

Mathematical models of trachoma transmission and control.

*Report on an International Trachoma Initiative sponsored workshop,
organised by Imperial College London.*

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1 Introduction

The International Trachoma Initiative (ITI) and Imperial College London are working on models of: 1) the spread of infection of ocular *Chlamydia trachomatis*; 2) the endemic distribution of infection in an age-structured community; 3) the clearance of infection and progression to disease in a population, and the endemic distribution of disease; 4) the progress within a population of the state of active disease and re-infection (or persistent infection) to the disease sequelae: trachomatous trichiasis, corneal opacity and blindness; and 5) control policies to interrupt transmission and reduce the number of cases of the disease sequelae.

The models under development at Imperial College (IC) fit into the WHO's activities for the Alliance for the Global Elimination of Trachoma by 2020 (GET 2020), whose mission is to eliminate the blinding form of trachoma by 2020. Any mathematical model that will help to

accomplish this mission must reproduce, to a level of accuracy agreed-upon by trachoma researchers and public health workers, the current knowledge of the relationship between infection and disease burden in trachoma endemic communities, as long as the model is validated using both pre- and post-control data. Models which, when they are calibrated to specific communities, faithfully reproduce infection and disease patterns can then be trusted to simulate through time the effect of various interventions such as antibiotic treatment and environmental components of the SAFE¹ strategy.

As an important part of this project, a workshop was organised at Imperial College, with the aim of consulting many of the foremost researchers and practitioners in trachoma disease and epidemiology to garner from them their advice on what should be included in trachoma models. The Imperial College team have been working on the project since November 2004 and a preliminary model exists; this model served as a focal point for discussion during the meeting, allowing participants to add or reduce complexity, or otherwise suggest alterations to the modelling approach. The participants of the workshop were informed that the goals would be the following:

- To review and reach consensus on the key features of *Chlamydia trachomatis* transmission and progression to disease, to allow the construction of policy relevant mathematical models;
- To identify outstanding issues that may need to be resolved to allow a mathematical model to be constructed and validated;
- To identify outstanding needs for empirical data collection and routes to collecting these data

The meeting took place at the main campus of Imperial College London, in South Kensington, London on 26th and 27th September 2005. The format was designed to emphasise discussion and come to an agreement, within the group of participants, on the set of important questions to be answered during the course of the meeting. Several invited presentations on topics relevant to modelling trachoma were given on the first day. At the beginning of the second day, a set of questions distilled from the first day's discussions were presented to the group and run through to ensure that everyone understood what needed to be answered and agreed on each question's relevance to trachoma modelling. The questions were then discussed by the group and a consensus opinion on each was reached. Summaries of the first day's presentations and the second day's discussions around the questions contained in each of five broad categories are outlined in this report.

¹ S—surgery for trichiasis, A—antibiotic treatment, F—facial cleanliness, E—environmental improvement.

2 Trachoma models

The IC model, as it currently stands, is a step up in complexity from the simplest possible design to model microparasitic infections. The simplest design involves two categories of host: susceptible and infected. The modelled population passes from one category to the next with a rate of transfer related to: 1) the number of people in the infected category i.e. this is a simple ‘mass action’ model in which it is assumed that the susceptibles come into contact with infecteds at a rate proportional to their numbers; and 2) the transmission rate i.e. the rate at which a contact between susceptible and infected successfully results in an infection. The model shown in Figure 1 adds several levels of susceptible and infected classes to the basic model and this allows it to clearly take into account the importance of reinfection in trachoma epidemiology. Individuals enter the model in susceptible class S_1 and they become infected, whereupon they progress to infected class I_1 ; they then recover at a rate dependent on function of the number of prior infections and enter class S_2 ; they then progress to subsequent infected and susceptible classes. This ‘ladder’ of infection—susceptible becoming infected and then recovering into the *next* susceptible class (rather than dropping back into the previous class, as would occur for an ‘SIS’ model)—forces the modelled population to retain a memory of the number of previous infections. This infection memory can then be used to advance the population along the route to disease sequelae.

Professor Taylor’s presentation on the first day of the meeting included a cartoon image of the relation between infection and active disease as well as the progressive path to scarring (and therefore disease sequelae) (Figure 2). This image was strikingly similar to the basic design of the current IC model, and the group agreed that reinfection is the path to worsening scarring (though there may be a distinct population subgroup whose propensity to scar appears to be linked to its inability to clear infection).

