

Coordinating COVID-19 Vaccine Evidence Development Efforts

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With widespread COVID-19 vaccination underway in the United States (U.S.), it is critically important to continue gathering evidence on vaccine safety, effectiveness, and access. Substantial vaccine surveillance and research efforts are ongoing among a broad range of federal and state agencies and private organizations, each capturing vaccination records and clinical real-world data (RWD) across varied populations. In addition, a range of researchers, health plans, health care systems, data networks, and registries can contribute to ongoing evidence development efforts. Given the variety of public and private evidence development efforts underway, coordinating efforts around high-priority questions and high-quality data and methods is critical to support confidence in COVID-19 vaccines and address vaccine hesitancy.

In January 2021, the Duke-Margolis Center for Health Policy (Duke-Margolis) and MITRE convened expert stakeholders to discuss ongoing vaccine evidence development efforts. Participants identified critical questions about vaccine safety, effectiveness, and access, and challenges impacting efforts to answer them. Participants then discussed steps that might be taken to meaningfully bolster evidence development efforts by improving coordination among stakeholders.

This issue brief describes some of the critical questions about vaccines identified during the January stakeholder discussion, identifies key data sources that can help answer these critical questions, and recommends actions that organizations capturing, sharing, and analyzing vaccine data can take to coordinate efforts and answer critical questions rapidly.

Critical Questions about COVID-19 Vaccine Safety, Effectiveness, and Access

COVID-19 vaccines from Pfizer, Moderna, and Johnson & Johnson received emergency authorization following rigorous clinical trials that assessed their safety and efficacy among tens of thousands of participants. However, critical questions about vaccine safety, effectiveness, and access will need to be answered through evidence development efforts that go beyond clinical trials. Answering questions that characterize the real-world effectiveness of vaccines and can inform both vaccination strategies and clinical decision-making. And efforts to do so require multiple data sources to monitor and characterize the impact of vaccinations across millions of individuals. Such large-scale evidence generation requires the combined efforts of state and federal government agencies like the FDA, CDC, and state health departments, as well as researchers, health plans, health systems, and academic medical centers.

Vaccine Safety

To date, clinical trials have established that COVID-19 vaccines are safe for administration among the general adult population. Yet ongoing study of vaccine safety is needed to identify and characterize less common adverse events and assess safety in populations that have not yet been studied in clinical trials.

Some vaccine safety questions are being addressed through ongoing clinical trials. Manufacturers' large clinical trials are following participants for two years after vaccination and will assess long term safety outcomes among participants. And newer clinical trials are underway to assess vaccine safety among both adolescents and younger children.

Beyond clinical trials, several ongoing surveillance efforts and safety studies can help investigators identify and follow-up on adverse events. The FDA, CDC, VA, CMS, and other public agencies are leveraging vaccine surveillance systems, health care claims, and clinical data to identify and investigate safety signals. Systems like V-safe and the Vaccine Adverse Event Reporting System (VAERS) can provide early indications of safety signals. And vaccine registries like Duke's HERO Registry can extend public agency efforts. Furthermore, the FDA's Biologics Effectiveness and Safety (BEST) program and Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system, along with the CDC's Vaccine Safety Datalink (VSD) provide vaccination records, clinical data, and health care claims data to identify and investigate vaccine safety signals. These systems offer more detailed data for thorough follow-up safety signal evaluations and can also contribute to investigations of vaccine effectiveness.

Importantly, a range of stakeholders beyond public agencies can cooperate to enhance data sharing and contribute to vaccine safety studies. Health plans, health systems, data networks, and registries can link and share their data with public agencies to support agencies' timely access to high-quality data from varied sources. The resulting datasets might include more detailed claims, clinical, and demographic data that covers longer time periods. Agencies can then use these comprehensive datasets to conduct broad and rapid assessments of vaccine safety in specific populations (like those with comorbidities and pregnant vaccine recipients) and to assess comparative safety among different vaccines.

Vaccine Effectiveness

Together with information on vaccine safety, questions of vaccine effectiveness can inform vaccination strategies and characterize the level, duration, and kind of protection vaccines offer. Both state and federal policymakers are interested in understanding whether vaccinations are making positive impacts, particularly among specific populations as vaccinations become more widespread. Are vaccines preventing severe COVID-19, hospitalization, and death? Are vaccines

effective against emerging concerning viral variants? Are vaccines protecting older adults, long-term care facility residents and staff, people with underlying health conditions, and people from racial and ethnic minorities? How do different vaccines compare? How long do vaccines provide protection? The answers to these questions may vary among the different vaccines and might influence how vaccines are distributed and administered. And the studies to answer these and other questions about vaccine effectiveness require appropriate data and methods.

