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Review

Trachoma: transmission, infection, and control

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Mass antibiotic treatment and facial cleanliness are central to WHO's strategy for the elimination of blindness caused by trachoma. Recent studies have highlighted the heterogeneous response of communities to mass treatment and the complex relation between infection with *Chlamydia trachomatis* and clinical disease. It is important to be able to explain these findings to predict and maximise the effect of treatment on active trachoma disease and blindness in the community. Here we review the immunobiology of trachoma and provide a simple conceptual model of disease pathogenesis. We show how incorporating this model into a mathematical framework leads to an explanation of the observed community distribution of infection, bacterial load, and disease with age. The predictions of the model and empirical data show some differences that underscore the importance of individual heterogeneity in response to infection. The implications of disease transmission and pathogenesis for trachoma control programmes are discussed.

Introduction

Trachoma is the most common cause of infectious blindness worldwide.[1] In 1996, WHO established the Alliance for the Global Elimination of Blinding Trachoma by the year 2020 (GET 2020), and recommended endemic countries to implement the SAFE strategy (surgery to correct distorted upper eyelids of patients with advanced disease; antibiotic treatment for the infection; facial cleanliness to reduce transmission; and environmental change to increase access to clean water and improve sanitation). Trachoma has recently been identified as a candidate for integrated control with other so-called neglected diseases.[2] A major component of the SAFE strategy is mass administration of the macrolide antibiotic azithromycin, which has been donated by Pfizer to national trachoma control programmes that are implementing the comprehensive strategy. This has provided the incentive to monitor the distribution of bacterial load in the community before and after treatment, and recent studies have measured the rate of reinfection after mass treatment in various epidemiological settings.[3,4] These studies have shown the heterogeneous response of communities to mass treatment, with the prevalence of infection in some communities showing a sustained reduction, whereas in other communities prevalence rapidly returns to pretreatment levels. Furthermore, the likely effect of a reduction in the incidence of infection on the occurrence of scarring and blindness in later years of life remains unclear. Understanding the relation between the distribution of infection and disease in the population, the role of heterogeneity in the environment and in behaviour, and the response of trachoma-endemic communities to mass treatment remains a major challenge.

We review trachoma immunobiology and mechanisms of disease pathogenesis, and show how these mechanisms lead to observed distributions of bacterial infection and disease in the population. We begin with a brief overview of trachoma immunology and then provide a simple conceptual model of pathogenesis in infected individuals. We then review data on the population distribution of infection, bacterial load, and clinical disease in trachoma-endemic communities. Inclusion of the simple conceptual model of pathogenesis in a mathematical model of transmission reproduces the observed population distributions of infection, bacterial load, active disease, and blindness by age in a series of illustrative fits. Although the general fit of this model to a set of available data is good, the discrepancies underscore the importance of heterogeneity in the immune response of individuals to repeated infection. The Review ends with a discussion of the implications for the effect of control programmes on blindness caused by trachoma.

Trachoma immunobiology and pathogenesis

Our understanding of human ocular *Chlamydia trachomatis* immunobiology rests heavily on research in animals, notably cynomolgus monkeys,[5] and on longitudinal studies of human trachoma pathogenesis in endemic communities.[6] Inference by analogy with animal models and human studies of the better-understood genital chlamydia infections has also played a central part.[7] However, inference from these different systems must be tentative, and indicates differences in host and pathogen biology. For example, interferon-γ-mediated degradation of tryptophan inhibits growth of ocular but not genital serovars of *C trachomatis*, since the latter are able to use indole as a substrate for tryptophan synthesis.[8] With this caveat in mind, we briefly describe the current paradigm for the protective and pathological immune response to ocular infection, some recent challenges to this paradigm, and the role of repeated infection in progression to scarring and blindness.

