TRANSMISSION DYNAMICS AND
CONTROL OF TRACHOMA

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ABSTRACT

Trachoma continues to be the leading cause of infectious blindness. Mass administration of antibiotics is part of the current control effort, an approach which is costly when drugs are not donated.

Trachoma has been shown to cluster by household and therefore this unit could be a means to target treatment. This thesis shows that active inflammatory disease is a more sensitive marker of infection within an individual’s household than just in that individual. The potential impact of a more efficient, targeted treatment of households with at least one member with active disease depends on the relative contributions of community and household transmission of infection.

A mathematical model of the household transmission of ocular *Chlamydia trachomatis* was fitted to detailed demographic and prevalence data from four endemic populations, two in The Gambia and two in Tanzania. Maximum likelihood estimates of the household and community transmission coefficients were obtained. The estimated household transmission coefficient exceeded both the community transmission coefficient and the rate of clearance of infection by individuals in three of the study populations, indicating persistent transmission of infection within households. Allowing children and adults to have a different duration of infection improved the fit of the model to the data in three populations.

For a given level of treatment coverage, targeting antibiotics to households with active disease was predicted to have similar post-treatment dynamics to those observed after mass treatment but to be much more drug sparing. Using available cost data this approach was shown to be more cost effective when antibiotics are not donated. If targeting increases treatment coverage of diseased households, it was found to be more effective and more cost-effective than mass treatment even if antibiotics are donated. Further work is now required to explore the feasibility of incorporating household targeted treatment into trachoma control programmes.
ACKNOWLEDGEMENTS

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# TABLE OF CONTENTS

Abstract ................................................................................................................................. 1
Acknowledgements ................................................................................................................ 2
Table of Contents ................................................................................................................... 3
List of Figures ....................................................................................................................... 6
List of Tables ......................................................................................................................... 8
List of Abbreviations ........................................................................................................... 10
Chapter 1 Introduction ......................................................................................................... 11
  Motivation ......................................................................................................................... 11
  Objectives ......................................................................................................................... 12
  Outline of thesis ............................................................................................................... 13
Chapter 2 Background to trachoma .................................................................................... 14
  Ocular infection and disease ............................................................................................ 15
    Aetiology ......................................................................................................................... 15
    Natural history of disease: Active trachoma through to blinding trachoma .................. 18
    Detection of ocular C. trachomatis Infection .................................................................. 22
    Transmission of ocular C. trachomatis ........................................................................... 23
    Immunity towards infection and immune-pathogenesis ................................................... 26
  Global burden of trachoma and current trachoma control effort ................................... 29
    Global burden ............................................................................................................... 29
    GET 2020 & SAFE strategy ......................................................................................... 30
    Current Control programmes ......................................................................................... 40
  Previous mathematical models of trachoma .................................................................... 41
Chapter 3 A Household mathematical model of transmission without immunity ................ 45
  Introduction to the importance of household transmission for infectious diseases ........ 46
  Description of household mathematical model of transmission without immunity ........ 48
Non age-structured model .............................................................................................................. 48
An extension to the model: age structure .................................................................................. 51
Estimation of transmission parameters ...................................................................................... 54

Chapter 4 Description of Data ................................................................................................. 59
Introduction to Data ................................................................................................................ 60
Data Collection ......................................................................................................................... 60
Data characteristics ................................................................................................................... 63
Infection and Disease ................................................................................................................ 63
Household Structure ................................................................................................................ 63
Missing data .............................................................................................................................. 64

Chapter 5 Estimation of household and community transmission ........................................... 68
Estimation of household and community transmission without age-structure ...................... 69
Methods ...................................................................................................................................... 69
Results ....................................................................................................................................... 71
Estimation of household and community transmission with age-structure ............................. 78
Methods ...................................................................................................................................... 78
Results ....................................................................................................................................... 79
Discussion .................................................................................................................................. 86
Estimates of household and community not accounting for differences in transmission by age 86
Estimates of household and community transmission accounting for differences in transmission by age ...................................................................................................................................... 88
Overall conclusion ...................................................................................................................... 90
Limitations ................................................................................................................................... 90

Chapter 6 Implications of household transmission .................................................................. 92
Methods ...................................................................................................................................... 93
Stochastic simulation model ....................................................................................................... 94
Results ....................................................................................................................................... 95
Discussion .................................................................................................................................. 99
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 2-1</td>
<td>Diagram of chlamydial development.</td>
<td>16</td>
</tr>
<tr>
<td>Figure 2-2</td>
<td>Global distribution of trachoma in 2009.</td>
<td>30</td>
</tr>
<tr>
<td>Figure 4-1</td>
<td>Geographic locations of the four populations from which demographic, C. trachomatis infection and trachoma disease data was collected.</td>
<td>61</td>
</tr>
<tr>
<td>Figure 4-2</td>
<td>Prevalence of ocular Chlamydia trachomatis infection in males and females, by age class, in the four communities.</td>
<td>66</td>
</tr>
<tr>
<td>Figure 4-3</td>
<td>Prevalence of active disease in males and females, by age class, in the four communities.</td>
<td>66</td>
</tr>
<tr>
<td>Figure 4-4</td>
<td>Fitted and observed household distributions..</td>
<td>67</td>
</tr>
<tr>
<td>Figure 5-1</td>
<td>Sensitivity of transmission parameter estimates to different values of the duration of infection.</td>
<td>73</td>
</tr>
<tr>
<td>Figure 5-2</td>
<td>Correspondence between the proportion of individuals infected in each age group (and proportion of households infected) in the four communities.</td>
<td>85</td>
</tr>
<tr>
<td>Figure 6-1</td>
<td>Proportion of incidence contributed per individual from a household of size $m$ (solid line) and the probability distribution $P(m)$ of a randomly chosen individual belonging to a household of that size.</td>
<td>96</td>
</tr>
<tr>
<td>Figure 6-2</td>
<td>Distribution of the average time households are infected for at equilibrium in four communities..</td>
<td>97</td>
</tr>
<tr>
<td>Figure 6-3</td>
<td>Comparison of the rate of return of infection after one round of mass treatment between the fitted model allowing for household and community transmission and a fitted model which only allows for homogeneous mixing of the population.</td>
<td>98</td>
</tr>
<tr>
<td>Figure 7-1</td>
<td>Sensitivity (A) and specificity (B) of trachoma active disease as a marker of infection in an individual or in the household.</td>
<td>106</td>
</tr>
<tr>
<td>Figure 7-2</td>
<td>Sensitivity and specificity of active disease as a marker of infection in the household (both limiting clinical diagnosis to children under 10 years old and assessing clinical disease in all ages) for four trachoma endemic communities.</td>
<td>107</td>
</tr>
<tr>
<td>Figure 7-3</td>
<td>The probability of a household having one or more members with active disease, given a certain number of infected individuals.</td>
<td>108</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 2-1 Proportion of ocular Chlamydia trachomatis isolates which are the dominant serovar or genovar in four communities in which strains were identified. ..........................17
Table 2-2 Pictures and description of each stage of the simplified grading system. ............21
Table 2-3 Summary of field studies in West and East Africa which have followed up the temporal changes in prevalence of infection compared to that at baseline after single or multiple MDA rounds with the antibiotic azithromycin.........................................................35
Table 3-1 Description of the possible nested models within the full age-structured SIS household model ..................................................................................................................54
Table 4-1 Demographic and prevalence data from the four populations examined for ocular Chlamydia trachomatis infection..................................................................................62
Table 4-2 The number of individuals and prevalence of infection for each age groups in four endemic communities .................................................................................................65
Table 5-1 Maximum likelihood estimates of the transmission parameters in four populations of West and East Africa..................................................................................................72
Table 5-2 Sensitivity of the transmission parameter estimates by definition of the ‘household’ unit .........................................................................................................................74
Table 5-3 Estimation of transmission parameters in four endemic populations excluding individuals from the populations that were not examined..........................................75
Table 5-4 Estimation of transmission parameters accounting for if infected individuals were half, equal or twice as likely to be sampled than uninfected individuals..........................76
Table 5-5 Comparison of the ICC from four populations endemic for trachoma with the mean simulated ICC. .......................................................................................................77
Table 5-6 Comparison of different transmission models fitted to C. trachomatis infection data. ...............................................................................................................................................80
Table 5-7 Maximum likelihood estimates of the transmission parameters for each of the four populations and nested models. ..................................................................................81
Table 7-1 The median number of: individuals who received azithromycin; individuals who were successfully cleared of infection; and infections averted from one hundred stochastic simulations.................................................................113
Table 8-1 Cost data from Mali used in this analysis. ................................................................. 121
Table 8-2 Cost data from Nepal used in this analysis. ............................................................. 121
Table 8-3 Cost-effectiveness of azithromycin MDA compared to targeted treatment of households with at least one member with trachoma active disease. ........................................ 124
Table 8-4 Cost-effectiveness of azithromycin MDA compared to targeted treatment of households with at least one member with trachoma active disease assuming azithromycin is donated ........................................................................................................................................ 125
Table 8-5 Cost-effectiveness of azithromycin MDA compared to targeted treatment of households with at least one member with trachoma active disease assuming azithromycin is purchased at the proprietary price. .............................................................................................................. 126
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIC</td>
<td>Akaike Information Criterion</td>
</tr>
<tr>
<td>CO</td>
<td>Corneal Opacity</td>
</tr>
<tr>
<td>GET 2020</td>
<td>Global Elimination of blinding Trachoma by 2020</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon-γ</td>
</tr>
<tr>
<td>ITI</td>
<td>International Trachoma Initiative</td>
</tr>
<tr>
<td>JHU</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>LCR</td>
<td>Ligase Chain Reaction</td>
</tr>
<tr>
<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
</tr>
<tr>
<td>MDA</td>
<td>Mass Drug Administration</td>
</tr>
<tr>
<td>MOMP</td>
<td>Major Outer Membrane Protein</td>
</tr>
<tr>
<td>NTD</td>
<td>Neglected Tropical Disease</td>
</tr>
<tr>
<td>SAFE</td>
<td>Surgery, Antibiotics, Face-washing and Environmental improvement</td>
</tr>
<tr>
<td>SANN</td>
<td>Simulated Annealing</td>
</tr>
<tr>
<td>SCI</td>
<td>Schistosomiasis Control Initiative</td>
</tr>
<tr>
<td>SIS</td>
<td>Susceptible – Infected - Susceptible</td>
</tr>
<tr>
<td>STH</td>
<td>Soil Transmitted Helminth</td>
</tr>
<tr>
<td>TF</td>
<td>Trachomatous inflammation - Follicular</td>
</tr>
<tr>
<td>TI</td>
<td>Trachomatous inflammation - Intense</td>
</tr>
<tr>
<td>TS</td>
<td>Trachomatous Scarring</td>
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<tr>
<td>TT</td>
<td>Trachomatous Trichiasis</td>
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<td>WHO</td>
<td>World Health Organization</td>
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</table>
CHAPTER 1 INTRODUCTION

Motivation
Trachoma is the leading infectious cause of blindness worldwide [1] and there are currently an estimated 46 million people with the active stage of the disease [2] which is caused by ocular infection with the bacterium Chlamydia trachomatis. It falls under the umbrella term ‘Neglected Tropical Diseases’ (NTDs) since the disease mostly affects impoverished populations in which people cannot afford treatment.

Azithromycin is the antibiotic most widely used for trachoma control, followed by tetracycline. Ideally, antibiotics would be administered to infected individuals. However identifying infected individuals is difficult because there is no available field-test for diagnosing infection and active trachoma (early disease) is a poor marker of infection in individuals. Hence, mass treatment is part of the current control effort but for countries which do not receive donated azithromycin this strategy can be expensive. The distribution strategy may also increase the selective pressure for the emergence of resistant bacteria.

Targeting treatment to the majority of infected individuals would reduce the number of antibiotics administered. As described in Chapter 2, trachoma clusters by household and antibiotics could be targeted to infected households. However, the potential impact of more efficient, targeted treatment of infected households depends on the relative contribution of community and household transmission of infection, which have not previously been estimated. The effectiveness of using active disease at the household level to identify infected households also remains to be estimated. Children are also believed to be a reservoir of infection and could be an alternative treatment target group.

Transmission between members of the same household is considered important for many infectious diseases. For some of these infections, such as influenza, understanding the contribution of transmission that occurs between household members has been crucial for planning interventions (this has been achieved using household mathematical models of the
transmission of infection). Household mathematical models of infection in their simplest form allow individuals to be infected by members of their own household or by members of their community at two different rates and either assume that when individuals recover from infection they are either protected from re-infection or are susceptible to re-infection. The majority of mathematical models used to understand transmission patterns or infer the potential effectiveness of household interventions to control infection, have focused on infections which result in a protective immune response. Although the mathematical behaviour of household models of infections without a protective immune response have been analysed, transmission parameters have not been estimated nor the resulting transmission implications examined.

Objectives
The work of this thesis aims to understand key factors affecting the transmission dynamics of trachoma and to use these to maximise the effectiveness of treatment strategies for the control of trachoma. The specific objectives are to:

- Estimate the contribution of transmission between members of the same household and that between households of the same population to the incidence of ocular C. *trachomatis* infection using cross-sectional data on the prevalence of infection from four endemic communities, two in West Africa (The Gambia) and two in East Africa (Tanzania) with and without accounting for differences in transmission by age
- Understand the implications of household transmission for the transmission dynamics of ocular C. *trachomatis*
- Investigate whether antibiotics can effectively be targeted to households with at least one member with active trachoma or to children only for the prevention of ocular chlamydial infection
- Calculate the cost-effectiveness of targeted household treatment compared with Mass Drug Administration (MDA) using available cost data
- Discuss the implications of the findings with respect to trachoma control, the limitations of the work and how the work can be extended in the future
Outline of thesis

Chapter 2 gives the background to trachoma, how it is caused and the current control effort. Chapter 3 describes the importance of household transmission for infectious diseases in general; the principles of a household model of transmission which assumes no protective immune response against re-infection; extensions to the model such as age-structure; and the methodology used in this work to estimate transmission parameters. Chapter 4 describes the four data sets to which the models are fitted to estimate the contribution of household transmission, and explores the possibility of household targeted intervention. In Chapter 5 the estimates of household and community transmission are presented and the implications of household transmission for transmission dynamics of trachoma are explored in Chapter 6. The effectiveness of targeted treatment of antibiotics to diseased households compared with the current control strategy of mass treatment in controlling infection is investigated in Chapter 7, and the cost-effectiveness of each strategy is estimated in Chapter 8. Finally the findings of this work are discussed in Chapter 9 in relation to future work.

I declare that the work presented in this thesis is of my own and that I have acknowledged the work of others where relevant.
CHAPTER 2 BACKGROUND TO TRACHOMA

The first section of this chapter gives an overview of the causative pathogen of trachoma, how the pathogen is believed to be transmitted, the immune response towards infection and the different disease stages of trachoma. The second section reviews the global burden and distribution of trachoma, the current trachoma control programmes and the strategies used for the control. The third section reviews previous mathematical models of trachoma.
Ocular infection and disease

Aetiology
The causative organism of trachoma is *Chlamydia trachomatis* (Chlamydiae: Chlamydiaceae); an obligate intracellular gram-negative, bacterial pathogen. There are nineteen serovars of the bacteria (antigenically distinct members of a species) but not all serovars cause trachoma as they each have different tissue tropisms. Ocular infection occurs with serovars A, B, Ba and C resulting in trachoma, whereas genital infection occurs with serovars D-K resulting in pelvic inflammatory disease and infertility [3]. Serovars A-K infect epithelial cells and are non-invasive whereas serovars L1, L2, L2a and L3 are invasive and cause the sexually transmitted disease known as lymphogranuloma venereum [3]. Genital-serovar ocular infection is self-limiting in adults and causes neonatal conjunctivitis in infants.

There are two bacterial states during the development cycle of *C. trachomatis*: elementary bodies and reticulate bodies. Elementary bodies are relatively small, metabolically inactive and extra-cellular. It is this state which infects new cells of the host or cells of a new host. Reticulate bodies are larger, metabolically active and intracellular and replicate within the host cell before transforming back to elementary bodies which are released to infect new cells. In cell culture the development cycle has been shown to occur within 42 to 72 hours [4]. A diagram of the development cycle is given in Figure 2-1.

A recently published study suggests that two other Chlamydiaceae species, *Chlamydia psittaci* and *Chlamydia pneumonia* may also cause trachoma [5] but this is only in one setting and needs to be investigated further in more trachoma endemic communities.
Genetic Diversity of C. trachomatis

Diversity of C. trachomatis has been traditionally characterised by changes in the Major Outer Membrane Protein (MOMP), encoded by the omp-A gene. MOMP accounts for 60% outer cell protein [7] (therefore it is likely to be exposed to the host’s immune system) and has four variable regions [8]. The different strains are defined by serovars and genovars. Originally the serovars were determined by antibody assays but more recently sequence motifs of the gene have been characterised. Genovars are defined as strains within a serovar that differ by one nucleotide substitution and are determined by sequencing [9].
Importance of genetic diversity of ocular *C. trachomatis*

A study which compared sequences from sixteen serovars (both genital and ocular) found 27.7% of the nucleotide sites of *omp*-A to be polymorphic, a degree of variability which is relatively high in comparison to that of house-keeping genes (for which 0 - 2% sites are polymorphic) [10], but the ratio of synonymous to non-synonymous substitution rate was shown to be 4.2 times higher, suggesting selection is conserving the phenotype. There is little current evidence for a large degree of genetic diversity in ocular Chlamydia. Three different studies [9,11,12] (of which one uses data from genital serovars) found evidence for purifying selection *i.e.* that new *omp*-A mutations are eliminated from the population of genovars. However two other studies which only compared nucleotide substitutions in trachoma serovars from cross-sectional data found over 80% of nucleotide substitutions resulted in amino acid change [13,14]. Although one study in Western Nepal suggests that genetic diversity increases with prevalence [15], four studies with varying levels of prevalence all have demonstrated that serovar A is far more prevalent than the B serovar and that within the serovars, one genovar dominates (Table 2-1) [9,11,13,16]. It is also uncommon for serovars A and C to be found in the same geographic region [9,11,13,15,16,17].

<table>
<thead>
<tr>
<th>Features of the study, country, and Reference</th>
<th>Proportion of dominant serovar</th>
<th>Proportion of dominant genovar</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 children Kongwa District, Tanzania [11]</td>
<td>0.77</td>
<td>0.50</td>
</tr>
<tr>
<td>Two villages, Egypt [13]</td>
<td>0.59</td>
<td>0.51</td>
</tr>
<tr>
<td>Two villages, The Gambia [16]</td>
<td>0.80</td>
<td>0.70</td>
</tr>
<tr>
<td>14 villages, Upper Saloum District, The Gambia [9]</td>
<td>0.87</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Table 2-1 Proportion of ocular *Chlamydia trachomatis* isolates which are the dominant serovar or genovar in four communities in which strains were identified.
Therefore although there is genetic diversity of \textit{omp-A} within the species of \textit{C. trachomatis}, there is limited diversity of \textit{C. trachomatis} in trachoma endemic regions when \textit{omp-A} is used as a marker of diversity. The role of the different serovars and genovars remains unclear. Phylogenetic analysis of \textit{omp-A} does not group the serovars by tissue tropism [10,18]. Andreasen and colleagues [9] found that there may be a difference between the two most dominant genovars with respect to virulence in their study site in The Gambia: genovar A1 was shown to be associated with clinical signs of active disease and have a relatively higher mean bacterial load whereas genovar A2 was more abundant (13% genovar A1 and 74% A2 of isolates at baseline) with a lower bacterial load. Individuals can be continuously re-infected with the same genovars [11,13,19] and multitypic infection has been shown to occur [11,19] but it remains unclear whether different serovars and genovars are independently transmitted from one another and whether the duration of infection differs between strains. As described above, genovars are defined as strains which differ by one nucleotide substitution. The studies which test for the presence of different genovars are mostly cross-sectional and do not consider whether each new genovar is a transient mutation or whether the genovar is viable and will be transmitted successfully.

Since the recent sequencing of the \textit{C. trachomatis} genome, ‘polymorphic membrane proteins’ (PmpA -> Pmpl) are also considered to be important surface-exposed proteins [20] which may interact with the immune system. Although this gene family has been shown to be a potential mechanism for antigenic variation in genital \textit{Chlamydia} [21], this has not been investigated in ocular chlamydial infections.

Natural history of disease: Active trachoma through to blinding trachoma

\textit{Active trachoma}

Ocular infection with \textit{C. trachomatis} leads to the development of conjunctivitis which on initial infection is likely to be self-limiting but on repeat infection may be manifest, according to the World Health Organization (WHO) simplified grading system [22], as: Trachomatous Inflammation – Follicular (TF) and/or Trachomatous Inflammation – Intense (TI) (Table 2-2). The presence of either or both of these two signs is referred to as ‘active disease’ or ‘active trachoma’. TF is considered a unique sign of current or recent infection with ocular \textit{C. trachomatis} whilst infection with other ocular pathogens can also lead to
signs of TI [23]. TF is defined as ‘the presence of five or more follicles at least 0.5 mm in diameter in the central part of the upper tarsal conjunctiva’ and TI is defined as ‘pronounced inflammatory thickening of the upper tarsal conjunctiva obscuring more than half the normal deep tarsal vessels’. The prevalence of active disease has been shown to peak in younger children and decline into adulthood [24,25,26].

Active disease is a poor marker of infection. A study of a Gambian cohort with frequent follow-up [27] has estimated the median incubation period to be 17 days and that active disease persists in individuals 4-5 weeks after infection is cleared. Michel and colleagues estimated the sensitivity of TF as a marker of infection to be 64% and the specificity to be 80% [28]. Field studies often record large differences between the prevalence of active disease and the prevalence of infection. *C. trachomatis* was not detected in ocular swabs taken from children aged 1-10 years old in a community in Nepal where the prevalence of active disease in that age group was 6% [29]. Comparable to this, a study in The Gambia found the overall prevalence of infection among children under 10 years of age in two regions to be 0.3% based on qualitative PCR testing of conjunctival swabs, whereas the prevalence of active disease in this age group was 10% [30]. After two rounds of mass treatment with azithromycin in a Tanzanian community, local elimination of infection occurred within five years after the first treatment with a sharp decline in infection in the first year whereas active disease remained after five years and decreased in prevalence much more steadily [31]. A review by Solomon and colleagues documents fifty studies which also provide evidence for the mismatch between disease and infection [32].

Across all ages, Grassly and colleagues found that the median duration of active disease is 21 weeks whilst the median duration of infection is 17 weeks [27]. However in this study the duration of infection was shown to be age dependent: the median durations of infection in 0-4 year olds, 5-14 year olds and ≥ 15 years old were estimated to be 15.4 weeks, 8.2 weeks and 7.6 weeks respectively.

**Chronic trachoma**

Although inflammation clears infection through an immune response, it leads to the development of a collagenous scar on the conjunctiva, known as Trachomatous Scarring (TS). Progression to severe scarring over many years, from multiple episodes of re-infection
and inflammation, results in the contraction of the upper eyelid which in turn causes the eyelashes to rub against the cornea, a phenomenon known as Trachomatous Trichiasis (TT). Continuous contact of the lashes with the cornea results in trauma and scarring which leads to blindness through the development of corneal opacity (CO) [33]. The manifestation of CO from TT is believed to be independent from further ocular C. trachomatis infection. TS, TT and CO are all permanent sequelae which are not associated with current or recent ocular chlamydial infection.

The prevalence of later chronic stages of trachoma increases with age. The prevalence of TT is approximately 2-10% in people mostly over the age of 15 [34,35,36] although in areas which have had extremely high rates of transmission TT can be found in children aged under 15 years old [37,38]. CO generally occurs in a small percentage of people (approximately 1-2%) [39,40]. Due to multiple re-infections causing disease progression, communities with relatively high active disease prevalence, which have not received prior intervention, are associated with relatively high chronic trachoma sequelae [35,37]. All stages of trachoma are higher in adult women compared to men [24,37,39,41,42]. This phenomenon is thought to occur because of the frequent exposure women have to children compared to men.

The disease stages TF, TI, TS, TT and CO constitute the five stages of the simplified grading system which was developed by the WHO to classify the stages of trachoma disease that can be identified easily in field settings [22] (Table 2-2). A more detailed classification of disease stages exists for research purposes [43].
<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal eye</td>
<td></td>
</tr>
<tr>
<td>Trachomatous inflammation – follicular (TF)</td>
<td>The presence of five or more follicles in the upper tarsal conjunctiva</td>
</tr>
<tr>
<td>Trachomatous inflammation – intense (TI)</td>
<td>Pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep tarsal vessels</td>
</tr>
<tr>
<td>Trachomatous scarring (TS)</td>
<td>The presence of scarring in the tarsal conjunctiva</td>
</tr>
<tr>
<td>Trachomatous trichiasis (TT)</td>
<td>At least one eyelash rubs on the eyeball</td>
</tr>
<tr>
<td>Corneal opacity (CO)</td>
<td>Easily visible corneal opacity over the pupil</td>
</tr>
</tbody>
</table>

Table 2-2 Pictures and description of each stage of the simplified grading system (adapted from [22]).
Detection of ocular *C. trachomatis* Infection

**Laboratory detection**

There is no gold standard laboratory test for the detection of ocular *C. trachomatis* [32]. Cell culture is considered to be 100% specific but is not 100% sensitive [44,45]. Other previous lab methodologies have included: microscopy with Giemsa staining, microscopy with immunofluorescence and enzyme immuno-assays but these all lack sensitivity [32]. Current scientific research studies use nucleic acid amplification tests to identify infected individuals. Qualitative Polymerase Chain Reaction (PCR) is the most widely method used, detecting a target sequence of the common cryptic plasmid of *C. trachomatis*, and is considered to be highly sensitive and specific. Quantitative PCR, which targets the *omp*-A gene on the bacterial chromosome, is less sensitive than qualitative PCR [46,47] since each bacterium has numerous cryptic plasmids per cell but only one chromosome; however, quantitative PCR is useful for estimating the distribution of bacterial load (the number of bacteria a person is infected with) among a population [48].

An alternative nucleic acid amplification test targets 16S rRNA which is expressed at relatively high levels in metabolically active replicating *Chlamydia* bacteria. Using a ‘home-brew’ kit to test for 16S rRNA, Burton and colleagues [49] found this test to be less sensitive than PCR amplification of *omp1* in 248 individuals from The Gambia. Conversely, two studies in Ethiopia [50,51] which tested for the presence of infection in 56 and 240 children respectively found 63% and 59% to be positive for infection using a commercially available rRNA based test compared to 39% and 28% found to be positive by PCR amplification of the cryptic plasmid. A contributing reason to explain the difference between The Gambian and Ethiopian studies is the different type of rRNA amplification methods used (home-brew versus commercial) in the two studies. Although there has been much more work on genital *Chlamydia*, indicating that the commercial rRNA amplification test has increased sensitivity and comparable specificity compared to PCR amplification of the cryptic plasmid, there needs to be further work to understand how these two tests differ in different trachoma endemic settings and what the epidemiological importance is of the reservoir of bacteria which are solely detected by rRNA tests.
Care has to be taken with all nucleic acid amplification tests as contamination occurs easily due to the test’s ability to detect very small levels of DNA. Therefore strict methods are carried out, such as changing gloves between obtaining each ocular swab, as a precaution to avoid contamination.

**Detection in the Field**

Nucleic acid amplification tests are not appropriate methods to test for the presence of infection for trachoma control programmes because the equipment is very expensive and not suitable for field settings. Instead, programmes rely on the presence of active disease, but, as explained earlier, this is a poor marker of infection. The only equipment required to diagnose active disease is a binocular loupe, aside from an optional pen-torch, and is therefore much cheaper for control programmes as it only requires trained personnel. The diagnosis could therefore be considered to be subjective but inter-observer agreement is normally tested in programme settings [23] and is generally high. A dipstick assay for rapid diagnosis of the presence of infection is currently being developed [28] but it is not yet available in an affordable or satisfactory format.

