Modelling disease persistence and elimination in low-transmission settings

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Summary

Background
Malaria and human African trypanosomiasis are two vector-borne diseases caused by protozoa. In Zanzibar, Tanzania, malaria persists at a low prevalence despite the implementation of vector control, passive surveillance, and reactive surveillance. Human movement, and subsequent case importation, is hypothesised to be a key driver of persistence. Human African trypanosomiasis prevalence is below 1000 globally and is targeted for elimination. However, treatment options were previously limited and the diagnosis process is invasive and painful. The introduction of a new oral treatment improves options for treatment but may have an impact on transmission, as compliance levels may be lower than with previous treatments.

Methods
Stochastic metapopulation models of disease transmission were used to explore a range of questions regarding malaria and human African trypanosomiasis transmission and elimination. A metapopulation model of malaria transmission was developed and parameterised to data from Zanzibar, Tanzania. It incorporated human movement and reactive case detection, and was used to investigate the impact of improvements to reactive case detection or treatment of imported cases on prevalence levels. The model was then expanded to include separate categories for imported, introduced, and indigenous cases, which allowed us to apply the WHO definition of malaria elimination (three years with no indigenous cases). An already established model of human African trypanosomiasis transmission was adapted to incorporate treatment by fexinidazole and potential non-compliance. This was used to test the potential impact of widespread versus limited access to fexinidazole under a range of compliance scenarios, and the potential impact of increased treatment seeking rates.

Results
The controlled reproduction number for malaria was estimated to be below the threshold value of 1 on both major islands of Zanzibar, confirming that importation is driving disease persistence. Reactive case detection is estimated to reduce malaria incidence by approximately 10% on Zanzibar. To achieve non-zero probabilities of elimination, infections in travellers need to be targeted, and onward transmission from imported cases needs to be reduced. Considering human African trypanosomiasis transmission, an increase of 20% in the passive detection rate is expected to counter a small negative impact of non-compliance to fexinidazole.

Conclusion
While reactive case detection is useful for surveillance and does reduce malaria incidence, the large number of low parasite density infections prevents reactive case detection from removing large parts of the parasite reservoir. The controlled reproduction number needs

to be kept well below 1 in order to minimise the chances of any imported cases leading to chains of transmission that lead to indigenous cases. A better understanding of treatment compliance with fexinidazole and changes in treatment seeking behaviour is necessary to better estimate the potential impact of fexinidazole on human African trypanosomiasis transmission in the Democratic Republic of the Congo.

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Contents

Chapter 1

Introduction

1.1 History of disease elimination and eradication

Humanity has always lived with disease. Diseases have helped shape the human genome, human behaviours, and the way society functions. While hunter-gatherers of the Paleolithic era also suffered from illnesses, the Agricultural Revolution brought humans together in a density that allowed many diseases to spread easily. Humans and pathogens have been co-evolving since the emergence of our species, with certain defenses against diseases written into our genomes. For example, the trypanosome lytic factor is a high density lipoprotein that protects humans against infections from parasites of the genus *Trypanosoma*. However, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* have evolved resistance to trypanosome lytic factors [1]. This allows them to infect humans and cause sleeping sickness. This ongoing evolution of pathogens against our defenses leads to the emergence of novel infectious diseases.

Our defenses go beyond genetics. Improved sanitation, living conditions, and publicly funded healthcare have led to significant declines in many transmissible diseases and increases in life expectancy [2]. The invention of vaccines and antibiotics has further added to our arsenal for strengthening the immune system and for combating illnesses when our immune systems prove insufficient. Progress towards the reduced burden of diseases raises the question of eradication: the global reduction of incidence of a disease to zero, such that intervention measures are no longer needed against it. Until now, only two diseases have been eradicated: smallpox and rinderpest.

Smallpox was a highly contagious disease caused by two variants of the variola virus. The classic symptoms were fever and distinctive fluid-filled blisters on the skin. The disease decimated populations when outbreaks occurred, killing 15-30% of patients infected by the variola *major* virus [3, 4]. The earliest records of the disease stem from Egyptian mummies that died of the illness. Smallpox spread from human to human through aerosol droplets, with no animal reservoirs. The disease led to the development of the first vaccine by Edward Jenner, using the observation that people who had previously been infected by cowpox typically had asymptomatic or very mild cases of smallpox. The use of this cowpox vaccine led to a dramatic decline in smallpox deaths and paved the way to eradication. However, this vaccine was damaged by heat and was only effective for 2-3 days. Development of a thermostable vaccine in the 1950s led to mass vaccination campaigns in tropical areas, overseen by the World Health Organization (WHO) through

the 'Intensified Smallpox Eradication Program'. Proof of vaccination was required for travel, and re-introduction remained a threat until herd immunity could be reached. The last case was reported in Somalia in 1977, and in 1980, WHO declared smallpox eradicated [4]. The global efforts to eradicate the disease led to the start of the Expanded Program on Immunization — national programmes for vaccinating children against polio, diphtheria, pertussis, tetanus and measles — and the subsequent fall in the global burden of vaccine-preventable diseases.

Rinderpest was a viral disease causing fevers, oral sores, diarrhoea and eventually death in cattle and buffaloes, severely impacting human livelihoods. The history of the disease is closely intertwined with humanity, with it spreading globally due to cattle trading and the movement of herds of cattle with invading armies [5]. As the disease infects other ungulates, transmission between wild and domestic animals was also common. Originating from somewhere in Central or South Asia, rinderpest spread to Russia, Europe, the Middle East and eventually Africa, where the lack of immunity led to 90% mortality rates [5, 6]. After significant investment in control efforts, including the use of a potent, thermostable vaccine, it was declared eradicated by the World Health Organization (WHO) in 2011, ten years after the last known case had been found in Kenya [5, 6].

There are some similarities and differences between these two cases of eradication that are worth noting. First of all, in both cases, a highly efficacious, thermostable vaccine was available [7]. No cold chain was required, making global distribution easier. Secondly, there was a global political will to eradicate the disease. Both diseases had high mortality rates and no effective treatments and thus posed a large societal burden. Finally, most cases were clearly symptomatic, making cases easier to find and isolate. In contrast, while smallpox had no animal reservoirs, rinderpest could spread from wild ungulates to domestic cattle. The nature of rinderpest meant that it mainly spread in high animal density settings and so domestic animals were the maintenance hosts [8]. Therefore, vaccinating domestic ungulates was sufficient to reach eradication. In general, effective interventions and high coverage levels are common themes between both eradication efforts. Similar efforts are being made for polio eradication, with the Global Polio Eradication Initiative leading the way with mass vaccination campaigns using an oral poliovirus vaccine for two out of three serotypes, and an inactivated poliovirus vaccine for the last serotype. Polio also has the trademarks of a disease that could be eliminated: it is transmitted directly between humans; its symptoms can be debilitating, leading to strong economic incentives and political will to eradicate the disease; and there are effective vaccines available [9, 10]. While two out of three serotypes have been eradicated, wild poliovirus type 1 is still endemic to Pakistan and Afghanistan. The lack of eradication in these two countries has led to a new case arising in Malawi in 2021, which had previously been declared polio-free. Similarly, five cases have been observed in Mozambique in 2022, despite not having had an indigenous case since 1993 [11, 12]. This demonstrates the need for ongoing surveillance until global eradication is reached, as, otherwise, diseases can be re-established due to importation. Additionally, a large fraction of infections are asymptomatic, but those infected are able to transmit polio, making surveillance more challenging than for smallpox.

In general, the trends in disease prevalence from endemicity to eradication tend to follow a pattern similar to that shown in Figure 1.1. I define the controlled reproductive number, R, as the number of cases arising from a single case in the absence of immunity, but in the presence of control interventions. A discussion of reproduction numbers can

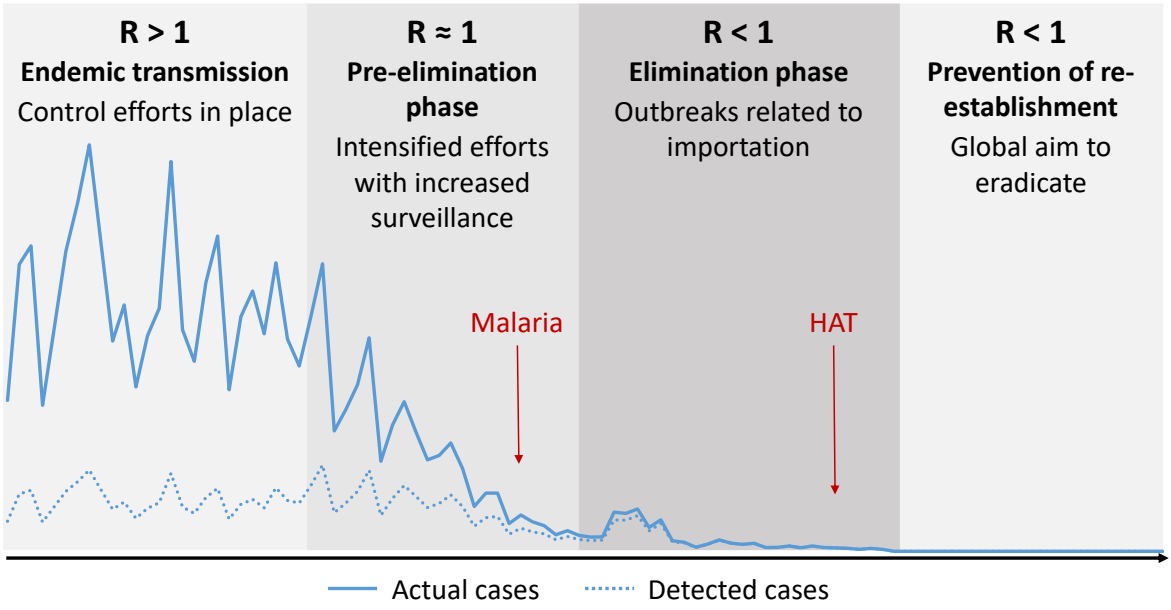

Figure 1.1: Stages towards disease elimination and eradication, with indicators of the current stage globally for malaria and human African trypanosomiasis (HAT). R indicates the reproductive number in that stage of transmission. Shading indicates the intensity of effort needed. Adapted from [14, 15, 16].

be found in Smith and Schapira (2012), covering the difference in basic, controlled, and effective reproduction numbers [13]. In the endemic transmission phase, each disease case would typically lead to more than one more such case in the absence of immunity, thus $R > 1$. There may be control efforts in place, but many cases are not reported and outbreaks are common. Diseases that are in this stage include dengue and influenza. As efforts intensify, the reproduction number may be brought down to 1, so each case typically leads to one more case. This stage, referred to as the pre-elimination stage in Figure 1.1, tends to see an improvement in surveillance efforts, with a larger proportion of cases being detected. Malaria is currently in this stage in many endemic countries and regions. When R is consistently kept below 1, in the 'elimination phase', the disease would die out without re-introduction from other regions. Following up imported cases and preventing further transmission becomes key, as does finding and treating any last cases that remain. Human African trypanosomiasis (HAT) can be thought to be in this stage, with fewer than 1000 cases reported globally per year. Finally, when elimination has been reached, i.e. there is no evidence of ongoing local transmission, there is still a need for strong surveillance to prevent the re-establishment of the disease. When all countries have reached elimination, the disease can be said to be eradicated. Only then can surveillance measures be relaxed.

Surveillance measures can include compulsory reporting of known disease cases, known as "notifiable diseases", actively searching for cases, or reactively searching for cases around areas known to have a case. HAT is a globally notifiable disease, and malaria is notifiable in many countries. Both active case detection and reactive case detection have historically been used to reduce disease transmission [17, 18, 19, 20]. However, as surveillance is resource-intensive, it is valuable to evaluate surveillance systems to assess how effective they are and how they can be improved.

1.2 Malaria

Malaria is a vector-borne infectious disease caused by protozoan parasites of the genus *Plasmodium* in humans. It is transmitted from human to human via female *Anopheles* mosquitoes. Historically, human malaria had a wide geographic distribution, but is now mostly present in Sub-Saharan Africa, South and Southeast Asia, and parts of South America [21]. The main symptom is febrile illness, with severe cases leading to respiratory distress, anaemia and cerebral malaria. While most cases are not fatal, fatality rates are highest amongst children under the age of 5, causing 7% of all deaths globally in this age group [22].

There have been two main global pushes towards malaria eradication. Firstly, in the 1950s with the Global Malaria Eradication Program, and then again from the Gates Malaria Forum of 2007 and the Sustainable Development Goals [23]. Interventions that aim to reduce the mosquito population and increase access to treatment have been used to substantially reduce the burden of the disease. However, progress is stalling and malaria sometimes persists in areas despite historically high levels of coverage of interventions.

Mathematical modelling can be a useful tool for gauging the potential impact of interventions and the likelihood of reaching elimination. Such models were developed for the context of Zanzibar, the United Republic of Tanzania, and used to assess the potential impact of improved reactive case detection and importation management on the chance of reaching malaria elimination. These models are presented in Chapters 2 and 3 of this thesis.

1.2.1 Malaria epidemiology and control

Five species of *Plasmodium* are known to cause malaria in humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. Of these, *P. falciparum* malaria is the most deadly. It is the primary species in Sub-Saharan Africa and in Tanzania, and is the focus of this thesis. It is spread by the bite of *Anopheles* mosquitoes, which injects sporozoites into the blood. These sporozoites then travel through the bloodstream to the liver, where they replicate asexually. After 5-10 days, the parasites then leave the liver as merozoites, enter the bloodstream, and invade red blood cells. Blood stage parasites cause clinical symptoms and death. A fraction of merozoites develop into gametocytes which, when ingested by mosquitoes upon taking a blood meal, combine in the mosquito midgut into zygotes. The zygotes then develop into oocysts, which rupture and release sporozoites, which then migrate to the mosquito salivary gland and continue the cycle [24].

Malaria symptoms can range from mild to severe, and typically include fever, headaches and tiredness. Vomiting and diarrhoea may also occur in uncomplicated malaria [25]. Children below the age of 5 are the most susceptible to severe malaria, which is characterised by symptoms such as severe malarial anaemia, respiratory distress and cerebral malaria. The majority of deaths also occur in this age group [22, 26]. Around 600,000 deaths occur globally due to the disease, with 91% of these deaths occurring in Africa. While still unacceptable, the malaria case incidence and mortality per 1000 population at risk have been falling steadily since the year 2000, with a slight rise in 2020 in part due to disruptions to services during the COVID-19 pandemic [27].

Part of this decline in case incidence and mortality can be attributed to the deployment of interventions against malaria. Malaria transmission can be reduced by targeting different stages of the infection cycle. Transmission from mosquitoes to humans can be reduced by reducing the mosquito biting rate by the use of insecticide-treated nets, or by killing mosquitoes before *Plasmodium* parasites have sufficient time to develop into sporozoites using insecticides sprayed inside the walls of homes (indoor residual spraying; IRS). Systematic reviews of insecticide-treated nets have found them to reduce cases of severe malaria by 45% and halve the incidence of uncomplicated *P. falciparum* episodes in children [28, 29]. Similarly, a systematic review of IRS found it to be particularly helpful in reducing the malaria burden in areas with a low entomological inoculation rate (less than 1 infectious mosquito bite received per person per year) [30]. Transmission can also be reduced by reducing the mosquito density through spraying larvicides on bodies of water where mosquito larvae develop [31]. Such interventions that target the mosquito lifespan, density, or biting rate are known as vector control. Alternatively, transmission can also be reduced by diagnosing and treating malaria patients promptly to reduce the time in which humans can transmit gametocytes to mosquitoes. In low-transmission settings, this may be done through reactive case detection (RCD). In RCD, the detection of a clinical malaria case at a health facility (known as the index case) sets off a cascade of events that lead to the testing and treatment of the index case's household members and neighbours.

The first attempts to globally eliminate malaria arose in the 1950s and 60s with the Global Malaria Eradication Programme (GMEP). The focus of GMEP was eliminating malaria from all areas outside of Africa by spraying homes with dichloro-diphenyl-trichloroethane (DDT), the most effective tool against malaria available at the time. While a significant burden reduction was achieved, malaria resurgence was seen in some areas which had interrupted transmission, in part due to the lack of surveillance activities [32]. For some years after GMEP, the focus shifted from malaria elimination to controlling the burden of disease. In the 1990s, the discussion of intensified malaria control was brought back onto the table, with the Millennium Development Goals aiming to, amongst other things, combat HIV/AIDS, malaria and other diseases. In particular, one of the targets of Goal 6 was to begin to reverse the upward trend in the incidence of malaria and other major diseases by 2015 [33]. The goal was achieved, with a 37% reduction in incidence and 58% reduction in mortality from 2000 to 2015 [34]. It was achieved in part due to the establishment of the Roll Back Malaria partnership, created to provide a platform for a globally coordinated effort to halve the burden of malaria between 1998 and 2010. In addition to this, the creation of The Global Fund to Fight AIDS, Tuberculosis and Malaria helped fill the funding gap between what was available and what was needed to achieve further burden reduction. A combination of efforts led to a steady decline in malaria cases per 1000 population at risk from 2000 to 2019 [27]. However, rising drug and insecticide resistance, loss of immunity, and disruptions to health systems due to COVID-19, have led to a rising incidence of malaria and a stagnation in the progress towards elimination.

1.2.2 Mathematical modelling of malaria

The first mathematical model of malaria was developed by Ronald Ross in 1911, shortly after the discovery of the malaria transmission cycle [35]. This model was further de-

veloped over time by George Macdonald, forming the Ross-Macdonald model that captures the transition of humans from a *susceptible* (uninfected) state, to an *infected* state, and then back to *susceptible*. Mosquitoes were also included in the model. They were modelled to transition from *susceptible*, to *exposed*, to *infected*. A variety of compartmental models emerged after this, with many other more complex factors such as age structure, geographic heterogeneity, and immunity being incorporated into the modelling framework [36]. To further incorporate heterogeneity and immunity at the individual level, agent-based modelling has been used widely in recent years for modelling malaria [37, 38, 39, 40].

Heterogeneity in transmission can lead to hotspots where the malaria prevalence is higher than in the general population. RCD is a strategy that targets such hotspots by focussing testing and treatment efforts around known malaria cases. RCD is a time- and labour-intensive intervention and a previous modelling study has suggested that it will likely only be effective in areas that historically had high transmission levels, but have recently seen a drop in transmission [41]. This is because RCD is useful for finding asymptomatic infections that would have otherwise been missed by the health system, whereas, in low transmission areas, most infections are expected to be symptomatic and so passive surveillance is most useful in finding and treating cases in the community. However, these assumptions contrast with study results from Zanzibar, Tanzania, where a large proportion of cases detected by quantitative polymerase chain reaction (qPCR) were asymptomatic and found to have parasite densities below the rapid diagnostic test (RDT) threshold for detection [42]. This is despite Zanzibar having had a low malaria prevalence for over 5 years at the time. Another modelling study found that RCD could contribute towards achieving elimination in low transmission settings [43]. However, this study did not consider case importation, which has been found to be a significant cause of malaria persistence in many low transmission settings [42, 44, 45, 46, 47]. Detection of imported cases at health facilities may trigger testing and treatment at the index household, but might not be associated with a local malaria hotspot.

Importation in the context of malaria elimination has been explored through modelling studies for a number of different settings [41, 45, 46, 48, 49]. Often, it is included as a constant rate of case importation parameterised to available data [41, 45, 50, 51]. Some metapopulation models contain connected patches where increases or decreases in malaria prevalence in one patch affect the importation rates in other patches [48, 49, 52]. While these models typically consider short-term human movement, some models include long-term migration as the main form of movement [53, 54]. Collectively, these models highlight the role played by case importation in malaria persistence and identify higher transmission regions that are the sources of infections for highly connected lower transmission areas.

1.2.3 Malaria control efforts in Zanzibar, Tanzania

Zanzibar is a semi-autonomous archipelago of islands in the United Republic of Tanzania. It has its own health ministry and malaria programme. Historically, the prevalence of malaria has been high in Zanzibar, with prevalence rates amongst 2–10 years olds above 50% [55]. However, since 2003, the prevalence has dropped substantially from the use of artemisinin-based combination therapies for treatment, increases in long-lasting insecticidal net usage, and indoor residual spraying [56]. In the 2017 Malaria Indicator Survey, the current prevalence among children aged 6–59 months as detected by RDT was estim-

ated to be 0.2% in Zanzibar, highlighting the significant progress that has occurred [57]. However, malaria continues to persist, in part due to repeated importation of infections from mainland Tanzania [45, 58, 59]. This high vulnerability (the number of imported cases arriving in an area over time), combined with a high receptivity (the presence of competent vectors for transmitting malaria) make reaching and sustaining elimination a challenge for Zanzibar.

The Zanzibar Malaria Elimination Program (ZAMEP) is in charge of malaria-related interventions and activities. Within their 2018–2023 strategic plan, ZAMEP aims to reach malaria elimination by 2023 by ensuring all clinical cases receive appropriate treatment, scaling up the use of piperonyl butoxide-treated bed nets (PBO nets) and IRS, and improving surveillance so all cases get classified as imported or locally transmitted [60].

To target foci of transmission, Zanzibar has implemented RCD across both major islands, Pemba and Unguja, since 2012. This programme has previously been evaluated in terms of operational coverage and timeliness and it was found that 35% of cases were followed up by a surveillance officer within 3 days, with public facilities performing better than private facilities [61]. It is unclear what proportion of the parasite reservoir is detected and treated with RCD and how improvements to the current surveillance-response system may affect the overall parasite prevalence in Pemba and Unguja.

1.3 Human African trypanosomiasis

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a vector-borne disease that is typically fatal in humans if left untreated. It is caused by the transmission of protozoan parasites of the species *Trypanosoma brucei* by tsetse flies of the genus *Glossina*. The majority of cases are caused by the subspecies *T. b. gambiense*, which will be the focus within this thesis. HAT caused by *T. b. gambiense* (gHAT) is mainly found in rural Central and West Africa and the main hosts are humans, with animal reservoirs likely playing a small role in transmission. In contrast, *T. b. rhodesiense* HAT is geographically located in rural East Africa and animal reservoirs are considered an important part of the transmission cycle. The two subspecies are morphologically identical and cause similar disease symptoms, except that *T. b. rhodesiense* HAT progresses much faster than gHAT. *T. b. gambiense* is better adapted to human hosts and can cause chronic illness that lasts for years, while *T. b. rhodesiense* is a mainly zoonotic disease with humans occasionally being infected [62]. When humans are infected, the disease progresses relatively rapidly and may be fatal within a few weeks of infection.

HAT is a neglected tropical disease (NTD), affecting mainly the rural poor of regions of sub-Saharan Africa where tsetse flies can proliferate. Control measures targeting tsetse vectors and treatment of patients have led to significant reductions in disease prevalence since the turn of the Century. The evolution of treatments over time has made treatment less toxic and more accessible. The Sustainable Development Goals agreed upon by the United Nations General Assembly aim for the interruption of transmission of gHAT and the elimination of *rhodesiense* HAT as a public health problem by 2030. In this thesis, I aim to use mathematical modelling to assess how a new oral treatment, fexinidazole, may affect gHAT transmission dynamics and the likelihood of elimination when considering potential reductions in treatment compliance and potential increases in treatment access.

1.3.1 gHAT epidemiology, treatment, and control

Transmission of *T. b. gambiense* to humans starts with a bite from a *Palpalis*-group species of tsetse fly [63]. Tsetse flies feed solely on blood, and inject trypomastigotes into the blood while feeding. These trypomastigotes then multiply in the blood until the host immune system produces antibodies against them. This leads to a reduction in parasite density, until a few of the trypanosomes begin to produce a different variant surface glycoprotein, and are then unaffected by the circulating antibodies. These then replicate until antibodies are produced against this specific glycoprotein. This cycle continues for the rest of the host's life, and the immune system is never able to fully eliminate the parasite [64]. If a tsetse fly feeds on an infected host, they take up some of the trypomastigotes, which then replicate in the fly midgut through binary fission. The trypanosomes then travel to the salivary glands of the fly, from where they are injected into the host when the fly takes a blood meal, completing the cycle [65].

Symptoms of gHAT can be classified into two stages: the haemolymphatic stage (stage 1) and the meningoencephalitic stage (stage 2). In the haemolymphatic stage, parasites are only present in the blood and lymphatic system. The main symptoms include intermittent, chronic fever, headaches, and enlarged lymph glands [62]. Other symptoms can include general fatigue, itchy skin and joint pain. Symptoms usually start 1–3 weeks after infection, and last for months to years [65]. The meningoencephalitic stage begins when the parasites cross the blood-brain barrier and invade the central nervous system. Symptoms in this stage gave rise to the disease name of 'sleeping sickness'. Disruption of cerebral functions typically first appears as changes in behaviour: the patient may become temperamental, careless, and confused [62]. Sleep becomes disordered, with patients sleeping during the day and staying awake at night. If left untreated, patients typically slip into a coma and die [66].

Diagnosis is typically through microscopic detection of trypomastigotes in lymph node aspirate, as the density of trypomastigotes in blood is often very low. The disease stage is determined by taking a sample of cerebrospinal fluid (CSF) and examining for the presence of trypomastigotes and an inflated white blood cell count [67]. If the white blood cell count is inflated or trypanosomes are present in the CSF, or both, then it is assumed that parasites have invaded the central nervous system and the disease has progressed to stage 2. Treatments for the disease were historically arsenic derivatives that aimed to kill the parasite before killing the patient. Thankfully, there has been significant progress in the area, with improved treatments, especially for *gambiense* HAT. Currently, the first stage of gHAT is typically treated with pentamidine, and the second stage with nifurtimox-eflornithine combination therapy (NECT). The fatality rate from treatment has dropped from 5-6% with melarsoprol (an arsenic derivative) to 0.5% with NECT [68]. In 2018, fexinidazole, the first oral treatment for gHAT, was approved for treatment of stage 1 and non-severe stage 2 cases [67]. Additionally, acoziborole, a new drug being developed through the Drugs for Neglected Diseases Initiative, may fulfill the need for a single-dose oral treatment for both stages of the disease. Acoziborole is currently undergoing Phase II/III trials [69].

The distribution of HAT cases is determined by the presence of tsetse flies. The flies typically live in forested areas and in vegetation near streams [65]. There were three major HAT epidemics in the 20$^{\text{th}}$ Century, with the most recent being in the 1990s [70]. In the latest epidemic, the prevalence was estimated to be 2% within the Democratic Republic of

the Congo (DRC), rising to up to 70% in some communities [71]. The disease devastates communities and livelihoods, contributing to poverty. For a long time, the disease was neglected, with resources being directed, instead, towards diseases with a larger global burden such as malaria and HIV. Sustained efforts to reduce HAT incidence, coordinated by WHO, have led to a large decline in HAT cases from the 1990s to the present. The number of cases reported annually dropped below 10,000 for the first time in 50 years in 2009, and below 1,000 in 2018 [72, 73]. Active screening and treatment of detected cases, general improvements in access to care for passively detected cases, vector control efforts targeting tsetse flies, and general bush clearing for farmland contributed to the decline of the disease [70, 72, 74]. Pesticides have been used to control tsetse fly populations, which had proven quite effective, as the tsetse fly has a long life cycle with relatively few offspring per female, especially compared to other insects. Novel interventions for tsetse fly control include "tiny targets", which are small insecticide-treated screens that kill tsetse flies. Use of these tiny targets has been shown to be highly efficacious in field trials, leading to a 90% decrease in the tsetse fly population [75].

1.3.2 Mathematical modelling of HAT

The first models of HAT were compartmental models adapted from early malaria models, as both are vector-borne diseases [63]. Rogers (1988) adapted the delay differential equation model of malaria by Aron and May (1982) to include animals as potential hosts and tsetse flies as the vectors [76, 77]. In this model, the two disease stages were not separated, and humans could recover from HAT and enter an immune state, from which they would slowly lose their immunity and return to the susceptible population [63, 76]. Artzrouni and Gouteaux (1996) also adapted the Ross-Macdonald model of malaria for use in testing control measures for gHAT [78, 79]. This model separated out the disease stages to some extent, with the assumption that those in the more severe second stage of the disease would no longer be infectious as they would either be at home or in a hospital and therefore not exposed to tsetse flies [79].

More recent models have incorporated further knowledge of disease characteristics, vector biology, and potential interventions into the model frameworks [80, 81, 82, 83]. These models are useful for assessing which parts of the disease transmission cycle may be most vulnerable to breakpoints, and which disease control interventions may be the most effective or cost-effective. Four independently developed deterministic models for gHAT transmission were compared as part of the NTD modelling consortium, in order to better understand how model structure and assumptions may impact results and policy recommendations [84]. The models were calibrated to HAT Atlas data from the former Bandundu province in DRC [85]. This analysis found that the models broadly agreed that the introduction of new interventions will likely lead to a decline in HAT incidence. In particular, vector control is likely to accelerate the time to elimination of transmission, and was found to be the intervention that had the largest impact on incidence [84]. A similar analysis across the same four models found that using case data that is separated by disease stage or using aggregate data made a difference to the outputs of the models, as the input parameters had different distributions depending on how much data was available [81]. Stochastic implementations of two models, developed by the University of Warwick and the Swiss TPH, were also used to predict the impact of COVID-19 on interruptions to active screening and passive surveillance. The key findings were that, as

the disease progresses slowly, disruptions to active screening and passive surveillance were not likely to lead to delays in the elimination of transmission of more than 2–3 years [86].

All four models assumed that all treatments were 100% successful, as the treatment is highly efficacious and is delivered in hospitals by trained healthcare staff. With the introduction of fexinidazole, which is taken orally over ten days and requires concomitant food intake to ensure adequate bio-availability, there is a possibility that the treatment will not cure everyone who receives it [67]. This could have a substantial impact on the time to elimination of transmission and is investigated further in this thesis.

1.4 Goals and objectives

When considering disease elimination and eradication, we typically see an increase in the resources needed to find and treat the last cases. Mathematical models can be used to help identify where resources are best targeted to maximise the impact of interventions, which is crucial in resource-constrained settings. Additionally, there may be interventions in place where small improvements are expected to have a substantial impact on disease transmission in the long run. Within this thesis, my goal is to study two diseases in elimination settings, to better understand what improvements to screening and treatment could be made, and to predict the potential impact of such changes.

The objectives of this thesis are to:

1. Estimate the effective reproductive number for malaria in the presence of case importation on Zanzibar, Tanzania, and the impact of interventions on malaria prevalence;

2. Estimate of the probability of reaching malaria elimination on Zanzibar when considering indigenous cases, as defined by WHO, under different intervention scenarios;

3. Estimate the potential impact of switching from the current standard HAT treatment to fexinidazole for stage 1 and non-severe stage 2 cases on disease transmission and the probability of reaching elimination.

Chapters 2 and 3 of this thesis focus on models for malaria transmission, looking at the impact of reactive and targeted interventions in the presence of ongoing human movement. Chapter 4 of this thesis uses a stochastic transmission model for HAT to explore the role of drug adherence and access to treatment on disease persistence, in the context of human African trypanosomiasis. Chapter 5 is a discussion of the findings of this thesis, its limitations, the broader context of reactive interventions, and the need for better data for these two diseases, albeit in different areas of the disease biology and epidemiology.

Chapter 2

The impact of reactive case detection on malaria transmission in Zanzibar in the presence of human mobility

2 The impact of reactive case detection on malaria transmission in Zanzibar in the presence of human mobility

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Abstract

Malaria persists at low levels on Zanzibar despite the use of vector control and case management. We use a metapopulation model to investigate the role of human mobility in malaria persistence on Zanzibar, and the impact of reactive case detection. The model was parameterized using survey data on malaria prevalence, reactive case detection, and travel history. We find that in the absence of imported cases from mainland Tanzania, malaria would likely cease to persist on Zanzibar. We also investigate potential intervention scenarios that may lead to elimination, especially through changes to reactive case detection. While we find that some additional cases are removed by reactive case detection, a large proportion of cases are missed due to many infections having a low parasite density that go undetected by rapid diagnostic tests, a low rate of those infected with malaria seeking treatment, and a low rate of follow up at the household level of malaria cases detected at health facilities. While improvements in reactive case detection would lead to a reduction in malaria prevalence, none of the intervention scenarios tested here were sufficient to reach elimination. Imported cases need to be treated to have a substantial impact on prevalence.

2.1 Introduction

Despite a global reduction in malaria burden in 2000–2015, improvements in case incidence have stagnated in the United Republic of Tanzania at around 6 million cases per year since 2010 [87]. Zanzibar, a semi-autonomous region of Tanzania, has seen a substantial decline in malaria prevalence since 2000 due to the use of long-lasting insecticidal nets (LLINs), indoor residual spraying (IRS) and artemisinin-based combination therapies (ACTs) [56]. These strategies have aided in reducing malaria prevalence by 10- to 23-fold as measured by rapid diagnostic tests (RDTs) and microscopy, with prevalence estimated to be below 5% [56, 88] on both main islands of Zanzibar: Unguja and Pemba.

Additionally, the Zanzibar Malaria Elimination Programme (ZAMEP) has implemented a reactive case detection (RCD) programme from 2012 onwards [61]. RCD involves following up clinical malaria cases that present at a health facility and testing their household members for malaria using RDTs. This helps to treat both asymptomatic cases, and symptomatic cases that may not report to a health facility, with the aim to reduce onward transmission. RCD has been implemented with varying levels of success in countries and regions with low malaria prevalence such as China [89], Eswatini [90, 91], India [92], and Zambia [93]. ZAMEP was aiming to achieve follow up for 100% of confirmed cases by 2018 [94], but analyses of health facility data suggests that only 35.3% of diagnosed cases are followed up at the household level within 3 days [61].

Despite these substantial efforts, elimination has not been achieved in Zanzibar. The persistence of a low level of transmission despite high coverage of interventions has been attributed to geographic foci of transmission, a reservoir of sub-patent infections that are not detected and eliminated by routine surveillance-response activities, and repeated importation of infections [56]. The impact of these factors on disease transmission can be studied through mathematical modelling. Failing to account for these factors when modelling the disease can lead to overly optimistic estimates of the time or resources

needed to eliminate malaria from a setting [56, 95].

Previous studies of RCD in Zambia and Namibia have suggested that it will only lead to malaria elimination in limited settings, particularly in areas that have reduced transmission recently [41, 43, 96, 97, 98]. The effectiveness of RCD can be improved by shifting to a reactive focal mass drug administration (rfMDA) programme, so that the probability of treating an infection is not dependent on the diagnostic test sensitivity [97, 98]. Diagnostic test sensitivity has been identified as a major impediment to RCD programmes in various settings, including Zanzibar [88], Zambia [93], and Eswatini [91], due to a high prevalence of very low density infections. Additionally, it has previously been suggested that RCD may not be useful in areas seeing large numbers of imported cases, as RCD relies on clusters of cases arising from local transmission [99]. On the other hand, as members of households often travel together, there is evidence that testing among the co-travellers of imported cases has a higher likelihood of yielding positive results [88]. Thus, it is unclear how useful RCD may be in the face of ongoing importation.

Previous studies of malaria importation have examined the impact of continuous importation of cases to Zanzibar from mainland Tanzania, where malaria prevalence is substantially higher [45, 58, 95, 100]. Parasite importation has also been shown to be an important factor for the persistence of malaria in settings outside of Tanzania [46, 101]. Churcher *et al* (2014) use branching process theory to calculate the reproduction number based on the proportion of detected cases that are classed as imported cases. If greater than 50% of detected cases are imported cases, the area is said to have a reproduction number below 1 and thus have halted endemic transmission [46], that is, indigenous incidence of malaria infection would not persist if all importation were halted [102]. Estimates of the proportion of clinical malaria patients in Zanzibar with a recent history of travel to mainland Tanzania have ranged from 9% to 49% [56, 88]. Whole genome sequencing of isolates from Zanzibar and mainland Tanzania has also highlighted the close relatedness of *Plasmodium falciparum* strains on Zanzibar and coastal Tanzania, suggesting some cases on Zanzibar have a recent history of importation [58].

A modelling analysis of malaria importation on Zanzibar has previously been conducted using mobile phone data to track human movement to and from mainland Tanzania [45, 59]. Using call data from the busiest period of travel to and from Zanzibar in 2008, Le Menach *et al* [45] estimated around 1.6 (falling within a range of 0–3.7) cases were imported per 1000 people per year to Zanzibar. The controlled reproductive number, R_c, is the expected number of secondary human infections stemming from one untreated infection in an area with vector control measures in place. R_c was estimated to be within 0—0.56 in urban Unguja, 0.71—0.91 in rural Unguja, and 0.92—0.98 in rural Pemba, using an adapted Ross-Macdonald model. Another study looking at quantifying migration across country borders in East Africa using census data suggests that the majority of case importation in Tanzania from long-term migration is likely to occur near country borders, away from Dar es Salaam and Zanzibar [103]. To the best of our knowledge, no modelling study has yet been conducted on quantifying the impact of reactive case detection on malaria transmission in Zanzibar, particularly in the presence of ongoing human movement and case importation rates that change in line with changes in prevalence in other areas.

In this paper, we use a compartmental metapopulation model to examine the impact of RCD and rfMDA, combined with ongoing short-term human movement, on the persistence of malaria in Zanzibar and the potential impact of treating imported cases. Using malaria

prevalence estimates for the islands of Pemba, Unguja and mainland Tanzania, along with data on the RCD programme, we consider the potential effects of improving or reducing the RCD programme currently in place, including changes in follow up, improvements in the number of cases reporting to health facilities, additional testing of neighbours of index cases, and shifting to an rfMDA intervention. We also consider possible synergies to be gained by combining rfMDA with treating neighbours as well as index households. Finally, combining the malaria prevalence estimates with travel history data, we estimate the likely impact of treating a proportion of imported infections on malaria prevalence on Zanzibar.

2.2 Methods

This analysis uses two main models: a compartmental susceptible-infected-susceptible (SIS) population model that was adapted to describe transmission dynamics in the presence of short-term human movement, and a stochastic implementation of this model including an ongoing RCD programme in Zanzibar. The first model is used to understand the role played by human movement in the persistence of malaria on the islands, and the second model is used to understand the impact of interventions strategies such as RCD and the treatment of imported cases in reducing the endemic equilibrium on the islands. Both models consisted of three patches: Pemba, Unguja, and mainland Tanzania.

2.2.1 Study setting

The Zanzibar archipelago lies to the east of the mainland of the United Republic of Tanzania. According to the 2012 census, the two main islands, Unguja and Pemba, had populations of 896,721 and 406,848, respectively. The islands are connected to mainland Tanzania via ferries and two airports (Fig. 2.1). In addition to this, there is regular small boat traffic between mainland Tanzania and Zanzibar, often by traditional dhows.

ZAMEP runs an RCD programme to effectively target test-and-treat efforts towards foci of infection. When patients on either island are diagnosed with malaria at a health facility, they should ideally be followed up within 3 days at their household by a district malaria surveillance officer (DMSO), and all household members should be tested with an RDT for malaria. Those who return a positive test result are treated with artesunate-amodiaquine and a single dose of primaquine. The Reactive Case Detection in Zanzibar: System Effectiveness and Cost (RADZEC) study included an examination of the operational coverage of the RCD programme [61]. Across the 150 public health facilities and 51 private health facilities, a mean of 32 and 12 malaria cases arrived at a health facility per district per month in Unguja and Pemba, respectively, corresponding to 6.4 cases per day in the whole of Unguja, and 1.6 in Pemba. Of those diagnosed at a health facility, 35.3% were followed up at the household by a district malaria surveillance officer within 3 days, 47.9% within 6 days, 59.9% within 15 days, and 62.0% within 21 days. The mean household size for index households was found to be 7.0 people per household on Pemba and 6.2 people per household on Unguja, including index cases [88].

This data, along with rolling cross-sectional survey data from the RADZEC study, were used to parameterise the RCD parameters in the model.

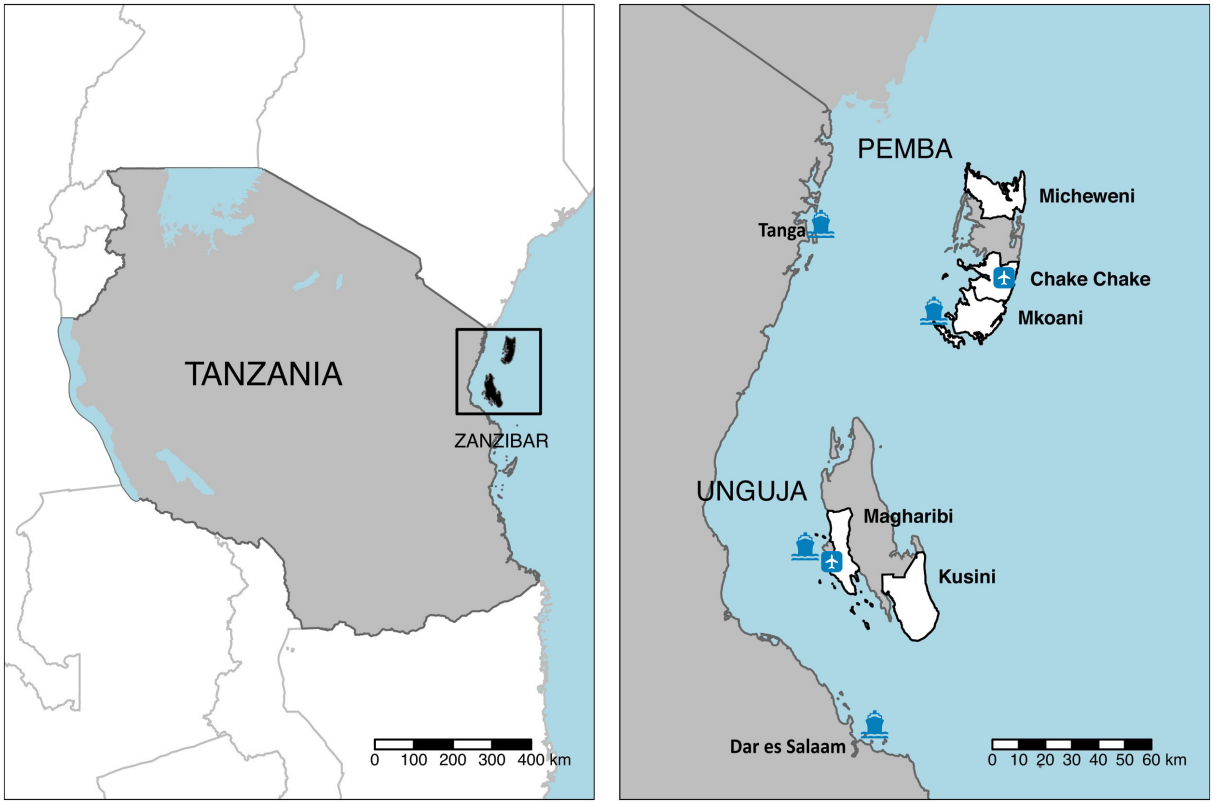

Figure 2.1: Map of Zanzibar, with the RADZEC study districts in white. Airports and ferry terminals are highlighted. Figure adapted from [88].

