Trachoma: The Forgotten Cause of Blindness

Beatriz Muñoz and Sheila West

INTRODUCTION

Trachoma, the second leading cause of blindness worldwide, continues to be hyperendemic in many areas of Africa, Asia, and the Middle East. Caused by an ocular infection with *Chlamydia trachomatis*, this chronic conjunctivitis results in more blindness than any other infectious eye disease. Once endemic in most countries, trachoma has largely disappeared from Europe and the Americas. Because of its disappearance from developed countries and its endemicity in the poorest of communities, trachoma has been largely forgotten as a public health issue. Communities with trachoma are often those with the fewest resources to take on health issues, and trachoma strikes the most vulnerable members of those communities—women and children. Second only to cataract as the leading cause of blindness, trachoma affects an estimated 300-500 million people of whom 5-7 million are blind (1).

In the last 10 years, there have been considerable advances in our understanding of the epidemiology and approaches to trachoma control that have major ramifications for public health measures against this disease. In this review, we summarize the characteristics of trachoma, the epidemiology and risk factors for the disease, and promising approaches to control strategies. The strides made in research on trachoma clearly warrant a reprioritization of this forgotten disease.

THE ORGANISM: *C. TRACHOMATIS*

*C. trachomatis*, the causative agent of trachoma, is an obligate intracellular organism that has no free living state. There is no known animal reservoir for human chlamydia infection. The chlamydia are given a place in their own order, chlamydials. The three species, *C. trachomatis*, *Chlamydia psittaci*, and *Chlamydia pneumoniae*, can be further separated into several serovars. Within *C. trachomatis*, the primary serovars responsible for trachoma are A, B, Ba, and C. The serovars D-K are associated with genital infections, and L1-L3 are the lymphogranuloma venereum serovars (2).

**Outer membrane proteins**

From an immunologic perspective, the outer membrane proteins on *C. trachomatis* are the principal antigens that distinguish the serovars. The major outer membrane protein is the immunodominant protein, accounting for 60 percent of the outer membrane proteins. In trachoma-endemic areas, Dean et al. (3) and Hayes et al. (4), in Tanzania and Gambia, respectively, have documented sequence polymorphism in the major outer membrane protein by demonstrating multiple genovars. These gene-typing studies indicate many more variants than previous studies of serovars have indicated; this antigenic variation may be the mechanism by which chlamydia escape immune surveillance and allow for multiple bouts of reinfection with the same serovar.

**Development cycle**

Chlamydia have a unique developmental cycle distinguished by two forms, the elementary body and the reticulate body. The elementary body is the metabolically inert, infectious particle that, through endocytosis, infects susceptible host cells. Endocytosis is followed by transformation of the elementary body into a reticulate body that is metabolically active and multiplies rapidly over the next 15 hours. Chlamydia lack a cytochrome system and cannot produce adenosine 5'-triphosphate (ATP); the host cell ATP is used to transport essential nutrients across the chlamydia cell wall. The reticulate bodies are noninfectious, but approximately 20 hours after infection, the reticulate bodies transform into elementary bodies. The reticulate bodies and elementary bodies are enclosed in an intracellular inclusion body, which can occupy up to 90 percent of the cell cytoplasm. With rupture of the cell,
infection of other cells by the newly transformed elementary bodies ensues. C. trachomatis targets columnar and squamocolumnar epithelial cells and is thus an infection of the conjunctiva, genital, respiratory, and intestinal tissues. Characteristics of the developmental cycle of chlamydia may well explain some features of infection, such as possible persistence.

Infection

A single episode of acute chlamydial infection, as seen in newborns in the United States, is not considered trachoma because there is virtually no risk of prolonged inflammation or the binding complications that characterize eyes exposed to multiple bouts of infection in trachoma-endemic areas. Repeated episodes of infection throughout childhood and young adulthood appear to be necessary to produce the complications seen in later life (5, 6). Repeated infection induces the immunopathology that characterizes the clinical signs of scarring, trichiasis, and entropion seen later in life.

CLINICAL SIGNS OF TRACHOMA

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 latter a marker for the intensity of the inflammation. Follicles are yellow or white “spots” in the tarsal conjunctiva and consist of lymphoid tissue containing B lymphocytes. Severe, inflammatory trachoma 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. Limbal follicles may appear, and new vessels develop, producing corneal pannus. Once the limbal follicles resolve, depressions remain on the cornea, resulting in the pathognomonic sign of trachoma, “Herbert’s pits.”

The community pool of active trachoma resides in the children, who may have ongoing signs of active trachoma as a result of repeated infections. The signs may never clear in children repeatedly exposed to C. trachomatis. In a cynomologus monkey model of trachoma, animals receiving weekly inoculations of C. trachomatis showed a waning of the severe inflammatory response after 2 months but maintained a follicular response as long as the reinoculation of the ocular challenge was maintained (6).