**Transmission of ocular C. trachomatis**

The bacteria are spread from one eye to another eye either by ‘fingers’ (i.e. an infected individual touches their eye, subsequently shakes hands with another individual who then touches their own eye), ‘fomites’ (e.g. a communal towel which is used from face to face) or eye-seeking flies (mechanical vectors). *Musca sorbens* (Diptera: Muscidae), the fly most commonly associated with the transmission of trachoma [52], breeds in human faeces and a lack of latrines has been shown to be associated with an increased risk of trachoma [53]. A study that caught flies leaving the faces of children in Ethiopia found 15% of them to be positive for ocular *C. trachomatis* [54]. Individuals with ocular discharge have been observed to have twice as many flies on their eyes as individuals without ocular discharge [52]. Two studies [55,56] in The Gambia found that communities that received three months and six months (respectively) of insecticide spraying had 75% and 55% fewer new cases of active trachoma respectively compared to communities with similar baseline prevalence that did not receive the intervention. However, another study found insecticide spraying did not improve trachoma control in addition to the distribution of antibiotics [57]. All three studies
reported significant large reductions in the fly population. Individuals with unclean faces are at an increased risk of active disease [58,59,60], although implementing face-washing alone has a moderate effect on reducing transmission [61]. Apart from the insecticide intervention studies, the relative contribution towards transmission of the different transmission routes has yet to be investigated in different geographic settings.

Definitions of endemicity levels

There are commonly three categories used to describe the endemicity of trachoma in a population: hypoendemic, mesoendemic and hyperendemic. The categories are based on the prevalence of active disease in a community. There are not strict thresholds for each category but generally hypoendemic is used to describe a population where the endemic prevalence of active disease is below 10%; a mesoendemic population has an endemic prevalence of active disease between 10% and 20% and a hyperendemic community has an endemic prevalence of active disease greater than 20% [62].

Heterogeneities of transmission

Age and sex

Children are considered to be the principal reservoir and source of infection in most communities. In most communities the prevalence of active disease has been shown to peak in younger children and decline into adulthood [24,25,26]. Schachter and colleagues [63] found that children were more likely to be re-infected after MDA with azithromycin compared to those older than 10 years. Children in two communities in Tanzania, one hyperendemic and the other mesoendemic, were shown to have higher bacterial loads than older individuals (90% of the chlamydial DNA isolated in both communities was from children younger than nine years-old) although this relationship did not hold for a hypoendemic community in The Gambia [48]. Re-analysis of a Gambian cohort with frequent follow-up has estimated the average duration of infection to be longer in children than in adults, contributing to the higher prevalence of infection among children in this community [27].

In general active disease and the prevalence of infection does not differ between male and female children, an exception being in Kongwa district in Tanzania in which 70% of children
with active disease were female [48]. However, the chronic sequelae occur more frequently in women (described earlier) suggesting they contribute more towards transmission over their lifetime due to the close contact they have with children [64].

Households
Clustering of active trachoma by household has been shown to occur in communities in Malawi [65], The Gambia [53,66], Tanzania [67] and Egypt [68]. In The Gambia, household clustering of *C. trachomatis* infection was also demonstrated. Further to this, it has been shown that individuals living with people who have active trachoma are more likely to have active disease than individuals who live with people without active disease [30,53,69,70]. Although these studies have been important in demonstrating that infection and disease cluster by household, or that sharing a house with an individual with active disease is a statistically significant risk factor for developing active trachoma, none of them have measured the amount of transmission that takes place within the household compared to the transmission that occurs between households. This is of obvious importance for understanding the dynamics of infection and implementing cost-effective control measures. In villages where within-household transmission is most important, a few households may account for most of the infection, and although prevalence may be low, persistence of infection can result from frequent re-infection of household members if not targeted for treatment.

Seasonality
There is evidence to show that signs of active trachoma may be strongly seasonal in some areas [71,72,73]. However, no studies have investigated directly whether the transmission of ocular *Chlamydia* infection is seasonal and inference directly from the active trachoma data has to be made with caution due to other seasonal ocular pathogens which can cause conjunctival inflammation [73,74]. The pattern of seasonal active trachoma differs by geographical community. In Nepal, active trachoma is higher in the wet season [72] but in Morocco it has been shown to be higher in the dry season [73]. It is plausible that transmission of ocular chlamydial infection is seasonal as the population dynamics of the mechanical fly vector has been shown to be seasonal and correlates with changes in active
trachoma prevalence [52,75]. Face-washing can reduce transmission [61] and the seasonal availability of water may also govern transmission.

Lee and colleagues [76] have developed a deterministic and stochastic model of seasonal trachoma transmission. Using this model they have inferred that there is a higher chance of eliminating infection when treatment is administered just before the trough of the low transmission season than at the peak of the high transmission season. Another analysis [77] however has indicated that treating with respect to seasonality is important only when the population size is large.

Other risk factors
Other factors which may influence the transmission of ocular chlamydia are altitude, cattle ownership and water hygiene practices. Prevalence of active trachoma has been shown to be associated with: low altitude [78] and this may be linked to abundance of *M. sorbens* [75] and cattle ownership [59,69,79] (cattle faeces provide breeding sites for *M. sorbens* flies [80]). There is contradictory evidence as to how water availability is related to the risk of having active trachoma. A larger distance to the water source has been shown to be associated with higher levels of active trachoma [81,82] but no association between the two has also been shown [30,83] and also a decreased risk of active trachoma has been found [40]. There is also mixed evidence as to whether the amount of water brought into the household is associated with active trachoma [81,84,85]. The conflicting findings are likely to arise due to the complex relationship between socio-economic standards of living, proximity to water and water practices.

Immunity towards infection and immune-pathogenesis
The immunity elicited from infection with *C. trachomatis* contributes both towards clearance of the infection and pathogenesis.

Infection
The immune response towards ocular *Chlamydia* infection is only partially effective. There is evidence for some acquired immunity: the average duration of infection and the bacterial load decrease with host age [27,48], whilst the inflammatory cytokine profile increases with
age [86]. However individuals are repeatedly infected [27,69,87] indicating that the immune response developed does not protect against re-infection. Infection is associated with the up-regulation of pro-inflammatory cytokines which elicit humoral and cell-mediated immune responses [3,88,89]. Although anti-chlamydial antibodies are produced, it is the cell-mediated response which is believed to be necessary for infection to be cleared [90].

Interferon-γ (IFN-γ) is a cytokine which is part of the pro-inflammatory response. As well as its immunomodulatory effects, the cytokine degrades the amino-acid tryptophan which is essential for bacterial growth. A study by Caldwell and colleagues demonstrates that genital serovars of *Chlamydia* evade this immune response by encoding a gene for an enzyme which synthesises tryptophan from a substrate, indole [91]. The authors suggest that this may provide a mechanism for persistent infection of genital serovars (persistent infection of genital serovars is loosely defined in the literature [92] but corresponds to an infection episode lasting longer than one year [93]). Ocular *Chlamydia* serovars lack the respective gene to synthesise tryptophan and therefore persistent infection by this method of immune evasion is not possible [91].

There is no conclusive evidence for persistent ocular *Chlamydia* infection. Some studies have found that some individuals in a community have active disease [94,95], or the same ocular serovar [96] at two survey time points and conclude these individuals could be persistently infected. However, the difference between two time points in one of the studies [95] was shorter than the recently estimated durations of infection and disease, and re-infection could have occurred in the other two studies [94,96] especially in the latter in which the two time points were three years apart. Another study [69] recorded active disease in children at four time points over a year and found 10% of children to have active disease every time, but again re-infection could have occurred. A study by Bobo and colleagues [19] tested children on a weekly basis for infection for three months and found 9 out of 53 children to be continuously infected. A further 9 children were found to have only a one week gap before re-infection which could have been a false negative due to the low sensitivity of the Ligase Chain Reaction Test (LCR) used to detect infection. However the observational time period was shorter than the estimated duration of infection. In the frequent follow-up study in The Gambia, which was used to estimate the duration of
infection by age [27], there were no individuals found to be constantly infected over the 6 month duration of the study.

If households are persistently infected once infection is introduced to a household, due to a high force of infection within the household, individuals will be re-infected more than other individuals in the community whose household does not have an infected member. Understanding the role of household transmission in trachoma endemic areas will help to comprehend how the observed persistent infection in individual people arises.

**Disease**

As well as eventually clearing infection, the elicited inflammatory immune response also leads to the progression of active disease (through the appearance of inflamed lymphoid follicles). Active disease is associated with pro-inflammatory cytokines even in the absence of infection [97]. The development of TS is thought to arise from repeat episodes of active disease through fibrogenic pathways [98].

Heterogeneous immune responses have been shown to occur within communities which result in different rates of chronic disease sequelae progression. These heterogeneities have been characterised by polymorphisms in genes encoding the inflammatory cytokines: Interleukin-10 [99], Tumour Necrosis Factor-α [100,101] and IFN-γ [102]; and in the Human Leukocyte Antigen which present pathogenic antigens and peptides to immune cells [103,104,105].

**Vaccine Development**

There is no effective vaccine to protect against ocular *Chlamydia* infection. Candidate vaccines were trialled twenty to forty years ago but were not successful because the resulting protection against infection was short-lived (less than a year) and in some of the studies the people who received the vaccine and subsequently challenged were hyper-sensitised, having more severe active trachoma than individuals who had not been vaccinated [106,107,108,109].
Global burden of trachoma and current trachoma control effort

Global burden
Trachoma continues to be the leading infectious cause of blindness worldwide [1]. Today the majority of affected populations are in developing countries [2], in areas where people cannot afford treatment, but until the early 20th century it was endemic in many regions of Europe and the United States of America [110,111,112]. It was recently estimated that 40.6 million people have active trachoma in 57 endemic communities and that approximately 50% of the active trachoma burden occurs in Ethiopia, India, Nigeria, Sudan and Guinea [2] (this is a large reduction compared with the estimate obtained in 2003 of 84 million people [113]). Trichiasis was estimated to occur in 8.2 million with 50% of the burden in China, Ethiopia and Sudan. However the authors comment that these estimates may have a large error due to the variation in methodologies used to obtain estimates in each country: Population-based surveys were carried out in some countries but with minimal coverage in some areas and projections were made for countries for which there were not enough data. China and India have the largest populations and the estimates of trachoma in these countries are therefore influential in the final estimate. A recent study in India found that a rural area considered to be hyperendemic for trachoma only had one village with the prevalence of TF above 10% in children [114]. Another caveat to the estimate of the global burden of trachoma is that it was calculated from prevalence estimates of countries considered to be endemic by the WHO. Burundi is not considered to be endemic for trachoma by the WHO but a recent prevalence survey identified relatively high levels of active disease in 1-9 year old children (Personal communication, Dr Marie-Alice Deville NTD Programme Manager for Burundi, Schistosomiasis Control Initiative). The most recent estimate of the number of people with blinding trachoma is 1.3 million made in 2002 [1]. Figure 2-2 is a map illustrating the trachoma endemic countries but it is important to consider that trachoma is not widespread throughout each endemic country but is focally distributed.
Visual impairment from trachoma can have a large impact on individuals’ lives including their mobility, psychological and social well being, finance and their mortality [115]. In 2004 the global burden of trachoma was estimated to be 1.3 million Disability Adjusted Life Years (DALYs) annually (as a comparison the burden of HIV was estimated to be 58.5 million DALYs) [116]. Burton and Mabey [115] report there are limitations to the trachoma DALY estimate as the population surveys which estimate the prevalence are not robust, the disability of having trichiasis was not included and it is not known how much blinding trachoma increases mortality (there is evidence that blindness increases mortality in rural communities in sub-Saharan Africa [117,118]).

**GET 2020 & SAFE strategy**

In 1996, a WHO - Alliance (a partnership of Member States, Non-governmental Development Organizations, Research Institutions, Philanthropic Foundations, and Industry) proposed the Global Elimination of blinding Trachoma by 2020 (GET 2020) [119] and the goal was made a resolution in the World Health Assembly, encouraging member states to work together with the alliance to achieve the target. The focus of the goal is to eliminate the blinding sequelae, not ocular *Chlamydia* infection, although infection will have to be largely reduced for the elimination of blinding sequelae to be sustained in the long term. For
a country to achieve elimination of blinding trachoma, a number of criteria have to be fulfilled: the prevalence of active disease in children aged 1-9 years must remain below 5% for three years; the prevalence of TT must be less than 1% and the prevalence of CO must remain below 0.01% [120]. Morocco was the first country to have achieved this since GET 2020 was established and the International Trachoma Initiative (ITI) predicts Ghana, Saudi Arabia and Mexico will achieve these goals by the end of 2010 [121].

The GET 2020 alliance advocates the ‘SAFE’ strategy (Surgery for trichiasis, distribution of Antibiotics, Facial cleanliness and Environmental improvements) for endemic countries to achieve their goal. The latter three components are directed at interrupting transmission. Each component is explained below. Before a control programme is commenced district and/or community prevalence estimates of TF and TT are obtained through cluster random sampling mapping [23].

_Surgery_

The in-turned eye lashes of trichiasis which scratch the cornea can be reversed by surgery, therefore preventing the development of later sequelae. The WHO recommends the ‘bilamellar tarsal rotation’ procedure [23] which can be carried out either by ophthalmic surgeons or nurses with comparable effectiveness [122]. The WHO advises surgery to be offered at health centres and at the community level, depending on the resources of the setting. However providing surgery at the community has been shown to have a higher uptake [123]. Recurrence of trichiasis after surgery does occur and the rate depends on the quality of the procedure and the level of trachoma endemicity. One study found 10% of individuals with recurrent trichiasis three months after surgery [122] and another found 60% of individuals three years after surgeries were performed [124]. The rate of recurrent trichiasis has been shown to be reduced if the antibiotic azithromycin is administered after surgery [125]. Evaluation of the full SAFE strategy three years after it commenced in five districts of the Amhara State in Ethiopia found that the reduction in prevalence of trichiasis is variable but large reductions are associated with a high coverage of surgeries [126].

_Antibiotics_

If the infection burden of ocular _Chlamydia_ is reduced then, in theory, individuals should have fewer episodes of active trachoma and therefore the blinding chronic disease sequelae
should be reduced in the long term, although there have been no longitudinal studies to test this.

Antibiotics recommended for trachoma control
There are two antibiotics recommended by the WHO to treat ocular Chlamydia infection: 1% tetracycline eye ointment which is applied twice a day for 6 weeks or a single oral dose of azithromycin (20mg/kg, with a maximum dose of 1g). The two antibiotics have been shown to have a similar efficacy in a research setting for clearing infection [127]. However, in an operational setting, tetracycline is much less effective in resolving active disease (prevalence of active disease 10 weeks after treatment was reduced by 51% in individuals assigned to the tetracycline arm of the study whilst it decreased by 68% in individuals in the azithromycin arm) [128] and this is attributed to the daily requirement of topical application for six weeks which can result in poor compliance. Azithromycin is therefore the preferred antibiotic of choice for control programmes [23]. A study in Tanzania, The Gambia and Egypt, which compared the change in prevalence of ocular Chlamydia in villages that received tetracycline with those that received azithromycin at the same time point, estimated azithromycin to be 95% efficacious in clearing infection whereas topical tetracycline was estimated to be 82% efficacious [63]. However, there has not been a clinical trial comparing azithromycin and placebo to determine the true efficacy of azithromycin as it is unethical to deny treatment when an alternative drug is available. There is no evidence to show azithromycin is harmful for pregnant women but it is not licensed for use during pregnancy [3]. The WHO recommends excluding infants younger than six months from receiving azithromycin and recommends tetracycline ointment to be given instead [23].

WHO guidelines for antibiotic distribution
The WHO recommends annual district-wide mass drug administration (MDA) of antibiotics for at least three years to members of districts in which the prevalence of TF in 1-9 year-olds is 10% or greater [23], along with the other three components of the SAFE strategy. After three years if the prevalence of TF in 1-9 year olds has not been reduced below 10% further rounds of MDA are advised. If the prevalence of TF in 1-9 year olds is below the 10% after three years, community prevalence surveys are advocated and if the prevalence of TF is
below 5% MDA is not required but above 5% annual MDA is required to bring the prevalence below 5%. At baseline if the district prevalence of TF is below 10% in 1-9 year olds, MDA is advised in communities within the district that have a prevalence of TF above 10% and the criteria followed as for districts to bring the prevalence of TF below 5% in the communities. For the communities with baseline prevalence of TF between 5% and 10% in 1-9 year olds the ‘F’ and ‘E’ components of the SAFE strategy are recommended with a reassessment of prevalence after three years. Communities with prevalence of TF below 5% in 1-9 years old ‘A’, ‘F’ and ‘E’ are not warranted [23].

Although the WHO recommends three annual rounds of MDA, with reassessment and possibly further annual rounds, the optimal frequency of MDA for different endemic settings remains to be elucidated. Some studies have investigated the possibility of eliminating infection with different frequencies and durations of MDA by following up the temporal dynamics of infection in populations following a baseline evaluation of the populations (summarised in Table 2-3). The conclusion drawn from these studies is that the WHO guidelines for MDA are not sufficient for control or elimination of infection in hyperendemic communities (those with prevalence of infection in 1-5 year olds above 30%) and that biannual treatment is a more appropriate strategy, although the response can be highly variable between villages. One round of MDA was not sufficient to control infection in any of the endemic settings. These findings concur with the predictions of a mathematical model [129](reviewed later in this chapter), which found that the WHO guidelines for frequency of MDA are likely to be adequate for communities with prevalence of infection < 35% but biannual MDA is better suited for communities with a prevalence above 50%. In the communities where infection was not eliminated, re-emergence of infection was rapid. Elimination of infection is not a goal of GET2020, but it should be controlled to a level (below 5%) at which individuals are not likely to develop blinding sequelae. However, the rapid re-emergence of infection illustrated by these studies highlights the importance of implementing the ‘F’ and ‘E’ components of the SAFE strategy to sustain the interruption of transmission.
<table>
<thead>
<tr>
<th>Community, country, reference</th>
<th>No. MDAs rounds</th>
<th>Baseline prevalence of Infection</th>
<th>End of follow-up time</th>
<th>Prevalence of infection at end of follow-up</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Saloum district, The Gambia [130]</td>
<td>1</td>
<td>7.2% (whole population)</td>
<td>17 months</td>
<td>2% [1.5 – 3.3]</td>
<td>Infection thought to be re-introduced into the community from members travelling to and returning from Senegal</td>
</tr>
<tr>
<td>Kahe Mpya sub-village, Tanzania [31,131]</td>
<td>2 (second after two years)</td>
<td>9.5% (whole population)</td>
<td>5 years</td>
<td>0%</td>
<td>Topical tetracycline ointment was given to individuals with active disease at follow up time points</td>
</tr>
<tr>
<td>Maindi village, Tanzania [70,132]</td>
<td>2 (second after 1.5 years)</td>
<td>57.0% (64.8% in 0-16 year-olds)</td>
<td>5 years</td>
<td>23.9% in 0-16 year-olds</td>
<td>Data at baseline thought to be unreliable due to PCR contamination</td>
</tr>
<tr>
<td>24 villages, Gurage Zone, Ethiopia [133]</td>
<td>1</td>
<td>56.3% in children 1-5 years old</td>
<td>6 months</td>
<td>11% in children 1-5 years old</td>
<td>Infection returned at an exponential rate of 12.3% per month</td>
</tr>
<tr>
<td>8 villages, Enemore/Ener district of the Gurage Zone, Ethiopia [134]</td>
<td>1</td>
<td>43.5% in 1-5 years old</td>
<td>2 years</td>
<td>11.3% in 1-5 years old</td>
<td>Twelve months after the MDA the prevalence of infection in 1-5 year olds was recorded in 15 villages which did not receive MDA as a control. The mean prevalence in these villages was 17.2% which is higher than the prevalence in the villages which received MDA at 12 months (6.7%).</td>
</tr>
<tr>
<td>16 villages, Goro district of the Gurage Zone, Ethiopia [135]</td>
<td>8 villages received two annual rounds and 8 villages received four biannual rounds</td>
<td>Annual treatment villages: 42.6% in 1-5 year olds Biannual treatment villages: 31.6% in 1-5 year olds</td>
<td>2 years</td>
<td>Annual treatment villages: 6.8% in 1-5 year olds (1 village had no infection) Biannual treatment villages: 0.9% in 1-5 year olds (6 villages had no infection)</td>
<td>3 of the 8 villages which received biannual treatment were followed up at 30 months. Prevalence of infection was assessed in the whole population and infection was eliminated in 1 village and in the other 2 villages; one and three individuals were infected [136]. Two of the biannual treatment villages with the highest baseline prevalence (48.3% &amp; 48.9%) received two further biannual MDA rounds and 42 months after baseline there was no infection in both villages [137].</td>
</tr>
<tr>
<td>16 villages, Enemore district of the Gurage zone, Ethiopia [138]</td>
<td>4 biannual rounds</td>
<td>63.5% in 1-5 year olds</td>
<td>3.5 years</td>
<td>2.6% in 1-5 year olds 6 months after the last round of MDA and 25.2% in 1-5 year olds at the end of follow-up</td>
<td>Collective analysis [139] of [133,134,135,138] (at 2 and 6 months after one MDA) indicates that coverage is a short term predictor of prevalence of ocular Chlamydia infection (2 months follow-up) whereas baseline endemicity is a short and long term predictor of infection.</td>
</tr>
</tbody>
</table>
Advantages and disadvantages of MDA

MDA is advocated because field-ready diagnostic tests for infection with *C. trachomatis* are currently unavailable and active disease is a poor marker for infection *i.e.* the aim of MDA is to give all members of a community antibiotics regardless of whether they are infected or not. However, not all infected individuals receive treatment because they either refuse or are away working or travelling. The WHO recommends a coverage level of at least 80% [23] though this is often difficult for control programmes to achieve [140]. Azithromycin is a well-tolerated drug [141] and therefore it is safe to administer to individuals even in the absence of infection. A recent study in 48 communities in Ethiopia has shown that another benefit of MDA with azithromycin is that it may decrease the odds of childhood mortality by 50% [142]. Although further work is required to investigate whether the same reduction in mortality can be achieved in different settings, a reduction in mortality is plausible as the antibiotic is effective against many other gram negative bacteria including *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilis influenza* and *Salmonella typhi* [143,144,145] and possibly some bacteria that cause diarrhoea [146], which can all result in mortality if the infections are not treated. Preliminary studies suggest there is some evidence to indicate the antibiotic may have anti-malarial effects [147,148,149,150,151]. However rigorous field trails are required to elucidate the anti-malarial effectiveness in different endemic settings.

There are two main disadvantages to MDA: it can be costly and may increase the chances of antibiotic resistant bacteria emerging. Providing antibiotics to the population of a district (or community depending on the endemicity level) annually for at least three years is extremely expensive, even when using the generic drug [152,153]. The burden of this cost has partially been alleviated by the donation of Zithromax® (Pfizer’s brand name for azithromycin) by Pfizer. The pharmaceutical company has already donated 145 million treatments in 18 countries. However, it is not known whether the donation is time-limited and there are over thirty remaining trachoma endemic countries that do not receive the donation. Aside from the cost of the antibiotics there are also costs associated with the distribution of the drugs

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Table 2.3 Summary of field studies in West and East Africa which have followed up the temporal changes in prevalence of infection compared to that at baseline after single or multiple MDA rounds with the antibiotic azithromycin

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35
from the central drug storage facility to the relevant districts and communities and the personnel (plus their training) that carry out the MDA campaigns [152,153,154].

The large number of people receiving azithromycin at one time creates a large selective pressure for the development of antibiotic resistant bacteria. Azithromycin-resistant ocular *C. trachomatis* isolates have not been found to date [155,156], but there is concern that resistance may occur in other bacterial species, in particular *S. pneumoniae* in which resistant isolates have been detected after MDA although they do not persist in the community [146,157,158]. However if resistant strains do emerge after MDA there is an argument that the prevalence of resistant isolates may return to baseline levels before the next annual treatment because trachoma-endemic populations do not normally have access to azithromycin aside from trachoma control programmes and there is likely to be a fitness cost associated with the resistant trait [159].

Targeting treatment to infected individuals

An antibiotic distribution approach which targeted treatment to those most likely to be infected and transmit the infection would potentially be much more cost-effective, using fewer doses of azithromycin and would reduce the pressure for the emergence of resistance. Two possible groups to target are infected households and children. Evidence as to why these groupings of individuals are considered core transmission groups is described earlier in this chapter (in the section about heterogeneities in transmission).

House and colleagues [160] investigated the effect of four MDAs with azithromycin at three month intervals to children aged 1-10 in 12 villages in Ethiopia. One year after baseline they found that the mean prevalence of infection in the older untreated age group had decreased by 47% and was statistically significantly lower than the prevalence of infection in the same age group of a comparable 12 villages which had not received any treatment. However implementation of MDA every three months is likely to be intensive for programmes on a country or district scale and it would be useful for the effect of other frequencies of children-targeted MDA to be investigated.

A study in nine villages in Mali [152] compared three distribution strategies: one round of MDA to all community residents; one round of MDA to children only under the age of 11;
and one round of treatment to households that had at least one child with active trachoma. The study found the former two strategies to have similar reductions in the prevalence of active trachoma twelve months later but the household strategy to be less effective (the odds of active trachoma in children one year after household-targeted treatment was found to be 1.56 compared to those which received mass treatment although the 95% confidence intervals include 1 [1-2.43]). Therefore further investigation is required to determine whether household targeted treatment is truly less effective than mass treatment in different endemic settings. The study also calculated the cost-effectiveness of the different strategies and using the cost per at risk person they found, assuming the antibiotics were not donated, household-targeted treatment to be most cost-effective. When repeating the analysis using the cost per person treated household-targeted treatment remained the most cost-effective strategy except in low transmission settings. However these cost analyses do not take into account the number of infections prevented in each strategy.

A study in Nepal [72] compared MDA of children to household targeted treatment of household members of all ages that had at least one child with active disease. The study found the two strategies not to be significantly different from one another in terms of the reduction in point prevalence of active disease six months after treatment or the costs involved [153] although the targeted household strategy used more resources. A study in Vietnam [161] examined dynamics of infection after two rounds of treatment of households that had at least one member aged between 5 and 15 years with active disease. The change in the prevalence of infection over two years after the last round of infection did not differ from a similar community that did not receive antibiotic intervention. However this is not surprising because the study used individuals between the age of 5 and 15 with active trachoma to identify households to receive treatment but by doing this the 0-5 years olds were missed, and this is known to be a key group in the transmission of ocular C. trachomatis.

If a dipstick assay to test individuals for infection in field settings with rapid results (also known as a point-of-care test) were to become available, Ray and colleagues [162] suggest that another method to reduce the total number of antibiotics administered to a community during a control campaign could be to ‘graduate’ communities. They define
graduating communities as ‘a point in time when a community will no longer receive mass antibiotic distributions because of evidence of infection is below a prescribed threshold’. They investigated this strategy using a stochastic mathematical model of transmission (reviewed later in this chapter) which was fitted to data from three populations with different endemicities from Tanzania, The Gambia and Ethiopia. The threshold for graduating communities was 5% and following three rounds of MDA with the graduating strategy their model predicted antibiotic usage to be reduced by 63%, 56% and 11% respectively in the three populations. The final prevalence of infection after the last round of treatment was estimated to be 0.3%, 3.9% and 14.4% compared with 0.03%, 2.4% and 12.9% respectively in communities using MDA without graduation. The model allowed for a constant exogenous infection rate which was fitted to the data. Tanzania had the highest exogenous infection rate, which could explain the difference in effectiveness of controlling infection between the two strategies in that setting (because graduated communities are quickly re-infected). Further work is required to trial this strategy when the dipstick analysis becomes available, along with a costing analysis to investigate in which settings it is more cost effective.

Summary of antibiotics for trachoma control
Azithromycin is the first-line antibiotic recommended for trachoma control by the WHO. At least three annual rounds of MDA is the advocated distribution strategy to communities that have a prevalence of TF greater than 10%, although several studies indicate that this frequency may not be sufficient. MDA can be costly and may increase the likelihood of the emergence of resistant bacteria but targeting treatment to core transmission groups could alleviate these problems. Field trials have demonstrated rapid re-emergence of infection after the final round of treatment and this can also be exacerbated by community members travelling to infected untreated communities and returning, importing infection back to the community [130]. Therefore it is essential that the ‘F’ and ‘E’ components of the SAFE strategy, improving the sanitation and hygiene of the communities, are implemented along with antibiotic distribution.
Facial hygiene

The aim of advocating face-washing is to remove the infectious ocular secretions on individuals’ faces thereby interrupting transmission. A review by Emerson and colleagues [163] list various studies which have found an association between dirty faces and active trachoma. Since the review was written, an association has been found in Southern Sudan [59] and studies in Niger [164] and India [114] also found an association between ocular C. trachomatis infection and individuals with dirty faces. There has been less evidence that people who wash their face more frequently are associated with a reduced risk of active trachoma. Only one study, in Sudan, has reported an association. There has been one intervention trial for face washing [61] in which a moderate effect on reducing transmission was found by face-washing although the authors noted that the trial was labour intensive and sustainable changes in individuals hygiene practices were difficult to achieve.

