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Impact of a Pandemic Outbreak on Vaccine Development Approach

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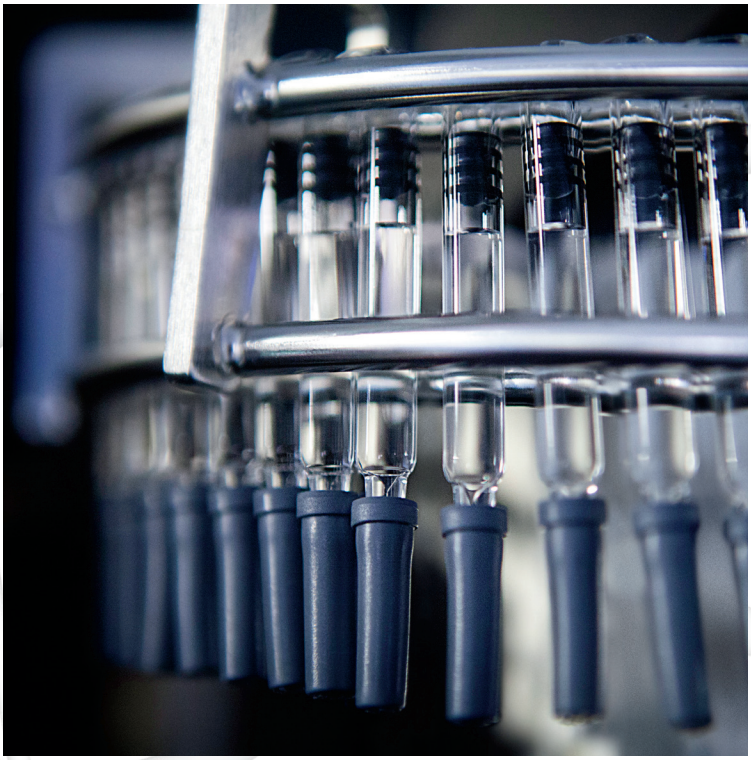

Over the past decade, outbreaks of H1N1 influenza, Sars-Cov, Ebola, and MERS have triggered several discussions about traditional vaccine development methods[1]. For example, new platform technologies, such as the use of messenger RNA (mRNA) vehiculated through lipid nanoparticles, have been introduced, stimulating scientific discussions. With the spread of SARS-CoV-2 intensifying, scientists, together with pharmaceutical companies, are reinventing the approach of how to bring these life-saving drugs to market faster without impacting product quality, safety, or efficacy.

This unprecedented data sharing and collaborative team effort is underway among various organizations, such as the World Health Organization[2], the Coalition for Epidemic Preparedness Innovations[3], the Milken Institute[4], and Biocentury, Inc[5]. The goal is to reduce approval time for a vaccine from 10+ years (traditional timeline) down to 12 to 18 months (see Figure 1).