2.2.2 RADZEC cross-sectional survey data

The rolling cross-sectional survey component of the RADZEC study was conducted between May 2017 and October 2018. It involved following DMSOs on visits to the households of patients diagnosed with malaria at a health facility (from now on referred to as the index case). A cross-sectional survey was conducted at these households, which included a questionnaire, RDT tests, and collecting blood samples for quantitative polymerase chain reaction (qPCR) tests. The survey included three types of households: index case households, neighbouring households, and a transect of households stemming from the index household. Neighbouring households consisted of the four households nearest to the index case household, and transect households consisted of five households along a 200m transect starting from the index household. The full survey details are described elsewhere [88].

The survey collected data on a range of factors including demographics, a recent history of illness, and detailed travel history from the last 60 days. The median trip length was found to be six nights.

Within the survey population, 12,487 residents were tested with RDTs for malaria and 6,281 with qPCR tests. The sensitivity of RDTs to detect qPCR-detectable infections was found to be 34% [88].

The malaria prevalence on each island was estimated by first taking the number of PCR-positive test results outside of the index household above a cut-off of 0.13 parasites/μl, below which the chance of false positive results increases. The number of people with

PCR-positive results in neighbouring and transect households was divided by the total number of people tested in neighbouring and transect households on each island to give the estimated prevalence on each island. Members of the index household were not included as this would have led to an artificial inflation of the malaria prevalence as index households contained a known malaria case (the index case) and had a higher likelihood of containing additional cases [88]. As this data was collected around the households of index cases, there was a possibility that the prevalence in this sample was still higher than in a random sample. At the same time, as this method directly excludes index cases and index households, where malaria prevalence is typically higher, there was a chance that the prevalence found in neighbouring and transect households would be an underestimate. In order to compare to a random sample, the qPCR prevalence in neighbouring and transect households in Micheweni district (north Pemba) in the RADZEC dataset was compared to the mean prevalence found by qPCR in a randomly sampled cross-sectional survey conducted in Micheweni in 2015 [56]. The prevalence in neighbouring and transect households in the RADZEC study was 1.8% (95% CI: 0.9-2.7), while the prevalence in the cross-sectional survey conducted in a random sample of households was 1.7% (95% CI: 1.1–2.4). This suggests that the positivity rate in neighbouring and transect households is a good approximation of the population prevalence.

The mean number of neighbours tested per index case was 20.4 in Pemba and 18.2 in Unguja. The ratio of cases amongst index household members compared to neighbouring and transect households was 3.2 in Pemba and 10.0 in Unguja. The ratio of cases in neighbouring households compared to neighbouring and transect households was 0.8 in Pemba and 1.3 in Unguja.

Travel data suggested that travellers spend similar numbers of nights in multiple parts of mainland Tanzania, so the malaria prevalence for 2-10 year old children across all of Tanzania, as estimated by the Malaria Atlas Project, was taken as the baseline for mainland Tanzania [104]. This is likely an overestimate of the population prevalence, as the prevalence in 2-10 year old children is typically higher than in the general population [105].

Time spent away from home, captured in the travel matrix θ_{ij} (see Table 2.1), was calculated by noting which proportion of nights in the last 60 nights were spent away from home amongst survey respondents from each patch and where they were spent, where i and j represent Pemba, Unguja and mainland Tanzania,

$$\theta_{ij} = \frac{\text{Mean number of nights a resident of } j \text{ spent in } i \text{ over the last 60 nights}}{60}. \quad (2.1)$$

where $\sum_{j=1}^{3} \theta_{ij} = 1$.

As we did not have data on travel to Zanzibar by residents of mainland Tanzania, we have assumed that the same number of person-nights are spent in total by residents of mainland Tanzania on Zanzibar as the other way around. Thus,

$$\begin{aligned} &\text{Proportion of time spent on mainland} \times \text{Population of each island} \\ &= \text{Proportion of time spent on each island} \times \text{Population of mainland.} \end{aligned}$$

Treatment was not included in the models outside of treatment due to RCD (which also includes treatment of the index case). Instead, the daily natural clearance rate was taken to be $(1/200)\text{day}^{-1}$ [36, 106].

2.2.3 Model description

Human movement was modelled using a deterministic SIS metapopulation model including three patches for Pemba, Unguja and mainland Tanzania. This was then extended to include stochasticity and the effects of RCD on Pemba and Unguja.

A model schematic can be found in Fig. 2.2.

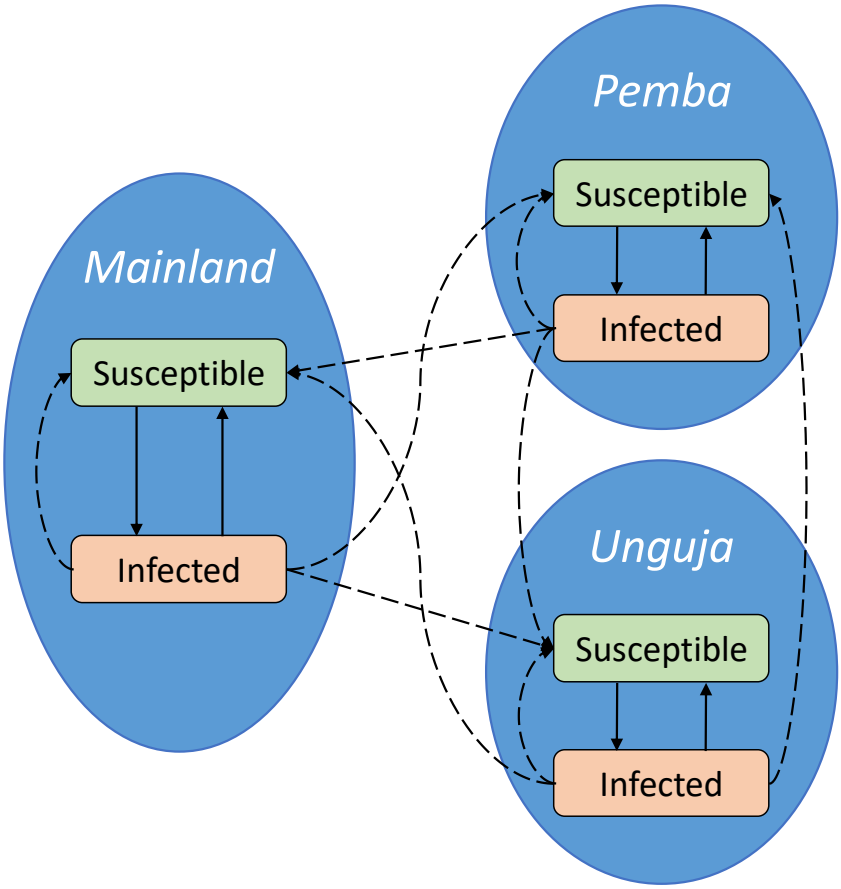

Figure 2.2: A schematic diagram of the model with two disease states in each patch. Solid arrows represent transitions between disease states, and dashed arrows represent transmission.

2.2.3.1 SIS model including human movement

Parameter or state variable	Description and units
I_k	Proportion of people who are infectious in patch k. Dimensionless.
I_k^*	Proportion of people who are infectious in patch k at equilibrium, before changes to ongoing interventions are applied. Dimensionless.
N_k	Total number of people in patch k. Humans.
β_k	The effective malaria transmission rate from humans to other humans in patch k. Day^{-1}.
θ_{ij}	The proportion of time the average resident of patch j spends in patch i. Dimensionless.
μ	Natural infection clearance rate. Day^{-1}.

Table 2.1: Descriptions of state variables and parameters for the SIS model with human movement.

The total number of people from patch j spending time in patch i, weighted by the amount of time they spend there, is given by $N_j\theta_{ij}$. Similarly, $N_j\theta_{ij}I_j$ gives the number of infected people from patch j spending time in patch i, weighted by the amount of time they spend there. When combined, the effective proportion of the population that is infectious in patch i is given by

$$A_i = \frac{\sum_{j=1}^{3} N_j\theta_{ij}I_j}{\sum_{j=1}^{3} N_j\theta_{ij}}. \tag{2.2}$$

A description of the parameters and state variables can be found in Table 2.1.

$\beta_i A_i \theta_{ik}$ is the contact rate between a susceptible individual from patch k and an infected individual in patch i. Summing over i gives the total rate at which a susceptible individual in patch k comes into contact with an infected person either in their own patch or another patch, and becomes infected,

$$B_k = \sum_{i=1}^{3} \left(\beta_i \left(\frac{\sum_{j=1}^{3} N_j\theta_{ij}I_j}{\sum_{j=1}^{3} N_j\theta_{ij}} \right) \theta_{ik} \right). \tag{2.3}$$

Eq. (2.3) is adapted from previous work by Ruktanonchai *et al* [49], accounting for both the infectious people moving in and out of patch k, as well as the time spent by residents of k in other patches.

Combining this with the proportion of susceptible individuals in patch k, which we represent as $S_k = 1 - I_k$, and allowing infected individuals to recover at the natural clearance rate of the disease gives the overall equation for the rate of change of I_k:

$$\frac{\mathrm{d}I_k}{\mathrm{d}t} = \sum_{i=1}^{3} \left(\beta_i \left(\frac{\sum_{j=1}^{3} N_j\theta_{ij}I_j}{\sum_{j=1}^{3} N_j\theta_{ij}} \right) \theta_{ik} \right) (1 - I_k) - \mu I_k. \tag{2.4}$$

We assume that the majority of trips are short-term trips and people retain the properties of their residential patch in terms of recovery rate and, in section 2.2.3.2, the RCD programme. Survey responses about travels in the last 60 days support the assumption of short trips.

We calibrated the model by assuming that malaria prevalence is at equilibrium. Under this assumption, we can calculate the transmission rate that would lead to the observed prevalence. Thus, setting the right hand side of Eq. (2.4) to 0,

$$\frac{\mu I_k^*}{1-I_k^*} = \sum_{i=1}^{3} \left(\beta_i A_i^* \theta_{ik}\right), k \in \{1,2,3\}, \tag{2.5}$$

where A_i^* is A_i at the equilibrium prevalence.

The transmission parameter, β, encompasses malaria transmission from humans to mosquitoes and back again, along with any malaria control strategies already in place. It can be derived as the solution to a set of simultaneous equations:

$$\begin{pmatrix}\beta_1\\ \beta_2\\ \beta_3\end{pmatrix} = \begin{pmatrix} A_1^*\theta_{11} & A_2^*\theta_{21} & A_3^*\theta_{31}\\ A_1^*\theta_{12} & A_2^*\theta_{22} & A_3^*\theta_{32}\\ A_1^*\theta_{13} & A_2^*\theta_{23} & A_3^*\theta_{33}\end{pmatrix}^{-1} \begin{pmatrix}\frac{\mu I_1^*}{1-I_1^*}\\ \frac{\mu I_2^*}{1-I_2^*}\\ \frac{\mu I_3^*}{1-I_3^*}\end{pmatrix}. \tag{2.6}$$

We then used the deterministic model to estimate the impact of human movement on malaria persistence on the islands of Pemba and Unguja. The impact of no human movement was modelled by keeping the calibrated transmission and recovery rates constant, but changing the time spent away from the home patch to 0 in all cases (i.e. $\theta_{ij} = 0$ for all $i \neq j$ and $\theta_{ij} = 1$ for all $i = j$ for $i, j \in 1, 2, 3$). This scenario acts as a counterfactual for deducing how human movement contributes to the persistence of malaria despite the current use of interventions.

2.2.3.2 SIS model including human movement and an RCD programme

Eq. (2.4) is modified in line with previous work by Chitnis *et al* [96] to include RCD. RCD is modelled by removing a number of infected individuals proportional to the number of infected people in that patch. The rate of change in I_k is now given by

$$\frac{\mathrm{d}I_k}{\mathrm{d}t} = \sum_{i=1}^{3}\left(\beta_i\left(\frac{\sum_{j=1}^{3} N_j\theta_{ij}I_j}{\sum_{j=1}^{3} N_j\theta_{ij}}\right)\theta_{ik}\right)(1-I_k) - (\mu+\varphi_k)I_k, \tag{2.7}$$

where φ_k is the rate of removing people from the infected class due to the RCD programme. This is the product of the number of cases followed up by the RCD programme per day, the mean number of household members in each index house, the ratio of positive tests in an index house versus the general population, and the test positivity rate, divided by the total population in that patch,

$$\varphi_k = \frac{\tau_k \nu_k \iota_k \rho}{N_k}. \tag{2.8}$$

Parameter descriptions can be found in Table 2.2. The number of cases followed up by the RCD programme per day depends on the number of infected people at any given time, the rate of seeking treatment, and the proportion of cases followed up by DMSOs,

$$\iota_k = \lambda_k \eta I_k N_k. \tag{2.9}$$

The rate of seeking treatment is assumed to be constant and is calculated from the observed number of cases arriving at the health facility at equilibrium,

$$\lambda_k = \frac{\iota_k^*}{\eta^* I_k^* N_k}. \tag{2.10}$$

The baseline value for the proportion of cases followed up by a DMSO at the index case household level, η^*, was taken to be the 3 day follow up rate: 35.3%.

Descriptions of RCD parameters can be found in Table 2.2.

Parameter	Description and units
φ_k	Treatment rate due to RCD programme in patch k. Day^{-1}.
φ_k^*	Treatment rate due to RCD programme at equilibrium in patch k. Day^{-1}.
τ_k	Ratio of malaria prevalence in individuals tested within the RCD programme as compared to the general population in patch k. Dimensionless.
ι_k	Number of cases followed up by a District Malaria Surveillance Officer per day in patch k. Humans per day.
ι_k^*	Number of cases followed up by a District Malaria Surveillance Officer per day at equilibrium in patch k. Humans per day.
ν_k	Number of people tested during follow up per index case in patch k. Dimensionless.
ρ	Rapid diagnostic test sensitivity. Dimensionless.
λ_k	The daily rate at which an infected individual seeks treatment in patch k. Day^{-1}.
η	The proportion of cases arriving at the health facility that are followed up by the DMSO. Day^{-1}.
η^*	The proportion of cases arriving at the health facility that are followed up by the DMSO within 3 days. Dimensionless.

Table 2.2: Descriptions of RCD programme parameters.

We compared testing only index household members in the RCD programme and testing both the index household and neighbours. When considering just index households, the targeting ratio was calculated by taking the ratio of the positivity rate, as measured by PCR, in index households compared to neighbouring and transect households. This was then adjusted in the model to ensure that a positive case was included for the index case, as often the index case had been treated by the time the DMSO followed up the case at the index household. The targeting ratio, $\tau^{(h)}$, given in Table 2.3 considers only the prevalence in index household members outside of the index case. When considering neighbouring households as well, the targeting ratio in neighbouring households

Variable or parameter	Mean values [95% CI]			Source
	Pemba	Unguja	Mainland	
I_k^*	1.36% [0.96-1.93]	1.18% [0.86-1.61]	7.79%	[88, 104]
N_k	406,848	896,721	43,625,354	[107]
θ_{ij}	$\begin{pmatrix} 0.991 & 0.004 & 5.7\times10^{-5} \\ 0.003 & 0.970 & 5.3\times10^{-4} \\ 0.006 & 0.026 & 0.999 \end{pmatrix}$			[88]
μ	0.005 day^{-1}	0.005 day^{-1}	0.005 day^{-1}	[36, 106]
$\tau^{(h)}$	3.2 [2.0-4.8]	10.0 [8.0-12.6]	N/A	[88]
$\tau^{(n)}$	0.7 [0.4-1.3]	1.3 [0.9-1.9]	N/A	[88]
$\nu^{(h)}$	7.0 [6.5-7.5]	6.3 [5.9-6.9]	N/A	[88]
$\nu^{(n)}$	20.4 [19.4-21.4]	18.8 [17.6-19.9]	N/A	[88]
ρ	34%	34%	N/A	[88]
η^*	35.3%	35.3%	N/A	[61]
η - range of values tested	0%, 35%, 48%, 60%, 62%, 100%	0%, 35%, 48%, 60%, 62%, 100%	N/A	Values based on DMSO follow up at the index case household level observed in [61]

Table 2.3: Variable and parameter values and sources. Where a range of parameter values were tested in the sensitivity analysis, the 95% confidence interval for the range of values tested is given. For θ_{ij}, the order of the rows and columns of the matrix correspond to Pemba, Unguja and mainland Tanzania.

was calculated by taking the ratio of PCR-positive cases in neighbouring households as compared to both neighbouring and transect households. We find that the likelihood of finding a case is 10 times higher in the index household than in a neighbouring household in Unguja, and 5 times higher in Pemba. The equation for φ_k was adapted to

$$\varphi_k = \frac{(\tau_k^{(h)}\nu_k^{(h)} + \tau_k^{(n)}\nu_k^{(n)})\iota_k\rho}{N_k}, \tag{2.11}$$

where the superscripts h and n refer to the index household and neighbouring households, respectively.

The RCD programme has been running on Zanzibar since 2012. We assume that the malaria prevalence has reached a steady state since the introduction of RCD. Case incidence data from 2012 to 2015 shows seasonal trends but relatively stable incidence over this time period [108]. Setting the right hand side of Eq. (2.7) to 0 and solving for β gives the transmission rates in the presence of an ongoing RCD programme,

$$\begin{pmatrix}\beta_1\\ \beta_2\\ \beta_3\end{pmatrix} = \begin{pmatrix}A_1^*\theta_{11} & A_2^*\theta_{21} & A_3^*\theta_{31}\\ A_1^*\theta_{12} & A_2^*\theta_{22} & A_3^*\theta_{32}\\ A_1^*\theta_{13} & A_2^*\theta_{23} & A_3^*\theta_{33}\end{pmatrix}^{-1} \begin{pmatrix}\frac{(\mu+\varphi_1^*)I_1^*}{1-I_1^*}\\ \frac{(\mu+\varphi_2^*)I_2^*}{1-I_2^*}\\ \frac{(\mu+\varphi_3^*)I_3^*}{1-I_3^*}\end{pmatrix}. \tag{2.12}$$

New interventions or potential changes to interventions are only simulated post-calibration. The transmission parameter on the three islands is unaffected by the new intervention, since all interventions considered here only target the infectious reservoir in humans and not the vectorial capacity.

2.2.3.3 Treatment of imported cases

Currently prophylaxis is not given to travellers when travelling to mainland Tanzania or vice versa. Similarly, there is no screen-and-treat programme for entrants to Zanzibar. We expanded our model to include treatment of imported cases as a potential intervention, in order to evaluate what proportion of cases must be treated to achieve different reductions in prevalence on Pemba and Unguja. Eq. (2.7) was modified to have a θ^{outbound}, which included treatment for mainland Tanzanians on their outbound journey to Zanzibar, and θ^{return} for Zanzibari residents that receive treatment on their return journey to Zanzibar. Thus Eq. (2.7) was modified to

$$\frac{\mathrm{d}I_k}{\mathrm{d}t} = \sum_{i=1}^{3}\left(\beta_i\left(\frac{\sum_{j=1}^{3}N_j\theta_{ij}^{\text{outbound}}I_j}{\sum_{j=1}^{3}N_j\theta_{ij}}\right)\theta_{ik}^{\text{return}}\right)(1-I_k) - (\mu+\varphi_k)I_k, \tag{2.13}$$

where

$$\theta^{\text{outbound}} = \begin{pmatrix}0.991 & 0.004 & (1-O)*5.7\times10^{-5}\\ 0.003 & 0.970 & (1-O)*5.3\times10^{-4}\\ 0.006 & 0.026 & 0.999\end{pmatrix}, \tag{2.14}$$

and

$$\theta^{\text{return}} = \begin{pmatrix}0.991 & 0.004 & 5.7\times10^{-5}\\ 0.003 & 0.970 & 5.3\times10^{-4}\\ (1-R)*0.006 & (1-R)*0.026 & 0.999\end{pmatrix}. \tag{2.15}$$

O represents the proportion of travellers from mainland Tanzania receiving treatment such that they are no longer infected upon entering Zanzibar, and R represents the proportion of Zanzibari residents receiving treatment such that they are no longer infected upon returning to Zanzibar.

2.2.4 Simulations

Stochastic simulations were only run with the model with RCD. In order to allow for small but finite populations of infectious individuals, a binomial tau-leap adaptation of the Gillespie algorithm was used to model Eq. (2.7) [109]. Following calibration, the current RCD programme (baseline of 35.3% follow up of index cases at index households only) was compared to a range of alternatives:

1. RCD at a range of levels of follow up (see Table 2.3 for values);
2. Expanding the RCD system to include follow up at four neighbouring households as well;
3. Doubling the daily treatment seeking rate;
4. rfMDA in the index household rather than test-and-treat;
5. Treating 50% of imported cases.

The effects of varying the proportion of cases followed up at the household level is tested by varying the follow up proportion between those seen in 3, 6, 15 and 21 days, as well as stopping the RCD programme altogether (no follow up) and perfectly following up every case. The potential benefits of testing and treating all neighbours in approximately four nearby households as well was considered. As the rate of seeking treatment amongst those infected is low, we tested doubling the daily treatment seeking rate (e.g. by promoting early treatment seeking or broader testing of patients at formal health facilities, or due to more individuals being symptomatic due to waning immunity). Additionally, rfMDA was modelled with the same parameters as for RCD, except the value of the test sensitivity was changed to 100%, as all index household members, infected or susceptible, would automatically receive treatment. Finally, treating 50% of cases imported onto the islands by either Zanzibari residents travelling to mainland Tanzania, or visitors from mainland Tanzania were also modelled ($O = R = 0.5$). 500 simulations were run for each combination of intervention parameters.

2.2.5 Impact of parameter uncertainty

The impact of parameter uncertainty was investigated by testing a range of parameter values in a sensitivity analysis. The values were based on the uncertainty in the sample data. The parameters varied and the distributions from which they were sampled were as follows:

- The equilibrium malaria prevalence on Pemba, $I_1^* \sim \text{Beta}(32, 2242)$;
- The equilibrium malaria prevalence on Unguja, $I_2^* \sim \text{Beta}(92, 3196)$;
- The targeting ratio in index households in Pemba, $\tau_1^{(h)} \sim \frac{\text{Beta(20,427)}}{I_1^*}$;
- The targeting ratio in index households in Unguja, $\tau_2^{(h)} \sim \frac{\text{Beta(64,470)}}{I_2^*}$;
- The targeting ratio in neighbouring households in Pemba, $\tau_1^{(n)} \sim \frac{\text{Beta(13,1147)}}{I_1^*}$;
- The targeting ratio in neighbouring households in Unguja, $\tau_2^{(n)} \sim \frac{\text{Beta(26,1619)}}{I_2^*}$;
- The number of people tested by the RCD programme in the index household in Pemba, $\nu_1^{(h)} \sim \text{Normal}(7.02, 0.24)$;
- The absolute number of people tested by the RCD programme in the index household in Unguja, $\nu_2^{(h)} \sim \text{Normal}(6.36, 0.25)$;

- The absolute number of people tested by the RCD programme in neighbouring households in Pemba, $\nu_1^{(n)} \sim \text{Normal}(20.36, 0.50)$;
- The absolute number of people tested by the RCD programme in neighbouring households in Unguja, $\nu_2^{(n)} \sim \text{Normal}(18.76, 0.58)$.

Subscripts of *1* and *2* indicate Pemba and Unguja, respectively. 100 random values were selected from these parameter distributions, and each set of values was simulated with five different seeds, forming a total of 500 simulations for each intervention. The 95% confidence intervals of the distributions used for these parameters can be found in Table 2.3.

2.3 Results

2.3.1 SIS model including human movement

The SIS transmission model described by Eq. (2.4) showed standard dynamics of reaching the equilibrium prevalence seen in the RADZEC study. When human movement was removed by changing the movement matrix, θ, to an identity matrix, the equilibrium prevalence dropped to zero on both Pemba and Unguja. This result is to be expected, as the calibrated transmission parameter is lower than the natural parasite clearance rate in both Pemba and Unguja. The calibrated values for β were 0.0048 (95% CI: 0.0044-0.0050), 0.0037 (95% CI: 0.0025-0.0.047) for Pemba and Unguja, respectively. R_c, given by the transmission rate divided by the recovery rate, was found to be 0.95 (95% CI: 0.88-1.00) on Pemba and 0.74 (95% CI: 0.50-0.94) on Unguja.

An analysis of the reproductive number of the whole system showed that the overall reproductive number is highly dependent on the transmission rate on mainland Tanzania. Details of this analysis can be found in Appendix Section A.1.

2.3.2 SIS model including human movement and an RCD programme

All simulations were initially calibrated to the baseline scenario of 35.3% follow up of index cases at the household level only. Year 0 is when the intervention is introduced.

Fig. 2.3 shows the timeseries expected from removing RCD that is currently in place. The proportion of index cases followed up by a DMSO was set to 0 from year 0. We observe a rise in the malaria prevalence until a new equilibrium is reached. The 50% and 95% confidence intervals of the 500 simulations at each time point are also included, alongside the median number of infected individuals. For illustration purposes, three individual stochastic simulations are also included to show how the malaria prevalence may vary within a single simulation. While individual simulations can fluctuate quite a lot, the median settles to a pseudo-equilibrium. We estimate that removing RCD would lead to a 10% increase in malaria prevalence on Pemba, and an 8% increase in prevalence on Unguja.

Fig. 2.4 shows the impact of increasing the proportion of cases followed up by a

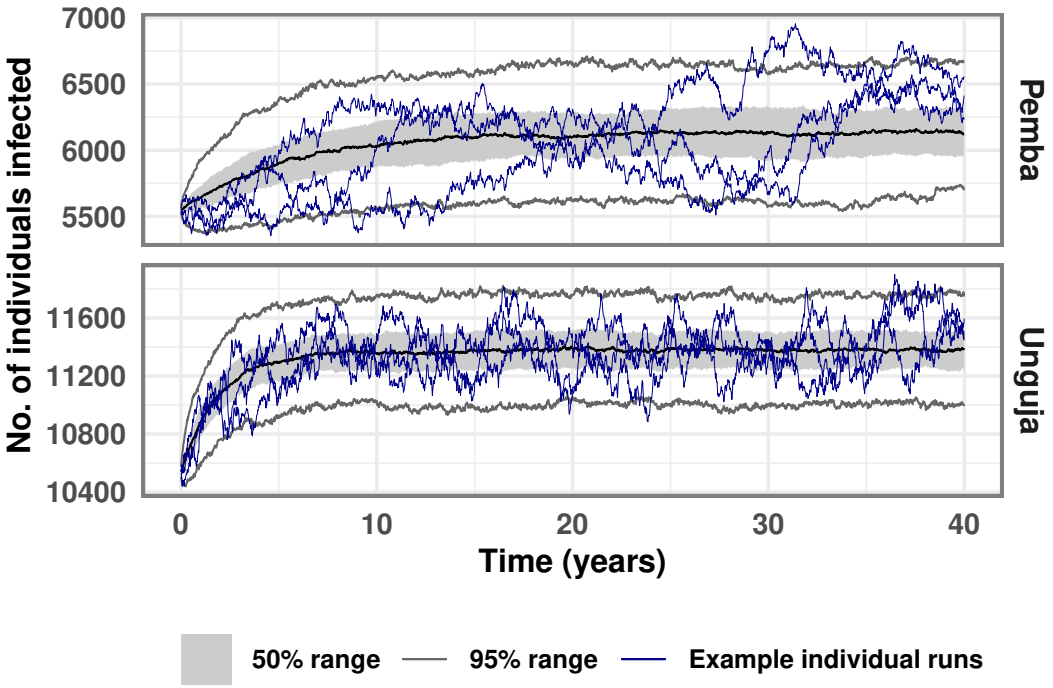

Figure 2.3: Timeseries of 500 stochastic simulations showing the median, 50% confidence interval, 95% confidence interval, and three individual simulation runs, for the scenario where all RCD is stopped at year 0.

DMSO in a timely manner from the 3-day follow up proportion of 35%, to the 21-day follow up proportion of 62%, and then to 100%. The final malaria prevalence reached under these intervention scenarios are compared to the baseline malaria prevalence (RCD with 35% of index cases followed up) and a counterfactual which indicates the pseudo-equilibrium reached when RCD is stopped (Fig. 2.3). Increasing follow up with no other changes to RCD has a very small effect on the final malaria prevalence reached after 40 years. Including 4 neighbouring households in RCD makes a negligible difference to the malaria prevalence. Shifting to rfMDA leads to some additional cases being treated due to the removal of testing. This decrease in prevalence is further compounded when combined with following up all index cases at the index household. Once again, including neighbouring households in rfMDA does not make a substantial difference. Doubling the rate at which infected people seek treatment and are identified as index cases leads to RCD finding and treating roughly twice as many cases. Finally, treating 50% of imported cases such that they cannot lead to further cases on Zanzibar led to large reductions in prevalence, with a 43% reduction in prevalence on Pemba and a 47% reduction in prevalence on Unguja.

Treating people who travel would need to achieve high coverage for both travellers to and from mainland Tanzania to achieve a substantial reduction in prevalence, as illustrated in Fig. 2.5. Time-series plots for a range of treatment proportions can be seen in Appendix Fig. A.1. Due to the transmission rate being substantially higher on Pemba than Unguja, even treating all malaria importations from mainland Tanzania would likely be insufficient to lead to elimination within 40 years on either Pemba or Unguja, as infections would be imported from Pemba to Unguja, sustaining transmission.

Fig. 2.6 shows the amount of resources needed for RCD and rfMDA when including or

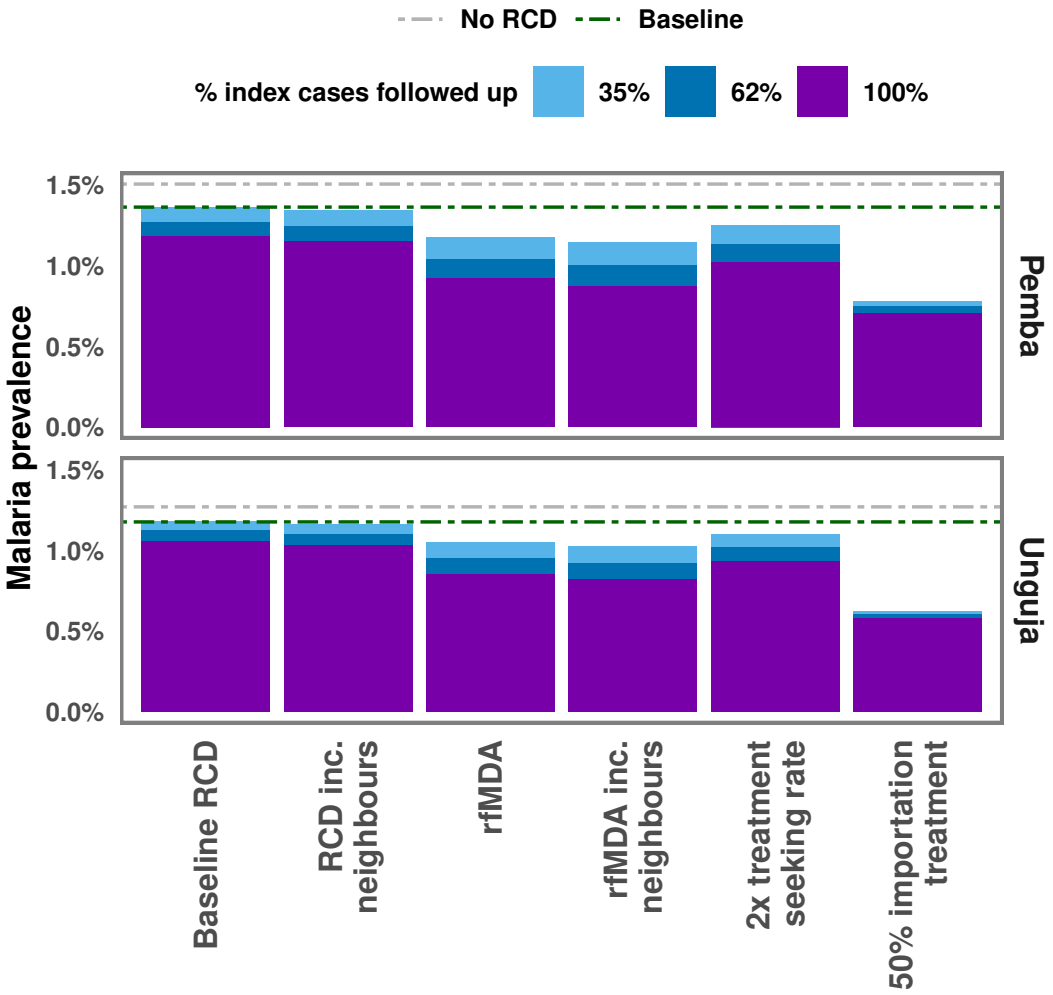

Figure 2.4: Median malaria prevalence reached after 40 years of simulations under different intervention scenarios and with different levels of follow up of index cases arriving at a health facility. Dashed lines indicate the baseline prevalence and the prevalence expected with no RCD. 'Baseline' refers to the malaria prevalence in the presence of RCD with 35% follow up of index cases, as observed in the RADZEC study.

not including neighbours, or when following up 100% of cases at the index household level. This figure does not consider the RDTs or ACTs needed outside of RCD (e.g. RDTs used to detect index cases in the health facility or ACTs distributed through pharmacies for malaria treatment outside of RCD). It also does not consider the additional personnel and time needed to expand RCD to include neighbours. In general, including neighbours leads to a much larger use of resources but with little gains in malaria prevalence reduction.

2.3.3 Impact of parameter uncertainty

Our analysis suggests that switching from RCD to rfMDA (at the same proportion of index cases followed up at the household level: 35.3%) has a similar impact as increasing the follow up proportion in the RCD programme to 100%, but neither increase the recovery

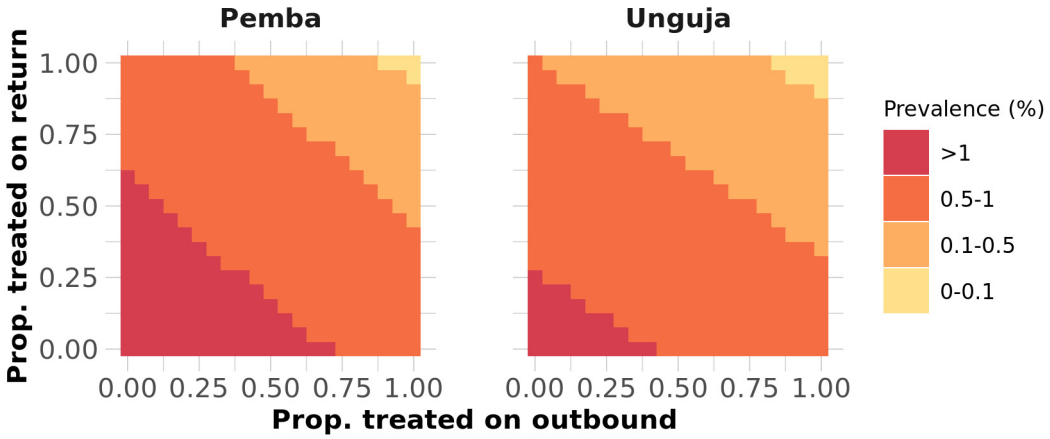

Figure 2.5: Heatmap showing the median final prevalence reached after 40 years out of 500 stochastic runs when treatment of travellers is included.

rate sufficiently to lead to elimination. A larger decrease in prevalence is seen if rfMDA is implemented with 100% of follow up at the index case household level, or if 50% of imported cases are treated. When parameter uncertainty is included in the simulations, we find that although the final prevalence reached in 40 years is sensitive to the varied parameters (see Fig. 2.7), the overall trends remained the same. It is worth noting that the median prevalence reached after 40 years across 100 parameter sets differs from the prevalence reached in previous figures due to the difference in the median and modal values of the parameter distributions (see Supplementary Information for details).

2.4 Discussion

Our results suggest that case importation and the low test sensitivity of RDTs in asymptomatic patients are the main factors that should be targeted to substantially reduce Zanzibar's malaria burden, while continuing to maintain the vector control measures that are currently in place. Removing the RCD programme would likely lead to an increase in malaria prevalence, but increasing follow up to cover all malaria cases arriving at a health facility would still be insufficient for reaching elimination. Treating imported cases, implementing rfMDA at the household level and increasing the rate at which infected people seek treatment would help reduce the endemic prevalence on both islands substantially. 100% imported case treatment is expected to reduce the prevalence below 1 case per 100,000 on Unguja and 1.4 cases per 10,000 population on Pemba, as Zanzibar acts as a sink for infections from mainland Tanzania, where prevalence is higher. This result assumes that all current measures are maintained. Relaxing interventions already in place may lead to the local reproduction number being higher than 1, and thus elimination would not be achieved even with treating 100% of imported cases.

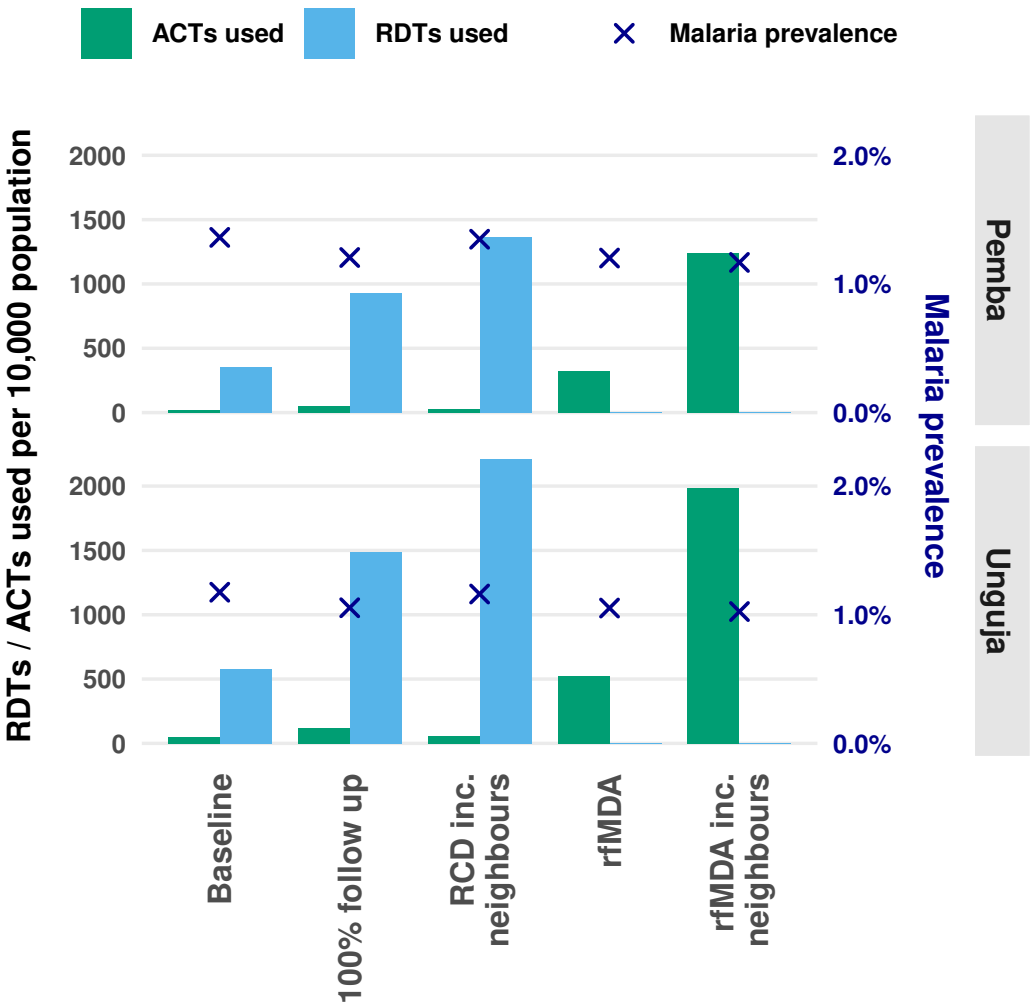

Figure 2.6: The cumulative number of RDTs and ACTs used per 10,000 population over 10 years since the start of interventions. Additionally, the crosses represent the malaria prevalence reached with that intervention. 'Baseline' refers to RCD with 35% follow up of index cases. '100% follow up' refers to RCD with 100% follow up of index cases. 'RCD inc. neighbours' refers to RCD with 35% follow up of index cases and testing and treatment at the index household and four neighbouring households. 'rfMDA' refers to 35% follow up and presumptive treatment of index household members. 'rfMDA inc. neighbours' refers to following up 35% of index cases and presumptive treatment of the index household and members of four neighbouring households. Note, this does not include RDTs used for diagnosing index cases, or ACTs used in malaria treatment outside of RCD.

As those residing in the same household as index cases are significantly more likely to test positive for malaria than those residing in neighboring households [88], the extra effort of testing neighboring residents makes little difference to overall transmission as compared to increasing follow up at the households of index cases. Expanding RCD to include neighbours requires extra resources and the reduction in malaria prevalence is minimal in comparison to the extra RDTs and human resources required. Nonetheless, surveillance is a key component of establishing when malaria elimination has occurred, so some form of passive or active surveillance is required to monitor cases. This can be

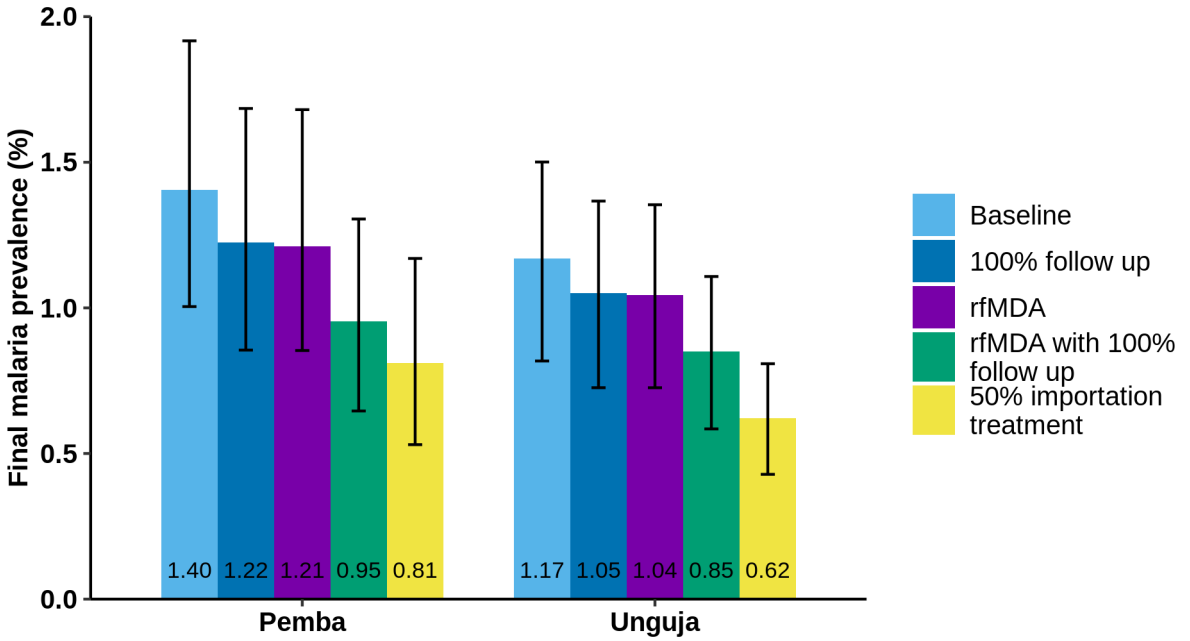

Figure 2.7: Bar chart showing the final equilibrium value after 40 years of the SIS model with the current RCD system (baseline), an RCD system with 100% follow up, replacing the RCD system with rfMDA, both replacing the RCD system with rfMDA and increasing follow up to 100%, and treating 50% of imported cases while maintaining the baseline RCD programme. The error bars here show the 95% confidence interval for both the stochastic variation and parameter uncertainty.

