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Number-needed-to-vaccinate calculations: Fallacies associated with exclusion of transmission

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ABSTRACT

Background: Number-needed-to-vaccinate (NNV) calculations are used with increasing frequency as metrics of the attractiveness of vaccination programs. However, such calculations as typically applied consider only the direct protective effects of vaccination and ignore indirect effects generated through reduction of force of infection (i.e., risk of infection in susceptible individuals). We postulated that such calculations could produce profoundly biased estimates of vaccine attractiveness.
Methods: We used mathematical models simulating endemic and epidemic diseases with a variety of epidemiological characteristics, and in the face of varying approaches to immunization, to evaluate biases associated with exclusion of transmission. We generated number-needed-to-vaccinate calculations using both traditional methods, and using a more realistic approach that defines this quantity as the ratio of cases prevented through vaccination (directly or indirectly) to individuals vaccinated. We quantified bias as the ratio of estimates produced using these two different methods.
Results: Across a range of simulated infectious diseases with variable epidemiological characteristics, and in the context of both pulsed vaccination and ongoing vaccine programs, traditional NNV calculations based on systems using plausible infectious disease parameters produced estimates biased by up to 3 orders of magnitude (i.e., 1000 fold). Unbiased NNV estimates were seen only in the context of diseases with extremely high reproductive numbers that could be prevented with highly efficacious vaccines.
Conclusions: When evaluated using mathematical models that simulate common vaccine-preventable diseases of public health importance, typical number-needed-to-vaccinate calculation produce marked over-estimates relative to NNV calculations incorporating the fundamental transmissibility of communicable diseases. NNV calculations should be used with caution and interpreted critically when used as metrics for the potential community-level impact of vaccination programs.

1. Introduction

Communicable diseases remain an important challenge for public health professionals around the world. Novel threats continue to emerge, and diseases previously identified as targets for elimination (measles, polio) have had resurgences in some jurisdictions over the past decade [1–3]. At the same time, emergence of novel vaccines and novel immune adjuvants [4,5], have presented communicable disease control agencies with an ever-wider array of tools for the control of such diseases. In an era of constrained costs, metrics of effectiveness and cost-effectiveness are helpful in informing decisions to adopt novel vaccines [6].

The "number-needed-to-vaccinate" (NNV) is an analogue of the number-needed-to-treat metric commonly used in pharmacoepidemiology [7]. NNV has been used to describe the potential impact of vaccination in controlling several communicable diseases, including human papillomavirus vaccine [8,9], influenza [10–12], pertussis [13] and pneumococcal disease [14,15]. NNV estimates are typically based on estimates of vaccine efficacy, or direct protection of vaccinated individuals, and as such ignore indirect effects of vaccination (e.g., reduction in secondary infections due to fewer infectious cases; protective effects of herd immunity) [16]. The failure to consider indirect vaccine effects may be unimportant when vaccine-preventable diseases are non-transmissible (e.g., as is the case with shingles [17] or tetanus). However, for communicable diseases, the impact of vaccination is a profoundly non-linear process, and the indirect effects of vaccination may far outweigh the direct effects that are incorporated into NNV calculations.

We noted that NNV calculations are likely to produce biased estimates of vaccine impact in populations, with the magnitude of bias likely to vary according to the epidemiological characteristics of the disease in question. NNV calculations that consider only protection derived from direct prevention of vaccinated

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individuals, conditional on a fixed incidence of infection in unvaccinated individuals, imply a constant force of infection (i.e., rate at which susceptible individuals become infected) with or without vaccination. Equilibrium incidence of infection is assumed to be perturbed only inasmuch as risk changes in a manner inversely proportional to vaccine efficacy. Similarly, as there is no dynamic perturbation of equilibrium via prevention of downstream cases, NNV calculations ignore time-at-risk, and the potential for prevention of extremely large numbers of cases through vaccine-derived elimination or eradication of infections.

We used mathematical models of infectious disease transmission that capture both direct and indirect vaccine effects with an aim to evaluate the nature and direction of bias associated with typical NNV calculations. We examined a variety of commonly encountered epidemiological circumstances related to disease natural history and transmissibility, population immunity, and whether the vaccine in question targets an epidemic or endemic disease.

2. Methods

2.1. Number needed to vaccinate

In its basic form, and ignoring indirect effects of vaccination, NNV can be conceptualized as the ratio of newly vaccinated individuals to cases prevented, *Nv*/*Nc*. *Nc* per dose of vaccine is simply

$$R_u - R_u(1 - E_v) \tag{1.0}$$

where R_u is the risk of disease in unvaccinated individuals, and E_v is efficacy of vaccination. Eq. (1.0) simplifies to $R_u E_v$. Traditional NNV calculations are often based on NNT estimates, and are written:

$$\text{NNV} = 1/(R_u - R_v) \tag{1.1}$$

where R_v is the risk among vaccinated individuals. Based on Eq. (1.0) this could equivalently be expressed as $1/R_u E_v$. Thus *Nc*/*Nv*, the number of cases prevented per vaccinated individual, can be written as either $R_u E_v$, or $R_u - R_v$, when indirect effects of vaccination are ignored.

