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The transmission mechanism theory of disease dynamics: Its aims, assumptions and limitations

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ABSTRACT

Most of the progress in the development of single scale mathematical and computational models for the study of infectious disease dynamics which now span over a century is build on a body of knowledge that has been developed to address particular single scale descriptions of infectious disease dynamics based on understanding disease transmission process. Although this single scale understanding of infectious disease dynamics is now founded on a body of knowledge with a long history, dating back to over a century now, that knowledge has not yet been formalized into a scientific theory. In this article, we formalize this accumulated body of knowledge into a scientific theory called the transmission mechanism theory of disease dynamics which states that at every scale of organization of an infectious disease system, disease dynamics is determined by transmission as the main dynamic disease process. Therefore, the transmission mechanism theory of disease dynamics can be seen as formalizing knowledge that has been inherent in the study of infectious disease dynamics using single scale mathematical and computational models for over a century now. The objective of this article is to summarize this existing knowledge about single scale modelling of infectious dynamics by means of a scientific theory called the transmission mechanism theory of disease dynamics and highlight its aims, assumptions and limitations.

1. Introduction

Despite the fact that there is now a large body of knowledge about the study of infectious disease dynamics using single scale mathematical and computational models, this vast knowledge has never been formalized into a scientific theory with a clear statement of aims, assumptions, and limitations. In this article, we formalize this existing knowledge about single scale modelling of infectious disease dynamics into a scientific theory called the transmission mechanism theory of disease dynamics and also explain its aims, assumptions, and limitations. Scientific theories have long been celebrated in the development of science. This is because science has progressed over time by being able to summarize our existing knowledge of natural phenomena using certain scientific theories. Two scientific theories that summarize our current understanding of

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infectious disease dynamics are (Garira, 2019): [a.] the transmission mechanism theory of disease dynamics - which is about single scale modelling of infectious disease dynamics, and [b.] the replication-transmission relativity theory of disease dynamics - which is about multiscale modelling of infectious disease dynamics. The article (Garira, 2019) mentions and describes the transmission mechanism theory of disease dynamics for the first time, but does not give a formal statement of the scientific theory. In this article, we give a formal statement of the transmission mechanism theory of disease dynamics for the first time, and also explain its aims, assumptions, and limitations. The transmission mechanism theory of disease dynamics states that at every scale of organization of an infectious disease system, disease dynamics is determined by transmission as the main dynamic disease process. Therefore, the transmission mechanism theory of disease dynamics is about our understanding of single scale dynamic interactions between an infectious agent such as bacteria, virus, fungi, helminths, prion, protozoa, or some mobile genetic elements with other living organisms and the environment.

The transmission mechanism theory implies that understanding infectious disease dynamics involves three types of scientific activities: [a.] developing an understanding of disease transmission process, [b.] identifying the scale at which this transmission process takes place, and [c.] developing a mathematical or computational model of disease dynamics at the identified scale that realistically incorporates the transmission process as the main dynamic disease process. This paper is structured as follows. In section 2, we discuss the aims and assumptions of the transmission mechanism theory. This is followed by section 3 where we discuss the formalization of this theory in mathematical terms. In section 4 we present two main limitations which undermine the usefulness and application of the transmission mechanism theory. To address one of these limitations we proposed a new single scale modelling science base for directly transmitted infectious disease systems where the inside-host environment's biological entities such as cells, tissues, organs, body fluids, whole body are considered as reservoirs of free-living infective pathogen in models of infectious disease dynamics that is comparable to an existing single scale modelling science base for environmentally transmitted infectious diseases where the outside-host geographical environment's physical entities such as soil, air, formites/contact surfaces, food and water are considered as reservoirs of free-living infective pathogen in models of infectious disease dynamics using malaria as an example in section 5. The new single scale malaria model is analyzed in section 6. We also discuss how the other limitation was recently addressed by revising and extending the transmission mechanism theory into a new theory of disease dynamics (Garira, 2019) called the replication-transmission relativity theory of disease dynamics in section 7. A summary of work in this article is given in section 8.

2. Aims and assumptions of the transmission mechanism theory

The transmission mechanism theory of infectious disease dynamics constitutes a body of knowledge that informs us about ways of defining what should be emphasized and measured in single scale mathematical and computational models of infectious disease dynamics. The theory requires measurement of transmission process as the main dynamic disease process. The aim of this infectious disease dynamics theory is to provide a unifying framework for the scientific practice of the study of infectious disease dynamics using single scale mathematical, statistical, and computational models. Its chief value and main intention is to unify disparity ideas into a united body of knowledge that allows understanding of single scale infectious disease dynamics in terms of transmission as the main dynamic disease process. The transmission mechanism theory is intended to provide a common basis for developing single scale mathematical and computational models of infectious disease dynamics. Therefore, the transmission mechanism theory of disease dynamics provides an important framework that helps to establish the intellectual foundations for the study of infectious disease dynamics using single scale mathematical, statistical, and computational models. This theory enables us to use single scale mathematical and computational models to derive meaning to control, elimination and even eradication of infectious diseases. This is achieved by first developing single scale mathematical and computational models of infectious disease dynamics and then convert these single scale models into metrics for disease control, elimination and even eradication. The theory makes the following four key assumptions:

[I.] **An infectious disease has two main forms of transmission mechanisms**: The transmission mechanism theory makes the assumption that infectious disease dynamics is a result of two main transmission mechanisms which are: [a.] environmental transmission mechanism, and [b.] direct transmission mechanism. In direct transmission mechanism, transmission of the infectious disease is mediated through direct contact of a susceptible host (cell, tissue, organ/microcommunity, organism, macrocommnity) with an infected host (cell, tissue, organ/microcommunity, whole organism, macrocommnity). However, in environmental transmission mechanism, transmission of the infectious disease is mediated through contact of a susceptible host (cell, tissue, organ/microcommunity, organism, macrocommnity) with an infectious agent in the environment or through contact with an environment which is contaminated with an infectious agent. These two main transmission mechanisms differ in the ways host infectiousness is defined:

[a.] *Environmental transmission mechanism*: In environmental transmission mechanism, host infectiousness is linked to the pathogen load. This transmission mechanism is based on making an explicit assumption about the link between infective pathogen load that the host (which can be a cell, a tissue, a organ/microcommunity, a whole organism, a macrocommunity) can excrete/shed into its external environment and infectiousness to other hosts (which can be cells, tissues, organs or microcommunities, whole organisms, communities).

[b.] *Direct Transmission mechanism*: In direct transmission mechanism, host infectiousness is linked to a disease class. This second transmission mechanism is based on avoiding explicit assumptions about the link between the

infective pathogen load and infectiousness, but instead assumes that disease severity is the one linked to pathogen load while making direct association between disease class of the host (which can be a cell, a tissue, an organ or a microcommunity, a whole organism, a macrocommunity) and infectiousness. In the simplest cases of this transmission mechanism only a single class of infectious individuals (cells, tissues, organs or microcommunities, whole organisms, macrocommunities) is assumed while the more elaborate versions of this transmission mechanism further subdivides infected individuals into different classes (highly infectious individual who are symptomatic, mildly infectious individuals who are asymptomatic, vaccinated individuals etc.) (Yang, 2000).

In some cases vector transmission is counted as a third type of disease transmission mechanism. But in the context of the transmission mechanism theory, vector-borne transmission is just one of the two forms of multi-host disease transmission which are: [a.] multi-host transmission in which the infectious agent needs at least two hosts to complete its life cycle, which is the vector-transmission mechanism, and [b.] multi-host transmission because of the generalist nature of the infectious agent. Vector transmission mechanism, which is a form of multi-host transmission can either be direct transmission as in the case of malaria (Agusto, Leite, & Orive, 2019) or it can be environmental transmission as in the case of schistosomiasis (Chiyaka & Garira, 2009). The only difference between vector transmission and other forms of transmission is that in vector transmission, two hosts are needed for the infectious agent to complete its life cycle: [a.] a definitive host, also sometimes called the primary host - in which the infectious agent becomes sexually matured and reproduces sexually, and [b.] an intermediate host also sometimes called the secondary host - in which an infectious agent passes through one or more asexual stages, mostly developmental stages.

[II.] **An infectious disease has seven main scales of organization at which single scale mathematical models can be developed**: This assumption makes the point that an infectious disease is a complex system and that in order to analyze infectious disease dynamics using single scale mathematical and computational models, this complexity has to be brought down to manageable levels by discretizing or decomposing an infectious disease into different discrete single scales of organization, so that at each singe scale of organization, disease transmission is the only main dynamic disease process. This assumption is informed by a pathogen-centred perspective of infectious disease dynamics.

Based on the structural organization of living organisms and their associated environments as habitats for infectious agents, we establish that an infectious disease can be discretized into seven main different single scales of organization which are: [a.] the cell scale, [b.] the tissue scale, [c.] the organ or microcommunity scale, [d.] the microecosystem scale, [e.] the whole organism scale, [f.] the macrocommunity scale, and [g.] the macroecosystem scale. Fig. 1 is a conceptual diagram illustrating the seven different single scales of organization of an infectious disease system. As shown in Fig. 1 these different single scales are hierarchically organized in both space and time so that along the hierarchy, as the spatial scale of the transmission process increases so does the time scale of the same transmission process. Inherent in this assumption is the idea that at each of these seven different single scales of organization, the dynamics of an infectious disease can be observed and analyzed independently by considering the transmission process as the only main dynamic disease process without reference to other scales at which other disease processes which influence the transmission process occur.

In what follows, we briefly describe each of the seven different single scales of organization of an infectious disease and also give some examples of single scale models of disease dynamics that have been developed in the past at each of the seven different single scales of organization based on the transmission mechanism theory.

[a.] *The cell scale*: At this scale of organization, single scale models of disease dynamics are developed incorporating either direct transmission or environmental transmission among a population of cells for a single pathogen species and single cell species context. At this scale of organization, transmission is considered to occur through local exchange of pathogen only either through direct contact between infected cells and susceptible cells - which is direct transmission, or through direct contact between susceptible cells and pathogen in the extracellular environment - which is environmental transmission. An example of a single scale model of disease dynamics incorporating direct transmission at cell scale of organization is (Culshaw, Ruan, & Webb, 2003). Another example of a single scale model at cell scale of organization incorporating environmental transmission is (Magombedze, Garira, & Mwenje, 2008).

[b.] *The tissue scale*: Single scale models of disease dynamics are developed at this scale of organization incorporating either direct transmission or environmental transmission among a population of tissues in the context of single pathogen species and single tissue species context. At this tissue scale of organization, transmission is considered to occur through local exchange of pathogen only either through direct contact between infected tissues and susceptible tissues - which is direct transmission, or through direct contact between susceptible tissues and pathogen in the inter-tissue environment - which is environmental transmission. Few models of disease dynamics have been developed at this scale of organization. The tissues usually considered in the development of models of infectious disease dynamics at this scale of organization are the granulomas (Shah, Pritt, & Alexander, 2017) or microabscess (Pigozzo, Macedo, Weber dos Santos, & Lobosco, 2012). A typical example of a single scale model developed at the tissue scale of organization incorporating direct transmission is (Gong, Linderman, & Kirschner, 2015).