Trachoma immunobiology

C trachomatis possesses a range of mechanisms to evade the immune response of the host, resulting in an infection that takes weeks to clear and that generates only partly protective immunity.[9] On initial infection, epithelial cells secrete cytokines that trigger inflammation and initiate recruitment of immune cells involved in the clearance of infection. Cellular immunity seems to be crucial for the resolution of infection: CD4 T-cell production of interferon γ has been shown to mediate immune clearance of *Chlamydia muridarum* in mice.[9] A preponderance of T-helper type 1 cell cytokines early in infection tends to polarise the response towards an inflammatory protective

immunity, whereas a greater involvement of T-helper type 2 cell cytokines can result in failure to clear infection.[10]

Acquired immunity from past infections appears to explain the shorter duration of infection observed in adults compared with children in a cohort study with frequent (fortnightly) follow-up visits.[11] Although children are highly exposed and reinfection may cause more frequent detection of infection at follow-up, a reanalysis of these cohort data suggests that incidence is not sufficiently high enough to explain, in isolation, the observed longer duration of infection at younger ages (Grassly et al, unpublished data). The acquired immune response seems to involve both cellular and humoral immune components.[9,12] The protective humoral immune response is targeted at the major outer membrane protein of *C trachomatis*, and raised concentrations of IgA antibodies have been shown to be associated with clearance of active trachoma in human beings.[13]

Acquired immunity is only partly protective against reinfection, and repeated episodes of infection have been reported in cohort studies from trachoma-endemic communities.[14,15] In mouse models of human genital infection, initial challenge results in rapid replication of bacteria resolving in around 4 weeks and, on re-challenge, around half the animals are completely protected.[7] Furthermore, in mice and human trials, vaccination with whole inactivated bacteria confers only partial protective immunity.[7,16]

Disease pathogenesis

Initial infection with ocular *C trachomatis* results in a self-limiting conjunctivitis that typically heals without permanent sequelae. However, this results in a hypersensitive state, such that subsequent infection results in more intense inflammation and faster clearance of bacteria.[11] Candidate antigens for inducing this hypersensitive state include the 60 kDa chlamydial heat shock protein, the major outer membrane protein surface antigen, and lipopolysaccharide from the bacterial cell membrane, although none of these antigens in isolation is sufficient to induce progressive disease.[17–19] Repeated infection results in chronic inflammation, visually apparent as inflamed lymphoid follicles when the upper eyelid is everted. In primates, repeated inoculation with *C trachomatis* results in an inflammatory response that may be sustained for as long as the monkey is inoculated.[20,21]

After years of reinfection and inflammation, scarring of the conjunctiva occurs, which, as it progresses, can cause the eyelashes to turn inwards and abrade the cornea, leading eventually to corneal opacity and blindness. The importance of reinfection for disease progression is reported in a study of Punjabi Indians living in Canada, who, despite signs of previous infection and trachomatous disease, failed to progress further in the absence of exposure to new bacterial inocula.[22]

WHO has devised a simplified system of clinically grading trachoma according to the severity of disease (panel). Because of the central role of reinfection to trachoma pathogenesis, rates of disease progression will depend on levels of exposure and hence overall prevalence of infection. We reviewed studies of the rate of progression from follicular or intense trachoma to scarring, trichiasis, and corneal opacity in different endemic communities (table 1). All cohort studies reporting rates of progression between disease sequelae were included. The rates given by these studies show the long timescales involved in progression to blinding trachoma and indicate the opportunity for surgical intervention.

