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A theoretical framework to identify invariant thresholds in infectious disease epidemiology

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HIGHLIGHTS

- Host heterogeneity modifies the relationship between R_0 and disease prevalence.
- Neglecting heterogeneity results in underestimated efforts to meet control targets.
- Invariant transmission thresholds are robust indicators for control planning.

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ABSTRACT

Setting global strategies and targets for disease prevention and control often involves mathematical models. Model structure is typically subject to intense scrutiny, such as confrontation with empirical data and alternative formulations, while a less frequently challenged aspect is the widely adopted reduction of parameters to their average values. Focusing on endemic diseases, we use a general transmission model to explain how mean field approximations decrease the estimated R_0 from prevalence data, while threshold phenomena – such as the epidemic and reinfection thresholds – remain invariant. This results in an underestimation of the effort required to control disease, which may be particularly severe when the approximation inappropriately places transmission estimates below important thresholds. These concepts are widely applicable across endemic pathogen systems.

1. Introduction

Traditional epidemiologic research classifies individuals by similarity of stipulated characteristics and conceives models for disease distribution in a population that is compartmentalized (Rothman, 2012). In infectious diseases, hosts move between compartments according to processes, such as disease progression and transmission, describing dynamic patterns of disease in the population (Anderson and May, 1991). The logic of compartmental study design motivates compartmental models calibrated by average parameters: the “mean field” approximation. Of particular interest from such models are threshold parameters, such as the basic reproduction number R_0, and the effective reproduction number R_e, which have become instrumental in the design and evaluation of control strategies (Diekmann et al., 1990; Becker et al., 1995; Anderson and May, 1991). Threshold parameters, generally dependent on model structure, can only be estimated indirectly and subject to assumptions whose impact is often unrecognized (Heffernan et al., 2005). Here we assess the behavior of transmission threshold parameters under heterogeneity in individual capacity to acquire immunity upon infection and in the rate at which contacts are made with other individuals.

Populations are undoubtedly composed of individuals that differ in their propensity to acquire infections and in their potential to transmit to others. Overall, variation results from a mix of genetic and environmental factors, including social and physical aspects. Due to demographic processes, differential selection is likely to occur within groups, resulting in patterns of disease for the population as a whole that differ from the

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expectation (Proscham and Sethuraman, 1976; Ball, 1985; Vaupel and Yashin, 1985). For this reason, variation in individual characteristics and group structure must be considered throughout the entire research process that establishes immunization practices, as recognized almost 50 years ago in a classical paper by Fox et al. (1971). Today there is an extensive literature dealing with mathematical analyses of how herd effects of vaccination programs help to reduce incidence and prevalence of infections among the human population. Until recently, most of this work has assumed that within each compartment, individuals are equally susceptible to infection, equally infectious if infected, and equally active in their social contacts. Although deviations of heterogeneous systems from mean field approximations have been well characterized mathematically for epidemic scenarios (Boylan, 1991; Andreasen, 2011; Clancy and Pearce, 2013; Katriel, 2012; Novozhilov, 2012), translations and applications in epidemiology research, especially with regards to endemic pathogens, remain limited. In this paper, we recall a few exceptions that are worth retaining before proceeding with general considerations on the relationship between threshold parameters and disease prevalence. Implication for disease control and elimination are discussed in Section 4.

2. Heterogeneity and transmission routes

2.1. Sexual transmission

Since the beginning of AIDS epidemic and the identification of the aetiological agent in the 1980s, it has been evident that heterogeneity in individual sexual behaviors must be considered in the interpretation of epidemiological data (Anderson et al., 1986; Hyman and Stanley, 1988). The notion is so consensual that most textbooks on infectious disease epidemiology written since then have a major chapter or section dedicated to heterogeneity in sexually transmitted diseases. Much research has been devoted to estimating such contact networks in diverse settings and with different methods in order to accurately predict HIV transmission dynamics (Leigh Brown et al., 2011; Jones and Handcock, 2003).

