

# Lessons from the pandemic: Responding to emerging zoonotic viral diseases—a Keystone Symposia report

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#### Abstract

The COVID-19 pandemic caught the world largely unprepared, including scientific and policy communities. On April 10–13, 2022, researchers across academia, industry, government, and nonprofit organizations met at the Keystone symposium “Lessons from the Pandemic: Responding to Emerging Zoonotic Viral Diseases” to discuss the successes and challenges of the COVID-19 pandemic and what lessons can be applied moving forward. Speakers focused on experiences not only from the COVID-19 pandemic but also from outbreaks of other pathogens, including the Ebola virus, Lassa virus, and Nipah virus. A general consensus was that investments made during the COVID-19 pandemic in infrastructure, collaborations, laboratory and manufacturing capacity, diagnostics, clinical trial networks, and regulatory enhancements—notably, in low-to-middle income countries—must be maintained and strengthened to enable quick, concerted responses to future threats, especially to zoonotic pathogens.

#### KEYWORDS

COVID-19, Ebola virus, infectious diseases, Lassa virus, Nipah virus, vaccines, zoonotic diseases

## INTRODUCTION

Over the past 20 years, the world has seen three major novel coronavirus outbreaks, SARS-CoV-1 in 2003, MERS-CoV in 2012, and SARS-CoV-2 in 2019. Despite repeated warnings that a coronavirus pandemic was likely, the world was in many ways caught off guard when SARS-CoV-2 took hold. The pandemic is now in its third year and has reached every corner of the globe. While some of the most pressing needs to control the pandemic have been addressed—effective vaccines and antivirals are available and diagnostic tests are available, though not readily accessible in some regions—it is useful to look back and see what can be learned from the world’s response to COVID-19 in terms of successes and remaining gaps.

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Diseases to discuss how the COVID-19 pandemic has changed preparedness for future pandemics and what lessons can be applied to known and unknown pathogen threats. Many symposium speakers focused on how the COVID-19 pandemic necessitated changes in public policies, clinical trial programs, regulatory processes, and capacity building, especially in low-to-middle income countries. They stressed that these changes must persist not only to facilitate a coordinated global response to future threats but also to strengthen healthcare systems in general to be more effective against routine healthcare needs. Symposium sessions were dedicated to early warning systems, rapid development and deployment of diagnostics, and efforts to reduce the manufacturing and development timelines of vaccines and therapeutics. While many speakers focused on COVID-19, several also discussed surveillance, research, and vaccine development efforts for other pathogens, including the Ebola virus, Lassa virus, and Nipah virus.

## KEYNOTE ADDRESS: LESSONS LEARNED FROM THE COVID-19 PANDEMIC

Anthony Fauci from the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) opened the meeting with a keynote address on what the COVID-19 pandemic has taught us about pandemic preparedness and response. Fauci called the pandemic “a totally historic, unprecedented outbreak” and lamented that even though the United States had been considered one of the most prepared countries, it suffered some of the highest infection and mortality rates. Fauci outlined seven lessons to take away from the COVID-19 pandemic (Figure 1).

1. The pandemic demonstrated the importance of global information and collaboration. For example, researchers in Wuhan, China quickly published the draft SARS-CoV-2 genome,<sup>1</sup> enabling researchers to begin working on what would ultimately prove to be highly effective vaccines. In addition, sharing surveillance data has been critical to identifying new variants—such as when South Africa first sounded the alarm about Omicron in late 2021—allowing countries to enhance their own surveillance measures.<sup>2</sup>
2. The pandemic revealed the importance of leveraging existing clinical trial infrastructure to ramp up clinical testing. In the United States, the NIH launched the COVID-19 Prevention Trials Network (COVPN) in July 2020 by merging pre-existing NIAID-funded networks.<sup>3</sup> This international network enabled the rapid roll-out of clinical trials for COVID-19 vaccines.
3. Fauci stressed the importance of basic biomedical research in vaccine development.<sup>4</sup> The COVID-19 vaccines were developed and approved in record time. However, they relied on decades of research in areas like structural vaccinology to identify optimal immunogens and in developing mRNA as a viable vaccine platform.
4. Preparing for the next pandemic requires continued surveillance and research into pathogens with pandemic potential. The World Health Organization (WHO) and other organizations have identified priority pathogens, including the Ebola virus, Zika virus, MERS-CoV, and SARS-CoV-2, to focus research efforts. Fauci also stressed the importance of a prototype pathogen approach, in which in-depth knowledge of a representative pathogen from a given family is leveraged to inform strategies and tools for related viruses.<sup>5</sup> In the case of COVID-19, prior experience with SARS-CoV-1 in 2002 and MERS-CoV in 2012 provided insights on effective approaches to SARS-CoV-2.<sup>6</sup> In February 2022, the NIAID published their Pandemic Preparedness Plan, which is heavily weighted toward the prototypes pathogen approach.<sup>7</sup>
5. Fauci stressed the importance of a One Health approach that centers the human–animal interface and the connection between human health, animal health, and the environment. COVID-19 is one of many examples demonstrating the impact of aggressive, damaging, and unbalanced interactions with nature that trigger new diseases.<sup>8</sup>
6. The COVID-19 pandemic was also another example of how longstanding systemic health and social inequities lead to disparities in health outcomes. In the United States, racial and ethnic disparities

## Lessons From COVID-19

- Global information sharing and collaborations are essential
- Existing clinical trial infrastructure should be utilized
- Prior scientific advances enable rapid vaccine development
- Prototype and priority pathogen approaches enable pandemic preparedness
- Continued surveillance of the human/animal interface is critical
- Longstanding systemic health and social inequities drive pandemic disparities
- Misinformation is the enemy of pandemic control

FIGURE 1

were seen in both SARS-CoV-2 infection and disease progression.<sup>9</sup> These may be a result of discrimination, limited healthcare access and use, or differences in occupation, education, income, and housing.

7. Finally, the pandemic revealed the power of misinformation. The Kaiser Family Foundation found that nearly 80% of people believe, or are unsure about, at least one common falsehood about COVID-19 or the vaccine—ideas such as vaccines contain microchips or cause infertility or death, or belief in the efficacy of fraudulent products and treatments.<sup>10</sup> Fauci tasked the audience to counter false information.

Over 2 years into the pandemic, it is clear that society must find a way to live with the virus long term. Several features of SARS-CoV-2 make eradication or elimination unfeasible—the virus has established animal reservoirs, it can rapidly mutate, acceptance of global vaccine campaigns has been challenging, and immunity wanes. The goal, therefore, is to return to a sense of normalcy where the virus no longer dictates everyday life. Eventually, effective treatments, intermittent vaccination, and routine respiratory hygiene may relegate SARS-CoV-2 to the likes of other respiratory viruses that we deal with daily.

## CEPI's response to the COVID-19 pandemic and future initiatives

William E. Dowling from the Coalition for Epidemic Preparedness Innovations (CEPI) described the organization's response to the COVID-19 pandemic and its plans. CEPI is a global partnership with a mission to stimulate and accelerate the development of vaccines against emerging infectious diseases and to enable access during outbreaks. Before COVID-19, CEPI was invested in priority pathogens, such as Lassa, MERS-CoV, Nipah, Chikungunya, and Rift Valley fever viruses. When SARS-CoV-2 emerged in January 2020, CEPI quickly shifted its focus to developing a vaccine, leveraging its MERS-CoV and Disease X efforts. Dowling stressed the importance of pre-existing partners to quickly pivot and ramp up SARS-CoV-2-related projects. Many activities were performed in parallel and at risk because the consequences of waiting were too high.

CEPI is part of the Access to COVID-19 Tools (ACT) Accelerator, a global collaboration to accelerate the development, production,

and equitable access to diagnostics, therapeutics, and vaccines. CEPI coleads the vaccine pillar of ACT, COVAX. As part of this effort, COVAX organized SWAT teams to conduct workshops with COVID-19 vaccine developers to identify and address challenges. Dowling stressed the importance of continuing these efforts as vaccine coverage is still inadequate in many parts of the world. Dowling described efforts as part of the Enabling Sciences team at CEPI to establish resources to directly compare vaccines developed by different entities, including the first WHO international standard for anti-SARS-CoV-2 immunoglobulin and a centralized laboratory network. The network is available for any COVID-19 vaccine in the preclinical-through-phase 3 stages. Researchers can also leverage the CEPI animal model network of high-containment labs for model development studies and vaccine testing.

Finally, Dowling described current and future CEPI efforts, dubbed CEPI 2.0. In response to the 100-Days Mission put forth at the 2021 G7 summit,<sup>11</sup> CEPI has set a goal of reducing the vaccine development timeline to 100 days.<sup>12</sup> Their plan includes developing a library of vaccines for known threats and the use of rapid response platforms that will allow rapid adaptation if related viruses emerge.

### Capacity building in West Africa—Experience from hemorrhagic fevers

Stephan Günther from the Bernhard Nocht Institute for Tropical Medicine (BNITM) described activities in West Africa, primarily Guinea, to address hemorrhagic fever. Günther described how the deployment of European Mobile Laboratories (EMLab) was instrumental during 2014–2016 Ebola virus disease outbreak. These mobile laboratories enable field operations for diagnostics of viral infectious diseases up to Risk Group 4, including Ebola virus, Lassa virus, Marburg virus, yellow fever virus, and now SARS-CoV-2. They are deployed based on a country request in response to outbreaks, usually under the WHO's Global Outbreak Alert and Response Network. To date, laboratory experts have been deployed with EMLab over 250 times.

Günther stressed that establishing decentralized laboratory capacity in communities most at risk and building capacity for in-country surveillance instead of external deployment is key to early detection and mitigating the impacts of an outbreak. After the 2014–2016 Ebola virus outbreak, one of the EMLabs was converted into a permanent, stationary lab for the diagnosis of hemorrhagic fever in the forest of Guinea. In February 2021, this lab detected a new Ebola virus outbreak, enabling a quick response by the WHO. As part of that response, BNITM deployed teams to Guinea to set up a permanent sequencing lab in the capital Conakry and to train local staff. The lab later sequenced SARS-CoV-2 variants in the region. The laboratory in forest Guinea also identified a single case of Marburg virus infection that, again, enabled quick action that ultimately limited the outbreak to a single index case. This decentralized, in-country surveillance capacity likely contributed to the stark contrast in disease and death between the 2014–2016 Ebola outbreak, which led to over 28,000 cases and 11,000 deaths, and the later 2021 outbreak, which was limited to 23 cases and 12 deaths.

### Leveraging academic health science centers to train for emerging pathogen outbreaks

Academic health science centers (AHSC) are in many ways well equipped to address pandemics. They employ experts in pathogen biology and infection control, have the means and expertise to develop and test countermeasures in animal models, are specialized in training, and typically form and maintain long-term capacity-strengthening collaborations. Despite these strengths, several obstacles limit AHSC involvement in outbreak responses. Experts often operate in silos and funding is project-specific and time-limited.

Dennis A. Bente from the University of Texas Medical Branch (UTMB) described programs and resources UTMB has developed to leverage its role as an AHSC and to contribute to pandemic preparedness and response. Owing to a long history of engagement with tropical medicine, global health, and high biocontainment research, UTMB was selected to host a national laboratory in 2005. The lab conducts cutting-edge research on animal reservoirs, spillovers, transmission, and countermeasures for high-consequence diseases. In addition, UTMB is home for the World Reference Center for Emerging Viruses and Arboviruses, which contains 7000 unique viral strains from almost 800 species, including 44 SARS-CoV-2 strains. Integral to the Galveston National Laboratory, a sophisticated high containment research facility on its campus, UTMB also runs a biocontainment care unit and training center for patients infected with high-consequence pathogens as well as a special pathogens program for clinical trials. The biosafety team has been instrumental in developing and validating protocols, such as an N95 decontamination and reuse program during COVID-19. Bente also described education and training programs at UTMB. They have developed a curriculum for graduate-level learners from diverse disciplines, including biomedical, social, clinical, public health, political, and environmental sciences, consisting of a simulated field experience of a Disease X outbreak and centered around One Health principles and outbreak investigation. Bente stressed the need to expand partnerships between national/international public agencies and AHSCs, to provide flexible funding, especially for educational programs, and to recognize public health response work done by academics.

### Challenges in infection control during the COVID-19 pandemic in India

Pragya Dhruv Yadav from the ICMR-National Institute of Virology, Ministry of Health & Family Welfare in India described some of the successes and challenges in India in addressing other viral outbreaks during the COVID-19 pandemic. Yadav stressed that the COVID-19 pandemic in many ways helped India realize its capabilities to scale-up in-country infrastructure for diagnostics, drug discovery, vaccine development and manufacturing, and personal protective equipment (PPE) manufacturing. India was quick to ramp up its vaccine manufacturing and clinical trial capacity in early 2020. As of April 2022, the Indian government has approved 10 COVID-19 vaccines, including COVAXIN®, an inactivated virus adjuvanted vaccine

developed by Bharat Biotech International Limited in collaboration with the Indian Council of Medical Research. The country has also demonstrated increased diagnostic and surveillance capacity for COVID-19, monitoring the Delta and Omicron waves and the impact of SARS-CoV-2 variants on vaccine-related immunity.<sup>13,14</sup>

Yadav also described the challenges the pandemic caused in effective surveillance of concomitant outbreaks. Outbreaks of Crimean Congo Hemorrhagic Fever (CCHF), Nipah virus, Zika virus, and H5N1 influenza virus occurred in India primarily during the Delta wave in the fall of 2021. Much of the healthcare workforce was mobilized to focus on COVID-19, limiting the surveillance efforts that likely led to underdiagnosis and underdetection during these outbreaks. For example, in 2019, 40 CCHF infections were detected in India. In contrast, only four infections were detected in 2020, despite the endemicity in Gujarat, Rajasthan state, and sero-surveillance data in livestock showing it is prevalent throughout the northern regions of the country. Lockdowns and travel limitations also put a hold on animal and bat survey studies to assess the prevalence of these zoonotic viruses. In addition, the lack of supplies and laboratory personnel negatively impacted laboratory diagnosis. Close-contact screening was also impacted by lockdowns and an overburdened workforce. This is especially critical given the common symptoms of COVID-19 and the Nipah virus infection. Despite these challenges, Yadav believes that India is better prepared to detect and respond to emerging/re-emerging threats. The country now has more than 3000 COVID-19 laboratories and enhanced hospital infrastructure. In addition, mobile BSL-3 facilities are being constructed for onsite sampling and testing in remote areas during outbreak situations and surveillance activities. This will undoubtedly be valuable, as the COVID-19 pandemic evolves during future outbreaks and epidemics.

## EARLY WARNING AND REPORTING FOR EMERGING ZOOONOTIC DISEASES

### Event-based surveillance and informal data sources for early epidemic awareness

In 1981, *MMWR* published what would become the sentinel report of the HIV/AIDS pandemic.<sup>15</sup> However, it would later be determined that HIV had been circulating since the 1930s, with widespread occurrences of AIDS in West Africa.

**Lawrence Madoff** from the University of Massachusetts Chan Medical School described the historical conditions that contributed to the delayed recognition of epidemics like HIV/AIDS and the growing importance of event-based surveillance and information data sources, such as social media, in the early detection of epidemics. There are many disincentives to report an infectious disease outbreak, as evidenced by the global reaction to South Africa when they first notified the world of the Omicron variant in late 2021.<sup>2</sup> In the 1980s, infectious disease surveillance was not a priority, and there was no international framework for disease reporting. Decades of research on vaccines and antibiotics had dramatically reduced infectious disease-related

mortality such that infectious diseases were not viewed as a major threat to public health. That attitude changed with the 1992 Institute of Medicine report *Emerging Infections: Microbial Threats to Health in the United States*.<sup>16</sup> In addition, the WHO revised International Health Regulations, which took effect in 2007, set up a framework for countries to report events that may constitute a public health emergency of international concern.<sup>17</sup>

Event-based, informal surveillance systems have increasingly been used to complement more traditional public health reporting systems to identify emerging outbreaks early. Madoff focused on the Program for Monitoring Emerging Diseases (ProMED), an electronic outbreak reporting service established in 1994.<sup>18</sup> ProMED has been the first outlet to publish reports of several outbreaks and epidemics, including cases of undiagnosed pneumonia in Wuhan, China based on social media and media outlets that would later be recognized as the beginning of the COVID-19 pandemic,<sup>19</sup> as well as cases related to the SARS-CoV-1 epidemic based on information from a reader who had read concerning information in a teacher chat room.<sup>20</sup> In addition to ProMED, other event-based surveillance systems include HealthMap, OIE-WAHIS, EMPRES-i+, and GISAIID. These surveillance systems can complement public health reporting, which while robust and accurate can also be slow and subject to broken links along the chain of communication. The WHO acknowledges the importance of these systems and provides member countries with guidance to establish their own systems in their 2008 report, *A Guide to Establishing Event-Based Surveillance*.<sup>21</sup> The WHO has also initiated the Epidemic Intelligence from Open Sources Program, which includes an accessible dashboard of infectious diseases drawn from a variety of sources.

## Preparing for the next coronavirus epidemic

**Lin-Fa Wang** from Duke–NUS Medical School discussed whether the world is prepared for the (nearly) inevitable emergence of a SARS-CoV-3 outbreak. Wang presented two possible scenarios for the next coronavirus outbreak—spillover from a natural animal reservoir, similar to what occurred with previous coronavirus epidemics, or reverse zoonotic transmission of SARS-CoV-2 from humans to animals and back to humans, which would be a unique event.<sup>22</sup> The chances of another sarbecovirus jumping from animals to humans is relatively high. Since 2020, more than a dozen new bat-borne coronaviruses related to SARS-CoV-2 have been identified in Asia.<sup>23</sup> Given that the bat species that harbors these viruses is found throughout Asia, Europe, and southern Africa, it seems only a matter of time until another virus spreads to humans. In the case of reverse zoonotic transmission, much of the focus has been on a theoretical transmission from bats.<sup>22</sup> However, Wang pointed to reports of widespread SARS-CoV-2 infection in white-tailed deer throughout the United States. Infection rates and trends suggest both active transmission among deer and multiple human-to-animal transmissions, making it feasible that deer may act as a new, manmade reservoir for SARS-CoV-2.

Wang also discussed work on understanding the impact of SARS-CoV-2 variants on vaccination immunity using a surrogate virus neutralization test to compare the ability of variants to escape neutralizing

antibody.<sup>24</sup> Wang showed that Omicron is unique among SARS-CoV-2 variants and animal sarbecoviruses in its ability to evade the neutralizing antibody response. They are now working on a pan-sarbecovirus vaccination strategy based on the detection of pan-sarbecovirus neutralizing antibodies in individuals previously infected with SARS-CoV-1 and vaccinated with the SARS-CoV-2 vaccine.<sup>25</sup> Wang showed unpublished data in mice of sequential vaccination with a SARS-CoV-2 vaccine followed by a SARS-CoV-1 vaccine. Wang hopes that this strategy may ultimately lead to the development of booster vaccines that elicit pan-sarbecovirus immunity in humans already vaccinated with current SARS-CoV-2 vaccines.

## A global systematic meta-analysis of SARS-CoV-2 seroprevalence studies

Rahul K. Arora from the University of Calgary and Maria Van Kerkhove from the WHO presented the results of a systematic review and meta-analysis of SARS-CoV-2 seroprevalence studies. Their study analyzed how seroprevalence has changed over time and across continents during the pandemic and included studies aligned to the standard, robust WHO UNITY serosurvey protocol.<sup>26</sup> Out of more than 73,000 abstracts screened, approximately 800 studies conducted from January 1, 2020 through March 4, 2022 were included in the analysis—43% of which were conducted in low-to-middle-income countries. The WHO and SeroTracker estimated that the global prevalence of seropositivity in October 2021 was approximately 67%—indicating that much of the world remained susceptible to severe disease.<sup>27</sup> Yet, seroprevalence varied throughout the world. It was lowest in the Western Pacific, perhaps due to the elimination strategy pursued in many countries in that region, and highest in high-income countries in the Americas. In Africa and Southeast Asia, increases in seroprevalence were largely driven by infections; in contrast, in high-income countries in Europe, the Americas, and the Western Pacific regions, vaccinations drove increased seroprevalence.<sup>27</sup> Arora also showed that SARS-CoV-2 cases were highly underestimated globally. Rates of underestimation varied by region and were highest in Africa.<sup>28</sup> Arora stressed that seroprevalence studies are crucial to understanding the true dynamics of SARS-CoV-2 infection and antibodies, thereby enabling better-informed decisions. The world developed considerable seroprevalence-study infrastructure during COVID-19—infrastructure that could be leveraged in the future for better serosurveillance for endemic diseases and emerging zoonotic viral diseases.

## Standardized seroprevalence data for SARS-CoV-2

May C. Chu and Thomas Jaenisch from the Colorado School of Public Health discussed the importance of standardized serosurveillance methods for SARS-CoV-2. While seroprevalence studies, like the one presented above by Arora, are critical to understanding trends in population burden and evolving immunity, the data are only as good as the tests used to assess seropositivity. In the case of SARS-CoV-2, over 500 serological assays have been developed. Chu and Jaenisch

are interested in identifying ways to harmonize surveillance results so that they can be compared, aligned, and provide meaningful insights. As a first step, they reviewed the SARS-CoV-2 literature for bridging studies—studies that include at least two serology test platforms for the same panel of samples. They identified approximately 350 such studies and qualitatively rated them on criteria such as the types of analyses performed, the use of calibration or reference samples, and the discussion of test limitations. Chu and Jaenisch are now working on more quantitative approaches to assess these studies to control for variability within and between studies, and correlations among tests in the same study, to eventually construct a synthetic reference standard to compare seroprevalence data over time and space.

## Nipah virus research and surveillance in Bangladesh

Nipah virus causes seasonal outbreaks in Bangladesh; fatality rates can be as high as 100%. Understanding the Nipah virus requires a true One Health approach to prevent spillover from the primary reservoir, *Pteropus medius*. Current surveillance efforts, effective at detecting hospital cases but may miss up to 50% of cases,<sup>29</sup> are largely focused on the western region of Bangladesh, which does not cover the entire range of either host or virus.<sup>30</sup>

Jonathan H. Epstein from the EcoHealth Alliance discussed how research can support surveillance efforts for Nipah virus. Epstein's group has worked to identify and confirm *P. medius* as the natural reservoir for Nipah virus. Longitudinal studies have shown that outbreaks in bats are associated with waning herd immunity rather than seasonal, as previously thought.<sup>31</sup> Additional work on human epidemiology identified characteristics associated with an individual's propensity to spread the Nipah virus.<sup>32</sup>

The government of Bangladesh has adopted an integrated approach to outbreak response, simultaneously investigating humans and bats during outbreaks to understand the relationship between the virus causing disease in humans and those circulating in bats. Epstein is currently involved in a 5-year project to better understand why Nipah outbreaks tend to localize to western Bangladesh, to assess Nipah virus genetic diversity and infection dynamics in bats throughout the country, and to better understand how viral genotype affects disease. Epstein stressed that the world is woefully underprepared for Nipah virus, or for any henipavirus strain with increased human-to-human transmissibility. Expanding surveillance efforts to regions where host and virus are known to occur alongside livestock and people, and making long-term investments in surveillance and spillover prevention, are needed to understand the diversity of these viruses, limit spillover, and scale up preparedness for future outbreaks.

## Microsoft Premonition—a scalable, sustainable platform to monitor the biome

Simon David William Frost from Microsoft Health Futures described how Microsoft Premonition can act as an early warning system for emerging diseases. Microsoft Premonition is a set of technologies

developed to monitor the biological environment in near real-time. It is first being assessed as a proof-of-concept to understand vector-borne diseases. One of the technologies within Microsoft Premonition is a cloud-based metagenomics pipeline that identifies species from high-throughput sequence data. Frost showed how this pipeline has been used to identify the presence of viruses in samples from patients with febrile illness in Nigeria, from bats, and from mosquitoes. Microsoft Health Futures is conducting a pilot study of environmental sensors that can detect and trap mosquitoes to assist in surveillance and vector control of West Nile virus in Texas. The goal is to eventually establish a global network of sensors that continuously samples the environment and provides real-time data about viruses and microbes in the area.

### **FIND: The 100-Days Mission for pandemic diagnostics**

Accurate diagnostics is a cornerstone of early pandemic response. During the COVID-19 pandemic, PCR tests were available within 64 days of the WHO announcing a public health emergency of international concern. Lateral flow tests became available within a year; and now, over 2 years after the pandemic began, genomic sequencing and at-home rapid testing are widespread, particularly in high-income countries. During the G7 summit in 2021, leaders tasked the scientific and research communities with shortening this timeframe even more. The summit put forth an ambitious, yet necessary, 100 Days Mission to have accurate rapid diagnostics, therapeutics, and vaccines ready to scale within 100 days of an outbreak.<sup>11</sup>

**Daniel G. Bausch**, from FIND, described the organization's plan to achieve the 100-day goal with regard to diagnostic testing. Achieving this milestone will require extensive preparation and changes to current global processes. During the early days of the COVID-19 pandemic, the development of diagnostic tests was hindered by slow access to samples and reference materials, lack of clear product requirements, and insufficient regulatory harmonization among countries. While many advances have been made, several low-to-middle-income countries still lack access to accurate tests and integration into surveillance networks. Overcoming these hurdles by setting up a framework for rapid sample sharing, a formalized global clinical trial network, and a collaborative regulatory processes is essential to streamline the diagnostics pipeline. FIND has defined 10 initiatives that revolve around accelerating research and development of novel diagnostic platforms, establishing clinical reference standards and sample access through a global biobanking network, streamlining evidence generation and regulatory approval, strengthening surveillance and community-based testing infrastructure, and establishing regional manufacturing bases. Bausch stressed that creating short-term systems meant to respond to one-off events is not a sustainable approach. Instead, FIND believes that outbreak preparedness relies on strengthening health systems—integrating programs and building capacity for endemic diseases and regularly actionable healthcare issues that are poised to pivot and scale to respond when a new threat arises.

### **Considerations for field-based laboratories**

**Lisa E. Hensley** from the NIAID, NIH described her experience setting up laboratories in Africa, with a focus on considerations for researchers when bringing diagnostics and research capabilities into the field. Hensley stressed that every situation is different in terms of mission, location, pathogen, scale, and speed. Successfully setting up a field laboratory requires understanding each of these elements while also being able to adjust to less-than-ideal circumstances and changing situations. In 2014, Hensley and her colleagues, including Joseph Fair, Randy Schoepp, and Joseph DiClaro, were instrumental in establishing the Liberian Institute of Biomedical Research (LIBR; now the recently established National Public Health Institute of Liberia) to establish in-country capabilities for Ebola testing. The goal was to set up a lab within 24 h at a facility previously used for HIV testing that local staff could continue to operate after the interim staff departed. Hensley described several challenges at such a site—for example, the lab was located in a relatively remote area, far from healthcare centers with poor-quality roads connecting it to the city. Delays in transporting samples can lead to delays in reporting results, which can affect both individual and public health responses. In addition, electricity, water, and communication systems can be unreliable. Other considerations include biosafety processes, such as the type of PPE to use and methods for proper waste disposal decontamination. The team developed systems to replace inconsistent paperwork and labeling with universal forms and standardized data management and result reporting to reduce inaccurate reports. Hensley noted that much has changed since they established the LIBR in 2014. Field laboratories are now more often involved in clinical research as well as public health responses, which presents its own opportunities and challenges. New technologies and better equipment, including point-of-care testing, as well as improvements in data reporting and capture, are more widely available. Perhaps most of all, there is increasing recognition and expectation of the high standards that can be achieved. Hensley stressed that the ability of these sites to rapidly pivot to COVID-19 underscores the need to establish and maintain long-term partnerships and clinical trial networks.

### **A bioluminescent biosensor for antibody detection**

Detecting pathogen-specific antibodies is important to understanding the prevalence of disease and a population's potential protection from it. The traditional method to detect antibodies, enzyme-linked immunosorbent assay (ELISA), is accurate and quantitative, but is also labor intensive.

**Éric Bergeron** from the Centers for Disease Control (CDC) described a new luminescent biosensor to detect antibodies directly from serum or plasma. The assay is based on NanoBit<sup>®</sup>, a bioluminescent platform, in which the NanoLuc<sup>®</sup> luciferase is split into two pieces. When these pieces are brought together in the presence of the NanoLuc substrate, a luminescent signal is generated. In this assay, each luciferase piece is

fused to the same pathogen antigen; if an antigen-specific antibody is present in the sample, it binds to two antigens, bringing together the luciferase halves. Bergeron showed how this assay has been applied to detect antibodies against the SARS-CoV-2 receptor-binding domain (RBD) antigen, as well as Ebola virus and Nipah virus antigens. The assay provides comparable sensitivity and specificity as ELISA but is simpler, has higher throughput, and can detect antibodies from any animal host, which is key for ecological studies of zoonotic diseases.<sup>33</sup>

## Assessing the quality of neutralization assays against SARS-CoV-2 variants

**Ioannis Sitaras** from Johns Hopkins University described work with the WHO Virus Evolution Working Group to review the literature on neutralization assays against SARS-CoV-2 variants using sera from vaccinated individuals. The group identified data for 72 observations and 1823 serum samples after primary vaccination of various vaccines and 47 observations and 1327 serum samples after boosting doses.<sup>35</sup> Most of the data were for the Moderna and Pfizer vaccines, while many other vaccines and vaccine combinations have comparatively limited data. Sitaras showed that the fold decrease in neutralizing antibodies against Omicron was higher and more variable for primary vaccination than for booster doses. This is not explained by waning immunity since most sera samples were collected at peak immunity. One possible explanation is that the percentage of responders—the percentage of samples that had detectable neutralizing antibodies against Omicron—was much lower following primary vaccination than after the booster dose (work in progress). Sitaras stressed that response rate is an important metric that should be evaluated and reported along with neutralization testing data. Another factor that could have contributed to the differences in fold-decrease between primary vaccination and boosters is study quality. Sitaras noted that many of the studies had inaccurate methodologies and/or incomplete reporting. Sitaras and colleagues developed a study reliability assessment tool to improve study comparability and increase the accuracy of fold difference calculations.<sup>34</sup>

## Prospective development of point-of-care tests

Many speakers throughout the session stressed the importance of early availability of diagnostic tests and strategies to decrease the time to develop such tests.

**Michael D. Gunn** from Duke University discussed an alternative approach, namely prospectively developing point-of-care antigen-based tests for pathogens with pandemic potential. Gunn addressed two key concerns to such an approach—the low sensitivity that often plagues point-of-care tests and the specific cause (agent) of the next outbreak is unknown. Gunn showed that highly sensitive tests can be developed by generating high-affinity diagnostic antibodies against targets present at high levels during infection. These antibodies can then be deployed onto high-sensitivity diagnostic platforms like the

D4 assay developed by Ashutoash Chilkoti at Duke University. The D4 assay consists of inkjet-printed antibody microarrays. The absence of background and strong signal contributes to its high sensitivity. Gunn's group has developed an Ebola D4 assay (EBOV D4) that targets a secreted glycoprotein and detects the four major Ebola strains with high sensitivity. In monkeys, EBOV D4 detected infection earlier than PCR-based tests.<sup>36</sup>

In terms of choosing a pathogen to target, Gunn noted that most pandemic threats will arise as genetic variants of known viruses. He recommended focusing efforts on diagnostics that are not affected by genetic variation. In the case of the Lassa virus, which is very genetically diverse, Gunn's group generated broadly reactive antibodies that should recognize any clinically relevant Lassa strain present in Africa. Gunn noted that this is one advantage of antigen-based tests over sequencing: antibodies recognize the three-dimensional structure of the antigen, which may be more highly conserved than a linear genetic sequence. Gunn proposed that broadly reactive diagnostic antibodies can be developed for all the pathogens on the WHO priority list using currently available technologies. These can be deployed onto high-sensitivity point-of-care assay platforms and distributed for use against current diseases. In the case of an outbreak, the tests can be validated against the new strain and widely distributed to help inform pandemic response efforts. Gunn noted that such a strategy would likely have been effective during the COVID-19 pandemic if a broadly reactive test against SARS-CoV-1 had been available.

## PATHOGEN BIOLOGY AND MODEL SYSTEMS

### Nonhuman primate models for Ebola and Lassa viruses

**Thomas W. Geisbert** from UTMB described work in nonhuman primate (NHP) models on hemorrhagic fever viruses, specifically Ebola and Lassa viruses. Geisbert described how different features of an animal model affect disease course. For example, the Ebola virus disease has a higher lethality rate in cynomolgus macaques than in rhesus macaques.<sup>36</sup> Other factors, such as the dose of the challenge virus and the route of exposure, can affect the timing of symptom onset and disease severity. Most studies in NHPs have focused on intramuscular (IM) injection, to mimic exposure via needle stick, or small particle aerosol exposure, to mimic potential bioterrorism threats. These routes of exposure show high rates of mortality but are not indicative of the primary means by which the Ebola virus is transmitted. Studies of mucosal exposure, which is the most common route of natural infection, are limited. Data from the initial Ebola virus outbreak in 1976 indicate that exposure via needle stick resulted in a shorter incubation period and higher mortality rate than mucosal exposure.<sup>37</sup> Geisbert showed that conjunctival exposure to the Ebola virus in cynomolgus macaques showed a delayed disease course and required a higher dose to produce uniform lethality than IM or small particle aerosol exposure. These data could have implications for patient management as they suggest that



the window of opportunity to provide treatment depends on the route of exposure.<sup>38</sup>

For Lassa virus, the main NHP model used is cynomolgus macaques as the virus does not cause high lethality in rhesus macaques. Similar to the Ebola virus, most studies on Lassa virus have focused on IM injection. Limited data on small particle aerosol exposure suggest that the disease course and lethality are similar for the two routes of exposure.<sup>39,40</sup> Most models of Lassa fever—and most vaccine and therapeutic studies—use a viral strain isolated from 1976 that belongs to lineage four.<sup>41</sup> Geisbert's group has isolated a more contemporary viral strain from lineage two and showed that it produces a highly lethal disease in cynomolgus macaques consistent with human Lassa fever.<sup>42</sup> They are also looking at the intranasal route of exposure to Lassa virus to see whether the disease differs based on the route of administration.

### Chimeric mouse models to understand the role of T cells in Ebola virus disease

NHP models are difficult to conduct—not all labs have the necessary expertise—and strict regulations can make it difficult to get such studies approved.

**César Muñoz-Fontela** from BNITM described work to develop mouse chimeric bone marrow models for filoviruses, with a focus on the Ebola virus. Muñoz-Fontela is interested in the role of T cell function in Ebola virus disease. T cell diversity and activity have been shown to correlate with disease outcomes in humans.<sup>43–45</sup> Developing a mouse model of Ebola virus disease is difficult as the virus does not cause disease in mice despite being able to replicate in them. Muñoz-Fontela's group has developed three mouse models with chimeric immune systems that can be leveraged to understand the role of T cells in Ebola virus disease. In the first model, immunosuppressed mice receive a bone marrow transplant from wild-type mice, resulting in an immunodeficient stromal compartment and wild-type immune system. Using this model, Muñoz-Fontela showed that the Ebola virus infects macrophages and dendritic cells. Dendritic cells are a key means by which the virus can migrate from sites of infection to the lymph nodes; in mice that survive, T cells are able to abrogate dissemination of the virus into the lymph nodes.<sup>46</sup> In a second model, immunocompromised mice are engrafted with human hematopoietic stem cells; this model recapitulates the human case fatality rate for different Ebola virus strains; Muñoz-Fontela showed that disease severity and mortality were associated with inflammation and colonization of the liver.<sup>47</sup> Finally, Muñoz-Fontela showed unpublished data from a mouse model designed to understand the memory immune response. He hopes that this model will be instrumental in identifying correlates of protection from vaccination and natural infection.

### Animal models to model immune imprinting for influenza virus

**Florian Krammer** from the Icahn School of Medicine at Mount Sinai described the use of animal models for the influenza virus, with a

focus on vaccine research. Many animal models have been developed to study influenza virus. These differ in their abilities to recapitulate human disease and assess transmissibility, as well as in practical aspects such as the cost and availability of genomic tools and reagents. For example, there are many good tools available to conduct studies on mice and NHPs; however, these animals do not transmit the virus. Of the animal models available, only pigs are a natural host for the influenza virus, yet immunologic tools and reagents for pigs are limited. Krammer focused primarily on using animal models to model pre-existing immunity. Humans are continually exposed to different influenza viruses either via natural infection or vaccination. According to Krammer, the first viral strain that people are exposed to affects their immunity going forward. For example, people born before 1957 were primarily first exposed to H1N1; this birth cohort, who are now aged 65 years and older, is less susceptible to hemagglutinin (HA) group 1 viruses and more susceptible to HA group 2 viruses. Conversely, younger individuals, who are more likely to have been initially exposed to H3N2, are more susceptible to HA group 1 viruses and less susceptible to HA group 2 viruses.<sup>48</sup> This immune “imprinting” is difficult to model in mice because repeat infection often induces cross-protective T cell responses across influenza A viruses, masking the impact of HA- or NA-based imprinting. Krammer's group has developed an animal model to mimic immune imprinting via influenza B viruses that express either H3 or H1. He showed that challenging mice with influenza H5N1 (a group 1 HA) after inoculation with either an H3- or H1-expressing virus recapitulates the effects of H1 imprinting—i.e., mice initially inoculated with H1-expressing virus were more resistant to disease than those inoculated with H3-expressing virus.<sup>49</sup> Krammer also described how differences in antibody features, the longevity of the immune response, and differential effects of adjuvants among animal models and humans must be taken into consideration in vaccine studies.

### NHP models for coronaviruses and henipaviruses

Developing new animal models will be a major bottleneck to achieving the 100-day goal for vaccines and therapies. One of the difficulties in generating a model for a new virus is that there are not a lot of data on the human disease to know what a successful model looks like.

**Emmie de Wit** from NIAID discussed work to create NHP models for COVID-19 and Nipah virus infection. When SARS-CoV-2 first emerged, de Wit's group leveraged their experience with MERS-CoV to develop an NHP model in rhesus macaques that recapitulates mild-to-moderate COVID-19, with similar virus shedding patterns as humans. The first data from macaques were shared with the U.S. government and the WHO in late February 2020,<sup>50</sup> and the model is now widely used to study the impact of SARS-CoV-2, as well as treatments<sup>51</sup> and vaccines.<sup>52,53</sup> De Wit noted that these data likely represent the fastest possible turnaround time from model development to in-human studies. For example, animal studies of the antiviral remdesivir began in early March 2020, and the USFDA granted emergency use authorization in May 2020. One drawback of this macaque model is that it does not recapitulate severe disease. De Wit's group has looked at differences in immune dynamics and disease course between young and old

animals to both understand why age is a risk factor for severe COVID-19 in humans and to see if they could model severe disease in animals. Unlike in humans, there were minimal differences in clinical disease and viral replication in old and young animals. However, older animals showed signs of delayed T cell responses and return to immune homeostasis.<sup>54</sup>

De Wit also shared work on animal models for Nipah virus infection and disease. The origin of several human Nipah virus cases was traced to the consumption of date palm sap contaminated with virus from bat excrement.<sup>55</sup> At the time, there was some skepticism over whether a respiratory infection could result from drinking/consumption. In a hamster model, de Wit validated that Nipah virus could cause a respiratory disease after drinking. De Wit's group also observed inefficient transmission between hamsters after inoculation by drinking, thus recapitulating the transmission patterns seen in humans.<sup>56,57</sup> Additional studies in hamsters showed that Nipah virus can enter the CNS through olfactory neurons early after infection, indicating that patients who present with symptoms may already have CNS involvement.<sup>58</sup> Effective treatments and vaccines must, therefore, consider the CNS impacts of Nipah virus as well as the respiratory effects. De Wit showed that treatment with remdesivir protects monkeys from lethal Nipah virus challenge; however, depending on the dose and timing, animals that survive still develop neurologic signs.<sup>59</sup> De Wit thinks this could be a model to study the neurologic impact of Nipah disease apart from the respiratory effects.

## SARS-CoV-2 antibodies and phagocytosis

Many antibody studies focus on their neutralization function, which is often associated with protection against infection; but antibodies have many other functions that may impact protection.<sup>60</sup>

**Pontus Nordenfelt** from Lund University presented data on the impact of anti-SARS-CoV-2 antibodies on phagocytosis. Nordenfelt showed that, somewhat paradoxically, spike-specific monoclonal antibodies inhibited phagocytosis at high concentrations, regardless of their neutralization ability. Consistent with this finding, in mice low-to-moderate doses of a monoclonal antibody treatment were effective at protecting animals against a lethal injection of SARS-CoV-2. High doses of the monoclonal antibody treatment, however, led to worse outcomes.<sup>61</sup> A similar dose relationship was seen in a phase 1 clinical trial of the antibody bamlanivimab.<sup>62,63</sup> Nordenfelt's group is working to understand how high antibody levels inhibit phagocytosis.

## COUNTERMEASURES: VACCINES, THERAPEUTICS, AND RAPID MANUFACTURING

### The Coronavirus Immunotherapeutic Consortium: Characterizing SARS-CoV-2 antibodies

**Erica Ollmann Saphire** from the La Jolla Institute for Immunology described the efforts of the Coronavirus Immunotherapeutic Con-

sortium (CoVIC) to evaluate antibody therapeutics for COVID-19 and identify likely effective combination therapies suitable for use in low-to-middle income countries. CoVIC is evaluating more than 400 candidate monoclonal antibodies from a range of sources, including SARS-CoV-1 and SARS-CoV-2 survivors, vaccinees, nanobodies, and engineered multivalent formats. Most of the antibodies were developed by industry, with a significant fraction coming from small companies and startups. Once they receive the antibodies, CoVIC sends them to various experts in the field to conduct functional analyses in parallel. The results are available via the CoVIC database.

Saphire discussed efforts to identify effective antibody combinations. Using high-throughput surface plasmon resonance-based competition analyses, researchers have classified antibodies into seven communities and additional subcommunities based on their epitope within the RBD of the spike protein.<sup>64</sup> These are functional subdivisions of the original four classes defined by Barnes et al.<sup>65</sup> Each community has a distinct footprint and competition profile. These definitions provide information on how the antibody will behave, for example, in terms of neutralization capacity against variants. When thinking about designing an antibody cocktail, it would likely be advantageous to choose those with different binding modes that do not compete for the same site on the spike protein. Neutralization assays showed that some antibody groups have reduced neutralization capacity against the Beta and Gamma variants, while others are relatively resistant to viral mutations. Epitope location is also correlated with neutralization ability. There was often a trade-off between robust neutralization and breadth across variants. Saphire noted that moving forward with an effective therapy will require finding a sweet spot that maintains both potency and breadth. Most antibodies have been evaluated in mice as a prophylactic treatment. These studies showed that certain epitope groups offer more robust *in vivo* protection. In general, the best antibodies have robust neutralization activity, but neutralization activity alone was not indicative of protection.

### The ChAdOx1 vaccine platform for COVID-19 and beyond

**Sarah C. Gilbert** from the University of Oxford discussed the development of the ChAdOx1 vaccine for COVID-19 and how the ChAdOx1 technology can be used to produce vaccines against other emerging pathogens. ChAdOx1 is an adenoviral vector in which the desired antigen is encoded into the viral genome and expressed by infected cells; modifications to the viral genome render it incapable of replicating. The use of a simian adenovirus avoids pre-existing immunity among vaccinees. The platform is easy to adapt to new and emerging pathogens as it only requires inserting the DNA sequence of the antigen gene of interest; the manufacturing process stays the same. Prior to SARS-CoV-2, ChAdOx1-vectored vaccines had been studied in phase 1 trials, demonstrating strong immunogenicity after a single dose and a consistent safety profile. The antigen in the COVID-19 ChAdOx1 vaccine is the SARS-CoV-2 spike protein without the prefusion stabilization mutations that have been used in other platforms. This native

spike antigen was shown to mimic the native spike receptor binding functionality and prefusion structure, as well as native receptor glycan modifications.<sup>66</sup> Gilbert stressed that an early partnership with AstraZeneca was key to ensuring sufficient manufacturing capacity. The company identified more than 25 supply partners across 15 countries to secure and establish a global supply. ChAdOx1 nCoV-19 is the most widely used vaccine worldwide, with over 2.8 billion doses delivered across 180 countries, with two-thirds of the doses provided to low-to-middle income countries. The vaccine is approved as a two-dose regimen, which was shown to maintain high antibody levels.<sup>67</sup> During the roll-out of the vaccine, rare cases of thrombosis with thrombocytopenia syndrome (TTS) were observed that were not seen in clinical trials.<sup>68</sup> Incidence of TTS is higher in northern European countries and lowest in Asia.<sup>69</sup> Researchers are working to understand whether there is a relationship between vaccination and TTS and to identify risk factors. Another evolving question is whether the vaccine will protect against new variants. Data show that it does protect against severe disease against the Alpha and Delta variants,<sup>70</sup> but continued research is needed as new variants emerge, immunity wanes, and people continue to get boosters.

Gilbert showed that the ChAdOx1 platform is being used to develop vaccines for other emerging pathogens. In livestock, a single dose of ChAdOx1 vaccine expressing the major glycoprotein of Rift Valley fever virus was 100% protective.<sup>71</sup> Vaccinating livestock for this virus can provide economic benefits while also preventing human exposure to the virus. Preclinical studies in NHsP have also demonstrated the ability of ChAdOx1-based vaccines to protect against Nipah virus<sup>72</sup> and Lassa virus.<sup>73</sup>

**Neeltje van Doremalen** from the NIAID presented data on a new version of ChAdOx1 that incorporates the SARS-CoV-2 Beta spike protein (AZD2816). Hamsters were vaccinated with either a single dose of AZD2816 or with a dose of the original ChAdOx1 COVID-19 vaccine (AZD1222) followed by AZD2816. Vaccinating with the Beta vaccine alone elicited higher levels of anti-Beta antibodies, while the dual vaccination strategy elicited similar antibody levels against ancestral, Beta, and Delta variants. Both vaccination strategies protected against challenges with the Beta and Delta variants. In both challenge groups, neutralizing antibody levels correlated with protection; however, binding antibodies correlated with protection only when challenged with the Delta variant (which was not part of either vaccine), but not the Beta variant. This suggests that other, non-neutralizing antibody properties may be more important to protect against variants not contained within the vaccine. Consistent with this, a single dose of AZD2816 induced high binding antibodies for the Omicron variant but few neutralizing antibodies. Despite the lack of neutralizing response, both AZD2816 and AZD1222 protected against infection from Omicron.<sup>74</sup>

### **Building on basic research to facilitate vaccine development**

**Kizzmekia S. Corbett** from the Harvard T.H. Chan School of Public Health discussed foundational research that enabled the rapid

development of COVID-19 mRNA vaccines.<sup>75</sup> Corbett highlighted the importance of a prototype pathogen approach to pandemic preparedness, championed by Barney Graham and discussed by Anthony Fauci in his keynote address. Before 2016, coronavirus vaccine development was plagued by low expression and instability of wild-type spike proteins.<sup>76</sup> Leveraging previous work showing that stabilizing the prefusion form of the RSV F protein increased its immunogenicity<sup>77</sup> and knowledge of the HKU1-spike protein structure,<sup>78</sup> the MERS-CoV spike was stabilized in its prefusion conformation. The stabilizing mutations, two prolines (2P) in the apex of the spike S2 region, increased immunogenicity. In mice, MERS S-2P elicited more robust neutralizing activity against multiple MERS strains compared to MERS S1 monomers or MERS spike wild-type trimers. Importantly, that foundational work showed that the 2P mutations were transferable into multiple Beta-CoV spikes, including SARS-CoV.<sup>79</sup> When SARS-CoV-2 emerged, analogous mutations were introduced into the spike protein to create a stabilized form, SARS-CoV-2 S-2P, that has been leveraged to develop mRNA vaccines, antibody treatments, and diagnostic tools. While several COVID-19 mRNA vaccines were developed in record time and are generally heralded as one of the key successes of the pandemic, Corbett noted that we could have been even more prepared if work to develop the MERS S-2P vaccine had continued to clinical trials. Corbett stressed the important relationship between structured-guided rational antigen design and viral immunology that enable the rapid development of highly effective vaccines.

### **Arevirumab-3: An antibody cocktail for Lassa fever**

**Luis M. Branco** from Zolgen Labs showed preclinical data for the antibody cocktail arevirumab-3. The antibodies within arevirumab-3 were identified from a group of human monoclonal antibodies isolated from Lassa fever survivors from Sierra Leone. Structural, *in vitro* virology, and *in vivo* studies suggest that monotherapy is ineffective and could lead to the escape of mutant viral strains.<sup>80-82</sup> Thus, a rationally designed cocktail of antibodies targeting nonoverlapping, complementary epitopes, and diverse mechanistic functions were derived for preclinical evaluation in relevant animal models of Lassa fever. In macaques, low-dose arevirumab-3 elicited 100% protection against lineage II and lineage III Lassa fever viruses after a single administration, even if given after the onset of clinical symptoms. While a dual antibody combination similarly elicited high levels of protection, Zolgen Labs is moving forward with the three-antibody cocktail to reduce the risk of escape mutants.<sup>83</sup> The company is planning a first-in-human phase 1 trial for arevirumab-3. Branco stressed that it no longer makes sense to disregard the development of potentially lifesaving, technologically advanced therapies for neglected tropical diseases. Lower costs and sufficient infrastructure and personnel in West Africa make it feasible to manufacture monoclonal antibody drugs regionally.<sup>84</sup>

### **MOPEVAC: A platform for arenavirus vaccines**

**Sylvain Baize** from the Institut Pasteur presented data on MOPEVAC<sub>NEW</sub>, a pentavalent live-attenuated vaccine against

new-world arenaviruses. MOPEVAC is a live-attenuated vaccine platform based on the Mopeia virus, an old-world arenavirus similar to Lassa fever virus but which does not cause disease in humans. The virus has been modified to both reduce virulence and increase immunogenicity. A Lassa-directed vaccine, MOPEVAC<sub>LAS</sub>, elicited both cellular and humoral immune responses in monkeys and demonstrated high levels of protection against challenges with Lassa fever virus.<sup>85,86</sup> Baize presented unpublished preclinical data on a MOPEVAC vaccine designed to protect against new-world arenaviruses, such as Machupo and Guanarito viruses.

### **Fiocruz: Capacity building in Brazil during COVID-19**

**Marco A. Krieger** from Fiocruz described the organization's efforts to spearhead the pandemic response and production of diagnostics, vaccines, and therapeutics in Brazil during the COVID-19 pandemic. Fiocruz was founded in 1900 to help address concurrent outbreaks of yellow fever, smallpox, and plague in Rio de Janeiro. Today, Fiocruz plays an extensive role in public health—its responsibilities include functions performed by the USNIH, USCDC, and USFDA—and is involved in research, education, and innovation from basic research to production. During COVID-19, Fiocruz was instrumental in facilitating a technology transfer with AstraZeneca to enable local production of the ChAdOx1 vaccine and deliver more than 150 million vaccine doses within the Brazilian public health system. Local vaccine production played an important role in the national vaccination program—the majority of vaccines produced in Brazil were delivered in the first half of 2021 when they were able to affect the course of the pandemic. Other COVID-19 initiatives included providing diagnostic support by producing molecular tests and training personnel; healthcare support by providing intensive care unit beds and supporting primary care; therapeutic research and production; public and media communications; and guidance materials for researchers and physicians. Krieger stressed that local access to innovations and new technologies is key to enabling countries like Brazil to face the challenges brought on by pandemics.

