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Fast Development of High-Quality Vaccines in a Pandemic



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The first reports of the virus SARS-CoV-2 emerged in late December 2019, which was followed by the subsequent global pandemic shutdown of March 2020. One key to stymie a pandemic is to make safe and effective vaccines available globally to attain herd immunity while minimizing death and suffering from the virus. Early in the pandemic, a COVID-19 vaccine seemed like a distant hope, with the most rapid turnaround for an expected vaccine quoted at 12 to 18 months from March 2020.¹ In general, the discovery and development of a vaccine takes 8 to 20 years, with anywhere from 2 to 10 years in the clinical trial phase.² Surprisingly, as of March 2021, three COVID-19 vaccines had received an emergency use authorization (EUA) in the United States; globally, there are six vaccines that have been approved or are under EUA. Across the globe at least 80 other vaccines are in clinical trials, and >170 vaccines are in preclinical evaluation. What models for vaccine development allowed for such success in such a short time period?

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Multiple infectious disease outbreaks in the past decade were catalysts for different groups to lay the necessary foundations before the COVID-19 pandemic. In 2017, the Coalition for Epidemic Preparedness Innovations (CEPI) with public and philanthropic funding from the Gates Foundation, the government of Norway, the Wellcome Trust and others, was established to accelerate vaccine development to emergent diseases and provide equitable access to vaccines during pandemics. Before COVID-19, the CEPI portfolio included vaccine development for Lassa virus, Middle Eastern respiratory virus, Ebola, Nipah virus, and “Disease X,” which is an unknown pathogen that could cause the next global pandemic. Using an “end-to-end” approach, CEPI strives to facilitate vaccine development and shepherd vaccines through the “valley of death” of development, clinical trials, and licensure.

The genetic sequence for SARS-CoV-2 was published on January 11, 2020; by January 23, with only 141 COVID-19 cases known worldwide, CEPI had deployed three vaccine programs to accelerate COVID-19 vaccines and was able to support nine candidate COVID-19 vaccines before Operation Warp Speed was established (Fig 1).

Operation Warp Speed, part of the US Department of Defense, was announced on May 15 and established the goal of delivering 300 million COVID-19 vaccines by January 1, 2021.³ This accelerated timeline was envisioned by overlapping vaccine development stages that historically occurred sequentially: research and development, preclinical trials, and Phase 1 clinical trials. Further, if a vaccine candidate was promising, Phase 2 and Phase 3 clinical trials would overlap, and vaccine candidate manufacturing would start, as opposed to waiting for the Phase 3 results. This overlap was possible with Operation Warp Speed encouraging public-private partnerships and providing >12 billion dollars to five different vaccine candidates.

The timeline for vaccine development was further accelerated with the rampant spread of SARS-CoV-2 that coincided with recruitment and follow-up of multiple Phase 3 trials. As more subjects were infected with SARS-CoV-2, the time needed to determine a difference between vaccine and placebo arms was shorter than initially projected.

