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Review

Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls

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ABSTRACT

Case-control studies are commonly used to evaluate effectiveness of licensed vaccines after deployment in public health programs. Such studies can provide policy-relevant data on vaccine performance under 'real world' conditions, contributing to the evidence base to support and sustain introduction of new vaccines. However, case-control studies do not measure the impact of vaccine introduction on disease at a population level, and are subject to bias and confounding, which may lead to inaccurate results that can misinform policy decisions. 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 planning, design and enrollment of cases and controls. Rigorous planning and preparation should focus on understanding the study context including healthcare-seeking and vaccination practices. Case-control vaccine effectiveness studies are best carried out soon after vaccine introduction because high coverage creates strong potential for confounding. Endpoints specific to the vaccine target are preferable to non-specific clinical syndromes since the proportion of non-specific outcomes preventable through vaccination may vary over time and place, leading to potentially confusing results. Controls should be representative of the source population from which cases arise, and are generally recruited from the community or health facilities where cases are enrolled. Matching of controls to cases for potential confounding factors is commonly used, although should be reserved for a limited number of key variables believed to be linked to both vaccination and disease. Case-control vaccine effectiveness studies can provide information useful to guide policy decisions and vaccine development, however rigorous preparation and design is essential.

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Contents

1. Introduction

Many new vaccines have been introduced into public health programs over the past decade and others are under development. Vaccines are generally licensed based on safety and efficacy as measured in randomized controlled trials. Once vaccines are introduced into public health programs, their performance under "real world" conditions also needs assessment [1], including among populations with subgroups that may have been excluded from pre-licensure trials (e.g., malnourished or HIV-infected), with more variable dosing schedules (e.g. age at administration, interval between doses, number of doses), against outcomes not included in randomized clinical trials (e.g. strain-specific protection or mortality), and over more extended periods of time.

Furthermore, some vaccines are licensed based on immunologic correlates of protection [2], and post-licensure evaluations provide important information about protection against disease endpoints. After vaccines have been introduced, conducting placebo-controlled trials is generally not considered ethical [3]. Observational post-licensure evaluations are important to underpin policy decisions on vaccine introduction, to optimize the vaccine program implementation, and to provide evidence for sustaining vaccine use and investment from governments and donors.

2. Efficacy, effectiveness and impact

'Efficacy', 'effectiveness' and 'impact' are sometimes used interchangeably in everyday language, but in the context of vaccine studies the terms have come to be used with distinctly different meanings (although not entirely consistently) [4–7]. Their usage in this document is defined below:

Efficacy is the percentage by which the rate of the target disease among those who are vaccinated according to the recommended schedule is reduced compared to the rate in similar unvaccinated persons. This is generally measured in the context of a placebo-controlled randomized trial as the "per protocol" efficacy (i.e. excluding persons who did not receive the recommended schedule), because the intention is to establish the biologic performance capacity of the product under optimal conditions.

Effectiveness measures the same percent reduction in the rate of disease as efficacy, but in the context of routine, real-world use of the vaccine. Vaccine effectiveness may be similar to the efficacy as measured in clinical trials. However, it often differs in magnitude because in routine use the population vaccinated includes some who may have a less robust immune response, and program implementation (e.g. cold-chain maintenance, dosing schedules) is more variable than in clinical trial settings.

Impact quantifies the reduction in disease at a population level following introduction of the vaccine [7]. Impact can be expressed as a percentage decline or as an absolute change in the rate of disease. It is determined by a combination of vaccine effectiveness, vaccine coverage in the population, and any herd effect (i.e. vaccination of part of the population leading to reduced transmission of the infection in the community, and thus lowered risk of disease in both vaccinated and unvaccinated persons) [8].

Studies of vaccine efficacy, effectiveness, and impact may use non-disease outcomes such as colonization as endpoints; however disease endpoints are more commonly used.

3. Observational methods to assess vaccine effectiveness and impact

Several observational epidemiologic methods are used to assess the impact of vaccination programs and the effectiveness of vaccines in routine use [4,5,9]. Examination of trends in disease incidence before and after vaccine introduction measures vaccination program impact. However this approach requires a stable, unchanged disease surveillance system before and after the introduction of vaccine. Interpretation of such studies can be challenging because of changes in measured disease incidence or the true disease incidence unrelated to vaccination. For example, changes in healthcare seeking behaviors can increase or decrease measured

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