University of Zululand

Theoretical modelling of temperature and rainfall influence on *Schistosoma species* population dynamics

BY

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DECLARATION

I, Tayo Alex ADEKIYA (Student No: 201633206), solemnly declare that the dissertation entitled **Theoretical modelling of temperature and rainfall influence on Schistosoma species population dynamics** submitted by the undersigned has been carried out under the supervision of Prof. Abidemi Paul Kappo and Prof Kazeem Oare Okosun in the Department of Microbiology and Biochemistry, University of Zululand and the Department of Mathematical Science, Vaal University of Technology. And this work had not been submitted to any university for any degree and the material used are acknowledge by references.

Candidate: Tayo Alex ADEKIYA

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Date:.....

DEDICATION

This project is dedicated to the Almighty God, the king of kings and the Lord of lords.

Also, to my Late father Elder S.A Adekiya.

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ABSTRACT

Schistosomiasis, otherwise known as snail fever or bilharzia, is caused by parasitic flatworms called schistosomes. In human, these schistosomes infected the intestines or the urinary tract where they develop to form other acute and chronic diseases which include fever, malaise, severe abdominal pain, skin rashes, liver disease, lung disease, intestinal disease and urinary tract disease depending on the schistosomes. The reoccurrence of Schistosoma infections over the years may result into cancer of the bladder, obstruction in urinary tract, portal or pulmonary hypertension and even death. This study was developed to investigate the influence of temperature and rainfall on population dynamics of *Schistosoma species* over South Africa. Also, to investigate time-dependent control strategies, so as to ascertain the best cost-effectiveness optimal control strategy for schistosomiasis eradication/control.

In this study, a deterministic schistosomiasis climate-based model was developed using differential equations. The numerical simulations of the system were done using MATLAB and Ferret software in order to examine the effect of climate variability on the transmission dynamics of schistosomiasis. Furthermore, a deterministic model for the transmission of schistosomiasis disease and optimal control analysis of the model was also derived and analyzed. The model is found to exhibit multiple equilibria, the necessary conditions for the optimal control of the disease was derived and analyzed. In addition, the cost-effectiveness of the controls was investigated in order to determine the most effective strategy to control the disease with minimum costs. Finally, the numerical solutions were presented.

Numerical simulations showed that the impact of climate change on population dynamics of schistosomiasis infection is greatly pronounced on the production, survivability and fecundity rate of both freshwater snails and schistosomes. It was also showed by the numerical simulations that all the strategies employed for schistosomiasis control have great effects both on the population of infected human and infected snail with control strategies B, D, F, G, I and J showed great decrease effects on the number of infected human population. In the cost-effectiveness of the control strategies, the results suggest that in the presence of limited resources, policy makers may adopt the strategy I (combination of the prevention, treatment and snail control) over J which includes additional cost of controlling loss of immunity. Finally, the model further suggested future opportunity for modification and refinement for the prediction of the effects of climate variability on the transmission dynamics of Schistosoma.

Keywords: Schistosomiasis, temperature, rainfall, climate change

LIST OF PUBLICATIONS AND CONFERENCES

Publications

1. **T.A. Adekiya**, A.P. Kappo, and K.O. Okosun. Temperature and rainfall impact on schistosomiasis. Global Journal of Pure and Applied Mathematics. Volume 14, Number 1 (2018), pp. 4966

2. **Tayo Alex Adekiya**, Raphael Taiwo Aruleba, Priscilla Masamba, Babatunji Emmanuel Oyinloye, Kazeem Oare Okosun and Abidemi Paul Kappo. Climate change and snail-schistosome cycle as predictors of transmission and biocontrol of Schistosomiasis in sub-Saharan Africa. Interdisciplinary Perspectives on Infectious Diseases. Submitted (4613804)

3. **T.A. Adekiya**, A.P. Kappo, K.O. Okosun Optimal control strategies and cost-effectiveness analysis of schistosomiasis model with vaccination. Scientific Reports. Submitted.

Conferences and Symposiums

1. **Tayo Alex Adekiya**, Kazeem Oare Okosun and Abidemi Paul Kappo. Theoretical modelling of temperature and rainfall impact on Schistosoma species population dynamics. 2017 Centre for High Performance Computing (CHPC) National Conference, Pretoria, South Africa 3-7 December 2017.

2. **Tayo Alex Adekiya**, Raphael Taiwo Aruleba, Abidemi Paul Kappo and Kazeem Oare Okosun. Influence of temperature and rainfall on Schistosomiasis transmission

in South Africa. Faculty of Science and Agriculture- Postgraduate Symposium, University of Zululand, KwaDlangezwa Campus, 29 September 2017. Page 37 of Abstract Book

3. **Tayo Alex Adekiya**. Mathematical modelling of temperature and rainfall influence on Schistosoma species population dynamics. The South African Medical Research Council, Parow Valley, Cape Town South Africa. Biomedical Research and Innovation Platform; Research Symposium 16 October 2017.

4. **Tayo Alex Adekiya**, Kazeem Oare Okosun and Abidemi Paul Kappo. The effects of temperature and rainfall variabilities on the population dynamics of schistosomiasis. South Africa Society of Biochemistry and Molecular Biology (SASBMB), in conjunction with the Federation on African Societies of Biochemistry and Molecular Biology (FASBMB), Potchefstroom, South Africa. July 8-11, 2018

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6. **Tayo Alex Adekiya**, Kazeem Oare Okosun and Abidemi Paul Kappo. Exploration of the impact of climate change on schistosomiasis transmission dynamics. 10thEuro-Global Conference on Infectious Diseases. Rome, Italy, September 26-29. Accepted

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Chapter 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Neglected tropical diseases (NTDs) are diseases which have been neglected for decades. They are a group of chronic infectious diseases affecting majorly over one billion people in sub-Sahara Africa and other poor societies of the world at large, who are considered to live below $2 per day and approximately, not less than two billion people are at high-risk of NTDs (Feasey *et al.,* 2009; Hotez *et al.,* 2009; Hotez *et al.,* 2007). NTDs cause over 534,000 deaths every year in sub-Sahara Africa and the world at large. In addition, they result in several disabilities and disfigure about 57 million people, before resulting in loss of life in chronic cases. NTDs have been shown to have great negative impact on health, financial and social economies of individual households and the government at large (Hotez and Kamath, 2009; Adenowo *et al.,* 2015; Martins-Melo *et al.,* 2016; Kappagoda and Ioannidis, 2014). In tropical regions, the prevalence of schistosomiasis is one of the most highly ranked and fast growing neglected tropical diseases (NTDs), due to change in

climatic factor, global warming, poor healthcare systems, poor sanitation, dilapidations in social infrastructures, increase in population and elevation in poverty level among people living in the region (Oyinloye *et al.,* 2014; Hotez *et al.,* 2007; Mangal *et al.,* 2008). Schistosomiasis is a common disease majorly found in tropical and subtropical regions such as Africa, Middle East and some areas of South America (Adenowo *et al.,* 2015; Oyinloye *et al.,* 2014; Gryseels *et al.,* 2006). Over the years, reports have shown that more than 218 million people are being affected by the epidemic of this deadly disease in not less than 78 countries of the world (Adenowo *et al.,* WHO, 2017). It has been shown to result into over 280,000 mortality rates annually and the increase in new cases of the infection have been documented to hit approximately over 700 million globally, most especially in areas where the disease is renowned to be easily transmitted (Adenowo *et al.,*; WHO 2014). This disease is mainly caused by the parasitic schistosome blood fluke both in humans and freshwater snails through its complete developmental cycle, which can easily result into several modifications leading to diverse conditions relating to the host (Hork *et al.,* 2015). Three main species of this parasite are majorly responsible for its hosting in humans. They include *Schistosoma mansoni, Schistosoma japonicum* and *Schistosoma haematobium.* However, the other two species *Schistosoma mekongi* and *Schistosoma intercalatum* in humans are more uncommon and restricted to a couple of nations (Colley *et al.,* 2014; Gryseels *et al.,* 2006). The epidemic of these parasites has been shown to result into complex or chronic diseases such as diarrhea, abdominal pain, presence of blood in stool, portal hypertension, liver cirrhosis, myeloradiculopathy, cercarial dermatitis, pneumonia, fever, splenomegaly, cancer of the bladder, hepatomegaly and premature death among others (Gryseels *et al.,* 2006; Lambertucci, 2010; WHO, 2014). As part of the measure to reduce the threat of schistosomiasis, administration of praziquantel (PZQ) has been adopted as the best treatment for this disease, likewise the reduction in transmission of the

disease through snail control and improvement in social infrastructure such as provision of portable water, sanitation of environment (Grimes *et al.,* 2015). Consequently, it is well known that environmental factors, due to variations in the season or changes in climatic factors such as temperature and rainfall play a major effect in the reappearance and dynamics of infectious diseases. Several studies have predicted climatic factors such as temperature, rainfall and other forms of climate conditions as potential factors that enhance the adequate production of schistosome parasite, the mortality and production of snails in the water-body (Barbosa *et al.,* 1985; Xue *et al.,* 2011; Zhou *et al.,* 2008). Some biological model-based experiment has shown that stages in the Schistosoma species, and several intermediates in the lifecycle of host snail as well as the rate of snail mortality are dependent on temperature sensitivity after several climate projections such as low, high and moderate warm climate (McCreesh *et al.,* 2015; McCreesh and Booth, 2014; Zhou *et al.,* 2008). However, the influence of temperature and rainfall on the life cycle and population dynamics of schistosomiasis over South Africa was investigated in this study because population dynamics is an essential factor in the risk of schistosomiasis. Also, in the transmission of schistosomiasis, it is important to investigate and understand the biology of schistosoma parasites and the snail intermediate hosts. Moreover, the significant role played by temperature and rainfall in both aquatic and adult stages of *Schistosoma species* in the snail intermediate hosts was also examined. Therefore, this present study developed an efficient and effective model that can predict *Schistosoma species* population dynamics, evaluate the optimal effectiveness of several control strategies. A framework model was also designed which can predict and accommodate the future incidence of schistosomiasis in the human population.

1.2 An Overview of Neglected Tropical Diseases

In some part of the African, Asian and American continents suffering from massive underdevelopment or are still developing, the major caused of chronic infectious diseases are NTDs. They are majorly caused by parasitic worms (helminths), viruses, bacteria and protozoa. The burden of NTDs in sub-Saharan African (SSA) is equivalent to one-half burden of malaria in SSA and double the burden of tuberculosis due to the neglect of these diseases for the top three pathologies: malaria, tuberculosis and HIV/AIDS (Hotez and Kamath, 2009). According to the World Health Organization (WHO), there are 17 majorly existing NTDs in the world, which includes schistosomiasis, buruli ulcer, rabies, lymphatic filariasis, onchocerciasis, trachoma, endemic treponematoses (Yaws), taeniansis/cysticerosis, leprosy, leishmaniasis, dracunculiasis, human African trypanosomiasis, echinococcosis, dengue and chukungunya fever, food-borne trematodiases, Chagas disease and soil transmitted helminthiases (STH) (Mackey *et al.,* 2014; Hotez *et al.,* 2016).

1.3 Occurrence, Distribution and Burden of NTDs in Sub-Sahara Africa

Several studies have shown NTDs in predominant conditions in over 500 million poor people in Africa. The disease burden put together is comparable to one and half burden of malaria in SSA and twice the burden of tuberculosis in this region (Hotez and Kamath 2009; Adenowo *et al.,* 2015). Over 85 % burden of NTDs result from infections of helminthes and hookworm, which is the major source of anemia in over 40 to 50 million school children and over 7 million of pregnant women in SSA. Schistosomiasis is the second most occurring NTDs in SSA, with approximately 93 % cases of the global infection

resulting in over 192 million people living with the disease (Hotez and Kamath 2009; Adenowo *et al.,* 2015). In order of importance, the prevalence of other NTDs ranges as follows: lymphatic filariasis, onchocerciasis, human trypanosomiasis and trachoma (Hotez and Kamath 2009). According to the 2013 manual for water, sanitation and hygiene (WASH) in South Africa, soil-transmitted helminthiasis (STH) and schistosomiasis among other NTDs are endemic in the country with at least over 5.2 million people at high-risk of each of this infection (Freeman *et al.,* 2013; WHO PCT, 2013). Therefore, as a measure to reduce the risk of NTDs in South Africa and to keep the country as one of the countries with lesser occurrence of the distribution and burden of NTDs in the world, there is need for further studies involving one of these diseases. Moreover, the National Master Plan for NTDs is yet to be launched publicly in South Africa; it is expected that this will help to target and control the prevalence of NTDs (Freeman *et al.,* 2013).

1.4 Schistosomiasis

Schistosomiasis, otherwise known as bilharzia, ranked 2nd among the group of NTDs. It is a chronic and acute disease majorly caused by three parasitic trematode flatworms of the schistosoma species namely: *Schistosoma mansoni, Schistosoma japonicum* and *Schistosoma haematobium* among others (Adenowo *et al.,* 2015; Colley *et al.,* 2014). Over the years, approximately 218 million people are being afflicted globally by this disease in 78 countries. In Africa, Eastern Asia and South America, approximately over 700 million are at the risk of Schistosoma infection (WHO, 2014). The infection results in acute sickness with symptoms such as malaise, fever and abdominal pain or skin rashes, while the chronic stage result in liver, intestinal, lung, urinary tract diseases depending on the infective species of the schistosome. Reoccurrence of schistosoma infection and

incomplete treatment for years, result in death due to obstruction in urinary tract, cancer of the bladder, pulmonary or portal hypertension and other severe complications (Gray *et al.,* 2011; Mostafa *et al.,* 1994; Samaras *et al.,* 2010; Zaghloul *et al.,* 2012; Groeneveld *et al.,* 1996).

1.4.1 Epidemiology of Schistosomiasis

IIn terms of public health challenge, schistosomiasis is a leading tropical disease, 2nd only to malaria. The African continent bears the highest brunt of this disease with no less than 46 countries having a high prevalence of this infection (Berge *et al.,* 2011; Steinmann *et al.,* 2009). The incidence of schistosomiasis varies significantly from one region to another due to the environmental factors and lifestyle of the dwellers of such areas (Oyinloye *et al.,* 2014). These areas are usually located around 36^0 North and South of the equator, having the most favourable freshwater temperature that enables the survival of the snail intermediate hosts of schistosomes in humans (Schutte *et al.,* 1994; Bica *et al.,* 2000). In sub-Sahara Africa, the burden of schistosomiasis is very high in young adults and children. Out of the total 207 million global burden of the infection, an estimated 192 million (93 %) cases occurs in SSA with Nigeria having the highest prevalence of 29 million, followed by the United Republic of Tanzania with a prevalence of 19 million. Additionally, Ghana, Democratic Republic of Congo has a prevalence of 15 million, while Mozambique presents a prevalence of 13 million of the disease (Adenowo *et al.,* 2015; Hotez and Kamath 2009). Approximately 112 million of schistosomiasis infections are caused by *Schistosoma haematobium*, which is greater than half of the total schistosomiasis infection. Furthermore, an annual 280,000 deaths due to the disease are caused by *S. mansoni* and *S. haematobium* (Mbabazi *et al.,* 2011).

1.4.2 Prevalence of Schistosomiasis in Sub-Sahara Africa

Despite a remarkable impact in the reduction and control of schistosomiasis around the world, the prevalence of schistosoma infection is still at an alarming rate in some parts of the world as shown in figure 1. In a study carried out in Nigeria, 2.3% of more than 1000 cases of an infected appendix had schistosome eggs found in histological sections, with 56 % of the cases owing to *S. mansoni*, 26 % to S. haematobium, and 19 % to co-infection by both species (Gali *et al.,* 2006). Also, in another related study carried out at the Ahmadu Bello University Teaching Hospital, Zaria, Nigeria, it was discovered that schistosomiasis of the appendix was common, out of 1,464 appendectomy specimens sampled (Ahmed *et al.,* 2014). In regions of high schistosomiasis endemicity, pulmonary hypertension, which is caused as a result of *S. mansoni* is very prominent (Lapa *et al.,* 2009).

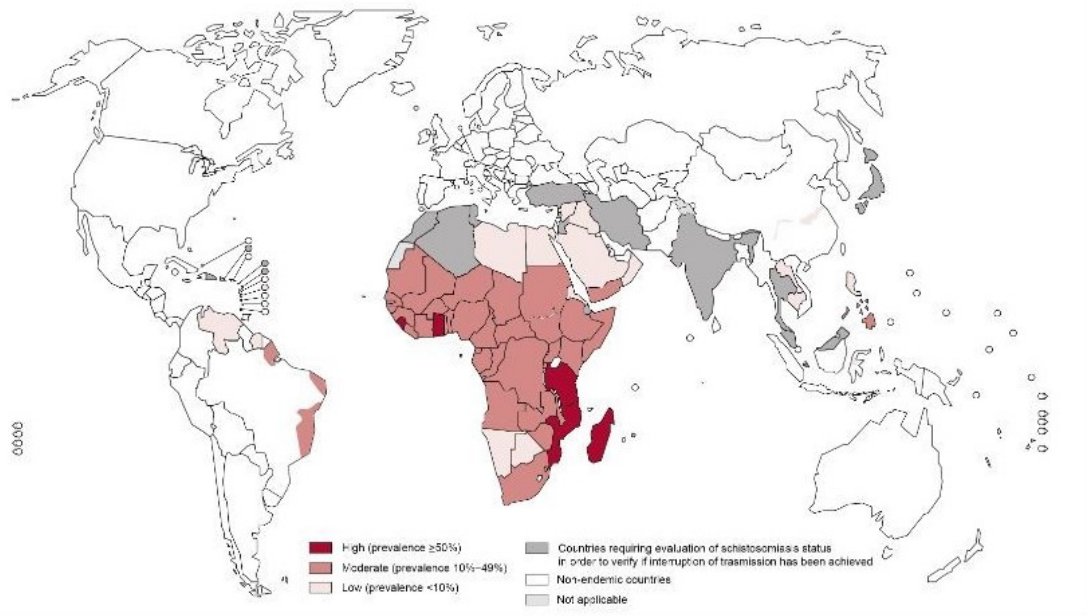

Figure 1.1: The Distribution of Schistosomiasis from different countries of the world (WHO Fact Sheet, 2014)

In Rwanda, it was discovered that 21.1 % of Lake Rweru dwellers presents with intestinal schistosomiasis; an indication of high prevalence of the disease in the region, which may occur as a result of lack in the availability of piped water in various communities of the region (Odiere *et al.,* 2012). Also, another study carried out in Mbita and some Islands not far from Lake Victoria in Kenya using school children with age ranges between 5 to 19 years, it was discovered there is high level of *S. mansoni* infection in these target areas with prevalence as high as 60.5 % (Ruberanziza *et al.,* 2013) In Sengerema District of North-West Tanzania, despite preventive and control measure put in place to reduce the prevalence of schistosomiasis infection in the area through medication, high prevalence level of *S. mansoni* infection was noted in a cross-sectional study of school children between the age range of 8 to 17 years (Mazigo *et al.,* 2010). In Ghana, the prevalence of schistosomiasis as reported in a study carried out among school children between ages 6 to 15 years residing in areas along Tono Irrigation Canal in North Ghana showed a 33.2 % occurrence of *S. haematobium* and 19.8 % *S. mansoni* infections. Added to this, the

authors noted high prevalence of schistosomiasis infection among males compared to their female counterparts, this might be due to longer contact with contaminated water with schistosomes (Anto *et al.*, 2013). The findings from another study in the Volta Basin of Ghana among adults, showed a high prevalence of urinary schistosomiasis of about 46.5 %, which indicates that the prevalence of Schistosoma infection is not temporal among adults (Yirenya-Tawiah *et al.,* 2011) In the Niakhar District of Senegal, 57.6 % prevalence of urinary schistosomiasis and a high level of *S. haematobium* infection of 185 eggs/ml were reported among age school children; this may be due to greater dependence of the dwellers on ponds and backwater for diverse household activities(Senghor *et al.,* 2014). In a demographic analysis, it was noted that high prevalence of schistosomiasis was common among children of household residing in an area close to a dam, high prevalence of 30.7 % urinary schistosomiasis was discovered among school age children population of age range between 3 to 16 years in Zenu, a village around the capital city of Ghana (Tetteh-Quarcoo *et al.,* 2013) More so, a prevalence of 1.0 % *S. mansoni* and 47.0 % *S. haematobium* infections was revealed in a national survey of soil helminth and schistosoma infections among school age children in Mozambique. In this study, it was observed that there is an increase in the infection of schistosomiasis as the years increase, as well as an increase in *S. haematobium* infection in the age group of 10 to 14 years. Further analysis from this study showed highest prevalence of schistosomiasis was observed in the male child compared to their female counterparts due to the longer time spent in ponds or dam infected with *Schistosoma species* (Augusto *et al.,* 2009). In Ethiopia, despite de-worming programs among school children in Zarima, a town northwest of the country, it was revealed that there is a 37.9 % increase in the prevalence of *S. mansoni* infection among the 319 primary school children sampled. High endemicity with *S. haematobium* infection was revealed in Barombi Kotto, South-West of Cameroun with prevalence of

69.17 % however, it was revealed that *B. globosus* intermediate host needed for the transmission of the disease was present in most lakes found in the area (Nkengazong *et al.,* 2013). In addition to this, high prevalence of *S. haematobium* 85.3 % and *S. mansoni* 53.8 % among school age children was revealed in a study carried out in the Agboville community of Cote d Ivoire (Muller *et al.,* 2011).

1.4.3 Epidemiology and Prevalence of Schistosomiasis in South Africa

In South Africa, *S. mansoni* and *S. haematobium* are the two most common *Schistosoma species*; their infections result in intestinal and urogenital schistosomiasis respectively (Appletona and Miranda, 2015). The endemic regions of the disease are in the east and the north of the country, which occupies about a quarter of the total land mass, with more than 5 million individuals diagnosed to be infected with the infection, which predominates among school-aged children (Mbabazi *et al.,* 2011; Saathoff *et al.,* 2004). Approximately, over 25.7 million South African are believed to be at risk of the disease due to climate change. More so, individuals whose occupations or activities put them in contact with surface water, such as agricultural workers, fishermen and miners are at high risk of the disease. Others include; women who come into contact with water during clothes washing and bathing, and children playing in water are also at risk of infection with schistosomiasis in South Africa (Magaisa *et al.,* 2015; Wolmarans and De Kock, 2009). In South Africa, the endemic of schistosomiasis is situated in the north-east and covers roughly one quarter of the country, with *S. haematobium* being the most prevalent species (Appletona and Miranda, 2015). In 1998, a pilot programme for helminth control was established by the Department of Health of the province of KwaZulu-Natal (KZN) in-conjunction with

the Department of Education, a programme which aimed at frequently treating primary school children for schistosome infection and intestinal helminth infections (Saathoff *et al.,* 2004).

The intermediate (snail) host of *S. haematobium*, *B. africanus* and *B. globosus* are closely related but differ in their physiological properties as *B. africanus* is better adapted to temperatures in the temperate and subtropical areas of the country southwards to the Kromme River in the Eastern Cape (25^oS), while *B. globosus* are better suitable to the high temperature in the north and north-east of the country (Appletona and Miranda, 2015). Hence, *B. globosus* is limited to the subtropical area of South Africa which comprises of Limpopo province, the middleveld and lowveld of Mpumalanga province, and Swaziland to the north-east corner of KwaZulu-Natal around latitude 28^oS. The intermediate (snail) host of *S. mansoni*, *B. pfeifferi* is widely distributed over Limpopo province, the north-eastern part of North West province, the middleveld and lowveld of Mpumalanga, the eastern half of Swaziland and the eastern half of KwaZulu-Natal. There is no occurrence of *B. pfeifferi* in the south of Port St Johns (a latitude of 31.6^oS). Unlike *B. globosus*, which is widely dispersed across tropical region in Africa (Appletona and Miranda, 2015). In a pilot study report among school age children in Eastern Cape Province of South Africa in 2010, a 73.3 % was observed; this high prevalence may be due to the small population size hence, further investigation in order to ascertain the impact of schistosomiasis in the area is of utmost importance (Meents and Boyles, 2010).

1.5 Causative Agents of Human Schistosomiasis

In humans, several causative agents of schistosoma infection have been shown to exhibit differences in strains, genera and species. These include immunogenicity, the rate of

transmission of infection and the rate at which schistosomes cause disease in the parasite populations (Gentile and Oliveira, 2008; Rollinson *et al.,* 1997). Evidence from literature averred there are five existing schistosome species namely *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma mekongi* and *Schistosoma intercalatum*,However, out of these five schistosome species, only three have been recognised and confirmed to be responsible for the pathology of schistosomiasis in humans (Ingram *et al.,* 2012; Oyinloye *et al.,* 2014). Studies have shown that 95 % of all schistosoma infections in humans are majorly caused by *Schistosoma mansoni* and *Schistosoma haematobium*, which are responsible for over 280,000 deaths every year (Alebie *et al.,* 2014; Mazigo *et al., 2010*; Mbabazi *et al.,* 2011). Due to their great significance in human schistosomiasis, *Schistosoma mansoni* and *Schistosoma haematobium* have gained more recognition than other Schistosoma species.

1.6 Schistosoma Life Cycle

Mature schistosomes are generally between 7 to 20 mm, normally whitish or grayish in colour, cylindrical in shape and possess two suckers region, reproductive organs, a tegument and digestive tract. This trematode is different from other types of trematodes due to being dioecious i.e. the worms possess distinct sexual dimorphism between both males and females. In this case, the male possesses gyneaphoric canal which makes it capable of griping the female counterpart who are normally thinner and longer (Gryseels *et al.,* 2006). Both the male and female schistosomes permanently embrace each other and live in the rectal venous plexus and vesical venous plexus for *S. haematobium*, *S. mansoni* and *S. japonicum* respectively. Schistosomes obtain all the necessary nutrients through the blood stage host and globulins by anaerobic glycolysis, while discharging

their waste back into the hosts body (Gryseels *et al.,* 2006; Adenowo *et al.,* 2015). The African specie of the female schistosome was discovered to generate hundreds of eggs per day, while the oriental species are able to produce thousands of eggs per day. The ovum of individual female schistosome is home to the miracidum larva and cilia through which proteolytic enzymes are generated to help the migration of eggs to the intestine or the hollow lumen of the bladder(Gryseels *et al.,* 2006). As depicted in figure 2, the eggs of the Schistosoma parasite are released through the urine and faeces of infected individuals to the surface of water bodies, resulting in the formation of miracidia through the help of light and chemical stimuli. The miracidia contaminate and penetrate freshwater snails, which serve as intermediate host to the parasite. Inside the snail, the miracidia go through asexual reproduction to generate multicellular sporocytes that later matures or grow to become cercaria larva with embryonic suckers and two divided tails. Thereafter, the infected snail releases the cercaria larvae after spending about 4-6 weeks inside the snail and these moves around for about 72 hours in order to come into contact with the human skin which is the definitive host (Gryseels *et al.,* 2006). The larvae form of the parasite penetrates the intact skins of individual human who washes, bathes, swims, fishes and does all sorts of ponds, streams and river related works where infected intermediate host snails exists (Gryseels *et al.,* 2006). Inside the host body, these larvae form of the parasite (cercaria) loses its tail to become Schistosomulum/Schistosomula; the mature worms then move to hepatic portal system, from where they grow within 4 to 6 weeks and perform their reproductive activities, later migrate to the intestine, urinary bladder, liver and the ureter. These mature worms produce and deposit numerous eggs; most of which pass through the faeces and urine of infected person back into the water bodies where they are hatched to release miracadium with the tendency to infect freshwater snail, leading to the continuation in the life cycle of Schistosoma parasite (Gryseels *et al.,* 2006; Oyinloye *et*

al., 2014).

