Modelling trachoma: infection, transmission and control

A report prepared for the International Trachoma Initiative

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Acknowledgements

This report presents a model of trachoma transmission and control developed during a two year project funded by the International Trachoma Initiative (ITI). It contains detailed description and validation of the model using data from trachoma endemic communities, and presents investigations into the impact of mass distribution of antibiotics on trachomatous infection and disease.

We would like to thank ITI not only for the financial support to carry out this project, but also for their continued engagement and collaboration on the research presented herein. In particular we would like to thank Jacob Kumaresan, Felicity Turner, Ibrahim Jabr and Jeff Mecaskey. We would also like to especially thank Matthew Burton and Anthony Solomon for sharing published and unpublished data from the Gambia and Tanzania used to validate the transmission model. We have also benefited greatly from discussion at two international meetings that focused on the epidemiology and control of trachoma. We would like to thank the participants at this meeting for their contribution to the modelling work presented in this report: Agatha Aboe, Wondu Alemayehu, Neal Alexander, Robin Bailey, Jaya Chidambaram, Michael Deming, Bruce Gaynor, Peter Kilima, Charles Knirsch, Tom Lietman, David Mabey, Silvio Mariotti, Beatriz Munoz, Mohammad Babar Qureshi, Serge Resnikoff, Hugh Taylor, Sheila West, Emily West-Gower. In the work that follows we attempted to follow advice from these meetings as closely as possible.

Manoj, Isobel, Maria-Gloria, Nick

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Executive summary

- It has been found that a simple mechanistic model of ocular infection with *C. trachomatis* adequately describes the major features of the epidemiology of trachoma. The model incorporates the natural history of infection and progress to the damaging disease sequelae through contact with infected members of the population and subsequent repeat infection.

- Model parameters were estimated by fitting to data from low (hypoendemic), medium (mesoendemic) and high prevalence (hyperendemic) communities. These fits demonstrate a shift in the peak prevalence towards younger ages as the estimated transmission parameter increases and individuals acquire immunity earlier.

![Graphs showing prevalence of infection in different communities]

The model adequately describes the prevalence of infection in different communities (a) Upper Saloum district, Gambia (hypoendemic); (b) Rombo district, Tanzania (mesoendemic); (c) Kongwa district, Tanzania (hyperendemic).

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• Three rounds of annual antibiotic treatment appear to be sufficient in the model to control infection in the hypo- and meso-endemic communities.

**Mesoendemic: Prevalence of infection after treatment**

![Graph showing prevalence of infection after treatment](image)

The infection prevalence is reduced to a very low value following three rounds of antibiotic treatment in a mesoendemic setting. The low prevalence level is sustained beyond the period of treatment.

• Prevalence levels of disease sequelae are also gradually reduced during and beyond the antibiotic treatment programme in the hypo- and meso-endemic communities. A sustained reduction, however, may require a reduction in the level of transmission, through the facial cleanliness (F) & environmental improvement (E) components of the SAFE strategy.

**Mesoendemic: Prevalence of disease sequelae following treatment**

![Graph showing prevalence of disease sequelae](image)

The age-dependent prevalence of disease sequelae (TS—trachomatous scarring; TT—trachomatous trichiasis; CO—corneal opacity) following three rounds of annual antibiotic treatment with a 97% coverage level in a mesoendemic setting. There are declines in prevalence over all ages following treatment. As the time since treatment increases, and the infection rebounds, the rate at which these prevalence levels drop decreases.
In the hypo- and mesoendemic settings, the incidence of corneal opacity declines below the guideline level of 1 incident case per year in a population of 10,000 for the achievement of GET 2020.

**Mesoendemic: Incidence of CO after treatment**

The time development of the incidence of CO in the mesoendemic setting following three annual antibiotic treatments. The incidence of CO drops below the threshold for control (indicated by the (red) dotted line at 0.01%).

Three annual antibiotic treatments are shown to fail to bring down the prevalence of infection for any appreciable period of time in the hyperendemic setting. The incidence of disease sequelae, and corneal opacity in particular, therefore also remain well above a level sufficient to achieve the GET 2020 goals.

**Hyperendemic: Incidence of CO after treatment**

The time development of the incidence of CO in the hyperendemic setting following various antibiotic treatment programmes, starting at time 0 years. The incidence of CO drops remains far from the threshold for control (indicated by the (red) dotted line at 0.01%).
The implementation of the F & E components of the SAFE strategy in a hyperendemic setting—in the model interpreted as a steady reduction of the transmission rate—is shown to reduce the force of infection so that the prevalence of infection can be brought down and perhaps eliminated, thereby allowing reductions in the disease sequelae.

**Hyperendemic:** Prevalence of infection after treatment

The prevalence of infection in a hyperendemic setting before and following 9 years of a reduction in the transmission rate (interpreted here as an F & E campaign) and three annual antibiotic treatments at 86% coverage. The first of the three antibiotic treatments is indicated by the (red) arrow.

- A high coverage level of antibiotic treatment is crucial for the successful control of infection. The effectiveness gain observed (measured by the reduction in the prevalence of infection) by increasing coverage from low levels is greater than the gain when coverage is higher.

**Hypoendemic:** Prevalence of infection with varying treatment coverage

The prevalence of infection, in a hypoendemic setting, 1 and 5 years after three rounds of antibiotic treatment with coverage given along the x-axis.
• The incorporation of active disease (TF/TI) into the model allows the simulation of 1) the presence of disease in the absence of infection and 2) the lag in the disappearance of the signs of disease once infection has been cleared following treatment. These model features may allow decision support when the prevalence of active disease is monitored as a proxy for infection in the wake of treatment programmes.

**Hypoendemic: TF/TI prevalence after treatment**

![Graph showing the development through time of the prevalence of infection and active disease for the model and recent baseline and post-treatment data from Upper Saloum District, Gambia\(^d\). The model replicates the observed disparity between infection and disease prevalence and the lag in disease decline following treatment.]

• This is the first model of infection and disease in trachoma to: 1) be fitted to the full-range of endemic settings across all ages and to replicate epidemiological patterns; 2) include the progress of individuals toward the trachomatous disease sequelae as well as the infected state; 3) examine the effect across ages of a variety of treatment programmes using both antibiotic treatment and transmission reduction through non-chemotherapeutic means; 4) explicitly include active disease as well as infected status.

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• As more data emerge from intervention trials and control programmes, the model presented here is capable of being newly calibrated to project the impact of treatment in trachoma-endemic communities to understand what needs to be done to achieve the GET 2020 goals of eliminating the most severe disease sequelae.
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1 Report structure

The first section of the report provides an outline of the age-structured model that has been built to represent trachoma infection and disease. The most important factor in building a mathematical model is to decide what are the crucial components determining the transmission dynamics of the infection and the effect on these dynamics of control interventions. The components of the model and their reasons for inclusion are outlined in this first section. Details are also given here of the datasets that were made available to the project. Using these data, the model is calibrated to a hypo-, meso- and hyperendemic setting and the resulting curves of the prevalence of infection are analysed. The way in which the model represents the disease sequelae is also explained here, along with a calibration of the model to the sequelae data of the three endemic settings.

The next section of the report explores a number of scenarios in which trachoma control interventions are implemented. The first of these is the simplest: antibiotic treatment over the entire population and the subsequent tracking of the age-dependent prevalence of infection as it rebounds over the course of a year. This is followed by a series of analyses of the effect of antibiotic treatment on the scarring disease sequelae, which are represented in the model as outlined in the first section. The gradual drops in prevalence of the sequelae, over time and age, are examined and the decreases in these values are also explored in the case of elimination of infection for the hypo- and meso-endemic communities. Next, the GET 2020 objectives, focusing on the disease sequelae, and in particular corneal opacity, are investigated by looking at the incidence of these disease states over time under various control scenarios. An attempt is made to look at the combined effect of other components of the SAFE strategy—namely the facial cleanliness (F) and environmental improvement (E) interventions—along with antibiotic treatment for a hyperendemic setting, where the prevalence of infection is extremely hard to reduce. The level of antibiotic coverage is also becoming an important area of concern in intervention trials and this level is systematically varied here to look at the way in which post-treatment infection prevalence varies with different coverage levels. Finally, the inclusion of active disease—trachomatous inflammation: follicular and/or intense—in the model allows the representation of the observations that 1) active disease and infection prevalence levels often are not the same and 2) active disease prevalence lags behind infection prevalence post-treatment.
Following this section, the report gives a more detailed account of two of the issues outlined in the first section, namely 1) the inclusion of the infection load in the model and how the load at the individual level influences the infection load distribution in the population and 2) the variation in the rate of recovery from infection with exposure to infections. These features of infection and disease are both dependent upon a gradually acquired immunity that clears infection more rapidly with increased exposure to infection; they play important roles in trachoma epidemiology and a model allows an analysis of exactly how they influence quantities such as the prevalence of infection.

The final section summarises the main points from the investigations detailed in the previous sections. This summary is carried out with the GET 2020 goals in mind and any policy-related implications are discussed here.

In addition to the main body of the report, an extensive set of Appendices are attached. These sections include specific details on: the mathematical background of the model; the model with added active disease state; a section on the relative importance of exposure and acquired immunity; and an excerpt from the Master’s degree dissertation of Ms. Isobel Blake, a Master’s degree student supervised by the trachoma modelling team at Imperial College London.
2 Model structure

The model representing ocular infection by *Chlamydia trachomatis* in a community setting is based upon the simple SIS framework (Anderson and May 1992), in which susceptible (S) individuals become infected through contact with infected (I) individuals before recovering again to a susceptible state. Initial infection and reinfection come about through direct contact with other infected members of the community, indirect contact through fomites or through facial contact with flies carrying bacteria. In endemic settings, disease progression appears to occur through multiple reinfection by the bacterium (Taylor, Johnson et al. 1987). This model takes account of the fundamental importance of multiple reinfection on disease progression by keeping track of the number of infections an individual has experienced (Figure 1). Conceptually, the model represents the ‘ladder’ of infection, with each ‘rung’ of the infection ladder corresponding to an additional cumulative infection with *C. trachomatis*. Susceptible states are denoted by $S_i$ and the infected states by $I_i$, with the subscript denoting the number of previous infections (full details of the model are given in Appendix A).

\[ S_i \xrightarrow{\lambda} I_i \xrightarrow{\nu_i} S_i \xrightarrow{\lambda} I_i \xrightarrow{\nu_i} S_n \xrightarrow{\lambda} I_n \]

**Figure 1** A simplified compartmental diagram showing the model described in the text. Each susceptible and infected compartment is connected to the compartment 'above' so that the population passes up a ladder of infection.
2.1 Demography

The demography of the population is carefully described in the model, since demographic effects are important in determining the prevalence levels of the more severe disease sequelae. These sequelae generally have higher prevalence levels at older ages and, once the population has been treated with antibiotic, the rate at which the prevalence levels decline depends upon mortality among older individuals. Calculations of the rate of decline of the sequelae with age, therefore, are dependent on correctly defining age-specific death rates.

Age-specific death rates and the crude birth rate for the Gambia and Tanzania were based on life table estimates for 2001 published by the WHO (WHO 2006). Figure 2 shows age-dependent forms of the death rates for the two countries from which trachoma baseline and treatment follow-up data were available for this project.

![Figure 2: Death rates used in the age-structured simulations](image)

**Figure 2** Death rates used in the age-structured simulations. These death rates have been plotted here for the mid-points of the age-groups of the model. The 2001 data were obtained from the WHO website (WHO 2006).

2.2 Rate of recovery from infection

The rates at which the population enters and exits the compartments illustrated in Figure 1 are the fundamental parameters that decide the equilibrium age distribution of susceptible and infected individuals. Several studies have postulated that the sequelae of trachoma are largely caused by immunopathological processes which increase in severity with increasing age (Abu el-Asrar, Geboes et al. 1998; Debattista, Timms et al. 2003; Brunham
and Rey-Ladino 2005). This idea is supported by work which shows that the duration of active disease and infection are both age-dependent, becoming markedly shorter with age (Burton, Holland et al. 2005; Grassly and Bailey In prep.). In this report we assume that acquired immunity results in an increasingly rapid rate of recovery from infection as the number of previous infections increases. The model parameter associated with a maturing immunity is the recovery rate $\nu_i$ from infection $I_i$; Appendix A gives details on how this rate changes with an increasing number of infections. The rate of recovery from infection approaches a limit at high numbers of infections, as shown in Figure 3.

The parameter values determining the rate at which the curve rises with infection number and the initial recovery rate was estimated by fitting the model to data on the prevalence of infection and recovery rate by age derived from intervention and cohort studies (as described in detail in section 6.2.2 and Appendix A).

![Figure 3](image_url)

**Figure 3** The function of recovery rate defined over compartment number ($i$). As the population progresses along the ladder of infection, the recovery rate increases to a saturation level. The parameters describing this relationship were estimated by fitting the model directly to age-specific prevalence data and data from cohort studies on the duration of infection as described in section 6.2.2.

### 2.3 Infection load

In trachoma-endemic communities, it has been observed that bacterial infection loads among individuals at young ages are often higher than those at older ages (Solomon, Holland et al. 2003). In the model presented here, it is assumed that the origin of this diminution of infection load with age lies in the acquired immune response to chlamydial
infection developed through bacterial reinfection. The mechanism for the lowering of the average load is the same as that responsible for the increase in recovery rate from infection: as individuals acquire a stronger clearing immune response, their average infection load drops. An exponential decay is used to represent the average infection load for an individual who has experienced a specific number of infections, as detailed in Appendix A.

The load enters the model as a proxy for the infectivity of individuals; therefore, those who have experienced few infections are more infectious than those who have experienced many. More details on the precise way in which load enters the model can be found in Appendix A. There are precedents for such a model structure in the literature on helminth infections, where acquired immunity to infection is developed with exposure, and therefore with age, and such models lead to lower microfilarial and worm burdens with age (Chan, Guyatt et al. 1994; Chan, Guyatt et al. 1995; Chan, Srividya et al. 1998; Norman, Chan et al. 2000). For these macroparasitic models, patterns of infection prevalence, intensity and infection-induced morbidity are found that are very similar to those seen in trachoma.

3 Data used to validate model and produce parameter estimates

The model was fit to pre-intervention prevalence and bacterial load data from different communities where the prevalence of active disease ranged between 8% and 36%. These data were provided by Dr. Matthew Burton (Upper Saloum district, Gambia) and Dr. Anthony Solomon (Rombo district, Tanzania) both at the London School of Hygiene and Tropical Medicine. In addition to these data, the published baseline survey of Dr. Emily West and co-workers (Kongwa, Tanzania) were also used (West, Munoz et al. 2005). These three data-sets constitute a range of initial levels of endemic prevalence of infection and disease as outlined in Table 1, excerpted from data given by Solomon et al. (Solomon, Holland et al. 2003):
### Table 1: An outline of the data from the three trachoma-endemic regions analysed in this report.

<table>
<thead>
<tr>
<th>Location</th>
<th>Infection prevalence</th>
<th>Active disease prevalence</th>
<th>Source</th>
<th>Endemicity level</th>
<th>Treatment coverage (first round)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Saloum district, Gambia</td>
<td>7%</td>
<td>8%</td>
<td>(Burton, Holland et al. 2005)</td>
<td>Hypoendemic (&lt;10% active disease)</td>
<td>83%</td>
</tr>
<tr>
<td>Rombo district, Tanzania</td>
<td>10%</td>
<td>18%</td>
<td>(Solomon, Holland et al. 2004)</td>
<td>Mesoendemic (10-20% active disease)</td>
<td>97%</td>
</tr>
<tr>
<td>Kongwa district, Tanzania</td>
<td>57%</td>
<td>36%</td>
<td>(West, Munoz et al. 2005)</td>
<td>Hyperendemic (&gt;20% active disease)</td>
<td>86%</td>
</tr>
</tbody>
</table>

The definitions of hypo-, meso- and hyperendemic prevalence levels used here differ slightly from those found in the literature\(^e\) (Lietman, Porco et al. 1999; Johnson and Mak 2003) (Table 1). The model outlined in section 2 generates age-specific prevalences of infection and its outputs can therefore be compared with the baseline data since these also vary with age. A least-squares expression was formulated to calculate the deviation of the results generated by the model from the datasets and, by minimising this expression simultaneously with respect to the principal parameters of the model, the values for the these parameters were obtained. The parameters that were determined through this fitting procedure are listed in Table 2. The full set of parameters from Table 2 can be determined from the data for the hyperendemic community and, once this full set has been determined, the parameters relating to the rate of recovery from infection were assumed to be fixed for subsequent fits of the model to meso- and hypoendemic data. This assumption stems from the idea that since the change in the rate of recovery is dependent upon the development of acquired immunity, it is a function only of the number of prior infections and it should therefore be independent of the trachoma-endemic level. The data available on the rate of recovery from infection relate to a hyperendemic community in the Gambia (Bailey, Duong et al. 1999), so the rate of recovery parameters are fitted along with the other

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\(^e\) It is with respect to the prevalence of active disease in children that areas are often characterised as hypo-, meso- and hyperendemic.
parameters by using the more current hyperendemic data i.e. the data from the Kongwa district, Tanzania.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu_0$</td>
<td>Rate of recovery from the first infection</td>
<td>1.2 per year (High value: 2.4 per year)</td>
</tr>
<tr>
<td>$\nu_1$</td>
<td>Rate of recovery from infection following a large number of prior infections</td>
<td>5.0 per year (High value: 18 per year)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>The exponential rate at which the rate of recovery changes from the lower to the higher rate</td>
<td>0.021 per infection</td>
</tr>
<tr>
<td>$\phi$</td>
<td>The rate of decay of infection load with number of prior infections</td>
<td>0.116 per infection</td>
</tr>
<tr>
<td>$\beta$</td>
<td>The transmission rate: the rate of transmission (per year) of infection between individuals</td>
<td>Hypo: 4.314 per year, Meso: 6.182 per year, Hyper: 21.814 per year</td>
</tr>
</tbody>
</table>

Table 2 Model parameters estimated directly from the intervention and cohort study data. Note the additional ‘high’ values for the rates of recovery from infection, from Bailey et al. (Bailey, Duong et al. 1999); these are mentioned in the text but the lower values are used for disease projections.

Parameters of the model not directly estimated during this fitting process are given in Table 3. These include those describing the population demography and the extent to which the contact process is assortative by age. We allow mixing patterns to vary between entirely random ($\varepsilon = 0$) and fully assortative ($\varepsilon = 0$), opting for an intermediate value in the studies presented in this report.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\varepsilon$</td>
<td>Mixing parameter determining degree of assortative/random mixing</td>
<td>0.5</td>
</tr>
<tr>
<td>$b$</td>
<td>Birth rate (per capita)</td>
<td>0.04 per year</td>
</tr>
<tr>
<td>$d$</td>
<td>Death rate (per capita)</td>
<td>See Figure 2</td>
</tr>
</tbody>
</table>

Table 3 Model parameters estimated independently.

4 Model fit to pre-intervention prevalence data

4.1 Prevalence of C. trachomatis infection

Following the fitting of the model to the datasets from the three endemic settings, the prevalence curves generated are shown in Figure 4: in each case, a close correspondence with the overall trend in the prevalence of infection with age is found. The prevalence of infection drops at higher ages, which is a consequence of the age-associated increase in the recovery rate from infection and the drop in infectivity with age: as an individual experiences an increasing number of infections, the model states that the time for recovery from each infection will reduce, and with this reduction in recovery time, more time will be spent by each individual being uninfected rather than being infected, thereby decreasing the prevalence of current infections among those who have experienced a large number of prior infections. The number of infections previously experienced is a close proxy for the age of an individual and so the prevalence of infection should drop with age in this model of trachoma. The relative effects on the prevalence of infection of the recovery rate and infectivity are explored in Appendix C.

Figure 4 shows two separate model fits to the data—one for which the values for the recovery rate from infection have been obtained from Bailey et. al (Bailey, Duong et al. 1999) and the other for which a lower recovery rate, obtained through fitting overall infection prevalence to post-treatment data (see section 6.2.2), is used. Comparing the model-generated curves using the high recovery rate data (Figure 4(I), the left column) with the data to which they have been fitted shows that the prevalence of infection at
young ages is greater than the data would suggest. The simplest explanation for this is that the change in the rate of recovery from infection between young ages and old (or, more correctly, from low infection numbers to high) may be too high in the models.

The infection prevalence appears to be humped at young ages (roughly 5 years) in the datasets used here. Such a peak implies that there are competing forces that are causing both more and fewer people to become infected, and that these forces balance each other out at the peak itself. The model-generated curves using the low recovery rates show peaks at young ages. Furthermore, the data also show some evidence of a peak shift (Woolhouse 1998) where, for higher transmission levels (Figure 4(c)(II)), the peak of infection is shifted toward younger ages. This effect is due to acquired immunity and it occurs when individuals experiencing high forces of infection develop a greater ability to clear infection at younger ages than those in lower force-of-infection environments; the prevalence of infection therefore drops from its peak level at younger ages. The observation of this phenomenon here lends further support to the importance of acquired immunity in trachoma epidemiology.

Due to the appearance of these peaks in prevalence at young ages and the better observed fits of the post-treatment infection and disease prevalence data, the lower recovery rates were selected for developing the model to take into account disease sequelae and to simulate control scenarios. Further details of post-treatment data-fitting are given in section 6.2.2.
I. High recovery rate

(a) Hypoendemic

(b) Mesoendemic

(c) Hyperendemic

Figure 4 Figures showing the model-generated prevalence of infection for the three data-sets at baseline (a) Upper Saloum district, Gambia (hypoendemic); (b) Rombo district, Tanzania (mesoendemic); (c) Kongwa district, Tanzania (hyperendemic). The figures on the left show the best fitting models using the recovery rate data of Bailey et.al (Bailey, Duong et al. 1999) and those on the right show the best fitting models using the lower recovery rates of Table 2.
4.2 Prevalence of disease sequelae

A simple model for the accumulation of trachomatous scarring (TS) is incorporated into the basic model by assuming that scarring increases with the number of reinfections. With worse scarring come the more severe disease sequelae, trachomatous trichiasis (TT) and corneal opacity (CO). For simplicity, it is assumed here that these conditions can coexist with one another i.e. a person may be graded with scarring; scarring and trichiasis; or scarring, trichiasis and corneal opacity. In each case, it is assumed that all disease sequelae less severe than the most severe present will also be detected (Figure 5).

![Figure 5](image)

**Figure 5** Schematic diagram showing the way in which the model is interpreted to determine the presence of disease sequelae: trachomatous scarring (TS), trachomatous trichiasis (TT), corneal opacity (CO). The simplest possible scheme is used: thresholds exist, along the ladder of infection, beyond which each of the sequelae are assumed to be present. Beyond the threshold corresponding to a specific sequela, that sequela is assumed to be present e.g. when the threshold for CO has been passed, all three sequelae are present.

4.2.1 Calculating the threshold number of infections for the disease sequelae

It remains to take the model, appropriately fit to each endemic setting, and to determine the threshold infection levels that need to have been experienced in order for individuals to show signs of each of the sequelae. These values are found by comparing the overall prevalence of each of the disease sequelae with the prevalence implied in the model by
different threshold numbers of infections. The threshold infection numbers that result in overall prevalence levels closest to those observed in the data are listed in Table 4. From the point of view of the natural history of the infection, disease and disease sequelae, these threshold values should not vary over the different endemicity levels. Individuals might be expected to start showing signs of each of the disease sequelae after the same number of infections regardless of the endemic environment in which they find themselves; they will experience the sequelae sooner where they are infected more frequently, but that is only because they experience a greater number of infections in the same amount of time as individuals in lower endemic environments. However, the datasets used here arise from areas which have been subject to varying amounts of prior intervention and secular trends, and so these numbers might be expected to turn out differently for each setting. In addition, it is likely that only a fraction of the population progresses to each of the disease sequelae, and this fraction may vary over communities due to factors such as genetic predisposition of the particular ethnic groups making up the population (Mozzano-Chamay, Mahdi et al. 2000; Alves, Medina et al. 2002).

