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A comparison of the test-negative and traditional case-control study designs with respect to the bias of estimates of rotavirus vaccine effectiveness

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ABSTRACT

Estimation of the effectiveness of rotavirus vaccines via the test-negative control study design has gained popularity over the past few years. In this study design, children with severe diarrhea who test positive for rotavirus infection are considered as cases, while children who test negative serve as controls. We use a simple probability model to evaluate and compare the test-negative control and the traditional case-control designs with respect to the bias of resulting estimates of rotavirus vaccine effectiveness (VE). Comparisons are performed under two scenarios, corresponding to studies performed in high-income and low-income countries. We consider two potential sources of bias: (a) misclassification bias resulting from imperfect sensitivity and specificity of the test used to diagnose rotavirus infection, and (b) selection bias associated with possible effect of rotavirus vaccination on the probability of contracting severe non-rotavirus diarrhea.

Our results suggest that both sources of bias may produce VE estimates with substantial bias. Particularly, lack of perfect specificity is associated with severe negative bias. For example, if the specificity of the diagnostic test is 90% then VE estimates from both types of case-control studies may underestimate the true VE by more than 20%. If the vaccine protects children against non-rotavirus diarrhea then VE estimates from test-negative control studies may be close to zero even though the true VE is 50%. However, the sensitivity and specificity of the enzyme immunoassay test currently used to diagnose rotavirus infections are both over 99%, and there is no solid evidence that the existing rotavirus vaccines affect the rates of non-rotavirus diarrhea. We therefore conclude that the test-negative control study design is a convenient and reliable alternative for estimation of rotavirus VE.

1. Background

Rotavirus is the leading cause of severe diarrhea among children worldwide and was estimated to cause 215,000 childhood deaths in 2013 [1]. To prevent the burden of severe rotavirus diarrhea (SRD), the World Health Organization recommends routine vaccination of all children worldwide. Two vaccines against rotavirus were licensed for use in 2006 and have been introduced in the national immunization programs of more than 85 countries by late 2017. In randomized clinical trials, the *efficacy* of these vaccines against severe rotavirus diarrhea ranged from 85% to 98% in high income settings to 50–64% in low income settings. While the exact reasons for this variable vaccine performance are not known, factors that may adversely affect the performance of these orally administered, live virus vaccines in low income settings – such as interference by concurrent enteric infections, malnutrition, high levels of maternal antibody, and interference with concurrently administered oral polio vaccine – likely play a role. Given this variable performance of rotavirus vaccines in clinical trials, evaluations of vaccine effectiveness (VE) in routine programmatic use in diverse range of settings are a public health priority.

As vaccination against rotavirus is now recommended globally, randomized placebo-controlled clinical trials to evaluate vaccine efficacy are challenging to conduct. Therefore, observational studies based on patients seeking care or hospitalized for SRD are the best options for obtaining estimates of rotavirus VE. Cohort studies are not widely feasible due to low incidence of SRD; therefore

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case-control study designs are most commonly used. In these studies, the odds of vaccination are compared between individuals who contracted SRD (cases) and control individuals. Controls should be representative of the source population that produces the cases and should be like cases with respect to covariates (potential confounders) that may affect the chances of vaccination and contracting the diseases of interest.

In *traditional case-control* (TCC) studies, controls are selected from the same community (e.g., children in the same neighborhood) as the cases. Over the past decade, a new type of case-control study has evolved. In these *test-negative control* (TNC) studies, individuals seeking care for clinical symptoms like those of the cases but who test negative for the pathogen of interest serve as controls. TNC studies have mainly been used to estimate influenza VE [2–5], but they are also being used to estimate VE against other diseases, including rotavirus. (Tate et al. [6], Schwartz et al. [7]). TNC studies are expected to reduce confounding bias because cases and controls have similar symptoms and therefore are likely to have similar care-seeking behaviors and may also be similar with respect to other characteristics, such as age, comorbidities or access to health care. Such studies are also logistically easier and more economical to conduct, as no external control group needs to be recruited. By collecting vaccination data prior to knowledge of the test results, bias in ascertainment of vaccination among cases and controls can be avoided through TNC studies.

