Modelling Malaria Transmission in Ndumo and Shemula, KwaZulu-Natal

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Declaration

I, the undersigned, hereby declare that the work contained in this research project is my original work, and that any work done by others or by myself previously has been acknowledged and referenced accordingly.

Signed by candidate

Mandisi Moya, 11 March 2021

Abstract

The KwaZulu Natal (KZN) province is the front runner for malaria elimination in South Africa. It accounts for a small proportion of the total number of malaria cases diagnosed in the whole country in recent times. This study focused on the key localities in the province, Ndumo, and Shemula which reported the highest number of local malaria cases between the years, 2014 and 2018. The study aimed at investigating and assessing the most influential factors that drive malaria in the localities and to represent the malaria key features such as treatment, imported cases, vector spraying, and vector/human relationships. The model used in the study examines the malaria behaviour at a smaller scale as other models mainly look at larger population sizes such as district level and provinces to find the most effective strategies as we move closer to elimination. The purpose of this was to understand how malaria will change in the future if the existing strategies change. It also aimed at studying impact these changes would have on the existing cases, as to whether there will be a rise or a drop with the existing intervention coverages. This was achieved by formulating an 11 compartmental population-based, non-linear stochastic ordinary differential equation model that will be used to simulate malaria transmission in the two localities to assess the potential impact of various policy interventions that may be used to achieve malaria elimination. It was also developed to assess the impact of policy interventions on imported infections, seasonal spraying, the effectiveness of reducing the current coverages over time, and to reach the goal of malaria elimination.

Based on our analysis, we deduced that to maintain a low number of malaria cases, it would be sufficient to employ the current coverages but to reduce the number of cases, we need to consider finding ways to increase the IRS efficacy. Thus, for IRS, we conclude that, to reduce the malaria cases to its minimum (even further to 0), we need to consider increasing both the IRS coverage and its efficacy closer to 100%.

With imported cases having a big impact on local cases, we concluded that we could reduce the number of local cases if we can control imported cases from other areas. Strategies such as the border clinics, screening at the border etc, would result in significant impact in the local malaria cases as we would eliminate one of the major contributors to existing malaria cases.

In conclusion, we believe that increasing our efforts on the existing interventions, would result

in a further decrease in the number of cases. Although one would argue that the investment is not worthwhile and that the decrease is redundant, and because of this, it is worth considering moving all those efforts towards the prevention of the more concerning variable; imported cases. In terms of local cases, we would then consider maintaining the current coverages. In that case, we should only treat those who require the treatment and spray the areas that still report cases.

Contents

Chapter 1

Introduction

Malaria is one of the most prevalent and deadly parasitic diseases in the whole world, affecting children under the age of 5, pregnant women, patients with human immunodeficiency virus (HIV) and the acquired immune deficiency syndrome (AIDS), tuberculosis, non-immune migrants, mobile populations and travellers [3], [32]. This life-threatening disease caused by the parasite is transmitted to humans through the infected female Anopheles mosquitos' bites referred to as malaria vector. There are only 5 species of parasites that spread and infect humans, with only two that pose the greatest threat to humans. The first is the Plasmodium falciparum (P.falciparum), the most prevalent malaria parasite on the African continent which is responsible for most malaria-related deaths in the whole world. The second is the Plasmodium vivax (P.vivax), the dominant malaria parasite in most countries outside of sub-Saharan Africa [1]. In the early stages, a person infected with malaria displays symptoms such as fever or headache. The symptoms usually appear within 10-15 days of being bitten by an infected mosquito. Following the appearance of symptoms, malaria can lead to death if not treated within 24 hours[3].

Malaria transmission is seasonal, limited to the warm and rainy summer months, cases start to rise in October, peaking in January and February, and waning towards May. Malaria is considered unstable and epidemic-prone. Malaria is sensitive to the climate, with Rainfall and Temperature acting as the main factors that drive the malaria epidemic. The number and survival of mosquitoes are affected by these climatic conditions which vary over time [2], [3]. Studies suggest that excessive rainfall has a major effect on malaria transmission and is known to increase transmission in the following ways [34], [35];

- with mosquitoes breeding in water, rainfall provides more opportunities for mosquitoes to breed as there are more water pools during rainy seasons, which leads to an increase in malaria vector population,

- due to high temperatures and humidity which is often associated with high rainfall, people tend to spend nights in cooler areas outside their houses or indoors with open windows, thereby increasing the change of being bitten by infected mosquitoes.
- and lastly, too much rain results in flooding and bad roads which in turn to hamper the movement of the teams that conduct the IRS in some communities.

Scaling up of interventions such as treatment, diagnosis, and prevention has reduced malaria burden by 11% globally from 239 to 219 million cases with incidence rate from 72 to 59 cases per 1000 population at risk, while the incidence at risk remained at 219 cases per 1000 population at risk in the sub-Saharan region between 2010 and 2017 [2], [1]. In 2018, the World Health Organisation (WHO) reported an estimate of 228 million malaria cases worldwide, with the number of deaths standing at approximately 405000. As stated, pregnant women and children are more at risk. Immunity to malaria in a pregnant woman is reduced by pregnancy, making her more vulnerable to the infection and putting her at a higher risk of contracting an illness, severe anaemia, and death. Maternal malaria delays the foetus growth which in turn increases the risk of immature delivery and low birth weight. Maternal malaria has been known as the leading cause of child mortality [2]. The WHO reported 11 million women that contracted malaria in areas of medium and high disease transmission in sub-Saharan Africa in 2019. As a result of this, approximately 900 thousand children were born with low birth-weight [2]. Children under the age of 5 were the most vulnerable affected by malaria. It was estimated that 271350 children died of malaria before their fifth birthday, accounting for 67% of the total deaths. The Africa region is reported to be the carrier of most of the cases reported in the world. During this period, the region was home to about 93% of malaria cases and 94% of malaria deaths.

Malaria in South Africa is identified as being substantially less prevalent than in other African regions. In South Africa malaria mainly takes place at the low-altitude areas of the northern and eastern parts of the country along the border with neighbouring countries including Mozambique, eSwatini, and Zimbabwe, with transmission taking place mainly in Limpopo, Mpumalanga and KwaZulu Natal provinces [1]. According to Silal et al. [3], approximately 95% of confirmed malaria cases are due to infections with Plasmodium falciparum in the country. Limpopo province has been reported with the highest incidence in the country because of its position in the high-risk malaria transmission zone bordering Mozambique, Zimbabwe, and Botswana, and KwaZulu Natal reported the least number of cases. The transmission is constant, peaking during and after warm rainy seasons, between September and May [4]. Its rate may vary in and between years depending on factors such as the amount of rain, air temperature, and other climatic conditions that could create a conducive environment [5].

In recent years, there was an expected and substantial increase in malaria-related morbidity and mortality in endemic regions of South Africa, with malaria cases increasing from 1377 in 2016 to 30558 in 2017 [6], despite all efforts that had been made in the country to control malaria over the past years (pre 2016), which lead to a significant decline in morbidity and mortality in the malaria risk regions [7]. Over the years, South Africa made use of several strategies to manage the malaria vector. These included epidemic preparedness, disease surveillance, indoor residual spraying, malaria advocacy and information, education, and communication.
Several studies stated that of the three malaria-endemic provinces in South Africa, the KwaZulu Natal Province (KZN) had the lowest number of reported malaria cases. Over the past decade, the province reported the fewest number of malaria cases diagnosed in South Africa each year, with most of these cases diagnosed in Umhlabuyalinga Municipality, a local municipality located at the eastern border of uMkhanyakude District, along the border with eSwatini and Mozambique. Several studies suggested that most of these cases are a result of imported malaria cases reported in the province each year. The province is the front runner for malaria elimination, it presented a steady decline in local cases over the years, from 102 to 35 malaria cases in the June 2010/July 2011 and June 2016/July 2017 seasons respectively [8]. This number continued to decrease until a rapid increase was noticed in 2018. This increase is suspected to have been influenced by the increase in cases reported in the neighbouring country, mostly Mozambique.

KZN is the closest to its target of eliminating malaria, as evidenced the fewest number of malaria cases out of the three provinces. Ndumo and Shemula localities were the biggest contributors to the malaria cases between 2014 and 2018 in the province. The two localities are in Jozini local municipality, located in uMkhanyakude district. In this study, we evaluated the impact any change in the interventions we have in place would have on malaria transmission as we move closer elimination. This was achieved by formulating a population-based, non-linear stochastic ordinary differential equation model that was used to simulate malaria transmission in the KwaZulu Natal province and assess the potential impact on malaria transmission of various policy interventions that may be used to achieve malaria elimination. This model was also used to assess the impact of policy interventions on imported infections, seasonal spray, the effectiveness of reducing the current coverages over time, and the goal of malaria elimination. This dissertation aims to model the malaria transmission within the two localities, and assess impact on transmission in the following actions were to be carried out:

- Reducing/increasing Indoor residual (IRS) as the localities move towards elimination.
- Reducing/increasing the number of imported cases into the localities.

Research questions

- What impact would the reduction in IRS coverage have on the local cases within the two localities? Would it result in malaria transmission persisting or remain the same?
- How much change would a reduction in the number of imported cases have on the local cases reported in the two localities? Would it result in fewer cases reported in the localities?

Chapter 2

Literature review

Malaria

Malaria is a global burden mostly affecting underdeveloped regions, especially sub-Saharan Africa despite scaling up interventions to reduce the malaria burden. The World Health Organisation (WHO) malaria report [3] states that at least 70% of the global malaria cases that occur, 67% resulted in deaths in 2019, mostly affecting young children and pregnant women. It was also stated that 229 million malaria cases were reported in 91 countries with approximately 409000 deaths [2], [1].

Biology of malaria

Malaria is a transmittable disease that occurs when a malaria parasite is transferred to a human through a female malaria-infected Anopheles mosquito bite, which simultaneously injects sporozoites into the skin. The process consists of 3 cycles which work concurrently, as shown in Figure 2.1. These cycles are referred to as Exo-erythrocytic (1 – 4 cycles), Erythrocytic (5 – 7 cycles) and Sporogonic cycles (8 – 12 cycles). The mosquito bite and sporozoites injection mentioned above are in cycles 1 and 2, respectively.

Once the sporozoites reach the liver, they invade hepatocytes and later sporozoites develop into liver schizonts and replicate asexually (3). After approximately 7 days of development, the schizotes rapture and release merozoites which later enter the peripheral bloodstream (4).

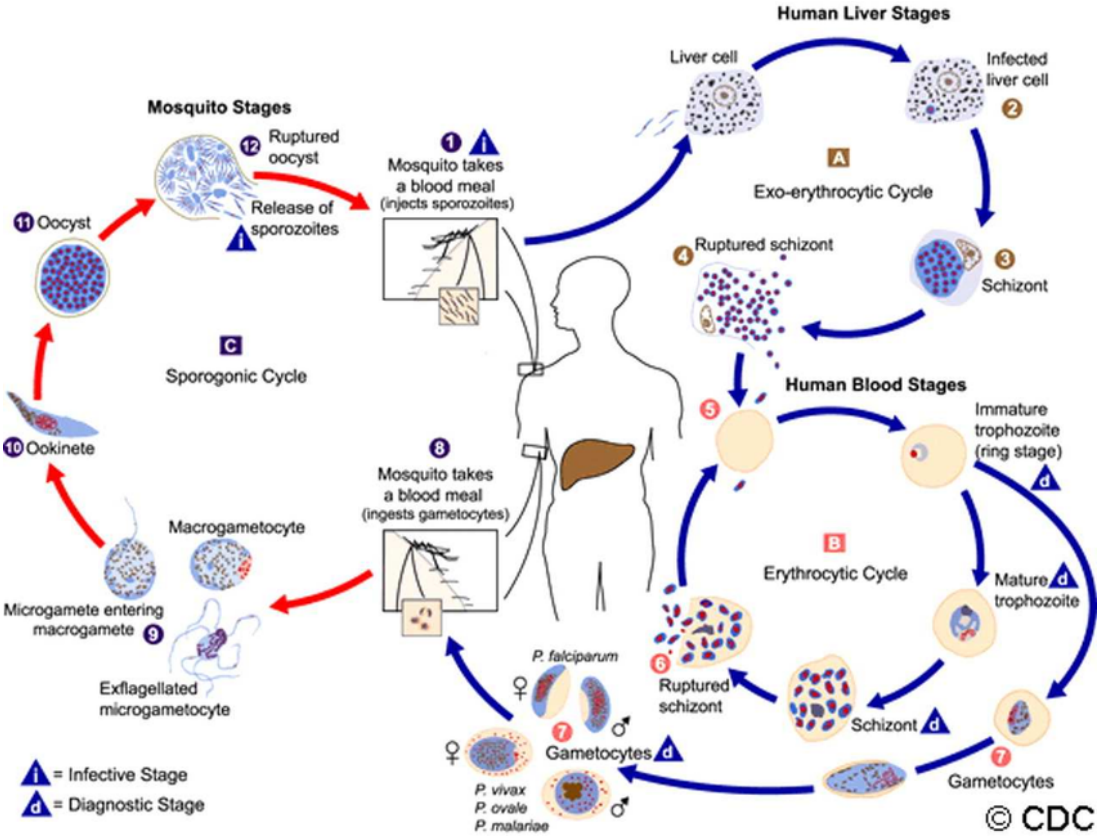


Figure 2.1: Malaria Life Cycle [30]

As soon as merozoites enter the bloodstream, they invade the circulating red blood cells. This causes the asexual cycle to start over (5). At stage 6, merozoites are raptured and released into circulation, starting a new process of asexual reproduction. This happens when the parasite progresses through the ring and trophozoite stages before replicating into about 8 to 32 daughter merozoites at the schizont stage within the period of 48 hours. In each cycle, few parasites produce progeny which differentiate the cycle into gametocytes (i.e. male and female forms) after splitting from the asexual replication. The parasites leave the cycle (B) and enter the extravascular space of the bone marrow, where gametocytes mature and progress within a period of 8-10 days (gametocytogenesis) (7). Even though the primary location of immature gametocytes is the bone marrow, they can be also found in other parts of the human body (i.e. spleen).

In stage 8, an Anopheles mosquito ingests gametocytes from an infected human during a blood meal in which a male and female gametocyte rapidly mature into gametogenesis (gametes). The male gametocyte divides into up to eight flagellated microgametes, whereas the female gametocyte develops into a single macrogamete (9). Fertilization of a macrogamete by a microgamete results in the formation of a zygote, which undergoes meiosis and develops into an invasive ookinete that penetrates the mosquito gut wall (10). The ookinete forms an oocyst within which the parasite asexually replicates, forming several thousand sporozoites (sporo-

gony) (11). Upon oocyst rupture, these sporozoites migrate to the salivary glands, where they can be transmitted back to the human host during a blood meal (12).

Interventions against malaria

South Africa and eSwatini, both low transmission countries, are aiming to eliminate malaria by 2020 and 2023 respectively [17, 18]. The two countries share a border with a southern coast country, Mozambique; a country with a high burden of malaria [19]. Overs the years, several interventions have been made available to mitigate and control malaria transmission, particularly in the South African endemic provinces, to eliminate malaria [1]. With these interventions in place, a significant decrease in the total number of local cases has been noticed [24]. These interventions include the Cross-border malaria control initiative which was mainly introduced to control malaria transmission and reduce the spread of Arteminism-resistant Malaria at the border districts. It is aimed at successful malaria control and elimination. The second initiative is called the Lubombo Spatial Development Initiative (LSDI). The programme was introduced in 1999 as a collaborative project to address the issue of high malaria transmission in economic and agricultural developing areas [16]. The programme aimed at:

- Reducing malaria incidence at the border areas of South Africa and eSwatini from 250/1000 to less than 20/1000 population,
- Reducing malaria infections rate from 625/1000 to 200/1000 population within the period of 3 years of initiative post its introduction,
- Developing a regional malaria control programme to cover 200000 sq. km,
- Developing a regional geographic information system (GIS)-based malaria information system (MIS) in the three countries,
- And establishing an effective treatment and definitive diagnosis through the roll-out of rapid diagnostic tests (RDTs) and artemisinin-based combination therapy (ACT) at all public health facilities [13, 21].

The malaria control initiative objectives were achieved within five years of its initial implementation [21]. It made a substantial decline in the malaria burden, improved the health quality of the targeted populations, and contributed to the economic productivity [22]. Due to financial constraints, the initiative was terminated in Mozambique in 2011, although the programme made a significant difference on malaria transmission.

After the termination of the LSDI, a substantial increase in the number of malaria cases was noticed and reported in different parts of the MOSASWA regions (Mozambique, South African,

and eSwatini), despite the sustained in-country implementation of malaria interventions in South Africa and eSwatini [11]. Few years post the LDSI termination, the MOSASWA initiative was introduced. It was built on the solid foundation of the LSDI, from which capacity still exists in all three affected countries for the implementation of strategies and management of the initiative. Although malaria cases in the MOSASWA region increased in the 2012 - 2017 period, numbers remain relatively low [13]. This initiative formed part of the border Elimination Eight (E8) which was a collaboration of eight southern countries that aimed at achieving a zero local malaria transmission in the four front-line countries (Botswana, Namibia, South Africa, and eSwatini) by 2020 and in the second line countries (Angola, Mozambique, Zambia, and Zimbabwe) by 2030.

Due to the implemented interventions in the three countries, a large decrease in malaria burden was noticed and is now limited to the border districts of South Africa and eSwatini. It was recognized that imported cases from malaria-endemic areas near these three countries were the main contributor that leads to an increase in the total number of diagnosed cases in different parts of the countries [13]. Despite all optimal malaria control that has been in place, there has been "increasing consensus that the disease incidence could only be further reduced by a regional approach to control" [13]. Indoor residual spraying (IRS) which is the main strategy used for vector control is undertaken in the three malaria-endemic provinces of South Africa. IRS is conducted yearly in the 3 malaria-endemic provinces (i.e. KwaZulu Natal, Limpopo, and Mpumalanga). The spraying season commences in August each year and ends the following year in March. The IRS malaria programme consists of two different types of chemical insecticides: dichloro-diphenyl-trichloroethane (DDT) and a synthetic pyrethroid. Both insectides are approved by World Health Organisation for malaria vector control. DDT and pyrethroids are used to spray walls made of porous materials such as mud or wood and plastered or painted walls respectively [26, 28].

In 2001, South Africa implemented rapid diagnostic tests (RDT) to diagnose malaria in endemic areas [6]. RDT is most effective in a primary care setting and is known as being easy to use as it does not need complicated technology and gives quick results [7]. Its ability to give precision and functionality can be affected by many factors which include storage, transport, manufacturing defects, and end-user performance [8].

Elimination

South Africa alone has malaria programmes that have been active for decades, with several interventions' available country-wide to eliminate and control malaria transmission [1]. These programmes were aimed at eliminating malaria in the whole country by 2018. The programmes

defined four elimination phases.
The step by step phases are explained as follow;

- To control to less than 5 positive cases per 1000 persons presenting with fever,
- To reduce to less than 1 case per 1000 persons at risk per year,
- To combine both phases listed above to prevent re-introduction aiming to maintain 0 malaria cases per 1000 persons at risk per year.

An illustration is shown below [40, 41]:

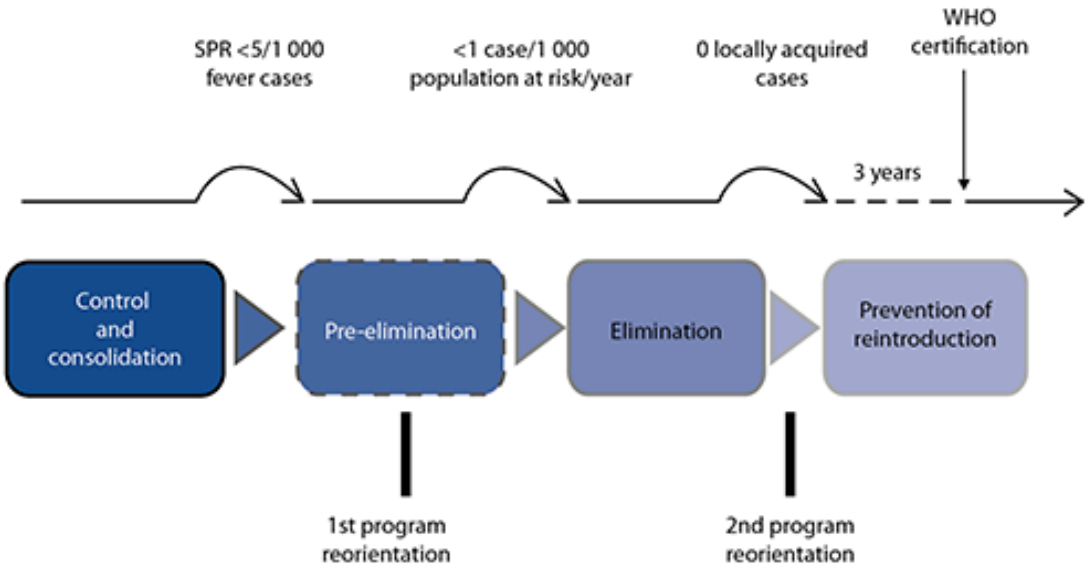


Figure 2.2: Malaria Elimination Phases [38]

The interventions used in the four listed phases include;

- Indoor residual house spraying (IRS),
- Treatment of uncomplicated malaria with Artemisinin Combination Therapy [ACT] as they are rapidly and reliably effective i.e. lumefantrine, chlorproguanil/dapsone, amodiaquine, mefloquine, piperaquine and sulfadoxine/pyrimethamine.

It has been reported that scaling up of these interventions could help in eliminating malaria and achieving the goal of maintaining zero malaria cases in South Africa [1]. The consensus at this point is finding the right places to treat and knowing which intervention is more effective to achieve the elimination goal. Malaria can be prevented using mosquito coils and repellents, spraying the insides of houses (where most Anopheles species feed and rest) with insecticides (indoor residual spraying) and by sleeping under the bed nets that have been treated with long-lasting insecticides [9]. Mass screening and treatment (MSAT) with effective anti-malarial drugs can also reduce malaria transmission [10].

Malaria Incidence and Control in Ndumo and Shemula, KZN

History

Since the last malaria epidemic that occurred in 2000, malaria incidence has decreased substantially in South Africa. By 2012, the country had already met the malaria elimination threshold of less than 5 cases per 1000 population at-risk set by the World Health Organisation (WHO) [12]. Several studies state that within the three malaria-endemic provinces in the country (South Africa), the KwaZulu Natal Province (KZN) is known to have the lowest number of reported malaria cases.

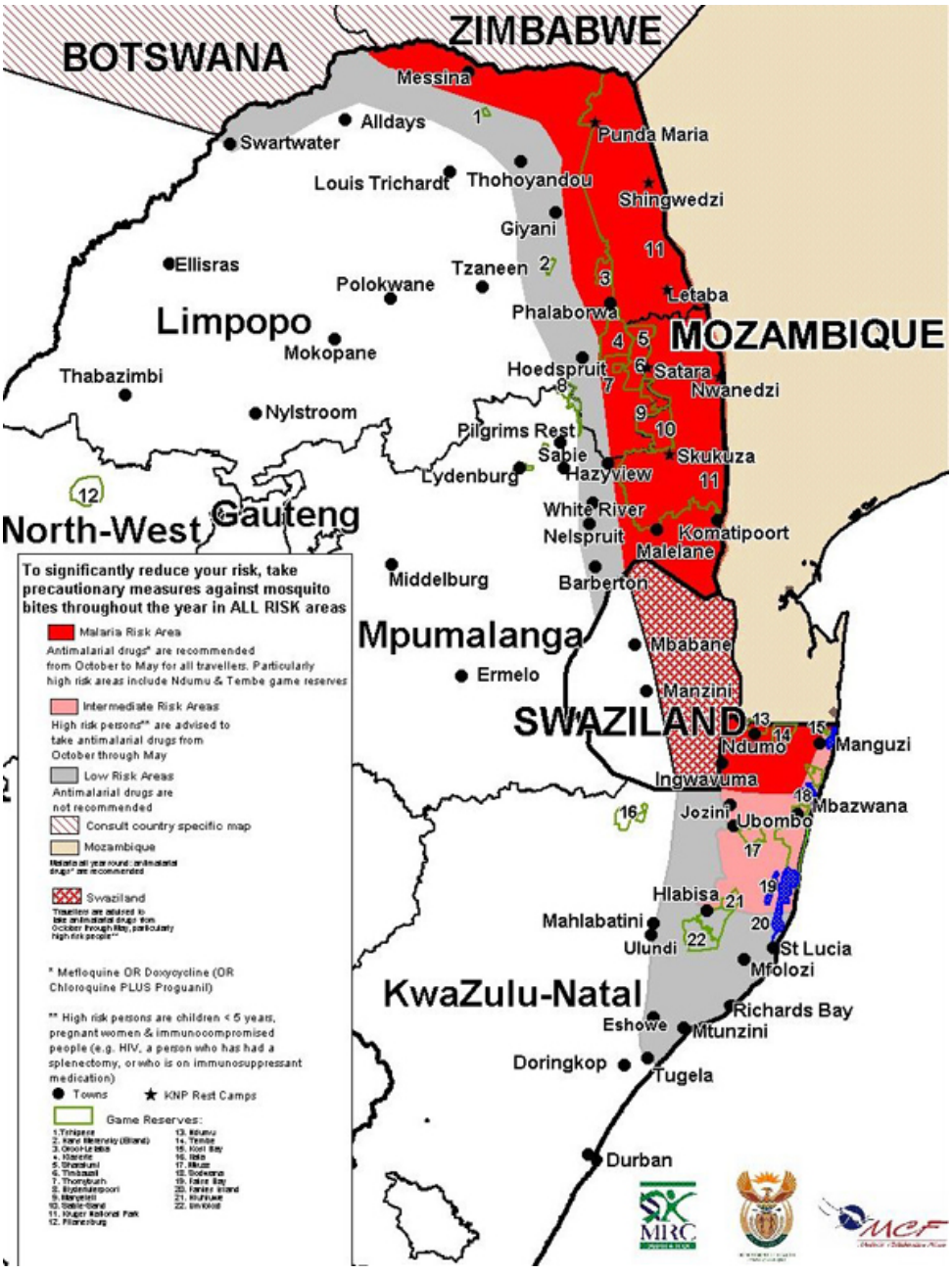


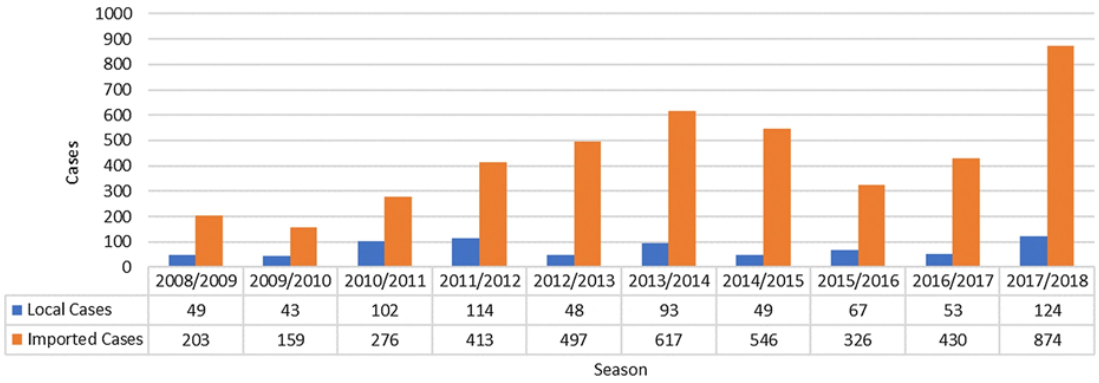
Figure 2.3: SA with neighbouring countries

Over the past decade, KZN reported the fewest number of malaria cases diagnosed in South

Africa each year, and most of these cases were diagnosed in uMhlabuyalinga Municipality, a local municipality located at the eastern border of uMkhanyakude District, along the border with eSwatini and Mozambique [1]. It was suggested that most of these cases are a result of imported malaria cases reported in the province each year. The Malaria Elimination 8 report [32] stated that approximately 77% of total malaria cases are diagnosed in travellers from neighbouring countries each year (imported cases). Malaria transmission in KZN is constant (seasonal), peaking during and after warm rainy seasons, between September and May [4].

Most of the malaria cases diagnosed in South Africa are Plasmodium Falciparum cases and are suspected to be associated with a severe and fatal disease. It was stated in some studies that most South Africans are non-immune to malaria which then puts them more at risk of contracting severe malaria [61, 62]. In the early 2000, malaria was a threat to human life in South Africans, and with this as an issue, several interventions were put in place to diagnose and manage the disease. The choice of antimalarial agents was dependent on the severity of the illness and the pattern of drug resistance of the parasite in the geographical area where malaria was acquired. South African public health uses a rapid diagnostic test to test whether an individual is malaria positive or negative. A theoretical detection threshold of 200 parasites/μL is employed. The test usually takes up to 20 minutes of processing time. Another strategy called Active case detection is used to identify the source of the infection which enables further screening and treating of symptomatic people. South Africa has changed treatment for symptomatic patients 3 times between 2002 and 2006 to cater for the increase in gametocyte, from sulphadoxine-pyrimethamine (SP) to SP-artesunate followed by SP-artesunate [13]. Indoor residual spraying (IRS) is one of the most used vector controls in the country [15].

Over the past decade, the local cases diagnosed in KwaZulu Natal have been making up only a small proportion of the total number of cases, with most of the cases being recorded as being imported from outside the borders of the country, mainly sourced from Mozambique (Figure 2.4). It is these imported cases that also cause secondary cases within the province. This is evidenced by the fact that as imported cases have increased, so have the number of local cases even though there was a marginal increase in the reported number of local cases in the last three malaria seasons [36]. Ndumo and Shemula localities are small regions located in the uMkhanyakude district. These localities were reported with the highest number of malaria cases between 2014 and 2018. It is suspected that the reason for the high incidence of malaria in the two regions may have been due to being close to the Mozambican border. Figure 2.3 shows the two localities.



	2008/2009	2009/2010	2010/2011	2011/2012	2012/2013	2013/2014	2014/2015	2015/2016	2016/2017	2017/2018
Local Cases	49	43	102	114	48	93	49	67	53	124
Imported Cases	203	159	276	413	497	617	546	326	430	874

Figure 2.4: Number of KZN local and imported cases

Mathematical Modelling Epidemiology

Since the development of the first dynamic model of smallpox by Bernoulli in 1760, various mathematical models have been employed to study infectious diseases [17] to reveal the underlying spread mechanisms that influence the transmission and control of these diseases. Among them, Kermack and Mckendrick [18] initiated the famous Susceptible, Infected and Recovered (SIR) type of compartmental model in 1927 for the plague studies in Mumbai and succeed in unveiling its epidemiological transition. Since then, mathematical modelling has become an important and useful tool to study the transmission and spread of epidemic diseases. The underlying equations for the SIR model are as follows:

$$\frac{dS}{dt} = -\beta.S.I$$
$$\frac{dI}{dt} = \beta.S.I - \frac{1}{\alpha}.I$$
$$\frac{dR}{dt} = \frac{1}{\alpha}.I$$

Where S is the susceptible population at risk of contracting malaria, I is the infectious population capable of infecting others, R is the recovered population and t is the time. β and $1/\alpha$ can be explained as the number of contacts per unit time and the rate of recovery, respectively. The model assumes the following about its population. That

- modelled population is a fixed population (N = S + I + R), where the members interact with one another equally.
- immigration and emigration are not permitted as it may accelerate the dynamics of the disease and death processes. Any inherent age, demographic and spatial structure are also ignored.

- immunity is permanent (i.e. once an infected individual recover from the disease, re-infections is not possible.
- all susceptible people within the population are equally likely to get infected.
- the incubation period of the infectious agent is instantaneous and the duration of infectivity is the same as the duration of the disease (one can be infectious only if one has the disease).
- that all the members that reside in one compartment are identical.
- that its proportions that flow through the compartments are continuous.
- the rate of recovery is fixed for everyone within the population; hence the average duration of infectiousness is α.

The SIR model was later extended to other models to consider other factors such as stages of immunity, vector/[athogen dynamics, super-infection, birth processes, death processes, age, gender, drug therapy, vaccines, vector control and spatial structure, migration [19]. The following are some examples of extensions to the SIR model:

- Susceptible-Infectious (SI) model, a model that does not take account of for Immunity,
- Susceptible-Exposed-Infectious-Recovered (SEIR) model, a model that allows individuals to be exposed to the disease before being infected, and
- Susceptible-Infectious-Recovered-Susceptible (SIRS) model. It allows individuals to have temporal immunity.

It is worth noting that the models of the same disease can be modelled with different structures etc.

Mathematical Modelling of Malaria

Over the years, researchers in biology have become aware of the importance and the role of mathematical modelling in modelling infectious disease and proving an explicit framework for understanding the disease transmission dynamics within and between hosts and parasites. Mathematical models incorporate several known clinical and biological information or features that are known to be important to the problem being investigated in the disease progression and dynamics.

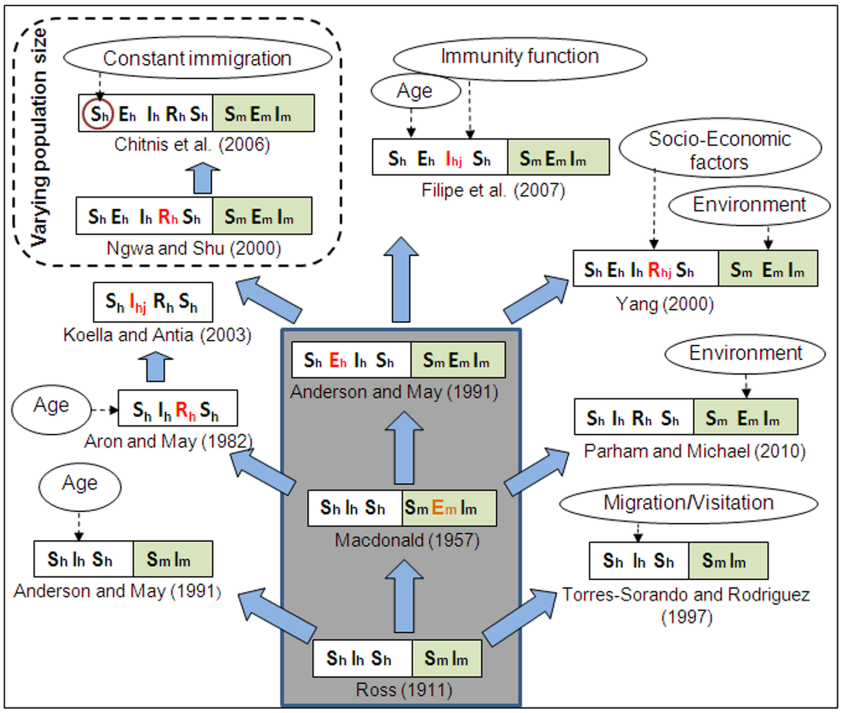


Figure 2.5: Evolution and grouping of different types of SEIR malaria models. Subscripts $'h'$ and $'m'$ stands for human and mosquito. Double-folded boxes are for both the human & mosquito population, and single fold boxes are only for human. First time addition of a new compartment is shown in red. The subscript $'j' = 1, 2, 3$ indicates further subdivision of the corresponding compartment. Three models inside the big grey box are considered as the Basic malaria models. Dotted arrows show the incorporation of complex factors in different models or specific compartments (circle). Total population size is constant for all models, except the ones inside the dashed box [22].

A model structure is dependent on the process being studied and aimed for extrapolation which then acts as an approximation to the complex reality. Based on the investigations done, these models can be fitted to observed cases, and further, make predictions on how the disease will occur in the future. Epidemiologists have widely made use of mathematical models as tools to predict infectious diseases epidemics and as a tool for guiding research for the eradication of malaria at present [16, 21].

Since a single infection does not guarantee permanent immunity, there has been a need to incorporate a flow between the recovered to the susceptible compartments (resulting in the SIRS model) and found the need to modify the basic Ross model to explain the effect of the age structure of prevalence [16], migration and visitation of people [24]. Several models were also put forward after Macdonald's model by combining additional complexities of human immunity, parasite diversity, and resistance, to explain large amounts of epidemiological data collected in Africa and other parts of the world [26, 28]. Figure 2.5 demonstrates these models which looks at different malaria aspects [22]. These aspects could include factors such as movement between populations (i.e. migration and/or immigration), drug therapy, socio-economic and

environmental factors. Several models have been published by several scientists that attempt to capture such complex factors as those described above. Examples of these models include those of:

- Yang, SEIR models for hosts and vectors (incorporating dynamics in an SEI model for mosquitoes) that incorporated socio-economic and environmental factors,
- Auger et al who extended the Ross-Macdonald model to several patches in a meta-population compartment,
- Torres-Sorando and Rodriguezwhich included the migration and visitation to the SIS model,
- Koella and Antia [14] which incorporated resistance to drug therapy and super-infection to the SIRS model.

Building a mathematical model that closely approximates reality is a complex task. To achieve this, one would have to include factors such as: how time progression in a human population is measured (i.e. discretely versus continuously), time-dependent rates and the degree of mixing in the model, randomness in the model, and/or how the population is described (individual membership or proportions of a population), etc [29]. There exist several population groups, each having a different behaviour and different abilities to transmit infection. Population-level models assume that populations are large enough to average out any deviations caused by the heterogeneity in individual behaviour. This assumption does not always stand, particularly if a rare disease is being modelled or in the case of malaria when elimination of the last-remaining infections is being explored. Unlike population models, Individual-Based Modelling (IBM) models the behaviour of individuals, thereby allowing the heterogeneous behaviour of individuals to be captured by the model [23].

Mathematical Modelling in Malaria in South Africa

Over the years, South Africa has made use of mathematical modelling in its goal to eliminate malaria. With KwaZulu Natal province as the front runner in eliminating malaria in the country, mathematical modelling has played a major role. Climate change is known as one of the contributors to new infections in the Sub-Saharan region (including a region containing KwaZulu Natal). Numerous climate-based malaria models have been developed to study malaria transmission. Examples of such applications were done in previous studies of Martens et al [33], Jetten et al [35], and Lindsay and Martens [34]. Climate data were used to simulate the relationship between climate variables and the basic reproduction rate of malaria.

In this study, we developed a model to study malaria transmission in the two most malaria-

endemic localities in KwaZulu Natal (Ndumu and Shemula localities) as they move near elimination. The model explores the different factors that drive infection in the two localities. Since malaria transmission is dependent on a vector (mosquitoes) and host (human) populations, we incorporated as many factors as possible which influence the change in malaria transmission. The focus of the modelling exercise is to understand the impact of importations and change in indoor spray. The aim was to build a model that mimics the nature of malaria to enable ourselves to understand how malaria transmission changes over time and how the measures put in place to reduce transmission and other factors that stimulate growth in the number of cases.

Chapter 3

Data Analysis

This chapter is aimed at reviewing the number of malaria cases reported in the most malaria-endemic localities in the KwaZulu Natal province, Ndumo and Shemula between 2010 and 2018 to acquire a better view of how malaria cases have changed as malaria interventions improved over time. To achieve this, we will evaluate the number of malaria cases diagnosed in South Africa, focusing on imported cases as they are known to have an immense impact on some areas in the country. We also review some of the factors that may have resulted in the increase in the total number of malaria cases towards the end of the period (between 2017 and 2018). To understand the incidence in the two localities, we evaluate malaria incidence dynamics over time, hence the review from the total of malaria cases diagnosed in the whole country zooming down to the cases in the two localities of interest.

Cases in South Africa

Figure 3.1 illustrates the number of malaria cases diagnosed in South Africa between 2010 and 2018. The dotted red line shows the total number of cases diagnosed in the country, regardless of the source of infection. The solid red line shows the number of only locally sourced cases diagnosed in South Africa. The blue line represents the proportion of locally sourced cases to the total number of cases in the province.

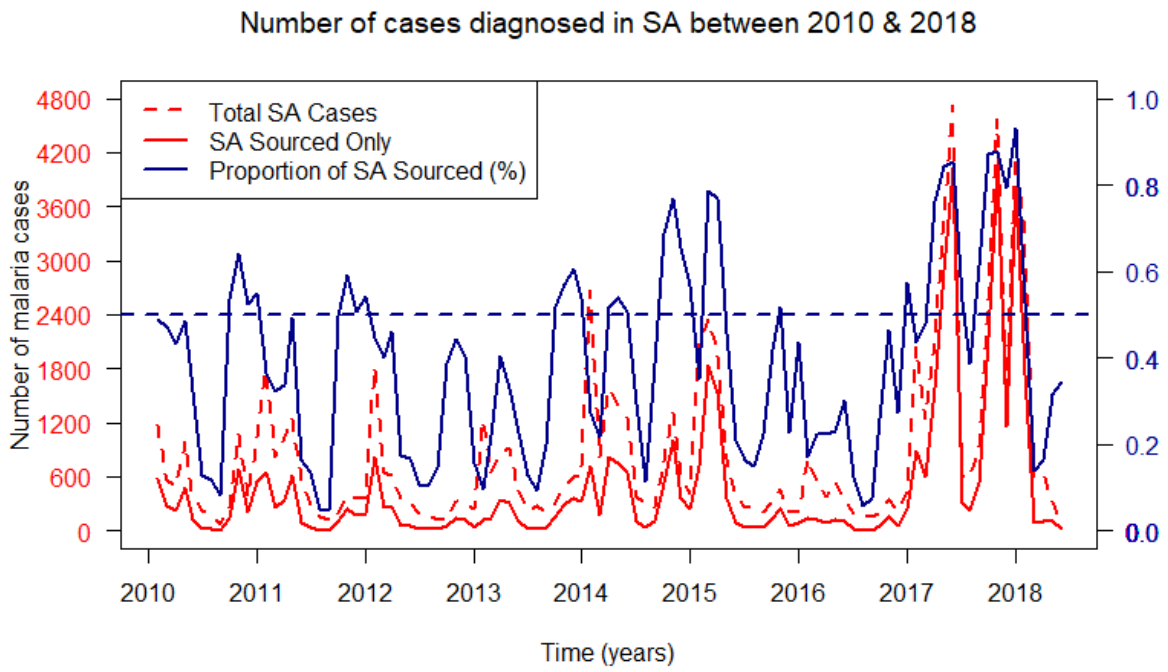


Figure 3.1: Malaria diagnosed in SA

The above plot shows that the total number of cases remained low over time, showing seasonality over time until a significant increase was noticed between 2017 and 2018. This may suggest an epidemic occurred during that period. Imported cases were almost equal to the local cases during the years of peak infection 2017 and 2018, however, they were the majority contributor for all the other years. Based on the number of locally sourced cases, shown in solid blue imported cases were the majority contributor to the number of cases diagnosed in the country, except for 2015 and the last two peaks shown in the graph. This suggests that imported cases are a problem in the country. The proportions show that when there was an increase in the whole country, the majority contributor were local malaria cases which were approximately 80% of the total number of cases diagnosed. This may have resulted from several factors such as incorrectly recording of the source of infection, where is an imported case is recorded as a local case when is it a sourced case. These errors can occur when a SA resident travels, then gets tested in SA but do not report the correct source of infection when asked. Despite the possible errors in the data, we will interpret the numbers as they are presented.

