



Developing a vaccine for SARS-CoV-2

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The world is in the midst of a viral pandemic caused by a novel coronavirus, SARS-CoV-2, that emerged in Wuhan, China in late 2019. In the four months since the first reported case, this virus has spread rapidly to 185 countries, and has infected >2.5M people worldwide, leading to 186,131 deaths. It is widely believed that the easiest way out of the crisis lies in the development of a vaccine. This has spurred more than 70 vaccine efforts worldwide. Without an effective vaccine, intermittent social distancing may be required into 2022 to achieve “herd immunity”.

What is a vaccine? A vaccine is a substance used to stimulate a specific and lasting immune response, usually against a pathogenic microbe. Vaccines comprise two key components: the **antigen payload** and the **delivery platform**. The antigen payload provides critical information to the host immune system about what the pathogen “looks like”, so that an immune response can be mounted. Often, but not always, the payload is the receptor that the microbe uses to mediate entry into host cells. The delivery platform is the vaccine format used to distribute that antigen to the immune system. Commonly-used platforms include dead (*inactivated vaccines*) or dampened (*live attenuated vaccines*) pathogen, purified pathogen fragments (*protein subunit vaccines*), and non-infectious pathogen particles (*virus-like particle vaccines*). Emerging platforms include recombinant virus vector systems (*replicating or non-replicating viral-vectored vaccines*) and nucleic acids (*RNA/DNA vaccines*). Some vaccines also contain an **adjuvant**, an additional substance used to non-specifically enhance host immunity.

Considerations for vaccine design. Vaccine development has three main considerations: 1.) is the vaccine safe? 2.) does it generate pathogen-neutralizing immunity? and 3.) can it be manufactured and delivered economically and to scale? To assess vaccine safety, dose-response studies are done first in rodent models, and then in non-human primates, before proceeding to Phase I clinical trial. Assessing vaccine efficacy usually encompasses both immunogenicity testing (does the vaccine generate humoral and cellular immunity against the pathogen?) and challenge studies (does vaccination protect against infection and disease?). These studies usually require animal models that are susceptible to pathogen infection, and then Phase II-III clinical trials. Manufacturing clinical-grade vaccine requires good manufacturing practice, which mandates strict adherence to quality control and assurance measures far exceeding standard laboratory practice. This requires specialized and very expensive manufacturing facilities.

Development of a SARS-CoV-2 vaccine. There is growing evidence that humans mount strong, neutralizing immune responses to SARS-CoV-2 infection. This is encouraging for vaccine developers and society at large. There are at least 76 vaccine candidates under development (<https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf>). The most common antigen payload is the SARS-CoV-2 spike (S) protein, which mediates entry into host cells *via* the ACE2 receptor, but some vaccines also incorporate viral N, M, E and/or other proteins/antigens. The platforms used span the gamut, from the commonly-used to emerging platforms described above. At least six vaccines are now in clinical trial, with the furthest along – an encapsulated mRNA vaccine developed by Moderna – leading the way, with some participants receiving 28-day booster vaccinations this week.

Most experts agree that many vaccines ought to be simultaneously developed, as we can't predict which, if any, will be safe and effective, or how efficiently they can be manufactured. One safety concern being given particular consideration during the developmental process is **vaccine-enhanced disease (VED)**, a phenomenon in which the immune system helps, rather than hinders, the virus infection. VED was observed with experimental vaccines targeting SARS and MERS and is being carefully monitored for in preclinical studies. Some important issues about vaccine efficacy include how long immunity to SARS-CoV-2 will last, and whether immune pressure will drive the emergence of resistant strains. Immunity to several other coronaviruses circulating in human populations is unfortunately quite fleeting. These, and other, issues will get worked out in a flurry of animal studies and clinical trials. Hopefully, one or several vaccines will emerge and be licensed within 12-18 months – which would be an unprecedented timeframe for vaccine development – and become widely available. Until then, wash your hands, wear your mask and keep your distance!