

Opinion

Coupled Heterogeneities and Their Impact on Parasite Transmission and Control

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Most host–parasite systems exhibit remarkable heterogeneity in the contribution to transmission of certain individuals, locations, host infectious states, or parasite strains. While significant advancements have been made in the understanding of the impact of transmission heterogeneity in epidemic dynamics and parasite persistence and evolution, the knowledge base of the factors contributing to transmission heterogeneity is limited. We argue that research efforts should move beyond considering the impact of single sources of heterogeneity and account for complex couplings between conditions with potential synergistic impacts on parasite transmission. Using theoretical approaches and empirical evidence from various host–parasite systems, we investigate the ecological and epidemiological significance of couplings between heterogeneities and discuss their potential role in transmission dynamics and the impact of control.

Transmission Heterogeneity in Host–Parasite Systems

Heterogeneity, broadly defined as the variability of a property of a system across space, time, and/or the system's individual constituents [1], is a pervasive feature of all host–parasite transmission systems. Empirical evidence shows that individual hosts can vary in their susceptibility to infection and parasite infectiousness or shedding rates (mediated by immunological factors or complex host–pathogen interactions); contacts between hosts or hosts and vectors tend to be highly variable in space and time and dependent on social, behavioral, or environmental conditions; and pathogen strains can vary in their level of virulence and transmissibility. One of the properties emerging from such individual, temporal, and spatial variability is the consistent finding of transmission heterogeneity (TH), in which certain individuals, locations, age or social groups, host species, or pathogen strains are responsible for a high proportion of overall transmission events [2–6]. Superspreading is an extreme case of TH in which a disproportionately large amount of transmission events are driven by very few individuals [7,8]. Theoretical and empirical studies indicate that interventions that account for TH can have a disproportionately high impact on pathogen transmission in comparison to blanket or random implementations [3,6,7,9]. While the public health impacts of TH have been extensively evaluated theoretically (e.g., [6,7,10–12]) and manifested in recent infectious disease outbreaks (e.g., the recent Ebola outbreak in West Africa [13]), the causal drivers leading to TH are not well understood. To better account for those extremely important yet rare contributors to transmission and improve disease prevention programs, two key questions will first need to be addressed: (i) Is TH the result of identifiable traits inherent to specific individuals and/or locations? (ii) Can we use such traits to predict TH across different epidemiological settings and time points?

Trends

The uneven contribution of certain individuals, locations, parasite strains, or reservoir host species to transmission – termed transmission heterogeneity – is a widespread attribute of most host–parasite systems.

Multiple conditions contributing to transmission heterogeneity can be correlated with each other, leading to non-linear impacts on parasite transmission potential (R_0).

Targeting epidemiologically relevant couplings can lead to more impactful control interventions.

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Given that TH can arise from a wide array of putative factors, a major challenge infectious disease researchers face when addressing these questions is the integration of available parasite-related information into a mechanistic framework that allows identification of the most epidemiologically relevant sources of heterogeneity [2,14,15]. When confronting mechanistic models of parasite transmission with epidemiological data, it also becomes apparent that there are often multiple factors that could potentially contribute to TH. The ways in which these factors interact to determine overall TH is a largely unexplored topic. Here, we introduce the concept of ‘coupled heterogeneities’ to capture the interrelated and complex interactions among conditions contributing to TH. We apply this concept to dengue virus (a multistrain, vector-borne viral pathogen with well-identified heterogeneities at the virus, mosquito vector, and human host levels) and expand it to other vector-borne and parasitic diseases to support the notion that accounting for the couplings between key heterogeneities could lead to a more effective mechanistic interpretation of parasite transmission dynamics and programs designed to prevent disease.

From Individual to Coupled Heterogeneities

Initial quantifications of TH by Woolhouse *et al.* [6] and Lloyd-Smith *et al.* [7] focusing on the role of individual heterogeneities, primarily contact rates and infectiousness, provide a foundation for understanding the role of functional heterogeneities (see Box 1 for a definition) in disease systems. Extensions of these seminal studies have led to the development of novel approaches for accounting for functional heterogeneities, including the explicit simulation of pathogen transmission within heterogeneous contact networks [16–18], the consideration of individual- and population-level variability in infectiousness [7,19–21], the evaluation of the role of spatial heterogeneity in the emergence of disease hotspots [5,22,23], and the evaluation of disease severity (or the inclusion of asymptomatic infections) in forecasts of pathogen transmission [24–26]. The magnitude of such effect is, however, compounded by correlations between functional heterogeneities. As Woolhouse *et al.* [6] note, ‘The magnitude of the effect of these other heterogeneities at the population level is unknown; but they will not decrease R_0 unless negatively correlated with the variables analyzed here. There may also be effects of “higher order” heterogeneities, all of which may further increase R_0 .’ This observation underscores a key, but poorly explored, aspect relevant for the identification of the drivers leading to TH; that is, the coupled nature of functional heterogeneities. Specifically, system properties may be strongly coupled with one another for a number of reasons, including multiple symptoms associated with disease manifestation, behavioral syndromes, or other phenotypic suites [27], or because of trade-offs in pathogen fitness [28]. As intimated by Woolhouse *et al.* [8], the sign of this coupling (positive or negative) between functional heterogeneities can significantly influence estimates of the basic reproduction number (R_0 , see Box 1 for a definition), or other measures of pathogen transmission.

