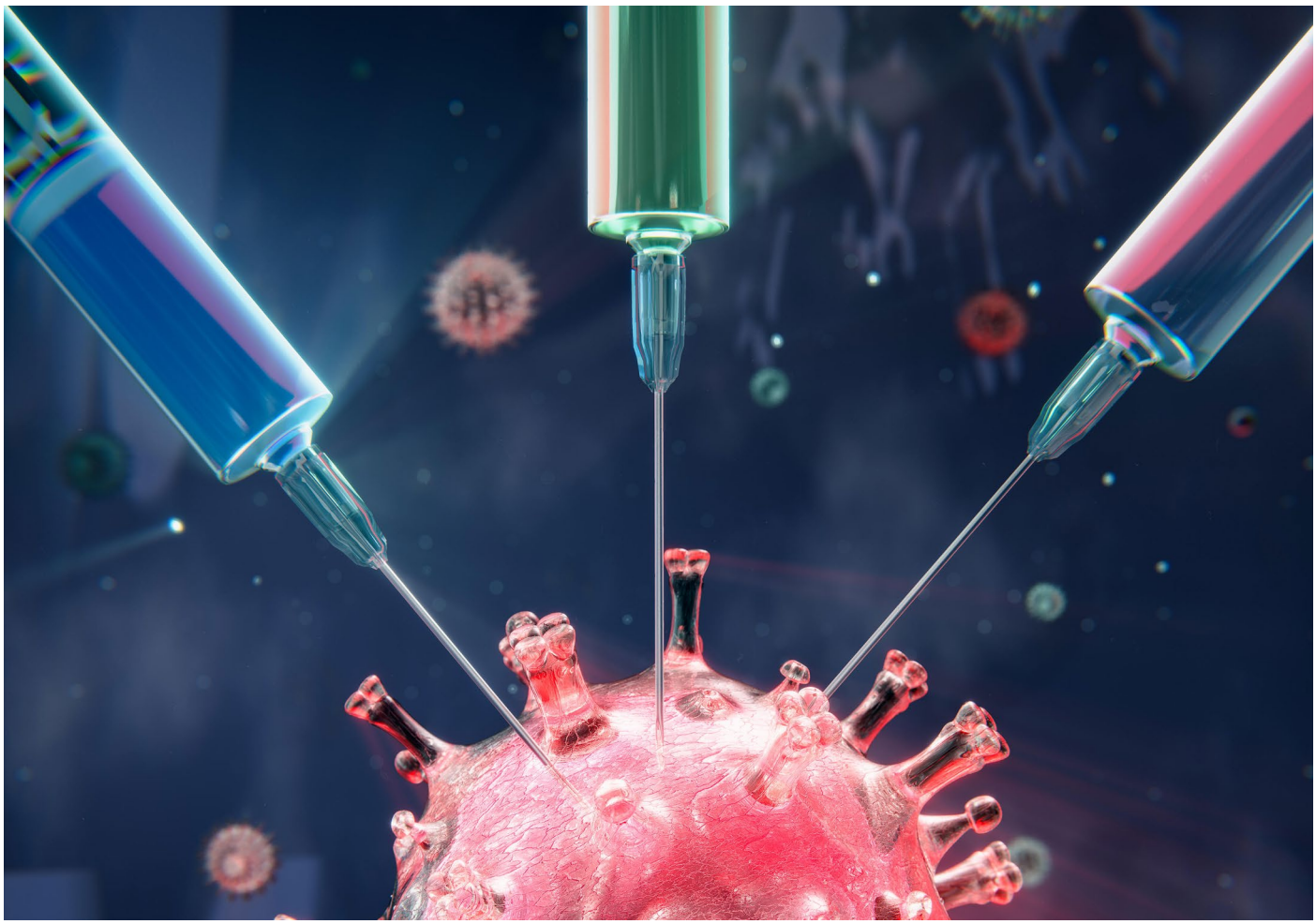

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The pandemic pipeline

Companies are doing their best to accelerate experimental drugs and vaccines for COVID-19 through the pipeline. Each faces its own set of challenges, but all agree on the need for a radical rethink of the clinical development process for pandemics.

John Hodgson

This week, Moderna Therapeutics' modified mRNA vaccine for COVID-19 began phase 1 clinical testing. From the first description of the novel coronavirus (SARS-CoV-2) genome on 10 January, it took the company just 42 days to produce the first batches of its vaccine (mRNA-1273), which encodes a prefusion-stabilized form of the SARS-CoV-2 spike (S) protein. If it can successfully negotiate safety and efficacy testing on a larger scale, batches of the mRNA vaccine could reach clinics as early as 2021. This will be too late for the current pandemic. And given that no mRNA vaccine has ever been approved, mRNA-1273 faces numerous challenges in clinical development and manufacture before it has the possibility of being made available for global immunization.

In the meantime, a host of other therapeutic modalities are being accelerated through discovery and development. Approved small molecules are already in use off label as adjunct therapies for critically ill patients (like Fujifilm Toyama Chemical's favipiravir), with several other experimental drugs (like Gilead's remesdivir) under investigation. Repurposed monoclonal antibodies (mAbs) developed against previous coronaviruses, such as severe acute respiratory syndrome (SARS) virus and Middle Eastern respiratory syndrome (MERS) virus, promise passive immunity

Box 1 | Supercharging drug repurposing

Of all the approaches available to the drug developer in the face of a pandemic, focused repurposing of approved small-molecule compounds has the best promise of early returns. According to Christian Gruber, CEO at Innophore in Graz, Austria, having an experimentally determined structure of the 3CL protease from the original SARS virus available was a boon to early computational drug design efforts against SARS-CoV-2.

Although generative machine learning approaches have been touted as a means for rapidly identifying lead compounds, from a medicinal chemistry standpoint there are clear limitations on the ability of artificial intelligence systems to design.

Mira Behnam is medicinal chemist whose 2016 PhD with Christian Klein at the Institute of Pharmacy and Molecular Biotechnology in Heidelberg University focused on the development of inhibitors for the flaviviral proteases from dengue, West Nile and Zika viruses. She says that although in silico methods are rapid, at present they tend to oversimplify the challenge for drug design. In the case of flavivirus proteases, they underestimate the complexity of both the initial target mechanism and the network of associated molecular interactions. The resulting compounds identified are unlikely to provide significant inhibition and will not become clinical candidates.

"Medicinal chemistry works better when the target is better understood," Behnam says. She believes that future AI should aim to produce more complex models that incorporate multiple factors affecting a target protein.

Behnam also thinks AI might also help identify broad-spectrum antivirals, as potential first lines of defense in emerging epidemics: "Most labs cannot cover more than a few different viruses, whereas finding a real broad-spectrum drug requires broader view of data and literature. This is where AI can be quite useful."

before vaccines come online. And in the wings newer experimental modalities, such as small interfering RNAs (siRNAs), virus-like particle or nanoparticle vaccines and DNA vaccines, are also waiting for their chance to contribute.

