COVID-19 Evidence Accelerator Collaborative

Diagnostics Evidence Accelerator #32

Thursday, *June 17, 2021, 12-1 PM ET*

Call Summary

Introduction to Diagnostics Evidence Accelerator Meeting #32

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

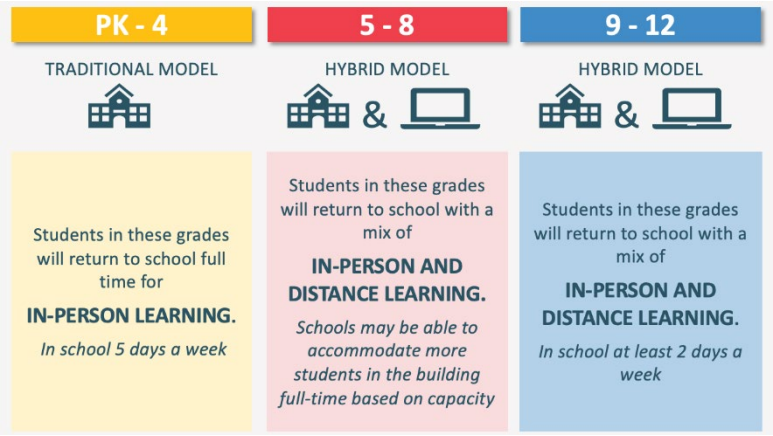
1. Overview of NOLA-PS COVID-19 Testing Strategy (Dina Hasiotis, New Orleans Public Schools)
2. Neutralizing Serology in the Setting of Vaccination (Dr. Richard Frank, et al., Siemens Healthineers)

As always, thank you to all of the analytic partners, strategic advisors, and scientific advisors that are participating in Project One of Diagnostics Evidence Accelerator.

Overview of NOLA-PS COVID-19 Testing Strategy (Dina Hasiotis, New Orleans Public Schools)

This presentation discussed the testing strategy that was administered in New Orleans Public Schools (NOLA-PS). The school district consists of 45,000 students and 78 schools. The students are primarily economically disadvantaged and students of color. This understanding and the understanding of how COVID-19 impacted different communities were the primary driving forces behind their problem-solving approach.

NOLA-PS opened schools through a phased process. Pre-Kindergarten through 4th grade students returned to in-person school first and then the higher grades. Distance learning was available for all students throughout the 2020-21 academic school year. The model can be seen in the figure below.



The reopening was facilitated by the Common Return to School Model, clear operational health and safety, standards and commitment to the standards, and COVID-19 testing strategy. The factors impacting testing were availability of funding; ability to ensure consistent and equitable resources, both responsive and routine; availability of end-to-end testing solutions, and demand and school capacity.

While keeping these barriers in mind, the school system was able to implement two testing strategies. The first strategy was the acute responsive testing. This strategy consisted of two parts. The first part, testing via hospital partnerships, the school system ensured that they had robust hospital partnerships. This allowed their students and families to connect to and access tests and medical care as schools reopened. The second part was on-site testing in school via rapid antigen testing using Abbott's BinaxNOW. Thirty-eight (38) schools participated in this responsive testing model. This model was used to test symptomatic students and faculty only. The second testing strategy that NOLA-PS implemented in January 2021, with the help of the Rockefeller Foundation was mobile routine testing. This strategy brought optional testing to student, school staff, school community.

Using the lessons learned, NOLA-PS is implementing new testing and vaccination strategies. They are implementing targeted on-site testing and mobile vaccination clinic for individuals that were disproportionately impacted by COVID-19. NOLA-PS is working on establishing partnerships with hospitals to administer the Pfizer and Johnson & Johnson COVID-19 for individuals who are 12 or older.