Imported cases

Imported malaria cases have become a threat in South Africa (SA) as they contribute a significant number of cases in the country and they act as a reservoir to many regions in the country. These cases can occur in several ways. Firstly, when an infected individual enters

the country (SA) without getting tested or when the individual is still in the asymptomatic stage, and who later gets bitten by a mosquito which then bites another person or persons resulting in the person or persons getting infected. Secondly, when a person residing in SA visits another region outside of SA and then gets infected before returning to the country and ends up infecting persons in SA upon return.

Figure 3.2 shows the number of imported cases diagnosed in South Africa between 2010 and 2018. The plot shows that there was a rise in the number of imported cases at the end of each year. This rise is higher than of the locally sourced malaria cases. This suggests that there is correlation between the increase in imported cases and locally sourced cases. A rise in the number of imported cases result in an increase in local cases as shown in figure 3.1. This was motivated by the lag which appears between the local and imported peaks.

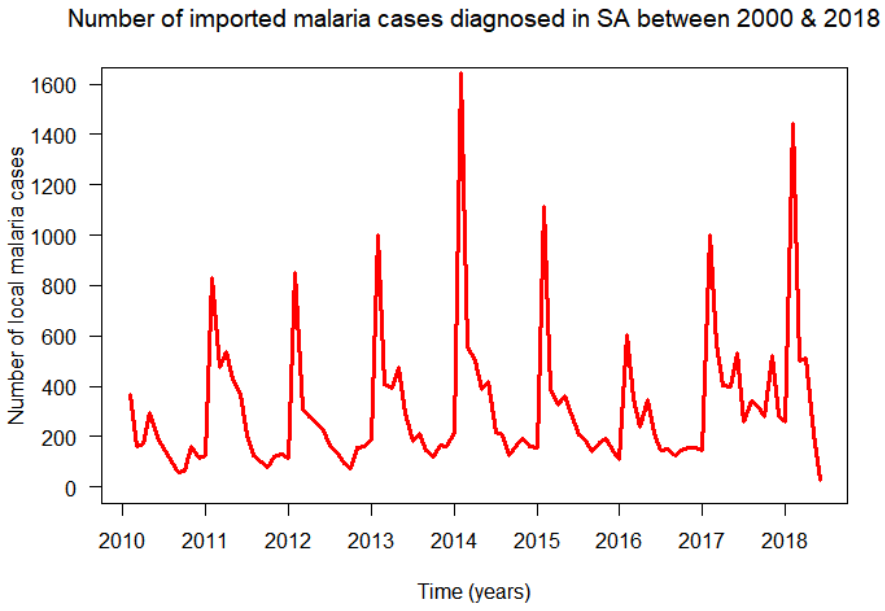


Figure 3.2: Imported cases diagnosed in SA

This plot also shows that imported cases contributes greatly to local cases as we can see that the number of sourced cases is way higher as compared to local sourced cases. This supports the hypothesis made that without imported cases, the goal of eliminating malaria in the country would easier to achieve. Although these numbers are much lower than cases diagnosed in the neighbouring countries (mostly Mozambique), these cases are high given that there are controls in place to prevent imported cases from entering the countries.

Malaria in KwaZulu Natal

Malaria Cases diagnosed in the whole of the KZN province

The KwaZulu Natal (KZN) province is the front runner for malaria elimination in South Africa. It accounts for a small proportion of the total number of malaria cases diagnosed in the whole country in recent times. Figure 3.3 shows the number of deaths (solid blue), severe cases (dashed blue) and malaria incidence (solid red) reported in the KwaZulu Natal province (KZN) between the years 2010 and 2018. The plot shows that the reported cases remained low between 2012 and the beginning of 2017 inclusively until a significant increase was noticed in the middle of 2017 and 2018. The rise in the number of KZN local cases seem to be proportional to the total number of imported cases diagnosed in the country as shown in Figure 3.2. Based on the plot, there is a lag between imported and local cases, suggesting that the rise of local incidence resulted from an increase in the number of imported cases. This then suggests that imported cases play a big role in the local incidence and without them, it seems safe to assume KZN would be able to eliminate malaria.

The plot (Figure 3.2) also shows that there were very few malaria death-related cases reported in KZN between 2010 and 2018. This demonstrates that malaria is manageable with existing interventions and controls in the province. As a result of data unavailability, the graph only illustrates severe malaria cases reported between 2015 and 2018. The data shows a constant behaviour in the number of malaria cases reported over time, except for a spike in 2014 and 2015 and an even larger spike in 2018 in both complicated (severe) and uncomplicated (symptoms show after 7-10 days after mosquito bite) cases. The malaria incidence and death behaviour are seasonal.

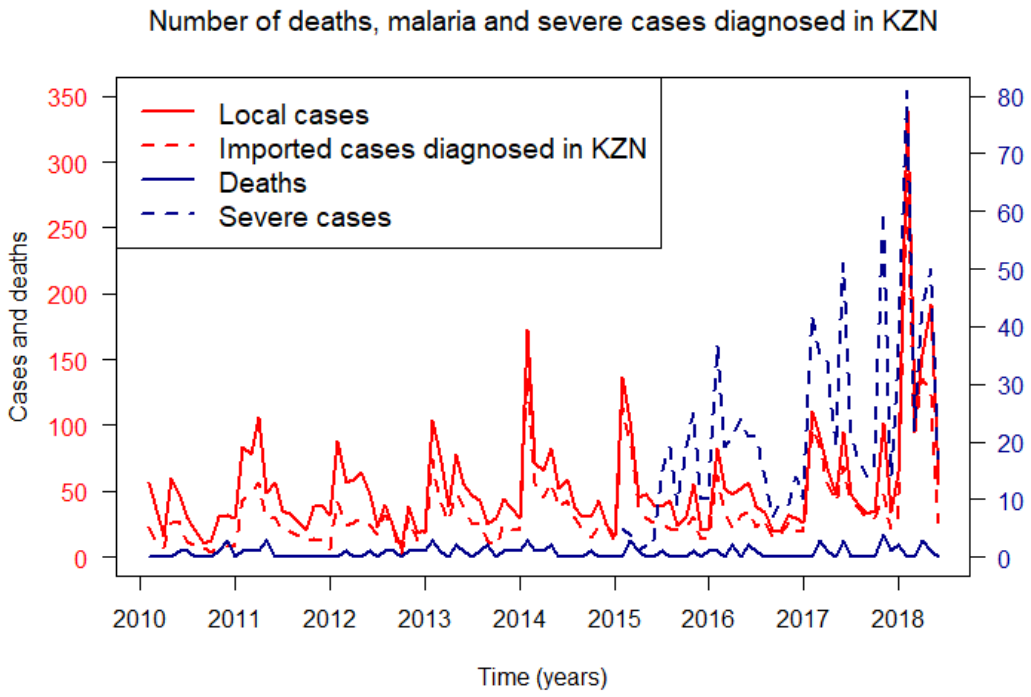


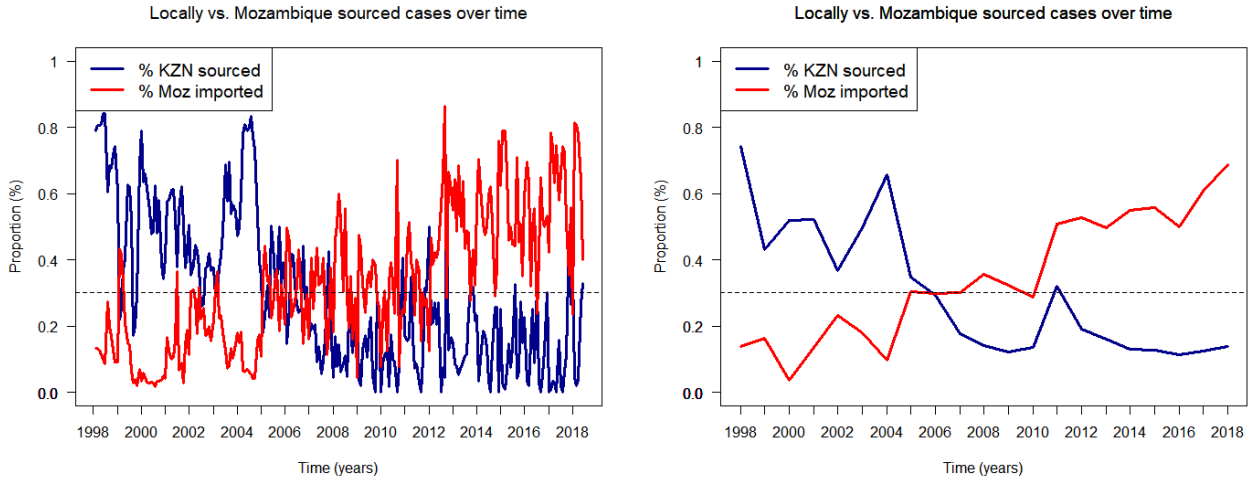
Figure 3.3: Malaria cases diagnosed in KZN

Based on the results shown in figures 3.2 and 3.3, similar patterns exist between imported and local cases, which indicate that imported cases have had a negative impact on local cases. By this is meant that when the other countries experience an increase in the number of malaria cases, the province realizes a rise in its incidence. It is important to note that most of Mozambique sourced cases diagnosed in the whole province were detected in Durban.

Imported cases sourced from the malaria-endemic regions outside of KZN are known to be the main source/contributor that drives infection in the province. These cases are known to have been sourced from malaria-endemic provinces within South Africa and International African countries, with the majority sourced from Mozambique. Figures 3.2 and 3.3 study the relationship between the locally sourced and imported cases to understand the impact of imported cases over time, mainly focusing on how local and imported cases have contributed to the total number of cases diagnosed in KZN.

The plot shows that in the late 90s and early 2000s, local cases were the majority contributor to the total number of malaria cases reported in KwaZulu Natal. They accounted for approximately 74% in 1998 and this number decreased overtime to 13% in the year 2018. This shows that when the number of locally transmitted cases drop, the number cases is expected to be significantly low (approximately zero) that transmission may even be considered eliminated. This also suggests that if we continue with the same control or put more effort, malaria transmission will be eliminated, more so if imported cases has dropped or prevented early.

Figures 3.4a and 3.4b illustrate the proportion contributed by both KZN local cases and imported cases from Mozambique diagnosed in KZN. It shows that about 20 years ago, locally sourced cases were the biggest contributor to the KZN malaria incidence. This number continued to drop over the years. By the beginning of 2018, the number had dropped by approximately 60%. In 2018, Mozambique imported cases had contributed about 70% to the total number of local cases. Based on the behaviour shown in the plot, it seems like this number will continue to rise in the future, meaning that Mozambique will be the main reservoir to the local cases. If this does not change, malaria elimination will be close to being impossible. The two subplots show the same thing; one shows the proportion contributed by local cases versus imported cases monthly and the other on an annual basis.



(a) Number of Locally vs. Mozambique sourced cases (Monthly)

(b) Number of Locally vs. Mozambique sourced cases (Yearly)

Figure 3.4: Distribution of local cases reported in KZN from January 2010-May 2018, grouped by method of detection, years and notification area for the top 5 localities)

Top 5 localities (2014 – 2018)

With malaria being a transmittable disease, the transmission rate in different areas depending on the location of the area in endemic areas, availability of preventative measures, how endemic the region is, etc.). It then makes sense that some localities in KwaZulu Natal will have more malaria cases than others. Below is a table that illustrates the top 5 localities reported with the highest number of local malaria cases reported between the years 2010 and 2018. The localities are Shemula (8.1%), Ndumo (7.9%), Mamfene (7.6%), Magwangwa (4.6%) and Othobothini (4.6%). The order ranks from the largest number of local malaria cases reported between 2014 and 2018 to the least number of cases reported. It also reports the total number of cases reported in the 5 localities within the period of 2010-2018 and 2014-2018, where the total number of cases includes imported cases sourced from other malaria-endemic international countries and

South African provinces.

Localities	**Total cases**		**Local cases**	
	2010-2018	2014-2018	2010-2018	2014-2018
Shemula	66	47	46	32
Ndumo	101	67	50	31
Mamfene	75	55	44	30
Magwanga	28	21	25	19
Othobothini	43	36	20	18

Table 3.1: Top 5 localities: Number of cases reported in the top 2010 to 2018, grouped by year and area

Based on the results, the province is very close to elimination given that the more endemic localities were reported with only an average of 37 local cases within a period of 7 years and 5 months. Out of the top 5 localities, 4 are located in the uMhlabuyalingana local municipality of uMkhanyakude district and has the highest number of cases in the province while the fifth, Othobothini is located in Jozini local municipality. All 5 localities are located along the Mozambique border. Overall, the 5 localities accounted for about 33% of the total local cases diagnosed in KZN.

Figure 3.5 shows the malaria incidence (red) and the number of malaria-related deaths (dark blue) reported in the top 5 localities. It shows that Shemula, Ndumo, and Othobothini localities did not report any deaths due to malaria during this period and very few deaths for the other 2 localities (Ndumo and Mamfene). Based on the plot, there were very few malaria death-related cases in the province between 2010. It also shows that malaria incidence was also low over the years, up until recent years where there was a rise in cases. This increase was not big given that the highest number reported was 14 cases. These results show that malaria incidence in the province is very low.

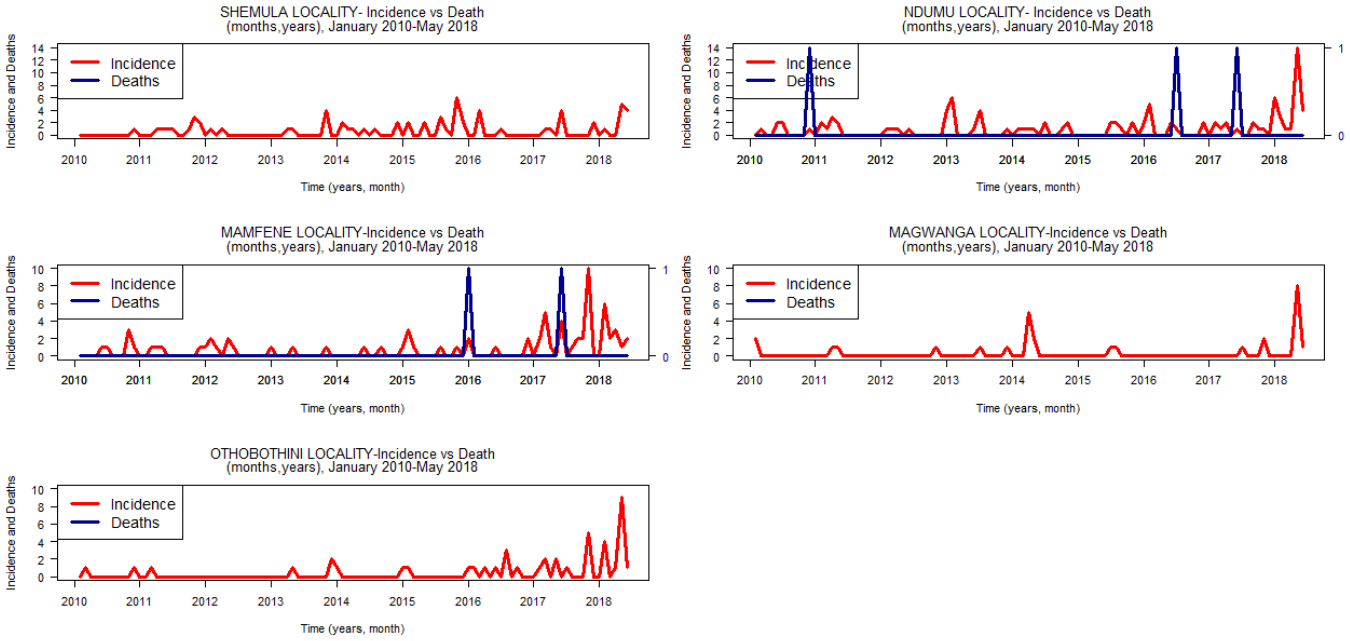
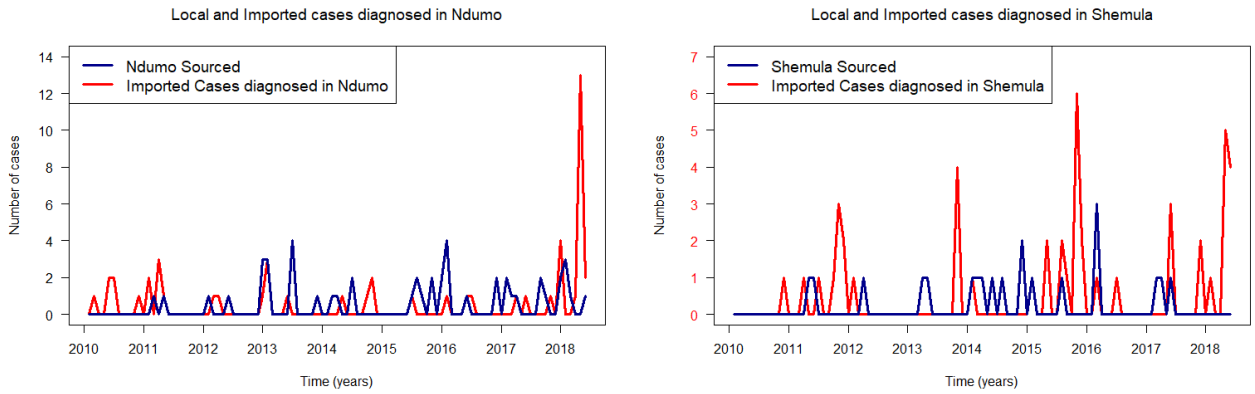


Figure 3.5: Deaths and incidence reported in the top 5 localities between 2010 and 2018

Ndumo and Shemula localities

Based on the above sub section, Ndumo and Shemula localities were the most malaria endemic areas in the province, accounting for approximately 16% of the total number of locally sourced cases between 2014 and 2018. The highest number reported during this period was 13 cases in both localities.

In this section, we aim at evaluating the two localities to better understand how malaria cases changed over time, focusing on both local and imported malaria cases. Figure 3.6a observes the number of locally sourced and imported cases diagnosed in Ndumo localities between 2010 and 2018. The plot shows that the number of local and sourced cases remained low between 2010 and towards the end of February 2018 until a sudden increase occurred in March 2018. Based on these results, imported cases seem to have had an indirect impact on several local cases since the increase was only realised on local cases. This indirect impact may have resulted from the free movement between regions (i.e. no borders: SA residents being allowed to move any were in the country. An example could be citizens seeking resources from other nearby areas). It is worth taking this factor into account since we are studying small populations. The majority of cases diagnosed in KZN were diagnosed in Durban, one of the biggest and busiest cities in the province. Since people move between regions, individuals residing in Ndumo could have contracted malaria during a visit to the city or other areas, and since an individual is diagnosed in Ndumo, it may be assumed the cases are local whereas it is imported cases.



(a) Number of malaria cases diagnosed in Ndumo (b) Number of malaria cases diagnosed in Shemula locality

Figure 3.6: Number of malaria cases at a locality level (Ndumo and Shemula)

Figure 3.6 illustrates the number of malaria cases reported in Shemula between 2010 and 2018. It shows that malaria cases reported in Shemula remained low with no dramatic increase over time, including sourced cases from other areas diagnosed in the locality. This suggests that the controls used to maintain low malaria incidence in the locality are effective, although it seems difficult to eliminate malaria (0 cases). It also suggests that there may be a gap in the controls which still introduces new cases. This may require an evaluation of the controls to understand why malaria cases still exist. This is even more important to look at, given that the most effective intervention, Indoor Residual Spraying (IRS) is employed in the localities and that its coverage is almost at its maximum (100%). Figure 3.7 shows the Ndumo and Shemula's IRS coverage over time. It shows that the Ndumo's coverage was approximately 100% during all spraying seasons, except for the year 2016 when the spraying coverage was reduced. By the end of the period we are focusing on, the coverage had gone back to 100%. On the other hand, the Shemula spraying coverage remained high throughout the whole period. It is worth noting that coverage between 2010 and 2012 remained at 0%. This might not mean that spraying did not occur during that period but rather missing data.

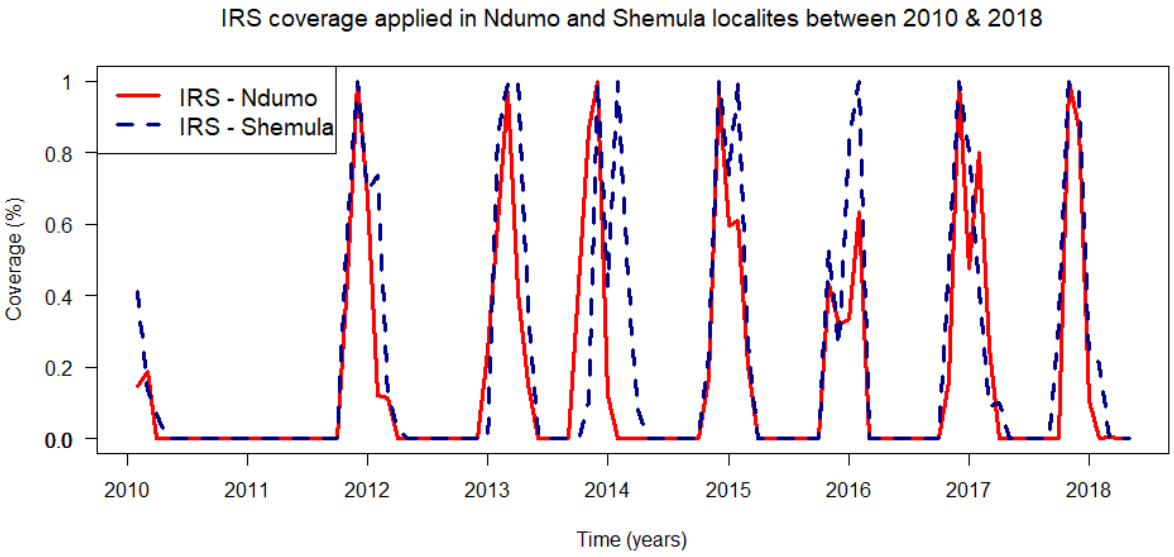


Figure 3.7: IRS coverage - Ndumo and Shemula

Data analysis summary

- This chapter analyses malaria dynamics in the KwaZulu Natal province between 2010 and 2018 to better understand the transmission in the 5 localities with the highest local malaria cases
- According to the data, most of the cases detected in KZN are imported cases from other areas outside of KZN. As malaria needs a reservoir of infection for transmission to persist, imported infections are contributing to the spread of local malaria.
- Malaria incidence in KZN is dispersed along the border, with few localities with local transmission.
- There have been very few imported cases that were detected reactively, though several were detected pro-actively. This suggests that many imported infections may be asymptomatic. Therefore, the infected do not feel sick and do not seek treatment, and therefore unknowingly contribute to the infectious reservoir. These may be the key drivers to why local infection persists in KZN.
- As can be seen from the Figures above, we have a seasonal pattern in the five localities though the peak of the season can be seen to occur at different times. A possible reason for this includes proximity to a national border or a large percentage of imported infections driving the local transmission.

Chapter 4

Dynamic Compartmental Model

The model is a deterministic non-linear differential equation representing the dynamics of the human population. We aim at employing this model to simulate malaria transmission in the top 2 malaria-endemic localities in KwaZulu Natal, Ndumo, and Shemula.

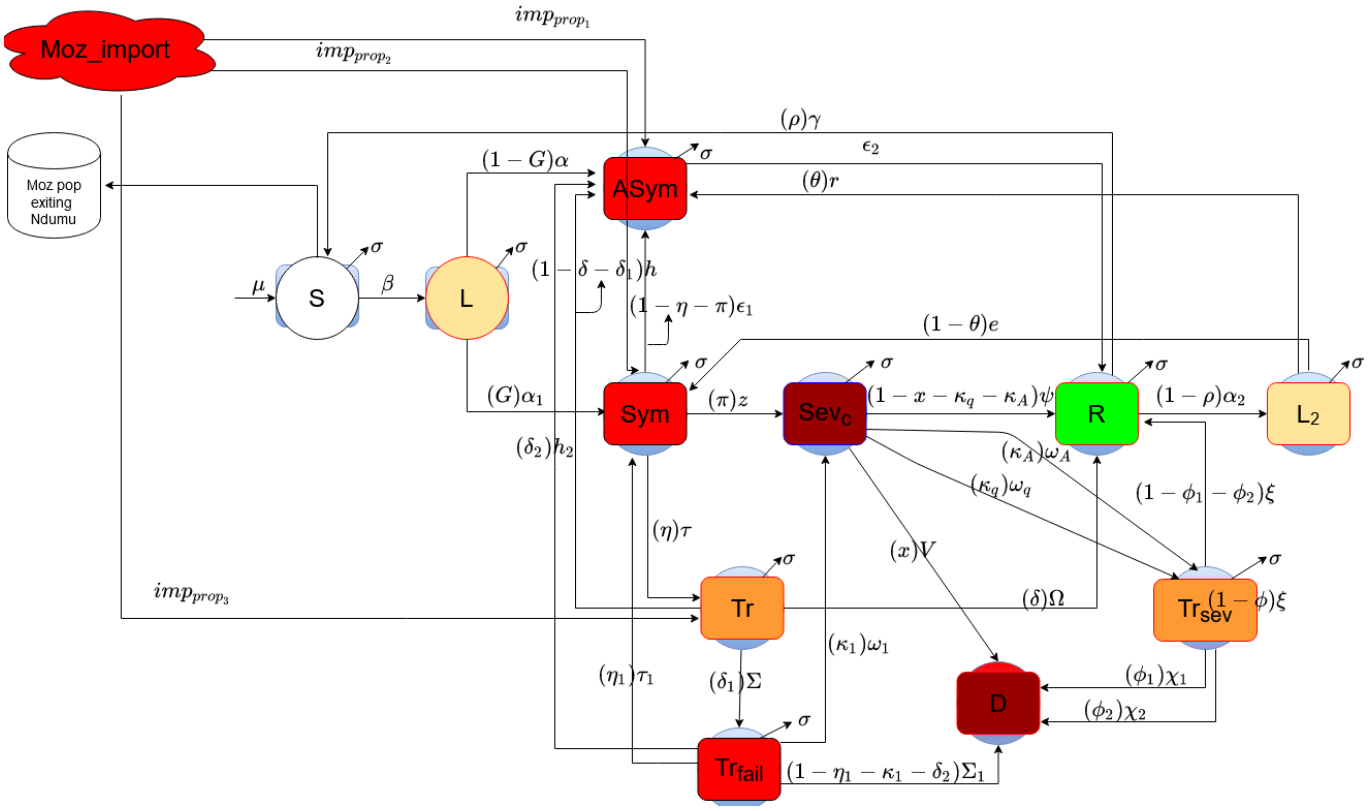


Figure 4.1: Model

The total population $N_n(t)$ is subdivided into distinct classes or compartments, for the infection and treatment stages. Each compartment is characterised by a heterogeneous mixing of individuals within it, while there is a homogeneous interaction of individuals between the

non-intersecting classes. Thus, each susceptible individual is assumed to have an equal chance of being infected by an infectious individual.

Formulation

The diagrammatic structure in Figure 4.1 represents a 13 compartmental dynamical system which is also represented by a set of Ordinary Differential Equations (ODE) with assumptions and determined parameters from previous studies and some estimated from collected data.

Model equations

The dynamical system described in Figure 4.1 is represented by the following ODE equations.

$$\frac{dS}{dt} = \left(\frac{1}{L_n}\right).N_n + (\gamma).\rho.R - \lambda_n.S - \left(\frac{1}{L_n}\right).S$$

$$\frac{dL}{dt} = \lambda_n.S - (1-G).\alpha.L - (G).\alpha_1.L - \left(\frac{1}{L_n}\right).L$$

$$\frac{dASym}{dt} = (1-G).\alpha.L + (\delta_2).h_2.Tr_{fail} + (1-\eta-\pi).\epsilon_1.Sym + (1-\delta-\delta_1).h.Tr + (\theta).r.L_2 - \epsilon_2.ASym - \left(\frac{1}{L_n}\right).ASym$$

$$\frac{dSym}{dt} = (G).\alpha_1.L + (\eta_1).\tau_1.Tr_{fail} + (1-\theta).e.L_2 - \eta.\tau.Sym - (\pi).z.Sym - (1-\eta-\pi).\epsilon_1.Sym - \sigma.Sym$$

$$\frac{dSev_c}{dt} = (\pi).z.Sym + (\kappa_1).\omega_1.Tr.fail - (x).V.Sev_c - (\kappa_q).\omega_q.Sev_c - (\kappa_A).\omega_A.Sev_c - (1-x-\kappa_q-\kappa_A).\psi.Sev_c - \left(\frac{1}{L_n}\right)Sev_c$$

$$\frac{dTr}{dt} = (\eta).\tau.Sym - (\delta).\Omega.Tr - (\delta_1).\Sigma.Tr - (1-\delta-\delta_1).h.Tr - \left(\frac{1}{L_n}\right).Tr$$

$$\frac{dTr_{sev}}{dt} = (\kappa_q).\omega_q.Sev_c + (\kappa_A).\omega_A.Sev_c - (\phi).\chi.Tr_{sev} - (1-\phi).\xi.Tr_{sev} - \left(\frac{1}{L_n}\right).Tr_{sev}$$

$$\frac{dTr_{fail}}{dt} = (\delta_1).\Sigma.Tr - (\kappa_1).\omega_1.Tr_{fail} - (\eta_1).\tau_1.Tr_{fail} - (\delta_2).h_2.Tr_{fail} - (1-\eta-\kappa_1-\delta_2).\Sigma_1.Tr_{fail} - \left(\frac{1}{L_n}\right).Tr_{fail}$$

$$\frac{dR}{dt} = (1-x-\kappa_q-\kappa_A).\psi.Sev_c + (\epsilon_2).ASym + (\delta).\Omega.Tr + (1-\phi).\xi.Tr_{sev} - (\rho).\gamma.R - (1-\rho).\alpha_2.R - \left(\frac{1}{L_n}\right).R$$

$$\frac{dL_2}{dt} = (1-\rho).\alpha_2.R - (1-\theta).e.L_2 - (\theta).r.L_2 - \left(\frac{1}{L_n}\right).L_2$$

$$\frac{dD}{dt} = (x).V.Sev_c + \phi.\chi.Tr_{sev} + (1-\eta-\kappa_1-\delta_2).\Sigma_1.Tr_{fail}$$

$$\frac{dCumInc}{dt} = \lambda_n.(S+R)$$

Where;

$$\lambda_n = (1 - IRS_{cov} * IRS_{eff}) .\beta_h.\beta_t. \left(\frac{ASym + Sym + Sev_c + Tr + Tr_{fail} + Tr_{sev}}{N_n} \right) \quad (4.1)$$

$\beta_t = \beta[amplit(1+cos(2\pi(t-\phi)))]$ is used as the seasonality function to simulate the model from 1950 to 1997 which assumes a periodic behaviour over time. The purpose of this was to stabilize the model before fitting it to the reported cases in the localities. Once the model has stabilized, we employ a rainfall driven model. This was achieved by standardising collected data from the two localities between 2010 and 2018 and employing a `spline` function build-in R to act as our seasonality function over time, with time and standardised rainfall data as arguments. The motive behind this was to make use of a factor that drives malaria in the localities to best mimic malaria incidence over time. Once the model has stabilized, this function acts as our seasonality function (β_t) from 2010. This was motivated by the similarities noticed between malaria incidence and rainfall in the localities, shown in Figure 5.7. The rainfall data is at a district level (uMkhanyakude district) as data at the locality level is unavailable. This then acts as a proxy of rainfall data to each locality, since rainfall in a district level is not far off to a locality level.

With regards to imported cases, we initially assumed that the proportion of imported cases are divided into the following buckets;

- 10% are untreated asymptomatic individuals that enter the locality,
- 40% are untreated Symptomatic individuals and
- 50% are treated individuals.

Model Variable definitions

The compartments includes:

Variable	Description
S	Susceptible population, individuals that are still naive to malaria.
L	Liver stage after infection for naive individuals
$ASym$	Asymptomatic stage
Sym	Clinical infection (Symptomatic)
Sev_c	Malaria severe stage
Tr	Population with clinical malaria in treatment (i.e. Coartem)
Tr_{sev}	Severe malaria population in treatment (i.e. Quinine or Artesunate)
Tr_{fail}	Asymptomatic population that failed treatment
R	Recovered population from malaria
L_2	Represents secondary infection liver stage
D	Malaria related deaths
Moz_{import}	Malaria cases sourced from Mozambique
$MozpopexitingNdumo$	The Mozambique population exiting the Ndumo locality

The total adult population at any given time t, is thus given by:

$$N_n = S + L + ASym + Sym + Sev_c + Tr + Tr_{sev} + Tr_{fail} + R + L_2 \tag{4.2}$$

Parameter Table

Parameter	Description	Value	Source
N_n	Locality population size	5631	[31]
L_n	Average life expectancy of the population	62	[37]
μ	Natural birth rate	$\frac{N_n}{L_n}$	Calculated from specified parameters
σ	Mortality rate	$\frac{1}{L_n}$	Calculated from specified parameters
β	Duration of the infection to the liver stage	2.5 days	Estimated from model fitting process
B_h	The transmission probability per contact from an infectious human to a susceptible mosquito	0.25%	Assumed
α	Rate of movement from the liver to Asymptomatic stage	7.5 days	[54]
α_1	Rate of movement from the Asexual to the Gametocyte stage stage	7 days	[46, 47]
G	Proportion of patients that move from the liver to the Symptomatic stage	90%	[49]
ϵ_1	Rate of movement from the liver stage to Symptomatic stage	0.7 weeks	[57]
π_i	Proportion of clinical infection that progresses to Severe malaria	$a_i * 0.125$	Derived from data
τ	Time to seek treatment for a patient in the Symptomatic stage	0.3 weeks	
η	Proportion of Symptomatic patients that receive treatment (Coartem)	70%	Derived from data
γ	Proportion of recovered individuals that become susceptible to malaria again	9.88%	[54]
ϵ_2	Rate of natural recovery to an Asymptomatic patients	26 weeks	[55]
z	Rate of movement from the Symptomatic to the Asymptomatic stage	10 days	[10, 55]
ω_q	Time for a patient with severe malaria to be treated with Quinine	55 days	[27, 39]

Continued on next page

Table 4.1 – *Continued from previous page*

Parameter	Description	Value	Source
ω_A	Time for a patient with severe malaria to be treated with Artesunate	10 days	[27]
κ_{qi}	Proportion of patients with severe malaria treated with Quinine	$a_i * 0.8804$	Derived from data
κ_{Ai}	Proportion of patients with severe malaria that are treated with Artesunate	$a_i * 0.1194$	Derived from data
x_i	Proportion of patients with untreated severe malaria dying due to malaria	$a_i * 0.8$	Derived from data
V	Death rate for patients with untreated severe malaria	4.5 days	Estimated from model fitting process
ψ	Time taken by a severe malaria patient to recover naturally	26 weeks	[55]
η_1	Proportion of patients that failed treatment moving back to the Symptomatic stage	70%	Estimated from model fitting process
Σ	Duration of treatment (Coartem) failure	8 days	Estimated from model fitting process
δ	Proportion of patients that recover from treatment (Coartem)	96%	Derived from data
δ_1	Proportion of patients who were treated with Coartem that became Asymptomatic	5%	[51]
ω_1	Rate of movement for patients that failed treatment which progresses to the severe stage	4 days	Estimated from model fitting process
κ_1	Proportion of patients that failed treatment that progress to the severe stage	12.5%	Derived from data
Ω	Recovery of recovery from treatment (Coartem)	7 days	
h	Rate of movement for patients under treatment (Coartem) moving to the Asymptomatic stage	18 days	
ρ	Duration of clinical immunity	5 years	[25]
χ_1	Time taken for a patient with severe malaria under treatment (Quinine) to die of malaria	5 weeks	Estimated from model fitting process
χ_2	Time taken for a patient with severe malaria under treatment (IV Artesunate) to die of malaria	6 weeks	Estimated from model fitting process

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Table 4.1 – *Continued from previous page*

Parameter	Description	Value	Source
ϕ_1	Probability that treated severe malaria progresses to death (Quinine)	22%	[**?** 43, 44]
ϕ_2	Probability that treated severe malaria progresses to death (IV artesunate)	15%	[**?** 43, 44]
ξ	Recovery rate for patients with severe malaria under treatment	55 days	[27, 39]
α_2	Probability of a secondary mosquito bite	22.22%	
θ	Proportion of patients that disease recurrence moving from the liver to the asymptomatic stage	90%	[56]
r	Rate at which patients that are having malaria again move back to the Asymptomatic stage (from liver stage)	19 days	Estimated from model fitting process
e	Rate at which patients that are having malaria again move back to the clinical stage (from liver stage)	18 days	Estimated from model fitting process
h_2	Rate of movement for patients that failed treatment (Coartem) move back to the Asymptomatic stage	70 days	Estimated from model fitting process
δ_2	Proportion of patients that failed treatment move back to the Asymptomatic stage	17.5%	Derived from data
Σ_1	Time taken for a patients that failed treatment to die of malaria	28 days	
IRS_{eff}	Indoor Residual Spraying (IRS) efficacy	38%	[51]
$amplit$	Amplitude of seasonal variation	2.7 na	Fitted by model
Imp_{prop_1}	Proportion of Asymptomatic patients that moved to Ndumo from Mozambique 1998-2018	10%	Derived from data
Imp_{prop_2}	Proportion of Symptomatic patients that moved to Ndumo from Mozambique 1998-2018	40%	Derived from data
Imp_{prop_3}	Proportion of Symptomatic patients on treatment that moved to Ndumo from Mozambique 1998-2018	50%	Derived from data

$\texttt{i} = \{1, 2, 3, 4\}$ `where` $1 = 1998 - 2007, 2 = 2008 - 2015, 3 = 2016 - 2018(3), 4 = 1988 - 1997$
The rate of movement for patients under treatment (Coartem) the asymptomatic stage, where a patient is from a treatment stage to not showing any signs of malaria is also incorporated in the model. This instance could be a case where a patient stops taking treatment before the pathogens clears up.

Model Building

There have been several studies done which aimed at finding the best strategies to help reduce and even eliminate the deadly disease that is malaria which have claimed people′s lives for years. These studies have found that malaria is dependent on several factors including environmental factors [51, 64]. Factors that have shown to have a greater impact and thus labelled as the main drivers of malaria transmission are temperature, rainfall, and imported cases. Studies suggest that malaria can be managed by having control measures available to reduce transmission. In this study, we aim at building a tool that can help in finding the best solution in treating malaria towards its elimination in Ndumo and Shemula localities in KZN by making use of previous studies and data. The model uses a combination of both parameters from previously published sources and parameters estimated from the model. It aims at mimicking the malaria cases reported in the locality to predict future malaria cases still to occur. The model incorporates factors such as rainfall, IRS coverage, treatment coverage, and imported malaria cases. We employed a parameter estimation technique to estimate the unknown parameter. The technique aimed at obtaining the most suitable parameters that would ensure coherence between model output and clinically observed data through modelling simulation. Even though many of the parameter values are clinically or experimentally estimated, the unknown parameters were obtained by fitting the model to real data, by employing scientific packages, built-in **R**. These packages are:

- the `deSolve` is for solving the initial value problems (IVP) of ordinary differential equations (ODE), differential algebraic equations (DAE), partial differential equations (PDE) and delay differential equations (DeDE). The system of differential equations is written as a function. The solvers may be used as part of a modeling package for differential equations, or for parameter estimation using any appropriate modelling tool for non-linear models in **R** such as the `optim` function. This is a package used to model a compartmental model over time.

- the `maxLik` which comprises a set of convenience tools and wrappers focusing on Maximum Likelihood (ML) analysis, and other optimization tasks, offering easy access to likelihood-specific features like standard errors or information matrix equality. It also comprises utilities that extract standard errors from the estimates. The package is used for model fitting purposes,

- the `bbmle` which is designed to simplify maximum likelihood estimation and analysis in **R**, extends and modifies the `mle` function and class in the `stats4` package that comes with **R** by default.

