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Review

Mathematical methods for scaling from within-host to population-scale in infectious disease systems

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ABSTRACT

Mathematical modellers model infectious disease dynamics at different scales. Within-host models represent the spread of pathogens inside an individual, whilst between-host models track transmission between individuals. However, pathogen dynamics at one scale affect those at another. This has led to the development of multiscale models that connect within-host and between-host dynamics. In this article, we systematically review the literature on multiscale infectious disease modelling according to PRISMA guidelines, dividing previously published models into five categories governing their methodological approaches (Garira (2017)), explaining their benefits and limitations. We provide a primer on developing multiscale models of infectious diseases.

1. Introduction: why develop multiscale modelling frameworks of infectious diseases?

Mathematical modelling of infectious diseases typically either focuses on the immunology or the epidemiology of the disease in question. Within-host models help us to understand the progression of an infection at an individual level, which can differ from person to person depending on specific immunology and can change according to age and co-morbidity status, for example. As shown in the schematic in Fig. 1, such models can cover multiple scales, from the molecular scale on the order of nanometres, to the organism scale on the order of metres. Within-host models are often designed with the purpose of better understanding disease progression to develop better and more personalised treatments, but importantly can also be used to better understand and represent changing infectiousness, and hence the transmission process inherent to between-host models.

Between-host models represent the transmission of pathogens and can therefore help predict the effectiveness of public health interventions. These models can represent processes between spatial scales of one metre and one or more kilometres (as suggested in Fig. 1). These two types of model (within-host and between-host) can also be linked together, to form a multiscale model, in which the dynamics at one scale can be linked to the dynamics of the other (Childs et al., 2019). This, in turn, can improve the predictions used to inform public health strategies, by adding patient-specific dynamics to population-level pathogen spread. Hereafter, such models will be referred to as multiscale modelling frameworks, to clearly differentiate between them and exclusively within- or between-host models.

Although the link between within-host and between-host dynamics is known to be important (Handel and Rohani, 2015), within-host and between-host models are not routinely connected to form multiscale modelling frameworks. One issue, which exemplifies the difficulties in connecting within- and between-host models, surrounds the linking of the pathogen load of an infectious individual to their subsequent infectiousness. It is often assumed that infectiousness is a linear function of pathogen load. For example, in the immuno-epidemiological framework introduced in Feng et al. (2012), V, the within-host viral load, evolves according to ordinary differential equations (ODEs), and is linked to β, the transmission rate at the between-host scale, via the equation: $\beta(V) = \beta V$. However, aside from modelling assumptions, the relationship between pathogen load and infectiousness has not been well-studied for most diseases. Another issue, which has yet to be fully resolved, is the degree to which infection – either of the individual themselves or of other individuals of whom they are aware – influences behaviour and subsequently impacts on between-host transmission (Guo et al., 2015; Sontag et al., 2022). Multiple types of modelling approaches, including ODEs, partial differential equations (PDEs), meta-population models and agent-based models (ABMs), are employed to investigate within-host or between-host dynamics, as we will explore in this review. Issues as to which is the most appropriate modelling paradigm, and how to link different modelling

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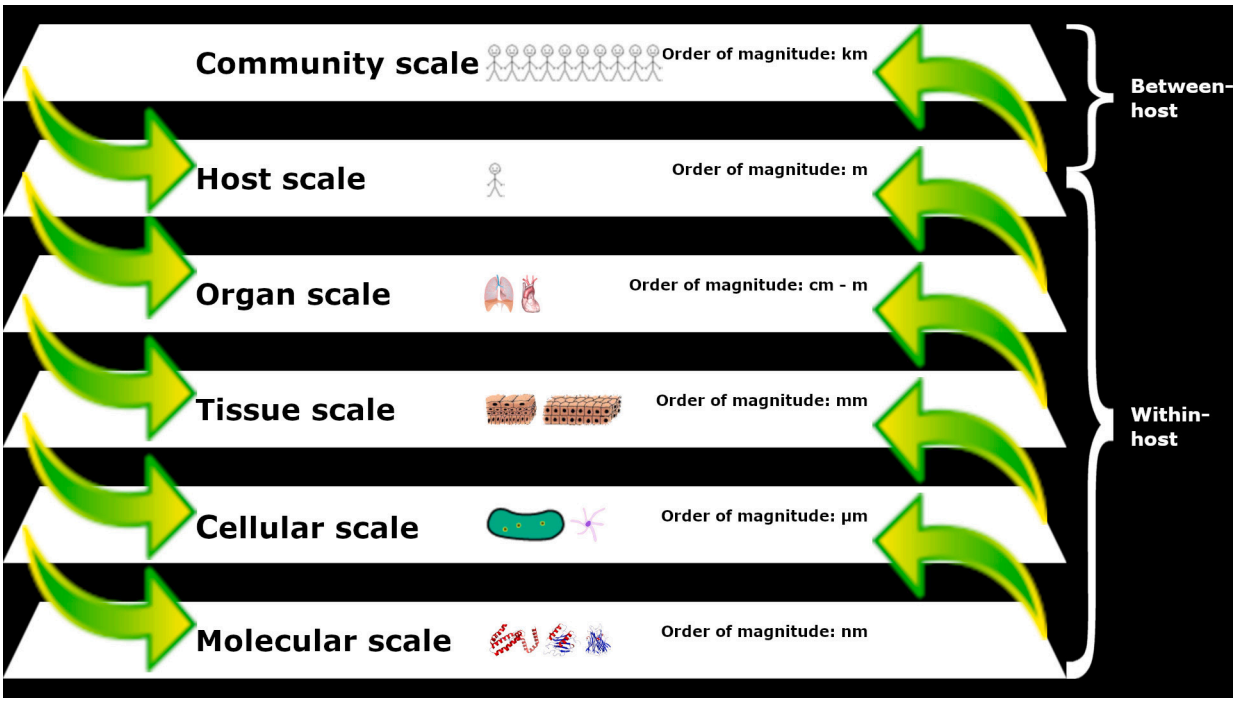

Fig. 1. Schematic showing the potential within-host and between-host scales that models of infectious disease can represent.

approaches across scales, are open questions with answers depending on the modelling context (Almocera and Hernandez-Vargas, 2018, 2019).