However, TNC studies may still be prone to selection bias, as controls may not represent the entire population that produces the cases. In particular, VE estimates from TNC studies will be biased if vaccination affects other pathogens that cause diseases that increase the likelihood of individuals to be included in the study as controls (by testing negative for the pathogen of interest) [8]. This may happen due to virus interference or cross-protection. Both types of case-control studies are prone to bias resulting from imperfect diagnostic tests and misclassification of vaccination status, but the extent of bias may differ.

In this work, we compare the biases associated with estimates of rotavirus VE against SRD from TNC and TCC studies. We focus on two sources of bias: (a) misclassification bias resulting from errors in the test for rotavirus infection (false positives or false negatives), and (b) bias associated with the possible effect of rotavirus vaccination on the probability of severe non-rotavirus diarrhea (SNRD).

2. Methods

We use a simplified version of the model developed by Shi et al. [9] to evaluate the bias of estimates of influenza VE from TNC and TCC studies. The general model consists of five steps: (1) assigning a binary covariate corresponding to a person's health status ('healthy' or 'frail); (2) vaccination; (3) developing illness (severe diarrhea, in our case) resulting either from the pathogen against which the vaccine is expected to protect (rotavirus, in our case) or from other pathogens (non-rotavirus infections, in our case); (4) seeking medical care (hospitalization, in our case); and (5) Testing positive or negative to the pathogen of interest. The probabilities of the possible outcomes in each step may depend on the outcomes of the previous steps. For example, the probability of being vaccinated may depend on health status, the probabilities of illness may depend on health status and vaccination status, etc. In this work, we do not account for a patient's health status, and we assume that the probability of seeking care (i.e., hospitalization) does not depend on the patient's vaccination status or on the etiology of her/his severe diarrhea. Below we describe the components of the model that are relevant to the current work.

2.1. Study designs

Children hospitalized because of severe diarrhea are tested for rotavirus infection. In the TNC study, children with severe diarrhea who test positive for rotavirus infection serve as cases while those who test negative become controls. In the TCC study, cases are again defined as children with severe diarrhea who test positive for rotavirus infection, while controls are children who did not develop severe diarrhea during the study period. We assume that eligible controls are randomly selected from the population that produces the cases.

2.2. Vaccination

A child is considered effectively vaccinated 14 days after completing a full course of the rotavirus vaccine. We assume that a child's vaccination status does not change during the study period and that the probability of a child with severe diarrhea being hospitalized does not depend on vaccination status.

2.3. True classification

A hospitalized study participant may suffer from either SRD or SNRD. The true etiology of infection is unknown before the child is tested.

2.4. Test for rotavirus infection

Children hospitalized for severe diarrhea are tested for rotavirus infection. We assume that the test's sensitivity and specificity do not depend on the child's vaccination status.

Our model includes the following **parameters**: The probability of being vaccinated (vaccine coverage), the probabilities of SRD and SNRD among vaccinated and unvaccinated children, and the diagnostic test's sensitivity and specificity. The true VE against SRD is defined as 100% times one minus the ratio of the risks (probabilities) of SRD in vaccinated and unvaccinated children. We consider two scenarios for the values of these parameters: Scenario A represents a high-income setting where incidence of SRD is relatively low and VE is relatively high, such as the U.S., while scenario B represents a low-income, high incidence setting such as sub-Saharan Africa. Table 1 lists the parameters and their values under both scenarios.

For each scenario we also consider a *baseline case* where the probability of SNRD in vaccinated children is the same as in unvaccinated children and the test's sensitivity and specificity are both set to 100% We only expect minimal bias (or no bias) under the baseline cases.

For each of the two case-control study designs we used the values of the parameters to calculate the probabilities that a randomly selected child is classified as either a vaccinated case, vaccinated control, unvaccinated case or unvaccinated control. The estimate of VE is then calculated as 100% times one minus the ratio of the odds of being vaccinated in cases and in controls. The bias of an estimate is the difference between the estimated VE and the true VE. Methods for calculating the bias of estimated VEs for a given array of the model's parameters have been developed by Shi et al [9]. A SAS program for calculating the bias under our model is available from the first author upon request.

We focused on two sources of bias: (1) lack of perfect sensitivity and specificity of the test for rotavirus infection, and (2) effect of the vaccine on the probability of contracting SNRD because of virus interference or cross-protection. For the second source of bias, the effect of the vaccine is quantified by the risk ratio comparing the probabilities of SNRD in vaccinated and unvaccinated. This risk ratio will be denoted RR(SNRD). For example, if the probability of

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