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A mathematical modelling framework for linked within-host and between-host dynamics for infections with free-living pathogens in the environment

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ABSTRACT

In this study we develop a mathematical modelling framework for linking the within-host and between-host dynamics of infections with free-living pathogens in the environment. The resulting linked models are sometimes called immuno-epidemiological models. However, there is still no generalised framework for linking the within-host and between-host dynamics of infectious diseases. Furthermore, for infections with free-living pathogens in the environment, there is an additional stumbling block in that there is a gap in knowledge on how environmental factors (through water, air, soil, food, fomites, etc.) alter many aspects of such infections including susceptibility to infective dose, persistence of infection, pathogen shedding and severity of the disease. In this work, we link the two subsystems (within-host and between-host models) by identifying the within-host and between-host variables and parameters associated with the environmental dynamics of the pathogen and then design a feedback of the variables and parameters across the within-host and between-host models using human schistosomiasis as a case study. We study the mathematical properties of the linked model and show that the model is epidemiologically well-posed. Using results from the analysis of the endemic equilibrium expression, the disease reproductive number R_0, and numerical simulations of the full model, we adequately account for the reciprocal influence of the linked within-host and between-host models. In particular, we illustrate that for human schistosomiasis, the outcome of infection at the individual level determines if, when and how much the individual host will further transmit the infectious agent into the environment, eventually affecting the spread of the infection in the host population. We expect the conceptual modelling framework developed here to be applicable to many infectious disease with free-living pathogens in the environment beyond the specific disease system of human schistosomiasis considered here.

1. Introduction

The disciplinary separation of immunology, epidemiology of infectious diseases and environmental health have hampered progress on research of infectious diseases. Because of this disciplinary separation, traditional approaches to studying infectious diseases through mathematical modelling are largely based on the idea that diseases consist of dynamic processes across temporal, spatial and biological scales and that specific models can be developed to study a particular disease system at a particular scale. Two dominant disciplinary fields that address the modelling of subsystems relevant to the study of infectious diseases include mathematical modelling of between-host dynamics of infectious disease transmission (see [1–9] and references therein) (mathematical models of infectious disease transmission) and mathematical modelling of within-host dynamics of infectious diseases (see [13–19] and references therein) (modelling pathogen–immune interactions). At the larger scale of mathematical modelling of between-host modelling of infectious diseases, models have been developed in the past to aid public health decision makers to make strategic decisions about control of infectious diseases (see for example [10–12] and references therein). The standard approach in these models is to classify the host population into compartments within which individuals behave homogeneously. These models have been used to aid understanding of the disease transmission dynamics and increase our capabilities for control of infectious diseases with fewer resources. At the smaller scale (pathogen–immune interactions level) of the within-host dynamics of

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infectious diseases, mathematical models have been developed to study the interaction of the pathogen and the immune system in order to elucidate the mechanisms and outcomes of infection within a single host (see for example [20] and references therein). These models are mainly based on ordinary differential equations describing the evolution in time of the number of immune cells, pathogens and target cells. However, we are still missing a general theory of how to link the within-host and between-host dynamics of infectious diseases. This situation has opened up gaps in knowledge and missed opportunities for understanding and predicting disease risks as well as designing interventions and preventive health programs. The general framework will greatly aid interpretation of data, and provide insight into a number of issues pertaining to infectious diseases such as persistence of infection, virulence and infectivity. From a theoretical point of view, the most appropriate way to facilitate the task of linking within-host and between-host dynamics of infectious diseases is to identify in each sub-system variables or parameters that affect the dynamics of the other sub-system, and then design a feedback of these variables or parameters across models in a consistent way. Therefore, capturing how the dynamics at a given scale affect and are affected by those at the other scale is the specific challenge at hand in the mathematical modelling of linked within-host and between-host dynamics of infectious diseases. Recent efforts to link the within-host and between-host dynamics of infectious diseases include [21–46]. In the context of deterministic mathematical modelling, we have, to date witnessed the development of four different coupling principles that organise and inform the research that lead to linked mathematical models of the within-host and between-host dynamics of infectious diseases which are as follows.

1. *Linked through nesting principles*: Here the linking of the within-host and between-host models is achieved through a nested modelling approach [27–36]. This is done in three stages. The first step in this approach is to develop a within-host model. The second step is to define an epidemiological model (between-host model). The third and final step is to nest the within-host model within an epidemiological model by linking the dynamics of the within-host model to the epidemiological model through either a structural variable or parameter of the epidemiological model. In the case of linking the within-host dynamics to an epidemiological model through a structural variable (of the epidemiological model), the epidemiological model must be structured through time-since-infection [34]. The time since-infection is then used as an independent variable in the immunological model, which is valid only in the infected epidemiological model compartment. In the case of linking within-host dynamics model to an epidemiological model through parameters, the parameters of the epidemiological model are expressed as functions of the dependent variables of the immunological model (within-host model). For example, transmission rate may be assumed to be a function of the parasite load, or disease induced mortality may be assumed to be a function of the parasite load and the immune system [33].
2. *Linked through network modelling principles*: This modelling framework is achieved through developing a within-host model first and then modify this model by placing each individual in the population within a simple randomly distributed network of N people such that the pathogen load variable of a given individual is linked with the pathogen load variable of adjacent individuals within the network [35–37]. This is achieved by making an assumption that the rate at which a person's incoming flow of free pathogen particles is proportional to the pathogen load of their neighbours.
3. *Linked through developing a within-host inspired between-host model*: In this modelling framework, the link is based on developing a physiologically structured epidemiological model [39–45]. The physiological aspect normally considered here is cellular and their genetic variations (immune response) and how they modulate infection and disease progression. Very often, this task is accomplished through subdividing the entire population of the hosts into various sub-classes corresponding to different levels of immune protection: naive or completely susceptible, completely or partially immune, vaccinated, immune compromised (e.g. due to HIV co-infection) or protected from infection due to certain genetic factors. Modelling the dynamics of the distribution of humans with regard to their immune status in this way is a critical step in understanding the relationship between the dynamics of recurrent infections and the dynamic variability of the acquired immunity to these diseases within a host population [44].
4. *Linked through environmental contamination*: This is the case for infections with free-living pathogens growing in the environment [46]. In this case, the disease triad: host, pathogen and a contaminated environment (such as water, air, food, soil, objects or contact surfaces) must be present and interact appropriately for the infectious disease to occur. The linking here of within-host and between-host dynamics is based on the idea that disease process time-scales here can be separated into three distinct times scales. The first disease process time scale is at the within-host (individual host) level. It is related to the reproductive cycle of the pathogen within the host and its interaction with the host immune system. This disease process typically occurs on a fast time-scale. The second disease process time-scale is the one associated with infection between individuals, that is, the epidemiological time-scale (between-host time scale) that takes place according to contacts of susceptible hosts and the free-living pathogen in the environment. This disease process typically occurs at an intermediate time-scale. The third disease process time-scale is the environmental time-scale. For infections with free-living pathogens in the environment, the environment is an important driver. For such infections, the pathogen may survive in the environment for some time, and further, the abundance of the pathogen in the environment is occasionally replenished by infectious hosts that excrete the pathogen into the environment. This disease process typically occurs at a slow time-scale. This third disease process time-scale is the key to providing a functional link for with-host and between-host models of infectious diseases. We show in this work that the linking of with-host model and between-host model is structured by both pathogen load within an infected host and the density/number of infected/infectious hosts. This linking approach of with-host and between-host models has been previously proposed in [46] based on an arbitrary functional form. Using human schistosomiasis as an example, we demonstrate the approach here based on explicit consideration of the biology of the disease. The focus in this work is on clarifying the determination of the functional form of the linkage between the within-host and between-host disease dynamics and how this encapsulates the underlying biology of the disease process.

The obvious distinction between models for other diseases and those infectious diseases with free-living pathogens in the environment is that the latter usually have at least one extra equation describing the dynamics of parasite in the environment. From a theoretical point of view, this paper is about the role this extra equation plays in linking the within-host and between-host dynamics of infectious diseases with free-living pathogens in the environment. This paper is organised as follows. In Section 2 we

discuss the different transmission cycles for infections with free-living pathogens in the environment. We further present the mathematical model of linked within-host and between-host dynamics of human schistosomiasis in Section 3 and also establish the feasible region of the solutions of the model in Section 3. In Section 4 we calculate the reproductive number of the model and use it to establish the local and global stability of the disease-free equilibrium. This is followed by Section 5 where we show the existence of the endemic equilibrium and go on to prove its local stability. The effects of the environment on the transmission of human schistosomiasis are discussed in Section 6. The model is analysed using numerical methods in Section 7 and the paper ends up with conclusions in Section 8.

2. Transmission of infections with free-living pathogens in the environment

For infectious diseases with free-living pathogens in the environment, the environmental influences (biological, geophysical, economic and social) on disease transmission chains are fundamental to understanding these complex diseases. An estimated 24% of the global disease burden and 23% of death can be attributed to environmental factors [47–53]. Infectious diseases with the largest absolute burden attributable to modifiable environmental factors include diarrhea, lower respiratory infections and malaria [47–50]. To reflect on the idea that the environment serves as a reservoir of infectious free-living pathogens for infection of human, animals and plants [54,55], we hypothesise four different groups of transmission cycles that result in infections with the environment acting as a reservoir of infectious free-living pathogens. Fig. 1 is a conceptual representation of the four different groups of transmission cycles for infections with free-living pathogens in the environment. The first group (see Fig. 1(a)) includes infectious diseases for which the environment (e.g. food, water, air, soil) play a significant role in the pathogen transmission cycle. Here transmission occurs between humans and the environment directly. No other host animal or vector are involved. The second group (see Fig. 1(b)) still includes infectious diseases for which the environment (as in the first group) still plays a significant role in the pathogen's transmission cycle. The difference with the first group is that although the environment still remains an integral part of the transmission chain, an animal host mediates the transmission. The third group (see Fig. 1(c)) still includes infectious diseases for which the environment (as in the second group) still plays a significant role in the transmission cycle. The difference with the second group is that although the environment still remains an integral part of the transmission chain, a vector (instead of an animal host) mediates the transmission. The fourth group (see Fig. 1(d)) includes some pathogens that cause zoonotic diseases. Here humans are the dead end hosts and no person-to-person transmission is possible. The group includes non-vector-borne zoonotic diseases in which pathogens are transmitted indirectly through the environment or directly from a host to the human.

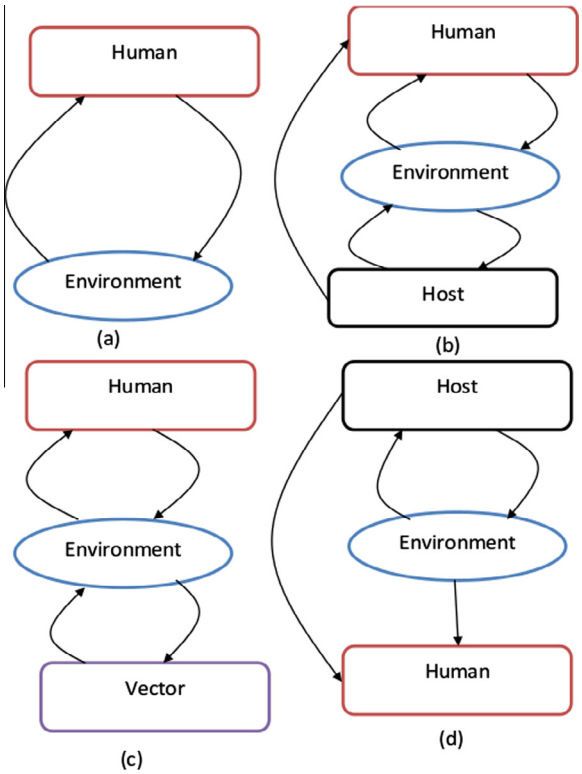

Fig. 1. A conceptual diagram showing the four different groups of transmission cycles for infections with free-living pathogens in the environment.

Human schistosomiasis was chosen in this study as a conceptual framework for the mathematical modelling of linked within-host and between-host dynamics of infections with free-living pathogens in the environment partly because of the simplicity of its transmission chain where the human and snail hosts do not interact with each other directly except through the shared schistosome parasites (see Fig. 1(c)) in the physical water environment and also partly because of the availability of preliminary work on single scale modelling approaches [19,58] of human schistosomiasis infection in an appropriate form for infections with free-living pathogens in the environment.

Human schistosomiasis, mediated by the water-borne schistosome parasite is a global health concern, being the third most devastating tropical disease in the world after malaria and intestinal helminthiasis [60–66]. Most schistosomiasis infections occur in resource-limited settings with more than 200 million people being infected with schistosomiasis of which 85% live in Africa, while globally an estimated 200,000 deaths are attributable to schistosomiasis annually [66,63]. The major forms of human schistosomiasis are caused by species of the water-borne flatworm or blood flukes called schistosomes, but the three most commonly found are *Schistosoma mansoni*, *Schistosoma japonicum*, and *Schistosoma haematobium*. *S. haematobium* affects the urinary tract and kidneys, as well as the reproductive systems and is concentrated in Africa and the Middle East. *S. mansoni* is the most widespread while *S. japonica* is primarily found in Asia and these two cause chronic hepatic and intestinal fibrosis [63]. The life cycle of the schistosome parasite is complex [60–66]. The complexity of the life cycle of the schistosome parasite includes three factors: (a) multiple interacting hosts (human and snail hosts), (b) multiple infective pathogenic species (miracidia and cercariae), and (c) structural complexity of the environmental domains (biological, geographical, economic, and social) in which transmission occurs. For more information about the complex life cycle of human schistosomiasis the published works [60–66] provide more details. Only a brief description is provided in this section. The reproductive cycle of schistosomiasis starts with parasitic worm eggs released into freshwater through faeces and urine. The schistosome eggs produced by the sexual stage leave people via urine or faeces, reach freshwater, shed their shells and hatch a ciliated free-swimming larva called a miracidium that seek out to infect certain species of snail that serve as intermediate host [66]. A miracidium that locates an appropriate species and genotype snail, penetrates and infects it, multiplies asexually through two larval stages into thousands of free-living cercariae that escape the snail and live

in water. The infected snails release cercariae 4–6 weeks after infection [63]. The cercariae swim until they encounter a skin of suitable warmth and smell, and infect humans by direct penetration of the skin. Once the cercariae penetrate the skin, they lose their tails and differentiate into larval forms called schistosomulae.

A schistosomulum spends several days in the skin before exiting via blood vessels traversing to the lung, where it undergoes further developmental changes. It then migrates via the systematic circulation to the liver where it settles, reaches sexual maturity and pairs. Only those worm pairs that reach the portal system of the liver mature into adults [63]. Thereafter, worm pairs migrate by the bloodstream to their definitive location; *S. mansoni* and *S. japonicum* to the small and large intestines and *S. haematobium* to the bladder and rectal veins [63]. The worms lay thousands of eggs that cause damage as they work through tissues. The eggs, which are highly antigenic and can induce an intense granulomatous response, migrate through the bowel or bladder wall to be shed via faeces or urine. The eggs, released into the water in urine or faeces, restart the cycle.

3. The mathematical model

The model that we formulate traces explicitly the life-cycle of the schistosome parasite in three different environments which are the physical water environment (which is also affected by the physical climatological environment), the physical land environment, the human biological environment (within-host parasite dynamics). The full model is based on monitoring the dynamics of the twelve populations at any time t which are susceptible humans $S_H(t)$, and infected humans $I_H(t)$ in the behavioural human environment, susceptible snails $S_V(t)$ and infected snails $I_V(t)$ in the physical water environment, cercariae $P_W(t)$, miracidia $M(t)$ and worm eggs $E_W(t)$, in the physical water environment, cercariae $P_H(t)$, immature schistosome worms $W_I(t)$, mature schistosome worms $W_P(t)$ and worm eggs $E_H(t)$ in the biological human environment (within host parasite dynamics) and worm eggs $E_L(t)$, in the physical land environment. A summary of model variables is given in Table 1 here, while a summary of parameter values is given in Tables 2–4 in Section 7.

We make the following assumptions for the model:

i. There is no vertical transmission of the disease.
ii. The transmission of the disease in the snail and human populations is only through contact with infective free-living pathogens (miracidia, $M(t)$ and cercariae $P_W(t)$ respectively) in the physical water environment.
iii. There is no immigration of infectious humans.
iv. Seasonal and weather variations do not affect snail populations and contact patterns.
v. Infected snails do not reproduce due to castration by the miracidia.
vi. There is no immune response in both snail and human populations.
vii. The human host is assumed to be healthy, has not been previously exposed to the disease and has no immunity to infection.
viii. Infected snails and humans do not recover naturally from the infection/disease.
ix. Mature worms $W_P(t)$, migrate from the liver only as pairs and that those that fail to locate a partner will, with time, die a natural death and therefore will not participate in producing eggs, making their contribution to pathology irrelevant.
x. When a mature worm dies, its former partner does not remate, and the contribution of the pair to pathology is lost, so we assume a pair death for mature worms for simplicity.