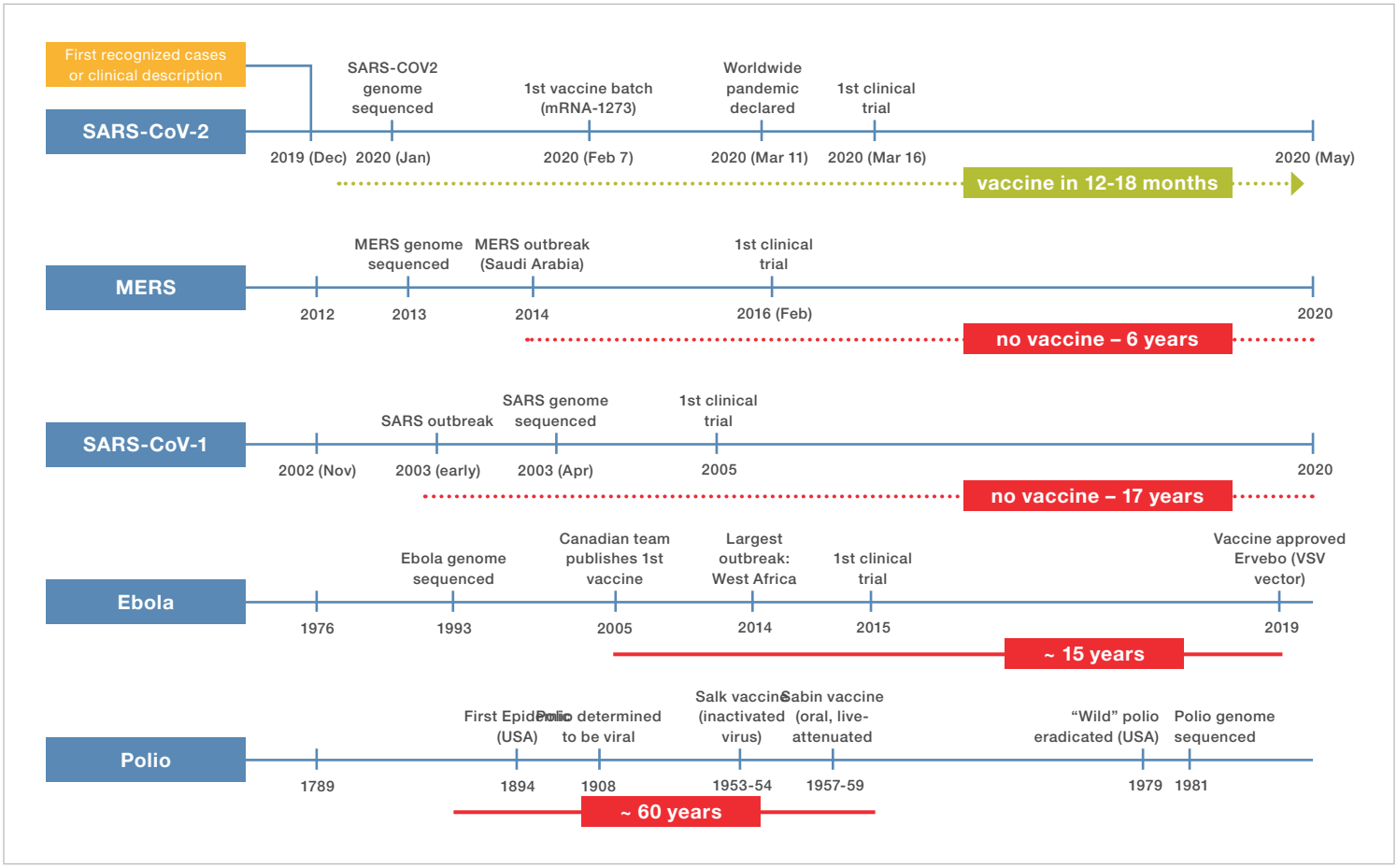

Figure 1[6]. Traditional timeframe for vaccine development and commercialization.

The ideal profile of a vaccine needs to take into consideration multiple aspects, including:

- A long-lasting immune response to protect individuals from the infection or minimizing its effects
- The insurgence of severe adverse effects upon administration has to be limited
- Logistics need to grant a worldwide distribution

However, several challenges with traditional methods need to be overcome in order to reduce the timeline for vaccine distribution. For example, the process today requires multiple activities, such as the development of a reliable and robust manufacturing process, selection of appropriate packaging components, and raw materials procurement. All of these carry significant risk, as they are performed before clinical trial outcomes are known. In addition, scale-up activities often begin even if full process development is not complete, reducing the confidence that a vaccine can successfully meet clinical study endpoints. The need for quick distribution of a vaccine for SARS-CoV-2 has brought these issues to the forefront, as billions of doses are expected for distribution in a compressed timeframe.

Vaccine platforms under development: implications on fill & finish services

Vaccines can be grouped into two families: classic and new-generation platforms (see Figure 2). There are pros and cons to both when it comes to manufacturing a finished product.

Classic platforms

Classic platforms are based on live attenuated or inactivated viruses, such as with the MMR and polio vaccines, which are protein virus or viral protein complexes formulated to simulate virus-like particles (VLPs). These platforms require dedicated, biosafety-level facilities to minimize the risk of the attenuated virus regaining virulence. Scale-up becomes extremely complex in this situation, as extensive safety testing is required before proceeding with large-scale production. In addition, several recombinant proteins must be produced simultaneously for virus-like particle vaccines. Despite these challenges, live or attenuated virus platforms are proven technologies with simple formulations stimulating a significant immune response, even in the absence of an adjuvant, which is typically required for a protein-based vaccine to induce a strong immune response toward the antigen following immunization. Some examples of a vaccine like this currently on the market include Gardasil to prevent papilloma virus infection, as well as the vaccines for diphtheria-tetanus-pertussis, Hepatitis A, and Hepatitis B.