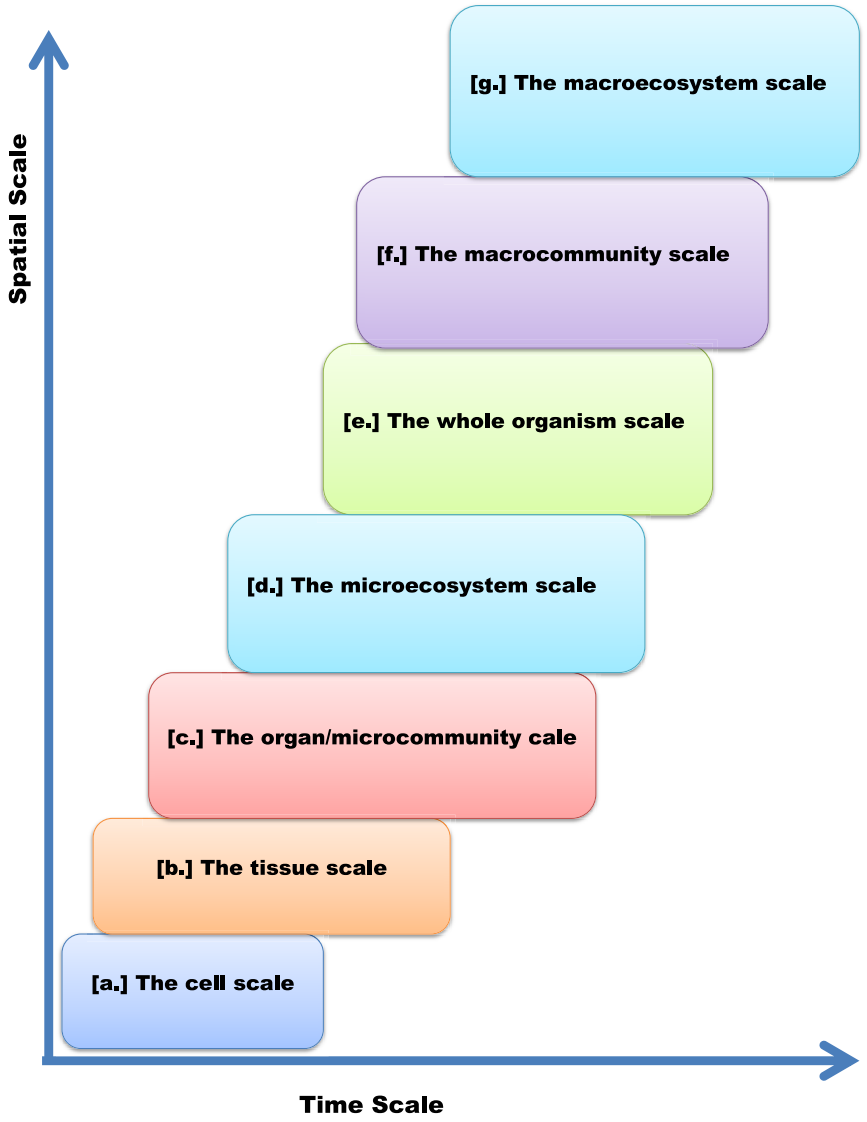


Fig. 1. A schematic diagram of the seven main different single scales of organization of an infectious disease system based on the transmission mechanism theory which are: [a.] the cell scale, [b.] the tissue scale, [c.] the organ/microcommunity scale, [d.] the microecosystem scale, [e.] the whole organism scale, [f.] the macrocommunity scale, and [g.] the macroecosystem scale. These scales are hierarchically organized in both space and time such that as the spatial scale of the transmission process increases, so does the time scale of the same transmission process.

[c.] *The organ/microcommunity scale*: At this scale of organization, single scale models of disease dynamics are developed based on either direct transmission or environmental transmission. At the organ scale, the different organs are considered as distinct pathogen microcommunities which is why this scale of organization is also called the micro-community scale. Within each organ as a distinct pathogen microcommunity, single scale models of disease dynamics are developed incorporating either direct transmission or environmental transmission among a population of tissues or cells in the context of single pathogen species and single tissue or single cell species context. Therefore, within each organ transmission is considered to occur through local exchange of pathogen only either through direct contact between infected tissues or cells and susceptible tissues or cells - which is direct transmission, or through direct contact between susceptible tissues or cells and pathogen in the inter-tissue environment or inter-cellular environment - which is environmental transmission. However, pathogen transmission between organs as distinct microcommunities is considered to occur through global exchange of pathogen between the different organs. The global exchange of pathogen between organs or microcommunities or microenvironments is usually through the circulatory system or

through the lymphatic system. For typical examples of single scale models developed at this scale organization see (Orwa, Mbogo, & Luboobi, 2018; Selemani, Luboobi, & Nkansah-Gyekye, 2017) for malaria infections and (Barker & Vaidya, 2020; Chen, Cheng, & Rong, 2019) for viral infections in the context of environmental transmission. Therefore, the main distinguishing feature for single scale models developed at this scale of organization is that they incorporate multiple microcommunities (i.e. the different organs).

[d.] *The microecosystem scale*: Single scale models of disease dynamics are developed incorporating either direct transmission or environmental transmission at this scale of organization like in the other three scales of observation (cell scale, tissue scale, organ scale). However, at the cell scale of organization and tissue scale of organization, the main distinction is that the single scale models are developed incorporating local pathogen transmission in the context of multiple pathogen species/strains and/or either multiple tissue species (for the tissue scale of organization) or multiple cell species (for the cell scale of organization). Further, the main difference between single scale models developed at organ/microcommunity scale of organization and this scale of organization is that the single scale models at this scale of organization are developed incorporating both local and global pathogen transmission in the context of multiple pathogen species/strains. Some examples of single scale disease transmission models developed at this scale of observation are (Browne, 2015; Dai & Zou, 2015; Koelle, Farrell, Brooke, & Ke, 2019; Murray & Perelson, 2005; Shiri, Garira, & Musekwa, 2005). Overall, for this scale of organization, single scale models of disease dynamics are developed in the context of multiple pathogen species/strains, and/or multiple cell species, and/or multiple tissue species.

[e.] *The whole organism scale*: At this scale of organization, single scale models of disease dynamics are developed using either direct transmission or environmental transmission among a population of whole organisms (humans, animals, vectors, or even plants) for a single pathogen species/strain, single organism species context. At this scale of organization, transmission is considered to occur through local exchange of pathogen only either through direct contact between infected organisms and susceptible organisms - which is direct transmission, or through direct contact between susceptible organisms and pathogen in the inter-whole organism macroenvironment - which is environmental transmission. The foundations of the mathematical formalization of the transmission mechanism theory were originally established at this scale of organization (Kermack & McKendrick, 1927; Ross, 1911), that is, the whole organism scale incorporating direct transmission. For examples of single scale models of infectious disease dynamics developed at this scale of organization in the context of environmental transmission see (Breban, 2013) and references therein. Because of the historical legacy of this scale of organization in single scale modelling of infectious disease dynamics, the term host scale is usually used to exclusively mean the whole organism scale of organization although in reality any of the seven different scales of organization can be considered as a host scale because each of the seven scales of organization of an infectious disease is potentially a different pathogen habitat.

[f.] *The macrocommunity scale*: At the macrocommunity scale as the scale of organization, the macroenvironment (geographical environment) is considered as consisting of different macrocommunities at which pathogen transmission occurs. Within each macrocommunity (local, national, regional, whole world) as a distinct pathogen macroenvironment or geographical environment as pathogen habitat, single scale models of disease dynamics are developed incorporating either direct transmission or environmental transmission among a population of whole organisms (humans, animals, vectors, or even plants) in the context of single pathogen species and single whole organism species context. Therefore, within each macrocommunity transmission is considered to occur through local exchange of pathogen only either through direct contact between infected whole organisms and susceptible whole organisms – which is direct transmission, or through direct contact between susceptible whole organisms and pathogen in the geographical environment's physical entities (water, soil, air etc.) - which is environmental transmission. However, pathogen transmission between different geographical environments as distinct macrocommunities is considered to occur through global exchange of infected whole organisms or free-living pathogen in the environment between the different macrocommunities. The global exchange of pathogen between different geographical environments or macrocommunities or macroenvironments is usually through travel, wind, migration, etc. For typical examples of single scale models developed at this scale of organization see (Arino, Sun, & Yang, 2016; Citron et al., 2021; Khatua, Kar, Nandi, Jana, & Kang, 2020; Zakary, Rachik, Elmouki, & Lazaiz, 2017) for direct transmission and (Mononen & Ruokolainen, 2017) for environmental transmission. Therefore, the main distinguishing feature for single scale models developed at this scale of organization compared to those developed at whole organism scale is that here they incorporate multiple macrocommunities (i.e. the different geographical environments).

[g.] *The macroecosystem scale*: Single scale models of disease dynamics are developed at this scale of organization incorporating either direct transmission or environmental transmission like in the whole organism scale and the macrocommunity scale. However, the difference between single scale models developed at whole organism scale and this scale of organization is that at this scale of organization the single scale models are developed incorporating local pathogen transmission in the context of multiple pathogen species and/or multiple whole organism species. Further, the main difference between single scale models developed at macrocommunity scale of organization and this scale of organization is that here single scale models are developed incorporating both local and global pathogen transmission in the context of multiple pathogen species and/or multiple host species. As examples of single scale models of disease dynamics developed at this scale of organization see (Bichara & Iggidr, 2018; Chen et al., 2020; Kucharski, Andreasen, & Gog, 2016; Rashkov & Kooi, 2021).

For these seven different main scales of organization we note that each of them can be considered as a different reservoir of an infectious agent or a habitat in which the infectious agent can live, grow, multiply, and be transmitted.

[III.] **Transmission process of disease is either through local transmission of pathogen only or through both local and global transmission of pathogen**: The transmission mechanism theory further makes the assumption that the transmission process of pathogen is either through local transmission of pathogen only or through both local and global transmission of pathogen. In the context of this assumption, local transmission of pathogen is through direct contact between an infected host (i.e. a cell, or a tissue, or a whole organism) and a susceptible host (i.e. a cell, or a tissue, or a whole organism) – for direct transmission or direct contact between a susceptible host (i.e. a cell, or a tissue, or a whole organism) and pathogen – for environmentally transmitted disease. However, global transmission of pathogen is through facilitated transport of pathogen between an infected host (i. e. a microcommunity, or a macrocommunity) and a susceptible host (i.e. a microcommunity, or a macrocommunity). At microcommunity scale the facilitated transport is through the circulatory system which encompasses the cardiovascular system and the lymphatic system – for humans and other animals and through the vascular system which encompasses the xylem and phloem – for plants. But, at macrocommunity scale the facilitated transport is through aerial means (i.e. through wind/air flow to different geographical areas of the community (local, national, regional, whole world), or hydrological means (i.e. through water flow) to different geographical environment (local level, national level, regional level) or through travel/migration (for human hosts and animal hosts) or export/import of food (for animal and plant hosts and their products). This implies that the seven scales of organization of an infectious disease system can be demarcated into three main groups depending on whether the transmission process involves either local transmission of pathogen only or both local and global transmission of pathogen. The three different groups are: [a.] a group of primary scales of organization (cell scale, tissue scale, whole organism scale) - at which transmission of disease is through local transmission of pathogen only, [b.] a group of secondary scales of organization (microcommunity scale, macrocommunity scale) - at which transmission of disease is through both local transmission of pathogen within each microcommunity or macrocommunity and global transmission of pathogen between microcommunities or macrocommunities, and [c.] a group of tertiary scales of organization (microecosystem scale, macroecosystem scale) - at which transmission of disease is the same as either at primary scales of organization or as at secondary scales of organization, except that it involves transmission of multiple pathogen species or strains and/or multiple whole organism species.

[IV.] **An infectious disease is caused by interaction of three main components which are the host, the pathogen and the environment**: The transmission mechanism theory is founded on another key assumption that in infectious disease dynamics, the transmission process, which is considered to be the main dynamic disease process, is a result of interaction between the host, the pathogen or mobile genetic elements, and the environment. This current understanding of causes of infectious diseases is based on the epidemiological triad theory which was formulated and developed by Frost in 1976 (Frost, 1976). The epidemiological triad theory states that an infectious disease system is a result of the interaction of three components which are: [a.] the host, [b.] the pathogen, and [c.] the environment (Frost, 1976). This understanding is a culmination of previous and now outdated series of infectious disease causation theories which were progressively refined, one after another, to explain the cause of infectious diseases (Garira, 2019). The initial infectious disease causation theory called demonic theory or punitive theory was based on the understanding that infectious diseases are attributed to a variety of spiritual and demonic forces including punishment from God for sinful behaviour or weak moral character or as a result of witchcraft. However, the miasmic theory, is the first infectious disease causation theory established in the era of modern medicine, which was founded on the understanding that infectious diseases are caused by natural processes and was based on the inference that the air arising from certain kinds of ground, especially low swampy areas was the cause of infectious disease. This was later replaced by the germ theory which postulate that infectious diseases are caused by germs/microbes/pathogens. The first expression of the germ theory of disease causation by Jacob Henle (1809–1885) came in 1840 and was developed further by Robert Koch (1843–1910), Joseph Lister (1827–1912), and Louis Pasteur (1822–1875) in the late nineteenth and early twentieth centuries (Brauer, Castillo-Chavez, & Feng, 2019). However, the epidemiological triad theory, introduced by Frost in 1976 (Frost, 1976) as an extension of the germ theory, constitutes the current and modern infectious disease causation theory. In the original formulation of the epidemiological triad theory, the host was interpreted to be whole organism (whole animal, whole human, etc.), but in the context of the transmission mechanism theory, it is interpreted to mean any of the seven scales of organization. This is because each of the seven scales of organization of an infectious disease system is potentially a pathogen habitat, that is, an environment in which pathogen can stay, replicate and be transmitted.

These four assumptions provide a foundation for the transmission mechanism theory of infectious disease dynamics.

