Trachoma: new assault on an ancient disease

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Abstract

Trachoma is the leading infectious cause of blindness worldwide. The World Health Organization (WHO) estimated that approximately 5.9 million persons are blind or have severe vision-loss as a result of trachoma, and another 10 million are at high risk. Trachoma preferentially affects the most deprived communities, and within these communities, women and children bear the brunt of the burden. In recent years, there has been a renewed focus on research and heightened enthusiasm for strengthening trachoma control programs in afflicted countries. WHO has convened an alliance of member countries, non-governmental organizations, and other partners for the Global Elimination of Blinding Trachoma by the year 2020, and endorsed the multi-faceted SAFE strategy for trachoma control. SAFE—Surgery, Antibiotics, Face-washing, and Environmental improvement—has incorporated sound research on elements likely to reduce trachoma, and trachomatis blindness, in endemic communities. This review summarizes current knowledge about trachoma and its causative agent, *Chlamydia trachomatis*, the epidemiology and risk factors for trachoma as a prelude to reviewing the SAFE strategy. While ongoing research to support the knowledge base for SAFE must continue to be a priority, the full implementation of SAFE is the best hope for countries to reduce the global burden of blindness from this preventable cause.
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1. Introduction

Trachoma is the leading infectious cause of blindness worldwide, affecting an estimated 300–500 million people of whom 5.9 million are blind (Thylefors et al., 1995). This chronic conjunctivitis, caused by repeated episodes of infection with *Chlamydia trachomatis*, preferentially affects women, and afflicts the most impoverished communities on earth. Once endemic in most countries, trachoma has largely disappeared from Europe and the Americas, the disappearance predating the advent of antibiotics. Famous hospitals established to treat trachoma and eye diseases of the poor, like Massachusetts Eye and Ear Infirmary and Moorfield's Hospital in London, saw little trachoma by the 1930s. In the United States, infection with *C. trachomatis* became better known as a sexually transmitted disease than as an ocular infection. However, trachoma continues to be hyperendemic in many of the poorest and most remote areas of Africa, Asia, Australia, and the Middle East. Within these areas, communities with trachoma are often those with the fewest resources to take on the myriad of health issues their residents face. Because of its absence in 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. The WHO alliance for the Global Elimination of Blinding Trachoma by the year 2020 (GET 2020) has endorsed a multi-faceted control program for use within countries endemic for trachoma.

To appreciate how formidable a foe trachoma is, it is necessary to have some understanding of the organism itself, the clinical disease at all stages, the epidemiology and the risk factors for this disease. With this background, the evidence base for the trachoma control strategy itself can be appreciated.

1.1. Historical perspective

Mankind has been afflicted with trachoma since ancient times. There is evidence of its existence in China as early as the 27th century BC (Al-Rifai, 1998). In Egypt, the features of trachoma were described in the Papyrus, a collection of writings by ancient Egyptian

physicians found by Ebers in 1889 (Duke-Elder, 1965); epilation devices used for removing inturning eyelashes, a consequence of trachoma, were present in Egyptian tombs as early as the 19th century BC (MacCallan, 1931). Ancient Greek physicians, including Hippocrates, wrote descriptions of treating trachoma and the chronic sequelae of infection (MacCallan, 1931; Mettler, 1947). In fact, trachoma is the derivation of the Greek word for "rough", or "swelling" (Duke-Elder, 1965).

Trachoma spread to Europe in the early 1800s. By 1897, the supervising Surgeon General of the United States stated that trachoma in immigrants to the United States was grounds for immediate denial of entry and return to the port of origin (Wyman, 1897). The United States Public Health Service spent more than 80% of its resources between 1897 and 1925 on medical inspections at seaports and borders, primarily for trachoma (Markel, 2000). Despite American public opinion that trachoma was a disease of poor immigrants, trachoma was already endemic in Native Americans and populations of Appalachia (Allen and Semba, 2002). Even early descriptions of the disease recognized that preventive or public health strategies were needed for control (Elliot, 1920; MacCallan, 1931; Wyman, 1897). In 1920, fly control and avoiding hand/eye contact were recommended as mechanisms to decrease the spread of infection, and current efforts to reduce transmission use this same approach (Elliot, 1920). A public health approach that treats trachoma not as a series of cases with disease but as a disease of the entire community is now viewed as the most effective way to control trachoma where it still exists.

1.2. Current prevalence

Although, trachoma is no longer a public health problem in most of the western world, it continues to be a major cause of blindness in the developing countries. Trachoma is still prevalent in large regions of Africa, the Middle East, Southwestern Asia, the Indian Subcontinent, Aboriginal communities in Australia, and there are small focuses of blinding disease in Central and South America (Thylefors et al., 1995).

In these countries, trachoma is more often found in rural, economically underdeveloped areas, where good

water supplies and basic sanitation services are lacking. Even within hyperendemic areas, trachoma clusters both at the neighborhood and at the household level (Bailey et al., 1989; Katz et al., 1988; West et al., 1991b). Trachoma is an infectious disease and transmission of infected ocular secretions can occur by sharing clothes, towels, or sleeping quarters. Therefore, trachoma is passed among family members, and in some settings, between families in households that are in close proximity (Bailey et al., 1989; Grayston et al., 1972).

The overall prevalence of trachoma globally is somewhat difficult to determine as many of the studies have been carried out in areas of countries known to be at high risk. Extrapolation to the entire country or even region may not be justified. For example, there are pockets of low levels of trachoma in poor areas of Sao Paulo, Brazil, but highly endemic trachoma in indigenous tribes of the Brazilian rain forest (Alves et al., 2002; Medina et al., 1992). Moreover, there are scant data on trachoma prevalence from India and China, countries with very large populations that could alter any estimates of global burden of trachoma. The WHO has developed a rapid assessment methodology for use by health officials within countries to identify regions and districts where trachoma is a public health problem, and rank the priority of districts for trachoma control activities. This technique, while valuable for assigning health priorities, has been mistakenly used in place of true prevalence surveys to provide estimates of prevalence of trachoma. Validation of the rapid assessment technique against true prevalence surveys even for ranking villages has shown about 60% agreement (Rabui, 2001), with correlations of 0.58 (Paxton, 2001). Summaries of trachoma prevalence surveys excluding rapid assessment results show that the burden of disease is primarily in Africa and the Middle East, although again if India and China are shown to have trachoma, even in pockets, the global burden could shift to these countries (West and Bailey, 2003). The prevalence of trachoma has been decreasing in The Gambia and Saudi Arabia, with reports of decreases in local areas in Malawi and Nepal (Baral et al., 1999; Dolin et al., 1998; Hoechsmann et al., 2001; Tabbara and al-Omar, 1997). In other locations, such as areas of Tanzania and Aboriginal communities in Australia, do not appear to have any evidence of decline in the prevalence (Schachter et al., 1999; Taylor, 2001; West et al., 1991b).

The burden of trachoma is measured not just in the prevalence, nor in the prevalence of blindness or visual loss due to trachoma. The economic costs of trachoma in endemic countries are estimated at an annual productivity loss of $2.9 billion, based on loss of vision (Frick et al., 2003a). The prevalent cases of visual loss are responsible for 39 million lifetime disability-adjusted life years (DALYs). These impacts are likely to be under-estimates, as trichiasis, even without vision loss, is associated with disability (Frick et al., 2001b).

2. Trachoma: clinical disease and infection

2.1. Stages of trachoma

In trachoma-endemic communities, trachoma should be considered a chronic disease. The community pool of active inflammatory trachoma (TI) resides in the children who may have persistent signs of active trachoma as result of repeated or persistent infections. The sequelae of repeated bouts of active trachoma are apparent in both young and older adults.

Active trachoma is a chronic, follicular conjunctivitis, characterized by an inflammatory response to a series of infections throughout childhood. Children with active trachoma present with follicles and papillae, the marker for the intensity of the inflammation. Follicles are yellow or white "spots" in the tarsal conjunctiva, and consist of tissue containing B lymphocytes. Severe, TI presents as thickening of the conjunctiva with inflammation obscuring the deep tarsal vessels. The presence of pus with severe inflammation usually indicates a bacterial infection, which may be co-incident. Corneal changes may occur during active inflammation, but these signs are not a sensitive indicator of trachoma. Limbal follicles may appear, and new vessels develop, producing corneal pannus. Once the limbal follicles resolve, depressions remain on the cornea, resulting in the pathognomic sign of trachoma, "Herbert's pits".