RCD or just case reporting, but RCD allows for the surveillance of asymptomatic cases as well.

Moving from RCD to rfMDA allows for the treatment of approximately three times more cases for any given prevalence, particularly low density infections that are less likely to be detected by RDT, but may still contribute to onward transmission. It is possible that early infections in neighbours are missed by RCD as the parasite density may be too low to be detected by RDTs. A previous field study compared RCD to rfMDA in the low malaria-endemic setting of Namibia and found a significant reduction in incidence in the rfMDA arm [98]. rfMDA in this context could also have a prophylactic effect, preventing onward transmission from the index case. However, rfMDA involves substantially greater use of ACTs than RCD. This may have a negative effect on parasite resistance [110, 111]. Increases in drug resistance may lead to increased treatment failure rates, leading to a resurgence in malaria prevalence, though this was not found to be a frequent cause of malaria resurgence in previous work [112].

These results are broadly in line with findings from other studies on RCD effectiveness in different settings. A recent study of mass drug administration campaigns in the Greater Mekong Subregion suggested that an RCD programme in the region would have missed 99.6% of *Plasmodium* infections [113]. When modelling RCD in southern Zambia, the number of people presenting to a health facility with malaria and being followed up was found to be a limiting factor for an RCD programme's success [43]. Similarly, an independent study of Zambia's reactive case detection system found that in low-transmission settings, improving case management (the rate at which patients seek treatment from

health facilities) would have a greater impact on onward transmission than further improving the RCD system [41]. Additionally, this study highlighted that in both low and high transmission settings, importation management was crucial for successful disease elimination. Similar results were found by Le Menach *et al* when examining malaria importation rates onto Pemba and Unguja in 2012 [45]. Our findings also show that importation management is key to interrupting transmission on Unguja and substantially reducing disease prevalence on Pemba. As the average time spent on mainland Tanzania is higher amongst Unguja residents in the sample, as compared to Pemba residents, the effect of importation was estimated to be larger on Unguja than on Pemba.

We calibrate the transmission rate based on the malaria prevalence in the three patches and the movement between the patches. We make the simplifying assumption that factors such as immunity profiles, healthcare access, and the proportions of patients who are asymptomatic are identical amongst travellers and non-travellers due to a lack of empirical data from Tanzania on these factors. This may not necessarily be true, as in some areas, migration is associated with less use of healthcare facilities and higher malaria risk profiles [114]. This would suggest that malaria in travellers might play a larger role in transmission than described in this study. On the other hand, repeated exposure to malaria among travellers might lead them to have greater levels of immunity than non-travellers, and so they may have lower parasite densities and, subsequently, lower infectiousness when infected. In that case, the impact of case importation may be smaller than described. We also assume that longer-term migrants do not play a significant role in case importation in Zanzibar. This is supported by a study looking at census data and malaria transmission rates in East Africa, which suggests that most migrants from high transmission areas settle near the borders of mainland Tanzania, but not many come to Zanzibar [103].

Reconstructing travel history data from survey responses is prone to underestimates of travel frequency, as certain trips may not be recalled. Thus, our estimate of the amount of time Zanzibari residents spend away from home are likely to be underestimates. Therefore, malaria importation is likely to play a larger role in malaria persistence than estimated here. We have also not considered the seasonal variation in travel. The busiest travel period typically falls between October and December, which coincides with the shorter period of seasonal rainfall [45, 56]. This variation throughout the year will also impact the rate of case importation into the region.

As RDTs typically detect cases with a higher parasite density, and cases with a higher parasite density are more likely to be symptomatic, RCD may, over time, lead to the infectious reservoir being skewed towards asymptomatic infections. In this model, we model all infections as having equal infectiousness, whereas these asymptomatic infections may have a lower infectiousness, and so the impact of RCD may be greater than that displayed here.

Additionally, we have assumed that malaria transmission is constant throughout the year on the islands. The data used in this study is averaged across both high and low seasons of transmission [88]. Seasonal transmission likely increases the importance of imported cases, as elimination may be achieved in the dry season, but cases are reintroduced in the wet season when the transmission rate is higher. Also, reactive vector control is another reactive intervention that may be considered in the wet season, which would involve spraying insecticide inside index and neighbouring households to prevent further transmission from known cases. A field study of reactive vector control found

adding it to RCD or rfMDA had an additional benefit in reducing malaria incidence in Namibia [98].

This analysis does not preclude the existence of smaller foci of transmission that could exist on these islands. Transmission is likely to be heterogeneous, with local sources and sinks of cases. As there was insufficient data on local movement patterns within each island, each island has been treated as homogeneous. Extending this analysis with other sources of data on travel, such as call record detail data, would allow for a finer-scale analysis of parasite sources and sinks.

Additionally, as the model presented here is an SIS model, it does not include the relationship between infection and disease, which would play a role in the effectiveness of an RCD programme that relies on patients seeking treatment. This should be considered in future work conducted in this area.

Here, we have defined malaria elimination as having zero malaria infections present on an island. In contrast, the World Health Organization defines a country to have eliminated malaria when they have zero indigenous cases for three consecutive years, allowing for some imported and introduced cases [87]. Thus, our definition of elimination is a stricter definition in comparison to the World Health Organization.

2.5 Conclusion

Our analysis suggests that the current interventions in place on Unguja have sufficiently reduced the transmission rate such that malaria elimination could be achieved in the absence of imported cases. On Pemba, the situation is less clear, though the mean controlled reproduction number is below 1. Current interventions should be maintained, and improvements to the surveillance-response system are expected to have an incremental effect on the malaria prevalence. Interventions with the most impact were found to be those that removed the majority of cases imported to the islands.

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Authors' contributions

AMD contributed to the conceptualization, methodology, formal analysis and writing of this manuscript; MAH and JOY contributed to the conceptualization and critically reviewed the manuscript; LS contributed to the investigation, data curation and critically reviewed the manuscript; BSF, AHA and AA contributed to the investigation and critically reviewed the manuscript; NC contributed to the conceptualization, methodology and supervision of the study, and critically reviewed the manuscript. All authors gave final approval for publication and agree to be held accountable for the work performed therein.

Chapter 3

Modelling the impact of interventions on imported, introduced and indigenous malaria infections in Zanzibar, Tanzania

3 Modelling the impact of interventions on imported, introduced and indigenous malaria infections in Zanzibar, Tanzania

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Abstract

Malaria cases can be classified as imported, introduced or indigenous cases. The World Health Organization's definition of malaria elimination requires an area to demonstrate that no new indigenous cases have occurred in the last three years. Here, we present a stochastic metapopulation model of malaria transmission that distinguishes between imported, introduced and indigenous cases, and can be used to test the impact of new interventions in a setting with low transmission and ongoing case importation. We use human movement and malaria prevalence data from Zanzibar, Tanzania, to parameterise the model. We test increasing the coverage of interventions such as reactive case detection; implementing new interventions including reactive drug administration and treatment of infected travellers; and consider the potential impact of a reduction in transmission on Zanzibar and mainland Tanzania. We find that the majority of new cases on both major islands of Zanzibar are indigenous cases, despite high case importation rates. Combinations of interventions that increase the number of infections treated through reactive case detection or reactive drug administration can lead to substantial decreases in malaria incidence, but for elimination within the next 40 years, transmission reduction in both Zanzibar and mainland Tanzania is necessary.

3.1 Introduction

Globally, the case incidence of malaria has fallen from around 81 cases per 1000 population at risk from the year 2000 to 59 in the year 2020. Within the same time frame, deaths per 100,000 population at risk have halved, falling from 30 to 15 [27]. As the burden of the disease falls, the number of countries looking to eliminate malaria grows. The World Health Organization (WHO) defines malaria elimination as the interruption of local transmission of a specified malaria parasite species in a defined geographical area as a result of deliberate activities [115]. WHO defines the interruption of local transmission as the reduction to zero incidence of indigenous cases, where it classifies *Plasmodium falciparum* malaria cases into the following categories: imported, introduced, indigenous, and induced, as defined in Table 3.1. Certification of malaria-free status by WHO requires the country to show three years of zero indigenous cases [116].

Term	Description
Imported case	Malaria case or infection in which the infection was acquired outside the area in which it is diagnosed
Introduced case	A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first-generation local transmission)
Indigenous case	A case contracted locally with no evidence of importation and no direct link to transmission from an imported case
Induced case	A case the origin of which can be traced to a blood transfusion or other form of parenteral inoculation of the parasite but not to transmission by a natural mosquito-borne inoculation

Table 3.1: WHO classification of malaria cases [116]. Furthermore, WHO defines a case as the occurrence of malaria infection in a person in whom the presence of malaria parasites in the blood has been confirmed by a diagnostic test [116]; therefore cases are defined on infection status and not on clinical symptoms.

So far, WHO has certified 40 countries as having eliminated malaria, with another 61 classified as either a country where malaria never existed or where malaria disappeared without specific measures [117]. In 93 countries, malaria remains endemic, though 47 of these countries reported fewer than 10,000 cases in 2020 [27]. As countries and regions head towards elimination, the focus of malaria programmes typically shifts from reducing the burden of the disease to reducing the rate of malaria transmission, finding and treating each remaining infection, and preventing the re-establishment of local transmission.

Since interventions do not have the same effect on the different categories of cases, different intervention approaches may be required depending on the composition of cases in a particular setting. Previous models of malaria importation have examined the presence of sources and sinks of malaria within a country [48, 49], the proportion of detected infections that must be imported infections to ensure that each infection typically leads to fewer than one subsequent infection [46], and the reproduction number in the absence of importation [45]. Wesolowski *et al* (2012) and Ruktanonchai *et al* (2016) studied the movement of malaria infections within Kenya and Namibia using mobile phone usage data to infer where malaria would not be sustained without ongoing importation of infections. Churcher *et al* (2014) used branching process theory to model the total number of infections stemming from a single malaria infection and used this to show that the reproductive number is likely to be below 1 in Eswatini. Le Menach *et al* (2011) used a combination of mobile phone data and ferry traffic data to estimate the per capita malaria importation rate for Zanzibar, Tanzania. From this, they concluded that the reproduction number for malaria was below 1 on both major islands of Zanzibar and that typically around 1.6 cases were imported from mainland Tanzania per 1000 inhabitants per year. However, they assumed a constant importation rate and only importation from mainland Tanzania, excluding the movement of infections between the islands.

Zanzibar is a semi-autonomous archipelago of islands in the Indian Ocean just south of the Equator. It consists of two main islands, Unguja and Pemba. Unguja has a population of close to a million, is more urban and has stronger connections and more movement with mainland Tanzania. Pemba has less than half the population of Unguja, is conversely more rural and has fewer connections with the mainland.

Zanzibar has seen a decline in malaria transmission since the year 2000 due to the intensive use of vector control and passive surveillance efforts [56]. However, progress has stagnated since around 2007, with malaria persisting at a low prevalence on both main islands. Reactive case detection (RCD), the active search for malaria infections following the detection of a clinical index case at a health facility, was introduced in 2012 to help find malaria infections within the community, particularly those that may be asymptomatic and thus missed by passive surveillance. In Zanzibar, approximately 35% of index cases are followed up at their household (referred to as the index household) within 3 days. Within the index household, everyone who consents is tested with a rapid diagnostic test (RDT) and those found to be positive for malaria are treated. This RDT was estimated to have a sensitivity of 34% as compared to quantitative polymerase chain reaction (qPCR). Previous modelling studies have highlighted that improvements to RCD and sustaining current levels of vector control and passive surveillance are likely insufficient for achieving elimination [118], and imported infections need to be targeted to prevent chains of transmission [45, 118]. However, all these studies defined elimination as zero malaria infections, irrespective of their classification, which is not realistic in areas with regular movement of people to and from neighbouring regions with ongoing endemic transmission. To our knowledge, no prior studies have modelled imported, introduced, and indigenous infections explicitly and examined the impact of interventions on these three categories of infections; therefore no previous work has been able to model the probability of elimination as defined by the WHO.

In this study, we explicitly model imported, introduced and indigenous separately to model the feasibility of achieving three years with no indigenous cases with current and potential future interventions to achieve the WHO standard for malaria-free certification. We do not include induced cases because they are responsible for less than 0.1% of all classified cases in Zanzibar (Abdul-wahid Al-mafazy, personal communication). We parameterise the model with data from 2017–18 from Zanzibar and analyse it to infer an estimate for the proportions of each category of infections on Pemba and Unguja. We then use this model to examine the impact of combinations of interventions such as improvements to reactive case detection (RCD), increasing the number of clinical cases detected in health facilities, switching to reactive drug administration (RDA), and treatment of imported infections. We also considered the impact of further reductions in transmission rates, both on Zanzibar and on the mainland, although we did not explicitly model the interventions that would lead to the reductions. The structure of this model allows us to explicitly model the probability of achieving the WHO definition of elimination — three years with zero new indigenous infections — as well as investigating the resulting changes in incidence on Zanzibar.

We follow WHO terminology in defining a malaria case as anyone infected with *P. falciparum* parasites, including both symptomatic and asymptomatic infections. However, we assume that diagnosis of cases only occurs in the patch of residence so we classify cases relative to their patch of residence: therefore we define imported infections as infections acquired when away from the area of residence; introduced infections as infections stemming from an imported infection, or from an infected visitor visiting the area of residence of the introduced infection; and indigenous infections as infections stemming from introduced or other indigenous infections. Thus, our definition of imported cases differs slightly from the WHO definition, as infected visitors are not counted as imported cases in the model (they would be classified as either an imported, introduced or indigenous case

in their area of residence depending on where they acquired the infection). Our definition of introduced and indigenous cases match the definitions used by WHO, although in our simulations we have knowledge of the position of cases in the chain of transmission, which is not always known by elimination programmes when classifying cases.

3.2 Results

Using our model, we estimate that 88% of new infections on Pemba are indigenous infections, 8% are introduced infections, and 4% are imported infections (Fig 3.1). On Unguja, we estimate that 56% of new malaria infections are indigenous infections, 25% are introduced infections, and 18% are imported infections. These results are not directly estimated from local case notification data, but rather an output of the model, arising from the travel history of survey respondents and the prevalence of malaria in the areas visited.

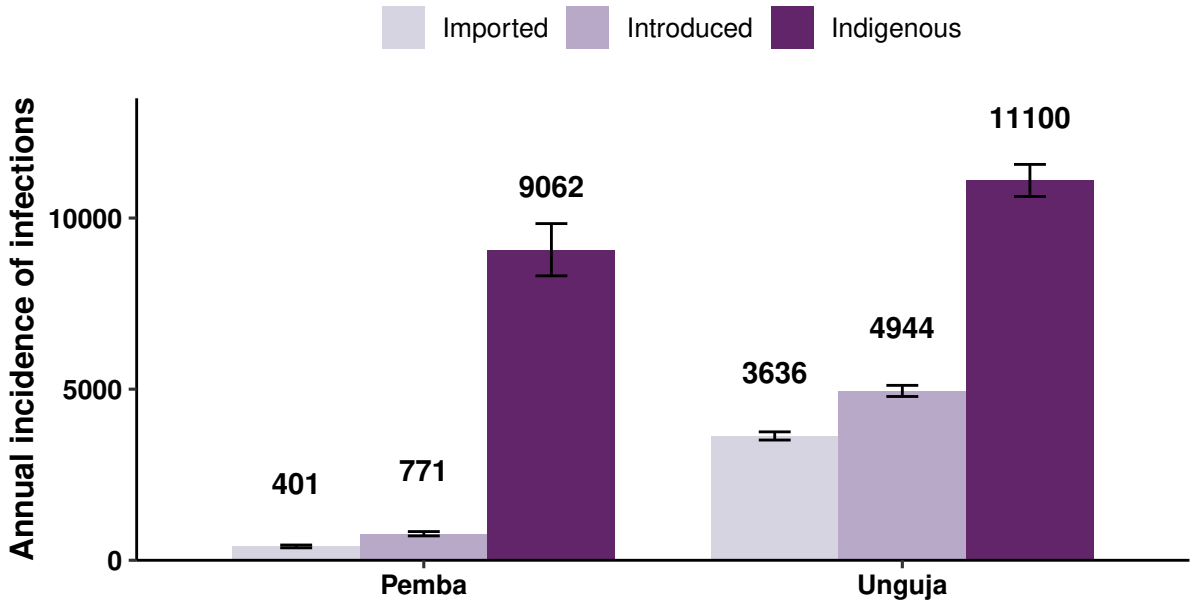

Figure 3.1: Median annual incidence of imported, introduced and indigenous malaria cases at baseline. Median annual incidence of imported, introduced, and indigenous infections on Pemba and Unguja at baseline. The height of the bar represents the median value across n=500 simulations. The error bars represent the 95% prediction interval of the annual incidence.

Previously, a simpler version of this model found the calibrated values for the effective daily transmission rate for each infected individual ($\boldsymbol{\beta}$) were 0.0048 day^{-1} (95% CI: 0.0044-0.0050) on Pemba and 0.0037 day^{-1} (95% CI: 0.0025-0.0.047) on Unguja [118]. The controlled reproductive number, given by the transmission rate divided by the recovery rate, was estimated to be 0.95 (95% CI: 0.88-1.00) on Pemba and 0.74 (95% CI: 0.50-0.94) on Unguja. These results remain unchanged by the extension of the model.

Removing RCD entirely is expected to lead to an increase in incidence of 10% in Pemba

and 5% in Unguja. Switching from RCD to RDA is expected to lead to the treatment of approximately three times as many infections in the population for a given malaria prevalence, since RDTs currently miss approximately two-thirds of qPCR-detectable infections [88]. In the model, we observe 12% fewer new infections in Pemba and 7% fewer new infections in Unguja when we switch from RCD to RDA. In Fig. 3.2, we show time-series plots for the impact of switching from RCD to RDA at year 0 on the three categories of infections, since this is an intervention that is currently being considered for implementation by the Zanzibar Malaria Elimination Program (ZAMEP). The impact of switching to RDA on the incidence of imported cases is minimal, as transmission for these cases typically occurs on mainland Tanzania, and RDA is being implemented in Zanzibar. The impact on the incidence of introduced cases is small, and the impact on indigenous cases is substantial on both Pemba and Unguja, as these transmission events occur on Zanzibar and so are reduced by the shift from RCD to RDA.

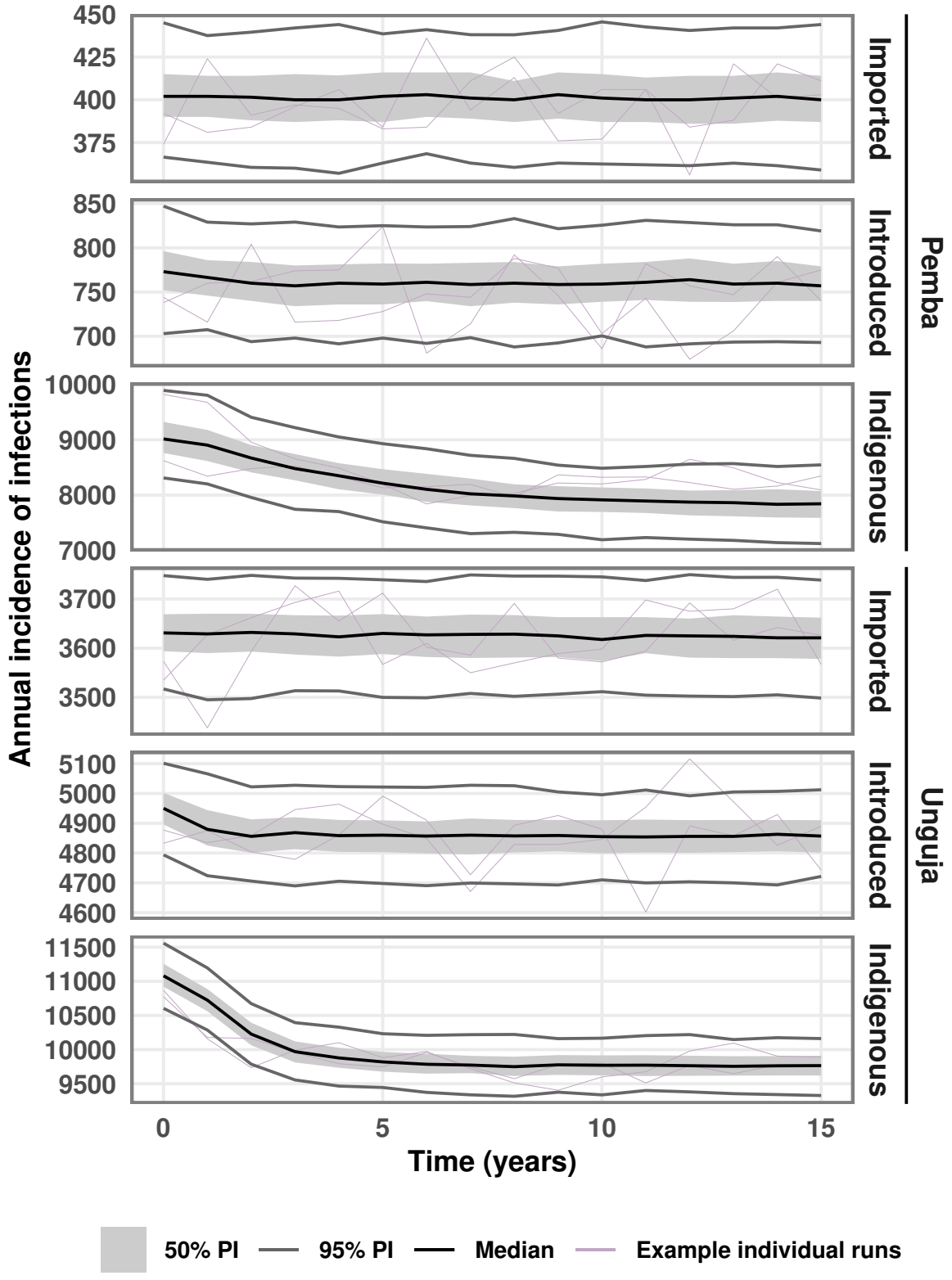

Figure 3.2: Simulated annual malaria incidence after switching from reactive case detection (RCD) to reactive drug administration (RDA). Time-series plot showing the median annual incidence of malaria infections across n=500 stochastic simulations, after switching from RCD to RDA in year 0. Grey shaded area indicates the interquartile prediction interval, and the grey lines indicate the 95% prediction interval of simulation results. Purple lines are examples of individual runs. 'PI' stands for prediction interval.

Fig. 3.3 shows the incidence of indigenous infections per 10,000 population in the 15^{th} year from the implementation of interventions. Most RCD-related interventions have a similar impact on the incidence of indigenous infections (Fig. 3.3A). Across all three categories of infections, increasing follow up of index cases from 35% to 100% is estimated to lead to an incidence reduction of 12% in Pemba and 7% in Unguja. Similarly, the median drop in incidence from a three-fold increase in the treatment seeking rate is estimated to be 12% in Pemba and 8% in Unguja. Including 100 neighbours in RCD is expected to have a smaller impact than other RCD-related interventions, with a 6% reduction in incidence in Pemba and a 4% reduction in Unguja. Treating infected travellers has the largest impact on transmission, with a 90% treatment proportion leading to an 85% reduction in incidence on Pemba, and an 89% reduction on Unguja.

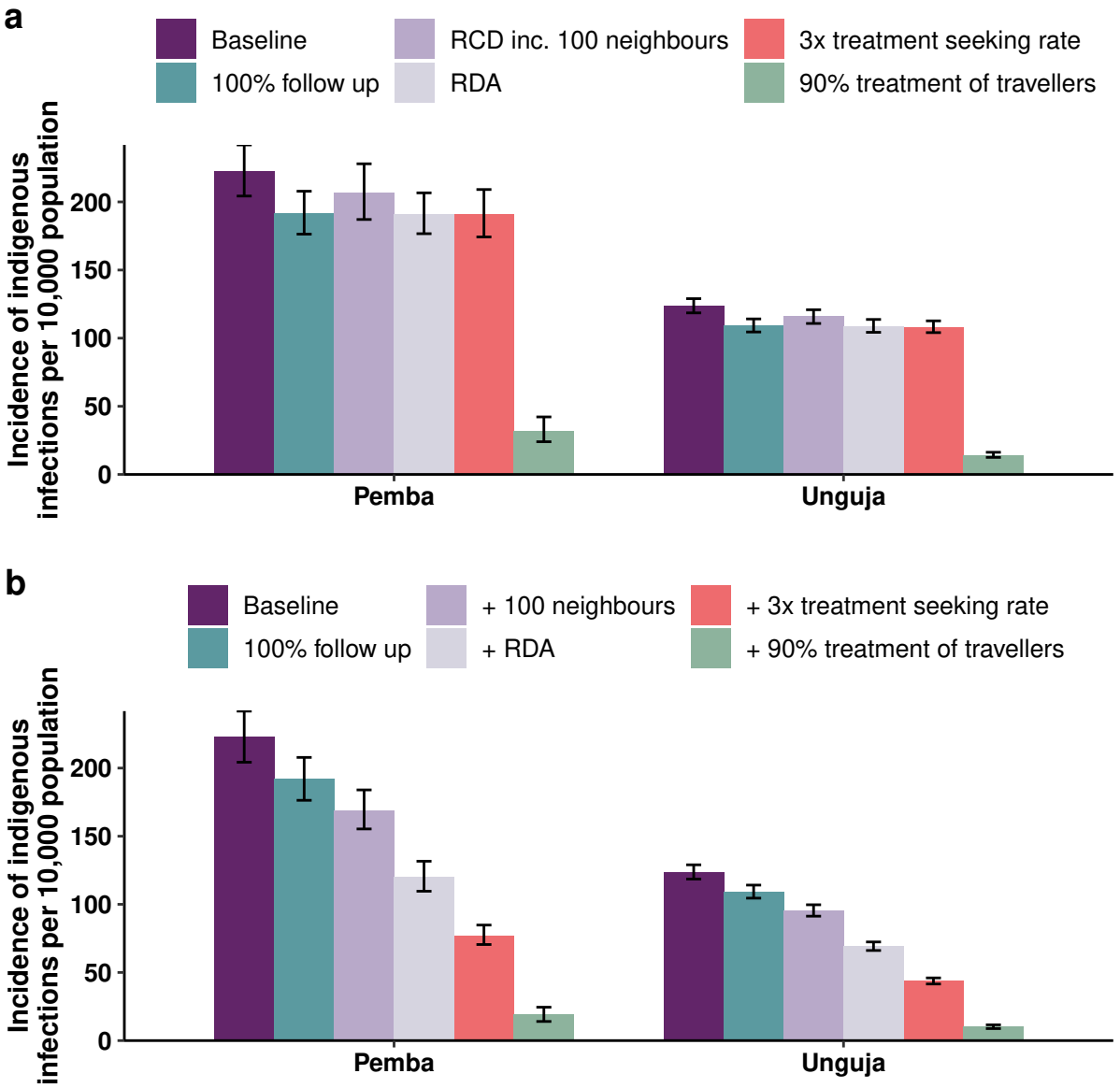

Figure 3.3: Simulated annual malaria incidence 15 years after the start of interventions. Median annual incidence of indigenous infections per 10,000 population in the 15th year after the start of interventions. The height of the bar represents the median value across n=500 simulations per intervention scenario. The error bars represent the 95% prediction interval in the annual incidence. 'Baseline' refers to RCD with 35% follow up of index cases at the index household. **a)** Bar plot showing the final incidence after the implementation of each intervention on its own (n=500 simulations per scenario). **b)** Bar plot showing the final incidence when, going from left to right, each new intervention is layered on top of the last intervention (n=500 simulations per scenario). 'RCD' stands for reactive case detection. 'RDA' stands for reactive drug administration.

Combining interventions can have a multiplicative effect on the reduction in incidence. Fig. 3.3B shows the impact of adding in new interventions on top of existing ones. Even without treating travellers, a 59% reduction in incidence amongst Pemba residents and a 40% reduction amongst Unguja residents can be achieved through the use of RDA with 100% follow up of index cases, including 100 neighbours in RDA, and increasing

the treatment seeking rate so that three times as many index cases are typically found in health facilities for a given malaria prevalence. Time-series plots of incidence for individual and combinations of interventions can be found in Figs S8-S12 in the Supplementary Information.

We then considered the impact of further reducing the transmission rate on Pemba and Unguja. We find a 50% reduction in the transmission rate is expected to lead to a 89% drop in incidence on Pemba and a 62% drop in incidence on Unguja. We additionally investigate the likelihood of reaching zero indigenous infections over three consecutive years. Fig 3.4 shows the percentage of the 500 simulations that reach zero indigenous infections over three years at each time point, defined as reaching elimination. When there is no transmission reduction, even when 100% of infected travellers are treated, by the 40^{th} year, 24% of simulations reached elimination in Unguja and 1% of simulations reached elimination in Pemba. Even with large reductions in transmission on Zanzibar, we see high probabilities of elimination only when all infected travellers are treated. This is due to the large numbers of imported infections and introduced infections stemming from visitors to both islands, but especially Unguja. Thus, even when 90% of travellers are treated, there are still sufficient numbers of imported infections that lead to onward transmission and eventually a handful of indigenous infections per year. Again, the results of combining all previously mentioned interventions with treatment of travellers and reductions in transmission can be found in Fig S13 in the Supplementary Information. We find combining treating 90% of travellers with a 90% reduction in transmission leads to a 99.5% reduction in incidence on Pemba and a 97.9% reduction in incidence on Unguja. The controlled reproduction number is below 1 for both islands, and this suggests that elimination should be achieved in the absence of importation. This is observed when the model is run for a longer period of time than 40 years (Fig S15 in the Supplementary Information). Within 100 years of treating all infected travellers from mainland Tanzania, both islands reach almost 100% probability of reaching elimination.

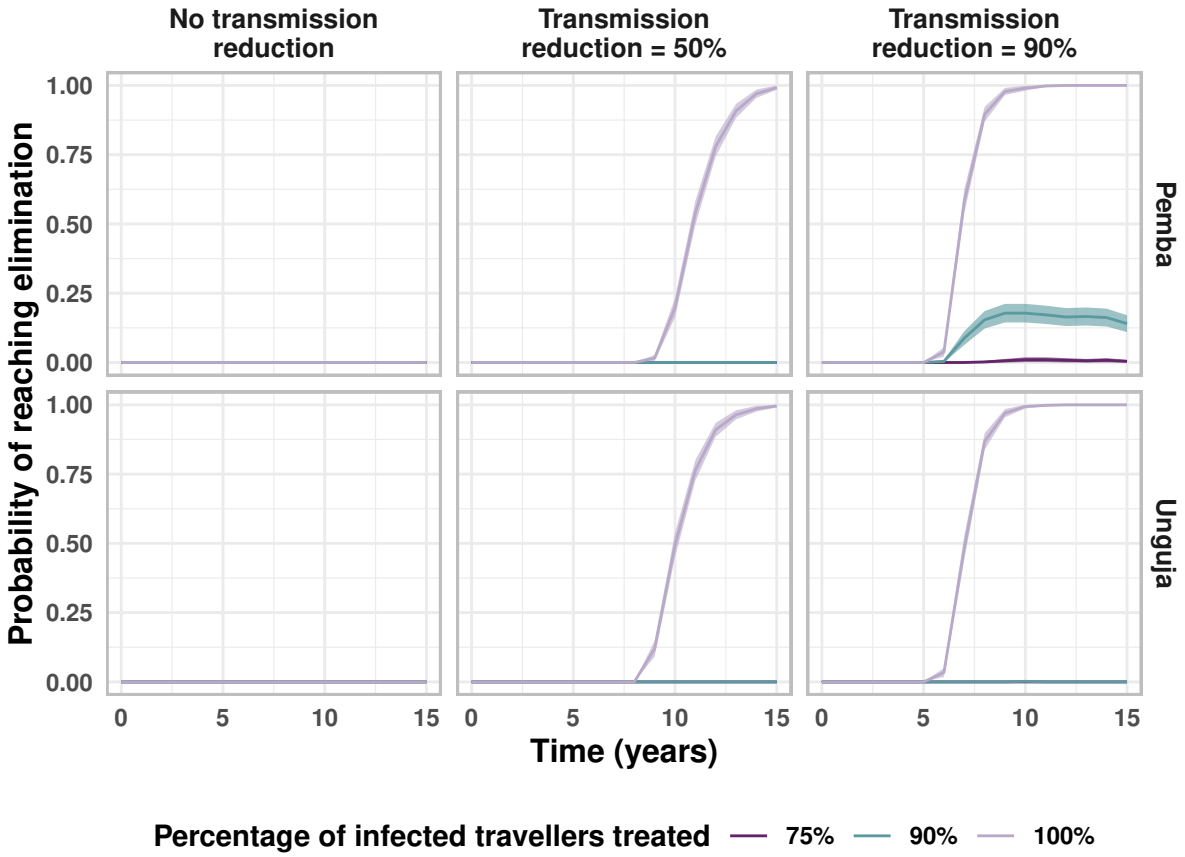

Figure 3.4: Proportion of stochastic simulations reaching elimination upon treating infected travellers and reducing transmission rates across Zanzibar. The central line is the proportion of n=500 simulations that reached elimination (3 years with zero indigenous infections). The shaded area indicates 95% confidence interval (calculated assuming a binomial proportion using a Normal approximation interval). We assume that only the baseline interventions (RCD for 35% of cases arriving at a health facility at the index household level only) are present and then simulate reducing the malaria transmission rate on Zanzibar and treating a proportion of infections imported from mainland Tanzania.

As giving treatment or chemoprophylaxis to 100% of travellers is difficult to achieve, we also considered a potential reduction in malaria transmission on mainland Tanzania, thus reducing the number of imported infections arriving on Zanzibar. As shown in Fig 3.5, a combination of a reduction in transmission on mainland Tanzania and on Zanzibar could lead to elimination on both Pemba and Unguja. The results from combining all previous interventions with transmission reduction on Zanzibar and mainland Tanzania can be found in Fig S14 of the Supplementary Information. The probability of elimination after 40 years is estimated to be 31% on Pemba and 71% on Unguja when there is a 30% reduction in transmission on mainland Tanzania but no reduction in transmission on Zanzibar, and all RCD-related interventions are set to the maximum value given in Table 3.2.

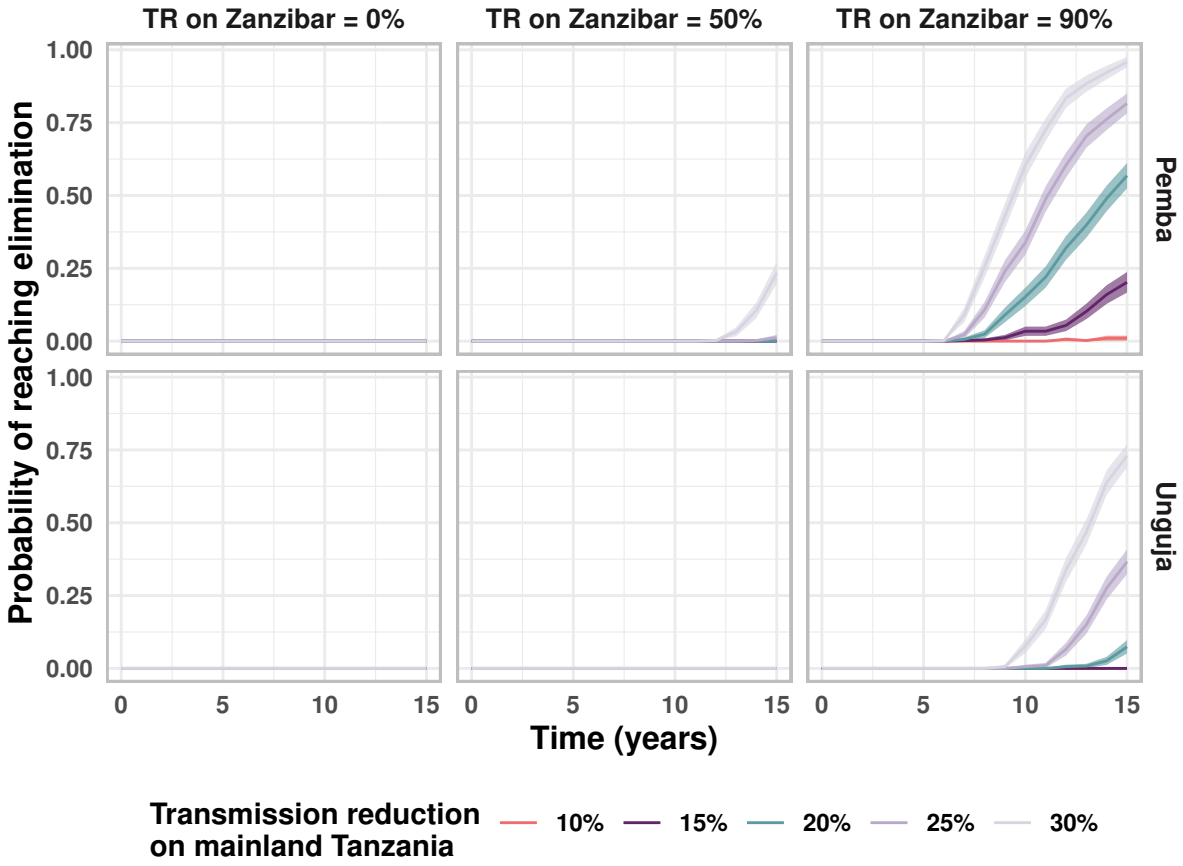

Figure 3.5: Proportion of stochastic simulations reaching elimination when transmission reductions on Zanzibar and mainland Tanzania are combined. The central line is the proportion of n=500 simulations that reached elimination (3 years with zero indigenous infections). The shaded area indicates 95% confidence interval (calculated assuming a binomial proportion using a Normal approximation interval). These simulations consider that baseline interventions are in place (RCD with follow up of 35% of cases at the index household level) and consider the impact of reducing the transmission rate on mainland Tanzania and combining this with a reduction in the transmission rate (TR) on the islands of Zanzibar. Interventions are introduced at time point 0.

Intervention	Baseline value	Intervention values
RCD follow up	$\eta = 35.3\%$	$\eta = [0\%, 100\%]$
Increase in treatment seeking rate	No increase	100% increase, 200% increase
RCD including follow up of X neighbours	$\nu = 0$ neighbours	$\nu =$ [20 neighbours, 100 neighbours]
Switching from RCD to RDA (modelled as change in test sensitivity, ρ)	$\rho = 34\%$	$\rho = 100\%$
Treating a proportion of infections brought on to Zanzibar	Prop. treated = 0	Prop. treated = [0.25, 0.50, 0.75, 0.90, 1]
Reductions in the malaria transmission rate on Zanzibar	$r_{\text{Zanzibar}} = 0$	$r_{\text{Zanzibar}} = [0.25, 0.50, 0.75, 0.90, 1]$
Reductions in the malaria transmission rate on mainland Tanzania	$r_{\text{Mainland}} = 0$	$r_{\text{Mainland}} = [0.10, 0.15, 0.20, 0.25, 0.30]$

Table 3.2: Baseline and intervention values for interventions simulated. Note, 'Zanzibar' refers to both Pemba and Unguja.

Additionally, the impact of changing the intervention parameters one at a time to see the impact on the final incidence of indigenous infections is explored in section S2.1 of the Supplementary Information. Increases in RCD-related interventions were found to lead to a linear decrease in malaria incidence, while the relationship between transmission reduction on Zanzibar and malaria incidence was found to be highly non-linear, with a small reduction in the transmission rate leading to large decreases in malaria incidence.

3.3 Discussion

We developed a model for estimating the proportions of infections observed in a region that are imported, introduced and indigenous, based on malaria prevalence and human movement data. This model can be applied to different settings and adapted to suit local interventions in place. We used this model to examine the role of imported infections in Zanzibar, a low prevalence region with substantial importation of malaria infections and a well-established RCD programme.

The malaria situation is quite different between the two major islands of Zanzibar, and so the intervention effects also differ across the two islands. In Unguja, and to a lesser extent on Pemba, repeated importation of infections and local transmission from infected visitors is driving malaria persistence. Improvements in RCD, coupled with treatment of travellers, could lead to substantial reductions in the incidence of malaria infections, including indigenous infections. In addition to this, RCD is a useful surveillance tool that can be used for confirming the lack of indigenous infections and allowing for certification of malaria elimination. However, the large number of imported and introduced infections estimated in the model means that unless all infections coming from mainland Tanzania to Zanzibar can be treated or prevented, elimination is unlikely to be reached in Zanzibar, even though very low incidence levels can be reached. Instead, our results suggest that the pursuit of malaria elimination must be a coordinated effort on a national scale.

Simulated decreases in the transmission rates on both Zanzibar and mainland Tanzania led to the largest reduction in malaria incidence and the highest likelihood of achieving malaria elimination on Zanzibar. Given that insecticide-treated nets and indoor residual spraying are already widely deployed in Zanzibar, further decreases in transmission rates may be difficult, but could potentially be achieved through novel supplementary vector control interventions such as volatile pyrethroid spatial repellents, odour-baited traps, and attractive targeted sugar baits. Transmission reduction could also be achieved with reactive vector control, which has shown promise in a field study in Namibia, especially when used in combination with RDA, and could be considered for deployment in a setting like Zanzibar [98].

Furthermore, these results assume all passive surveillance and vector control measures that are already in place are maintained, and that there is no significant malaria importation from outside of mainland Tanzania. Given that elimination is not currently certified by WHO at sub-national level, Zanzibar could only become certified by WHO when mainland Tanzania also has no community transmission and an application for elimination certification could be made for the entire United Republic of Tanzania [119].