Through this effort NOLA-PS was able to learn valuable lessons. Those lessons are listed below:

- Delivering end-to-end testing services is important. Piecemeal options and resources are not a support and understanding that schools and school systems are not equipped to do this work.
- Providing schools with only the best testing resources available is crucial. Our customers are savvy consumers and only deserve the best.
- Ensuring your state authorizations reflect your best thinking on how to use testing resources. Conflicting messages only create more challenges for school systems and waste precious time, therefore EUA language is very meaningful to school and district legal teams.
- Ready resources to bring responsive, rapid testing and mobile vaccine options to schools when needed can be beneficial. Under-resourced communities in particular need rapid testing and vaccines on-site and on-call. Without this, it can be difficult to combat a pandemic.
- Setting statewide expectations and provide standard communication tools for schools to implement is helpful. Given pandemic and testing fatigue and vaccine hesitation, broader, bolder strategies and communication tools are needed. School systems need to feel safe as they roll out options, especially routine or surveillance protocols.
- Be cognizant of what is truly at stake. This work is fundamental to building and maintaining trust at the ground-level.

<u>Questions and Answers:</u>

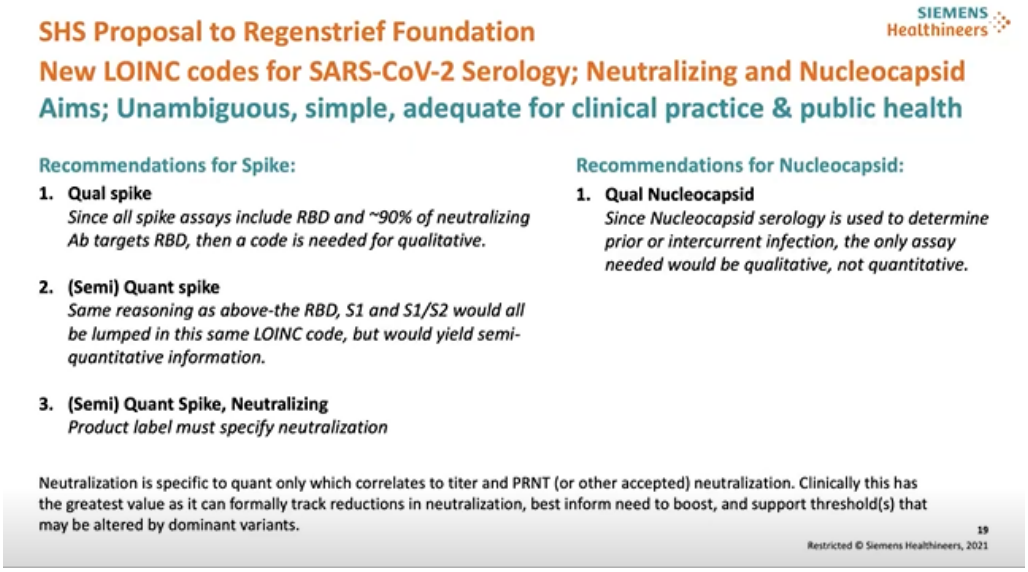
- Were symptomatic students required to be tested? Could parent/guardian refuse permission?
- What were the discussions you had for opt-in vs. opt-out during the regular school year? In our school district, opt-in was confusing and led to slow sign-up.
    - The NOLA-PS required testing. Opt-out testing was not something the schools felt comfortable doing legally. This said, it looks like some schools are interested in opt-out testing for unvaccinated individuals in the fall.
- What happened when you received a positive PCR result?
    - We went through the regular protocols for positive results (reporting to State Department of Health, district, and close contacts). NOLA-PS was able to do some responsive testing for close contacts as well.
- Are there publications that the Accelerator community can read regarding this topic?

    - Rockefeller commissioned a cross-site qualitative evaluation to better understand feasibility and acceptability of testing in K-12. NOLA, and 5 other jurisdictions are included in the report.
    - Rockefeller commissioned a RAND compilation of promising practices in K-12. They conducted a review of Covid-19 testing programs implemented by K-12 schools nationwide and a deep dive of 10 schools, districts, and states who were early adopters of Covid-19 testing. The community can read more about the practices here.
- Did you do any pooled testing or just stick to individual level?
    - No pooled testing due to costs and the fact that we couldn't find a partner willing to double swab the pools. NOLA-PS did test pooled testing with a small group in December, but it created a lot of anxiety in the school given that they wouldn't be able to identify positive individuals for 4+ days after testing
- Will lab-based Antigen testing play any role in the summer or fall, or just PCR?
    - NOLA-PS will likely focus on PCR. Lab-based antigen tests take quite a while to implement (~30 minutes per student testing), so we are unable to implement at the scale needed in a school
- If vaccines are authorized for adolescents and pediatrics will that change your testing program?
    - Not right now, when there are more individuals get vaccinated, then we will re-evaluate the testing program.