At any time t, new recruits enter the human and snail populations through birth at constant rates Λ_H and Λ_V respectively. There is a constant natural death rate μ_H and μ_V in the human and snail populations respectively. Infected human hosts have an additional mortality of δ_H. Similarly, infected snails have an additional mortality δ_V. $N_H(t)$ is the total human population and is given by

$$N_H(t) = S_H(t) + I_H(t). \tag{3.1}$$

Susceptible humans acquire schistosomiasis through infection by cercariae in the physical water environment at rate $\lambda_H(t)$ where

$$\lambda_H(t) = \frac{\beta_H P_W(t)}{P_0 + \epsilon P_W(t)}, \tag{3.2}$$

with β_H being the maximum rate of exposure; ϵ is the limitation of growth velocity of cercariae with the increase of cases; P_0 is the half saturation constant. From the functional response, we notice that at low parasite densities, contacts are directly proportional to host densities.

$N_V(t)$ is the total snail population and is given by

$$N_V(t) = S_V(t) + I_V(t). \tag{3.3}$$

Similarly, susceptible snails acquire schistosomiasis through infection by miracidia in the physical water environment at rate $\lambda_V(t)$ where

$$\lambda_V(t) = \frac{\beta_V M(t)}{M_0 + \epsilon M(t)}, \tag{3.4}$$

with β_V being the maximum rate of exposure; ϵ is the limitation of growth velocity of miracidia with the increase of cases; M_0 is the half saturation constant. From the functional response, we also notice that at low parasite densities, contacts are directly proportional to host densities.

Table 1
Summary of variables used in the model.

Variable	Variable description	Initial value
$S_H(t)$	The susceptible human population size in the behavioural human environment	200,000
$I_H(t)$	The infected human population size in the behavioural human environment	2000
$S_V(t)$	The susceptible snail population size in the physical water environment	40,000
$I_V(t)$	The infected snail population size in the physical water environment	3000
$P_H(t)$	The cercariae population size in the biological human environment	200
$W_I(t)$	The immature worm population size in the biological human environment	30
$W_P(t)$	The mature worm population size in the biological human environment	0
$E_H(t)$	The worm eggs population size in the biological human environment	0
$E_L(t)$	The worm eggs population size in the physical land environment	40
$E_W(t)$	The worm eggs population size in the physical water environment	40
$M(t)$	The miracidia population size in the physical water environment	20
$P_W(t)$	The cercariae population size in the physical water environment	50

Table 2
Between-host parameter values for model system (3.9).

Para-meter	Meaning	Initial value	Range explored	Units	Source/rational
Λ_H	Supply of susceptible humans	800	800–1600	humans day^{-1}	Assumed
Λ_V	Supply of susceptible snails	2500	2500–5000	snails day^{-1}	Assumed
μ_H	Natural death rate of humans	0.0000384	0.0000384–0.14	day^{-1}	[67]
μ_V	Natural death rate of snails	0.0014	0.000569–0.9	day^{-1}	[59]
δ_H	Disease induced death rate of humans	0.0013699	0.0039–0.039	day^{-1}	[64]
δ_V	Disease induced death rate of snails	0.002	0.002–0.05	day^{-1}	[56]
β_H	Maximum exposure rate of Humans	0.028	0.028–0.122	day^{-1}	[56]
β_V	Maximum exposure rate of Snails	0.000127	0.000127–0.0012	day^{-1}	[56]

Table 3
Within-host parameter values for model system (3.9).

Para-meter	Description	Initial value	Range explored	Units	Source/rational
α_C	Migration rate of cercariae from skin to lung	0.33	0.33–0.997	day^{-1}	Estimated
μ_C	Natural death rate of cercariae	0.003	0.003–0.004	day^{-1}	Estimated
α_I	Migration rate of immature worms from skin to lungs	0.0004	0.0004–0.4	day^{-1}	Estimated
μ_I	Natural death rate of immature worms	0.000685	0.0005–0.5	day^{-1}	[65]
α_P	Migration rate of mature worms from skin to lungs	0.0004	0.0004–0.4	day^{-1}	Estimated
μ_P	Natural death rate of mature worms	0.000183	0.000183–0.0003	day^{-1}	[62]
N_P	Number of eggs produced	300	300–2000	worm^{-1} day^{-1}	[58]
α_E	Excretion rate of eggs into environment	0.0004	0.0004–0.4	day^{-1}	Estimated
μ_E	Natural death of worm eggs	0.0025	0.000685–0.005	day^{-1}	[66]

Table 4
Free-living pathogens and their associated environmental parameter values for model system (3.9).

Para-meter	Description	Value	Range explored	Units	Source/rational
μ_L	Death rate of eggs on land	0.2	0.142857–0.5	day^{-1}	[19]
α_W	Rate at which eggs hatch in water	0.05	0.05–0.0625	day^{-1}	[57]
μ_W	Death rate of eggs in water	0.11	0.11–0.833	day^{-1}	[57]
N_W	Number of miracidia produced from each worm egg	110	110–500	day^{-1}	[57]
μ_M	Death rate of miracidia	2.2	2–2.66	day^{-1}	[57]
γ_S	Rate at which infected snails become cercariae shedding	0.02	0.0119–0.04	day^{-1}	[56]
μ_S	Rate at which cercariae die	0.4	0.33–0.5	day^{-1}	[65,56]
N_S	Number of cercariae produced	4128	2476–8400	snail^{-1} day^{-1}	[56]
M_0	Saturation constant of miracidia	100^{500}	–	–	Estimated
P_0	Saturation constant of cercariae	100^{6}	–	–	Estimated
ϵ	Limitation of growth velocity of cercariae with the increase of cases	0.6	–	–	Estimated

Considering the average cercariae population within a single infected human host $P_H(t)$, we note that this population is generated following uptake of cercariae through cercariae skin penetration of the human host. In the general population, this uptake of cercariae through skin penetration is actually the transmission of the cercariae pathogen from the physical water environment to susceptible humans at a rate of $\lambda_H(t)S_H(t)$ resulting in $I_H(t)$ infected humans. Therefore, in general, a single susceptible human host will uptake cercariae at an average rate of

$$\frac{\lambda_H(t)S_H(t)}{I_H(t)}, \tag{3.5}$$

where $\lambda_H(t), S_H(t)$ and $I_H(t)$ are as defined previously. In our modelling of the mean cercariae population within a single infected human host $P_H(t)$, we further assume that the event of cercariae uptake through skin penetration of a single human host in a population with $S_H(t)$ susceptible humans, $I_H(t)$ infected humans and $P_W(t)$ cercariae load happens through a single transition defined by

$$\begin{aligned}(S_H(t), I_H(t), P_W(t)) &\to (S_H(t)-1, I_H(t)+1, P_W(t))\\ &= (S_h(t), I_h(t), P_W(t)).\end{aligned} \tag{3.6}$$

Therefore, the average rate of uptake of cercariae by a single susceptible human host through skin penetration is modelled by $\lambda_h(t)S_h(t)$ resulting in one infected human host where

$$\lambda_h(t) = \frac{\beta_H P_W(t)}{(P_0 + \epsilon P_W(t))I_h(t)}, \quad S_h(t) = S_H(t) - 1,$$
$$I_h(t) = I_H(t) + 1. \tag{3.7}$$

In Eq. (3.7) β_H, ϵ and P_0 remain as in the previous definitions. This implies that the mean cercariae population within a single infected human host $P_H(t)$, increases at a variable mean rate given by

$$\frac{\lambda_H(t)S_h(t)}{I_h(t)} = \lambda_h(t)S_h(t). \tag{3.8}$$

Skin penetration by cercariae causes a local inflammatory response evidenced by a rash, called swimmer's itch, which is believed to involve immediate and delayed hypersensitivity reactions. The mean cercariae population within a single infected human host $P_H(t)$, is assumed to decay through natural death at a constant rate μ_C and to exit the skin to the lung via blood vessels at a rate α_C, where they undergo developmental changes to become immature worms.

The mean population of immature worms $W_I(t)$, within a single infected human host is generated following developmental changes undergone by cercariae to become immature worms at a rate α_C. These immature worms are assumed to die naturally at a rate μ_I and migrate to the liver at a rate α_I.

The mean population of mature worms $W_P(t)$, within a single infected human host is generated following developmental

changes undergone by immature worms to become mature worms at a rate $\frac{\alpha_I}{2}$. These developmental changes result in immature worms reaching sexual maturity, pairing up and then migrating, through the blood stream to their definitive locations. The introduction of the fraction $\frac{1}{2}$ multiplying the parameter α_I models the pairing of immature worms on reaching sexual maturity. We assume that mature worms die naturally at a rate μ_P and migrate to their definitive locations at a rate α_P.

The mean population of schistosome eggs $E_H(t)$, within a single infected human host is generated through each worm pair laying an average of N_P eggs per day having migrated to its definitive location at a rate α_P. We model the rate at which these eggs die inside the human body by the parameter μ_E and the rate at which they are excreted by the human host into the physical land environment by α_E.

The population of schistosome eggs $E_L(t)$, contaminating the physical land environment is generated following excretion of schistosome eggs by the human host in either urine or faeces into the physical land environment. We note that each infected human host excretes these eggs at a rate $\alpha_E E_H(t)$ and for a total of $I_h(t)$ infected humans, the rate of contamination of the physical land environment by schistosome eggs becomes $I_h(t)\alpha_E E_H(t)$. These schistosome eggs are assumed to die naturally at a rate μ_L and to be washed away by running water into the physical water environment at a rate α_L.

The population of schistosome eggs $E_W(t)$, in the physical water environment is generated following inflow of schistosome eggs in running water from the contaminated physical land environment into the physical water environment at a rate α_L. We assume that these eggs die naturally in the physical water environment at a rate μ_W and hatch at a rate α_W releasing an average of N_W miracidia per egg into the physical water environment.

The population of miracidia $M(t)$, in the physical water environment is generated through each egg hatching an average of N_W miracidia with eggs hatching at an average rate of α_W so that the total miracidia population in the physical water environment is modelled by $N_W\alpha_W E_W$. We assume that miracidia in the physical water environment die naturally at a rate μ_M.

The cercariae population $P_W(t)$, in the physical water environment, is generated through shedding of cercariae by infected snails at an assumed rate of $N_S\gamma_S$, where N_S is the number of cercariae shed by each snail per day and γ_S is the rate at which infected snails become cercariae shedding. These cercariae are further assumed to have an average life span of $\frac{1}{\mu_S}$. Putting together the above formulations and assumptions gives the following system of differential equations:

$$
\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H - \lambda_H S_H - \mu_H S_H,\\
\frac{dI_H}{dt} &= \lambda_H S_H - (\mu_H + \delta_H) I_H,\\
\frac{dS_V}{dt} &= \Lambda_V - \lambda_V S_V - \mu_V S_V,\\
\frac{dI_V}{dt} &= \lambda_V S_V - (\mu_V + \delta_V) I_V,\\
\frac{dP_H}{dt} &= \lambda_h S_h - (\alpha_C + \mu_C) P_H,\\
\frac{dW_I}{dt} &= \alpha_C P_H - (\alpha_I + \mu_I) W_I,\\
\frac{dW_P}{dt} &= \frac{\alpha_I}{2} W_I - (\alpha_P + \mu_P) W_P,\\
\frac{dE_H}{dt} &= N_P \alpha_P W_P - (\alpha_E + \mu_E) E_H,\\
\frac{dE_L}{dt} &= I_h \alpha_E E_H - (\alpha_L + \mu_L) E_L,\\
\frac{dE_W}{dt} &= \alpha_L E_L - (\alpha_W + \mu_W) E_W,\\
\frac{dM}{dt} &= N_W \alpha_W E_W - \mu_M M,\\
\frac{dP_W}{dt} &= N_S \gamma_S I_V - \mu_S P_W.
\end{aligned} \tag{3.9}
$$

The model flow diagram is depicted in Fig. 2, and the associated parameters are given in Tables 2–4.

3.1. Feasible region of the equilibria of the model

All parameters and state variables for model system (3.9) are assumed to be non-negative to be consistent with human and animal populations. Further, it can be verified that for model system (3.9), all solutions with non-negative initial conditions remain bounded and non-negative.

Letting $N_H = S_H + I_H$ and adding equations 1 and 2 in system (3.9) gives

$$\frac{dN_H}{dt} \leqslant \Lambda_H - \mu_H N_H.$$

This implies that

$$\lim_{t\to\infty} \sup(N_H(t)) \leqslant \frac{\Lambda_H}{\mu_H}. \tag{3.10}$$

Similarly, letting $N_V = S_V + I_V$ and adding equations 3 and 4 in system (3.9) gives

$$\frac{dN_V}{dt} \leqslant \Lambda_V - \mu_V N_V. \tag{3.11}$$

This implies that

$$\lim_{t\to\infty} \sup(N_V(t)) \leqslant \frac{\Lambda_V}{\mu_V}. \tag{3.12}$$

Using Eqs. (3.10) and (3.12) similar expressions can be derived for the remaining model variables. Hence, all feasible solutions of system (3.9) are positive and eventually enter the invariant attracting region

$$
\begin{aligned}
\Omega = \{(S_H, I_H, S_V, I_V, P_H, W_I, W_P, E_H, E_L, E_W, M, P_W) : 0 \leqslant S_H + I_H \leqslant M_1,\\
0 \leqslant S_V + I_V \leqslant M_2, 0 \leqslant P_H \leqslant M_3, 0 \leqslant W_I \leqslant M_4,\\
0 \leqslant W_P \leqslant M_5, 0 \leqslant E_H \leqslant M_6, 0 \leqslant E_L \leqslant M_7,\\
0 \leqslant E_W \leqslant M_8, 0 \leqslant M \leqslant M_9, 0 \leqslant P_W \leqslant M_{10}\},
\end{aligned} \tag{3.13}
$$

where

$$
\begin{aligned}
M_1 &= \frac{\Lambda_H}{\mu_H},\\
M_2 &= \frac{\Lambda_V}{\mu_V},\\
M_3 &= \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_4 &= \frac{\alpha_C}{\alpha_I + \mu_I} \cdot \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_5 &= \frac{1}{2} \cdot \frac{\alpha_I}{\alpha_P + \mu_P} \cdot \frac{\alpha_C}{\alpha_I + \mu_I} \cdot \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_6 &= \frac{N_P \alpha_P}{\alpha_E + \mu_E} \cdot \frac{1}{2} \cdot \frac{\alpha_I}{\alpha_P + \mu_P} \cdot \frac{\alpha_C}{\alpha_I + \mu_I} \cdot \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_7 &= \frac{\alpha_E}{\alpha_L + \mu_L} \cdot \frac{N_P \alpha_P}{\alpha_E + \mu_E} \cdot \frac{1}{2} \cdot \frac{\alpha_I}{\alpha_P + \mu_P} \cdot \frac{\alpha_C}{\alpha_I + \mu_I} \cdot \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_8 &= \frac{\alpha_L}{\alpha_W + \mu_W} \cdot \frac{\alpha_E}{\alpha_L + \mu_L} \cdot \frac{N_P \alpha_P}{\alpha_E + \mu_E} \cdot \frac{1}{2} \cdot \frac{\alpha_I}{\alpha_P + \mu_P} \cdot \frac{\alpha_C}{\alpha_I + \mu_I} \cdot \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_9 &= \frac{N_W \alpha_W}{\mu_M} \cdot \frac{\alpha_L}{\alpha_W + \mu_W} \cdot \frac{\alpha_E}{\alpha_L + \mu_L} \cdot \frac{N_P \alpha_P}{\alpha_E + \mu_E} \cdot \frac{1}{2} \cdot \frac{\alpha_I}{\alpha_P + \mu_P} \cdot \frac{\alpha_C}{\alpha_I + \mu_I} \cdot \frac{1}{\alpha_C + \mu_C} \cdot M_{11},\\
M_{10} &= \frac{N_S \gamma_S}{\mu_S} \cdot \frac{\Lambda_V}{\mu_V}\\
M_{11} &= \frac{\beta_H N_S \gamma_S \Lambda_V (\Lambda_H - \mu_H)}{(P_0 \mu_S \mu_V + \epsilon N_S \gamma_S \Lambda_V)(\Lambda_H + \mu_H)}, \quad \text{for} \quad \Lambda_H > \mu_H.
\end{aligned} \tag{3.14}
$$

