Haber et al. (1) have made a careful and detailed study of the effects of disease prior to an outbreak on estimates of vaccine efficacy following the outbreak. Their calculations are based on the assumption that the vaccine affords "all or nothing" protection, that is, that a proportion of vaccinees are wholly protected against infection while the remainder are totally unprotected. One issue of considerable practical importance in estimating vaccine efficacy in outbreak investigations is whether to include or exclude individuals infected prior to the attack rate denominators. The authors review various options and conclude that, under most circumstances, including prior cases in the denominators will not produce serious bias.

However, previous work (2) has shown that, while this is indeed correct for "all or nothing" vaccines, it is not so for other types of vaccines. In particular, for so-called "leaky" vaccines in which the effect of vaccination is to reduce disease incidence in all vaccinees, without giving complete protection to any, considerable bias may occur resulting in low or even negative vaccine efficacies in outbreaks or long-term follow-up studies of age-specific efficacy.

For example, consider a secondary school outbreak of pertussis in 15-year-old students. Suppose, for simplicity, that vaccination took place close to birth, that the average age of pertussis prior to the outbreak was 10 percent, and that the vaccine efficacy is 80 percent, reducing the annual incidence to 2 percent. By the age of 15 years, 22.3 percent (100 exp(-0.1 X 15)) of those unvaccinated are susceptible, compared with 74.1 percent (100 exp(-0.2 X 0.1 X 15)) of those vaccinated. The vaccine efficacy during the outbreak (which is the age-specific efficacy at the age of 15 years) calculated by including prior cases in the attack rate denominators is then 34 percent (100 X (1 - (0.2 X 0.741)/0.223)), rather than 80 percent. If the average annual incidence in the 0- to 15-year age group had been 15 percent, the observed efficacy during the outbreak would have been negative: -21 percent.

This simple example demonstrates the considerable effect of the vaccine mechanism on vaccine efficacy estimates derived in outbreaks, especially those occurring many years after vaccination when there has been ample opportunity for natural exposure to infection. In practice, reliable knowledge of prior infections is rarely available, so that it is not possible to exclude prior cases from attack rate denominators. In these circumstances, in the absence of detailed knowledge about vaccine mechanisms, low vaccine efficacies obtained in outbreak investigations should not hastily be ascribed to low or declining vaccine effectiveness.

REFERENCES
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