Multiple infections or prolonged, severe infection is often followed by evidence of scarring of the conjunctiva. Even in late childhood and early adulthood, the scarring may be prominent and obscure evidence of active disease, although in some cases of scarring without evidence of active disease, there is laboratory evidence of C. trachomatis infection (7, 8). By middle age, for some cases, the scarring is significant enough to cause trichiasis, or inturned eyelashes. Trichiasis, and entropion, eventually require lid surgery to correct the eyelashes rubbing on the globe and to prevent visual loss from corneal opacification.

The visual loss from trachoma is due to irreversible corneal damage. The damage is believed 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. Inturned eyelashes abrade the corneal surface, which may be drier than normal, and allow secondary infections. Ultimately, the cornea develops opacities and the destruction is irreversible.

The World Health Organization has published a simple classification scheme for assessing trachoma in community-based surveys (table 1) (9). 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 TF and/or TI. Those with TI have severe inflammation, are more likely to have a laboratory test positive for C. trachomatis, and thus need prompt treatment; the prevalence of TT indicates the backlog for surgical services; and the prevalence of CO is an indication of the potential impact of trachoma on visual impairment in the community. The World Health Organization trachoma grading scheme is reliable, is easy to teach to eye health workers, and has been used in a number of surveys (10). For rapid assessment of the magnitude of the problem of active trachoma and for planning eye care services for the

**TABLE 1. World Health Organization simplified trachoma grading classification system**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF</td>
<td>Follicular trachoma: the presence of five or more follicles in the upper tarsal conjunctiva of at least 0.5 mm</td>
</tr>
<tr>
<td>TI</td>
<td>Inflammatory trachoma: pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels</td>
</tr>
<tr>
<td>TS</td>
<td>Trachomatous scarring: the presence of easily visible scarring in the tarsal conjunctiva</td>
</tr>
<tr>
<td>TT</td>
<td>Trichiasis: evidence of at least one eyelash touching the globe; evidence of recent removal of intumescence of eyelashes is also graded as TT</td>
</tr>
<tr>
<td>CO</td>
<td>Corneal opacity: the presence of easily visible corneal opacity that obscures at least part of the pupillary margin</td>
</tr>
</tbody>
</table>
They are expensive and can be labor intensive when between 100 and 200 epithelial cells are needed from the membrane protein fluorescent-tagged antibody. Best staining with species-specific and antimajor outer tertiary bodies in conjunctival smears may be made by mydial infections have been used widely in the diagnosis of chlamydia, using other techniques have positive for C. TRACHOMATIS culture as the "gold standard," although the newer techniques are clearly more sensitive.

The diagnosis of infection with C. trachomatis in the laboratory can be done by examining 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 follicular trachoma no longer have an agent; the follicular reaction takes time to resolve once the agent is gone. Moreover, subclinical or preclinical 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 and can change the sensitivity of, for example, tissue culture by as much as 50 percent. Many of the studies have used Chlamydia culture as the "gold standard," although the newer techniques are clearly more sensitive.

Early laboratory tests for C. trachomatis included direct smears of conjunctival swabs stained with iodine or Giemsa. Giemsa staining is fast, economical, and more sensitive than iodine; however, it has a low overall sensitivity, around 30 percent, even in the presence of severe disease (11, 12).

Tissue culture is considered the most specific test. Ideally, the sensitivity of tissue culture should be 90 percent or better, but sensitivity is highly dependent on the degree to which strict requirements for transport and storage are maintained (7, 11, 13). Moreover, negative cultures in clearly symptomatic individuals positive for Chlamydia using other techniques have been reported (7, 11).

Direct antigen detection tests for diagnosing chlamydial infections have been used widely in the diagnosis and screening of sexually transmitted diseases. They are expensive and can be labor intensive when used for trachoma surveys. Identification of elementary bodies in conjunctival smears may be made by staining with species-specific and antimajor outer membrane protein fluorescent-tagged antibody. Between 100 and 200 epithelial cells are needed from the ocular sample before the sample is deemed adequate for antigen testing. In a large prevalence study of trachoma in Tanzania, Taylor and colleagues (7) found 11.3 percent of specimens to be inadequate. In this same study, the sensitivity of direct fluorescent antibody testing against culture was 88 percent and specificity was 87.5 percent. Direct fluorescent antibody requires a highly trained observer and can be subjective; however, it has the advantage over nonmicroscopic antigen detection tests that the adequacy of the sample can be determined. The enzyme-linked immunosorbent assay (ELISA) has a sensitivity compared with culture of anywhere from 66 to 100 percent, with a specificity of 90–99 percent (8, 11, 14, 15). Some lipopolysaccharide-specific ELISA testing does cross-react with other microorganisms, and false-positive tests can result unless confirmatory tests are also done.