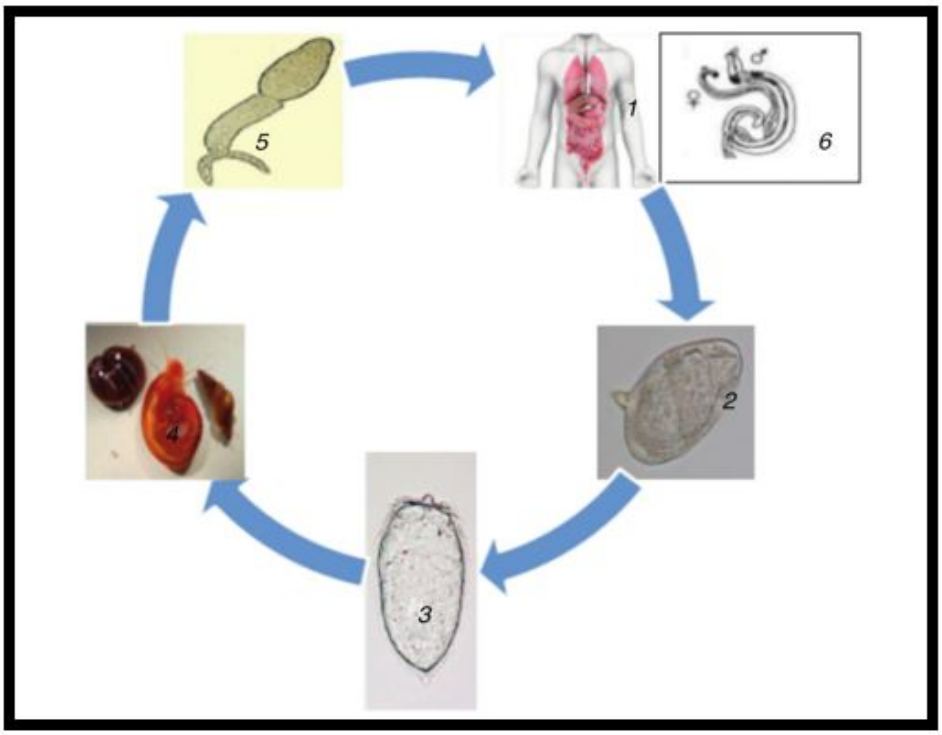

Figure 1.2: Schistosoma Life cycle *1. Definitive host, 2. Schistosome eggs discharged in faeces or urine of definitive host, 3. Free-swimming miracidia from eggs, 4. Intermediate host, 5. Cercaria (infiltrates skin, loses its tail and transforms into schistosomulum), 6. Paired adult worm (schistosomulum migrates to the hepatic portal system; adult worms mature in pairs in the veins surrounding the bladder, intestines or liver. They produced eggs, most of which are eliminated in urine or faeces of definitive host to the environment. The eggs hatch liberating miracidia to restart the life cycle (Oyinloye et al., 2014).*

1.7 Schistosomiasis and Cancer

Several studies have linked cancer of the bladder to urinary schistosomiasis which is caused by *S. heamatobium* infection (Mostafa *et al.,* 1994; Samaras *et al.,* 2010). It accounts for about 30 % of total cancer cases and is more prevalent in men than women (Mostafa *et al.*, 1994). Recently, the International Agency for Cancer Research (IACR) in

conjunction with the World Health Organization (WHO) ranked *S. haematobium* as one of the prominent cancer-causing agents (Shaker *et al.,* 2011; Vennervald and Polman, 2009). Also, other Schistosoma infections (*S. mansoni* and *S. japonicum*) have been associated with several types of cancers such as liver, cervical, intestine, uterus and in addition, colorectal carcinomas (Madbouly *et al.,* 2007; Samaras *et al.,* 2010). However, the cellular and molecular mechanism by which Schistosoma parasite initiates cancer formation is not very well understood (Botelho *et al.,* 2010).

Consequently, the role of Schistosoma infection has been observed in several studies to have resulted in the formation of chronic inflammatory reactions and irritation in the bladder, which results into the generation of endogenous free radicals (neutrophils and macrophages) (Marletta, 1988; Rosin *et al.,* 1994a; Rosin *et al.,* 1994b; Zaghloul, 2012). On the other hand, endogenous radicals are considered to play an essential role in cancer initiation process through the production of N-nitrosamines; a carcinogenic compound (Marletta, 1988; Zaghloul, 2012). N-nitrosamines may cause detrimental effects on cells through the exchanges of sister chromatids, mutations in the cells and disruptions of DNA strands, which in turn results into malignant formation (Oyinloye *et al.*, 2014; Shacter *et al.*, 1988; Weitberg, 1989; Weitzman and Stossel, 1981).

Moreover, the activities of inflammatory cells have also been shown to associate with the activation of procarcinogens into carcinogenic compounds, for example activation of polycyclic aromatic hydrocarbons and aromatic amines (O'Brien, 1988; Oyinloye *et al.,* 2014).

Studies by Mostafa and colleagues (1994) and Lehman and co-workers (1973) show that there is an elevated level in the activities of N-nitrosamines, as well as an observable increase in the levels of nitrate-reducing bacteria in the urine of Schistosoma-infected individuals when compared to normal individuals without infection of the Schistosoma

parasite. This indicates that in the generation of cancer of the bladder, Schistosoma infection plays a crucial role through the formation of N-nitrosamines (Michaud *et al.,* 2007; Samaras *et al.,* 2010).

1.8 Factors affecting population dynamics of schistosomiasis transmission

The occurrence and reoccurrence of Schistosomiasis is a public health issue that the entire world ought to be bothered about presently and in future due to the high impact of climatic factors on the transmission of infectious diseases. Several factors have been associated and generally recognized as potential factors that may aid the transmission dynamics of schistosomiasis. These include environmental factors such as rainfall, temperature and vegetation coverage, as well as socio-economic factors (Brooker, 2002; Mao, 1990). In some parts of the world where schistosomiasis is endemic, population dynamics in the transmission of schistosomal infections have been linked to some human activities that create or impact snail habitat such as the building of irrigation system, construction of dams and reservoirs for electricity generation, agricultural and other domestic purposes resulting in the alteration of the ecosystem (Fenwick *et al.,* 2009). In some parts of sub-Saharan Africa such as Ghana, Senegal, Mali, Cameroun, Cote dIvoire and Namibia, the significant increase in the number of urinary schistosomiasis cases has been linked to the construction of dams (Olveda *et al.,* 2013). In another related study, it was assumed that approximately 106 million (13.6%) people that are susceptible to schistosoma infection are currently living closer to areas where huge dam or reservoirs are constructed, as well as areas covered by irrigation schemes (Steinmann *et al.,* 2006). A study carried out in two zones of Zambia that varies in temperature and rainfall, established human activities

such as cassava production and cattle rearing; among rural dwellers have a significant impact on the transmission of schistosomiasis. It was further averred that physicochemical factors such as water flow velocity, heavy metals, condition of water and type of substrate caused by human activities are likely to play a tremendous role in the transmission of schistosomiasis (Monde *et al.,* 2016).

1.9 Effects of climate change

Over the years, rapid changes in climate factors caused by global warming have been recognized and shown to have great impact on several aspects of public health, such as transmission dynamics of vector-borne diseases like malaria, schistosomiasis, leishmaniasis, and African trypanosomiasis among others (Fernndez *et al.,* 2009; Mendelsohn and Dawson, 2008; Trrup *et al.,* 2011). This has called for a collective adoption of a resolution on climate change and health-related issues by the World Health Organization Assembly in 2008 in order to strengthen the World Health Organization (WHO). Climate change such as temperature and rainfall influence the suitability of freshwater bodies to host both snail population and parasites, which may alter or modify geographical distribution of schistosomiasis.

1.9.1 Effects of temperature on population dynamics of Schistosomiasis transmission

In 2008, Mangal and co-workers observed there might be some negligible factors in the prevalence of schistosomiasis such as temperature and other factors, which increase the mortality and morbidity of the disease as a result of increase in disease burden. Their study ascertained that increase in temperature has a negative impact on population dy-

namics of schistosomiasis transmission (Mangal *et al.,* 2008). They demonstrated that multiple increases in the burden of Schistosomiasis (especially *S. mansoni*) infection in prevalent regions correlated with an increase in temperature from 20^{o}C to 30^{o}C. They further showed that there was drastic decrease in the burden of the infection when temperature was increased above 30^{o}C, which may be due to increase in the mortality rate of the snail intermediate host (Mangal *et al.,* 2008).

In Eastern Africa, effect of climate change has been predicted as strong agents that increase the transmission of *S. mansoni* (McCreesh *et al.,* 2015). Designed model sensitivity to temperature and an agent-based model involves both the life cycles of the snail intermediate host and the *S. mansoni* parasite. The model predicted temperature as a suitable factor for the transmission of schistosomiasis in some areas and that it increased the prevalence of the transmission dynamics of the parasite in eastern Africa (McCreesh *et al.,* 2015).

McCreesh and Booth (2014) observed increase in water temperature is a suitable potent population dynamic for transmission of *S. mansoni* in eastern Africa. It was ascertained in their experiment that warm water has several effects on both snails and parasites depending on abiotic properties of the water body. This experimental model observation involved the sensitivity of temperature to *S. mansoni* and its effect on the life cycle of the *Biomphalaria pfeifferi* snail intermediate host (McCreesh and Booth, 2014). Additionally, it was observed the population of snails remain constant between temperatures ranging between 15^{o}C to 31^{o}C; there is a decrease in snail population when there is a slight change in temperature below or above 14^{o}C or 32^{o}C. The highest risk of infection was observed in humans between the hour of 1 pm and 6 -10 pm in stagnant water with temperatures from 16^{o}C to 18^{o}C, while in flowing water the temperature ranges between 20 - 25^{o}C at around 12 noon - 4 pm (McCreesh and Booth, 2014).

In China, climate change has been shown to have a great impact in the transmission of Schistosomiasis. This is as a result of a development-derived biology model, which shows the development of *S. japonicum* inside *Oncomelania hupensis* snail intermediate host depends on a temperature threshold of 15.4^{o}C. It was also observed that half of the snail hibernated at temperature of 5.8^{o}C which affects the fecundity rate of the snails (Zhou *et al.,* 2008).

In cold-blooded animals, temperature is a positive factor that enhances their development. A significant fall in temperature below a considerable threshold i.e. the lowest developing temperature otherwise known as biological zero will result in an alteration in the development of cold-blooded animals (Kotl *et al.*, 2016; Damos and Savopoulou-Soultani, 2011). The development of larvae stage in Schistosoma within the snail intermediate host follows the same rule of lowest developing temperature with cold-blooded animals. This lowest developing temperature is recognized as the hibernating temperature for the snail, in which there is a drastic drop in the metabolic rate of snails (Yang, 2006).

1.9.2 Effects of rainfall on population dynamics of Schistosomiasis transmission

Rainfall is another climatic factor with significant impact on the transmission of schistosomiasis infection. This was demonstrated in a study carried out in transmission sites closer to three villages in the lower delta of the Senegal River. This study revealed there is an abundant increase in the population of *Biomphalaria pfeifferi*, which is the prospective intermediate host of *S. mansoni* during the rainy period, while there is limited distribution of *Bulinus globosus* the intermediate host of *S. haematobium*, which means that there is an increase in transmission of *S. haematobium* during the dry period (Ernould *et al.,*

1999).

In another related study, Xue and colleagues (2011) established that rainfall is another climatic factor that is extensively responsible for the accumulation of sufficient surface water in ponds. This factor enhances and provides breeding sites for snail production. This may be due to the increase runoff in the water volume that is channelled through irrigation canals, which may in turn result in the elevation level in the flow velocities. In addition, it can relatively increase higher values, which cause unstable shear that can alter the survival of cercaria (Xue *et al.,* 2011)

1.9.3 Climate change mediation of cercarial production in schistosome life cycle

Climate change caused by fluctuation in temperature above or below the optimal temperature has a major influence on egg production by freshwater snail which in turn, has detrimental effect on the production of juvenile worms by freshwater snails. The temperature of the water body directs the rate at which parasites develop within the snail intermediate host, as well as the infection rate of cercaria with very pronounced and clear impact on the trematodal fluke life cycle. Generally, in trematodes transmission life cycle, molluscs (e.g. snails) are normally the intermediate hosts in which multiple copies and relatively large numbers of infectious stage cercaria are produced; an essential and imperative component in the schistosoma parasite transmission. After the formation of cercariae, it penetrates the definite host, where it gets to mature into worms in the form of blood flukes (Schistosomatidae). The entire process, even with the production of cercariae in the Schistosoma transmission life cycle is directly influenced by temperature and increase in output production of cercaria within the ranges of temperature where both

the parasite and the host survive, is habitually coupled with the increase in temperature (Kalinda *et al.,* 2016).

An increase in temperatures during the production of cercariea from snails does not only assist in triggering this production process, increases and hastens up the production rate of cercariae inside the snail hosts through the increase of metabolic activity of the intermediate host and more prominently, the increase in vitality. The net result of raising environmental temperatures will along these lines be more prominent in increasing the production number of cercaria in the intermediate snail host in aquatic environments (Poulin, 2006).

1.10 Role of mathematical modelling in disease epidemiological studies

Mathematical modelling is a system used in describing real life problems in both mathematics language and concepts. The use of mathematical modelling takes several methods which include statistical models, dynamical systems, theoretic models or differential equations (Willems and Polderman, 2013). The applications of modelling have been proved very useful in natural sciences such as biology, meteorology, and earth sciences among others. Additionally, its role in the field of engineering, social science, medicine, physical system control and risk management cannot be over emphasized (Wolkenhauer *et al.,* 2013; Marino *et al.,* 2014; Cacciabue, 2013; Hughes *et al.,* 2015). Also, mathematical modelling plays important role in the prevalence of infectious diseases. It is useful in investigating or examining and quantifying the effect and cause of spread of infectious diseases (Funk *et al.,* 2010; May, 2004). Models can also be helpful in decision-making due to projected results generated such as changes in the pattern of disease spreads due

to interventions (Huppert and Katriel, 2013).

Abiodun and colleagues (2016) used a mathematical model to study and examine the influence of temperature and rainfall on the population dynamics of *Anopheles arabiensis*. The results of their study precisely quantified the impacts of seasonal changes on the population dynamics of *A. arabiensis* and the vector (mosquito) over the study area. Added to this, they showed the simulated larval density creates a curve, which correlated with other observable data as seen in some other studies. They further averred that their model was developed to efficiently predict the population dynamics of *A. Arabiensis* in other to assess various strategies that can be effective in the control of malaria. Also, the model was designed to accommodate dynamics in human population to predict the future incidence of malaria (Abiodun *et al.,* 2016). More so, studies have been carried out on the outbreak of cholera, control strategy and population dynamics, co-infection of cholera with malaria using mathematical models. This study was carried out to have the full understanding of the effect, causes of cholera and co-infection with other diseases such as malaria. Modelling have also been used to highlight how cholera and co-infections with other diseases can be managed and prevent future occurrence (Chao *et al.,* 2013; Obeng-Denteh *et al.,* 2015; Okosun and Makinde, 2014). Other studies in which the impact of modelling has been examined in controlling the population dynamics of diseases include tuberculosis (TB) and HIV (Magombedze *et al.,* 2010; Roeger *et al.,* 2009; Zwerling *et al.,* 2015).

Mangal and colleagues (2008) modelled the effect of temperature on the worm burden and prevalence of schistosomiasis for optimal disease control strategy. It was observed that the burden of Schistosoma reached the climax at a temperature of 30^oC and drastically reduces when the temperature is raised to 35^oC. Therefore, it was concluded that the best stable temperature for the prevalence of schistosomiasis ranges between 20^oC to

35^oC, and that the best optimum temperature for the survival of Schistosoma parasite is 20^oC, which is the temperature that the parasite can survive at, which can be helpful in the disease control. In another related study by McCreesh and Booth (2014), the temperature-sensitive stage of *S. mansoni* and the life cycle of its *Biomphilaria pfeifferi* intermediate host were simulated. It was observed the infection of *S. mansoni* in rivers and lakes was very high ranging between 15 - 19^oC and 20 - 25^oC respectively meaning the survivability of snail reduces drastically outside the temperature range of 14^oC - 26^oC. In like manner, an epidemiological model was developed by Ngarakana-Gwasira and colleagues (2016) to improve the prediction of the influence of climatic factors on the population dynamics and disparity of schistosomiasis strength in Zimbabwe. The study observed that the best temperature for the transmission of schistosomiasis in that region ranges between 18^oC to 28^oC and the optimal temperature for schistosoma transmission in this region was about 23^oC. Additionally, it was observed that the schistosoma infection in snails increase at 22^oC when compared to other temperature like 20^oC and 25^oC, and that the schistosoma parasite died when the temperature was raised to 30^oC (Ngarakan-Gwasira *et al.*, 2016). Therefore, this present study was aimed at theoretical modelling of temperature and rainfall influence on Schistosoma species population dynamics in South Africa, and adopted the schistosomiasis sub-model as highlighted in Okosun and Smith (2017), by incorporating climate parameters.

1.11 Problem Statement

In the next century, climate warming due to changes in climatic factors is expected to have an enormous influence on the interactions between pathogens and their hosts. Over the years, vector-borne diseases have been shown to be particularly sensitive to a warm

atmosphere, because temperature changes can lead to alteration in the rate of vector development, change in geographical distribution and can modify the transmission dynamics of diseases. Since schistosomiasis is recognized to be one of the neglected tropical and vector-borne diseases affecting both freshwater snails and humans, increase in population dynamics of this infection is likely to spread, and the elevation in the risk of infection has been predicted worldwide, especially with 25.7 million South Africans at risk of the disease due to climate change (Magaisa *et al.,* 2015; Wolmarans and De Kock, 2009). Therefore, this present study was designed to develop an effective and efficient model that can predict the population dynamics of *Schistosoma species*, evaluate the effectiveness of several control strategies, and develop a framework model that can predict and accommodate future incidence of schistosomiasis in human population dynamics.

1.12 Research Aim

The aim of this study was to model the influence of temperature and rainfall on population dynamics of *Schistosoma species* over South Africa.

1.13 Research Objectives

The specific objectives of this research include:

i. Design of an effective and efficient model to predict population dynamics of *Schistosoma species* and to evaluate the effectiveness of several control strategies

ii. Developed a human-snail model to under-study the impact of temperature and rainfall on the population dynamics of Schistosomiasis

iii. Developed and validated snail-human Schistosomiasis model over epidemic regions in South Africa

iv. The application of the snail-human Schistosomiasis model on the effect of climate variability on Schistosomiasis epidemics over South Africa

v. Identification of novel methods that evaluate several control strategies for schistosomiasis disease

vi. Used optimal control theory to determine the best cost effectiveness that can eliminate the disease.

1.14 Climate Data

In this study, the observational re-analysis crossbreed datasets for day by day precipitation, least and most extreme daily temperature was considered over the study area for the period 20022004. Therefore, Princeton University Global Meteorological Forcing Dataset for land surface display created by the Terrestrial Hydrology Research Group of Princeton University was used. Additionally, the present study was in accordance with previous studies that the population dynamics of diseases is basically driven mainly by climatic factors.

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Chapter 2

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Climate change and the snail-schistosome cycle as a predictors of transmission and bio-control of Schistosomiasis in sub-Saharan Africa

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Abstract

In the next century, global warming due to changes in climatic factors is expected to have an enormous influence on the interactions between pathogens and their hosts. Over the years, the rate at which vector-borne diseases and their transmission dynamics modify and develop have been shown to be highly dependent to a certain extent, on changes in temperature and geographical distribution. Schistosomiasis has been recognized as a tropical and neglected vector-borne disease whose rate of infection have been predicted to be elevated worldwide, especially in sub-Saharan Africa; the region currently with the highest proportion of people at risk, which is further exacerbated partially by change in climate. This review not only suggests the need to develop an efficient and effective model which will predict Schistosoma spp. population dynamics but seeks to evaluate the effectiveness of several current control strategies. The design of a framework model to predict and accommodate the future incidence of schistosomiasis in human population dynamics in sub-Saharan Africa is proposed. The impact of climate change on schistosomiasis transmission as well as the distribution of several freshwater snails responsible for the intermediate hosting of Schistosoma parasites in the region is also reviewed. Lastly, this article advocates a bid to model the prediction of several bio-control mechanisms for schistosomiasis in sub-Saharan Africa to deal with re-infection of the disease despite treatment with praziquantel, the first-line treatment drug for schistosomiasis.

Keyword: *Biomphalaria spp, Bulinus spp*, cercariae, climate change, Schistosomiasis, sub-Saharan Africa,

Running title: Relationship between climate change and schistosomiasis transmission.

2.1 Introduction

Neglected tropical diseases (NTDs) are a group of chronic infectious diseases that have been ignored for several decades, but which typically affect poor people who live on wages below US$2 per day, particularly those living in poor rural areas as well as destitute urban regions with limited access to public health facilities, which are prominent in sub-Saharan Africa (SSA) [1, 2]. Over 500 million people in this region alone bear the full impact of these diseases which hold significant influence on the health, social, financial and economic status of both governments and households. Currently, there are 19 diseases categorized as NTDs namely; buruli ulcer, chagas disease, cysticercosis, dengue fever, dracunculiasis (guinea worm disease), echinococcosis, fascioliasis, human African trypanosomiasis (African sleeping sickness), leishmaniasis, leprosy (hansen's disease), lymphatic filariasis, onchocerciasis, rabies, schistosomiasis, soil-transmitted helminths (STH) (ascaris, hookworm, and whipworm), trachoma and yaws, river blindness and hydatid disease.

Schistosomiasis, otherwise known as bilharzia, is identified as the second most widespread NTD in SSA after hookworm infections [3]. It is a parasitic infection which results in acute and chronic disease, caused by trematode flatworms of the Schistosoma genus. The disease has dire consequences on agricultural yields and grave effects on the life and development of school children and pregnant women in affected regions. The five causative agents identified as the main instigators of schistosomiasis are *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Schistosoma mekongi* and *Schistosoma intercalatum*. The first three are the most common and predominantly liable for hosting, transmitting and enhancing the occurrence of the infection in humans, while the last two are rare species that are restricted to a few central African countries [4].

The life cycles of all the *Schistosoma spp* are all similar yet very complex as the parasite

alternates between two hosts: the intermediate (snail) and the definitive (human) host. Infection in the definitive host is associated with several diseases such as malaise, skin rashes, fever and abdominal pain in an acute situation, while the chronic state of the disease may result in liver, lung, intestinal or urinary tract diseases, which are highly dependent on the species one is infected with. Reoccurrence of infection over the years may additionally cause cancer of the bladder, pulmonary hypertension and blockage in the urinary tract that may ultimately lead to other related complications and even death. In recent times, several studies [5-9] have deduced that climate and the changes associated with it such as temperature change, precipitation, humidity, flooding, salinity and drought have adverse effects on the Schistosoma life cycle, especially in sub-Saharan Africa. Hence, understanding the relationship between the variability in climate change and the life cycle of the schistosome worm will be a promising and predictive target in the control of schistosomiasis in the sub-Saharan Africa region.

2.2 Impact of climate change on NTDs and human health in sub-Saharan Africa

The progression or increase in population dynamics of various health-related issues in SSA can be linked to a number of climatic variations, which include changes in temperature, rainfall or precipitation, air movement, drought, flooding, salinity and others [5, 8-10]. According to the 2013 Policy Brief Report of the African Climate Policy Centre (ACPC) on the issues of climate change and health in Africa, it was stated that climate change in SSA will not only present health consequences but will also have adverse effects on the economic growth and development of certain SSA countries, while mounting additional impact on environmentally related issues [11]. This is due to the vulnerability of SSA

countries to climate change as compared to other continents in the world. This susceptibility is due to the existence of high levels of poverty, armed conflict and weak institutions in SSA which limit the capacity of African countries to deal with the additional health challenges posed by climate change [11]. It was further averred that the level and category of health-related issues caused by climate change in SSA is significantly different from one community or region to another. This diversity is as a result of microclimate differences, geographic and socio-economic factors, accessibility and availability to quality health infrastructure as well as underlying epidemiology and communication capabilities [2]. The influence of climate change in human health can either be direct or indirect; such changes include elevated levels of mortality and morbidity, disease patterns and incidence such as cancer of the skin, thermal stress, eye diseases, allergic disorders, cardio-respiratory diseases, malnutrition, inaccessibility to food and water, famine, droughts, infectious diseases due to migration and the increase in population dynamics of vector and water-borne diseases [12]. The most important impacts of climatic change on human health include increase in the prevalence of NTDs, malaria, malnutrition, diarrhea and meningitis [12]. Several studies have confirmed the impacts of climate change on the incidence of cholera in SSA [13, 14]. In an annual study carried out in Lusaka, Zambia by Fernndez and co-workers on the influence of climate change on the evolution of cholera, it was observed that the number of people affected with cholera due to an increase in temperature levels for six weeks after the rainy season, which consisted of high levels of rainfall for three weeks, increased by 4.9%. It was therefore posited that this region might be further confronted with an increase in the number of cholera cases within the three weeks of rainfall [13]. In another related study carried out in Kwazulu-Natal, South Africa by Mendelsohn and Dawson, it was observed that an increase in the sea surface temperature and precipitation caused by climate change correlated with the prevalence of cholera in the

area [15]. In a model study done in Tanzania, Trrup and co-workers [16] incorporated historical data on climate change and the incidence or burden of cholera together with socio-economic data as the control. It was observed that a 1^oC increase in temperature significantly increased the risk of cholera by 15 - 29%. Based on their model, the authors projected that an increase in temperatures between 1 2^oC will increase the prevalence of cholera in Tanzania by the year 2030 with a increment between 0.32 - 1.4% [16].

In addition, the malaria burden in SSA has also been attributed to climatic change; it was observed that the increase in endemic transmission and spread of malaria in disease-free regions correlated with an increase in temperature between 32 - 33^oC [17]. On the other hand, the spatial distribution of anopheline larval habitats in the western Kenyan highlands correlated with change in topography and the effects of land cover types [18]. In another model study carried out by Ngarakana-Gwasira and co-workers [19], it was observed that an increase in both the reproduction and transmission dynamics of the falciparum parasite correlated with a change in climatic factors such as rainfall and temperature. It was averred that the malaria burden is likely to increase, not only in East Africa but also in the tropics and the highland regions of SSA, while reduction in falciparum malaria will be experienced in Northern Africa [19]. A recent study carried out in the KwaZulu-Natal Province, South Africa observed that the increase in population dynamics of *Anopheles arabiensis* is dependent on seasons and that the increase in population dynamics of the malaria vector additionally depends on climatic factors such as temperature and rainfall [20].

Other studies in which the effects of climate change have been examined on health-related issues include the prevalence of meningitis in North-west Nigeria [21], the increase in cerebrospinal meningitis in Ghana as well as the threat of diarrheal disease in Botswana [22, 23]. Therefore, climate change should also be seen as a potential factor that enhances

the increase in the population dynamics of schistosomiasis in SSA. Transmission of this infection relies on the presence of an intermediate host in the form of freshwater snails. Thus, the following sub-topics will expand more on the effects of climate variability on snail fecundity, production and mortality.

2.3 Snail as an intermediate in the transmission of Schistosomiasis

Two hosts are known to be important for the spread of schistosomiasis; the intermediate and the definitive host. The asexual phase of the parasite takes place within the snail, while the sexual phase takes place in humans. Within the definitive host are generations of fertilized schistosome eggs which are released through human feces or urine into freshwater where they hatch into free-living ciliated organisms called miracidia; this is the first larval phase of the parasite, with the ability to penetrate and infect aquatic snails that serve as the intermediate host to the parasite. Once in the intermediate host, the miracidia continue their lifecycle to produce multiple cercariae which is the second larval stage of the parasite and these have the ability to penetrate and infect human skin once in contact with infested waters.