In order to aid the development of new multiscale modelling frameworks of infectious disease, we conducted a literature review of the current state of the field. We performed a structured search on Google Scholar, following the PRISMA guidelines for a systematic review (Moher et al., 2009), and found multiple examples of multiscale (known variably as immuno-epidemiological or within-host-to-between-host) models for specific infectious diseases, as well as generic approaches at these different scales that could apply to a range of diseases. We reviewed these models, discussing the modelling approaches employed, and the benefits and drawbacks of these frameworks. To our knowledge, this is the first systematic review of multiscale modelling frameworks of infectious disease that link the within-host and between-host scales and uses the categorisations of the methodological approaches to multiscale epidemic modelling previously defined by Garira (2017), with a focus on the methodologies used to link the scales. The categorisations are discussed further in Section 3. Our aim with this review paper is to provide a resource that can guide epidemiological modellers, by helping them to understand the range of different approaches to multiscale infection modelling.

Throughout the remainder of this article, we outline and contrast the wide variety of different approaches that have been taken with regards to multiscale modelling of infectious diseases. Specifically, the article is structured as follows: Section 2 demonstrates the potential organisational levels of multiscale modelling frameworks and specifies the organisational level investigated in this review; in Section 3 we define the five categories of multiscale modelling framework considered in this review; in Section 4 we outline the methodology of the systematic review; in Sections 5 to 9 we present the examples we identified in our systematic review of the five types of multiscale modelling frameworks defined by Garira (2017), specifically: individual-based multiscale modelling frameworks in Section 5; nested multiscale modelling frameworks in Section 6; embedded multiscale modelling frameworks in Section 7; hybrid multiscale modelling frameworks in Section 8; and coupled multiscale modelling frameworks in Section 9. We conclude in Section 10 with a short discussion of the state of the field and suggest open problems for epidemiological modellers to address in the future.

2. Potential organisational levels of a multiscale modelling framework

As is shown in Fig. 1, infectious diseases can impact multiple spatial scales; these spatial scales are spread over multiple organisational levels (Garira, 2017), as shown in Fig. 1. Humans, as hosts of infectious diseases that make up the population (between-host) scale (i.e. the focus of host-level multiscale modelling frameworks), are made up of organs. These organs in turn are composed of different types of tissue; cells are the building blocks of tissues and are in turn, roughly speaking, collections of molecules. At the highest scale, communities of humans are an additional potential organisational level (Garira, 2018, 2019). While there is substantial complexity in within-host infection dynamics (as illustrated in the different levels in Fig. 1), mathematical modelling requires simplification of complex biological processes. For that reason, modellers often simplify this complexity by considering "within-host" and "between-host" infection dynamics, where the within-host scale comprises processes occurring from the molecular to the organism scale (as shown in Fig. 1). We therefore focus in this review on within-host and between-host dynamics.

3. Types of multiscale modelling framework

Five types of multiscale modelling framework have previously been identified: individual-based; nested; embedded; hybrid; and coupled (Garira, 2017). Each of these approaches have been used to link the within-host and between-host scales (Garira, 2017):

- **Individual-based multiscale modelling frameworks** see the between-host variables determined by the characteristics of each host: individuals are considered as discrete entities, and are given pre-determined properties and rules to follow.

Table 1
Records included in this review paper after following PRISMA guidelines. Some records could be placed into multiple categories, and so are referenced multiple times in this table.

Type	References
Individual-based	Parra-Rojas et al. (2018), Vickers and Osgood (2014), Yang et al. (2018), Du et al. (2020), Steinmeyer et al. (2010), Lukens et al. (2014), Hay et al. (2020), Sun et al. (2016), Musundi et al. (2022) Chen et al. (2020), Waites et al. (2022), Van Dorp et al. (2014), Nguyen et al. (2018), Park et al. (2013), Schreiber et al. (2021), Marrec (2020), Sieben et al. (2022), Pereira et al. (2021), Griffiths (2013)
Nested	Almocera and Hernandez-Vargas (2018), Almocera and Hernandez-Vargas (2019), Schreiber et al. (2021), Chhetri et al. (2021) Prakash et al. (2020), Mafunda (2018), Hart et al. (2020), Oganga (2021), Heffernan and Keeling (2009), Booton et al. (2019) Oganga et al. (2020), Garira and Mathebula (2020), Cai et al. (2020), Tuncer et al. (2016), Handel et al. (2013), Wang and Tang (2017), Shen et al. (2019a), Lou et al. (2015), Musundi (2021), King et al. (2009), Bhattacharya and Martcheva (2016) Gulbudak and Browne (2020), Azevedo et al. (2018), Shen et al. (2019b), Mathebula (2018), Legros and Bonhoeffer (2016), Li et al. (2021), Martcheva and Li (2013), Hu and Lou (2016), Agusto et al. (2019), Nikin-Beers (2018), Bosia (2017)
Embedded	Feng et al. (2012), Garira (2019), Yang et al. (2018), Nguyen et al. (2018), Marrec (2020), Pereira et al. (2021), Griffiths (2013), Mathebula (2018), Agusto et al. (2019), Wang et al. (2022), Garira and Chirove (2020), Xue and Xiao (2020) Wang and Wang (2017), Makhuvha (2019), Ratchford and Wang (2019), Ratchford and Wang (2020), Mobisa (2019), Mohsen and Naji (2020), Aili et al. (2023), Fotsa-Mbogne et al. (2021), Banerjee et al. (2020), Hite and Cressler (2018), López et al. (2022)
Hybrid	Nguyen et al. (2018), Park et al. (2013), Schreiber et al. (2021), Marrec (2020), Cai et al. (2020), Tuncer et al. (2016), Handel et al. (2013), Wang and Tang (2017), Shen et al. (2019a), Lou et al. (2015) Musundi (2021), King et al. (2009), Bhattacharya and Martcheva (2016), Gulbudak and Browne (2020), Azevedo et al. (2018), Shen et al. (2019b), Li et al. (2021), Martcheva and Li (2013), Hu and Lou (2016)
Coupled	Hay et al. (2020), Schreiber et al. (2021), Marrec (2020), Sieben et al. (2022), Pereira et al. (2021), Griffiths (2013), Bhattacharya and Martcheva (2016), Gulbudak and Browne (2020), Azevedo et al. (2018), Shen et al. (2019b), Mathebula (2018) Legros and Bonhoeffer (2016), Li et al. (2021), Martcheva and Li (2013), Hu and Lou (2016), Agusto et al. (2019), Nikin-Beers (2018), Bosia (2017), Hite and Cressler (2018), López et al. (2022), Barfield et al. (2018), Gulbudak (2020)

- In **nested multiscale modelling frameworks**, the within-host scale is connected to the between-host scale unidirectionally: the between-host scale is influenced by the within-host scale, but the within-host scale is not influenced by the between-host scale.
- By comparison, **embedded multiscale modelling frameworks** allow for information to flow in both directions: there is cyclical feedback between the within-host and between-host scales.
- Each of the previous three approaches typically only consider one mathematical formalism (the same at both scales); **hybrid multiscale modelling frameworks** explicitly use different mathematical representations at each scale (for example, ODEs at one scale and PDEs at another scale).
- Furthermore, whilst the previous four types of multiscale modelling framework normally consider just one strain of one pathogen affecting one type of host in one environment, **coupled multiscale modelling frameworks** allow for multiple strains, pathogens, hosts and environments.