3. Formalization of the transmission mechanism theory in mathematical terms

Scientific theories do not always have to be formalized in mathematical terms in order to be useful. The theory of evolution formulated and developed by Charles Darwin (Darwin, 1909, pp. 95–96) is a successful theory although Darwin never

formalized it in mathematical terms. However, the formalization of a theory in mathematical terms is often interpreted as a sign of a maturing theory. Most of the knowledge about single scale mathematical and computational modelling of infectious disease dynamics which has now accumulated over time is based on the application of the transmission mechanism theory in its classical form. The classical transmission mechanism theory is about single scale modelling of infectious disease dynamics at whole organism scale such as whole human scale or whole animal scale. The two basic assumptions of the classical transmission mechanism theory are that: [a.] an infectious disease consists of only one scale of organization, which is, the whole organism scale, and [b.] there is only one form of transmission mechanism of infectious disease, which is direct transmission. The classical transmission mechanism theory excludes the following: [a.] the dynamics at the other six scales of organization of an infectious disease system, which are part of assumption II, [b.] environmental transmission which is part of assumption I, and [c.] assumption IV of the transmission mechanism theory in its entirety. It considers that transmission is a result of interaction between infected whole organism and susceptible whole organism. However, the single scale modelling of infectious dynamics based on the classical transmission mechanism is knowledge that has been inherent in modelling directly transmitted infectious disease dynamics, at least since Daniel Bernoulli developed a dynamic single scale model of smallpox transmission and control in 1766 (Bernoulli, 1766; Dietz & Heesterbeek, 2002). A remarkable contribution to the formalization of the classical transmission mechanism theory in mathematical terms was further contributed by En'ko in Russian in 1889 (En'ko, 1989; Dietz, 1988). In addition, Hamer published a measles transmission model in 1906 (Hamer, 1906) which for the first time proposed that the spread of infection should depend on the number of susceptible individuals and the number of infective individuals. Hamer's important contribution to the mathematical formalization of the classical transmission mechanism theory was the suggestion for the use of the mass action law to model the rate of new infections, an idea which has been basic in compartmental models to this day. This was followed by Ross's malaria transmission dynamics models in 1911 (Ross, 1911). These precursor mathematical ideas were unified by Kermack and McKendrick in their seminal papers (Kermack & McKendrick, 1927) into an idea now more widely known as mathematical epidemiology by 1933, which completed the formalization of the classical transmission mechanism theory in mathematical terms. In particular, the Kermack-McKendrick foundations for mathematical formalization of the classical transmission mechanism theory incorporates direct transmission by categorizing the human population into three discrete disease states, which are: Susceptible (S), Infected (I), and Recovered (R), thus the name SIR-type models as given by single scale model system (3.1). In this single scale modelling framework susceptible individuals (S_H) are assumed to become infected through direct contact with infectious individuals (I_H) at a variable rate $\lambda(I_H)$, with susceptible individuals dying naturally at a constant rate μ_H. Infectious individuals are assumed to recover (R_H) at a constant rate γ_H with lifelong immunity, and experience disease induced death at a constant rate δ_H. The constant rate γ_H is interpreted that $1/\gamma_H$ is the average amount of time spent in the infectious class before an individual recovers. Therefore, the foundations of the formalization of the classical transmission mechanism theory in mathematical terms incorporating direct transmission and population demography resulted in a SIR-type single scale model (3.1):

$$\text{Direct transmission single scale model of disease Dynamics} \begin{cases} 1.\ \dfrac{dS_H(t)}{dt} = \Lambda - \beta_H\lambda(I_H)S_H(t) - \mu_H S_H(t), \\ 2.\ \dfrac{dI_H(t)}{dt} = \beta_H\lambda(I_H)S_H(t) - [\mu_H + \delta_H + \gamma_H]I_H(t), \\ 3.\ \dfrac{dR_H(t)}{dt} = \gamma_H I_H(t) - \mu_H R_H(t). \end{cases} \tag{3.1}$$

Improvements in development of SIR-type single scale model framework resulted in models that decompose a population of organisms into four main disease states: susceptible-exposed-infectious-recovered (SEIR)-type framework where the exposed class consists of individuals who are infected but not yet infectious. With time, the classical transmission mechanism theory matured and also enlarged the number of scales of organization from the initial one (i.e. the whole organism scale) at which transmission process can be considered in the development of infectious disease models to a total of seven scales of organization as illustrated in Fig. 1. The developments in SEIR-type model framework resulted in several different types of single scale models of disease dynamics based on classical transmission mechanism theory by compartmentalizing the population of hosts (cells, tissues, organs/microcommunities, organisms, macrocommunities) into susceptible - exposed-infected - recovered (SEIR), and variations of this paradigm (SI, SIS, SEI, SEIS, SIR, SIRS, SEIRS, etc.) at each of the seven scales of organization (the cell scale, the tissue scale, the whole organism scale, etc.) of an infectious disease system. Some of the different single scale models of disease dynamics that can be developed at each of the seven scales of organization of an infectious disease system as illustrated in Fig. 1 include (Garira, 2013): [i.] SEIR models, [ii.] SEIRS models, [iii.] SI models, [iv.] SIR models, [v.] SIRS models, and [vii] SIS models.

The final step in the formulation and development of the transmission mechanism theory was the establishment of assumption IV in the form of a theory - the epidemiological triad theory in 1976 (Frost, 1976). This was followed by formalization of the transmission mechanism theory in mathematical terms in which single scale models of disease dynamics were developed by assuming that the macroenvironment or geographical environment's physical entities such as soil, air, formites/contact surfaces, food and water are the reservoir of infective pathogen in the community. For such single scale models pathogen load in the macroenvironment is explicitly incorporated into the model (Breban, 2013). This then extends

single scale models for directly transmitted infectious diseases based on susceptible, exposed, infected, recovered, (SEIR) and variations of this paradigm (SI, SIS, SIR, etc.) to single scale models for environmentally transmitted infectious diseases based on susceptible, exposed, infected, recovered, pathogen load (SEIRP) and variations of this paradigm (SIP, SISP, SIRP, etc.) in which pathogen load is explicitly incorporated. The mathematical formalization of the transmission mechanism theory and classical transmission mechanism theory resulted in the development of several metrics for quantifying disease control, elimination and even eradication, the most important being the following five disease transmission metrics: [a.] prevalence and incidence (Boshuizen et al., 2017), [b.] the reproductive number (Van den Driessche & Watmough, 2002), [c.] the pathogen load, [d.] the endemic equilibrium, and [e.] the sensitivity index. However, at this stage, the mathematical technology for the application of the transmission mechanism theory in the development of single scale models incorporating direct transmission does not incorporate assumption IV of the transmission mechanism theory. In section 5 we present a new single scale modelling framework that overcomes this limitation of the application of the transmission mechanism theory.

4. Limitations of the transmission mechanism theory of disease dynamics

The transmission mechanism theory has two main limitations which have undermined its usefulness and application which are: [I.] lack of a unified and standardized single scale modelling framework for both direct and environmental transmission mechanisms, and [II.] inability to account for pathogen replication in models of infectious disease dynamics. In what follows, we briefly describe each of them.

[I.] **Lack of a unified and standardized single scale modelling framework for both direct and environmental transmission mechanisms**: This is because the mathematical technology for development of single scale models of directly transmitted infectious disease systems is still not yet fully developed to encapsulate all the four basic assumptions of the transmission mechanism theory. Only single scale models for environmentally transmitted diseases are based on the transmission mechanism theory in its present form. Because of this difference, there is currently no unified single scale modelling framework for both environmental transmission and direct transmission. This limits the application of the transmission mechanism theory in the following ways:

[a.] *Different mathematical formalisms are used to represent direct transmission and environmental transmission in single scale mathematical models*: Single scale models of directly transmitted infectious diseases are based on susceptible, exposed, infected, recovered (SEIR) and variations of this paradigm (SI, SIS, SIR, etc.). However, single scale models for environmentally transmitted infectious diseases are based on susceptible, exposed, infected, recovered, pathogen load (SEIRP) and variations of this paradigm (SIP, SISP, SIRP, etc.) so that pathogen load is explicitly incorporated into models at each of the seven scales of organization of an infectious disease system. Current single scale models for disease dynamics incorporating direct transmission violate assumption IV of the transmission mechanism theory. The greatest limitation of these single scale models is that they do not explicitly incorporate the assumption of disease causation. For assumption IV of the transmission mechanism theory, infection is understood to be caused by the interaction of pathogen, host, and environment (sometimes called the epidemiological triad). However, single scale compartment models for directly transmitted infectious diseases focus only on host populations. Pathogens, the actual cause of infectious diseases, are only modelled implicitly.

[b.] *Different metrics of transmission are used to represent direct transmission and environmental transmission in single scale mathematical models*: There are two types of transmission metrics in single scale disease modelling. First, there are those metrics which represent transmission mechanism in the single scale model. Second, there are those metrics which are derived from the single scale models. For metrics derived from a single scale model, current definition of control, elimination and eradication for these single scale models incorporating direct transmission is in terms of prevalence and incidence (Dowdle, 1998). However, the definition of control, elimination and eradication for single scale models incorporating environmental transmission is in terms of pathogen load. This is more appropriate since the most sure way to eradicate a disease is to eradicate the infectious agent. Since the transmission mechanism theory is about disease dynamics incorporating either direct transmission or environmental transmission, or both there is currently no common definition for control, elimination and eradication that can be generalized to these two forms of transmission of an infectious disease system.

In the following section we propose a new single scale modelling framework that overcomes this limitation by using pathogen load as a common metric of disease dynamics at all scales of organization of an infectious disease system. Currently, single scale models of infectious disease systems incorporating direct transmission define disease burden in terms of incidence and prevalence (Dowdle, 1998). However, for some infectious diseases prevalence is not very informative, as the infectivity of individuals depends more on pathogen load than on whether one is infected or not. Further more, incidence is difficult to measure directly. More importantly, the use of pathogen load as a measure of disease burden also enables us to use a common metric for disease dynamics and burden across scales. In addition, pathogen load also combines information from prevalence.

[II.] **Inability to account for pathogen replication in models of infectious disease dynamics**: In infectious disease dynamics, transmission by itself is determined by the collective output of infectious material by the individuals (cells, or tissues, or organisms, etc.) that constitute the population, which in turn is decided by each individual's pathogen replication. This implies that in infectious disease dynamics, there is mutual interaction between the influence of pathogen replication and pathogen transmission. Therefore, in order to understand infectious disease dynamics we need a fuller understanding of the replication-transmission cycle. However, the characteristic scale at which pathogen transmission often does not match with the characteristic scale at which pathogen replication often occurs (Garira, 2019, 2020). This means that the replication-transmission cycle in infectious disease dynamics is a multiscale cycle involving pathogen replication at one scale and pathogen transmission at another scale.

In single scale models of infectious disease dynamics based on transmission mechanism theory, details of pathogen replication-transmission interactions are not modelled explicitly. Instead, pathogen replication is only represented phenomenologically by a single parameter. Because of this limitation, it is not possible to investigate infectious disease dynamics under constraints that are imposed by pathogen replication using models based on the transmission mechanism theory. By failing to incorporate details of pathogen replication processes, single scale models of infectious disease dynamics based on the transmission mechanism theory only make reference to the complexity of an infectious disease system under consideration without incorporating the exact content of the complexity. However, these single scale models occupy a central position in scientific investigations of infectious disease dynamics whenever a quick means is needed to represent an infectious disease system quantitatively for both basic science and practical applications. In the following section, we present a new single scale modelling framework that provides a common way of representing transmission for all forms of transmission mechanisms - environmental transmission and direct transmission to address the first limitation of the transmission mechanism theory.

