

# Vaccine Epidemiology: Efficacy, Effectiveness, and the Translational Research Roadmap

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(See the article by Curns et al, on pages 1617–1624.)

Despite the rather short history of vaccination, compared with the millennia of various human plagues and pestilences, more than a dozen major infectious diseases (most notably, smallpox, poliomyelitis, rabies, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b disease, measles, mumps, and rubella) have been controlled in many parts of the world [1]. The recently licensed rotavirus vaccines show great promise in this new century for controlling an infection which leads to 25,000–50,000 hospitalizations, nearly 400,000 emergency room visits, and 400,000 medical care visits of children in the United States annually, while at the same time leading to nearly 600,000 deaths worldwide [2–5].

As each new vaccine is considered for licensure, the most basic of questions is perhaps the most complex to answer: “How well does the candidate vaccine prevent the disease for which it was devel-

oped?” In this issue of *the Journal*, Curns et al [6] estimate that pentavalent rotavirus vaccine use has decreased hospitalization rates for acute gastroenteritis among children in the United States aged <5 years by 45%, including those who were either too young or too old to be eligible for vaccination. A monovalent rotavirus vaccine is also licensed for use in the United States [2, 3] but was not available during the study period.

The Curns et al [6] study is timely and important and also highlights the distinction between the epidemiologic concepts of vaccine efficacy and vaccine effectiveness [7–12]. These often confused terms fit well into the new paradigm of translational research discussed below.

The mathematical deduction of protective vaccine efficacy is nearly 100 years old, having been proposed by Greenwood and Yule in 1915 for inactivated whole cell cholera and typhoid vaccines [13]. Vaccine efficacy is best measured by double-blind, randomized, clinical controlled trials, such as those performed for both the pentavalent and monovalent rotavirus vaccines [14, 15]. Such vaccine efficacy trials represent the “best case scenarios” of vaccine protectiveness under controlled conditions and are commonly required before a new vaccine is licensed by the Food and Drug Administration and other global regulatory authorities [7]. The outcome data (vaccine efficacy) generally are expressed

as a proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV) study cohorts and can be calculated from the relative risk (RR) of disease among the vaccinated group with use of the following formulas [7, 9, 12]:

$$\text{Efficacy} = \frac{\text{ARU} - \text{ARV}}{\text{ARU}} \times 100$$

and

$$\text{Efficacy} = (1 - \text{RR}) \times 100 .$$

The advantages of a vaccine efficacy study include rigorous control for biases afforded by randomization, as well as prospective, active monitoring for disease attack rates and careful tracking of vaccination status; often there is, at least for a subset of the study population, laboratory confirmation of the infectious outcome of interest and a sampling of vaccine immunogenicity. The major disadvantages of vaccine efficacy trials are the complexity and expense of performing them, especially for relatively uncommon infectious outcomes for which the sample size required is driven upwards to achieve clinically useful statistical power.

Vaccine efficacy studies can measure outcomes beyond disease attack rates, including hospitalizations, medical visits, and costs. The external validity of the results of a vaccine efficacy study to a larger,

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nonstudy population may be lowered by differences between the study cohort and the population as a whole. For example, a rotavirus vaccine might be efficacious in a study population restricted to certain inclusion and exclusion criteria but might be less effective in a population at large which is different in critical ways from the study cohort.

Vaccine effectiveness is often confused with vaccine efficacy (in fact, one former designation for it was “field efficacy”) but should be viewed as a distinctly different, although related, concept [7–12]. Essentially, vaccine effectiveness is a “real world” view of how a vaccine (which may have already proven to have high vaccine efficacy) reduces disease in a population. This measure can assess the net balance of benefits and adverse effects of a vaccination program, not just the vaccine itself, under more natural field conditions rather than in a controlled clinical trial. Vaccine effectiveness is proportional to vaccine potency (ie, vaccine efficacy) but is also affected by how well target groups in the population are immunized (which itself may reflect difficulties in maintaining proper storage conditions of a vaccine, such as the cold chain, access to health care, and vaccine cost), as well as by other nonvaccine-related factors that influence the real-world outcomes of hospitalizations, ambulatory visits, or costs.

Several study designs may be used to measure vaccine effectiveness [7–9, 11, 12]. Perhaps the most familiar is the ret-

rospective case control analysis, in which the rates of vaccination among a set of infected cases and appropriate controls are compared [8, 9, 12]. The outcome data (vaccine effectiveness) are expressed as a rate difference, with use of the odds ratio (OR) for developing infection despite vaccination:

$$\text{Effectiveness} = (1 - \text{OR}) \times 100 .$$

A less well-known type of study design to measure vaccine effectiveness is the “indirect cohort” or “quasi-cohort” study, in which different responses in the same vaccinated population are examined [8]. For example, an analysis of the vaccine effectiveness of pneumococcal polysaccharide vaccine examined all invasive pneumococcal disease in a population cohort and compared the rates of vaccine-serotype infection and nonvaccine-serotype infection (assuming that no protection against nonvaccine serotypes was afforded by vaccination), providing an indirect estimate of vaccine effectiveness [16]. Another uncommon type of vaccine effectiveness study is the “case-coverage” or “case-cohort” method, in which vaccination rates among cases are compared with those in a similar cohort (which may include individuals who develop cases) over a defined period of time [9, 11, 17]. The fourth type of vaccine effectiveness study, used by Curns et al [6] to assess the impact of rotavirus vaccine, is ecologic or observational in nature, examining changes in dis-

ease burden over time (eg, before and after introduction of routine vaccination) [7]. This common type of study may use laboratory-based diagnostics or large-scale databases containing billing codes or *International Classification of Diseases, 9th Edition, Clinical Modification* (ICD-9-CM) discharge codes.

The “real world” view afforded by vaccine effectiveness data is desirable in planning public health initiatives, an advantage (along with a simpler and less costly study design) that makes these studies attractive. However, many biases (some of which are difficult to detect) can affect vaccine effectiveness studies, such as differential case ascertainment in vaccinated and unvaccinated groups, differences in susceptibility or exposure of some groups in the population to infection, differences in health care utilization (unrelated to vaccination) between vaccinated and unvaccinated populations, undetected loss to follow-up from migration, and assumptions made during statistical analysis. Thus, vaccine effectiveness studies have the benefit of using real-world outcomes but also possess challenges in distinguishing vaccine-related effects from other potential confounders that may affect the same outcomes.

Recently, experts have lamented the slow translation of knowledge from scientific discovery to the improvement of public health and have described translational research as a 2-step process (termed T1 and T2 research), to speed

**Table 1. Pentavalent Rotavirus Vaccine Development as an Example of Pediatric Translational Research**

Selected studies	Design	Research nomenclature		
		Clinical trial phase	IOM translational definition	Expanded translational definition
[28, 29]	Product discovery	Basic science, preclinical	T1	T1
[14, 30]	Safety	I	T1	T1
[14, 30]	Immunogenicity	II	T1	T1
[14, 30]	Efficacy	III	T2	T2
[6, 23, 24, 26, 27]	Effectiveness	IV	T2	T3
[4, 31–35]	Disease burden, population outcome, policy impact, cost-benefit, cost-effectiveness	...	T2	T4

**NOTE.** IOM, Institute of Medicine.

the application of basic knowledge to public health practice [18, 19]. This re-engineering of the clinical research enterprise comprises a large part of the National Institutes of Health Roadmap for future research [20]. A newer definition of translational research proposes 4 steps, which fit nicely together within the continuum of vaccine research [21].

Table 1 compares these 3 paradigms of research—the classical phases of vaccine and drug testing, the recent Institute of Medicine definition of translational research (T1-T2 model), and the newer expanded definition of translational research (T1-T4 model)—with use of rotavirus vaccine research as a template. In the classic Phase I through Phase IV clinical trials, safety, immunogenicity, efficacy, and post-licensure effectiveness of a rotavirus vaccine are assessed, respectively. In the Institute of Medicine translational definition, T1 research includes safety and immunogenicity trials. In the expanded translational definition, T4 studies first demonstrate the burden of rotavirus disease. Basic science research then develops a rotavirus vaccine, and T1 research trials (Phase I-II) evaluate vaccine safety and immunogenicity. T2 efficacy research measures vaccine efficacy of the rotavirus vaccine in controlled prelicensure clinical trials, and T3 research uses a method such as a case-control design to measure post-licensure vaccine effectiveness. Finally, T4 research, such as the Curns et al study [6], may assess the overall population-wide burden of acute gastroenteritis, attempting to distinguish the impact of rotavirus vaccine from the underlying burden of hospitalizations or other outcomes.

Because of the challenge of T3 and T4 translational studies, multiple sources of data and numerous studies are generally needed to establish vaccine effectiveness and population-wide disease burden reduction attributable to a vaccine. In this case, a strength of the Curns et al study design is the population coverage of nearly 50% of children in the United States; however, weaknesses include the absence of

direct data on individual virologic diagnosis and vaccination status, as well as possible case ascertainment bias of relevant hospitalizations classified as “short-stay observation” not being included in certain ICD-9-CM discharge code databases [22]. Population-based, laboratory-confirmed, case-control studies should allow a more precise definition of the contribution of decreasing rotavirus gastroenteritis to all-cause gastroenteritis [4].

The work of Curns et al [6] adds a powerful piece to the multifaceted answer to the question, Does rotavirus vaccine protect against rotavirus infection in the United States population at large? Recent laboratory [23–25] and insurance claim database [26] studies, and a single-city, 1-season case-control study [27] support Curns et al’s [6] affirmative answer and attest to the power of T1–T4 translational research as it applies to childhood vaccines.

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