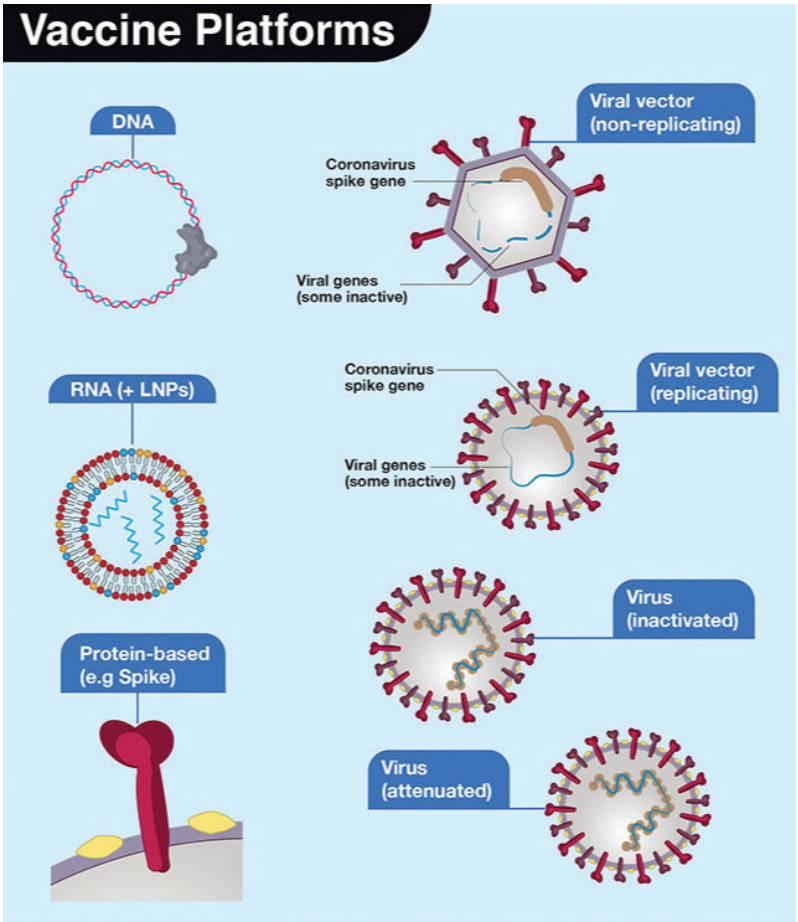

Figure 2[6]. Examples of platforms currently under investigation for SARS-CoV-2 treatment.

New-generation platforms

New-generation platforms offer a significant advantage in vaccine development, as they can be developed using only genetic sequence information. Because these DNA- and RNA-based platforms require only laboratory synthesis and not culture or fermentation, they can quickly provide a lead, allowing a candidate to go from initial development to early clinical trials in about 16 weeks. The process begins with virus genetic information encoded in DNA and then transcripted into mRNA, which is responsible for virus protein codification. The RNA vaccine is commonly injected into the muscle using a liposome-based formulation, known as lipid nanoparticle, or a polycation-based nanoparticle for mutation. Once inside the cells, the ribosomes produce the protein encoded by the RNA sequence, which, for the COVID-19 vaccine, is the spike protein on the SARS-CoV-2 virus surface. The produced protein antigen then induces the immune response likely required to gain immunity against the virus. Unfortunately, these kinds of vaccines are less stable than the classical ones and require refrigeration at -70°C, limiting distribution when an appropriate cold chain infrastructure is not available.

Among the emerging technologies transforming vaccine development are viral vectors, which also play a fundamental role in the race for the SARS-CoV-2 vaccine. Vaccines based on viral vectors offer a high level of protein expression and long-term stability and can induce a strong immune response. Viral vector-based vaccines encode the viral gene of interest into one of several well-characterized vectors, such as adenovirus (Ad) and vesicular stomatitis virus (VSV). These vaccines can be either replicating or non-replicating. Replicating vector vaccines infect cells in which the vaccine antigen is produced and more infectious viral vectors are then able to infect new cells, producing the vaccine antigen. With a replicating virus as a vector, many more cells would be infected, increasing the immune system's exposure. To develop a replicating viral vector, researchers manipulate the viruses so that they are unable to replicate at their full capacity and therefore cannot cause disease. For some viruses, researchers remove some of their genetic material, which in turn slows down their replication rate and minimizes their ability to cause disease. This allows the immune system to eventually catch up - typically within a few weeks - and rid the body of the viral vector. Non-replicating vector vaccines initially enter cells and then produce the vaccine antigen without new virus particles being formed. This platform has the potential to be manufactured on a large scale. The adenovirus vector, for example, can be grown in cells and used for various vaccines by adding the appropriate genetic information, which instructs them to generate SARS-CoV-2 protein and stimulate an immune response. Preexisting immunity to the specific viral vector can attenuate immunogenicity, which needs to be addressed in early-stage trials. Another advantage of these viral vector-based vaccines is that a single dose can be sufficient for protection, as in the case of the vesicular stomatitis virus-based Ervebo vaccine against the Ebola virus.[7]

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New development strategy deployed to address the SARS-CoV-2 pandemic

Vaccine development is a complex and costly undertaking that is incredibly risky, as the majority of vaccine candidates fail during preclinical and Phase I development. Classical, rational, and systematic approaches to the development of vaccine formulations cover biophysical characterization, stabilizer screening, adjuvant interactions, sterile filtration, container interactions, and stability studies. Each of these components occurs over multiple phases in a linear sequence of development and are complimentary to one another (see Figure 3).

