Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
"Road to Recovery: Ramping Up COVID-19 Vaccines, Testing, and Medical Supply Chain"
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The Honorable Frank Pallone, Jr. (D-NJ)

1. With the rise of new COVID-19 variants, it will also be crucial to improve our understanding of the impact these variants have on infections, testing, and vaccines. This will require updating our surveillance of the virus, including through genetic sequencing. You noted in your testimony that we are currently only sequencing about 3,000 specimens out of 1.4 million positive tests. What percentage of specimens should we be sequencing, and can you describe what a coordinated national system for sequencing would look like?

A pathogen surveillance system that will keep Americans safe will need to focus on improving the (1) data collection and data systems, (2) workforce and resources to sustain the system, (3) analytical tools (both genomic and phenotypic), and (4) decision-support capabilities.

Some experts have estimated that sequencing 5 percent of representative samples of identified COVID-19 cases would enable the detection of a new variant when the variant represents about 0.1 percent to 1.0 percent of the country's cases. The CDC has taken steps recently to augment the number of specimens sequenced. CDC's SPHERES program, a consortium of sequencing labs around the country, aims to sequence 20,000 samples per month. The U.K. is aiming to sequencing 10 percent of SARS-CoV-2 positive samples.

There are many U.S. laboratories capable of performing sequencing work, in universities, medical centers, private sector clinical labs, etc., as well as government labs, such as the CDC. One of the most logistically challenging aspect of SARS-CoV-2 sequencing is gathering sufficient numbers of clinical samples from individuals testing positive to make sequencing cost-effective. (Sequencing machines can process thousands of samples at once). New Mexico, for example, has agreed to sequence samples from several other western states.

Another issue is timeliness of results. From the time patients are tested to the collection of clinical samples and delivery to sequencing facilities, to sequencing, to reporting results to local

health departments and to the CDC takes days. Ideally, results would be reported within a time frame that is "epidemiologically actionable" – i.e., within 24-48 hours of patient testing. The material and personnel costs of sample collection and sequencing must also be considered, as well as supply chain sustainability and the consequences of re-directing sequencing activity from ongoing studies and clinical work.

The Honorable Lisa Blunt Rochester (D-DE)

1. Because of the disparate access to testing in underserved communities, but also due to a lack of consistent decision-making and guidance out of the federal government, there are a lot of unknowns about the specific impact COVID is having in such communities. I have also heard very little about how high-quality antibody testing can be better deployed in any of these national or state testing plans discussed to date. I have heard very little about what the actual plan is for figuring out how long these vaccines are going to work, or whether there is any variability based on age, or race or ethnicity or co-morbid conditions that impact communities of color. I understand the initial tests FDA let on the market were of varying quality, but now that there are highly specific options out there, how can they be deployed by the new Administration moving forward especially in assessing variability in vaccine response across the population?

For diagnostic and screening tests, the CDC should develop, with input from the FDA, testing guidance so clinicians, public health practitioners and the public are informed of optimal testing strategies for particular scenarios (i.e., screening asymptomatic individual after exposure, pre- and post-travel testing, surveillance testing at the workplace, etc.). There is also a need to provide clearer and more useful explanations about COVID-19 test results to members of the public.

There is little role for antibody-based testing now other than for epidemiological purposes. A positive antibody test does not mean someone is protected from COVID-19 infection. Even individuals who recovered from COVID-19 need to be vaccinated to be optimally protected from re-infection.

Rapid read-out, point-of-use diagnostic tests are being used to screen asymptomatic people in workplaces, schools, etc. One key challenge for public health has been capturing diagnostic test results and analyzing all the aggregate data to guide the public health response. Missing, delayed and incomplete data has hampered the public health response. While mandated by the CARES Act, its enforcement has been limited. This problem will only grow as more tests become available directly to the consumer. Tests that are marketed directly to consumers should include mechanisms to automatically report the results to public health systems. Accurate data reporting is essential for monitoring the trends of disease spread, identifying hot transmission spots, and guiding resource allocation. There remains a need for innovation around ensuring data capture that enhances local, state, and national response.

