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The influence of incomplete case ascertainment on measures of vaccine efficacy

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ABSTRACT

Background: Motivated by the unexplained variation in the performance of some vaccines across different settings, we extend previous theoretical work to consider the potential impact of incomplete case ascertainment on measures of vaccine efficacy (VE), which is more likely in subclinical or clinically unimportant infections, such as rotavirus gastroenteritis.
Methods: By simulating the measurement of VE under outbreak conditions using a discrete time stochastic SIR model, we compare three commonly used measures, VE_{Risk}, VE_{Rate}, and VE_{Hazard}, calculated respectively based on risk ratio, rate ratio and hazard ratio of disease. We investigate how these measures are influenced by factors such as biological activity, action mechanism of vaccine, proportion of cases ascertained, and underlying force of infection.
Results: Under plausibly low levels of ascertainment, the group with the most infections, and therefore the most missed cases, has the most falsely inflated denominator, producing similar rates in the control and intervention groups. As a result, VE_{Rate} and VE_{Hazard} will underestimate the true VE compared to high case ascertainment scenarios. Furthermore, the extent of underestimation is greater for *leaky* vaccine models with lower biological protective effects and under conditions which are conducive to high transmission.
Conclusions: This study demonstrates that a biologically active vaccine may produce a low measured VE under a range of epidemiological, vaccine-related and logistical conditions. Low case ascertainment may partly explain the observed heterogeneity in the performance of rotavirus vaccine across different settings, and should be considered in the design and interpretation of future field trials.

1. Introduction

Evidence that a vaccine can help reduce burden of disease is a prerequisite for introducing the vaccine into a specific region. Because previous rotavirus vaccine candidates have failed in resource-poor settings, the World Health Organization initially delayed prequalification of both the HRV vaccine (GSK, Rotarix) and the PRV (Merck, Rotateq) until supportive clinical trial data was available from resource-poor settings [1]. This motivated our study to better understand the unexplained variation in the performance of some vaccines across different settings, for which we chose to use rotavirus as an illustrative example.

While most rotavirus infections are benign, rotavirus is nonetheless the leading cause of severe gastroenteritis among young children [2–4]. Implementation of rotavirus vaccine programs have been highly successful in high-income settings with evidence of both direct and herd protection [5,6]; however, like many other enteric vaccines, rotavirus vaccines have been associated with lower measured vaccine efficacy (VE) in resource-poor settings with the heaviest rotavirus burden [4,7]. The estimated VE based on the risk ratio of severe disease for RV1 in field trial in Malawi, for example, was only 49% [8]. Notwithstanding differences in the research design across studies, this is lower than estimates from South Africa (54–61%) and considerably lower than that in the US, Australia, Latin America and Europe (80–95%) [9–12]. Among Aboriginal children in Australia's Northern Territory with historically very high rates of rotavirus infection [13], lower

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than expected effectiveness was observed during a widespread outbreak [14].

To understand the impact of vaccination during both pre-licensure vaccine trials and post-licensure evaluation of vaccine programs, the reasons underlying the observed variation in measured VE across settings need to be better understood [1,4,15]. There is some evidence that this variation can be partly explained by reduced immune responses to vaccination in resource-poor settings [1,16], with malnutrition, maternal factors (like breast milk antibodies) and enteric co-infections proposed as mechanisms [17]. Part of the variation in estimated VE may be attributable to incorrect inferences about the biological activity of vaccines based on population studies. The biological activity of a vaccine can be defined as some measure of vaccine-induced reduction in the risk of an individual acquiring infection when exposed to an infective agent. The measured VE of a vaccine might not directly measure its biological activity, since the former is measured in aggregate at the population level rather than at the individual per-exposure level, and can therefore be influenced by disease transmission, which can be dynamically affected by herd immunity and other population level factors [18].

At the population level, VE is usually expressed as a function of the comparative probability of infection among vaccinated and unvaccinated individuals. Different effect measures are not interchangeable in the context of vaccine evaluation, displaying different characteristics depending on the balance of 'leaky' versus 'all-or-nothing' protective mechanisms [18–21]. A vaccine which is conceptually 'leaky' acts homogenously among vaccine recipients by reducing the probability of transmission of infection per potentially infectious contact; a vaccine that acts in a conceptually 'all-or-nothing' manner completely protects some vaccine recipients while providing no protection to the remainder. It has been demonstrated that measuring VE as a function of the cumulative incidence (*i.e.*, 1 – risk ratio) provides a time-invariant measure of the proportion of vaccinated individuals protected for an all-or-nothing vaccine, while VE measured as a function of the proportionate reduction in cases per person-time at risk (*i.e.*, 1 – rate ratio) provides a time-invariant measure of the reduction in the probability of transmission per infectious contact for a leaky vaccine [20,22].