5. A common framework for formalization of the transmission mechanism theory in mathematical terms using malaria as a paradigm

While the formalization of the transmission mechanism theory in mathematical terms incorporating environmental transmission is now well established, the mathematical technology frontier is still limiting the application of the theory to direct transmission. Single scale modelling of infectious disease dynamics incorporating direct transmission is still based on the classical transmission mechanism theory – which excludes assumption IV of the transmission mechanism theory. As a result there is no common single scale modelling framework with a common metric for host infectiousness or disease transmission for both directly transmitted diseases and environmentally transmitted diseases. For directly transmitted diseases, incidence and prevalence are the most common metrics of infectiousness while for environmentally transmitted diseases pathogen load is used as the metric for infectiousness. This presents difficulties in modelling infectious disease systems with multiple transmission mechanisms such as cholera. In an effort to address this limitation of the transmission mechanism theory we propose a new single scale modelling science base for directly transmitted diseases similar to an existing single scale modelling science base for environmentally transmitted infectious diseases. The approach develops a single scale modelling science base for directly transmitted infectious disease systems where the inside-whole organism scales of organization of an infectious disease system (i.e. cell scale, tissue scale, organ/microcommunity scale, microecosystem scale, whole organism scale) are the reservoir of infective pathogen in infectious disease dynamics, that is comparable to an existing single scale modelling science base for environmentally transmitted infectious diseases where the outside-whole organism scales of organization of an infectious disease system (i.e. macrocommunity scale, macroecosystem scale) are the reservoir of infective pathogen in infectious disease dynamics. This then extends standard single scale disease dynamics models based on susceptible, exposed, infected, recovered (SEIR) and variations of this paradigm (SI, SIS, SIR, etc.) for directly transmitted infectious diseases to disease dynamics models similar to existing single scale models for environmentally transmitted infectious diseases based on susceptible, exposed, infected, recovered, pathogen load (SEIRP) and variations of this paradigm (SIP, SISP, SIRP, etc.) where pathogen load is explicitly incorporated into models at each of the seven scales of organization of an infectious disease system. To illustrate the new single scale modelling framework, we first develop the single scale malaria model based on the classical transmission mechanism theory, and then show how this model is modified to encapsulate all the four basic assumptions of the transmission mechanism theory.

5.1. The single scale malaria model based on classical transmission mechanism theory

To illustrate the new modelling framework applied to malaria disease, we first develop a submodel for malaria transmission in the human population, and another submodel for malaria transmission in the mosquito population. We further integrate these two submodels into a single scale malaria model based on classical transmission mechanism theory. Then we show how the single scale malaria model based on classical transmission mechanism theory is extended to incorporate pathogen load so that it is finally based on the transmission mechanism theory.

[I.] **Direct transmission of malaria in the human population**: This sub-model is described by an SIS model. The sub-model is formulated based on monitoring the dynamics of two populations which are susceptible humans S_H, and infected humans I_H so that the total human population is given by $N_H = S_H + I_H$. We make the following assumptions for this sub-model.

[a.] There is no herd immunity in the human population as a result of prior exposure to the malaria infection or vaccination.

[b.] The infected human population can recover naturally from malaria infection.

[c.] The transmission parameter λ_V is a function of the number of infected mosquitoes so that $\lambda_V = \lambda_V(I_V)$.

[d.] The dynamics of S_H and I_H are assumed to occur at time scale t so that $S_H = S_H(t)$ and $I_H = I_H(t)$.

Based on these assumptions the malaria transmission dynamics model using the whole human scale as the scale of observation and the macrocommunity scale as scale of analysis becomes

$$\text{Direct transmission model of malaria among humans} \begin{cases} 1.\ \dfrac{dS_H(t)}{dt} = \Lambda_H - \beta_V \lambda_V(I_V) S_H(t) - \mu_H S_H(t) + \gamma_H I_H, \\ 2.\ \dfrac{dI_H(t)}{dt} = \beta_V \lambda_V(I_V) S_H(t) - [\mu_H + \delta_H + \gamma_H] I_H(t). \end{cases} \tag{5.2}$$

The first equation in sub-model system (5.2) describes the dynamics of susceptible humans. The population of susceptible humans is assumed to increase at a constant rate Λ_H through birth. This population is depleted through infection of susceptible humans at a variable rate $\lambda_V(I_V)$ and natural death at a constant rate μ_H. The population of susceptible humans also increases through natural recovery of infected individuals at a rate γ_H. The second equation in sub-model system (5.2) describes the dynamics of infected humans. This population increases through infection of susceptible humans and decreases through natural death at a rate μ_H, through disease induced death at a rate δ_H and through natural recovery at rate γ_H.

[II.] **Direct transmission of malaria in the mosquito population**: This sub-model is described by an SI model and describes the transmission of malaria parasite from infected humans to susceptible mosquitoes. We make the following assumptions for this sub-model.

[a.] The infected mosquitoes do not recover naturally from malaria infection.

[b.] The transmission parameter λ_H is a function of the number of infected humans so that $\lambda_H = \lambda_H(I_H)$.

[c.] The dynamics of S_V and I_V are assumed to occur at time scale t so that $S_V = S_V(t)$ and $I_V = I_V(t)$.

Based on these assumptions the malaria transmission dynamics model using the whole mosquito scale as the scale of observation and the macrocommunity scale as the scale of analysis becomes

$$\text{Direct transmission model of malaria among mosquitoes} \begin{cases} 1.\ \dfrac{dS_V(t)}{dt} = \Lambda_V - \beta_H \lambda_H(I_H) S_V(t) - \mu_V S_V(t), \\ 2.\ \dfrac{dI_V(t)}{dt} = \beta_H \lambda_H(I_H) S_V(t) - [\mu_V + \delta_V] I_V(t). \end{cases} \tag{5.3}$$

The first equation in sub-model system (5.3) describes the dynamics of susceptible mosquitoes. The first term on the right-hand side of this equation models the increase of susceptible mosquitoes through birth. The susceptible population of mosquitoes decreases through natural death at a constant rate μ_V, and through infection by humans at a variable rate $\lambda_H(I_H)$. The second equation in sub-model system (5.3) describes the dynamics of infected mosquitoes. The population of infected mosquitoes increases through infection of susceptible mosquitoes at a variable rate $\lambda_H(I_H)$. The same population decreases through natural death at a constant rate μ_V and also through infection induced death at a constant rate δ_V.

Putting together all these various derivations and assumptions the complete single scale model for malaria transmission dynamics at the whole organism scale of observation (human organism and mosquito organism) and the community scale of analysis becomes

$$\text{Malaria model based on classical transmission mechanism theory} \begin{cases} 1.\ \dfrac{dS_H(t)}{dt} = \Lambda_H - \beta_V \lambda_V(I_V) S_H(t) - \mu_H S_H(t) + \gamma_H I_H, \\ 2.\ \dfrac{dI_H(t)}{dt} = \beta_V \lambda_V(I_V) S_H(t) - [\mu_H + \delta_H + \gamma_H] I_H(t), \\ 3.\ \dfrac{dS_V(t)}{dt} = \Lambda_V - \beta_H \lambda_H(I_H) S_V(t) - \mu_V S_V(t), \\ 4.\ \dfrac{dI_V(t)}{dt} = \beta_H \lambda_H(I_H) S_V(t) - [\mu_V + \delta_V] I_V(t). \end{cases} \tag{5.4}$$

We now re-cast this single scale model of malaria into the proposed new single scale modelling framework.

5.2. Malaria model in the proposed new single scale modelling framework based on transmission mechanism theory

The new single scale malaria model development involves making assumptions that infected hosts (humans and mosquitoes) in the community are homogeneous and unevenly distributed microbial habitats. In particular, we assume that host infectiousness is constant for a given host, for the entire duration of host infectiousness, but may vary among hosts in a discrete way, for example by distinguishing several disease classes of hosts, so that average host infectiousness determined by average within-whole human pathogen load (N_h) and by average within-whole mosquito pathogen load (N_v) may be calculated. In this case, details of pathogen-immune system interactions which characterizes the replication and persistence of the pathogen at within-whole human scale and within-whole mosquito scale are not modelled explicitly. Instead, their interaction is reflected in the parameters N_h and N_v. We then establish the relationship between N_h and N_v and the parameters of the human-to-mosquito and mosquito-to-human malaria parasite transmission at macrocommunity scale which are $\lambda_V(I_V)$ and $\lambda_H(I_H)$. Details of the specific derivations and assumptions are as follows.

[a.] We assume that the transmission parameter in the mosquito-to-human malaria transmission sub-model, λ_V is not just a function of the infected vector population alone $I_V(t)$, but of both the infected vector population $I_V(t)$ and the average sporozoite population N_v within each infected mosquito so that $\lambda_V = \lambda_V(N_v I_V(t))$. The net effect of this assumption is to up-scale individual mosquito infectiousness N_v to population level or community level infectiousness $N_v I_V(t)$. In addition, we interpret the quantity $N_v I_V(t)$ to be a new variable at the macrocommunity scale, as the scale of analysis, which we now denote by $P_V(t)$ so that $P_V(t) = N_v I_V(t)$, which is a product of the average individual infected mosquito's sporozoite load and the number of infected mosquitoes. Here, $P_V(t)$ is the total infectious reservoir of mosquitoes at the macrocommunity scale, as the scale of analysis, which we refer to in this study as community sporozoite load. In terms of community sporozoite load, the transmission parameter for mosquito-to-human malaria transmission sub-model becomes $\lambda_V = \lambda_V(P_V(t))$. We further assume a Holling type II functional form of the function $\lambda_V(P_V)$ so that the force of infection, denoted here by $\lambda_V(t)$, associated with infectivity of the community to humans becomes

$$\lambda_V(t) = \frac{\beta_V P_V(t)}{P_0 + P_V(t)}, \tag{5.5}$$

where β_V is the exposure rate to a community with a population $P_V(t)$ of sporozoites per unit time, P_0 is the community sporozoite load that yields 50 percent chance of getting a human host infected with malaria after a bite by a mosquito in a particular community and

$$\lambda_V(P_V(t)) = \frac{P_V(t)}{P_0 + P_V(t)}, \tag{5.6}$$

is probability that a random bite by a mosquito vector in a particular community with a community sporozoite load $P_V(t)$ will infect the individual with malaria in that community. The transmission rate of malaria (5.6), which we also refer to as infectivity response functions of malaria is a probability and can be modelled by any functions $\lambda_V(P_V(t))$ with the specification that $\lambda_V : [0, \infty) \to [0, 1]$ represents the probability that a random bite of a human host by the mosquito host in a particular community with community sporozoite load $P_V(t)$, will infect the human host in that community. Since the function $\lambda_V(P_V(t))$ is a probability, it must have the following properties:

a. Property I: The probability of infection vanishes in absence of pathogen [i.e. $\lambda_V(0) = 0$] and approach 1 as the community sporozoite load becomes large [i.e. $\lim_{P_V(t) \to \infty} \lambda_V(P_V(t)) = 1$];
b. Property II: The probability of infection $\lambda_V(P_V(t))$ increases with the community sporozoite load $P_V(t)$, that is, $\lambda'_V(P_V(t)) > 0$, where prime denotes derivative with respect to the argument.

In the context of the proposed new modelling framework, any function, $\lambda_V(P_V(t))$, with the above properties can be used in place of those derived from Holling type I functional form (5.6). However, $P_V(t)$, is a new variable at macrocommunity scale which we have just introduced. In order to derive the differential equation governing $P_V(t)$, then the rate of change of community sporozoite load $P_V(t)$, in the entire community made of $I_V(t)$ unevenly distributed microbial (sporozoite) habitats/environments in the community becomes

$$\frac{dP_V(t)}{dt} = N_v \alpha_v I_V(t) - \alpha_V P_V(t), \tag{5.7}$$

where α_V is the rate of sporozoite elimination at macrocommunity scale as the scale of analysis so that the process of sporozoite elimination of community sporozoite load at macrocommunity scale as the scale of analysis takes an average of $1/\alpha_V$ days. Since $P_V(t)$ is the total infectious reservoir of mosquitoes in a particular community defined here as community sporozoite load, then $1/\alpha_V$ days is the average time to eliminate the total infectious reservoir of mosquitoes and render all mosquitoes in a particular community non-infectious. Taking into account these derivations and assumptions the mosquito-to-human malaria transmission sub-model becomes

$$\begin{cases} 1.\ \dfrac{dS_H(t)}{dt} = \Lambda_H - \dfrac{\beta_V P_V(t)}{P_0 + P_V(t)} S_H(t) - \mu_H S_H(t) + \gamma_H I_H(t), \\ 2.\ \dfrac{dI_H(t)}{dt} = \dfrac{\beta_V P_V(t)}{P_0 + P_V(t)} S_H(t) - [\mu_H + \gamma_H + \delta_H] I_H(t), \\ 3.\ \dfrac{dP_V(t)}{dt} = N_v \alpha_v I_V(t) - \alpha_V P_V(t). \end{cases} \tag{5.8}$$

Community sporozoite load (CSL) $P_V(t)$, which is also a measure of the total infectious reservoir of mosquitoes in the community, is defined in this study as an aggregate population-level biomarker of a community's sporozoite burden over a specific time period and is being proposed in this study as a useful metric for assessing the overall impact of malaria health interventions targeted at the mosquito vector or the uptake of malaria interventions targeted at the mosquito vector and quantifying their impact on transmission of malaria from mosquitoes to humans. We therefore propose that this new public health measure of malaria transmission should be operationalized in the assessment of the path from control to elimination for malaria transmission in a particular community as [i.] an indicator of a community's level of infectiousness and transmission probability of malaria to humans, [ii.] a measure of the effectiveness of malaria interventions targeted at the mosquito vector, and [iii.] a proximal maker of malaria incidence among mosquitoes and their potential to propagate malaria to humans.