One of the earliest theoretical explorations of coupled heterogeneities was provided by Dietz [29] in a model for schistosomiasis transmission. Specifically, he extended Barbour’s [30] formulation of the classic Ross–Macdonald model for malaria transmission to include a correlation structure between two functional heterogeneities: times for which different individuals are exposed to parasites at water ponds (heterogeneity in susceptibility) and rates at which different hosts contaminated ponds (parasite shedding rates, i.e., heterogeneity in infectiousness). Dietz’s findings, summarized in the following formula,

$$R_0^{(\text{heterogeneous})} = R_0^{(\text{homogeneous})} (1 + SD_{\text{heterogeneity1}} SD_{\text{heterogeneity2}} \rho_{\text{het1,het2}})$$

concluded that the impact of the modeled heterogeneities on R_0 depends on their magnitudes (quantified by their standard deviations, SDs) and the correlation between them ($\rho_{\text{het1,het2}}$). Later, Koella [31] followed Dietz’s approach by extending Dye and Hasibeder’s [32] formulation of R_0 for malaria transmission (developed to better account for heterogeneous biting) to include a covariance structure between three functional heterogeneities: biting rate, host susceptibility, and duration of infectiousness [31]. Both theoretical approaches arrived to a similar conclusion:

Box 1. System Properties and Functional Heterogeneities Relevant for Dengue Virus Transmission

All individual-level, temporal, or spatial attributes of potential epidemiological interest (e.g., parasitemia, duration of infectiousness, spatial distribution of people and households) can be referred to as 'system properties' of a particular disease system [1]. For dengue virus (DENV), the most important mosquito-borne viral infection of humans [69], a wide array of system properties at the human, virus, vector, and environmental levels have been identified as crucial for persistent virus transmission (Figure 1). At the virus level, each of the four DENV serotypes elicits different immune responses in humans [70,71], as well as variable effects on vector competence [20,72]. Spatial and temporal variability in productivity of larval habitats and abundance of the primary worldwide vector, *Aedes aegypti* [73], together with variations in adult *Ae. aegypti* longevity, impact vector survival, extrinsic incubation period of the virus, and, consequently, transmission probability [74]. Temperature fluctuations impact *Ae. aegypti* vectorial capacity [75], and immune and/or serotype-specific interactions within human hosts can impact disease severity and, likely, the individual infectiousness of humans to mosquitoes [35,76]. Mosquito dispersal and human movement and other behavioral responses to infection are key determinants of effective human–mosquito contacts and thus virus transmission [77,78].

If system properties vary from individual to individual, location to location, or over time in a way that impact an epidemiological or ecological measure such as vectorial capacity or transmission potential (e.g., the basic reproduction number of the pathogen, R_0 , defined as the expected number of secondary cases produced by a single infection in a completely susceptible population), then we refer to this variability as 'functional heterogeneity' [1]. For dengue, several functional heterogeneities have been identified (black bold font text in Figure 1). They involve heterogeneous biting, variability in human infectiousness to mosquitoes, disease-related behavioral response, herd immunity, vector competence and incubation periods in humans and mosquitoes, and human daily movement patterns. Some system properties cannot be predicted exactly but their variability may be accurately described through probability distributions. Such properties can be said to exhibit 'stochastic variability'. Stochastic variability can emerge from environmental stochasticity (e.g., increase in mosquito larval habitats due to a scattered rain event), measurement error (which can increase the variability in estimates of a system property), or sampling bias (which can lead to an incomplete characterization of a system property). Thus, TH is determined by a combination of functional heterogeneities specific to a given transmission system and stochastic variability that obscures and potentially alters the relationship between functional heterogeneities and TH. We further posit that focusing research efforts on the quantification of couplings between functional heterogeneities with strong influence in DENV transmission could increase our ability to develop realistic estimates of pathogen transmission and innovative concepts for disease prevention.