Environmental Improvement

As described earlier, the fly M. sorbens is believed to be an important mechanical vector of ocular C. trachomatis infection, and it breeds in human and some animal faeces. Part of the ‘E’ component of the SAFE strategy is directed at reducing the fly population to reduce transmission. Pit latrines prevent adult flies emerging from faeces in which the larvae survive and there have been many risk factor analyses that show the use of pit latrines to be associated with a decreased risk of active trachoma [60,163], although this is true only when community members understand the need to use them. However there has only been one randomised control trial to assess the impact of pit latrines on the reduction of active trachoma prevalence. The provision of pit latrines (of which 98% were used) reduced the fly population by 30% relative to the control but the prevalence of active trachoma was only reduced by 1.26% (absolute value) which was statistically non-significant [56]. The baseline active trachoma prevalence was relatively low (6%) and it would be useful for there to be another trial in a hyperendemic area where flies may contribute more to transmission.

Another approach to control the fly population is insecticide spraying but as described earlier, this technique has been found to have mixed results. Animals, such as cattle, could be moved further away from households as the flies also breed in their faeces but this intervention has not been trialled.
‘Environmental improvement’ can also include the provision of clean water, to enable face-washing, and education programmes to help affected communities understand how the disease is caused and how to prevent the spread of infection. Part of a small study in Mali [165] compared the change in active trachoma prevalence over 6 months in one village that received no intervention to one village that received a weekly community education programme informing the women and children of the importance of family hygiene and sanitation and how it can reduce trachoma. The study found the incidence of active trachoma to be reduced by two-thirds in the village which received the education programme compared to the control village. However an education programme is only effective if villages have the facilities, such as latrines, to improve their sanitation [166].

A study in Vietnam [167] in two comparable mesoendemic villages over three years, in which one village received the full SAFE strategy and the other the ‘S’ and ‘A’ components only, found that implementation of the ‘F’ and ‘E’ attributed an additional absolute 6% decline in the prevalence of active trachoma in children under the age of 15. Trachoma disappeared from Europe and the United States of America without MDA, through improvements in hygiene and sanitation. It is unlikely that the current trachoma endemic countries will have huge changes in their hygiene and sanitation in the next decade and so the full SAFE strategy is essential to work towards the GET 2020 goal.

Current Control programmes
Trachoma control has been implemented through highly focused and vertical programmes including those by the International Trachoma Initiative (ITI), which currently facilitates control in eighteen countries [168]. ITI was founded in 1998 during which it began to implement the SAFE strategy in five endemic countries: Ghana, Mali, Morocco, Tanzania and Vietnam [169]. By 2005 ITI was facilitating trachoma control programmes in 11 countries, working with the national governments and partners to implement the SAFE strategy [170]. In 2009 ITI merged with ‘The Task Force for Global Health’ and its main mission is to manage the supply chain of Pfizer’s Zithromax® donation, advocate for the elimination of blinding trachoma and to collaborate with partners to achieve all components of the SAFE strategy [171]. Sightsavers International focuses on providing azithromycin and tetracycline to communities that do not have access to donated Zithromax® and it provides training of
ophthalmic nurses to carry out surgery for trichiasis, whilst working with local partners for the ‘F’ and ‘E’ SAFE components [172]. Helen Keller International trains health workers to perform trichiasis surgery and works with communities to improve health education [173], collaborating with partners to improve sanitation. The Carter Center’s trachoma control programme operates in six African countries in conjunction with the ministries of health, providing support for all four parts of the SAFE strategy. It assists with the mapping of trachoma, provides trichiasis surgeries, distributes antibiotics and disseminates health education through community leaders, teachers and radio broadcasts. Family hygiene is promoted through training women in soap preparation and the programme also trains masons to build latrines [174].

It has recently been suggested that trachoma control should be integrated with that of other NTDs for which MDA (with affordable/donated safe drugs) is feasible and/or underway (e.g., schistosomiasis, onchocerciasis, lymphatic filariasis and the soil-transmitted helminths (STHs)). The Schistosomiasis Control Initiative (SCI), hosted at Imperial College, has begun to roll out this approach in Niger, Burkina Faso, Tanzania, Uganda, Burundi and Rwanda. Integrated control is advocated on the basis that it would improve efficiency and effectiveness in both delivering treatment packages and their subsequent monitoring and evaluation over and above vertical programmes [175]. The development of such an integrated approach could allow a greater proportion of people infected with trachoma to be treated highlighting the need to improve our current understanding of the dynamics of transmission and the effect on such dynamics of control interventions so that treatment can be administered in the most effective way to individuals and populations. Results of integrated control programmes have yet to be published, with the exception that mapping the prevalence of trachoma and schistosomiasis can successfully be combined [176].

**Previous mathematical models of trachoma**

Modelling the transmission of infectious diseases mathematically can have several useful applications: hypotheses can be tested on patterns/routes of transmission and the development of disease; values of key transmission parameters can be estimated; and
resulting simulations can be used to guide policy in the control of infectious diseases [177,178].

The first mathematical model of trachoma [179] divided the population into three states: susceptible individuals to active trachoma, individuals with active trachoma and individuals with ‘healed’ trachoma (which would now correspond to the chronic sequelae), therefore assuming a direct relationship between infection and active disease and that protective immunity develops after one infection. Individuals were assumed to be infected at a constant rate and recovery at constant rates. Therefore many of the assumptions of this model do not reflect the natural history of trachoma. The model outputs corresponded with data from Taiwan that showed active disease occurring in the younger population and ‘healed’ trachoma increasing with age. However, the model substantially overestimated the prevalence of active trachoma in the 15-20 years age group and underestimated prevalence in the 5-10 years age group. This can be explained as the result of the assumptions of a recovery rate that is independent of age and complete protective immunity.

More recently published mathematical models of trachoma have all been based upon the Susceptible→Infected→Susceptible (SIS) model, in which the population is categorised into two groups - individuals susceptible to infection (S) or infected individuals (I) - and infected individuals recover to become susceptible again. This type of model has been used due to the evidence for the partial protective immune response that does not protect against re-infection (described earlier). In the simplest form of the framework, susceptible individuals become infected at a rate $\beta \frac{I(t)}{N}$ (where $\beta$ is the transmission coefficient, a product of the contact rate per person per unit time and the probability that infection is transmitted with contact, $I$ is the number of infected individuals at time $t$, and $N$ is the size of the population) and infected individuals recover from infection at a rate $\gamma$ per unit time which is the reciprocal of the mean duration of infection [178].

Analysis of an age-structured SIS deterministic model of trachoma [129] found that the frequency of MDA required to eliminate infection from a community increases with the initial doubling time (the time taken for the number of infected individuals to double at the beginning of an epidemic). The model allowed for age-dependent transmission coefficients
and a recovery rate independent of age (which ranged from 1/9 to 1/17 weeks). MDA was implemented in the model by shifting the infected individuals whom are successfully treated to the susceptible state. It was fitted to a range of the prevalence of active trachoma by age class in different countries. The analysis also showed that if only children ≤ 10 years only receive MDA, more frequent rounds of MDA are required to eliminate infection. The model may have overestimated the contribution towards infection of adults by assuming a constant rate of recovery independent of age; nevertheless the work was important in demonstrating that annual rounds of MDA will not be effective in controlling trachoma in hyperendemic settings.

Three variants of this model, which all limit the population to children only, have been used to explore seasonal transmission [76], stochasticity of post-MDA dynamics [180] and ‘graduating’ communities [162]. The recovery rate in these models was estimated from the baseline prevalence and rate of re-emergence of infection at 2 and 6 months after one round of MDA. These estimates were 0.023 per week for the first study, 0.017 per week for the second study and 0.037, 0.052 & 0.0123 per week for the three populations in the third study. The corresponding durations of infection are 43, 59 and 27, 19 & 81 weeks. The majority of these values do not correspond with the estimated values of the duration of infection (see the section on the natural history of trachoma) from a longitudinal study with frequent follow-up of individuals. There are two explanations for this discrepancy: either there is heterogeneity in the duration of infection between endemic settings, to date there only remains only one longitudinal study, although the variation between 17 weeks and a year is relatively large; or certain heterogeneities, not captured in a simple SIS model, may be important in the transmission of the bacteria, causing the true rate of re-infection to be slower than that predicted by simpler models (and therefore the estimated duration of infection would be longer). Examples of these heterogeneities are large levels of household transmission with low levels of community transmission, in which infection is limited to a few households and individuals make few contacts with these household causing an initial slow spread across the community [181]; or strain diversity with incomplete cross-immunity, in which each strain has a relatively low $R_0$ (the mean number of secondary infections caused from a primary case in an entirely susceptible population) and therefore
low prevalence and rate of emergence but cumulatively across strains the infection has a relatively high prevalence [182].

Another caveat to the three models is that they limit the population to only children because children are considered to be a main reservoir of infection. However individuals over the age of 10 years have been shown to be infected, especially in lower prevalence settings, and are therefore likely to contribute towards transmission. Depending on the level of this contribution infection could be more difficult to eliminate in the whole population than what a model limited to children predicts.

Nevertheless, the three models have been important for trachoma control programmes by showing that: if transmission is seasonal it will be most effective for MDA to be timed just before the low season; the prevalence of infection in two communities with the same endemic prevalence can re-emerge in different ways after an MDA round due to stochastic fluctuations; and that graduating communities is a potential method to reduce the number of antibiotics used in control programmes.

Another model of trachoma is again based on the SIS framework and is modified to incorporate the trachoma chronic sequelae. The model is age-structured and the number of infections experienced are tracked [62] so that individuals progress up a ‘ladder’ of infection. Infectivity and the recovery rate are functions of the number of prior infections to reflect the partial immune response i.e. infectiousness decreases and the rate of recovery increases as the number of prior infections increases. TS and TT occur once individuals experience a certain threshold of prior infections and CO develops at a constant rate from TT. The model was fit to the age-distribution of chlamydial load in a hyperendemic setting [183] along with the age-distribution of the duration of infection[27] and the age-distribution of infection in three endemic settings. The thresholds for chronic sequelae were fitted to data on the prevalence of sequelae by age form a hyperendemic setting and the model fit well to all the age-distributions. Analyses of the model outputs indicate that if infection is eliminated there will be a lag in the elimination of the sequelae because without surgery TT remains until the mortality of affected individuals. If infection re-emerges after MDA rounds, little impact will be observed in the control of the chronic sequelae (Dr Manoj Gambhir, personal communication).
CHAPTER 3 A HOUSEHOLD MATHEMATICAL MODEL OF TRANSMISSION WITHOUT IMMUNITY

This chapter gives an overview of the importance of transmission between members of the same household for infectious disease epidemiology. It then describes a household mathematical model of transmission which allows individuals to be re-infected (i.e. no protective immune response, as observed for ocular C. trachomatis) with and without age-structure, followed by the methods to estimate the respective transmission parameters for a given community. The model without age-structure has been described previously [184,185] (with the exception of the coefficient for density dependence of within household transmission), whereas the model with age-structure has not been described elsewhere.
Introduction to the importance of household transmission for infectious diseases

Transmission between members of the same household is considered to be important for many infections such as influenza [186,187,188], *Streptococcus pneumoniae* [189], *Staphylococcus aureus* [190] and *Mycobacterium tuberculosis* [191] and leads to the aggregation of disease among households. For some of these infections, such as influenza, understanding the contribution of transmission that occurs between household members, using a household mathematical model of transmission, has been crucial for understanding the impact of potential interventions, including targeted control policies such as vaccinating members of large households [192] (or dependent children as a proxy for large households [193]); and quarantining household members [187,194,195]. A household transmission model for variola minor virus [196], has demonstrated that when choosing the optimal vaccination strategy, the most effective one is that in which vaccination is targeted at individuals living in larger households (compared to smaller households), rather than random vaccination individuals of households.

The basic reproduction number $R_0$, defined as the mean number of secondary infections caused from a primary case in an entirely susceptible population with homogeneous mixing of individuals [178], is a key parameter for understanding the dynamics of infection for a given infectious disease. When it is greater than one an epidemic can occur. However $R_0$ is not appropriate for populations with relatively high levels of household transmission as individuals do not mix randomly and the number of susceptibles in households with an index case quickly depletes. Instead, another parameter $R^*$, which is defined as the mean number of households infected following the introduction of a single infected individual to a randomly chosen household, can be used to understand whether an epidemic can take-off (*i.e.* if it is greater than one) [184].

Household mathematical models of infection in their simplest form allow individuals to be infected by members of their own household or by members of their community at two different rates. They assume when individuals recover from infection they are either protected from re-infection or a susceptible to re-infection. The majority of mathematical models used to understand transmission patterns or infer household interventions have
focused on infections which result in a protective immune response e.g. [186,187,188,192,193,194,195,197,198].

Although the mathematical behaviour of household models of infections without a protective immune response have been analysed [184,185] the transmission parameters have not been estimated for any infections and the resulting transmission implications been examined. There also remains a debate as to whether transmission within households is frequency dependent (the average number of household contacts is independent of the number of people in a household) or density dependent (the average number of household contacts increases with number of people in a household) for different infectious diseases. Some models of influenza transmission assume density dependent within household transmission [188,193,199] while in another study frequency dependent household transmission of influenza provided a better fit to longitudinal data [186]. Frequency dependent household transmission of pneumococcal infection has also been shown to occur [189].

Theoretical work by Hiebeler [181] on the household SIS model suggests that a population with highly efficient household transmission and extremely low community transmission (but unrealistic large household sizes) will have a relatively low rate of emergence of infection compared to a population which mixes homogeneously with the same endemic prevalence (assuming no protective immune response towards infection). Previous models of trachoma that have been used to understand optimal control strategies assume homogeneous mixing of the population and it is therefore important to understand how the transmission dynamics differ between these two assumptions for trachoma endemic communities.
**Description of household mathematical model of transmission without immunity**

**Non age-structured model**

A household mathematical model of transmission in which individuals are re-infected is an extension of the SIS model, has previously been described by Ball [184] and Neal [185].

The probability that a household of size $m$ (number of people in a household) has $j$ infected individuals (and $m - j$ susceptible individuals) at time $t$ is given by $z^{(m)}_j(t)$ and can be characterised by a time-inhomogeneous Markov chain. The Markov assumption is that the future evolution only depends on the current state and is independent of the previous states.

A susceptible individual can be infected from either an infected member of the community (global transmission) at a rate: $\beta_G \nu$, in which $\beta_G$ is the global transmission coefficient and $\nu$ is the prevalence of infection in the community; or from an infected member of the same household (local transmission) at a rate: $\frac{j \beta_L}{(m-1)}$, in which $\beta_L$ is the local transmission coefficient. $\beta_L$ is multiplied by either the number of infected individuals in the household, $j$, if transmission is assumed to be density dependent (the average number of contacts per individual increases with household size, corresponding to $w = 0$), or the fraction of infected individuals in the household $\frac{j}{m-1}$, representing that the average number of contacts per individual is constant, regardless of household size, and corresponding to $w = 1$.

The parameter $w$ is therefore the coefficient for density dependence, which in the application described we allow to vary on a continuous scale with $w \geq 0$. Incorporating this parameter which allows the level of frequency / density dependent within household transmission is an extension to Ball and Neal’s model.

Individuals recover from infection at a rate $\gamma$, taken as the reciprocal of the mean duration of infection. Births and deaths are not included in the model because the duration of infection is relatively short compared to the average human life expectancy.
A household at time $t$ can be in one of $\{0,1,...,m\}$ states, which correspond to the number of infected individuals a household contains at that time. We can write the Kolmogorov forward difference-differential equation for $z^{(m)}_0(t)$, $z^{(m)}_1(t)$ and $z^{(m)}_2(t)$:

$$\frac{d}{dt}z^{(m)}_0(t) = -m\beta_0\nu z^{(m)}_0(t) + \gamma z^{(m)}_1(t)$$ (3-1)

$$\frac{d}{dt}z^{(m)}_1(t) = m\beta_0\nu z^{(m)}_0(t) - \gamma z^{(m)}_1(t) - (m-1)\left(\beta_0\nu + \frac{\beta_l}{(m-1)^\nu}\right)z^{(m)}_1(t) + 2\gamma z^{(m)}_2(t)$$ (3-2)

$$\frac{d}{dt}z^{(m)}_2(t) = (m-1)\left(\beta_0\nu + \frac{\beta_l}{(m-1)^\nu}\right)z^{(m)}_1(t) - 2\gamma z^{(m)}_2(t) - (m-2)\left(\beta_0\nu + 2\frac{\beta_l}{(m-1)^\nu}\right)z^{(m)}_2(t) + 3\gamma z^{(m)}_3(t)$$ (3-3)

and therefore we can write the Kolmogorov forward difference-differential equation for $z^{(m)}_j$:

$$\frac{d}{dt}z^{(m)}_j(t) = (m-j+1)\left(\beta_0\nu + (j-1)\frac{\beta_l}{(m-1)^\nu}\right)z^{(m)}_{j-1}(t) - j\gamma z^{(m)}_j(t) - (m-j)\left(\beta_0\nu + j\frac{\beta_l}{(m-1)^\nu}\right)z^{(m)}_j(t) + (j+1)\gamma z^{(m)}_{j+1}(t)$$ (3-4)

where $j \leq m$; $m = 1,2,...$; $j = 0,1,...,m$ and $z^{(m)}_{m+1} = z^{(m)}_{-1} = 0$

At endemic equilibrium, assuming the number of households $n$ is large ($n \to \infty$), solving
\[
\frac{d}{dt} z_j^{(m)}(t) = 0, \text{ leads to the recursion:}
\]
\[
z_j^{(m)} = \frac{(m - j + 1) \left( \beta_j \nu + (j - 1) \frac{\beta_i}{(m - 1)^w} \right)}{j \gamma} z_{j-1}^{(m)}
\]
\[j = 1, 2, \ldots, m,\]

where
\[
z_0^{(m)} = 1 / \left( 1 + \sum_{j=1}^{m} \prod_{i=0}^{j-1} \frac{(m - i) \left( \beta_j \nu + i \frac{\beta_i}{(m - 1)^w} \right)}{(i + 1) \gamma} \right)
\]

The prevalence of infection in the community described by equations (3-5) and (3-6) is
\[
\theta(\nu) = \frac{\sum_{m=1}^{\infty} \sum_{j=0}^{m} z_j^{(m)} j \varphi_m}{\sum_{m=1}^{\infty} \varphi_m m}
\]

where \(\varphi_m\) is the fraction of households of size \(m\) in the population. Solving equations (3-5) and (3-6) therefore requires the implicit equation \(\theta(\nu) = \nu\) to be satisfied at equilibrium.

If a household of size \(m\) is initially infected then \(R^{(m)}\) is
\[
R^{(m)} = \frac{\beta_G (m - 1)!}{\gamma} \frac{\rho_m^i}{\rho_m^{i-1}} \sum_{i=0}^{m-1} \frac{\rho_m^i}{i!}
\]

where
\[ \rho_m = \frac{(m-1)^\gamma}{\beta_L} \]  

(3-9)

and \( R_c \) is the mean across all individuals according to their probability of being in a household of a given size,

\[ R_s = \sum_{m=1}^{\infty} \frac{m \varphi_m R_c^{(m)}}{\sum_{m=1}^{\infty} \varphi_m} = \sum_{m=1}^{\infty} \varphi_m \frac{\beta_G}{\gamma} \left( \frac{m!}{\rho_m ^{m-1}} \right) \sum_{i=0}^{m-1} \frac{\rho_m^i}{i!} \sum_{m=1}^{\infty} \varphi_m m \]  

(3-10)

An extension to the model: age structure
An extension to this SIS household model is to include age structure of the population. The population is structured into households and into two age classes: ‘children’, \( c \), and ‘adults’, \( a \). In each household there are \( m_c \) children and \( m_a \) adults; \( j_c \) infected children and \( j_a \) infected adults; and \((m_c - j_c)\) susceptible children and \((m_a - j_a)\) susceptible adults.

In this case, a susceptible individual of age class \( y \) is infected by a member of their own household (local transmission) of age class \( x \) at a rate \( \frac{\beta_{Lxy} j_x(t)}{(m_c - 1)\rho_y} \) or by a member of their community (global transmission) of age class \( x \) at a rate \( \beta_{Gxy} v_x(t) \). The subscripts \( x \) and \( y \) can indicate either \( c \) or \( a \), and when \( x = y \), \( v = 1 \) and when \( x \neq y \), \( v = 0 \). \( \beta_{Lxy} \) is the local transmission coefficient and \( \beta_{Gxy} \) is the global transmission coefficient. Function \( v_x(t) \) is the global prevalence of infection in the population of age class \( x \) as a function of time \( t \).

There are therefore eight potential transmission parameters (\( \beta_{Lcc}, \beta_{Lca}, \beta_{Lau}, \beta_{Lac}, \beta_{Gcc}, \beta_{Gca}, \beta_{Gaa} \) and \( \beta_{Gac} \)) to estimate. A susceptible child in a household of size \( m_c + m_a \) is infected at a rate \( \lambda_c \), where \( \lambda_c = \frac{\beta_{Lcc} j_c}{(m_c - 1)^w} + \frac{\beta_{Lac} j_a}{m_c w} + \beta_{Gcc} v_c + \beta_{Gac} v_a \). A susceptible adult in a household of size \( m_c + m_a \) is infected at a rate \( \lambda_a \), where
\[ \dot{\lambda}_a = \frac{\beta_{Loc} j_a}{(m_a - 1)^2} + \frac{\beta_{Lac} j_c}{m_c} + \beta_{Gaa} \gamma_a + \beta_{Gca} \gamma_c. \]

Children recover from infection at a rate \( \gamma_c \) and adults at a rate \( \gamma_a \). Depending on assumptions there are a total of nine possible models that are nested in the most general model (described in Table 3-1). In model 4 adults are assumed to be \( \theta \) times as infectious as children and in model 5 adults are assumed to be \( \theta \) times as susceptible as children (where \( \theta \) lies between 0 and \( \infty \)). In those two models, the contact rate differs for household and community transmission but does not differ by age class.

The transmission dynamics within each household are described by a multi-state Markov model. The number of infected adults \( j_a \) and children \( j_c \), together with the number of children \( m_c \) and adults \( m_a \) in a household determine the state of the system at time \( t \). For convenience we index this state by the function \( s(t) = j_a(t)(m_a + 1) + j_c(t) \). The total number of possible states a household can be in is given by \( (m_c + 1)(m_a + 1) \). The Markov transition intensities \( q_{rs}(t) \) are determined by the instantaneous rate of infection among children \( (m_c - j_c) \dot{\lambda}_c \) (when \( s = r + 1 \)) and adults \( (m_a - j_a) \dot{\lambda}_a \) (when \( s = r + m_c + 1 \)), and the rate of recovery of children \( j_c \gamma_c \) (when \( s = r - 1 \)) and adults \( j_a \gamma_a \) (when \( s = r - m_c - 1 \)).

Collectively, the transition intensities form a matrix \( Q(m_c, m_a) \) whose rows sum to zero so that \( q_{rs} = -\sum_{s \neq r} q_{rs} \). The remaining matrix elements are zero. This matrix is completely determined by ten parameters: the eight transmission parameters and the two recovery rate parameters \( (\beta_{Loc}, \beta_{Lac}, \beta_{Lac}, \beta_{Gaa}, \beta_{Gca}, \beta_{Gaa}, \beta_{Gac}, \gamma_a, \gamma_c) \). The matrix defining the transition probability of a household (of size \( m_c + m_a \)) being in state \( s \) at a time \( t + u \) in the future, given the state at time \( u \) is \( r \), is given by:

\[
P(t, m_c, m_a) = \text{Exp}(tQ),
\]

where \( \text{Exp} \) is the matrix exponential function. The probability of a household being in state \( s \) at endemic equilibrium, \( z_s^{(m_c, m_a, j_c, j_a)} \) is determined by the corresponding diagonal entry of \( P(t, m_c, m_a) \) as \( t \to \infty \).
It was not possible to solve the endemic equilibrium for this model analytically but numerical methods can be used to find $P(t,m_c,m_a)$ from $Q(m_c,m_a)$ as $t \to \infty$. As the

<table>
<thead>
<tr>
<th>Model No.</th>
<th>Description</th>
<th>Model equations</th>
<th>Recovery rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Homogeneous mixing of the population. Children and adults recover at the same rate.</td>
<td>$\beta_{Lcc} = \beta_{Lca} = \beta_{Laa} = \beta_{Lac} = 0$</td>
<td>$\gamma_c = \gamma_a$</td>
</tr>
<tr>
<td>2</td>
<td>Household and community transmission. Children and adults recover at the same rate.</td>
<td>$\beta_{Lcc} = \beta_{Lca} = \beta_{Laa} = \beta_{Lac}$</td>
<td>$\gamma_c = \gamma_a$</td>
</tr>
<tr>
<td>3</td>
<td>Household and community transmission. Children recover more slowly than adults.</td>
<td>$\beta_{Lcc} = \beta_{Lca} = \beta_{Laa} = \beta_{Lac}$</td>
<td>$\gamma_c &lt; \gamma_a$</td>
</tr>
<tr>
<td>4</td>
<td>Household and community transmission. Adults are $\theta$ times as infectious as children.</td>
<td>$\beta_{Lcc} = \beta_{Lca}$, $\beta_{Laa} = \beta_{Lac} = \theta \beta_{Lcc}$</td>
<td>$\gamma_c &lt; \gamma_a$</td>
</tr>
<tr>
<td>5</td>
<td>Household and community transmission. Adults are $\theta$ times as susceptible as children.</td>
<td>$\beta_{Lcc} = \beta_{Lca}$, $\beta_{Laa} = \beta_{Lac} = \theta \beta_{Lcc}$</td>
<td>$\gamma_c &lt; \gamma_a$</td>
</tr>
<tr>
<td>6</td>
<td>Household and community transmission. Adults have a different infectiousness to that of children and this may differ between household and community transmission.</td>
<td>$\beta_{Lcc} = \beta_{Lca}$, $\beta_{Laa} = \beta_{Lac}$, $\beta_{Gcc} = \beta_{Gca}$, $\beta_{Gaa} = \beta_{Gac}$</td>
<td>$\gamma_c &lt; \gamma_a$</td>
</tr>
</tbody>
</table>
|   | Household and community transmission. Adults have a different susceptibility from that of children and this may differ between household and community transmission. | $\beta_{Lcc} = \beta_{Lac}$
$\beta_{Laa} = \beta_{Lca}$
$\beta_{Gcc} = \beta_{Gac}$
$\beta_{Gaa} = \beta_{Gca}$ | $\gamma_c < \gamma_a$ |
|---|---|---|---|
|   | Household and community transmission. Adults and children are equally susceptible and infectious but there are different contact rates between adults $\rightarrow$ adults, adults $\rightarrow$ children, children $\rightarrow$ adults and children $\rightarrow$ children. | $\beta_{Lac} = \beta_{Laa} = \beta_{Lca}$
$\beta_{Gac} = \beta_{Gaa} = \beta_{Gca}$ | $\gamma_c < \gamma_a$ |
|   | The transmission rates of an infected individual infecting a susceptible individual of age classes: adults $\rightarrow$ adults, adults $\rightarrow$ children, children $\rightarrow$ adults and children $\rightarrow$ children differ for both household and community transmission. | $\beta_{Lcc}, \beta_{Laa}, \beta_{Lca}, \beta_{Lac}$
$\beta_{Gcc}, \beta_{Gaa}, \beta_{Gca}, \beta_{Gac}$ | $\gamma_c < \gamma_a$ |

Table 3-1 Description of the possible nested models within the full age-structured SIS household model

Time step, $\delta t$, $\rightarrow 0$, the diagonal entries of $P_{rr}(t)$, can be approximated to be $1 + q_{rr} \delta t$ and the other entries $p_{rs}(t) \approx q_{rs} \delta t$. At endemic equilibrium, $z_{s}(m_c, m_u, \ldots)$ corresponds to the normalised left eigenvector, with an eigenvalue of 1, of the approximated transition probability time matrix $P(t, m_c, m_u)$.

