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The Importance of Environmental Interventions in Eliminating Trachoma Infection in Africa: The Case of Gashoho Health District, Burundi

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The importance of environmental interventions in eliminating Trachoma infection in Africa: the case of Gashoho Health District, Burundi

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THESIS DECLARATION FORM

DECLARATION

This is to certify that the thesis entitled "The importance of environmental interventions in eliminating Trachoma Infection in Africa: the case of Gashoho Health District, Burundi", submitted to the University of Notre Dame Australia, in partial fulfillment of the requirements for the award of the degree of *Doctor of Philosophy*, is my own work has not been submitted and will not be submitted either in part or in full, for the award of any other degree or diploma in this institute or any other institute or university.

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ABSTRACT

Gashoho Health District, Burundi, has not achieved the World Health Organisation (WHO) target of elimination of the blinding infectious disease, trachoma, by 2020. The work in this thesis addresses this problem using three different approaches.

Firstly, a cross-sectional study was undertaken to establish the current trachoma prevalence in Gashoho and whether poor sanitation was a risk factor for infection. 468 individuals from 117 households across four villages were clinically examined for signs of trachoma infection, and completed a questionnaire about environmental risk factors. The current prevalence of trachoma in Gashoho was 7.9% (95 % CI 5.0 - 10.6%). Children under 9 years old had an overall prevalence of 19.5% (95% CI 13.7-26.4%). Household access to a sanitary toilet almost halved the odds of trachoma infection (OR 0.437, 95 % CI 0.256 - 0.743).

Then, mathematical models based on the SIS framework, but incorporating environmentally mediated transmission, were utilised to explore whether improved sanitation might eliminate trachoma in Gashoho. Stability analysis showed the existence of two basic reproductive numbers, R_{0H} and R_{0E}, governing human-to-human and environmentally mediated transmission. Persistence of trachoma was shown to depend on the sum of these quantities exceeding one. Numerical simulations suggested that the elimination of trachoma was possible in Gashoho, given environmental interventions that increased pathogen clearance from the environment.

To complete the work in the thesis and allow rapid translation of the results into policy and practice, a new method of monitoring and evaluation of environmental interventions was proposed. Using computational and algebraic methods, Stratified Truncated Sequential Sampling was developed to link monitoring in individual villages to policy decisions at the Health District level.

In conclusion, this thesis generates new knowledge and methods for improving trachoma control efforts in Gashoho Health District, Burundi.

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LIST OF PUBLICATIONS

A number of publications and presentations arose from this thesis. At the time of submission, one paper has been published:

- Ndisabiye D, Gahungu A, Kayugi D, Waters EK. Association of environmental risk factors and trachoma in Gashoho Health District, Burundi. African Health Sciences. 2020 Apr 20;20(1):182-9.

This paper comprises part of chapter 3.

In addition, one paper has been submitted and is under review at the time of submission:

- Ndisabiye D, Gore RG, Waters EK, Sidhu H. Do environmental reservoirs of infection drive Trachoma transmission Burundi? A mathematical modelling study. ANZIAM J.

This paper comprises part of Chapter 4.

In addition, work from the thesis has been included in oral presentations at the following conferences:

- Ndisabiye D. Estimating the basic reproductive number (R0) of Trachoma in Burundi. 4^{th} Workshop on Mathematical Modelling in Biology and Medicine, University of Wollongong, November 2018.

- Ndisabiye D. Do environmental reservoirs of infection drive Trachoma transmission Burundi? A mathematical modelling study. 5^{th} Workshop on Mathematical Modelling in Biology and Medicine, University of Wollongong, December 2019.

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List of Terms and Abbreviations

N N T B P National Neglected Tropical Disease and Blindness Program

AMR antimicrobial resistance

ANOVA Analysis Of variance

CD4 cluster of differentiation 4

CI Confidence Interval

CMI Cell Mediated Immune

CO cornea opacity

CT Chlamydia trachomatis

DFE Disease free equilibrium

DNA Deoxyribonucleic acid

EB elementary body

EE endemic equilibrium

FOI Force of Infection

IgA immunoglobulin A

ITI International Trachoma Initative

GEE Generalized Estimating Equation

GET2020 global elimination of trachoma by 2020

MDA mass drug administration

MG Mycoplasma genitalium

ODE Ordinary Differential Equations

RB reticulate body

R_0	Basic reproductive number
R_{0H}	Basic reproductive number for the human to human transmission
R_{OE}	Basic reproductive number for the environmentally mediated transmission
SAFE	Surgery Antibiotic Facial cleanliness Environment improvement
SIS	Susceptible-Infected-Susceptible
STD	Sexually Transmitted Disease
STSS	Stratified Truncated Sequential Sampling
TF	Trachomatous Follicular
TI	Trachomatous Inflammatory
TSS	Truncated Sequential Sampling
TT	Trachoma triachiasis
WHO	World Health Organisation

CHAPTER 1

Introduction

1.1 About this thesis

The work contained in this thesis arose directly from my clinical experience after completing my medical degree in Burundi in 2008. When working as a general practitioner in hospitals, I treated many children with chronic conjunctivitis as a direct effect of trachoma. In 2014, I was transferred to the Burundi Ministry of Health in a managerial role after completing a Masters of Public Health and Environment. Through my new role and study, I appreciated the importance of and lack of academic interest in environmental factors in the transmission of neglected chronic diseases. I decided, in particular, that I wanted to complete research into the environment and trachoma, and to raise awareness of its importance to eliminating the disease.

The purpose of this thesis was then to document the current prevalence of trachoma in Gashoho Health District, Burundi, and to identify whether new interventions targeting environmental risk factors for trachoma transmission among might help eliminate trachoma. The World Health Organisation has set the target of 2020 as the date of the Global Elimination of Trachoma worldwide (GET2020), and suggested the SAFE (Surgery, Antibiotic,Facial cleanliness , Environment improvement) strategy as a mean of achieving this. Yet, as 2020 draws to a close, this has not been achieved. Trachoma is still present in some countries and not always uniformly distributed in endemic areas, moreover, local environmental factors influencing its prevalence are not yet adequately understood. Determining which risk factors are most important to the persistence of trachoma may help to better understand its transmission, why the current interventions have not been successful in eradicating the disease, and help to determine the appropri-

ate level at which to target control interventions.

This work has been proposed, conceived and carried out in conjunction with two Burundian doctors both working for National Neglected Tropical Disease and Blindness Program, one from the national level and another one from Gashoho Health District. They are both co-authors in our first publication which arose from this thesis (reproduced in Chapter 3). Given that this project involved people dealing day to day with trachoma, it has the opportunity of including fresh ideas representing exact concerns encountered by public health managers at all levels and most importantly, it has the opportunities of implementation of recommendations arising from it. Reflecting this background, the thesis approaches trachoma infection from a distinctly public health perspective and employs mathematical and computational tools to reach its conclusions. It used algebra and computer simulation to assess the applicability of a Stratified Truncated Sequential Sampling (STSS) for the monitoring and evaluation of a public health intervention aiming the reduction of trachoma prevalence. After these explorations, it ultimately provides realistic and achievable recommendations.

1.2 Thesis outline

The thesis comprises an introduction in Chapter 1, a literature review presented in Chapter 2, four chapters describing the results of research undertaken within duration of candidature, and a conclusion summarising the results with full consideration of the limitations of the research and suggestions for future work.

The literature review commences with a historical overview of trachoma infectious disease, from the first description of trachoma by ancient authors through to modern insights into the parthenogenesis of the disease, clinical diagnostic approaches, and management. In doing so, it describes the variable clinical presentations of trachoma infection and their division into clinical stages. It also presents the biology of the microbial agent and the clinical biology of the infection. The treatments currently available and the public health management approach to the disease is then discussed. The global epidemiology is described in general and particularly with reference to Africa and Gashoho Health District in Burundi. A number of gaps in the public health man-

agement of trachoma in Burundi are identified and these form the basis of Chapter 3.

Chapter 3 describes the methodology used in the investigation of trachoma prevalence and common risk factors associated to the active disease, and presents the results observed on the field. A cross-sectional study was carried out to investigate the relationship between environmental risks factors and the prevalence of trachoma. To achieve this, a representative sample of the population was obtained, clinical examinations performed, and a questionnaire on the existence and knowledge of environmental risk factors for trachoma was completed by participants. The infectious status of participants was classified according to the capacity of transmission of trachoma as defined by WHO (World Health Organisation). To explore the data, descriptive statistics and generalized estimating equations were used. This study provided an updated estimate of the prevalence of trachoma in Gashoho, and an estimate of how much environmental risk factors were associated with trachoma infection. It was concluded that the persistence of trachoma in Gashoho Health District may well be due to environmental factors, as the odds of trachoma infection per individual per household almost doubled depending on household access to sanitary toilet facilities.

Based on the information and results obtained in Chapter 3, Chapter 4 uses mathematical modelling to assess the extent to which further reductions in trachoma prevalence might be obtained if an environmental intervention targeting sanitation was added to antibiotic distribution in Gashoho. To do so, a model based on the Susceptible-Infected-Susceptible (SIS) scheme was developed, as the SIS model was most suitable for modelling trachoma infection given its ecology and clinical history. A system of ordinary differential equations (ODEs) including both person to person and environmentally mediated transmission was developed, and the stability of the system of equations was analysed using the Jacobian matrix. The model revealed the existence of two basic reproductive numbers – one describing the effectiveness of human to human transmission, termed R_{0H}, and the other the infections resulting from environmentally mediated transmission, termed R_{0E}. Most importantly the model found that even after the elimination of human to human transmission by antibiotic distribution, environmentally mediated transmission was still able to cause endemic infection in the human

population. Analysis of the model showed that eradication of trachoma in Gashoho was only possible if environmental improvement targeting sanitation was implemented.

Chapter 5 improves the model presented in Chapter 4, by incorporating in the model the demographics and an age structure. The age structured model reproduces key features of trachoma epidemiology. 1) The age profile of infection prevalence, demonstrated the existence of different basic reproductive numbers in the age structured groups; 2) The existence of the disease in one age group can drive the disease in the other age group even in the absence of risk factors in the other age group; 3) The environmental risk factors remained. The model with demographics confirmed the existence and the persistence of the two basic reproductive numbers. The R_{0H} representing the human to human transmission and the R_{0E} representing the environmentally mediated transmission. In the age structured model contrarily, to the model in Chapter 4 and in the model with demographics where the stability was analysed using the Jacobian matrix, it uses the numerical simulation to find the critical values values where the model shifts from one equilibrium to the other (DFE: Disease Free Equilibrium to EE: Endemic Equilibrium or vice versa). This chapter further proves that, the persistence of trachoma in Gashoho Health District is heavily influenced by the improvement of the environment.

Chapters 4 and 5 suggested that trachoma could only be eliminated in Gashoho if environmental improvement, specifically sanitation, was implemented in a systematic way. Chapter 6 presents a novel strategy to monitor and evaluate the success of such a public health intervention across the many villages in the district. The strategy forms the final novel contribution of the thesis, but perhaps the one most important for policy and practice: Stratified Truncated Sequential Sampling (STSS). This method is based on avoiding the necessity of calculation of the required sample size, which often results in the need to collect larger samples than are possible in a low-resource setting such as Gashoho Health District. STSS achieves this by assessing whether a desired threshold of precision has been obtained in a prevalence estimate, after each data point is collected. When the threshold is reached, sampling is ceased. The STSS method presented in this chapter is shown to provide the basis for a rapid and reliable survey method for

monitoring the effect of health programs aimed at reducing trachoma prevalence, and reliably classifies sites as low, moderate or high prevalence. By achieving this outcome using small sample sizes, a substantial decrease in the amount of time and resources required for surveillance is obtained, making this method much more suitable for trachoma surveillance in Gashoho than other methods. It is hoped that this method might be employed in Gashoho for trachoma surveillance in the near future.

Chapter 7 summarises the results of the preceding chapters, and the limitations of the methods employed. It suggests ways in which future work could extend the work in this thesis to more complex scenarios and different applications, and suggests a number of new avenues for research.

CHAPTER 2

Literature Review

2.1 Background

Trachoma, an infectious condition of the eye causing blindness, is one of the oldest scourge, well detailed in the Egyptian Ebers Papyrus in 1900 BC and was also known to Hippocrates [5]. The disease used to be endemic in Europe until well into the twentieth century, and immigrants to the USA were screened for trachoma by examination of the everted upper eyelid on arrival at Ellis Island, New York. Those in whom the characteristic appearance of trachoma was observed were put on the next boat and sent back to Europe, so great was the fear of what was clearly recognised to be a contagious condition [6]. Many of the eye hospitals in Europe were founded specifically to treat trachoma, and in 1937 the physician Duke-Elder, who developed early treatments for the disease, stated that " *its importance as a source of human suffering, as a cause of blindness, and as a national economic loss over large tracts of the world's surface, is second to none among diseases of the eye* " [7]. Trachoma has now disappeared from Western Europe and North America as a result of improved living standards, but unfortunately there are many parts of the world where living standards have not improved, and where trachoma remains a problem. Australia is the only developed country where trachoma is still endemic. It disappeared from urban Australia in early 20^{th} century, but now it is still endemic in remote aboriginal communities [8]. According to WHO 93% of the worlds' population at risk of trachoma (170 million) live in Africa and it is in Africa where 72% of the global burden of trichiasis is found [9]. Trachoma remains the third commonest cause of blindness worldwide after cataract and glaucoma. The treatment for trachoma recommended by Duke-Elder, copper sulphate, was also used by the ancient Egyptians [10]. But there have been several major advances in our under-

standing of the disease, and in 1997 the World Health Organisation announced a new initiative to eliminate trachoma as a cause of blindness by the year 2020 [10], known by the acronym GET2020 (Global Elimination of Trachoma by 2020). As the year 2020 draws to an end, however, the goals of the program have not been met, and the aspirational date of 2030 has now been given to meet the goals of GET2020 [11, 12]. Therefore, in this thesis, which deals with specific questions about the strategy, references to the GET2020 are understood to apply to the strategy's continued use until 2030 as well.

The failure of GET2020 is intimately associated with the fact that trachoma is a disease of poor individuals, and in endemic areas infected people tend to be clustered among the most vulnerable and poorest families [13, 14]. The transmission of the disease is believed to be from one eye to another, however, the importance of inanimate objects such as (clothes, eye make up), flies, or aerosol transmission through secretions of infected individuals in this process is still not understood [15]. A number of studies [16, 17, 18, 19] have incriminated indigence, access to water, the quantity of water available per family, the existence of flies, and the absence of hygiene as the major risk factors of trachoma. The distribution of water to families affected by trachoma is impossible; it is not financially accessible, and supplying piped water at the family level is not the least cost effective public health programs either [20]. The presentation of the association between trachoma infection and unclean faces inspired another control technique: health education to encourage parents to keep their children's faces clean by regular washing. To be successful, interventions based on behaviour change must involve the community and have its full support; the success of community based approaches has been demonstrated in both Africa and Asia [21].

2.2 Chlamydia cell biology, immunology and pathogenesis

Human pathogenic chlamydia species are members of a successful and unique lineage of bacteria, and chlamydial species cause a wide range of diseases in both animals and humans [22]. Of particular concern, *C. trachomatis* is an endemic infection, and the leading cause of preventable blindness, in many developing countries [9]. Moreover, it

is a frequent cause of sexually transmitted disease (STD) in developed countries [23]. There are many clinical presentations of chlamydial STD including pelvic inflammatory disease, infertility and ectopic pregnancies [24]. Chlamydiae have been common human pathogens for a long time and have been the subject of much research attention. The biology of some species such as *Chlamydia pneumoniae* is well understood and a vaccine does exist [25, 26]. However, problems still exist in combating the variants responsible for trachoma, as the bacterium has special properties that make it difficult to eradicate, including from environmental reservoirs.

One of the great mysteries of trachoma is that, despite the fact it has not developed resistance to widely used antibiotics,and in fact is still extremely susceptible to them, it has continued to persist as an endemic infection [27]. Antibiotic chemotherapy is mostly a powerful tool to treat initial infection but has not yet shown any use in preventing the ocular complications of repeated infection [28]. Often trachoma infections do not have symptoms and therefore, go with undiagnosed and not treated, which may create a state of chronic inflammation and irreversible complications [29]. In most areas, with limited access to medical facilities and diagnosis technologies also inhibit adequate exploration and management. Recurrent infections are frequent, and the chances of developing irreversible ocular complications (e.g., blindness) increases with multiple infections [30]. These obligate intracellular bacteria develop within a membrane bound vacuole termed the inclusion, and their existence within the inclusion defines much about the biology of the bacterial lineage. The challenges to understanding and preventing chlamydial disease are amplified by the difficulties of working with an obligate intracellular bacterial species, in which the development of a practical system of genetic manipulation is only in its infancy [31]. The complexity of the chalymydial life cycle is described in brief below.

C.trachomatis has a unique biphasic life cycle, involving:

1. an extra-cellular, infective but non-replicative, environmentally resistant electron dense cell type called the elementary body (EB) [32, 33].

2. a metabolically active replicative form, termed the reticulate body (RB) [27].

In the extra-cellular EB, DNA exists in a highly condensed state bound by chlamydial histone-like proteins. The transition from EBs to the metabolically active replicative form, termed the reticulate body (RB), takes place entirely within a membrane bound vesicle within the host, termed an inclusion body [27]. The process starts within the first few hours of infection and is characterized by decondensation of the chromosome, loss of infectivity and an increase in the organism's size [34]. The RBs multiply by binary fission until late in infection. Around about 18 hours after infection, several numbers of RBs begin to change back to EBs, which accumulate in the lumen of the inclusion as the remaining RBs continue to multiply. The inclusion body has numerous mechanisms to increase pathogenicity and avoidance of the host immune response, which may contribute to chalmydias continuing to cause severe organ damage, despite effective treatments. *C.trachomatis* is a Gram-negative bacteria which is an obligate intra-cellular pathogen. In its developmental cycle *C.trachomatis* alternates between two different morphological forms; the first form is the infectious which employs the extracellular elementary body (EB) and the second is the replicating form using the intracellular reticulate body (RB). The EB envelope is extremely resistant to degradation in the extracellular environment [35, 36]. The understanding of human ocular *C. trachomatis* infection is heavily based on research in animals, such as monkeys and guinea pigs [37], and on longitudinal studies of trachoma infection in humans in endemic areas [38]. Inference, by analogy, from animal models and human studies of the well understood genital chlamydia infections has also brought a considerable contribution. However, such efforts have identified key differences in host and pathogen biology. For example, interferon-γ-mediated immune responses targeting tryptophan metabolism inhibit growth of ocular, but not genital, variants of *C. trachomatis*, since the latter are able to use multiple substrates to derive tryptophan [39]. This is just one example of how ocular variants of *C.trachomatis* have developed unique mechanisms to evade the host immune response, resulting in an infection which may take weeks to recover from and which generates, at best, only partially protective immunity [40]. Despite the relative lack of adaptive immunity, cell-mediated immunity does appear to be critical for the resolution of infection. CD4 T-cell production of T-helper type 1 cell cytokines such as interferon γ has been proved to mediate immune clearance of *Chlamydia muridarum* in mice. On the other hand, up-regulation of T-helper type 2 cell cytokines may result

in failure to clear infection [41].

2.3 The natural history of trachoma infection and clinical aspects

Since the consequences of trachoma infection evolve through the life span, beginning with repeated conjunctival infection with *Chlamydia trachomatis*,and concluding in the development of conjunctival scarring [42], the signs and symptoms of infection also vary [1, 43].

The clinical signs and symptoms of active trachoma infection (follicular and papillary inflammation) are most commonly found in younger children [13]. Active infection is described as repeated periods of chronic conjunctivitis. Follicles are defined as epithelial collections of lymphoid cells and appear as tiny, yellow- white excavations on the conjunctival tissues of the upper lid when it is everted [44]. Papillary hypertrophy which is an oedema of tiny vessels surrounded by oedema also happens and may obstruct the deep tarsal vessels if severe enough. Vascular infiltration of the upper cornea (pannus) can potentially appear in active infection, however, it does not often affect vision [42]. People may be without symptoms or only report minor symptoms, even when clear signs of infection are obvious. When patients do report symptoms, these can be similar to those found in most types of conjunctivitis such as: tearing, discomfort,redness, photophobia and scant muco-purulent discharge [1, 45].

Recurrent and long lasting periods of trachoma infection may develop in the scarring and ultimately in blindness. In the early stages, conjunctival scarring is found in the subtarsal of the conjunctiva, which can range from a few linear or stellate scars to thick, distorting bands of fibrosis [46]. Contraction of this scar tissue is the origin of entropion (in turning of the eyelids) and trichiasis (eyelashes touching the eyeball) which is usually painful [47]. Eventually, corneal opacification leads to the blinding end-stage of the disease. This is probably occurs due as a result of multiple insults to the cornea: mechanical trauma from lashes, secondary bacterial or fungal infection and a dry ocular surface [48, 49]. Blindness from trachoma is irreversible [50].

Over the years, various grading systems for trachoma have been proposed. The one which is currently used by trachoma control programmes is the 1987 WHO simplified grading system for district level interventions [51, 52]. The clinical phases of trachoma and their management are summarised in Table 2.1.

Table 2.1 Clinical stages of trachoma and their management, adapted from [1, 2].

	Stage	Description	Management
Active trachoma	Follicular trachoma (TF)	5 or more follicles of > 4mm on upper tarsal conjuctiva	Antibiotics
	Inflammatory trachoma (TI)	Inflammation and thickening of the eyelid, obscuring more half of the normal vision	
Irreversible trachoma (trichiasis)	Trachomatous conjunctival scarring (TS)	The presence of easily visible scars in the conjunctiva	Surgery
	Trachomatous trichiasis (TT)	≥ 1 eyleash rubbing on the cornea or evidence of recent removal of turned-in eyelashes	
	Corneal opacity (CO)	Blurring of the pupil margin	

2.4 Management of the disease

The Alliance for the Global Elimination of Blinding Trachoma has set the goal of 2020 for the global elimination of trachoma (GET2020). The aim is to control trachoma through the SAFE strategy: implementation of surgery (S) for trichiasis, antibiotics (A) to treat infection, facial cleanliness (F), and environmental improvements (E) to reduce transmission [53]. The SAFE strategy, dependent on the initial prevalence of blindness and infection, can be used with the primary aim of:

1. preventing vision loss and blindness;

2. decreasing the prevalence of infection below 5%, the level at which trachoma is no longer considered to be endemic; or

3. achieving total elimination of trachoma from a low prevalence population [54].

For areas where trachoma is recognized as endemic in the community, such as Gashoho, the urgency is to decrease the potentiality of visual impairment, trichiasis or blinding i.e. to deploy the S component of the SAFE strategy. Then the next stage is to decrease the severity of the infection and reduce the transmission of *C.trachomatis* by mass antibiotic distribution (the A component). Interventions may after that be undertaken to suppress the risk factors that amplify transmission of the disease, by actions that promote the improvement of the environment (E) and cleaning the face (F). SAFE therefore describes a comprehensive plan of interventions, implemented in a community, to treat the different stages of trachoma and address the risk factors predisposing to disease transmission [55]. Each of the components of the strategy is now described in more detail.

2.4.1 Surgery for trichiasis

Many different procedures have been described to correct trichiasis. The two surgical methods now most commonly used are [56]:

1. Division of the upper-eyelid tarsal plate with external rotation of the distal margin by use of three or four sutures (tarsal rotation) gave the best results, with at least 70% success at 6 to 24 months after surgery.

2. Some programmes have advocated repeated epilation for patients who have only a few in-turned eyelashes and no evidence of damage to the cornea.

Studies in Africa suggest that if patients with trichiasis are identified in a community and asked to attend a nearby health facility for surgery, fewer than one in three attend[57, 58, 59]. Bowman and co-workers showed that surgery offered in the village at no cost had a better acceptance rate [60]. An eye nurse working in Tanzania did tarsal rotation in the community and reported 80% success at 2 years, and more than 95% success if successful outcomes included one or two lateral in-turned eyelashes not

touching the cornea [61].

In conclusion, the surgery part of SAFE, as implemented in Burundi, includes recognition of patients with trichiasis and treating them by the rotation of tarsal, in the community, by competent surgeons, the procedure was almost free of charge. Importantly, surgery targets only the late effects of trachoma infection, and does not impact active trachoma prevalence or transmission (see Table 2.1). As such, surgery is administered independently of interventions targeting active infection and transmission: the A, F, and E components of the SAFE strategy.

2.4.2 Antibiotics

The recommended treatment for active trachoma is topical tetracycline, twice per day and for 6 weeks. Tetracycline ointment is irritating and difficult to use, especially in infants, so compliance is poor [62]. Randomised controlled trials have established that one 20 mg/kg dose of azithromycin is at least as effective as supervised application of tetracycline ointment. When tubes of ointment are simply given to patients and parents for use at home, single-dose azithromycin is more effective, particularly for individuals with intense inflammation (TI) [63]. Azithromycin has the added benefit of treating extra ocular reservoirs of chlamydial infection, and although there must be caution to avoid emergence of resistance in chlamydia and other bacteria, current evidence supports the use of azithromycin [64]. Pfizer (a pharmaceutical company), through the International Trachoma initiative, have generously donated azithromycin for use in the SAFE programmes in countries where azithromycin is not yet available or affordable. An annual mass drug administration (MDA) with oral azithromycin for a minimum of 3 years is recommended for communities where the initial prevalence of the clinical sign trachomatous inflammation follicular (TF) (Active trachoma) is 10% in children aged 1 to 9 years, with a recommended coverage of 80% of the whole community [65]. In low prevalence settings this usually leads to a considerable and sustained reduction in *C.trachomatis* infection prevalence over time, however in highly endemic areas infection is more likely to reemerge shortly after MDA [66]. Signs of inflammatory infection are reported to persist longer than infection itself at both the individual and population levels, resulting in the observation of clinical signs in the absence of infection [67]. The

association between clinical signs and *C.trachomatis* infection in communities prior to MDA also decreases after treatment [68].

Who should receive treatment? Suggested strategies include: all children; all inhabitants of any household which has an individual with TF or TI; and all inhabitants of a village with endemic trachoma. If antibiotics are given only to individuals with clinical evidence of TF or TI and their families, reinfection is likely to occur more rapidly. Therefore, the consensus is to treat all inhabitants of a village with endemic trachoma. However, this may be an inappropriate strategy for a community with a low frequency of active disease. Mass treatment requires more antibiotic, but may be a more effective and cost-effective approach for communities with moderate or high frequency of active disease. Recent studies have shown that children younger than 5 years of age have the highest ocular chlamydial loads, and even those younger than 1 year old constitute a significant reservoir of infection [69].

How often should antibiotic distribution be done? Initial models for determining treatment frequency are yet to be validated. Currently, annual treatment is recommended, but treatment should probably be given more often in populations with high rates of trachoma transmission and perhaps less often in populations where trachoma is on the wane. Thus, azithromycin is an important new tool for the control of active disease and reduction in disease transmission. Optimum use of the antibiotic needs to be defined for communities with high, moderate, and low prevalences [70].

Despite the central place of mass administration of azithromycin in the SAFE strategy, it is not without problems. There is a fear that widespread use of any antibiotic may drive the development of anti-microbial resistance, a major public health concern in its own right [71]. There is, as yet, no evidence to suggest MDA of azithromycin at the community-level leads to increased azithromycin resistance in ocular Chlamydia trachomatis infection. However, there are data supporting an association of MDA with the emergence of resistance in non-target *Sterptococcus* and *Staphylococcus* organisms. For example, macrolide-resistant *Streptococcus pneumoniae* has isolated from the nasopahrnyx in some settings [72]. While studies carried out in Tanzania, Nepal and The

Table 2.2 Algorithm for annual mass drug administration to target active trachoma, according to the field prevalence surveys, as outlined in [3, 4]. The evaluation of prevalence being based in children under 9 years old per community

Prevalence of TF in 1-9 Y.O at baseline	Frequency of treatment with oral azithromycin
10 % or greater	Antibiotic annually for all residents for three years. Then survey again if : 1. prevalence is 10% or greater : repeat treatment for three years again and reassess 2. prevalence is less than 10%, then survey to determine the prevalence at community level, for communities : a) with less than 5% : stop treatment b) with 5% or greater : treatment until prevalence falls below 5%
<10%	Survey at community level, for communities with: 1. 10% or greater, annual treatment for three years. Then survey, if prevalence : a) Less than 5% treatment can be stopped. b) 5% or greater treatment should be continued until the prevalence falls below 5% 2. In the communities where the prevalence is between 5 - 10%. F and E should be implemented for three years then survey, if : a) prevalence between 5 - 10% F and E should be continued b) prevalence less than 5% F and E can be stopped
<5%	The implementation of A, F and E component is not a priority.

Gambia have shown no evidence of such resistance following a single treatment round [73], other studies in Tanzania, Nepal and Australia suggest resistance does emerge after just one or two annual rounds of mass treatment [74]. Further studies in Ethiopia have documented increased macrolide resistant pneumococci isolated following four rounds of MDA given at 3 month intervals and following six biannual rounds over a period of 3 years [75].

Staphylococcus aureus colonization is a risk factor for many conditions ranging from skin and soft tissue infections in children to invasive disease such as neonatal sepsis, bacteraemia and endocarditis [76]. Evidence proves that both the prevalence and the proportion of resistant strains are higher after three rounds of azithromycin treatment

[77]. That highlights the need for continued antimicrobial resistance monitoring in communities receiving azithromycin treatment at the community-level [78], and further supports an increased emphasis on the F and E components of the SAFE strategy to limit, as much as possible, the need for antibiotic distribution.

2.4.3 Facial cleanliness

Anecdotal reports have suggested that face washing protects against trachoma, and observational studies have shown that unclean faces are associated with TF and TI [1, 79, 80].Studies comparing interventions with antibiotic treatment alone versus antibiotic treatment combined with an intensive health education programme about facial cleanliness [81, 82, 83, 84] showed that antibiotics lowered the frequency of TF and TI in all communities, but that active disease returned towards pre-treatment levels by 12 months. Epidemiological information of this sort has informed the emphasis on using F and E strategies, rather than antibiotics, to try to further reduce prevalence in moderate areas (5-10% prevalence; see table 2.2). The health education programme prolonged the reduction in the prevalence of severe trachoma (TI): this difference between intervention and control groups was significant. Although no significant effect on the prevalence of TF at 1 year could be attributed to health education in this study, the education programme significantly increased the proportion of sustained clean faces in children, and clean faces were protective against TF and TI [85].

Transmission may be limited if ocular and nasal secretions are removed by keeping faces washed and clean; a number of cross-sectional studies have shown that children with clean faces are less likely to have trachoma [86, 87, 88]. Cross-sectional surveys have shown a positive association between the distance to the water source and the prevalence of active trachoma both in the household and in children [89, 90]. The quantity of household water also predicts the prevalence of trachoma in a variety of settings [91]. The prevalence of trachoma is associated with distance, or time taken to walk, to the nearest water supply [16]. In that way it is assumed to be related to the amount of water that individuals can carry home per trip [91]. It is believed that up to a particular threshold the distance or time to water source does not affect the amount of water brought into the household or its subsequent use, while above this level, distance

to water source corresponds with a drop in the amount of water carried [17, 91].

2.4.4 Environmental improvement

The environmental component of the SAFE strategy is the most undefined, but probably the most important part of it. This can be justified by the fact that trachoma was eradicated in European countries and in North America as standard living conditions improved, not because of mass antibiotics distribution or surgery [1, 92, 93]. While socioeconomic conditions remains at a low level in most of trachoma endemic regions, targeted public health interventions have been suggested to suppress the risk of infection by ocular *C. trachomatis* . They include environment improvement through, for example, increasing access to water, use of latrines and other fly control interventions, and moving animals away from the household environment; education, both general and specific for trachoma; and improved local economy leading to better living conditions [94]. A number of studies found that insecticide spraying or provision of latrines could produce a reduction in flies (specifically the eye-seeking *Musca sorbens*), which in turn produces a reduction in active trachoma and in diarrhoeal disease [95, 96, 97, 98].

The fly *Musca sorbens* has long been considered as a vector of hyperendemic trachoma and associated bacterial conjunctivitis in the rural communities of developing countries. It has been noted that in these areas a seasonal increase in the prevalence of these infections coincides with an increase in the fly population. In trachoma endemic areas, flies are frequently seen clustering around the face and eyes of children where they feed on mucus and discharge [99]. For the eye-seeking fly *M. sorbens*, the vector of trachoma, its preferred breeding medium is isolated human faeces lying on the ground. For that reason pit latrines are being promoted as part of the environmental improvement component of the SAFE strategy for trachoma control as a means of controlling *M.sorbens* [100]. The rationale of this is that M. sorbens is believed to breed in solid faeces lying on the ground, but does not breed in latrines, so long as the contents liquefy rapidly. In Egypt, less trachoma was found in households in which simple pit latrines were present and this may be because they reduce the *M.sorbens* population by restricting its breeding habitat [101]. Any measures that can reduce fly-eye contact are likely to be of public health benefit in the control of trachoma and, therefore, the

importance of flies should be incorporated into health/hygiene promotion programmes and school curricula. Though eyelid surgery and antibiotic treatment make an immediate impact, the ultimate success of the SAFE strategy for trachoma control is likely to depend on finding sustainable ways of reducing trachoma transmission. The neglected area of fly control deserves some attention [97].

There are a number of unanswered questions from these studies, however. It is not clear whether provision of latrines or insecticide use is more effective at limiting fly populations, although, logically it would seem removing breeding grounds for flies such as unsanitary toilets would be more effective as it would have a long-term rather than transitory effect on fly populations. It might also reduce the transmission of *C. trachomatis* on fomites and contaminated fingers and hands. At the moment, however, it is not possible to confirm the hypothesis that provision of sanitary toilets would have the largest effect on reducing trachoma transmission, because the magnitude of the increase in risk of trachoma infection associated with unsanitary toilets (the effect size) has not been established. Establishing this effect size is one of the main aims of Chapter 3 of this thesis.

2.5 The African context

In Africa there are 27.8 million cases of active trachoma, which represent 68.5% of the global prevalence. This figure includes 3.8 million cases of trichiasis, which is 46.6% of their global prevalence. Moreover, trachoma is believed to be endemic in 33 of the 56 countries in Africa, including Burundi, and the highest prevalence of active trachoma and trichiasis in the world is in the Sahel area of West Africa and Savannah areas of East and Central Africa [102]. Whilst population level prevalence is now less than 50% in all areas [103, 104, 105], the prevalence of active infection in 1 – 9 year-old children in these regions is very high. For example South Sudan (83%), Ethiopia (64%), Guinea (50%), Uganda (37%), Chad (38%), Central Africa Republic (38%), and Tanzania (32%) [106]. Studies in Gambia, Cameroon, and Nigeria also showed that the overall prevalence of active trachoma in children aged 1–9 years of age were 3.8%, 12%, and 37.7%, respectively [107, 108, 109].

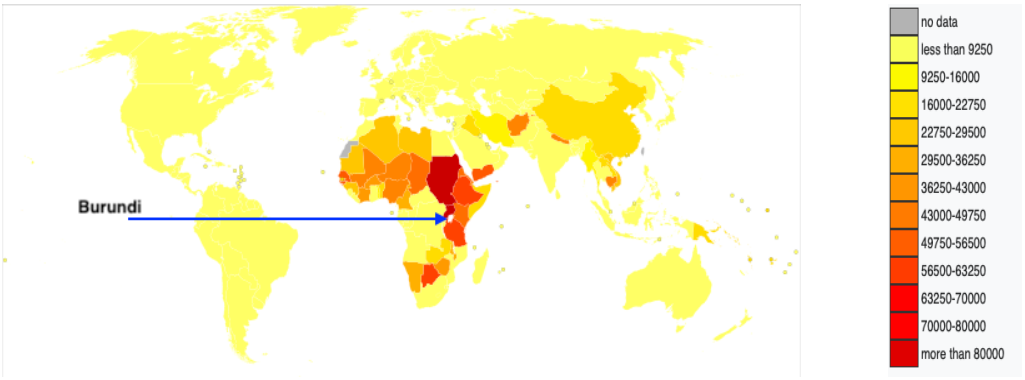

Fig. 2.1 Age-standardised disability-adjusted life year rates from Trachoma by country (per 100,000 inhabitants) in 2004. Blue arrow indicates location of Burundi (shown in white, indicating the absence of data). Map created by Lokal Profil, and used and edited in accordance with the terms of the Creative Commons Attribution-Share Alike 2.5 Generic (CC BY-SA-2.5) license. License terms and original image hosted at: `https://commons.wikimedia.org/wiki/File:All_Causes_world_map_-_DALY_-_WHO2004.svg`.

The endemic nature of trachoma transmission in Africa is undoubtedly facilitated by the presence of the environmental risk factors discussed above. A scarcity of clean water is suspected to promote trachoma transmission, because less water is available to use for cleaning the face of infectious secretions [110, 111]. Similarly, limited access to sanitary toilet facilities increases faecal contamination of the environment, therefore promoting the breeding of the fly *M. sorbens* [85, 112], as previously described. In most African countries to date, however, only the antibiotics component of the SAFE strategy has been systematically implemented [113, 114]. Measures for increasing face-washing or environmental improvement have been neglected, in part because of the lack of evidence regarding the magnitude of the association between these risk factors and trachoma prevalence [114]. Increased attention is now being given to these components of the SAFE strategy as the current approach has not achieved the elimination targets. Given its African context, this thesis will contribute to the body of research that is now investigating whether increased attention to the E component, in particular, can assist in achieving GET2020 at some point in the future.

2.6 The local context: Burundi and Gashoho

There is some uncertainty about the current prevalence of trachoma in Burundi, where this thesis particularly focuses. In Burundi in 2007, a rapid assessment for trachoma was performed, in which an average of 50 adults and 50 children aged 1–9 years per community were examined ($n = 2,253$ children, $n = 1,845$ adults) [115]. This survey revealed the presence of active trachoma in the country but did not clarify its magnitude. Till November 2009, there was no data of trachoma available for the WHO see Fig.2.1. It followed a more detailed survey in 2009–2010, in which 20,659 children were examined in 11 districts. Results from this survey demonstrated a prevalence of children with follicular trachoma (TF) above 10% in three districts. An extension of this survey to eleven other districts also showed TF above 10% in the Rutana district, the prevalence of unclean faces was also $> 10\%$ [116]. Till current time, the fight against trachoma in Burundi is done based on data from the eleven districts while Burundi counts in total 45 health districts. Moreover, logistic constraints and health policy problems (lack of evidence on the real magnitude of trachoma for the whole country, lack of clear policies specific to local conditions, lack of interest and prioritisation of other disease with potential of emergency or epidemic) have led to sub-optimal implementation of the SAFE strategy. Burundi has only adopted the antibiotics component of the SAFE strategy, likely due to its perceived higher compliance and lower cost of this strategy in the communities. In contrast, the E component is less well understood, as described above, but is also a multi-factorial public health intervention requiring ongoing education, resourcing and behavioural change. It is therefore more complex to implement than antibiotics, but neglecting this component may hamper elimination of the disease. This is evidenced in Gashoho Health District, which is the focus of the work in this thesis. Even though Gashoho is located in the Muyinga province, which was targeted for mass azithromycin distribution from 2010-2014 [115], trachoma remains endemic in Gashoho. Therefore, this thesis will explore the extent to which environmental interventions, in particular, might assist in controlling trachoma in Gashoho.

2.7 The role of mathematical models in the study of trachoma

2.7.1 The role of mathematical models in epidemiology

Mathematical modelling is the process of using mathematics to make predictions about the real-world, to understand situations and to assist in making decisions. It is the bridge between the real world and mathematics, whose theoretical and numerical analysis provides insight, answers, and guidance useful for the originating application [117]. When reviewing modelling, it is helpful to identify broad categories of models. Classification of individual models into these categories tells us immediately some of the essentials of their structure. One division between models is based on the type of outcome they predict. Deterministic models ignore random variation, and so always predict the same outcome from a given starting point, depending only on the parameter values.On the other hand, stochastic models incorporate random or systematic variation, and are more unpredictable in nature as they do not generate the same outcome for the same initial conditions. In this way, they may be used to predict the distribution of possible outcomes from a single parameter set [118].

Stochasticity can be a major driving force in the behaviour of epidemics, and yet it is one of the most difficult concepts to deal with mathematically. There are two main forms of stochasticity that can be distinguished [118]:

- demographic stochasticity, which arises from variability within the host population (also called random error or noise); and
- environmental stochasticity (comes from sources external to the population).

Due to limitations on project time, this thesis will not formulate stochastic models, but will to a degree evaluate the possible range in magnitude of environmental influences on the population by thorough sensitivity analysis and model fitting.

A second approach to distinguishing between types of models is to consider the type of problems that the model seeks to understand. A model which begins with equations corresponding to an underlying or higher-level process, then refines these based on low-level data, is called a mechanistic model, because they seek to better understand the

mechanisms through which data is produced [119, 120]. Statistical models, in contrast, begin with low-level data and seek to develop over-arching models explaining variability in the data, without necessarily making inferences about the causal mechanisms by which changes to the system occur. Instead, it is merely noted that they do occur, and the model tries to account quantitatively for changes associated with different conditions [121, 122].

Trachoma modelling studies exist both in statistical and mechanistic types, with the latter being arguably more valuable, as they aim to understand the dynamics and/or the control of *C.trachomatis*. Mechanistic models of trachoma transmission have used both deterministic and stochastic approaches [123, 124, 125]. The diversity of mathematical modelling studies examining trachoma dynamics and control at the population level are explored chronologically below.

2.7.2 Mechanistic models of trachoma transmission

The first mechanistic or mathematical model of trachoma appeared in 1966 and was investigating the force (the rate at which susceptible individuals acquire an infectious disease) of infection and the changes in the risk of infection and in the disease picture over time [5]. It used data from Taiwan to fit a catalytic model; this model, whilst bearing some similarities to the foundational epidemic growth model of Bernoulli [126], is unique, and is worthy of brief discussion. The authors assumed that

- the population is constantly exposed to a force of infection which does not vary in the age-band under investigation, 0-64 years
- that the evidence of effective contact is definite and remains so for life.

The catalytic curve (that is, the evolution of the proportion of individuals of a given age who have been exposed to the disease (are either infective or have already had the infection and are immune). This type of model is described in a monograph) developed from these assumptions was then described by the equation:

$$y = 1 - e^{-rt} \quad (y = 0 \text{ at } t = 0), \tag{2.1}$$

where y is the fraction of the population diagnosed, e the base of the natural logarithm, r the force of infection in terms of effective contacts per year per unit of population (effective contact means a contact sufficient to produce infection if the subject is susceptible), and t is age.

Another study in 1973 used a more elaborate model to attempt to determine the general usefulness of catalytic models in assessing change in the rate of acquiring clinical trachoma following a programme of intensive control [127]. It concluded that a single catalytic curve based on just one force of infection parameter r was an inadequate model for planning or measuring the results of trachoma control programs. The later paper suggested that two or perhaps more age groups, experiencing different forces of infection, were required for the catalytic-type model for this purpose. Where the age band should be divided to provide the two groups and what forces of infection should be used for each are admittedly parameters that could be obtained by iteration, then

$$y = \frac{a}{a-b}(e^{-at} - e^{-bt}) \qquad (y = 0 \text{ at } t = 0) \tag{2.2}$$

where a is the force of infection experienced by a given age group, in terms of effective contacts per year per unit of population, and b the rate at which active trachoma progresses into healed (and non-infectious) trachoma [127]. Whilst this model was more realistic than that of (2.1) [5], it did not see widespread use or further development.

Clearly, these historical models are very different to those currently used in infectious disease modelling. These days, when we think of mathematical models of infectious disease, we think of differential equation models of the kind now common in mathematical epidemiology, i.e. mechanistic rather than statistical models. These usually employ ordinary differential equations and divide populations into compartments such as susceptible (S), infectious (I) and recovered (R) individuals [118]. The first attempts to apply these sort of models to trachoma did not occur until the early 1990s, and not until 1999 was the first model of this type published in a peer-reviewed academic journal [128].

In 1999 the WHO recommended mass antibiotic distribution in endemic communi-

ties [128], as noted above. Based on the fact that mathematical models were used in the pharmacology to assess how often an antibiotic should be administered, mathematical models began to be used to assess how often community wide treatment would need to be repeated in order to eliminate trachoma in an endemic community. An age structured model based on the susceptible–infectious–susceptible (SIS) framework, but assuming partial immunity for older individuals was developed by [128]. Partial immunity was hypothesised to occur through two mechanisms. Either older individuals might, on average, have a decreased susceptibility to the infection, or, older individuals might, on average, clear the infection faster [128]. Analysis of this model recommended that periodic treatment would reduce the prevalence based on the prevalence at the baseline. This model influenced the algorithm for periodic antibiotic distribution based on initial prevalence, as shown in table 2.2.

In 2005 a new deterministic SIS model was used to determine which season annual mass antibiotic treatments was the best to be administered in so that the probability of elimination of trachoma can be maximised. The model found that treating three months before the low season resulted in elimination in the shortest period of time. Treating three months before the high season was the least effective. This seasonal pattern was found by monitoring the length of time for elimination in 75%, 90%, and 95% of the communities. The 95% confidence interval for the average time until elimination in a certain percentage of villages at any time-point ranged from ± 2 months to ± 5 months. Therefore, ideally the treatment should be administered before the low season to have the greatest chance of locally eliminating the infection [129]. In 2007 a literature review focused on the understanding of immunobiology of trachoma by incorporating immunological principles into a mathematical framework leading to a new model of the observed community distribution of infection, bacterial load, and disease, based on age [125]. The SIS model framework was again used and showed that trachoma disease progression is intimately linked with the immune response provoked by initial and subsequent ocular infections by *C trachomatis*. The model showed that population subgroups may exist who are genetically predisposed to acquire the infection in the first place, and then to develop severe scarring sequelae on continued exposure to infection [125].

In the same year a stochastic version of the SIS model previously developed in [129], was developed and used data collected from 16 villages in Ethiopia to calibrate a mathematical model that incorporates the effects of chance. The fundamental issue is that the goal is to control the infection but, not to completely eliminate it. Therefore, a single mass antibiotic distribution can dramatically reduce the prevalence of infection in a village. However, if infection is not eliminated in every single community, it is likely to return back, therefore, repeated treatments are often required. Policy makers are reluctant to distribute antibiotics indefinitely, there is a need of a proven long–term rationale for continuing antibiotics. The model demonstrated that the average prevalence of infection across all villages progressively decreased after each treatment, as long as the frequency and coverage of antibiotics are sufficient. Infection could be eliminated in more villages at each round of treatment. However, in the communities where infection was not eliminated, it returned back to the same average level. Simulations suggested that a biannual treatment plan implemented for 5 years would lead to elimination in 95% of all villages.

The model was developed to determine whether a local elimination was possible, and if so, in what time frame. The mathematical models did indeed prove that elimination was possible condition to repeated treatments [130]. In 2008 an age structured model of ocular infection with *C. trachomatis* was developed and fitted with parameters estimated to the pre-intervention ocular chlamydial infection prevalence from three geographically-separate sites in The Gambia and Tanzania, representing areas of low, moderate and high endemicity. Insights from the model help explain observed age-profile patterns of infection prevalence in these settings [124]. In 2010 a mathematical model was developed to allow the impact of control programmes on infection and blinding disease sequelae to be predicted. The model had a structure that allows an important aspect of trachoma pathogenesis to be taken into account, namely the effect of repeated cycles of infection and recovery leading to scarring and the damaging disease sequelae [131].

In 2013 GET2020 had dramatically reduced the community prevalence of infection,

and some were arguing that lowered prevalence of infection may lead to reductions in immunity [132, 133, 134], and that less immunity may in turn lead to increased transmission from what infection remains. A stochastic model was then developed and used data collected from a 3- year antibiotic treatment program (a 32-community, cluster-randomized clinical trial in Tanzania) to assess whether or not transmission actually increases during elimination campaigns. The model found that the basic reproductive number was decreased, and that there was no evidence supporting any increase in transmission over the course of the program, therefore, there was no loss of immunity when the infection is decreased in the population [135].

Since 2014 mass oral azithromycin distributions have continued to dramatically reduce the prevalence of trachoma in some countries (Nepal, Mexico, Ghana, Uganda, and the Gambia) [136]. Mathematical transmission models have continued to be used to understand the effects of these programs, and to estimate the prevalence of infection immediately after treatment, and found the effective field efficacy of antibiotic (proportion of individuals who cleared the infection given a certain coverage) in a community [4, 137].

Unfortunately, despite the large number of mathematical models suggesting the efficacy of mass drug administration in eliminating trachoma, in 2020, trachoma remains endemic in many places. The failure of the SAFE strategy to achieve elimination of trachoma by 2020 (GET2020) in many places has not gone unnoticed by mathematical modellers. In 2019, a consortium discussion group on trachoma conducted a review of mathematical modeling and quantitative studies, and recommended the extension of the GET2020 target until 2030. Mathematical modelling and current surveillance data continues to suggest that elimination of trachoma as a public health problem is feasible, and indeed this has already been achieved by some formerly endemic countries such as Ghana, Gambia, and Uganda [11]. However, in areas with long-term persistence that have relied only upon mass antibiotic administration (e.g. Ethiopia), this has not been sufficient to achieve elimination of trachoma as a public health issue. The consortium found that mass drug administration should be supplemented with additional tools to help to eliminate the transmission of infection, including more intensive efforts

to promote facial cleanliness and environmental improvement (the F and E components of SAFE). The optimal ways to do so, however, remain unclear. Unfortunately, to date it has been challenging to measure or model the true impact of F and E interventions and their potential role in helping to reduce transmission, due to lack of data [11, 138]. Mathematical models of the effects of environmental improvement in particular have been neglected. A mathematical modelling study by modifying their β parameter rather than introducing a new compartment to the model structure, suggested that infection could be controlled more readily if treatment was combined with enhanced F and E[139]. In the light of this study the model which will be developed in this work includes an environmental compartment to permit more comprehensive study of the importance of the E component of SAFE strategy.

In summary, despite an abundance of mathematical models of antibiotic distribution to control trachoma, there has been a lack of attention given to developing mathematical models of the non-pharmaceutical components of the SAFE strategy. In particular, there is no mathematical model evaluating the role played by the improvement of sanitation to reduce environmentally mediated transmission, and potentially to achieve GET2020, which has yet not been achieved by prioritising mass antibiotic administration, despite the positive predictions of mathematical models.

2.8 Data sources for mathematical models of trachoma

2.8.1 Problems with existing data

The collection of routine high quality baseline data and data from the monitoring and evaluation, to parametise mathematical models which target to inform public health policies on the reduction and the control of trachoma are very limited [12]. This comes with consequences for mathematical modellers, who therefore need to collect data themselves, or collaborate with other groups who have conducted the study [140]. Given the large range of settings around the world where trachoma is endemic (with respect to climatic, ecological and social differences), it does not seem appropriate that models parameterised primarily with data from Africa be used to make accurate and informative projections about the transmission dynamics of infection occurring in other

endemic regions such as Southeast Asia or Latin America where infection is also endemic [139], or vice versa. However, the majority of studies have calibrated using the data from Gambia, Tanzania and Ethiopia [123]. Given a large geographical variety of trachoma distribution and the non negligible heterogeneity in transmission of the infection within-countries, modelling studies should be investigating the dynamics of the infection at the global level, also trying to trying to understand the spatial differences in trachoma transmission that exists within a country. However, current progress remains limited given the scarce availability of data from regions outside of a few key transmission areas, primarily in sub-Saharan Africa, where research studies have been conducted [141]. Moreover, modelling is often the final activity performed in such a partnership, and constitutes a secondary analysis of the data, following a primary analysis that includes the evaluation of risk factors for disease, and a pre- and post-intervention description of infection and disease prevalence. This has meant that modelling and quantitative analysis have not been systematically used as an integrated part of trachoma control programmes. Whether the methodology applied to estimate these parameters is approached through Maximum Likelihood Estimation [124, 140] the aim of these studies remains the same, which is, to understand the intensity of transmission and the amount of effort required in order to control infection [84].

With reference to this thesis, at the time the PhD project commenced there was no up to date data on the prevalence of trachoma in Gashoho. Indeed, in Burundi, data were lacking such that its trachoma status cold not be represented in a worldwide map Fig.2.1. Therefore, in Chapter 3 of this thesis, we undertook a field study to obtain up–to–date data as a preliminary to the mathematical and computational work in subsequent chapters.

2.8.2 Methodological approaches to data collection in low-resource settings

2.8.2.1 Overview

Since communities with trachoma are largely underprivileged and most frequently located in remote rural areas of developing countries, data collection commonly faces logistical problems. Good research data has the attributes of precision (repeated samples from the same population will yield similar estimates), and accuracy (sample estimates

of population parameters are close to the true value) [142]. Precision and accuracy are both increased by collecting large sample sizes, but in low-resource contexts, this is not usually possible [143]. Instead, epidemiological studies in low-resource settings need to provide the best estimates possible given relatively limited sampling capacity [144]. A number of methods have been developed for such settings, particularly for conducting real-time surveillance and sampling, and these are reviewed below. Some familiarity with these methods is important, as they underpin the ultimate recommendations made by this thesis for surveillance to be conducted after implementing any environmental interventions in Gashoho (see Chapter 6).

2.8.2.2 Population-based prevalence surveys

Despite difficulties with sample sizes and resourcing, population-based surveys are still occasionally used in the estimation of prevalence in trachoma endemic regions [145, 146]. The most commonly used population-based survey design for trachoma prevalence estimation is cluster random sampling. A random selection of 30 sites (termed "clusters") is made [147], where the sample size required for each cluster with a desired level of statistical significance and power is given by

$$n = \frac{Z^2 p(1-p)}{d^2}, \tag{2.3}$$

where n is the number of individuals sampled per cluster; Z is the coordinate of the standard normal probability distribution function corresponding to a significance level α (for example if $\alpha = 0.05$, $Z = 1.96$); *p* is the expected prevalence of the disease; and d is statistical precision, such that $1 - d$ equals statistical power. Thus, as the desired level of significance and power increase, the sample size n per cluster increases.

Cluster Random Sampling is efficient in that only enumeration of the population in the selected cluster is required to develop a sampling frame, rather than a complete population census. Furthermore, cluster random samples can be used for multiple indicators at the same time, e.g. assessment of active trachoma, trichiasis and community risk factors. The main drawbacks are the requirement for *a priori* estimates of prevalence, and power, which have significant effects on the ultimate sample size calculation.

These requirements usually result in large sample size requirement [148], which may be difficult to gather in low resource settings, particularly when repeated sampling is required (i.e. for monitoring or evaluating interventions).

2.8.2.3 Trachoma rapid assessment

Trachoma rapid assessment (TRA) was devised in 1999 and was conceived as an elegant and powerful tool to use for a rapid assessment of active trachoma in children, trichiasis in women and environmental risk factors [149]. This tool utilises a convenience sample to identify high-risk communities, suggesting that at least fifty children between 1 to 9 years are needed for an assessment of current prevalence. It is based on community participation and it is believed to provide a simple way of determining whether or not trachoma is endemic in a particular community. TRA has been advocated as a practical tool for ranking communities, thus facilitating prioritization of interventions in affected areas. However, TRA is not based on probability sampling, and cannot be regarded as population representative [150]. Even though the technique was not conceived to replace proper surveys, TRA data are frequently presented as yielding reliable prevalence estimates. In addition, field trials suggest that the method has low precision (large differences between repeated samples), adding further doubt regarding its accuracy and reliability [151], especially for monitoring and evaluation.

2.8.2.4 Acceptance sampling for trachoma rapid assessment

Acceptance sampling for trachoma rapid assessment uses lot quality-assurance sampling (LQAS) principles and is believed to allow the identification and classification of communities that have low or high prevalence of trachoma [152]. Lot Quality Assurance Sampling was developed in the manufacturing industry for the control of the quality of products in factories, and has been used for public health purposes to evaluate immunization coverage and disease prevalence. The main outcome of this methodology is to determine if a batch or lot of goods is acceptable or not acceptable by taking a sample of items, calculating the probability of items being defective, and defining what risk of a defect going undetected is acceptable given the economic advantage of not having to inspect every item. The decision value is the number of defective items that need to be found before a lot is deemed unacceptable; in infectious disease applications,

a defective item is a case of disease.

This survey design, unlike those above, does not have a fixed sample size, and sampling may stop once the number of defects (cases) allowed has been exceeded [153].For infectious disease applications, LQAS is based on the probability of finding d or more infected people in a randomly chosen area ("lot"), defined as

$$\begin{aligned} P(a) &= \frac{n!}{a!(n-a)!} \\ &= p^a q^{n-a}, \end{aligned} \tag{2.4}$$

where p represents the true prevalence in the area, $q = 1 - p$ is the complement of the prevalence, n is the sample size (number of people sampled in the area), a is the number of non-infected individuals in the sample, so that d is estimated to bed $d = n - a$. The choice of parameters defines two "stopping rules": sampling stops when either the maximum sample size (n) is met or the number of defects allowed in the sample (d) is exceeded. If the maximum sample size (n) is met without the number of defects allowed in the sample (d) being exceeded, the sampled population is classified as having a low prevalence of defects. If the number of defects allowed in the sample (d) is exceeded the sample is classified as being of high prevalence. The main concern with this kind of sampling is that whilst it can estimate that the prevalence exceeds the threshold, as defined by the quantities n and d, it is not possible either to estimate the prevalence of infection or to state the precision of such estimates, thus their reliability is not always clear.

Therefore, a new version of LQAS with additional decision rule was developed to provide specified levels of error for each classification. It is based on prior definitions of acceptable type I and type II error rates, denoted by α and β, which represent the probability of falsely classifying a lot as defective or not defective, respectively. Based on the *a priori* definitions of α and β, (2.4) was transformed into two new equations,

$$\begin{aligned} P(X < d | n\ , p_u \geq 70\%) &\leq \alpha, \\ P(X \geq d | n\ , p_L \leq 40\%) &\leq \beta, \end{aligned} \tag{2.5}$$

where X is the number of cases observed, 70% and 40% represent the thresholds for classifying the prevalence of cases as high or low, based on a specific public health scenario [154], and other values have their previous meanings. The use of these equations is best demonstrated by an example. Consider a situation where the maximum sample size desired is $n = 20$, with $\alpha + \beta \leq 0.20$. Simultaneously solving (2.5) to minimise both α and β identifies an optimal value of $d = 12$. This results in a probability $P(X < 12|20, P_u = 70\%) = 0.113$ high prevalence areas as low, and a probability $P(X \geq 12|20, p_L = 40\%) = 0.057$ of falsely classifying low prevalence areas as high, with $\alpha + \beta = 0.17$. Unfortunately, this plan always requires $n = 20$ to be collected in order to make the classifications with appropriate precision.

Both forms of LQAS show the potential of more complicated sampling schemes to minimise sample size, and thus, to be suited for rapid assessment of disease prevalence in settings with limited resources. Unfortunately, at present LQAS is only applicable in local settings, such as villages. As yet, no method exists for translating the results of methods such as LQAS, carried out in individual villages, to higher-level population units such as districts or countries, where health policy decisions are often made, whilst preserving the desired levels of accuracy and precision. This limits the potential of LQAS to transform policy and practice at higher decision making levels.

As can be seen, all of the above methods have some problems. Chapter 6 develops a new method for conducting surveillance in Gashoho, which is based on repeated, stratified sampling, but also allows the results to be translated to the Health District level, where they may more easily inform policy and practice. The method described in chapter 6 may well be one of the first major contributions from this thesis to be transferred into policy in Gashoho.

2.9 Conclusion

In this chapter, the facts that contribute to maintaining trachoma as the leading cause of preventable blindness have been reviewed. Despite the lack of good data in some locations, trachoma is believed to be endemic in 33 of the 56 countries in Africa, including Burundi. The highest prevalence of active trachoma and trichiasis remains in the Sahel

area of West Africa and Savannah areas of East and Central Africa [102]. In Burundi, trachoma is still believed to be endemic in Gashoho Health District, where this study is focused, although the true prevalence is unknown as contemporary data are lacking. This is despite Gashoho having been a focus of trachoma control efforts (mainly antibiotic distribution) for almost a decade.

The World Health Organisation (WHO) set the global elimination of trachoma by 2020 (GET2020), but this goal has still not been attained – a revised target of 2030 has been set for GET2020. The SAFE strategy is promoted by the WHO as a means of achieving GET2020 and comprises: surgery for trichiasis (S), antibiotics (A), and promotion of face-washing (F) and environmental improvements (E) to suppress transmission. As shown in this literature review, the endemic nature of trachoma transmission in Africa is facilitated by the presence of environmental risk factors that are common in the developing world. Limited access to sanitation increases faecal contamination of the environment, therefore promoting the breeding of the fly *M. sorbens*, which is a vector for trachoma [85, 112]. The actual magnitude of the association between poor sanitation and tracoma transmission, however, remains unclear, as does the capacity of environmental interventions targeting sanitation to control the disease.

To address the gaps in knowledge identified in this review, the following research questions were developed:

1. What is the current prevalence of trachoma in Gashoho Health District?
2. What is the magnitude of the association between poor sanitation and trachoma infection?
3. Can environmental interventions to improve sanitation help in eliminating trachoma?
4. How should the effectiveness of environmental interventions be monitored?

Research questions 1 and 2 are answered in Chapter 3 of this thesis, which describes the results of a field study conducted in Gashoho. Research question 3 is explored in Chapters 4 and 5, using mathematical modelling. Research question 4 is addressed in

Chapter 6, where algebraic and computational approaches are used to develop a surveillance plan for Gashoho going into the future.

In summary, this thesis addresses important knowledge gaps identified in the literature. It uses a variety of methods to address these problems, and culminates in presenting strategies with clear applications for policy and practice in Gashoho Health District in the short- to medium-term.

CHAPTER 3

Association of Environmental Risk Factors and Trachoma In Gashoho Health District, BURUNDI

3.1 Introduction

As discussed in section 2.4.4, the magnitude of the increase in risk of trachoma infection associated with unsanitary toilets (the effect size), whilst thought to be important in the persistence of the disease in developing countries, has not been established. In the context of Gashoho Health District, Burundi, estimating this effect size is made more difficult due to the lack of recent epidemiological data. The lack of information on the effect size and the prevalence of trachoma in Gashoho makes mathematical modelling of interventions targeting the environment in Gashoho almost impossible.

Therefore, this chapter, as a preliminary step to other work in the thesis, aims to:

1. gather up to date epidemiological information on the prevalence of trachoma in Gashoho; and
2. estimate the effect size associated with unimproved environment in Gashoho, and thus, provide information on the potential reduction in trachoma transmission that might be achieved by targeting the environment.

To achieve these aims, conventional epidemiological survey methods were used.

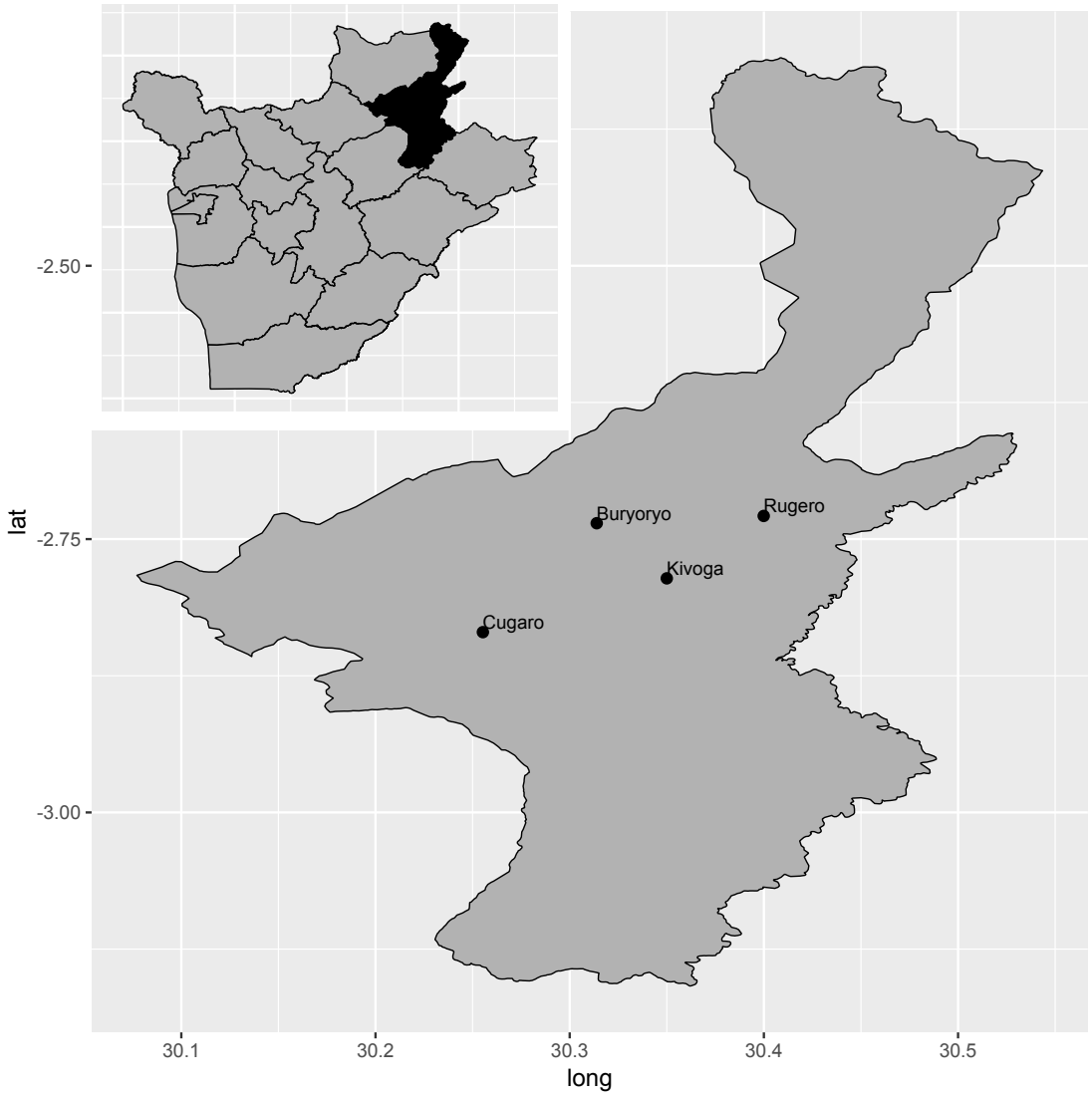

Fig. 3.1 Geographical representation of the locations within the Gashoho Health District where the data collection was carried out. The top left hand side map shows the map of Burundi and the location of Muyinga Province where Gashoho district belongs. The other map shows the borders of Gashoho District and positions of the four villages which have been surveyed.

3.2 Methods

3.2.1 Study design

This is a cross sectional study to investigate the relationship between environmental risks factors and the prevalence of trachoma, using convenience samples from four clinics in the Gashoho health district. The method of Walter et al [155] was used to calculate the sample size required for specified levels of the type I and type II error. A minimum sample size of 350 individuals across 4 villages was required to detect moderate differences in prevalence with 5% precision (type I error) and 80% power (1 - type II error). Community members were informed of the location of the clinic by the local town crier/ drum man, which is a common means of transmitting messages in African communities that do not have universal radio, television, internet or newspaper access [156]. The study was carried out in April during the Easter school holidays, when school aged children could attend the clinics. April falls during the wet season in Burundi, and is warm and humid with most of the year's rain (1.2 m on average) falling during the wet season. Attendees at the clinics were invited to participate in the study. Participant information was provided in the local language Kirundi; it was emphasised that participation in the study did not influence access to the care offered by the clinics. Each participant aged over 18 years was responsible for providing their own consent. Where adults attended with children in their care, they were asked to provide consent for their children's clinical data to be included in the study. The field survey received ethical approval from the Gashoho Health District, Neglected Tropical Diseases Program, and the University of Notre Dame Australia (HREC Approval Number 017167S). The work in this chapter was supported by funding from the School of Medicine, Sydney, at the University of Notre Dame Australia. The ethics application, ethics approval documents, and funding information, are included as appendices.

3.2.2 Study location

The health district of Gashoho is located in the middle of the province of Muyinga, north Burundi (see Figure 3.1). The population of Burundi is estimated at 11,400,379 people, of whom 87% live in rural villages, similar to the study sites. 50.8% of the population are female, and 49% of the population is aged under 15 years of age. 83%

have access to clean water, but only 39% of the population have access to sanitary toilets [157, 158].

3.2.3 Data collection

Data was collected in clinics established in the four villages as part of the normal work of the National Integrated Neglected Tropical Diseases Blindness Program and Health District's Trachoma Control Initiative. Two clinical investigators (Drs Athanase Gahungu and Donatien Kayugi) set up clinics to offer trachoma screening according to WHO guidelines in the four villages within the Health District: Kivoga and Rugero (Gashoho council area), and Cugaro and Buryoryo (Gasorwe council area). All individuals who attended the clinics consented to participate in the study. They received the standard clinical management provided in all trachoma clinics run by the district. Participants were examined clinically for the presence of trachoma and its clinical stage, and if found to have active trachoma (inflammatory or follicular stages), were prescribed antibiotics by a single dose of azithromycin at a dose of 20 mg/kg for children and of 1 g for adult as recommended by WHO. Individuals with trichiasis or cornea opacity (called irreversible trachoma) were referred for surgery. Those individuals who agreed to participation in the study had their infectious status, age, and sex recorded. Infectious status is defined as the presence of clinical trachoma, based on the assumption that individuals with ocular secretions have the capacity to transmit trachoma.

In addition, the adults from each household were surveyed to assess their knowledge about the importance of face-washing and sanitation in transmitting trachoma. In addition, the composition of each household, its access and proximity to clean water, and its access to sanitary toilet facilities was recorded. Clean water was defined as piped water to a yard, access to a public tap or standpipe, a household tube well or a bore hole, or a protected dug well. Sanitary toilets were defined as a flush toilet, a piped sewer, septic tank, ventilated pit latrine, or a pit latrine with slab. The survey instrument is included in the appendices.

3.2.4 Data analysis

Differences in the prevalence of binary trachoma risk factors (gender, household access to improved water, household access to improved toilets) and active or irreversible trachoma between villages and districts were analysed using chi square. Differences in demographics (mean household age, mean household size, mean proportion of the population below 9 years old, distance to clean water) between villages and districts were analysed using one-way ANOVA. Responses to survey questions about knowledge of trachoma were analysed using descriptive statistics.

Generalised estimating equations (GEE) were used for analysis of the association between risk factors and active trachoma per individual per household, since the infectious status of individuals who lived within the same household was correlated with risk factors at the household level (access to clean water or toilets). To conduct the analysis in SPSS, household was set as the subject level variable, and each individual within the household was set as the within subject variable. The initial GEE model included individuals' age, household distance to clean water, household access to improved water, and household access to improved toilet facilities as independent variables and active trachoma (any, or none) as the dependent variable was used to determine the association between these predictors and active trachoma in any member of a household. Individuals with irreversible trachoma (trichiasis or corneal opacity) were excluded from the analysis. A logistic link function was used because of the binary nature of the dependent variable. All two-way interactions were included in the initial model, and backwards elimination was used to remove non-significant variables step-wise.

SPSS version 25.0 for Mac OSX (IBM, Armonk, New York) was used for the analysis and difference was considered as statistically significant at p value < 0.05. The p-value is the probability of obtaining results at least as extreme as the observed results of a statistical hypothesis test, assuming that the null hypothesis is correct. The p-value is used as an alternative to rejection points to provide the smallest level of significance at which the null hypothesis would be rejected. A smaller p-value means that there is stronger evidence in favor of the alternative hypothesis.

Table 3.1 Characteristics of the sample drawn from each village (SD= standard deviation, CI= confidence interval,YO= Years old).

	Buryoryo	Cugaro	Kivoga	Rugerero	overall
Age mean(SD)	19.30 (1.31)	23.69 (1.84)	19.46 (1.34)	22.48 (1.74)	21.10 (0.78)
<9 YO proportion (95% CI)	39.3% (30.8-4.83)	30.7% (22.3-40.1)	35.1% (27.3-43.5)	33.6% (25.6-42.4)	34.8% (30.6-39.2)
Gender	M(53.0%) F(47.0%)	M(48.9%) F(51.1%)	M(48.9%) F(50.4%)	M(49.6%) F(50.4%)	M(50%) F(50%)
Household size (Median and range)	4(2-9)	5(2-8)	6(3-12)	5(2-10)	5(2-12)
Number of household	30	25	25	27	117
Number of individuals	117	101	131	119	469

3.3 Results

468 individuals from 117 households attended the clinics, and all consented to participate in the study. The number of households and individuals surveyed in each village is given in Table 3.1.

There were no significant demographic differences between villages. The average age of participants for the four villages was 21.10 with a standard deviation (SD) of 0.78. The proportion of participants under 9 years old in total was 34.8% with a CI confidence interval (30.6-39.2). Males and females equally participated in our study. These results are summarised in Table 3.1.

The overall prevalence of any trachoma in the sample was estimated at 7.9%, 7.1% of which was active trachoma (see Table 3.2). In children under nine years old the prevalence was 19.5%. Most active trachoma was inflammatory rather than follicular. The prevalence of corneal opacity or trichiasis was 0.9% overall but Kivoga had zero cases, whilst Buryoryo had a prevalence of 1.7% There were no significant differences between villages in any of these estimates.

There was no statistically significant difference in the proportion of households that had access to clean water or toilets see Table 3.2, however, the mean distance to clean water (for households that had access) significantly differed between villages ($p < .001$), with distances varying from 150 to 500 meters. Overall, 73.8% of surveyed

Table 3.2 Percentage (95% CI) of people with trachoma and without access to clean water or sanitation.

	Buryoryo	Cugaro	Kivoga	Rugero	Overall
Any trachoma	8.5 (4.5-14.6)	8.9 (4.5-15.6)	7.6(4.0-13.1)	6.7 (3.2-13.1)	7.9 (5.0-10.6)
Active trachoma	6.8 (3.3-12.5)	7.9 (3.8-14.8)	7.6 (4.0-13.1)	5.9 (2.7-11.2)	7.1(5.0-9.6)
Corneal Opacity or trichiasis	1.7 (0.4-5.4)	1(0.1-4.5)	0.0	0.8 (0.1-3.9)	0.9 (0.3-2.0)
Active trachoma (<9 YO)	17.1 (8.0-30.6)	24.1 (11.5-41.6)	19.5 (9.7-33.5)	18.5 (8.6-32.8)	19.5 (13.7-26.4)
Inflammatory trachoma(<9 YO)	12.2 (4.8-24.7)	17.2 (6.9-33.7)	14.6 (6.3-27.7)	13.2 (5.2-26.5)	14.1 (9.2-20.4)
Follicular trachoma(9 YO)	4.9 (1.0-14.9)	6.9 (1.5-20.3)	4.9 (1.0-14.7)	5.3 (1.1-15.8)	5.4(2.6-9.9)
No access to sanitary toilets	70.0 (52.3-84.0)	84.0 (66.3-94.3)	68.0 (48.5-83.6)	74.1 (55.7-72.9)	73.8 (64.9-81.4)
No access improved water	50.0 (32.8-67.2)	72.0 (52.7-86.5)	60.0 (40.6-77.3)	55.6 (37.1-72.9)	58.9 (49.4-67.9)

Table 3.3 Significant predictors of trachoma infection in the final model (OR= odds ratio, CI= confidence interval).

	P value	OR	95% CI
Age	0.004	0.918	0.866-0.972
Access to sanitary toilet	0.002	0.437	0.256-0.743

household and 74.3% surveyed individuals reported no access to improved toilets. An average of 58.9% (95% CI 49.4-67.9%) of households reported no access to clean water. 100% of adults agreed or strongly agreed that frequent face washing was important in reducing the risks of trachoma. However, none of them identified sanitation as being associated with trachoma transmission. In the final GEE model, only an individual's age and the household's access to sanitary toilet facilities were significant predictors of active trachoma in any household member see Table 3.3. Access to a sanitary toilet more than halved the odds of an individual within the household having trachoma, making this the most significant modifiable risk factor for active trachoma.

3.4 Discussion

This chapter is of a capital importance for this thesis, in the sense that it provides up-to-date data, which will form the basis for the more mathematical work in the remaining chapters. It provides estimates of key parameters, such as the association between poor sanitation and infection, which can be used to calibrate models and estimate the effect of interventions. In addition, current estimates of the trachoma prevalence in Gashoho were gathered, which can serve as initial conditions when modelling the likely impact of such interventions. Mathematical models are more accurate and better able to inform public health policy, if the data used to parametise them reflects the reality in the field. As such, this chapter carries out important work in translating the results of the thesis into policy and practice.

The work in this chapter confirmed that trachoma remains a public health issue in the remote communities of Gashoho Health District. The prevalence of active trachoma in Gashoho remains over the GET2020 target of 5% required for elimination. The overall prevalence of 7.9 % (95% CI 5.0-10.6 %) was not significantly different from the previously reported prevalence [159], suggesting little improvement, despite ongoing distribution of antibiotics in accordance with the SAFE strategy. In some villages, about 1% of individuals had corneal opacity or blindness. These findings are practically unchanged from those reported in 2011 [116]. Children aged under nine years were important drivers of transmission, with the prevalence of active trachoma in this group being 19.5%, with most cases being the more infectious inflammatory stage. This is also reflected in the protective association between increasing age and active trachoma (OR 0.918 for each additional year of age). These findings are similar to those previously reported in [115], and reflect the underlying natural history of disease, which consists of repeated episodes of active trachoma during childhood and the accumulation of scar tissue leading to potential blindness in adulthood [109].

It has been suggested that further reductions in trachoma prevalence in Burundi depend on emphasising face–washing and environmental improvements, including to sanitation [115]. In Gashoho health district, the study found evidence that there was

knowledge of the importance of face–washing, but, contradicting some previous studies, access to clean water was not associated with an increased risk of active trachoma. This result may reflect the knowledge–based motivation of villagers to maintain good facial hygiene even where access to water is difficult. On the other hand, villagers had very poor knowledge about the role of sanitation in preventing the spread of trachoma, despite the most significant predictor of trachoma status in our sample being access to sanitary toilets. Individuals living in households with access to sanitary toilet facilities more than halved their risk of active trachoma. Access to an improved toilet, unlike face-washing, does not require behaviour modification; people will use them if they are available. This, in conjunction with a hypothetical impact on fly populations, may explain why access to improved toilets led to a significantly reduced risk of active trachoma in our sample, even in the absence of knowledge about poor sanitation being a risk factor. Further research is required to establish whether this association may have implications for trachoma control.

These results, taken together, indicate that whilst there are high levels of awareness of the importance of face-washing in Gashoho Health District, and this may have ameliorated the risks associated with poor access to clean water, there is substantial room to improve the population's knowledge about the role of environmental sanitation in reducing the risk of experiencing active trachoma. Household access to sanitation almost halved the risk of trachoma infection (per individual for household) even in the absence of improved knowledge. Future efforts at controlling trachoma in the Gashoho Health District should focus on improving sanitation. The large effect size associated with access to improved toilets shown in our study suggests that targeting this risk factor might be associated with a significant reduction in the risk of active trachoma. Importantly, the proportion of individuals in our sample without access to sanitary toilets was similar to the national average of 39%, suggesting that the results of this study have implications for Burundi as a whole.

Mathematical models will be employed to investigate how much reduction in trachoma incidence might be associated with improved sanitation and whether focusing on environmental improvement alone might be sufficient to reduce the prevalence of

trachoma to the less than 5% target required for elimination. There were a number of limitations to this study. First, whilst the study included four villages and two council areas to try to improve generalisability, it is possible that the four villages surveyed may not be representative of the rest of Burundi with respect to trachoma prevalence and risk factors. However, the prevalence of trachoma in these villages was similar to that reported in studies across Burundi previously; this suggests that the findings of this study are similar to other areas of the country. A second limitation relates to the timing of the survey; it is possible that the effect size associated with poor sanitation might be different in the dry season from the wet season. However, the main mode of transmission associated with poor sanitation is likely to be vector borne transmission (flies). Flies would become more active during the dry season, potentially increasing the association between poor sanitation and infectious status. Future studies in the dry season should be conducted to examine this hypothesis. Finally, the study reported in this chapter was limited because the relationship between improved toilets and trachoma status depended on self-reported data. It would have been desirable for surveyors to have obtained information on sanitation and access to clean water by visiting households. Unfortunately, financial constraints made this impossible, as it would have required the employment of more research staff for a longer time. Future research should validate our findings by more in depth observations in the field.

3.5 Conclusion

This Chapter makes three novel contributions. First, it provides up-to-date information on the prevalence of trachoma in Gashoho Health District, which is estimated at around 8% at a population level (but close to 20% in children under 9 years of age). Secondly, it estimates, for the first time in the literature, the size of the association between poor sanitation and trachoma infection. Household access to sanitary toilets almost halved the risk of infection per individual, per household. Poor access to sanitary toilet facilities was the most significant modifiable risk factor identified in this study. The third contribution was to highlight the knowledge gap of villagers regarding the role that sanitation played in preventing trachoma. Given the large effect size associated with sanitation in the absence of knowledge, potentially, public information campaigns focused on hand washing and hygienic use of toilets could increase the protective effect

of sanitary toilets even further.

This chapter reinforced the conclusion, made anecdotally by clinicians in Gashoho, that efforts to eliminate trachoma in Gashoho Health District should focus on improving sanitation (the E component of the SAFE strategy). In subsequent chapters, these results are used to develop mathematical models to estimate the potential effect of interventions targeting poor sanitation, and whether these could result in elimination of trachoma in Gashoho, which has not occurred so far using antibiotics alone to reduce person-to-person transmission.

CHAPTER 4

Do Environmental Reservoirs of Trachoma Infection Drive Trachoma Transmission in Burundi? A Mathematical Modelling Study.

4.1 Introduction

The results presented in the previous Chapter showed the magnitude of trachoma risk factors in Burundi and highlighted the importance of the environmental risk factors in the occurrence of trachoma. The improvement of the environment in the context of trachoma can be the access to clean water or the access to sanitary toilets. In Gashoho Health District, the access to clean water was sufficient, however, there was a lack of sanitary toilets. For instance, the odds of acquiring trachoma infection in the household was doubled given the absence of unimproved sanitation [160]. This supported the hypothesis that non-improved sanitation provides a significant environmental reservoir for *Chlamydia trachomatis* [141], the obligate intracellular spirochete which is the bacterium [161] in the cause of trachoma. The indirect route of trachoma transmission can then be described as pathogens deposited in the environment by flies and picked up by susceptible individuals through inanimate objects. This chapter develops new mathematical models to assist in understanding the main routes of transmission of active trachoma, so that the transmission can be reduced or stopped, thereby reducing the number of people in 51 countries (currently estimated at 232 million) who are at risk of blindness due to the complications of trachoma infection [159]. Furthermore, this chapter develops models to assist in achieving the Global Elimination of trachoma by 2020 (GET2020) goals set by the World Health Organization (WHO) (reduction in prevalence in endemic regions to $< 5\%$ by 2020). As described previously, the SAFE strategy, which comprises surgery for trichiasis, antibiotics for active infection, facial

cleanliness and environmental improvement is recommended as a means of achieving this target [162], and will be investigated especially with respect to its E component, the importance of which was identified in Chapter 3. The antibiotics component of the strategy is delivered via mass administration of annual single dose of 20mg/kg of the macrolide antibiotic azithromycin at annual intervals until a prevalence less than 5% is reached at community level [3, 4]. The International Trachoma Initiative (ITI) recommended then that at least a coverage of 90% of the population should be reached during mass antibiotic administration to lower the risk of recurrent endemic infection [163, 164, 165], see Section 2.4

Whilst antibiotic administration reduces the number of infected people, in endemic areas, person–to–person transmission is not the only means of trachoma transmission. There is substantial evidence that environmental measures targeting sanitation and vector–borne transmission might be just as, or even more, important for long term elimination [166]. Provision of sanitary toilets or latrines appears to be associated with a lower prevalence of active trachoma. Improved sanitation undoubtedly reduces vector–borne transmission; flies act as mechanical vectors of disease by picking up pathogens from infectious material and transferring them to an uninfected host. Elimination of faecal matter in the environment, which flies breed in, reduces the fly population, hence, reducing vector-borne transmission [167]. The evidence that flies are vectors of trachoma has been strengthened by intervention studies. In Gambia, one study found that a reduction in the community prevalence of active trachoma was associated with fly control of 61% (odds ratio of 0.39 [95% CI 0.20 – 0.77] p=0.007). Moreover, the number of new cases was significantly lower in the intervention villages than controls [98]. In Egypt, less trachoma was found in households in which simple pit latrines were present and this was related to the reduction of the fly population by restricting its breeding habitat [95]. Nonetheless, focusing on vector–borne transmission only may underestimate the potential contributions of improved sanitation to trachoma control [168], as sanitation may reduce other modes of transmission such as self inoculation (analogous to fecal–oral transmission), or transmission via fomites.

Although the mechanisms of environmentally mediated trachoma transmission are

well explained, to the best of our knowledge no mathematical modelling studies have been conducted to investigate its contribution to trachoma endemicity. Mathematical modelling can be a powerful tool to study the transmission of infectious diseases [169], including trachoma [125, 170]. In this chapter, we use mathematical modelling, calibrated to field data, to investigate whether environmental transmission could explain the persistence of trachoma in a health district in Burundi.

In Burundi, trachoma is endemic in 11 districts , which are home to almost 2 million people [116]. More concisely, in three districts, the district- prevalence level of TF in 1 –9 year–olds was $>10\%$, classed as high prevalence by the WHO [3, 4]. Based on these results the study recommended the commencement of trachoma control activities, with implementation of the SAFE strategy. Unfortunately, despite over a decade of control efforts, there has been little change in the prevalence of trachoma in Burundi [160]. It is proposed that the reason for failure of the control efforts might be a lack of attention to the environmental improvement component of the SAFE strategy. Therefore, an improved understanding of the transmission dynamics and ecology of trachoma in Burundi might help to improve the control, and consequently the elimination of disease. Mathematical models are potentially valuable tools for this purpose [169]. In this chapter a mathematical model which includes an environmental transmission component to further investigate its place in the dynamic of trachoma infection will be developed. More specifically, the model will be used to assess how much improvement we need to make in order to achieve the target of Global Elimination of trachoma by 2020 (GET 2020).