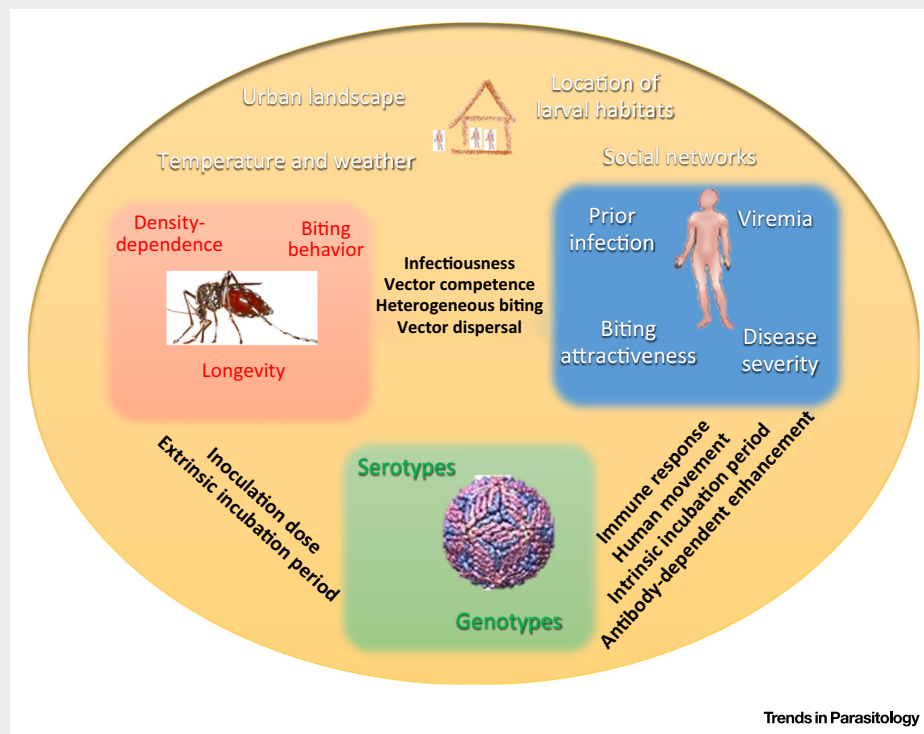
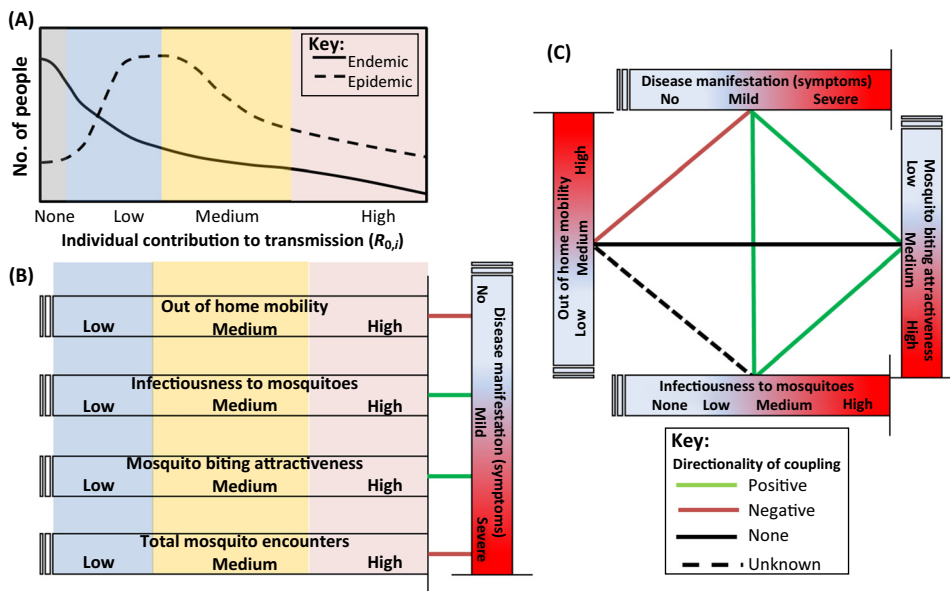


Figure 1. System Properties Responsible for Dengue Virus Transmission. Colored boxes identify specific traits known to vary in space (yellow), time or among individual people (blue), mosquitoes (red), or viruses (green). Black bold font text identifies functional heterogeneities known to have a direct impact in virus pathogen transmission and propagation.

positive correlations between two heterogeneous system properties increase R_0 relative to the situation in which the properties vary independently or do not exhibit heterogeneity, whereas negative correlations have the opposite effect. Here, we build on these findings by calling attention to these and other effects of coupling between heterogeneities, and we use dengue as a case study to investigate the empirical plausibility and epidemiological significance of coupled heterogeneities.