The model was simulated using several assumed parameters, within realistic biological and epidemiological ranges. We restricted our simulation to the particular incidence of malaria in the two malaria-endemic localities in KZN, for which some parameters are known. IThe parameters include demographic parameters such as: μ, σ and β. The model was ran on date from 1950 to reach a steady-state before being fitted to data from 2010. The model with the estimated parameter values is then run for a further three years to be further validated by comparison to data between 2018 and 2020.

Model assumptions

Several assumptions were made in the model:

- The liver stage of the infection acts as a delay in the flow between the susceptible and blood-stage compartments.
- An asymptomatic case while infectious, does not seek treatment but will just recover at an assumed recovery rate.
- With KZN being a low transmission environment, immunity and super-infection are rare and are excluded from the model.
- The types of imported cases that were detected or reported in the localities are untreated (asymptomatic and symptomatic) and treated infected cases. This assumption is based on the fact that asymptomatic travellers do not feel sick and will not seek treatment. Additionally symptomatic travellers may not always have access to or feel comfortable to make use of public health facilities owing to xenophobia/illegal travel status. Since we are interested in malaria, we disregarding malaria-free individuals entering the locality as they do not possess any threats.
- Although the seasonal nature of transmission is incorporated in the model, the mosquito population is not modelled directly as it is assumed that the mosquito dynamics operate on a faster time-scale than the human dynamics and as such, the mosquito population can be considered to be at equilibrium concerning changes in the human population.

Assumptions made about the model parameters:

- With rainfall being one of the main drivers of the mosquito population, we have allowed rainfall to be the driver of infection in the model over time as a mosquito would have to bite a human for a case to occur. This was further supported by observed rainfall data that shows that there is volatility in the reported number of cases which mimics the volatility in rainfall (i.e. an increase in rainfall leads to an increase in the reported

number of cases and vice versa, with a lag). We have therefore allowed the two localities past rainfall data to be our seasonality function. The relationship is shown in Figure 5.7. This is at a district-level data. The data was supplied by the department of health, SA.

- Treatment coverages; for both severe and clinical malaria cases are fixed over three different periods, with each coverage fixed for a period of time (years). We assumed that symptomatic and severe cases had the same treatment coverage for all three periods. Figures aligning these assumptions are as follow: The coverages prior 2010, between 2010 & 2016 and post 2016 are assumed to be 60%, 80% and 95% respectively. This assumes that the treatment coverages were kept constant during these periods, regardless of the disease level in the different areas within the two localities. The data was supplied by the department of health, SA.

- The assumptions made about treatment in the model are based on existing and used treatment types, Coartem, Artesunate and Quinine. Coartem is used to treat symptomatic patients whereas Artesunate and Quinine treat severe cases.

- The Indoor Residual Spraying (IRS) efficacy has been kept constant at 38% (provided by an expect) for the whole period.

- We have assumed that only patients that die due to malaria are patients with severe malaria, who are either on treatment, not on treatment, or patients who have failed treatment. The fatality rates are assumed to vary over time.

- Patients who have had malaria before cannot be susceptible but will be on the second kind of the liver stage (i.e. Stage L_2 on Figure 4.1). This then means patients with the second infection can only move from liver stage to either being symptomatic or asymptomatic. At this stage, patients are assumed to have immunity.

- Since the KwaZulu Natal province has effective controls available, a higher malaria intervention coverage, and a high detection rate to reduce malaria transmission as compared to Mpumalanga and Limpopo, we have assumed that reporting rate to be 100%.

- Figure 5.7 illustrates the relationship between Rainfall recorded in Ndumo locality and malaria incidence reported in Ndumo and Shemula localities between 2010 and 2018. The purpose of this graph is to illustrate the similar behaviour between the rainfall and incidence in the localities. This association suggests that the mosquito population increases when there are large pools of water available for mosquitoes to breed, which then leads to malaria incidence increasing. The opposite applies when there is very little or no rainfall available. Given that other factors play a role in the change in the number

of cases recorded every year, we have also included other factors such as interventions, importation, etc.

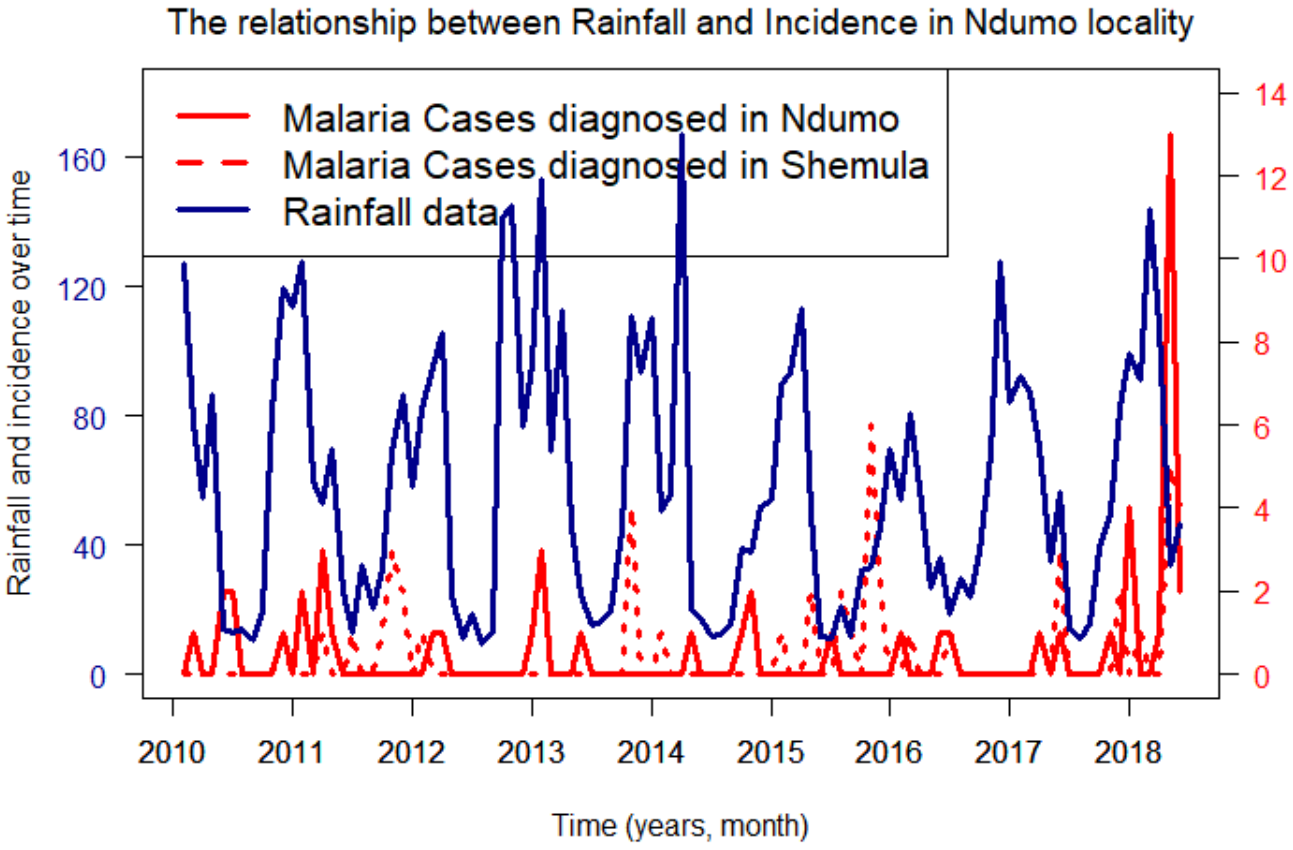

Figure 4.2: Relationship between cases reported in Ndumo, Shemula and rainfall recorded overtime

Transmission Model

This chapter aims at demonstrating the results produced from the malaria transmission model described in Chapter 4. The model assumes that the individuals within each compartment in the two populations have a homogenous behaviour. Imported malaria from neighbouring countries and localities are incorporated into the model. This is important as imported cases comprise a large proportion of reported cases. The model is built to model the two localities namely, Ndumo and Shemula, respectively. These two localities are the top 2 localities in KZN which were reported with the highest number of cases between 2014 and 2018. The model is developed for both localities with each divided into 13 compartments representing the different stages individual(s) would go through during the stages of an infection. The stages includes stages such as an individual(s) that is susceptible (S) to malaria, liver stages (L), treatment stages (Tr, Tr_{fail}) etc (please refer to Figure 4.1). As much as the behaviour between the two

localities is very closely related since they are very close to each other, the model parameters are different. However, some parameters used are assumed to be the same because of data unavailable such as rainfall which is available at district level but not at a locality level.

To mimic the seasonality behaviour that shows in the reported malaria cases in both localities, we have used a `cos` function in the model which assumes fixed and unfixed parameters for the purposes of stabilizing the model before the model simulation starts. This was done to allow the model to reach a steady-state, where the model stabilizes. As a result of our data being available as of the beginning of 1998, we started our simulation from 1998 to 2018. After the model had stabilized, we used available data for the main factors that drive malaria infection which incorporates Indoor Residual Spraying, imported cases, rainfall, and malaria treatment. It is crucial to include such factors as there is a directly proportional relationship between malaria cases and interventions used to reduce the number of cases.

The model illustrated in Figure 4.1 is built to model different compartments that represent population sizes for the different model is the force of infection, which is the rate at which susceptible individuals acquire malaria. In our model, we have formulate malaria stages that occur over time. A key component of the transmissiond the force of infection for 2 time periods, before and after 1998. The force of infection function is presented as β_t. Before 1998 we used the `cos` function to achieve the malaria seasonality depicted by the malaria incidence. The seasonal function is represented as follow:

$$\beta_t = \beta[amplit(1 + cos(2\pi(t - \phi)))]$$

and as of January 1998, we fitted a cubic smoothing spline (i.e. `spline()` function in `R`) to the standardized rainfall data using a Maximum Likelihood approach. Based on how rainfall behaved in the district the 2 localities are located in, we have used the UmKhanyakude district rainfall as the seasonality function for both localities. The parameter λ_n (see Equation 4.1) which represent the force of infection is estimated through the data fitting process with initial values from previously published sources. Therefore, rainfall acts as a seasonal function in the model for both localities. See Chapter 4 for more information.

Chapter 5

Results

Background

The KwaZulu Natal (KZN) province has been for more than a decade a front runner to malaria elimination, with the fewest malaria cases reported in the 3 malaria-endemic province in South Africa. Within KZN, Ndumo and Shemula localities ranked the highest number of cases between 2014 and 2018 which makes them the top 2 localities in the province. Both these localities are located in the uMhlabuyalingana municipality which is located in the uMkhanyakude district. uMkhanyakude district is located along the borders of the most malaria prevalent countries, eSwatini and Mozambique. The objective of this chapter is demonstrate the model illustrated in figure 4.1 that is fitted to the top-ranked localities in the province. We were aiming at fitting a model to the data for the 2 localities with fixed and estimated parameters. The goal was to fit a model to the data that we could use in the future to assist in finding the best strategies to eliminate malaria in the 2 localities and the province as a whole.

Data fitting

The model is fitted to monthly treated case data from January 2010 to March 2018, and validated with data from April 2018 to June 2020. The data was provided by the department of health and the ethical approval was obtained.

Ndumo locality

Ndumo locality reported the highest number of malaria cases between 2014 and 2018. Although this locality had the highest number of cases, the number of cases remained low over the years, with a maximum of 13 malaria cases reported in March 2018.
The table showing all the parameters fitted by the model, with their corresponding simulated

interval, the range at which the parameter can vary during simulation. The confidence bands represent the interval within which a model parameter value can vary without the model returning unrealistic values.

Parameter	Description	Value	Sim interval
B_h	The transmission probability per contact from an infectious human to a susceptible mosquito	9.65%	$[5.3\%, 14.0\%]$
G	Proportion of patience that move from the liver to the Symptomatic stage	67.24%	$[40.3\%, 94.1\%]$
ϵ_1	Rate of movement from the liver stage to Symptomatic stage	0.14 weeks	$[306.5, 459.7]$
π_1	Proportion of clinical infection that progresses to Severe malaria (1998-2007)	0%	$[0.0\%, 0.0\%$
π_2	Proportion of clinical infection that progresses to Severe malaria (2008-2015)	11.93%	$[9.5\%, 14.3\%]$
π_3	Proportion of clinical infection that progresses to Severe malaria (2016-2018(3))	2.65%	$[2.1\%, 3.2\%]$
π_4	Proportion of clinical infection that progresses to Severe malaria (1988-1997)	99.92%	$[99.9\%, 99.9\%]$
η	Proportion of Symptomatic patience that receive treatment (Coartem)	91.4%	$[82.3\%, 100\%]$
γ	Proportion of recovered individuals that become susceptible to malaria again	1.33%	$[0.7\%, 1.9\%]$
ϵ_2	Rate of natural recovery to an Asymptomatic patients	1.05 weeks	$[1.05, 1.05]$
z	Rate of movement from the Symptomatic to the Asymptomatic stage	2.5 days	$[117.7, 176.5]$
ω_q	Time for a patient with severe malaria to be treated with Quinine	8.68 days	$[42.1, 42.1]$
ω_A	Time for a patient with severe malaria to be treated with Artesunate	1.27 days	$[287.1, 287.1]$
κ_{q1}	Proportion of patients with severe malaria treated with Quinine(1998-2007)	15.19%	$[8.4\%, 22.0\%]$
κ_{q2}	Proportion of patients with severe malaria treated with Quinine (2008-2015)	72.55%	$[72.3\%, 72.3\%]$

Continued on next page

Table 5.1 – *Continued from previous page*

Parameter	Description	Value	Sim interval
κ_{q3}	Proportion of patients with severe malaria treated with Quinine(2016-2018(3))	98.59%	[97.6%, 97.6%]
κ_{q4}	Proportion of patients with severe malaria treated with Quinine(1988-1997)	0.47%	[0.3%, 0.67%]
κ_{A1}	Proportion of patients with severe malaria treated with Artesunate (1998-2007)	24.42%	[13.4%, 35.4%]
κ_{A2}	Proportion of patients with severe malaria treated with Artesunate (2008-2015)	16.10%	[8.9%, 23.3%]
κ_{A3}	Proportion of patients with severe malaria treated with Artesunate (2016-2018(3))	7.29%	[7.3%, 7.3%]
κ_{A4}	Proportion of patients with severe malaria treated with Artesunate (1988-1997)	0.52%	[0.29%, 0.76%]
x_1	Proportion of patients with untreated severe malaria dying due to malaria (1998-2007)	69.30%	[55.2%, 83.2%]
x_2	Proportion of patients with untreated severe malaria dying due to malaria (2008-2015)	51.43%	[51.3%, 51.3%]
x_3	Proportion of patients with untreated severe malaria dying due to malaria (2016-2018(3))	25.80%	[25.1%, 25.1%]
x_4	Proportion of patients with untreated severe malaria dying due to malaria (1988-1997)	73.99%	[59.2%, 88.8%]
V	Death rate for patients with untreated severe malaria	6 days	[59.9, 59.9]
ψ	Time taken by a severe malaria patient to recover naturally	0.2 weeks	[253.7, 253.7]
τ_1	Rate of movement for patients that failed treatment moving to the Symptomatic stage	94.23 days	[95.3, 251.3]
η_1	Proportion of patients that failed treatment moving back to the Symptomatic stage	91.14%	[82.3%, 100%]
Σ	Duration of treatment (Cortem) failure	2.96 days	[67.8, 178.8]
δ_1	Proportion of treated (Coartem) patients that become Asymptomatic again	3.20%	[2.6%, 3.8%]
ω_1	Rate of movement for patients that failed treatment that progresses to the severe stage	12 days	(16.7, 44.1)

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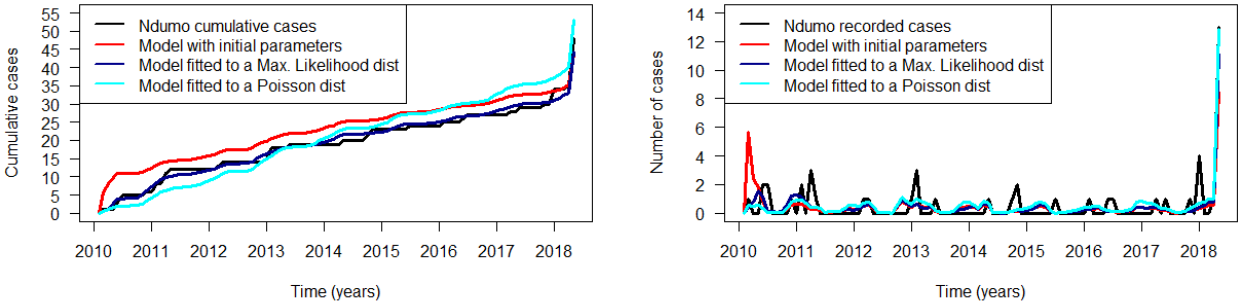
Table 5.1 – *Continued from previous page*

Parameter	Description	Value	Sim interval
κ_1	Proportion of patients that failed treatment that progress to the severe stage	10.45%	$[8.36\%, 12.5\%]$
Ω	Recovery of recovery from treatment (Coartem)	2.59 days	$[1.8, 4.7]$
h	Rate of movement for patients under treatment (Coartem) moving to the Asymptomatic stage	14.7 days	$[10.1, 26.7]$
ρ	Duration of clinical immunity	$\frac{1}{12.34}$ years	$\left[\frac{1}{10.3}, \frac{1}{15.4}\right]$
χ_1	Time taken for a patient with severe malaria under treatment (Quinine) to die of malaria	1.4 weeks	$[1.1, 1.7]$
χ_2	Time taken for a patient with severe malaria under treatment (IV Artesunate) to die of malaria	1.7 weeks	$(1.4, 2.0)$
ϕ_1	Probability that treated severe malaria progresses to death (Quinine)	3.84%	$[3.1\%, 4.6\%]$
ϕ_2	Probability that treated severe malaria progresses to death (IV artesunate)	3.69%	$[3.0\%, 4.4\%]$
ξ	Recovery rate for patients with severe malaria under treatment	192.49 days	$[132.8, 350.0]$
α_2	Duration before an individual gets a mosquito bite again	37.56%	$[30.1\%, 45.1]$
θ	Proportion of patients that get a recurrence of the disease moving from the liver to the clinical stage	99.03%	$[99.0\%, 99.0\%]$
r	Rate at which patients that are having malaria again move back to the Asymptomatic stage (from liver stage)	2.92 days	$[2.0, 5.3]$
e	Rate at which patients that are having malaria again move back to the clinical stage (from liver stage)	158.64 days	$[109.4, 288.4]$
h_2	Rate of movement for patients that failed treatment (Coartem) move back to the Asymptomatic stage	0.30 days	$[0.2, 0.6]$

Continued on next page

Table 5.1 – *Continued from previous page*

Parameter	Description	Value	Sim interval
δ_2	Proportion of patients that failed treatment move back to the Asymptomatic stage	0.6%	$[0.5\%, 0.7\%]$
Σ_1	Time taken for a patients that failed treatment to die of malaria	30.71	$[25.6, 38.4]$



(a) Malaria cummulative cases

(b) Monthly malaria cases

Figure 5.1: Reported malaria cases reported in Ndumo vs. fitted model

Figure 5.1 shows the mathematical model fitted to the number of malaria cases diagnosed in Ndumo locality between 2010 and 2018. The objective of this plot is to demonstrate the method that fits the model to the data best, between Maximum likelihood and Poisson distribution methods. The Maximum Likehood method is a "statistical technique which is aimed at estimating the parameters of a probability distribution by maximizing a likelihood function, so that under the assumed statistical model the observed data is most probable" [59]. The Poisson distribution fitting method is also a statistical method that "expresses the probability of a given number of events occurring in a fixed interval of time or space if these events occur with a known constant mean rate and independently of the time since the last event" [60]. The method is used to overlook the discrete cases that occur on a monthly basis.

Based on the results, the maximum likelihood method is the best fit for the model. We used the Akaike information criterion (AIC) [50] which estimates the likelihood of a model to predict and estimate the future values. It is an estimator of prediction error and thereby relative quality of statistical models for a given set of data. The AIC estimates the relative amount of information lost by a given model: the less information a model loses, the higher the quality of that model [58]. Because the AIC of the Maximum Likelihood method was lower than of the

Poisson method, it is the best method between the two (744.2 vs. 1750.4, respectively). The two plots illustrate the cumulative and monthly cases reported in the locality, respectively.

Through model fitting, the following fit represented by Figure 5.7 was achieved. The fit is an approximation of the reported Ndumo malaria cases. At the end of the period, the cases seem to have changed and an increase is realised. This could mean that one of the factors mentioned above has had a significant impact on the existing malaria cases reported. As much as the number of imported malaria cases reported in the locality remained low, a significant rise in the number of imported cases was noticed in KZN as a whole. It is worth noting that just because the majority of malaria cases were not diagnosed in the Ndumo locality, there could have been interactions between individuals from Ndumo locality and from surrounding areas that reported the highest number of imported cases. This could then mean that there was an issue with reporting.

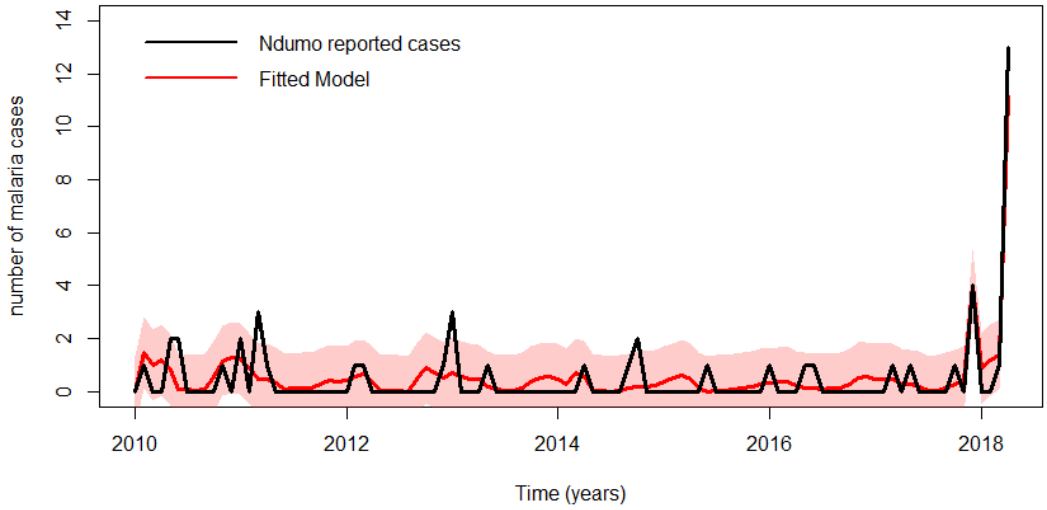


Figure 5.2: Mathematical model fitted to reported malaria cases in Ndumo locality between 2010 and 2018

With IRS being one of the most effective techniques used to prevent and reduce the malaria burden, it is worth analysing the behaviour as changes are expected to occur in the future. Figure 5.3 and Figure 5.4 explore these possible adjustments in malaria cases as the IRS coverages and its efficacy vary using the best-fitted parameter values. Figure 5.4 is a magnification of the plots in 5.3 covering the period from May 2018 to December 2022. Malaria elimination has been a long-lived dream in the country, hence we are very interested in understanding how much an increase in the IRS coverage will impact the local cases. Based on the calculations from the obtained data, the maximum reported IRS coverage was 62%. The plots in Figure 5.3 and Figure 5.4 show how malaria cases in the locality will change as the IRS coverage is

increased to 80% solid red and 100% dashed red, while keeping the IRS efficacy at the reported proportion of 38% during the spraying seasons. The model shows that there would be a reduction in the number of malaria cases if the coverage were increased to 80%. This is also the case when coverage is increased to 100% (meaning that all households are sprayed). However, the decrease is not substantial. This suggests that spraying more structures in the locality while everything else is kept constant will not help eliminate malaria but will help in reducing existing cases. Similarly, it would be interesting to see how the number of malaria cases would change if spraying no longer took place in the locality while everything else was kept the same. This is represented by the dotted red line in the plot. The plot shows that this would result in the number of cases rising. It suggests that there would be an insignificant rise in the local cases when the IRS coverage is low in the first few years but over time, it would be significant.

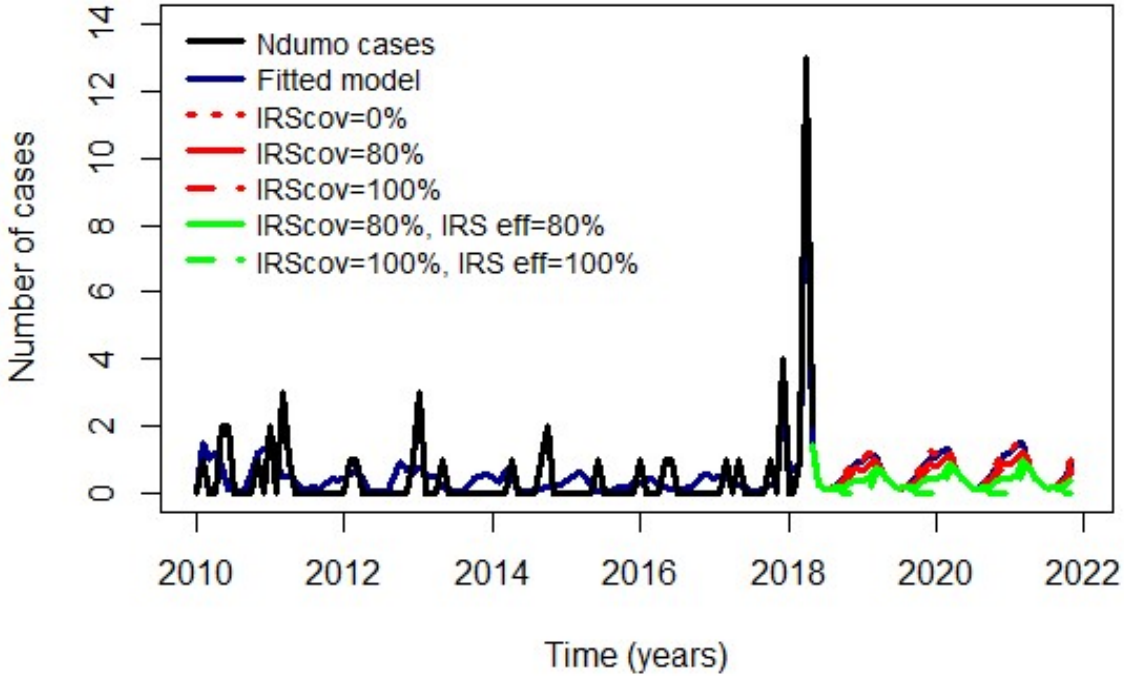


Figure 5.3: IRS scenario analysis

In the interest of seeing real change in the number of reported cases, we must carry out an analysis of the efficacy of the techniques employed to fight the malaria burden. Based on results, we can conclude that the impact made when the spraying coverage is increased whilst the other methods (including the efficacy not changing) remain the same, is somewhat redundant as it may result in wastage of resources. This is based on the fact that the change in the number of cases in the locality does not change even when the IRS coverage and its efficacy have increased. Therefore, we have also analysed the impact that would have been made when the IRS coverage would be kept at 80% while the efficacy is also fixed at 80% (represented by solid green). Note that in the dotted and solid red lines in the plot, the efficacy is kept at 385%. We also looked

at the case when the coverage is kept at 100% and efficacy is also kept at 100% (represented by dashed green) respectively. The model suggests that a big change would occur in the number of malaria cases when the coverage and efficacy would be increased at the same time. This shows that to achieve a significant reduction in the number of local malaria cases, we need to invest time and money in improving the IRS efficacy. The analysis showed that if we only invest in increasing the IRS coverage, we there will not be an impact made as the results showed that not much change would occur if the change is made to IRS coverage. This, of course, would not only happen with the IRS coverage, the other methods need more attention and to be reviewed further to understand how best we can use our intervention to manage low local cases and to reach the stage of elimination.

Overall, the number of malaria cases in the locality remained low. This shows that strategies used in the locality and the province as a whole have been effective in reducing the disease spread and local cases influenced by imported cases. However, we can see that if we were to keep our efforts the same over a long period we would either stand a chance of maintaining the existing malaria cases or risk an increase in the number of cases as the population will have low immunity. In that case, we need to find the best ways to use the strategy in which we would be able to maintain the existing cases or better still reduce cases without additional resources e.g. 100% IRS coverage and 100% efficacy.

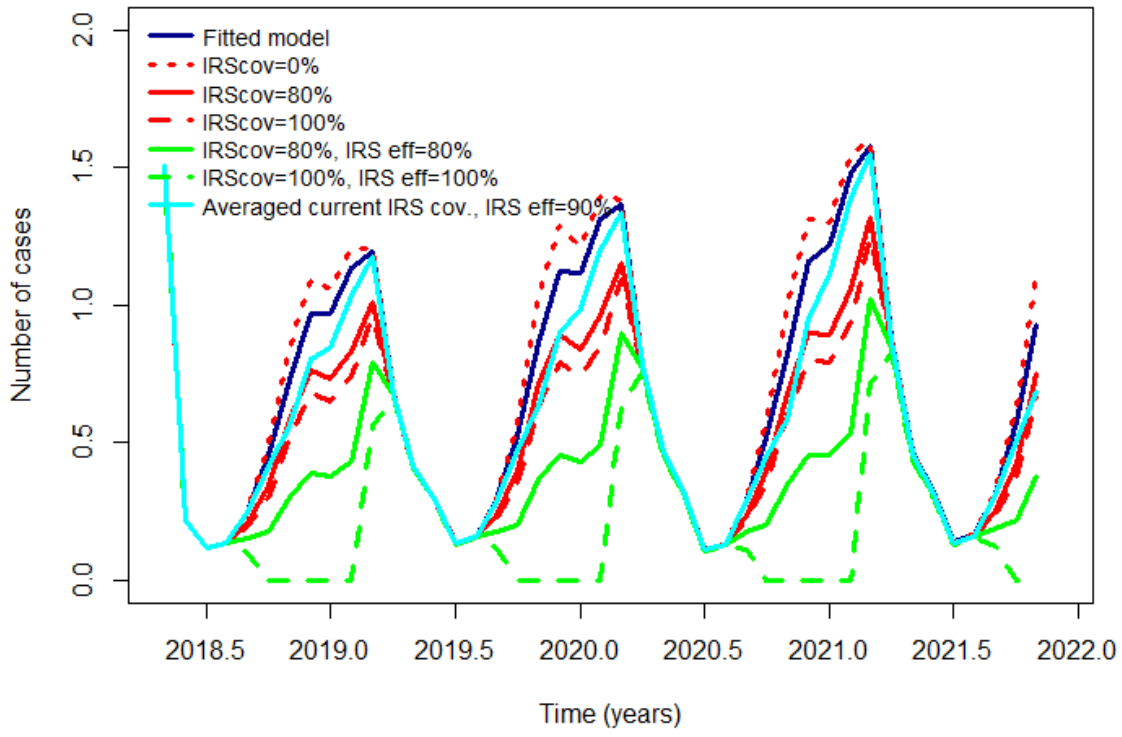


Figure 5.4: A zoomed-in plot to show the unclear plots in figure 5.3

To further our analysis, we took into account the number of imported cases in the locality which heavily depend on the prevalence of malaria cases in the neighbouring regions and countries. Figure 5.10 illustrates how an increase in the number of imported cases might impact local cases in the Ndumo locality in the future. The results show that as the imported cases rise, the higher chances of the local malaria cases increasing. Although the increase will be lower when the IRS coverage and efficacy are high, there will still be a rise in the number of malaria cases. This shows that we should not only focus on the interventions that prevent transmissions within the province but also invest in preventing imported cases from rising.

The analysis explores and compares the predicted local cases when the imported cases are 10 and 20 times larger than current cases to find out how much impact do imported cases have on local case.It was also show how the number of local cases would change if imported cases were to be eliminated. These values for the two scenarios were chosen over using proportions due to the low number of imported cases in the locality. The results clearly show that with a further rise in imported cases, an increase in the number of local cases can be expected in the future. This can prolong the time to malaria elimination. This scenario demonstrates how sensitive the local transmission is to imported malaria at this stage of the path to malaria elimination.

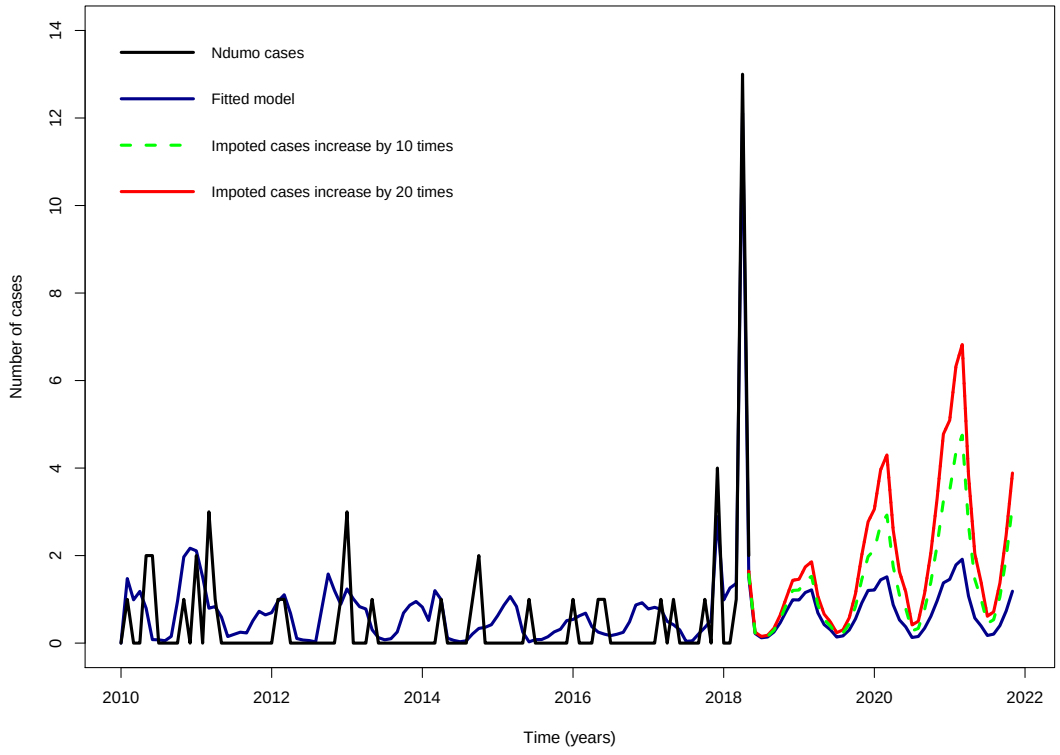


Figure 5.5: Mathematical model demonstrating local cases as imported cases rise

Shemula locality

The parameters were obtained from published sources and model fitting and are presented in the table below:

Parameter	Description	Value	Sim interval
β	Duration of the infection to the liver stage	44.4 days	$[2.2, 86.6]$
B_h	The transmission probability per contact from an infectious human to a susceptible mosquito	3.1%	$[0.2\%, 6.1\%]$
G	Proportion of patience that move from the liver to the Symptomatic stage	100.0%	$[100.0\%, 100.0\%]$
ϵ_1	Rate of movement from the liver stage to Symptomatic stage	52.8 weeks	$[, 52.8, 52.8]$
π_1	Proportion of clinical infection that progresses to Severe malaria (1998-2007)	100%	$[100.0\%, 100.0\%]$
π_2	Proportion of clinical infection that progresses to Severe malaria (2008-2015)	0.06%	$[0.0\%, 0.1\%]$
π_4	Proportion of clinical infection that progresses to Severe malaria (1988-1997)	99.85%	$[99.8\%, 99.8\%]$
τ	Time to seek treatment for a patient in the Symptomatic stage	0.011 weeks	$[0.01, 0.011]$
η	Proportion of Symptomatic patience that receive treatment (Coartem)	$1.1 \times 10^{-6}\%$	$[1.1 \times 10^{-8}\%, 2.3 \times 10^{-6}\%]$
γ	Proportion of recovered individuals that become susceptible to malaria again	70.27%	$[42.2\%, 98.4\%]$
ϵ_2	Rate of natural recovery to an Asymptomatic patients	2.6×10^{-9} weeks	$[1.3 \times 10^{-10}, 5.1 \times 10^{-9}]$
z	Rate of movement from the Symptomatic to the Asymptomatic stage	0.009 days	$[0.007, 0.01]$
ω_A	Time for a patient with severe malaria to be treated with Artesunate	0.37 days	$[0.3, 0.6]$
κ_{q1}	Proportion of patients with severe malaria treated with Quinine(1998-2007)	99.9%	$[99.9\%, 99.9\%]$
κ_{q2}	Proportion of patients with severe malaria treated with Quinine (2008-2015)	27.91%	$[0.6\%, 55.3\%]$

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Table 5.2 – *Continued from previous page*

Parameter	Description	Value	Sim interval
κ_{q3}	Proportion of patients with severe malaria treated with Quinine(2016-2018(3))	$1.1 \times 10^{-18}\%$	$[2.2 \times 10^{-20}\, 2.2 \times 10^{-18}\%]$
κ_{q4}	Proportion of patients with severe malaria treated with Quinine(1988-1997)	23.98%	[0.5%, 47.5%]
κ_{A1}	Proportion of patients with severe malaria treated with Artesunate (1998-2007)	1.24%	[0.0%, 2.4%]
κ_{A2}	Proportion of patients with severe malaria treated with Artesunate (2008-2015)	1.02%	[0.0%, 2.0%]
κ_{A4}	Proportion of patients with severe malaria treated with Artesunate (1988-1997)	99.99%	[100.0%, 100.0%]
x_1	Proportion of patients with untreated severe malaria dying due to malaria (1998-2007)	$1.5 \times 10^{-4}\%$	$[3.0 \times 10^{-6}\%, 3.0 \times 10^{-4}\%]$
x_2	Proportion of patients with untreated severe malaria dying due to malaria (2008-2015)	35.53%	[0.7%, 70.4%]
x_3	Proportion of patients with untreated severe malaria dying due to malaria (2016-2018(3))	99.41%	[99.4%, 99.4%]
x_4	Proportion of patients with untreated severe malaria dying due to malaria (1988-1997)	$2.0 \times 10^{-23}\%$	$[2.0 \times 10^{-25}\%, 4.0 \times 10^{-23}\%]$
ψ	Time taken by a severe malaria patient to recover naturally	93.7 weeks	[48.1, 150]
τ_1	Rate of movement for patients that failed treatment moving to the Symptomatic stage	1.13 days	[0.7, 3.8]
η_1	Proportion of patients that failed treatment moving back to the Symptomatic stage	$1.1 \times 10^{-6}\%$	$[1.1 \times 10^{-8}\%, 2.3 \times 10^{-6}\%]$
δ	Proportion of patients that recover from treatment (Coartem)	99.41%	

Continued on next page

Table 5.2 – *Continued from previous page*

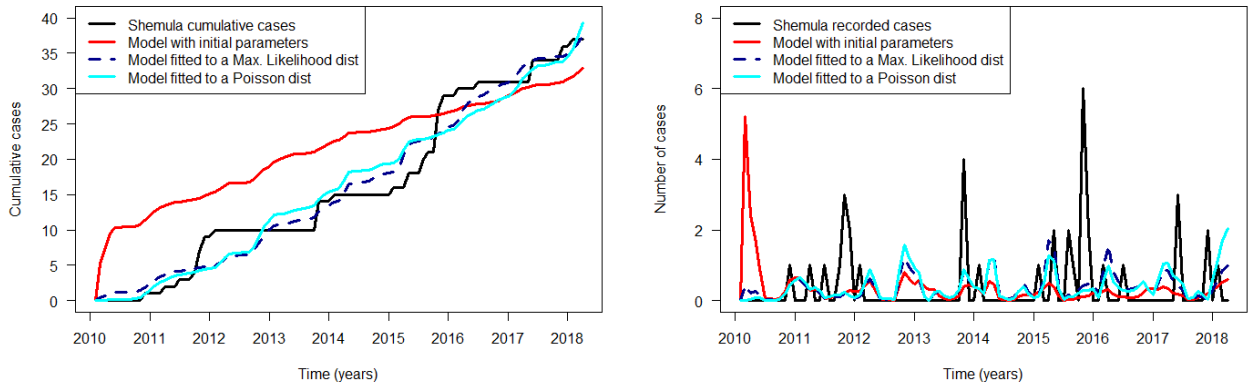
Parameter	Description	Value	Sim interval
δ_1	Proportion of treated (Coartem) patients that become Asymptomatic again	99.99%	$[100.0\%, 100.0\%]$
ω_1	Rate of movement for patients that failed treatment that progresses to the severe stage	0 days	$[0.0, 0.004]$
κ_1	Proportion of patients that failed treatment that progress to the severe stage	100.00%	$[100.0\%, 100.0\%]$
Ω	Recovery of recovery from treatment (Coartem)	0.0052 days	$[0.005, 0.005]$
h	Rate of movement for patients under treatment (Coartem) moving to the Asymptomatic stage	0.0682 days	$[0.07, 0.07]$
ρ	Duration of clinical immunity	$\frac{1}{45.4}$ years	$[\frac{1}{45.4}, \frac{1}{45.4}]$
χ_1	Time taken for a patient with severe malaria under treatment (Quinine) to die of malaria	0.1489 weeks	$[0.08, 7.45]$
χ_2	Time taken for a patient with severe malaria under treatment (IV Artesunate) to die of malaria	0.2526 weeks	$[0.13, 5.05]$
ϕ_1	Probability that treated severe malaria progresses to death (Quinine)	0.10%	$[0.0\%, 0.2\%]$
ϕ_2	Probability that treated severe malaria progresses to death (IV artesunate)	22.65%	$[22.7\%, 22.7\%]$
α_2	Duration before an individual gets a mosquito bite again	32.5%	$[16.3\%, 48.8\%]$
θ	Proportion of patients that get a recurrence of the disease moving from the liver to the clinical stage	88.80%	$[88.8\%, 88.8\%]$
r	Rate at which patients that are having malaria again move back to the Asymptomatic stage (from liver stage)	0.0015 days	$[0.0015, 0.0015]$

Continued on next page

Table 5.2 – *Continued from previous page*

Parameter	Description	Value	Sim interval
e	Rate at which patients that are having malaria again move back to the clinical stage (from liver stage)	0 days	$[0, 0]$
δ_2	Proportion of patients that failed treatment move back to the Asymptomatic stage	$6.8 \times 10^{-10}\%$	$[6.8 \times 10^{-12}\%, 1.4 \times 10^{-9}\%]$
Σ_1	Time taken for a patients that failed treatment to die of malaria	0.0203%	$[0.02, 0.02]$

With the use of packages available in `R`, we were able to fit the model in 4.1 to the data representing the number of malaria cases reported in Shemula between 2010 and 2018. The charts **??** and **??**illustrate the results fitting the model to the data using the maximum likelihood estimation and Poisson distribution method.