4.2 Model description

The Susceptible–Infected–Susceptible scheme (SIS), where infected hosts become susceptible once again after recovering from infection [124], is used to evaluate the implementation of the SAFE strategy in Gashoho Health District. The SIS scheme is suitable for trachoma because it is apparent that the symptomatic state can reoccur within the same individual and that any immunity conferred is at best partial [128, 171]. The basic SIS model does not account for the fact that the incidence of trachoma infection increases with age, however, so a number of age-structured models have been utilized

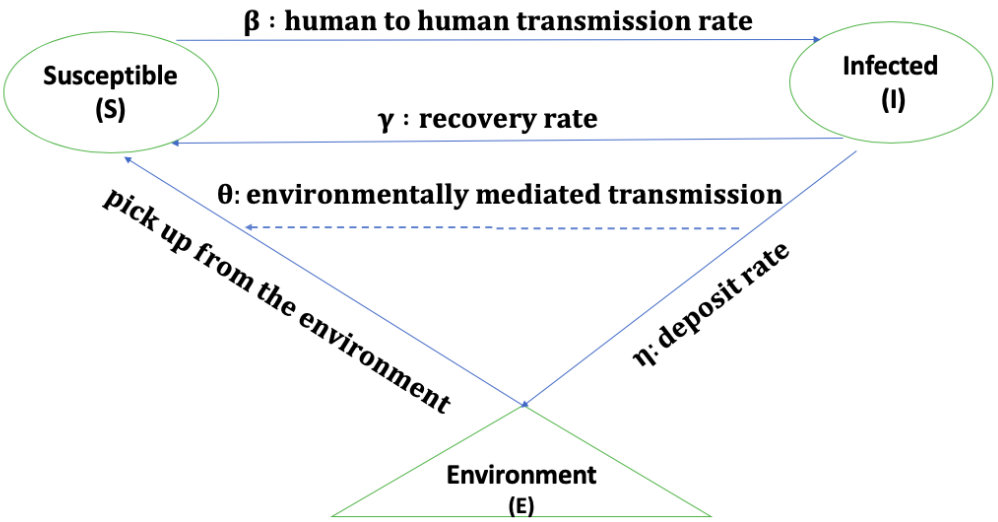

Fig. 4.1 Trachoma transmission model, including both human-to-human and environmentally mediated transmission.

to study the disease [124, 125]. Since this current study is phenomenological in nature, with the main focus being studying the mechanistic role of environmentally-mediated transmission in driving endemic disease, we have chosen to simplify our study by not using an age-structured model at this time. We will examine how incorporating age–structure into our model affects the results in a later chapter. We justify this decision because, biologically, there is no increase in immunity associated with age, and, more importantly, in Gashoho, trachoma control initiatives are implemented without consideration of age. Given the clinical history of the infection, it was necessary to make further simplifying assumptions. Specifically, the model will only include individuals with active trachoma (TI and TF; see Table 2.1), as only these individuals contribute to the transmission of the infection. Individuals with irreversible trachoma are not included in the model, as these clinical presentations are best considered as complications from repeated infection, and individuals in these states do not contribute to the spread of the infection [172]. A simplified schematic of the proposed model is presented in Fig. 4.1.

The approach to modelling an acute infection with trachoma in the human population differs from previous models of ocular infection with *C. trachomatis*, since it includes a compartment representing viable pathogen subsisting in the environment,

for example, in proximity to unimproved latrines which provide an environment for pathogens to proliferate and interact with human hosts and vectors. In the model, susceptible people (S) may become infected through contact with infected individuals (I) at rate β; alternatively, they may become infected via contact with viable pathogen in environmental reservoirs E (latrines) at rate θ. The rate parameter θ operationalises multiple possible modes of transmission, for example: physical contact with contaminated waste by individuals then touch their eyes or face, and vector-driven transmission where flies carry pathogen on their bodies to the eyes of an infected individual. These modes of transmission are combined into one parameter for simplicity of the model. The parameter η represents the rate at which infected individuals shed pathogen into the environment, and the rate parameter μ operationalises the multiple ways by which the environmental pathogen load might be reduced, including by improved sanitation. The unit of time is assumed to be one day, the shortest increment of time that would be useful in most practical applications of this model. The model described visually in Fig.4.1 corresponds to the system of ordinary differential equations (ODEs),

$$\begin{cases} \frac{dS}{dt} &= -\beta SI + \gamma I - \theta SE \\ \frac{dI}{dt} &= \beta SI + \theta SE - \gamma I \\ \frac{dE}{dt} &= \eta I - \mu E. \end{cases} \tag{4.1}$$

Assuming a constant human population size of $N = S + I$, the system (4.1) can be reduced to a new one consisting of two equations

$$\begin{cases} \frac{dI}{dt} &= \beta NI - \beta I^2 + \theta NE - \theta EI - \gamma I \\ \frac{dE}{dt} &= \eta I - \mu E. \end{cases} \tag{4.2}$$

The system of equations (4.2) has two equilibrium solutions (recall that an equilibrium point is defined as the variation d over time equals zero $\frac{d}{dt}$=0); a disease free equilibrium $(0, 0)$ and an endemic equilibrium,

$$\begin{pmatrix} \hat{I} \\ \\ \hat{E} \end{pmatrix} = \begin{pmatrix} \frac{\beta N\mu + \theta\eta N - \gamma\mu}{\beta\mu + \theta\eta} \\ \\ \frac{\eta}{\mu}\left(\frac{\beta N\mu + \theta\eta N - \gamma\mu}{\beta\mu + \theta\eta}\right) \end{pmatrix}. \tag{4.3}$$

The stability of the disease free equilibrium (DFE) is studied first. Evaluated at the DFE, the Jacobian of (4.2) is

$$J(0,0) = \begin{bmatrix} \beta N - \gamma & \theta N \\ \eta & -\mu \end{bmatrix}. \tag{4.4}$$

For stability, the trace of (4.4),

$$\text{Tr}(0,0) = \beta N - \gamma - \mu, \tag{4.5}$$

must be negative. This condition is satisfied subject to

$$\frac{\beta N}{\gamma} < 1 + \frac{\mu}{\gamma}. \tag{4.6}$$

The stability of the DFE also requires that the determinant of (4.4), $Det(0,0)$, is positive, where

$$Det(0,0) = -\beta N\mu + \gamma\mu - \theta\eta N. \tag{4.7}$$

This condition is satisfied subject to

$$\frac{\beta N}{\gamma} < 1 - \frac{\theta\eta N}{\gamma\mu}. \tag{4.8}$$

Considering the two conditions (4.6) and (4.8), and given that only positive parameter values are meaningful, it is apparent that the condition (4.6) is satisfied whenever (4.8) is true. Therefore, for the DFE to be stable, it is sufficient to consider only the inequality (4.8). It is useful to reorganise (4.8) as

$$\frac{\beta N}{\gamma} + \frac{\theta\eta N}{\gamma\mu} < 1. \tag{4.9}$$

This formulation of (4.8) suggests that the ratios function as basic reproduction numbers in our model. The basic reproductive number, R_0, is usually defined as the expected number of secondary infections arising from a single individual during his or her entire infectious period in a wholly susceptible population [173]. The quantity R_0 is often used as a bifurcation parameter in many mathematical models; if $R_0 < 1$, then the infection

cannot be transmitted effectively and will not become endemic or cause an epidemic, whereas when $R_0 > 1$, endemic or epidemic transmission is possible [174]. Equation (4.9), on the other hand, can be expressed in terms of two quantities that behave similarly to the traditional definition of R_0, and hence can be viewed as basic reproduction numbers. Let R_{0H} denote the expected number of secondary infections caused by one infectious individual in a wholly susceptible population, as per the normal definition of R_0. Further, let R_{0E} denote the expected number of infections caused by one unit of pathogen in the environment, in a wholly susceptible population. Further, let

$$R_{0H} = \frac{\beta N}{\gamma} \quad \text{and} \quad R_{0E} = \frac{\theta \eta N}{\gamma \mu}, \tag{4.10}$$

such that the inequality (4.9) can be reduced to

$$R_{0H} + R_{0E} < 1. \tag{4.11}$$

The inequality (4.11) shows that not only both R_{0H} and R_{0E} must be reduced to < 1, but their sum must also be < 1 for the eradication of trachoma,with the condition on R_{0E} showing the vital role of environmental improvement in the SAFE strategy. While $R_{0H} < 1$ may be attained using antibiotics, R_{0E} can only be reduced using environmental improvement.

The stability of the endemic equilibrium (EE) is now considered. The Jacobian of (4.2), evaluated at $(\hat{I}, \hat{E})$ is

$$J(\hat{I}, \hat{E}) = \begin{pmatrix} -\frac{\beta^2 N\mu^2 + 2\beta N\mu\theta\eta - \beta\mu^2\gamma + \theta^2\eta^2 N}{(\beta\mu+\theta\eta)\mu} & \frac{\theta\eta\mu}{\beta\mu+\theta\eta} \\ \eta & -\mu \end{pmatrix} \tag{4.12}$$

Stability requires that the trace of (4.12),

$$\text{Tr}(\hat{I}, \hat{E}) = -\left(\frac{\beta^2 N\mu^2 + 2\beta N\mu\theta\eta - \beta\mu^2\gamma + \theta^2\eta^2 N + \theta\eta\mu^2 + \beta\mu^3}{(\beta\mu + \theta\eta)\mu} \right). \tag{4.13}$$

is < 0. The denominator of (4.13) is positive by definition for realistic parameter values, so the trace will be negative when the numerator of (4.13) is also positive noting the

negative sign on the RHS of (4.13), which occurs subject to:

$$\beta N\mu + \theta\eta N - \gamma\mu > 0. \tag{4.14}$$

The stability of the endemic equilibrium further requires that the determinant of (4.2) evaluated at the endemic equilibrium, $\det(\hat{I}, \hat{E})$, be positive. Since $\det(\hat{I}, \hat{E})$ can be simplified to

$$\det(\hat{I}, \hat{E}) = \beta N\mu + \theta\eta N - \gamma\mu. \tag{4.15}$$

satisfying the inequality (4.14) is sufficient for stability. Nonetheless, it is convenient to rearrange the inequality as

$$\frac{\beta N}{\gamma} + \frac{\theta\eta N}{\gamma\mu} > 1, \tag{4.16}$$

which is the reciprocal condition to (4.9), and thus clearly shows the dynamics. If R_{0H} and R_{0E} are the number of new infections produced in a wholly susceptible population by an infected individual and a unit of pathogen in the environment, as defined previously in (4.10), then (4.16) can be expressed as

$$R_{0H} + R_{0E} > 1. \tag{4.17}$$

It is important to note the additive action of R_{0i} where $i = E, H$ from (4.17) on the existence of an endemic equilibrium, the sum of R_{0i} needs to be > 1 regardless whether any or both of them is < 1. Hence, even in the absence of productive person to person transmission, a contaminated environment can drive endemic disease. These results reinforce the importance of environmental improvement in ensuring that the SAFE strategy is effective.

When $R_{0H} > 1$ and $R_{0E} < 1$, the system tends towards the second equilibrium point due to person to person transmission only; if $R_{0H} < 1$ but $R_{0E} < 1$, residual pathogen in the environment may be sufficient to cause endemic disease in the human population. In the first case, antibiotic administration will constitute a successful control measure, but in the second case, environmental improvement will need to be employed to control

the disease. If all $R_{0i} > 1$, the endemic equilibrium is stable, and both antibiotics and environmental improvement will be required to eliminate disease.

4.3 The relationship between prevalence and basic reproduction numbers at endemic equilibrium

In this section, it is shown that prevalence (the proportion infected) when (4.2) is at the endemic equilibrium approximates the relation [118],

$$\frac{I}{N} = 1 - \frac{1}{R_{0H} + R_{0E}}. \tag{4.18}$$

This relation was derived based on the assumption

1. R_0 is approximately the rate at which secondary cases are produced times average infectious period.

2. The proportion of susceptible individuals at endemic equilibrium is the inverse of R_0.

That the relation holds in general is seen by using the assumption of constant population size

$$N = I + S. \tag{4.19}$$

Dividing (4.19) through by N gives

$$1 = \frac{I}{N} + \frac{S}{N}, \tag{4.20}$$

and substituting the proportion of susceptible individuals $\frac{S}{N}$ in (4.20) by $\frac{1}{R_0}$ and re-arranging gives

$$\frac{\hat{I}}{N} = 1 - \frac{1}{R_0}, \tag{4.21}$$

thus proving the relation between R_0 and prevalence in general.

This relation is now proved specifically for the system (4.2) at the endemic equilibrium by noting that

$$\frac{1}{R_0} = 1 - \frac{\hat{I}}{N}, \tag{4.22}$$

and using the value $\hat{I}$ at the endemic equilibrium, (4.3). Recalling that

$$\hat{I} = \frac{\beta N\mu + \theta\eta N - \gamma\mu}{\beta\mu + \theta\eta}, \tag{4.23}$$

then

$$\begin{aligned}
\frac{\hat{I}}{N} &= \frac{1}{N}\left(\frac{\beta N\mu + \theta\eta N - \gamma\mu}{(\beta\mu + \theta\eta)}\right) \\
&= \frac{1}{N}\left(\frac{N(\beta\mu + \theta\eta) - \gamma\mu}{(\beta\mu + \theta\eta)}\right) \\
&= \frac{1}{N}\left(N - (\frac{\gamma\mu}{(\beta\mu + \theta\eta)}\right) \\
&= 1 - \frac{\gamma\mu}{N(\beta\mu + \theta\eta)}.
\end{aligned} \tag{4.24}$$

Substituting (4.24) into (4.22) gives

$$\frac{1}{R_0} = 1 - \left(1 - \frac{\gamma\mu}{N(\beta\mu + \theta\eta)}\right) \qquad = \frac{\gamma\mu}{N(\beta\mu + \theta\eta)}. \tag{4.25}$$

From (4.25),

$$\begin{aligned}
R_0 &= \left(\frac{\gamma\mu}{N(\beta\mu + \theta\eta)}\right)^{-1} \\
&= \frac{N(\beta\mu + \theta\eta)}{\gamma\mu} \\
&= \frac{\beta N}{\gamma} + \frac{\theta\eta N}{\gamma\mu}.
\end{aligned} \tag{4.26}$$

Thus, for this model, the value of R_0 that determines the prevalence of infection amongst humans at endemic equilibrium is the sum of R_{0H} and R_{0E}, as defined in (4.10).

This finding has important implications for relating the field data collected in Chapter 3 to the model, and for understanding the inability of the GE2020 strategy to control

trachoma. If, at endemic equilibrium, both R_{0H} and R_{0E} are > 1 individually (a possible solution to the model), such that $R_{0H} + R_{0E} > 2$, then the prevalence, based on eqs. (4.21) and (4.26) would be $> 50\%$. No recent studies, including that contained in Chapter 3, report prevalences above 50% for trachoma [103, 104, 105]. Therefore, we can deduce that the scenario where both R_{0H} and R_{0E} are > 1 is not realistic.

In part, since this implies that one of R_{0H} or R_{0E} must be < 1, this may reflect the partial success of GET2020. Since GET2020 has resulted in frequent delivery of the antibiotics component of the SAGE strategy, it is possible that R_{0H} is now < 1 in many locations, where, nonetheless, trachoma persists. Therefore, the relation between prevalence, R_{0H} and R_{0E}, gives further evidence that to eliminate trachoma, targeting environmentally mediated transmission is required.

The model (4.3) was fitted to the endemic equilibrium by setting γ and N constant, whilst varying the values of other parameters. The recovery rate γ was fixed at 0.017, based on clinical data [130], and the population size was fixed at $N = 1000$. Other parameters, represented by the vector $\hat{p} = (\beta, \theta, \eta, \mu)$ were varied. Latin hypercube sampling was used to generate random values of each parameter, and then (4.2) was solved numerically for all possible combinations of these parameter values to identify all parameter combinations yielding solutions within the 95% confidence interval for field prevalence in Gashoho from [160]. All simulations utilised initially conditions of 1 infected person and zero pathogen in the environment, and were conducted using the *library(deSolve)* in R version 10.14.6 on Mac OSX Mojave, with a time-step of one day. Results of these simulations are shown in Fig. **??**, which shows that for scenarios where $1.107646637 > R_{0H} + R_{0E} > 1.051710284$, the prevalence at endemic equilibrium fell was not significantly different to the field prevalence in Gashoho of 7.9% (95% CI 5 - 9.6) [160]. Multiple regression was used for sensitivity analysis of the results presented in Fig. **??**, with prevalence at endemic equilibrium as the dependent variable and R_{0H} and R_{0E} as independent variables. The interaction between the two dependent variables was modelled as an additive effect. This regression-based sensitivity analysis showed that only the sum $R_{OH} + R_{0E}$, and not the individual reproduction numbers R_{0H} and R_{0E}, were significant predictors of prevalence at endemic equilibrium. Standardised

Table 4.1 Parameters corresponding to stability of the disease free equilibrium (a), and three stable endemic scenarios (b, c, d), each of which approximate the target prevalence in Gashoho. Results for each scenario are shown in Fig. 4.2. As it can be seen in the table all the parameters are fixed except μ, this done on the purpose of highlighting the importance of the environment in the transmission of trachoma.

Parameter	a	b	c	d
β	0.0000056	0.000000012	0.0000129	0.00001729
θ	0.004	0.004	0.004	0.004
η	0.013	0.013	0.013	0.013
μ	5	2.8	9	40
R_{0H}	0.329411765	0.000705882	0.758823529	1.017058824
R_{0E}	0.611764706	1.092436975	0.339869281	0.074783301
$R_{0H} + R_{0E}$	0.941176471	1.093142856	1.09869281	1.093529412

regression coefficients from the sensitivity analysis are shown in Tab. 4.1.

4.4 Application of the model to Gashoho Health District

Numerical methods were utilized to fit the model to recent field data from Gashoho, Burundi [160]. In Gashoho, as in other parts of the country, pockets of endemic trachoma occur in rural locations [116]. The main reason for the clustering of trachoma in rural areas is believed to be a lack of sanitation [175, 176]. The prevalence of trachoma and its associated risk factors were recently studied in four villages (117 households, 468 individuals) in Gashoho Health District, with results described in Chapter 3 of this thesis [160]. Recall from Chapter 3 that the prevalence of active trachoma was 7.9% (95% CI 5.0 – 10.6) overall, and 19.5% (95% CI 13.7 – 26.4) in children aged 1–9 years. Individuals in households with access to improved sanitation were found to have almost half the odds of trachoma infection (OR =0.437, 95% CI 0.256–0.743). These results are in line with those from several other epidemiological studies from the region. One study in Tanzania found a similar negative association between sanitary toilets and trachoma infection (OR=0.49, 95% CI 0.26 – 0.93) [177]. Another study in Guinea Bissau revealed that the presence of flies around a latrine was independently associated with trachoma infection with an odds ratio of 2.1 (95% CI 1.1 – 3.8) [111]. All of these findings suggest that aside from person-to-person transmission, the persistence of trachoma in Gashoho Health District may well be maintained (at least in part) by

environmentally mediated transmission. The mathematical model described above was therefore fitted to the field prevalence data [160], and the possible impact of sanitation programs on endemic trachoma, using parameters derived from the odds ratios identified in the aforementioned studies.

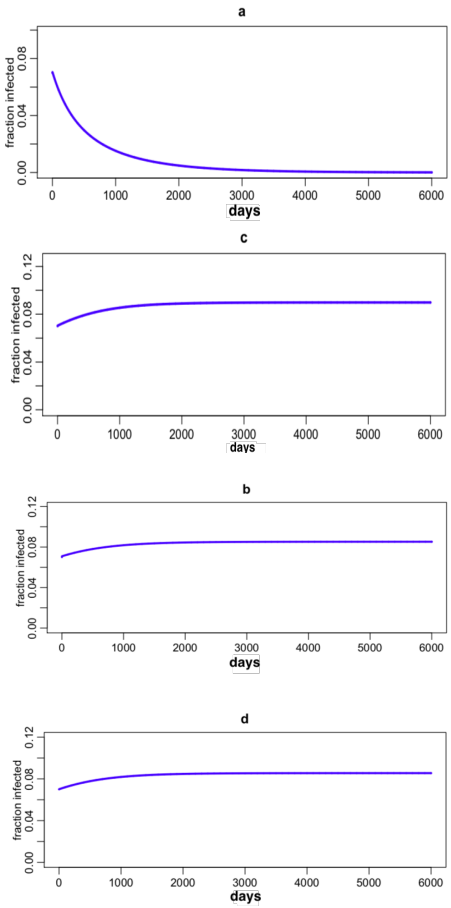

Fig. 4.2 Proportion of the population infected under different basic reproduction numbers corresponding to the scenarios from Table 4.1, namely: a) $R_{0H} + R_{0E} = 0.941176471$, $R_{0E} = 0.611764706$, $R_{0H} = 0.329411765$; b) $R_{0H} + R_{0E} = 1.09314286$, $R_{0E} = 1.09243697$, $R_{0H} = 0.00070588$; c) $R_{0H} + R_{0E} = 1.09869281$, $R_{0E} = 0.33986928$, $R_{0H} = 0.75882353$; d) $R_{0H} + R_{0E} = 1.09352941$, $R_{0E} = 0.07647059$, $R_{0H} = 1.01705882$.

The model (4.3) fitted to the DFE and endemic equilibrium by setting γ and N constant, whilst varying the values of other parameters. The recovery rate γ was fixed at 0.017 per day, based on clinical data [130], and the population size was fixed at $N = 1000$. Other parameters, represented by the vector $\hat{p} = (\beta, \theta, \eta, \mu)$ were varied for different scenarios. To fit the DFE, values of $\hat{p}$ were identified that satisfied the constraint $R_{0H} + R_{0E} < 1$. To fit (4.3) to the endemic equilibrium, we assumed

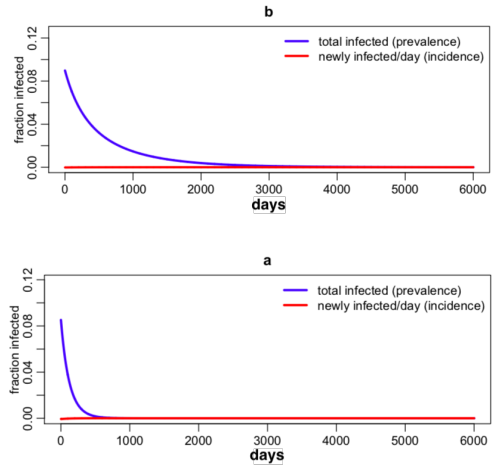

Fig. 4.3 Time (days) to elimination for when environmental improvement is implemented in endemic populations from Fig. 4.2. Environmental improvement is operationalised by doubling the value of μ whilst holding other parameters constant. **Plot 4.3 a)**: Initial conditions and parameters correspond to the endemic equilibrium from Fig. 4.2 b); **Plot 4.3 b)**: Initial conditions correspond to the endemic equilibrium from Fig.4.2 c).

that the average prevalence of trachoma in Gashoho is 7.9%, as reported in our recent cross-sectional study [160]. The values of $\hat{p}$ were varied to model the following three scenarios satisfying $R_{0H} + R_{0E} > 1$:

1. $R_{0H} + R_{0E} = 1.0931$, $R_{0E} = 1.0924$, $R_{0H} = 0.0007$;
2. $R_{0H} + R_{0E} = 1.0986$, $R_{0E} = 0.3398$, $R_{0H} = 0.7588$;
3. $R_{0H} + R_{0E} = 1.0935$, $R_{0E} = 0.0764$, $R_{0H} = 1.0170$.

Results for these simulations are presented in Fig. 4.2, where plot 4.2 (a) shows the results for the DFE, and plots 4.2 (b-d) correspond to the three scenarios satisfying the endemic equilibrium as listed above. Parameter values used for each scenario are given in Table 4.1.

We did not attempt to fit the model to a situation where both R_{0E} and R_{0H} exceeded 1, since this would give result in a prevalence exceeding 50%, which did not agree with our observations from the field data (see Chapter 3), or other epidemiological data (see section 4.3 above).

To explore the possible effect of improvements in sanitation on trachoma control, we drew on the results of our field study, which showed that improved sanitation almost halved the odds of trachoma transmission. We operationalised this effect in simulations by doubling the environmental clearance rate μ, given initial conditions equal to the endemic equilibrium. Simulations were conducted using the *library(deSolve)* in R version 10.14.6 on Mac OSX Mojave, with a time-step of one day. Initial conditions for the simulations corresponded to the number of susceptible and infected individuals, and units of pathogen in the environment, at endemic equilibrium for scenarios b) and c) from Table 4.1. Parameter values, except μ, were also taken from Table 4.1. We did not simulate scenario d) from 4.1 as the value of R_{0E} was already close to zero in this scenario.

4.5 Results

Figure 4.2 affirms the results of our stability analysis, showing, in scenario (a), that where both R_{0H} and R_{0E} and their sum are < 1, the system converges upon the DFE. Scenarios b) and d) illustrate that having either R_{0H} or R_{0E} is able to cause the persistence of the infection in the human population. Scenario (c) shows that if the sum of R_{0H} and R_{0E} is not < 1 the disease will persist in the population even if individually each R_{0i} is < 1. In each of these three endemic scenarios, we were able to approximate the target prevalence of 7.9% derived from our field data see Fig. 4.2.

Figure 4.3 shows the possible impact of an intervention improving sanitation on trachoma endemicity in Gashoho. The effect size of the environmental improvement intervention was estimated from field studies showing an approximate halving of the odds of acquiring infection associated with improved sanitation [111, 177, 160]. This effect was modelled by using solutions of the simulations corresponding to scenarios (b) and (c) in Fig.4.2 as initial conditions, then doubling the parameter μ to operationalise the effect size observed in the field, whilst holding all other parameters constant. After implementing this modification to μ, R_{0E} was reduced from 1.0924 to 0.5469244 for scenario b) and from 0.3398 to 0.1699346 in scenario c). In both scenarios, the overall R_0 was reduced to less than one – from 1.093142857 to 0.5469244 in scenario b), and from 1.09869281 to 0.9287582 in scenario c). These results show that increases in the

value of μ, modelling the effect attributable to improved sanitation, result in eventual eradication of trachoma. More importantly, elimination (defined by the WHO as $<$ 5% prevalence and no active transmission (zero incidence) was attained within 1–2 years in these simulations. These numerical results are in agreement with both our stability analysis and the clinical consensus that eradication or further reductions in the prevalence of trachoma in Gashoho depends upon improvements in sanitation [160].

4.6 Discussion

This chapter makes two new contributions. Firstly by analysing the stability at the endemic equilibrium, therefore, revealing the rationale of the persistence of trachoma in Gashoho Health District. Second it proved that the elimination of trachoma is possible subjected to the improvement of the environment. The World Health Organization (WHO), with many other organizations and public health services, have been implementing programs designed to eliminate trachoma infection, using the SAFE strategy. A cornerstone of the SAFE strategy is the mass administration of systemic antibiotics, which is generally being implemented appropriately in Burundi [178]. Despite this, trachoma has remained endemic in some areas, which has drawn attention to the fact that the environmental improvement component of the SAFE strategy is not being implemented [178, 179, 128]. An increasing number of epidemiological studies have sought to quantify the impact of unimproved environment as a risk factor for trachoma infection and to gain a better understanding of how improved sanitation might contribute to trachoma control [180, 181, 182]. To date, however, very few mathematical modelling studies have been conducted to consider the effect of non pharmaceutical interventions (and particularly the F and E components of the SAFE strategy) in helping to reduce transmission. There remains a substantial need for mathematical models of trachoma transmission that focus on these areas [123].

In this chapter, we aimed to fill this gap by not only developing a new model, but calibrating it to data recently obtained in the field from one of the endemic areas in Burundi, Gashoho Health District. The model developed in this chapter expands upon the usual SIS framework by adding an environmental reservoir of infection. A deterministic model was used because, even though all epidemics are inherently stochastic at the

individual level, endemic infections (such as trachoma) affecting large numbers of people will approximate a suitably defined deterministic model [183]. Subsequent linear stability analysis demonstrated that trachoma elimination cannot be achieved as long as there is non improvement of the environment. This finding is supported by other studies which found that measures such as provision of latrines has important effects on vector borne transmission, for example, reducing the fly population, and is therefore effective in decreasing the transmission of the infection [184]. Improved sanitation probably also impacts transmission via other routes, however, because our field data showed that access to sanitary toilet facilities reduced transmission at the household level rather than population level, where impacts on vector-borne transmission would tend to be seen [160]. Most likely, improved sanitation reduces transmission at the household level by limiting contact transmission between persons, self-inoculation and transmission via fomites. The work in this chapter therefore sought to operationalise multiple modes of transmission to fully capture the potential benefits of improved sanitation on the transmission of trachoma. Therefore, though numerous vector-borne transmission models exist in the literature, we chose to use a more phenomenological approach, since emphasising vector-borne transmission might underestimate the other ways in which sanitation impacts transmission [168]. Furthermore, environmental improvements will not only reduce trachoma transmission, but will also provide some other health benefits to households and communities, for example a reduction in the incidence of diarrhea. Our modelling approach was also designed to facilitate use of the model in examining these potential other benefits of sanitation in future work. In addition, the model may be applicable to other diseases where environmentally mediated transmission is important, but which do not confer long term immunity. Whilst many models incorporating environmentally mediated transmission have been developed for cholera, these are significantly different from our model because cholera is a vaccine preventable disease, whereas trachoma is not. Hence, cholera models incorporate long term immunity and are of an SIR type [185], whereas our model accommodates repeated infection by using a SIS framework. Hence, the model presented in this chapter differs in key aspects from those previously described in the literature and makes a novel contribution.

Nonetheless, our model has a number of limitations, though these can be addressed

in future research, and some are addressed in the following chapter. The use of the SIS framework, though employed by other authors [186], is an oversimplification, since it omits the clinical consequences of repeated infection (corneal opacity and trichiasis), as well as the reduction in the risk of infection with age. Future work should improve the model by incorporating temporary or partial immunity, as well as an age-structured implementation [124].

Additionally, we did not simulate the effect of interventions targeting the pick-up rate θ or the deposit rate η, but only those that removed pathogen load from the environment. Furthermore, we did not distinguish between the different modes of pathogen acquisition (fomites, physical contact, vector borne, etc.) operationalised by the parameter θ. Future research should develop our model by including public health interventions targeting either the pick up rate θ or the deposit rate η, and the different modes of transmission operationalised using these parameters. Future studies should also explore the persistence of the causative agent of trachoma in the environment, and the exact magnitude in reduction that can be achieved by improving environmental conditions to reduce transmission [123].

Trachoma infection is strongly age dependent, suggesting age-specific contact rates, it can be studied with models formulated as ordinary differential equations (ODEs) with distinct variables to describe the size of groups such as susceptible, exposed and infectious, with possibly several compartments to further divide these groups. The ODE formulation assumes that all individuals within a compartment behave identically, regardless of how much time they have spent in the compartment. For instance, it assumes that all individuals in an infectious compartment have the same level of infectiousness, and also that the waiting times in each compartment are exponentially distributed by the dynamic of active trachoma as it is the one which is related to the environmental factors under investigation.

4.7 Conclusion

Trachoma, caused by infection with *C.trachomatis* is the leading cause of preventable blindness worldwide. Its transmission is believed to be from human to human by close

contact, by the arthropod vector *Musca sorbens*, and from environmental reservoirs to humans via fomites and personal contact. The WHO has popularised the SAFE strategy (surgery, antibiotics, facial cleanliness, environment) to eliminate trachoma, but the components have not been equally emphasised in the field. In particular, the environmental improvement component has been neglected in parts of Africa where the disease remains endemic, such as Burundi, as shown in Chapter 3. This chapter makes several new contributions to the study of trachoma.

The chapter describes a new model of trachoma infection incorporating environmentally mediated transmission, and calibrates it to recently obtained field data from Gashoho Health District, Burundi. We demonstrated that where environmentally mediated transmission contributed more than one infection on average in a susceptible population ($R_{0E} > 1$), improvement of the environment is essential for successful elimination. It was further shown that it is not possible to fit this model to field data if both R_{0E} and R_{0E} are > 1. Therefore, the results in this chapter support the hypothesis that environmentally mediated transmission is a major factor in trachoma transmission. This agrees with the results of Chapter 3, which found that access to sanitary toilet facilities reduced the odds of trachoma infection per person, per household, by almost half. Therefore, the contributions of this chapter strongly support the arguments of other researchers that only by full application of the SAFE strategy in Burundi, emphasising environmental improvement, can the WHO's trachoma elimination targets be achieved [159, 11, 116, 115].

However, to assist in stability analysis, some important simplifications were made when constructing the model in this chapter. One of these was failing to consider the age-dependent nature of transmission, and how demographics (birth and death rates) might affect the results. The following chapter addresses these limitations by developing versions of the model incorporating demographics and age-structure.

CHAPTER 5

Age Structured Trachoma Model

5.1 Introduction

In the previous chapter, the role played by the lack of an improved environment in the transmission of active trachoma was demonstrated by development of a new model. It established the existence of two basic reproduction numbers and showed that, even in the absence of human-to-human transmission, environmentally mediated transmission could maintain trachoma at endemic levels. However, the model in the previous chapter employed a number of simplifying assumptions, and omission of birth and death rates. This chapter, will present an improved model by including demographics and age structure, which more accurately reflect the association between age and trachoma infection in low-resource, endemic settings.

In communities where trachoma is endemic [187, 188], infection usually begins in childhood and repeated episodes of infection cause corneal abrasion and ultimately blindness due to corneal opacity at older age [44, 189]. Active trachoma is more commonly observed in children and irreversible trachoma in older individuals [190, 191]. In the previous chapter, the dynamics of the infection at the population level were modelled, and the potential reduction in the prevalence of active disease following improvement of the environment was estimated. However, the model did not take into account the important effects of demographics and age on infection and disease of the apparent reduction in the prevalence of active trachoma that is observed with age [192]. There is a growing body of evidence that indicates that *C.trachomatis* infections are most prevalent in individuals under 9 years old, including the results presented in Chapter 3 of this thesis and published in African health science [160]. The overall prevalence of

active trachoma in children varies widely from region to region, but the age distribution of prevalence is relatively consistent: The prevalence of active trachoma typically peaks from the ages of 3–5 years and then declines monotonically to a very low level in adulthood [128]. Thus for public health and mathematical modelling purposes two different age groups in regards to the strength of transmission of trachoma should be distinguished–individuals under and over 9 years of age.

5.1.1 Modelling approach

In this chapter, before analysing a model with two age groups, however, a model incorporating birth and death rates and conservation of population size is first studied. Birth and death rates are related to the incidence of the more severe disease sequelae, such as blindness, which only occurs in older individuals. This model with births and deaths, because of its relative simplicity, can be analysed using both numerical methods and linear stability analysis. Linear stability analysis shows how the results demonstrated in the previous chapter are affected by incorporating demographics. However, birth-death models with conserved population are not suitable to address more complex questions, such as how the dynamics of trachoma infection are related to the high mortality rate in infants and high birth rates in developing countries [193].

Therefore, the model with births and deaths is further developed to include age groups. Due to its complexity, this model is only studied using numerical methods. However, its realism is evaluated by fitting the model to the age-specific, pre-intervention ocular chlamydial infection prevalence in Gashoho, as described in Chapter 3, with age-specific incidence and rates of recovery from infection. Insights from both of these models should help to explain the observed age-profile patterns of infection prevalence in these settings. Furthermore, these models should assist in understanding how different age groups might benefit from environmental interventions targeting sanitation.

5.2 Model with births and deaths

5.2.1 Mathematical Model

The SIE model of Chapter 4 is first made more complex by adding density dependent birth and death rates. In this new model it is assumed that the total number of the population is constant, where the parameter ϕ is the birth and death rate in susceptible individuals as well as in the infected individuals, assuming that the birth rate is equal to the death rate, to maintain constant population size. All other parameters are the same as in the previous model and they keep the same meaning. The system of ODEs (ordinary differential equations) governing the model is given as

$$\begin{cases} \dfrac{dS}{dt} = -\beta SI + \gamma I - \theta SE + \phi N - \phi S \\ \\ \dfrac{dI}{dt} = \beta SI + \theta SE - \gamma I - \phi I \\ \\ \dfrac{dE}{dt} = \eta I - \mu E. \end{cases} \tag{5.1}$$

5.2.1.1 Jacobian matrix and equilibrium points

The Jacobian matrix of (5.1) is

$$J = \begin{pmatrix} -\beta I - \theta E - \phi & -\beta S + \gamma & -\theta S \\ \\ \beta I + \theta E & \beta S - \gamma - \phi & \theta S \\ \\ 0 & \eta & -\mu \end{pmatrix}. \tag{5.2}$$

The system of equations (5.1) has two equilibrium points: a disease free equilibrium (DFE), $(N, 0, 0)$; and a second solution where the disease is endemic in both the human population and the environment, $(\hat{S}, \hat{I}, \hat{E})$.

At the endemic equilibrium point for both basic reproductive numbers: in human and in the environment. The equilibrium value of pathogen density in the environment

is found by setting the third line of (5.1) to zero, giving

$$\hat{E} = \frac{\eta \hat{I}}{\mu}. \tag{5.3}$$

To determine the value of $\hat{S}$ at that endemic equilibrium point, we substitute (5.3) into the equation describing the variation of infected individuals of (5.1), giving:

$$\beta S\hat{I} + \theta S(\frac{\eta \hat{I}}{\mu}) - \gamma \hat{I} - \phi \hat{I} = 0$$

$$\beta S\hat{I} + \theta S(\frac{\eta \hat{I}}{\mu}) = \gamma \hat{I} + \phi \hat{I}$$

$$S\left(\beta + \frac{\theta\eta}{\mu}\right) = \gamma + \phi$$

$$\hat{S} = \frac{\gamma + \phi}{\beta + \frac{\theta\eta}{\mu}} \tag{5.4}$$

Using the assumption of a constant population, $I = N - S$, so from (5.4),

$$\hat{I} = N - \frac{\gamma + \phi}{\beta + \frac{\theta\eta}{\mu}}. \tag{5.5}$$

Now substituting (5.5) into (5.3)

$$\hat{E} = \frac{\eta}{\mu}(N - \frac{\gamma + \phi}{\beta + \frac{\theta\eta}{\mu}}). \tag{5.6}$$

Thus the endemic equilibrium point is

$$\begin{pmatrix} \hat{S} \\ \\ \hat{I} \\ \\ \hat{E} \end{pmatrix} = \begin{pmatrix} \frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}} \\ \\ N - \frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}} \\ \\ \frac{\eta}{\mu}(N - \frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}}) \end{pmatrix} \tag{5.7}$$

5.2.1.2 Stability at the DFE

The Jacobian matrix (5.2) evaluated at the DFE is

$$J(N,0,0) = \begin{pmatrix} -\phi & -\beta N + \gamma & -\theta N \\ \\ 0 & \beta N - \gamma - \phi & \theta N \\ \\ 0 & \eta & -\mu \end{pmatrix} \tag{5.8}$$

By expanding down the first column it is clear than one of the eigenvalues is $-\phi$. For physically meaningful cases, this eigenvalue is always negative. Hence the stability of the DFE is dependent on the eigenvalues of the 2X2 matrix located at the bottom right of (5.8), that is

$$\begin{pmatrix} \beta N - \gamma - \phi & \theta N \\ \\ \eta & -\mu \end{pmatrix}. \tag{5.9}$$

Hence the requirements for the DFE to be stable are that the trace of the 2×2 matrix defined in (5.9) be < 0, and that the corresponding determinant to be > 0.

For the trace to be < 0, it is required that

$$\beta N - \gamma - \phi - \mu < 0$$

which can be written as

$$\frac{\beta N}{\gamma + \phi} < 1 + \frac{\mu}{\gamma + \phi}. \tag{5.10}$$

For the determinant (5.9) to be > 0, it is required that

$$-\mu\beta N + \mu\gamma + \mu\phi - \theta N\eta > 0,$$

which can also be written as

$$\frac{\beta N}{\gamma + \phi} < 1 - \frac{\theta N\eta}{\mu(\gamma + \phi)} \tag{5.11}$$

Note that the above condition automatically ensures (5.10). The DFE point is therefore stable, with all eigenvalues having negative real part when (5.11) holds. Notice that, similarly to the model without births and deaths presented in the last chapter, (5.11) can be interpreted in terms of two basic reproductive numbers:

$$R_{0H} = \frac{\beta N}{\gamma + \phi} \tag{5.12}$$

representing human to human transmission, and

$$R_{0E} = \frac{\eta\theta N}{\mu(\gamma + \phi)} \tag{5.13}$$

representing environmentally mediated transmission. Hence, from (5.11) we have the requirement that $R_{0H} + R_{0E} < 1$, which echoes the condition on the DFE for the model without demographics, presented in the previous chapter.

Once again, for the DFE to be stable, both human to human and environmentally

mediated transmission, as represented by R_{0H} and R_{0E} need to be less than one, both individually and cumulatively. The clinical implications of this are that for trachoma to be eradicated in Gashoho Health District, a mass antibiotic administration is required to keep the rate of productive human to human transmission (R_{0H}) sufficiently low to prevent the rise of new cases and the contamination of the environment; and the environmentally mediated transmission (R_{0E}) requires public health interventions to increase the removal rate μ as much as possible so that the conditions for pathogens to breed are kept at a minimum level. This stability condition is similar to those for the model without births and deaths presented in the previous chapter. In Gashoho, as described in Chapter 3, it is likely that antibiotic distribution is sufficient to maintain $R_{0H} < 1$. Therefore, further reductions in prevalence are likely to require focusing on reducing the basic reproduction number for environmentally mediated transmission, R_{0E}.

5.2.1.3 Stability at the endemic equilibrium point

For completeness, the stability of the endemic equilibrium is now studied. The Jacobian matrix (5.2), evaluated at the endemic equilibrium, (5.7), is

$$J(\hat{S},\hat{I},\hat{E}) = \begin{pmatrix} -\beta\hat{I} - \theta\hat{E} - \phi & -\beta\hat{S} + \gamma & -\theta\hat{S} \\ \beta\hat{I} + \theta\hat{E} & \beta\hat{S} - \gamma - \phi & \theta\hat{S} \\ 0 & \eta & -\mu \end{pmatrix}, \tag{5.14}$$

The characteristic polynomial for the endemic equilibrium satisfies

$$det \begin{pmatrix} -\beta\hat{I} - \theta\hat{E} - \phi - \lambda & -\beta\hat{S} + \gamma & -\theta\hat{S} \\ \beta\hat{I} + \theta\hat{E} & \beta\hat{S} - \gamma - \phi - \lambda & \theta\hat{S} \\ 0 & \eta & -\mu - \lambda \end{pmatrix} = 0, \tag{5.15}$$

where λ are the eigenvalues of the Jacobian matrix (5.14). By expanding down the first column of (5.15) it can be shown that the eigenvalues must satisfy the equations

$$(\lambda + \phi)(\lambda^2 + a_1\lambda + a_0) = 0 \tag{5.16}$$

where

$$a_1 = \beta(\hat{I} - \hat{S}) + \theta\hat{E} + \phi + \mu + \gamma$$

$$a_0 = \beta\mu(\hat{I} - \hat{S}) + \theta(\hat{E}\mu - \hat{S}\eta) + \mu(\phi + \gamma) \tag{5.17}$$

From (5.16) it is clear one of the eigenvalues is $-\phi$, which, for physically meaningful parameter values must always be negative. Hence, for the endemic equilibrium to be stable, we require both a_1 and a_0 to be positive. First, consider a_1, as expressed in (5.17). Substituting $\hat{S}, \hat{I}$ and $\hat{E}$ in (5.17) by their corresponding values from (5.7) gives,

$$a_1 = \beta\left(N - \frac{\gamma+\phi}{\beta + \frac{\theta\eta}{\mu}} - \frac{\gamma+\phi}{\beta + \frac{\theta\eta}{\mu}}\right) + \frac{\theta\eta}{\mu}\left(N - \frac{\gamma+\phi}{\beta + \frac{\theta\eta}{\mu}}\right) + \phi + \mu + \gamma. \tag{5.18}$$

Then, extending (5.18) becomes

$$a_1 = \frac{\mu^3\beta + \mu^2\theta\eta + 2\theta\eta N\beta\mu + \theta^2\eta^2 N + \beta^2\mu^2 N - \phi\mu^2\beta - \gamma\mu^2\beta}{(\beta\mu + \theta\eta)\mu}. \tag{5.19}$$

For physically meaningful parameters, the denominator is always positive. Hence for a_1 to be > 0 the numerator has to be positive. In other words,

$$\mu^3\beta + \mu^2\theta\eta + 2\theta\eta N\beta\mu + \theta^2\eta^2 N + \beta^2\mu^2 N - \phi\mu^2\beta - \gamma\mu^2\beta > 0. \tag{5.20}$$

Equation (5.20) can be grouped as

$$(\mu\beta + \theta\eta)\left[\mu^2 + N(\theta\eta + \mu\beta)\right] > \mu^2\beta(\phi + \gamma); \tag{5.21}$$

therefore,

$$\frac{N\beta}{\phi+\gamma}+\frac{N\theta\eta}{\mu(\phi+\gamma)}>\frac{\mu\beta}{\mu\beta+\theta\eta}-\frac{\mu}{\phi+\gamma}$$
$$\frac{N\beta}{\phi+\gamma}+\frac{N\theta\eta}{\mu(\phi+\gamma)}>1-\frac{\theta\eta}{\mu\beta+\theta\eta}-\frac{\mu}{\phi+\gamma}. \tag{5.22}$$

Now consider $a_0 > 0$ as defined in (5.17).

$$\beta\mu\left(N-\frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}}-\frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}}\right)+\phi\left(\frac{\eta}{\mu}(N-\frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}})\right)-\left(\frac{\gamma+\phi}{\beta+\frac{\theta\eta}{\mu}}\eta\right)+\mu(\phi+\gamma)>0 \tag{5.23}$$

which after some simplification results in

$$N\beta\mu+N\theta\eta-\gamma\mu-\phi\mu>0$$
$$\frac{N\beta}{\phi+\gamma}+\frac{N\theta\eta}{\mu(\phi+\gamma)}>1 \tag{5.24}$$

According to (5.14), the stability of system (5.1) at the endemic equilibrium is then based upon the two conditions (5.22) and (5.24). It is important to realise that satisfying (5.24) satisfies (5.22) as well. Therefore, the endemic equilibrium is stable whenever the condition in (5.24), which is the reciprocal condition to (5.11), is satisfied. Given the definitions from (5.12) and (5.13), (5.11) is satisfied subject to

$$R_{0H}+R_{0E}>1, \tag{5.25}$$

echoing the condition on the endemic equilibrium for the system without demographics presented in the previous chapter. Thus, if (5.24) does not hold the endemic equilibrium point shifts towards the DFE. This kind of situation might occur if a public health intervention targeting the increase of μ (improvement of the environment) was undertaken. Notably, as for the system without demographics, the endemic equilibrium can persist for even if both R_{0H} and R_{0E} are each < 1; so long as their sum exceeds 1, the endemic equilibrium can persist. Elimination thus depends on on reducing all modes of transmission, so as to reduce the overall R_0 below one so that the equilibrium point shifts from the endemic to the disease free equilibrium point.

Overall, as for Section 5.2.1.2, the endemic equilibrium point is similar to that in the previous chapter, except that the birth and death rate ϕ now appears in the numerator. The most important point is that when demographics are included in the model, the persistence of trachoma in Gashoho Health District is still dependent upon the improvement of sanitation as demonstrated in (5.24), where μ is the removal rate of pathogen from the environment. If environmental improvement is implemented, thus increasing μ, R_{0E} reduces, which can shift the equilibrium moves towards the DFE, contingent upon satisfying (5.11). The analysis of the endemic equilibrium again confirms that sanitation is crucial for reducing trachoma prevalence in Gashoho Health District and for achieving GET2020.

5.3 The relationship between prevalence and basic reproduction numbers at the endemic equilibrium

In this section, it is demonstrated that prevalence (the proportion infected) when (5.1) is at endemic equilibrium still approximates the relation

$$\frac{\hat{I}}{N} = 1 - \frac{1}{R_{0H} + R_{0E}}. \tag{5.26}$$

when demographics are included in the model. This result complements that from Section 4.3.

Recall from Section 4.3 that this relation depends on two assumptions:

1. R_0 is approximately the rate at which secondary cases are produced times average infectious period;

2. The proportion of susceptible individuals at endemic equilibrium is the inverse of R_0.

That the relation holds in general is seen by using the assumption of constant population size

$$N = I + S \tag{5.27}$$

, and dividing (5.27) through by N, gives

$$1 = \frac{I}{N} + \frac{S}{N}. \tag{5.28}$$

Substituting the proportion of susceptible individuals, $\frac{S}{N}$ in (5.28), by $\frac{1}{R_0}$ and rearranging gives

$$\frac{I}{N} = \frac{N}{N} - \frac{1}{R_0}$$

then,

$$\frac{\hat{I}}{N} = 1 - \frac{1}{R_0} \tag{5.29}$$

. thus proving the relation between R_0 and prevalence in general.

This relation is now proved specifically for the system (5.1) at the endemic equilibrium by noting that

$$\frac{1}{R_0} = 1 - \frac{\hat{I}}{N}. \tag{5.30}$$

and using the value $\hat{I}$ at the endemic equilibrium (5.7). Recalling that

$$\hat{I} = N - \frac{\gamma + \phi}{\beta + \frac{\theta\eta}{\mu}} \tag{5.31}$$

then

$$\begin{aligned} \frac{\hat{I}}{N} &= \frac{1}{N}\left(N - \frac{\mu(\gamma+\phi)}{\beta\mu + \theta\eta}\right) \\ &= 1 - \left(\frac{\mu(\gamma+\phi)}{N\beta\mu + N\theta\eta}\right). \end{aligned} \tag{5.32}$$

Substituting (5.32) into (5.30) gives

$$\frac{1}{R_0} = 1 - \left(1 - \frac{\mu(\gamma+\phi)}{N\beta\mu + N\theta\eta}\right) \qquad = \frac{\mu(\gamma+\phi)}{N\mu\beta + N\theta\eta} \tag{5.33}$$

from (5.33),

$$R_0 = \left(\frac{\mu(\gamma + \phi)}{N\beta\mu + N\theta\eta} \right)^{-1}$$

$$= \frac{N\mu\beta + N\theta\eta}{\mu(\gamma + \phi)}$$

$$= \frac{\mu\beta N}{\mu(\gamma + \phi)} + \frac{\theta\eta N}{\mu(\gamma + \phi)}$$

$$= \frac{\beta N}{\gamma + \phi} + \frac{\theta\eta N}{\mu(\gamma + \phi)} \tag{5.34}$$

Thus, for this model, the value of R_0 that determines the prevalence of infection amongst humans at endemic equilibrium is the sum of R_{0H} and R_{0E}, as defined in (4.10)

This finding has the same implications for relating the field data collected in Chapter 3 to the model with demographics as in Section 4.3. If, at endemic equilibrium, both R_{0H} and $R_{0E} > 1$ (a possible solution to the model), such that R_{0H} + $R_{0E} > 2$, then the prevalence, based on equations (5.29) and (5.34) would be $> 50\%$. No recent studies, including that contained in Chapter 3, report prevalences above 50% for trachoma. Therefore, we can deduce that the scenario where R_{0H} and $R_{0E} > 1$ is not realistic for the model with, as well as without, demographics.

Again, since this implies that one of R_{0H} or R_{0E} must be < 1, this may explain the at best partial success of GET2020. Since GET2020 has resulted in frequent delivery of the antibiotics component of the SAFE strategy, it is possible that R_{0H} is now < 1 in many locations in which trachoma persists to be an endemic disease. Therefore, the relation between prevalence, R_{0H} and R_{0E}, gives further evidence that to eliminate trachoma, targeting the environmentally mediated component of trachoma transmission is required.

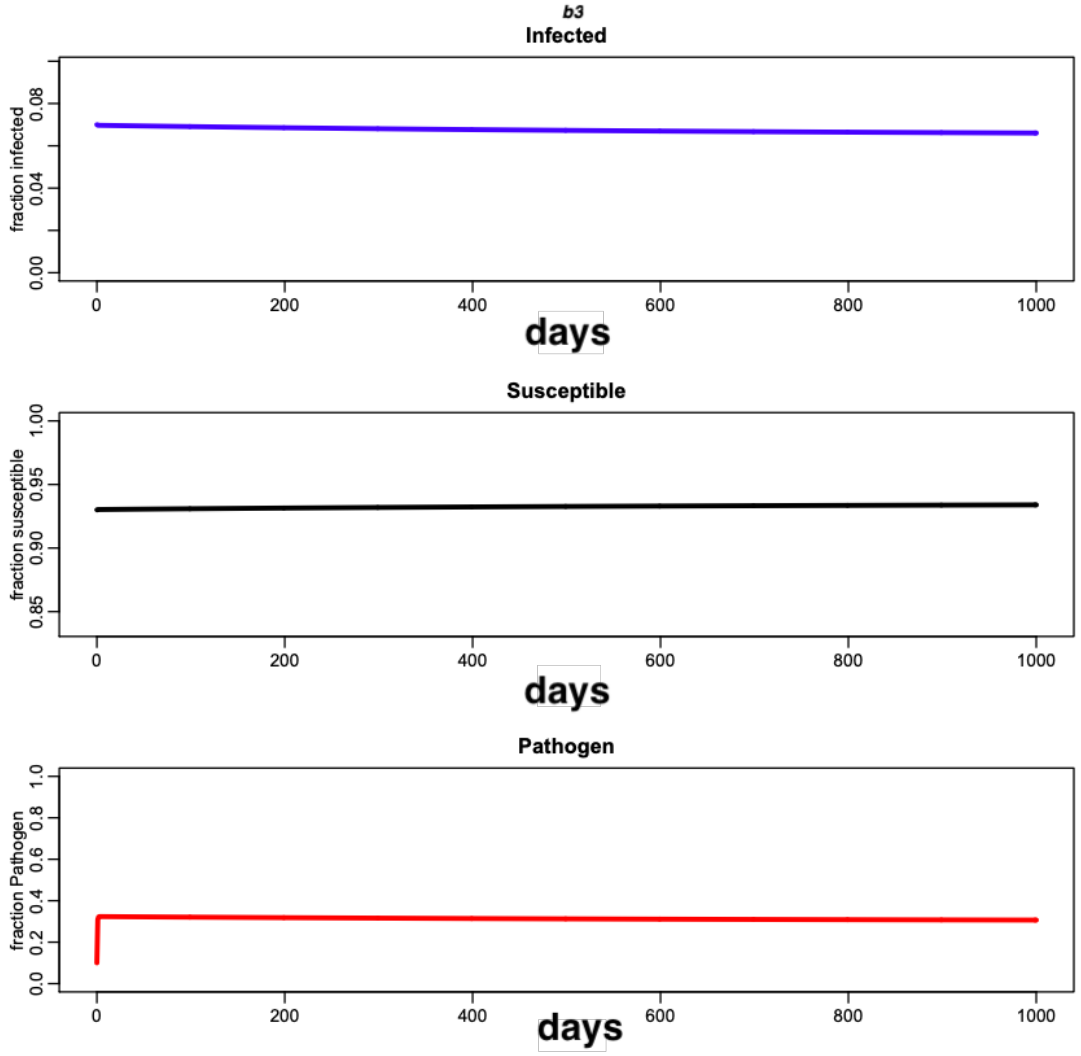

Fig. 5.1 The time to reach endemic equilibrium for pathogens, and the proportion of susceptible and infected individuals, and units of pathogen in the environment at endemic equilibrium, when $R_{0H} + R_{0E}$= 1.06902318, R_{0H}=0.00069031 and R_{0E}=1.06833287 (scenario b in Table5.1. Initial conditions were $I_0 = 70$ ($N = 1000$) and $E_0 = 0.1$.

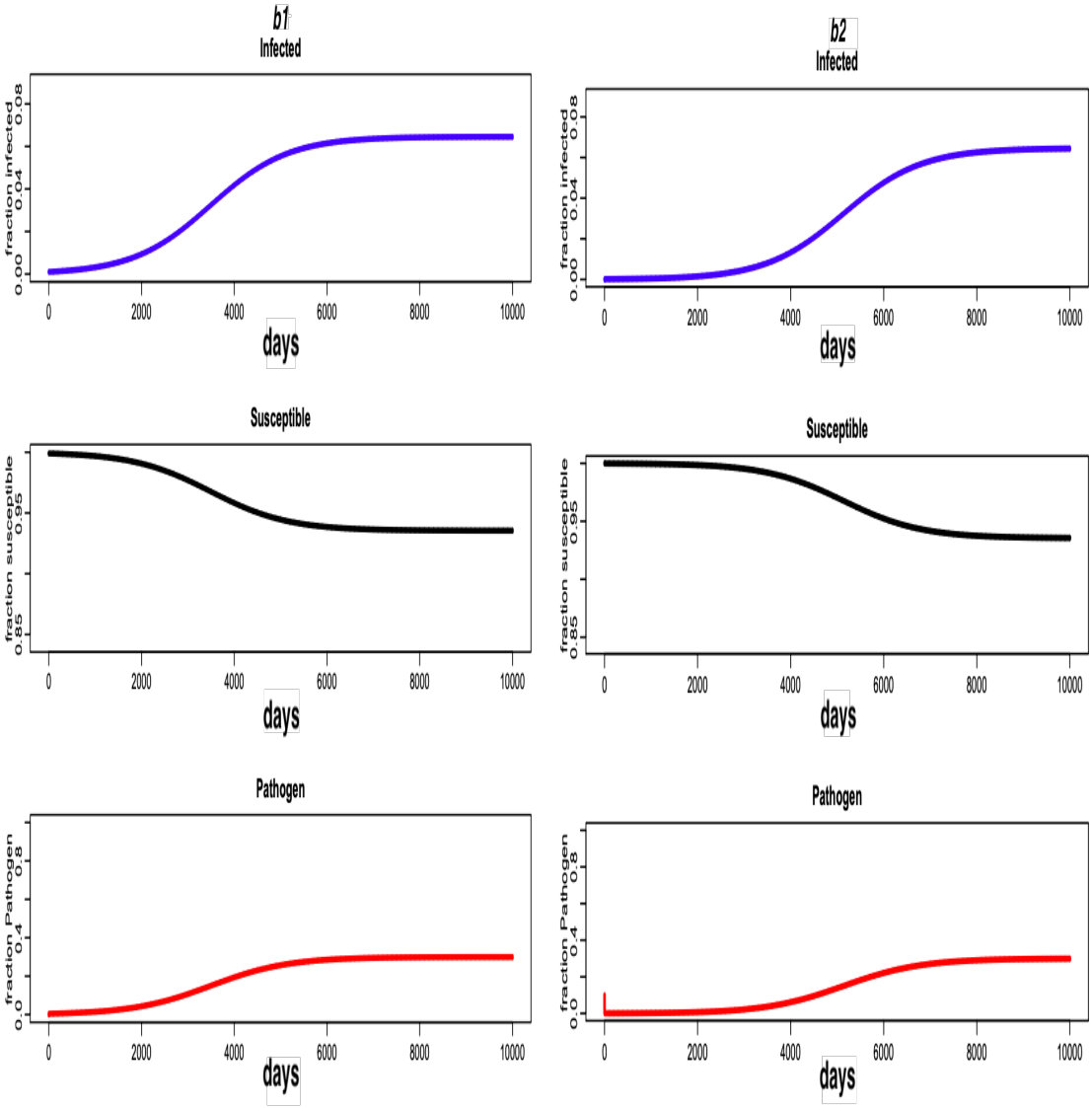

Fig. 5.2 Time to attain the endemic equilibrium with $R_{0H} + R_{0E} = 1.06902318$, corresponding to the parameters for scenario b) in Table 5.1. For plot b1) the initial conditions are one infected individual and zero units of pathogen in the environment. For plot b2) there are initially zero infected individuals and 0.1 units of pathogen in the environment.

Table 5.1 Parameters corresponding to stability of the disease free equilibrium (a), and three stable endemic scenarios (b, c, d), each of which approximate the target prevalence in Gashoho. As it can be seen in the table all the parameters are fixed except μ, this done on the purpose of highlighting the importance of the environment in the transmission of trachoma.

Parameter	a	b	c	d
γ	17×10^{-3}	17×10^{-3}	17×10^{-3}	17×10^{-3}
β	$5.6 \times 10^{-}5$	1.2×10^{-8}	12.9×10^{-5}	1.729×10^{-5}
θ	4×10^{-3}	4×10^{-3}	4×10^{-3}	4×10^{-3}
η	1.3×10^{-2}	1.3×10^{-2}	1.3×10^{-2}	1.3×10^{-2}
μ	5	2.8	9	40
ϕ	3.8356×10^{-4}	3.8356×10^{-4}	3.8356×10^{-4}	3.8356×10^{-4}
R_{0H}	0.32214345	6.9031×10^{-4}	0.742080448	0.9946179
R_{0E}	0.598266408	1.06833287	0.332370227	0.0747833
$R_{0H} + R_{0E}$	0.920409858	1.06902318	1.074450675	1.0694012

5.3.1 Simulation of the model

5.3.1.1 Simulation methods

To complete the exploration of a possible effect of improvements in sanitation on trachoma control, simulations were conducted adding the demographics to the initial model presented in Chapter 4. Once again, the *library(deSolve)* in R version 10.15.4 on Mac OS Catalina was used to solve the system of equations, with a time-step of one day. Numerical simulations were employed to calibrate the model to the adequate field data of Gashoho Health District. The same parameters used to fit the model in the previous chapter were used plus the demographic parameter ϕ which represents the birth and deaths rates.

The model was (5.1) fitted to the DFE and endemic equilibrium by setting γ , ϕ and N constant, whilst varying the values of other parameters. The recovery rate γ was fixed at 0.017 based on clinical data [130], ϕ at 0.00038356 and the population size was fixed at $N = 1000$. Other parameters, represented by the vector $\epsilon = (\beta, \theta, \eta, \mu)$ were adjusted to fit different scenarios. To calibrate the DFE (5.11), values of ϵ were chosen that satisfied the constraint of $R_{0H} + R_{0E} < 1$. To fit (5.24) to the time to the endemic equilibrium, we used the average prevalence of trachoma in Gashoho (7.9%), as reported in Chapter 3 [160].

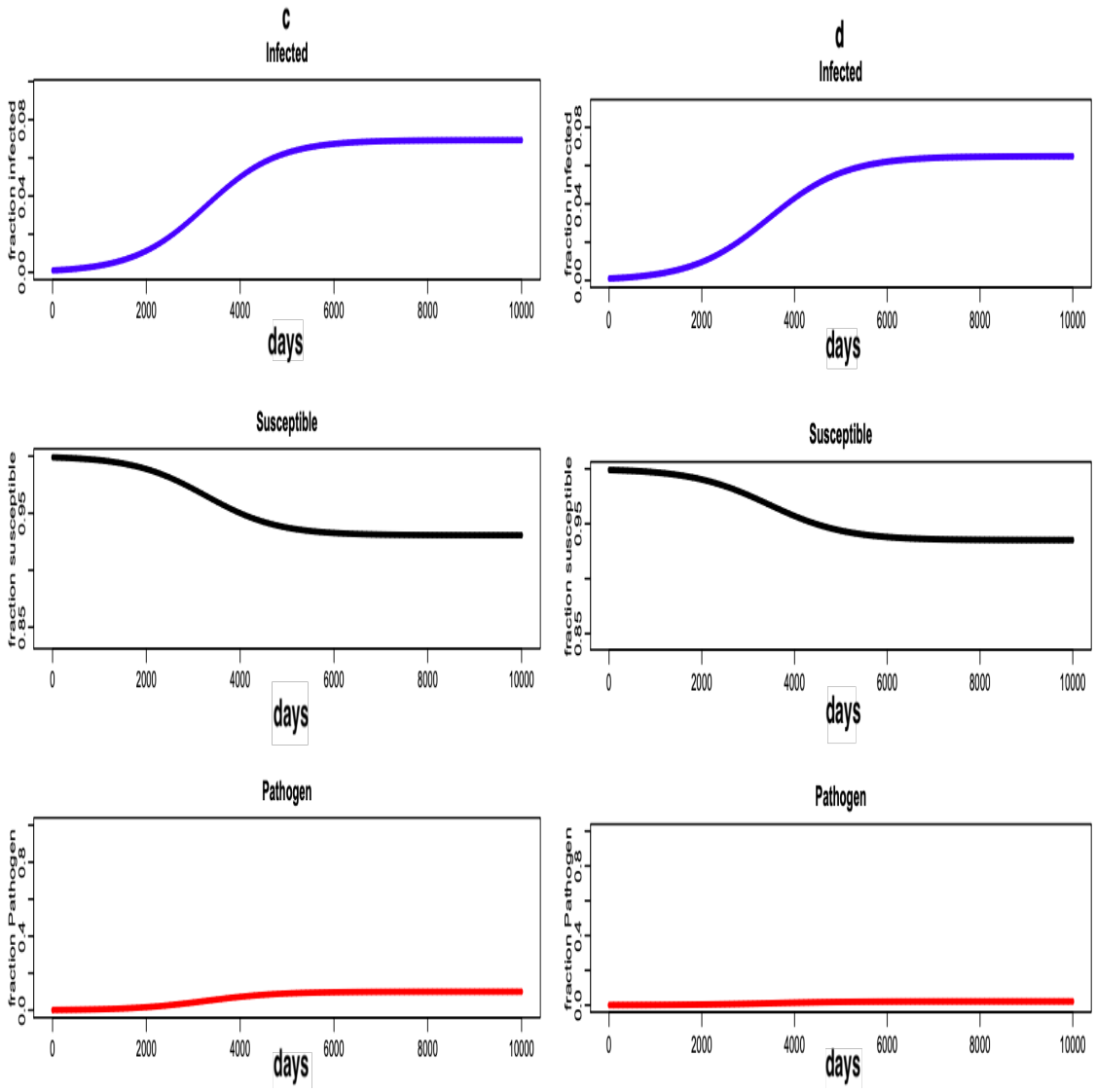

Fig. 5.3 Time needed to reach the endemic equilibrium, with parameters corresponding to scenarios c) and d) from Table 5.1; note that in scenario c) R_{0E} is less than in scenario d). For both plots, initial conditions were 1 infected individuals and 0 units of pathogen in the environment with $N = 1000$.

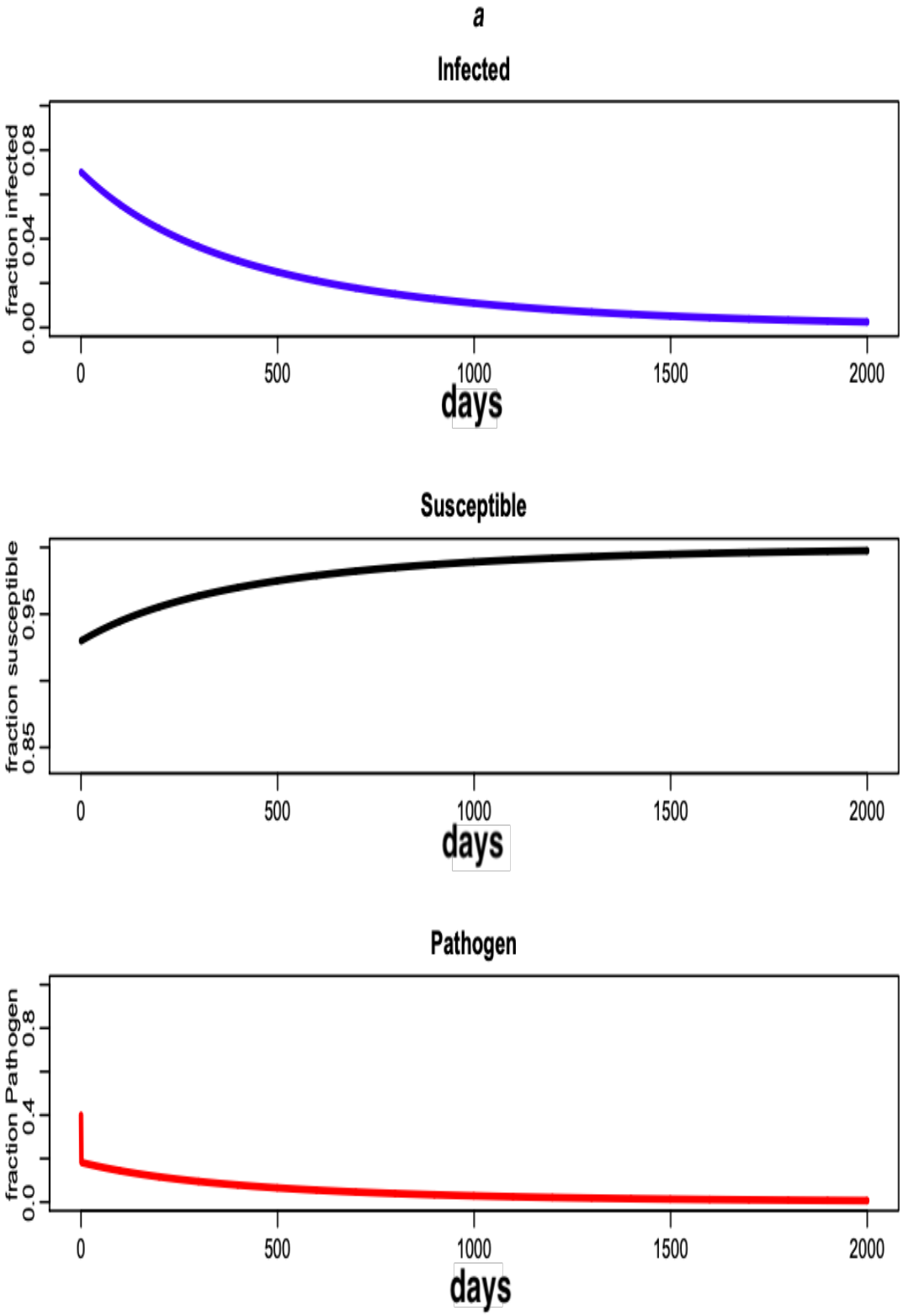

Fig. 5.4 Time to reach disease free equilibrium from endemic equilibrium, given an intervention that increases μ,with initial conditions of $I_0 = 70$ individuals ($N = 1000$ and $E_0 = 0.4$.

Figure 5.1 shows that even if R_{0H} is close to zero but R_{0E} is greater than one, the disease will persist in the population. Moreover, under these conditions, whether pathogen is introduced into the environment or an infected individual is introduced into a susceptible population, the disease will quickly become endemic. Similarly, Fig. 5.3 shows that even if both R_{0H} and R_{0E} are less than one, corresponding to scenario (c) and (d) from Table 5.1, if their sum is greater than one the disease will persist in the population. These findings validate that even after including demographics, the most important consideration for whether trachoma will become endemic is whether as long $R_{0H} + R_{0E}$ is $>$ or < 1.

5.3.1.2 Simulation results

Figure 5.5 shows that for $R_{0H} + R_{0E} < 1$ (scenario a in Table 5.1, and both individual $R_{0i} < 1$, the system tends to the disease free equilibrium. In addition, Figure 5.5 gives an indication of the time that may be needed to eliminate trachoma infection in Gashoho Health District. Since it begins with initial conditions corresponding to a high prevalence (close to that in under 9 year old children), it can be considered a rough estimate of the time to eliminate disease if $R_{0H} + R_{0E}$ are reduced to < 1 by an intervention. The figure shows that even with a high initial prevalence, such as 15%, trachoma can be eliminated over several years if the overall ($R_{0H} + R_{0E}$) is < 1. The proportion of infected individuals is reduced to $< 5\%$ (low prevalence within 400 days, with almost total elimination of disease within 2.5 years.

Figure 5.1 shows that scenario b) from Table 5.1, an endemic equilibrium based on $R_{0E} > 1$ and $R_{0H} < 1$, can be fitted to the field prevalence in Gashoho reported in Chapter 3, using equation (5.26). This affirms that environmentally mediated transmission can sustain the endemic prevalences observed in Gashoho. Figure 5.2 shows the time required to reach this endemic equilibrium for different initial conditions. When one infected individual and zero units of pathogen were introduced into the population, the endemic equilibrium was reached slightly earlier than when no infected individuals, but 0.1 units of pathogen, were present. This highlights that even though R_{0H} can be negligible in value (as in scenario b) from Table 5.1), human to human transmission

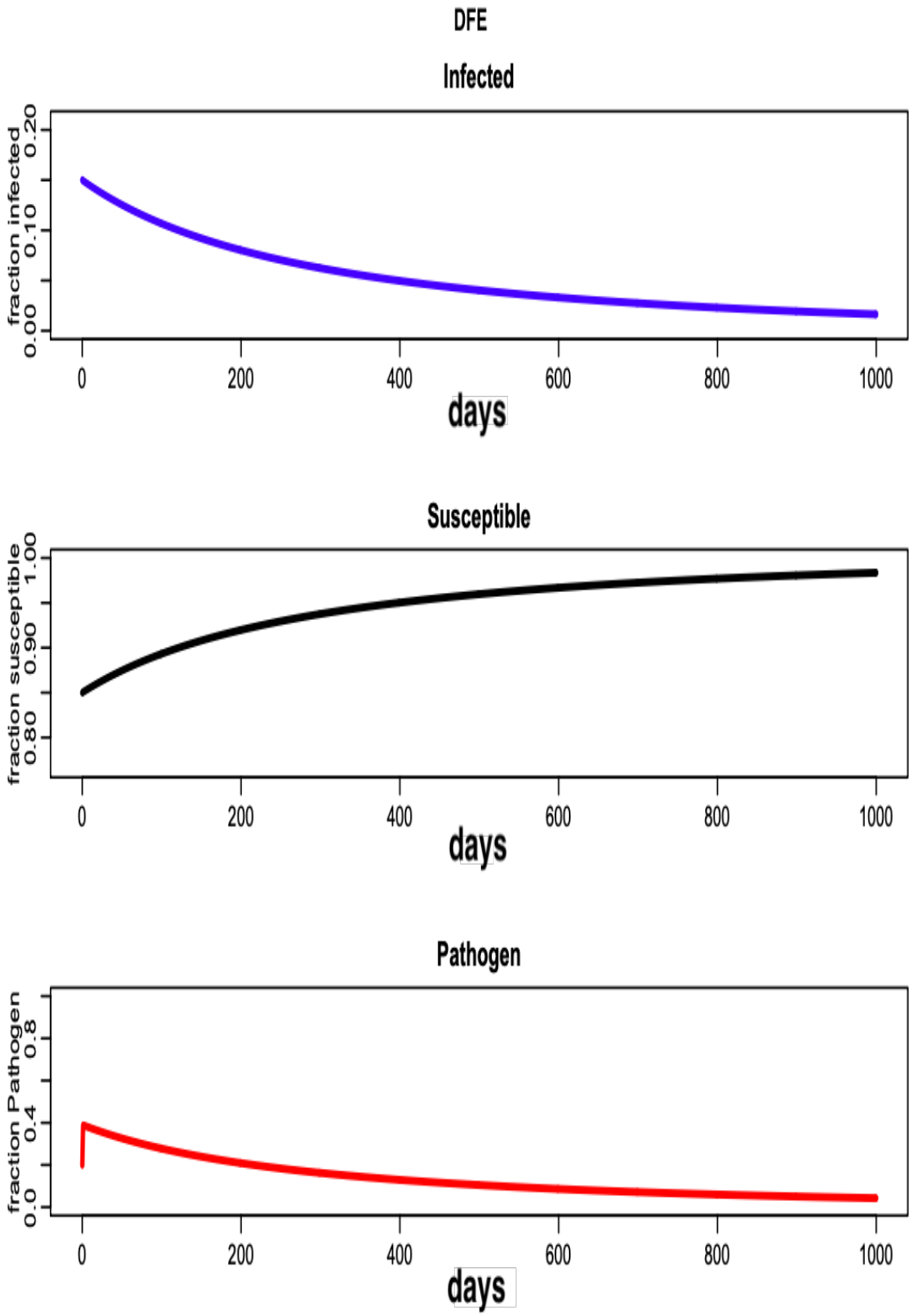

Fig. 5.5 Time to reach the disease free equilibrium using parameters in scenario (a) of Table 5.1 ($R_{0H} + R_{0E} = 0.920409858$), with initial conditions of 150 infected individuals ($N = 1000$)) and 0.1 units of pathogen in the environment.

still plays an important role in the dynamics of the system. This finding re-emphasises the importance of the need of association of the two components of the SAFE strategy (Antibiotics and Environment improvement) to successfully reduce the prevalence of trachoma in Gashoho Health District.

Figure 5.3 shows the time to reach the endemic equilibrium for scenarios c) and d) from Table 5.1. Again, the endemic equilibrium proportion of infected individuals can be fitted to approximately the prevalence in Gashoho [160], affirming that, as for the model without age-structure, any one of the three endemic scenarios b, c or d), might well approximate the situation in the Gashoho Health District. In both scenarios c) and d), neither R_{0H} or R_{0E} are greater than one. R_{0E} is larger in scenario c) than in scenario d), and vice versa for R_{0H}, since in both scenarios $R_{0H} + R_{0E} > 1$. As in the model without age structure presented in the previous chapter, in scenarios c) and d) despite neither R_{0H} nor $R_{0E}1$ being greater than one, and regardless of which R_{0i} is larger, the system will always tend towards endemic infection in the human population, as long as the overall R_0 is > 1. Therefore, once again, when planning interventions, the sum of reproductive numbers needs to be considered in planning.

Figure 5.4 shows the possible impact of an intervention improving sanitation on trachoma endemicity in Gashoho. The effect size of the environmental improvement intervention was estimated from field studies showing an approximate halving of the odds of acquiring infection associated with improved sanitation. This effect was modelled by using solutions of the simulations corresponding to scenario (b) from Table 5.1, shown in Fig. 5.1, as initial conditions, then doubling the parameter μ to operationalise the effect size observed in the field, whilst holding all other parameters constant. After implementing this modification to μ, R_{0E} was reduced from 1.068332874 to 0.598266408. In both scenarios, increases in the rate of μ corresponding to field estimates of the effect size attributable to improved sanitation resulted in eventual eradication of trachoma. More importantly, elimination (defined by the WHO as $< 5\%$ prevalence and no active transmission (zero incidence) was attained within 1–2 years in these simulations. These numerical results are in agreement with both our stability analysis and the clinical consensus that eradication or further reductions in the prevalence

of trachoma in Gashoho depends upon improvements in sanitation [160]. The scenario where the individual R_{0H} is > 1 was not explored as the model assumed a successful cure of antibiotic in the community.

However, the model has some limitations, it would have been interesting to have the knowledge of the proportion of pathogens in the environment at the time when endemicity is reached, so that we can fit the model and accurately predict after how long the recurrence of trachoma is expected if only antibiotic is distributed in the population.

5.4 The model with age groups

5.4.1 Model development

The model is a system of equations which governs the dynamic of the exploited age-structured population model. To analyse the addition of age structure to the transmission of trachoma infection in Burundi, we assume a two age group model: group 1, children under 9 years old, and group 2, older children and adults older than 9 years of age.

The person-to-person transmission in this age structured population occurs at four different rates governed by the Who Acquires Infection From Whom (WAIFW) matrix,

$$\left(\begin{array}{c|cc} & I_1 & I_2 \\ \hline S_1 & \beta_{11} & \beta_{21} \\ S_2 & \beta_{12} & \beta_{22} \end{array}\right), \tag{5.35}$$

where β_{11} is the transmission rate within group 1, β_{22} the transmission rate within group 2 ,β_{21} is the transmission rate from group 2 to group 1, β_{12} is the transmission

rate from group 1 to group 2. The ODEs describing this system are,

$$\begin{cases} \frac{dS_1}{dt} &= -\beta_{11}S_1I_1 + \gamma I_1 - \theta S_1 E - \beta_{21}S_1I_2 + \phi N - \phi_1 S_1 - \psi S_1 \\ \frac{dI_1}{dt} &= \beta_{11}S_1I_1 + \beta_{21}S_1I_2 + \theta S_1 E - \gamma I_1 - \phi_1 I_1 - \psi I_1 \\ \frac{dS_2}{dt} &= -\beta_{22}S_2I_2 + \gamma I_2 - \theta S_2 E - \phi_2 S_2 - \beta_{12}S_2I_1 + \psi S_1 \\ \frac{dI_2}{dt} &= \beta_{22}S_2I_2 + \beta_{12}S_2I_1 + \theta S_2 E - \gamma I_2 - \phi_2 I_2 + \psi I_1 \\ \frac{dE}{dt} &= \eta I_1 + \eta I_2 - \mu E \end{cases} \tag{5.36}$$

where γ the recovery rate per unit time, ϕ is the birth rate, ϕ_1 is death rate in group 1, ϕ_2 is death rate in group 2, and ψ is the development rate from group 1 to group 2. The other parameters are similar to those used in the previous model and they keep the similar meaning.

5.4.2 Equilibrium point and Jacobian matrix

Under the assumption of a constant population size N and constant group sizes N_1 and N_2 results in the relations

$$\begin{cases} N &= S + I \\ S &= S_1 + S_2 \\ I &= I_1 + I_2 \end{cases} \tag{5.37}$$

Then, setting (5.36) at zero for I_1,I_2 and E equal zero. The first equation of (5.36) gives

$$\begin{aligned} \phi N &= \hat{S}_1(\phi_1 + \phi) \\ \hat{S}_1 &= \frac{\phi N}{\phi_1 + \psi} \end{aligned} \tag{5.38}$$

the size of the first age group. The third line gives

$$\begin{aligned} \phi_2 \hat{S}_2 &= \psi \hat{S}_1 \\ \hat{S}_2 &= \frac{\psi}{\phi_2} \left[\frac{\phi N}{\phi_1 + \psi} \right] \end{aligned} \tag{5.39}$$

The system of (5.36) has then as DFE point

$$(\hat{S}_1, 0, \hat{S}_2, 0, 0) \tag{5.40}$$

where $\hat{S}_1$ and $\hat{S}_2$ are given in (5.38) and (5.39) respectively. From (5.40), to ensure that the equality $\hat{S}_1 + \hat{S}_2 = N$ is kept valid, the death rate is further expressed as follow :

$$\phi = \left[\frac{\phi_1 + \psi}{\phi_2 + \psi} \right] \phi_2. \tag{5.41}$$

5.4.3 The Jacobian matrix

The Jacobian matrix from (5.36) is given as ,

$$J = \begin{pmatrix} -\beta_{11}\hat{I}_1 - \theta\hat{E} - \beta_{21}\hat{I}_2 - \phi_1 - \psi & -\beta_{11}\hat{S}_1 + \gamma & 0 & -\beta_{21}\hat{S}_1 & -\theta\hat{S}_1 \\ \beta_{11}\hat{I}_1 + \beta_{21}\hat{I}_2 + \theta\hat{E} & \beta_{11}\hat{S}_1 - \gamma - \phi_1 - \psi & 0 & \beta_{21}\hat{S}_1 & \theta\hat{S}_1 \\ \psi & -\beta_{12}\hat{S}_2 & -\beta_{22}\hat{I}_2 - \theta\hat{E} - \phi_2 - \beta_{12}\hat{I}_1 & -\beta_{22}\hat{S}_2 + \gamma & -\theta\hat{S}_2 \\ 0 & \beta_{12}\hat{S}_2 + \psi & \beta_{22}\hat{I}_2 + \beta_{12}\hat{I}_1 + \theta\hat{E} & \beta_{22}\hat{S}_2 - \gamma - \phi_2 & \theta\hat{S}_2 \\ 0 & \eta & 0 & \eta & -\mu \end{pmatrix}. \tag{5.42}$$

The stability of (5.42) is now assessed at the disease free equilibria with respect to (5.41)

5.4.4 Stability at the disease free equilibrium

Evaluated at the disease free equilibrium, the Jacobian (5.42) is given as

$$J = \begin{pmatrix} \phi_1 - \psi & -\beta_{11}\hat{S_1} + \gamma & 0 & -\beta_{21}\hat{S_1} & -\theta\hat{S_1} \\ 0 & \beta_{11}\hat{S_1} - \gamma - \phi_1 - \psi & 0 & \beta_{21}\hat{S_1} & \theta\hat{S_1} \\ \psi & -\beta_{12}\hat{S_2} & -\phi_2 & -\beta_{22}\hat{S_2} + \gamma & -\theta\hat{S_2} \\ 0 & \beta_{12}\hat{S_2} + \psi & 0 & \beta_{22}\hat{S_2} - \gamma - \phi_2 & \theta\hat{S_2} \\ 0 & \eta & 0 & \eta & -\mu \end{pmatrix}. \tag{5.43}$$

The characteristic polynomial of (5.43) is of the form,

$$(\lambda + \phi_1 + \psi)(\lambda + \phi_2)(\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0) = 0, \tag{5.44}$$

where λ is the eigenvalue of (5.43). Hence, from (5.44) two of the eigenvalues are $-\phi_1 - \psi$ and $-\phi_2$ which are both always negative for physical meaningful parameters. Therefore, the stability of the DFE is dependent upon the roots of the cubic of (5.44). Here, the coefficients of the cubic are given as:

$$a_2 = 2\gamma + \phi_1 + \phi_2 + \mu + \psi - \beta_{11}\hat{S_1} - \beta_{22}\hat{S_2}, \tag{5.45}$$

$$\begin{aligned} a_1 = (\psi + \phi_1)(\mu + \gamma) &- \beta_{11}\hat{S_1}(\mu + \gamma + \phi_2) \\ &- \beta_{22}\hat{S_2}(\psi + \gamma + \phi_1) \\ &- \beta_{21}\hat{S_1}(\beta_{12}\hat{S_2} + \psi) \\ &+ \beta_{22}\hat{S_2}(\beta_{11} - \mu) \\ &- \theta\eta(\hat{S_1} + \hat{S_2}) \\ &+ \phi_2(\gamma + \phi_1 + \mu) + 2\gamma\mu + \gamma^2, \end{aligned} \tag{5.46}$$

and

$$\begin{aligned} a_0 = &- \beta_{11}\hat{S}_1\mu(\gamma+\phi_2) - \theta\hat{S}_1\eta(\phi_2+\beta_{21}\hat{s_2}) \\ &- \beta_{12}\hat{S}_2\hat{S}_1(\beta_{21}\mu+\theta\eta) \\ &- \theta\hat{S}_1\eta(\gamma+\psi) \\ &+ \theta\hat{S}_2\eta(\beta_{11}\hat{S}_1-\phi_1) \\ &- \psi\beta_{21}\hat{S}_1\mu + \phi_2\mu(\gamma+\psi) \\ &+ \hat{S}_1\beta_{22}\hat{S}_2(\theta\eta+\beta_{11}\mu) \\ &+ \gamma\mu(\psi+\phi_1+\gamma) \\ &+ \phi_1\phi_2\mu - \beta_{22}\hat{S}_2\mu(\psi+\phi_1+\gamma) \\ &- \hat{S}_2\eta\theta(\gamma+\psi). \end{aligned} \tag{5.47}$$

For the DFE to be stable, a_0, a_1 and a_2 must all be positive, which ensures the eigenvalues have negative real parts. Unfortunately, given the complexity of the expressions for a_0, a_1 and a_2 a numerical approach had to be used to determine the conditions for the stability of the DFE.