The new tests for C. trachomatis, DNA amplification or the polymerase chain reaction (PCR) and ligase chain reaction tests, are highly promising and gaining wide acceptance. A number of in-house polymerase chain reaction tests have been used for detecting C. trachomatis using labeled DNA probes that detect specific nucleotide sequences to ribosomal RNA, and commercial kits are available. The tests are highly sensitive and specific for C. trachomatis, ranging in sensitivity from 98 to 100 percent with 99–100 percent specificity (13, 14, 16). Chlamydial PCR tests were evaluated in trachoma endemic regions of Tanzania and The Gambia (14, 16). In both studies, the PCR test was more sensitive than other laboratory techniques. In Tanzania, positive results were obtained in 95 percent of those with severe trachoma and 54 percent of those with follicular trachoma. In The Gambia, 85 percent of those with severe disease were PCR positive, and 69 percent of those with mild disease were positive. In both studies, between 8 percent (The Gambia) and 24 percent (Tanzania) of those without trachoma were also positive; in Tanzania, 70 percent of those cases were mild, having one to four 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 cases who were PCR positive but clinically negative were either incubating the disease or were such mild cases that they did not meet the World Health Organization definitions of trachoma.

Use of these newer diagnostic agents has energized the epidemiologic studies of trachoma because it has enabled more detailed studies of the relationship between infection and clinical disease and investigations into the role of persistent or latent infection and the risk of scarring.
IMMUNITY

The acquisition of repeated infections with *C. trachomatis* in trachoma endemic areas suggests the absence of any long-lasting protective immunity. Neutralizing antibodies against the major outer membrane protein have been shown to protect against infection in the laboratory, but the extent of natural immune response in producing some protection is not well clarified (17). The understanding of host defense mechanisms that promote the persistence or eliminate the growth of *C. trachomatis* is essential for the design of an effective vaccine. Specifically, research should focus on clarifying the role of Th1-like responses in clearance of infection as well as the role of Th-2 responses in producing more severe disease.

In animal models, immunity was shown to be short lived and serotype specific (18, 19). Reinfection with a different serovar tends to raise antibody responses to the previous serovar (20). There is no evidence that tear antibodies confer protection against chlamydial infection (21, 22). Byrne and Krueger have shown that gamma interferon inhibits chlamydial growth and viability in cell cultures and probably serves as one host defense mechanism (23).

In fact, the immune response may well be responsible for the serious clinical manifestations of trachoma. Severe inflammation may be the result of a delayed hypersensitivity response in ocular tissues elicited by the 57-kD chlamydial heat shock protein (24-26). Some data from cell cultures suggest a role of cytokines in inducing the fibrogenesis characteristic of the submuco-osal fibrosis in chronic sequelae of trachoma (27). Data from a trachoma region in The Gambia suggest that the peripheral blood lymphocyte proliferative responses in subjects with scarring showed a predominantly Th2-type response to a range of chlamydial antigens. This response suggests that chronic sequelae of infection can occur in individuals who have an immune response that prevents clearance (28).

Genetic polymorphism

Currently there is considerable interest in characterizing the genetic variation in the omp1 gene (which encodes the major outer membrane protein) in *Chlamydia*. It is possible that variants are selected by immune pressure and escape from immune surveillance, which would help explain recurrent infections. Such findings have major implications for vaccine development using the major outer membrane protein as a candidate. In a study in The Gambia, Hayes and coworkers (29) found variants of *C. trachomatis* in two villages where surveys were conducted on selected individuals over a year. During that period of time, four genovar variants accounted for 89 percent of infections, although the introduction of novel variants was observed. The data do suggest that there was insufficient immune response to clear the infecting variant for the majority of those with recurrent infection at follow-up. Similar studies on samples from Tunisia and from Tanzania have shown genovar variants in those populations (3, 30).

Persistency

There is controversy over the role, if any, of persistent infection as a factor in the pathogenesis of trachoma. Electron micrographic studies have shown that in cell culture systems, some epithelial cells contain aberrant, nonculturable, reticulate body-like structures that may represent persistent or latent infection (31). Such forms may play a role in heightened hypersensitivity to infection or may explain why conjunctival scarring should proceed in the absence of demonstrable infection. The findings of Mabey et al. (32) and Taylor et al. (7)—that in those with no inflammatory disease, scarring was associated with antigen positivity—tend to support this conjecture. However, studies of migrant Sikh Indians showed that those with previous trachoma who moved to Canada (an area with no trachoma) had no additional cases of disease, suggesting that relapse or persistence is not a major factor in recurrent disease (33). Further work, especially in the demonstration of persistent or latent forms in vivo, is needed.

