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 effect. (Change "effect" to "efficacy", being consistent with the term VE introduced in the second paragraph of Introduction.) (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.

Keywords: Vaccine effectiveness; Mathematical modelling; Incomplete ascertainment; Outbreak; Leaky vaccine; All-or-nothing vaccine

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 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 homogeneously 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 $\Delta R_{U \text{ or } V}$ and $\Delta I_{U \text{ or } V}$ be the number of newly recovered and infected infants, respectively, during the time interval Δt :

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

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

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

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

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

And the size of each subpopulation in the next iteration $t + 1$ is,

$$S_{U,(t+1)} = S_{U,t} - \Delta I_U$$

$$S_{V,(t+1)} = S_{V,t} - \Delta I_V$$

$$R_{U,(t+1)} = R_{U,t} + \Delta R_U$$

$$R_{V,(t+1)} = R_{V,t} + \Delta R_V$$

$$I_{U,(t+1)} = I_{U,t} + \Delta I_U - \Delta R_U$$

$$I_{V,(t+1)} = I_{V,t} + \Delta I_V - \Delta R_V,$$

where λ represents the force of infection among unvaccinated infants, determined by contact and transmissibility parameter β and the proportion of the population being infected at given time t , $\frac{I_{U,t} + I_{V,t}}{N}$.

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

Table 1 Variables and parameters.

Variable	Description
S_U	Unvaccinated susceptible individuals
S_V	Vaccinated susceptible individuals
F	Fully protected individuals by vaccination
I_{Ua}	Unvaccinated infections that are ascertained

I_{Un}	Unvaccinated infections that are not ascertained	
I_{Va}	Vaccinated infections that are ascertained	
I_{Vn}	Vaccinated infections that are not ascertained	
R_{Ua}	Unvaccinated and immunised individuals after recovery from ascertained infections	
R_{Un}	Unvaccinated and immunised individuals after recovery from unascertained infections	
R_{Va}	Vaccinated and immunised individuals after recovery from ascertained infections	
R_{Vn}	Vaccinated and immunised individuals after recovery from unascertained infections	
Parameter	Description	Default value by scenario
N	Total size of the study population	10,000
β	Transmission probability per-infectious-contact	0.6
γ	Rate of recovery	$0.2, R_0 = \beta/\gamma = 3$
θ	Biological activity of a leaky vaccine: reduction in the probability of transmission of infection for each contact between a vaccinated and an infectious individual	0.8 for a leaky vaccine, and 0 for an all-or-nothing vaccine
η	Biological activity of an all-or-nothing vaccine: proportion fully protected by vaccination	0 for a leaky vaccine, and 0.8 for an all-or-nothing vaccine.
α	Proportion of infection ascertained	0.1

In the alternative all-or-nothing vaccine model, we assume a proportion η of all vaccine recipients, denoted by F , are fully protected by immunisation while the rest, $1 - \eta$, experience primary vaccine failure and remain just as susceptible as unvaccinated infants. Given that only a small proportion of rotavirus infections are likely to be ascertained as cases, we introduce an additional parameter α to represent the proportion of infections that are ascertained. Ascertained and unascertained cases are denoted by subscripts a and n , respectively.

2.2 Measures of vaccine effect

Several outcome measures have been used in the analysis of clinical trials and post licensure evaluation of vaccines, namely the risk ratio, the rate ratio, and the hazard ratio of infection among vaccinated versus unvaccinated individuals [20,25]. The risk ratio compares the ratio of the average cumulative risk of infection between groups. The rate ratio compares instead the average rate of infection in susceptible individuals expressed, for example, as infections per person days at-risk. The hazard ratio compares the average instantaneous risk of infection (the hazard) among susceptible individuals in the two groups over the study period. The equations below show how VE is calculated as a function of these distinct measures at the end of an outbreak $t = T$:

$$VE_{\text{Risk}} = 1 - risk\ ratio = 1 - \frac{R_{Va,T}}{R_{Ua,T}};$$

$$VE_{\text{Rate}} = 1 - rate\ ratio = 1 - \frac{R_{Va,T} / \sum_{t=1}^{t=T} [S_{V,t} + F_t + R_{Vn,t}]}{R_{Ua,T} / \sum_{t=1}^{t=T} [S_{U,t} + R_{Un,t}]};$$

$$VE_{\text{Hazard}} = 1 - hazard\ ratio = 1 - e^{V\acute{a}c}, \text{ here we used a Cox proportional hazard model, including only an indicator variable for vaccination status (} V\acute{a}c), \text{ to obtain maximum likelihood estimates of the hazard ratios (} e^{V\acute{a}c}).$$

