Global Vaccine Safety Assessment

Challenges and Opportunities

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The Need for Vaccine Safety Research and Programs

Childhood mortality has decreased substantially in the last 25 years.[1] For example, the global under-five mortality rate has decreased from 90 to 56 deaths per 1000 live births.[2] This includes a 99% reduction in incidence rates of devastating, yet vaccine preventable diseases, in countries with established immunization programs. Thus, vaccination remains an important public health tool for the prevention of suffering, disability and death in children.[3] Moreover, although most drugs are given to a relatively small number of children with disease, vaccines are administered to almost all and usually healthy children. This underscores the ethical dimension of global immunization programs and the importance of appropriate benefit–risk research and monitoring to support immunization as a population-based public health intervention.

Vaccine benefit–risk research attempts to balance the desirable effects (benefits) and undesirable effects (risks) of vaccines. However, balancing benefits with risks is complex. It includes weighing the suspected risks associated with *acquiring* immunity by wild-type infection against giving a vaccine and therefore *inducing* immunity. The harm or risk of the vaccine itself (eg, because of product characteristics) or by the mode of dissemination and administration (eg, programmatic errors) is generally inferred from the presence of adverse events following immunization (AEFI). AEFI are defined by the Council for International Organizations of Medical Sciences and the World Health Organization (WHO) as "any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of a vaccine."[4] This definition highlights that the establishment of a causal association between a vaccine and an AEFI requires more than their temporal association. In addition, to determine true or perceived risks, understanding the potential pathophysiological mechanisms of vaccine adverse events is necessary.

Whether risk is real or perceived, public confidence is increasingly important to maintain the sustainability of immunization programs, especially in a world of growing rapid global information sharing. Therefore, maintaining public confidence has to be based on readily available, harmonized and high-quality data on the epidemiology and burden of both vaccine preventable diseases and adverse events. To address these issues, partners of the Brighton Collaboration Network have developed and are developing standardized case definitions, harmonized study methods and protocols, common data models, shared tools and infrastructures for data management and analyses, innovative methods for public and social media monitoring, harmonized approaches to clinical management of AEFI and networks and training materials for knowledge transfer and capacity building.[5]

The Framework of Vaccine Safety Research

The basic pillars of vaccine safety research and monitoring are signal detection, signal verification, hypothesis testing and causality assessment. The overall safety profile of a vaccine reflects the safety knowledge throughout its life cycle from preclinical investigations through postapproval. A safety signal has been defined by the WHO as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."[6] Signal detection during prelicensure occurs in clinical trials, whereas postapproval signals primarily arise by the public or social media or are detected by a spontaneous reporting system. Signal verification is typically based on the rapid epidemiological studies comparing the observed rates of AEFI with expected background incidence rates of the event and other sensitivity analyses around these measures. Hypothesis testing is based on more sophisticated and usually large epidemiological studies aimed at quantifying measures of

relative and attributable risk by optimizing control for bias and confounding. Finally, causality assessment rests on studies investigating the pathophysiological and immunological mechanisms.

The Challenges of Vaccine Safety Research

Risk Identification and Response

Key challenges in vaccine safety monitoring begin first with the identification of risks. The risks need to be detected, and most countries rely on passive pharmacovigilance by spontaneous reporting of healthcare providers. However, WHO estimates that only 35% of 192 countries had an adequately functioning system for monitoring AEFI in 2012. Although the value of spontaneous reporting systems is evident, the quality of available data is limited because of incomplete reports and underreporting, even in established immunization programs.[7] Improving national signal detection capacity without the ability to adequately respond to signals can potentially jeopardize immunization programs. Therefore, it is particularly important to build capacity for rapid signal verification, hypotheses testing and effective communication in low- and middle-income countries where new vaccines (eg, against malaria) will increasingly be investigated and introduced into national programs before they get introduced in high-income countries.

Methodological Considerations

Typically, pharmacoepidemiological assessments of risk focus on the assessment of probability. Regardless of the risk estimate, the methods are not designed to infer a causal association as, for example, laid out by Hill[8] and Rothman.[9] Results from observational studies (eg, case control, cohort, self-controlled case series), however, may yield high-quality estimates of risk when carefully addressing the statistical conditions as described by Cox and Hinkley.[10] Quantifying residual bias and confounding is a key methodologically challenge. Determining acceptable risk and quantifying benefit–risk ratios as a dynamic measure changing over time is another key challenge. Thus, adequate design and implementation of vaccine safety studies require highly specialized pharmacoepidemiological knowledge, experience and approaches.