EPIDEMIOLOGY OF TRACHOMA

History

Civilizations have been afflicted with trachoma since ancient time (34). In Egypt, the features of trachoma were described in the Ebers Papyrus, a collection of writings by ancient Egyptian physicians (35); epilation devices used for removing inturned eyelashes were present in Egyptian tombs as early as the nineteenth century B.C. (36). Trachoma is a derivation of the Greek word for “rough,” or “swelling” (35), and ancient Greek physicians, including Hippocrates, wrote descriptions of treating trachoma and the chronic sequelae of infection (36-38).

In the early 1800s, Egypt became a military battle ground for England, France, and Turkey; and trachoma quickly spread to Europe. Much of the blindness attributed to trachoma was probably gonococcal conjunctivitis, but simultaneous infection with trachoma was likely (36). Public health strategies to control the spread of infection were described in the early 1900s (36, 38-40). In 1920, Elliot recommended...
trying to control the fly population and avoiding hand/eye contact as mechanisms to decrease transmission (40).

**Prevalence**

Although trachoma has largely disappeared from 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, and Aboriginal communities in Australia. In addition, there are small foci of blinding disease in Central and South America (41). Within these countries, trachoma is more common in the particularly 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 (42–44). Trachoma is an infectious disease, and transmission 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 (45). The variation in trachoma prevalence between neighborhoods in the same village can be several-fold (42).

Crowded living conditions in the family unit appear to increase the risk of trachoma. With increasing numbers of persons per sleeping area, the prevalence of active trachoma has been shown to increase (43, 46, 47). The association is logical, as there is more exposure to infection or disease via close contact (32, 48). A large family per se is not necessarily a risk factor for active trachoma in children (49, 50). Rather, the risk appears to be related to the likelihood of contact with an infected individual, and larger families are more likely to have preschool children who have the highest prevalence of infection. Thus, several studies have found that mothers of children with trachoma are more likely themselves to have active disease, compared with women who either did not take care of children or whose children did not have trachoma (51–53). In studies of maternal genital infection as a source of trachoma, Brunham et al. (54) found no evidence that maternal or perinatal transmission of *C. trachomatis* was an important determinant of infection or disease in children.

The stability and endemicity of the disease in the community largely determines the age distribution of the individual signs of trachoma. In hyperendemic areas, active disease is most common in preschool children, with prevalences as high as 60–90 percent (42, 55). The prevalence of active trachoma decreases with increasing age, with less than 5 percent of the adults showing signs of active disease (42). In areas where trachoma has been endemic for a long period of time, conjunctival scarring increases with age and is as high as 90 percent in some areas (55). Although rates of active disease are roughly similar in male and female children, the later sequelae of trichiasis and entropion and corneal opacities due to trachoma are more common in women than in men (42, 55, 56). In one location in Egypt, 75 percent of the women and 50 percent of the men older than 45 years had trichiasis or entropion (55). A typical pattern of the age and sex distribution of active and chronic trachoma for a hyperendemic area can be illustrated by figure 1.

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 is present only in adults (57, 58). The prevalence of trichiasis and corneal opacities due to trachoma in adults reflects past episodes of disease when this cohort were children. While the blinding complications may continue to be a problem for generations previously exposed, the low or absent incidence of active disease in children is a good indicator of the future absence of blinding disease.

In areas in which trachoma is not a blinding condition, the prevalence of active disease in preschool children is less than 30 percent, and the average age of peak prevalence is greater than in hyperendemic areas. Although the prevalence of scars still increases with age, the presence of trichiasis and corneal opacities is rare (32, 43) (table 2).