Infections which are asymptomatic or mild and clinically unimportant are assumed to be immunising but not ascertained as cases. Although naturally immune, such infants would be considered susceptible for the purpose of calculating the VE measures.

2.3 Simulation and output variables

We start with a population that is naïve (completely susceptible) to infection, and introduce one infection in the unvaccinated ascertained group ($I_{Ua, (t=0)} = 1$) to initialise a simulation run where there is always half the population vaccinated ($S_{V, (t=0)} = 5,000$, $S_{U, (t=0)} = 4,999$). Each simulation is run until there is no longer a source of infection in the population ($I_{Ua,t} + I_{Un,t} + I_{Va,t} + I_{Vn,t} = 0$). Under these stochastic processes, not every introduction results in take-off (sustained transmission) and therefore an outbreak. We empirically define that an *outbreak* occurs if a simulation run accumulates at least 20 infected infants; a histogram of the final number of cases for all simulations can be found in Appendix A. The proportion of simulated introductions resulting in an outbreak and the mean VE measures (VE_{Risk} , VE_{Rate} , VE_{Hazard}), with associated 95% confidence intervals, are reported based on 10,000 simulation runs under default parameter values (Table 1) unless specified otherwise. All simulations and analyses were conducted in R [26].

3 Results

While the aggregated number of infected infants increases, the disease dynamic was consistent as the population size increases under both the leaky and all-or-nothing models (Fig. 2), so we fixed our study population size at $N = 10,000$. In observational studies, an outbreak might not be identified if only a few infections are ascertained. However, with a high force of infection ($R_0 = 3$) the chance of failing to meet this threshold is low (<0.4%, see Table 2) even if the proportion of infections ascertained is low.

Fig. 2 Dynamics of rotavirus infections under various vaccine action mechanisms for three different sizes of study population. The biological activity of both leaky (top) and all-or-nothing (bottom) vaccines was assumed 80%. The mean number of infections was calculated based on outbreaks occurred out of 100 simulation runs, stratified by unvaccinated (grey) or vaccinated (black) and unascertained (dashed) or ascertained (solid). Left: $N = 1,000$, Middle: $N = 5,000$, Right: $N = 10,000$. All other parameters are as given in Table 1.

Table 2 Mean measures of VE based on default parameters as given in Table 1 unless specified otherwise, 10,000 simulation runs.

VE measures \ Scenario	Leaky, $\alpha = 1$ [95CI]	All-or-nothing, $\alpha = 1$ [95CI]	Leaky, $\alpha = 0.1$ [95CI]	All-or-nothing, $\alpha = 0.1$ [95CI]
Risk of outbreaks	0.4925	0.4929	0.4968	0.4956
Ascertained outbreaks	0.4925	0.4929	0.494	0.4918
VE_{Risk}	0.6557 [0.6554, 0.6560]	0.8001 [0.8000, 0.8002]	0.6550 [0.6545, 0.6555]	0.7996 [0.7992, 0.7999]

VE_{Rate}	0.8352 [0.8350, 0.8354]	0.9023 [0.9021, 0.9025]	0.6734 [0.6730, 0.6739]	0.8113 [0.8110, 0.8116]
VE_{Hazard}	0.8011 [0.8003, 0.8018]	0.8758 [0.8753, 0.8762]	0.6665 [0.6660, 0.6670]	0.8065 [0.8061, 0.8068]