[b.] Finally, we assume that the transmission parameter in the human-to-mosquito malaria transmission sub-model, λ_H is not just a function of the infected human population alone $I_H(t)$, but of both the infected human population $I_H(t)$ and the average gametocyte population N_h within each infected human so that $\lambda_H = \lambda_H(N_h I_H(t))$. The net effect of this assumption is also to up-scale individual human infectiousness N_h to population level or community level infectiousness $N_h I_H(t)$. In addition, the quantity $N_h I_H(t)$ is also a new variable at macrocommunity scale as the scale of analysis which we now denote by $G_H(t)$ so that $G_H(t) = N_h I_H(t)$, which is a product of the average individual infected human's gametocyte load and the number of infected humans. Here $G_H(t)$ is the total infectious reservoir of humans in the community which we refer to in this study as community gametocyte load. In terms of community gametocyte load, the transmission parameter for human-to-mosquito malaria transmission sub-model becomes $\lambda_H = \lambda_H(G_H(t))$. We further also assume a Holling type II functional form of the function $\lambda_H(G_H)$ so that the force of infection, denoted here by $\lambda_H(t)$, associated with infectivity of the community to mosquito becomes

$$\lambda_H(t) = \frac{\beta_H G_H(t)}{G_0 + G_H(t)}, \tag{5.9}$$

where β_H is the exposure rate to a community with a population $G_H(t)$ of gametocytes per unit time, G_0 is the community gametocyte load that yields 50 percent chance of getting a mosquito vector infected with malaria after a bite of a human host by a mosquito in a particular community and

$$\lambda_H(G_H(t)) = \frac{G_H(t)}{G_0 + G_H(t)}, \tag{5.10}$$

is the probability that a random bite of a human host by a mosquito vector in a particular community with a community gametocyte load $G_H(t)$ will infect the mosquito with malaria in that community. Similarly, the transmission rate of malaria (5.10), which we also refer to as infectivity response function of malaria is a probability and can be modelled by any function $\lambda_H(G_H(t))$, with the specification that $\lambda_H : [0, \infty) \to [0, 1]$ represents the probability that a random bite of a human host by a mosquito host in a particular community with community gametocyte load $G_H(t)$, will infect the mosquito host in that community. Equally, since the function $\lambda_H(G_H(t))$ is a probability, it must have the following properties:

a. Property I: The probability of infection vanishes in absence of pathogen [i.e. $\lambda_H(0) = 0$] and approach 1 as the community gametocyte load becomes large [i.e. $\lim_{G_H(t)\to\infty} \lambda_H(G_H(t)) = 1$];

b. Property II: The probability of infection $\lambda_H(G_H(t))$ increases with the community gametocyte load $G_H(t)$, that is, $\lambda'_H(G_H(t)) > 0$, where prime denotes derivative with respect to the argument.

In the context of the proposed new modelling framework, any function, $\lambda_H(G_H(t))$, with the above properties can be used in place of those derived from Holling type I functional form (5.10). However, because $G_H(t)$, is also a new variable at macro-community scale as the scale of analysis which we have just introduced. In order to derive the differential equation governing $G_H(t)$, since at any time t we have a total of $I_H(t)$ of these contaminated habitats/environments contaminated with an average of N_h gametocytes, then the rate of change of community gametocyte load, $G_H(t)$ in the entire community made of $I_H(t)$ homogeneous and unevenly distributed microbial (gametocyte) habitats/environments in the community becomes

$$\frac{dG_H(t)}{dt} = N_h\alpha_h I_H(t) - \alpha_H G_H(t), \tag{5.11}$$

where α_H is the rate of elimination of this total infectious reservoir of humans in the community so that the process of gametocyte elimination in a particular geographical area/country/community takes an average of $1/\alpha_H$ days. Since $G_H(t)$ is the total infectious reservoir of humans in a particular community defined here as community gametocyte load, then $1/\alpha_H$ days is the average time to eliminate the total infectious reservoir of humans and render all humans in a particular community non-infectious to mosquitoes. Taking into account these derivations and assumptions the human-to-mosquito malaria transmission sub-model becomes

$$\begin{cases} 1.\ \dfrac{dS_V(t)}{dt} = \Lambda_V - \dfrac{\beta_H G_H(t)}{G_0 + G_H(t)} S_V(t) - \mu_V S_V(t), \\ 2.\ \dfrac{dI_V(t)}{dt} = \dfrac{\beta_H G_H(t)}{G_0 + G_H(t)} S_V(t) - [\mu_V + \delta_V] I_V(t), \\ 3.\ \dfrac{dG_H(t)}{dt} = N_h\alpha_h I_H(t) - \alpha_H G_H(t). \end{cases} \tag{5.12}$$

The total infectious reservoir of the scale of analysis $G_H(t)$ when the whole human scale is the scale of observation, which is also a measure of the total infectious reservoir of humans in the community - because the community scale is the scale of analysis, is defined in this study as an aggregate population-level biomarker of a community's gametocyte burden over a specific time period and is being proposed in this study as a useful public health measure of malaria transmission for assessing the overall impact of malaria health interventions targeted at the human host or the uptake of malaria interventions targeted at the human host and quantifying their impact on transmission of malaria from humans to mosquitoes. We therefore propose that this new measure should be operationalized in the assessment of the path from control to elimination for malaria transmission in a particular community as [a.] an indicator of a community's level of infectiousness and transmission probability of malaria to mosquitoes, [b.] a measure of the effectiveness of malaria interventions targeted at the whole human scale as the host, and [c.] a proximal maker of malaria incidence among humans and their potential to propagate malaria to mosquito vectors.

Putting together all the various derivations and assumptions the complete single scale model for malaria transmission dynamics at the whole organism scale of observation (whole human scale and mosquito scale) and the macrocommunity scale of analysis based on the transmission mechanism theory becomes

Single scale malaria model based on transmission mechanism theory

$$\begin{cases} 1.\ \dfrac{dS_H(t)}{dt} = \Lambda_H - \dfrac{\beta_V P_V(t)}{P_0 + P_V(t)} S_H(t) - \mu_H S_H(t) + \gamma_H I_H(t), \\ 2.\ \dfrac{dI_H(t)}{dt} = \dfrac{\beta_V P_V(t)}{P_0 + P_V(t)} S_H(t) - (\mu_H + \delta_H + \gamma_H) I_H(t), \\ 3.\ \dfrac{dP_V(t)}{dt} = N_v\alpha_v I_V(t) - \alpha_V P_V(t), \\ 4.\ \dfrac{dS_V(t)}{dt} = \Lambda_V - \dfrac{\beta_H G_H(t)}{G_0 + G_H(t)} S_V(t) - \mu_V S_V(t), \\ 5.\ \dfrac{dI_V(t)}{dt} = \dfrac{\beta_H G_H(t)}{G_0 + G_H(t)} S_V(t) - (\mu_V + \delta_V) I_V(t), \\ 6.\ \dfrac{dG_H(t)}{dt} = N_h\alpha_h I_H(t) - \alpha_H G_H(t), \end{cases} \tag{5.13}$$

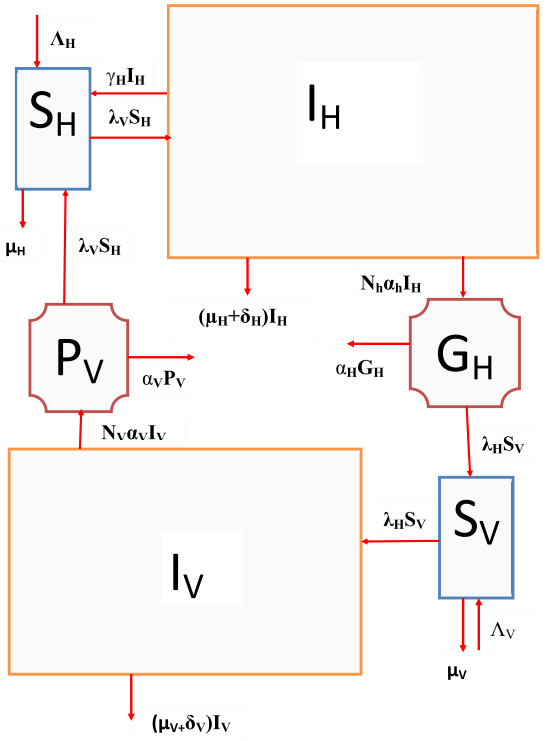


Fig. 2. A conceptual diagram of the new single scale model of malaria transmission dynamics (5.13) based on the transmission mechanism theory using the whole organism scale (whole human scale and whole mosquito scale) as the scale of observation and the macrocommunity scale as the scale of analysis.

This new single scale modelling framework encapsulate all the four basic assumptions of the transmission mechanism theory. Fig. 2 is a flow diagram of the single scale model system (5.13) for malaria based on the transmission mechanism theory.

6. Analysis of the proposed new single scale model for malaria

We now provide some qualitative analysis of the single scale malaria model (5.13) in this section. The same simple methods for analyzing current single scale models of disease dynamics based on classical transmission mechanism theory are applicable to the proposed new single scale modelling framework based on transmission mechanism theory. (see Table 1)

6.1. Basic properties of the single scale malaria model

Since the single scale malaria model (5.13) describes human, mosquito, and malaria parasite populations, all parameters in the model are non-negative. It can be easily be shown using basic methods etablished for analyzing current single scale models of disease dynamics based on classical transmission mechanism theory that given non-negative initial values ($S_H(0)$, $I_H(0)$, $P_V(0)$, $S_V(0)$, $I_V(0)$, $G_H(0)$), the solution/trajectories ($S_H(t)$, $I_H(t)$, $P_V(t)$, $S_V(t)$, $I_V(t)$, $G_H(t)$) of the single scale malaria model (5.13) will remain positive for all $t \geq 0$, so that the model is consistent with biological reality. Similarly, using the basic methods etablished for analyzing current single scale models of disease dynamics based on classical transmission mechanism theory, the boundedness of solutions of the single scale malaria model (5.13) can be shown by splitting the single scale model variables into four parts, namely the human population, mosquito population, community gametocyte load and community sporozoite load. Then, consider the biologically feasible region consisting of

$$\Omega = \Omega_H \times \Omega_V \times \Omega_G \times \Omega_P \subset \mathbb{R}_+^2 \times \mathbb{R}_+^2 \times \mathbb{R}_+ \times \mathbb{R}_+, \tag{6.14}$$

where

$$\begin{cases} \Omega_H &= \left\{\left(S_H, I_H\right) \in \mathbb{R}_+^2 : 0 \leq N_H \leq \dfrac{\Lambda_H}{\mu_H}\right\}, \\ \Omega_V &= \left\{\left(S_V, I_V\right) \in \mathbb{R}_+^2 : 0 \leq N_V \leq \dfrac{\Lambda_V}{\mu_V}\right\}, \\ \Omega_G &= \left\{G_H \in \mathbb{R}_+ : 0 \leq G_H \leq \dfrac{N_h \alpha_h \Lambda_H}{\mu_H \alpha_H}\right\}, \\ \Omega_P &= \left\{P_V \in \mathbb{R}_+ : 0 \leq P_V \leq \dfrac{N_v \alpha_v \Lambda_V}{\mu_V \alpha_V}\right\}, \end{cases} \tag{6.15}$$

So that $N_H(t) = S_H(t) + I_H(t)$, $N_V(t) = S_V(t) + I_V(t)$. Thus, the region Ω attracts all non-negative solutions. Therefore, it is sufficient to consider the dynamics of the flow generated by the single scale model (5.13) in Ω. In this region, the single scale model is epidemiologically and mathematically well-posed. Thus, every solution of the single scale model (5.13) with initial conditions in Ω remains in Ω for all $t > 0$. Therefore, the ω-limit set of the single scale model (5.13) is contained in Ω.

