



COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #26

Thursday, March 18, 2021, 12:00-1:00PM ET

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 26

This week's Diagnostics Evidence Accelerator meeting consisted of 2 presentations:

1. Trajectory of SARS-CoV-2 Pandemic (Herbert (Skip) Virgin, Vir Biotechnology)
2. Interoperability: Impetus for Change (David McClintock, University of Michigan and Thomas Durant, Yale University)
3. Introducing "Heidi for Vaccines" and the Vaccines Evidence Accelerator (Gina Valo and Donna Rivera, FDA)

As always, thank you to all of the analytic partners, strategic advisors, and scientific advisors that are participating in this project. As of the week of March 15, 2021, we are on step 6 where accelerators are revising Aim 1 manuscript on testing characterization and on step 9 where accelerators are running their Aim 2 analysis.

Trajectory of SARS-CoV-2 Pandemic (Herbert (Skip) Virgin, Vir Biotechnology)

During a pandemic, variants are expected to emerge. The major factors that determine how a virus varies during a pandemic are the intrinsic error rate of viral polymerase, size of the pandemic; fitness of variant viruses in transmission and replication; virus coverage; virulence of variant viruses; availability of immunocompromised host for prolonged infection; immune selective pressure and full pressure awaiting herd immunity; evolution outside of humans may allow introduction new strains; and unexplored role of variation outside of spike which is a key weakness in knowledge.

The structure of the spike protein was shown to illustrate how a virus mutates. There are approximately 722,055 sequenced viruses in the GISAID database, which is estimated conservatively to be only about .6% of viruses that have occurred in humans thus far. Additionally, 71% of the known sequences come from only 4 countries, which together make up approximately 7% of the world's population. With travel, the variants will continue to spread and we will not know where the variants are due to the mixing of the population and low sequencing coverage across many countries. Later in the meeting another illustration of the spike protein was shown. In that diagram, Accelerators were able to see where the mutations are located on the spike protein. These mutations enhance growth in different animals such as gorillas, mice and minks. Therefore, it is speculated that variants are not just a human problem, they could be a mammalian problem.

During the meeting, a graph was shown that illustrates the prevalence of sequences from variants of concern that are added to the GISAID databases. Since the beginning of the pandemic, there are increasing numbers of sequences from variants being added to the database. These variants are unstable (can continue to mutate), therefore there is a greater chance of mutations. Additionally, some of the variants such as a newly reported relative of the UK variant, are a hybrid of two variants (the original UK strain with a key mutation also observed in the South African Strain) potentially making them highly transmissible and enhancing the potential to evade immunity.

There was discussion of a paper that is published in the Lancet that discusses how important variants are. The study was conducted in Manaus, Brazil where they saw a surge in cases in May 2020. Once a mask mandate was implemented in the town, there was a downward trend in the number of cases. By analyzing a sample of the population donated blood, researchers saw that 76% of the population had natural immunity to the SARS-CoV-2 virus. In January 2021, there was an additional surge in the number of cases, therefore the residents were faced with a variant of the SARS-CoV-2 virus, which appeared to cause a greater number of reinfections. Another paper published in the New England Journal of Medicine noted that the AstraZeneca vaccine is only 10-30% effective against the South African strain.

There was a discussion about how the mutations are not stable, and therefore can change in the future based on mutations and external circumstances. Data was presented from a paper showing that the UK variant (B.1.1.7) was neutralized by serum from recipients of the BNT162b2 mRNA vaccine. However, since the UK variant picked up an amino acid sequence also observed in the South African variant, there is a decrease in the effectiveness of serum from recipients of the BNT162b2 mRNA vaccine against this new virus. The presentation ended with the a discussion of a [paper](#) published on the dual function monoclonal antibodies VIR-7831 and VIR-7832, demonstrating potent in vitro and in vivo activity against SARS-CoV-2 variants. Additionally, there was a [press release](#) from Vir Biotechnology that discusses interim data which prompted the Independent Data Monitoring Committee (IDMC) to stop enrollment due to evidence of efficacy for VIR-7831 against COVID-19.

Interoperability: Impetus for Change (David McClintock, University of Michigan and Thomas Durant, Yale University)

The presentations discussed the interoperability for lab values. There were multiple subspecialty practices within the health care system that have requested external lab results to be included within their local electronic health record (EHR). This would allow physicians to create and assess medications used in long term patient care plans; timely adjust medication dosing for patients; allow patients to get labs drawn/performed close to home; instead of traveling to hospital draw sites; and allow patients to choose the laboratory that will provide the best insurance coverage per their specific plan.

There are more than 22,500 estimated patient-prescribed immunosuppressive medications within institutions and more than 17,000 active patients on immunosuppressive medications requiring medication monitoring in the EHR. Also, there are more than 10 different drug classes requiring monitoring and more than 30 different immunosuppressive medications prescribed in 161 ambulatory care units (ACUs). Therefore, there was an extreme need for including external lab results in the HER.

