

IAVI Report

A microscopic image of HIV virus particles, showing several spherical particles with a textured surface, colored in shades of red, orange, and blue, set against a dark background.

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**Applying decades of
experience battling
HIV to COVID-19**

FROM THE EDITOR

When Bill Gates delivered a TED talk in 2015, he warned that the world was not ready for the next pandemic. Many others have issued similar warnings, some on the [pages of this publication](#). *Vanity Fair* recently referred to Gates, Mike Osterholm, and Seth Berkley (see page 17), among others, as “[Coronavirus Cassandras](#),” and asked why the world didn’t heed their warnings.

But while it certainly does seem that the world was unprepared from a public health perspective, scientists were ready. Within days—hours even—scientists around the world shifted their focus to combatting COVID-19. The genetic sequence of the new coronavirus was published within two weeks of when the first cases emerged, setting off a race to develop vaccines and therapies. And now, seven months later, there are 139 vaccine candidates in preclinical development and 26 already in clinical trials. There are also dozens of monoclonal antibodies to SARS-CoV-2 in development for both treatment and prevention, as well as numerous other diagnostics and novel and re-purposed therapeutics. The scientific understanding of this new virus is unfolding at an unprecedented pace.

Many of the scientists contributing to these efforts have honed the technologies and expertise being applied to COVID-19 in their decades-long quest to thwart HIV. In

this issue, we focus on some of the critical contributions that HIV researchers are making in both vaccine and monoclonal antibody development (see page 4 and page 12). We also talk with Seth Berkley, chief executive officer of Gavi, the Vaccine Alliance, about their efforts to ensure equitable global access to eventual COVID-19 vaccines (see page 17), as well as investigate how many experts are urging the world to prepare now for the next pandemic, even as this one continues to unfold (see page 22).

I recognize that there is no shortage of reading material, scientific or otherwise, on COVID-19. But my hope is that this issue emphasizes how the impressively rapid scientific response to this novel pathogen was facilitated by the investment and innovation in HIV and other viruses that remain global public health burdens. I also hope it makes the case for continuing basic research and vaccine development efforts so we can win the battle against all microbes. To quote a blog post by Max Roser of the University of Oxford and founder and director of [Our World in Data](#), “our best hope is science.”

We all hope that this collective scientific effort will bring this pandemic, which has now taken the lives of nearly 700,000 people, to an end as quickly and definitively as possible. If science is our best hope, we are in good hands.

—Kristen Jill Kresge



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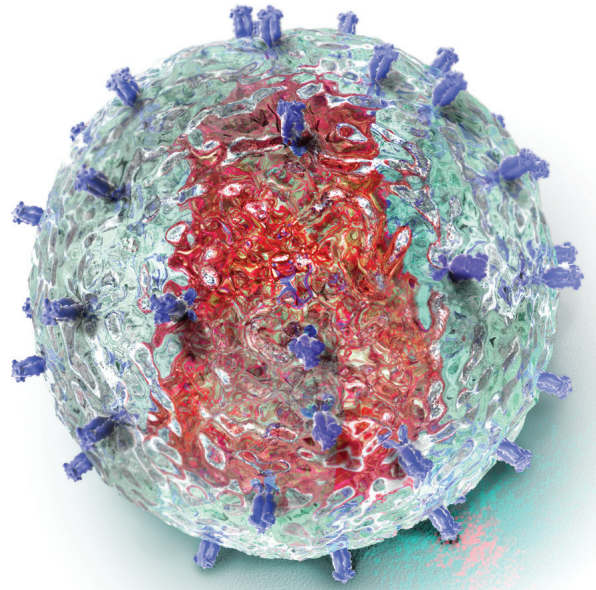
IN THIS ISSUE

4 The race is on
Scientists are applying decades of HIV research experience to the development of SARS-CoV-2 vaccines in the race to end the pandemic.

12 Monoclonal antibodies and their potential role in combatting COVID-19
Numerous monoclonal antibodies are already in development for both treatment and prevention. There are many unanswered questions, but, if they work, antibodies may play a role in ending this pandemic and in responding to future viral outbreaks.

17 Finding a global solution for a global problem
An interview with Seth Berkley, chief executive officer of Gavi, the Vaccine Alliance.

22 In the midst of a pandemic and preparing for the next
SARS-CoV-2 is the first Disease X. There will certainly be others. Will the world be better prepared for the next one?



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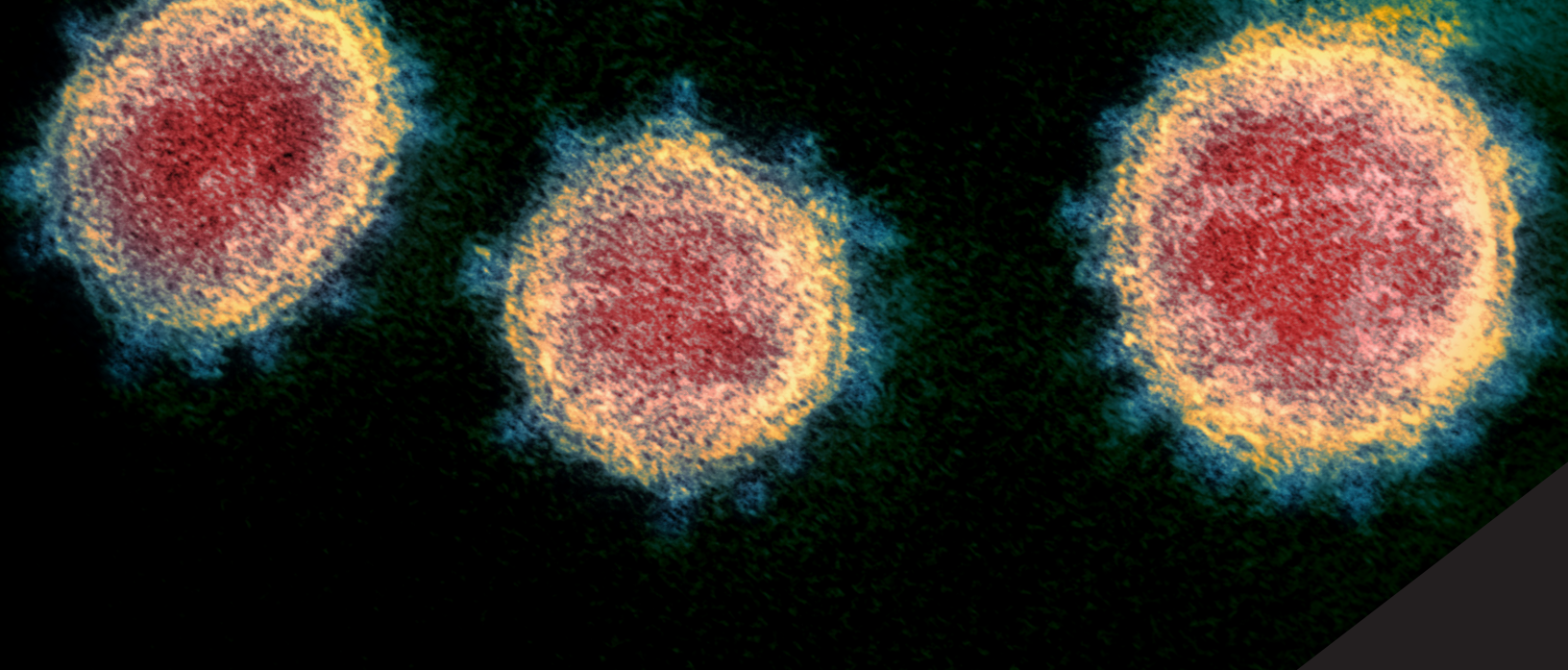
ON THE COVER

Novel Coronavirus SARS-CoV-2. This transmission electron microscope image shows SARS-CoV-2—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient in the U.S. Virus particles are shown emerging from the surface of cells cultured in the lab. The spikes on the outer edge of the virus particles give coronaviruses their name, crown-like. Image captured and colorized at NIAID's Rocky Mountain Laboratories in Hamilton, Montana. Credit: NIAID

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THE RACE IS ON

Scientists are applying decades of HIV research experience to the development of SARS-CoV-2 vaccines in the race to end the pandemic.

By Michael Dumiak

The astonishing and frightful course of the COVID-19 pandemic that has so far killed nearly 700,000 people and infected 18 million changes daily. What has not changed is the pace of the response to this new virus.

A frantic race is on to develop vaccines and therapies against SARS-CoV-2, drawing heavily on experience with other pathogens. Much of the laboratory expertise and infrastructure supporting the development, testing, and evaluation of COVID-19 vaccine candidates—as well as understanding the virus and its pathogenesis—was developed in the long struggle against HIV/AIDS and the quest to develop an HIV vaccine, alongside influenza and, more recently, Ebola and Zika. But as in the early days of HIV, there is still an enormous amount to learn.

Dan Barouch started work on SARS-CoV-2 even before the virus had a name. On a mild weekend in January, his group held its annual Barouch Lab Retreat, at which his 60-member research lab at Harvard Medical School's Beth Israel Deaconess Medical Center and Ragon Institute of Massachusetts General Hospital, MIT, and Harvard reviews the year's previous work and sets goals for the next. They talked that Friday afternoon about the concerning cluster of pneumonias being reported in Hubei Province, China, particularly in the large city

of Wuhan, where official figures at the time reported 41 cases and one death—though Wuhan officials later conceded to these figures being under-reported. Already in the first week of January, Barouch and his team feared the outbreak could get far worse. They knew the cause was a coronavirus, but its genome had not yet been reported.

“After we'd all gone home, the sequence was posted and we started work on it immediately,” Barouch recalls. Yong-Zhen Zhang of Shanghai's Fudan University uploaded the sequence accession MN908947 from the Wuhan outbreak to GenBank on January 10. It drew immediate attention from scientists around the world. That evening Barouch had key researchers in his group start analyzing the sequence. “We worked through the weekend on developing sequences,” Barouch says. “On Monday we started making vaccine constructs.”

Other scientists throughout the HIV field also turned their attention to SARS-CoV-2, as did their colleagues across the infectious disease spectrum. With decades of expertise, researchers in the HIV field were particularly well-placed to contribute. Six months later, even as the pandemic still has the world in its grip, scientific research on the new pathogen continues at a jaw-dropping pace. There are now more than 160 vaccine candidates in

development and dozens of neutralizing antibodies targeting the virus under consideration for potential treatments or preventives (see page 12).

There are also numerous efforts to understand how this virus can go virtually unnoticed in some people and cause severe disease or even death in many others. “What’s puzzled or disturbed me the most,” the National Institute of Allergy and Infectious Diseases’ director, Anthony Fauci, said recently, “is that I have never seen a virus in which the same pathogen—with little change—ranges from no symptoms in up to 40 percent of individuals, mild illness in others requiring virtually no care, with others going to bed at home for weeks, and some requiring hospitalization, oxygen, intubation, and a variety of other interventions, and in fact causes death in a substantial proportion of those at risk.” The case fatality rate is estimated at around 2.3 percent based on more than 72,000 infections reported by the Chinese Center for Disease Control and Prevention. But given all the variables, it is difficult to put a precise number on how lethal the disease is (*Nature* 582, 467, 2020).