It is worth noting that these types of multiscale modelling framework are not mutually exclusive. Depending on the linking mechanism and the number of mathematical modelling approaches, host species, pathogens, and strains used at each scale, certain multiscale modelling frameworks could be assigned to multiple categories. Having said this, there are clear distinctions between the types, such that no one type of multiscale modelling framework is a strict subset of another type. We acknowledge that other methods of categorisation could be used, one of which is discussed in the following paragraph.

Consideration should be given as to whether a multiscale approach linking the within-host and between-host scales is 'essential' or not (Mideo et al., 2008). The term essential here refers to multiscale immuno-epidemiological models for which the within-host and between-host scales affect each other, meaning an explicit representation of both scales is necessary to capture the full dynamics. If the link is only in one direction (i.e. the within-host scale affects, but is subsequently unaffected by, the between-host scale), the multiscale modelling framework is referred to as 'inessential', as one could simplify the scheme by reducing the model to a single-scale between-host representation. Broadly speaking, the embedded multiscale modelling frameworks (reviewed in Section 7), and some of the hybrid multiscale modelling frameworks (reviewed in Section 8), would fit the definition of 'essential'; individual-based and nested multiscale modelling frameworks (reviewed in Sections 5 and 6, respectively) would typically be considered 'inessential' (Garira, 2017).

The benefits and drawbacks of each type of multiscale modelling framework are discussed in Section 10, and are summarised in Table 7 in Section 10.

4. Systematic review methodology

There are four stages that should be followed to conduct a systematic review, according to the PRISMA guidelines (Moher et al., 2009). The first stage is identifying potential records to be included in the review, either from a structured search of an academic database or from other sources; the second is screening the records identified and removing any duplicates; the third is making a determination as to which records are eligible for the review being carried out; and the fourth is including the eligible records and analysing the results.

We conducted a structured search on Google Scholar, using the search terms *("individual based" OR nested OR embedded OR hybrid OR coupled) AND ("infectious disease" OR "infectious diseases") AND (multiscale OR "multi scale") AND ("immuno epidemiological" OR "host level" OR ("within host" AND "between host"))*. This search returned 367 papers that were potentially eligible.

Papers were deemed eligible if they presented both a within-host model and a between-host model, and/or a multiscale modelling framework, and were related to the spread of pathogens among human hosts (other hosts could be considered provided human hosts were accounted for). Additionally, we required the multiscale modelling frameworks to be unique, so papers were excluded if they contained the same multiscale modelling framework as another paper already deemed eligible (these were typically papers by the same authors), and that there should be a quantitative link between the within-host and between-host scales. Review papers, retracted papers and partially/wholly inaccessible records were also excluded at this stage, which meant that 304 papers were discarded for failing to satisfy at least one of the specified criteria. This left 63 papers eligible for our review. Another 5 papers that we were already aware of were also included (Feng et al., 2012; Van Dorp et al., 2014; Pereira et al., 2021; Oganga et al., 2020; Banerjee et al., 2020) (4 did not include the term "multiscale" or alternative spellings; 1 does not appear to be within Google Scholar's index), for a total of 68 papers. All of the papers are listed in Table 1 according to the type of multiscale modelling framework.

It is worth acknowledging here that other papers that would have been deemed eligible may have been missed, due to the search terms

Table 2
Examples of the technical features of different individual-based multiscale modelling frameworks.

Feature	Example	Reference
Within-host pathogen load for each individual as solution of ODE	$\frac{dZ_i}{dt} = c_i B - \xi_i Z_i$ $i = 1, \ldots, N$: ith individual Z_i: pathogen load of individual i B: environmental pathogen load c_i: transfer rate of environmental pathogens to individual i ξ_i: removal rate of pathogen from individual i	Yang et al. (2018)
Behaviour at between-host scale determined by individual's age of infection	$c(t - t_0^i) = \begin{cases} c1, & \text{Primary stage;} \\ c2, & \text{Asymptomatic stage;} \\ c3, & \text{AIDS stage.} \end{cases}$ c: frequency of high-risk behaviours t_0^i: time at which individual i was infected	Sun et al. (2016)

that were chosen. We chose search terms such that each identified paper should specifically be a multiscale model of infectious disease, with within-host and between-host scales, and belong to one of the types of multiscale modelling framework previously identified (Garira, 2017). However, as this categorisation of multiscale modelling frameworks was taken from a paper published in 2017, any papers published before that may be excluded, due to the authors of those papers being unaware of, and thus not using, the terminology that would later be used to describe their models. Having said this, whilst we appreciate there are limitations to our search criteria, we believe they are reasonable, and that we have been sufficiently specific.

Furthermore, some between-host models attempt to incorporate within-host models without explicitly representing the within-host scale. For example, a compartmental between-host model may include separate compartments for symptomatic and asymptomatic individuals (Lovell-Read et al., 2021), or hosts at different stages of infection, reflecting different within-host dynamics between individuals. To be clear, such papers are excluded from this systematic review: the within-host scale had to be explicitly represented.

In the following five sections, we present the examples identified in our systematic review of the five types of multiscale modelling framework defined by Garira (2017). In addition, we have picked representative examples of the technical details of such multiscale modelling frameworks; these have been included in Tables 2–6.

5. Individual-based multiscale modelling frameworks

Although multiple modelling techniques have been developed for scaling from within-host individual-based models to between-host models (some of which are presented in Table 2), relatively few multiscale individual-based modelling frameworks exist in the literature. The first models that were developed in this category considered used ODEs at the within-host scale, linking these to network models at the between-host scale (Parra-Rojas et al., 2018; Vickers and Osgood, 2014). The two scales were linked in these models by making transmission a function of the pathogen load.

One individual-based multiscale modelling framework of cholera transmission dynamics gave each individual unique within-host dynamics by setting their internal pathogen concentration to be determined by the solution of an ODE, where the transfer rate of cholera from the environment into the individual was varied for each host (Yang et al., 2018). The authors used an embedded multiscale modelling framework: each individual shed bacteria into the environment, where indirect transmission could occur, and the within-host pathogen load was impacted by the environmental pathogen load (Yang et al., 2018).

Other individual-based multiscale modelling frameworks used a within-host ODE model to determine pathogen load and symptoms, whilst an ABM was used at the between-host scale (Du et al., 2020; Steinmeyer et al., 2010; Lukens et al., 2014; Sun et al., 2016); some authors contrasted the results of these models against deterministic between-host models for comparison (Du et al., 2020; Steinmeyer et al., 2010). To link the scales, it was usually assumed that the transmission rate was a function of pathogen load (Du et al., 2020) and, for some models, other factors such as symptoms, contact type (Lukens et al., 2014), host immunity (Steinmeyer et al., 2010), or behaviour (e.g. condom use when considering HIV) (Sun et al., 2016). However, one model chose to make transmission a function of multiple factors other than pathogen load: binding avidity of viruses, immunity, infection history and antigenic distance (Hay et al., 2020). As the virus in this model was allowed to adapt over time, this also counts as a coupled multiscale modelling framework. In most of these models, an agent transitioned from exposed to infectious once the infection level passed a certain threshold value (Lukens et al., 2014; Steinmeyer et al., 2010).

A more flexible approach was introduced by Chen et al., in which individual hosts, as well as environments and vectors, were considered as "patches", and the pathogen load of each patch was governed by an ODE (Chen et al., 2020). Each patch was allocated its own pathogen replication rate and death rate, whilst each possible between-patch transmission had its own transmission rate. In this sense, the between-host scale was an emergent property of the within-host scale.

In contrast to the individual-based multiscale modelling frameworks with deterministic within-host models previously mentioned, Musundi et al. used a stochastic within-host model which was linked to a PDE between-host model (Musundi et al., 2022). Susceptible individuals could have pathogens within them; they transitioned to infectious if their pathogen load progressed beyond a critical threshold.

A flexible approach was developed by Waites et al. (2022). A rule-based modular multiscale modelling framework was presented, in order to explore how the adaptive immune response at the within-host scale impacted on the transmission dynamics at the between-host scale for a viral infectious disease; the paper was developed with COVID-19 in mind. In the absence of an immune response, viral load replication was captured by a logarithmic counter of the total population: at a certain rate, the logarithm of the viral population increased by one. If an individual had a virus population of any size, their B-cell population would be activated; these would then produce antibodies. The affinity of virus-specific B-cells increased proportionally with the viral load, and antibodies were produced at a rate proportional to the affinity of the individual's B-cells. The viral load decreased linearly with the size of the antibody population, and if it was sufficiently low, it could be eradicated at a constant rate. If there was no virus population left, an individual's antibody count could wane over time at a constant rate. These within-host dynamics were connected to the between-host dynamics by determining whether individuals were susceptible, infectious or removed according to the sizes of their virus and B-cell populations. Between-host transmission from an infectious individual was proportional to that infectious individual's viral load.

The last individual-based multiscale modelling framework, which was used to model HIV-1 infection, used ABMs at both within-host and between-host scales. It was developed to determine whether the within-host scale or the between-host scale was more important in terms of evolutionary selection (Van Dorp et al., 2014). HIV-1 virions were the "agents" in the within-host dynamics, whilst individuals in the between-host dynamics could be either susceptible or infectious. At the within-host scale, the discrete events that could take place included the virus evolving a mutation that allowed for immune escape or reversing a deleterious mutation that previously took place. The disease state of an infectious host could be one of acute, asymptomatic or AIDS, with constant transition rates from acute to asymptomatic and AIDS to death; the transition rate from asymptomatic to AIDS, however, was dependent on the viral load. At the between-host scale, an infectious individual could transmit the disease to a susceptible individual or die from the infection; a susceptible individual was created if death

occurred, to keep the total population size constant. The method for determining which discrete event happened next was based on the Sellke construction, a generalisation of the Gillespie algorithm allowing for non-exponential waiting times (Sellke, 1983).

The models in this section have treated each individual as a separate entity, but this may lead to substantial computational complexity, as discussed above. The next two sections consider models that do not explicitly represent each host: embedded multiscale modelling frameworks, and first, nested multiscale modelling frameworks.

6. Nested multiscale modelling frameworks

In the articles we identified involving nested multiscale modelling frameworks, the most common mathematical framework at both scales was ODEs (Almocera and Hernandez-Vargas, 2018, 2019; Chhetri et al., 2021; Prakash et al., 2020; Mafunda, 2018; Hart et al., 2020; Oganga, 2021; Heffernan and Keeling, 2009; Booton et al., 2019; Oganga et al., 2020; Garira and Mathebula, 2020). The link between the scales was typically achieved by making the transmission rate at the between-host scale a function of the pathogen load at the within-host scale (Almocera and Hernandez-Vargas, 2018, 2019; Chhetri et al., 2021; Hart et al., 2020; Oganga, 2021; Booton et al., 2019; Oganga et al., 2020). The functions used to link within-host pathogen load to between-host transmission rate were frequently assumed to be linear (Almocera and Hernandez-Vargas, 2018; Hart et al., 2020; Booton et al., 2019); in other cases, logistic (Almocera and Hernandez-Vargas, 2018) and other saturating functions (Almocera and Hernandez-Vargas, 2018, 2019; Oganga, 2021; Oganga et al., 2020) were chosen. Alternatively, the total pathogen load produced by an infected host at the within-host scale was found by integrating the area under the pathogen load curve; this quantity was either implemented as a proxy for the direct transmission rate (Chhetri et al., 2021), or was used to determine how many pathogens were shed into the environment, leading to direct (Mafunda, 2018) or indirect transmission to susceptible hosts (Garira and Mathebula, 2020; Prakash et al., 2020), depending on the pathogen in question. Other linking mechanisms identified in our review included making the transmission rate, exposed period and infectious period depend upon the level of immune memory prior to exposure (Heffernan and Keeling, 2009), and making the mortality rate a function of the equilibrium amount of susceptible cells (Booton et al., 2019). Some examples of these linking mechanisms can be found in Table 3.