There are 2 processes to create an External Lab Interoperability: importing external lab values and using external lab values. For importing external lab values, there were many options. The first option was to manually result entry group that was established. This required using reports that are received via electronic fax and email. It was mentioned that through this method, there were varying turn around

times for different services. Finally, the results are entered at the component level, therefore they can enter discrete values, look at trends, and able to used for CDS tools. The values are designated as “EX” labs for external lab values. The second option was to use CareEverywhere (Epic’s Health Information Exchange) for automatic loading of external lab results already present. This was only mapped at the chart level. In order to map them at the patient level, they had to take additional steps and effort. The third option that they could use was the Michigan Health Information Network (MiHIN). It included real time data, external lab results, and data from non-Epic institution that are not eligible for CareEverywhere. The way that this model works is that organizations will send information to the MiHIN HIE, the data will be filtered through MiHIN HIE, and matched with the patient. The method that was chosen was a hybrid MiHIN and CareEverywhere. However, this would bring in duplicates into the data presenting additional measures to eliminate the duplicates.

Therefore, interoperability is not easy. Researchers will need a prioritized list of tests and assays that clinicians use and the granularity at which they will need them at to include into the system. Additionally, they will need to build each external lab test for each organization, and repeat this for each new test added. In order to do this, the external lab resulting requires additional resources such as 2 FTE for dedicated external result setup and configurations and continued maintenance. Also, there is a need for a review process by labs and clinicians in order to make sure the technical pieces are appropriate.

Example of how interoperability works in the context of COVID-19 was provided. In the first example shown, the presenters were asked develop a solution to identify patients under investigations (PUI). The solution that they developed was to link a specific test in the EHR with a Rule Out COVID-19 test. When this test is ordered, patients would automatically be placed on a COVID-19 isolation precaution and patient’s chart will be updated with a blue banner. Rules were attached to this to indicated what precautions should be taken. If the test is positive, the blue banner will stay for 10 days to indicate an isolation precaution. If the initial test is positive and then the subsequent test is negative, then the blue banner stays for 10 days unless it is manually removed by the infection prevention team. If the test is negative, then the blue banner is removed automatically and the patient is removed from isolation precautions. However, there can be confusion that occurs in this process. If the lab result was positive, but the patient had a negative test the day before, and the subsequent is negative, then the question of should the patient be in isolation remains. Additionally, questions about the test such as was a point of care test given or was it from a less sensitive assay arise.

In their second example, the presenters discussed COVID-19 direct admits. Bed management would review the inbound cases for COVID-19 clearance. They would also have a list of acceptable tests that can be used with the exception of tests which are less sensitive. An example was presented where a patient is transferred from another hospital and a diagnostic test has been conducted. At the new hospital, providers will have to ask if they can use the diagnostic test conducted at the other hospital or administer a new test. Also, if the diagnostic test conducted at the first hospital is positive and at the second hospital is negative, then what should a provider do. These questions still remain and need work.

Introducing “Heidi for Vaccines” and the Vaccines Evidence Accelerator (Gina Valo and Donna Rivera, FDA)

The Hypothetical Patient “Heidi” was previously used as a model to understand the importance for connecting the pipes for real-world performance of diagnostic tests. Now that there are vaccines that are receiving an EUA, interoperability becomes an important topic for vaccine data . There are three foundational phases for collection of data in the vaccine space(pre-vaccine, vaccination, and post-

vaccine long term monitoring). The pre-vaccine phase consists of collecting any data on prior exposure or treatment for COVID. The vaccination phase includes vaccine administration specific data (type, dose, date, and demographics) as well as initial side effect monitoring. The post vaccine long-term monitoring phase consists of long-term safety data and understanding the duration of immunity.

The Accelerator community was introduced to:

- Maya, a 48-year-old Hispanic female healthcare worker. After recovering from COVID-19, she moved for a new job and received the COVID-19 vaccine. Therefore, Maya's healthcare data is located in her previous city and in her new city.
- Steve is a 56-year-old White male Veteran. His data is captured through the VA EHR system. Steve enrolled in a vaccine clinical trial where his vaccine data was captured carefully.
- Carol is a 60-year-old White Female grocery worker. She received her vaccine at the Department of Health because it was the only place she could access an appointment. She receives medical care across various healthcare settings. Therefore, having an RWD data aggregator to link this data may be useful.
- Miles is a 78-year-old Black male and is professor. Miles represents the individuals who do not receive the vaccine due to multifaceted reasons. Miles has excellent access to care; however, he has vaccine hesitancy due to not only previous, but current contexts of structural inequity.

Heidi also received her vaccine at a stadium. However, due to her receiving her vaccine at a local stadium, the data is not captured well in the data system.