Fauci was addressing a two-day virtual scientific meeting dedicated to COVID-19 in mid-July as part of the International AIDS Society’s (IAS) biennial conference. His long career in infectious diseases stretches back to the late 1960s and is indelibly marked by his work on HIV/AIDS. Now his role in communicating about and in helping coordinate the U.S. response to the COVID-19 pandemic has made him a household name. IAS president Anton Pozniak said it is no surprise that those on the frontlines of the HIV response—with four decades of experience fighting a pandemic—are able to draw on their skills to speed the development of vaccines and antibodies against this novel virus. It’s because of this experience that IAS decided to host the virtual COVID conference.

This isn’t the first time HIV researchers have turned to battling a coronavirus. When the first SARS outbreak sparked 18 years ago, some HIV researchers trained their efforts on combatting this novel pathogen.

David Ho of Rockefeller University, a driving force behind the introduction of protease inhibitors and combination antiretroviral therapies that are the hallmark of today’s successful HIV treatment, was one of them. Ho consulted with then-Health Minister Zhang Wenkang of China when the viral gene sequence of SARS-CoV-1 was posted, months after

the first case reports, and got to work on it. “I realized that we have a much better chance of fighting this virus than we do HIV, especially in terms of vaccine development. But we didn’t have samples, we didn’t have virus or even a proper facility. I was driving to work one day and heard on the radio that the sequence was posted. We looked at the sequence that same day and realized that now we could tackle the envelope of the protein of this virus, and from that we could branch off into therapeutics and vaccine,” Ho told *TREAT Asia Report* in June 2003. “Based on animal coronavirus work, we know a vaccine is possible. It will be principally based on neutralizing antibodies and I already knew from colleagues in Hong Kong that patients who recovered developed neutralizing antibodies. So we made the synthetic gene and we’re moving ahead with the vaccine work now.”

Sounds familiar. Yet the would-be SARS-CoV-1 vaccine never materialized. In large part this was because the outbreak died out, leaving no possibility for the extensive trials needed for testing potential vaccines, and then funding and therefore interest also drifted away, directed to other priorities.

Anne de Groot, chief executive and science officer of the biotech company EpiVax, published a commentary in mid-2003 under the banner “How the SARS vaccine effort can learn from HIV—speeding towards the future, learning from the past,” (*Vaccine* 21, 4095, 2003). As leader of the TB/HIV research laboratory at Brown University at the time, she outlined lessons learned from HIV vaccine development and called for SARS-specific reagents to be collected and shared as part of an effort to develop a vaccine, or at least viable candidates.

Nearly 20 years later, de Groot once again sees hard-won HIV expertise as relevant to SARS-CoV-2. “During SARS-1 people still questioned the validity of computational vaccinology. We’re in a different decade. People recognize the value; we have 10 vaccine collaborations now with different companies wanting to access our tools to rapidly develop a vaccine. I don’t have to advocate for that anymore.”

But even armed with advanced technologies researchers are challenged by the basic and devilish questions posed by SARS-CoV-2. “This is an RNA virus, and we’ve learned so many times before that we’ve failed to address the actual correlates of immunity,” de Groot says. “The correlates for RNA viruses—what are they?”

Why SARS-CoV-2 spread so far

SARS-CoV-2 is the third novel coronavirus to spread among humans over the last two decades. In late 2002, SARS-CoV-1 caused an outbreak that started in the city of Foshan, China, near Hong Kong. Over eight months, SARS-CoV-1 killed 774 people, infected 8,000, and spread to 29 countries. Ten years later Saudi Arabia documented the first known case of infection with Middle East Respiratory Syndrome (MERS) coronavirus, with further outbreaks emerging in South Korea in 2015, and again in Saudi Arabia in 2018.

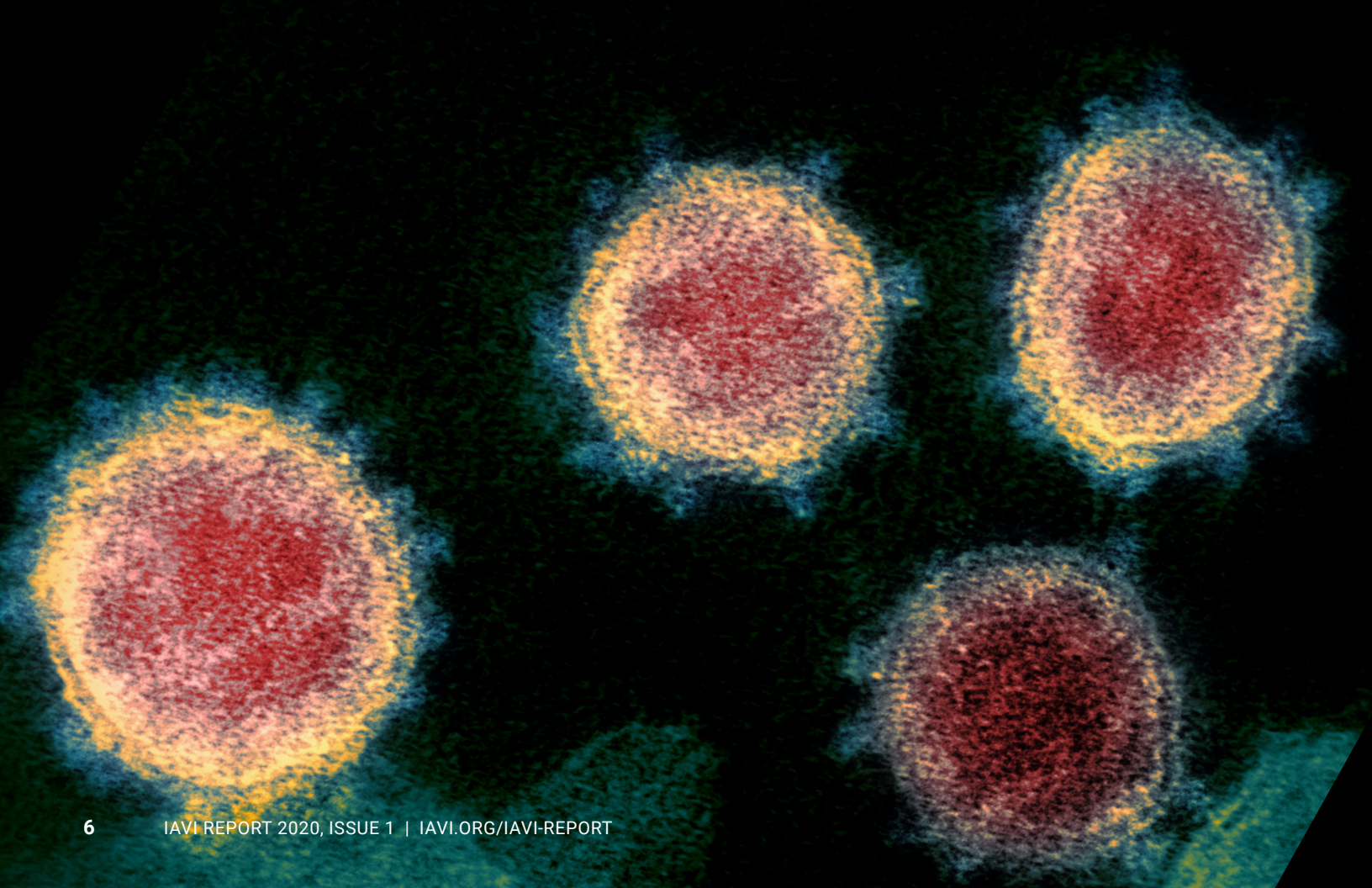
Now there is SARS-CoV-2, a cousin of SARS-CoV-1, with some important differences. As with all coronaviruses,

CoV-2 has an unusually large genome for an RNA virus. This appears to allow the virus to adapt quickly to new hosts and infect and replicate in more tissue types. Coronavirus expert Eric Snijder at Leiden University figures its large genome may also allow the virus to replicate in host cells more easily.

SARS-CoV-2, unlike many RNA viruses, also carries an enzyme that serves a proofreading function, moderating or correcting the replication errors—the mutations—that viruses make while reproducing. While rapid mutation can confer advantages to viruses in eluding immune defenses (notably so in the case of HIV, a retrovirus) or by making a virus more

transmissible or virulent, rapid mutation in a virus more often leads it to an evolutionary dead end: an ineffective collection of mistakes. Unfortunately, proofreading probably keeps CoV-2 from winding up there.

As with CoV-1, CoV-2 codes for its structure through the last third of its genome, with four conserved proteins as a result: Spike (S), Membrane (M), Envelope (E), and the virus Nucleocapsid (N). But one essential difference between the two cousins is that CoV-2 proved to be less lethal than its predecessor. As a result, CoV-2, while still deadly, is spreading much further than the first, which burned itself out in a little over a year. ■



Neutralizing antibody responses directed to the receptor binding domain (RBD) of the Spike protein (see image below) appear to develop at higher levels in individuals with more severe disease. Precisely what amount of antibody is needed to protect against infection, though, is among many unknowns. Researchers are also attempting to determine what role T-cell responses may play in immunity, and whether T-cell responses to SARS-CoV-1 that seem to persist for long periods may impact susceptibility to SARS-CoV-2 infection (*Nature* <https://doi.org/10.1038/s41586-020-2550-z> (2020)).

Meanwhile, early data is just starting to emerge for some of the vaccine candidates that entered clinical trials with record speed in the weeks after the pandemic began. And while many of the candidates appear to induce neutralizing antibodies, it's too soon to tell whether these levels of antibodies will be sufficient to protect against infection: only Phase III efficacy trials, some of which are already underway, can answer that question. Durability of the antibody responses following natural infection and vaccination is also an open question, one that researchers can only answer with time. Although it may feel like this pandemic has been with us for quite a while, it has only been seven months.

