COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #21

Thursday, *December 17, 2020, 12:00-1:00PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting 21

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

1. National Football League COVID-19 Monitoring Program (Christina Mack, IQVIA and Allen Sills, NFL)
2. NCI SARS-CoV-2 Serology Studies (Doug Lowy, National Cancer Institute)

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 December 11, 2020, we are on step 4 where accelerators are refining Aim 2: Positive Percent Agreement & Risk of Seropositivity protocol.

National Football League COVID-19 Monitoring Program (Christina Mack, IQVIA and Allen Sills, NFL)

The NFL/NFLPA has three main goals: 1) to create a safe environment for its players, coaches, and staff; 2) to model and amplify public health messages; and 3) to share lessons learned with the public health community. Through the NFL/NFLPA 2020 season COVID-19 Monitoring Program, it has developed a longitudinal COVID-19 database that covers the 32 teams or "mini-communities" that are part of the NFL. This has provided the League with insights into real-world effectiveness of COVID-19 monitoring, mitigation and diagnostic testing strategies. There are 3 components of the Program: screening and testing, behavioral protocols, and active contact tracing. All of these elements must work together to create a monitoring and surveillance system that enables safe return to sport, in large part identifying cases early and preventing transmission.

The Program has resulted in a comprehensive linked database of real-world data joining testing results, symptomology and wearable devices that provide exposure information. The NFL is administering daily PCR tests which are coupled with ad hoc antigen point of care (POC). There is near-complete follow up with case adjudication in the 32 NFL teams, as this is largely an employee population with comprehensive monitoring and care. To date, the NFL has administered approximately 870,000 PCR tests across more than 15,000 individuals in 5 months. Through this, it has produced key findings with important implications for public health along with practical application to broad populations. These include: 1) the type of PCR machine matters, 2) quantitative values (cycle thresholds) are instructive and can be used as a guide for diagnoses and patient management, 3) antigen POC tests failed to detect virus early in infected patients, and 4) wearable devices are essential tools in understanding exposure and transmission. NFL/NFLPA Protocols have evolved empirically over the season, driven by analytics

and ongoing expert review of real-world evidence; this has been key to having effective operational protocols in this unprecedented season.

In the NFL-NFLPA screening and testing protocol, there are 5 laboratory sites and 3 diagnostics platforms across a central lab provider (BioReference). In 2 sites, if the sample is positive on the Roche platform, then the sample is rerun on the Hologic machine, which allows comparison of the sensitivity and specificity of the machines. In one lab of the labs, the sample is run on a ThermoFisher platform and in two labs the sample is run on a Hologic platform. The NFL has administered approximately 6,200 PCR tests per day to 70-89 players and 125-233 staff members per club. The key takeaway is platform-specific variance in positive predictive value (PPV). A second key takeaway is that CT values from the Roche machine provided a guide for interpretation and clinical decision making. Finally, antigen POC tests may not detect infection early in cases where PCR was able.

The NFL/NFLPA behavioral protocols mandate and enforce: extensive restriction in facilities, during travel and at hotels, which include but are not limited to 1) wearing masks at all times, 2) physical distancing, 3) limited meal-room facilities, 4) lowered room capacities, 5) employee tier structures with safety-focused inter-tier restrictions, 6) seating charts during travel, and 7) wearable proximity devices worn at all times in facilities and during travel. The contact tracing protocol uses linked wearable proximity device data with PCR test results available through an integrated database, which provides positive case notification and contact tracing on a real-time, actionable basis. It also allows for monitoring of protocol compliance. The key points from contact tracing are that testing alone is not sufficient, and wearable device data can is helpful, but not sufficient for contact tracing; in-depth interviews are also necessary. Adhering to protocols and thorough contact tracing can prevent and/or minimize outbreaks.

NCI SARS-CoV-2 Serology Studies (Doug Lowy, National Cancer Institute (NCI))

NCI COVID-19 response consists of foundational serology through the Serological Sciences Network (SeroNet), clinical & translational serology, support for cancer research and care amid the pandemic, and additional COVID-19 research. NCI received supplemental funding from Congress to develop, validate, improve, and implement serological testing and associated technologies. For one of NCI's response to the pandemic, they are using SeroNet which has a goal to increase national capacity for serological testing and advance our understanding of all aspects of the immune response to SARS-CoV-2 to enable development of therapies and vaccines. Also, NCI is evaluating antibody test performance with the FDA. The have evaluated more than 100 serology tests and provide test performance data to the FDA. This has fostered an interaction between NCI and devices. NCI has developed a reference serology standard which can be used for benchmarking antibody studies.