Over the years, not less than 350 species of snails have been identified to have veterinary and medical importance [24]. In the life cycle of the Schistosoma worm, four genera of snails have been identified to serve as intermediate hosts for the parasite which include *Bulinus, Biomphalaria, Tricula* and *Oncomelania*. These snails species can be sub-divided into two groups based on their habitats: *Bulinus* and *Biomphalaria* snails, also known as aquatic snails, have the ability to live and survive under water but generally cannot endure and survive elsewhere for longer periods of time, while *Oncomelania* and *Tricula* snails

can adjust and survive both within and outside water [25].

2.3.1 Distribution of Bulinus species in sub-Saharan Africa

Bulinus is a group of freshwater snails of the gastropod genus, which belongs to the Planorbidae family. It is composed of four groups of species: *B. africanus, B. forskalii, B. reticulatus* and *B. tropicus* (or *B. truncates* complex), which are all sub-divided into 37 species with some species responsible for the intermediate hosting of *S. intercalatum* and *S. haematobium* larval parasites. In SSA, over 112 million cases of urogenital schistosomiasis are caused by *S. haematobium*, which accounts for about 50% of the total incidence of infection in this region [26]. This may be largely due to the wide geographical distribution of the *Bulinus spp.* (its intermediate host) in this region with the snail mostly endemic to Cameroon, Egypt and Senegal.

The transmission of urinary schistosomiasis within and between SSA countries is significantly different and is dependent on the functions the various *Bulinus species* perform within one ecological region to the other. For instance, the transmission of urinary schistosomiasis in Senegal is mainly caused by *B. senegalensis, B. umbilicatus, B. truncatu* and *B. globosus* snail species [27]. The location of the parasite transmission consists of ponds and their prevalence depends on rainfall. In Cameroon, the transmission of this disease predominantly involves *B. truncates*, while in Southern Africa *B. africanus* and *B. globosus* have been recognized to be responsible for the transmission of *S. haematobium* and a less-recognized specie *S. mattheei* [28, 29]. The disparity in the role of *Bulinus species* in the transmission of urinary schistosomiasis was highlighted in a recent study by Zein-Eddine and co-workers [30]. In this study, significant differences was observed in the genetic features of seven *Bulinus spp.* examined within three areas of high prevalence of *Bulinus spp* in sub-Saharan Africa (Cameroon, Egypt and Senegal). Added to this, these

observed differences are indicative of the various roles exhibited by the snail species in the transmission of schistosomiasis [30].

2.3.2 Distribution of Biomphalaria species in sub-Saharan Africa

Biomphalaria belongs to the genus of freshwater gastropod snails, which are members of the Planorbidae family. They are otherwise known as Taphius and serve as intermediate hosts for the transmission of *S. mansoni* infection leading to intestinal schistosomiasis. Biomphalaria snails are usually found in freshwater or tropical pond water within sub-Saharan Africa and South America or in subtropical regions within a 30^o latitude radius [31]. Several Biomphalaria species are known to survive within and outside freshwater habitats for a long time [32].

There are several existing Biomphalaria species which are known vectors in the transmission of intestinal schistosomiasis worldwide; 22 of which have been recognized in America, while 12 dominant species have been discovered in SSA [33]. Egypt particularly, houses two special hybrid species: *B. alexandrina* and *B. glabrate* [34]. Currently, four other species *B. pfeifferi, B. tenagophila, B. straminea* and *B. glabrate* recently extended their natural homes to some SSA countries and subtropical regions such as in Egypt, Congo, Florida, Texas, Hong Kong and Louisiana [31]. Studies have shown that *Biomphalaria species* love to reside in slow-moving and minimal wave-acting waters, and in some cases prefer to stay in ponds or pools where they exhibit a high degree of tolerance to changes in temperature. This condition seems pleasant to the production of miracidia, which seek out and penetrate these snails to form cercariae [35]. In sub-Saharan Africa, studies have shown that the wide geographical distribution of *S. mansoni* is closely related to the number of predisposed Biomphalaria snail species to the parasite, which assists in its asexual reproductive phase (sporocysts) [36].

2.3.3 Distribution of Oncomelania and Tricula species in sub-Saharan Africa

Oncomelania and Tricula belong to freshwater gastropoda snails, which are members of the Planorbidae family. There are two existing species of the Oncomelania genus: *O. hupensis* and *O. minima*. Tricula comprises of twenty species under the Triculinae subfamily, which is the largest endemic freshwater snails discovered in the world [37]. Sub-species of Oncomelania have been identified to play a role in the transmission of *S. japonicum*. In the same vein, Tricula species are known vectors in the transmission of *S. megonki, S. sinensium* (only in rodents), *S. malayensis* and some other Schistosoma infections in humans and other animals in Asia, most especially in China, Philippines, Malaysia and Thailand. Other Oncomelania species that have been recognized include *O. lindoensis, O. shini* and *O. sakuyamai*, which serve as intermediate hosts in the transmission of S. japonicum in Japan and the Sulawesi region of Indonesia [38, 39].

Generally, a typical Oncomelania snail can live and survive in swamps, wetlands and shallow lakes. A study in Asia has shown that the increase in *S. japonicum* transmission is often tied to irrigated rice farms [40]. Over the years, the taxonomy of Oncomelania in Asia has been challenged due to the disparity in the genetic features and differences in the operculum and shell sculpture; for instance, these snails may either exhibit smooth, varix or ridged shells. At the moment, the prevalence of Oncomelania and Tricula snail species has not been reported in sub-Saharan Africa; this may be due to climate variability, which exerts enormous influence in increasing flooding in this region. Therefore, it is surmise to state that an increase in flooding activities in SSA may result in severe health challenges including serious increases in schistosomiasis outbreaks. Several studies have shown that during floods, many people come into contact with snail-infested waters [3, 8, 10]. An

increase in water flow causes a rise in water velocity, which ultimately enhances contact between miracidia and their snail intermediate hosts. This is one of the routes by which climate change impact schistosomiasis transmission, most especially in SSA. Therefore, it necessary to discuss the impact of variable climate change factors on the transmission of schistosomiasis in SSA.

2.4 Impact of climate change on schistosomiasis transmission in sub-Saharan Africa

Climate variability has been predicted as a potential factor that may influence the transmission of schistosomiasis [3, 9, 10]. Variations in the weather conditions have been recognized to have significant impact on the lifespan (mortality) and fecundity rate of both snails and worms during the schistosome life-cycle [41]. Hence, the role of climate change factors such as alterations in temperature, rainfall/precipitation, flood, drought and pH among others as depicted in the model shown in Figure 1 will be discussed in the following sections of this article.

2.4.1 Effect of changes in temperature on the intermediate host in schistosomiasis transmission

It is believed an increase in global temperature has a pronounced effect on the interactions that takes place among organisms in an ecosystem [12]. An increase in temperature has been suggested to drive the complex interactions that occurs between schistosomes and their snail intermediate host. As shown in figure 1, the exact effect of an increase in tem-

perature in SSA on the Schistosoma snail intermediate host of the parasite may influence growth, distribution, survival and fecundity rate, as well as make unfavourable, breeding conditions for both freshwater snails and the schistosomes themselves, which may in turn affect the population dynamics of Schistosomal infections in SSA depending on snail types of snails and schistosome species present in the area. As observed in a number of studies on the eradication of schistosomiasis in certain parts of SSA, it has been shown that increase in temperature can eventually lead to a decrease in mortality rates of snails [5, 42]. Additionally, a rise in temperature may increase the infective stages of the parasite due to an increase in snail production and decrease in the growth and developmental rate of the parasite.

The rate at which the miracidia penetrate snails, as well as the release of cercariae into the larval stage of the parasite and its penetration into the skin of the definitive host are temperature-dependent [42]. The production of cercariae within the intermediate host is assisted by an increase in temperature, which does not only help the production of cercariae but also plays a significant role in increasing the metabolic activity, energy and vitality of the snail to intensify the rate of cercarial production within the snail [41]. Studies have shown that the fecundity, survival and mortality rate of several intermediate hosts of schistosomes and the developmental rate of the worm within the host, acclimatization or adjustment to a particular environment were dependent on change in temperature [5, 32, 43].

McCreesh and Booth [42] developed an agent-based model of temperature-sensitive stages of *Schistosoma mansoni* and the life cycle of the *Biomphalaria pfeifferi* snail. It was discovered that the number of snails approximately remained constant between 15 31^{o}C; any temperature outside this range saw a steep decrease in the number of intermediate hosts. This implies the snail population lacks the ability to survive beyond this tempera-

ture range. Added to this, it was observed that the time needed for the snail population to decrease with a simultaneous increase in temperature ranged from 46 - 176 days, at a temperature between 14 - 26^{o}C. More so, the highest at-risk temperature range for infection with schistosomes in calm waters for humans was shown to be 16 - 18^{o}C, around 1pm and between 6pm - 10pm. However, the highest risk of infection in flowing waters was determined to be between 20 - 25^{o}C, between 12pm - 4pm. On the whole, the authors showed the risk of infection increases suddenly as the temperature increases beyond the minimum degree required for continued transmission.

More so, Appleton and Eriksson [44] investigated the role of temperature fluctuations above optimal levels and the effect on the fecundity of *Biomphalaria pfeifferi*, the snail specie responsible for *S. mansoni* transmission. They observed the fecundity rate for freshwater snails decreased drastically as the temperature increases above 27^{o}C, which is believed to be the optimal temperature for snail fecundity [44]. In the same vein, at temperatures above optimal level, snails with shell height ranging between 1.5 - 2.5mm failed to produce multiple eggs. Moreover, the survival rate of the snails reduced drastically, which in turn affected the production of the *S. mansoni* worms.

2.4.2 Effect of changes in rainfall on the intermediate host in schistosomiasis transmission

The effect of changes in rainfall/precipitation on population dynamics or in the transmission of schistosomiasis in SSA cannot be over-emphasized. Although, the mechanism by which rainfall affects the prevalence of schistosomiasis in the region is not well understood, it is believed that an increase and decrease in water levels occur because of

rainfall patterns. A quantitative analysis of change in the inter-annual total rainfall of Ga District in Ghana showed the total rainfall and number of rainy days correlated with the prevalence of schistosomiasis in the area [45]. Furthermore, it was shown that years with reduced amounts of rainfall correlated with a low prevalence of schistosomiasis, while years with moderate as well as high rainfall correlated with a high prevalence of schistosomiasis. However, no significant association was made between the amount of rainfall and the disease itself [45].

In another related study conducted in Ethiopia by Xue and co-workers [9], it was established that rainfall is a prominent climatic factor responsible for the increase in population dynamics of schistosomiasis through the accumulation of sufficient surface water in ponds. An increase in rainfall promotes and provides breeding space for the snail population due to an increase in the volume of runoff waters that are channelled through irrigation canals. This may in turn increase flow velocities thereby promoting contact between the parasite and its intermediate host. An increase in water levels due to high rainfall may also cause turbulent shear thereby altering the survival rate of cercariae through which the transmission of the disease is enhanced [9].

In years past, the considerable differences in the distribution of the Schistosoma parasite in certain areas was observed to depend on the amount of rainfall, the periods of dry and rainy seasons, as well as the intervals between these seasons [46]. During prolonged dry periods, there is an observable dry-out in the natural habitats of snails, which may in turn result in the death of those that hosts the parasite [47]. In SSA, the distribution of the *Schistosoma species* varies depending on the amount of rainfall. This was observed in a study conducted in three villages in the lower delta region of Senegal by Ernould and co-workers [48]. It was discovered that during rainy periods, there was a drastic increase in the population dynamics of *Biomphalaria pfeifferi*, the prospective intermediate host of

S. mansoni when compared to *Bulinus globosus*, the intermediate host of *S. haematobium*; this suggested an increase in the transmission of *S. haematobium* during the dry period [48].

2.4.3 Effect of flooding on the intermediate host in schistosomiasis transmission

Similar to an increase in rainfall, SSA is expected to experience an increase in the population dynamics of schistosomiasis due to an increase in flooding activities caused by temperature variability, which has been suggested to have a serious impact on health and availability to limited resources [49]. During flooding, a huge number of people encounter contaminated water resulting in infection with the schistosome parasite [8, 10]. This assertion was supported by the observation of Wu and co-workers [50] who elucidated that the dispersal patterns of intermediate snail hosts with respect to acute and chronic infections caused by the parasite in the Peoples Republic of China was related to flooding. It was observed that the habitats of snails present during the years when flooding occurred were 2.6 - 2.7 times larger than in those years when water levels were normal. Additionally, the re-emergence of snails was observed due to floods in habitats where the snail population have been previously reported to be eliminated. According to Wu and his colleagues, both the density and infection rate of snails infected with the parasite dropped during the first two years after the floods, while in the third year, a significant increase was observed in the infection and density of snails to the parasite [50]. This observation was supported by results from some mathematical models created by Longxing and co-workers [8] in their study conducted in Anhui Province of the Peoples Republic of China that showed how floods act on the stability of an endemic equilibrium. The numerical simulation and

generated data revealed there would be an extremely serious schistosomiasis outbreak in the study area about three years after the flood. It was further observed that there was a marked increase in the number of acute schistosomiasis cases in the years characterized by the floods, with an average increase of about 2.8 times more cases as compared to years with normal water levels [50].

It would therefore be safe to conclude that due to the increase in flooding activities in the SSA countries with reported cases of schistosomiasis such as Nigeria, South Africa, Niger, Senegal, Kenya, Malawi, Angola and Zimbabwe among others, there may eventually be an increase in the occurrence of new habitats for both snails and schistosomes, as well as reoccurrence of snails in some areas where they have previously been reported to be eliminated.

2.4.4 Effect of drought on the intermediate host in schistosomiasis transmission

Drought is a climatic factor with a significant impact on the socio-economic and health related issues of an individual and the society at large. Some of these effects include lack of water and food, increase in diseases caused by airborne particles such as smoke and pollen, valley fever caused by fungi, germy hands, mosquito-borne diseases, as well as recreational injuries among others [51]. This type of climatic factor may have futuristic effects on the population dynamics of schistosomiasis in SSA because certain snail intermediate hosts such as Oncomelania, actually have the ability to withstand and survive dry environments for extended periods of time due to their operculum, which is capable of closing shell during periods of drought for as long as 2 - 4 months [52]. However, prolonged drought in some countries like Nigeria, Ethiopia and Zimbabwe, has resulted

in a remarkable reduction in the prevalence of schistosomiasis due to a decrease in the reproductive and survival rate of snails responsible for intermediate hosting of the parasite in those areas, as well as the decrease in the transmission sites of infections [36, 53, 54]. Studies have shown that during aestivation, uninfected snails have the ability to withstand longer periods of drought than infected snails [36, 55]. This implies that during drought, infected snails die off and this alters the transmission of schistosomiasis in drought-stricken areas [7, 36, 55]. Mutuku and co-workers [36] analyzed temporal changes on the spatial transmission pattern of *S. haematobium* worms on different age groups and their relationship to ponds infested with Bulinus snails in coastal Kenya. It was observed that the ponds dried up and hence, there were no sources of infection; very few or none of the snails that infested the ponds in the past were detected during the major drought between 2001 and 2009. It was further observed that the hydrological changes and the long-term drought resulted in the absence of Bulinus snails nine months after the pond had been refilled [36].

In another related study by Senghor and co-workers [7], the impact of drought on the snail intermediate hosts of urogenital schistosomiasis in Niakhar, West-Central Senegal was studied. It was observed that out of the two Bulinus species (*B. senegalensis* and *B. umbilicatus*) collected in the study area, only *B. senegalensis* was found in all sampled 17 sites, while *B. umbilicatus* was found in only one out of the 17 surveyed sites. In the years 2012 and 2013, a total number of 1032 and 8261 *B. senegalensis* were collected respectively, while a total of 901 out of the 1032 and 6432 of the 8261 snails were tested for *Schistosoma spp.* infection within the stipulated time periods. On the other hand, a total number of 58 and 290 *B. umbilicatus* snails were also collected during the years 2012 and 2013 respectively, while a total number of 58 and 281 snail species were tested for infection, within the respective designated time periods [7]. A 0.0% and 0.12% over-

all cercarial shedding percentage was observed for *B. senegalensis*, as well as 13.79% and 4.98% for *B. umbilicatus* during these years. It was further posited that individual *Bulinus species*, ranging between 7 - 9.9mm in size, were present in the month of July; 63.6 % and 57.8 % for *B. senegalensis* and *B. umbilicatus* respectively. For the first time, this study reported that *B. umbilicatus* can maintain Schistosoma larvae for as long as 7 months of drought thereby resulting in the transmission of schistosomiasis in early July, leading to an increased risk of schistosomiasis transmission in the study area [7]. Therefore, it is safe to deduce that prolonged drought periods for more than 9 months can result in the eradication of schistosomiasis transmission in some parts of SSA, while drought periods lasting less than 7 months can aid the transmission of the disease in other parts of the region due to maintenance of the larval stage.

2.4.5 Effect of pH and conductivity on the intermediate host in schistosomiasis transmission

Physico-chemical parameters such as pH and conductivity in relation to climatic factors are known to have a considerable influence on the population dynamics of schistosomiasis transmission in SSA. In simple terms, pH is the presence of hydrogen ions in water or soil and the amount of acidity in water is measured by the pH. The acidity or pH of water differs greatly from one region to another and is highly dependent on climatic change. Due to global warming, there is a strong release of carbon dioxide into the atmosphere by the ocean leading to a decrease in pH of about 0.28 - 0.7U, which influences the acidity of the ocean with a pH increment between 7.4 -7.8 [56]. An increase in precipitation is expected to result in the acidification of the atmosphere or the oceans, which can pose a serious threat to marine organisms through tropic interactions and biodiversity caused

by calcification [57].

This type of environmental condition has been shown to influence the population dynamics of several diseases that include the infection and lysogenizing of recipient cells or hosts by *Vibrio cholera* [14]. However, it has been shown that *V. cholerae* has the ability to survive high-level pH of host cells [14]. Abnormal vaginal discharge also falls under infections or diseases caused by changes in pH, which in this case has effects on the vaginal flora [58]. There are only a few studies that have shown the influence and interaction between change in pH and its resultant effect on parasites and their hosts. In an extensive study conducted by Koprivnikar and co-workers [59] on the effects of temperature, salinity and pH on the rate of survival and activity of marine cercariae, it was discovered that pH on its own cannot alter the survival of cercariae but in association with salinity and time. The study further showed the survival and active rate of cercariae only occurs at a high pH of 8.2 [59].

Other studies that have been conducted elucidating the nexus between change in pH and the intermediate hosts of schistosomiasis, includes one carried out in Uganda by Rowel and co-workers [6]. It was shown that physico-chemical factors such as pH and conductivity do influence Biomphalaria populations and infections. Disparity in the population dynamics of Biomphalaria from one location to another was observed but depended on the lake and the pH. In both Lake Albert and Lake Victoria, a positive relationship between Biomphalaria population and infections was observed, while in Lake Albert, a negative relationship with conductivity was observed. It was further stated that out of all the Biomphalaria snails collected from Lake Albert, 8.9% were infected with digenetic trematodes, 15.8% shed *S. mansoni* cercariae, while 84.2% were infected with non-human-infective cercariae. On the other hand, from Lake Victoria, 2.1% of all collected Biomphalarias-nails were infected with digenetic trematodes with 13.9% of them shedding *S. mansoni*

cercariae, 85.7% shedding non-human-infective cercariae, and 0.4% of the infected snails shedding both types of cercariae [6].

In a related study by Marie and co-workers [60], the physical and chemical properties of water quality on the density and distributions of some freshwater snails collected from eight different streams within the Egyptian governorate were investigated. Within these eight streams, there was an observable production of snail species at a wide-water pH range with the highest percentage ranging between pH 7.6 - 8.5, which is similar to that obtained by Ntonifor and Ajayi [61] which showed that the pH ranges that harbours snail production falls between pH 7.2 and 10.9. A fluctuation in the pH below or above 7.0 and 9.0 results in a decrease in snail production from 68.94% to approximately 1.35% and 13.28% respectively [60]. It was further observed that *B. alexandrina* snails were the most enumerated snail species with the ability to tolerate and adapt to various environmental circumstances. This concurs with the work of Kazibwe and co-workers [62] where they observed that the abundance of *B. sudanica* negatively correlated with pH levels. Other previous studies have shown the abundance of *B. alexandrina* and B͡. truncatus snails at pH of 6.0 - 6.5 and pH of 6.9 - 7.2 [63, 64].

2.4.6 Effect of salinity on the intermediate host in schistosomiasis transmission

Salinity is another important climatic factor with considerable influence on the population dynamics of schistosomiasis. The variability in climatic factor caused by global warming can result in the elevation of sea levels which can in turn raise the salinity of water bodies in coastal regions [65]. It was hypothesized by Ramasamy and Surendran [65] that an increase in the level of saline water bodies in coastal regions correlates to a rise in sea

levels leading to an elevation in the densities of salinity-tolerant vectors, which in turn result in the adjustment of freshwater vectors (snails) to breed in saline/brackish waters. Among study that have focused on the impact of salinity on parasites, it has been shown that cercariae possess high tolerance to salinity fluctuation and their production from the intermediate host can be influenced by it [66]. A decline in cercariae production occurs as salinity concentration reduces.

Moreover, the overall impact of high salinity has been associated and more favourable towards schistosome parasites rather than their intermediate snail hosts [67]. Thompson [68] and Paraense [69] observed B. straminea and B. glabrata freshwater snails have the ability to survive in saline water of about 5.0ppt in coastal regions. It was further observed that S. mansoni eggs from these coastal regions have the ability to hatch in saline water of 6.0 ppt [70]. Mostafa [71] carried out a study to ascertain the effect of salinity on the survival of *Biomphalaria arabica*, the intermediate host of *S. mansoni* in Saudi Arabia from fresh water bodies by collecting and exposing the snails to NaCl concentrations of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, as well as series of concentrations lying between the one that produced 100% mortality and the preceding one. Results from this study showed *B. arabica* snails remain alive in 5 NaCl concentration and at 7.2 NaCl concentration, 100% mortality occurred. He further averred that in the presence of water lettuce, *B. arabica* showed pronounced resistance to increase in salinity, which may account for the abundance of *B. arabica* in the study area. Support for these findings comes from the study of Neto and co-workers [72] in which the effects of biological, physical and chemical factors on breeding sites in Porto de Galinhas, Brazil was studied. It was shown that salinity indices up to 1003d, is non-infective on the snail species and the *S. mansoni* strain, which have been highly adapted to coastal environments with high salinity.

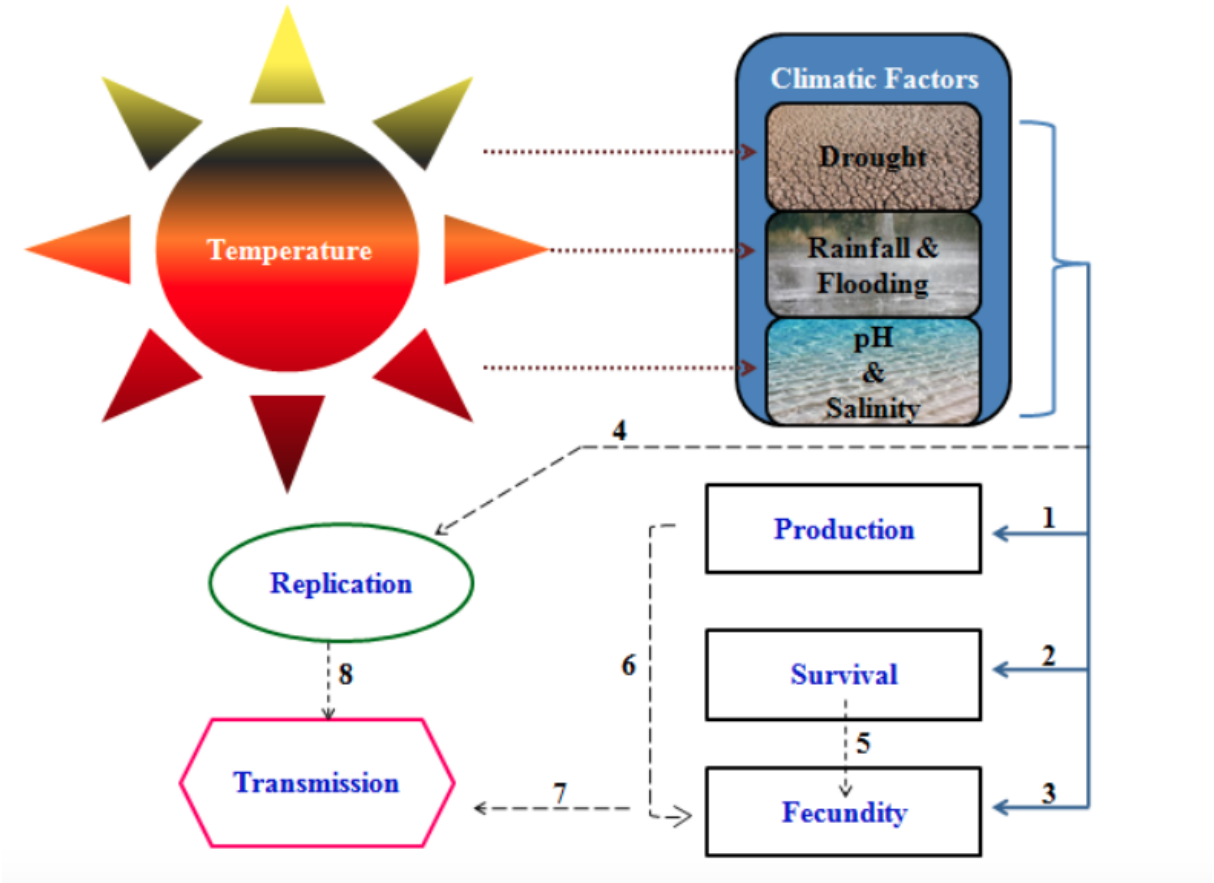

Figure 2.1: Proposed model eliciting effects of change in climatic factors on Schistosomiasis transmission. *1. Changes in climatic factors are essential determinant in the production and development of snails as well as the production and development time of miracidia and cercaria in the intermediate host (snails) and in freshwater depends on climate variability, 2. The survival rate of snails as well as miracidia and cercaria in freshwater and intermediate host depends on change in climatic factors, 3. Climate changes pose a serious influence on fecundity of the snails and hatching of schistosomes eggs into miracidia, 4. Replication of miracidia in the intermediate host to form sporocyte which in turn produce cercaria, 5. Increase in survival rate leads to an increase in fecundity rate, 6. Climate change enhances the rapid reproduction of snails also, the rapid metamorphosis of miracidia into cercaria in the intermediate host, 7. Increase in fecundity rate of snails enhances the transmission of schistosomiasis by increasing the*

production number of cercaria within snails, 8. The cercaria penetrate into the definitive human host, thereby metamorphosing into schistosomula that develop into adult worm which lay eggs that are responsible for the morbidity and mortality resulting from this disease.

2.5 CONCLUSION AND FUTURE PERSPECTIVES

Modelling is a valuable tool that is useful in studying the prevalence of infectious diseases and can be used to investigate and quantify the cause and effects of the spread of infectious diseases [73]. Huppert and Katriel [74] considered modelling as a useful tool for developing disease prevention and control measures because it has value in predicting the likely outcome of a population level in order to implement different control measures. Moreover, modeling can also be helpful in decision making with regards to epidemiological issues such as changes in the spread of disease pattern [74]. Added to this, modelling has also been used to tackle the influence of temperature and rainfall on the transmission dynamics of diseases such as the evolution of cholera epidemics in Lusaka, Zambia [13], dynamics of poliomyelitis outbreaks [75], as well as the outbreaks of smallpox in realistic urban social networks [76], di1fferent smallpox epidemics in England [77] and responses to a smallpox epidemic in France; taking into account uncertainty factors [78]. The technique has also been used to gain great insights into the transmission dynamics of tuberculosis [79], as well as the transmission and bio-control of trypanosomiasis using trypanocides or insecticide-treated livestock [80].