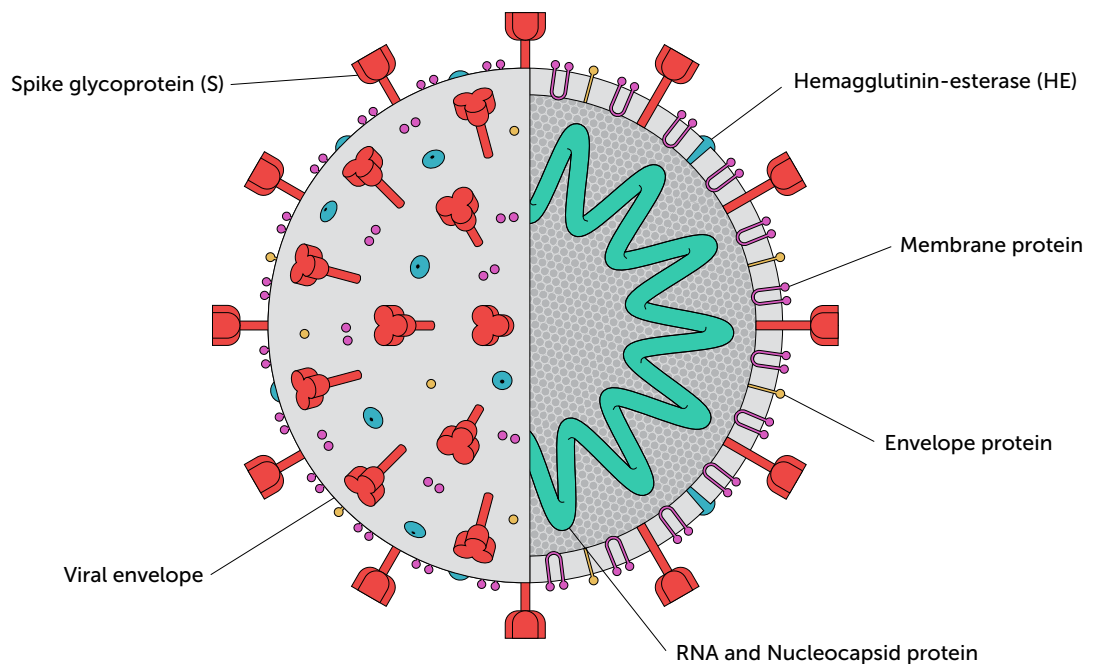
A critical set of tools for answering many of these questions are the assays that measure and characterize experimental data. Some of the most important assays gauge neutralizing antibody responses to SARS-CoV-2—and key protocols for these assays are being developed and rigorously validated in HIV researcher David Montefiori's lab at the Human Vaccines Institute at Duke University. This kind of formal validation documents the reliability of the methods and data produced and could speed regulatory approval for a future vaccine.

Like Barouch, Montefiori watched with alarm as the initial outbreak spread in waves around the world. He was hoping that other labs would do what his does for HIV, only for

CoV-2. But as lockdown clamped in March, he saw stringent clinical assay validation was not happening at the pace or scale needed to take on the job for the drug and vaccine clinical trials that would surely come.

So Montefiori began work on a SARS-CoV-2 neutralization assay, a cell-based diagnostic that shows exactly how potent an antibody is in interfering with or shutting down a virus. “We struggled with it for a while, like everybody else,” he says. He got input from Barouch, for example, on how the Harvard labs were working with their neutralization assays. Working with the U.S. National Institutes of Health's (NIH) Vaccine Research Center, the Duke lab received plasmids that express the Spike protein for the CoV-2 virus that emerged in Wuhan, optimized to improve gene expression and transcription.

The coronavirus Spike is the primary target for neutralizing antibodies: it is the crown-like profusion on the surface of the virus, which it uses to bind its receptor and enter host cells. While there is research suggesting more complete strategies for targeting CoV-2's M and N proteins could be useful (*Cell* 181, 1489, 2020), the neutralizing antibodies that have been identified from infected individuals primarily target the RBD region of the viral Spike. Accordingly, most of the vaccine candidates in development that do not contain whole viruses are based on the Spike protein.



Regardless of where they bind to Spike, Montefiori's assay measures how well neutralizing antibodies block infection of cells.

Montefiori also obtained human tissue cell lines transfected with the enzyme ACE2, the receptor found on the surface of many types of organ and tissue cells that CoV-2 Spike uses to infect human cells. Huihui Mou and Mike Farzan, infectious disease specialists at Scripps Research in Florida who also work on HIV, observed that ACE2 was involved in viral entry during the first SARS outbreak in 2002 and have been working with the cells ever since. Farzan sent cells to Duke.

Montefiori maintains an online library full of protocols, decades in the making, that are the overarching guide for HIV neutralization assays: The Standardized Assessments of Neutralizing Antibodies for HIV/AIDS Vaccine Development. Now he wants to see this kind of library established for CoV-2 assays. But instead of taking years to do this, he's hoping to accomplish it in a matter of months. "We're using our HIV assay program as a model," he says.

Establishing these libraries for SARS-CoV-2 will require identifying assays that have a high likelihood of predicting the efficacy of neutralizing antibodies in the serum of infected people and in volunteers in vaccine trials. This will be vital, given the Duke labs will run the neutralizing assay programs for Phase III trials of COVID-19 vaccines that are being prioritized by U.S. government-supported research efforts.

HIV clinical trial networks are also now being used for SARS-CoV-2 vaccine research. The U.S. government's Operation Warp Speed is placing billions of dollars in federal resources into developing COVID-19 countermeasures. It has made the Fred Hutchinson Cancer Research Center—and the large network of clinical trial sites that it administers with the NIH through the HIV Vaccine Trials Network (HVTN)—a locus for SARS-CoV-2 vaccine testing. This is part of what Larry Corey, former director the Fred Hutchinson Cancer Research Center and current codirector of the HVTN, Fauci, and others outlined in their "strategic approach" to COVID-19 vaccine R&D published at the end of May (*Science* 368, 948, 2020). By early June, Corey and Fauci were discussing how to mobilize multiple 30,000-volunteer clinical trials and operate them

simultaneously. The Fred Hutchinson Center is now the operations hub for the U.S. federal COVID vaccine trials program.

The HVTN extends over 46 sites within the U.S.; the Caribbean nations of Jamaica, Haiti, the Dominican Republic, and Trinidad and Tobago; Peru; Brazil; Switzerland; and in the sub-Saharan African countries of Malawi, Mozambique, South Africa, Tanzania, Zambia, and Zimbabwe. The network is directed by NIAID and funded through the NIH and the Bill & Melinda Gates Foundation. Tapping into this and the other clinical trials networks, Corey says, brings global reach across both hemispheres and a community for whom outreach to all different kinds of populations is second nature.

South Africa is a case in point. Working between home and a lab under half-lockdown in Johannesburg, Penny Moore, a virologist and associate professor at the National Institute for Communicable Diseases and University of the Witwatersrand, is bracing for a rise in local SARS-CoV-2 rates. "Cape Town was the area of greatest concern. Now it's very much Johannesburg and its surrounding area," she says. "I think we're about to get the brunt of it."

By now she has adapted to running a lab under trying conditions. Moore works on lineage and evolution of broadly neutralizing HIV antibodies and on tailoring vaccine immunogens. Her lab is working in shifts structured to allow for greater social distancing; people come in at odd hours and bioinformatic analysis and computational biology is done at home. Since March, Moore's lab has been applying its expertise to CoV-2. The same technologies used to study antibody responses to HIV are now being used to study the overall humoral immune response to SARS-CoV-2, including identifying the viral epitopes that are targeted by protective antibodies. She is working on both vaccine-related research and also on potential passive immunization with neutralizing antibodies.

Moore is also working closely with Montefiori's group on aligning the CoV-2 assay protocols. She says the widespread collaboration among labs around the world working on HIV, particularly in regions of the world that are hardest hit by the virus, has allowed for the creation of networks that can help speed things along. "For many years we've tried so hard to make sure that the things we measure can be done in multiple laboratories across the world," she says. "We very much

walked into the CoV-2 pandemic knowing how important that is. That's led to an advantage we would not have had without the HIV networks.”

It is still the early days of the pandemic in many ways, yet there are already 26 vaccine candidates in clinical trials, with another 139 under preclinical study—as well as a growing set of monoclonal antibodies being developed for therapeutic or prophylactic use. Early trial results for CoV-2 candidates are starting to trickle in and a handful of candidates are already being tested in Phase III efficacy studies (*Lancet*; *NEJM*; *medRxiv*).

Several vaccine strategies are being used by scientists around the world, including replicating and nonreplicating viral vectors, messenger RNA (mRNA) and DNA-based designs, as well as recombinant proteins (see page 10). Each has their pros and cons: nucleic-acid based vaccines, for example, are faster to develop and make than viral vector or protein-based vaccines, but there are no licensed vaccines using this approach. Protein vaccines are considered a more tried and true approach but are initially slower to develop.

Corey and others say that in all likelihood stopping the pandemic is going to require more than one vaccine. He and other public health experts such as the University of North Carolina's Ralph Baric, a longtime coronavirus researcher, point out that the threshold for reaching 70 percent herd immunity—considered by some to be what is needed to keep the spread of CoV-2 in check—means vaccinating between 4.4 billion and 5 billion people. Not only could that require more than one vaccine, the vaccines and other preventives, including monoclonal antibodies, will need to be applied strategically to have the biggest impact in the shortest time.

All of the vaccine platforms in development for COVID are also being explored in HIV research (see *Coding for Protection, IAVI Report, Vol. 22, No. 3, 2018*; *Proven against Ebola, a vector shows its broader potential, IAVI Report, Vol. 23, No. 2, 2019*). “There was no way we could have moved so swiftly for COVID-19 vaccine development if it weren't for our HIV work. All the platforms, all the systems have been put in place for HIV,” Barouch says.

Barouch helped develop an HIV vaccine candidate with Janssen Vaccines & Prevention, part of the

Janssen Pharmaceutical Companies of Johnson & Johnson, that is now being tested in a Phase II and a Phase III trial (see *Taking the next step with the mosaic HIV vaccine candidate, IAVI Report, Vol. 23, No. 2, 2019*). The vaccine employs an adenovirus serotype 26 (Ad26) viral vector—the same one Barouch and his colleagues have used for experimental vaccines against Zika and for Janssen's Ebola vaccine, which now looks set to be approved by the European Union and pre-qualified by the World Health Organization.

Now the U.S. Biomedical Advanced Research and Development Authority (BARDA) and Johnson & Johnson are collaborating to develop an Ad26 viral-vector-based COVID-19 vaccine and have already pledged to supply a billion doses of it for global distribution on a nonprofit basis. The vaccine candidate went into human trials in mid-July in Belgium and in the U.S., with a large-scale, 30,000-volunteer Phase III efficacy study expected to launch in September.

A recent study from Barouch and colleagues provides preclinical evidence for pursuing this approach (*Nature* <https://doi.org/10.1038/s41586-020-2607-z> (2020)). In this study, researchers evaluated seven different Ad26-vec-tored vaccine candidates encoding the CoV-2 Spike protein in non-human primates. Each of the candidates elicited neutralizing antibody responses and provided either complete or near-complete protection against CoV-2 infection with a single dose. The leading candidate employs the full-length Spike with mutations that make the immunogen more stable, according to Barouch.

A single-dose vaccine against COVID-19 would obviously be preferable to multi-dose formulations given the huge numbers of people who need to be vaccinated. But two-dose regimens may elicit higher antibody levels.

