

Perspectives

Progress of Active Surveillance for Vaccine Safety in China

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Vaccination is one of the most cost-effective interventions for saving lives and promoting public health. The coronavirus disease 2019 (COVID-19) pandemic is providing a stark reminder of the importance and power of vaccines (1). However, vaccines can cause harm, and their rare safety concerns have increased in relative visibility as successful control and prevention of vaccine preventable diseases has diminished awareness of these diseases. Vaccine hesitancy — the reluctance or refusal to be vaccinated despite the accessibility of vaccines — has been called one of the top ten threats to global health (2). This threat has stalled or even reversed some progress in preventing disease through immunization. To address public concern and maintain confidence in vaccines, comprehensive and reliable evidence is crucial, including evidence from clinical trials, passive safety surveillance, and active safety surveillance (3). Among the methods used to monitor the safety of vaccines, active surveillance is the predominant means to discover and assess causal association between vaccines and adverse events. In this article, we briefly summarize policies, capabilities, and influences of active vaccine safety monitoring in China.

POLICIES FOR ACTIVE SURVEILLANCE

In 2019, the World Health Organization (WHO) Global Vaccine Safety Blueprint 2.0 initiated a Global Vaccine Safety Ecosystem and prioritized active surveillance and causality assessments for the next ten years (4). The WHO also upgraded evaluations of the National Regulatory Systems (NRS) with a new Global Benchmarking Tool, highlighting risk — benefit balance and active vigilance for vaccine safety concerns. Additionally, the first and overarching strategic priority in the new Immunization Agenda 2030 (IA2030) is to ensure that immunization programs are an essential part of primary healthcare and universal health coverage (1). A key focus of IA2030 is continuous monitoring of vaccine safety with effective responses to vaccine safety concerns.

In China in 2019, the Law on Drug Administration underwent a major revision that strengthened regulation of pharmacovigilance, market authorization holders (e.g., manufacturers), and market authorization application procedures. The Law on Vaccine Administration of China, enacted in 2019, stipulates strict management of vaccine safety by requiring whole-process, end-to-end supervision and a secure digital tracking system. To enforce these laws, the State Council of China launched a new campaign — Opinions of Comprehensively Strengthening the Capacity of Drug Supervision — that includes the construction and promotion of NRSs, digital supervision throughout the life cycles of vaccines, and scientific action planning for supervision. It is laudable that the “14th Five-Year Plan” of China expressly continues the national Expanded Program on Immunization and appeals to the health community to achieve IA2030 goals.

PROGRESS IN ACTIVE SURVEILLANCE

Active vaccine safety surveillance is the active monitoring of post-vaccination clinical manifestations of each dose administered in a defined population; it enables precise estimation of the incidence of adverse events relative to baseline levels and assessment of potential causal relationships (5). Given the shortcomings of passive surveillance, researchers began turning to electronic health data for monitoring vaccine safety starting in the late 1980s. A few countries established national active surveillance systems as integral parts of their immunization program. According to the characteristics of their electronic health data, these systems can be categorized into three groups: population-, hospital-, and vaccination-based systems.

Population-Based Active Surveillance

The Vaccine Safety Datalink (VSD) was the first large-scale population-based active surveillance (PBAS) system in the world. VSD has well-defined target

populations that include vaccinated and unvaccinated persons with individual-level linking of comprehensive medical records to vaccination histories (6). In VSD, all essential information is available from Health Maintenance Organizations' records systems. Thus, the denominator of cohorts, vaccination statuses, and occurrences of clinical events are all captured through database linkages. In addition to VSD, in 2009, the United States developed another nationally-representative program, called for Post-Licensure Rapid Immunization Safety Monitoring program (PRISM), which used 9 immunization information systems and 4 national health insurers' data to cover 38 million individuals in active safety surveillance of influenza H1N1 pandemic vaccine (7).

