COMMENT

COVID-19 vaccines: breaking record times to first-in-human trials

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The twenty-first century has come with a new era in vaccinology, in which recombinant genetic technology has contributed to setting an unprecedented fast pace in vaccine development, clearly demonstrated during the recent COVID-19 pandemic.

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COVID-19 is caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). As of 15th April 2020, the World Health Organization (WHO) has reported over 1.7 million cases of COVID-19 and 100,000 deaths worldwide1. The virus can be transmitted by patients with or with no symptomatology, thus making the control of this disease outbreak a challenging task due to the lack of a specific treatment or vaccine2. Without an efficacious licensed vaccine, control of the pandemic relies on self-isolation to prevent close contact with other people and basic measures such as hand washing. Quarantine is efficacious but causes major disruption to the economy of people and countries3. Therefore, development of a safe and effective vaccine against COVID-19 is an urgent public health priority.

Over the last century, control of epidemics has been achieved successfully thanks to vaccines developed using various technologies, predominantly by classic pathogen inactivation or attenuation. This has worked efficiently for Cholera, Typhoid, Polio, Measles, Plague or Tetanus. Conjugate-vaccines and subunit vaccines have also provided effective triumphs in vaccinology for pneumonia, sepsis and meningitis4. The pace of these vaccine developments is comparatively slow to that imprinted by 21st-century vaccines that use recombinant genetic technology. During the recent pandemic of COVID-19, six vaccine candidates encoding or presenting SARS-CoV-2 antigens have entered phase I clinical trials to assess their safety and immunogenicity, including those based on mRNA (NCT04283461), adenoviral vector 5 (NCT04313127); chimpanzee adenoviral vector ChAdOx1 (NCT04324606), DNA (NCT04336410), a lentiviral vector (NCT04276896) and artificial antigen-presenting cells or aAPC (NCT04299724). Despite the fact that most of these COVID-19 vaccine candidates are being evaluated in phase I trials, some are experimental (DNA/RNA vaccines) and may have a longer journey ahead to achieve licensure. Available information indicates that various candidates express the COVID-19 spike (S) glycoprotein to neutralise the virus and prevent attachment to the human angiotensin converting enzyme II (ACE2) receptor, known to be the co-receptor for viral entry of SARS-CoV-25.

The mRNA1273-COVID-19 vaccine has set a record time by reaching trials (NCT04283461) in only 69 days after the identification of the SARS-CoV-2 as the causative agent of the current outbreak2. This is in contrast to the lack of a specific treatment or vaccine2. Without an efficacious licensed vaccine, control of the pandemic relies on self-isolation to prevent close contact with other people and basic measures such as hand washing. Quarantine is efficacious but causes major disruption to the economy of people and countries3. Therefore, development of a safe and effective vaccine against COVID-19 is an urgent public health priority.

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NCT02840487). Dengue Virus has been in circulation for more than a century and a tetravalent live attenuated vaccine produced by Sanofi Pasteur has only been authorized by the European Medicine Agency in 2018. However, the very first clinical trial was done during the World War II by Albert Sabin, who used a Dengue virus originally attenuated in mice. The first chikungunya vaccine tested in humans in the late 60’s used a formalin-inactivated virus, which was subsequently abandoned for new vaccine platforms such as a virus-like particle (VLP) platform (NCT01489358), which has showed high titers of neutralizing antibodies in recipients after a second dose. The first Zika DNA vaccine reached trials in August 2016, 9 years after ZIKV outbreak in part of the Federated States of Micronesia, 3 years after the major epidemic in French Polynesia in October 2013 but just 6 months after WHO declaration as the Public Health Emergency of International Concern (PHEIC) on February 2016, highlighting the advances in the modern vaccine development in urgent need. A Zika DNA vaccine delivered in a split-dose needle freeway, was able to induce six times higher immune responses compared to a single-dose delivery via needle and syringe and therefore moved into an international placebo-controlled phase 2 efficacy trial.