Neutralizing Serology in the Setting of Vaccination (Dr. Richard Frank, et al., Siemens Healthineers)

This presentation focused on the issues surrounding the clinical imperatives for neutralizing serology as a biomarker of vaccine effectiveness. The presenters also reviewed laboratory reporting codes discerning Neutralizing from Nucleocapsid; published evidence of neutralizing serology following vaccination; serology as an efficacy endpoint in SARS-CoV-2 vaccine trials; and special populations which need boosting.

LOINC codes are important in determining clinical practice of ordering the right test and determining results. Siemens developed a proposal to Regenstrief Institute regarding the recommendations for new LOINC codes for SARS-CoV-2 serology and neutralizing and nucleocapsids. The recommendations can be seen in the screenshot below.



Siemens is collaborating with the CDC and SeroNet to determine if a routine assay can determine individuals who are likely to be immune, and if so, then can the assay determine the level of immunity. This analysis has to be conducted using the immunoassay and PRNT which is the gold standard for neutralizing antibody response. In collaboration with the CDC, they received 30 samples from individuals who recovered. They extracted S1 RBD, N protein, S1, S2, S1/S2 (full length) from each patient sample. This was sent to the CDC to perform PRNT using neat serum and purified antibodies.

The conclusion was that a significant quantitative correlation was observed for anti-RBD and anti-S1 (which contains the full-length RBD) antibodies and PRNT50 neutralization titers. No similar correlation was observed for either anti-N protein antibodies or anti-S2 antibodies, indicating a lack of significant neutralizing potency with antibodies to these targets.

This supports sCOVG index as a surrogate for PRNT to monitor humoral response in COVID-19 patients, vaccinated individuals, and selection of convalescent plasma for COVID-19 therapy. The World Health Organization (WHO) developed a standard that can be used to harmonize the different assays. This is done on the sCOVG index.

While the public health community correctly points out that a definitive level of protective antibody (i.e., a “threshold”) has yet to be established from either recovered infection or vaccination, abundant data show a strong correlation between anti-RBD levels (and anti-spike which contains RBD) and neutralizing antibody titers. Studies indicate the RBD antibodies provide as much as 90% of the neutralizing activity. The CDC study data presented extends these findings by isolating subsets of antibody from convalescent patients and correlating those target-specific antibodies to PRNT50 titers. While much of the published data in-vitro correlates to PRNT and pseudoviral neutralization assays, infusion of neutralizing antibody into naïve animal models has shown a dose-dependency with antibody levels (as measured by both anti-RBD and anti-spike assays) and protection with subsequent viral challenge. This implies a significant if not exclusive role for antibody in a protective response, as cellular immunity clearly plays a role as well. Even without comprehensive data for antibody threshold or quantifying contributions from cellular immunity, antibody testing has proven advantageous when used in a population subset relative to vaccination/need to boost in other viral infections. Examples include both hepatitis B (example healthcare workers, immunocompromised individuals etc. where levels of

antiHBs are used to guide vaccination/boost decisions) and Rubella (example expectant mothers are boosted if Rubella IgG level is absent or below a defined threshold). Khoury DS et al. has extended this potential utility for antibody testing to SARS-CoV-2 (both vaccination and natural infection). This study employed mathematical modeling populated with antibody data for seven different vaccines and convalescent plasma (using geometric mean titers to produce a relative comparison as antibody assays differed between datasets). Key findings included that high levels of antibody were linked to protection from infection (sterilizing immunity) while lower levels were more permissive of breakthrough infection but associated with significant protection from severe disease. Additionally, levels of antibody relative to variant infection may need to be higher to confer similar levels of protection and vaccine efficacy was correlated with antibody levels. The authors concluded that neutralization level is highly predictive of immune protection and that antibody levels may serve as a correlate of protection and be highly useful in vaccine deployment strategies. Quote from the paper; "This analysis suggests that the mean in vitro neutralization level of a vaccine measured early after vaccination is predictive of the subsequent protective efficacy…".