Using the threshold infection numbers in Table 4, the curves shown in Figure 6 are produced. In Figure 6(a) and (b), the age-dependent prevalence levels generated by the model are close to those observed in the datasets, another encouraging validation of the model. The dataset used for the hyperendemic setting, while from the same district in Tanzania as the baseline set of West et al. (West, Munoz et al. 2005), was collected several years ago and, given that this model is calibrated with the current dataset, the disparity between model and data is expected. Nevertheless, sequelae projections generated by the model in the hyperendemic case were considered useful guidelines for the study of the prevalence and incidence dynamics following treatment.
<table>
<thead>
<tr>
<th>Hypoendemic</th>
<th>Baseline Prevalence</th>
<th>Threshold no. infections</th>
<th>Baseline Prevalence</th>
<th>Threshold no. infections</th>
<th>Baseline Prevalence</th>
<th>Threshold no. infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoendemic</td>
<td>14.0%</td>
<td>7</td>
<td>1.9%</td>
<td>11</td>
<td>1.5%</td>
<td>12</td>
</tr>
<tr>
<td>Mesoendemic</td>
<td>11.2%</td>
<td>10</td>
<td>1.5%</td>
<td>15</td>
<td>0.4%</td>
<td>18</td>
</tr>
<tr>
<td>Hyperendemic</td>
<td>25.7%</td>
<td>47</td>
<td>4.7%</td>
<td>91</td>
<td>1.4%</td>
<td>117</td>
</tr>
</tbody>
</table>

Table 4 The overall prevalence of each of the disease sequelae and the threshold number of infections necessary to be surpassed by individuals in the fitted models such that these prevalence levels are matched most closely. Values are given here for the 3 settings analysed in this report. The hypo- and mesoendemic data were made available by the currently active projects of Dr. Matthew Burton and Dr. Anthony Solomon, but the hyperendemic data were obtained from a study in the same district as the current intervention trial of West et al. (West, Munoz et al. 2005) approximately 10 years ago (Munoz, Aron et al. 1997).
Figure 6 The age-dependent prevalence of the disease sequelae for each of the endemic settings analysed in this report. Model-generated curves are shown along with the data provided by (a) Dr. Matthew Burton, (b) Dr. Anthony Solomon both of LSHTM; (c) data from (Munoz, Aron et al. 1997), which were collected from the same district as the data of West et al. (West, Munoz et al. 2005) several years ago, hence the mismatch between the model output (calibrated to the current datasets) and the earlier data.
5 Modelling the control of trachoma

The model can be run to simulate control scenarios based on the parameters estimated from different prevalence settings. These simulations can be used to examine the effect of, for example, antibiotic treatment or steady environmental improvements on the prevalence of infection and more severe disease sequelae. Since the GET 2020 goals are based on targets relating to the elimination of the blinding sequela of trachoma by 2020, such scenario modelling can be valuable. In the sections that follow, the models are subjected to many control sequences and they are analysed to inform possible policy choices.

5.1 The effect of treatment on the prevalence of infection by age

At the time of treatment, a proportion of individuals (given by the fraction: efficacy × coverage) has been treated so that their bacterial carriage is nil and, in the model, they are moved from their infected state back into the susceptible state. In Figure 7, the plots at time \( t=0 \) show that the prevalence of infection in all age groups has dropped to a much lower level than before treatment (shown by the dotted line). Figure 7 also shows the time development of the prevalence of infection from an initial time point at which mass antibiotic administration (MDA) has occurred. The efficacy, for an individual case, of a single dose of azithromycin is taken to be 95% (Bailey, Arullendran et al. 1993; Schachter, West et al. 1999) and the community coverage level achieved is assumed to be the same as the level documented in published materials summarised in Table 1. A comparison of the spreading of infection throughout the population following mass treatment illustrates the following main points:

- Because the prevalence of infection in children is higher than in the rest of the population, the same percentage reduction in the infected individuals in each age-group will leave a larger proportion of children still infected post-treatment than the rest of the population.
- The rate at which infection returns to children is greater than for the rest of the population. This is most easily seen for the hyperendemic setting, where, in addition to the post-treatment prevalence of infection being greater in children than adults, the return to pre-treatment levels of infection is particularly rapid in those under 10 years old. There are two reasons for this: the rate of recovery from
infection in children is lower than for adults and, therefore, children retain their infections for greater lengths of time causing greater prevalence levels; the second reason is dependent on the comparatively greater infectivity of children than adults in the model. Since children are assumed to interact more frequently with those their own age ($\varepsilon = 0.5$), this greater infectivity leads to a greater probability of becoming infected and, therefore, a greater prevalence. Appendix C shows that the greater infectivity among children is very similar to the effect of an increased exposure to infection in children compared with adults.

- The rate of re-emergence of infection into the hyperendemic setting is much greater than the corresponding rates for the hypo- and mesoendemic settings. In fact, there appears to be very little return of infection in the hypo- and mesoendemic settings. This is a consequence of the fact that the transmission rate necessary to fit the pre-treatment age-dependent prevalence of infection is much smaller for the hypo- and meso endemic settings and the infection rebound rate, being largely dependent on this transmission rate, is therefore also small.

- One year following treatment, infection has returned to its pre-treatment level in the hyperendemic setting. Without additional control measures, such as the F and E components of the SAFE strategy, annual treatments will not be sufficient to locally eliminate the infection.

- For the hypo- and mesoendemic settings, the return of infection is minimal. The prevalence of infection in all age-groups is reduced to below 5%, and either further treatments or the implementation of the F and E components of the SAFE strategy will serve to drive the infection to very low levels and possibly elimination.
Figure 7 The prevalence of infection with age over the course of a year following a single antibiotic treatment with coverage given by Table 1.

5.2 The effect of treatment on the prevalence of more severe disease sequelae

The impact of antibiotic treatment on the prevalence of infection in a population is immediate as infection is cleared from treated individuals. The dynamics of the return of infection to the community after treatment is important, with the overall rate of this return (as well as the age-varying rates; see Section 5.7) providing information on the number and frequency of treatments necessary for the elimination of infection as well as the possibility
of targeting specific age-groups. However, the indirect effects of antibiotic treatment include the reduction in the prevalence of more severe disease sequelae such as trichiasis and corneal opacity. Since it is these sequelae that are of concern—and the GET 2020 goals aim to eliminate the worst of these damaging effects—it is important to examine these sequelae in the model. The model structure allows such an examination by tracking the number of individuals who have progressed beyond the threshold for TS, TT and CO (see section 4.2). In the model, a round of antibiotic treatment shifts a proportion of the population from the infected class back into the closest susceptible class. This has the effect of arresting the progress of individuals along the ladder of infection and also reducing the force of infection experienced by the population. Section 4.2 outlines the procedure that has been adopted to calibrate the model to the prevalence data available for the disease sequelae. The age-dependent prevalence curves obtained from the model, using the resulting threshold values for the number of infections for each of the disease sequelae, appear to correspond well with the quantitative values as well as the shape of the data (see Figure 6).

5.2.1 Prevalence of disease sequelae after three annual treatments

Once a steady endemic prevalence has been reached, the model can be subjected to three rounds of annual antibiotic treatment in each of the three endemic settings, corresponding to the WHO protocol (WHO 2006) (though the WHO recommendations for the hypoendemic community would be the implementation of the facial cleanliness (F) and environmental improvement (E) interventions since the prevalence is under 10% but greater than 5%). Figure 8 illustrates the outcome of three annual antibiotic treatments on the age-dependent prevalence of each of the disease sequelae. In the hypo- and mesoendemic settings, prevalence levels decrease with time at a rate which peaks about 5 years after the final treatment. At this time, with very few infected people remaining in the population, there are few new cases of TS, TT or CO and, assuming the irreversibility of these states of disease, the drops in prevalence are due to mortality of those currently afflicted. In the hyperendemic setting, however, rapid return of *C. trachomatis* infection means that the prevalence of the more severe disease sequelae are little affected by just 3 rounds of treatment with antibiotic.

In the model presented here, infection is never completely eliminated and prevalence will eventually return to pre-treatment levels. The rate of decline in prevalence of the severe
sequelae therefore slows over time and also eventually returns to the pre-treatment level. It is, however, possible for a large drop in the prevalence of infection to result in local elimination of the bacteria. In this case, in the absence of the reintroduction of infection, prevalence of the disease sequelae will continue to drop at the most rapid rate observed in Figure 8(a,b). Figure 9 illustrates this by continuing annual treatments for 10 consecutive years, which is equivalent to eliminating infection for this period in the hypo- and mesoendemic settings. As expected, the prevalence of disease sequelae continues to steadily fall with time and there is no slowing of this decline after 20 years in the hypo- and mesoendemic settings.
Figure 8 The age-dependent prevalence of disease sequelae following three rounds of annual antibiotic treatment with coverage levels given by Table 1; (a) and (b) show declines in prevalence over all ages following treatment. As the time since treatment increases, and the infection rebounds, the rate of decline of these prevalence levels decreases. There is very little change in prevalence at all ages in (c), the hyperendemic setting.
5.2.2 Disease sequelae incidence levels following treatment

The drop in prevalence observed following three annual treatments in the hypo- and mesoendemic settings (Figure 8(a) and (b)) indicates that the model predicts fewer cases of disease sequelae will occur for a period of time during and following treatment but prior to the rebound of infection to its pre-treatment level. However, should infection be maintained at very low levels, or entirely eliminated, the model predicts that the number of cases of disease sequelae will drop to zero, though this may take many years since it is assumed here that the accumulation of scarring, trichiasis and corneal opacity is irreversible. Of course, this is not strictly true, and refinements can be made to take into account trichiasis surgery. In addition, this model does not include progress along the path to more severe disease sequelae without the stimulus of constant reinfection, which is a possibility either through the process of severe scarring leading to trichiasis or through an ongoing fibrosis induced by an initial set of infections but not requiring reinfection (Burton, Bowman et al. 2006).

This simplest model, however, can still be used to account for those individuals who are prevented from progressing to worse sequelae through the interruption of the repeat infection process. Table 5 gives values for the percentage of the population that constitutes newly incident cases of disease sequelae in settings in which there have been three annual rounds of treatment with mass distributed azithromycin or no antibiotic treatment. The population fractions are calculated with respect to the total population immediately after the time of the third and final antibiotic treatment. This table shows that there are very large differences between the with- and without-treatment incidences of each of the disease sequelae in the hypo- and mesoendemic settings up to 10 years following treatment, when the incidence level of the sequelae are still 20 times smaller with treatment than without in the hypoendemic setting and 6 times smaller in the mesoendemic setting. The results for the hyperendemic setting show that the incidences are essentially the same with and without treatment.\(^f\)

\(^f\) Note that the slightly larger value of the incidence with treatment than without in the hyperendemic setting is a result of the rapid rebound of infection following treatment, which often slightly overshoots its pre-treatment value before returning to this value.
Figure 10 illustrates the incidence of TS over time during and following three rounds of annual antibiotic treatment. The drop in the incidence to almost zero in the hypo- and mesoendemic cases is clear, and this very low incidence is sustained for a considerable period of time following treatment. This raises the possibility of local elimination of infection particularly if the intervention is accompanied by implementation of the F and E components of the SAFE strategy (Chidambaram, Lee et al. 2005). The hyperendemic TS incidence is very clearly harder to reduce through the same antibiotic treatment regime. A rough measure of the number of cases of TS averted by the treatment is given by the area of the graphs between the solid line (with treatment) and the dotted line (without treatment) and this area is significantly smaller in the hyperendemic setting than in the hypo- or mesoendemic settings.