NCI collaborated with HealthVerity to write a manuscript titled *Real-world data suggest antibody positivity to SARS-CoV-2 is associated with a decrease risk of future infection*. The main question they looked at is whether serum antibodies that develop after SARS-CoV-2 infection are associated with a decreased risk of reinfection. The secondary question is whether we can use anonymized "real world data". The HealthVerity data ecosystem provides an infrastructure to connect data from over 75 unique data sources, uses a secure encrypted linkage process, permits access to the broad categories of data on millions of individuals, and uses anonymized but linkable commercial laboratory data, Medical claims, and EMR data. HealthVerity SARS-CoV2 has serum antibody tests on approximately 4 million patients and viral RNA tests on approximately 20 million patients. They have conducted more than 5 million antibody tests and the average positivity rate is 11.13%. For the diagnostic test, more than 31 million

tests have been administered and the average positivity rate is 8.59%. NCI is able to adjust for underlying comorbidities.

For the study design, the index event had 88.3% antibody-negative, 11.6% antibody-positive, and 0.1% inconclusive patients. The study index date for each patient was the date of first SAR-CoV-2 antibody test after January 8, 2020. The follow up period was captured in 30-day increments after index date to monitor viral RNA shedding (NAAT). This represents ongoing viral shedding or new infection. This was compared to NAAT positivity (proxy for re-infection) rates for index antibody-negative and antibody-positive patients. There were more female patients in the study. Most of the patients were from the northeast because of the availability for testing and antibody IgG tests were administered more.

They saw that there were similar rates over multiple 30-day intervals for index antibody-negative patients and progressively declining rate for index antibody-positive patients. Diagnostic viral RNA test results for subsequent 30-day intervals after index antibody test showed progressive decrease in ratio of positive viral RNA among index AB-negative antibody-positive and antibody-negative AB+/Ab- (95% CI). The vast majority of viral RNA tests were triggered by symptoms. Also, they found that progressive time-dependent reduction in ratio of viral RNA positivity rates between antibody-positive and antibody-negative patients at index (from 2.85 at 0-30 days to 0.1 at >90 days) is consistent with seropositivity being associated with protection against symptomatic re-infection. Reduced infection rate among antibody-positive patients was not attributable to them getting fewer viral RNA tests. Instead they had more tests per person than antibody-negative people. Also, the inferred level of protection could be an overestimate or an underestimate. An overestimate could lead to possible confounding biases from observational study. In an underestimate, if antibody-positive people thought they were immune, they might have engaged in riskier behavior. Finally, the increased rate of NAAT positivity observed within the first 30 days of a positive index antibody test is consistent with persistent shedding of viral RNA.

The conclusions that could be drawn from their study are the presence of antibodies to SARS-CoV-2 is associated with a reduced risk of developing a subsequent symptomatic SARS-CoV-2 infection and the observed decrease during the >90 day period was approximately 10-fold. However, these data cannot address whether exposure to SARS-CoV-2 in antibody-positive people may develop asymptomatic viral infection when they are exposed to the virus. The remaining issues are that these data cannot address whether antibody-positive people might have asymptomatic viral shedding when they are exposed to the virus. We do not know how long seroprotection will last, whether antibody-positive people who become antibody-negative are still protected, and whether patients whose first infection is asymptomatic will be protected from new infections. These questions could lead to future research and collaboration.

From the Chat Box

National Football League (NFL) COVID-19 Monitoring Program (Christina Mack, IQVIA and Allen Sills, NFL):

- Is the wearable just for contact tracing or are their biosensors embedded?
    - The wearable devices is just for contact tracing and proximity wearing device. However, teams have been using it to for prophylactic purposes too. it allows the clubs to modify their routines and change behavior.
- Do you continue daily testing even after a person comes back as positive?
    - No, but they do test in the days after their test results for confirmatory purposes.