As we have seen, nested multiscale modelling frameworks only allow for information to flow in one direction: from the within-host scale to the between-host scale. The next section reviews models that also have information flow from the between-host scale to the within-host scale: embedded multiscale modelling frameworks.

7. Embedded multiscale modelling frameworks

For embedded multiscale modelling frameworks, the most frequent mathematical formalism at both scales was again ODEs (Wang et al., 2022; Garira, 2019; Garira and Chirove, 2020; Xue and Xiao, 2020; Wang and Wang, 2017; Makhuvha, 2019; Ratchford and Wang, 2019, 2020; Mobisa, 2019; Mohsen and Naji, 2020; Aili et al., 2023; Fotsa-Mbogne et al., 2021; Feng et al., 2012; Banerjee et al., 2020). In such models, the within-host dynamics linked to the between-host dynamics bidirectionally. In multiple models, the transmission rate of infectious individuals (Wang and Wang, 2017) (and pre-symptomatic individuals in one case (Wang et al., 2022)) was a function of their pathogen load, which in turn depended on contact rate with infectious individuals in HIV-specific models (Xue and Xiao, 2020; Mobisa, 2019). In some models, the pathogens in the environment at the between-host scale could be transmitted to the host, subsequently impacting the pathogen load at the within-host scale (Wang et al., 2022; Wang and Wang, 2017; Makhuvha, 2019; Ratchford and Wang, 2019, 2020; Fotsa-Mbogne et al., 2021). Pathogens could be shed into the environment by infectious individuals in some models (Wang and Wang, 2017; Makhuvha, 2019; Ratchford and Wang, 2019; Fotsa-Mbogne et al., 2021), and in one case, a cyclical feedback loop was implemented by allowing the internal pathogen load to increase due to uptake of environmental pathogens (Aili et al., 2023). The disease-induced death rate of individuals with AIDS was defined in one model of HIV as a function of pathogen load.

Table 3
Examples of the technical features of different nested multiscale modelling frameworks.

Feature	Example	Reference
Between-host transmission as a linear function of within-host pathogen load	$\beta(\tau) = kV(\tau)$ β: expected infectiousness V: expected viral load τ: days since infection	Hart et al. (2020)
Between-host transmission as a saturating function of within-host pathogen load	$\lambda(L^*) = \frac{aL^*}{L^*+b}$ λ: transmission rate L^*: equilibrium viral load a: maximum transmission rate b: half saturation constant	Oganga et al. (2020)
Area under the within-host pathogen load curve as a proxy of between-host infectivity	$N_h = \frac{\alpha \int_{d_1}^{d_2} U^* ds}{y+\mu_v}$ N_h: area under viral load curve α: burst rate of infected cells d_1: beginning of infection d_2: end of infection U^*: infected cells s: within-host time scale y: immune response μ_v: death rate of virus	Chhetri et al. (2021)

However, some authors linked the scales by introducing a cyclical feedback loop between host-pathogen dynamics and the number of infectious individuals at the between-host scale (Mohsen and Naji, 2020; Feng et al., 2012). In order to model the variability in immune response across the population, one model constructed the bidirectional link by making the number of susceptible individuals at the between-host scale a function of the initial viral load at the within-host scale. If the initial viral load to which an individual was exposed was small enough, the individual would never be susceptible to the disease if they had a "strong" immune response. The initial viral load was in turn dependent upon the number of infectious individuals at the between-host scale (Banerjee et al., 2020). Finally, some models accounted for the possibility of super-infection by linking the between-host scale to the within-host scale. This was achieved by allowing individuals to uptake virions from/shed virions into the environment (Garira, 2019). In one coupled multiscale modelling framework, infected vectors could shed virions into the environment (Garira and Chirove, 2020). Some examples of these linking mechanisms can be found in Table 4.

Up until now, the multiscale modelling frameworks described have been concerned with just one mathematical formalism at both scales. In the next section, we will explore the frameworks that have been developed with different formalisms used to represent each scale: hybrid multiscale modelling frameworks.[1]

8. Hybrid multiscale modelling frameworks

Hybrid multiscale modelling involves the use of different modelling approaches at different scales (some examples of which are presented in

[1] Individual-based multiscale modelling frameworks can also use different formalisms to represent each scale. However, they will always represent each individual within a population separately, whereas hybrid multiscale modelling frameworks do not necessarily always do this.

Table 4
Examples of the technical features of different embedded multiscale modelling frameworks.

Feature	Example	Reference
Increase in within-host pathogen load over time as a function of between-host contacts with infectious individuals	$\frac{dV}{dt} = c_1 p_1 \frac{I}{N} + c_2 p_2 \frac{A}{N} + ...$ V: viral load c_1: contacts with infecteds p_1: virus released by infecteds I: infected individuals N: total population size c_2: contacts with AIDS patients p_2: virus released by AIDS patients A: AIDS patients	Xue and Xiao (2020)
Number of susceptible individuals as a function of within-host pathogen load (which is a function of infectious individuals)	$S(v_0) = \begin{cases} S_1, & v_0 < \hat{v}_0 \\ S_2, & v_0 \geq \hat{v}_0 \end{cases}$ $v_0(I) < \hat{v}_0,\ I < I_c$ $v_0(I) \geq \hat{v}_0,\ I \geq I_c$ S: susceptible individuals v_0: initial viral load S_1: susceptibles with weak immune response S_2: total susceptibles $\hat{v}_0$: critical viral load I: infected individuals I_c: critical number of infecteds	Banerjee et al. (2020)
Environmental dynamics linking within-host and between-host dynamics	$\frac{dB}{dt} = \xi(Z)I - \delta B$ B: environmental pathogen load Z: within-host pathogen load I: infectious individuals ξ: pathogen shedding rate δ: pathogen degradation rate	Wang and Wang (2017)

Table 5
Examples of the technical features of different hybrid multiscale modelling frameworks. For more details, see the references.