6.2. Determination of the basic reproductive number

An important question in malaria elimination is: how far has efforts to eliminate malaria at a particular scale of analysis gone and how much more remains to be done? If a strategy for control interventions is such that a particular scale of analysis has achieved $R_0 < 1$, then it is possible that maintaining current coverage levels of interventions would continue to reduce malaria transmission at a particular scale of analysis. However, if $R_0 > 1$, this gives way to an increase of malaria transmission at a particular scale of analysis. To obtain the reproductive number of the single scale model system (5.13) we first obtain the disease-free equilibrium point by setting the left-hand side of this model equal to zero and also assume that $I_H = P_V = I_V = G_H = 0$ for the community scale as the scale of analysis. Thus we get

$$E^0 = (S_H^0, I_H^0, P_V^0, S_V^0, I_V^0, G_H^0) = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0, 0\right), \tag{6.16}$$

where E^0 denotes the disease-free equilibrium of the single scale malaria model (5.13). The local asymptotic stability of E^0 can be established using the basic reproductive number. In this study, we calculate the basic reproduction number of the model system (5.13) by using the next generation matrix approach (Van den Driessche & Watmough, 2002) as appropriate for single scale models based on the transmission mechanism theory. In this case, the second and the third equations of the model system (5.13) form a subsystem that describes the generation and transition of infectious humans and the community pathogen load that are used to calculate $\mathcal{R}_0$. The Jacobean matrix associated with the linearized subsystem evaluated at the disease free equilibrium point, E^0, of the model system (5.13) is given by

$$J(E_0) = \begin{pmatrix} -(\mu_H + \delta_H + \gamma_H) & \dfrac{\beta_V \Lambda_H}{P_0 \mu_H} & 0 & 0 \\ 0 & -\alpha_V & N_v \alpha_v & 0 \\ 0 & 0 & -(\alpha_V + \delta_V) & \dfrac{\beta_H \Lambda_V}{G_0 \mu_V} \\ N_h \alpha_h & 0 & 0 & -\alpha_H \end{pmatrix}. \tag{6.17}$$

Then, $J(E^0)$ is decomposed into two matrices F and V such that $J(E^0) = F - V$, where F is the transmission and non-negative matrix describing the generation of secondary infections, and V is the transition and non-singular matrix, describing the changes in individual states such as removal by death, recovery or excretion of malaria parasite into the scale of analysis by infected humans and mosquitoes in the community. We can give two different biological interpretations of the disease compartments and hence different next generation matrices from (6.17), to get two different $\mathcal{R}_0$ expressions for the single scale compartmental model (5.13) as follows.

[a.] *Assume that the community pathogen load is an extended state of host infectiousness*: This assumption holds since we upscaled individual host infectiousness (i.e. $N_h\alpha_h$ and $N_v\alpha_v$) to population level infectiousness (i.e. G_H and P_V). In this case, the shedding of malaria parasite (i.e. $N_h\alpha_h$ and $N_v\alpha_v$) is placed in the V matrix rather than in the F matrix, so the basic reproduction number of the single scale malaria model (5.13) becomes

$$R_0^I = \rho(F_I V_I^{-1}) = \sqrt[2]{\left[\frac{N_h\alpha_h}{(\mu_H+\delta_H+\gamma_H)}\frac{\Lambda_V\beta_H}{\mu_V\alpha_H G_0}\right]\left[\frac{N_v\alpha_v}{(\mu_V+\delta_V)}.\frac{\Lambda_H\beta_V}{\mu_H\alpha_V P_0}\right]}. \tag{6.18}$$

[b.] *The community is assumed to act as a reservoir of the infective pathogen*: This assumption also holds since $N_h\alpha_h$ and $N_v\alpha_v$ are the rates that describe how much malaria pathogen load each infected individual (mosquito or human) contributes to the community pathogen load during their entire period of infectiousness. In this case, the shedding rates of malaria parasite (i.e. $N_h\alpha_h$ and $N_v\alpha_v$) are placed in the F matrix rather than in the V matrix, so that the basic reproduction number of the single scale malaria model (5.13) becomes

$$R_0^{II} = \rho(F_{II} V_{II}^{-1}) = \sqrt[4]{\left[\frac{N_h\alpha_h}{(\mu_H+\delta_H+\gamma_H)}\frac{\Lambda_V\beta_H}{\mu_V\alpha_H G_0}\right]\left[\frac{N_v\alpha_v}{(\mu_V+\delta_V)}.\frac{\Lambda_H\beta_V}{\mu_H\alpha_V P_0}\right]}. \tag{6.19}$$

Therefore, the basic reproductive number $\mathcal{R}_0^I$ or $\mathcal{R}_0^{II}$ in the human-to-human or mosquito-to-mosquito for malaria transmission.

We can make use of the reproductive number, $\mathcal{R}_0$ to show the existence of the endemic equilibrium of single scale malaria model (5.13). Let $E^* = S_H^*, I_H^*, P_V^*, S_V^*, I_V^*, G_H^*$ be the endemic equilibrium of the single scale malaria model (5.13). We can easily express $S_H^*, P_V^*, S_V^*, I_V^*, G_H^*$ in terms of I_H^* in the form

$$\begin{cases} S_H^*(I_H^*) = \dfrac{[\Lambda_H-\gamma_H I_H^*][B+CI_H^*]}{B\mu_H+(A+C\mu_H)I_H^*}, \quad S_V^*(I_H^*) = \dfrac{\Lambda_V[\alpha_H G_0+N_h\alpha_h I_H^*]}{\mu_V\alpha_H G_0+DI_H^*}, \\ I_V^*(I_H^*) = \dfrac{\Lambda_V N_h\alpha_h\beta_H I_H^*}{[\mu_V+\delta_V][\mu_V\alpha_H G_0+DI_H^*]}, \\ P_V^*(I_H^*) = \dfrac{N_v\alpha_v\Lambda_V N_h\alpha_h\beta_H I_H^*}{\mu_V[\mu_V+\delta_V]+D[\mu_V+\delta_V][\mu_V+\beta_H]\alpha_V I_H^*}, \\ G_H^*(I_H^*) = \dfrac{N_h\alpha_H I_H^*}{\alpha_H}, \quad \lambda_V^*(I_H^*) = \dfrac{AI_H^*}{[B+CI_H^*]}, \quad \lambda_H^*(I_H^*) = \dfrac{N_h\alpha_h\beta_H I_H^*}{\alpha_H G_0+N_h\alpha_h I_H^*}, \end{cases} \tag{6.20}$$

Where

$$\begin{cases} A=\beta_V N_v\alpha_v\Lambda_V.N_h\alpha_h\beta_H, \quad B=\mu_V[\mu_V+\delta_V]\alpha_H G_0\alpha_V P_0, \\ C=N_v\alpha_v\Lambda_V.N_h\alpha_h\beta_H+N_h\alpha_h\alpha_V P_0[\mu_V+\delta_V][\mu_V+\beta_H], \quad D=N_h\alpha_h[\mu_V+\beta_H]. \end{cases} \tag{6.21}$$

Substituting the expressions in (6.20) in the equation for I_H which is given by

$$\frac{dI_H}{dt} = \lambda_V S_H - [\mu_H+\delta_H+\gamma_H]I_H,$$

At the endemic equilibrium we get:

$$I_H^* = \frac{\mu_H(\mu_H+\delta_H+\gamma_H)B[R_0^2-1]}{A\gamma_H+[A+C\mu_H][\mu_H+\delta_H+\gamma_H]}, \tag{6.22}$$

where A, B, and C are as defined by the expressions (6.21). We can easily deduce from expressions (6.22) and (6.20) that there exists one unique endemic equilibrium for model system (5.13) whenever $\mathcal{R}_0 > 1$ whenever $I_H^* < \Lambda_H/\gamma_H$.

6.3. Numerical study of the single scale malaria model

In this subsection, we perform numerical simulations of the single-scale malaria model (5.13) using the parameter values given in Table 2. We illustrate the influence of parameters (α_v, α_h, β_H, β_V) on the four model variables (I_H, G_H, I_V, P_V).

Fig. 3 shows the evolution of [a.] population of infected humans I_H, [b.] population of infected mosquitoes I_V, [c.] community gametocytes load G_H, and [d.] community sporozoite load P_V for different values of α_h: $\alpha_h = 0.4$, $\alpha_h = 0.6$, $\alpha_h = 0.8$. Here α_h models the rate at which gametocytes develop and become infectious to mosquitoes. These results show that as the rate at which gametocytes develop and become infectious to mosquitoes (α_h) increases, malaria disease transmission in the

Table 1
Table of variables and their description for the single scale malaria model (5.13). For this single scale malaria model, the scale of analysis is the macrocommunity scale.

No	Variable	Description
1	$S_H(t)$	Population of susceptible humans at time t
2	$I_H(t)$	Population of infected humans at time t
3	$G_H(t)$	Total infectious reservoir of humans (gametocyte load) of the scale of analysis at time t
4	$P_V(t)$	Total infectious reservoir of mosquitoes (sporozoite load) of the scale of analysis at time t
5	$S_V(t)$	Population of susceptible mosquito vectors at time t
6	$I_V(t)$	Population of infected mosquito vectors at time t

community also increases. Overall, Fig. 3 shows that interventions that reduce the rate of development of gametocytes to become infectious reduces malaria transmission at macrocommunity scale as the scale of analysis. Therefore, the use artemisinin-based combination therapy (ACT) which reduce the productions of gametocytes will likely to reduce the malaria disease transmission.

Fig. 4 shows the evolution of [a.] population of infected humans I_H, [b.] population of infected mosquitoes I_V, [c.] community gametocytes load G_H, and [d.] community sporozoite load P_V for different values of for different values α_v: $\alpha_v = 0.25$; $\alpha_v = 0.45$ and $\alpha_v = 0.85$. In this case α_v models the rate at which sporozites develop to become infectious to humans. Fig. 4 shows that as the rate at which sporozoites develop and become infectious to humans (α_v) increases, malaria disease transmission at macrocommunity scale also increases. Overall Fig. 4 shows that interventions that reduce the rate of development of sporozites to become infectious to mosquitoes reduces malaria transmission at macrocommunity scale. Therefore, the use of artemisinin-based combination therapy (ACT) which reduce the productions of gametocytes which later develop into sporozoites will likely reduce the transmission of malaria disease at macrocommunity scale.

Fig. 5 shows the evolution of [a.] population of infected humans I_H, [b.] population of infected mosquitoes I_V, [c.] community gametocytes load G_H, and [d.] community sporozoite load P_V for different values of β_H: $\beta_H = 0.356$, $\beta_H = 0.456$, $\beta_H = 0.556$. Here β_H models the contact rate of community gametocyte load with susceptible mosquitoes. The results in Fig. 5 show that as the contact rate of susceptible mosquitoes (β_H) with infectious reservoir of humans increases, malaria transmission at macrocommunity scale also increases. Overall, the results in Fig. 5 indicate that the use of Long-lasting insecticidal nets (LLINs) which reduce contact between susceptible mosquitoes with infectious reservoir of humans have an beneficial impact of reducing malaria disease transmission at macrocommunity scale.

Fig. 6 show the evolution of [a.] population of infected humans I_H, [b.] population of infected mosquitoes I_V, [c.] community gametocytes load G_H, and [d.] community sporozoite load P_V for different values of β_V: $\beta_V = 0.32135$, $\beta_V = 0.42135$, $\beta_V = 0.52135$. In this case β_V models the contact rate of susceptible humans with infectious reservoir of mosquitoes. Fig. 6 shows that as contact rate of susceptible humans with infectious reservoir of mosquitoes (β_V) increases, malaria transmission at macrocommunity scale also increases. Overall, the results in Fig. 6 indicate that the use of Long-lasting insecticidal nets (LLINs) which reduce contact between susceptible humans with infectious reservoir of mosquitoes have an beneficial impact of reducing malaria disease transmission at macrocommunity scale.

By using pathogen load as a common metric of disease dynamics at all levels of organization of an infectious disease, this would ensure a common metric of control, elimination and eradication of disease in terms of pathogen load. Currently, models of infectious disease dynamics incorporating direct transmission define disease burden in terms of incidence and prevalence (Dowdle, 1998). As a result, it is currently not easy to compare disease burden based on models for direct transmission and environmental transmission because these two different modelling frameworks use different metrics for disease burden. Further, for some infectious diseases prevalence is not very informative, as the infectivity of individuals depends more on pathogen load than on whether one is infected or not. Incidence is difficult to measure directly. More importantly, the use of community pathogen load as a measure of disease burden also enables us to use a common metric for disease dynamics and burden across scales for both directly transmitted diseases and environmentally transmitted diseases. Further, community pathogen load also combines information from prevalence. Therefore, the numerical results of the single scale model of malaria disease system given in this section cannot be compared with other numerical results for single scale malaria models which are developed based on SEIR models and variations of this paradigm (SI, SIS, SIR, etc.) because of differences in metrics for measuring disease burden.

7. The replication-transmission relativity theory as the modern theory of disease dynamics

Although science has progressed over time by being able to summarize our existing knowledge of natural phenomena using certain scientific theories, it must be made clear that our description of natural phenomena using scientific theories is a dynamic process because these scientific theories often only adequately describe the phenomenon studied up to a certain time. As time progresses, new knowledge often emerges as we extend the domains of observation to improve the accuracy of measurement. In this dynamic picture of science, the transmission mechanism theory of disease dynamics remained unaltered for almost a century. However, the transmission mechanism theory met its first obstacles, because of the knew knowledge related its limitations as explained in Section 4, that it is anable to account for pathogen replication in models of

Table 2
Parameters values of model of malaria and their description.