**Estimation of transmission parameters**

Maximum likelihood can be used to estimate the transmission parameters for a given community for which the data includes information on the number of people infected in each household and the household size. Here we describe estimating parameters assuming the data are cross-sectional and the infection in the community is at endemic equilibrium.

**Likelihood for the non-age structured SIS household model**

The likelihood, $L$, of observing a household of size $m$, with $j$ individuals infected is given by $L = z_{j}^{(m)}$ and the total log-likelihood is the summation of $\ln L$ across all households.

It may occur that a small number of individuals recorded as living in the household, from a census, are not tested for the presence of infection, for example due to refusal or because
they were away travelling. The sensitivity of the estimates of transmission parameters to
the inclusion of these individuals as members of the household, such that they may have
contributed to transmission, can be examined. If there are $\sigma$ members of a household
tested for infection and an additional $m-\sigma$ individuals who are not tested for infection but
who contribute to transmission, the probability that $h$ individuals are found positive in the
sample, given that $j$ members of the overall household of size $m$ are actually infected
(according to a hypergeometric distribution [200]) is:

$$
P(H = h \mid j, \sigma, m) = \binom{j}{h} \binom{m-j}{\sigma-h} \binom{m}{\sigma}^{-1}$$  \hspace{1cm} (3-11)

In this case the likelihood for each household can be modified such that

$$
L = \sum_{j=0}^{m} \left[ z_j^{(m)} P(H = h \mid j, \sigma, m) \right]$$  \hspace{1cm} (3-12)

This assumes that infected individuals are equally likely to be sampled as uninfected
individuals. A non-central hypergeometric distribution [200] can be used to explore this
assumption. In this case, a relative weighting, $\omega$, is given to infected individuals indicating
how likely is was that they were sampled compared to uninfected individuals i.e. if $\omega = 2$,
infected individuals are twice as likely to be sampled than uninfected individuals.

Therefore the probability that $h$ individuals are found positive in the sample is now given
as:

$$
P(H = h \mid j, \sigma, m) = \frac{\omega^h \binom{j}{h} \binom{m-j}{\sigma-h}}{\sum_{a=0}^{\sigma-1} \omega^a \binom{j}{a} \binom{m-j}{\sigma-a}}$$  \hspace{1cm} (3-13)
**Likelihood of the age-structured SIS household model**

The likelihood, $L$, of observing a household of size $m_c + m_a$, in state $s$ at equilibrium for a given set of model parameters is $L = z^x_{s,m_c,j_c,j_a}$. The total log likelihood is the summation of $\ln L$ over all households. If there are adults and children who were not tested for infection in the data that are assumed to be equally likely to be infected as adults and children in the household who were tested for infection the probability that $h_x$ individuals of age category $x$ were found positive given that $j_x$ individuals were actually infected is given by equation (3-8) for each age group. The probability that a household was in state $S$ is therefore,

$$P(S = s \mid j_c, j_a, \sigma_c, \sigma_a, m_c, m_a) = P(H_c = h_c \mid j_c, \sigma_c, m_c) P(H_a = h_a \mid j_a, \sigma_a, m_a).$$  \hspace{1cm} (3-14)

The likelihood for a household is modified such that,

$$L = \sum_{x=(m_c+1)(m_a+1)} \left[ z^x_{s,m_c,j_c,j_a} P(S = s \mid j_c, j_a, \sigma_c, \sigma_a, m_c, m_a) \right].$$  \hspace{1cm} (3-15)

**Methods to maximise the likelihood**

Finding the values of transmission parameters which give the maximum log-likelihood is an optimisation problem for which there are many algorithms available. The choice of algorithm depends on whether the log-likelihood surface contains local maxima as well as the global maximum. An outline of commonly used algorithms is given below, summarised from [201] and [202].

‘Grid Search’ method

A crude method to find the maximum log-likelihood is ‘Grid Search’ in which the log-likelihood is evaluated for different combinations of parameters however this is very time consuming and therefore unfeasible if there are multiple parameters. For example if there are three parameters and the log-likelihood is evaluated for one hundred values of each of the parameters the log-likelihood will be evaluated 1,000,000 times. If the log-likelihood is evaluated for few combinations of parameters, the maximum is unlikely to be found.
‘Derivative–based’ methods
For smooth log-likelihood surfaces, with no local maxima, it is possible to use algorithms which are derivative based to find the maximum. At the maximum point of the log-likelihood surface the gradient (first derivative) will be zero, termed a stationary point of the surface, and the algorithms are designed to converge towards that point. An example of a derivative based algorithm is Newton’s method: the algorithm uses the first and second derivatives at each iterative step to take a series of steps closer towards the closest stationary point of the log-likelihood surface. The quasi-Newton method (also known as the ‘BFGS’ method) and ‘generalised reduced gradient non-linear optimisation’ algorithm approximate the second derivates through evaluating consecutive gradient vectors rather than computing them at every iteration. These methods are not appropriate for calculating the global maximum log-likelihood for surfaces in which there are local maxima as the local maxima will also have first derivatives of zero.

‘Derivative-free’ methods
‘Derivative-free’ based algorithms can be more computationally more intensive than ‘derivative-based’ methods but can be more robust when there are many parameters that determine the likelihood surface.

The ‘Nelder-Mead’ method (also known as the downhill simplex method) finds the closest minimum of the negative log-likelihood by moving downhill from a starting point, without making assumptions about the surface of the likelihood. At every iterative step the Nelder-Mead method constructs a simplex on the likelihood surface (a higher-dimensional analogue of a triangle) with $n + 1$ parameter combinations that form the vertices of the simplex where $n$ is the number of parameters to be estimated. The log-likelihood is evaluated at each vertex and the vertex with the worst log-likelihood is moved at every iterative step (through reflection, expansion or contraction) according to a set of rules until the simplex becomes sufficiently small and changing the vertices does not result in an improvement in the log-likelihood.

Simulated annealing method (SANN) is the most reliable algorithm for finding the global maximum when there are local maxima but it is very computationally intensive. The principles of the algorithm are taken from thermodynamics of annealing molten metals to
solids during which if the liquid metal is cooled slowly the atoms arrange themselves to a minimum energy state resulting in a pure crystal whereas if the molten metal is cooled quickly a sub-optimal energy state is reached and the metal is weaker in structure. Even at a low temperature there may be a chance of a system being in a higher energy state than the minimum state. The SANN algorithm aims to find the global minimum of a function. There are variants of the algorithm but the one described here is that described by Belisle [203,204]. It evaluates the negative log-likelihood (-L₁) of the initial starting parameters and also the negative log-likelihood (-L₂) of nearby new parameter values (determined by a Gaussian Markov kernel with a scale proportional to the temperature). If -L₂ < -L₁ the new parameters are accepted and the process repeated whereas if -L₂ > -L₁, the new parameters are accepted if \( e^{-\Delta(-L)/k} \) is less than a random number generated between 0 and 1 (where \( k \) is the temperature which is a logarithmic decline function:

\[
k = \frac{k_{start}}{\log\left(\frac{\left(\mu - e\right)}{\mu}\right)}
\]

where \( \mu \) is the number of function evaluations at each temperature, \( k_{start} \) is the starting temperature, and \( i \) is the iteration number). Therefore if the algorithm is converging towards a local minimum there is a chance it can ‘jump’ out and continue to find the global minimum. The declining logarithmic function of the temperature allows a high chance of accepting a ‘worse’ log-likelihood at the beginning of the algorithm whereas later in the algorithm there is less of a chance. The process is repeated until the difference in the two negative log-likelihood is smaller than a given threshold or the maximum number of iterations is reached.
CHAPTER 4 DESCRIPTION OF DATA

This chapter describes the four data sets for which, in subsequent chapters, the contribution of household transmission is estimated and the effectiveness of targeted intervention strategies are explored. Two of the data sets are from populations in The Gambia (West Africa) and two are from Tanzania (East Africa). They are kindly shared with us by collaborators at the London School of Hygiene and Tropical Medicine and Johns Hopkins School of Public Health. Each data set consists of approximately 1000 individuals and contains detailed demographic, infection and disease data.
Introduction to Data

The work described in this thesis is a new analysis of previously collected data from four populations believed to be endemic for ocular *Chlamydia trachomatis* infection. Two are from The Gambia (Upper Saloum district which lies in the ‘Central River Division’ of the country and Jali village in Kiang West district which is part of the ‘Lower River Division’) and two from Tanzania (Kahe Mpya sub-village, which is located on the north-eastern slopes of Mount Kilimanjaro and Maindi village which is situated on the Masai Steppe in a dry area of central Tanzania) (Figure 4-1). Data were collected by groups led by the London School of Hygiene (LSHTM) and Johns Hopkins University (JHU), with whom we are collaborating for the modelling of trachoma transmission. The names of our collaborators who shared each data-set, the year the data were collected along with the original references are given in Table 4-1. The data presented here is cross sectional, prior to any intervention and each data-set is part of a follow-up study which assesses the impact of mass distribution of azithromycin (except for Jali village in which follow-up occurred without intervention).

Data Collection

Individuals of all ages from the four endemic populations were examined for trachoma and tested for the presence of ocular *C. trachomatis*. Sterile swabs were passed four times over the upper tarsal conjunctiva (of the left eye in Upper Saloum district and Jali village and the right eye in Kahe-Mpya sub-village and Maindi village). Standard precautions were taken to prevent contamination and the swabs were frozen before being analysed in the laboratory. PCR amplification of a target sequence in the common cryptic plasmid of the bacteria was used to test for the presence of chlamydial infection (Amplicor PCR assay by Roche Molecular Systems, NJ, USA was used except for the swabs from Jali for which the assay was not available at the time of the study and the protocol by Sriprakash and Macavoy was followed [205]). In one community, Maindi village, the presence of infection was based on quantitative PCR amplification of the *omp*-1 gene. Ocular disease was assessed by trained ophthalmologists and observers using an x2 binocular loupe and pen torch. In The Gambia the more detailed clinical diagnosis “FPC” system [43] was used but subsequently
converted to the simplified WHO grading system [22] for this analysis. In Tanzania the simplified grading system was used. Active disease was defined as the presence of TF and / or TI. Detailed information on the bedroom (Upper Saloum District, Kahe Mpya sub-village and Jali village only), household (Upper Saloum District, Kahe Mpya sub-village and Maindi village only), compound (Jali village and Upper Saloum district only), balozi (Kahe Mpya sub-village and Maindi village only) and village (Upper Saloum district) of the individuals examined was recorded; along with a number of other risk factor for trachoma. Characteristics of these populations and detailed methods have been reported previously [47,53,70,131].
<table>
<thead>
<tr>
<th>Population and reference of study</th>
<th>Year at baseline</th>
<th>Data shared by:</th>
<th>No. individuals in population</th>
<th>No. individuals tested for chlamydial infection at baseline</th>
<th>Prevalence of infection (%)</th>
<th>Prevalence of active disease (%)</th>
<th>Mean household size (number)</th>
<th>Percentage of households infected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, Upper Saloum District, The Gambia [53]</td>
<td>2001</td>
<td>Matthew Burton (LSHTM)</td>
<td>1595</td>
<td>1319</td>
<td>7.2</td>
<td>7.7</td>
<td>13.6</td>
<td>24.8</td>
</tr>
<tr>
<td>Jali village, Kiang West District, The Gambia [47]</td>
<td>1991</td>
<td>Robin Bailey (LSHTM)</td>
<td>844</td>
<td>752</td>
<td>22.1</td>
<td>15.2</td>
<td>17.3</td>
<td>73.5</td>
</tr>
<tr>
<td>Sub-village of Kahe Mpya, Rombo District, Tanzania [131]</td>
<td>2000</td>
<td>Anthony Solomon (LSHTM)</td>
<td>978</td>
<td>956</td>
<td>9.5</td>
<td>20.4</td>
<td>5.3</td>
<td>30.0</td>
</tr>
<tr>
<td>Maindi village, Kongwa District, Tanzania [70]</td>
<td>2000</td>
<td>Sheila West (JHU)</td>
<td>1017</td>
<td>783</td>
<td>36.0</td>
<td>38.3</td>
<td>4.7</td>
<td>60.4</td>
</tr>
</tbody>
</table>

Table 4-1. Demographic and prevalence data from the four populations examined for ocular *Chlamydia trachomatis* infection. NOTE The household unit for Jali village was a compound as household data was unavailable. We are also grateful to David Mabey, head of the trachoma group at LSHTM, for sharing all the data.
Data characteristics

Infection and Disease

The prevalence of infection and active disease in each community is given in Table 4-1. In the work which follows, the data is split into two age groups: individuals younger than ten years old and individuals ten years old and older. The number of individuals in each age group and the respective prevalence of infection and disease are presented in Table 4-2. The prevalence of infection does not differ largely between males and females in the two different age groups (Figure 4-2) nor does the prevalence of active disease (Figure 4-3). The exception to this is Maindi village in which the prevalence of active disease is much greater in females than males, particularly in children. A previously higher exposure to infection by female children could explain this prevalence discrepancy (since the duration of active disease is relatively long (described earlier)).

Household Structure

A household census was undertaken in each of the four populations at the start of the studies, prior to disease and infection data collection, and the size of each household is defined as the number of residents of each household as determined by the census.

In The Gambia one household or a cluster of households forms a compound, a unit which is fenced off from the rest of a community. In Upper Saloum district the household unit ranges from 1-55 individuals and the compound ranges from 2-77 individuals. In Jali village the compound unit ranges from 4-70 individuals (household data unavailable). In Tanzania, the household unit is the ‘kaya’, (ranging from 1 to 14 individuals) and on average the unit is smaller than the household unit in The Gambia (Table 4-1). Kayas which are situated within the same geographical zone are grouped into a ‘balozi’ and share a balozi leader. The mean household size and the percentage of households infected are given in Table 4-1.

The negative binomial distribution [206] can be fitted to the household size distribution of each community by obtaining maximum likelihood estimates of the inverse overdispersion parameter, \( k \) (when \( k \to 0 \) the distribution is overdispersed and when \( k \to \infty \) the distribution follows a Poisson distribution). Confidence intervals for the estimates of \( k \) are
calculated by assuming that \(-2^* (\ln L)\) is approximately \(\chi^2\) (chi-squared) distributed. The probability mass function used for the negative binomial is [206]:

\[
P(M = 0) = \left(1 + \frac{\bar{m}}{k}\right)^{-k}
\] (4-1)

and when \(m > 0\)

\[
P(M = m) = \left(\frac{k + m - 1}{m} \left(\frac{\bar{m}}{\bar{m} + k}\right) P(M = (m - 1))
\] (4-2)

where \(\bar{m}\) is the (arithmetic) mean household size (see Table 4-1).

The household size distribution and fitted distributions are given in Figure 4-4 and the respective estimates for \(k\) are (95% CI denoting 95% confidence intervals): \(k = 3.95\) [95% CI: 2.85 – 5.49], and \(k = 1.86\) [1.21 – 2.76], for respectively Upper Saloum district and Jali village (The Gambia), and \(k \to \infty\) for both Kahe Mpya sub-village and Maindi village (Tanzania).

**Missing data**

A number of individuals were members of the respective population, determined by the census, but were not observed due to absenteeism and refusal. The total population size and the total number of individuals which were observed are given in Table 4-1. Table 4-2 shows the number of individuals observed in each age group.
<table>
<thead>
<tr>
<th>Population</th>
<th>Individuals &lt;10 years old</th>
<th>Individuals &gt;= 10 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number in population</td>
<td>Number in population</td>
</tr>
<tr>
<td></td>
<td>No. tested for chlamydial</td>
<td>No. tested for chlamydial</td>
</tr>
<tr>
<td></td>
<td>infection (%)</td>
<td>infection (%)</td>
</tr>
<tr>
<td></td>
<td>Prevalence of infection (%)</td>
<td>Prevalence of infection (%)</td>
</tr>
<tr>
<td></td>
<td>Prevalence of active disease (%)</td>
<td>Prevalence of active disease (%)</td>
</tr>
<tr>
<td>Upper Saloum District, The Gambia</td>
<td>600</td>
<td>995</td>
</tr>
<tr>
<td></td>
<td>544</td>
<td>795</td>
</tr>
<tr>
<td></td>
<td>9.0</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>15.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>304</td>
<td>542</td>
</tr>
<tr>
<td></td>
<td>294</td>
<td>458</td>
</tr>
<tr>
<td></td>
<td>40.1</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>40.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Sub-village of Kahe Mpya, Tanzania</td>
<td>362</td>
<td>616</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>596</td>
</tr>
<tr>
<td></td>
<td>15.8</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>42.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Maindi village, Tanzania</td>
<td>363</td>
<td>654</td>
</tr>
<tr>
<td></td>
<td>293</td>
<td>490</td>
</tr>
<tr>
<td></td>
<td>47.1</td>
<td>24.9</td>
</tr>
<tr>
<td></td>
<td>39.6</td>
<td>16.8</td>
</tr>
</tbody>
</table>

Table 4-2 The number of individuals and prevalence of infection for each age groups in four endemic communities
Figure 4-2 Prevalence of ocular *Chlamydia trachomatis* infection in males and females, by age class, in the four communities. Error bars indicate 95% binomial confidence intervals.

Figure 4-3 Prevalence of active disease in males and females, by age class, in the four communities. Error bars indicate 95% binomial confidence intervals.
Figure 4-4 Fitted and observed household distributions. The inverse overdispersion parameter, $k$, was estimated to be with 95% confidence intervals (CI) $k = 3.95$ [95% CI: 2.85 – 5.49], $k = 1.86$ [1.21 – 2.76], $k = \infty$ and $k = \infty$ for, respectively, Upper Saloum district, Jali village, Kahe Mpya and Maindi village, where $k = \infty$ corresponds to a random or Poisson distribution.
CHAPTER 5 ESTIMATION OF HOUSEHOLD AND COMMUNITY TRANSMISSION

Targeting treatment to infected households would be more efficient than MDA and would reduce the selective pressure for resistant bacteria. However the potential impact on the reduction of infection depends on the relative contribution of community and household transmission of infection, which have not previously been estimated.

Here I estimate the level of transmission between members of the same household and that between households of the same population using cross-sectional data on the prevalence of ocular *C. trachomatis* infection from four endemic communities, two in West Africa (The Gambia) and two in East Africa (Tanzania).

In the first section of this work household and community transmission is estimated ignoring differences in transmission by age (i.e. using the non-age structured household SIS model described in Chapter 3). I also estimate whether household transmission is frequency or density dependent. The sensitivity of the estimates of the transmission parameters to following assumptions is explored: duration of infection; definition of a household; contribution of missing data. Finally, the correspondence between the data and the model is assessed. In the second section of this work, household and community transmission is estimated allowing for different assumptions of transmission by adults and children (described using the age-structured model described in Chapter 3) and the most parsimonious model which best explains the observed data is identified.

The results from the non-age structured household SIS model have been presented as a Research Article in PLoS NTDs [207] (a copy of this paper is at the end of this thesis).
Estimation of household and community transmission without age-structure

Methods
Maximum likelihood was used to estimate $\beta_G$, $\beta_L$ and $w$ (using the likelihood function defined earlier in equation 3-12) simultaneously for four populations described in Chapter 4. The ‘generalised reduced gradient algorithm’ optimisation algorithm, i.e. the ‘Solver’ ‘Add-in’ in Excel was used to maximise the likelihood and all three parameters were constrained to be greater than zero. The mean duration of infection was assumed to be 17.2 weeks based on cohort studies of infection with frequent follow-up [27] and $\nu$ was taken to be the prevalence of infection in the cross-sectional survey (i.e. infection in the communities is assumed to be at endemic equilibrium). The sensitivity of the estimates to the assumed mean duration of infection was examined for a range of plausible values (12 – 24 weeks) [27]. Confidence intervals (CI) for each parameter were calculated by assuming that $-2(\ln L)$ is approximately $\chi^2$ (chi-squared) distributed [208]. We tested the hypothesis of density dependence in the contact rate by estimating parameter $w$ and its confidence intervals; the null hypothesis of density dependence ($w = 0$) was contrasted with the alternative hypothesis of ($w > 0$). Frequency dependence in the contact rate is inferred when $w=1$.

The impact of different definitions of a ‘household’ on the estimates of $\beta_G$, $\beta_L$ and $w$ was examined, from bedroom, household, compound and village for the Upper Saloum District; room and compound for Jali village; room, kaya and balozi for Kahe Mpya sub-village and kaya and balozi for Maindi village.

The impact of excluding the individuals who were not examined at the moment of sampling on the estimates of the three transmission parameters was assessed. When accounting for the missing individuals, we assume individuals were missing at random i.e. infected individuals were equally likely to be sampled as uninfected members. The sensitivity of this assumption was examined by re-estimating the parameters if infected individuals were twice or half as likely to be sampled using the non-central (Fisher) hypergeometric
distribution [200] (described earlier) and these estimates were compared to the original estimates.

The appropriateness of the household SIS model of *C. trachomatis* transmission was assessed by simulating the number of people infected at endemic equilibrium and the household to which they belong under the model using the estimated parameters. The underlying household size distributions were based on a negative binomial distribution fit to the data from each community (described earlier in Chapter 4). Comparison of the model simulations with the observed data was based on the mean intraclass correlation coefficient for the prevalence of infection within households (ICC). The ICC provides a quantitative measure of similarity between individuals within groups and is based upon the comparison of within- and between-group sums of squares from an analysis of variance [209]:

\[
ICC = \frac{MS_b - MS_w}{MS_b + (n_0 - 1)MS_w}.
\]  

(5-1)

MS\(_b\) and MS\(_w\) are the between-group and within-group mean squares from a one way analysis of variance of binary data where

\[
n_b = \frac{1}{(k-1)} \left[ N - \sum_{i=1}^{k} \frac{n_i^2}{N} \right],
\]

(5-2)

\[
N = \sum_{i=1}^{k} n_i,
\]

(5-3)

\[
MS_b = \frac{1}{(k-1)} \left[ \sum_{i=1}^{k} \frac{Y_i^2}{n_i} - \frac{1}{N} \left( \sum_{i=1}^{k} Y_i \right)^2 \right]
\]

(5-4)

and

\[
MS_w = \frac{1}{(N-k)} \left[ \sum_{i=1}^{k} Y_i \right] - \sum_{i=1}^{k} \frac{Y_i^2}{n_i}.
\]

(5-5)

The number of groups (*i.e.* households) is denoted by \(k\) and the \(i\)th group contains \(n_i\) individuals each having a binary response (infected or uninfected). \(Y_i\) denotes the total number of infected individuals in group \(i\).
One thousand stochastic simulations were run for each setting using the numerical integration package Berkeley Madonna™ [210].

Results

The estimates for the global and local transmission coefficients (\( \beta_G \) and \( \beta_L \)) along with the density-dependent coefficient, \( w \) and the household reproduction number \( R_c \) are given in Table 5-1 along with their 95% confidence intervals. In Jali the compound unit was used because household data were unavailable. Estimates of the rate of household transmission were large and \( \beta_L \) was greater than \( \beta_G \) in three of the four populations. The two populations in The Gambia had higher estimates of \( \beta_L \) and lower estimates of \( \beta_G \) compared to the two populations in Tanzania. Estimates of \( w \) were close to 1, and the 95% CIs included 1, consistent with frequency-dependent transmission, such that the number of contacts made by an infected individual was not larger in bigger households. Estimates of \( R_c \) were all above 1. Jali village had the highest estimate of \( R_c \) and Kahe Mpya sub-village had the lowest.
### Table 5-1 Maximum likelihood estimates of the transmission parameters in four populations of West and East Africa.

<table>
<thead>
<tr>
<th>Population</th>
<th>Global transmission coefficient, $\beta_G$ [95% CI]</th>
<th>Local transmission coefficient, $\beta_L$ [95% CI]</th>
<th>Coefficient for density dependence, $w$ [95% CI]</th>
<th>$R^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, Upper Saloum</td>
<td>0.29 [0.16 – 0.51]</td>
<td>7.09 [3.58 – 13.73]</td>
<td>1.22 [0.99 – 1.45]</td>
<td>1.25</td>
</tr>
<tr>
<td>District, The Gambia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>0.76 [0.39 – 1.40]</td>
<td>4.01 [1.81 – 7.38]</td>
<td>1.05 [0.84 – 1.23]</td>
<td>2.81</td>
</tr>
<tr>
<td>Sub-Village of Kahe Mpya,</td>
<td>1.73 [1.18 – 2.37]</td>
<td>1.57 [0.29 – 5.31]</td>
<td>0.89 [0.06 – 1.63]</td>
<td>1.18</td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maindi village, Tanzania</td>
<td>1.70 [1.15 – 2.46]</td>
<td>3.06 [1.14 – 6.18]</td>
<td>0.88 [0.41 – 1.26]</td>
<td>2.65</td>
</tr>
</tbody>
</table>

**NOTE** The transmission parameters were obtained by fitting the non-age structured model of household transmission of ocular *C. trachomatis* to the baseline data summarised in Table 4-1.

The estimates of $\beta_G$ and $\beta_L$ were sensitive to changes in the duration of infection, whereas the estimates of $w$, $R$, and the ratio $\beta_G / \beta_L$ were not affected by changes in the duration of infection (Figure 5-1).
As the definition of a household unit becomes smaller in size (from village to compound; balozi to household; kaya to room), the proportion of units with at least one infected individual decreases. The estimate of $\beta_0$ increased as the definition of the household unit became smaller in size and the estimates of $\beta_k$ and $R_c$ decreased (except for $\beta_i$ in the Upper Saloum District) and $w$ remained approximately constant (Table 5-2).
<table>
<thead>
<tr>
<th>Community</th>
<th>Unit</th>
<th>Fraction of units infected</th>
<th>$\beta_G$ [95% CI]</th>
<th>$\beta_L$ [95% CI]</th>
<th>$w$ [95% CI]</th>
<th>$R*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jali village, Jali village, The Gambia</td>
<td>Village</td>
<td>0.50</td>
<td>0.03 [0.006 – 0.09]</td>
<td>6.25 [3.42 – 11.52]</td>
<td>1.11 [0.99 – 1.14]</td>
<td>$\rightarrow\infty$</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>Compound</td>
<td>0.24</td>
<td>0.12 [0.05 – 0.24]</td>
<td>8.35 [4.79 – 14.08]</td>
<td>1.21 [1.07-1.36]</td>
<td>1.35</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>Household</td>
<td>0.25</td>
<td>0.29 [0.16 – 0.51]</td>
<td>7.09 [3.58 – 13.73]</td>
<td>1.22 [0.99 – 1.45]</td>
<td>1.25</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>Room</td>
<td>0.10</td>
<td>1.34 [0.97 – 1.81]</td>
<td>2.68 [1.24 – 5.51]</td>
<td>0.93 [0.57 – 1.45]</td>
<td>1.07</td>
</tr>
<tr>
<td>Kahe Mpya sub-village, Kaya village, Tanzania</td>
<td>Compound</td>
<td>0.73</td>
<td>0.76 [0.39 - 1.40]</td>
<td>4.01 [1.81 – 7.38]</td>
<td>1.05 [0.84 – 1.23]</td>
<td>2.81</td>
</tr>
<tr>
<td>Kahe Mpya sub-village, Tanzania</td>
<td>Room</td>
<td>0.30</td>
<td>1.66 [1.18 – 2.27]</td>
<td>1.74 [0.56 – 3.91]</td>
<td>0.63 [0.12 – 1.04]</td>
<td>1.76</td>
</tr>
<tr>
<td>805</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>805</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5-2 Sensitivity of the transmission parameter estimates by definition of the 'household' unit
Exclusion of the individuals who were not examined at the moment of sampling but were members of households in the four populations does not change the parameter estimates significantly (Table 5-3). In general estimates of $\beta_G$ were slightly increased and estimates of $\beta_L$ were slightly decreased. Assuming infected individuals to be more or less likely to be sampled did not alter the parameter estimates significantly either (Table 5-4).

