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VACCINE INSIGHTS

SPOTLIGHT ON:

COVID-19: how is the pandemic changing the vaccines space?

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VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

A new chapter for the COVID-19 pandemic – and for the vaccines space

Charlotte Barker & Fred Cassels

"...after the series of epidemics and pandemics the world has seen in recent decades, we cannot afford to let the current momentum diminish."

FOREWORD

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Welcome to the inaugural issue of *Vaccine Insights*, and our Spotlight exploring how the COVID-19 pandemic has changed – and is still changing – the vaccine field.

Contributors to this Spotlight represent some of the world's leading authorities on COVID-19. Along with an army of government, industry, academic and non-profit scientists, they have worked tirelessly from the moment a novel coronavirus was identified in Wuhan in December 2019. SARS-CoV-2 was sequenced within weeks, clinical trials of vaccine candidates began three months later, and the first COVID-19 vaccines were licensed for use just 11 months after the viral genome was published.

In large part due to those vaccines, we are moving into a new phase of the pandemic. At this unique moment in the pandemic – and in history – we feel that the time is right to take stock, consider lessons learned, and look ahead to what will be needed to counter new COVID-19 variants and future pandemic viruses. In this issue, we ask leading experts in all areas of vaccine development, manufacture, and delivery to share their thoughts in a series of articles and interviews.

Nick Jackson (Clover Biopharmaceuticals, formerly Coalition for Epidemic Preparedness Innovations, CEPI) sets the scene with an overview of how the vaccines space has been changed by the pandemic to date – from the meteoric rise of mRNA vaccines to an influx of new companies into the industry, with the technology platform 'toolbox' having grown considerably in the process.

Anthony Fauci (NIH) has been at the heart of the COVID-19 response in the US – in an interview, he lays out the key lessons governments and funders must heed if they are to protect the public from future pandemic threats. He introduces several threads that run throughout the issue, including the need for sustained investment in pandemic preparedness and vaccine research, the importance of developing strategies to tackle mis/disinformation, and the increasing focus on broadly protective vaccines.

After an mRNA vaccine made history by becoming the first approved vaccine for COVID-19, there has been great excitement about the potential of this platform technology – we sat down with RNA pioneer Drew Weissman (University of Pennsylvania) to get his thoughts on the past, present, and future of RNA vaccines.

A recurring theme from our contributors was the role of regulators in accelerating vaccine approvals – in our Expert Roundtable video and transcript, we bring together Peter Marks (FDA), Marco Cavaleri (EMA), Carla Vinals (Moderna), and Adam Hacker (CEPI) to discuss how regulators adjusted and adapted to pandemic conditions, and what that means for vaccine developers going forward.

Analytical development is one area where vaccine developers can avoid regulatory delays – Anna Särnefält and Ingrid Kromann (CEPI) urge developers to start early and think ahead in assay development.

An area that is garnering attention from regulators, researchers, and developers alike is correlates of protection (CoPs). Peter Gilbert (Fred Hutchinson), Stanley Plotkin (University of Pennsylvania), and Peter Dull (Bill and Melinda Gates Foundation) are three of the world's leading experts on CoPs for vaccines and they join us for an Expert Roundtable to discuss the nuances around the use of CoPs and, importantly, how CoPs can be used for regulatory decision-making.

Of course, the story – and the challenges – didn't end with the regulatory approval of COVID-19 vaccines. Tracing the journey from approvals to 'shots in arms,' Michael Angelastro and Robert Johnson (Biomedical Advanced Research and Development Authority, BARDA) describe the US government's approach to supply chain management, while Darin Zehrung (PATH) discusses the unique challenges of delivering pandemic vaccines in lower- and middle-income countries (LMICs). mRNA vaccines, in particular, have challenging ultra-low temperature storage and transport requirements. In the next phase of the pandemic, cheaper and more easily stored vaccines are likely to gain importance, says

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Biological E's Vikram Paradkar, in an article describing the development of the company's $2/dose adjuvanted protein subunit vaccine, CORBEVAX™.

COVID-19 vaccination rates remain low in many LMICs, and Jerome Kim (International Vaccine Institute) and Maria Elena Bottazzi (Baylor College of Medicine) offer six key lessons to achieve more equitable vaccine delivery in future pandemics. Emily Adhikari (University of Texas Southwestern Medical Center) et al highlight another group underserved in this pandemic – pregnant and lactating women – and call for more inclusive clinical trials.

The impact of COVID-19 goes beyond the morbidity and mortality of acute disease. With millions worldwide suffering ongoing respiratory and neurological symptoms, Peter Hotez (Baylor College of Medicine) and members of the Lancet COVID-19 Commission ask whether vaccination should be considered as a preventative or therapeutic option for 'long-COVID.'

Next, we turn our attention to future threats. We appear to be moving toward endemicity, but new variants can still pose fresh challenges, and the prevalence of coronaviruses in key zoonotic reservoirs (most notably bats, with many introductions of bat-related viruses into humans annually) means that a new human coronavirus pandemic is inevitable. After decades of studying coronaviruses, Ralph Baric (University of North Carolina) believes our best hope for the future lies in developing multiple lines of defense, including development of broadly protective vaccine strategies. It's a sentiment echoed by zoonotic disease expert Linfa Wang (Duke-NUS Medical School), who cautions that development of broadly protective coronavirus vaccines will be a stepwise process, but whose lab is developing a promising pan-sarbecovirus vaccine.

The deadliest pandemic since the 1918 pandemic influenza, COVID-19 has touched all our lives. But will the world remember the hard-won lessons our contributors have shared, including the importance of long-term investment into pandemic preparedness and vaccine development? Will changes to the vaccine industry wrought by the pandemic last? As Philip Dormitzer (GSK) points out, interest in – and funding for – vaccines has historically been cyclical. But after the series of epidemics and pandemics the world has seen in recent decades, we cannot afford to let the current momentum diminish.

We believe that the vaccines space is entering an exciting new chapter. *Vaccine Insights* will continue the story, with upcoming Spotlights offering insights into vaccine formulation and administration, preclinical and clinical research, what's next for RNA vaccines, and the future of vaccine manufacturing. We hope you'll join us!

BIOGRAPHIES

Charlotte Barker, Editor, *Vaccine Insights*

Charlotte Barker is an experienced writer and editor with a passion for communicating the latest scientific advances. As Editor of *Vaccine Insights*, she works with a variety of stakeholders to generate timely, accessible content for readers engaged in vaccines development and manufacture around the world. Charlotte has worked in scientific and medical publishing for 17 years, most recently as Associate Content Director at Texere Publishing, maintaining high editorial standards and a unique voice across publications covering analytical chemistry, translational science, and pharmaceutical manufacturing. She began her career at Future Science Group, where she managed Medline-indexed journals including *Regenerative Medicine* and *Bioanalysis*.

Fred Cassels, Global Head for Enteric and Diarrheal Diseases, Center for Vaccine Innovation and Access, PATH

Fred Cassels is Global Head for Enteric and Diarrheal Diseases (EDD) at the Center for Vaccine Innovation and Access at PATH. Projects within the EDD group encompass vaccine discovery, proof of concept, process development, cGMP manufacture, Phase 1–4 clinical trials, licensure,

and introduction – all for the benefit of low- and middle-income countries. Previously, Fred was Chief of the Enteric and Hepatic Diseases Branch, Division of Microbiology and Infectious Diseases (DMID), NIAID. While at DMID, Fred also served as the SARS and Influenza Vaccines program officer.

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COMMENTARY

COVID-19: how is the pandemic changing the vaccines space?

Nicholas Jackson

The COVID-19 pandemic has brought both immense challenges and exciting innovations to the vaccines field, from the meteoric rise of mRNA vaccines to an influx of new companies – but what scientific or business changes have had the greatest impact?

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Before one can address this pertinent question, one must recall the status of the vaccine field and industry prior to the SARS-COV-2 pandemic. Despite decades of development, viral vector platforms had only achieved licensed indications against Ebola virus disease [1]. mRNA platforms had yet to demonstrate sufficient immunogenicity and acceptable tolerability in clinical trials [2]. Our understanding of the molecular mechanisms of adjuvants had advanced significantly, yet few novel adjuvants were licensed [3]. Our global response to the 2009 influenza A (H1N1) pandemic had exposed inequity in access to vaccines in developing countries, with developed countries placing orders that secured the vast majority of available products from manufacturers [4]. The development of vaccines typically required a decade or more of resources and 'Emergency Use Authorization' (EUA) had been granted only a handful of times in the first 16 years following enactment (for 2009 H1N1 vaccines and – pursuant to an amendment allowing for preemptive EUAs – to authorize countermeasures in anticipation of MERS, Ebola, and Zika). Globally, four large multinational vaccine companies existed (Merck, Pfizer, Sanofi, and GSK) and the Developing Country Vaccine Manufacturing Network (DCVMN) included 43 members in 14 territories [5]. Economically, vaccine R&D investment in high-income countries (HICs) was largely driven by new first-in-class vaccine candidates against

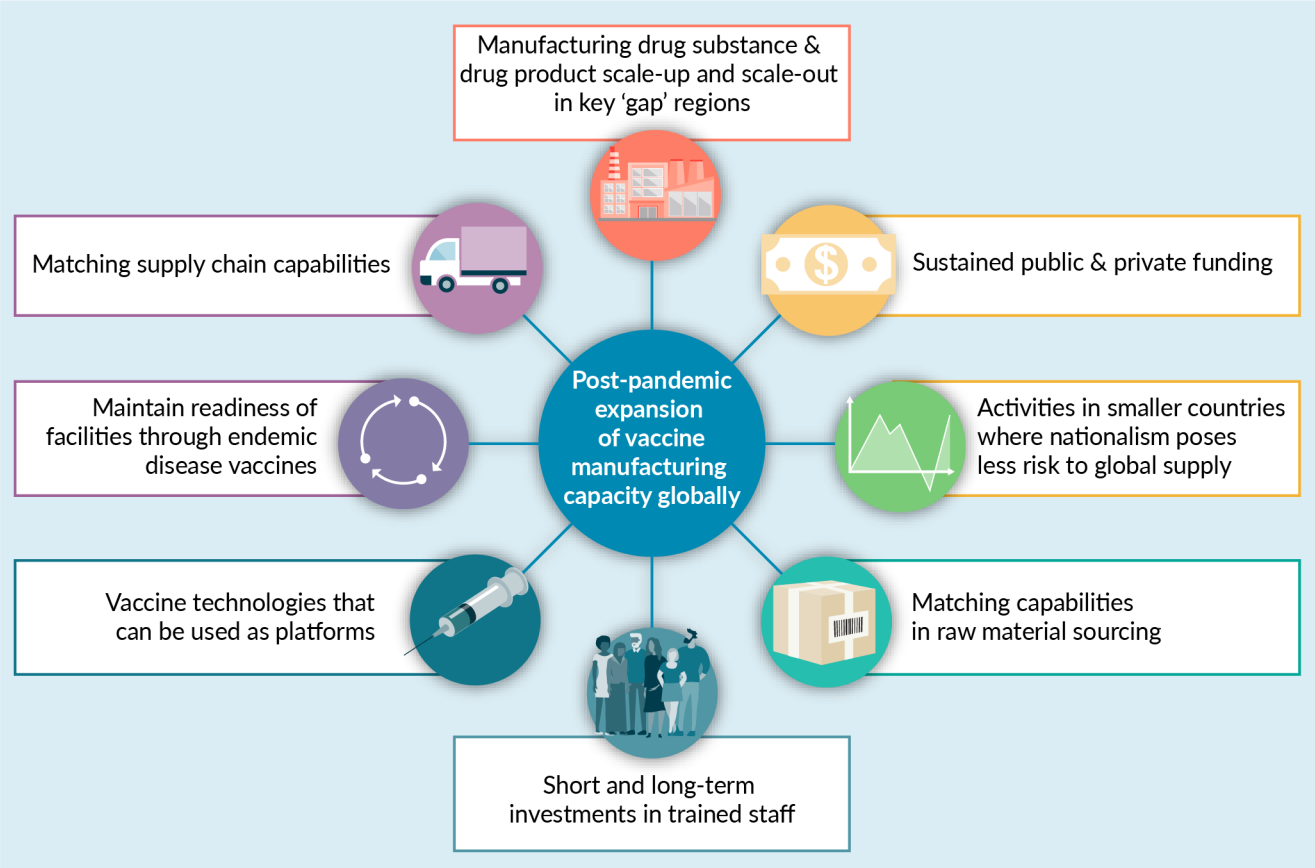
endemic diseases or clinically differentiated next-generation versions of existing vaccines. Few organizations pursued epidemic or pandemic vaccine preparedness; notably the Biomedical Advanced Research and Development Authority (BARDA), the National Institute of Allergy and Infectious Diseases (NIAID), and the Centre for Epidemic Preparedness and Innovation (CEPI). Turning then to our question: how is the pandemic changing the vaccine field?

AN EXPANSION OF MANUFACTURING CAPABILITIES & CAPACITY

Arguably the greatest limitation for COVID-19 vaccine development, licensure, and the initial phases of access has been manufacturing. Prior to the pandemic, manufacturers were annually producing around 5 billion doses [6]. Expansive efforts missed initial forecasts in 2020 but delivered, through 2021, in excess of 11 billion doses of COVID-19 vaccine alone [7]. However, these impressive achievements exposed numerous shortfalls: a restrictive reliance on a limited geographical footprint of production, raw material shortages, a fundamental lack of qualified and trained individuals to support scale-up and scale-out activities, and nationalism resulting in export bans (India, EU, and the US implemented regulations imposing export restrictions on COVID-19 vaccines or ingredients) [8]. As a consequence, numerous organizations, companies, and countries are now striving to expand the geographical placement of manufacturing capabilities to positively disrupt the normal 'north-to-south' supply of existing and new vaccines and thereby improve equitable access (Figure 1) [9–12]. This will only achieve success if appropriate quality

FIGURE 1

Multiple components are required to successfully expand global vaccine manufacturing footprint for improved future responses.



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systems and trained staff remain in place, with regular sus+tained manufacturing campaigns to ensure any given facility retains operational compliance. Equally, it requires longevity in public and private support. It is crucial to note that platform systems will have distinct differences under expansion efforts (Table 1). In general, platform technologies such as mRNA and adenoviral vectors enable multi-production manufacturing within the same facility, unlike recombinant proteins or pathogen-based products, since the manufacturing processes are the same from upstream production to downstream purification and formulation.

In addition to supply, there is also a stark realization that mass delivery and administration is another part of the success equation regionally (Box 1). The challenges of massive distribution under appropriate cold-chain requirements to varying points of vaccination necessitates the adaptation of primary healthcare systems in many countries to be ready

BOX 1

The challenges of mass vaccination exemplify the significant needs for future investment to ensure better readiness.

- Reliable and consistent procurement
- Cold chain supply and storage capabilities
- Inventory management systems
- Prioritization of vaccinees
- Notifications for vaccinees
- Suitable points of vaccination
- Trained staff
- Waste management
- Vaccination history tracking and regional uniformity
- Pharmacovigilance surveillance
- Overcoming hesitancy
- Equitable access for all vulnerable populations & minorities

TABLE 1

Key vaccine technologies viewed from a post-pandemic perspective.

Vaccine technology	Advantages	Limitations	Suitability for global expansion[1]	LMIC suitability[2]
Protein/adjuvant	Long pedigree of efficacy & safety Typically best-in-class tolerability Trimerization technologies Thermal stability (typically 2–8°C) Large volume manufacturing	Longer manufacturing timelines In some cases, need for adjuvant other than alum	++	+++
mRNA	Rapid construct generation *In vitro* transcription production simplicity & rapidity Platform application enabling multi-production manufacturing within the same facility.	Safety signals recently observed for SARS-COV-2 indication Thermal stability requiring ultra-cold chain for supply Tolerability profile currently unfavourable	+++	+(+)[3]
Viral vector	Strength in eliciting T-cell immunity Platform application enabling multi-production manufacturing within the same facility Thermal stability (typically 2–8°C) Large volume manufacturing	Considered less potent at eliciting humoral responses Pre-existing immunity to vector Safety signals recently observed for SARS-COV-2 indication	++	++
Inactivated vaccine	Ease of production & large volume manufacturing Low cost of goods Safety Presents whole virion immunogens	Poorly immunogenic versus other technologies Structural damage to epitopes	+	+++

1. Defined based on considerations cited in Figure 1.
2. Defined as combination of factors including but not limited to, more optimal cold chain requirements, cost of goods and volumes.
3. LMIC suitability would significantly improve if thermal stability could be increased, and cost of goods reduced.

as rapid response vaccination outlets in the future.

INVESTMENT TO IMPROVE VACCINE RAPID RESPONSES TO FUTURE OUTBREAKS

Greater recognition of zoonotic spillover events and their potential to result in the next viral pandemic has refocused vaccine R&D efforts on 'Disease X' to be better prepared for future outbreaks. New approaches include efforts by CEPI to generate libraries of widely available mRNA vaccines against prioritized pathogen threats, which would have three potential future uses:

- Against a matched emergent pathogen with a monovalent formulation
- Against a closely matched pathogen with a monovalent or multivalent formulation
- To serve as a prototype to accelerate the development of a new matching construct.

A pertinent example of the latter utility is the prior work done on MERS that pioneered our understanding of immunogen design and the crucial need to stabilize the S protein in the right conformation, which served as a prototype for the rapid work on the SARS-COV-2 S protein immunogen [13]. The NIAID has also initiated plans for pandemic preparedness in which ten priority viral families (Arenaviridae, Filoviridae, Flaviviridae, Paramyxoviridae, Picornaviridae, Togaviridae, Phenuiviridae, Peribunyaviridae, Nairoviridae, and Hantaviridae) [14] will be targeted for

- Basic and translational research
- Animal models to support development
- Prototypic vaccine R&D.

Setting a new bar from the availability of the SARS-COV-2 genetic sequence to the first EUAs in around 300 days has provided the impetuous for the vaccine field to further improve upon this historically rapid vaccine development. Only influenza vaccine development, as part of strain adaptation, has proceeded more rapidly. CEPI is investing in the aspiration of a '100-Day' vaccine rapid response [15]. While this laudable goal may not be applicable or feasible for all emergent pathogens, it will potentially shape the vaccine landscape in terms of novel pre-prepared development pathways and new regulatory pathways [16].

NEW PLATFORM TOOLS FOR VACCINE R&D & MOMENTUM FOR NEW VACCINE INDICATIONS

In terms of technology platforms, the 'toolbox' for future vaccine indications has significantly grown. mRNA delivered in lipid nanoparticles (LNPs), and adenoviral vectors, all expressing full-length SARS-COV-2 S protein, have proven efficacious, with a safety and tolerability profile acceptable for the prevention of COVID-19 disease. It remains to be seen whether these platforms will prove equally successful against other pathogens, particularly in terms of safety and tolerability, when alternative platforms can provide comparable efficacy with a superior safety, tolerability, and cold-chain supply profile. A new novel adjuvant (TLR7/8 agonist) used in a licensed COVID-19 vaccine, and the expanded use of the novel existing adjuvant CpG (TLR9 agonist), will surely find utility as immunopotentiators for other new vaccines [17,18]. Combining these and other new technologies with new ways of approaching development, a new era of vaccine R&D is already evident in the field; beyond SARS-COV-2, there are at least 17 completed or ongoing clinical studies investigating mRNA vaccines against other infectious diseases [19]. Moderna, for example, has two modified mRNA non-replicating vaccine constructs in Phase 3 trials against RSV and CMV. It should also be noted that numerous efforts are pursuing innovative broadly protective SARS-COV-2, sarbecovirus, and betacoronavirus candidate vaccines.

While the pandemic has punctuated efforts on viral vaccines, the advancement of

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bacterial vaccines remains essential and has also gained recent momentum. The 'silent' pandemic of deaths associated with rapidly increasing bacterial anti-microbial resistance [20] is driving new efforts in vaccine R&D; for example, Janssen's Phase 3 efficacy trial against extraintestinal pathogenic *Escherichia coli* [21]. The Bill and Melinda Gates Medical Research Institute is conducting TB epidemiology studies on the path to conducting a large pivotal field efficacy trial for its M72-adjuvanted candidate vaccine for the prevention of disease in Mycobacterium tuberculosis-infected individuals.