Serology can play an important role in supporting the vaccine studies that are taking place in the pediatric space, vaccine boosters, and phase 3 and 4. The FDA released guidance that stated that it would be possible to approve a vaccine with serology as an endpoint. The data captured can provide evidence of safety and effectiveness. Due to this, Moderna and Pfizer are using this to capture antibody levels as a measure of safety and effectiveness. Additionally, there are two booster studies, Moderna Booster study and NIAID Sponsored Booster Study that are using serology as their endpoint.

Siemens has been speaking to experts in the field – clinicians such as infectious disease physicians and rheumatologists, as well as virologists, immunologists and medical laboratory directors - about SARS-CoV-2 serology testing as an accessible method to measure immune response. These experts provided input into a vendor-agnostic educational position paper that Siemens published on SARS-CoV-2 serology in the setting of vaccination and affirmed that serology is especially useful in certain populations at risk of not producing any immune response, or an adequate immune response, after vaccination. The individuals may remain vulnerable to infection and disease or become vulnerable to infection again sooner. These patient populations include solid organ transplant recipients, dialysis, inflammatory bowel disease, oncology, rheumatology disorders, and other patients on immunomodulating drugs, based on data published to date (see bibliography in slides). Several clinical trials are occurring to address these populations, to supplement earlier clinical trial data where these patients were excluded. There are other factors that may compound in these patients, such as older age or obesity. This data and the input Siemens received from the experts in the field points to serology as a useful and readily accessible method for assessing adequate neutralizing response and duration after infection and vaccination, including potential need to boost. Some physicians are already putting this into practice for these patient populations even without a solid, single threshold of immunity, to semi-quantitatively assess this indicative part of the immune response.

Literature for Special Populations

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2) Grupper, A. et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. Am J Transplant. 2021;00:1–8. https://doi.org/10.1111/ajt.16615
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7) Grupper, A. et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. CJASN Apr 2021; https://doi.org/10.2215/CJN.03500321
8) Torreggiani, M. et al. Neutralizing SARS-CoV-2 antibody response in dialysis patients after the first dose of the BNT162b2 mRNA COVID-19 vaccine: the war is far from being won. Kidney Int. 2021 Jun;99(6):1494-1496. https://doi.org/10.1016/j.kint.2021.04.010
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11) Agha, M. et al. Suboptimal response to COVID-19 mRNA vaccines in hematologic malignancies patients. medRxiv. 2021 Apr 7. https://10.1101/2021.04.06.21254949
12) Massarweh, A. et al. Evaluation of Seropositivity Following BNT162b2 Messenger RNA Vaccination for SARS-CoV-2 in Patients Undergoing Treatment for Cancer. JAMA Oncol. Published online May 28, 2021. https://10.1001/jamaoncol.2021.2155
13) Monin, L. et al. "Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study." The Lancet. Oncology, vol. 22,6 765–778. 27 Apr. 2021 https://doi.org/10.1016/S1470-2045(21)00213-8
14) Herishanu, Y. et al. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. Blood. 16 Apr. 2021. https://doi.org/10.1182/blood.2021011568
15) Terpos, E. et al. Low Neutralizing Antibody Responses Against SARS-CoV-2 in Elderly Myeloma Patients After the First BNT162b2 Vaccine Dose. Blood, blood.2021011904. 16 Apr. 2021, https://doi.org/10.1182/blood.2021011904
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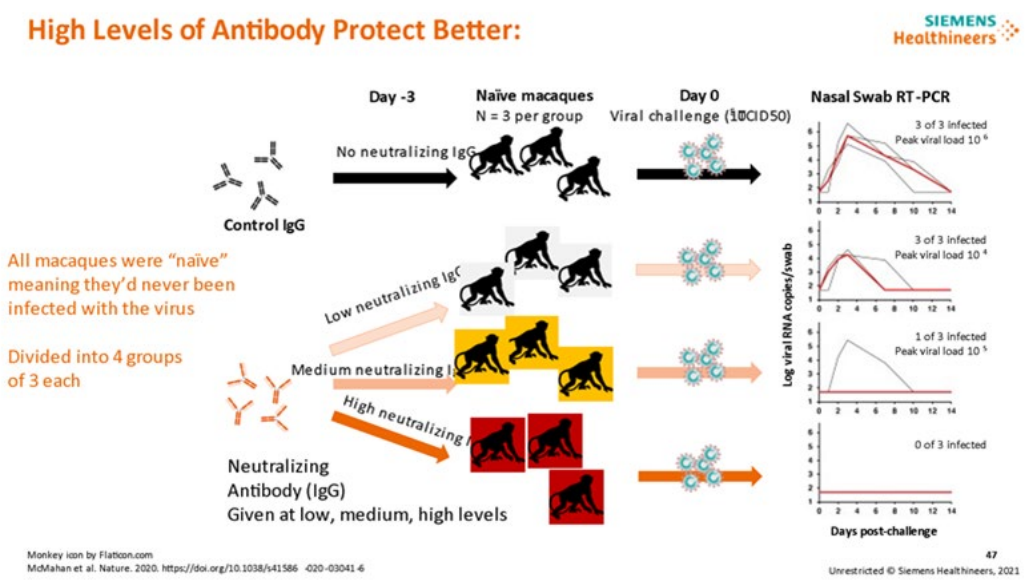
Questions and Answers:

- If the patient does seroconvert, then do they produce enough antibodies?
    - We do not have definitive knowledge of what the threshold is, but more is better. This continuum is demonstrated in the Khoury paper; the higher the neutralizing capability, the greater the protection, from a reduction of symptoms at low levels to complete protection at higher levels
- Is there any guidance from FDA, CDC, or vaccine manufacturers regarding boosters?
    - No, those studies are in progress. However, they may not provide sufficient information to understand to whom and when boosters should be administered, which would leave us in the same situation we were when the pandemic started, prioritizing by general risk factors like age and chronic disease.
- What do we know about transmissibility with certain antibody titers?
    - Evidence indicates that higher viral loads are associated with increased likelihood of transmission, so anything that reduces viral load would be expected to reduce transmission. Data also indicate that the level of neutralizing antibodies limits both infection and viral load and, therefore, by inference, neutralizing antibodies would reduce transmission. Supportive data include:
        - A primate model in which naïve macaques were infused with neutralizing antibody from convalescent macaques prior to viral challenge. Infused antibody levels were categorized as low, medium, or high. In this model, adaptive cellular immunity is not operative. Results, published in Nature, demonstrated dose-dependent effect of antibody on both viral load and the ability to infect.



- PRNT and other neutralization assays indicate a high correlation between infectivity in-vitro and neutralizing antibody.
- Similar in-vitro data show neutralizing antibodies limit infection with variants though higher levels of antibody may be necessary. Vaccine efficacy studies show the risk of infection drops precipitously >2-weeks post 2nd dose, at which point a significant increase in neutralizing antibodies was observed in the dose-ranging trials.
- The vast majority of neutralizing antibodies (estimate ~90%) are to epitopes within the Receptor Binding Domain (RBD). The levels of RBD antibody correlate best with neutralization of virus.
- Finally, RBD and other spike assays detect the polyclonal response. Data show neutralization may be reduced but isn't lost with variants, consistent with the polyclonal response.
- Which specific serology test (LOINC code) would you suggest front-line clinicians order to assess level of protection in patients who have been vaccinated?
    - #2 or #3, one of the (semi) quantitative assays for neutralizing antibodies. This includes the group of assays collectively known as "spike" assays (for S1, S1-S2, or S1-RBD). These antibodies are known to be neutralizing, which is the basis for the choice of vaccine targets

Next Steps

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

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