For vaccine breakthrough cases, the CDC should launch a national surveillance effort to sequence the virus of anyone who develops COVID-19 even after being fully vaccinated. This is important to monitor for vaccine failure that may occur because of waning immunity or because of less protection afforded by the authorized vaccines against the emerging variants of concern.

2. What steps need to be taken by FDA and CDC go about establishing a threshold neutralizing antibody level for protection against COVID-19?

Establishing such a threshold will require clinical research data demonstrating whether there is a threshold at which individuals are likely to be protected from SARS-CoV-2.

The Honorable Brett Guthrie (R-KY)

1. There is growing concern that some of the new strains are more resistant to existing antibody therapies.

    a. Do we have the right set of therapies ready to use or will we need additional ones in our stockpile?

The United States lacks a strong therapeutic armamentarium against COVID-19. Although we were very hopeful, the antibody-based therapies have not been successful in treating sicker, hospitalized patients. Thankfully, clinical trials are demonstrating that several monoclonal antibodies are useful in preventing disease progression in certain high-risk individuals. Nevertheless, most antibody-based therapies are vulnerable to emerging variants that carry mutations that evade or reduce neutralization by these types of therapies. It is possible to develop new antibody therapies that would be effective against variants, but ways of testing such therapies more quickly are needed.

The NIH should establish a national capability for the rapid conduct of streamlined, pragmatic, randomized clinical trials, like what the U.K. has established, to evaluate promising treatments in a suite of common or platform trials that share a common control group. We all hope that the most promising therapies will work but we can't be sure until we study them in properly designed clinical trials. Learning what works and what doesn't is an urgent matter. Broad utilization of unproven therapies, even under FDA's Emergency Use Authorization framework, may end up hurting patients and delays our ability to learn what treatments are most effective.

I'm encouraged that the Biden administration is providing $3.2B to support development of small molecule drugs to address coronaviruses in general. Investments should also include antiviral drugs that may have activity against multiple pathogens. While these are sometimes harder to identify, the time is now to develop these types of drugs in earnest since we do not know what the next pandemic pathogen could be.

    b. Do you know if additional antibody therapies are currently under development to respond to these emerging strains and if so, what the status of those therapies are?

Some companies are developing new versions of their monoclonal antibodies to help address the emerging variants. However, the role of highly specific monoclonal antibodies is limited in the treatment of COVID-19 and stand to benefit only a small subset of people (i.e., those with risk factors and who have not developed their own antibodies, and only if the drug is administered soon after infection). However, at least one company, Vir, has a monoclonal antibody, Vir-7831, that seems to retain activity against the variants now circulating as it targets a more conserved part of the SARS-CoV-2. The company is working on formulating the product for intramuscular delivery, which obviates the need for infusion centers that have proven to be a rate-limiting step in the timely delivery of these types of drugs to those who stand to benefit.

c. Can you explain why it is important to have a strong portfolio of therapeutics available, even as more people are able to get vaccinated and what can we be doing to better support the development of new therapies?

No vaccine is 100% effective or work equally well in all patient populations. Patients need access to safe and effective treatments if they become infected. The United States has a formidable and vibrant biomedical research enterprise, but it lacks a national capability to conduct pragmatic, yet rigorous clinical trials required for evaluating the merits of promising treatments quickly. As a result, only a small fraction of patients diagnosed with COVID-19 enroll in a clinical study. The more patients that can be enrolled in such studies, the quicker we can identify winning therapies. I'm encouraged that the Biden administration is providing $3.2B to support development of small molecule drugs to address coronaviruses in general. Investments should also include antiviral drugs that may have activity against multiple pathogens.

2. Last year, Congress provided millions of dollars to be spent on domestic manufacturing capabilities. Focusing on vaccines and therapeutics, how do you suggest we encourage private sector entities to build additional manufacturing capacity or adopt technologies that allow for production to be quickly ramped up in order to respond to future public health emergencies?

