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Optimal prophylactic vaccination in segregated populations: When can we improve on the equalising strategy?

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ABSTRACT

One of the fundamental problems in public health is how to allocate a limited set of resources to have the greatest benefit on the health of the population. This often leads to difficult value judgements about budget allocations. However, one scenario that is directly amenable to mathematical analysis is the optimal allocation of a finite stockpile of vaccine when the population is partitioned into many relatively small cliques, often conceptualised as households. For the case of SIR (*susceptible–infectious–recovered*) dynamics, analysis and numerics have supported the conjecture that an equalising strategy (which leaves equal numbers of susceptible individuals in each household) is optimal under certain conditions. However, there exists evidence that some of these conditions may be invalid or unsuitable in many situations. Here we consider how well the equalising strategy performs in a range of other scenarios that deviate from the idealised household model. We find that in general the equalising strategy often performs optimally, even far from the idealised case. However, when considering large subpopulation sizes, frequency-dependent transmission and intermediate levels of vaccination, optimality is often achieved through more heterogeneous vaccination strategies.

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Introduction

Mathematical modelling has had a profound influence on public health associated with infectious diseases; most public-health decisions are now supported by detailed mathematical predictions that quantify the incremental costs and benefits of any new policy. This is particularly true for changes to vaccination programs (including the introduction of new vaccines) where there are potentially many subtle non-linearities between the distribution of vaccine and the public-health benefits (Anderson and May, 1983; Bansal et al., 2006; van Hoek et al., 2011). In principle the aim of this modelling for vaccination is relatively simple: to find a strategy that produces the maximum reduction in cases (and in particular severe health outcomes) for a given cost (Woodhall et al., 2009; Baguelin et al., 2010; Klepac et al., 2011; Brown and Jane White, 2011). Yet despite this apparent simplicity, determining the optimal policy is highly computationally intensive due to the vast range of strategies that can be investigated (Dushoff et al., 2007; Hall et al., 2007; Keeling and White, 2011). In addition when there are multiple desirable outcomes, it is generally impossible to optimise all of them simultaneously and a careful definition of the objective is required (Hollingsworth et al., 2011).

The ground-breaking work of Ball et al. (1997), Ball and Lyne (2002) is seen as offering one of the few explicit and rigorous results in this complex field. In this work it was demonstrated that an equalising strategy was optimal for control of an SIR-type infection in a population segregated into households (or component subpopulations) of just 2, 3 and 4 individuals. Further, it was conjectured, supported by extensive numerics, that this result holds for all subpopulation sizes. Here an equalising strategy is one which leaves an equal number of individuals susceptible in each household (or subpopulation) irrespective of the size of the household (e.g. all households of size 3 or more are left with just 3 susceptible individuals). However, the results are more precise and constrained than usually appreciated (Ball et al., 1997; Ball and Lyne, 2002). Firstly, they only strictly apply to density-dependent transmission, which in the household context means that the risk of transmission between any two members of the household is independent of household size. However, data from detailed household

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studies of influenza suggest that the rate of transmission between any two household members decreases monotonically with household size (Cauchemez et al., 2004, 2009; House et al., 2012). Secondly, optimality refers to maximising the reduction in early household-to-household transmission (the between-household reproductive number or $R_\star$) for a given supply of vaccine; equivalently, this allows the calculation of the minimal amount of prophylactic vaccine required to reduce the reproductive number to one, and hence prevent a large-scale outbreak of infection. Therefore the equalising strategy does not necessarily hold for on-going vaccination during an outbreak, nor does it necessarily protect the most people from infection when there is insufficient resources to reach the elimination threshold (Hollingsworth et al., 2011).

Although the equalising strategy and results in this paper are generally expressed in terms of household-based transmission, the implications are more wide ranging. Our findings apply to any population that can be modelled in a metapopulation format: multiple distinct relatively small subpopulations with strong transmission within the subpopulations but weaker transmission between them. The only other condition is that there must be a large number of these subpopulations such that we can take expectations of their behaviour. As such the models formulated here equally apply to human populations aggregated into schools, hospitals and local communities, livestock aggregated into farms, or wildlife that can be spatially aggregated into regions of suitable habitat. Therefore, although for brevity and historical consistency, we refer to households throughout this paper the findings hold for any appropriate grouping or subpopulation.