Multiple infections over time and/or prolonged, severe infections are followed by evidence of scarring of the conjunctiva. As early as childhood and early adult hood, the scarring may be clearly evident. In some cases of scarring without evidence of active disease there is still laboratory evidence of *C. trachomatis* infection (Mabey et al., 1987; Munoz et al., 1999; Taylor et al., 1989a). As scarring becomes more extensive, trichiasis, or inturned eyelashes, develops. Trichiasis, and entropion, eventually requires lid surgery to correct the eyelashes rubbing on the globe and prevent visual loss from corneal opacification.

Corneal damage from trachoma, which leads to the visual consequences with this disease, is felt to be the result of multiple processes. Scarring may affect the meibomian orifices and result in atrophy of the gland and development of features of dry eye; similarly, the lacrimal ducts may be affected resulting in aqueous deficiency (Tabbara and Bobb, 1980). The cornea is thinner in eyes with trachomatous scarring, showing damage to the cornea even prior to trichiasis (Guzey et al., 2002). Inturned eyelashes abrade the compromised corneal surface and allow secondary infections. Ultimately, the cornea develops opacities that are

Table 1
World Health Organization simplified trachoma grading classification system

Sign	Description
TF	Follicular trachoma: The presence of five or more follicles in the upper tarsal conjunctiva of at least 0.5 mm
TI	Inflammatory trachoma: Pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels (not to be confused with scarring, which may also obscure the tarsal vessels). TI may be severe enough to obscure follicles
TS	Trachomatous scarring: The presence of easily visible scarring in the tarsal conjunctiva
TT	Trichiasis: Evidence of at least one eyelash touching the globe. Evidence of recent removal of inturned eyelashes is also graded as TT
CO	Corneal opacity: The presence of easily visible corneal opacity which obscures at least part of the pupillary margin

irreversible. These eyes are not good candidates for corneal grafts, and attempts at transplant often fail.

In 1987, the WHO published a simple classification scheme for assessing trachoma based on clinical signs (see Table 1) (Thylefors et al., 1987). Each of the signs has relevance for understanding the epidemiology of trachoma in a population. The prevalence of active disease is represented by the proportion of the population with follicular trachoma (TF) and/or TI; those with TI are most infectious and need prompt treatment; the prevalence of TT provides an indication of need for surgical services; and the prevalence of corneal opacity (CO) is an indication of the magnitude of impact of trachoma on the blindness rates in the community. The WHO trachoma grading scheme is reliable, easy to teach to eye nurses and other eye health workers, and has been used in a number of surveys (Taylor et al., 1987b). For research purposes, there are more complicated grading systems available which have more detailed levels of severity for each sign, but the reliability of the more complex schemes is correspondingly lower (Dawson et al., 1981). There is value in the use of more detailed determination of the severity of trichiasis, as severity is related to uptake of surgery and recurrence following surgery (Reacher et al., 1992). Severity is related to the number of lashes touching the globe, the location of the lashes (central versus nasal or temporal), the presence of lashes touching the cornea, and the degree of entropion (Melese et al., 2003; Merbs et al., 2004; West et al., 2004a).

2.2. Chlamydia trachomatis: the pathogen

The causative agent of trachoma, C. trachomatis, is an obligate intracellular organism with no known animal reservoir. Chlamydiae are eubacteria, and are given a place in their own order, Chlamydiales. C. trachomatis contains three biovars, two of which are causative agents for human disease, the trachoma and lymphogranuloma biovars. Within the trachoma biovar, the primary serovars responsible for trachoma are A, B, Ba, and C, while the serovars D–K are associated with genital infections. The genome of C. trachomatis (serovar D) has been sequenced and contains a 1,042,519 base pair chromosome with 894 likely protein-coding genes (Stephens, 1998). Of interest, the ocular serovars appear to carry a deletion or frame-shift mutation in the gene encoding tryptophan synthesis, such that ocular strains cannot use exogenous indole to synthesize tryptophan (Caldwell et al., 2003; Fehlner-Gardiner et al., 2002). The sequencing project has provided considerable insight into the biology of the organism.

The trachoma serovars target columnar and squamo-columnar epithelial cells, and are thus infections of the conjunctiva, genital, respiratory, and intestinal tissues. Chlamydiae have a unique developmental cycle distinguished by two specialized forms. The elementary body (EB) is the metabolically inert, infectious particle which infects host cells. Through invagination of the host cell membrane, the EBs are encased in a vesicle that matures into the inclusion body. The chlamydial inclusion avoids host cell lysosomal killing by inhibiting phago-lysosome fusion. Once inside, transformation of the EB into a reticulate body (RB) occurs. The RB, although non-infectious, is metabolically active and multiplies rapidly over the next 15–30 h. Chlamydiae were previously considered to be unable to synthesize ATP, which was felt to be the main feature of its obligate intracellular parasitism. However, while recent genome studies have identified genes which are likely to code for proteins involved in acquiring ATP from the host cell, they have also suggested, paradoxically, that Chlamydiae have the enzymes required for ATP synthesis (Iliffe-Lee and McClarty, 1999; Stephens, 1998). Approximately 18–30 h after infection, the RBs begin transformation into EBs. The RBs and EBs remain enclosed in the inclusion, which can occupy up to 90% of the cell cytoplasm. At 40–48 h post-infection, the cell will lyse, releasing EBs into the extracellular space to infect other cells.

In vitro, exogenous immune factors such as the T-cell cytokine interferon gamma cause differentiation into a non-infectious, non-metabolically active, but persistent, state. While in this persistent state, the aberrant Chlamydia appear to express inflammatory proteins, and some researchers suggest this is a major route by which the pathology of chronic Chlamydia infection occurs (Beatty et al., 1994). Such forms may play a role

in heightened hypersensitivity to infection, or explain why conjunctival scarring should progress in the absence of demonstrable infection. Findings that in those with no inflammatory disease, scarring was associated with chlamydial antigen positivity tends to support this conjecture (Mabey et al., 1992; Taylor et al., 1989a). Infection was a strong predictor of progression to scarring and trichiasis in cohorts followed in Tanzania (Munoz et al., 1999; West et al., 2001). The finding of genotypic evidence for the same organism in women who were infected at time points years apart is additional evidence for a role of persistent infection in the pathogenesis of trachoma (Smith et al., 2001). Further work on characterizing persistent infection, and its role in driving the progression of trachoma, needs to be done.

In the last several years, exciting research on the active interaction of Chlamydia with the host cell has emerged, including data suggesting that Chlamydia do not induce, and in fact may resist, apoptosis (Dean and Powers, 2001; Fan et al., 1998), and that Chlamydiae possess a gene which may function to reduce HLA expression by the host cell (Zhong et al., 2001).

The outer membrane of *C. trachomatis* contains many principal antigens from an immunologic perspective, and mediates adhesion between the Chlamydia and the host cell. The major outer membrane protein (MOMP, also called *omp1*) is immunodominant in the humoral immune response, accounting for 60% of the outer membrane proteins. Epitopes with MOMP have been studied as candidates for sub-unit vaccine development. The antigenic heterogeneity as a result of diversity in the four variable domains of MOMP is the basis for the distinction of *C. trachomatis* into different serovars. Genotyping studies, typically of the *ompA* gene which codes for *omp1*, done in trachoma-endemic areas suggest that a number of genovars may be present within a given serovars, implying more variants than previously known on the basis of serovar studies; however, most of the polymorphisms are based on point mutations (Dean et al., 1992; Hayes et al., 1992; Hseih et al., 2001). One prospective study of children with infection over time indicated evidence for drift in the *omp1* genotypes, but also found children with the same *omp1* genotype over time (Hseih et al., 2001). The polymorphism is hypothesized to be a mechanism by which Chlamydia escape immune surveillance, and may be an explanation for multiple bouts of re-infection with the same serovar.

2.3. Detection of infection

There are many techniques which have been used to diagnosis infection with *C. trachomatis* in the laboratory. These include cytological examination of stained slides of conjunctival swabs, growing the organism in tissue cultured cells, or detection of antigen or nucleic acids. Serologic tests or tear tests for antibody are not helpful for determining current infections.