Exposure varies across communities, both in terms of age and residential structure, and infection clusters within families residing in the same household.[29] However, some infected hosts are more likely to experience severe disease than others,[6,30] which may in part be explained by heterogeneity in host genotype. Certain HLA alleles seem to be more frequently associated with scarring disease, potentially mediated through cytotoxic T-cell activity.[31,32] Increased concentrations of tumour necrosis factor, indicating specific alterations in the gene coding for this inflammatory cytokine, have also been associated with severe disease,[33] and certain interleukin-10 promoter genetic sequences have been shown to be correlated with conjunctival scarring.[31] Furthermore, some ethnic groups seem to be at greater risk of severe disease than others, suggesting a possible role for host genetic factors in disease.[14]

Latent bacteria

Recently, a subset of the host population has been found to be unable to clear infection, and rather than repeated infection driving disease progression, the persistent release of antigen by uncleared bacteria has been proposed to lead to progressive disease.[6,34,35] This

***Panel*: WHO clinical disease grading of trachoma**

Trachomatous inflammation, follicular (TF)
At least five follicles (of at least 0·5 mm in diameter) on upper tarsal conjunctiva

Trachomatous inflammation, intense (TI)
Papillary hypertrophy and inflammation covering more than half of deep tarsal vessels

Trachomatous scarring (TS)
Clear trachomatous scarring of upper tarsal conjunctiva

Trachomatous trichiasis (TT)
One, or more than one, eyelash rubbing on the eyeball or signs of the eyelash's removal

Corneal opacity (CO)
Corneal opacity caused by trachoma, some of which obscures the pupil

Adapted from Taylor.[23]

hypothesis is difficult to prove or disprove because its signature—persistent, unchanging bacterial serotypes through the course of disease—is also expected as a consequence of the spatial clustering of transmission.[36] In genital infections, interferon-γ-rich environments can induce bacterial persistence,[8,37,38] with the continued presentation of antigens such as the 60 kDa chlamydial heat shock protein by this persistent form.[7,8,17,36,39,40]

An alternative mechanism for disease pathogenesis has been proposed in which infected epithelial cells produce pro-inflammatory chemokines, cytokines, and growth factors.[34] In this mechanism, the host-acquired immune response has a secondary role in inflammation and scarring, but the primary source of chronic and proliferative cell damage is the infected epithelial cells. This hypothesis can be tested in future research by observing the response profile to infection, which should differ from a pure immune system response if its origin is largely non-immune.

Epidemiology of infection and disease

In trachoma-endemic communities, the prevalence of active disease (follicular and intense) generally peaks sharply among children aged 1–5 years, in whom it can be higher than 50%,[41,42] and drops to substantially lower levels in adults, often around (or less than) one-tenth of its peak level. Most cases of active disease in adults are in women, who are in more frequent contact with infectious children, for whom they are the primary caretakers.

The prevalence of infection in communities has recently been studied by use of PCR techniques, whose sensitivity is greater than Giemsa staining, culture, and direct fluorescent antibody procedures previously used.[5,30,43–45] Surprisingly, these studies have found large numbers of PCR-positive adults and a tendency towards a roughly constant prevalence of infection with age. Furthermore, they have indicated the extent of the discrepancy between infection and disease, with typically about one-third of those with active disease showing no detectable infection, and one-third of those with laboratory evidence of infection being classified as clinically well.

Many of the cases of clinical disease in the absence of infection are explained by the kinetics of disease pathogenesis, in which inflammatory disease may persist long after infection has been cleared.[5,46,47] The large number of cases of infection without clinical disease is more puzzling. Reasons for this disparity may include, on the one hand, false positives for infection, either because of cross-contamination during examination or poor test specificity, both of which have been identified as potential problems in some early studies, and, on the other hand, low sensitivity of the WHO simplified grading system. (This simplified system was never devised for detailed studies of the relation between infection and disease, and will grade many cases as clinically normal when there are, for instance, less than five inflamed follicles.) A recent study that used

