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An elaboration of theory about preventing outbreaks in homogeneous populations to include heterogeneity or preferential mixing

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HIGHLIGHTS

- Population-immunity thresholds are useful only in homogeneous, proportionally-mixing populations.
- Meta-population effective reproduction numbers, $\mathfrak{R}_v$, and related quantities always are useful.
- Heterogeneity in variables affecting sub-population reproduction numbers is relevant.
- Together with preferential mixing among sub-populations, such heterogeneity increases $\mathfrak{R}_v$.
- The partial derivatives of $\mathfrak{R}_v$ with respect to sub-population immunities indicates the optimal strategy.

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ABSTRACT

The goal of many vaccination programs is to attain the population immunity above which pathogens introduced by infectious people (e.g., travelers from endemic areas) will not cause outbreaks. Using a simple meta-population model, we demonstrate that, if sub-populations either differ in characteristics affecting their basic reproduction numbers or if their members mix preferentially, weighted average sub-population immunities cannot be compared with the proportionally-mixing homogeneous population-immunity threshold, as public health practitioners are wont to do. Then we review the effect of heterogeneity in average *per capita* contact rates on the basic meta-population reproduction number. To the extent that population density affects contacts, for example, rates might differ in urban and rural sub-populations. Other differences among sub-populations in characteristics affecting their basic reproduction numbers would contribute similarly. In agreement with more recent results, we show that heterogeneous preferential mixing among sub-populations increases the basic meta-population reproduction number more than homogeneous preferential mixing does. Next we refine earlier results on the effects of heterogeneity in sub-population immunities and preferential mixing on the effective meta-population reproduction number. Finally, we propose the vector of partial derivatives of this reproduction number with respect to the sub-population immunities as a fundamentally new tool for targeting vaccination efforts.

1. Introduction

Human populations are heterogeneous, but all differences need not be modeled to answer any specific question. Immunity to vaccine-preventable diseases, for example, is heterogeneous within the United States (Fig. 1). Can differences among and within states be ignored in establishing vaccination coverage targets or monitoring progress in attaining them? The function used routinely for that purpose, the population-immunity threshold, involves the basic reproduction number, denoted $\mathfrak{R}_0$. As this quantity is derived from a mathematical model, ascertaining its adequacy amounts to determining if the model from which it was derived is sufficiently detailed.

Mechanistic models are hypotheses about processes underlying natural phenomena. Simplicity is a virtue because it facilitates their evaluation. But the only way to ensure that one's model is not too simple is to compare results with those from models that include additional details that might affect them. In transmission modeling, one generally distinguishes sub-populations whose

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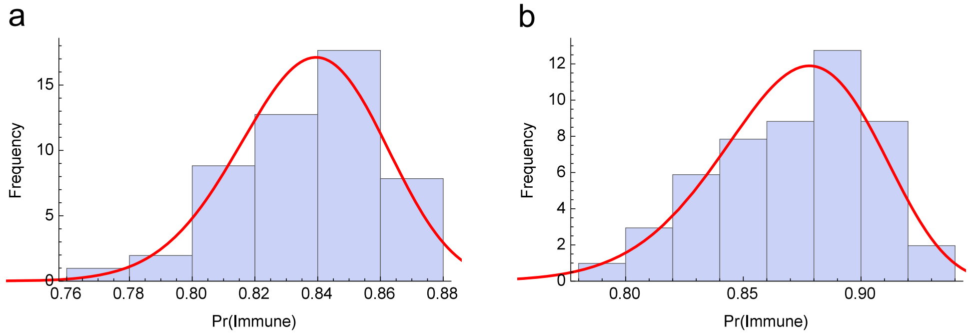

Fig. 1. Immunity to measles in the United States among (a) children aged 19–35 months and (b) adolescents aged 13–17 years for all 50 states and the District of Columbia from the 2012 National Immunization Surveys (http://www.cdc.gov/vaccines/imz-managers/coverage/nis/child/2012-released.html). Immunity was estimated as proportions of children with at least one and adolescents with two or more doses of MMR vaccine times efficacies of 92% and 95%, respectively. The curves are fitted beta distributions having shape parameters $\alpha=208.39$ and $\beta=40.65$ for children and $\alpha=83.98$ and $\beta=12.52$ for adolescents. Insofar as some adolescents have had one dose of MMR, (b) under-estimates their immunity to measles.

members have characteristics with which their risks of being infected or infecting others vary (e.g., age, gender, location). Levins (1969) coined the term meta-population for any population whose members could be so stratified, although his own applications involved spatially-stratified populations.