Understanding vaccine effectiveness against concerning viral variants is critical to informing vaccination strategies and vaccine development programs. Understanding concerning viral variants presents a particular challenge that requires genomic sequencing data and thoughtful evaluation. Accordingly, the CDC has increased its genomic sequencing capacity and is partnering with clinical organizations across the U.S. to bolster viral surveillance. State public health agencies, health plans, and health systems are beginning to work together to identify vaccine failures (when vaccinated individuals become sick with COVID-19) by coordinating vaccination and clinical data, and can ensure relevant clinical samples are sequenced. Together, genomic and clinical data offer opportunities to characterize vaccine effectiveness against concerning viral variants that might differentially impact individuals among varied populations and geographies.

Similarly, understanding the comparative effectiveness of COVID-19 vaccines can also inform vaccination strategies and ongoing vaccine development. Although clinical trial results provide initial indications of vaccine efficacy, as vaccines are administered more widely their real-world effectiveness must also be investigated. Stakeholders are interested in understanding whether particular vaccines are more or less effective among different demographic groups. And understanding whether concerning viral variants impact the effectiveness of different vaccines might determine where and to whom particular vaccines are distributed. Already, manufacturers are testing whether adding booster doses to existing regimens can provide enhanced protection and are updating existing vaccines to target concerning viral variants.

Access to Vaccines and Equitable Vaccination Strategies

Vaccine evidence development efforts can also answer questions about access to vaccines and equitable vaccination strategies. Public health officials planning vaccination programs and evaluating outcomes need to understand current and upcoming vaccine supply and who is receiving vaccinations. Accordingly, regardless of where vaccinations occur, appropriate data needs captured and recorded within state immunization information systems that facilitate data sharing between health systems, health plans, and public health agencies (as allowed by law). Analyzing the data among such systems can help public health officials identify and respond to disparities among populations characterized by race, ethnicity, age, geography, and other factors. And as vaccination programs expand, efforts to capture and share vaccination data must

expand as well. Vaccinations will increasingly occur among additional community settings and health care sites (like primary care offices). Public health agencies can prepare these sites to capture and share vaccination data, especially as the entire adult population, adolescents, and younger children become eligible for vaccination.

Data Sources for Vaccine Evidence Development

A variety of data sources can contribute to evidence development that addresses important outstanding questions about vaccines, including RWD sources, registries, and surveys. Each data source offers information relevant to multiple vaccine-related questions.

RWD sources may be best equipped to quickly answer vaccine-related questions. Vaccination data from health care claims and clinical data from electronic health records can be quickly captured and analyzed on a massive scale. Already, large data networks like the N3C, PCORnet, OHDSI, Epic's Cosmos, and the FDA's BEST program are aggregating RWD from several health plans and health systems. And encouraging cooperation among an even broader set of data owners and networks might offer investigators the capability to aggregate enough data to answer questions about smaller demographic groups where evidence of vaccine safety, effectiveness, and access is currently limited.

Registries are another method by which RWD is being captured expressly for the purpose of assessing vaccine safety and effectiveness. Multiple registries are collecting demographic data describing participants and allowing vaccinated individuals to report side effects and adverse events. The CDC's V-safe registry has been used by over 1 million individuals to report adverse events following vaccination. And the HERO Registry has enrolled thousands of health care workers to capture similar safety data, as well as data about vaccine hesitancy, pregnancy, and longer-term outcomes. Registries offer the capability to capture RWD that may not be included among existing databases. For example, a registry might capture viral genomic sequencing data from community test sites or from patients admitted to hospitals with COVID-19, enabling investigators to characterize the impact of concerning viral variants on disease transmission and vaccine effectiveness.

Survey data can reveal concerns and questions regarding vaccine safety and effectiveness that are important to the public and help characterize the impact of vaccination programs. The Delphi Group at Carnegie-Mellon University has partnered with Facebook to run a massive daily survey that captures data through questions designed collaboratively among a consortium of academic partners and public health officials. The survey data provides information about the spread of COVID-19 and its effect on individuals in the U.S. This survey data can forecast viral transmission and inform research efforts that inform public health messaging, combat vaccine hesitancy, and aim to answer other important questions.

While each of these data sources are substantial and growing, concerns regarding data reliability, data latency, and data linkages are relevant. To reach the scale required to identify rare events and rapidly answer questions about vaccine safety and effectiveness among smaller populations, complete data on as many vaccinations as possible must be captured and subsequently shared and evaluated in a reliable manner.

