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Date of submission: 8 June 2020

Date of acceptance: 17 July 2020

Date of online publication: 1 August 2020

Title

Where in the world is the COVID-19 vaccine?

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Author biography

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SUMMARY OF ARTICLE

The following article explores the novel coronavirus SARS-CoV-2, the global race to develop a vaccine and the many challenges faced by researchers during this unprecedented time. With a focus on the eight most promising vaccine candidates currently in clinical evaluation around the world, the results from the early stages of human trials are discussed and the difficulties faced by those at the forefront are brought to light.

Learning Points:

1. Vaccine development is a rigorous process spanning over many years in order to ensure maximum safety, tolerability, and efficacy.
2. The need for a vaccine to protect against SARS-CoV-2 has sparked ground-breaking research worldwide with over 100 candidate vaccines currently in progress.
3. The acceleration of the Phase I, II, and III clinical trials raises concerns for the safety of the new vaccine.

Keywords:

vaccine, vaccination, COVID-19, Coronavirus, SARS-CoV2

Word Count:

2130

Introduction

In December 2019, an outbreak of severe viral pneumonia of unknown origin was reported in the city of Wuhan, China. A novel coronavirus Severe Acute Respiratory Syndrome–Coronavirus 2 (SARS-CoV-2) was isolated on January 7th and subsequently sequenced on January 11th 2020 [1]. By the end of January, cases were appearing outside China and it was evident that local transmission had occurred in 18 countries, sparking travel bans, whole city lockdowns, and social distancing restrictions [1]. On March 11th, the World Health Organisation (WHO) declared the coronavirus disease of 2019 (COVID-19) outbreak as a pandemic [1]. As of May 20, over 5 million cases in 187 countries have been reported with more than 325,000 deaths [2]. Development of a vaccine is crucial to provide adequate herd immunity to mitigate the spread of SARS-CoV-2, especially as there is no current effective treatment. Almost overnight, researchers were faced with the near-impossible task of developing a vaccine to protect against a poorly understood virus in the midst of a pandemic. The following article explores COVID-19, vaccine development, the global race to find a solution, and the many challenges faced by researchers during this unprecedented time.

The virus responsible for COVID-19

COVID-19 refers to the disease caused by infection from the virus SARS-CoV-2. SARS-CoV-2 is a member of the *Coronaviridae* family meaning “crown-like” due to the appearance of the S spike surface proteins that surrounds the single-stranded RNA virus [1]. Coronaviruses are commonly found in animals but have been previously identified in humans, and four circulating human coronaviruses are known to cause the common cold [1]. Past epidemics, SARS (caused by SARS-CoV-1) and Middle East respiratory syndrome (caused by MERS-CoV), were caused by coronavirus infections [3].

The virus, transmitted through droplet, direct, or fomite contact spread, primarily affects the respiratory system. An individual infected by SARS-CoV-2 can be asymptomatic or may experience mild symptoms including fever, sore throat, dry cough, fatigue, loss of smell, and myalgia. In severe cases, the individual may require mechanical ventilation [4]. The mortality rate has been shown to increase with age and co-morbidities. That said, cases of the disease have been reported in all age groups, further pushing the need for a vaccine that is distributable on an immense global scale [4].

A guide to vaccine development

Vaccine is derived from the Latin word *vacca* meaning “cow” after Edward Jenner discovered in the late 18th century that cowpox protected against smallpox. A vaccine contains antigens that stimulate the immune system against a pathogen in order to prevent the development of an infectious disease thus developing active acquired immunity by exposing the body to components or attenuated forms of infectious agent [5]. Most vaccines are combined with adjuvants in order to increase the immune response and ensure longer lasting immunity [6].

A vaccine takes on average 10 to 15 years of research and testing before it becomes readily available to the public [7]. To add to this immense investment, only 6% of vaccine candidates progress from pre-clinical studies to licensure [8]. The candidate must successfully pass through all stages of development: exploratory, pre-clinical, clinical development, regulatory review and approval, manufacturing, and quality control [9]. Initial research establishes the biological feasibility of the trial vaccine. Pre-clinical testing confirms efficacy, toxicity, and pharmacokinetic properties in animal and in vitro studies. Once the vaccine candidate has shown to be safe in animals, it progresses to clinical studies on human volunteers, in three sequential phases. The first phase (Phase I) assesses the safety of the vaccine within a small cohort of less than 100 healthy volunteers. Phase II expands testing to a larger population and

once deemed safe, Phase III trials is implemented to test the vaccine candidate to thousands of subjects, of varying health status, to confirm safety and determine efficacy. The current cost of developing a new vaccine from concept to market costs between 200 and 500 million US dollars [8]. As of May 15th 2020, eight candidate vaccines against SARS-CoV2 entered into clinical evaluation and another 110 are in preclinical evaluation. Amongst the global efforts there could be just a handful that will be ultimately successful.

