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Perspective

**Developing Covid-19 Vaccines at Pandemic Speed**

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he need to rapidly develop a vaccine against SARS-CoV-2 comes at a time of explosion in basic scientific understanding, including

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in areas such as genomics and structural biology,

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

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 epi- demics of H1N1 influenza, Ebola, Zika, and now SARS-CoV-2. An H1N1 influenza vaccine was de- veloped relatively rapidly, largely because influenza-vaccine technol- ogy was well developed and key regulators had previously decided that vaccines made using egg- and cell-based platforms could be li- censed under the rules used for a strain change. Although a mono- valent H1N1 vaccine was not avail- able before the pandemic peaked in the Northern Hemisphere, it was available soon afterward as a stand-alone vaccine and was ulti- mately incorporated into commer- cially 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 reallo- cated funds that had been com- mitted to vaccine development, leaving manufacturers with finan- cial losses and setting back other vaccine-development programs.

Development of an Ebola vac- cine by the Public Health Agency of Canada had been on hold when the 2013–2016 Ebola outbreak be- gan. The U.S. government provid- ed funding to accelerate the vac- cine’s development, which was ultimately transferred to Merck. The company continued develop- ment even when the outbreak end- ed, and stockpiles of investigation- al product were available for use

and Drug Administration at the end of 2019 and in several Afri- can countries thereafter. Some companies working on Ebola vac- cines have received external sup- port and invested their own funds to continue development. Even with successful development and licensure, however, the prospect that commercial markets will sus- tain 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 patho- gens. Vaccine and biotech com- panies have been investing heavily in such approaches, with support from the U.S. government and other funders. The National In- stitute of Allergy and Infectious

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Diseases has led an initiative to support early development of plat- forms and test them against “pro- totype pathogens” from various viral families.1

Our organization, the Coalition for Epidemic Preparedness Innova- tion (CEPI), an international non- governmental organization fund- ed by the Wellcome Trust, the Bill and Melinda Gates Foundation, the European Commission, and eight countries (Australia, Bel- gium, Canada, Ethiopia, Germany, Japan, Norway, and the United Kingdom), is supporting develop- ment of vaccines against five epi- demic pathogens on the World Health Organization (WHO) pri- ority list. We aim to develop re- serves of investigational vaccines for each pathogen after such vac- cines have completed phase 2a trials, expecting that they will undergo clinical trials during fu- ture outbreaks. CEPI also supports development of platform technol- ogies to prepare for “Disease X”

— a newly emerging epidemic disease, such as Covid-19. An ideal platform would support de- velopment from viral sequencing to clinical trials in less than 16 weeks, demonstrate elicitation of consistent immune responses across pathogens, and be suit- able for large-scale manufactur- ing using a pathogen-agnostic platform.

Multiple platforms are under development. Among those with the greatest potential for speed are DNA- and RNA-based plat- forms, followed by those for de- veloping recombinant-subunit vac- cines. RNA and DNA vaccines can be made quickly because they require no culture or fermenta- tion, instead using synthetic pro- cesses. 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 tri- als, and regulators have experi- ence in reviewing clinical trial applications and with associated manufacturing of the vaccines.

Use of next-generation sequenc- ing and reverse genetics may also cut development time of more conventional vaccines during epi- demics. The table lists major platform types and examples of SARS-CoV-2 vaccine types being developed on each. A more com- plete 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 prom- ising immunogen for protection, optimizing antigen design is criti- cal to ensure optimal immune response. Debate continues over the best approach — for exam- ple, targeting the full-length pro- tein 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 en- hancement. Such an adverse effect may be associated with a type 2 helper T-cell (Th2) response. Hence, testing in a suitable ani- mal model and rigorous safety monitoring in clinical trials will be critical. (It is still too early to define good animal models; rhe- sus macaques appear quite prom- ising, as do hamsters and ferrets [unpublished data].) If adjuvants are required to generate a suffi- cient immune response or for dose sparing, those triggering a Th1 response and demonstrating

a high neutralizing-antibody re- sponse are theoretically more like- ly to be protective and avoid the risk of immunopathology. How- ever, 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 estab- lished. As with naturally acquired infection, the potential duration of immunity is unknown; simi- larly, whether single-dose vac- cines will confer immunity is un- certain.