<table>
<thead>
<tr>
<th>Community</th>
<th>Global transmission coefficient, $\beta_G$ [95% CI]</th>
<th>Local transmission coefficient, $\beta_L$ [95% CI]</th>
<th>Coefficient for density dependence, $w$ [95% CI]</th>
<th>$R^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, Upper Saloum District, The Gambia</td>
<td>0.36 [0.21 – 0.59]</td>
<td>5.90 [2.86 – 11.91]</td>
<td>1.17 [0.91 – 1.42]</td>
<td>1.21</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>0.89 [0.48 – 1.56]</td>
<td>3.76 [1.63 – 7.15]</td>
<td>1.04 [0.82 – 1.24]</td>
<td>2.53</td>
</tr>
<tr>
<td>Sub-Village of Kahe Mpya, Tanzania</td>
<td>1.73 [1.23 – 2.36]</td>
<td>1.64 [0.32 – 5.51]</td>
<td>0.91 [0.09 – 1.65]</td>
<td>1.21</td>
</tr>
<tr>
<td>Maindi village, Tanzania</td>
<td>1.64 [1.21 – 2.19]</td>
<td>2.87 [1.25 – 5.40]</td>
<td>0.92 [0.49 – 1.28]</td>
<td>1.84</td>
</tr>
</tbody>
</table>

Table 5-3: Estimation of transmission parameters in four endemic populations excluding individuals from the populations that were not examined.
<table>
<thead>
<tr>
<th>Community</th>
<th>Weighting of how likely infected individuals were sampled compared to uninfected individuals</th>
<th>Global transmission coefficient, $\beta_G$ [95% CI]</th>
<th>Local transmission coefficient, $\beta_L$ [95% CI]</th>
<th>Coefficient for density dependence, $w$ [95% CI]</th>
<th>$R^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, The Gambia</td>
<td>0.5</td>
<td>0.29 [0.15 – 0.50]</td>
<td>7.39 [3.72 – 14.20]</td>
<td>1.23 [1.01 – 1.46]</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.29 [0.16 – 0.51]</td>
<td>7.09 [3.58 – 13.73]</td>
<td>1.22 [0.99 – 1.45]</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.30 [0.17 – 0.51]</td>
<td>6.80 [3.49 – 13.37]</td>
<td>1.21 [0.99 – 1.44]</td>
<td>1.23</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>0.5</td>
<td>0.76 [0.38 – 1.41]</td>
<td>4.06 [1.84 – 7.42]</td>
<td>1.05 [0.84 – 1.23]</td>
<td>2.98</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.76 [0.39 – 1.40]</td>
<td>4.01 [1.81 – 7.38]</td>
<td>1.05 [0.84 – 1.23]</td>
<td>2.81</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.78 [0.41 – 1.41]</td>
<td>3.92 [1.78 – 7.34]</td>
<td>1.05 [0.84 – 1.23]</td>
<td>2.61</td>
</tr>
<tr>
<td>Sub-Village of Kahe Mpya, Tanzania</td>
<td>0.5</td>
<td>1.73 [1.22 – 2.39]</td>
<td>1.54 [0.28 – 5.28]</td>
<td>0.88 [0.05 – 1.62]</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.73 [1.18 – 2.37]</td>
<td>1.57 [0.29 – 5.31]</td>
<td>0.89 [0.06 – 1.63]</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.72 [1.18 – 2.36]</td>
<td>1.59 [0.30 – 5.38]</td>
<td>0.90 [0.07 – 1.64]</td>
<td>1.18</td>
</tr>
<tr>
<td>Maindi village, Tanzania</td>
<td>0.5</td>
<td>1.74 [1.16 – 2.59]</td>
<td>3.06 [1.13 – 6.15]</td>
<td>0.87 [0.39 – 1.25]</td>
<td>2.86</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.70 [1.15 – 2.46]</td>
<td>3.06 [1.14 – 6.18]</td>
<td>0.88 [0.41 – 1.26]</td>
<td>2.65</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1.63 [1.12 – 2.36]</td>
<td>3.13 [1.20 – 6.28]</td>
<td>0.90 [0.44 – 1.29]</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Table 5-4 Estimation of transmission parameters accounting for if infected individuals were half, equal or twice as likely to be sampled than uninfected individuals
The average ICCs from the model simulations were in agreement with the ICCs calculated from the data, suggesting that the simple SIS model of household transmission captures much of the dynamics of *C. trachomatis* infection in these communities (Table 5-5).

<table>
<thead>
<tr>
<th>Community</th>
<th>ICC from data</th>
<th>Mean simulated ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, Upper Saloum District, The Gambia</td>
<td>0.26</td>
<td>0.23</td>
</tr>
<tr>
<td>Jali village, The Gambia</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>Sub-village of Kahe Mpya, Tanzania</td>
<td>0.11</td>
<td>0.12</td>
</tr>
<tr>
<td>Maindi village, Tanzania</td>
<td>0.14</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 5-5 Comparison of the ICC from four populations endemic for trachoma with the mean simulated ICC. **NOTE** – ICC = Intraclass correlation coefficient, with the mean ICC calculated from running 1000 stochastic simulations. The stochastic simulations used the estimated household transmission parameters and the fitted household size distribution described in Chapter 3.
Estimation of household and community transmission with age-structure

Methods

Estimation

The age-structured SIS household model of transmission allows for different rates of household and community transmission for two different age classes. We chose the two age classes to be individuals aged 0-9 and those greater or equal to ten years old as children under the age of 10 are considered to be the principle reservoir of infection. The characteristics of each age group are given in Chapter 4, Table 4-2.

Maximum likelihood methods were used to estimate model parameters from the cross-sectional, pre-intervention data on the prevalence of infection, assuming that infection was at endemic equilibrium (the likelihood is defined earlier, equation 3-15). The child-, \( \gamma_c \), and adult-specific, \( \gamma_a \), recovery rates were taken as the reciprocals of the estimated average durations of infection for the two age categories in a Gambian cohort with frequent follow-up [27]: \( 1/\gamma_c = 18.6 \text{ weeks} \), and \( 1/\gamma_a = 7.1 \text{ weeks} \). The average duration of infection, \( 1/\gamma \), was assumed to be 17.2 weeks for the non-age-structured model [27]. We assume frequency dependent transmission of infection (\( w = 1 \)), in agreement with the results for the non-age structured model, such that the hazard of infection is proportional to the fraction of contacts that are infectious (rather than number). The other transmission parameters were constrained to be greater than zero. The variance of each parameter estimate was obtained from the diagonal entries of the inverted Hessian matrix of the maximized log-likelihood [201]. Approximate confidence intervals were calculated assuming a normal distribution on the log-scale for the parameters.

The transmission model was written in R (version 2.7.2) [203]. To ensure that a global maximum likelihood was found, optimization was restarted at different parameter values and robustness of the estimate was examined under both Nelder-Mead and simulated-annealing algorithms from the ‘optim’ package.

Model selection

Incorporating two age groups and household structure into a model of ocular chlamydial transmission allows for up to eight transmission parameters to be estimated. However
simpler models are special cases within this eight transmission parameter model (Table 3-1). For each dataset, the Akaike Information Criterion (AIC) was used to identify the most parsimonious yet adequate model [211]. The AIC is given by \( AIC = -2L + 2k \), where \( L \) is the total log-likelihood and \( k \) is the number of parameters estimated. When comparing two models, a difference greater than 10 between the respective AICs is considered as empirical evidence in favour of the model with the lower AIC value [211].

Results
Table 5-6 shows the AIC of each model for each community and the parameter estimates for the different models are given in Table 5-7. Model 5 has the lowest AIC for Upper Saloum district and Jali village (where \( \theta \) equals 1.48 and 0.47 respectively, corresponding to the relative susceptibility of adults compared to children). Model 3 had the lowest AIC for Kahe Mpya sub-village and Model 4 had the lowest AIC for Maindi village (where \( \theta \) equals 0.00001, corresponding to the relative infectiousness of adults compared to children).

However there is only enough empirical support for the model with the lower AIC when the difference between the model with the lowest AIC and the AIC of a simpler model is greater than or equal to 10 [211]. The difference in AIC values between models 1 (homogeneous mixing of the population with no age structure) and 2 (household and community transmission, no age structure) is much larger than 10 in all four datasets in favour of model 2, and so there is support for a model with household and community transmission. There is also support for including age structure in addition to household structure when the model includes a shorter duration of infection for older individuals compared with younger individuals (model 3). The exception is the Upper Saloum District in The Gambia; in this case the difference in the AIC values is less than ten between models with or without explicit age structure. The reduction in the AIC between model 3 and a model where the transmission rates depend on the age of the susceptible and the infectious individual (models 4-9) is not large enough for there to be empirical support for any of these models in Kahe Mpya sub-village and Maindi village. Only in Jali village, is the reduction in the AIC between models 5 and 3 large enough for there to be support for model 5.
The ratio between household transmission coefficients and community transmission coefficients remained similar in each setting after accounting for differences in transmission by age.

<table>
<thead>
<tr>
<th>Model</th>
<th>Description of model</th>
<th>Number of parameters estimated</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Upper Saloum district</td>
<td>Jali village</td>
</tr>
<tr>
<td>1</td>
<td>Homogeneous mixing of the population. Children and adults have the same recovery rate.</td>
<td>1</td>
<td>462</td>
</tr>
<tr>
<td>2</td>
<td>Household and community transmission. Children and adults have the same recovery rate.</td>
<td>2</td>
<td>305*</td>
</tr>
<tr>
<td>3</td>
<td>Household and community transmission. Children recover from infection at a slower rate than adults.</td>
<td>2</td>
<td>301</td>
</tr>
<tr>
<td>4</td>
<td>Household and community transmission. Adults have a different infectiousness than children</td>
<td>3</td>
<td>302</td>
</tr>
<tr>
<td>5</td>
<td>Household and community transmission. Adults have a different susceptibility than children</td>
<td>3</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>Household and community transmission. Adults have a different infectiousness than children but this may differ between household and community transmission.</td>
<td>4</td>
<td>304</td>
</tr>
<tr>
<td>7</td>
<td>Household and community transmission. Adults have a different susceptibility to children but this may differ between household and community transmission.</td>
<td>4</td>
<td>302</td>
</tr>
<tr>
<td>8</td>
<td>Household and community transmission. Adults and children are equally susceptible and infectious but there are different contact rates between adults→ adults, adults→ children, children→ adults and children→ children.</td>
<td>6</td>
<td>306</td>
</tr>
<tr>
<td>9</td>
<td>The transmission rates of an infected individual infecting a susceptible individual of age classes: adults→ adults, adults→ children, children→ adults and children→ children differ for both household and community transmission.</td>
<td>8</td>
<td>307</td>
</tr>
</tbody>
</table>

Table 5-6 Comparison of different transmission models fitted to C. trachomatis infection data. The Akaike Information Criterion (AIC) values are shown for each model and each of the four endemic communities under investigation. The smallest AIC value for each community is indicated in italics. If there is a difference greater than or equal to 10 between two AIC values there is enough empirical support for the model with the lower AIC value [211]. The model with enough empirical support is indicated by an asterisk (*).
Table 5-7 Maximum likelihood estimates of the transmission parameters for each of the four populations and nested models. An explanation of each of the different transmission models is given in Table 3-1 and Table 5-6. The numbers in square brackets denote 95% confidence intervals.

Upper Saloum district, The Gambia

<table>
<thead>
<tr>
<th>Model number</th>
<th>$\beta_{Lcc}$</th>
<th>$\beta_{Lca}$</th>
<th>$\beta_{Laa}$</th>
<th>$\beta_{Lac}$</th>
<th>$\beta_{Gcc}$</th>
<th>$\beta_{Gca}$</th>
<th>$\beta_{Gaa}$</th>
<th>$\beta_{Gac}$</th>
<th>$\theta$</th>
<th>$\ln L$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.62</td>
<td>$[1.60 - 1.65]$</td>
<td>$\beta_{Gcc}$</td>
<td>$\beta_{Gca}$</td>
<td>$\beta_{Gac}$</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>1.78</td>
<td>$[1.71 - 1.86]$</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Lcc}$</td>
<td>0.20</td>
<td>$[0.17 - 0.23]$</td>
<td>$\beta_{Gcc}$</td>
<td>$\beta_{Gca}$</td>
<td>$\beta_{Gac}$</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>2.52</td>
<td>$[2.44 - 2.60]$</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Lcc}$</td>
<td>0.26</td>
<td>$[0.23 - 0.30]$</td>
<td>$\beta_{Gcc}$</td>
<td>$\beta_{Gca}$</td>
<td>$\beta_{Gac}$</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>0.37</td>
<td>$[0.34 - 0.40]$</td>
<td>$\beta_{Lcc} * \theta$</td>
<td>$\beta_{Lcc} * \theta$</td>
<td>0.04</td>
<td>$[0.03 - 0.04]$</td>
<td>$\beta_{Gcc} * \theta$</td>
<td>$\beta_{Gca} * \theta$</td>
<td>$\beta_{Gac} * \theta$</td>
<td>20.88</td>
</tr>
<tr>
<td>5</td>
<td>2.13</td>
<td>$[1.77 - 2.56]$</td>
<td>$\beta_{Lcc} * \theta$</td>
<td>$\beta_{Lcc} * \theta$</td>
<td>0.24</td>
<td>$[0.15 - 0.37]$</td>
<td>$\beta_{Gcc} * \theta$</td>
<td>$\beta_{Gca} * \theta$</td>
<td>$\beta_{Gac} * \theta$</td>
<td>1.48</td>
</tr>
<tr>
<td>6</td>
<td>0.37</td>
<td>$[0.35 - 0.40]$</td>
<td>$\beta_{Lcc}$</td>
<td>7.74</td>
<td>$[6.64 - 9.02]$</td>
<td>$\beta_{Lac}$</td>
<td>$\beta_{Gcc}$</td>
<td>0.01</td>
<td>$[0.00 - 5e+17]$</td>
<td>$\beta_{Gca}$</td>
</tr>
<tr>
<td>7</td>
<td>1.96</td>
<td>$[1.56 - 2.46]$</td>
<td>$\beta_{Laa}$</td>
<td>3.35</td>
<td>$[2.52 - 4.46]$</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Gaa}$</td>
<td>0.21</td>
<td>$[0.17 - 0.26]$</td>
<td>$\beta_{Gcc}$</td>
</tr>
<tr>
<td>8</td>
<td>1.88</td>
<td>$[0.78 - 4.51]$</td>
<td>2.42</td>
<td>$[1.02 - 5.72]$</td>
<td>4.44</td>
<td>$[1.86 - 10.61]$</td>
<td>$\beta_{Lca}$</td>
<td>0.45</td>
<td>$[0.19 - 1.08]$</td>
<td>0.05</td>
</tr>
<tr>
<td>9</td>
<td>3.04</td>
<td>$[2.69 - 3.45]$</td>
<td>3.72</td>
<td>$[1.68 - 8.21]$</td>
<td>3.25</td>
<td>$[0.90 - 11.79]$</td>
<td>$\beta_{Laa}$</td>
<td>0.09</td>
<td>$[0.00 - 4e+01]$</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Jali village, The Gambia

<table>
<thead>
<tr>
<th>Model number</th>
<th>$\beta_{Lcc}$</th>
<th>$\beta_{Lca}$</th>
<th>$\beta_{Laa}$</th>
<th>$\beta_{Lac}$</th>
<th>$\beta_{Gcc}$</th>
<th>$\beta_{Gca}$</th>
<th>$\beta_{Gaa}$</th>
<th>$\theta$</th>
<th>$\ln L$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.94 [1.89 - 2.01]</td>
<td>$\beta_{Gcc}$</td>
<td>$\beta_{Gcc}$</td>
<td>NA</td>
<td>NA</td>
<td>-198.10</td>
</tr>
<tr>
<td>2 1.63 [1.29 - 2.05]</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Lcc}$</td>
<td>0.45 [0.25 - 0.79]</td>
<td>$\beta_{Gcc}$</td>
<td>$\beta_{Gcc}$</td>
<td>NA</td>
<td>NA</td>
<td>-178.34</td>
</tr>
<tr>
<td>3 2.35 [1.85 - 2.98]</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Lcc}$</td>
<td>$\beta_{Lcc}$</td>
<td>0.65 [0.37 - 1.13]</td>
<td>$\beta_{Gcc}$</td>
<td>$\beta_{Gcc}$</td>
<td>NA</td>
<td>NA</td>
<td>-144.33</td>
</tr>
<tr>
<td>4 0.56 [0.03 - 9.04]</td>
<td>$\beta_{Lcc}^* \theta$</td>
<td>$\beta_{Lcc}^* \theta$</td>
<td>$\beta_{Lcc}^* \theta$</td>
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Kahe Mpya sub-village, Tanzania

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Maindi village, Tanzania

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The median prevalence of infection from 100 simulations from the transmission model with the most support corresponds well with the prevalence of infection in each age group for all four data-sets (Figure 5-2).

Figure 5-2 Correspondence between the proportion of individuals infected in each age group (and proportion of households infected) in the four communities (error bars are 95% binomial confidence intervals) with the median of 100 simulations of the model of transmission with the most empirical support (Table 5-6).
Discussion

Estimates of household and community not accounting for differences in transmission by age

Clustering of infection by household is an important epidemiological feature of many communicable diseases and is thought to be a key characteristic of trachoma. However, the magnitude of transmission of *C. trachomatis* between individuals belonging to the same household and that between individuals living in different households but the same community, have not previously been estimated. Here they were estimated in four different populations by fitting a household model of transmission to prevalence data using maximum likelihood estimation.

The variation of the results within the two countries and the small number of populations studied in each country make inter-country comparisons difficult. Generally, the two populations studied in The Gambia were estimated to have higher local (household) and lower global (community) transmission compared to the two populations in Tanzania i.e. household transmission was estimated to be more efficient in The Gambia than Tanzania. The higher household transmission in The Gambia is not intuitive from the differences in geographical distances between households in the two countries. Households are further apart in the Tanzanian populations than those in The Gambia and from this one may think community transmission to be lower in Tanzania. However our work indicates community transmission to be higher in Tanzania. This may be explained by differences in their community structure: Individuals in The Gambia live in much larger households which cluster together to form large compounds. The larger size of the living unit may limit the number of contacts made with the rest of the community therefore sustaining transmission within the household. This is supported by the results of the sensitivity analysis of the household unit definition, which indicate that the smaller the unit, the higher the estimated amount of global (community) compared to local transmission.

The estimates of the transmission coefficients are less certain for the Tanzanian populations than for the Gambian ones because there are fewer large households, which contribute most information to the estimate of household transmission.
Estimates of the density dependence of transmission found that $w$ was close to 1 in all communities, with the 95% confidence intervals containing 1. This indicates that individuals typically have a fixed number of contacts per household regardless of household size (i.e. the risk of infection is proportional to the fraction of infective individuals in a household, rather than the number) and that prevalence of infection within a household would not increase linearly with household size. This phenomenon has also been shown for other infections, such as Streptococcus pneumoniae and influenza virus [186,189]. The estimate of $w$ from the data from Upper Saloum district is slightly higher than the other estimates ($w = 1.22$), resulting in a slight decline in the number of contacts per individual with household size, although the confidence intervals include 1. This may be explained by differences in human behaviour between study sites, especially as the household unit is relatively large.

In all of the populations, the household reproductive number $R_h$ was estimated to be greater than 1, indicating sustained transmission. The estimates of $R_h$ were not linearly correlated with endemic prevalence. The highest $R_h$ estimate was for Jali village whereas Maindi village had the highest endemic prevalence. However $R_h$ is an average across all households in a population and Jali village has an overdispersed household size distribution (i.e. most households will have a relatively low $R_h^{(m)}$ and a few households will have a relatively high $R_h^{(m)}$) whereas Maindi village has a Poisson distribution of household sizes.

Results from the sensitivity analysis of the definition of a household unit show that when the definition of the household unit is relatively large (e.g. a village in Upper Saloum), $R_h \rightarrow \infty$. This is because the expected final size of the number of infections following a single introduction within a village tends to infinity because of repeated re-infection and a smaller probability of stochastic extinction in this larger unit. The relationship between $R_h$ and prevalence is further complicated by the non-random mixing of individuals between villages, which we have not considered in this simple model.

Estimates of the household and community transmission coefficients were sensitive to the duration of infection whereas the ratio between the two coefficients, $w$ and $R_h$, remained unchanged. The reason why the household and community transmission coefficients were
sensitive to the duration of infection is that the longer individuals are infected for (and therefore infectious), the lower the contact rate has to be to achieve a given endemic prevalence. The ratio between the two transmission coefficients determines the level of clustering of infection within certain households.

The compound was used as the household unit in Jali as household information was not available. A compound is a fenced household or a collection of a small number of households and therefore was a fair approximation to make. From analogy with the transmission estimates in Upper Saloum district, $\beta_L$ could be expected to be slightly reduced and $\beta_G$ increased if household data were available for Jali village.

The number of individuals not examined, but part of the study population, varied between the communities. Infection with ocular C. trachomatis is not debilitating and so there is not a reason to believe that infected individuals are more or less likely to remain in the household and be sampled. For clarity, I examined how the transmission parameter estimates would differ if infected individuals were twice or half as likely to be sampled compared with uninfected individuals. This resulted in only very small changes in the estimates. Excluding the missing data from the analysis had a bigger impact on the transmission estimates but overall this was still only a marginal change and the same relationships between the transmission parameters hold (i.e. $\beta_L > \beta_G$ in three of the four communities and $w \approx 1$).

The good correspondence between the summary statistics of the data (particularly the ICC) and of the model simulations indicates that the model is a reasonable description of the household transmission of ocular chlamydial infection. A reason why the two values for the ICC do not correspond exactly is that the ICC calculated for the data does not take into account the missing individuals.

Estimates of household and community transmission accounting for differences in transmission by age

Children are considered to be a reservoir of ocular C. trachomatis infection. In this section of work the level of household and community transmission was estimated, accounting for differences in transmission between adults and children. A suite of models were used with
different levels of complexity, ranging from the most simple SIS model with no age structure and homogenous mixing through to a model with children having a longer duration of infection than adults and different transmission rates of household and community transmission, depending on the age of the susceptible and infectious individual. The AIC was used to determine the most parsimonious model for each setting.

In all four datasets there was strong evidence for differences in household and community transmission parameters. Three out of four communities also had strong evidence for children having a longer duration of infection than adults. The exception was Upper Saloum District, which had a very low prevalence of infection (7%) and therefore older individuals may not have been sufficiently exposed to infection for a partially protective immune response to develop that would reduce the duration of infection. In addition, prevalence of infection does not decline with age in this population [53].

Out of the further levels of complexity that were incorporated into the model, there was only enough empirical support for adults (individuals aged ≥ 10 years old) being half as susceptible to infection as children in Jali village. This is likely to reflect behavioural differences that put these individuals at lower risk, but could also result from partially-protective immunity to infection (and indeed the inflammatory cytokine profile does increase with age [86]). Including this and other levels of complexity did not provide strong evidence for a better explanation of the data in the other communities.

The estimate for the relative susceptibility of adults for Kahe Mpya sub-village was also below 1 but for Maindi village and Upper Saloum district the estimates were above 1, indicating adults are more susceptible than children. There were mixed results for the estimates of the infectiousness of adults compared to children whereby adults were estimated to be more infectious than children in the two populations from The Gambia and vice versa in the two populations from Tanzania. There were not consistent patterns in the estimated mixing rates between the different age groups across the four communities. The behaviour and hygiene practices may differ in the four populations however the 95% confidence intervals were wide for the transmission parameters, indicating the statistical power was too low to obtain reliable estimates.
To understand how transmission rates differ between adults and children, data from much larger populations are required. Each household in the data contributes to the total log likelihood. Therefore, the larger the number of households in the data, the more augmented true differences will be between model likelihoods. This in turn would increase the difference in AIC values between two models.

Overall conclusion
In conclusion I show that different rates of household and community transmission and with the greater contribution of children to transmission (by having a longer duration of infection) are important characteristics of transmission of *C. trachomatis* in four diverse communities. The implications of different levels of household transmission are addressed in the next chapter.

Limitations
There are some caveats to our model of transmission. The household model used in this work assumes that all individuals mix homogeneously outside their household at the same rate (specific to each setting), such that each household is at equal risk of infection. This is likely to be a simplification e.g. people in Maindi village could mix more with people in their balozi than people in other balozis and some individuals are likely to mix with more people than others (e.g. balozi leaders). However, due to the small size of the four populations this was an adequate assumption to make. The small size of the populations did not allow for biological or behavioural heterogeneities within each age group to be explored. There was not enough evidence to support adults having a different relative infectiousness compared to children. The model was not fitted to infectious load data because it remains to be elucidated as to how the number of bacteria harboured from a swab exactly relates to infectiousness. Once this relationship is better understood differences in infectiousness between the age groups can be explored further. Despite these caveats, the correspondence between the ICC from the model simulations and the data indicate that the model is a reasonable description of the household transmission of ocular chlamydial infection.
In the age structured model, individuals do not move from one age group to the next but this is a reasonable simplification as the time spent in the lower age group (ten years) by each individual is far longer than the average duration of infection. If ageing of the population was to be included into the model, births and deaths would be included too and incorporation of these parameters would result in the household characteristics changing over time, resulting in a much more complicated model and possibly less tractable results.

The age-structured model only contained two age groups, implying, for example, that somebody fifty years old has the same transmission patterns as a fourteen year old. However, if more age groups were included many more transmission parameters would be required to be estimated and the size of the data was already not large enough to obtain reliable estimates for two age groups. Much of the trachoma literature states differences between children under the age of ten and older individuals in terms of risk of infection. Furthermore the WHO guidelines use this age threshold for measuring whether communities warrant receiving mass antibiotic treatment. I did not perform a sensitivity analysis on the age threshold determining ‘adults’ and ‘children’ due to the computationally intensive nature of estimating transmission parameters for each community for all the different models.

Accurate testing of individuals for ocular chlamydial infection was assumed, including the absence of contamination of conjunctival swabs. Cross-contamination of samples is a risk when using PCR techniques but standard precautions were taken to prevent this [47,48]. The four populations were assumed to be at endemic equilibrium for ocular C. trachomatis transmission. This assumption was made because none of the communities had received any interventions to reduce transmission. It is possible that a secular trend in the improvement of sanitation may have been occurring; more so in the lower endemicity communities but there is no data to show such trends. If these trends were true, the transmission parameters would need to decrease per unit of time.
CHAPTER 6 IMPLICATIONS OF HOUSEHOLD TRANSMISSION

It is important to understand the implications of various levels of household transmission both for the epidemiology and the control of trachoma.

In this chapter, the contribution of transmission between members of the same household and that between households of the same population to the incidence of ocular *C. trachomatis* infection is examined. The role of household size (number of people in a household) is also investigated to assess whether individuals from larger households contribute more towards transmission than smaller households. The implications of household transmission in terms of persistence of infection within households are investigated through inferences of the relationship between the estimated transmission parameters and stochastic simulations of the household model. Finally the difference between a transmission model with high household transmission and relatively low community transmission and a model which allows for community transmission only (homogeneous mixing) is explored as the latter has been assumed in previous models of trachoma to understand optimal control strategies. All these implications are discussed in relation to the efficient control of ocular *C. trachomatis* and blinding trachoma.

The estimates of the proportion of incident infections due to transmission within the household and the contribution to transmission by household size are presented in the PLoS NTDs Research Article [207].
Methods

The implications of household transmission are considered using the simple SIS household model without age structure with parameter estimates given in Chapter 5).

The incidence of ocular C. trachomatis from transmission between members of the same household by households of size \( m \), \( C_L^{(m)} \), is given by:

\[
C_L^{(m)} = \sum_{j=0}^{\lfloor m-1 \rfloor} \left( m - j \right) \frac{j}{(m-1)} \beta_{\text{L}} \varphi_{m} z_{j}^{(m)}.
\]

The incidence from transmission between members of the community by households of size \( m \), \( C_G^{(m)} \), is given by:

\[
C_G^{(m)} = \sum_{j=0}^{\lfloor m-1 \rfloor} \left( m - j \right) v \beta_{\text{G}} \varphi_{m} z_{j}^{(m)}.
\]

(The definitions of parameters are given in Chapter 3.)

The contribution to transmission by households of size \( m \), \( \tau_{m} \), is given by:

\[
\tau_{m} = \frac{C_L^{(m)} + \mu_{m} \sum_{m=0}^{m=\infty} C_G^{(m)}}{\sum_{m=1}^{m=\infty} C_L^{(m)} + \sum_{m=1}^{m=\infty} C_G^{(m)}}.
\]

The parameter \( \mu_{m} \) corresponds to the proportion of global prevalence attributed by households of size \( m \). Therefore the proportion of transmission contributed by an individual from a household of size \( m \), is given as:

\[
\varphi_{m} m \sum_{m=\infty}^{\infty} \left( \tau_{m} / \varphi_{m} \right).
\]
**Stochastic simulation model**

Stochastic simulations were used to examine the time a household is infected for and to compare the rate of return of infection after intervention of the fitted SIS household model to a model with homogeneous mixing of the population.

