COVID-19 Evidence Accelerator Collaborative

Lab Meeting # 29

Thursday, March 18th, 2021 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting 29

March 18th included the first edition of the vaccines workstream of the accelerator. To kick-off the meeting we listened to a conversation between Dr. Michael Osterholm of the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota and Dr. Patrick Ryan of OHDSI. They discussed where we are today in our effort to vaccinate against COVID-19 and what data can support our work to ensure vaccines continue to help fight COVID-19. Next, Dr. Steve Anderson of the Office of Biostatistics and Epidemiology at the Center for Biologics Evaluation and Research (CBER) provided an overview of government efforts to monitor and evaluate the safety and efficacy of COVID-19 vaccines in the United States. He gave an in-depth look at ongoing near real-time analyses that will help to identify safety signals and understand how these vaccines are performing in the real-world. Finally, Dr. Donna Rivera of FDA's Oncology Center of Excellence (OCE) provided a few hypothetical examples of real-world data at the patient-level and discussed how these data flows can inform our ongoing analyses of COVID-19 vaccines.

We Have Vaccines – Now What?

Michael Osterholm, Center for Infectious Disease Research and Policy, University of Minnesota
Interviewed by Patrick Ryan, OHDSI
For more, see our "Putting Our Heads Together" Blog article featuring the interview with Dr. Osterholm.

Key Challenges Going Forward:

- A lot of people over the age of 65 still have not been vaccinated. As we expand eligibility for the vaccine it will be increasingly difficult for this at-risk population to get it. As variant cases surge, we do not know what will happen to this at-risk group and we have not prepared vaccine distribution for what this surge could be like.
- We also do not understand how vaccines are affected by new variants in Brazil, in South Africa, and elsewhere. We need to have a discussion more focused on strategic vaccination against variants in these countries. If we do not work to control variant cases in low and middle-income countries through vaccination, variant cases will spin out of control and risk impacting the success we have seen from these vaccines so far.

- As variant cases surge, we need to take a futuristic view of how we will manufacture and continue to monitor and develop vaccines.
- We have additional questions about the safety of these vaccines for pregnant women, young children, etc., but we have been able to answer questions quickly and effectively about the relative safety and efficacy of these vaccines.
- Data from other countries where there are different approaches to vaccinating (such as, one dose or smaller doses) can be an adjunct source of information for considering these issues. We also need to be able to capture data in more real time to help answer some of these questions.
- We need a rapid system for evaluating data. For example, when these vaccines were being considered for Emergency Use Authorization (EUA), variants were not as clear of a presence in the data challenge. Now, there is a whole new data set that has come forward. We do not have a system that enables us to evaluate these data in a comprehensive manner as the data quickly changes.

An Update of FDA Monitoring COVID-19 Vaccine Safety

Steve Anderson, Center for Biologics Evaluation and Research (CBER), Office of Biostatistics and Epidemiology [Slides are available HERE]

US Surveillance Monitoring Systems

- There are four US Government large-linked medical data systems used for monitoring and surveillance of vaccines in the United States.
    - FDA Surveillance Program, CDC's Vaccine Safety Datalink (VSD), the VA's EHR & data warehouse, Defense Medical Surveillance System

FDA-CMS Vaccine Safety Partnership

- This partnership between FDA and CMS on vaccine safety began in 2002.
- These data, which consist of claims data with access to medical charts, cover nearly all 55 million elderly (>=64 years old) US beneficiaries and represent a variety of healthcare settings including inpatient and outpatient care.

Rapid-cycle Analysis (RCA)

- FDA-CMS system uses RCA which allows near-real time surveillance of vaccine safety.
- Process of the RCA - identified 15 possible Adverse Events of Special Interest (AESIs), waited until there were sufficient vaccine counts in the CMS database to support these analyses, evaluated background rate information for each AESI, now in the process of conducting the RCA using CMS data.
- The working list of AESIs identified for the RCA includes Guillain-Barre syndrome, Bell's Palsy, Anaphylaxis, Encephalomyelitis, Narcolepsy, Appendicitis, Non-hemorrhagic Stroke, Hemorrhagic Stroke, Acute myocardial infarction, Myocarditis/Pericarditis, Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Disseminated intravascular coagulation (DIC), Immune thrombocytopenia (ITP), Transverse Myelitis, and Multisystem Inflammatory Syndrome.
- Vaccine count as of February 27, 2021 in CMS Medicare data was at 9.0 million doses total (includes both Pfizer and Moderna vaccines).

Background Rate Analyses for AESIs

- Background rates provide information on the expected rate or estimate of a baseline for comparison for each AESI.
- Unlike active monitoring for influenza vaccines which has a strong historical base on background rates for the comparator groups, COVID-19 vaccines are new and therefore lack historical information. As a result, they require new background rates generation for the deliberate selection of comparator groups.
- AESIs (n=15-18) background rates may vary by population and time period.
    - Populations: adults aged 65+ years vs. influenza vaccinees 65+ years
    - Time periods: pre-COVID (2018-2019) vs. peri-COVID-19 (March 2020-October 2020)
- The pandemic impacted healthcare utilization and AESI rates (e.g. heart attacks were underreported by half) during peri-COVID-19 period (March – December 2020).
    - Evaluation for populations and time periods allows for more reliable safety signal detection and generation. Assessment of background rates allows approximation of the true AESI rates.
- For all AESIs, pre-COVID-10 background rates among adults 65+ years were selected.
- AESI rates did recover to pre-COVID-19 levels by December 11, 2020. Background rates will be standardized to the distribution of COVID-19 vaccinees by select demographic characteristics (e.g., nursing homes, age, sex, race/ethnicity for CMS).