2.2. Models and representation of disease natural history

We sought to explore the relationship between traditional representations of NNV (NNV static or NNVs), and NNV projections that would be derived using more realistic models that capture the fundamental tendency towards "non-independence" of communicable diseases (NNV dynamic or NNVd), by constructing a series of compartmental dynamic transmission models [18]. Such models represent the epidemiology of infectious diseases as a series of transitions between mutually exclusive health states. We constructed susceptible-infectious-removed (SIR) models, as well as susceptible-infectious-susceptible (SIS) models, to represent both diseases where infection is followed by durable immunity (e.g., measles or mumps) and those where infection is not followed by durable immunity, whereas vaccination does produce a durable immune response (e.g., effects produced by conjugate vaccines against *Hemophilus influenzae* group B or *N. meningitidis* group C.

A basic description of these models is as follows (see Supplementary material for additional details). For SIR systems, we can characterize the epidemiology of disease based on the following three ordinary differential equations:

$$\frac{dS}{dt} = -\beta SI + \mu N - \varpi(VE)S - \mu S \tag{2.0}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I \tag{2.1}$$

$$\frac{dR}{dt} = \gamma I + \varpi(VE)S - \mu R \tag{2.2}$$

here β represents a transmission parameter, γ is the rate of recovery from disease, ϖ is the rate of vaccination, and *VE* is vaccine efficacy. For simplicity, we refer to vaccine efficacy and assume 100% vaccine coverage in all scenarios. However, one could equivalently consider a 100% efficacious vaccine with the *VE* value reflecting the proportion of the population vaccinated. The parameter μ represents birth and death rates in a population at (demographic) equilibrium and $N = (S + I + R)$. Disease-related mortality is considered rare and is ignored. For SIS systems in which durable immunity is achievable only through vaccination:

$$\frac{dS}{dt} = -\beta SI + \mu N - \varpi(VE)S + \gamma I - \mu S \tag{3.0}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I \tag{3.1}$$

$$\frac{dV}{dt} = \varpi(VE)S - \mu V \tag{3.2}$$

here *V* represents the vaccinated state. We used these models to perform simulations in which basic reproductive numbers (R_0, the number of new cases created by a single primary case in a susceptible population), time horizons, population immune status, and levels of vaccine coverage were varied. It should be noted that in a homogeneously mixed population, vaccine coverage and efficacy are interchangeable, such that, for example, the impact of 100% coverage with a 70% efficacious vaccine will be equivalent to 70% coverage with a 100% efficacious vaccine.

For each simulation, we calculated the ratio of NNV estimated using traditional methods (e.g., Eq. (1.0) above) and based on dynamic methods (estimated as the ratio of vaccine doses to cases prevented). We estimated divergence in NNV estimates as the ratio of NNVs to NNVd.

We performed these simulations for each of the following scenarios:

2.2.1. Endemic disease

(a) Short-term effects with pulsed vaccination: The simplest scenario to be considered is a disease that is endemic, such that the equilibrium prevalence of susceptibles is $1/R_0$ [18]. We consider a dynamic population structure with life expectancy of 65 years, and introduce an instantaneous "pulse" of vaccination at the beginning of the scenario for variable fractions of the population.

(b) Longer-term effects with ongoing vaccination: Once instituted, immunization programs for endemic diseases are likely to be ongoing. We modified scenario 1.a. by following the initial pulse of vaccination with immunization of a fixed fraction of the population at birth, so that the total fraction of the population immunized did not decrease over time.

(c) Diseases with limited natural immunity: Several encapsulated bacterial pathogens (e.g., *N. meningitidis*, *H. influenzae*) are associated with repeated carriage states that resolve without durable immunity [19]. A small subset of individuals colonized with these pathogens experience clinically apparent disease. Newer adjuvanted vaccines provide durable immunity to carriage of these pathogens. We evaluated such a scenario using a simple susceptible-infectious-susceptible (SIS) model in which vaccine associated immunity was lifelong and considered NNV over a 20-year time horizon. NNV calculations were based only on observed symptomatic cases of disease that would be apparent to public health surveillance systems. We structured our model to simulate a pathogen like *N. meningitidis*, with a duration of carriage = 9 months, a low basic reproductive number (1.1) and a low risk of symptomatic infection among colonized individuals (1/10,000) [20,21].