These stories have key differences in care setting that cause variance in RWD fitness for use. From Maya's story, we can learn about the real-world utilization of vaccines (demographics, geographic and temporal patterns, vaccine compliance) as well as studying long-term safety and real-world duration of immunity. From Steve, we can learn about vaccine efficacy, and initial vaccine safety through the trial data. Carol represents the potential for disconnected data and provides insight into how we can derive fit for purpose questions from disparate sources (inpatient, Department of Health, and outpatient) or , if there use of an RWD aggregator additional questions across data or longitudinally can be answered. Capturing RWD provides a unique collaborative opportunity to gain knowledge which can build evidence and potentially improve outcomes, especially in the context of increasing vaccine confidence .

From the Chat Box

- An accelerator asked if we are getting better coverage from other than the four countries
 - The presenter responded no we are not. That are major sequencing centers around the world that are collecting this data is important. The presenter mentioned that the UK variant and the South Africa Variant are more virulent therefore, spread easily.
- Another accelerator asks if the presenter can address the New York Variant that was mentioned as very concerning.
- Does the graph of mutants represent all variants or variants of concern? The presenter would expect lots of variants, but the ones of concern are those that we really want to focus on as they are related to the effectiveness of the vaccine or impact on pathogenicity or infectivity.
 - There is a development of machine learning to predict variants, therefore there will be technology that can predict from current data what a virus will do in the future. The virus will tell us what the important variants are. In the variations, our immune system and

behavioral changes are putting pressure on the virus. The virus already has variations and when there is a new selective pressure (e.g. vaccines), then the new variants come out.

- One accelerator commented that the graph shows 80% are new variants is scarier if those are variants of concern that impact vaccine performance, immunity, pathogenicity.
- Another accelerator stated we need to be able to characterize the clinical features of newly identified COVID-19 viral variants to understand the danger associated with them. We can now make therapy decisions based on nucleotide coding and sequence alterations that maintain a stable representation as more data are collected (once the data management hurdles were overcome) and apply that knowledge to identify new COVID-19 viral mutations. In contrast to what the U.S. can accomplish with our currently dysfunctional EHRs, there are countries that sequence 50% of the virus isolates and can promptly link them to clinical data to know which variants are associated with particular clinical profiles, a task that requires the maintenance of a high level of clinical data veracity that we cannot reach because of our non-interoperable EHR systems.
- A speaker asked how do we think about describing SARS-CoV2 vaccine immunity? Is it antibody (spike or neutralizing)? Is it T-Cell? or is it both? T-cell might not be specific to SARS CoV2 or vaccine. On the other hand, we wouldn't expect antibody to virus to be consistently elevated, right?
- Another speaker asked if the lab results at the University of Michigan and Yale University were exchanged using HL7 v2.x.
 - The presenter responded yes, they are. They receive the lab results from MiHIN via HL7 and then use that version to put them back in the EHR.
- A participant asked wouldn't be easier for all, if we would have comprehensive lab data collection standards.
 - The presenter responded ideally, we would have a national patient identifier to make patient matching easier (right now we have to compare at least 5 if not 7 or more patient identifiers to ensure the patients match), in addition to standardized HL7 formats for sending lab results to HIEs, followed by incentives for hospitals to adopt these standardized formats.
- Another invitee stated that it's helpful to understand why this is so difficult and to imagine how that same level of effort has to happen across every institution.
- A speaker stated that emphasizing the amount of manual effort needed to do this with existing processes and tools. There is a lack of understanding on both what and how to do this and there is a belief that this is easy and consistent. It would be great to see some kind of working group that is cross industry to see where things can be cross utilized.
- An accelerator stated that standardized test names with greater adoption of LOINC by vendors (to make sure all labs use the right LOINC code for each test/assay) is also key, along with the ability to send additional test data, e.g. sensitivity, specificity, PPV, NPV for a lab's assay would help to determine how well clinicians can trust the test.
 - In response to this, an accelerator states LOINC is great only IF people use it and map the right codes. When they have to guess, the standard fails...we had CBC mapped to an umbilical cord blood gas purely by human error, confusing clinicians.
 - Another accelerator commented stating we have recommending submission of LOINC as part of clinical trial data to FDA (for CDER and CBER) <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-submission-loinc-codes-regulatory-applications-us-food-and-drug-administration>.
- Another accelerator stated that from a patient perspective that this would be good information to have too - as an evolution of records - where patients can see what is happening with themselves.

Hard to explain to a clinician what has happened when you don't even have access to your OWN information in a format that is easy to use and transferrable.

- A speaker said interoperability issues are equally challenging with the health plans and the longitudinal data that supports FDA Sentinel Surveillance activities. As we shift to vaccine discussion linkage of IIS to various data sources is critical prior PRISM work on vaccine data linkage: <https://pubmed.ncbi.nlm.nih.gov/23129683/>.
- An accelerator states health plans are obtaining claims from mass vaccination sites. CVS billed for administration in nursing homes through pharmacy claims and for Medicare in Part B claims. There is a difference between RWD aggregator from Health Plan (Anthem, Aetna, Optum, Humana).

Next Steps

- Continue making data connections through the Evidence Accelerator and through www.EvidenceAccelerator.org.

Next Meeting: Thursday, April 1, 2021 12-1 pm ET