of these increases has been relatively small in comparison with the magnitude of decrease in IPD.

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**Pitfalls in Case-Control Studies of Vaccine Effectiveness**

To the Editor—Barricarte et al. [1] concluded that vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7) is associated with a 6-fold increased risk of invasive pneumococcal disease (IPD) caused by non-PCV7 serogroups. This conclusion contrasts with other studies that found little or no increased risk of non-PCV7-type IPD among healthy vaccinated children [2–6]. We believe that the analysis and inferences by Barricarte et al. [1] have 2 important limitations.

First, methodological biases and uncontrolled confounding may explain some of the study findings. In observational studies of vaccine effectiveness, the non-random allocation of vaccination introduces bias regarding who receives—and who is recorded to have received—vaccine. Vaccination status was collected from a Primary Care registry, but there is no statement about the completeness of vaccination among children with non–PCV7-type IPD derived from active, population-based surveillance among vaccinated and unvaccinated subjects. If case reporting and isolate submission improved over time, this should have been controlled for in the analysis (see p. 151 of the work by Rothman and Greenland [9]).

Second, the authors do not adequately guide the interpretation of the reported OR, which is only a relative measure of increased risk. For example, a 10-fold increase in an uncommon disease can represent substantially less in absolute case numbers than a 2-fold increase in a common disease. The authors’ discussion suggests that the 6-fold increased odds of vaccination among children with non–PCV7-type IPD provides information about the absolute rate increase in the population. However, documenting such an increase would require knowing rates of non–PCV7-type IPD derived from active, population-based surveillance among vaccinated and unvaccinated children. The authors’ conclusion that “the overall effectiveness of PCV7 for IPD prevention may be greatly reduced” [1, p. 1436] is therefore not supported by their data.

The preponderance of evidence shows that pneumococcal conjugate vaccines have overwhelming benefits for public health in various settings and with a range of vaccine coverage [2, 4–6, 10, 11]. Surveillance for pneumococcal disease caused by non-PCV7 serotypes, as the authors of this report have done, is critical for the monitoring of vaccine impact. As national immunization programs consider the use of pneumococcal conjugate vaccines, we urge readers to consider the full scope of
published observations and to use caution when interpreting findings inconsistent with other evidence.

Acknowledgments


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Reply to Bernaola et al. and Moore et al.

To the Editor—The points made by Bernaola et al. [1] are interesting and some that we also considered [2]. The 7-valent pneumococcal conjugate vaccine (PCV7) is dispensed in pharmacies in Navarre, Spain, but it is administered in primary health care centers. All doses administered are recorded in the patient’s computerized clinical history, which automatically updates the vaccination registry. The number of doses of PCV7 recorded represents 98.7% of the doses sold. The vaccination status was ascertained in a blind review of the registry. Any bias would be small and nondifferential—that is, toward the null effect.

Our study was individually matched, both in design and analysis. The failure to adjust for chronic diseases, socioeconomic class, breast-feeding, day care attendance, or exposure to tobacco smoke is a potential limitation [2]. There are 4 reasons showing that, in the case of our analysis, the lack of adjustment does not have an important effect on the conclusions. First, none of the case patients had a previous pathology for which PCV7 would be especially indicated. Second, we found both an important protective effect of PCV7 against vaccine and vaccine-related serotypes and an increased risk from nonvaccine serogroups. It seems highly unlikely that, with the use of the same design, confounding factors would explain a risk of invasive pneumococcal disease (IPD) from nonvaccine serogroups 6 times higher among vaccinated children without the reduction of the estimated effectiveness against vaccine serotypes. Third, to evaluate the possibility that the selection of controls could have given rise to confounding in one analysis but not in the other, we repeated the 2 analyses by comparing the case patients in each one with the pooled control subjects, and the conclusions were unchanged. Fourth, exposure to tobacco smoke, lack of breast-feeding, and low socioeconomic class have been related with a higher incidence of IPD and may be also associated with a lower probability of being vaccinated. Thus, this bias would overestimate the effectiveness of the vaccine.

We interpret the OR as a relative risk. Children who received at least 1 dose of vaccine had a 6-fold greater risk of IPD due to nonvaccine serogroups than did those who were not vaccinated, and complete vaccination was associated with a 13-fold higher risk of developing IPD caused by non-PCV7 serogroups.

The results are consistent with those of the active population-based surveillance of IPD in children aged <5 years. In the same period, the incidence of IPD from vaccine serotypes decreased by 69%, the incidence of cases from non-PCV7 serotypes showed a nonstatistically significant increase of 36%, and the overall incidence of IPD showed a nonsignificant decrease of only 12% [3].

We agree with Moore et al. [4] that our results [2] are somewhat different from those of other published studies. The effectiveness of PCV7 depends greatly on local factors; therefore, the discrepancy with what has been found in other places is not an argument against the validity of our results.

In 2000, before the licensure of PCV7, an active population-based surveillance of IPD was initiated in Navarre. All pneu-