The global race for a vaccine

COVID-19 vaccine developers worldwide are currently attempting an unprecedented feat: the conception, production, and worldwide distribution of a vaccine against a novel virus in a matter of months. International organisations such as the WHO, the Coalition for Epidemic Preparedness Innovations (CEPI), the Gates Foundation, and the Global Alliance for Vaccines and Immunization (GAVI) are funding the most promising of the candidate vaccines [10]. As of May 15th 2020, there are eight vaccines in clinical evaluation [11]. These eight candidates cover an array of vaccine platforms: two non-replicating viral vector by CanSinoBio (Tiajin, China) and The University of Oxford (Oxford, England), three inactivated virus by Sinopharm (Shanghai, China) and Sinovac (Beijing, China), two RNA by Moderna (Massachusetts, United States) and BioNTech (Mainz, Germany), and one DNA vaccine by Inovio Pharmaceuticals (Pennsylvania, United States).

Gene based vaccines using nucleic acids constitute a relatively new approach in the realm of vaccinology. This format is conveniently fast to produce, easy to modify, and safe to administer. The disadvantages however are that they are less efficient [2] and currently there are no licensed nucleic acid vaccines anywhere in the world [9]. Moderna in the United States have shown promising results with a lipid nanoparticle-encapsulated mRNA vaccine, mRNA-1273 [12]. mRNA-1273 carries the genetic code

for producing a portion of the SARS-CoV-2 spike protein. When injected, the vaccine is incorporated into the host cells to produce the viral protein antigen. The host immune system recognises the antigen to be foreign and develops an immune response against it. The vaccine candidate has entered into Phase II trials and, if effective, is hoping to be licensed as soon as 2021. German company BioNTech/Pfizer has entered Phase I/II trials with a mRNA-based vaccine similar to Moderna. The trial involves 7,600 subjects who will be given the mRNA vaccine BNT162b1 in 4 dosing regimens [12]. The US company Inovio Pharmaceuticals are currently working on the only DNA based vaccine to reach clinical trials. INO-4800 is a DNA plasmid vaccine delivered by electroporation [13]. It is more difficult for DNA to enter into cells, so subjects are given a small electrical impulse to open the cell membrane pores [14]. In April, Inovio entered into phase I and has plans to enter into phases II/III in June [13].

Viral vector vaccines have been highly efficacious in the past few decades. Vectors use harmless genetically modified viruses to mimic SARS-CoV-2 to trigger an immune response. This method has seen recent success in the development of *Ervebo*, an Ebola Zaire vaccine licensed in 2019 [15]. The disadvantage of this method is that pre-existing immunity to the vector (eg. Adenovirus or Vesticular stomatitis virus) can diminish the immune response. The University of Oxford Jenner Institute were initially at the forefront of the race with their vaccine candidate ChAdOx1, a non-replicating vectored vaccine using a weakened version of a common chimpanzee adenovirus. The results from animal trials have revealed that ChAdOx1 decreased disease severity but was unable to prevent infection in six rhesus macaque monkeys [16]. The risk with delivering this vaccine would be that immunised individuals, whilst protected from the disease, are still capable of transmitting the virus to others. The vaccine candidate still progressed into Phase I trials in April which confirmed the safety and tolerability of the candidate and Phase II is currently underway [17]. CanSino Biologics in China have developed another

adenovirus vector vaccine Ad5-nCoV, similar to ChAdOx1, which entered Phase II in Wuhan in April [13]. This was the first vaccine to enter the second phase of clinical trials.

Inactivated virus vaccines have become increasingly popular. There is pre-existing commercial experience with this method and capacity for large scale production. Chinese company Sinovac Biotech have recently published positive results with their inactivated virus vaccine PiCoVacc in eight rhesus macaque monkeys which were protected from SARS-CoV-2 infection with no known side effects [18]. It is still uncertain if monkeys are the best animal model and if the number involved in this study was too small to produce statistically significant results. Sinovac have progressed to Phase I/II with a favourable safety and tolerability profile as well as a simple manufacturing process making this candidate the most promising in China. They have already begun manufacturing thousands of vaccines to give high risk individuals if human trials are successful [18]. Similarly, Wuhan Institute of Biological Products/ Sinopharm have been approved for Phase II trials with another chemically inactivated virus formerly known as COVID-19 vaccine. China is expected to have five candidate vaccines in clinical studies by the end of May [10].

The challenges of developing a vaccine against SARS-CoV-2

With 20,000 new cases daily and a rising death toll, the need to develop a vaccine against SARS-CoV-2 has never been greater. In addition to the prevention of infection, other factors that need consideration include the safety and durability of immunity, as well as the speed, scale, and cost of manufacture of the vaccine [19].