With the advent of extremely sensitive tests for detection of chlamydial DNA, the establishment of a "gold standard" for determining the sensitivity and specificity of laboratory tests for *C. trachomatis* has become more complicated. Comparison against the clinical signs of disease is not optimal because many cases of TF no longer have agent; the follicular reaction appears to take significant time to resolve once the agent is gone. Moreover, sub-clinical or pre-clinical infections are a well-recognized entity, and a laboratory test may well be positive in the absence of clinical signs. The sensitivity and specificity of the tests are affected greatly by the collection, handling, and storage of the samples in the field and in the laboratory. For example, poor handling of specimens for tissue culture can change the sensitivity by as much as 50%. Many of the studies have used Chlamydia culture as the gold standard, although the newer techniques are clearly more sensitive.

The nucleic acid amplification tests are currently in wide use and are exquisitely sensitive. In Tanzania, positive results were obtained in 95% of those with severe trachoma (TI) and 54% of those with TF (Bobo et al., 1991). In The Gambia, 85% of those with severe disease were PCR positive and 69% of those with mild disease were positive (Bailey et al., 1994a). In both studies, between 8% (The Gambia) and 24% (Tanzania) of those without trachoma were also positive; in Tanzania, 70% of those cases were mild, having 1–4 follicles. In The Gambia, the clinically negative subjects who were PCR positive were more likely to develop signs of trachoma from 1 to 6 months later. These findings suggest that some of the PCR positive–clinically negative cases are either incubating the disease or are such mild cases that they do not meet the WHO definitions of trachoma.

Commercially available assays target DNA sequences in the Chlamydia plasmid, which is present at 7–10 copies per EB. Thus, these tests theoretically can detect less than one EB in a sample. PCR techniques require meticulous attention to the handling of specimens in order to avoid contamination, as false positivity can easily result. The commercially available tests are relatively expensive, especially for typical countries with trachoma. Facilities for processing specimens are also not readily available. For low to medium trachoma areas (less than 40% prevalence in children), pooling multiple specimens into a single test is a feasible approach for prevalence studies (Diamant et al., 2001).

Uses of these newer diagnostic agents, and tests that quantify the load of infection, have energized the epidemiological studies of trachoma because it has enabled more detailed studies of the relationship between infection and clinical disease, risk of transmission, and effect of treatment on Chlamydia load within

communities (Bird et al., 2003; Burton et al., 2003; Solomon et al., 2003; West et al., 2004e). Mass treatment of communities, where infection falls dramatically, appears to have little effect on the follicular sign of trachoma, with prevalences of TF only slightly lower at 1 year with very low levels of infection. Treatment disturbs the relationship equilibrium between infection and clinical disease, such that monitoring TF even out to a year post-treatment, is not a reliable indicator of infection within the community (Bird et al., 2003). This prolongation of follicles was not predicted by monkey models of trachoma, where the follicular response was maintained only as long as ocular challenge with agent was maintained (Taylor et al., 1982). Clinically, severe, TI is more highly associated with infection even after treatment, and better mirrors infectious status in trachoma-endemic areas (Burton et al., 2003; West et al., 2004e).

For monitoring the effect of antibiotic intervention in trachoma-endemic communities, the development of an inexpensive, simple, sensitive and specific test for Chlamydia infection would be highly desirable, one that could be implemented in the countries themselves without the need for expensive equipment.

2.4. Immune responses

The clinical signs of trachoma associated with infection by *C. trachomatis* are a reflection of the immune response to the organism. Scarring is the result of immunopathology induced by repeated, or persistent, episodes of infection. A single episode of acute chlamydial conjunctivitis, as seen in newborns in Europe and North America, is not considered trachoma because there is virtually no risk of the blinding complications that characterize eyes exposed to multiple or prolonged bouts of infection in trachoma-endemic areas. The prolonged exposure to infection throughout childhood and young adult hood appear to be necessary to produce the complications seen in later life (Grayston et al., 1985; Taylor et al., 1982, 1989a). The importance of innate and adaptive immune responses in trachoma and the extent to which variations in this host immune response might assist in explaining the variation in scarring, or persistent infection, is incompletely understood, and an area of active research.

The acquisition of repeated infections, even with the same genovar, suggests the absence of any long-lasting protective immunity. Neutralizing antibodies against MOMP have been shown to protect against infection in the laboratory, but the extent of a natural protective immune response is not clear (Zhang et al., 1987). However, there is evidence that an immune response to *C. trachomatis*, expressed through either resistance to, or resolution of, infection, is induced. Research has shown that signs of active disease, ocular

chlamydial infection, and high loads of organism are more common in children than in adults in trachoma-endemic settings. While adults may have less exposure to infection, they may also be protected, at least partially, from reinfection by prior exposure, and have been shown to have a shorter duration of disease (Bailey et al., 1999).

Both innate and adaptive immune responses are invoked during *C. trachomatis* infection. Chlamydia-infected cells produce a number of cytokines and chemokines including Interleukin-8, a powerful neutrophil attractant (Rasmussen et al., 1997).

MOMP is the immunodominant antigen in inducing antibody response to infection. While neutralizing antibodies against MOMP have been shown to protect against infection in the laboratory, it is not clear that antibodies generated during natural infection produce protection (Zhang et al., 1987). Though antibody responses are found in ocular secretions, there is scant evidence that they confer protection against chlamydial infection (Bailey et al., 1993; Treharne et al., 1978).

The cellular immune response may be both helpful and harmful. Lymphocyte proliferative responses, reflecting class-II restricted CD4+ memory or effector T-cell responses to chlamydial antigens are readily demonstrable in humans with trachoma (Mabey et al., 1991). Subjects who spontaneously cleared their disease had enhanced lymphoproliferative responses to chlamydial antigens compared to those with persistent disease whose responses were reduced (Bailey et al., 1995). At the same time, the scarring manifestations of trachoma may also result from the cellular immune response. Peripheral blood lymphocyte proliferative responses were reduced in scarred subjects compared to controls and showed a predominantly Th2 type response to a range of chlamydial antigens (Holland et al., 1993). Together with observations that scarred subjects may be more likely to be infected, suggests that some chronic sequelae of infection occur in individuals who have an immune response that fails to clear infection. Subjects with scarring trachoma have been found to have increased mRNA transcripts of TGF-beta (Bobo et al., 1996) a fibrogenic cytokine which may induce polarization towards Th2 responses.

Severe inflammatory trachoma may be the result of a delayed hypersensitivity response in ocular tissues elicited by the 57 kDa chlamydial heat shock protein (hsp 60) (Morrison et al., 1989; Taylor et al., 1987a; Watkins et al., 1986). This protein is a 'chaperonin' whose relative expression is increased under stress such as that induced by gamma interferon, which also induces the formation of persistent, aberrant organism (Beatty et al., 1993). This may explain the finding of serological responses to hsp 60 in subjects with damaging sequelae of chlamydial infection, including trachomatous scarring (Peeling et al., 1998).

3. Risk factors for trachoma

Trachoma remains a blinding disease in communities where the living conditions facilitate constant exposure to infection and continuous transmission among family members. The age and gender distributions of the various clinical manifestations of the signs of trachoma are important descriptors of the trachoma burden within the community. Determinations of the specific factors which increase the risk of trachoma have guided the current recommendations for intervention strategies to control the disease.

The age distribution of the different signs of trachoma depends in part on the stability and endemicity of the disease in the community. In hyperendemic areas, active disease (TF/TI) is most common in pre-school children, with prevalences as high as 60–90% (Courtright et al., 1989; West et al., 1991b). The prevalence of active trachoma decreases with increasing age, with less than 5% of the adults showing signs of active disease (West et al., 1991b). However, the prevalence of active trachoma reflects both the incidence and duration of disease. The duration of disease has been shown to decline strongly with increasing age (Bailey et al., 1999). Moreover, in the older population, a higher proportion of clinical presentation was TI rather than the more prolonged TF seen in younger children. While pre-school children clearly carry the burden of chlamydial infection within communities, adults have infection, often sub-clinical infection as well (Burton et al., 2003). These data suggested that while the incidence rate of disease lower in adults compared to children, the much lower prevalence rates in adults is also a function of the much shorter duration of disease.