**Risk factors**

In hyperendemic areas, preschool children have the highest rate of trachoma, and a significant decline in the prevalence is observed after the age of 10 years for both males and females. The prevalence of chronic trachoma (scars, trichiasis, and corneal opacities) increases with age and reflects the accumulated experiences with reinfection. As a general pattern, females...
<table>
<thead>
<tr>
<th>Location (reference no.)</th>
<th>Date of survey</th>
<th>No. examined</th>
<th>Active disease</th>
<th>Scars</th>
<th>Trichiasis</th>
<th>Type of survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>1991</td>
<td>1,841</td>
<td>2-5 years</td>
<td>13</td>
<td>≥15</td>
<td>0.6</td>
</tr>
<tr>
<td>Sabou region (103)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
<td>0</td>
</tr>
<tr>
<td>Egypt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nile Delta (55)</td>
<td>1987</td>
<td>1,138</td>
<td>3 years</td>
<td>59</td>
<td>≥25</td>
<td>0.6</td>
</tr>
<tr>
<td>Qalyub (104)</td>
<td>1984</td>
<td>777</td>
<td>Primary school</td>
<td>26</td>
<td>0.6</td>
<td>Not stated</td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sidamo (46)</td>
<td>1988</td>
<td>1,222</td>
<td>5-9 years</td>
<td>29</td>
<td>≥45</td>
<td>11</td>
</tr>
<tr>
<td>Gambia</td>
<td>1984</td>
<td>950</td>
<td>4-7 years</td>
<td>29</td>
<td>≥20</td>
<td>25</td>
</tr>
<tr>
<td>Jali (32, 43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>1977-1981</td>
<td>13,803</td>
<td>0-4 years</td>
<td>59</td>
<td>Overall</td>
<td>5</td>
</tr>
<tr>
<td>Endemic areas (57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>1983</td>
<td>7,079</td>
<td>1-2 years</td>
<td>49</td>
<td>≥15</td>
<td>29</td>
</tr>
<tr>
<td>Lower Shire Valley</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>1991</td>
<td>1,185</td>
<td>0-9 years</td>
<td>31</td>
<td>≥10</td>
<td>15</td>
</tr>
<tr>
<td>Quarazate Province</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥10 years</td>
<td>4</td>
</tr>
<tr>
<td>(105)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>1986</td>
<td>5,574</td>
<td>3 years</td>
<td>68</td>
<td>≥15</td>
<td>8</td>
</tr>
<tr>
<td>Dodoma region (42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥15 years</td>
<td>3.5</td>
</tr>
<tr>
<td>Sudan</td>
<td>1992</td>
<td>616</td>
<td>0-15 years</td>
<td>65</td>
<td>Sample of “displaced persons”</td>
<td></td>
</tr>
<tr>
<td>Omuruman County (106)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>1985</td>
<td>6,777</td>
<td>0-5 years</td>
<td>18</td>
<td>≥6</td>
<td>7</td>
</tr>
<tr>
<td>Luapula Valley (107)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥6 years</td>
<td>0.6</td>
</tr>
<tr>
<td>Middle East</td>
<td>1982-1983</td>
<td>9,058</td>
<td>All ages</td>
<td>15</td>
<td>All areas</td>
<td>0.7</td>
</tr>
<tr>
<td>Israel West Bank, Gaza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(108)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>1980s</td>
<td>18,679</td>
<td>Primary school</td>
<td>9.5</td>
<td></td>
<td>Random selection, elementary schools</td>
</tr>
<tr>
<td>Al-Ahsa (109)</td>
<td></td>
<td></td>
<td>children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Territory</td>
<td>1985 and later</td>
<td>NS†</td>
<td>Children</td>
<td>5-69</td>
<td></td>
<td>Community-wide surveys</td>
</tr>
<tr>
<td>(110)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal Communities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Australia</td>
<td>1984-1985</td>
<td>547</td>
<td>0-9 years</td>
<td>12</td>
<td></td>
<td>Not stated; school and preschool children</td>
</tr>
<tr>
<td>Gollfield and Kimberly Regions (111)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central and South America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>1993</td>
<td>1,097</td>
<td>0-10 years</td>
<td>25</td>
<td>≥40</td>
<td>100</td>
</tr>
<tr>
<td>Chiapas (54)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>1986</td>
<td>2,008</td>
<td>3-4 years</td>
<td>7</td>
<td>≥10</td>
<td>0.5</td>
</tr>
<tr>
<td>Bebedouro (48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural area</td>
<td>1989</td>
<td>950</td>
<td>4-11 years</td>
<td>6</td>
<td></td>
<td>Random sample of school children</td>
</tr>
<tr>
<td>Northern São Paulo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(112)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Age at peak prevalence, or if not, specific age group.
† NS, not specified.

**Epidemiol Rev** Vol. 19, No. 2, 1997
appear to be at a higher risk of having every sign of trachoma compared with males, especially the blind- stages of trichiasis and corneal opacities (32, 42, 43, 59). 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 (52).

Trachoma remains a blinding disease in communities where the living conditions facilitate continuous transmission of *C. trachomatis* among family members. Determination of the specific factors that increase the risk of trachoma may lead to intervention strategies to control the disease. Below we review some of the environmental and personal factors that appear to affect the risk of active trachoma.

**Water availability and use**

Poor hygienic conditions due to lack of available water have long been associated with the risk of trachoma. Several studies have found a positive association between the distance from the household to the water source and the prevalence of active trachoma (48, 59–61). Clearly the distance to water can place constraints on the amount of water brought to the house, and water becomes a scarce resource whose use for hygiene purposes may be limited.