Private sector participation is essential to creating a manufacturing ecosystem that's better prepared for tomorrow's public health emergencies. Leading talent and cutting-edge manufacturing technologies, platforms, and processes will be just as important as physical infrastructure.

Historically, limited market incentives have precluded biopharmaceutical manufacturers from investing in the innovation and capacity required for more effective rapid response mechanisms. Today's system is oriented towards discovering new drugs as quickly as possible and bringing them to market. There is little incentive for contract development and manufacturing organizations (CDMOs) or pharmaceutical companies to spend time or resources developing innovative manufacturing processes ahead of a specific product or to take a risk on a novel platform or technology. This dynamic is exacerbated by the lack of regulatory mechanisms to qualify manufacturing technologies outside of product approval processes.

Importantly, expanding existing manufacturing capacity is not sufficient. The current system is reliant on extremely skilled talent and large-scale bioreactors and can only be scaled to a certain point. New technologies are needed that can overcome existing inefficiencies via completely new ways to make vaccines and therapeutics that make it easier to make these complicated products at cost, at speed, and at scale.

U.S. government partnership can help catalyze a modern biomanufacturing ecosystem by providing:

- Near-term investment to offset the cost of new infrastructure, upgrade existing capacity, and advance breakthrough manufacturing technologies.
- Long-term investment in basic and applied research and development for advanced manufacturing technologies.
- Long-term contracts providing commitments to purchase critical vaccines and therapeutics and to the requisite infrastructure for production.
- Tax credits, subsidies, financing, and other support measures for building, modernizing, or revitalizing infrastructure, investing in new technologies, and training the future workforce.
- A regulatory and policy environment that supports greater manufacturing adaptability, including safe and rapid site changes and the adoption of new manufacturing processes and platforms.
- The convening of stakeholders from across government, industry, and academia to collaborate on challenging policy and science problems.

3. While this Committee has long had an interest in exploring ways to increase domestic manufacturing for certain medical products, the COVID-19 pandemic has highlighted even further the desire for a more robust domestic manufacturing infrastructure.

    a. How can we best invest in building and maintaining an advanced manufacturing infrastructure to be better prepared for future pandemics?

The COVID-19 pandemic has highlighted longstanding vulnerabilities and inefficiencies in our current manufacturing ecosystem. Insufficient biopharmaceutical manufacturing, particularly for complex biologics (large molecule vaccines and therapeutics), holds readiness at risk and prevents the discoveries of today from reaching patients as quickly and cost effectively as possible.

True preparedness cannot be accomplished through a one-off program or by building in a single stand-alone government facility reserved for emergencies. This would only enhance current supply chain vulnerabilities by consolidating emergency capacity in a single node that could be shut down by a climate event, such as the winter storm recently seen in Texas, or adversary attack. Reserve capacity of this type would also suffer from long lead times to activate the facility in times of need, outdated technologies, and talent that is not trained in leading systems and methods.

As the U.S. looks to build out its domestic production capabilities in the aftermath of COVID-19, it must develop a next generation manufacturing ecosystem that can keep pace with advances in biological sciences and adapt to potential future threats. Rapid, multi-modality manufacturing capacity is vital to creating pathogen-agnostic preparedness for the next pandemic or biological event. At least one company, Resilience Inc., has been established recently and proposes to do just that. We cannot predict what the next threat may be so we must have the systems and tools to quickly counter the widest range of possible disease threats.

The Federal government could set a broad mandate for bolstering U.S. biopharmaceutical manufacturing through sustained investment in manufacturing science, public-private partnerships that create a network of agile capacity, and future-oriented systems that allow us to create lasting preparedness and not a band-aid for today's capacity. A robust network of flexible capacity able to pivot production provides continuous, real-time biopharmaceutical manufacturing capacity with the latest technologies and leading talent that can be available in times of crisis. By also serving industry, the model saves tax-payer dollars and fuels local and national economies through high-paying manufacturing jobs.

b. Do you know if there are there real or perceived regulatory barriers at FDA that prevent investment in advanced manufacturing or maintaining excess capacity that could be activated quickly and flexibly during times of drug shortages or national emergencies?