NEW PLAYERS BRINGING INNOVATION & INCREASED COMPETITION

Comparable to the HIV-1/AIDS pandemic that peaked in the 1990s, COVID-19 will likely drive a decade of innovation in the field of prophylaxis. New players have rapidly emerged, bringing innovation and healthy competition to a vaccine industry that had narrowed in prior decades [22]. Moderna is one example of a company that has emerged from pandemic vaccine development and licensure as a new contender, particularly in the United States, with over 1,800 employees, scaled-out production, and mRNA vaccines in development against 12 different virus targets. Numerous companies are advancing promising next-generation structured-array nanoparticles seeking SARS-COV-2 and other infectious disease indications [23,24]. Economically, the legacy of large public and private investments during the pandemic in these and a plethora of other vaccine organizations and their platforms will transform the vaccine landscape. Consequently, the field will need much support from the existing and next generation of talented vaccine researchers, developers, and manufacturers.

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INTERVIEW

Guiding America through a pandemic

Charlotte Barker, Editor, *Vaccine Insights* speaks with **Anthony Fauci,** Director of the National Institute of Allergy and Infectious Diseases (NIAID) and the Chief Medical Advisor to the US President.

For the public and scientists alike, presidential advisor and leading infectious disease expert Anthony Fauci has been the face of the USA's pandemic response, calmly outlining the latest scientific advances and public health advice through two years of social and political turmoil. As we reach an apparent turning point in the COVID-19 pandemic, we sit down with Dr Fauci to find out his lessons learned and priorities for the future.

ANTHONY S FAUCI has been the director of NIAID since 1984, where he oversees an extensive portfolio of basic and applied research to prevent, diagnose, and treat established and emerging infectious diseases and immune-mediated illnesses.He has advised seven presidents on domestic and global health issues and was one of the principal architects of the President's Emergency Plan for AIDS Relief (PEPFAR), a program that has saved millions of lives throughout the developing world. He is currently the Chief Medical Advisor to President Joe Biden. Dr Fauci is the recipient of numerous prestigious awards, including the Presidential Medal of Freedom (the highest honor given to a civilian by the President of the United States), the National Medal of Science, and the Lasker Award for Public Service. Dr Fauci is also the longtime chief of the NIAID Laboratory of Immunoregulation and has made many contributions to basic and clinical research on the pathogenesis and treatment of immune-mediated and infectious diseases, including developing therapies for formerly fatal inflammatory vascular diseases such as polyarteritis nodosa. Dr Fauci has made seminal contributions to the understanding of how HIV destroys the body's immune defenses and continues to devote much of his research to the immunopathogenic mechanisms of HIV infection and the scope of the body's immune responses to HIV.

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Q What are the biggest lessons that we should take from the COVID-19 pandemic?

AF: One of the key lessons is the importance of long-term investment in basic and clinical biomedical research. The one outstanding success story of this pandemic has been the development of highly effective and safe vaccines within a timeframe that is unprecedented in the history of vaccinology.

"The one outstanding success story of this pandemic has been the development of highly effective and safe vaccines within a timeframe that is unprecedented in the history of vaccinology."

Within a few days of the identification of the sequence of the novel coronavirus in early January, the development of the COVID-19 vaccines began. Sixty-five days later, Phase 1 clinical trials in humans began, and soon thereafter Phase 3 clinical trials involving tens of thousands of people were underway, leading to the emergency-use authorization of vaccines before the end of November 2020. People often ask, "When most vaccines take five or more years from starting development to being shown safe and effective, how did you do it in 11 months?" Of course, vaccine scientists know that this capability didn't arise overnight. There were decades of investment in basic and clinical research – from the original work on the fundamental concept of mRNA as a vaccine platform, to research by NIAID showing that the stabilized pre-fusion spike protein is the optimal immunogen.

The first pandemic coronavirus (SARS-CoV-1) in 2002, and Middle East Respiratory Syndrome (MERS) in 2012, also got us geared up to begin pursuing work on coronaviruses as a pandemic threat. These outbreaks acted as a warning sign, which we fortunately responded to.

We need to continue to invest in this work and take a prototype pathogen approach, to gain fundamental core information about various families of pathogens and learn about the commonalities among them, including pathogenic mechanisms, immune correlates of protection, animal models, and optimal vaccine platforms. When we get hit with the next pandemic, we do not know what family of virus it may spring from, so we need to be prepared for any eventuality.

Even though we have learned from history and acquired knowledge about many types of outbreaks, this particular virus has humbled us.

Q What areas of research should we be focusing on?

AF: We must continue to invest in fundamental, basic, undifferentiated research. Obviously, we must also fund research that is directed towards pandemic preparedness and specific classes of microbes. However, the realization that mRNA can serve as a highly effective vaccine platform started two decades ago with the targeted modification of RNA molecules.

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The same holds true for immunogen design – a stabilized prefusion spike protein was found to be the optimal immunogen before its use in a COVID-19 vaccine. Only later did it become clear that it was applicable to COVID and lead to great success in the development of a vaccine.

My concern is that in the push for immediate results that are readily recognized to be applicable, basic research is sometimes neglected. Much of my own research is directed toward a particular clinical and public health problem, the pathogenesis of HIV disease. However, I appreciate the importance of letting investigators pursue their interests. The history of biomedical research is filled with examples of research findings that were undifferentiated at first but turned out to be critical in solving a real-world public health problem.

Q What are the research priorities for SARS-CoV-2 vaccines?

AF: Currently, we have very effective vaccines for SARS-CoV-2, but we have an issue with the durability of the response. People who get vaccinated have a high degree of an effective response, and then after several months, the durability of that protection against infection – and to a lesser extent hospitalization – reduces. That is something we need to work on, either by developing different platforms or mixing and matching platforms – starting with an mRNA vaccine followed by a booster of a vaccine of a different platform, such as a subunit protein plus adjuvant, a viral-like particle, or a nanoparticle. It is a continuous and iterative process, which is why we are actively pursuing these different platforms such as nanoparticles, virus-like particles, and vector-expressed immunogens.

Another issue is that while these vaccines protect well against systemic disease and hospitalization, they are less successful at protecting against symptomatic infection. People who are vaccinated and have gotten boosted do not usually get seriously ill, but they do get infected and often get symptoms. We need to start thinking about developing a nasally or orally administered vaccine, which induces not only systemic but also mucosal immunity, to protect against both infection and transmission.

Q How do you rate prospects for a broadly protective coronavirus vaccine?

AF: We are not going to get a universal coronavirus vaccine the first time we take a swing at it. We still do not know what the proper immunogen would be to develop the broader response to cover all the viruses within a particular group. Once we know what that immunogen is, we still need to find out if it is immunogenic enough to produce a powerful and durable immune response.

It is going to be an incremental process that is iterative and progressive. The first goal would be to get a pan-SARS-CoV-2 vaccine that is equally effective against all identified and unidentified variants. If we are successful in that, then we might want to pursue a vaccine that covers all sarbecoviruses (SARS-CoV-1 and SARS-CoV-2). The next step would be to get a vaccine against all beta-coronaviruses. But we are still very much in the discovery phase.

Q What should be done and by whom to ensure global COVID-19 vaccine equity?

AF: Dating back to when I helped develop the President's Emergency Plan for AIDS Relief (PEPFAR) program, I have felt strongly that the developed world, including the US, has a moral obligation to pursue global equity in the accessibility of life-saving interventions. We have a disease that is global in impact, yet we have profound disparities in the availability of life-saving interventions, including vaccines, therapies, and diagnostics. The solution is a commitment on the part of upper- and middle-income countries to not only make interventions such as vaccines and therapies available to lower-income countries but to help them to build their own capacity to manufacture and distribute those interventions within their own countries.

"Misinformation and disinformation are the banes of public health efforts... Unfortunately, social media spreads misinformation much more effectively than it spreads correct information."

Q You have seen first-hand the damage that misinformation and disinformation about vaccines can do. How can we mitigate the impact?

AF: Misinformation and disinformation are the banes of public health efforts. I do not have an easy answer to this, except to say that the best way to counter misinformation and disinformation is to flood the system with correct information. Unfortunately, social media spreads misinformation much more effectively than it spreads correct information. I can only attest that it is a serious problem, and it has in many respects interfered with an adequate public health response to the pandemic.

Q Would you say we are transitioning from the pandemic to the endemic phase of COVID-19?

AF: Yes, but with a caveat. I look at outbreaks like this in five separate brackets: the full-blown pandemic phase, the deceleration of the pandemic to a lesser outbreak, control, and then if you are lucky, elimination, and eradication.

There is no chance we are going to eradicate SARS-CoV-2. We have only eradicated one human virus in history: smallpox. I also do not think that there is any possibility we will eliminate SARS-CoV-2 like we have eliminated measles in the US. The measles virus has limited antigenic drift – the virus that was circulating 25 years ago is essentially the same virus that is circulating today. We also had universal vaccine coverage and acceptance for measles, which we do not have with SARS-CoV-2. In addition, vaccine-induced or infection-induced immunity to measles has a very long duration, often for life. With SARS-CoV-2, we

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not only have a virus that continues to evolve with new variants, and a short duration of immunity, but we also have a degree of vaccine hesitancy that makes universal vaccination problematic, if not impossible.

That brings us to control. Right now (March 18, 2022) in the US, we are down from close to a million infections per day to 20–30,000. Cases, hospitalizations, and deaths are down. If we can keep them at this low level and get to a point where the presence of the infection in society is not disrupting our lives, both economically and socially, some people would call that going from the pandemic to the endemic phase.

However, we must not accept a level of endemicity that confers high viral burden, morbidity, and mortality. We should aim for SARS-CoV-2 to be no more threatening to us than any of the other infectious respiratory diseases that we deal with such as RSV, parainfluenza, or influenza. Also, we must continue to address the issue of 'long COVID'.

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EXPERT ROUNDTABLE

Vaccine development in the COVID-19 era: regulatory challenges & innovation

Peter Marks, Marco Cavaleri, Carla Vinals & Adam Hacker

How have regulators evolved to meet the need for rapid vaccine development during the pandemic – and what does that mean for the regulatory landscape going forward? Here, four experts who have played key roles in the regulatory response to COVID-19 come together to discuss the key issues.

PETER MARKS is Director of the Center for Biologics Evaluation and Research (CBER) and Acting Director, Office of Vaccines Research and Review (OVRR) at the FDA. He joined the FDA in 2012 as Deputy Center Director for CBER and became Center Director in 2016. He has been Acting Director for OVRR since 2021. He is board-certified in internal medicine, hematology, and medical oncology, and before joining the FDA, he held a variety of leadership roles in academic medicine and the pharmaceutical industry – most recently as the leader of Yale University's Adult Leukaemia Service and Chief Clinical Officer of Smilow Cancer Hospital.

MARCO CAVALERI is the Head of Biological Health Threats and Vaccines Strategy at the European Medicines Agency (EMA). He is the Chair of the EMA COVID-19 Task Force and responsible for EMA activities for emergent pathogens, vaccines, and antimicrobial resistance. Marco is a pharmacologist who spent several years in industry R&D, mainly in preclinical and clinical development of anti-infectives, before the EMA in 2005. In 2009 he was appointed Head of Section for Anti-infectives and Vaccines in the Safety & Efficacy Sector, Human Medicines Development and Evaluation Unit

CARLA VINALS is Head of Regulatory Affairs for Infectious Diseases at Moderna, Inc. She has been in the pharmaceutical industry for 26 years, and her career has been devoted to vaccine development. Carla joined Moderna in 2020, as the company was preparing for Phase 3 trials of its COVID-19 vaccine. Carla and her team are now supporting two large multinational Phase 3 studies for RSV and CMV vaccines, and ongoing programs targeting respiratory viruses, latent viruses, and pandemic preparedness

FRED CASSELS (MODERATOR) is Global Head for Enteric and Diarrheal Diseases (EDD) at the Center for Vaccine Innovation and Access at PATH. Projects within the EDD group encompass vaccine discovery, proof of concept, process development, cGMP manufacture, Phase 1-4 clinical trials, licensure, and introduction – all for the benefit of low- and middle-income countries. Previously, Fred was Chief of the Enteric and Hepatic Diseases Branch, Division of Microbiology and Infectious Diseases (DMID), NIAID. While at DMID, Fred also served as the SARS and Influenza Vaccines program officer

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Q You are all part of a COVAX working group on correlates of protection (CoPs) – what is the structure of the group and how does it exert its influence?

PD: The CoPs working group falls under the COVAX pillar of the Access to COVID-19 Tools (ACT) Accelerator. COVAX is the vaccines initiative that was co-convened by WHO, Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI), and UNICEF. Within the COVAX pillar, CEPI and BMGF managed a Clinical SWAT team, which organized and coordinated R&D to move vaccines as quickly as possible through the development space [1]. Within the Clinical SWAT were several working groups, one of which is a CoP working group, of which we are all members. We essentially repurposed a Gates Foundation advisory group on CoPs to work on COVID-specific correlates activity.

Our efforts were focused on facilitating the conversation around the evidence on CoPs to accelerate product development and bring other developers forward as quickly as possible. We led conversations about where we are on the journey to identifying CoPs through workshops to accelerate new vaccines into use [2]. We also tried to publish the evidence as it became available and encouraged developers to make their data available as soon as possible so it could be part of the conversations around CoPs.

Q How does the working group define a CoP for vaccines in general, and specifically for SARS-CoV-2?

SP: Defining CoPs is critical to vaccine development against any disease but has been particularly important for SARS-CoV-2 due to the urgency to develop vaccines. CoPs are important not simply for basic knowledge, but also because they enable the correct antigen choice to protect against a particular disease, as exemplified by COVID-19.

A CoP is an immune response that is statistically interrelated with protection. In vaccinology, one can have correlates that are absolute – if an individual has that response, they are fully protected. Alternatively, a correlate may be relative – a higher level is more protective than a lower level.

regulatory decisions. In Europe, we do not have emergency-use authorization, at least at the central level, but we used the conditional marketing authorization route in the most flexible way we could [2].

I would also echo Adam's comments about international cooperation and the fact we have been able to discuss the regulatory requirements on a more global scale.

CV: The frequent contact between the applicant and the agencies has been paramount, including rolling reviews. We also very much appreciated the fact that guidelines have been issued very fast and with a good level of alignment between the various regulators around the world, which is unprecedented. To add to the list, remote good practice inspections have also been very useful.

Q In terms of speeding up vaccine approvals during the pandemic, are there any aspects that could be further accelerated, and how could that be accomplished?

CV: I would suggest four areas where we could do even better. First, on the topic of generating evidence specifically, further clarification of requirements for authorization and licensure ahead of time would be useful to help design the right studies the first time and as fast as possible. Developing master protocols would also be very useful. In particular, defining the minimum amount of required safety data, in terms of numbers of subjects and length of exposure post-vaccination to avoid multiple data cuts in study databases. Harmonizing requirements across geographies as much as possible, from an operational perspective, would also accelerate the process, alongside Clinical Trials Application harmonization.

Last but not least, we have been experiencing a specific bottleneck in sample testing. The generation of neutralizing antibody data specifically for COVID vaccine programs has been critical and there is room for further discussion in terms of what surrogates we could use to help us accelerate the process in future.

In terms of the dossier preparation, pre-defining a simplified dossier structure that is compatible with fast submission timelines would be of benefit, although I would add that all agencies have been extremely flexible in terms of the format and types of data submitted.

In terms of preparing the launch of the product, pre-defining exemptions and deferrals, such as product presentation, harmonizing requirements for electronic labeling, defining common pandemic packages, and preestablishing digital solutions for the prescribing information would help speed the process. Finally, accelerating the review

"...further clarification of requirements for authorization and licensure ahead of time would be useful to help design the right studies the first time and as fast as possible."

– Carla Vinals

and approval of the artwork for the label of the product would help finish the process as soon as possible.

MC: Carla raised an important point around inspection. Reliance on inspections done by other agencies is something that we have to work on, particularly in the context of an emergency such as a pandemic, to avoid delays in the regulatory process. We have seen some significant delays due to this. We need to ensure that all the clinical studies that would underpin an authorization are conducted in accordance with good clinical practice (GCP) so, in many cases, we wanted to look at the data ourselves, but this takes a lot of time – we need to find a better way so we can be faster in concluding on all aspects relating to GCPs.

In terms of having protocols already prepared, CEPI and others have been working on this, but it is very difficult when you are facing a new pathogen to fix everything in advance. While all the work in the preparedness stage is fundamental, and we need to spend much more time on this in future, you cannot cover everything. There will still be a lot of uncertainties.

When it comes to safety, we, as regulators, have some idea of the basic numbers that would constitute an acceptable safety database. We have to look at each product individually and if something emerges that is of concern, then the safety database will have to be enlarged accordingly.

It is difficult to be definitive in all these areas, but we should try our best to set up criteria and schemes that could allow a portfolio of options for clinical development ahead of the next crisis.

PM: As we think about preparing for the next crisis, for me it comes down to manufacturing capacity, manufacturing capacity, and manufacturing capacity! Many, many people around the globe need vaccines now, and expanding manufacturing capacity will also help us ramp up for future pandemics. If there is anything that the current crisis has brought home to me, it is that we are limited by our quality manufacturing capacity around the globe.

AH: In normal times, regulators generally do not require alignment of different aspects of development programs between different developers. In an outbreak situation, it is very helpful to have the same endpoints in the clinical trials as it allows comparisons to be made. Similarly, if you use the same assays, for example, the WHO international standards for neutralizing antibodies, it allows comparison of the results to be made across studies, at least on an immunogenicity

"As we think about preparing for the next crisis, for me it comes down to manufacturing capacity, manufacturing capacity, and manufacturing capacity! Many, many people around the globe need vaccines now, and expanding manufacturing capacity will also help us ramp up for future pandemics."

– Peter Marks

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level. Those aspects are important to enable comparisons of the results, which is important for policy decisions, and enable changes in regulatory requirements, for example acceptability of immunobridging, as early as possible in the pandemic.

Looking at where developers need additional help or where things have taken longer than they could have, building out manufacturing capacity means that developers have to move their production process into different facilities. We have seen some organizations that have been very good at technology transfers and comparability, but we have seen others where this has not worked so well. This can cause significant delays with the ramp-up of capacity. Furthermore, splitting the developer's resources to manage technology transfers across multiple facilities can lead to further delays.

There are opportunities to look at how labeling is managed to get maximum supply into countries. Being able to put the manufacturing date on the label rather than the expiry date allows flexibility in pandemic conditions where stability data is being developed in real-time. If you put the manufacturing date on the packaging then a QR code, for example, can be used to consult electronic labelling where expiry dates can be updated regularly; whereas if you put an expiry date, even if an extension is approved, it may not be possible to update the packaging with the revised expiry date and it will then look like the material has expired. This has caused terrible problems in low and middle-income countries, which do not want to use what looks like an expired product. Utilizing manufacturing date rather than expiry date would really help here.

Q What challenges are posed for developing and regulating second-generation vaccines given the increasing seroprevalence of COVID-19 in the community?

PM: The challenges for developing second-generation vaccines are several-fold and improvements in any one of these aspects would be a win. First, there is the breadth of protection – what varieties of coronaviruses are we going to be significantly protected against by that vaccine? Then, there is the depth of protection – can we get protection to 95%, not just against the original variant, but also against all the different variants that come along?

There is also the addition of protection against transmission. This is a high bar, but if we could have vaccines that were more protective against transmission, perhaps by providing mucosal immunity, that would be a great thing.

Finally, there is the challenge of getting vaccines that are simpler to use; for example, one dose that can be administered very simply and inexpensively. We would love to have a vaccine that is inexpensive enough to see it globally deployed in low-, middle-, and high-income countries.

In a Utopian world, we would have all of those. But if you could improve even some of these, you would still have a better second-generation vaccine.

MC: I completely agree with Peter. Once we have more seropositivity in the population because of vaccination or natural infection, we will shift focus to understanding who will require re-vaccination. This means putting in place an adequate vaccination strategy for re-vaccination of those that might suffer the consequences of being re-exposed to the virus over time. At the same time, we should not forget that younger people who have been naïve to the virus might not ever be exposed to it, so we will also need a strategy for priming younger people, similar to what we do in influenza.

Another issue besides the breadth of coverage is the duration of protection. This seems to be quite problematic with the current vaccines, which are very good at the peak of the immune response, but the protection seems to wane fairly rapidly. Developing vaccines that could lead to a higher level of protection for a longer period could be very important.

One ambition is to have vaccines that would cover not just SARS-CoV-2 and all its variants, but also other coronaviruses and therefore would also be helpful in terms of preparedness. We must invest in this area even if we recognize that it is not easy to achieve.

AH: Most of the attention of second-generation vaccine developers will be the development of booster vaccination. Developers will need to include a relatively homogenous population in their studies, including individuals who are similar with regard to history of vaccination, and history of infection and so on – ensuring similar subjects are recruited is increasingly challenging as seroprevalence from prior infection increases.