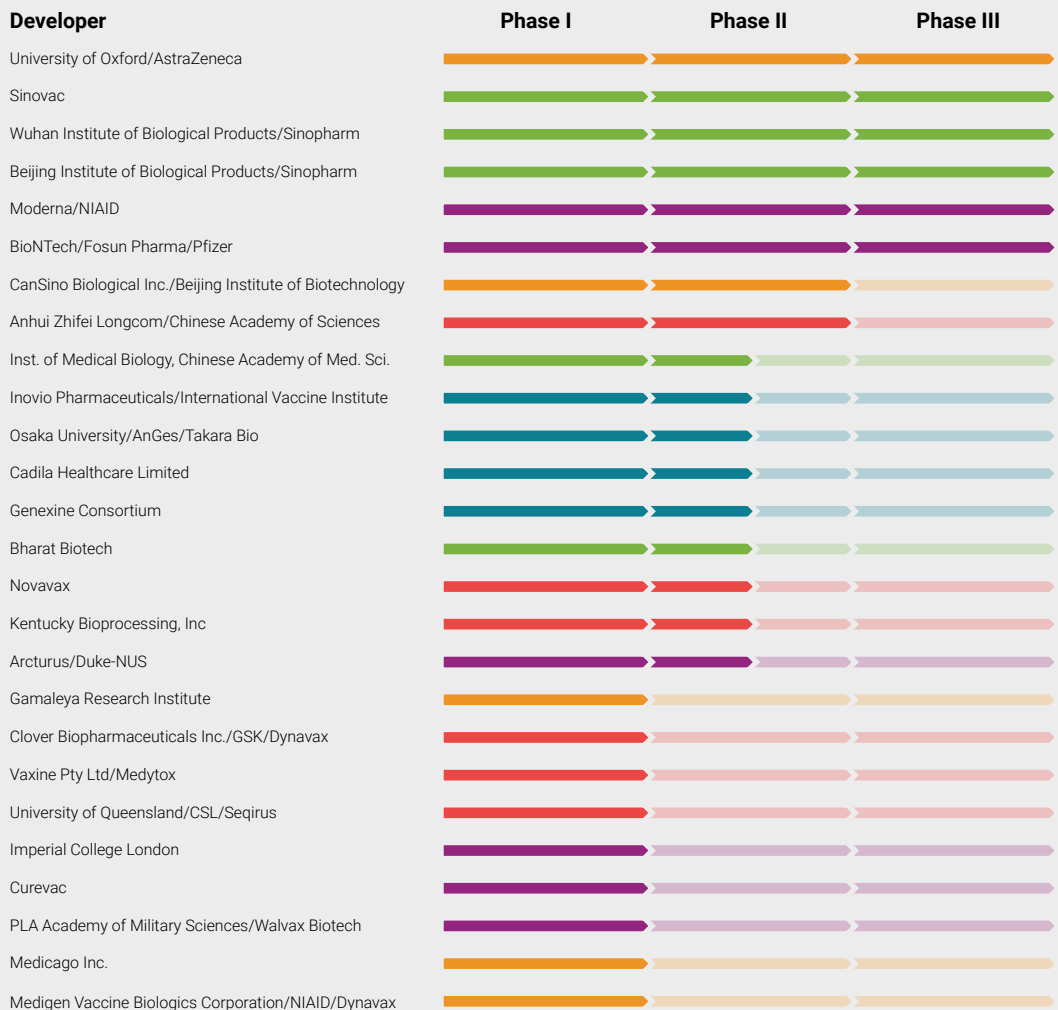
In a prior study, Barouch showed that CoV-2 infection in non-human primates induces immune responses that protect against re-infection (*Science* DOI:10.1126/science.abc4776). The jury is still out on whether the same is true in humans. Another important question is how durable these immune responses are. Studies indicate that serum antibody levels in individuals infected with SARS-CoV-2 diminish rapidly (<https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930196-1>; <https://>

165 COVID-19 vaccines are currently in development

These fall into 9 different product categories:

- Non-replicating viral vector
- Protein subunit
- Live-attenuated virus
- Replicating viral vector
- RNA
- Virus-like particle
- Inactivated virus
- DNA

26 Vaccines are in clinical testing



139 Vaccines are in preclinical development

Source: WHO Draft landscape of COVID-19 candidate vaccines, 28 July 2020

www.nejm.org/doi/pdf/10.1056/NEJMc2025179), although whether immune memory is enduring is not yet understood (*Science* DOI:10.1126/science.abc6284 (2020)).

Non-human primates don't get very sick from SARS-CoV-2 and therefore may not be the most reliable animal model for human infection. Barouch is also planning to evaluate other animal models, such as Syrian hamsters, which do develop severe COVID-19. Finding the one best suited for SARS-CoV-2 is still a matter of inquiry. Every virus is unique, Barouch says, but so far, the immune responses to CoV-2 appear to be somewhat predictable and he thinks that monkey studies can show that neutralizing antibodies are a good biomarker for vaccines and correlate with protection.

In addition to Ad26, other vaccine platforms in development for HIV are also being applied to COVID. mRNA approaches—the platform pursued against CoV-2 by Moderna, BioNTech, and Germany's CureVac, among others—gained currency in recent years in efforts to develop vaccines and therapies against HIV, prostate and lung cancers, and Zika. A partnership between Merck and IAVI is developing experimental vaccine candidates to CoV-2 based on a recombinant vesicular stomatitis virus (rVSV) vector, variations of which are also in development for HIV, Lassa virus, and Marburg virus. Merck's vaccine against Ebola was the first-ever licensed rVSV vaccine, approved last December (see *Proven against Ebola, a vector shows its broader potential*, IAVI Report, Vol. 23, No. 2, 2019).

Andrew Ward, professor in the department of integrative structural and computational biology at Scripps Research in La Jolla, CA, says that every cutting-edge vaccine platform was co-opted for work on SARS-CoV-2. "It's one of the greatest experiments of my lifetime," he says.

Robin Shattock, a professor at Imperial College in London who has long worked in the HIV field on EU-backed experimental vaccine candidates, is heading up development efforts for a self-amplifying RNA-based vaccine candidate against CoV-2. Shattock and his team, like many others, worked at breakneck speed and had their first coronavirus vaccine candidate formulation worked up in the lab within two weeks after the viral genome was posted. It's expected to be tested in a large human

efficacy trial starting in October. It will be conducted in the U.K. and Uganda, where Pontiano Kaleebu, director of the Uganda Virus Research Institute in Entebbe, is helping to manage the country's response to COVID-19. Kaleebu is helping advance COVID vaccine candidates, something he has been doing for HIV over the better part of the last two decades. "Most of the capacity we have in the lab, in terms of studying immune responses, studying viruses, sequencing, all that has been built here through HIV, as well as other infectious diseases. But largely HIV."

Expertise gained in HIV work will undoubtedly continue to support efforts to understand CoV-2 and deliver research data on key aspects for the fight against the virus. Viral evolution, and the resulting variability, is a mainstay in the HIV field, given a foe that is the ultimate shapeshifter. Bette Korber, a computational molecular biologist at Los Alamos National Laboratory with a long record as an HIV researcher, catalogued a protein shift underway in the novel coronavirus that seems to be asserting itself as a dominant strain, one step removed from its emergent Wuhan form (*Cell* <https://doi.org/10.1016/j.cell.2020.06.043>).

All viruses mutate, and in most cases—excluding hypervariable viruses like HIV and influenza—it is harmless or even beneficial to the host. But vaccine developers clearly need to track the mutations. de Groot, whose EpiVax firm is designing CoV-2 epitopes for a vaccine candidate using its immunoinformatics tools, recalls this from the first SARS outbreak. "It's not really fair to look back on these last five months and say that CoV-2 is not going to shape-shift. I think it will," she says. "One vaccine will not be the solution. We will have to look at conserved epitopes, both B-cell and T-cell epitopes, and at how viruses escape immune defense."

Though a vaccine preventing HIV remains elusive, the field is rich with results and practical expertise—and researchers are applying this expertise in the effort to beat COVID-19. Scientists are fond of pointing to the importance of basic research and how difficult it is to get funding for and attention to it. The contribution coming from the HIV field in the effort to smother the COVID pandemic may be making that case for them. ■

Michael Dumiak, based in Berlin, reports on global science, public health, and technology.

Monoclonal antibodies and their potential role in combatting COVID-19

Numerous monoclonal antibodies are already in development for both treatment and prevention. There are many unanswered questions, but, if they work, antibodies may play a role in ending this pandemic and in responding to future viral outbreaks.

By Kristen Jill Kresge

In January, James Crowe and his lab at Vanderbilt University were gearing up to do their second simulation of a viral pandemic. The goal of this simulation was the same as the one they conducted in 2019: to isolate and test human antibodies against a virus as quickly as possible, part of an overall effort to develop a platform for rapidly developing monoclonal antibodies in preparation for future outbreaks.

Their first simulation, or sprint, as they call it, used the mosquito borne Zika virus as a model global outbreak. With Zika, Crowe, who is the director of the Vanderbilt Vaccine Center, and colleagues were able to go from a blood sample of someone who was infected with the virus to showing that monoclonal antibodies against Zika could completely protect non-human primates from infection in just 78 days.

That's why they call it a sprint. Typically, these efforts might have taken nearly a year—more of a jog than a sprint. But for this work, sponsored by the Defense Advanced Research Projects Agency (DARPA), part of the U.S. Department of Defense, speed is a guiding principle. Crowe's group is one of the grant recipients of [DARPA's Pandemic Protection Platform program](#), which has set ambitious targets for a rapid response to viral pathogens. The program aims to develop platforms to develop countermeasures to any known or new infectious threat within 60 days.

The second sprint for Crowe and his team was designed to test their neutralizing antibody discovery platform against a potential global outbreak of bird flu, a pathogen many scientists thought might be the source of the next pandemic.

But what was intended to be a simulation quickly became reality, albeit with a different virus. “Just as we were gearing up to launch that sprint in the third week of January, we decided on the fly that this coronavirus could become not just a regional outbreak, but a global pandemic,” says Crowe, referring to the now ubiquitous SARS-CoV-2.

They spent a week debating whether to switch the focus of the sprint to this new human coronavirus, for which the genomic sequence was just published. It meant starting from scratch—they had no reagents or cells prepared in advance, and no virus. “Fortunately, we decided to do this,” Crowe says.

They activated their efforts in January and received a blood sample from what Crowe says was likely the first SARS-CoV-2 infected U.S. citizen, someone who had recently returned from Wuhan, China, where the outbreak originated. The sample was collected from this individual around eight days after infection, flown to Nashville, Tennessee, and hand delivered to Crowe at his home. With that, Crowe's team was up and running. Or rather, sprinting.

They obtained another blood sample in mid-March, and just 18 days later identified their lead antibodies (*Nat. Med.* <https://doi.org/10.1038/s41591-020-0998-x>). These neutralizing antibodies against SARS-CoV-2 were transferred to pharmaceutical partners, including AstraZeneca, for development just over three weeks after Crowe's group obtained the sample. “We later did non-human primate studies and achieved 100 percent protection just like we did with Zika,” he notes. “Those antibodies look fantastic.”

What was at one time an unthinkable timeline was achieved partly because they took many risks, Crowe says. “You can't do science as usual in a sprint. You have to change your mindset to move as quickly as possible and do science in a different way. Once we got going, it became clear that every step of the process could be shortened.” He also credits DARPA for their support in developing their methodologies, which was another reason they could isolate and test these neutralizing antibodies so quickly. “We activated very early and we had a platform in place.” The fact that this work was occurring while an actual pandemic was unfolding was another motivating factor. “We wanted to go faster this time because it was real,” he says. “Everyone is going as fast as they can.”

