Editorial

COVID-19 vaccine: The all-important timelines

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A COVID-19 vaccine provides acquired immunity against COVID-19[1]. Prior to COVID-19 pandemic, knowledge about the coronavirus structure was extrapolated from prior encounters with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)[1]. To date, there is no safe and effective SARS vaccine[2]. There is also no proven MERS vaccine[3]. After severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in December 2019[4], its genetic sequence was published on 11 January 2020, triggering an international response to prepare for an outbreak and hasten the development of a vaccine[5]. In February 2020, World Health Organization (WHO) stated that it did not expect a vaccine against SARS-CoV-2 to become available before 18 months[6]. The rapid infection rate of COVID-19 worldwide during early 2020 stimulated international alliances and government efforts to urgently organize resources to make multiple vaccines on shortened timelines[7].

Phase I trials test primarily for safety and preliminary dosing in a few dozen healthy subjects, while Phase II trials evaluate immunogenicity, dose levels and adverse effects of the candidate vaccine, in hundreds of people[8,9]. A Phase I–II trial consists of preliminary safety and immunogenicity testing and is typically randomized and placebo-controlled[9]. Phase III trials involve more participants at multiple sites, include a control group, and test effectiveness of vaccine to prevent the disease, while monitoring for adverse effects at optimal dose[8,9]. Definition of vaccine safety, efficacy, and clinical endpoints in a Phase III trial may vary between trials of different companies, such as defining degree of side effects, infection or amount of transmission, and whether the vaccine prevents moderate or severe COVID-19 infection[10-12]. By mid-December 2020, 57 vaccine candidates were in clinical research, including 40 in Phase I–II trials and 17 in Phase II–III trials[1].

Geopolitical issues, safety concerns for vulnerable populations, and manufacturing challenges for producing billions of doses are compressing schedules to shorten the standard vaccine development timeline, in some cases combining clinical trial steps over months, a process typically conducted sequentially over years[13]. In the haste to provide a vaccine on a rapid timeline for the COVID-19 pandemic, developers and governments are accepting a high risk of 'short-circuiting' or 'fast-tracking' the vaccine development process[14], with one industry executive saying: "The world crisis is so big that each of us will have to take maximum risk now to put a stop to this disease"[14]. Multiple steps along the entire development path are evaluated, including level of acceptable toxicity of vaccine, targeting vulnerable populations, need for vaccine efficacy breakthroughs, duration of vaccination protection, special delivery systems (oral or nasal, rather than injection), dose regimens, stability and storage characteristics, emergency use authorization, all before formal licensing, optimal manufacturing for scaling to billions of doses, and dissemination of licensed vaccine[15]. Timelines for conducting clinical research, normally a sequential process requiring years, are being compressed into safety, efficacy, and dosing trials running simultaneously over months, potentially compromising safety assurance[13,14].

A multinational collaboration, including the WHO, the Coalition for Epidemic Preparedness Innovations (CEPI), Global Alliance for Vaccination and Immunisation (GAVI), the Gates Foundation, and governments, formed the Access to COVID-19 Tools (ACT) Accelerator, to raise financial support of accelerated research and development, production, and globally-equitable access to COVID-19 tests, therapies, and licensing of vaccines, which are in a specific development programme called the COVAX Pillar[16,17]. The COVAX Pillar has the goal of facilitating licensure of several COVID-19 vaccines, influencing equitable pricing, and providing equal access for up to 2 billion doses by the end of 2021 to protect frontline healthcare workers and people with high-risk of COVID-19 infection, particularly in low-to-middle income countries

Effectiveness of a new vaccine is defined by its efficacy[18]. In the case of COVID-19 specifically, a vaccine efficacy of 70% may be enough to stop the pandemic, but if it has only 60% efficacy, outbreaks may continue; an efficacy of less than 60% will not provide enough herd immunity to stop the spread of the virus alone[15].

On 24 June, 2020, China approved 2 inactivated virus vaccines for emergency use in high-risk occupations[19]. On 11 August, 2020, Russia approved its Sputnik V vaccine for emergency use[20]. In the US, emergency use authorization (EUA)

facilitates availability and use of medical countermeasures, including vaccines, during public health emergencies, like COVID-19 pandemic[21]. Once EUA is issued by the US Food and Drug Administration (FDA), the vaccine developer is expected to continue Phase III clinical trials to finalize safety and efficacy data, leading to application for licensure (approval) in the US[21]. Pfizer-BioNTech submitted EUA request to FDA for Tozinameran (mRNA Vaccine BNT162b2) on 20 November, 2020[22]. On 2 December, 2020, the UK Medicines and Healthcare products Regulatory Agency (MHRA) gave Pfizer–BioNTech vaccine temporary regulatory approval[23], becoming the first country in the Western world to approve the use of any COVID-19 vaccine. On 11 December, 2020, the US FDA granted EUA for Pfizer-BioNTech vaccine tozinameran[24]. A week later, they granted EUA for Moderna vaccine (mRNA-1273), making US the first country to authorize 2 vaccines for public use[25]. On 30th December, 2020, the UK's MHRA approved use of the Oxford University /Astra Zeneca's Covid-19 vaccine[26]. On 31st December, 2020, WHO granted emergency validation to Pfizer-BioNTech vaccine[27]. On 3rd January, 2021, India approved 2 Covid vaccines, the Oxford Astra Zeneca and another vaccine made by the Indian firm Bharat Biotech[28]. On 22nd January 2021, the National Medicines Regulatory Authority (NMRA) of Sri Lanka granted Emergency Use Authorization for the Oxford Astra Zeneca vaccine[29]. On 28th January 2021 India donated 500,000 doses of the AstraZeneca "Covishield" vaccine to Sri Lanka[30]. On 29th January 2021, Sri Lanka's COVID-19 vaccination drive was launched at the National Institute of Infectious Diseases[31]. On 17th February 2021, WHO approved the emergency use of AstraZeneca vaccine giving the green light for it to be rolled out globally through COVAX[32].

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