Parameter	Description	Initial Value	Range	Units	Source
Λ_V	Recruitment rate of mosquitoes.	6000	5000–7000	Mosquitoes per day	Agusto et al. (2019)
β_V	Contact rate of susceptible humans with the infectious reservoir of mosquitoes.	0.52135	2.7×10^{-3}–0.64	day^{-1}	Garira and Mathebula (2019)
μ_V	Natural death rate of mosquitoes.	0.12	0.033–0.3	day^{-1}	Garira and Mathebula (2019)
δ_V	induced death rate of infected mosquitoes.	4.26×10^{-6}	4.26×10^{-6}–5.33×10^{-6}	day^{-1}	Garira and Mathebula (2019)
P_0	Half saturation constant associated with the infection of humans.	1×10^8	1×10^6–5×10^8	day^{-1}	Garira and Mathebula (2019)
N_v	Number of sporozoites available for excretion	3000	100–4000	Sporozoites per day	assumed
α_V	Rate of clearance of community sporozoite load.	0.3	0.09–0.99	day^{-1}	Garira and Mathebula (2019)
α_v	Shedding rate of sporozoites	0.25	0.016–1.0	day^{-1}	Garira and Mathebula (2019)
Λ_H	Recruitment rate of humans.	1000	100–1200	humans per day	Agusto et al. (2019)
β_H	Contact rate of susceptible mosquitoes with the infectious reservoir of humans.	0.356	0.072–0.64	day^{-1}	Agusto et al. (2019)
μ_H	Natural death rate of humans.	4.002×10^{-5}	1×10^{-5}––0.9	day^{-1}	Garira and Mathebula (2019)
δ_H	induced death rate of infected humans.	0.0027	1×10^{-15}–0.0027	day^{-1}	Garira and Mathebula (2019)
γ_H	Recovered rate from infection.	0.25	0.0014–0.7	day^{-1}	Garira and Mathebula (2019)
G_0	Half saturation constant associated with the infection of mosquitoes.	5×10^8	1^6–5×10^9	day^{-1}	Garira and Mathebula (2019)
N_h	Number of gametocytes available for excretion	2000	10–3000	gametocytes per day	assumed
α_H	Rate of clearance of community gametocytes load.	0.913	4.67×10^{-5}––0.913	day^{-1}	Garira and Mathebula (2019)
α_h	Shedding rate of gametocytes	0.4	0.01–0.9	day^{-1}	Garira and Mathebula (2019)

infectious disease dynamics. The challenges precipitated by the need to ccount for pathogen replication in models of infectious disease dynamics, required the development of a new theory that accounts for multiscale description of infectious disease dynamics through extension of the transmission mechanism theory. The extension of the transmission mechanism theory into a new theory for multiscale description of infectious disease dynamics was recently accomplished through formulating a new theory that required the union of two scales at a level of organization of an infectious disease system: a microscale as a scale of observation where pathogen replication often occurs and macroscale as another scale of observation where pathogen transmission often occurs. This theory, called the replication-transmission relativity theory (Garira, 2019), resulted in the multiscale description of infectious disease phenomena involving the simultaneous description of both the pathogen transmission and pathogen replication (Garira, 2020). The main limitation of the transmission mechanism theory of disease dynamics is that it tends to disjoint these two scales of organization in order to simplify representation and understanding of infectious disease dynamics and focus exclusively on macroscale as the only scale of organization in disease dynamics. Fig. 7 is a conceptual representation of the replication-transmission relativity theory of infectious disease dynamics.

The replication-transmission relativity theory of disease dynamics (Garira, 2019), which states that at any level of organization of an infectious disease system there is no privileged or absolute scale which would determine disease dynamics, only interactions between the microscale and macroscale identifies an infectious disease system as a complex system which is organized into seven main hierarchical levels at which host-pathogen interactions can play out (Garira, 2019, 2020): [I.] the cell level - with within-cell scale and between-cell scale as the microscale and macroscale respectively, [II.] the tissue level - with the within-tissue scale as the microscale and between-tissue scale as the macroscale, [III.] the organ/microcommunity level - where the within-microcommunity scale is the microscale and between-microcommunity scale is the macroscale, [IV.] the microecosystem level - with within-microecosystem scale and between-microecosystem scale as the microscale and macroscale respectively, [V.] the whole organism level - where the within-whole organism scale is the microscale and between-whole organism scale is the macroscale, [VI.] the macrocommunity level - with within-macrocommunity scale and between-macrocommunity scale as the microscale and macroscale respectively, and [VII.] the macroecosystem level - where the within-macroecosystem scale is the microscale and between-macroecosystem scale is the macroscale. As illustrated in Fig. 7, the theory makes the point that in multiscale dynamics of infectious diseases, there is an interacting multiscale cycle of four processes which are [a.] infection/super-infection by pathogen process, [b.] pathogen replication process, [c.] pathogen

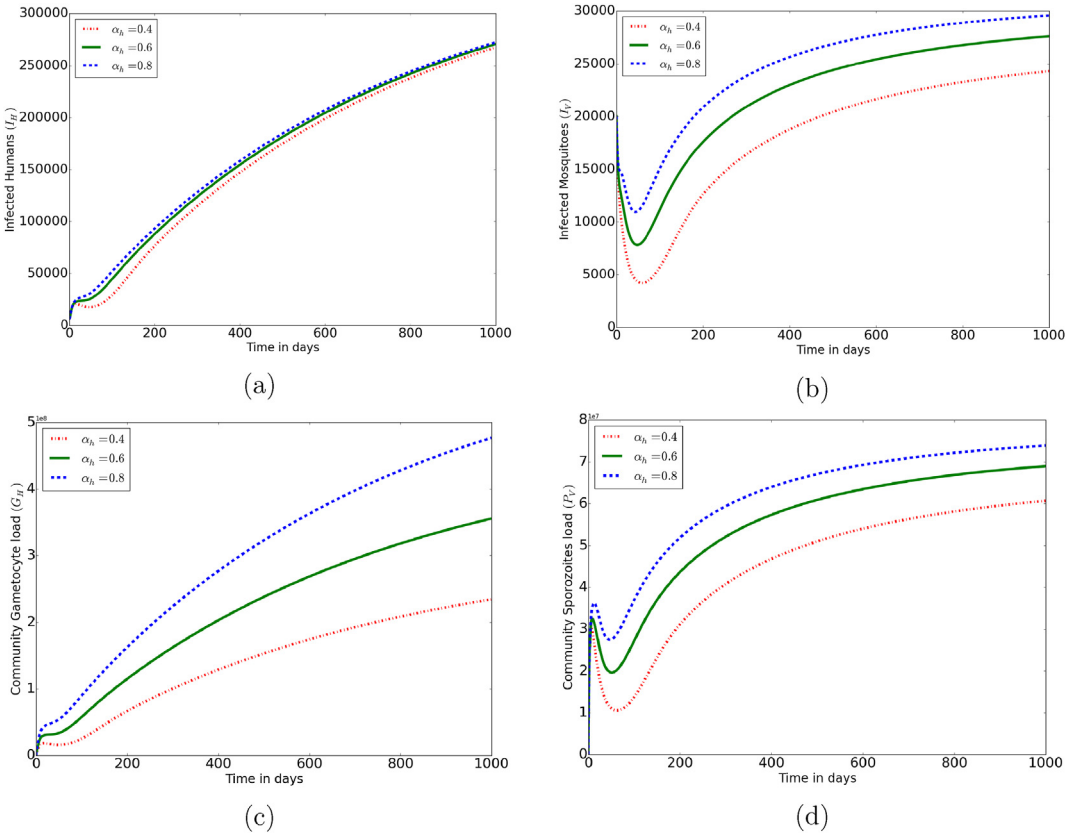


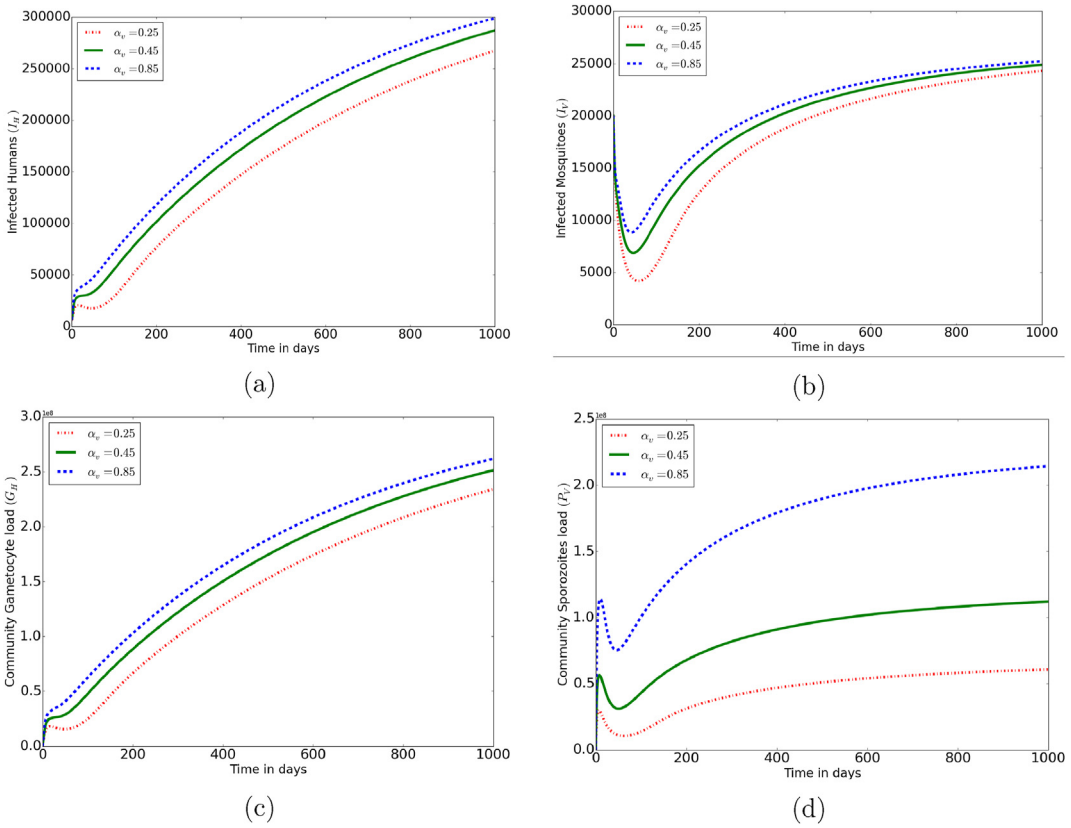
Fig. 3. The evolution of [a.] population of infected humans I_H, [b.] population of infected mosquitoes I_V, [c.] community gametocytes load G_H, and [d.] community sporozoite load P_V for different values of α_h: $\alpha_h = 0.4$, $\alpha_h = 0.6$, $\alpha_h = 0.8$.

shedding/excretion process, and [d.] pathogen transmission process, which is repeated sequentially at each level of organization of an infectious disease system. These four processes are key to understanding infectious disease dynamics using multiscale modelling methods.

The passage from transmission mechanism theory of disease dynamics to the replication-transmission relativity theory of disease dynamics shares features that are common to all such transitions in which an old scientific theory gives way to a new one. In almost every situation where this transition occurs there is usually a domain D_n of phenomena described by the new theory and a subdomain D_o wherein the old theory is reliable to a given accuracy. In the case of infectious disease dynamics, the domain D_n represents the level of multiscale observation described by the replication-transmission relativity theory, where D_n is a union of the microscale as a scale of organization where pathogen replication often occurs and macroscale as a scale of organization where pathogen transmission often occurs. However, the subdomain D_0 represents the macroscale, the scale of organization where pathogen transmission occurs and is thus described by the transmission mechanism theory. Therefore, unlike the transmission mechanism theory which brings down the complexity of an infectious disease system to manageable levels by discretizing or decomposing the infectious disease system into hierarchical scales of organization, each of which can be analyzed independently using single scale modelling methods, the replication-transmission relativity theory enables us to bring down the complexity of an infectious disease system to manageable levels by discretizing or decomposing an infectious disease system into hierarchical levels of organization, each of which consisting of a microscale and a macroscale, which can be analyzed independently using multiscale modelling methods.