	Length of study	Frequency of follow-up	Study population	Disease incidence [% transition (95% CI)] and duration	Country	Disease prevalence
Bowman et al[34]	12 years	One at 12 years	639 with TS	TS to visual impairment/blindness, 17% (13–21); TT to visual impairment/blindness, 15% (4–35).	The Gambia	10%
Bowman et al[24]	1 year	6 months and 12 months	190 with TT; all ages, both sexes	In 12 months: minor TT to major TT, 33% (21–47); unilateral TT to bilateral TT, 46% (31–61); incident CO to progressive CO, 10% (5–17).	The Gambia	..
Burton et al[25]	4 years	One at 4 years	154 with TT in one or both eyes	In eyes in 4 years: major trichiasis to CO, 10%; minor trichiasis to CO, 5%; minor trichiasis to major trichiasis, 37%; no trachiasis to trichiasis, 29%.	The Gambia	Baseline active 8%
Muñoz et al[26]	5 years, 10 years	One at 5 years and 10 years	6038 women, all ages	In 5 years (one age-range, others given in paper): TS to TT (15–19 years), 3%. In 10 years: TT to CO (15–24 years), 27%.	Tanzania	Hyperendemic
Muñoz et al[27]	7 years	One at 7 years	523 women with TS from 11 villages; >18 years	TS to TT: <20 years, 7%; 20–29 years, 7%; 30–39 years, 7%; 40–49 years, 10%; 50–59 years, 9%; ≥60 years, 20%.	Central Tanzania	Hyperendemic
Taylor et al[28]	1 year	Every 3 months	53 children from 9 families; age 0–14 years, both sexes	Number in 1 year: no disease to TF/TI, 7/53; TF/TI to no disease, 13/53.	Tanzania	Hyperendemic; peak TF/TI prevalence in children aged 5 years >90%
West et al[6]	7 years	Four exams over 1 year at baseline then once at 7 years	98 children with constant severe trachoma; 96 without; age 1–7 years	Constant severe trachoma to TS (or worse): 1–3 years, 18%; 4–7 years, 40%. Less severe trachoma to TS (or worse): 1–3 years, 11%; 4–7 years, 8%.	Central Tanzania	Hyperendemic; 60%

CO=corneal opacity. TF=trachomatous inflammation, follicular. TI=trachomatous inflammation, intense. TS=trachomatous scarring. TT=trachomatous trichiasis. ..=not reported.

Table 1: **Studies reporting progression between trachoma disease sequelae**

	Infection positivity by DNA methods	Infection load distribution	Clinical disease (follicular and intense)	Context and comments
Burton et al[4] (Solomon et al[30])	7% of all ages by qualitative PCR	Mean load in each age-group is fairly constant, but most of load is in <20 year-olds	8% active disease	Upper Saloum district, The Gambia; 14 villages, 1319 individuals examined at baseline.
Melese et al[49]	56·3% of those aged 1–5 years by PCR	..	..	Gurage zone, Ethiopia; 1322 children.
Solomon et al[30]	9·5% of all ages by PCR	Youngest age-groups have highest loads, several with four orders of magnitude greater than older ages	20·4% active disease	Rombo district, Tanzania; one village, 956 individuals tested at baseline.
West et al[3] (Solomon et al[30])	57% of all ages by PCR	Skewed towards young ages; 71% of those with above median infection load are <15 years	38% active disease (77% prevalence in <8 years)	Kongwa, Tanzania; 873 individuals examined.

..=not reported.

***Table 2*: Studies reporting clinical disease levels and PCR measurements for infection**

quantitative PCR for 16S RNA expression has shown that many individuals positive by qualitative DNA-based PCR in fact have low bacterial gene expression.[48] Instances that are positive according to DNA-based PCR may therefore in some cases represent continuous passive inoculation of the eye with bacteria in the environment, rather than actively replicating infections.

Several studies have used quantitative DNA-based PCR to examine the distribution of bacterial load in the community. These studies reveal substantial heterogeneity, with the heaviest bacterial loads concentrated among young children (table 2). In extreme cases, nearly 50% of all the bacteria in the sample—the community bacterial load—may be harboured by children aged under 1 year.[30] Adult loads are generally lower than those of children, presumably because of effective acquired immunity, although there is often a small proportion of adults with high loads.[45] Again, interpretation of these results should be made with some caution in view of the potential for cross-contamination of samples, although this may be unimportant in these more recent studies, in which more care has been taken in the handling of samples.