Within the results, we observe that while RCD-related parameter values are higher in Unguja (e.g. a higher treatment seeking rate, larger targeting ratio), and so the total rate of removal of infections (φ) is higher on Unguja, removing RCD (modelled as a counterfactual scenario) would lead to a larger relative increase in malaria incidence on Pemba than on Unguja. We expect this is due to the higher transmission rate on Pemba than on Unguja. This highlights that even if RCD does not necessarily find and remove many cases, the effects of RCD compound over time and it can still have a substantial effect, particularly in higher transmission settings. However, the larger proportion of imported infections and smaller proportion of indigenous infections on Unguja suggests importation plays a larger role in sustaining transmission on Unguja than on Pemba. Treating infections in travellers is expected to have a large effect on malaria incidence, but there may be challenges in implementing border screening, as infected travellers with short trip lengths may not have RDT-detectable levels of parasite density upon entry to Zanzibar. Additionally, treating 75% to 100% of infected travellers is likely not feasible without more drastic measures such as mass drug administration to travellers. Targeting interventions such as chemoprophylaxis or awareness campaigns towards travellers to or from high-risk areas within mainland Tanzania may be more feasible and cost-effective. Further research in this area is needed to better quantify what these effects may be.

In general, we see that combinations of interventions have a compounding effect on incidence. For example, improvements to RCD such as a combination of switching to RDA, following up all index cases promptly, and increasing the rate at which infected individuals seek treatment, can lead to large declines in malaria incidence on both islands (50% reduction on Pemba and 33% reduction on Unguja). We see that including neighbours leads to relatively small gains as the frequency of infections amongst neighbours was found to be very low in the RADZEC survey data, similar to the general population prevalence [88]. Including 100 neighbours in RCD would require a large amount of extra effort on the part of surveillance officers as many neighbouring houses would need to be visited and many more tests would need to be conducted. This result is in line with a previous modelling study that used an individual-based model for malaria to investigate the relationship between the search radius and the entomological inoculation rate (EIR) [43]. Reiker *et al* (2019) found that at low EIR, increasing the search radius (i.e. the number

of neighbours tested and treated) made no difference to the time to elimination [43].

The results shown here only consider stochastic uncertainty in the model. When uncertainty in the parameter values used is also included, the median final prevalence reached in each of the intervention scenarios remains the same but the confidence intervals widen, with substantial overlap. Nonetheless, the probability of reaching elimination does not change substantially. Details on how parameter uncertainty was included and the results from this analysis can be found in section S2.2 of the Supplementary Information.

RDA would likely confer some kind of a prophylactic effect in individuals given presumptive treatment, and may thus lead to a larger impact than that modelled here. On the other hand, since our model does not include acquired immunity, we assume that all malaria infections are equally likely to transmit malaria, regardless of parasite density. There is some evidence to suggest that individuals with lower parasitemia, who are more likely to show up as negative on an RDT, have lower gametocytemia and thus are less infective to mosquitoes than RDT positive individuals [120, 121]. In this case, the impact of RCD may be underestimated by the model and the impact of a switch to RDA may be overestimated.

A previous study from Zambia found that the targeting ratio, the ratio of malaria prevalence in those tested and treated in RCD as compared to the general population, increases with decreasing prevalence, i.e. the clustering of infections increases as prevalence falls [96]. In this study, since we had no data on the impact of changing prevalence on the targeting ratio, we assumed a constant targeting ratio. In section S2.4 of the Supplementary Information, we compare the impact of a fixed targeting ratio to one that varies according to the function fitted in Chitnis *et al* (2019). We find a minor improvement in the impact of RCD with a targeting ratio that increases with decreasing prevalence.

We define the term imported infection as relative to the patch of residence, where patch refers to either Pemba, Unguja or mainland Tanzania. Thus, only residents of Pemba or Unguja who are infected while away from their patch of residence are counted as imported infections on Zanzibar in the model. In terms of reporting, it is likely that a resident of mainland Tanzania who experiences malaria symptoms and seeks treatment while they are in Zanzibar would be classified and recorded as an imported infection in Zanzibar. Thus, we do not expect our model's estimates of imported infections to necessarily match with local records. Indeed, in the ZAMEP 2019-2020 Annual Report, it is estimated that 43% of cases are imported cases within the Malaria Case Notification database [122]. In comparison, we estimate that approximately 13% of new malaria infections amongst Zanzibari residents were acquired outside of Zanzibar in 2017–18. This discrepancy may arise due to a number of reasons, such as a change in travel patterns or malaria transmission rates from 2017 to 2020, or because cases may be acquired locally but still reported as imported if there is a history of travel, or because of a large number of mainland Tanzania residents seeking treatment for malaria while on Zanzibar. Such infected visitors would not be counted as imported cases within our model. However, transmission from such infected visitors is included as leading to introduced infections, if they infect a local resident on the patch they are visiting, and so our estimates of introduced and indigenous infections match WHO definitions [116]. At any given time, the number of imported infections and the number of infected visitors on each of the three patches were estimated to be similar, so they contribute similarly to new infections (see Table S3 in the Supplementary Information). Therefore, roughly half of the introduced

infections can be attributed to transmission from imported infections and half to transmission from infected visitors. Additionally, as infected visitors contribute to the force of infection in the area that they are visiting, they can infect a susceptible traveller from the same area of residence as themselves. For example, two travellers from patch k, one susceptible and one infected, may travel together and transmission may occur between them when on patch j. In the model, the newly infected person would be counted as an imported case on patch k. This follows from the fact that transmission occurred via vectors on patch j, and imported cases are defined as cases arising from transmission away from the area of interest.

In these simulations, we assume that transmission restarts upon the incidence of a single indigenous infection. However, WHO allows for the presence of some indigenous infections after certification of elimination, as long as there are not more than three indigenous infections in one focus per year over three consecutive years [115]. As of yet, no country that has been certified malaria free has lost this status, suggesting that once elimination is reached, community transmission rarely restarts. A comparison of a transient and a cumulative probability of elimination is included in section S2.5 of the Supplementary Information.

This model assumes homogeneous mixing in each patch, with all individuals in a patch equally likely to become infected or to transmit an infection. However, heterogeneous biting rates would lead to a variation of the reproduction number within each patch [123, 124]. Including such heterogeneity is likely to make elimination even more difficult than our analysis suggests. However, heterogeneity in travel risk may make it easier to target travellers from high endemicity areas and allow for a larger impact on transmission with lower coverage.

In conclusion, the results of this study suggest that the largest group of infections on both major islands of Zanzibar are indigenous infections despite each infection typically leading to fewer than one new infection on both islands (i.e. the controlled reproduction number is estimated to be below 1 on both islands). The malaria burden on Zanzibar can be reduced substantially through a combination of interventions such as improvements to RCD and targeting treatment, chemoprophylaxis and bite avoidance measures towards travellers importing infections from mainland Tanzania. However, malaria elimination on Zanzibar will be difficult to achieve without a reduction in malaria prevalence on mainland Tanzania, highlighting the need for a coordinated effort within the United Republic of Tanzania to achieve elimination.

3.4 Methods

We extend a stochastic metapopulation model described in [118] to include separate compartments for imported, introduced and indigenous malaria infections. The model is parameterised to malaria prevalence and travel history data from the Reactive Case Detection: System Effectiveness and Cost (RADZEC) study conducted on Zanzibar and Malaria Atlas Project estimates of malaria prevalence for mainland Tanzania [88, 61, 104]. Data from a cross-sectional survey conducted during RCD, and extended to neighbours and a transect of households extending from the index household, inform the estimates of the population prevalence and increase in prevalence in index households and neighbouring

households [88]. Results from a data audit conducted on the Malaria Case Notification register of Zanzibar inform estimates of the number of clinical cases typically reported at health facilities and the proportion of cases followed up [61]. The population prevalence at baseline for Pemba and Unguja is estimated by the prevalence of qPCR-detectable infections in neighbouring and transect households. The results from Micheweni, Pemba, from this dataset was compared to the PCR-detectable prevalence in a random sample in Micheweni in another study, and was found to be comparable [56, 118, 88]. Malaria Atlas Project estimates of malaria prevalence in 2–10 year olds for the whole of Tanzania was used as the baseline prevalence on mainland Tanzania, as the RADZEC data on travel to mainland Tanzania suggested that residents of Zanzibar travel to many parts of mainland Tanzania, so the overall prevalence for Tanzania was taken in order to not assume travel to specifically high or low prevalence areas [88, 104]. Further details of data collection can be found in Stuck *et al* (2020) and van der Horst *et al* (2020), and details of parameterisation can be found in Das *et al* (2022) [118, 88, 61].

The model is based on a system of ordinary differential equations that include susceptible and infected humans in three patches, representing the islands of Pemba and Unguja, and mainland Tanzania. We include short term human movement between the patches. Amongst infected humans, there are separate compartments for imported, introduced and indigenous infections on each patch. A schematic of the model is shown in Fig 3.6.

Movement model

If we first consider that there is just one patch and no human movement, but rather a constant rate of imported infections, the rate of change of imported infections can be described by:

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \delta - \mu P, \tag{3.1}$$

where P is the number of imported infections, δ is the rate of importation per unit time, and μ is the recovery rate.

If these imported infections then transmit the infection to other susceptible residents, the new infections would be classified as introduced infections according to WHO. The rate of change of introduced infections can be described by:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \beta P \frac{S}{N} - \mu T, \tag{3.2}$$

where T is the number of introduced infections, β is the malaria transmission rate, S is the number of susceptible residents, and N is the total number of residents.

Further transmissions from these introduced infections lead to the second generation of infections from the original imported infections and are classified as indigenous infections by WHO. Similarly, further transmissions from indigenous infections lead to more indigenous infections. Thus, the rate of change of indigenous infections can be described by:

$$\frac{\mathrm{d}D}{\mathrm{d}t} = \beta (T + D) \frac{S}{N} - \mu D, \tag{3.3}$$

where D is the number of indigenous infections.

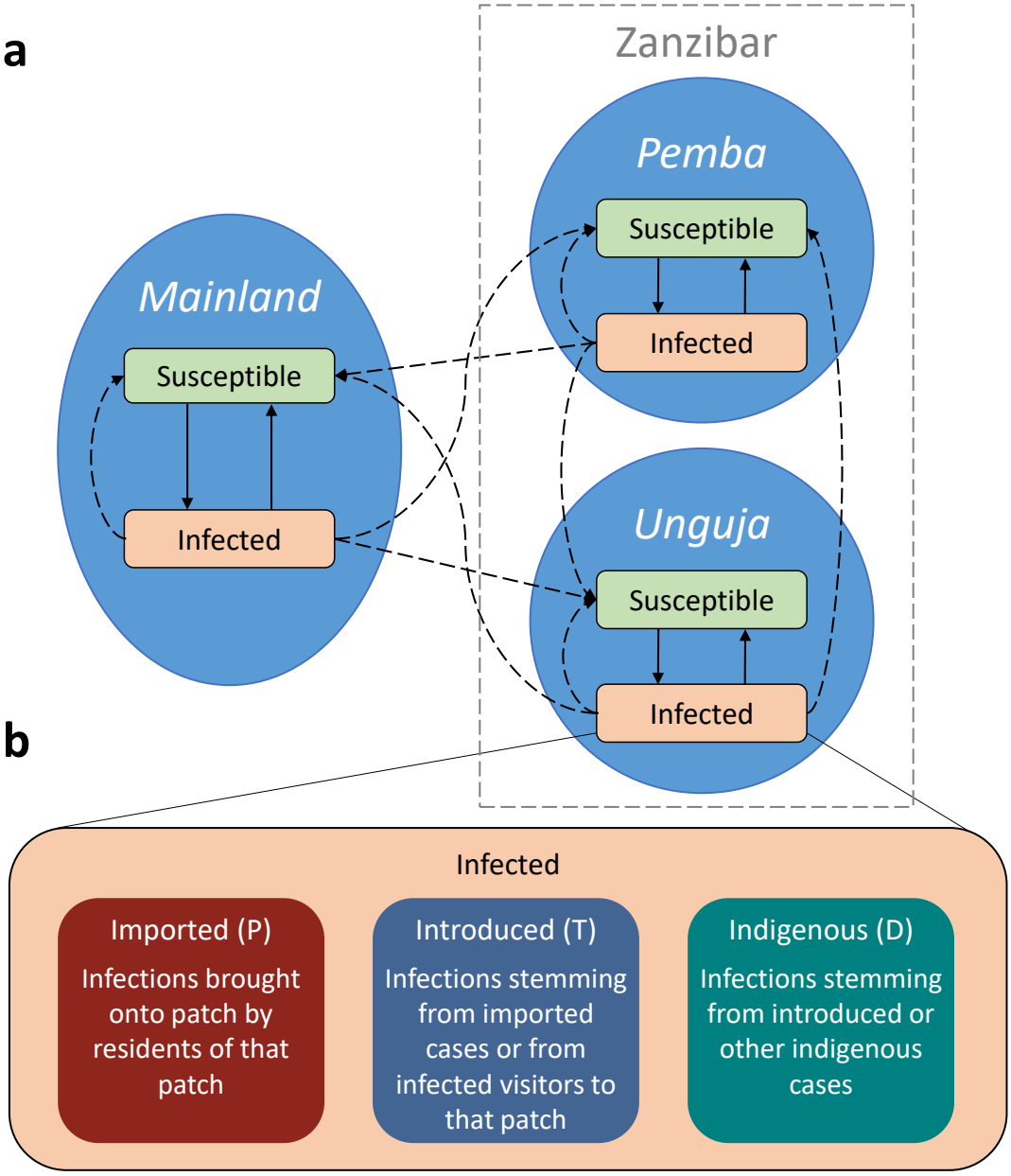

Figure 3.6: Description of model patches and compartments, including sub-compartments for different categories of infections. a) A schematic diagram of the model with two disease states in each patch. Solid arrows represent transitions between disease states, and dashed arrows represent transmission. **b)** A diagram of how the infected compartment is further divided into three sub-compartments comprising of imported, introduced and infected infections. Letters in brackets indicate state variable name in equations. These sub-compartments exist for all three patches.

We then combine this framework for classifying infections into separate categories depending on where they are acquired and their position in the chain of transmission with a model for describing the movement of infection between patches [118]. Human mobility can be modelled with either an Eulerian perspective (where hosts explicitly move between patches) or a Lagrangian perspective (where hosts are fixed to their patch but can transmit infection between patches) [52]. In this model, we use a Lagrangian approach

and label individuals by their patch, but allow them to contribute to transmission in other patches. The force of infection in any patch is therefore dependent on the malaria prevalence in all patches. This model is better suited to consider the short-term movement of people, which is expected to increasingly play a significant role in malaria persistence in low transmission areas [48, 49, 46, 45, 125]. As the median trip length in the Reactive Case Detection in Zanzibar: System Effectiveness and Cost (RADZEC) study was 6 days, we assume the majority of travel takes the form of short trips, and individuals retain the properties of their home patch [88].

We define a resident as someone who has lived in that patch for over 60 days, as the RADZEC travel data comes from questions regarding travel in the last 60 days. We define a visitor as someone who is temporarily visiting a patch other than their patch of residence. This is captured in the parameter θ_{ij}, which gives the proportion of time the average resident of patch j spends on patch i. Imported infections are defined as those where someone travelled away from their patch of residence, became infected with malaria while away, and then returned to their home patch infected. The rate of susceptible residents becoming imported infections is given by the proportion of the force of infection that they are exposed to when away from their home patch. Thus, the force of infection leading to imported infections in patch k, λ_k^P, is given by:

$$\lambda(t)_k^P = \sum_{i \neq k}^{n} \left(\beta_i \left(\frac{\sum_{j=1}^{n} N_j \theta_{ij} I(t)_j}{\sum_{j=1}^{n} N_j \theta_{ij}} \right) \theta_{ik} \right). \tag{3.4}$$

We sum over all $i \neq k$ to get a total exposure away from home. In the context of Zanzibar and mainland Tanzania, the number of patches is set to 3, i.e. $n = 3$.

This is then combined with a recovery term that accounts for the natural clearance of infections and clearance due to reactive case detection to give:

$$\frac{\mathrm{d}P_k}{\mathrm{d}t} = \sum_{i \neq k}^{n} \left(\beta_i \left(\frac{\sum_{j=1}^{n} N_j \theta_{ij} I_j}{\sum_{j=1}^{n} N_j \theta_{ij}} \right) \theta_{ik} \right) S_k - (\mu + \varphi_k) P_k. \tag{3.5}$$

Introduced infections in patch k have either been infected from imported infections on patch k (residents of k), or from visiting malaria infections who are residents of one of the other patches (who may be classified as an imported, introduced or indigenous infection on their patch of residence). Thus, the force of infection leading to introduced infections is given by the sum of the exposure of susceptible residents of k to imported infections residing in patch k, and the exposure to infected individuals from other patches visiting patch k:

$$\lambda(t)_k^T = \beta_k \left(\frac{\theta_{kk} P(t)_k + \sum_{j \neq k}^{n} N_j \theta_{kj} I(t)_j}{\sum_{j=1}^{n} N_j \theta_{kj}} \right). \tag{3.6}$$

The first term within the brackets is the contribution to the force of infection from imported infections amongst residents of patch k, and the second term is the contribution to the force of infection from all infected visitors who are visiting patch k (hence, we sum over $j \neq k$).

Finally, when there is further transmission from introduced infections or indigenous infections that are residents of patch k while they are in patch k, these lead to new indigenous infections. If they are not on patch k during the time of transmission, they

would lead to introduced infections in another patch if they infect a resident of that patch, or an imported infection if they infected another visitor to that patch. Thus, the force of infection term leading to indigenous infections is:

$$\lambda(t)_k^D = \beta_k \left(\frac{\theta_{kk}(T(t)_k + D(t)_k)}{\sum_{j=1}^{n} N_j \theta_{kj}} \right). \tag{3.7}$$

When the transmission terms for introduced and indigenous infections are also combined with recovery terms, the full sets of equations becomes:

$$\frac{\mathrm{d}P_k}{\mathrm{d}t} = \sum_{i \neq k}^{n} \left(\beta_i \left(\frac{\sum_{j=1}^{n} N_j \theta_{ij} I_j}{\sum_{j=1}^{n} N_j \theta_{ij}} \right) \theta_{ik} \right) S_k - (\mu + \varphi_k) P_k, \tag{3.8}$$

$$\frac{\mathrm{d}T_k}{\mathrm{d}t} = \beta_k \left(\frac{\theta_{kk} P_k + \sum_{j \neq k}^{n} N_j \theta_{kj} I_j}{\sum_{j=1}^{n} N_j \theta_{kj}} \right) \theta_{kk} S_k - (\mu + \varphi_k) T_k, \tag{3.9}$$

$$\frac{\mathrm{d}D_k}{\mathrm{d}t} = \beta_k \left(\frac{\theta_{kk}(T_k + D_k)}{\sum_{j=1}^{n} N_j \theta_{kj}} \right) \theta_{kk} S_k - (\mu + \varphi_k) D_k, \tag{3.10}$$

where $I_k = (P_k + T_k + D_k)/N_k$ for $k \in \{1, 2, 3\}$, i.e. the proportion of infected residents on each patch k, $n = 3$, and φ_k represents the clearance rate due to RCD (this is described in more detail in Eq. (3.11)). State variable and parameter descriptions for Eqs. (3.8)-(3.10) can be found in Table 3.3.

State variable or parameter	Description and units
	State variables
P_k	Number of imported infections in patch k. Humans.
T_k	Number of introduced infections in patch k. Humans.
D_k	Number of indigenous infections in patch k. Humans.
	Parameters
N_k	Total number of people in patch k (assumed to be constant). Humans.
β_k	The effective malaria transmission rate from humans to other humans in patch k. Day^{-1}.
θ_{ij}	The proportion of time the average resident of patch j spends in patch i. $\sum_i \theta_{ij} = 1 \; \forall j$. Dimensionless.
μ	Natural infection clearance rate. Day^{-1}.
$\tau_k^{(h)}$	Ratio of malaria prevalence in the index household tested in RCD as compared to the general population in patch k.
$\tau_k^{(n)}$	Ratio of malaria prevalence in neighbouring households tested in RCD as compared to the general population in patch k.
$\nu_k^{(h)}$	Number of people tested in the index household during follow up per index case in patch k. Dimensionless.
$\nu_k^{(n)}$	Number of people tested in neighbouring households during follow up per index case in patch k. Dimensionless.
ρ	Rapid diagnostic test sensitivity. Dimensionless.
η	The proportion of cases arriving at the health facility that are followed up. Dimensionless.
ξ_k	The daily rate at which an infected individual seeks treatment in patch k. Day^{-1}.
	Derived parameters
S_k	Number of susceptible humans in patch k, i.e $S_k = N_k - P_k - T_k - D_k$. Humans.
I_k	Proportion of humans who are infectious in patch k, i.e. $(P_k + T_k + D_k)/N_k$. Dimensionless.
φ_k	Treatment rate due to RCD programme in patch k. Day^{-1}.
ι_k	Total number of cases arriving at a health facility in patch k. Humans per day.

Table 3.3: Descriptions of state variables, parameters, and derived parameters used in the model.

The effective transmission rate, $\boldsymbol{\beta}$, is estimated from the malaria prevalence, movement rates and RCD activities present on each of the three patches [118]. At equilibrium, the system of ordinary differential equations can be rearranged to a set of simultaneous equations, which can then be solved for $\boldsymbol{\beta}$ when $\mathbf{I}$, $\mathbf{N}$, $\boldsymbol{\theta}$ and $\boldsymbol{\varphi}$ are known [118]. The transmission parameter, $\boldsymbol{\beta}$, incorporates the baseline transmission potential, ongoing vector control activities, and ongoing passive surveillance.

Reactive case detection

RCD is a form of contact tracing where, due to the mosquito-borne nature of malaria, the focus is on geographically nearby contacts. Thus, nearby contacts of a known malaria case are followed up, tested for malaria, and treated if found to be positive. In Zanzibar, this involves following up index cases and testing and treating their household members. The per capita rate of treatment due to RCD is:

$$\varphi_k(t) = \xi_k \eta \nu_k^{(h)} \tau_k^{(h)} I_k(t) \rho, \tag{3.11}$$

where ξ_k is the rate at which infected individuals seek treatment at a health facility, η is the proportion of index cases that are investigated at the index household level [61], $\nu_k^{(h)}$ is the size of the index household, $\tau_k^{(h)} I_k$ is the inflated prevalence amongst index household members, and ρ is the rapid diagnostic test (RDT) sensitivity [88]. ξ_k was derived from health facility data on the median number of malaria cases recorded per month per district on Pemba and Unguja, which was scaled by the number of districts on each island and 30 days in a month [61]. $\nu_k^{(h)}$ was estimated by calculating the mean index household size from RADZEC data [88]. $\tau_k^{(h)}$ was calculated by taking the mean number of infections found in an index household, dividing by the index household size, and taking the ratio of the prevalence in the index household to the malaria prevalence in the general population [88]. The baseline values for these parameters can be found in Table 3.4.

Variable or parameter	Pemba	Unguja	Mainland	Source
I_k^*	1.36%	1.18%	7.79%	[88, 104]
N_k	406,848	896,721	43,625,354	[107]
θ_{ij}		Pemba / Unguja / Mainland		[88]
		Pemba: 0.991, 0.004, 5.7×10^{-5}		
		Unguja: 0.003, 0.970, 5.3×10^{-4}		
		Mainland: 0.006, 0.026, 0.999		
μ	0.005 day^{-1}	0.005 day^{-1}	0.005 day^{-1}	[126, 127]
$\tau_k^{(h)}$	3.2	10.0	N/A	[88]
$\tau_k^{(n)}$	0.7	1.3	N/A	[88]
$\nu_k^{(h)}$	7.0	6.3	N/A	[88]
$\nu_k^{(n)}$	20.4	18.8	N/A	[88]
ρ^*	34%	34%	N/A	[88]
η^*	35.3%	35.3%	N/A	[61]
ξ^*	2.9×10^{-4} day^{-1}	6.1×10^{-4} day^{-1}	N/A	[88, 61]

Table 3.4: Variable and parameter values at baseline and sources. The superscripts (h) indicates the index household and (n) indicates neighbouring households.

When neighbours are also included in RCD, the rate of treatment due to RCD is modified to the following:

$$\varphi_k(t) = \xi_k \eta (\nu_k^{(h)} \tau_k^{(h)} + \nu_k^{(n)} \tau_k^{(n)}) I_k(t) \rho, \tag{3.12}$$

where the superscripts (h) refers to the index household and (n) refers to the neighbouring households.

The daily number of malaria cases recorded in health facilities is:

$$\iota_k = \xi_k I_k N_k, \tag{3.13}$$

where $I_k N_k$ is the total number of infected people on patch k and ξ_k is the rate at which each infected person seeks treatment at a health facility and is diagnosed with malaria, as described earlier. We note that this rate is relatively low since many infections are likely to be asymptomatic and may never seek treatment in the course of the infection. The daily number of malaria cases recorded at a health facility is estimated from data on the median number of cases reported per district per month on Pemba and Unguja [61]. By assuming that this is the value of ι_k^* at baseline and assuming equilibrium prevalence, we estimate that the treatment seeking rate is:

$$\xi_k = \frac{\iota_k^*}{I_k^* N_k}, \tag{3.14}$$

where an asterisk indicates the value of that parameter at baseline.

Model simulations

Eqs. (3.8)-(3.10) were simulated using a binomial tau-leap adaptation of the Gillespie algorithm [109]. The initial conditions were set such that all infections were indigenous infections, and then the model was run for ten years to allow it to reach an equilibrium of imported, introduced and indigenous infections. After this, interventions were introduced and simulations were run for another 40 years. Simulations were repeated 500 times to account for stochastic variation. In all figures, interventions are introduced in year 0, which is calibrated to data from 2017–18. Note, in some figures, results are displayed for the first 20 years from the start of interventions. Simulations were run using Python version 3.6.6 and Numba version 0.39.0. Figures were plotted in R version 4.1.2, using ggplot2 version 3.3.5.

Model with interventions

The baseline model was expanded to include the following interventions:

1. RCD at a range of levels of case follow up. At baseline, 35% of malaria cases diagnosed at a health facility are followed up at the index household level within 3 days [61].

2. RCD with follow up of neighbouring households. Currently, neighbours are not generally included in RCD in Zanzibar. We test the impact of including individuals in neighbouring households in testing and treatment upon investigation of the index case.

3. Switching from RCD to RDA. Currently, an RDT is used to diagnose malaria in those followed up by RCD. This RDT is estimated to have a sensitivity of 34% as compared to qPCR due to a high frequency of low parasite density infections [88].

Switching to RDA means that the RDT is no longer used during follow up and all members of the household are given presumptive treatment.

4. RCD at a range of levels of treatment seeking. At baseline, the rate of seeking treatment is 2.9×10^{-4} per day in Pemba and 6.1×10^{-4} per day in Unguja. We test the impact of increasing the treatment seeking rate of infected individuals. For example, this could be due to waning immunity and thus a higher proportion of symptomatic infections in the population, broader screening measures in health facilities, or including pharmacies or drug stores in the case notification system.

5. Treatment and prevention of a proportion of infections brought on to Zanzibar by travelling humans (either residents or visitors). This could be through prevention measures such as chemoprophylaxis or bite avoidance measures for Zanzibari residents when visiting mainland Tanzania or treatment of mainland residents on arrival at Zanzibar. In order to be concise, this intervention is referred to as treatment of travellers.

6. Reductions in the malaria transmission rate on each of the islands of Zanzibar, potentially through intensified vector control, i.e. $\beta_{\text{Zanzibar}}^{\text{intervention}} = \beta_{\text{Zanzibar}}(1-r_{\text{Zanzibar}})$, where r refers to the reduction in vectorial capacity, and the subscript Zanzibar refers to either Pemba or Unguja.

7. Reductions in the malaria transmission rate on mainland Tanzania potentially through intensified vector control, i.e. $\beta_{\text{Mainland}}^{\text{intervention}} = \beta_{\text{Mainland}}(1 - r_{\text{Mainland}})$.

Interventions 1 to 6 were applied simultaneously to the Pemba and Unguja patches. Interventions 1 to 4 are collectively referred to as RCD-related interventions. Baseline and intervention values simulated can be found in Table 3.2.

Details of how the interventions were included in the model are described in Section S1.1 of the Supplementary Information.

Data availability

The data and code needed to run this model are available on GitHub and deposited in the Zenodo database under accession code https://doi.org/10.5281/zenodo.7782511. Publicly available data from the Malaria Atlas Project was also used to parameterise the model. This data can be found at https://data.malariaatlas.org. No data was specifically collected for this study.

Code availability

The data and code needed to run this model are available on GitHub and deposited in the Zenodo database under accession code https://doi.org/10.5281/zenodo.7782511. Modelling, data analysis and plotting were conducted using Python version 3.6.6, numba version 0.39.0, R version 4.1.2 and ggplot2 version 3.3.5.

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Author contributions statement

AMD was responsible for study conceptualisation, developing the methods and data analysis, writing, editing and reviewing the manuscript. MWH was responsible for study conceptualisation, and contributed to writing, reviewing and editing the manuscript. JOY was responsible for study conceptualisation, and contributed to writing, reviewing and editing the manuscript. LS was responsible for collecting the data used in this study, and contributed to writing, reviewing and editing the manuscript. BSF was responsible for collecting the data used in this study, and contributed to writing, reviewing and editing the manuscript. AHA was responsible for collecting the data used in this study, and contributed to writing, reviewing and editing the manuscript. AA was responsible for collecting the data used in this study, and contributed to writing, reviewing and editing the manuscript. NC was responsible for study conceptualisation, developing the methodology, supervision, and contributed to writing, reviewing and editing the manuscript.

Competing interests statement

The authors declare no competing interests.

Chapter 4

Modelling the impact of fexinidazole use on human African trypanosomiasis (HAT) transmission in the Democratic Republic of the Congo

4 Modelling the impact of fexinidazole use on human African trypanosomiasis (HAT) transmission in the Democratic Republic of the Congo

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Abstract

Gambiense human African trypanosomiasis is a deadly disease that has been declining in incidence since the start of the Century, primarily due to increased screening, diagnosis and treatment of infected people. The main treatment regimen currently in use requires a lumbar puncture as part of the diagnostic process to determine disease stage and hospital admission for drug administration. Fexinidazole is a new oral treatment for stage 1 and non-severe stage 2 human African trypanosomiasis. The World Health Organization has recently incorporated fexinidazole into its treatment guidelines for human African trypanosomiasis. The treatment does not require hospital admission or a lumbar puncture for all patients, which is likely to ease access for patients; however, it does require concomitant food intake, which is likely to reduce adherence. Here, we use a mathematical model calibrated to case and screening data from Mushie territory, in the Democratic Republic of the Congo, to explore the potential negative impact of poor compliance to an oral treatment, and potential gains to be made from increases in the rate at which patients seek treatment. We find that reductions in compliance in treatment of stage 1 cases are projected to result in the largest increase in further transmission of the disease, with failing to cure stage 2 cases also posing a smaller concern. Reductions in compliance may be offset by increases in the rate at which cases are passively detected. Efforts should therefore be made to ensure good adherence for stage 1 patients to treatment with fexinidazole and to improve access to care.

Author summary

Sleeping sickness is a parasitic disease present in parts of Central and West Africa that is fatal if left untreated. Current case management requires unpleasant procedures such as a lumbar puncture and intravenous drug administration, but has high compliance rates as the treatment is given by hospital staff to patients. In this study, we explore the impact of a new oral treatment on compliance rates for treatment using a mathematical model fitted to data on sleeping sickness cases and screening activities. We also look at the possibility of patients being more likely to seek and access treatment since the new treatment can be used without a lumbar puncture if the patient does not display clinically severe symptoms. We find that reduced compliance, especially from patients suffering from the first less severe stage of the disease, will lead to more sleeping sickness cases and delay elimination, but increases in the number of patients seeking treatment will likely counter effects of reduced compliance.

4.1 Introduction

Human African trypanosomiasis (HAT) is a vector-borne neglected tropical disease mainly affecting people in rural settings in sub-Saharan Africa. Two subspecies of *Trypanosoma brucei*, *T. b. gambiense* and *T. b. rhodesiense*, cause the slower and faster progressing forms of the disease, respectively. The *gambiense* form of the disease (gHAT) accounts for $\sim 98\%$ of reported cases, with its greatest burden being in the Democratic Republic of the Congo (DRC) [73]. Nonetheless, the burden of disease has reduced significantly since the turn of the Century, with the global number of cases reported to the World Health Organization (WHO) falling from 26,872 in 2001 to 876 in 2019 [128]. While this drop may be due to falling rates of active screening or case reporting, a modelling analysis using Bayesian inference techniques suggested that these declines represent a true reduction in case incidence [129]. WHO has set the goal of interrupting transmission of gHAT by 2030 [130]. Actively screening at-risk populations for cases has formed the main control measure for gHAT.

Disease progression occurs in two stages: the first stage is the haemolymphatic stage, consisting of milder symptoms such as headaches and fever; the second stage is the meningo-encephalitic stage, where the parasites cross the blood-brain barrier, leading to neuropsychiatric disorders and eventual death if left untreated. Disease staging is required to define treatment, and is determined via examination of the cerebrospinal fluid obtained through a lumbar puncture. The recommended treatment for gHAT that is currently in use consists of daily intramuscular injection of pentamidine for seven days for stage 1 of the disease, and oral nifurtimox and intravenous eflornithine combination therapy (NECT) over ten days for stage 2, both requiring patient hospitalisation [67, 131].

Fexinidazole is a 10-day oral treatment for both stages of the disease. In November 2018, fexinidazole received a positive opinion by the European Medicines Agency for the treatment of both the first stage and second stage of gHAT in adults and children aged 6 years and older with a body weight of 20 kg or more. In December 2018, marketing authorisation was granted within the DRC. Recently, fexinidazole has been included in the WHO guidelines for the treatment of gHAT [67]. This new treatment presents significant advantages over the current treatment in terms of easier administration, a less unpleasant experience for patients and removing the need for a lumbar puncture in less severe cases. Although fexinidazole is an excellent drug for stage 1 and early stage 2 of the disease, a higher treatment failure rate was observed for late-stage 2 patients, where there is substantial parasite presence in the central nervous system. In these cases, treatment with NECT is recommended. Thus, patients only need a lumbar puncture if a clinical assessment suggests there is a chance of severe stage 2 HAT. As fexinidazole requires treatment for 10 consecutive days and food intake prior to drug administration to ensure efficacy, there is a concern that compliance may be lower than in the current treatment, which is administered via intramuscular injection or intravenous infusion by healthcare professionals. Finally, it is possible that, due to the easier logistics from a health facility perspective and less unpleasant treatment from a patient perspective, the rate of passive detection, i.e. detection at health center level and not by screening via a dedicated mobile team, may increase with the introduction of fexinidazole. This is in line with previous studies of patient preferences for anticancer treatments, which found a strong preference for oral chemotherapy as compared to chemotherapy administered via injections or infusions [132, 133, 134].

Active case detection forms the most widespread strategy for reducing the disease burden in the DRC. However, as a vector borne disease, gHAT may also be controlled by interventions that target tsetse flies. Interventions such as Tiny Targets offer a promising method of dramatically reducing the vector population, leading to large reductions in disease prevalence. Previous field studies conducted with Tiny Targets in Yasa Bonga, DRC, Boffa, Guinea, and Mandoul, Chad, measured reductions of 85%, 80% and 99.9% respectively [135, 136, 137]. In line with these findings, respective vector control activities are currently ongoing in several active foci of the DRC. Previous modelling studies have also suggested that vector control could be a highly effective intervention against gHAT [81, 138, 139]. In our work, we have chosen to focus on medical interventions, since that is where fexinidazole will likely play a role.

In this study, we use a previously described and calibrated mathematical model for gHAT to explore how a reduced compliance to fexinidazole, as compared to the current treatment, may impact gHAT transmission. Furthermore, we consider the impact of potential increases in passive detection on mitigating the impact of non-compliance on transmission levels.

4.2 Materials and methods

4.2.1 Model description and parameterisation

We adapted the stochastic formulation of the population-based gHAT transmission and control model described in [140], which builds on previous work [80, 81]. A schematic of the model is shown in Fig 4.1, and a description of the corresponding state variables is given in Table 4.1. The model is based on a system of ordinary differential equations that include tsetse flies, humans in multiple disease stages, and two risk settings. The low risk and high risk settings represent the 'village' and 'plantation' settings, respectively. Some individuals are modelled to travel between the two, and we assume those in the high risk setting do not participate in active screening, as there is an opportunity cost to screening [141, 142]. Vectors are assumed to only be susceptible to infection when they are in the teneral stage of development, i.e. during their first bloodmeal. This period lasts approximately 5 days and causes the so called teneral effect seen in infectivity amongst tsetse flies [143]. After this, they enter a mature, non-teneral stage in which we assume they are no longer susceptible to infection. While there is evidence that wild animals and livestock can harbour *T. b. gambiense* trypanosomes, it is unclear whether they contribute to disease transmission [144, 145]. Previous modelling analyses have suggested that observed case data can be similarly explained by either including or excluding non-human host reservoirs that contribute to transmission [82, 83]. Taking this into account, we have made a simplifying assumption that tsetse flies can take bloodmeals from non-human hosts, but non-human hosts do not contribute to further transmission. However, it is worth noting that feeding on non-human animals helps to sustain the local tsetse fly population.

A deterministic version of the model was fitted using a Bayesian approach to screening data and staged reported case data from both active and passive surveillance from Mushie territory in the DRC from 2000 to 2018 [72, 85]. This was then projected forward using

stochastic simulations to 2040, with fexinidazole being introduced in 2021. Projections used the mean number of people screened annually by active screening between 2014 and 2018, leading to a decreasing active screening rate as the population size increases. The passive detection rate, i.e. the rate at which patients are removed from the infected compartments due to seeking treatment at a health centre, was kept constant at the 2018 rate from 2019 onwards. Parameters such as the ratio of humans in the high to low risk settings, the rate of passive detection between 2000 and 2018, the ratio of vectors to humans, and the diagnostic specificity were fitted using a Bayesian approach and an adaptive Metropolis-Hastings Markov chain Monte Carlo approach was used to sample from the posterior distributions. Forward simulations were then run from 2000 to 2040 using the direct method of the Gillespie algorithm [146], implemented in a combination of R and C++ using the 'Rcpp' package. Further information on model assumptions, parameterisation and calibration can be found in Appendix C.

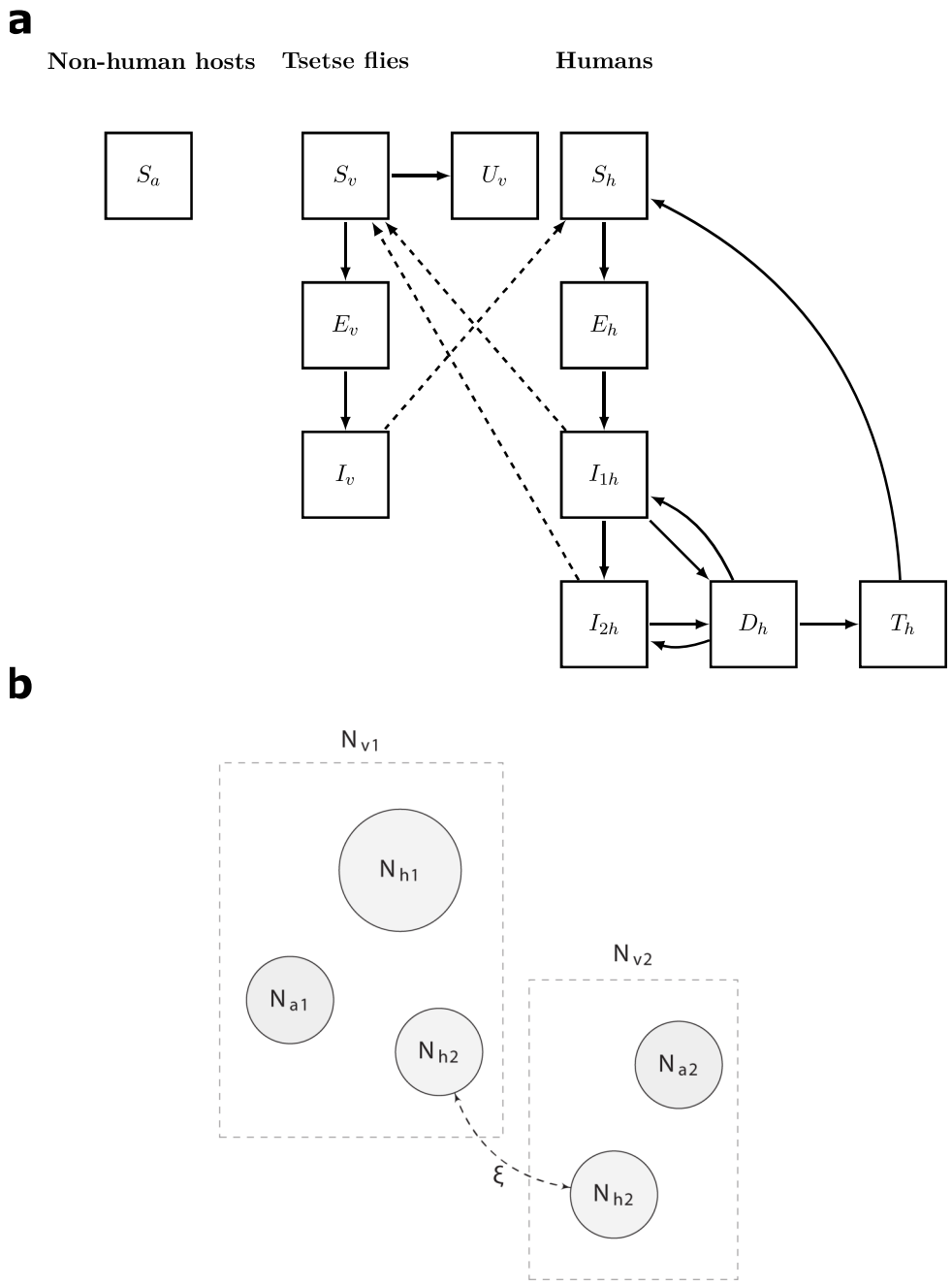

Figure 4.1: Overview of the model compartments and model structure.
a Compartments within model. Solid lines depict transitions between compartments, while dashed lines represent transmission. State variable descriptions can be found in Table 4.1. Non-human hosts can receive bites from tsetse flies, but are assumed to not carry or transmit the disease. Figure adapted from [80]. **b** Overall model structure. The model consists of low and high risk settings, with some movement between these settings by high risk individuals. The compartmental diagram showing disease stages corresponds to the high transmission setting (with Nv2). In the low transmission setting, there is one population of tsetse flies (Nv1) feeding on both high and low risk humans. The full system is therefore 22-dimensional and can be found in Appendix C.

