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Perspective

Developing Covid-19 Vaccines at Pandemic Speed

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The need to rapidly develop a vaccine against SARS-CoV-2 comes at a time of explosion in basic scientific understanding, including in areas such as genomics and structural biology, that is supporting a new era in vaccine development. Over the past decade, the scientific community and the vaccine industry have been asked to respond urgently to epidemics of H1N1 influenza, Ebola, Zika, and now SARS-CoV-2. An H1N1 influenza vaccine was developed relatively rapidly, largely because influenza-vaccine technology was well developed and key regulators had previously decided that vaccines made using egg- and cell-based platforms could be licensed under the rules used for a strain change. Although a monovalent H1N1 vaccine was not available before the pandemic peaked in the Northern Hemisphere, it was available soon afterward as a stand-alone vaccine and was ultimately incorporated into commercially available seasonal influenza vaccines.

Vaccines for the severe acute respiratory syndrome (SARS), Ebola, and Zika did not follow a similar path. The SARS and Zika epidemics ended before vaccine development was complete, and federal funding agencies reallocated funds that had been committed to vaccine development, leaving manufacturers with financial losses and setting back other vaccine-development programs.

Development of an Ebola vaccine by the Public Health Agency of Canada had been on hold when the 2013–2016 Ebola outbreak began. The U.S. government provided funding to accelerate the vaccine's development, which was ultimately transferred to Merck. The company continued development even when the outbreak ended, and stockpiles of investigational product were available for use in the recent outbreaks in the Democratic Republic of Congo. The vaccine received conditional marketing authorization from the European Medicines Authority and approval from the U.S. Food and Drug Administration at the end of 2019 and in several African countries thereafter. Some companies working on Ebola vaccines have received external support and invested their own funds to continue development. Even with successful development and licensure, however, the prospect that commercial markets will sustain multiple vaccines for which relatively few doses may need to be manufactured seems dim.

Reviews of the experience with H1N1 vaccine have stressed the need for novel development-and-manufacturing platforms that can be readily adapted to new pathogens. Vaccine and biotech companies have been investing heavily in such approaches, with support from the U.S. government and other funders. The National Institute of Allergy and Infectious

Diseases has led an initiative to support early development of platforms and test them against "prototype pathogens" from various viral families.[1]

Our organization, the Coalition for Epidemic Preparedness Innovation (CEPI), an international nongovernmental organization funded by the Wellcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries (Australia, Belgium, Canada, Ethiopia, Germany, Japan, Norway, and the United Kingdom), is supporting development of vaccines against five epidemic pathogens on the World Health Organization (WHO) priority list. We aim to develop reserves of investigational vaccines for each pathogen after such vaccines have completed phase 2a trials, expecting that they will undergo clinical trials during future outbreaks. CEPI also supports development of platform technologies to prepare for "Disease X" — a newly emerging epidemic disease, such as Covid-19. An ideal platform would support development from viral sequencing to clinical trials in less than 16 weeks, demonstrate elicitation of consistent immune responses across pathogens, and be suitable for large-scale manufacturing using a pathogen-agnostic platform.

Multiple platforms are under development. Among those with the greatest potential for speed are DNA- and RNA-based platforms, followed by those for developing recombinant-subunit vaccines. RNA and DNA vaccines can be made quickly because they require no culture or fermentation, instead using synthetic processes. Developers' and regulators' experience with these platforms for personal oncology vaccines can facilitate rapid testing and release. There are no approved RNA vaccines to date, but RNA vaccines have entered clinical trials, and regulators have experience in reviewing clinical trial applications and with associated manufacturing of the vaccines.

Use of next-generation sequencing and reverse genetics may also cut development time of more conventional vaccines during epidemics. The table lists major platform types and examples of SARS-CoV-2 vaccine types being developed on each. A more complete and continually updated list is available from the WHO.[2]

Even with novel platforms, SARS-CoV-2 vaccine development poses challenges. First, although the virus's spike protein is a promising immunogen for protection, optimizing antigen design is critical to ensure optimal immune response. Debate continues over the best approach — for example, targeting the full-length protein or only the receptor-binding domain.

Second, preclinical experience with vaccine candidates for SARS and the Middle East respiratory syndrome (MERS) have raised concerns about exacerbating lung disease, either directly or as a result of antibody-dependent enhancement. Such an adverse effect may be associated with a type 2 helper T-cell (Th2) response. Hence, testing in a suitable animal model and rigorous safety monitoring in clinical trials will be critical. (It is still too early to define good animal models; rhesus macaques appear quite promising, as do hamsters and ferrets [unpublished data].) If adjuvants are required to generate a sufficient immune response or for dose sparing, those triggering a Th1 response and demonstrating a high neutralizing-antibody response are theoretically more likely to be protective and avoid the risk of immunopathology. However, data and careful regulatory review will be needed.

Third, although correlates of protection may be inferred from experience with SARS and MERS vaccines, they are not yet established. As with naturally acquired infection, the potential duration of immunity is unknown; similarly, whether single-dose vaccines will confer immunity is uncertain.