The antibodies from Crowe's group are among dozens that are now in various stages of preclinical and clinical development to potentially treat or prevent COVID-19. AstraZeneca has announced plans to begin a clinical trial this summer testing a combination of two of the monoclonal antibodies they licensed from Crowe's efforts. ID Biologics, a biotechnology company founded by Crowe, is also developing a SARS-CoV-2 monoclonal antibody licensed from Vanderbilt.

Other monoclonal antibodies are already in clinical trials. In July, Regeneron started a Phase III trial in collaboration with the U.S. National Institute of Allergy and Infectious Diseases (NIAID) testing a combination of two of the company's antibodies for prevention in 2,000 individuals at 100 sites in the U.S. The company also initiated an adaptive Phase II/III therapeutic trial testing these same antibodies in both hospitalized and non-hospitalized patients with COVID-19 at 150 sites in the U.S., Brazil, Mexico, and Chile. Lilly is also testing their lead monoclonal antibody, identified by AbCellera, in a Phase III trial in partnership with NIAID, and are developing and testing another monoclonal antibody with the Chinese company Junshi Biosciences.

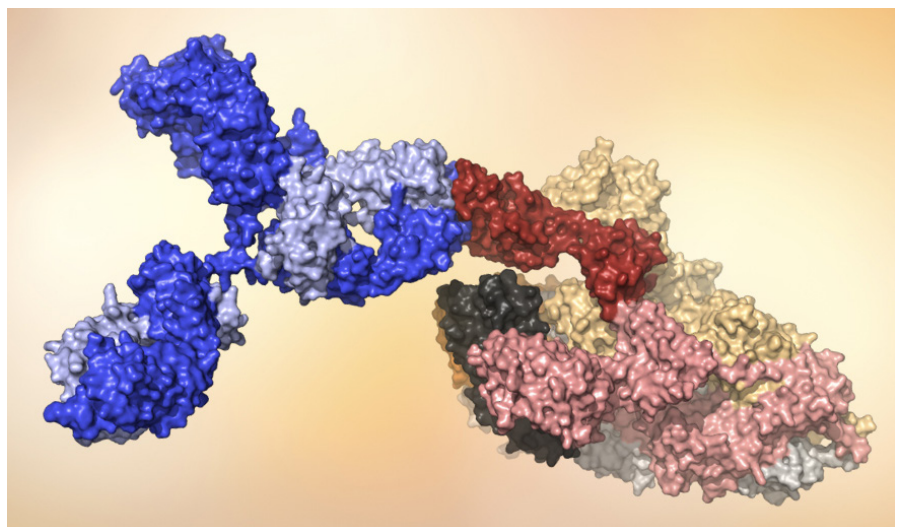
Several other groups and companies also rapidly mobilized to identify neutralizing antibodies against SARS-CoV-2, some of which are now being developed as potential products with various partners. Scripps Research, IAVI, and the University of California San Diego School of Medicine isolated potent neutralizing antibodies against SARS-CoV-2 from blood samples collected from patients infected with the virus, mapped the targets on the virus where these antibodies bind, and showed protection from disease in an animal model all within seven weeks (*Science* DOI: 10.1126/science.abc7520).

Even with these rapid-fire advances, there still are many open questions about neutralizing antibody responses to SARS-CoV-2. Researchers still don't know what levels of antibodies are required to protect against infection, or how durable monoclonal antibodies will be in humans. But, as with vaccines, clinical trial data showing whether these monoclonal antibodies are effective could be available before the end of the year. These findings may help solidify the role monoclonal antibodies can play in treating and preventing both existing and emerging infectious diseases.

Monoclonal antibodies are a large and growing market. More than 75 monoclonal antibody products have now been approved by the U.S. Food and Drug Administration. Of those, only a few are used to treat or prevent infectious diseases, namely anthrax, respiratory syncytial virus, and *Clostridium difficile* (*JAMA* 324(2), 131, 2020). But even before SARS-CoV-2, numerous monoclonal antibodies against several viruses, including Ebola, influenza, Zika, and HIV, were in development. "Increasingly, antibodies are the future of preventing and treating infectious diseases," says Crowe.

The interest in developing monoclonal antibodies for infectious diseases is largely a result of advances that have made antibodies easier to identify, select, optimize, and manufacture (*NEJM* 378, 1469, 2018). During and following the deadliest Ebola outbreak in history, which took place from 2014-2016, monoclonal antibodies were developed as potential therapies. A cocktail of three mouse-human chimeric antibodies known as ZMapp was tested during that outbreak, but did not provide a statistically significant benefit. Since then, researchers have identified multiple other monoclonal antibodies against Ebola, some of which are single antibodies, making them easier and less expensive to manufacture, and some that may work against multiple virus strains (*NEJM* 378, 1469, 2018).

Dozens of monoclonal antibodies are also in development for HIV. The results of the most



A human antibody (blue) attaches to the receptor binding domain (red) on SARS-CoV-2. Model courtesy of the laboratory of Dennis Burton, chairman and professor, Scripps Research, and scientific director of the IAVI Neutralizing Antibody Center.

advanced clinical trials are expected this October. Two Phase IIb trials conducted by the HIV Vaccine Trials Network, known as the Antibody Mediated Prevention or AMP studies, enrolled more than 4,600 volunteers in the U.S., Brazil, Peru, Switzerland, and sub-Saharan Africa.

These trials are testing whether a single broadly neutralizing antibody (bnAb) against HIV (known as VRC01, which binds the CD4 binding site on HIV and was discovered by scientists at the Vaccine Research Center at NIAID) is effective at preventing infection. Many other bnAbs are also in development, many of which are combinations that target multiple sites of vulnerability on the virus and that are optimized to be both longer lasting and more potent.

In fact, many of the technologies developed and honed from work on HIV are now being brought to bear on SARS-CoV-2, both in vaccine development (see page 4) and in antibody discovery. “HIV research has paved the way in terms of technology development,” says Andrew Ward, a professor in the department of integrative

structural and computational biology at Scripps Research. Scientists from Tsinghua University in Beijing were the first to isolate neutralizing antibodies from SARS-CoV-2-infected patients (*Nature* <https://doi.org/10.1038/s41586-020-2380-z>) and they did so using a strategy first used to isolate and screen for HIV neutralizing antibodies (*J. Virol. Methods* 158(1-2), 171, 2009; *Cell* 181, 1458, 2020).

Lessons learned from studying HIV and other viruses are also being applied to SARS-CoV-2 by many of the same research groups, including Ward’s. “If you look at the important discoveries, a substantial number are by researchers who work on HIV,” says Rogier Sanders, professor of virology at the Academic Medical Center at the University of Amsterdam, whose group has also identified potent neutralizing antibodies from

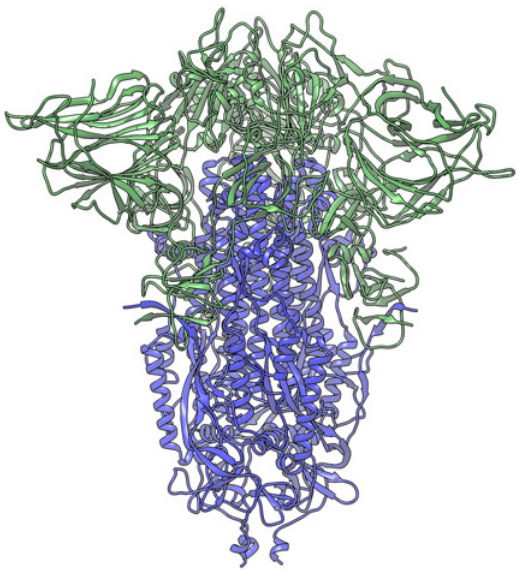
COVID-19 patients (*Science* DOI:10.1126/science.abc5902).

“Once you put the core technology in place, you can just swap out the virus,” says Joseph Jardine, director of product discovery and optimization at IAVI. “We were able to leverage our existing technologies for HIV and snakebite envenoming and rapidly apply them to a different disease.” When they did, they were reminded why HIV is so challenging. “SARS-CoV-2 is a much easier problem,” says Jardine.

For years, HIV vaccine researchers were stymied by their inability to stabilize the virus’ floppy trimeric Envelope protein. But with SARS-CoV-2, researchers were able to rapidly stabilize the crown-like Spike protein (*Science* 367, 1260, 2020) on the surface of the virus that is the primary target of neutralizing antibodies (*Cell* DOI:<https://doi.org/10.1016/j.it.2020.03.007>). Ward says it was just a little over a month after the full genomic sequence of SARS-CoV-2 was published that the cryogenic electron microscopy structure of the Spike protein was available. This was thanks, in large part, to work by Ward and colleagues, who had previously resolved the structure of the trimeric Spike protein for a common-cold causing strain of human coronavirus (*Nature* 531(7592), 118, 2016). It turned out that the stabilizing mutations they used for that coronavirus were also applicable to SARS-CoV-2 and this rapidly propelled the development of vaccine constructs and the isolation of antibodies against Spike.

HIV proves to be a more intractable virus than SARS-CoV-2 in other ways too. “Even with a stabilized HIV trimer it is hard to identify neutralizing antibodies,” says Sanders, whereas with SARS-CoV-2, neutralizing antibodies that are capable of clearing the virus develop in the vast majority of infected individuals. And by comparison to HIV, these antibodies were relatively easy to isolate from convalescent sera. Jardine says his lab produced over 2,000 monoclonal antibodies targeting six different epitopes on the SARS-CoV-2 Spike protein.

The neutralizing antibodies against SARS-CoV-2 also appear to be easier for the immune system to make, another factor that sets it apart from HIV. Jardine and Crowe both say that the SARS-CoV-2 neutralizing antibodies they have identi-



In this cryogenic electron microscope image of a SARS-CoV-2 Spike protein side view, the S1 section of the Spike is shown in green and the S2 portion is shown in purple. This unique two-piece system has shown itself to be relatively unstable. A new mutation has appeared in the viral variant most common in New York and Italy that makes this Spike both more stable and better able to infect cells. Credit: Andrew Ward lab, Scripps Research

fied have few, if any, mutations. Most differ by only 2 percent from the initial round of antibodies generated by the immune system in response to the virus, what are referred to as germline antibodies.

By contrast, many of the HIV-specific bnAbs are extensively mutated—some differ from germline antibodies by as much as 30 percent. This extensive level of mutation is a result of sustained viral exposure, which triggers the B cells that give rise to antibodies to undergo repeat rounds of somatic hypermutation in the germinal centers of lymph nodes. For HIV, the process of somatic hypermutation is what leads B cells to produce antibodies that can neutralize a wide swath of the many viral variants in circulation. This doesn't appear necessary for SARS-CoV-2. “You don't need a lot of mutations and in some cases, you may not need any,” says Jardine, to have an effective immune response against the virus. At least for now.