The skewing of infection load towards children is more marked in communities in which active disease is hyperendemic (active disease prevalence in children more than 50%).[50] In lower prevalence communities, a more even distribution of bacterial load is found, with fewer of the high-load infections occurring in young children.[30] This is consistent with the lower cumulative exposure to infection experienced by adults in these communities and the correspondingly lower levels of acquired immunity. Similar patterns of infection prevalence and intensity are observed in parasitic infections such as helminths and malaria.[51] The intracellular replication of *Chlamydia* spp results in production of large numbers of infectious elementary bodies, and individuals with high loads are likely to be responsible for most new infections in a population.

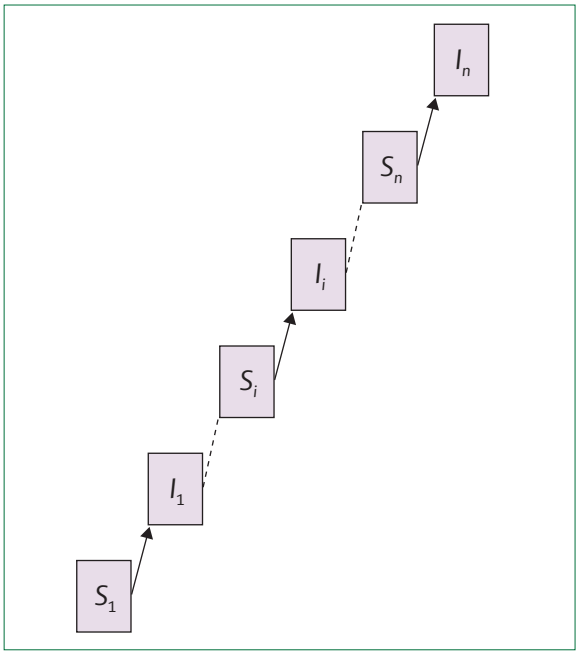

***Figure 1*: A simplified compartmental diagram of the susceptible-infected model of infection**
Each susceptible and infected compartment is connected to the compartment above so that the population passes up a ladder of infection (see webappendix for details). i=number of previous infections. I_i=infected stage i. S_i=susceptible stage i.

National surveys often report specific clinical diagnoses by age, largely according to the WHO grading system.[42,52–55] These surveys report very low levels of conjunctival scarring, corneal opacity, and blindness in the youngest age-groups, with the prevalence of these severe disease sequelae rising steeply with age. Corneal opacity and blindness constitute a small fraction of overall disease for older individuals, whereas scarring often becomes, at older ages, commensurately prevalent with active disease at younger ages.[56,57] In general, the higher the prevalence of active disease in the community, the higher the