Figure 1 is a conceptual summary of known or hypothesized relationships between functional heterogeneities and TH that are typical of dengue transmission systems. The distribution of the number of secondary infections generated by any one individual in a population could be a function of a specific confluence of functional heterogeneities that lead to some individuals contributing more to transmission, infecting more mosquitoes, and thus generating a higher number of secondary infections (Figure 1A). For instance, a negative coupling between out-of-home human mobility and disease severity may result in severely ill individuals reducing their movement because of fever, fatigue, and other symptoms, and, perhaps, reducing the overall number of mosquito encounters within their infectious period across their activity space (Figure 1B). Dengue disease severity may be positively coupled with viral titer [34,35] and thus overall infectiousness to mosquitoes. Owing to increases in body temperature and lethargy, we may also expect disease severity to be positively correlated with attractiveness to mosquitoes



Trends in Parasitology

Figure 1. Coupled Heterogeneities in Dengue Virus Transmission. (A) The contribution of each individual in a population to dengue virus (DENV) transmission (expressed as the individual-level R_0 , $R_{0,i}$, defined as the expected number of secondary infections produced by each individual in a fully susceptible population) may differ between endemic and epidemic settings due to the levels of virus circulation and the proportion of individuals that are immune to the circulating serotype(s). With endemic transmission, the distribution of $R_{0,i}$ is significantly biased towards zero (due to the high proportion of immune individuals), whereas during epidemics a much larger proportion of the population contributes to transmission. Despite this difference, the expected distribution of $R_{0,i}$ allows grouping the individual contribution of individuals to transmission as poor (blue box), intermediate (yellow box), and high (red box). (B) Multiple functional heterogeneities can lead to this uneven distribution of $R_{0,i}$. As an extreme example, individuals with high out-of-home mobility, high infectiousness to mosquitoes, and high mosquito attractiveness will infect more mosquitoes and contribute more to transmission compared with individuals in the low end of the spectrum for these characteristics. Such heterogeneities are not independent from each other. For instance, disease manifestations (severity of dengue infection) may be correlated with multiple conditions, positively (green lines) or negatively (orange lines). (C) Diagram outlining what is known about the correlation structure among various sources of heterogeneity in DENV transmission.

and mosquito feeding success (Figure 1B). Figure 1C summarizes all known couplings between the four functional heterogeneities considered here.

To focus on a specific example with plausible couplings between heterogeneities, in Box 2 we consider a simplified model wherein either positive or negative coupling between infectiousness and host–vector contact clearly impacts R_0 . Even in this basic example, different couplings can

Box 2. Moving Beyond Single Heterogeneities

Consider a host population with four distinct types representing a two-by-two combination of high and low states of infectiousness to vectors (q_h, q_l) and high and low contact with vectors when sick (γ_h, γ_l) (Figure 1A). Heterogeneity in the latter is assumed to derive from heterogeneity in the proportion of time that individuals spend at home versus elsewhere. If we consider only a single type of vector and assume that encounters between vectors and hosts are well mixed, then R_0 is

$$R_0 = \frac{k^2 V D(\gamma)}{\delta \xi} \left(\frac{\gamma_h q_h}{H_{hh}} + \frac{\gamma_h q_l}{H_{hl}} + \frac{\gamma_l q_h}{H_{lh}} + \frac{\gamma_l q_l}{H_{ll}} \right)$$

where parameters are defined in Table 1 ([32,79]). We explored two aspects of coupling between heterogeneities in infectiousness and contact with vectors: (i) the direction of coupling (three scenarios in Figure 1A, with shaded boxes denoting which types are present), and (ii) the overall extent of heterogeneity (from left to right in Figure 1B). Colors in Figure 1A,B are coordinated across the three scenarios (i.e., positive, blue; none, black; negative, red), with Figure 1A indicating the proportion of individuals of each type that are present in a population under each scenario. For example, under the positive coupling scenario, the only individuals present are those who either have high contact and high infectiousness or low contact and low infectiousness. Positive coupling increases R_0 , negative coupling decreases R_0 , and no coupling leads to no change in R_0 (Figure 1B). As the overall extent of heterogeneity increases (i.e., as lows become lower and highs become higher), differences due to either positive or negative coupling lead to increasingly large departures in R_0 relative to the situation in which the heterogeneities are uncoupled (from left to right in Figure 1B). Intuitively, a decrease in R_0 in the presence of negatively coupled heterogeneities can be thought of as a consequence of the two heterogeneities canceling each other out. In an extreme example, if highly infectious hosts are never bitten by vectors, then transmission cannot occur, despite the presence of highly infectious hosts. Applying similar intuition, positive coupling leads to ‘superspreaders’ that are capable of individually contributing far more to transmission than individuals who possess either high infectiousness or high contact, but not both. Although infectiousness and contact may be much more continuous than ‘low’ and ‘high’, the qualitative results about the effects of negative and positive couplings on R_0 are general. Coupling between other heterogeneities, such as contact rates when sick versus healthy, may lead to different results and merit further theoretical investigation.