8. Discussion and conclusions

In this article we presented a theory of single scale modelling of infectious disease dynamics called the transmission mechanism theory of disease dynamics and explained its aims, assumptions and limitations. This theory states that at every scale of organization of an infectious disease system, disease dynamics is determined by transmission as the main dynamic process. It is a scientific theory that has matured substantially over the past century and has established an enduring framework for the study of infectious disease dynamics using single scale mathematical and computational models. The single scale models developed based on the transmission mechanism theory occupy a central position in scientific



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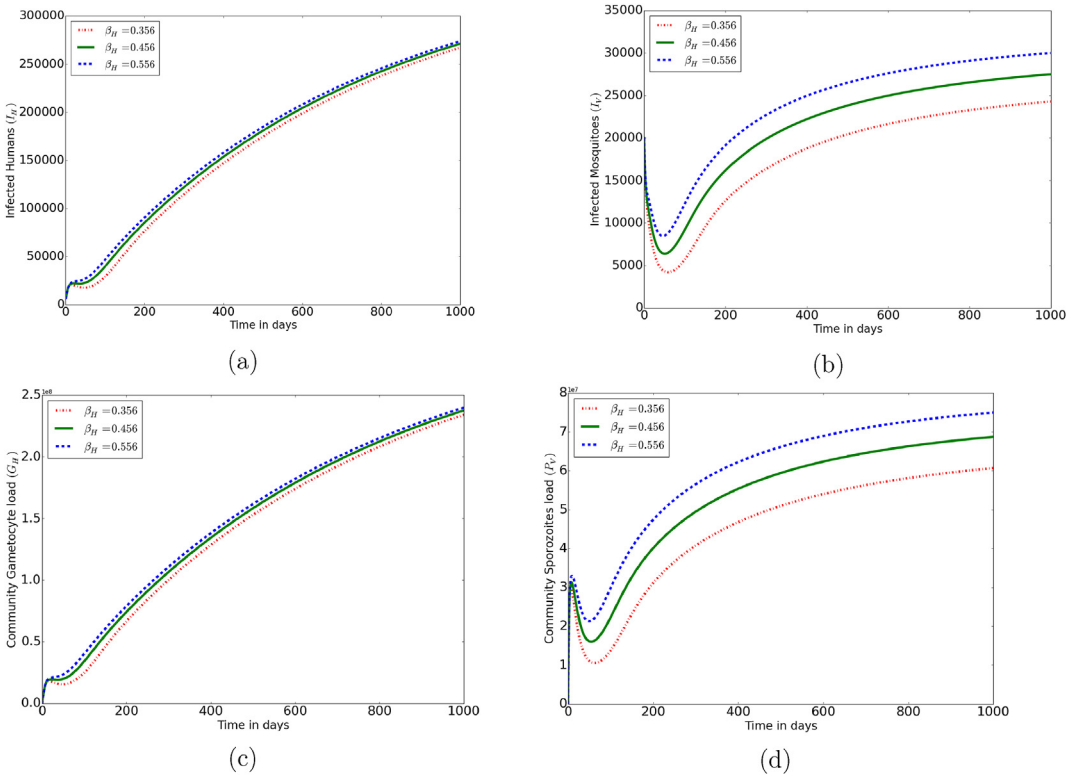
investigations whenever a quick means is needed to represent an infectious disease system quantitatively for both basic science and practical applications. However, we established that the transmission mechanism theory has limitations which undermine its usefulness and application. First, there is lack of a unified and standardized single scale modelling framework for both direct and environmental transmission. Second, the theory does not account for pathogen replication in single scale models of infectious disease dynamics. In an effort to address the first limitation of the transmission mechanism theory we proposed a new single scale modelling science base for directly transmitted diseases similar to an existing single scale modelling science base for environmentally transmitted infectious diseases. The new method development for single scale models of directly transmitted infectious diseases proposed in this study is based on introducing pathogen load as a common metric of disease transmission across all the seven scales of organization of an infectious disease system, which is then used to define the force of infection and transmission probability. This then extends standard single scale infectious disease models based on susceptible, exposed, infected, recovered (SEIR) and variations of this paradigm (SI, SIS, SIR, etc.) for directly transmitted infectious diseases to infectious disease models similar to existing single scale models for environmentally transmitted infectious diseases based on susceptible, exposed, infected, recovered, pathogen load (SEIRP) and variations of this paradigm (SIP, SISP, SIRP, etc.) in which pathogen load in the environment is explicitly incorporated into models of infectious disease dynamics. The usefulness of such single scale models is that they are predictive models of pathogen load whose usefulness is three-fold: [a.] as a metric for assessing the effectiveness of treatment, [b.] as an indicator of a scale of analysis's level of infectiousness and transmission probability, and [c.] as a proximal marker for infectious disease incidence and potential epidemic propagation. While the example given in this study is specific to malaria, the new single scale modelling framework is general enough and is in principle applicable to other directly transmitted infectious disease systems.

We also described how a new theory of infectious disease dynamics - called the replication-transmission relativity theory (Garira, 2019) was formulated and developed by revising and extending the transmission mechanism theory to address it limitations. The basic principle behind the replication-transmission relativity theory is that it establishes that at every level of organization of an infectious disease system there is a replicative-transmission cascade in which a pathogen replicates at microscale while there is transmission at macroscale. This theory provides formal methodology, of describing the multiscale dynamics of infectious disease systems through the use of formal mathematics (Garira, 2017, 2018, 2020). It marks a breakthrough in a decades long quest to build a working theory of the multiscale modelling of infectious disease dynamics. The replication-transmission relativity theory ripped the entire fabric of the transmission mechanism theory which has been



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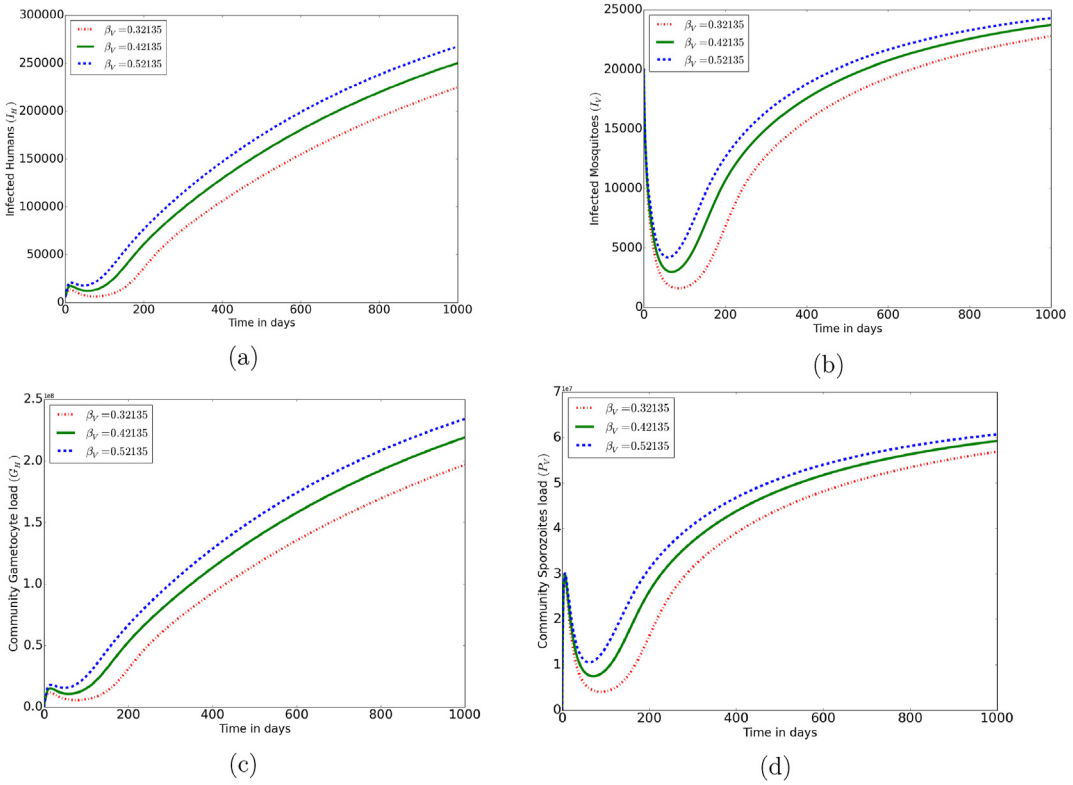

Fig. 6. The evolution of [a.] population of infected humans I_H, [b.] population of infected mosquitoes I_V, [c.] community gametocytes load G_H, and [d.] community sporozoite load P_V for different values of β_V: $\beta_V = 0.32135$, $\beta_V = 0.42135$, $\beta_V = 0.52135$.

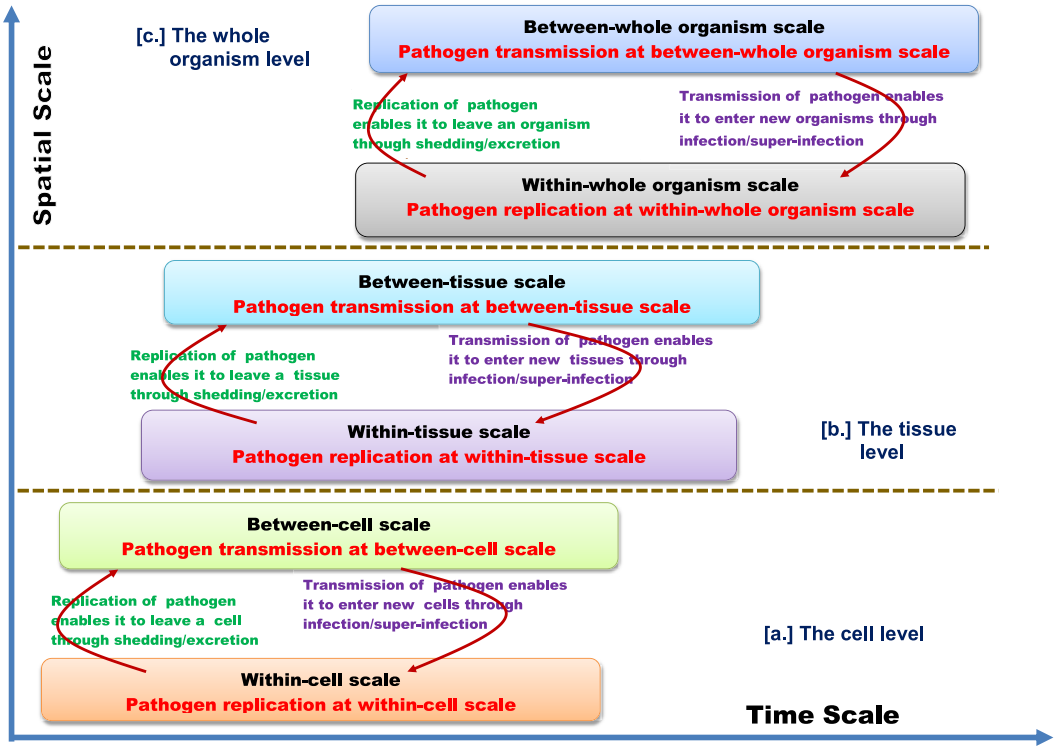

Fig. 7. A conceptual representation of the replication-transmission mechanism theory of infectious disease dynamics at [a.] the cell level - which consists of within-cell scale as the microscale and between-cell scale as the macroscale, [b.] the tissue level - which consists of within-tissue scale as the microscale and between-tissue scale as the macroscale, and [c.] the whole organism level - which consists of within-whole organism scale as the microscale and between-organism scale as the macroscale. The theory makes the point that in multiscale dynamics of infectious diseases, there is an interacting multiscale cycle of four processes which are [a.] infection/super-infection by pathogen process, [b.] pathogen replication process, [c.] pathogen shedding/excretion process, and [d.] pathogen transmission process, which is repeated sequentially at each level of organization of an infectious disease system.

in existence at least since Daniel Bernoulli developed a dynamic model of smallpox transmission and control in 1766 (Bernoulli, 1766). This modern theory demolished the notion that transmission is the only main dynamic process in infectious disease dynamics. We anticipate that this landmark theory will uncannily transform mainstream thinking about multiscale modelling of infectious disease dynamics from a complex systems perspective. We therefore, issue a "call to arms" against pathogenic infections using complex systems approaches based on multiscale modelling as part of our armory involving four multiscale modelling approaches (Garira, 2020): [a.] mathematical-based multiscale models, [b.] computational-based multiscale models, [c.] empirical-based multiscale models, and [d.] data-based multiscale models to forge a interdisciplinary alliance in characterizing the multiscale dynamics of infectious systems.

Declaration of competing interest

The authors declare no competing non-financial/financial interests.

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