Recommendations

Addressing critical questions about vaccine safety, effectiveness, and access to vaccinations requires timely high-quality data, reliable data infrastructure, and robust methods. During the stakeholder discussion, participants identified several challenges impacting vaccine evidence development and strategies to overcome them. The following recommendations are informed by this discussion.

First, researchers should take care when identifying, investigating, and communicating vaccine safety signals to avoid false positives that might cause harm. Because millions of individuals will be vaccinated, a significant number of adverse events are expected. However, many or most reported or recorded adverse events will not be caused by vaccines. To help determine whether vaccines are causing adverse events, agencies like the FDA and CDC have designed robust methods to determine the background rate of adverse events among populations, particularly for adverse events of special interest (AESIs). Importantly, the data and methods applied toward vaccine safety studies must be highly reliable and fit for purpose, and vaccine data must be high-quality and frequently updated when possible. Efforts like BEST, PRISM, and the VSD have been carefully designed to enable reliable rapid cycle analyses (or sequential analyses) that can detect safety signals, and facilitate follow-up to determine whether vaccines might be responsible for such signals. These systems will inform public health communications about the safety of COVID-19 vaccines. When investigating safety signals, stakeholders must take care to apply rigorous research methods that can reliably determine whether adverse events are attributable to vaccines.

Second, government agencies, researchers, health systems, and health plans should collaborate to identify and prioritize critical questions about vaccine safety, effectiveness, and access. Stakeholders are asking similar questions about vaccine safety, effectiveness, and access. By prioritizing questions with the greatest potential public health impact, stakeholders might obtain meaningful answers more quickly. Furthermore, the data required to answer particular questions frequently exists among multiple stakeholders who might be working independently on similar issues, where cooperation might offer efficiencies. As such, there should be greater effort to identify specific questions and research, either through collaborations with government agencies like FDA and CDC, or through a clearinghouse-like

structure that can facilitate the cooperative prioritization of critical questions about vaccines and centralize the organization of evidence development efforts. Public-private partnerships and organizations like the COVID-19 Vaccine Evidence Accelerator, organized by FDA and the Reagan-Udall Foundation, offer opportunities for such collaboration.

Third, the federal government, states, health systems, and health plans should improve data sharing on vaccinations. Data on vaccinations is captured among diverse stakeholders and linking data among them has been challenging. For example, data from vaccinations that occur beyond traditional health care sites does not reliably flow into claims databases and is not always made available to health plans and health systems. Although much of this vaccination data is available in state immunization information systems, health systems have expressed difficulty ensuring that data is reliably shared with and retrieved from these systems. Stakeholders are taking steps to improve data sharing and reduce data latency. For example, health plans are actively working with CMS to ensure vaccination data on Medicare beneficiaries can be captured and shared. And in some states vaccination records within immunization information systems are being linked with COVID-19 case data, enhancing immunization information systems' utility for vaccine evidence development. But more effort is needed to support data sharing, reduce data latency, and ensure that both vaccination and clinical data are available to federal and state public health agencies, researchers, and health care providers, potentially through additional public-private cooperation.

Finally, health systems, health plans, and other data owners and users should adopt standards such as common data models and common methods for conducting analyses and reporting results. Such standards can help stakeholders aggregate data from different sources and scale their evidence development efforts. To standardize clinical data, PCORnet created a subset of its common data model to streamline its data partners' adoption of COVID-19 data elements and enable more frequent data refreshes and analyses. And the N3C established an effort to aggregate RWD from its partners' electronic medical records by transforming different data models into a harmonized OMOP data set. To encourage common analytical methods, approaches like the Regan-Udall Foundation's evidence accelerator might advance methodological coordination among public and private partners. These common data models and methods can better aggregate and leverage substantial clinical, claims, and registry data sources and yield reliable, actionable insights more quickly than might be achieved through smaller research efforts.

Conclusion

The expert stakeholder discussion led by Duke-Margolis and MITRE revealed challenges limiting large-scale evidence development and next steps to address them. Stakeholders must

coordinate to answer questions about vaccines that promise immediate public health impact, use reliable data and methods for evidence development, improve data linkages, and adopt common data standards and methods. And U.S. government agencies including the FDA, CDC, CMS, and others can consider actions that support such coordination. Organizations capturing vaccine data and developing evidence have an opportunity to take these steps and answer critical questions about vaccines quickly and efficiently.

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