Perspectives

The Importance of Active Surveillance in the Assessment of Vaccine Safety

Steven Black[1,2,#]

Vaccines are among the most effective public health interventions (*1*). However, vaccines can potentially cause harm. To minimize risk, proactive regulation of drugs and vaccines was implemented globally beginning in the 1950s. With new requirements for safety evaluation also came new regulations for routine post-marketing surveillance. Developments in ways to code adverse events emerged through the 1960s and 1970s and continue today, and drug and vaccine adverse event passive-reporting systems have been established in more than 100 countries. While modern vaccine pharmacovigilance includes signal-detection using spontaneous reporting, these reports can only identify possible safety signals but cannot be used to estimate risk or to evaluate a possible causal association (*2*).

Before receiving licensure, vaccines have been assessed for efficacy, quality, and safety in phase III clinical trials. These studies are traditionally viewed as the gold standard for vaccine outcomes, but they are limited in their sample size from a few hundred individuals to tens of thousands and to the types of populations included. In addition, the ability of the trials to detect rare, or very rare, events or longer-term outcomes in follow-ups of individuals is usually limited (*3*).

This is where post-marketing active surveillance based on observational studies is critical as the importance of these studies in complementing clinical trials is well-established. Observational studies in vaccine safety include a range of methodologies that compare the occurrence of outcomes of interest between people exposed and unexposed to a vaccine. Over the past 25 years, the ability to conduct observational studies and adjust for bias, most often using computerized clinical data, has evolved to a point that large observational studies can be used to assess even very rare vaccine safety outcomes. Traditional methods have used cohort and case-control designs, but more recent designs, such as the self-controlled case series, have been used in overcoming potential bias (*4*).

While large observational studies on post-licensure vaccine safety have focused on potential associations with rare events, they can also assess differences between vaccine brands and formulations and possible risks in special sub-populations such as pregnant women or HIV-infected individuals. For example with rare events, such as Guillain-Barre Syndrome, detecting a 2-fold increased relative risk with a background incidence of 1/100,000 would require a study of more than 4.7 million people. This would be impossible in a clinical trial (*5*), but by using large clinical datasets, however, such an association can be assessed. Access to clinical data that includes the potential outcomes of interest, information on the vaccination status of individuals, and the ability to link the information in these datasets using a common patient identifier is required. The same infrastructure at many sites has been used to conduct formal phase IV studies mandated by regulatory agencies.

The globalization of vaccine manufacturing has increased the need to assure that vaccines shipped globally are both safe and perceived as safe by the public. Because vaccine safety scares are now also global in scope, a global approach is warranted. To address this need, the Global Vaccine Data Network was established in 2019 with two goals: to facilitate global collaborative studies of vaccine safety to increase their statistical power and to assist in developing infrastructure for the conduct of active surveillance observational studies in key areas of the world. The GVDN network is based in New Zealand and includes scientists from 17 countries, including two from China, with expertise in conducting large observational studies of vaccine safety. At present, the network is developing a protocol to assess the risk of Guillain-Barre Syndrome following the influenza vaccine and to assess possible genetic risk factors for Guillain-Barre disease. Because of the global scope of the network, the study will be able to compare risk between different types of influenza vaccines and in different populations.

In China, there has been a dramatic increase in

vaccine manufacturing for both the domestic and international markets, and there is increasing recognition that infrastructure to conduct state-of-the-art active surveillance of vaccine safety using phase IV observational studies is vital for maintaining public confidence and to meet international regulatory standards and expectations. Fortunately, in China there are locations with comprehensive computerized clinical datasets that include both clinical outcomes as well as vaccination status. This opens the possibility of using sentinel active surveillance in these select areas should a decision be made to develop this infrastructure. Such a sentinel approach was used by US CDC in establishing the Vaccine Safety Datalink (VSD) project in the US that now routinely conducts vaccine safety studies of all new vaccines used in the US (*3*). The VSD has conducted numerous vaccine safety studies to address concerns raised through passive surveillance and issues of concern to the public including autism following MMR vaccine, multiple sclerosis following hepatitis B vaccine, and chronic arthritis following rubella vaccine (*6*). The active surveillance studies have been able to reject each of the original concerns.

In summary, the assessment of vaccine safety post-licensure requires both passive reporting systems for signal detection and active surveillance based upon observational studies for assessment of possible associations. The globalization of vaccine manufacturing and the emergence of many manufacturers in China and other countries means that such assessments can no longer be done exclusively in North America or Europe where such studies have traditionally been conducted. Because of the internet, vaccine safety scares and concerns spread widely and now require a coordinated and rapid global response to avoid declines in vaccine uptake and resulting increases in vaccine preventable diseases. The availability of computerized clinical data in many countries and this need for a global coordinated response has fostered the development of the Global Vaccine Data Network. Within China, the components and expertise exist to develop an active surveillance system for vaccine safety post-licensure. Developing this infrastructure would help manufacturers meet phase IV regulatory requirements to assess vaccine safety and would help appropriately address vaccine safety concerns in China.

Corresponding author: Steven Black, stevblack@gmail.com.

[1] Global Vaccine Data Network, USA; [2] Cincinnati Children's Hospital, USA.

Submitted: November 18, 2019; Accepted: December 02, 2019

References

1. Bloom DE, Canning D, Weston M. The value of vaccination. World Economics-Henley on Thames 6.3 (2005):15.
2. Jones JK, Kingery E. History of Pharmacovigilance. In: Andrews EB, Moore N, editors. Mann's Pharmacovigilance 2014:11 – 24.
3. Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS, et al. Vaccine safety datalink project: A new tool for improving vaccine safety monitoring in the United States. Pediatrics 1997;99(6):765 – 73. http://dx.doi.org/10.1542/peds.99.6.765.
4. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res 2009;18(1):7 – 26. http://dx.doi.org/0.1177/0962280208092342.
5. Strom BL, Kimmel SE, Hennessy S. Textbook of pharmacoepidemiology. Wiley Online Library 2013.
6. McNeil MM, GeeJ, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine 2014;32(42):5390 – 8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6727851/.