(a) Malaria cummulative cases

(b) Monthly malaria cases

Figure 5.6: Reported malaria cases reported in Shemula vs. fitted model

Figure 5.6a shows the cumulative cases for the 8-year period. The plot compares he quality of fit obtained for manual, maximum likelihood and Poisson distribution fitting. Figure 5.6b on the other hand compares the performance of the three models to model the monthly malaria cases recorded in the Shemula locality over time. Based on the results, the Maximum likelihood method produces more accurate results as compared to the Poisson distribution method since the AIC (510.2) for the Maximum Likelihood method was lower than of the Poisson method (560.3). As a result, we will use the model produced by the Maximum likelihood method in

terms of both predicting and carrying out sensitivity analysis.

Looking at how the total number of malaria cases in the locality has changed over the years, the number of cases reported in the respective years have decreased significantly, with monthly cases ranging between 0 and 6, with 6 cases being the maximum number of malaria cases reported between 2010 and 2018. Figure 5.7 shows how well the predictions of the best fitted model compare with the actual recorded malaria cases in Shemula between 2010 and 2018.

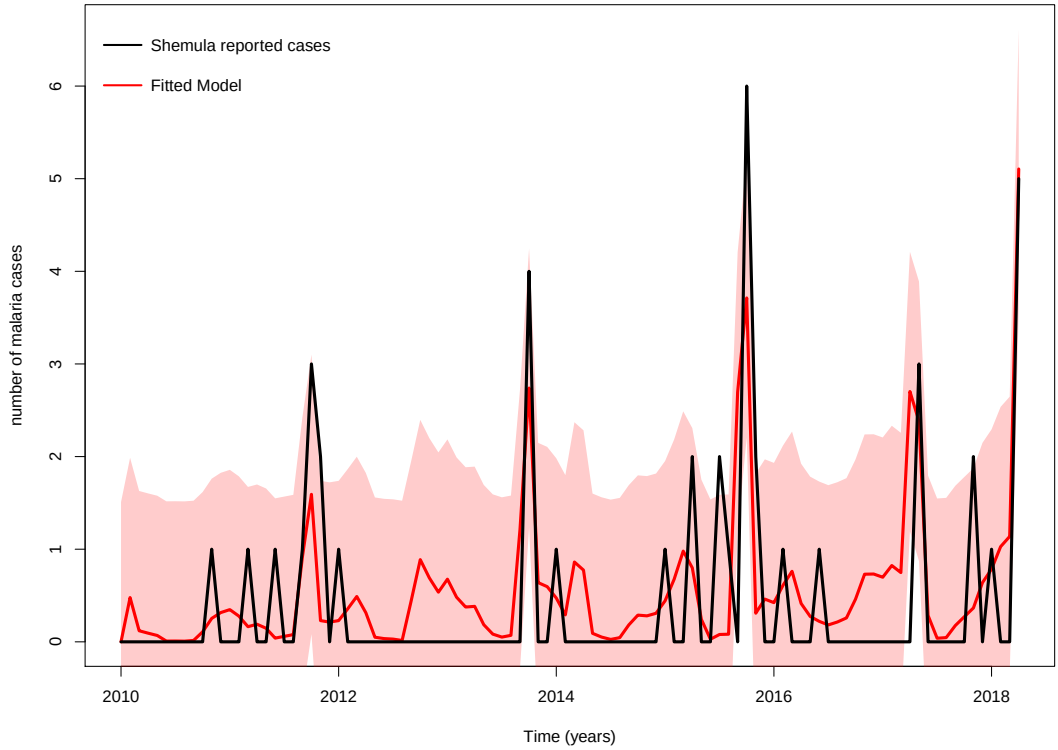


Figure 5.7: Mathematical model fitted to reported malaria cases in Shemula locality overtime

As for the Ndumo locality, we also carried out an analysis to understand any changes that would occur when the Indoor Residual Spraying (IRS) would be adjusted. Based on the results produced in figure 5.8, the impact would be very similar to the one of the Ndumo locality; an increase in the IRS coverage results in a decrease in the number of reported malaria cases and vice versa. Although there is a positive change in the number of cases, the impact is insignificant. However, when its efficacy is high, there seems to be a significant change in the number of cases reported. This then suggests that it is important to also invest time in making sure that the strategy is effective instead of putting more effort into spraying more structures in the surrounding areas. Moreover, since the strategy has been effective for decades, it is critical that we enforce the existing interventions to prevent reinfection.

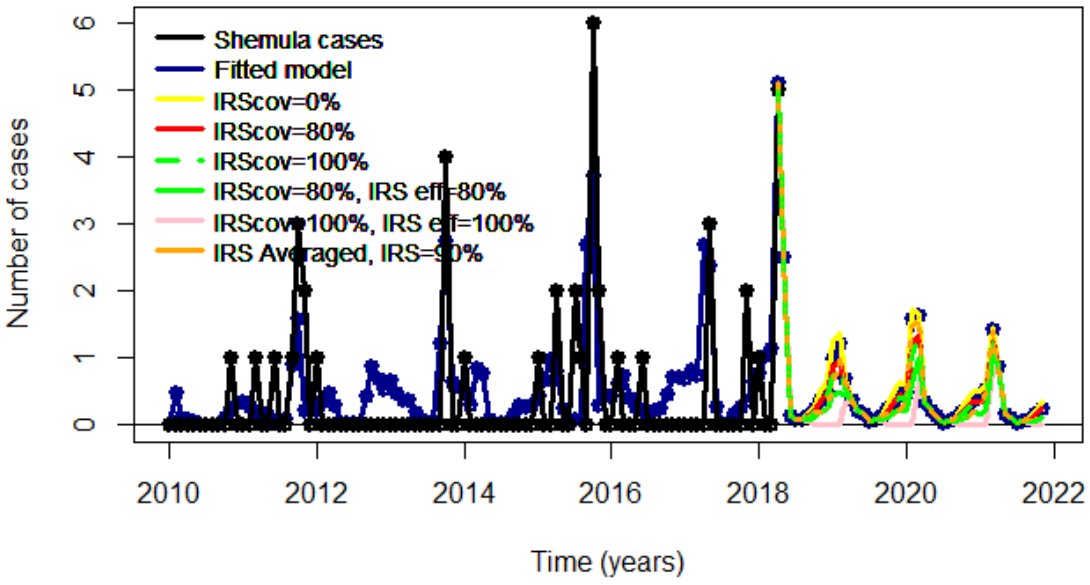


Figure 5.8: IRS scenario analysis closer to the predictions

Figure 5.9 aims at showing a better view of the results produced in figure 5.8, starting from May 2018 to December 2022

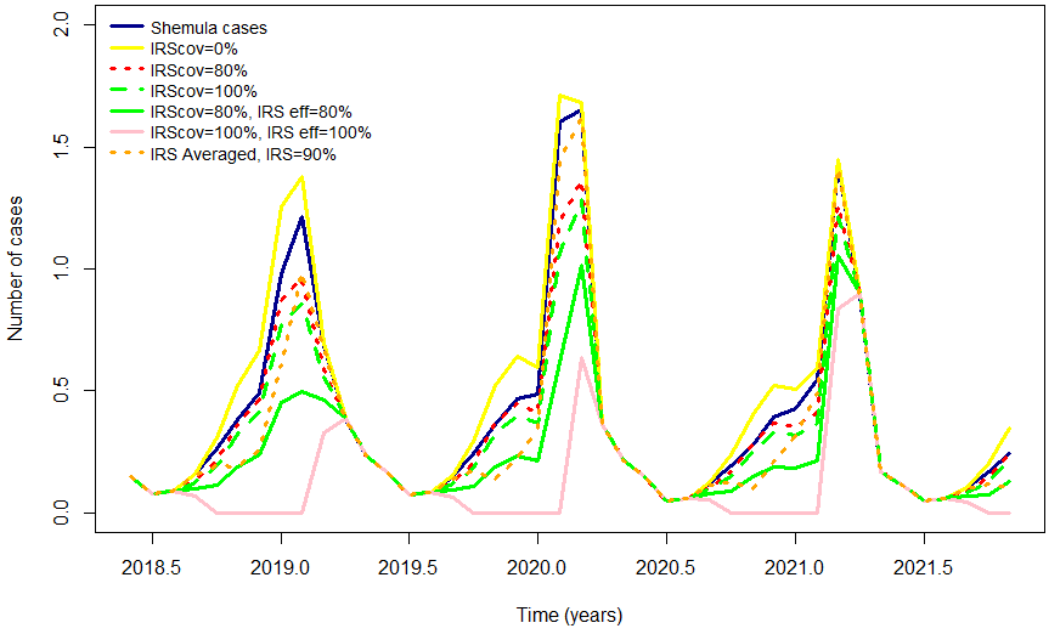


Figure 5.9: A zoomed-in plot to show the unclear plots in figure 5.8

Figure 5.10 shows how Shemula locality malaria cases would change if the reported number of imported cases were to increase in the future. The analysis mainly focused on imported cases as they would have a major impact on the existing cases. Similarly to the results obtained in the Ndumo locality model, the local malaria cases seem to decrease as the IRS coverage is increased and vice versa. However, the difference is insignificant. Based on the analysis, for the results to drop significantly, it is crucial that we also consider increasing the IRS efficacy as higher efficacy has proven to have a positive impact on the number of local cases. It is crucial that we also improve other interventions in place to achieve total elimination of the disease. As the population in the country and from the neighbouring countries interact as they move from one place to the next for jobs and others for other reasons, a rise in the number of imported cases is expected. Therefore, the country as whole needs to increase its effort to prevent transmission caused by movement between different regions. We do believe that instead of only preventing the local infections, we also assist neighbouring countries that still have high numbers of cases to reduce the prevalence. This would be beneficial as we would prevent the problem at the source.

The results also showed that local malaria tend to increase as the number of imported cases rise. However, the increase for Shemula locality would be lower than it is for the Ndumo locality. The analysis showed that for the number of local cases to increase as a result of a rise in the number of imported, there would have to be a significant rise in the number of imported cases, more especially if the controls in place are still as effective. This further shows that investing more time in our controls, increases the chances of preventing imported cases from affecting local cases. Therefore, it is worthwhile maintaining the existing strategies and interventions.

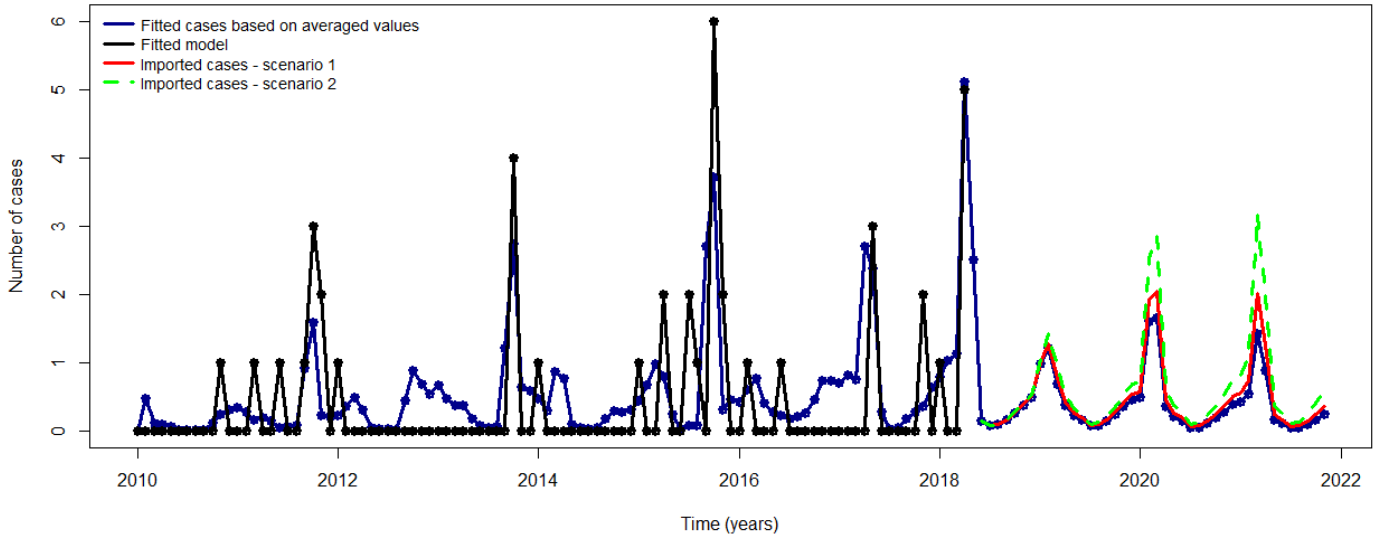


Figure 5.10: Mathematical model demonstrating local cases as imported cases rise

Summary

For over a decade, the malaria prevalence remained low in the two provinces. Although the number of malaria cases reported in KZN increased at the beginning of 2018, the cases reported in the two localities remained low. We could assume that the rise in imported cases reported in the province did not impact the local malaria cases. However, there was an increase in the number of cases reported in the Ndumo locality. Since most of the imported cases were reported in the busiest cities in the province, e.g. Durban, there could have been indirect transmissions that lead to malaria rising. In the analysis, we explored these possibilities to build the model with real-life situations. Some of the imported cases were likely asymptomatic meaning that they could not have been detected during testing. Based on the analysis done which explores how the cases will change from March 2018 to the end of 2022 as the Indoor Residual Spraying change over time. The results show that only increasing our effort in spraying while the efficacy remains the same, will not eliminate malaria in the two localities, but will reduce it by a small proportion. This then further show that it is important that we distribute the effort evenly between the most effective interventions when considering increasing coverages and the efficacy of each strategy. As the results have shown, we will achieve a significant reduction in the number of malaria cases when both the IRS coverage and its efficacy is high. It is, however, important to keep the number of imported cases low as they will affect the number of local cases. To keep the imported cases low, we would also have to increase our efforts in the border clinics as they play a major role in preventing malaria cases from entering the country.

Chapter 6

Sensitivity Analysis

In determining the best model parameters for the two localities, it is necessary to know the relative importance of the different factors responsible for malaria transmission. Sensitivity indices enable us to measure the relative change in a state variable when a parameter change occurs. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter.[47]. The transmission is mainly driven by the force of infection (β_t), which is driven by other factors such as rainfall data. To study the sensitivity of the model parameters, we made use of the uniform distribution method which enabled each parameter be varied within 45% of its fitted value. These indices will assist in telling us how crucial each parameter is to disease transmission and prevalence. Sensitivity analysis is mostly used to understand how robust the model is to the predicted parameter values. This is of great importance since there are usually errors in data collection and presumed parameter values).

Figure 6.1 illustrates the sensitivity analysis plot which shows the 95% confidence band for the number of malaria cases reported in Ndumo locality. The 95% confidence interval for the malaria incidence was generated in a simulation in which all parameters in the model were varied about their fitted values by randomly sampling from appropriate uniform distributions. The confidence interval computation was obtained by making use of the following formula:

$$\bar{X} \pm Z\frac{s}{\sqrt{n}}$$

where;

- $\bar{X}$ is the mean value of the incident values produced by the randomised model at every time point,

- $Z = 1.96$ is the Z-value (from the Z-table),
- s is the standard deviation calculated from the incident values produced at each time step and
- $n = 144$ is the number of observations (number of months between January 2010 to December 2020)

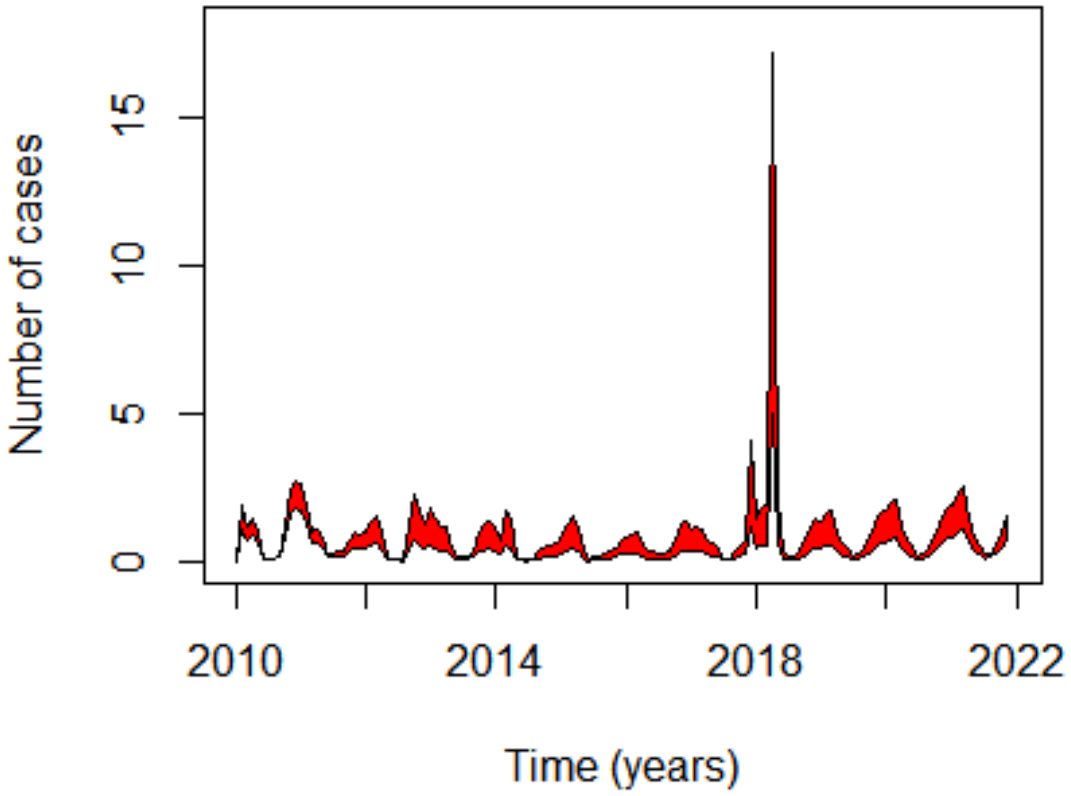
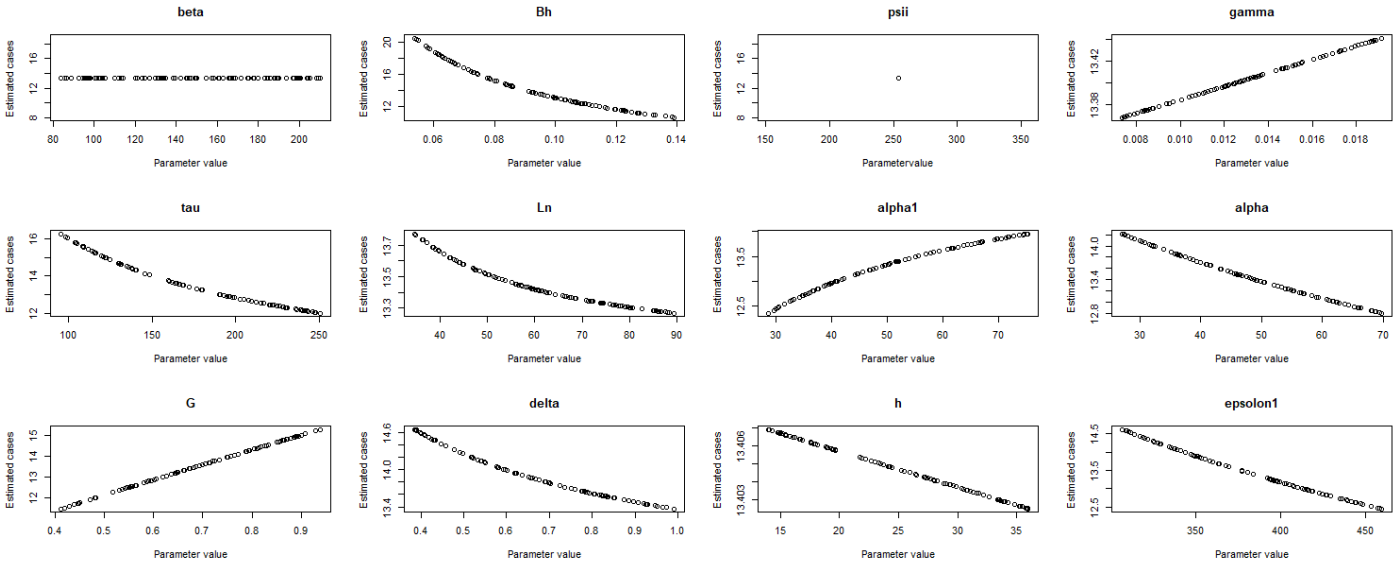


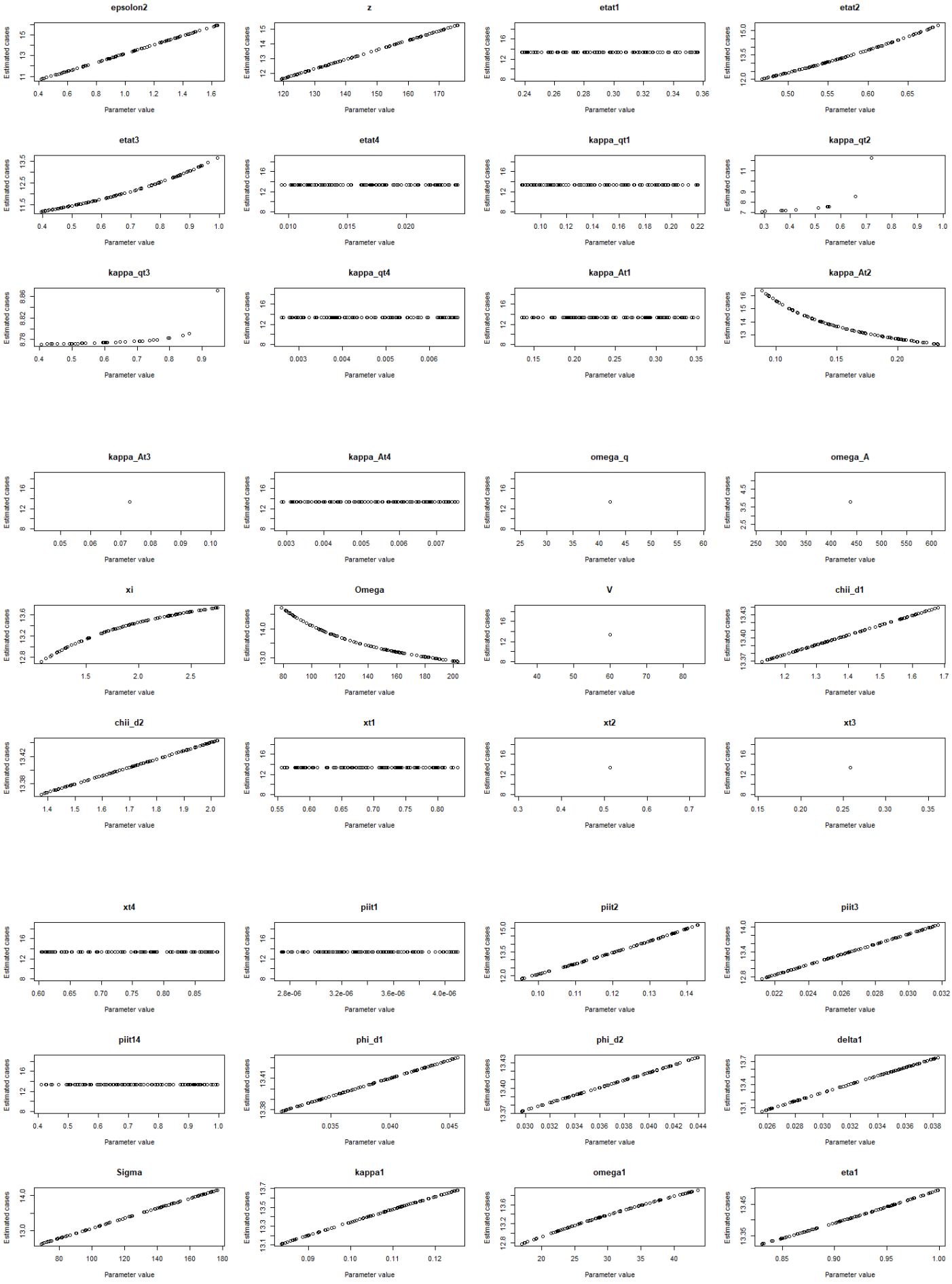
Figure 6.1: Ndumo Sensitivity Analysis Plot

Figure 6.2 shows the 95% confidence interval results of the model sensitivity based on 100 simulation runs. The plot shows how much the malaria incidence varied as the parameter values changed. The sensitivity analysis shows that out of the 60 parameter values, 5 parameters values were the most sensitive parameters as they led to unrealistic values whenever a change occurred within each parameter value. These are the parameters; ψ, ω_q, ω_A, κ_{A3} and V (please see Table 4 for definitions). The model also shows moderate sensitivity to changes in parameter values based on proportion (%). These include ϵ_1, ϵ_2, Σ_1, δ, z, η_3, κ_{q3} and κ_{q4} (see Table 4 for definitions).

The parameter simulations assisted us in understanding how much the estimated malaria cases as of March 2018 will vary as each parameter change as per the given interval. The results illustrated in Figure 8.1 show that some parameters are more sensitive than others, and also with some that are not sensitive at all. During the analysis, we realised that any change in the fitted parameter lead to the model producing unrealistic values. These are parameters such as ψ, κ_{q3}, κ_{A3} etc. Some of the parameters vary more often during the simulation. These are parameters such as B_h, ϵ_2, τ, G etc. It also showed that some parameters are not sensitivity at all; L_n, h, ϕ_{d1}. The baseline value to the sensitivity analysis was 13, the estimated cases for March 2018. Please refer to Table 4 for parameter definitions.

Below, Figure 6.4 illustrates the impact each parameter have on the model as each parameter value changes in the Ndumo locality model. The plot shows how the number of estimated cases varies as each parameter value changes randomly, with the values moving up and down within the defined range. This was done at a parameter level. This was to investigate which parameters are sensitive to change which would result to the model being unstable.

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Estimated cases
Parameter value

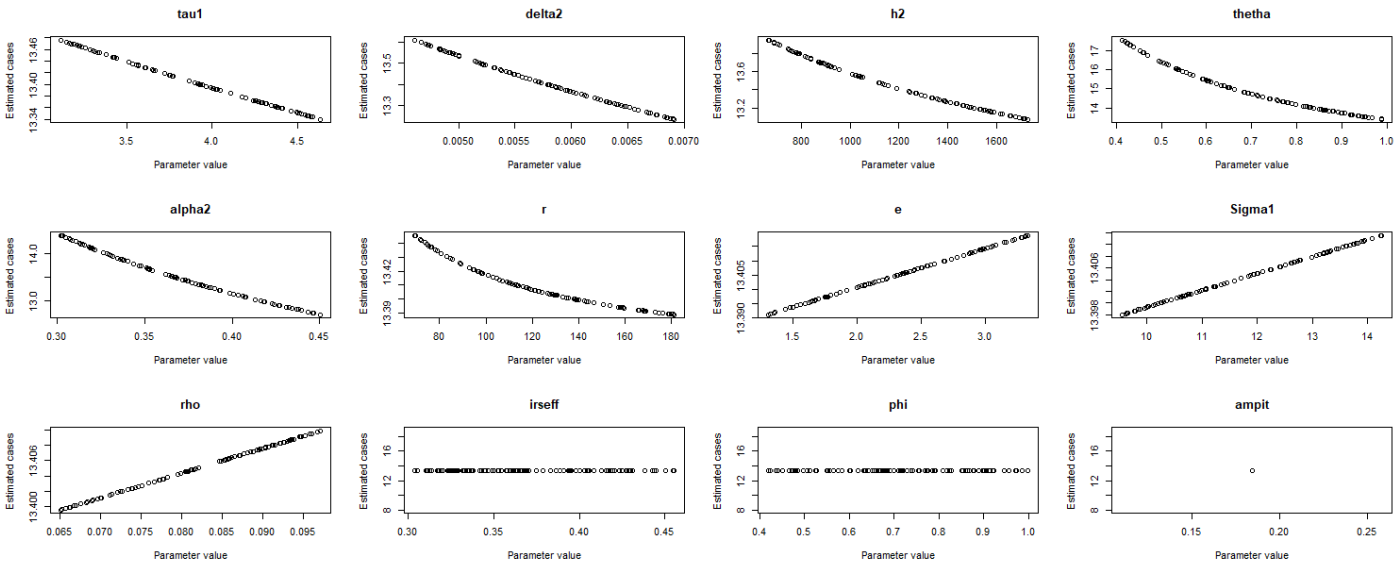


Figure 6.2: A multivariate sensitivity analysis plot which simulates the model parameters several times - Parameter impact to model

The same method used for the Ndumo locality in studying the sensitiveness of the model parameters is also employed in the Shemula locality. The results show that there are some parameter values to which the model tends to be sensitive. This happens at different levels. It shows to be extremely sensitive to some of the model parameters whilst it is just mild sensitive to some parameter values and others not showing any sensitiveness. Figure 6.3 shows the sensitivity plot that aims at illustrating the confidence band of the fitted malaria cases as the model parameters are randomly being generated from a uniform distribution and fitting the model at each time step (100 times).

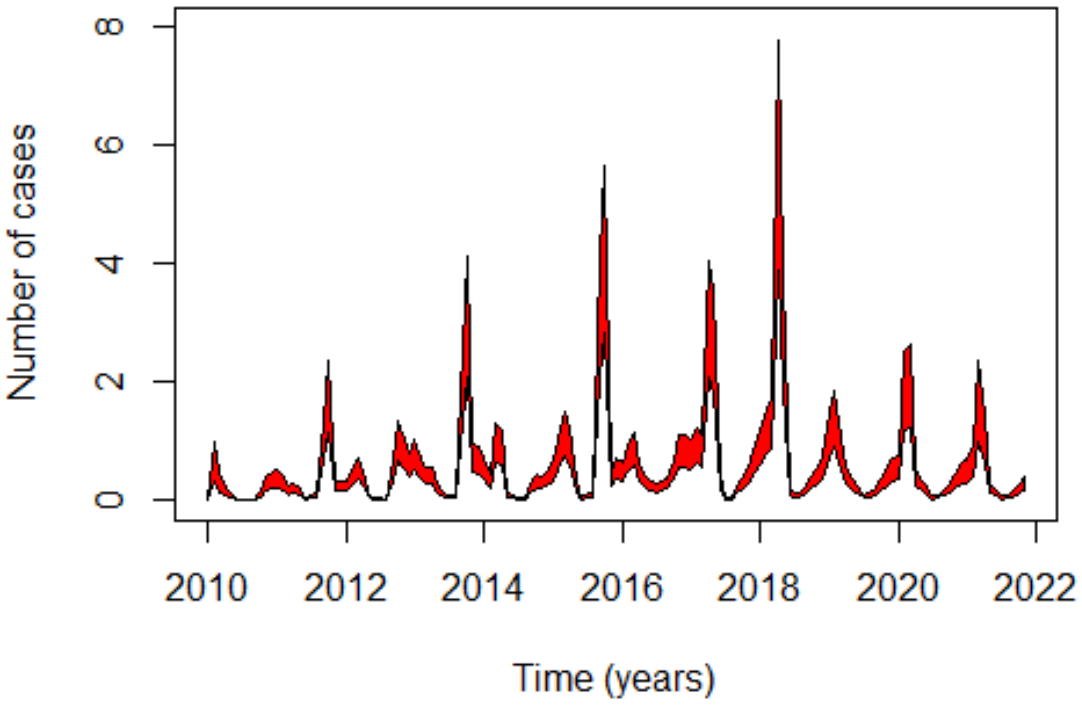
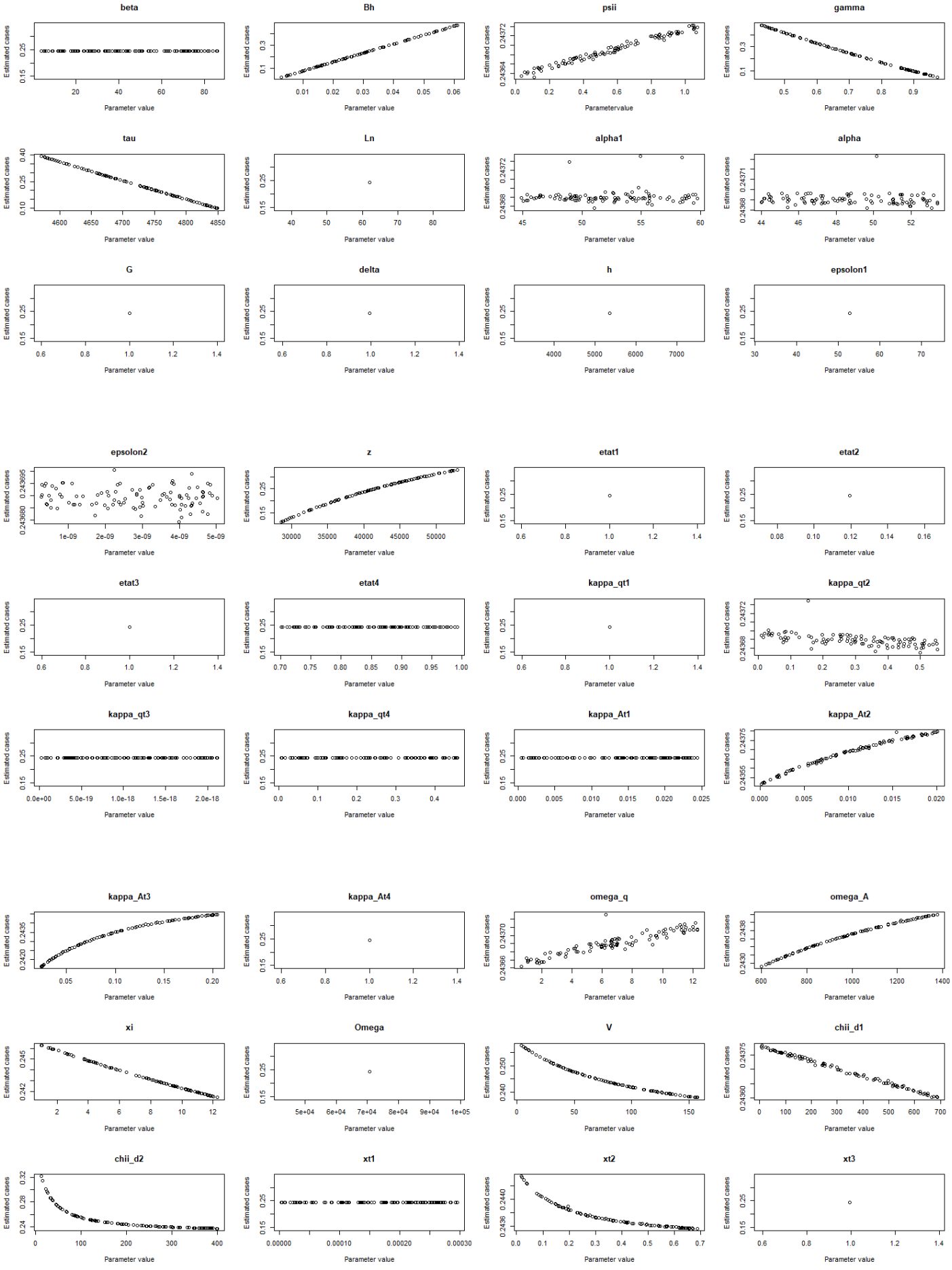


Figure 6.3: Shemula Sensitivity Analysis Plot

Figure 6.3 aimed at demonstrating the sensitiveness of each parameter as they vary on the respective parameter intervals.

During model simulation (Figure 8.1), all parameter values were varied several times for over a specified interval to investigate the sensitiveness of parameter values. Although the parameter values were varied and chosen randomly from the interval, we found that for some parameters values there was a little or no change in the number of estimated cases whereas for other parameters the estimated cases would be more distributed. For example for θ the estimated cases ranged between 13 and 18 when the parameter was allow to vary whereas for η_1 the value remained as 14.

Below, figure 6.4 illustrates the impact each parameter have on the model as each parameter value changes in the Shemula locality model. The results show that an increase or a decrease in the parameter may either result to an increase or decrease in the estimated monthly cases. It also shows that the estimated value can be random as the parameter value changes.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kappa_qt1
kappa_qt2
kappa_qt3
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kappa_At1
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kappa_At4
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Estimated cases
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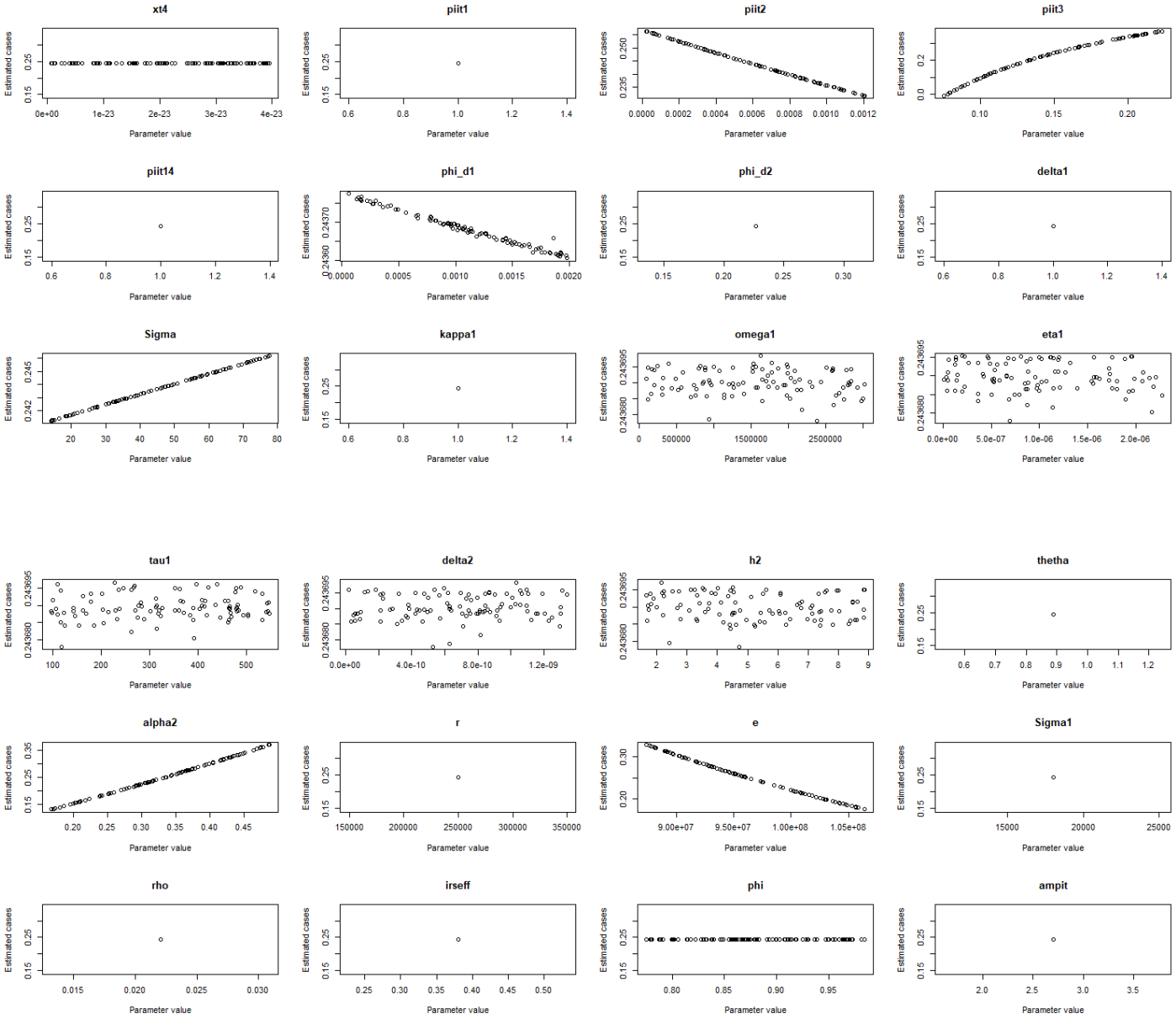

Figure 6.4: A multivariate sensitivity analysis plot which simulates the model parameters several times - Parameter impact to model

Chapter 7

Discussion and Conclusion

The results show that there is potential for a rise in the number of malaria cases should there be a decrease in the current coverages. For instance, if the Indoor Residual Spraying would stop completely, the impact would be significant. Conversely, throughout the analysis, we have realised that there is a possibility to reach the goal of malaria elimination in the two localities, Ndumo and Shemula, even in the whole province. For this to happen, we would have to put in more effort in using the most effective strategies available. The results show that most of the strategies in place have had a significant impact on the number of cases since they have managed to maintain a low number of malaria cases in the top 2 malaria prevalent localities in the KwaZulu Natal province with a maximum of 13 monthly cases. To maintain low numbers of malaria cases going forward, we have to retain and/or reinforce the current coverages. This is important given that the change in the number of cases depends on factors such as Indoor Residual Spraying (IRS), IRS efficacy, Rainfall, and Imported Cases.

Firstly, we try to understand how an increase of IRS coverage from the current maximum of 62% to 80% and 62% to 100% would impact the number of cases. The results show that, everything else remaining the same, increasing the IRS coverage from 62% to 80% results in a significant impact on the number of local cases, however the impact is relatively indistinguishable to that of increasing the IRS coverage from 62% to 100%. As much as an increase in the current coverages would result in a decrease in the number of local cases in the future, we need to consider applying strategies that will be impactful without any wastage of resources. Based on this, it would be economical to have a coverage of 80% than 100%. Moreover, we deduce that, to maintain the low number of malaria cases, it would be sufficient to use the current coverages but to reduce the number of cases, we need to consider finding ways to increase the IRS's efficacy. Thus, for IRS, we conclude that, to reduce the malaria cases to its minimum (even further to 0), we need to consider increasing both the IRS coverage and its efficacy closer

to 100%.

Secondly, we studied the impact of imported cases on the number of local cases. Imported cases have been known to be one of the major contributors to malaria transmission in the country. Thus, it is worth analysing the effect it has had in the past and how it would affect the local number of cases in the future as the existing strategies adjust. During our analysis, we considered instances where imported cases increase and instances where there are 0 imported cases meaning that individuals who travel from other regions would be screened and treated before entering the localities (100% efficacy in imported cases prevention). The results showed that if there would be a rise in the number of cases in the neighbouring malaria prevalent regions (neighbouring countries and South African regions), there would be an increase in the number of malaria-infected individuals entering the region, which would result in a rise in the number of local cases. This is likely to happen if the coverages of existing strategies are dropped. To prevent a major increase in the number of local malaria cases, it is vital that we either maintain or increase our efforts in preventing imported cases from affecting local cases. This may even result in the number of local cases decreasing as there are other techniques in place which aim at reducing local cases. Moreover, to reduce the probability of local cases increasing as a result of a rise in the number of cases in the neighbouring countries, we need to ensure 100% enforcement of existing strategies which are aimed at ensuring that all individuals entering the country are screened and treated to avoid any possible transmissions. These are strategies such as the border clinics. This would have a significant difference in the local malaria cases as we would eliminate one of the major contributors to existing malaria cases. This may even lead to the elimination of malaria in the two localities.

In conclusion, it is important that we increase our efforts in ensuring that we retain and/or strengthen the existing strategies. As the results have shown that there is both potential of an increase and a decrease in the number of local malaria cases, and the number of cases being consistent in the future depending on several factors. These possibilities can occur when the efforts in the strategies in place have either increased, decreased, or remained the same, respectively. This then shows us that since we have managed to maintain a low number of cases over the years until March 2018 (when a sudden increase occurred), we can continue maintaining low cases by continuing to make use of the existing strategies provided that the number of cases in the neighbouring regions remains low and/or strategies used to prevent imported cases also do not change. It is concerning to know that there is a possibility of a rise in the number of cases. To avoid this from happening we need to invest in increasing our coverages and find ways to increase the efficacy of our strategies. The model showed that this would have a significant impact on the existing number of cases as they would move closer to

0 cases a month. It is also worth noting that malaria cases in each locality in KZN are very low. This then means that an investment of more money and time would result in a further decrease in the number of cases. One would argue that the investment is not worthwhile and that the decrease is redundant, and because of this, it is worth considering moving all that effort towards the prevention of the more concerning variable; imported cases. In terms of local cases, we would then consider maintaining the current coverages. In that case, we should only treat those who require the treatment and spray the areas that still report cases.

Limitations

The model in this study particularly aimed at a closer view of the monthly local malaria cases in the two key localities in KZN. Although other models, mainly look at larger regions such as districts and provinces, the model focused on representing the key features of malaria vector/human relationship, treatment, imported cases, and vector spraying. This is crucial as having a bird eyes view might not always give a clear idea of the malaria behaviour over time. This also plays a major role in terms of finding the best ways to reduce malaria transmission. The data analysis showed that the averaged monthly cases are very low as some localities have reported very low malaria cases. When averaging, we miss out on several factors that result in a rise to the existing cases. This could occur as localities reach elimination. The impact of imported cases, spraying, etc are more likely to be affected by random events than average trends. Therefore, a granular approach ensures that we find strategies that prevent the transmission at the source by understanding how malaria cases change in the key localities and in understanding the factors that resulted in the localities having high malaria cases.

The model has some limitations; as the localities are extremely small relative to the size of the province with a population of 5831 (Ndumo) and 2495 (Shemula), it becomes a challenge in building a model that mimics the malaria cases. This is even more of a challenge as data for some of the parameters such as Rainfall data were not available at a locality level but rather at a district level. For future work, we would recommend the use of locality level specific data as it would give more accurate results. Also, since we are aware that malaria transmission can occur as a result of movement between different regions, it is worth looking at building a meta-population model that would include movement between the neighbouring localities and countries such as Mozambique. Another limitation of the study was we did not evaluate the impact of increasing coverage of the other interventions for several such as of data unavailability.

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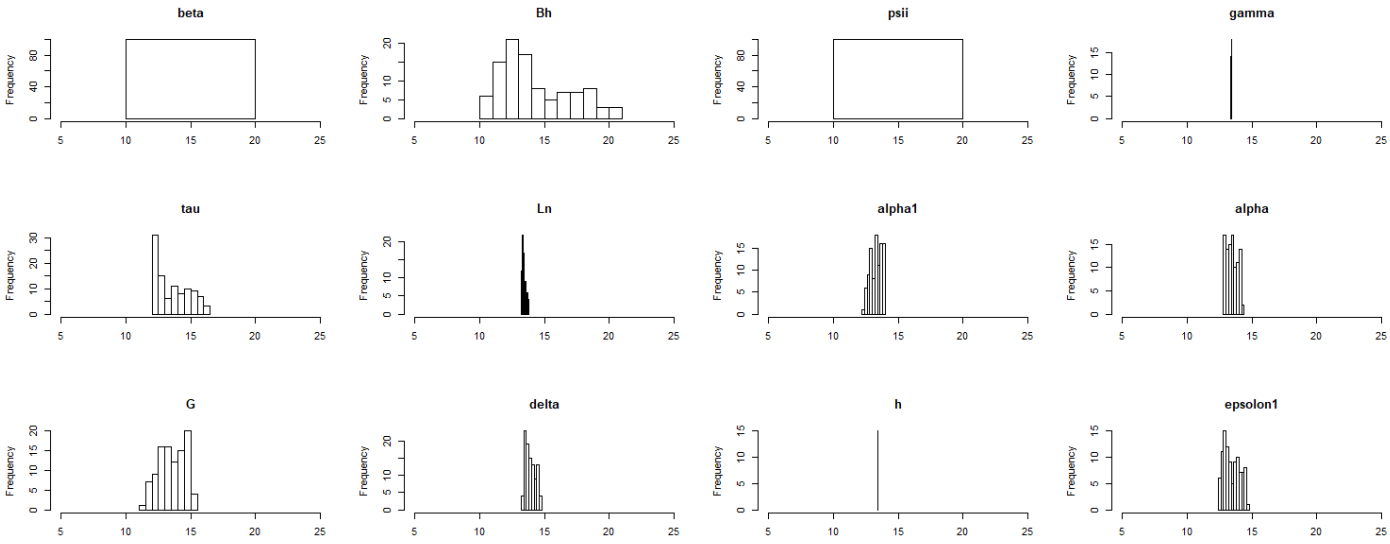
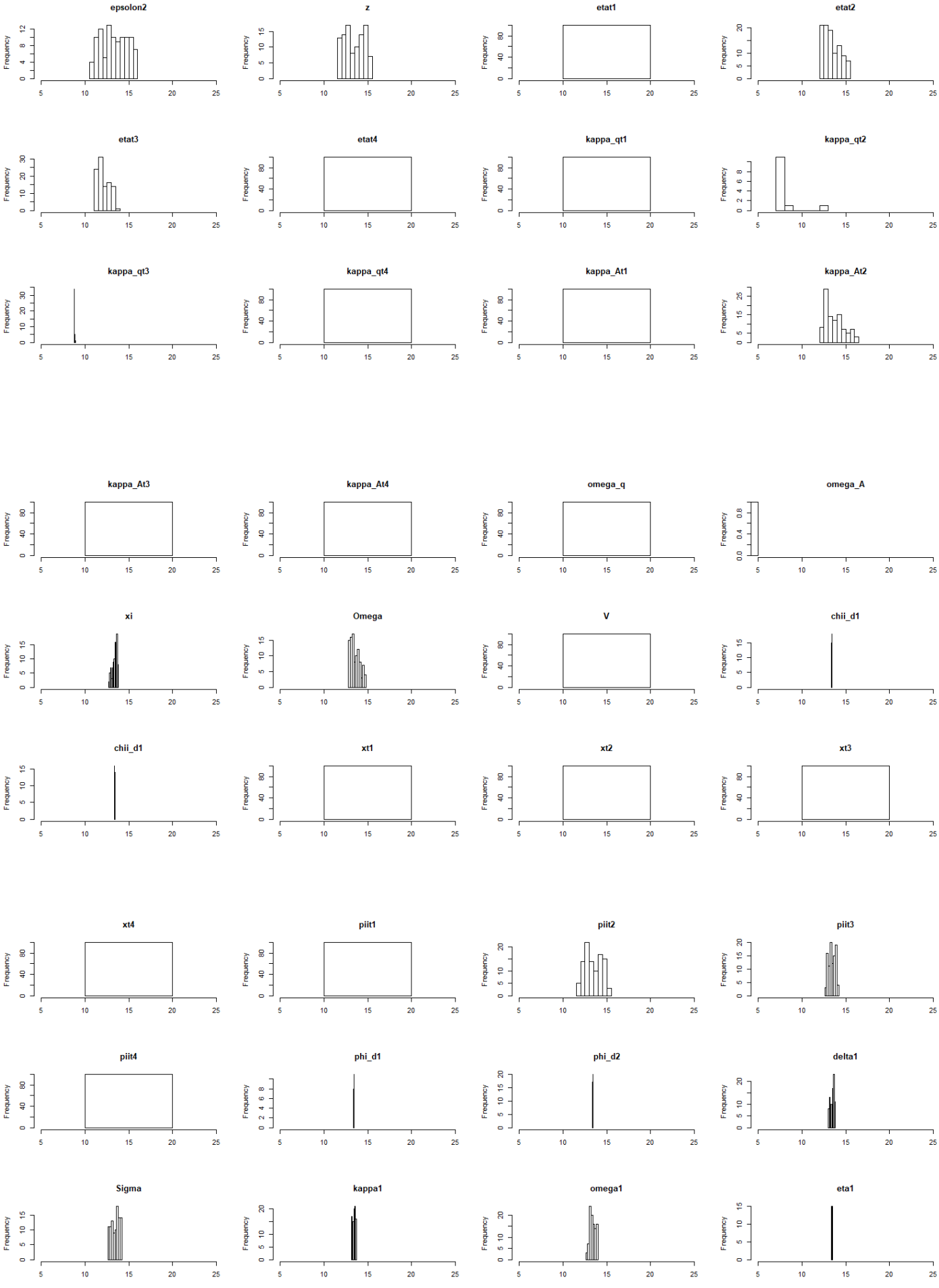
Chapter 8

Appendix A. Sensitivity Analysis Graphs




epsolon2
z
etat1
etat2
etat3
etat4
kappa_qt1
kappa_qt2
kappa_qt3
kappa_qt4
kappa_At1
kappa_At2
kappa_At3
kappa_At4
omega_q
omega_A
xi
Omega
V
chii_d1
chii_d1
xt1
xt2
xt3
xt4
piit1
piit2
piit3
piit4
phi_d1
phi_d2
delta1
Sigma
kappa1
omega1
eta1
Frequency

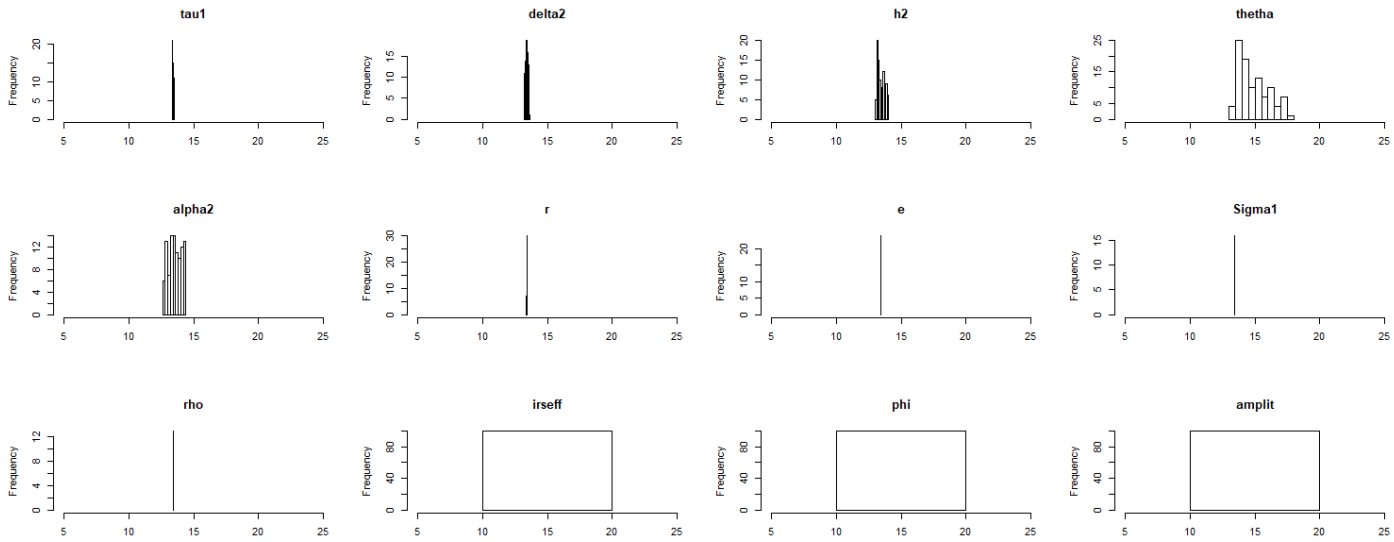
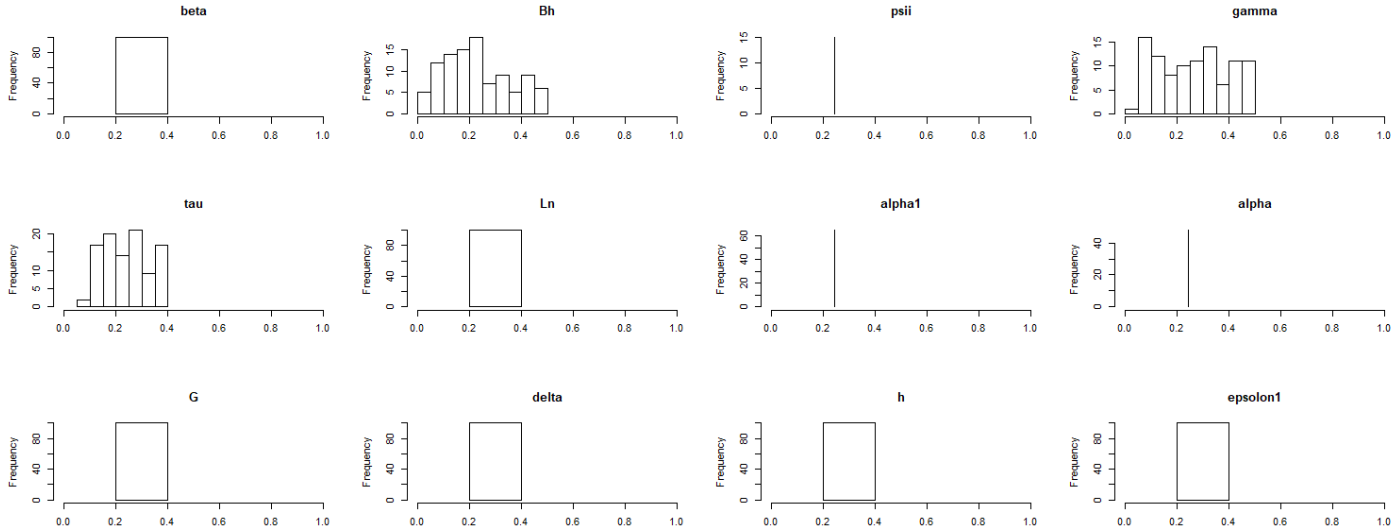
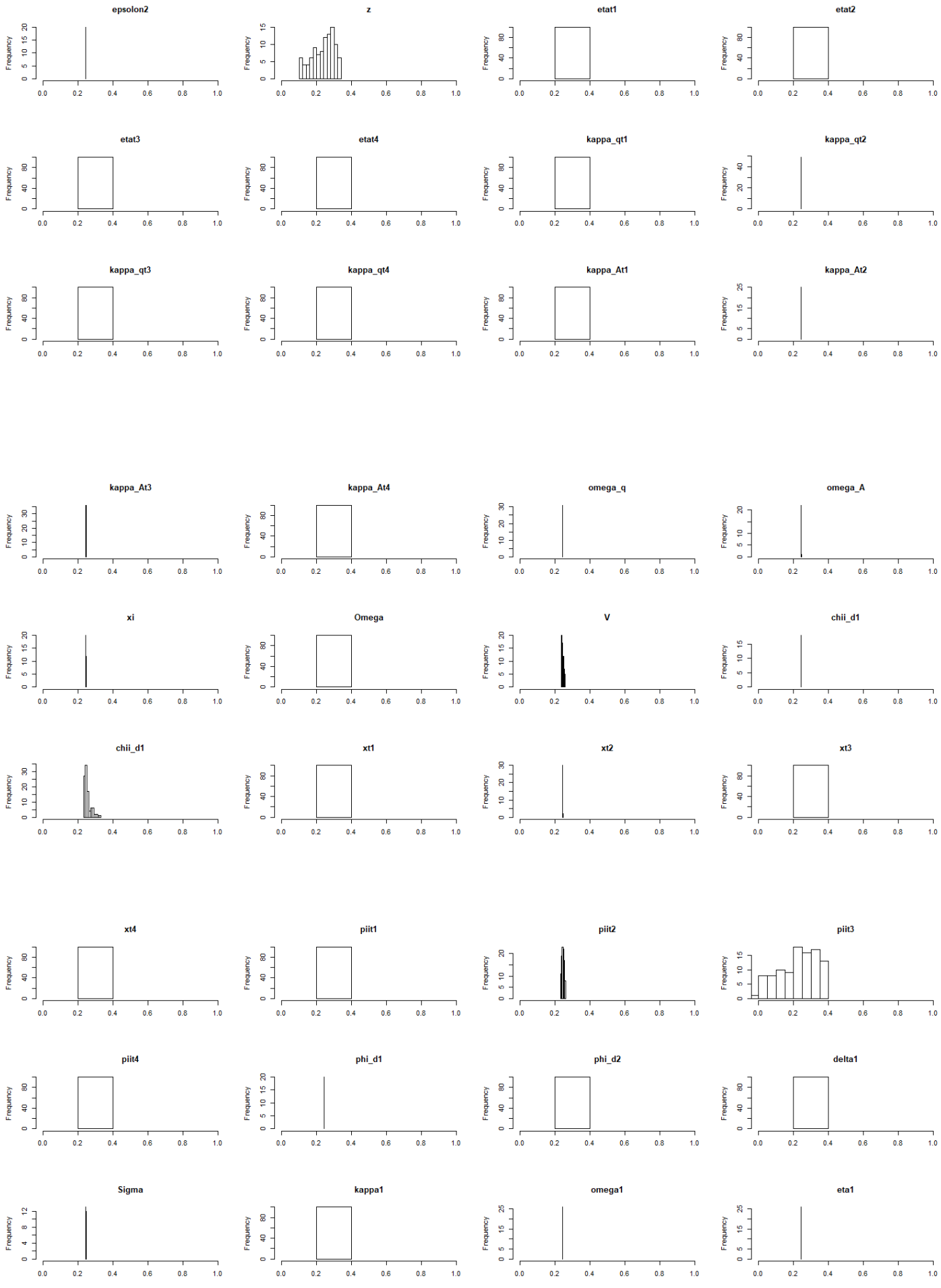


Figure 8.1: A multivariate sensitivity analysis plot which simulates the model parameters several times




epsolon2
z
etat1
etat2
etat3
etat4
kappa_qt1
kappa_qt2
kappa_qt3
kappa_qt4
kappa_At1
kappa_At2
kappa_At3
kappa_At4
omega_q
omega_A
xi
Omega
V
chii_d1
chii_d1
xt1
xt2
xt3
xt4
piit1
piit2
piit3
piit4
phi_d1
phi_d2
delta1
Sigma
kappa1
omega1
eta1
Frequency

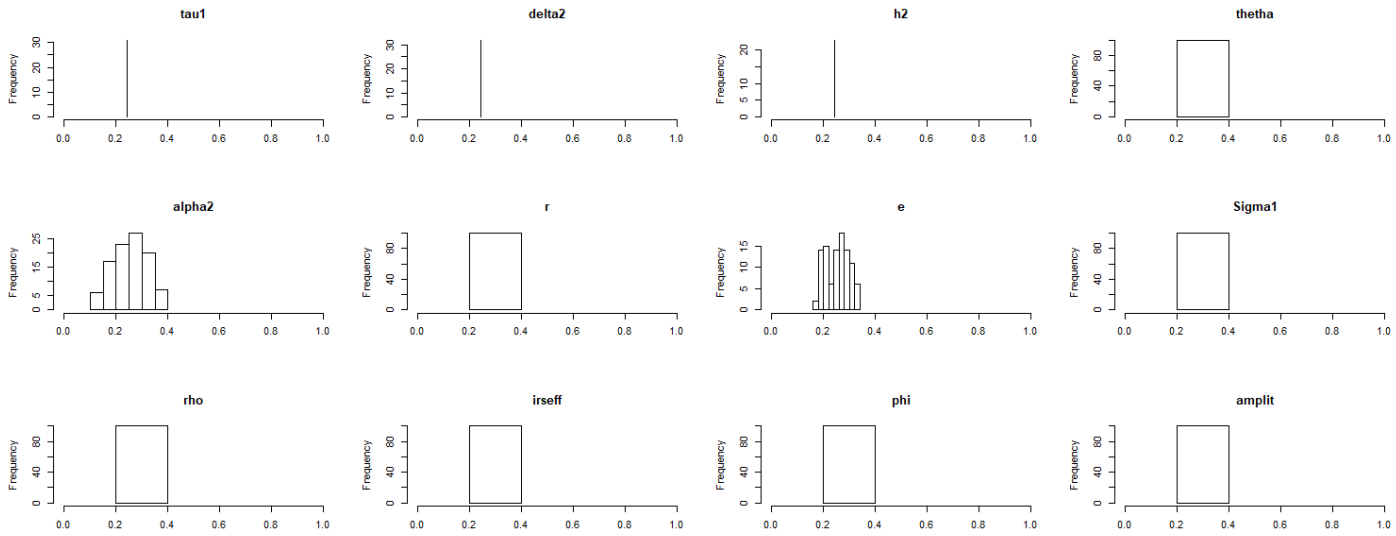


Figure 8.2: A multivariate sensitivity analysis plot which simulates the model parameters several times