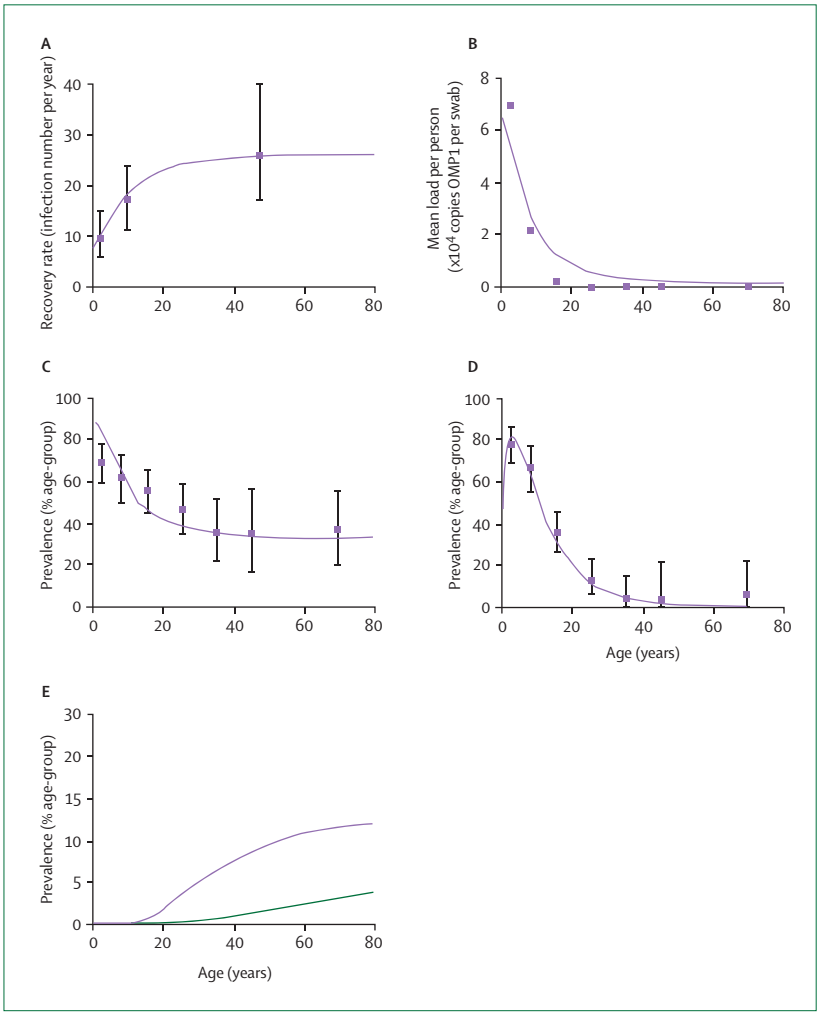

***Figure 2*: Simultaneous fit of a simple mathematical model to data on age-specific profiles**
(A) Rate of recovery from infection, with values from Bailey and colleagues[11] (mean duration of infection for the 0–4-year age-group, 5·5 weeks; 5–14 years, 3·0 weeks; ≥15 years, 2·0 weeks). (B) Bacterial load in female patients measured by DNA-based quantitative PCR tests.[61] (C) Prevalence of infection for female patients measured by qualitative PCR.[61] (D) Prevalence of active disease for female patients measured as follicular and follicular ± intense.[61] (E) Model-generated prevalence of disease sequelae. (C, D) Error bars represent exact 95% CIs, assuming a random sample of population infection and disease prevalence, respectively. (D) The predicted age profiles of active disease and (E) severe disease sequelae (scarring [purple line] and more severe sequela [green line]) are also shown; their method of calculation is outlined in the webappendix. The model outputs represent the best fit to the published data (purple squares). Reducing the transmission parameter in the model produces patterns of infection load, and infection and disease prevalence consistent with observations from lower prevalence settings (data not shown). OMP1=outer membrane protein 1.

See Online for webappendix

prevalence of disease sequelae, which is as expected if repeated infection is required for disease progression.[58–60]

Mathematical model of trachoma

The central importance of previous exposure to an individual's biological and clinical response to reinfection can be captured in a simple mathematical model. This model corresponds with a simple susceptible–infected model of infection,[51] but in which each compartment is indexed by the number of previous infections (figure 1). As individuals progress up this ladder of infection, an acquired immune response is assumed to result in more rapid clearance of infection, reduced bacterial load, and more severe disease, in agreement with our understanding of chlamydia immunobiology (webappendix). The probability of infection transmission from an infected individual by direct contact, fomites, or flies is assumed to be proportional to the bacterial load.