Every product class has different strengths and faces different challenges in reaching the clinic. As companies scramble to form new consortia and partnerships that meld discovery and manufacturing expertise, tried-and-tested small molecule and mAb development programs look the most likely to provide the fastest route to a first line of treatments. It may be that machine learning can supercharge such discovery programs (see Box 1). But it is becoming increasingly clear that the biggest problem for drug and vaccine makers is not which therapeutic or vaccine platform to pursue. It is that conventional clinical development paths are far too lengthy and cumbersome to address the current public health threat. Several groups are now exploring how to retool the development process to find solutions.

Arrested development

Commercial biopharmaceutical discovery is a less than ideal vehicle for responding to an outbreak of a new viral pathogen spreading like wildfire through an immunologically naive population. Drug manufacturers are accustomed to navigating a regulatory and clinical development process that typically takes years, sometimes a decade or more; similarly, regulators have little experience for drug development in the context of a pandemic. There is no accelerated pathway for COVID-19 or any other emerging infectious disease.

A second problem is that for antiviral R&D, funding needs to be not only available when the pathogenic threat is clear and present but also sustained in between outbreaks. "In pharma, everything takes time, and it takes longer if you have to start from zero," says John Rex, an infectious diseases physician and operating partner with Advent Life Sciences in London. Thus, novel antiviral discovery and development against COVID-19, or any other emerging pathogen for that matter, faces a problem of basic economics: there are no market mechanisms for unpredictable outbreaks.

Rex sees close parallels between the situation in epidemic preparedness and his own preoccupation over several decades — preventing antibiotic overuse and the emergence of antimicrobial resistance. "Both these things," he says, "are true honest-to-God market failures. They meet the three technical tests for market failure [positive externalities, negative externalities and non-excludability], meaning that government intervention has to be the way you get things done." Robin Shattock, director of the Future Vaccine Manufacturing Hub at Imperial College in London, agrees. "You need a flu vaccine every season and that's great commercially. But a successful outbreak vaccine kills the outbreak and suddenly, there's no market!"

This is certainly how things were back in 2002–2003 for the original outbreak of SARS. A single phase 1 drug study (NCT00215826) and two phase 1 vaccine studies ran to completion. Both vaccines were well tolerated and induced neutralizing antibodies. But the SARS epidemic ended by the time the products were developed, so neither was tested under natural challenge.

In addition, John Rex argues that, since 2003, the 'Tamiflu incident' in the late 2000s set back efforts to construct the non-market mechanisms that might have helped address infectious disease outbreaks. Fearing an overwhelming outbreak of avian influenza, health authorities in the United States, France, Germany, the United Kingdom and elsewhere stockpiled Basel, Switzerland-based Hoffmann-La Roche's approved antiviral Tamiflu (oseltamivir). But when the pandemic failed to materialize and governments were left with warehouses full of unused antivirals, "there was a lot of hand-wringing," says Rex. "Officials felt cheated, 'ripped off' by pharma rather than being happy the pandemic didn't occur."

Rex believes that governments should regard effective antivirals and vaccines not as a burdensome drain on limited resources, but rather much as householders regard insurance policies and fire extinguishers: as products we buy hoping never to have to use.

Non-market funding mechanisms

Fast forward to 2020 and a few non-market mechanisms are starting to appear. The Oslo-based Coalition for Epidemic Preparedness Innovations (CEPI), the Platform for European Preparedness Against Re-Emerging Epidemics (PREPARE) out of Antwerp, Belgium, and the US Defense Advanced Research Projects Agency (DARPA)'s Pandemic Prevention Platform (P3) program are three of the most prominent.

CEPI was established in 2017 and since then has attracted over $750 million in funding from the governments of Australia, Belgium, Canada, Ethiopia, Norway, Germany, Japan and the United Kingdom and from the Bill & Melinda Gates Foundation and the Wellcome Trust. Its original remit was to fund industry and academic groups to develop vaccines for emerging infections, and it came into being after the disastrous 2014–2015 Ebola outbreak in West Africa, according to director of vaccine research and development Melanie Saville.

Box 2 | Preparing for a pathogen

One shortcut in preparedness for disease outbreaks is to recognize the shape of the likely threat. This is why one of the early decisions at CEPI was to lay out strategies to deal with the next major infectious disease epidemic, 'Disease X'. Back in October 2018, CEPI's director of vaccine development, Melanie Saville, outlined her organization's thinking at a technical summit meeting held in upstate New York, stating that a new disease emerges every four months on average and that Disease X was likely to be zoonotic in origin.

The research groups in DARPA's P3 had the challenge of providing passive immune protection "against any pathogen." But Greg Sempowski, director of the Duke Human Vaccine Institute (DHVI), one of the groups involved, said that the scope of the likely threat in reality was narrower than the brief. "It's not coming from Mars, right?" he says. "It was going to be some variation of a relatively known virus family, and that's exactly what this is."

"Coronaviruses are endemic in lots of animal species and can spill over into humans," says Sarah Gilbert, leader of the vaccine and emerging pathogen program at the Jenner Institute "so it wasn't a really big surprise that it was a coronavirus causing this outbreak."

Anticipating certain classes of viruses as likely threats is useful, but it is even more useful to be able to monitor the precise character of viruses as they move within and around natural and intermediate animal reservoirs. At present, the best example of this approach occurs in seasonal influenza, where detecting the appearance of new combinations of hemagglutinin and neuraminidase antigens in domestic animals and birds is used to direct interventions, such as culling or the design of annual vaccines.

The field systems for monitoring virus transmission and evolution of coronavirus and other emergent pathogens are underdeveloped, but rapid genome sequence technologies make it plausible to broaden the scope and frequency of sampling in likely animal reservoirs. Vincent Munster's group at NIAID's virus ecology unit in Hamilton, Montana, studies infectious viruses in animal reservoirs and how information on the way they move into human population can guide intervention strategies. He says that it might be possible to greatly improve the monitoring systems in the chain of infections that leads to outbreaks. "We would need a system which links genotype to phenotype in a way which would keep up with the generation of the sequence data," he says.

At present, though, only rarely is it possible to link sequence data to physiological characteristics of potentially infectious viruses. For instance, the receptor-binding domains of SARS-CoV-2 looked similar to those in SARS-CoV, and, says Munster, "it was reasonable to assume it would bind human ACE2." Such a marker in an animal virus might have been a hint about its zoonotic potential. However, the relationship is not simple: many SARS-like viruses also use ACE2 and their epidemic potential is much more limited.

In theory, Munster says, better mechanisms for tracking the evolution of molecular details could help anticipate whether emergent viruses might have the capacity to infect the lower and/or upper respiratory tract or block host innate immune systems, factors that influence subsequent transmission patterns and pathogenicity. "But typically there are hundreds of specific virus–host interactions, and at the moment do not know which are specific or important for spillover/zoonotic transmission."

"Despite a decade of research, there were no clinically tested [Ebola] vaccines when the outbreak occurred," she says. "Market forces had failed, and there was clearly a need for an organization that could focus on vaccine development for emergent infections."

CEPI now funds the development of 17 vaccines against 5 priority pathogens, but it also funded programs for unknown future emergent pathogens — programs for 'Disease X'. 'Disease X' now has a name: COVID-19.

In the European Union, there is also an overarching program called PREPARE, which mobilized a series of project grants from the European Union's Innovative Medicines Initiative to establish a network 1,000 hospitals and 900 first-line diagnostic laboratories in 42 countries in Europe. "PREPARE worked because it acted ahead of time," says the program's coordinator, Herman Goossens from the University of Antwerp Vaccine and Infectious Disease Institute in Antwerp, Belgium. In its "peacetime activities" (before the COVID-19 outbreak), PREPARE provided its network with, among other things, protocols for pathogen diagnosis based on RT-PCR and registered clinical trial methodologies for each center.

"If there was going to be a pandemic, then it was likely to be a respiratory virus," Goossens explained, "so our focus was acute respiratory infections in the ICU [intensive care unit] and in primary care." In 2016, PREPARE set up the REMAP-CAP trial (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), the main point of which was to capture the clinical outcomes of physician-prescribed interventions for respiratory infections. The result of REMAP-CAP will show, at least in the European, Australian and New Zealand centers involved, which of the many conventional treatments that are being used in the current outbreak were most effective.

In the United States, DARPA has a different target. The groups funded under P3 have been challenged to develop platforms that could provide antibody protection to military personnel rapidly after receiving a sample from DARPA. Moreover, because P3 is a pandemic program, the platform set up has to be capable of responding to any pathogen (see Box 2).

Working against the clock

CEPI's "aspirational goal" is to go from virus sequence to phase 1 trial of vaccine candidates in 16 weeks — "a real test," Saville concedes. The DARPA P3 timetable is even more stringent: 60 days. "If we had had countermeasures within 60 days with previous outbreaks — H1N1 swine flu in 2009 and Ebola in 2014–2016 — we could have potentially made a difference," says P3 lead Amy Jenkins, "and it is also technically very challenging."

For both DARPA and CEPI, these time constraints disqualify many of biotech's approaches to therapeutic or vaccine development.

Designing specific antivirals is perfectly possible in a longer timeframe that allows cycles of structurally guided medicinal chemistry followed by preclinical and human safety testing. But even there, trying to accommodate the range of organisms that might turn up by designing broad-spectrum antivirals is not facile, as Christian Klein, a medicinal chemist at the Institute of Pharmacy and Molecular Biotechnology at Heidelberg University in Germany, points out. "To some extent 'broad' is connected to 'non-specific', and that opens another can of worms," he says.

DARPA has favored mAbs as passive immunity agents since around 2011 because of their selectivity, safety and relatively long persistence in the body. But at that time,

the most advanced processes for identifying neutralizing antibodies and manufacturing them took at least two years. This was electrically fast by industry standards, says Jenkins, but "obviously not a rapid response."

Monoclonals turn to nucleic acids

Even if getting a phase 1 trial and investigational new drug (IND) application continues to get faster — these days it can be as fast as 12 months — DARPA has a keen interest in new technologies that can slash preclinical development times for mAb programs targeting emerging pathogens. One such technology is nucleic-acid-encoded mAbs (Table 1).

First demonstrated as effective against human immunodeficiency virus (HIV) in 2009 by Philip Johnson and colleagues at the University of Pennsylvania, the approach was further refined by David Baltimore's group at Caltech for use against influenza in 2013. Using an adeno-associated virus to deliver to muscle nucleic acid encoding two broadly neutralizing mAbs, Baltimore's team demonstrated that long-lasting (11-month) immunity from influenza virus infection could be achieved in mice.

While these early studies all employed DNA as the encoding nucleic acid, more recent efforts have taken the concept further, substituting mRNA for DNA. Messenger RNA has the advantage of immediate protein production in the cytosol and reduced concerns over genomic integration. In 2017, another University of Pennsylvania group led by Drew Weissman collaborated with Vancouver-based Acuitas Therapeutics to show that modified mRNA encoding neutralizing antibodies could protect mice against HIV challenge.

DARPA seized on these findings as evidence that mRNA-encoded mAbs could fulfil its P3 goals. One of its earlier programs, ADEPT (Autonomous Diagnostics to Enable Prevention and Therapeutics), had shown that rapidly identifying neutralizing antibodies could provide a protective response in animals. But the brief under P3 was to incorporate other technology elements — notably, DNA or mRNA design and manufacturing — into robust packages. P3 had four 'shots on goal' with projects at two industrial groups and two US academic centers: Vancouver, Canada-based AbCellera in partnership with Ichor Medical Systems, Cambridge, UK-based AstraZeneca's Medimmune unit, the Duke Human Vaccine Institute (DHVI) and Vanderbilt University.

The core of the antibody discovery platform at AbCellera is a credit-card-sized microfluidic device containing around 100,000 chambers, each nanoliter-sized. The system is seeded with a blood sample from one convalescent patient who has recovered from infection. "The small chamber volumes mean that it only takes ten minutes to an hour for antibody concentrations to build to levels that we can test for target binding," says Ester Falconer, AbCellera's head of research and development.

AbCellera has already demonstrated that it can meet DARPA's stringent schedule, although not for coronavirus. Last year, the company tested its system using a donor sample from a patient who had recovered from influenza. Within one day of screening, the company discovered 191 distinct antibodies and isolated "many dozens" of potent neutralizing antibodies that proved protective in a mouse model of influenza. "All of that happened in less than 55 days," says Falconer, "and the simulation was quite close to what we're now attempting with COVID-19." On 11 March, Eli Lilly announced its intention to co-develop the COVID-19 mAbs discovered by AbCellera.

In contrast to AbCellera's effort, the P3 program at Duke anticipated that little would be known about the emergent infection. With a facility licensed for work on level 3 pathogens, part of DHVI's routine role is to provide cultures of pathogens, such as West Nile virus or dengue virus, to other investigators within the NIH research family. But for P3, the requirement was to develop systems that are pathogen-agnostic. "It is not possible to know what the virus might be or its optimal culture conditions," says DHVI director Greg Sempowski. "So we built a platform with multiple cell lines that would grow the virus in vitro."

Downstream from that, the group developed an epitope-agnostic method using fluorescence-activated cell sorting to selected pathogen-specific B cells. The route from there to the mRNA agent end-product involved a series of relative standard molecular workflows: PCR reactions to isolate heavy- and light-chain variable regions, Gibson assembly (joining multiple DNA fragments simultaneously) into expression vectors with common constant regions, and transient expression to produce antibodies for virus binding and neutralization assays. Simultaneous sequencing of the inserts provides the grist to allow the Duke mRNA delivery to linearize the sequence, manufacture purified mRNA and formulate it in lipid before in vitro functional or preclinical testing.

It's quick, but does it work?

Validation for DARPA's concept of passive immune protection comes in the form of AstraZeneca's Synagis, says the agency's Amy Jenkins. Synagis (palivizumab) is a humanized immunoglobulin G (IgG)-1κ mAb against an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). "Every winter, we give premature infants … palivizumab so they do not get RSV." mAb against an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). "Every winter, we give premature infants … palivizumab so they do not get RSV." Palivizumab is as safe as placebo and reduces RSV-related hospitalization in newborns by 40–80%, according to a 2014 metastudy. That study also suggests that passive protection with 15 mg/kg of a single mAb is effective — that's a 50-mg dose for a premature baby but a gram for a 75-kg man or woman at the same dosing rate.

Little is known definitively about the effective dose of protective mAbs outside RSV. According to ClinicalTrials.gov, there are over 100 phase 2 studies looking at mAbs against viral infections, but none in phase 3.

There is also the question of whether mRNA- or DNA-encoded mAbs, compared with a conventional mAb provided as a protein product, is expressed at therapeutic levels, at which it can elicit the required protective response. "This was an unheard-of technology a few years ago," Amy Jenkins says, "We have done a phase 1 safety study; we believe that that antibody is expressed at a level that would be protective, but we haven't done the efficacy model. We still do not have efficacy data for a DNA- or an RNA-encoded antibody."

There are similar questions over DNA and mRNA vaccines, which constitute half of the half dozen eggs in CEPI's COVID-19 basket. (Table 2) Will they be expressed in a manner that they elicit protective antibody responses across the global population in different genetic backgrounds and in individuals of all ages? CEPI's recent funding call for COVID-19 is supporting work on such approaches in at least three biotech firms — CureVac of Tübingen, Germany, Inovio Pharmaceuticals, and Moderna — as well as groups at the Universities of Oxford in the United Kingdom and Queensland in Australia.

Nucleic acid vaccines' moment

CureVac has found itself at the center of an alleged and unseemly turf war between the US and German governments. Shortly after appearing at a roundtable of top biopharma leaders with President Trump in March, CureVac CEO Daniel Menichella left the company and was replaced by original founder Ingmar Hoerr. Hoerr stepped back after a week for medical reasons, reportedly not COVID-related, and acting CEO Franz-Werner Haas stepped in. In mid-March, stories circulated that Trump offered funds

Table 1 | Selected experimental therapies under development for COVID-19

Company	Modality	Status	Partners
RNAi			
Alnylam Pharmaceuticals	Aerosolized delivery of siRNA chemistry optimized for lung uptake	Alnylam has synthesized 350 siRNAs to SARS-CoV2;Vir will conduct in vitro and in vivo testing	Vir Biotechnology
Sirnaomics	Respiratory-specific siRNA formulation that is delivered by a customized handheld nebulizer device	Preclinical	
Recombinant proteins			
Apeiron Biologics (Vienna)	Recombinant ACE2 enzyme (APN01; binds virus in circulation and blocks entry)	24 patients in randomized, unblinded clinical trial in China	
Monoclonal antibodies			
AbCellera Biologics (Vancouver, British Columbia, Canada)	Fully human IgG1 mAbs targeting SARS-CoV-2 developed from polyclonal antibodies identified in sera of convalescent patients	Discovered 500 unique antibodies from one patient with COVID-19	Eli Lilly for manufacture and scale-up
Beijing Defengrei Biotechnology	Fully human IgG1 mAb targeting complement factor 5a	Approved for phase 1 clinical trials in China in February 2020	
EUSA Pharma (Hemel Hempstead, UK)	Sylvant (siltuximab), human IgG1κ mAb against IL-6	Observational case–control study in patients with respiratory symptoms	Papa Giovanni XXIII Hospital (Bergamo, Italy)
Harbour Biomed (Shanghai)	Fully human IgG1 mAb (47D11) targeting the full-length spike (S) proteins of SARS-CoV and SARS-CoV-2	Antibody reformatted from chimeric mAb identified via SARS2-S1 subunit screening in hybridomas derived from mice engineered with two human heavy and light chains and a rat constant region (H2L2)	Research partnership with Mount Sinai Health System
ImmunoPrecise Antibodies (Victoria, British Columbia, Canada)	Fully human IgG1 mAbs targeting multiple undisclosed epitopes (polytope) on SARS-CoV-2	Reactive B cells were profiled in animals immunized with designed SARS-CoV-2 target antigens (e.g., S protein or Nsp15) and phage display used to identify neutralizing mAbs that show broad cross-species reactivity, which are reformatted as fully human molecules	EVQLV to provide computational antibody design expertise to optimize novel mAbs. Ligand Pharmaceuticals to combine its OmniMab platform with B Cell Select and DeepDisplay antibody technologies.
InflaRx (Jena, Germany)	Fully human IgG1 mAb against complement factor 5a	Approved for clinical trial in China	
Vir Biotechnology	Human IgG1 mAbs targeting SARS-CoV-2 developed from polyclonal antibodies identified in sera of convalescent patients	Vir has also identified two mAbs targeting the human angiotensin-converting enzyme ACE2 receptor	WuXi and Biogen to provide scale-up/manufacturing in China and United States, respectively
Others			
NanoViricides	SARS-CoV-2 S protein chemically attached to virucidal nanomicelle flexible polymer and polyethylene glycol	Testing candidates in culture	
Pharmamar (Madrid)	Aplidin natural product from marine tunicate *Aplidium albicans*, targeting elongation factor 1A	Positive in vitro studies against SARS-CoV-2–related coronavirus, requesting IND from regulators in mid-March	

Does not include polyclonal or IgG products extracted from convalescent patient serum. Sources: BioWorld, company sites, Thomson Cortellis, PubMed

to bring CureVac and its COVID-19 mRNA vaccine exclusively to the United States. But in a press conference on March 18, Haas said that they cannot "confirm or reject" that they had any offer by the president. CureVac's main backer, software billionaire Deitmar Hopp, said that the vaccine should be available "not only regionally, but to people all over the world …."

Around the same time, another German mRNA vaccine developer, Mainz-based BioNTech, clinched a $135 million deal with Fosun Pharma in Shanghai to co-develop its product against SARS-CoV-2. In return, Fosun will share gross profits from sales of the vaccine in China together with clinical trial, regulatory and commercial assistance to advance the vaccine.