<table>
<thead>
<tr>
<th></th>
<th>% of population newly experiencing disease sequelae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TS W/out treatment</td>
</tr>
<tr>
<td>Hypoendemic 1 yr</td>
<td>0.42</td>
</tr>
<tr>
<td>5 yrs</td>
<td>2.22</td>
</tr>
<tr>
<td>10 yrs</td>
<td>4.78</td>
</tr>
<tr>
<td>Mesoendemic 1 yr</td>
<td>0.40</td>
</tr>
<tr>
<td>5 yrs</td>
<td>2.14</td>
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<tr>
<td>10 yrs</td>
<td>4.62</td>
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<tr>
<td>Hyperendemic 1 yr</td>
<td>1.21</td>
</tr>
<tr>
<td>5 yrs</td>
<td>6.43</td>
</tr>
<tr>
<td>10 yrs</td>
<td>13.84</td>
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</tbody>
</table>

Table 5 Table showing the incident cases of the disease sequelae for each of the three prevalence levels and for three periods of time (1yr, 5yrs and 10yrs). The incidence is expressed as a percentage of the population at the time of the third treatment if there were three treatments, and at the equivalent time when there was no treatment.
Figure 9 Plots illustrating the effect on trachomatous scarring (TS) for three endemic settings following ten rounds of annual antibiotic treatment. The treatment coverage is given in Table 1 and the antibiotic efficacy is 95%.

Figure 10 The development through time of the incidence of trachomatous scarring (TS) in three endemic settings, with and without three annual rounds of azithromycin treatment. The times at which azithromycin is administered to the population—with coverage levels given by Table 1 and efficacy set at 95%—are shown as the (red) arrows. The incidence scale adopted for the three settings is the same in each case.
5.3 What would it take to achieve the GET 2020 goals?

The main GET 2020 goal—the elimination of incident blindness from trachoma by 2020 (Frick, Hanson et al. 2003)—is linked, in the model, to the interruption of the transmission of infection and the slowing or stopping of progress along the ladder of infection. A simplifying assumption of the model is that reinfection is the only means by which an individual can progress through a sufficient number of cumulative infections, beyond which scarring, trichiasis and corneal opacity will result. In reality, it is also possible that individuals who have progressed to the level of trachomatous trichiasis may continue to deteriorate to the point of corneal opacity and blindness without further infection—trichiasis causes problems mechanically and the cornea can be damaged without fresh disease episodes (Burton, Bowman et al. 2006). A small adjustment to the model to include the ongoing progress toward corneal opacity without infection could be made, but data are scarce on these rates (Burton, Bowman et al. 2005) and so it is assumed here that this process is partially taken into account in the calculation of the threshold values for the number of infections necessary before each of the disease sequelae are exhibited (see Table 4). The threshold values calculated for the model are probably slightly lower than they would be if the disease sequelae were purely the result of repeat infection.

With this caveat in mind, the GET 2020 goal essentially becomes the elimination of incident cases of blindness due to reinfection by *C. trachomatis*. The WHO Report of the 2nd Global Scientific Meeting on Trachoma (WHO 2003) states that trachoma as a blinding disease has been controlled when under 1 case of corneal opacity due to trachoma is detected per year in a population of 10,000. The incidence of trachomatous scarring given by the model is shown in Figure 10 and, similarly, the incidence of corneal opacity can also be determined over time. Figure 11(a) and (b) show the development of the incidence of corneal opacity over time for the meso- and hyperendemic settings. The incidence is scaled as a percentage of the total population at the beginning of the year and the threshold for the control of blinding trachoma is shown as a dotted line across the plot (at 0.01%). Both scenarios are very similar to those shown for TS, trachomatous scarring (in Figure 10), and now it can be seen that the threshold for control is crossed for the mesoendemic setting (and, therefore, *a fortiori*, for the hypoendemic setting) but that in the hyperendemic setting, even for the strongest of all of the control options shown—biannual antibiotic administration over 10 years—the threshold for control remains very far off.
This is a powerful illustration of the difficulty of controlling trachoma in hyperendemic settings; without more fundamental changes to the transmission environment of trachoma—such as the implementation of the rest of the SAFE strategy—it will be very difficult to achieve the GET 2020 goals.

Figure 11 The time development of the incidence of corneal opacity: (a) In the mesoendemic setting, three annual antibiotic treatments lead to a drop in the incidence of CO below the threshold for control (indicated by the (red) dotted line at 0.01%); (b) A variety of treatment regimes fail to cause the incidence of CO to drop below the threshold for control, even the most intensive, which is 20 biannual treatments. Note that the incidence of CO drops immediately with treatment and, following a rebound once treatment has halted, then drops to a lower value again; both effects are explored in the text.

It should also be noted that, in Figure 11(a) and (b), there is both an immediate and a long-term impact of treatment on the incidence of CO. The immediate impact is caused by the arrest of the progress of individuals along the ladder of infection as soon as treatment is administered. After treatment, those individuals who were on the threshold of CO then cross the threshold and develop symptoms. The long-term effect occurs due to the overall reduction in the force of infection over the whole population at every stage of disease prior to CO. The slowing of all of these individuals along their path means that, due to the mortality of the people showing the signs of the later stages of TT, there are also fewer to replace them and fewer to cross the threshold into CO. Both of these effects are crucial in maintaining a low value of the incidence of CO.
5.4 The F & E components of the SAFE strategy, and secular trends

A few studies have shown falls in the prevalence of infection and disease that have occurred either disproportionately with respect to the antibiotic treatment administered (Jha, Chaudary et al. 2002) or even entirely without antibiotics (Dolin, Faal et al. 1997). The elimination of ocular chlamydial infection from many countries in which it was previously endemic preceded the widespread use of antibiotic treatment for trachoma and was probably related to economic and infrastructural improvement. The facial cleanliness (F) and environmental improvement (E) components of the SAFE strategy seek to lower the level of bacterial transmission so that 1) antibiotic treatment has a greater impact or 2) the infection is driven to extinction without the need for antibiotic. In section 5.2 and section 5.3, it has been shown that in hyperendemic settings, even when the treatment regime is very intensive, infection may rebound too quickly to reduce the incidence of the disease sequelae by anything but a small value. In such cases, the F and E components of the SAFE strategy would appear to be crucial.

The model as it currently stands includes all elements contributing to transmission in an umbrella term, the transmission rate; it is this rate that would be reduced by the F and E components of the SAFE strategy. There may also be effects relating to, for example, the predisposition among certain populations to acquire infection, become highly infective and subsequently develop disease and scarring sequelae, and these can affect the value of the transmission rate. However, if it is assumed for simplicity that these factors are constant over all communities, any change in the transmission rate can be attributed to environmental factors and how these factors affect the chance of becoming infected. Background secular trends (e.g. non-programmatic environmental improvements, washing practices, fly density reduction) would be similarly modelled as reductions in the model transmission rate.

Figure 12 illustrates how the steady-state prevalence of infection varies with the transmission rate in the hyperendemic setting. As the transmission drops from its hyperendemic value (giving an initial prevalence of >50%), the steady-state prevalence gradually declines. This decline becomes more rapid as the transmission rate drops to around one quarter of its initial value. The prevalence reductions following this level of transmission rate decline are much larger and imply that F & E campaigns need to
persevere to considerably decrease the transmission rate before antibiotic coverage will have a large effect.

Figure 12 The steady-state prevalence of infection as the transmission rate is reduced from its initial value, appropriate to a hyperendemic setting, to zero 10% at a time. The prevalence initially drops more slowly than it does when the transmission rate reaches small values.

The importance of the F and E components of the SAFE strategy is highlighted in Figure 13. Here an F & E programme is performed for 9 years prior to the first of three annual antibiotic treatments (a 10th F & E, or transmission reduction, year coincides with the first antibiotic administration). When the rate of transmission decline is 5% or 7% per year, the effectiveness of the antibiotic treatments remain low and infection prevalence quickly rebounds. However, when the rate of reduction is 9% per year, reducing the transmission rate by 81% before the first antibiotic round, the effect of antibiotics is very large. The effectiveness of antibiotic treatments may therefore be multiplied many times if an F & E programme has reduced the transmission by a sufficient amount beforehand.
Figure 13 The prevalence of infection before and following 9 years of a reduction in the transmission rate (interpreted here as an F & E campaign) and three annual antibiotic treatments at 86% coverage. The model is initially calibrated to simulate the hyperendemic setting. The first of the three antibiotic treatments is indicated by the (red) arrow. There is a marked change in the effectiveness of treatment when the aggressiveness of the F&E campaign is increased from 7% to 9% per year.

5.5 Treatment coverage levels and the prevalence of infection

A larger level of treatment coverage will clearly lead to a more effective campaign against the infection. But the precise way in which coverage levels influence the effectiveness is important: it may be possible to find a coverage level beyond which the infection and the disease sequelae fall rapidly. Figure 14 illustrates the effect on the overall prevalence of infection 1 and 5 years following three annual antibiotic treatments as the coverage of these treatments is raised from 50% to 95%. In the hypo- and mesoendemic cases, the post-treatment prevalence levels are seen to drop almost linearly with coverage level, though with slightly diminishing returns to a coverage increase beyond 80%. The hyperendemic case actually shows a slight increase in final prevalence for greater coverage levels, and this strange outcome can be explained by the rapid infection rebound experienced in the hyperendemic setting, a rebound that overshoots the starting prevalence resulting in a greater final level.

The outcome measure used here, namely the post-treatment prevalence of infection, may not be the best to give information on how much easier the infection will be to control following three rounds of treatment since this is strongly connected with the transmission...
environment. However, the observation of a larger initial drop in prevalence when coverage is close to 50% is an important consideration for cost-effectiveness calculations.

### 5.6 The effect of treatment on active disease

The assessment of the level of trachoma in an area—a community, district, or country—is usually conducted on the basis of clinical examination. Since the primary method for the treatment of trachoma is antibiotic for the bacterial infection, the relation between infection and disease is important. In addition to the model presented in section 2, which takes into consideration only the infected state, a second model has been constructed to account for active disease (TF/TI). The details of this model are given in Appendix B.

Figure 15 shows the model-generated prevalence levels of active disease and infection and the data to which the model was fitted, for the three endemic settings. The model curves show the two key features of the kinetics of trachoma infection and disease as it affects trachoma epidemiology: 1) the prevalence of infection is different from the prevalence of disease; in this model, the prevalence of disease is always assumed to be higher than that of infection; and 2) once antibiotic treatment has been administered, the prevalence of infection drops to a low level immediately, while the prevalence of active disease lags behind infection at a somewhat higher level.

Figure 15 (d) shows the ratio of the prevalence of infection and disease through time for each of the endemic models. Treatment causes a sharp drop in the ratio, which then returns to its pre-treatment level. For the cases in which the model represents the true endemic situation, it can therefore be expected that, following treatment, an adjustment might be made to the measured prevalence of active disease (obtained through clinical examination) to arrive at an estimate of the remaining infection. Easy-to-use field tests for determining the level of infection are certainly more reliable for this measurement (Michel, Solomon et al. 2006) but, while these tests are not widely available, the conversion of active disease prevalence to an estimate of infection prevalence would be useful.
Figure 14 The change in the overall prevalence of infection 1 and 5 years after three rounds of antibiotic treatment with coverage given along the x-axis. The prevalence observed following treatment is plotted against coverage. Initial values of prevalence are (a) 8.5%, (b) 12.1%, (c) 50.7%. In a) the hypoendemic and b) the mesoendemic settings, the trend is close to linear, though with slightly bigger gains in prevalence decline for increases from the 50% coverage mark. In c) the hyperendemic setting, the prevalence has returned to its original value by 1 year following treatment.
Figure 15 The development through time of the prevalence of infection and active disease for the model and recent baseline and post-treatment data (Solomon, Holland et al. 2004; Burton, Holland et al. 2005; West, Munoz et al. 2005) in each of three endemic settings ((a), (b) and (c)). (d) shows the ratio of the prevalence of infection and disease through time in each of the endemic settings. Treatment causes a sharp drop in the ratio followed by a steady rise to its pre-treatment level.