Then, I would turn to the greatest need, which is in low and middle-income countries where there have been very low levels of vaccination, and yet high levels of infection. Here, the primary series of individuals who have not had a prior infection is not so relevant. Rather, it's about vaccine regimens for individuals who have had a prior infection. We have not tackled the regulatory requirements in that setting, rather we are looking more to policy to help establish what would be the most appropriate regimens, but these decisions and recommendations need to be based on data. CEPI is investing in this area and hopes the data will support such recommendations.

CV: I agree with the other panelists about the growing importance of boosters versus primary vaccinations as it becomes more difficult to study a second-generation vaccine in a primary vaccination setting, given the high seroprevalence. Also, the difficulty is that seroprevalence is very heterogeneous, because of the different etiologies – infection versus vaccination, different types of vaccines, and different dosages. It becomes very complex to find a homogeneous population to study when developing a second-generation vaccine.

In the absence of a correlate of protection, we also have to ask the question: what do you compare to? This question has been evolving in the last year or so and is something that we are still in the middle of trying to figure out, along with how we can best capture the breadth and duration of protection. Moving beyond focusing on the peak immune response against the variant contained in the vaccine, how do we include those additional important features in a second-generation vaccine? How do we make sure we are not throwing out a good candidate by focusing too much on one specific attribute? These are all questions that will need to be discussed intensely in the coming weeks.

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Q What do you anticipate will be the role of immuno-bridging studies in licensing new vaccines?

MC: This is going to happen very soon; from our perspective, we are already there. We are already discussing with developers how to design trials looking to immuno-bridging to gather approvals of these new vaccines, including the area of boosters, as that is where most of these vaccines will be used.

We do not have an immune correlate of protection established, but it would not be the first time that we have used immunogenicity data to infer a level of protection. This is an approach that has been used in other cases, like pertussis and influenza. The right comparator must be taken on board, to give us sufficient reassurance that the new vaccine will elicit an immune response that will be as protective as already-approved vaccines.

Neutralizing antibodies have been generally agreed by the scientific community to be the best immune marker to use in these immuno-bridging exercises. Some researchers have also proposed using binding antibodies, but emerging data from studies with Omicron suggest they could be misleading. We also have the usual dilemma – to what extent to factor in the role of T cell responses. No doubt they are going to be important, but it is difficult to quantify them or to establish any relationship between CD4 or CD8 T cell response versus protection. We believe that using neutralizing antibodies will be sufficient.

PM: There may be some nuances, but by and large, things are very similar at the FDA. We will look at each individual candidate based on its background and make a decision; however, there is no escaping that immuno-bridging is going to be a very important part of what we are doing moving forward.

CV: I agree that immuno-bridging is not going away any time soon, and carefully defining the controls and comparators is going to be paramount. I also think that a broader discussion on defining correlates of protection is merited. Correlates of protection in vaccine science have been a holy grail, often studied but never achieved! It's a Catch-22 situation – correlates of protection need clinical efficacy data to be generated, but if sponsors invest in those studies to identify correlates of protection, it would benefit other manufacturers. Therefore, there is not always an incentive for manufacturers to emphasize developing correlates of protection. I think there needs to be a joint effort from industry, manufacturers, regulators, and not-for-profit organizations, to generate the

"Neutralizing antibodies have been generally agreed by the scientific community to be the best immune marker to use in these immuno-bridging exercises. Some researchers have also proposed using binding antibodies, but emerging data from studies with Omicron suggest they could be misleading."

– Marco Cavaleri

necessary data for correlates of protection to be useful for everybody and potentially some incentives for industry to put more effort into this.

AH: To speak to Carla's point, there is a need for a standardized assay that is used consistently by developers to allow comparisons and allow the data pools to be much larger. Developers are already doing immuno-bridging studies. It was realized that vaccine efficacy studies with clinical endpoints were going to be increasingly challenging as rates of infection and vaccination increased. There have been some initial approvals based on immunobridging, such as Biological E's Corbevax vaccine, approved in India, and Valneva, approved in Bahrain. Other approvals will follow.

The challenge will come for those vaccine modalities that do not necessarily trigger a significant neutralizing antibody response, such as mucosal-administered vaccines. There is no clear answer there, except turning towards clinical endpoints and transmission studies – until we unravel cell-mediated immunity markers that can give some indication of what is going on, we have still got some way to go.

Q What is the role of real-world evidence and observational studies in supporting regulatory decision-making, now and in future?

PM: The pandemic has shown us that while there is a place for rigorous randomized clinical trials, there is also a place for real-world evidence. There seems to be this idea that you are either in the real-world evidence camp or the randomized clinical trial camp. As with many things in life, the truth is somewhere in between. We have seen what real-world evidence can bring us, including some of the data from studies in Israel and the US, looking at the protection of the population over time, as well as looking at safety events.

AH: We need to evaluate those observational studies to learn how good they have been in terms of confirming vaccine efficacy, particularly for epidemic preparedness. If we get a worse epidemic in the future, we will want to do vaccine development much faster. Does that give us time to do formal vaccine efficacy studies? At some point, you may want to deploy earlier. A partial deployment, gathering observational data as it is rolled out, can give answers much quicker than conducting a Phase 3 vaccine efficacy trial. Such early deployment may afford the opportunity of limiting the spread of an

"If we get a worse epidemic in the future, we will want to do vaccine development much faster... At some point, you may want to deploy earlier. A partial deployment, gathering observational data as it is rolled out, can give answers much quicker than conducting a Phase 3 vaccine efficacy trial."

– Adam Hacker

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epidemic. We need to nail that question of how we can use observational data for the confirmation of decisions that have been made by the regulators for licensure.

CV: This pandemic has been unique in generating vast amounts of real-world evidence data, and we have been witnessing what I could call a 'reverse regulatory pathway.' Countries have made decisions based on scientific arguments, public health arguments, or pragmatism to recommend the use of vaccines in different ways, beyond what was approved from a regulatory standpoint; for example, determining dose intervals, or how to do boosting. Then the real-world data were generated and used in supporting regulatory action and, most importantly, spread evidence around the world, from country to country [3]. That is a very interesting model that merits further exploration. Going forward, real-world evidence will become more and more reliable and will play a bigger role.

MC: I completely agree that real-world evidence, at least for vaccines, played an important role in the context of this pandemic. We have already used real-world evidence for vaccines in the past on a few occasions, and this shows there is even more room for using it. In the post-approval phase, real-world data will become very important, and that is why the EMA is engaging with the European Center for Disease Prevention and Control to build infrastructure in Europe for continuously running effectiveness studies for all the vaccines that we are using [4].

Of course, we must always be cognizant of the quality of this data, the methodology being used, and the data collection. But for vaccines, these data are interpretable and can be used. I also deal with therapeutics for COVID-19, and I would be more cautious in using real-world evidence for any regulatory decision in this area because the potential impact of biases can be enormous and can lead to misleading results. We must be careful how we use these approaches, but in the context of vaccines, observational studies are here to stay, and we should learn how to use them even better [5,6].

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VACCINE INSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

Analytical development for rapid response vaccines: start early, think ahead

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Manufacturing & Supply Chain Division Coalition for Epidemics Preparedness Innovations (CEPI), Norway

VIEWPOINT

"As highlighted by the COVID-19 pandemic, early analytical development is key for the rapid scale-up of new vaccines. Careful consideration of assay development throughout the pipeline can expedite technology transfer, avoid costly missteps, and produce vaccines faster to fight future pandemics."

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The COVID-19 pandemic prompted laboratories around the globe to start developing vaccines against SARS-CoV-2. One important lesson from this unprecedented effort is that to achieve worldwide mass vaccination in record time, an early focus on assay development is key.

The analytical toolbox, comprising of all analytical methods needed to evaluate a vaccine candidate, is crucial for taking a vaccine from idea to commercialization – proving that it is safe and efficient by quantitatively testing critical quality attributes (CQA) such as potency, content, purity, etc, and characterizing the product according to regulations [1].

Most CQA assays are product- and/or platform-specific and need to be developed accordingly [2]. The time and effort required to develop appropriate methods – including reagents and reference standards – that can be qualified and validated, should not be underestimated. The earlier these assays can be utilized, the more relevant data can be generated to support a regulatory filing. This is vital if we are to meet the Coalition for Epidemic Preparedness Innovations (CEPI)'s goal of developing a vaccine in 100 days [3].

The first emergency use authorization for a COVID-19 vaccine was issued less than a year after the pathogen was identified. To make this possible, activities normally done sequentially have been performed in parallel (at financial risk to developers and other funders) without compromising safety; for example, scaling up manufacturing at the same time as conducting early-stage clinical studies. Developers conducted multiple tech transfers to scale up and scale out their manufacturing, usually to several countries, resulting in astonishing 13 billion COVID-19 vaccine doses produced in 2021 [4]. If rapid analytical methods were in place to support some of those time-consuming tech transfer steps, our response to the next pandemic could be even faster.

Products developed during a pandemic need to be as well characterized as those following a 'normal' timeline, so reliable analytics to ensure product quality and comparability, as well as proving lot-to-lot consistency, are essential. To match the manufacturing capacity and mitigate potential testing bottlenecks, tech transfer of analyses to multiple quality control laboratories, in addition to tech transfers to national release laboratories, were undertaken. This can be a laborious task and must be well managed to keep to tight timelines. The sooner new laboratories can initiate their work, the lower the risk of causing delays in getting vaccines to the world.

It is a regulatory requirement to show comparability between the materials used throughout clinical development of a product [5,6], thereby demonstrating comparability between the different manufacturing scales used for generating material – from small-scale preclinical toxicity studies to pilot-scale GMP clinical trial material, and ultimately to commercial scale. Any process modification or formulation change between these stages must also be covered by the CQA comparability exercise, to avoid costly and time-consuming clinical bridging.

Establishing stability indicating CQA assays is a particular priority. Allowing time for release testing by the manufacturer and national release laboratories, and global distribution, at least 6 months shelf life is required to make any vaccine viable. Robust assays to measure the physicochemical and biological stability of the drug substance and drug product over time when manufacturing material for Phase 1 clinical trials will generate real-time data in support of a longer shelf life when filing for licensure. Particularly in an outbreak situation, being able to initiate relevant stability studies, including transport simulations, as soon as possible enables a longer shelf life and increased usability of the vaccine.

CEPI has co-hosted several workshops with the Bill & Melinda Gates Foundation addressing various Chemistry Manufacturing and Controls (CMC) issues throughout the pandemic. The importance of addressing

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CQA at an early stage was covered at the 'Best practices for tech transfer workshop' [7].

In conclusion, robust analytical methods are needed early on in vaccine development. Assays showing that the products used in clinical studies are comparable to the product manufactured at different scales and sites are crucial. These assays are also key to demonstrating that the vaccine is safe and efficient when used – and a delay in assay development could delay product launch. To fight future pandemics and achieve CEPI's 100 days aspiration, the global health community must come together to ensure we have robust assays and other analytical tools at the ready.

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INTERVIEW

Vaccine R&D in the post-COVID-19 era

Charlotte Barker, Editor, Vaccine Insights **speaks with Philip Dormitzer**, Senior Vice President and Global Head of Vaccines Research and Development, GSK

Having played a key role in the development of Pfizer's mRNA COVID-19 vaccine, Philip Dormitzer is now heading up vaccines R&D at GSK – we sat down with him to discuss speeding up vaccine development, the future of RNA vaccines, and how the pandemic has shaken up the industry.

PHILIP DORMITZER recently joined GSK as Global Head of Vaccines Research and Development. Previously, he was Chief Scientific Officer for Viral and RNA Vaccines at Pfizer, where he led programs that included the Pfizer-BioNTech RNA-based COVID-19 vaccine collaboration. Previously, he held positions at Novartis Vaccines that included Head of US Research and was the founding member of the Novartis Viral Vaccine Research Center in Cambridge, MA. In 2009, his research team supported the development and licensure of three H1N1v influenza pandemic vaccines in what remains the most rapid vaccine response in history. Before joining industry, Dr Dormitzer was an Assistant Professor of Pediatrics at Harvard Medical School and led a structural virology laboratory, which, with collaborators, determined the structures of the rotavirus neutralization antigens.

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Q How would you describe the status of the vaccine industry before and after the COVID-19 pandemic hit?

> "Now it is recognized that, at least in a pandemic situation, you can develop a vaccine much faster than was ever believed possible."

PD: Pre-pandemic, there was a common acceptance of the notion that it takes many years to develop a vaccine. Now it is recognized that, at least in a pandemic situation, you can develop a vaccine much faster than was ever believed possible. When the first projections for COVID-19 vaccine timelines came out, the press, the government, and academics, all thought that it was ridiculous over-promising. However, it turned out that the predictions were right; the outcome was far quicker than anyone expected.

Before COVID-19, at least in the US and Europe, there were just four major vaccine producers. There were challengers – including vaccine companies in India, China, Indonesia, and Brazil – but generally, the big four were not concerned that they might be disrupted by upstarts. COVID-19 has certainly shaken things up. The vaccine landscape today is more diverse, as those who were able to move quickly during the pandemic became much bigger vaccine companies in terms of production. As we leave the pandemic and COVID-19 vaccines become a less prominent part of the landscape, it will be interesting to see to what degree things go back to the way that they were. Whatever happens, I do not expect the industry to look the same in a few years.

The notion that you could have a vaccine frozen at -70°C and mass distribute it seemed impossible before the pandemic. It's not yet clear whether these supply chains will carry over to the post-pandemic era, but we now know that when circumstances demand it, the degree to which vaccine production can be scaled up is tremendous.

Q Hiring qualified staff was a challenge for the vaccine industry pre-pandemic – has COVID-19 changed that?

PD: There is no question that people who know how to make vaccines are in demand right now, and that makes hiring a challenge. The best way for a company to attract great staff is by having an exciting offering. Vaccines is a mission-driven field – salary and benefits are important, but people also want to enter a program that will be important for human health, so it is important to create that vision and show your employees that they can have a big impact in this field.

Q Will the current interest in – and funding for – vaccine development last?

PD: Interest in vaccines R&D is cyclical. The first big wave of innovation in this century came in the aftermath of the fear generated by highly pathogenic avian influenza and

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biodefence concerns following anthrax attacks in the early 2000s. Medical countermeasures took on new significance, and the US government – via BARDA – invested massively in vaccine innovation. Then, we entered a 'shaking out' period when support for vaccine research declined, and funding became competitive. The COVID-19 pandemic led to a rebirth of vaccine innovation, creating another wave of interest in vaccines – scientifically, economically, and in terms of public health. Vaccines were always interesting from a primary public health perspective, but now other aspects are coming to the fore, such as technical innovation, defense, and huge economic interest.

Interest won't be at the current fever pitch forever, but I do think the setpoint has changed in the past few decades, as we've been hit by a series of epidemics and pandemics – HIV, Ebola, Influenza, SARS, and COVID-19. We have seen nothing of the magnitude of the current pandemic since 1918, but inevitably there will be more pandemics in the future.

Q What were the most important factors that allowed COVID-19 vaccines to be developed in less than a year?

PD: First, RNA technology has been a genuine advance. Second, there was a willingness to invest at tremendous risk. Third, there was a real partnership between regulators and vaccine companies to respond to this huge public health outbreak. We saw the world's first Phase 1/2/3 trials, which went seamlessly and were frequently revised as new variants or populations came up. This involved very rapid action from regulators as well as from companies. Normally, you would accumulate data over a long period, put together a file, and it would take its place in a queue to be considered. In this case, data was evaluated in real-time; as soon as the data were ready, they were sent to regulators and reviewed immediately. It was a dynamic process, not the usual batch-by-batch process.

Q How could we make the process even faster when facing the next potential pandemic?

PD: The power of a platform is important. If we find ourselves facing another coronavirus, we can move much faster now we know how to make coronavirus vaccines. The response to the 2009 flu pandemic took less than half the time of COVID-19 because we already had flu vaccines, we had regulatory pathways, and people had anticipated flu pandemics. For mRNA vaccines, the rate-limiting step is often synthesizing sufficient quantities of DNA at a suitable level of quality, so there is room for technological innovation too.

There are some things you can do faster, but other things are more difficult because we – rightly – have high standards for safety and efficacy. For example, you need large clinical trials to detect rare adverse events, which can be difficult to predict. As advanced as machine learning is, and as informative as preclinical animal studies can be, we still need sizeable human trials to ensure safety. However, correlates of protection could reduce the size of efficacy trials in some cases.

Correlates of protection are already used for existing vaccines; for example, in influenza, we use hemagglutination inhibition antibody titers. However, these correlates are crude

tools, and we still do not fully understand the underlying mediators of protection. When a new vaccine is similar to an existing vaccine with an established correlate, we can expect a better immune response to translate to better protection – but if something new comes along, that is more of a challenge. It is a remarkably complex subject and there is still much debate about the role of T cells and mucosal immunity.

"Reactivity to RNA is still quite high, which people tolerated during the pandemic, but are less likely to tolerate when the threat is not as great."

Q What role do you anticipate RNA vaccines will play in the future of the vaccine industry?

PD: We know RNA technology is great for pandemic response, and we are now exploring what it can do for other fields. Multiple companies are looking at influenza as a target for RNA vaccines because the virus changes every year. We're effectively responding to a new epidemic every year, so the ability to move quickly and change rapidly is important, and RNA vaccines can help achieve that.

However, there are challenges. Reactivity to RNA is still quite high, which people tolerated during the pandemic, but are less likely to tolerate when the threat is not as great. Another major issue is temperature stability, which is improving incrementally, but requires more work. It is possible that if the issues with temperature stability and reactogenicity can be solved, we could see RNA vaccines become much more widespread. However, at this point, we cannot say whether the advantages outweigh the disadvantages of RNA for many indications.

As the new kid on the block, it is exciting to see what RNA vaccines can do, but that does not mean that other vaccine platforms are no longer relevant. In many cases, older platforms may still be the right solution. Post-pandemic, we will want better tolerated, more temperature stable COVID-19 vaccines, and more traditional vaccine platforms have real advantages. Plus, some vaccines cannot be produced via RNA; for example, glycoconjugate vaccines, which are highly effective against bacteria.

Q What are your priorities at GSK for the next few years?

PD: We aim to develop vaccines against important public health threats. Pre-pandemic, GSK was the leading vaccine company globally and we intend to regain that position through R&D. I believe GSK has a key role to play in pandemic preparedness, with a wide range of platforms, including RNA, as well as a global reach in terms of the production and distribution of vaccines.

There is still room for more COVID-19 vaccines, even in the late pandemic and post-pandemic era. The vaccine response to COVID-19 was much more rapid and effective in

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developed countries than in lower- and middle-income countries, and RNA vaccines are not necessarily the best solution in countries where maintaining cold chains is challenging.

In the coming months, we look forward to announcing the results of our Phase III trial of a respiratory syncytial virus (RSV) vaccine in older adults. This could be a tremendously important new vaccine, as RSV has a significant impact on older adults around the world. Later this year, we will release results from a pivotal trial of our menABCWY vaccine, which covers a wide range of serotypes of meningococcal bacteria that impact young adults and infants.

We are expanding our research in what else vaccines can do, not only as prophylactics but also as therapeutics, particularly for recurrent infectious conditions. We are seeing increasing problems with antimicrobial resistance, and, with a slowing antibiotic pipeline, we are investigating what role vaccines could have in addressing that.

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Discussion of the impact of RNA technology on vaccines.

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EXPERT ROUNDTABLE

Correlates of protection for SARS-CoV-2 vaccines

Peter Dull, Stanley A Plotkin, Peter Gilbert & Fred Cassels

Vaccine Insights brought together three leading experts to discuss how the COVID-19 pandemic has advanced our understanding of correlates of protection – and where further research is needed.

PETER DULL is Deputy Director, Integrated Clinical Vaccine Development, Vaccine Development & Surveillance at the Global Health Division of the Bill & Melinda Gates Foundation, where he provides technical and strategic guidance on clinical development to the Foundation's program strategy teams (Pneumonia, Enteric and Diarrhea Diseases, Malaria, and others) and external partners. He joined the foundation after 10 years at Novartis Vaccines and Diagnostics where he was the Clinical Franchise Head for Meningitis and Sepsis Vaccines. During the COVID-19 pandemic, he co-led the COVAX Clinical SWAT team, providing product-agnostic support to developers to accelerate vaccine licensure and WHO pre-qualification with a focus on vaccines primarily targeting low-income countries.

STANLEY A PLOTKIN is an Emeritus Professor at the University of Pennsylvania. Previously, he was Professor of Pediatrics and Microbiology at the University of Pennsylvania, Professor of Virology at the Wistar Institute, and Director of Infectious Diseases and Senior Physician at the Children's Hospital of Philadelphia. For seven years he was Medical and Scientific Director of Sanofi Pasteur and is now a consultant to vaccine manufacturers and non-profit research organizations. He developed the rubella vaccine now in standard use throughout the world, is a co-developer of the pentavalent rotavirus vaccine, and has worked extensively on the development and application of other vaccines.