In trachoma hyperendemic areas, there appears to be a sub-group of children who respond to infection by consistently mounting a severe, inflammatory response (West et al., 1996). In a longitudinal study in Tanzania, about 10% of pre-school children had TI at three to four of the examinations over the course of 1 year (constant TI). These children were shown to maintain high levels of Chlamydia and seemed unable to resolve either infection or disease (Bobo et al., 1997). They tended to be female and to live in families where their siblings had trachoma. Moreover, the 7-year incidence of scarring in those with constant, TI was almost five times greater than in children without constant TI (but who had episodes of trachoma) (West et al., 2001). Differing immune responses to chlamydial infection may explain the more severe consequences of repeated or persistent infection, as it is likely that this sub-group of children represent those who go on to develop the blinding complications of disease. Control of blinding trachoma does not rest on identifying these persons, but preventing exposure through treatment and decreasing transmission within their communities.

In areas where trachoma has been endemic for a long period of time, the presence of conjunctival scars increases with age, and the prevalence in those 25 and older could be as high as 90% (Courtright et al., 1989). A typical pattern of the age and sex distribution of active and chronic trachoma for a hyperendemic area can be illustrated by the data from a survey of 20 villages in Tanzania (Fig. 1).

In areas in which trachoma is mesoendemic, the prevalence of active disease in pre-school children is less than 30%, and the average age of peak prevalence is older than in hyperendemic areas. Although, the prevalence of scars still increases with age, the presence of severe scarring, trichiasis, and COs is rare (Dolin et al., 1998; Mabey et al., 1992). Such communities are not considered at great risk of blinding trachoma.

In areas where active trachoma has largely disappeared, a different pattern of the presentation of trachoma is observed. The prevalences of lid scarring and chronic sequelae are more common than active disease, and trachoma may be present only in adults (Schwab et al., 1995; Tabbara and Ross-Degan, 1986). The prevalence of trichiasis and COs due to trachoma in adults largely reflect childhood exposure to past episodes of disease and likely some persistent infection in the adults. While the blinding complications may continue to be a problem, the low or absent incidence of active disease in children is a good indicator of the future absence of blinding disease as a public health problem.

As a general pattern, female children may have similar or only slightly higher rates of active trachoma, but the later sequelae of scarring, trichiasis and entropion, and COs due to trachoma, are more common in women than in men (Mabey et al., 1992; Schwab et al., 1995; Tielsch et al., 1988; West et al., 1991b). This excess risk among women is believed to be related to their relatively continuous close contact with young children, who are the main reservoir of infection (Congdon et al., 1993). However, a recent study of women with chronic ocular
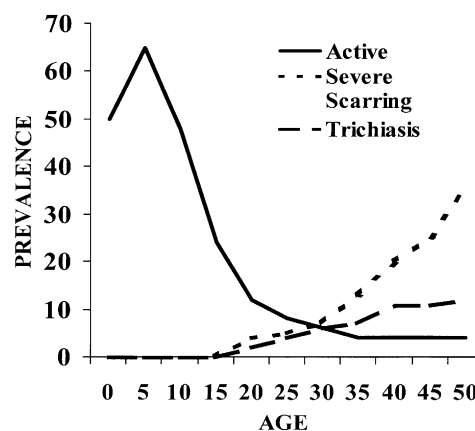

Fig. 1. Age distribution of various stages of trachoma.

Chlamydia infection found genotypic evidence for persistent infection, and found no obvious household source for repeated infection (Smith et al., 2001). While re-infection from exposures to other household members is a likely contributor to the blinding sequelae in women, it appears that persistent infection in those exposed may also be an important factor.

3.1. Risk factors for active trachoma

In addition to age and sex, environmental factors that increase the risk of active trachoma have been identified, and these have informed the development of control strategies for the community risk of trachoma.

3.1.1. Water

Several studies have found a positive association between the distance from the household to the water source and the prevalence of active trachoma (Luna et al., 1992; Prost and Negrel, 1989; Schemann et al., 2002; Taylor et al., 1989b; Tielsch et al., 1988). In Tanzania, those households located more than 2 h from water not only had more trachoma but also more TI and more disease in the younger children (Taylor et al., 1989b). Water is used for personal hygiene, washing of dishes, clothes, and other articles. Clearly, the distance to water can place constraints on the amount of water brought to the house, and use for purposes other than drinking or cooking may be limited.

The availability of water for a household is only one component of water use; another important factor is the household decision on how water is to be utilized. In a large prevalence study, although distance to water was related to trachoma, 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 (West et al., 1989, 1991b). The authors suggest that behavioral factors around water utilization are more important for trachoma than total amount of water available. A case-control study in The Gambia found that after controlling for family size, distance to water, and other socioeconomic factors, families with trachoma used less water for washing children than did the control families without trachoma, regardless of the amount of water available for consumption (Bailey et al., 1991).

In general, in areas in which trachoma is endemic, communities with inadequate access to water are more likely to have higher trachoma prevalence (Ballard et al., 1983; Marx, 1989; Tielsch et al., 1988), and such communities are at higher risk of other health conditions as well. The provision of a stable water supply does not necessarily ensure that trachoma rates will decline. The decision to use water to improve hygienic conditions is very complex in these communities, and is

clearly an important factor as well (McCauley et al., 1990). Water provision to communities with no water is an expensive infrastructure development program that must be justified on the basis of a host of public health problems, not just trachoma control.

3.1.2. Personal hygiene

In general, poor hygienic conditions favor the transmission of *C. trachomatis* through contact with ocular and other secretions (Jones, 1980). Several studies have been carried out to identify the specific components of hygienic conditions associated with a lower risk of active trachoma. These include use of handkerchief, use of towels, and face washing practices in children.

In Tanzania, a large cross-sectional study found a protective effect against both trachoma and TI with the use of handkerchief for nose blowing and a towel for drying one's face (Taylor et al., 1989b). This finding is somewhat paradoxical, since handkerchiefs and towels would seem to enhance transmission of secretions, especially if used among many family members. Since only a few families had either a handkerchief or towel in this study, 5–7% of families, it may be likely that these items were a marker for families with better hygiene practices overall. The use of towels or handkerchiefs was not related to trachoma in Mexico (Taylor et al., 1985) or in Mali (Schemann et al., 2002).

The ocular and nasal secretions of pre-schoolchildren in trachoma areas are clearly a potential source of infection (Bobo et al., 1991; West et al., 1993). Improving facial cleanliness may decrease the likelihood of transmission from these secretions. 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. In studies in Malawi, Tanzania, and Brazil, the self-report of frequency of washing children's faces was not related to the prevalence of trachoma (Luna et al., 1992; Taylor et al., 1989b; Tielsch et al., 1988) although in Mexico and Mali, there was a modest association (Schemann et al., 2002; Taylor et al., 1985).

However, observations of clean faces on children has been consistently linked to lower prevalence of trachoma (Guraksin and Gullulu, 1997; Schemann et al., 2002; Taylor et al., 1989b; West et al., 1991a, 1996). A longitudinal study of children at two time points 6 years apart found that children with unclean faces who had clean faces at follow up were far less likely to have TI at follow up, odds ratio of 0.21, compared to children who had unclean faces at both time points, even adjusting for baseline trachoma status (Hsieh et al., 2000).

The specific elements of an unclean face that were related to the risk of trachoma were studied in children in Tanzania and included 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 to children without these signs (West et al., 1991a). Dust was a fairly ubiquitous sign, and not a good indicator of hygiene; even after face washing, dust returned quickly to children's faces in these environments.

While face washing obviously has no effect the course of disease, it may reduce the likelihood of auto-reinfection or transmission of infection to others. A randomized, community-based intervention trial was conducted in Tanzania to test the effectiveness of a community-based, participatory program to improve face washing following mass antibiotic treatment in communities (Lynch et al., 1994; West et al., 1995). Children who kept their faces clean were about half as likely to have trachoma at the end of the 1-year follow up, and a third as likely to have TI, as children who did not have clean faces (West et al., 1995). The difficulties of carrying out such an intensive behavioral intervention were evident, and it is not clear how much more effective other, less intense program would be.