The remarkable speed with which scientific leaders have readied a COVID-19 vaccine illustrates what is possible with unprecedented public-private partnership and regulatory engagement and flexibility. However, there are regulatory challenges preventing similar speed, flexibility, and innovation in manufacturing.

The current regulatory regime focuses on the approval of individual products. While this has been successful in bringing safe and effective products to market, it does not incentivize investments in new manufacturing technologies that bring enhanced safety, transparency, and quality controls. Product developers take on extensive risk when advancing novel products towards and through clinical trials. Because the FDA does not review manufacturing technologies without a specific product, the only way a new technology would demonstrate compliance to the broader industry is by an individual product developer taking on additional risk.

For products that are already approved, changing the manufacturing location or technique requires FDA review each time. While appropriate to ensure product integrity, there is no system in place to "pre-qualify" multiple facilities in the face of potential disruptions, nor facility agnostic technology. There is also no expedited pathway for manufacturing supplements that use technologies already familiar to the FDA. Combined, the existing framework prevents novel manufacturing technologies moving from research projects to commercial applications as quickly as possible and provides a disincentive for investments in new technologies that can better support preparedness.

Last month, the National Academies of Medicine published an extensive report entitled "Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations." This report made several recommendations that would help bring manufacturing innovations to fruition faster and change the incentive structure, whether effectuated by Congress or by the FDA under their current regulatory flexibilities. Of particular importance are the following recommendations:

- Advance innovative mechanisms for evaluating technology outside product approvals.
- Expand the scope and capacity of the Emerging Technology Program and the Emerging Technology Team.
- Increase external engagement to facilitate innovation and increase awareness of readiness to evaluate innovative technology.

4. Are there lessons learned from our response to the pandemic that could be extended beyond the public health emergency to support new drug manufacturing innovation, make review processes more efficient, and increase collaboration and communication between FDA and drug manufacturers?

Please see response to question 3.

5. How should Congress balance investments in short-term COVID product production with a strategic longer-term approach to pandemic preparedness?

These short-term investments have been crucial to saving lives and helping restore our economy. There have been many lessons accrued over the course of the COVID-19 pandemic that should be incorporated into a longer-term strategy. The private sector must remain engaged in bio-preparedness even after the immediate emergency subsides, not only because of its collective capacity and bandwidth, but also because it is where innovation resides. Careful attention should be given to supply chain resilience. A resilient supply chain requires more than onshoring manufacturing capacity. It requires a deep understanding of the supply networks and the application of cutting-edge and flexible technologies, including synthetic biology, to manufacture goods on short notice. For example, Antheia, a synthetic biology company based in California, is developing technology that can enable more resilient and agile advanced manufacturing processes for domestic production of key APIs in life-saving medicines.

6. According to Harvard Professor Michael Mina, the appropriate use of rapid antigen tests can curb the spread of COVID, because they are inexpensive, easily scalable, take just minutes to process, and can target populations with higher rates of infection who are unable to access a hospital or lab. They detect people who are currently infectious, so identifying and isolating these individuals could quickly break the chain of transmission. Despite all of this, there is a large misunderstanding of rapid tests.

    a. Can you discuss how rapid tests could be used as a public health screening tool?

Rapid tests could play an important role in curbing the pandemic if they are deployed as a screening tool in many different environments. To work, they need to be conducted frequently. For example, individuals must be able to access an antigen test every three or four days to identify they are

contagious soon after they are exposed and before they spread to others. While there is some evidence that weekly screenings could be effective, the increase in frequency is optimal to break the chain of transmission. As such, affordability is also key. At home testing of just one test currently costs $25-100, which is out of reach for mot.

One thing that is often overlooked in the discussion around rapid tests is the importance of data reporting. Missing, delayed and incomplete data has hampered the public health response. While mandated by the CARES Act, its enforcement has been limited. This is unfortunate since accurate reporting of mass-testing could allow for a more proactive response. Accurate data reporting is essential for monitoring the trends of disease spread, identifying hot transmission spots, and guiding resource allocation. There remains a need for innovation around ensuring data capture that enhances local, state, and national response.

An option that hasn't been discussed readily is increasing access to at-home testing via the provision of kits that contain multiple antigen tests but doing so in a way that is affordable enough for all Americans. One promising company ContagionNet, by DataRobot, is proposing to provide households with antigen tests in a kit format where individuals can be tested every couple of days to increase the accuracy of the assay and ensure the identification of the contagious period before they have an opportunity to spread the infection to others. Companies should submit data to the U.S. FDA to make sure their screening tests perform as intended.

b. How can we better utilize rapid tests in school and work settings and not just focus on PCR tests?

Antigen tests and PCR tests are different tools. While PCR can be highly accurate and detect and amplify small amounts of SARS-CoV-2 RNA, it is not positioned well to help reduce transmission rates. It is typically expensive, requires trained personnel and laboratory equipment to administer, and the time to turnaround results can be several days. Therefore, PCR tests are much better positioned to confirm someone is sick as opposed to stopping or slowing the spread. Today, antigen screening is better poised as a way to stop transmission. In the future, we should expect tests that retain the accuracy of PCR tests and the convenience, speed, and ease of use as antigen tests.

Antigen tests can be used to screen people upon entry into a space or event or provided to children to take at home on a regular basis. This is being done right now in the Philadelphia region with Assisting Childhood Education through Increase Testing or Project (ACE-IT), which aims to reduce the risk of the spread of COVID-19 within schools. ACE-IT is a collaboration with the Children's Hospital of Philadelphia, PA-Department of Public Health, United States Digital Services, DataRobot, and Southwest Texas Regional Advisory Council. The program serves staff and students in school districts across the five-county southeastern Pennsylvania region. As of March 12, over 300 schools in the Philadelphia area have been reopened for in person-learning and over 300,000 tests have been conducted under the program. A similar program is being launched in Seattle, and a playbook has been developed for how this can be done for every county and metro in the country.

The United Kingdom is about to roll out mass testing to reopen all schools. The students will then get kits so they can test themselves at home. The U.K. government has distributed nearly 57 million rapid test kits to schools across the country.

Similar programs, screening upon entry or ensuring the ability to check for contagiousness at home, can be done as part of re-opening congregate work settings. Companies should submit data to the U.S. FDA to make sure their screening tests perform as intended.

The competitor to antigen-based testing is broad access to lab PCR testing using pooled samples. Although time to result is significantly longer, accuracy is improved. All strategies should be considered.

7. Serology tests continue to be underutilized, even though they are an important tool in understanding the true spread of the virus. They could be also useful at the patient level - for example, if a patient presents with a heart condition, lung condition, diabetes, their doctor may want to know if they had COVID and developed their condition because of the infection.

    a. In your opinion, should appropriate use of serology testing be further leveraged in a testing strategy?

Serology testing is a useful public health tool but of limited utility for testing of individuals. The most valuable tests are the ones that lead to a specific course of action. The results of a serology test, whether positive or negative, do not tend to inform courses of action, such as a decision to isolate, quarantine, or be vaccinated.

    b. Would it make sense to include a COVID serology test in wellness panels, for example?

As I described above, the results of a serology test do not impact individual decision-making and has little use for wellness panels.

8. Some serology tests can measure the approximate level of antibodies in a person's body. These tests can potentially be used to track the immune response to a COVID vaccine – helping to identify when a booster shot may be needed among other benefits.

    a. How should these tests be leveraged as part of the vaccine roll-out and follow-up?

There is no role for antibody tests to be used in the vaccine roll-out or follow-up. There is insufficient data to rely on antibody levels to inform vaccine boosting strategies.