### **Conducting vaccine trials amid the COVID-19 pandemic**

**Sue Ann Costa Clemens** from Oxford University gave important insight on the clinical and operational aspects of conducting a large vaccine clinical trial with high quality and fast enrollment amid the COVID-19 pandemic. Clemens noted that, in one sense, science moved too fast: vaccine candidates were developed in record time, but there was globally insufficient infrastructure to conduct in-parallel, large-scale clinical trials needed to ensure their safety and efficacy for registration purposes. The development of a global clinical trial network focusing on LMICs paved the way for regulatory and ethics committees to quickly approve vaccine trials and for expedient enrollment of thousands of volunteers. Other pandemic-related challenges included

building new investigational sites and addressing a lack of medical protection, equipment, devices, and laboratory material, all while ensuring this new infrastructure adhered to social distancing guidelines while facilitating connectivity between sites in the midst of travel and flight restrictions. Setting up such a large quality trial network also required extensive capacity building—training personnel and building up laboratory capacity. As part of the Bill & Melinda Gates Foundation site readiness program, Clemens and the team prepared and trained for four months, establishing 22 clinical trial sites in seven Latin American countries. At their peak, these sites recruited up to 22,000 subjects per month, contributing to the global network of sites at the COVAX website. These initiatives were key to quickly bringing vaccines to the world population, saving millions of lives. During the pandemic, the time from getting a trial protocol approved to opening a site could be as short as 44 days. Clemens echoed Krieger's earlier sentiment, noting that much of the initial trial funding in Brazil was provided by Brazilian philanthropy and local institutions, highlighting the importance of local support and capacity building. Now that the main push to build research capacity and set up clinical trial sites is over, the infrastructure and resources are being used to address key scientific questions using real-world data, such as the persistence of immunity among vaccinees, the impact of variants on immunity, how booster doses affect protection, and expanding knowledge of vaccination and therapeutics in high-risk groups, such as pediatrics and pregnant women. Clemens is confident that the COVID-19 experience will have lasting impact on future surveillance, research, development, and therapeutic manufacturing capacities. Global collaborations, partnerships, and networks for research and development can continue to be leveraged for new challenges and to improve and accelerate regulatory submissions and reviews as well as technology transfers from industry and academia to local sites. Coupled with the fact that many areas now have a more experienced workforce and increased laboratory capacity, Clemens is hopeful that the COVID-19 pandemic will leave us better prepared to face current and future healthcare challenges.

### **Improving vaccine manufacturing to achieve the 100-Days Mission**

**Renske Hesselink** from CEPI discussed the organization's efforts to decrease vaccine manufacturing timelines to achieve the 100-Days Mission put forth at the 2021 G7 summit. Regarding vaccines, critical points along the chemistry, manufacturing, and controls (CMC) process occur at the beginning of the process—e.g., to develop processes to manufacture materials suitable for first-in-human studies—and at the end—e.g., scaling up manufacturing and technology transfers are critical to producing doses for phase 3 trials and commercialization as well as to ensure equitable access around the world. Estimates indicate that currently available technologies can decrease vaccine development timeline to approximately 250 days. It is clear, therefore, that new technologies and innovations are needed.<sup>12</sup> CEPI has conducted an assessment of current vaccine platforms to identify the critical paths and timelines from a CMC perspective to generate a first clinical trial

material (CTM). Among the platforms, RNA-based platforms are the fastest, with the potential to produce a first CTM within 30 days of access to the viral genome, given that certain criteria are met. This timing is consistent with achieving the 100-Days Mission. Other vaccine platforms, such as viral vectors and protein-based vaccines, take longer to develop the first CTM—up to approximately 60 days under appropriate conditions. Hesselink stressed that speed is not the sole consideration, however. Given that different vaccine platforms will generate different immune responses and have different safety profiles, it is important to continue to develop and optimize a range of vaccine platforms. In addition to new technologies, investments in infrastructure, a trained workforce, regulatory strategies, and a robust supply chain are needed to ensure that the resources are available to scale-up vaccine manufacturing. One of the key challenges of the pandemic has been to ensure equitable access to vaccines in low-to-middle income countries. Factors, such as thermostability, cost, and ease of administration, are key to achieving this. Hesselink described a project with CEPI and the company MedInstill to develop a multidose injection system that holds 200 vaccine doses as a low-cost alternative to single-dose glass vials.

### Improving clinical trial design: Tools from the COVID-19 Therapeutics Accelerator

Dan Hartman from the Bill & Melinda Gates Foundation described the efforts of the COVID-19 Therapeutics Accelerator (CTA), a collaboration across public and private sectors to address bottlenecks and gaps along the research and development chain. The goal of the CTA is ultimately to accelerate the development of and access to COVID-19 therapeutics, with a focus on low-resource settings while establishing sustainable infrastructure for ongoing healthcare needs and future pandemics. Hartman stressed that the CTA has a novel approach to drug development founded on transparency, agility, speed, flexibility, and global access. Hartman focused on the CTA's efforts to address issues with poorly designed clinical trials. The USFDA estimated that of more than 2500 trial arms among COVID-19 trials, only 5% were adequately powered and randomized.<sup>87</sup> To address this problem, the CTA has created tools for clinical researchers to design robust, well-powered trials that are able to address the scientific question being studied. These tools are available on the Design, Analyze, Communicate (DAC) website (<https://dac-trials.tghn.org/>) and include trial simulation tools, a protocol library, and an assessment questionnaire that covers a range of topics important for trial design. Hartman showed details from the TOGETHER Trial, an adaptive platform study that investigated the effect of 11 repurposed interventions in newly diagnosed, high-risk patients with COVID-19, including fluvoxamine,<sup>88</sup> interferon-lambda,<sup>89</sup> ivermectin,<sup>90</sup> and sabizabulin.<sup>91</sup> Adaptive platform trials, like TOGETHER, can be more efficient than other clinical trial designs—data are routinely reviewed in real-time, enabling investigators to adapt the trial to efficacy and safety signals and multiple prospective therapies are tested against a single control group, obviating the need to conduct individual studies for each agent.

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### COMPETING INTERESTS

R.K.A. is a Fellow at Flagship Pioneering. He was previously a Technical Consultant for the Bill and Melinda Gates Foundation Strategic Investment Fund, is a minority shareholder of Alethea Medical, and was a former Senior Policy Advisor at Health Canada; each of these relationships is unrelated to the present work. S.G. owns stock in Vaccitech, a company using ChAdOx1 to develop vaccines, and is named as an inventor on patents covering the ChAdOx1 technology and the ChAdOx1 Covid vaccine.

The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays, NDV-based SARS-CoV-2 vaccines, and influenza virus vaccines, which list Florian Krammer as coinventor. Mount Sinai has spun out a company, Kantaro, to market serological tests for SARS-CoV-2. F.K. has consulted for Merck and Pfizer (before 2020) and is currently consulting for Pfizer, Seqirus, 3<sup>rd</sup> Rock Ventures, and Avimex. The Krammer laboratory is also collaborating with Pfizer on animal models of SARS-CoV-2, has historically collaborated with GSK on influenza virus vaccines, and is currently collaborating with Dynavax on influenza virus vaccine development.

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