RNA vaccine giant Moderna has already announced interim data from it phase 1 data for its cytomegalovirus (CMV) mRNA vaccine (mRNA-1647), which comprises a mixture of six mRNAs, five of which encode subunits of the CMV pentamer complex and one of which encodes the glycoprotein B. Participants were randomized to receive either placebo or 30, 90, 180 or 300 micrograms of mRNA-1647 given at zero, two and six months. The interim analysis showed that after the third and final dose of the vaccine, participants achieved neutralizing antibody titers against CMV as well as glycoprotein B T-cell reactivity, with

Table 2 | Selected vaccines under development for COVID-19

Sponsor	Modality	Status	Partners
Altimmune	Single-dose intranasal replication-defective adenovirus vector vaccine incorporating the SARS-CoV-2 S protein	Design and synthesis completed; moving toward animal testing and manufacture. Phase 1 trial planned for mid-August.	None
Arcturus	Self-transcribing and replicating RNA (STARR) vaccine expressing undisclosed epitope(s) delivered by lipid nanoparticle comprising 50% ionizable amino lipid or MC3, 7% 1,2-distearoyl-*sn*-glycero-3-phosphocholine, 40% cholesterol and 3% 1,2-dimyristoyl-*sn*-glycerol, methoxypolyethylene glycol	Manufacturing stage	Duke-NUS Medical School (Singapore) will provide rapid screening technology; $10 million in funding from Singapore government
BioNTech (Mainz, Germany)	mRNA vaccine (BNT162) expressing codon-optimized undisclosed SARS-CoV-2 protein(s) encapsulated in 80-nm ionizable cationic lipid/ phosphatidylcholine/ cholesterol/polyethylene glycol–lipid nanoparticles	Clinical testing to begin late April	Pfizer extends 2018 influenza agreement to work on COVID-19 candidate; Fosun Pharma, which paid $50 million in equity with a further $85 million in milestones, will collaborate in running clinical trials in China
(Sichuan) Clover Biopharmaceuticals (Chengdu, China)	Recombinant SARS-CoV-2 S protein trimer subunit vaccine	In preclinical testing with GlaxoSmithKline's pandemic adjuvant technology	Partnered with GlaxoSmithKline, which provides pandemic adjuvants platform comprising squalene, DL-α-tocopherol and polysorbate 80
Codagenix	Computationally designed and recoded live attenuated SARS-CoV-2 vaccine	Multiple codon-deoptimized SARS-CoV-2 vaccine candidate genomes designed on the basis of multiple genome sequences	Serum Institute of India to scale-up manufacture
CureVac (Tübingen, Germany)	Protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s)	Phase 1 in June or July	$8.3 million in funding from CEPI
Generex Biotechnology	Undisclosed SARS-CoV-2-derived synthetic peptide conjugated at N terminus to the C terminus of the key moiety of the major histocompatibility complex class II–associated invariant chain (Ii protein) containing a four-amino-acid (LRMK) modification (Ii-Key)	Human trials in June	EpiVax provides epitope prediction; Institute of Shandong Academy of Sciences tests the reactivity of candidate peptides in blood samples collected from convalescent patients
GeoVax	Modified vaccinia Ankara virus-like particle vaccine based on Wuhan strain of SARS-CoV-2	Candidates in animal studies	BravoVax (Wuhan, China) to provide manufacturing and clinical testing
Heat Biologics	Heat-shock protein gp96 complexed with undisclosed SARS-CoV-2 peptide(s)	Program announced March 3	
iBio	Platform based on *Agrobacterium*-transformed tobacco for producing virus-like particle with undisclosed SARS-CoV-2 peptide(s) combined with its lichenase carrier immunostimulatory adjuvant	Program announced in February	Partnering with Beijing CC- Pharming, which has previous MERS vaccine experience
Inovio Pharmaceuticals	Electroporated DNA vaccine INO-4800 encoding SARS-CoV-2 S protein	Trials to begin in April in United States followed by China and South Korea; 3,000 doses available	Beijing Advaccine Biotechnology partnering for trials in China and Gates Foundation for Celletra electroporation device; funding from CEPI ($9 million) and Gates Foundation ($5 million)
Janssen (Johnson & Johnson)	Single-dose intranasal recombinant adenovirus vaccine incorporating undisclosed SARS-CoV-2 protein using human retinal cell line (Per.Co6) scale-up technology	Seven constructs being tested in mice; phase 1 testing anticipated in October 2020 to February 2021	BARDA
LineaRx	Electroporated linear DNA vaccine	Four candidates of linear DNA vaccine based on S protein and selected epitopes ready for testing by the beginning of May or June	Takis Biotech (Rome) to clinical test candidates in Italy
Medicago (Quebec City)	Undisclosed recombinant SARS-CoV-2 protein virus-like particles produced in tobacco	Virus-like particles produced within 20 days; preclinical testing ongoing with clinical trials to begin summer 2020	Laval University Infectious Disease Research Centre

Continued

Table 2 | Selected vaccines under development for COVID-19 (Continued)

Sponsor	Modality	Status	Partners
Moderna	mRNA vaccine encoding SARS-CoV-2 S protein encapsulated in ionizable lipid, distearoyl phosphatidylcholine, cholesterol and polyethylene glycol lipid	Phase 1 testing under way	NIAID, CEPI
Novavax	Nanoparticle vaccine displaying SARS-CoV 2 S protein with saponin-based (Matrix-M) adjuvant	Animal testing of candidates underway	$4 million in funding from CEPI
Sanofi (Paris)	Recombinant vaccine of undisclosed SARS-CoV-2 protein(s) expressed in baculovirus system	Advancing preclinical candidate; clinical trial to begin between March and August 2021	BARDA
Tonix Pharmaceuticals	Live-attenuated modified horsepox vaccine expressing undisclosed SARS-CoV-2 protein(s) (TNX-1800)	Pre-IND in February 2020	Collaboration with non-profit Southern Research
University of Queensland (Brisbane, Australia)	Recombinant subunit vaccine of SARS-CoV-2 S protein locked in prefusion conformation by polypeptide moiety (molecular clamp)	Preclinical as of mid-March	CEPI; Dynavax Technologies to provide Toll-like receptor 9 agonist adjuvant CpG 1018; GlaxoSmithKline to provide pandemic adjuvants platform (squalene, DL-α-tocopherol and polysorbate 80); CSL (Parkville, Australia) to provide MF59 adjuvant (containing squalene in citric acid buffer with stabilizing nonionic surfactants Tween 80 and Span 85)
Vaxart	Oral recombinant adenovirus 5 vector vaccine of undisclosed SARS-CoV-2 protein(s) aimed at mucosal immune response	Preclinical as of mid-March	
Vaxil Biotherapeutics (Ness Ziona, Israel)	Human signal peptide domain complexed with undisclosed SARS-CoV-2 protein(s) as vaccine	Vaccine candidate identified by in silico analysis as of mid-March	
Zydus Cadila (Ahmedabad, India)	Electroporated DNA vaccine and live attenuated recombinant measles vaccine vector of undisclosed SARS-CoV-2 protein(s)		

Sources: BioWorld, company sites, Thomsen Cortellis, PubMed

relatively minor adverse events including fever, headache, myalgia and chills.

With these data in hand, Moderna's phase 1 submission for its anti-SARS-CoV-2 vaccine mRNA-1273 is also testing a broad dosing range — from 25 to 250 micrograms. That, says Melanie Saville, is what one would expect. "It is important to have a range, especially in an outbreak, because we know that number of doses will be an issue." The first of 45 patients in that trial was dosed on 16 March.