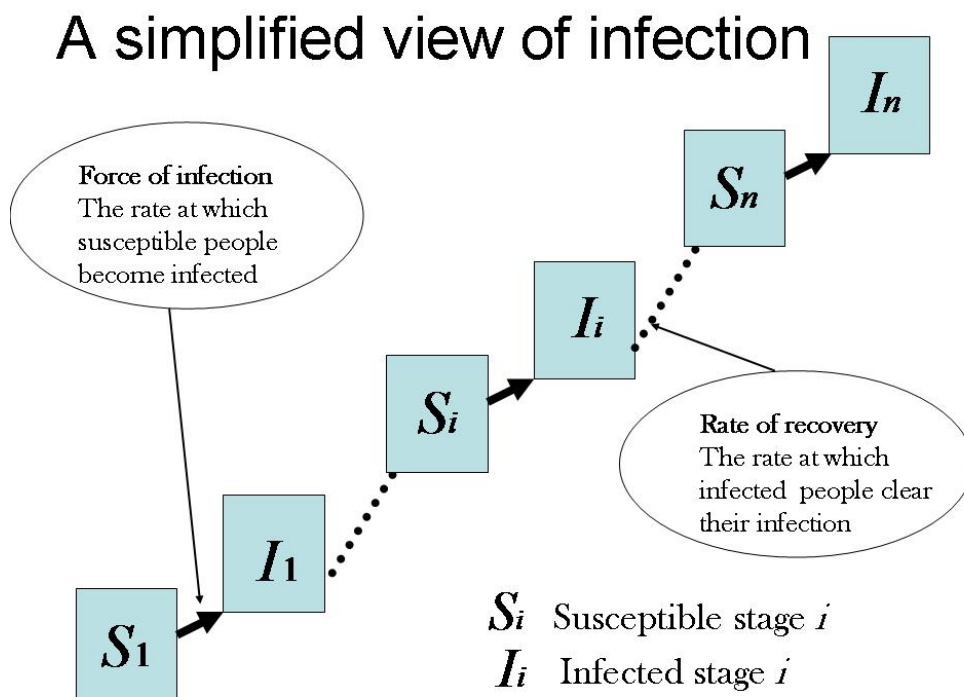


Figure 1 Simplified view of the current IC model for trachoma infection in a population flowing through each of the compartments.

Development of Trachoma

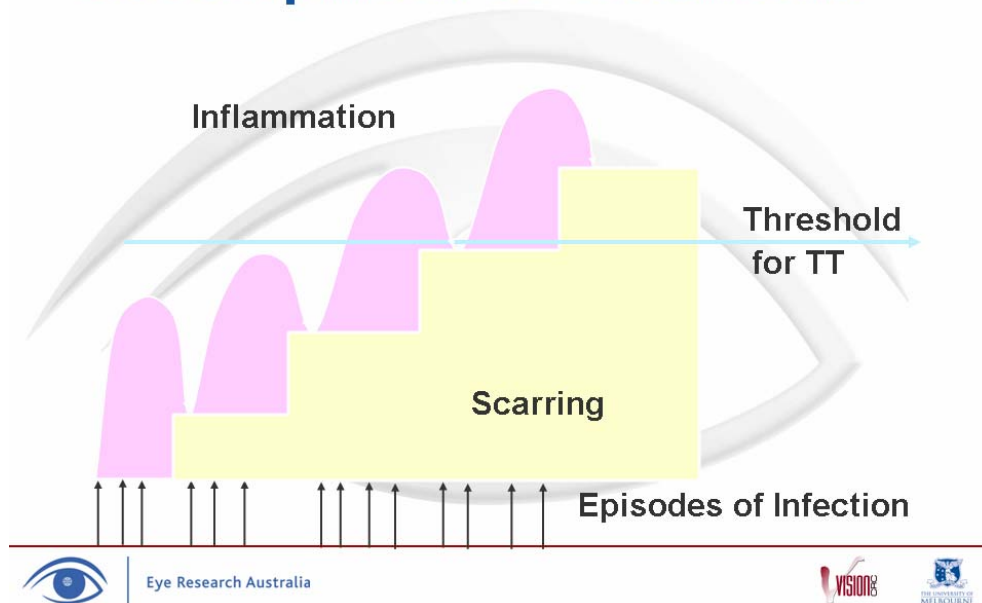


Figure 2 Professor Taylor's schematic diagram illustrating the relationship between infection episodes (arrows), inflammatory disease brought on by infection (pink humps), and incremental scarring (yellow steps).

