Occupational Medicine 2021;**71**:115–117
Advance Access publication on 18 March 2021 doi:10.1093/occmed/kqaa208

EDITORIAL

The vaccination clinic 2021

At the time of writing (November 2020), we appear to be near to the global discovery, manufacture and, ultimately, mass deployment of a successful vaccine for SARS-CoV-2.

There has been unprecedented global collaboration between governments, academia, industry and various others, including participants in clinical trials who have put themselves forward on all our behalf. The World Health Organization lists 48 candidate vaccines in clinical development, with 11 vaccines in Phase III clinical trials [1].

While traditional vaccine development can take 15–18 years, the development of a vaccine for SARS-CoV-2 has progressed rapidly. However, research into SARS-CoV-1 (2002–04), with which SARS-CoV-2 has about 80% similarity, has been progressing since 2002. Such has that advantage been, that the SARS-COV-2 's' or spike protein had already been identified as a potential target for a corona virus vaccine by the time SARS-CoV-2's genetic sequence was known in January 2020. Thus, researchers in 2020 have been able to build on that knowledge to progress vaccine development for this pandemic. Science has also progressed on the back of our combined experience with the swine flu pandemic (2009), MERS (2012) and Ebola outbreaks (2014) [2,3].

Other factors have contributed to this compressed time line. Vaccine researchers and developers have adopted and adapted existing investigative and manufacturing processes. Vaccine developers and public organizations have also committed enormous sums to allow the usually sequential traditional vaccine development stages (design and exploration; pharmaceutical process development; *in vitro*/*in vivo* pre-clinical testing and toxicology; Phase I–III clinical trials) to run in parallel. Progression through clinical trial stages has been achieved over 8 months since Phase I trials began in March 2020. Vaccine manufacturers have scaled up production in anticipation of scientific success much earlier than is usual in traditional development [4].

Additionally, medicines regulators across the world have committed to real-time regulatory review of incoming data during the vaccine development process outlined above. This allowed Phase III trials to start, based on satisfactory results on interim analysis of Phase I/II data. That being said, vaccines for SARS-CoV-2 need to meet the same safety, quality and efficacy standards that apply to all medicines [5,6]. It remains to be seen whether the type of authorization granted is an emergency or conditional authorization given the pandemic, and it must be noted that a disadvantage to this compressed timeline is that long-term data on the duration of induced immunity from SARS-CoV-2 vaccination to date are as yet unknown.

A vaccine is designed to present an inactive SARS-CoV-2 antigen to the immune system, such that the immune system mounts a successful immune response to neutralize it. There are traditional vaccines in the pipeline and novel vaccine types that have not been authorized in humans before. The type of antigen presented to our immune system may be based on whole virus SARS-CoV-2, or just on components of SARS-CoV-2. A look at the WHO draft landscape [1] gives an indication of the vaccine types under development, which may be categorized as whole virus, viral vector, nucleic acid and protein-based vaccine types [4,7,8].

Whole virus vaccines are manufactured by traditional vaccine technology and there are many existing vaccines made in this way, for example, for polio, rabies and influenza. As these vaccines need infectious virus to begin with, this type of manufacture may need Biosafety Level 3 standard facilities and extensive safety testing which are costly, time-consuming and large-scale operations. These whole virus vaccines may be inactivated (rendered non-infectious by means of chemicals, heat or irradiation) or weakened/attenuated by repeated propagation in animal or human cell cultures which results in mutations, limiting ability to cause disease. They remain immunogenic although sometimes requiring an immune adjuvant to boost their efficacy.

In the case of viral vector vaccines, a different, weakened virus (e.g. adenovirus, which has long use in gene therapies) is genetically engineered, so that it can produce SARS-CoV-2 antibodies when introduced into the body. These vaccines also have a biosafety risk, are time-consuming to manufacture and are costly, with some requiring deep freeze. They can be replicating (the viral vector genome is intact, so the viral lifecycle continues, including viral assembly and shedding in recipient cells), hence no adjuvant is needed. They may otherwise be non-replicating (no genetic instructions for viral assembly and shedding), which may be safer for immunocompromised patients but may require booster doses in future. However, if the vaccinee has already been exposed to the viral vector in these vaccines, their

immune system can mount a response against the vaccine and blunt its effectiveness.