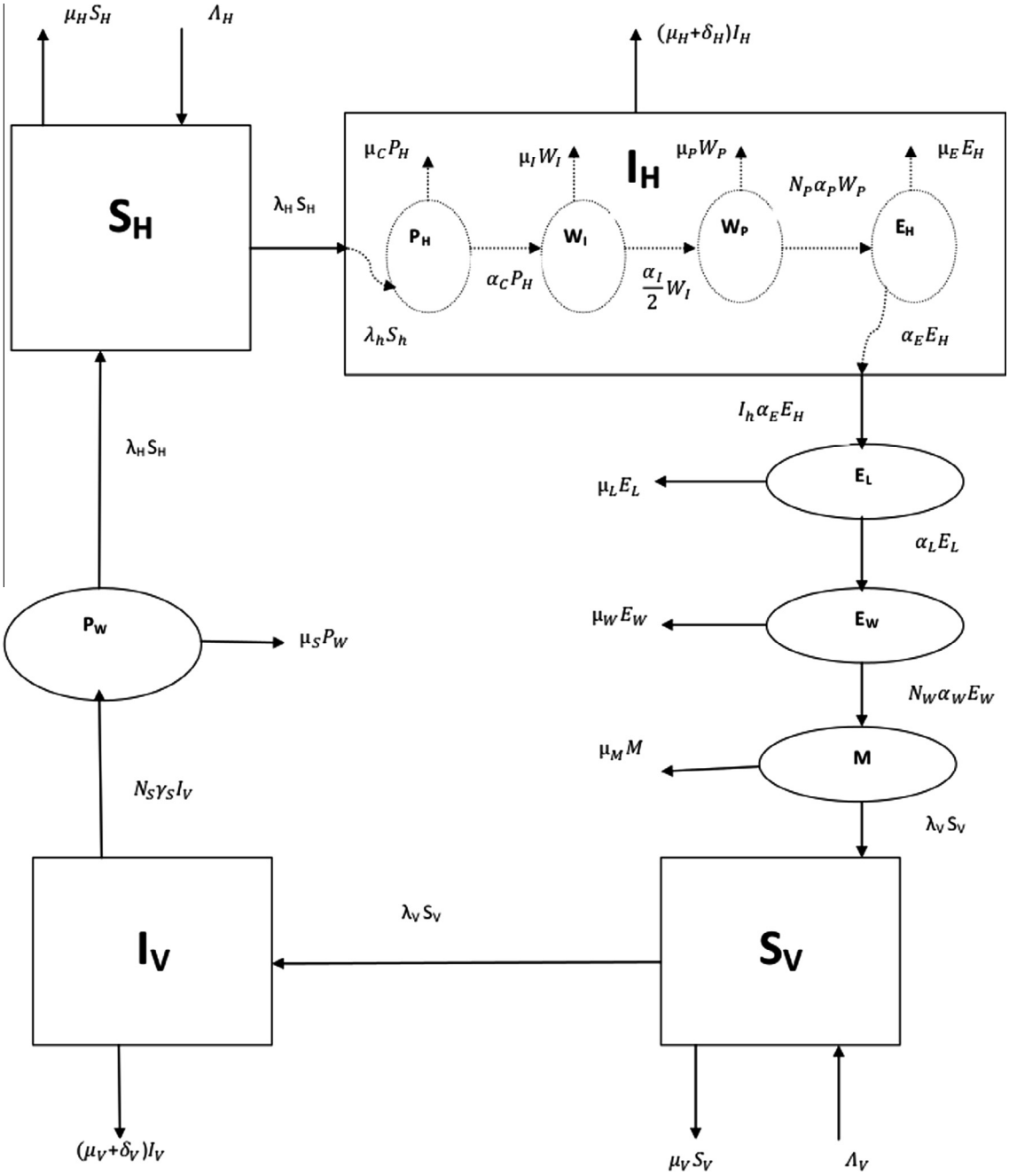

Fig. 2. A conceptual diagram of the mathematical model of linked with-host and between-host dynamics of human schistosomiasis.

Thus, whenever $\Lambda_H > \mu_H, \Omega$ is positively invariant and attracting and it is sufficient to consider solutions of model system (3.9) in Ω. Existence, uniqueness and continuation results for system (3.9) hold in this region and all solutions starting in Ω remain there for all $t \geqslant 0$. Hence, model system (3.9) is mathematically and epidemiologically well-posed and it is sufficient to consider the dynamics of the flow generated by model system (3.9) in Ω. We shall assume in all that follows (unless stated otherwise) that $\Lambda_H > \mu_H$.

4. Determination of disease free equilibrium and its stability

The equilibrium states of the model are obtained by setting the right-hand side of system (3.9) to zero. The system admits two equilibrium states which are the disease-free equilibrium and the endemic state. At the disease-free equilibrium, there is no cercariae, miracidia, worms and eggs and hence no infection in the human and snail populations. Thus, the model system (3.9) has a disease-free equilibrium given by

$$\begin{aligned} E^0 &= (S_H^0, I_H^0, S_V^0, I_V^0, P_H^0, W_I^0, W_P^0, E_H^0, E_L^0, E_W^0, M^0, P_W^0), \\ &= \left(\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0, 0, 0, 0, 0, 0, 0, 0, 0\right). \end{aligned} \tag{4.15}$$

The key parameter in many epidemic models which identifies the most important factors in the disease transmission cycle is the basic reproductive number, R_0, which we calculate in the next sub-section.

4.1. The model reproductive number

The reproductive number R_0, defined as the average number of secondary infections produced by a single infectious host, introduced into a totally susceptible population [68–73] is one of the most important tools in the analysis of disease outbreak. For most disease outbreaks, if $R_0 < 1$, then the outbreak will disappear with time, whereas if $R_0 > 1$, then the outbreak will persist at endemic levels. In the context of human schistosomiasis infection, the quantity R_0 defines the expected number human/snail schistosomiasis infections generated by a single human/snail during the entire period of infectiousness of the human/snail introduced in a completely susceptible human/snail population. Therefore, in this case R_0 quantifies transmission of schistosomiasis from human to human or snail to snail. This is because of the fact that starting from a single infected human, schistosomiasis has to go through a snail before it can infect another human. Similarly, starting from a single infected snail, schistosomiasis has to go through a human being before it can infect another snail. We use the next generation operator approach to calculate the basic reproduction number [73]. Model system (3.9) can be written in the form

$$\begin{aligned}\frac{dX}{dt} &= f(X,Y,Z),\\ \frac{dY}{dt} &= g(X,Y,Z),\\ \frac{dZ}{dt} &= h(X,Y,Z),\end{aligned} \tag{4.16}$$

where

$$\begin{aligned}X &= (S_H, S_V),\\ Y &= (I_H, I_V, P_H, W_I, W_P, E_H, E_L, E_W),\\ Z &= (M, P_W).\end{aligned} \tag{4.17}$$

Components of X denote the number of susceptibles, while components of Y represent the number of infected individuals that do not transmit the disease. Components of Z represent the number of individuals capable of transmitting the disease. Following [73] we define $\tilde{g}(X^*, Z)$ by

$$\begin{aligned}\tilde{g}(X^*,Z) = (&\tilde{g}_1(X^*,Z), \tilde{g}_2(X^*,Z), \tilde{g}_3(X^*,Z), \tilde{g}_4(X^*,Z), \tilde{g}_5(X^*,Z), \tilde{g}_6(X^*,Z),\\ &\tilde{g}_7(X^*,Z), \tilde{g}_8(X^*,Z)),\end{aligned} \tag{4.18}$$

with

$$\begin{aligned}\tilde{g}_1(X^*,Z) &= \frac{\beta_H \Lambda_H P_W}{\mu_H(\mu_H+\delta_H)(P_0+\epsilon P_W)},\\ \tilde{g}_2(X^*,Z) &= \frac{\beta_V \Lambda_V M}{\mu_V(\mu_V+\delta_V)(M_0+\epsilon M)},\\ \tilde{g}_3(X^*,Z) &= \frac{1}{\alpha_C+\mu_C}\cdot F_H,\\ \tilde{g}_4(X^*,Z) &= \frac{1}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot F_H,\\ \tilde{g}_5(X^*,Z) &= \frac{1}{2}\cdot\frac{1}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot F_H,\\ \tilde{g}_6(X^*,Z) &= \frac{1}{2},\frac{1}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot F_H,\\ \tilde{g}_7(X^*,Z) &= \frac{1}{2}\cdot\frac{1}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot F_W,\\ \tilde{g}_8(X^*,Z) &= \frac{1}{2}\cdot\frac{1}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot F_W,\end{aligned} \tag{4.19}$$

where

$$\begin{aligned}F_H &= \frac{\beta_H(\Lambda_H-\mu_H)(\mu_H+\delta_H)P_W}{\mu_H(\mu_H+\delta_H)(P_0+\epsilon P_W)+\beta_H\Lambda_H P_W},\\ F_W &= \frac{\beta_H(\Lambda_H-\mu_H)P_W}{\mu_H(P_0+\epsilon P_W)}.\end{aligned} \tag{4.20}$$

Let $A = D_Z h(X^*, \tilde{g}(X^*,0), 0)$ and further assume that A can be written in the form $A = M - D$, where $M \geqslant 0$ and $D > 0$, a diagonal matrix. Then A becomes

$$A = \begin{bmatrix} -\mu_M & \frac{C_H}{P_0} \\ \frac{C_V}{M_0} & -\mu_S \end{bmatrix}, \tag{4.21}$$

where

$$\begin{aligned}C_H &= \frac{1}{2}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta_H(\Lambda_H-\mu_H)}{\mu_H},\\ C_V &= \frac{\beta_V N_S \gamma_S \Lambda_V}{\mu_V(\mu_V+\delta_V)}.\end{aligned} \tag{4.22}$$

Since $A = M - D$, we deduce matrices M and D to be

$$M = \begin{bmatrix} 0 & \frac{C_H}{P_0} \\ \frac{C_V}{M_0} & 0 \end{bmatrix}, \quad D = \begin{bmatrix} \mu_M & 0 \\ 0 & \mu_S \end{bmatrix}. \tag{4.23}$$

The basic reproductive number is the spectral radius (dominant eigenvalue) of the matrix MD^{-1}, that is,

$$R_0 = \rho(MD^{-1}). \tag{4.24}$$

In this case,

$$R_0 = \sqrt{\frac{C_H}{P_0\mu_S}\cdot\frac{C_V}{M_0\mu_M}} = \sqrt{R_{0H}R_{0HS}} = \sqrt{R_{0WH}R_{0SH}R_{0HS}}. \tag{4.25}$$

In Eq. (4.25), the quantity R_{0HS} is interpreted as follows. Consider a single newly infected human host entering a disease-free population of snails at equilibrium. This individual is still present and infectious and the expected number of snails infected by this human is approximately

$$R_{0HS} = \frac{\beta_V N_S \gamma_S \Lambda_V}{M_0\mu_M\mu_V(\mu_V+\delta_V)}. \tag{4.26}$$

Therefore, the human to snail transmission coefficient R_{0HS} is composed of between-host disease parameters only. Similarly, in Eq. (4.25), the quantity R_{0H} is interpreted as follows. Consider a single newly infected snail host entering a disease-free population of humans at equilibrium. This snail is still present and infectious and the expected number of humans infected by this snail is approximately

$$\begin{aligned}R_{0H} = &\frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{1}{2}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\\ &\cdot\frac{\beta_H(\Lambda_H-\mu_H)}{P_0\mu_H\mu_S}, = R_{0WH}R_{0SH}.\end{aligned} \tag{4.27}$$

From Eq. (4.27) we deduce that the snail to human transmission coefficient R_{0H} is a product of two other transmission coefficients which are the between-host (snail to human) transmission coefficient R_{0SH} and the within-host (within-human) R_{0WH} which are given by

$$R_{0SH} = \frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\beta_H(\Lambda_H-\mu_H)}{P_0\mu_H\mu_S}, \tag{4.28}$$

and

$$R_{0WH} = \frac{1}{2}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I},\frac{\alpha_C}{\alpha_C+\mu_C}, \tag{4.29}$$

respectively.

Therefore, the basic reproductive number R_0, given by

$$R_0 = \sqrt{R_{0WH}R_{0SH}R_{0HS}}, \tag{4.30}$$

is composed of both within-host and between-host disease parameters, and R_{0HS}, R_{0SH} and R_{0WH} are given by Eqs. (4.26), (4.28) and (4.29) respectively.

From the expression for R_0 in Eq. (4.30) we make the following deductions.

a. The between-host transmission parameters (snail to human and human to snail) such as supply of new susceptible snails Λ_V and humans Λ_H, contact rate between hosts (snails and humans) and infected waters β_V and β_H, the rate at which schistosome eggs in water hatch to become miracidia $N_W\alpha_W$, the rate at which infected snails contaminate the physical water environment with cercariae $N_S\gamma_S$ all contribute to the transmission of human schistosomiasis. Therefore, control measures such as killing of snails by use of molluscicides and reducing contact between the human and snail hosts and infected waters through educating the public may help to reduce human schistosomiasis transmission.
b. The within-host transmission parameters (within the human host) such as the rates at which (a) cercariae within the human host become immature worms $\alpha_C, (b)$ immature worms become mature worms $\frac{\alpha_I}{2}, (c)$ mature worms lay eggs $N_P\alpha_P$ and the rates at which the cercariae within the human host and the worms die all contribute to the transmission of human schistosomiasis. Therefore immune mechanisms that kill cercariae and worms and destroy eggs within the human host and also treatment intended to kill mature worms may help to reduce human schistosomiasis transmission.

Therefore, we conclude that both epidemiological (between-host) and immunological (within-host) factors affect the transmission of human schistosomiasis.

4.2. Local Stability of the disease free equilibrium

From Theorem 4.2 of van den Driesche and Watmough [70], if the basic reproduction number R_0 is less than one, then the disease free equilibrium is locally asymptotically stable and the disease cannot invade the population. This is summarised in the following theorem.

Theorem 4.1. *The disease free equilibrium point E^0, of model system (3.9) is locally asymptotically stable whenever $R_0 < 1$ and unstable otherwise.*

Proof. The proof is not needed since local stability of the disease free equilibrium is a consequence of Theorem 4.2 in van den Driessche and Watmough [70]. □

4.3. Global stability of the disease free equilibrium

Theorem 4.2 in [70] establishes that the disease free equilibrium is locally asymptotically stable whenever $R_0 < 1$ and unstable when $R_0 > 1$. In this section, we list two conditions that if met, also guarantee the global asymptotic stability of the disease free state. We write system (3.9) in the form:

$$\begin{aligned}\frac{dX}{dt} &= F(X,Z),\\ \frac{dZ}{dt} &= G(X,Z), \quad G(X,0)=0,\end{aligned} \tag{4.31}$$

where $X = (S_H, S_V)$ comprises of the uninfected components and

$$Z = (I_H, I_V, P_H, W_I, W_P, E_H, E_L, E_W, M, P_W), \tag{4.32}$$

comprises of infected and infectious components.

$$E^0 = (X^*, 0) = \left(\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0, 0, 0, 0, 0, 0, 0, 0\right), \tag{4.33}$$

denotes the disease free equilibrium of the system. To guarantee global asymptotic stability, the conditions $(H1)$ and $(H2)$ below must be met [73].

H1. For $\frac{dX}{dt} = F(X,0), X^*$ is globally asymptotically stable (g.a.s),

H2. $G(X,Z) = AZ - \hat{G}(X,Z), \hat{G}(X,Z) \geqslant 0$ for $(X,Z) \in \mathbb{R}^+_{12}$ where $A = D_Z G(X^*, 0)$ is an M-matrix and R^+_{12} is the region where the model makes biological sense.

In our case,

$$F(X,0) = \begin{bmatrix} \Lambda_H - \mu_H S_H \\ \Lambda_V - \mu_V S_V \end{bmatrix}, \tag{4.34}$$

and

$$A = \begin{pmatrix} a_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_H \Lambda_H}{P_0\mu_H} \\ 0 & a_2 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_V \Lambda_V}{M_0\mu_V} & 0 \\ 0 & 0 & a_3 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_H(\Lambda_H - \mu_H)}{P_0\mu_H} \\ 0 & 0 & \alpha_C & a_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\alpha_I}{2} & a_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & N_P\alpha_P & a_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_E & a_7 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \alpha_L & a_8 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & N_W\alpha_W & -\mu_M & 0 \\ 0 & N_S\gamma_S & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_S \end{pmatrix}. \tag{4.35}$$

where

$$\begin{aligned} a_1 &= -(\mu_H + \delta_H),\\ a_2 &= -(\mu_V + \delta_V),\\ a_3 &= -(\alpha_C + \mu_C),\\ a_4 &= -(\alpha_I + \mu_I),\\ a_5 &= -(\alpha_P + \mu_P),\\ a_6 &= -(\alpha_E + \mu_E),\\ a_7 &= -(\alpha_L + \mu_L),\\ a_8 &= -(\alpha_W + \mu_W). \end{aligned} \tag{4.36}$$

$$\hat{G}(X,Z) = \begin{bmatrix} \left(\frac{\Lambda_H}{P_0\mu_H} - \frac{S_H}{P_0+\epsilon P_W}\right)\beta_H P_W \\ \left(\frac{\Lambda_V}{M_0\mu_V} - \frac{S_V}{M_0+\epsilon M}\right)\beta_V M \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}. \tag{4.37}$$

Since $\left(S^0_H = \frac{\Lambda_H}{\mu_H}\right)\frac{1}{P_0} \geqslant \frac{S_H}{P_0+\epsilon P_W}$ and $\left(S^0_V = \frac{\Lambda_V}{\mu_V}\right)\frac{1}{M_0} \geqslant \frac{S_V}{M_0+\epsilon M}$, it is clear that $\hat{G}(X,Z) \geqslant 0$ for all $(X,Z) \in \mathbb{R}^+_{12}$. It is also clear that matrix A is an M-matrix since the off diagonal elements of A are non-negative. We state a theorem which summarises the above result.