PETER GILBERT is a Professor of Biostatistics at the Fred Hutchinson Cancer Research Center and the University of Washington. He focuses on the statistical design and analysis of randomized clinical trials of vaccines for HIV, SARS-CoV-2, malaria, and other infectious pathogens. He specializes in statistical methods and data analyses of these trials to understand how immune responses to vaccination and genetic features of infectious pathogens impact the protective level of the vaccine, so-called "immune correlates of protection analyses" and "sieve analyses." Peter is Principal Investigator of the Statistical Data Management Center for the NIAID-sponsored HIV Vaccine Trials Network and has co-led statistical science research for the US government-sponsored COVID-19 vaccine clinical research program.

FRED CASSELS (MODERATOR) is Global Head for Enteric and Diarrheal Diseases (EDD) at the Center for Vaccine Innovation and Access at PATH. Projects within the EDD group encompass vaccine discovery, proof of concept, process development, cGMP manufacture, Phase 1-4 clinical trials, licensure, and introduction – all for the benefit of low- and middle-income countries. Previously, Fred was Chief of the Enteric and Hepatic Diseases Branch, Division of Microbiology and Infectious Diseases (DMID), NIAID. While at DMID, Fred also served as the SARS and Influenza Vaccines program officer

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Q You are all part of a COVAX working group on correlates of protection (CoPs) – what is the structure of the group and how does it exert its influence?

PD: The CoPs working group falls under the COVAX pillar of the Access to COVID-19 Tools (ACT) Accelerator. COVAX is the vaccines initiative that was co-convened by WHO, Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI), and UNICEF. Within the COVAX pillar, CEPI and BMGF managed a Clinical SWAT team, which organized and coordinated R&D to move vaccines as quickly as possible through the development space [1]. Within the Clinical SWAT were several working groups, one of which is a CoP working group, of which we are all members. We essentially repurposed a Gates Foundation advisory group on CoPs to work on COVID-specific correlates activity.

Our efforts were focused on facilitating the conversation around the evidence on CoPs to accelerate product development and bring other developers forward as quickly as possible. We led conversations about where we are on the journey to identifying CoPs through workshops to accelerate new vaccines into use [2]. We also tried to publish the evidence as it became available and encouraged developers to make their data available as soon as possible so it could be part of the conversations around CoPs.

Q How does the working group define a CoP for vaccines in general, and specifically for SARS-CoV-2?

SP: Defining CoPs is critical to vaccine development against any disease but has been particularly important for SARS-CoV-2 due to the urgency to develop vaccines. CoPs are important not simply for basic knowledge, but also because they enable the correct antigen choice to protect against a particular disease, as exemplified by COVID-19.

A CoP is an immune response that is statistically interrelated with protection. In vaccinology, one can have correlates that are absolute – if an individual has that response, they are fully protected. Alternatively, a correlate may be relative – a higher level is more protective than a lower level.

To understand CoPs, it is important to acknowledge the difference between mechanistic and non-mechanistic correlates. A mechanistic correlate is an immune response that is biologically responsible for protection, whereas a non-mechanistic correlate is a biomarker that we can use quantitatively but is not the biological reason for protection. Defining the importance of neutralizing antibodies in the case of COVID-19 was critical to the further progress of vaccine development and the choice of effective vaccines.

Q How do CoPs inform our approach to SARS-CoV-2 vaccine development?

SP: The development of vaccines against COVID-19 was brilliant. Vaccines were developed in a short period of time, and that success was based on animal and *in vitro* studies showing that the neutralizing antibodies could protect in *in vitro* tissue culture assays and experimental animals. When studies were done in human populations, it became clear that those with higher neutralizing responses were better protected than those with lower neutralizing responses. Therefore, one could distinguish between experimental vaccines based on their ability to produce those antibodies.

Of course, the immune system is complex and other responses may have their importance. However, it became clear that the vaccines that produce high levels of neutralizing antibodies gave the best efficacy in clinical tests. Therefore, one can use that index to study newer vaccines.

Q Can CoPs be used to license a new vaccine in the absence of Phase 3 placebo-controlled efficacy trials?

PG: I think of a CoP as an immune biomarker that can be used to predict the level of efficacy a vaccine provides against a clinically meaningful endpoint such as symptomatic or severe disease. The goal of a CoP is to be able to predict vaccine efficacy and not need to run randomized, placebo-controlled efficacy trials, which are currently the gold standard to prove vaccine efficacy, but are very large, expensive and time consuming.

To be able to use a CoP to license a vaccine without a Phase 3 trial, there needs to be evidence that the CoP works as a predictor of vaccine efficacy. Regulatory agencies have come up with different mechanisms to do this. The traditional approval pathway requires validation that the biomarker is a reliable predictor of vaccine efficacy. Then, a vaccine can be approved based on a non-inferiority study to show that the distribution of immune response for the new vaccine is

"To be able to use a CoP to license a vaccine without a Phase 3 trial, there needs to be evidence that the CoP works as a predictor of vaccine efficacy."

– Peter Dull

non-inferior to the distribution of immune response for another licensed vaccine for which the immune correlate was validated.

If there is good evidence that the immune marker is reasonably likely to predict vaccine efficacy but it hasn't been fully established, regulatory agencies have accelerated approval mechanisms, and can now approve vaccines based on the distribution of the marker being high enough in vaccinees. However, post-approval clinical endpoint studies are required to confirm the efficacy directly. Ideally, those would be randomized studies comparing different vaccines head-to-head.

Meningococcal C conjugate (Men-C) vaccines provided a precedent of a vaccine approval based on a CoP, where a Phase 3 trial was not done. Here, there was a CoP that had been established for another licensed vaccine for the same disease endpoint. Flu is another precedent, where each year the new flu strain vaccine is approved based on the hemagglutination inhibition (HAI) titer CoP without needing to run a new randomized Phase 3 trial to validate that vaccine.

PD: We must also recognize that it is not as black and white as whether we can or cannot trust a CoP. Many of these decisions are made in the context of a risk-benefit assessment that regulators, and the global community, are willing to accept.

In the example of Men-C vaccines that Peter Gilbert described, the rate of disease is extremely low, so you are simply not going to get a vaccine approval unless you apply a CoP. We had to collectively look at the evidence and make an assessment to go ahead and license and confirm efficacy post-licensure with confirmatory studies.

SARS-CoV-2 has offered an amazing opportunity to generate data. I don't think scientists could have ever dreamed of acquiring the type and amount of data around correlates that we now have and will continue to get from the COVID-19 experience.

Q How does the application affect the type of validation that is needed? What are the limits of CoPs?

PG: It is important to note that a CoP is not just a single thing. We are generally trying to predict vaccine efficacy in a context that we were not able to study in the original Phase 3 trials. When planning validation for a CoP, we must consider the type of bridging we are trying to do.

It might be taking a vaccine that was proven efficacious in one population and bridging it to another population, for example from adults to children. Other types of bridge could be between an existing and new strain of the virus or a modified dose of a vaccine.

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>
> **– Peter Gilbert**

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We also must consider endpoints and timing. A CoP against symptomatic COVID-19 might be different from a CoP against severe COVID-19, or viral load. Predicting vaccine efficacy three months after vaccination might be different than predicting vaccine efficacy 9–12 months post-vaccination.

To give an example, if we are trying to bridge to new variants that might emerge later on, the type of validation we want is a series of randomized, placebo-controlled trials, with variability in the types of SARS-CoV-2 variants that are breaking through. Estimates of vaccine efficacy against several different lineages allow for meta-analyses that compare the vaccine response for each vaccine against each of the lineages. From that, we can piece together a model of efficacy by strain-specific antibody and strain-specific COVID-19. But for different types of bridging, the approach might be different.

The limitations of CoP depend on how long the bridge is. If you are taking an identical vaccine for an identical population and creating a new vaccine lot, this makes for a very short bridge with a limited level of validation. However, if you are bridging on many different components, such as a new population, a different circulating variant, or a different vaccine platform, the bridge will be much longer. The longer the bridge, the harder it will be to prove that you can get a high level of predictiveness for a correlate. In those settings, you need more validation data.

SP: In trying to identify correlates, we are trying to simplify something that is very complex. The immune system has a lot of redundancy and many immune responses can be measured. People often object to looking for correlates because the immune system is complex, and many kinds of responses are important. But the practical point is that if you have a correlate, you can make predictions. We are trying to extract what is most important, rather than focusing on the complexity of the immune system.

Q How can CoPs be applied for decision-making in different settings, such as public health?

PD: There is nuance around CoPs, which comes back to the question of what you are going to use it for, and who is going to use it. CoPs may be used for regulatory purposes, to license a vaccine or immuno-bridge down to a younger age group. However, there are more pragmatic cases. For example, the WHO may want a CoP to help them recommend the timing and need for a booster dose – that is a difficult question to answer. Neutralizing antibodies decline from their peak rather rapidly but whether you need a booster dose now depends on what you are trying to prevent.

In the setting of an individual clinician or patient who wants to know if they need a booster, it depends on the patient, their age, whether they are immunocompromised, and their titer levels. The studies we've discussed may not inform that conversation as clearly as they would for a regulator or a general booster dose recommendation for a whole population. The answer to 'Do you have a correlate?' depends heavily on the intended use.

PG: When we consider statistical analysis to understand how well correlates predict, we think of two types of correlates. One is the antibody marker measured shortly after vaccination, used as a predictor of the COVID-19 endpoint over the follow-up time. The other is modeling the antibody over time and trying to pinpoint the antibody level near exposures that cause COVID-19 illness. Those require different statistical methods and different planning. In one case you only have to measure antibodies at one timepoint, whereas in the other case you have to measure antibodies at many sampling time points. If the objective is to define a trigger for when you should get a booster dose, performing a longitudinal study to pinpoint the antibody near exposure is more informative.

SP: This is an important issue in vaccinology, which goes beyond COVID-19. For example, the mumps vaccine does not give prolonged high levels of immunity. Efficacy must be evaluated over long periods, as well as in different situations. Identifying the correlate is useful not only acutely, but also over the lifetime of the vaccine.

Q We have mainly discussed neutralization antibodies. How do other aspects of immunity, such as T cells and Fc-mediated effector functions, fit into the conversation about CoPs?

SP: Even considering antibody responses, we measure these by neutralization, which is totally artificial. You take a fixed amount of virus, and you put it together with variable amounts of serum, and you extract an answer that indicates functionality. However, this is only distantly related to what is going on in the body. In reality, there are not only neutralizing responses but also binding antibodies and Fc effector antibodies which contribute to the response. They are not primary correlates, but there is evidence, for example, that neutrophil phagocytosis is an important function of Fc effector antibodies.

With respect to T cells, we need CD4 T cells to develop antibodies, so they could be considered a CoP. But there are other functions of CD4 T cells, some of which we barely know how to measure. Meanwhile, there is good evidence in primates that CD8 T cells are important in recovery from and suppression of SARS-CoV-2 infection. There is evidence that CD8 T cell responses are poor in the elderly, which could be a partial explanation as to why COVID-19 is severe in the elderly.

My final point is that we are insufficiently informed about immunoglobulin A (IgA) and other mucosal responses. We need to know more about those if we are to develop better vaccines against SARS-CoV-2.

PD: One of the reasons our CoP working group has continued despite licensure of multiple vaccines is because of the 'Holy Grail' search for a T-cell correlate. We are continuing to solicit collaborators to help us do the gold-standard breakthrough analysis we need. This requires the right samples, collected at the right time, prior to a disease outcome.

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We think severe disease is linked to T cells, but we need further analysis to have bulletproof evidence of the contribution of T cells to protection against severe disease. We cannot get a solid look at a T cell CoP for severe disease because we do not have the samples yet.

Q How do CoPs translate between the different SARS-CoV-2 variants?

PG: Up to Omicron, the data were encouraging on the use of the neutralization marker to predict the efficacy of vaccines against variants. We saw this in various data analyses of the Phase 3 trials and observational studies. We can characterize for each vaccine the neutralization level to a panel of variants. Based on how much the neutralization gets abrogated against a given variant, we can predict how much the vaccine efficacy against the variant should be abrogated compared to against the original vaccine strain lineage. The validation data from Phase 3 and other studies confirm that so far.

Omicron has many more mutations from the vaccine strain than the other variants, and because it is still relatively recent, the question of how well the neutralization CoP model is going to carry over to Omicron is still open. We will have data for this, as the Phase 3 trials supported by the US Government stored samples from trial participants 2–4 weeks after booster doses, when many Omicron breakthrough cases are happening. We will be able to directly study antibodies to Omicron as a CoP against Omicron COVID-19.

We tend to think about correlates against a specific variant or specific lineage, which is always going to be a moving target. There are many discreet genotypes of SARS-CoV-2. Our goal is not to find a correlate for each specific genotype, but to gain a more generalizable model. This will allow us to take a given virus and score it by its predicted neutralization sensitivity to vaccinee sera. Then, we can learn how the correlate works for viruses defined on a neutralization score scale. This will be a better biomarker going forward because it does not require a separate correlation analysis for every genotype. We will be able to use all the cases in the analysis and this biomarker of the virus scoring its antigenic distance to a vaccine insert strain.

SP: It will certainly be important to be able to manage the multiple mutations that will continue to occur in the SARS-CoV-2 virus. One avenue of active research is the development of a broader, pan-sarbecovirus vaccine that would allow us to be ready for the next variant, whenever that occurs. I am optimistic that will be feasible and many groups are working on that.

> "One avenue of active research is the development of a broader, pan-sarbecovirus vaccine that would allow us to be ready for the next variant, whenever that occurs. I am optimistic that will be feasible and many groups are working on that."
>
> **– Stanley A Plotkin**

Q How confident can we be in applying CoPs to vaccine development for future pandemic viruses?

PD: Going beyond COVID-19, into the next pandemic, we have to be bolder. If we are to have a hope of reaching a 100-day target to develop, scale-up, and move a new vaccine into the community, we must lean into neutralizing antibodies. Unless there is something mechanistically odd about the new pathogenic virus and how it infects humans, we must take a chance.

We will do the safety studies in advance, but we must scale these products in advance of that and confirm with test-negative design, post-licensure studies. My takeaway from this pandemic is that, hopefully, the next time we will do it even quicker.

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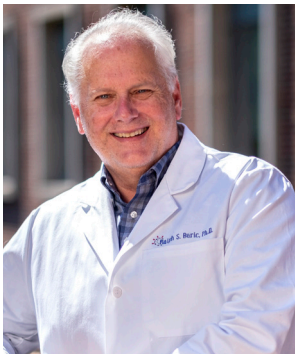
VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

Developing broadly protective strategies to protect against future pandemic threats

Ralph Baric
Gillings School of Global Public Health



"To protect ourselves from future coronavirus pandemics, we need strategies that are proven effective against a broad range of coronaviruses."

VIEWPOINT

Vaccine Insights 2022; 1(1), 59–65
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On March 28 2022, Charlotte Barker, Editor, *Vaccine Insights*, spoke to Ralph Baric about developing broadly protective drugs, antibodies, and vaccines. This article has been written based on that interview.

As we start to look beyond the COVID-19 pandemic, it's clear that another human coronavirus – even another sarbecovirus – could emerge from animal reservoirs at any time. If we are to be prepared for the next pandemic threat and avoid another global shutdown, we must invest in developing broadly protective drugs, antibodies, and vaccines.

Today, virtually everyone has heard of coronaviruses. But back in the early 1980s, when I was looking for my first postdoc position, coronaviruses sparked my interest partly because they were undiscovered territory. We knew that they had a large genome, but not how large, and we had no idea of the sequence, how they regulated the expression of their genes, or even how they replicated. I was fascinated by virus replication and began to study the fundamental mechanisms of how coronaviruses replicate in cells and cause disease.

At the time, the impact of coronaviruses on society was mostly as significant animal pathogens affecting economically important farm animals. Two human coronaviruses were known to cause mild upper and lower respiratory tract infections but were not considered serious health threats. Lists of emerging viruses of concern in the 1980s and 1990s would not have contained a single coronavirus. However, there were early warning signs.

In the 1990s, our group started asking fundamental questions about how coronaviruses moved between species, working with the mouse hepatitis virus (MHV) coronavirus, which was only known to affect mice and was believed to have no capacity to replicate in any other species. But when we co-cultured MHV in the presence of hamster cells, we found that the virus could adapt and replicate to a very high titer [1]. Further analysis revealed that it took as little as two mutations for the virus to adapt to a new host species and that cross-species transmission was facilitated via receptor orthologs – receptors in different species that evolved from a common ancestral gene and share a similar function [2]. MHV uses a mouse C-CAM receptor molecule for docking and entry but can adapt to use C-CAM molecules from other species, including hamster and human cell lines. Mutations in the viral fusion machinery can further enhance cross-species transmission [3]. Simultaneously, several new coronavirus infections of economically important farm animals were also recognized, including porcine epidemic diarrhea virus, porcine respiratory coronavirus, and others, that demonstrated that this virus family was very efficient at altering host range and colonizing new species.

In 2003, less than 4 years after we published our work on MHV cross-species transmission, a sarbecovirus that became known as SARS-CoV emerged and spread to 29 countries, killing hundreds. With 8000 cases and a nearly 10% mortality rate, the scientific community began to take coronaviruses more seriously as pandemic threats. Two additional human coronaviruses, NL63 and HKU1, were identified during this time and there was a realization that this virus family could cause more serious disease, especially in infants and the elderly.

SARS-CoV originated in bats, where it used bat angiotensin 1 converting enzyme (ACE) 2 receptors for docking and entry. During the expanding 2002–2003 epidemic, mutations evolved in the spike gene which enhanced the virus's ability to use human ortholog ACE 2 receptors for entry – just like MHV in our earlier studies. Additional mutations occurred within the S2 region of the spike protein gene, which regulates a second important species-specific regulatory element – the ability of the virus to fuse and inject nucleic acid into the target cell. Much later, it was revealed that many SARS-CoV-like bat coronaviruses had an intrinsic capacity to use human, bat, and other mammalian species' ACE2 receptors, priming them for cross species transmission and future emergence events [4]. Sarbecoviruses represented a clear and present danger to global health.

After the MERS coronavirus outbreak in 2012, research in the area ramped up as it become clear that it was only a matter of

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time before a pandemic coronavirus emerged. When that threat was realized in late 2019 with SARS-CoV-2, earlier work from our group and others allowed the scientific community to respond rapidly.

A CLEAR & PRESENT DANGER

Four contemporary human coronaviruses infect most people across the globe every few years, generally causing only upper respiratory tract infections (Figure 1), at least three of the four trafficked from bats to humans at various points over the last 600–700 years. We cannot know what spectrum of disease was seen in human populations when these coronaviruses first emerged, but modern coronavirus pandemics suggest that in a naive population, coronaviruses cause the most severe disease in the elderly. When a coronavirus emerges from a zoonotic reservoir, there are a large number of elderly individuals who are highly susceptible and poised for severe disease, so we would expect to see high rates of morbidity and mortality in the elderly. As that group becomes infected and the survivors develop immunity through natural infection or vaccination, the virus evolves in response to herd immunity in the population. Since immunity typically wanes more quickly in the nose and upper respiratory tract than in the lower respiratory tract, we expect virus infection to become a mostly upper respiratory tract event over time – i.e., a common cold virus – although we can expect several waves of pandemic disease before this event occurs, each with a reduced mortality rate compared with previous waves.

However, while we anticipate that SARS-CoV-2 will eventually become just another common cold, new coronaviruses can (and likely will) emerge from zoonotic reservoirs. How many coronaviruses in the zoonotic reservoir can infect humans? After the emergence of SARS and MERS, our group identified other bat SARS coronaviruses that were distinct from the 2003 and 2019 strains but could replicate exceptionally well on primary human lung cells [5–7].