FDA RCA using CMS Data

- Foundational work on counts monitoring, descriptive analyses, background rates are completed.
- RCA runs are under way and quality control checks are being performed on initial runs.
- Conducting runs every week to achieve near real-time monitoring.

Surveillance Study Protocols

1. Background Rates of AESI for COVID-19 Vaccine Safety Monitoring
    - **a.** Final protocol posted on bestinitiative.org and study complete
2. COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol
    - **a.** Final protocol posted, analysis currently underway with input from background rates study, weekly vaccine counts being updated.
3. COVID-19 Vaccine Safety Surveillance: Inferential Study Master Protocol
    - **a.** Protocol to be posted
4. Performance of Claims-based COVID-19 Diagnosis Code Using SARS-CoV-2 Nucleic Acid Amplification Test Results
    - **a.** Protocol to be posted
5. Future Protocols that are in Development
    a. COVID-19 Vaccine Safety Study to verify potential vaccine safety signals
    b. COVID-19 Vaccine Safety Study
        i. Effectiveness by vaccine, dose, duration between doses, duration of protection, comparative effectiveness

Next Steps for Active Safety Monitoring

- ≥ 65 years old monitoring analyses underway in CMS Medicare data

- 18-64 years old additional rapid cycle analyses in development, planning to start analyses in April
- Conduct brand specific analyses for each AESI – risk intervals, quality assurance, patient profile analyses, etc.

Challenges

- Vaccine Confidence & Hesitancy
    - Vaccines have different risk/benefit considerations than therapeutics – risk tolerance may be lower for vaccines.
        - Concerns about false positive results from poorly conducted studies.
        - False 'signals' can have a huge impact on vaccine confidence & hesitancy.
        - Rare adverse events are generally not detected in clinical trials.
- Data Systems
    - Not all claims and EHR data systems can be used to address safety or effectiveness regulatory questions.
    - There are limitations in data – populations, care settings, clinical details provided, data lag, linkage of vaccinations to inpatient outcomes, power to detect rare adverse events.
    - Need to think about how to improve data systems and government systems such as BEST to improve our ability to study vaccine safety and effectiveness.

Needs

- High quality data, tools and methods with quality control steps to support regulatory decision making.
- Data on millions of vaccine recipients to evaluate rare adverse events.
- Ability to conduct chart review and confirm rare outcomes.
- Improve capture of COVID-19 vaccine exposures.

<u>Vaccine Real-World Data</u>

Donna Rivera, Oncology Center of Excellence

Foundations for Collecting Real-World Vaccine Data

- There are three phases for collection of real-world vaccine data:
    - Pre-Vaccine (90 days) – COVID diagnostic test results, clinical encounters, treatment for COVID.
    - Vaccination (Interim Monitoring) – vaccine information (type, dose, data, demographics), side effects, adverse drug events, clinical encounters
    - Post-Vaccine Long Term Monitoring (Safety data and duration of immunity) – patient generated, clinical encounters, antibody test results and date of test, occupation exposure risk level, COVID diagnostic test results and date, symptoms, treatments, location.
- There are many timepoints in the timeline of vaccination where data can be generated.
- Considerations for what data to look at & where the data come from will be different depending on the patient.

Hypothetical Patient Examples

- The hypothetical scenarios presented demonstrate just a few of the challenges to providing vaccines in diverse settings each presenting different considerations for longitudinal data monitoring.
- **Maya** – 48-year-old Hispanic female, healthcare worker (high-risk of exposure), contracted COVID, later received vaccine
    - Inpatient care data from when she was hospitalized and sick with COVID can be used for pre-vaccine real-world data.
    - Centralized data from the HMO that administered her vaccine, where she works/receives healthcare can be used for interim monitoring (vaccination) & Post-vaccine long term monitoring.
- **Steve** – 56 year old white male, veteran, enrolled in clinical trial for COVID vaccine
    - Centralized data capture from care at the VA can be used for real-world data on pre-vaccine, vaccination, and post-vaccine long term monitoring.
    - RCT case report forms from Steve's time in the clinical trial can be used for interim monitoring (vaccination) and for post-vaccine long term monitoring.
- **Carol –** 50-year-old white female, grocery store worker in the rural Midwest, vaccinated by the department of public health
    - Carol received care across a variety of settings – inpatient care, department of public health, and outpatient care.
        - Pre-vaccine – inpatient care data
        - Interim vaccine monitoring – department of public health that administered her vaccine
        - Long term monitoring – outpatient care
    - Because she received care across many different settings, a real-world data aggregator could be used to help link data across these settings and better understand the full story.
- **Heidi**
    - Found her vaccine going to a local/state website.
    - Data not captured in the current system.
- **Miles** – Represents the many patients not currently vaccinated due to access/equity issues, vaccine hesitancy, etc.
    - Black male professor with good access to care but is understandably skeptical to get vaccinated because of historical ethical issues in drug development.

Sources for Real-World Data

- **Centralized data from HMOs** – Real-world utilization, demographics (increased generalizability), geographic and temporal patterns, long-term safety including adverse events, vaccination compliance (getting second dose), real-world duration of immunity.
- **RCT Case Report Form data –** vaccine efficacy, efficacy to variants, initial vaccine safety (PK/PD, dosing, clinical), immunogenicity assessments, post-market requirements, post-market commitments, safety analysis by serostatus
- When these data sources are linked with a RWD aggregator it is possible to tell the complete story and answer more questions:

- **Inpatient** – clinical data on HCRU, encounters, demographics
- **Departments of Public Health** – vaccine, type, date, demographics
- **Outpatient –** clinical data (may vary by specialty) on routine care, HCRU, encounters, demographics