It is therefore necessary to use modeling in order to ascertain how climate change influences the population dynamics and transmission pattern of schistosomiasis in SSA as well as predict the potential distribution of the spread of this infection. In addition to this, the

uncertainties in using climate change information and schistosomiasis models in mapping the disease over sub-Saharan Africa needs to be urgently predicted, as well as several bio-control measures for the disease in sub-Saharan Africa such as the development of vaccines and new drug formulations capable of blocking re-infection after treatment and resistance of schistosomes to praziquantel. Moreover, other measures needed to be put in place in order to lessen the burden of schistosomiasis in SSA includes: an improvement and consistency in climate surveillance systems, execution of vaccination campaigns in target regions once vaccines is developed, sensitization of the public about the disease and its impacts on public health and public health policies, as well as improvement in support towards schistosomiasis research in order to better understand the current and possible future distribution of the disease.

In conclusion, the role of climate variability on the population dynamics of schistosomiasis transmission in SSA cannot be over-emphasized. The impact of climate change on population dynamics of schistosomiasis infection is greatly pronounced on the production, survivability and fecundity rate of both freshwater snails and schistosomes. Therefore, all hands must be on deck in order to develop several effective and efficient models capable of predicting the population dynamics of the Schistosoma species, as well as map the areas or regions in which climate change will have a profound impact on schistosomiasis transmission in sub-Saharan Africa.

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Chapter 3

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Temperature and rainfall impact on schistosomiasis

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Abstract

In this paper, we present a deterministic schistosomiasis climate based model, in order to examine the effect of climate variability on the transmission dynamics of schistosomiasis. Firstly, we explore the theoretical mathematical analysis of the schistosomiasis model dynamics. The model equilibrium states are then analyzed and the disease-free equilibrium is proved to be locally asymptotically stable when the respective epidemic basic reproduction number (R_{sc}) for the model is less than unity. The model further exhibit backward bifurcation phenomena, the implication of this occurrence is that the classical epidemiological requirement for effective eradication of the disease, $R_{sc} < 1$, is no longer sufficient, even though necessary. Secondly, we presented the numerical simulations. Our results show that climate change enhances the reproduction number of schistosomes and the reproduction rate of snails.

AMS subject classification: 49K05, 49K15, 49S05.

Keywords: Schistosomiasis, temperature, rainfall, basic reproduction number, sensitivity analysis, cercariae, mathematical model, population dynamics, numerical simulations.

3.1 Introduction

Schistosomiasis, also known as bilharzia, happens to be one of the groups of neglected tropical diseases (NTDs), ranked second most prevalent among NTDs ([10,11]). Schistosomiasis, is caused by flatworms belonging to a class of trematode within the phylum, Platyhelminthes and genus *schistosoma*. The life cycle of *Schistosoma* species is related to each other but, they are biologically complex whereby they alternate between two

hosts; the intermediate (snail host) and the definitive (human) host, as well as two free-living transmission stages; cercariae and miracidia. Also, the parasite requires distinct environments ([12,13,14]).

Humans are the principal definitive host of the five notable *Schistosoma* species which are; *Schistosoma haematobium, Schistosoma mansoni, Schistosoma japonicum, Schistosoma intercalatum and Schistosoma mengiko* ([12,13,14]). The infections caused by these parasites result into chronic and acute diseases which include fever, abdominal severe pain, malaise, skin rashes, liver disease, intestinal disease, lung disease and urinary tract disease depending on the *Schistosoma* species. The reoccurrence of *Schistosoma* infections over the years may result into cancer of the bladder, obstruction in urinary tract, portal or pulmonary hypertension and even death ([15,16,17,18,19]).

Over the years, *Schistosoma* infection has been estimated to affect over 218 million people who are in need of preventive treatment and over 800 million people are at high risk of the infection in not less than 78 countries of the world; most of these countries fall within Africa, Eastern Asia and South America [20]. There is a significant difference in the prevalence of schistosomiasis from one area to another due to environmental and ecological factors, and activities embarked upon by the residents of that area [10]. It has been observed that the prevalence of schistosomiasis in an endemic area normally fall within the equator at 36^o north and south; this region of equator has a favourable condition that enhances the survivability of freshwater snails (intermediate host) ([21,22,10]).

In Africa, the burden of *Schistosoma* infection is alarming among children of school age, women and young adults, accounting for about 93% (192 million) of the total world estimated cases of schistosomiasis. In the African nations, the prevalence of *Schistosoma* infection is very high in Nigeria, with Tanzania taking the second lead, followed by Ghana, Mozambique and Democratic Republic of Congo (DRC) ([11,23]). Addition-

ally, countries within African and Asian continents are presently experiencing flooding as a result of change in temperature which may pose serious challenges to good health and available limited resources. Studies have shown that flood leads to a serious outbreak of schistosomiasis ([2,14,3]). During flooding, majority of people comes in contact with contaminated water, leading to a higher proportion being infected by schistosomes ([2,14,3]). Consequently, the impact of climate change parameters such as temperature, precipitation, flood and other climatic factors have been postulated as potential factors that may influence the transmission of schistosomiasis ([25,26,2]). Added to that, variations in weather conditions have been recognized to have significant impact on lifespan or mortality and fecundity rate of both snails (intermediate host) and *Schistosoma* species in *schistosoma* lifecycle [27]. Although, the exact mechanism by which precipitation affects the population of infectious stage of *Schistosoma* parasite (cercaria) is not well understood [28]. Xue and co-workers, 2011, observed that the total monthly and time series of precipitation obtained through rain gauge and four different satellites has been shown to have a significant negative correlation in the transmission of schistosomiasis. They further observed that an increase in rainfall can lead to turbulence with increasing rate of velocity of water flow which can kill the cercaria as a result of high shears.

An important tool in gaining insight to dynamics of disease transmission is mathematical modelling. It is also very useful in the decision-making processes with regards to intervention mechanisms for infectious diseases control. Just for example, the first mathematical models of malaria transmission was developed by Ross in 1911 [34]. He focused on mosquito population control, and he proved that, for the disease to be eliminated, the population of mosquito should be brought below a certain threshold. Further studies by Koella and Anita [38] included a latent class for mosquitoes. They examined different scenarios to curtailing the spread of resistance and also studied the sensitivity of

their results to the model parameters. While in Nikolaos et al. [36] the authors proposed detailed analysis of a dynamical model in order to describe pathogenesis of HIV infection. In Chiyaka *et al.*[1], the authors constructed a deterministic mathematical model to study the transmission dynamics of schistosomiasis by incorporating the miracidia and cercariae dynamics. Also, a mathematical model for the human-cattle-snail transmission of schistosomiasis was presented by Chen *et al.*[35]. In [32], the authors considered the co-infection of malaria and schistosomiasis. These studies have used mathematical modelling by ignoring the influence of climate variables in their models. But recently, in [31], the authors studied influence of temperature and rainfall on the population dynamics of Anopheles arabiensis and in [33], the modelling and analyzes of the impact of temperature and rainfall on mosquito population dynamics over Kwazulu-Natal, South Africa was presented. Their model consisted of six ordinary differential equations that describe susceptible and infected human, cattle and snail sub-populations. While Longxing *et al.* [3] went further to examined a mathematical model of schistosomiasis transmission under flood in Anhui province. The authors developed a biology-driven model to assess the potential impact of rising temperature on the transmission of schistosomiasis in China [37]. While in [39], an agent-based model of the temperature-sensitive stages of Schistosoma was investigated.

However, studying the relationship between the production of snails, *Schistosoma* species and climate change can be helpful in ascertaining the population dynamics of the snails and *Schistosoma* parasite, as well as a futuristic prediction of areas with high risk of *schistosoma* infections. Therefore, the aim of this present paper is to design a deterministic schistosomiasis based model detailing the influence of temperature and rainfall on population dynamics of the Schistosoma parasite. In addition, the influence of temperature and rainfall on the breeding site dynamics of the parasite will be considered. As a result of the significant burden of diseases associated with vector-borne diseases in the developing

countries, it is very important to incorporate issues of climate change into public health policies [29].

This paper is arranged as follows: Section 2 is concentrated on the model formulations and the assumptions underlying the model. In Section 3, we present the analysis of the model, while in Section 4, we present the numerical results and discussions. The conclusions is finally presented in Section 5.

3.2 Model Formulation

The model total population denoted by N_h is sub-divided into sub-classes of Susceptible humans S_h, the individuals infected with schistosomiasis I_{sc}, the Individuals who recovered from schistosomiasis R_s. Such that, we have $N_h = S_h + I_s + R_s$. Also, we have the total snail vector population, denoted by N_{sv}, sub-divided into Susceptible snails S_{sv}, the snails infected with schistosomiasis I_{sv}. Thus, $N_{sv} = S_{sv} + I_{sv}$.

The model is given by the following system of ordinary differential equations:

$$\begin{cases} \frac{d}{dt}S_h = & \Lambda_h + \epsilon R_s - \lambda_1 S_h - \mu_h S_h \\ \frac{d}{dt}I_{sc} = & \lambda_1 S_h - (\omega + \mu_h + \eta) I_{sc} \\ \frac{d}{dt}R_s = & \omega I_{sc} - (\epsilon + \mu_h) R_s \\ \\ \frac{d}{dt}S_{sv} = & B(t) - \lambda_2 S_{sv} - \mu_{sv} S_{sv} \\ \frac{d}{dt}I_{sv} = & \lambda_2 S_{sv} - \mu_{sv} I_{sv} \end{cases} \tag{3.1}$$

where,

$$\begin{aligned} \lambda_1 = \frac{\lambda I_{sv}}{N_h}, \quad \lambda_2 = \frac{\lambda_s I_{sc}}{N_h} \\ B(t) = B_m \frac{e^{-c(T-T_0)}}{1 + e^{a+bP(R,T)}} \end{aligned} \tag{3.2}$$

where, $B(t)$ and Λ_h are the reproduction rate of snail and human birth rate respectively. The schistosomiasis related death rate is denoted by η. The immunity waning rate is represented as ϵ and while ω is the recovery rate. Also, μ_h and μ_{sv} are respectively the humans and snails mortality rates.

Furthermore, the term $P(R,t)$ is the daily average precipitation, and B_m is the maximum reproduction rate, while T_0 is the optimum reproduction temperature $(20-25^oC)$, where a and b are the logistic parameters.

Table 3.1 lists the parameter descriptions and values used in the numerical simulation.

Parameter	Description	value	Reference
λ	schistosomiasis transmissibility to humans	0.406 day^{-1}	[30]
λ_s	schistosomiasis transmissibility to snails	0.615 day^{-1}	[1]
μ_h	Natural death rate in humans	0.00004 day^{-1}	[7]
μ_{sv}	Natural death rate in snails	0.000569 day^{-1}	[1,30]
Λ_h	human birth rate	800 people/day	[1]
ω	recovery rate of schistosomiasis-infected individual	0.0181 day^{-1}	assumed
η	schistosomiasis-induced death	0.0039 day^{-1}	[1]

Table 3.1: Parameters in the model.

Table 3.2: Parameters of the schistosomiasis model

Description of parameter	Symbol	Value	Ref
snail reproduction rate	$B(t)$	$B_m \frac{e^{-c(T-T_0)}}{1+e^{a+bP(R,T)}}$	[3]
Precipitation	$P(R,T)$	$R_0T_0\left(1+R_1T_1 sin\left(\frac{2\pi T}{365}\right)\right)$	[6,8,9]

3.3 Analysis of the schistosomiasis model

3.3.1 Positivity and boundedness of solutions

For the transmission model (2.1) to be epidemiologically meaningful, it is important to prove that all solutions with non-negative initial data will remain non-negative for all time.

Theorem 3.4. If $S_h(0), I_{sc}(0), R_s(0), S_{sv}(0), I_{sv}(0)$ are non negative, then so are $S_h(t), I_{sc}(t), R_s(t), S_{sv}(t)$ and $I_{sv}(t)$ for all time $t > 0$. Moreover,

$$\limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h} \text{ and } \limsup_{t\to\infty} N_s(t) \leq \frac{B_m}{\mu_{sv}}. \tag{3.3}$$

Furthermore, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. If $N_s(0) \leq \frac{B_m}{\mu_{sv}}$, then $N_s(t) \leq \frac{B_m}{\mu_{sv}}$.

The feasible region for system (2.1) is therefore given by

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_s \subset R \tag{3.4}$$

where

$$\mathcal{D}_h = \{(S_h, I_{sc}, R_s) \in R_+^3 : S_h + I_{sc} + R_s \leq \frac{\Lambda_h}{\mu_h}\}$$

$$\mathcal{D}_s = \{(S_{sv}, I_{sv}) \in R_+^2\}.$$

Note that $\mathcal{D}$ is positively invariant.

Proof. Let

$$t_1 = \sup\{t > 0 : S_h, I_{sc}, R_s, S_{sv} \text{ and } I_{sv} \text{ are positive on } [0, t]\}.$$

Since $S_h(0), I_{sc}(0), R_s(0), S_{sv}(0)$ and $I_{sv}(0)$ are non-negative, $t_1 > 0$. If $t_1 < \infty$, then, by using the variation of constants formula to the first equation of the system (2.1), we have

$$S_h(t_1) = \mathcal{U}(t_1, 0)S_h(0) + \int_0^{t_1} \Lambda_h \mathcal{U}(t_1, \tau)d\tau$$

where $\mathcal{U}(t,\tau) = e^{-\int_\tau^t (\lambda_1+\mu_h)(s)ds}$.

This implies that $S_h(t_1) > 0$. It can be shown in the same manner that this is the case for the other variables. This contradicts the fact that t_1 is the supremum because at least one of the variables should be equal to zero at t_1. Therefore $t_1 = \infty$, which implies that S_h, I_{sc}, R_s, S_{sv} and I_{sv} are positive for all $t > 0$.

For the second part of the proof, adding the last two equations of system (4.1), we obtain $\frac{dN_s}{dt} = B_m - \mu_{sv}N_s$. This implies that $N_s(t) = N_s(0)e^{-\mu_{sv}t} + \frac{B_m}{\mu_{sv}}(1 - e^{-\mu_{sv}t})$. Thus $\limsup_{t\to\infty} N_s(t) = \frac{B_m}{\mu_{sv}}$. Moreover, if $N_s(0) \leq \frac{B_m}{\mu_{sv}}$, then $N_s(t) \leq \frac{B_m}{\mu_{sv}}$.

From the first three equations of (2.1), we have $\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \eta I_{sc}$. Since $0 < I_{sc} \leq N_h$, then

$$\Lambda_h - (\mu_h + \eta)N_h \leq \frac{dN_h}{dt} \leq \Lambda_h - \mu_h N_h.$$

By using a standard comparison theorem [24], we obtain

$$N_h(0)e^{-(\mu_h+\eta)t} + \frac{\Lambda_h}{\mu_h+\eta}(1 - e^{-(\mu_h+\eta)t}) \leq N_h \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t}).$$

This implies that

$$\frac{\Lambda_h}{\mu_h+\eta} \leq \liminf_{t\to\infty} N_h(t) \leq \limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}.$$

The other cases are similar.

Moreover, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. This establishes the invariance of $\mathcal{D}$ as required.

□

From this theorem, we see that system (2.1) is epidemiologically feasible and mathematically well-posed in $\mathcal{D}$.

3.4.1 The disease-free equilibrium (DFE) stability analysis

The schistosomiasis model (2.1) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\mathcal{E}_{0c} = (S_h^*, I_{sc}^*, R_s^*, S_{sv}^*, I_{sv}^*) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{B(t)}{\mu_{sv}}, 0\right).$$

We established the linear stability of $\mathcal{E}_{0c}$ by using the next generation operator method described in Driessche and Watmough [18] on the model (2.1).

Hence, we have the reproduction number of the schistosomiasis model (2.1), which is denoted by $\mathcal{R}_{sc}$, given by

$$\mathcal{R}_{sc} = \sqrt{\frac{B(t)\lambda\lambda_s\mu_h}{\Lambda_h(\eta+\omega+\mu_h)\mu_{sv}^2}}, \tag{3.5}$$

By using the Theorem 2 presented in Driessche and Watmough [5], we established the following result: The DFE is locally asymptotically stable whenever $\mathcal{R}_{sc} < 1$ and unstable otherwise when $\mathcal{R}_{sc} > 1$.

Sensitivity indices of R_{sc} to model parameters

Here, we derive the sensitivity of R_{sc} in (3.3) to each of the 8 different parameters. However, for parameters whose expression for their sensitivity indices are complex, we evaluate the sensitivity indices of these parameters at the baseline parameter values as given in Table (1). The sensitivity index of R_{sc} with respect to λ, for example is,

$$\Upsilon_{\lambda}^{R_{sc}} \equiv \frac{\partial R_{sc}}{\partial \lambda} \times \frac{\lambda}{R_{sc}} = 0.5 \tag{3.6}$$

The detailed sensitivity indices of R_{sc} resulting from the evaluation to the other parameters of the model are shown in Table 3.

	Parameter	Description	Sensitivity index 10^oc	Sensitivity index 25^oc
1	$P(R,T)$	precipitation	-1.97	-4.99
2	b	logistic parameter	-1.97	-4.99
3	c	weight constant	-1.0	-2.5
4	μ_{sv}	snail mortality	-0.5	-0.5
5	λ	prob. of humans getting infected	0.5	0.5
6	λ_s	prob. of snail getting infected	0.5	0.5
7	B_m	max. reproduction rate of snail	0.5	0.5
8	Λ_h	human birth rate	-0.5	-0.5
9	μ_h	humans mortality rate	0.499	0.499
10	ω	recovery from schisto	-0.4106	-0.4106
11	η	schisto-induced death	-0.0885	-0.0885
12	a	logistic parameter	-0.15	-0.15

Table 3.3: Sensitivity indices of R_{sc}

Table 3 shows the parameters, arranged from the most sensitive to the least. For $R_{sc} < 1$, the most sensitive parameters are the precipitation, logistic parameter, snail mortality rate, the probability of a snail getting infected with schistosoma and the reproduction rate of snail ($P(R,T)$, b, μ_{sv}, λ_s and $B(t)$, respectively). Since $\Upsilon_{\mu_{sv}}^{R_{sc}} = -0.5$, increasing (or decreasing) the snail mortality rate μ_{sv} by 10% decreases (or increases) R_{sc} by 5%. In the same way, increasing (or decreasing) the prob. of snails getting infected with schistosoma, λ_s, by 10%, increases (or decreases) R_{sc} by 5%. By increasing (or decreasing) the precipitation $P(R,T)$ by 10% decreases (or increases) R_{sc} by 49.9% (25^oc) and R_{sc} by 19.7% (10^oc) respectively.

3.4.2 Existence of endemic equilibrium

The schistosomiasis-only model has a unique endemic equilibrium if and only if $\mathcal{R}_{sc} > 1$.

Proof. Using the schistosomiasis force of infection λ_1^* from (2.2), the endemic equilibrium point satisfies the following polynomial:

$$P(\lambda_1^*) = \lambda_1^* \left[A(\lambda_1^*)^2 + B(\lambda_1^*) + C\right] = 0 \tag{3.7}$$

where

$$\begin{aligned}
A &= \Lambda_h \mu_{sv}(\mu_h + \epsilon + \omega)[\lambda_s(\epsilon + \mu_h) + (\epsilon + \omega + \mu_h)\mu_{sv}] \\
B &= (\epsilon + \mu_h)\Lambda_h(\omega + \mu_h)\frac{\mu_{sv}^2}{\mu_h}\Big(\epsilon(m + \mu_h) + \mu_h(\eta + \omega + \mu_h)\Big)[R_f - \mathcal{R}_{sc}^2], \\
C &= \mu_{sv}^2 \Lambda_h(\epsilon + \mu_h)^2(\eta + \omega + \mu_h)^2(1 - \mathcal{R}_{sc}^2) \\
R_f &= \frac{\mu_h[\lambda_s(\epsilon + \mu_h) + 2(\epsilon + \omega + \mu_h)\mu_{sv}]}{\mu_{sv}(\epsilon(\eta + \mu_h) + \mu_h(\eta + \omega + \mu_h))}
\end{aligned}$$

□

1. If $R_f \geq 1$, then system (2.1) exhibits a transcritical bifurcation.

2. If $R_f < 1$, then system (2.1) exhibits a backward bifurcation.

Proof.

1. For $R_f \geq 1$, we obtain when $\mathcal{R}_{sc} > 1$ that $C < 0$. This implies that system (2.1) has a unique endemic steady state. If $\mathcal{R}_{sc} \leq 1$, then $C \geq 0$ and $B \geq 0$. In this case, system (2.1) has no endemic steady states.

2. For $R_f < 1$, we have the following cases:

i. If $\mathcal{R}_{sc} > 1$, then $C < 0$, so system (2.1) has a unique endemic steady state.

ii. If $\mathcal{R}_{sc} \leq \sqrt{R_f}$, then both B and C are positive, implying that system (2.1) has no endemic steady states.

iii. If $\sqrt{R_f} < \mathcal{R}_{sc} < 1$, then $C > 0$ and $B < 0$ while the discriminant of (3.5), $\Delta(\mathcal{R}_{sc}) \equiv B^2 - 4AC$, can be either positive or negative. We have $\Delta(1) = B^2 > 0$ and $\Delta(\sqrt{R_f}) = -4AC < 0$; it follows that there exists $\mathcal{R}_{0sc}$ such that $\Delta(\mathcal{R}_{0sc}) = 0$, $\Delta(\mathcal{R}_{sc}) < 0$ for $\sqrt{R_f} < \mathcal{R}_{sc} < \mathcal{R}_{0sc}$ and $\Delta(\mathcal{R}_{sc}) > 0$ for $\mathcal{R}_{0sc} < \mathcal{R}_{sc}$. This, together with the signs of B and C, imply that system (4.1) has no endemic steady states when $\sqrt{R_f} < \mathcal{R}_{sc} < \mathcal{R}_{0sc}$, one endemic steady state when $\mathcal{R}_{sc} = \mathcal{R}_{0sc}$ and two endemic steady states when $\mathcal{R}_{0sc} < \mathcal{R}_{sc} < 1$.

□

The existence of two endemic equilibria for $\mathcal{R}_{sc}$ in $(\mathcal{R}_{0sc}, 1)$ is established by Proposition 1. To investigate the stability of these equilibria we use the centre manifold method by Castillo-Chavez and Song [4].

Backward bifurcation analysis of the model

By aplying the centre manifold theory on the system (2.1), we can prove the existence of backward bifurcation. Using Center Manifold theorem [4], first we carry out the bifurcation analysis by re-arranging and modifying model variables (2.1) by letting $x_1 = S_h$, $x_2 = I_{sc}$, $x_3 = R_s$ and $x_4 = S_{sv}$, and $x_5 = I_{sv}$. Also, using the vector notation $X = (x_1, x_2, x_3, x_4, x_5)^T$, the model (2.1) can then be formulated as $dX/dt = F(x)$,

with $F = (f_1, f_2, f_3, f_4, f_5)^T$ given in the following:

$$\begin{aligned}
\frac{dx_1}{dt} &= \Lambda_h + \epsilon x_3 - \lambda_1 x_1 x_5 - \mu_h x_1 \\
\frac{dx_2}{dt} &= \lambda_1 x_1 x_5 - (\mu_h + \omega + \eta) x_2 \\
\frac{dx_3}{dt} &= \omega x_2 - (\mu_h + \epsilon) x_3 \\
\frac{dx_4}{dt} &= B(t) x_2 - \lambda_2 x_2 x_4 - \mu_{sv} x_4 \\
\frac{dx_5}{dt} &= \lambda_2 x_2 x_4 - \mu_{sv} x_5
\end{aligned} \tag{3.8}$$

where

$$\lambda_1 = \frac{\lambda x_5}{x_1 + x_2 + x_3}; \quad \lambda_2 = \frac{\lambda_s x_2}{x_1 + x_2 + x_3}$$
$$\lambda = \lambda^* = \frac{\lambda_s \mu_h B(t)}{\Lambda_h \mu_{sv}^2 (\eta + \omega + \mu_h)}.$$

Evaluating the Jacobian matrix at the disease-free equilibrium of the model (2.1) at $\mathcal{E}_{0c}$, choosing λ as the bifurcation parameter and solve $\mathcal{R}_{sc} = 1$, we have

$$J = \begin{pmatrix}
-\mu_h & 0 & \epsilon & 0 & -\lambda \\
0 & -(\eta + \omega + \mu_h) & 0 & 0 & -\lambda \\
0 & \omega & -(\epsilon + \mu_h) & 0 & 0 \\
0 & -\frac{\lambda_s B(t) \mu_h}{\mu_{sv} \Lambda_h} & 0 & -\mu_{sv} & 0 \\
0 & \frac{\lambda_s B(t) \mu_h}{\mu_{sv} \Lambda_h} & 0 & 0 & -\mu_{sv}
\end{pmatrix}$$

The Jacobian matrix J has one simple zero eigenvalue and while the remaining eigenvalues have negative real parts. Therefore, the center manifold theory is appropriate to be used to analyze the dynamics of the system (2.1). For the case when $\mathcal{R}_{sc} = 1$, the Jacobian matrix J has a right eigenvector denoted by W, which is express as $W = [w_1, w_2, w_3, w_4, w_5]^T$. These are

$$w_1 = -\left(\frac{\Lambda_h (\epsilon\eta + \mu_h(\epsilon + \eta + \omega + \mu_h)) \mu_{sv}^2}{B(t) \lambda_s \mu_h^2 (\epsilon + \mu_h)} \right),$$

$$w_2 = \frac{\Lambda_h \mu_{sv}^2}{B(t)\lambda_s \mu_h}, \quad w_3 = \frac{w_2 \omega}{(\epsilon + \mu_h)}, \; w_4 = -w_5,$$

$$w_5 = w_5 > 0$$

and the left eigenvector denoted by V, is express as $V = [v_1, v_2, v_3, v_4, v_5]$. These are

$$v_1 = v_3 = v_4 = 0, \; v_2 = \frac{B(t)\lambda_s \mu_h}{\Lambda_h \mu_{sv}(\eta + \omega + \mu_h)}$$

After rigorous computations, we get a and b

$$a = 2v_5 w_4 w_2 \frac{\lambda_s \mu_h}{\Lambda_h} - 2v_2 w_5 \frac{\lambda \mu_h}{\Lambda_h}(w_2 + w_3) - 2v_5 w_2 \frac{\lambda_s B(t) \mu_h^2}{\mu_{sv} \Lambda_h^2}(w_1 + w_3 + w_2) - v_5 w_3 w_4 \frac{\lambda_s \mu_h^2}{\Lambda_h^2}$$

and

$$b = w_5 \frac{B(t)\lambda_s \mu_h}{\Lambda_h \mu_{sv}(\eta + \omega + \mu_h)}$$

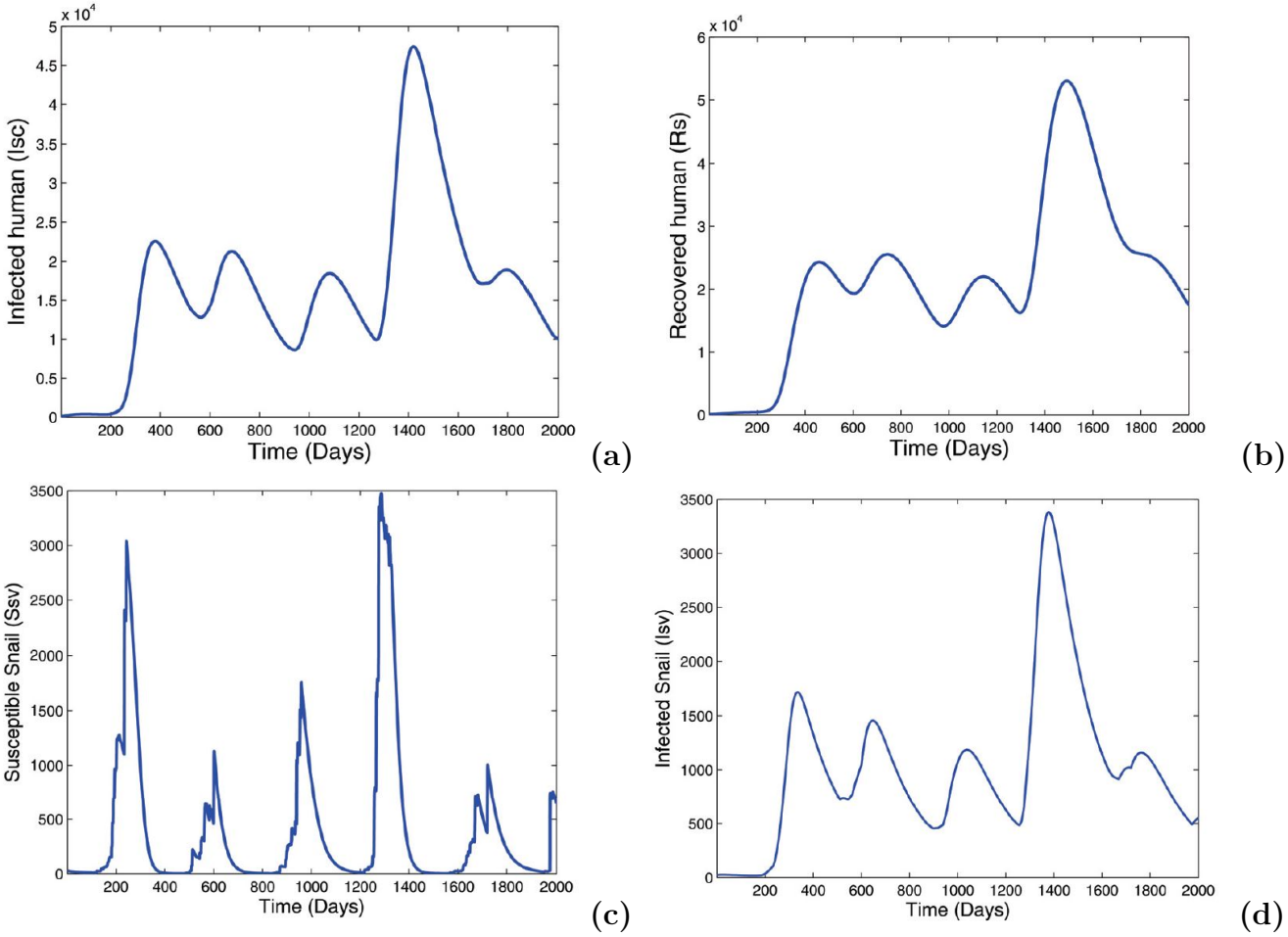

Figure 1: Simulations of the model showing the effect of temperature on the population dynamics.