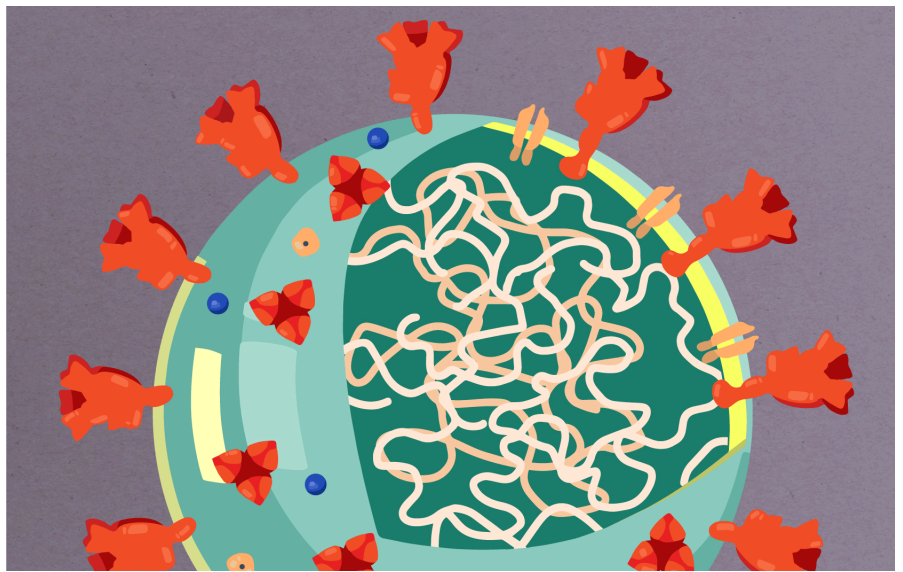
SARS-CoV-2 has a much slower mutation rate than HIV. Only one dominant mutation has been observed so far, though it does seem to have an impact on the infectivity of the virus (*Cell* DOI:<https://doi.org/10.1016/j.cell.2020.06.043>). Researchers are already considering the extent to which SARS-CoV-2 may further mutate and how this may allow the virus to escape from neutralizing antibody responses. “The potential of it becoming an issue is always there,” says Sanders.

In a recent preprint publication, researchers from Rockefeller University showed they could readily generate mutated variants of the SARS-CoV-2 Spike protein that allow it to escape antibody neutralization in laboratory experiments (DOI: <https://doi.org/10.1101/2020.07.21.214759>). These mutations, though not common, can already be detected in populations where the virus is circulating. To ward against the potential of viral escape, the Rockefeller researchers suggest combinations of monoclonal antibodies targeting distinct epitopes on the virus may be more favorable than single monoclonal antibody products.

But Crowe says that the best neutralizing antibodies that his group has identified target multiple epitopes on the receptor binding domain (RBD) region of the virus, and this limits the virus' ability to mutate. Crowe's lab has identi-

fied two neutralizing antibodies that simultaneously bind distinct epitopes on RBD and synergistically neutralize the virus (*Nature* <https://doi.org/10.1038/s41586-020-2548-6>).

“The virus has relatively little leeway to change those contact residues; otherwise it will lose receptor binding and thus it will not be a fit virus. My opinion is that it is not likely that the right antibodies that only contact the receptor binding domain are going to be susceptible to escape, and that it is likely that monotherapy will be sufficient for those particular antibodies.”



The bulbous projections seen on the outside of the coronavirus are Spike proteins (red-orange). This fringe of proteins gives the virus its crown-like appearance under the microscope, from which the Latin name *corona* is derived. The Spike proteins act as grappling hooks that allow the virus to latch onto host cells and crack them open for infection. Illustration by Hailee Perrett, Ward Lab, Scripps Research.

However, Crowe acknowledges that it is a theoretical possibility that escape mutants will occur for all RNA viruses, including SARS-CoV-2, and therefore some of his partners are moving forward with a combination of monoclonal antibodies. “I think that's logical, but the downside is that now you have twice the manufacturing costs and more than twice the complexity.”

Manufacturing monoclonal antibodies at the scale needed for SARS-CoV-2 is a big issue. The Margolis Center for Health Policy at Duke University [published a policy paper in June](#) reviewing the capacity for manufacturing monoclonal anti-

bodies for COVID-19 and the potential demand for these antibodies in North America and Europe. But the need for effective COVID-19 therapies and preventives extends well beyond those continents. And making them affordable at a global scale is an important issue.

Monoclonal antibodies are typically produced in Chinese hamster ovary (CHO) cells. However, many alternatives are already in use or in development, including using plants, algae, and fungi to produce antibodies. Nucleic acid technologies, both DNA and messenger RNA (mRNA), are also being utilized to deliver monoclonal antibodies. Crowe says there isn't enough CHO cell manufacturing capacity on the planet to satisfy the global need for COVID-19 antibodies, which is why his company, ID Biologics, is pursuing some alternate production platforms, including using tobacco plants or mRNA delivery systems.

Even so, Ward is skeptical about whether large-scale production of antibodies for SARS-CoV-2 is practical. "In all likelihood there will be a few antibodies that are really good, but implementation is problematic," he says. "The doses they are going to work at are pretty impractical."

This is why some researchers are now engineering SARS-CoV-2 monoclonal antibodies in an effort to improve both their potency and extend their half-life, thereby limiting the dose required for the antibodies to be effective. "It's very useful to have more potent antibodies because the more potent they are, the less you will need, and then the less expensive it will be to make," says Sanders.

And the less expensive antibodies are, the more applicable they will be for global use. "We're looking to see how we can make them available in low- and middle-income countries as quickly as possible," says Jardine, who is applying his expertise in engineering HIV monoclonal antibodies to devise even better antibodies against COVID-19 than those the immune system naturally generates. "The immune system doesn't try to make an antibody that's easy to manufacture," he jokes. "We'd love to have antibodies that neutralize more potently."

Jardine wanted to test this optimization approach so he started with an antibody against SARS-CoV-1, the first of three novel coronaviruses that

has infected and spread among humans in the past two decades. The SARS-CoV-1 antibody Jardine used could bind SARS-CoV-2, but it didn't bind with high enough affinity to be able to neutralize the new coronavirus. So he engineered three variants of the original SARS antibody by introducing various mutations. The resulting antibodies had a much higher binding affinity to SARS-CoV-2—and more than a 1,000-fold improvement in potency. "If you increase the affinity of a neutralizing antibody, you typically will increase its potency as well. It turns out that this works quite well," he says.

Next Jardine wants to see if they could achieve a similar boost in potency starting with monoclonal antibodies that are already able to neutralize SARS-CoV-2. "Antibody optimization has huge potential in a lot of different fields," he says, and COVID-19 is providing an interesting opportunity. "If we can make these antibodies available and affordable globally, we should be able to do it for HIV."

Typically, half-life is harder to control, but researchers are also introducing mutations into the Fc portion of SARS-CoV-2 antibodies in an effort to extend their durability as well. In some cases, it is the same mutations that are being introduced into HIV bnAbs to extend their half-life (*Nature Biotechnology* 28, 157, 2010). "These antibodies are all going to have 90-day half-lives," Crowe says.

With those attributes, Crowe sees monoclonal antibodies as being a critical component in the response to the COVID-19 pandemic. He even thinks they may have advantages over the antibodies generated by the immune system. "The potency, efficacy, and half-life could exceed that of vaccines," he says. But Ward is less optimistic. "They're great on paper," he says, "but I don't see how they make a big difference in the end."

As with many things in this pandemic, only time will tell. If clinical trials show these monoclonal antibodies are effective for treating and/or preventing COVID-19, some scientists are hopeful they will be a complementary approach to vaccines in mitigating this pandemic, and others to come. Ward agrees that in some populations, including the elderly, who are at particularly high risk from developing deadly complications from COVID-19 disease, and individuals who are immune compromised, antibody prophylaxis may hold promise. ■

INTERVIEW

Finding a global solution for a global problem

An interview with Seth Berkley, chief executive officer of Gavi, the Vaccine Alliance

By Kristen Jill Kresge

In the pages of *IAVI Report*, and countless other places around the globe, Seth Berkley doesn't require an introduction.

The founder and former president and CEO of IAVI is a visionary who has spent much of his career promoting the development of new vaccines and implementing immunization programs that benefit the world's poorest people. Since leaving IAVI in 2011, Berkley has led Gavi's largest expansion, which has resulted in the immunization of an additional 300 million of the poorest children across the globe, preventing five to six million deaths in the process. He is relentless in his commitment to public health and travels almost non-stop, at least he used to pre-COVID. Like all of us, he is spending much more time at home these days.

Since its inception in 2000, Gavi has facilitated the immunization of more than 760 million children worldwide, averting a staggering 13 million deaths from vaccine-preventable diseases. Nearly 90 percent of the world's children now receive at least one round of childhood vaccines, almost half of them as a result of Gavi-supported immunization programs. They aren't stopping until they reach them all.

That mission has become even more complicated in light of the ongoing COVID-19 pandemic. As airports and countries around the world shut down in an effort to limit the spread of SARS-CoV-2, public health programs, including Gavi-supported immunization programs, faced multiple setbacks. This hasn't yet resulted in widespread outbreaks of vaccine-preventable infectious diseases, but it is still too soon to judge the widespread impact of this pandemic. At the virtual COVID-19 Conference held July 10-11 in conjunction

with the International AIDS Society's conference, Bill Gates warned of another consequence—the disruption in HIV/AIDS treatment programs that could prevent people from receiving life-saving anti-retroviral therapy.

Amidst all of this, Berkley's commitment is unwavering. In June, with the world in the throes of the pandemic, the U.K. hosted the Global Vaccine Summit, an effort to replenish Gavi's financing through commitments from world leaders. It was overwhelmingly successful—31 donor governments, and eight foundations, corporations, and organizations pledged more than US\$8.8 billion to Gavi, exceeding the replenishment target.

In addition to ensuring that 100 percent of the world's children receive at least one round of routine immunizations, Gavi, along with the Coalition for Epidemic Preparedness Innovations (CEPI) and the World Health Organization, is now also helping coordinate the development, manufacturing, and eventual access to COVID-19 vaccines through the COVAX facility (see *COVAX: Facilitating global vaccine access*, page 21). The goal of the facility is to accelerate the development and manufacturing of COVID-19 vaccines and to distribute them globally to the individuals at highest risk in an effort to halt the pandemic as quickly as possible. It will allow even the poorest countries to access vaccines. The idea of distributing vaccine doses equitably based on need and not the ability to pay is one of Gavi's core missions. “Unless everyone is protected, we are all at risk,” Berkley said.

I spoke recently with him to discuss the COVID vaccine pipeline, the COVAX facility, Gavi's focus after the replenishment, and his hopes and fears during this pandemic. An edited version of our conversation appears below.



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I hope we can get back to understanding the importance of trying to solve this problem for everyone. It is a global problem that needs a global solution.

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Are you optimistic about the prospects for COVID-19 vaccine development?