Variable	Description
S_a	Number of non-human hosts
S_v	Number of susceptible vectors
E_v	Number of exposed vectors
I_v	Number of infected vectors
U_v	Number of non-teneral vectors
S_h	Number of susceptible humans
E_h	Number of exposed humans
I_{1h}	Number of infected humans in stage 1
I_{2h}	Number of infected humans in stage 2
D_h	Number of diagnosed humans
T_h	Number of treated humans

Table 4.1: Description of model state variables. These variables exist for both the high and low risk settings.

4.2.2 Fexinidazole parameters and assumptions

Currently, it is unclear what proportion of patients in each stage will receive fexinidazole versus pentamidine or NECT, and the likely level of compliance. Thus, we have considered a range of values for the three parameters used to model fexinidazole treatment:

- **Compliance:** The proportion of patients receiving fexinidazole who comply with treatment guidelines sufficiently to be treated. The values simulated here were 25%, 50%, 75% and 100%.
- **Stage 1 access:** The proportion of patients in stage 1 of the disease, detected either through active screening or passive surveillance, receiving fexinidazole rather than the current treatment. The values simulated here were 25%, 50%, 75% and 100%.
- **Stage 2 access:** The proportion of patients in stage 2 of the disease, detected either through active screening or passive surveillance, receiving fexinidazole rather than the current treatment. The values simulated here were 25%, 50%, and 75%.

Efficacy of fexinidazole and the current treatment are assumed to be equal for stage 1 HAT, as both have efficacies above 95% and have not been compared in a head-to-head trial [67]. For stage 2 of the disease, a head-to-head comparator trial of fexinidazole versus NECT showed that NECT had an efficacy of 98% and fexinidazole an efficacy of 91% [147]. A reduction in relative efficacy of 7.1% has been included in the model for stage 2 patients receiving fexinidazole.

Five scenarios were selected from the full-factorial combination described above for further analysis (Table 4.2). In the model, a 100% compliance to fexinidazole has the same effect on transmission as the recommended treatment that is currently in use, independent of the proportions of stage 1 or stage 2 cases treated with fexinidazole; this is the so called “full compliance" scenario in Table 4.2. “Worst case" scenarios were scenarios with the lowest compliance (25%) and either widespread use of fexinidazole for stage 1 cases (100%), for stage 2 cases (75%), or both. An additional scenario with widespread

access to fexinidazole in both stages (75% for stage 1 and 50% for stage 2) and high compliance (75%) was also included as a baseline for what may be the usage of the drug given WHO guidelines are followed ("high compliance" scenario). Widespread access was considered appropriate as active detection leads to cases being reported earlier in the disease progression. This is reflected in the high ratio of cases detected through active screening versus passive surveillance seen in the data. Thus, we expect the majority of diagnosed cases will be detected before late stage 2, and so can be treated with fexinidazole.

Scenario	Compliance	Access in stage 1	Access in stage 2	Description
Full compliance	100%	75%	50%	Perfect compliance, same as current treatment
High compliance	75%	75%	50%	Imperfect, but high, compliance, with widespread access to fexinidazole
Worst case — stage 1	25%	100%	25%	Poor compliance and widespread use for stage 1 patients
Worst case — stage 2	25%	25%	75%	Poor compliance and widespread use for stage 2 patients
Worst case — both stages	25%	100%	75%	Poor compliance and widespread use for patients in both stages

Table 4.2: Scenarios considered in modelling the impact of fexinidazole use on the transmission of gHAT.

It is possible that with a logistically simpler and less unpleasant treatment, a larger number of health facilities will be able to administer the treatment. Additionally, the possibility to avoid a lumbar puncture will likely lead to less stigma around being tested for the disease. This may lead to an increase in the rate of passive detection. Increases of 20%, 50% and 100% in the passive detection rate in both stages from 2021 onward were explored. The corresponding percentage of patients accessing treatment via passive detection, rather than active screening, disease progression or death, are given in Table 4.3 considering active screening rates in 2021. These values change over time in the low risk setting as the active surveillance rate decreases over time.

Setting	Increase in passive detection rate (%)	Corresponding percentage of patients of that setting and stage receiving treatment through passive detection (%)
Low risk - stage 1	[0, 20, 50, 100]	[19, 22, 26, 32]
Low risk - stage 2	[0, 20, 50, 100]	[51, 55, 61, 67]
High risk - stage 1	[0, 20, 50, 100]	[25, 28, 33, 40]
High risk - stage 2	[0, 20, 50, 100]	[55, 60, 65, 71]

Table 4.3: Increases in passive detection rate and corresponding percentage of patients in each setting and disease stage receiving treatment while in that stage.

4.3 Results

4.3.1 Impact of reduced compliance

As expected, the greatest reduction in incidence between 2021 and 2040 is achieved with perfect compliance and is at least equivalent to continuing the use of the current treatment regimen (Fig 4.2). In comparison, in the worst case scenario (low compliance and extended use of fexinidazole in both stages), we see a delay of 7 years in achieving elimination of transmission when considering the median incidence, as compared to the full compliance scenario. Widespread use of fexinidazole in stage 1 in low compliance scenarios (worst case - stage 1 and worst case - both stages) has a larger overall negative impact on transmission, likely because stage 1 cases that are not effectively treated can potentially transmit the disease to susceptible individuals for a longer period than stage 2 non-compliants. While attention should be paid towards treatment adherence regardless of stage in line with WHO recommendations [67], this result suggests that compliance in stage 1 patients is especially important for reducing further transmission of the disease.

While the median simulated incidence is declining for all scenarios (Fig 4.2b), there are some potential parameter sets where low compliance leads to an increase in cases (Fig 4.2a). This is because the observed historic data is compatible with parameters that would lead to an increase in disease incidence if compliance with treatment was low. This result suggests that the situation should be monitored closely after the introduction of fexinidazole, and an increase in cases may indicate that drug compliance is low.

4.3.2 Improvements in passive detection rate

The issue of non-compliance is likely to be countered by the increased number of patients who access treatment, particularly those in an early stage of the disease. Increasing the passive detection rate by $\sim 20\%$ is expected to be sufficient to ensure a similar trend in incidence and probability of elimination of transmission in the “high compliance" scenario as expected with the current treatment (Fig 4.3, black dashed line versus green line).

Nonetheless, if compliance is low and access to fexinidazole for both stages is high, even after doubling the passive detection rate, a substantial drop in the probability of

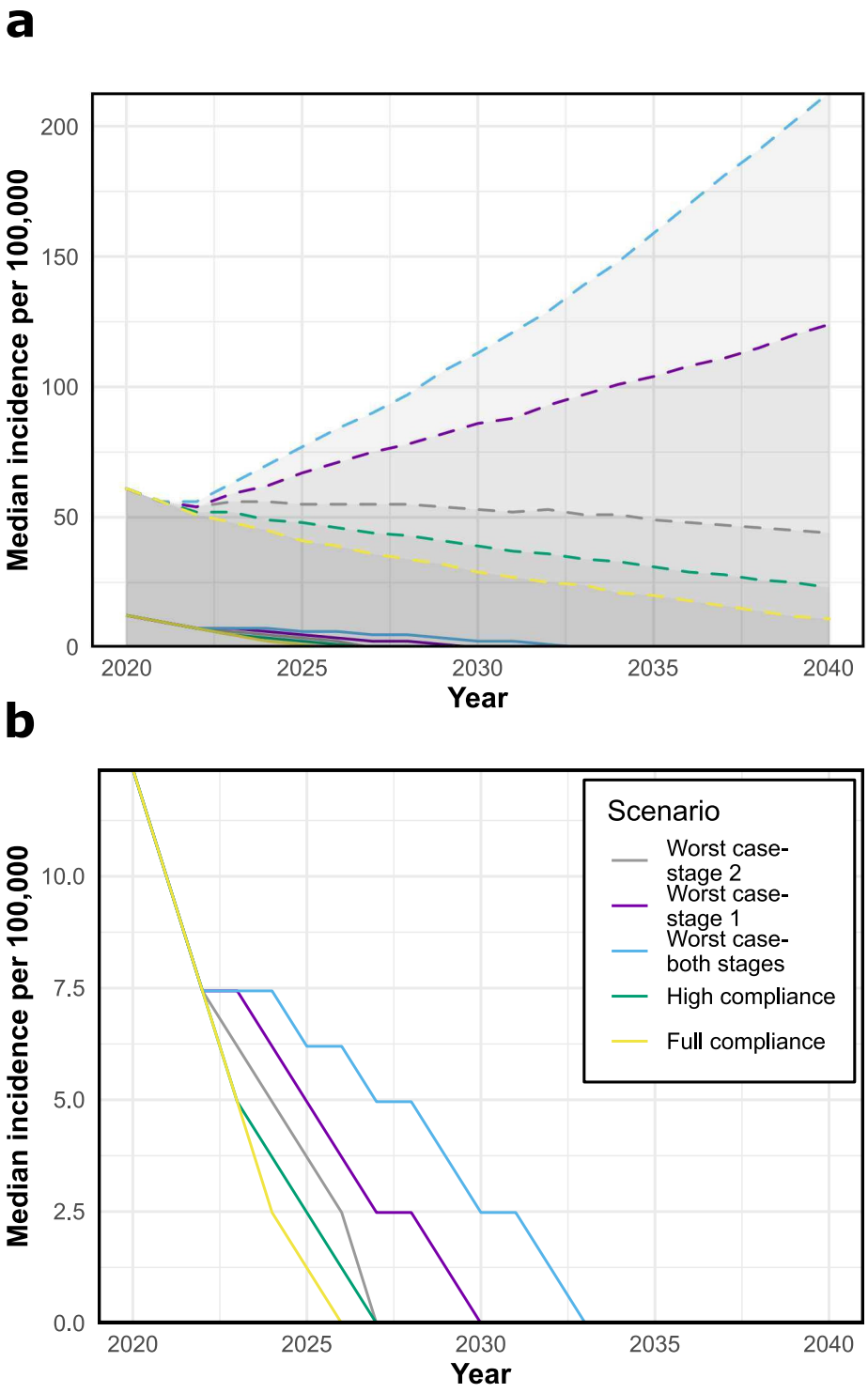

Figure 4.2: gHAT incidence per 100,000 at various fexinidazole compliance and use levels. Fexinidazole has been modelled to be introduced from 2021. Descriptions of the scenarios can be found in Table 4.2. **(a)** The median incidence including the 95% confidence intervals (shaded area bounded by dashed lines of the same colour). **(b)** The median incidence per 100,000 for each scenario. Note the different scales on the y-axis for the two plots.

the elimination of transmission over time is expected. The probability of elimination of transmission (EOT) for any given year is defined as the proportion of simulations which have reached zero exposed and infected humans and vectors by that year. The probability of EOT by 2030 is 65% if the treatment regimen that is currently in use is continued with no increase in passive detection (Fig 4.4, black dashed line). However, in the worst case scenario, even when the passive detection rate is 200% of the current passive detection rate, the WHO target of EOT by 2030 is achieved in only 50% of the simulations (Fig 4.4, light blue line).

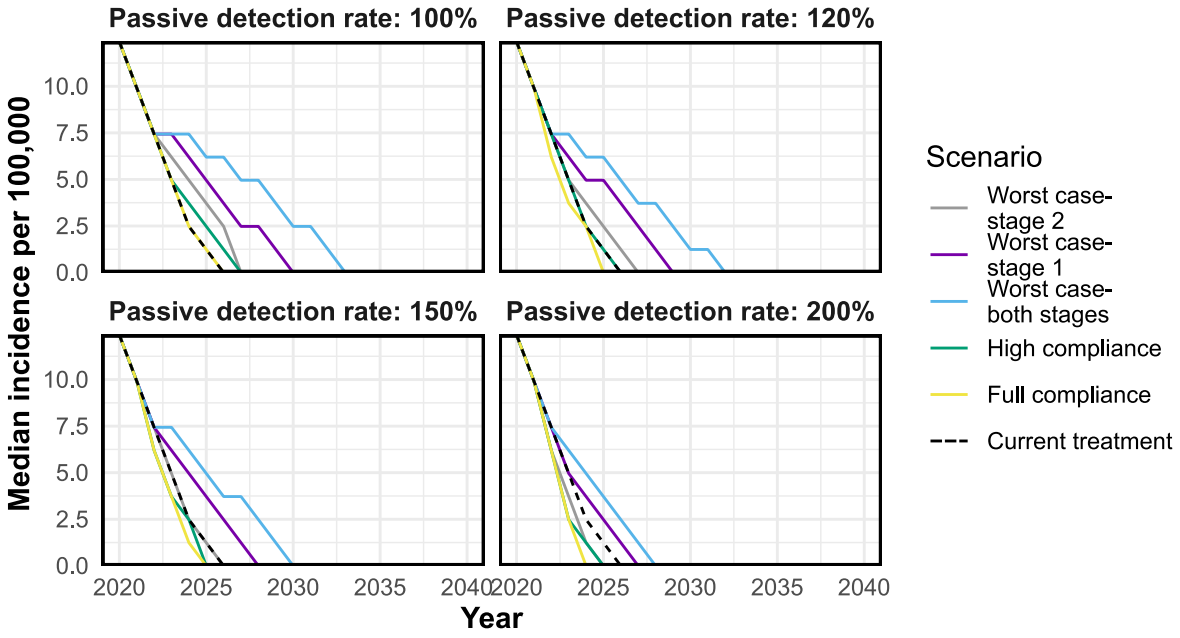

Figure 4.3: The time-series of median incidence per 100,000 population at increasing passive detection rates. Descriptions of the scenarios can be found in Table 4.2. The dashed black line corresponds to the current treatment (equivalent to 100% compliance and no increase in the passive detection rate). Fexinidazole has been modelled to be introduced from 2021.

4.4 Discussion

The effect of fexinidazole on gHAT transmission depends on treatment adherence and the proportion of diagnosed patients that receive the drug. If compliance is low, particularly in stage 1 patients, fexinidazole could have a substantial negative impact on the decline in gHAT incidence seen in recent years. The possibility of achieving the WHO 2030 goal of elimination of transmission is expected to decrease with low compliance and widespread use of fexinidazole. This would be due to the higher number of incompletely treated patients potentially contributing to transmission, with stage 1 patients typically contributing for longer to further transmission than stage 2 patients. However, if compliance is high, especially if it also leads to more patients arriving at health facilities for diagnosis, then the impact of fexinidazole may be a positive one. In a near-elimination disease setting such as the case of HAT in the DRC, it is expected that at some point,

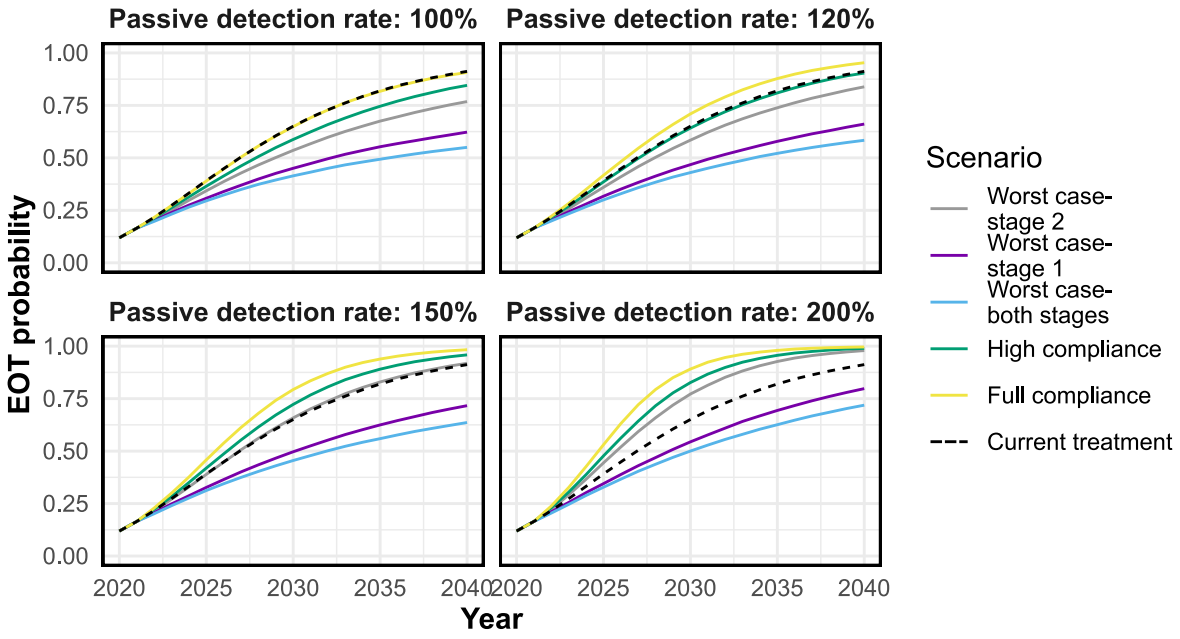

Figure 4.4: The probability of the elimination of transmission (EOT) at increasing passive detection rates. This probability of EOT reflects our uncertainty in the setting (the uncertainty in parameter values from our best fits to the data) and inherent stochastic variation. Mathematically, it is calculated as the proportion of all simulation runs (including different parameterisations and random seeds) that have reached zero exposed and infected humans and vectors by that year. Descriptions of the scenarios can be found in Table 4.2. The dashed black line corresponds to the current treatment (equivalent to 100% compliance and no increase in the passive detection rate). Fexinidazole has been modelled to be introduced from 2021.

active screening is likely to be scaled back as it is a resource-intensive intervention. With this, the relative importance of passive detection will increase, as that will be the main mechanism by which cases are detected and treated. An oral treatment that can be administered in the primary care setting, such as fexinidazole, may remove some barriers to self-presentation at health centres. Firstly, patients would have to travel less far on average to receive treatment if more health facilities could provide HAT treatment, particularly for the second stage of the disease [148]. In 2018, it was estimated that while 696 facilities in the DRC could provide a diagnosis of HAT, only 191 health facilities could provide treatment for second-stage HAT with NECT [72]. Secondly, fear of lumbar punctures was also identified as a reason why some patients avoid HAT screening [141]. This would no longer be necessary for non-severe HAT cases that qualify for fexinidazole treatment. Other factors that may improve passive detection include ensuring that indirect costs for treatment are affordable [141, 149]. Removing the need for a lumbar puncture and hospitalisation would help to reduce the cost faced by patients for HAT treatment. Finally, administering fexinidazole would require fewer healthcare resources than the current treatment pathway, which has been previously highlighted as a challenge to controlling the disease [150].

WHO guidelines recommend fexinidazole only when there is confidence in concomitant food intake and confidence in full adherence. Following these guidelines would likely lead

to high levels of compliance, averting the worst case scenarios presented in this study. Until now, no study has reported on adherence to fexinidazole treatment, and studies on adherence to other oral treatment in rural African settings for diseases such as malaria and HIV treatment show a high variability in compliance, which depends on multiple factors including gender, age, education level and side effects among others [151, 152, 153, 154]. A systematic review of interventions to promote patient adherence to antimalarial medication found a significant increase in adherence when treatment was observed by a medical professional [155]. It is difficult to predict at this stage the likely impact of an oral treatment such as fexinidazole on the passive detection rate. However, if it increases the rate at which patients seek diagnosis and treatment, then the effects of lower treatment compliance may be mitigated by increases in the proportion of patients receiving treatment.

It is worth noting that non-compliance will lead to patients being reported as treated when they may in fact still be infectious. Thus, the number of successfully treated cases may differ from the number of cases reported through official channels. In line with WHO guidelines, we would recommend follow up of cases treated by fexinidazole to confirm that the treatment was successful and to detect any relapses early. However, this may prove challenging in rural settings where gHAT is prevalent. Additionally, as a monotherapy, there is a change of the emergence of resistance, which may occur faster in the presence of widespread non-compliance. Fexinidazole-resistant trypanosomes have already been generated *in vitro*, showing 11-fold resistance to fexinidazole as compared to wild strains [156]. Resistance to fexinidazole and nifurtimox appears to occur through similar mechanisms, as drug activation in both cases relies on a single enzyme in the trypanosome, and so differences in resistance emergence have not been included in the present study.

While we have focused on medical intervention and access to care in this study, we would recommend that any medical interventions should continue to be complemented with vector control, where logistically and economically feasible. This will increase the chance of reaching EOT by 2030, as vector control strategies have previously been tested with modifications of this model for other health zones and the results suggest that vector control could substantially improve the probability of reaching EOT [81]. As the fitted ratio of vectors to humans is similar between low and high risk settings (see Appendix C), the effect of vector control would likely be similar across settings, with the potential to have a larger effect on disease incidence in high risk settings where active screening is not prevalent.

Another limitation of this study is that it does not consider disruption to ongoing control activities due to the 2019 coronavirus disease (COVID-19) pandemic. Active screening was suspended in the DRC in 2020 due to the pandemic. A previous study conducted with this model and another stochastic model that was independently developed for gHAT suggested that if the disruption was to continue until the end of 2021, a delay of 2-3 years in achieving EOT would be expected [86]. The likely effect of this disruption would be to reduce the probabilities of EOT by 2030 presented in this paper, but the overall trends would remain the same.

4.5 Conclusion

In conclusion, this study highlights the need for careful monitoring of compliance with the use of an oral medication such as fexinidazole for the treatment of HAT. Reduced compliance in stage 1 patients is expected to lead to increased incidence and delays in achieving HAT elimination. Reduced compliance in stage 2 patients plays less of a role. Potential increases in the passive case detection rate would be sufficient to offset any increases in transmission due to poor treatment adherence in stage 1 patients. Although further studies are required to better quantify the likely effect of fexinidazole on drug compliance and the rate of passive detection, efforts should particularly focus on ensuring high compliance in stage 1 patients and improving passive case detection for all patients.

Acknowledgments

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Chapter 5

Discussion

5.1 Summary of findings

This thesis aimed to model the impact of new interventions in disease elimination settings. The interventions included reactive case detection for malaria, importation management, and a new, oral treatment for human African trypanosomiasis.

In order to study the impact of reactive interventions in a low malaria transmission setting with ongoing importation, we developed a stochastic metapopulation model of malaria transmission that included human mobility and reactive case detection and parameterised it to malaria prevalence and human movement data from Zanzibar, Tanzania. The effective human-to-human malaria transmission rate was calibrated to available data and compared to the recovery rate. This analysis suggested that the controlled reproduction number for malaria was below 1 on both Pemba and Unguja, the two major islands of Zanzibar. Thus, we conclude that human movement and importation is driving malaria persistence in Zanzibar. The model was further extended to differentiate between imported, introduced and indigenous cases, allowing for the monitoring of indigenous infections. As the WHO defines elimination as three years with zero indigenous cases, this allowed us to estimate the probability of reaching a state where zero indigenous cases have been observed for three years under various intervention scenarios.

Within the context of Zanzibar, the model was used to estimate the potential impact of changes to the current RCD program, such as following up more symptomatic cases, switching to reactive drug administration, and including neighbours of the household containing the symptomatic case in test-and-treat strategies. The main findings were that RCD generally does not find or remove the majority of infections in the population. Changes to RCD were each likely to have a small impact if implemented on their own, and a substantial impact if all implemented together. Additionally, the model was used to estimate the potential impact of interventions outside of RCD, such as treating infected travellers, broader screening for malaria at health facilities to detect more cases and trigger RCD, and reducing the malaria transmission rate. The key findings were that increasing the number of index cases found would have a relatively small effect on malaria incidence, and treating infected travellers or reducing the transmission rate is expected to have a dramatic effect on the incidence of indigenous cases. This occurred either through reducing the number of imported cases arriving in Zanzibar, or by preventing further transmission from such cases.

In summary, policymakers should focus on the following if the aim is to reduce malaria incidence in Zanzibar:

- Increasing the detection of malaria infections (e.g. through including pharmacies and other healthcare providers in malaria case notification);
- Increasing the follow up of passively detected cases such that 100% of such cases trigger RCD;
- Rather than testing and treating within the index household, switch to reactive drug administration (presumptive treatment of all household members).

The areas of focus when aiming for elimination of malaria on Zanzibar should be the following:

- Increasing vector control activities to minimise local transmission in Zanzibar;
- Increasing vector control activities in high transmission areas within mainland Tanzania, from where most imported and introduced cases arise;
- Targeting treatment efforts towards travellers from high transmission areas within mainland Tanzania (either mainland Tanzania residents from these regions or Zanzibar residents visiting these areas for shorter trips).

For investigating the impact on HAT transmission expected from switching to fexinidazole from pentamidine and NECT, we expanded an existing stochastic metapopulation model for HAT transmission to include the potential for treatment by fexinidazole. The main changes included modelling potentially reduced adherence to treatment in both disease stages, and lower treatment efficacy in second-stage patients when treated with fexinidazole. We also considered potential increases in the passive detection rate with the introduction of fexinidazole.

The key findings were that reduced compliance with fexinidazole may slow down or even undo some of the impressive progress made towards eliminating HAT over the last two decades. In particular, focus should be placed on compliance in stage 1 patients treated with fexinidazole, as these patients have longer to potentially transmit HAT if not cured. Potential increases in the rate at which patients seek or access treatment may help mitigate any decreases in compliance, but a better understanding of realistic changes in both compliance rates and passive detection rates in the field are needed to better understand the likely impact of introducing fexinidazole as the standard of care. As the first oral treatment for HAT, fexinidazole has undoubtedly a more pleasant and convenient mode of administration than pentamidine or NECT. It does not require hospital admission, though daily observed therapy is recommended. Such innovations in drugs that lead to lower costs and more pleasant treatment should be encouraged, but possible issues with adherence, and its impacts on cure rates and further transmission, need to also be taken into account when long-term goals of disease elimination are being considered.

5.2 Limitations of this research

Within the malaria models presented in Chapters 2 and 3, there are several key limitations that may affect our results and the conclusions we draw from them. Previous analysis of malaria fevers in two districts in Zanzibar showed significant variation in the course of a year, and a correlation with rainfall [56]. Such seasonal patterns will likely affect which interventions may be more useful for achieving elimination. For example, it may be feasible for malaria transmission to be interrupted in the dry season, and then the focus may need to be on preventing re-establishment of transmission in the wet season through intensified vector control. Seasonality may also pose challenges in terms of the number of District Malaria Surveillance Officers needed to follow up all malaria index cases. More human resources will likely be needed in times of high transmission than during times of low transmission. This requires a flexible workforce that can assist elsewhere in the dry season, and be available for RCD in the wet season. If this is not feasible, it is possible that while 100% follow up of index cases can be achieved in the dry season, a lower proportion of cases may be followed up in the wet season because there are more index cases than DMSO capacity for follow up. Nonetheless, as the malaria burden decreases, we would expect to see a decrease in the number of passively detected cases, and following up all cases would become easier. Seasonal fluctuations in travel patterns may make it easier to treat a large proportion of infected travellers, as intensive border screening may only be needed for a fraction of the year to test and treat the majority of travellers. Data such as ferry traffic between Zanzibar and mainland Tanzania could be used to estimate the busiest periods of travel and target interventions to this time.

WHO does not currently recommend border screening as an intervention [157]. This is largely because there have been no field studies looking at the impact of border screening on malaria prevalence, and with porous land borders, high coverage is expected to be difficult to achieve. WHO does, however, conditionally recommend targeting identifiable groups of travellers who are arriving or returning from malaria-endemic areas. This could be implemented in Zanzibar by targeting messaging around malaria prevention or testing upon arrival or return towards travellers from highly endemic areas within mainland Tanzania. This may already prevent the majority of parasite importation to Zanzibar. Future work should consider the feasibility of proposed interventions and, if possible, be backed up with field data on realistic coverage levels and the method of implementation. For example, presumptive treatment or chemoprophylaxis amongst travellers returning from highly endemic areas may reduce the movement of parasites more than broader testing with low-sensitivity RDTs and low coverage levels. Such data would help inform potential ranges of intervention parameter values, such as the maximum proportion of infected travellers that can realistically be treated. Additionally, WHO highlights the need for more research into the proportion of imported cases found and treated using border screening, as compared to all imported cases. A model such as presented in Chapter 3 can be used to estimate the expected number of imported cases in a time period, based on travel patterns and malaria prevalence, and data on the number of imported cases identified by border screening could be compared to the model output to get an estimate of the intervention efficiency.

We make the assumption in both malaria models that travellers are no different to the general population of their patch of residence. We assume they have the same recovery rates, the same probability of infection, and the same likelihood of being treated by RCD,

whereas this may not be true in reality. A study of migrants and travellers in Cambodia estimated that migrant workers were in general more vulnerable to malaria and may have poorer access to healthcare, particularly those working in remote, forested areas [114]. These are details that are currently not captured in the models presented but may make a difference to the final incidence of infections estimated under different intervention scenarios.

In comparison, within the HAT model, we model commuters separately, including a higher risk of infection and exclude this population from active screening. This separation requires more data on such segments of the population and some parameters may still need to be estimated or fitted, such as the increased exposure to tsetse flies. Additionally, within the HAT model, we assume that there is a sub-population that always travels, and the other residents never travel. However, we expect that these assumptions likely have a small impact on the incidence rates observed in the model. Comparisons across model structures would allow for a better understanding of the magnitude of the impact of such assumptions on our results. Such comparisons between models have been conducted previously for another HAT model and have shown that structural choices around aspects such as heterogeneity in exposure to tsetse bites or animal reservoirs can make a large difference to predictions of when elimination is likely to be achieved [82]. Ensemble modelling requires a lot of extra time and effort but can help highlight the structural uncertainties present in a model.

When modelling RCD for malaria, it is worth considering the time taken from infection to disease symptoms, and from disease symptoms in the primary case to secondary infections having a blood parasite density that is measurable by RDT. It may be that following up index cases within three days may be too soon after infection for secondary infections to test RDT-positive. Thus, they may not receive treatment during follow up, but then go on to develop malaria and contribute to onward transmission. Modelling gamma-distributed infection lengths through the use of multiple infected 'tunnel' states and modelling RDT sensitivity as a function of time since the detection of the index case may allow for some of these factors to be incorporated into a population model. However, the last suggestion would make the assumption that infections found in the index household are all secondary infections stemming from the index case, whereas they may have been acquired from co-travelling with the index case, or around the same time as when the index case was infected. Stuck *et al* (2020) found that, in Zanzibar, co-travellers of imported cases were approximately twice as likely to be infected as non-co-travelling household members [88]. This suggests that a proportion of the infections detected by RCD are likely not secondary infections stemming from the index case, but rather infections that were also acquired during travel. Similarly, prompt follow up allows for finding infections that were acquired locally at the same time as the index case.

We do not consider the prophylactic effect of RDA within our models. The prophylactic effect of presumptive treatment is part of the reason why RDA is conditionally recommended by WHO for reducing malaria transmission [157]. By not including this, we likely underestimate the effectiveness of RDA in reducing transmission. In order to include a prophylactic effect, we would need to expand the model to include a gamma-distributed time spent protected by RDA, during which non-infected individuals would move from the susceptible class to a treated class, and then return to the susceptible class after this time. We could even consider potentially modelling multiple rounds of RDA within the same households to see if imperfect coverage plays a large role in ongoing

transmission, though this would be challenging to do accurately in a population model as we cannot track who has previously received RDA. An individual-based model where we can monitor which household each person belongs to and their treatment history would be necessary.

Within the HAT model presented in this thesis, there are aspects such as asymptomatic infections and animal reservoirs that are not included that may lead to the persistence of HAT transmission [145]. Including such aspects would likely decrease our estimates of the probability of elimination, similar to the results found by Rock *et al* (2015) [82]. However, considering the sustained decline in HAT transmission observed over the last 30 years through mainly active and passive surveillance, it is likely that such cryptic reservoirs are not leading to the majority of cases, as neither of these interventions targets such reservoirs. Nonetheless, while such reservoirs may only contribute a small amount to transmission, they may be sufficient to allow for the persistence of HAT in areas that would otherwise reach elimination. Better data on the frequency of cryptic reservoirs and the magnitude of their contribution to transmission is required to better understand how big a role they may play in disease persistence.

Looking to the future, acoziborole is a single-dose oral treatment for HAT that is in late-stage clinical trials. If acoziborole is shown to be safe and efficacious in Phase III clinical trials and receives approval, it would greatly reduce concerns around compliance as the treatment regimen consists of only one dose. The model presented in Chapter 4 could easily be adapted to model the introduction of acoziborole in the future. Compliance rates would likely be higher with acoziborole than with fexinidazole, the efficacy as compared to pentamidine and NECT would need to be adjusted according to trial results, and the access to treatment would need to be adjusted in line with WHO guidelines. The estimate of the prophylactic period for the drug would also need to be adjusted, and if the drug is exceptionally safe as compared to previous treatments, has a low probability of developing resistance, and has a particularly long prophylactic period, there may be some possibility of using it for prophylaxis or presumptive treatment in high-risk groups. Again, the current model can be adapted to include such interventions.

5.3 The role of reactive interventions in disease elimination settings

Reactive interventions are used in disease control in two main settings: for early outbreaks in a mostly naïve population, i.e. at the start of an epidemic, and to find and treat the last cases of a disease when approaching elimination.

Contact tracing is a reactive intervention for diseases spread by direct contact. During the COVID-19 pandemic, rigorous contact tracing led to fewer new infections and deaths [158]. Similarly, contact tracing is an essential part of outbreak containment measures for Ebola [159]. Contact tracing works well when most cases are symptomatic, the majority of cases are followed up, and quarantining of all contacts is feasible or accurate tests can be used to determine which contacts were infected and which were not. Timing of testing can play a role in the effectiveness of contact tracing, where testing at the point when pathogen densities are high enough to be detected on a test will increase the chances of finding all secondary infections. Similarly, different estimates of the

serial interval may influence the optimal length of the quarantine period for contagious diseases [160]. However, in the case of COVID-19, contact tracing alone was typically insufficient to prevent outbreaks. Instead, we saw that the countries that closed borders (stopping importation) or imposed lockdowns (reducing the transmission rate) had the most success with preventing large outbreaks of COVID-19 [161]. These outcomes are quite similar to the findings presented in this thesis.

When considering reactive case detection in malaria, we are looking to use it in the other main setting: to achieve disease elimination and prevent the re-establishment of transmission. Malaria also comes with the added challenge of being a vector-borne disease, therefore isolation is not a feasible control measure. Instead, we must rely on tests, and, ideally, these tests should be rapid and inexpensive, thus RDTs are used. RDTs have a detection limit of approximately 100 parasites per micro-litre of blood [162, 163]. Data from controlled human malaria infection trials suggests that at least six days need to pass from infection until the blood parasite density crosses 100 parasites/µl in non-immune individuals [164]. This time may be longer in patients with immunity, as may be seen in malaria-endemic areas. Nonetheless, it may be better to conduct RCD at least sixteen days after the detection of the initial case, accounting for both a minimal extrinsic incubation period of ten days in mosquitoes [165], and the time taken to develop a patent infection in humans, to increase the likelihood that any secondary infections are detectable, rather than within three days as modelled in this thesis. However, delays in conducting RCD mean that these secondary infections have longer to transmit malaria before they are detected, which may reduce the effectiveness of the intervention. Additionally, infections within the same generation as the index case are also left untreated for sixteen days in this case. There is also the potential for greater resistance from the community if RCD is conducted in a delayed manner rather than promptly. It may seem like malaria is not a priority for the Ministry of Health, or that it is not very concerning to have malaria. On the other hand, a two-week delay between detection of the index case and follow up may act as a notice period, so more household members or neighbours may be present for testing, as absence has previously been noted as the main reason for not participating in RCD [98]. Further research is needed into the community-level acceptability of delayed reactive case detection, and also the optimal delay period between the detection of the index case and follow up in order to minimise the impact of both first-generation and secondary infections.

In contrast, reactive vector control may be more effective if follow up is conducted in a timely manner. It can be assumed that an index case is likely infectious to mosquitoes by the time they are diagnosed with malaria at a health facility. In this case, some secondary infections may be prevented by prompt IRS within the index household and neighbouring households. The long-lasting effects of the typical insecticides used in IRS should prevent further transmission from any secondary infections within the household sprayed [98]. Of course, outdoor biting from mosquitoes may still lead to further transmission, so reactive vector control may be best suited to areas with *Anopheles* species that mostly bite indoors. Reactive vector control could also take the form of larviciding in villages with higher than average reporting of malaria cases. While larviciding has been shown to reduce malaria incidence in clinical trials [31], there is a lack of research regarding larviciding as a potential reactive intervention. Similarly, there are novel vector control tools in development and use, such as attractive targeted sugar baits, odour-baited traps, transfluthrin-treated eave ribbons, and topical repellents, that could be used as reactive interventions, particularly

in areas with high densities of outdoor biting mosquitoes [166, 167, 168].

Reactive case detection is not commonly used in HAT surveillance and control. RCD was trialled for HAT in Côte d'Ivoire in 2012, with 79 cases detected over the last 12 years being followed up and members of the household and neighbours being tested for HAT [169]. The results of RCD were compared to the efficacy of active screening in the same area. RCD found more HAT cases than active screening, despite testing fewer individuals. There are two key implications from the findings of this study: firstly, RCD may find more cases because there is more clustering of cases around index cases, secondly, going to the household of the index case and to their neighbours may be an easier way to screen high risk individuals than setting up temporary testing centres and requesting that people go there for screening. The first point is supported by evidence that having family members with a history of HAT infection is associated with being diagnosed with HAT [170, 171, 172, 173]. The second point is supported by evidence that the mean attendance rate for active screening was around 74% in 1997-98 in DRC, with considerable variation between villages [142, 169]. Some of the reasons for non-attendance at screening rounds included not seeing HAT as a concern, accessibility, the opportunity cost of going to screening, and false beliefs around lumbar punctures leading to impotence [142]. All of these points can be better addressed by door-to-door screening where a surveillance officer goes to the household of the patient and can explain directly why screening is necessary and clarify any misconceptions.

When considering the implementation of reactive case detection in HAT, the same challenge is present as in malaria: the optimal gap between detection of the initial case and reactive screening is unclear. *Gambiense* HAT is a much slower-progressing disease than malaria, and the field study by Koffi *et al* (2016) found all parasitologically confirmed RCD-detected cases near the homes of index cases identified ten years ago. A ten-year gap is not practical from a programmatic perspective, particularly for a disease that is targeted for elimination by 2030. Another study, conducted in DRC, used reactive screening at the village level to search for more cases within the village of the index case and neighbouring villages, with follow up being conducted some months after the detection of the index case [20]. Similar to Koffi *et al* (2016), Lumbala *et al* (2020) found that reactive screening detected more patients per person screened than active screening. These cases were also approximately three times as likely to be in stage 1 of the disease as cases that were passively detected [20]. This further suggests that the efficacy of RCD for HAT may not be so sensitive to the time to follow up as it is for malaria.

Given HAT is a vector-borne disease, reactive vector control could also be considered as a reactive intervention. Vector control through the use of 'tiny targets' has shown promising results in different settings and is sometimes a part of standard HAT control measures [75, 136, 137]. Blanket coverage using vector control is considered impractical as a transmission reduction strategy, but targeted use of vector control in transmission hotspots may be a cost-effective method of reducing HAT incidence [75, 174, 175]. Additionally, vector control would limit transmission from any potential animal reservoirs.

It is worth recognising that reactive interventions are resource-intensive and become more expensive per case found as prevalence decreases. Nonetheless, surveillance is necessary for gathering evidence of elimination, and reactive interventions can be paired with surveillance to bring about targeted action from the data gathered through surveillance and monitoring.

5.4 The uses of compartmental models for infectious disease modelling

As the computing power and speed of computers and high-performance computing clusters continue to grow, there is a trend within the field of disease modelling towards the use of individual-based models. These models simulate individuals and their interactions, drawing parameter values for aspects such as transmission rates and recovery rates from distributions. As individuals are tracked, a disease history can be maintained, and this history can impact the likelihood of the next event happening. Individual-based models can capture heterogeneous biting patterns, travel patterns and treatment seeking behaviours more easily than compartmental models. However, these models can be difficult to parameterise and require richer datasets to make the most of the extra functionality that individual-based models can offer. In comparison, compartmental models can often be easier to parameterise, as they typically contain fewer parameters. Additionally, the simplicity of compartmental models can allow the user to focus on the research question of interest, such as connectivity between populations, without the model quickly becoming computationally expensive. It is also easier to use compartmental models to estimate population-wide parameters such as the reproduction number of a disease, which can provide insights into the likely trajectory of a disease without further simulation. Finally, as compartmental models are typically built on an underlying system of differential equations, it can be easier to interpret outputs and check if they make intuitive sense. When results do not agree with intuition, it is possible to analyse the equations to see if the behaviour of the model can be expected under certain circumstances, or if there may be an error in the coding of the model. For example, states may be observed in susceptible-infected-susceptible compartmental models where the basic reproductive number is below 1, but an endemic equilibrium persists (a backward bifurcation). However, this phenomenon is often only observed under a very specific and unlikely set of parameter values, such as higher transmission rates for partially immune or vaccinated individuals [176, 177]. As models become more complex, it can become more challenging to confirm if unintuitive results are to be expected, or if they arise due to unrealistic assumptions or human error in coding.

Nonetheless, individual-based models can capture many aspects of the disease biology that are difficult to include in compartmental models and could be particularly useful in the context of a disease such as HAT, where there is considerable heterogeneity in risk factors and biting exposure [175]. Looking to the future, an individual-based model for HAT could be used to explore the potential impact of heterogeneity in infection risk, immunity and treatment seeking behaviour in greater detail.

5.5 The need for better data

Malaria and HAT are both vector-borne diseases caused by protozoa. They are diseases of poverty, associated with rural areas. There is no vaccine that provides long-lasting sterile immunity available for either disease. However, our understanding of the biology of malaria is vastly better than that of HAT. We have a relatively good understanding of the disease transmission cycle, the parasite biology, the vector biology and the within-host

dynamics of malaria. This allows for better targeting of interventions towards transmission breakpoints. For HAT, much of this is unknown. For example, there is evidence that some patients can harbour transmissible *T. b. gambiense* parasites on the skin [178]. Capewell *et al* (2016) were able to demonstrate that mice with trypanosomes on the skin were able to transmit the parasites to tsetse flies. If this is also possible for humans, this could be a mechanism of persistence that allows for continued transmission of HAT in areas where symptomatic cases have not been reported for a long time. However, we do not know what proportion of all infections may be such asymptomatic infections.