The simulation model was based on the one described in section non-age structured model and was written in the R programming language [203]. Each household, \( i \), is divided into two state variables: susceptible individuals, \( H_{i,1} \) and infected individuals, \( H_{i,2} \). The number of new infections, \( I_i \), and recoveries, \( R_i \), from infection were assumed to be binomially distributed (number of trials, probability):

- \( I_i(t) \sim \text{binomial}(H_{i,1}(t), \lambda(t)\delta t) \)
- \( R_i(t) \sim \text{binomial}(H_{i,2}(t), \gamma\delta t) \)

Where \( \lambda \) is the force of infection given by:

\[
\lambda = \frac{\beta_L H_{i,2}}{H_{i,1} + H_{i,2}} + \frac{\sum_{i=1}^{n} H_{i,1}}{\sum_{i=1}^{n} (H_{i,1} + H_{i,2})}
\]

and \( \gamma \) is the recovery rate (\( n \) is the number of households).

- Therefore \( H_{i,1}(t + dt) = H_{i,1}(t) + R_i(t) - I_i(t) \), and
- \( H_{i,2}(t + dt) = H_{i,2}(t) + I_i(t) - R_i(t) \).

**Simulating the duration that a household is infected for**

From this point on the ‘duration a household is infected for’ refers to the time period during which a household has at least one infected individual since the first infected person became infected. For each community the model was run for five hundred years (\( i.e. \) one simulation) and the mean time each household was infected for over this period was calculated and the distribution across households was plotted.
Rate of return of infection after intervention

The model was run to equilibrium and one round of mass treatment was implemented in which the aim is to treat everyone in the community but a certain proportion, $1 - \eta$, of individuals are missed. The number of infected individuals treated $H_{i,t}^{\text{treated}}$ was assumed to be distributed as $H_{i,t}^{\text{treated}} \sim \text{binomial}(H_{i,t}(t), \eta)$. Parameter $\eta$ (therapeutic coverage) was set to equal 0.80. Azithromycin was assumed to be 95% efficacious in clearing the infection [63,127]. The number of successfully treated individuals was binomially distributed with a probability of 0.95 and was sampled from the number of infected individuals selected for treatment. Successfully treated individuals at the time of treatment were transferred from the infected household state variable to the susceptible state variable. The model was run for a further 10 - 15 years to record the return of infection. One hundred stochastic simulations were run and the median at each time point was calculated. This was repeated using a transmission model that assumes homogeneous mixing of the population (i.e. $\beta_L = 0$ and $\beta_L$ was estimated for each community as described earlier in Chapter 3).

Results

An average of 71% of incident infections over the four communities was the result of transmission within the household (with a range of 48% (in Kahe Mpya sub-village) - 91% (in Upper Saloum district)). Individuals from larger households were estimated to contribute more to incidence than those from smaller households (Figure 6-1). This effect saturates for large households (> 15 individuals) and reverses somewhat at very large household sizes in Upper Saloum District where the estimate of $\nu$ (>1) is consistent with a decline in the number of infectious contacts with increasing household size. (As a comparison, if homogeneous mixing were to be assumed, individuals would contribute the same amount to transmission, regardless of household size).

Persistent infection within households is inferred in three communities (the exception being Kahe Mpya sub-village) as $\beta_L > \gamma$ (Table 5-1). This means that for the time that an individual is infected (and infectious) they will infect more than one susceptible individual in their household on average, thereby sustaining transmission within the household. In Kahe Mpya sub-village the transmission parameters imply that an infected individual recovers faster.
than the rate at which they mix with other individuals in their household (and infection is transmitted on contact) meaning that, on average, they infect less than one susceptible individual in their household, thereby not sustaining transmission within the household.

Figure 6-1 Proportion of incidence contributed per individual from a household of size \( m \) (solid line) and the probability distribution \( P(m) \) of a randomly chosen individual belonging to a household of that size based on the negative binomial distribution in a) The Gambia – the black lines correspond to Upper Saloum district and the red lines correspond to Jali village; and b) Tanzania – the black lines correspond to Kahe Mpya sub-village and the red lines correspond to Maindi village.
The median time a household is infected for is greater than the individual duration of infection in all four communities (Figure 6-2). The three communities with high levels of household infection have a median household duration of infection greater than one year. Infection persists for the longest in households in Jali, with an overdispersed distribution. Upper Saloum district and Maindi village have a similar distribution of the duration whilst households in Kahe Mpya sub-village are infected for a much shorter length of time and there is less variability between households.

![Figure 6-2: Distribution of the average time households are infected for at equilibrium in four communities.](image)

Communities with relatively high household transmission (Upper Saloum and Jali) have a slightly slower rate of return of infection than comparable populations in which transmission solely occurs through homogeneous mixing of the population ($\beta_L = 0$ and $\beta_G = 3.24, 3.88, 3.34$ and $4.72$ for Upper Saloum, Jali, Kahe Mpya and Maindi respectively) (Figure 6-3).
Figure 6-3 Comparison of the rate of return of infection after one round of mass treatment between the fitted model allowing for household and community transmission and a fitted model which only allows for homogeneous mixing of the population. The solid black line corresponds to the homogeneous mixing model and the blue dashed line corresponds to the household SIS model. Both lines are median values of 100 stochastic simulations at every time point.
Discussion

An average of 71% of incident infections were the result of transmission within the household across the four endemic communities, indicating the important role of household transmission in the repeat infections with *C. trachomatis* that result in progression to trachomatous scarring and blindness. In all four populations, individuals who live in relatively large households (*i.e.* with many individuals) contribute more to incidence than those who live in households with fewer individuals (although in Upper Saloum district this effect reverses for very large households due to \( w \) being greater than one).

Further to this, in the two Gambian populations and in Maindi village, Tanzania, the household transmission coefficient was estimated to be greater than the rate of recovery from infection, such that sustained transmission within the household is possible. In other words, the expected duration that a household is infected will be significantly longer than an individual’s duration of infection, despite eventual stochastic extinction. The median household duration of infection was estimated to be greater than a year for the three communities with relatively high household transmission, by simulating under the stochastic model. The duration of household infection depends on both the endemic prevalence and the level of household transmission. For instance, Upper Saloum district and Maindi village are predicted to have a similar duration of household infection. Upper Saloum district has the lowest endemic prevalence of infection but a high level of household transmission whereas Maindi village has the highest endemic prevalence but lower level of household transmission than Upper Saloum district. Measuring this duration would be difficult in the field as it would require frequent follow-up of individuals for an extremely prolonged amount of time, especially in a setting such as Jali village in which some households are predicted to be infected for many years.

Kahe Mpya sub-village was estimated to have a low level of household transmission with \( \beta_L < \gamma \), and the results from the stochastic simulations predicted the majority of households in this setting to be infected for less than one year, indicating that households are not persistently infected in this setting. This may be the result of a difference in social behaviour of this community or perhaps a difference in the fly population that may act as a
mechanic vector of trachoma. Interestingly, infection was successfully eliminated from this community after two mass treatments with azithromycin and multiple targeted treatment of active disease with topical tetracycline at follow-up time points [31].

Using parameters estimated from Jali village, some households were predicted to be persistently infected for at least one hundred years. During such a long period of time the household size is likely to change due to births, deaths, immigration and marriages and these rates are likely to influence how long the infection persists for inside the house (for instance if the household becomes smaller in size infection may persist for a shorter amount of time or may increase as the household becomes larger through marriage and the birth of new children). Nevertheless, the results of this work are important in illustrating potentially how long households can be persistently infected for in trachoma endemic settings.

This work shows that persistence of ocular C. trachomatis infection within households is common in different trachoma endemic settings. An important epidemiological implication of this finding is that individuals in a persistently infected household are more likely to be re-infected than other members of the community and so they may be more likely to develop the later trachoma disease sequelae. Persistent infection within households is a possible explanation for the observations of ‘continuously’ infected individuals in cohort studies (described earlier in Chapter 2). Persistent infection within households will result in members of infected households being re-infected at a higher rate than other individuals in the community whose household does not have an infected member and with infrequent follow-up, this could appear as ‘continuous’ infection in a cohort study.

The resulting persistence of infection within households permits epidemic spread following the introduction of infection into a household (i.e. $R > 1$) even if the community transmission coefficient is low. Gradual spread across communities over the course of about one year has been observed following community-wide treatment in several studies [70,130,135,212]. Such gradual spread is difficult to reconcile with the estimated, rather short duration of infection of individuals with ocular C. trachomatis. This work shows that allowing for household transmission does reduce the rate of re-emergence of infection in areas with relatively high household transmission but this alone is unlikely to be sufficient to explain the observed gradual spread of infection after community-wide treatment.
Additional factors such as genetic diversity (as explained on page 43, although there is currently limited evidence for large genetic diversity of ocular chlamydia), or waning immunity (i.e. if after treatment, the observed relatively short duration of infection in adults increased in length back to that observed in children, through lack of exposure to infection after treatment, but this has not been investigated) could also contribute to the observed gradual spread of infection.

Persistence of infection within households has consequences for trachoma control. Part of the current strategy is mass administration of antibiotics but high coverage rates are difficult to achieve [140]. If some infected members do not receive antibiotics, infection will quickly spread to other household members acting as a reservoir of infection to the rest of the community. We show that individuals from large households contribute more towards transmission than smaller households and therefore mass treatment could be limited to households over a certain size. However denying treatment to smaller families is not ethical. In the previous chapter it was demonstrated that high household transmission leads to clustering of infection by household. Targeting treatment to infected households could be a drug-sparing and potentially more cost-saving approach to controlling *C. trachomatis* infection and this question is explored in subsequent chapters of this thesis.
CHAPTER 7 TARGETING ANTIBIOTICS FOR CONTROL OF OCULAR C. TRACHOMATIS

MDA of antibiotics to control ocular C. trachomatis can be expensive for countries that do not receive donated drugs and it increases the selective pressure for resistant bacteria. An antibiotic distribution approach which targets treatment to those most likely to be infected could potentially be much more cost-effective and use fewer doses of azithromycin. The work in the previous two chapters demonstrates that intra-household transmission of ocular C. trachomatis is very efficient, leading to clustering of infection by household. Therefore antibiotics could be targeted to infected households, (if active disease can be used to identify infected households). An alternative approach to targeting treatment would be to limit treatment to children because they are the principal reservoir and source of infection in most communities.

In this chapter the most parsimonious models selected in Chapter 5 for each of the four populations examined in this thesis are used to compare the effectiveness of targeted treatment to eliminate ocular C. trachomatis with mass distribution of antibiotics. Targeted treatment scenarios examined include targeting households with at least one member with active disease or targeting treatment to children only. The effectiveness of each treatment scenario is measured by comparing the post-treatment infection dynamics, estimating the probability of eliminating infection and estimating the number of incident infections averted. The predicted number of individuals receiving antibiotics is recorded. The accuracy of using active disease to identify infected households is also calculated for the four populations. As a household targeted approach may increase the coverage of infected individuals receiving antibiotics, the effectiveness of the treatment scenario is investigated with two levels of coverage (80% and 100%).
The household SIS model assumes that each household has an equal risk of becoming infected. In reality it is likely that this will differ between households for example due to differences in hygiene practices. Sensitivity analysis of this assumption is performed to understand how it influences effectiveness of the different treatment scenarios.

Methods

Sensitivity and Specificity of Active Disease as a Marker of Infection
The sensitivity and specificity of active disease (TF and TI) as a marker of infection were calculated among individuals in each community. I also calculated the sensitivity and specificity of active disease exhibited by at least one member of a household as a marker for infection of at least one household member (which we refer to as the household sensitivity and specificity). This was done for disease in all ages and limiting assessment to children under the age of 10 years old.

Stochastic Simulations
In Chapter 2, Model 2 for Upper Saloum district, Model 5 for Jali village and Model 3 for the other two Tanzanian populations were shown to be the most parsimonious yet adequate models for the distribution of ocular C. trachomatis infection in the respective communities. These models were simulated using the estimated parameters for each community to compare the effectiveness of alternative treatment strategies. The simulation model was written in the R programming language [203]. Each household, indexed by \( i \), is divided into four state variables: susceptible children, \( H_{i,1} \), infected children, \( H_{i,2} \), susceptible adults, \( H_{i,3} \), infected adults, \( H_{i,4} \). The number of new infections, \( I_{i,y} \), and recoveries, \( R_{i,y} \), from infection in both age groups were assumed to be binomially distributed (number of trials, probability), where \( y \) is the age group index:

- \( I_{i,c}(t) \sim \text{binomial}(H_{i,1}(t), \lambda_c(t)\delta t) \) and \( I_{i,a}(t) \sim \text{binomial}(H_{i,3}(t), \lambda_a(t)\delta t) \)
- \( R_{i,c}(t) \sim \text{binomial}(H_{i,2}(t), \gamma_c\delta t) \) and \( R_{i,a}(t) \sim \text{binomial}(H_{i,4}(t), \gamma_a\delta t) \)
Therefore $H_{i,t} (t + dt) = H_{i,t} (t) + R_i (t) - I_{i,c} (t),$

$H_{i,t} (t + dt) = H_{i,t} (t) + I_{i,c} (t) - R_i (t)$

$H_{i,t} (t + dt) = H_{i,t} (t) + R_i (t) - I_{i,c} (t)$ and

$H_{i,t} (t + dt) = H_{i,t} (t) + I_{i,c} (t) - R_i (t)$

**Implementation of Treatment**

The model was run to equilibrium and at chosen time points (depending on the level of endemicity) treatment was implemented. The outcome of three annual rounds of azithromycin treatment was investigated in all four populations as this is the number of treatment rounds recommended by the WHO prior to re-assessment of the prevalence of active disease. Three treatment strategies were investigated:

a) Mass treatment in which the aim is to treat everyone in the community but a certain proportion, $1 - \eta$, of individuals missed;

b) Targeted treatment of households with one or more members presenting with active disease in a household but a proportion of individuals ($1 - \eta$) are missed;

c) Targeted treatment of households with one or more member presenting with active disease and all members within such household are treated;

d) Mass treatment of only children aged <10 years, assuming a certain proportion, $1 - \eta$, are missed.

The number of individuals treated in each state variable $H_{i,t}^{treated}$ in each strategy were assumed to be distributed as:

a) $H_{i,t}^{treated} \sim \text{binomial} \left( H_{i,t} (t), \eta \right)$

b) $H_{i,t}^{treated} \sim \text{binomial} \left( H_{i,t} (t), \eta \phi \right)$

c) $H_{i,t}^{treated} \sim \text{binomial} \left( H_{i,t} (t), \phi \right)$ and

d) $H_{i,t}^{treated} \sim \text{binomial} \left( H_{i,t} (t), \eta \right)$. 


Parameter $\eta$ (therapeutic coverage) was set to equal 0.80. Parameter $\phi$ indicates whether a household has one or more individuals with active disease (which is referred to as a ‘diseased’ household); $\phi=1$ if the household is ‘diseased’ and $\phi=0$ if the household has no diseased individuals. The probability that a household is ‘diseased’ $\omega_j(t)$, as a function of the number of infected individuals at time $t$, was calculated from the data for each of the four communities. At each treatment time $\phi$ was determined for each household: $\phi \sim \text{binomial}(1, \omega_j(t))$.

Azithromycin was assumed to be 95% efficacious in clearing the infection [63,127]. The number of successfully treated individuals was binomially distributed with a probability of 0.95 and was sampled from the number of infected individuals selected for treatment. Successfully treated individuals at the time of treatment were transferred from the respective age-class infected household state variable to the corresponding susceptible state variable.

One hundred simulations were run for each strategy and the effectiveness of each strategy was evaluated through comparing: i) the resulting post-treatment dynamics; ii) the proportion of simulations which resulted in local elimination of infection; and iii) the number of incident infections averted between the start of treatment and five years after the last treatment round.

The probability of eliminating infection was calculated as the proportion of 100 stochastic simulations which resulted in elimination of infection.

**Household heterogeneity**

Accounting for variation in transmission parameters among households (for example because of differences in hygiene) was explored. Each household was assigned a relative transmission potential, $\pi_i$, which was sampled from the negative binomial distribution (to reflect overdispersion in household hygiene) with a mean of 1 and a overdispersion parameter $\kappa$. The child and adult forces of infection for each household were modified to be $\pi_i^c$ and $\pi_i^a$. Parameter $\kappa$ was varied to explore the effect of different levels of overdispersion. The role of overdispersion was examined in Jali village as an example.
Results

In all four communities the sensitivity of active disease as a marker of infection was higher at the household level than that at the individual level. By contrast, specificity was lower (Figure 7-1). Limiting clinical diagnosis to children under the age of 10 years resulted in a similar household sensitivity and specificity compared to undertaking clinical diagnosis in all age groups (Figure 7-2).

Figure 7-1 Sensitivity (A) and specificity (B) of trachoma active disease as a marker of infection in an individual or in the household. Results are shown for four trachoma endemic communities in West and East Africa (Upper Saloum and Jali in The Gambia, and Kahe-Mpya and Maindi in Tanzania). Error bars indicate 95% binomial confidence intervals. The symbols * , ** and † indicate statistical significance (p = 0.05, 0.01 and 0.001 respectively) between the individual and the household level using Fisher’s exact test.
Figure 7-2 Sensitivity and specificity of active disease as a marker of infection in the household (both limiting clinical diagnosis to children under 10 years old and assessing clinical disease in all ages) for four trachoma endemic communities. Error bars individuate 95% binomial confidence intervals. There is no statistical significant difference between assessing active disease in children under ten years old and assessing disease in all ages (Fisher’s exact test \( p > 0.05 \)).

The probability of a household having at least one member with active disease for each community is given in Figure 7-3. In all four communities a household with at least three infected individuals is likely \( (p = 1 \) with lower bound confidence intervals ranging between 0.63 and 0.85 across the communities) to have at least one member with active disease.
The probability of a household having one or more members with active disease, given a certain number of infected individuals, calculated for the four trachoma endemic populations described in chapter 4. Error bars denote 95% binomial confidence intervals.

Three annual rounds of treatment were predicted to be not enough to interrupt transmission in Maindi village (Figure 7-4) (i.e. no simulations resulted in elimination of infection) and so six bi-annual rounds were investigated for this transmission setting.

Figure 7-4 Three annual rounds of different treatment scenarios in Maindi village. Blue – MDA with 80% coverage, Red – Treatment targeted at households with one or more individuals with active disease and 80% of individuals in each household are reached, Green – Treatment targeted at households with one or more individuals with active disease and 100% of individuals in each household are reached, Purple – MDA of children under the age of 10 years old with 80% coverage. Treatment rounds commence at time = 0. 100 stochastic simulations were run for each scenario and the median of these simulations at each time point are displayed here. The probability of eliminating infection for each treatment scenario was 0.
Targeting treatment to households, in which at least one resident has active disease, gives similar post-treatment dynamics as MDA (Figure 7-5). The household-targeted approach has a slightly higher rate of return of infection and therefore the probability of eliminating infection five years after the last treatment round is somewhat lower. However if all individuals in targeted households are treated, then the probability of eliminating infection greatly increases. Limiting MDA to children under the age of ten does result in an initial decrease in the prevalence of infection in the untreated older population (Figure 7-6) but the probability of eliminating infection in the whole community is greatly reduced compared to the other treatment scenarios investigated (Figure 7-5). There is a relatively smaller difference in effectiveness between the different treatment scenarios in the communities with relatively low baseline prevalence (Upper Saloum district and Kahe-Mpya sub-village) but household-targeted treatment, treating all household members remains to be the most effective treatment scenario.
Figure 7-5 Comparison of MDA with targeted treatment of households with at least one member with active disease and MDA of children <10 years old only. Blue – MDA with 80% coverage, Red – Treatment targeted at households with one or more individuals with active disease and 80% of individuals in each household are reached, Green – Treatment targeted at households with one or more individuals with active disease and 100% of individuals in each household are reached, Purple – MDA of children under the age of 10 years old with 80% coverage. Treatment rounds commence at time = 0. Upper Saloum district, Kahe Mpya sub-village and Jali village have three annual treatment rounds, Maindi village has six biannual rounds. 100 stochastic simulations were run for each scenario and the median of these simulations at each time point are displayed here. The bar charts show the probability of eliminating infection from the community for each treatment scenario.
Figure 7-6 Dynamics of the prevalence of infection in two age groups when only children < 10 years receive MDA. The lines are median values of 100 stochastic simulations. The black line corresponds to prevalence in ‘children’ < 10 years and the grey line corresponds to ‘adults’, aged ≥ 10 years old.

Targeting antibiotics to households with at least one member with active disease results in a similar number of infected individuals clearing infection compared to MDA, assuming that in the two treatment scenarios a certain proportion of the population misses treatment. However for the household targeted approach there is a large reduction in the number of susceptible individuals receiving treatment and hence the overall number of antibiotics distributed is reduced (Table 7-1). If a household targeted approach improves the coverage of infected individuals the number of incident infections averted is largely increased. As I have shown that targeting MDA to children under the age of 10 years is not as effective in reducing the prevalence of ocular C. trachomatis I have not shown the numbers of people receiving antibiotics in the simulations.

Accounting for overdispersion in transmission parameters among households resulted in faster return of infection for all treatment strategies and the probability of eliminating
infection was lower five years after the last treatment round (Figure 7-7). However, the relationship between the treatment scenarios remained unchanged.

**No Heterogeneity**

**Slight Heterogeneity**

**Strong Heterogeneity**

Figure 7-7 Role of heterogeneity of household transmission parameters. Blue – Mass treatment with 80% coverage, Red – Treatment targeted at households with one or more individuals with active disease but 80% of individuals in each household receive treatment, Green - Treatment targeted at households with one or more individuals with active disease and 100% of individuals in each household are treated, Purple – MDA of children under the age of 10 years old with 80% coverage. Treatment rounds occur at times = 0, 1 and 2. The model fitted to Jali village was used as an example as it has reasonably high baseline prevalence and a large amount of household transmission. The bar chart shows the probability of eliminating infection after three rounds of household targeted treatment for communities with varying levels of heterogeneity of household susceptibility. Slight heterogeneity corresponds to an overdispersion parameter, \( \kappa' \), of 5 and strong heterogeneity corresponds to \( \kappa' = 1.5 \).
<table>
<thead>
<tr>
<th></th>
<th>Upper Saloum district – 3 annual treatment rounds</th>
<th>Jali village – 3 annual treatment rounds</th>
<th>Kahe Mpya – 3 annual treatment rounds</th>
<th>Maindi village – 6 biannual treatment rounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDA 80% coverage</td>
<td>Household-targeted 80% coverage</td>
<td>Household-targeted 100% coverage</td>
<td>MDA 80% coverage</td>
</tr>
<tr>
<td>Total number of individuals receiving azithromycin</td>
<td>3,822 [3,780 – 3,870]</td>
<td>1,877 [1,703 – 2,031]</td>
<td>2,033 [1,998 – 2,061]</td>
<td>2,349 [2,312 – 2,385]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,165 [1,954 – 2,338]</td>
<td>1,504 [1,386 – 1,611]</td>
<td>1,190 [1,108 – 1,265]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,441 [1,258 – 1,648]</td>
<td>1,462 [1,361 – 1,550]</td>
<td>4,877 [4,807 – 4,947]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2,033 [1,954 – 2,338]</td>
<td>1,441 [1,258 – 1,648]</td>
<td>4,877 [4,807 – 4,947]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,702 [1,555 – 1,847]</td>
<td>1,750 [1,697 – 1,820]</td>
<td>2,237 [2,186 – 2,282]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,702 [1,555 – 1,847]</td>
<td>1,750 [1,697 – 1,820]</td>
<td>2,237 [2,186 – 2,282]</td>
</tr>
<tr>
<td>Number of incident infections averted between the start of treatment and five years after the last round of treatment</td>
<td>2,314 [1,914 – 2,807]</td>
<td>2,176 [1,708 – 2,653]</td>
<td>2,169 [1,833 – 2,665]</td>
<td>2,340 [2,155 – 2,680]</td>
</tr>
</tbody>
</table>

Table 7-1: The median number of: individuals who received azithromycin; individuals who were successfully cleared of infection; and infections averted from one hundred stochastic simulations. The numbers in square brackets give the inter-quartile range.
Discussion

The success of targeting treatment for trachoma control depends on the target group containing the large majority of infected individuals. Burton and colleagues [53] previously found that if antibiotics were given to members of a compound where one or more individuals showed signs of active disease then 95% of infected individuals would receive treatment in Upper Saloum district. Here we show, in different settings with a wide range in the prevalence of infection, that selecting households with one or more members with active disease identifies a high proportion of infected households (and therefore infected individuals). Even if diagnosis of active disease is limited to children living in a household, infected households can mostly be identified. The low sensitivity of active disease as a marker of infection in individual and the variability of this sensitivity between settings highlights how inappropriate it is to directly target treatment to individuals with active disease.

Targeting treatment to these households is an approach that lies in the middle of a range of treatment strategies between one which treats infected individuals only (which is currently unfeasible due to the low sensitivity of active disease as a marker for infection at the individual level and the lack of an available point-of-care test), and one of mass treatment of the whole population, which can be very expensive unless antibiotics are donated.

Numerical simulation of *C. trachomatis* transmission in an age and household structured population indicated that targeting antibiotics to households with at least one member with active disease has a similar effect to MDA. Active disease is not 100% sensitive as a marker of infection at the household level and this explains the (small) differences observed between the two strategies. However, we show that household targeted treatment results in a large reduction in the number of uninfected individuals receiving antibiotics compared to MDA.

If all members of visited households are treated (as a result of the visit by the treatment team, rather than centralised distribution during MDA), boosting treatment coverage, there is a much higher chance of eliminating infection from the community in all settings, illustrating how successful targeting treatment to households could be. The success of this approach will depend on the extent of household transmission and the degree to which
household visits can boost treatment coverage. For example, in a community such as Kahe Mpya where household transmission is limited, this approach is less effective. Baseline surveys of the prevalence of disease could be used as an indicator for the likely degree of household transmission, enabling the selection of communities that would benefit from a targeted approach. That targeted treatment can boost treatment coverage is indicated by the results of a trial of targeted treatment in Nepal [72]. In contrast, a large effort is typically required to achieve high coverage levels for MDA control programs [140]. Analogy can be drawn with other disease control programmes, such as vaccination for polio and measles, in which a house-to-house strategy of administering vaccination achieves much higher coverage than a fixed point campaign [213,214]. Whether all household members can be reached with one household visit remains to be investigated. Two visits may be necessary to increase the coverage.

In low prevalence settings the additional benefits of treating all household members is less apparent in our simulations because we investigated the effect of three annual rounds of treatment (WHO guidelines [23]), which are sufficient for any treatment scenario to have a greater than 50% chance at eliminating infection in these settings.

Limiting treatment to children is another way to target treatment. Our models predict that the prevalence in adults declines when children under the age of ten are treated, in agreement with House et al. [160], but this strategy is not as effective as MDA or household-targeted treatment because the probability of eliminating infection is reduced in all four communities. As explained in Chapter 5, infectious load was not incorporated into the model as the relationship with infectivity requires further investigation. Infectious load has been shown to be higher in children and if this is correlated with infectivity, targeting children only could have a bigger impact. Women could be included along with children in the target group as explored in a Malian study [152]. However we did not investigate this strategy because the number of transmission parameters to be estimated would be too large for the size of our dataset and the prevalence of infection did not differ largely between males and females in the study communities [48] (Figure 4-2). Besides, there is considerable risk that specifically excluding adult males from treatment schedules would jeopardise community support for drug distribution.
Two field studies have compared targeted treatment of households to MDA: one in Nepal [72] and one in Mali [152]. The study in Nepal [72,153] compared MDA of children to household targeted treatment of all ages and found the two strategies not to be significantly different from one another in terms of the reduction in point prevalence of active disease six months after treatment. The Mali study [152] found household-targeted treatment to be less effective than MDA of the whole population with respect to the reduction of active disease prevalence one year after one round of treatment (although the age-adjusted odds ratio for prevalence active disease after household targeted treatment in relation to MDA was 1.56 with 95% confidence intervals of 1.00-2.43 indicating the strategies could have had the same outcome). Our model allows for stochastic events and we present the median outcomes of the strategies. The broad inter-quartile ranges of the simulations in the four endemic settings suggest that if single simulations are compared either strategy could appear more effective than the other e.g. if MDA was compared to household targeted treatment in a small number of comparable populations (such as the Mali and Nepalese studies) the rate of re-emergence of mass treatment could be relatively low and that of mass treatment could be relatively high, due to stochastic fluctuations in the transmission and recovery rates, giving a conclusion that MDA was more effective than household targeted treatment. If this comparison was made over many populations, however, there would be little difference between the two treatment scenarios.