This also meant that it was not possible to solve for R_{0H} and R_{0E} algebraically. Since the hypothesis under investigation in the thesis is the role played by the environment in the transmission of trachoma, we instead used the parameter μ, which represents impact of sanitation on trachoma transmission, as a surrogate for R_{0E}. By varying the value of μ, whilst holding other parameters constant, we sought to illustrate that the key finding from the simpler models (that improved sanitation is essential for eliminating trachoma) also held true for the more complex age-structured variant.

5.4.5 Simulation of the cubic roots of the polynomial

Based on the results of the previous Chapters, it has been hypothesised and demonstrated that, the success in the elimination of trachoma in Gashoho Health District, is most likely related to the persistence of the development of pathogens in the environment. The rationale for that is that, despite the mass antibiotic administration has been successfully distributed as recommended by GET 2020 [115], trachoma is still

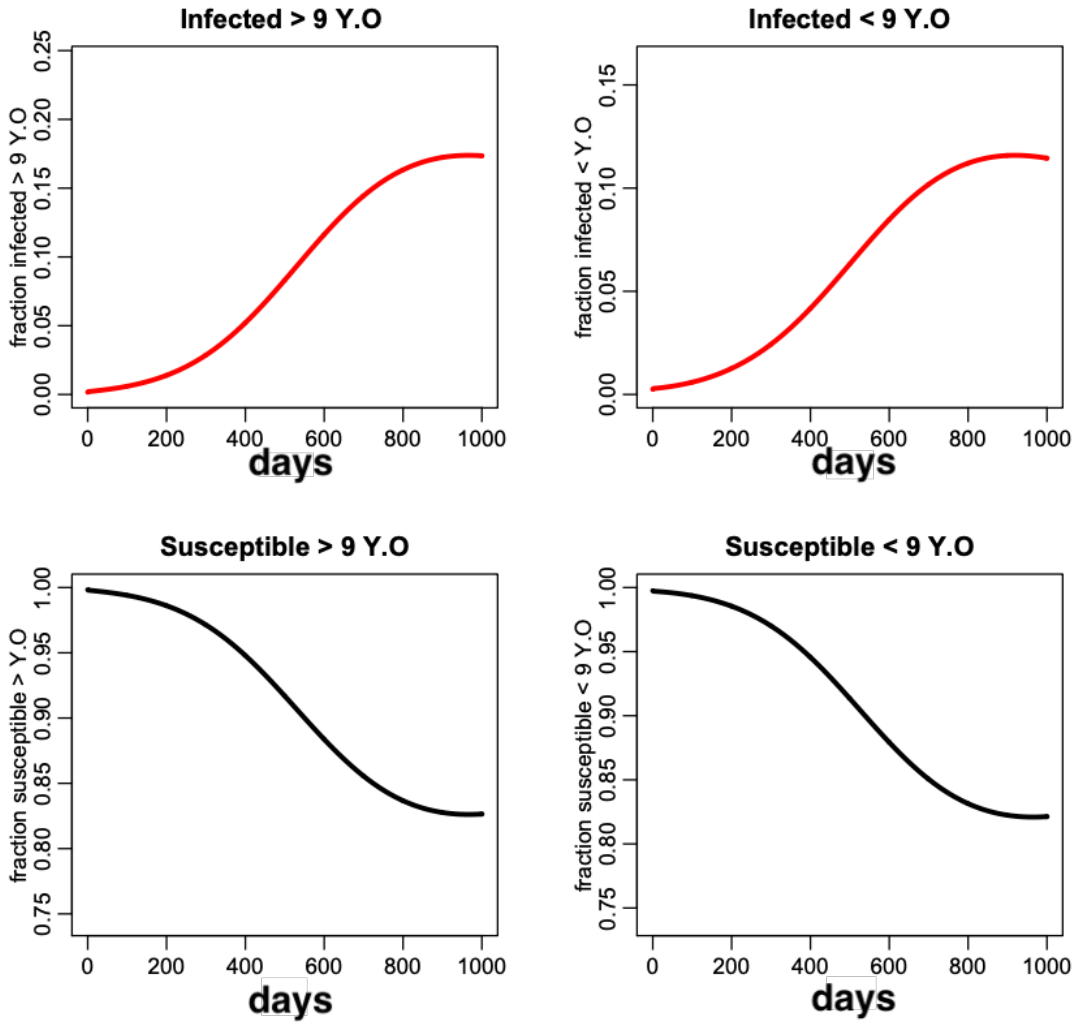

Fig. 5.6 The change in the proportion of infected and susceptible individuals over time after introduction of 1 infected individual in each age group. Parameters correspond to those supporting a stable endemic state in Table 5.2, including $\mu = 2.8$ to reflect inefficient removal of pathogen from the environment.

endemic in Gashoho Health District. Therefore, on the assumption of the absence of the human to human transmission due to a successful antibiotic treatment, the only remaining root of transmission is therefore the environmentally mediated transmission as shown in Chapter 4. Thus, simulating the shift of stability is reduced to assessing when a_0, a_1 and a_2 are all positive, given the increase of μ the removal rate while the other parameters are kept unchanged. μ was incremented on a step of one in the range from -5 to $+20$. It important to clarify that negative values of μ are not realistic, but are used to make the graphical representation of the results easier to interpret, since the coefficients of the cubic change signs very close to zero (see) figure 5.7.

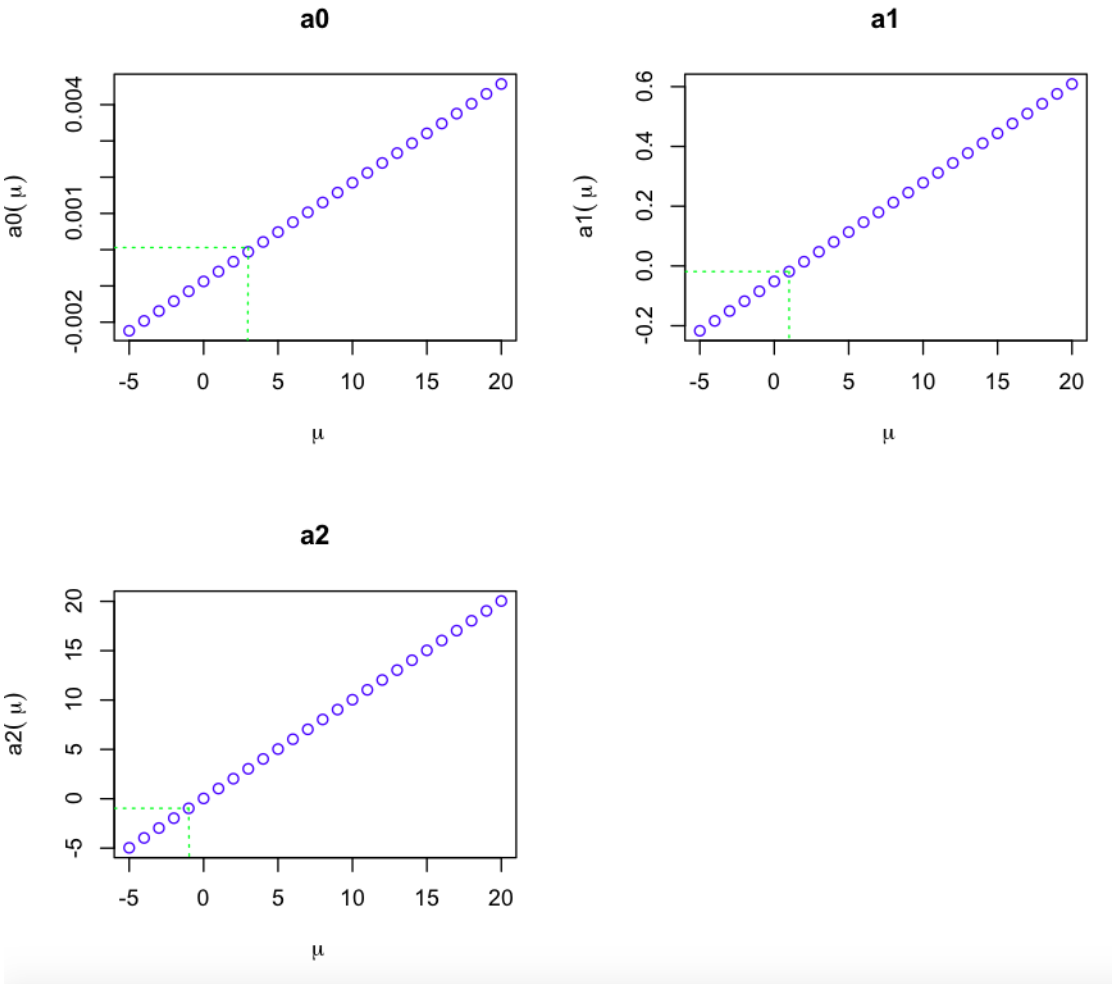

Fig. 5.7 The variation of a_0, a_1 and a_2 given decreasing values of μ.The green boxes show the value of μ where each parameter changes sign from positive to negative, and hence, where the DFE becomes unstable and vice versa.

5.4.6 Effect of the cubic roots on stability of the disease free equilibrium

Fig. 5.7 shows that the cubic root a_2 is always positive for meaningful values of μ. Since a_1 is the first cubic root to change sign, it is the key inequality for determining whether the system shifts from the endemic to the disease-free state. The simulation was started with negative values of the removal rate μ. Even though unrealistic in nature, this helped to make more obvious when the changes in signs of the coefficients of the cubic (5.44) occur. It is apparent that increasing the removal rate μ facilitates ($R_{0E} \to 0$), such that environmentally mediated transmission is eliminated as a source of persistent infection. Once the removal rate μ has reached a critical threshold where the pathogens are adequately removed the stability shifts from the endemic equilibrium to disease free equilibrium. From there on wards the disease free equilibrium is stable. For that situation to occur, all the coefficients a_0, a_1 and a_2 need to be positive.

5.5 Simulation of the model

To complete the exploration of a possible effect of improvements in sanitation on trachoma control, given age structure, the effect of reducing environmentally mediated transmission on different age groups was investigated numerically. Simulations were conducted using the `library(deSolve)` in R version 10.15.4 on MacOS Catalina, with a time-step of one day. The same parameters (5.1) used to fit the model with demographics were used, with the following exceptions.

The transmission parameters were necessarily adjusted to conform to (5.35), with the greatest transmission rate being between children. The value of β_{11} was estimated to be close to the transmission rate, β, used in chapter 4 and presented in Table 5.1. From chapter 3, active trachoma is extremely prevalent in children under 9 years old while it is rare in individuals older than 9 years old. It was, therefore, logical to set the other transmission parameters β_{12} , β_{22} , and β_{21} close to zero to truly reflect the data observed in the field. The parameter values used are provided in Table 5.2.

In addition, the demographic parameters ψ , ϕ , ϕ_1 and ϕ_2, which represent the growth

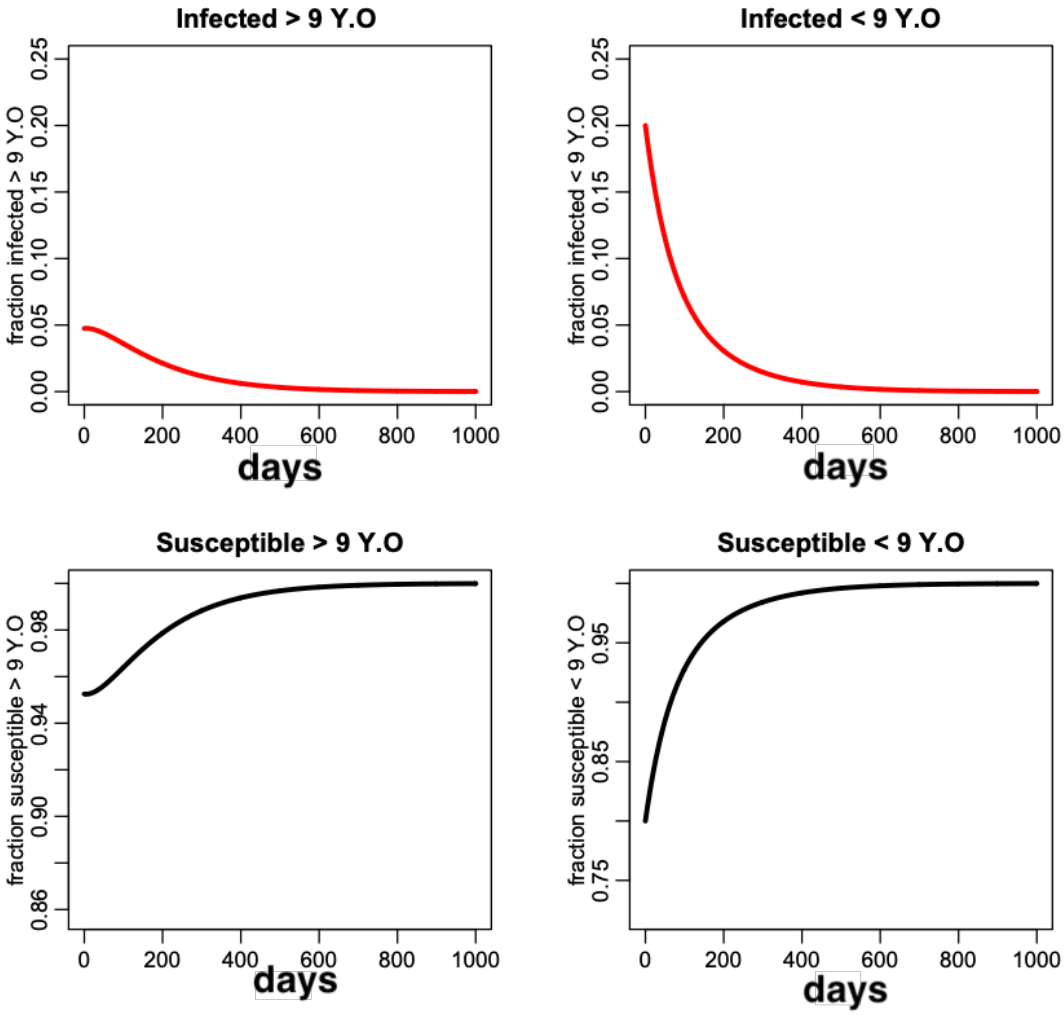

Fig. 5.8 The reduction in the proportion of infected and susceptible individuals in the two age groups after introduction of an environmental intervention to improve sanitation. Initial conditions approximated the endemic prevalences observed in the field; $I_1 = 0.048$, $I_2 = 0.20$. Parameter values correspond to those for the DFE in Table 5.2, which include $\mu = 5$ to reflect efficient removal of pathogen from the environment.

Table 5.2 Final parameter values used in the simulation of the age structured model, with all the parameters being fixed except β_{11} and μ

Parameter	DFE	EE
N_1	400	400
N_2	600	600
ϕ_1	1.60274×10^{-4}	1.60274×10^{-4}
ϕ_2	1.60274×10^{-4}	1.60274×10^{-4}
β_{11}	5.6×10^{-6}	1.2×10^{-8}
β_{12}	4.62×10^{-9}	4.62×10^{-9}
β_{21}	1.48×10^{-9}	1.48×10^{-9}
β_{22}	1.45×10^{-9}	1.45×10^{-9}
η	13×10^{-4}	13×10^{-4}
θ	4×10^{-3}	4×10^{-3}
μ	5.0	2.8

rate (movement from age group 1 to age group 2), birth rate, death rate in age group 1, and death rate in age group 2, respectively, had to be set to approximate population dynamics whilst preserving constant population size. The values of these parameters were based on the most recent general census data from Burundi [194], with the final values provided again in Table 5.2.

5.6 Results and discussion

Figure 5.8 shows the possible impact of an intervention improving sanitation on trachoma endemicity in Gashoho. The effect size of the environmental improvement of an intervention was taken from section 5.4.6 showing at which level of the removal rate μ the intervention is likely to achieve the target of trachoma elimination. This effect was modelled by using solutions of the simulations corresponding to figure 5.6 as initial conditions, then using the value of μ as in 5.7 to operationalise the effect attributable to sanitation observed in the field, whilst holding all other parameters constant. After implementing this modification, infection is eliminated and the DFE is reached in the age groups within two years. In both age groups, increases in the rate of μ corresponding to field estimates of the effect size attributable to improved sanitation resulted in eventual eradication of trachoma. The rate of decline was initially greater in group 1 (< 9 y.o.), probably since transmission was greatest in this group, thus most impacted by interventions reducing transmission. Ultimately, the prevalence in the two age groups equalised at around 400 days. The less dramatic decrease in the older age group 2 (> 9 y.o.) might also reflect the fact that there is intimate contact between infected children and their carers.

These numerical results are in agreement with both the stability analysis presented in the previous sections and Chapter, and the clinical consensus, reflected in the results from Chapter 3, that eradication or further reduction in the prevalence of trachoma in Gashoho depends upon improvements in sanitation. In accordance with the results shown in previous sections, this may happen rapidly. In figure 5.6 by introducing one infected individual and zero pathogens in the environment, the endemicity is reached in three years. Fig.5.6 does not reflect the reality on the ground in the sense that, the

age group 1 and age group 2 all approach the same level of endemic prevalence. Given that algebraic solution of the age-structured model was not possible and that time was limited, the parameter sets leading to more realistic prevalences in group 1 and group 2 could not be established, but will be explored in future work.

5.7 Conclusion

This chapter makes a number of new contributions. First, a model with demographics was developed which included the birth and death rate to account for the replenishment of the susceptible population. It is a major contribution as it helps to understand the dynamic and the persistence of active trachoma in the population. It is expected that, the active infection of trachoma will die out as former children grow up into older children and adults. Unfortunately, the disease is still prevalent in Gashoho Health District due to the replenishment of the population. Second, the age structured model, structuring the population in two age groups with different transmission and demographics parameters. As Chapter 3 demonstrated the predominance of active trachoma in infants aged under years old, it is important then to explore the role played by age in the fight for the elimination of trachoma.

The first contribution of this chapter is the development of the model with demographics. The stability analysis of the model at the DFE and the EE revealed again the existence of two basic reproductive numbers with demographics, R_{0H} representing the human to human transmission and R_{0E} representing the environmentally mediated transmission. This is in agreement with Chapter 4 as the two emphasise in the importance of improved sanitation in the elimination of trachoma.

The second contribution was developing the age structured model. Whilst it was not possible to solve this model analytically, numerical results were in broad agreement with those for the previous model and the model in Chapter 3. The age-structured model also gave new insights. Most importantly, the numerical simulations showed that the improvement of the environment by sanitation affected the two age groups differently. The decrease of the infection in the under 9 years old is slower than older individuals, however the improvement of the environment affected the two age groups.

This chapter proved the importance of the environmentally mediated transmission of trachoma in Gashoho Health District. Regardless of whether the initial model presented in Chapter 4 has the demographics or has age structured included, environmentally mediated transmission is still a major source of infection in the trachoma transmission model. Environmentally mediated transmission must be reduced by interventions targeting sanitation for trachoma to be eliminated in Gashoso and the goals of GET2020 met. The following chapter explores how such an intervention, if introduced, might be evaluated in a low resource setting such as Gashoho, given constraints on conducting population level surveillance for a complex intervention.

CHAPTER 6

Stratified Truncated Sequential Sampling (STSS): A novel strategy for evaluating trachoma control initiatives in Gashoho Health District, Burundi

6.1 Introduction

The purpose of this chapter is to evaluate practical methods for evaluating environmental interventions for trachoma, were these to be implemented in Gashoho based on the findings from previous chapters. Chapter 3 of this thesis presented the results of a cross-sectional study of trachoma conducted in Gashoho Health District to explore the association between cases of active trachoma per household and environmental risk factors. Recall that the overall prevalence of active trachoma was found to be 7.9% (95% CI 5.0-9.6%), with 19.5% (95% CI 13.7-26.4%) in children under nine years old and the occurrence of trachoma was highly associated with access to sanitary toilets, which more than halved the odds of active trachoma (OR 0.43, 95% CI 0.25-0.74%)[160]. Then, in Chapter 4, a mathematical model exploring how an environmental intervention based on targeting this association was developed. Stability analysis and numerical simulations suggested that an environmental improvement intervention focused on improved sanitation was essential for the eradication of trachoma in Gashoho. More complex models incorporating births, mortality, and age-structure were developed in Chapter 5. Stability analysis and numerical results again showed that limiting environmental transmission was essential for controlling trachoma in Gashoho. These results, presented in previous chapters, all reinforced the need for an optimal implementation of the SAFE strategy (S = surgery, A = antibiotics, F = facial washing, E = environmental improvement) by the World Health Organization to achieve its target of global elimination of trachoma by 2020 (GET2020) [195]. Nonetheless, at present, environ-

mental improvement is neglected in Burundi especially in Gashoho Health District, where trachoma remains endemic [196]. This chapter therefore examines how such an intervention should be evaluated, if the results from previous chapters are acted upon and the SAFE strategy fully implemented in Gashoho.

Should an environmental improvement intervention be implemented, its impact will need to be subject to real-time, repeated, surveillance to ensure that it is making a meaningful contribution to the task of meeting the GET2020 targets (which other interventions have not yet done). Whilst a number of approaches exist for conducting surveillance of this type, unfortunately, existing methods usually provide estimates of prevalence at only a village or household level, without a clear way of extrapolating their estimates to a district or country level [197, 198, 199, 153]. In Burundi, administrators demand health data collated at the district level, meaning that any sequential sampling method used will need to provide district level extrapolations whilst also capturing clinically meaningful variation between sites (see) figure 6.3. Therefore, evaluation schemes for new environmental intervention need to be stratified to identify areas where implementation is less successful, and where additional infrastructure, education or clinical support are required. However, the use of stratified ecological data to provide a statistical framework for extrapolating between the site and district level presents severe challenges with respect to confounding, particularly with respect to avoiding the ecological fallacy termed "Simpson's paradox."

Confounding is a common issue in the analysis and interpretation of data. Confounding occurs when both an exposure and outcome are dependently related to a third variable [200]. An understanding of confounding is essential to study design, data analysis, and interpretation of resulting estimates. Simpson's paradox is an extreme example of confounding, which occurs when trends or effects observed within strata are reversed across strata [201, 202], due to the fact that the process of allocating observations to strata acts as a confounding variable [200]. Failing to account for the existence of the paradox can pose problems for practical decision making based on stratified data collection as the confounding factor will potentially bias the results due to a lack of representative sample.

The probability of Simpson's paradox occurring is arguably increased in low resource settings. When conducting a surveillance and evaluation program, low resource settings face particular problems in balancing sampling precision and sampling effort [203]. Ideally, the 30 cluster method as suggested by WHO would be the most recommended [204]. However, if the setting is poorly resourced, and the nature of the surveillance or evaluation program demands repeated or stratified sampling, the costs of such an intensive approach may be prohibitive, then alternative methods are needed [205, 206]. This is particularly true if it is to be applied to the monitoring of environmental interventions, which are usually implemented unevenly from the outset [207], and whose effectiveness often differs between sites [208]. In such instances the trends are to test limited clusters due to the constraints of the budget [209]. Then, if the results are aggregated in the traditional manner, the data may potentially include confounding variables due to interactions between individual and ecological level factors or unequal sample sizes unaccounted for within aggregate data [210]. This can be minimised by increasing the number of clusters [211].

The current chapter, therefore, proposes a new strategy for arriving at district level estimates based on repeated sampling of lower level strata, based on applied probability and vector arithmetic. The new strategy, called stratified truncated sequential sampling (STSS), consists of a combination of:

1. conventional truncated sequential sampling (TSS, explained below) applied within a number of strata (here, villages within a health district); and

2. a novel vector-based method to support decision making at the district level, based on the results of TSS across a number of strata.

This new STSS approach, we argue, accounts for clinically meaningful variations in prevalence between sites, whilst also providing an acceptably precise but simple and elegant method for clinical decision making at the district level. This chapter concludes with an elegant example of using foundational mathematical principles to solve an important real world problem, and is of particular interest in Gashoho Health District.

6.2 Decision making using STSS

6.2.1 Classification at the village level using classic truncated sequential sampling (TSS)

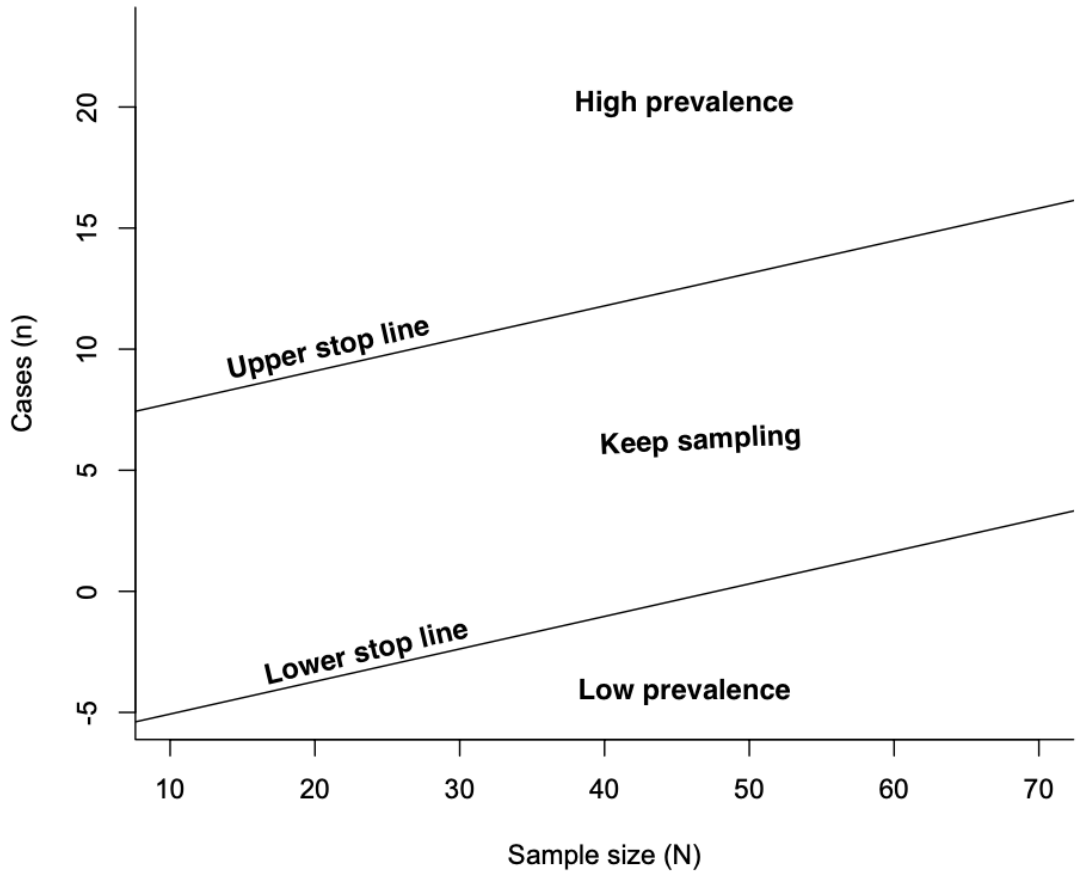

Fig. 6.1 The method of sampling using SPRT, as given in (6.1)–(6.3). Classifications of low or high prevalence can only be made when when the number of cases falls outside the two lines. Otherwise, sampling is continued until this occurs.

The original TSS method is a special form of Wald's sequential probability ratio test (SPRT) [212], which was designed to avoid the necessity of calculating required sample sizes whilst accurately classifying the prevalence of defects within a sample.

To minimise sample size, SPRT and related methods such as TSS rely on the difference between nominal precision (the precision one wants to achieve, analogous to *a priori* precision in a standard sample size calculation) and achieved precision.

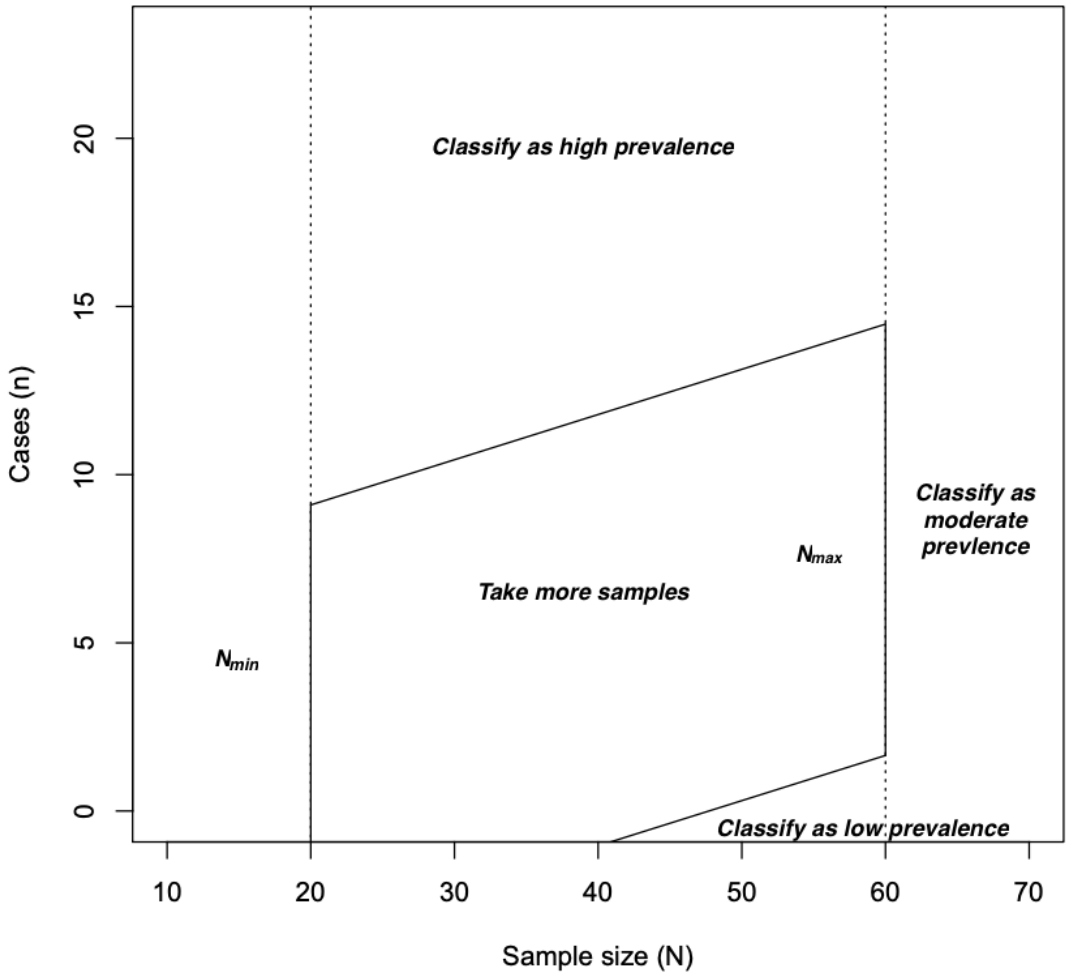

Fig. 6.2 A graphical representation of truncated sequential sampling (TSS). Classifications of high and low prevalence can be made by comparing the position at a point (N, n) to the position of the upper or lower stop lines after the starting sample size (N_{min}) has been collected. Sampling continues as long as the number of cases (n) is between the solid lines. The sampling is terminated if the number of cases (n) falls above or below the stop lines in the area demarcated by dotted lines, and a classification of low or high prevalence is made. A classification of moderate prevalence is made and sampling is stopped (truncated) when the maximum sample size (N_{max}) has been collected in which case the prevalence is classified as moderate. In this illustrative example N_{min} was set at 20 and N_{max} at 60.

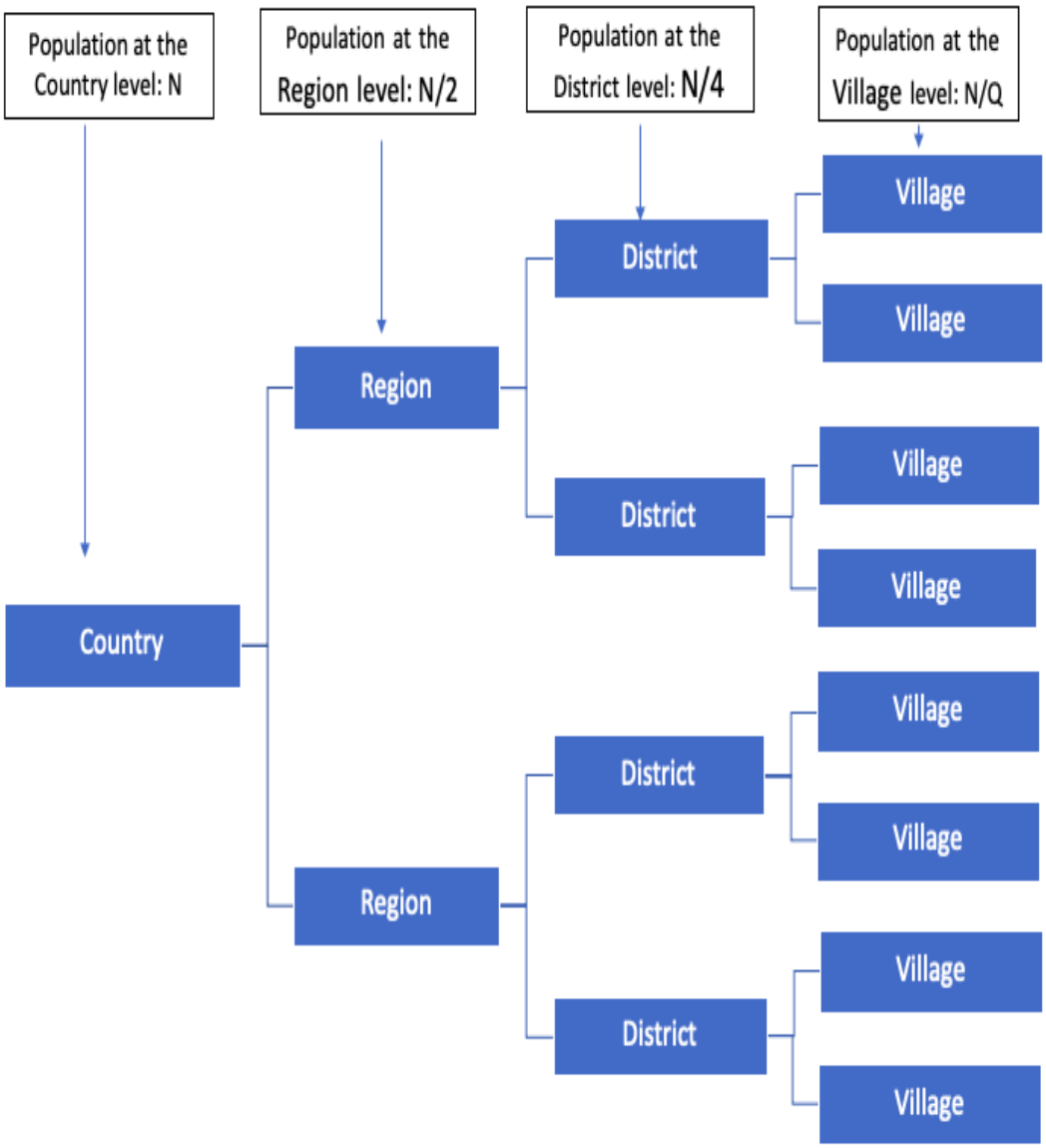

Fig. 6.3 Schematic of stratification of a populations and relationship between strata for the implementation and the reporting of health interventions in Burundi.

Achieved precision, unlike nominal precision, will vary with each sample taken, and using achieved rather than nominal precision as a marker of adequate sample size can reduce the overall sample size required in many instances [213]. For example, consider tossing a coin to estimate whether it is fair (that is, the probabilities of heads (H) and tails (T) results are each 0.5). Compare two samples of ten coin tosses, where the first sample is T,H,T,H,T,H,T,H,T,H, and the second sample is H,H,H,T,H,T,T,T,H,H. The first sample will estimate that the coin is likely to be fair with considerably more precision than the second sample. If an additional coin toss was added to the second sample, yielding T, the achieved precision in estimating whether the coin is fair would, however, increase. SPRT is based upon this concept of incrementally adding observations until the achieved precision meets or exceeds a desired threshold level, which ultimately has the effect of selecting the smallest possible sample size whilst guaranteeing a minimal level of precision [212].

As shown in Fig. 6.1, SPRT utilises two "stop lines" demarcating whether a given sample contains a high or low prevalence of some characteristic.[1] Each time the sample size increments by one (x axis in Fig. 6.1), the cumulative number of cases (infected individuals- y axis) is examined to see whether it lies above, below, or between the two stop lines. If the number of cases lies below or above these stop lines, sampling is stopped and prevalence is classified as low or high with a specified degree of precision. If the number of cases lies between the stop lines, sampling continues until prevalence can be classified as either high or low [212]. The reliability of classifications can be depended on because the equations for the stop lines include the desired threshold values of type I (α) and type II (β) error rates, such that errors will not exceed these levels. The intercept for the lower stop line in Fig. 6.1 is:

$$C_{lower} = \ln(\frac{\beta}{1-\alpha}) / \ln(\frac{p_2(1-p_1)}{p_1(1-p_2)}); \tag{6.1}$$

[1] In industrial applications, this method is used to determine whether a lot contains an excessively large number of defects (i.e., is of poor quality) or an exceptionally low number of defects (i.e., is of high quality).

the intercept for the upper stop line is:

$$C_{upper} = \ln(\frac{1-\beta}{\alpha}) / \ln(\frac{p_2(1-p_1)}{p_1(1-p_2)}); \tag{6.2}$$

and the slope of both lines is

$$m = \ln(\frac{1-p_1}{1-p_2}) / \ln(\frac{p_2(1-p_1)}{p_1(1-p_2)}). \tag{6.3}$$

In these equations, p_1 is the value below which the prevalence is classified as low, and p_2 is the value above which prevalence is classified as high.

Sampling based on the SPRT, as shown in Fig. 6.1, has some limitations for public health surveillance. Whilst in general it conserves sample size, if the difference between p_1 and p_2 is not large, it is possible for sampling to continue for a long time without making a classification. This limits the use of the method in very low-resource contexts, where resources for collecting large samples do not exist. Therefore, a modification to the SPRT consisting of two truncations of the stop lines was suggested, and called truncated sequential sampling (TSS) [214]. These truncations guarantee collection of a relatively small sample size, whilst preserving the reliability of classifications made based upon equations (6.1)–(6.3). Because of its emphasis on reducing the collected sample size, TSS is particularly well suited for use in surveillance in low-resource settings where wasted sampling effort might consume costly resources.

The manner in which the TSS method is applied to disease surveillance at a given site is shown graphically in Figure 6.2. Briefly, in TSS, as compared to SPRT (see Fig. 6.1, a minimum sample size (N_{min}) is chosen and collected (20 individuals in the case of Fig. 6.2). This lower truncation is represented graphically by a vertical line bisecting the stop lines. Similarly, a maximum sample size (N_{max}) is determined at which sampling will be stopped (truncated). This truncation is again represented graphically by a vertical line bisecting the stop lines. The area in between the lines of truncation and the stop lines forms a polygon, as shown clearly in Fig. 6.2.

Compared to SPRT (see Fig. 6.1), the area in which sampling is continued is dramat-

ically reduced in size in TSS, as the sample size is only incremented when the number of cases, n, for a given value sample size N, falls within the limits of the polygon. If, at N_{max}, the number of cases does not fall outside the polygon, then prevalence is classified as moderate. The optimum values of N_{min} and N_{max} for a given public health application are determined using computer simulation and convention [214, 213]. It is important to understand that equations (6.1)–(6.3) remain the governing equations for TSS, though their domain is truncated, effectively rendering them piece wise continuous equations of straight lines. For trachoma, the values of p_1 and p_2 in these equations are determined by the particular public health context. For example the WHO's Neglected Tropical Diseases (NTD) program has determined that an area with less than 5% has low prevalence of trachoma, therefore $p_1 = 0.05$, whilst an area with between $5 - 10\%$ has moderate prevalence and area with more than 10% has high prevalence, thus $p_2 = 0.10$. The significance of these values is that if prevalence is above 0.05, then mass administration of antibiotics needs to occur according to the SAFE strategy [93, 215].

The limitation of TSS, to be addressed in this chapter, is that it only provides an estimate of prevalence at a single site, such as a village. However, in Burundi, decisions about trachoma management, including starting or stopping mass antibiotic distribution is based on classifying prevalence within a district that includes multiple villages. This means that any surveillance method has to be able to reliably convert estimates from villages into a district level estimates, to prevent errors in decision making at the district level that would result in inadequate or excessive treatment [106].

6.2.2 Classification at the district level based on TSS – stratified TSS (STSS)

To study the conditions under which errors in decision making at the district level can arise from implementing TSS, and to develop protocols for arriving at reliable classifications of prevalence within the district to guide interventions, graphical methods employing 2-dimensional vectors are employed. The method is depicted graphically in Figure 6.4 and described algebraically below.

Based on equations (6.1)–(6.3), the lower stop line has equation

$$f_{low}(N) = C_{lower} + mN, \tag{6.4}$$

and the upper stop line has the formula

$$f_{high}(N) = C_{upper} + mN, \tag{6.5}$$

where

$$N = \sum_{q=1}^{Q} N_q, \tag{6.6}$$

is the sample size collected during an iteration of TSS in $Q \geq 1$ villages.