Other emerging diseases that have caused major epidemics are Haemorrhagic fever viral diseases such as Ebola, Crimean-Congo fever and Lassa fever. These have taken more than three decades to get to the first-in-human assessment (NCT00072605, NCT03020771, NCT03805984) (Fig. 1) but unfortunately not all of them have described safety and tolerability results yet. However, the rVSV-Ebola vaccine candidate based on a live, attenuated recombinant vesicular stomatitis virus vector produced by Merck has progressed beyond I/II/III clinical trials receiving approval by the US FDA in December 2019; whereas a viral-vectorized Ebola vaccine candidate consisting of Ad26/MVA has now completed phase III trial (NCT02543567). Initial vaccine clinical trials may not always lead to a successful license but can pave the way to the success of future vaccines in acquiring the license. The great majority of licensed vaccines are based in inactivation/attenuation pathogens which lengthen the development, cost and production of the vaccine. Recombinant viral vectored, DNA/RNA and protein technologies are setting the fastest records in vaccine development but just a selected few have been licensed so far for veterinary use only, since, for humans some vaccines have not met some regulatory requirements for approval and commercialization yet but international emergencies like the current COVID-19 could provide a final push towards obtaining licensure. This highlights the potential of vaccinology to make fast progress when appropriate international support exists, proving that when there is a will, there is a way.

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REFERENCES
1. WHO COVID-19 dashboard. https://covid19.who.int/. (2020).
2. Rothe, C. et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2001468.
3. Wilder-Smith, A. & Freedman, D. O. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J. Travel. Med. 2020. https://doi.org/10.1093/ijtmyktaa020.
4. Bhurani, V., Mohankrishnan, A., Morrot, A. & Dalai, S. K. Developing effective vaccines: cues from natural infection. Int. Rev. Immunol. 37, 249–265 (2018).
5. Zhou, P. et al. A pneumonia outbreak associated with a novel coronavirus of probable bat origin. Nature. 579, 270–273 (2020).
6. Wang, C., Horby, P. W., Hayden, F. G. & Gao, G. F. A novel coronavirus outbreak of global health concern. Lancet Lond. Engl. 395, 470–473 (2020).
7. Vitelli, A. et al. Chimpanzee adenoviral vectors as vaccines—challenges to move the technology into the fast lane. Expert Rev. Vaccines 16, 1241–1252 (2017).
8. Zaki, A. M., van Boheemen, S. & Bestebroer, T. M., Osterhaus ADME, Fouchier RAM. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N. Engl. J. Med 367, 1814–1820 (2012).
9. Rosling, L. & Rosling, M. Pneumonia causes panic in Guangdong province. BMJ. 326, 416 (2003).
10. Ashburn, P. M. & Craig, C. F., US Army Board for the Study of Tropical Diseases. Experimental investigations regarding the etiology of dengue fever. 1907. J. Infect. Dis. 189, 1747–1783 (2004).
11. Ross, B. W. The Newala epidemic. III. The virus: isolation, pathogenic properties and relationship to the epidemic. J. Hyg. (Lond.) 54, 177–191 (1956).
12. Sergon, K. et al. Seroprevalence of Chikungunya virus (CHIKV) infection on Lamu Island, Kenya, October 2004. Am. J. Trop. Med. Hyg. 78, 333–337 (2008).
13. Duffy, M. R. et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N. Engl. J. Med. 360, 2536–2543 (2009).
14. Dick, G. W. A., Kitchen, S. F. & Haddow, A. J. Zika virus. I. Isolations and serological specificity. Trans. R. Soc. Trop. Med. Hyg. 46, 509–520 (1952).
15. Dick, G. W. A. Zika virus. II. Pathogenicity and physical properties. Trans. R. Soc. Trop. Med. Hyg. 46, 521–534 (1952).
16. Sabin, A. B. Research on dengue during World War II. Am. J. Trop. Med. Hyg. 1, 30–50 (1952).
17. Harrison, V. R., Eckels, K. H., Bartelloni, P. J. & Hampton, C. Production and evaluation of a formalin-killed Chikungunya vaccine. J. Immunol. Baltim. Md. 1950 107, 643–647 (1971).
18. Chang, L.-J. et al. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. Lancet Lond. Engl. 384, 2046–2052 (2014).
19. Gaudinski, M. R. et al. Safety, tolerability, and immunogenicity of two Zika virus DNA vaccine candidates in healthy adults: randomised, open-label, phase 1 clinical trials. Lancet. 391, 552–562 (2018).
20. Pattyn, S., van der Groen, G., Jacob, W., Piot, P. & Courtelle, G. Isolation of Marburg-like virus from a case of haemorrhagic fever in Zaire. Lancet Lond. Engl. 1, 573–574 (1977).
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COMPETING INTERESTS
The authors declare no competing interests.