5.7 Age-targeted treatment

Among the strategies for treating chlamydial infection, aside from the mass treatment of as large a fraction of the entire community as possible, there are options that target specific sections of the community most likely to harbour high infectious loads. The modelling of protocols in which household members of those who show signs of active trachoma are treated requires a model more fine-grained than the model examined here. However, it is instructive to look at the selective treatment of children and the impact of this treatment on the prevalence of infection in the whole community. Figure 7 illustrates the effect over time of the treatment of the whole community at a level of coverage given by Table 1. This
figure shows that in the case of a hypo- and mesoendemic setting, the return of infection is very slow (infection remaining under 5% at all ages after 1 year), but that, after 1 year, the hyperendemic community has already returned to its pre-treatment prevalence of infection. It is likely that the treatment of 0-9 year old children would be a less effective strategy than community-wide treatment in all cases. However, because much of the community infection load is concentrated among children, it is not obvious that the treatment of children alone will not be effective enough.

Figure 16 The age-dependent prevalence of infection following a single treatment of the 0-9 year old children in a hyperendemic setting. The coverage and efficacy have been set to 100% here to illustrate more clearly the effect of treating the 0-9 year group.

The results shown in Figure 16 and Figure 17 (a) illustrate the impact of treatment of the population between 0-9 years. For the purpose of this illustration, the efficacy and coverage of the round of treatment have both been set to 100%, which, while unrealistic, clarifies the dynamical picture. At the time of treatment, all individuals up to and including the age of 9 years have been treated so that their bacterial carriage is nil and, in the model, they are moved from their infected state back into the susceptible state. The plot at time \( t=0 \) shows that the prevalence of infection in all people under 9 years is zero while the prevalence of infection for those over this age remains as it was prior to treatment (dotted line). As time progresses, the prevalence of infection in the 0-9 year olds rises as these children come into contact with older infected people. Because the youngest children had, in general, experienced fewer infections than older children at the time that they were treated, they have lower levels of acquired immunity. They therefore clear infection more slowly and have higher bacterial loads when infected, resulting in a more rapid increase in the prevalence of infection among these children (Figure 16).
The dotted curves in Figures 16 and 17 represent the age-dependent infection prevalence prior to treatment. By comparison with the solid curve, it can be seen that a treatment round administered to children under 10 years not only reduces prevalence among these children (direct impact) but also decreases the prevalence of infection among those of all ages (indirect impact). Moreover, the size of this impact can be significant. By removing infectious children from the population adults benefit because they are less likely to come into contact with an infectious source. Because the younger children tend to harbour greater bacterial loads, a large portion of the community infection load has been eliminated by treating these children.

In the hypoendemic setting (Figure 17) the impact on those from older ages is also clear, with prevalence levels continuing to drop at the 1 year mark post-treatment. The re-emergence of infection for the treated individuals is considerably slower in this case, as would be expected, because the force of infection from those left untreated is so much lower than the hyperendemic situation; this is because there are far fewer people remaining
infected following treatment and also the transmission level is much smaller, so that there are fewer infection transmitting contacts between those susceptible and those infected. It is interesting to look at the prevalence of infection in the hypoendemic community following two further annual treatments of exactly the same kind as the initial treatment (Figure 17(b)): it can be seen that the level of infection in the community continues to drop and is below 5% at the 3 year mark. With additional measures to reduce the transmission rate, it would seem that elimination of infection would be possible under this treatment regime.
6 Acquired immunity and the natural history of infection

6.1 Infection load

The infection load plays an important role in the model presented here: the infectivity of individuals is considered to be linearly proportional to the bacterial load they harbour. Infectivity is calculated by dividing the infection load per individual, in a particular age-group, by the maximum load per individual in the hyperendemic setting. Since PCR measurements are now providing measurements of the infection loads at various intervention study sites, new data are becoming available to include in models. The procedure for including the infection load in the model is outlined here, along with the epidemiological consequences.

6.1.1 Infection load with age

The data used for fitting the infection load distribution were provided at the individual level by Dr. Matthew Burton and Dr. Anthony Solomon of the London School of Hygiene and Tropical Medicine, and at the age-group level in the published data of Dr. Emily West et al. (West, Munoz et al. 2005), and were aggregated into age-categories with roughly equal numbers of individuals in each category. As explained in Section 2.3, the infection load is assumed to drop exponentially with the number of prior infections suffered. Comparison of the quantities of the \textit{omp1} gene, obtained through PCR, between different studies is not completely reliable, but the results obtained here are reasonable and allow the infectivity of individuals to be calibrated.

The reason that it is assumed average infection load drops with age is the same as the reason the rate of recovery increases with age: the acquired immune response clears infection more efficiently and quickly with increased prior exposure. In the case of the rate of recovery, the model states that this value increases with each new infection and that the rate of increase is independent of the level of endemicity in the population. Therefore, this principle should also apply to the infection load: its rate of decay with infection number should also be independent of endemic level. If the rate of decay of infection load from the
A hyperendemic fitted model is applied to the hypo- and mesoendemic models, the results shown in Figure 18 are produced. The curve for the hyperendemic setting declines much more steeply than the hypo- and mesoendemic curves. These are the load curves that are applied in the model when it is used to explore control scenarios.

![Figure 18](image_url)

**Figure 18** The model-generated curves for the infection load with age. Here, the recovery rate has been set to a lower value than that found by Bailey et al. (Bailey, Duong et al. 1999), in accordance with the post-treatment fits to data of section 6.2.2. In addition, these curves have been fit to the data by fixing the decay rate of the load function so that this rate is found when fitting the hyperendemic curve and fixed to this value for the hypo- and mesoendemic curves.

### 6.1.2 The population distribution of infection load

Infection load is expected to decline with an increasing number of prior infections due to the acquired infection-clearing immune response elicited on repeat infection. The available data appear generally to support this idea (Burton, Holland et al. 2003; Solomon, Holland et al. 2003). In the models studied here, the average infection load per person plays a central role in the transmission of infection: those with a high infection load are more likely to pass on their infection than those with a low load. Figure 19 shows that the distribution of infection load over the population varies such that, for hyperendemic communities, the majority of individuals have a low load and fewer have higher loads whereas, for the hypoendemic case, the load is more evenly distributed across the population. Such a variation in the load distribution across different prevalence settings has recently been observed (Solomon, Holland et al. 2003) and the simple inclusion of the biologically plausible idea of an average load drop with an increasing number of prior infections gives rise to this observed phenomenon.
Figure 19 Model-generated infection load distribution for the three endemic settings studied in this report. Individuals have a wide variety infection loads in the hypoendemic setting, less of a variety in the mesoendemic setting and there is a clear skew toward a large number of individuals having a very low infection load in the hyperendemic setting.
6.2 Rate of recovery from infection

6.2.1 Rate of recovery with age using the available data

Since the data available for the recovery rate were collected in a hyperendemic community\(^8\), the model was initially fit to these recovery rate data along with the prevalence and infection load data from Kongwa district, Tanzania (West, Munoz et al. 2005), also a hyperendemic region. The rationale for using the hyperendemic data is that it is assumed in the model that the particular distribution of recovery time with age is dependent upon the number of prior infections that have been experienced by individuals of a particular age, and this number of prior infections will itself be dependent upon the overall level of transmission in the population. In hyperendemic communities, there will be a large level of infection transmission, reflected by a high value for the transmission parameter, and so it is in these communities that the data for the age-distribution of recovery rate will be best modelled. Figure 20 illustrates the point: the model-generated curve of the recovery rate with age for the hyperendemic region fits the data very well; the plots of recovery rate against age for the hypo- and mesoendemic region data show that the rates remain very low and rise very little at even the oldest ages. This phenomenon is a consequence of the fact that the population in hypo- and mesoendemic settings has experienced considerably fewer infections, on average over a lifetime, than in the hyperendemic case.

![Figure 20](image)

*Figure 20* The model-generated development of recovery rate with age for three levels of endemicity. Note the substantially lower levels of recovery rate at the lower levels of endemicity. The model was fit to the data displayed as filled squares.

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\(^8\) The Gambian study, from which this rate of recovery data comes, was carried out in an area in which 29% of the individuals tested started off with active disease. According to the definitions given in Table 1, this is classed as a hyperendemic region and it is therefore considered appropriate to use this dataset for the model along with data from the other hyperendemic dataset used here, namely the data from Kongwa district, Tanzania.
6.2.2 Determining the rate of recovery from infection

The estimates for the recovery rates, from infection and disease, of Bailey et al. (Bailey, Duong et al. 1999) imply that if an average individual, on reaching the age of 15, were to be immediately reinfected following recovery from each previous infection, he could suffer and clear 25 infections per year, a number that amounts to around 1000 infections over 50 years, by the time this individual reaches 65 years. It is unlikely that a person will be infected so often, particularly at older ages when the rate of contact between individuals may drop and also—as is included in the model—when mixing is to some degree assortative, (within age groups) the bacterial load transferred may be too small to result in an effective replicating chlamydial infection and instead may simply constitute a passive inoculation with no pathological effects. Burton et al. (Burton, Holland et al. 2006) supports the idea that these low load transfers are not causative of active disease, inflammation and, therefore, scarring. So, while the rate of reinfection (the force of infection) may be lower than that required to support such a large average number of annual infections, it still needs to be sufficiently large to sustain an endemic population prevalence of infection or disease sometimes as high as 70% (Lansingh, Weih et al. 2001). It remains to assess whether these lifetime numbers of infections are plausible. In communities such as those located in the Kongwa district of Tanzania (West, Munoz et al. 1996; West, Munoz et al. 2005; West, Munoz et al. 2005), it is possible that contact rates, either directly, person to person, or through face-wiping with cloths or skirts (Prof. H.Taylor—personal communication), infection loads, and transmission probabilities are sufficiently high to cause people to become infected very often.

An epidemic of an infection can provide a set of data to supplement the endemic prevalence data and allow the parameters of models to be better estimated (see e.g. for the recent SARS outbreak (Anderson, Fraser et al. 2004)). While the data available for trachoma do not include infectious epidemic outbreaks, post-treatment follow-up data on the returns of infection and disease comprise a very similar dataset that can be useful for parameter estimation.

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6.2.3 Fitting to post-treatment data

Because pre-treatment endemic scenarios may be fitted to the model with non-unique sets of parameters, more information is needed to choose among these parameter values. Overall prevalence levels of infection give information about the ratio $\beta/\nu$ (the transmission rate divided by the recovery rate from infection) and not the values of the parameters themselves (though the positions of the peaks in the infection prevalence curves give more information). However, if a version of the infection ladder model is fitted to pre- and post-treatment data, the extra information contained therein should help to narrow down the choices of $\beta$ and $\nu$.

Figure 21 shows the prevalence of infection generated by a non age-structured version of the model for two different sets of values for the transmission rate and the rate of recovery from infection. These model results are shown imposed upon the data from follow-up examinations for the three districts—representing the three levels of prevalence analysed in this report. The dotted lines, representing model results for the recovery rates of Bailey et al. (Bailey, Duong et al. 1999), fit the initial prevalence levels well, but once the antibiotic treatment has been administered and the prevalence has substantially dropped, they predict a much more rapid rate of return of infection, in the meso- and hyperendemic cases, than has been so far observed (Solomon, Holland et al. 2004; Burton, Holland et al. 2005). In the hypoendemic community the sustained decline in prevalence is adequately described by the model.

