COVID 19 vaccine trials: Where are we?

Narmada Fernando

Institute of Biochemistry, Molecular Biology and Biotechnology, University of Colombo

Coronavirus-induced disease 2019 (COVID 19) was first reported in Wuhan, China in December 2019 and subsequently spread worldwide. SARS-CoV2 virus is a single stranded RNA virus which is the etiological agent of this respiratory disease spread rapidly. Statistics revealed that 29,698,932 individuals have been infected by SARS-CoV2 virus from 213 countries and territories with 938,104 deaths (as of 15th of September 2020). The globe has experienced two major corona virus outbreaks during the twenty years prior to COVID 19 outbreak. In 2002, a fast spreading respiratory infection was reported namely, severe acute respiratory syndrome (SARS) and the corona virus which caused this illness was named as SARS-CoV. Many countries were affected by the SARS and the total number of cases reported was above 8000 with 774 deaths (1). Thereafter, the world experienced the second corona virus-induced disease known as Middle East respiratory syndrome (MERS). Unlike SARS or COVID 19, MERS was reported only from the Middle-East region in the Arab. MERS resulted more deaths (858) despite the less number of infected cases (nearly 2500) compared to SARS (2). Apart from these three corona viruses, a number of human corona viruses are known to cause mild cold conditions and cases have been reported from Sri Lanka as well (3). However, of the three serious corona virus-induced diseases, COVID 19 is the only disease reported in Sri Lanka.

Successful prior studies on vaccine development against a virus in the same viral family of any new virus accelerate the novel vaccine development by provision of a platform for clinical trial approaches. However, in the case of COVID 19, no prior studies had been successful against the other viruses in the same family. Moreover, although SARS-CoV and MERS-CoV epidemics occur a considerable time prior to the occurrence of COVID 19 pandemic, production of a vaccine against SARS-CoV2 virus has not been supported by the attempts taken to produce an effective vaccine against SARS-CoV or MERS-CoV. The reason behind this was that none of the trials conducted against SARS-CoV or MERS-CoV could advance beyond the phase I safety. By the same token, no vaccines are available for other human coronaviruses as well (3).

Of more than 200 vaccine trials which are being conducted against SARS-CoV2, nearly one fifth has shown to be successful in pre-clinical phase and are in the clinical phase of development. Six leading phase III vaccine trials are reported as of early September 2020 escalating the hope of an effective vaccine against COVID 19 in near future (4). These vaccines are developed based on different strategies with a variety of vaccine candidates including modified RNA (Candidate mRNA-1273), whole organism (Candidate CoronaVac) and recombinant vaccines using vectors (Candidates Ad5-nCoV and AZD1222) (3, 4). Mode of action of the vaccine is based on the vaccine strategy as mechanisms involved in rising and maintenance of immunity by each type of vaccine candidate may be different.

The strategies which have already been used for vaccine development are an important context to be reviewed. In RNA vaccine, the injected viral RNA is taken up and viral proteins will be translated by the recipient's cells. RNA vaccines are well advantageous compared to most of conventional vaccine strategies. The production of RNA vaccines is much cheaper and faster compared to traditional vaccine strategies. Therefore, it is expected to allow quick responses to outbreaks like COVID 19. However, there are no RNA vaccines available for human use up to date (5). Therefore, more studies are much needed for better understanding of potential side effects and evidence on long term efficacy. Two approaches that are being followed as whole organism vaccines are based on live attenuation and inactivation of the virus. Use of these as vaccines also has a mix of advantages and disadvantages. Live attenuated vaccines include the live organism which has been chemically or physically treated to suppress the disease-causing ability. As the treated weaken organism is still capable of multiplying inside the recipient body, a single dose of vaccination is sufficient to provide a long-term (maybe life-long) protection. However, the process of attenuation must be done perfectly in order to minimize the risk of

reversal of the attenuated organism to pathogenic form. Genetic engineering is a promising solution to produce attenuated organisms irreversibly. Removal of genes which are essential for virulence or growth in selected types of cells increases the safety of the live attenuated vaccines. Injection of inactivated (killed) virus is potent in inducing immune response at least for some of the viral antigens. Relative safety, stability and ease of storage are advantageous over the need of booster doses and higher cost of production. Recombinant vector vaccines are safer and effective in inducing long term immunity. The genes encode key antigens of the desired organism are inserted into another attenuated virus or bacteria in the development of recombinant vector vaccines. This application maintains the advantage of live attenuated vaccines while avoiding the risk of reversal to pathogenic form (6). Apart from these strategies, trials are in operation to develop vaccines using protein subunits and with modifications of standard approaches.

Vaccines are administered through different routes to have high vaccine efficacy while minimizing the possible adverse reactions. Oral (by mouth), subcutaneous (into the area just beneath the skin), intramuscular (into muscle tissue), intradermal (into skin layers) and intranasal (into nose) are the standard routes of vaccine administration (6).

The process of development of a vaccine for any novel disease is challenging. Limited knowledge on viral biology and immune responses against a novel virus make the process more challenging. Already available knowledge on molecular virology, viral biology of SARS-CoV and MERS-CoV had enormously contributed for the immediate development of vaccine candidates that are being trialled (3). Studying subjects from different ethnic groups and geographical locations in vaccine trial is important in order to determine the effectiveness and the safety of the novel vaccine (7). The existing logistic and travel limitations may have a negative impact on trialling out the novel vaccines on a variety of ethnic groups. Further, it is not possible to conclude about the efficacy or safety of any developed vaccine until the results of phase III trials are analysed. Outcomes of successful phase III trials will provide answers for standard questions such as the strength of the dose, level of immune response induced and need of booster doses.

A vaccine comes to the market succeeding at laboratories and clinical testing set-ups for decades. However, in the case of COVID 19, it has been estimated that the time required for an effective vaccine to be available for community would be 12-18 months from the commencement of vaccine trials. If ongoing phase III clinical trials success as anticipated, curtailing the rapid spread of SARS-CoV2 will not be impossible. People who survived from this serious pandemic will witness the fastest-ever development of an effective vaccine through endless and tremendous work done by trial volunteers, scientists and health professionals.

References

1. de Wit E, van Doremalen N, Falzarano D, Munster VJ. 2016. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 14:523-34.
2. Organization WH. 2020. Middle East respiratory syndrome coronavirus (MERS-CoV). https://www.who.int/emergencies/mers-cov/en/. Access date 18/09/2020
3. Diamond MS, Pierson TC. 2020. The Challenges of Vaccine Development against a New Virus during a Pandemic. Cell Host Microbe 27:699-703.
4. Craven J. COVID-19 vaccine tracker, Regulatory Focus, https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker. Access date 17/09/2020
5. L B. 2018. RNA Vaccines: An introduction. University of Cambridge. https://www.phgfoundation.org/briefing/rna-vaccines. Access date 17/09/2020
6. Owen JA PJ, Stanford SA, Jones PP. 2013. Kuby Immunology. 7th edNew York: WH Freeman and Company.
7. Dutta AK. 2020. Vaccine Against Covid-19 Disease - Present Status of Development. Indian J Pediatr 87:810-816.

Dr Narmada Fernando *obtained the BSc from the University of Colombo, Sri Lanka and PhD from the Institute of Biochemistry, Molecular Biology and Biotechnology, University of Colombo, Sri Lanka. She is a Senior Lecturer at the Institute of Biochemistry, Molecular Biology and Biotechnology, University of Colombo, Sri Lanka.*