This simple model may be fit to cross-sectional or time-series data by the age distribution of infection, bacterial load, active disease, and/or more severe disease sequelae, thus allowing the estimation of parameters describing the relation between rates of clearance of infection or bacterial load and the number of previous infections. We provide a fit of the model to illustrative data collected in a high prevalence trachoma-endemic community (figure 2). Such a close fit of our simple model is reassuring, and suggests that the current paradigm for chlamydia pathogenesis is broadly correct. However, there are some interesting discrepancies. First, the predicted prevalence of active disease in the model drops to zero for older ages, whereas it continues to be reported among a small fraction of older individuals in most trachoma-endemic communities (figure 2). This could be the result of heterogeneity in exposure to infection or the response of individuals to infection, such that a small number are unable to resolve infection and show persistent clinical symptoms. Second, the predicted prevalence of severe disease sequelae in the model rises rather more steeply with age than is commonly observed in endemic settings (figure 2). This might again indicate heterogeneity, missing from the model, in the response of individuals to infection, with some more prone to scarring and progressive disease than others.

Trachoma control

Mass antibiotic administration programmes, using oral azithromycin (at 20 mg/kg bodyweight, up to a 1 g single dose), are being rolled out across Africa,[62] with the aim of eliminating the blinding form of trachoma by 2020. Theoretical and empirical studies are addressing the following key factors: the frequency with which antibiotic treatment needs to be administered to eliminate the infection from a community; the rate at which infection will re-emerge if not eliminated; the main routes and sources for reinfection; and the relative rates of disappearance of infection and disease.

Among the theoretical studies, the deterministic mathematical model of Lietman and colleagues[63] investigates how often antibiotic treatment would need to be administered, and at what level of community coverage, to eliminate *C trachomatis* infection in a closed population. Because such models do not take into account the stochastic nature of infection in communities, infection always re-emerges at a rate characterised by the initial doubling time (IDT) of the prevalence of infection in the community. The IDT, in turn, can be used to calculate quantities such as the

necessary treatment frequency for consistent (monotonic) prevalence decline.[63] This method has been put to the test in the Gurage zone of Ethiopia,[49] where the required treatment frequency for elimination was estimated at 12 months, provided that 80% of the population is treated, and without immigration of *C trachomatis* carriers. The IDT is a function of the basic reproduction number,[51] R_0, which can be estimated from the level of endemic infection observed in communities. In general, the higher the level of endemic infection, the shorter the IDT, the higher the value of R_0, and the faster the infection will re-emerge.[63] However, the relation between R_0 and endemic prevalence is complicated by heterogeneity in exposure and the ability to clear infection. Furthermore, the assumption of endemic equilibrium is rarely met. Therefore, in addition to indicating the average behaviour of the host–pathogen system, models of trachoma epidemiology and control will need to capture individual (or household) variability in transmission variables for these models to become truly useful at informing control policy.

Among the empirical studies, we summarise salient findings of longitudinal investigations of trachoma control after a single dose of azithromycin in endemic communities (ie, without re-treatment) in The Gambia,[4] and in Tanzania.[3,64] Burton and colleagues[4] found that most of the antibiotic-treated villages (oral azithromycin and topical tetracycline ointment, with a therapeutic coverage of 83% of the total population for the former) resolved their baseline infections, and by 12 months after treatment, the overall infection levels had become substantially lower than those at baseline. By contrast, those villages experiencing appreciable contact with untreated communities increased their level of infection 2 months after treatment, although subsequently, levels of infection also decreased well below those recorded at baseline.

West and colleagues[3] found that, after an initial large drop in infection prevalence (from a high baseline of more than 50%), there was evidence of a rise in infection levels by 18 months after treatment. Risk-factor analysis revealed that travelling outside the village did not increase the risk of incident infection by 12 months after treatment, but that if another household member had a high infection load 2 months after treatment, then incident infection in the same household became more likely. Individuals with high infection loads within households therefore seem to be of primary concern to the success of community-based treatment. This study may also indicate that those with high pretreatment bacterial loads may respond less well to treatment and become sources of subsequent reinfection.[3]

Burton and colleagues[4] and Solomon and colleagues[64] have also examined the change in infection and disease prevalence after mass antibiotic treatment. Community infection load (measured as the geometric mean bacterial load over all measurements taken in the village) decreased fairly consistently on follow-ups after treatment, but prevalence of active disease (both inflammatory and follicular) took much longer to decline. This discrepancy in the dynamics of infection and disease after treatment may be explained by the time taken for disease resolution after antibiotic treatment.