    - Once the individual has a confirmed case of COVID-19, then that individual is out of the testing protocol and they are tested for 90 days and then come back into the daily testing protocol.
    - They are doing whole genome sequencing on the positive samples to understand transmission.
- Did you use same PCR kits on different instruments or, for ex. Roche kits with Roche Instruments, Thermo kits with Thermo instruments?
    - Yes. It is the same equipment.
- 1-2 day advanced detection of virus in Roche - do the CT values during that early time suggest viral levels significant for transmission?
    - Since they are testing daily, they are able to see viral levels significant for transmission.
- What happens in the event of noncompliance for testing, masking, etc.?
    - There is no option to not test and if someone missed the test, then they are not allowed to play. One thing that motivated clubs are the competitive advantage. If the team is healthy, then they will have an advantage. They are not going to make decisions based on money and all of the decisions will be made based on medical data.
- How do you define recovery to allow players to resume normal activities? Resolution of symptoms or a negative test or something else?
    - They follow the CDC guidelines on return. They do not require a negative test for return and they continue to monitor symptomology.
- Do you have a protocol or recommendation algorithm for how often people should be practically testing (e.g. considering costs and convenience outside of the NFL bubble). If negative for early detection + prevention? Presumably if positive then they may not need daily testing and a recommendation may be made as to threshold guides for next test.
- How expensive is all this? What can be extrapolated to general population?
- What about POOLING. It seems the guidance to pool samples for analysis on the Roche would hinder your sensitivity while rendering the Ct values less useful. Also, what was your false positive result rate for high value Cts? Did you have folks that tested x1 positive on PCR but never tested positive again?
- How "closed" were the communities of ~200 individuals each, aside from interacting with each other?
- Have you seen any correlations between testing data (CT level, days between exposure and first positive, etc.) and whether a patient develops symptoms?
- An accelerator shared regarding whole genome sequencing, interesting article recently in Nature about genetic mechanisms in COVID responses; https://www.nature.com/articles/s41586-020-03065-y

<u>NCI SARS-CoV-2 Serology Studies (Doug Lowy, National Cancer Institute (NCI))</u>

- Were the antibody tests used centrally calibrated by the same positive and negative controls and high and low standards?
    - All of the tests used have EUA and they have good sensitivity and specificity.
- What was the percentage of patients being Ab positive after PCR positive?
    - The investigators have not been able to analyze this but are looking forward to working with HealthVerity to answer these questions.
- Did you correlate the levels of PCR positivity with the levels of antibodies or antibody types?
    - This is not have been part of the authorization for the tests tha have been administered.

- Was the pilot study only on cancer patients?
    - This pilot study did not only include cancer patients.
- What can be done to design a pragmatic long-term observational registry to follow the Ab+ patients for a longer period of time? This group of individuals is an important group to study to discern whether they are naturally protected from subsequent COVID infections.
    - They are looking forward to doing that.
- The presenter's colleague stated that HealthVerity has been pleased to work on this important project, along with our collaborator Aetion, with NCI.
- Are these antibody tests measuring the same antigens?
    - No, there are all sorts of antibodies used commercially.
- Have you/ are you planning to assess the impact of care-seeking behavior and test prescribing behavior on the data (e.g., an individual who tested positive for SARS-CoV-2 before may be less likely to be tested again in the next 90 days even if they develop symptoms consistent with COVID-19)?
    - This could be envisioned for the future.
- Curious how you're thinking about these questions for people who receive the vaccine?
    - The presenter asked if there any data on vaccinated individuals? There is data from Europe that the levels of anti-spike Abs in vaccinated individuals may be much higher than natural infections.
- Do you have information on indication for antibody testing - could it be related to duration of symptoms or other disease related factors?
    - An accelerator stated that the Diagnostics Evidence Accelerator have examined factors associated with antibody testing!
    - They are going to be addressing this in a future collaboration with HealthVerity.
- An accelerator wondered what would be the most practical strategy for return to normal; i.e. environmental controls, redesigning air-conditioning systems and the use of UV light to decrease contamination of environment, especially offices etc.? Any practical ways of detecting the virus in the environment?

Next Steps

- Continue making data connections through the Evidence Accelerator.

Next Meeting: Thursday, January 7, 2021 12-1 pm ET