2.2. Vector transmission

Relatively recently, Smith et al. (2005) developed a mathematical framework that allows the estimation of heterogeneity in malaria infection rates from the relationship between parasite rates and entomological inoculation rates in multiple populations. The model was fitted to data from more than 90 localities, a distribution of individual susceptibilities was estimated, and the implications for disease control were discussed for this vector-transmitted disease. Notably, this heterogeneity was later found to greatly enlarge the range of R_0 for malaria transmission (Smith et al., 2007), and entered the discussion of control strategies aiming at $R_0 < 1$.

2.3. Airborne transmission

The study of heterogeneity in airborne diseases has been less explored since parameter estimation becomes more difficult, although heterogeneity in social contacts, for example, has started to be recognized (Mossong et al., 2008). A prominent case in the topic is tuberculosis (TB), a disease transmitted by droplet nuclei carrying *Mycobacterium tuberculosis* secreted from patients with pulmonary TB when coughing, sneezing, spitting and other respiratory acts. These tiny droplets disperse throughout the air of enclosed spaces, such as rooms and buildings, and transmission occurs when they are inhaled by another person. Epidemiologic studies implicate the droplet nucleus mechanism in the transmission of tuberculosis, measles, influenza and many other infections of the respiratory tract (Riley, 1974).

Over the years several authors have independently challenged the mean field approximation in TB transmission systems. Murphy et al. (2002) evoked different genetic susceptibility distributions, demographic factors, and transmission intensity, to explain the wide variation in endemic TB levels between countries. Gomes et al. (2012) analyzed published data relating the reinfection proportion among recrudescences and TB incidence to estimate the decomposition into low and high risk groups that could best reproduce the worldwide dataset. Similarly, an independent study based in the city of Rio de Janeiro, Brazil (Dowdy et al., 2012), estimated relative contributions of high and low risk groups compatible with global estimates. Heterogeneity in propensity of infectious individuals to cause secondary cases has also been postulated to explain the observed skewness in genotypic cluster size distributions of *M. tuberculosis* (Vynnycky et al., 2001; Ypma et al., 2013) and outbreak dynamics in a number of directly transmitted diseases (Lloyd-Smith et al., 2005).

3. Endemic diseases and threshold parameters

The approaches used by Smith et al. (2005) in malaria, and Gomes et al. (2012) in tuberculosis, have a similar strategy of fitting a relatively simple model simultaneously to epidemiological data from multiple populations to infer common underlying heterogeneities. This enables the simultaneous estimation of key threshold parameters and the exploration of implications for disease control in specific settings (Gomes et al., 2014). We proceed by defining two threshold parameters of interest in the context of the mean field susceptible-infected-recovered (*SIR*) model, and then by analyzing the effects of adding heterogeneity incrementally.

3.1. Mean field SIR

To define the threshold parameters and their behavior under individual heterogeneity, we rely on a minimal *SIR* model, which describes the rates of change in the proportions of the population that are susceptible (S), currently infected (I), and recovered (R) by the system of differential equations:

$$\begin{aligned}\frac{dS}{dt} &= \mu - \lambda S - \mu S\\ \frac{dI}{dt} &= \lambda(S+\sigma R) - (\gamma+\mu)I\\ \frac{dR}{dt} &= \gamma I - \lambda\sigma R - \mu R,\end{aligned} \tag{1}$$

where $\lambda = \beta I$ is the *per capita* rate of infection (force of infection) given an effective contact rate, β, between susceptible and infected individuals, γ is the rate at which individuals recover from infection, μ is the birth rate, here assumed equal to the death rate, and σ is the relative susceptibility of recovered individuals with respect to those who have never encountered the pathogen.

The system has two threshold parameters:

1) The epidemic threshold (Becker et al., 1995), above which epidemics occur and infection remains endemic, is given by $R_0 = 1$, where R_0, defined as the average number of secondary infections generated by one infectious individual in a totally susceptible population, is given by $R_0 = \beta/(\gamma+\mu)$;
2) The reinfection threshold (Gomes et al., 2004, 2005), above which epidemics occur and infection remains endemic in a population where all individuals have previously experienced