Here, it is clear that the coefficient b is positive and it is the sign of a that will determine the backward bifurcation of the model (4.1).

Backward bifurcation has been studied for schistosomiasis and some other diseases by many authors ([1,12,32]). The occurrence of such bifurcation only suggests that eradication of schistosomiasis is achievable only when the (constant) controls are greater than a critical value less than one. Hence, this implies that for the disease not to become endemic again, treatment or intervention controls must be maintained at this level for

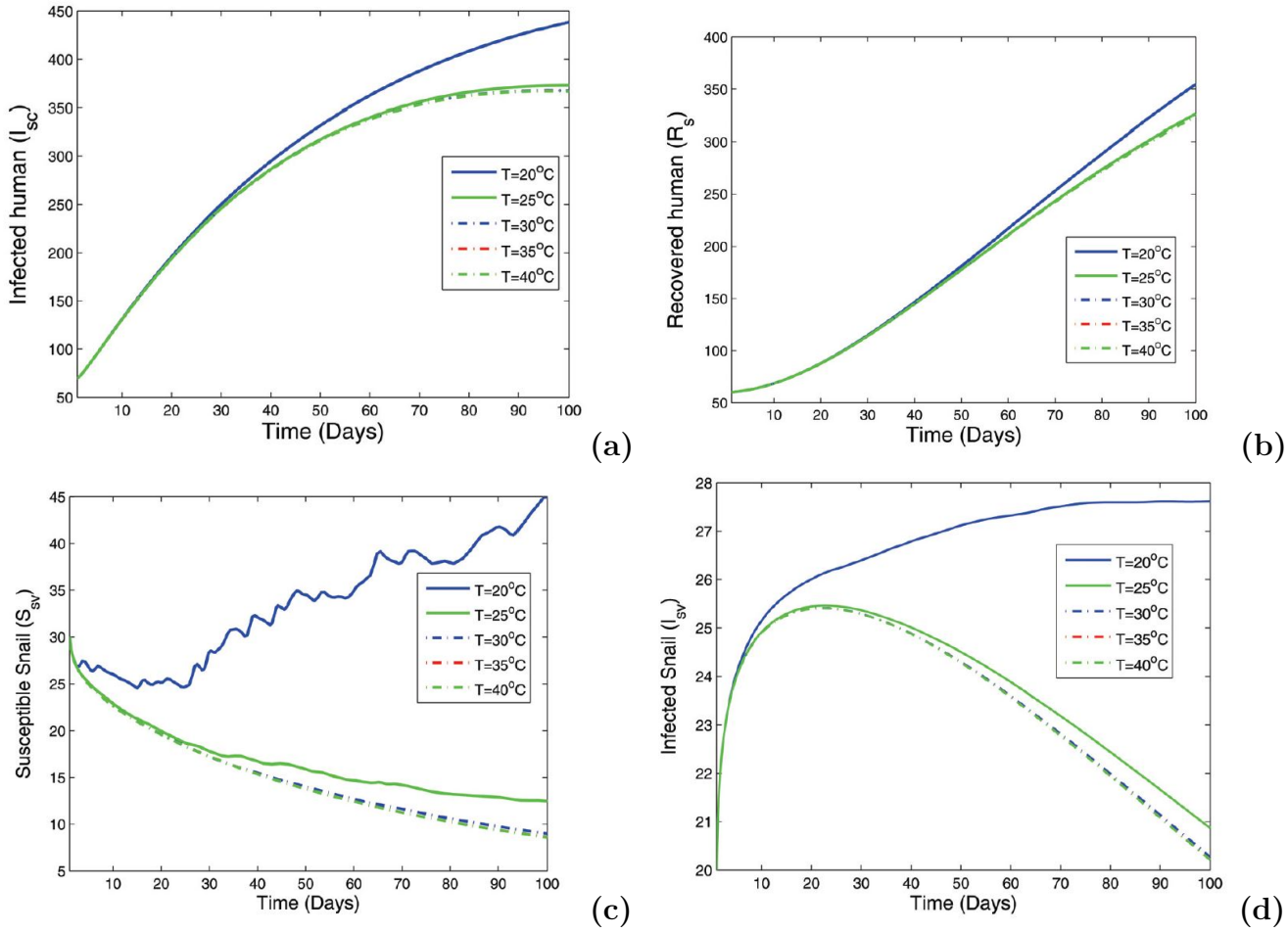

Figure 2: Sensitivity of the model dynamics to temperature. The effect of constant temperature on (a) the infected humans, (b) the recovered humans, (c) the susceptible snails and (d) the infected snails

all time. This is because the system will ultimately re-stabilize at its previous endemic steady state when intervention is stopped.

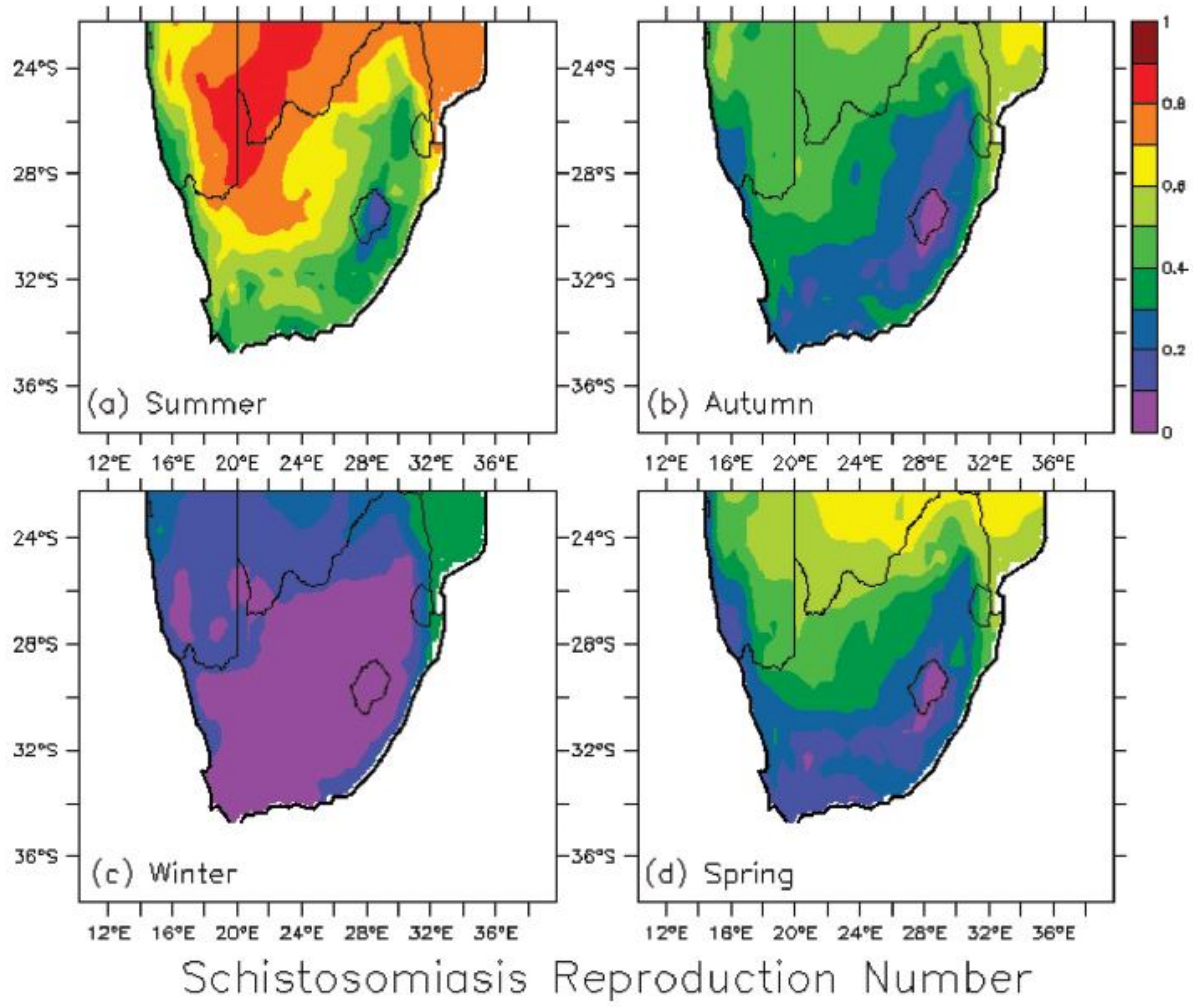

Figure 3: Spatial distribution of the Schistosomiasis reproduction number over South Africa

3.5 Numerical Results and Discussions

In this study, we simulated the snails reproduction rate and *schistosoma* reproduction number spatially over South Africa for December $2000 - 2002$ was done by running the model over the daily temperature of 1.0^o spatial resolution of the dataset. The results obtained are shown in Figures (3 - 4), suggesting why schistosomiasis transmission is seasonal. It is noticed that snails reproduce more during summer period (December - February), while there are still some snails producing during spring (September - Novem-

ber) and autumn (March - May). The results further gave a clear indication that climate variability contributes to the increase in the reproduction number of schistosomes.

3.5.1 Model sensitivity to parameters

From the population dynamics results, we observed as shown in Figure (1) that the susceptible snails population present a very strong seasonal variability within the period.

In other to gain better understanding of the relationship between temperature and the humans-snails dynamics, we carried out both humans and snails populations sensitivity to temperature and this is presented in Figure (2). In other to achieve this, we assume that for the first 100 days, the temperature is constant while we vary rainfall. In each of the population class, the dynamics of the disease is examined using the following temperature range: $20, 25, 30, 35$ and 40^oC. We observed that the disease dynamics are more sensitive to temperature at 20^oC.

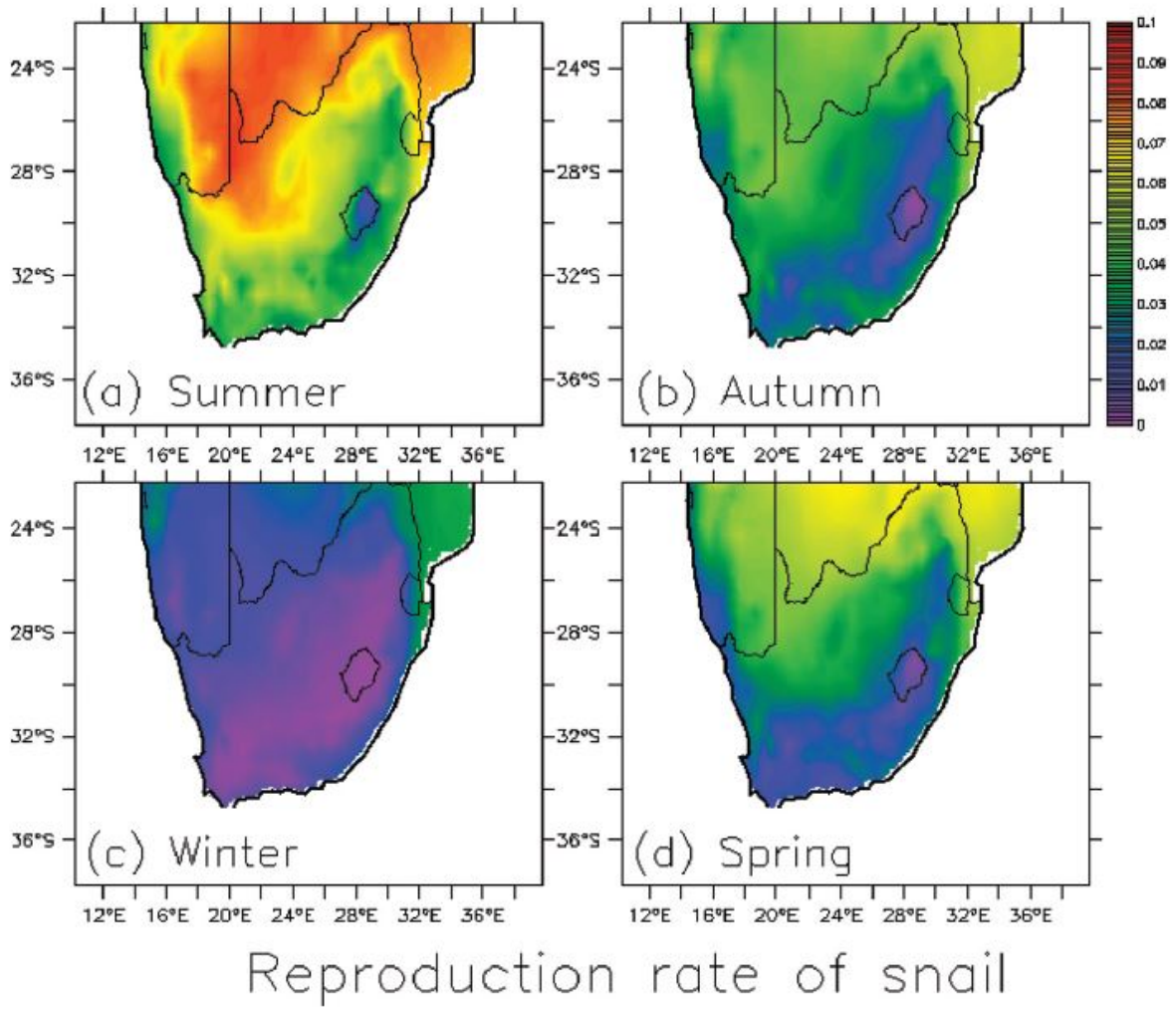

Figure 4: Spatial distribution of the snails reproduction rate number over South Africa

3.6 Conclusion

We have in this study, investigated a climate-based mathematical model in order to examine the impact of temperature and rainfall on schistosomiasis transmission. From the numerical simulations, we found that in the presence of climate variability, the increases observed in schistosomes reproduction number and the snails reproduction rate are associated with the increase in the climate parameter values. The model further suggested future opportunity for modification and refinement, for the prediction of the effects of climate variability on the transmission dynamics *schistosoma*. From the sensitivity analysis

of R_{sc} to other model parameters, the reproductive number R_{sc} is more sensitive to the precipitation ($P(R,T)$) and the reproduction rate of snails and probability of infections. The model further exhibit backward bifurcation phenomena.

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Chapter 4

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Optimal control strategies and cost-effectiveness analysis of schistosomiasis model with vaccination

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Abstract

Schistosomiasis, otherwise known as snail fever or bilharzia, is caused by parasitic flatworms called schistosomes. In humans, schistosomes infect the intestines or the urinary tract where they develop to form the disease with symptoms such as fever, malaise, severe abdominal pain, skin rashes, liver disease, lung disease, intestinal disease and urinary tract disease depending on the schistosome specie. The reoccurrence of Schistosoma infections for years may result into cancer of the bladder, obstruction in urinary tract, portal or pulmonary hypertension and even death. This study was developed to investigate time-dependent control strategies, in order to ascertain the best optimal strategy for schistosomiasis control. In this study, a deterministic model for the transmission of schistosomiasis disease was derived and analyzed, followed by optimal control analysis of the model. The model was found to exhibit multiple equilibria. Conditions for the optimal control of the disease was further derived and analyzed as well. Additionally, cost-effectiveness of the controls in order to determine the most effective strategy to control the disease with minimum costs was investigated. Finally, numerical solutions were presented showing all strategies employed for schistosomiasis control have great effects both on the population of infected humans and infected snails. Importantly, control strategies B, D, F, G, I and J showed drastic decrease in the number of infected human population. For cost-effectiveness of the control strategies, our results suggest that in the presence of limited resources, policy makers may adopt the I (combination of the prevention, treatment and snail control) over J which includes additional cost of controlling loss of immunity by vaccination.

Keywords: Schistosomiasis, optimal control, stability analysis

4.1 Introduction

Schistosomiasis, otherwise known as bilharzia or snail fever, is caused by parasitic flatworm which belongs to the genus of schistosomes. Majority of people living in the poorest regions of the worlds are vulnerable to this parasitic infection, and the endemicity of this disease is very pronounced in sub-Saharan Africa, and some other regions in South America, Southeast Asia and the Middle East. Some of the common symptoms of schistosomiasis include abdominal pain, blood in the urine and stool, diarrhea, difficulties in learning and stunted growth in children; reoccurrence and untreated infection results into cancer of the bladder and liver damage ([1]). In adults, long-time exposure of this disease may cause reproductive health diseases and predispose sufferers to HIV AIDS among other diseases. The life cycle of the three major schistosomes (*Schistosoma mansoni, Schistosoma haematobium* and *Schistosoma japonicum*) both in the intermediate snail host and definitive human host are similar but biologically complex, the life cycle begins with the defecation of infected eggs in faeces or urine of an infected human into freshwater sources, which after several hours the eggs are hatched into miracidia and then penetrate into an intermediate host (freshwater snail) where it develops into sporocytes which in turn produce cercaria. The cercaria penetrate an intact skin of the definitive human host where its transformed into schistosomula that develops into adult worms which lay eggs and continue the life cycle ([1]).

Several preventive and control measures have been employed over the years in eradicating and lessen the burden of this disease include the control of freshwater snail via: environmental control which comprises of temperature, current speed of water, water

chemistry, light and shade, as well as association of snails with plants ([2, 3, 4, 5, 6]). Other preventive control measures via intermediate snail host include; the use of molluscicides which can either be chemical (bayluscide, derivative of N-p-substituted phenyl uracil-5-sulphonamide, anilofos, fenitrothion, eugenol and thymol) or plants (*Solanum nigrum, Ambrosia maritime, Thymelaea hirsute, Peganum harmala* and *Callistemon lauceolatus*) as toxic agents against freshwater snail and the schistosomes ([7, 8]). In addition, biological control which involve the use of different organisms such as Trematocranus-placodon fishes (e.g tilapia fish) and Cairinamaschata (muschovy ducks) as predators of freshwater snail ([9]). Host parasite relationship is another control measure used in controlling the burden of this disease by making the freshwater snails to develop resistance to some schistosomes infection via the activation of cytokines such as TNF-α and IL-1 ([10]). Other internal defence protein response in molluscan control is up-regulation of granularin a protein with phagocytotic activity against foreign particles. Increase in the dose or amount of schistosome in the freshwater is another means of controlling the intermediate snail host ([11]). Additionally, genetic control is another means of controlling schistosomiasis intermediate snail host, by changing the strain of highly susceptible snails to non-susceptible ones and releasing the snails that are resistance to schistosome parasite into natural habitats such as, freshwater ([12]). In the human host, praziquantel remain the only effective control in treating schistosomiasis, and it has been shown over the years that schistosomes have developed resistance against praziquantel as well as been unable to kill the immature worms in the human host.

Mathematical modelling has been a significant tool in understanding the dynamics of infectious disease transmission, it has also been a helpful tool in decision making processes through the development of an intervention mechanisms that can be used in the control of diseases. Over the years, several studies have employed mathematical modelling

methods in studying the causes and population dynamics of infectious diseases, as well as identifying the best control and cost-effective strategies in treatment and management of infectious diseases. The impact of chemotherapy on optimal control of malaria dynamics with infective treatments, introduction of infected immigrants and the use of insecticides against population dynamics of mosquitoes was described in a mathematical model carried out by Makinde and Okosun [13]. They observed immigrants who are infected with malaria has no considerable influence in the transmission of malaria, provided there is an existence of an effective treatment and mosquito control. They further averred that, the combination of treatment of infectives, assessment of infected immigrants and the use of insecticides in killing mosquitoes results in a better and effective control in the transmission of malaria.

Okosun and Makinde [14] considered a hepatitis C virus (HCV) deterministic model, where they studied the best optimum control in treatment of HCV and the screening of immigrants on the spread of HCV in a homogeneous population that has constant immigration of susceptible. The results from their work suggests that the strategy of treating both chronic and acute-infected people should be improved, where there is lack of adequate resources; because, the implementation of immigrants screening and treatment of chronic and acute-infected individuals combined, will results into an additional cost for the treatment of the disease ([14]). In another related study Okosun and co-workers in [15] carried out an optimal control and cost-effectiveness analysis of three malaria preventive measures (spraying of mosquitos with insecticides, use of treated bednets and possible treatment of infected individual). They discovered that the total cost for applying treated bednets and treatment of an infected individuals is not effective in eliminating malaria but sustainable. Also, they found out that the combination of spraying mosquitoes with insecticides for 57 days at 100% and the use of 100% treatment for 20 days was very

effective in eliminating malaria. Likewise, the use of the three controls (use of 100% treated bednets for 18 days, use of 100% insecticides spray and 87% use of treatment) can also be very effective in eliminating the disease though, its requires an unnecessary additional cost when compared to the strategy that uses insecticides spray and treatment of infected individuals. Interestingly and according to their model, they concluded that the combination of the three control strategies is the most cost-effective out of all the strategies employed in eliminating malaria ([15]).

Recently, this tool was used to present a deterministic schistosomiasis climate-based model, which was employed to examine the impact of climate variability on the transmission dynamics of schistosomiasis. In the study, it was observed that climate change poses great influence on the reproduction number of both schistosomes and freshwater snails([1]). Zhang and co-workers [16], developed a partial differential equations of schistosomiasis age-based system model in human hosts and its application in treatment strategies incorporating the human definitive host the and intermediate snail host. The study suggested that the strategies of controlling the disease should focus on the rate of infection in age group maybe the most successive strategy in schistosomiasis treatment. However, they did not consider costs that will be effective in controlling a given age-dependent or the development of possible resistance of the parasite to chemotherapy ([16]). Liang and co-workers [17], using a calibration approach and a mathematical model integrating various field data, designed as strategies control in the feasibility of characterizing site-specific schistosomiasis transmission in endemic villages of south-western Sichuan, China showed a viable control strategy is important in lowering schistosomiasis transmission, and that the population dynamics can be reduced by focusing on snail control, chemotherapy and egg control ([17]).

In this paper, several controls were introduced into existing schistosomiasis climate-

based model in order to understand the best control strategy in dealing with the transmission of the disease. Four control strategies: vaccination campaign and sensitization of the public (possible vaccination), Schistosomiasis prevention (environmental control) , schistosomiasis treatment (available drugs) and snail control (molluscicides)were employed to determine time-dependent control strategies in order to ascertain the optimal control strategy for schistosomiasis control.

Therefore, this manuscript is arranged as follows: the formulations and descriptions with the appropriate assumptions peculiar to the model is presented in Section 2. The mathematical analysis of the model is elucidated in Section 3 - 5. Section 6 depict the optimal control analysis while numerical results and discussion are presented in Section 7. The overall conclusion of the paper is presented in Section 8.

4.2 Mathematical Model Formulation

A total human population $N(t)$ at time t is partitioned into individuals who are susceptible $S_h(t)$, those infected individuals $I_h(t)$, recovered individuals $R_h(t)$ and vaccinated individuals $V_h(t)$.

Thus, $N_h(t) = S_h(t) + I_h(t) + R_h(t) + V_h(t)$.

While the total vector (snail) population $N_s(t)$ at time t is partitioned into susceptible snails $S_s(t)$, those infected snails $I_s(t)$.

Thus, $N_s(t) = S_s(t) + I_s(t)$.

The model is given by the following system of ordinary differential equations:

$$\begin{cases} \frac{d}{dt}S_h = & (1-u_1)\Lambda_h + \epsilon R_h - (1-u_2)\lambda_1 S_h - \mu_h S_h + \kappa V_h \\ \frac{d}{dt}I_h = & (1-u_2)\lambda_1 S_h + b(1-u_2)\lambda_1 V_h - (u_3\omega + \mu_h + \eta)I_h \\ \frac{d}{dt}R_h = & u_3\omega I_h - (\epsilon + \mu_h)R_h \\ \frac{d}{dt}V_h = & u_1\Lambda_h - (\kappa + \mu_h)V_h - b(1-u_2)\lambda_1 V_h \\ \\ \frac{d}{dt}S_s = & \Lambda_s - (1-u_2)\lambda_2 S_s - u_4\mu_s S_s \\ \frac{d}{dt}I_s = & (1-u_2)\lambda_2 S_s - u_4\mu_s I_s \end{cases} \tag{4.1}$$

where,

$$\lambda_1 = \frac{\lambda I_s}{N_h}, \quad \lambda_2 = \frac{\lambda_s I_s}{N_h} \tag{4.2}$$

where, Λ_s and Λ_h are the reproduction rate of snail and human birth rate respectively. The schistosomiasis related death rate is denoted by η. The immunity waning rate is represented as ϵ and while ω is the recovery rate. Also, μ_h and μ_s are respectively the humans and snails mortality rates.

Furthermore, κ is the vaccination waning rate and b is the modification parameter.

Table 4.1 lists the parameter descriptions and values used in the numerical simulation.

4.3 Analysis of the schistosomiasis model

4.3.1 Positivity and boundedness of solutions

For the transmission model (4.1) to be epidemiologically meaningful, it is important to prove that all solutions with non-negative initial data will remain non-negative for all time.

Theorem 4.4.