It is worth stressing that the equalising strategy and any improvements outlined in this paper make the simplifying assumption that all individuals in the population are equal apart from their household composition. In practice, for human populations, both age and underlying health status dominate the consequences of infection and hence the need to protect by vaccination. Therefore it should be stressed that strategies purely based on household size are idealisations and alternative targeting should often take priority. However, there are at least two scenarios with this understanding could be practically useful. Firstly, once the most vulnerable or high risk members of the population are protected, the equalising strategy may provide a means of slowing or containing epidemic spread when the number of vaccine doses are limited. Secondly, for livestock infections individual-level heterogeneity is generally less of a consideration, so targeting based purely on animal numbers may be effective especially when dealing with a costly vaccine.

Here we examine both analytically and numerically the generality of the equalising strategy. We first review the previous work and methodology (Ball et al., 1997; Ball and Lyne, 2002) before considering the relevance of the equalising strategy for populations that do not obey density-dependent transmission, while maintaining the same condition for optimality. We then numerically explore the use of the equalising strategy under alternative optimisation criteria.

The traditional equalising strategy

We first define the stochastic *SIR* model in an infinitely large population of households to set the nomenclature and parameters of the system. Throughout this paper we formulate and simulate models that are Markovian in nature (i.e. transitions occur as stochastic rates that only depend on the current state of the system, such that there is no historical knowledge), whereas the original work on the equalising strategy held for any form of transmission dynamics (Ball et al., 1997; Ball and Lyne, 2002). While this explicit decision about the nature of the system is necessary to produce our quantitative comparison of vaccination priorities, we believe that the qualitative findings will hold more generally. We define the model in terms of the transitions between states and the rates at which these transitions occur. There are three possible transitions within a household of size n:

External Infection
$$(S, I, R) \quad \to (S-1, I+1, R) \quad \text{Rate} = \quad \alpha_n \bar{I} S$$
Internal Infection
$$(S, I, R) \quad \to (S-1, I+1, R) \quad \text{Rate} = \quad \beta_n I S$$
Recovery
$$(S, I, R) \quad \to (S, I-1, R+1) \quad \text{Rate} = \quad \gamma_n I$$

where S, I and R ($S+I+R=n$) refer to the number of susceptible, infectious and recovered/resistant individuals in a household, while α, β and γ capture the rates of external transmission, internal transmission and recovery; $\bar{I}$ is the proportion of the population that is infected, which is calculated as the weighted average over all households. We further define h_n to be the proportion of households containing n individuals. Throughout we make the natural assumptions that α and γ are not dependent on household size, although we retain the dependence in the equations as much as possible. We note here that the action of vaccination is to successfully immunise susceptible individuals, effectively turning them into recovered individuals; hence as we are considering prophylactic vaccination (before an outbreak) we assume the action of vaccination is to begin an epidemic with a mixture of susceptible and recovered individuals in each household.

Here we have allowed the fundamental rates to be functions of the household size, n; this is in contrast to the earlier modelling studies where these rates where assumed independent of the household size (Ball et al., 1997; Becker and Starczak, 1997; Ball and Lyne, 2002). We now need to introduce some epidemiological notation; when $\beta_n = \beta$ then transmission increases with the number of individuals in the household and such transmission is known as density dependent (even though it arises when the parameter is independent of population size), in contrast when β_n is a function of the household size n the transmission is referred to as frequency dependent. The independence of parameters from household size (and hence the assumption of density-dependent transmission) made in previous work has an important epidemiological consequence: the rate of transmission between susceptible and infected individuals does not depend on the number of recovered individuals in the household. Therefore rather than considering the behaviour of a household of type (S, I with $R = n - S - I$), in the limited case where independence is assumed, it is sufficient to consider a smaller household of size $S+I$ without any recovered individuals.

Following the work of Ball et al. (1997), Ball and Lyne (2002), the following statements must hold for the equalising strategy to be optimal:

(i) given two households of size n and two doses of vaccine, it is better to vaccinate one individual in each household rather than two individuals in a single household, for all n; and,
(ii) given a household of size n, a household of size $n+1$, and single dose of vaccine, it is better to vaccinate an individual in the household of size $n+1$, for all n.

Here, 'better' and 'optimal' are defined with respect to minimising the expected number of secondary households infected. To generate the mathematics equivalent to these two verbal conditions, requires us to consider the household reproductive number,

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