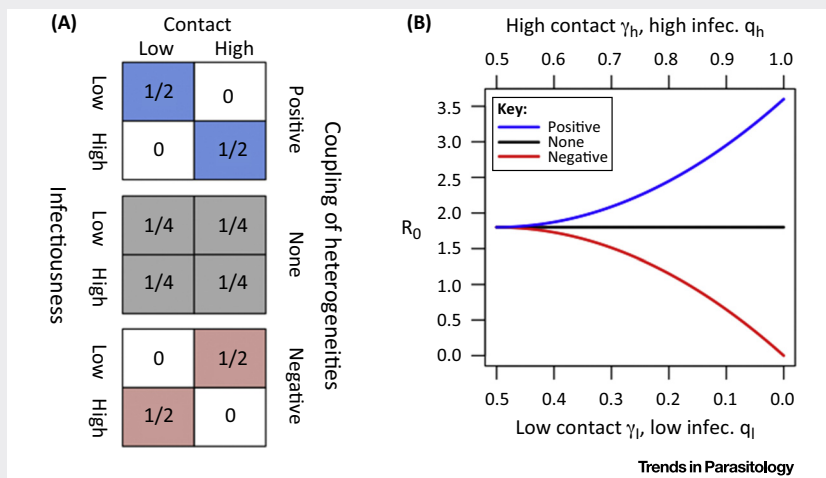


Figure 1. Epidemiological Impact of Coupling Contact Rates and Infectiousness. (A) The proportion of the population assigned to each of four types (i.e., low–low, low–high, high–low, high–high) under different scenarios about coupling. (B) Effects of positive (blue), negative (red), or no (black) coupling on R_0 given different levels of heterogeneity in contact when sick and infectious. The extent of heterogeneity in contact and infectiousness are assumed to be equal under a given scenario (i.e., at a given point on the x-axis in B). The overall extent of heterogeneity – that is, how low is low and how high is high – is increased from left to right on the x-axis in (B).

Table 1. Parameter Definitions and Specific Values for the Model in Box 2

Symbol	Definition	Value
K	Vector biting rate	0.3
V	Vector density	1.0
Δ	Vector death rate	0.15
P	Vector-to-host infectiousness	0.5
Q	Host-to-vector infectiousness	0–1
γ	Host-vector contact rate	0–1
ε	Host recovery rate	0.33
H	Host density	1.0

lead to differing conclusions regarding transmission potential and the difficulty associated with parasite elimination; increasing it in one case and decreasing it in another. Another implication of this simple model is that if heterogeneities are negatively coupled, targeting control efforts on individuals who are at the upper extreme with regard to one heterogeneity may have no net effect if those individuals are simultaneously at the lower extreme with regard to another epidemiologically relevant heterogeneity. Similarly, benefits of targeted control on a single heterogeneity that is positively coupled with another should yield greater marginal returns on control than if the heterogeneities were uncoupled. Without a mechanistic understanding of couplings, incorrect predictions of control impacts and biased inferences about drivers of transmission could be commonplace (particularly if, after the consideration of couplings, transmission systems respond much differently to perturbation than we think). Given that multiple functional heterogeneities are present in dengue transmission systems (Box 1), it is critical that future research address the population-level effect of coupled heterogeneities so that interventions can be designed and deployed to take better advantage of the inner workings of this complex transmission system.

Empirical Support for Coupled Heterogeneities

The perspectives emerging from the study of within-host dynamics and ecological immunology are beginning to shed light on the complexities associated with the process of host infection and parasite transmission [14,36], providing fertile ground for the study of couplings among functional heterogeneities across a range of disease systems. Such insights are also changing the field of epidemiological modeling by providing a higher level of granularity in the elaboration of model parameters contributing to TH, the evolution of virulence, and the impact of interventions [2,14,37–39]. For instance, the recognition that pathogen transmission is dependent on trade-offs between individual-level factors affecting infectiousness or parasite load (driven by disease severity, immune response, genetic attributes of the host, and/or pathogen, etc.) and host behavioral changes exerted by those conditions (e.g., changes in mobility or frequency of contacts, behavior change due to vaccination, etc.) is beginning to gain traction as an important factor driving parasite transmission dynamics and evolution [14,37].