In view of the weak connection between the results of clinical examination and the laboratory-confirmed presence of infection, the development of a relatively cheap, easy-to-use, sensitive, and reliable field test for the detection of *C trachomatis* infection would be useful. Recent testing of a point-of-care assay in a resource-constrained setting found a sensitivity and specificity of 84% and 99%, respectively, for infection by qualitative PCR.[65,66] After being thoroughly assessed in the field, assays such as this may allow better identification of communities that require mass antibiotic treatment (currently judged by the prevalence of active disease in children),[4,67] and allow the monitoring of the effect of treatment on overall levels of infection and transmission.

Conclusions

Trachoma disease progression is intimately linked with the immune response provoked by initial and subsequent ocular infections by *C trachomatis*. Exposure to infection tends to be highly heterogeneous within communities, and additionally, population subgroups may exist who are genetically predisposed to acquire the infection in the first place, and then to develop severe scarring sequelae on continued exposure to infection. The reasons for this predisposition to scarring sequelae are currently thought to be linked with immune responses to reinfection that are more damaging to tissue than the responses of those who experience less trachomatous scarring after the same level of exposure. For those with a more damaging response, a state of hypersensitivity to one or more bacterial antigens is attained wherein a reintroduction of antigen leads to an immune hyperreaction, rapid clearance of bacteria, and disappearance of active disease, but also severe tissue damage in the wake of this clearance. This hypersensitive state does not require continued chlamydial infection, and occasional exposure to antigen might be sufficient to lead to the prolonged inflammation that results in scarring.

Ocular infection with *C trachomatis* precedes subsequent disease and disease often persists beyond bacterial clearance; these infection and disease kinetics explain the many observations in which one of either disease or infection is observed without the other. Clinical examination is currently the only cost-effective method for determining infection prevalence in a community. However, at the individual level clinical diagnosis will miss many cases of infection. Rapid point-of-care assays for the presence of infection address this problem, and may be useful in the future, depending on feasibility and affordability in field situations.

Recent efforts to interrupt transmission of ocular *C trachomatis* by use of azithromycin have resulted in

Search strategy and selection criteria

Studies for this Review were obtained by searching the PubMed database by use of the search terms "trachoma AND (progression OR natural history)" and "trachoma AND infection AND PCR". All cohort studies that reported rates of progression between disease sequelae were included, but only those studies (and the studies to which they referred) in which DNA-based PCR was used were included. No date or language restrictions were set in the search.

new data that document infection and disease prevalence before and after a single-dose treatment. These data show the following: (1) declines in active disease typically lag behind declines in the prevalence of infection after treatment; (2) infection may re-emerge after treatment from low, residual levels or after reintroduction from other areas; (3) high treatment coverage among communities may result in sustained reductions of infection and disease; (4) a population subgroup carrying a high infectious load may respond poorly to treatment and constitute reinfection sources; and (5) the frequency of treatment required for local elimination of infection is dependent on initial endemic levels.

The availability of new data from qualitative and quantitative PCR tools, collected before and during trachoma control programmes, are providing much valuable information on ocular infection with *C trachomatis* at individual and community levels. Mathematical models of trachoma transmission and control, of a kind able to incorporate these new data, are being developed with the aim of informing control policy for the achievement of the GET 2020 goal.

Our framework has, thus far, focused on feasibly reproducing the progression of individuals through the infection ladder that seems to characterise the epidemiology of trachoma and the progression to ocular disease. Future models will need to be parameterised and fitted to both endemic and post-treatment data to predict the frequency and duration of mass antibiotic administration programmes in settings with different forces of infection, and to identify which members of the community may need to be targeted to reduce reinfection sources that may threaten the overall success of local elimination efforts.

Conflicts of interest

We declare that we have no conflicts of interest.

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