Theorem 4.2. *The fixed point $E^0 = \left(\frac{\Lambda_H}{\mu_H}, 0, \frac{\Lambda_V}{\mu_V}, 0, 0, 0, 0, 0, 0, 0, 0\right)$ is a globally asymptotically stable (g.a.s) equilibrium of system (3.9) if $R_0 < 1$ and the assumptions $(H1)$ and $(H2)$ are satisfied.*

5. The endemic equilibrium state and its stability

At the endemic equilibrium both humans and snails are infected by cercariae and miracidia respectively and the endemic equilibrium is given by

$$E^* = (S_H^*, I_H^*, S_V^*, I_V^*, P_H^*, W_I^*, W_P^*, E_H^*, E_L^*, E_W^*, M^*, P_W^*). \tag{5.38}$$

We give expressions for the endemic equilibrium and their interpretations in the following subsections and also prove its existence.

5.1. The endemic equilibrium

The endemic value of susceptible humans is given by

$$S_H^* = \frac{\Lambda_H}{\mu_H + \lambda_H^*}. \tag{5.39}$$

We deduce from Eq. (5.39) that the equilibrium state associated with susceptible humans is proportional to the average time of stay in the susceptible compartment and the rate of supply of new susceptibles through birth. Individuals exit this compartment either through death or infection. The endemic value of infected humans is given by

$$I_H^* = \frac{\lambda_H^* S_H^*}{\mu_H + \delta_H} = \frac{\Lambda_H \lambda_H^*}{(\mu_H + \delta_H)(\mu_H + \lambda_H^*)}. \tag{5.40}$$

We note from Eq. (5.40) that the infected population at the endemic equilibrium is directly proportional to three quantities: the average time of stay in the infected compartment, the rate of infection of susceptibles and the number/density of susceptible hosts. The quantity of infected snails at endemic equilibrium is given by

$$S_V^* = \frac{\Lambda_V}{\mu_V + \lambda_V^*}. \tag{5.41}$$

Eq. (5.41) implies that at equilibrium, the susceptible snail population equals the product of the average time of stay in this compartment and the rate of supply of new susceptibles through birth. At endemic equilibrium, the population of infected snails is given by

$$I_V^* = \frac{\lambda_V^* S_V^*}{\mu_V + \delta_V} = \frac{\Lambda_V \lambda_V^*}{(\mu_V + \delta_V)(\mu_V + \lambda_V^*)}. \tag{5.42}$$

Therefore, infected snail population's endemic equilibrium value is a product of three quantities: the average life span of infected snails, the rate of infection of snails and the number/density of susceptible snails.

By setting

$$Z_H^* = \Lambda_H - (\mu_H + \lambda_H^*) > 0,$$

the endemic equilibria for $P_H^*, W_I^*, W_P^*, E_H^*, E_L^*, E_W^*$ and M^* can be expressed in terms of this quantity as follows. The average population of cercariae within a single infected human host at endemic equilibrium is given by

$$P_H^* = \frac{\lambda_h^* S_h^*}{\alpha_C + \mu_C} = \frac{1}{\alpha_C + \mu_C} \cdot \frac{(\mu_H + \delta_H)\lambda_H^* Z_H^*}{\Lambda_H \lambda_H^* + (\mu_H + \delta_H)(\mu_H + \lambda_H^*)}. \tag{5.43}$$

The endemic equilibrium of the average cercariae population inside a single human host is directly proportional to the life span of cercariae within a single infected human host and the rate of infection of a single susceptible to become an infected human host. Thus immune pressures that destroy cercariae within an infected human

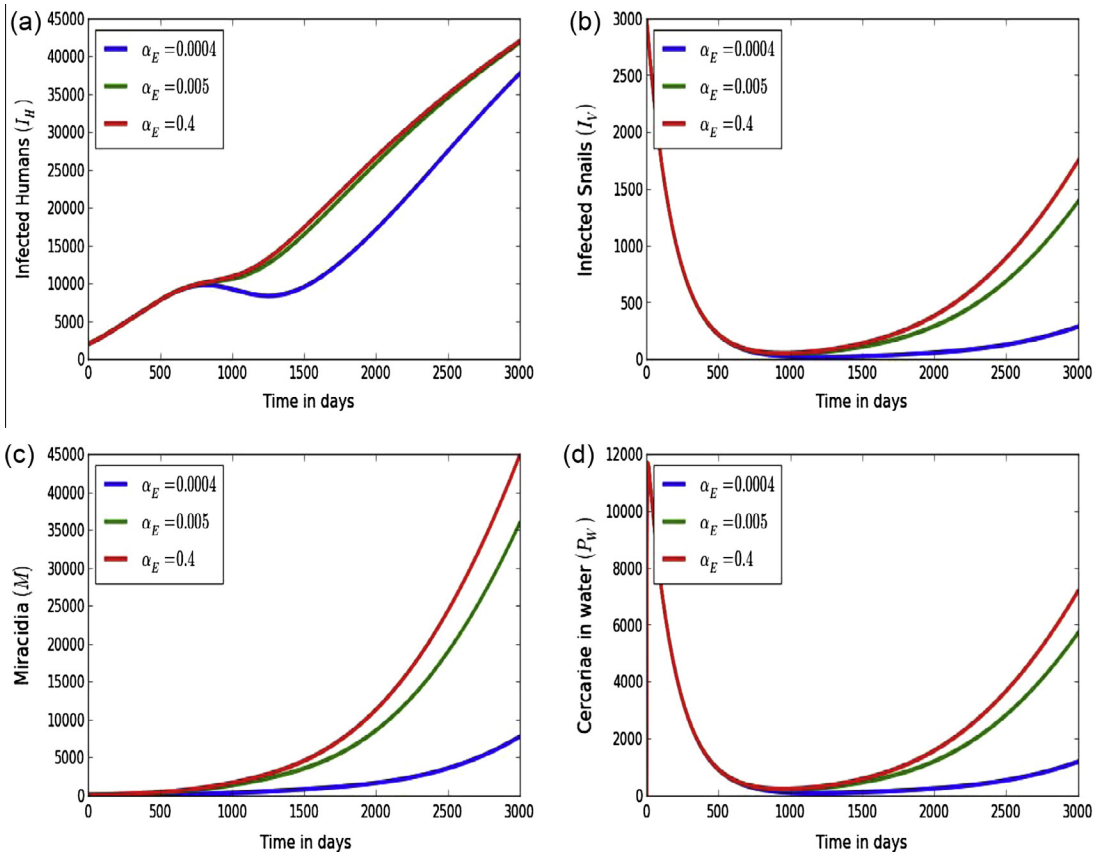

Fig. 3. Simulations of model system (3.9) showing the evolution with time of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of rate of excretion of worm eggs by an infected human, $\alpha_E : \alpha_E = 0.0004, \alpha_E = 0.005$ and $\alpha_E = 0.4$.

host reduce cercariae endemic equilibrium. This expression implies a link between within-host cercariae dynamics and human population dynamics. The population of immature worms within a single infected human host at endemic equilibrium is given by

$$W_I^* = \frac{\alpha_C P_H^*}{\alpha_I + \mu_I} = \frac{1}{\alpha_I + \mu_I} \cdot \frac{\alpha_C}{\alpha_C + \mu_C} \cdot \frac{(\mu_H + \delta_H)\lambda_H^* Z_H^*}{\Lambda_H \lambda_H^* + (\mu_H + \delta_H)(\mu_H + \lambda_H^*)}. \tag{5.44}$$

Therefore, the population of immature worms at endemic equilibrium increases with an increase in the average life-span of immature worms and the rate at which cercariae become mature worms. Therefore, treatment and immune responses focused on killing cercariae and immature worms reduce the endemic equilibrium associated with immature worms within a human host. The population of mature worms within a single infected human host at endemic equilibrium is given by

$$\begin{aligned} W_P^* &= \frac{1}{2} \cdot \frac{\alpha_I W_I^*}{\alpha_P + \mu_P}, \\ &= \frac{1}{2} \cdot \frac{1}{\alpha_P + \mu_P} \cdot \frac{\alpha_I}{\alpha_I + \mu_I} \cdot \frac{\alpha_C}{\alpha_C + \mu_C} \cdot \frac{(\mu_H + \delta_H)\lambda_H^* Z_H^*}{\Lambda_H \lambda_H^* + (\mu_H + \delta_H)(\mu_H + \lambda_H^*)}. \end{aligned} \tag{5.45}$$

We conclude from Eq. (5.45) that the rate at which paired immature worms become mature worms and the life-span of mature worms determine the level of endemic equilibrium associated with mature worms within a human host. Therefore, immune responses and treatment aimed at killing mature worms reduce the endemic equilibrium. The average schistosome egg population within a single infected human host at endemic equilibrium is given by

$$\begin{aligned} E_H^* &= \frac{N_P \alpha_P W_P^*}{\alpha_E + \mu_E}, = \frac{1}{2} \cdot \frac{1}{\alpha_E + \mu_E} \cdot \frac{N_P \alpha_P}{\alpha_P + \mu_P} \cdot \frac{\alpha_I}{\alpha_I + \mu_I} \cdot \frac{\alpha_C}{\alpha_C + \mu_C} \\ &\quad \cdot \frac{(\mu_H + \delta_H)\lambda_H^* Z_H^*}{\Lambda_H \lambda_H^* + (\mu_H + \delta_H)(\mu_H + \lambda_H^*)}. \end{aligned} \tag{5.46}$$

Eq. (5.46) implies that at equilibrium the average schistosome egg population within an infected human host is directly proportional to the average egg life span and worm fecundity. Thus, immune responses which reduce worm fecundity and those that destroy eggs within an infected human host reduce the endemic equilibrium associated with worm eggs. The population of schistosome eggs on the physical land environment at the endemic equilibrium is given by

$$\begin{aligned} E_L^* &= \frac{\alpha_E E_H^* (I_H^* + 1)}{\alpha_L + \mu_L}, \\ &= \frac{1}{2} \cdot \frac{1}{\alpha_L + \mu_L} \cdot \frac{\alpha_E}{\alpha_E + \mu_E} \cdot \frac{N_P \alpha_P}{\alpha_P + \mu_P} \cdot \frac{\alpha_I}{\alpha_I + \mu_I} \cdot \frac{\alpha_C}{\alpha_C + \mu_C} \cdot \frac{\lambda_H^* Z_H^*}{(\mu_H + \lambda_H^*)}. \end{aligned} \tag{5.47}$$

We deduce from Eq. (5.47) that the life span of eggs, the rate at which each infected human host excrete schistosome eggs and the total number of humans infected by schistosomiasis all influence the endemic equilibrium associated with schistosome eggs in the physical land environment. Therefore, atopy aspects [38] reduce the endemic equilibrium of schistosome eggs in the physical land environment. The endemic equilibrium of schistosome eggs in the physical water environment at is given by

$$E_W^* = \frac{\alpha_L E_L^*}{\alpha_W + \mu_W} = \frac{1}{2} \cdot \frac{1}{\alpha_W + \mu_W} \cdot \frac{\alpha_L}{\alpha_L + \mu_L} \cdot \frac{\alpha_E}{\alpha_E + \mu_E} \cdot \frac{N_P \alpha_P}{\alpha_P + \mu_P} \cdot \frac{\alpha_I}{\alpha_I + \mu_I} \cdot \frac{\alpha_C}{\alpha_C + \mu_C} \frac{\lambda_H^* Z_H^*}{(\mu_H + \lambda_H^*)}. \tag{5.48}$$

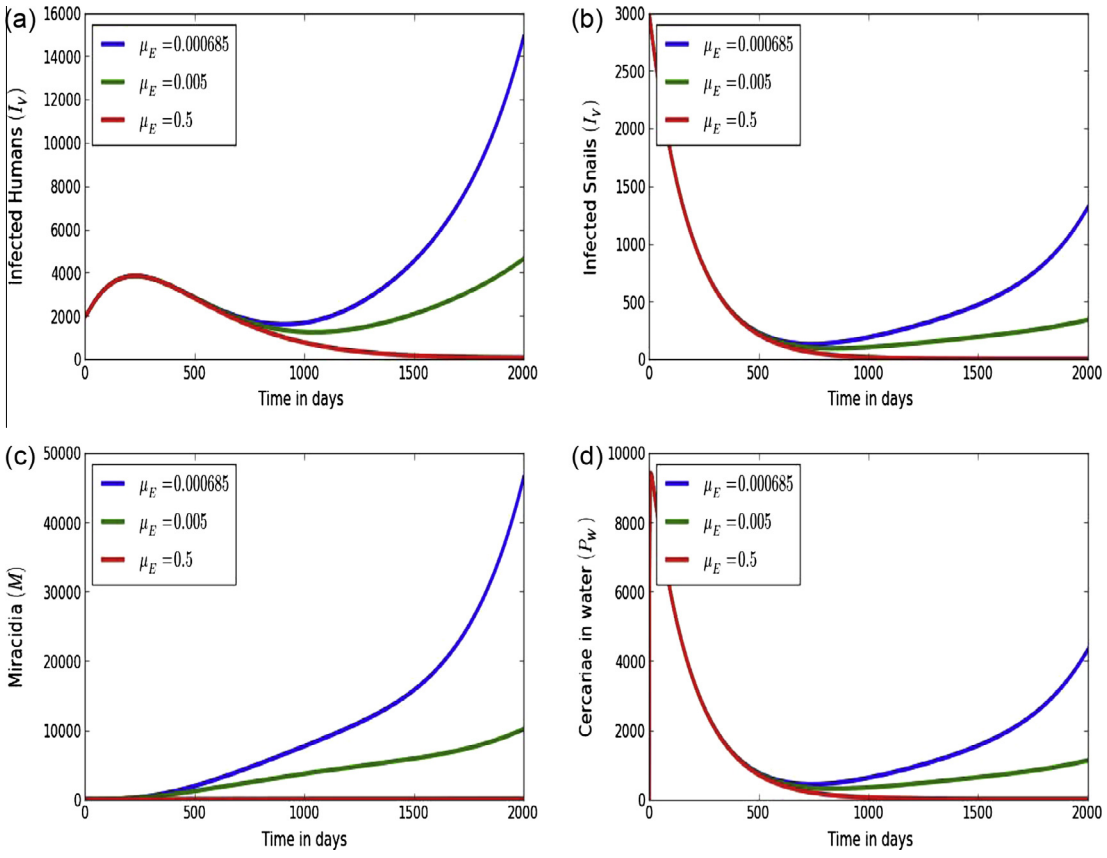

Fig. 4. Simulations of model system (3.9) showing the evolution with time of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of natural death of worm eggs, $\mu_E : \mu_E = 0.00685, \mu_E = 0.005$ and $\mu_E = 0.5$.

Eq. (5.48) indicates that the endemic schistosome egg population in the physical water environment is influenced by the average life span of the eggs and the rate at which the eggs are transported into physical water environment by flowing water. Therefore, rainfall conditions which wash away the schistosome eggs into the physical water environment affect the transmission of human schistosomiasis. The endemic equilibrium value associated with miracidia in the physical water environment is given by

$$M^* = \frac{N_W\alpha_W E_W^*}{\mu_M} = \frac{1}{2}\cdot\frac{N_W\alpha_W}{\mu_M}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\lambda_H^* Z_H^*}{(\mu_H+\lambda_H^*)}. \tag{5.49}$$

We note from Eq. (5.49) that the life span of miracidia and worm fecundity all directly influence the endemic levels of miracidia in the physical water environment. The cercariae population in the physical water environment at endemic equilibrium is given by

$$P_W^* = \frac{N_S\gamma_S I_V^*}{\mu_S} = \frac{\Lambda_V N_S\gamma_S\lambda_V^*}{\mu_S(\mu_V+\delta_V)(\mu_V+\lambda_V^*)}. \tag{5.50}$$

From Eq. (5.50), we conclude that the life span of cercariae in the physical water environment and the rate at which infected snails shed cercariae in the physical water environment reduce the endemic equilibrium. Thus, interventions intended to kill snails, particularly infected snails reduce schistosomiasis transmission.