The lowest value for the rate of recovery given in the literature is 0.1 per person month or, roughly, 1.2 per person year (Lee, Chidambaram et al. 2005), a rate that was computed from early rate-of-return of infection data from a study in Ethiopia (Melese, Chidambaram et al. 2004). This corresponds to an average duration of infection of about 10 months. If the lowest value of the rate of recovery from infection is fixed at 1.2 per person year a much better fit is obtained for the meso- and hypoendemic communities, shown in Figure 21(a) and (b) as the solid black lines.

More data are required to determine properly the recovery rate but here it will be assumed that the lowest rate is 1.2 per person year. The highest rate of recovery is assumed to be 5 per person per year; this rate has been harder to determine: post-treatment fits show that it lies between the lowest value and around 13 per person per year. A compromise upper-end
recovery rate of 5.0 per year (see Table 2) is therefore chosen and, given that post-
treatment results appear fairly close to observed values using this level, it appears to be
valid. The poor fit obtained for the hyperendemic data Figure 21, even when using the
lower recovery rates, suggests that either the initial level of infection measured is actually
too high\(^i\) or that secular trends in hygiene, face washing or fly density are concomitantly
reducing the transmission rate (Appendix D).

\(\text{Figure 21} \) Fitted, simplified non age-structured, model prevalence of infection curves pre- and post-
treatment. The data were available at baseline (0 years) and for the points afterward. The data
points shown prior to baseline were added to ensure a good fit to the pre-treatment endemic
setting. The solid line is the fit using the lower values of the recovery rate from infection (see Tab-
le 2), and the dotted line is the fit when the higher values of Bailey et al. (Bailey, Duong et al. 1999)
are used.

\(^i\) Not an unlikely possibility since PCR contamination may have been very common before stringent
precautions were taken.
6.2.4 Stochastic model outcomes

The post-treatment follow-up data observed for the intervention trials analysed in this report, when fitted to the model, suggest that the rates of recovery from infection reported by Bailey et al. (Bailey, Duong et al. 1999) are too high. It is possible that the model-generated outcomes, which represent the *average* outcome expected, given the pre- and post-treatment conditions, might simply not be observed due to the randomness of the real world. The slower observed rate of return of infection might simply be a random fluctuation. By looking at the results of a *stochastic* model it is possible to count the number of times the model replicates observed data instead of following the average path.

In Appendix D, an excerpt from a Master’s degree dissertation on trachoma by Ms. Isobel Blake, these outcomes are examined and it is found that for the hypo- and mesoendemic settings, a large proportion of the stochastic outcomes, using the lower recovery rates, appear to be very similar to the datasets; a much smaller proportion of the outcomes, using the higher recovery rates, follow the trajectory of the data. In the hyperendemic case, the stochastic outcomes using both low and high recovery rates remain significantly different to the observed data. Again, suggesting that either the initial level of infection measured is too high or that secular trends in hygiene, face washing or fly density are concomitantly reducing the transmission rate. In all three settings, elimination of infection occurs considerably more frequently in the hypo- and mesoendemic than the hyperendemic case.
7 Conclusions

This report has detailed the development of a model for ocular infection with C. trachomatis in a community setting. The model is based upon the idea of a ‘ladder’ of infection in which people progress to greater numbers of infection when they come into contact with infected members of the population. With increasing numbers of infections, individuals in the model become progressively more scarred and develop the damaging disease sequelae. The model is shown to adequately represent the epidemiological patterns of trachoma, namely: the prevalence of infection and disease sequelae at all ages and across various endemic settings; active disease and infection prevalence differences pre- and post-treatment; and the lag of active disease behind infection prevalence post-treatment.

When the model is fit to baseline infection prevalence data from recent antibiotic intervention trials in three endemic settings, the resulting age-dependent prevalence curves show magnitudes over all ages that are very close to the observed data and a peak in the prevalence of infection is found for young children. The shifting of this peak to slightly younger ages for environments in which the force of infection is greater is indicative of the acquisition of immunity with increasing exposure to infection. This feature is replicated in the model where acquired immunity is captured as more rapid rate of clearance of infection with increased exposure.

In keeping with the WHO recommendations, in hypo- and mesoendemic settings three rounds of annual antibiotic treatment appear to be sufficient to control the infection: prevalence drops to very low levels for considerable periods of time. In these settings, the prevalence levels of the disease sequelae are also gradually reduced during and well after the antibiotic treatment programme, though treatment may need to be supplemented by a reduction in the level of transmission, through the facial cleanliness (F) and environmental improvement (E) components of the SAFE strategy, to ensure that infection does not rebound. The WHO antibiotic treatment regime was tested on the hypoendemic community, even though it is not strictly recommended, to compare its outcome with the meso- and hyperendemic setting.

Crucially, in hypo- and mesoendemic settings, the incidence of corneal opacity is also seen to decline below the guideline level for GET 2020 of 1 incident case per year in a population of 10,000. While the incidence rebounds following the treatment regime (though some years afterward) the reduction of the force of infection in the population causes the incidence to fall again; in real communities it seems likely that the infection
would be driven sufficiently low to be driven to extinction or, if not, an F and E campaign may well drive infection away, and thereby sustain the elimination of the blinding sequela.

By contrast, it is found in hyperendemic settings, that a variety of antibiotic treatment regimes (up to and including 20 biannual treatments) are shown to fail to bring down the prevalence of infection for a period of time sufficient to have any lasting effect on the disease sequelae. Very few cases of scarring, trichiasis and corneal opacity are seen to be averted by these treatment programmes and the GET 2020 goals in this setting would seem to be very difficult to achieve.

However, when a sustained F and E campaign is simulated in a hyperendemic setting—by enforcing a steady reduction of the transmission rate on an annual basis—it is shown that the force of infection is reduced so that the prevalence of infection can be brought down and perhaps eliminated, thereby allowing reductions in the disease sequelae. In the successful control scenario simulated in this report, transmission rate reductions are performed at 9% per year for 9 years, before antibiotic treatment is introduced, so that the total reduction in transmission is 81%; the remaining transmission is at a level closer to what might be expected for a meso- or hypoendemic setting. The impact of antibiotic treatment is considerably greater following these annual reductions in transmission than for reductions slightly smaller than these; 7% per year for 9 years, for example, is considerably less effective as an adjunct to antibiotic treatment.

The need for a high coverage level of antibiotic treatment is currently a subject of interest among those involved in intervention trials and in hypo- and mesoendemic settings and here it is shown that a high coverage is indeed crucial for the successful elimination of infection. The gain in the effectiveness of the treatment programme (measured by the reduction in the prevalence of infection) observed by gradually increasing coverage from a starting low level is greater than the gain when coverage starts off at a higher level. Again, however, in the hyperendemic setting, the rebound of the infection prevalence is extremely rapid and the useful analysis of coverage is not permitted.

A variant of the main age-structured model is also presented in which active disease (TF/TI) is explicitly included. The model allows the simulation of 1) the presence of disease in the absence of infection and 2) a lag in the disappearance of the signs of disease once infection has been cleared following treatment. Because of the lack of a one-to-one mapping between those who are infected and those who show signs of active disease, this model may be useful in providing decision support when the prevalence of active disease is monitored as a proxy for infection in the wake of treatment programmes. At these times, it
becomes necessary to understand how effective a treatment programme is with respect to the elimination of infection and clinical exam may be the only way of assessing this.

The model, once it has reached a steady state, produces an infection load distribution that broadly follows the distribution observed in a variety of endemic settings: in hypoendemic settings, the number of people with high loads is close to the number with medium and low loads; whereas in hyperendemic settings, the load distribution is strongly skewed toward those with low loads, with only a few people having high loads. The incorporation of infection load into models of trachoma is certainly important and this report has outlined a preliminary approach to its inclusion.

This is the first model of infection and disease in trachoma to: 1) be fitted to the full-range of endemic settings across all ages and to replicate epidemiological patterns; 2) include the progress of individuals toward the trachomatous disease sequelae as well as the infected state; 3) examine the effect across ages of a variety of treatment programmes using both antibiotic treatment and transmission reduction through non-chemotherapeutic means; 4) explicitly include active disease as well as infected status. As more data emerge from intervention trials and control programmes, the models presented in this report are capable of being fit to this new data to allow projections to be made of the impact of treatment in trachoma-endemic communities. This may help guide programmes in achieving the elimination of blindness due to trachoma.
8 References


Grassly, N. and R. L. Bailey (In prep.). "Is there an effective adaptive immune response to ocular Chlamydia trachomatis infection?"


9 Appendix A: Mathematical model description

The SI model used here channels the population through successive susceptible and infected stages, indexed by the parameter \( i \), as illustrated in Figure 1. Each susceptible \((S_i)\) and infected \((I_i)\) compartment is connected to the next compartment ‘above’ it so that individuals pass up a ‘ladder’ of infection. The following partial differential equations describe the flow from one compartment to another in continuous age and time, both of which are discretised for the computer simulation.

\[
\frac{\partial S_i(a,t)}{\partial t} + \frac{\partial S_i(a,t)}{\partial a} = -\beta S_i(a,t) \sum_j \rho_j I_j(a',t) da' - \mu(a)S_i(a,t) + \nu_{i-1}I_{i-1}(a,t)
\]

\[
\frac{\partial I_i(a,t)}{\partial t} + \frac{\partial I_i(a,t)}{\partial a} = \beta S_i(a,t) \sum_j \rho_j I_j(a',t) da' - \mu(a)I_i(a,t) - \nu I_i(a,t)
\]

Here, \( S_i \) and \( I_i \) are functions of age \( a \) and time \( t \); \( \beta \) is the transmission parameter from susceptible to infected states; \( w(a,a') \) is a mixing matrix (in the discretised version) describing the rate of mixing between individuals of age \( a \) and \( a' \)

\[
w(a,a') = \varepsilon \delta_{a,a'} + (1-\varepsilon) \sum_a N_{a'} \delta_{a,a'},\quad \text{where} \ \delta_{a,a'} \text{ is the Kronecker Delta (Boas 1983); } N_{a'} \text{ is the number of individuals of age } a' \text{ and } \varepsilon \text{ is a mixing parameter ranging from 0 (random) to 1 (assortative), here set to 0.5); } \rho_j \text{ is the infectivity of infected individuals in compartment } I_j; \ \mu(a) \text{ is the death-rate at age } a \text{ obtained from the 2001 WHO Gambian and Tanzanian life tables (WHO 2006); and } \nu_i \text{ is the recovery rate of individuals in compartment } I_i.

The recovery rate per individual \( \nu_i \) from infection \( i \) is assumed to follow an exponential function of \( i \) that begins at an initial rate \( \nu_0 \) and saturates at a maximum rate \( \nu_1 \):

\[
\nu_i = (\nu_0 - \nu_1) e^{-\gamma i} + \nu_1
\]
The exponent $\gamma$ is the parameter over which this function is fitted to the data of Bailey et al., (Bailey, Duong et al. 1999).

The infectivity of an individual $\rho_j$ is assumed to be linearly proportional to the bacterial load $l_i$, which is assumed to be a function of the number of previous infections experienced by that individual, in agreement with the observed decline in load with age in trachoma-endemic communities.(Solomon, Holland et al. 2003; Solomon, Holland et al. 2004; Burton, Holland et al. 2005; West, Munoz et al. 2005). An exponential function is chosen such that the load declines from its initial value $l_o$ as below:

$$l_i = l_0 e^{-\phi i}$$

The parameter $\phi$ can be estimated from age-stratified data on bacterial load (e.g. the model is fit to the data of West et al.(West, Munoz et al. 2005)). The load, when normalised to lie between 0 and 1, then becomes the infectivity $\rho_j$ of the population in compartment $i$. 


10 Appendix B: Active disease model

10.1 The addition of a diseased class

The inclusion of a diseased stage in the natural history of trachoma, in addition to infected and susceptible stages, is necessary to investigate the pre- and post-treatment dynamics of active disease. Infection and disease are not perfectly correlated in trachoma, and the age-structured model outlined in the earlier sections implicitly assumes that they are, an assumption that allows the model to explore, with great simplicity, the epidemiological patterns of trachoma. However, the inclusion of a stage in which individuals are diseased would allow the exploration of: 1) the consequences of the existence of a proportion of the population that is diseased without being infected; 2) the time-lag between the onset of infection and the manifestation of disease (as well as the lag between the cessation of infection and disease), which is of particular importance when infection in a community has been treated by antibiotic administration and, while the infection load may drop substantially, the signs of disease remain among many members of the population. In order to investigate these phenomena, a second model was constructed.