3 Questions for discussion

The second day's discussions focused on several questions on which the group attempted to reach consensus. These questions were arranged into four categories, spanning the research areas of infection/disease and epidemiology most relevant to the improvement of models. The questions were devised by the IC team following the first day's presentations and they ran as follows:

3.1 Natural History

- What is the relationship between infection & disease upon first and subsequent ocular infections? Can we derive a cartoon representation showing this relationship for 1st, 2nd, 3rd, etc. infections over time post-challenge, analogous to data from animal models (including best estimate of the duration of infection and of disease)?
- Do host genetics play a role in this response?
- Is there immunity to re-infection?
- How many infections are needed to progress to scarring? What is the role of host genetics or other factors in the heterogeneity of rates of progression to scarring?
- What is the rate of progression from scarring to TT and TT to blindness and how is this influenced by re-infection?
- What is the role of other bacterial pathogens in progression from scarring to blindness?

3.2 Epidemiology

- In our simple model we assume the force of infection experienced by a ‘susceptible’ individual is a function of the ocular load of their contacts and mixing patterns by age. We do not assume a change in contact rate by age and are still able to reproduce observed patterns of infection and disease? Is this reasonable?
- Do we need to model gender effects at the level of transmission? Does the data exist to parameterise a model with gender-specific transmission?
- Are there well-established patterns of community load with age and gender in low, medium, and high (disease) prevalence communities?

3.3 Heterogeneity

- Clustering of infection and heterogeneity in transmission result in faster rebound from a given endemic prevalence than in a homogeneous population. What are the best estimates of clustering of infection and which level is most important (household, village, other geographic structure, etc.)?
- Does the degree of heterogeneity in community load vary with level of endemicity?

3.4 Persistence

- Is persistence common, what determines persistence and are persistent, non-replicating *Chlamydia* refractory to treatment with azithromycin?
- Are low load (persistent?) infections likely to contribute to transmission?
- Is persistence a significant factor in the progression to scarring and blindness? What fraction of individuals develop persistent infection?
- Are chronic severe infections due to heterogeneity in exposure or host-related factors?

At the beginning of the day, during a run-through of the questions, a fifth question-category was added to the existing four:

3.5 Intervention

- How does treatment affect our conclusions above?
- What is the effectiveness of the components of the SAFE strategy?
- Can we use the model to examine surveillance and sampling strategies pre and post-intervention?

4 Summary of discussions

An outline of the discussions around the above questions is given in what follows.

4.1 Summary of the discussion on disease natural history

It is important, in modelling interventions against blinding trachoma, to understand the processes relating infection with *C. trachomatis* to trachoma disease and disease sequelae because clinical examination (as well as other rapid assessment techniques) of individuals should lead to diagnoses of disease that will be useful in assessing the level of infection in a community; this allows the determination of which communities to treat and when to stop treatment. By assessing the level of infection, and which members of the community are harbouring the infection, interruption of onward transmission can be attempted. Correctly modelling the progression of disease among those infected will allow any interventions simulated in a model to take into account, for example, the possible re-emergence of infection from those left untreated due to their lack of clinical signs or infection-positive status at the time of treatment.

The duration of an episode of infection and active disease seems to decrease with age and the reason for this decrease may be one or a combination of: 1) the strength of the immune response to chlamydial infection increases with each exposure, thereby shortening episodes of infection with age (and the number of exposures); 2) the rate at which individuals are exposed to infection decreases with age so that it appears as if, for young age-groups, those who are suffering from prolonged episodes of active disease are actually being frequently re-infected, maintaining their current disease episode, while clearing the infection in a shorter time than it takes them to clear disease [1]. Professor Taylor's monkey model results powerfully support hypothesis (2) while Dr. Bailey's Gambian cohort [2] results back hypothesis (1). Figure 3 shows the results for a monkey model in which the animal is repeatedly challenged with inoculum: the results for primary infection are very similar to secondary (and subsequent) infection, though the indicators of follicular and inflammatory disease appear more severe for the first inoculation. The monkey model results also show that follicular disease is maintained while re-infection continues (see Professor Taylor's presentation), but that the infection load drops to a very low value and inflammatory disease declines following the first few inoculations. These results indicate that an adaptive immune response is at work, but that it is a short-term response which does not change with subsequent inoculations.

