COVID-19 Evidence Accelerator Collaborative

Lab Meeting 45

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

Call Summary

Overview of Lab Meeting 45

Lab Meeting 45 focused on several groups' efforts to monitor the safety and effectiveness of COVID-19 vaccinations using real-world data (RWD). First, we heard from Dr. Nicola Klein of Kaiser Permanente about the Vaccine Safety Datalink (VSD) and use of Rapid Cycle Analyses to identify and describe potential safety concerns and vaccine uptake. Next, Dr. Steven Brunelli of DaVita, Inc. gave an overview of results from analyses exploring the effectiveness and comparative effectiveness of vaccines among dialysis patients. Dr. Eduardo Lacson, Jr. of Dialysis Clinic, Inc. finished out the meeting with his presentation of findings on vaccine effectiveness and durability among patients with End-Stage Renal Disease (ESRD) receiving hemodialysis.

Monitoring COVID-19 Vaccine Safety in Near Real-Time in 5–11-Year-Olds with the Vaccine Safety Datalink (VSD): Leveraging Clinical Systems

Nicola Klein, MD, PhD, Kaiser Permanente

Importance of Monitoring Vaccine Safety

- Public assurance that safety problems, if they arise, will be detected ASAP.
- Rapid cycle analyses can detect problems quickly and can addressed concerns arising from elsewhere.

The Vaccine Safety Datalink (VSD)

- Collaborative project between the Centers for Disease Control & Prevention (CDC) and 9 integrated healthcare organizations across the US representing 12 million+ individuals
- Distributed Data Model – each site collects and stores their own data locally, specific data points submitted to central hub to answer questions that arise

Rapid Cycle Analysis

- Rapid Cycle Analyses (RCA) – conducted weekly to monitor the safety of several routine vaccines as well as vaccines against COVID-19.
    - VSD's RCAs are best suited for outcomes that are:
        - Clinically well-defined & coded in the electronic medical records (EMRs)
        - Acute onset (I.e., within a few days or weeks of vaccination)
        - Serious
- Aims of VSD RCAs:
    a. Monitor the safety of COVID-19 vaccines on a weekly basis using pre-specified outcomes of interest among VSD members.
    b. Describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity.

Outcomes for COVID-19 Vaccine Safety RCA Surveillance

- Surveillance of COVID-19 vaccines began in December 2020
- Monitoring 23 serious outcomes with varying levels of understanding/concern
    - **Inclusion in prior vaccine safety studies**: acute disseminated encephalomyelitis, anaphylaxis, encephalitis/myelitis, Guillain-Barre syndrome, etc.
    - **Hypothetical concerns regarding association with COVID-19 disease:** acute myocardial infarction, acute respiratory distress syndrome, disseminated intravascular coagulation, multisystem inflammatory syndrome, etc.
    - **Outcomes due to emerging concerns:** cerebral venous sinus thrombosis, myocarditis/pericarditis, thrombosis with thrombocytopenia syndrome
    - **Imbalances in Phase III COVID-19 Vaccine clinical trials:** appendicitis, Bell's palsy

Chart Review & Adjudication Process

- Case(s) are identified within an "appropriate" time interval following COVID-19 vaccination.
- Within a week, a quick chart review is performed to determine if the case is an incident with symptom onset after the vaccination.
    - Case meets VSD incident definition --> included in weekly RCA.
    - Case does not meet the VSD incident definition --> excluded from all future RCAs.
- Case continues to full chart abstraction/adjudication after the appropriate time has passed (varies by outcome) from the initial date of diagnosis.
    - Delay in abstraction/adjudication allows time for diagnostic information and follow-up visits to accumulate in the medical record.
- To allow for balance between quick chart-confirmed and complete follow-up for each week's analyses, weekly VSD includes a mix of:
    - All cases confirmed after full chart abstraction/adjudication
    - All quick-reviewed cases pending full chart abstraction

RCA Surveillance Analytic Strategy

- Primary analysis: the number of outcomes observed in the risk interval (1-21 days) after COVID-19 vaccination were compared to the number expected.
- Expected was derived from "vaccinated concurrent comparators" who were in a comparison interval (days 22-42) after COVID-19 vaccination.
- On each day that an outcome occurred, vaccine recipients who were in their risk interval were compared with similar vaccine recipients who were concurrently in their comparison interval.
    - Comparisons adjusted by age, sex, race/ethnicity, VSD site, calendar date.