Now define a positional vector in 2 dimensional space, having origin at $(0, 0)$, and terminating at the point (N_q, n_q), which represents the sample size and number of cases when sampling using TSS is terminated in a village q. The vector for a particular village q is therefore given by

$$\vec{p_q} = (N_q, n_q). \tag{6.7}$$

Where TSS is implemented in $Q > 1$ villages, there is a resultant vector

$$\vec{P} = (\sum_{q=1}^{Q} N_q, \sum_{q=1}^{Q} n_q), \tag{6.8}$$

Graphically, comparing the value of $\sum_{q=1}^{Q} n_q$ in (6.8) to the values of the stop lines (6.4) and (6.5) at the same point N gives the district a classification of low, moderate, or high prevalence according to the following rules:

1. If
$$\sum_{q=1}^{Q} n_q < f_{low}\left(\sum_{q=1}^{Q} N_q\right)$$
the district is of low prevalence;

2. If

$$\sum_{q=1}^{Q} n_q > f_{high} \left(\sum_{q=1}^{Q} N_q \right)$$

the district is of high prevalence; or, if

3.

$$f_{low} \left(\sum_{q=1}^{Q} N_q \right) < \sum_{q=1}^{Q} n_q < f_{high} \left(\sum_{q=1}^{Q} N_q \right)$$

the district is of moderate prevalence.

Based on this decision framework for the district, there are two possible error types arising from Simpson's paradox that it is important to consider:

1. All villages are classified as low prevalence using TSS, but the district is classified as moderate or high prevalence.

2. No villages are classified as high prevalence using TSS, but the district is classified as high prevalence.

These two errors have clinically important consequences. The first error would result in a district continuing to receive mass drug administration when it is not indicated, wasting valuable and costly resources. The second type of error will not have immediate clinical consequences, as any district of moderate or high prevalence should receive mass drug administration; but it would have longer term implications for evaluation and planning, as it would potentially conceal real advances made in reducing prevalence. This could, for example, result in inaccurate appraisal of the performance of novel sanitation interventions, when considered at the district level. This might lead to premature scaling back of interventions perceived to not be of real benefit, when in fact they were having a modest impact.

The first scenario, where all villages are classified as low prevalence using TSS, but the district is classified as moderate or high prevalence, is considered first. Recall that the maximum possible value of the lower stop line in TSS for a single village occurs at N_{max} (see Fig. 6.2). Whilst the stop line (6.4) is a continuous function of N_{max}, the actual number of observed cases n is an integer. Define n_{low} as an integer, which is the highest integer value of n that is less than the quantity expressed in equation (6.4).

Thus, n_{low} is the maximum number of cases at which a village can be classified as low prevalence using TSS.

Let TSS be implemented in $Q > 1$ villages, to provide a district classification. Let every village have n_{low} cases from N_{max} observations, the maximum number at which a village can still be classified as of low prevalence, such that for each sampled village the result of TSS can be represented in two dimensional space by the vector

$$\vec{p_q} = (N_{max}, n_{low}). \tag{6.9}$$

Given (6.8) the resultant vector is

$$\vec{P} = (QN_{max}, Qn_{low}), \tag{6.10}$$

which is its largest attainable value given the constraint that all villages contain n_{low} cases.

For the classification error 1 to occur in this scenario, the value of the lower stop line (6.4) evaluated at QN_{max} must exceed Qn_{low}. Since n_{low} is defined as the highest integer less than the value of (6.4), then Qn_{low} is always less than (6.4) evaluated at QN_{max}. Therefore, if all villages are of low prevalence, a classification of the district as high or moderate prevalence cannot occur.

Therefore, misclassifications of moderate or high prevalence at the district level can never be made using our implementation of TSS if all villages are classified as low, see figure 6.4. This result is important because if a district can confidently be classified as low prevalence, mass antibiotic distribution can be stopped within that district. Thus, if this decision can be made with certainty, it will allow valuable financial resources to be redirected from stockpiling antibiotics towards other pressing health concerns. This vector algebraic proof does not, however, account for incorrect classifications of villages as low using TSS at the village level. Were such errors to be common, the usefulness of the vector decision making method for the district level would be reduced. The likely frequency of such errors will be studied later in this paper.

Table 6.1 Mean sample size collected over 10,000 resampling iterations.

Distribution	Villages	Classification	Sample size needed to make the classification	
			Mean	St.dev
Uniform	4	**High**	39.11	9.58
		Moderate	40.83	9.30
		Low	39.17	8.53
	5	**High**	40.70	9.38
		Moderate	40.89	10.32
		Low	38.86	10.22
	6	**High**	38.15	9.83
		Moderate	40.07	9.40
		Low	41.59	8.60
	7	**High**	37.81	9.58
		Moderate	38.02	9.58
		Low	39.83	8.88
Beta	4	**High**	40.14	9.87
		Moderate	39.06	10.03
		Low	40.14	9.87
	5	**High**	38.63	10.62
		Moderate	37.48	9.55
		Low	37.88	9.80
	6	**High**	35.95	10.22
		Moderate	37.77	9.87
		Low	35.25	10.17
	7	**High**	37.53	9.32
		Moderate	36.34	9.49
		Low	35.57	9.32

Now, consider the second type of error where all villages are to be classified as moderate or low prevalence by TSS, yet the resultant vector representing the district level classification terminates above the upper stop line (6.5) resulting in a classification of high prevalence for the district. Recall that the maximum number of samples collected in TSS for a given village occurs at N_{max}, where a classification of moderate prevalence is made when the number of positive cases in the village, n_q, is less than (6.5) and greater than (6.4) evaluated at N_{max}. Since the actual number of observed cases in village, n_q, must be an integer, there exists an integer $f_{low}(N_{max}) < n_{mod} < f_{high}(N_{max})$ such that n_{mod} is the maximum number of cases at which a village can be classified as moderate prevalence using TSS. If TSS is implemented in $Q > 1$ villages, to provide a district classification, and every village has n_{mod} cases from N_{max} observations, the

resultant vector for the district is

$$\vec{P} = (QN_{max}, Qn_{mod}), \tag{6.11}$$

If a misclassification of high prevalence is to occur when all villages are moderate or low prevalence, the vector (6.11) must intersect the upper stop line, which will occur if Qn_{mod} is greater than (6.5) evaluated at QN_{max}.

The possibility of such an error can be easily demonstrated graphically. Given two vectors mod_1 and mod_2, the resultant vector intersects the upper stop line and the intersection occurs, resulting in the district being classified as high, as shown in Fig. 6.4. The clinical implications of such an error are however much less critical than with a misclassification of low prevalence. For both moderate and high prevalence districts, current protocols demand mass administration of antibiotics. The fact that the vector decision making tool has an algebraically demonstrated propensity for misclassifying districts of moderate prevalence as being of high prevalence is therefore not a contraindication to its use in public health.

In summary, the vector elaboration of TSS, STSS, is a promising way of classifying districts as low prevalence or not based on TSS carried out at the village level. Algebraically, it is clear that so long as the rate of mistakenly classifying villages as low is negligible, the vector based classification method for classifying districts should not result in many incorrect classification of low prevalence at the village level. Thus, the STSS method, comprising TSS in multiple villages and a vector based method for district classification, could feasibly be employed to inform policy decisions around ceasing mass drug administration when all sampled villages are of low prevalence according to TSS. Clearly, it is not safe to stop mass drug administration if all villages are not of low prevalence, given that classification errors can occur at the district level even in the simplest case where all districts are of moderate prevalence. The STSS method developed here could be used in surveillance of new environmental interventions aimed at reducing trachoma prevalence in the Gashoho Health District, again provided that incorrect classification of low prevalence do not occur frequently at the district level. The likely real world performance of the STSS method is now further studied using computer simulation to estimate village and district error rates in empirically informed

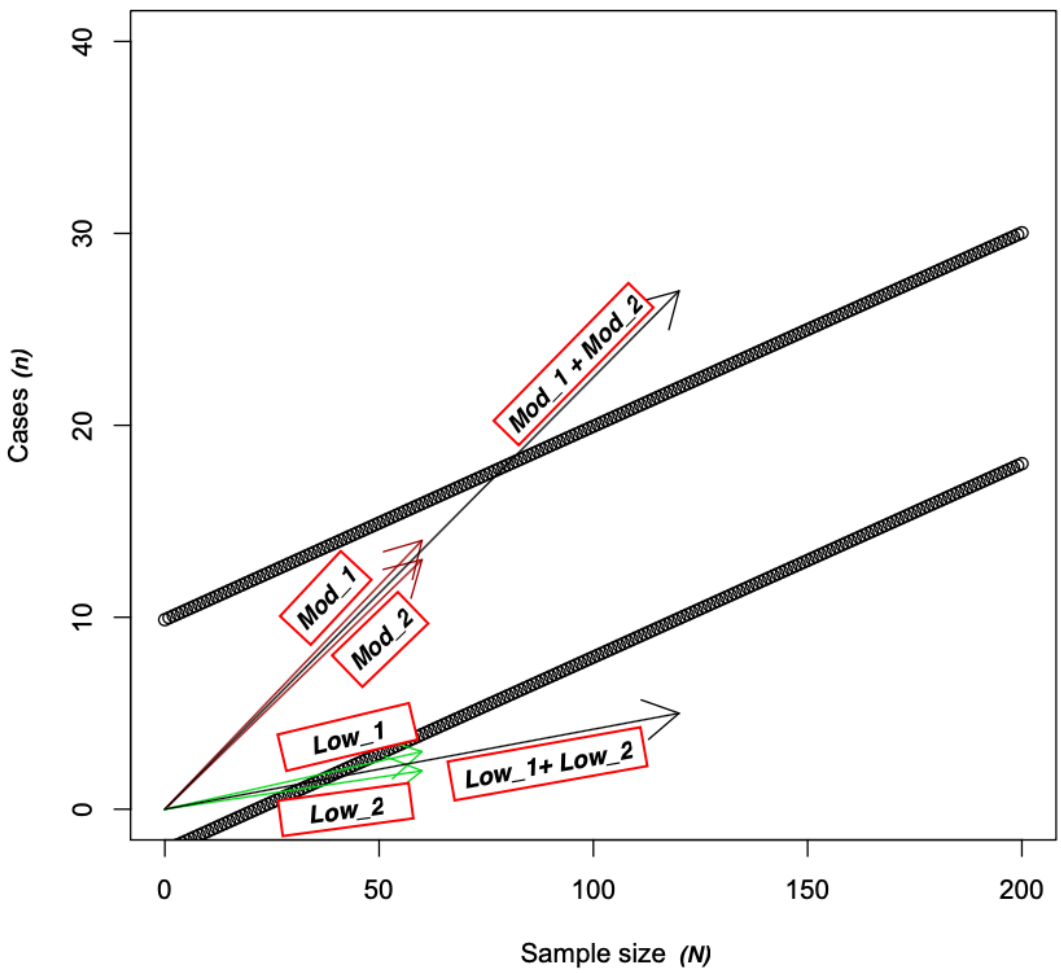

Fig. 6.4 Illustration of resultant vectors for classification of trachoma prevalence at the district level. Parameter values are $\alpha = 0.0005$, $\beta = 0.2$, $p_1 = 0.05$, and $p_2 = 0.1$. The vectors mod_1 and mod_2 terminate at points (60,14) and (60,13), and the vectors low_1 and low_2 at (60,3) and (60,2), where 60= N_{max}.

scenarios.

6.3 Simulations

6.3.1 Rationale

To investigate the likely real-world decision making performance of the above STSS strategy, simulations were undertaken, using empirically derived parameters. The general process of using computer simulation to assess the performance of the sampling plan is known as validation, and is a widely accepted method for studying decision making tools used in public health, particularly for low resource settings. Sampling plans validated by computer simulation are in use by the WHO for multi-drug resistant TB,

trachoma, and HIV surveillance in many low resource settings [216, 217, 218, 219]. In this validation exercise, simulations assessed the likely achieved (vs nominal) precision of sampling estimates, mean sample size collected, and frequency of incorrect decisions within strata, and hence the reliability of the STSS method for overall decision making at the health district level.

6.3.2 Computational methods

6.3.2.1 Data generation

Three different combinations of variables parameters were used in the simulation for α and β are the maximum permissible rates of type I (false positives) and type II (false negatives) errors, as formulated in (6.1) – (6.3). In the context of TSS, a false positive is interpreted as a classification of prevalence that is high or moderate when the actual prevalence is low, and a false negative is interpreted as a classification of low prevalence when the real prevalence is moderate or high. The significance of this interpretation is that classifications of moderate or high prevalence indicate that antibiotic distribution in communities should be continued, whilst a classification of low prevalence means that antibiotic distribution should be ceased, which could be devastating if a community in fact was suffering disease at endemic levels. For the first scenarios α statistical significance and β statistical power were taken from the commonly used rate, the other two scenarios, β was chosen so that the nominal statistical power exceeded the commonly used standard. The rationale for emphasising the value of β in simulations is to minimize the risk of false negative classifications. With false negatives interpreted as described above, so that negative (low) classifications result in not supplying antibiotics to infected people, the clinical result of a false negative is more severe than that of a false positive (higher) classification. The three scenarios of α and β errors used in simulations were:

1. α = 0.05 and β = 0.20
2. α = 0.10 and β = 0.10
3. α = 0.05 and β = 0.15.

For each of the scenarios above, the prevalences of trachoma across villages were drawn from two different probability distributions, namely:

- Trachoma prevalence distributed uniformly between villages, so that all prevalences between 0% and 15% (mean of 7.9% and a (95% CI 7,5 - 8,2)) were equally likely to occur; and
- Beta distributed prevalence, where prevalences between villages followed a Beta distribution defined on the interval $[0, 1]$ with parameters $\texttt{shape1} = 0.38, \texttt{shape2} = 4.0$ in *R* syntax.

These two distributions were chosen for different reasons. The uniform distribution was used to ensure that the performance of the STSS method was assessed across the range of possible prevalence levels, in particular across a broader range of low prevalences. Whilst low prevalences are not currently observed in the field, it is predicted that improved sanitation will result in low prevalence, so adequate performance of the surveillance plan in the low prevalence range is obligatory. The Beta distribution, on the other hand, was chosen to simulate the range of prevalences currently observed empirically in the Gashoho Health District. The Beta distribution used had a mean of 7.4 % and a 95 % CI of 7.2–7.6, which closely approximated the empirically observed distribution of trachoma in Gashoho Health District. As reported by [160] Gashoho Health District had an overall mean prevalence of 7.9% (95% CI 5.7-10.6%), with no significant differences between surveyed villages, reflecting the endemic nature of the disease. Based on the lack of significant differences between villages, the assumption that prevalence in each village was drawn from the same sampling distribution was accepted. The similarity between the Beta distribution employed and the empirical data was verified using the function `prop.test` in R, which showed that the distribution of prevalences across villages observed in the field was not statistically different from that modelled by the specified Beta distribution (p-value = 0.8669). Therefore, the Beta distribution parameterised above, was regarded as a good approximation of the empirical sampling distribution of Trachoma prevalence between villages in the Gashoho Health District.

From each of these two different distributions, $d = 1, 2$, where $d = 1$ is the uniform distribution and $d = 2$ the beta distribution, $V_d = 20$ representative quantiles were generated using Latin hypercube sampling, using *randomLHS* function in R programming language. Each of the V_d quantiles was then used as the success probability for a binomial distribution to generate 1,000 random binary values, with each value representing

the Trachoma infection status (0 = susceptible) of a person in village $v_d = 1, \ldots, V_d$.

Unique combinations of binomial prevalence data from $Q = 4, 5, 6$ or 7 villages, distributed according to V_d, were computed using *Combn* function in R, parameterised as

$$C(V_d, Q) = \binom{V_d}{Q} = \frac{V_d!}{(V_d - Q)!Q!}. \tag{6.12}$$

Simulation was then used to assess how well the STSS approach performed in classifying trachoma prevalence, both within each of Q villages, and for decision making at the district level, with district estimates being represented in simulations by each unique combination $C(V_d, Q)$.

6.3.2.2 TSS simulation at the village level

Recall that the STSS scheme uses classic TSS, given by (6.1) – (6.3), to classify prevalence at the village level. The implementation of these equations is illustrated in figure 6.2. Custom code for simulating the use of TSS to classify prevalence within Q villages in each unique combination of villages $C(V_d, Q)$ was developed, using code from [220] as a basis. The code was initially developed in R [221], but ultimately transferred into plain C for increased computational speed, and is available at [222]. Fixed values were used during simulations for all parameters from equations (6.1) – (6.3), except for α and β, where three different scenarios were modelled, as listed on page 113. Values of fixed parameters are given in Table 6.2. Further information on the values of parameters p_1 and p_2 is given on p. 116. The values of the fixed parameters N_{min} and N_{max} require further explanation. The starting sample size $N_{min} = 20$ was chosen based on convention and anecdotal experience. The choice of starting sample size does not, in any case, affect the eventual classification by TSS. The maximum sample used for truncation was $N_{max} = 60$, or three times the minimum sample size. Previous authors have trialled maximum sample sizes of $25 - 60$ when evaluating TSS, and found that sample sizes above 47 were adequate [213, 214].

Using these parameters, in each of Q villages in each unique combination of preva-

Table 6.2 Values of fixed parameters used in simulations.

Parameter	Values	Explanation
N_{min}	20	Starting sample size per village
N_{max}	60	The maximum sample size per village
p_1	0.05	The threshold value below which local prevalence is classified as low
p_2	0.10	The threshold value above which local prevalence is classified as high

lences from each distribution $C(V_d, Q)$, the sampling scheme was simulated 100 times, and the results recorded. For each village, the proportion of times the prevalence was classified as low, moderate or high and the sample size required to make each classification. The rate at which incorrect classifications were made for each village over all sampling iterations was also calculated and related to achieved precision (expressed in terms of achieved type I and type II error rates) to assess the performance of the method. Incorrect classifications were further sub-categorised as incorrect classifications of low, moderate or high prevalence. Gross misclassifications were distinguished from other sorts of classification errors, where gross misclassifications were those in which a village with clearly high prevalence was classified as having low prevalence, or the other way around. The rate at which each of these types of gross misclassification occurred for each village was also recorded and the results tabulated in table 6.3.

6.3.2.3 Simulation at the district level

Having obtained results for each of Q villages for each unique combination of prevalences from each distribution ($C(V_d, Q)$), the use of STSS's novel vector based approach (see page 108) to reach a classification for the district containing the villages was then simulated. To assess the probability of misclassifications at the district level, using STSS in $Q = 4, 5, 6$ or 7 villages per district, two functions were used.

Let x_q be one of $X \in (0, Q_c)$ villages with an estimated prevalence in the low range (i.e. each $x_q \in X$ has $n/N \leq p_0$, $p_0 = 0.05$), where Q_c is a unique combination of Q villages and prevalences drawn from $C(V_d, Q)$, as defined in (6.12). X relates to grand mean of each unique combination $C(V_d, Q)$ by the weighted empirical distribu-

tion function,

$$\hat{F}_{Q_c}(p_0) = \frac{X}{Q_c} = \frac{1}{Q_c} \sum_{x_q=1}^{X \leq Q_c} x_q \leq 0.05. \tag{6.13}$$

where the grand mean is calculated by

$$\frac{1}{Q} \sum_{q=1}^{Q} p_q, \tag{6.14}$$

p_q being the estimate of the prevalence in each village.

The function (6.13) was implemented in R using the `ewcdf` command for each unique combination of Q villages from each distribution, $C(V_d, Q)$. If the vector-based classification was perfect in practice, as in theory, then (6.13) would correspond to the rate at which a district with prevalence equal to the grand mean would be classified as low.

Unfortunately, the classification of prevalence for each village is not perfect, but its performance can be estimated using simulations at the village level as described in Section 6.3.2.2. Let g_q be the probability of a village q being classified as low in all of the 100 iterations conducted as described in Section 6.3.2.3 above. It follows that the probability of Q villages from a district being classified as low always using the vector-based method is

$$G = \prod_{q=1}^{Q} g_q. \tag{6.15}$$

If sampling at the village level was perfect, (6.15) would equal (6.13) for every grand mean of villages (6.14). In practice, for each grand mean across each combination of Q villages from each distribution, $C(V_d, Q)$, the probability of classifying a district as low was less than (6.13), as reflected in the values of g_q calculated from the village-level results as described in 6.3.2.2. The difference between the functions (6.13) and (6.15) was recorded for each unique combination of villages and prevalences, $C(V_d, Q)$, and used to assess the performance of STSS at classifying districts with grand means over

Table 6.3 Rates and type of misclassification for each probability distribution and for each combination of type I and II errors for the TSS classifier at the village level: HWL= the classification is made as high prevalence while the true prevalence is low; LWH= the classification is made as low prevalence while the true prevalence is high.

		Any mis classification				Gross mis-classification		
Distribution	**True prevalence**	$Scenario_1$	$Scenario_2$	$Scenario_3$		$Scenario_1$	$Scenario_2$	$Scenario_3$
	High	1.73%	$5.38\%.10^{-1}$	1.00%	**HWL**	$2.75\%.10^{-2}$	$2.48\%.10^{-2}$	$3.42\%.10^{-2}$
Beta	**Moderate**	3.18%	2.38%	3.08%	**LWH**	1.98%	1.32%	1.68%
	Low	17.43%	6.23%	11.48%				
	High	1.99%	2.43%	9.56%				
Uniform	**Moderate**	8.51%	9.44%	9.56%	**HWL**	$4.48\%.10^{-3}$	$4.47\%.10^{-3}$	$2.75\%.10^{-2}$
	Low	22.43%	2.61%	2.90%	**LWH**	5.44%	6.14%	6.44%

Q sampled villages, with the grand mean given by (6.14).

6.3.3 Results of simulation studies

6.3.3.1 Importance of the sampling distribution

The underlying sampling distribution giving rise to V_d had a significant effect on the accuracy of classification or prevalence at the village level. The TSS sampling strategy did not perform well in the Uniform distribution in all scenarios. For instance in the low range prevalence the plan returned over 22 % , of any misclassification for scenario1 and more than 6% of gross misclassification for the same scenario. In the high range prevalence scenario1 returned with less than 2% of any misclassification and over 4% of gross misclassification. Scenario3 returned over 9% of any misclassification and over 2% of gross misclassification.

The TSS sampling plan performed better in the Beta distribution where in the low range prevalence scenario1 resulted in 17% of any misclassification and less than 2% of gross misclassification. Scenario3 resulted in slightly over 11% of any misclassification and less than 2% of gross misclassification.

In the high prevalence range, scenario1 returned less than 2% of any misclassification and less than $2 \times 10^{-2}\%$ of gross misclassification. Scenario3 returned with 1% of any misclassification and slightly more than $3 \times 10^{-2}\%$ of gross misclassification.

Overall, the results indicate that the STSS methods performs better in the Beta distribution using the parameters for scenario2 which returned 6.23% of any misclassification

and less than 2% of gross misclassification in the low range prevalence, and less than $6\% \times 10^{-1}$ of any misclassification and less than $3\% \times 10^{-2}$ of gross misclassification in high range prevalence. Therefore, for the remaining results of 6.3, only curves from the beta distribution with 90% significance and 90% power scenario will be presented.

It is worth noting that there were no significant differences in average sample size collected regardless of classification or underlying distribution between villages (with average mean sample size of 39 and s.d of 10; see Table 6.1). This shows that TSS fulfills its promise of minimising sample size regardless of the underlying prevalence.

6.3.3.2 Classification of district level prevalence

In Section 6.2.2 above, it was shown algebraically that the vector-based approach to district classification will always classify a district as low prevalence when all sampled villages in the district are classified as low prevalence. This would make the scheme effectively perfect at classifying districts of low prevalence, and suggest that it would be ideal for conducting surveillance of an intervention that aimed to reduce the prevalence of trachoma to below the low threshold. Unfortunately, not all classifications of low prevalence at the village level are correct, as shown in Table 6.3. This results in less than perfect classifications of districts as low prevalence using STSS, as shown in Fig. 6.5. The solid lines in Fig. 6.5 were generated using equation (6.13), which shows the proportion of villages with a given grand mean of having at least one village of moderate or high prevalence(> 0.05). The probability is zero at grand mean of 0.0, and reaches 1.0 for grand means above $p_1 = 0.10$, the threshold for classifications of high prevalence. The dotted lines in the same figure were generated using equation (6.15), and show the probability of classifying a district as low prevalence using the vector-based component of STSS, for a given grand mean. This probability is one when the district grand mean is zero and zero when the grand mean is $> p_1$, the threshold for high prevalence (0.10). The results from Fig. 6.5 for four and seven villages are now compared below.

Both the probability of having at least one village of moderate or high prevalence and the probability of classifying the district of low prevalence when all villages are

classified as low by TSS, for a given grand mean, differ according to the number of villages sampled per district. For instance, Fig. 6.6 (a) shows that for four villages, the probability of classifying the district as low when the district mean (grand mean) is 5% is around 20%, while the probability of having at least one village of moderate or high prevalence for the same grand mean (blue line) is around 22%. In other words, the vector-based classification of district prevalence in STSS makes errors in classifications of low prevalence about 2% of the time, when TSS estimates from four villages per district are available. The same Fig.6.6 scenario (b), shows that for seven villages, the probability of classifying the district as low when the district mean (grand mean) is 5%, is around 3% (red line) while the probability of having at least one village of moderate or high prevalence for the same grand mean is around 18% (blue line). Clearly, the performance of the vector-based classification is superior when seven villages are used, and the chance of inaccurately classifying a district as being of entirely low prevalence (the first instance of Simpson's Paradox defined on page 108 is very small.

6.4 Discussion

This chapter makes a number of new contributions. Firstly, a new-vector based method was developed for combining estimates from TSS in a number of villages to classify prevalence within districts. The vector-based method was developed and evaluated algebraically, which suggested that it would perform very well when the goal of surveillance was to correctly identify whether districts that had received new interventions were reduced to low prevalence. This combination of using TSS within strata and the vector based method to aggregate strata was called STSS. Secondly, the performance of STSS was assessed using simulation populations. These results confirmed that the STSS scheme might be used to monitor the outcomes of environmental interventions in Burundi, but that the population distribution of infection and the number of villages used as sub-strata affected performance significantly. The biggest limiting factor on performance was the distribution of prevalence between villages, which substantially affected the performance of STSS.

The first contribution of this chapter, the development of vector-based method to

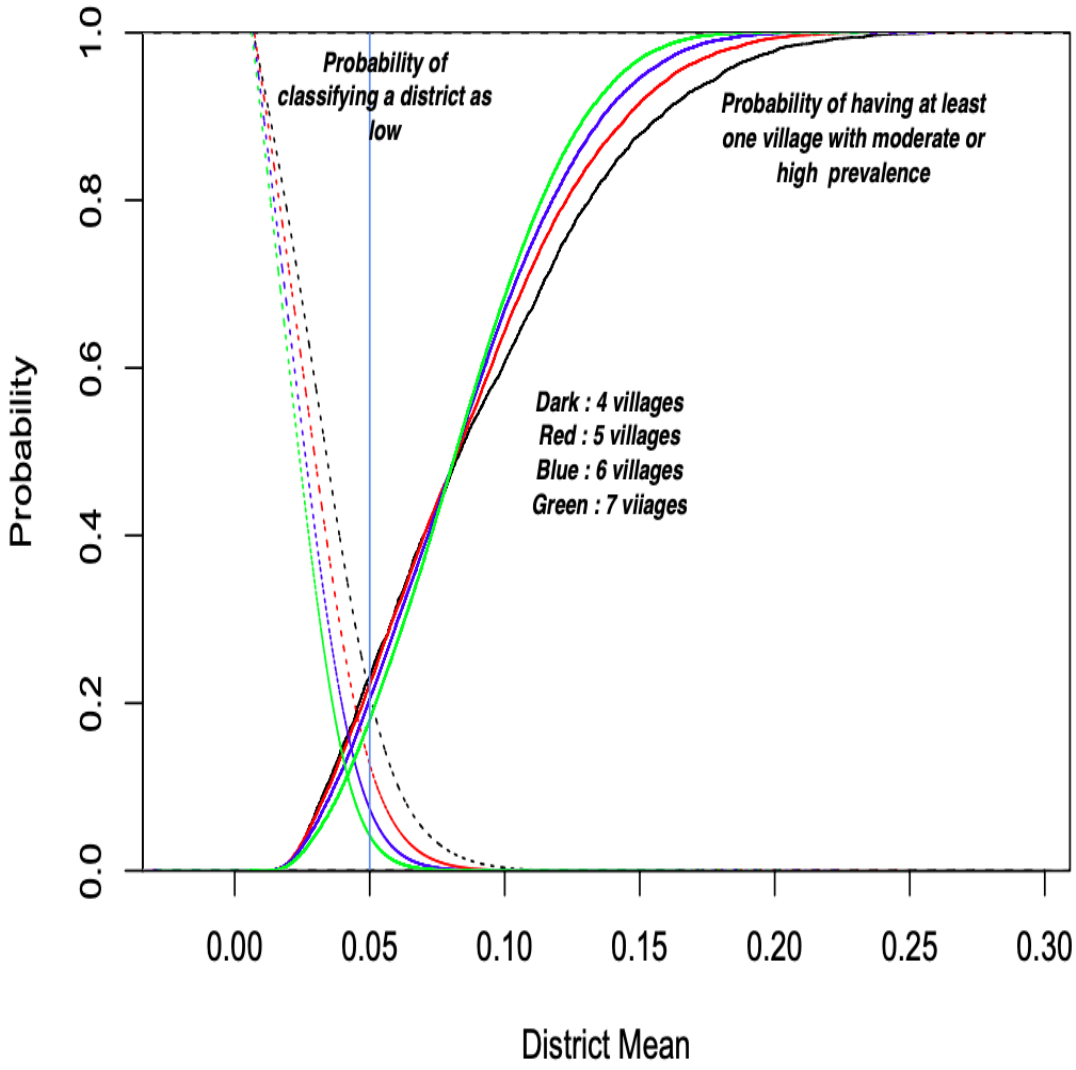

Fig. 6.5 Performance of STSS for decision making at the district level. Dotted lines show the probability of a district being classified as low prevalence, based on a sample of $Q = 4$–7 villages with a given grand mean (the x-axis value). The solid lines shows probability of each combination of Q villages used to estimate district prevalence, with a particular grand mean, having at least one village that is actually of moderate or high prevalence.

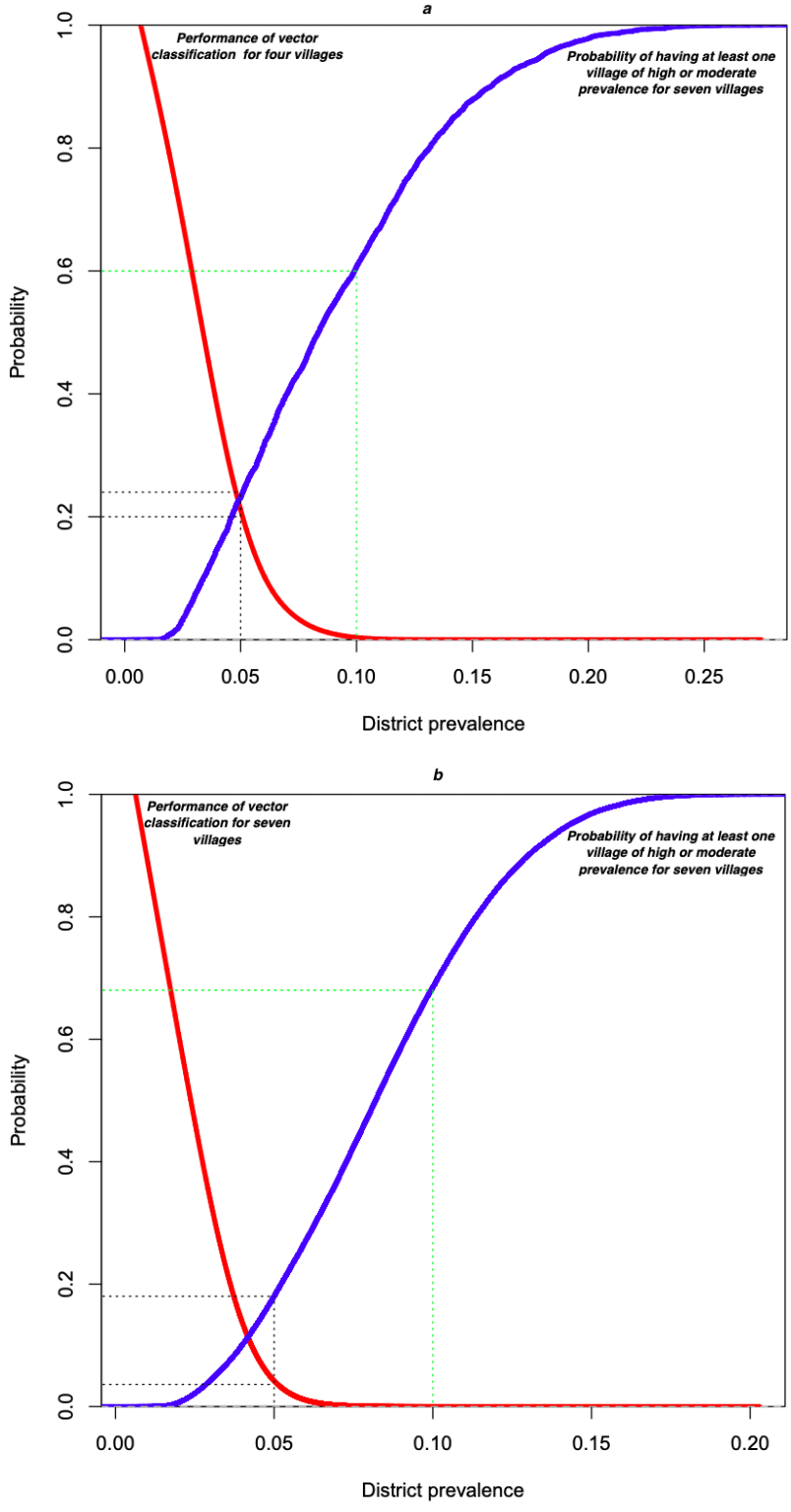

Fig. 6.6 Performance of the of the vector-based component of STSS when used to classify district prevalence based on four (a) and seven (b) villages. The red line represents the probability of STSS classifying the district as low prevalence, while the blue line represents the probability of having at least one village of moderate or high prevalence in a district sample with a given grand mean.

provide public-health classifications at the district level based on surveys at the village level, is a promising way of dealing with an important problem. The potential for the aggregation of data to result in errors in decision-making is a major concern and was investigated in some other studies such as in [223], demonstrating that the growing availability of micro–level data creates challenges for decision makers in terms of choosing the right level of data aggregation for inference and decisions. A particular type of error of concern for decision-makers is Simpson's paradoxes, which arises when traits that occur within strata disappear or change when strata are aggregated. Detecting whether Simpson's paradox occurs in a data set used for decision making is therefore critical.

In this work a vector-classification method for identifying Simpson's Paradox, inspired by [224], was shown to produce acceptably low rates of Simpson's Paradox. Two different instances of Simpson's Paradox were explored, as outlined on page 108. First, we examined the scenario where one or more villages are classified as being of moderate or high prevalence, but the district was classified as low prevalence. Secondly we examined the scenario where no-villages were classified as being of high prevalence, but the district was classified as being of moderate prevalence. In regards to second instance of Simpson's paradox, it occurs only in the moderate range prevalences when the aggregation reaches a certain value, then after that point the classification of high prevalence is certain. However, this instance of Simpson's paradox does not have major clinical implications as the protocol for managing trachoma in both moderate and high prevalence areas is the same – mass drug administration.

The most harmful kind of misclassification is obviously the first kind, when STSS classified a district as having a " low " prevalence when one or more villages in the district were classified as being of moderate or high prevalence, since this will mean stopping mass drug administration in these villages when they actually require it, according to WHO protocols. Numerical simulation reveals a negligible amount of misclassification of this kind when seven villages per district were sampled, and about a 2% chance of misclassification when four villages were sampled (see Fig. 6.4). It is clear that, the probability of misclassification decreases as we increase the number of vil-

lages involved in the evaluation process. However, maximising the number of villages surveyed is not always possible in settings with limited resources, so it is comforting that even when just four villages were surveyed, the performance of STSS was good. This means that the STSS method may have an important clinical role in the monitoring of public health interventions orientated in the reduction of trachoma prevalence as low prevalences are the measure of successful interventions and the trigger for ceasing regional drug administration, so need to be classified accurately. Figure 6.4, taken with our algebraic results, shows that STSS can classify low prevalence districts with confidence, subject to correct classifications at the village level. Provided there is confidence in the TSS classifications at the village level, mass antibiotics distribution can then confidently be stopped in districts classified as low using STSS.

Within villages, TSS performed well when the distribution of prevalences between villages was described by the Beta distribution, but did not perform well when prevalence was distributed uniformly – particularly when prevalence was around the threshold of 5%. Fortunately, the empirical results from Chapter 3, [160] and the fundamentals of dynamical systems analysis suggest that the Beta distribution, rather than the uniform distribution, is most realistic. Firstly the Beta distribution was calibrated to the field data collected in [160], so we are confident that it captures the variation between endemic sites. Secondly, when dynamical systems shift between equilibria, they do not necessarily do so in a linearly decreasing way, suggesting that all values around a threshold point would not have a uniform chance of occurring. Public health data show that when successful contraventions are implemented against infectious diseases, the underlying dynamical system switches rapidly from an endemic state to the disease free state [225, 226]. For instance in Enemore (Ethiopia) where the prevalence of active trachoma in children aged 1 to 5 years old dropped from 43.5% to 5.1% in only two months after a single dose of antibiotic [225], the same results were observed in Tanzania where the prevalence of infection was reduced from 57% to 12% within 2 months [226]. Thus, the Beta distribution is more realistic than the uniform distribution, because it has more points in the endemic (8% prevalence) region than around the transitional range of prevalences at the 5% region.

The STSS method developed in this chapter therefore has substantial promise, having acceptable accuracy in realistic scenarios, whilst minimising sampling effort. It would be best used in situations where the classification of the prevalence of a condition into categories or classes (for example, high and low prevalence) provides sufficient information on which to base decisions to take specific actions. This approach could be adopted, for example, in many national programs such as HIV, tuberculosis and trachoma control programs. In addition, these results suggest that the STSS classifier could be most efficiently employed by using it only for monitoring and evaluation in low resource settings, where only a classification of the prevalence level is needed to commence or to stop an intervention such as mass antibiotic administration. The rationale is that the method avoids the calculation of the sample size required and other parameter values to specify the null and alternative values of significance level and power as are usually required [227], and thus tends to minimise sample size whilst not sacrificing achieved precision.

This method can also be used in any other circumstances in which the monitoring of a disease is an important issue, but where limited resources do not allow a full-scale surveillance to be undertaken. The low sample size and few villages (strata) requirement means that such a method would be suitable for use in low-resource settings in developing countries, for disease like trachoma, where a full scale up of the SAFE strategy is being implemented. And multiple surveys over time are required to keep track of the achievements of the program. For instance, in the case of trachoma where at each prevalence level a specific management is recommended, a necessity of a practical and reliable method for surveillance is needed [228]. The method can be used in several settings. The application of the method in the field does not require the use of computers for data entry and analysis. Data analysis consists of applying stopping rules to collected data then assess class level according to the threshold values p_1 and p_2 . This may be done using graphical devices or by the use of a tabular data collection and analysis form such as that shown in Figure 6.2. Application of the sampling plan using a tabular data collection and analysis form involves recording the cumulative number of cases found in the sample against the size of the survey sample taken as data are collected. The choice of data collection and analysis device should be informed by the

familiarity with the graphical representation of number (that is, the ability to accurately plot points onto graphs and to read values from graphs using the two-dimensional Cartesian coordinate system) amongst survey staff, which should not be taken for granted and is likely to vary from setting to setting. The development of simple tools (for example, formulae, algorithms or computer programs) to assist the development of such sampling plans could be the subject of further work. In this chapter we explored the usefulness TSS as a mean of monitoring and evaluation, but a number of other stratified sampling schemes have been proposed (e.g. the cross-sectional survey, especially the 30 cluster-sampling schemes with 210 respondents [229, 230], the LQAS with multiple sampling plans which is an extension to the usual LQAS method to accommodate more than one stopping rule [231, 214, 153, 232, 154]). All those schemes have proved their efficiency in sample size saving and would be worth exploring them in future work. This limits the uniqueness of STSS as the only possible scheme in the surveillance of public health intervention. This method has not been tested on the ground, however a research protocol of a stepped wedge randomised control trial of a rural sanitation intervention (as suggested in [160]) to reduce active trachoma infection in Gashoho Health District is being prepared and will be evaluated using the scheme proposed in this chapter.

6.5 Conclusion

The STSS method developed in this chapter could provide the basis for a rapid and reliable survey method for the monitoring and evaluation of a health program such as trachoma to classify an area as low, moderate or high prevalence. Prevalence surveys commonly rely upon classical statistical approaches in which sample sizes are fixed in advance of data collection according to the expected prevalence and the level of precision or error required [233]. The new method appears to be an alternative approach in which the sample size is not fixed in advance at the village level and provides a clear method of extrapolating the results at the district level according to the villages involved in the evaluation. Therefore, the stratified truncated sequential sampling (STSS) approach represents a practical scheme for conducting surveillance activities such as monitoring and evaluation of trachoma in a setting with limited resources. It avoids the need to meticulously calculate a priori sample size and is acceptably accurate given realistic distributional assumptions.

CHAPTER 7

Conclusion and future direction

7.1 Overview

This thesis investigated the reasons why the leading cause of preventable blindness worldwide, trachoma, continues to persist in the Gashoho Health District, Burundi. Classical epidemiological methods were used to understand the magnitude of risk factors associated with trachoma infection in Gashoho Health District. Then, mathematical modelling was employed to assess how significant environmentally mediated transmission of trachoma was, compared to transmission arising from mixing between susceptible and infected individuals. The use of an SIS model incorporating environmentally mediated transmission represents a novel approach to understanding the persistence of trachoma infection in this local context, which is nonetheless similar to many other local settings in Africa. Finally, computational methods were used to derive a new sampling method for the monitoring and evaluation of an eventual public health intervention targeting the reduction of trachoma.

The contributions made in this thesis fall broadly into three areas. Firstly, the thesis establishes the importance of the relationship between trachoma infection and unimproved environment, to better understand the role of unimproved sanitation in the persistence of trachoma infection as a public health concern in a low resource, African setting. Secondly, the thesis comprehensively analyses mathematical models incorporating the relationship between trachoma infection and unimproved sanitation, and shows the implications of this relationship for policy makers. Specifically, it is shown that improved sanitation is essential to eliminate trachoma.

Finally, following from the previous results from this research program, methods for conducting surveillance of interventions to improve sanitation were developed. These new methods give policy makers a tool to evaluate, in the short term, whether the reductions in trachoma prevalence predicted by the mathematical models in this thesis are being reflected in the field situation. These three major contributions are reviewed in more detail below.

7.2 Contributions to the epidemiology of trachoma infection

The thesis makes several contributions to trachoma epidemiology:

- it provides an updated estimate of the prevalence of trachoma in Gashoho Health District
- it estimates the magnitude of the association of unimproved sanitation at the household level and trachoma infection in Gashoho Health District.

These contributions arose from the first phase of the research in this thesis (fieldwork undertaken in Gashoho Health District), the results of which are presented in Chapter 3. These showed empirically that household access to sanitary toilets almost doubled the odds of a household member acquiring trachoma infection. In addition, this work reaffirmed that trachoma infection was concentrated in children under 9 years old. These results will inform practical recommendations about how the risk factor can be modified to achieve GET 2020 targets.