In order to accelerate the development of the vaccine, clinical trials are no longer following a step-by-step approach but rather occurring simultaneously. Accelerating a decade-long process does not come

without substantial costs and safety concerns. A major concern with the accelerated trial periods is that the vaccine could lead to a dangerous phenomenon known as antibody dependant enhancement (ADE). ADE is poorly understood but refers to a condition where antibody levels are low and unable to neutralise the virus subsequently leading to increased infectivity and virulence if infected. The vaccine in this circumstance could worsen the disease severity [20]. At present there is a lack of strong evidence supporting the role of ADE in humans, however, animal studies on cats vaccinated against feline coronavirus showed significantly poorer outcomes in those vaccinated compared to the unvaccinated cats implicating the involvement of ADE [16].

Smaller trials cohorts can omit rare complications. During a swine flu outbreak in USA in 1976 an emergency vaccine was administered to 45 million people in a 10-week period. They later discovered a rare association with the nervous system disorder, Guillain-Barre Syndrome [21]. This unfortunate event raises the importance of Phase IV studies and post-marketing surveillance which will be more important than ever if a COVID-19 vaccine is fast-tracked and widely distributed.

A suggested strategy to accelerate the testing process of candidate vaccines is with controlled human challenge trials. This involves administering the experimental vaccine to a small number of healthy subjects then exposing them to the SARS-CoV-2 virus. Replacing Phase III testing with this trial could significantly accelerate the development process as usually scientists must wait for patients to naturally encounter the virus to check the efficacy of the vaccine [22]. This type of trial has been performed in the past for malaria, typhoid, and influenza [22]. These infectious diseases, however, have had treatments readily available if necessary whereas COVID-19 does not, thus raising a number of ethical issues if challenge trials were to proceed.

Current data has found only minor genetic drift during the current SARS-CoV-2 pandemic which shows promise that a vaccine based on the current strain will still be effective on strains in 12 months [23].

There is speculation that SARS-CoV-2 may not be eradicated completely in which case it could develop into a seasonal circulating virus similar to influenza [24].

Even when a vaccine is shown to be effective, a major challenge lies in meeting global production and equitable distribution. With nearly eight billion people in the world at risk of COVID-19, the necessary facilities capable of meeting the production demand do not exist. It is important to take into account that existing manufacturers cannot cease the production of other fundamental vaccines, such as measles, in order to produce the SARS-CoV-2 vaccine. Many researchers are calling for larger investment into the development and distribution of vaccines moving forward [25]. This pandemic has revealed the worldwide need for more facilities capable of developing and producing vaccines, as well as more advanced technology for health surveillance. The popular phrase “health is wealth” alludes to the inherent relationship between public health and the economy. It is estimated that this pandemic may cost the global economy up to four trillion dollars [26]. Investing in vaccine development is costly and requires global political will and vision but could ultimately prevent the devastating economic impact in the long term [27].

Conclusion

Promising research into vaccine development is being conducted worldwide. Nonetheless, the future of the COVID-19 vaccine remains filled with uncertainty. With novel platforms and international cooperation, researchers are confident that within two years, there may be a vaccine developed which

can be administered to high risk individuals, such as the elderly and health care workers. Until then, we continue to rely on surge hospital capacity and public mitigation strategies.

Conflict of interest

None.

Funding

None.

Acknowledgement

With thanks to the team at AMSJ for their assistance in the editing of this article.

Author's contribution

This article was written by Clara Dahlenburg.