The three-stage model of infection and disease in Professor Taylor's recent *Lancet Infectious Diseases* review article [1], namely, an infection incubation period, then 'frank disease' and infection together, and, finally, infection clearance but disease persistence, was agreed-upon by the group as the sequence in which these events occur. When an individual is susceptible to infection, this state does not preclude the possibility of suffering from active disease, and, again, this is consistent with Professor Taylor's monkey model in which the animal requires repeated re-infection, even when diseased, to maintain disease or to harbour a non-zero infection load (as detectable by culture or by other means).

Professors West and Muñoz's studies [3-5] have brought to light a subsection of the population that persistently suffers from intense inflammatory trachoma and this group also, in general,

harbours a larger infection load than non-persistent-TI peers. The explanation for the existence of this group may be genetic—it seems to consistently constitute 10% of the children under study (in these particular studies). Within this group, the reason for the observation of persistent infection may be: 1) a latent infection comes about, in which the bacterial load becomes non-replicating but continues to present antigen to the host, resulting in severe active disease; 2) the hosts are more susceptible to re-infection and are less able to clear infection than their peers and so their infection persists. True persistent infections—i.e. case (1)—in which *Chlamydia* are viable but non-cultivable have only rarely been observed, and even in these cases generally for non-trachomatis *Chlamydia* species or in genital rather than ocular infections.

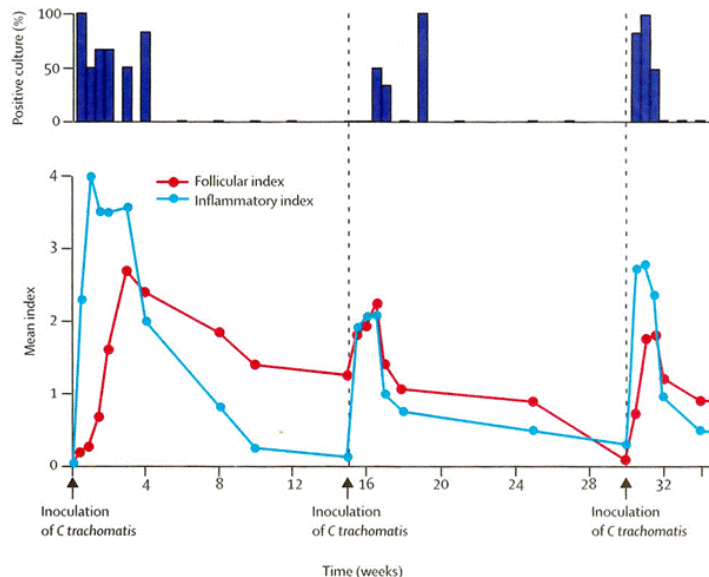
Various rates of progression from active disease to the disease sequelae were presented. Professors West and Muñoz's studies looked at a Tanzanian group of pre-school children over a 7 year period and found that, for children with constant severe trachoma—defined as those suffering from TI on three or more examinations out of four at the beginning of the study—29.2% became scarred, whereas 9.6% of those without constant severe trachoma became scarred. Richard Bowman et al.'s 12 year follow-up work in the Gambia measured the rate of progression from TS to further disease sequelae: 6.4% developed TT; 5.96% developed CO; 16.51% developed visual impairment/blindness. Another study headed by Richard Bowman showed that, over a year, 33% of subjects progressed from minor TT to major TT and in 36% progression of corneal scarring occurred.

It seems that the subgroup, identified by Professors West and Muñoz, that experiences some form of persistent infection, progresses more rapidly through the disease sequelae and that the time during which individuals remain in the TI disease category—high, by definition, for the persistently infected subgroup—is strongly correlated with scarring sequelae. However, Dr. Bailey cautioned against the firmness of this conclusion by suggesting that this duration may not be the most important correlate of scarring; for example, inoculum size may be equally, or more, important.

