Case-Control Studies to Assess the Effectiveness of Vaccines

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Received May 19, 2014; accepted May 26, 2014; electronically published June 30, 2014.

Before a vaccine is approved for general use, its protective efficacy must be demonstrated, usually in a double-blind, randomized clinical trial, the gold standard for scientific validity [1]. Randomization assures lack of bias in allocation of the exposure (vaccine), whereas blinding assures lack of bias in ascertainment of the outcome (infection). Nevertheless, there are a number of disadvantages, both practical and scientific, to randomized clinical trials to assess the efficacy of vaccines [2]. Because large samples and relatively prolonged follow-up may be necessary for adequate statistical power, these studies are extremely expensive. To limit costs, they often are conducted in select populations with an unusually high incidence of the infection of interest. These and other factors, such as the carefully controlled conditions of an experimental study, may lead to questions about the generalizability of the results of such trials to target populations that differ from that in which the trial was conducted. In addition, because clinical trials of experimental vaccines usually are conducted for only a relatively short period, the efficacy of the vaccine over time rarely is assessed.

Case-control studies, a type of nonexperimental study that may be subject to a number of potential biases, nonetheless may be very useful to answer questions about the efficacy of a vaccine in actual practice (also termed “effectiveness”) once it has been approved, including the vaccine’s effectiveness in subgroups of patients and its effectiveness over time [2, 3]. I will demonstrate that it is possible to incorporate strategies to minimize bias and to assess the potential effects of bias to help to assure the validity of case-control studies of the effectiveness of vaccines. Methods to minimize bias in case-control studies include prospective identification of a consecutive series of potential case subjects, random selection of controls from a list of potential controls, matching of controls to cases on potential confounders such as age and socioeconomic status, and use of statistical techniques, such as stratification or logistic regression, to adjust for differences in potential confounders between cases and controls. However, even with the use of such techniques, one cannot be sure that bias has not affected the results. Although it is not possible to allocate subjects randomly in observational studies (leading to uncertainty about the effects of unrecognized confounders), use of “sham” outcomes (which should not be affected by the exposure of interest) and of “sham” exposures (which should not affect the outcome of interest) provide an opportunity to assess whether bias might have affected the results of the study [6].

In a case-control study of the effectiveness of pneumococcal polysaccharide vaccine (PPV23), we showed that the vaccine was effective against infections caused by serotypes included in the vaccine; however, using identical methods to identify cases with invasive pneumococcal infections and matched controls without pneumococcal infections, the vaccine was not effective against infections caused by serotypes not in the vaccine (a sham outcome) [7]. If the difference between cases with infections due to serotypes in the vaccine and their matched controls in the odds of having received PPV23 were due to bias, one might expect to see a similar (erroneous) difference between cases infected by serotypes not in the vaccine and their matched controls. We also assessed the odds of having received influenza vaccine (a sham exposure), a vaccine that was also indicated for all subjects. Unlike for PPV23, there was no statistically significant difference in the odds of having received influenza vaccine between cases and matched controls, additional evidence that the apparent effectiveness of PPV23 was not a result of bias [7].

We also conducted a case-control study to assess the effectiveness of varicella vaccine over time [8, 9]. The efficacy
of this vaccine was never assessed in a randomized clinical trial in the target population (healthy children) in the United States. In this study, potential cases were identified by active, prospective surveillance of pediatric practices in southern Connecticut for patients who might have varicella (most were diagnosed over the telephone by their pediatricians). We obtained samples from the skin lesions of potential cases that were tested by polymerase chain reaction (PCR) assay for varicella-zoster virus (VZV). Controls were children without varicella, identified by computer logs and matched to the case by age and pediatric practice. We found that the vaccine’s overall effectiveness was 87%, although its effectiveness declined substantially from year 1 after vaccination (97%) to years 2–8 after vaccination (84%; P < .01). As would be expected, the vaccine was not effective against potential cases whose PCR assay for VZV was negative (in effect, a sham outcome), and there was no significant difference in the odds of immunization with measles-mumps-rubella vaccine (a sham exposure), a vaccine administered at about the same age as varicella vaccine. These findings support the validity of the original result.

To test the validity of the case-control method of assessing a vaccine’s effectiveness, a “sham” study was conducted [6]. A case-control study that demonstrated the effectiveness of *Haemophilus influenzae* type b (Hib) vaccines against invasive Hib infections was replicated using identical methods, except that the “case” subjects in the sham study were children with invasive infections due to *Streptococcus pneumoniae*, an infection that should not be affected by vaccines against Hib. If the apparent effectiveness of Hib vaccines were attributable to bias, then in the sham study it should erroneously appear that Hib vaccines were effective in preventing invasive pneumococcal infections. Using identical methods to identify cases and matched controls and to document prior immunization, we showed that Hib vaccines were not effective in preventing invasive pneumococcal infections, but they were effective in preventing invasive infections due to Hib, additional evidence that supports the validity of the case-control method of assessing a vaccine’s effectiveness [6].

Sham studies can also be useful for assessing the feasibility of conducting a future case-control study of the effectiveness of a vaccine and in assessing possible sources of bias. This strategy was demonstrated by a sham study to assess the possibility of conducting a case-control study of rotavirus vaccine after it is introduced in rural Kenya [10]. Case-control studies are a valuable tool to answer questions about the effectiveness of vaccines that cannot be addressed by a randomized clinical trial. When possible, sham outcomes or sham exposures should be incorporated into the design of observational studies to help to assess the validity of their results.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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