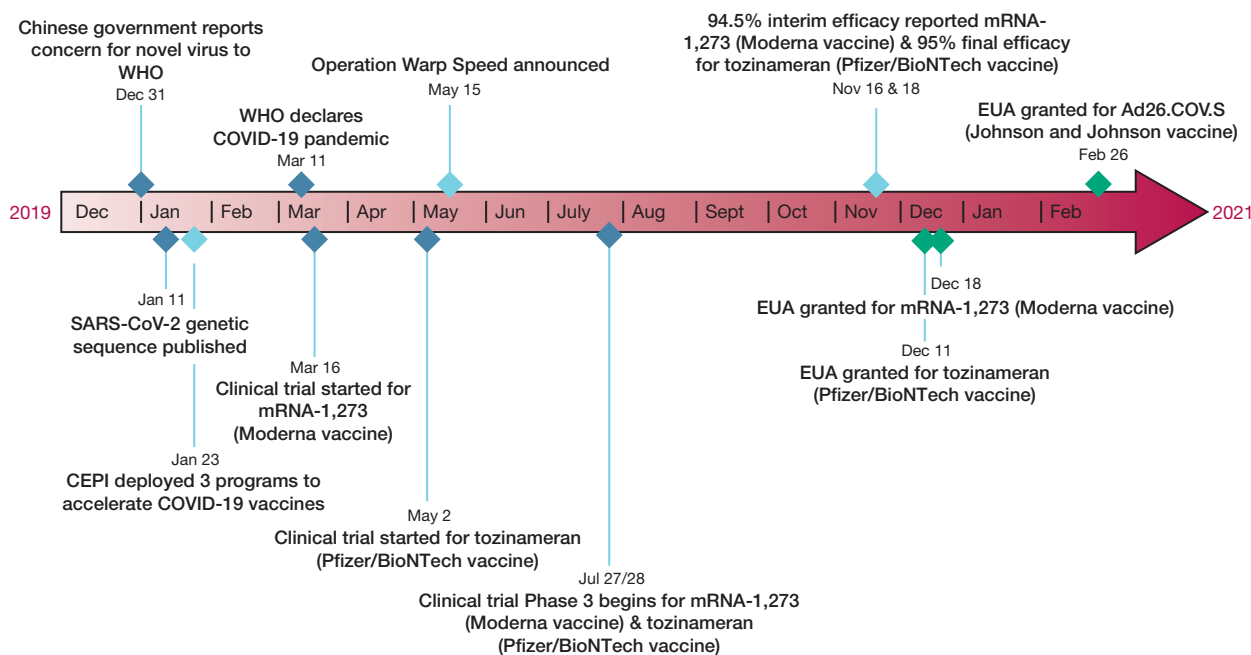


Figure 1 – Timeline of COVID-19 vaccine development. CEPI = Coalition for Epidemic Preparedness Innovations; EUA = emergency use authorization; mRNA = messenger RNA; WHO = World Health Organization.

Advances in vaccine technology have also been vital in the rapid development of multiple effective vaccines. Although the idea for messenger RNA (mRNA) vaccines has been around for >30 years, early experiments were limited due to the toxicity of the initial lipid delivery system. The transition to lipid nanoparticle technology as a delivery system allowed the relatively large and positively charged mRNA molecules to be endocytosed successfully into cells. In the case of the Moderna vaccine (Moderna Inc), a candidate was determined within days after the genetic sequence was released, and the first-in-human clinical trials started 66 days after the sequence was released.⁴

Another prominent platform-based technology in COVID-19 vaccines is the adenovirus viral vector. Because adenoviruses elicit robust T-cell responses, the use of an adenovirus viral vector in vaccines was attempted for HIV vaccines in the early 2000s but was not successful. Because there is a high prevalence of preexisting immunity to adenovirus 5 in the community, researchers looked to other adenoviruses as potential vaccine vectors. Oxford-AstraZeneca or AZD1222 vaccine uses a chimpanzee adenovirus AZD1222/ChAdOx1 that cannot replicate in humans.⁵ The use of a chimpanzee adenovirus is helpful because humans would not have prior immunity to this virus. If a patient had preexisting immunity to the adenovirus, the immune response may be directed against the viral

vector, as opposed to the desired antigen. The Johnson & Johnson vaccine adenovirus 26.COV2.S uses a modified adenovirus 26 (Ad26) that cannot replicate in humans with a target sequence to a stabilized prefusion spike protein. Few people have preexisting immunity to Ad26. The first adenovirus vaccine that used Ad26 was approved in July 2020 by the European Union for Ebola outbreaks.

Adenovirus viral vectors work because the genetic sequence for the spike protein is encoded onto double-stranded DNA and is inserted into an adenovirus. The adenovirus, once endocytosed, deposits the DNA into the nucleus, leading to the desired sequence being transcribed and transplanted into the desired protein sequence. Similar to mRNA vaccines, this is a platform-based technology so that the target sequence of DNA can be modified easily to target a new or emerging pathogen. However, unlike mRNA vaccines, the temperature restrictions for adenovirus vaccines are less stringent. Limitations of this platform might be difficulties in scaling viral vector production and prior exposure to the viral vector that could reduce vaccine effectiveness.

In the development and licensure of the three vaccines approved in the United States, although the steps for approval were done contemporaneously, no steps were missed in the scientific assessment of these vaccines. After transparent and rigorous review by the Federal Drug Administration, EUA was granted on December

11, 2020, for tozinameran (Pfizer/BioNTech vaccine), on December 18, 2020, for mRNA-1273 (Moderna vaccine), and on February 26, 2021, for Ad26.COV.S (Johnson and Johnson vaccine).

Though these effective vaccines have been developed in record time without compromise of scientific integrity, these are not the last vaccines that we will need. Future vaccines, either for new variants of SARS-CoV-2 or for other diseases such as malaria, HIV, or TB likely will benefit from both platform-based technology and organizational support that navigate a vaccine candidate from discovery to equitable distribution.

References

1. Vazquez M. Task force health expert contradicts Trump about coronavirus vaccine timing. *CNN*. 2020. <https://www.cnn.com/2020/03/02/politics/donald-trump-coronavirus-vaccine-push-back/index.html>. Accessed March 5, 2020.
2. Heaton PM. The Covid-19 vaccine-development multiverse. *N Engl J Med*. 2020;383(20):1986-1988.
3. Trump Administration Announces Framework and Leadership for 'Operation Warp Speed' [press release]. May 12, 2020 U.S. Department of Defense, Washington, DC.
4. Corbett KS, Edwards DK, Leist SR, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature*. 2020;586(7830):567-571.
5. Farina SF, Gao GP, Xiang ZQ, et al. Replication-defective vector based on a chimpanzee adenovirus. *J Virol*. 2001;75(23):11603-11613.