VIEWPOINT

Postapproval Vaccine Safety Surveillance for COVID-19 Vaccines in the US

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Since January 2020, more than 7.8 million cases of coronavirus disease 2019 (COVID-19) and 215 000 deaths have occurred in the US. In response to the pandemic, vaccine development has been moving at record speed through strong public or private partnerships, with nearly 200 vaccine candidates in development or in trials. In the US, 8 vaccine candidates have received federal support under Operation Warp Speed, and 4—from Moderna, Pfizer/BioNTech, Oxford/AstraZeneca, and Janssen—have entered phase 3 trials. Vaccines will be critical for the prevention and control of COVID-19 in the US and worldwide, yet these efforts cannot succeed without public confidence in a vaccination program. Demonstrating vaccine efficacy and safety during clinical trials and implementing a robust postlicensure vaccine safety monitoring system as the vaccine is deployed in larger, more diverse populations is central to public confidence and enabling timely and accurate policy decisions for population-level use.

In response to the 2009 H1N1 pandemic and informed by prior experience during the 1976 swine flu vaccination program, the US government assembled a coordinated response to monitor the safety of H1N1 vaccines by convening a Federal Immunization Safety Task Force, composed of numerous federal agencies.[1] Led by the National Vaccine Program Office, a harmonized national plan was developed for monitoring vaccine safety that involved a public-private partnership.[2] The H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG) was established as an independent body to review vaccine safety–related data on the 2009 H1N1 vaccine as it became available.[1] Importantly, VSRAWG provided transparent and timely communication about vaccine safety as data accumulated and vaccines were broadly distributed in the population.

The Advisory Committee on Immunization Practices (ACIP) initially convened the COVID-19 Vaccine Safety Technical (VaST) Working Group in June 2020 to advise the ACIP COVID-19 Vaccine Workgroup and the full ACIP on the safety of COVID-19 vaccines in development and postapproval. The group includes scientific expertise in coronavirus immunology, clinical trials, postmarket vaccine safety surveillance, risk communication, public health, and clinical medicine, as well as federal partners (Centers for Disease Control and Prevention [CDC], US Food and Drug Administration [FDA], Department of Defense [DoD], Veterans Administration [VA], Indian Health Service [IHS]) with long-standing experience in vaccine safety surveillance. The objectives of the VaST Working Group are to review and interpret preapproval and postapproval COVID-19 vaccine candidate safety data and provide guidance on presenting safety data to ACIP and the general public. More specifically, VaST is reviewing the capabilities and protocols of existing and novel vaccine safety surveillance systems that will be engaged in COVID-19 vaccine safety. A brief overview of key considerations for postauthorization/postlicensure safety surveillance is outlined below, as a starting point for public discussions about plans for COVID-19 vaccine safety monitoring.

In addition to phase 4 studies to monitor safety and effectiveness, passive and active safety surveillance systems serve critical functions in ensuring vaccine safety and maintaining vaccine confidence (eTable in the Supplement). The Vaccine Adverse Event Reporting System (VAERS) is a passive surveillance system that relies on reporting by patients or family members, health care professionals, or manufacturers to capture temporally associated, potential adverse events after vaccination.[3] VAERS is comanaged by the FDA and CDC and serves as an early warning system for potential safety signals that may be temporally related to vaccines. The rapid identification of an intussusception signal after widespread use of rotavirus vaccines in infants exemplifies the essential role of passive surveillance in the US.[4]

To rapidly evaluate safety signals, however, active vaccine safety surveillance systems are essential. The Vaccine Safety Datalink is a 30-year collaboration between the CDC and 9 health systems that use health care encounter data and electronic medical records to capture data on vaccines and potential outcomes of interest in a well-defined population of approximately 11.3 million insured patients, with near real-time capabilities for signal detection, signal refinement, and signal evaluation. Similarly, the VA has well-established capabilities to track and monitor vaccine adverse events using an active surveillance system that can detect safety signals in near real time and conduct signal refinement and signal evaluation activities through electronic medical record review in approximately 6.4 million veterans. In addition, the FDA-Centers for Medicare & Medicaid Services (CMS) active surveillance program, established in 2008, is currently enabled for near real-time safety surveillance of CMS claims data for more than 50 million beneficiaries older than 65 years, including approximately 650 000 nursing home residents. These well-established active safety surveillance systems form the foundation of monitoring COVID-19 vaccine safety.

Novel approaches to complement existing safety surveillance systems are also being explored. Given the need for real-time visibility and to maximize efficiency, several large systems are developing capabilities for enhanced passive surveillance. This approach will leverage systems designed to track COVID-19 vaccine administration and pair them with standardized reporting mechanisms for potential adverse events, such as

VAERS. Similar to VAERS, reporting by patients, clinicians, or health systems is needed to identify and report potential adverse events. An advantage of enhanced passive surveillance, however, is the potential availability of denominator data (ie, number of doses administered in that population) to estimate rates of potential adverse events in targeted populations.

Health care personnel may be among the first to receive COVID-19 vaccines, and monitoring safety in this population will be vital. The CDC's National Healthcare Safety Network (NHSN) conducts surveillance for health care–associated infections in US health care facilities such as acute care hospitals and long-term care facilities (ie, nursing homes, assisted living and residential care, chronic care facilities, and skilled nursing facilities), with a goal of supporting benchmarking and improvement efforts. NHSN routinely collects annual aggregate data on health care personnel influenza vaccination rates and is currently exploring the additional capture of COVID-19 vaccination rates. Capabilities for enhanced monitoring of early COVID-19 vaccine recipients (eg, essential workers) through smartphone or web-based surveys are also being developed to capture potential adverse events following vaccination. Additionally, the DoD and IHS have the ability to track vaccine administration in their respective populations. The DoD plans to conduct enhanced passive surveillance through the Vaccine Adverse Event Clinical System for military personnel. The IHS has established an interagency collaboration with the CDC to support enhanced passive surveillance through VAERS, including prospective surveillance of vaccine sentinel events, for the American Indian/Alaska Native populations.

Clinical consultation is also being planned to support the response to emerging safety issues. The Clinical Immunization Safety Assessment Project, established in 2001, will serve as a clinical resource for clinicians who need guidance for individual patients with possible adverse events temporally associated with COVID-19 vaccination. The DoD will also support clinical consultations through their Regional Vaccine Safety Hubs for causality assessment.

Given the large number of vaccine candidates under consideration, adverse events of special interest (AESIs) may be classified as general, platform-specific (eg, mRNA, protein, viral vector), or population-specific (eg, older adults, children, pregnant women). A harmonized list of prioritized AESIs will enhance comparability across different surveillance systems and enable timely evaluation of potential safety signals. Short-term AESIs (eg, within 6 weeks of vaccination) may be considered for near real-time safety surveillance, whereas AESIs with longer latency periods may require different methodologic approaches and systems to evaluate potential safety issues. AESIs are likely to include allergic, inflammatory, and immune-mediated reactions, such as anaphylaxis, Guillain-Barré syndrome, transverse myelitis, myocarditis/pericarditis, vaccine-associated enhanced respiratory disease, and multisystem inflammatory syndrome in children.

Similar to the FDA guidance on clinical and immunologic end points for COVID-19 vaccine efficacy, guidance on harmonized safety end points is needed for phase 3 and phase 4 clinical trials. The FDA typically advises a minimum population size of approximately 3000 individuals for prelicensure assessments of vaccine safety.[5] In contrast, phase 3 clinical trials for COVID-19 vaccines are enrolling or plan to enroll between 30 000 to 50 000 individuals each, providing the largest databases on prelicensure vaccine safety to date and an opportunity to better understand safety profiles within and across vaccine candidates prior to approval.

A coordinated approach and harmonized safety end points are also needed across multiple postapproval safety surveillance systems. A strategic approach to vaccine safety monitoring will generate data needed to support timely decision-making; however, this will require strong collaboration between federal agencies, academic institutions, and global vaccine safety partners, with input from industry and data and safety monitoring boards on clinical trial findings. Statistical signals are often anticipated during surveillance; however, signals can be spurious because of suboptimal comparison groups, miscoded outcomes in electronic data, inability to adjust for all relevant confounders for each unique adverse event on a weekly basis, multiple testing, or chance.[6] To speed the time from signal identification to signal evaluation, harmonized protocols are needed to explore whether findings are similar across multiple safety surveillance systems and whether those findings are validated through medical record review and epidemiologic studies.

The likely number and diversity of new COVID vaccines that will be developed, including those using novel vaccine platforms, presents new challenges. To maintain public trust and support vaccine policies, a dynamic, robust, and ongoing assessment of the benefit-risk balance of available vaccines is needed.[7] Well-established safety surveillance systems are being strengthened and will remain the cornerstone of COVID-19 vaccine safety monitoring. Novel approaches are in development to enrich safety surveillance in the early phases of vaccine deployment. Coordination of postapproval vaccine safety monitoring efforts through harmonized protocols and outcomes will enable timely identification and evaluation of safety signals. Confidence in vaccines, and therefore a successful vaccination program, can only be attained when there is transparency in the process of decision-making, awareness of how vaccine safety will be monitored, and timely communication about safety monitoring and the benefit-risk balance of COVID-19 vaccines.

ARTICLE INFORMATION

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