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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

Winston Garira *, Dephney Mathebula, Rendani Netshikweta

Modelling Health and Environmental Linkages Research Group (MHELRG), C/o Department of Mathematics and Applied Mathematics, University of Venda, Private Bag X5050, Thohoyandou 0950, South Africa

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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

* Corresponding author.
E-mail address: winston.garira@univen.ac.za (W. Garira).

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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