3.1.3. Flies

One of the earliest risk factors noted for trachoma was the presence of flies (Jones, 1980; Weir, 1952; Wilson, 1932). In endemic trachoma areas, epidemics of bacterial conjunctivitis and increases in the prevalence of active trachoma have been observed following peaks in the fly population (Dawson et al., 1976; Gupta and Gupta, 1970). Furthermore, studies have found an association between fly density in the household or the presence of flies on children's faces and presence and severity of trachoma (Brechner et al., 1992; Schemann et al., 2002; Taylor et al., 1989b; West et al., 1991a). Flies can 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 (Forsey and Darougar, 1981). In Tanzania, the presence of flies was a risk factor not only for active disease, but also for infection with *C. trachomatis* (West et al., 1991c), which supports an active role for flies in transmission. Clean faces also appear to be less of a fly attractant than unclean faces, providing additional support for improving hygiene practices.

In a pilot trial in The Gambia to investigate the association of flies with trachoma, one member of each pair of villages in a mesoendemic area received 3 months of spraying with deltamethrin to control flies (Emerson et al., 1999). Muscid flies were the targets of the intervention, especially *Musca sorbens*, the fly most commonly found in contact with eyes. After 3 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. Another randomized trial in a set of hyperendemic communities demonstrated a drastic reduction in flies over a 1-year period of intense spraying as well, but failed to find any effect on trachoma (West et al., 2004c). The lack of efficacy may reflect the multiple routes of transmission that are likely operating in these hyperendemic communities, such that other factors may be as effective for transmission as well. Flies are not the only source of transmission, as others have found trachoma where the fly populations are absent (Taylor et al., 1985) or less intense (Reinhards et al., 1968).

Regardless, environmental control of flies is desirable from a number of other public health perspectives, where flies are associated with other diseases. The presence of human and animal waste in the household environment, leading to ideal fly breeding sites, is markers for disease, including trachoma. Environmental control of flies, from a public health perspective, should be encouraged.

3.1.4. Latrines

The presence of a functional latrine near the house has been associated with lower trachoma prevalence in several different countries (Burton et al., 2003; Courtright et al., 1991; Schemann et al., 2002; Taylor et al., 1989b; Tielsch et al., 1988). *M. sorbens*, the eye-seeking fly, breeds preferentially in solid human feces on the ground, but feces within a latrine does not support breeding (Emerson et al., 2001). Thus, removal of human feces through appropriate construction and use of latrines may decrease the fly population, leading to less trachoma in settings where transmission by flies is important (Emerson et al., 2001). This hypothesis is being tested in a community-based clinical trial.

The latrine may also be a marker for families who have better hygiene practices overall. In Egypt, presence of a latrine was related to other measures of higher socioeconomical status, such as more professional occupation and more education of the head of the household, more large farm animals and bigger farming plots (Courtright et al., 1991).

3.1.5. Cattle

The presence of cattle pens and cattle ownership has been associated with trachoma in some African countries (De Sole, 1987; Taylor et al., 1989b), but not in others (Schemann et al., 2002). In arid environments, cattle droppings create an optimal environment for breeding flies, especially *M. domestica* although not a preferred site for *M. sorbens*. The presence of cattle is not just a simple marker for flies, as flies and cattle ownership were independent predictors of TI in Tanzania (Taylor et al., 1989b). In some societies, cattle are a sign not only of traditional wealth, but also of families with traditional lifestyles living in unhygienic

circumstances, and who are the most resistant to adopting new practices. The cattle pens are close to the house, and in some cases the animals live in the house at night to avoid thievery.

3.1.6. Crowding

Crowded living conditions in the family unit seem to increase the risk of trachoma. The number of persons per sleeping room (Bailey et al., 1989; Sahlu and Larson, 1992) shows a positive association with the prevalence of active trachoma. The increasing risk with increasingly crowded conditions is logical, as there is more exposure to infection or disease via close contact with infected individuals or diseased individuals through the sharing of sleeping rooms (Luna et al., 1992; Mabey et al., 1992). A large family per se is not necessarily a risk factor for trachoma in children (Assaad et al., 1971; Barenfanger, 1975). Rather, the risk appears to be related to the likelihood of contact with an infected individual, and larger families are more likely to have pre-school children who are the reservoir of infection. Thus, several studies have found that mothers of children with trachoma are more likely themselves to have active disease, compared to women who either did not take care of children or whose children did not have trachoma (Congdon et al., 1993; Schemann et al., 2002; Taylor, 1958; Taylor et al., 1985).

3.1.7. Nutritional deficiencies

Three cross-sectional surveys have found an association of active trachoma in children with evidence for vitamin A deficiency (Katz et al., 1988; Lietman et al., 1998; Schemann et al., 2001), although another found no evidence for an association (Fine and West, 1997). These two diseases are more frequent in impoverished communities, so it is not surprising that they may cluster. Vitamin A deficiency affects the immune system, and may compromise host clearance of infection, which could explain the association as well (Nauss and Newberne, 1985; Semba et al., 1992).

3.2. Risk factors for scarring and trichiasis/entropion

The sequelae of active trachoma (trichiasis, entropion, and COs) appears in young adulthood and in middle aged persons. In some areas, severe scarring can appear in children (Dawson et al., 1989), but the prevalence of severe scarring is usually low in children and increases with age. Because of the long time course from repeated or prolonged active infection in childhood to the development of blinding sequelae in middle aged adults, there are few good longitudinal study of risk factors for scarring or trichiasis/entropion. This area is of considerable interest because although the majority of children in trachoma hyperendemic areas have active disease, only a small percentage go on to develop the

blinding complications and there are only limited data to suggest who is at risk.

Ongoing infection is suspected to play an active role in the continued pathogenesis of scarring (Ward et al., 1990). Clinically inapparent infection has been found in adults with conjunctival scarring living in hyperendemic communities (Mabey et al., 1992; Taylor et al., 1989a). Even if the load is low in adults, the presence of antigen may continue to drive the progression to severe scarring and trichiasis (Bailey et al., 1994b; Burton et al., 2003; Solomon et al., 2003; West et al., 2004a, e). In addition, the sub-group in the population who, when infected, cannot seem to clear infection and have constant TI are at three-fold increased risk of scarring (West et al., 2001). The immune response also likely plays a role in scarring. Immunogenetic polymorphisms affecting host responses to infection have been shown to be differentially distributed in cases of scarring compared to controls (Conway et al., 1996, 1997; Mozzato-Chamay et al., 2000). In all such studies, it is uncertain whether the associations themselves reflect susceptibility, or whether the polymorphism studied is merely in linkage with a true susceptibility allele elsewhere on the same chromosome.

Although, the prevalence of active trachoma is similar for males and females in childhood, adult women are at much greater risk of developing the blinding complications of trachoma than are adult men (Courtright et al., 1989; West et al., 1991b). This increased risk has been explained by the women's close contact with small children, who are the main reservoir of infection, and active disease in adults is highly associated with being caretakers of children with trachoma (Congdon et al., 1993). In a longitudinal study of women with C. trachomatis infection 3 years after baseline, the women who were still infected were more likely to be living in a household with children of whom one or more were also infected (Smith et al., 2001). However, 47% of the women with chronic infection had no obvious household source of infection. The fact that 73% were infected with the same ompA genotype as at baseline suggests that most of the infections were persistent.

Repeated or persistent infections in adulthood, many of which may be clinically inapparent, could be a factor involved in the ongoing process of scarring and development of trichiasis. Chronically infected women were five times as likely to have trichiasis compared to women without chronic infection (Smith et al., 2001). A 7-year follow up study of 1026 women revealed that infection was associated with a 2.5-fold increased risk of trichiasis (Munoz et al., 1999). The 7-year incidence rate in women with scars was 9.2%, and virtually none of the women without scars at baseline developed trichiasis (0.6%). Incident trichiasis was also associated with having active trachoma at baseline, lending further support for the role of infection and immune response in

the development of trichiasis. In The Gambia, where trachoma rates are substantially lower, the 12-year progression from scarring to trichiasis in a cohort of 326 persons was 6.4%, about half that of Tanzania in an older cohort which also included men (Bowman et al., 2001).