Figure 3[8]. Traditional vaccine development approach.

The decision to invest in capacity for the manufacture of billions of doses has occurred concomitantly with clinical trials and process development, rather than the traditional linear time-consuming pathway. It's imperative that there is a positive and fully transparent approach among clinical, manufacturing, and development departments to optimize the final formulation as well as its size and strength.

Equipment is established before there is sufficient knowledge about the final product characteristics. Creating an effective and adaptable approach to development and manufacturing is a key factor in successfully accomplishing scale-up and validation of future commercial vaccines.

The response of the pharmaceutical industry to fight SARS-CoV-2 infections has inspired new approaches for generating an effective vaccine. Despite the unprecedented challenges presented by this pandemic, an exceptional effort from the scientific community resulted in a vaccine that is being quickly and globally distributed. The progress thus far has created the basis for an innovative technology transfer sequence that can quickly tackle potential new future pandemic future pandemic emergencies, and has established a new and proactive approach to managing the unpredictable demand of life-saving products.

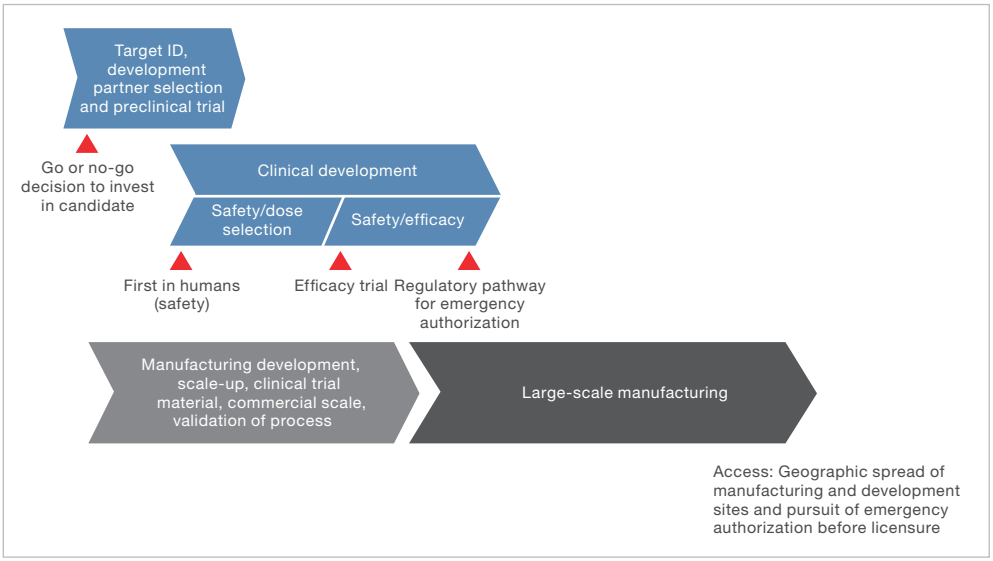

Figure 4[9]. New paradigm in vaccine development.

1 *Next-generation vaccine platforms for COVID-19,* Debby van Riel and Emmie de Wit, Nature Materials | VOL 19 | August 2020 | 810–820 |

2 https://www.who.int/emergencies/diseases/novel-coronavirus-2019/globalresearch-on-novel-coronavirus-2019-ncov

3 https://cepi.net/covid-19/

4 https://milkeninstitute.org/covid-19-tracker

5 https://www.biocentury.com/coronavirus

6 *A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic,* Colin D. Funk, Craig Laferrière and Ali Ardakani, Frontiers in Pharmacology, June 2020 | Volume 11 | Article 937

7 The COVID-19 vaccine development landscape, Tung Thanh Le, Zacharias Andreadakis, Arun Kumar, Raúl Gómez Román, Stig Tollefsen, Melanie Saville and Stephen Mayhew, Nature Reviews | Drug DISCOVery, volume 19 | May 2020 | 305 -306

8 Investing in Vaccines for the Developing World, PATH, April 2015.

9 Developing Covid-19 Vaccines at Pandemic Speed, Nicole Lurie, M.D., M.S.P.H., Melanie Saville, M.D., Richard Hatchett, M.D., and Jane Halton, A.O., P.S.M., The NEW ENGLAND JOURNAL of MEDICINE, May 21, 2020, 1969-1973.

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