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Opinion

Coupled Heterogeneities and Their Impact on Parasite Transmission and Control

Gonzalo M. Vazquez-Prokopec,[1,2,*] T. Alex Perkins,[2,3] Lance A. Waller,[4] Alun L. Lloyd,[2,5] Robert C. Reiner Jr,[2,6] Thomas W. Scott,[2,7] and Uriel Kitron[1,2]

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.

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 nonlinear impacts on parasite transmission potential (R_0).

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

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?

[1]Department of Environmental Sciences, Emory University, Atlanta, GA, USA
[2]Fogarty International Center, National Institutes of Health, Bethesda, MD, USA
[3]Department of Biological Sciences and Eck Institute for Global Health, University of Notre Dame, Notre Dame, IN, USA
[4]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, USA
[5]Biomathematics Graduate Program and Department of Mathematics, North Carolina State University, Raleigh, NC, USA
[6]Department of Epidemiology and Biostatistics, Indiana University, Bloomington, IN, USA
[7]Department of Entomology and Nematology, University of California Davis, Davis, CA, USA

*Correspondence:
gmvazqu@emory.edu
(G.M. Vazquez-Prokopec).

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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,

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

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: