DCRI THINK TANKS
FROM INSIGHT TO ACTION

Preparing for the Next Pandemic: From EUA to Beyond

May 11-12, 2022

EXECUTIVE SUMMARY

BACKGROUND

Over the past two years, the COVID-19 pandemic, and its constant unpredictability, has become a frequent topic of discussion. The May 2022 DCRI Think Tank session on "Preparing for the Next Pandemic: From EUA to Beyond" brought together thought leaders from academia, clinical practice, industry, the US Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) to share firsthand, expert knowledge on the effective and ineffective strategies learned during the COVID-19 pandemic. The Think Tank focused on Emergency Use Authorization (EUA), diagnostics, therapeutics, vaccines, clinical trials, and how these all play a role in overall pandemic preparedness.

WELCOME AND OVERVIEW

Co-hosts Susanna Naggie (Duke University) and Rajesh Gandhi (Harvard University) welcomed the attendees and commended them on their tremendous response efforts around COVID-19, as well as their unique expertise and experience that has become critical in chartering the course forward for the next pandemic. The co-hosts encouraged attendees to reflect on the key lessons learned from the COVID-19 pandemic, and other epidemics such as HIV/AIDS and Viral Hepatitis, and to brainstorm effective strategies that make equity and fairness the central response to future public health crises.

SESSION I: EUAs AND BEYOND FOR DIAGNOSTICS AND THERAPEUTICS

EUAs

Shanti Narayanasamy (Duke University) started the session off by providing an introduction and historical overview on the FDA's Emergency Use Authorization (EUA). First established by the Project BioShield Act of 2004, EUAs were designed to facilitate the availability and use of

medical countermeasures (MCMs) needed during Public Health Emergencies (PHEs), such as drugs, vaccines, diagnostic tests, and medical equipment. The use of EUAs enables activities that would otherwise violate provisions of the Federal Food, Drug, and Cosmetic (FD&C) Act, allowing the FDA to authorize products for use to diagnose, prevent, and treat. Criteria for issuance of an EUA includes: (1) reason to believe that the product "may be effective" in preventing, diagnosing, or treating serious or life-threatening diseases or conditions, (2) the known and potential benefits of the product outweigh the known and potential risks, and (3) there is no adequate, approved, and available alternative to the product. Over the course of the COVID-19 pandemic, EUAs have been issued for therapeutics, vaccines, and devices (over-the-counter (OTC) testing, respiratory protective devices, surgical masks, face shields, etc.). For example, two COVID vaccines – one manufactured by Pfizer, the other by Moderna – were EUA approved based on Phase 3 trial data. Also, to note, Vaccine EUAs differ greatly from Vaccine Biological License Applications (BLAs). For instance, with EUAs for COVID-19 vaccines, the FDA required a follow up for 50% of the participants for 2 months. In contrast, the FDA required a follow up for 50% of participants for 6 months under BLAs. Secondly, in vaccine BLAs the FDA requires more data throughout the vaccine development process, along with thorough facility inspections

Diagnostics

Moderator Chris Woods (Duke University) introduced the panelists and encouraged attendees to think about how diagnostics has become an integral component of the COVID-19 pandemic.

Panelist Sarah Turbett (Harvard University) offered an academic perspective, beginning with a detailed overview of the SARS-CoV-2 (Coronavirus) diagnostics timeline. In early 2020, the US Department of Health and Human Services (HHS) determined that diagnostic testing was essential in addressing the rapid emergence of SARS-CoV-2. The CDC created the first test (SARS-CoV-2 PCR test) which received EUA approval fairly quickly, but due to complications there were significant delays in distribution. State Public Health Laboratory (SPHL) testing was inadequate based on demand and there was no commercial or reference lab testing available. This prompted the need to develop a test for hospitals, communities, and public health laboratories which led to the blueprint for a diagnostic Laboratory Developed Test (LDT). The main hurdle experienced during LDT development was scarcity. These deficiencies included lack of proper instrumentation, reagents and consumables, clinical samples to test, and workforce due to performing clinical testing and LDT development simultaneously. Collaborations with research techs aided in addressing these needs to perform LDT validation. Once completed, a limit of detection, accuracy, and reproducibility were able to be performed as outlined by the FDA. Now with a test that works, an EUA submission had to be completed. Although there were less regulatory requirements and paperwork, the unfamiliarity of the EUA process still

presented complications. Another hurdle was to initiate more training to increase the scale of the LDT and overall capacity. To illustrate, the first LDT could only produce 20 tests/day and was primarily manual. Quality assurance and competency assessments were also established to ensure accuracy and comfortability for the technologists performing the tests. In March 2020, the LDT went live, serving a critical role in the Remdesivir trials. The main ask was "who needs this test the most?" The test became useful and allowed for a lot of participants to be enrolled, and now Remdesivir has become standard of care. Even still the issue of scarcity remained as demand for testing increased throughout different communities. Luckily, around the same time, many commercial developers received EUA for their tests, increasing capacity of high throughput testing significantly, which allowed the use of more familiar platforms and the ability to perform more tests at once with less labor. In addition, results were electronically recorded into medical records as opposed to manual entry during the initial stages of testing. A downfall, however, was that every other clinical laboratory in the country was also using these same diagnostic tests which, again, led to shortages in supply. Due to specific regulatory components with limited flexibility, clinical labs were on tight allocation only performing a certain number of tests per day. This caused many to expand outside of the commercial manufactures that were normally used, mixing and matching based on what was available. Heading into summer of 2020, we began witnessing lower prevalence rates and EUAs being established for other types of tests such as pooling. On the other hand, new challenges started arising in clinical labs as it related to workforce and other testing. Since commercial manufacturers were focused on SARS-CoV-2 testing, it started taking away from other tests that were needed for routine clinical care. As we were returning back to a state of normalcy, this also meant that the need for all routine clinical tests was increasing again. With this increased demand, we saw shortages of basic necessities like blood plates, MRSA screening agar, etc. Outsourcing of certain tests increased due to the lack of workforce available to perform the tests, impacting patient care overall. When the first variant emerged with Alpha in fall of 2020, variant surveillance for new SARS-CoV-2 mutations became imperative, to ensure tests were still working properly and that new mutations were identifiable. As therapeutics started to emerge, we had to consider how therapies would be appropriately tailored? In our current state, we see that access to testing is better, but not perfect or equal across the country. There are still many areas where it takes days to receive a PCR test. Clinical labs have authorized, reliable testing available, but are still plagued by reagent and consumable shortages. Regulatory components remain challenging because we don't have bandwidth to pivot quickly. There is dire need for continued diagnostic development in rapid/point-of-care (POC) testing. Lastly, the clinical lab work force remains the biggest hurdle to overcome – "we just don't have enough people to get the testing done." A few suggested solutions – better infrastructures; training across many disciplines; streamlined regulatory processes; and collaboration between industry, government, researchers, and clinical labs.

Panelist Timothy Stenzel (FDA) offered a regulatory perspective, summarizing the FDAs commitment to address one of the most challenging PHEs we have seen, both nationally and globally. At the start of the pandemic, it was discovered that many clinical labs and manufacturers were unaware of the opportunity to submit tests to the FDA. With this knowledge, the FDA issued a new policy informing clinical labs that diagnostic tests were welcome to help expedite testing capacity in the US. Within the first week of the new policy's issuance, the FDA received seven submissions from labs that had already developed tests. Towards the end of February 2020, the FDA had engaged with over 100 test developers. On March 16, 2020, FDA updated the Feb. 29 policy and expanded to kit manufacturers of diagnostic tests, which allowed States to oversee the tests being developed by clinical labs in their jurisdictions. Since the start of the pandemic, the FDA has authorized over 470 unique tests (of the over 2,500 submitted) with majority of them being molecular diagnostic tests, and receives 100+ EUA test applications per month. There are a diverse set of tests available such as antigen diagnostic tests, molecular diagnostic tests, serology tests, and other immune response tests. The real success behind this outcome comes from government funding, which provided manufacturers with the right incentive and security to proceed with producing massive amounts of tests. Lessons the FDA identified regarding EUA and diagnostic testing include the following. First, US government and international partners should establish a plan for sharing clinical specimens as soon as a PHE emerges. Second, keep testing warm and waiting for potential pandemics. Presetting funding and authorization for a small number of well-designed, validated diagnostic tests, manufacturers, and POC tests – that can run on common high-throughput platforms – will help us meet our goal of distributing large amounts of diagnostic tests in a shorter period of time. Third, create a common legislative framework. This may limit the confusion on regulation and ensure all clinical tests are accurate and reliable. Fourth, clinical community should understand test performance and how to use information in patient care. We witnessed a lot of cavities including misuse of tests (particularly communication and education of serology tests), gaps in understanding of testing, and clear communication for all Americans (lay persons). Lastly, a commitment to increasing access and ensuring reliability of COVID-19 tests moving forward.

Gavin Cloherty (Abbott), discussed the critical bottlenecks that industries faced in the development of diagnostic tests and the solutions that were used to counteract them amid the pandemic. The first challenge was, do we act or not? From a business perspective, there can be serious consequences that come with delaying projects and pipelines for other products that the physicians they serve both need and want. The second challenge was lack of information and samples. There was limited knowledge and information regarding COVID-19 compared to the wealth of knowledge and information that typically exists for other viruses. Using the "building the plane while it's taking off" approach, Abbott removed all standard stops and were dedicated to developing tests promptly in the beginning, while figuring out the specific details of how to use the tests later. Starting off with molecular tests, testing was being completed in

several months compared to the normal testing process being completed and approved in a process of 3-5 years. As a result, Abbott had 12 tests developed and approved within the first year of the pandemic. This illustrates the success of a collaborative framework within an organization. Ongoing partnership, dialogue, and collaboration with the FDA was also key. Understanding that viruses adapt was fundamental. Using the same surveillance program for COVID-19 that's been used for other viruses helped us to understand how COVID-19 was evolving. The third challenge was understanding the utility of these tests and addressing misinformation as diagnostic tests were being developed. This included discussions such as POC tests vs. Lab PCR, how to use the tests properly, when to use the right test, how to interpret results, etc. Industries have commended the FDA on balancing the need to make diagnostic test available with analytical data as numerous tests were being developed. A suggested opportunity involves Pharma working more closely with diagnostics, particularly in accessing samples and data, so that the correlates of protection can be examined. This would be valuable because as the pandemic progresses, the population being studied for the vaccine disappears as more people become infected. Actively having industry involved in the public health space was novel compared to it usually being at arm's length.

Discussion

Attendees revisited the topic of scarcity, more specifically sample scarcity, and reagent and diagnostics availability which impacted the development and distribution of diagnostic tests. Strategies we can use to address scarcity in the next pandemic include: (1) keep test manufacturing warm and consider the entire supply chain and scalability, (2) use of commercial manufacturers are key as well as continued flexibility among some of those components under the EUA, (3) sharing validation materials across institutions rather than having institutions go through each process individually, and (4) create a stockpile of common designs that have been agreed upon and can be customized between commercial manufacturers.

How do we address public misinformation? One concept that attendees discussed was establishing a pre-identification of manufacturers who can respond to misinformation quickly. Time Stenzel spoke to the FDA's strategy of providing as much specific information as possible to healthcare providers and consumers early on. An improvement to this strategy is to provide lay-friendly information to ensure understanding across all audiences.

Many smaller, underserved communities who don't have the money and/or resources have experienced lack of access to diagnostic testing. How do we address these health disparities in our communities? Sarah Turbett spoke to larger organizations performing testing for smaller community laboratories, emphasizing the importance of infrastructure and trained personnel.

Tim Stenzel stressed opportunities to build off of, and enhance, national efforts of providing free at-home testing. It was also discovered, however, that many encountered difficulties using these at-home tests due to obstacles such as physical impairments/disabilities, misuse of tests,

and lack of understanding. How can we make these at-home tests easier so that everyone can have equal access to testing? As a follow up question, Esther Krofah (FasterCures) asked attendees to consider: With regards to consumers, how can the lessons learned from at-home testing during the pandemic be applied to testing for other routine clinical conditions such as strep throat or flu? The pandemic has spotlighted opportunities to transition many tests into the home setting. Tim Stenzel highlighted other FDA authorized at-home testing, such as pregnancy tests, insulin pumps, diabetes tests/wearables, which have all experienced similar processes. One of the most important factors is to continue efforts of maintaining test safety and effectiveness.

Therapeutics

Co-moderators Rajesh Gandhi and Roy Gulick (Weill Cornell) introduced the panelists on therapeutics and facilitated the discussion.

Mark Denison (Vanderbilt University) provided an academic perspective on therapeutics, discussing the strategies for therapeutic discovery early in the pandemic and how it evolved over time. The concept of high throughput screening and repurposing played a huge role in therapeutic discovery in the pandemic and was highly supported. The foundation of all approved or EUA antivirals involves pre-SARS-CoV-2 science and data on CoV inhibition, and have been worked on for a long time. To illustrate, nirmatrelvir was studied during the SARS-CoV epidemic; remdesivir was initially studied beginning in 2014, and was published between 2017 and 2020; and molnupiravir contains early evidence in targeted studies that began in 2016. It's important to note, the evolution of testing. We now have access to structures of key enzymes and exceptional biochemical systems for targeted and high throughput testing, broad animal models, better rationale for drugs, comparative testing of drugs, reporter viruses, and published data on EUA/NDA (New Drug Application) antivirals. The use of these various testing strategies should be encouraged. What do we do with post-EUA and novel compounds? As we think about post-EUA, we also need to think about ways we can continue providing fundamental data. We may have data going forward in some compounds that might have additional mechanisms. We should be looking at ways to incentivize across academia, regulatory, and industry that encourages the use of combination therapies over monotherapies. It would also be most beneficial to have companies collaborate, rather than having various companies working on different compounds.

Peter Stein (FDA) began by re-emphasizing the criteria for EUA issuance and the differences between the NDA/BLA and EUA. When comparing approval standards between NDA/BLA and EUA, the first requires substantial evidence of effectiveness, while the second is based upon the totality of scientific evidence. An additional difference is that the EUA standard is discretionary

(stating *may* authorize not *must* authorize) whereas the NDA/BLA is nondiscretionary. It is important to note that due to the dynamic, evolving nature of the pandemic, EUAs are not a "fixed" standard. In other words, the FDA will periodically review the circumstances and appropriateness of an EUA. This flexibility component helps to best address the current needs of a pandemic, and involves balancing early access against uncertainties. Revisions or revocation of an EUA can take place if circumstances warranting issuance no longer exist, criteria for issuance of the EUA are no longer met, and/or other circumstances make revision or revocation appropriate to protect the public health or safety. A few additional key lessons learned by the FDA include the following. First, regulatory tools and trial capacity are needed early. It's important to ensure infrastructure, networks, and resource availability. Second, organization and prioritization of clinical trial efforts are essential and are needed nationally and globally. Third, rapid initiation of clinical trials needs to be balanced with study design and implementation quality. Master protocols and platform trials are important, but must also be efficient. Finally, attention to the timeline of drug availability needs to be a high-level focus, and channels of communication to (and from) health care providers (HCPs) and patients are essential, especially when dealing with rapidly evolving information.

Phil Pang (Vir Biotechnology) transitioned the discussion into an industry perspective, focusing on issues and opportunities to discuss monoclonal antibodies (mAbs) as pandemic therapeutics. The first issue consisted of affordability and availability. What is the best strategy to support the development and availability of new medicines? Government funding was essential in the pandemic, but where the government spent funding might not have been optimal. Prioritizing government support for US manufacturing over platform trial support may better accelerate medicines. If the focus is to conduct platform studies, then we should consider focusing instead on more expensive and challenging trials. The second issue involved thousands of competing clinical trials that slowed progress. The opportunity: establish a sponsor prioritization mechanism based on a transparent, minimum criteria that rewards innovation and capability. By putting one in place, this would help reduce regulatory bottlenecks. Third, given the amount of at-risk dollars, companies want to know what the target is. Is greater transparency regarding EUA standards (for initiation, maintenance, and reauthorization) possible? With greater transparency and proper understanding, sponsors are encouraged to spend more at-risk funding leading to enhanced speed. The final issue: lacking mAb correlates of protection. How do we reconcile *in vitro* data with conflicting *in vivo* data? Why does neutralization appear to take precedence? This provides opportunity to develop a shared understanding of the biology of mAbs, and how they work, leading to more, faster, and highly efficacious medicines.

JR Dobbins (Eli Lilly) contributed to the industry perspective by discussing supply considerations for a pandemic. What do we manufacture? This involves selecting mAb sequence to achieve desired activity and early identification of the target product profile. How fast can it be

manufactured? How much do we manufacture? It is key that we identify and address the global demand, process transfer to multiple manufacturing sites, and evaluate internal vs. external capacity and supply availability. Product quality is our "North Star." All batches should be manufactured to meet established product quality criteria. A few regulatory challenges that need to be further considered are: uncertainty in applicable regulatory requirements, pathways, and timelines during the pandemic, urgent overlapping global health authority submissions and interactions, and divergent health authority expectations. A major opportunity is to establish streamlined global regulatory pathways to ensure timely delivery of supply to patients. How do we refine processes for holding timely Industry/Health Authority interactions globally? How do we leverage reliance/harmonization concepts to expedite reviews and minimize divergence?

Discussion

Attendees discussed flexibility within the current standard of care. Peter Stein noted the FDA's stance on taking a broad view of what adequate therapy is. The goal is to have a number of readily available therapeutic options due to both the virus' evolving nature and scarcity challenges.

An obstacle we witnessed with combination therapy is that different companies were making different compounds. How do we get different companies to work together on combination therapy studies? Phil Pang mentioned how companies have discussed this concept before and that ultimately it boils down to financial incentives. There needs to be an ideal framework across companies as to what the target goal is. Are we developing for a virus evolving within a person, or in billions of people around the world at the same time? Are we going for breadth or barrier to resistance, and which matters more in a timely fashion?

SESSION II: VACCINE AND FUTURE PANDEMICS

Vaccines

Moderator Tony Moody (Duke Human Vaccine Institute) introduced the session and facilitated the discussion.

Panelist Lindsey Baden (Harvard University) shared an academic perspective on COVID-19 vaccine development. Key concepts we should ponder are: how do we know there is a new pathogen, and how do we respond? How do we communicate about a new pathogen? – Should it be free and open discourse, or can this lead to confusion and altered purposes? How do we

prioritize in the beginning of a pandemic? – Shouldn't our clinical studies involve the use of forward-looking modern technology? In the vaccine world, consider which reagents are made in weeks and which ones take months or years. This implies what flexibility we have. How do we think about data from other communities with candidate immunogens that may work, but the data upon which they are based may not be easily understood/have confidence in? When there is a new pathogen we feel led to respond to, how do we choose the correct immunogen to target? It is important to understand how spike proteins work, where its vulnerabilities are, how it can be stabilized, etc. Lastly, how do we bring communities together to be able to respond quickly? It may be beneficial to have a government-supported infrastructure that includes harmonized efficacy trials, collaborative clinical trial networks, centralized labs, data and safety monitoring board, and between-trial statistical groups for correlates of protection. How can we leverage these different structures to enable learning across domains instead of having studies that are completed in isolation? We need to find ways to more rapidly interrogate and share different types of data. From a research perspective, it is important that in the beginning measurable, relevant endpoints are developed to ensure objective data, confidence, and reliability. At first, it was unclear how the SARS-CoV-2 pathogen behaved and what illness looked like. In retrospect, our primary endpoint consisted of prevention of molecularly confirmed illness. Although this endpoint still has its shortcomings, it has stood the test of time and exemplifies the value of defining endpoints and goals of vaccines. During the Phase 3 vaccine efficacy trial, known as COVE, timelines were slowed down to ensure enrollment included diverse populations representative of our nation's population. We need to make sure our studies are equitable, fair, and inclusive, representing everyone being affected by the illness. Truth and inclusivity help build trust between HCPs, patients, academia, sponsors, etc. and provides a better understanding of safety and efficacy over time. As we recall other events that took place during the pandemic – such as food and toiletry shortages and civil unrest spurred by the murder of George Floyd – we must also be attentive to how present economic, social, and political climates reflects what is taking place in our communities with our staff/clinicians, patients, and their families. Mistrust due to social forces around us needs to be addressed and overcome in order to improve inclusivity and get the answers we need. As we review vaccine development timelines we must ask ourselves, do we wait to proceed until each phase is completed or do we do things at risk? It is a very complex arena where choices are done at-risk and we as a community have to determine which are the best choices to make. For instance, if we invest billions of dollars into a vaccine, and it works, then we will be upset if it is not available for everyone, but if the vaccine does not work, then we will be upset that we spent billions of dollars on manufacturing. After receiving EUA approval, there was discussion about what to do with the placebo recipients. How do we do studies ethically? How do we harmonize this incomplete portfolio of information that has been developed as a result of the pandemic?

Panelist Peter Marks (FDA) offered a regulatory perspective on COVID-19 vaccine development. Over time the FDA's role with vaccines has included: strain selection and reference standard production, lot release, evaluation of safety and efficacy, post-market surveillance, advancing vaccine technology, and ensuring public confidence in vaccines. In response to vaccine development skyrocketing during the pandemic, FDA provided two guidance documents. One on the development and licensure of vaccines to prevent COVID-19, and the second on EUA for vaccines to prevent COVID-19. The goal was to provide recommended steps manufacturers can take regarding COVID-19 vaccine development that would secure the public's confidence on the vaccine's safety and effectiveness. FDA based authorization on clear and compelling efficacy in large, well-designed Phase 3 clinical trials. Clear guidance to manufacturers on expectations has been extremely helpful. In addition, ongoing timely communication with manufacturers was incredibly beneficial for product development, for both COVID-related and Non-COVID related products. How can we implement this in future product development even after the pandemic? Maximal transparency for the public, through advisory committees and document postings, has been helpful, but how do we go about this transparency in order to educate? Sometimes just having the facts without understanding them can lead to miscommunication. Despite its challenges, the EUA has proved itself to be a worthy piece of legislation attributed to its adaptability, flexibility, and agility. EUAs can appropriately apply to different product classes, adapts to the specific nature of the emergency, and changes can be made rapidly as new data emerges.

Speaking on behalf of the Advisory Committee on Immunization (ACIP), Panelist Sara Oliver (ACIP- CDC) discussed the parallel evolution of the SARS-CoV-2 virus and COVID-19 vaccines, the importance of creating simplistic vaccine policies that require continued evaluation of COVID-19 epidemiology and vaccine effectiveness, and ensuring that these policies are easy to communicate and implement in order to optimize uptake ("Vaccines on the shelves don't save lives, vaccines in arms do!") Established in 1964, the ACIP's primary role is to provide advice and guidance to the CDC Director on the most effective ways to prevent vaccine-preventable diseases in the U.S. ACIP deliberations include: consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of evidence being reviewed, economic analyses and implementation issues. During the COVID-19 pandemic, the ACIP also added an equity domain. Since authorization of COVID-19 vaccines in December 2020, ACIP has held 17 public meetings compared to their standard 3 meetings held per year pre-pandemic. During these meetings, considerable discussions were held on topics such as: Phase 3 clinical trial data for COVID-19 vaccines, updated COVID-19 epidemiology, post-authorization safety data, benefit risk analyses for use of COVID-19 vaccines, real-world vaccine effectiveness data, implementation considerations for COVID-19 vaccines, vaccine uptake, acceptance, intent to vaccine data, and clinical considerations for use of COVID-19 vaccines. Revisiting the importance of defining the goal of a vaccine, do we want the primary goal of COVID-19 vaccines to be prevention of infection and transmission, or prevention of severe

diseases? Some viable solutions regarding future vaccine doses include the following. First, prevention of infection/transmission may be time-limited. Future doses could potentially require timing of vaccine roll-out prior to increases in COVID-19 cases. Second, prevention of severe disease is more durable and allows flexibility in timing of future vaccine roll-out. Third, preserving capacity of healthcare infrastructure which has proven to be important. Lastly, data may support different recommendations for general population and vulnerable populations, and it is important to have COVID-19 vaccine policy that is simple.

Panelists Joanne Waldstreicher (Johnson & Johnson) and Brett Leav (Moderna) offered an industry perspective on vaccine development. (Brett Leav) Due to the necessity of the pandemic, one of the biggest challenges was conducting vaccine development using a parallel structure. In other words, "everything everywhere all at once." To illustrate, Moderna was able to determine an effective and safe vaccine dose for the Phase 2 study, while also preparing vaccine formulation for the Phase 3 study. This varies greatly from clinical development that is typically performed in series where one study informs the next after all observations have been completed. Committing to ensuring diversity and inclusion is another important factor. Reemphasizing Dr. Baden's points, it was critical in the development of the COVE study to ensure that the population of participants who enrolled represented the population of the country, especially concerning underserved populations (African Americans, Latinx, comorbidity populations) who would be disproportionately impacted by COVID-19. One of the biggest achievements from the COVE study, based off of Moderna's findings, was that the study population accurately represented US populations at-risk for COVID-19, from diverse racial and ethnic populations to individuals with pre-existing medical conditions. A hopeful success from clinical data shows that the multivalent vaccine containing the Beta variant generated a higher immune response against all three COVID-19 variants that have been tested so far, compared to a prototype boost with 1273 or spike backs.

(Joanne Waldstreicher) Johnson & Johnson's single dose vaccine enabled better transportation, opportunities to meet the needs of low- and middle-income countries, and led to the launch of the Sisonke study – which provided 500,000 healthcare workers in South Africa with access to an effective vaccine. All of these examples demonstrate the need to balance global vs. national needs. During the pandemic we witnessed a lot of unprecedented collaboration across academia, industry, government, and communities. In the long run, it may have been better to perform a platform trial. If we had, a few benefits would have been minimization of the number of placebo participants, streamlined clinical trial site preparation, and allowance for comparisons across studies, populations, and variants. Perhaps in the future, setting up a platform infrastructure could help us enable and accelerate development. We saw how harmonization and aligning study endpoints helped save time. Developing study center qualification criteria and training materials across all different sites would also be helpful. If concordance can be shown, the FDA should consider developing centralized confirmatory testing for the primary endpoint. An important outcome from the pandemic was the criticality

of the safety infrastructures that we have in the US established by the FDA and CDC. These spontaneous reporting systems provided insight into emerging safety issues quicker than existing real-world data systems. Opportunities to enhance the current system starts with decentralizing, meaning we should streamline processes of sharing critical data to cut back on time and redundancy, especially in the case of a pandemic. For future pandemics, is there a way where we can work together? Could there be a global safety database with controls so all critical parties can come together and have access to the data? With it being so many collaboratives, what are ways we can work together and have a unified approach to safety surveillance and sharing safety data? We can also use the same approach with real-world data. There are opportunities to also learn from other countries and their response to the pandemic. Even if we cannot all work as a federated network, we could still try defining case definitions, phenotype characterization, background incidences, and analytic methodology for real-world data studies, ahead of time, to help us save time and cost, and still have a series of unified approaches.

Discussion

The idea of having a common case definition is popular opinion, but it can become difficult trying to define a case while also trying to intervene on the case. How do we define a pandemic in real-time? How do we define cases and success when having an incomplete picture of what the pandemic looks like? Lindsey Baden and others agreed that we have to, first, begin by reflecting on what our goals are and what we are trying to achieve.

Adrian Hernandez (Duke Clinical Research Institute) asked attendees to also consider how do we define the inflection point of when to sound the alarm? When referring to triggering alarms, how many false alerts can one tolerate? How many viruses could potentially be emerging each day? Peter Marks suggested that the solution may be similar to the specific criteria we see in how we prepare for natural disasters. For instance, a hurricane watch is issued when a tropical cyclone poses a *possible* threat, a hurricane warning is issued when hurricane conditions are *expected* somewhere within the specified area, and then you have the *actual* hurricane. In addition, Brett Leav spoke on the SpillOver model, a risk-assessment tool developed by the University of California at Davis, used to evaluate zoonotic spillover and the risks of certain pathogens. Systems such as these can also apply to how we define the inflection points of viruses that could lead to pandemics. There are different pressures of novel pathogens that require different responses depending on the level of morbidity.

Attendees discussed the importance of community engagement and earning trust in communities. Trust is fostered through transparency, the use of creative, nontraditional communications strategies, long-term relationship building, sustained investment within communities, and commitment to meeting community needs.

Esther Krofah reflected on the public's perception of the acceptability of COVID-19 vaccines. Which approach is better? – Educating and engaging with the public as clinical trials are developing, or waiting until clinical trials are completed before informing the public. Sarah Tweedy noted how the pandemic has shifted the way health professionals and the public engage. There is now a greater understanding of clinical trials, both positive and negative perceptions. How do we continue to use this opportunity to engage and educate the public on clinical trials? Peter Marks presented another key learning regarding tensions between political organizations and public health organizations in the US, and how this impacted the public's perception resulting in more challenges. From the standpoint of the public, sometimes the public health and political organizations are all grouped under one umbrella.

As a follow up question, Adrian Hernandez asked attendees: should we be thinking of creative, nontraditional ways to communicate with the public? What about the use of different channels? The platform for how we communicate has changed. Observations and discussions are being exposed and aired to the public immediately, whereas before, observations were discussed for years within the scientific process and then presented to the public.

Sara Oliver noted that, over the course of the pandemic, it was also discovered that people like to receive information from people who look and sound like them. It is important to branch out into communities, building relationships with community partners and local health departments who feel empowered to have discussions and answer the community's questions.

Esther Krofah noted that the engagement and investment established in communities during the pandemic must be sustained. In some communities, investment and resources have already been pulled back which heightens mistrust, rather than eliminating it.

Attendees also discussed global health equity. What can we do now to take advantage of global equity and responsiveness before momentum slows? It seems people were responding urgently in the beginning of the pandemic, but as it has progressed, that same urgency appears to have dissipated. How does this play into community engagement?

Peter Marks raised the issue of weaknesses in global manufacturing. It may be best to remediate the deficit in manufacturing capabilities across each continent to help alleviate global vaccine equity.

Standing Up Clinical Trials during a Pandemic

Co-moderators Susanna Naggie and Adrian Hernandez introduced the panelists and facilitated the discussion.

Panelist Mark Sulkowski (John Hopkins University) provided an academic perspective on clinical trials' response to the COVID-19 pandemic and addressed the unique characteristics stemming from COVID-19 clinical research. In early 2020 there were many challenges such as diverse patient population, no expert investigators or established treatments, innumerable hypotheses, repurposed faculty and staff, and limited centralized resources. A couple initial observations included: realizing the disproportionate impact of positive COVID-19 cases on the Latinx community (specifically in the Maryland areas) and mismatch between patients and clinical trial capacity throughout the pandemic. In Spring 2020 there were more patients than Principal Investigators (PIs) and staff, and then in Fall 2020 there were more PIs and staff than patients. Johns Hopkins had several different COVID-19 committees a part of their COVID-19 response. These committees included a steering committee, outpatient clinical research units (CRUs), a clinical research coordinating committee (CRCC), a data research evaluation committee (CARE), and a biospecimen repository committee. Their CRCC's rationale for prioritizing studies involved enhancing research participation across their entire health system, prioritizing studies for emergency IRB, being sensitive to rapidly emerging data, limiting the number of treatment trials that are supported, controlling how investigators are engaged, and avoid overwhelming patients with multiple requests regarding research participation. Additionally, 10 guiding principles for clinical prioritization, similar to some of the themes discussed earlier, were collaboration, equity, prioritization, transparency, balanced portfolio, and scientifically and ethically sound research. The COVID-19 Outpatient CRUs created medical isolation units (PODS) near COVID-19 testing centers as drive-up locations that involved infusion capability and specimen collection. Since May 2020, there has been more than 2,057 participant visits. From this we learn that the public responds well to the convenience of driving up and participating in these clinical studies. The Recruitment Innovation Unit coordinated innovative recruitment and community engagement opportunities alongside hospitalized patients, ambulatory patients, and community partners that worked really well. For example, the COVID-19 HOPE registry, a centralized patient-centric recruitment registry, resulted in over 15,000 participants supporting 31 COVID-related studies through recruitment coordinated on Microsoft Teams. Partnership with Centro SOL aided in promoting vaccination education and testing physically in the community at local churches and markets. Community engagement should be viewed as a key element that needs to be maintained in the research community. Overall, participants, investigators, research team members, and sponsors need easier, adequately funded, well-designed clinical trials. How do we maintain preparedness? Overtime we see limited funding and committee participation to maintain PHE readiness. How do we stay ready, and how do we afford to do that?

Speaking on behalf of the NIH, Panelist John Beigel (NIH) shared insight on the Adaptive COVID-19 Treatment Trial (ACTT) studies. The first strength was being early. The ACTT studies began when there were only 30 official cases in the US. The second strength was access to many sites. The NIH had 93 sites participate in one or more stages, known networks were used, and they

engaged many new sites. The third strength involved having highly motivated investigators who wanted to participate in trials. The fourth strength was the National Institute of Allergy and Infectious Diseases (NIAID) made funding available with straight forward approvals. Unique NIH funding mechanisms were also used which involved the Federally Funded Research Development Center (FFRDC) compared to grant funding which is not as fast or flexible. Another strength was early and frequent engagement with the FDA and expedited engagement of international sites. The Pre-Investigational New Drug Application (IND) was reviewed in 3 days, IND reviewed in 2 days, and received EUA 12 days after the Data and Safety Monitoring Board (DSMB) recommended NIAID unblind the trial. In addition, protocol development was quick. Synopsis was developed in 4 days, full protocol developed in under 2 weeks, and balanced data/specimens with ease of implementation. The guiding question was, how can we collect minimal amount of data that is easily extractable from medical records? On the other hand, there were also many pitfalls. First, ACTT sites were approached by many different studies and tried to perform too many trials. Second, some investigators participated in multiple studies and some focused on ACTT with authorship correlating to enrollment. Third, hospitals had different strategies such as limited enrollment and specific allocation of patients to trials. Finally, ACTT studies received a lot of criticism due to initial results being conveyed via press release. Moving forward, it may be more beneficial to consider larger trials with mortality endpoints whereas ACTT focused on early answers with clinically important endpoints. Also, pre-conceived notions about the risk of immuno-suppression was a limitation.

Panelists Lothar Roessig (Bayer) and Sarah Tweedy (Pfizer) provided an industry perspective. (Lothar Roessig) A few highlighted success factors Bayer observed include the following. First, was the collaborative study approach between Academic Research Organization & Pharma Co, and public research funding agencies. Thanks to a collaborative study framework, rapid contracting and initiation were enabled. Second, there was a pre-existing network of sites and investigators. This contributed to accelerated committee formation, protocol development, feasibility check, and study start-up. To illustrate, it only took 29 days from concept to FPFV in the ACTT program. Third, having an adaptive study design. With pre-specified protocol modifications, this allows for quick responses to the evolving pandemic dynamics and scientific insights. Lastly, have a multifactorial design. There were also key barriers to address within the regulatory and ethics approval process, uncertainties around study design assumptions, and international clinical trial infrastructure. First, while most Health Authorities (HAs) compressed review timelines, the standard sequential approach country by country remained cumbersome and redundant, too long for a pandemic situation. Also, equipoise considerations varied widely among jurisdictions. A consensus is needed when approved and established drugs are used in a pandemic response situation. Second, there was dynamically evolving knowledge about pathogens and its epidemiology. We should establish reference centers/consultations and alignment processes to support trialists. Lastly, to create a unified mechanism to facilitate large,

multi-country, multi-institutional collaborations instead of multiple parallel, overlapping, underpowered, and underfunded studies. In addition, larger studies tend to last longer too.

(Sarah Tweedy) Pfizer had to shift the way managed clinical trials were managed in response to the impacts of the pandemic. Business continuity and the use of pandemic planning were critically important. How do you equip yourself to respond to the unexpected? We also had to learn how to run through a rapid, large, and robust development plan under the umbrella of a single protocol. Now, in the span of 2 years, we can see the results of our studies with 4.9 billion people fully vaccinated in the world and 11 billion doses administered. What exactly did we do to get these results? What do we do moving forward? What should we do again? The cautionary tale is that we have to know how to pivot and have readily available resources at our fingertips that we can leverage in order to deliver solutions. A guiding principle is anchoring to the idea of being led by the science. It was vital to have real-time access to data since we were learning as we were responding to the pandemic. From a clinical research perspective, we learned it was important to share our data on an ongoing basis. EUA is the end of the first chapter, not the end of the story. How do we go from an EUA to full licenseship? We also had to become use to, and respond to, the public and media's interest in clinical trials. This provides us with the opportunity to help drive education in our communities around clinical research. It became interesting to see how clinical trials interacted with the public and what this may mean moving forward. For instance, there was a Pfizer clinical trial participant who shared her story as an opinion piece in the NY times.

Discussion

Attendees discussed the importance of combining clinical studies and pursuing more efficient ways to design vaccines in the future in terms of speed, and labor- and resource-intensity.

Alice Pau (NIH) reflected on the various responsibilities PIs, Study Coordinators, Nurses, and other health professionals experienced at the height of the pandemic. In addition to operating clinical trials, we witnessed capacity issues in our hospitals while taking care of patients. Can data collection be compromised due to how busy health professionals were, and how does this potentially compromised data impact our secondary and primary endpoints?

Roy Gulick described a classic tension in clinical trials between the need for data that can support drug approval vs. the need for data that helps inform strategies about the best management of patients. RECOVERY, a study that employed the use of the National Health Service (NHS) in the UK, has been extraordinary in the number of answered questions they have led us to, often strategy-related answers rather than specific drug approval. Should we develop a platform similar to RECOVERY in the US? In response, John Beigel spoke on the US' need for infrastructure. Part of RECOVERY's success was their access to their electronic medical record, any site, and follow up on mortality end points, whereas the US does not have a unified medical record.

Another tension attendees discussed was that between clinical trials being considered too long vs. too short, and ways to balance out the process. Over the course of the pandemic, as mortality rates were rapidly increasing and accelerated results were needed to help inform decision making, there was concern of clinical trial development taking too long. On the other hand, however, moving quickly through clinical trial development contributed to concerns such as not having enough information and the overall safety of products. One solution is that we have to make decisions based on the information we have, while including mortality endpoints. In hindsight, the accelerated mortality rates led to the pace of enrollment being faster than expected. Another solution involves sticking to our guiding principles and a collaborative framework in order to stay on track and prevent any undercutting. Norman Stockbridge (FDA) pointed out how this tension is the same for all drug development and should be considered regarding every decision throughout the clinical development process, with or without a pandemic.

Adrian Hernandez wrapped up the discussion asking the session's panelists to share one thing they would write into a Defense Production Act to help prepare for future pandemics. In response, the overall themes were (1) to create "go teams" that can be turned on and off, (2) incrementally invest in improvements during down times that can be adequately amplified when it comes time to respond, (3) review Israel's example of providing data and apply those learnings, and (4) establish a national health system with a unified, real-time database to help advance public health structures, especially clinical trials.

SESSION III: PANDEMIC PREPAREDNESS

Moderator Lesley Curtis (Duke Clinical Research Institute) introduced the panelists and facilitated the discussion.

Panelist Mark McClellan (Duke-Margolis) began the session by providing an academic perspective on pandemic preparedness. Thanks to a lot of progress in many dimensions of synthetic biology, we have learned that we need a biomedical response enterprise from the beginning in any future pandemic. This means having reliable tests available at scale, targeted treatments like monoclonals, oral therapies that can work against a broad range of viruses, and vaccines that can all be ready in a matter of a few weeks or months. This has already been captured in the 100-day pandemic response plan established by the Office of Science and Technology Policy (OSTP), it just has not been effectively implemented yet. One of the key features of pandemic response going forward is moving from a linear process to a hyper-parallel process. There were a lot of steps from a regulatory standpoint, nationally and internationally, to lay out clear expectations of what a promising vaccine candidate needed for EUA. Setting clear expectations is important because the EUA is such a flexible standard. The

best way we can improve the EUA process is to improve the underlying evidence that is available to inform the EUA process. Thanks to a platform approach, we were able to jumpstart large clinical trials fairly quickly and gain compelling evidence. Although we did not receive as much data as we would have compared to a full approval, such as long-term effects and a more comprehensive understanding of rare safety effects, manufacturing, and quality issues, this data can still be obtained in follow up studies. There may be opportunities for clarifications on FDA vs. CDC roles and appropriate expertise. A lot of ACIP leadership of the CDC were comprised of people with expertise in childhood vaccines which differed from the expertise of the FDA's vaccine review advisory committee, VRBPAC. As a nation, there are also gaps that can be improved upon. The first is that we lack steps for further evidence development on products after approval. It has been challenging for the US to perform efficient real-world data practices for larger studies, such as the ability to track patients longitudinally, apply rigorous data standards, and understand the completeness of the data. These components can be very hard to study in smaller, randomized clinical trials. Second, is that we have a fragmented system that did not do an adequate job of generating evidence quickly. The US led the world in COVID-19 cases, but not in enrollment and participation in reliable clinical evidence development efforts. Less than 1% of hospitalized patients participated in consent, active, randomized trials, and according to a study released by the Clinical Trials Transformation Initiative (CTTI), of the patients who were enrolled in COVID-19 trials only about 26% participated in randomized, adequately-powered trials. This is also opportunity to push POC trial capabilities, similar to the ACTIV studies and other US POC initiatives, since there is potential to develop off-the-shelf treatments quickly in response to new variants or threats. A third parallel stream to an effective pandemic response is scale. There is a lot of planning underway now to build more robust, resilient, and domestic supply chains, and change our models concerning surge responses. Experiences from the pandemic has shifted our thinking to build more capacity into our manufacturing base to help assure we have more supplies on hand in the future. It is not enough to accelerate availability of vaccines, diagnostics, and therapeutics. We have to have a public health and healthcare system that is able to use it. Today, we are having trouble providing access to resources, not because we don't have some supply, but because of lack of delivery capacity, trust, and system engagement.

Panelist Stacey Adam (Foundation for the National Institutes of Health [FNIH]) offered a regulatory perspective on pandemic preparedness by providing in depth insight into the strengths and weaknesses of the NIH ACTIV studies. ACTIV is a large public-private partnership that brought together stakeholders for a parallel effort on evidence development for COVID-19 therapeutics. The collaborative framework among partners worked exceptionally well, due in part to partners coming forward, with a willingness to participate and contribute agents, time, and resources. Government funding also played a key role in majority of ACTIV studies. In total, ACTIV brought together 8 government, 4 nonprofits, and over 20 industry partners in the span of a month. Another component of ACTIV's collaborative framework was the development of 4