Chapter 9

Appendix B. Model Code

9.1 Model Fitting

```
library(deSolve)
library(readxl)
library(xlsx)
library(maxLik)
library(bbmle)
library("openxlsx")
#Data fitting
rm(list=ls())
data<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/Total_local_cases1_Shemula.xlsx", sheet = 1, startRow = 1, colNames = TRUE)
data_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/Total_local_cases1_1_Shemula.xlsx", sheet = 1, startRow = 1, colNames = TRUE)
climatedata<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/chirps_Shemula.xlsx", sheet= 1, startRow = 1, colNames = TRUE)
climatedata_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/chirps_1_Shemula.xlsx", sheet= 1, startRow = 1, colNames = TRUE)
```

```
13 climatedata1<-read.xlsx("C:/Users/mandi/OneDrive - University of
     Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
     chirps_Shemula.xlsx", sheet= 2, startRow = 1, colNames = TRUE)
14 climatedata1_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
     Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
     chirps_1_Shemula.xlsx", sheet= 2, startRow = 1, colNames = TRUE)
15 data_IRScov<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape
     Town/Dissertation/Thesis Work/Model building/Start Afresh/IRScov
     data incomplete1_averrm8_Shemula.xlsx", sheet = 1, startRow = 1,
     colNames = TRUE)
16 data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
     Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
     IRScov data incomplete1_averrm8_1_Shemula.xlsx", sheet = 1,
     startRow = 1, colNames = TRUE)
17 Imported_shemula<-read.xlsx("C:/Users/mandi/OneDrive - University of
     Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
     Malaria cases imported diagnosed in Shemula.xlsx", sheet = 1,
     startRow = 1, colNames = TRUE)
18 Imported_shemula_1<-read.xlsx("C:/Users/mandi/OneDrive - University
     of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh
     /Malaria cases imported diagnosed in Shemula_1.xlsx", sheet = 1,
     startRow = 1, colNames = TRUE)
19 Multi<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/
     Dissertation/Thesis Work/Model building/Start Afresh/Incidence
     multiplier.xlsx", sheet = 1, startRow = 1, colNames = TRUE)
20 Multi_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape
     Town/Dissertation/Thesis Work/Model building/Start Afresh/
     Incidence multiplier_1.xlsx", sheet = 1, startRow = 1, colNames =
     TRUE)
21
22 # Defining functions for Vector dynamics
23 climatedata$ts          <- with(climatedata, seq(0,30.33333,1/12))
24 climatedata_1$ts          <- with(climatedata_1, seq(0,8.33333,1/12)
     )
25 climatedata1$ts          <- with(climatedata1, seq(0,30.33333,1/12))
```

```
26 climatedata1_1$ts            <- with(climatedata1_1, seq(0,8.33333,1/
       12))
27 data_IRScov$ts             <- with(data_IRScov, seq(0,30.33333,1/12))
28 data_IRScov_1$ts             <- with(data_IRScov_1, seq(0,8.33333,1/12)
       )
29 Imported_shemula$ts1 <- with(Imported_shemula, seq(0,30.34,1/12))
30 Imported_shemula_1$ts1 <- with(Imported_shemula_1, seq(0,8.34,1/12))
31 Multi$ts1 <- with(Multi, seq(0,30.33333,1/12))
32 Multi_1$ts1 <- with(Multi_1, seq(0,8.33333,1/12))
33
34 R_interpol_s                 <- with(climatedata,approxfun(ts,
       Umkhanyakude_rain,rule=1,method='linear'))
35 R_interpol_s_1                <- with(climatedata_1,approxfun(ts,
       Umkhanyakude_rain,rule=1,method='linear'))
36 R_stdinterpol_s               <- with(climatedata1,approxfun(ts,
       Umkhanyakude_std,rule=1,method='linear'))
37 R_stdinterpol_s_1              <- with(climatedata1_1,approxfun(ts,
       Umkhanyakude_std,rule=1,method='linear'))
38 IRSinterpol_s                 <- with(data_IRScov,approxfun(ts, Shemula
       ,rule=1,method='linear'))
39 IRSinterpol_s_1                <- with(data_IRScov_1,approxfun(ts,
       Shemula,rule=1,method='linear'))
40 Imported_shemula_s  <- with(Imported_shemula,approxfun(ts1,Shemula,
       rule=1,method='linear'))
41 Imported_shemula_s_1  <- with(Imported_shemula_1,approxfun(ts1,
       Shemula,rule=1,method='linear'))
42 Multi_s  <- with(Multi,approxfun(ts1,Multi_X,rule=1,method='linear')
       )
43 Multi_s_1 <- with(Multi_1,approxfun(ts1,Multi_X,rule=1,method='
       linear'))
44
45 require(deSolve)
46 sir <- function(t,x,parms){
47   Sn <- x[1];L <- x[2];ASym<-x[3];Sym<-x[4];Tr<-x[5];Trfail<-x[6];
       Ssev<-x[7];Trsev<-x[8];D<-x[9];Rn<-x[10];LV<-x[11];CumInc<-x
       [12]
```

```
48  with(as.list(parms),
49       {
50         R_s = R_interpol_s(t)
51         R_s_std = R_stdinterpol_s(t)
52         IRScov = IRSinterpol_s(t)
53         Moz_Imported_Shemula= Imported_shemula_s(t)
54         Multiplier = Multi_s(t)
55
56         #print(R_s_std)
57         I=ASym+Sym+Ssev+Tr+Trfail+Trsev
58         N=Sn+L+ASym+Sym+Ssev+Tr+Trfail+Trsev+Rn+LV
59         # Fix the driver of infection as it will be the determiner
               of how change infections changes over t
60         betat<- beta*((amplit*(1+cos(2*pi*(t-phi))))*(t<10) + (t
               >=10)*(R_s_std)) #*(spline(t[577:820],R_s_std,xout=(t-
               phi))$y)))
61
62         lambdamh.n <- Multiplier*(1-IRScov*irseff)*Bh*betat*(I/N)
63         #Conditions on the treatment coverages
64         if( t >= 10 & t< 22) {x_sev=xt1}
65         else if (t>=22 & t<28) {x_sev=xt2}
66         else if (t>=28 & t<=30.25) {x_sev=xt3}
67         else (x_sev=xt4)
68
69         if(t >=10 & t< 22) {kappa_q=kappa_qt1}
70         else if (t>=22 & t<28) {kappa_q=kappa_qt2}
71         else if (t>=28 & t<=30.25) {kappa_q=kappa_qt3}
72         else (kappa_q=kappa_qt4)
73
74         if( t >=10 & t< 22) {kappa_A=kappa_At1}
75         else if (t>=22 & t<28) {kappa_A=kappa_At2}
76         else if (t>=28 & t<=30.25) {kappa_A=kappa_At3}
77         else (kappa_A=kappa_At4)
78
79         if( t >=10 & t< 22) {eta=etat1}
80         else if (t>=22 & t<28) {eta=etat2}
```

```
81          else if (t>=28 & t<=30.25) {eta=etat3}
82          else (eta=etat4)
83
84          if( t >=10 & t< 22) {pii=piit1}
85          else if (t>=22 & t<28) {pii=piit2}
86          else if (t>=28 & t<=30.25) {pii=piit3} #else if (t>=66 & t
              <=68.4) {pii=piit3}
87          else (pii=piit4)
88
89          dSn    <- (N/Ln) + (gamma)*rho*Rn - lambdamh.n*Sn - (1/Ln)*
              Sn -  Moz_Imported_Shemula
90          dL     <- lambdamh.n*Sn - (G)*alpha1*L - (1-G)*alpha*L - (1/
              Ln)*L
91          dASym <- (1-G)*alpha*L + (1-eta-pii)*epsolon1*Sym + (1-
              delta-delta1)*h*Tr + (delta2)*h2*Trfail + (thetha)*r*LV
               - epsolon2*ASym - (1/Ln)*ASym + 0.1*Moz_Imported_
              Shemula
92          dSym   <- (G)*alpha1*L + (eta1)*tau1*Trfail  + (1-thetha)*e*
              LV - (pii)*z*Sym - (eta)*tau*Sym - (1-eta-pii)*epsolon1*
              Sym - (1/Ln)*Sym + 0.4*Moz_Imported_Shemula
93          dTr    <- (eta)*tau*Sym - (delta)*Omega*Tr - (delta1)*Sigma*
              Tr - (1-delta-delta1)*h*Tr - (1/Ln)*Tr + 0.5*Moz_
              Imported_Shemula
94          dTrfail <- (delta1)*Sigma*Tr - (eta1)*tau1*Trfail - (kappa1
              )*omega1*Trfail - (delta2)*h2*Trfail - (1-eta1-kappa1-
              delta2)*Sigma1*Trfail - (1/Ln)*Trfail
95          dSsev <- (pii)*z*Sym + (kappa1)*omega1*Trfail - (kappa_q)*
              omega_q*Ssev - (kappa_A)*omega_A*Ssev - (x_sev)*V*Ssev -
               (1-x_sev-kappa_q-kappa_A)*psii*Ssev - (1/Ln)*Ssev
96          dTrsev <- (kappa_q)*omega_q*Ssev + (kappa_A)*omega_A*Ssev -
               (phi_d1)*chii_d1*Trsev - (phi_d2)*chii_d2*Trsev - (1-
              phi_d1-phi_d2)*xi*Trsev - (1/Ln)*Trsev
97          dD     <- (phi_d1)*chii_d1*Trsev + (phi_d2)*chii_d2*Trsev +
              (x_sev)*V*Ssev +(1-eta1-kappa1-delta2)*Sigma1*Trfail
98          dRn    <- (1-x_sev-kappa_q-kappa_A)*psii*Ssev + epsolon2*
              ASym + (1-phi_d1-phi_d2)*xi*Trsev + (delta)*Omega*Tr - (
```

```
            gamma)*rho*Rn - (1-gamma)*alpha2*Rn - (1/Ln)*Rn
99          dLV   <- (1-gamma)*alpha2*Rn - (1-thetha)*e*LV - (thetha)*r
              *LV - (1/Ln)*LV
100         dCumInc  <- lambdamh.n*(Sn+Rn) # this needs attention
101         res <- c(dSn, dL, dASym, dSym, dTr, dTrfail, dSsev, dTrsev,
              dD, dRn, dLV, dCumInc)
102         list(res)
103       })
104 }
105
106 a1 = 0.6; a2 = 0.8;a3 = 0.95; a4 =  0.05
107 parms <- c(beta=365.25/62,Bh=0.25,psii=52/26,gamma=0.0988,tau=52/
      0.3,Ln=62,alpha1=365.25/7,alpha=365.25/7.5,G=0.9,delta=0.96,h
      =365.25/18,
108           epsolon1=52/0.9,epsolon2=52/26,z=365.25/10,etat1=a1,etat2
                =a2,etat3=a3,etat4=a4,kappa_qt1=a1*0.8804,kappa_qt2=a2
                *0.8804,
109           kappa_qt3=a3*0.8804,kappa_qt4=a4*0.8804,kappa_At1=a1*
                0.1196,kappa_At2=a2*0.1196,kappa_At3=a3*0.1196,kappa_
                At4=a4*0.1196,
110           omega_q=365.25/55,omega_A=365.25/10,xi=365.25/55,Omega
                =365.25/70,V=365.25/4.5,chii_d1=52/5,chii_d2=52/6,xt1
                =0.8*0.8,
111           xt2=0.7*0.8,xt3=0.6*0.8,xt4=0.95*0.8,piit1=0.7*0.125,
                piit2=0.6*0.125,piit3=0.5*0.125,piit4=0.8*0.125,phi_d1
                =0.22,phi_d2=0.15,
112           delta1=0.05,Sigma=365.25/8,kappa1=0.125,omega1=365.25/4,
                eta1=0.70,tau1=365.25/7,delta2=0.175,h2=365.25/70,
                thetha=0.9,alpha2=1/4.50,
113           r=365.25/19,e=365.25/18,Sigma1=365.25/28,rho=1/5,irseff
                =0.38,phi=0.005/12,amplit=2.7)
114 ts <- seq(0,30.33333,1/12)
115 x0 <- c(2495-20-2-10,2,0,20,10,0,0,0,0,0,0,0)
116 stateMatrix <- ode(y=x0, ts, sir, parms)
117 colnames(stateMatrix) <- c("t","Sn", "L", "ASym", "Sym", "Tr", "
      Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
```

```
118
119 plot(stateMatrix[,"t"], stateMatrix[,"Sn"], type="l", lwd=2,
120       xlab="t", ylab="Population Size",ylim=c(1,3500))
121 lines(stateMatrix[,"t"], stateMatrix[,"L"], col="red", lwd=2)
122 lines(stateMatrix[,"t"], stateMatrix[,"ASym"], col="green", lwd=2)
123 lines(stateMatrix[,"t"], stateMatrix[,"Sym"], col="cyan", lwd=2)
124 lines(stateMatrix[,"t"], stateMatrix[,"Tr"], col="blue", lwd=2)
125 lines(stateMatrix[,"t"], stateMatrix[,"Trfail"], col="yellow", lwd
    =2)
126 lines(stateMatrix[,"t"], stateMatrix[,"Ssev"], col="orange", lwd=2)
127 lines(stateMatrix[,"t"], stateMatrix[,"Trsev"], col="darkblue", lwd
    =2)
128 lines(stateMatrix[,"t"], stateMatrix[,"D"], col="pink", lwd=2)
129 lines(stateMatrix[,"t"], stateMatrix[,"Rn"], col="darkgrey", lwd=2)
130 lines(stateMatrix[,"t"], stateMatrix[,"LV"], col="brown", lwd=2)
131 #lines(stateMatrix[,"t"], stateMatrix[,"CumInc"], col="brown", lwd
    =2)
132 legend("topright", c("Sn", "L", "ASym", "Sym", "Tr", "Trfail", "Ssev
    ", "Trsev", "D", "Rn", "LV"), col=c("black","red","green","cyan",
    "blue","yellow","orange","darkblue","pink","darkgrey","bisque"),
    lwd=1, horiz = T)
133
134 tim = seq(0, 30.2,1/12)
135 inc<-c(stateMatrix[1,"CumInc"])
136 for (tt in 2:length(tim)){
137   inc<-c(inc,stateMatrix[tt,"CumInc"] - stateMatrix[tt-1,"CumInc"])
138 }
139 par(mfrow=c(1,1))
140 plot_t<- seq(1988+1/12, 2018+2/12,1/12)
141 plot_t1<- seq(2010, 2018+2/12,1/12)
142 # plot(plot_t,data$Shemula[1:364], type = "o", col='blue', lwd=2,lty
    =1,ylim=c(0,185))
143 # lines(plot_t[1:364],inc[1:364], col='red', ty = 'o', lwd=2,lty=1)
144 # abline(h=95)
145
146 #Cummulative Incidence
```

```
147 par(mfrow=c(1,1))
148 plot(plot_t[1:363], cumsum(data$Shemula[1:363]), type="l", lwd=2,
      xlab="Time", ylab="Incidence",ylim=c(0,11000)) #cum incidence
149 lines(plot_t[1:363], stateMatrix[1:363,13], ty='l', col="red",lwd=3,
      lty=2) #first fit
150
151 cumbombay <- cumsum(data_1$Shemula[1:100]) #cumsum(bombay)
152 weeks_fit <- seq(0,8.2,1/12)
153
154 sir_fit <- function(t,x,parms){
155   Sn <- x[1];L <- x[2];ASym<-x[3];Sym<-x[4];Tr<-x[5];Trfail<-x[6];
        Ssev<-x[7];Trsev<-x[8];D<-x[9];Rn<-x[10];LV<-x[11];CumInc<-x
        [12]
156   with(as.list(parms),
157        {
158          R_s_1 = R_interpol_s_1(t)
159          R_s_std_1 = R_stdinterpol_s_1(t)
160          IRScov_1 = IRSinterpol_s_1(t)
161          Moz_Imported_Shemula_1= Imported_shemula_s_1(t)
162          Multiplier = Multi_s_1(t)
163          #print(R_s_std)
164          I=ASym+Sym+Ssev+Tr+Trfail+Trsev
165          N=Sn+L+ASym+Sym+Ssev+Tr+Trfail+Trsev+Rn+LV
166          # Fix the driver of infection as it will be the determiner
               of how change infections changes over t
167          betat<- R_s_std_1 #beta*((amplit*(1+cos(2*pi*(t-phi))))*(t
               <10) + (t>=10)*R_s_std_1) #*(spline(t[577:820],R_s_std,
               xout=(t-phi))$y)))
168          lambdamh.n <- Multiplier*(1-IRScov_1*irseff)*Bh*betat*(I/N)
169          #Conditions on the treatment coverages
170          if( t <= 6) {x_sev=xt2}
171          else (x_sev=xt3)
172
173          if(t <= 6) {kappa_q=kappa_qt2}
174          else (kappa_q=kappa_qt3)
175
```

```
176         if( t <= 6) {kappa_A=kappa_At2}
177         else (kappa_A=kappa_At3)
178
179         if( t <= 6) {eta=etat2}
180         else (eta=etat3)
181
182         if( t <= 6) {pii=piit2}
183         else (pii=piit3)
184
185         dSn    <- (N/Ln) + (gamma)*rho*Rn - lambdamh.n*Sn - (1/Ln)*
                Sn -  Moz_Imported_Shemula_1
186         dL     <- lambdamh.n*Sn - (G)*alpha1*L - (1-G)*alpha*L - (1/
                Ln)*L
187         dASym <- (1-G)*alpha*L + (1-eta-pii)*epsolon1*Sym + (1-
                delta-delta1)*h*Tr + (delta2)*h2*Trfail + (thetha)*r*LV
                 - epsolon2*ASym - (1/Ln)*ASym + 0.1*Moz_Imported_
                Shemula_1
188         dSym   <- (G)*alpha1*L + (eta1)*tau1*Trfail  + (1-thetha)*e*
                LV - (pii)*z*Sym - (eta)*tau*Sym - (1-eta-pii)*epsolon1*
                Sym - (1/Ln)*Sym + 0.4*Moz_Imported_Shemula_1
189         dTr    <- (eta)*tau*Sym - (delta)*Omega*Tr - (delta1)*Sigma*
                Tr - (1-delta-delta1)*h*Tr - (1/Ln)*Tr + 0.5*Moz_
                Imported_Shemula_1
190         dTrfail <- (delta1)*Sigma*Tr - (eta1)*tau1*Trfail - (kappa1
                )*omega1*Trfail - (delta2)*h2*Trfail - (1-eta1-kappa1-
                delta2)*Sigma1*Trfail - (1/Ln)*Trfail
191         dSsev <- (pii)*z*Sym + (kappa1)*omega1*Trfail - (kappa_q)*
                omega_q*Ssev - (kappa_A)*omega_A*Ssev - (x_sev)*V*Ssev -
                 (1-x_sev-kappa_q-kappa_A)*psii*Ssev - (1/Ln)*Ssev
192         dTrsev <- (kappa_q)*omega_q*Ssev + (kappa_A)*omega_A*Ssev -
                 (phi_d1)*chii_d1*Trsev - (phi_d2)*chii_d2*Trsev - (1-
                phi_d1-phi_d2)*xi*Trsev - (1/Ln)*Trsev
193         dD     <- (phi_d1)*chii_d1*Trsev + (phi_d2)*chii_d2*Trsev +
                (x_sev)*V*Ssev +(1-eta1-kappa1-delta2)*Sigma1*Trfail
194         dRn    <- (1-x_sev-kappa_q-kappa_A)*psii*Ssev + epsolon2*
                ASym + (1-phi_d1-phi_d2)*xi*Trsev + (delta)*Omega*Tr - (
```

```
            gamma)*rho*Rn - (1-gamma)*alpha2*Rn - (1/Ln)*Rn
195         dLV    <- (1-gamma)*alpha2*Rn - (1-thetha)*e*LV - (thetha)*r
              *LV - (1/Ln)*LV
196         dCumInc  <- lambdamh.n*(Sn+Rn) # this needs attention
197         res <- c(dSn, dL, dASym, dSym, dTr, dTrfail, dSsev, dTrsev,
              dD, dRn, dLV, dCumInc)
198         list(res)
199       })
200 }
201
202 require(bbmle)
203 # likelihood function
204 sirLL <- function(logbeta,lBh,logpsii,lgamma,logtau,logLn,logalpha1,
      logalpha,lG,ldelta,logh,logepsolon1,logepsolon2,logz,letat1,
      letat2,letat3,letat4,lkappa_qt1,
205                   lkappa_qt2,lkappa_qt3,lkappa_qt4,lkappa_At1,lkappa
                        _At2,lkappa_At3,lkappa_At4,logomega_q,logomega_
                        A,logxi,logOmega,logV,logchii_d1,logchii_d2,
206                   lxt1,lxt2,lxt3,lxt4,lpiit1,lpiit2,lpiit3,lpiit4,
                        lphi_d1,lphi_d2,ldelta1,logSigma,lkappa1,
                        logomega1,leta1,logtau1,ldelta2,logh2,lthetha,
207                   lalpha2,logr,loge,logSigma1,lrho,lirseff,lphi,
                        logamplit,logSn0,logL0,logSym0,logTr0) {
208   parms <- c(beta=exp(logbeta),Bh=plogis(lBh),psii=exp(logpsii),
        gamma=plogis(lgamma),tau=exp(logtau),Ln=exp(logLn),alpha1=exp(
        logalpha1),alpha=exp(logalpha),
209               G=plogis(lG),delta=plogis(ldelta),h=exp(logh),epsolon1=
                    exp(logepsolon1),epsolon2=exp(logepsolon2),z=exp(
                    logz),etat1=plogis(letat1),etat2=plogis(letat2),
210               etat3=plogis(letat3),etat4=plogis(letat4),kappa_qt1=
                    plogis(lkappa_qt1),kappa_qt2=plogis(lkappa_qt2),
                    kappa_qt3=plogis(lkappa_qt3),kappa_qt4=plogis(lkappa
                    _qt4),
211               kappa_At1=plogis(lkappa_At1),kappa_At2=plogis(lkappa_
                    At2),kappa_At3=plogis(lkappa_At3),kappa_At4=plogis(
                    lkappa_At4),omega_q=exp(logomega_q),omega_A=exp(
```

```
                logomega_A),
212             xi=exp(logxi),Omega=exp(logOmega),V=exp(logV),chii_d1=
                exp(logchii_d1),chii_d2=exp(logchii_d2),xt1=plogis(
                lxt1),xt2=plogis(lxt2),xt3=plogis(lxt3),xt4=plogis(
                lxt4),
213             piit1=plogis(lpiit1),piit2=plogis(lpiit2),piit3=plogis(
                lpiit3),piit4=plogis(lpiit4),phi_d1=plogis(lphi_d1),
                phi_d2=plogis(lphi_d2),delta1=plogis(ldelta1),Sigma=
                exp(logSigma),
214             kappa1=plogis(lkappa1),omega1=exp(logomega1),eta1=
                plogis(leta1),tau1=exp(logtau1),delta2=plogis(
                ldelta2),h2=exp(logh2),thetha=plogis(lthetha),alpha2
                =plogis(lalpha2),
215             r=exp(logr),e=exp(loge),Sigma1=exp(logSigma1),rho=
                plogis(lrho),irseff=plogis(lirseff),phi=plogis(lphi)
                ,amplit=log(logamplit))
216   x0 <- c(Sn=exp(logSn0), L=exp(logL0),0, Sym=exp(logSym0), Tr=exp(
        logTr0),0,0,0,0,0,0,0)
217   out <- ode(y=x0, weeks_fit, sir_fit, parms)
218   SD <- sqrt(sum((cumbombay-out[,13])^2)/length(weeks_fit) ) #The
        scale of 1 to 99 was removed for the second approx. to run.
        Rewrite it again once it hs worked!!!
219   -sum(dnorm(cumbombay, mean=out[,13], sd=SD, log=TRUE))
220 }
221
222 fit <- mle2(sirLL,start=list(logbeta=log(365.25/62),lBh=qlogis(0.25)
      ,logpsii=log(52/26),lgamma=qlogis(0.0988),logtau=log(52/0.3),
      logLn=log(62), #1:6
223                               logalpha1=log(365.25/7),logalpha=log(365.25/
                                  7.5),lG=qlogis(0.9),ldelta=qlogis(0.96),
                                  logh=log(365.25/18), #7:11
224                               logepsolon1=log(52/0.9),logepsolon2=log(52/
                                  26),logz=log(365.25/10),letat1=qlogis(a1),
                                  letat2=qlogis(a2), #12:16
225                               letat3=qlogis(a3),letat4=qlogis(a4),lkappa_
                                  qt1=qlogis(a1*0.8804),lkappa_qt2=qlogis(a2
```

```
                *0.8804),lkappa_qt3=qlogis(a3*0.8804), #
                17:21
226             lkappa_qt4=qlogis(a4*0.8804),lkappa_At1=
                qlogis(a1*0.1196),lkappa_At2=qlogis(a2*
                0.1196),lkappa_At3=qlogis(a3*0.1196), #
                22:25
227             lkappa_At4=qlogis(a4*0.1196), #26
228             logomega_q=log(365.25/55),logomega_A=log
                (365.25/10),logxi=log(365.25/55),logOmega=
                log(365.25/70), #27:30
229             logV=log(365.25/4.5),logchii_d1=log(52/5),
                logchii_d2=log(52/6), #31:33
230             lxt1=qlogis(0.8*0.8),lxt2=qlogis(0.7*0.8),
                lxt3=qlogis(0.6*0.8), #34:36
231             lxt4=qlogis(0.95*0.8),lpiit1=qlogis(0.7*
                0.125),lpiit2=qlogis(0.6*0.125),lpiit3=
                qlogis(0.5*0.125),lpiit4=qlogis(0.8*0.125)
                , #37:41
232             lphi_d1=qlogis(0.22),lphi_d2=qlogis(0.15),
                ldelta1=qlogis(0.05),logSigma=log(365.25/
                8),lkappa1=qlogis(0.125),logomega1=log
                (365.25/4), #42:47
233             leta1=qlogis(0.70),logtau1=log(365.25/7),
                ldelta2=qlogis(0.175),logh2=log(365.25/70)
                ,lthetha=qlogis(0.9),lalpha2=qlogis(1/
                4.50), #48:53
234             logr=log(365.25/19),loge=log(365.25/18),
                logSigma1=log(365.25/28),lrho=qlogis(1/5),
                lirseff=qlogis(0.38),lphi=qlogis(0.005/12)
                , logamplit=log(2.7), #54:60
235             logSn0=log(2495-20-2-10),logL0=log(2),logSym0
                =log(20),logTr0=log(10)), #61:64
236         method="Nelder-Mead",
237         control=list(maxit=1E5,trace=0),
238         trace=FALSE)
239 summary(fit)
```

```
240 # Save a single object to a file
241 saveRDS((fit), "Shemula Max_Fit.rds")
242 # Restore it under a different name
243 my_data <- readRDS("Shemula Max_Fit.rds")
244
245 theta <- as.numeric(c(exp(coef(fit)[1]),plogis(coef(fit)[2]),exp(
      coef(fit)[3]),plogis(coef(fit)[4]),exp(coef(fit)[5:8]),plogis(
      coef(fit)[9:10]),
246                       exp(coef(fit)[11:14]),plogis(coef(fit)[15:26])
                          ,exp(coef(fit)[27:33]),plogis(coef(fit)
                          [34:44]),exp(coef(fit)[45]),plogis(coef(fit
                          )[46]),
247                       exp(coef(fit)[47]),plogis(coef(fit)[48]),exp(
                          coef(fit)[49]),plogis(coef(fit)[50]),exp(
                          coef(fit)[51]),plogis(coef(fit)[52:53]),
248                       exp(coef(fit)[54:56]),plogis(coef(fit)[57:59])
                          , exp(coef(fit)[60:64])) )
249
250 parms_1 <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10],h=theta[11],
251             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1=
                theta[15],etat2=theta[16],etat3=theta[17],etat4=theta
                [18],kappa_qt1=theta[19],kappa_qt2=theta[20],
252             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_At4
                =theta[26],omega_q=theta[27],omega_A=theta[28],
253             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],xt3
                =theta[36],xt4=theta[37],piit1=theta[38],
254             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=theta
                [48],
255             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=theta
                [52],alpha2=theta[53],r=theta[54],e=theta[55],Sigma1=
```

```
                theta[56],rho=theta[57],irseff=theta[58],phi=theta
                [59],amplit=theta[60])

par_comparison <- cbind(parms,parms_1) #comapare parameters before
    and after before fitting model
times <- seq(0, 8.2,1/12)
x0_1 <- c(theta[61:62],0,theta[63:64],0,0,0,0,0,0,0)
stateMatrix1 <- ode(y=x0_1, times, sir_fit, parms_1)
colnames(stateMatrix1) <- c("time","Sn", "L", "ASym", "Sym", "Tr", "
    Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")

tim <- 1:99
inc_1<-c(stateMatrix1[1,"CumInc"])
for (tt in 2:length(tim)){
  inc_1<-c(inc_1,stateMatrix1[tt,"CumInc"] - stateMatrix1[tt-1,"
      CumInc"])
}

plot_time<- seq(1988+1/12, 2018+3/12,1/12)
plot_time1<- seq(2010, 2018+2/12,1/12)
par(mfrow=c(1,1))
plot(plot_time1[1:99], cumbombay[1:99], type="o", lwd=2, xlab="Time"
    , ylab="Incidence",ylim=c(0,50)) #cum incidence
lines(plot_time1[1:99], stateMatrix1[,13], type="o",col="green") #
    MLE fit

#Incidence
plot(plot_time[264:363], data$Shemula[264:363], type="l", lwd=2,
    xlab="Time", ylab="Incidence",ylim=c(0,8)) #cum incidence
#lines(plot_time[264:363], inc[264:363], ty='l', col="red",lwd=3,lty
    =2) #first fit
lines(plot_time1[1:99], (inc_1[1:99]), type="l",col="green",lwd=3,
    lty=1) #MLE fit

#Maximum Likelihood second FIT
fit2 <- mle2(sirLL,
```

```
282                 start=as.list(coef(fit)),
283                 fixed=list(logSn0=coef(fit)[61],
284                            logL0=coef(fit)[62],
285                            logSym0=coef(fit)[63],
286                            logTr0=coef(fit)[64]),
287                 method="Nelder-Mead",
288                 control=list(maxit=1E5,trace=2),
289                 trace=TRUE)
290
291 summary(fit2)
292
293 theta_2 <- as.numeric(c(exp(coef(fit2)[1]),plogis(coef(fit2)[2]),exp
        (coef(fit2)[3]),plogis(coef(fit2)[4]),exp(coef(fit2)[5:8]),plogis
        (coef(fit2)[9:10]),
294                         exp(coef(fit2)[11:14]),plogis(coef(fit2)
                                [15:26]),exp(coef(fit2)[27:33]),plogis(coef
                                (fit2)[34:44]),exp(coef(fit2)[45]),plogis(
                                coef(fit2)[46]),
295                         exp(coef(fit2)[47]),plogis(coef(fit2)[48]),exp
                                (coef(fit2)[49]),plogis(coef(fit2)[50]),exp
                                (coef(fit2)[51]),plogis(coef(fit2)[52:53]),
296                         exp(coef(fit2)[54:56]),plogis(coef(fit2)
                                [57:59]), exp(coef(fit2)[60:64])) )
297
298 parms_2 <- c(beta=theta_2[1],Bh=theta_2[2],psii=theta_2[3],gamma=
        theta_2[4],tau=theta_2[5],Ln=theta_2[6],alpha1=theta_2[7],alpha=
        theta_2[8],G=theta_2[9],delta=theta_2[10],h=theta_2[11],
299                 epsolon1=theta_2[12],epsolon2=theta_2[13],z=theta_
                        2[14],etat1=theta_2[15],etat2=theta_2[16],etat3=
                        theta_2[17],etat4=theta_2[18],kappa_qt1=theta_2[19],
                        kappa_qt2=theta_2[20],
300                 kappa_qt3=theta_2[21],kappa_qt4=theta_2[22],kappa_At1=
                        theta_2[23],kappa_At2=theta_2[24],kappa_At3=theta_
                        2[25],kappa_At4=theta_2[26],omega_q=theta_2[27],
                        omega_A=theta_2[28],
```

```
301                 xi=theta_2[29],Omega=theta_2[30],V=theta_2[31],chii_d1=
                        theta_2[32],chii_d2=theta_2[33],xt1=theta_2[34],xt2=
                        theta_2[35],xt3=theta_2[36],xt4=theta_2[37],piit1=
                        theta_2[38],
302                 piit2=theta_2[39],piit3=theta_2[40],piit4=theta_2[41],
                        phi_d1=theta_2[42],phi_d2=theta_2[43],delta1=theta_
                        2[44],Sigma=theta_2[45],kappa1=theta_2[46],omega1=
                        theta_2[47],eta1=theta_2[48],
303                 tau1=theta_2[49],delta2=theta_2[50],h2=theta_2[51],
                        thetha=theta_2[52],alpha2=theta_2[53],r=theta_2[54],
                        e=theta_2[55],Sigma1=theta_2[56],rho=theta_2[57],
                        irseff=theta_2[58],phi=theta_2[59],amplit=theta_
                        2[60])
304
305 par_comparison <- cbind(parms,parms_1,parms_2) #comapare parameters
        before and after before fitting model
306 times <- seq(0, 8.2,1/12)
307 x0_2 <- c(theta_2[61:62],0,theta_2[63:64],0,0,0,0,0,0,0)
308 stateMatrix2 <- ode(y=x0_2, times, sir_fit, parms_2)
309 colnames(stateMatrix2) <- c("time","Sn", "L", "ASym", "Sym", "Tr", "
        Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
310
311 inc_2<-c(stateMatrix2[1,"CumInc"])
312 for (tt in 2:length(tim)){
313   inc_2<-c(inc_2,stateMatrix2[tt,"CumInc"] - stateMatrix2[tt-1,"
          CumInc"])
314 }
315
316 plot(plot_time1[1:99], cumbombay, type="l", lwd=2, xlab="Time", ylab
        ="Incidence",ylim=c(0,40)) #cum incidence
317 plot(plot_time[264:362], stateMatrix[264:362,13], ty='l', col="red",
        lwd=3,lty=2) #first fit
318 lines(plot_time1[1:99], stateMatrix1[,13], type="l",col="green") #
        MLE fit
319 lines(plot_time1[1:99], stateMatrix2[,13], type="l",col="blue") #MLE
         second fit
```

```
320
321 #Incidence
322 plot(plot_time1[1:99], data_1$Shemula[1:99], type="l", lwd=2, xlab="
      Time", ylab="Incidence",ylim=c(0,10)) #cum incidence
323 lines(plot_time[1:99], inc[264:362], ty='l', col="red",lwd=3,lty=2)
      #first fit
324 lines(plot_time1[1:99], inc_1, type="l",col="green",lwd=3,lty=2) #
      MLE fit
325 lines(plot_time1[1:99], inc_2, type="l",col="blue",lwd=3,lty=1) #MLE
       second fit
326
327 #Possion distriution method
328 sirLL2 <- function(logbeta,lBh,logpsii,lgamma,logtau,logLn,logalpha1
      ,logalpha,lG,ldelta,logh,logepsolon1,logepsolon2,logz,letat1,
      letat2,letat3,letat4,lkappa_qt1,
329                         lkappa_qt2,lkappa_qt3,lkappa_qt4,lkappa_At1,
                              lkappa_At2,lkappa_At3,lkappa_At4,logomega_q,
                              logomega_A,logxi,logOmega,logV,logchii_d1,
                              logchii_d2,
330                         lxt1,lxt2,lxt3,lxt4,lpiit1,lpiit2,lpiit3,lpiit4,
                              lphi_d1,lphi_d2,ldelta1,logSigma,lkappa1,
                              logomega1,leta1,logtau1,ldelta2,logh2,lthetha,
331                         lalpha2,logr,loge,logSigma1,lrho,lirseff,lphi,
                              logamplit,logSn0,logL0,logSym0,logTr0) {
332   parms_2 <- c(beta=exp(logbeta),Bh=plogis(lBh),psii=exp(logpsii),
        gamma=plogis(lgamma),tau=exp(logtau),Ln=exp(logLn),alpha1=exp(
        logalpha1),alpha=exp(logalpha),
333                     G=plogis(lG),delta=plogis(ldelta),h=exp(logh),
                          epsolon1=exp(logepsolon1),epsolon2=exp(logepsolon2
                          ),z=exp(logz),etat1=plogis(letat1),etat2=plogis(
                          letat2),
334                     etat3=plogis(letat3),etat4=plogis(letat4),kappa_qt1=
                          plogis(lkappa_qt1),kappa_qt2=plogis(lkappa_qt2),
                          kappa_qt3=plogis(lkappa_qt3),kappa_qt4=plogis(
                          lkappa_qt4),
```

```
335                     kappa_At1=plogis(lkappa_At1),kappa_At2=plogis(lkappa_
                            At2),kappa_At3=plogis(lkappa_At3),kappa_At4=plogis
                            (lkappa_At4),omega_q=exp(logomega_q),omega_A=exp(
                            logomega_A),
336                     xi=exp(logxi),Omega=exp(logOmega),V=exp(logV),chii_d1
                            =exp(logchii_d1),chii_d2=exp(logchii_d2),xt1=
                            plogis(lxt1),xt2=plogis(lxt2),xt3=plogis(lxt3),xt4
                            =plogis(lxt4),
337                     piit1=plogis(lpiit1),piit2=plogis(lpiit2),piit3=
                            plogis(lpiit3),piit4=plogis(lpiit4),phi_d1=plogis(
                            lphi_d1),phi_d2=plogis(lphi_d2),delta1=plogis(
                            ldelta1),Sigma=exp(logSigma),
338                     kappa1=plogis(lkappa1),omega1=exp(logomega1),eta1=
                            plogis(leta1),tau1=exp(logtau1),delta2=plogis(
                            ldelta2),h2=exp(logh2),thetha=plogis(lthetha),
                            alpha2=plogis(lalpha2),
339                     r=exp(logr),e=exp(loge),Sigma1=exp(logSigma1),rho=
                            plogis(lrho),irseff=plogis(lirseff),phi=plogis(
                            lphi),amplit=log(logamplit))
340   x0 <- c(Sn=exp(logSn0), L=exp(logL0),0, Sym=exp(logSym0), Tr=exp(
          logTr0),0,0,0,0,0,0,0)
341   out <- ode(y=x0, weeks_fit, sir_fit, parms_2)
342   -sum(dpois(cumbombay[1:99], lambda=out[1:99,13], log=TRUE))
343 }
344
345 fit.pois <- mle2(sirLL2,
346                  start=list(logbeta=log(365.25/125),lBh=qlogis(0.25)
                         ,logpsii=log(52/26),lgamma=qlogis(0.0988),logtau
                         =log(52/0.3),logLn=log(62), #1:6
347                                     logalpha1=log(365.25/7),
                                        logalpha=log(365.25/7.5),
                                        lG=qlogis(0.9),ldelta=
                                        qlogis(0.96),logh=log
                                        (365.25/18), #7:11
348                                     logepsolon1=log(52/0.9),
                                        logepsolon2=log(52/26),
```

```
                logz=log(365.25/10),letat1
                =qlogis(a1),letat2=qlogis(
                a2), #12:16
349             letat3=qlogis(a3),letat4=
                qlogis(a4),lkappa_qt1=
                qlogis(a1*0.8804),lkappa_
                qt2=qlogis(a2*0.8804),
                lkappa_qt3=qlogis(a3*
                0.8804), #17:21
350             lkappa_qt4=qlogis(a4*0.8804),
                lkappa_At1=qlogis(a1*
                0.1196),lkappa_At2=qlogis(
                a2*0.1196),lkappa_At3=
                qlogis(a3*0.1196), #22:25
351             lkappa_At4=qlogis(a4*0.1196),
                 #26
352             logomega_q=log(365.25/55),
                logomega_A=log(365.25/10),
                logxi=log(365.25/55),
                logOmega=log(365.25/70), #
                27:30
353             logV=log(365.25/4.5),logchii_
                d1=log(52/5),logchii_d2=
                log(52/6), #31:33
354             lxt1=qlogis(0.8*0.8),lxt2=
                qlogis(0.7*0.8),lxt3=
                qlogis(0.6*0.8), #34:36
355             lxt4=qlogis(0.95*0.8),lpiit1=
                qlogis(0.7*0.125),lpiit2=
                qlogis(0.6*0.125),lpiit3=
                qlogis(0.5*0.125),lpiit4=
                qlogis(0.8*0.125), #37:41
356             lphi_d1=qlogis(0.22),lphi_d2=
                qlogis(0.15),ldelta1=
                qlogis(0.05),logSigma=log
                (365.25/8),lkappa1=qlogis
```

```
                                                    (0.125),logomega1=log
                                                    (365.25/4), #42:47
357                                                 leta1=qlogis(0.70),logtau1=
                                                    log(365.25/7),ldelta2=
                                                    qlogis(0.175),logh2=log
                                                    (365.25/70),lthetha=qlogis
                                                    (0.9),lalpha2=qlogis(1/
                                                    4.50), #48:53
358                                                 logr=log(365.25/19),loge=log
                                                    (365.25/18),logSigma1=log
                                                    (365.25/28),lrho=qlogis(1/
                                                    5),lirseff=qlogis(0.38),
                                                    lphi=qlogis(0.005/12),
                                                    logamplit=log(2.7), #54:60
359                                                 logSn0=log(2495-20-2-10),
                                                    logL0=log(2),logSym0=log
                                                    (20),logTr0=log(10)), #
                                                    61:64
360                         method="Nelder-Mead",
361                         control=list(maxit=1E5,trace=0),
362                         trace=FALSE)
363
364 summary(fit.pois)
365
366 theta_3 <- as.numeric(c(exp(coef(fit.pois)[1]),plogis(coef(fit.pois)
      [2]),exp(coef(fit.pois)[3]),plogis(coef(fit.pois)[4]),exp(coef(
      fit.pois)[5:8]),plogis(coef(fit.pois)[9:10]),
367                               exp(coef(fit.pois)[11:14]),plogis(coef(fit.
                                      pois)[15:26]),exp(coef(fit.pois)[27:33]),
                                      plogis(coef(fit.pois)[34:44]),exp(coef(
                                      fit.pois)[45]),plogis(coef(fit.pois)[46])
                                      ,
368                               exp(coef(fit.pois)[47]),plogis(coef(fit.pois
                                      )[48]),exp(coef(fit.pois)[49]),plogis(
                                      coef(fit.pois)[50]),exp(coef(fit.pois)
                                      [51]),plogis(coef(fit.pois)[52:53]),
```

```
369                                exp(coef(fit.pois)[54:56]),plogis(coef(fit.
                                       pois)[57:59]), exp(coef(fit.pois)[60:64])
                                       ) )
370
371 parms_3 <- c(beta=theta_3[1],Bh=theta_3[2],psii=theta_3[3],gamma=
        theta_3[4],tau=theta_3[5],Ln=theta_3[6],alpha1=theta_3[7],alpha=
        theta_3[8],G=theta_3[9],delta=theta_3[10],h=theta_3[11],
372                 epsolon1=theta_3[12],epsolon2=theta_3[13],z=theta_
                        3[14],etat1=theta_3[15],etat2=theta_3[16],etat3=
                        theta_3[17],etat4=theta_3[18],kappa_qt1=theta_3[19],
                        kappa_qt2=theta_3[20],
373                 kappa_qt3=theta_3[21],kappa_qt4=theta_3[22],kappa_At1=
                        theta_3[23],kappa_At2=theta_3[24],kappa_At3=theta_
                        3[25],kappa_At4=theta_3[26],omega_q=theta_3[27],
                        omega_A=theta_3[28],
374                 xi=theta_3[29],Omega=theta_3[30],V=theta_3[31],chii_d1=
                        theta_3[32],chii_d2=theta_3[33],xt1=theta_3[34],xt2=
                        theta_3[35],xt3=theta_3[36],xt4=theta_3[37],piit1=
                        theta_3[38],
375                 piit2=theta_3[39],piit3=theta_3[40],piit4=theta_3[41],
                        phi_d1=theta_3[42],phi_d2=theta_3[43],delta1=theta_
                        3[44],Sigma=theta_3[45],kappa1=theta_3[46],omega1=
                        theta_3[47],eta1=theta_3[48],
376                 tau1=theta_3[49],delta2=theta_3[50],h2=theta_3[51],
                        thetha=theta_3[52],alpha2=theta_3[53],r=theta_3[54],
                        e=theta_3[55],Sigma1=theta_3[56],rho=theta_3[57],
                        irseff=theta_3[58],phi=theta_3[59],amplit=theta_
                        3[60])
377
378 par_comparison <- cbind(parms,parms_3) #comapare parameters before
        and after before fitting model
379 times <- seq(0, 8.2,1/12)
380 x0_3 <- c(theta_3[61:62],0,theta_3[63:64],0,0,0,0,0,0,0)
381 stateMatrix3 <- ode(y=x0_3, times, sir_fit, parms_3)
382 colnames(stateMatrix3) <- c("t","Sn", "L", "ASym", "Sym", "Tr", "
        Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
```

```
383
384 stateMatrix <- ode(y=x0, times, sir_fit, parms)
385 colnames(stateMatrix) <- c("t","Sn", "L", "ASym", "Sym", "Tr", "
    Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
386 tim = seq(0, 8.2,1/12)
387 inc<-c(stateMatrix[1,"CumInc"])
388 for (tt in 2:length(tim)){
389   inc<-c(inc,stateMatrix[tt,"CumInc"] - stateMatrix[tt-1,"CumInc"])
390 }
391
392 inc_3<-c(stateMatrix3[1,"CumInc"])
393 for (tt in 2:length(tim)){
394   inc_3<-c(inc_3,stateMatrix3[tt,"CumInc"] - stateMatrix3[tt-1,"
      CumInc"])
395 }
396
397 #Poission Likelihood second FIT
398 fit.pois2 <- mle2(sirLL2,
399               start=as.list(coef(fit.pois)),
400               fixed=list(logSn0=coef(fit.pois)[61],
401                          logL0=coef(fit.pois)[62],
402                          logSym0=coef(fit.pois)[63],
403                          logTr0=coef(fit.pois)[64]),
404               method="Nelder-Mead",
405               control=list(maxit=1E5,trace=2),
406               trace=TRUE)
407
408 summary(fit.pois2)
409
410 theta_4 <- as.numeric(c(exp(coef(fit.pois2)[1]),plogis(coef(fit.
    pois2)[2]),exp(coef(fit.pois2)[3]),plogis(coef(fit.pois2)[4]),exp
    (coef(fit.pois2)[5:8]),plogis(coef(fit.pois2)[9:10]),
411                           exp(coef(fit.pois2)[11:14]),plogis(coef(fit.
                                  pois2)[15:26]),exp(coef(fit.pois2)
                                  [27:33]),plogis(coef(fit.pois2)[34:44]),
                                  exp(coef(fit.pois2)[45]),plogis(coef(fit.
```

```
                                pois2)[46]),
412                           exp(coef(fit.pois2)[47]),plogis(coef(fit.
                                pois2)[48]),exp(coef(fit.pois2)[49]),
                                plogis(coef(fit.pois2)[50]),exp(coef(fit.
                                pois2)[51]),plogis(coef(fit.pois2)
                                [52:53]),
413                           exp(coef(fit.pois2)[54:56]),plogis(coef(fit.
                                pois2)[57:59]), exp(coef(fit.pois2)
                                [60:64])) )
414
415 parms_4 <- c(beta=theta_4[1],Bh=theta_4[2],psii=theta_4[3],gamma=
      theta_4[4],tau=theta_4[5],Ln=theta_4[6],alpha1=theta_4[7],alpha=
      theta_4[8],G=theta_4[9],delta=theta_4[10],h=theta_4[11],
416               epsolon1=theta_4[12],epsolon2=theta_4[13],z=theta_
                    4[14],etat1=theta_4[15],etat2=theta_4[16],etat3=
                    theta_4[17],etat4=theta_4[18],kappa_qt1=theta_4[19],
                    kappa_qt2=theta_4[20],
417               kappa_qt3=theta_4[21],kappa_qt4=theta_4[22],kappa_At1=
                    theta_4[23],kappa_At2=theta_4[24],kappa_At3=theta_
                    4[25],kappa_At4=theta_4[26],omega_q=theta_4[27],
                    omega_A=theta_4[28],
418               xi=theta_4[29],Omega=theta_4[30],V=theta_4[31],chii_d1=
                    theta_4[32],chii_d2=theta_4[33],xt1=theta_4[34],xt2=
                    theta_4[35],xt3=theta_4[36],xt4=theta_4[37],piit1=
                    theta_4[38],
419               piit2=theta_4[39],piit3=theta_4[40],piit4=theta_4[41],
                    phi_d1=theta_4[42],phi_d2=theta_4[43],delta1=theta_
                    4[44],Sigma=theta_4[45],kappa1=theta_4[46],omega1=
                    theta_4[47],eta1=theta_4[48],
420               tau1=theta_4[49],delta2=theta_4[50],h2=theta_4[51],
                    thetha=theta_4[52],alpha2=theta_4[53],r=theta_4[54],
                    e=theta_4[55],Sigma1=theta_4[56],rho=theta_4[57],
                    irseff=theta_4[58],phi=theta_4[59],amplit=theta_
                    4[60])
421
```

```
422 par_comparison <- cbind(parms,parms_1,parms_2,parms_3,parms_4) #
      comapare parameters before and after before fitting model
423 x0_3 <- c(theta_4[61:62],0,theta_4[63:64],0,0,0,0,0,0,0)
424 stateMatrix4 <- ode(y=x0_3, times, sir_fit, parms_4)
425 colnames(stateMatrix4) <- c("time","Sn", "L", "ASym", "Sym", "Tr", "
      Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
426
427 inc_4<-c(stateMatrix4[1,"CumInc"])
428 for (tt in 2:length(tim)){
429   inc_4<-c(inc_2,stateMatrix4[tt,"CumInc"] - stateMatrix4[tt-1,"
        CumInc"])
430 }
```

9.2 Model Prediction Scenarios

```
1 library(deSolve)
2 library(readxl)
3 library(xlsx)
4 library(maxLik)
5 library(bbmle)
6 library("openxlsx")
7 #Data fitting
8 rm(list=ls())
9 data_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town
    /Dissertation/Thesis Work/Model building/Start Afresh/Scenarios_
    NDUMO/Total_local_cases1_1_Ndumo.xlsx", sheet = 1, startRow = 1,
    colNames = TRUE)
10 climatedata_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/chirps_1.xlsx", sheet= 1, startRow = 1, colNames
    = TRUE)
11 climatedata1_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/chirps_1.xlsx", sheet= 2, startRow = 1, colNames
    = TRUE)
12 data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
```

```
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1.xlsx", sheet =
    1, startRow = 1, colNames = TRUE)
#data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1_0.0%.xlsx",
    sheet = 1, startRow = 1, colNames = TRUE)
#data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1_80%.xlsx",
    sheet = 1, startRow = 1, colNames = TRUE)
#data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1_100%.xlsx",
    sheet = 1, startRow = 1, colNames = TRUE)
#Imported_Ndumo_1<-read.xlsx("C:/Users/mandi/OneDrive - University
    of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh
    /Scenarios_NDUMO/Malaria cases imported diagnosed in Ndumo_1_
    Increase.xlsx", sheet = 1, startRow = 1, colNames = TRUE)
Imported_Ndumo_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
     Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/Malaria cases imported diagnosed in Ndumo_1_
    Original.xlsx", sheet = 1, startRow = 1, colNames = TRUE)

# Defining functions for Vector dynamics
climatedata_1$ts           <- with(climatedata_1, seq(0,12-1/12,1/12)
    )
climatedata1_1$ts           <- with(climatedata1_1, seq(0,12-1/12,1/
    12))
data_IRScov_1$ts           <- with(data_IRScov_1, seq(0,12-1/12,1/12)
    )
Imported_Ndumo_1$ts1 <- with(Imported_Ndumo_1, seq(0,12-1/12,1/12))

R_interpol_s_1               <- with(climatedata_1,approxfun(ts,
    Umkhanyakude_rain,rule=1,method='linear'))
R_stdinterpol_s_1            <- with(climatedata1_1,approxfun(ts,
```

```
    Umkhanyakude_std,rule=1,method='linear'))
IRSinterpol_s_1                <- with(data_IRScov_1,approxfun(ts,
    Ndum1,rule=1,method='linear'))
Imported_Ndumo_s_1  <- with(Imported_Ndumo_1,approxfun(ts1,Ndumo,
    rule=1,method='linear'))

cumbombay <- cumsum(data_1$Ndumo) #cumsum(bombay)
weeks_fit <- seq(0,12-2/12,1/12) #seq(0, 12-1/12,1/12)
times <- seq(0, 12-1/12,1/12) #seq(0, 12-1/12,1/12)
tim <- 1:144 #1:144

sir_fit <- function(t,x,parms){
  Sn <- x[1];L <- x[2];ASym<-x[3];Sym<-x[4];Tr<-x[5];Trfail<-x[6];
      Ssev<-x[7];Trsev<-x[8];D<-x[9];Rn<-x[10];LV<-x[11];CumInc<-x
      [12]
  with(as.list(parms),
       {
         R_s_std_1 = R_stdinterpol_s_1(t)
         IRScov_1 = IRSinterpol_s_1(t)
         Moz_Imported_Ndumo_1= Imported_Ndumo_s_1(t)
         I=ASym+Sym+Ssev+Tr+Trfail+Trsev
         N=Sn+L+ASym+Sym+Ssev+Tr+Trfail+Trsev+Rn+LV

         #Conditions on the treatment coverages
         if( t <= 6) {x_sev=xt2}
         else (x_sev=xt3)

         if(t <= 6) {kappa_q=kappa_qt2} #This is the problem
         else (kappa_q=kappa_qt3)

         if( t <= 6) {kappa_A=kappa_At2}
         else (kappa_A=kappa_At3)

         if( t <= 6) {eta=etat2}
         else (eta=etat3)