Similarly, we know that pigs, goats and sheep in Cameroon have previously tested PCR-positive for *T. b. gambiense* [179, 180], but we do not know how much such animal reservoirs contribute to transmission, or if they are even able to infect tsetse flies. If they can infect flies and contribute significantly to transmission, it would likely make a substantial difference to the estimated time to reach elimination under different intervention scenarios, and so such transmission events should be included in HAT disease models. In order to parameterise such transmission, we need data on the frequency of co-location between humans and animals in different settings and the probability of transmission upon co-location. These factors can be hard to parameterise, and model fitting can allow us to estimate potential values for these parameters that agree with the observed data on case incidence. However, when many parameters are fitted together, there can be problems of identifiability, where many combinations of values for the unknown parameters are equally likely to lead to the data observed.

In contrast, we have excellent data on HAT cases that have been detected, due to the toxic nature of past treatments for the disease and the need to avoid unnecessary treatment. The HAT Atlas is built by systematic data collection regarding every HAT case detected worldwide, including georeferencing at the village level [85]. This detailed mapping of case distributions meant that, despite gaps in our knowledge regarding the disease biology, interventions could be targeted towards transmission hotspots, and control strategies could be evaluated. For example, cases were typically found in the earlier stages of the disease in villages that were part of active screening efforts [85]. Our lack of understanding of the disease biology can sometimes prove a challenge: in some areas where interventions such as active screening and treatment have been repeatedly implemented, such as Mbini in Equatorial Guinea, HAT case numbers appear to be stable in the HAT Atlas data [85]. This would suggest that the current strategy for HAT control in such areas should be revisited. However, without a better understanding of what is causing the epidemiological pattern to remain so stable, it is difficult to gauge which interventions are worth trying in such areas. At most, the HAT Atlas data could be used to compare the population census to the number of people screened during active screening to assess whether poor coverage is the issue.

In comparison, while many countries with high transmission levels of malaria keep some form of a national register of malaria case numbers, under-reporting is common, with estimates of the proportion of cases missed ranging from 15% to 80% [181, 182, 183]. This is often due to private clinics and pharmacies not needing to report cases to the national register. Under-reporting can be especially common in areas with high transmission rates and subsequently strong immunity profiles. Many infections may be asymptomatic or mild and therefore not be reported to the formal healthcare system. This may make it look like such areas have a low malaria prevalence, when, in reality, the area has high levels of local transmission and may also be a source of infections for lower-transmission

areas nearby. Surveys such as the Malaria Indicator Survey (MIS) or the Demographic and Health Survey (DHS) can provide some insight into the true malaria prevalence or incidence in an area. However, these surveys typically use RDTs or microscopy to diagnose malaria, which can have a low sensitivity in settings where low parasite density infections are common. Thus, testing even a random sample of households may not yield a good measure of the true malaria prevalence in an area. Stronger notification systems, which include reporting of malaria cases detected at pharmacies and private health facilities as well as public health facilities, are needed to have better estimates of case numbers. Additionally, more surveys need to be conducted that use PCR for the detection of infections, in order to better gauge the frequency of low parasite density infections. Given that RDT sensitivity as compared to PCR is estimated to be as low as 10% in some settings [184], and that, in some samples, over 40% of RDT-negative, PCR-positive infections also contained gametocytes [185], it is crucial to better estimate the frequency of low parasite density infections in elimination settings, and ensure this parasite reservoir is removed.

Better diagnostics and case reporting would also reduce unnecessary use of antimalarials. Resistance to artemisinin derivatives is spreading, and the situation is becoming slowly reminiscent of the late 1980s and early 1990s, where *Plasmodium falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine, mefloquine and quinine was a huge challenge to treating severe malaria cases [186]. This was alleviated through the introduction of artemisinin. Resistance to artemisinin and its derivatives arose soon after, first in Asia, and then in Africa [187]. Reducing unnecessary exposure to ACTs is a key part of prolonging the effective lifespan of ACT drugs. In Dar es Salaam, it was observed that less than 10% of outpatient fevers in children were due to malaria [188]. Such cases highlight the value of testing for malaria before distributing antimalarials to febrile patients. Overall, better testing and reporting of malaria cases would not only help with disease modelling, but also with targeted disease control and slowing the spread of ACT resistance.

5.6 Future directions for research

As diseases approach elimination, the cost per case found and treated tends to increase. A better understanding of disease biology, transmission dynamics and the potential impact of interventions would likely help us to compare methods of reaching disease elimination and eradication, particularly in terms of speed and cost-effectiveness. There are many aspects of the disease biology and intervention dynamics of both malaria and HAT that could benefit from further study. Here, I only focus on directions for future research that pertain to the key questions I have explored in this thesis: reactive interventions, human mobility, and access to treatment with novel drugs.

Reactive vector control (RVC) could be a promising intervention for reducing transmission in vector-borne diseases, as vectors typically have to bite twice to transmit a disease, providing two opportunities to interrupt transmission. Malaria transmission models could be used to explore the potential impact of reactive vector control as compared to reactive case detection. A field study of RVC conducted in Namibia observed that adding RVC to RCD led to a similar reduction in malaria incidence as switching from RCD to RDA [98]. Expanding the models presented in this thesis to include mosquitoes would

require detailed information on the mosquito species, density, and biting patterns present in Zanzibar, but then could be used to evaluate the potential impact of introducing RVC in Zanzibar.

We currently do not have a good estimate of the optimal time to follow up cases in RCD. This may depend on if the case is likely an imported case or a locally acquired infection. Further study into the proportions of cases detected that are acquired elsewhere or locally acquired could help inform the optimal time at which follow up should be conducted to find the most new cases, ideally before symptoms become severe or significant transmission can occur.

As humans become more mobile, it is worth investigating how frequent travellers may differ from non-travellers within a population, to better assess whether there may be subgroups or behaviours that could be targeted by interventions. The effectiveness of measures such as border screening, travel advice around protection against mosquito bites, and chemoprophylaxis adherence should be studied in the field to better gauge what can realistically be achieved in terms of treating and preventing infections in travellers. Surveys conducted on modes of transportation or at ports of entry would be helpful for understanding where people travel to and from, and the precautions they typically take against malaria.

Similarly, it would be helpful to better understand the risk factors and tsetse density that workers who move regularly between 'village' and 'plantation' settings in HAT-endemic areas are exposed to, both at work and when commuting. As mobile phones become more ubiquitous, anonymised data from calls, messages and internet usage could be used to better understand travel patterns to identify sources and sinks of disease transmission [48, 49, 59]. Additionally, census data could be used to identify longer-term migration patterns [103], which may be useful for slower-progressing diseases such as HAT.

The use of novel drugs such as fexinidazole in clinical settings for HAT should be monitored to estimate the likely adherence rates, in order to assess whether any non-compliance will likely have an effect on the predicted time to reach gHAT elimination. Additionally, it would be worth asking passively detected patients, particularly in the second stage of the disease, what the main barriers they faced in accessing treatment were. A better understanding of what prevents patients from being diagnosed earlier would help us to better target such barriers and thus reduce the length of time the average patient remains infectious.

Conclusion

The contents of this thesis highlight the use of stochastic models of disease transmission in guiding thinking around new interventions and policy-making in low transmission settings for diseases approaching elimination. Such models are useful for exploring a range of intervention scenarios quickly and inexpensively, and can provide insights into data gaps that need to be filled. They can be especially useful in the context of disease elimination, where the cost associated with finding each remaining case grows as prevalence decreases. Human African trypanosomiasis is closer to elimination than malaria and potentially represents the situation that malaria may be in within ten to twenty years' time. Local, national and regional elimination and preventing the re-establishment of diseases is the essential first step towards eradication.

We developed two models for malaria transmission focusing on human mobility and reactive case detection in Zanzibar, Tanzania. Upon calibration to movement and prevalence data, our results suggest that the effective reproduction number in the absence of importation is significantly below 1 on the larger island of Unguja, and likely below 1 on the smaller island of Pemba (the 95% confidence intervals include the threshold value of 1). Improvements to reactive case detection are unlikely to result in interruption of transmission, and most infections are not found by reactive case detection. A novel model for distinguishing between imported, introduced and indigenous cases was used to confirm if combinations of interventions in Zanzibar could lead to the WHO definition of malaria elimination: three years with zero indigenous cases. We find that the reactive intervention scenarios modelled can substantially reduce malaria incidence, particularly when used in combination, but disease elimination was highly unlikely using reactive interventions. This is in part due to a drop in the number of index cases found as the malaria prevalence drops. In contrast, interventions that prevented new infections from arriving in Zanzibar, either through treatment of travellers or preventing infections in travellers in the first place, and interventions that reduced onward transmission from any imported cases that did arrive in Zanzibar, were the ones that had non-zero probabilities of reaching elimination in the next 40 years. We show that the effective reproduction number must be kept well below 1 to prevent the incidence of indigenous infections in the face of ongoing importation. There is a need for a better understanding of the true malaria prevalence and frequency of travel in both the area of interest and the areas to which they are linked in the model, in order to better estimate the potential impact of various intervention scenarios on the probability of reaching elimination.

We find that fexinidazole may have a positive or negative effect on human African trypanosomiasis transmission, depending on who receives the drug, compliance levels, acceptability of the new treatment within the community and changes in treatment-seeking behaviour. Oral medication, when administered correctly, could help speed up the

progress towards sleeping sickness elimination in the Democratic Republic of the Congo. There is a need for better data on fexinidazole adherence and any potential changes to the passive detection rates of the disease from the introduction of fexinidazole, in order to better gauge the likely impact of this new drug.

While both diseases are targeted for elimination, the tools that have allowed us to eradicate smallpox and rinderpest, such as effective vaccines that provide long-lasting sterile immunity, are not yet available for malaria or sleeping sickness. We must understand the mechanisms of disease persistence, and then look at the tools available and consider the most efficient and targeted ways of deploying them such that elimination, and eventually eradication, can be achieved.

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Appendices

Appendix A

Chapter 2 Supplementary Information

A.1 The controlled reproduction number for the whole system

The controlled reproduction number for the whole system, R_s, gives the expected number of secondary infections arising across all three patches from a primary infection when interventions are in place. R_s was calculated by taking the spectral radius of the next generation matrix [176, 189]. Note, R_s is different to the local controlled reproductive number on each island given in the main text, R_c, as that is calculated by taking the ratio of the transmission and recovery rates on each island.

The equation for the rate of change of infected individuals (Eq. 2.4) can be linearised by decomposing the Jacobian matrix into two matrices describing the transmission events leading to new infections, $\mathbf{F}$, and the recovery events leading to removal from the infected class, $\mathbf{V}$:

$$\frac{\mathrm{d}\vec{I}}{\mathrm{d}t} = (\mathbf{F} - \mathbf{V})\vec{I}, \tag{A.1}$$

where

$$F_{ij} = \sum_{k=1}^{3} \left(\frac{\beta_k N_j \theta_{kj} \theta_{ki}}{\sum_{l=1}^{3} N_l \theta_{kl}} \right), \tag{A.2}$$

and

$$V_{ij} = \begin{cases} \mu & i = j, \\ 0 & i \neq j. \end{cases} \tag{A.3}$$

The next generation matrix, $\mathbf{K}$, is given by

$$\mathbf{K} = \mathbf{F}\mathbf{V}^{-1}. \tag{A.4}$$

R_s is equal to the spectral radius of $\mathbf{K}$.

In order to investigate the potential impact of changing transmission levels on mainland Tanzania, the value of β_{mainland} was varied between 0.004 and 0.0054 and R_s was re-calculated.

The results are shown in Fig. A.1. While the value for the transmission rate on mainland Tanzania is below the transmission rate on Pemba, the spectral radius of $\mathbf{K}$ is dominated by the ratio of the transmission and recovery rates on Pemba. Once the transmission rate on the mainland approaches that of Pemba, the mainland transmission rate becomes the dominant factor in determining the spectral radius of $\mathbf{K}$. After this point, we see a linearly increasing relationship between the mainland transmission rate and the controlled reproductive number of the system.

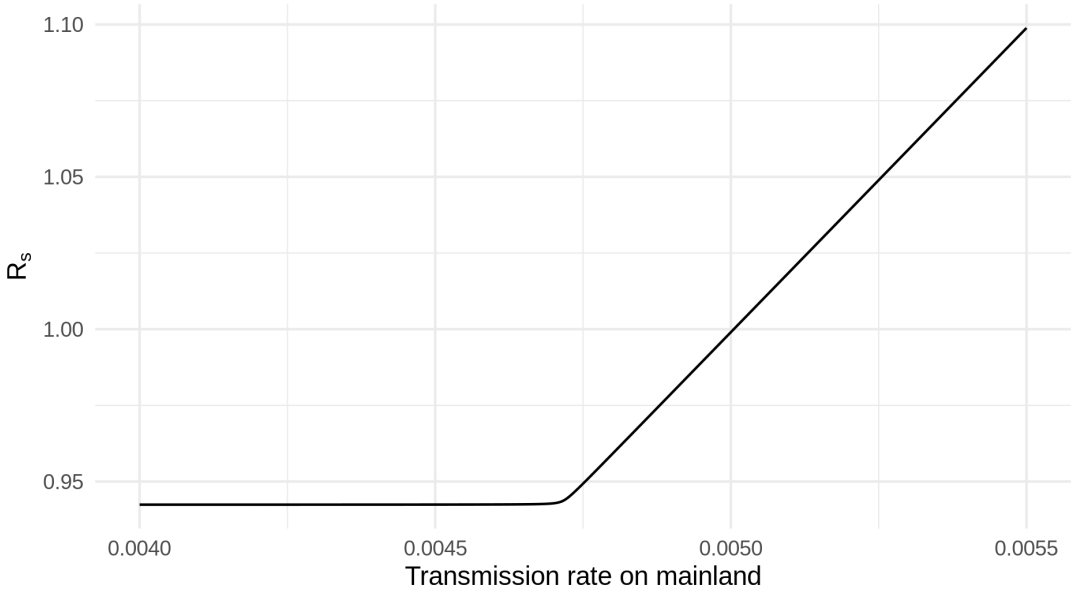

Figure A.1: Plot showing the relationship between the transmission rate on mainland Tanzania, and the controlled reproductive number of the whole system.

A.2 Treatment of imported cases

Treatment of imported cases leads to a shift in the equilibrium prevalence observed on each island. Fig. A.2 shows the timeseries plots for reaching equilibrium for the following proportions of treatment of outbound travellers from the mainland to Zanzibar, O, and travellers from Zanzibar on their return to Zanzibar, R, assuming the baseline level of RCD is maintained:

- $O = R = 0.25$,
- $O = R = 0.5$,
- $O = R = 0.75$,
- $O = R = 1$.

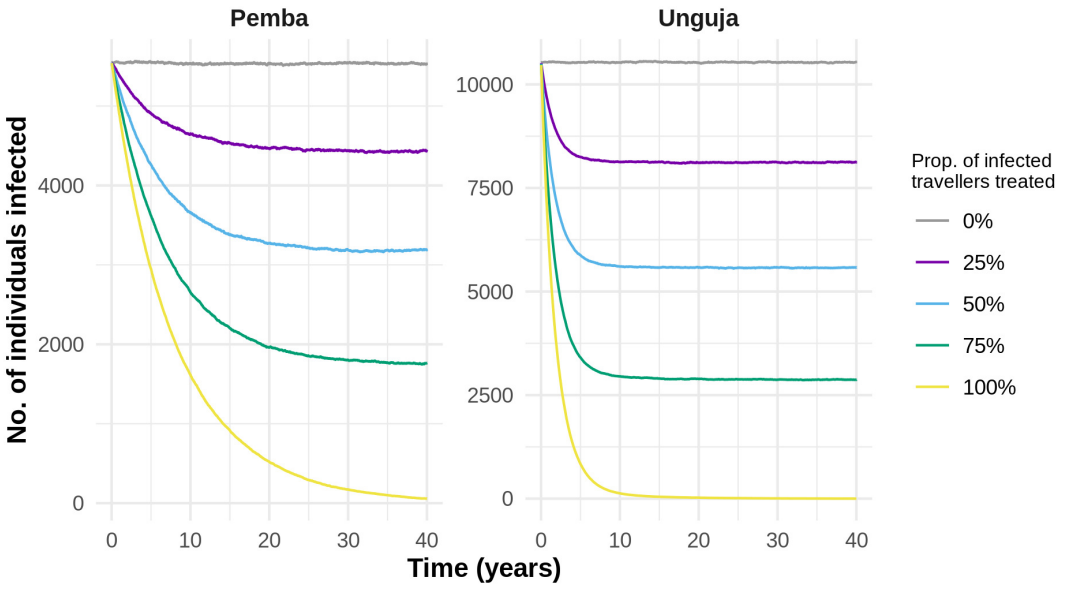

Figure A.2: 7-day moving average of the median of 500 stochastic simulations for an SIS model of RCD for Pemba and Unguja comparing different levels of treating infected travellers, assuming baseline RCD is maintained. Here, the value given as the proportion of travellers treated account for both travellers from the mainland and travellers from Zanzibar.

Appendix B

Chapter 3 Supplementary Information

B.1 Methods

B.1.1 Modelling of interventions

B.1.1.1 RCD at a range of levels of follow up

The percentage of malaria cases diagnosed at a health facility that are followed up by a District Malaria Surveillance Officer is given by η. η is varied between 0% and 100% to model the extreme values of removing RCD altogether, and perfect follow up of all cases diagnosed at a health facility.

B.1.1.2 RCD at a range of levels of treatment seeking

The rate at which people seek treatment is 2.9×10^{-4} per day in Pemba and 6.1×10^{-4} per day in Unguja. This was calculated by considering the median number of malaria infections diagnosed at a health facility per month per district on Pemba and Unguja, and scaling by the number of districts and 30 days in a month [61]. This was increased by a factor of 2 or 3 as to simulate increase in treatment as an intervention.

B.1.1.3 RCD with follow up of neighbours

Currently, neighbours are not included in RCD. We simulated the testing and treatment of 20 and 100 neighbours, as well as the index household. From the RADZEC study data, we estimated that the targeting ratio amongst neighbouring households is around 0.7 (95% confidence interval (CI): 0.4–1.3) in Pemba and 1.3 (95% CI: 0.9–1.9) in Unguja.

Thus, the RCD term was modified to

$$\varphi_k = \rho I_k(\tau_k^{(h)}\nu_k^{(h)} + \tau_k^{(n)}\nu_k^{(n)})\eta\xi_k, \tag{B.1}$$

with $\nu_k^{(n)}$ either 20 or 100.

B.1.1.4 Switching from RCD to RDA

When modelling RDA, we considered that all index household members and neighbours (when included) would receive treatment regardless of disease status. Thus, the diagnostic test sensitivity, ρ, was changed from 34% to 100%.

B.1.1.5 Treatment of a proportion of cases brought on to Zanzibar by travelling humans (either residents or visitors)

Currently prophylaxis is not provided to travellers to mainland Tanzania. Similarly, there is no screen-and-treat programme for entrants to Zanzibar. We include treatment of imported cases as a potential intervention in our model, in order to evaluate what proportion of cases must be treated to achieve different reductions in prevalence on Pemba and Unguja [118]. We modify Eq. (4) in the main text to have a θ^{outbound}, which includes treatment for visitors from mainland Tanzania on their outbound journey to Zanzibar, and θ^{return} for Zanzibari residents that receive treatment on their return journey to Zanzibar. Thus the base form of the equation becomes

$$\frac{\mathrm{d}I_k}{\mathrm{d}t} = \sum_{i=1}^{3}\left(\beta_i\left(\frac{\sum_{j=1}^{3} N_j\theta_{ij}^{\text{outbound}} I_j}{\sum_{j=1}^{3} N_j\theta_{ij}}\right)\theta_{ik}^{\text{return}}\right)(1-I_k) - (\mu+\varphi_k)I_k, \tag{B.2}$$

where

$$\theta^{\text{outbound}} = \begin{pmatrix} 0.991 & 0.004 & (1-O)*5.7\times10^{-5} \\ 0.003 & 0.970 & (1-O)*5.3\times10^{-4} \\ 0.006 & 0.026 & 0.999 \end{pmatrix}, \tag{B.3}$$

and

$$\theta^{\text{return}} = \begin{pmatrix} 0.991 & 0.004 & 5.7\times10^{-5} \\ 0.003 & 0.970 & 5.3\times10^{-4} \\ (1-R)*0.006 & (1-R)*0.026 & 0.999 \end{pmatrix}. \tag{B.4}$$

O represents the proportion of travellers from mainland Tanzania receiving treatment such that they are no longer infected upon entering Zanzibar, and R represents the proportion of Zanzibari residents receiving treatment such that they are no longer infected upon returning to Zanzibar. We always simulate equal proportions of outbound and return cases being treated (i.e. $O = R$)

B.1.1.6 Reductions in the malaria transmission rate

The rate at which malaria is transmitted from one human to another can be reduced through vector control interventions such as the use of long-lasting insecticidal nets, indoor residual spraying and larval source management. As we do not explicitly model mosquitoes or the vectorial capacity, we reduce the transmission parameter, β, to simulate increases in vector control.

Thus, for this intervention, β is replaced by $\beta(1-r)$ where r is the reduction in vectorial capacity. As vectorial capacity is proportional to the number of susceptible humans

infected by an infected human per day, β is proportional to the vectorial capacity, and any reduction in β could arise from a proportional reduction in the vectorial capacity [190]. Values ranging from 0.25 to 0.9 were tested for r on Pemba and Unguja, and values ranging from 0.1 to 0.3 for r on mainland Tanzania.

B.2 Results

B.2.1 Comparison of interventions

The impact of each intervention alone was tested by changing one factor at a time and plotting the final equilibrium reached 40 years after the introduction of the intervention. All other factors were held at their baseline value, given in Table 3 in the main text. The results from this analysis are shown in Fig B.1. Most intervention parameters had an approximately linear relationship with malaria incidence, but the relationship between the percentage of travellers treated and the incidence of infections was mildly concave, and the relationship between a reduction in the malaria transmission rate in Zanzibar and the incidence of infections was steeply curved. This suggests that even small increases in vector control may have a disproportionately large impact with regards to reducing malaria incidence on Zanzibar.

B.2.2 Impact of parameter uncertainty

Parameter uncertainty was considered in the same way as described in Das *et al* (2022) [118]. Simulations were run with a range of parameter values based on the uncertainty in the data. The parameters varied and the distributions from which they were sampled were as follows:

- The equilibrium malaria prevalence on Pemba, $I_1^* \sim \text{Beta}(32, 2242)$;
- The equilibrium malaria prevalence on Unguja, $I_2^* \sim \text{Beta}(92, 3196)$;
- The targeting ratio in index households in Pemba, $\tau_1^{(h)} \sim \frac{\text{Beta}(20,427)}{I_1^*}$;
- The targeting ratio in index households in Unguja, $\tau_2^{(h)} \sim \frac{\text{Beta}(64,470)}{I_2^*}$;
- The targeting ratio in neighbouring households in Pemba, $\tau_1^{(n)} \sim \frac{\text{Beta}(13,1147)}{I_1^*}$;
- The targeting ratio in neighbouring households in Unguja, $\tau_2^{(n)} \sim \frac{\text{Beta}(26,1619)}{I_2^*}$;
- The number of people tested by the RCD programme in the index household in Pemba, $\nu_1^{(h)} \sim \text{Normal}(7.02, 0.24)$;
- The number of people tested by the RCD programme in the index household in Unguja, $\nu_2^{(h)} \sim \text{Normal}(6.36, 0.25)$;
- The number of people tested by the RCD programme in neighbouring households in Pemba, $\nu_1^{(n)} \sim \text{Normal}(20.36, 0.50)$;

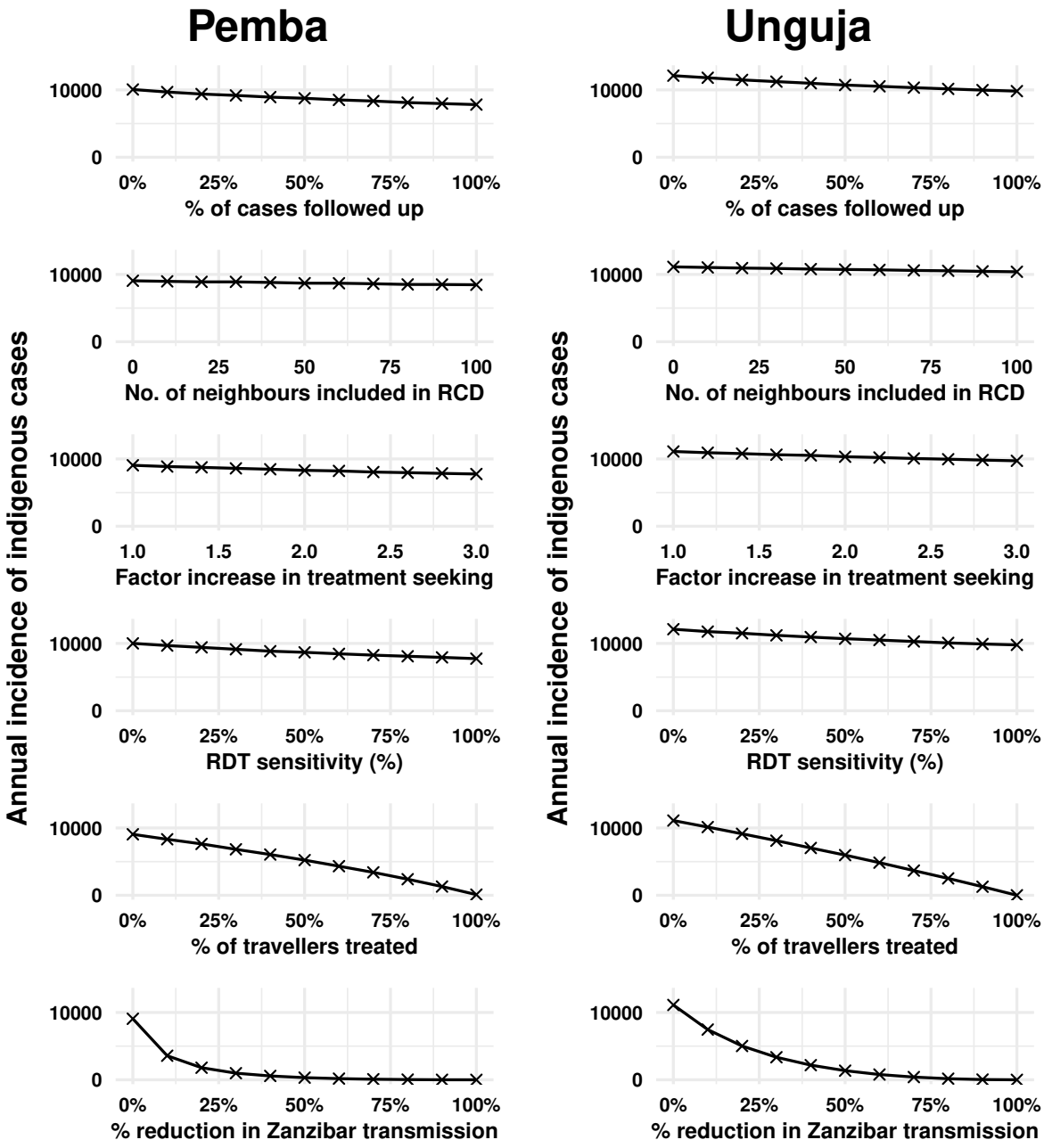

Figure B.1: Median yearly incidence of indigenous cases out of 500 simulations in the 40^{th} year after the start of each intervention. At each point, only the parameter on the x-axis has been changed, with all other parameters remaining at the baseline value. RCD: reactive case detection; RDT: rapid diagnostic test.

- The number of people tested by the RCD programme in neighbouring households in Unguja, $\nu_2^{(n)} \sim \text{Normal}(18.76, 0.58)$.

Subscripts of *1* and *2* indicate Pemba and Unguja, respectively. Parameter values with the 95% interval values can be found in Table B.1.

100 random values were selected from these parameter distributions, and each set of values was simulated with five different seeds, forming a total of 500 simulations for each intervention scenario. The final equilibrium value reached for a range of interventions,

Variable or parameter	Mean values [95% CI]			Source
	Pemba	Unguja	Mainland	
I_k^*	1.36% [0.96-1.93]	1.18% [0.86-1.61]	7.79%	[88, 104]
N_k	406,848	896,721	43,625,354	[107]
θ_{ij}		Pemba / Unguja / Mainland		[88]
		Pemba: 0.991, 0.004, 5.7×10^{-5}		
		Unguja: 0.003, 0.970, 5.3×10^{-4}		
		Mainland: 0.006, 0.026, 0.999		
μ	0.005 day^{-1}	0.005 day^{-1}	0.005 day^{-1}	[36, 106]
$\tau_k^{(h)}$	3.2 [2.0-4.8]	10.0 [8.0-12.6]	N/A	[88]
$\tau_k^{(n)}$	0.7 [0.4-1.3]	1.3 [0.9-1.9]	N/A	[88]
$\nu_k^{(h)}$	7.0 [6.5-7.5]	6.3 [5.9-6.9]	N/A	[88]
$\nu_k^{(n)}$	20.4 [19.4-21.4]	18.8 [17.6-19.9]	N/A	[88]
ρ^*	34%	34%	N/A	[88]
η^*	35.3%	35.3%	N/A	[61]
ξ^*	2.9×10^{-4} day^{-1}	6.1×10^{-4} day^{-1}	N/A	[61, 88]

Table B.1: Variable and parameter values at baseline and sources. Where a range of parameter values were tested in the uncertainty analysis, the 95% confidence interval for the range of values tested is given. The superscripts (h) and (n) indicate the index household and neighbouring households, respectively.

along with the uncertainty stemming from both the parameter and stochastic variation, is shown in Fig B.2. The impact of parameter uncertainty on the probability of reaching elimination was also examined and found to be minor (see Fig B.3). Even when parameter uncertainty is included, elimination is only observed when there is 100% importation treatment in the absence of transmission reduction interventions.

B.2.3 Sensitivity analysis

A sensitivity analysis was conducted using the Sobol method to characterise the impact of parameter variation on model outputs. 32,768 parameter values were sampled from uniform distributions for each parameter using Saltelli sampling [191, 192]. The bounds of the uniform distributions corresponded to 95% confidence intervals found in the literature or, when such bounds were not available, the point estimate of the parameter ±50%. Upper and lower bounds and data sources can be found in Table B.2. The upper bound of the proportion of time spent by mainland Tanzania residents on Pemba and Unguja was calculated by scaling the upper bound from Le Menach *et al* (2011) by the proportion of people residing on mainland Tanzania as compared to Pemba or Unguja. The model was then run using these parameter sets and a different seed for each parameter set, and

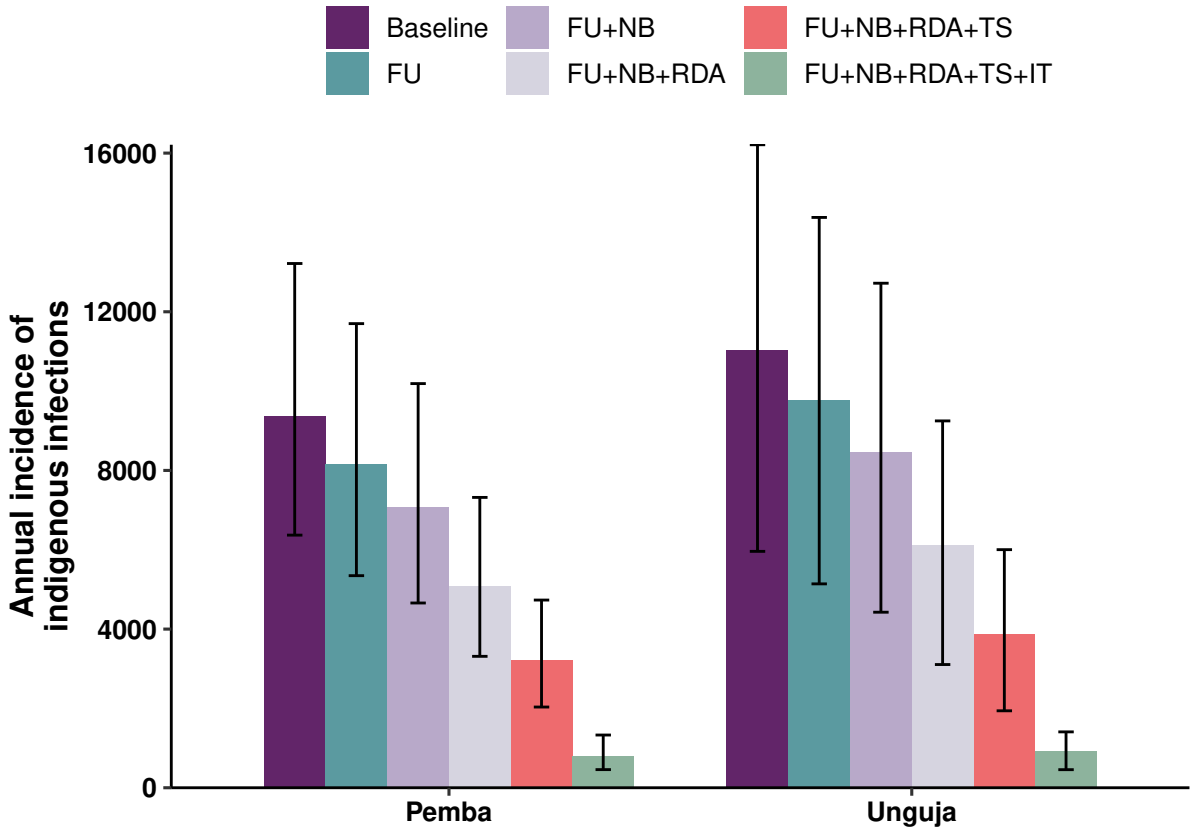

Figure B.2: Bar chart showing the median yearly incidence of indigenous infections 40 years after the start of interventions (i.e. once equilibrium is reached). The error bars indicate the 95% confidence for both the parameter and stochastic uncertainty. FU: 100% follow up; NB: 100 neighbours included in testing and treatment; RDA: reactive drug administration; TS: three times the baseline treatment seeking rate; IT: treatment of 90% of travellers arriving on Zanzibar.

the outputs were used to calculate Sobol indices. First order and total Sobol indices were calculated using the SALib package (version 1.4.5) in Python [192].

This analysis suggests that the main outputs of malaria prevalence and the annual incidence of indigenous infections are most sensitive to the estimates of the transmission parameter (Fig B.4 and B.5). As these are back-calculated from the baseline malaria prevalence, the need for accurate estimates of the prevalence in the general population is important for a correct estimate of the effective human-to-human malaria transmission rate. An accurate estimate of the baseline prevalence is also key to estimating the probability of elimination being reached under different intervention conditions.

B.2.4 The impact of a fixed versus a varying targeting ratio

The targeting ratio is calculated from the RADZEC study data and is assumed to be fixed in the main text, regardless of the population malaria prevalence. This implies that cases do not become more clustered as the disease prevalence falls. In comparison, Chitnis *et al* (2019) consider a targeting ratio that varies depending on prevalence and

Parameter	Point estimate	Lower bound	Upper bound	Reference
Transmission rate on Pemba (β_{Pemba})	0.0048	0.0024	0.0072	±50%
Transmission rate on Unguja (β_{Unguja})	0.0037	0.0019	0.0056	±50%
Transmission rate on mainland Tanzania (β_{Mainland})	0.0054	0.0027	0.0081	±50%
Mean duration of infection ($1/\mu$)	200	184	237	[126]
Targeting ratio on Pemba ($\tau^{(h)}_{\text{Pemba}}$)	3.1	2.0	4.8	RADZEC data ([88])
Targeting ratio on Unguja ($\tau^{(h)}_{\text{Unguja}}$)	10.1	8.0	12.7	RADZEC data ([88])
Treatment seeking rate on Pemba (ξ_{Pemba})	2.9×10^{-4}	1.5×10^{-4}	4.4×10^{-4}	±50%
Treatment seeking rate on Unguja (ξ_{Unguja})	6.1×10^{-4}	3.1×10^{-4}	9.2×10^{-4}	±50%
RDT sensitivity (ρ)	34%	0%	100%	Full range
Follow up of index cases (η)	35%	0%	100%	Full range
Movement from Pemba to Unguja (θ_{UP})	0.0032	0.0016	0.0048	±50%
Movement from Pemba to mainland Tanzania (θ_{MP})	0.0061	0	0.12	[45]
Movement from Unguja to Pemba (θ_{PU})	0.0039	0.0019	0.0058	±50%
Movement from Unguja to mainland Tanzania (θ_{MU})	0.026	0	0.12	[45]
Movement from mainland Tanzania to Pemba (θ_{PM})	5.7×10^{-5}	0	0.0011	[45]
Movement from mainland Tanzania to Unguja (θ_{UM})	5.3×10^{-4}	0	0.0025	[45]

Table B.2: Parameter bounds for sensitivity analysis.

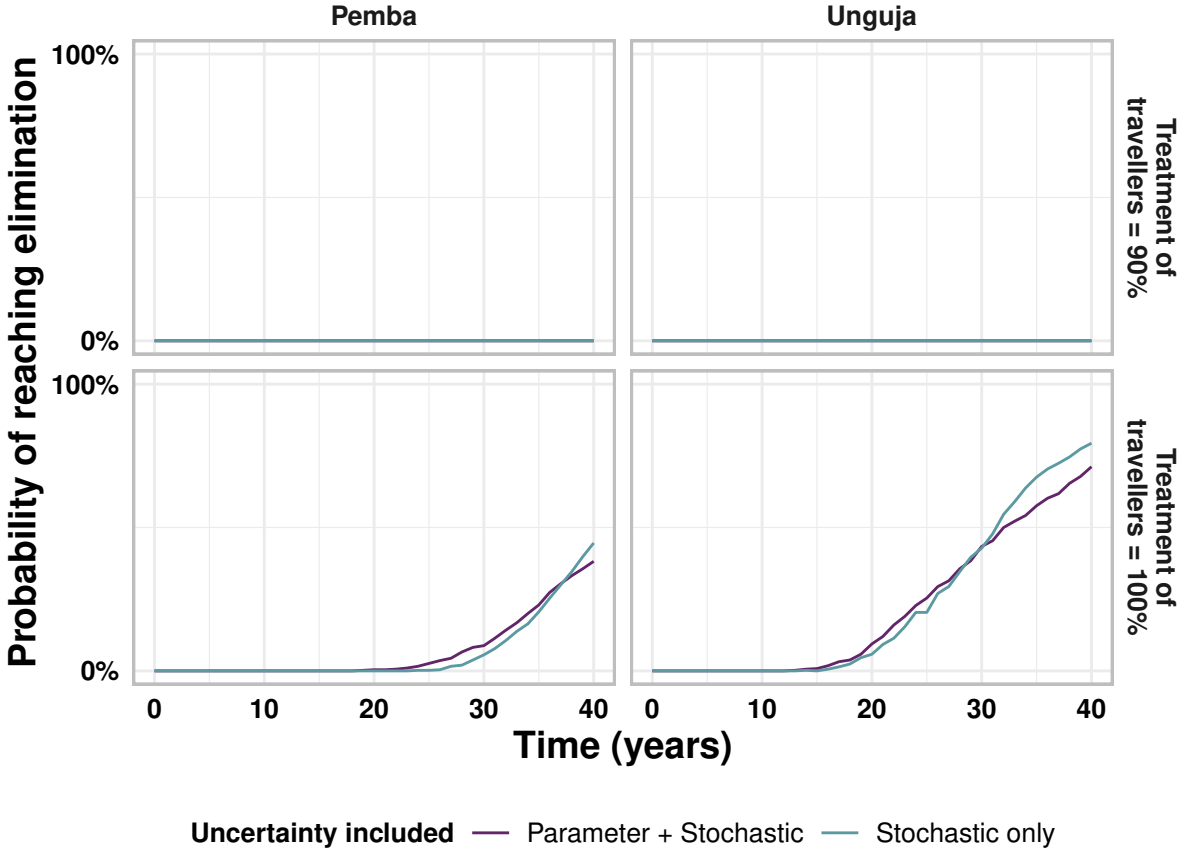

Figure B.3: Proportion of stochastic simulations reaching elimination (three years with zero indigenous cases), starting from the introduction of all RCD-related interventions and treatment of imported cases, comparing stochastic uncertainty to the combination of parameter and stochastic uncertainty.

the number of people tested, with the ratio of malaria infections amongst those tested as compared to the general population decreasing as prevalence and the number of people tested increases [96]. The following function was found to best estimate the targeting ratio, τ, for geo-located prevalence data collected in Zambia:

$$\tau(\nu, I) = \exp\left((-\alpha_1 \ln(I) + \frac{\alpha_2}{\nu} - \frac{\alpha_3}{\nu}\ln(I))\frac{N-\nu}{N}\right) \mid \tau(\nu, I) \geq 1, \tag{B.5}$$

where τ is the targeting ratio, ν is the number of people tested, not including the index case, N is the total population, and α_1, α_2 and α_3 are fitted parameters with values $\alpha_1 = 0.23$ (95% credible interval (CI): 0.16, 0.29); $\alpha_2 = -1.40$ (CI: -2.77, -0.02) and $\alpha_3 = 2.87$ (CI: 1.13, 4.59) [96].

In order to compare running the model with a fixed targeting ratio and a varying targeting ratio, we take the function from Chitnis *et al* (2019) that is fitted to data from Zambia, and apply a scaling factor to adjust the targeting ratio so that the targeting ratio matches between Eq. (B.5) and the targeting ratio for the index household in the RADZEC data ($\tau^{(h)}$ in the main text). Thus, the equation we used to generate a varying τ was given by

$$\tau(\nu, I) = A\exp\left((-\alpha_1 \ln(I) + \frac{\alpha_2}{\nu} - \frac{\alpha_3}{\nu}\ln(I))\frac{N-\nu}{N}\right) \mid \tau(\nu, I) \geq 1, \tag{B.6}$$

where A was calculated to be 0.19 for Pemba and 0.42 for Unguja, in order to match the targeting ratios calculated by Eq. (B.6) and the targeting ratio seen in the RADZEC study data. Thus, as the malaria prevalence decreases due to the introduction of new interventions, the targeting ratio increases and the effectiveness of RCD increases.

Running the model with a varying τ and a fixed τ, we see that the difference in the targeting ratio is not substantial even when considering the maximum RCD interventions tested i.e. RDA with triple the usual treatment seeking rate and 100 neighbours included in treatment (see Fig B.6). These interventions maximise the effect of the targeting ratio and so are the ones where we'd expect to see the largest difference between the blue and purple lines in Fig B.6. When RCD finds and treats a lot of cases, a targeting ratio that improves as the prevalence falls can provide an optimistic outlook of potentially eliminating malaria earlier than when considering a fixed targeting ratio, which makes the more conservative assumption of no increase in case clustering as prevalence decreases. Nonetheless, given the difference is small, we have used a fixed targeting ratio for all simulations shown in the main text.