However, other research suggests that the availability of water may be less of a factor than household decisions on how water is to be utilized. In a large prevalence study, West et al. (42, 62) found that although distance to water was related to trachoma, there was no relationship to 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. In addition, Bailey et al. (63) found in a village in The Gambia 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. In general, in areas where trachoma is endemic, communities with a poor water supply are more likely to have higher trachoma prevalence (58, 64, 65), but the provision of adequate water 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 (66).

**Files**

One of the earliest risk factors noted for trachoma was the presence of flies (67–69). Eye-seeking flies can carry *C. trachomatis* on their legs and in the contents of their proboscis. Their ability to act as physical vectors for the transmission of infection has been demonstrated in laboratory settings by Forsey and Darougar (70). In Tunisia and India, epidemics of bacterial conjunctivitis and increases in the prevalence of active trachoma have been observed after peaks in the fly population (71, 72). Furthermore, studies in Tanzania have found an association between fly density in the household or the presence of flies on children's faces and the presence and severity of trachoma (61, 73, 74) as well as infection with *C. trachomatis* (75). However, flies are probably not the most important source of transmission, as others have found trachoma where the fly populations are absent (51) or less intense (76).

**Cattle**

Although cattle are not a reservoir or a physical vector for *Chlamydia* infection, the presence of cattle and cattle ownership has been associated with trachoma in some African countries (61, 77). In arid environments, cattle droppings create an optimal environment for breeding flies, and this has been the explanation for the association of cattle with trachoma. However, flies and cattle were independent predictors of severe trachoma in Tanzania, which suggests that cattle ownership is a marker for other important factors (61). In some societies, cattle not only are a sign of traditional wealth but also mark families with traditional lifestyles who tend to have the poorest living conditions.

**Hygiene**

In general, poor hygienic conditions favor the transmission of *C. trachomatis* through contact with ocular and other secretions that carry the infection (69). Several studies have been carried out to identify the specific hygiene practices associated with a lower risk of active trachoma. These studies have evaluated the use of latrines, handkerchiefs, and towels as well as face washing in children.

The presence of a functional latrine near the house has been associated with lower trachoma prevalence in several different countries (59, 61, 78). The mechanism by which the presence of a latrine would decrease trachoma is not entirely clear. In Egypt, Courtright et al. (78) found that the presence of a latrine was related to other measures of higher socioeconomic status, such as higher occupational level and more education of the head of the household, more large farm animals, and larger farming plots.
In Tanzania, a large cross-sectional study found a protective effect against both trachoma and severe trachoma with the use of a handkerchief for nose blowing and a towel for drying one's face (61). This finding is somewhat paradoxical, since handkerchiefs and towels would seem to enhance transmission of secretions, especially if used among many family members (79, 80). It may be likely that these items, which were rarely used in general, were a marker for a few families with better hygiene practices overall.

One potential source of infection is obviously the ocular and nasal secretions of preschool children (16, 81, 82). Decreasing the presence of these secretions by improving facial cleanliness may lessen the likelihood of transmission. However, determining 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 three studies, the self-reported frequency of washing children’s faces was believed to be unreasonably high, and was not related to the prevalence of trachoma (48, 59, 61). In one study, there was a modest association (51). In the Tanzanian study, investigators asked questions about face washing and also observed children’s faces in the home. Children who had clean faces were less likely to have trachoma or severe trachoma compared with children who had unclean faces (61). Further research determined the specific elements of an unclean face that were related to the risk of trachoma in children. Of the four elements studied (flies, nasal discharge, food on the face, and dust), children having flies on the face and nasal discharge had a twofold increased risk of active trachoma compared with children who did not have these signs (73).

The data from Tanzania suggest that children with clean faces were less likely to have trachoma; however, cross-sectional data are not sufficient evidence that improving face washing is protective. Face washing obviously has no effect on the course of disease but may reduce the likelihood of autoinfection or transmission of infection to others. To test the effectiveness of face washing, a randomized, community-based intervention trial was conducted in Tanzania by West and colleagues (83). Mass antibiotic treatment at one time point was offered to the entire study population in an effort to reduce the load of infection in each community. Six villages were randomly assigned to either mass treatment alone or mass treatment plus an intensive participatory face-washing campaign that involved the entire community. One year after mass treatment, children who kept their faces clean were about one half as likely to have trachoma, and one third as likely to have severe trachoma, as children who did not have clean faces (84, 85). The difficulties of carrying out a behavioral intervention were evident, but such an approach is likely to be more sustainable for communities with trachoma than the constant provision of antibiotic treatment.