If $S_h(0), I_h(0), R_h(0), V_h(0), S_s(0), I_s(0)$ are non negative, then so are $S_h(t), I_h(t), R_h(t), R_h(t), S_h(t)$

Parameter	Description	value	Reference
λ	schistosomiasis transmissibility to humans	0.406 day^{-1}	[21]
λ_s	schistosomiasis transmissibility to snails	0.615 day^{-1}	[22]
μ_h	Natural death rate in humans	0.00004 day^{-1}	[23]
μ_{sv}	Natural death rate in snails	0.000569 day^{-1}	[22, 21]
Λ_h	human birth rate	800 people/day	[22]
ω	recovery rate of schistosomiasis-infected individual	0.0181 day^{-1}	assumed
η	schistosomiasis-induced death	0.0039 day^{-1}	[22]
κ	vaccination waning rate	0.001 day^{-1}	assumed

Table 4.1: Parameters in the model.

and $I_s(t)$ for all time $t > 0$. Moreover,

$$\limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h} \text{ and } \limsup_{t\to\infty} N_s(t) \leq \frac{B_m}{\mu_{sv}}. \tag{4.3}$$

Furthermore, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. If $N_s(0) \leq \frac{\Lambda_s}{\mu_s}$, then $N_s(t) \leq \frac{\Lambda_s}{\mu_s}$.

The feasible region for system (4.1) is therefore given by

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_s \subset R_+^4 \times R_+^2 \tag{4.4}$$

where

$$\mathcal{D}_h = \{(S_h, I_h, R_h, V_h) \in R_+^3 : S_h + I_h + R_h + V_h \leq \frac{\Lambda_h}{\mu_h}\} \tag{4.5}$$

$$\mathcal{D}_s = \{(S_s, I_s) \in R_+^2\}. \tag{4.6}$$

Note that $\mathcal{D}$ is positively invariant.

Proof. Let Since $S_h(0), I_h(0), R_h(0), V_h(0), S_s(0)$ and $I_s(0)$ are non-negative, $t_1 > 0$. If $t_1 < \infty$, then, by using the variation of constants formula to the first equation of the

system (4.1), we have

$$S_h(t_1) = \mathcal{U}(t_1, 0)S_h(0) + \int_0^{t_1} (1 - u_1)\Lambda_h \mathcal{U}(t_1, \tau)d\tau$$

where $\mathcal{U}(t, \tau) = e^{-\int_\tau^t (\lambda_1 + \mu_h)(s)ds}$.

This implies that $S_h(t_1) > 0$. It can be shown in the same manner that this is the case for the other variables. This contradicts the fact that t_1 is the supremum because at least one of the variables should be equal to zero at t_1. Therefore $t_1 = \infty$, which implies that S_h, I_h, R_h, V_h, S_s and I_s are positive for all $t > 0$.

For the second part of the proof, adding the last two equations of system (4.1), we obtain $\frac{dN_s}{dt} = \Lambda_s - \mu_s N_s$. This implies that $N_s(t) = N_s(0)e^{-\mu_s t} + \frac{\Lambda_s}{\mu_s}(1 - e^{-\mu_s t})$. Thus $\limsup_{t\to\infty} N_s(t) = \frac{\Lambda_s}{\mu_s}$. Moreover, if $N_s(0) \leq \frac{\Lambda_s}{\mu_s}$, then $N_s(t) \leq \frac{\Lambda_s}{\mu_s}$.

From the first three equations of (4.1), we have $\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \eta I_h$. Since $0 < I_h \leq N_h$, then

$$\Lambda_h - (\mu_h + \eta)N_h \leq \frac{dN_h}{dt} \leq \Lambda_h - \mu_h N_h.$$

By using a standard comparison theorem [19], we obtain

$$N_h(0)e^{-(\mu_h+\eta)t} + \frac{\Lambda_h}{\mu_h + \eta}(1 - e^{-(\mu_h+\eta)t}) \leq N_h \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t}).$$

This implies that

$$\frac{\Lambda_h}{\mu_h + \eta} \leq \liminf_{t\to\infty} N_h(t) \leq \limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h}.$$

The other cases are similar.

Moreover, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$. This establishes the invariance of $\mathcal{D}$ as required.

□

From this theorem, we see that system (4.1) is epidemiologically feasible and mathematically well-posed in $\mathcal{D}$.

4.4.1 The Disease-free equilibrium (DFE) stability analysis

The schistosomiasis model (4.1) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\mathcal{E}_{0c} = (S_h^*, I_h^*, R_h^*, V_h^*, S_s^*, I_s^*) = \left(\frac{(\kappa + (1-u_1)\mu_h)\Lambda_h}{\kappa + \mu_h}, 0, 0, \frac{u_1\Lambda_h}{\kappa + \mu_h}, \frac{\Lambda_s}{\mu_s}, 0 \right).$$

We established the linear stability of $\mathcal{E}_{0c}$ by using the next generation operator method described in Driessche and Watmough [18] on the model (4.1).

Hence, we have the reproduction number of the schistosomiasis model (4.1), which is denoted by $\mathcal{R}_{sc}$, given by

$$\mathcal{R}_{sc} = \sqrt{\frac{\Lambda_s \lambda \mu \left(u_2 - 1\right)^2 \lambda_s \left(\Lambda_h u_1 (b\mu + \kappa) + \Lambda_h \left(1 - u_1\right)(\kappa + \mu)\right)}{\Lambda_h^2 u_4^2 (\kappa + \mu)\mu_v^2 \left(\eta + \mu + u_3\omega\right)}}, \tag{4.7}$$

By using the Theorem 2 presented in Driessche and Watmough [18], we established the following result: The DFE is locally asymptotically stable whenever $\mathcal{R}_{sc} < 1$ and unstable otherwise when $\mathcal{R}_{sc} > 1$.

4.4.2 The Endemic equilibrium (DE) stability analysis

Next we calculate the endemic steady states. Solving system (4.1) at the equilibrium we obtain $\lambda_1^* = 0$ (which corresponds to the DFE) or

$$A_1\lambda_1^{*4} + A_2\lambda_1^{*3} + A_3\lambda_1^{*2} + A_4\lambda_1^{*2} + A_5 = 0 \tag{4.8}$$

$$
\begin{aligned}
A_1 &= b^2(1-u_2)^4 u_4\mu_v(\Lambda_h(1-u_1)+\Lambda_s u_1^2(\mu+u_3\omega+\epsilon)((1-u_2)\lambda_s(\mu+\epsilon) \\
&+ u_4\mu_v(\mu+u_3\omega+\epsilon)) \\
A_2 &= -b\Lambda_h(u_2-1)^3(-b\Lambda_s\lambda(u_2-1)^2\lambda_s(\mu+\epsilon)(\mu u_3\omega+(\eta+\mu)(\mu+\epsilon)) \\
&- 2u_4^2\mu_v^2(\mu+u_3\omega+\epsilon)(u_1(\mu+\epsilon)(b(\Lambda_h(\eta+\mu)-\mu\Lambda_h)+\Lambda_h(\kappa+\mu) \\
&- \Lambda_h(\eta+\kappa+\mu))-\Lambda_h u_3\omega(b(\mu+\epsilon)+\kappa+\mu)-\Lambda_h(\mu+\epsilon)(b(\eta+\mu)+\kappa+\mu)) \\
&+ u_4\mu_v(-u_1(\mu+\epsilon)(b(\Lambda_h(\eta+\mu)-2\mu\Lambda_h)+2\Lambda_h(\kappa+\mu)-\Lambda_h(\eta+2\kappa+\mu)) \\
&+ u_3\omega(\mu u_1((-b-2)\Lambda_h+2b\Lambda_h+\Lambda_h)+\Lambda_h(b(\mu+\epsilon)+2(\kappa+\mu))) \\
&+ \Lambda_h(\mu+\epsilon)(b(\eta+\mu)+2(\kappa+\mu))))
\end{aligned}
\tag{4.9}
$$

and

$$
\begin{aligned}
A_3 = (u_2-1)^2(((((b^2(\eta+\mu)^2 + 4b(\kappa+\mu)(\eta+\mu) + (\kappa+\mu)^2)(\epsilon+\mu)^2 \\
&+ \omega u_3(2(\epsilon+\mu)((\epsilon+\mu)(\eta+\mu)b^2 + 2(\kappa+\mu)(\epsilon+\eta+2\mu)b + (\kappa+\mu)^2) + (b^2(\epsilon+\mu)^2 \\
&+ 4b(\kappa+\mu)(\epsilon+\mu) + (\kappa+\mu)^2)\omega u_3))\Lambda_s^2 - 2u_1(((\eta+\mu)(\Lambda_s(\eta+\mu) - \Lambda_h\mu)b^2 + (4\Lambda_s(\eta+\mu)(\kappa+\mu) \\
&- \Lambda_h(4\mu^2 + 4(\eta+\kappa)\mu + \eta(\eta+3\kappa)))b - (\kappa+\mu)(\Lambda_h(\eta+\kappa+\mu) - \Lambda_s(\kappa+\mu)))(\epsilon+\mu)^2 \\
&+ \omega u_3((\epsilon+\mu)((\epsilon+\mu)(2\Lambda_s(\eta+\mu) - \Lambda_h(\eta+2\mu))b^2 + (4\Lambda_s(\kappa+\mu)(\epsilon+\eta+2\mu) \\
&- \Lambda_h(8\mu(\kappa+\mu) + \eta(3\kappa+4\mu) + \epsilon(\eta+4(\kappa+\mu))))b - (\kappa+\mu)(\Lambda_h(\eta+2(\kappa+\mu)) \\
&- 2\Lambda_s(\kappa+\mu))) + (\Lambda_s - \Lambda_h)(b^2(\epsilon+\mu)^2 + 4b(\kappa+\mu)(\epsilon+\mu) + (\kappa+\mu)^2)\omega u_3))\Lambda_s \\
&+ u_1^2((b^2(\Lambda_h\mu - \Lambda_s(\eta+\mu))^2 + (\Lambda_s(\kappa+\mu) - \Lambda_h(\eta+\kappa+\mu))^2 + 2b(2\mu^2(\Lambda_s - \Lambda_h)^2 \\
&+ 2(\eta+\kappa)\mu(\Lambda_s - \Lambda_h)^2 + \eta(2\kappa\Lambda_s^2 - \Lambda_h(\eta+3\kappa)\Lambda_s + \Lambda_h^2\kappa)))(\epsilon+\mu)^2 \\
&+ (\Lambda_s - \Lambda_h)\omega u_3(2(\epsilon+\mu)((\epsilon+\mu)(\Lambda_s(\eta+\mu) - \Lambda_h\mu)b^2 + (2\Lambda_s(\kappa+\mu)(\epsilon+\eta+2\mu) \\
&- \Lambda_h(4\mu(\kappa+\mu) + \eta(\kappa+2\mu) + \epsilon(\eta+2(\kappa+\mu))))b - (\kappa+\mu)(\Lambda_h(\eta+\kappa+\mu) - \Lambda_s(\kappa+\mu))) \\
&+ (\Lambda_s - \Lambda_h)(b^2(\epsilon+\mu)^2 + 4b(\kappa+\mu)(\epsilon+\mu) + (\kappa+\mu)^2)\omega u_3)))u_4^2\mu_v^2 \\
&+ (\epsilon+\mu)(u_2-1)\lambda_s(((-\epsilon-\mu)(\Lambda_h\mu(\Lambda_h\mu - \Lambda_s(\eta+\mu))b^2 + (2(\eta+\mu)(\kappa+\mu)\Lambda_s^2 \\
&- \Lambda_h(4\mu^2 + 2\eta\mu + 5\kappa\mu + 3\eta\kappa)\Lambda_s + \Lambda_h^2(2\mu^2 + 2\eta\mu + 3\kappa\mu + \eta\kappa))b \\
&+ (\Lambda_s(\kappa+\mu) - \Lambda_h\kappa)(\Lambda_s(\kappa+\mu) - \Lambda_h(\eta+\kappa+\mu))) + (\Lambda_s - \Lambda_h)(\Lambda_h\mu(\epsilon+\mu)b^2 \\
&+ (\Lambda_h(2\mu^2 + \epsilon\mu + 3\kappa\mu + 2\epsilon\kappa) - 2\Lambda_s(\epsilon+\mu)(\kappa+\mu))b - (\kappa+\mu)(\Lambda_s(\kappa+\mu) - \Lambda_h\kappa))\omega u_3)u_4\mu_v u_1^2 \\
&+ (-b\Lambda_s\lambda(\epsilon+\mu)(\eta+\mu)(2\Lambda_s\kappa + (b+2)\Lambda_s\mu - \Lambda_h(2\kappa + 2b\mu + \mu)) \\
&+ b\Lambda_s\lambda\mu(-2\Lambda_s(\kappa+\mu) + \Lambda_h(2\kappa+\mu) + b(\Lambda_h(\epsilon+2\mu) - \Lambda_s(\epsilon+\mu)))\omega u_3 \\
&+ b\Lambda_s\lambda u_2((\epsilon+\mu)(\eta+\mu)(2\Lambda_s\kappa + (b+2)\Lambda_s\mu - \Lambda_h(2\kappa + 2b\mu + \mu)) \\
&+ \mu((\Lambda_s - \Lambda_h)(b\epsilon + 2\kappa) + ((b+2)\Lambda_s - (2b+1)\Lambda_h)\mu)\omega u_3) + \Lambda_s((-\epsilon-\mu)(\Lambda_h\mu(\eta+\mu)b^2 \\
&+ (\Lambda_h(4\mu^2 + 2\eta\mu + 5\kappa\mu + 3\eta\kappa) - 4\Lambda_s(\eta+\mu)(\kappa+\mu))b + (\kappa+\mu)(\Lambda_h(\eta+2\kappa+\mu)
\end{aligned}
\tag{4.10}
$$

and also

$$
\begin{aligned}
A_4 = (u_2-1)(\mu+\epsilon)(-(u_2-1)\lambda_s(u_1(u_3\omega(\Lambda_s\lambda\mu(b^2\mu\Lambda_h(\mu+\epsilon)+b(\Lambda_h(3\kappa\mu+2\mu^2+2\kappa\epsilon+\mu\epsilon)\\
-\quad 2\Lambda_h(\kappa+\mu)(\mu+\epsilon))-(\kappa+\mu)(\Lambda_h(\kappa+\mu)-\kappa\Lambda_h))+\Lambda_h u_4(\kappa+\mu)\mu_v(\mu+\epsilon)(2\Lambda_h(\kappa+\mu)\\
-\quad \Lambda_h(b\mu+2\kappa+\mu)))+\Lambda_s\lambda u_2((\eta+\mu)(\mu+\epsilon)(\Lambda_h(\kappa+\mu)(2b\mu+\kappa+\mu)-\Lambda_h(\kappa(3b\mu+\mu)\\
+\quad b(b+2)\mu^2+\kappa^2))-\mu u_3\omega(b^2\mu\Lambda_h(\mu+\epsilon)+b(\Lambda_h(3\kappa\mu+2\mu^2+2\kappa\epsilon+\mu\epsilon)-2\Lambda_h(\kappa+\mu)(\mu+\epsilon))\\
-\quad (\kappa+\mu)(\Lambda_h(\kappa+\mu)-\kappa\Lambda_h)))-(\eta+\mu)(\mu+\epsilon)(\Lambda_s\lambda(\Lambda_h(\kappa+\mu)(2b\mu+\kappa+\mu)\\
-\quad \Lambda_h((3b+1)\kappa\mu+b(b+2)\mu^2+\kappa^2))-\Lambda_h u_4(\kappa+\mu)\mu_v(2\Lambda_h(\kappa+\mu)-\Lambda_h(b\mu+2\kappa+\mu))))\\
-\quad \Lambda_h(\kappa+\mu)(\Lambda_s\lambda((\eta+\mu)(-\mu-\epsilon)(2b\mu+\kappa+\mu)-\mu u_3\omega(2b(\mu+\epsilon)+\kappa+\mu))\\
+\quad \Lambda_s\lambda u_2(\mu u_3\omega(2b(\mu+\epsilon)+\kappa+\mu)+(\eta+\mu)(\mu+\epsilon)(2b\mu+\kappa+\mu))\\
+\quad \Lambda_h u_4(\kappa+\mu)\mu_v(\mu+\epsilon)(\eta+\mu+u_3\omega))-\Lambda_h(b\mu+\kappa)))\\
-\quad 2u_4^2(\kappa+\mu)\mu_v^2(-\Lambda_h)(\eta+\mu+u_3\omega)(u_1(\mu+\epsilon)(b(\Lambda_h(\eta+\mu)-\mu\Lambda_h)+\Lambda_h(\kappa+\mu)\\
-\quad \Lambda_h(\eta+\kappa+\mu))+u_3\omega(-\Lambda_h)(b(\mu+\epsilon)+\kappa+\mu)-\Lambda_h(\mu+\epsilon)(b(\eta+\mu)+\kappa+\mu)))
\end{aligned}
$$

$$
H_5 = \Lambda_h^2 u_4^2(\kappa+\mu)^2\mu_v^2(\mu+\epsilon)^2(\eta+\mu+u_3\omega)^2\left(1-R_{sc}^2\right) \tag{4.11}
$$

Remark: The system (4.1) has a unique endemic equilibrium E^* if $R_{sc} > 1$ and Cases 1-3 (as declared in Table 1) are satisfied. It could have more than one endemic equilibrium if $R_{sc} > 1$ and Case 4 is satisfied; it could have 2 endemic equilibria if $R_{sc} < 1$ and Cases 2-4 are satisfied.

Theorem 4.5.

The system (4.1) has a unique endemic equilibrium E^* if $R_{sc} > 1$ and Cases 1-3 and 6 are satisfied; it could have more than one endemic equilibrium if $R_{sc} > 1$ and Cases 4, 5, 7, and 8 are satisfied; it could have 2 or more endemic equilibria if $R_{sc} < 1$ and Cases 2-8 are satisfied.

Table 1, shows the existence of multiple endemic equilibria when $R_{sc} < 1$. The Table suggests the possibility of backward bifurcation, where the stable DFE coexists with a stable endemic equilibrium, when the reproduction number is less than unity. Thus, the occurrence of a backward bifurcation has an important implications for epidemiological control measures, since an epidemic may persist at steady state even if $R_{sc} < 1$.

4.6 Analysis of optimal control

In this section, we make use of optimal control techniques applying Pontryagins Maximum Principle in order to arrive at the indispensable conditions for the optimal control that seeks to examine believers on unbelievers. We include time-dependent controls into system (4.1) to establish the optimal strategy or mechanism for controlling the unbelievers. Hence, we obtain,

Table 4.2: Number of possible positive real roots of $P(\lambda_1)$ for $R_{sc} > 1$ and $R_{sc} < 1$

Cases	A_1	A_2	A_3	A_4	A_5	R_{sc}	Number of sign change	Number of positive real roots
1	+	+	+	+	+	$R_{sc} < 1$	0	0
	+	+	+	-	-	$R_{sc} > 1$	1	1
2	+	-	-	-	+	$R_{sc} < 1$	2	0, 2
	+	-	-	-	-	$R_{sc} > 1$	1	1
3	+	+	-	-	+	$R_{sc} < 1$	2	0, 2
	+	+	-	-	-	$R_{sc} > 1$	1	1
4	+	-	+	-	+	$R_{sc} < 1$	4	0, 2,4
	+	-	+	-	-	$R_{sc} > 1$	3	1, 3
5	+	-	-	+	+	$R_{sc} < 1$	2	0, 2
	+	-	-	+	-	$R_{sc} > 1$	3	1, 3
6	+	+	+	-	+	$R_{sc} < 1$	2	0, 2

$$
\begin{cases}
\frac{d}{dt}S_h = & (1-u_1)\Lambda_h + \epsilon R_h - (1-u_2)\lambda_1 S_h - \mu_h S_h + \kappa V_h \\
\frac{d}{dt}I_h = & (1-u_2)\lambda_1 S_h + b(1-u_2)\lambda_1 V_h - (u_3\omega + \mu_h + \eta) I_h \\
\frac{d}{dt}R_h = & u_3\omega I_h - (\epsilon + \mu_h) R_h \\
\frac{d}{dt}V_h = & u_1\Lambda_h - (\kappa + \mu_h) V_h - b(1-u_2)\lambda_1 V_h \\
\\
\frac{d}{dt}S_s = & \Lambda_s - (1-u_2)\lambda_2 S_s - u_4\mu_s S_s \\
\frac{d}{dt}I_s = & (1-u_2)\lambda_2 S_s - u_4\mu_s I_s
\end{cases}
\tag{4.12}
$$

The control functions, $u_1(t), u_2(t), u_3(t)$ and $u_4(t)$ are bounded, Lebesgue integrable functions. Control u_1 is the effort designed to vaccination. The control u_2 deals with the effort required to prevent infection. The control u_3 is the effort to treat and u_4 is effects targeted against snails.

$$
J(u_1, u_2, u_3, u_4) = \int_0^{t_f} \left(AI_h + BI_s + \frac{C}{2}u_1^2 + \frac{D}{2}u_2^2 + \frac{E}{2}u_3^2 + \frac{D}{2}u_2^2 + \frac{E}{2}u_4^2 \right) dt, \tag{4.13}
$$

where t_f denotes the final time and the coefficients, A, B, C, D, E, F are balancing cost factors as a result of scales and significance of the five portions of the objective function. We desired to seek an optimal control, u_1^*, u_2^*, u_3^* and u_4^* in a way that

$$
J(u_1^*, u_2^*, u_3^*, u_4^*) = \max_{\mathcal{U}} J(u_1, u_2, u_3, u_4). \tag{4.14}
$$

where $U = \{(u_1, u_2, u_3, u_4)$ in a way u_1, u_2, u_3, u_4 are measurable with $0 \leq u_1 \leq 1,\ 0 \leq u_2 \leq g_2,\ 0 \leq u_3 \leq g_3,$ and $0 \leq u_4 \leq g_4,$ for $t \in [0, t_f]\}$ is the control set. The vital conditions that an optimal solution must have is emanated the Pontryagin et al. [25] Maximum Principle. This principle changes (4.1) - (4.2) into a type of problem which

minimizes pointwise a Hamiltonian H, with regard to u_1, u_2, u_3 and u_4,

$$\begin{aligned} H &= AI_h + BI_s + \tfrac{C}{2}u_1^2 + \tfrac{D}{2}u_2^2 + \tfrac{E}{2}u_3^2 + \tfrac{D}{2}u_2^2 + \tfrac{E}{2}u_4^2 \\ &+ \lambda_{S_h}\{(1-u_1)\Lambda_h + \epsilon R_h - (1-u_2)\lambda_1 S_h - \mu_h S_h + \kappa V_h\} \\ &+\lambda_{I_h}\{(1-u_2)\lambda_1 S_h + b(1-u_2)\lambda_1 V_h - (u_3\omega + \mu_h + \eta)I_h\} \\ &+\lambda_{R_h}\{u_3\omega I_h - (\epsilon+\mu_h)R_h\} \\ &+\lambda_{V_h}\{u_1\Lambda_h - (\kappa+\mu_h)V_h - b(1-u_2)\lambda_1 V_h\} \\ &+\lambda_{S_s}\{\Lambda_s - (1-u_2)\lambda_2 S_s - u_4\mu_s S_s\} \\ &+\lambda_{I_s}\{(1-u_2)\lambda_2 S_s - u_4\mu_s I_s\} \end{aligned} \tag{4.15}$$

where $\lambda_{S_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{V_h}, \lambda_{S_s}$ and λ_{I_s} represent the adjoint variables or co-state variables. The system equations is arrived at by considering the right partial derivatives of the Hamiltonian (4.15) with regard to the corresponding state variable.

Theorem 4.7. Given optimal controls $u_1^*, u_2^*, u_3^*, u_4^*$ and solutions

$S_h, I_h, R_h, V_h, S_s, I_s$ of the associated state system (4.12)-(4.15) that minimizes $J(u_1, u_2, u_3, u_4)$ over Γ. Then there exists adjoint variables

$\lambda_{S_h}, \lambda_{I_h}, \lambda_{R_h}, \lambda_{V_h}, \lambda_{S_s}, \lambda_{I_s}$ satisfying

$$\frac{-d\lambda_i}{dt} = \frac{\partial H}{\partial i} \tag{4.16}$$

where $i = S_h, I_h, R_h, V_h, S_s, I_s$ and with transversality conditions

$$\lambda_{S_h}(t_f) = \lambda_{I_h}(t_f) = \lambda_{R_h}(t_f) = \lambda_{V_h}(t_f) = \lambda_{S_s}(t_f) = \lambda_{I_s}(t_f) = 0 \tag{4.17}$$

and

$$u_1^* = \min\left\{1, \max\left(0, \overline{2C}\right)\right\} \tag{4.18}$$

$$u_2^* = \min\left\{1, \max\left(0, \frac{}{2D}\right)\right\}, \tag{4.19}$$

$$u_3^* = \min\left\{1, \max\left(0, \frac{}{2E}\right)\right\}, \tag{4.20}$$

$$u_4^* = \min\left\{1, \max\left(0, \frac{}{2F}\right)\right\}, \tag{4.21}$$

Proof: Corollary 4.1 of Fleming and Rishel [20] provides possible condition for existence of an optimal control based on convexity of the integrand of J with regard to u_1, u_2, u_3 and u_4, a *priori* boundedness of the state solutions, and the *Lipschitz* characteristics of the state system with respect to the state variables. The Hamiltonian function determined at the optimal control level gives the governing adjoint variables.

Solving for the values of u_1^*, u_2^* and u_3^* with respect to the constraints, the characterization (4.12-4.15) can be arrived at as

In the next section, we shall discuss extensively the numerical simulations which depend on the optimality of the model exploring various strategies of the optimal controls u_1u_2 and u_3.

4.8 Numerical Simulations

We begin by presenting an extensive discussion on the numerical solutions obtained as a result of the optimality of the system and the associated results of changing the optimal controls u_1, u_2, u_3 and u_4, the parameter selections, in addition to the appropriate interpretations from different cases. The numerical simulation solutions are undertaken using MATLAB 10.0 version. The optimality system, which comprises the state system and the adjoint system, was computed to determine the optimal control solution. The optimality system solution was determined employing a fourth-order Runge-Kutta iterative

scheme. The adjoint equations were computed using the backward fourth-order Runge-Kutta scheme taking into account the recent solutions of the state equations which depend on the transversality conditions (4.17). The controls results were revised employing a convex combination of the previous controls and the value obtained from the characterisations. This activity was carried on and the iterations were terminated if the values of the unknowns at the previous iterations were similar to the ones arrived at the current iteration [14, 15].

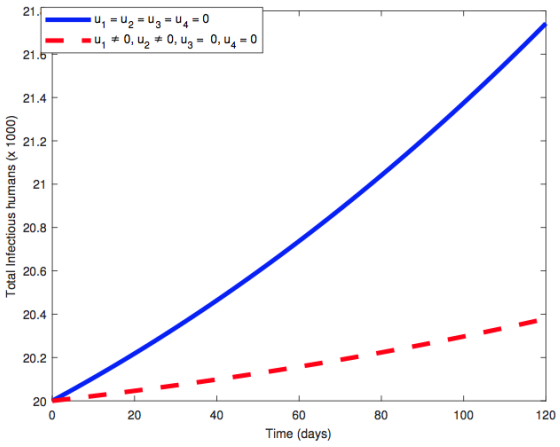
Table shows parameters and values used in the numerical simulation of the model. The following weight constants were considered: $a_1 = 40,\ a_2 = 110$, and $b_1 = 200,\ b_2 = 180,\ b_3 = 500$.

The table (4.1) shows the parameters and values used for the numerical simulation.