Feature	Example	Reference
ODE within-host model, network between-host model	$\frac{dV}{dt} = r_V V(1 - \frac{V}{K_V})(\frac{V}{I_n + V})(1 - \frac{Ab}{K_{Ab}})$ $p_{I_i} = V(t_i)/K_V,\ p_{I_i} \in [0,1]$ $p_{S_j} = f_S(\text{age}_j),\ p_{S_j} \in [0,1]$ $p_{i,j} = p_{I_i} p_{S_j}$ V: viral load p_{I_i}: transmission potential of infectious node i p_{S_j}: susceptibility of neighbouring node j $p_{i,j}$: transmission probability	Nguyen et al. (2018)
ODE within-host model, PDE between-host model	$\frac{dU}{dt} = -kUV$ $\frac{dX}{dt} = kUV - \delta X$ $\frac{dV}{dt} = pX - c_w V$ $\frac{dS(t)}{dt} = -S(t)(b_2 P(t) + \int_0^\infty b_1(a) I(t,a) da)$ $I(t,0) = S(t)(b_2 P(t) + \int_0^\infty b_1(a) I(t,a) da)$ $\frac{\partial I(t,a)}{\partial t} = -\frac{\partial I(t,a)}{\partial a} - g(a) I(t,a)$ $\frac{dP}{dt} = \int_0^\infty w(a) I(t,a) da - c_b P$ U: uninfected cells X: infected cells V: viral load S: susceptible individuals I: infectious individuals P: environmental pathogens t: time a: age of infection k: infection rate δ: death rate of infected cell p: production rate of virions c_w: virus clearance rate b_1: direct transmission rate b_2: environmental infection rate g: rate of recovery w: rate of shedding c_b: virus decay rate in the environment	Handel et al. (2013)

Table 5). Nguyen et al. used a compartmental ODE within-host model and a network ABM at the between-host scale (Nguyen et al., 2018). We note that some models fall into multiple categories of multiscale model. In particular, as well as being a hybrid model, this model is also an embedded and individual-based model. Scales were linked by assuming that an infectious individual's transmission potential was linearly proportional to their current viral load, and that the initial viral load of a newly infected individual was related to the transmission potential of the person transmitting the pathogen to them.

Similarly, Park et al. used an ODE within-host model and linked it to a stochastic between-host transmission model (Park et al., 2013). The model linked the scales by having the evolutionary rate of one strain becoming dominant within a host at the between-host scale determined by the number of infectious cells infected with the original strain multiplied by various within-host parameters (Park et al., 2013).

Other hybrid multiscale modelling frameworks also used ODE models at the within-host scale, but chose PDE models for the between-host scale (Cai et al., 2020; Tuncer et al., 2016; Handel et al., 2013; Wang and Tang, 2017; Shen et al., 2019a; Lou et al., 2015; Musundi, 2021; King et al., 2009; Bhattacharya and Martcheva, 2016). All of these frameworks were also examples of nested multiscale modelling frameworks. The transmission rates in many models were functions of the pathogen load (Wang and Tang, 2017), although one model made transmission also depend upon the number of infectious individuals (Musundi, 2021). This function was typically set to be saturating (Cai et al., 2020; Tuncer et al., 2016; Lou et al., 2015); one model defined a linear relationship between the two (Bhattacharya and Martcheva, 2016), and some models considered multiple functions to define the link connecting within-host pathogen load and between-host transmission (Handel et al., 2013; Shen et al., 2019a; King et al., 2009). One model also made shedding of bacteria into the environment a function of bacterial load (Wang and Tang, 2017). Additionally, in some instances, other epidemiological functions were set to be functions of the host-pathogen dynamics: the recovery rate (Cai et al., 2020; Tuncer et al., 2016); the disease-induced death rate (Cai et al., 2020; Tuncer et al., 2016; Bhattacharya and Martcheva, 2016; Lou et al., 2015); the shedding rate (Cai et al., 2020); and the treatment rate (Lou et al., 2015).

The previous four sections (5–8) have focused on investigating the impact of one strain of one infectious pathogen on one host population in one environment. The last type of multiscale modelling frameworks, explored in the next section, have more than one strain/pathogen/host population/environment; they are known as coupled multiscale modelling frameworks.

9. Coupled multiscale modelling frameworks

Many coupled multiscale modelling frameworks could also be categorised as hybrid: they frequently employ ODEs at the within-host scale and PDEs at the between-host scale (Gulbudak and Browne, 2020; Azevedo et al., 2018; Shen et al., 2019b; Li et al., 2021; Martcheva and Li, 2013; Hu and Lou, 2016; Bhattacharya and Martcheva, 2016). Other coupled multiscale modelling frameworks that would also qualify as hybrid saw the within-host scale dynamics determined by ODEs whilst the model at the between-host scale was stochastic (Schreiber et al., 2021; Marrec, 2020). Two strains of a pathogen were incorporated at the within-host scale in each of these models (Schreiber et al., 2021; Marrec, 2020); at the between-host scale, an individual-based approach was taken. Similarly, in an example of an individual-based

Table 6
Examples of the technical features of different coupled multiscale modelling frameworks.

Feature	Example	Reference
Different strains of the same pathogen	$E = b_w v_w(t) + b_m v_m(t)$ E: effective viral load of an individual v_w: viral abundance of wild type v_m: viral abundance of mutant strain b_w: wild type transmission probability b_m: mutant strain transmission probability	Schreiber et al. (2021)
Different species infected by the same pathogen	$N_{BH}(t) = S_H(t) + I_H(t) + R_H(t)$ $N_M(t) = S_M(t) + I_M(t)$ $N_{BH}(t)$: total human population $N_M(t)$: total mosquito population $S_H(t)$: susceptible human population $I_H(t)$: infected human population $R_H(t)$: recovered human population $S_M(t)$: susceptible mosquito population $I_M(t)$: infected mosquito population	Agusto et al. (2019)

multiscale modelling framework, Sieben et al. linked an ODE within-host model (with multiple strains of a disease taken into account) to an ABM for between-host transmission (Sieben et al., 2022). The probability of between-host transmission, and the amount of pathogens of a given strain subsequently transmitted, was a function of that strain's pathogen load.

Other coupled multiscale modelling frameworks have employed ODE models at both the within-host and between-host scales (Mathebula, 2018; Legros and Bonhoeffer, 2016; Hite and Cressler, 2018; Agusto et al., 2019; López et al., 2022; Bosia, 2017). Mathebula modelled two different diseases, malaria and schistosomiasis, separately (Mathebula, 2018); multiple other authors also investigated malaria (Legros and Bonhoeffer, 2016; Agusto et al., 2019; López et al., 2022), while Hite and Cressler explored two strains of parasites (Hite and Cressler, 2018) and Bosia created an HIV multiscale modelling framework with multiple strains (Bosia, 2017). Both humans and mosquitoes were included at the between-host scale of the malaria models, compartmentalised into susceptible and infectious individuals (Mathebula, 2018; Legros and Bonhoeffer, 2016; Agusto et al., 2019; López et al., 2022).

