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EDITORIAL

Vaccines for SARS coronavirus 2 and the new normal in vaccinology

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes an acute infection that is controlled by the immune response. The virus has a dominant surface protein that is highly immunogenic and it can be presumed that neutralising antibodies will prove to be the correlate of protection, supported by cell-mediated immunity.[1] It should therefore be straightforward to produce a vaccine against this novel virus.

This perspective has turned out to be true, but it is the pace with which the vaccines have been prepared and delivered that is spectacular. Consider that the vaccine made against the 2009 influenza H1N1 pandemic virus was delivered in record time, yet the first wave of cases had been and gone before it could be deployed.[2] Influenza vaccine has the distinct advantage that its licensure is based on a variation from the existing product licence and so can circumvent much of the long, detailed regulatory review needed for a new vaccine. Credit should be given to the flexibility shown by expert regulators prepared to conduct rolling review of the process of licencing each SARS-CoV-2 vaccine rather than waiting for massive files of data to be delivered to them at one timepoint. Major credit should also be given to the developers of novel vaccine platforms who accelerated their plans to bring us vaccines to protect against coronavirus disease 2019 (Covid-19) well before the traditional methodology, such as killed vaccine, live-attenuated vaccine or recombinant glycoprotein plus adjuvant were able to deliver. One platform is based on RNA technology while the second utilises recombinant adenovirus, neither of which has previously led to a licenced vaccine product.[3-6]

By modifying RNA to enhance expression of the encoded desired immunogen, a chemically defined path to making vaccines from far fewer and less complex molecules has been provided, including the characteristic of self-amplification by including the option of encoding an RNA polymerase within the RNA molecule.[7] Degradation after injection is reduced and uptake into target cells is increased by physical incorporation of the modified RNA into lipid nanoparticles.

By using adenovirus as a vector, recombinant spike protein of SARS-CoV-2 is presented to the immune system. To avoid the problem of pre-existing immune responses to the vector neutralising the inoculum, the Oxford group used a chimpanzee adenovirus while the Russian Sputnik vaccine used human adenovirus 5 then human adenovirus 26 in a prime-boost strategy.[5,6]

What does this amazing progress tell us about the next steps in vaccinology? First, we should consider these two new platforms to be top of the list when considering how to develop a new vaccine against the next novel virus. This does not mean that conventional routes of vaccine production should be discarded; a killed vaccine may well have a role for nonenveloped viruses that grow well in cell cultures, such as in the successful vaccine for hepatitis A. However, the major assumption for deriving live-attenuated vaccine strains—that they should give better immune responses than nonreplicating preparations—should no longer be taken for granted, given the excellent humoral and cell-mediated immune responses generated by the new RNA and recombinant adenovirus vaccines. Second, we cannot allow a return to the old ways of taking decades to develop new vaccines. Not only does this increase the cost of the final product, it impairs the assessment of cost-effectiveness. Vaccines frequently offer excellent value for money but get held back when the net present value of their future medical benefits is calculated. The reason is that public bodies making investment decisions discount the value of the future benefits to compensate for the disappointment of having to wait for their delivery. This process automatically disadvantages products with a long lead time, like conventional vaccines. The 'new normal' that we return to after lockdown will not include every aspect of the steps taken to procure SARS-CoV-2 vaccines during a pandemic, but some should be used again. For example, countries preordering doses of a vaccine if it proves to satisfy defined criteria of safety and efficacy will support the investment decisions of vaccine manufacturers. We should encourage our individual countries to rally round the list of viral diseases that the World Health Organisation would like to see controlled and tackle them one by one. My preference for the next acute virus infection spread by the respiratory route that causes serious disease with unmet medical need and has a prominent glycoprotein protruding through its lipid envelope would be respiratory syncytial virus, but readers may prefer alternative targets.

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REFERENCES

1. Khan MM, Noor A, Madni A, Shafiq M. Emergence of novel coronavirus and progress toward treatment and vaccine. *Rev Med Virol*. 2020;30(4):e2116.

2. Rappuoli R, Dormitzer PR. Influenza: options to improve pandemic preparation. *Science*. 2012;336(6088):1531-1533.
3. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416.
4. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
5. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2020.
6. Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*. 2021;397(10275):671-681
7. Wadhwa A, Aljabbari A, Lokras A, Foged C, Thakur A. Opportunities and challenges in the delivery of mRNA-based vaccines. *Pharmaceutics*. 2020;12(2):102.