In China, a study demonstrated that the regional health information platform (RHIP) of Ningbo City could actively monitor human papillomavirus (HPV) vaccine safety; however, due to low HPV vaccine coverage, the system was limited to hypothesis testing (8). In the future, strength-of-association analyses will be conducted for vaccines having high coverage levels among Ningbo infants, and, for vaccines with low coverage, by integrating data from multiple RHIPs to provide sufficient sample sizes for assessment of causal relationships. Fortunately, the number of RHIPs having similar capabilities as Ningbo's has increased to 38 cities this year. For methodology- and information-intensive PBAS analyses, active vaccine safety monitoring research organizations should offer maximum methodological support to regulatory departments-up to and including leading or assisting with specific studies, as VSD often does in the US.

Hospital-Based Active Surveillance

Due to limitations of enhanced passive surveillance, Canada determined in the 1980s that monitoring serious vaccination-related adverse events could be conducted at hospitals, and thus became a pioneer of hospital-based active surveillance (HBAS) for vaccine safety (9). However, at that time, it was not feasible to start open-ended monitoring of all events due to the tremendous workload and paucity of readily-available timely vaccination records. The project therefore initially targeted surveillance of acute neurological hospital admissions and discharges. Cases-only study designs were usually used to evaluate associations because data collection could be limited to cases of interest and their vaccination histories — both of which could be obtained using case report forms. Some studies proved to be alternatives to cohort designs,

especially for high-coverage vaccines (10).

In China, a nested case-control study to assess risk of Guillain-Barre Syndrome (GBS) following influenza vaccination was conducted in 74 hospitals in Jiangsu Province; the study showed no association of GBS within the six months of vaccination (11). Some national hospital-based sentinel networks for active surveillance of influenza-like illness or adverse drug reactions (ADR) have existed for several years. It is commendable that the innovative China Hospital Pharmacovigilance System for ADR discovery uses intelligent search and reports assistance to promote efficiency and quality. In the future, these networks may become foundations for active vaccine safety surveillance, especially when records can be linked with individual-level immunization information system data.

Vaccination-Based Active Surveillance

Some projects have created an electronic vaccination follow-up system using email, text messages, or smartphone APPs to obtain potential adverse event reports following each dose of vaccine (12). Such a system can be considered a single-arm cohort study facilitated by novel information techniques for vaccination follow-up, or an active extension to passive vaccine safety surveillance augmenting data access for key stakeholders.

In China, cohort-based adverse event monitoring studies are widely used, especially for new vaccines like COVID-19 vaccines (13). These studies have clear advantages because they provide complete and valid vaccination records coupled with a full range of adverse events reporting — like clinical trials do. In developing and using these systems in the future, it will be essential to ensure sensitivity, data quality, and validity of captured events. For example, the efficiency of detecting rare, serious adverse events could be frustratingly low, challenging validity of estimates. Thus far, however, these systems play the basic role of signal detection, and few have clarified causal relationships between vaccines and rare or serious adverse events. However, these vaccination follow-up designs have only recently been developed and validated as good options for assessing associations in cohorts (10).

OPPORTUNITIES AND THE WAY FORWARD

It is imperative to establish robust national active

vaccine safety surveillance in China, especially in an era of global attention to efficacy, adverse events, licensing, and roll-out of COVID-19 vaccines. Long-term success depends on sustained support from regulations, policies, and finance, as well as collaborative efforts of regulatory departments, research organizations, and data owners. Considering the potential of available databases and the merits of various methods, we believe that in China today, vaccination-based models can be used for signal detection, and population- and hospital-based models are more reliable and practical for evaluating causality.

Without doubt, active surveillance for vaccine safety in China can and will make a difference in global health. The entire world is becoming a community with a shared destiny in public health. China, as the world's largest country, would make a great contribution to global disease prevention by achieving all IA2030 goals. Evidence from active vaccine safety surveillance in China would not only boost confidence in vaccines around the world but also would support use of Chinese vaccines to further increase global vaccine availability and vaccination coverage. Therefore, with the goal of improving global public health, let us build upon lessons learned and set out on a course to make active vaccine safety surveillance a reality in China.