10.2 The structure of the disease model

Due to the added complexity of investigating the effect of a diseased stage, this second model is not age-structured. While the added richness of analysis afforded by age-structure is missing from this model, the increased speed of execution allows for a rapid sequence of fits to available data. The addition of the new diseased class allows the model population to include members who are diseased without at the same time being infected. However, for simplicity, individuals cannot be infected without showing clinical signs of disease. The aim here is to include a diseased class, since it is clinical disease (TF/TI) that is measured—more frequently than the infection prevalence—to determine the level of trachoma in a community.

Figure 22 illustrates the model; the main features distinguishing it from the age-structured model described in section 2 are: 1) the diseased-only state and 2) the new path that individuals can take to advance along the ladder of infection from the diseased-only state,
bypassing a recovered state, and straight into the next infected-and-diseased state above. The addition of a new way in which individuals can progress along the infection ladder is intended to allow for the possibility that, even after antibiotic distribution has reduced the level of infection in the community, disease remains, and there may be individuals who continue to experience disease for a considerable time, possibly even progressing in the severity of the disease they experience. This addition is intended to also capture the lag between the clearance of infection and the eventual clearance of disease from a community. Figure 22 shows that this additional path along the ladder is dependent upon the prevailing force of infection in the population, but that only a fraction of the already-diseased population, denoted by $f$, will follow this path.

Figure 22 Diagram showing a model that includes a diseased-only class, as well as an infected and diseased class. This model allows the population to clear the infection yet still show signs of disease, a phenomenon commonly observed in field-studies.

10.3 Fitting the model to data

The model was fitted to the data available from the three studies used previously for the age-structured model, namely, Upper Saloum district, Gambia (hypoendemic at baseline); Rombo district, Tanzania (mesoendemic at baseline); and Kongwa district, Tanzania (hyperendemic at baseline). Pre- and post-treatment data were used to determine the parameter values of the model using least squares fitting of the model-generated time-dependent infection and disease prevalence to the data for these values. The compartments
shown in Figure 22 represent a particular level of the ladder of infection and should have been labelled with subscripts $i$ as for the earlier model (Figure 1) but, for simplicity, these have been suppressed here. The values of the model parameters, obtained through fitting to the pre- and post-treatment data, are listed in Table 6.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu_0$</td>
<td>Rate of recovery from the first infected-and-diseased state</td>
<td>1.2 per year</td>
</tr>
<tr>
<td>$\nu_1$</td>
<td>Rate of recovery from infected-and-diseased state following a large number of prior infections</td>
<td>5.0 per year</td>
</tr>
<tr>
<td>$\rho_0$</td>
<td>Rate of recovery from the first diseased-only state</td>
<td>0.86 per year</td>
</tr>
<tr>
<td>$\rho_1$</td>
<td>Rate of recovery from diseased-only state following a large number of prior infections</td>
<td>5.0 per year</td>
</tr>
</tbody>
</table>
| $f$       | Fraction of the diseased population advancing to the next state without recovery | Hypo: very low (<0.01)  
Meso & Hyper: high (>0.99) |
| $\beta$   | Transmission rate: the rate of transmission (per year) of infection between individuals | Hypo: 1.89 per year  
Meso: 3.25 per year  
Hyper: 5.71 per year |

Table 6 The parameters used for the active disease model. These parameters were obtained by fitting the model to the pre- and post-treatment data of the three endemic settings analysed in this report. Note that the rate of recovery from the diseased-only state, denoted by $\rho$, represents the total rate at which individuals recover from this state.

The parameter values for the fraction of the population advancing along the ladder of infection without recovery, obtained through fitting to the pre- and post-treatment data, show that there is no clear conclusion for this fraction. The model-generated pattern obtained with the extreme values of 0 and 1 (close to the values actually obtained through fitting) give very similar outcomes.
Using these parameter values, the model generates outcomes for the trajectory of the prevalence of active disease (TF/TI) and infection pre- and post-treatment. The results of these simulations are shown in section 5.6.


11 Appendix C: The relative dependence of exposure and acquired immunity on prevalence

Figure 23 illustrates the relationship between prevalence and age for three model set ups: 1) no load dependence on the infectivity of individuals AND no infection dependence on the rate of recovery from infection—this means that individuals who have experienced a large number of infections are considered to be just as infective, and their recovery time from infection is exactly the same, as those who have experienced few; 2) no load dependence but an infection number dependence of the recovery time from infection; 3) a load-dependent infectivity but no infection-number dependence of the recovery rate from infection. In each of these cases, the parameter governing the mixing matrix, $\varepsilon$, was set to 1, the assortative extreme, in which each age group was only interacting with other members of its own group. Fixing the mixing matrix parameter to its extreme value excluded the effects of age mixing on the resulting epidemiology of the infection. With this enforcement, it became possible to examine the effect solely of a load-dependent infectivity and an infection-dependent recovery time.

It can be seen that the effects of these two model features are very similar—they both cause the prevalence of infection to decline with age and they both do this in such a way as to cause a peak to occur in the age-dependent prevalence of infection. The declining recovery time (or increasing recovery rate) with number of previous infections has an immediately understandable effect on the prevalence; because the force of infection experienced by uninfected individuals is the same, no matter how old they are, an increase in the recovery rate from each subsequent infection will result in there being fewer people infected at any given time at older than at younger ages. The load dependence-effect is also clear; older people have generally been exposed to a greater number of infections than younger people and—despite there being, in this scenario, no change in recovery rate with age—the infectivity of older people, on average, is much lower than that of younger people; when, therefore, the interactions were confined to those in the same age-group the force of infection was significantly reduced in older age groups, thereby reducing the prevalence of infection at these ages.
While some of the available data suggest an increase in the recovery rate from infection with age (Bailey, Duong et al. 1999), a higher level of exposure to infection at younger ages would also result in similar epidemiological patterns i.e. young-age peaks in the age profiles of infection and active disease. If both acquired immunity and a higher level of contact between those in the younger age groups were both operating, then the difference in the prevalence of infection at young and old ages would be expected to be even greater than is seen and so would the discrepancy between the data and the model-generated curves. However, it is difficult to disentangle the effects of age-related differences in exposure to infection and acquired immunity. While current evidence seems to suggest that, in trachoma, an acquired immune response is developed (Bailey, Duong et al. 1999; Grassly and Bailey In prep.), there probably are also age-related exposure differences and further studies are needed to clarify this issue.

The immunity effect is almost completely equivalent to one in which the rate of exposure to infection reduces with age. Models for helminthic infections, and their resulting morbidity, such as those for schistosomiasis and lymphatic filariasis (Chan, Guyatt et al. 1994; Chan, Guyatt et al. 1995; Norman, Chan et al. 2000) often include age-related exposure as well as the effects of age-dependent acquired immunity and these models attempt to disentangle these two effects from one another, finding that their result on the overall prevalence of infection and morbidity is very similar.
12 Appendix D: Excerpts from the Master’s degree dissertation of Ms. Isobel Blake

The following excerpts have been made from the Master’s thesis of Ms. Isobel Blake. Ms. Blake worked under the supervision of the Imperial College London, Department of Infectious Disease Epidemiology team which worked on the ITI/Imperial College project. The model developed in the thesis was a non age-structured version of the model outlined in the main body of the report. The sections excerpted here involve the fitting of the model to intervention data and the analysis of a stochastic version of the model in which each model run is different from every other, and it is possible for the infection to become extinct when the number of infected individuals becomes very low. There is a possibility that the outcomes observed post-treatment in the intervention trials included in this report might be explained as particular realisations from a whole spectrum of possible outcomes of control interventions on the communities and districts. This spectrum of outcomes is explored in the following sections from the thesis. The parameters referred to in the main text as $\nu_0$ and $\nu_i$ are, in the excerpt here, referred to as $\nu_0$ and $\nu_n$.

12.1 Fitting to Intervention Data and Subsequent Inference of the Recovery Rate

12.1.1 Deterministic Model

When fitting the value of $\nu_0$ to intervention data (described in table 2), but constraining the estimate to lie within previous estimates of the parameter, the optimised values of $\nu_0$ always were 1.2 person\(^{-1}\) year\(^{-1}\) regardless of the values of the decays constant $\gamma$ and $\nu_n$ (table 8). If the value of $\nu_0$ was not constrained then the optimised value always tended towards zero. The mean $\nu$ estimate was relatively close to the value of $\nu_0$, highlighting the fact that value of $\nu_0$ has more influence in determining the transmission of trachoma and hence is more important to fit to the data than $\nu_n$. An increased value of $\gamma$ (recovery rate decay constant) gave a larger fitted value of $\beta$ which in turn increased the rate of re-emergence of infection (approximated by $\beta/\nu$ (mean $\nu$)). Setting the value of $\nu_n$ to five compared to ten, decreased the rate of infection re-emergence. Values of $\nu_0 = 1.2$ and $\nu_n = 5$ (or 10) gave a slower rate of re-emergence of infection compared to using the revised Bailey estimates\(^{18}\) but the rate of re-emergence of infection was still faster than in the intervention studies (figure 8).
### Table 8

Fitted values of $\nu_0$ and $\beta$ to intervention data;\textsuperscript{12-14,73} described in section 5.2. The value of $\nu_0$ was constrained to lie between previous estimates of the parameter (table 3). The value of the recovery rate decay constant $\gamma$ was varied between 0.001 and 0.1 and $\nu_n$ was set at both 5 and 10 person\textsuperscript{-1} year\textsuperscript{-1}. Efficacy was set at 95\% and the coverage was set to the level of therapeutic coverage described in the respective intervention study.

<table>
<thead>
<tr>
<th>Data set</th>
<th>$\nu_n = 10$</th>
<th>$\nu_n = 5$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\nu_0$</td>
<td>$\beta$</td>
</tr>
<tr>
<td><strong>$\gamma = 0.001$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saloum District, The Gambia</td>
<td>1.2</td>
<td>2.13</td>
</tr>
<tr>
<td>Rombo District, Tanzania</td>
<td>1.2</td>
<td>4.61</td>
</tr>
<tr>
<td>Kongwa, Tanzania</td>
<td>1.2</td>
<td>51.79</td>
</tr>
<tr>
<td><strong>$\gamma = 0.01$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saloum District, The Gambia</td>
<td>1.2</td>
<td>2.35</td>
</tr>
<tr>
<td>Rombo District, Tanzania</td>
<td>1.2</td>
<td>6.55</td>
</tr>
<tr>
<td>Kongwa, Tanzania</td>
<td>1.2</td>
<td>189.31</td>
</tr>
<tr>
<td><strong>$\gamma = 0.1$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saloum District, The Gambia</td>
<td>1.2</td>
<td>4.48</td>
</tr>
<tr>
<td>Rombo District, Tanzania</td>
<td>1.2</td>
<td>27.69</td>
</tr>
<tr>
<td>Kongwa, Tanzania</td>
<td>1.2</td>
<td>462.50</td>
</tr>
</tbody>
</table>
Figure 8 Prediction of the change in prevalence of infection after MDA in hypo-, meso- and hyperendemic communities using the fitted recovery rates ($v_0 = 1.2$ person$^{-1}$ year$^{-1}$ and $v_n = 5$ or 10 person$^{-1}$ year$^{-1}$) and the revised Bailey estimates ($v_0 = 2.4$ person$^{-1}$ year$^{-1}$ and $v_n = 18$ person$^{-1}$ year$^{-1}$). Predicted results are compared to recent intervention data, described in section 5.2. $\beta$ was fitted to endemic prevalence of infection levels prior to treatment. Efficacy was set at 95% and the therapeutic coverage was set to the level of coverage described in the respective intervention study.
12.1.2 Stochastic Model

Stochastic simulations were run using the fitted estimates of $\beta$, $v_0 = 1.2 \text{ person}^{-1} \text{ year}^{-1}$ and setting $v_n = 5 \text{ person}^{-1} \text{ year}^{-1}$.

