COVID-19 vaccines: how did we do so well?

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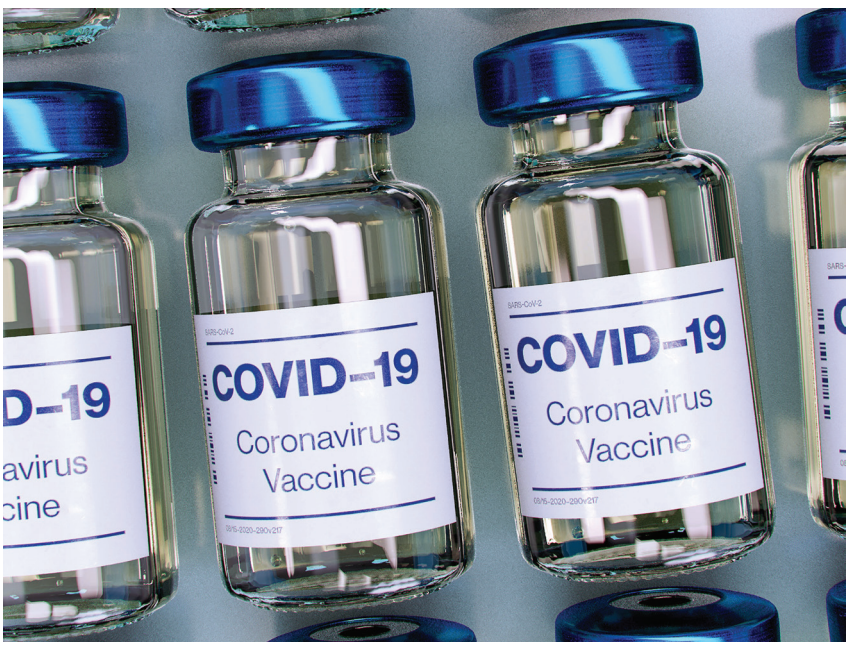
Although SARS-CoV-2 was relatively easy to design a vaccine against, the speed at which COVID-19 vaccines have been developed and deployed was surprising. Nevertheless some canny planning along with decades of investment in biomedical research and health informatics, as well as eventually learning from previous disease outbreaks, all helped in the endeavour.



The development and roll-out of the COVID-19 vaccines has been rapid. This speed was possible due to numerous factors including the virus profile, new advancements and investment, and lessons from previous pandemics. Photo by Daniel Schludi on Unsplash

It would probably be fair to say that the speed of development and roll-out of COVID-19 vaccines has taken most people by surprise, although the reasons for this may differ depending on whether you are a scientist, a clinician, a politician or a member of the public. As an immunologist working on vaccine design and evaluation for more than 30 years, I was not particularly surprised that designing an effective vaccine against SARS-CoV-2 turned out to be quite so straightforward (for reasons that I explain below), but I have been amazed at how quickly the vaccines moved through clinical trials, how rapidly manufacturing capacity has been scaled up, and how efficiently the population is being vaccinated.

Vaccine development and production

The streamlining of the clinical trials pipeline has been a real eye-opener and will, I think, lead to long-lasting changes in how we do things. Rather than taking each phase of the process as an independent project, with each stage requiring entirely separate justification, funding and formal review, we have realised that with careful sequencing and appropriate stage-gate review, the different phases can be planned as a single integrated package, with considerable savings in time and effort.

Vaccine manufacturing is an inherently risky business proposition,[1] and manufacturing capacity has been a headache for public health systems around the world for many years, with interruptions to supply regularly holding up vaccination programmes.

Although supply has improved in recent years with the advent of lower-cost manufacturing in emerging economies such as India, China and Brazil, the speed at which the technology for producing COVID-19 vaccines has been transferred to manufacturing plants across the globe has been impressive.

The efficiency of roll-out in the UK, on the other hand, reflects in part the financial gamble taken by the Vaccines Taskforce to invest in the manufacture of numerous vaccine candidates long before their clinical efficacy was known; this has ensured early access

to large volumes of vaccine as soon as regulatory approval was granted. In addition, the UK's major investments in electronic health data collection and sharing have allowed us to prioritise people for vaccination on the basis of their individual risk, and the universal reach of our NHS has enabled us to contact people and invite them for vaccination.

The virus itself

But, without vaccines of proven efficacy there would be no vaccination programme. So, how did we get to the point of having so many approved COVID-19 vaccines within a year of the start of the pandemic? Firstly, we were lucky that SARS-CoV-2 turned out to be a rather easy target for vaccine development.

SARS-CoV-2 is a relatively simple virus (its genome codes for just a dozen viral proteins) and having only very recently jumped from its original animal host, it is still evolving to be a truly human pathogen. It has not yet had time to find ways to evade our immune systems, although the emerging viral variants with enhanced transmission and reduced sensitivity to neutralising antibodies are clear evidence that such evolution is well underway.

SARS-CoV-2 is also very similar to viruses such as SARS and MERS for which prototype vaccines had already been developed.

New vaccine technology

Secondly, there has been huge investment over recent decades in new approaches to making vaccines. The historic approach of using attenuated or killed whole pathogens to induce a protective immune response (as for polio, measles, mumps and rubella) has been supplemented by a subunit approach, where one or more fragments of the virus is produced as a standalone antigen and incorporated into an immunogenic carrier or adjuvant. For example, the hepatitis B vaccine, which used recombinant DNA technology to produce HBV surface antigen in bacteria, was launched in the mid-1980s and was the first of this new generation of 'designer' vaccines. More recent examples include vaccines for meningococcal and pneumococcal disease.