7.3 Contributions to mathematical modelling of trachoma

Deterministic models have a long history of being applied to the study of infectious disease epidemiology. Many earlier studies were confined to establishing criteria for the stability of the infection-free steady state and existence of an endemic steady state, perhaps in simple cases with explicit expressions for the proportion susceptible, prevalence of infection and herd immunity. Studies of the endemic state involve demographic processes that occur at a different (and longer) time scale, as well as epidemiological processes. Important concepts for structured populations such as age-shift and core

groups are fundamental insights that arise from this analysis, so even though disease transmission is in principle a discrete stochastic process, deterministic modelling offers a fruitful avenue to study problems of endemicity.

The mathematical work contained in this thesis is, therefore, a first attempt at modelling the elimination of trachoma transmission using non-pharmaceutical means. This differs from other mathematical modelling work by

- including parameters representing environmentally mediated transmission, and the control of this mode of transmission;
- extending mathematical models of infectious disease by including a compartment representing persistence of pathogen in the environment;
- demonstrating the existence of two basic reproductive numbers R_{0H} representing the human to human transmission and R_{0E} representing the environmentally mediated transmission; and
- incorporating demographics and the age-dependent nature of trachoma infection into a model using two age groups, one for children under 9 years old and the other for individuals aged over 9 years old.

The significance of the incorporation of an environmental component into a trachoma transmission model should not be understated. The WHO recommendation of the elimination of trachoma via GET2020, suggest the use of the SAFE strategy framework, and so far the non pharmaceutical component of the strategy have benefited limited mathematical interest. Establishing the series of mathematical steps underlying trachoma transmission model is a key contribution to the general ecology literature because it bolsters the confidence in the applicability and feasibility of the SAFE strategy in the elimination of trachoma. It is also an important step in familiarising researchers outside of public health with the SAFE strategy. This will assist mathematical modellers to engage with this important public health issue.

The work shows the dependence of trachoma endemicity upon two basic reproductive numbers, R_{0H} representing human to human transmission, and R_{0E} environmentally mediated transmission; these two reproductive numbers are shown to have an

additive effect. The elimination of the human to human transmission by administration of mass antibiotic treatment at the community scale have been proved to be efficient by several previous studies [172, 234, 235]. However, these earlier works failed to show mathematically how R_{0E} relates to the persistence of trachoma infection in the community. By elucidating the mathematical details, this thesis paves the way for greater appreciation of the relationship between the overall R_0 and the environmentally mediated transmission R_{0E}.

The simple mathematics relating R_{0E} and R_{0H} to the overall R_0 in the dynamics of the transmission model suggests that for the elimination of trachoma in Gashoho Health District, each R_{0i} needs to be less than one and the overall R_0 needs to be less than one as well, otherwise the disease will persist in the community. The application of the environmentally mediated transmission models to the understanding of disease progression in the population is not unprecedented. Environmentally mediated transmission has been used to model the transmission of cholera in Zambia [236, 237], and it has also been used to model the persistence of vector borne disease in Australia [238]. However, these papers have not parameterised environmentally mediated transmission in terms of a basic reproductive number, with implications for planning and evaluating large scale health program. This thesis is different from these papers, in that it uses the concept of environmentally mediated transmission to discuss planing and evaluating non-pharmaceutical interventions to control trachoma transmission in Gashoho Health District.

The thesis makes one further mathematical contribution. The work available in trachoma infectious disease modelling deal with modelling transmission in heterogeneous populations [123, 139]. There has, however, been little emphasis in these publications on the how the inherently age dependent nature of trachoma infection relates to environmentally mediated transmission, and whether interventions targeting environmental transmission benefit some groups more than others. Chapter 3 showed that most active trachoma infection in Gashoho Health District occurred in individuals under 9 years old. This work informed the age-structured model developed in Chapter 5, which sought to understand how transmission in different age groups might be impacted an intervention

targeting the improvement of the sanitation. Chapter 5 showed that even if an intervention affects all age groups evenly, transmission in different age groups may decline at different rates. This shows the importance of determining whether homogeneous or age-structured models are more appropriate to studying particular interventions targeting trachoma transmission. My results also reinforce those of Pinsent et al. [139] which recommends that in high and moderate transmission settings, both MDA and enhanced F and E are needed for sustained control. The model proposed in this work went beyond their approach and derived an environmental basic reproductive number to quantify the magnitude of the importance the environmental risk factors.

7.4 Contributions to policy and evaluation

The final contribution, but by no means the least important, of the thesis is the development of a tool for monitoring and evaluation of new trachoma control programs. This tool, presented in chapter 6 classifies a district, the unit of health policy in Burundi, as having a low, moderate or high prevalence of trachoma. A public health intervention targeting the elimination of trachoma will require a real time evaluation to see if the program is meeting its target. The WHO recommendation for mass antibiotic administration is for areas with high prevalences greater or equal to 10%, but limited tools exist for evaluating whether interventions are succeeding at reducing trachoma prevalence to close to zero. Additionally, the reporting system in Burundi is done at the District level, so such an evaluation instrument will need to provide reliable estimates of low trachoma prevalences (<10%) at the district level. In addition, these instruments need to be appropriate for low-resource settings, where collecting repeated, large samples is not feasible. Unfortunately, the existing tools for sampling in low-resource can only provide estimates at the village level without a clear way of extrapolating the results at the district level. The new scheme presented in chapter 6 (STSS) was developed to assist public health policy makers in evaluating whether an intervention was reducing trachoma prevalence to low levels, or not, and to do so using low sample sizes that enable repeated surveys. STSS is an elaboration of truncated sequential sampling (TSS), where, after TSS is conducted in individual strata (such as villages), the results are aggregated using vector algebra and compared to graphical decision rules.

Recall that for the monitoring and evaluation of a public health intervention targeting the elimination of trachoma, the interest is focused in areas with prevalence less than 5%, where antibiotic administration is stopped and further reductions need to be achieved by other interventions (for example, those targeting sanitation). The results in chapter 6 demonstrate, using algebraic and simulation methods, that STSS is both efficient and reliable when it comes to classifying an area as of low prevalence. For instance, if four villages are involved in the process of monitoring and evaluation, and if all villages are classified by TSS as of low prevalence, STSS shows that the district can confidently be classified as of low prevalence. But, if one of them is classified by TSS as other than low prevalence, the district cannot then be classified as low prevalence. Therefore, antibiotics would not be stopped in any district where one surveyed village had moderate or high prevalence. The simulation of the sampling plan also showed, that by increasing the number of villages involved in the monitoring and evaluation, the probability of having an accurate classification of the district also increased. Nonetheless, the results strongly suggested that four villages were sufficient to make reliable classifications at the district level. The much smaller sample size required to carry out the sampling in four rather than seven villages means that the plan has real potential to be used for policy making decisions in Burundi in the short term.

7.5 Future Directions

Based on the observed trends of trachoma in many developing countries, it is clear that current public health efforts are not having the desired effect on trachoma control in general. The work presented here suggests that these efforts may in fact be unintentionally contributing to the persistence of trachoma. The results from this thesis demonstrated that without improved sanitation, trachoma may be expected to persist in Burundi. Unfortunately the current control policies may focus on the antibiotics component only, and neglect the environmental measures as they first, seem harder to implement and second have long term results. However, a number of questions remain. The results of the research questions posed in this thesis, along with the findings of other mathematical modeling suggest several avenues of future research. Additionally, the work presented in this thesis has a number of limitations that could be improved upon in future research.

The use of the SIS framework was an oversimplification, and future research should extend the model to incorporate at least temporary or partial immunity. The rationale being that, the immune response to *C.trachomatis* provides an incomplete protection and is accepted to be important in the natural history of trachoma. Such as tissue damage and blinding complications, whist, protective immune effects and disease pathogenesis in trachoma is still not well understood. Paradoxically, where the "immunological paradigm" suggests that the disease pathology is a result of cell mediated immune responses against targeted chlamydial antigens and the "cellular paradigm" says that the infected epithelial cell responses drive pathology through expression of various mediators. This paradox creates an ambiguity on the role played by the immune system and the cell in active and scarring trachoma. A mathematical modelling exploring both ways to illustrate the importance of each component to predict the occurrence of a particular clinical manifestation is needed [40].

Given that scarring and blindness are caused by repeated episodes of conjunctival infection with *C.trachomatis*, whilst the effects of public health interventions to control the active disease at the population level can be promptly evaluated, the effects on severe ocular sequelae will need a long term to be assessed. A mathematical model of trachoma infection and evolution of the disease to predict the impact of interventions on the prevalence of blinding trachoma should then be developed in future research. The model would be based on the concept of multiple reinfections yielding progressively to conjunctival scarring, trichiasis, corneal opacity and blindness. It would also use some aspects of trachoma natural history, like a considerable rate of recovery from infection and a reduction of within-host bacterial load with subsequent episodes of infection, which is believed to depend upon an acquired immunity that clears infection more rapidly for older individuals [124].

Another important avenue of future research is modelling the potential public health impact of different interventions targeting either the pick–up rate η or the deposit rate θ, such as insecticide spraying for flies and face washing [95]. Indeed the relationship between trachoma, the presence of flies and other environmental risk factors such as

water availability appears to be complex. The presence of flies on the face of children was one of the earliest risk factors observed for trachoma, therefore, it has been suggested that flies could act as vectors for transmission of *C. trachomatis*. This association between the presence of flies on children's faces and the occurrence of trachoma has been reported in several studies. Flies can then be a physical vector for transmission of *C.trachomatis* and their control may be followed by a significant decrease in trachoma prevalence [239].

This modelling might occur in conjunction with the development of new models for the life cycle of Chalmydia in the extra-cellular environment. Recall, from Section 2.2 that the infectious part of the *C. trachomatis* life cycle occurs in an environmentally resistant form called the elementary body (EB) [27]. Numerous mathematical models have been developed to explore how a single EB adapts in the extra-cellular environment to form a pathogenic inclusion body within the host (e.g. [171, 240]. To date, however, all of these models have investigated the reaction of the human body to the pathogen in its extra-cellular environment, and none have been developed to model the strategies that the chalmydial EB uses to survive in environmental reservoirs such as latrines and fecal matter (another kind of extra-cellular environment). This is surprising, given that resistance to environmental degradation is such an important part of Chalmydia's ability to undergo environmentally mediated transmission [27]. This is an important gap that should be investigated in future studies. Future single cell models of how Chlamydia survives outside the host in the environment would be useful for developing new interventions to target environmentally mediated transmissions, and for developing more precise parameter values for the environmental transmission parameters μ , θ and η used in the models from this thesis.

An assessment of cost-effectiveness of trachoma control measures comparing different interventions targeting the improvement of the environment and lost productivity associated with blindness should also be considered. Cost effectiveness analyses can provide valuable inputs to these decisions by identifying the most efficient ways of delivering prevention, diagnosis, and treatment services at different levels of resource availability. The project would address the question of what are the costs and effects of

prevention, early detection, management, and rehabilitation of visual impairment, both individually and in the community [241].

In this thesis we explored the usefulness of the newly developed STSS as a mean of monitoring and evaluation, but a number of other stratified sampling schemes have been proposed [229, 230] such as LQAS with multiple sampling plans which is an extension to the usual LQAS method to accommodate more than one stopping rule [153, 154, 214, 231, 232]). More direct comparisons between the STSS and LQAS schemes in field settings would be worth exploring in future work.

7.6 Conclusions

This thesis found that, currently Gashoho Health District in Burundi had not met the GET 2020 target set by the WHO, and that trachoma remained at endemic levels. The results of this thesis support the hypothesis that sub-optimal implementation of the SAFE strategy, especially with regard to its environmental (E) component, is a major factor in this poor outcome. With this background, the thesis made a number of new findings that established parameters, expectations and protocols for planning and evaluating environmental interventions targeting trachoma.

This thesis provided new, up-to-date data regarding the prevalence of trachoma in Gashoho Health District and demonstrated the importance of sanitation in the persistence of trachoma infection in Gashoho Health District, using a cross-sectional study. This study found that the odds of acquiring the disease for an individual in a household doubled given the absence of improved sanitation.

From these results, a mathematical model using the SIS framework was developed, which also included environmentally mediated transmission. The stability analysis using the Jacobian matrix showed the existence of two basic reproductive numbers: R_{0H} representing human to human transmission, and R_{0E} representing environmentally mediated transmission. The existence of an endemic equilibrium was proved where $R_{0H} + R_{0E} > 1$, and the endemic equilibrium was successfully fitted to field data from Gashoho. The possibility of elimination where $R_{0H} + R_{0E} < 1$ was shown,

as well as that environmental interventions might facilitate elimination by increasing the removal rate of pathogen from the environment, μ. Subsequently, these results were shown to hold for more complex versions of the model incorporating demographics and age structure.

Public health interventions targeting the removal rate, such as improved sanitation, were suggested as a mean of achieving the GET 2020 targets in Gashoho Health District. Such interventions would need real time evaluation to check whether their potential (as suggested by mathematical models) was realised in the field. To that end the stratified truncated sequential sampling (STSS) method was developed to provide the basis for a rapid and reliable survey method for monitoring and evaluation. Using STSS, unlike other sequential sampling approaches, it is possible to classify the prevalence of trachoma as low, moderate or high at both the level of individual, local communities and at the district level. Thus, development of the STSS method facilitates the monitoring of interventions at the district level, where health policy regarding trachoma monitoring is set. By ultimately providing a strategy for monitoring and evaluation of new interventions (as well as data and mathematical models for planning them), this thesis makes an important contribution to combating trachoma in Gashoho Health District, with immediate potential for translation into policy and practice in Burundi. More broadly the methodology and the results of this thesis can ultimately be applied in areas where trachoma is still endemic, with the aim of eliminating trachoma by the new deadline of 2030.

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Appendices

The Appendices contain documents related to the conduct of the field study and project. Specifically, they contain

1. Grant Approval letter: The field research comprising chapter 3 was funded partially by the School of Medicine, Sydney, at the University of Notre Dame Australia. Dr Edward Waters won a grant from the School in 2017 to support the costs involved in undertaking the field work for chapter 3. This attachment is to acknowledge the support from the school.

2. Ethics Application Form for Notre Dame: the application to undertake the field work contributing to chapter 3

3. Attachment to Ethics Application: Project Proposal

4. Ethics Approval from Gashoho Health District: approval to undertake the field work in Gashoh Health District, presented in chapter 3.

5. Ethics Approval from the National Neglected Tropical Diseases Initiative in Burundi: This approval was granted to enable their clinical team to participate in the work included in chap 3.

6. Ethics approval from University of Notre Dame

7. Participant Information sheet:(in three languages: English,French and Kirundi) The document was used to clarify the information which will be collected then receive their consent from the participants.

8. Questionnaire: The form used to collect the data used in chapter 3

Appendix A

Grant Approval

THE UNIVERSITY OF NOTRE DAME AUSTRALIA

OFFICE OF THE DEAN
SCHOOL OF MEDICINE, SYDNEY

160 Oxford Street, Darlinghurst, NSW, 2010
(PO BOX 944) Broadway, New South Wales, 2007
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ABN: 69 330 643 210
CRICOS PROVIDER CODE: 02651D

3 July 2017

Re: 2017 Research Fund Support

To: Dr Edward Waters

Dear Edward,

Thank you for your interest in the 2017 SoMS Research Support. I am pleased to advise that your application was successful.

The School is able to support your project titled **Modelling Thracomiasis in Africa: Infection, transmission and control. Case Study in Burundi, Gashosho Health District** for the amount of **$4,200**.

The School supports your project with the following provisos:

- a summary of expenses is provided at the end of the project, during 2017;
- a report/paper of the project is submitted at the end of the project, during 2017.

Congratulations and best wishes with your Research Project.

Yours sincerely,

Professor Christine Bennett AO
Dean

Appendix B

Notre Dame Ethics Application Form

Important Information for Applicants

1. This application form is to be used by researchers seeking a full HREC ethical review for research involving human participants.

2. Download a new form from the HREC - ethics application forms webpage to ensure that you are using the most current version of this form.

3. Handwritten applications will not be accepted.

4. Please respond concisely to all applicable sections, using plain language wherever possible.

5. Type an X in checkboxes that apply.

6. Provide all necessary attachments where indicated.

7. The *National Statement on Ethical Conduct in Human Research (2014)* (NS) provides the primary guidelines for this application. Hyperlinks to relevant chapters are included throughout the application.

8. Other national guidelines can be found at the HREC - Useful Links page.

9. UNDA research policies can be found at the HREC - Policies and Guidelines page.

   In particular read Policy: Ethics Approval for Research Involving Humans and Guideline: Applying for Ethics Approval (Full Ethical Review).

10. If you already have HREC approval from another institution, you may be eligible for "Cross Institutional Recognition". Contact the Research Ethics Officer for more information.

11. Your completed application must be submitted to your School Research Committee (SRC) for review, together with all attachments. The SRC will forward your application to the Research Office for a full ethical review by the HREC.

12. RESEARCH MUST NOT COMMENCE UNTIL WRITTEN APPROVAL HAS BEEN PROVIDED BY THE HREC.

13. The HREC will not grant retrospective ethics approval.

Application for Full Ethical Review of a Research Project involving Human Participants

HREC Reference Number *(Research Office use only)*

1. Project Title:

Trachoma control in Burundi: Understanding the importance of environmental determinants of infection

2. **Project Type:** (Type X to options that apply)

X Student Research Project
PhD Honours
X Masters Postgraduate Diploma
Other

X Staff Research Project

3.

1.3 Expected commencement date for data collection: November 2017

Estimated project completion date: January 2018

1.4 School / Institute:	School of Medicine, Sydney

1.5 Research Team Details

a) Chief Investigator / Supervisor: *[must be UNDA staff member with ultimate responsibility for the research]*

Name	DR EDWARD WATERS		
Mailing Address	School of Medicine, 160 Oxford St Darlinghurst 2010		
UNDA Email	edward.waters@nd.edu.au	**Phone**	0425567655
Describe what this researcher will do in the context of this project.	The supervision of the research, with input into and approval of the research methodology, data collection and data analyses, co-authorship of journal articles. Mentoring the student and the team in the field during the data collection.		
Describe the relevant experience this researcher has specific to this project.	10 years of experience in utilizing and designing sampling programs and surveys, including design, implementation of, and analysis of sampling programs and surveys in low resource settings (Papua New Guinea, People's Democratic Republic of North Korea). >22 published journal articles, roughly half of these using sequential sampling or survey based methodologies.		

b) Student:

Title and Name	DESIRE NDISABIYE		
Mailing Address	School of Medicine, 160 Oxford St Darlinghurst NSW 2010		
Email	desire.ndisabiye1@my.nd.edu.au	**Phone**	0426903000
Describe what this researcher will do in the context of this project	Co-designer of sequential sampling plan. Coordination of field data collection, and analyzing these data to make inferences about the relative importance of environmental and vector-borne Trachoma transmission in Burundi.		
Describe the relevant experience this researcher has specific to this	7 years of experience as a medical practitioner in Burundi. Masters of Public Health and Environment (University of Nancy, France) Current Masters by research student		

c) Co-Investigator

Title and Name	Dr GAHUNGU Athanase		
Mailing Address			
Email	gathanase@ymail.com	**Phone**	+257 75 593 844
Describe what this researcher will do in the context of this project.	Coordinating all the activities, relating to the recruitment of the participants including: selection of the villages to be sampled, information of the participant and local authorities.		
Describe the relevant experience this researcher has specific to this project.	Dr Athanase GAHUNGU is the head of Gashoho health District, he is experienced in community communication and in the community health.		

d) Co-Investigator

Title and Name	Dr DONATIEN KAYUGI		
Mailing Address			
Email	drakayugi@yahoo.fr	**Phone**	+257 79 569 551
Describe what this researcher will do in the context of this project	Dr Donatien KAYUGI is from the National Integrated Neglected Tropical Diseases and Blindness Program of Burundi. He will coordinate all the activities on the field, including: sampling, treatment of positive cases, data entry.		
Describe the relevant experience this researcher has specific to this	Dr Donatien KAYUGI is the Assistant Coordinator of the National Integrated Neglected Tropical Diseases and Blindness Program of Burundi, he has been attending many conferences on Trachoma, among them, one in Sydney in May 2015.		

(Copy and paste boxes for additional researchers)

1.6 Use of Independent Contractors / Assistants

Will parts of this project be carried out by anyone not listed in the research team?

(e.g. participant recruitment, interviewing, questionnaire design, data analysis, sample testing etc)

X YES NO If YES, who is/are the independent contractor/s and describe what he/she will do in the context of this project.

[Ensure that any independent contractor/s will be engaged on the basis of relevant qualifications/experience and understands the requirements as outlined in the approved ethics protocol.]

Field data collection will be undertaken by the National Integrated Neglected Tropical Diseases and Blindness Program of Burundi. Co-investigators Dr Donatien Kayugi and Dr Athanase Gahungu will lead this work, and act as clinicians (for diagnosing the presence and stage of trachoma infection and prescribing antibiotic treatment where required). They will supervise a team of surveyors who will administer all parts of the paper survey except the clinical diagnosis, and computer data entry personnel, who will transcribe data from paper surveys to electronic form.

1.7 Research Project Location

a) Will the research project be undertaken on-site at The University of Notre Dame Australia?

YES X NO If NO, provide details of the off-campus location and its suitability for the purposes of this research.

The project will be carried out in the Gashoho Health District in Burundi, as the main purpose of the research project is to describe the dynamics of Trachoma in this country.

b) Is permission required to gain access to another location/organization/institute?

x YES NO If YES, specify from whom and attach a copy of the approval letter when available.

As the field work for this project will be coordinated in conjunction with a team from the National Integrated Neglected Tropical Diseases and Blindness Program carrying out its usual work in the Gashoho Health District, permission from these organizations is required and has been obtained. The research team has submitted the research proposal to the Research Committee of the National Integrated Neglected Tropical Diseases and Blindness Program and to the representatives of the Gashoho District. All of these organizations have reviewed the Project Proposal and provided the approvals attached.

c) Is this a multi-centre research project?

*[Refer to **NS 5.2.8**]*

(i.e. involving hospitals, in collaboration with researchers from other institutions, undertaken by new UNDA staff/student who have transferred with existing research projects etc.)

X YES NO If YES, provide details on all participating sites.

Gashoho Local Health District (Dr Athanase GAHUNGU), National Integrated Neglected Tropical Diseases and Blindness Program of Burundi (Dr Donatien KAYUGI).

1.8 Other HREC Approvals

*[Refer to **NS 5.2.8**]*

a) Does this project have approval by another HREC/s?	x	YES		NO
b) Will this project be submitted to another HREC/s for review?		YES	X	NO

If you answered YES to either, provide the name of the HREC/s, and indicate the status of the application at each (i.e. submitted, approved, deferred or rejected). Attach copies of any correspondence. Indicate which committee you consider to be the primary HREC for this project and why.

The program of research has already received ethical review by the National Integrated Neglected Tropical Diseases and Blindness Program of Burundi and from the Gashoho Health District (not Australian HRECs, but the local ethics governance structures).

1.9 Funding

[Refer to NS 5.2.7]

Is this research project being funded?

x YES NO If YES, provide details of amount and source of funds.

$4200 Australian dollars from a School Research grant from the School of Medicine, Sydney, at Notre Dame University.

1.10 Monitoring of Research Conduct

[Refer to NS Chapter 5.5 regarding researchers' responsibilities for monitoring of research projects.]

How will the Chief Investigator/Supervisor monitor the conduct of the research team to ensure that the research project complies with the protocol set out in this application, the University policy Code of Conduct for Research and the National Statement?

The local team of co-investigators, the lead investigator/ supervisor and the student will have regular phone/ Skype conversations to make sure that the research is being ran correctly as planned, and in accordance with section 5 of the National Statement on monitoring research projects. Any significant alterations to protocol or observed problems will be responded to by pausing data collection and reapplying to HREC.

2. Project Details

2.1 Keywords

Provide a list and definitions for any technical terms and acronyms which may assist the HREC to understand this application.

Term	Lay Explanation
Sequential sampling	Sequential sampling involves the iterative collection of sampling units, testing of a hypothesis. This allows sampling to be terminated immediately when the outcome of a hypothesis test is known with a desired degree of precision, minimizing the sample size collected.
Truncated Sequential Sampling (TSS)	Used to test the hypothesis of whether the prevalence of an infectious disease is low, medium or high at a single site.
Stratified Sequential Sampling (STSS)	An adaptation of TSS proposed for use at different sites that may have significantly different prevalence of some disease.
SAFE Strategy	World Health Organization (WHO) initiative for Trachoma elimination by 2020. Comprises the targeted delivery of Surgery, Antibiotics, Face washing and Environmental (SAFE) interventions.

2.2 Aims of and Justification for the Research Project

[*Refer to NS Section 1 , 5.2.5, 5.2.6]*

- **State clearly the aims and significance of the project.**
- **Where relevant, state the specific hypothesis or research questions.**
- **Provide a brief description of relevant background, current research/literature review and justification as to why this research is important.**

Blinding Trachoma is a communicable disease caused by the bacterium *Chlamydia trachomatis* and ranked among the WHO's National Integrated Neglected Tropical Disease and Blindness Program, signifying the need for further research. Initial infection with ocular *Chlamydia trachomatis* results in a self-limiting conjunctivitis, but repeated infection results in chronic inflammation, visually apparent as inflamed lymphoid follicles when the upper eyelid is lifted. After years of re-infection and inflammation, scarring of the conjunctiva occurs, which, as it progresses, can cause the eyelashes to turn inwards (Trichiasis) and scratch and damage the cornea, leading eventually to corneal opacity and blindness.

The **SAFE** strategy (**S**urgery for Trichiasis, **A**ntibiotics to treat *Chlamydia trachomatis* infection, **F**acial cleanliness, and **E**nvironmental improvement) was developed to reduce the transmission of *Chlamydia trachomatis* from one person to another, but has been implemented incompletely in many low resource settings. In Burundi and many other African countries, only the "Antibiotics" component of the SAFE strategy is employed, likely due to perceived higher compliance and the lower cost of this part of the strategy in the relevant communities. However, the effectiveness of this partial implementation of SAFE at reducing Trachoma has not been investigated in Burundi. The current prevalence of Trachoma and Trichiasis is unknown, nor is it apparent how much (if any) further reduction in prevalence could be gained by fully implementing the strategy. Implications for antibiotic resistance have also not been addressed. The current MSc project will investigate these issues, and will provide recommendations for policy and practice improvements in the field.

The Aims of the Masters project are:

1. to evaluate the efficacy of a Trachoma control program using only the Antibiotics component of the SAFE strategy, compared to the full SAFE program, using field data and computer simulation;

2. to recommend improvements to policy and practice to improve the efficacy of Trachoma control in settings that only partially implement the SAFE strategy.

3. to quantify the morbidity associated with blinding Trachoma in Burundi, and its prevalence. Whilst assumed to be in line with other similar African countries, no current country specific data exist.

The Burundi government has expressed interest in utilizing the results of the research project to inform policy and practice, as our study is the first that is specific to the situation in Burundi. The collection of field data in Burundi gives the project a high level of credibility in the eyes of the community it serves, and will assist in translating the results of the research project into policy and practice in a way that will have a significant impact on health in an under-served and disadvantaged population.

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2.3 Research Project Design and Methodology

[*Refer to NS Section 3 on Ethical considerations specific to research methods.]*

a) What data collection technique/s will be used? *[Type X to all options that apply]*

Questionnaire/s	x
Interview/s and/or focus group/s *(NS 3.1)*	
Observation of participants *(NS 3.1)*	
Audio- and/or video-taping participants	
Information sourced from a databank *(NS 3.2)*	

Medical, physiological and/or psychological testing *(NS 3.3)* ***See Q 2.4***	x
Collection of and/or or use of human biospecimen/s (e.g. cells, blood, saliva) ***See Q 2.4*** *(NS 3.4)*	
Collection of and/or use of genetic material *(NS 3.5)*	
Other (*provide details below in b*)	

b) Clearly describe the proposed research project design and methodology.

- **Describe the procedures/tasks which participants will be asked to take part in step-by-step.**
- **If sourcing data from a databank, describe the data that will be collected and used for this project.**
- **Outline how the data will be analysed.**

Survey sites

A cluster sampling methodology will be employed, so that the variability in the prevalence of Trachoma and risk factors in different areas of Burundi can be estimated. We aim to:

- Survey two villages in each of two districts (four villages total)
- Collect 50 survey forms in each village (no more than one survey per household)

These numbers were calculated using the method of Walter et al. (1998) (further details of this power calculation provided in section 3c below)

Clinical examination and participant recruitment

In each village, the clinical investigators will set up a clinic to offer Trachoma screening (and treatment if necessary). The setting up of the clinic is part of the normal work of the clinical investigators in their roles in the National Integrated Neglected Tropical Diseases Blindness Program's and Health District's Trachoma control initiative.

Routine clinical examination for Trachoma or Trichiasis will be offered in the clinic to all members of each village as part of the normal work of Trachoma control. Members of the village found to be infected with Trachoma will be prescribed antibiotics, and those with Trichiasis will be referred for surgery (the clinical investigators from the Program and Health District are not surgeons). Community members will be informed of the location of the clinic by the local town crier/ drum man, which is a common means of transmitting messages in African communities that do not have universal radio, television, internet or newspaper access (Ugboajah 1982; Wilson 1989).

All adults who attend the clinic will be invited to complete the survey. Due to this recruitment method, it is possible that either more or less people in each village than the nominal required sample size of 50 per village will wish to participate. If less than 50 but more than 46 wish to participate, this will not affect our statistical power, as we have already incorporated a buffer as previously described. If less than 46 participate, resampling will be conducted, by enlisting the town crier to broadcast the need for further participants. Participants recruited via resampling will be appropriately weighted in data analysis to account for a different probability of inclusion in the sample (see data analysis section below). If more than 50 wish to participate, we will allow this, as this will improve our power (make it higher by increasing total sample size). We are satisfied that be these methods, we should achieve our required number of participants for statistical validity.

Modifications to the recruitment process for illiterate participants

Some potential participants will not be able to read or write, so for these participants a modified procedure for obtaining informed consent will be employed. When inviting these individuals to participate, one of the clinical investigators (Dr Kayugi or Dr Gahungu) will read verbatim the participant information form to them. If the person wishes to participate, the consent form will also be read to them verbatim. If the person still wishes to join the study, an ink finger print will be used to sign the consent form in lieu of a signature. Once the investigator has obtained informed consent, they will record the Trachoma status of the household

members on the survey form. Another member of the survey team will ask the participant the remaining questions and record their responses.

Survey design

The survey comprises two parts. Firstly, some minimal demographic information will be collected: the gender and age of the respondent, the number of people in their house-hold and their genders and ages, and the number of these confirmed as having Trachoma or Trichaisis blindness by the clinical investigators, Dr Kayugi and Dr Gahungu. Secondly, information about the household's face washing and environment (the F and E component of the SAFE strategy) will be collected to determine whether known risk factors for Trachoma are present. Taken together, these two parts of the survey will enable the investigators to:

1. Estimate the prevalence of Trachoma and Trichiasis across the survey sites and thence for Burundi as a whole
2. Estimate the prevalence of environmental risk factors for Trachoma and face-washing in Burundian households, and the association of these risk factors with disease

The estimate of prevalence (point 1 above) will be particularly robust as the cluster sampling procedure described above will allow researchers to estimate not only the variance in Trachoma prevalence within villages but between villages and districts, giving an estimate of how prevalence will be distributed at the country level.

The estimated prevalence of risk factors (point 2 above) will allow the investigators to determine how much Trachoma prevalence could be reduced by full implementation of the SAFE strategy, focusing on the F (face-washing) and E (environmental improvement) components.

Data analysis

Prevalence will be estimated using the methods of Clark and Steel (2007). Associations between face-washing and environmental risk-factors and trachoma infection status will be determined using hierarchical logistic regression, with random effects to account for variance between households and districts. The nlme package in R will be used to fit the models. Associations will be considered statistically significant at the $p<0.05$ level.

2.4 Clinical, Health and Epidemiological Research

[Refer to NS Chapter 3.3 regarding Interventions and therapies.]

a) Will the research project involve non-treatment or placebo control conditions? *[Refer to NS 3.3.10]*

YES x NO If YES, provide details below.

b) Will the research project include any interventions and/or therapies, including non-clinical trials and innovations? *[Refer to NS 3.3]*

YES NO X If YES, provide details below.

Participants will be recruited from individuals who are receiving Trachoma screening (via physical examination) and treatment (antibiotics, or referral for surgery) as part of a clinic set up by the National Integrated Neglected Tropical Diseases and Blindness Program and Health District. Whilst participation in the research project is voluntary and separate from this clinic (treatment and screening are offered to all, whether they participate in the survey or not), due to the close alignment of the activities (research project and the clinical work of the investigators) we acknowledge the risk that some participants may perceive that completion of the survey is connected to receiving treatment or screening. To minimize this risk, investigators will start by screening and administrating treatment for Trachoma before any activities related properly to the current survey.

c) Is this research project a clinical trial? *[Refer to NS 3.3]*

YES	NO X	If YES, Clinical trials must be registered in a publically accessible register (NS 3.3.12) such as the Australian New Zealand Clinical Trials registry and ClinicalTrials.gov. Provide registration details below.

d) Will the research project involve the collection and/or use of human biospecimens? *[Refer to NS 3.4]*

YES	x NO	If YES, complete Appendix A and attach to this application.

e) Will the research involve the extraction and/or use of human genetic material? *[Refer to NS 3.5]*

YES	NO x	If YES, complete Appendix A and attach to this application.

f) Will the research involve administering chemical compounds, drugs or biological agents or use of devices already registered on the Australian Register of Therapeutic Goods (ARTG)?

[Refer to Therapeutic Goods Administration.]

YES	x NO	If YES, provide details below and attach a copy of the product information provided by the TGA.

g) Will the research involve administering chemical compounds, drugs or biological agents or use of devices not registered on the Australian Register of Therapeutic Goods (ARTG)?

YES	NO x	If YES, provide details below and refer to the TGA website for information regarding the Clinical Trial Exemption (CTX) and Clinical Trial Notification (CTN) schemes.

h) Will the research involve use of ionising radiation e.g. X-Rays?

YES x NO If YES, provide details below and attach a copy of the radiation dose and risk assessment by the Radiation Safety Officer.

i) Will the research involve any other physically invasive procedures?

YES NO X If YES, provide details below.

3. Participant Details and Recruitment Strategy

*[Refer to **NS Section 4** on Ethical consideration specific to participants.]*

3.1 Target Participant Group

a) Indicate the targeted participant group (Type X to all options that apply)

(*Expand any responses as necessary in the space provided at b)*

i. Students or staff of this University	
ii. Adults (over the age of 18 years and competent to give consent)	x
iii. Women who are pregnant (NS 4.1) DO WE NEED TO INCLUDE WOMEN WHO ARE PREGANT?	
iv. Children/legal minors (anyone under the age of 18 years) (NS 4.2) [1]	
v. People in dependent or unequal relationships (NS 4.3)	
vi. People highly dependent on medical care (NS 4.4)	
vii. People whose primary language is other than English (NS 5.2.16)	X
viii. People with a cognitive impairment, an intellectual disability or mental illness (NS 4.5)	
ix. People who are pensioners or welfare recipients	
x. People with a physical disability	
xi. People who may be involved in illegal activities (NS 4.6)	

xii. People who are incapable of providing informed consent (NS 2.2.12)	
xiii. Aboriginal and/or Torres Strait Islander people and/or communities (NS 4.7) [2]	
xiv. People in other countries (NS 4.8)	X
xv. People identifiable by their membership of a cultural, ethnic or minority group	
Other *[Provide details below in b]*	

[1] Adults in any employment involving direct contact with children are subject to the Child Protection Legislation and Working with Children Check relevant to the jurisdiction of the State in which the research will be carried out. (WA, NSW)

Attach a copy of a WWCC for all researchers directly interacting with children under the age of 18 years in this project.

For more information on ethical conduct when researching about children, go to Child Ethics.

[2] Research affecting the health and wellbeing of Aboriginal people and communities must have approval from the relevant HREC in your state **(WAAHEC, AH&MRC**). For more information on ethical conduct when researching about Aboriginal people go to **AIATSIS**.

b) Provide details of your participant group including number required, age range and source.

If sourcing data from a databank, describe the participants, whose data will be used for this project.

[If you ticked iv in a), provide details about the awareness and comprehension levels of the participants and how parents will be involved.]

[If you ticked xiii, xiv and/or xv in a), provide details about how cultural sensitivities will be considered and how opinions, expectations and the effects of the research on the participants and their communities will be taken into account.]

All participants will be adults over the age of 18 living in households in one of the four surveyed villages. They will be citizens of Burundi; whose official language is French and whose native language is Kirundi. Three members of the research team are native Burundians and fluent in both French and Kirundi. Copies of the survey form will be provided in French and Kirundi for use in the field, as well as in English for review by HREC.

Each completed survey form will contain details about one household, and be completed by one or more adult members of the household. If multiple adults attend the clinic together and agree to participate, separate consent forms will be taken, even though they complete only one survey for their household. Names of household members will not be recorded and surveys will be de-identified when entered into electronic format.

The Trachoma status of household members will be ascertained during clinical examinations carried out in the National Integrated Neglected Tropical Diseases Blindness Program clinic.

Only adults who give informed consent will have their Trachoma infection status recorded on the survey form.

No minor children will be participants, but the Trachoma status of all members of the household (some of whom may be minors) will be recorded on the survey form. Permission from an adult (a parent of carer) will be sought before recording the Trachoma infection status of children who live in the household on the survey form.

c) Provide justification for the number of participants you intend to recruit.

If sourcing data from a databank, provide a number of records/files you will need in order to achieve your aims.

[Refer to the NS Chapter 1.1 on Research Merit and Integrity and 5.2.5, 5.2.6]

For qualitative studies: Justification can include optimum size for focus groups, accepted norms of a field, recruitment of an entire cohort, number of interviews likely to lead to saturation etc.

For quantitative studies: Justification of sample size is usually based on a power calculation. (Consult a statistician if unsure or use an online sample size calculator e.g. http://powerandsamplesize.com/)

Sample size estimation and power calculation for household studies using cluster samples are complex and a range of formulas and methods are available. We calculated sample size using the method of Walter et al. (1998). According to this method, for a power of 0.8 at a significance level of 0.05, we need to collect 46 surveys to per village for a total sample size across four villages of 183. However, in order to account for the possibility that some villages might supply less than 46 participants, negatively affecting power, we added a buffer to our total sample size of 50 per village, or 200 surveys in total, to retain power if numbers between villages are unequal.

3.2 Community Engagement

*[Refer to the 2.2.13 where others need to be involved in participation decisions and NHMRC **Model Framework for Consumer and Community Participation in Health and medical Research** and NS 4.2.3, 4.7.10*

Have you consulted with the community/group or a representative of the community/group to which the research outcomes pertain?

(e.g school principal, school teachers/parents, Aboriginal elder, Aboriginal advisory group, CEO of a community support group etc.)

YES X	NO	If Yes, describe this consultation and provide a copy of a support letter from the relevant community/group leader.

Letters of approval from community organizations are attached.

3.3 Dependent/Unequal Relationships

*[Refer to **NS Chapter 4.3** on people in dependent or unequal relationships.]*

Are any of the participants in a dependent or unequal relationship with any of the researchers named in this application? (e.g. teacher/student, doctor/patient, lecturer/student, counsellor/client)

YES	If Yes, explain the dependent/unequal relationship and the steps to be taken by the researchers to ensure that participation is purely voluntary and not adversely affected by the relationship.

The clinical examination of participants will be conducted by the two medical doctors who are also named researchers. Whilst participation in the project is purely voluntary and will not affect the provision of medical treatment by the clinicians, it is noted that the context in which participant recruitment is carried out (Trachoma clinic of the National Integrated Neglected Tropical Diseases and Blindness Program) may give the impression that reception of free medical treatment is linked to participating in the project. To minimize this risk, we have emphasized in the participant information sheet the separation between these activities, and that participants will be able to access free medical services and treatment whether or not they complete a survey.

3.4 Participant Recruitment

a) Indicate the method of recruitment (Type X to all options that apply)

Mail out	
Advertisement e.g. poster, flyers, online, newspapers	
Email	
Telephone	
Social media e.g. Facebook	
Participants from a previous study	
Contact details obtained from public documents e.g phone book	
Contact details obtained from private sources e.g employee list, membership database	
Recruitment carried out by researcher/s	
Recruitment carried out by third party e.g employer, doctor, sponsor	
Snowball i.e. participants suggest other potential participants	
Advertisement through a local community advertiser	x

b) Provide details of recruitment strategies

*[Refer to NS **Section 3.3.6** and relevant Chapters in **Section 4**.]*

Explain step by step how participants will be invited to participate and by who.

Attach a copy of your advertisement, flyer, letter, email etc. to the application.

As described above, the setting up of the Neglected Integrated Tropical Disease and blindness Program Clinic in each village will be announced by the local town crier/ drum man. The town crier/ drum man will walk all the way around the village at approximately 5:00 AM on each day the clinic is operating, beating his drum and announcing that “There is a team from Bujumbura that is examining eyes, anyone wanting to get examined is welcomed to the Clinic”. Individuals who attend the clinic will be invited to complete the survey by the clinical investigators, as described above.

3.5 Payment or Incentives offered to Participants

*[Refer to **NS 2.2.10 and 2.2.11** on reimbursing participants]*

Do you propose to pay, reimburse or reward participants?

YES NO X If Yes, how, how much and for what purpose? Please justify the approach below.

4. Risk and Risk Management

*[Refer to **NS Chapter 2.1** regarding risk and benefit.]*

4.1 Risk Profile

Does the research project involve procedure/s that may cause any of the following harms in your participants and/or others? [Type X to all options that apply].

Physical harm e.g. injury, illness, pain, side-effects etc.	
Psychological harm e.g. anxiety, emotional distress, diminished self-esteem, embarrassment, shame, regret etc.	
Social harms e.g. damage to social networks or relationships with others, discrimination in access to benefits, services, employment or insurance, social stigmatization etc.	
Economic harms e.g. direct or indirect cost of participation.	
Legal harms e.g. discovery and/or prosecution of criminal conduct	

4.2 Potential Risks to Participants

List, as far as possible (even if unlikely) all potential risks to participants (or others associated with the project) and the setting in which the project is conducted.

Trachoma is an infectious disease. Whilst all possible infection control measures will be taken to avoid the spread of infection between infected and uninfected study participants, a theoretical possibility of transmission whilst attending the Clinic in which the project is set remains.

It is theoretically possible that the Trachoma status of an individual could be disclosed to someone who is not aware of it during this project, for example, a member of one household may read or overhear the survey of another.

4.3 Managing Potential Risks

Describe what measures you have in place to

a) Minimize each of the identified potential risks to participants and

b) Manage any harms or adverse effect a participant may experience arising from their involvement in the project.