In the hypoendemic setting, the change in prevalence of infection after one MDA with azithromycin in the Saloum district, The Gambia\textsuperscript{12} (figure 9a) lies within the range of values predicted by the simulations. In the mesoendemic data (Rombo district, Tanzania)\textsuperscript{13} after two MDAs, elimination of infection was achieved but this is not the case in 30% of the simulations (figure 9b). In the hyperendemic setting, the rate of return of infection was much higher in the all of the simulations compared to that of the Kongwa, Tanzania data (figure 9c). Therefore if the recovery rates are $v_0 = 1.2 \text{ person}^{-1} \text{ year}^{-1}$ and $v_n = 5 \text{ person}^{-1} \text{ year}^{-1}$ then the results from the intervention data for the hypo- and mesoendemic communities could have been a stochastic effect. This is not true for the hyperendemic community.
Figure 9 Comparison of stochastic simulations from the model of the change in prevalence of infection after MDA and field data from hypo-, meso-, and hyperendemic areas (described in section 5.2). The red line represents the results from the field data, the grey lines represent the 50 simulations from the model and the purple line corresponds to the median of the simulations. $\beta$ was fitted to the endemic prevalence of each community. $v_{0} = 1.2$ person$^{-1}$ year$^{-1}$ and $v_{n} = 5$ person$^{-1}$ year$^{-1}$. The efficacy of azithromycin was assumed to be 95% and the therapeutic coverage was set to what the authors stated they achieved in each respective field study. The number MDAs implemented is the same as in the field studies. The model was run deterministically to reach endemic equilibrium before stochasticity and treatment were introduced.
12.2 What Can Be Learnt From The Model? Messages for Control Programmes

12.2.1 The Effect of Three Annual MDAs

The effects of three annual MDAs (as advised by the WHO) on the prevalence of infection and disease sequelae were investigated in the model both deterministically (figure 10) and stochastically (figure 11). Hypo-, meso- and hyperendemic areas were all investigated with this treatment regime (the WHO does not advise this strategy for hypoendemic areas but this area was investigated for completeness). The results using the recovery rates from section 5.3.2.1 \( (\nu_0 = 1.2 \text{ and } \nu_n = 5 \text{ person year}^{-1}) \) were compared to using Bailey’s revised estimates of the recovery rates \( (\nu_0 = 2.4 \text{ and } \nu_n = 18 \text{ person year}^{-1}) \).

**Deterministic Model**

Annual MDA was implemented at time = 0, 1 and 2 years in the model. In all scenarios and levels of endemicity, infection, after treatment, re-emerges after the initial drop, to a peak which is approximately twice that of its endemic level, before returning to endemic equilibrium. When using the faster recovery rates, the re-emergence of infection occurs earlier in time and at a faster rate. As the level of endemic prevalence of infection increases, the rate of re-emergence of infection after treatment also increases. The fitted value of \( \beta \) at endemic equilibrium was larger in magnitude when using the faster recovery rates.

The effect on disease sequelae is less pronounced as the severity of the disease increases. The prevalence of TS decreases after the three rounds of treatment until a lag after the re-emergence of infection, after which the prevalence of TS returns to its endemic level. When the lower recovery rates were used in the model, the decline in the prevalence of TS was greater than when using the faster recovery rates because the re-emergence of infection did not happen until a later time point. Similarly the decline in prevalence of TS was greatest in the hypoendemic area as infection took the longest time to re-emerge in this area. The prevalences of TT and CO decreased by less than 1% and therefore remained approximately constant, regardless of treatment.

**Stochastic Model**

Two hundred simulations were run and the resulting prevalences of infection and disease at 1, 5 and 20 years after the third MDA of three annual MDAs were recorded and plotted in histograms (figure 11).
a) Infection

*Hypoendemic community*

The first year after the third annual MDA, 89% of the simulations resulted in elimination of infection from the community when using either set of recovery rates. Twenty years after the treatments, 98% and 97% of the simulations resulted in elimination of infection using the lower and higher recovery rates respectively. The remaining simulations resulted in prevalences of \(0\%-20\%\]. The number of extinctions did not increase by more than 1% between five and twenty years after treatment.

*Mesoendemic community*

Again, the majority of simulations resulted in the elimination of infection one year after the three annual MDAs when using either sets of recovery rates in the model. Five years after the treatments 95% and 92% of simulations resulted in elimination of infection using the lower and higher recovery rates respectively. These percentages did not increase in value twenty after the MDAs. The remaining simulations resulted in prevalences of \(0\%-30\%\].

*Hyperendemic community*

The difference in using the two sets of recovery rates is more pronounced in the hyperendemic area. When using the lower recovery rates, a year after the last MDA 58% of the simulations resulted in elimination of infection, which increased to 78% five years after the MDAs. In comparison, using the higher recovery rates in the model resulted in elimination of infection in only 25% of the simulations one year after the treatments. Five years after treatment, this percentage had only increased to 26%. In both scenarios the number of extinctions did not increase by more than 1% between 5 and 20 years after the three MDAs.

b) Disease Sequelae

In all three endemic settings with both sets of recovery rates, the distributions of the disease sequelae prevalences from the two-hundred stochastic simulations appear to be normally distributed around the endemic equilibrium prevalence of the sequela in question at one and five years after the three annual MDAs. The exception to this is the hypoendemic setting in which TS (using the lower recovery rates) and CO are normally distributed around the adjacent bin to the endemic equilibrium prevalence. In the hypoendemic and mesoendemic settings the mean of the distribution, from the simulations,
of the prevalence of TS and TT decrease by 2% and 0.5% respectively, twenty years after the three annual MDAs, irrespective of the recovery rates used. The distribution of CO does not change after the three annual MDAs. While in the mesoendemic setting, a few of the simulations (2% using either recovery rates) result in elimination of CO, in the hyperendemic setting, only when using the lower recovery rates do the distributions of the three disease sequelae decrease in prevalence, twenty years after the three MDAs.
Figure 10: The effect of three annual MDAs in hypo-, meso- and hyperendemic areas using two sets of recovery rates predicted by the deterministic model ($\nu_0 = 1.2 \nu_n = 5$ person year$^{-1}$ from section 5.3.2.1 and $\nu_0 = 2.4 \nu_n = 18$ person year$^{-1}$ revised Bailey estimates$^{10}$). The values of $\beta$, $m$, $p$ and $q$ were fitted to the endemic prevalence levels of infection and disease sequelae from the Saloum district, The Gambia (14 villages)$^{12}$, Rombo district, Tanzania$^{14}$ and the Jimma zone, Ethiopia$^{23}$ (in which the prevalence of TF/TI was assumed to be equivalent to the prevalence of infection) for hypo-, meso and hyperendemic areas respectively. The three annual treatments occur at time = 0, 1 and 2, which is shown on the graphs by the area shaded grey. Efficacy of azithromycin was assumed to be 95% and the therapeutic coverage of the population with MDA was assumed to be 90% at each distribution.
Figure 11a) Hypoendemic area
Figure 11b) Mesoendemic area
The effect of three annual MDAs in hypo-, meso- and hyperendemic areas on the prevalence of infection and disease sequelae at 1, 5 and 20 years after the last MDA, using two sets of recovery rates predicted by stochastic simulations ($v_0 = 1.2, v_n = 5$ person year$^{-1}$ from section 5.3.2.1 and $v_0 = 2.4, v_n = 18$ person year$^{-1}$ revised Bailey estimates). The model was run deterministically to reach endemic equilibrium, after which the model was run stochastically. At the same time point, switching to the stochastic model, the three annual treatments were introduced. 200 simulations were run for each endemic setting with each set of recovery rates. The resulting prevalences of infection and disease sequelae at 1, 5 and 20 years after the third
annual MDA were recorded and plotted in a histogram. The values of $\beta$, $m$, $p$ and $q$ were fitted to the endemic prevalence levels of infection and disease sequelae from the Saloum district, The Gambia (14 villages)$^{12}$, Rombo district, Tanzania$^{14}$ and the Jimma zone, Ethiopia$^{23}$ (in which the prevalence of TF/TI was assumed to be equivalent to the prevalence of infection) for hypo-, meso- and hyperendemic areas respectively. The efficacy of azithromycin was assumed to be 95% and the therapeutic coverage of the population with MDA was assumed to be 90% at each distribution. The pink cross corresponds to the endemic prevalence of infection and disease sequelae that the model was fitted to. The numbers on the x-axis correspond to the bin of less than or equal to the category.

12.3 What other factors not captured in the deterministic model account for the slow rate of re-emergence of infection after MDA seen in the field?

There are at least four possibilities. Firstly, the model assumes that trachoma infection in the communities is at endemic equilibrium, prior to interventions. However, as previously discussed, the community in the Saloum district and the Rombo district may have been experiencing secular trends and so infection may have been declining in prevalence anyway, regardless of the introduction of MDA.

Secondly, the endemic prevalence of the Kongwa, Tanzania area was 57%. This value is an extremely high proportion of the population to be infected, especially as a large proportion of the adult population was infected, considering an enhanced immune response in the older ages, and so may have resulted from cross contamination between samples from individuals when detecting whether individuals were infected using PCR, or from the detection of transient bacteria.\textsuperscript{79} If the endemic prevalence of infection prior to MDA was in fact lower, then the recovery rate would not need to be so small to fit to the endemic prevalence and the very slow rate of re-emergence of infection.

Thirdly, the slow re-emergence of infection in the studies may have been a stochastic effect. Running the model stochastically, using the lowest estimate of $v_0$ from the literature, does result in the majority of the simulations from the hypoendemic and mesoendemic settings after MDA to have slower rates in the re-emergence of infection or elimination (in the case of the mesoendemic community with two rounds of MDA). The simulations from the hyperendemic community always had a larger rate of re-emergence of infection than in the data from Kongwa, Tanzania, supporting the hypothesis that the baseline endemic
prevalence was inaccurately measured. Therefore the results of the intervention studies from the hypo and mesoendemic settings may have been due to chance. In a study, which monitored the change in prevalence in children (so not appropriate to fit this model to) after a single MDA in 24 Ethiopian villages, it was found that in some villages infection was eliminated, in others the prevalence hovered below 20% and in others the prevalence of infection increased rapidly. Lietman argues that they all had similar pre-treatment levels and were located within close proximity of each other and so the differences between villages in the change in prevalence are due to chance effects. Therefore, to be able to fit the recovery rates to intervention studies, a much larger sample of studies is required, measuring the change in prevalence in the whole population. Currently this data is not available but this study illustrates there is an urgency for its collection.

Finally, a change in the diversity of the C. trachomatis genovars may affect the rate of return of infection after treatment. There are at least ten different genovars (which are determined by the outer membrane protein ompA) and it is thought that the bacteria have a competitive advantage if they infect a host that has previously only been infected by a different strain. It has been shown that communities with a high prevalence of infection also have a high diversity of strains compared to communities with a low prevalence of infection. At the time of MDA with azithromycin, the diversity of strains may be reduced below a certain threshold in which the remaining strains do not have the same competitive advantage in infected individuals and so the infection may be eliminated in the community (the Allee effect) or may take a longer time than expected when not taking account of the competitive advantage of strains i.e. the slow rate of re-emergence of prevalence of infection in the results of the intervention studies might be accounted for by a reduction in diversity of C. trachomatis, especially in the Kongwa, Tanzania data which was hyperendemic before MDA. There is currently one study that has investigated the effect of MDA with azithromycin on the change in diversity of C. trachomatis. After one MDA there was much less diversity, with 90.5% of cases with the same genovar type compared with 74% at baseline.