Elsewhere, Inovio is developing a DNA vaccine (INO-4800) against SARS-CoV-2. Last September, Inovio's partner in emergent diseases, GeneOne Life Sciences of Seoul, South Korea, published phase 1 data on a DNA vaccine for MERS (GLS-5300) that uses a similar technology. That vaccine which showed a robust immune response following a dose-escalation protocol of 0.67, 2 or 6 milligrams via one-milliliter intramuscular injections at baseline, week 4 and week 12 followed immediately by co-localized intramuscular electroporation. Participants showed both antibody and a cellular response, but it remains unclear whether that response is protective.

Not all vaccine platform technologies are equally immunogenic, says Sarah Gilbert, vaccines group head the Jenner Institute in Oxford. Under an $19 million 2018 agreement with CEPI, Jenner together with Janssen Vaccines & Prevention of Leiden in the Netherlands is developing adenoviral-vector vaccines against MERS, Nipah virus infection and Lassa fever. In March, CEPI added SARS-CoV-2 to the roster. Gilbert argues that DNA and RNA vaccines are relatively simple and easy to make but, as in effect 'dead vaccines', tend to need two or three doses, even where the intracellular uptake of a DNA vaccine has been boosted through electroporation. "With replication-deficient adenovirus, a single dose is usually effective," she says.

Safety issues

Vaccine safety is one aspect that will need particular attention, says Robin Shattock. "When you think about developing a vaccine for global use, you have to do a lot of work to make sure it's safe. And you have to remember that you're using a vaccine in a population where maybe the fatality rate is 1 or 2%. It may be lower for people who are below the age of 60. So most people are not going to have any complications from the infection itself. You need to make sure that the vaccine isn't going to cause any problems in that population at all."

This is pertinent as previous coronavirus vaccines have not all proven appropriate or even safe. In one case, ferrets administered a recombinant SARS-CoV S protein vaccine based on a modified vaccinia virus Ankara and subsequently challenged with SARS-CoV not only were not protected but also exhibited an immunopathologic liver reaction — termed antibody dependent enhancement (ADE). This ADE problem had been previously seen in a US trial of a formalin-inactivated RSV vaccine in infants in the 1960s and resulted in the 2017 withdrawal in the Philippines of Dengvaxia, a live-attenuated tetravalent vaccine against dengue fever produced by Sanofi.

Even though there was not much follow-through of vaccine candidates following the SARS outbreak, two separate SARS vaccines did make it through phase 1 trials: one used inactivated SARS virus and the other used recombinant spike protein formulation. Both led to a T-helper type 2 cell-shifted immune responses and were well tolerated. However, in subsequent studies, mice inoculated with either vaccine and then challenged with SARS-CoV displayed hypersensitivity, resulting in severe immunopathology. The SARS vaccines were only safe as long as no virus challenge occurred.

Gilbert says these findings are reason enough "for caution in proceeding to application of a SARS-CoV vaccine in humans." And it will be essential for any SARS-CoV2 vaccine program that these effects be ruled out.

Everything depends specifically, Gilbert says, on how strong a response is protective against SARS-CoV2. For some infections — Nipah virus in humans or Hendra virus in horses — very low neutralizing antibody titers protect. But with SARS-CoV-2, she says, "we don't know how strong an immune response will be necessary. We don't know the correlates of protection for any human coronaviruses, despite the fact that we have SARS and MERS; and there are four other circulating human coronaviruses [causing some cases of the common cold] that we know very little about."

Antibody manufacturers up their game

Although CEPI's mAb programs have focused on nucleic-acid-encoded molecules, most of the industry's manufacturers make mAbs by an entirely different means: Chinese hamster ovary (CHO) cell lines, which at large scale (>100 liters) can generate grams of mAb product in a single batch. Two of the biotech sector's flagship companies, Regeneron and Biogen, have recently announced programs against COVID-19 using such technology.

On 2 March, Regeneron president and CEO Leonard Schleifer stated in a televised White House meeting that his company could start producing 200,000 doses per month of an investigational COVID-19 antibody therapy by August. Two days later, Regeneron announced that the US Department of Health and Human Services would expand an existing research funding agreement with the company to use its human antibody discovery platform, VelociSuite, to develop new coronavirus treatments. Investors welcomed the news, pushing the company's market cap up by a massive $10–12 billion.

The VelociSuite platform is based on mice engineered with a humanized immune system that can be challenged with all or parts of a virus of interest and used to generate fully human mAbs. Importantly, antibodies from this platform have already been used in a phase 1 study in MERS (from which there are as yet no published results). Regeneron's earlier preclinical studies showed that two neutralizing antibodies used prophylactically reduced MERS viral load and lessened respiratory disease in mice and marmosets. On 17 March, Regeneron said its researchers have isolated hundreds of SARS-CoV-2-neutralizing, fully human antibodies from its mice and other antibodies from people who have recovered from the virus.

In a separate program, Regeneron is also collaborating with Sanofi to start clinical testing of its rheumatoid arthritis drug Kevzara (sarilumab), an anti-interleukin-6 receptor IgG1 mAb, as a potential therapy to address the cytokine storm and excessive inflammation that can arise following SARS-CoV-2 infection.

Elsewhere, Biogen, whose leadership has been severely affected by the COVID-19 outbreak at the company's annual strategy meeting in Boston, signed a letter of intent on 12 March with California startup Vir Biotechnology for the development and clinical manufacturing of the latter's COVID-19 mAbs.

Vir is focused on developing monotherapies and combinations targeted against infectious agents, including hepatitis B virus, HIV, RSV, influenza, CMV, norovirus and rabies virus. A unicorn startup founded with a massive funding tranche of more than $500 million, it has built a portfolio of over 40 products on the basis of its human-derived mAb technology (brought on board from its acquisition of Humabs BioMed), computational mAb design expertise (through partnership with Visterra) and CMV-vector-based vaccine technology obtained through acquisition of TomegaVax in 2017.

When Vir announced in late January that it was tackling SARS-CoV-2, its stock leapt from around $12 to over $20 a share. The startup's program aims to repurpose mAbs identified from the convalescent serum of individuals infected with SARS-CoV in the previous outbreak during the noughties; it has been searching for variants of these molecules that bind to the new SARS-CoV2. In recent weeks, it announced it is working with the US National Institute of Allergy and Infectious Diseases (NIAID) to identify and optimize antibody combinations against SARS-CoV-2, SARS-CoV, MERS-CoV and other types of coronavirus.

The startup is not only working with Biogen. In February, it announced a collaboration with WuXi Biologics in Shanghai to develop and manufacture two mAbs against SARS-CoV2. This partnership, and that with Biogen, is typical of the types of collaboration springing up in industry to link discovery and development expertise (see Box 3), although in this case Vir CEO George Scangos already had strong links to Biogen: from 2010 to 2017 he served as Biogen CEO. Scangos is also chairing a committee at the Biotechnology Innovation Organization (BIO) focused on coordinating the industry's COVID-19 response.