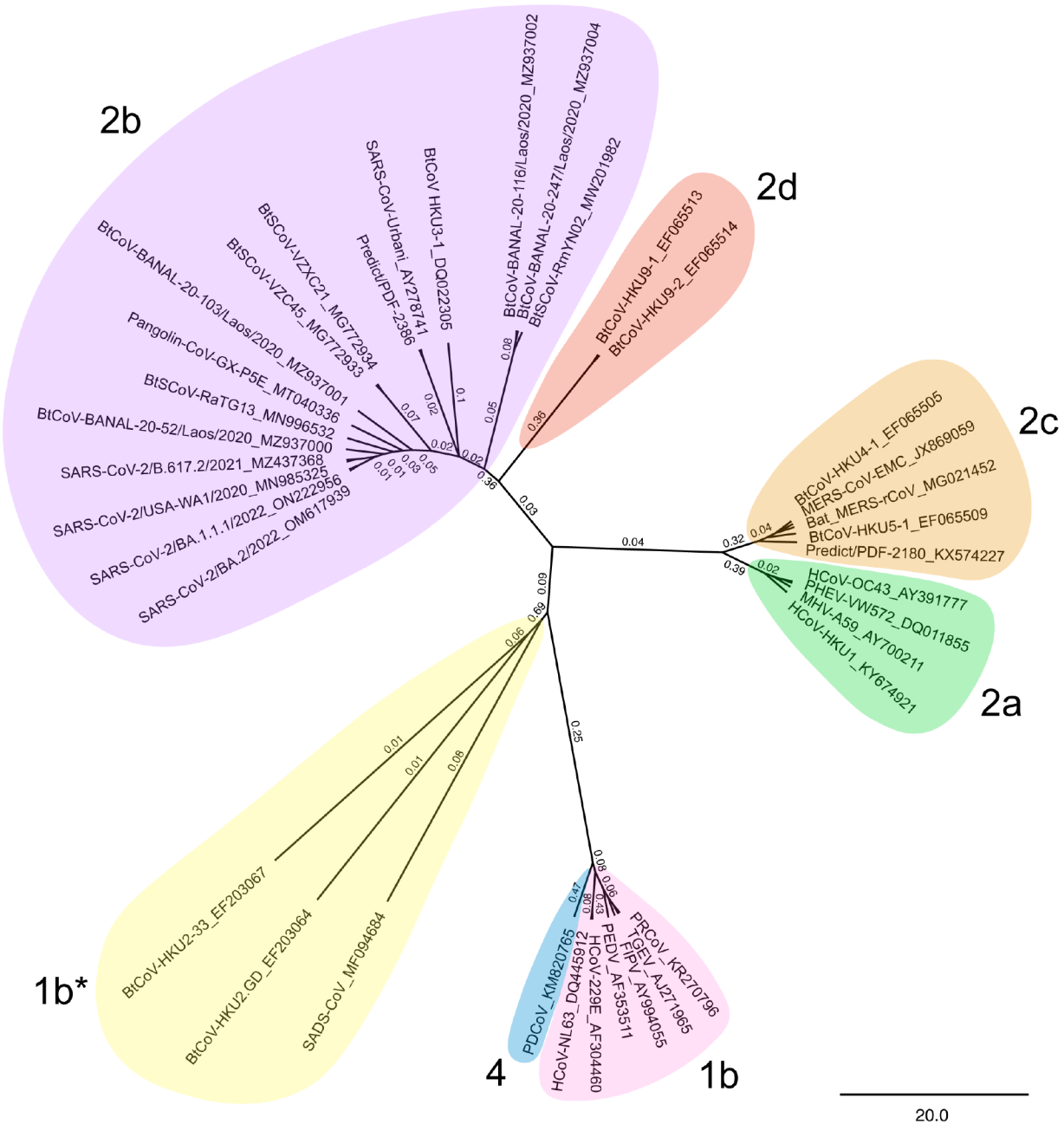
All of the closest animal relatives of SARS-CoV-2 have been identified in bats and pangolins from Southern China and Southeast Asia. For transmission to occur, a human must come into close contact with a bat or pass-through species that has an active coronavirus infection capable of making the jump. However, people who live near sites in Southeast Asia where bats overwinter in large numbers have a high prevalence of antibodies against bat SARS coronaviruses, indicating that cross-species transmission is not a rare event. Indeed, it's thought that there are as many as 50,000 introductions of bat-related viruses into humans in Southeast Asia every year [8]. Most of these events don't cause outbreaks, due to another bottleneck – the ability to transmit between humans, which only a small number of coronaviruses possess – but it is only a matter of time.

BUILDING BROADER LINES OF DEFENSE

To protect ourselves from future coronavirus pandemics, we need strategies that are proven effective against a broad range of coronaviruses. First, we need orally administered, broad-based drugs that can treat all coronavirus infections and reduce mortality. By building on our work on coronavirus replication, we have been able to contribute to the development of three such drugs – remdesivir and the oral drug molnupiravir, which are already on the market, and pegylated interferon lambda, which is showing great promise in clinical trials. Other groups contributed Paxlovid (nirmatrelvir and ritonavir), an orally administered protease inhibitor that is extremely potent against SARS-CoV2 infection. These drugs demonstrate that successful treatment strategies can be developed against the virus and that investment is warranted. Importantly, COVID-19 and other emerging viruses can elicit immunopathologic disease, requiring future investment in host-based therapies to treat long-COVID and other inflammatory based complications of infection.

FIGURE 1

The Coronavirus family tree.



Spike phylogeny of representative coronaviruses. The Spike protein sequences of selected coronaviruses were aligned and phylogenetically compared. Coronavirus genera are grouped by classic subgroup designations (1b, 2a-d, and 4). Sequences designated as 1b* group with other 1b viruses when proteins other than Spike are compared. Branches in each tree are labeled with consensus support values. Sequences were aligned using free end gaps with the Blosum62 cost matrix in Geneious Prime 2022. The tree was constructed using the neighbor-joining method based on the multiple sequence alignment, also in Geneious Prime. Numbers following the underscores in each sequence correspond to the GenBank Accession number. The radial phylogram was exported from Geneious and then rendered for publication using Adobe Illustrator 2022.

The second line of defense comes from broad-based therapeutic antibodies that work against whole lineages, including sarbecoviruses. The Omicron variant has reformulated our thinking on what is considered a broad-based therapeutic antibody and how to identify them – it has been a frustrating setback, but ultimately it will allow us to identify

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better broad-based therapeutic antibodies, many of which are currently being developed and moved into the clinic.

The third line of defense for future generations is a broadly protective vaccine. Our group, and others, have been involved in multiple efforts to develop a pan-sarbecovirus vaccine. First, we collaborated with Barton Haynes and his lab at Duke University. They identified a highly conserved epitope present on all known sarbecoviruses and targeted the immune response to that epitope using a nanoparticle-based vaccine. In mice and non-human primates, the vaccine was successful against multiple heterogeneous strains of sarbecoviruses, supporting the concept [9].

The second approach, which we pursued in our own lab, takes advantage of the modular design of the spike glycoprotein, which consists of an N terminal domain (NTD), a receptor-binding domain (RBD), and an S2 domain. As modular units, these domains can be recombined between strains and produce chimeric immunogens with modules from multiple strains, all of which have neutralizing epitopes, increasing the breadth of that immunogen to cover many more strains. By multiplexing that with other chimeric spike glycoproteins, we hope to focus the immune response on conserved elements, while simultaneously broadening the type-specific response to many different strains. Our multiplexed mRNA-based vaccines produce very robust and uniform neutralizing responses against all available sarbecovirus strains [10].

The third approach, led by Neil King and David Veesler at the University of Washington, involved nanoparticle-based vaccines incorporating RBDs from multiple strains of sarbecovirus. Many neutralizing epitopes are located in the RBD region and by mixing RBDs from very different strains the vaccine achieves a broad, type-specific response and enhances the response to the conserved epitopes that are present on each of those RBDs [11].

Our previous work identifying heterogeneous bat sarbecoviruses that could replicate in both human cell cultures and mice allowed us to test these vaccines against a diverse array of SARS-related viruses. All three strategies work well in mouse models and are now moving into trials with primates.

Developing a pan-sarbecovirus vaccine is achievable, but a vaccine covering all beta or alpha coronaviruses, or a true universal coronavirus vaccine, will take significant investment into basic science. We need more research into the diversity of bat coronaviruses poised for cross-species transmission, more and better animal models of human disease, and a better understanding of the receptors used by bat coronaviruses as they traffic between species. We also need to understand the evolutionary trajectories of new SARS-CoV-2 variants of concern and model platforms to evaluate vaccine performance against these newly emerged strains. Additional funding for identifying broadly conserved B and T cell epitopes across multiple coronaviruses will also be important. In my view, that investment is worthwhile since it is directly portable to many other highly variable and rapidly emerging RNA viruses that could threaten human populations.

NO ROOM FOR COMPLACENCY

In the 21st century, we have experienced the emergence of 10–12 outbreak, epidemic, or pandemic viruses in less than 20 years. These have arisen from diverse RNA virus families like flaviviruses, alphaviruses, filoviruses, coronaviruses, and noroviruses. Several other RNA virus families are also poised to emerge and cause global suffering. Human populations are at an all-time high, interactions between humans and wildlife are increasing, and we have the capacity for almost instantaneous global movement of human populations. All of those factors help to maximize virus movement out of animal reservoirs and into human populations – and that reservoir contains many viruses that can produce much more serious and devastating pandemics than COVID-19. We need to invest in public health infrastructure and in developing broad-acting drugs, therapeutics, antibodies, and vaccines.

The COVID 19 scientific response, rolling out efficacious vaccines, drugs, and therapeutic antibodies, is a triumph of decades of investment in basic and applied biomedical research by the US and global community. We have overhauled infrastructure and introduced new platforms for vaccines, all of which will put us in a better position when we're inevitably faced with the next pandemic, which will certainly occur in the 21st century. But we can't stop there – we must continue to build on these achievements. Just as our group's decades-long research on coronavirus transmission and evolution is contributing to the fight against COVID-19 today, the work done by scientists around the world in the coming years will doubtless find application in future pandemics. We need to be ready with small molecule inhibitors and broad-based vaccines, while building rapid response platforms to get discoveries from the bench to the clinic. Microbes have amazing powers of evolution, but we have science, creativity, and forward-thinking. Let's use them to improve global public health.

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INTERVIEW

In search of vaccinology's Holy Grail: developing a pan-sarbecovirus vaccine

Charlotte Barker, Editor, *Vaccine Insights* **speaks with Linfa Wang,** Professor of the Emerging Infectious Diseases Programme at Duke-NUS Medical School, and Executive Director of the Programme for Research in Epidemic Preparedness and Response (PREPARE), Singapore.

A leading researcher in emerging infectious diseases, Linfa Wang was on a work trip to Wuhan in January 2020 and witnessed the early days of the COVID-19 pandemic firsthand. Back in his lab at Duke-NUS Medical School, Singapore, he set to work developing a new assay that makes it easier to detect neutralizing antibodies for SARS-CoV-2 and other sarbecoviruses. Now, Wang and his team are developing a pan-sarbecovirus vaccine – with help from survivors of the 2003 SARS outbreak.

LINFA WANG is a Professor in the Programme in Emerging Infectious Diseases at Duke-NUS Medical School and the Executive Director of the Programme for Research in Epidemic Preparedness and Response (PREPARE), Singapore. He is one of the world's leading experts in zoonotic diseases, bat immunology, and pathogen discovery. He is a member of multiple WHO committees on COVID-19 and his recent research contributions include developing antibody-based serological tests to detect the SARS-CoV-2 virus, and the early and successful culture of the virus. His team is currently focusing on research into the origin of SARS-CoV-2, developing assays to better assess vaccine efficacy, and a novel vaccination strategy to broaden protective immunity against future variants and emerging SARS-related coronaviruses. His work has been recognized internationally through various international awards, numerous invited speeches at major international conferences, and more than 500 scientific papers.

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Q What was your entry point into infectious disease research?

LW: It was more accident than design! I did an undergraduate degree in biology and a PhD in biochemistry and molecular biology. I had zero formal training in infectious disease but got a job at the Australian Animal Health Laboratory, which is a Biosafety Level (BSL)-3 and -4 lab, carrying out livestock infectious disease research. Within a few years, the Hendra virus outbreak happened in Australia, and I found myself at the center of the first major bat-borne zoonotic virus of the century [1]. I quickly became fascinated by bats and their unique ability to host viruses, and later made the breakthrough discovery that bats are the host of viruses closely related to SARS-CoV responsible for the 2003 SARS outbreak [2].

"Live animal trading involves transporting animals over large distances and under stress. When animals become stressed, their viral load goes up (just as it does in humans)... this makes live animal trading a flashpoint for zoonotic transmission."

Q Coronaviruses are found in a tremendous variety of animals. What species are most likely to generate the next pandemic?

LW: Many sarbecoviruses such as SARS-CoV-2 use the ACE2 receptor for cell entry, which is highly conserved across different mammals. Before the COVID-19 pandemic, most people believed that bats were the key natural reservoir of zoonotic coronaviruses. However, it's now clear that pangolins, civets, raccoon dogs, mink, and deer are all mammals that in theory could be the intermediate hosts to bring about the next coronavirus pandemic.

SARS-CoV-2 can spill over from animal to human, or spill back from human to animal. At this point, SARS-CoV-2 has infected at least a dozen different animal species, from wild bats to farmed mink. In the USA, white-tailed deer have acquired SARS-CoV-2 from humans (an "unnatural" reservoir) and now demonstrate infection rates of 40–80%, including almost all the variants found in humans.

In terms of region, I would say Asia is likely to remain a hotspot, due to the number and diversity of bat species, and the prevalence of legal live animal markets. Live animal trading involves transporting animals over large distances and under stress. When animals become stressed, their viral load goes up (just as it does in humans). Together with close contact between animals and humans, this makes live animal trading a flashpoint for zoonotic transmission.

Q Could we design an early warning system?

LW: That is a difficult dream. There are multiple levels of pandemic preparedness. One is prevention, involving disease surveillance to identify any high-risk viruses found in animals

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that come into close contact with humans. Secondly, an early warning system in hospitals can identify unusual cases and report them to an international network – an INTERPOL for pandemic threats. Viruses are our common enemies, and now that we can communicate in real-time around the globe, it makes sense to fight them together. However, this would require international cooperation between governments as well as scientists, and geopolitics makes this challenging.

Q Another line of defense could be broadly protective coronavirus vaccines – how can we achieve that goal?

LW: If early warning and containment strategies fail, the only thing left is to apply countermeasures – vaccines and therapeutics that limit human morbidity and mortality. During the COVID-19 pandemic, we have already achieved a milestone for humankind – producing and distributing a vaccine in 10 months. However, the virus will continue to mutate and if our vaccines fail to protect against new variants, we will be forever one step behind. This is where broadly protective coronavirus vaccines become important.

We cannot expect to immediately develop a pan-coronavirus vaccine; instead, I expect the development of broadly protective vaccines to be a stepwise process, with each generation of vaccines offering protection against a wider range of coronaviruses. We knew early on that the first-generation vaccines, developed using the original Wuhan variant, would not protect us forever. One approach is to develop second-generation vaccines targeting specific variants, such as Omicron. With mRNA platforms offering a 90-day turnaround for a new vaccine, this initially seemed plausible, but the rapid spread of new variants has proven the concept not as practical as originally hoped.

My group is now working on a third-generation vaccine, which protects against all sarbecoviruses, including SARS-CoV, SARS-CoV-2, and potentially new SARS-related coronaviruses that might emerge in future. Looking further ahead, we hope that fourth-generation vaccines will target all beta-coronaviruses, including MERS, and the fifth generation will be a truly pan-coronavirus vaccine. I don't believe we can realistically develop a fifth-generation vaccine now, but a third-generation vaccine is feasible in the near-term.

Q Tell us more about the pan-sarbecovirus vaccine your group is working on...

LW: The Hendra virus that I worked on earlier in my career is related to another zoonotic bat-borne virus first found in Malaysia and Singapore – the Nipah virus. These two viruses differ in their genome by around 20–30%, similar to the difference between SARS-CoV and SARS-CoV-2, and the vaccine we developed against Hendra virus also protected against Nipah virus [3]. When COVID-19 emerged, I thought back to that experience and asked myself: could survivors of the SARS outbreak 17 years ago hold clues to defeating COVID-19 in 2020? We quickly confirmed that, unlike Hendra and Nipah, SARS-CoV infection did not protect against SARS-CoV-2. Today, we know that coronavirus immunity is

very specific – even different SARS-CoV-2 variants lead to reduced vaccine protection. But questions still lingered in my mind.

In May 2021, we got the chance to vaccinate a number of SARS survivors with first-generation COVID-19 vaccines. We knew that they would generate a high level of SARS-CoV-2 neutralizing antibodies, but would COVID-19 vaccination also boost their levels of SARS-CoV antibodies? And could this affect immunity to other sarbecoviruses?

We were well-positioned to answer these questions because we had already developed a surrogate virus neutralization assay platform to detect antibodies against many different sarbecoviruses in one assay [4]. Even without access to the virus itself, we can use the sequence to engineer the receptor-binding domain and do neutralization tests, without the risks of working with a live virus. With just a few microliters of blood, we can now measure neutralizing antibodies against 20different sarbecoviruses.

Our study vaccinating SARS survivors for COVID-19 showed that they produced broadly neutralizing antibodies, capable of neutralizing all of the sarbecoviruses we tested against – an effect we call cross-clade boosting [5]. This was a real Eureka moment! There was a lot of interest in our work from vaccine developers and international organizations.

The next questions were obvious: can we achieve cross-clade boosting of broadly neutralizing antibodies by vaccination only, rather than infection? And can we reverse the order, generating immunity to SARS-CoV-2 first, then boosting for SARS-CoV, given that most of the world population would have immunity against SARS-CoV-2 by either vaccination or infection?

We designed a vaccine containing the full spike protein sequences from multiple viruses in the SARS-CoV-1 clade, including human and bat virus sequences. We vaccinated mice with two doses of an approved human COVID-19 vaccine and two months later, gave them our boosting vaccine candidate based a consensus SARS-CoV-1 clade virus sequence. The results bore out our earlier findings beautifully – the vaccination and boosted mice could neutralize all sarbecoviruses in our assay at the time.

Then, Omicron emerged, and we found that this product of human transmission and immune selection could reduce the effect of the broadly neutralizing antibodies generated by cross-clade boosting [6]. This was disappointing; however, our goal remains to have a vaccine ready for the next variant or new zoonotic sarbecovirus.

Q What's next for this work?

LW: We want to make a real impact on the current pandemic and play a role in preventing the next coronavirus pandemic. This means making our cross-clade boosting virus vaccine a reality and we believe this is achievable in the very near future. The three platforms already in use for COVID-19 vaccines are mRNA, protein subunit, and

"Even without access to the virus itself, we can use the sequence to engineer the receptor-binding domain and do neutralization tests, without the risks of working with a live virus."

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viral vectors. We are working on all three approaches right now to deliver these pan-sarbecovirus virus vaccines, as the platform could affect factors such as efficacy, vaccine acceptance, transport, and vaccine equity.

The ultimate test of protection is a clinical trial. However, it is difficult to perform a classic Phase 3 clinical trial of a booster pan-sarbecovirus vaccine considering there are so many first-generation vaccines in human application and the many different variants in circulation. A more realistic approach would be to measure immunity using various assays to assess both the potency and breadth simultaneously.

The international community is working very hard to develop the next-generation vaccine. But the goalposts have shifted. Many people have been vaccinated (with various combinations of vaccines) or exposed to COVID-19, which makes booster vaccines difficult to test. We have to find a new way to deal with a new virus and this will require some flexibility from regulators.

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VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

Lessons from COVID-19 & poverty-associated infectious disease vaccines for future epidemic & pandemic preparedness

Jerome H Kim & Maria Elena Bottazzi

VIEWPOINT

"[The] gap in vaccine equity has resulted in additional deaths, trillions of dollars' worth of economic damage, and the generation of increasingly resistant variants of concern"

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Vaccine development for COVID-19 and poverty-associated infectious diseases face a range of challenges – some very different, some with significant overlap. Here, we identify six key mutually instructive lessons that should be applied if we are to respond more efficiently and equitably to the next epidemic or pandemic threat.

From the initial description of an unknown respiratory illness in China in December 2019 to the emergency use approval of multiple COVID-19 vaccines in November-December 2020, the accelerated development of vaccines against SARS-CoV-2, using innovative (mRNA, adenoviral vectors, DNA) and standard (whole inactivated virus, protein-based) vaccine platforms has been remarkable and unprecedented, taking research discoveries from the laboratory to licensure in less than one year [1,2].

However, although nearly 12 billion doses of these vaccines have been administered, only 15.9% of people in low-income countries have received at least one dose, which highlights that more than 80% of people in low-income countries have yet to be vaccinated [3]. This gap in vaccine equity has resulted in additional deaths, trillions of dollars' worth of economic damage, and the generation of increasingly resistant variants of concern [4]. At the same time, endemic and poverty-associated infectious diseases (PAID) have continued to weigh heavily on low- and middle-income countries (LMICs) [5,6]. Looking at vaccine development for both COVID-19 and PAID, several observations highlight common problems and offer mutually instructive lessons (Table 1).