There is accruing evidence that individuals who have had COVID-19 may only need one dose of the mRNA-based vaccines. Even if the U.S. where to adopt such a strategy, it would likely rely on a history of a positive COVID-19 test. It would be impractical to do an antibody test on everyone before vaccinating.

    b. Do you see a benefit to tracking the durability of the immune response, particularly considering some of the mutated strains like those from South Africa, Brazil, or United Kingdom?

Yes, we must track the durability of protection, carefully monitor for vaccine failures, and asses the prevalence of vaccine-failures that are due to infection with variant strains.

The Honorable Michael C. Burgess, M.D. (R-TX)

1. The current vaccine distribution chain only involves one distributor. Have there been capacity issues with distribution that could be solved by involving more private distribution companies? Are there certain areas, for example rural, that are more difficult to reach under the existing distribution channels?

I am not aware that the distribution chain only involves one distributor. I strongly believe in leveraging all capabilities that exist in the private sector to allow for a more timely and robust public health response, and allow for vaccine to reach all areas of the United States.

The Honorable Neal P. Dunn, M.D. (R-FL)

1. What steps should the Biden administration take to guarantee that leading American vaccine and vaccine raw material manufacturers will be approached by the Administration's COVID-19 Response Team to ensure that our Nation's vaccine manufacturing capacity and supply chain can meet expected demands and that Americans have timely access to a vaccine?

    a. What recommendations do you have for the Biden administration to sustain those relationships and engagement strategies post the COVID-19 pandemic to make certain we have rapid vaccine manufacturing capabilities for potential future pandemics and other global health challenges?

The Biden administration is reportedly looking at end-to-end solutions for rapid vaccine manufacturing for both the current pandemic and what infrastructure needs to be supported now so that we do not find ourselves in the same situation in the future. The solutions are complex. We need to increase capacity for raw materials, consumables and equipment in addition to capacity for drug substance and drug product. The key will be sustainment of these efforts when the pandemic wanes. Please also refer to my answers to questions 2-5, above, posed by the Honorable Brett Guthrie.

2. What steps should the Administration's COVID-19 Response Team take to ensure that drug identification platforms that can help to protect the public from the next pandemic will be funded over the next few years?

    a. As we continue in the fight against COVID-19 and witness the rise of new virus variants, would you support the development of an oral broad-spectrum host direct antiviral (HAD) for immediate deployment in response to viruses, their variants and other potential pathogens?

Theoretically, yes. In practice, these types of therapies have eluded us. For example, randomized controlled clinical trials have shown that neither ivermectin nor colchicine are effective in the treatment of COVID-19. Most drugs that appear to be active in cell lines or even in animal models do not work when subjected to proper clinical trials. It is critical to expand our national capability for the study of such promising therapies.

The Biden administration is providing $3.2B to support development of small molecule drugs to address coronaviruses in general. Those can be considered pan-coronavirus antiviral drugs. Investments should also include antiviral drugs that may have effectiveness against multiple pathogens. While these are sometimes harder to identify, the time is now to develop these types of drugs in earnest since we don't know what the next pandemic pathogen could be.

3. Given that Federal, state, and local officials are grappling with the effects of vaccine shortages, lack of transparency about stockpiles, and instability in the supply chain, what steps should the Administration's COVID-19 Response Team take to introduce additional COVID-19 vaccine candidates into market that are easier to distribute, remain stable at more favorable temperatures and only require a single dose?

From public reports, the administration is taking all of the necessary steps to secure COVID vaccines to all Americans who want them. On February 27, 2021, the U.S. FDA issued an emergency use authorization (EUA) for the Johnson & Johnson vaccine. This is the third EUA for a COVID-19 vaccine and the first for a vaccine that can be stored and distributed at refrigerator temperatures between 2°C and 8°C (36°F and 46°F) and requires a single dose. From public reports, mRNA-based vaccine companies are working on strategies that could improve the thermostability of their vaccines. Given the breadth of technologies in the U.S. Government supported COVID vaccine portfolio, and the emergency of variants, there could be a greater focus on the development of universal coronavirus vaccines that could address all of the different species and variants of coronaviruses.