found to have the lowest TT recurrence rate and was therefore endorsed by the WHO.[50] Many trachoma endemic countries have insufficient ophthalmologists to perform the volume of surgery to deal with the backlog of unoperated trichiasis. Therefore, many programmes train nurses and other para-medical staff to perform lid surgery with comparable outcomes to ophthalmologists.[51] The uptake of surgery, which has been low in many areas, is often greater when offered at community level.[52]

A major problem limiting the effectiveness of surgery is the recurrence of trichiasis following surgery, which can be as high as 40–60%.[53] Various factors may contribute: the choice of procedure, suture type, inter-surgeon variability, infection and the pre-operative disease severity. Trials examining whether peri-operative antibiotic (azithromycin) reduces the risk of recurrence found that for hyperendemic regions, this adjunctive therapy reduced recurrence but this was not the case in meso-endemic settings.[31,54] There is a need for additional research to develop approaches to improve the long-term surgical outcome. Despite these disappointing results, there can be a small improvement in vision following surgery of about a line of Snellen visual acuity.[31,50]

Antibiotic in trachoma control

Antibiotic therapy has been used for many decades to reduce burden of infection at the individual and community level. It is hoped that this in turn reduces the drive to progressive trachomatous scarring, although there is currently little direct evidence to support this. There are several key issues related to antibiotics which have bearing on how they should be used.

Which antibiotic should be used against *C. trachomatis*?

A number of different antibiotics have anti-chlamydial activity and have been used for treatment of trachoma. Currently, the most commonly used options are tetracycline eye ointment applied twice a day for 6 weeks or a single oral dose of azithromycin (20 mg/kg up to a maximum dose of 1 g). Tetracycline has been in routine use for five

decades in trachoma control. There is limited placebo-controlled trial data demonstrating limited efficacy of this antibiotic in the treatment of active trachoma.[55] These studies were conducted at a time when the standard practice was to only treat individuals with signs of active disease. This approach would have probably left a large pool of untreated infected individuals within a community to subsequently re-infect treated individuals, undermining the effectiveness of the intervention.

Azithromycin was directly compared with topical tetracycline in several trials and found to be equally effective.[56] In the largest of these studies (ACT) conducted in three endemic countries, mass community-wide treatment produced a marked reduction in the prevalence of chlamydial infection, which was sustained for 12 months of the study.[14] Similar responses have been observed in subsequent studies.[19,28] In an operational comparison of azithromycin and tetracycline, the former was found to be significantly more effective in the case of severe inflammatory trachoma.[57] This probably reflects the poor compliance with a 6 week course of tetracycline ointment, which is messy and sometimes irritating. Currently 12 trachoma endemic countries are receiving azithromycin as part of a philanthropic donation from the manufacturer (Pfizer Inc.).

Azithromycin is not licensed for the use during pregnancy. However, there is currently no evidence that it is harmful. Moreover, in a large trial of the presumptive treatment of sexually transmitted infections during pregnancy, the use of azithromycin in combination with other antibiotics was associated with more favourable outcomes for both the mother and the child.[58] The Centre for Disease Control supports this view and recommends azithromycin for treating *C. trachomatis* infection during pregnancy.[59] Azithromycin is not used in infants under the age of 6 months. This group was recently demonstrated to be significant reservoir of infection and therefore important to treat. The WHO currently recommends that a 6 week course of topical tetracycline be used for infants under 6 months.

Who should receive antibiotic treatment?

It is increasingly appreciated that there can be a major mismatch between the signs of active trachoma and the detection of chlamydial infection (Relationship between clinical signs and infection). This is a particular problem for control programmes in determining who should be offered antibiotic treatment; if only those with signs of trachoma are given antibiotic, many infected individuals with significant loads of infection would be left untreated.[10] The WHO currently recommends that mass community-wide treatment should be used (Box1).