5.2. The Existence of the endemic equilibrium state

In this section we present some results concerning the existence of an endemic equilibrium or constant solution for model system (3.9). To do this we shall make use of a threshold parameter, which we have already denoted by R_0.

Theorem 5.1. *The model (3.9) formulated in terms of proportions has at least one endemic equilibrium solution given by*

$$E^* = (S_H^*, I_H^*, S_V^*, I_V^*, P_H^*, W_I^*, W_P^*, E_H^*, E_L^*, E_W^*, M^*, P_W^*), \tag{5.51}$$

with $S_H^*, I_H^*, S_V^*, I_V^*, P_H^*, W_I^*, W_P^*, E_H^*, E_L^*, E_W^*, M^*, P_W^*$ *all non-negative, whose existence and properties are determined by the threshold parameter* R_0 *where*

$$R_0 = \sqrt{\frac{N_S\gamma_S\beta_V\Lambda_V}{\mu_V\mu_M M_0(\mu_V+\delta_V)}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\beta_H(\Lambda_H-\mu_H)}{2P_0\mu_H\mu_S}}. \tag{5.52}$$

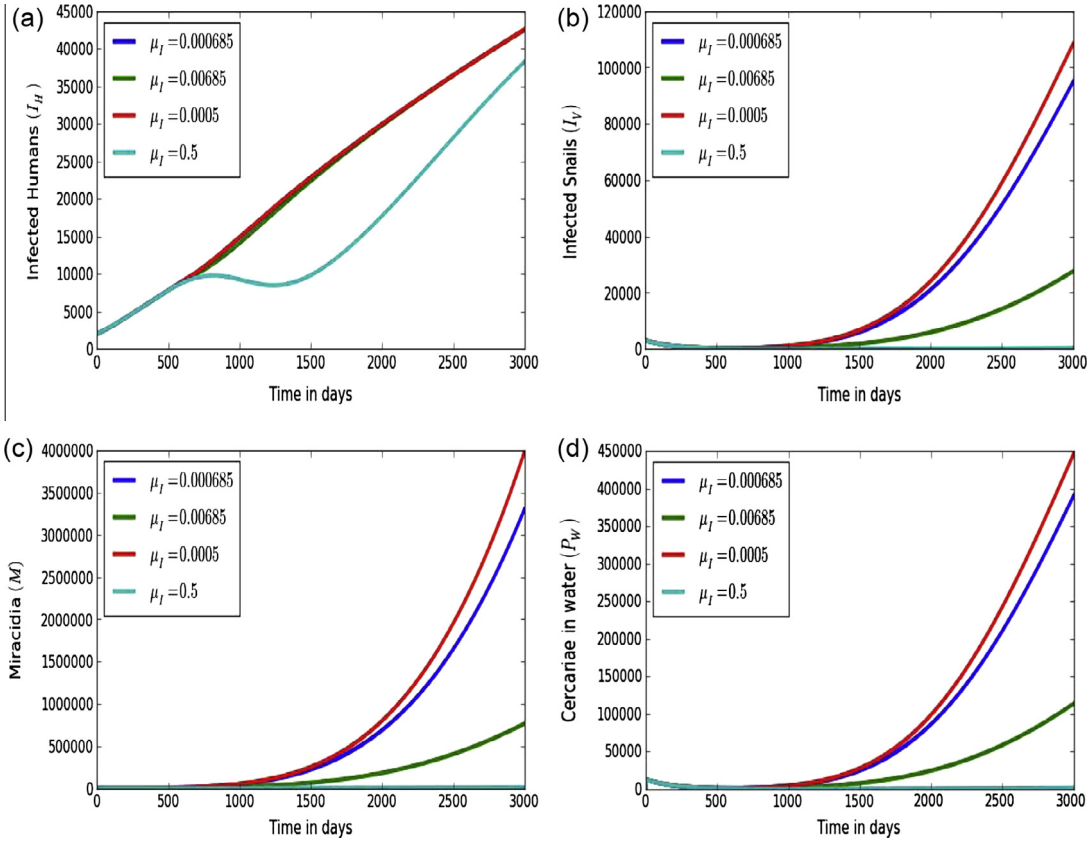

Fig. 5. Graphs of numerical solutions of model system (3.9) showing propagation of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of natural death rate of immature worms, $\mu_I : \mu_I = 0.000685, \mu_I = 0.0005, \mu_I = 0.00685$ and $\mu_I = 0.5$.

Proof. Let $E^* = S_H^*, I_H^*, S_V^*, I_V^*, P_H^*, W_I^*, W_P^*, E_H^*, E_L^*, E_W^*, M^*, P_W^*$ be a constant solution of the model system (3.9). We can easily express $S_H^*, I_H^*, S_V^*, P_H^*, W_I^*, W_P^*, E_H^*, E_L^*, E_W^*, M^*, P_W^*$ in terms of I_V^* in the form

$$
\begin{aligned}
S_H^*(I_V^*) &= \frac{\Lambda_H(P_0\mu_S + \epsilon N_S\gamma_S I_V^*)}{\mu_H(P_0\mu_S + \epsilon N_S\gamma_S I_V^*) + \beta_H N_S\gamma_S I_V^*},\\
I_H^*(I_V^*) &= \frac{1}{\mu_H+\delta_H}\cdot\frac{\beta_H\Lambda_H N_S\gamma_S I_V^*}{\mu_H(P_0\mu_S + \epsilon N_S\gamma_S I_V^*) + \beta_H N_S\gamma_S I_V^*},\\
S_V^*(I_V^*) &= \frac{\Lambda_V(M_0 + \epsilon Q_V Z_V^*)}{\mu_V(M_0 + \epsilon Q_V Z_V^*) + \beta_V Q_V Z_V^*},\\
P_H^*(I_V^*) &= \frac{1}{\alpha_C+\mu_C}\cdot\frac{Z_V^*}{I_H^*+1},\\
W_I^*(I_V^*) &= \frac{1}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{Z_V^*}{I_H^*+1},\\
W_P^*(I_V^*) &= \frac{1}{2}\cdot\frac{1}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{Z_V^*}{I_H^*+1},\\
E_H^*(I_V^*) &= \frac{1}{2}\cdot\frac{1}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{Z_V^*}{I_H^*+1},\\
E_L^*(I_V^*) &= \frac{1}{2}\cdot\frac{1}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot Z_V^*,\\
E_W^*(I_V^*) &= \frac{1}{2}\cdot\frac{1}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot Z_V^*,\\
M^*(I_V^*) &= \frac{1}{2}\cdot\frac{1}{\mu_M}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot Z_V^*,\\
P_W^*(I_V^*) &= \frac{N_S\gamma_S I_V^*}{\mu_S}\\
\lambda_H^*(I_V^*) &= \frac{\beta_H N_S\gamma_S I_V^*}{P_0\mu_S + \epsilon N_S\gamma_S I_V^*},\\
\lambda_V^*(I_V^*) &= \frac{\beta_V Q_V Z_V^*}{M_0 + \epsilon Q_V Z_V^*},
\end{aligned}
\tag{5.53}
$$

where

$$
Z_V^* = \frac{\beta_H N_S\gamma_S I_V^*}{P_0\mu_S + \epsilon N_S\gamma_S I_V^*}\cdot\frac{(\Lambda_H-\mu_H)(P_0\mu_S + \epsilon N_S\gamma_S I_V^*) - \beta_H N_S\gamma_S I_V^*}{\mu_H(P_0\mu_S + \epsilon N_S\gamma_S I_V^*) + \beta_H N_S\gamma_S I_V^*},
$$

$$
Q_V = \frac{1}{2}\cdot\frac{1}{\mu_M}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}.
$$

Substituting the expressions in (5.53) in the equation for I_V which is given by

$$
\frac{dI_V}{dt} = \lambda_V S_V - (\mu_V+\delta_V)I_V,
$$

at the endemic equilibrium we get:

$$
I_V^*\left[A{I_V^*}^2 + BI_V^* + C\right] = 0, \tag{5.54}
$$

where

$$
\begin{aligned}
A &= (N_S\gamma_S)^2(\beta_V+\epsilon\mu_V)(\mu_V+\delta_V)Q_V\left[\beta_V^2 + \epsilon\beta_H(\Lambda_H-\mu_H)\right]\\
&\quad + \epsilon(N_S\gamma_S)^2(\beta_V+\epsilon\mu_H)(\beta_V+\epsilon\mu_V)(\mu_V+\delta_V),
\end{aligned}
\tag{5.55}
$$

$$
\begin{aligned}
B &= (1-R_0^2)P_0^2\mu_S^2 + \beta_H(\Lambda_H-\mu_H)N_S\gamma_S(\beta_V+\epsilon\mu_V)(\mu_V\\
&\quad + \delta_V)Q_V P_0\mu_S + P_0\mu_S(\mu_V+\delta_V)M_0\mu_V N_S\gamma_S(\beta_V+\epsilon\mu_H)\\
&\quad + \beta_V^3(N_S\gamma_S)^2\Lambda_V Q_V,
\end{aligned}
\tag{5.56}
$$

and

$$
C = (1-R_0^2)P_0^2\mu_S^2(\mu_V+\delta_V)M_0\mu_V N_S\gamma_S\epsilon\mu_H. \tag{5.57}
$$

Eq. (5.54) can be written in the form

$$
A\cdot I_V^*\left[{I_V^*}^2 + E_V I_V^* + F_V\right] = 0, \tag{5.58}
$$

where $E_V = \frac{B}{A}$ and $F_V = \frac{C}{A}$. Note that $A > 0$ for all values of R_0 and $C < 0$ for $R_0 > 1$ while B can be positive or negative for $R_0 > 1$.

Eq. (5.58) gives $I_V^* = 0$, which corresponds to the disease-free equilibrium point and

$$
I_V^* = \frac{1}{2}\left[-E_V \pm \sqrt{E_V^2 - 4F_V}\right] > 0, \tag{5.59}
$$

for the endemic equilibrium. Since $F_V < 0$ for $R_0 > 1$, we can easily deduce from expression (5.59) that only one positive endemic equilibrium exists for $R_0 > 1$. Consequently, there exists one unique endemic equilibrium for model system (3.9) whenever $R_0 > 1$. □

Apart from the fact that the endemic equilibrium values represented by expressions (5.53) as well as expressions (5.38)–(5.49), (and) (5.50) synthesize important elements of human schistosomiasis transmission processes, we note that the between-host endemic expressions for

$$
S_H^*, I_H^*, S_V^*, I_V^*, E_L^*, E_W^*, M^*, P_W^* \tag{5.60}
$$

are determined by both within-host disease parameters and between-host disease parameters and in turn, the within-host endemic expressions for

$$
P_H^*, W_I^*, W_P^*, E_H^* \tag{5.61}
$$

are also determined by both the within-host disease parameters and between-host disease parameters. This confirms the reciprocal influence of within-host and between-host transmission dynamics of human schistosomiasis.

5.3. Local stability of the endemic equilibrium

Theorem 5.1 has established the existence of a unique endemic equilibrium for model system (3.9) without providing any information about its stability. We make use of a bifurcation approach to address this concern [70–76]. Center Manifold Theory has been used to determine the local stability of a non-hyperbolic equilibrium (linearisation matrix has at least one eigenvalue with zero real part) [70–76]. We now employ the Center Manifold Theory [75] to establish the local asymptotic stability of the endemic equilibrium of model system (3.9).

In order to apply the Center Manifold Theory, we make the following simplifications and change of variables. Let $S_H = x_1, I_H = x_2, S_V = x_3, I_V = x_4$, $P_H = x_5, W_I = x_6, W_P = x_7, E_H = x_8$, $E_L = x_9, E_W = x_{10}, M = x_{11}$ and $P_W = x_{12}$ so that $N_H = x_1 + x_2$ and $N_V = x_3 + x_4$. Further, by using the vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12})^T$, model system (3.9) can be written in the form $\frac{d\mathbf{x}}{dt} = F(\mathbf{x})$ with

$$
F(\mathbf{x}) = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12}), \tag{5.62}
$$

such that

$$
\begin{aligned}
\frac{dx_1}{dt} &= \Lambda_H - \lambda_H x_1 - \mu_H x_1,\\
\frac{dx_2}{dt} &= \lambda_H x_1 - (\mu_H+\delta_H)x_2,\\
\frac{dx_3}{dt} &= \Lambda_V - \lambda_V x_3 - \mu_V x_3,\\
\frac{dx_4}{dt} &= \lambda_V x_3 - (\mu_V+\delta_V)x_4,\\
\frac{dx_5}{dt} &= \lambda_h S_h - (\alpha_C+\mu_C)x_5,\\
\frac{dx_6}{dt} &= \alpha_C x_5 - (\alpha_I+\mu_I)x_6,\\
\frac{dx_7}{dt} &= \frac{\alpha_I}{2}x_6 - (\alpha_P+\mu_P)x_7,
\end{aligned}
$$

$$\frac{dx_8}{dt} = N_P\alpha_P x_7 - (\alpha_E + \mu_E)x_8,$$
$$\frac{dx_9}{dt} = I_h\alpha_E x_8 - (\alpha_L + \mu_L)x_9,$$
$$\frac{dx_{10}}{dt} = \alpha_L x_9 - (\alpha_W + \mu_W)x_{10},$$
$$\frac{dx_{11}}{dt} = N_W\alpha_W x_{10} - \mu_M x_{11},$$
$$\frac{dx_{12}}{dt} = N_S\gamma_S x_3 - \mu_S x_{12}, \tag{5.63}$$

where,

$$\lambda_H(t) = \frac{\beta_H x_{12}(t)}{P_0 + \epsilon x_{12}(t)}, \quad \lambda_V(t) = \frac{\beta_V x_{11}(t)}{M_0 + \epsilon x_{11}(t)}. \tag{5.64}$$

The method involves evaluating the Jacobian matrix of the system (5.63) at the disease-free equilibrium E^0 denoted by $J(E^0)$. The Jacobian matrix associated with equation system (5.63) at E^0 is given by

$$J(E^0) = \begin{pmatrix}
-\mu_H & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{\beta_H\Lambda_H}{P_0\mu_H} \\
0 & b_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_H\Lambda_H}{P_0\mu_H} \\
0 & 0 & -\mu_V & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{\beta_V\Lambda_V}{M_0\mu_V} & 0 \\
0 & 0 & 0 & b_2 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_V\Lambda_V}{M_0\mu_V} & 0 \\
0 & 0 & 0 & 0 & b_3 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_H(\Lambda_H-\mu_H)}{P_0\mu_H} \\
0 & 0 & 0 & 0 & \alpha_C & b_4 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \frac{\alpha_I}{2} & b_5 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & N_P\alpha_P & b_6 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_E & b_7 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_L & b_8 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & N_W\alpha_W & -\mu_M & 0 \\
0 & 0 & 0 & N_S\gamma_S & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_S
\end{pmatrix}, \tag{5.65}$$

where

$$b_1 = -(\mu_H + \delta_H),$$
$$b_2 = -(\mu_V + \delta_V,)$$
$$b_3 = -(\alpha_C + \mu_C),$$
$$b_4 = -(\alpha_I + \mu_I),$$
$$b_5 = -(\alpha_P + \mu_P),$$
$$b_6 = -(\alpha_E + \mu_E),$$
$$b_7 = -(\alpha_L + \mu_L),$$
$$b_8 = -(\alpha_W + \mu_W). \tag{5.66}$$

From expression (4.30) the reproductive number of system (5.63) is

$$R_0 = \sqrt{\frac{N_S\gamma_S\beta_V\Lambda_V}{\mu_V\mu_M M_0(\mu_V+\delta_V)} \cdot \frac{\alpha_C}{\alpha_C+\mu_C} \cdot \frac{\alpha_I}{\alpha_I+\mu_I} \cdot \frac{N_P\alpha_P}{\alpha_P+\mu_P} \cdot \frac{\alpha_E}{\alpha_E+\mu_E} \cdot \frac{\alpha_L}{\alpha_L+\mu_L} \cdot \frac{N_W\alpha_W}{\alpha_W+\mu_W} \cdot \frac{\beta_H(\Lambda_H-\mu_H)}{2P_0\mu_H\mu_S}}. \tag{5.67}$$

Now let us consider $\beta_V = k\beta_H$, regardless of whether $k \in (0,1)$ or $k \geqslant 1$ and let $\beta_H = \beta^*$. Taking β^* as the bifurcation parameter and if we consider $R_0 = 1$, and solve for β^*, we obtain

$$\beta^* = \sqrt{\frac{\mu_V\mu_M M_0(\mu_V+\delta_V)}{kN_S\gamma_S\Lambda_V} \cdot \frac{\alpha_C+\mu_C}{\alpha_C} \cdot \frac{\alpha_I+\mu_I}{\alpha_I} \cdot \frac{\alpha_P+\mu_P}{N_P\alpha_P} \cdot \frac{\alpha_E+\mu_E}{\alpha_E} \cdot \frac{\alpha_L+\mu_L}{\alpha_L} \cdot \frac{\alpha_W+\mu_W}{N_W\alpha_W} \cdot \frac{2P_0\mu_H\mu_S}{(\Lambda_H-\mu_H)}}. \tag{5.68}$$

Note that the linearised system of the transformed Eq. (5.63) with bifurcation point β^* has a simple zero eigenvalue. Hence, the Center Manifold Theory [75] can be used to analyse the dynamics of (5.63) near $\beta_H = \beta^*$.