The importance of both uniform definition and ascertainment of cases has been addressed in the design of vaccine studies [23], recognising that cases of infection may be incompletely ascertained because not all are captured whether by active follow-up or by passive clinical or laboratory surveillance systems [21]. Only a fraction of rotavirus infections result in moderate to severe symptoms requiring medical evaluation, and therefore only a minority are likely to be ascertained as cases in the absence of meticulous monitoring [24]. Under-ascertainment of infection is inevitable for many vaccine preventable diseases, and yet the potential for this to influence VE measures has not been explored. We therefore extend previous theoretical work to consider the potential impact of incomplete ascertainment of infection on the archetypal vaccine models.

We established an epidemiological model that describes rotavirus outbreaks among infants where vaccines are given to half of the study population. By measuring VE as a function of either the risk ratio, rate ratio or hazard ratio, this model approximates typical randomised field trials or non-randomised case-control or cohort studies to evaluate rotavirus vaccines. By investigating how different measures of VE are sensitive not only to various biological activities of vaccine but also different levels of completeness of infection ascertainment, we explore the extent to which low estimates of VE in low-resource settings might be partly explained as artefacts of the statistical models used and analytical factors, rather than true differences in the biological activity of the vaccine.

2. Methods

2.1. Stochastic modelling of vaccine trial during rotavirus outbreak

We use discrete-time stochastic models based on a Susceptible-Infected-Recovered structure to simulate the transmission of rotavirus between individuals in a closed population. We make the assumption that outbreaks occur over such a brief period (weeks to months) that births, deaths, inward and outward migrations, and waning immunity are negligible. If the average duration of infectiousness $1/\gamma$ is taken to be five days and we assume that the basic reproduction number $R_0 = 3$, then the probability of effective transmission per-day between two infants is $\beta = R_0\gamma = 0.6$. R_0 is defined as the average number of secondary cases of infection caused by a single case of infection in an entirely susceptible population. Sensitivity analyses with smaller values of R_0 are also investigated given that reported R_0 for rotavirus in unvaccinated young children is estimated as slightly above 1 in middle- to high-income settings [24].

We begin with a *leaky* vaccine model that assumes vaccination protects all vaccine recipients in an identical multiplicative way. A constant number N of infants is assumed in a study population who at any point in time during the study are either susceptible (S) to rotavirus, infected and infectious (I), or no longer susceptible because of immunity upon recovery from natural infection or vaccination (R) (Fig. 1 and Table 1). Time t is measured in days, a small enough increment to reasonably assume that all modelled rates stay constant within each step and that multiple events cannot occur to the same individual in the same step. Half of N infants at $t = 0$ are unvaccinated (labelled U) and half are vaccinated (labelled V) before the start of an epidemic outbreak. Thus our population is divided into six disjoint subgroups according to the health status of infants with respect to pathogen (S, I or R) and vaccination status (U or V). Let θ denote reduction in the probability of transmission of infection (β) for each contact between a vaccinated susceptible infant (S_V) and an infectious infant (I_V or I_U) compared with a similar contact made between an unvaccinated susceptible infant (S_U) and an infectious infant. Let $\Delta R_{U\ or\ V}$ and $\Delta I_{U\ or\ V}$ be the number of newly recovered and infected infants, respectively, during the time interval Δt:

$$\Delta R_U \sim Binomial\ (I_{U,t}, \gamma\Delta t)$$

$$\Delta R_V \sim Binomial\ (I_{V,t}, \gamma\Delta t)$$

$$\lambda = \beta\frac{I_{U,t} + I_{V,t}}{N}$$

$$\Delta I_U \sim Binomial\ (S_{U,t}, \lambda\Delta t)$$

$$\Delta I_V \sim Binomial\ (S_{V,t}, (1-\theta)\lambda\Delta t)$$

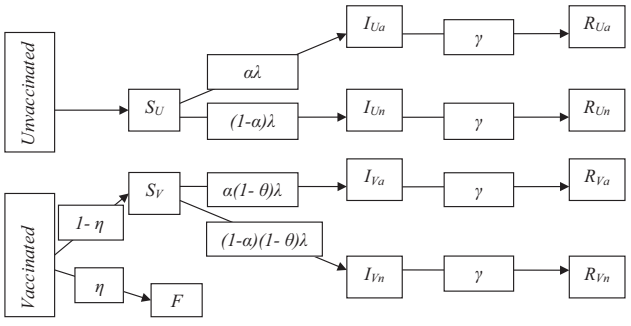

Fig. 1. Model structure. Description and default choice of values of all variables and parameters are provided in Table 1.