Evidence from multiple host–parasite systems emphasize the epidemiological impact of couplings among disease severity, infectiousness, parasite load, and host behavior. A recent empirical evaluation of TH in amphibian-parasitizing trematodes used mechanistic experiments manipulating host size, behavior, and immunity to evaluate their impact in parasite burden. Aggregation of parasites within hosts was dependent on the occurrence of particular dyads, of which those including reductions in host behavior (inactivity simulating presence of a predator) had the highest influence on patterns of parasite aggregation [40]. For malaria, expanding mathematical models by compartmentalizing the human reservoir into multiple subclasses with

different infectiousness and exposure profiles (e.g., uninfected, subpatent, asymptomatic, and symptomatic) may allow for better estimates of disease burden and the impact of interventions [24,25]. Submicroscopic gametocyte carriers (individuals that transmit the sexual stage of the *Plasmodium* parasite infectious to mosquitoes) are primarily asymptomatic and have a lower infectiousness to mosquitoes compared with symptomatic individuals with microscopically detectable malaria infections [41]. Coupling disease severity status, infectiousness, and localized exposure to mosquito bites is thus an important new frontier for malaria modeling [5,42], as is the identification of parasite transmission hotspots [22,25]. A survey performed during the 2009 influenza pandemic showed that sick individuals had significantly fewer contacts compared with healthy individuals, leading to the general notion of a negative coupling between contact rates and disease severity [43].

Owing to the role of multiple dynamic, interacting populations of different types of hosts (i.e., insect and human), many vector-borne and zoonotic systems are more complex than those in which transmission is direct and restricted solely to human–human contact networks [44]. In particular, reservoir host heterogeneity is a significant functional heterogeneity for zoonotic systems. The aggregation of ticks in specific rodent species, age groups, and individuals leads to heterogeneous bacteremia of *Borrelia burgdorferi*, *Babesia microti*, and *Anaplasma phagocytophilum*, and these heterogeneities appear to be explained by system properties such as high population density, small body size, and short generation time [9,45,46]. In the USA, American robins (*Turdus migratorius*) were identified as potential superspreading species for West Nile virus (WNV) transmission in the East and Midwest [47,48], but not in the Southeast [49]. This difference in epidemiological role of robins may be due to intrinsic (heterogeneity in infectiousness, e.g., [50,51]) and extrinsic (avian community composition and bird–mosquito encounters, e.g., [48]) factors. Thus, to understand how much host heterogeneity matters for the dynamics of zoonotic parasites, more information will be needed on the structure and magnitude of couplings between heterogeneities with an influential role connecting individual reservoir host traits to reservoir species (and potentially vector species) community assemblages [44].

These examples point to the value of explicitly understanding how pathogen load, host immunity, symptom severity, and host behavior combine to drive TH. Whether such information could lead to improved disease management strategies (e.g., by identifying and targeting those individuals that disproportionately contribute to TH [3,6,7]) will depend on the impact of such couplings at the population or community levels. In an elegant assessment of the role of anthelmintic treatment on the regulation of the host immune response system by parasitic worms on *Mycobacterium bovis* (bovine tuberculosis) infected African buffalo, Ezenwa and Jolles [52] showed that treatment significantly increased buffalo survival (i.e., a positive individual-level impact), leading to an increase in the duration of bovine tuberculosis infectiousness and an eightfold increase in R_0 in *M. bovis*, that is, a negative population-level impact. Thus, defining the quantitative link between functional heterogeneities and pathogen transmission will depend on carefully collected data, proper statistical and quantitative approaches, and the evaluation of the individual- and population/community-level implications of couplings for pathogen transmission and disease management.

Data and Quantitative Challenges to Reveal Coupled Heterogeneities

The empirical quantification of the structure of couplings between functional heterogeneities will require complex study designs focusing on within-host dynamics but also capturing interindividual variability embedded in host populations. Such data needs can be best met if studies track (either experimentally or observationally) traits responsible for pathogen infection dynamics, the structure of contacts leading to pathogen propagation, the host behavioral attributes that may be influenced by infection, and the environmental context within which transmission occurred. Experimental infection studies have provided evidence of couplings among heterogeneities in

non-human infectious diseases and parasites (e.g., [40,50,53]). For human infectious diseases, however, experimental infection studies are unethical, rarely capture disease-related behavioral attributes of individual hosts, and often involve small sample sizes. Longitudinal cohort studies examining naturally infected individuals to quantify infection-related quantities (e.g., pathogen load, immune response, symptoms), together with the structure of their contact networks and behavioral responses to infection represent a more amenable design to the study of coupled heterogeneities. Datasets meeting such criteria are now being generated for malaria and dengue, as well as other infectious agents (e.g., [20,41,54,55]).