Vaccine development is a lengthy, expensive process. Attrition is high, and it typically takes multiple candidates and many years to produce a licensed vaccine.[3] Because of the cost and high failure rates, developers typically follow a linear sequence of steps, with multiple pauses for data analysis or manufacturing-process checks. Developing a vaccine quickly requires a new pandemic paradigm (see diagram), with a fast start and many steps executed in parallel before confirming a successful outcome of another step, hence resulting in elevated financial risk. For example, for platforms with experience in humans, phase 1 clinical trials may be able to proceed in parallel with testing in animal models.

As soon as China announced that a novel coronavirus had been identified as the cause of the Wuhan outbreak, CEPI contacted its partners that were developing MERS vaccines or working on novel platforms. With the potential for further financial support, they and others began vaccine development as soon as the first gene sequence was posted, and development is proceeding quickly. Moderna's mRNA-based SARS-

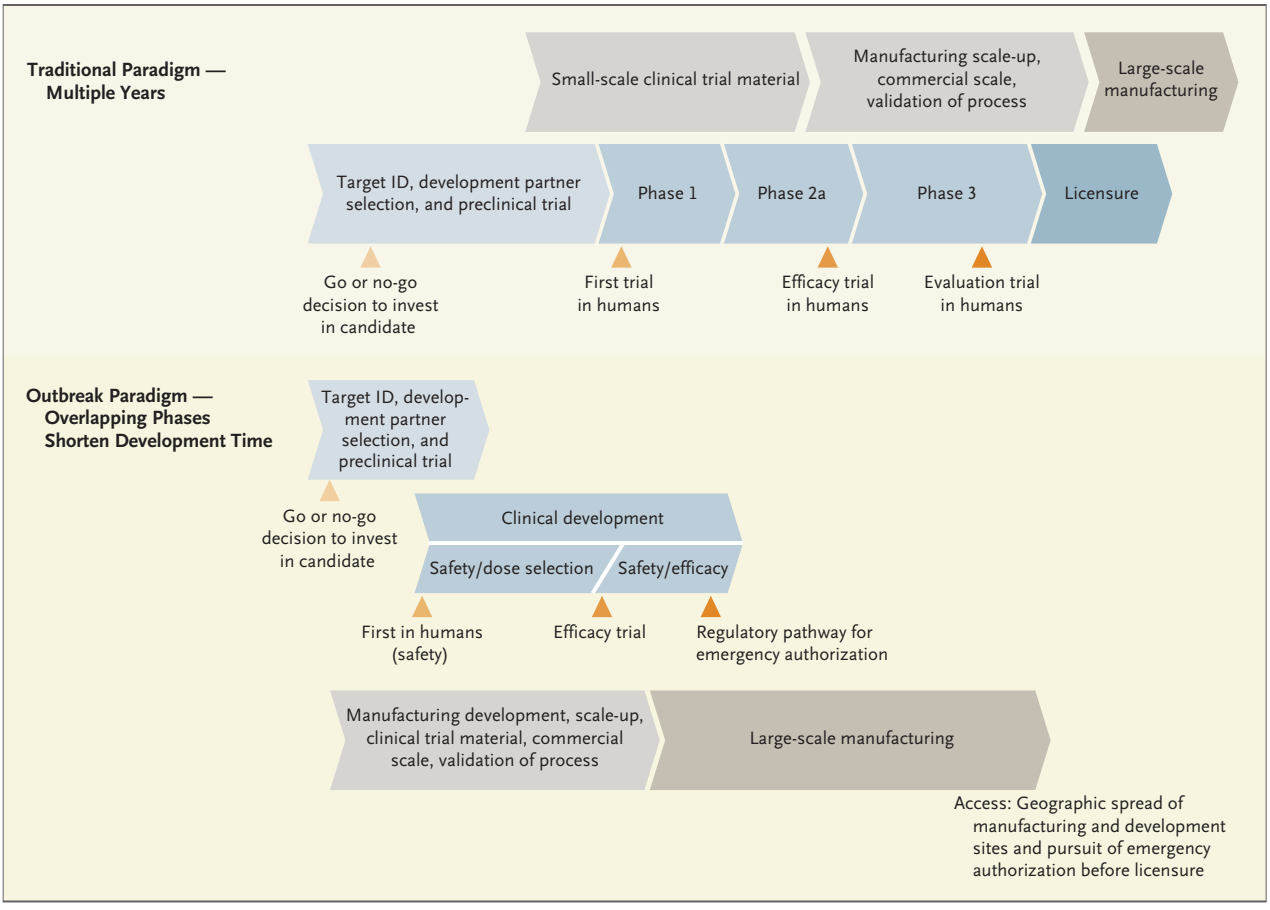
Vaccine Platforms, Their Attributes, and the Status of Vaccine Candidates.*