A case-control study of trichiasis in women in Tanzania found trichiasis cases was more likely to report a group of factors during childbearing years that are indicators of poor living conditions. Having no adult education, living in poor housing, sleeping in rooms with a cooking fire, and having five or more deaths among their children were all associated with an increased risk of developing trichiasis (Turner et al., 1993). It is of interest that Sarkies (1967) found carbon particles embedded in the fibrotic conjunctiva of entropion cases undergoing surgery in South Africa. Whether or not dust or smoke from the cooking fire could be a factor in scarring of trichiasis is unclear.

The progression of trichiasis to CO was studied in a sample of 20 patients from The Gambia examined 12 years apart. In all, 20% went on to develop central CO over the 12-year period, and 15% developed visual loss (Bowman et al., 2001). Since blindness is associated with a higher mortality in African patients, compared to those without visual loss, the rate of progression to visual loss may be even higher in the 31 cases of trichiasis who were lost to follow up.

The disability associated with trichiasis is not confined to those with visual loss however. Limitations in the daily activities of village life were found, for women especially, in those with trichiasis but no visual loss (Frick et al., 2001b). For men and women, having trichiasis and visual loss was 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 associated with the visual loss from trichiasis. Moreover, it points to the necessity of targeting surgery for trichiasis well in advance of visual loss to restore function.

4. Trachoma control: SAFE strategy: Surgery/Antibiotics/Face-washing/Environmental change

Based on the current understanding of the epidemiology of trachoma and its risk factors, the WHO has recommended the use of "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, Face washing and Environmental change to reduce transmission. The implementation is critically important, as the temptation is strong to follow a more medically oriented model of concentration on provision of surgery and antibiotics with 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 place to reduce blinding trachoma so that it is no longer a public health problem. The WHO alliance for the GET 2020 is a consortium of countries, non-governmental organizations, universities and other interested parties dedicated to decreasing the burden of trachoma by implementing the SAFE strategy. Details on the rationale for each component of the SAFE strategy are described below.

4.1. Surgery

Even if current control strategies are 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 (Courtright et al., 1989; Taylor, 1993). About 1% per year of persons with scars in endemic communities will develop trichiasis (Bowman et al., 2001; Munoz et al., 1999). Many patients with trichiasis will epilate to provide relief of symptoms, but the efficacy of this procedure in prevention of CO or visual loss is unknown. Epilation is a temporary measure, as the eyelashes re-grow and the hard stubble new growth may be more abrasive if it touches the cornea than the original lash. Moreover, one-third of those with trichiasis of less than five lashes touching the globe and who were advised to epilate rather than have surgery went on to develop severe trichiasis in 1 year (Bowman et al., 2002). Other procedures to ablate the lash, such as cryotherapy, electrolysis, and laser, have also been shown to have high recurrence rates and need multiple treatments for effectiveness (Reacher et al., 1992).

There are a number of different surgical techniques that have been used to correct trichiasis (Adamu and Alemayehu, 2002; Reacher et al., 1992). 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 1 year (Reacher et al., 1992), and in 88% up to 3 months (Adamu and Alemayehu, 2002). However, in areas in which trachoma is endemic, patients with trichiasis often have very limited if any access to an ophthalmologist. In a study from Tanzania, after proper training by an ophthalmologist, an eye nurse successfully performed trichiasis surgery using the tarsal rotation technique in makeshift theatres in the local communities (Bog et al., 1993). In areas in which trachoma is endemic and very few ophthalmologists are available, ophthalmic nurses or

medical assistants are trained to perform trichiasis surgery, and training manuals and videos are available from the WHO (Reacher et al., 2002).

Recurrence of trichiasis following surgery is a 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 about 17% per year (Bog et al., 1993; Khandekar et al., 2001; Negrel et al., 2000; Reacher et al., 2002). Recurrence rates increase with longer follow up time; some have reported rates as high as 55% with a median follow up of 7 years (Bowman et al., 2000a; Ezz et al., 2001; Khandekar et al., 2001; West et al., 2004a). Some of the recurrence is surgery related, which is apparent within a short time following surgery. For example, recurrence at 3 months has been reported at 8% (Bowman et al., 2000b), 10–12%, the latter depending on the severity of trichiasis prior to surgery (Adamu and Alemayehu, 2002). In a study of recurrence in Tanzania, recurrence differed by eye and by location, prompting the authors to suggest surgical factors that could explain some of the differences in recurrence (Merbs et al., 2004). Recurrence is also higher in those for whom repeat surgery is attempted, as these are more difficult cases to correct (Reacher et al., 1992).

Incident recurrence following surgery continues over time in many locales in the years following surgery, suggesting other factors, such as ongoing exposure to *C. trachomatis* infection, are also important. Two studies have found that surgical patients residing in areas with high trachoma rates were more likely to have recurrence (Khandekar et al., 2001; West et al., 2004a). In addition, surgical cases who lived in households where at least one member had active infection were more likely to have recurrence (West et al., 2004a). Trichiasis cases with recurrence are more likely to have ocular inflammation resembling TI, but this could be the result of the recurrence as well as a preceding infection (Bowman et al., 2000a; West et al., 2004a). These data provide further support to the hypothesis that ongoing exposure to infection is a factor in both the development of trichiasis and recurrence following surgery. A large clinical trial of antibiotics after trichiasis surgery in Ethiopia will provide more definitive data on the role of infection with *C. trachomatis* in recurrence.

Availability of surgical services 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 women with trichiasis to whom surgery was offered opted to have the operation in a 2-year period, and 27% by 7 years. The main barriers were perceived cost, and lack of accessibility to the health facilities (Oliva et al., 1997; West et al., 1994). In this environment, cost includes cost of transport, food, and costs of 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 (Rabiu and Abiose, 2001). 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 and increase uptake (Bowman et al., 2000b). In The Gambia, Frick et al. (2001c) have shown that the productivity gains from the additional surgeries done because the surgeries were carried out in the village exceed the costs of moving the surgery to the local level. However, surgical acceptance drops off markedly with the institution of cost-recovery schemes, which increases the cost barrier, regardless of location. Cost was the single biggest impediment to surgical uptake reported in a series from The Gambia, where estimated costs were $6 for a bilateral case in an area where about half of the adults have an income of less than $150 per year (Bowman et al., 2002).

Because women have higher risk of trichiasis, countries offering surgical services need to be certain of gender equity in access and receipt of surgery. Gender-specific barriers to surgery, such as lack of child care, have been documented (Oliva et al., 1997). A recent review of the proportion by gender receiving surgery, compared to the proportion in the community with trichiasis in the country programs of Vietnam and Tanzania revealed no evidence of inequity (West et al., 2004f). However, the gender ratio in other countries suggest inequity, and reasons for this need to be identified (Ezz et al., 2001).

4.2. Antibiotics

The use of antibiotics for trachoma control is intended to reduce the community pool of infection. Although, it is argued that trachoma disappeared in the United States prior to antibiotics and thus they are not a necessary component, the disappearance of trachoma took many years and coincided with massive socio-economic development, a boon that is unlikely to occur for trachoma-endemic communities. A number of studies have been done showing equivalency of various antibiotics in reducing infection in clinical cases, but the two antibiotics in most frequent use are topical tetracycline eye ointment, once a day for 4–6 weeks, or (for countries in a special donation program) a single dose of azithromycin. Although, either regimen is clinically effective in combating infection, re-infection is very likely to occur if only isolated, clinically apparent, cases within these communities are treated.

In practice, azithromycin, with its ease of one dose administration and lack of significant side effects, is preferred over the 6 weeks of an oily, stinging eye ointment that temporarily clouds vision and for which compliance with full treatment cannot be assured

(Fraser-Hurt et al., 2001). Azithromycin also has secondary benefits for the community as well. Children who took azithromycin for trachoma had fewer fever, diarrheal, and vomiting episodes, and a modest beneficial effect on indices of malaria, compared to children who took topical tetracycline ointment in a randomized trial in The Gambia (Sadiq et al., 1995; Whitty et al., 1999). A decrease in the prevalence of impetigo for 10 days following treatment has also been reported from Nepal in a group of children receiving azithromycin (Fry et al., 2002). Antibiotic treatment of either whole communities or selected groups considered at high risk is the current recommendation, and once yearly treatment has been shown to be effective in reducing the infectious burden from 2 to 12 months post-treatment, with evidence of re-emergence in some settings (Fraser-Hurt et al., 2001; West et al., 2004e).