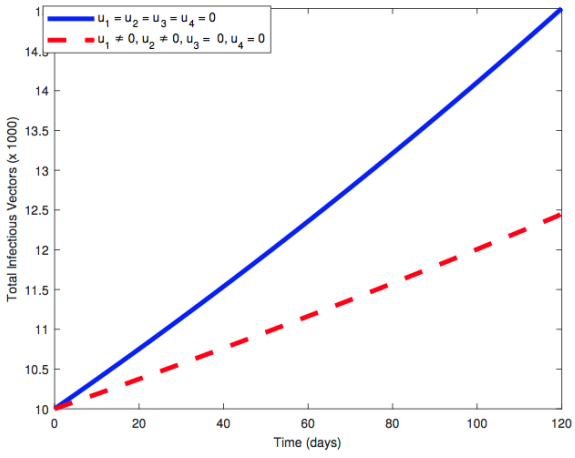
- Strategy A: combination of vaccination and prevention.
- Strategy B: combination of vaccination and treatment.
- Strategy C: combination of vaccination and snail control.
- Strategy D: combination of prevention and treatment.
- Strategy E: combination of prevention and snail control.
- Strategy F: combination of treatment and snail control.
- Strategy G: combination of vaccination, prevention and treatment.
- Strategy H: combination of vaccination, prevention and snail control.
- Strategy I: combination of prevention, treatment and snail control.
- Strategy J: combination of vaccination, prevention, treatment and snail control.

4.8.1 Vaccination (u_1) and Prevention (u_2) control only

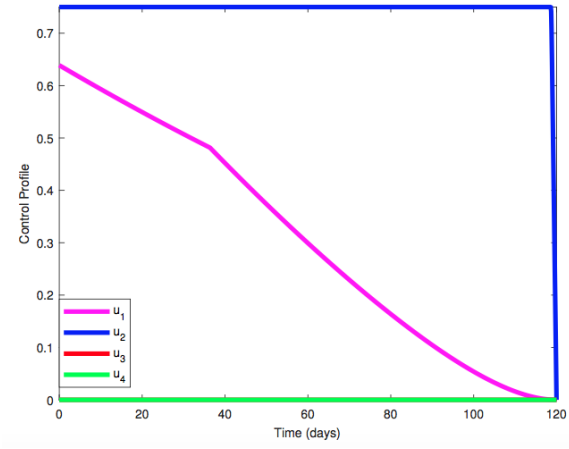
In this strategy, the use of vaccination as a means of control u_1 and prevention control u_2 are employed in order to optimize the objective function J while we set the use of treatment u_3 and snail control u_4, to zero. It was shown in figure 1a and b that due to the control strategies, the number of infected humans (I_h) and infected vectors (snail) (I_s) decreases. This indicates that eliminating the spread of schistosomiasis in human population through the means of vaccination and prevention would lead to an indirect decrease in the number of infected snail population. The control profile in figure 1 c shows that the schistosomiasis vaccination control u_1 decrease gradually from 64% to the lower bound during the entire 120 days of intervention. And the prevention control u_2 should be maintained at a maximum effort for the entire duration of the intervention.



(a)



(b)



(c)

Figure 1: Simulations of the model showing the effect of vaccination and prevention only on transmission

4.8.2 Vaccination (u_1) and Treatment (u_3) only

The use of vaccination control u_1 and treatment control u_3 are used to optimize the objective function J while prevention control u_2 and snail control u_4 was set to be zero. We observed in figure 2 a and b that in the presence of these two control strategies, there is a drastic decrease in the number of infected human population (I_h) and a great significant decrease in infected snail population (I_s). This implies that, the use of vaccination and treatment controls in infected human population will put an end to the spread of the disease and in turn, lead to great decrease in infected snail population as shown in figure 2b. From the control profile shown in figure 2 c, the results suggest that in using this strategy, the vaccination control u_1 should be decrease gradually from 44% during the first 40day and reduce drastically for the remaining 80days. While control u_3 treatment level should be maintain at a maximum effort during the application of the intervention.

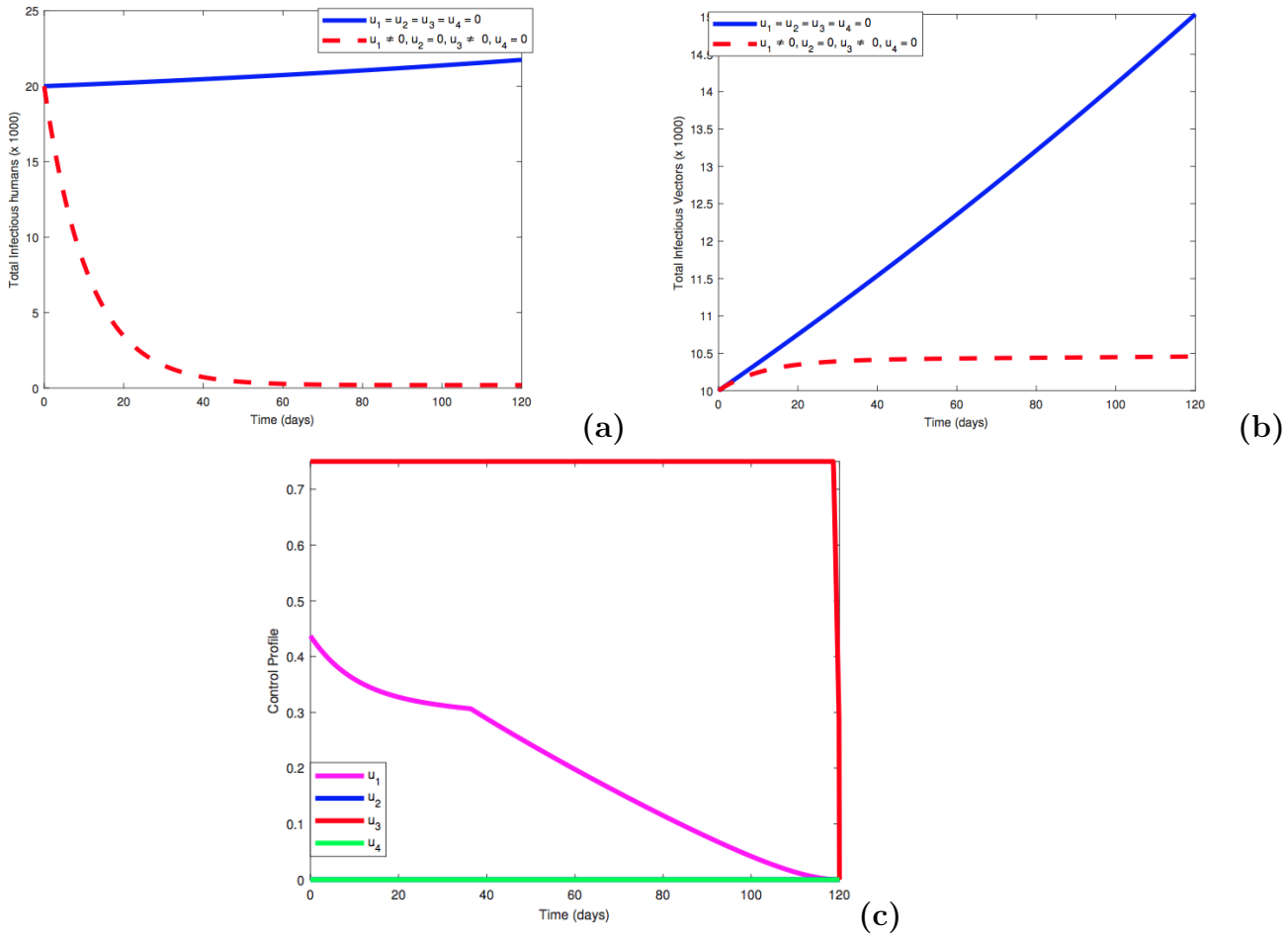


Figure 2: Simulations of the model showing the effect of vaccination and treatment only on transmission

4.8.3 Vaccination (u_1) and Snail control (u_4) only

In this strategy, we optimize the objective function J using vaccination control u_1 and snail control u_4 while the prevention control u_2 and treatment control u_3 is set to be zero. We observed in figure 3a and b that this control strategy has a considerable influence on the number of infected human population (I_h) and caused a drastic decrease in the number of infected snail population. Figure 3 c shows that the schistosomiasis vaccination control u_1 level should be reduce from 55% to the lower bound during the entire duration of the intervention. While the level of the snail control u_4 should be maintained until 117days of the intervention.

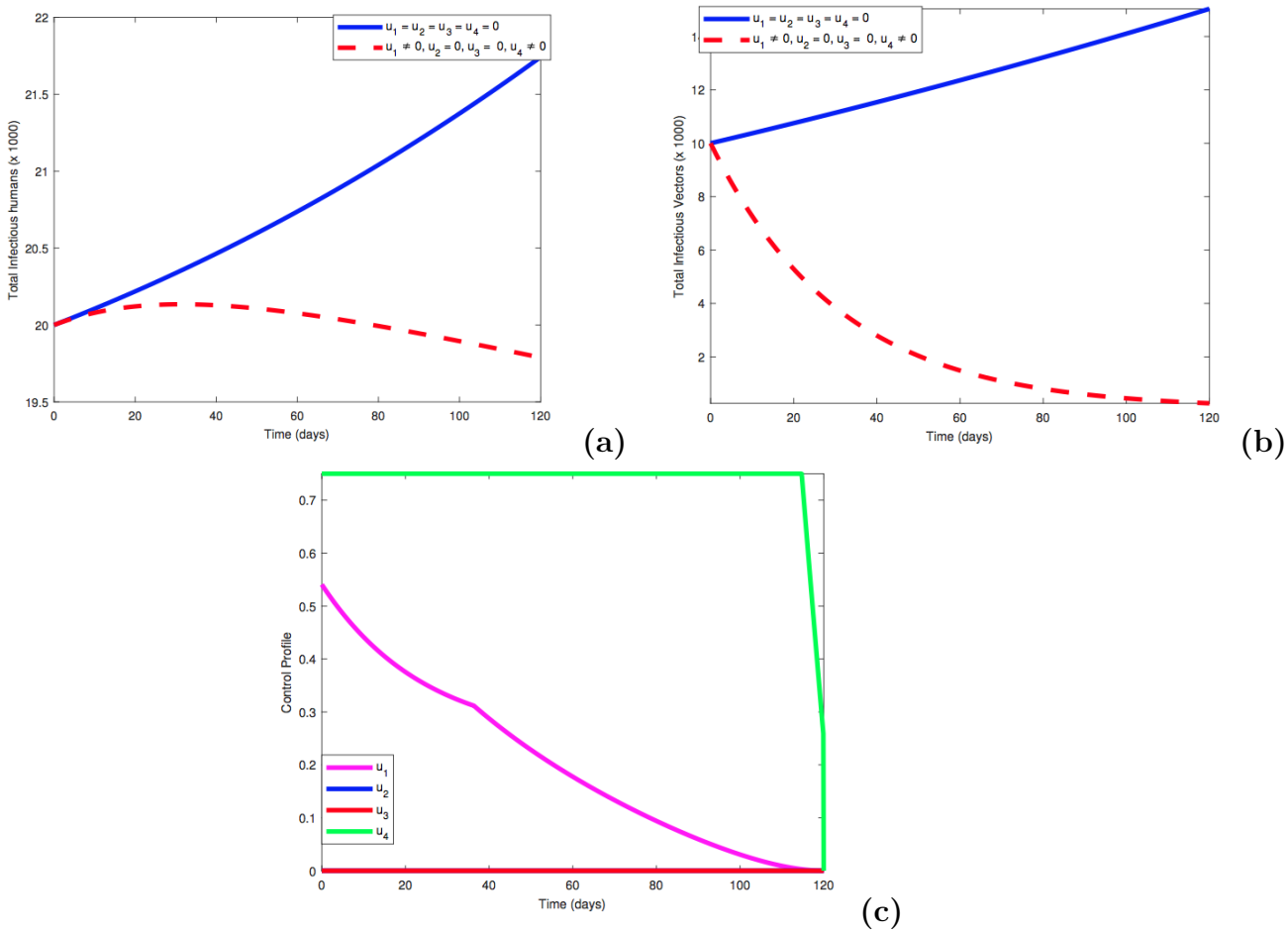


Figure 3: Simulations of the model showing the effect of vaccination and snail control only on transmission

4.8.4 Prevention (u_2) and Treatment (u_3) only

We employed prevention control u_2 and treatment control u_3 in this strategy to optimize the objective function J. It was observed in figure 4a and b that in the presence of these control strategies, the number of infected human population (I_h) decrease drastically, also, there is a great decrease in the number of infected snail population (I_s). This indicates that, the use of these control strategies will eradicate the spread of this disease in human population and cause a great decline in the number of infected snail population. The

control profile in figure 4 c stipulate that both the strategy prevention u_2 and treatment u_3 control level should be maintain at a maximum level for about 117 to 118days for the entire period of intervention.

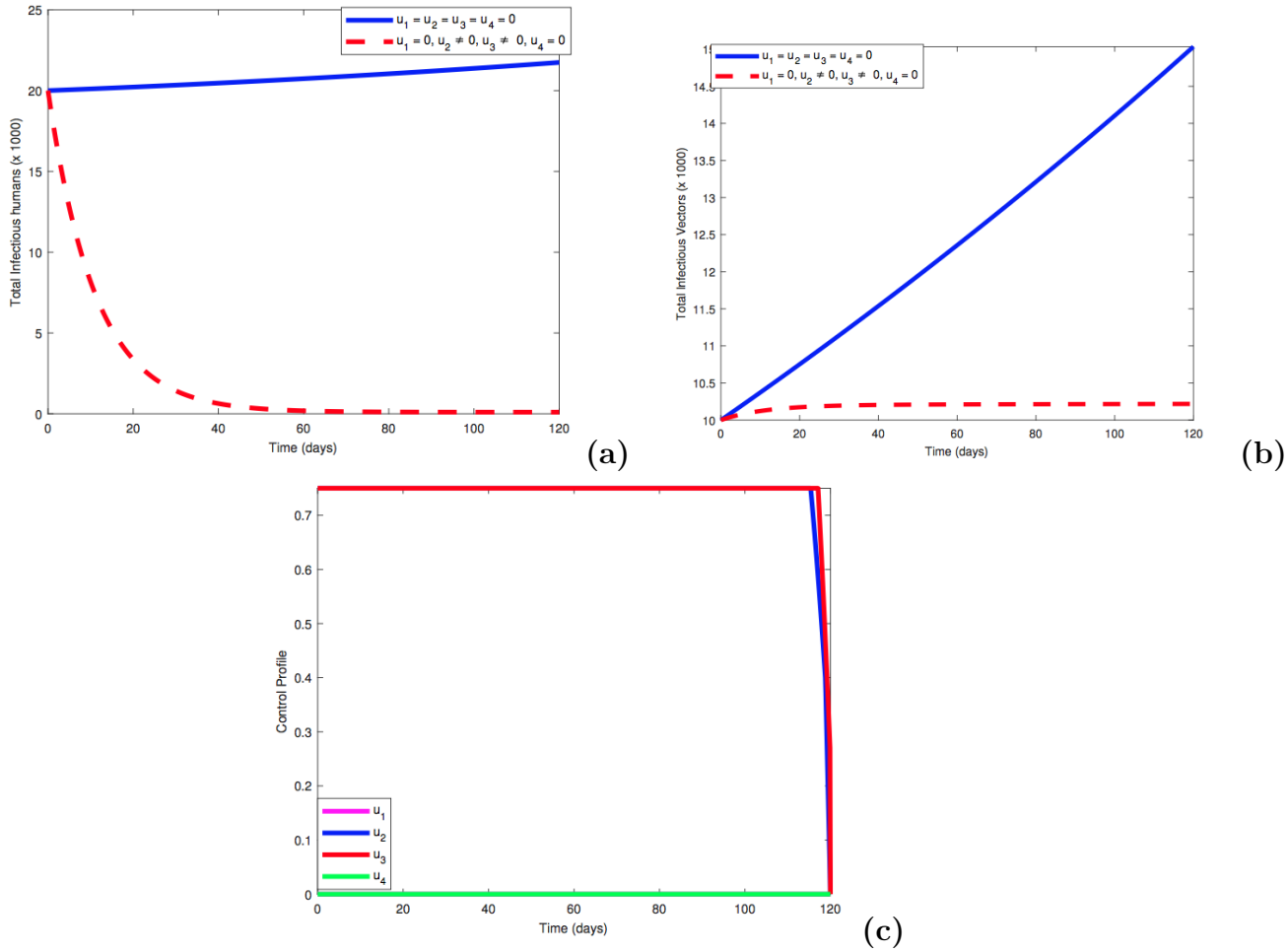


Figure 4: Simulations of the model showing the effect of treatment and prevention only on transmission

4.8.5 Prevention (u_2) and Snail control (u_4) only

In this strategy, we introduced prevention control u_2 and snail control $u_4$bn so as to optimize the objective function J whereas we set vaccination control u_1b and treatment control u_3 to zero. We observed in figure 5a and b that the introduction of this control

strategy has a significant effect on infected human (I_h) population as well as poses a great considerable influence on the number of the infected snail (I_s) in the population. This is an indication that, the combination of prevention control and snail control strategy may alter the transmission of schistosomiasis by eliminating the snail which serve as intermediate host for the disease. The control profile in figure 5 c suggest that the control u_2 ought to be kept at a maximum level of 100% for about 92days and gradually decrease to 30% and kept same within the whole period of 120days. While control u_4 level should be kept at a maximum level of 100% for about 116days and reduces gradually to 30% which should be maintain throughout the entire 120days of the intervention.

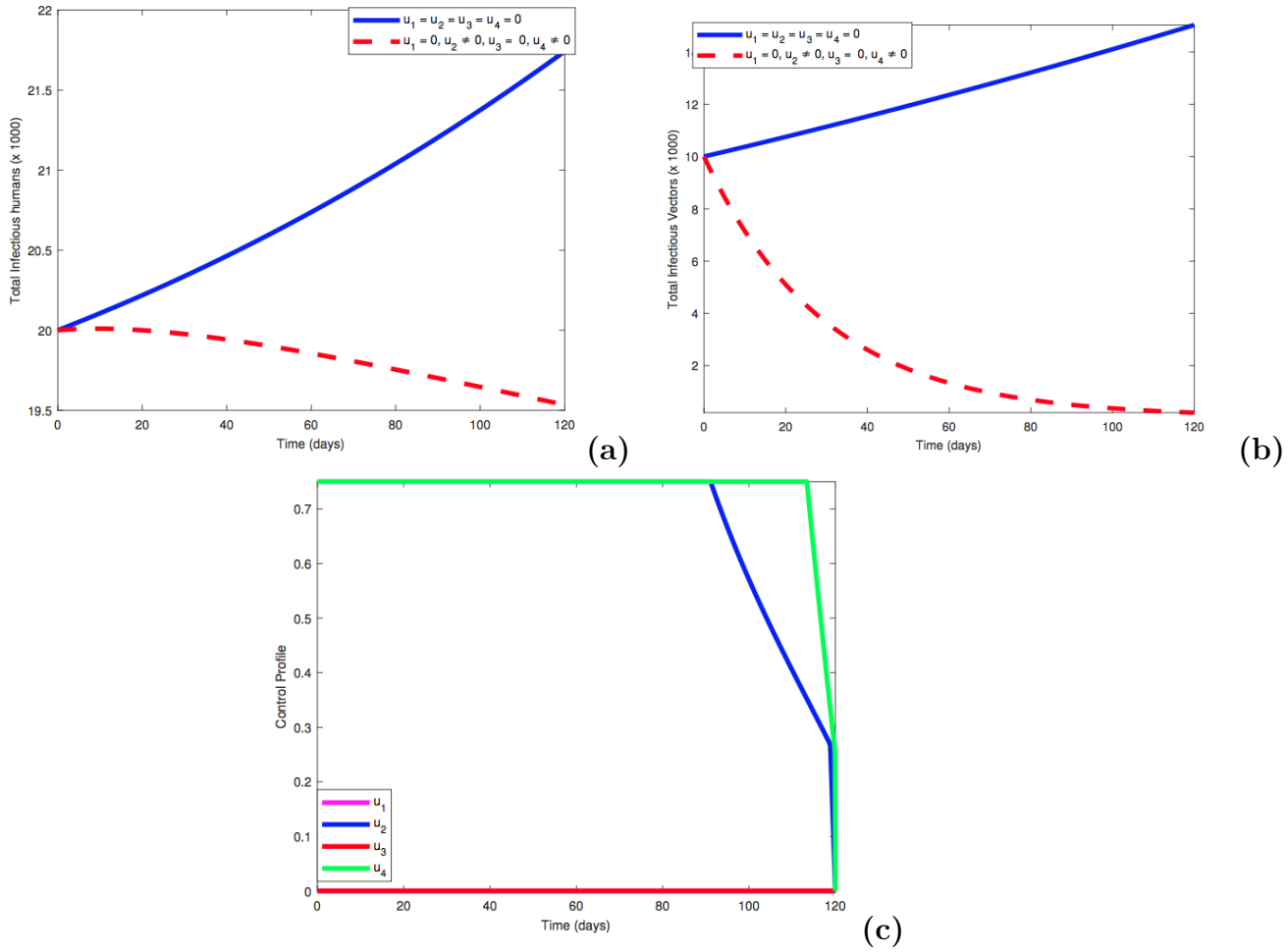
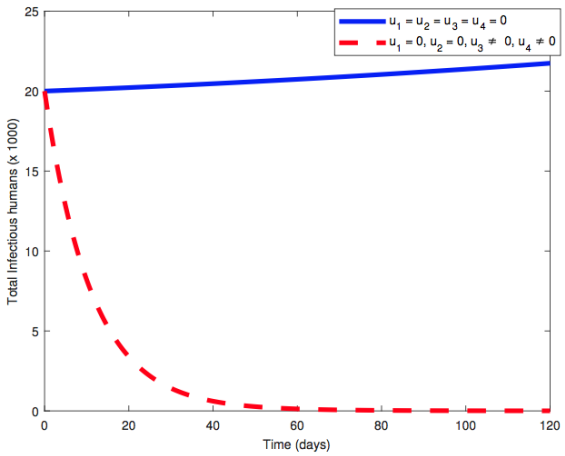


Figure 5: Simulations of the model showing the effect of snail control and prevention only

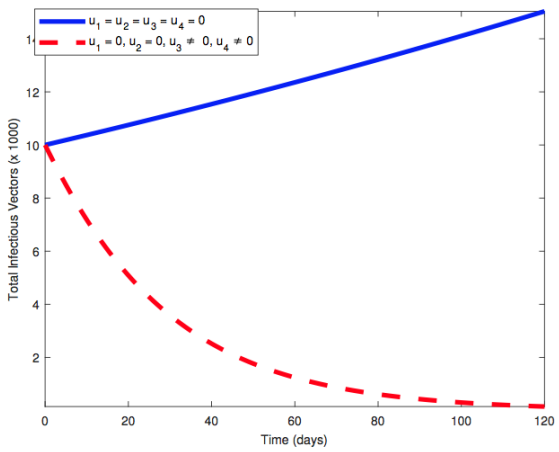
on transmission

4.8.6 Treatment (u_3) and Snail control (u_4) only

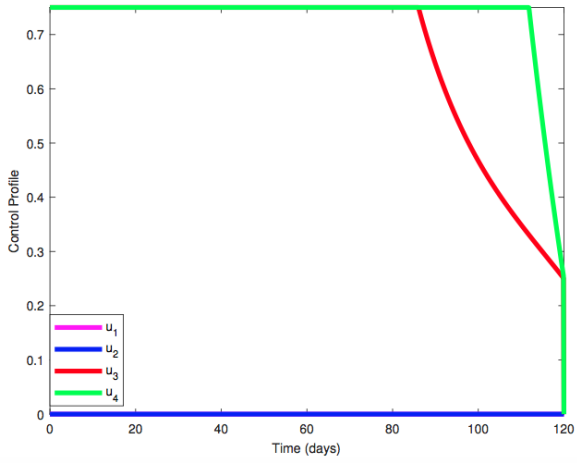
In this approach, the use of treatment control u_3 and snail control u_4 was adopted to optimize the objective function J while the use of vaccination control u_1 and prevention control u_2 was set to be zero. It was observed in figure 6a and b that this control strategy poses a great significant impact on the number of infected human (I_h), moreover, the number of infected snail (I_s) decreases drastically. This great observable decrease in the number of infected human maybe due to the accurate completion in the dose of treatment which may in turn leads to the elimination of the disease as seen in figure 6a. From the control profile shown in figure 6 c, the results indicate that the use of schistosomiasis treatment u_3 control should be maintain at a maximum level of 100% for about 87days and start to decline to 30% and maintain same within the entire 120days of the intervention while the snail control u_4 should be kept at a maximum level of 10% for about 113 - 116days and gradually reduce to 30% for the entire 120days.



(a)



(b)



(c)

Figure 6: Simulations of the model showing the effect of snail control and treatment only on transmission

4.8.7 Vaccination, Prevention and Treatment (u_1, u_2, u_3)

In this strategy, the use of vaccination control u_1, prevention control u_2 and treatment control u_3 are employed in order to optimize the objective function J while we set the snail control u_4, to be zero. It was shown in figure 7a and b that due to the control strategies, the number of infected humans (I_h) in the population diminish and eventually become eliminated from the system, more so, the number of infected vectors (snail) (I_s) decreases. The control profile in figure 7 c show that vaccination u_1 control gradually decrease from about 34 - 35% during the first 40days and there was a significant reduction for the remaining 80days of the intervention. In prevention u_2 control, it was observed that the level of the control should be kept at 100% for about 115days. While treatment u_3 control level should be maintain at a maximum level of 100% for about 118days of the entire intervention. This result is an indicative that, the combination of these control strategies may eradicate the spread of the disease.

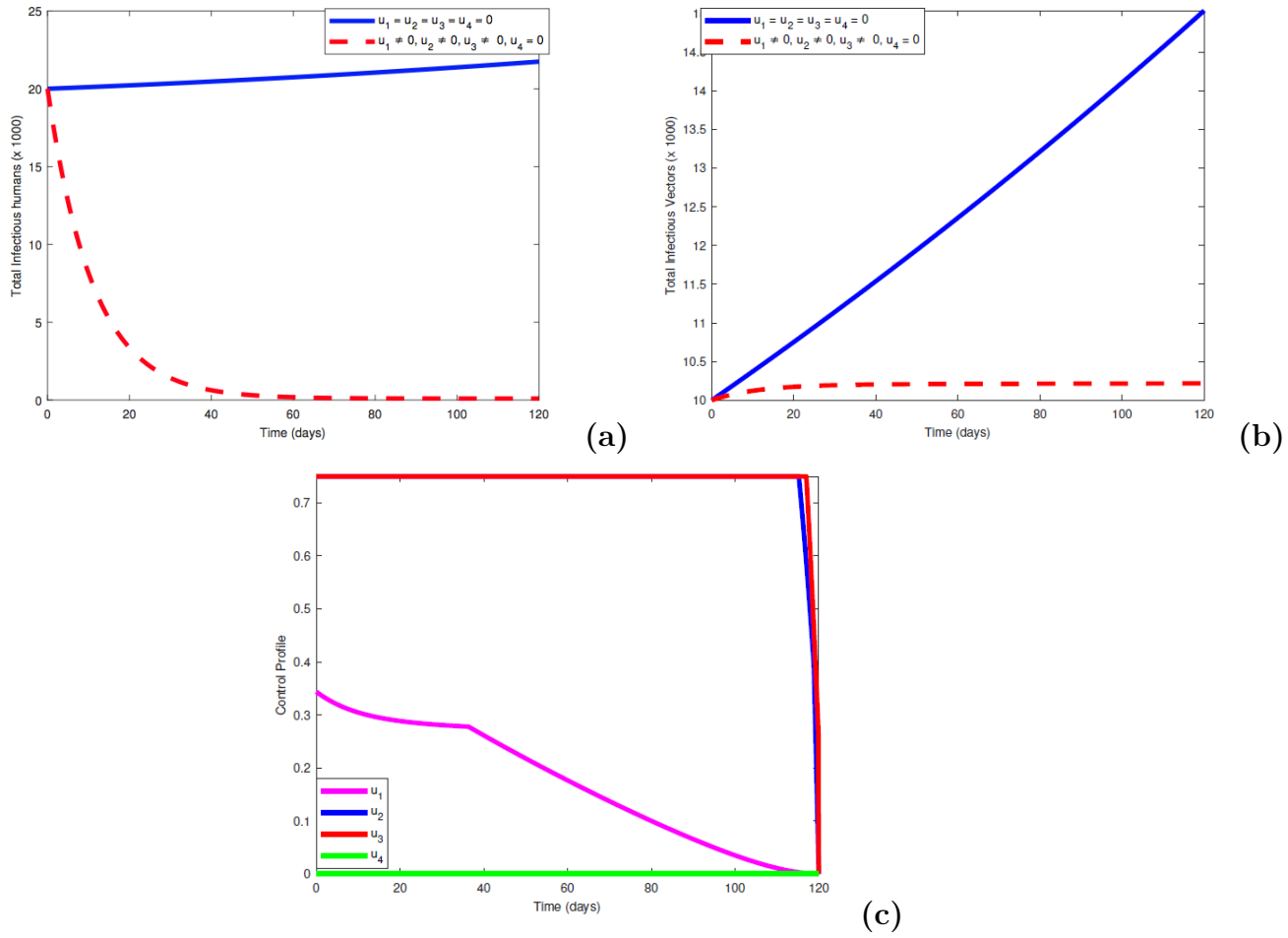


Figure 7: Simulations of the model showing the effect of vaccination, prevention and treatment on transmission

4.8.8 Vaccination, Prevention and Snail control (u_1, u_2, u_4)

In this approach, the use of vaccination control u_1, prevention control u_3 and snail control u_4 was adopted to optimize the objective function J while the use of treatment control u3 was set to be zero. We observed in figure 8a and b that this control strategies pose a significant effect on the number of infected human (I_h), and the number of infected snail (I_s) decreases and consistency in this approach as shown in figure 8b may eliminate infected snail (I_s) population as time goes on. For the control profile shown in figure 8c, the results show that vaccination u_1 control should be reduce gradually from 39% during the 37days of the intervention and drastically reduce to lower bound for the remaining days.

