Methods in vaccine effectiveness and safety studies: A critical need for vaccine confidence

As currently designed, vaccines have as their goal the conversion of a generally healthy but susceptible host, into a host protected against a disease (for which the vaccine is being administered) to which the host may be exposed to at a future date. To this end, a high bar for effectiveness, efficacy, and safety of vaccines is appropriate. Interest in efficacy and safety is not confined to scientists and health care providers, but also to the general public. Indeed, absent data demonstrating both safety and efficacy, such vaccines will neither be recommended by physicians, nor utilized by the public. Measuring safety and effectiveness is not, however, inherently straightforward. Done correctly, increased confidence and widespread adoption of a vaccine may ensue. Done poorly, or incorrectly, years of misperceptions and “active disuse” of a vaccine may result. Recent examples include vaccine safety fears and controversies regarding the possible occurrence of Guillain–Barre syndrome after pandemic influenza vaccine, or fears about autism spectrum disorders among intended recipients of MMR vaccines. These controversies started with anecdotal observations, and proceeded to various types of study designs often of low or misleading quality. Because the science of methods in vaccine safety and effectiveness continues to evolve, “gold standard” study design and methods have not yet been widely disseminated and put into place by scientific journals and routinely utilized by journal editors and reviewers. Worse, the print and broadcast media often misinterpret or wrongly report such observations, decreasing public confidence in vaccines. As a result, confusion ensues and poorly designed studies are published that add to the fears and confusion about a vaccine’s safety or efficacy. Indeed, recent papers and commentaries on the “new decade of vaccines” have emphasized the importance of vaccine confidence, and the scientific and social challenges we face in developing and utilizing new vaccines [1,2]. Sound study design methods for vaccine safety and effectiveness are essential to physician and public confidence in vaccines.

As a remedy for this situation, we are excited to announce a new section for VACCINE entitled, “Methods in Vaccine Effectiveness and Safety Studies.” In recent years, a confluence of circumstances has led to a proliferation of observational vaccine safety and effectiveness studies. These include the widespread adoption of electronic health records, increased interest among investigators in following large cohorts for epidemiologic studies on the influences of vaccination on health, and many large vaccine safety initiatives in the U.S. These include such representative initiatives as the Vaccine Adverse Event Reporting System (VAERS) [3], Vaccine Safety Datalink (VSD) [4], Post-licensure Rapid Immunization Safety Monitoring (PRISM), and the mini-sentinel/sentinel initiative [5] sponsored by the U.S. Food and Drug Administration.

These initiatives provide new opportunities and challenges for studies of vaccine safety, effectiveness, and efficacy. For example, the availability of electronic health records provides for the near real-time passive surveillance of adverse events that come to medical attention [6]. Moreover, the large sample sizes, often obtained through distributed data networks, present the opportunity to address safety and effectiveness in ways barely imaginable 20 years ago. These capabilities, however, also present challenges since traditional epidemiologic methods may not be capable of fully exploiting the potential of these data.

Indeed, we are seeing new methodologic developments in a variety of settings to address these challenges. For example, new study designs such as a case-centered approach are being proposed and tested [7]. The multiple testing problems due to the increased chance of making a type-1 error inherent to sequential looks for adverse events following vaccination are challenging as well. To this end, new analytic strategies are being utilized [8,9]. The reliance upon passive surveillance through administrative data and electronic health records raises questions about the validity of coding, necessitating new efforts to investigate their completeness and accuracy [10,11]. And as signals are observed, new questions arise about how best to use information generated from these studies.

While these developments are rapidly expanding, much of the developing literature in this regard is not readily accessible to vaccinologists. Analytic method papers tend to be published in statistical journals, often buried among theoretical papers and filled with technical jargon and mathematical formulas. Design method papers may be published in epidemiology journals, hidden among papers of very diverse diseases and outcomes. In all, the application to vaccinology may not be highlighted or readily accessible. Thus, such papers could potentially miss the very audience that most needs the information for designing appropriate vaccine safety and efficacy studies and interpreting their results.

In this new proposed section, we hope to publish 1–2 articles per month, as full or brief reports, or even as reviews. These papers should be written for the general vaccine audience, making their content accessible to methodologists and non-methodologists alike. In some cases, we will include an accompanying invited editorial comment about the significance of new methods and designs for vaccinology development.

We believe our readers will find this information useful, both as they design their own studies and interpret the findings of others. Further, we hope that as new study designs and methods mature,
gold standards will develop that elevate the science and make data that supports or rejects the safety and effectiveness of a given vaccine more understandable. As always, we solicit your opinion and advice as we embark on the launch of this new section.

References


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