In particular, Theorem 4.1 in Castillo-Chavez and Song [74], reproduced below as Theorem 5.2 for convenience, will be used to show the local asymptotic stability of the endemic equilibrium point of (5.63) (which is the same as the endemic equilibrium point of the original system (3.9), for $\beta_H = \beta^*$).

Theorem 5.2. *Consider the following general system of ordinary differential equations with parameter ϕ:*

$$\frac{dx}{dt} = f(x,\phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}, \quad \mathbb{f} : \mathbb{C}^2(\mathbb{R}^2 \times \mathbb{R}), \tag{5.69}$$

where 0 is an equilibrium of the system, that is $f(0,\phi) = 0$ for all ϕ, and assume that

A1. *$A = D_x f(0,0) = ((\partial f_i/\partial x_j)(0,0))$ is linearisation of system (5.63) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A, and other eigenvalues of A have negative real parts,*

A2. *matrix A has a right eigenvector u and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} u_k v_i v_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$
$$b = \sum_{k,i=1}^{n} u_k v_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{5.70}$$

The local dynamics of (5.63) around 0 are totally governed by a and b.

i. *$a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium.*
ii. *$a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;*
iii. *$a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable and a positive unstable equilibrium appears;*
iv. *$a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable*

In order to apply the above theorem, the following computations are necessary (it should be noted that we are using β^* as the bifurcation parameter, in place of ϕ in Theorem 5.2).

Eigenvectors of J_{β^*}: For the case when $R_0 = 1$, it can be shown that the Jacobian of (5.63) at $\beta_H = \beta^*$ (denoted by J_{β^*}) has a right eigenvector associated with the zero eigenvalue given by $u = [u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9, u_{10}, u_{11}, u_{12}]^T$, where

$$u_1 = -\frac{\beta^*}{P_0\mu_H}\cdot\frac{\Lambda_H}{\mu_H},$$

$$u_2 = \frac{\beta^*}{P_0\mu_H}\cdot\frac{\Lambda_H}{\mu_H+\delta_H},$$

$$u_3 = -\frac{\mu_S(\mu_V+\delta_V)}{N_S\gamma_S\mu_V},$$

$$u_4 = \frac{\mu_S}{N_S\gamma_S},$$

$$u_5 = \frac{1}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H},$$

$$u_6 = \frac{1}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H},$$

$$u_7 = \frac{1}{2}\cdot\frac{1}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H},$$

$$u_8 = \frac{1}{2}\cdot\frac{1}{\alpha_E+\mu_E}\cdot\frac{\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H},$$

$$u_9 = \frac{1}{2}\cdot\frac{1}{\alpha_L+\mu_L}\cdot\frac{N_P\alpha_P}{\alpha_E+\mu_E}\cdot\frac{\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H},$$

$$u_{10} = \frac{1}{2}\cdot\frac{1}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_P\alpha_P}{\alpha_E+\mu_E}\cdot\frac{\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H},$$

$$u_{11} = \frac{1}{2}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_P\alpha_P}{\alpha_E+\mu_E}\cdot\frac{\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\beta^*(\Lambda_H-\mu_H)}{P_0\mu_H\mu_M} = \frac{R_{0H}\mu_S}{\mu_M},$$

$$u_{12} = 1. \tag{5.71}$$

Further, the left eigenvector of $J(E^0)$ associated with the zero eigenvalue at $\beta_H = \beta^*$ is given by $v = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}]^T$, where

$$v_1 = 0,$$
$$v_2 = 0,$$
$$v_3 = 0,$$
$$v_4 = \frac{M_0\mu_V\mu_M}{\beta_V N_S\gamma_S},$$
$$v_5 = \frac{1}{2}\cdot\frac{\alpha_C}{\alpha_C+\mu_C}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W},$$
$$v_6 = \frac{1}{2}\cdot\frac{\alpha_I}{\alpha_I+\mu_I}\cdot\frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W},$$
$$v_7 = \frac{N_P\alpha_P}{\alpha_P+\mu_P}\cdot\frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W},$$
$$v_8 = \frac{\alpha_E}{\alpha_E+\mu_E}\cdot\frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W},$$
$$v_9 = \frac{\alpha_L}{\alpha_L+\mu_L}\cdot\frac{N_W\alpha_W}{\alpha_W+\mu_W},$$

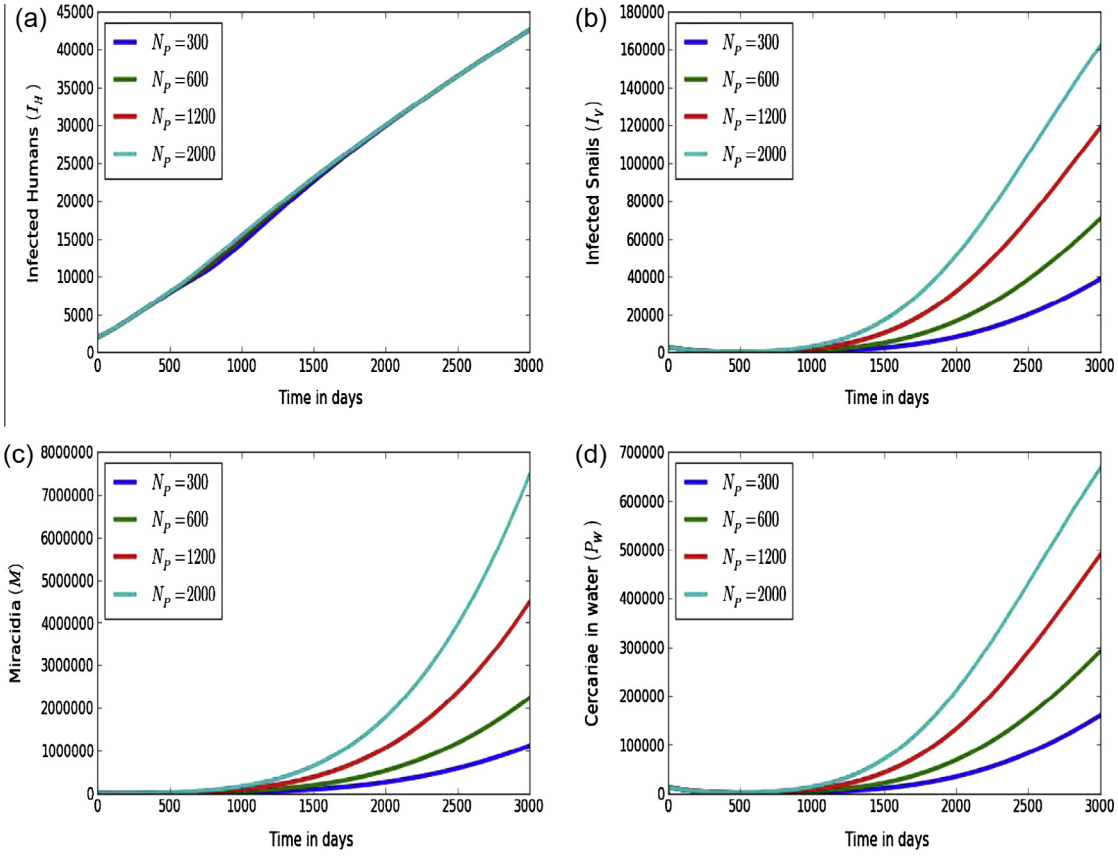

Fig. 6. Graphs of numerical solutions of model system (3.9) showing propagation of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of the rate of mature worm fecundity within an infected human, $N_P : N_P = 300, N_P = 600, N_P = 1200$, and $N_P = 2000$.

$$v_{10} = \frac{N_W \alpha_W}{\alpha_W + \mu_W},$$
$$v_{11} = 1,$$
$$v_{12} = \frac{M_0 \mu_V \mu_M (\mu_V + \delta_V)}{k\beta^* \Lambda_V N_S \gamma_S} = \frac{1}{R_{0HS}}. \tag{5.72}$$

Computation of bifurcation parameters a and b:

The sign of a is associated with the following non-vanishing partial derivatives of F:

$$\frac{\partial^2 f_4}{\partial x_3 \partial x_{11}} = \frac{\partial^2 f_4}{\partial x_{11} \partial x_3} = \frac{\beta_V}{M_0},$$
$$\frac{\partial^2 f_4}{\partial x_{11}^2} = -\frac{2\epsilon\beta_V}{M_0^2}$$
$$\frac{\partial^2 f_5}{\partial x_1 \partial x_{12}} = \frac{\partial^2 f_5}{\partial x_{12} \partial x_1} = \frac{\beta_H}{P_0},$$
$$\frac{\partial^2 f_5}{\partial x_{12}^2} = -\frac{2\beta_H \epsilon (\Lambda_H - \mu_H)}{P_0^2 \mu_H}.$$
$$\frac{\partial^2 f_5}{\partial x_2 \partial x_{12}} = \frac{\partial^2 f_5}{\partial x_{12} \partial x_2} = -\frac{\beta_H \epsilon (\Lambda_H - \mu_H)}{P_0 \mu_H},$$
$$\frac{\partial^2 f_9}{\partial x_2 \partial x_8} = \frac{\partial^2 f_9}{\partial x_8 \partial x_2} = \alpha_E. \tag{5.73}$$

Substituting Eq. (5.73) into Eq. (5.70), we get

$$a = -\frac{2R_{0H}\mu_S^2}{M_0 \mu_M}\left[\frac{k\beta^* \Lambda_V + \epsilon R_0^2 \mu_V^2}{R_{0HS} \Lambda_V \mu_V}\right] - \frac{2R_{0H}\mu_S^2}{P_0}\left[\frac{\beta^* \Lambda_H}{\mu_H(\Lambda_H - \mu_H)} + \epsilon\right],$$
$$= -2R_{0H}\mu_S^2\left[\frac{k\beta^* \Lambda_V + \epsilon R_0 \mu_V^2}{M_0 \mu_V \mu_M \Lambda_V R_{0HS}} + \frac{\beta^* \Lambda_H + \epsilon \mu_H (\Lambda_H - \mu_H)}{P_0 \mu_H \mu_S (\Lambda_H - \mu_H)}\right] < 0. \tag{5.74}$$

For the sign of b, it is associated with the following non-vanishing partial derivatives of F,

$$\frac{\partial^2 f_4}{\partial \beta^* \partial x_{11}} = \frac{k\Lambda_V}{M_0 \mu_V},$$
$$\frac{\partial^2 f_5}{\partial \beta^* \partial x_{12}} = \frac{\Lambda_H - \mu_H}{P_0 \mu_H}. \tag{5.75}$$

It follows from the above expression that

$$b = \frac{2R_{0H}}{\beta^*} > 0. \tag{5.76}$$

Thus, $a < 0$ and $b > 0$. Using Theorem 5.2, item (iv), we have established the following result which only holds for $R_0 > 1$ but close to 1.

Theorem 5.3. *The unique endemic equilibrium guaranteed by Theorem 5.2 is locally asymptotically stable for $R_0 > 1$ near 1.*

6. The effect of environment

The model system (3.9) presented in this work does not explicitly incorporate environmental factors such as the effect of climatological environment. But with minor modifications, the model can incorporate climate change. First consider the two forces of infection which appear in model system (3.9) which are

$$\lambda_H(t) = \frac{\beta_H P_W(t)}{P_0 + \epsilon P_W(t)}, \tag{6.77}$$

and

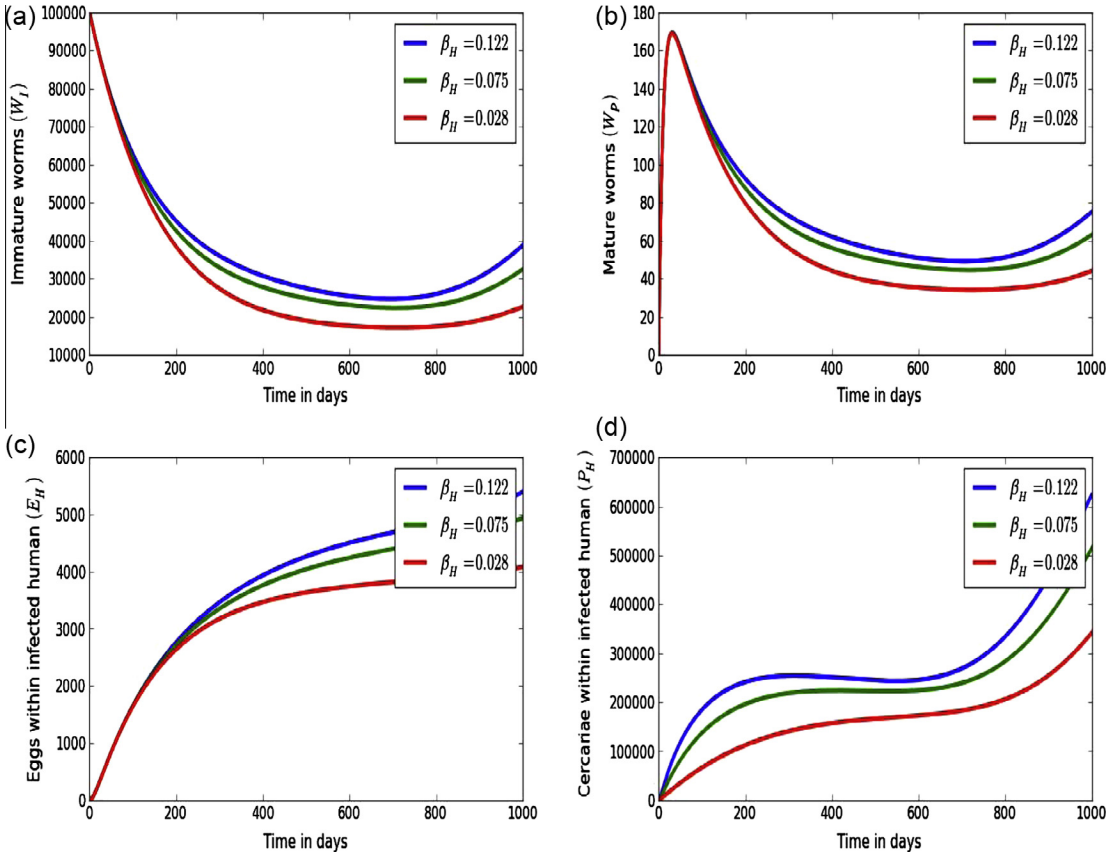

Fig. 7. Graphs of numerical solutions of model system (3.9) showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of the infection rate of humans by cercariae, $\beta_H : \beta_H = 0.028, \beta_H = 0.075$, and $\beta_H = 0.122$.

$$\lambda_V(t) = \frac{\beta_V M(t)}{M_0 + \epsilon M(t)}. \tag{6.78}$$

Then consider the water level in which cercariae, miracidia and snails live and where infections of both humans and snails take place. Assume that the water volume can be described by the following ordinary differential equation:

$$\frac{dW}{dt} = P + S - DW. \tag{6.79}$$

where P is precipitation, S is water flow rate upstream into the site of infection and D is drainage rate of water downstream from the site of infection per volume of water W. Using the volume of water, W, we can modify the two previous forces of infection to become:

$$\lambda_H(t) = \frac{\beta_H P_W(t)}{K_H W + \epsilon P_W(t)}, \tag{6.80}$$

and

$$\lambda_V(t) = \frac{\beta_V M(t)}{K_V W + \epsilon M(t)}. \tag{6.81}$$

where K_A and K_V are constants that re-scale water volume so that transmission of infection from the water to humans and snails occurs at 50% of the maximum rate of $K_H W$ and $K_V W$ respectively. In the absence of seasonal variations in water flow or precipitation, the equilibrium water level becomes:

$$W^* = \frac{P+S}{D}. \tag{6.82}$$

Thus, in the absence of seasonal variations in water flow and precipitation, the two forces of infection become:

$$\lambda_H(t) = \frac{\beta_H P_W(t)}{K_H W^* + \epsilon P_W(t)}. \tag{6.83}$$

$$\lambda_V(t) = \frac{\beta_V M(t)}{K_V W^* + \epsilon M(t)}. \tag{6.84}$$

and if we define

$$K_H W^* = P_0, \quad K_V W^* = M_0, \tag{6.85}$$

then, we are back to original model Eq. (3.9), and all the results we have obtained so far and in particular equilibrium solutions and the reproductive number remain the same except that P_0 and M_0 are now given a new interpretation in those results of re-scaled water volume in which infection of both humans and snails occur. With this new interpretation of P_0 and M_0 and the results obtained from the analysis of the model, we make the following deductions:

a. The forces of infection λ_H and λ_V, are inversely proportional to P_0 and M_0 respectively. Therefore, the force of infection experienced by humans and snails is higher when water levels are low, than when they are high.
b. The reproductive number R_0, is inversely proportional to P_0 and M_0. Therefore, schistosomiasis outbreaks in regions close to rivers, streams and ponds are in constant tension between temperatures, which tend to stimulate growth of the free-living infective pathogens in the physical water environment (cercariae and miracidia), and increased water volumes, which tend to buffer infections.