B.2.5 The impact of varying the definition of malaria re-establishment

Currently, we consider a simulation to have reached elimination when three years have passed with zero incidence of indigenous cases. However, if an indigenous case appears after this three year period, we count this as malaria re-establishment and thus losing 'eliminated' status. In contrast, the World Health Organization defines the minimum indication of re-establishment of transmission as *'the occurrence of three of more indigenous malaria cases of the same species per year in the same focus, for three consecutive years'* [115]. Since no country that has been certified as malaria-free has lost certification, we additionally modelled the impact of assuming that once a region eliminates malaria, it stays malaria-free. Out of the 500 simulations, when a simulation reaches three years with zero incidence of indigenous cases, we assume it remains at zero indigenous cases indefinitely into the future. The probability of reaching elimination is shown in Fig B.7, with the assumption of remaining malaria-free after elimination labelled as 'cumulative' and the more strict definition of malaria re-establishment (losing 'eliminated' status after the appearance of one indigenous case) labelled as 'transient'. We observe that in the majority of cases, the definition of re-establishment does not impact the proportion of runs reaching elimination. Only in the case where the number of indigenous cases is typically zero, but not always (90% importation treatment with 90% reduction in the transmission rate on Pemba) does the definition of re-establishment make a substantial difference to the number of runs reaching elimination.

	Number of imported cases	Number of infected visitors
Pemba	216	234
Unguja	1888	1829

Table B.3: Median number of imported cases and infected visitors present on each patch at equilibrium.

B.3 Additional figures

B.3.1 Time-series plots for individual interventions

B.3.2 Figures with all previously introduced interventions also in place at maximum values

B.3.3 Probability of elimination over a longer period of time with 100% treatment of travellers

B.4 Additional tables

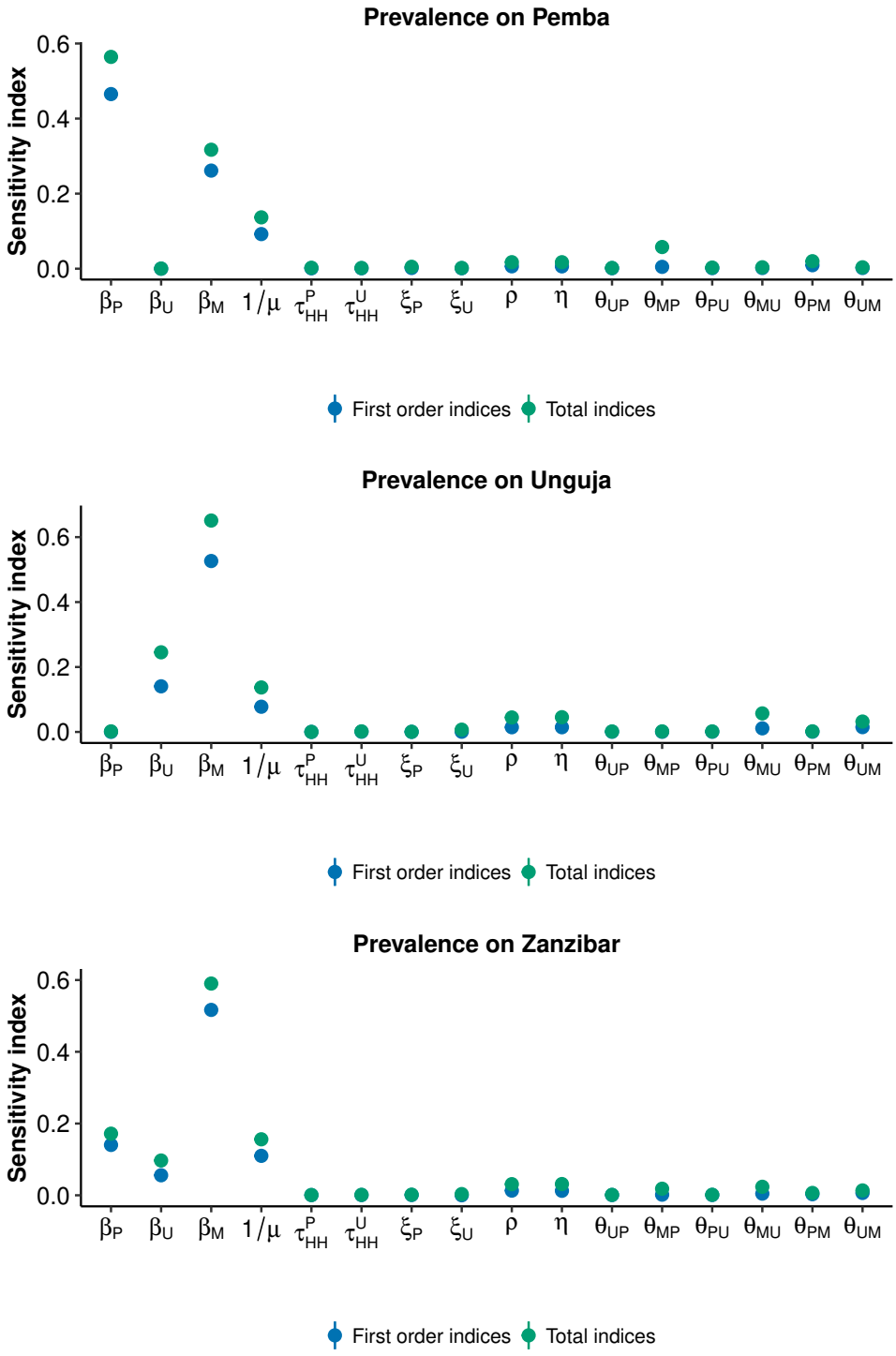

Figure B.4: First order and total Sobol indices for each parameter tested when the overall malaria prevalence is considered as the output. Note, the 95% confidence intervals are smaller than the point sizes and so are not visible. The model output of malaria prevalence on Zanzibar as a whole was calculated by multiplying the expected prevalence on each island by the population size of each island, summing to get the total number of infected people on both islands, and then dividing by the summed population across both islands.

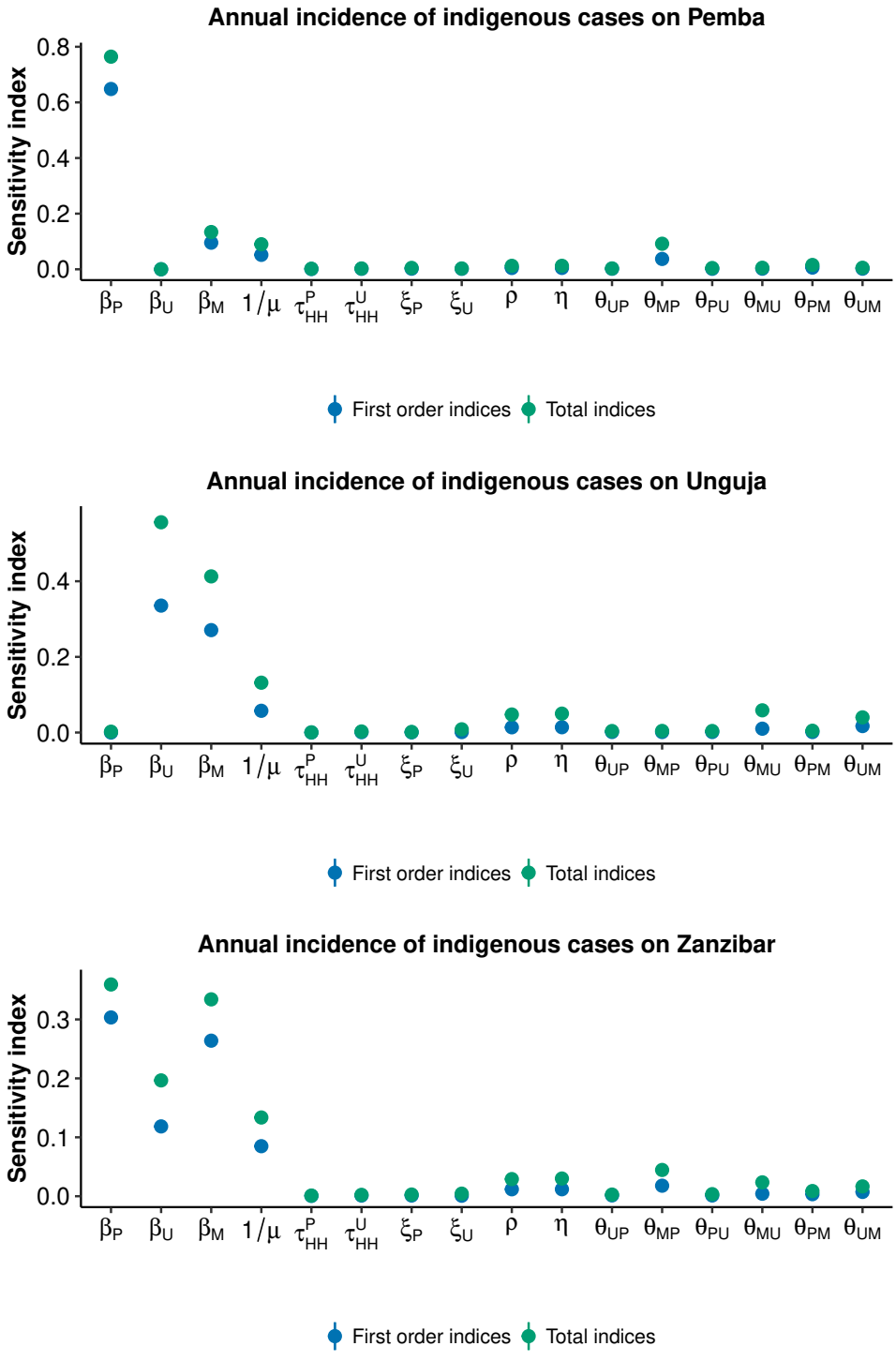

Figure B.5: First order and total Sobol indices for each parameter tested when the annual incidence of indigenous cases is considered as the output. Note, the 95% confidence intervals are smaller than the point sizes and so are not visible. The total incidence of indigenous cases for Zanzibar as a whole was calculated by summing the incidence of indigenous cases on each island.

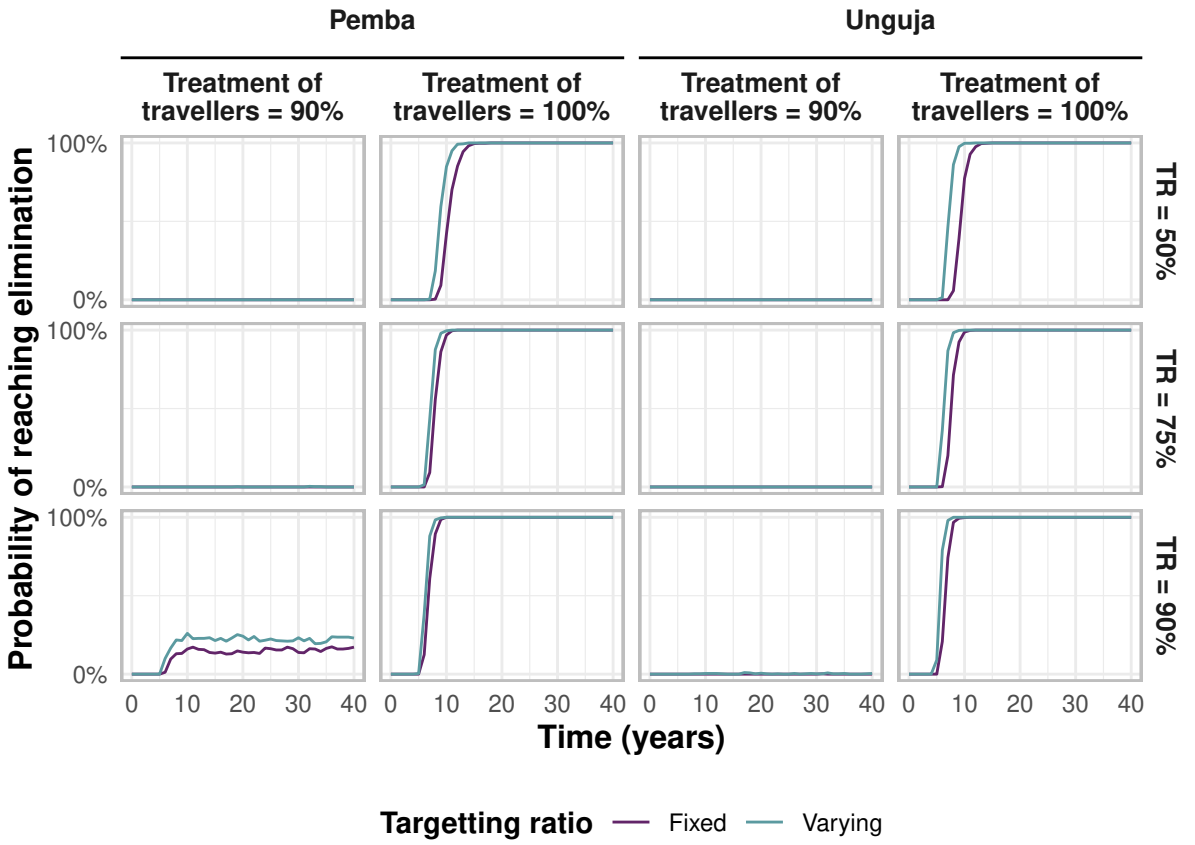

Figure B.6: Proportion of stochastic simulations reaching elimination (three years with zero indigenous cases), starting from the introduction of all RCD-related interventions, comparing a more conservative definition of the targeting ratio, where the ratio is constant regardless of prevalence, and a definition where the targeting ratio increases as the malaria prevalence decreases.

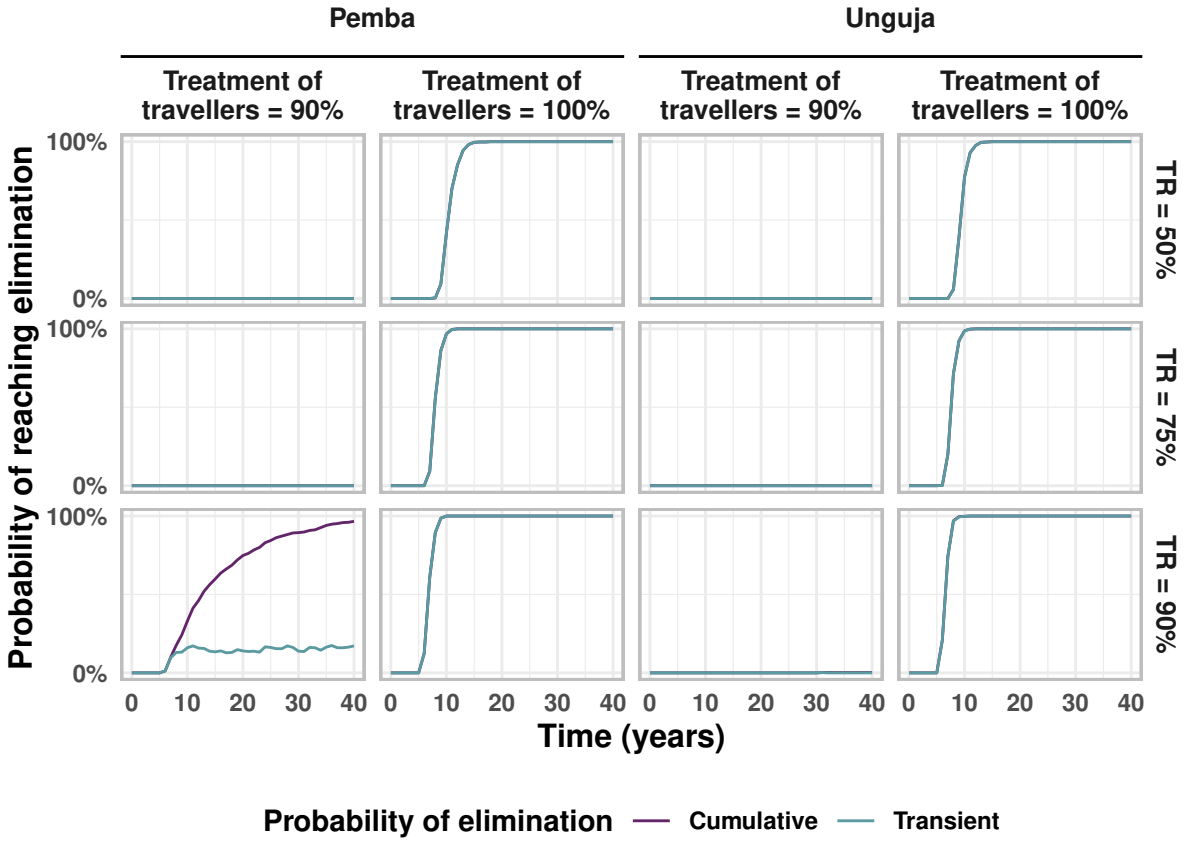

Figure B.7: Proportion of stochastic simulations reaching elimination (three years with zero indigenous cases), starting from the introduction of all RCD-related interventions and treatment of imported cases, comparing a transient probability of elimination (where 'eliminated' status is lost after the appearance of one indigenous case), to a cumulative probability of elimination (once a simulation reaches elimination, it stays malaria-free with zero indigenous cases). 'TR' stands for transmission reduction.

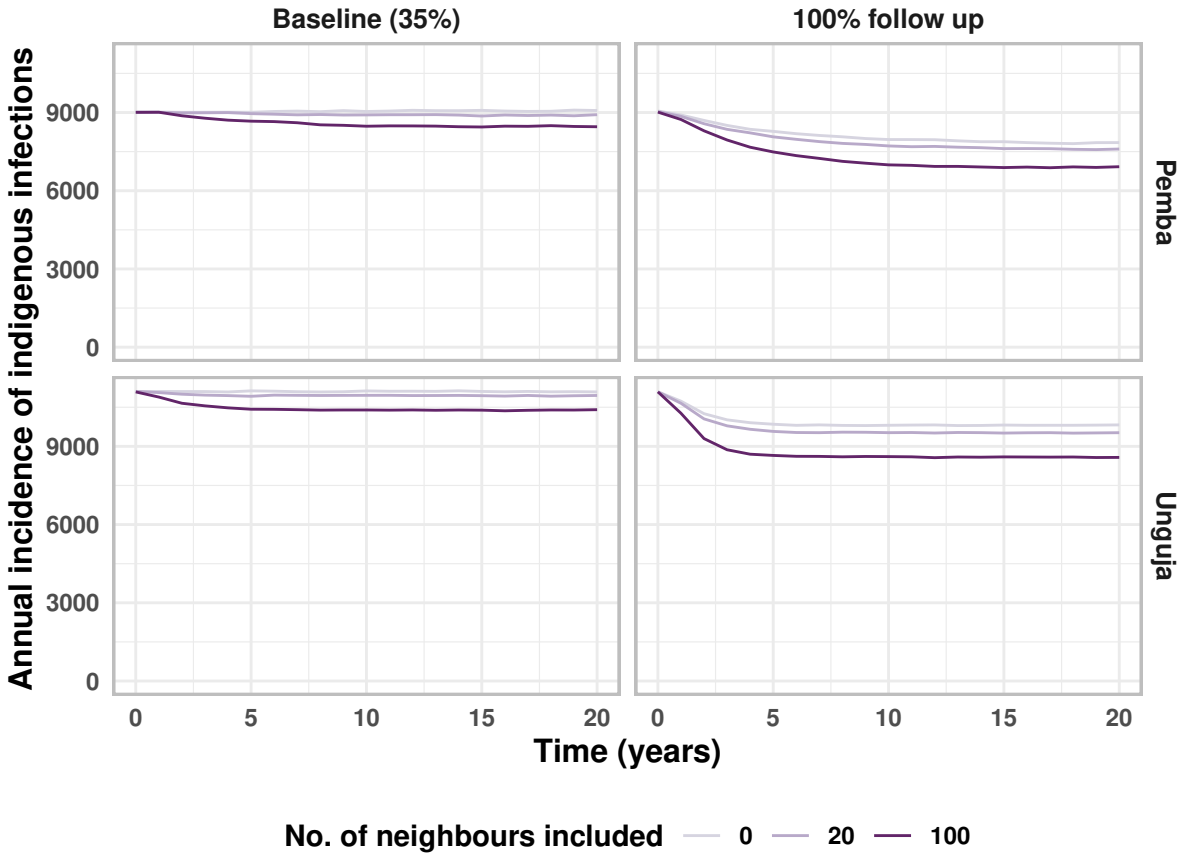

Figure B.8: Median annual incidence of infections comparing the current RCD system to a system where 100% of malaria cases diagnosed at a health facility are followed up at the index household level and a range of number of neighbours are included in RCD.

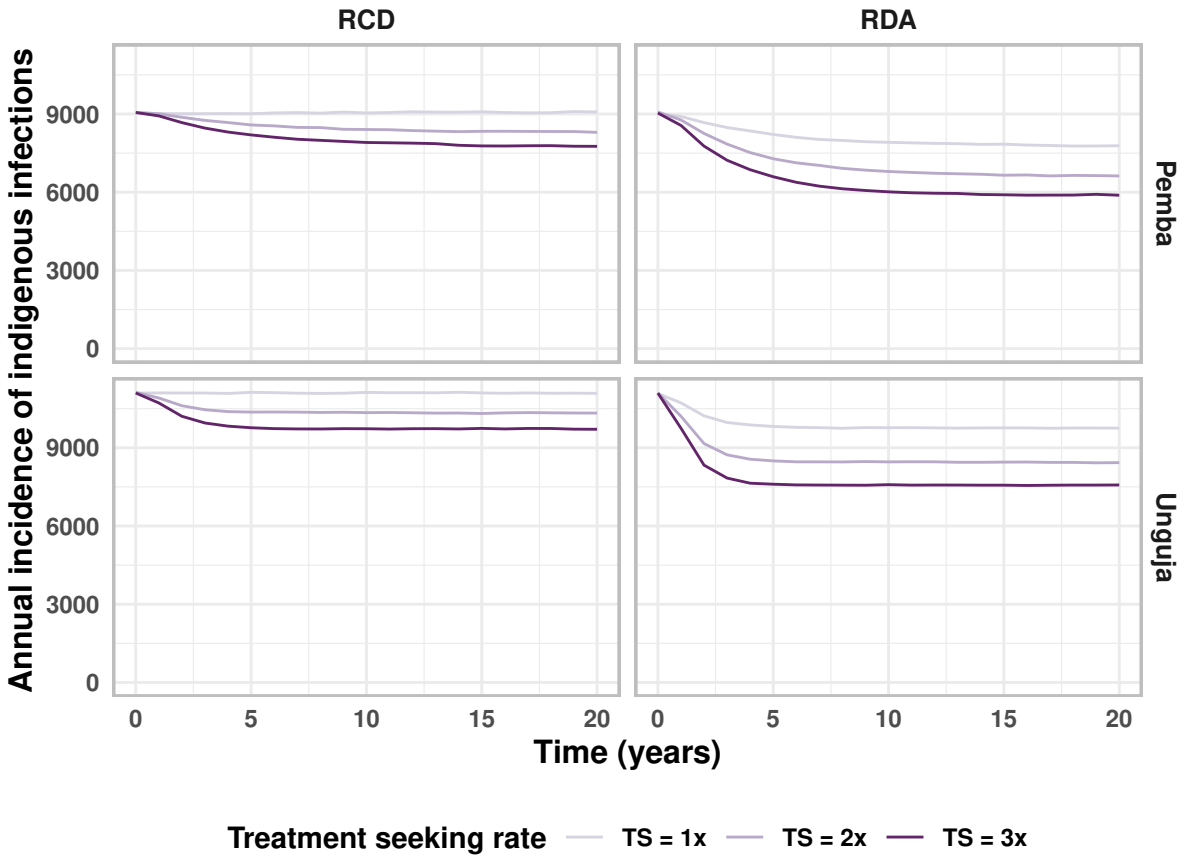

Figure B.9: Median annual incidence of infections comparing the current RCD system to reactive drug administration (in reaction to detecting a case at a health facility, upon follow up, testing is skipped and antimalarials are given to all index household members) and increases in the rate at which people seek treatment (treatment seeking is abbreviated as 'TS').

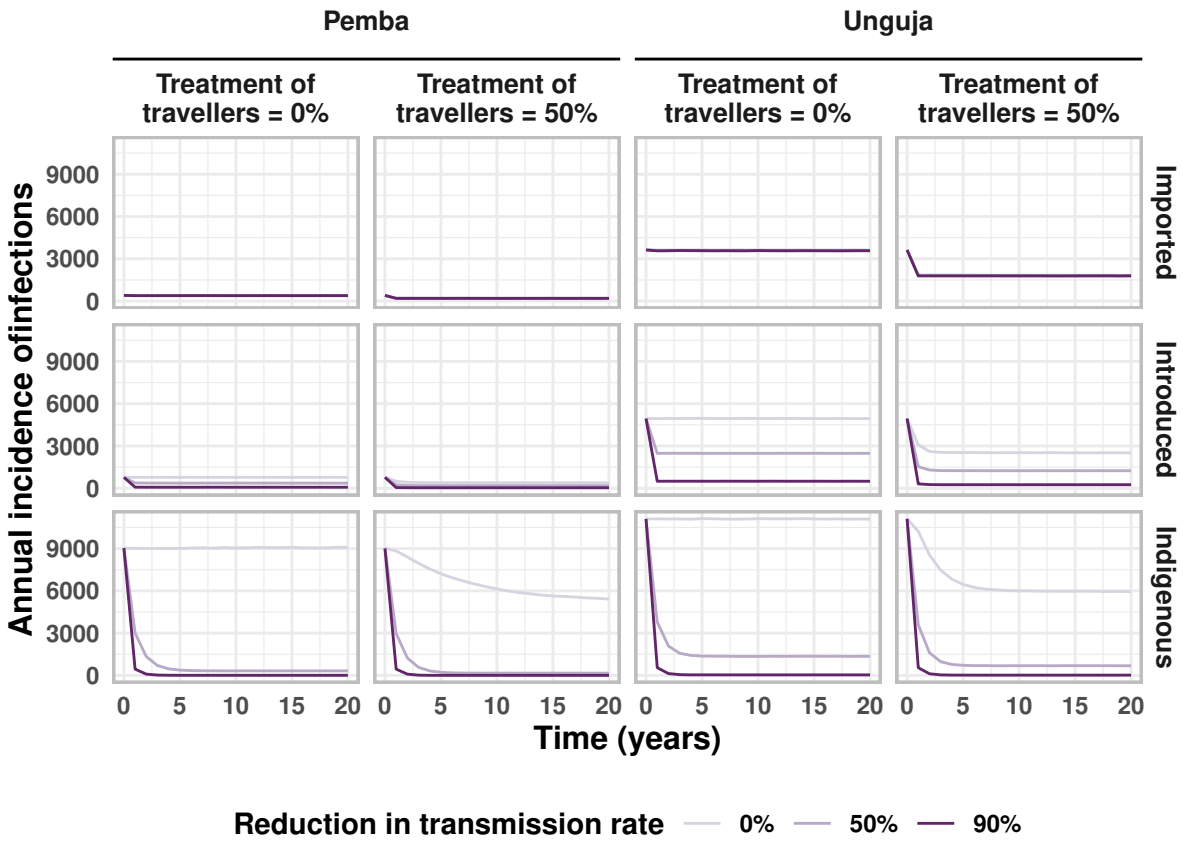

Figure B.10: Median annual incidence of indigenous infections comparing the baseline interventions (RCD for 35% of cases arriving at a health facility at the index household level only) to also treating a range of proportions of infected travellers, as well as vector control to reduce the malaria transmission rate on Zanzibar.

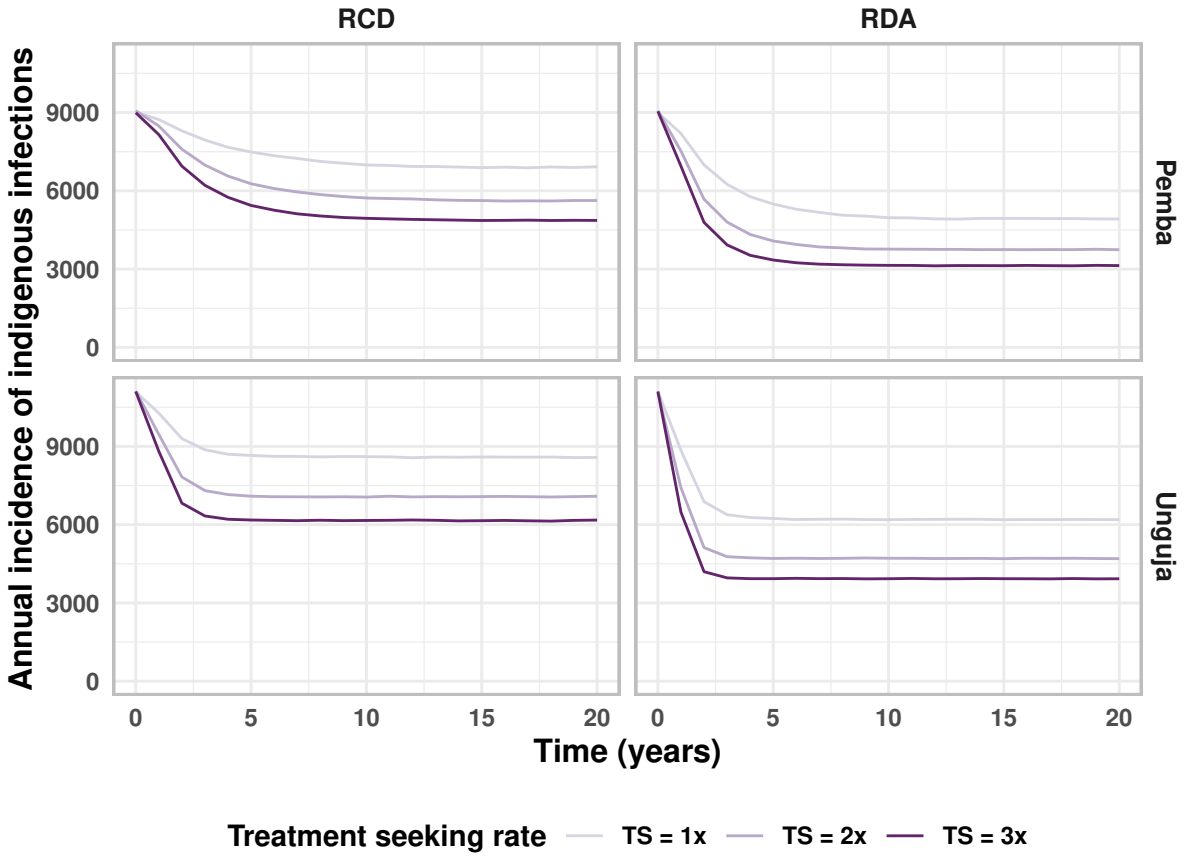

Figure B.11: Median incidence of infections from 500 stochastic simulations comparing the current RCD system with 100% follow up of cases and 100 neighbours being included in testing and treating to reactive drug administration (in reaction to detecting a case at a health facility, upon follow up, testing is skipped and antimalarials are given to all index household members and 100 neighbours) and increases in the rate at which people seek treatment (treatment seeking is abbreviated as 'TS').

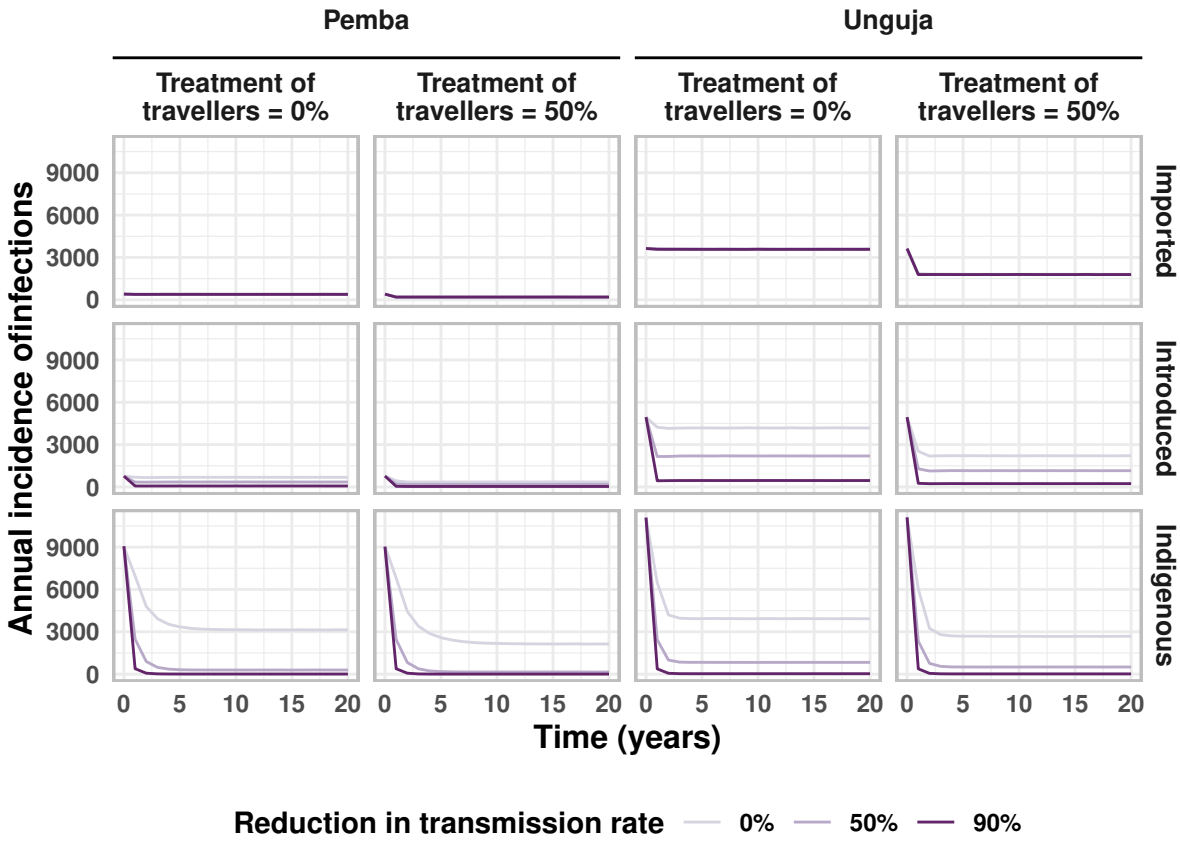

Figure B.12: Median incidence of infections from 500 stochastic simulations comparing the impact of treating imported cases and reducing the malaria transmission rate on Zanzibar (both Pemba and Unguja). Here, we assume all RCD-related interventions (100% follow up of all cases, treatment of the index household and 100 neighbours in RDA, treatment seeking rate increased to 3 times the baseline rate) are also in effect.

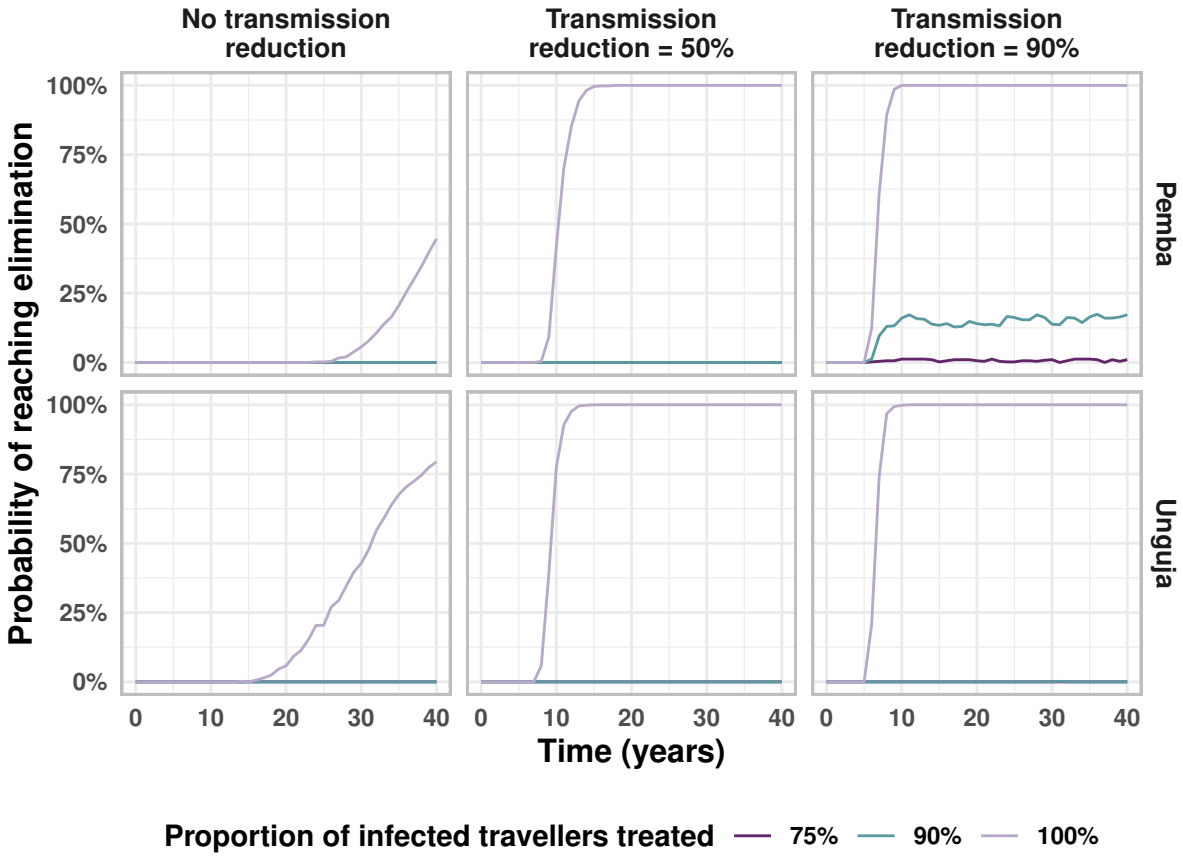

Figure B.13: Proportion of stochastic simulations reaching elimination (three years with zero indigenous cases), starting from the introduction of interventions. We assume that the maximum values of all RCD-related interventions (100% follow up of all cases, treatment of the index household and 100 neighbours in RDA, treatment seeking rate increased to 3 times the baseline rate) are present and then simulate reducing the malaria transmission rate and treating a proportion of cases imported from mainland Tanzania.

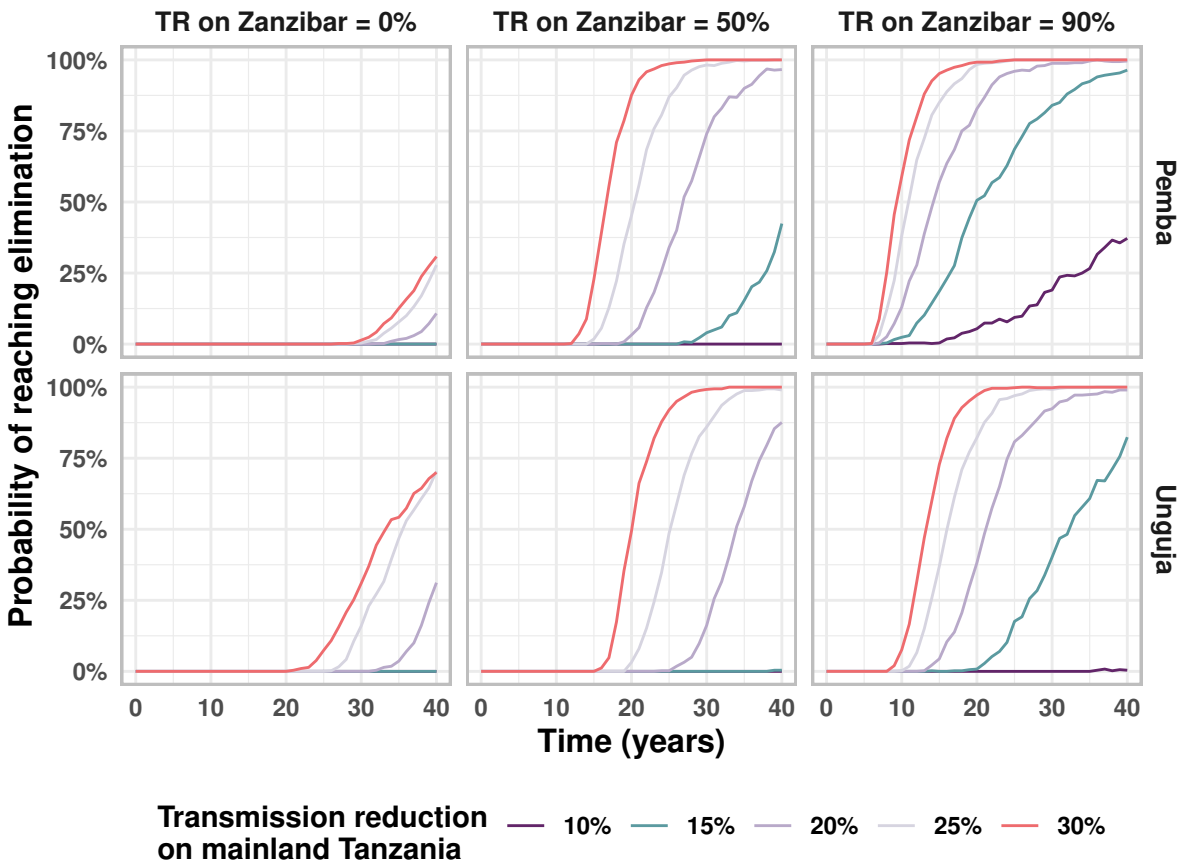

Figure B.14: Proportion of stochastic simulations reaching elimination (three years with zero indigenous cases), starting from the introduction of interventions. We assume that the maximum values of all RCD-related interventions (100% follow up of all cases, treatment of the index household and 100 neighbours in RDA, treatment seeking rate increased to 3 times the baseline rate) are present and then simulate reducing the malaria transmission rate on both Zanzibar and mainland Tanzania.

