



EDITORIALS

Developing a vaccine for covid-19

Old and new strategies are being investigated in an unprecedented worldwide effort

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The rapidly developing covid-19 epidemic has stimulated an enormous effort to develop vaccines against the coronavirus SARS-CoV-2. At least six vaccine candidates have entered clinical trials across the globe, with more than 80 other candidates reported to be in preclinical stages.¹ This means many different approaches are being moved forward at the same time. However, the road to successful vaccine licensure is treacherous, and only a handful of these vaccines may make it.

No vaccines are currently licensed for any of the other coronaviruses affecting humans—SARS-CoV-1, MERS-CoV, and minor cold viruses. Economic reasons are undoubtedly a major factor for the absence of these vaccines, but vaccine design is also a challenge; immune responses to natural coronavirus infections can be short lived, and some trial vaccines for SARS-CoV-1 raised safety concerns in animal models.² The development of a SARS-CoV-2 vaccine therefore may not be straightforward.

The multiple strategies to vaccine development for covid-19 include both traditional methods and next generation techniques. Historically, vaccines comprised inactivated whole virus, attenuated virus (less virulent but still immunogenic), or parts or subunits of the virus. Live vaccines are not likely to be attempted for covid-19 for safety reasons, but an inactivated whole virus vaccine has been taken through to preclinical trials in primates.³ When challenged with SARS-CoV-2, vaccinated macaques were protected from severe disease and cleared the virus within a week, whereas macaques receiving placebo developed severe interstitial pneumonia. A phase I-II human trial of this inactivated vaccine is now underway in China.⁴

Spike protein

Many other efforts are currently focused on the spike protein in SARS-CoV-2. This protein is part of the outer layer of the virus and is critical for entry into cells. Antibodies that target the spike protein can block virus entry, potentially inhibiting subsequent virus replication.⁵ The genetic sequence of the spike protein was released internationally on 10 January 2020, providing a blueprint for vaccine development.^{6,7}

Widely reported UK contributions towards a SARS-CoV-2 vaccine are based on the spike protein. Scientists at the University of Oxford have modified a chimp adenovirus vector

to carry the spike protein gene. When the adenovirus invades human cells, the spike protein will be produced, becoming a potential target for an immune response. The clinical trial for this vaccine started on 23 April and plans to recruit over 1000 volunteers.⁸

The use of messenger RNA as a vaccine is a relatively new strategy, and no licenced vaccines have yet used this method. The concept is simple though—inject mRNA coding for the spike protein and let the host make the protein. One advantage of this approach is a reasonably straightforward route to manufacture, allowing rapid scaling up of production. The first mRNA vaccine entered clinical trials in the US six weeks ago, and preliminary results are eagerly awaited. Related work is ongoing at Imperial College London, with promising results in mice released at the end of April.⁹

Other vaccine strategies under consideration include injecting DNA coding for the spike protein or the actual spike protein (“recombinant protein”). Others are using just the tip domain of the spike protein as this is the part that targets the receptors on human cells. Examples of these approaches are likely to enter phase I clinical trials this year.

Repurposing other vaccines

Repurposing vaccines to treat covid-19 is being considered as an alternative means of virus control. Hundreds of vaccines are licensed worldwide for non-coronavirus pathogens, and associations have been made between general vaccine uptake in a country and covid-19 severity.

The current frontrunner is the BCG vaccine, normally directed against tuberculosis. BCG vaccine can stimulate broad, innate components of the immune system, offering some protection against a range of diseases from influenza to bladder cancer.^{10,11} Several studies have now proposed an epidemiological link between population BCG coverage and reduced covid-19 incidence at a country level.^{12,13} Although several rebuttal studies have also been published, at least five clinical trials are now recruiting healthcare workers to investigate whether BCG protects them against covid-19.¹⁴

Other potential repurposed vaccines include the oral polio vaccine¹⁵ and the MMR vaccine.¹⁶ All these existing vaccines

have the advantage that they can begin phase III trials immediately as safety (phase I) and immunogenicity (phase II) have already been established. However, evidence for their use must be regarded as tenuous at this point.

Which vaccine will make it successfully through clinical trials first? It's too early to tell, and in an ideal world we would have several safe and effective vaccines. No single vaccine will be suitable for everyone, everywhere. Access will be particularly challenging for low income countries, where financial support will be essential.

Having choice will also increase the scale of overall production, using a variety of manufacturing options. While fast tracking research and development is an option in all well resourced countries, the most realistic time frame for the production at scale of any safe and effective vaccine against covid-19 still stands at over a year.

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