COVID-19 vaccines for rapid global impact

Writing in early January 2021, less than a year from the disclosure of the SARS-CoV-2 coronavirus genome sequence, it is truly extraordinary that three vaccines have been developed, with impressive efficacy results published [1–3], licensure confirmed in many countries, and these are being administered to millions of people to help contain the worst pandemic for over a century. Three other vaccines, from Russia and China [4–6], are also being deployed and likely to have similar high efficacy and two further vaccines [7,8] from Janssen and Novavax are completing phase III trials. This editorial aims to the review some of this progress with a focus on the Oxford/AstraZeneca vaccine which, the Jenner Institute has been centrally involved with.

Once it became clear in late January 2020 that the new SARS-CoV-2 coronavirus was spreading internationally, and had a substantial *R* value indicting high transmissibility, with infection also from asymptomatic subjects; numerous biotech companies, academic groups and, later, large pharma companies initiated development programmes aiming to provide an effective vaccine. Estimates of time frames for showing efficacy in humans, by different experts, ranged from September 2020 to late 2021, although doubters pointed out that, generally, vaccine development takes closer to 10 years. In Oxford we had the opportunity to build on a technology platform of simian adenovirus vectored vaccines and clinical experience of rapid trial responses to swine flu and Ebola outbreaks over the previous 11 years [9–11].

Vaccine Approaches

Recombinant adenoviral vectored vaccines, first tested in clinical trials in the early 1990s, have been part of several of the largest efforts to develop HIV, malaria and Ebola vaccines [12–14]. They are licensed for the latter and, prior to 2020, had been administered to over 100 000 subjects [7] with long-term follow-up for safety.

Chimpanzee adenoviruses were first tested clinically from 2007 at Oxford [13], attempting to overcome the recognised reduction in immunogenicity associated with pre-existing anti-vector immunity to human adenoviruses. These simian vectors, which are overlapping in their phylogeny with human adenoviruses, are now the basis of clinical development programmes at Oxford University, or its spin-off company Vaccitech, for sixteen disease indications, and have been in clinical trials sponsored by three major pharma companies with over 5000 vaccinees evaluated prior to 2020 [9]. They have several advantages including a 'plug and play' approach allowing antigens to be rapidly inserted into and

expressed by the adenoviral genome, complete replication incompetence in humans, scalable manufacturing processes and established utility with a single dose. They have been principally adopted for their exceptional capacity to induce $CD8^+$ T cell responses but also induce potent antibodies [15].

For COVID-19, human adenoviruses have been developed by Janssen [7], CanSino [16] in China and the Gamaleya Institute in Moscow [4] and, like the Oxford/AstraZeneca ChAdOx1 vaccine [17], these viral vectors express the full length SARS-CoV2 spike protein and showed efficacy in pre-clinical studies in non-human primates.

A second class of vaccine is based on the new RNA vaccine technology, which like adenoviral vectors allows rapid generation of vaccines, which induce potent antibodies. High level efficacy against COVID-19 in humans has been reported [2,3] but these vaccines have unusual freezing requirements for storage, limited long-term safety data and some challenges for very large scale manufacture. Imperial College, London and Curevac in Germany are also developing RNA vaccines for COVID-19.

Several vaccines have also been developed by the classical approach of inactivating the SARS-CoV-2 virus and then mixing this with an adjuvant (Sinopharm, SinoVac, Valneva, Bharat). Sinopharm [5] and Sinovac [6] have reported high efficacy in phase III trials by press release with publications awaited. It is unclear what the potential for manufacturing billions of doses by this approach is as viral growth rates may be limiting.

Finally, production of the spike protein *in vitro* and use of this with an adjuvant is a standard vaccine approach and Novavax Inc have reported strong immunogenicity with a saponin adjuvant [8], with efficacy data expected soon. A GSK–Sanofi joint project has been delayed until late 2021 by sub-optimal immunogenicity in older adults.