**Extraocular infections**

In trachoma-endemic areas, children with active ocular Chlamydia infection are also likely to have extraocular chlamydial infections (81, 82). Autoreinfection from extraocular sources of Chlamydia infection may be one source of transmission and may explain why treatment with topical antibiotic ointment is effective for only a short time. However, in a study of the effect of mass topical treatment in a village in Tanzania, West et al. (81) found that the incidence rate of new infections was similar in those who had a positive nasal specimen at baseline compared with those who had a negative nasal specimen. Moreover, a positive ocular specimen at baseline was not predictive of the risk of a new infection after treatment, suggesting that these new infections were not the result of a latent or persistent infection. The use of a systemic antibiotic compared with a topical treatment for trachoma in children in a study in The Gambia did not lower the reemergent rates of infection at follow-up (86). These two studies suggest that the source of Chlamydia reinfection after treatment is not likely to be extraocular sources. The epidemiology of reinfection of trachoma will be enhanced considerably with the use of the newer technology for genovar determination since more precise studies of the source of infection will be possible.

**Risk factors for sequelae**

Trichiasis, entropion, and corneal opacities can be the sequelae of active trachoma in childhood. These complications appear in young adulthood and in middle age. In some areas, severe scarring can appear in children, but the prevalence of severe scarring is usually low in children and increases with age. Because of the long time course from repeated active infections in childhood to the development of blinding sequelae in middle-aged adults, there are few longitudinal studies of risk factors for scarring and none for trichiasis/entropion. In fact, the pathophysiologic change from scarring to trichiasis and visual loss have not been clearly defined. This area is of considerable interest because, although the majority of children in trachoma endemic areas have active disease, only a small percentage go on to develop the blinding complications.

The detection of chlamydial antigen or DNA suggests that cryptic infection may continue to drive the
progression to severe scarring and trichiasis (87). Clearly, prospective studies are needed to determine the importance of cryptic or persistent infection in the development of blinding complications of trachoma.

It is clear that adult women are at much greater risk of developing the blinding complications of trachoma than are adult men (42, 55). 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 almost entirely confined to caretakers of children with trachoma (52). However, a case-control study of risk factors for trichiasis in women by Turner et al. (88) did not find any association with years of exposure to child care activities, although exposure to children with active trachoma could not be ascertained retrospectively.

The same study found that trichiasis cases were more likely than controls to report poor living conditions during childbearing years. 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 (88). The association with cooking fire is of interest because others have found carbon particles imbedded in the fibrotic conjunctiva of entropion cases undergoing surgery in South Africa (89). Whether dust or smoke from the cooking fire could act as a mechanical irritant in the development of trichiasis is unclear.

**MATHEMATICAL MODELS FOR TRACHOMA**

The development of quantitative models that will integrate a variety of information from epidemiologic studies into a single system is currently underway. These models must identify optimal community-specific intervention strategies that have the potential to control or eradicate trachoma as a public health problem. Early catalytic models were developed in the late 1960s to evaluate reductions of trachoma (90, 91); however, these models describe rates of incidence and recovery for a given epidemiologic situation, without the characterization of the dynamics of transmission needed to understand the contribution of different types of interventions. Currently, simulation models are being developed that take into consideration population structure as well as environmental conditions to estimate the force of infection, likelihood of chronic sequelae, and effect of interventions (92, 93).

**STRATEGIES FOR TRACHOMA CONTROL**

Trachoma must be viewed as a community disease, not as a series of cases, in order to develop effective public health measures for control. As with other infectious diseases that have been controlled, a vaccine against *Chlamydia* would be ideal; however, efforts to date to create a vaccine against chlamydial infection have been unsuccessful. Attempts were made to develop chlamydial vaccines by using killed elementary bodies, but these first generation vaccines resulted in even more severe disease than naturally acquired infection; any protection conferred was against the immunizing serovar (94). Apparently, the vaccine acted to potentiate the effects of infection by sensitizing the subjects. The evidence in humans is not convincing, and researchers are again raising the issue of the value of killed vaccines in conferring immunity (95).

Clearly, an effective vaccine will have to elicit a protective immune response across multiple serovars, without sensitizing the recipient. Rational approaches to the design of a vaccine await further research on the development of genetic systems for chlamydia and studies clarifying human correlates of protective immunity (95).

Based on our current knowledge, a public health approach to trachoma control for hyperendemic areas should consist of three components: first, the provision of safe, effective, and inexpensive antibiotics to reduce the pool of infection in the community; second, health education about face washing to decrease transmission; third, the provision of surgery for trichiasis to prevent visual impairment. Trachoma control programs that do not have all three components will be unsuccessful in ultimately reducing the burden of visual impairment in the community for the long run.