The risk of transferring trachoma infection between participants during examination or attendance in the Clinic will be minimized by appropriate infection control procedures, specifically:

- The use of new gloves for the clinical examination of each participant.
- Washing hands between each clinical examination
- The use of disposable instruments where these are required
- Safe disposal of all consumables (cotton wool, gloves, instruments etc.) in a receptacle for potentially contaminated clinical waste

The risk of inadvertent disclosure of Trachoma status will be minimized by conducting surveys in a private location, and secure storage of survey forms.

4.4 Benefits versus Potential Risks

Outline the benefits of the study to the community (and participants, if applicable), relative to the potential risks to participants.

At the level of the community and more broadly, the benefits of the research are:
1. better understanding of the factors promoting the spread of trachoma in the community
2. More efficient surveillance mechanisms
3. Recommendations for limiting the spread of the trachoma

At the level of the individual, the risks of participating are:
1. Contracting Trachoma
2. Having their Trachoma status become known to another individual in the community

To appreciate the magnitude of these risks vs benefits in the local context, it should be noted that the study is being conducted in small, tightly knit communities where there is endemic spread of Trachoma in the community setting. Furthermore, Trachoma can present with obvious physical symptoms. Therefore, the risk of both transmission and knowledge of an individual's Trachoma status are more likely to occur as a natural consequence of living in the setting than they are in the context of the study.

Furthermore, it is important in understanding the risks vs benefits to note that Trachoma is not a disease to which shame or stigma is attached (unlike, for example HIV).

On balance, we feel the benefits of the study far outweigh the risks.

4.5 Potential Risks to Researchers

Outline any significant risks to researchers associated with the project and the setting in which the project is conducted and explain how these risks can be minimized and managed should they occur.

(e.g. personal safety overseas, in-home visits, travelling to rural areas or needle injury, exposure to bio specimens etc.)

It is theoretically possible that clinical investigators could accidently touch the eye secretions of participant, and then infect themselves if they do not adhere to proper clinical infection control procedures, for example, by not washing their hands and then touching their own eyes. However, the examiners are all experienced clinicians who understand infection control, so this risk is practically zero.

5. Information for Participants and Participation Consent

[Refer to NS Chapter 2.2 regarding general requirements for consent and 5.2.16 regarding participants' interests.]

5.1 Information for Participants

a) Will you be providing participants with information in a written Participant Information Sheet?

X YES NO If No, provide details of the protocol you will use to explain the research project to participants and invite their participation?

However, some potential participants may not be able to read and/ or write. In this case, the researcher, will read the information sheet and consent form to the participant verbatim. If the participant agrees to participate, she/he will give her/his signature via a finger print as described above. A member of the field team will read to the participant the questions of the questionnaire verbatim and record their answers verbatim.

b) Will arrangements be made to ensure that participants who have difficulty understanding English can comprehend the information provided about the research project?

YES X NO If Yes, what arrangements have been made? If No, provide reasons.

The questionnaire and the consent form will be translated into French and in Kirundi

5.2 Participant Information Sheet

(Please use the UNDA participant information sheet template located at http://www.nd.edu.au/research/hrec/apply.shtml)

Not Applicable

Confirm that the Participant Information Sheet will include: [Type X to all that apply]

The University of Notre Dame Australia logo / letterhead	X
A short project title and details of the research aims	X
Names, contact details and school affiliation for all researchers involved	X
Study level if it is a student research project	X
An explanation of what each participant is expected to do and an estimate of the time commitment involved	X
An acknowledgement of any audio-recording, video-recording or photographs and how this material will be used	X
Objective description of any risks involved and the procedures in place to minimise and manage these	X
An explanation of arrangements for the protection of confidentiality of data, who will have access to the data and a statement that confidentiality of information provided is subject to legal limitations (see * below)	X
A clear statement that if participants are in a dependent/unequal relationship with any of the researchers, involvement in the project will not affect ongoing assessment/grades/ management or treatment of health	X
A clear statement that participation in the project is voluntary and that participants are free to withdraw consent at any time, and to withdraw any unprocessed data previously supplied	X
Any plans to make the data available (in non-identifiable form) to other researchers for future research	X
An acknowledgement of any sources of funding for the research	X
State that the project has received ethical clearance by the UNDA HREC and approval reference number	X
A footnote explaining complaints procedures as follows*; If participants have any complaint regarding the manner in which a research project is conducted, it should be directed to the Executive Officer of the Human Research Ethics Committee, Research Office, The University of Notre Dame Australia, PO Box 1225 Fremantle WA 6959, phone (08) 9433 0943, research@nd.edu.au*	X

[* – it is possible for data to be subject to subpoena, freedom of information request or legal reporting obligations. Depending on the research proposal you may need to specifically state these limitations on confidentiality]

PLEASE ATTACH A COPY OF THE PARTICIPANT INFORMATION SHEET TO YOUR APPLICATION

5.3 Obtaining Participant Consent

a) How will each participant's consent be established? [Type X to all options that apply]

Signing and returning a Consent Form	X	Returning an anonymous survey	
Verbal agreement		Waiver of consent	
Recorded agreement		Opt-out	
By a person with lawful authority to consent (e.g.parent/guardian)		Finger print	x

b) If participants are unable to give informed consent, explain who will consent on their behalf and how such consent will be obtained and recorded. (NS 2.2.12, 4.4, 4.5)

No minor children will be participants, but the Trachoma status of all members of the household (some of whom may be minors) will be recorded on the survey form. Permission from an adult (a parent of carer) will be sought before recording the Trachoma infection status of children who live in the household on the survey form.

c) If you are using an opt-out approach, please justify why according to <u>each condition outlined</u> in NS Sections 2.3.6 – 2.3.8.

d) If you are seeking a waiver of consent, please justify why according to <u>each condition outlined</u> in NS Sections 2.3.10 and 2.3.11.

(Use of identifiable patient data from hospitals or clinic databases without patient consent requires justification for a consent waiver.)

5.4 <u>Deception or Concealment</u>

*[Refer to **National Statement Section 2.3.1 – 2.3.5** regarding limited disclosure.]*

Will the true purpose of the research, or the collection of data itself, be concealed from participants or will participants in any way be deceived?

YES x NO

If you answered YES, provide a clear justification. You will also need to provide participants with details of the deception in a debriefing and give them the opportunity to withdraw their data if they wish to do so.

5.5 Consent Form

(Please use a UNDA Consent form template found at http://www.nd.edu.au/research/hrec/apply.shtml)

Not Applicable

Confirm that the Consent Form will include: [Type X to all that apply]

The University of Notre Dame Australia logo / letterhead	x
Include the title of the project and names of researchers	x
State that the project is for research purposes	X
State that involvement in the project is voluntary and that participants are free to withdraw at any time and free to withdraw any unprocessed identifiable data previously supplied.	X
Outline particular requirements of participants (e.g whether interviews are to be audio and/or video-taped).	X
Include arrangements to protect the confidentiality of data	X
Include advice that there are legal limitations to data confidentiality (see * below)	X
If the sample size is small confirm that this may have implications for protecting the identity of the participants	N/A
Any plans to make the data available (in non-identifiable form) to other researchers for future research	N/A
Be retained by the researcher (once signed and returned)	X

[* – it is possible for data to be subject to subpoena, freedom of information request or legal reporting obligations. Depending on the research proposal you may need to specifically state and explain these limitations on confidentiality]

PLEASE ATTACH A COPY OF THE CONSENT FORM TO YOUR APPLICATION

6. Privacy, Data Management & Dissemination of Research Outcomes

6.1 Federal Privacy Legislation

This section applies to medical research that involves access to personal information held by agencies where identified information needs to be used without consent from the individual/s involved. Refer to Guidelines approved under Section 95A of the Privacy Act 1988

	Yes	No
a) Is this project medical or health research (including epidemiological research)?	Y	
If Yes, will you require the use or disclosure of information from a Commonwealth agency?		N
If Yes, will the information be identifiable?		N
If Yes, will you be obtaining consent from the individuals to whom the information relates?	Y	

b) Is this research relevant to public health or safety or to the management, funding or monitoring of a health service? Y

If Yes, does the research involve the collection, use or disclosure of information from a private sector organisation? N

If Yes, will you be collecting, using or disclosing health information? Y

If Yes, will consent be obtained from the individuals to whom the health information relates? Y

If you answered YES to collecting identifiable information and NO to obtaining consent, complete *Appendix B* and attach to this application.

c) If you answered Yes to collecting personal health information, outline exactly what information will be sought and the number of records to be accessed.

The Trachoma status of individuals will be determined during clinical examination in the National Integrated Neglected Tropical Disease and Blindness Program Clinics.

(d) If you are not seeking consent from individuals to use their identifiable health information, justify why identifiable information is necessary and why written consent will not be obtained from individual participants.

6.2 Data Storage and Security

*[Refer to Chapter 2 of the **Australian Code for the Responsible Conduct of Research** and University policy '**Code of conduct for research'**]*

There is no name on the questionnaire (survey form).
The name is only on the consent form.

a) How will the identity of participants be protected during the research project and dissemination of project outcomes?

b) How and where will data be stored securely during the research project?

As the field work will be made by the staff members of the National Integrated Neglected Tropical Disease and Blindness Program, the physical copies of the surveys will be stored in the same way they store other data, i.e. in locked cabinets for five years. The electronic data (survey results entered into a spreadsheet) will be held both IN Burundi and locally at The Unviersity of Notre Dame Australia on password protected computers and in password protected files, for a period of five years.

c) How and where will the data be stored <u>following completion</u> of the research project? Will any identifiable data be stored?

The only identifiable materiel is the consent form, otherwise, no one will be capable to recognize which survey form belongs to which participant.

d) Will the data be used for future research or potentially be made available to other researchers?

YES x NO If Yes, describe what data and what consideration has been given to participant consent.

e) How long will the data collected during the research project be retained after the research project?

The data will be kept securely for five years in accordance with regulations.

6.3 <u>Dissemination of Research Project Outcomes</u>

a) How will the research project outcomes be disseminated at the end of the project?

[E.g. thesis, journal article, book, web page, conference paper, the media etc.]

[Refer to Chapter 4 of the Australian Code for the Responsible Conduct of Research and University policy 'Code of conduct for research']

The research outcomes will be disseminated as a thesis and journal article at the end of study period of the student.

b) What feedback will be provided to the participants and how will this feedback be given?

[*Refer to **NS 1.5**]*

The results of the project will be communicated back to participants in community meetings and presentations by the National Integrated Neglected Tropical Diseases and Blindness Program.

7. Conflict of Interest & Other Ethical Considerations

*[Refer to **NS Chapter 5.4** regarding conflicts of interest and university policy '**Code of Conduct for Research**'.]*

7.1 <u>Potential Conflict of Interest</u>

Is there any affiliation or financial interest for researchers in this research project or its outcomes or any circumstances which might represent a perceived, potential or actual conflict of interest?

YES x NO If Yes, give details below and explain how your participants will be informed of the conflict of interest.

7.2 Other Ethical Issues

Are there any further ethical considerations relevant to this research project and the researchers involved?

YES x NO If Yes, provide details below.

8. Declaration by the Research Team

The information contained herein is, to the best of my/our knowledge and belief, accurate.

I/We apply for approval to conduct the research. If approval is granted, it will be undertaken in accordance with this application and the *National Statement on Ethical Conduct in Human Research, The University of Notre Dame Australia's policies and guidelines* and the *Australian Code for the Responsible Conduct of Research*.

All researchers listed section 1 must sign this declaration:

Name of Researcher	**Signature of Researcher**	**Date**

9. Declaration by School Research Committee (SRC)

Applications not approved by the SRC will not be considered

The SRC has reviewed this project and considers the methodological/technical and ethical aspects of the proposal to be appropriate to the tasks proposed.

YES NO

The SRC considers that the researcher has the necessary qualifications, experience and facilities to conduct the research set out in the attached application, and will be able to deal with any emergencies and contingencies that may arise.

YES NO

SRC Comments/Provisos:

Name of SRC Chair	
Signature	
Date	

Note: If the SRC Chair is also a named researcher on this project, the declaration must be signed by another authorised member of the SRC.

The SRC must forward the original application, including attachments to the Research Ethics Officer for assessment by the HREC.

10. Checklist

Please check that the following documents are attached to your application.

(Please note that where questionnaire or interview questions are submitted in draft form, a copy of the final documentation must be submitted for final approval when available)

Documents	Yes	Draft	Final	N/A
External approvals related to the research (Section 1.7)				
Approvals/Correspondence from other HREC/s (Section 1.8)				
Reference List (Section 2.2)				
Data Collection Tools (Section 2.3)				
Appendix A – human biospecimens (Section 2.4 d, e)				
Product Information from TGA (Section 2.4f)				
Radiation dose and risk assessment (Section 2.4g)				
Working with Children Check (Section 3.1iv)				
HREC approval from WAAHEC or AH&MRC (Section 3.1xiii)				
Community Engagement information (3.2)				
Recruitment advertisement, approvals (Section 3.4b)				
Debriefing Material (Section 5.4)				
Participant Information Sheet (PIS) (Section 5.2)				
Consent Form (Section 5.4)				
Appendix B – personal health information				

Appendix C

Ethics application – attached project proposal

MODELLING TRACHOMA IN AFRICA*: infection, transmission, and control. CASE STUDY OF BURUNDI, GASHOHO HEALTH DISTRICT.*

INVESTIGATORS:

INTERNAL: EDWARD WATERS (Lecturer), DESIRE NDISABIYE (MSc student)

EXTERNAL: DONATIEN KAYUGI, ATHANASE GAHUNGU

1. Background and rationale

Blinding Trachoma is a communicable disease ranked among the WHO's Neglected Tropical Disease (NTDs), signifying the need for further research. Initial infection with ocular *Chlamydia trachomatis* results in a self-limiting conjunctivitis, but repeated infection results in chronic inflammation, visually apparent as inflamed lymphoid follicles when the upper eyelid is averted. After years of re-infection and inflammation, scarring of the conjunctiva occurs, which, as it progresses, can cause the eyelashes to turn inwards (Trichiasis) and abrades the cornea, leading eventually to a corneal opacity and blindness.

The **SAFE** strategy (**S**urgery for Trichiasis, **A**ntibiotics to treat *Chlamydia trachomatis* infection, **F**acial cleanliness, and **E**nvironmental improvement) was developed to reduce the transmission of *Chlamydia trachomatis* from one person to another, but has been implemented incompletely in many low resource settings. In Burundi and other African countries, only the "Antibiotics" component of the SAFE strategy is employed, likely due to its perceived higher compliance and the lower cost of this strategy in the relevant communities. However, the effectiveness of this partial implementation of SAFE has not been investigated, nor is it apparent how much improvement could be gained by a full implementation of the strategy. Implications for antibiotic resistance have also not been addressed. The current MSc project will investigate these issues from a modelling perspective, and will provide recommendations for policy and practice improvements in the field, however, at present, these will only be based on data that is freely available and not specific to the situation in Burundi. The Burundi government has expressed interest in utilising the results of the research project to inform policy and practice, provided the results of the modelling can be demonstrated to be relevant to the specific situation in Burundi. The collection of field data could make the model much better calibrated to the specific situation in Burundi, and assist in translating the results of the research project into policy and practice in a way that will have a significant impact on health in an under-served and disadvantaged population.

2 The Aims

The Aims of the existing MSc project are:

1) develop and validate optimal Trachoma surveillance strategies using computer simulation;

2) to evaluate the efficacy of a Trachoma control program using only the Antibiotics component of the SAFE strategy, compared to the full SAFE program, using a new mathematical model;

3) if appropriate, to recommend improvements to policy and practice to improve the efficacy of Trachoma control in settings that only partially implement the SAFE strategy.

The incorporation of field research into the research program, which is dependent upon funds, would enable the following additional aims to be addressed:

4) to validate the newly developed surveillance strategies in the field as well as by using computer simulation

5) To optimize the recommendations arising from the mathematical modelling to the situation in Burundi by fitting the model to empirical data from the field.

6) to quantify the morbidity associated with blinding Trachoma in Burundi, and its prevalence. Whilst assumed to be in line with other similar African countries, no current country specific data exist.

3 Methods

a. Data collection

Data will be collected by officials from the Health District of Gashoho, using a Stratified form of Truncated Sequential Sampling(STSS). Non-stratified versions of truncated Sequential sampling (TSS) were previously developed and validated Waters et al. and Myatt and Bennett , but the STSS is a new method that has previously not been validated for use in the field.

TSS and STSS are sampling protocols designed to minimize sampling intensity by assessing whether the desired precision in a prevalence estimate has been attained after each data point is collected. Because of their emphasis on reducing the collected sample size whilst ensuring a desired precision is achieved, these methodologies are particularly well suited for use in low-resource settings where wasted sampling effort consumes costly resources.

The novel component of STSS is stratifying the population to which TSS sampling protocol is to be applied, in order to accurately estimate the different prevalences of Trachoma in different areas. STSS is a form of multi-stage sampling, which will 1) determine a number of villages (per council area – see below) to survey for Trachoma, then 2) apply TSS, to determine the number of people to sample within each village. Each person sampled will be

asked to complete an oral questionnaire (see below), which will collect information on their infection status with respect to Trachoma and their exposure to known risk factors.

The optimal number of villages (per council area) to be included in the survey can be estimated using computer simulation only (original MSc proposal), but additional confidence can be gained by field validation. A simple rule of thumb that has been used with two-stage lot quality assurance sampling (a method with some similarities to STSS) is four villages, but it is not clear whether this is optimal or merely convenient.

We propose to establish the optimal number of villages to survey in the Health District of Gashoho. Initially, four villages in Gashoho will be selected using simple random sampling (four villages overall, as per the rule of thumb), and Trachoma prevalence and risk factors will be assessed in each village by administering the survey. The between-villages variance in Trachoma prevalence will be calculated, and the optimal number of villages that would need to be sampled to ensure precision in the field estimated using the two-stage sampling stop line calculated by Kuno .

This field-work will be carried out by Public Health Officers from Burundi's NTD Program, led by a physician, in conjunction with local teams from the Health District of Gashoho led by the head of the District, will conduct the survey. The role of the research student will be to design the sampling methodology and the survey itself, to train the head of the field survey in STSS (training manuals and video conference), and subsequently to analyze the data. The student will not return to Burundi to collect the data himself. The head of the field survey team will be the physician from the NTD Program (Dr KAYUGI Donatien). Full ethics approval will be sought from the University of Notre Dame Australia and the Local Health District.

c. Data analysis

Simulation modelling will be used to characterize the error associated with the optimal number of villages surveyed. As described in (1,3), the optimal number of strata (villages) required to minimize the risk of underestimating Trachoma prevalence (a type II error or else negative) needs to be determined. In brief, 1,000 simulated populations with more and less than the optimal number of villages will be generated with different levels of variability in Trachoma prevalence between villages. Let P be the pair of values denoting the number of villages to be sampled in the first and second council districts. Latin hypercube sampling will be used to generate 500 sets of values of P. For each set of values for P, the STSS plan will be simulated 1,000 times on each of the 1,000 populations using three different nominal type II error levels, making 3,000,000 times 500 or 150 million simulated sampling events. The results of these simulated sampling events will be analyzed using R to determine the optimal number of villages to minimize the chance of making a type II error during sampling.

The survey will also collect data on risk factors for Trachoma. The association between risk factors and Trachoma prevalence in each village will be using multinomial logistic regression, with type of trachoma (none, TF, TI, TS, TT) as the response variable and village name; age; sex; other family members infected; latrine improvements; presence of garbage; presence of improved water sources; and distance of improved water sources as predictors. Initially, logistic regression models will be computed for each of the predictors combined with village name (to account for between groups variance). Significant predictors ($p<0.05$) in these models will be retained and combined into an overall model with multiple predictors.

Questionnaire

First, we would like to ask you some questions about yourself and your household.

What is your gender?

How old are you?

How many people live in your household?

How many of these are adults?

How many of these are children?

Please make sure the doctor completes the form on the back page.

Now, we will ask some questions to help us understand how we can help to control trachoma in your village.

Thinking about toilets, does your household use (tick all that apply):

Flush toilet
Piped sewer
Septic tank
Ventilated latrine pit latrine
Pit latrine with slab
A public or shared flush toilet
A pit latrine without a slab
Open defecation

Thinking about water, does your household get its water from (tick all that apply):

Piped water to the house
Piped water to the yard
A public tap or standpipe
A tube well or bore hole
A protected dug well
An unprotected dug well
A protected spring
An unprotected spring
Roof harvested rainwater
Surface water
River water
A cart with a tank
A tanker truck

Thinking now about Trachoma, consider your level of agreement with the following statements:

	Strongly agree	Agree	Don't know/ unsure	Disagree	Strongly disagree
It is very important to wash your face whenever it is dirty					
Open garbage is important in spreading trachoma					
I wash my kids' faces every day					

Sharing towels and pillows is not important in spreading trachoma					

Thinking about the most important thing in spreading trachoma, would it be?

Washing the face regularly	Sheep
Open garbage	Sharing towels and pillows
Flies	Using dirty water
Touching dogs and sheep	Eating unwashed fruit
Working without shoes	

Clinical information

Trachoma status of household members (completed by clinician):

Person	Adult/ child	Male/ female	Type of trachoma (TF, TI, TS, TT)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Appendix D

Ethics Approval Gashoho District

REPUBLIC OF BURUNDI

Muyinga, the 09./.7../2017

MINISTRY FOR INTERNAL AFFAIRS AND PATRIOTIC TRAINING

PERMISSION FOR THE FIELD WORK

The Gashoho and Gasorwe Commune Administrators, elected officials and representative of the people of their communities, have reviewed the research proposal of Ndisabiye Desire, Masters student at the University of Notre Dame Australia, entitled "Modelling Trachoma in Africa: Infection, Transmission and Control".

In addition to the research supervisor, Dr Edward Waters, also at Notre Dame, the project has two local co-investigators: Dr Athanase Gahungu from the Gashoho Local Health District and Dr Donatien Kayugi from the National Neglected Tropical Diseases Program.

This is to certify that the methodology, ethical aspects, and benefits of the proposed research program have been assessed by the Neglected Tropical Disease Program.

We certify that the proposed research project meets local ethical requirements pertaining to research projects led by students.

The potential benefits of the proposed research program are extensive, given the high morbidity associated with Trachoma in Burundi, and we are pleased for the research to be carried out.

We give the permission for this field work to be conducted in the area of the Gashoho Local Health District, so long as field work is supervised by National Tropical Disease Program physician Dr Donatien Kayugi or the Gashoho Local Health District chief Dr Athanase Gahungu.

THE GASHOHO COMMUNE

ADMISTRATOR

Désiré BIGIRIMANA

THE GASORWE COMMUNE
ADMISTRATOR

REPUBLIQUE DU BURUNDI
PROVINCE MUYINGA

Appendix E

Ethics Approval from The National Neglected Tropical Disease

REPUBLIC OF BURUNDI

Bujumbura, the ..8../..8.../2017

MINISTRY OF THE PUBLIC HEALTH
AND THE FIGHT AGAINST AIDS
GENERAL DIRECTION OF HEALTH SERVICES
AND THE FIGHT AGAINST AIDS
PROGRAMS AND PROJECTS OF HEALTH DIRECTION
NATIONAL INTEGRATED NEGLICTED TROPICAL
DISEASES AND BLINDNESS PROGRAM

REF: 633.2/58/PNIMTNC/2017

PERMISSION FOR THE FIELD WORK

The National Integrated Neglected Tropical Diseases and Blindness Program of Burundi has reviewed the research proposal of Ndisabiye Desire, Masters student at the University of Notre Dame Australia, entitled "Modelling Trachoma in Africa: Infection, Transmission and Control". In addition to the research supervisor, Dr Edward Waters, also at Notre Dame, the project has two local co-investigators: Dr Athanase Gahungu from the Gashoho Local Health District and Dr Donatien Kayugi from the National Neglected Tropical Diseases Program.
This is to certify that the methodology, ethical aspects, and benefits of the proposed research program have been assessed by the Neglected Tropical Disease Program.
We certify that the proposed research project meets local ethical requirements pertaining to research projects led by students.
The potential benefits of the proposed research program are extensive, given the high morbidity associated with Trachoma in Burundi, and we are pleased for the research to be carried out.
We give the permission for this field work to be conducted in the area of the Gashoho Local Health District, so long as field work is supervised by National Tropical Disease Program physician Dr Donatien Kayugi or the Gashoho Local Health District chief Dr Athanase Gahungu.

THE NATIONAL INTEGRATED NEGLICTED TROPICAL DISEASES AND BLINDNESS PROGRAM DIRECTOR

Dr Victor BUCUMI

TCI:
- Health Services and the Fight Against AIDS General Director
-Programs and Projects of Health Director

Appendix F

Notre Dame Ethics approval

THE UNIVERSITY OF NOTRE DAME AUSTRALIA

19 Mouat Street (PO Box 1225) Fremantle WA 6959
+61 8 9433 0555 | enquiries@nd.edu.au

16 November 2017

Dr Edward Waters & Mr Désiré Ndisabiye
School of Medicine
The University of Notre Dame Australia
P.O Box 944
Broadway NSW 2007

Dear Edward and Désiré,

Reference Number: 017167S

Project title: "Trachoma control in Burundi: Understanding the importance of environmental determinants of infection."

Your response to the conditions imposed by the university's Human Research Ethics Committee, has been reviewed and assessed as meeting all the requirements as outlined in the *National Statement on Ethical Conduct in Human Research* (2007, updated May 2015). I am pleased to advise that ethical clearance has been granted for this proposed study.

Other researchers identified as working on this project are:

Name	School/Centre	Role
Dr Gahungu Athanase	Gashoho Health District, Burundi	Co-Investigator
Dr Donatien Kayugi	National Integrated Neglected Tropical Diseases and Blindness Program of Burundi	Co-Investigator

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

On behalf of the Human Research Ethics Committee, I wish you well with your study.

Yours sincerely,

Dr Natalie Giles
Research Ethics Officer
Research Office

Cc: Prof George Mendz, SRC Chair, School of Medicine Sydney

Appendix G

Ethics application

PARTICIPANT INFORMATION SHEET

Modeling Trachoma in Africa: Infection, Transmission and Control: Case Study of Burundi, Gashoho Health District.

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?

The research project:

1) Will test new ways of collecting information on how many people have trachoma in Burundi;

2) Test whether Burundi's Trachoma control strategy is working;

3) Help us to understand how to control Trachoma Better in the future.

Who is undertaking the project?

This project is being coordinated by Désiré Ndisabiye, a Master of Sciences student at the University of Notre Dame Australia (UNDA). My supervisors are Dr Edward Waters from School of medicine, UNDA, along with Dr Donatien Kayugi from National Integrated Neglected Tropical Diseases and Blindness Program of Burundi and Dr Gahungu Athanese from Gashoho Health District.

What will I be asked to do?

If you consent to take part in this research study, you will be asked to answer survey questions about your family's experience of Trachoma and risk factors for this disease. Completion of the survey should take no more than 30 minutes.

Are there any risks associated with participating in this project?

We do not anticipate any risk to you in participating in this project. If you experience any anxiety or stress during the clinical examination or when answering the survey questions, please let us know and we can arrange for you to access support from the Gashoho Hospital.

What are the benefits of the research project?

This project has a number of benefits for your community, your family and yourself as an individual. It will help your community to better understand its experience of Trachoma infection, as well as evaluating current approaches to managing Trachoma, and suggesting improved strategies. At a more personal level, you and your family members will have the opportunity to receive a medical treatment for trachoma if, during participation in the project, you or your family members are found to be infected.

What if I change my mind?

Participation in this study is completely voluntary. Even if you agree to participate, you can withdraw from the study at any time without discrimination or prejudice. Withdrawal will not affect you or your family member's receipt of medical treatment (past or future) from the National Integrated Neglected Tropical Disease and Blindness Program clinic. If possible, your data will be deleted and excluded from the study at the time you withdraw. However, if you withdraw after your information has been de-identified, it will not be possible to exclude your data from the study at that stage.

Will anyone else know the results of the project?

Information gathered about you will be held in strict confidence. This confidence will only be broken if required by law. Survey responses will be de-identified; researchers at the University of Notre Dame Australia will not know who you are whilst analyzing the data. Once the study is completed, the data will be stored securely in the School of Medicine at The University of Notre Dame Australia, as well as by the National Integrated Neglected Tropical Disease and Blindness Program, for at least a period of five years. The results of the study may be published in academic journals or book chapters, and will form part of the Masters thesis submitted by Ndisabiye Desire.

The field work will be done by two physicians listed as investigators and other technicians from the National Integrated Neglected Tropical Disease and Blindness Program and Health District of Gashoho. During the Survey, we have explained that Trachoma is not a disease subject of discrimination like HIV or others, however, the clinic and the survey will be run in two different rooms by different investigators. The data will be collected, manipulated and kept in the same department in the National Integrated Neglected Tropical Disease and Blindness Program and in the Gashoho Health District.

Will I be able to find out the results of the project?

The National Integrated Neglected Tropical Disease and Blindness Program in Burundi will provide community leaders in each participating village with a summary of the findings. You can expect to receive this feedback in the middle of 2018.

Who do I contact if I have questions about the project?

If you have any questions about this project please feel free to contact me at desire.ndisabiye1@my.nd.edu.au. You can also contact my supervisors: Edward Waters at edward.waters@nd.edu.au, Dr Donatien Kayugi at drakayugi@yahoo.fr or +257 79 56 95 51 or Dr Athanase Gahungu at gathanase@ymail.com or +257 75 59 38 44. We are happy to discuss with you any concerns you may have about this study.

Also in Burundi, the following people are available to be contacted to answer any questions you have: Désiré Bigirimana (Administrator of Gashoho commune) +257 79 927 696 and Jean Claude Barutwanayo (Administrator of Gasorwe commune) +257 79 587 711.

What if I have a concern or complaint?

The study has been approved by the Human Research Ethics Committee at The University of Notre Dame Australia (approval number 017167S). If you have a concern or complaint regarding the ethical conduct of this research project and would like to speak to an independent person, please contact Notre Dame's Ethics Officer at (+61 8) 9433 0943 or research@nd.edu.au. Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

How do I sign up to participate?

If you are happy to participate, please sign both copies of the consent form, keep one for yourself and give the other copy to the field research team along with the survey form.

Thank you for your time. This sheet is for you to keep.

Yours sincerely,

Désiré Ndisabiye

Cher participant,

Vous êtes invité à participer au projet de recherche décrit ci-dessous.

De quoi parle le projet?

Le projet de recherche étudie [décris le projet, ses buts et objectifs, pourquoi il est /ou, devrait être important pour les participants et ce que vous espèrez réaliser.

Le projet de recherche

1) examinera les nouveax moyens de collect d'information sur le nombre de personnes porteur de trachome au Burundi.

2) examiner si la strategie de lute contre le trachome au Burundi fonctionne bien.

3) nous aider à comprendre comment on pourrait mieux contrôler le trachome dans l'avenir.

Qui entreprendront le projet?

Ce projet est coordonné par [DESIRE NDISABIYE], [MASTER OF SCIENCE] étudiant à l'Université de Notre Dame en Australie, sous la supervision du [DR EDWARD WATERS], ainsi que [Dr DONATIEN KAYUGI]. D'autres personnes sont egalement impliquées, tels que le Dr ATHANSE GAHUNGU ETC

Qu'est-ce qu'on attend de moi ?

Si vous consentez à participer à cette étude, vous devrez répondre aux questions des enquêteurs sur vous et l'expérience de votre famille en matière du trachome et de facteurs de risque pour cette maladie. La durée de l'enquête ne devrait pas dépasser 30 minutes.

Y a-t-il des risques associés à la participation à ce projet?

Choisis une option

Il est possible que vous puissiez vous sentir inconfortable ou mal à l'aise pendant l'examen clinique et / ou en répondant aux questions du sondage. Si ces sensations persistent même après la fin de la session, des dispositions seront prises pour que vous puissiez avoir accès aux services de l'hôpital de Gashoho.

Quels sont les avantages de ce projet de recherche?

Ce projet présente un certain nombre d'avantages pour votre communauté, votre famille et vous-même en tant qu'individu. Cela aidera votre communauté à mieux comprendre son expérience à l'infection par le Trachome, ainsi qu'à évaluer les approches actuelles de la gestion du Trachome et à proposer des stratégies pour les améliorées. À un niveau plus personnel, vous et les membres de votre famille auront la possibilité de bénéficier d'un traitement médical pour le Trachoma si, lors de la participation au projet, vous et/ou un de membres de votre la famille sont infectés.]

Et si je change d'avis?

La participation à cette étude est totalement volontaire. Même si vous acceptez de participer, vous pouvez vous retirer de l'étude à n'importe quel moment sans discrimination ni préjugé. Le retrait ne vous affectera ni à vous ni à aucun membre de votre famille par rapport au traitement médical gratuit (dans le passé ou dns l'avenir) de la clinique du Programme National Intégré pour les Maladies Tropicales Négligées et la cécité. Si possible, vos données seront supprimées et exclues de l'étude au moment de votre retrait. Toutefois, si vous vous retirez après que vos informations ont été déjà codées, il ne sera pas possible d'exclure vos données de l'étude à ce stade.

Est-ce que quelqu'un d'autre connaîtra les résultats du projet?

Les informations recueillies sur vous seront tenues en toute confidentialité. Cette confidence ne sera rompue que si la loi le requiert. Les réponses aux enquêtes seront désidentifiées; Les chercheurs de l'Université de Notre-Dame d'Australie ne sauraient pas savoir qui vous êtes en analysant les données. Une fois l'étude terminée, les données recueillies auprès de vous seront désidentifiées et stockées en toute sécurité à l'École de médecine de l'Université de Notre Dame en Australie, ainsi qu'au Programme National Intégré pour les Maladies Tropicales Négligées et la Cécité , pendant au moins cinq ans années. Les résultats de l'étude peuvent être publiés dans des revues académiques ou des chapitres de livres et feront partie de la thèse de Masters présentée par Ndisabiye Desire.

Le travail sur terrain sera executé par deux médecins qui sont sur la liste comme des co-chercheurs en collaborations avec les techniciens du Programme National Integré pour les Maladies Tropicales Negligées et la Cécité et du District Sanitaire de Gashoho. Pendant l'enquênte , comme nous l'avions expliqué, le Trachome n'est pas une maladie pourlaquelle on peut discriminer quelqu'un comme le VIH ou autre, néanmoins, les examens Clinique et l'enquête se derouleront dans deux pièces differentes par differents chercheurs. Les données seront collectées, manupulées et conservées dans le même service au Programme National Intégré pour les Maladies Topicales Negligées et la cécité dans le District Sanitaiere de Gashoho.

Pourrais-je connaître les résultats du projet?

Le Programme National Intégré pour les Maladies Tropicales Négligées et la Cécité du Burundi fournira aux leaders communautaires dans chaque village qui a participé un résumé des résultats. Vous pouvez vous attendre à recevoir ces resultats au milieu d'année 2018.

A qui dois-je contacter si j'ai des questions sur le projet?

Si vous avez des questions sur ce projet, n'hésitez pas à contacter moi-même [téléphone / courrier électronique] ou mon superviseur, ######, [téléphone / email] (ne pas donner votre contact personnel ou vos coordonnées personnelles). Mon superviseur et moi-même sommes heureux de discuter avec vous des préoccupations que vous pourriez avoir à propos de cette étude.

Et si j'ai des problèmes ou des plaintes?

L'étude a été approuvée par le Human Research Ethics Committee de l'Université Notre Dame en Australie (numéro d'homologation #######). Si vous avez une préoccupation ou une plainte concernant la conduite éthique de ce projet de recherche et souhaitez parler à une personne indépendante, veuillez vous addresser au responsable de l'éthique de Notre Dame au (+61 8) 9433 0943 ou à research@nd.edu.au. Toute plainte ou préoccupation sera traitée en toute confidence et entièrement étudiée. Vous serez informé du résultat.

Comment me faire enregistrer pour participer?

Si vous souhaitez de participer, signez les deux exemplaires du formulaire de consentement, conservez-le pour vous-même et donnez l'autre copie à l'équipe de recherche de terrain ainsi que le formulaire de sondage.

Merci pour votre temps. Cette feuille est à conserver.

Cordialement,

Désiré Ndisabiye

Ncuti,

Murasabwe kwitaba ubutumire mwa hahwe kuvyerekeye umugambi wubushakashatsi ukurikira.

Uyomugambi uvuga iki?

Uwo mugambi wubushakashatsi utegekanya,

1) Gutegura n'ukwemeza imigambi ngenderwako mugucungera ingwara itera uruhumyi Trachome.

2) Gusuzuma uburyo bukoreshwa mukurwanya indwara ya trachome mu Burundi

3) kurondera ibiharuro kuri iyo ndwara , bizodufasha kugwanye uyomugera muri kazoza.

Nibande bazorangura uyo mugambi?

Uyo mugambi uzokurikiranwa na [DESIRE NDISABIYE], [MASTER OF SCIENCE] umunyeshure kuri kaminuza Notre Dame muri Australiya, akurikiranwa na [DR EDWARD WATERS], na [Dr DONATIEN KAYUGI]. Hazoba harimwo n'abandi nka Dr ATHANSE GAHUNGU ETC

Munyitezeko iki ?

Ni mwemera ata gahato kuja muri kino cirwa, muzosabwa kwishura kubibazo vyabo bashakashatsi, kuco muzi ni co umuryango wanyu uzi kuvyerekeye trachome hamwe nibitera iyo ndwara ya trachome. Umwany bizotwara ntuzorenga iminota mirongo itatu.

Hari ingorane bitera kuwugiye muri uwomugambi?

Birashoboka ko ugira umwitwarariko urenze gato mugihe bazoba bariko baragusuzuma canke mugihe uriko urishura kubibazo vya bashakashatsi. Wunvise ugumye utamerewe neza inyuma yokubonana nabo bashaka shatsi, ingingo zikenewe zose zizofatwa kugira uvanwe murico kibanza atoco urinze kuriha.

Inyungu zuyo mugambi ni izihe?

Uyu mugambi ufise inyingu Atari nke mukibano canyu, kumiryango yanyu no kurimwebwe nyene ubwanyu. Bizotuma mukibano mutahura gusumba ivyerekeye ingwara itera uruhumyi trachome, nokumenya kugenzura uburyo buhari bwokurwanya uyo mugera utera iyo ngwara, noguterera uburyo mwibaza bwoba bubereye bwokurwanya iyo ngwara. Kuvyumwihariko , mwebwe canke umwe mu muryango wanyu uwuzoba arwaye azoronswa umuti wiyo ndwara kubuntu.

Mpinduye Iciyunviro naho?

Kuja muri uyo mugambi ni kubugombe bwumwumwe wese. Nubwo mwekwemera kujamuri uyo mugambi , mushobora gusokokora umwanya uwariwo wose , kandi bibizotuma uca ukumirwa canke ngo winubwe. Kugosokora ntaco bizohindura kurimwebwe canke kuri uwariwe wese mu muryango wanyu kuvyerekeye ivyo guhabwa umuti kubuntu. Bigikunda muzoca mukurwa no murutonde rwaba zokurikiranwa. Ariko ni mwahitamwo gusokora urutonde rumaze guhinyikwa ntibizoba bigikunda ko tubakuramwa.

Hari uwundi azomenya ibipimo vyuwa pimwe muri uwumugambi?

Ibipimo hamwe namakuru yose muzoba mwatubwiye bizoguma mwibanga. Ibanga rizomenwa bisabwe namategeko honyene. Inyishu muzokwishura zizonyegezwa , abashakashatsi bo kuru kaminuza ya Notre Dame yomuri Australie nabene ntibazoshobora kumenya abo umwewese ico ari mugihe bazoba bariko barahinyanyura ivyavuye murico cirwa. Icirwa nicahera, inyishhu mwatanze zizoshingurwa ahadata mugisata cubuvuzi kuri kaminuza Notre Dame muri Australie no mumugambi wigihugu ujejwe kurwanya indwara zititahweho bikwiye, nimiburiburi ikiringo cimyaka itanu. Ibizova muri icocirwa bizotangazwa mibimenyesha makuru vya kaminuza canke mubigabane vyibitabu , bikaba bizokwandikwa mugitabu coguheza amashule ya master ya Ndisabiye Desire.

Umuntu azomenya gute inyishu zavuye muri ico cirwa?

Umugambi wigihugu ujejwe kurwanya irwara zititaweho uzoha icegeranyo cico cirwa imboneza mubaremesha kiyako mugacimbiri kose kaserukiwe mucirwa. Icocegeranyo mwocitega umwaka 2018 ugezze hagati.

Umuntu afise ikibazo cerekeye ico cirwa yobaza inde?

Mufise ikibazo ntimuze mutinye kumbaza kuri telephone yanje ……. Canke iyo ntwara …….

Uwuntwara najewe nyene tuzoba turi niteka ryukubakira nokuganira namwe kuco arico cose.

Ufise ibibazo canke ingorane?

Icirwa caremejwe numugwi ujejw ivya akaranga kuri kaminuza ya Notre Dame muri Australie (nomero……..). Nimwaba mufise ikibazo canke umwitwarariko, ukaba wifuza kuganira numuntu ataho yegamiye kuvyerekeye akaranga kajanye n”ico cirwa , murakura kuri (+618)94330943 canke research@nd.edu.au. Ibirego vyose bizokwihwezwa mwibanga ntangere, mukazomeshwa ivyavuyemwo.

Nogira gute kugira ngo nje muri icocirwa?

Mwipfuza kuja muri ico cirwa , ni mutere umukono kuri izo mpapuporo zibiri zemeza kumweye atagahato, muce mugumya rumwe , urundi muruhe uyu murwi uriko uragira ico cirwa.

Murakoze kukanya mwaduhaye

Appendix H

Questionnaire

Questionnaire[1]

First, we would like to ask you some questions about yourself and your household.

What is your gender?

How old are you?

How many people live in your household?

How many of these are adults?

How many of these are children?

Please make sure the doctor completes the form on the back page.

Now, we will ask some questions to help us understand how we can help to control trachoma in your village.

Thinking about toilets, does your household use (tick all that apply):

Flush toilet
Piped sewer
Septic tank
Ventilated latrine pit latrine
Pit latrine with slab
A public or shared flush toilet
A pit latrine without a slab
Open defecation

Thinking about water, does your household get its water from (tick all that apply):

Piped water to the house
Piped water to the yard
A public tap or standpipe
A tube well or bore hole
A protected dug well
An unprotected dug well

[1] To be read verbatim to participants by a member of the research team if participant cannot read

A protected spring
An unprotected spring
Roof harvested rainwater
Surface water
River water
A cart with a tank
A tanker truck

Thinking now about Trachoma, consider your level of agreement with the following statements:

	Strongly agree	Agree	Don't know/ unsure	Disagree	Strongly disagree
It is very important to wash your face whenever it is dirty					
Open garbage is important in spreading trachoma					
I wash my kids' faces every day					
Sharing towels and pillows is not important in spreading trachoma					

Thinking about the most important thing in spreading trachoma, would it be?

Washing the face regularly	Touching dogs or sheep

Open garbage	Sharing towels and pillows
Flies	Using dirty water
Working without shoes	Eating unwashed fruit

Clinical information

Trachoma status of household members (completed by clinician):

Person	Adult/ child	Male/ female	Type of trachoma (TF, TI, TS, TT)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			