COVID-19 Evidence Accelerator Collaborative

Lab Meeting 52

Thursday, May 19th, 2022, 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting 52

Lab Meeting 52 included two presentations on how "signals" in real-world data can help assess the safety and effectiveness of COVID-19 vaccines. First, Dr. Chathuri Daluwatte of Sanofi discussed how social media traffic can provide be used to monitor and identify concerns circulating in the public about the safety of COVID-19 vaccines. Second, Dr. Peter Gilbert of the University of Washington provided an overview of work identifying immune correlates of protection (CoP) of mRNA vaccines against COVID-19 variants. Following Dr. Gilbert's presentation, the group discussed how real-world and observational studies can be designed to include consideration of CoP.

Web and Social Media Listening Using AI/NLP for COIVD-19 Vaccine Safety Monitoring

Dr. Chathuri Daluwatte & Dr. Alena Khromava, Sanofi

Social Media for Vaccine Insights

- There is a time gap between the occurrence of an event and reporting in of an adverse event (AEs) in traditional AE reporting systems
- More consumers are using social media to share vaccine experiences
- Web and social media listening using AI/ML can efficiently provide insights about AEs related to COVID vaccines and information on consumer concerns about vaccine safety

Soteria App

- The Soteria App captures insights on consumer concerns and vaccine safety signals from 190 countries in 61 languages
    - Data gathered weekly from social media sites including Twitter
    - Several NLP modules such as the AE model, lexical models to detect special populations and vaccine brands, databases for MedDRA vocabulary and weekly counts
    - Trends by vaccine brand, company, and mechanism, country, MedDRA level, and special populations (pregnant and pediatrics)
- Insights gathered help adjust signal detection strategies and communication to external stakeholders, contributing to increased confidence in vaccine monitoring and safety
    - Presented using visual analytics

Example Insights

- How often did patients talk about COVID-19 vaccine safety topics?
    - Using Soteria, generated a unique dataset on patient voice on safety topics around COVID vaccines
    - Looking at the distribution of number of mentions with an AE (detected as MedDRA PT) between November 202 and April 2022, there were many mentions in 2021 and less in 2022

- Carditis, myocarditis, hyperthermia, fatigue, and headache were leading AEs for mRNA COVID-19 vaccines mentioned for pediatric group
    - Results concordant with published results on AEs for US adolescents 12-17 years old who received Pfizer-BioNTech COVID vaccine (dizziness, syncope, nausea, headache, fever)
    - Top 5 serious reports in the US VAERS system including chest pain, increased troponin, myocarditis, increased CRP & negative SARS-CoV-2 test result

Immune Correlates of Protection (CoP) in the Moderna COVE Study and CoP for Variants

Dr. Peter Gilbert, University of Washington

Challenging to Approve All Efficacious Vaccines Based on Randomized Placebo Controlled Trials

- >100 unapproved candidate COVID vaccines in clinical testing
- Placebo controlled RCTs are becoming rare
- Alternative approaches to approval:
    - Active comparison arm Phase 3 trial with a clinical endpoint (non-inferiority design)
    - Immune marker surrogate endpoint trial
        - Could potentially support accelerated approval if marker is reasonably likely to predict vaccine efficacy but not yet scientifically well established

Sources of Evidence for Validating an Immune Correlate

1. Natural history studies – showing the marker is a correlate of risk of the clinical endpoint
2. Post-approval epidemiological studies – supporting the marker is a correlate of risk and a correlate of protection
3. Immunoassay/biomarker development
4. Studies supporting the marker (partially) captures a mechanism of protection
5. Meta-analysis of multiple phase 3 VE trials
6. Analyses of individual phase 3 VE trials showing evidence for the marker as a correlate of risk and a correlate of protection

COVE Trial: High mRNA-1273 Vaccine Efficacy

- Demonstrated the Moderna COVID vaccine was highly efficacious for preventing COVID over the first 2-3 months following dose 2
- Four antibody markers assessed as immune correlates:
    - Binding antibody (bAb) Assays: bAb to Spike, bAb to RBD
    - Neutralizing antibody (nAb) Assays: PsV nAb ID50 titer, PsV nAb ID80 titer
- First immune correlates paper provided results from Stage 1 of the trial which focused on blinded placebo for ~peak Ab short-term follow-up correlates analyses
- Stage 2 was open-label, post-crossover, post-dose three, and will provide data on post PDV breakthrough cases and Ab over time as correlates:

Numbers of Per-protocol Baseline Negative Vaccine Recipients with Antibody Data	
Group	Number
Breakthrough cases for analyses of Day 29 markers	46
Breakthrough cases for analyses of Day 57 markers	36
Non-cases in the immunogenicity subcohort (stratified random sample)	1005

Day 29 marker analyses: Include all cases >=7 days post Day 29 visit
Day 57 marker analyses: Include all cases >=7 days post Day 57 visit

Analyses

- Antibody levels lower in vaccine breakthrough cases than vaccine non-cases
- Statistical Inference about immune correlates:
    - Correlates of Risk (CoR) – How well do post-vaccination antibody markers predict COVID occurrence? (inference on statistical association parameters)
    - Correlates of Protection (CoP) – How well do post-vaccination antibody markers predict or cause vaccine efficacy against COVID? (inference on causal effect parameters)
- Applications of Immune Correlates
    - Validating an immune correlate is a central goal of vaccine research
        - One of the 14 'grand challenges of global health' of the NIH & Gates Foundation (for HIV, TB, Malaria)
    - Immune correlates are useful for: shortening trials and reducing costs, guiding iterative development of vaccines between basic and clinical research, guiding regulatory decisions, guiding immunization policy, bridging efficacy of vaccines in new settings

Summary of COVE Results Under the Neutralization CoP Model

- VE as a function of vaccinee Day 57 PsV nAb ID50 titers:
    - Positive δ: saturates to ~100%
    - Negative δ: stable, ranging from ~70%-90%
- Bridging VE to variants based on ID50 titer indicates VE drops no lower than 70%
- For delta, VE estimated to be 85%-90%, across three sub-variants studied by the Montefiori Lab
- For omicron, VE estimated to be ~75% against sub-variants with 30-40 fold reduction in nAb ID50 titer compared to D614G
- Ongoing validation of nAb ID50-CoP model for predicting CoP
    - Adding estimates of variant-specific VE from test negative design observational studies
    - Quantify accuracy of CoP-predicted VE

Discussion

- It is important to think about real-world studies as complementary to randomized trials
    - Observability of exposure, observability of outcomes, and what questions/how we ask questions are key considerations in the design of quality real-world/observational studies
- Potential value of linking clinical trials to real-world data – for example, take a clinical trial cohort, de-identify and connect to RWD, follow longitudinally
- Test negative designs to learn about CoP
- One challenge is finding the exact patients you're looking for, RWD can be used to think about inclusion/exclusion criteria on a broader scale and can help to identify a greater volume of patients which is important for CoP and CoR studies