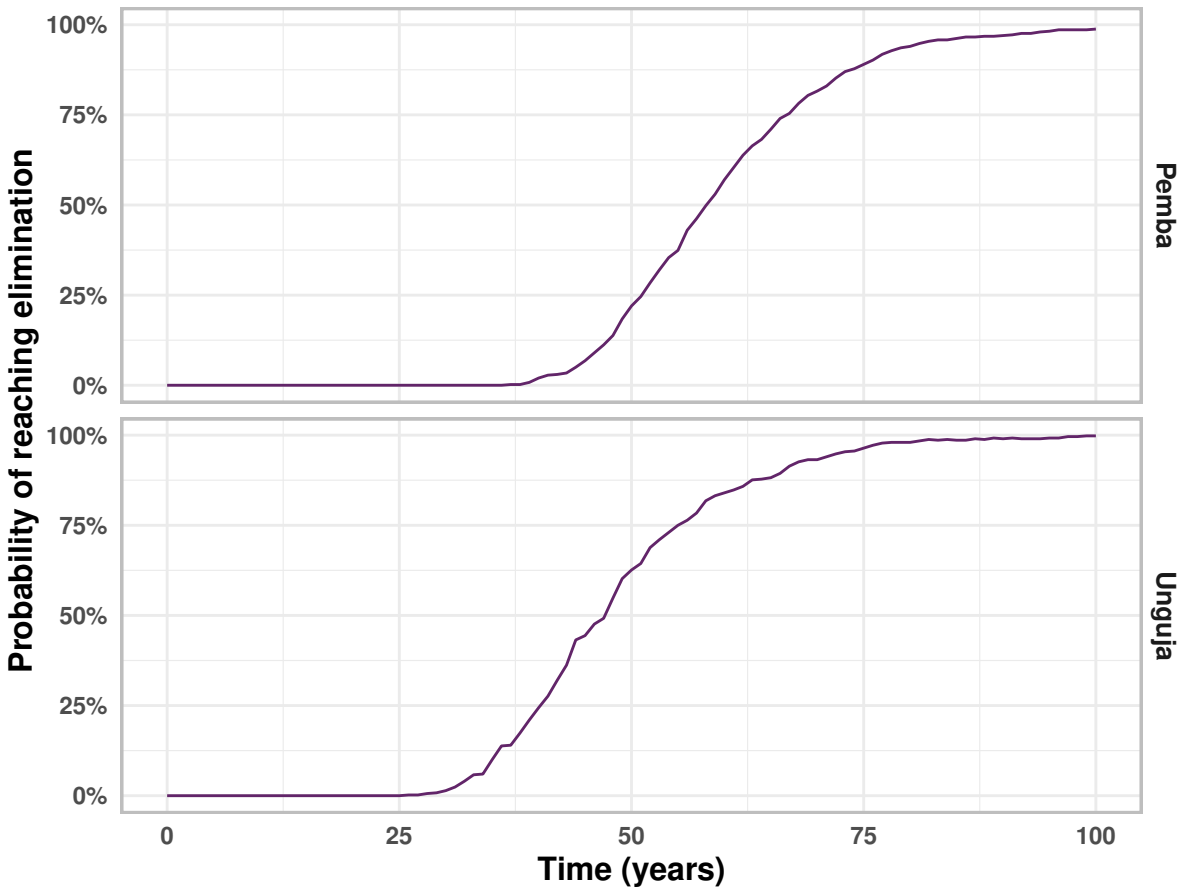

Figure B.15: Proportion of stochastic simulations reaching elimination (three years with zero indigenous cases) when 100% of infected travellers from mainland Tanzania are treated, starting from year 0. We assume that all other interventions are at baseline values (RCD for 35% of cases arriving at a health facility at the index household level only).

Appendix C

Chapter 4 Supplementary Information

C.1 Model description

C.1.1 Deterministic model

This description is adapted from [81, Supplementary data].

The deterministic model used here was presented and described in [86] and is a variant of the HAT transmission model originally published in [80] and [81]. The model consists of a system of coupled ordinary differential equations (ODEs), with compartments for tsetse, non-human and human populations. These three different host types are modelled for two different settings corresponding to a low transmission area (e.g. the village, L) and a high transmission area (such as river banks or plantations, H) that enable accounting for heterogeneity in exposure to tsetse bites. The population size for tsetse, non-human hosts or humans in each setting i ($i = \{L, H\}$) is assumed to be stable by allowing the associated birth terms to compensate deaths in all the compartments. Tsetse and non-human host populations always stay within their setting (for example, tsetse in low transmission settings always remain in the low transmission setting and non-human hosts in high transmission settings always remain in the high transmission setting). Similarly, humans in low transmission settings always remain in low transmission setting. However, humans in the high transmission setting move back and forth between the high and low transmission settings spending a fixed amount of time in each one (to model, for example, the movement of high risk individuals between villages and plantations) — as shown in Figure C.1.

Five compartments describe humans in any of the two settings: susceptible (S_{hi}); exposed or incubating (E_{hi}); infected with the first stage of the disease (I_{h1i}); infected with the second stage of the disease, where trypanosomes have reached the cerebro-spinal fluid (I_{h2i}); and treated (T_{hi}). The total human population in setting i is $N_{hi} = S_{hi} + E_{hi} + I_{h1i} + I_{h2i} + T_{hi}$. Humans can simultaneously belong in the diagnosed compartment (D_{hi}) and one of the infected stages, from which, depending on drug compliance, they may either move on to the treated compartment, or remain in the infected compartment.

Tsetse populations are divided into susceptible (S_{vi}); teneral (U_{vi}); exposed (E_{vi}); and

infected (I_{vi}), so that the vector population is $N_{vi} = S_{vi} + U_{vi} + E_{vi} + I_{vi}$.

As in [81], in this model implementation: *i)* non-human hosts do not contribute to transmission, thus non-human host populations are modelled as constant parameters, N_{ai}, and only form a sink for tsetse bite; *ii)* both stages (rather than only stage 1) of the disease are exposed to tsetse fly bites; *iii)* an additional compartment in the vector dynamics, U_i, accounts for the teneral effect — a reduction of infectivity with time — such that on average tsetse are only infectious for the first five days after emergence. These changes were made with respect to the original version [80] to provide a more realistic representation of the transmission dynamics. A schematic of the model is shown in Figure C.1.

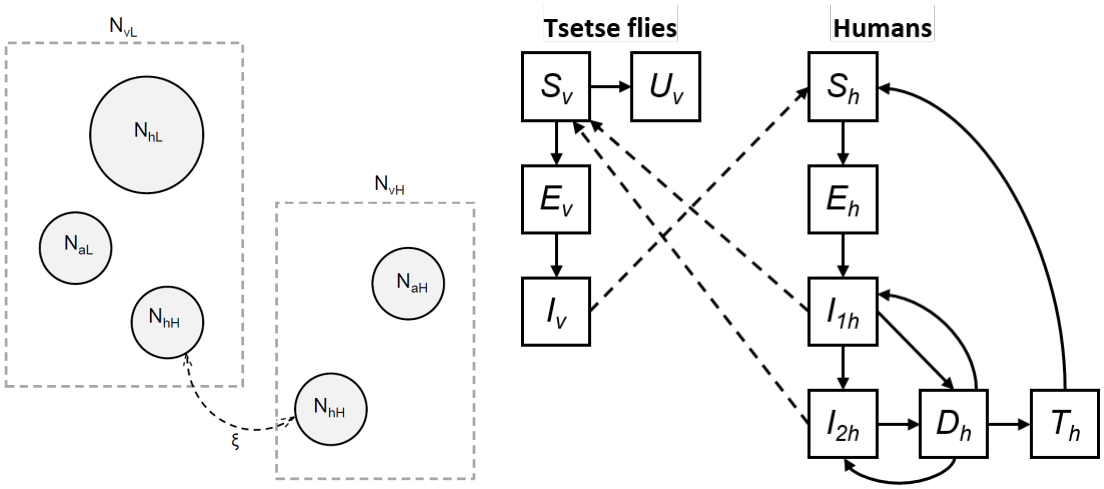

Figure C.1: Schematic of the model. Left: model population structure. Human populations are composed by a stationary population (N_{hL}) that remains in low exposure habitats (e.g., a village), and a smaller population (N_{hH}) which commute and spend a proportion ξ of their time in a potentially high exposure setting (e.g., a plantation). Each habitat also contains tsetse (N_{vL} and N_{vH}) and non-human vertebrate animal populations (N_{aL} and N_{aH}). Right: schematic of infection dynamics, subscripts $i = \{L, H\}$ were removed for easy reading. Compartmental diagram highlights the transmissions between states of infection of the tsetse and human populations, with solid lines indicating transition between compartments, and dashed lines representing transmission rates. Non-human hosts cannot transmit infection thus acting as a sink for tsetse bite. Note that in the low-risk transmission setting, both human populations are exposed to tsetse bites. Figure adapted from [80].

C.1.1.1 Model equations

The model dynamics are described by sets of ODEs for humans, vectors and non-human hosts. Descriptions of state variables and parameters can be found in Tables C.1, C.2 and C.4. A description of r_{as} and r_{pd} can be found in sectionC.1.2.

Humans, low risk setting:

$$
\begin{aligned}
\frac{dS_L}{dt} &= \beta_L + \delta T_L - \mu S_L - \lambda_L I_{v_L} S_L \\
\frac{dE_L}{dt} &= \lambda_L I_{v_L} S_L - (\mu + \eta) E_L \\
\frac{dI_{1L}}{dt} &= \eta E_L - (\mu + \gamma) I_{1L} - (r_{as} + r_{1pd}) I_{1L} + (1 - \psi)(r_{as} + r_{1pd}) \phi_1 I_{1L} \\
\frac{dI_{2L}}{dt} &= \gamma I_{1L} - (\mu + \mu_\gamma) I_{2L} - (r_{as} + r_{2pd}) I_{2L} + (1 - e\psi)(r_{as} + r_{2pd}) \phi_2 I_{2L} \\
\frac{dD_{1L}}{dt} &= (r_{as} + r_{1pd}) I_{1L} - \psi (r_{as} + r_{1pd}) \phi_1 I_{1L} - (r_{as} + r_{1pd})(1 - \phi_1) I_{1L} \\
&\quad - (1 - \psi)(r_{as} + r_{1pd}) \phi_1 I_{1L} \\
\frac{dD_{2L}}{dt} &= (r_{as} + r_{2pd}) I_{2L} - e\psi (r_{as} + r_{2pd}) \phi_2 I_{2L} - (r_{as} + r_{2pd})(1 - \phi_2) I_{2L} \\
&\quad - (1 - e\psi)(r_{as} + r_{2pd}) \phi_2 I_{2L} \\
\frac{dT_L}{dt} &= \psi (r_{as} + r_{1pd}) \phi_1 I_{1L} + (r_{as} + r_{1pd})(1 - \phi_1) I_{1L} + e\psi (r_{as} + r_{2pd}) \phi_2 I_{2L} \\
&\quad + (r_{as} + r_{2pd})(1 - \phi_2) I_{2L} - (\mu + \mu_t + \delta) T_L
\end{aligned}
$$

where

- ϕ_i (for either low-risk or high-risk setting) is the proportion (range to determine between 0 and 1) of cases treated with fexinidazole (i.e. those who do not fall into the following categories: children $<$ 6 years; patients weighing $<$ 20kg; pregnant women in the first trimester; advanced stage 2 cases). $\phi_1 > \phi_2$ as advanced stage 2 patients must follow the current treatment.
- ψ (for either low-risk or high-risk setting) is the proportion of cases that comply with fexinidazole treatment sufficiently to count as full compliance.
- e is the relatively reduction in fexinidazole efficacy for treatment of stage 2 HAT as compared to NECT.
- For both active screening and passive detection, we assume perfect compliance to the current first-line treatment, the lesser compliance to fexinidazole is represented by a factor ψ between 0 and 1 such that this proportion of patients receiving fexinidazole comply with treatment and moved to the treated stage (same for stage 2). The remaining $1 - \psi$ proportion of patients treated with fexinidazole do not comply and remain infected despite having been diagnosed.

Related to the force of infection,

$$\lambda_L = \frac{bf\theta_{v_L h_L}}{N_L}$$

where the probability of biting a human for the vector population in the low risk setting, N_{vL}, can be split in two: $\theta_{v_L h_L}$ and $\theta_{v_L h_H}$, defined as:

$$\theta_{v_L h_L} = \frac{\sigma N_L}{\sigma(N_L + (1 - \xi) N_H) + \sigma_{aL} N_{aL}}$$

$$\theta_{v_L h_H} = \frac{\sigma(1-\xi)N_H}{\sigma(N_L + (1-\xi)N_H) + \sigma_{aL}N_{aL}},$$

and the probability of biting a non-human host for the vector population in the low risk setting is:

$$\theta_{v_L a_L} = \frac{\sigma_{aL}N_{aL}}{\sigma(N_L + (1-\xi)N_H) + \sigma_{aL}N_{aL}}.$$

Note that

$$\beta_L = \mu(S_L + E_L + I_{1L} + I_{2L} + T_L) + \mu_\gamma I_{2L} + \mu_t T_L.$$

and that N_L indicates the part of the population exposed to bites,

$$N_L = S_L + E_L + I_{1L} + I_{2L}.$$

Humans, high risk setting:

$$\begin{aligned}
\frac{dS_H}{dt} &= \beta_H + \delta T_H - \mu S_H - \lambda_{H1} I_{v_L} S_H - \lambda_{H2} I_{v_H} S_H \\
\frac{dE_H}{dt} &= \lambda_{H1} I_{v_L} S_H + \lambda_{H2} I_{v_H} S_H - (\mu + \eta) E_H \\
\frac{dI_{1H}}{dt} &= \eta E_H - (\mu + \gamma) I_{1H} - r_{1pd} I_{1H} + (1-\psi) r_{1pd} \phi_1 I_{1H} \\
\frac{dI_{2H}}{dt} &= \gamma I_{1H} - (\mu + \mu_\gamma) I_{2H} - r_{2pd} I_{2H} + (1 - e\psi) r_{2pd} \phi_2 I_{2H} \\
\frac{dD_{1H}}{dt} &= r_{1pd} I_{1H} - \psi r_{1pd} \phi_1 I_{1H} - r_{1pd}(1-\phi_1) I_{1H} - (1-\psi) r_{1pd} \phi_1 I_{1H} \\
\frac{dD_{2H}}{dt} &= r_{2pd} I_{2H} - e\psi r_{2pd} \phi_2 I_{2H} - r_{2pd}(1-\phi_2) I_{2H} - (1 - e\psi) r_{2pd} \phi_2 I_{2H} \\
\frac{dT_H}{dt} &= \psi r_{1pd} \phi_1 I_{1H} + r_{1pd}(1-\phi_1) I_{1H} + e\psi r_{2pd} \phi_2 I_{2H} + r_{2pd}(1-\phi_2) I_{2H} \\
&\quad - (\mu + \mu_t + \delta) T_H
\end{aligned}$$

with

$$\begin{aligned}
\lambda_{H1} &= \frac{bf\theta_{v_L h_H}}{N_H} \\
\lambda_{H2} &= \frac{bf\theta_{v_H h_H}}{N_H}.
\end{aligned}$$

where the probability of biting a human for the vector population in the high risk setting, N_{vH}, is $\theta_{v_H h_H}$:

$$\theta_{v_H h_H} = \frac{\sigma\xi N_H}{\sigma\xi N_H + \sigma_{aH} N_{aH}},$$

and the probability of biting a non-human host for the vector population in the high risk setting is $\theta_{v_H a_H}$:

$$\theta_{v_H a_H} = \frac{\sigma_{aH} N_{aH}}{\sigma \xi N_H + \sigma_{aH} N_{aH}}.$$

Note that

$$\beta_H = \mu N_H + \mu_\gamma I_{2H} + \mu_t T_H.$$

Non-human hosts, low risk setting:

$$\frac{dS_{aL}}{dt} = \beta_{aL} + \delta_a R_{aL} - \mu_{aL} S_{aL} - \lambda_{aL} I_{v_L} S_{aL} \tag{C.1}$$
$$\frac{dE_{aL}}{dt} = \lambda_{aL} I_{v_L} S_{aL} - (\mu_{aL} + \eta) E_{aL} \tag{C.2}$$
$$\frac{dI_{aL}}{dt} = \eta E_{aL} - (\mu_{aL} + \gamma_{aL}) I_{aL} \tag{C.3}$$
$$\frac{dR_{aL}}{dt} = \gamma_{aL} I_{aL} - (\mu_{aL} + \delta_a) R_{aL} \tag{C.4}$$

with

$$\lambda_{aL} = \frac{b f \theta_{v_L a_L} c_{aL}}{N_{aL}}.$$

Non-human hosts, high risk setting:

$$\frac{dS_{aH}}{dt} = \beta_{aH} + \delta_a R_{aH} - \mu_{aH} S_{aH} - \lambda_{aH} I_{v_H} S_{aH} \tag{C.5}$$
$$\frac{dE_{aH}}{dt} = \lambda_{aH} I_{v_H} S_{aH} - (\mu_{aH} + \eta) E_{aH} \tag{C.6}$$
$$\frac{dI_{aH}}{dt} = \eta E_{aH} - (\mu_{aH} + \gamma_{aH}) I_{aH} \tag{C.7}$$
$$\frac{dR_{aH}}{dt} = \gamma_{aH} I_{aH} - (\mu_{aH} + \delta_a) R_{aH} \tag{C.8}$$

with

$$\lambda_{aH} = \frac{b f \theta_{v_H a_H} c_{aH}}{N_{aH}}.$$

Note, $c_{aL} = c_{aH} = 0$ so non-human hosts can receive bites, but do not become infected.

Vectors, low risk setting:

$$\frac{dS_{vL}}{dt} = \beta_{vL} - \mu_v S_{vL} - w_{LL}(I_{1L} + I_{2L})S_{vL} - w_{LH}(I_{1H} + I_{2H})S_{vL} - w_{aL}I_{aL}S_{vL} - \alpha S_{vL} \tag{C.9}$$

$$\frac{dE_{vL}}{dt} = w_{LL}(I_{1L} + I_{2L})S_{vL} + w_{LH}(I_{1H} + I_{2H})S_{vL} + w_{aL}I_{aL}S_{vL} - (\mu_v + \nu)E_{vL} \tag{C.10}$$

$$\frac{dI_{vL}}{dt} = \nu E_{vL} - \mu_v I_{vL} \tag{C.11}$$

$$\frac{dU_{vL}}{dt} = \alpha S_{vL} - \mu_v U_{vL} \tag{C.12}$$

with

$$w_{LL} = f\theta_{v_L h_L}\frac{1}{N_L}c_h \tag{C.13}$$

$$w_{LH} = f\theta_{v_L h_H}\frac{1}{N_H}c_h \tag{C.14}$$

$$w_{aL} = c_{aL}f\theta_{v_L a_L}\frac{1}{N_{aL}}. \tag{C.15}$$

Note: currently $c_h = c_1 = c_2$ so tse-tse have no particular preference on biting stage I or II infected humans.

Vectors, high risk setting:

$$\frac{dS_{vH}}{dt} = \beta_{vH} - \mu_{vH} S_{vH} - w_{HH}(I_{1H} + I_{2H})S_{vH} - w_{aH}I_{aH}S_{vH} - \alpha S_{vH} \tag{C.16}$$

$$\frac{dE_{vH}}{dt} = w_{HH}(I_{1H} + I_{2H})S_{vH} + w_{aH}I_{aH}S_{vH} - (\mu_v + \nu)E_{vH} \tag{C.17}$$

$$\frac{dI_{vH}}{dt} = \nu E_{vH} - \mu_v I_{vH} \tag{C.18}$$

$$\frac{dU_{vH}}{dt} = \alpha S_{vH} - \mu_v U_{vH} \tag{C.19}$$

with

$$w_{HH} = f\theta_{v_H h_H}\frac{1}{N_H}c_h \tag{C.20}$$

$$w_{aH} = c_{aH}f\theta_{v_H a_H}\frac{1}{N_{aH}}. \tag{C.21}$$

C.1.1.2 Stochastic implementation

This description is adapted from [81, Supplementary data].

Epidemiological deterministic models, including previous implementations of this model [80, 81, 84], have the shortcoming that they do not capture rare events and do no account for the discrete nature of populations, and are therefore unable to reproduce the transition between extremely low prevalence and zero transmission. For such situations, a discrete stochastic model formulation is more suitable as it captures the stochastic nature of events involved in transmission dynamics while producing integer outputs (e.g. number of cases and new infections here) that enable a clearer definition of elimination of transmission (and subsequent forecasting of elimination timelines) than in deterministic ODE models where arbitrary thresholds must be defined.

In the stochastic formulation of the ODE model described in C.1.1, we model all human host, non-human host and tsetse fly populations as discrete numbers, and all individuals move probabilistically between compartments at varying intervals of time. Any process governing the HAT transmission dynamics is considered stochastic, with terms in the compartmental model being now considered as probabilities at which an event occurs.

We implemented the direct method of the stochastic simulation algorithm (SSA; also known as Gillespie method [146]). In the direct method of the SSA, all possible events in the HAT transmission dynamics have an associated rate given by the associated term in the deterministic ODEs. For example, if γ represents the rate at which humans infected in the stage 1 of the disease (I_1) move to the second stage of the disease (I_2), thus γI_1 represents the rate R for the event "progression to stage 2 of the disease".

In order to simulate one stochastic realisation under the direct method, for i possible events with associated rate R_i, at any time t:
(a) we determine the time $t+\tau$ at which the next event happens, with τ an exponentially distributed random number scaled by the sum of all process rates, $\Sigma_i R_i$; and
(b) we decide which that event will be: the event that happens next is obtained through drawing a process randomly from all possible processes according to their respective probabilities given by $R_i / \sum_j R_j$.

In the present analysis, 1000 posterior parameter sets (see section C.2) were used along with the fixed parameters to obtain 100,000 realisations of the stochastic model (100 realisations for each parameter set).

Simulations up to 2000 were deterministic, i.e. by numerical solving the ODE system, with further projections using the stochastic implementation described in this section.

The deterministic model output at 2000 was scaled up to follow the population growth trajectory of Mushie territory and rounded to integer values before running stochastic simulations of the forward discrete model. Simulations from 2000 to 2018 were run using parameters calibrated to data, and then projected forward until 2040 including reductions in the active screening rate (see section C.1.2) and maintaining the passive detection rate seen in 2018.

The discrete stochastic model was run until 2040 in order to allow evaluation of elimination of transmission (EOT) (Figure 4 in the main text), with EOT defined as the point where there are no exposed or infected humans or vectors present in the simulation.

C.1.2 Screening

This description is adapted from [86, Supplementary data].

Active screening was modelled via a constant annual active detection rate r_{as} that removes infected people only from the low risk setting. As in previous works, we followed [78] to relate a proportion, d, of humans effectively screened in a given year and the annual removal rate r_{as} as $d = 1 - e^{-r_{as}}$, leading to $r_{as} = -\ln(1-d)$. For the model fitting, screening levels were informed from data, and estimates for the health zone population in 2015 were taken from [193], and projected backwards and forward in time assuming a 3% annual growth rate. For model projections, the mean number of people screened from the last 5 years of available data (2014-2018) was used to define d, with an ongoing 3% growth rate in the total population (leading to a continuing decrease in the proportion of the population screened).

Passive detection is represented by a continuous stage-specific detection rate, $r1$ and $r2$ for stage 1 and stage 2 respectively, and removes infected people from both low- and high-risk settings. Relying on previous work [81], improvement to passive detection was assumed for the data period. We modelled improvement for the number of years $y > 0$ after 2000 as a logistic function:

$$\begin{aligned} r1(y) &= 365 \times r1_{\text{const}} + \frac{\Delta r_1}{1 + \exp(-\alpha_{\text{pd}}(y - x_0 + 1))}, \\ r2(y) &= 365 \times r1_{\text{const}} \times c2 + \frac{\Delta r_1 + \Delta r_2}{1 + \exp(-\alpha_{\text{pd}}(y - x_0 + 1))}, \end{aligned}$$

where $r1_{\text{const}}$ and $c_2 \times r1_{\text{const}}$ are the constant daily passive detection rates in stage 1 and stage 2 respectively for any time before 2000, and Δr_1, Δr_2, α_{pd} and x_0 are parameters defining the profile of the logistic curve. All parameters in the expression above are fitted to the health zone level data. For model projections, we assumed passive detection rates $r1$ and $r2$ continue at the highest level from 2000-2018.

Additionally, due to changes to the method of confirming positive HAT cases, including video evidence of moving parasites, a perfect specificity of 100% was assumed from 2017 onwards. This is reflected in the cases seen, as there is a drop in reported cases observed from 2017 onwards.

Our model assumes that before 2000 only passive detection was ongoing, at constant rates, and that active screening activities started in 2000, the initial year for which there is available data on active screening.

C.2 Fitting procedure

Twelve parameters were fitted using annual case data from Mushie territory for the period 2000–2018. The deterministic model was first run to reach equilibrium prevalence of infection assuming only constant passive screening before 2000, when the fitting starts. The data that was fitted separated reported cases into those from active screening and passive detection, and provided information on staging in the years from 2015 onward. Fitting was performed via an adaptive Metropolis-Hastings Markov chain Monte Carlo (MCMC) approach using the following log-likelihood function:

$$
\begin{aligned}
LL(\theta|x) = \; & \log(P(x|\theta)) \\
& \propto \sum_{i=2000}^{2018} \Bigg(\log\left[\text{NegBin}\left(A_{d1}(i) + A_{d2}(i); A_{m1}(i) + A_{m2}(i), \kappa_{\text{AS}}\right)\right] \\
& \quad + \; \log\left[\text{NegBin}\left(P_{d1}(i) + P_{d2}(i); P_{m1}(i) + P_{m2}(i), \kappa_{\text{PD}}\right)\right] \Bigg) \\
& \quad + \sum_{i=2015}^{2018} \Bigg(\log\left[\text{Bin}\left(P_{d1}(i); P_{d1}(i) + P_{d2}(i), \frac{P_{m1}(i)}{P_{m1}(i) + P_{m2}(i)}\right)\right] \\
& \quad + \log\left[\text{Bin}\left(A_{d1}(i); A_{d1}(i) + A_{d2}(i), \frac{A_{m1}(i)}{A_{m1}(i) + A_{m2}(i)}\right)\right] \Bigg),
\end{aligned}
$$

where A_{d1}: stage 1 reported cases (active screening); A_{d2}: stage 2 reported cases (active screening); P_{d1}: stage 1 reported cases (passive detection); P_{d2}: stage 2 reported cases (passive detection); A_{m1}: stage 1 reported cases from the model (active screening); A_{m2}: stage 2 reported cases from the model (active screening); P_{m1}: stage 1 reported cases from the model (passive surveillance); P_{m2}: stage 2 reported cases from the model (passive surveillance); κ_{AS}: shape parameter for the negative binomial distribution for annual number of cases detected through active screening; and κ_{PD}: shape parameter for the negative binomial distribution for annual number of cases detected through passive detection.

The two terms in the first sum represent the total number of active and passive cases in the data, respectively, modeled as a negative binomial with mean equal to the number of cases from the differential equation model. The two terms in the second sum represent the proportion of cases in stage 1, modeled as a binomial in which the probability of stage 1 is the proportion from the differential equation model (and the number of trials is from the data of total number of cases). Since we only have staged data from 2015 onwards, those terms only contribute to the log likelihood in those years.

To sample from the posterior distribution, determined by the likelihood function and the prior distributions, we used an adaptive Metropolis-Hastings MCMC algorithm – the accelerated shaping algorithm [194]. We ran two independent chains of the algorithm to corroborate convergence for the sampling. We used a burn-in period of 2000 steps and then ran the chain for 20,000 steps, which was thinned to every other sample. For the proposal distribution, we used a multivariate Normal distribution (truncated with the bounds given in Table C.3), with a covariance matrix that adapts to predict the shape and scale of the posterior distribution as the algorithm proceeds. The adaptation improves the efficiency of proposing new samples so that there are neither excessive rejections nor acceptances in the algorithm. Finally, to improve mixing further, we used the two covariance matrices from this first set of runs in a second round of two independent chains with the same burn-in and sampling strategy. With this second set, we visually checked that there was good mixing. The parameters used in the forward projections are based on the first chain of this second set of runs.

C.2.1 Fixed parameters, priors and posterior distributions

Descriptions of state variables are given in Table C.1. Descriptions and values of all fixed parameters are given in Table C.2, and descriptions and prior distributions for all fitted parameters are given in Table C.3 and Table C.4 respectively.

Notation	Description
S_i	Number of susceptible humans in risk setting i
E_i	Number of exposed humans in risk setting i
I_{1i}	Number of infected humans in stage 1 in risk setting i
I_{2i}	Number of infected humans in stage 2 in risk setting i
D_{1i}	Number of diagnosed humans in stage 1 in risk setting i
D_{2i}	Number of diagnosed humans in stage 1 in risk setting i
T_i	Number of treated humans in risk setting i
S_{ai}	Number of susceptible non-human hosts in risk setting i
E_{ai}	Number of exposed non-human hosts in risk setting i
I_{ai}	Number of infected non-human hosts in risk setting i
R_{ai}	Number of removed non-human hosts in risk setting i
S_{vi}	Number of teneral vectors in risk setting i
E_{vi}	Number of exposed vectors in risk setting i
I_{vi}	Number of infected vectors in risk setting i
U_{vi}	Number of non-teneral vectors in risk setting i

Table C.1: State variables in the model. Notation and a brief description of the state variables. $i = L, H$, representing the low and high risk settings respectively.

Parameter	Unit	Prior Distribution and Bounds
κ	-	Unif$[0, 1]$
log(VHL)	-	N$(1.1, 0.05)$ in [0,log(100)]
log(c_1)	-	Gamma$(1, 1)$ in [0,log(50)]
logit(spec)	-	Unif[logit(0.998), logit(0.9999)]
$r1_{\text{const}}$	day^{-1}	Unif$[0, 10^{-3}]$
log(c_2)	-	Gamma$(1, 1)$ in [0,log(50)]
Δr_1	year^{-1}	Unif$[0, 2.5]$
Δr_2	year^{-1}	Unif$[0, 2.5]$
x_0	-	Gamma$(10, 0.06)$ in $[0, 19]$
α_{pd}	-	Unif$[0.1, 5]$
κ_{as}	-	Gamma$(23.5, 3)$
κ_{pd}	-	Gamma$(23.5, 3)$

Table C.3: Priors for fitted parameters. Non-uniform priors were additionally truncated with values given in brackets. Gamma priors are written with arguments of shape and scale.

Table C.2: Model parameterisation (fixed parameters). Notation, a brief description, and the used values of fixed parameters.

Notation	Description	Value
α	Rate at which tsetse become non-teneral (i.e. cannot get infectious)	73 year^{-1} assumed
A/H_1	Density of non-human hosts relative to humans in area L	1.35 [80]
A/H_2	Density of non-human hosts relative to humans in area H	1.5 [80]
b	Proportion of infective bites leading to infection in humans	0.433 [80]
c_h	Proportion of bites on an infective human that lead to a mature infection in flies	0.065 [76]
c_{ai}	Proportion of bites on an infective non-human hosts of type i that lead to a mature infection in flies	0
δ	Rate at which treated humans return to the susceptible class	2.19 year^{-1} [141]
η	Rate at which hosts move from the incubating stage	31.025 year^{-1} [76]
f	Inverse of duration of feeding cycle; or biting rate	121.545 year^{-1} [195]
γ	Rate of progression to stage 2 in humans	0.6939 year^{-1} [196]
μ	Death rate of humans due to natural causes	0.01666 year^{-1} [197]
μ_γ	Disease-induced death rate or rate of leaving the recovered state for humans	1.4484 Year^{-1} [196]
μ_t	Death rate of humans due to treatment	0 year^{-1} assumed
μ_v	Death rate of tsetse	10.95 year^{-1} [76]
ν	Inverse of the extrinsic incubation period	12.41 year^{-1} [198]
σ	Biting preference for humans	0.326 [80]
σ_{ai}	Biting preference for non-human host in the setting i	0.8/0.396 assumed
ξ	Proportion of time spent i the high risk region by commuters	0.698 [80]
sensitivity	Diagnostics sensitivity (active screening)	0.91 [199]

Table C.4: Model parameterisation (posteriors of fitted parameters). Notation, a brief description, and representative percentiles of the posterior distributions for fitted parameters. Here logarithm always refers to the natural logarithm.

Notation	Description	Posterior (median [95% CI])
κ	Ratio of humans in the high- to low-exposure environment	8.25 [3.82,11.6]$\times 10^{-2}$
log(VHL)	Log ratio of vectors to humans in low-exposure environment (VHL)	1.053 [0.974, 1.445]
$\log(c_1)$	Log ratio of the ratio of vectors to humans in the high exposure environment to the ratio of vectors to humans in the low exposure environment	6.585 [0.547, 17.02]$\times 10^{-2}$
spec*	Diagnostic specificity (active screening)	0.9991 [0.9990, 0.9992]
$r1_{\text{const}}$	Daily passive detection rate for stage 1 (pre-2000)	3.62 [1.92,5.78]$\times 10^{-4}$
$\log(c_2)$	Log ratio of passive detection for stage 2 to stage 1 (pre-2000)	0.559 [0.036, 1.773]
Δr_1	Amount passive detection in stage 1 improves	9.978 [4.402, 17.16]$\times 10^{-2}$
Δr_2	Amount passive detection in stage 2 improves (in addition to improvement of stage 1)	1.444 [0.646, 2.314]
x_0	Turning point (years since 1999) for logistic improvement in passive detection	13.24 [6.44, 18.76]
α_{pd}	Steepness in logistic improvement of passive detection	0.578 [0.182, 0.962]
κ_{as}	Overdispersion parameter (active screening)	34.04 [19.56, 56.49]
κ_{pd}	Overdispersion parameter (passive detection)	61.45 [39.13, 91.33]

* The specificity parameter, spec, was sampled in the logit scale, however posterior estimates are shown here in the model scale for clarity.

C.2.2 MCMC outputs

The MCMC outputs shown in Figures C.2 correspond to 10,000 post burn-in samples.

C.2.2.1 Posterior densities

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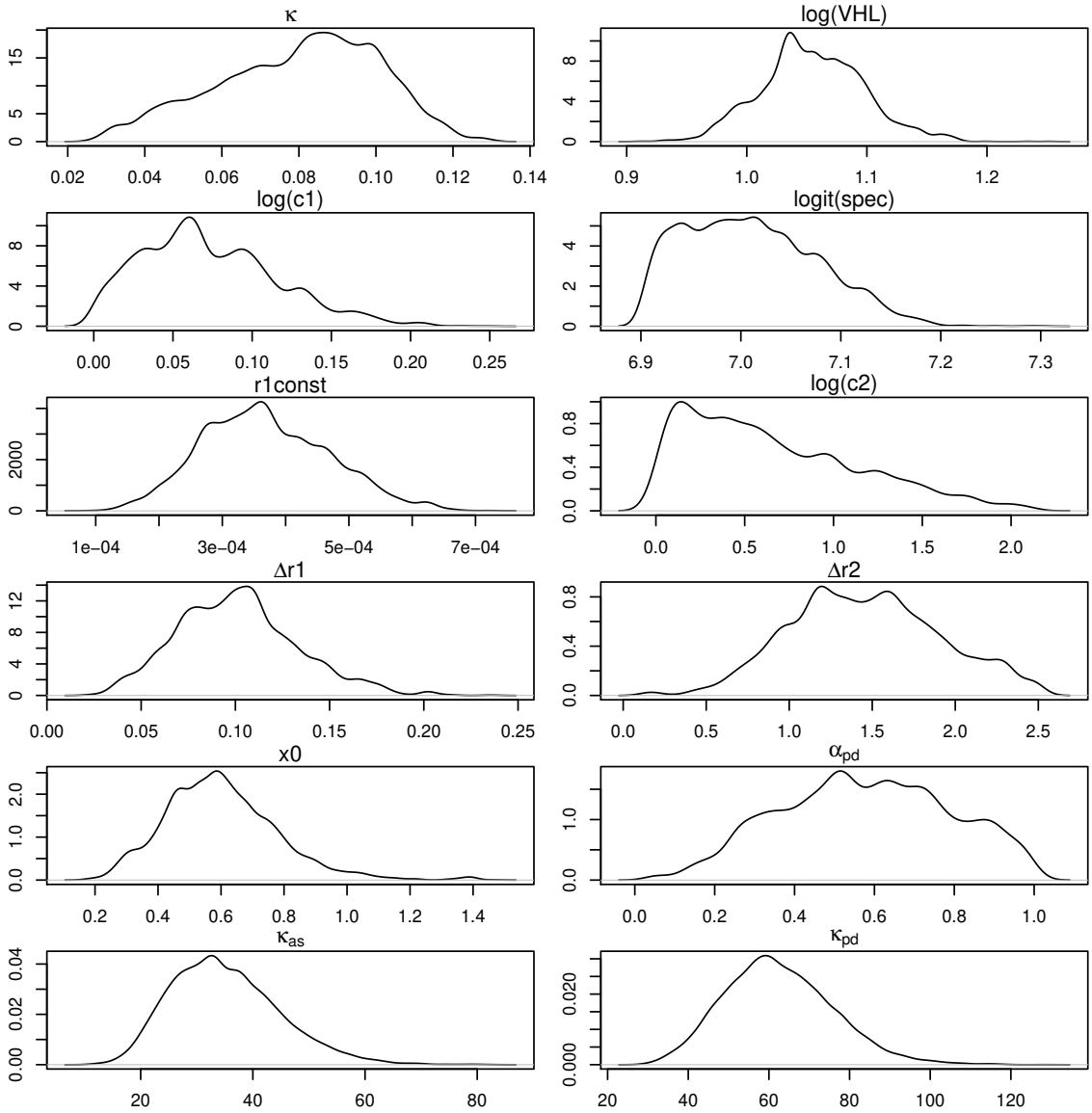

Figure C.2: Posterior density of fitted parameters for Mushie territory.

C.2.2.2 Model fit to reported case data

Figure C.3 shows the model fit to Mushie territory. The deterministic model simulations used 10,000 MCMC posterior samples.

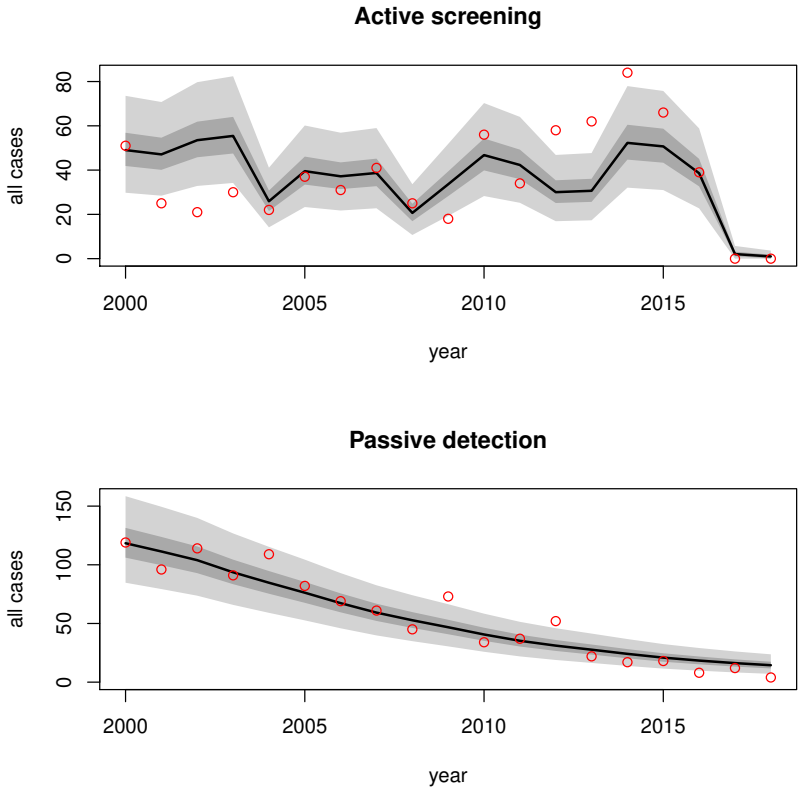

Figure C.3: Model fit to reported case data for Mushie territory. Shaded regions indicate (2.5,97.5) and (25,75) percentiles.

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EXPERIENCE

SEPTEMBER 2019 – OCTOBER 2022

PHD CANDIDATE, SWISS TROPICAL AND PUBLIC HEALTH INSTITUTE, ALLSCHWIL, SWITERLAND

Used stochastic metapopulation models to explore the impacts of new interventions and improvements to current interventions on diseases approaching elimination. Focus of work was on the impact of reactive case detection and human movement on malaria transmission in Zanzibar, Tanzania, and the impact of fexinidazole use on human African trypanosomiasis transmission in the Democratic Republic of the Congo. Models built in Python, R and C++.

SEPTEMBER 2018 – AUGUST 2019

ASSOCIATE, CONSULTING SERVICES, IQVIA, BASEL, SWITZERLAND

Assisting in problem analysis and decision making for large and mid-sized pharmaceutical companies.

EDUCATION

JUNE 2018

M.SCI, NATURAL SCIENCES (SYSTEMS BIOLOGY), UNIVERSITY OF CAMBRIDGE

Class: 2.1
Courses taken included: bioinformatics methods for data acquisition and handling, mathematical modelling and analysis of networks.
Master's project focused on modelling antigenic variation in *P. falciparum*, with the aim of identifying network properties of PfEMP1 sequences associated with severe forms of malaria. Extensively used Python and Cytoscape.

JUNE 2017

BA, NATURAL SCIENCES (PHYSICS), UNIVERSITY OF CAMBRIDGE

Class: 2.1
Courses taken included: thermal and statistical physics, special and general relativity, advanced quantum physics, optics and electrodynamics, astrophysical fluid dynamics, particle and nuclear physics, soft condensed matter, physics education

PUBLICATIONS

Das AM, Hetzel MW, Yukich JO, Stuck L, Fakih BS, Al-mafazy AH, Ali A, Chitnis N. (2023) "Modelling the impact of interventions on imported, introduced and indigenous malaria infections in Zanzibar, Tanzania." *Nature Communications* 14:2750. https://doi.org/10.1038/s41467-023-38379-8

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Das AM, Chitnis N, Burri C, Paris DH, Patel S, Spencer SEF, Miaka EM, Castaño MS. (2021) "Modelling the impact of fexinidazole use on human African trypanosomiasis (HAT) transmission in the Democratic Republic of the Congo." *PLOS Neglected Tropical Diseases* 15(11): e0009992.
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https://doi.org/10.1093/cid/ciaa933

PRESENTATIONS

April 2022. "Simulating malaria elimination strategies in Zanzibar, Tanzania." Presented to the Zanzibar Malaria Elimination Program.

November 2021. "Modelling malaria elimination strategies for Zanzibar, Tanzania." Poster presentation at the American Society of Tropical Medicine and Hygiene 2021 Conference.

January 2021. "Modelling the impact of fexinidazole use on gHAT transmission in the DRC." Presented at the LCNTDR & The HAT Platform Scientific Research Meeting 2021.

September 2020. "The impact of human mobility on malaria transmission in Zanzibar." Presented at the Malaria Modelling Consortium Summer Lightning Talk Series.

April 2020. "Modelling potential effects of fexinidazole on sleeping sickness transmission in the DR Congo." Presented at the NTD Modelling Consortium Technical Meeting 2020.

SKILLS

- Languages: English, Bengali, Hindi, German
- Computing: Python, R, C++, Excel, LaTeX