jraas

Journal of the Renin-Angiotensin-Aldosterone System
April-June 2020: 1–3

DOI: 10.1177/1470320320926902
journals.sagepub.com/home/jra
SAGE

COVID-19: The race for a vaccine

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Vaccines can take more than a decade to develop in a safe and effective manner. Candidate vaccines must first demonstrate efficacy in laboratory-based studies prior to toxicity testing in animals. In early-phase clinical trials, the vaccine must be tested for safety (Phase I), and efficacy and adverse events (Phase II) before entering large-scale clinical trials (Phase III). There is a high level of attrition as vaccines pass through the various stages of clinical trials because of either safety concerns or lack of efficacy, or both. It is thus difficult to fast-track vaccine development.

The coronavirus disease 2019 (COVID-19) pandemic is accelerating the slow process of vaccine development, but how long will it be until we can effectively vaccinate populations? This article looks at how the industry is responding to the COVID-19 outbreak in the race for a vaccine.

Current vaccine candidates

According to the World Health Organization (WHO), there are 70 vaccines in development against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the COVID-19 outbreak, with three already in clinical trials.[1] The Coalition for Epidemic Preparedness Innovations (CEPI), a foundation that receives donations to finance independent research projects to develop vaccines against emerging infectious diseases, is currently working with nine companies, all of which are having to adapt to accelerate their vaccine-development process.[a]

The first stage of vaccine development is research intensive and involves the identification of natural or synthetic antigens based on the viral protein. Within a week of sequencing the SARS-CoV-2 genome, Chinese scientists had shared this publicly.[2,3] Sharing the viral genome globally has allowed for an acceleration of the early development stage. Researchers at Imperial College London, for example, took just two weeks from receiving the genome to producing a candidate vaccine.[4]

Another way of accelerating the development process is to run trials in parallel. Researchers at the University of Oxford have begun testing a vaccine candidate that uses a chimpanzee adenovirus vector in healthy human volunteers.[5] The same vaccine underwent animal trials during the recruitment phase of the human study. This is unusual, as animal studies should normally be completed before human trials can begin. However, the chimpanzee adenovirus vector has been studied extensively and used safely in thousands of subjects in vaccines targeting more than 10 different disease types.[6] This makes it easier to justify the accelerated move to human testing. Regulatory approval can also be accelerated if similar products have previously been approved.

For similar reasons, many companies are also repurposing vaccines. In the two recent outbreaks of coronavirus infection, severe acute respiratory syndrome (SARS) which caused an epidemic in the early 2000s and Middle East respiratory syndrome (MERS) which caused multiple outbreaks between 2015 and 2018, work which had started on vaccines was subsequently stopped when the epidemics were successfully contained. Inovio Pharmaceuticals had already initiated work on a DNA vaccine for MERS prior to the COVID-19 outbreak, allowing the company to develop a potential vaccine for COVID-19 rapidly.[7] Sanofi is repurposing a SARS protein vaccine,[8] and Novavax are working on several repurposed vaccines that will reportedly be ready for human trials in spring 2020.[9,10]

As well as the more traditional techniques being used, such as live-attenuated and recombinant vaccines, RNA vaccines are being used to develop a vaccine against SARS-CoV-2. These are faster and cheaper to develop than the more traditional vaccines, as there is no requirement to grow large amounts of the virus in the lab, which overcomes manufacturing hurdles. However, no RNA vaccine has to date been approved for use, and the safety of such vaccines is unknown at present. Moderna administered the first dose of their novel RNA vaccine to a human participant on 16 March and currently has 45 participants

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[a]University of Oxford, Institut Pasteur, University of Hong Kong, Novavax, Inc, University of Queensland, Moderna and the National Institute of Allergy and Infectious Diseases, CureVac, and Inovio.

enrolled in clinical trials.[11] However, they expect the trials to continue into next year. Although the vaccine may have been quicker to develop, they cannot circumvent the necessary steps to show the vaccine is safe and effective.

One step that can potentially be fast-tracked is authorisation. The European Medicines Agency (EMA) has regulatory mechanisms in place to speed up development and approval. The PRIME scheme was launched to provide early and enhanced scientific and regulatory support to medicines that have the potential to address unmet medical needs. Developers of medicines and vaccines benefitting from PRIME will be eligible for accelerated assessment, reducing the time frame for the EMA to review applications for market authorisation. The EMA can also grant a conditional marketing authorisation for vaccines where the benefits of immediate availability outweigh the risks of less comprehensive data than normally required. Developers working on vaccines that could be used for the prevention of COVID-19 are encouraged to contact the EMA and discuss their research as soon as possible.[12] Once a safe and effective vaccine has been developed, there are further hurdles, including large-scale manufacturing. Many organisations researching a vaccine do not have the required manufacturing capacity. Vaccine development is high risk, with many candidates failing to reach clinical application. Further, manufacturing facilities tend to be tailored to specific vaccines. Scaling up these facilities when the future deployment of a vaccine is still in the uncertain early stages is not commercially viable. However, CEPI can shoulder some of this risk by providing funding not only to research facilities developing vaccine candidates but also to manufacturing facilities in parallel. At the same time as clinical trials are taking place in Oxford, production of the vaccine is being scaled up ready for larger trials and possible future deployment.[5] With early-stage scale-up, researchers can ensure that sufficient doses will be available as soon as possible if the trials prove that the vaccine is safe and effective.

Current issues

Researchers in Beijing studied the viral genome from 103 infected patients and identified two types of the virus: S and L.[13] At present, scientists do not know how the underlying genetic differences in the two strains relate to disease severity. Genetic analysis from a man in the USA who tested positive in January has shown that it is possible to be infected by both strains. Any vaccine candidate will have to target features present in both strains in order to be effective. The genetic differences between the two strains are small at present and unlikely to affect the production of proteins that act as antigens to promote an immune response. Genetic diversity does not necessarily mean the virus is changing. However, we can expect more strains to emerge. It is generally agreed that once infected, individuals are unlikely to be infected again, unless the virus mutates to overcome host immunity. It is possible that this selection process will lead to an outbreak of a new strain in a similar fashion to seasonal influenza. As is the case with influenza, new variants can emerge that infect individuals, whether or not they have been infected in the past. This will clearly have an impact on the long-term efficacy of vaccines currently in development.

Acknowledgements

This brief commentary was published on the Fieldfisher website (www.fieldfisher.com) on 7 April 2020.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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