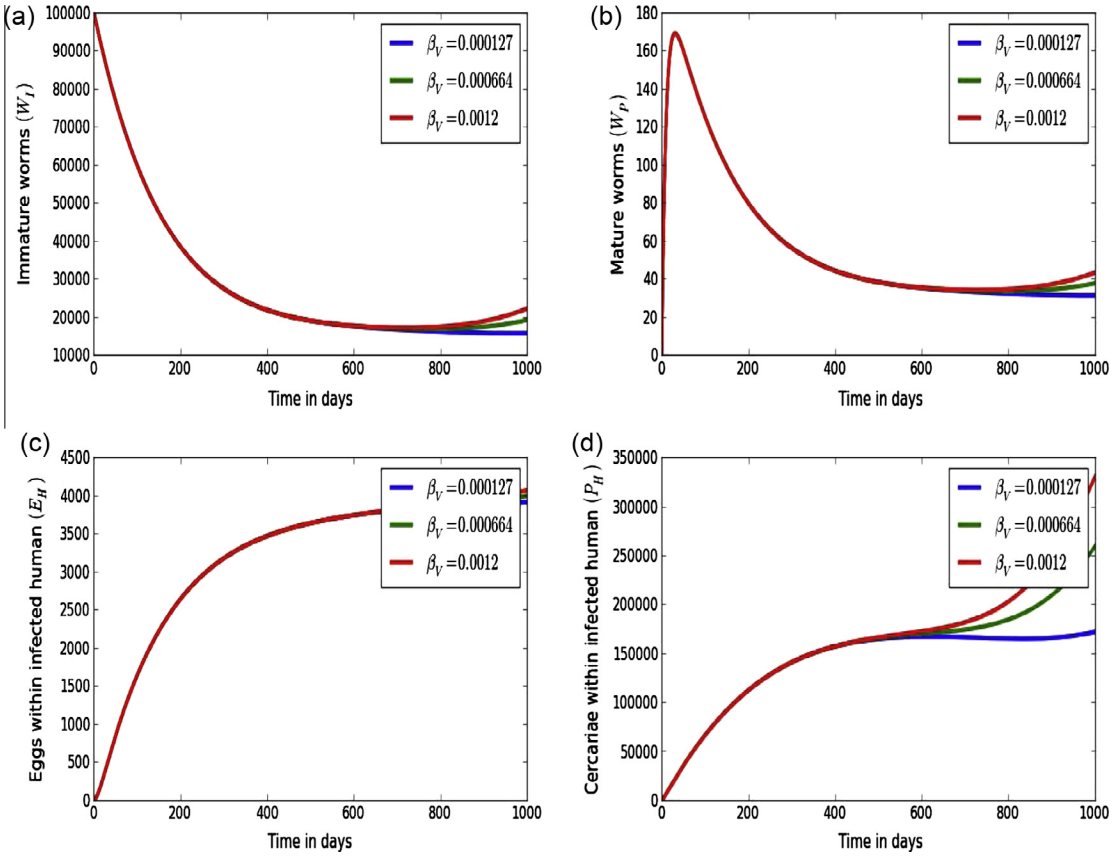

Fig. 8. Graphs of numerical solutions of model system (3.9) showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of the infection rate of snails by miracidia, $\beta_V : \beta_V = 0.000127$, $\beta_V = 0.000664$, and $\beta_V = 0.0012$.

7. Numerical simulations

In this section, we present numerical simulations of model system (3.9) in order to illustrate some of the analytical results obtained in this paper. The main objective here is to illustrate qualitatively the influence of the various within-host disease parameters on between-host model variables and in turn, the influence (qualitatively) of the between-host disease parameters on within-host model variables.

7.1. Methods

The numerical simulations were done using a set of within-host and between-host parameters in Tables 2–4 and initial values given in Table 1. The values of the model parameters are either from published literature or from estimations as values of some parameters are generally not reported in literature. For those parameters which are not reported in literature, their values were only indirectly approximated from inferences reported in the published literature. The model system (3.9) is simulated using Python version V2.6 on the Linux operating system. We used the odeint function in the scipy.integrate package in python.

7.2. Results

In the following, we present the results of the simulations for model system (3.9) in graphical form.

Fig. 3 illustrates the solution profiles of the population of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of rate of excretion of worm eggs by an infected human, $\alpha_E : \alpha_E = 0.0004, \alpha_E = 0.005$ and $\alpha_E = 0.4$. The results demonstrate a correlation between within-host disease processes and between-host disease transmission. In particular, the results show that higher rates of worm eggs excretion results in increased populations of infective parasites (miracidia and cercariae) in the physical water environment and a noticeable increase in infected snails. Therefore, improvements in individual sanitation (which reduce environmental contamination with worm eggs) are good for the community because they reduce the risk of human schistosomiasis transmission to the general public.

Fig. 4 illustrates the solution profiles of the population of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of natural death of worm eggs, $\mu_E : \mu_E = 0.00685, \mu_E = 0.005$ and $\mu_E = 0.5$. The numerical results show that the within-host process of death of worm eggs affect transmission of the disease in the population. Increased death of worm eggs reduces transmission of the disease at population level. Therefore, immune mechanisms which enhance the killing of worm eggs within an infected individual reduce transmission risk of the disease within a community.

Fig. 5 shows graphs of numerical solutions of model system (3.9) showing propagation of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of natural death rate of immature worms, $\mu_I : \mu_I = 0.000685, \mu_I = 0.0005, \mu_I = 0.00685$ and $\mu_I = 0.5$. The results in Fig. 5 shows that an increase in the death rate of immature worms

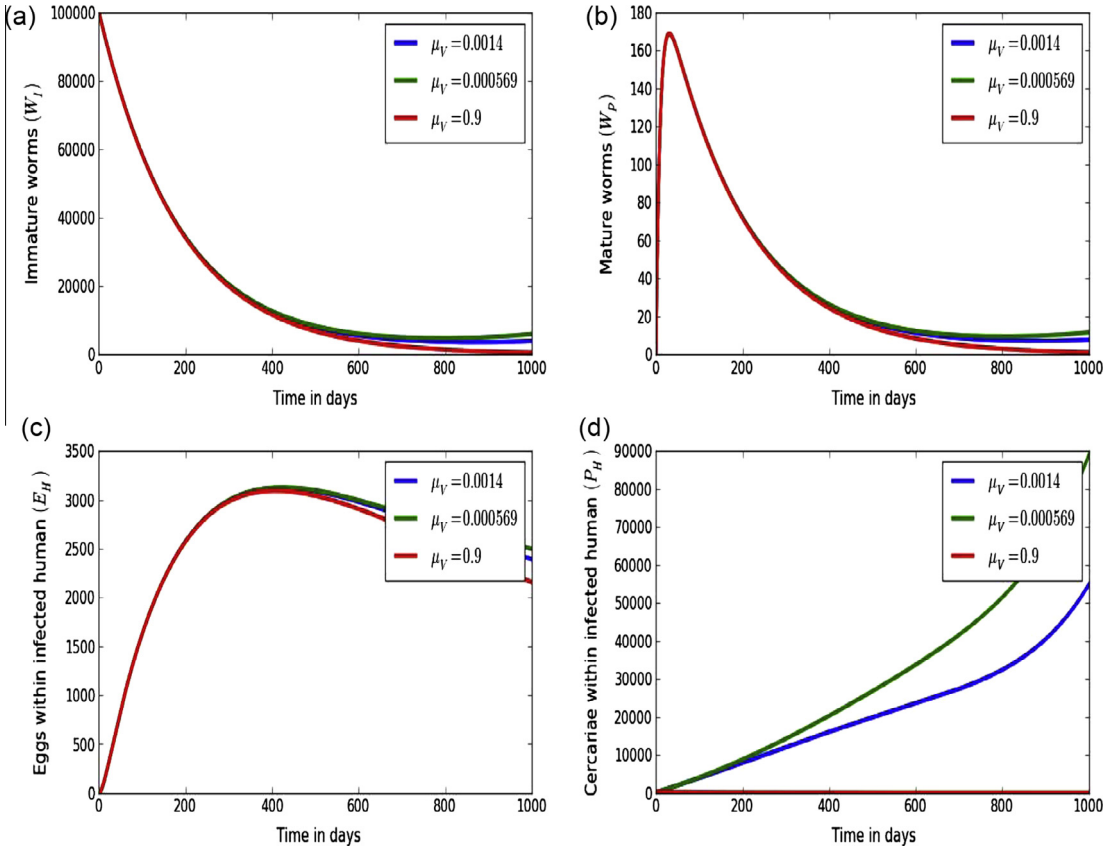

Fig. 9. Graphs of numerical solutions of model system (3.9) showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of natural death rate of snails, $\mu_V : \mu_V = 0.000569, \mu_V = 0.0014$, and $\mu_V = 0.9$.

within an infected individual reduces the transmission risk of human schistosomiasis at population level. Therefore immune mechanisms which kill immature worm within an infected individual have an epidemiological influence on human schistosomiasis transmission.

Fig. 6 shows graphs of the numerical solutions of (a) infected humans (I_H), (b) infected snails (I_V), (c) miracidia (M) in the physical water environment, and (d) cercariae (P_W) in the physical water environment for different values of the rate of mature worm fecundity within an infected human, $N_P : N_P = 300$, $N_P = 600, N_P = 1200$, and $N_P = 2000$. We observe from Fig. 6 that an increase in production worm eggs per day by each worm pair of mature worms increases the transmission risk of human schistosomiasis. Therefore, immune mechanisms which reduce worm fecundity within an infected individual reduce the transmission risk of human schistosomiasis in the community.

Fig. 7 shows graphs of numerical solutions of model system (3.9) showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of the infection rate of humans by cercariae, $\beta_H : \beta_H = 0.028$, $\beta_H = 0.075$, and $\beta_H = 0.122$. The results show qualitatively the influence of between-host disease process on within-host schistosomiasis infection intensity. In this case, as transmission rate of disease in the community increases, the within-host infection intensity of schistosomiasis also increases. The numerical results demonstrate that the transmission of disease at the population level influence the dynamics within an infected individual. Therefore, human behavioural changes which reduce contact with infected water bodies reduce the infection intensity at individual level. Equally, good sanitation practices by the community which reduce contamination of water bodies reduce the intensity of infection humans at individual level.

Fig. 8 illustrates graphs of numerical solutions showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of the infection rate of snails by miracidia, $\beta_V : \beta_V = 0.000127$, $\beta_V = 0.000664$, and $\beta_V = 0.0012$.

The numerical results in Fig. 8 illustrate that an increase in the rate of infection of snails by miracidia in the physical water environment increases the infection intensity for humans at individual level. This demonstrates the influence of between-host disease transmission parameters on within-host infection intensity. Therefore, public health interventions intended to reduce transmission risk of human schistosomiasis to snails also reduce the disease intensity with an infected individual. The numerical results in Fig. 8 shows direct relationship between population level transmission of the disease and the within-host infection intensity.

Fig. 9 illustrates graphs of numerical solutions showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of natural death rate of snails, $\mu_V : \mu_V = 0.000596, \mu_V = 0.0014$ and $\mu_V = 0.9$. The numerical results in Fig. 9 shows direct relationship between public health interventions intended to reduce snail population (such as killing snails using molluscicides) and infection intensity within an infected individual. This is in agreement with analytical results

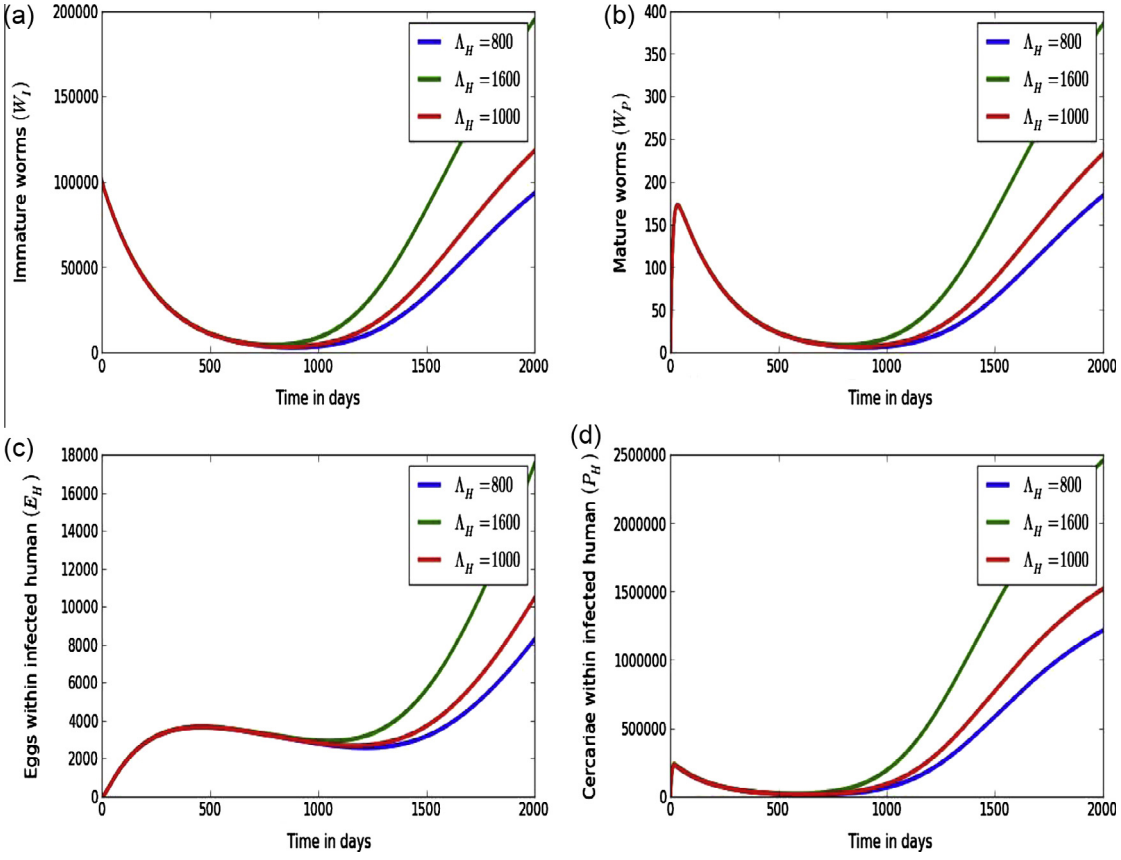

Fig. 10. Graphs of numerical solutions of model system (3.9) showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of recruitment rate of new susceptible humans, $\Lambda_H : \Lambda_H = 800, \Lambda_H = 1000$, and $\Lambda_H = 1600$.

which show influence of between-host disease parameters on within-host disease processes. Here the numerical results show that the death of snails μ_V, reduce the intensity of the disease with an infected individual. Therefore, public health interventions intended to kill snails have beneficial effect on an individual through reduced infection intensity.

Fig. 10 shows graphs of numerical solutions showing propagation of (a) immature worms within an infected human (W_I), (b) mature worms within an infected human (W_P), (c) worm eggs within an infected human (E_H), and (d) cercariae within an infected human (P_H), for different values of recruitment rate of new susceptible humans, $\Lambda_H : \Lambda_H = 800, \Lambda_H = 1000$, and $\Lambda_H = 1600$.

We note from Fig. 10 that the supply of new human susceptibles increases the intensity of humans at individual level. This again confirms the influence of between-host disease parameters on within-host disease processes. But overall, the numerical results presented in this section show bi-directional influence of within-host and between-host disease process on human schistosomiasis transmission.

