EDITORIAL

Nonspecific Effects of Vaccines

David Goldblatt, MBChB, PhD; Elizabeth Miller, FRCPath

Vaccination is one of the great public health achievements of the last 100 years.[1] The development of vaccination has led to the eradication of smallpox, the reduction of the worldwide incidence of polio by 99%, and the control of measles, with a 74% decline in global measles deaths since 2000.[2]

With the decline in vaccine-preventable diseases that were once major causes of morbidity and mortality and with the availability of many new vaccines, some targeting diseases that are not major causes of morbidity and mortality in developed countries, public opinion has at times focused on the possible adverse events associated with vaccination rather than their benefit. In recent years these have included high-profile concerns surrounding the association of autism with either combined live viral vaccines (measles-mumps-rubella [MMR]) or preservatives (thimerosal) in combination vaccines. Both associations have now been refuted following careful scientific studies.[3] Unexpected benefits of vaccination have also been reported but have attracted less attention. These include the apparent effect of live vaccines such as measles and BCG on reducing mortality from infections other than measles or tuberculosis.[4]

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Much of the evidence for nonspecific effects of vaccines comes from the group headed by Peter Aaby and relates to developing-country settings. In this issue of *JAMA*, the question is examined in a high-income country (Denmark), using hospital admissions for any infection as an outcome. In an observational study, Sørup and colleagues[5] tested the hypothesis that the incidence of infectious disease admissions in the second year of life differs according to whether a live vaccine (MMR) or an inactivated vaccine containing diphtheria, tetanus, pertussis, polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib) was the most recent vaccine received. The recommended schedule in Denmark during the study period was DTaP-IPV-Hib given at 3, 5, and 12 months, followed by MMR at 15 months. The majority of children in the study cohort (456 043) received the vaccines in the recommended order, but in approximately 4% (19 219), MMR was given after the second dose of DTaP-IPV-Hib and the third dose either not given or delayed until after the MMR had been given (the reversed-schedule cohort). In the recommended-schedule cohort, the rate of admissions for any infection was 8.9 per 100 person-years in children receiving MMR most recently vs 12.4 per 100 person-years in children receiving DTaP-IPV-Hib most recently, for an adjusted incidence rate ratio of 0.86 (95% CI, 0.84-0.88). The potential for bias was recognized, so analyses were conducted using available information on potential confounding variables, which had little effect on the results—the apparent reduced risk associated with MMR remained, whether MMR was given after the second or third DTaP-IPV-Hib dose.

A concern with such observational studies is that they are inevitably subject to various sources of bias and confounding, and past experience indicates the need for caution when interpreting apparent nonspecific protective effects of vaccines.[6] Black et al[7] found an association between both MMR and diphtheria-tetanus-pertussis (DTP) vaccines and reduced risk of subsequent invasive bacterial infection after adjustment for available covariates such as socioeconomic status, race, and day care attendance. However, additional analyses adjusting for well-care visits abolished the apparent protective relationship. Hviid et al,[8] using the same Danish data source as Sørup et al with adjustment for similar covariates but over a slightly different period, also found an apparent association between childhood vaccination and reduced risk of a variety of viral and bacterial infections. However, unlike in the current study, these were for both MMR and DTP vaccines.

Although the potential for residual confounding in such observational studies cannot be excluded, apparent protective associations between MMR and risk of admission for bacterial and viral infections have also been found using the self-controlled case series method, which automatically adjusts for individual-level confounding.[9,10] Such studies were designed to test the hypothesis that MMR or other combination vaccines might increase the risk of infection based on the "immune overload" hypothesis and the reported protective associations received little attention. The new Danish findings relate specifically to the vaccine sequence and assessed whether the differential outcomes for the association between inactivated vaccines and infectious disease admissions reported in observational studies in developing countries could be seen in a developed country. Additional studies in similar high-income settings are needed to confirm the findings before the association is accepted as causal and, to avoid publication bias, it is important that studies with both positive and negative findings are submitted for publication.

No prospective studies designed to explore the immunological mechanisms underlying the apparent reduction in infection syndromes not targeted by the administered vaccine have been published. Theoretical possibilities include the mediation of the apparent effect by antibodies, T cells, or innate immunity. Antibody responses after vaccination are in general highly specific for the immunizing antigens. Nonspecific antibody responses, as a result of polyclonal stimulation, have been suggested as a mechanism for maintaining serological memory[11] and could theoretically lead to nonspecific protec-

tive effects. However, few studies designed to identify such antibodies have been positive.[12] Heterologous T-cell immunity could provide a mechanism whereby vaccines protect against infections that are not targeted by the vaccine. Naturally occurring cross-reactive $CD8^+$ T cells in humans recognizing 2 dissimilar HLA-A2-presented influenza A- and Epstein Barr virus-derived antigens illustrate the theoretical possibility that this may occur after immunization.[13] Although innate immunity was considered not critical for antigen-specific immunity and to lack the capacity for immune memory, recent evidence is emerging of the innate immune system displaying memory as a result of earlier infection or vaccination. This phenomenon is likely mediated by cytokines such as IL-17,[14] natural killer cells, or both.[15]

The possible implications of any such nonspecific vaccine effects for the infant immunization schedule remain unclear. If such effects are documented with robust evidence, the infant immunization schedule might need to be adjusted, because minor modifications to the routine immunization schedule could further reduce childhood mortality.[4] However, vaccine schedules have evolved over time to provide optimal safety and direct protection from the vaccines administered and to ensure compatibility with other vaccines in the schedule. Changes to schedules should only follow careful evaluation in well-designed studies, preferably in both high- and low-morbidity settings and with careful attention to confounding variables.

To this end, the WHO Strategic Advisory Group of Experts recently decided to revisit the issue of nonspecific effects of vaccines as part of its continued appraisal of important issues that could be relevant to inform global immunization policy. Systematic reviews of all available epidemiologic and immunologic evidence relevant to the issue of the nonspecific effects of vaccines on childhood mortality will be undertaken to decide whether current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation.[16] The study by Sørup et al is a further contribution to this body of literature. Although reanalysis of the available evidence is important, the ability to properly control for bias and confounding in observational studies is often limited, and without randomized controlled trials specifically designed to test the hypothesis, the issue of nonspecific effects of vaccines may remain subject to continuing debate.

ARTICLE INFORMATION

Author Affiliations: Immunobiology Unit, UCL Institute of Child Health and Great Ormond Street Children's Hospital, London, United Kingdom (Goldblatt); Immunisation, Hepatitis and Blood Safety Department, Public Health England, Colindale, London, United Kingdom (Miller).

Corresponding Author: David Goldblatt, MBChB, PhD, Immunobiology Unit, UCL Institute of Child Health and Great Ormond Street Children's Hospital, 30 Guilford St, London WC1N 1EH, United Kingdom (d.goldblatt@ucl.ac.uk).

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