Yes and no. If it turns out that the Spike protein on SARS-CoV-2 is the right target, then the fact that we have about 160 vaccines in development says to me that we have a pretty diverse and wide set of approaches, and so I think it is likely that some will work. But there is that caveat. If it turns out that the Spike protein isn't the right antigen, then there are very few candidates that are not based on that.

The second point would be that we don't know whether we will be able to get protection in all age groups, including the elderly, and we don't know how long the protection will last. We also don't know if this coronavirus is going to be like seasonal coronaviruses, and therefore, you can get re-infected, or if there will be long-term immunity, etc. There are a lot of other questions too, but in terms of getting immunologic protection from the vaccine, I'm optimistic assuming that Spike is the right target.

You seemed to be one of the first people to raise the issue of equitable access to an eventual vaccine. What steps is Gavi taking to ensure that vaccines, when available, are not just accessible to those countries who can afford to pay for them?

When the pandemic started, we thought about the need to have an advanced market commitment (AMC) for the Gavi countries, because as the poor-

est countries in the world they would not have the resources to be able to compete with other countries. Those are traditionally the countries we think about. But it became quite clear over time that there was a risk that even if there was adequate financing for Gavi countries, that given the intense global desire for a COVID-19 vaccine and the fact that in the first 18 months there is no way there is going to be excess vaccine, there was a good chance that even if a country had the money they could end up not being able to access a vaccine.

So that made us pivot and starting thinking about how we might supply vaccines globally to a subset of the population to try to control the pandemic, which from a public health point of view is the efficient way to do it, rather than taking a nationalistic approach to protecting just your own people. Obviously if a few countries buy 100 percent of the vaccine for their entire population, then in the early days there will be no vaccine for anybody else.

That pivot was important because it led to the design of the COVAX facility, which went beyond the AMC that we also launched. The idea of the COVAX facility was to try to create a place that other countries could self-finance vaccines as part of an overall portfolio. The idea is that if we can get enough countries interested, then we could scale up production adequately and make sure that there is a vaccine available for developed and developing countries.

So that covers all countries?

All countries. The idea is that low- and lower-middle-income countries fall into the AMC, which would be the normal Gavi mechanism. We are still debating whether to also include the 12 International Development Association-eligible small countries that are mostly small island states. Then the upper-middle income countries and high-income countries are eligible to procure the self-financed vaccine, hopefully with a tiered approach that would allow people to be able to afford vaccines.

Speaking of affordable vaccines, what are your thoughts about the price of an eventual COVID-19 vaccine?

We had to estimate prices in our models and for fundraising, but since we have no idea which vaccine is going to work—whether it is going to be one, two, or three doses, or what the manufacturing yield is going to be, etc.—it is impossible to come up with a price. We just used a weighted average price of \$10 a dose as a proxy for about what it will cost.

Certainly, there are many approaches that are in the pipeline that would not be extraordinarily expensive to make, and then there are some that might be expensive to make, so we've been pragmatic. Not all manufacturers are the same. A big manufacturer might be able to say we can do this at cost, plus some minimal amount, rather than not for profit. But there are other groups that are small, venture-backed companies that frankly can't say that. They would need to have some type of return, and then the challenge would be to structure a tiered price that would give the companies a return that would be appropriate—not excessive, but appropriate—and would do it in a way that was fair for all countries. We are trying to be pragmatic because of course we want access to whatever vaccines are worth having access to.

And how are you thinking about the manufacturing of vaccines?

We're thinking about it from large companies, contract manufacturers, and from the developing countries vaccine manufacturers network, working closely with CEPI. CEPI is setting up relationships for particular approaches, but if those approaches were to fail, they are trying to be in a position to capture the manufacturing, or vials, or goods that are necessary to produce a vaccine and use them for another candidate. One of the challenges with vac-

cine nationalism is not only that you might have access to just a couple of vaccine approaches and those vaccines might not work, but also, if every country is going out and trying to produce their own vaccines and many of them are going to fail, then you can end up in a situation where you use up all of the manufacturing resources. And then when you have a successful vaccine or vaccines that are the ones that should be scaled up for everybody, there won't be enough facilities or the products you need to make those vaccines successfully. That would obviously be a tragedy.

Do you think that there is an appropriate balance in the vaccine pipeline between candidates that are quick to develop and those that are more likely to succeed?

Well, there are two critical truths here. One is that we need vaccines quickly because of the state of the global pandemic. The second is that we also need vaccines that work and are usable. To do that, you want a full portfolio of vaccines. CEPI's philosophy is to try to have different types of vaccines. Some are going to take longer to make; others like Moderna's mRNA vaccine candidate, which was the leader in terms of speed, was being tested in humans in 63 days. But there are also no licensed mRNA products, and with these new approaches there are concerns about what the regulatory pathway will be and the process of scaling up manufacturing to produce large volumes.

The question, in a sense, is are we talking about the tortoise or the hare here because you don't want to exclude either from the race. That is why it is important to still focus on products that are going to take longer to do the bioengineering for in the beginning—like a live-attenuated vaccine or live-vectored approaches. We need to make sure that we're paying attention to the full range of approaches. What may end up happening is that we will have a first phase of vaccines that will be used acutely to try to control the pandemic, and then these will be followed by a second phase of vaccines that might be easier to use, more immunogenic, work better in the elderly, or be single dose rather than multi-dose.

You've spent so much of your life trying to convince the world to focus on vaccines and now everyone is talking about vaccines!

Except for the people who are talking about how they would never take a COVID vaccine.

Well there is that issue too. Why do you think there is still so much vaccine skepticism?

It's interesting. I have no answer for this. I think that there is fear out there. But my assumption is that when you have a vaccine that works and people start using it, and those people are being followed and it is shown to be safe, and those people are then able to resume a normal life, I have to hope that this will flip and substantial numbers of people who are nervous now become less reticent to be vaccinated.

There is always a small group who are never going to take vaccines, then there are those people who love and trust vaccines and will take them, and then there's that group in the middle. What we're looking at is the group in the middle. You want to make sure you move those people toward wanting vaccines and not in the other direction.

How has COVID-19 affected the implementation of Gavi-supported immunization programs? Have you seen a spike in vaccine-preventable diseases because of COVID-related interruptions?

Yes. We don't know the full extent of the interruptions yet, but the numbers are quite dramatic—73 percent of countries have had outreach impacted and 63 percent of countries have had a moderate impact on routine vaccinations. Of course, we don't have real-time monitoring everywhere, so we can't give up-to-the-minute statistics, but clearly it has had a big effect.

The hope is that there was a dip and that now those numbers will come back up again as people get used to the situation. But the immunization rates may not go up quite as high because people may be holding their families back, and you also may have a slower process with people using PPE [personal protective equipment] etc. The hope is that we can keep population immunity at a high enough level that we don't have outbreaks. But we've already seen a range of outbreaks occur so far. We haven't yet seen massive full-country outbreaks, but if you think about it, it's only been about three months of reduced uptake, and so it is still early days. One of the questions is whether we will be able to do catch-up campaigns in the near future, or is this interruption going to last for a substantial period, in which case we would have to worry.

Just in terms of the supply chain, we had a period where airports were shut down and we were wor-

ried about stock outs all over the place. Now we're almost back to the same shipment levels as before the pandemic began and we are catching up on back-up shipments.

And in the midst of all this you held the Global Vaccine Summit, which was a resounding success. What are Gavi's priorities coming out of the summit?

Well, the core of the replenishment was laid out pre-COVID and it really had a few major points of focus.

We've made it to the point where 90 percent of children receive at least one dose of routine immunizations, and that's extraordinary. Now the focus is on that last 10 percent, the so-called zero-dose children, two-thirds of whose families live below the poverty line. Those families live in places where there are no health services at all, so if the children get sick, they are more likely to die. And if an epidemic starts there, it is more likely to spread. The radical idea was to reach that last 10 percent or get as close as possible to universal access between now and the end of the Sustainable Development Goals in 2030.

But these vaccines don't deliver themselves, so in order to do that you have to build a health system for that last mile. This has many positive effects because those are the areas with the highest mortality rates. So the core of Gavi 5.0 is built around this idea of going not just nationally, but sub-nationally, working with countries to focus on using local data to identify where the clusters of zero-dose children are and to really begin to have indicators that look at how many of them you've reached, and in the process leave behind health systems that extend beyond vaccines. That's the plan. Now, of course, we are starting with many more zero-dose children and many more under-immunized children as a result of COVID, so the first question is, how long will it take for us to get back to baseline? But the core strategy stays the same.

Ironically, the other part of the strategy was to strengthen our work around epidemics and to have better stockpiles and surveillance so that we are better prepared to deal with global health emergencies, which we know are evolutionarily certain to occur. The idea was that given global warming, increased urbanization, and increased population density, we are going to see more outbreaks that we need to be prepared for. And I think that will obviously be important going forward.

The additional financing we received is quite important because we had cut back on some of our previous ambitions when we added inactivated polio vaccine into the core of Gavi. As a result, we cut about \$600 million out of our health systems financing effort. This new round of funding is going to allow us to get back to full financing and really try to drive things forward. We haven't fully decided what the additional money will be used for, but a substantial portion will be on this sub-national effort to go the last mile and reach the zero-dose children.

These are strange times. What keeps you up at night?

I used to worry about the replenishment and securing funding in the time of COVID. But now, to be honest, what keeps me up at night is that we're at a

tipping point. This is a global pandemic that started from a small outbreak in Wuhan, China, and spread to 180 countries in three months and we are now seeing this kind of nationalism occurring. It is certainly possible that a nationalistic approach could result in a dozen or two dozen countries buying up all the doses of vaccine, leaving none left for the rest of the world. This is not a great idea, not just from an equity point of view or a humanitarian point of view, but also from a public health point of view. If you have massive outbreaks of virus circulating, adapting to humans, mutating, and then spreading, you're never going to solve this. I worry about a world where governments are focusing on vaccinating every person in their own country, and everywhere else people are dying. I hope we can get back to understanding the importance of trying to solve this problem for everyone. It is a global problem that needs a global solution. ■

COVAX: Facilitating global vaccine access

The rapid pace of COVID-19 vaccine development is unprecedented. Scientists across the globe are developing, testing, and preparing to manufacture billions of doses of vaccines in mere months—dramatically faster than decades typically required to bring successful vaccine products to market. Just six months after the sequence of the novel coronavirus was made available, there are more than 160 vaccine candidates in various stages of pre-clinical and clinical development.

Not all of these vaccines will work. But to ensure that those that do can be manufactured at huge scale as soon as they are shown to be effective, companies are investing in and scaling up manufacturing processes now, much earlier in the clinical development process than would normally be the case. They are doing this in many cases with huge amounts of government support. Every country is interested in gaining early access to vaccines that are shown to be effective and many wealthy nations are investing heavily in the development of specific candidates.