There are some caveats to the model of transmission and hence these results. When fitting the model to the data we assumed that infection was at endemic equilibrium in the four populations as they had not received prior interventions; however, there could have been a downward secular trend. This would result in a decrease in the transmission parameters over time which would in turn, increase the probability of eliminating infection in all treatment scenarios. The model assumes that individuals mix homogeneously outside their household with a rate specific to each endemic setting and that each household is at equal risk of becoming infected. Sensitivity analysis of the latter assumption found that increasing the level of heterogeneity in the household transmission parameters resulted in a faster rate of return of infection after treatment with a lower probability of eliminating infection for each treatment strategy. Further studies are needed to quantify differences in households’ risk of becoming infected. We have assumed that the relationship between
active disease and infection remains constant after treatment. This requires further investigation because during a (temporary) reduction in transmission, individuals will not be infected so frequently and therefore their immune system may not be hyper-sensitised resulting in a delay in the development of active disease. However, the sensitivity of active disease as a marker for infected households was estimated to be less variable across different endemicities than the sensitivity of active disease as a marker of infection in individuals. Consequently, if the relationship between active disease and infection does change after antibiotic distribution the change may be less marked in households. Other caveats to the model have been discussed in Chapter 5.

In conclusion the work of this chapter has shown that targeting antibiotics to households with at least one individual with active disease is as effective as MDA in the reduction of ocular *C. trachomatis* or better if it increases the coverage of infected individuals. This targeted approach also results in a large reduction in the number of antibiotics distributed to a community and therefore has the potential to be more cost effective, a question that is addressed in the next chapter. Targeting MDA to children only is predicted to be not as effective as MDA to all ages, even when accounting for differences in the contribution towards transmission by adults and children. However the role of infectious load in transmission needs to be understood to fully assess the effectiveness of this treatment scenario.
CHAPTER 8 ESTIMATING THE COST-EFFECTIVENESS OF HOUSEHOLD TARGETED TREATMENT

In Chapter 7, targeting antibiotics to households with at least one member with active disease was shown to be drug sparing and as effective as MDA in eliminating infection or more effective if coverage of infected individuals is increased. The large decrease in the number of individuals requiring antibiotics in the targeted strategy could mean that this approach is more cost-effective. However, there are other costs associated with implementing each strategy that may differ between the two strategies. Therefore these costs have to be accounted for when assessing the cost-effectiveness of each treatment strategy. Costs include the number of personnel required to implement each strategy (for instance in the household strategy personnel will need to be trained to assess active disease), transport costs and opportunity costs (the cost to treatment-recipient individuals foregoing work to receive treatment). Two studies have published these costs: one in Mali [152] and one in Nepal [153].

In this chapter I calculate the cost per incident infection averted of targeted household treatment compared with MDA using previously published data on the costs of these interventions [152,153] and the stochastic simulations of these strategies for four diverse trachoma endemic communities, summarised in Table 7-1. The cost per incident infection averted is calculated both from the public health control programme perspective (assuming drugs are purchased at the generic price and that the government contributes to some of the cost of the programme) and the societal perspective (taking into account opportunity costs). The analysis is also performed assuming the antibiotics are either donated or bought at the proprietary price.
Methods

Cost data
The costs were taken from two published studies in Mali [152] and Nepal [153], which compared household-targeted treatment of all ages to mass treatment (of children in Nepal, all ages in Mali) and are summarized in Table 8-1 and Table 8-2. The cost data were collected in 2000 and 1998 respectively for the Nepalese and Malian studies. The costs are adjusted to a value closer to that of the present day’s value using the most recent available consumer price index (CPI) [215,216,217]. Costs included the generic and proprietary price of azithromycin per tablet, drug delivery costs per population size, and opportunity costs (the amount of money not earned per recipient whilst they attend the treatment campaign). Drug delivery costs were higher for household targeted treatment as they accounted for the extra resources required to identify and treat diseased households. Delivery costs in the Mali study consisted of governmental (salaries and vehicle investment) and distribution (dispatching, training of nurses and other health workers, per diems and fuel) costs specific to each strategy. Delivery costs in the study from Nepal were composed of salary and transportation costs and not the training of health workers. The delivery costs were higher for household-targeted treatment as they accounted for the extra training and salaries of nurses to diagnose trachoma in Mali and the increase in transport costs in Nepal (in this study two trips per community were assumed for this strategy: one for screening and one for treatment).

Estimation of total costs for the different treatment scenarios
The costs were applied to the resulting median and quartiles of 100 stochastic simulations of each treatment scenario (summarised in Table 7-1).

The total cost of azithromycin was calculated by multiplying the median number of individuals receiving treatment by the price per tablet and the mean number of tablets received in that age-group. The delivery costs were scaled linearly to the size of the population in the four endemic areas under study and were assumed to occur at each round of treatment. We assumed that opportunity costs were incurred by the median number of individuals receiving treatment who were aged ≥ 10 years and that mass treatment cost half a day’s wages (to collect drugs from distribution point) and household-targeted treatment
cost one hour’s wages (administered at time of second visit), (as stated in the Mali study). The per child costs from the Nepal data were assumed to be equivocal to per person costs. A discount rate of 3% per year was applied to all future costs. Two estimates of total drug costs, delivery costs and opportunity costs were obtained using the two different sets of cost data and the mean cost of the two was calculated. The two estimates were taken to be the lower and upper bounds for the different costs.

Cost-effectiveness ratio
The incremental cost-effectiveness ratio was calculated as the sum of total azithromycin costs, delivery costs (and opportunity costs, depending on the perspective), divided by the total number of incident infections averted from the start of treatment through to five years after the last treatment compared with the ‘doing nothing’ scenario.

Lower and Upper bounds for cost-effectiveness ratios
The cost-effectiveness intervals were defined using a conservative approach, such that lower bounds were estimated by calculating the incremental cost-effectiveness ratio for each simulation using the lower costs estimates and taking the lower quartile of these ratios. The Upper bounds were estimated by calculating the incremental cost-effectiveness ratio for each simulation using the upper costs estimates and taking the upper quartile of these ratios.
### Table 8-1 Cost data from Mali [152] used in this analysis.

<table>
<thead>
<tr>
<th>Cost (US$)</th>
<th>1998</th>
<th>Adjusted to 2007 US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic cost per tablet*</td>
<td>0.43</td>
<td>0.50</td>
</tr>
<tr>
<td>Government cost for mass treatment per community of 510,000 people</td>
<td>1,000</td>
<td>1,160</td>
</tr>
<tr>
<td>Government cost for household-targeted treatment per community of 510,000 people</td>
<td>10,000</td>
<td>11,600</td>
</tr>
<tr>
<td>Distribution cost for mass treatment per community of 510,000 people</td>
<td>20,000</td>
<td>23,200</td>
</tr>
<tr>
<td>Distribution cost for targeted treatment per community of 510,000 people</td>
<td>18,000</td>
<td>20,880</td>
</tr>
<tr>
<td>Opportunity cost per adult per day</td>
<td>0.55</td>
<td>0.64</td>
</tr>
</tbody>
</table>

*The proprietary cost per tablet is not given.

### Table 8-2 Cost data from Nepal [153] used in this analysis.

<table>
<thead>
<tr>
<th>Cost (US$)</th>
<th>2000</th>
<th>Adjusted to 2007 US$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic cost per tablet</td>
<td>0.64</td>
<td>0.99</td>
</tr>
<tr>
<td>Proprietary cost per tablet</td>
<td>6.22</td>
<td>9.66</td>
</tr>
<tr>
<td>Total distribution and governmental cost for mass treatment per child</td>
<td>0.049</td>
<td>0.08</td>
</tr>
<tr>
<td>Total distribution and governmental cost for targeted treatment per child</td>
<td>0.066</td>
<td>0.10</td>
</tr>
<tr>
<td>Adult wage per hour</td>
<td>0.09</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Calculation of mean number of tablets received by each age category

The mean number of tablets received by each age-group was calculated from a large data-set (~ 5000 individuals) for which the age and number of tablets received (determined by weight) was recorded.

Data

A village-wide trachoma prevalence survey was undertaken in Kahe village, Rombo district, Tanzania, as a prelude to the longitudinal studies of Kahe Mpya sub-village described elsewhere [131]. Every non-pregnant resident of Kahe Mpya was offered a single oral dose of approximately 20mg/kg azithromycin (to a maximum of 1g). An initial round of balozi-to-balozi visits was conducted, after giving notice to residents that antibiotic would be available at their balozi leader’s house on a specified day. Several mop-up exercises were then undertaken in an attempt to make sure that no-one who wanted treatment missed out. Azithromycin treatment was directly observed in every instance. In accordance with national treatment guidelines, women who said they were pregnant and children under the age of twelve months were offered two tubes of 1% tetracycline eye ointment, in place of azithromycin. Including treatment with either (oral) azithromycin or (topical) tetracycline, the total number of individuals treated in Kahe village was 5,016 against a denominator of 5,853, giving overall treatment coverage of 85.7%.

Calculation

The data were split into the two age classes used in this work and the mean number of azithromycin tablets received in each age class was calculated. Individuals aged 10 years or older received a mean of 3.43 azithromycin tablets and those under the age of 10 received a mean of 1.02 tablets.
Results

Assuming 80% therapeutic coverage and that azithromycin is not donated, household-targeted treatment was predicted to be more cost-effective than MDA in all four communities (Table 8-3). A household-targeted approach results in a similar number of infected individuals receiving antibiotics as MDA but reduces the number of antibiotics given to uninfected individuals. Including opportunity costs slightly improves the cost-effectiveness of the targeted approach (Table 8-3). We did not calculate the cost-effectiveness of targeting treatment to children because the model simulations showed it to be the least effective of the four treatment scenarios at controlling infection.

If a visit to a household facilitates treatment of all members, then there is a large increase in the number of incident infections averted compared with either MDA or targeted approaches with 80% coverage. As a result, the household targeting strategy in which all members of diseased households are treated is significantly more cost-effective in the areas with high baseline prevalence.

In this analysis the cost of the antibiotics was the dominating cost as in each of the four communities the estimated cost of generic antibiotics was at least one order of magnitude higher than the delivery cost. If the analysis is repeated but instead it is assumed that the drugs are donated, household targeted treatment is still found to be more cost effective than MDA but only if opportunity costs are included (Table 8-4). If the antibiotics are purchased at the proprietary price a household targeted approach is always more cost effective (Table 8-5).
<table>
<thead>
<tr>
<th></th>
<th>Upper Saloum district – 3 annual treatment rounds</th>
<th>Jali village – 3 annual treatment rounds</th>
<th>Kahe Mpya – 3 annual treatment rounds</th>
<th>Maindi village – 6 biannual treatment rounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDA 80% coverage</td>
<td>Household -targeted 80% coverage</td>
<td>Household -targeted 100% coverage</td>
<td>MDA 80% coverage</td>
</tr>
<tr>
<td>Cost effectiveness ratio (2007 US$ per infection averted)</td>
<td>excluding opportunity costs</td>
<td>3.1 [1.8 – 5.0]</td>
<td>1.7 [1.0 – 2.7]</td>
<td>1.7 [1.1 – 2.6]</td>
</tr>
<tr>
<td></td>
<td>including opportunity costs</td>
<td>3.6 [2.0 – 5.7]</td>
<td>1.8 [1.1 – 2.8]</td>
<td>1.8 [1.1 – 2.7]</td>
</tr>
</tbody>
</table>

Table 8-3 Cost-effectiveness of azithromycin MDA compared to targeted treatment of households with at least one member with trachoma active disease. Costs are in 2007 US$. Costs are given as the mean of the total costs estimated from the two different cost studies and scaled to the respective medians from stochastic model simulations (summarised in Table 7-1) with the numbers in square brackets giving the lower and upper bounds. The average total cost was divided by the median effectiveness (number of incident infections averted) from the simulations to give a cost-effectiveness ratio, with the numbers in square brackets giving lower and upper bounds.
### Table 8-4 Cost-effectiveness of azithromycin MDA compared to targeted treatment of households with at least one member with trachoma active disease assuming azithromycin is donated

<table>
<thead>
<tr>
<th></th>
<th>Upper Saloum district – 3 annual treatment rounds</th>
<th>Jali village – 3 annual treatment rounds</th>
<th>Kahe Mpya – 3 annual treatment rounds</th>
<th>Maindi village – 6 biannual treatment rounds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost effectiveness</strong></td>
<td>MDA 80% coverage Targeted 80% coverage Targeted 100% coverage</td>
<td>MDA 80% coverage Targeted 80% coverage Targeted 100% coverage</td>
<td>MDA 80% coverage Targeted 80% coverage Targeted 100% coverage</td>
<td>MDA 80% coverage Targeted 80% coverage Targeted 100% coverage</td>
</tr>
<tr>
<td><strong>US$ per infection averted</strong></td>
<td>excluding opportunity costs</td>
<td>including opportunity costs</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.12 [0.08 – 0.18]</td>
<td>0.18 [0.11 – 0.28]</td>
<td>0.15 [0.10 – 0.24]</td>
<td>0.07 [0.04 – 0.10]</td>
</tr>
<tr>
<td></td>
<td>0.57 [0.31 – 0.87]</td>
<td>0.23 [0.15 – 0.36]</td>
<td>0.21 [0.14 – 0.32]</td>
<td>0.33 [0.20 – 0.49]</td>
</tr>
</tbody>
</table>
### Upper Saloum district – 3 annual treatment rounds

<table>
<thead>
<tr>
<th>MDA 80% coverage</th>
<th>Targeted 80% coverage</th>
<th>Targeted 100% coverage</th>
</tr>
</thead>
</table>

### Jali village – 3 annual treatment rounds

<table>
<thead>
<tr>
<th>MDA 80% coverage</th>
<th>Targeted 80% coverage</th>
<th>Targeted 100% coverage</th>
</tr>
</thead>
</table>

### Kahe Mpya – 6 biannual treatment rounds

<table>
<thead>
<tr>
<th>MDA 80% coverage</th>
<th>Targeted 80% coverage</th>
<th>Targeted 100% coverage</th>
</tr>
</thead>
</table>

### Total cost of azithromycin assuming proprietary tablets are used (2007US$)

<table>
<thead>
<tr>
<th></th>
<th>Cost effectiveness ratio (2007 US$ per infection averted)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>excluding opportunity costs</td>
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<tr>
<td></td>
<td>including opportunity costs</td>
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<tr>
<td></td>
<td>39.2 [32.7 – 46.9]</td>
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<tr>
<td></td>
<td>39.6 [32.9 – 47.6]</td>
</tr>
<tr>
<td></td>
<td>20.5 [18.2 – 23.8]</td>
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<tr>
<td></td>
<td>20.6 [18.2 – 23.9]</td>
</tr>
<tr>
<td></td>
<td>20.5 [18.7 – 23.2]</td>
</tr>
<tr>
<td></td>
<td>22.6 [18.6 – 26.3]</td>
</tr>
<tr>
<td></td>
<td>22.9 [18.8 – 26.7]</td>
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<td></td>
<td>22.6 [18.6 – 26.3]</td>
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<tr>
<td></td>
<td>17.9 [16.4 – 19.4]</td>
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<tr>
<td></td>
<td>7.5 [7.5 – 7.6]</td>
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<tr>
<td></td>
<td>7.5 [7.5 – 7.6]</td>
</tr>
<tr>
<td></td>
<td>21.2 [19.0 – 25.6]</td>
</tr>
<tr>
<td></td>
<td>12.2 [11.2 – 15.8]</td>
</tr>
<tr>
<td></td>
<td>12.6 [11.6 – 14.3]</td>
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<tr>
<td></td>
<td>18.6 [15.5 – 20.9]</td>
</tr>
<tr>
<td></td>
<td>14.4 [12.5 – 15.8]</td>
</tr>
<tr>
<td></td>
<td>5.1 [4.7 – 7.0]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cost effectiveness ratio (2007 US$ per infection averted)</th>
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<tbody>
<tr>
<td></td>
<td>excluding opportunity costs</td>
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<tr>
<td></td>
<td>including opportunity costs</td>
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<td></td>
<td>39.6 [32.9 – 47.6]</td>
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<tr>
<td></td>
<td>20.6 [18.2 – 23.9]</td>
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<tr>
<td></td>
<td>20.6 [18.8 – 23.3]</td>
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<tr>
<td></td>
<td>22.9 [18.8 – 26.7]</td>
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<td></td>
<td>22.6 [18.6 – 26.3]</td>
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<tr>
<td></td>
<td>18.0 [16.5 – 19.5]</td>
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<tr>
<td></td>
<td>7.5 [7.5 – 7.6]</td>
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<tr>
<td></td>
<td>21.4 [19.2 – 26.0]</td>
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<td></td>
<td>12.2 [11.3 – 15.9]</td>
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<tr>
<td></td>
<td>12.6 [11.7 – 14.4]</td>
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<tr>
<td></td>
<td>18.8 [15.6 – 21.2]</td>
</tr>
<tr>
<td></td>
<td>14.3 [12.5 – 15.9]</td>
</tr>
<tr>
<td></td>
<td>5.1 [4.7 – 6.9]</td>
</tr>
</tbody>
</table>

Table 8-5 Cost-effectiveness of azithromycin MDA compared to targeted treatment of households with at least one member with trachoma active disease assuming azithromycin is purchased at the proprietary price.
Discussion

Targeted treatment to households with at least one member with active disease was shown, in Chapter 7, to use fewer antibiotics than MDA and be as effective as MDA in reducing the prevalence of ocular *C. trachomatis* or more effective if the coverage of infected individuals is increased. In this chapter, using available cost data on the two distribution scenarios, the household targeted approach is predicted to have a lower cost per infection avoided compared with MDA when antibiotics are not donated (as antibiotics are the dominating cost). Even if antibiotics are donated, opportunity costs incurred by individuals taking time to collect tablets from the MDA program can result in household targeted treatment being more cost-effective.

If a household targeted approach to administering antibiotics increases coverage in those households, the cost per incident infection averted is greatly reduced in high prevalence areas due to the increase in the number of incident infections averted. In low prevalence settings the additional benefits of treating all household members is less apparent in our simulations because we investigated the effect of three annual rounds of treatment (WHO guidelines [23]), which are enough for any treatment scenario to have a greater than 50% chance at eliminating infection in these settings. *(N. B. The baseline prevalence of active disease (Table 4-1) in the four communities is above the current threshold for MDA [23] with the exception of Upper Saloum district).*

In this analysis I assume that targeting treatment to diseased households does require more resources than MDA as trained ophthalmic nurses are required to assess the disease status of each household and this increase in personnel will require extra transport costs. The cost data used in our analysis were taken from two published studies [152,153], which both included the extra delivery costs incurred by implementing targeted household treatment, and was scaled to the size of the communities, to which the model simulations were based, assuming individuals of all ages were screened for active disease in the simulations. The delivery costs of targeting treatment to diseased households could be reduced in a number of ways that need to be researched further: treatment could be administered in the same visit as when individuals are screened, thereby reducing transport and salary costs; village volunteers could be trained to assess clinical disease (a scheme which has been trialled with
success in Ghana [218]) to reduce the costs of ophthalmic nurses; and screening could be limited to children under the age of ten: we have shown here that this approach has the same sensitivity as screening all ages but could reduce the time taken screen villages (and therefore potentially the cost). The difference in cost between screening all ages and just children remains to be investigated.

The original analysis of the data from Nepal [153] found no significant difference in the costs of MDA and household-targeted treatment but the targeted approach did result in higher delivery costs (however this study compared MDA to children only with household targeted treatment of all ages). The original analysis of the Mali data [152] found household targeted treatment to be more cost effective except in low transmission settings (both including and excluding the cost of antibiotics). Using cost data from these two studies but applying it to the stochastic model simulations; I find household targeted treatment to be more cost-effective than MDA in all settings if antibiotics are not donated. If opportunity costs are considered, I find this to be true as well when antibiotics are donated. A difference between this work and the previous cost analyses is that here the cost is calculated as a cost per incident infection averted over five years rather than a change in point prevalence between baseline and one time point. Measuring the number of infections avoided is not feasible in the field but measuring the cost-effectiveness this way from model simulations gives a better insight into impact of each treatment scenario on cumulative exposure to infection and therefore the ocular disease process.

Limitations
There are some caveats to this cost analysis: The delivery costs were scaled linearly to the size of each community and there may be some costs that are not appropriate to scale in this way. However, the two cost studies were the only published cost data at the time of our study. This work has investigated the cost-effectiveness of a household-targeted approach in populations of approximately 1,000 people. If such an approach were to be implemented on a country-wide scale, economies of scale will have to be considered e.g. a large number of nurses (or volunteers) will have to be trained for screening and there may be societal costs incurred as such personnel may stop working on other health programmes. Health
system infrastructure may need to be improved to roll out such approach and the feasibility of these needs to be considered. These limitations require further exploration.

The cost data was collected for one round of treatment. For two endemic settings I investigated the cost-effectiveness of multiple rounds of treatment of household-targeted treatment. The only cost that I took to be variable over multiple treatment rounds was the cost of antibiotics; all other costs I assumed to be fixed. However this may not be the case. As prevalence decreases, fewer antibiotics will be required for the household targeted strategy and this may reduce the transport costs. Training of personnel may also be a variable cost if less training is required for subsequent rounds of treatment. Opportunity costs and salary costs are likely to remain as fixed costs. Further investigation is required into how costs change over multiple treatment rounds.

I assumed that individuals aged ten years or over received a mean of 3.4 tablets whilst those aged under ten years received one. This is a simplification and does not include azithromycin suspension given to younger children and topical tetracycline given to infants under 6 months. However, this would increase the total cost of antibiotics further, making targeted treatment more cost effective. There may also be costs associated with treating 100% of members of targeted diseased households that we have not included in our analysis of this scenario. The costs involved in treatment scenarios are likely to vary from country to country and by size of the community treated. Further studies are required to investigate these differences. However these differences will have to vary by at least one order of magnitude for the delivery costs to become greater than the current cost of generic antibiotics.

Some trachoma endemic populations are currently receiving azithromycin as part of integrated Neglected Tropical Disease control programmes. If trachoma control continues to be part of such programmes the feasibility of incorporating household-targeted treatment into the programme will also need to be considered.

(The caveats to the model of transmission described in Chapter 5 also apply to the results of this chapter).
Conclusion
The WHO recommends targeted treatment for households containing cases of active trachoma in communities where the prevalence of disease in children aged 1-9 years is between 5 and 10%. In The Gambia, it is policy to treat household contacts of children with active trachoma even when the prevalence is less than 5% in the community (Personal communication, Mr Ansumana Sillah, Manager, Gambian National Eye Care Programme). In the previous chapter I showed that targeting treatment to households which have at least one resident with active trachoma is drug sparing and as effective as MDA in a diverse variety of settings including those with prevalence greater than 10%. Furthermore, this strategy can be more effective if it increases the coverage of infected individuals. In this chapter I have shown that household targeted treatment has the potential to be more cost effective. The results indicate a need for studies to explore whether household targeted treatment can improve coverage levels of infected individuals and a need to collect more cost data on the logistics of scaling-up such an approach in a variety of settings. Once this has been done, countries with limited antibiotic resources can consider adopting household-targeted treatment with azithromycin for trachoma control.
CHAPTER 9 OVERALL CONCLUSION AND FUTURE WORK

Summary of results
In this thesis I estimate the level of transmission of ocular C. trachomatis which occurs between members of the same household and that which occurs between members of the community in four trachoma-endemic populations, using a household-structured mathematical of transmission with and without age structure. Within-household transmission was estimated to be typically efficient but the level of household transmission was shown to vary between the communities (i.e. within household transmission was found to be higher in The Gambia than Tanzania).

Individuals from larger households were estimated to contribute more to transmission than individuals from smaller households. High within-household transmission was shown to result in persistent infection within infected households and also to result in a slightly reduced rate of emergence of infection compared to a population with the same endemic prevalence but that mixes homogeneously.

Incorporating two age categories into the model with children contributing more to infection then adults (through having a longer duration of infection), provides a better fit to the distribution of infection among individuals in the four individuals in three of the four communities. In one community adults were estimated to be less susceptible to infection than children.

The sensitivity and specificity of households with at least one member with active disease as a marker for infected households was shown to be relatively high, demonstrating that a potential method of targeting antibiotics could be to distribute them only to households with active disease. Model simulations predicted this antibiotic distribution scenario to be as effective as the current approach of mass treatment in the elimination of infection or more effective if it increases the coverage of infected individuals. Using cost data from two
published studies the household-targeted approach was predicted to be more cost-effective than mass treatment if antibiotics are not donated.

Targeting mass treatment to children was predicted to be less effective than mass treatment to all ages and for this reason the cost-effectiveness of this approach was not explored.

These findings are not only relevant for epidemiology and control of trachoma but also may have implications for understanding the transmission of other infectious pathogens which do not elicit a protective immune response and the disease clusters by household.

**Future Work**

As described in earlier chapters, there are some caveats to the model of transmission I have used in this thesis. These could be explored in more detail in future but more field data needs to be collected.

The number of bacteria obtained from one swab of the eye, also known as ‘infectious load’, has been shown to be higher in children than adults in cross sectional surveys and therefore it could be inferred that children are more infectious than adults. However how ‘infectious load’ relates to transmissibility remains to be elucidated. It is also not yet known how ‘infectious load’ fluctuates during the course of infection. Frequent swabbing throughout the duration of infection would be required to assess this.

Genetic diversity was not incorporated into the model of transmission because there is currently evidence to suggest limited diversity of *C. trachomatis* in trachoma endemic regions when *omp-A* is used as a marker of diversity. Other surface exposed proteins of genital *C. trachomatis* strains have been shown to be polymorphic but this has not yet been test for ocular strains. The level of genetic diversity is important to understand because if these genes are polymorphic in trachoma-endemic populations with incomplete cross-immunity between strains, a high prevalence of overall infection can be achieved by a number of strains with relatively low $R_0$ [182]. This would result in a low rate of emergence of infection after treatment, in agreement with the data, and would imply easier control of infection using antibiotics.
The force of infection in the model encompassed transmission by all routes: ‘flies, fingers and fomites’. The contribution by each route is likely to vary for each transmission setting and has not yet been estimated in a community. Installation of latrines and promotion of their usage is part of the trachoma control effort to decrease the fly population. It would be interesting to know how the relative levels of community and household transmission would change if the fly population were to be substantially reduced in a community through such interventions (and how this effect varies in different settings).

This thesis examines data from four diverse populations with varying prevalence of disease and different levels of household transmission. Two are from East Africa and two from West Africa. Trachoma occurs in many developing countries with different cultures, household characteristics, hygiene practises, and geographical characteristics (hence differences in fly populations), potentially resulting in different transmission patterns. It would be interesting to extend the analyses to populations from other continents.

This thesis has focused on infection and active disease. In 1996 the WHO and partners established the goal of Global Elimination of blinding trachoma by the year 2020. An extension to the work of this thesis could be to include the development of the later disease sequelae into the model of transmission to investigate the impact of household transmission on the distribution and development of blindness within communities. I have estimated infection to persist within a household, indicating that individuals in particular households may be at higher risk of developing the later disease sequelae than individuals in other households.

As described in Chapter 8, before targeted treatment of households with active disease can be considered a cost-effective strategy to reduce the prevalence of ocular C. trachomatis, there needs to be a better understanding of how the costs would vary in different settings and countries and whether they are reduced at subsequent treatment rounds. There may also be further ways to reduce the cost of the strategy compared to the current published cost data. From analogy with other disease intervention programmes, there is reason to believe targeting antibiotics to households may increase the coverage in these households (and subsequently infected individuals) compared to MDA. This requires investigation.
Some populations may be more suited to household-targeted treatment than others. The data used in this thesis did not include a population with low household transmission and relatively high endemic prevalence. If such a setting does occur then a large proportion of households may be infected and so a household-targeted approach may not be appropriate. Therefore the suitability of the approach needs to be considered in other settings.