Hite and Cressler explored the evolution of the amount of resources available to humans/parasites, as well as the number of susceptible hosts and those infected by either strain Hite and Cressler (2018). For the schistosomiasis framework, the within-host model considered different compartments of infective parasitic agents, whilst the between-host scale had humans and snails as potential hosts, both of which could be susceptible or infected; additionally, different parasitic infective agents were considered in the environment (Mathebula, 2018).

Instead of ODEs, both Barfield et al., and Gulbudak used PDEs at both scales (Barfield et al., 2018; Gulbudak, 2020). At the between-host scale, two host species in competition with each other were considered in Barfield et al.'s model; Gulbudak had human and vector populations as susceptible species (Gulbudak, 2020). The scales were linked in both models by setting multiple parameters at the between-host scale (namely the transmission rate, disease-induced death rate and recovery rate) to depend on the within-host variables.

The model developed by Nikin-Beers simplified the within-host dynamics by approximating the viral loads for individuals infected with either dengue fever or dengue hemorrhagic fever via triangular distributions; this was then linked to a PDE between-host scale model (Nikin-Beers, 2018). The compartments considered at the between-host scale were susceptible, infectious and recovered; these were further subdivided according to which of two strains a host was infected with first: one could only become infected with the other strain once they had fully recovered from the first they were exposed to, giving eight compartments in total.

The scales were linked for most of these models by making at least one of the between-host model parameters a function of the within-host variables, such as antibody levels (Gulbudak and Browne, 2020), pathogen load (Azevedo et al., 2018; Shen et al., 2019b; Mathebula, 2018; Legros and Bonhoeffer, 2016; Schreiber et al., 2021; Li et al., 2021; Martcheva and Li, 2013; Hu and Lou, 2016; Agusto et al., 2019; Nikin-Beers, 2018; Hu and Lou, 2016). Additionally, multiple frameworks set the disease-induced death rates of hosts (as well as the human recovery rate from malaria in multiple frameworks) to be functions of the infective agents (Mathebula, 2018; Li et al., 2021; Martcheva and Li, 2013; Agusto et al., 2019), whilst Bosia allowed for strains to evolve as part of the within-host dynamics (Bosia, 2017). In this sense, these multiscale modelling frameworks could also be categorised as nested.

However, some coupled multiscale modelling frameworks were embedded rather than nested. The schistosomiasis model developed by Mathebula was an embedded multiscale modelling framework: parasite loads within a human host could increase based on contact with the parasite in the environment, whilst more parasites could be excreted by an infectious host back into the environment (Mathebula, 2018). Hite and Cressler's framework also qualified as an embedded multiscale modelling framework: the between-host transmission rate and virulence were functions of parasite load, whilst a host's internal energy could increase with resource consumption (Hite and Cressler, 2018). Agusto et al. created an embedded model by having the parasite loads in both humans and mosquitoes increase as a function of the number of infectious hosts (Agusto et al., 2019). López et al. made their malaria multiscale modelling framework an embedded one by making the transmission rate a function of the proportion of infected target cells. Additionally, the within-host pathogen load was allowed to increase as a function of infected mosquitoes (López et al., 2022). Marrec had the amount of pathogens of a given strain transmitted during between-host transmission depend on the within-host proportion of pathogens that are drug-resistant; the amount of pathogens of each strain transmitted to a new host determined the initial conditions of their within-host dynamics (Marrec, 2020).

Finally, multiple authors developed individual-based coupled multiscale modelling frameworks to investigate tuberculosis (Pereira et al., 2021) and parasitic infections (Griffiths, 2013). The between-host scale models were ABMs, and were linked to deterministic within-host dynamics. In Griffiths's model, two strains of parasites (one of which was treated and one of which was not) were included, along with a specific immune response to each strain and resources available for the parasite, at the within-host scale (Griffiths, 2013). In Pereira et al.'s framework, drug-resistant and drug-sensitive strains of *Mycobacterium tuberculosis* (*Mtb*) were considered (subdivided into active and dormant bacteria) (Pereira et al., 2021).

Both of these last two models were also embedded multiscale modelling frameworks. Adult parasites produced eggs that contributed to the environmental pool of parasites at the between-host scale of the parasitic infections model by Griffiths; this environmental pool could then be ingested and initiate infections in other hosts at the within-host scale (Griffiths, 2013). Pereira et al., meanwhile, made the amount of pathogens transmitted at the between-host scale a function of the pathogen load of the transmitter's within-host dynamics; each agent was either susceptible, latently infected or actively infected (with either drug-sensitive or drug-resistant strains in both the final two categories), depending on their within-host pathogen load. The within-host dynamics were then affected by the pathogens transmitted to them at between-host scale, as super-infection was incorporated (Pereira et al., 2021).

Some examples of the technical features of coupled multiscale modelling frameworks are presented in Table 6.

10. Discussion

In this review article, we have summarised different types of multiscale models of pathogen transmission. These types are: individual-based, nested, embedded, hybrid and coupled.

The main advantage that individual-based multiscale modelling frameworks have over the other categories is the ability to incorporate individual heterogeneity at the within-host scale by giving individuals properties that are not grouped together and can be uniquely changed over time (Garira, 2017). Not everybody's immune system is equally capable of dealing with invading pathogens, and some of the models in this review have considered this, for example by changing the uptake rate of environmental pathogens (Yang et al., 2018), having an individual's immune response depend upon their own infection history (Hay et al., 2020), or having the pathogens themselves evolve and adapt to the immune system (Van Dorp et al., 2014). Similarly, not everybody is equally likely to be infected; modelling between-host scale transmission on a network can account for this, whereas other types of multiscale model cannot capture this in the same way. Another benefit of individual-based models is their relatively simple interpretation (Garira, 2017): depending on the audience the model is to be presented to, the fact that many of these models can be described in terms of agents and rules rather than equations may help with improving understanding of the modelling approach. Additionally, publicly accessible modelling software incorporating individual-based modelling approaches is available (e.g. NetLogo Tisue and Wilensky, 2004), although we note that the development of further user-friendly software for running multiscale transmission models is a key area for future research. We also note that the level of detail included in individual-based models tends to lead to greater computational cost (Garira, 2017). Keeping these costs down may mean that substantial simplification of the within-host dynamics is required.