4.1.1 Action points for models (regarding the natural history of disease)

- Include, in the mixing matrix, a strong grading of exposure levels from children to adults: children have much higher rates of contact and therefore transmission than adults.
- Test the consequences of including a recovery rate from infection and disease that increases with age, as opposed to one that remains constant with age.
- Test for the inclusion of a class (approx. 10% of children) who harbour persistent infection either through 1) a latent infection that cannot be cleared and that causes severe inflammatory disease or 2) an increased transmission rate of infection i.e. a greater force of infection.
- Calibrate the model so that the rate of progression to disease sequelae matches the data.

Primary and Secondary Inoculation



Eye Research Australia



Figure 3 Professor Hugh Taylor's monkey model results, showing that disease is sustained only when the animal is repeatedly challenged with inoculum; bacterial carriage seems to drop to a very low level and inflammatory disease also declines shortly after inoculation. The severity of subsequent episodes of disease appears to drop after the first inoculation as does the duration.

4.2 Summary of the discussion on epidemiology

Gender effects were considered important in the epidemiology of trachoma, largely because women looking after small children remain in a high exposure environment much longer than men. The importance of this difference in exposure should be captured by a trachoma model.

The force of infection should be greater among younger age-groups than older, but the main reason for this may not be to do with the difference in average infection load between young and old people, which is the case for the IC model as it currently stands. Indeed, Dr. Bailey and Dr. Alexander pointed out that the downward trend, with age, in average load per person, as measured by quantitative PCR (qPCR) [6-8], is not very significant in recent studies. In the current IC model, the transmission rate of infection is proportional to the average infection load per individual, and this may be a valid approximation to a true load distribution in which there are a few very young people who harbour an extremely high load and also very few older people whose loads can be large.

New results from the reverse transcription-PCR (RT-PCR) technique [9] as outlined by Dr. Burton, may give a better indication of viable infection and therefore those members of the population who are infective. Those carrying an infection that is detectable by qPCR but is very low do not appear on the equivalent RT-PCR plot, which picks up RNA indicating bacterial metabolic activity, and, since the mechanism by which the detected RNA is produced requires live, probably infectious,

bacterial organisms to be present, the RNA studies may be the better indicators of infectious community bacterial load (see Figure 4). It may, therefore, be necessary to look at qPCR data again to subtract those with very low, and non-infective, loads; or, it may also be possible to assess load distributions, for the purposes of improving models, by looking at disease distribution data over age-groups.

The transmission rate should, however, decrease from children to adults but the main effect driving this change is probably the rate of exposure—i.e. contact—between individuals in each age-group, and not due to the average infection load per individual and this load’s effect on the infectivity variation with age. The model currently contains an expression for the infectivity proportional to the average load per capita for each age-group, and Professor Taylor suggested that this infectivity might be modified so that, instead of proportionality, a sigmoid or step function would govern this link. Such a function would have effectively two states: 1) with very little infectivity in those with very low infection loads and 2) roughly constant infectivity for higher load individuals. This scheme takes into account the idea that very low bacterial loads, as measured by quantitative PCR, are possibly non-replicating and therefore non-infectious but that higher loads are infectious, and the load itself does not alter the infectivity. Higher loads may be more available in ocular discharge and other facial areas and may affect the level of infectivity and this idea needs to be investigated.

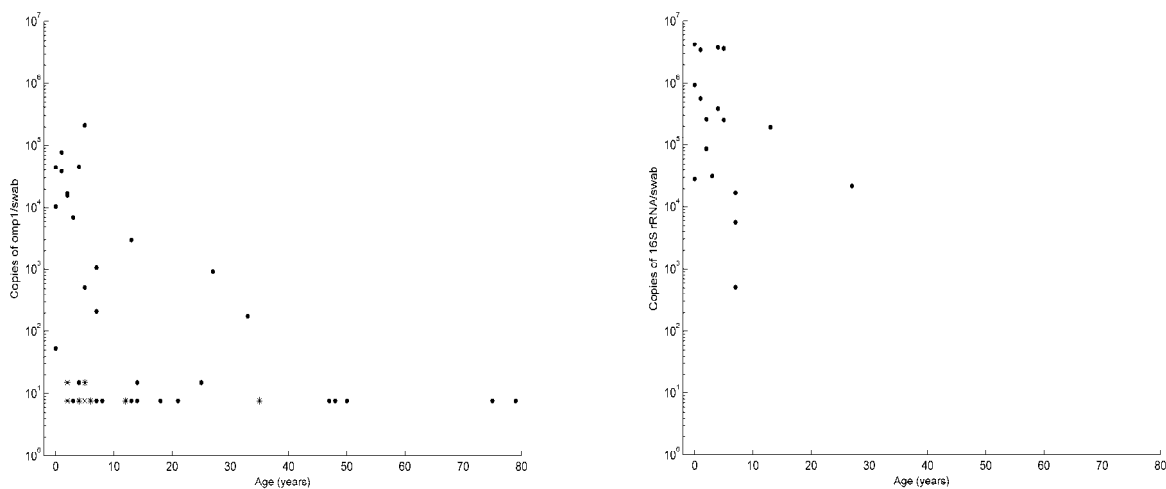


Figure 4 Plots by Dr. Burton et al. [9] showing the community chlamydial load with age as measured by quantitative PCR (left) and RT-PCR (measuring RNA) (right). Each spot represents the swab count for an individual.

4.2.1 Action points for models (regarding epidemiology)

- Divide the population into male and female classes, with appropriate infection transmission rates for each class over age-groups.
- Vary the transmission rate over ages to take into account properly the very large variation in exposure levels between children and adults.
- Test the sensitivity of the model to the dependence of infectivity on the average transmission load at each age. The infectivity should be proportional to the infection load.
- Incorporate some of the new 16S rRNA data on the presence of infectious bacterial organism into the model; investigate ways of adjusting the qPCR data in the light of new RNA results.

4.3 Summary of the discussion on heterogeneity

The group agreed that spatial clustering is a very important phenomenon in trachoma epidemiology and that any realistic model should be built to emphasise the most important transmission block, namely the household. There should be some level of inter-household transmission but the intra-household transmission is much more significant. Even in densely populated communities, it has been found that the main route of transmission is within households. There was some disagreement about the best way to measure levels of clustering within households and communities, but the intracluster correlation coefficient (ICC) may be a good first approach for surveys in which it is calculated.

Professor West has worked on studies in which the time between incident infections within and between households are measured and these results may be used for calibrating the clustered models e.g. [10].

Genetic heterogeneity should also be included in future models in the way that is outlined in previous sections i.e. using the data from Professors West and Muñoz's studies on the subgroup more likely to be persistently infected, with high infection load, and more likely to progress to scarring sequelae. According to the studies of Professors West and Muñoz, good predictors of a positive infection test at a follow-up to a baseline measure are: 1) the individual was infected at baseline, and/or that the individual was suffering from TI; 2) the household in which the individual lives had at least one other infected individual. In addition, they have observed that when more than one member of a household is infected, all members generally harbour bacteria of the same genotype. These observations are further evidence of household clustering.

4.3.1 Action points for models (regarding heterogeneity)

- Investigate ways of including the household clustering risk factor into the model and potentially use intracluster correlation coefficient calculations.

4.4 Summary of the discussion on persistence

Again, the issue of the subgroup of the population that is more likely to be infected and be suffering from TI on examinations subsequent to baseline, was discussed. Whether this population's mechanism for maintaining infection and disease is due to a genuine bacterial latent state; a greater susceptibility to reinfection; or an inability to clear infection once it has taken hold is not yet known. This population is also more likely to fail to respond fully to treatment, and so any treatment scenarios modelled should allow for a 80-90% efficacy, with the high-risk subgroup being the treatment-failing group.

Professor Lietman's models have incorporated antibiotic mass treatment by removing infection from a large proportion of the population. The possibility of removing a large proportion of the infection from each member of the population might also be investigated.

4.4.1 Action points for models (regarding persistence)

- The subgroup more at risk of high infection loads, disease and scarring should fail treatment with a high probability.