Recently, Ball et al. (2014) noted that the meta-population framework may preserve analytic tractability, unlike alternative means of incorporating salient structural heterogeneity, namely agent-based or network models. But they describe several challenges for modelers, among them clarifying the usefulness and limitations of systems of weakly coupled sub-populations in modeling the spread of infections. Coupling strength determines a continuum whose limiting meta-populations behave as one or as multiple independent sub-populations. Here we endeavor to consolidate and extend the contributions of others who have considered intermediate situations.

Rates of person-to-person contact may vary with population density (e.g., be greater in urban than rural areas). They may also vary with personal characteristics (e.g., be greater among schoolchildren than younger and older people). The effect of such heterogeneity on $\mathfrak{R}_0$, defined as the average number of secondary infections caused by a newly infectious person on introduction to a wholly susceptible population, was studied by Dietz (1980), Anderson et al. (1986), May and Anderson (1988), and Diekmann et al. (1990). These authors showed that, when mixing among sub-populations is proportional, $\mathfrak{R}_0$ varies with the contact rate's variance and mean.

Nold (1980) developed a more general mixing framework in which a fraction of one's contacts is reserved for members of one's own group and the complement is distributed proportionately among groups. Jacquez et al. (1988) allowed this fraction to vary among groups. Barbour (1978), Dye and Hasibeder (1986), Hasibeder and Dye (1988), and Adler (1992) showed that $\mathfrak{R}_0$ attains its maximum when individuals having high average *per capita* contact rates mix exclusively with each other.

May and Anderson (1984a, 1984b), Hethcote (1978), and Hethcote and van Ark (1987) considered heterogeneity in immunity. They concluded that the immunity above which newly introduced infectious persons would not cause outbreaks, to which we refer as the naïve population-immunity threshold, was greater in heterogeneous populations than apparent if homogeneity was incorrectly assumed. But Hethcote and van Ark argued that the difference was modest if contact rates were not too dissimilar. None of these authors considered preferential mixing.

Recently, Fine et al. (2011) reviewed the history and applications of the population-immunity threshold,[1] which was derived from a model of a proportionally-mixing homogeneous population. In the next section, we define a meta-population model and mixing function with which to evaluate the utility of this threshold when mixing is preferential or sub-populations are heterogeneous with respect to characteristics affecting their basic reproduction numbers.

2. Methods

We employ the simplest meta-population model capable of informing vaccination policy to illustrate the effects of heterogeneity in sub-population contact rates and immunities, together with preferential mixing, on the effective reproduction number. A glossary accompanies this section.

Our model comprises n sub-populations in which people are susceptible, S_i, infected and infectious, I_i, or removed, R_i (from the infection process by virtue of immunization or immunity following infection), μ is both the birth and death rate (introducing susceptible people without changing population size), p_i are proportions immunized at birth, λ_i are *per capita* forces (or hazard rates) of infection among susceptible people, and γ is the recovery rate. The rates μ and γ are the reciprocals of life expectancy and the mean infectious period, respectively.

$$\begin{aligned}
\frac{dS_i}{dt} &= \mu N_i(1-p_i)-(\lambda_i+\mu)S_i\\
\frac{dI_i}{dt} &= \lambda_i S_i-(\gamma+\mu)I_i,\\
\frac{dR_i}{dt} &= \mu N_i p_i+\gamma I_i-\mu R_i,\\
N_i &= S_i+I_i+R_i, \quad i=1,\dots,n
\end{aligned}$$

The force of infection among susceptible members of sub-population i, $\lambda_i := a_i\beta\sum_{j=1}^{n} c_{ij}(I_j/N_j)$, where β is the probability of infection upon contacting an infectious person, a_i is the average contact rate in sub-population i (activity henceforth), c_{ij} is the proportion of the ith sub-population's contacts that are with members of the jth sub-population, I_j/N_j is the probability that a proportionally encountered member of sub-population j is infectious, and n is the number of sub-populations.

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[1] We reserve the term "herd immunity" for the indirect effect of vaccination, a reduction in the force of infection experienced by unvaccinated members of a population by virtue of the vaccination of others.