The model of transmission that I used in this thesis assumed that each household in a community has an equal chance of becoming infected. Sensitivity analysis showed that if certain houses have higher risk of becoming infected than others (e.g. due to differences in hygiene) then in these settings infection becomes more difficult to eliminate. If there was a way of identifying high risk households and efforts were increased to ensure these households were screened and all members treated if positive, control of infection could be easier than in homogeneous populations.

These questions could be addressed by carrying out trials of household targeted treatment in different transmission settings, collecting detailed cost and coverage data, with frequent follow-up between treatment rounds.

Conclusion
In conclusion the work in this thesis has demonstrated the importance of within household transmission of ocular C. trachomatis for the epidemiology and control of trachoma. Targeted treatment of households with active trachoma is predicted to be as effective as and potentially more cost-effective than the current antibiotic distribution strategy of mass treatment, supporting the implementation of pilot studies to examine cost-effectiveness at a larger scale in endemic communities.
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APPENDIX

This section contains a copy of my PLoS Neglected Tropical Diseases Research Article ‘Estimating Household and Community Transmission of Ocular Chlamydia trachomatis’.
Estimating Household and Community Transmission of Ocular *Chlamydia trachomatis*

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Abstract

**Introduction:** Community-wide administration of antibiotics is one arm of a four-pronged strategy in the global initiative to eliminate blindness due to trachoma. The potential impact of more efficient, targeted treatment of infected households depends on the relative contribution of community and household transmission of infection, which have not previously been estimated.

**Methods:** A mathematical model of the household transmission of ocular *Chlamydia trachomatis* was fit to detailed demographic and prevalence data from four endemic populations in The Gambia and Tanzania. Maximum likelihood estimates of the household and community transmission coefficients were obtained.

**Results:** The estimated household transmission coefficient exceeded both the community transmission coefficient and the rate of clearance of infection by individuals in three of the four populations, allowing persistent transmission of infection within households. In all populations, individuals in larger households contributed more to the incidence of infection than those in smaller households.

**Discussion:** Transmission of ocular *C. trachomatis* infection within households is typically very efficient. Failure to treat all infected members of a household during mass administration of antibiotics is likely to result in rapid re-infection of that household, followed by more gradual spread across the community. The feasibility and effectiveness of household targeted strategies should be explored.

Introduction

Trachoma is the leading cause of infectious blindness worldwide. Eight million people are visually impaired from the disease and a further 46 million people with active disease are in need of treatment to prevent blindness [1]. Mass drug administration (MDA) with antibiotics (predominantly azithromycin but also topical tetracycline) is one of the four arms of the SAFE strategy, advocated by the World Health Organization (WHO) to control trachoma with the aim of Global Elimination of Blinding Trachoma by 2020 (GET 2020). Large scale vertical control programmes currently operate, such as those through the partners of the International Trachoma Initiative, and control efforts are expected to expand when trachoma control is integrated with that of other neglected tropical diseases [2].

The presence of active disease is currently used to guide trachoma control programs and to evaluate the success of interventions. The WHO advises that if the prevalence in a district of trachomatous inflammation follicular (TF) in a district among 1–9 year-old children is ≥10%, annual treatment of the district along with face-washing and environmental improvement should occur for at least three years until the prevalence of active disease in that age group is reduced to less than 5% [3]. However there is a loose relationship between an individual showing signs of active disease and being infected with the causative bacterium of trachoma, *Chlamydia trachomatis*. There is typically a lag before the appearance of active disease after an individual has been infected and a persistence of active disease after infection resolves [4,5]. Signs of conjunctival inflammation may also be the result of other bacterial infections or mechanical irritation [6] and even after infection is eliminated from a community, some individuals may still show signs of active disease [7]. Therefore the proportion of individuals with active disease may not correspond to the proportion of individuals with infection. This was recently illustrated by a study in The Gambia in which the overall prevalence of infection among children under 10 years of age in...
Here we examine the contribution of transmission between members of the same household and that between households of the same population to the incidence of ocular C. trachomatis infection using cross-sectional data on the prevalence of infection from four endemic communities, two in West Africa (The Gambia) and two in East Africa (Tanzania). We discuss the implications of our findings for the resurgence of infection after community-wide treatment and the potential for targeted treatment of households to reduce infection efficiently.

Methods

Data

Individuals of all ages from four endemic populations (Upper Saloum District and Jali village in The Gambia and Kahe Mpya and Maindi villages in Tanzania) were examined and conjunctival swabs taken to test for the presence of chlamydial infection using PCR amplification of a target sequence in the common cryptic plasmid of the bacteria. In one community, Maindi village, the presence of infection was based on quantitative PCR amplification of the ompl1 gene. Detailed information on the bedroom (Upper Saloum District, Kahe Mpya sub-village and Jali village only), household (Upper Saloum District, Kahe Mpya sub-village and Maindi village only), compound (Jali village and Upper Saloum district only), balozi (Kahe Mpya sub-village and Maindi village only) and village (Upper Saloum district) of the individuals examined was recorded; along with a number of other risk factor for trachoma and clinical signs of disease. Characteristics of these populations and detailed methods have been reported previously [15,19,22,23].

The study in Upper Saloum district was approved by the Gambian Government/Medical Research Council Joint Ethics Committee (SCC 856) and the London School of Hygiene and Tropical Medicine Ethics Committee. Written informed consent was obtained from all individuals. The Kahe Mpya study was approved by the London School of Hygiene and Tropical Medicine committee and the Kilimanjaro Christian Medical Centre, Tanzania. Written consent was obtained. The study in Maindi village was approved by the Johns Hopkins Institute Review Board and the Tanzanian National Institute for Medical Research; all participants provided oral informed consent. Both IRBs approved oral informed consent because many of the rural villagers are illiterate and asking them to sign a document they cannot read is unethical; in the past, unscrupulous persons have had them sign official “documents” that were really signing away their land. Oral consent was witnessed and documented by a member of the team on a study document. These three studies were done in accordance with the Helsinki Declaration. The study in Jali received ethical approval from the joint Gambia Government and Medical Research Council Ethics Committee (SCC 508). All subjects gave oral informed consent that was witnessed and signed by the witness following the standard consent procedures at the time.

Household Model of Transmission

Trachoma is a disease in which a fully protective immune response against re-infection is not elicited and so individuals can be repeatedly infected [18,24]. We therefore chose to describe transmission using a simple Susceptible→Infected→Susceptible (SIS) model, in which the population is categorised into two groups - individuals susceptible to infection (S) or infected individuals (I) - and infected individuals recover to become susceptible again. Household SIS models have been previously examined by Ball [25] and Neal [26].

Author Summary

Trachoma is a major cause of blindness worldwide and results from ocular infection with the bacterium Chlamydia trachomatis. Mass distribution of antibiotics in communities is part of the strategy to eliminate blindness due to trachoma. Targeted treatment of infected households could be more efficient, but the success of such a strategy will depend on the extent of transmission of infection between members of the same household and between members of the community. In this work, we estimated the magnitude of household and community transmission in four populations, two from The Gambia and two from Tanzania. We found that, in general, transmission of the bacteria within households is very efficient. In three of the four populations, persistent infection within households was predicted by the high level of household transmission (a phenomenon observed in longitudinal studies of trachoma). In all of the studied populations, individuals who live in households with more individuals contribute more to the number of new infections in the community than those who live with fewer individuals. Further studies are required to identify and examine household-targeted approaches to treatment.

two regions was 0.3% based on qualitative PCR testing of conjunctival swabs, whereas the prevalence of active disease in this age group was 10.4% [8].

Control programmes that have used MDA as part of their control strategy have had some success [9], and people may also benefit from other bacterial infections being cleared by the antibiotic. Although most antibiotics are currently donated, donation is not universal and is likely to be time-limited. There are also many costs associated with delivering antibiotics in rural settings [10,11]. Furthermore, MDA results in many uninfected individuals receiving treatment and could promote antibiotic resistance among other bacterial infections such as Streptococcus pneumoniae [12]. Targeted treatment to those infected would reduce the number of drug doses required, potentially reducing the cost of MDA. However, the loose relationship between infection and active disease makes targeted treatment of individuals with active disease ineffective at the population level. Targeting households with at least one member with active disease may be more effective since infection clusters by household [13] and so asymptomatic infections are more likely to be treated. In The Gambia, this strategy has been used as national policy in communities with less than 5% of TF among children aged 1–9 years old (Personal communication, Mr Ansumana Sillah, Manager, Gambian National Eye Care Programme).

Clustering of active trachoma disease by household has been shown to occur in a number of communities [13–17] and individuals living with people who have active trachoma are more likely to have active disease than individuals who live with individuals without active disease [15,18–20]. Furthermore, in Jali village in The Gambia, the same serovar of C. trachomatis was predominantly found within a household even though three serovars were present in the community [21], suggesting that transmission between members of the same household is more common than between other members of the community with different serovars. However, the rates of transmission between individuals of the same household and between members of the same community have not been estimated and little is known about the likely impact of targeted treatment of households on transmission of C. trachomatis.
The probability that a household of size \( m \) has \( j \) infected individuals (and \( m-j \) susceptible individuals) at time \( t \) is given by \( P_j^{(m)}(t) \). A susceptible individual can be infected from either an infected member of the community (global transmission) at a rate: \( \beta_G v \), in which \( \beta_G \) is the global transmission coefficient and \( v \) is the prevalence of infection in the community; or from an infected member of the same household (local transmission) at a rate: \( \beta_L \frac{m-j}{m-1} \), in which \( \beta_L \) is the local transmission coefficient. \( \beta_L \) is multiplied by either the number of infected individuals in the household, \( j \), if transmission is assumed to be density dependent (the average number of contacts per individual increases with household size, corresponding to \( w=0 \)), or the fraction of infected individuals in the household \( \frac{m-j}{m-1} \), representing that the average number of contacts per individual is constant, regardless of household size, and corresponding to \( w=1 \). The parameter \( w \) is therefore the coefficient for density dependence, which in the application described we allow to vary on a continuous scale with \( w=0 \). Individuals recover from infection at a rate \( \gamma \), taken as the reciprocal of the average duration of infection. Births and deaths are not included in the model because the duration of infection is relatively short compared to the average human life expectancy. We can write the difference-differential equation for \( P_j^{(m)}(t) \),

\[
\frac{d}{dt} P_j^{(m)}(t) = \begin{cases} 
(m-j+1) \left( \beta_G v + (j-1) \frac{\beta_L}{(m-1)} \right) P_{j-1}^{(m)}(t) - j \gamma P_j^{(m)}(t) 
\end{cases} 
\]

where \( j \leq m; \ m=1,2,\ldots\ j=0,1,\ldots m \) and \( P_{m+1}^{(m)} = P_{-1}^{(m)} = 0 \).

At endemic equilibrium, assuming the number of households \( n \) is large (\( n \to \infty \)), solving \( \frac{d}{dt} P_j^{(m)}(t) = 0 \), leads to the recursion:

\[
P_j^{(m)} = \frac{(m-j+1) \left( \beta_G v + (j-1) \frac{\beta_L}{(m-1)} \right) P_{j-1}^{(m)}}{j \gamma} 
\]

where

\[
P_0^{(m)} = \frac{1}{\left( 1 + \sum_{i=1}^{m} \Pi_{i=0}^{m-i-1} \frac{(m-i) \left( \beta_G v + i \frac{\beta_L}{(m-1)} \right)}{(i+1) \gamma} \right)} 
\]

The prevalence of infection in the community described by equations (2) and (3) is

\[
\theta(v) = \frac{\sum_{j=1}^{\infty} \sum_{m=1}^{\infty} P_j^{(m)} \phi_m}{\sum_{m=1}^{\infty} \phi_m n^m} , 
\]

where \( \phi_m \) is the fraction of households of size \( m \) in the population. Solving equations (2) and (3) therefore requires the implicit equation \( \theta(v) = v \) to be satisfied at equilibrium.

An epidemic can occur when the household basic reproduction number \( R_e \) is greater than 1 [25]. \( R_e \) is defined as the mean number of households infected following the introduction of a single infected individual to a randomly chosen household. It is analogous to the basic reproduction number \( R_0 \) in a non-structured, randomly mixing population [27]. If a household of size \( m \) is initially infected then \( R_e^{(m)} \) is

\[
R_e^{(m)} = \frac{\beta_G (m-1)!}{\gamma} \frac{\prod_{i=0}^{m-1} \rho_m}{m^m} . 
\]

where

\[
\rho_m = \frac{(m-1)^w \gamma}{\beta_L} , 
\]

and \( R_e \) is the average across all individuals according to their probability of being in a household of a given size,

\[
R_e = \sum_{m=1}^{\infty} \frac{m \phi_m R_e^{(m)}}{\sum_{m=1}^{\infty} \phi_m m^m} 
\]

Maximum likelihood was used to estimate \( \beta_G \), \( \beta_L \) and \( w \) simultaneously. The likelihood, \( L \), of a household of size \( m \), with \( j \) individuals infected is given by \( L = P_j^{(m)} \) and the total log-likelihood is the summation of \( \ln L \) across all households.

The duration of infection was assumed to be 17.2 weeks based on cohort studies of infection with frequent follow-up [4] and \( v \) was taken to be the prevalence of infection in the cross-sectional survey (i.e. infection in the communities, prior to antibiotic intervention, is assumed to be at endemic equilibrium). The sensitivity of the estimates to the assumed duration of infection was examined for a range of plausible values (12–24 weeks) [4]. Confidence intervals (CI) for each parameter were calculated by assuming that \( -2^{\chi^2} \) (chi-squared) distributed [28]. We therefore tested the hypothesis of density dependence in the contact rate by estimating parameter \( w \) and its confidence intervals; the null hypothesis of density dependence (\( w=0 \)) was contrasted with the alternative hypothesis of frequency dependence (\( w=1 \)), by ascertaining whether the confidence intervals around the estimate included 0 or 1.

A small number of individuals were not tested for the presence of infection, due to refusal or because they were away travelling. The sensitivity of the estimates to the inclusion of these individuals as members of the household such that they may have contributed to transmission was examined (Text S1). If there were \( s \) members of a household tested for infection and an additional \( m-s \) individuals who were not tested for infection but who contribute to transmission, the probability that \( y \) individuals were found positive in the sample, given that \( j \) members of the overall household of size \( m \) were actually infected (according to a hypergeometric distribution [29]) is:

\[
P(Y = y | j, s, m) = \frac{\binom{j}{y} \binom{m-j}{s-y}}{\binom{m}{s}} . 
\]
In this case the likelihood for each household can be modified such that

$$L = \sum_{y=0}^{\infty} \left( \frac{\mu^y}{y!} \right) p(Y = y | \mu, \lambda).$$

This assumes that infected individuals are equally likely to be sampled as uninfected individuals. The sensitivity of this assumption was explored using the non-central hypergeometric distribution [29] (Text S1).

The impact of different definitions of a ‘household’ on the estimates of $\beta_G$, $\beta_L$ and $w$ was examined, from bedroom, household, compound and village for the Upper Saloum District; room and compound for Jali village; room, kaya and balozi for Kahe Mpya sub-village and kaya and balozi for Maindi village. (See below in the Results section for the definitions of ‘kaya’ and ‘balozi’).

Model Fit

The appropriateness of the household SIS model of *C. trachomatis* transmission was assessed by simulating the number of people infected at endemic equilibrium and the household to which they belong under the model using the estimated parameters and assuming a negative binomial distribution for the underlying household size distribution (with inverse over-dispersion parameter $k$ equal to (95% CI denoting 95% confidence intervals): $k = 3.95$ [95% CI: 2.85–5.49] and $k = 1.86$ [1.21–2.76], for respectively Upper Saloum district and Jali village (The Gambia), and $k \to \infty$ for both Kahe Mpya and Maindi village (Tanzania), where $k = \infty$ corresponds to a random or Poisson distribution; see Text S1). The probability mass function used for the negative binomial is [30]:

$$P(M = 0) = \left( 1 + \frac{m}{k} \right)^{-k}$$

and when $m > 0$

$$P(M = m) = \left( \frac{k + m - 1}{m} \right) \left( \frac{\mu}{\mu + k} \right) P(M = (m - 1)),$$

where $\mu$ is the (arithmetic) mean household size (Table 1). Comparison of the model simulations with the observed data was based on the mean intraclass correlation coefficient for the prevalence of infection within households (ICC). The ICC provides a quantitative measure of similarity between individuals within groups and is based upon the comparison of within- and between-group sums of squares from an analysis of variance [31]. One thousand stochastic simulations were run for each setting using the numerical integration package Berkeley Madonna [32].

**Results**

**Community Structure and Prevalence of Infection**

In The Gambia one household or a cluster of households forms a compound, a unit which is fenced off from the rest of a community. In Upper Saloum district the household unit ranges from 1–55 individuals and the compound ranges from 2–77 individuals. In Jali village the compound unit ranges from 4–70 individuals (household data unavailable). In Tanzania, the household unit is the ‘kaya’, (ranging from 1 to 14 individuals) and on average the unit is smaller than the household unit in The Gambia (Table 1). Kayas which are situated within the same geographical zone are grouped into a ‘balozi’ and share a balozi leader. The number of individuals examined in each community along with the prevalence of infection among households and among individuals is given in Table 1.

**Estimates of Household Transmission**

The estimates for the global and local transmission coefficients ($\beta_G$ and $\beta_L$) along with the density-dependent coefficient, $w$ and the household reproduction number $R_h$ are given in Table 2 along with their 95% confidence interval. In Jali the compound unit was used because household data were unavailable. The estimates of $\beta_G$ and $\beta_L$ were sensitive to changes in the duration of infection, whereas the estimates of $w$, $R_h$ and the ratio $\beta_G/\beta_L$ were not affected by changes in the duration of infection (Text S1). Estimates of $w$ were close to 1, and in all of the four populations the 95% CIs included 1, consistent with frequency-dependent transmission, such that the number of contacts made by an infected individual was not larger in bigger households. Estimates of the rate of household transmission were large and $\beta_L$ was greater than $\beta_G$ in three of the four populations. In all four, individuals from larger households were estimated to contribute more to incidence than those from smaller households (Figure 1). This effect reverses somewhat at very large household sizes in Upper Saloum District where the estimate of $w$ ($>1$) is consistent with a decline in the number of infectious contacts with increasing household size. An average of 71% of incident infections were the result of transmission within the household (with a range of 48%–91%) in the four populations.

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**Table 1.** Demographic and prevalence data from the four populations examined for ocular *Chlamydia trachomatis*.

<table>
<thead>
<tr>
<th>Population and reference of study</th>
<th>Year at baseline</th>
<th>No. individuals in population</th>
<th>No. individuals tested for chlamydial infection at baseline</th>
<th>Prevalence of infection (%)</th>
<th>Mean household size (number)</th>
<th>Percentage of households infected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jali village, Kiang West District, The Gambia [22]</td>
<td>1991</td>
<td>844</td>
<td>752</td>
<td>22.1</td>
<td>17.3</td>
<td>73.5</td>
</tr>
<tr>
<td>Sub-village of Kahe Mpya, Rombo District, Tanzania [23]</td>
<td>2000</td>
<td>978</td>
<td>956</td>
<td>9.5</td>
<td>5.3</td>
<td>30.0</td>
</tr>
<tr>
<td>Maindi village, Kongwa District, Tanzania [19]</td>
<td>2000</td>
<td>1017</td>
<td>783</td>
<td>36.0</td>
<td>4.7</td>
<td>60.4</td>
</tr>
</tbody>
</table>

NOTE: The household unit for Jali village was a compound as household data was unavailable.

doi:10.1371/journal.pntd.0000401.t001
Table 2. Maximum likelihood estimates of the transmission parameters in four populations of West and East Africa.

<table>
<thead>
<tr>
<th>Population</th>
<th>Global transmission coefficient, $\mu_g$ [95% CI]</th>
<th>Local transmission coefficient, $\mu_l$ [95% CI]</th>
<th>Coefficient for density dependence, $w$ [95% CI]</th>
<th>$R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, Upper Saloum District, The Gambia</td>
<td>0.29 [0.16–0.51]</td>
<td>7.09 [3.58–13.73]</td>
<td>1.22 [0.99–1.45]</td>
<td>1.25</td>
</tr>
<tr>
<td>Jali village, Kiang West District, The Gambia</td>
<td>0.76 [0.39–1.40]</td>
<td>4.01 [1.81–7.38]</td>
<td>1.05 [0.84–1.23]</td>
<td>2.81</td>
</tr>
<tr>
<td>Sub-Village of Kahe Mpya, Rombo District, Tanzania</td>
<td>1.73 [1.18–2.37]</td>
<td>1.57 [0.29–5.31]</td>
<td>0.89 [0.06–1.63]</td>
<td>1.18</td>
</tr>
<tr>
<td>Maindi village, Kongwa district, Tanzania</td>
<td>1.70 [1.15–2.46]</td>
<td>3.06 [1.14–6.18]</td>
<td>0.88 [0.41–1.26]</td>
<td>2.65</td>
</tr>
</tbody>
</table>

NOTE: The transmission parameters were obtained by fitting the model of household transmission of *C. trachomatis*, described in the main text, to the baseline data summarised in Table 1.

doi:10.1371/journal.pntd.0000401.t002

Figure 1. Proportion of incidence contributed per individual from a household of size $m$ (solid line) and the probability distribution of a randomly chosen individual belonging to a household of that size, $P(m)$, based on the negative binomial distribution in (A) The Gambia – the black lines correspond to Upper Saloum district and the red lines correspond to Jali village; and (B) Tanzania – the black lines correspond to Kahe Mpya sub-village and the red lines correspond to Maindi village.

doi:10.1371/journal.pntd.0000401.g001
The estimate of $\beta_G$ increased as the definition of the household unit became smaller in size (from village to compound; balozi to household; kaya to room) and the estimates of $\beta_I$ and $R$, decreased (except for $\beta_I$ in the Upper Saloum District) and $w$ remained approximately constant (Text S1). Exclusion of the individuals who were not examined at the moment of sampling but were members of households in the four populations does not change the parameter estimates significantly (Text S1). Assuming infected individuals to be more or less likely to be sampled did not alter the parameter estimates significantly either (Text S1).

Model Fit
The average ICCs from the model simulations were in agreement with the ICCs calculated from the data, suggesting that the simple SIS model of household transmission captures much of the dynamics of C. trachomatis infection in these communities (Table 3).

Discussion
Clustering of infection by household is an important epidemiological feature of many communicable diseases and is thought to be a key characteristic of trachoma. However, the magnitude of transmission of C. trachomatis between individuals belonging to the same household and that between individuals living in different households but the same community have not, to our knowledge, previously been estimated. Here they are estimated in four different populations by fitting a household model of transmission to prevalence data using maximum likelihood estimation. In these communities an average of 71% of incident infections were the result of transmission within the household, indicating the important role of household transmission in the repeat infections with C. trachomatis that result in progression to trachomatous scarring and blindness. In all four populations, individuals who live in relatively large households (i.e. with many individuals) contribute more to incidence than those who live in households with fewer individuals. Further to this, in the two Gambian populations and in Maindi village, Tanzania, the household transmission coefficient was estimated to be greater than the rate of recovery from infection, which contribute more to incidence than those who live in households with fewer individuals. Further to this, in the two Gambian populations and in Maindi village, Tanzania, the household transmission coefficient was estimated to be greater than the rate of recovery from infection, such that sustained transmission within the household is possible (Table 2). This indicates that individuals who were not examined at the moment of sampling but were members of households in the four populations does not change the parameter estimates significantly (Text S1). Assuming infected individuals to be more or less likely to be sampled did not alter the parameter estimates significantly either (Text S1).

Table 3. Comparison of the ICC from four populations endemic for trachoma with the mean simulated ICC.

<table>
<thead>
<tr>
<th>Community</th>
<th>ICC from data</th>
<th>Mean simulated ICC [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 villages, Upper Saloum District, The Gambia</td>
<td>0.26</td>
<td>0.23 [0.23–0.24]</td>
</tr>
<tr>
<td>Jali village, Kiang West District, The Gambia</td>
<td>0.10</td>
<td>0.08 [0.08–0.08]</td>
</tr>
<tr>
<td>Sub-village of Kahe Mpya, Tanzania</td>
<td>0.11</td>
<td>0.12 [0.12–0.13]</td>
</tr>
<tr>
<td>Maindi village, Tanzania</td>
<td>0.14</td>
<td>0.15 [0.15–0.16]</td>
</tr>
</tbody>
</table>

NOTE: ICC = Intraclass correlation coefficient, with the mean ICC calculated from running 1000 stochastic simulations. The stochastic simulations used the estimated household transmission parameters (Table 2) and the fitted household size distribution (main text).

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of household size (i.e. the risk of infection is proportional to the fraction of infective individuals in a household, rather than the number). This phenomenon has also been shown for other infections, such as *Streptococcus pneumoniae* and influenza virus [40,41]. The estimate of $w$ from the data from Upper Saloum district is slightly higher than the other estimates ($w = 1.22$), resulting in a slight decline in the number of contacts per individual with household size, although the confidence intervals include 1 (Figure 1).

The household model used in this work assumes that all individuals mix homogeneously outside their household at the same rate (specific to each setting), such that each household is at equal risk of infection. It ignores any protective immunity against reinfection, does not include infection with different serovars, and assumes that an individual’s age does not affect their duration of infection or risk of acquiring infection. It also assumes that each infected individual is equally infectious and does not therefore take into account that some individuals harbor a much higher number of bacteria than others. These assumptions are simplifications of disease transmission and natural history, and in particular, neglect the differences between adults and children in their contribution to transmission. Children have a longer duration of infection and a higher prevalence of infection than adults. Children may also have a different within/between household contact pattern than adults. However, the correspondence between the model simulations and the data indicate that the model is a reasonable description of the household transmission of ocular chlamydial infection. Further work will examine in more detail the contribution of individuals of different ages to the transmission of ocular *Chlamydia* within households. We have assumed accurate testing of individuals for ocular chlamydial infection and that there was no contamination of the conjunctival swabs. Although, cross-contamination of samples is a risk when using PCR techniques, standard precautions were taken to prevent this [22,42].

The strategy of mass antibiotic treatment to control trachoma can be costly [10], may result in antibiotic treatment of uninfected individuals and may increase the chance of antibiotic resistance developing, as observed for other bacterial infections [43–46]. A control approach which minimises the number of antibiotic doses given out in a community but still has similar effects in reducing prevalence in a community compared to mass distribution would therefore be advantageous. In this paper we have quantified the amount of household and community transmission for the first time and have shown that this leads to persistently infected households in 3 of the 4 study populations. Furthermore, in all four such populations, individuals living in larger households contributed more to transmission than those living in smaller households (Figure 1). This suggests a potential role for the targeted treatment of households more likely to harbor infection.

Two field studies have explored the use of the household as the unit for targeting treatment and come to differing conclusions. In Nepal, the reduction in prevalence of active disease after community-wide treatment and after targeted treatment of households containing children showing active disease were not significantly different [47]. In Mali, treatment of those households where at least one child had active disease was significantly less effective at controlling active disease than mass treatment [48]. However, these two studies used active disease as an indicator for treatment and therefore may have missed some children who would have been infected but without showing signs of active disease [4,5]. Other methods of targeted treatment could also be explored, such as the use of a dipstick assay for rapid diagnosis of the presence of infection, which is currently being developed [49].

The critical role of the household in the transmission and persistence of trachoma demonstrated by our study, along with the high cost of community-wide antibiotic treatment, highlight both the potential and the need for targeted approaches for the treatment of ocular chlamydial infection. Further studies are needed to identify efficient and effective methods to achieve this.

**Supporting Information**

**Text S1**

Found at: doi:10.1371/journal.pntd.0000401.s001 (0.18 MB DOC)

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**Author Contributions**

Conceived and designed the experiments: MJB RLB AWS BM MJH SW. Analyzed the data: IMB NCG. Wrote the paper: IMB. Conceived and designed the experiments: MJB RLB AWS SW BM MJH DCWM MG MGB NCG. Performed the experiments: MJB RLB AWS SW BM MJH DCWM MG MGB NCG. Analyzed the data: SW BM MJH DCWM MG MGB NCG. Wrote the paper: IMB.

**References**