4.5 Summary of the discussion on intervention

Gambian studies in which flies were controlled and the prevalence of trachoma was monitored 3 months later found significant declines following the control programme [11]. A similar study in a hyperendemic area of Tanzania, however, has shown no effect of fly control, even when the fly density dropped to almost zero. For the purposes of model-building, it was agreed that a transmission term should subsume the effects of fly and environmental factors, there being no easy and clear way of explicitly including these effects otherwise. Currently, therefore, the available data does not justify the approach of dividing the transmission parameter into components that will take into account environmental and fly control.

Antibiotic treatment with azithromycin or tetracycline affects the infection load and so those community members who harbour the highest infection load will most likely have the highest infection load following treatment. It is not necessarily the case, therefore, that the high-infection load risk group harbours an infection that is refractory to treatment.

The rates of the re-emergence of infection in communities are beginning to be measured; some measurements have been carried out by Professor West and these focus on the rate of intra- versus inter-household re-emergence. Professor Lietman's studies have also begun to look at re-emergence on a village and multiple village level.

4.5.1 Action points for models (regarding intervention)

- Models need to be run for various intervention scenarios such as mass antibiotic treatment and treatment of specific age-groups, including the effects of less-than-100% effective treatment.
- Need to include varying levels of treatment coverage (e.g. 80% coverage is the norm in reality).

5 References

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6 Appendix 1: List of participants

David Mabey	(London School of Hygiene and Tropical Medicine)
Tom Lietman	(University of California, San Francisco)
Robin Bailey	(London School of Hygiene and Tropical Medicine)
Hugh Taylor	(University of Melbourne)
Sheila West	(Johns Hopkins University)
Beatriz Munoz	(Johns Hopkins University)
Matthew Burton	(London School of Hygiene and Tropical Medicine)
Neal Alexander	(London School of Hygiene and Tropical Medicine)
Manoj Gambhir	(Imperial College London)
Maria-Gloria Basáñez	(Imperial College London)
Nicholas Grassly	(Imperial College London)
Silvio Mariotti	(World Health Organisation)
Felicity Turner	(International Trachoma Initiative)
Jacob Kumaresan	(International Trachoma Initiative)
Charles Knirsch	(Pfizer, Inc.)

7 Appendix 2: Meeting Agenda

The focus of this meeting will be oriented toward sketching a simple but sufficient description of the epidemiology and immunology of trachoma. A second meeting will be held in 2006 to identify how such a model can be used in the planning and motivation of policy.

Each speaking slot includes time for a short discussion.

Day 1

9:00 Welcome from ITI / Imperial College

Introduction

Morning chair: Silvio Mariotti

9:10 Why use mathematical models for trachoma epidemiology?—Nicholas Grassly

9:25 Review of the main research and policy questions—David Mabey

9:55 The uses of models for policy—Maria-Gloria Basáñez

10:15 Some simple approaches to modelling trachoma—Manoj Gambhir

10:35 *Coffee/tea*

Infection and disease

11:00 ITI programmes, modelling, and the future of trachoma research—Jacob Kumaresan / Felicity Turner

11:25 The connection between infection and disease—David Mabey

11:50 What are we measuring with PCR for *Chlamydia trachomatis*?—Matthew Burton

12:15 Discussion

12:30 *Lunch*

Disease pathogenesis

Chair: David Mabey

1:45 The role of immune response and immunopathology—Hugh Taylor

2:10 The role of re-infection and persistent infection—Sheila West

2:35 Host genetic factors and immune response to infection with *Chlamydia trachomatis*—Robin Bailey

3:00 Discussion

3:15 *Coffee/tea*

Models and control

Chair: Sheila West

3:40 Modelling the influence of household clustering on the control of trachoma with antibiotics—Neal Alexander

4:05 Trachoma infection and disease control—Tom Lietman

4:30 Discussion and summary of the day

5:00 Wrap-up

Day 2

The participants will be split into two working groups, each of which will discuss the main research areas of trachoma epidemiology—as outlined in the discussions on the first day—with the focus on simplifying each of these issues so as to build a mathematical model. Following a half-day of discussion and the formulation of a set of actions, each group will present its recommendations. The whole set of attendees will then combine these recommendations to form an action plan for further work on trachoma models.

Coffee, tea and lunch are scheduled as for day 1