The U.S. government, for example, is supporting a range of vaccine candidates

through its Operation Warp Speed initiative, which aims to deliver 300 million doses of a safe and effective COVID-19 vaccine by January 2021 as part of its overall effort to speed the development and access to COVID-19 vaccines, therapeutics, and diagnostics. This effort is backed by almost \$10 billion in funding allocated by Congress. The U.K. and other European governments are also supporting development of priority vaccine candidates and making deals directly with vaccine companies to secure vaccine supply for their citizens.

But instead of each nation negotiating independently to guarantee access to eventual vaccines, some are calling for a more equitable approach. Speaking at the International AIDS Society's virtual COVID-19 Conference in July, Bill Gates called for a large, fair global distribution system for COVID-19 vaccines similar to what has been developed for HIV/AIDS treatments. He said that global cooperation is necessary and that "leaders need to make decisions based on equity, not just market-driven forces."

This is where the COVAX facility comes in. With support from the World Health

Organization, the Coalition for Epidemic Preparedness Innovations, and Gavi, the COVAX facility is meant to provide equitable access to vaccines. It works by pooling resources from participating countries to support a broader range of vaccine candidates than any one of the countries could manage on their own. Should one or more of these vaccines be proven safe and effective, the COVAX facility aims to distribute two billion doses equitably among countries that contributed to the COVAX facility by the end of 2021. Developing countries that would otherwise be unable to afford the vaccine will receive doses through Gavi's donor-supported COVAX Advance Market Commitment, which aims to secure \$2 billion in funding so the poorest countries can also have access to COVID-19 vaccines.

An editorial in *The Lancet* (*Lancet* 395, 1883, 2020) called the COVAX facility and Advance Market Commitment "commendable," and a "step in the right direction," saying that "controlling the pandemic demands global cooperation... resources must be pooled and shared." ■

THE NEXT DISEASE X

In the midst of a pandemic and preparing for the next

SARS-CoV-2 is the first Disease X. There will certainly be others. Will the world be better prepared for the next one?

By Michael Dumiak

Peter Piot is only a few months into his recovery from COVID-19. But even as the pandemic rages on, he is already thinking ahead to the next one.

“We need to plan for the next epidemic *now*. This is the time to make sure we don’t commit the same mistakes in not investing in epidemic preparedness,” he said at the virtual COVID-19 Conference, part of the International AIDS Society’s biennial conference.

Piot, director of the London School of Hygiene and Tropical Medicine and a widely known epidemiologist who was among a group of researchers that discovered Ebola virus, spent a week in the hospital in mid-March after becoming infected with SARS-CoV-2, the coronavirus that causes COVID-19. Even a month later it still left him breathless to climb a flight of stairs.

But by mid-July Piot was well enough to advise the research community, and his advice was to take a long-term view. Piot has described long-term epidemic responses before, as when he joined the editorial board for the journal *AIDS* (*AIDS* 26, 1199, 2012). Long term, Piot thinks the world will be living with SARS-CoV-2, while also facing other now-unknown pandemic threats. These threats are referred to as Disease X, an uncharacterized but potentially deadly pathogen that finds its way into humans and spreads. SARS-CoV-2 is the first Disease X, but there will be more.

The Disease X concept sprang into being during the 2014-2016 Ebola outbreak in West Africa, says John-Arne Røttingen, chief executive of the Research Council of Norway and a

member of the World Health Organization’s (WHO) scientific advisory board for its research and development initiative, the R&D Blueprint. In 2015 as part of its analysis of what was happening before and during the Ebola outbreak, WHO set out to try to prepare a list of pathogens with the potential to cause major international public health emergencies. These pathogens were considered priorities for vaccine development. Added to this menacing roster—amid viruses like Hendra, Nipah, and the coronavirus that causes Middle East Respiratory Syndrome (MERS)—the Disease X was placed as something like a wild card.

The R&D Blueprint eventually led to the 2017 launch at the World Economic Forum in Davos of CEPI, the Coalition for Epidemic Preparedness Innovations, a grant-making, nonprofit organization which funds basic research and early clinical vaccine trials aimed at developing a reserve of potential vaccine candidates against a set of epidemic-prone infectious diseases—selected from the R&D Blueprint roster—that can be developed quickly in the event of outbreak (*Science* 350, 170, 2015; *A Crisis Gives You Wings, IAVI Report*, Vol. 21, No. 1 2017).

CEPI was inspired by the pathway that led to vaccines against Ebola, one of which is now licensed (ERVEBO); the other, a two-component vaccine (Zabdeno and Mvabea) was recently approved for marketing by the European Commission. Though these did not come from CEPI, what became ERVEBO made use of a pre-existing candidate that had laid dormant for years until the West Africa outbreak once again drew attention to the virus.

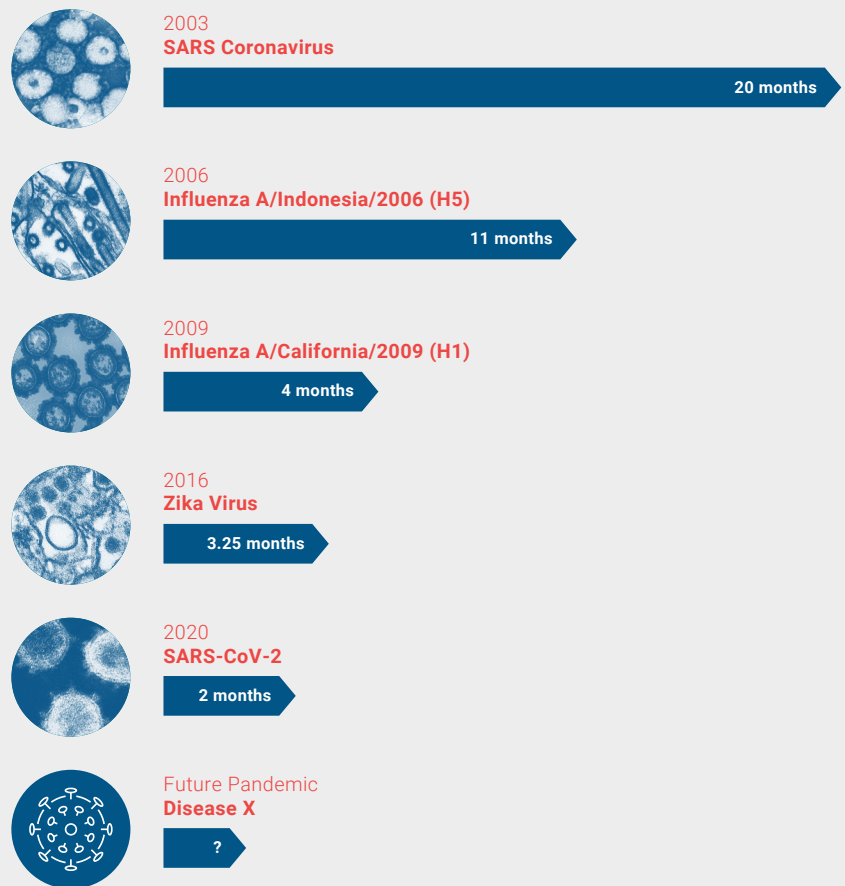
CEPI started by investing in efforts to develop vaccine against MERS, Nipah, Lassa, Rift Valley Fever, and Chikungunya viruses. When SARS-CoV-2 arrived—and fit the bill as Disease X—they quickly funded several vaccine efforts against this virus, including development partnerships with CureVac, Inovio, Insitut Pasteur, Novavax, the University of Oxford, Moderna, the University of Hong Kong, and the University of Queensland.

The WHO convened an R&D summit in Geneva in mid-February at which the group took stock of available knowledge and identified common research areas. These are the kind of measures CEPI’s Nicole Lurie, a former U.S. Assistant Secretary for Preparedness and Response, says are vital to what in her view is a new era in vaccine development, one that can meet a Disease X—or even two Disease X’s at once, or a Disease X and a flu outbreak at the same time. In “Developing COVID-19 Vaccines at Pandemic Speed,” Lurie lays out a vision of ideal vaccine platforms that can support development from viral sequencing to clinical trials in less than 16 weeks, alongside capabilities for boosting and accelerating manufacturing capacities, putting funding in place, and running multiple clinical trial phases at the same time, all in parallel (*NEJM* 382, 1969, 2020).

The Blueprint group also developed and promoted similar steps, such as laying the groundwork to quickly launch large-scale, flexible clinical trials for therapeutics. “The Blueprint mechanisms had already started working on coronavirus by early January,” Røttingen says. “It is the first clearly defined new pathogen, Disease X, and the general protocols for clinical trials were being worked into more specific therapeutic clinical studies.” The SOLIDARITY trial, a flexible, so-called adaptive multi-armed trial of COVID-19 therapies launched in mid-March.

Lurie sees this as the beginning of what she describes as a new “pandemic paradigm,” with Phase I trials and animal studies taking place simultaneously and investments flowing into producing vaccine doses even before they are proven to work. But considering a future that may well produce another Disease X, Lurie emphasizes the need for investing in better and speedier manufacturing technologies and creating global systems for mobilizing resources and finances.

Time from Viral Sequence Selection to First Phase I Clinical Trial



Source: Adapted from *JAMA* 319 (14), 1431, 2018.

Since 2003, when SARS-CoV-1 first emerged, the response to emerging viral pathogens has become much faster. But experts still see room for improvement before the next Disease X hits humans.

Lurie describes preparedness—against a future Disease X and all kinds of hazards—as a continuous activity, one requiring a research plan (*NEJM* 368(13), 1251, 2013). For now, it’s important to figure out how to get experimental vaccines and therapies to trial sites during the ongoing pandemic and utilize existing trial networks. “They need the capability to stand up pretty quickly,” she says.

As seen on a smaller scale during the Ebola outbreak, when some of these techniques proved effective, adaptive trials are an important component of an emergency response. As is proving the case with COVID, a pandemic fluctuates. Researchers have already fretted about this in the

U.K. and in parts of the U.S. and China, only for those concerns to dissipate as infection rates spike. A clustered trial can be designed to adapt to fluctuating infection rates. The SOLIDARITY trial is doing this, Røttingen says: it started out early on in Europe, but as rates have waned there, most of the recruitments shifted to Asia and Latin America. The network now extends to Iran, Indonesia, Philippines, India, and several South American countries.

It's already possible to see measures in place in the race against COVID-19 that will be used for future preparedness. Much of this has to do with scientists rapidly mobilizing to develop vaccine candidates, antibodies, and drugs, and testing them in adaptive clinical trials in record time. Only when the next Disease X comes, Piot says the response will have to be better than what happened with COVID. "When you look at the inter-

national rankings of countries in terms of epidemic preparedness, those who were at the top have done the worst."

The Bill & Melinda Gates Foundation strategist and immunologist Shmona Simpson identifies challenges to preparedness that span preclinical, clinical, and manufacturing phases of product development, including low sample and reagent availability to begin with (*Lancet* 20, 108, 2020).

"This is a wake-up call. I think all countries will increase their own investments in their national preparedness and response capabilities," Røttingen says. "I hope they will be willing to invest in collective mechanisms, because that is needed. And we should definitely plan for a pandemic influenza." ■

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