These tried and tested approaches are being used for COVID-19 vaccines – the Valneva, Sinovac and Sinopharm vaccines all use inactivated SARS-CoV-2 virus and Novavax has developed a protein subunit vaccine – but the pandemic has provided the impetus for fast-tracking some newer vaccine platform technologies. Viral-vectored vaccines, such as the Oxford AstraZeneca, Sputnik V and Johnson & Johnson/Janssen vaccines, use a harmless adenovirus to carry the genetic code of the viral spike protein into our cells where our own cellular machinery translates it into spike protein, triggering anti-spike immunity.

Attenuated adenovirus-vectored vaccines have been under development for many years but, prior to COVID-19, had only been approved for vaccination against Ebola[2] – another recent example of a deadly epidemic driving vaccine innovation. The entirely new 'kid-on-the-block', however, is mRNA vaccine technology. The Pfizer/BioNtech and Moderna COVID-19 vaccines are the first mRNA vaccines ever approved and implemented. In both cases, the RNA code for the virus spike protein is encased in fat droplets, called liposomes. As with the viral vectored vaccines, this tricks our cells into synthesising the spike protein so that we make antibodies and T cells to fight off any subsequent infection.

Learning from the past

And last, but by no means least, the public health community learned a very important lesson from the Ebola epidemic in West Africa in 2014–2016, namely that we lacked a vaccine against Ebola simply because no-one had considered it a sufficient priority to produce one.

Prototype Ebola vaccines had been languishing for decades in laboratory freezers on three continents but progressing them to even pre-clinical trials required a major financial investment and any subsequent development was dependent upon interest from potential manufacturers.[3] Neither the money nor the industrial partners were available because the sporadic and limited nature of Ebola outbreaks made it a poor commercial prospect (prior to 2014 there had been only a dozen or so outbreaks since Ebola was first described in 1976, the largest of which is believed to have killed approximately 250 people).

The 2014 outbreak changed all that, leading to the recognition that epidemic preparedness required governments and philanthropic organisations to invest not just in vaccine development and manufacture for diseases with known epidemic potential, but also in generic vaccine platforms that could be rapidly deployed to respond to the emergence of previously unknown pathogens. In 2016, the then Department of Health established the UK Vaccines Network to invest in vaccine platform development and manufacturing in the UK and, in 2017, a group of international funders, including the Bill and Melinda Gates Foundation and Wellcome, established the Coalition for Epidemic Preparedness and Innovation (CEPI) with similar aims and a global remit.

Limited side-effect profile

Despite my optimism that SARS-CoV-2 vaccine development would prove to be relatively uncomplicated, I was as relieved as anyone when the first reports of the safety, immunogenicity and protective efficacy of both the mRNA and the modified adenovirus vaccines began to emerge in the autumn of 2020. No matter how straightforward the project might have seemed, vaccine development can throw up unexpected and unwelcome complications leading to delays in

vaccine roll-out, vaccine recall or discontinuation of a vaccine programme. Within the last couple of decades, highly effective vaccines against dengue fever,[4] seasonal influenza[5] and rotavirus[6] have been found to induce uncommon but potentially serious side-effects in specific groups of people. This has necessitated reformulation or withdrawal of these vaccines or has restricted the use of the vaccines in certain demographics.

In the case of SARS-CoV-2 the major concerns were not just how effective the vaccines would be in preventing infection, severe disease and death but also whether they would increase the risk of immune-mediated pathology. The severe, lower respiratory tract pathology caused by SARS-CoV-2 is, in part, mediated by the host's inflammatory response, and there was at least a theoretical risk that immunisation could enhance rather than reduce this response. Thankfully, this has not been the case.

Furthermore, some viruses induce antibodies that do not effectively neutralise the virus, but rather enhance viral infection of host cells: antibody-coated virus particles bind to immunoglobulin receptors on host cells triggering endocytosis of the virus.[7] Antibody-dependent enhancement (ADE) of virus infectivity can occur with RSV and measles, and has been the main stumbling block in rolling out Dengue vaccines in endemic countries. Importantly, ADE has also been described for several coronaviruses including those that cause SARS, MERS and feline infectious peritonitis. To date, there have been no reports of significant ADE after COVID-19 infection or vaccination, which has been a huge relief, but monitoring continues.

While frequent severe adverse events that might preclude wide-scale vaccine implementation have thankfully not been seen, the recent data linking two adenovirus vectored vaccines (AstraZeneca and Johnson&Johnson/Janssen) with rare cases of thrombocytopaenia and atypical blood clots are a timely reminder that we must remain vigilant for rare but life-threatening side-effects that could not have been predicted from clinical trials. The aetiology of these rare adverse events is not yet confirmed, but autoantibodies have been detected in some cases and treatment with polyclonal immunoglobulin seems to be beneficial.

Summary

In summary therefore, if vaccine deployment is indeed the turning point for the COVID-19 pandemic it will be the culmination of decades of investment in biomedical research and health informatics: our (belated) ability to learn from previous disease outbreaks, and some canny investments by the Vaccine Taskforce. However, it will also be because SARS-CoV-2 proved to be rather easy to vaccinate against. For that, we should be very grateful.

Declaration of interests

The author is a member of the UK Vaccines Network, the UKRI COVID-19 taskforce and the COVID-19 working group of the British Society for Immunology.

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