Oligonucleotide therapies on the radar

Vir also announced 4 March that its 2017 agreement with Alnylam Pharmaceuticals to develop RNA interference (RNAi) oligonucleotide therapies against infectious agents would be expanded to include SARS-CoV-2. Alnylam has already synthesized over 350 siRNAs against all available RNA genomes of SARS-CoV and SARS-CoV-2. Following in vitro potency testing, Vir will undertake preclinical testing for antiviral activity and lead selection and also spearhead downstream clinical development and commercialization. Before trials begin, Alnylam has an opt-in right for a 50–50 share of profits and losses associated with the program.

Elsewhere, Sirnaomics, a company that previously developed siRNA drugs for the 2003 SARS-CoV outbreak, H5N1 influenza and other respiratory viral infections, has also initiated an COVID-19 program focused on its respiratory-specific siRNA formulation that is delivered by a customized handheld nebulizer device.

As yet, there has been comparatively little attention to RNAi programs for SARS-CoV-2, which is surprising as many of the early commercial RNAi programs were directed against viruses, such as RSV or CMV.

According to Kevin FitzGerald, CSO at Alnylam, "RNAi is a powerful, natural cellular mechanism that is uniquely suited as an antiviral strategy." Like antisense oligonucleotides (ASOs), the sequence-based approach for RNAi therapeutics allows quick design and testing of molecules with potent antiviral activity. Oligonucleotide chemistry is also well established and generally consistent from one product to another, which simplifies manufacture compared with more complex protein biologics. What's more, current siRNA chemistries provide "exceptional stability, even at room temperature, potentially obviating the need for a cold chain and thus facilitating distribution," says FitzGerald. Nucleotide chemistry may also offer "the potential to accelerate timelines

Box 3 | Collaboration, networks and partnerships

"There is a very coordinated [US] government response to this right now..." says Amy Jenkins, the lead for DARPA's P3 program. "Just with coronavirus, I have at least ten phone calls a week with BARDA and the Assistant Secretary of Preparedness and Response." Those are just the standing calls, she says, and then there are supplementary calls with the National Institutes of Health and others with BARDA (the Biomedical Advanced Research Development Authority). Outside the United States, DARPA channels its interactions with WHO through colleagues in the US Department of Health and Human Services and works closely with CEPI, whose director, Richard Hatchett, was the former director at BARDA. Its networks extend to other centers in Europe and Asia, notably with Department of Defense OCONUS laboratories (Outside of Continental United States). "There are lot of moving parts," says Jenkins, "but it all works."

Melanie Saville at CEPI believes that it is "critically important" to have formed relationships prior to any outbreak not only with overarching bodies like the WHO but also with "downstream people" such as regulators and those who will deploy the vaccines. "Having the network in place and engaging with all the stakeholders ahead of time is really important," she says, "You don't want to be exchanging business cards during a during an emergency or during an outbreak."

Pre-formed relationships have been important in biotech's response to COVID-19. Regeneron and its long-term development partner for its biologicals outside North America, Sanofi, began a clinical program to evaluate Regeneron's approved IL-6-receptor-blocking rheumatoid arthritis drug Kevzara against COVID-19 after the reported success of another IL-6-receptor blocker, tocilizumab, originally developed by Tokyo-based Chugai and Roche of Basel, Switzerland.

Vir Biotechnology CEO George Scangos has been leveraging connections in the industry to help propel COVID-19 projects forward. Vir and Alnylam already had a development deal in infectious diseases focused on hepatitis B dating back to 2017, sharing post-phase 2 option rights 50–50. The two companies expanded that deal on 4 March to take forward a collection of siRNA candidates that Alnylam produced to target SAR-CoV-2 and other coronaviruses.

Then on 12 March Vir announced that Biogen, based in Cambridge, Massachusetts, had committed to being its North American development and clinical manufacturing partner for the proprietary anti-SARS-CoV-2 mAbs that Vir isolated from convalescing patients who had COVID-19. Personal connectivity provided the trust to bring a deal together quickly and to allow both companies to begin work before the legal niceties of the deal were completed. The Biogen deal complemented Vir's earlier (25 February) development and clinical manufacturing agreement with WuXi Biologics covering greater China.

Similarly, BioNTech will co-develop and distribute its experimental COVID-19 mRNA vaccine, BNT162, with Pfizer, its existing partner for the development of mRNA influenza vaccines. The worldwide deal with Pfizer excludes China, for which BioNTech has partnered with the Shanghai Fosun Pharmaceutical Group.

for CMC and preclinical development," he adds, with the caveat that it is too early to comment on what a preclinical and clinical development plan for an RNAi therapeutic targeting SARS-CoV-2 might look like.

A final advantage of oligonucleotides is that they can be designed to target highly conserved regions of a virus. "Small interfering RNAs could have cross-reactivity against related viral strains, may continue to remain effective as a virus mutates in the community, and potentially could have activity against a future novel, but related, emergent virus (e.g., SARS-CoV-2 and SARS-CoV)," says FitzGerald.

For respiratory infections, the big question, though, is delivery. Here again, progress is already being made. Last June, at the 3rd International Conference on the Long and the Short of Non-Coding RNAs in Chania, Crete, Alnylam presented mouse data in which aerosolized delivery to the lungs via a pressurized syringe showed similar potency and duration of activity to those of *N*-acetylgalactosamine-conjugated siRNA molecules delivered subcutaneously and targeted to the liver. According to FitzGerald, "The current set of siRNA molecules against SARS-CoV-2 comprises modifications designed to enhance lung delivery."

Similarly, published preclinical and clinical results in cystic fibrosis also give confidence that naked phosphorothioate ASOs with three constrained ethyl residues at each terminus (the 3–10-3 gapmer configuration) could be administered as antivirals by aerosol for lung disease. Although Ionis Pharmaceuticals currently has no SARS-CoV-2 program underway, according to executive chairman Stan Crooke, "if coronavirus infects airway and pulmonary parenchymal cells, then we would use aerosol delivery, which has been shown to work well in clinical trials of our ASOs."

Extending plug and play

Automation and turnkey systems seem destined to become an increasing factor of the technological response to outbreaks. In 2018 Robin Shattock spoke at the Davos World Economic Forum about the idea that the best way of getting a vaccine delivered wherever it was needed was to use a dispersed mechanism. "The key criteria would be ease of production," he said. "You need a system that is easy to standardize, with a small footprint. Rather than a manufacturing plant the size of a warehouse, it might be the size of two shipping containers." A similar idea of distributed vaccine manufacturing has previously been proposed by J. Craig Venter, with an oligonucleotide-assembly platform under development by Dan Gibson's group at SGI-DNA.

