



## COVID-19 Evidence Accelerator Collaborative

### Diagnostics Evidence Accelerator #14

Thursday, September 17, 2020, 12:00-1:00PM ET

#### Call Summary

#### Introduction to Diagnostics Evidence Accelerator Meeting 14

This week's Diagnostics Evidence Accelerator meeting consisted of 4 presentations.

1. Clinical Utilization of SARS-CoV-2 Serology Tests (Jim Freeman, Siemen Healthineers)
2. RADx Update (Rachael Fleurence, NIH)
3. Tracking COVID-19, Influenza and RSV (John Tamerius, Quidel Virena)
4. Parallel Analysis Project One Update (Carla Rodriguez-Watson, Foundation and Gina Valo, FDA)

#### Clinical Utilization of SARS-CoV-2 Serology Tests (Jim Freeman, Siemen Healthineers)

The central theme of this presentation was that not all serology assays are the same. The three main differences are; the specificity ranges from 95-99.8%, qualitative vs quantitative, and whether they measure antibodies which only bind some part of the virus, or instead actually neutralize the virus, which is the mechanism by which immunity is conferred.

Test performance can vary by prevalence even when using a "good test". If the researchers are looking at a serology assay that has a specificity of 95.0% and the prevalence of the population is 5%, then the positive predictive value (PPV) is 50% compared to a serology assay that has a specificity of 99.9% in the same population, the PPV is greater than 90%. Therefore, the specificity of a serology assay is an important factor in receiving the right answers.

Serology assays are being created using nucleocapsid protein, Receptor Binding Domain (RBD) protein, spike protein (S1 and S2) and only S1 on the Spike protein. The spike protein is divided into 2 regions, S1 and S2 domains. The RBD is located on the S1 region. Antibodies against the viral protein are produced early into the infections and are produced in similar concentrations. IgM and IgG antibodies show up 7 days after the onset of symptoms and the concentration increases at a fast rate, therefore, the question that we need to answer is how long antibodies last in the human body. This requires an assay which is quantitative.

The antibody response will be underestimated by tests for anti-N. There was a discussion of research conducted surrounding serology testing. [Grandjean et al.](#) found that the half-life of the N-antibody was significantly shorter than that of the Spike protein and the RBD protein. [Fenwick, C et al.](#) saw a similar finding in the anti-N antibody response which will underestimate the proportion of virus exposed individuals compare to anti-S antibody response. Antibodies to RBD that are associated with neutralizing

activity form in response to both infections and vaccination. The Moderna mRNA vaccine produced neutralizing antibodies in human volunteers. In the preliminary report conducted by [Jackson et al](#), “the mRNA-1273 vaccine was immunogenic inducing robust binding antibody responses to both full-length S-2P and receptor-binding domain in all participants after the first vaccination in a time- and dose-dependent fashion”. There is a strong neutralizing response seen in patients that are older than 55 years of age. In another study conducted by [Premkumar, L. et al. \(2020\)](#) supports the use of RBD antigens in diagnostic assay. Also, their results provided strong support for the use of RBD based antibody assays for population level surveillance and a correlate of neutralizing antibody levels in people that have recovered from infections.

All antibodies bind some protein in the virus but only a subset actually neutralize the virus. Neutralization is the mechanism by which immunity is conferred. In another publication, the researchers found that there was a “significant correlation between neutralizing antibody titers and AUC of anti-S-RBD IgG, but not of anti-NP IgG...” ([Ni et al., 2020](#)). Anti-Spike proteins and anti-nucleocapsid were present in the seroconversion but only the anti-Spike proteins were able to neutralize the virus. Both N and S proteins elicit an antibody response with similar kinetics though not all infections produce similar levels of antibodies.

Cross-reactivity with antibodies to other influenza viruses can confound interpretation of some assays. N protein and full-length Spike (S1/S2) antibody assays may have greater risk of cross-reactivity. [Ng, K et al \(2020\)](#) reported that there was cross reactivity with IgG antibody to seasonal coronavirus for SARS-CoV-2 assay that included S2 or N. [Premkumar, L et al. \(2020\)](#) found that people who have been exposed to acute common HCoV infections do *not* have detectable levels of cross reactive antibodies to the recombinant RBD of SARS-CoVs.

The best immunoassays to use in an acute setting are RBD and Nucleocapsid based assays to aid in diagnosis. To see if a patient is recovered, an IgG assay works best. To assess potential immunity such as individuals that have been vaccinated, the best assay to use is the IgG or total antibody assay. It is important to use receptor binding domain assays because those are the protein determinant of the virus that elicit a neutralizing response. It is important to know which assay was used to conduct the test, however, there is no determination of a LOINC code for assay methodology which does not provide data for assay design. HHS announced new laboratory data reporting for COVID-19 testing to be implemented by August 1, 2020, but the new guidelines are missing assay methodology. The data mining that is required are inadequate to do the type of trending that may be necessary.

### **RADx Update (Rachael Florence, NIH)**

The goal for the RADx initiative is to accelerate innovation, development, commercialization and implementation of COVID-19 testing. Their approach is to fund programs that they have developed such as RADx-tech, RADx-ATP, RADx-UP, RADx-rad, and coordinate with other government agencies such as HHS, DoD, FDA, BARDA, and CDC. The team published a paper in July 2020 called “Rapid Scaling up Covid-19 Diagnostic Testing in the United States- The NIH RADx Initiative” which provides an overview of the program and potential challenges.

