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The Enigma of Alternative Childhood Immunization Schedules

What Are the Questions?

ALTERNATIVE CHILDHOOD IMMUNIZATION schedules have emerged as a distinct phenomenon in response to parental concerns about the safety of the US immunization schedule and its component vaccines. Some alternative schedules have been put in writing,[1] many more are ad hoc, and all endorse a spacing out, a delaying, or a forgoing of at least some vaccines (which is contrary to what is jointly recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians). None of these alternative schedules have been tested for their safety and efficacy.

See also page 274

Evaluating alternative schedules, however, is not easy. The first challenge is to determine the questions of interest. Two seem to be paramount: (1) What is the risk of acquiring vaccine-preventable disease for children on alternative schedules compared with children on the recommended schedule? (2) How do the risks of early- or late-onset vaccine-related adverse events for children on alternative schedules compare with those for children on the recommended schedule? Arguably, the dominant issue is whether any alternative schedule adequately protects a child—and thereby the child's community—from each of the vaccine-preventable diseases, so it therefore seems essential to answer the first question first. Only after it is proven that an alternative schedule does not substantially increase the risk of an individual acquiring a vaccine-preventable disease does it seem reasonable to study that schedule's safety profile.

Beyond determining the research question, formidable methodological challenges await.[2] First, at a minimum, alternative schedules must be precisely defined, the specific intervals and timing of vaccines within these schedules clearly identified, and children correctly classified as actually being on an alternative schedule. Second, the lack of one dominant type of alternative schedule imposes its own constraints on the ability to study them, and grouping several schedules together can be problematic. For instance, to justify a randomized con-

trolled trial comparing the recommended schedule for childhood immunization with any alternative immunization schedule, there must be an apparent balance of risks and benefits (ie, equipoise) between the two. This assessment is both difficult to make if the comparison group includes different types of alternative schedules and is, at best, controversial enough such that other study designs are likely to be employed. Third, to detect rare events associated with alternative schedules, such as some disease outcomes or vaccine-related adverse effects, the use of a large, integrated immunization database like the Vaccine Safety Datalink is required. In this issue of the journal, Glanz et al[3] illustrate the Herculean effort required to overcome some of these challenges.

The study by Glanz et al[3] also begs the fundamental question that has implications for immunization policy. What does it mean to simply consider a research agenda on immunization schedules that deviate from the recommended one? Doing so involves a willingness to scrutinize something sacred in pediatric preventive care and public health. This requires both caution and courage. Inevitably, just raising the question will provoke discussions—between doctors and parents, policy makers and the public—about the value and timing of each dose in the current recommended schedule. The current schedule will be deconstructed, and any of it that appears mysterious will result in further inquiry. For instance, what accounts for the variation in childhood vaccine schedules between countries? In the first year of a child's life, why is the diphtheria and tetanus toxoids and acellular pertussis vaccine recommended in Sweden at the ages of 3, 5, and 12 months, in the United Kingdom at the ages of 2, 3, and 4 months, and in the United States at the ages of 2, 4, and 6 months? How much of this variation in spacing of vaccines is rooted in tradition—borne out by experience—rather than differences in vaccine formulations and disease incidence?

There is also the question of utility: given the methodological limitations and hurdles to studying alternative schedules and the fact that only a minority of parents use them, is the juice worth the squeeze? There may well be more important uses of limited research and public heath resources. The Institute of Medicine Committee on Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule is conducting an independent assessment of the feasibility of studying health outcomes in children who were vaccinated according to the recommended schedule and those who were not. It is anticipated that the committee's report will be available soon.

Prudence demands that attention be paid to avoiding unintended consequences similar to those that stemmed from the 1999 decision to remove thimerosal from infant vaccines.[4] Although this action was taken as a precaution and to maintain public confidence in the safety of infant immunization, it escalated concerns about vaccine safety and nurtured discontent regarding immunization.[5] It would be disastrous to have the consideration of a research agenda on the immunization schedule reinforce the perverse perception that the recommended schedule is not safe.

History is filled with examples in which the field of medicine was reluctant to entertain alternative scientific hypotheses. Sometimes it was right to remain reluctant (eg, autistic enterocolitis), and sometimes it was not (eg, miasmas as the cause of cholera). The study by Glanz et al[3] pushes us closer to a point where reluctance may no longer be tolerable. Parents and clinicians seek guidance, and there is no better guidance than high-quality scientific evidence. It behooves immunization scientists and policy makers to continue this pursuit, deliberately but decidedly. Defining the questions of greatest importance would be a good start.

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