A Missing Dimension in Measures of Vaccination Impacts

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Immunological protection, acquired from either natural infection or vaccination, varies among hosts, reflecting underlying biological variation and affecting population-level protection. Owing to the nature of resistance mechanisms, distributions of susceptibility and protection entangle with pathogen dose in a way that can be decoupled by adequately representing the dose dimension. Any infectious processes must depend in some fashion on dose, and empirical evidence exists for an effect of exposure dose on the probability of transmission to mumps-vaccinated hosts [1], the case-fatality ratio of measles [2], and the probability of infection and, given infection, of symptoms in cholera [3]. Extreme distributions of vaccine protection have been termed leaky (partially protects all hosts) and all-or-nothing (totally protects a proportion of hosts) [4]. These distributions can be distinguished in vaccine field trials from the time dependence of infections [5]. Frailty mixing models have also been proposed to estimate the distribution of protection from time to event data [6,7], although the results are not comparable across regions unless there is explicit control for baseline transmission [8]. Distributions of host susceptibility and acquired protection can be estimated from dose-response data generated under controlled experimental conditions [9–11] and natural settings [12,13]. These distributions can guide research on mechanisms of protection, as well as enable model validity across the entire range of transmission intensities. We argue for a shift to a dose-dimension paradigm in infectious disease science and community health.

Natural Transmission

We consider a minimal susceptible (S) and infected (I) model [14] of pathogen transmission in a host population to explore population effects of protection conferred by a vaccine (or other preventive measure, such as symbionts) against infection, under different assumptions about how this is distributed among individuals. We consider that infection is lifelong, and that there is no naturally acquired immunity.

Vaccines that provide leaky protection against infection act by reducing susceptibility to a factor σ that is distributed among individuals according to a probability density function q(x), where 0 ≤ x ≤ 1. Denoting by i_v(x) the densities of hosts who are vaccinated and have susceptibility factor x, the integral

\[ I_v = \int_0^1 i_v(x) \, dx \]

represents the proportion of hosts who are infected despite being vaccinated. Assuming no effect on infectiousness, the per capita rate of infection among totally susceptible individuals is given by \( \lambda = \beta (I + I_v) \), where \( \beta \) is the effective contact rate.

Figure 1A shows, for the distributions q(x) represented on the right, equilibrium curves describing prevalence of infection versus transmission intensity measured by \( R_0 \), the basic reproduction number. The curves for extreme cases of vaccines that confer equal protection to all or total protection to some and none to others are depicted by the higher (red) and lower (blue) curves, respectively. Intermediate curves represent scenarios in which susceptibility follows a beta distribution with fixed mean and increasing variance from top to bottom. Prevalence curves become shallower with heterogeneity and converge to the same level as transmission increases, except in the all-or-nothing extreme, in which the prevalence cannot surpass the susceptible fraction, irrespective of transmission intensity. Although the impact of protection appears to increase with polarization of effects, the endemic curves do not converge uniformly to their all-or-nothing homologue. In the absence of unequivocal empirical evidence for the idealized all-or-nothing mode of action, we suggest modifying the terminology to include polarized distributions more generally.

Experimental Challenge

Infection in a controlled experimental setting is modeled by describing infected proportions in terms of challenge dose. Adopting standard formulations [15–17], the mean number of infecting pathogens is \( pd \), where \( d \) is the number of pathogens challenging the host, and \( p \) is the probability of infection for each pathogen; the number of infecting pathogens per host has a Poisson distribution with mean \( pd \). In the homogeneous case, the probability


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dose-response manner by intervention (colored). Hosts are challenged with a range of pathogen doses, under a model in which the intervention reduces susceptibility to a line that represents the scenario without intervention. Colored lines assume susceptibility factors distributed with mean 0.5 in all cases and variance \( \sim lsv \), \( \sim mI \), \( \sim dSv \), respectively, where \( d \) is the number of pathogens the host is challenged by and \( p \) is the probability of infection for each pathogen. Colored lines assume susceptibility factors distributed with mean 0.5 in all cases and variance 0 (red), 0.05 (orange), 0.1 (green), 0.2 (cyan), and 0.25 (blue). Red and blue at the extremes are discrete, while the intermediate cases are continuous.

Figure 1, and the circles indicate the location of the extreme homogeneous distributions used in Figure 1, and the diagonal indicates the location of the symmetric distributions used in Figure 1 and the circles indicate the location of the uniform distribution (gray square), showing good discriminatory power in the region of parameter space where uncertainty is greatest. This analysis suggests a promising approach for classifying intervention effects in controlled experimental settings and using this as action of interventions, such as vaccines. Given the lack of uniform convergence to all-or-nothing as the leaky mode becomes increasingly polarized, we have classified beta distribution shapes according to polarization (Figure 2). The dashed line along the diagonal indicates the location of the extreme homogeneous (red) and all-or-nothing (blue) distributions. The power to identify polarized distributions is analyzed in Figure S1, focusing on a vicinity of the uniform shape (gray square), showing good discriminatory power in the region of parameter space where uncertainty is greatest. This analysis suggests a promising approach for classifying intervention effects in controlled experimental settings and using this as
prior information for further study in natural settings [18].

Supporting Information

Figure S1 Power analysis to identify polarized intervention effects. Simulated sets of dose-infectivity data were generated and used to estimate model parameters (Figure S2), assuming the host susceptibility of the intervention group described by a beta distribution, \(q(x)\), with shape parameters positioned as a grid in a square neighborhood of the uniform distribution (Figure S1).

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