```

```
58          if( t <= 8.33333333) {irseff=0.38}
59          else (irseff=0.9)
60
61          if( t <= 6) {pii=piit2}
62          else (pii=piit3)
63
64          if( t <= 6) {aa=1}
65          else (aa=1)
66
67          if( t >= 7.83333333 & t< 7.91666667) {mult=2.4}
68          else if(t >= 8.16666667 & t<= 8.25) {mult=5.3} #
69          else if(t >= 0 & t<= 0.58333333) {mult=1} #
70          else if(t > 8.25 & t<= 8.33333333) {mult=2.9} #
71          else if(t > 8.33333333){mult=1.4}
72          else (mult=1.3)
73
74          #Fix the driver of infection as it will be the determiner
               of how change infection changes over t
75          betat <- mult*R_s_std_1 #beta*((amplit*(1+cos(2*pi*(t-phi))
               ))*(t<10) + (t>=10)*R_s_std_1) #*(spline(t[577:820],R_s_
               std,xout=(t-phi))$y)))
76          lambdamh.n <- (1-IRScov_1*irseff)*mult*Bh*betat*(I/N)
77
78          dSn    <- (N/Ln) + (gamma)*rho*Rn - lambdamh.n*Sn - (1/Ln)*
               Sn -  aa*Moz_Imported_Ndumo_1
79          dL     <- lambdamh.n*Sn - (G)*alpha1*L - (1-G)*alpha*L - (1/
               Ln)*L
80          dASym <- (1-G)*alpha*L + (1-eta-pii)*epsolon1*Sym + (1-
               delta-delta1)*h*Tr + (delta2)*h2*Trfail + (thetha)*r*LV
                - epsolon2*ASym - (1/Ln)*ASym + 0.1*aa*Moz_Imported_
               Ndumo_1
81          dSym   <- (G)*alpha1*L + (eta1)*tau1*Trfail  + (1-thetha)*e*
               LV - (pii)*z*Sym - (eta)*tau*Sym - (1-eta-pii)*epsolon1*
               Sym - (1/Ln)*Sym + 0.4*aa*Moz_Imported_Ndumo_1
82          dTr    <- (eta)*tau*Sym - (delta)*Omega*Tr - (delta1)*Sigma*
               Tr - (1-delta-delta1)*h*Tr - (1/Ln)*Tr + 0.5*aa*Moz_
```

```
            Imported_Ndumo_1
83          dTrfail <- (delta1)*Sigma*Tr - (eta1)*tau1*Trfail - (kappa1
              )*omega1*Trfail - (delta2)*h2*Trfail - (1-eta1-kappa1-
              delta2)*Sigma1*Trfail - (1/Ln)*Trfail
84          dSsev <- (pii)*z*Sym + (kappa1)*omega1*Trfail - (kappa_q)*
              omega_q*Ssev - (kappa_A)*omega_A*Ssev - (x_sev)*V*Ssev -
               (1-x_sev-kappa_q-kappa_A)*psii*Ssev - (1/Ln)*Ssev
85          dTrsev <- (kappa_q)*omega_q*Ssev + (kappa_A)*omega_A*Ssev -
               (phi_d1)*chii_d1*Trsev - (phi_d2)*chii_d2*Trsev - (1-
              phi_d1-phi_d2)*xi*Trsev - (1/Ln)*Trsev
86          dD     <- (phi_d1)*chii_d1*Trsev + (phi_d2)*chii_d2*Trsev +
              (x_sev)*V*Ssev +(1-eta1-kappa1-delta2)*Sigma1*Trfail
87          dRn    <- (1-x_sev-kappa_q-kappa_A)*psii*Ssev + epsolon2*
              ASym + (1-phi_d1-phi_d2)*xi*Trsev + (delta)*Omega*Tr - (
              gamma)*rho*Rn - (1-gamma)*alpha2*Rn - (1/Ln)*Rn
88          dLV    <- (1-gamma)*alpha2*Rn - (1-thetha)*e*LV - (thetha)*r
              *LV - (1/Ln)*LV
89          dCumInc  <- lambdamh.n*(Sn+Rn) # this needs attention
90          res <- c(dSn, dL, dASym, dSym, dTr, dTrfail, dSsev, dTrsev,
               dD, dRn, dLV, dCumInc)
91          list(res)
92        })
93  }
94
95  #For saved parameters purposes
96  Max_Ndumo_1 <- read.xlsx("C:/Users/mandi/OneDrive - University of
      Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
      Scenarios_NDUMO/Fitted_Parameter_values_Max1_Ndumo.xlsx", sheet =
       1, startRow = 1, colNames = FALSE)
97  #
98  Max_Ndumo_1_par <- as.vector(Max_Ndumo_1[,1])
99  theta <- as.numeric(c((Max_Ndumo_1_par[1]),(Max_Ndumo_1_par[2]),(Max
      _Ndumo_1_par[3]),(Max_Ndumo_1_par[4]),(Max_Ndumo_1_par[5:8]),(Max
      _Ndumo_1_par[9:10]),
100                       (Max_Ndumo_1_par[11:14]),(Max_Ndumo_1_par
                            [15:26]),(Max_Ndumo_1_par[27:33]),(Max_
```

```
                                Ndumo_1_par[34:44]),(Max_Ndumo_1_par[45]),(
                                Max_Ndumo_1_par[46]),
101                           (Max_Ndumo_1_par[47]),(Max_Ndumo_1_par[48]),(
                                Max_Ndumo_1_par[49]),(Max_Ndumo_1_par[50])
                                ,(Max_Ndumo_1_par[51]),(Max_Ndumo_1_par
                                [52:53]),
102                           (Max_Ndumo_1_par[54:56]),(Max_Ndumo_1_par
                                [57:59]), (Max_Ndumo_1_par[60:64])))
103
104 parms_1 <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10],h=theta[11],
105                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                      =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                      theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
106                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                      [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                      At4=theta[26],omega_q=theta[27],omega_A=theta[28],
107                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                      [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                      xt3=theta[36],xt4=theta[37],piit1=theta[38],
108                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                      theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                      theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                      theta[48],
109                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                      theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                      Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                      theta[59],amplit=theta[60])
110
111 x0_1 <- c(theta[61:62],0,theta[63:64],0,0,0,0,0,0,0)
112 stateMatrix1 <- ode(y=x0_1, times, sir_fit, parms_1)
113 colnames(stateMatrix1) <- c("time","Sn", "L", "ASym", "Sym", "Tr", "
      Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
114
115 inc_1<-c(stateMatrix1[1,"CumInc"])
```

```
116 for (tt in 2:length(tim)){
117   inc_1<-c(inc_1,stateMatrix1[tt,"CumInc"] - stateMatrix1[tt-1,"
        CumInc"])
118 }
119
120 plot_time<- seq(2010, 2018+4/12,1/12)
121 plot_time1<- seq(2010, 2022-1/12,1/12) #2022-1/12,1/12)
122 plot_time2<- seq(2018+4/12, 2022-1/12,1/12) #2022-1/12,1/12)
123
124 par(mfrow=c(1,1))
125 plot(plot_time1, stateMatrix1[1:144,"CumInc"], type="l", lwd=2, xlab
      ="Time", ylab="Incidence",ylim=c(0,84)) #cum incidence
126 lines(plot_time, cumbombay[1:101], type="l",col="green") #MLE fit
127 #Incidence
128 plot(plot_time1, (inc_1), type="l", col="darkblue",lwd=3,lty=1, xlab
      ="Time (years)", ylab="Number of cases",ylim=c(0,14)) #cum
      incidence
129 #IRS Coverage and Efficacy
130 lines(plot_time, data_1$Ndumo[1:101], type="l",col=1,lwd=3,lty=1) #
      IRS cov = Averaged over the last 3 years
131 lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
      =20,lty=3) # IRS cov = 0%
132 lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
      =20,lty=1) #IRS cov = 80%
133 lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
      =20,lty=2) #IRS cov = 100%
134 lines(plot_time2,inc_1[101:144], type = "l", col="green", lwd=3,pch
      =20,lty=1) #IRS cov = 80%, irs eff = 80%
135 lines(plot_time2,inc_1[101:144], type = "l", col="green", lwd=3,pch
      =20,lty=2) #IRS cov = 100%, irs eff = 100%
136 lines(plot_time2,inc_1[101:144], type = "l", col="cyan", lwd=3,pch
      =20,lty=1) #IRS cov = Averaged, irs eff = 90%
137 legend("topleft", c("Ndumo cases", "Fitted model","IRScov=0%","
      IRScov=80%","IRScov=100%","IRScov=80%, IRS eff=80%","IRScov=100%,
       IRS eff=100%"), col=c("black","darkblue","red","red","red","
      green","green"), lty=c(1,1,3,1,2,1,2),lwd=3, horiz = F,bty="n",x.
```

```
    intersp = 0.5,cex=0.9)
#Imported cases change
lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
    =20,lty=1) # Increase by times 20
lines(plot_time2,inc_1[101:144], type = "l", col="cyan", lwd=3,pch
    =20,lty=1) #Reduction by 70%
lines(plot_time2,inc_1[101:144], type = "l", col="green", lwd=3,pch
    =20,lty=2) #Increase by times 20, while IRS cov = 20%, eff = 38%
legend("topleft", c("Fitted cases based on averaged values", "Fitted
     model","Impoted cases increase by 10 times","Impoted cases
    increase by 20 times"), col=c("black","darkblue","green","red"),
    lty=c(1,1,2,1),lwd=3, horiz = F,bty="n",x.intersp = 0.5,cex=0.9)

#Zoom out the plot
#Incidence
plot(plot_time2, (inc_1[101:144]), type="l", col="darkblue",lwd=3,
    lty=1, xlab="Time (years)", ylab="Number of cases",ylim=c(0,2)) #
    cum incidence
#IRS Coverage and Efficacy
lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
    =20,lty=3) # IRS cov = 0%
lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
    =20,lty=1) #IRS cov = 80%
lines(plot_time2,inc_1[101:144], type = "l", col="red", lwd=3,pch
    =20,lty=2) #IRS cov = 100%
lines(plot_time2,inc_1[101:144], type = "l", col="green", lwd=3,pch
    =20,lty=1) #IRS cov = 80%, irs eff = 80%
lines(plot_time2,inc_1[101:144], type = "l", col="green", lwd=3,pch
    =20,lty=2) #IRS cov = 100%, irs eff = 100%
lines(plot_time2,inc_1[101:144], type = "l", col="cyan", lwd=3,pch
    =20,lty=1) #IRS cov = Averaged, irs eff = 90%
legend("topleft", c("Fitted model","IRScov=0%","IRScov=80%","IRScov
    =100%","IRScov=80%, IRS eff=80%","IRScov=100%, IRS eff=100%", "
    Averaged current IRS cov., IRS eff=90%"), col=c("darkblue","red",
    "red","red","green","green","cyan"), lty=c(1,3,1,2,1,2,1),lwd=3,
    horiz = F,bty="n",x.intersp = 0.5,cex=0.9)
```

```
155
156 #Incidence
157 g_range1<-range(0,seq(0,14,2))
158 plot(inc_1[1:100], type = "l", col="darkblue",ylim = g_range1,
159       lwd=3, axes=F,ann=F,pch=20,lty=1)
160 axis(1, at=0:12*12, lab=c("2010", "2011","2012","2013", "2014", "
      2015", "2016", "2017", "2018","2019", "2020", "2021", "2022"))
161 axis(2,las=1, at=2*0:g_range1[2],col.axis="black")
162 axis(4,las=1, at=2*0:g_range1[2],col.axis="black")
163 lines(data_1$Ndumo[1:100], type = "l", col="red", lwd=3,pch=20,lty
      =1)
164
165 box()
166 legend("topleft", c("Ndumo reported cases", "Fitted Model"), col=c("
      black","darkblue"), lty=c(1,1),lwd=2, horiz = F)
167 #title(main="Local and Imported cases diagnosed in Ndumo", col.main
      ="black",font.main=1)
168 title(ylab="Number of cases")
169 title(xlab = "Time (years)")
170 #lines(inc_1[101:144], type = "l", col="red", lwd=3,pch=20,lty=1)
171
172 #Plot with confidence bends
173 #----------------------------
174 # confidence interval of the best predictions:
175 cl <- 0.95 # confidence level
176 cl <- (1 - cl) / 2
177 time_points <- seq(2010, 2018+3/12,1/12)
178 best_predictions <- inc_1[1:100]
179 Inc_data <- data_1$Ndumo[1:100]
180 SD <- sqrt(sum((Inc_data-best_predictions)^2)/length(weeks_fit
      [1:100]))
181 lwr <- qnorm(p = cl, mean = best_predictions, sd = SD)
182 upr <- qnorm(p = 1 - cl, mean = best_predictions, sd = SD)
183 # layout of the plot:
184 plot(time_points, time_points, ylim = c(0, max(upr)), type = "n",
185       xlab = "Time (years)", ylab = "number of malaria cases")
```

```
186 # adding the predictions' confidence interval:
187 sel <- time_points >= 1 # predictions start from the second data
    point
188 polygon(c(time_points[sel], rev(time_points[sel])), c(upr[sel], rev(
    lwr[sel])),
189         border = NA, col = adjustcolor("red", alpha.f = 0.2))
190 # adding the model's best predictions:
191 lines(time_points, best_predictions, col = "red", lwd=3)
192 lines(time_points, data_1$Ndumo[1:100], type="p", pch =19, col = "
    black",cex =1.35)
193 legend("topleft", c("Ndumo reported cases", "Fitted Model"), col=c("
    black","red"),lwd=2, horiz = F, bty="n",x.intersp = 0.5)
194 colnames(stateMatrix1) <- c("t","Sn", "L", "ASym", "Sym", "Tr", "
    Trfail", "Ssev", "Trsev", "D", "Rn", "LV", "CumInc")
195
196 plot(stateMatrix1[,2], col="black", lwd=2, ylim=c(-200,5200),ty="l")
197 lines(stateMatrix1[,3], col="red", lwd=2,ty="l")
198 lines(stateMatrix1[,4], col="green", lwd=2,ty="l")
199 lines(stateMatrix1[,5], col="cyan", lwd=2,ty="l")
200 lines(stateMatrix1[,6], col="yellow", lwd=2,ty="l")
201 lines(stateMatrix1[,7], col="orange", lwd=2,ty="l")
202 lines(stateMatrix1[,8], col="darkblue", lwd=2,ty="l")
203 lines(stateMatrix1[,9], col="pink", lwd=2,ty="l")
204 lines(stateMatrix1[,10], col="darkgrey", lwd=2,ty="l")
205 lines(stateMatrix1[,11], col="brown", lwd=2,ty="l")
206
207 Value_1 <- read.xlsx("C:/Users/mandi/OneDrive - University of Cape
    Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/Fitted_Parameter_values_Max1_Ndumo.xlsx", sheet =
     2, startRow = 1, colNames = TRUE)
208
209 lower<-Value_1$`Value_5`
210 upper<-Value_1$Upper_value
211
212 analysis_factor <- 5
213 #Sensitivity Analysis
```

```
214 for ( i in 1:analysis_factor){
215     parms_e <- c(beta=runif(1,lower[1],upper[1]),Bh=runif(1,lower
        [2],upper[2]),psii=runif(1,lower[3],upper[3]),gamma=runif(1,
        lower[4],upper[4]),tau=runif(1,lower[5],upper[5]),Ln=runif(1,
        lower[6],upper[6]),alpha1=runif(1,lower[7],upper[7]),alpha=
        runif(1,lower[8],upper[8]),G=runif(1,lower[9],upper[9]),delta
        =runif(1,lower[10],upper[10]),h=runif(1,lower[11],upper[11]),
216                 epsolon1=runif(1,lower[12],upper[12]),epsolon2=runif
                    (1,lower[13],upper[13]),z=runif(1,lower[14],upper
                    [14]),etat1=runif(1,lower[15],upper[15]),etat2=
                    runif(1,lower[16],upper[16]),etat3=runif(1,lower
                    [17],upper[17]),etat4=runif(1,lower[18],upper[18])
                    ,kappa_qt1=runif(1,lower[19],upper[19]),kappa_qt2=
                    runif(1,lower[20],upper[20]),
217                 kappa_qt3=runif(1,lower[21],upper[21]),kappa_qt4=
                    runif(1,lower[22],upper[22]),kappa_At1=runif(1,
                    lower[23],upper[23]),kappa_At2=runif(1,lower[24],
                    upper[24]),kappa_At3=runif(1,lower[25],upper[25]),
                    kappa_At4=runif(1,lower[26],upper[26]),omega_q=
                    runif(1,lower[27],upper[27]),omega_A=runif(1,lower
                    [28],upper[28]),xi=runif(1,lower[29],upper[29]),
218                 Omega=runif(1,lower[30],upper[30]),V=runif(1,lower
                    [31],upper[31]),chii_d1=runif(1,lower[32],upper
                    [32]),chii_d2=runif(1,lower[33],upper[33]),xt1=
                    runif(1,lower[34],upper[34]),xt2=runif(1,lower
                    [35],upper[35]),xt3=runif(1,lower[36],upper[36]),
                    xt4=runif(1,lower[37],upper[37]),piit1=runif(1,
                    lower[38],upper[38]),piit2=runif(1,lower[39],upper
                    [39]),
219                 piit3=runif(1,lower[40],upper[40]),piit4=runif(1,
                    lower[41],upper[41]),phi_d1=runif(1,lower[42],
                    upper[42]),phi_d2=runif(1,lower[43],upper[43]),
                    delta1=runif(1,lower[44],upper[44]),Sigma=runif(1,
                    lower[45],upper[45]),kappa1=runif(1,lower[46],
                    upper[46]),omega1=runif(1,lower[47],upper[47]),
                    eta1=runif(1,lower[48],upper[48]),tau1=runif(1,
```

```
                    lower[49],upper[49]),
220                 delta2=runif(1,lower[50],upper[50]),h2=runif(1,lower
                    [51],upper[51]),thetha=runif(1,lower[52],upper
                    [52]),alpha2=runif(1,lower[53],upper[53]),r=runif
                    (1,lower[54],upper[54]),e=runif(1,lower[55],upper
                    [55]),Sigma1=runif(1,lower[56],upper[56]),rho=
                    runif(1,lower[57],upper[57]),irseff=runif(1,lower
                    [58],upper[58]),phi=runif(1,lower[59],upper[59]),
                    amplit=runif(1,lower[60],upper[60]))
221   run_d<- ode(y=x0_1, times, sir_fit, parms_e)
222   lines(run_d[,2], col="black", lwd=2)
223   lines(run_d[,3], col="red", lwd=2)
224   lines(run_d[,4], col="green", lwd=2)
225   lines(run_d[,5], col="cyan", lwd=2)
226   lines(run_d[,6], col="yellow", lwd=2)
227   lines(run_d[,7], col="orange", lwd=2)
228   lines(run_d[,8], col="darkblue", lwd=2)
229   lines(run_d[,9], col="pink", lwd=2)
230   lines(run_d[,10], col="darkgrey", lwd=2)
231   lines(run_d[,11], col="brown", lwd=2)
232 }
233
234 CIdata<-NULL
235 for ( i in 1:analysis_factor){
236   parms <- c(beta=runif(1,lower[1],upper[1]),Bh=runif(1,lower[2],
        upper[2]),psii=runif(1,lower[3],upper[3]),gamma=runif(1,lower
        [4],upper[4]),tau=runif(1,lower[5],upper[5]),Ln=runif(1,lower
        [6],upper[6]),alpha1=runif(1,lower[7],upper[7]),alpha=runif(1,
        lower[8],upper[8]),G=runif(1,lower[9],upper[9]),delta=runif(1,
        lower[10],upper[10]),h=runif(1,lower[11],upper[11]),
                    epsolon1=runif(1,lower[12],upper[12]),epsolon2=runif
                    (1,lower[13],upper[13]),z=runif(1,lower[14],upper
                    [14]),etat1=runif(1,lower[15],upper[15]),etat2=
                    runif(1,lower[16],upper[16]),etat3=runif(1,lower
                    [17],upper[17]),etat4=runif(1,lower[18],upper[18])
                    ,kappa_qt1=runif(1,lower[19],upper[19]),kappa_qt2=
```

```
                runif(1,lower[20],upper[20]),
238             kappa_qt3=runif(1,lower[21],upper[21]),kappa_qt4=
                runif(1,lower[22],upper[22]),kappa_At1=runif(1,
                lower[23],upper[23]),kappa_At2=runif(1,lower[24],
                upper[24]),kappa_At3=runif(1,lower[25],upper[25]),
                kappa_At4=runif(1,lower[26],upper[26]),omega_q=
                runif(1,lower[27],upper[27]),omega_A=runif(1,lower
                [28],upper[28]),xi=runif(1,lower[29],upper[29]),
239             Omega=runif(1,lower[30],upper[30]),V=runif(1,lower
                [31],upper[31]),chii_d1=runif(1,lower[32],upper
                [32]),chii_d2=runif(1,lower[33],upper[33]),xt1=
                runif(1,lower[34],upper[34]),xt2=runif(1,lower
                [35],upper[35]),xt3=runif(1,lower[36],upper[36]),
                xt4=runif(1,lower[37],upper[37]),piit1=runif(1,
                lower[38],upper[38]),piit2=runif(1,lower[39],upper
                [39]),
240             piit3=runif(1,lower[40],upper[40]),piit4=runif(1,
                lower[41],upper[41]),phi_d1=runif(1,lower[42],
                upper[42]),phi_d2=runif(1,lower[43],upper[43]),
                delta1=runif(1,lower[44],upper[44]),Sigma=runif(1,
                lower[45],upper[45]),kappa1=runif(1,lower[46],
                upper[46]),omega1=runif(1,lower[47],upper[47]),
                eta1=runif(1,lower[48],upper[48]),tau1=runif(1,
                lower[49],upper[49]),
241             delta2=runif(1,lower[50],upper[50]),h2=runif(1,lower
                [51],upper[51]),thetha=runif(1,lower[52],upper
                [52]),alpha2=runif(1,lower[53],upper[53]),r=runif
                (1,lower[54],upper[54]),e=runif(1,lower[55],upper
                [55]),Sigma1=runif(1,lower[56],upper[56]),rho=
                runif(1,lower[57],upper[57]),irseff=runif(1,lower
                [58],upper[58]),phi=runif(1,lower[59],upper[59]),
                amplit=runif(1,lower[60],upper[60]))
242     run_d<- ode(y=x0_1, times, sir_fit, parms)
243     CIdata<-cbind(CIdata,run_d[,13])
244 }
245
```

```
Incidence <-NULL
for(i in 1:analysis_factor){
  inc_1<-c(CIdata[1,i])
  for (tt in 2:144){
    inc_1<-c(inc_1,CIdata[tt,i] - CIdata[tt-1,i])
  }
  Incidence<-cbind(Incidence,inc_1)
}

plot_time<- seq(2010, 2018+4/12,1/12)
plot_time1<- seq(2010, 2022-1/12,1/12) #2022-1/12,1/12)

#Incidence
plot(plot_time1,Incidence[,1], type="l", col="darkblue",lwd=3,lty=1,
     xlab="Time (years)", ylab="Number of cases",ylim=c()) #cum
    incidence
for(j in 2:analysis_factor){
lines(plot_time1, Incidence[,j], type="l",col=j,lwd=3,lty=1) # IRS
    cov = Averaged over the last 3 years
}

CIsd<-CIuci<-CIlci<-NULL
CIMean<-rowMeans(Incidence)
for (i in 1:(dim(Incidence)[1])){
  CIsd[i]<-sd(Incidence[i,])
  CIuci[i]<-CIMean[i]+1.96*CIsd[i]/sqrt(analysis_factor)
  CIlci[i]<-CIMean[i]-1.96*CIsd[i]/sqrt(analysis_factor)
}

plot(plot_time1, CIMean, type="l",ylim=c(0,18), ylab="Number of
    cases", xlab="Time (years)",lwd=1)
lines(plot_time1, CIlci, col="red2",lwd=1)
lines(plot_time1, CIuci, col="red",lwd=1)
```

9.3 Sensitivity Analysis

```
library(deSolve)
library(readxl)
library(xlsx)
library(maxLik)
library(bbmle)
library("openxlsx")
#Data fitting
rm(list=ls())
data_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town
    /Dissertation/Thesis Work/Model building/Start Afresh/Scenarios_
    NDUMO/Total_local_cases1_1_Ndumo.xlsx", sheet = 1, startRow = 1,
    colNames = TRUE)
climatedata_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/chirps_1.xlsx", sheet= 1, startRow = 1, colNames
    = TRUE)
climatedata1_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/chirps_1.xlsx", sheet= 2, startRow = 1, colNames
    = TRUE)
data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1.xlsx", sheet =
    1, startRow = 1, colNames = TRUE)
#data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1_0.0%.xlsx",
    sheet = 1, startRow = 1, colNames = TRUE)
#data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1_80%.xlsx",
    sheet = 1, startRow = 1, colNames = TRUE)
#data_IRScov_1<-read.xlsx("C:/Users/mandi/OneDrive - University of
    Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/IRScov data incomplete1_averrm8_1_100%.xlsx",
    sheet = 1, startRow = 1, colNames = TRUE)
```

```
#Imported_Ndumo_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/Scenarios_NDUMO/Malaria cases imported diagnosed in Ndumo_1_Increase.xlsx", sheet = 1, startRow = 1, colNames = TRUE)
Imported_Ndumo_1<-read.xlsx("C:/Users/mandi/OneDrive - University of Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/Scenarios_NDUMO/Malaria cases imported diagnosed in Ndumo_1_Original.xlsx", sheet = 1, startRow = 1, colNames = TRUE)

# Defining functions for Vector dynamics
climatedata_1$ts           <- with(climatedata_1, seq(0,12-1/12,1/12))
climatedata1_1$ts          <- with(climatedata1_1, seq(0,12-1/12,1/12))
data_IRScov_1$ts           <- with(data_IRScov_1, seq(0,12-1/12,1/12))
Imported_Ndumo_1$ts1 <- with(Imported_Ndumo_1, seq(0,12-1/12,1/12))

R_interpol_s_1             <- with(climatedata_1,approxfun(ts, Umkhanyakude_rain,rule=1,method='linear'))
R_stdinterpol_s_1          <- with(climatedata1_1,approxfun(ts, Umkhanyakude_std,rule=1,method='linear'))
IRSinterpol_s_1            <- with(data_IRScov_1,approxfun(ts, Ndum1,rule=1,method='linear'))
Imported_Ndumo_s_1  <- with(Imported_Ndumo_1,approxfun(ts1,Ndumo, rule=1,method='linear'))

cumbombay <- cumsum(data_1$Ndumo) #cumsum(bombay)
weeks_fit <- seq(0,12-2/12,1/12) #seq(0, 12-1/12,1/12)
times <- seq(0, 12-1/12,1/12) #seq(0, 12-1/12,1/12)
tim <- 1:144 #1:144

sir_fit <- function(t,x,parms){
  Sn <- x[1];L <- x[2];ASym<-x[3];Sym<-x[4];Tr<-x[5];Trfail<-x[6];
    Ssev<-x[7];Trsev<-x[8];D<-x[9];Rn<-x[10];LV<-x[11];CumInc<-x
    [12];CumTr<-x[13]
```

```
37  with(as.list(parms),
38       {
39         R_s_std_1 = R_stdinterpol_s_1(t)
40         IRScov_1 = IRSinterpol_s_1(t)
41         Moz_Imported_Ndumo_1= Imported_Ndumo_s_1(t)
42         I=ASym+Sym+Ssev+Tr+Trfail+Trsev
43         N=Sn+L+ASym+Sym+Ssev+Tr+Trfail+Trsev+Rn+LV
44
45         #Conditions on the treatment coverages
46         if( t <= 6) {x_sev=xt2}
47         else (x_sev=xt3)
48
49         if(t <= 6) {kappa_q=kappa_qt2} #This is the problem
50         else (kappa_q=kappa_qt3)
51
52         if( t <= 6) {kappa_A=kappa_At2}
53         else (kappa_A=kappa_At3)
54
55         if( t <= 6) {eta=etat2}
56         else (eta=etat3)
57
58         if( t <= 8.33333333) {irseff=0.38}
59         else (irseff=0.38)
60
61         if( t <= 6) {pii=piit2}
62         else (pii=piit3)
63
64         if( t <= 6) {aa=1}
65         else (aa=1)
66
67         if( t >= 7.83333333 & t< 7.91666667) {mult=2.4}
68         else if(t >= 8.16666667 & t<= 8.25) {mult=5.3} #
69         else if(t >= 0 & t<= 0.58333333) {mult=1} #
70         else if(t > 8.25 & t<= 8.33333333) {mult=2.9} #
71         else if(t > 8.33333333){mult=1.4}
72         else (mult=1.3)
```

```
73
74          #Fix the driver of infection as it will be the determiner
                of how change infection changes over t
75          betat <- mult*R_s_std_1 #beta*((amplit*(1+cos(2*pi*(t-phi))
                ))*(t<10) + (t>=10)*R_s_std_1) #*(spline(t[577:820],R_s_
                std,xout=(t-phi))$y)))
76          lambdamh.n <- (1-IRScov_1*irseff)*mult*Bh*betat*(I/N)
77
78          dSn    <- (N/Ln) + (gamma)*rho*Rn - lambdamh.n*Sn - (1/Ln)*
                Sn -  aa*Moz_Imported_Ndumo_1
79          dL     <- lambdamh.n*Sn - (G)*alpha1*L - (1-G)*alpha*L - (1/
                Ln)*L
80          dASym <- (1-G)*alpha*L + (1-eta-pii)*epsolon1*Sym + (1-
                delta-delta1)*h*Tr + (delta2)*h2*Trfail + (thetha)*r*LV
                 - epsolon2*ASym - (1/Ln)*ASym + 0.1*aa*Moz_Imported_
                Ndumo_1
81          dSym   <- (G)*alpha1*L + (eta1)*tau1*Trfail  + (1-thetha)*e*
                LV - (pii)*z*Sym - (eta)*tau*Sym - (1-eta-pii)*epsolon1*
                Sym - (1/Ln)*Sym + 0.4*aa*Moz_Imported_Ndumo_1
82          dTr    <- (eta)*tau*Sym - (delta)*Omega*Tr - (delta1)*Sigma*
                Tr - (1-delta-delta1)*h*Tr - (1/Ln)*Tr + 0.5*aa*Moz_
                Imported_Ndumo_1
83          dTrfail <- (delta1)*Sigma*Tr - (eta1)*tau1*Trfail - (kappa1
                )*omega1*Trfail - (delta2)*h2*Trfail - (1-eta1-kappa1-
                delta2)*Sigma1*Trfail - (1/Ln)*Trfail
84          dSsev <- (pii)*z*Sym + (kappa1)*omega1*Trfail - (kappa_q)*
                omega_q*Ssev - (kappa_A)*omega_A*Ssev - (x_sev)*V*Ssev -
                 (1-x_sev-kappa_q-kappa_A)*psii*Ssev - (1/Ln)*Ssev
85          dTrsev <- (kappa_q)*omega_q*Ssev + (kappa_A)*omega_A*Ssev -
                 (phi_d1)*chii_d1*Trsev - (phi_d2)*chii_d2*Trsev - (1-
                phi_d1-phi_d2)*xi*Trsev - (1/Ln)*Trsev
86          dD     <- (phi_d1)*chii_d1*Trsev + (phi_d2)*chii_d2*Trsev +
                (x_sev)*V*Ssev +(1-eta1-kappa1-delta2)*Sigma1*Trfail
87          dRn    <- (1-x_sev-kappa_q-kappa_A)*psii*Ssev + epsolon2*
                ASym + (1-phi_d1-phi_d2)*xi*Trsev + (delta)*Omega*Tr - (
                gamma)*rho*Rn - (1-gamma)*alpha2*Rn - (1/Ln)*Rn
```

```
88            dLV    <- (1-gamma)*alpha2*Rn - (1-thetha)*e*LV - (thetha)*r
                 *LV - (1/Ln)*LV
89            dCumInc  <- lambdamh.n*(Sn+Rn) # this needs attention
90            dCumTr = (eta)*tau*Sym + (kappa_q)*omega_q*Ssev + (kappa_A)
                 *omega_A*Ssev
91            res <- c(dSn, dL, dASym, dSym, dTr, dTrfail, dSsev, dTrsev,
                  dD, dRn, dLV, dCumInc, dCumTr)
92            list(res)
93          })
94  }
95
96  Max_Ndumo_1 <- read.xlsx("C:/Users/mandi/OneDrive - University of
       Cape Town/Dissertation/Thesis Work/Model building/Start Afresh/
       Scenarios_NDUMO/Fitted_Parameter_values_Max1_Ndumo.xlsx", sheet =
        1, startRow = 1, colNames = FALSE)
97  #
98  Max_Ndumo_1_par <- as.vector(Max_Ndumo_1[,1])
99  theta <- as.numeric(c((Max_Ndumo_1_par[1]),(Max_Ndumo_1_par[2]),(Max
       _Ndumo_1_par[3]),(Max_Ndumo_1_par[4]),(Max_Ndumo_1_par[5:8]),(Max
       _Ndumo_1_par[9:10]),
100                         (Max_Ndumo_1_par[11:14]),(Max_Ndumo_1_par
                               [15:26]),(Max_Ndumo_1_par[27:33]),(Max_
                               Ndumo_1_par[34:44]),(Max_Ndumo_1_par[45]),(
                               Max_Ndumo_1_par[46]),
101                         (Max_Ndumo_1_par[47]),(Max_Ndumo_1_par[48]),(
                               Max_Ndumo_1_par[49]),(Max_Ndumo_1_par[50])
                               ,(Max_Ndumo_1_par[51]),(Max_Ndumo_1_par
                               [52:53]),
102                         (Max_Ndumo_1_par[54:56]),(Max_Ndumo_1_par
                               [57:59]), (Max_Ndumo_1_par[60:64])))
103
104 parms_1 <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
       tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
       [9],delta=theta[10],h=theta[11],
105                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                       =theta[15],etat2=theta[16],etat3=theta[17],etat4=
```

```
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
106             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
107             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
108             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
109             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
110
111 x0_1 <- c(theta[61:62],0,theta[63:64],0,0,0,0,0,0,0,0)
112 run_d <- ode(y=x0_1, times, sir_fit, parms_1)
113 pop<-run_d[,2]+run_d[,3]+run_d[,4]+run_d[,5]+run_d[,6]+run_d[,7]+run
    _d[,8]+run_d[,9]+run_d[,10]+run_d[,11]+run_d[,12]
114
115 plot_time<- seq(2010, 2018+4/12,1/12); plot_time1<- seq(2010, 2022-1
    /12,1/12) #2022-1/12,1/12)
116 plot_time2<- seq(2018+4/12, 2022-1/12,1/12) #2022-1/12,1/12)
117
118 plot(plot_time1,run_d[,2], col="red", ylim=c(0,15000), type="l",
    main="Ndumo Model")
119 lines(plot_time1,run_d[,3], col="blue")
120 lines(plot_time1, run_d[,4], col="green")
121 lines(plot_time1,run_d[,5], col="cyan")
122 lines(plot_time1,run_d[,6], col="blue")
123 lines(plot_time1,run_d[,7], col="yellow")
124 lines(plot_time1, run_d[,8], col="orange")
125 lines(plot_time1,run_d[,9], col="darkblue")
126 lines(plot_time1,run_d[,10], col="pink")
127 lines(plot_time1,run_d[,11], col="darkgrey")
```

```
128 lines(plot_time1,run_d[,12], col="bisque")
129 lines(times,pop,type="l")
130 legend("topright", c("Sn", "L", "ASym", "Sym", "Tr", "Trfail", "Ssev
    ", "Trsev", "D", "Rn", "LV"),
131         col=c("black","red","green","cyan","blue","yellow","orange","
            darkblue","pink","darkgrey","bisque"), lwd=1, horiz = T)
132 #Outcomes
133 plot(plot_time1,run_d[,13],type="l")
134 lines(plot_time1,run_d[,14], col="red")
135 plot(plot_time1,run_d[,14]/run_d[,13], col="purple", type="l")
136 trtprop<-run_d[length(run_d[1:143,1]),14]/run_d[length(run_d
    [1:143,1]),13]
137
138 Value_1 <- read.xlsx("C:/Users/mandi/OneDrive - University of Cape
    Town/Dissertation/Thesis Work/Model building/Start Afresh/
    Scenarios_NDUMO/Fitted_Parameter_values_Max1_Ndumo.xlsx", sheet =
     2, startRow = 1, colNames = TRUE)
139 lower<-Value_1$`Value_5`
140 upper<-Value_1$Upper_value
141 analysis_factor <- 100
142
143 #One at a time sensitivity analysis
144 betasens<-NULL
145 for (i in 1:analysis_factor){
146   parms <- c(beta=runif(1,lower[1],upper[1]),Bh=theta[2],psii=theta
      [3],gamma=theta[4],tau=theta[5],Ln=theta[6],alpha1=theta[7],
      alpha=theta[8],G=theta[9],delta=theta[10],h=theta[11],
147             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
148             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
149             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
150                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
151                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
152   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
153   betasens<-rbind(betasens, c(parms[1], run_d[length(run_d[1:143,1])
          ,14]/run_d[length(run_d[1:143,1]),13]))
154 }
155
156 Bhsens<-NULL
157 for (i in 1:analysis_factor){
158   parms <- c(beta=theta[1], Bh=runif(1, lower[2], upper[2]), psii=theta
          [3], gamma=theta[4], tau=theta[5], Ln=theta[6], alpha1=theta[7],
          alpha=theta[8], G=theta[9], delta=theta[10], h=theta[11],
159                 epsolon1=theta[12], epsolon2=theta[13], z=theta[14], etat1
                        =theta[15], etat2=theta[16], etat3=theta[17], etat4=
                        theta[18], kappa_qt1=theta[19], kappa_qt2=theta[20],
160                 kappa_qt3=theta[21], kappa_qt4=theta[22], kappa_At1=theta
                        [23], kappa_At2=theta[24], kappa_At3=theta[25], kappa_
                        At4=theta[26], omega_q=theta[27], omega_A=theta[28],
161                 xi=theta[29], Omega=theta[30], V=theta[31], chii_d1=theta
                        [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                        xt3=theta[36], xt4=theta[37], piit1=theta[38],
162                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
163                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
164   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
```

```
165   Bhsens<-rbind(Bhsens, c(parms[2],run_d[length(run_d[1:143,1]),14]/
          run_d[length(run_d[1:143,1]),13]))
166 }
167
168 psiisens<-NULL
169 for (i in 1:analysis_factor){
170   parms <- c(beta=theta[1],Bh=theta[2],psii=runif(1,lower[3],upper
          [3]),gamma=theta[4],tau=theta[5],Ln=theta[6],alpha1=theta[7],
          alpha=theta[8],G=theta[9],delta=theta[10],h=theta[11],
171                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                      =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                      theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
172                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                      [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                      At4=theta[26],omega_q=theta[27],omega_A=theta[28],
173                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                      [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                      xt3=theta[36],xt4=theta[37],piit1=theta[38],
174                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                      theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                      theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                      theta[48],
175                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                      theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                      Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                      theta[59],amplit=theta[60])
176   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
177   psiisens<-rbind(psiisens, c(parms[3],run_d[length(run_d[1:143,1])
          ,14]/run_d[length(run_d[1:143,1]),13]))
178 }
179
180 gammasens<-NULL
181 for (i in 1:analysis_factor){
182   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=runif(1,
          lower[4],upper[4]),tau=theta[5],Ln=theta[6],alpha1=theta[7],
          alpha=theta[8],G=theta[9],delta=theta[10],h=theta[11],
```

```
183                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
184                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
185                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
186                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
187                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
188   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
189   gammasens<-rbind(gammasens, c(parms[4],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
190 }
191
192 tausens<-NULL
193 for (i in 1:analysis_factor){
194   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=runif(1,lower[5],upper[5]),Ln=theta[6],alpha1=theta[7],
          alpha=theta[8],G=theta[9],delta=theta[10],h=theta[11],
195                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
196                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
197                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
198                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
199                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
200   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
201   tausens<-rbind(tausens, c(parms[5], run_d[length(run_d[1:143,1])
          ,14]/run_d[length(run_d[1:143,1]),13]))
202 }
203
204 Lnsens<-NULL
205 for (i in 1:analysis_factor){
206   parms <- c(beta=theta[1], Bh=theta[2], psii=theta[3], gamma=theta[4],
          tau=theta[5], Ln=runif(1, lower[6], upper[6]), alpha1=theta[7],
          alpha=theta[8], G=theta[9], delta=theta[10], h=theta[11],
207                 epsolon1=theta[12], epsolon2=theta[13], z=theta[14], etat1
                        =theta[15], etat2=theta[16], etat3=theta[17], etat4=
                        theta[18], kappa_qt1=theta[19], kappa_qt2=theta[20],
208                 kappa_qt3=theta[21], kappa_qt4=theta[22], kappa_At1=theta
                        [23], kappa_At2=theta[24], kappa_At3=theta[25], kappa_
                        At4=theta[26], omega_q=theta[27], omega_A=theta[28],
209                 xi=theta[29], Omega=theta[30], V=theta[31], chii_d1=theta
                        [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                        xt3=theta[36], xt4=theta[37], piit1=theta[38],
210                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
211                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
212   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
```

```
213   Lnsens<-rbind(Lnsens, c(parms[6],run_d[length(run_d[1:143,1]),14]/
          run_d[length(run_d[1:143,1]),13]))
214 }
215
216 alpha1sens<-NULL
217 for (i in 1:analysis_factor){
218   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=runif(1,lower[7],upper[7]),
          alpha=theta[8],G=theta[9],delta=theta[10],h=theta[11],
219               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
220               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=theta[28],
221               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
222               piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
223               tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
224   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
225   alpha1sens<-rbind(alpha1sens, c(parms[7],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
226 }
227
228 alphasens<-NULL
229 for (i in 1:analysis_factor){
230   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=runif(1,lower
          [8],upper[8]),G=theta[9],delta=theta[10],h=theta[11],
```

```
231                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
232                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
233                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
234                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
235                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
236   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
237   alphasens<-rbind(alphasens, c(parms[8],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
238 }
239
240 Gsens<-NULL
241 for (i in 1:analysis_factor){
242   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=runif
          (1,lower[9],upper[9]),delta=theta[10], h=theta[11],
243                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
244                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
245                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
246                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
247                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
248   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
249   Gsens<-rbind(Gsens, c(parms[9], run_d[length(run_d[1:143,1]),14]/
          run_d[length(run_d[1:143,1]),13]))
250 }
251
252 deltasens<-NULL
253 for (i in 1:analysis_factor){
254   parms <- c(beta=theta[1], Bh=theta[2], psii=theta[3], gamma=theta[4],
          tau=theta[5], Ln=theta[6], alpha1=theta[7], alpha=theta[8], G=theta
          [9], delta=runif(1, lower[10], upper[10]), h=theta[11],
255                 epsolon1=theta[12], epsolon2=theta[13], z=theta[14], etat1
                        =theta[15], etat2=theta[16], etat3=theta[17], etat4=
                        theta[18], kappa_qt1=theta[19], kappa_qt2=theta[20],
256                 kappa_qt3=theta[21], kappa_qt4=theta[22], kappa_At1=theta
                        [23], kappa_At2=theta[24], kappa_At3=theta[25], kappa_
                        At4=theta[26], omega_q=theta[27], omega_A=theta[28],
257                 xi=theta[29], Omega=theta[30], V=theta[31], chii_d1=theta
                        [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                        xt3=theta[36], xt4=theta[37], piit1=theta[38],
258                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
259                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
260   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
```

```
261   deltasens<-rbind(deltasens, c(parms[10],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
262 }
263
264 hsens<-NULL
265 for (i in 1:analysis_factor){
266   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=runif(1,lower[11],upper[11]),
267                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                      =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                      theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
268                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                      [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                      At4=theta[26],omega_q=theta[27],omega_A=theta[28],
269                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                      [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                      xt3=theta[36],xt4=theta[37],piit1=theta[38],
270                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                      theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                      theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                      theta[48],
271                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                      theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                      Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                      theta[59],amplit=theta[60])
272   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
273   hsens<-rbind(hsens, c(parms[11],run_d[length(run_d[1:143,1]),14]/
          run_d[length(run_d[1:143,1]),13]))
274 }
275
276 epsolon1sens<-NULL
277 for (i in 1:analysis_factor){
278   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
```

```
279                 epsolon1=runif(1,lower[12],upper[12]),epsolon2=theta
                        [13],z=theta[14],etat1=theta[15],etat2=theta[16],
                        etat3=theta[17],etat4=theta[18],kappa_qt1=theta[19],
                        kappa_qt2=theta[20],
280                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
281                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
282                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
283                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
284   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
285   epsolon1sens<-rbind(epsolon1sens, c(parms[12],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
286 }
287
288 epsolon2sens<-NULL
289 for (i in 1:analysis_factor){
290   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
291                 epsolon1=theta[12],epsolon2=runif(1,lower[13],upper
                        [13]),z=theta[14],etat1=theta[15],etat2=theta[16],
                        etat3=theta[17],etat4=theta[18],kappa_qt1=theta[19],
                        kappa_qt2=theta[20],
292                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
293                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
```

```
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
294             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
295             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
296   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
297   epsolon2sens<-rbind(epsolon2sens, c(parms[13],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
298 }
299
300 zsens<-NULL
301 for (i in 1:analysis_factor){
302   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
303             epsolon1=theta[12],epsolon2=theta[13],z=runif(1,lower
                [14],upper[14]),etat1=theta[15],etat2=theta[16],
                etat3=theta[17],etat4=theta[18],kappa_qt1=theta[19],
                kappa_qt2=theta[20],
304             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
305             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
306             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
307             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
```

```
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
308   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
309   zsens<-rbind(zsens, c(parms[14],run_d[length(run_d[1:143,1]),14]/
          run_d[length(run_d[1:143,1]),13]))
310 }
311
312 etat1sens<-NULL
313 for (i in 1:analysis_factor){
314   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
315                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                   =runif(1,lower[15],upper[15]),etat2=theta[16],etat3=
                   theta[17],etat4=theta[18],kappa_qt1=theta[19],kappa_
                   qt2=theta[20],
316                kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                   [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                   At4=theta[26],omega_q=theta[27],omega_A=theta[28],
317                xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                   [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                   xt3=theta[36],xt4=theta[37],piit1=theta[38],
318                piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                   theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                   theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                   theta[48],
319                tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                   theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                   Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                   theta[59],amplit=theta[60])
320   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
321   etat1sens<-rbind(etat1sens, c(parms[15],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
322 }
323
324 etat2sens<-NULL
```

```
325 for (i in 1:analysis_factor){
326   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
327               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=runif(1,lower[16],upper[16]),etat3=
                  theta[17],etat4=theta[18],kappa_qt1=theta[19],kappa_
                  qt2=theta[20],
328               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                  [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                  At4=theta[26],omega_q=theta[27],omega_A=theta[28],
329               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                  [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                  xt3=theta[36],xt4=theta[37],piit1=theta[38],
330               piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                  theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                  theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                  theta[48],
331               tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                  theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                  Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                  theta[59],amplit=theta[60])
332   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
333   etat2sens<-rbind(etat2sens, c(parms[16],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
334 }
335
336 etat3sens<-NULL
337 for (i in 1:analysis_factor){
338   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
339               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=theta[16],etat3=runif(1,lower[17],
                  upper[17]),etat4=theta[18],kappa_qt1=theta[19],kappa
                  _qt2=theta[20],
```

```
340                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
341                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
342                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
343                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
344   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
345   etat3sens<-rbind(etat3sens, c(parms[17],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
346 }
347
348 etat4sens<-NULL
349 for (i in 1:analysis_factor){
350   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
351                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        runif(1,lower[18],upper[18]),kappa_qt1=theta[19],
                        kappa_qt2=theta[20],
352                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
353                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
354                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
```

```
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
355             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
356   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
357   etat4sens<-rbind(etat4sens, c(parms[18],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
358 }
359
360 kappa_qt1sens<-NULL
361 for (i in 1:analysis_factor){
362   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
363             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=runif(1,lower[19],upper[19]),
                kappa_qt2=theta[20],
364             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
365             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
366             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
367             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
368   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
369   kappa_qt1sens<-rbind(kappa_qt1sens, c(parms[19],run_d[length(run_d
```

```
      [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
}

kappa_qt2sens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                   =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=runif(1,
                    lower[20],upper[20]),
                kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=theta[28],
                xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
                piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
                tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
  run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
  kappa_qt2sens<-rbind(kappa_qt2sens, c(parms[20],run_d[length(run_d
      [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
}

kappa_qt3sens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
```

```
387                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
388                 kappa_qt3=runif(1,lower[21],upper[21]),kappa_qt4=theta
                        [22],kappa_At1=theta[23],kappa_At2=theta[24],kappa_
                        At3=theta[25],kappa_At4=theta[26],omega_q=theta[27],
                        omega_A=theta[28],
389                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
390                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
391                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
392   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
393   kappa_qt3sens<-rbind(kappa_qt3sens, c(parms[21],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
394 }
395
396 kappa_qt4sens<-NULL
397 for (i in 1:analysis_factor){
398   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
399                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
400                 kappa_qt3=theta[21],kappa_qt4=runif(1,lower[22],upper
                        [22]),kappa_At1=theta[23],kappa_At2=theta[24],kappa_
                        At3=theta[25],kappa_At4=theta[26],omega_q=theta[27],
                        omega_A=theta[28],
401                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
```

```
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
402             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
403             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
404   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
405   kappa_qt4sens<-rbind(kappa_qt4sens, c(parms[22],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
406 }
407
408 kappa_At1sens<-NULL
409 for (i in 1:analysis_factor){
410   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
411             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
412             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=runif
                (1,lower[23],upper[23]),kappa_At2=theta[24],kappa_
                At3=theta[25],kappa_At4=theta[26],omega_q=theta[27],
                omega_A=theta[28],
413             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
414             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
415             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
```

```
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
416   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
417   kappa_At1sens<-rbind(kappa_At1sens, c(parms[23],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
418 }
419
420 kappa_At2sens<-NULL
421 for (i in 1:analysis_factor){
422   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
423             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=runif(1,lower[24],upper[24]),kappa_
                    At3=theta[25],kappa_At4=theta[26],omega_q=theta[27],
                    omega_A=theta[28],
424             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
425             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
426             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
427   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
428   kappa_At2sens<-rbind(kappa_At2sens, c(parms[24],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
429 }
430
431
432 kappa_At3sens<-NULL
```

```
433 for (i in 1:analysis_factor){
434   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
435               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
436               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=runif(1,lower
                    [25],upper[25]),kappa_At4=theta[26],omega_q=theta
                    [27],omega_A=theta[28],
437               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
438               piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
439               tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
440   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
441   kappa_At3sens<-rbind(kappa_At3sens, c(parms[25],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
442 }
443
444 kappa_At4sens<-NULL
445 for (i in 1:analysis_factor){
446   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
447               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
448               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
```

```
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=runif(1,lower[26],upper[26]),omega_q=theta[27],
                omega_A=theta[28],
449             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
450             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
451             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
452   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
453   kappa_At4sens<-rbind(kappa_At4sens, c(parms[26],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
454 }
455
456 omega_qsens<-NULL
457 for (i in 1:analysis_factor){
458   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
459             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
460             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=runif(1,lower[27],upper[27]),
                omega_A=theta[28],
461             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
462             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
```

```
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
463             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
464   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
465   omega_qsens<-rbind(omega_qsens, c(parms[27],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
466 }
467
468 omega_Asens<-NULL
469 for (i in 1:analysis_factor){
470   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
471             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
472             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=runif(1,
                    lower[28],upper[28]),
473             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
474             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
475             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
476   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
477   omega_Asens<-rbind(omega_Asens, c(parms[28],run_d[length(run_d
```

```
      [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
}

xisens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
              epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                 =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                  theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
              kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                  [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                  At4=theta[26],omega_q=theta[27],omega_A=theta[28],
              xi=runif(1,lower[29],upper[29]),Omega=theta[30],V=theta
                  [31],chii_d1=theta[32],chii_d2=theta[33],xt1=theta
                  [34],xt2=theta[35],xt3=theta[36],xt4=theta[37],piit1
                 =theta[38],
              piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                  theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                  theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                  theta[48],
              tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                  theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                  Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                  theta[59],amplit=theta[60])
  run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
  xisens<-rbind(xisens, c(parms[29],run_d[length(run_d[1:143,1]),14]
      /run_d[length(run_d[1:143,1]),13]))
}

Omegasens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
```

```
495                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
496                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
497                 xi=theta[29],Omega=runif(1,lower[30],upper[30]),V=theta
                        [31],chii_d1=theta[32],chii_d2=theta[33],xt1=theta
                        [34],xt2=theta[35],xt3=theta[36],xt4=theta[37],piit1
                        =theta[38],
498                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
499                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
500   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
501   Omegasens<-rbind(Omegasens, c(parms[30],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
502 }
503
504 Vsens<-NULL
505 for (i in 1:analysis_factor){
506   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
507                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
508                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
509                 xi=theta[29],Omega=theta[30],V=runif(1,lower[31],upper
                        [31]),chii_d1=theta[32],chii_d2=theta[33],xt1=theta
```

```
                [34],xt2=theta[35],xt3=theta[36],xt4=theta[37],piit1
                =theta[38],
510             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
511             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
512   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
513   Vsens<-rbind(Vsens, c(parms[31],run_d[length(run_d[1:143,1]),14]/
        run_d[length(run_d[1:143,1]),13]))
514 }
515
516 chii_d1sens<-NULL
517 for (i in 1:analysis_factor){
518   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
519             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
520             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
521             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=runif
                (1,lower[32],upper[32]),chii_d2=theta[33],xt1=theta
                [34],xt2=theta[35],xt3=theta[36],xt4=theta[37],piit1
                =theta[38],
522             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
523             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
```

```
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
524   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
525   chii_d1sens<-rbind(chii_d1sens, c(parms[32],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
526 }
527
528 chii_d2sens<-NULL
529 for (i in 1:analysis_factor){
530   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                  theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
531             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                  [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                  At4=theta[26],omega_q=theta[27],omega_A=theta[28],
532             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                  [32],chii_d2=runif(1,lower[33],upper[33]),xt1=theta
                  [34],xt2=theta[35],xt3=theta[36],xt4=theta[37],piit1
                  =theta[38],
533             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                  theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                  theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                  theta[48],
534             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                  theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                  Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                  theta[59],amplit=theta[60])
535   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
536   chii_d2sens<-rbind(chii_d2sens, c(parms[33],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
537 }
538
539 xt1sens<-NULL
540
```

```
541 for (i in 1:analysis_factor){
542   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
543               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                  theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
544               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                  [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                  At4=theta[26],omega_q=theta[27],omega_A=theta[28],
545               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                  [32],chii_d2=theta[33],xt1=runif(1,lower[34],upper
                  [34]),xt2=theta[35],xt3=theta[36],xt4=theta[37],
                  piit1=theta[38],
546               piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                  theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                  theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                  theta[48],
547               tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                  theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                  Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                  theta[59],amplit=theta[60])
548   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
549   xt1sens<-rbind(xt1sens, c(parms[34],run_d[length(run_d[1:143,1])
        ,14]/run_d[length(run_d[1:143,1]),13]))
550 }
551
552 xt2sens<-NULL
553 for (i in 1:analysis_factor){
554   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
555               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                  theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
556               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
```

```
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
557             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=runif(1,
                lower[35],upper[35]),xt3=theta[36],xt4=theta[37],
                piit1=theta[38],
558             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
559             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
560   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
561   xt2sens<-rbind(xt2sens, c(parms[35],run_d[length(run_d[1:143,1])
        ,14]/run_d[length(run_d[1:143,1]),13]))
562 }
563
564 xt3sens<-NULL
565 for (i in 1:analysis_factor){
566   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
567             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
568             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
569             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=runif(1,lower[36],upper[36]),xt4=theta[37],piit1
                =theta[38],
570             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
```

```
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
571             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
572   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
573   xt3sens<-rbind(xt3sens, c(parms[36],run_d[length(run_d[1:143,1])
        ,14]/run_d[length(run_d[1:143,1]),13]))
574 }
575
576 xt4sens<-NULL
577 for (i in 1:analysis_factor){
578   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
579             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
580             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
581             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=runif(1,lower[37],upper[37]),piit1
                =theta[38],
582             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
583             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                theta[59],amplit=theta[60])
584   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
585   xt4sens<-rbind(xt4sens, c(parms[37],run_d[length(run_d[1:143,1])
```

```
      ,14]/run_d[length(run_d[1:143,1]),13]))
}

piit1sens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
              epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                 =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                 theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
              kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                 [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                 At4=theta[26],omega_q=theta[27],omega_A=theta[28],
              xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                 [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                 xt3=theta[36],xt4=theta[37],piit1=runif(1,lower[38],
                 upper[38]),
              piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                 theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                 theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                 theta[48],
              tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                 theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                 Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                 theta[59],amplit=theta[60])
  run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
  piit1sens<-rbind(piit1sens, c(parms[38],run_d[length(run_d
      [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
}

piit2sens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
```

```
603                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
604                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
605                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
606                 piit2=runif(1,lower[39],upper[39]),piit3=theta[40],
                        piit4=theta[41],phi_d1=theta[42],phi_d2=theta[43],
                        delta1=theta[44],Sigma=theta[45],kappa1=theta[46],
                        omega1=theta[47],eta1=theta[48],
607                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
608   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
609   piit2sens<-rbind(piit2sens, c(parms[39],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
610 }
611
612 piit3sens<-NULL
613 for (i in 1:analysis_factor){
614   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
615                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
616                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
617                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
618                 piit2=theta[39],piit3=runif(1,lower[40],upper[40]),
                        piit4=theta[41],phi_d1=theta[42],phi_d2=theta[43],
                        delta1=theta[44],Sigma=theta[45],kappa1=theta[46],
                        omega1=theta[47],eta1=theta[48],
619                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
620   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
621   piit3sens<-rbind(piit3sens, c(parms[40],run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
622 }
623
624 piit4sens<-NULL
625 for (i in 1:analysis_factor){
626   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
627                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
628                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
629                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
630                 piit2=theta[39],piit3=theta[40],piit4=runif(1,lower
                        [41],upper[41]),phi_d1=theta[42],phi_d2=theta[43],
                        delta1=theta[44],Sigma=theta[45],kappa1=theta[46],
                        omega1=theta[47],eta1=theta[48],
631                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
632   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
```

```
633   piit4sens<-rbind(piit4sens, c(parms[41],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
634 }
635
636 phi_d1sens<-NULL
637 for (i in 1:analysis_factor){
638   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
639                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
640                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=theta[28],
641                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
642                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    runif(1,lower[42],upper[42]),phi_d2=theta[43],delta1
                    =theta[44],Sigma=theta[45],kappa1=theta[46],omega1=
                    theta[47],eta1=theta[48],
643                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=theta[60])
644   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
645   phi_d1sens<-rbind(phi_d1sens, c(parms[42],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
646 }
647
648 phi_d2sens<-NULL
649 for (i in 1:analysis_factor){
650   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
```

```
651                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
652                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
653                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
654                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=runif(1,lower[43],upper[43]),delta1
                        =theta[44],Sigma=theta[45],kappa1=theta[46],omega1=
                        theta[47],eta1=theta[48],
655                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
656   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
657   phi_d2sens<-rbind(phi_d2sens, c(parms[43],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
658 }
659
660 delta1sens<-NULL
661 for (i in 1:analysis_factor){
662   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
663                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
664                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
665                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
666                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=runif(1,lower[44],
                        upper[44]),Sigma=theta[45], kappa1=theta[46], omega1=
                        theta[47], eta1=theta[48],
667                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
668   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
669   delta1sens<-rbind(delta1sens, c(parms[44], run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
670 }
671
672 Sigmasens<-NULL
673 for (i in 1:analysis_factor){
674   parms <- c(beta=theta[1], Bh=theta[2], psii=theta[3], gamma=theta[4],
        tau=theta[5], Ln=theta[6], alpha1=theta[7], alpha=theta[8], G=theta
        [9], delta=theta[10], h=theta[11],
675                 epsolon1=theta[12], epsolon2=theta[13], z=theta[14], etat1
                        =theta[15], etat2=theta[16], etat3=theta[17], etat4=
                        theta[18], kappa_qt1=theta[19], kappa_qt2=theta[20],
676                 kappa_qt3=theta[21], kappa_qt4=theta[22], kappa_At1=theta
                        [23], kappa_At2=theta[24], kappa_At3=theta[25], kappa_
                        At4=theta[26], omega_q=theta[27], omega_A=theta[28],
677                 xi=theta[29], Omega=theta[30], V=theta[31], chii_d1=theta
                        [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                        xt3=theta[36], xt4=theta[37], piit1=theta[38],
678                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        runif(1,lower[45],upper[45]), kappa1=theta[46], omega1
                        =theta[47], eta1=theta[48],
679                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
680   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
```

```
681   Sigmasens<-rbind(Sigmasens, c(parms[45],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
682 }
683
684 kappa1sens<-NULL
685 for (i in 1:analysis_factor){
686   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
687                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                   =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                   theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
688                kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                   [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                   At4=theta[26],omega_q=theta[27],omega_A=theta[28],
689                xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                   [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                   xt3=theta[36],xt4=theta[37],piit1=theta[38],
690                piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                   theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                   theta[45],kappa1=runif(1,lower[46],upper[46]),omega1
                   =theta[47],eta1=theta[48],
691                tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                   theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                   Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                   theta[59],amplit=theta[60])
692   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
693   kappa1sens<-rbind(kappa1sens, c(parms[46],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
694 }
695
696 omega1sens<-NULL
697 for (i in 1:analysis_factor){
698   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
```

```
699                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
700                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
701                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
702                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=runif(1,lower[47],
                        upper[47]),eta1=theta[48],
703                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                        theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                        Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                        theta[59],amplit=theta[60])
704   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
705   omega1sens<-rbind(omega1sens, c(parms[47],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
706 }
707
708 eta1sens<-NULL
709 for (i in 1:analysis_factor){
710   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
711                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
712                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
713                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
714                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        runif(1, lower[48], upper[48]),
715                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                        Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                        theta[59], amplit=theta[60])
716   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
717   eta1sens<-rbind(eta1sens, c(parms[48], run_d[length(run_d[1:143,1])
          ,14]/run_d[length(run_d[1:143,1]),13]))
718 }
719
720 tau1sens<-NULL
721 for (i in 1:analysis_factor){
722   parms <- c(beta=theta[1], Bh=theta[2], psii=theta[3], gamma=theta[4],
          tau=theta[5], Ln=theta[6], alpha1=theta[7], alpha=theta[8], G=theta
          [9], delta=theta[10], h=theta[11],
723                 epsolon1=theta[12], epsolon2=theta[13], z=theta[14], etat1
                        =theta[15], etat2=theta[16], etat3=theta[17], etat4=
                        theta[18], kappa_qt1=theta[19], kappa_qt2=theta[20],
724                 kappa_qt3=theta[21], kappa_qt4=theta[22], kappa_At1=theta
                        [23], kappa_At2=theta[24], kappa_At3=theta[25], kappa_
                        At4=theta[26], omega_q=theta[27], omega_A=theta[28],
725                 xi=theta[29], Omega=theta[30], V=theta[31], chii_d1=theta
                        [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                        xt3=theta[36], xt4=theta[37], piit1=theta[38],
726                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
727                 tau1=runif(1, lower[49], upper[49]), delta2=theta[50], h2=
                        theta[51], thetha=theta[52], alpha2=theta[53], r=theta
                        [54], e=theta[55], Sigma1=theta[56], rho=theta[57],
                        irseff=theta[58], phi=theta[59], amplit=theta[60])
728   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
```

```
729   tau1sens<-rbind(tau1sens, c(parms[49],run_d[length(run_d[1:143,1])
          ,14]/run_d[length(run_d[1:143,1]),13]))
730 }
731
732 delta2sens<-NULL
733 for (i in 1:analysis_factor){
734   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
735                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                   =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                   theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
736                kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                   [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                   At4=theta[26],omega_q=theta[27],omega_A=theta[28],
737                xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                   [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                   xt3=theta[36],xt4=theta[37],piit1=theta[38],
738                piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                   theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                   theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                   theta[48],
739                tau1=theta[49],delta2=runif(1,lower[50],upper[50]),h2=
                   theta[51],thetha=theta[52],alpha2=theta[53],r=theta
                   [54],e=theta[55],Sigma1=theta[56],rho=theta[57],
                   irseff=theta[58],phi=theta[59],amplit=theta[60])
740   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
741   delta2sens<-rbind(delta2sens, c(parms[50],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
742 }
743
744 h2sens<-NULL
745 for (i in 1:analysis_factor){
746   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
```

```
747                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
748                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
749                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
750                 piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                        theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                        theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                        theta[48],
751                 tau1=theta[49],delta2=theta[50],h2=runif(1,lower[51],
                        upper[51]),thetha=theta[52],alpha2=theta[53],r=theta
                        [54],e=theta[55],Sigma1=theta[56],rho=theta[57],
                        irseff=theta[58],phi=theta[59],amplit=theta[60])
752   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
753   h2sens<-rbind(h2sens, c(parms[51],run_d[length(run_d[1:143,1]),14]
          /run_d[length(run_d[1:143,1]),13]))
754 }
755
756 thethasens<-NULL
757 for (i in 1:analysis_factor){
758   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
759                 epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                        =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                        theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
760                 kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                        [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                        At4=theta[26],omega_q=theta[27],omega_A=theta[28],
761                 xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                        [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                        xt3=theta[36],xt4=theta[37],piit1=theta[38],
```

```
762                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
763                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        runif(1, lower[52], upper[52]), alpha2=theta[53], r=
                        theta[54], e=theta[55], Sigma1=theta[56], rho=theta
                        [57], irseff=theta[58], phi=theta[59], amplit=theta
                        [60])
764   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
765   thethasens<-rbind(thethasens, c(parms[52], run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
766 }
767
768 alpha2sens<-NULL
769 for (i in 1:analysis_factor){
770   parms <- c(beta=theta[1], Bh=theta[2], psii=theta[3], gamma=theta[4],
          tau=theta[5], Ln=theta[6], alpha1=theta[7], alpha=theta[8], G=theta
          [9], delta=theta[10], h=theta[11],
771                 epsolon1=theta[12], epsolon2=theta[13], z=theta[14], etat1
                        =theta[15], etat2=theta[16], etat3=theta[17], etat4=
                        theta[18], kappa_qt1=theta[19], kappa_qt2=theta[20],
772                 kappa_qt3=theta[21], kappa_qt4=theta[22], kappa_At1=theta
                        [23], kappa_At2=theta[24], kappa_At3=theta[25], kappa_
                        At4=theta[26], omega_q=theta[27], omega_A=theta[28],
773                 xi=theta[29], Omega=theta[30], V=theta[31], chii_d1=theta
                        [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                        xt3=theta[36], xt4=theta[37], piit1=theta[38],
774                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                        theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                        theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                        theta[48],
775                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                        theta[52], alpha2=runif(1, lower[53], upper[53]), r=
                        theta[54], e=theta[55], Sigma1=theta[56], rho=theta
                        [57], irseff=theta[58], phi=theta[59], amplit=theta
```

```
                    [60])
776   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
777   alpha2sens<-rbind(alpha2sens, c(parms[53],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
778 }
779
780 rsens<-NULL
781 for (i in 1:analysis_factor){
782   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
783                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                   =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                   theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
784                kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                   [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                   At4=theta[26],omega_q=theta[27],omega_A=theta[28],
785                xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                   [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                   xt3=theta[36],xt4=theta[37],piit1=theta[38],
786                piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                   theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                   theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                   theta[48],
787                tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                   theta[52],alpha2=theta[53],r=runif(1,lower[54],upper
                   [54]),e=theta[55],Sigma1=theta[56],rho=theta[57],
                   irseff=theta[58],phi=theta[59],amplit=theta[60])
788   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
789   rsens<-rbind(rsens, c(parms[54],run_d[length(run_d[1:143,1]),14]/
          run_d[length(run_d[1:143,1]),13]))
790 }
791
792 esens<-NULL
793 for (i in 1:analysis_factor){
794   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
```

```
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
795               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
796               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=theta[28],
797               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
798               piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
799               tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=runif(1,
                    lower[55],upper[55]),Sigma1=theta[56],rho=theta[57],
                    irseff=theta[58],phi=theta[59],amplit=theta[60])
800   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
801   esens<-rbind(esens, c(parms[55],run_d[length(run_d[1:143,1]),14]/
        run_d[length(run_d[1:143,1]),13]))
802 }
803
804 Sigma1sens<-NULL
805 for (i in 1:analysis_factor){
806   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
807               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
808               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=theta[28],
809               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
```

```
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
            piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
            tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=runif(1,lower[56],upper[56]),rho=theta[57],
                irseff=theta[58],phi=theta[59],amplit=theta[60])
  run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
  Sigma1sens<-rbind(Sigma1sens, c(parms[56],run_d[length(run_d
      [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
}

rhosens<-NULL
for (i in 1:analysis_factor){
  parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
      tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
      [9],delta=theta[10], h=theta[11],
            epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
            kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                At4=theta[26],omega_q=theta[27],omega_A=theta[28],
            xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                xt3=theta[36],xt4=theta[37],piit1=theta[38],
            piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                theta[48],
            tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                Sigma1=theta[56],rho=runif(1,lower[57],upper[57]),
```

```
                irseff=theta[58],phi=theta[59],amplit=theta[60])
824   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
825   rhosens<-rbind(rhosens, c(parms[57],run_d[length(run_d[1:143,1])
          ,14]/run_d[length(run_d[1:143,1]),13]))
826 }
827
828 irseffsens<-NULL
829 for (i in 1:analysis_factor){
830   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
          tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
          [9],delta=theta[10], h=theta[11],
831                epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                   =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                   theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
832                kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                   [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                   At4=theta[26],omega_q=theta[27],omega_A=theta[28],
833                xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                   [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                   xt3=theta[36],xt4=theta[37],piit1=theta[38],
834                piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                   theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                   theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                   theta[48],
835                tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                   theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                   Sigma1=theta[56],rho=theta[57],irseff=runif(1,lower
                   [58],upper[58]),phi=theta[59],amplit=theta[60])
836   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
837   irseffsens<-rbind(irseffsens, c(parms[58],run_d[length(run_d
          [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
838 }
839
840 phisens<-NULL
841 for (i in 1:analysis_factor){
842   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
```

```
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
843             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                  theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
844             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                  [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                  At4=theta[26],omega_q=theta[27],omega_A=theta[28],
845             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                  [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                  xt3=theta[36],xt4=theta[37],piit1=theta[38],
846             piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                  theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
                  theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                  theta[48],
847             tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                  theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                  Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                  runif(1,lower[59],upper[59]),amplit=theta[60])
848   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
849   phisens<-rbind(phisens, c(parms[59],run_d[length(run_d[1:143,1])
        ,14]/run_d[length(run_d[1:143,1]),13]))
850 }
851
852 amplitsens<-NULL
853 for (i in 1:analysis_factor){
854   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
855             epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                  =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                  theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
856             kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                  [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                  At4=theta[26],omega_q=theta[27],omega_A=theta[28],
857             xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
```

```
                    [32], chii_d2=theta[33], xt1=theta[34], xt2=theta[35],
                    xt3=theta[36], xt4=theta[37], piit1=theta[38],
858                 piit2=theta[39], piit3=theta[40], piit4=theta[41], phi_d1=
                    theta[42], phi_d2=theta[43], delta1=theta[44], Sigma=
                    theta[45], kappa1=theta[46], omega1=theta[47], eta1=
                    theta[48],
859                 tau1=theta[49], delta2=theta[50], h2=theta[51], thetha=
                    theta[52], alpha2=theta[53], r=theta[54], e=theta[55],
                    Sigma1=theta[56], rho=theta[57], irseff=theta[58], phi=
                    theta[59], amplit=runif(1,lower[60],upper[60]))
860   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
861   amplitsens<-rbind(amplitsens, c(parms[60], run_d[length(run_d
        [1:143,1]),14]/run_d[length(run_d[1:143,1]),13]))
862 }
863
864 par(mfrow=c(3,4))
865 hist(betasens[,2], xlim=c(5,25), main="beta", xlab=" ")
866 hist(Bhsens[,2], xlim=c(5,25), main="Bh", xlab=" ")
867 hist(psiisens[,2], xlim=c(5,25), main="psii", xlab=" ")
868 hist(gammasens[,2], xlim=c(5,25), main="gamma", xlab=" ")
869 hist(tausens[,2], xlim=c( 5, 25), main="tau", xlab=" ")
870 hist(Lnsens[,2], xlim=c( 5, 25), main="Ln", xlab=" ")
871 hist(alpha1sens[,2], xlim=c( 5, 25), main="alpha1", xlab=" ")
872 hist(alphasens[,2], xlim=c( 5, 25), main="alpha", xlab=" ")
873 hist(Gsens[,2], xlim=c( 5, 25), main="G", xlab=" ")
874 hist(deltasens[,2], xlim=c( 5, 25), main="delta", xlab=" ")
875 hist(hsens[,2], xlim=c( 5, 25), main="h", xlab=" ")
876 hist(epsolon1sens[,2], xlim=c( 5, 25), main="epsolon1", xlab=" ")
877 hist(epsolon2sens[,2], xlim=c( 5, 25), main="epsolon2", xlab=" ")
878 hist(zsens[,2], xlim=c( 5, 25), main="z", xlab=" ")
879 hist(etat1sens[,2], xlim=c( 5, 25), main="etat1", xlab=" ")
880 hist(etat2sens[,2], xlim=c( 5, 25), main="etat2", xlab=" ")
881 hist(etat3sens[,2], xlim=c( 5, 25), main="etat3", xlab=" ")
882 hist(etat4sens[,2], xlim=c( 5, 25), main="etat4", xlab=" ")
883 hist(kappa_qt1sens[,2], xlim=c( 5, 25), main="kappa_qt1", xlab=" ")
884 hist(kappa_qt2sens[,2], xlim=c( 5, 25), main="kappa_qt2", xlab=" ")
```

```
885 hist(kappa_qt3sens[,2], xlim=c( 5, 25), main="kappa_qt3", xlab=" ")
886 hist(kappa_qt4sens[,2], xlim=c( 5, 25), main="kappa_qt4", xlab=" ")
887 hist(kappa_At1sens[,2], xlim=c( 5, 25), main="kappa_At1", xlab=" ")
888 hist(kappa_At2sens[,2], xlim=c( 5, 25), main="kappa_At2", xlab=" ")
889 hist(kappa_At3sens[,2], xlim=c( 5, 25), main="kappa_At3", xlab=" ")
890 hist(kappa_At4sens[,2], xlim=c( 5, 25), main="kappa_At4", xlab=" ")
891 hist(omega_qsens[,2], xlim=c( 5, 25), main="omega_q", xlab=" ")
892 hist(omega_Asens[,2], xlim=c( 5, 25), main="omega_A", xlab=" ")
893 hist(xisens[,2], xlim=c( 5, 25), main="xi", xlab=" ")
894 hist(Omegasens[,2], xlim=c( 5, 25), main="Omega", xlab=" ")
895 hist(Vsens[,2], xlim=c( 5, 25), main="V", xlab=" ")
896 hist(chii_d1sens[,2], xlim=c( 5, 25), main="chii_d1", xlab=" ")
897 hist(chii_d2sens[,2], xlim=c( 5, 25), main="chii_d1", xlab=" ")
898 hist(xt1sens[,2], xlim=c( 5, 25), main="xt1", xlab=" ")
899 hist(xt2sens[,2], xlim=c( 5, 25), main="xt2", xlab=" ")
900 hist(xt3sens[,2], xlim=c( 5, 25), main="xt3", xlab=" ")
901 hist(xt4sens[,2], xlim=c( 5, 25), main="xt4", xlab=" ")
902 hist(piit1sens[,2], xlim=c( 5, 25), main="piit1", xlab=" ")
903 hist(piit2sens[,2], xlim=c( 5, 25), main="piit2", xlab=" ")
904 hist(piit3sens[,2], xlim=c( 5, 25), main="piit3", xlab=" ")
905 hist(piit4sens[,2], xlim=c( 5, 25), main="piit4", xlab=" ")
906 hist(phi_d1sens[,2], xlim=c( 5, 25), main="phi_d1", xlab=" ")
907 hist(phi_d2sens[,2], xlim=c( 5, 25), main="phi_d2", xlab=" ")
908 hist(delta1sens[,2], xlim=c( 5, 25), main="delta1", xlab=" ")
909 hist(Sigmasens[,2], xlim=c( 5, 25), main="Sigma", xlab=" ")
910 hist(kappa1sens[,2], xlim=c( 5, 25), main="kappa1", xlab=" ")
911 hist(omega1sens[,2], xlim=c( 5, 25), main="omega1", xlab=" ")
912 hist(eta1sens[,2], xlim=c( 5, 25), main="eta1", xlab=" ")
913 hist(tau1sens[,2], xlim=c( 5, 25), main="tau1", xlab=" ")
914 hist(delta2sens[,2], xlim=c( 5, 25), main="delta2", xlab=" ")
915 hist(h2sens[,2], xlim=c( 5, 25), main="h2", xlab=" ")
916 hist(thethasens[,2], xlim=c( 5, 25), main="thetha", xlab=" ")
917 hist(alpha2sens[,2], xlim=c( 5, 25), main="alpha2", xlab=" ")
918 hist(rsens[,2], xlim=c( 5, 25), main="r", xlab=" ")
919 hist(esens[,2], xlim=c( 5, 25), main="e", xlab=" ")
920 hist(Sigma1sens[,2], xlim=c( 5, 25), main="Sigma1", xlab=" ")
```

```
921 hist(rhosens[,2], xlim=c( 5, 25), main="rho", xlab=" ")
922 hist(irseffsens[,2], xlim=c( 5, 25), main="irseff", xlab=" ")
923 hist(phisens[,2], xlim=c( 5, 25), main="phi", xlab=" ")
924 hist(amplitsens[,2], xlim=c( 5, 25), main="amplit", xlab=" ")
925
926 par(mfrow=c(3,4))
927 plot(betasens[,1],betasens[,2], main="beta", xlab="Parameter value",
      ylab="Estimated cases")
928 plot(Bhsens[,1],Bhsens[,2], main="Bh", xlab="Parameter value", ylab=
    "Estimated cases")
929 plot(psiisens[,1],psiisens[,2], main="psii", xlab="Parametervalue",
    ylab="Estimated cases")
930 plot(gammasens[,1], gammasens[,2], main="gamma", xlab="Parameter
    value", ylab="Estimated cases")
931 plot(tausens[,1], tausens[,2], main="tau", xlab="Parameter value",
    ylab="Estimated cases")
932 plot(Lnsens[,1], Lnsens[,2], main="Ln", xlab="Parameter value", ylab
    ="Estimated cases")
933 plot(alpha1sens[,1], alpha1sens[,2], main="alpha1", xlab="Parameter
    value", ylab="Estimated cases")
934 plot(alphasens[,1], alphasens[,2], main="alpha", xlab="Parameter
    value", ylab="Estimated cases")
935 plot(Gsens[,1], Gsens[,2], main="G", xlab="Parameter value", ylab="
    Estimated cases")
936 plot(deltasens[,1], deltasens[,2], main="delta", xlab="Parameter
    value", ylab="Estimated cases")
937 plot(hsens[,1], hsens[,2], main="h", xlab="Parameter value", ylab="
    Estimated cases")
938 plot(epsolon1sens[,1], epsolon1sens[,2], main="epsolon1", xlab="
    Parameter value", ylab="Estimated cases")
939 plot(epsolon2sens[,1], epsolon2sens[,2], main="epsolon2", xlab="
    Parameter value", ylab="Estimated cases")
940 plot(zsens[,1], zsens[,2], main="z", xlab="Parameter value", ylab="
    Estimated cases")
941 plot(etat1sens[,1], etat1sens[,2], main="etat1", xlab="Parameter
    value", ylab="Estimated cases")
```

```
942 plot(etat2sens[,1], etat2sens[,2], main="etat2", xlab="Parameter
      value", ylab="Estimated cases")
943 plot(etat3sens[,1], etat3sens[,2], main="etat3", xlab="Parameter
      value", ylab="Estimated cases")
944 plot(etat4sens[,1], etat4sens[,2], main="etat4", xlab="Parameter
      value", ylab="Estimated cases")
945 plot(kappa_qt1sens[,1], kappa_qt1sens[,2], main="kappa_qt1", xlab="
      Parameter value", ylab="Estimated cases")
946 plot(kappa_qt2sens[,1], kappa_qt2sens[,2], main="kappa_qt2", xlab="
      Parameter value", ylab="Estimated cases")
947 plot(kappa_qt3sens[,1], kappa_qt3sens[,2], main="kappa_qt3", xlab="
      Parameter value", ylab="Estimated cases")
948 plot(kappa_qt4sens[,1], kappa_qt4sens[,2], main="kappa_qt4", xlab="
      Parameter value", ylab="Estimated cases")
949 plot(kappa_At1sens[,1], kappa_At1sens[,2], main="kappa_At1", xlab="
      Parameter value", ylab="Estimated cases")
950 plot(kappa_At2sens[,1], kappa_At2sens[,2], main="kappa_At2", xlab="
      Parameter value", ylab="Estimated cases")
951 plot(kappa_At3sens[,1], kappa_At3sens[,2], main="kappa_At3", xlab="
      Parameter value", ylab="Estimated cases")
952 plot(kappa_At4sens[,1], kappa_At4sens[,2], main="kappa_At4", xlab="
      Parameter value", ylab="Estimated cases")
953 plot(omega_qsens[,1], omega_qsens[,2], main="omega_q", xlab="
      Parameter value", ylab="Estimated cases")
954 plot(omega_Asens[,1], omega_Asens[,2], main="omega_A", xlab="
      Parameter value", ylab="Estimated cases")
955 plot(xisens[,1], xisens[,2], main="xi", xlab="Parameter value", ylab
      ="Estimated cases")
956 plot(Omegasens[,1], Omegasens[,2], main="Omega", xlab="Parameter
      value", ylab="Estimated cases")
957 plot(Vsens[,1], Vsens[,2], main="V", xlab="Parameter value", ylab="
      Estimated cases")
958 plot(chii_d1sens[,1], chii_d1sens[,2], main="chii_d1", xlab="
      Parameter value", ylab="Estimated cases")
959 plot(chii_d2sens[,1], chii_d2sens[,2], main="chii_d2", xlab="
      Parameter value", ylab="Estimated cases")
```

```
960 plot(xt1sens[,1], xt1sens[,2], main="xt1", xlab="Parameter value",
      ylab="Estimated cases")
961 plot(xt2sens[,1], xt2sens[,2], main="xt2", xlab="Parameter value",
      ylab="Estimated cases")
962 plot(xt3sens[,1], xt3sens[,2], main="xt3", xlab="Parameter value",
      ylab="Estimated cases")
963 plot(xt4sens[,1], xt4sens[,2], main="xt4", xlab="Parameter value",
      ylab="Estimated cases")
964 plot(piit1sens[,1], piit1sens[,2], main="piit1", xlab="Parameter
      value", ylab="Estimated cases")
965 plot(piit2sens[,1], piit2sens[,2], main="piit2", xlab="Parameter
      value", ylab="Estimated cases")
966 plot(piit3sens[,1], piit3sens[,2], main="piit3", xlab="Parameter
      value", ylab="Estimated cases")
967 plot(piit4sens[,1], piit4sens[,2], main="piit14", xlab="Parameter
      value", ylab="Estimated cases")
968 plot(phi_d1sens[,1], phi_d1sens[,2], main="phi_d1", xlab="Parameter
      value", ylab="Estimated cases")
969 plot(phi_d2sens[,1], phi_d2sens[,2], main="phi_d2", xlab="Parameter
      value", ylab="Estimated cases")
970 plot(delta1sens[,1], delta1sens[,2], main="delta1", xlab="Parameter
      value", ylab="Estimated cases")
971 plot(Sigmasens[,1], Sigmasens[,2], main="Sigma", xlab="Parameter
      value", ylab="Estimated cases")
972 plot(kappa1sens[,1], kappa1sens[,2], main="kappa1", xlab="Parameter
      value", ylab="Estimated cases")
973 plot(omega1sens[,1], omega1sens[,2], main="omega1", xlab="Parameter
      value", ylab="Estimated cases")
974 plot(eta1sens[,1], eta1sens[,2], main="eta1", xlab="Parameter value"
      , ylab="Estimated cases")
975 plot(tau1sens[,1], tau1sens[,2], main="tau1", xlab="Parameter value"
      , ylab="Estimated cases")
976 plot(delta2sens[,1], delta2sens[,2], main="delta2", xlab="Parameter
      value", ylab="Estimated cases")
977 plot(h2sens[,1], h2sens[,2], main="h2", xlab="Parameter value", ylab
      ="Estimated cases")
```

```
978 plot(thethasens[,1], thethasens[,2], main="thetha", xlab="Parameter
      value", ylab="Estimated cases")
979 plot(alpha2sens[,1], alpha2sens[,2], main="alpha2", xlab="Parameter
      value", ylab="Estimated cases")
980 plot(rsens[,1], rsens[,2], main="r", xlab="Parameter value", ylab="
      Estimated cases")
981 plot(esens[,1], esens[,2], main="e", xlab="Parameter value", ylab="
      Estimated cases")
982 plot(Sigma1sens[,1], Sigma1sens[,2], main="Sigma1", xlab="Parameter
      value", ylab="Estimated cases")
983 plot(rhosens[,1], rhosens[,2], main="rho", xlab="Parameter value",
      ylab="Estimated cases")
984 plot(irseffsens[,1], irseffsens[,2], main="irseff", xlab="Parameter
      value", ylab="Estimated cases")
985 plot(phisens[,1], phisens[,2], main="phi", xlab="Parameter value",
      ylab="Estimated cases")
986 plot(amplitsens[,1], amplitsens[,2], main="ampit", xlab="Parameter
      value", ylab="Estimated cases")
987 #Multivariate sensitivity
988 data<-NULL
989 #runs
990 for (i in 1:10){
991   parms <- c(beta=theta[1],Bh=theta[2],psii=theta[3],gamma=theta[4],
        tau=theta[5],Ln=theta[6],alpha1=theta[7],alpha=theta[8],G=theta
        [9],delta=theta[10], h=theta[11],
992               epsolon1=theta[12],epsolon2=theta[13],z=theta[14],etat1
                    =theta[15],etat2=theta[16],etat3=theta[17],etat4=
                    theta[18],kappa_qt1=theta[19],kappa_qt2=theta[20],
993               kappa_qt3=theta[21],kappa_qt4=theta[22],kappa_At1=theta
                    [23],kappa_At2=theta[24],kappa_At3=theta[25],kappa_
                    At4=theta[26],omega_q=theta[27],omega_A=theta[28],
994               xi=theta[29],Omega=theta[30],V=theta[31],chii_d1=theta
                    [32],chii_d2=theta[33],xt1=theta[34],xt2=theta[35],
                    xt3=theta[36],xt4=theta[37],piit1=theta[38],
995               piit2=theta[39],piit3=theta[40],piit4=theta[41],phi_d1=
                    theta[42],phi_d2=theta[43],delta1=theta[44],Sigma=
```

```
                    theta[45],kappa1=theta[46],omega1=theta[47],eta1=
                    theta[48],
996                 tau1=theta[49],delta2=theta[50],h2=theta[51],thetha=
                    theta[52],alpha2=theta[53],r=theta[54],e=theta[55],
                    Sigma1=theta[56],rho=theta[57],irseff=theta[58],phi=
                    theta[59],amplit=runif(1,lower[60],upper[60]))
997   run_d<- ode(y=x0_1, times = times, func = sir_fit, parms = parms)
998   data<-rbind(data, trtprop=c(parms,run_d[length(run_d[1:143,1])
          ,13]))
999 }
1000
1001 lm1<-lm(data[,14]~data[,1:13], data=as.data.frame(data))
1002 library(QuantPsyc)
1003 lm2<-lm.beta(lm1)
1004 stdcoeff<-cbind(sort(abs(lm2), decreasing = T))
1005 stdcoeff
```