For countries planning an implementation of an antibiotic program, the first question is whom to treat. In areas with hyperendemic communities, those with prevalence >20%, the recommendation is to cover everyone in the community. However, azithromycin is under Federal Food and Drug Administration Class B for use in pregnant women (no studies to prove absence of teratogenecity). So, despite azithromycin as the first choice for treatment of sexually transmitted *C. trachomatis* regardless of pregnancy, this block has prevented many countries from permitting azithromycin use in pregnant women in the village. Unfortunately, this ban translates into inadequate treatment of women for trachoma. Also, in some countries azithromycin is not provided to children less than 1 year of age, and this age group is not only infected but they harbor significant infectious loads (Solomon et al., 2003).

Concern has been expressed that, in villages that are mesoendemic or hypoendemic, mass treatment would result in the provision of antibiotic to a majority of persons who had no infection. The positivity rate for infection, for example, in villages studied in The Gambia was only 7%, contrasted with 57% in Tanzania (Solomon et al., 2003). Alternatives to mass treatment that have been proposed are treatment only of children, or children with trachoma and their families (Holm et al., 2001; Laming et al., 2000). In hypoendemic villages in Nepal (where the prevalence in children of trachoma was 16%), both approaches reduced infection and active disease at 6 months post-treatment in children, but the targeted approach was more costly (Frick et al., 2001a). In hypoendemic villages in The Gambia, treatment of children only would miss a sizeable proportion of the infection in the village, which did not vary by age (Burton et al., 2003). The authors recommend treatment of all household members of clinically active cases, which would cover 96% of infection (as well as 67% of residents of the village). There are no long-term data on the effectiveness of these

alternative treatment strategies on trachoma in the community. In the hyperendemic communities in Tanzania, only mass treatment of communities would reach most cases of infection and cases with heavy loads; various targeted approaches either left a significant fraction of those infected without treatment, or covered such a high percentage of the community that mass treatment was simply deemed to be easier to implement (West et al., 2004b). Ideally, program planners should have data on the trachoma and infection rates within their communities if they are considering other than mass treatment, to be sure that sizable proportions of person with infection are not being missed because they are not clinically apparent or are not within the age group targeted.

Another pressing question is the frequency of treatment. Country programs are managing once yearly treatments, with varying success at reaching target coverage of 80%. More frequent treatment has been suggested to be more effective in reducing infection over time in hyperendemic countries, based on mathematical modeling (Lietman et al., 1999) but there are no data on the effectiveness, or cost-effectiveness, of other more frequent approaches.

The frequency of treatment in part depends on the effectiveness of yearly treatment on trachoma and infection in these communities. In a study in Nepal, of a mesoendemic village, three annual rounds of treatment for children resulted in marked drop of active disease and only one child left infected (Gaynor et al., 2003b). Despite high antibiotic coverage in hyperendemic communities, there is evidence that infection re-emerges (West et al., 2004e), and even after yearly rounds, the decline in active trachoma is relatively modest (West et al., 2004d).

Although, the precise reasons for re-emergent trachoma following community-based treatment are not clear, 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 infection and disease at follow up (Schachter et al., 1999; West et al., 2004e). Theoretically, infection should decline and disappear with 100% compliance (Lietman et al., 1999), but in practice that level is never achieved in programs, which strive to cover 80% of target persons each year (West et al., 2004d). Those who have not received treatment are at risk of maintaining their infection over time, and transmitting it to others (West et al., 2004e). For example, children age less than 6 months who do not receive azithromycin can have very heavy loads capable of transmission (Solomon et al., 2003). Second, populations in these communities are very mobile, with in migration of individuals who can bring in new disease, and returning community members who acquire infection outside. Such sources

were not important in a study of re-emergent infection in a treated community in Tanzania (West et al., 2004e) but may be important in other communities where intermingling is more intense. Third, in trachoma-endemic areas, children with active ocular Chlamydia infection also have extra-ocular Chlamydia infections (Malaty et al., 1981; West et al., 1993). Auto-reinfection from extra-ocular sources of Chlamydia infection may be one source of re-emergent infection. However, one study of the effect of mass topical treatment found that the incidence rate of new infections was similar in those who had a positive nasal specimen at baseline compared to those who had a negative nasal specimen (West et al., 1993). The use of a systemic antibiotic compared to a topical treatment for trachoma in a research setting with high compliance was equally effective in reducing ocular infection (Schachter et al., 1999). Such data suggest that the source of Chlamydia re-infection following treatment is not likely to be extra-ocular sources. Fourth, inadequately treated persons who harbor large loads of infection may continue to be infected and infective. A study following mass treatment in Tanzania found that effectiveness (defined as no evidence of infection at 2 months following treatment) of treatment with a single dose of azithromycin declined with increasing load of infection at baseline (West et al., 2004b). Very young children not only had heavy loads prior to treatment but also accounted for most of the heavy loads of infection in the community after treatment, despite proper dosing. Further follow up is needed to determine if there is resistance to azithromycin, or if higher dosing levels are indicated.

Is it possible that mass treatment programs may be fostering azithromycin resistant micro-organisms? In countries that have used tetracycline eye ointment for decades, resistant *C. trachomatis* has not been reported, and does not appear to be an issue. In countries that have mass treatment with azithromycin, there are no reports of clinically significant *C. trachomatis* resistance. In part, this may be due to the infrequent administration of mass treatment programs, once per year. Other micro-organisms could potentially develop resistance from treatment with systemic antibiotics as well, and research has investigated the effect of mass treatment on *Streptococcus pneumoniae*. This organism, a relatively common respiratory pathogen, is subject to documented resistance to macrolides (Oster et al., 1999). In an Australian aboriginal community, resistant strains of *S. pneumoniae* were found prior to treatment with azithromycin in 2% of isolates in children, increased to 55% of isolates at 3 weeks, and declined to 5.9% of isolates at 6 months post-treatment (Leach et al., 1997). The investigators did not evaluate whether or not clinical disease with resistant organisms had increased. Others have also evaluated changes in the carriage rate of *S. pneumoniae* and noted a transient increase

(Chern et al., 1999; Morita et al., 2000) but the clinical significance of resistant isolates is unclear. In a follow up of children in Nepal given azithromycin, no isolates where found that were resistant to *S. pneumoniae*; the authors caution that the study was underpowered (Gaynor et al., 2003a). Nevertheless, the findings are consistent with a transient rise of resistant, yet less fit, organism whose presence wanes once antibiotic pressure is removed (Gaynor et al., 2003a). In another study in Tanzania, there were no resistance strains prior to mass treatment, and only one isolate with resistance 6 months after treatment (Batt et al., 2003). At present, monitoring activities are ongoing, but it is felt that antibiotic resistance is not a serious problem for trachoma control efforts.

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 (Solomon et al., 2001). A comparison of using community volunteers versus village government leaders to recruit families for mass treatment in communities in Tanzania showed higher coverage rates for women and children in villages under the community volunteer program (Lynch et al., 2003). Research showing that for children over age two, height can be used as a proxy for weight in dosing azithromycin also simplifies the logistics of providing treatment (Munoz et al., 2003). The temptation to institute a cost-recovery mechanism to cover either distribution or treatment should be carefully considered in light of data showing that households with greatest risk of active trachoma were those least willing to pay for treatment (Frick et al., 2003b). Indicators of less cash availability and lower socioeconomic status were associated with decreased willingness to pay, and these are markers of households with trachoma. Planners must consider a trade-off of a less effective coverage of key members of the community (and effect on program success) balanced against budgetary concerns. Approaches to research on cost-effectiveness of various strategies for delivery of the antibiotic component have been described, and the importance of donation of azithromycin (rather than purchasing the antibiotic) is key to keeping it at reasonable cost (Frick and West, 2001). Fortunately, the major manufacturer of azithromycin, Pfizer Inc., has announced the provision of antibiotic without charge as its donation program, thereby removing a significant element of cost in the cost-effectiveness equation.