Technology	Attributes				Candidates in Preclinical Development	Candidates in Phase I
	Single Dose	Licensed Platform	Speed	Current Scale		
DNA	No	No	Fast	Medium	Inovio Pharmaceuticals Takis/Applied DNA Sciences/Evvivax Zydus Cadila	
Inactivated	No	Yes	Medium	Medium to high	Sinovac	
Live attenuated	Yes	Yes	Slow	High	Codagenix/Serum Institute of India	
Nonreplicating vector	Yes	No	Medium	High	GeoVax/BravoVax Janssen Pharmaceutical Companies University of Oxford Altimmune Greffex Vaxart ExpresS2ion	CanSino Biologics (ChiCTR20000 30906)
Protein subunit	No	Yes	Medium to fast	High	WRAIR/U.S. Army Medical Research Institute of Infectious Diseases Clover Biopharmaceuticals Inc/GSK Vaxil Bio AJ Vaccines Genrex/EpiVax/University of Georgia Sanofi Pasteur Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine iBio/CC-Pharming	
Replicating viral vector	Yes	Yes	Medium	High	Zydus Cadila Institut Pasteur/Themis Tonix Pharma/Southern Research	
RNA	No	No	Fast	Low to medium	Fudan University/Shanghai JiaoTong University/RNACure Biopharma China CDC/Tongji University/Stermina Arcturus/Duke-NUS Imperial College London Curevac BioNTech/Pfizer	Moderna/NIAID (NCT04283461)
Uncertain					University of Pittsburgh University of Saskatchewan ImmunoPrecise MIGAL Galilee Research Institute Doherty Institute Tulane University	

* Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.

CoV-2 candidate entered a phase 1 clinical trial on March 16, less than 10 weeks after the first genetic sequences were released; the first phase 1 trial with a nonreplicating vector-based vaccine has regulatory clearance to start phase 1 studies in China. Other phase 1 trials of nucleic acid vaccines are expected to start in April.

For some candidates, additional clinical trial material for phase 2 studies is being manufactured now; proceeding rapidly beyond phase 2 trials means manufacturing will need to be scaled up to commercial levels before substantial safety and immunogenicity data are available. Building manufacturing capacity can cost hundreds of millions of dollars. Furthermore, for novel platform technologies, most of which are unlicensed, large-scale manufacturing has never been done, so facilities capable of producing large quantities of product must be identified, technologies transferred, and manufacturing processes adapted, all without know-



Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm.

The pandemic paradigm requires multiple activities to be conducted at financial risk to developers and manufacturers and without knowing whether the vaccine candidate will be safe and effective, including very early manufacturing scale-up to commercial scale before establishment of clinical proof of concept. ID denotes identification.

ing if the vaccine candidate is viable.

It's far from certain that these new platforms will be scalable or that existing capacity can produce sufficient quantities of vaccine fast enough. It's therefore critical that vaccines also be developed using tried-and-true methods, even if they may take longer to enter clinical trials or to result in large numbers of doses.

Conducting clinical trials during a pandemic poses additional challenges. It's difficult to predict where and when outbreaks will occur and to prepare trial sites to coincide with vaccine readiness for testing. In addition, if multiple vaccines are ready for testing in the second half of 2020, it will be important not to crowd sites or burden countries and their ethics and regulatory authorities with multiple trials, as happened with Ebola therapeutics during the 2013–2016 outbreak.

Moreover, in a high-mortality situation, populations may not accept randomized, controlled trials with placebo groups; although other approaches that address such concerns may be scientifically feasible, they're typically not as fast, and the results can be harder to interpret.[4] This problem can sometimes be overcome by comparing outcomes with early vaccination versus delayed vaccination, as in the "Ebola ça suffit!" trial. One possible way forward would be to test several vaccines simultaneously in an adaptive trial design using a single, shared control group, so that more participants would receive an active vaccine.[5] This approach has advantages but can be logistically and statistically complex, and developers often avoid trials that may generate head-to-head comparative data.

CEPI, as a relatively new organization, had not established financial mechanisms and instruments to support development of

pandemic vaccines and will need to raise additional funds to see SARS-CoV-2 vaccines through the development and scale-up manufacturing processes. Although as many as several million vaccine doses may become available as a by-product of development, in a pandemic situation, once vaccine candidates are proved safe and effective, doses must be manufactured in large quantities. Though some high-income countries may pay for development and manufacture with their own populations in mind, there's no global entity responsible for financing or ordering vaccine manufacture. Discussions with global stakeholders about organizing and financing large-scale vaccine manufacturing, procurement, and delivery are under way.

Finally, pandemics will generate simultaneous demand for vaccines around the world. Clinical and serologic studies will be needed to confirm which populations remain at highest risk once vaccines are available and could form the basis for establishing a globally fair vaccine-allocation system. Some Group of Seven countries have already called for such a global system, whose planning must start while vaccine development proceeds.

Though it's unlikely, if the pandemic appears to abruptly end before vaccines are ready, we should continue developing the most promising candidates to a point at which they can be stockpiled and ready for trials and emergency authorization should an outbreak recur. A global financing system that supports end-to-end development and large-scale manufacturing and deployment, ensures fair allocation, and protects private-sector partners from significant financial losses will be a critical component of future pandemic preparedness.

Disclosure forms provided by the authors are available at NEJM.org.

From the Coalition for Epidemic Preparedness Innovations, Oslo.

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