separate working groups. These groups included (1) a pre-clinical group to help prioritize and oversee pre-clinical resources and development, (2) a vaccine group that arranged for main players to conduct common protocol and harmonize endpoints, and (3) a clinical therapeutics working group and (4) clinical trial capacity group who, hand-in-hand, performed a landscape analysis of all NIH networks to assess site capacity, site readiness, agents for COVID-19 treatment, and design master protocols to place them within. Coordination with international partners was kept throughout every process of development. Contrary to popular belief, ACTIV ended up launching 11 master protocols in 2 years and enrolled nearly 20,000 patients across these protocols. ACTIV's master protocols were sub divided under the assumption that this would help move processes quicker to get through regulatory approval. However, in retrospect, we learn that fewer master protocols, preferably 2-3, may have been more beneficial. Regarding agents used in ACTIV studies, 40 out of 800 evaluated agents were selected, and 25 out of the 40 selected have been completed to date. Initially, ACTIV studies received criticism because of the agents that were selected. Under ACTIV's established criteria, certain agents were chosen based on whether or not other companies were already studying certain agents. The objective was to avoid covering those same agents being covered by others and potentially discover new mechanisms. Looking back, we see how preconceived notions regarding agent selection might have been a bit limiting. We also learned that just because a trial opens, does not mean enrollment will be rapid or that evidence will be received in a timely manner. To the notion of creating fewer master protocols, moving forward, there are plans in place to collapse ACTIV 1,3, and 5 (inpatient protocols) together into a single network and launch a comprehensive pan-respiratory disease platform called STRIVE. The first 2 agents are under evaluation and will be brought through on existing funding, while contemplations on various funding sources are being considered. Action is also being taken to sponsor and facilitate collaboration with companies to combine data with ACTIV studies to produce a comprehensive patient level analysis on virologic endpoints. Current efforts, like RECOVER and the Antiviral Program for Pandemics (APP), are being developed to address both the long-term effects of the COVID-19 pandemic, such as long COVID, and to prepare for future PHEs.

Panelist Ola Vedin (Boehringer Ingelheim) provided an industry perspective, reflecting on data, regulatory innovation, and collaboration. An initial observation was the use of short decision pathways at Boehringer Ingelheim. Between the development teams and senior management there were no committees. As a result, decision making was rapid, teams were empowered, and there was clarity on prioritization and resource commitment aiding in Boehringer Ingelheim's overall teamwork structure. In regards to data, we need to go back and review what data was useful, what data did we miss, and how can we best collect data going forward? How does our data needs evolve over time? In the context of trust in our communities, what is the best way to disseminate/present data? Creativity is key in how we choose to disseminate data to our communities. Regulatory guidance has been very helpful. For instance, we saw guidance from the FDA and the European Medicine Agency (EMA) on how to keep current trials

running through the pandemic. On the same note, we also learned that a generalized and adaptable guidance can still be useful, and that guidance does not always have to be disease specific. Efficient communication with health authorities has been key, but discrepancies between national and international health authorities can be an issue that has no meaningful impact on patient safety or interpretation. Innovation has played a huge role in how we conduct our clinical trials. A success and opportunity are the use of registries and the potential to cultivate registry-based randomized trials to assess pandemic-related treatments and interventions. Cross-industry collaboration is not always easy, but it is feasible. The recipe for success and preparedness is to learn from all of these developments during COVID, apply them into the traditional drug development ecosystem, resulting in a more sustainable solution making us more prepared for the next pandemic.

Discussion

Attendees discussed potential incentives to maintain the public-private partnerships that have been established over the course of the pandemic. Phil Pang noted that the best strategy to maintain these partnerships are to develop win-win incentives. To illustrate, he then proposed the idea to develop a single contract with every academic site onboard. Companies would then be more likely to pay to access this centralized system network, rather than having to go through individual trial networks where contracting with academic centers can become time-consuming. Ola Vedin and Joanne Waldstreicher argued that incentives do not always have to be profit-based. Potential incentives can also be centered around the idea of partners coming together to discover better ways to collaborate and help move research forward.

"Keeping things warm," such as testing, partnerships, infrastructure, and funding, to ensure readily available resources for future pandemics was another reoccurring topic. Attendees discussed the importance of presenting tangible benefits as a catalyst to ensure ongoing engagement and prevent appetites to invest from disappearing due to competing priorities. Lothar Roessig pointed out the opportunity of advertising our learnings from the pandemic as a success story on collaboration and acting as a consortium in order to keep resources warm. Susanna Naggie and others suggested that maybe we should take a different approach and think outside the box. Instead of primarily focusing on keeping things warm for pandemics, we should focus on addressing critical disease needs and pivot as needed, going into each situation with a prioritization mindset.

Towards the end of the discussion Lesley Curtis asked attendees to reflect on all of the lessons learned and share one thing that we should begin today to prepare for the next pandemic? Most common responses included harmonization and the designing of a global infrastructure to address global equity, generating innovative win-win incentives for every group involved (industry, academia, community, etc.), and sustaining collaborative public-private partnerships

to increase trust with communities and decrease overall pandemic response time. Additional thoughts that were shared involved strategies to help teach communities about clinical research, the organization of multiple institutions to create a centralized database system, developing a safe harbor for research production to eliminate risk, and establishing sustainable infrastructures that will keep resources warm and ready for the next pandemic and beyond.

TAKEAWAYS

- Collaboration among industry, academia, government, and community partners – at national and international levels – played a huge role in the accelerated development of vaccines, therapeutics, and clinical trials over the course of the pandemic. How can we strengthen these public-private partnerships? How can we utilize platform trials?
- Keep things warm. Implementing an infrastructure/s that sustains readily available resources (testing, community engagement/partnerships, funding, etc.) will help us ensure a prepared response in a timelier matter.
- Prioritization is key when it comes to clinical trial efforts, resource availability, sustaining our workforce, and determining where government funding will be allocated.
- We need to consider creating some sort of centralized network with streamlined processes of sharing critical data to enable learning across domains and cut back on time and redundancy/overlapping. How can we develop a global infrastructure to harmonize processes?
- The flexibility, adaptability, and agility of EUAs was extremely beneficial.
- Ensuring diversity, equity, and inclusion in our clinical studies is critical to fostering trust, sustaining community engagement, and receiving accurate study results to adequately meet the needs of our communities, especially at-risk and underserved populations. We also need to be aware of the economic, social, and political climates that are affecting our staff, clinicians, patients, and their families.
- Sustained community engagement built on long-term relationships, transparent communication, and commitment to meeting community needs is imperative to building and maintaining trust.
- Utilize creative, nontraditional opportunities and strategies to both engage and teach our communities about clinical research to eliminate mistrust, gaps, and misinformation.