Box 1 WHO recommendation for antibiotic treatment for trachoma

1. Determine the district-level prevalence of TF in 1–9-year-old children
   (a) If this is 10% or more, conduct mass treatment with antibiotic throughout the district
   (b) If this is less than 10%, conduct assessment at the community level in areas of known disease
2. If assessment at the community level is undertaken
   (a) in communities in which the prevalence of TF in 1–9-year-old children is 10% or more, conduct mass treatment with antibiotic
   (b) in communities in which the prevalence of TF in 1–9-year-old children is 5% or more, but less than 10%, targeted treatment should be considered
   (c) In communities in which the prevalence of TF in 1–9-year-old children is less than 5%, antibiotic distribution is not recommended

Frequency and duration of treatment

It remains uncertain how often and for how long mass antibiotic therapy needs to be given to endemic populations to achieve control of the disease. Several studies have reported significant reductions in the prevalence of disease and infection following a single dose of azithromycin.[14,19,28] However, the impact is not 100% and in some studies there has been rapid re-emergence of infection.[19,60] This is probably due to a combination of inadequate treatment coverage, introduction of new chlamydial infections and primary treatment failures. A mathematical model antibiotic treatment for trachoma control suggests that for hyperendemic regions (>50%), mass antibiotic treatment would probably be needed twice a year and for regions with moderate prevalence (<35%), annual treatment is possibly sufficient.[61] There are no long-term data to guide programmes as to how long mass antibiotic treatment should be given and this remains a difficult area that requires further research. The current recommendation from the WHO is that three annual rounds of mass treatment should initially be given. After this, the community should then be re-assessed to see whether the prevalence of active disease has dropped sufficiently to discontinue treatment.

Resistance and side effects

Repeated mass distribution of a broad spectrum antibiotic such as azithromycin raises the possibility of driving the selection of antibiotic resistance. For *Chlamydia trachomatis*, this does not seem to be a significant issue. Of greater concern is the potential for non-chlamydial bacteria, such as *Streptococcus pneumoniae* to develop resistance. This question is being monitored, but to date shifts in resistance patterns have been short term and not thought to be clinically significant.[62,63]

Azithromycin is a well-tolerated drug which has proven to be safe in mass distribution programmes. In formal studies, Azithromycin-treated individuals have 20% fewer fever and headache episodes and 40% fewer diarrhoea and vomiting episodes compared with those receiving topical tetracycline.[64] There is also a beneficial effect on malaria, with a reduction in parasite counts, splenomegaly and the prevalence of febrile parasitaemia in azithromycin-treated individuals.[65]

Facial cleanliness and environmental improvements

The F&E components of the SAFE strategy are primarily targeting the transmission of *C. trachomatis* between individuals. Numerous epidemiological studies have found an association between dirty faces and active trachoma in children.[20] It was suggested that by washing away potentially infected ocular secretions, the transmission of *C. trachomatis* to others might be interrupted. To test this hypothesis, a community randomized trial of an intensive participatory face-washing strategy was conducted in Tanzania and found a moderate reduction in severe inflammatory trachoma (TI) in the intervention villages.[66,67] On the basis of this study, the promotion of face washing was incorporated into the SAFE strategy.

Eye-seeking flies are a common feature of many trachoma endemic communities and have long been considered a potential vector. *Chlamydia trachomatis* was found (by PCR) on 15% of flies caught leaving faces of children in a study from Ethiopia.[68] A community randomized trial was conducted in the Gambia to test the hypothesis that controlling the fly population could suppress the transmission of *C. trachomatis* and reduce the prevalence of active trachoma.[21] Communities were randomized to one of the three arms: (1) insecticide spray, (2) latrine provision and (3) control. Latrine provision removes faecal material from the environment and breeding sites for flies. Both intervention arms of this study resulted in a significant reduction in the number of flies caught on children's faces, although only in the spray villages was this sufficient to significantly suppress the prevalence of active trachoma. A community randomized controlled trial conducted in Tanzania did not find that the addition of insecticide spraying to azithromycin distribution improved trachoma control.[69]

Many trachoma control programmes actively advocate for general improvements in water supply (for face washing) and sanitation (to suppress fly populations). This drive has fortunately coincided with the setting of the United Nations' Millennium Development Goals (MDG). The target for the seventh MDG is to halve the number of people without safe water and basic sanitation by 2015. This means that

many more organizations and resources are being mobilized in this endeavour than would have been the case for trachoma control alone.

The future of trachoma control

In previously endemic countries in Europe and elsewhere, trachoma declined in the face of general improvements in living conditions and health. Such changes are beginning to happen in some parts of currently endemic countries. However, for many communities it may take many decades for general improvements in living standards to happen and to have an impact on trachoma. Therefore, it is necessary to pro-actively implement the SAFE strategy as the best validated approach to control this blinding disease. The limited published data on the impact of implementing the SAFE strategy indicate that even in some of the most highly endemic regions, such as South Sudan, significant reductions in the prevalence of active disease can be achieved.[70]

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