

LETTERS

VACCINATION AND RISK OF ALLERGIC DISEASE

In "Vaccination and Allergic Disease: A Birth Cohort Study," McKeever et al. reported strong crude and adjusted associations of vaccinations with asthma and eczema.¹ After stratifying on frequency of general practitioner (GP) visits, however, and finding that the strong associations were mostly confined to the lowest-frequency stratum, they concluded that ascertainment bias explains the associations in the total population. On the basis of their data and other studies, including ours,² they write, "current vaccination practices do not have an adverse effect on the incidence of allergic disease." However, a conclusion equally consistent with the evidence is that vaccinations may have adverse effects in at least some children.

First, the authors' interpretation of their stratified results may be misleading. Stratifying on a predictor of ascertainment does not always reduce ascertainment (misclassification) bias,³ and misclassification of both outcomes would have to be severely differential by vaccination status in the lowest GP-visit stratum to be consistent with their interpretation. Furthermore, the association between GP visits and outcome events may also reflect the effect of the latter on the former, which

means stratifying on visit frequency would increase bias if GP consultation is also associated with vaccination status. If visit frequency is affected by the outcome events, as expected, and assuming no confounding or other bias, then the crude associations are the best effect estimates.⁴ Moreover, consulting frequency may reflect true modifiers of the vaccination effects, rather than being only markers of ascertainment. Because of the imprecise estimation of effects within strata, the results are also consistent with vaccination effects in children with more frequent GP visits.

Regarding our study,² McKeever et al. state, "in general [Hurwitz and Morgenstern] found no association between vaccination and allergic disease." In fact, we detected associations between vaccination and allergy symptoms (adjusted odds ratio [OR]=1.63; 95% confidence interval [CI]=1.05, 2.54) and history (OR=1.69; 95% CI=1.10, 2.59), and we could not rule out effects on physician-diagnosed asthma. In its review of immunizations and immune dysfunction, the Institute of Medicine correctly reported that our findings favor an effect of diphtheria and tetanus toxoids and pertussis (DTP) or tetanus vaccination on clinical history of allergic disorder and cited inadequate literature to accept or reject a causal relation between immunizations and asthma.⁵

Addressing the possible causal role of vaccinations in subsequent allergic disease is difficult. Ethical issues preclude long-term randomized placebo-controlled trials, and estimates from observational studies are fraught with potential biases and alternative explanations. The current evidence, however, suggests that vaccinations may or may not increase the risk of allergic diseases. To conclude otherwise is misleading. ■

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doi: 10.2105/AJPH.2004.050583

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MCKEEVER ET AL. RESPOND

We thank Hurwitz and Morgenstern for their interest in our recent work in what has become a controversial area of research with a number of interesting methodological problems.

The authors' first point is that misclassification of both asthma and eczema status would have to be severely differential by vaccination status to produce the results we reported. In fact, our data demonstrate that this is likely to be the case, since the incidence of asthma among children not vaccinated with diphtheria, polio, pertussis, and tetanus (DPPT) vaccine in the lowest general practitioner (GP)-visit stratum was 0.3 per 100 person-years, which is very low and out of keeping with the other data. A similar pattern for rate of disease has been demonstrated for measles-mumps-rubella (MMR) vaccine, as well as for eczema and vaccination status, and we believe the most likely explanation is a marked underdiagnosis of allergic disease in children who do not regularly visit their GPs. In other words, children who do not visit their GPs are the

ones who are not vaccinated and are not being diagnosed with other diseases.

We agree with Hurwitz and Morgenstern's second point, that being diagnosed with an allergic disease might have increased an individual's frequency of GP visits and biased our results. For this reason, we excluded any visits for allergic disease when determining the level of GP visits. In addition, only GP consultations before diagnosis of allergic disease were counted. It seems unlikely to us that frequency of GP consultation reflects a true biological modifier of the vaccination effect; it seems far more likely that the difference in effect by level of health care use is due to bias.

In their own study, Hurwitz and Morgenstern found a significant impact of vaccination on allergy symptoms and history.¹ However, they found no evidence of an association between vaccination status and asthma, hay fever, severe allergic reaction, any allergy or allergic reaction, sinusitis or sinus problems, or wheezing or whistling. These findings are consistent with the conclusion of the Institute of Medicine review (cited by Hurwitz and Morgenstern) that the evidence for a link between vaccination and allergic disease is at best weak.² Furthermore, this review did not include an ecological study,³ a case-control study,⁴ and a longitudinal study,⁵ all of which failed to demonstrate a relationship between vaccination and allergic disease.

In summary, we believe the most likely explanation for our finding is that routine vaccination against DPPT and MMR does not increase the incidence of allergic disease, and this conclusion is consistent with the bulk of the available evidence. ■

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doi: 10.2105/AJPH.2004.050997

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