Resource Limitations

Comprehensive vaccine safety monitoring requires a series of technical and resource conditions, well-characterized data sources and analytic capacity. However, the availability of these components in many countries is limited. For instance, serious adverse events are rare, and therefore, large sample sizes are needed to demonstrate a significantly increased risk. Phase III clinical trials typically include 5000–10,000 subjects and may include up to 60,000 subjects, but study populations of 50 to >100 million subjects may be required to quantify risk of rare and serious AEFI with sufficient power. Regional and global infrastructures enabling data sharing will become increasingly important.

Developing Areas of Vaccine Safety Research

In addition to population-based data, internationally concerted and harmonized assessment of individual patients with AEFI is needed as modeled by the Clinical Immunization Assessment Centers in the United States.[11] A detailed investigation of patients with AEFI may lead to the identification of genetic susceptibility, biomarkers of unintended immune response (eg, excessive inflammatory response, molecular mimicry, bystander effects) and possibly screening tests for subpopulations at risk of developing AEFI.

Adverseomics is an emerging field utilizing high-throughput technologies including genome-wide association studies, transcriptomics and proteomics to investigate AEFI.[12,13] Combining such approaches with the power of clinical data in large healthcare databases will require large international multidisciplinary teams and can yield unprecedented insights in the etiology and pathogenesis of AEFI but also enlighten our understanding of immune responses in general. This is particularly true when we change the common paradigm of inference and take vaccination as a model for investigating human immune responses by capitalizing on the large number of exposed subjects with known type, quantity and time of administration of antigen, adjuvant and other excipients in the vaccines. This may address the need to understand the role of (epi-)genetic differences among individuals in the pathogenesis of serious AEFI.

Methods and models for the quantification and prediction of harm are very limited in today's vaccine safety risk assessment frameworks. This is yet another area of research emerging to improve personalized and population-level decision making based on the vaccine benefit–risk research.

Outlook and Opportunities for Vaccine Safety Monitoring

However, it is possible to address the challenges we face and build on opportunities. The feasibility of a concise infrastructure for international data sharing including common protocols, common data models, common case definitions, common data processing and transfer software, and shared guidance for data collection has been demonstrated. For example, a collaborative case-control study investigating the risk of Guillain–Barré syndrome after pandemic influenza vaccine was conducted across European member states participating in the Vaccine Adverse Events Surveillance and Communication consortium.[14,15] The feasibility of global collaboration and data sharing across continents has also been demonstrated as a proof of concept.[16]

The key opportunities to improve the resource limitations and methods in vaccine safety research are the availability of population-based electronic individual level immunization data and validated methods for assessing risk in low- and middle-income countries where vaccines will increasingly be launched first, before global introduction and access. At the time of launching an immunization program, reliable target population-based background rates of key AEFI should be available to promote rapid vaccine benefit–risk evaluations.[17] This is facilitated by having detailed and structured documentation of medical events and health interventions in electronic health information systems including information on vaccine target diseases and potential AEFI.

Building international frameworks for continuous monitoring of vaccine benefits and risks throughout the vaccine life cycle is paramount, given that vaccine safety assessment requires a global, multistakeholder approach as part of worldwide immunization programs. Accelerated Development of Vaccine Benefit-Risk Collaboration in Europe is European project addressing this need by bringing together health professionals, regulatory agencies, public health institutions and vaccine manufacturers to create a framework, methods and data sharing platform to support rapid vaccine benefit–risk decision making. It is likely to set the stage for future developments.[18]

Finally, understanding the drivers and patterns of public confidence is critical for evaluating the source and nature of vaccine safety concerns as well as for communication of risk by healthcare providers, public health agencies, regulatory agencies and manufacturers.

Vaccine safety research is now recognized as a key component of effective, responsible and sustainable implementation of immunization programs.[19] An increased and well-coordinated global effort promoting the science and building the required structures and processes is timely and needed to overcome the current challenges.

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