Shattock, Venter and Gibson are not the only ones thinking along those lines. CureVac has been using conventional manufacturing methods to develop mRNA vaccines against a range of viral infections, such as yellow fever, Lassa fever and MERS. But in February 2019 CEPI awarded CureVac a $34 million contract to develop a prototype 'RNA printer': a transportable, 'end-to-end' mRNA printing facility to deliver formulated vaccine quickly as part of an outbreak response.

The idea is that, as soon as an emerging pathogen has been identified or sequenced, a number of RNA vaccines would be designed and rapidly validated, and then the RNA printer would be used to produce a clinic-ready vaccine. The original goal for CureVac and CEPI was to develop a robust system operating in an automated or semiautomated manner remote from any conventional manufacturing facility to deliver the company's rabies vaccine. "In the current situation, you might put a container like that in Wuhan, or Italy or South Korea, where people need to be protected," says CureVac's head of vaccines, Lidia Oostvogels. "We expect to be able to make 100,000 vaccine doses in such a machine."

The RNA printer will not be ready for the current outbreak, however: CureVac only started development a year ago. Oostvogels

expects validation of the system only in 2021. In the meantime, CEPI has contracted CureVac to produce an mRNA coronavirus vaccine through more conventional manufacturing.

Quality in short order

There may be other places in clinical testing, manufacturing controls, quality assurance and product formulation where development times can be cut. As Gilbert puts it: "Normally, if we make a batch of vaccine for a phase 1 trial, we're looking at five to six months of getting it tested afterward to go back the MHRA [UK Medicines and Healthcare Products Regulatory Agency]." Much of this time is spent running old-fashioned and painstaking in vitro and in vivo tests.

One way to speed things up is have rolling testing, rather than a plodding progression of sequential testing whereby tests can only be done one after another. New technology can also help. According to Gilbert, "there's a move to use deep sequencing methods" and high-throughput analytics to characterize products. "But those need to be developed and validated," she says. If this could be achieved, not only vaccine manufacture but also quality control testing could be accelerated.

Many of these aspects have started to be investigated in the context of small batches of personalized vaccines used in cancer treatment. According to Gilbert, the new wave of cancer vaccines uses rapid readouts to ensure the identity and the purity of the product. "Is it exactly the right sequence? Is it all exactly the right sequence? Have you got any mixtures in there in there?" she asks. Sequencing can often provide a rapid answer for nucleic acid vaccines.

Personalized vaccine manufacturing also needs to be fast. Testing cannot last for more than six months as it does in the conventional paradigm. It also needs to be low cost. "The personalized cancer vaccine is going to be expensive anyway, but if you need the full testing package that we would normally do for phase 1, batches would end up [costing] tens of thousands of pounds. You simply can't spend that on each personalized cancer vaccine." Gilbert argues that these streamlined methods used for personalized cancer vaccines could be repurposed for the development of outbreak countermeasures.

"In a small way, all over the world, that process is already starting to happen," she says. "I think for outbreak pathogens … the question is 'who is prepared to put the money up?' All of these technical hurdles can be overcome. We can build a manufacturing plant. We can do rapid release testing. But it's got to be funded."

Missed opportunities

The reappearance of a coronavirus outbreak was predictable. "We've had MERS, SARS and now we've got COVID-19. Right now, we don't know what we need to protect in terms of immune response to protect against any of them. But if we can work out what protects against SARS-CoV-2, it will help with MERS vaccine, for example, and it will help with developing vaccines against other coronaviruses. The specific antigens would be different, but we'd know how to do it," says Gilbert.

In this respect, the lack of a concerted and sustained effort from funding agencies to address the pandemic threat is a missed opportunity. When the original SARS epidemic went away, all SARS vaccine work suddenly stopped. There were also lost opportunities in terms of logging immunological profiles of those who survived severe infections — or indeed of those who didn't. "It would have been useful to know how vaccines from related organisms might provide emergency protection," says Gilbert. "If we had had a SARS vaccine, we could have tried it for COVID-19. We don't know if Japanese encephalitis vaccine might have protected against West Nile outbreaks, or chikungunya against o'nyong nyong," she says.

In due course, financial institutions and economic strategists will make reasoned and detailed estimates of the costs the COVID-19 outbreak. For now, though, we can extrapolate from previous episodes.

The 2014 West African Ebola outbreak cost over $50 billion in lost productivity and reduction in economic growth, and that largely in countries with low gross domestic product per capita. For the original SARS outbreak, the Asian development bank estimated the economic cost at $10–15 billion, largely due to reduced tourism and travel restrictions in the nations most affected. Other estimates that examined trade and travel more globally came up with higher numbers for SARS: $30–100 billion, roughly $3–10 million per reported case. The 2015 outbreak of MERS in South Korea was confined to just 186 confirmed cases with 38 deaths, but the response to it, which involved school closures and cancellation of public events, had an economic cost of around $10 billion, more than $50 million per case.

These analyses suggest that the cost of the present outbreak could stretch well beyond a trillion dollars worldwide — more if COVID-19 doesn't recede or recedes more slowly than SARS.

Current spending on epidemic preparedness prevention pales into insignificance against these numbers. The budget for the establishing and running the diagnostic and clinical coordination network in the PREPARE program was €10–20 million ($11–22 million). Now that the extent of the COVID-19 outbreak has pushed the project beyond its peacetime funding, Herman Goossens and his colleagues have asked for an additional €5 million ($5.5 million) from the European Union's Horizon 2020 program. "It's so frustrating. So much money is lost and we have to beg for €5 million. But it is what it is," he says resignedly.

In the longer term, though, Goossens would like to see preparedness efforts move away from grant-based 'bootstrapping' to more permanent solutions that properly represent the commitment that governments are now expressing. He is working with the management consultancy firm Deloitte on developing business models to create a sustainable public–private infrastructure to support epidemic responses: inevitably, that work in preparing for preparedness is being grant-funded by the European Union, within a scheme called ECRAID (European Clinical Research Alliance on Infectious Diseases).

CEPI has outlined costings for completion its vaccine programs for COVID-19: "To build capacity to have multiple millions of doses available within 12–18 months, recognizing that not all approaches will make it to the end, would be about $2 billion," Saville says. The organization has published a breakdown of those figures that shows it plans to take up to eight candidates into phase 1, progressing up to six into a phase 2/3 trial and registering up to three of those. Funding that clinical effort would require a doubling or tripling of the money CEPI has raised since its foundation in 2017.

More recently, and perhaps ironically, a new non-market vehicle has been launched — the COVID-19 Therapeutics Accelerator. With a total of $125 million committed by the Bill & Melinda Gates Foundation, the Wellcome Trust and the Mastercard Impact Fund, the accelerator will test existing small molecules and mAbs against SARS-CoV-2 and work with regulators to bring effective molecules to patients within a year.

From a research community perspective, the time to ask for the technical preparedness resources is now, right in the midst of the outbreak. "Never let a good crisis go to waste," urges John Rex. "The message of Ebola, SARS and SARS-CoV-2 is that we're going to see these things emerge. The only antidote is being ready." ❐

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