Nested multiscale modelling frameworks of infectious diseases are typically preferable to other types in the sense that they tend to be the simplest to analyse (Garira, 2017). As there is only one direction for information to flow between scales, authors can find summary measures at the within-host scale and use these to evaluate the between-host dynamics at a single time scale: determining the area under the pathogen load curve and setting that as a proxy for the transmission rate is an example of this simplification (Chhetri et al., 2021). Such a simplification is usually made when the assumption that within-host dynamics occur on a faster time scale than between-host scale dynamics is a valid one.

The cyclical feedback of information between scales in embedded multiscale modelling frameworks makes them a more biologically realistic approach than nested multiscale modelling frameworks. An open question is whether to include super-infection in infectious disease models, the answer to which will often depend upon the host-pathogen-environment system being modelled (Gog et al., 2015), but embedded multiscale modelling is a suitable framework to use when it is necessary to include super-infection. Typically, mathematical models that ignore super-infection are easier to analyse, so there is a valid question as to whether the increased complexity is needed. However, when a bidirectional link is included, it is not always clear how best to capture this cyclical feedback between scales (Garira, 2017). In particular, the linking of mechanisms from the between-host scale to the within-host scale varied considerably across the papers in this review. Some chose to make the link via pathogens in the environment (e.g. Wang and Wang, 2017), whereas others made within-host pathogen load dependent upon the number of infectious individuals (e.g. Xue and Xiao, 2020; Banerjee et al., 2020).

Hybrid multiscale modelling frameworks, in which different types of mathematical model are used at the within-host and between-host scales, allow for greater flexibility than using a single modelling approach. Factors such as population size and density will determine whether, for example, an ODE model or an ABM will be more or less suitable, and what may be suitable at one scale is not guaranteed to be optimal at the other. Hybrid multiscale modelling frameworks can lead to efficient computation. The main issue with this type of multiscale modelling framework is the increased complexity in having to run multiple mathematical model types: each of these types will require different methods that may need to be simulated separately (Garira, 2017).

Coupled multiscale modelling frameworks are ideal when considering a unified public healthcare approach (Garira, 2017). It is not necessarily the case that an individual can only be infected with one pathogen, or one pathogen strain, at a time. Coupled multiscale modelling frameworks can allow policymakers to determine which strain poses the greatest threat, for example, and therefore which to prioritise when making decisions. However, it is important to take into account that the order of infection of different pathogens/strains can lead to different within-host dynamics and, subsequently, different disease outcomes. If they are to prove more useful than independent multiscale modelling frameworks of different pathogens/strains, coupled multiscale modelling frameworks need to account for this factor; this may lead to more complexity, and more difficulty in uniquely determining model parameters, for example.

10.1. Future challenges

One of the issues that will need further exploration in multiscale modelling going forwards is how to best capture the impact of human behaviour on pathogen transmission (Childs et al., 2015). Handel and Rohani explored how the interactions between pathogen load, symptoms, and immune responses impact not only an infected host's infectiousness, but also their behaviour, and consequently their potential to transmit the pathogen (Handel and Rohani, 2015). Host behaviour was shown to be impacted by pathogen load, symptoms and immune response, and trade-offs between contact rates and symptoms were investigated. The review concluded that, although differences in transmission potential between infected hosts have been recognised, more data will be needed, and models will require further development (e.g. mapping from infection dynamics to host behaviour and subsequently transmission potential) to make additional advances.

Another issue is the exact relationship between pathogen load and infectiousness; as seen throughout this review, the link between scales is often achieved by making the transmission rate of a pathogen a function of the within-host pathogen load (Childs et al., 2015; Gog et al., 2015; Hart et al., 2023). The studies reviewed by Handel and Rohani suggested that, although pathogen load is linked to host infectiousness, it is often a poor predictor when viewed in isolation from other factors. Symptoms can also play an important role in determining the infectiousness of a host (Hart et al., 2019), and for some diseases, transmission only appears to be possible if symptoms are present (although this is not always the case Hart et al., 2021). The relationship between pathogen load and infectiousness is explored, but quantitative mappings between these variables remain unknown for many pathogens (Handel and Rohani, 2015). One of the few diseases where this relationship has been more thoroughly explored is HIV: Fraser et al. found that an increasing Hill function gave the closest fit between viral load during the asymptomatic phase and infectiousness (Fraser et al., 2007). As a greater viral load leads to a reduced time period in the asymptomatic phase of HIV, transmission potential was maximised for medium viral loads (Fraser et al., 2007). Similarly, the relationship between pathogen load and infectiousness has been investigated recently for SARS-CoV-2 (Ke et al., 2021).

Some of these issues could be addressed by the conceptual framework introduced by Handel and Rohani, which maps out the relationship between quantities that describe within-host infection, such as pathogen load, symptoms, the infected host's immune response and any changes in their behaviour, and transmission potential. In this framework, at different time points, an infected host has infection-related quantities (e.g. pathogen load, components of immune response

Table 7
Benefits and drawbacks of each type of multiscale modelling framework.

Type	Pros	Cons
Individual-based	Individual heterogeneity Simple to understand	Greater computational cost
Nested	Simple to analyse	Potential lack of realism
Embedded	Feedback between scales	Harder to analyse
Hybrid	Greater flexibility	Increased complexity
Coupled	Unified approach	Increased complexity

and symptoms) measured before they are exposed to susceptible hosts. Over time, as different numbers of susceptible hosts become infected at each time point sampled, the authors were able to deduce the relationship between the within-host infection dynamics and infectiousness. Although such a framework is feasible, it would prove logistically difficult to implement, as it would require a large number of volunteers for replacement of contacts (Handel and Rohani, 2015).

10.2. Conclusion

In this review paper, we have considered different approaches for multiscale immuno-epidemiological modelling. Each of these approaches have advantages and disadvantages, and the exact framework to use depends on the host-pathogen-environment system being studied. Multiscale models enable population-scale predictions to be improved, as they allow a greater level of detail and mechanistic knowledge than single-scale models, and they allow for reciprocal feedback between the within-host and between-host scales to be included. This facilitates the study of how epidemiological or evolutionary mechanisms at one scale affect dynamics at another scale. We have summarised the multiscale modelling approaches that are currently available, and hope that this review is a useful resource for epidemiological modellers who want to learn more about multiscale modelling. Given the large number of publications on this subject in recent years, this is an emerging research topic.

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CRediT authorship contribution statement

James W.G. Doran: Conceptualization, Writing – original draft, Writing – review & editing. **Robin N. Thompson:** Writing – review & editing. **Christian A. Yates:** Conceptualization, Supervision, Writing – review & editing. **Ruth Bowness:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

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