Vaccine development is a lengthy, expensive process. Attri- tion is high, and it typically takes multiple candidates and many years to produce a licensed vac- cine.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 vac- cine quickly requires a new pan- demic paradigm (see diagram), with a fast start and many steps executed in parallel before con- firming a successful outcome of another step, hence resulting in elevated financial risk. For exam- ple, for platforms with experi- ence 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 poten- tial for further financial support, they and others began vaccine de- velopment as soon as the first gene sequence was posted, and development is proceeding quick- ly. Moderna’s mRNA-based SARS-

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 ge- netic sequences were released; the first phase 1 trial with a non- replicating vector-based vaccine has regulatory clearance to start phase 1 studies in China. Other phase 1 trials of nucleic acid vac- cines 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 manufac- turing will need to be scaled up to commercial levels before sub- stantial safety and immunogenic- ity 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 manufac- turing has never been done, so facilities capable of producing large quantities of product must be identified, technologies trans- ferred, and manufacturing pro- cesses adapted, all without know-

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| **Traditional Paradigm —** Manufacturing scale-up, Large-scale  **Multiple Years** Small-scale clinical trial material commercial scale, manufacturing  validation of process  Target ID, development partner Phase 1 Phase 2a Phase 3 Licensure selection, and preclinical trial  Go or no-go First trial Efficacy trial Evaluation trial decision to invest in humans in humans in humans  in candidate |
| **Outbreak Paradigm —** Target ID, develop-  **Overlapping Phases** ment partner  **Shorten Development Time** selection, and  preclinical trial  Go or no-go Clinical development decision to invest  in candidate Safety/dose selection Safety/efficacy  First in humans Efficacy trial Regulatory pathway for (safety) emergency authorization  Manufacturing development, scale-up,  clinical trial material, commercial Large-scale manufacturing scale, validation of process  Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure |

**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 pro- duce sufficient quantities of vac- cine fast enough. It’s therefore critical that vaccines also be de- veloped 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 dur- ing a pandemic poses additional challenges. It’s difficult to pre- dict 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 therapeu- tics during the 2013–2016 out- break.

Moreover, in a high-mortality situation, populations may not ac- cept randomized, controlled trials with placebo groups; although other approaches that address such concerns may be scientifi- cally feasible, they’re typically not as fast, and the results can be harder to interpret.4 This problem can sometimes be over-

come by comparing outcomes with early vaccination versus de- layed vaccination, as in the “Ebola ça suffit!” trial. One possible way forward would be to test several vaccines simultaneously in an adap- tive 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 logis- tically and statistically complex, and developers often avoid trials that may generate head-to-head comparative data.

CEPI, as a relatively new orga- nization, had not established fi- nancial mechanisms and instru- ments to support development of

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pandemic vaccines and will need to raise additional funds to see SARS-CoV-2 vaccines through the development and scale-up manu- facturing 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 manufac- tured in large quantities. Though some high-income countries may pay for development and manu- facture with their own popula- tions in mind, there’s no global entity responsible for financing or ordering vaccine manufacture. Discussions with global stake- holders about organizing and financing large-scale vaccine man- ufacturing, procurement, and de- livery are under way.

Finally, pandemics will gener- ate simultaneous demand for vac- cines around the world. Clinical and serologic studies will be

needed to confirm which popula- tions remain at highest risk once vaccines are available and could form the basis for establishing a globally fair vaccine-allocation sys- tem. Some Group of Seven coun- tries have already called for such a global system, whose planning must start while vaccine develop- ment 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 stock- piled and ready for trials and emergency authorization should an outbreak recur. A global fi- nancing system that supports end-to-end development and large- scale manufacturing and deploy- ment, 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 Prepared- ness Innovations, Oslo.

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