Summary of Current Results

- No safety signals for any outcome in the 21-days after both mRNA doses in the overall VSD population, including all ages >=12 years.
    - Surveillance ongoing for all COVID vaccines
- 12–39-year-old subgroup had an elevated rate ratio for myocarditis/pericarditis after both mRNA vaccines 0-21 days after vaccination, especially days 0-7
- Pfizer and Moderna mRNA vaccines were associated with myocarditis/pericarditis in persons aged 12-29.
- In the VSD, rate of anaphylaxis after mRNA vaccines is ~5 cases/million doses.

Planned Pediatric RCA

- Weekly sequential analyses
    - Ages 5-11

    - Risk Intervals same as for RCA in >= 12 years population (1-21 days post-vaccination, 1-42 days post-vaccination)
    - Signaling criteria P<.0064
- Weekly Subgroup Analyses
    - Ages 5-11, 12-15, 16-17, 18-39
    - Myocarditis (chart confirmed)
    - Risk Intervals 0-7 days, 0-21 days, 1-21 days, 8-14 days, 15-21 days
- One-time analysis
    - 12-15 – All outcomes
    - 16-17 – All outcomes
    - Risk intervals 1-21 days, 1-42 days

Key Takeaways

- Integrated clinical healthcare systems are critical to near real-time vaccine safety monitoring
- VSD surveillance complements other vaccine safety monitoring systems in the US
- Flexibility & access to good data is key
    - Can rapidly add new outcomes in response to emerging concerns
    - Access to comprehensive medical record and rapid case confirmation when appropriate
- Important to focus on appropriate comparators
    - Primary analyses used vaccinated rather than unvaccinated comparators
    - Unvaccinated comparators can be helpful initially to supplement primary analyses, comparisons between recent & more remote vaccine recipients would be expected to be more similar than with unvaccinated individuals
- Helpful that analyses compared similar vaccine recipients (in risk and comparison intervals) on the same calendar date
    - Avoids biases arising from variations in healthcare use throughout the pandemic and day-to-day variations
    - Comparators similar in demographic characteristics to the case

<u>SARS-CoV-2 Vaccine Effectiveness & Comparative Effectiveness Among Dialysis Patients</u>

Steven Brunelli, MD, MSCE, DaVita, Inc.

Vaccine Effectiveness: BNT162b2 & mRNA-1273

- Methods
    - Retrospective, observational cohort
    - Accrued 1/1/2021 - 2/25/2021
        - Vaccinated (received first-dose of vaccine)
        - Unvaccinated (did not receive first dose of vaccine through corresponding date)
        - Index = date of first shot
    - Matching: BNT162b2 (up to 1:4); mRNA-1273 (up to 1: 3)
        - Date of first vaccine dose, US state, prior COVID, propensity score (age, sex, race, diabetes, BMI, dialysis attendance)
    - Follow-up: Through 4/30/21
        - Censoring for death, loss to follow-up, receipt of vaccine (for unvaccinated)
        - PCR-confirmed cases
        - Peri-COVID hospitalization, mortality

- Results
    - BNT162b2, N=12,169; Unvaccinated, N=44,377
    - mRNA-1273, N=23,037; Unvaccinated, N=64,243
    - Low rates of pts. lost to follow-up for both comparisons
    - Characteristics of vaccinated/unvaccinated groups balanced for both comparisons
    - Both BNT162b2 and mRNA-1273 are potently associated with lower rates of clinically manifested COVID-19, as well as lower rates of peri-COVID-19 hospitalization and mortality.
    - Limitations:
        - Non-randomized study (residual bias/confounding)
        - Did not study asymptomatic viral carriage/shedding
        - Short-term follow-up: no ability to study durability
        - Head-to-head comparisons of the two vaccines ill-advised

Comparative Effectiveness: Ad26.COV2.S vs. BNT162b2

- Methods
    - Retrospective, Observational Cohort
    - Accrued 1/1/2021 - 5/18/2021
        - Included pts. Who were vaccinated with Ad26.COV2.S or received first-dose of BNT162b2
        - Index = date of first shot
    - Matching 1:1
        - Date of first vaccine dose, US state, prior COVID, age, race
    - Follow-up through 9/28/2021
        - Censoring for death, loss to follow-up
        - PCR confirmed cases
- Results
    - All Patients/COVID Naïve Patients
        - BNT162b2: N=2659/N=2465
        - Ad26.COV2.S: N=2659/N=2465
    - Well-balanced cohorts (slight imbalance in housing vacancy rates favored against Ad26 cohort – 9.7% vs. 10.4%)
    - Ad26 and BNT162b2 appear equivalent in reducing clinical cases of COVID-19 at each week interval (1-3, 4-6, 7+ weeks)
    - Worst case scenario is ~.6 additional cases of COVID-19 per week per 1000 patients vaccinated with Ad26
    - Limitations:
        - Non-randomized study (residual bias/ confounding)
        - Did not study asymptomatic viral carriage/shedding
        - Limited sample size: no ability to study hospitalization/mortality