References

- [1] Amanat F, Krammer, F. SARS-CoV-2 Vaccines: Status Report. *Immun.* 2020;52(4), 583–9. <https://doi.org/10.1016/j.immuni.2020.03.007>
- [2] COVID-19 CORONAVIRUS PANDEMIC. (2020). Retrieved 21 May 2020, from <https://www.worldometers.info/coronavirus/>
- [3] Purcell D, Quinn K. Where are we at with developing a vaccine for coronavirus? [Internet]. 2020. Retrieved 10 May 2020, from <https://www.doherty.edu.au/news-events/news/where-are-we-at-with-developing-a-vaccine-for-coronavirus>
- [4] Q&A on coronaviruses (COVID-19) [Internet]. 2020. Retrieved 16 May 2020, from <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-coronaviruses>
- [5] DerSarkissian, C. What is the definition of vaccine? [Internet]. 2020. Retrieved 10 May 2020, from <https://www.webmd.com/cold-and-flu/qa/what-is-the-definition-of-vaccine>
- [6] The Australian Immunisation Handbook. Australian Government Department of Health. <https://immunisationhandbook.health.gov.au/>. Published 2020. Accessed July 14, 2020.
- [7] Vaccine Testing and Approval Process | CDC [Internet]. 2020. Retrieved 20 May 2020, from <https://www.cdc.gov/vaccines/basics/test-approve.html>
- [8] Serdobova I, Kieny MP.). Assembling a global vaccine development pipeline for infectious diseases in the developing world. *Am J Public Health.* 2006;96(9), 1554–9. <https://doi.org/10.2105/AJPH.2005.074583>
- [9] The Drug Development Process - Step 3: Clinical Research [Internet]. 2018. Retrieved 20 May 2020, from <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research>
- [10] Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M *et al.* The COVID-19 vaccine development landscape [Internet]. 2020. Retrieved 20 May 2020, from <https://www.nature.com/articles/d41573-020-00073-5>
- [11] CEPI publishes analysis of COVID-19 vaccine development landscape [Internet]. 2020. Retrieved 15 May 2020, from https://cepi.net/news_cepi/cepi-publishes-analysis-of-covid-19-vaccine-development-landscape/
- [12] Callaway, E. Coronavirus vaccine trials have delivered their first results — but their promise is still unclear [Internet]. 2020. Retrieved 15 May 2020, from <https://www.nature.com/articles/d41586-020-01092-3>
- [13] Draft landscape of COVID-19 candidate vaccines [Internet]. 2020. Retrieved 15 May 2020, from <https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines>
- [14] Funk CD, Laferrière C, Ardakani A. A Snapshot of the Global Race for Vaccines Targeting SARS-CoV-2 and the COVID-19 Pandemic. *Front Pharmacol.* 2020;11(937). doi:10.3389/fphar.2020.00937.
- [15] Prevention and Vaccine | Ebola (Ebola Virus Disease) [Internet]. Centers for Disease Control and Prevention. <https://www.cdc.gov/vhf/ebola/prevention/index.html>. Published 2019. Accessed July 14, 2020.
- [16] Garber K. Coronavirus vaccine developers wary of errant antibodies [Internet]. 2020. *Nature.com.* <https://www.nature.com/articles/d41587-020-00016-w>. Accessed July 14, 2020.
- [17] Thomas, T. The Oxford Vaccine Centre COVID-19 Phase I Clinical Trial Explained [Internet]. 2020. Retrieved 16 May 2020, from <https://www.covid19vaccintrial.co.uk/phase-i-trial-explained>
- [18] Cohen, J. COVID-19 vaccine protects monkeys from new coronavirus, Chinese biotech reports [Internet]. 2020. Retrieved 20 May 2020, from <https://www.sciencemag.org/news/2020/04/covid-19-vaccine-protects-monkeys-new-coronavirus-chinese-biotech-reports>
- [19] National Press Club. National Press Club Address - In Conversation with Jane Halton of CEPI [Video]. 2020. Retrieved from <https://iview.abc.net.au/show/national-press-club-address/series/0/video/NC2012C004S00>
- [20] Xu, Jianqing. SARS-CoV-2: an unknown agent and challenges in vaccine development. *J BioX Res.* 2020;3(1), p3-5 doi: 10.1097/JBR.0000000000000063
- [21] Fineberg H. Swine flu of 1976: lessons from the past [Internet]. 2009. Retrieved 16 June 2020, from <https://www.who.int/bulletin/volumes/87/6/09-040609/en/>
- [22] Covidnautilus. What is a "human challenge trial," and could it solve the coronavirus vaccine problem? [Internet]. Nautilus. 2020. <https://coronavirus.nautil.us/what-is-a-human-challenge-trial-and-could-it-solve-the-coronavirus-vaccine-problem/>. Published 2020. Accessed July 14, 2020.
- [23] Corey BL, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. *Science* (New York, N.Y.). 2020;eabc5312. Advance online publication. <https://doi.org/10.1126/science.abc5312>
- [24] Pratt, E. COVID-19 Could Become a Seasonal Illness: What We'll Need to Do [Internet]. 2020. Retrieved 20 May 2020, from <https://www.healthline.com/health-news/covid19-could-become-seasonal-just-like-the-flu>
- [25] Albert H. Will Covid-19 Change the Face of Vaccine Development? [Internet]. 2020. Retrieved 16 June 2020, from <https://www.labiotech.eu/medical/coronavirus-vaccine-covid-19/>
- [26] Alegado S, Bloomberg. Coronavirus Pandemic Could Cost the World \$4.1 Trillion [Internet]. 2020. Retrieved 20 May 2020, from <https://time.com/5814933/coronavirus-pandemic-cost-4-trillion/>
- [27] Chaiechi T. How COVID-19 is affecting our economy [Internet]. 2020. Retrieved 16 June 2020, from <https://www.jcu.edu.au/this-is-uni/articles/how-covid-19-is-affecting-our-economy>