Given complete infection ascertainment ($\alpha = 1$), the measures of VE monotonically increase for biologically more active vaccines with $VE_{Risk} < VE_{Hazard} < VE_{Rate}$ regardless of the action mechanism (Fig. 3). VE_{Risk} approximates the biological activity η for an all-or-nothing vaccine (right panel, black) and underestimates the biological activity θ for a leaky vaccine (left panel, black). VE_{Rate} overstates the biological effect of all-or-nothing vaccine with more profound effects when θ (Change " θ " to " η ", sorry for this typo.) is low (right panel, dark grey), and slightly over-estimates that of leaky vaccine when θ is relatively high (left panel, light grey). VE_{Hazard} approximates θ of a leaky vaccine (left panel, light grey) and overestimates η of an all-or-nothing vaccine (right panel, light grey). However, these patterns no longer hold when the force of infection (R_0) is low and ascertainment of infection is not complete. Using the leaky vaccine model as an illustrative example in Fig. 4, we demonstrate that the underestimation effect of VE_{Risk} on θ diminishes as R_0 decreases (left panel). In addition, VE_{Hazard} no longer approximates θ but overestimates it when the force of infection is small (right panel, $R_0 = 1.5$) and underestimates it if (add " R_0 is high and " the proportion of infection ascertainment (α) is low (right panel, light (Change "light" to "black", sorry about the typo.) and dark grey).

Fig. 3 VE measures are influenced by the action mechanism and the biological activity of vaccine under complete infection ascertainment ($\alpha = 1$). The mean VE measures were calculated based on outbreaks occurred in 10,000 simulation runs. All other parameters are as given in Table 1.

Fig. 4 VE measures are influenced by the force of infection R_0 and the proportion of infection ascertained α . We considered three different values for $R_0 = 1.5, 2.2$ and 3 using different transmission parameter $\beta = 0.3, 0.44$ and 0.6 , respectively. The mean VE measures were calculated based on outbreaks occurred in 10,000 simulation runs. The biological activity of the leaky vaccine was assumed 80%. All other parameters are as given in Table 1.

We looked further into how well various VE measures reflect the biological activity of a vaccine with different mechanisms (θ or η) and under different ascertainment rates (α). For a given level of biological activity, $\theta, \eta = 0.8$, the estimated VE varies from 0.66 to 0.90 depending on choice of measurement (VE_{Risk} , VE_{Rate} or VE_{Hazard}), mechanism of vaccine action (leaky or all-or-nothing), and proportion of infections ascertained ($\alpha = 1$ or 0.1) (Table 2). In particular, low ascertainment has almost no impact on measures of VE_{Risk} , but VE_{Rate} and VE_{Hazard} are both reduced by incomplete ascertainment with a greater impact on leaky than on all-or-nothing vaccines. More detailed analyses are included in Appendix B. Epidemiological factors and logistical factors interactively contribute to estimates of VE.

4 Discussion

The observed heterogeneity in the performance of a number of vaccines like rotavirus vaccine across different settings are poorly understood but often attributed to reduced immune responses in resource-poor settings [1]. We developed a stochastic epidemiological model to investigate non-immune factors that potentially contribute to this observation. We replicated earlier work, which showed how VE measures are not interchangeable in regard to the vaccine’s leaky and all-or-nothing protective characteristics [20,25], and extended it by demonstrating how measures of VE can be further confounded by incomplete case ascertainment, which can be substantial for some vaccine preventable diseases. For an all-or-nothing vaccine, VE measured as a function of the risk ratio of infection provides a valid estimate of the proportion of vaccinated children fully protected, regardless of the proportion of infections ascertained. However, under most other combinations of vaccine mechanism and choice of VE measure, estimated VE will either systematically underestimate or overestimate the biological activity of a vaccine. More importantly, we have shown that a vaccine demonstrating identical immune protective effects across populations can have varying estimates of VE in different settings depending on the choice of VE measure and the proportion of infections ascertained.