Experience with Bamlanivimab in Hemodialysis Patients

- Methods
    - Patient population – adults on hemodialysis (HD), newly diagnosed with COVID-19, not hospitalized

- Procedures
    - Bamlanivimab administered intravenously as single dose over 60 minutes
    - Patients monitored for at least 1 hr. after administration
    - Adverse Events (AE): fever, chills, hives, rash, hypotension, headache, nausea, fatigue, dizziness, angioedema, muscle pain, or throat irritation
    - Serious Adverse Events (sAE): anaphylaxis or any condition requiring use of epinephrine injection or albuterol, was sent to the ED, or was hospitalized
- Results
    - 277 patients with newly diagnosed COVID received a single-dose of Bamlanivimab at DaVita (1/1/2021 – 4/16/2021)
        - Mean age 60.4 years
        - 46.2% female
    - There were 0 AEs or sAEs documented in the 1-hour post-administration observation window.
    - Mean follow-up, 84 days
        - 25.6% of patients (71/277) hospitalized; about half (34/71) within the first 14-days after receipt of Bamlanivimab.
        - 5.4% of patients (15/277) died.

<u>COVID-19, Vaccination Against SARS-CoV-2 and Outcomes in Patients with End-Stage Renal Disease (ESRD) on Maintenance Dialysis</u>

Eduardo Lacson, Jr., MD, MPH, FACP, Dialysis Clinic, Inc. (DCi), Clinical Science & Quality Initiatives

COVID for Patients with ESRD

- Patterns of spread through the HD community are similar to spread through the general population
- Outcomes reflect those of the elderly population, but are worse due to:
    - Varying levels of immunocompromise
    - More comorbidities among ESRD patients
    - High morbidity for nursing home residents
    - February 2020 – June 2020 – 400+ COVID positive patients on HD
        - 67% hospitalized
        - Overall death rate = 24.9% (109 deaths/438 infected HD patients)
    - February 2020 – November 2021 – 3800+ COVID positive patients on HD
        - Hospitalization rates down to ~50%
        - Overall death rate decreased to 19.1%

COVID-19 Vaccines

- Clinical trials for vaccines excluded patients with ESRD
- DCi protocol created and offered to clinicians to monitor receptor binding domain spike-1 IgG antibodies (RBD-S1-IgG Ab) using Seimens Advia Centaur sCOVG
- Monthly monitoring timing with routine monthly blood draws; stop after 2 months with negative tests or 12 months (initial protocol)

Results

- Most dialysis patients developed an antibody response after receiving a COVID vaccine, 10-15% of HD patients did not.
    - Only 30% response rate for patients receiving J&J, stopped administering after data from 400 patients.
    - Immune response tended to rapidly wane overtime in HD patients.
- Vaccine Effectiveness
    - Highest rate of COVID-19 among HD patients that were unvaccinated (3.35 events/10,000 patient days), lowest rate among those that received 2-doses of Moderna's COVID-19 vaccine (.91 events/10,000 patient days)
        - Similar patterns for COVID-related hospitalizations – highest risk among unvaccinated HD patients, lowest risk among Moderna recipients.
    - Currently in the process of formally assessing vaccine effectiveness
        - Separating pre-Delta variant period from post-Delta variant period (Delta dominant)
        - Adjusting for time from full vaccination to account for waning immune response
- Antibodies & Breakthrough Infections
    - 85% (23/27) of Breakthrough cases at RBD-S1-IgG Ab <2
        - 52% never developed antibody levels
        - 26% had antibody levels that waned to below 2 before infection
        - 7% had only 1 sAb value before infection
        - 15% had Ab level >2 at the time of COVID-19 diagnosis
    - All severe (hospitalized) cases occurred at Ab <6 (<7 with new assay)
    - 67.5% of cases still at <2 and all COVID-related deaths at <1