4.3. Face washing and environmental change

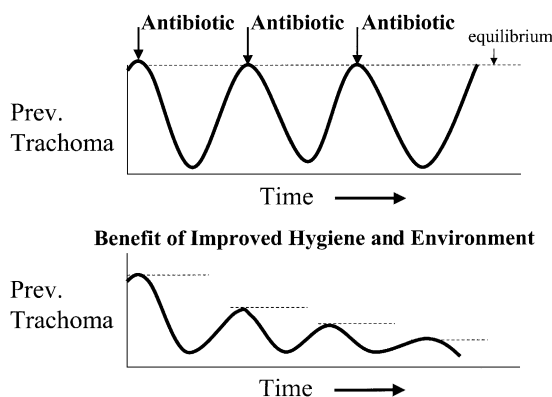While antibiotic use alone has been shown to make dramatic, short-term reductions in the reservoir of

Fig. 2. Why "F and E" with an effective antibiotic?

infection in trachoma-endemic communities, no long-lasting change in the dynamics of transmission, or the ecology, of trachoma has occurred in these villages—just the amount of agent has decreased. Without efforts to reduce the transmission of C. trachomatis, there is concern that the disease will re-emerge over time. A theoretical construct for the importance of the "F and E" components of SAFE is shown in Fig. 2. In essence, C. trachomatis reaches equilibrium within the community, based on multiple sources of, and ease of, transmission. While mass treatment disturbs this equilibrium and reduces the pool of infection, if nothing within the community changes, residual infection within the community or infection brought in from outside will be subject to the same transmission forces and result in return to equilibrium levels. This may happen over a short period of time or may take years. If, however, there are community efforts to reduce transmission through hygiene or reduction of other routes, then the equilibrium point is reset, such that re-emergence is never to pre-treatment levels. Over time, the combination of reduction in infection with resetting of this equilibrium within the community should lead to sustained trachoma control. This construct has not been formally tested, but evidence for its validity is found in the outcome of the face washing trial in Tanzania, where following mass treatment with eye ointment, children with clean faces were much less likely to have trachoma after 1 year compared to the children with unclean faces (West et al., 1995).

Although, the evidence base is not as strong for the F and E components of the SAFE strategy as for the surgery and antibiotic components (Emerson et al., 2000), caution is indicated in expecting behavior changes or environmental improvements to have the same drastic reductions in short periods of time as that seen with antibiotics. Part of the challenge for research in the area of "F and E" lies in the differing ecology for trachoma within the communities, which makes generalizing findings and strategies difficult. Clearly, the frequency of exposure and transmission is much greater

in locations like Tanzania or Ethiopia, where the prevalence of trachoma in children may be above 60%, compared to villages in Nepal or The Gambia, with a prevalences of 30% or less. The differing findings of the impact of intense fly control, which reduced trachoma in villages in The Gambia but had no effect on trachoma in Tanzania, may well reflect the relative importance of flies, among other routes of transmission, in the trachoma environment, in those settings.

Another challenge lies in translating effects observed under research conditions to programs that will be effective in village conditions. This is especially difficult when the effect requires behavior change, as evinced by 20 years of smoking cessation programs. The randomized trial of a participatory approach to improving face washing practices in villages in Tanzania was preceded by extensive ethnographic research to understand the barriers, perceptions, and constraints for village residents (Lynch et al., 1994; McCauley et al., 1990, 1992). In particular, demonstrations of how little water is needed to clean a face, and how many faces can be cleaned with a liter or less of water were powerful messages. Despite this intensive effort involving village and neighborhood meetings, school programs, and other supporting efforts, clean faces improved in the intervention villages from 4% to 27%. While even this modest improvement was associated with a reduction in trachoma and TI at 1 year, sustainable community involvement likely would be needed for any long-term effect on behavior change.

Much of the epidemiologic data point to decreases in trachoma in connection with improved hygiene, provision of latrines, and access to water. Therefore, these elements constitute the focus of the "F and E" components of SAFE, and indeed provide significant public health benefits for communities quite apart from any effect on trachoma.

From an implementation perspective, a significant challenge for trachoma control program managers will be the integration of persons skilled in community development of water and sanitation into the country strategy. Trachoma control is often part of the medical sector, or preventive health sector of Ministries of Health, which typically do not have jurisdiction over water or sanitation development, or school programs. Coordination and multi-sector partnerships are necessary to implement the components of SAFE at the community level. 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 (Sutter and Ballard, 1978, 1983). 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.

4.4. Vaccine

Efforts to create a vaccine against chlamydial infection have been unsuccessful to date. Attempts were made to develop chlamydial vaccines by using killed elementary bodies, but their use resulted in even more severe disease than naturally acquired infection; any protection conferred was against the immunizing serovar (Grayston and Wang, 1975). Apparently, the vaccine acted to potentiate the effects of infection by sensitizing the subjects. Clearly, an effective vaccine will have to elicit a protective immune response across multiple serovars, without sensitizing the recipient. Researchers are currently using a variety of antigenic challenges, ranging from whole, non-viable organism to DNA vaccine designs. Sub-unit vaccine designs based on MOMP have produced short-term protection only, and is serovar specific. Moreover, research that focuses on the sub-unit approach faces the considerable challenge of appropriate delivery vehicles and adjuvants that will boost protective immunity. In murine models, the most promising work has resulted when MOMP was in a non-denatured conformation and a TH1 T-cell response was obtained. However, while immunity has been associated in mouse models with a TH1 response (Cain and Rank, 1995), no such consistent finding has been demonstrated in human infection. A detailed review of the challenges and state of vaccine development against Chlamydia is presented by Igietseme et al. (2003).

Development of a vaccine against *C. trachomatis*, while challenging, is a high priority. Even a partially protective vaccine has been predicted, through computer modeling, to have a substantial effect on reducing infections globally (de la Maza and de la Maza, 1995). At present, control of trachoma through a vaccine strategy appears to be several years away.

5. Future directions

Basic and applied research into chlamydial ocular infection, and trachoma, is essential for the elimination of blinding trachoma as a public health problem. Trachoma is an ancient disease and, despite its disappearance from much of the world, is tenacious and patient; it is not liable to vanish completely without a sustained effort. It should be noticed that the strides made by basic scientists into the molecular biology and immunology of *C. trachomatis* are prodigious, and findings from these disciplines will greatly inform vaccine development and the future directions of the

epidemiological investigations. At the same time, the renewed interest in trachoma control and implementation of the SAFE strategy worldwide has been the result of clinical investigations providing the evidence base and rationale for the elements of SAFE.

Future research in trachoma should provide knowledge that contributes to the prevention, treatment, and control of this blinding disease. Priorities include the following:

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. Although, the current surgical technique is easy and effective, the rate of recurrence is relatively high. Other procedures, which can be carried out under field conditions, should be studied compared to proven surgeries using clinical trial methodology.
2. It is becoming increasingly clear that sub-sets of the population are at greater risk of intense trachoma, and the immune response clearly features in those who appear to develop persistent disease compared to those who clear infection. Further work is indicated to determine host factors that predict persistence and drive scarring and trichiasis in these communities.
3. Operational research on alternative strategies for implementation of the SAFE strategy, with appropriate evaluation, is critically important for the cost-effective implementation of trachoma control programs. For example, optimal but feasible coverage rates for antibiotic treatment of communities have not been determined, and the number of years that mass treatment must be included in programs or when an alternative approach is indicated are unknown. In particular, strategies to "graduate" villages from mass treatment and targeted, vertical, programs are urgently needed.
4. Further research in chlamydial genomics and proteomics are needed to identify likely gene products that may be reasonable vaccine candidates. Major research efforts are also needed in the development of effective delivery systems for such vaccines. Strategies for vaccine programs must also be considered, as the target group for sexually transmitted Chlamydia is different than the target group for trachoma, which begins in infancy.

The gauntlet has been laid down by The WHO—elimination of blinding trachoma by the Year 2020. The field of trachoma control has been energized by the recent large-scale donation program of azithromycin, and the formation of the alliance to foster progress in the implementation of the SAFE strategy in member countries. General consensus holds that the SAFE strategy is a safe bet for success, but diligence in implementation of the full strategy, and ongoing

research to provide data on the most effective trachoma control program, will be necessary to assure victory over this preventable cause of blindness.

Acknowledgements

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