The overall goal of RADx-ATP is to increase testing capacity. They awarded 7 high-throughput labs and 1 point-of-care organizations with funding to further the goal. RADx-ATP is continuing to work with the RADx Program Core Services to mitigate supply chain and regulatory issues. With that goal in mind, RADx-ATP has reached many milestones. The milestones that they have reached are achieving testing

capacity that have been reached by 5 of the 8 awardees. The RADx Core Services and ATP Coordination reduced reliance on constrained supplies and identification of alternative vendors to help address short-term scaling barriers. Finally, NIH-FDA Regulatory Partnership continues to prioritize RADx EUA submissions with the support of RADx Core Services.

The goals for the next 3 months are to continue working with the Core Services teams to help scale testing efforts. Also, coordinate and guide the companies through challenges in achieving EUA for expanding the use cases to saliva-based testing or at-home testing. Finally, in preparation for flu season, RADx-ATP will support the awardees as they move to incorporate influenza A and B testing along with COVID-19 testing in a single kit. Their identified challenges are to identify digital health platform that can provide connectivity among test results, EHR, and public health organizations. RADx developed a test called Accula and they are working with the GATES Foundation to integrate with POC test results. An app was developed to upload images of test results which can be transmitted. This will allow them to be able to collect point-of-care testing data. Laboratories are reporting data to the state, but data completed at POC may be incomplete or not linked to test results. Point of Care test data is uneven. Data solution include apps and readers and transmission from the analyzer. They are looking for strategies for at home test without readers, balancing low-cost, frequency and ease of use with possible underreporting of results.

### **Tracking COVID-19, Influenza and RSV (John Tamerius, Quidel, Virena)**

Quidel has developed immunofluorescent analyzers called Sofia and Sofia 2 for their assays. The analyzers connect to the LIS system directly. They have a data management system called Virena which is HIPAA compliant, therefore, the patient deidentified data is being transmitted to public health laboratory, CDC, and clinical centers using their system.

Virena was developed for two primary purposes: 1. to enable health system personnel to monitor Sofia/Sofia2 test results, including review of QC data, calibration, operator performance, and assay results and use at each facility, and 2. to permit patient de-identified data to be sent to public health agencies and government for monitoring infectious diseases regionally and nationally. This system has been used to track influenza and RSV. For COVID-19, Quidel developed the Sofia SARS Antigen FIA and received its EUA on May 8th, 2020. It adapted the Virena system to collect and transmit Sofia SARS Antigen FIA test results which are transmitted to public health agencies, healthcare systems, and other organizations.

The number of test results received per day by Virena has exceeded 30,000 since they launched Sofia SARS Antigen FIA on May 9, 2020. They have data on the positivity rate per day by Sofia SARS Antigen FIA. The positivity rate peaked on June 21 and has plateaued between 7% and 10% nationally. On September 11, 2020 the positivity rate was 6.1%. They have data at the state, county, and facility level. With the Virena system, you can see the number of tests and positivity rate on a map. The system is monitoring Influenza A, Influenza B, and COVID-19. They submitted a pre-EUA for a triplex test to detect Influenza A, Influenza B, and COVID-19 with one specimen type.

The data that is missing from the Virena system is patient information such as demographics, symptoms, and medical history. In order to enhance the utility of Virena, Quidel is working closely with the CDC and APHL to further facilitate delivery of Virena data to the CDC and other HHS divisions. In addition, Quidel is in discussion with four middleware companies to investigate the linking of Virena's patient-de-identified data and patient-identified EMR data as it is conveyed daily to State DOHs and to the CDC. The

Virena system is housed by the Sofia and Sofia 2 immunofluorescence Analyzers and by Solana—an HDA molecular assay. An advanced multiplex PCR, Savanna, coming in 2021, will also employ Virena, emphasizing Quidel's commitment to enhancing the availability of both near real-time test results and patient identifiable data in support of public health and other national goals.

### **Parallel Analysis Project One Update (Carla Rodriguez-Watson, Foundation and Gina Valo, FDA)**

As of the week of the September 14, 2020, we are on step 2 where we are developing a protocol for aim 1 test characterization. The data will include patients from all ages in outpatient, inpatient, emergency departments, and group living. Our next goal is to refine the protocol and continue working towards answering questions from Project One. As always, thank you to all of the analytic partners, strategic advisors, and scientific advisors that are participating to help us with Project One.

#### **From the Chat Box**

- A caller emphasized that understanding the range of serology tests is key to the developing RWD plans.
- Regenstrief Institute, developer of LOINC, would probably be interested in learning of the antibody distinction. LOINC is developed further only upon request from the industry.
  - A representative from Regenstrief stated that they would be happy to coordinate a call to discuss this.
- A caller suggested that perhaps just in time for consideration in vaccination campaigns, in which vaccine could be spared if the patient already is immunocompetent - and those who were not, the baseline would serve to affirm seroconversion, for the benefit of reassuring the subject and for assessing efficacy of the vaccine
- Another caller stated that it is very useful in vaccinated recipients to be able to tell if they become infected with the actual SARS-CoV-2 virus. We and many other places like the NIH have brought up anti-N to help monitor vaccine recipients even though it is less correlated with immunity, etc.
- A caller suggested that some of the "bad" features of anti-N like rapid decay can be useful for other clinical purposes. For example, anti-N re-elevations can signal re-infection.

#### **Next Steps**

- Continue making data connections through the Evidence Accelerator

**Next Meeting: Thursday October 1, 2020 12-1 pm ET**