Although antibiotics are effective in combating infection, reinfection is very likely to occur if only cases are treated. Antibiotic treatment of either whole communities or selected groups considered at high risk has been used in an attempt to reduce the risk of blinding disease. These approaches are effective in reducing infection and transmission in the short term. However, a long-lasting effect has not been attained when they are used as the only mode of control (71, 81, 86). Eradication failures have been attributed to poor compliance with the treatment regimen, the fact that the topical treatment may not be effective if extracocular sites of infection exist, the lack of treatment of infectious but clinically inapparent cases, and the reintroduction of trachoma through in-migration of active cases.

Recently, Bailey and coworkers (86) found that a new antibiotic, azithromycin, taken orally in a single dose, is as effective against ocular *Chlamydia* infection as 6 weeks of topical tetracycline. There are several advantages of this new drug: First, a single dose is effective and easy to administer, so there is the potential for achieving the high levels of compliance.
required for successful control programs. Second, systemic therapy with minimal side effects would be more effective than topical treatment for the eradication of infection in any extracocular reservoir. However, even with systemic antibiotics, a control program that must plan for the constant provision of medicine because reemergence occurs does not constitute a sustainable approach.

The disappearance of blinding trachoma from several countries in the Western world occurred before the availability of effective drug therapy. The disappearance paralleled economic development and improvement in housing, sanitation, and personal hygiene (69). Thus, it appears that environmental changes and alterations in lifestyle have a more sustainable impact on trachoma and point to the need for health education strategies for trachoma control. After the identification of key environmental and personal factors that are involved in maintaining transmission of active disease, community intervention programs that are culturally appropriate and targeted to the modification of these key factors should be developed and implemented.

In the transmission of trachoma, the role played by factors such as towel sharing, frequency of face washing, and presence of flies around the home appears to be understood by members of communities with trachoma. Therefore, Sutter and Ballard (96) in South Africa introduced the idea of “self-help” in the prevention of disease and found it could be very effective in areas where trachoma is hyperendemic. The formation of local women’s groups that not only were able to identify and treat the clinical signs of active trachoma but also were motivated to improve personal hygiene in their communities was the key element of the success of trachoma control in the Transvaal region of South Africa (97).

A community intervention trial carried out in Tanzania aimed to improve facial cleanliness in children after one mass treatment campaign was successful in reducing the levels of severe active trachoma up to a year after intervention (84, 85). In this trial, the key element was the active participation of the entire community through an intense education campaign to create awareness of first, the blinding consequences of the trachoma; second, the role that hygiene factors play in the transmission of the disease; and third, the importance of keeping children’s faces clean to avoid cycles of infection and reinfection with Chlamydia. The sustainability of this type of intervention requires a high level of involvement and support from the entire community (83).

Control strategies incorporating health education and antibiotics together are effective in reducing active trachoma in children, but the third arm—surgical intervention—must also be available because trichiasis will continue to exist in the adult population as a result of previous years of exposure to trachoma (55, 98). A number of different surgical techniques have been used to correct trichiasis (99). In particular, Reacher et al. (99) showed that tarsal rotation, when performed by an ophthalmologist, was effective in correcting 80 percent of minor and major cases of trichiasis studied for up to 1 year. However, in areas in which trachoma is endemic, patients with trichiasis often have very limited, if any, access to an ophthalmologist, so other health personnel should be trained. In Tanzania, after proper training by an ophthalmologist, eye nurses can successfully perform trichiasis surgery using the tarsal rotation technique in makeshift theaters in the local communities (100). Ophthalmic nurses or medical assistants can be trained to perform trichiasis surgery, and training manuals and videos are available from the World Health Organization (101).

Availability of trained personnel does not necessarily ensure that patients will use the services. In Tanzania, even after patients were aware that surgery was available and could prevent vision loss, compliance with surgery was very low: Only 18 percent of women with trichiasis to whom surgery was offered opted to have the operation in a 2-year period. The main barriers were perceived cost and lack of accessibility to the health facilities (102). In this environment, cost includes transportation, food, and expenses of an accompanying person who acts as a caretaker. Such factors must be considered when implementing an effective surgical program.

This three-pronged public health approach to sustainable trachoma control does not offer a quick and easy solution to trachoma. Unlike vitamin A capsules for xerophthalmia or ivermectin for onchocerciasis, there is no “magic bullet” for trachoma. Clearly, more research is needed on the immunopathology of trachoma, risk factors for the blinding complications, and strategies for effective intervention. Because trachoma afflicts the least empowered members of communities who are the most resource poor, the disease continues to be the most important, if forgotten, infectious cause of blindness in the world.

REFERENCES

3. Dean D, Schachter J, Dawson C, et al. Comparison of the