COVID-19 vaccines were developed and tested rapidly. This required that sufficient funding for de-risking the vaccine development process be made available early (Table 1: Lesson 1). The Coalition for Epidemic Preparedness Innovations (CEPI) made roughly US$1.5 billion available before the end of January 2020 [3,7], and by May 2020 [7], Operation Warp Speed provided $20 billion in funding [8]. Contrast those amounts with the 2017 budget for vaccines for *Streptococcus pyogenes*, which kills 500,000 annually: approximately US$1 million [9]. Furthermore, in aggregate, only US$17 million was invested in vaccine research and development for neglected diseases between 2007 and 2020 [10]. Funding matters.

For COVID-19, unprecedented concurrent, coordinated, and expedited review procedures instituted by regulatory agencies

TABLE 1

Lessons learned from COVID-19 and poverty-associated infectious disease (PAID) vaccine development to enable future efficient and equitable epidemic or pandemic responses.

Lesson	Category	What we learned
1	Funding	Early, continuous, and sustainable funding for de-risking of the vaccine development pathway is needed
2	Regulatory	Concurrent and expedited regulatory review procedures instituted globally are essential. This should include close coordination between regulatory agencies and other actors such as governmental agencies, industry, non-profits, and academics.
3	Manufacturing capacity	Large multinationals and small and medium biotechnology companies, as well as the Developing Country Vaccine Manufacturing Network (DCVMN), need an equal share of the funding for production accountability
4	Equity and access	The pace and cost of introduction for vaccines developed for PAIDs need to be revisited to enable better equity and access in LMICs
5	Absorption capacity	An adaptable framework for setting efficient supply chains, staffing, equipment, and data collection, with strategic communications and community engagement are key for successful vaccination
6	Leadership	Coordinated and clear accountability is needed to plan and execute end-to-end, without incoordination delay

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around the world enabled rapid, safe, and efficacious vaccine development (Table 1: Lesson 2). Products that were safe and immunogenic moved quickly to safety and efficacy testing and emergency approval. Joint consultations around theoretical safety concerns such as antibody-dependent enhancement and vaccine-associated enhanced respiratory disease created consensus around the minimization of risk. Similar urgency does not accompany PAID vaccine development, though these diseases (including HIV, TB, and malaria) kill 4–5 million people every year [11] – moving forward and for a 'new normal,' there should be an effort to apply these lessons for greater benefit.

Delays in scaling vaccine manufacturing are highlighted in Table 1: Lesson 3. If the early heroes of COVID-19 vaccine development were biotechnology companies (BioNTech, Moderna, Novavax) and atypical or small vaccine manufacturers (AstraZeneca, Janssen) – companies that had limited (if any) commercially approved vaccine production – manufacturing capacity and scalability were a known concern. Large multinational vaccine companies (Merck, GSK, Sanofi) with known vaccine manufacturing capabilities, tried to enter early in the COVID-19 vaccine development landscape but either discontinued further development or were delayed due to scientific or logistical challenges [12,13]. On the other hand, the vaccine companies that provide more than 75% of vaccines used globally in pediatric extended programs of immunization – the network of developing country vaccine manufacturers (DCVMs) [14] – were not a part of the initial funding distribution. Some DCVMs performed contract manufacturing (Serum Institute, Butantan), but why were DCVMs not included in the initial funding for the development of COVID-19 vaccines? Ultimately, whole inactivated virus vaccines from Chinese companies, Sinopharm and Sinovac, provided 4 billion doses in 2021, yet neither company received support from global funders. Interestingly, protein-based or subunit vaccines, a technology that is in the sweet spot of production for many DCVMs, were also not supported early in the pandemic [1].

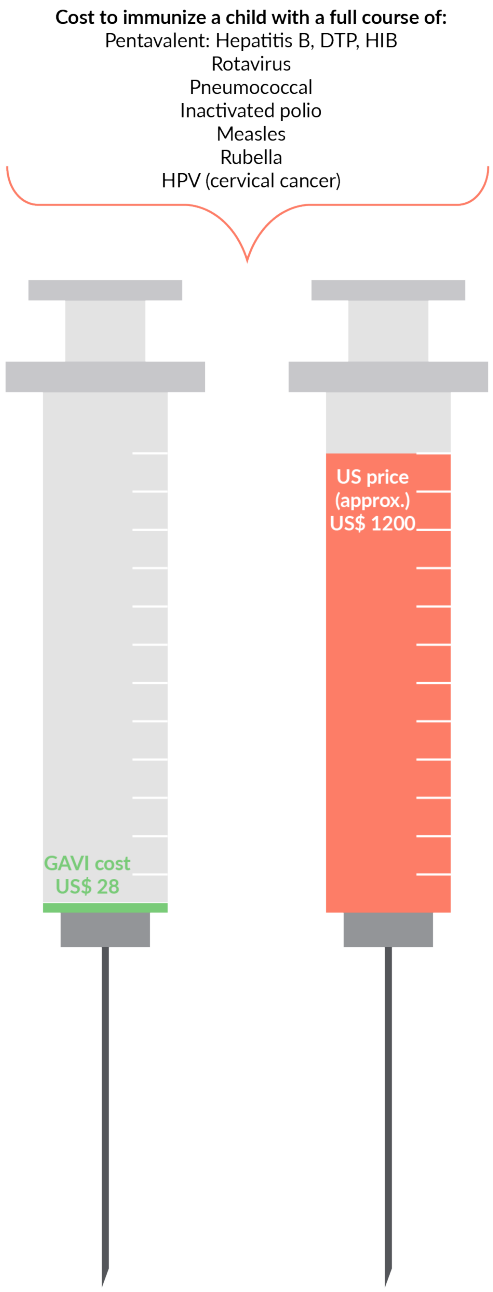
Lesson 4 is equity and access (Table 1: Lesson 4) [15,16]. Despite the establishment of the COVAX facility to ensure that countries receive 20% of their required doses by the end of 2021, delivery was 50% short of the 2 billion vaccine dose goal [17,18]. Equity and access for the LMICs, however, are always issues for vaccines that are developed in high-income countries (HICs); 15 years after the approval of the rotavirus vaccine, 60% of the world's children have not been fully vaccinated. Vaccines developed for PAIDs have a slower pace of introduction, requiring World Health Organization (WHO) regulatory approval, a recommendation from the Strategic Advisory Group of Experts in immunization (SAGE), and application to and negotiations with GAVI, to ensure that vaccines are: (1) needed; (2) wanted; (3) appropriately utilized (see Table 1: Lesson 5 for COVID-19 vaccines in LMICs).

The vaccines produced by DCVMs for extended programs of immunization are inexpensive; the GAVI average cost for to fully vaccinate a child for nine key pathogens is US$28, compared to an equivalent cost of US$1,100 in the USA (Figure 1). Cost limits access and the greatest burden of unvaccinated children is in middle-income, non-GAVI countries.

Lesson 5 comprises the issues associated with absorption capacity (Table 1: Lesson 5) [19] that effectively hinder vaccination. Staffing, logistics, competing priorities, perception of risk, and vaccine hesitancy are typical public health considerations for routine immunization – but these are particular issues when numbers are greater, perception of risk is low, and misinformation rife. For PAID vaccines, demonstrating the burden of disease is important for Ministries of Health; demonstrating cost-effectiveness is necessary for Ministries of Finance. The diagnostics gap (the difference in the number of tests done in HIC versus LMIC) has meant that African countries (and others) were unaware of the true burden of disease and death [20]. Convincing countries to vaccinate against

FIGURE 1

The GAVI average cost to fully vaccinate a child for nine pathogens compared to an equivalent cost in the USA.



Data from Gavi, the Vaccine Alliance, 29 January 2019.

COVID-19 when disease, cost, and need are not clear, and implementation of vaccination might disrupt other prioritized public health campaigns has been difficult; a lesson learned from vaccine control of PAIDs in LMICs.

The final lesson (Lesson 6) is leadership. There was no end-to-end leadership for COVID-19, no overarching control and guidance from vaccine development through manufacturing and global use. In the maelstrom of competing political, societal, and economic issues during the SARS-CoV-2 pandemic it is easiest to focus on development, supply, or vaccination, in isolation, but ultimately, impact on disease and death is the key metric. To have impact efficiently, we have to plan and execute end-to-end, without incoordination delay. With PAID vaccines, we have experienced this lesson frequently – for example, in the delayed recommendations for malaria and hepatitis E vaccines. Incoordination delay in COVID-19 vaccine supply, equity, and delivery was another lesson paid in unnecessary disease and death.

Leadership, whether a part of an existing organization or constituted ad hoc, should come from an entity that has negotiated terms of reference for responsibility, accountability, and funding commensurate with the task and is empowered to mobilize necessary resources to ensure speedy equity and access to innovative technologies, preventive and therapeutic. Given the complexities, this could take years, but given the human, economic and political cost of the COVID-19 pandemic, would be effort well spent.

To sum up, the continuum of development of vaccines against COVID-19 and PAIDs has taught us several lessons. The road ahead is still steep and has many roadblocks but moving forward the global community should work sedulously on solutions in anticipation of the next epidemic or pandemic, in the hope that we might respond more humanely, efficiently, and equitably to ensure that all populations will have access to life-saving vaccines.

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INTERVIEW

RNA vaccines: past, present & future

Charlotte Barker, Editor, *Vaccines Insights* speaks with **Drew Weissman,** Roberts Family Professor in Vaccine Research, Perelman School of Medicine, University of Pennsylvania

RNA vaccianes have been one of the success stories of the COVID-19 pandemic – but the platform has not always been so popular with vaccine developers. We caught up with RNA pioneer Drew Weissman to find out how RNA vaccines went from out in the cold to the hottest technology around – and why this is only the start.

DREW WEISSMAN is a professor of medicine at the Perelman School of Medicine at the University of Pennsylvania. In collaboration with Dr Katalin Karikó, he discovered the ability of modified nucleosides in RNA to suppress activation of innate immune sensors and increase the translation of mRNA containing certain modified nucleosides. The nucleoside-modified mRNA-lipid nanoparticle vaccine platform that Dr Weissman's lab created is used in the first two authorized COVID-19 vaccines by Pfizer/BioNTech and Moderna. They continue to develop other vaccines that induce potent antibody and T cell responses with mRNA-based vaccines. In 2021, Drs Weissman and Karikó were awarded the prestigious Lasker–DeBakey Clinical Medical Research Award for their work on modified mRNA vaccines. Dr Weissman is a member of The American Association of Immunologists, the American Federation for Clinical Research, and the Association of American Physicians. He received his graduate degrees from Boston University School of Medicine.

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Q How did your interest in RNA begin?

DW: I started my post-graduate career in Anthony Fauci's lab at the National Institute of Health (NIH), where I studied HIV immunopathogenesis and dendritic cells as antigen-presenting cells. In 1997, I came to the University of Pennsylvania to start my own lab and pursue my interest in making vaccines using dendritic cells. We got our hands on peptides and DNA, and we were interested in using RNA since it had already been used for vaccines. That is when I met Katalin Karikó.

> "I tested [RNA with pseudouridine and other modifications] in dendritic cells and found that the modifications got rid of the inflammation."

Kati had been working with RNA for years in tumor cell lines. She was able to transfect the cells but was never able to take it any further. She provided RNA, which I added to my dendritic cells, and we discovered that RNA is highly inflammatory. That was unexpected and led to years of investigation, while we tried to figure out the underlying mechanisms. Our collaboration has continued ever since.

Q How did you come up with the idea of using pseudouridines to reduce the inflammatory response?

DW: To understand why it was inflammatory, we took RNA from different parts of human and bacterial cells, and split them into RNA fractions, including ribosomal RNA (rRNA), nuclear RNA, and transfer RNA (tRNA). We tested them all individually and found that the bacterial RNA was highly inflammatory, whereas tRNA was not inflammatory at all. The difference is that up to 25% of the nucleosides in tRNA are modified, whereas bacterial RNA has very few of these modifications. This led us to hypothesize that nucleoside modification affected the inflammatory potential of the RNA. Kati made RNA with pseudouridine and other modifications, which I tested in dendritic cells and found that the modifications got rid of the inflammation.

Q That discovery turned out to be a real breakthrough – what was the response from the scientific community at the time?

DW: The night before our paper [1] was going to be published, I told Kati that soon our phones would be ringing off the hook because anybody with an interest in RNA would want to use this technology. But the phone never rang – in fact, it was years before people were interested. We were surprised, but we never stopped working.

I think people had been burned by RNA in the past and were not interested in trying again. RNA is a real pain to work with, as it degrades quickly, and you have to set up your lab in a very specific way to work with it.

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Q Fast-forwarding to early 2020, did you realize immediately that RNA vaccines could be harnessed to fight COVID-19?

DW: By the start of the pandemic, my lab had been working on RNA vaccines for decades and had published work showing that modified RNA/lipid nanoparticles (LNPs) were an incredibly potent vaccine platform. In a 2017 study, we immunized macaques with a single dose of RNA/LNP Zika vaccine and it protected them from infection [2] – that had never been seen before with any Zika vaccine, so we knew that it was incredibly potent. As soon as COVID-19 was identified as a coronavirus, we knew an RNA vaccine would work because people had already made coronavirus vaccines. We knew how to make the vaccine and we made it with RNA.

My family gives me a hard time because they had to come and tell me the results of the first Phase 3 clinical trial [3] – I had not seen them as I was already busy working on a pan-coronavirus vaccine. But I was incredibly excited because I knew that the vaccine would work and that it would be approved soon to start addressing the pandemic.

Until that point, we had made RNA vaccines for around 20 different pathogens, and nearly every one of them gave 100% protection in animal models. I knew that no respiratory vaccine had ever given protection above 70–75% so I wasn't expecting more than that, but based on all our previous animal studies, I was hoping for 95–100% protection. So I was happy to see the Phase 3 results showed over 94% efficacy.

Q Now that the efficacy and safety of RNA vaccines are established – what's next?

DW: We started working on a pan-coronavirus vaccine in the spring of 2020. The thinking was that there had been three coronavirus epidemics in the past 20 years, so there were going to be more. We knew that variants were going to appear in the future, and we hoped a pan-coronavirus vaccine could tackle this.

Making a universal coronavirus vaccine is very difficult. There are likely tens of thousands of different coronaviruses, some of which can infect people. We had to look at all the coronaviruses that had the potential to infect people and find conserved regions that we could put into a vaccine to protect against all of them. It took supercomputers looking at hundreds of thousands of sequences, but we have now published details of two immunogens, both of which work well and will be taken into clinical trials [4,5].

We also have a universal influenza vaccine, a genital herpes vaccine, and a malaria vaccine, all soon to start clinical trials [6,7,8].

Q What are the key areas for further study in RNA vaccines?

DW: Certainly, finding better delivery systems is going to be important, whether that is improving the LNP or finding something completely different. We and others are working on improving the LNPs. We have made some that are 5–10-times more potent than those currently in use, and we hope to move them to clinical trials soon. We are also

working on other formulations that will be as effective, but cheaper and easier to make and have fewer adverse events.

The biggest challenge is antigen/immunogen design. We already have vaccines for all the diseases that vaccines work well for, such as measles, mumps, and tetanus. Now we have to start working on vaccines for intractable diseases, such as HIV, hepatitis C, malaria, tuberculosis, and cancer. Here, RNA gives a lot of advantages in potency, but we do need better immunogens to make the vaccines more effective, especially for diseases where the envelope proteins mutate rapidly. We are collaborating with other groups to combine RNA technology with improved immunogen design [9]. We are starting the Penn Institute for RNA Innovation. It will combine all RNA research, including basic science and clinical development, and everything in between, in one center to promote interactive research.

"Now we have to start working on vaccines for intractable diseases... RNA gives a lot of advantages in potency, but we do need better immunogens to make the vaccines more effective, especially for diseases where the envelope proteins mutate rapidly"

Q Some vaccine developers are working on self-amplifying RNA – is this a promising avenue for the future?

DW: BioNTech did a four-arm Phase 1 clinical trial for coronavirus; two of the arms were modified RNA, one was an unmodified RNA similar to CureVac, and one arm was a self-amplifying RNA. Self-amplifying RNA gave good T cell responses but there was zero antibody response. Other companies have tried to use self-amplifying RNA as a booster and that works better, giving some antibody responses, but I suspect they are no better than modified RNA and probably worse.

Q What are the biggest lessons that we need to take from the pandemic?

DW: Certainly, it has pushed RNA into everybody's vocabulary and allowed regulators to easily approve new RNA vaccines. This will make development and production going forward much simpler.

A big problem we're facing is the anti-vax movement, and how they've been allowed to take over social media and spread misinformation, to the point that around 40% of Americans refuse to take a COVID-19 vaccine. I spend a lot of my evenings and weekends talking to groups of hesitant people. I will not talk to people who do not believe in science because they are not going to listen to me, but I do talk to people who simply do not know or understand the science. Other people are telling them that RNA vaccines will change their DNA

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or give them cancer, and I have a chance to explain the science in words they understand and help them see that the vaccine is safe and incredibly effective.

It's not just the public that does not trust in science. The prior administration decimated public health budgets and was completely unprepared for a pandemic because they, in part, did not believe in the science. Many politicians are great at hindsight but not very good at looking to the future and preparing. Scientists know what you have to do to be ready; convincing the politicians who have the money and the power to do it is a different thing. We need more reasonable politicians, or we need to do a better job convincing them of the importance of pandemic preparedness.

Q Another big challenge is getting COVID-19 vaccines to the entire world. Could you tell me about the work you have been doing in Thailand?

DW: I started working with scientists at Chulalongkorn University, Thailand, five years ago on a variety of RNA vaccines and therapeutics. In the early spring of 2020, they realized any vaccine made in the West would take many years to get to Southeast Asia. They were not willing to wait, and their government was willing to fund their own vaccine. So, we made a Thai mRNA–LNP vaccine and a GMP production site in Thailand big enough to produce the vaccine for all of Southeast Asia. The vaccine is in Phase 3 clinical trials, and we hope it will be available soon. We also set up a GMP site in South Africa and we are adding more around the world so that local governments can have control over their own vaccine production.

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SPOTLIGHT

Developing a protein subunit vaccine for COVID-19

Vikram Paradkar
Biological E Limited

"...we believe that the platform that we have developed ... can be adapted to develop a pan-coronavirus vaccine, provided we can develop the right antigen design."

VIEWPOINT

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Charlotte Barker, Editor, *Vaccine Insights,* spoke with Vikram Paradkar about developing a protein subunit vaccine for COVID-19 on April 8, 2022. This article was written based on that interview.

Supplied to the Indian government at $2 per dose, the recombinant protein subunit vaccine Corbevax has been administered to 100 million people. This article will discuss the rationale behind the choice of platform, immunogen, and adjuvants.

Biological E is one of the first biologic companies established in India and has been developing and manufacturing vaccines for more than 50 years. Pre-pandemic the company delivered more than 500 million vaccine doses per year to over 100 countries, with major products including pentavalent vaccine, DTP, TT and Td vaccines, and measles–rubella vaccines. When the COVID-19 pandemic was declared in February 2020, it was immediately apparent that only vaccines would be able to overcome this pandemic, and Biological E decided early on to focus on developing a protein subunit-based vaccine – Corbevax.

The vaccine entered Phase 1/2 trials in November 2020 and Phase 2/3 trials in June 2021. India's National Regulatory Authority granted an emergency use authorization (EUA) for adults on 28 December 2021, with EUAs for 12–18-year-olds and 5–12-year-olds granted in February and April 2022, respectively.

While mRNA and adenovirus vector vaccines were the first to be approved and have played a key role, the more traditional technology of protein subunit vaccines has important advantages. The safety profile of protein subunit vaccines is excellent, and we have seen very few adverse events, with none of the cardiovascular or blood clotting adverse events seen with mRNA and adenoviral vaccines, respectively. In three Phase 2/3 clinical trials, more than 3,500 subjects ranging in age from 5 to 80 years have received Corbevax with no reported Grade 3 or Serious Adverse Events, or adverse event of special interest. Another issue with mRNA vaccines, in particular, is that while the initial antibody response is greater than other vaccines, it wanes after a few months, requiring repeated boosters. Follow-up of clinical trial subjects receiving Corbevax indicates that good levels of immunity are preserved for at least 6 months, and possibly longer – if confirmed in larger post-marketing studies, this could be an important advantage for protein subunit formulations. Finally – and perhaps most important on a global scale – protein subunit vaccines can be manufactured at a large scale with well-established technologies, making them affordable. Biological E is supplying this vaccine to the government of India at around $2 a dose – the lowest price for a COVID-19 vaccine globally.

While protein subunit vaccines are well-established technology, every new vaccine presents challenges, and this project was no exception.

SELECTING THE IMMUNOGEN

One approach would be to use the entire spike protein as an antigen, but the SARS-CoV-2 spike protein is very large (1273 amino acids), meaning that the microbial systems the company currently uses for vaccine manufacturing would have been unable to produce the protein efficiently. We needed to find a smaller – but still immunogenic – fragment of the spike protein.