As adequate data become available, the quantification of the ecological and epidemiological role of coupled heterogeneities will strongly rely on quantitative approaches involving both statistical models of observed associations and mathematical models to illustrate the impact of propagating uncertainty through the dynamic system [56]. Here we highlight three classes of analytical approaches and the potential strengths and challenges each brings to the quantification and understanding of the epidemiological role of couplings (Table 1). Importantly, each class of

Table 1. Quantitative Approaches to Unveil the Epidemic Role of Coupled Heterogeneities

Analytical Approach	Analytical Goals and Challenges	Example Approaches and Potential Insights into Coupled Heterogeneities
Theoretical (Mathematical)	<p>Goals:</p> <ul style="list-style-type: none"> Quantification of general properties (e.g., R_0) derived from dynamic systems adjusted for coupled heterogeneities. Can capture stochastic variability. Closed form analytical solutions. <p>Challenges:</p> <ul style="list-style-type: none"> Complexity of model limited by analytical tractability. Most past work limited to individual heterogeneities. Generalizability of group level results in individual dynamics with more complex transmission heterogeneities. 	<p>Patch and Metapopulation Models</p> <ul style="list-style-type: none"> Assessment of spatial heterogeneities due to neighborhood and population-level couplings (e.g., movement as a function of disease severity class or infectiousness and severity class). <p>Household Models</p> <ul style="list-style-type: none"> Allow heterogeneity in contact between risk categories (e.g., between household members and community members). Could allow assessment of role of heterogeneities impacting the relative time spent with household members compared with community members. Extensions to other risk categories possible. <p>Network Models</p> <ul style="list-style-type: none"> Allow assessment of coupling heterogeneities between risk factors and individual attributes of the contact network (e.g., edge/node weights).
Hybrid (Simulation)	<p>Goals:</p> <ul style="list-style-type: none"> Quantify impact of changes in dynamic parameters (e.g., through heterogeneity or intervention) by simulating complex individual-level dynamics. Generates realizations of the modeled process allowing quantification of changes, variability, and patterns due to predefined coupled heterogeneities. <p>Challenges:</p> <ul style="list-style-type: none"> How to best define coupled heterogeneities. Simulation of correlated values? Functional associations? Must assess sensitivity to model assumptions and potential impact of model misspecification for the coupled heterogeneities. 	<p>Individual-Based Models</p> <ul style="list-style-type: none"> Allow implementation of complex couplings of heterogeneities but require clear specification of the couplings and the heterogeneities (dependent on statistical/mathematical quantification of relationships between heterogeneities). Provide the largest flexibility in accounting for couplings. Allow for parameter uncertainty estimations. Coupling between contacts and other functional heterogeneities easily modeled through network models. <p>Bayesian Mechanistic Inference (Mechanistic TSIR Models, Approximate Bayesian Computation)</p> <ul style="list-style-type: none"> Allow combining equation-based simulations with data.

Table 1. (continued)

Analytical Approach	Analytical Goals and Challenges	Example Approaches and Potential Insights into Coupled Heterogeneities
	<ul style="list-style-type: none"> • Impact of model assumptions may be difficult to assess. • Complexities in parameter estimation to capture complex relationships. • Uncertainty quantification of impact of coupled heterogeneities. 	<ul style="list-style-type: none"> • Could address coupled heterogeneities through specific equations and mathematical structures or through multivariate random effects with coupling defined via the covariance between random effects.
Empirical (Statistical)	<p>Goals:</p> <ul style="list-style-type: none"> • Data-based estimation of associations between risk factors and probability of infection, adjusted for coupled heterogeneities. • Model coupled heterogeneities through correlated error terms, often via random effect distributions. <p>Challenges:</p> <ul style="list-style-type: none"> • Repeated measures, temporal, spatial, and spatiotemporal correlations. • Measurement error. • Confounding factors (measured and unmeasured). • Typical data (e.g., number of reported cases per day) may be insufficient to support accurate and precise estimates of the underlying structure of the coupled heterogeneities. • Computational complexity. • Limitations in data availability. 	<p>Structural Equation Models</p> <ul style="list-style-type: none"> • Allow specification of families of coupled heterogeneities. • May be very difficult to fit. <p>Hierarchical Models (Multilevel Models, Random Effects)</p> <ul style="list-style-type: none"> • Allow multilevel impacts. • Allow adjustment for repeated measures on the same individual. • Allow use of random effects to assess both group-level average associations and individual-level variation from the group-level average. • Could address coupled heterogeneities through multivariate random effects with coupling defined via the covariance between random effects. • Allow temporal, spatial, and spatiotemporal correlations in outputs. <p>Measurement Error Models</p> <ul style="list-style-type: none"> • Can allow coupled heterogeneities in risk factors through correlated measurement error models. • Could be incorporated into hierarchical models above.

quantitative analysis brings different strengths and challenges, and all three will provide valuable insight into the nature and impact of coupled heterogeneities.