Whereas, the prevention u_2 control level should be maintain at maximum level of 100% for about 90days and start to decline drastically to approximately 27% and maintain same for the entire 120days. In the same manner, snail control u4 level should be maintain at maximum level for about 112days and decrease drastically to 30% and maintain same for 120days of the intervention.

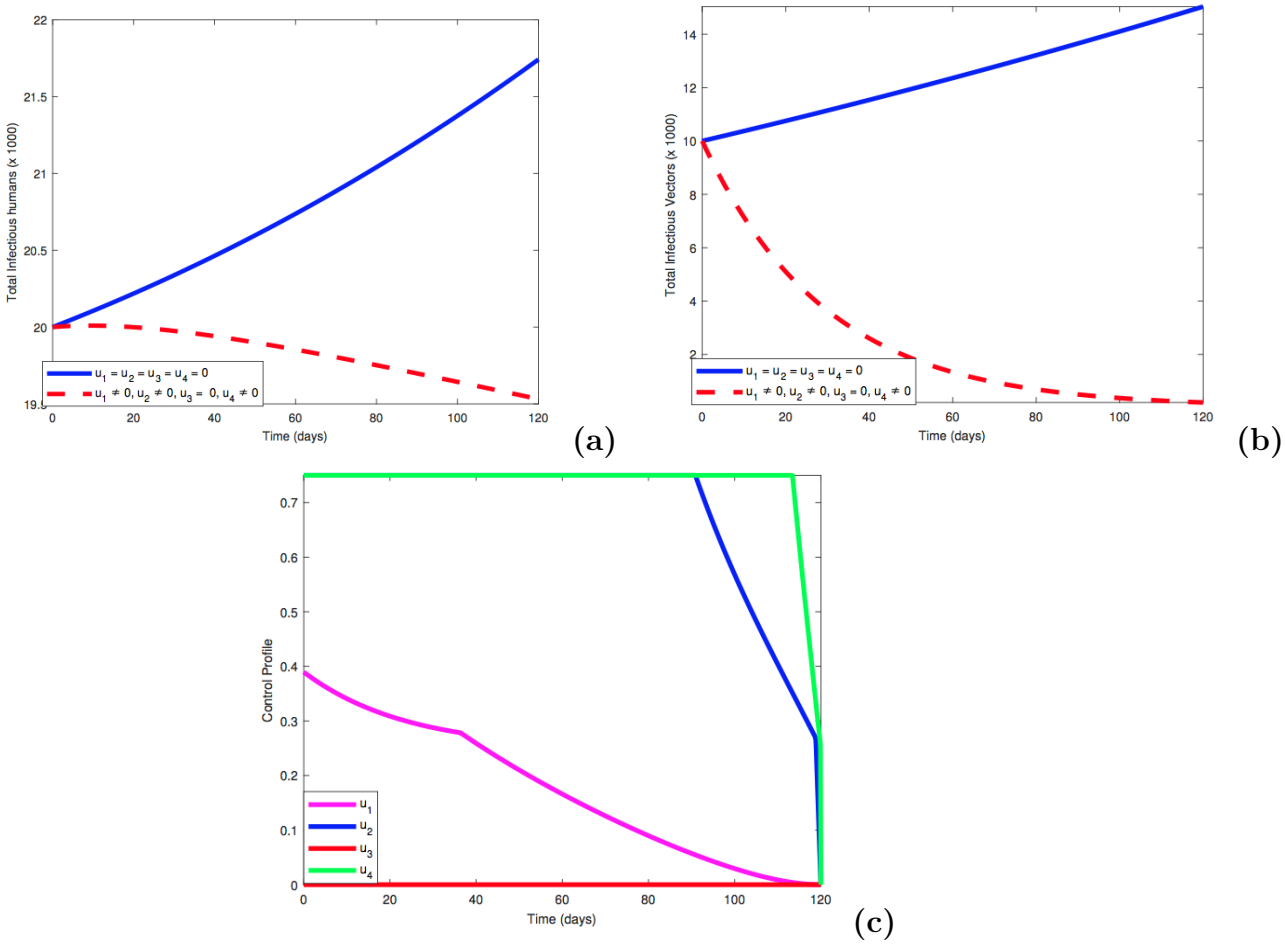
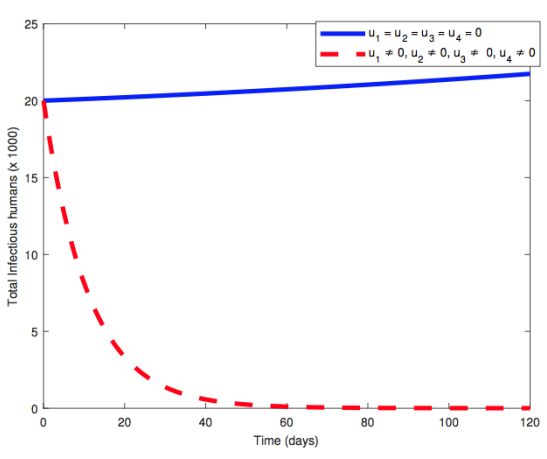


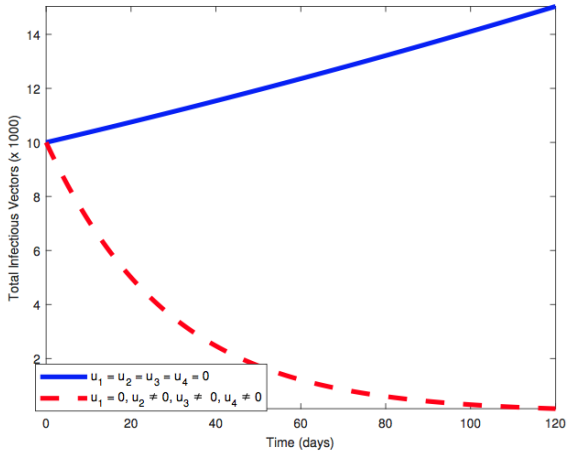
Figure 8: Simulations of the model showing the effect of vaccination, prevention and snail control on transmission

4.8.9 Prevention, Treatment and Snail control (u_2, u_3, u_4)

The provision of prevention control u_2, treatment control u_3 and snail control u_4 are used to optimize the objective function J while we set vaccination control u_1 to be zero. We observed in figure 9a and b that this control strategy a great significant effect on the number of infected human (I_h) and infected snail (I_s). This indicates that the continuous use of these control strategies may eliminate the spread of this disease in infected human (I_h) and infected snail (I_s) population as shown in figure 9a and b. The control profile in figure 9c show that schistosomiasis prevention u_2 control should be maintain at 100% for about 35days of the intervention and gradually decrease to 25% and keep same for 120days of the whole intervention. Treatment u_3 control level should be maintain at maximum level for 80days and gradually decrease to about 25% and maintain same for 120days. While snail control u_4 should be kept at 100% for approximately 112days and drastically reduce to 25% and keep same level for the period of 120days of the whole intervention.



(a)



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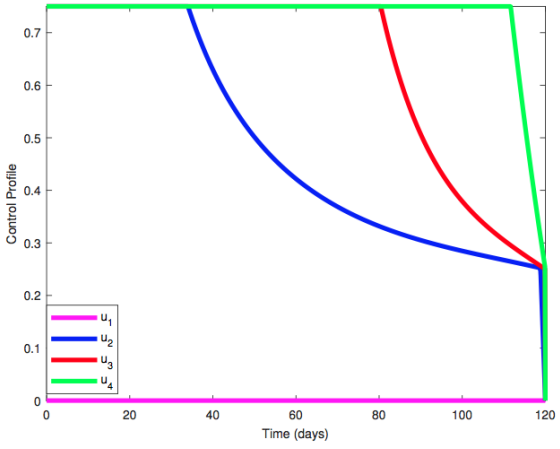

(c)

Figure 9: Simulations of the model showing the effect prevention, treatment and snail control on transmission

4.8.10 Vaccination, Prevention, Treatment and Snail control (u_1, u_2, u_3, u_4)

In this strategy, we use all the four controls u_1, u_2, u_3 and u_4 to optimize the objective function J. We observed in figure 10a and b that due to the control strategies, the number of infected human (I_h) and infected snail (I_s) population decreases greatly in the system. This shows that the adoption of these control strategies may eliminate the spread of schistosomiasis. From the control profile shown in figure 10c, the results stipulate that the application of this intervention requires that the vaccination u_1 control reduce gradually from 28% during the first 37days and drastically decrease for the remaining days of the intervention. Whereas, the prevention u_2 control level should be kept at maximum level for 35days and start to decline gradually to about 30% and maintain same for the entire 120days. Treatment u_3 control level should be maintain at maximum level for 80days and reduce gradually to 30% for the whole period of the intervention. The result also shows that snail control u_4 should be employ for about 110days at maximum level and reduce gradually to 30% for 120days and maintain same level for the entire period of the

intervention.

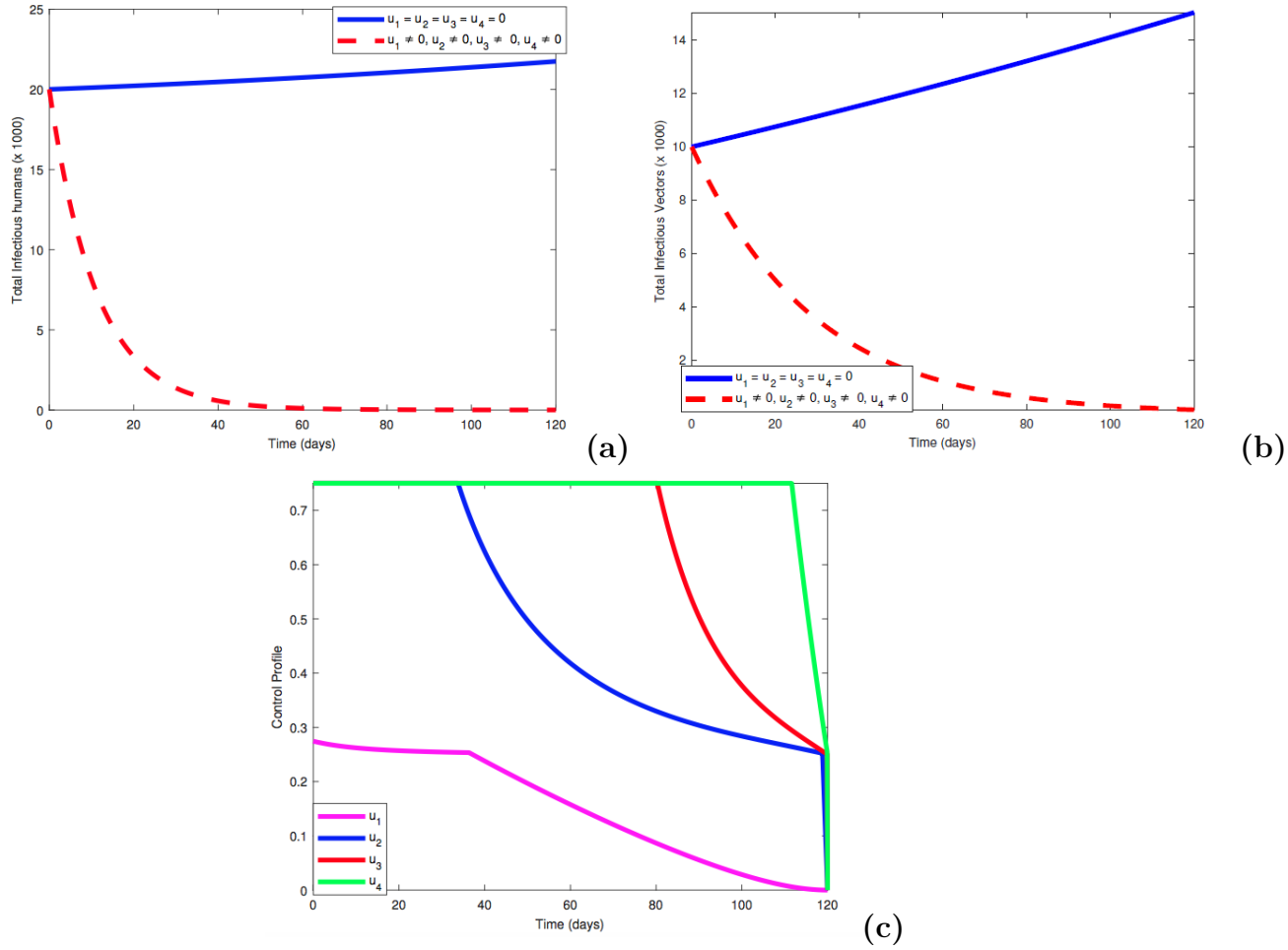

Figure 10: Simulations of the model showing the effect of all controls on transmission

4.9 Cost-Effectiveness Analysis

In order to quantify the cost-effectiveness of the control strategies, the cost effectiveness ratio of these strategies is examined. So that we can draw our conclusions. Using Average Cost-Effectiveness Ratio (ACER) which deals with a single intervention and evaluates that intervention against its baseline option (e.g. no intervention or current practice). It is calculated by dividing the net cost of the intervention by the total number of health

outcomes prevented by the intervention (see [15]) and using the parameter values as in table (4.1).

Strategies	Total infection averted	Total costs ($)	ICER
Strategy B	$25,000$	$2630	9.506
Strategy D	$25,200$	$3560	
Strategy G	$25,300$	$3970	
Strategy F	$34,700$	$3360	
Strategy I	$34,800$	$4460	
Strategy J	$34,800$	$4819	

The ICER, is calculated as follows:

$$\begin{aligned} \text{ICER(B)} &= \tfrac{25{,}000}{2630} = 9.506 \\ \text{ICER(D)} &= \tfrac{25{,}200-25{,}000}{3560-2630} = 0.0606 \end{aligned} \tag{4.22}$$

The comparison between strategies B and D shows a cost saving of $0.0606 for strategy D over strategy B. The lower ICER for strategy D indicates that strategy B is "strongly dominated". That is, strategy B is more costly and less effective than strategy D. Therefore, strategy B is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs ($)	ICER
Strategy D	$25,200$	$3560	7.0787
Strategy G	$25,300$	$3970	0.2439

The comparison between strategies D and G shows a cost saving of \$0.2439 for strategy G over strategy D. Similarly, the high ICER for strategy D indicates that strategy D is "strongly dominated". That is, strategy D is more costly and less effective than strategy G. Therefore, strategy D is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs (\$)	ICER
Strategy G	$25,300$	\$3970	6.3728
Strategy F	$34,700$	\$3360	-15.4098

The comparison between strategies G and F shows a cost saving of $\$ - 15.4098$ for strategy F over strategy G. The negative ICER for strategy F indicates that strategy G is "strongly dominated". That is, strategy G is more costly and less effective than strategy F. Therefore, strategy G is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs (\$)	ICER
Strategy F	$34,700$	\$3360	10.3274
Strategy I	$34,800$	\$4460	0.0909

The comparison between strategies F and I shows a cost saving of \$0.0909 for strategy I over strategy F. Similarly, the high ICER for strategy F indicates that strategy F is "strongly dominated". That is, strategy F is more costly and less effective than strategy I. Therefore, strategy F is excluded from the set of alternatives so it does not consume limited resources.

We recalculate ICER

Strategies	Total infection averted	Total costs ($)	ICER
Strategy I	$34,800$	$4460	7.8027
Strategy J	$34,800$	$4819	0

With this result, we conclude that strategy there is no significant different between strategy I and J. Since the ICER for strategy J is zero, therefore is strategy J is not more cost-effective than strategy I. It is clear therefore that strategy I and J can achieve the same results, hence we suggest that strategy I be adhere in order to minimize cost due to lose of immunity control.

4.10 Conclusion

In this study, we have derived and analyzed a deterministic model for the transmission of schistosomiasis and also performed optimal control analysis of the model. Furthermore, the various conditions for the optimal control of the disease were derived and analyzed. We showed the existence of multiple endemic equilibria when $\mathcal{R}_{sc} < 1$, suggesting the possibility of backward bifurcation, whereby the stable DFE co-exists with a stable endemic equilibrium when the reproduction number is less than unity. The occurrence of a backward bifurcation observed has an important implication for epidemiological control measures and effective eradication of schistosomiasis, Ro should be less than a critical value less than one. Also, achieving this may be too expensive, because it means that for steady and constant controls, there is a need to keep employing all the control measures: prevention, vaccination, treatment and snail control. Optimal control techniques and time-dependent controls as way of eradicating the disease in a limited time were applied showing that disease eradication will be possible and optimal in the human population

when one of the control strategies is employed.

However, where there is limited budget or resources to implement the control strategies, it is therefore imperative to determine the most effective strategy to control the disease with minimum costs. In conclusion, this study suggests that where there are limited resources, public health policy makers may adopt disease control strategy that combines prevention, treatment and snail control over that which combine vaccination, prevention, treatment and snail control. This is due to the additional cost of controlling loss of immunity by vaccination.

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Author Contributions

The authors have contributed equally for the production of this manuscript.

Conflicts of Interest: There is no competing interest regarding the production of this manuscript.

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Chapter 5

GENERAL DISCUSSION

The crippling impact from schistosomiasis and its complications triggered by fragile socio-economic factors, poor public health care and environmental factors among others is at an alarming rate in sub-Sahara Africa and other poor nations of the world. Recently, it has been hypothesized that in the next century, global warming will pose a serious threat on disease pathogens and their animal or human hosts. Schistosomiasis is a vector and water-borne disease whose transmission has been predicted to be strongly dependent on climate variability. Thus, the current study presents the theoretical modeling of temperature and rainfall on schistosomiasis population dynamics over South Africa.

Chapter one of this dissertation is a compilation of the full insight into the introduction, problem statement, research questions, aim and objectives of the study. In chapter two, an article elucidating the relationship between climate change and snail-schistosome cycle as predictive targets in reducing and controlling schistosomiasis transmission was reviewed. In this article, the mechanism of how climate variability plays a major role in the reoccurrence of schistosomiasis and the exponential increase in population dynamics of the disease transmission, as well as outbreaks of the disease in SSA was reviewed. More so, it was averred that the impact of climate change on the population dynamics of schistosomiasis

may support the schistosome parasite life cycle through the production, survivability and mortality or fecundity rate of both freshwater snails (Bulinus, Biomphalaria, Oncomelania and Tricula) and schistosomes (*S. mansoni, S. japonicum, S. haematobium*) in the water body. This assertion was supported by several biological and experimental models, which showed that different stages of Schistosoma species in freshwater, and the lifecycle of *Schistosoma species* in the snail intermediate host, as well as the rate of mortality in snails is temperature sensitive and dependent.

Furthermore, the effect of temperature and rainfall on schistosomiasis transmission over South Africa was investigated in chapter three. In this chapter, it was discovered that temperature fluctuations over South Africa will enhance the population dynamics of the disease. More so, it was observed that freshwater snail hosts are more susceptible to seasonal variability within the period of 2000 days thereby, posing great influence on snail population dynamics. The sensitivity of both human and snail population to temperature was carried out in order to have better understanding of the relationship between temperature and human-snail dynamics. Here, it was shown that schistosomiasis dynamics is more sensitive to 20^oC when compared to other temperatures of 25, 30, 35 and 40^oC, which correlates with other experimental schistosomiasis-based models in which the optimum temperature for the reproductive, mortality and growth rates of freshwater snail falls within 19.9^oC 22^oC (Barbosa *et al.,* 1986; Kubiriza *et al.,* 2010; McCreesh *et al.,* 2014; Okeeffe, 1985).

Additionally, the seasonal cycles of infectious diseases have been ascribed to changes in the atmospheric conditions, which alter the behavioural conditions of the intermediate host (Dowell, 2011). In view of this, the seasonality of schistosomiasis transmission over South Africa was determined using numerical simulation by studying the behavioural condition of freshwater intermediate snail hosts for the disease. Results from this study

found out that there is more reproduction or fecundity of snails during summer (December to February), little reproduction or fecundity of snails during spring (September to November) and autumn (March to May), while there was no production of snails during winter (June to August). This may be due to inability of snails to withstand high cold conditions during winter periods hence; they undergo a process called overwintering to keep them alive during this period. This result is in agreement with other studies that have shown the effects of low temperatures to have diminishing survival rates of snails (*B. globosus, B. africanus* and *B. pfeifferi*). Hence, in order for the snails to survive and acclimatize to low temperatures as experienced during winter, there is need to increase the production of low molecular weight compounds (Matsukura *et al.,* 2008; Wada and Matsukura, 2011), which are known to prevent protein denaturation by hydrogen-bonding, averts membrane damage by inhibiting lipid phase transition, and also reduces cuticular water loss by binding water at the cuticular basement of the membrane, thereby favouring the survival of snails. In addition, up-regulation of heat shock proteins in molluscs assist the tolerance to both low and high-temperatures as they help in repairing or preventing thermal damage to proteins (Wada and Matsukura, 2011). The physiological increase in the concentration of glycerol in form of polyol and decrease in glycogen concentration in bodies of cold-tolerant snails help them to withstand the winter season (Matsukura *et al.,* 2008; Wada and Matsukura, 2011).

In the same vein, several control measures were introduced into the existing schistosomiasis climate-based model formulated in chapter three and was described in chapter four. This was done in order to understand the best control strategies to eradicate the transmission of the disease. The four control measures studied include vaccination (production of vaccine, campaign and sensitization of the public about vaccine), prevention (environmental control), treatments (administration of available drugs) and snail control

(the use of plant molluscicides). These control strategies were considered to be time-dependent in order to ascertain the best optimal control strategy for the eradication of schistosomiasis. After performing the stability analysis of the model, it was discovered there is an existence of multiple endemic equilibra when $\mathcal{R}_{sc} < 1$, suggesting the possibility of backward bifurcation when the stable disease-free equilibrium co-exist with a stable endemic equilibrium when the reproduction number is less than 1. The presence of backward bifurcation found in the stability analysis of the endemic equilibrium is an essential indication that the system possesses an epidemiological control, which will be effective in controlling the population dynamics of schistosomiasis. This is due to the fact that for a disease-free equilibrium of the model to be epidemiological relevant, the Ro should be less than a critical value below 1. Thereafter, a time dependent optimal control technique was employed in determining the best optimal control strategies that can wipe out the disease within a short period of time. This is done because the application of all the proposed or introduced control may be costly to achieve due to steady and constant implementation. Thus, it was observed from the control analysis that the eradication of the disease will be possible and optimal in human population when one of these control strategies is employed B, D, F, G, I and J. Although, the best control strategies with minimum cost in a situation where there is limited budgets or resources in eradicating the disease transmission was determined using cost-effectiveness study. Here, it was discovered that control strategy I (combination of prevention, treatment and snail control) will save more cost where there are limited resources over J (combination of vaccination, prevention, treatment and snail control), which includes an additional cost for vaccination to activate immune response. This is needed for as times goes by, vaccination may undergo what is known as immune waning. This study perfectly corroborated results from other studies which have shown diverse effects of vaccination or vaccine on normal immune response

against pathogens (Barbarossa and Rost, 2015; Hamami *et al.,* 2017; Kontio *et al.,* 2012; Leuridan *et al.,* 2010). In particular, Leuridan and co-workers (2010) investigated the duration of the presence of early waning of maternal antibodies to measles elimination in infants from five hospitals in Antwerp, Belgium. It was shown from this study that there are significantly fewer IgG antibodies in vaccinated women when compared with naturally immune women. More so, the infants of vaccinated women possess significantly lower antibody concentrations when compare to the infants of naturally immune women, and that the presence of maternal antibodies endured for a median of 2.61 to 3.78 months for the infants of naturally infected women, while the infants of vaccinated women could only endure for 0.97 months (Leuridan *et al.,* 2010).

5.1 CONCLUSION

This study has examined the impact of temperature and rainfall on schistosomiasis transmission using a climate-based mathematical model, as well as the impact of treatment, prevention, vaccination and snail control was investigated on the burden of schistosomiasis. Moreover, the cost-effectiveness and the determination of appropriate optimal control strategy for schistosomiasis eradication were also examined. Numerical simulations generated results that gave a clear indication that climate variability contributes to the increase in the reproduction number of schistosomes and snails. It was also observed that the transmission of the disease is seasonally dependent. On the whole, it can be concluded from the numerical results and cost effectiveness analysis that the optimal strategy to effectively and efficiently control schistosomiasis is the combination of prevention, treatment, vaccination and snail control and in a situation where there are limited resources; a strategy combining prevention, treatment and snail control may be adopted

by policymakers.

5.2 FUTURE STUDY AND RECOMMENDATION

The present study did not consider the influence of factors such as drug resistance on the population dynamics of schistosomiasis if incorporated into the model. This is necessary as drug resistance is able to influence the susceptibility of freshwater snail to this factor. Co-infection is another factor whose effect on infectious diseases population dynamic cannot be overemphasizing in the present day. Therefore, the study of co-infection of schistosomiasis with morbidities like HIV/AIDS, cancer, tuberculosis and listeriosis among others, will allow for better understanding and best control strategy to manage schistosomiasis. Other further studies include, the examination and prediction of possible genetic modifications and biochemical changes of *Schistosoma. species* due to temperature and rainfall.

Additionally, based on the findings of this present study, it can be recommended that knowledge concerning schistosomiasis; the impact of the disease, motivation and intervention, as well as behavioural change will lead to a better and effective eradication of the disease. Therefore, all hands must be on desk in order to develop and design new therapeutic drug that can cater for infection and re-infection of schistosomiasis, as well as drugs that can reduce the burden of resistance by schistosomes against praziquantel. More so, plants with molluscicidal activities should be identified, especially around water banks where transmission of schistosomes is suspected, in order to reduce the population of freshwater snails.

5.3 References

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