The Baylor College of Medicine and Texas Children's Hospital carried out work in 2010 on the SARS-CoV-1 virus receptor-binding domain (RBD), which binds to the ACE-2 receptor in human cells to mediate cell entry and were able to demonstrate in animal studies that it was a good vaccine candidate [1]. We established research collaborations with a number of academic labs investigating the RBD as a vaccine candidate and evaluated the nature of the protein and the recombinant microbial strains used to produce them, including conducting animal studies with several different RBD proteins [2]. Ultimately, BioE licensed the *Pichia Pastoris* strain producing the RBD of SARS-CoV-2 from Baylor College of Medicine and Texas Children's Hospital.

The RBD fragment is small and easy to handle, and we expected that this vaccine would be easier to develop than a complex and heavily glycosylated spike protein in terms of consistent manufacturing. As it is a small fragment of the spike protein (around 20%), we were apprehensive about whether it would generate an immune response and

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demonstrate protection. However, our own animal studies confirmed the earlier studies from Baylor College of Medicine, and the Adjuvanted-RBD vaccine demonstrated good neutralization of the SARS-CoV-2 virus, giving us reasonable confidence that a vaccine derived from RBD would have enough immunologically relevant epitopes. That conclusion has been borne out in the clinic, with a good immune response offered by Corbevax as well as other RBD-based vaccines such as those developed by Findlay Institute in Cuba and Anhui-Zhifei of China [3,4].

SELECTING ADJUVANTS

The selection of adjuvants is critical for protein subunit vaccines. The safety profile of the adjuvants, compatibility between antigen and adjuvants, and the reactogenicity of the resulting vaccine must all be carefully considered.

RBD as a protein is not immunogenic in itself so it must be adjuvanted for the immune system to recognize it. We evaluated various adjuvants including aluminum hydroxide (alum), one of the most common adjuvants in vaccines, squalene- and saponin-based adjuvants, and CpG 1018, an emerging oligonucleotide adjuvant used by Dynavax in their vaccine for hepatitis B. In mouse studies, each adjuvant alone was only moderately successful; however, when alum and CpG were tested in combination they gave a significant synergistic response and the desired Th1-skewed immune response to avoid antibody-mediated disease enhancement (a lingering concern for several types of vaccines). At least three other vaccines developed against COVID-19 in the same timeframe (from Clover, Medigen, and Valneva) have also chosen to adjuvant with alum and CpG, suggesting that this has been a universal finding.

MANUFACTURING & SCALE-UP

The key to scalability is consistency in the manufacturing process. It is difficult, expensive, and time-consuming to make changes at full scale. We manufacture the RBD protein antigen of Corbevax in a recombinant yeast expression system that our team has significant experience with, and which does not require complex infrastructure. This tried and trusted protein manufacturing process is the key reason we can supply large quantities of Corbevax so cost-efficiently.

Yeast expression systems inherently have good scalability and productivity, but the magnitude of the scale-up required for RBD antigen production was substantial. That led to some challenges from a logistics perspective to our current manufacturing facilities, such as the ability to supply a large quantity of oxygen to fermenters to support growth, handling of methanol required for fermentation, etc. However, with some retrofitting, these issues were quickly resolved, and we are now producing Corbevax at close to 100 million doses per month, using our existing facilities.

LOOKING AHEAD

With the data from our pediatric trials [5], Corbevax received a EUA from India's National Regulatory Authority in April 2022 that covers vaccination from age 5 years and above, and with additional clinical trials, we hope to gain approval for younger children and infants. Currently, young children do not seem to be severely affected by COVID-19, but it is impossible to predict how new variants will affect vulnerable populations. Protein subunit vaccines are routinely administered as childhood vaccinations (e.g., hepatitis B) and are proven to be safe and effective in children and infants. We are also in the process of obtaining WHO-EUL and registering the vaccine in multiple countries. Corbevax is now approved in Botswana for ages 12 years and above and is under consideration for the 16 countries that form the Southern African Development Community. The Indian government initiated a vaccination campaign in children aged 12, 13 and

14 years with Corbevax on March 16, 2022 – to date, approximately 50 million doses of Corbevax have been administered and 15 million children have completed two-dose primary vaccination with minimal adverse events following immunization and no adverse events of special interest. This is one of the largest pediatric COVID-19 vaccination campaign worldwide.

Despite being such a small subunit protein, RBD is a vital part of the interaction of the virus with the ACE-2 receptor, and the antibodies generated appear to have significant cross-neutralizing potential for the variants already in circulation. However, there is a need to develop vaccines that can protect against variants that could emerge in the future. Future variants are not easy to predict. However, we believe that the platform that we have developed – a protein subunit plus alum and CpG adjuvants – can be adapted to develop a pan-coronavirus vaccine, provided we can develop the right antigen design. Options we are exploring include multivalent vaccines, a multi-epitope antigen, or a synthetically derived protein subunit.

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VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

COMMENTARY

Should we vaccinate against long-COVID?

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The primary goal of current COVID-19 vaccination programs is preventing hospitalizations and deaths from acute disease. However, an important additional role for vaccination could be in preventing or treating post-acute COVID-19 syndrome, known as long-COVID. Here, we outline the burden of long-COVID, discuss the limited evidence currently available on the impact of vaccination on the syndrome, and propose next steps to further our understanding of this important issue.

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According to the European Centre for Disease Control and Prevention, the most cited goal of COVID-19 vaccinations has been the prevention of hospitalizations and deaths due to COVID-19, but depending on the levels and type of protective immunity achieved, vaccination could also potentially prevent SARS-2 coronavirus (SARS-CoV-2) infection and interrupt disease transmission [1]. In addition, a more nuanced, yet vital role for vaccination could be in the prevention of the post-acute COVID-19 syndrome, often referred to as 'long-COVID'.

The case definition of long-COVID is undergoing refinement as we learn more about the natural history of COVID-19 caused by

a series of variants of concern, but it generally refers to the persistence of symptoms beyond the 3–4 week period when it is no longer routine to isolate intact, replication-competent SARS-CoV-2 [2].The World Health Organization (WHO) describes long-COVID in terms of a "post COVID-19 condition" that "occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last two months and cannot be explained by an alternative diagnosis" [3]. Some investigators further differentiate persistent symptoms as subacute COVID-19, occurring 4–12 weeks after the acute infection, and those ascribed to a lingering and chronic post-COVID-19 syndrome that extends more than 12 weeks beyond the acute period (and which cannot be linked to an alternative diagnosis). The US Centers for Disease Control and Prevention (CDC) define a post-COVID condition as an "umbrella term" for a range of health conditions that are present four or more weeks post-infection with SARS-CoV-2. Shown in Box 1 is a list of long-COVID-defining conditions from the US CDC. Some investigators prefer to categorize these conditions by systems, including cardiopulmonary sequelae with tachycardia, dyspnea, persistent cough, and an ongoing oxygen requirement; hematological with thrombotic events; renal insufficiency; arthralgias, myalgias and other rheumatologic symptoms; and neuropsychiatric disturbances associated with 'brain fog', fatigue, mood disturbances, and anosmia or dysgeusia [2,4,5], among others. Furthermore, there is the potential role of persistence of virus and/or viral antigens in many of these organs.

BOX 1

Long-COVID-defining conditions from the US CDC.

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise and/or poor endurance
- 'Brain fog' or cognitive impairment
- Cough
- Chest pain
- Headache
- Palpitations and/or tachycardia
- Arthralgia
- Myalgia
- Paresthesia
- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Lightheadedness
- Impaired daily function and mobility
- Generalized pain
- Rash (e.g., urticaria)
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities
- Depression

Adapted from [6].

BRAIN FOG

The neurologic complications linked to long-COVID may rank among the most concerning. A UK biobank of more than 40,000 brain scan images collected prior to COVID-19 pandemic made it possible to study almost 400 of those individuals who subsequently tested positive for SARS-CoV-2, together with an almost equal number of matched controls. The findings were striking and included significant gray matter degeneration and a neuroimaging pattern resembling that linked to cognitive declines seen in extreme aging or even Alzheimer's disease [7]. The underlying mechanisms are under investigation, but so far have been attributed to viral neuroinvasion, hypoxia and oxidative stress, or neuroimmunologic phenomena including microglial cell activation, neuronophagia, microglial nodules, and autoantibodies [8,9].

Such dire findings could emphasize the importance of vaccinating individuals to prevent long-COVID, especially to prevent chronic

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neurological complications and deterioration. A comprehensive analysis of data from electronic health records of almost 300,000 COVID-19 patients (mostly in the US), found that a third exhibit at least one feature of long-COVID in a 3–6 month window post-infection (including cognitive declines and anxiety or depression), with the highest risk in those with severe illness [10]. Younger long-COVID patients suffer predominantly from anxiety, depression, and headaches, as well as abdominal symptoms, compared to cognitive symptoms, fatigue, pain, and difficulties in breathing in older patients [10]. Data are mostly lacking for children less than 12 years of age, and there are widely divergent estimates on the health impact of long-COVID in these groups [11].

THERAPEUTIC VS PREVENTATIVE VACCINE

Given the important health and socioeconomic consequences of long-COVID, especially those related to neurologic complications and cognitive declines, there is an urgent need to study the potential benefits of COVID-19 vaccines for long-COVID. Current COVID-19 vaccines have two potential uses in this context.

The first use is as a therapeutic vaccine. This concept is based on anecdotal evidence and a few reported non-peer-reviewed studies from the UK-based longcovidSOS [12], together with hypotheses that long-COVID may in some cases be linked to the persistence of the virus or potentially delayed clearance of virus fragments [13]. In such cases, boosting antivirus immunity through immunization could accelerate patient recovery. Immunizing long-COVID patients with either mRNA or adenovirus-vectored COVID-19 vaccines was shown to be safe, offering slight improvements in terms of symptom resolution [14]. A large French study of a national cohort of patients with long COVID (known as ComPaRe) found that patients vaccinated with one of the available vaccines, including ChAdOx1 nCoV-19 (Astra Zeneca), BNT162b2 mRNA (Pfizer-BioNTech), Ad26.COV2. S (Johnson & Johnson), or mRNA-1273 (Moderna) vaccines, showed improvements relative to those unvaccinated in terms of symptoms and remission rate [13]. However a US-based study reported aberrant T cell memory responses following vaccination in long-COVID patients, suggesting that protection against re-infection in the long term may be impaired [15].

The other use for a vaccine is to prevent infection and, if infected, to prevent progression to long-COVID. In the UK, those fully vaccinated (two doses) with ChAdOx1, BNT162b2, or mRNA-1273 were found to exhibit a 50% reduction in the risk of developing long-COVID [16]. But, there is urgency to conduct additional studies.

NEXT STEPS

The prospect of establishing a therapeutic versus preventive vaccination indication and strategy against long-COVID is potentially attractive, but success on this front will require further clinical studies and information. Strict case-definitions of long-COVID are still lacking, as is epidemiologic information on the groups at highest risk or the extent to which younger groups, including children and adolescents, suffer from this condition. Furthermore, the healthcare community does not have consensus guidelines that can be used to treat long-COVID patients. Clinical guidelines must also be developed as the number of long-COVID patients continues to rise. Also complicating the disease burden assessments of long-COVID is the unknown frequency of this condition following mild versus severe illness. The absence of long-COVID biomarkers is yet another issue and a barrier to sorting out whether long-COVID is the consequence of host inflammatory processes – such as microglial activation in the brain – or whether it reflects active viral persistence.

Without the information outlined above, it is difficult to design the optimal studies

needed to pin down or confirm an impact of vaccination on long-COVID. This is also a barrier to assessing the cost-effectiveness of long-COVID vaccinations. However, consideration of long-COVID may prove to be essential for approving future COVID-19 vaccines, including additional primary series or booster doses [17]. Ultimately, preventing COVID-19 hospitalizations and deaths may not be sufficient if the disease impact of long-COVID turns out to be substantial or results in life-long impairments and disabilities. Assembling a consensus panel or charging immunization technical advisory groups such as the CDC's Advisory Committee on Immunization Practices (ACIP) to make recommendations on this issue may represent a logical first step.

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Will the COVID-19 pandemic lead to a rebirth of research and education on vaccinations in pregnancy?

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VIEWPOINT

"Consistent, clear messaging from professional societies, regulatory and funding agencies, physicians, public health and community leaders, and pregnant women themselves ... will help change the culture of fear and misinformation surrounding research and pregnancy."

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Pregnant and lactating women are routinely excluded from clinical trials, including those of vaccines, despite being at increased risk from infectious diseases. The COVID-19 pandemic has brought this omission into the spotlight, with exclusion from clinical trials followed by low vaccination levels amongst pregnant women contributing to maternal and fetal deaths. We hope the pandemic will act as a wake-up call to implement longstanding recommendations to integrate pregnant and lactating women into clinical studies.

Over the past 2 years, we have learned of the morbidity of the SARS-CoV-2 virus among pregnant women. Increased risks for severe illness and subsequent obstetric morbidity and mortality among pregnant women, particularly those infected with the more transmissible Delta (B.1.617.2) variant, have been well documented [1]. We have also seen the toll that the pandemic has taken on pregnant women and obstetrician–gynecologists, in the anxiety over being exposed to the virus while receiving or providing necessary prenatal or obstetric care, and the adaptation and perseverance required to continue these necessary services [2].

When two mRNA vaccines against SARS-CoV-2 first became available in the United States, obstetrician-gynecologists had no data with which to advise patients on the safety or efficacy of these vaccines in pregnant patients. The absence of evidence was frustrating, but not surprising. Despite recommendations presented to Congress in 2018 by the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to integrate pregnant and lactating women into the clinical research agenda and remove regulatory barriers to their inclusion, the status quo remained [3]. Pregnant and lactating women were excluded from the earliest COVID-19 vaccine trials, and the consequences were far-reaching.

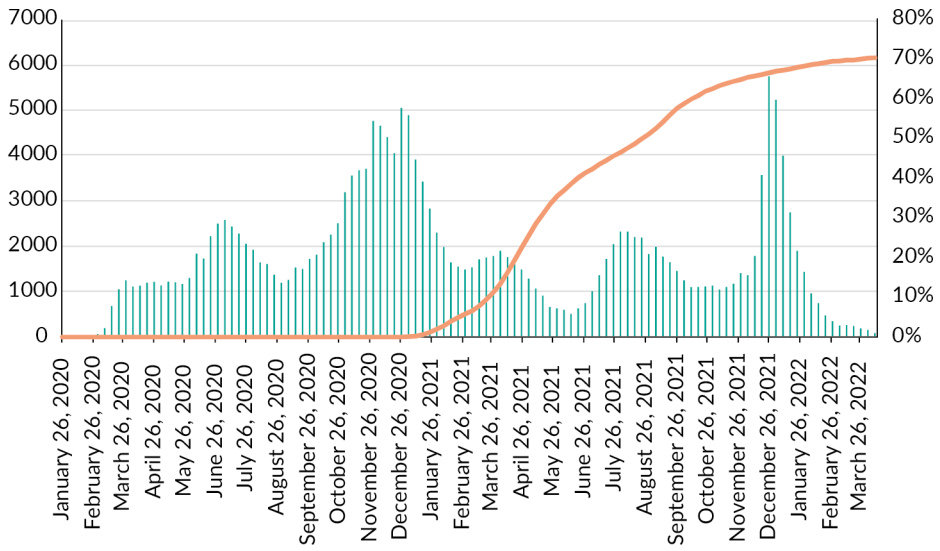
With public health messaging about COVID-19 vaccines evolving as surges came and went, seeds of confusion and doubt – as well as conspiracies – were sewn and grew like weeds, including amongst pregnant and lactating women [4]. Distrust in medicine among vulnerable and historically disadvantaged communities [5], as well as conspiracies spread by those in positions of power, presented challenges that have required nuanced approaches to address [6]. Vaccination rates began to increase in 2021, in part driven by those vaccinated prior to pregnancy, and in part due to the concerns related to COVID infection in pregnancy, especially related to severity of the infection with the Delta variant (Figure 1) [7]. Before we can expect a change in public perception, re-education on the basic principles and benefits of vaccination is needed, for both physicians and the general public.

As we enter the third year of the pandemic, obstetrician-gynecologists have an opportunity to re-emphasize prenatal discussions on the maternal and neonatal benefits of recommended vaccinations during pregnancy. Currently, influenza, tetanus–diphtheria–pertussis (Tdap), and COVID-19 immunizations are recommended specifically in pregnant women, for both maternal and neonatal protection [9]. Some vaccines (such as hepatitis B [10]) are now recommended for all adults, and others are recommended for adults with risk factors (such as pneumococcal vaccination for adults with diabetes or other chronic conditions [11]). Obstetrician-gynecologists and public health experts must take on the challenge of ensuring patients understand the benefits of vaccination – the health of our patients is worth the effort.

Moving forward, as we attempt to replace misinformation with truth grounded in science, we must also raise awareness among patients and their physicians about the importance of including pregnant and lactating women in observational studies and clinical trials of vaccines and therapeutics [12].

FIGURE 1

COVID cases and % vaccinated in pregnant women.



Data from [8].

Imperative to this effort is to proactively address ethical considerations and liability concerns for industry, as well as facilitate the implementation of feasible and uniform design standards which have already been proposed [13,14]. These include standardized collection of information on pregnancies through registries and rigorously designed cohort studies and clinical trials, increased safety monitoring for interventional studies, collection of cord blood at delivery, and collection of data on pregnancy outcomes, and infant outcomes up to a year of age [15].

Ideally, pharmacokinetic sampling of both maternal blood and breast milk to establish dosing information in pregnant and lactating women should be integrated into prenatal, delivery, and postpartum encounters. This would facilitate outreach to and enrollment of patients who become pregnant while participating in a trial, or who choose to participate in a study while pregnant or lactating. It is not lost on us as physicians that without such data, it is essentially an experiment with each dose, and a disservice to our patients. To this end, robust collaboration is needed between federal and state leaders, industry, academic institutions, local obstetrician-gynecologists, and the pregnant women they serve. Importantly, public trust must be earned (again) through ethical and patient-centered research, with politics left out of the process.

If we are to improve the health of mothers and babies, adherence to the principles of ethical research – respect for persons through informed consent, beneficence through risk–benefit balance, maintenance of confidentiality, and justice in equitable inclusion without exploitation – is the way forward. Advocacy and public support for the inclusion of pregnant and lactating patients in studies of vaccines and therapeutic agents will be needed. Consistent, clear messaging from professional societies, regulatory and funding agencies, physicians, public health and community leaders, and pregnant women themselves about the existence of rigorous safety and ethics standards will help change the culture of fear and misinformation surrounding research and pregnancy. When – not if – we face another pandemic infectious disease, obstetrician-gynecologists will then be better prepared to advise and protect our patients.

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VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

COMMENTARY

COVID-19 vaccine supply chain management: a LMIC perspective

Darin Zehrung

Delivering millions of doses of emergency vaccines – many requiring ultra-low-temperature storage and transport – in a pandemic is a challenge anywhere. But lower- and middle-income countries (LMICs) face additional challenges, and vaccination rates in many regions remain low. This article describes efforts by PATH's Medical Devices and Health Technologies program to help address COVID-19 vaccine supply chain challenges in LMICs.

On May 6, 2022, Charlotte Barker, Editor, *Vaccine Insights*, spoke to Darin Zehrung (Global Program Leader, Medical Devices and Health Technologies, PATH) about the group's work during the pandemic. This article has been written based on that interview.

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PATH's Medical Devices and Health Technologies Program works to support formulation development, packaging delivery technology, drug product presentation, and the logistics of vaccine supply and distribution for immunization programs in low- and middle-income countries (LMICs). With long-running projects on vaccine technologies and the cold chain, the MDHT Program was well-positioned to provide input into the COVID-19 pandemic response.

Early in the pandemic, we worked with the Bill and Melinda Gates Foundation (BMGF) and the Coalition for Epidemic Preparedness Innovations (CEPI) to map out the landscape for drug substance, drug product, packaging, and delivery technology in LMICs. Given the global nature of the vaccine production and

distribution supply chain, vaccine manufacturers and logistics companies were simultaneously working to secure access to needed components and materials to meet demand from both high-income countries (HICs) and LMICs, leading invariably to some diminished efficiencies in terms of global coordination. When the COVID-19 Vaccines Global Access (COVAX) Facility was established by Gavi, the Vaccine Alliance, CEPI, and WHO, alignment among global stakeholders greatly improved and we continued to support global COVID-19 vaccination efforts in a number of areas.