Within empirical statistical models, extensions to consider complex correlation structures between covariates are technically straightforward but often computationally intensive (e.g., structural equation models [57], hierarchical and measurement error models [58]). Such approaches could provide information on both the epidemiological role of couplings and the functional relationship between heterogeneities after accounting for stochastic effects embedded within the random effects of a model [33,59]. Unfortunately, applications of such methodologies to identify coupled heterogeneities in real datasets are rare. One exception is the use of time-varying frailty models to explore the effect of host heterogeneities in the force of infection of infectious diseases occurring sequentially on the same individual [60,61]. The basic assumption of this approach is that high correlation in the occurrence of two infections within the same individual should be found for parasites that share a similar route of transmission (as a result of shared conditions associated with exposure such as social contacts, mobility, etc.). Such correlations can be equivalent to couplings between functional heterogeneities, and frailty models allow embedding individual-level covariates in the estimation of force of infection [60,61]. The observational nature of the data and the non-unique links between pattern and process mentioned earlier, however, can create challenges in both the statistical identifiability of parameters and the interpretation of the output of dynamic models. Coupling empirical

quantifications with simulation or modeling could help overcome some of the challenges outlined for statistical approaches (e.g., [62]).

Simulation-based analyses (especially with individual-based models [63] or mechanistic Bayesian approaches) allow for a high level of flexibility in the consideration of couplings. Such approaches can play a crucial and complementary role relative to other quantitative approaches, because they allow for the impacts of a nearly endless variety of couplings to be explored. The strength of simulation models is their ability to facilitate the development of biological intuition and to assess the quantitative plausibility of the impacts of coupled heterogeneities on epidemiological outcomes. Confronting these models with data can be challenging, however, and development of simulation models always involves a cost associated with obtaining sufficient data to parameterize them. Estimation of covariance structure between heterogeneities (e.g., disease severity and infectiousness) by fitting simulation models to empirical data will be crucial before these or any other models can be used to accurately and reliably predict dynamics. Simulations evaluating the role of uncertainty in estimation of couplings [64] could, however, provide critical insights about their role in overall model performance, as well as to identify data needs to improve the measurement of heterogeneities.

Approaches that utilize somewhat simpler, but nonetheless mechanistic, mathematical models will encounter significant analytical challenges in terms of mathematical tractability once multiple heterogeneities and their couplings are accounted for. Nonetheless, they also represent a crucial tool in the theoretical exploration of the role of couplings, as outlined in [Box 2](#). Extensions of classic modeling frameworks to incorporate couplings (e.g., metapopulation, household, or network models) are possible [65,66]. As we point out in [Table 1](#), there is considerable room for improvement in the thoughtful design of epidemiological, statistical, and theoretical studies and, importantly, the interactions of the three toolsets to focus insight on these challenging problems.

Concluding Remarks

The time is ripe for more explicit consideration of the ecological and epidemiological role of coupling between functional heterogeneities in host–parasite transmission systems. As disease ecoparasitologists searching for traits responsible for TH and researchers focusing on understanding within-host dynamics converge in their questions, data, and analytical methodologies, there is an emerging need for a framework that enables them to consider the role of multiple, overlapping, and correlated sources of heterogeneity. Given the potential synergistic, antagonistic, or additive role of such couplings, the empirical quantification of the functional relationship among heterogeneities and the influence they may have on parasite transmission metrics (e.g., R_0 , outbreak size distribution, vectorial capacity) should become a focus for future research. Hypothetically, intervention strategies that simultaneously target couplings that act synergistically could have a higher impact than if only one source of heterogeneity is targeted in isolation (e.g., individuals who engage in risky sexual behaviors may have sex with more partners and also be less likely to use condoms). Similarly, couplings that contribute disproportionately to transmission could be exploited by evolving parasites that are constantly exploring new opportunities for maximizing fitness [67,68]. Such possibilities will not come about though without carefully developed field studies and advances in quantitative methods that allow for a comprehensive mechanistic understanding of the epidemiological and evolutionary mechanics of coupling between functional heterogeneities. Forthcoming endeavors along these lines have the potential to contribute to a range of timely questions (see Outstanding Questions) that must be addressed before the promise of leveraging knowledge of heterogeneities for improved control and evolutionary management can be realized.

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Outstanding Questions

To what extent is TH a function of individual-level characteristics, coupled heterogeneities, or stochastic variation?

Within a host species, how do within-individual and (meta) population level interactions couple?

If significant couplings are identified and predicted to have a disproportionate role in the emergence of TH: How will such information be used to develop rational disease mitigation strategies that take such information into consideration to identify those who disproportionately contribute to transmission?

Can disease mitigation strategies that target coupled heterogeneities be more efficacious than those focused on individual traits?

Can couplings among specific heterogeneities modulate rates of pathogen evolution?

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