The novel nucleic acid vaccines contain DNA or RNA genetic instructions for a SARS-CoV-2 antigen, e.g. the spike protein. Once the DNA or RNA instructions get into host cells, the vaccinee's own cellular machinery will make the antigen. On release from the cell, it is expected that the antigen will prompt an immune system response. There is no licensed vaccine in humans using this technology to date. Their advantage is that, as only genetic material is required to make them, rather than whole virus in large amounts, they can be made quickly and in a cost-effective manner. The DNA vaccines may, however, require a medical device to improve their uptake into cells by a process known as 'electroporation', which may limit widespread use in the community. In RNA vaccines, the RNA is enclosed within a lipid nanoparticle, or coat, which aids entry into the host cell, but stability of this type of vaccine requires deep-freeze storage conditions.

Protein-based vaccines, a type of subunit vaccine, are made from purified antigenic fragments of the whole virus. These smaller components focus on the spike protein itself or possibly only its receptor-binding domain. Due to their nature, this type of vaccine is often boosted with adjuvants and multiple doses might be needed. Alternatively, the protein-based vaccine may contain a virus-like particle—an empty shell or external layer of the virus without any genetic instructions internally. While they are non-infectious, they can trigger a strong immune response as there are multiple immune targets on the virus surface, but they are structurally more complex to make than the subunit or split antigen type.

When considering these four vaccine types, there is a trade-off between their ability to prompt a satisfactory immune response versus their tolerability. Ultimately, only the ongoing Phase III trials will determine if the vaccines in development for SARS-CoV-2 provide the necessary protection in a safe and effective manner. The next hurdle, should these Phase III trials prove satisfactory will be the twin challenges of mass deployment and uptake across the globe.

It is vaccination rather than vaccines themselves that will bring an end to this pandemic [9]. Presuming SARS-CoV-2 vaccine authorization, success will require that a sufficient number of the world's population is vaccinated such that herd immunity is achieved over the next 1–2 years. Estimating the level of herd immunity required is a complex calculation based on a number of assumptions, such as vaccine efficacy, duration of immunity provided and the virus' reproduction or R number. Governments and public bodies around the world are already well into the detail of designing pandemic vaccination campaigns to best achieve herd immunity [10].

Regarding mass deployment, vaccine manufacturers and component support companies are scaling up production, hoping that scarce raw materials will not prove to be a limiting pinch point over time. Those in procurement are working on vaccine availability, likely to come in waves, which will necessarily inform prioritization. Cold chain requirements will have a major impact on feasible distribution planning. The work of vaccination campaigns likely encompasses policy and procedure, vaccinator training, vaccination clinic resourcing and data management at population level.

Monitoring and evaluation of vaccines for adverse drug reactions are paramount, and in this global pandemic, there will be an onus on all health care professionals to look for, ask about and report adverse drug reactions as never before [11]. Understanding that not all possible side effects may have occurred in the clinical trials to date, health professionals must be vigilant and prompt in reporting, particularly to determine whether antibody-dependent enhancement of disease is a feature as has been observed in SARS, MERS and other respiratory viral infections [12].

In the short term, the goal has been the discovery, manufacture and mass deployment of a safe and efficacious vaccine. The best-case scenario is a range of vaccines against SARS-CoV-2, whether novel or traditional, with indications that cover all population subgroups. Moving from vaccines to vaccination, possibly the most important goal now is mass deployment of clear, consistent, communication with the intended recipient, from trusted sources, to ensure that the entire population has confidence in the plan. We must ensure that the amazing efforts made, and terrible hardships endured, by so many in the year 2020 are not wasted, for want of the right message.

Competing interests

N.K. is a Medical Assessor with the Health Products Regulatory Authority (HPRA), Dublin, Ireland. The views expressed are the author's own views and are not made on behalf of the HPRA.

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