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Review

Case-control vaccine effectiveness studies: Data collection, analysis and reporting results

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ABSTRACT

The case-control methodology is frequently used to evaluate vaccine effectiveness post-licensure. The results of such studies provide important insight into the level of protection afforded by vaccines in a 'real world' context, and are commonly used to guide vaccine policy decisions. However, the potential for bias and confounding are important limitations to this method, and the results of a poorly conducted or incorrectly interpreted case-control study can mislead policies. In 2012, a group of experts met to review recent experience with case-control studies evaluating vaccine effectiveness; we summarize the recommendations of that group regarding best practices for data collection, analysis, and presentation of the results of case-control vaccine effectiveness studies. Vaccination status is the primary exposure of interest, but can be challenging to assess accurately and with minimal bias. Investigators should understand factors associated with vaccination as well as the availability of documented vaccination status in the study context; case-control studies may not be a valid method for evaluating vaccine effectiveness in settings where many children lack a documented immunization history. To avoid bias, it is essential to use the same methods and effort gathering vaccination data from cases and controls. Variables that may confound the association between illness and vaccination are also important to capture as completely as possible, and where relevant, adjust for in the analysis according to the analytic plan. In presenting results from case-control vaccine effectiveness studies, investigators should describe enrollment among eligible cases and controls as well as the proportion with no documented vaccine history. Emphasis should be placed on confidence intervals, rather than point estimates, of vaccine effectiveness. Case-control studies are a useful approach for evaluating vaccine effectiveness; however careful attention must be paid to the collection, analysis and presentation of the data in order to best inform evidence-based vaccine policies.

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Contents

1. Introduction

New vaccines are licensed based on the results of randomized controlled trials demonstrating safety and efficacy. Yet even after licensure, there are often questions about how well a vaccine protects against disease in a "real world" context because of differences in epidemiologic contexts, host factors affecting immune response, vaccine implementation (e.g. varying dosing schedules), and the potential for waning immunity over time [1]. The case-control method is commonly used to estimate effectiveness after a vaccine has been implemented in a public health system; recent examples include evaluations of vaccines against *Haemophilus Influenzae* type B (Hib) [2–13], *Streptococcus pneumoniae* [14–21], influenza [22], rotavirus [23–36], and cholera [37–39]. The results of case-control vaccine effectiveness studies can complement and extend the data generated by clinical trials.

However the potential for bias and confounding are important limitations to the case-control method [40,41]. In 2012, a group of experts met to review recent experience with case-control studies evaluating the effectiveness of several vaccines; here we summarize the recommendations of that group regarding best practices for data collection, analysis and interpretation. (A separate paper provides an overview of the case-control method for evaluating vaccine effectiveness and reviews planning, design, and the identification and enrollment of cases and controls.) While case-control vaccine effectiveness studies have been carried out in countries of all income levels, this review focuses on their implementation in resource-poor settings.

2. Assessment of vaccination status

Vaccination status is the primary exposure of interest for case-control vaccine effectiveness studies, but it can be challenging to assess it accurately [42]. Misclassification of vaccination status can affect the VE estimates in various ways. Non-differential misclassification of vaccination status (i.e. cases and controls have similar risks of misclassification) will bias the effectiveness estimate towards the null [41]. Differential misclassification (i.e. vaccine classification errors have different probabilities in cases and controls) can bias the effectiveness estimate towards or away from the null, or even result in a negative VE, giving the false impression that vaccinated are at greater risk of the target disease than unvaccinated [41]. The same strategies to obtain vaccination history should be used for both cases and controls. Equal, intense effort must be made to obtain vaccination histories from all cases and controls [40,43], and those efforts should be clearly documented and reported.

Preferred sources of vaccination data are family-held vaccine records, clinic records, immunization registry data, or other written documentation of vaccines received and the dates on which they were administered. Doses not recorded on these documents are assumed to have not been received; although this assumption may be incorrect if recordkeeping is poor. Parent reporting of routine infant immunizations received, without written verification, may be unreliable [44]. However, if parents report receipt of no vaccines of any type or receipt of only birth doses, such a history may be valid even in the absence of written confirmation since unvaccinated children rarely will have family-held records and generally parents are unlikely to state that the child is unvaccinated when in fact he or she did receive vaccines. Because excluding unvaccinated children will lead to bias, children with a parental report of having received no routine vaccines beyond birth doses should be included and considered to have received no doses of the vaccine of interest. All eligible cases and controls should be enrolled regardless of whether a documented vaccination history is available at the time of enrollment. Although those lacking a confirmed vaccination history (other than unvaccinated children) will be excluded from primary analyses because of missing data, the proportion of enrolled children for whom vaccination history could not be obtained should be described in the results, and sensitivity analyses used to assess the impact of missing data on the effectiveness estimates (see Section 5).

Investigators should endeavor to understand factors associated with vaccination card availability and retention in the study setting, and whether those factors may also be linked to risk of disease or likelihood of vaccination [45]. In preparation for the study, efforts can be made to improve availability of cards and/or the quality and completeness of data in the clinic records. If vaccine histories are unavailable for a sizeable proportion of children in the area (e.g. $\geq$5–10%), then efforts should be made to assess differences between children with and without documented histories. If important differences exist with regards with risk factors for disease, then a case-control study in that context is likely to yield biased effectiveness estimates. Case-control studies may not be a valid method for evaluating VE in settings where more than a small fraction of children lack a documented immunization history.

Abstracting vaccination data from family-held cards or clinic records is not always straightforward and can be a source of bias. Copies of the vaccination data source (e.g. digital photo, photocopies, or scanned images of the card or record) are extremely useful for controlling data quality. Copies can be used for double-abstraction (e.g. by two independent observers), which may improve the quality of data, particularly in settings where interpretation of information in the record may be challenging, for example, where parental-held records have no dedicated space for a new vaccine or for vaccines administered during campaigns. Copies potentially allow for blinding with regard to case or control status for the person abstracting the vaccination data [40]. Vaccine