DELIVERY TECHNOLOGIES

Through BMGF funding and in cooperation with Gavi, United Nations Children's Fund (UNICEF), and the United States Agency for International Development (USAID), the team modeled the global syringe market for both auto-disable (AD) and re-use prevention (RUP) safety-engineered syringes utilized in LMIC immunization programs. This included engagement with industry to determine current production capacity and lead times, and how to increase capacity to meet projected global market needs in LMICs.

We also worked with the WHO to overcome a specific gap in the syringe market that was identified. The Pfizer-BioNTech vaccine is delivered in 0.3 ml doses, which is an atypical dose volume when compared to the standard dose volumes delivered in LMIC immunization programs. This vaccine also required reconstitution with diluent at the point of delivery. AD and RUP syringes are purchased by UN agencies and prequalified by WHO for use in immunization programs (routine or mass immunization) in LMICs to prevent re-use of syringes which will result in disease transmission. However, the standard volume for the AD syringes currently used in immunization programs is 0.5 ml, and 0.3 ml syringes were not previously WHO prequalified and available for UN agency procurement. Working in support of WHO, we helped to rapidly develop a performance qualification (PQ) specification for 0.3 ml auto-disable syringes and supported two manufacturers to achieve PQ.

The PATH team also worked with CEPI to evaluate designs for a multi-dose pouch technology, developed by MEDInstill and designed for mass vaccination, with a lower per-dose cold chain footprint than traditional vials. Our calculations estimated that the per-dose cold chain volume for the 200-dose pouch would be even lower than a 20-dose vial in terms of cold chain footprint (1.4 cm^3 vs 2.14 cm^3 per dose), and significantly less than a one or two-dose vial. This pouch technology holds 200 doses and has a connected multi-dose syringe to allow rapid administration. The PATH Living Labs human-centered design teams in Zambia and Kenya worked to provide user and stakeholder feedback on the design, which is now being transferred to the Institut Pasteur de Dakar to be scaled up, with a goal of delivering up to 300 million doses per year [1].

This is an important precedent-setting technology transfer in delivery and packaging innovation for vaccines in Africa. Over the years, there has been interest in building further capacity for vaccine manufacturing in the continent, which the pandemic has further catalyzed, culminating in a goal that 60% of the vaccines delivered in Africa will be manufactured in Africa by 2040 [2].

COLD CHAIN MODELING

PATH has a long history of cold chain modeling. When the pandemic hit, our forecast models used country-level data to calculate the existing cold chain space as well as needs for additional cold chain equipment (CCE) for emergency vaccines, even before some vaccine candidates for COVID-19 were known. These gap analyses helped donors understand the scale of need for different CCE strategies, with almost 200 scenarios in our model. Combining this with current

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procurement plans, we were able to model the outstanding global CCE gaps more precisely. This work has helped organizations like Gavi and UNICEF better prepare for requests from countries for CCE support. We have also been able to model CCE procured under pandemic response and allocate portions for routine immunization needs in the future.

With mRNA vaccines for COVID-19 requiring ultra-low temperatures (ULT), PATH supported organizations including BMGF, UNICEF Supply Division, Gavi, World Bank, COVAX, and CEPI with detailed ULT vaccines forecasts for the 92 countries eligible for COVID-19 vaccines via the COVAX Advance Market Commitment.

In the ULC arena, there were few facilities with existing equipment and those were almost entirely at national-level stores. The 2014–2016 Ebola outbreak and subsequent distribution of the Ervebo vaccine meant that ULT equipment was in place in some African nations, but in many cases, this equipment was no longer fully functional. ULT devices are more sensitive than traditional cold chain equipment, so additional generators and climate control equipment were included in the modeling to ensure protection of the ULT freezers and, ultimately, the vaccines.

Since our models have facility-level visibility, we were able to model scenarios for ULT CCE devices in terms of number of units, storage volume needs, as well as cost for LMICs. Once funding or vaccine allocation ceilings were applied, we were also able to help forecast outstanding gaps in need, so countries could look to other donors. For example, we were able to model national to regional, or national to district scenarios and the associated costs.

LESSONS LEARNED

The COVID-19 pandemic has emphasized the importance of vaccine developers being in close communication with global health stakeholders such as WHO, UNICEF, and Gavi, so that there are no surprises, as there was with the 0.3ml dose volume for the Pfizer vaccine. Vaccine manufacturers spend tremendous resources and many years conducting research into different formulation possibilities and getting through the preclinical stage into clinical studies; however, the consideration of final packaging and delivery format for optimal use in LMIC immunization programs is oftentimes considered late in the development process. Continued strengthening of the relationship between pharmaceutical developers and manufacturers and the global stakeholder community will help to address such gaps in the future.

LOOKING TO THE FUTURE

As the pandemic shifts to a different phase, we need to be ready for whatever the new normal turns out to be – be it for vaccine manufacturers, global stakeholders, or country-based immunization programs. If new variants of concern emerge and vaccine demand increases once more, we need to be ready. We also need to prepare for a future where the virus is endemic and seasonal vaccines are delivered globally, similar to influenza vaccines. This requires more work on the logistical side, including the cold chain and the role and fit of emerging delivery technologies such as microneedle patches when considered in complement with existing tools. Microneedle patches not only have the benefit of easy administration but also the potential for a formulation with enhanced thermostability, further reducing the impact on the cold chain.

Fortunately, the PATH MDHT program team was well-positioned to support the pandemic response, building upon our work over the past decades. The PATH team will continue to be at the ready, furthering our contribution to successful packaging, delivery, and uptake by immunization programs of future routine and pandemic vaccines. We hope that by our commitment to continuous improvement, we can ensure that the world will be ready for future challenges to come.

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VACCINEINSIGHTS

COVID-19: HOW IS THE PANDEMIC CHANGING THE VACCINES SPACE?

SPOTLIGHT

COMMENTARY

COVID-19 vaccine supply chain management: a US perspective

Michael Angelastro & Robert A Johnson

The COVID-19 pandemic has had a dramatic impact on vaccine industry supply chains. Reliance on just-in-time supply chains and limited capacity posed challenges for vaccine manufacturers as they rapidly and dramatically scaled-up production. Supply chain management and expansion are as important as vaccine development itself, and here we outline how the US Government has worked with multiple stakeholders to support supply chains and maximize 'shots in arms' – and what is needed to ensure we are better prepared for future outbreaks.

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VACCINE SUPPLY CHAIN & COVID-19

The dramatic impact of the COVID-19 pandemic on supply chains has been well documented, cutting across almost all industries, including vaccine manufacturing [1–3]. Many industrial manufacturing efforts, including the vaccine industry, not only rely on a 'just-in-time' supply chain but also have little idle excess manufacturing capacity (buildings, equipment, etc.) [4]. This business approach left vaccine manufacturers, like manufacturers of other COVID-19 countermeasures such as diagnostics and personal protective equipment (PPE), with the twin challenges of supply chain and capacity limitations while needing a dramatic increase

in production. Continued efforts throughout the COVID-19 response have improved the supply chain and manufacturing efforts for COVID-19 countermeasures. The large-scale COVID-19 vaccine production achieved in 2021 – estimated at greater than 11 billion doses, relative to the estimated 5 billion doses for all vaccines produced annually pre-COVID – underscores industry's success in managing and expanding the supply chain to support the pandemic response [5–7].

EARLY ACTIONS

Vaccine funders and developers understood from the start that supply chain management and expansion to produce, first, hundreds of millions and, eventually, billions of vaccine doses were as important as vaccine development itself. While the use of vaccine platform approaches greatly facilitated identification of key raw materials and other supplies, challenges were numerous, particularly for mRNA vaccines, which until that time had not been produced at a large scale [8,9]. The global biopharmaceutical reliance on customized, single-use technology, often sourced from just one or two manufacturers, was consistently the most challenging segment of the supply chain to manage.

While each vaccine developer company established and expanded its supply chain, the US Government (USG) had a central role in supply chain management within the United States throughout the response. This role included coordinated efforts not just to balance domestic COVID-19 vaccine production but also to support international COVID-19 vaccine production efforts and minimize the supply chain impact on production of other life-saving vaccines and therapeutics.

For almost two years, the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Health and Human Services (HHS)-Department of Defense (DOD) Joint Partnership, Operation Warp Speed (later the COVID-19 Countermeasure Acceleration Group) had a staff of over 30 individuals, including 'persons-in-plant' at key manufacturing facilities, working every day with hundreds of suppliers, distributors, developers, and manufacturers to coordinate the just-in-time production and supply of well over a thousand individual items. The Defense Production Act (DPA) authorities were utilized to prioritize key supplies and materials to support and prevent stoppage of COVID-19 vaccine production. The use of DPA was carefully managed, and priority ratings were removed from contracts as soon as sufficient supplies to support manufacturing were obtained. Part of managing the DPA activities included working with global partners to facilitate international COVID-19 vaccine production and avoid inventory shortfalls of other life-saving vaccines and therapies. This intensive focus on supply chain management allowed the rapid scale-up and continuous cGMP production of COVID-19 vaccines in less than a year – significantly better than the more than 5 years typically expected for manufacturing and scale-up of this size [10].

INDUSTRIAL BASE EXPANSION

Supply chain optimization of existing capacity was complemented with significant investments by the United States and other governments, vaccine developers, supply chain manufacturers, and others [11] in the expansion of capacity through the entire length of the supply chain for vaccine manufacturing, distribution, and administration [12]. Detailed knowledge of the supply chain was and remains critical for these capital investments to have a significant impact. Investments must focus on the goal of producing, delivering, and administering more vaccines. Otherwise, increasing capacity at one point in the supply chain can simply move the production chokepoint to a different step in the process without increasing actual vaccine production.

An example of the end-to-end requirement is the supply chain supporting final container fill/finish, distribution, and administration. While much attention was given early on to

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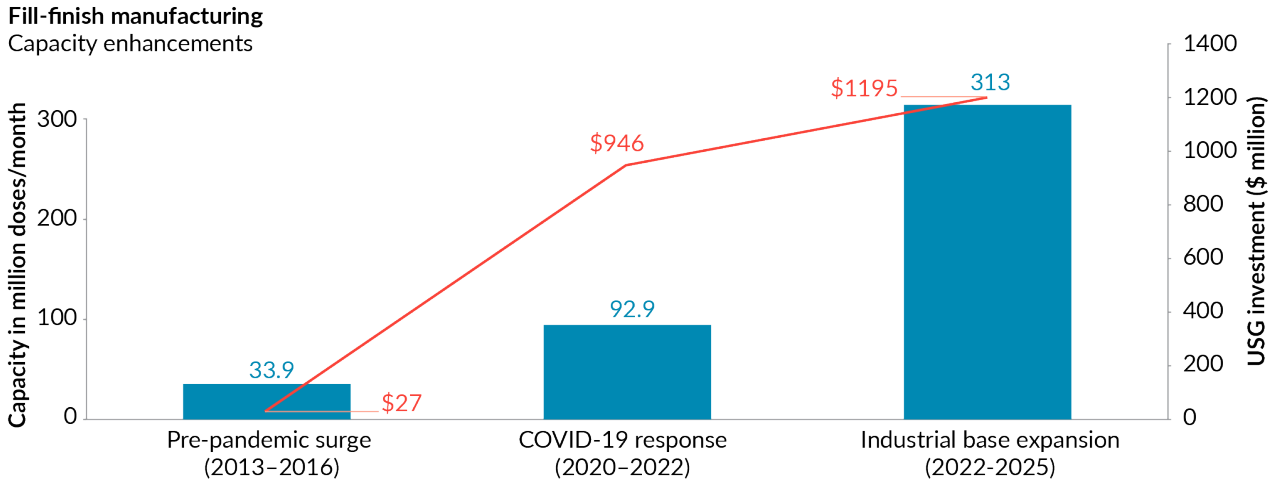
the shortage of fill/finish capacity, of equal importance were the many components required for filling, including vials, stoppers, caps, as well as upstream components, such as the specialized glass tubing needed to make the vials, the distribution capability, and administration supplies [8]. Increasing capacity at just one of these steps alone has little overall impact on 'shots in arms'; only by expanding all steps in the process could the goal of increasing vaccine administration rate be achieved. To address the requirement, BARDA made a series of capacity expansion investments in fill/finish capability (Figure 1), glass tubing and other components necessary to make vials (Figure 2), and needles and syringes (N/S) production capacity (Figure 3), particularly 1 mL low dead volume (LDV) N/S. The early BARDA investments in the LDV N/S proved particularly timely. As the LDV N/S became the only configuration that provided the needed flexibility to accurately administer vaccine in increments of 0.05mL as well as minimize wastage, the capacity expansion allowed supply to better match demand. Both attributes were critical to maximizing the number and timing of vaccine availability, an important lesson learned for future pandemic preparedness. When coupled with additional investments by the USG, vaccine developers, and others in a) distribution capacity and capability and b) pre-packaged kits containing ancillary supplies to administer vaccine, including N/S, these investments resulted in a dramatic increase in the ability to fill/finish, deliver, and administer vaccine.

Finally, a key component of the success of this and other BARDA-funded supply and capacity expansion efforts was the close collaboration between BARDA and several organizations within the DOD, including the Air Force, and the Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense, and Army Contracting Command (ACC). Early during the pandemic response, DOD entered into an agreement to support HHS contracting needs for the COVID-19 response. This was done in large part because of DOD's authorities, existing flexible funding mechanisms that could be immediately utilized to support the COVID-19 response, and expertise in industrial base capacity mobilization. As with OWS, the linking

FIGURE 1

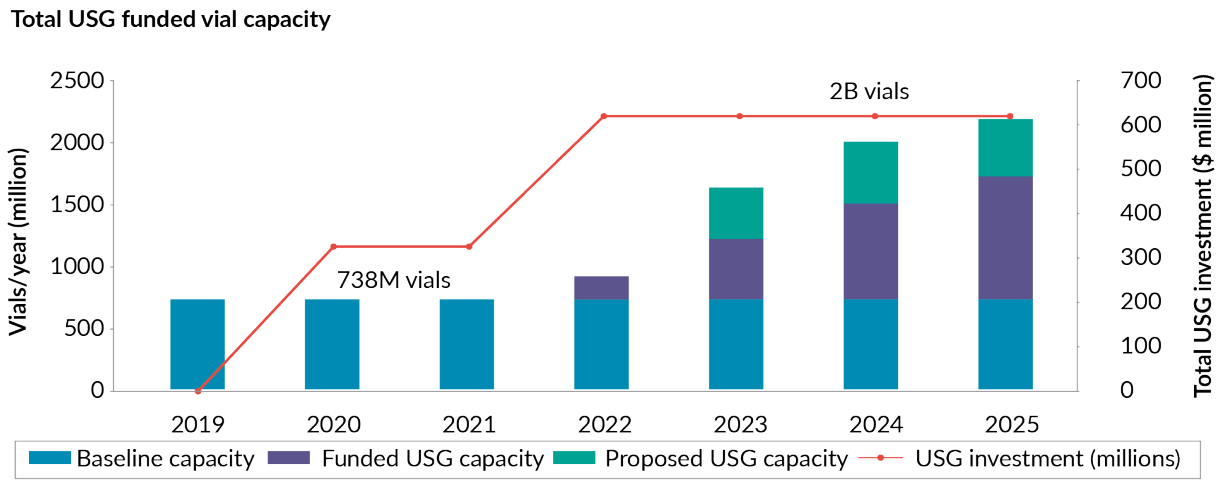
Comparison of investments in sterile injectable fill-finish capacity versus vaccine production capacity (historical data based on market research).



Compared to pre-pandemic surge (2013-2016, based on market research by BARDA) in fill-finish investment ($27M) that enabled production of 33.9M doses/month, investments during the COVID-19 response ($946M from 2020-2022) and anticipated future industrial base expansion investments ($1,195M from 2022-2025) have and will continue to increase production capacity by an order of magnitude (313M doses/month).

FIGURE 2

USG domestic annual vial capacity and total USG investment.



While baseline capacity (based on market research by BARDA) remains at 738M vials annually (blue bars), funded USG domestic capacity (purple bars) and proposed USG capacity (green bars) – made possible by sustained shared investment (red line) – are expected to increase vial production capacity through 2025, with total annual production capacity surpassing 2B vials of various formats and sizes.

of expertise across both Departments accelerated the overall contracting process, resulting in more awards made earlier, which facilitated alleviating the many supply constraints.

CURRENT STATUS

Today, the supply chain still has points of significant concern, and stocks of key supplies remain low, but global investments in almost all aspects of the vaccine manufacturing supply chain have made great inroads and alleviated many of the issues that impeded vaccine production early during the response [11,13,14]. However, vigilance is key as manufacturers prepare for the possible need for a strain change, or a multi-valent COVID-19 vaccine [15,16], either of which could result in a sharp uptick in manufacturing, fill/finish, and distribution/administration demand.

LOOKING TO THE FUTURE

Improved pandemic preparedness requires capacity that will exceed typical vaccine demand. Sustaining this manufacturing capacity and equipment comes with a significant cost – buildings, equipment, experienced staff, and corresponding supply chain. Already in other fields, such as PPE and diagnostics, capacity built to address COVID-19-driven demand has been shuttered and, in most cases, cannot be rapidly restarted. In some situations, the infrastructure is lost (i.e., facility/equipment is re-purposed). Even if the facility and equipment are still in place, re-start times will be lengthy as staffing, raw materials, and supply needs will all have to be addressed to re-establish the capability. If we are to avoid repeating past challenges, pandemic response capacity requirements must be defined, and sustainable mechanisms to fund the capability must be identified.

This challenge presents opportunities to address global challenges to routine vaccines. For example, through public-private partnerships, the pandemic response capacity could manufacture vaccines for domestic or global public health that would otherwise not be commercially viable. Careful inventory management would be critical to avoid a shortage of vaccines if manufacturing had to be switched to produce a pandemic vaccine. The twin challenges

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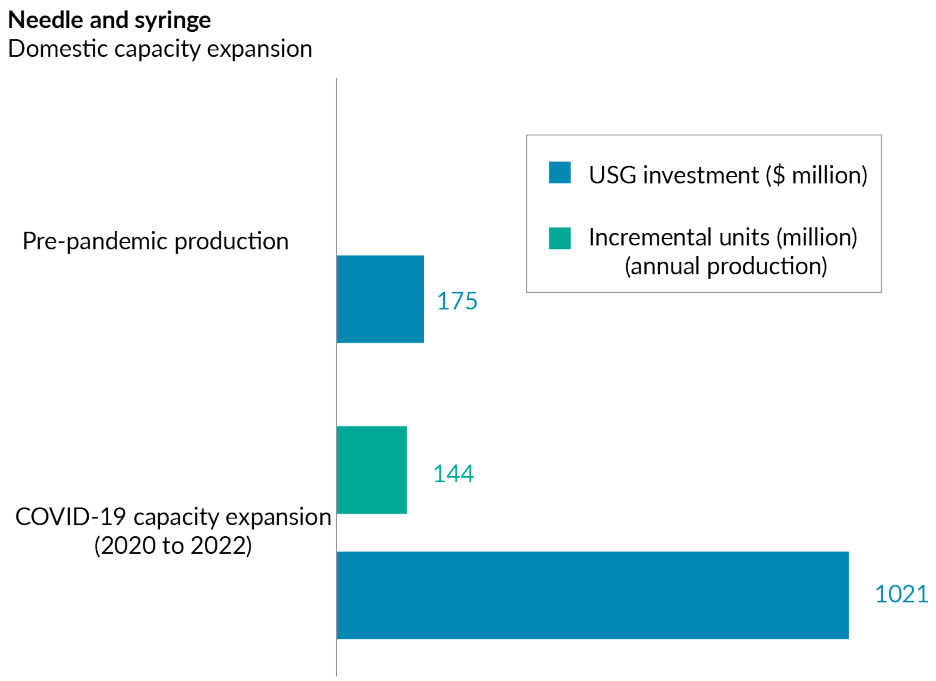
FIGURE 3

Needle and syringe production before and after the COVID-19 pandemic.



A comparison of pre-pandemic needle and syringe production (175M incremental units annually based on market research by BARDA) against production during the COVID-19 capacity expansion period (2020-2022) (1,021M incremental units annually) that was bolstered by recent USG investment ($144M) highlights the importance of continued USG investment in domestic capacity expansion for needles and syringes.

of few suppliers and lack of standardization of equipment and supplies, particularly disposable supplies, have no easy solution given the complexity of biological manufacturing and challenges with any change to the manufacturing process. Increased inventory of raw materials will be an important risk mitigation step until other solutions are identified.

Finally, we must continue to be forward-leaning, looking beyond the current supply chain. As vaccine platforms and delivery approaches evolve, so too will the supply chain requirements. We must monitor this evolution and ensure that the corresponding supply chain is adequate. Transformative vaccine technologies will only help blunt the next pandemic if the capability exists to rapidly produce, distribute, and administer the vaccine in large quantities.

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