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REFERENCES

1. The Lancet. 2021: the beginning of a new era of immunisations? *Lancet* 2021;397(10284):1519. [http://dx.doi.org/10.1016/S0140-6736\(21\)00900-4](http://dx.doi.org/10.1016/S0140-6736(21)00900-4).
2. The Lancet Child & Adolescent Health. Vaccine hesitancy: a generation at risk. *Lancet Child Adolesc Health* 2019;3(5):281. [http://dx.doi.org/10.1016/S2352-4642\(19\)30092-6](http://dx.doi.org/10.1016/S2352-4642(19)30092-6).
3. Black S. The importance of active surveillance in the assessment of vaccine safety. *China CDC Wkly* 2019;1(2):26 – 7. <http://dx.doi.org/10.46234/ccdcw2019.009>.
4. World Health Organization. Global vaccine safety blueprint 2.0 background research. Geneva: World Health Organization; 2019 Jul. Report No.: WHO/MVP/EMP/SAV/2019.03. Prepared by Deloitte Consulting LLP. https://www.who.int/vaccine_safety/publications/2019_Landscape_Analysis.pdf?ua=1. [2021-07-01].
5. Crawford NW, Clothier H, Hodgson K, Selvaraj G, Easton ML, Buttery JP. Active surveillance for adverse events following immunization. *Expert Rev Vaccines* 2014;13(2):265 – 76. <http://dx.doi.org/10.1586/14760584.2014.866895>.
6. 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. *The Vaccine Safety Datalink Team. Pediatrics* 1997;99(6):765 – 73. <http://dx.doi.org/10.1542/peds.99.6.765>.
7. Nguyen M, Ball R, Midthun K, Lieu TA. The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring program: strengthening the federal vaccine safety enterprise. *Pharmacoepidemiol Drug Saf* 2012;21(S1):291 – 7. <http://dx.doi.org/10.1002/pds.2323>.
8. Liu ZK, Zhang L, Yang Y, Meng RG, Fang T, Dong Y, et al. Active surveillance of adverse events following human papillomavirus vaccination: feasibility pilot study based on the regional health care information platform in the city of Ningbo, China. *J Med Internet Res* 2020;22(6):e17446. <http://dx.doi.org/10.2196/17446>.
9. Scheifele DW, Halperin SA, Gold R, Samson H, King A. Assuring vaccine safety: a celebration of 10 years of progress with the IMPACT project. *Paediatr Child Health* 2002;7(9):645 – 8. <http://dx.doi.org/10.1093/pch/7.9.645>.
10. Baker MA, Lieu TA, Li LL, Hua W, Qiang YD, Kawai AT, et al. A vaccine study design selection framework for the postlicensure rapid immunization safety monitoring program. *Am J Epidemiol* 2015;181(8):608 – 18. <http://dx.doi.org/10.1093/aje/kwu322>.
11. Chen Y, Zhang JL, Chu XH, Xu YL, Ma FB. Vaccines and the risk of Guillain-Barré syndrome. *Eur J Epidemiol* 2020;35(4):363 – 70. <http://dx.doi.org/10.1007/s10654-019-00596-1>.
12. Pillsbury A, Cashman P, Leeb A, Regan A, Westphal D, Snelling T, et al. Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015. *Euro Surveill* 2015;20(43):30050. <http://dx.doi.org/10.2807/1560-7917.ES.2015.20.43.30050>.
13. Yang ZN, Zhao YY, Li L, Gao HD, Cai Q, Sun XX, et al. Evaluation of safety of two inactivated COVID-19 vaccines in a large-scale emergency use. *Chin J Epidemiol* 2021;42:1 – 6. <http://dx.doi.org/10.3760/cma.j.cn112338-20210325-00249>. (In Chinese).