8. Conclusions

The major innovation proposed in this paper is the adoption of a linked modelling framework of the within-host (disease processes within a single host) and between-host (population transmission) dynamics of infectious diseases. While the building blocks (within-host model and between-host model) are specific to human schistosomiasis, the framework approach is general and is in principle reproducible with other infectious diseases with free-living pathogens in the environment. We established, using results from the analysis of the endemic equilibrium expression, the disease reproductive number R_0, and numerical simulations of the full model for the linked within-host and between-host models of human schistosomiasis, the individual's epidemiological status and transitions are determined by the within-host dynamics whose outcome feeds forward in the population dynamics of human schistosomiasis and that in turn, episodes of transmission of human schistosomiasis at both the human and snail host population levels feed back to the within-individual-host through environmental contamination with infectious schistosome parasite. We also illustrated how the alternative hosts (human and snail) affect parasite dynamics (cercariae and miracidia). The results are significant for the current ongoing efforts to develop new theoretical modelling frameworks of the ecology and evolution of infectious diseases. Overall, we anticipate these initial results to be central in articulating an integrated, more refined diseases control theory of the reciprocal influence between public health interventions to control diseases which are focused on communities and populations on one hand and medical interventions to treat diseases which are focused on the well-being of the individual on the other hand. In the context of human schistosomiasis, these initial findings suggest that there are important medical planning consequences to consider during the processes of epidemiological planning and vice versa in that a treatment that cures a patient of human schistosomiasis is equally good for both the patient and the general public because this patient no longer posses a transmission risk for human schistosomiasis to the public.

References

[1] W. Garira, The dynamical behaviours of diseases in Africa, in: P. Joachim, Carmel M. Martin (Eds.), Handbook of Systems and Complexity in Health Sturmberg, Springer, 2013. ISBN 978-1-4614-4997-3.

[2] C. Chiyaka, W. Garira, S. Dube, Mathematical modelling of the impact of vaccination on malaria epidemiology, Theor. Diff. Equat. Anal. 1 (1) (2007). 28–58.a.

[3] C. Chiyaka, J.M. Tchuenche, W. Garira, S. Dube, A mathematical analysis of the effects of control strategies on the transmission dynamics of Malaria, Appl. Math. Comput. 195 (2) (2008) 641–662.

[4] Z. Mukandavire, K. Bowa, W. Garira, Modelling circumcision and condom use as HIV/AIDS preventive control strategies, Math. Comput. Model. 46 (11) (2007) 1353–1372. disease parameters. Mathematical Biosciences and Engineering 2(4), 811–832.

[5] Z. Mukandavire, W. Garira, Effects of public health educational campaigns and the role of sex workers on the spread of HIV/AIDS among heterosexuals, Theor. Popul. Biol. 72 (3) (2007) 346–365.

[6] Z. Mukandavire, W. Garira, Sex-structured HIV/AIDS model to analyse the effects of condom use with application to Zimbabwe, J. Math. Biol. 54 (5) (2007) 669–699.

[7] Z. Mukandavire, W. Garira, Age and sex structured model for assessing the demographic impact of mother-to-child transmission of HIV/AIDS, Bull. Math. Biol. 69 (6) (2007) 2061–2092.

[8] C.P. Bhunu, Z. Mukandavire, W. Garira, M. Zimba, Tuberculosis transmission model with chemoprophylaxis and treatment, Bull. Math. Biol. 70 (4) (2008) 1163–1191.

[9] C.P. Bhunu, W. Garira, Modelling the transmission of multidrug-resistant and extensively drug-resistant TB, in: J.M. Tchuenche, Z. Mukandavire (Eds.), Advances in Disease Epidemiology, Nova Science Publishers, 2009, pp. 195–220. ISBN: 160741452X.

[10] M.J. Keeling, P. Rohani, Modeling Infectious Diseases in Humans and Animals, Princeton University Press, 2008.

[11] F. Brauer, C. Castillo-Chavez, Mathematical Models in Population Biology and Epidemiology, Springer, 2011.

[12] O. Diekmann, J.A.P. Heesterbeek, Mathematical Epidemiology of Infectious Diseases, vol. 146, Wiley, Chichester, 2000.

[13] G. Magombedze, W. Garira, E. Mwenje, Modelling the human immune response mechanisms to Mycobacterium tuberculosis infection in the lungs, Math. Biosci. Eng. 3 (4) (2006) 661–682.

[14] G. Magombedze, W. Garira, E. Mwenje, In-vivo mathematical study of co-infection dynamics of HIV-1 and Mycobacterium tuberculosis, J. Biol. Syst. 16 (03) (2008) 357–394.

[15] C. Chiyaka, W. Garira, S. Dube, Modelling immune response and drug therapy in human malaria infection, Comput. Math. Methods Med. 9 (2) (2008) 143–163.

[16] T. Shiri, W. Garira, S.D. Musekwa, A two-strain HIV-1 mathematical model to assess the effects of chemotherapy on, 2005

[17] G. Magombedze, W. Garira, E. Mwenje, Modelling the immunopathogenesis of HIV-1 infection and the effect of multidrug therapy: the role of fusion inhibitors in HAART, J. Math. Biosci. Eng. 5 (3) (2008) 485–504.

[18] W. Garira, S.D. Musekwa, T. Shiri, Optimal control of combined therapy in a single strain HIV-1 model, Electron. J. Diff. Eq. 2005 (52) (2005) 1–22.

[19] E.T. Chiyaka, G. Magombedze, L. Mutimbu, Modelling within host parasite dynamics of schistosomiasis, Comput. Math. Methods Med. 11 (5) (2010) 255–280.

[20] M. Nowak, R.M. May, Virus Dynamics: Mathematical Principles of Immunology and Virology: Mathematical Principles of Immunology and Virology, Oxford University Press, 2000.

[21] D.A. Bundy et al., Immunoepidemiology of lymphatic filariasis: the relationship between infection and disease, Immunol. Today 12 (1991) A71–A75.

[22] D.A.P. Bundy, G.F. Medley, Immunoepidemiology of human geohelminthiasis: ecological and immunological determinants of worm burden, Parasitology 104 (Suppl.) (1992) S105–S119.

[23] M.E.J. Woolhouse, A theoretical framework for the immunoepidemiology of helminth infection, Parasite Immunol. 14 (1992) 563–578.

[24] S. Gupta, K.P. Day, A theoretical framework for the immunoepidemiology of Plasmodium falciparum malaria, Parasite Immunol. 16 (1994) 361–370.

[25] B. Hellriegel, Immunoepidemiology – bridging the gap between immunology and epidemiology, Trends Parasit. 17 (2) (2001) 102–106.

[26] M.G. Roberts, The immuno-epidemiology of nematode parasites of farmed animals: a mathematical approach, Parasit. Today 15 (6) (1999) 246–251.

[27] M.A. Gilchrist, A. Sasaki, Modeling host-parasite co-evolution: a nested approach based on mechanistic models, J. Theor. Biol. 218 (2002) 289–308.

[28] N. Esposito, C. Rossi, A nested-epidemic model for the spread of hepatitis C among injecting drug users, Math. Biosci. 188 (2004) (117, 2917).

[29] D. Coombs, M.A. Gilchrist, C.L. Ball, Evaluating the importance of within-and between-host selection pressures on the evolution of chronic pathogens, Theor. Popul. Biol. 72 (4) (2007) 576–591.

[30] J. Dushoff, Incorporating immunological ideas in epidemiological models, J. Theor. Biol. 180 (3) (1996) 181–187.

[31] B.T. Grenfell, O.G. Pybus, J.R. Gog, J.L. Wood, J.M. Daly, J.A. Mumford, E.C. Holmes, Unifying the epidemiological and evolutionary dynamics of pathogens, Science 303 (5656) (2004) 327–332.

[32] N. Mideo, S. Alizon, T. Day, Linking within- and between-host dynamics in the evolutionary epidemiology of infectious diseases, Trends Ecol. Evol. 23 (9) (2008) 511–517.

[33] F.A. Milner, L.M. Sega, Integrating immunological and epidemiological models, in: 18th World IMACS/MODSIM Congress, Cairns, Australia, 13–17 July 2009, 685–690. <http://mssanz.org.au/modsim09>.

[34] M. Martcheva, An Immuno-epidemiological Model of Paratuberculosis, in: AIP Conference Proceedings, International conference; 3rd, Application of

Mathematics in Technical and Natural Science, vol. 1404(1), 2011, pp. 176–183.
[35] D.M. Vickers, N.D. Osgood, A unified framework of immunological and epidemiological dynamics for the spread of viral infections in a simple network-based population, Theor. Biol. Med. Model. 4 (49) (2007) 1–13.
[36] Z. Feng, J. Velasco-Hernandez, B. Tapia-Santos, M.C.a. Leite, A model for coupling within-host and between-host dynamics in an infectious disease, Nonlinear Dyn. 68 (2012) 401–411.
[37] H. Tuckwell, L. Toubiana, J. Vibert, Spatial epidemic network models with viral dynamics, Phys. Rev. E 57 (1998) 2163–2169.
[38] N. Rujeni, N. Nausch, C.D. Bourke, N. Midzi, T. Mduluza, D.W. Taylor, F. Mutapi, Atopy is inversely related to schistosome infection intensity: a comparative study in Zimbabwean Villages with distinct levels of *Schistosoma haematobium* infection, Int. Arch. Allergy Immunol. 158 (3) (2012) 288–298.
[39] J. Lama, V. Planelles, Host factors influencing susceptibility to HIV infection and AIDS progression, Retrovirology 4 (1) (2007) 52.
[40] C. Chiyaka, W. Garira, S. Dube, Transmission model of endemic human malaria in a partially immune population, Math. Comput. Model. 46 (5) (2007) 806–822.
[41] H.M. Yang, H.M. Yang, Malaria transmission model for different levels of acquired immunity and temperature-dependent parameters (vector), Revista de Saúde Pública 34 (3) (2000) 223–231.
[42] J. Tumwiine, J.Y.T. Mugisha, L.S. Luboobi, A mathematical model for the dynamics of malaria in a human host and mosquito vector with temporary immunity, Appl. Math. Comput. 189 (2) (2007) 1953–1965.
[43] A.C. Ghani, C.J. Sutherland, E.M. Riley, C.J. Drakeley, J.T. Griffin, R.D. Gosling, J.A. Filipe, Loss of population levels of immunity to malaria as a result of exposure-reducing interventions: consequences for interpretation of disease trends, PLoS One 4 (2) (2009) e4383.
[44] M. Martcheva, S.S. Pilyugin, An epidemic model structured by host immunity, J. Biol. Syst. 14 (02) (2006) 185–203.
[45] T. Kostova, Persistence of viral infections on the population level explained by an immuno-epidemiological model, Math. Biosci. 206 (2) (2007) 309–319.
[46] Z. Feng, J. Velasco-Hernandez, B. Tapia-Santos, A mathematical model for coupling within-host and between-host dynamics in an environmentally-driven infectious disease, Math. Biosci. 241 (1) (2013) 4917.
[47] A. Pruss-Ustum, C. Corvalan, Preventing Disease Through Healthy Environments: Towards an Estimate of the Environmental Burden of Disease, World Health Organization, Geneva, 2006. <http://www.who.int/quantifyingehimpacts/publications/preventingdisease.pdf>.
[48] A. Pruss-Ustum, C. Corvalan, How much disease burden can be prevented by environmental interventions?, Epidemiology 18 (1) (2007) 167–178
[49] K.R. Smith, K.R. Smith, F.C. Corvalan, T. Kjellstrom, How much global ill health is attributable to environmental factors?, Epidemiology 10 (5) (1999) 573–584
[50] World Health Organization: Environmental Burden of Disease Series. Geneva, 2007. <http://www.who.int/quantifyingehimpacts/national>.
[51] M. Bani-Yaghoub, R. Gautam, D. Dpfer, C.W. Kaspar, R. Ivanek, Effectiveness of environmental decontamination as an infection control measure, Epidemiol. Infect. 140 (3) (2012) 542.
[52] C.A. Gilligan, An epidemiological framework for disease management, Adv. Bot. Res. 38 (2002) 1–64.
[53] World Health Organization: World Health Report, Reducing Risks, Promoting Healthy Life, Geneva, 2002. <http://www.who.int/whr/2002>
[54] T. Caraco, I.N. Wang, Free-living pathogens: life-history constraints and strain competition, J. Theor. Biol. 250 (3) (2008) 569–579.
[55] M. Boots, A general host-pathogen model with free-living infective stages and differing rates of uptake of the infective stages by infected and susceptible hosts, Res. Popul. Ecol. 41 (2) (1999) 189–194.
[56] T.D. Mangal, S. Paterson, A. Fenton, Predicting the impact of long-term temperature changes on the epidemiology and control of schistosomiasis: a mechanistic model, PLoS One 3 (1) (2008) e1438.
[57] J. Wu, R. Dhingra, M. Gambhir, J.V. Remais, Sensitivity analysis of infectious disease models: methods, advances and their application, J. R. Soc. Interface 10 (86) (2013) 20121018.
[58] E.T. Chiyaka, W. Garira, Mathematical analysis of the transmission dynamics of schistosomiasis in the human–snail hosts, J. Biol. Syst. 17 (03) (2009) 397–423.
[59] S. Riley, H. Carabin, C. Marshall, R. Olveda, A.L. Willingham, S.T. McGARVEY, Estimating and modeling the dynamics of the intensity of infection with *Schistosoma japonicum* in villagers of Leyte, Philippines. Part II: intensity-specific transmission of *S. japonicum*. The schistosomiasis transmission and ecology project, Am. J. Trop. Med. Hyg. 72 (6) (2005) 754–761.
[60] D.R. Coon, Schistosomiasis: overview of the history, biology, clinicopathology, and laboratory diagnosis, Clin. Microbiol. Newsl. 27 (21) (2005) 163–168.
[61] S. Liang, D. Maszle, R.C. Spear, A quantitative framework for a multi-group model of *Schistosomiasis japonicum* transmission dynamics and control in Sichuan, China. Acta Trop. 82 (2) (2002) 263–277.
[62] Z. Feng, A. Eppert, F.A. Milner, D.J. Minchella, Estimation of parameters governing the transmission dynamics of schistosomes, Appl. Math. Lett. 17 (10) (2004) 1105–1112.
[63] B. Gryseels, K. Polman, J. Clerinx, L. Kestens, Human schistosomiasis, The Lancet 368 (9541) (2006) 1106–1118.
[64] A.N.A. Hussein, I.M. Hassan, R. Khalifa, Development and hatching mechanism of Fasciola eggs, light and scanning electron microscopic studies, Saudi J. Biol. Sci. 17 (3) (2010) 247–251.
[65] R.C. Spear, A. Hubbard, S. Liang, E. Seto, Disease transmission models for public health decision making: toward an approach for designing intervention strategies for Schistosomiasis japonica, Environ. Health Perspect. 110 (9) (2002) 907.
[66] P. Jordan, G. Webbe, R. Sturrock, Human Schistosomiasis, CAB International, Wallingford, 1993.
[67] F.A. Milner, R. Zhao, A deterministic model of schistosomiasis with spatial structure, Math. Biosci. Eng. 5 (3) (2008) 505–522.
[68] M. Bani-Yaghoub, R. Gautam, Z. Shuai, P. van den Driessche, R. Ivanek, Reproduction numbers for infections with free-living pathogens growing in the environment, J. Biol. Dyn. 6 (2) (2012) 923–940.
[69] D.L. Smith, F.E. McKenzie, R.W. Snow, S.I. Hay, Revisiting the basic reproductive number for malaria and its implications for malaria control, PLoS Biol. 5 (3) (2007) e42.
[70] P. Van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180 (1) (2002) 29–48.
[71] O. Diekmann, J.A.P. Heesterbeek, J.A.J. Metz, On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations, J. Math. Biol. 28 (4) (1990) 365–382.
[72] J.M. Hyman, J. Li, An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations, Math. Biosci. 167 (1) (2000) 65–86.
[73] C. Castillo-Chavez, Z. Feng, W. Huang, On the computation of R_0 and its role in global stability, in: C. Castillo-Chavez, S. Blower, P. van den Driessche, D. Kirschner (Eds.), Mathematical Approaches for Emerging and Re-emerging Infectious Diseases Part 1: An Introduction to Models, Methods and Theory, The IMA Volumes in Mathematics and Its Applications, vol. 125, Springer-Verlag, Berlin, 2002, pp. 229–250.
[74] C. Castillo-Chavez, B. Song, Dynamical models of tuberculosis and their applications, Math. Biol. Eng. 1 (2) (2004) 361–404.
[75] J. Carr, Applications Centre Manifold Theory, Springer-Verlag, New York, 1981.
[76] J. Dushoff, W. Huang, C. Castillo-Chavez, Backwards bifurcations and catastrophe in simple models of fatal diseases, J. Math. Biol. 36 (1998) 227178.