The difference between leaky and all-or-nothing vaccine models has been explored extensively by mathematically modelling their distinctive direct biological action mechanisms on individuals under various population mixing patterns and vaccine coverage [27-30]. It is known that when all infections are ascertained, VE_{Rate} *overstates* the biological effect for all-or-nothing vaccines, while VE_{Risk} *understates* the biological effect of leaky vaccines. Longini and colleagues proposed means to estimate VE based on survival curves for incidence data during epidemics (VE_{Hazard}), which they considered preferable to that derived from cumulative attack rate data (VE_{Risk}) [31]. In addition, VE_{Rate} has also been frequently used in clinical trials to compare the average rate of infection for vaccinated and unvaccinated populations [21]. We have shown that under plausible conditions, the estimated VE of a vaccine with an 80% protective effect (leaky or all-or-nothing) could range from 66 to 90% depending on the choice of VE measure and epidemiological factors. This finding compliments recent studies that assessed how population-level vaccine effects can be influenced by a range of disease and vaccine-related factors [16,18].

Incomplete ascertainment of infection may occur for many vaccine preventable infections either because the spectrum of severity includes mild or asymptomatic infection, or because of limitations in access to laboratory confirmation or insensitivity of laboratory assays. This is the case for rotavirus and is also likely to be true for pertussis, mumps, rubella, influenza, and tuberculosis. We emphasise that missing clinically insignificant infection should not necessarily be considered a failure of the study design, but this does need to be borne in mind when interpreting vaccine effect estimates and comparing VE estimates across different studies. If previously infected infants (whether ascertained as cases or not) are no longer at risk of clinically significant infection because of naturally acquired immunity, the proportion of children remaining ‘susceptible’ who are, in fact, immune increases over time.

If 10% of infections are ascertained during an outbreak (even lower ascertainment is plausible for rotavirus [24]), our simulations suggest that measured VE cannot be used directly to infer the biological protective effect of a vaccine. VE measures could either understate or overstate the biological effect, interactively influenced by different vaccine-related and epidemiological factors. When ascertainment is low, the unvaccinated group has the most infections and, therefore, the most missed cases and the number of ‘susceptibles’ most inflated by naturally immune individuals over time. As a result, VE_{Rate} and VE_{Hazard} will become progressively smaller (towards a null effect). The extent of underestimation is greater for leaky vaccines with lower biological protective effects and under epidemiological conditions which are conducive to high transmission. These findings highlight the importance of well-defined VE measures and prudent understanding of setting-specific factors that can be influential in the interpretation of the biological activity of vaccines. In particular, we caution against making uncritical inferences about biological activity of vaccines (including of waning efficacy) on the basis of population-based effect measures.

These effects are distinct from conventional sources of selection, information and confounding biases which can further distort effect measures from observational studies and from improperly conducted or controlled clinical trials. That is, the issues discussed here apply equally to well conducted randomised and blinded field trials as they do to observational studies. Rotavirus was used as an illustrative example, however, the findings are generalisable to other vaccine preventable disease scenarios. We have kept the model simple to focus on the role of infection ascertainment in evaluating vaccine effects. Further research is necessary to investigate the effect of changing demographics, mixing of low and high infection risk groups, as well as factors that might change the proportion of infections ascertained over time. These models can also be extended to investigate combined biological activity such as vaccines with combined leaky and all-or-nothing effects.

5 Conclusion

The measured effect of a vaccine can vary depending on the choice of effect measure and a range of epidemiological, vaccine-related and logistical conditions, including the proportion of infections ascertained as cases. By demonstrating this concept using a stochastic transmission model, we may partly explain the observed heterogeneity in the performance of rotavirus vaccine across different settings, which represents an example that should be generalisable to many other infectious disease scenarios. This work should guide the design and interpretation of future vaccine trials.

Conflicts of interests

None declared.

Author contributions

Y.W., T.L.S. and J.A.M. developed the model. Y.W. performed analysis and wrote the manuscript; E.S.M. contributed to the interpretation of results; T.L.S. initiated and supervised the project. All authors made substantial contribution to manuscript writing and approved the submission of the manuscript.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2018.04.046>.

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Appendix A. Supplementary material

[Multimedia Component 1](#)

Supplementary Figs. S1–S4

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