Safety

Safety data across large numbers of phase I–III trials now appears generally reassuring [1–3]. For example, over 60 000 subjects have been enrolled in trials of the Oxford/AstraZeneca vaccine in the UK, Brazil, South Africa, Kenya, the USA, India and Japan with a well-tolerated safety profile and no vaccine-attributed serious adverse events. The newer RNA vaccines are showing a satisfactory safety profile across many tens of thousands of subjects. These will need longer-term follow-up to exclude rare late adverse events beyond the three months median follow-up reported in recent analyses [2,3]. There were initial concerns that inactivated

SARS-CoV-2 virus vaccines might generate a Th2-biased immune response with a risk of immunopathology but this does not appear to be an issue in humans to date.

Efficacy

The most important measure of the efficacy of a vaccine against COVID-19 is its ability to provide high level protection against severe disease and death. Importantly, for all the vaccines that have been licensed or reported efficacy data this appears to be close to 100% [1–3,6]. This is excellent news for global health and suggests that a low level of vaccine-induced immunity in humans is able to protect well against lower respiratory tract infection and pneumonia, as suggested by animal studies.

In contrast, perhaps the most difficult endpoint for a vaccine to protect well against is colonisation of the upper respiratory tract as suggested by experience with vaccines against other respiratory pathogens. Few developers have attempted to measure this endpoint, which requires regular swabbing of asymptomatic trial participants. The Oxford-led UK trial of the ChAdOx1 vaccine has now evaluated over such 200 000 swabs and initial data suggest that there is indeed some efficacy, at least with the most immunogenic vaccination regimen [1].

The easiest endpoint to measure, and the most widely used, has been efficacy against clinical COVID-19 with the great majority of these cases being of mild disease and not requiring hospital admission. The RNA vaccines from Pfizer/Biontech and Moderna show very high efficacy (94–95%) on this measure, at least over three months of follow-up [2,3] and unpublished results from the Gamaleya, Sinovac and Sinopharm vaccines [4–6] are also high at 78–92% on this measure. But different endpoints used in different trial protocols and different lengths of follow-up make direct comparisons of efficacy very difficult. For example, the Oxford/AstraZeneca vaccine, which has been assessed with a range of immunisation regimes, shows different levels of efficacy according to the regime assessed. With just a single dose efficacy was 73% over the 12-week period from day 22 after immunisation [Table 10, Ref. 18]. For two dose regimens immunogenicity increased markedly with a booster dose, particularly if this was delayed for about 12 weeks (an eight-fold rise) rather than <6 weeks (a three-fold rise) [Table 3, Ref. 18]. The length of the interval between doses appears to largely explain differences in efficacy between two dose regimes ranging from 63% to 90% [1] and this underpins the recent decision in the UK to prioritise use of a 12-week interval between doses [18].

Across trials and vaccine types better efficacy appears to correlate well with total antibody titres to the spike protein and these levels of binding antibody in ELISA assays correlate with levels of neutralising antibodies. However, roles for T cell immunity and other responses cannot be excluded and are being assessed in ongoing searches for immune correlates of vaccine-induced efficacy. Trials continue to evaluate the durability of vaccine-induced immune responses.

Deployability and Global Impact

With several vaccines now increasingly available for use after regulatory approvals the focus is shifting to the challenges of rapid vaccine deployment. This is impacted by the thermostability of the vaccine, which is not a significant issue for all except the RNA vaccines which require freezers and complex cold chains. A larger issue is the rate at which vaccines can be supplied in various countries. It has long been clear that COVID-19 requires global control with billions of people likely to want two doses of a vaccine this year. No vaccine of any type has ever been supplied at a scale of half a billion doses in a year, but perhaps 5 billion people may want a COVID-19 vaccine in 2021, totalling 10 billion doses. The largest number of doses contracted to date is just over 3 billion, for the Oxford/AstraZeneca vaccine, which has manufacturing efforts ongoing in about fifteen countries. But other vaccines, cumulatively, could meet the remaining dose requirements if equitable access can be achieved. As many as nine vaccines could well be licensed and start deployment in various countries by March if current progress is sustained. This would be an unprecedented achievement of great public health and economic importance.

If many billions of doses can be distributed this year, to save huge numbers of lives and end the pandemic, that would be a fitting complement to the remarkable speed achieved in developing several vaccines to licensure in 2020.

Conflict of Interest

The author is Director of the Jenner Institute at Oxford University, one of the team developing the Oxford/AstraZeneca vaccine, and a co-founder of Vaccitech Ltd.

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