GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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COVID-19 vaccine: Potential candidates, achievements, and challenges

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GSC Biological and Pharmaceutical Sciences, 2021, 15(03), 102–109

Publication history: Received on 26 April 2021; revised on 04 June 2021; accepted on 07 June 2021

Article DOI: https://doi.org/10.30574/gscbps.2021.15.3.0145

Abstract

Severe acute respiratory syndrome [SARS]-CoV-2, which is the causative agent of Coronavirus Disease 2019 [COVID-19] disease, has engulfed more than 2.4 million people and still counting. As this pandemic is at its peak and is responsible for more than 100 million infected people worldwide, there is an urgent need to develop an effective vaccine to stop the COVID-19 disease. More than 220 vaccine candidates are in the pre-development stage while 15 candidates are in the developmental stage, from which Pfizer/BioNTech, Moderna, and some other vaccines have received approval by some countries for emergency use only. Fever, tiredness, headache, joint pain, swelling at the injection site and some other common effects have been found by using these vaccines. Efficacy, rapid mass production, and long-term immunity as well as acceptance of vaccination by society are the main challenges in developing a safe vaccine against COVID-19 despite the fact that some vaccines have over 90% efficiency against COVID-19 and are useful in developing immunity as well.

Keywords: Coronavirus disease; Major Challenges; Society perception; Vaccines; World responses

1. Introduction

Since the last month of 2019, there has been an outbreak of Covid-19 disease which was first reported in Wuhan, a city in China [1]. The World Health Organization (WHO) identified SARS-CoV-2 as the causative agent for the pandemic, which is responsible for 2.39 million deaths and more than 108.8 million confirmed cases as of 13 February 2021 [2, 3]. SARS-CoV-2 is a single-stranded, positive-sense RNA virus and contains four major structural proteins, envelop protein, nucleocapsid protein, membrane protein, and spike proteins that are found on the surface of SARS-CoV-2 [4].

A variety of vaccines are under development which include protein-based vaccines, non-replicating viral vector vaccines, and weakened virus vaccines [5, 6]. However, there is real novelty representation by Deoxyribonucleic acid [DNA] or Ribonucleic acid [RNA]-based vaccines [5]. But RNA vaccines are not approved in humans, but there are seven COVID-19 RNA vaccine candidates that are being tested in medical trials [7]. Global researchers are working hard to develop an effective vaccine against SARS-CoV-2, and most experts believe that a vaccine will be available by the middle of 2021 [8, 9]. But it requires several years to develop an effective and safe vaccine [10]. By December 23, 2020, there were two hundred and eighty-seven vaccine candidates, of which two hundred and twenty-four are in the pre-development stage while 15 candidates have reached the development stage [11]. One vaccine in the United Kingdom while two vaccines in the United States have been accepted for emergency use against COVID-19 [12]. Because of the novelty of SARS-CoV-2, some approved vaccines are available, but there is an urgent need to develop an effective and safe vaccine to prevent and control future outbreaks [13].

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1.1. RNA Vaccines

It is a new generation of vaccines in which all the ingredients can be prepared chemically [14]. The mode of action of RNA vaccines is shown in Figure 1.

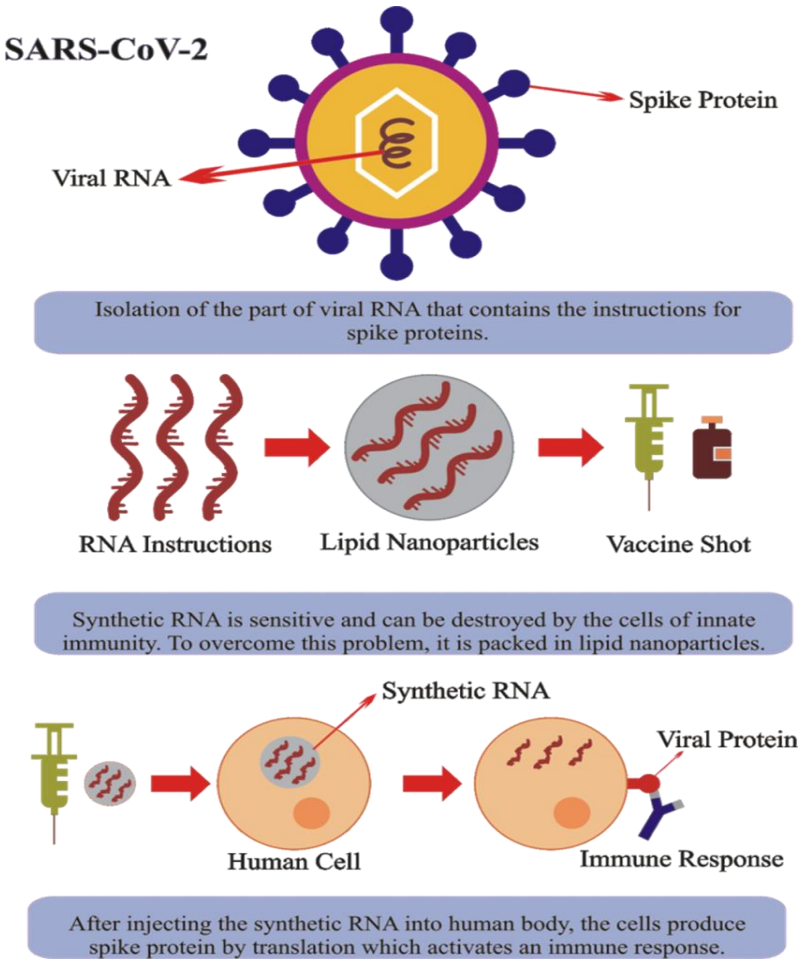

Figure 1 Mode of action of RNA Vaccine
Source: Royal Society of Chemistry (URL: https://www.compoundchem.com/2020/12/02/rna-vaccines/)

2. Moderna

The RNA-based vaccine which was first used for human trials on March 16, 2020, is Messenger RNA [mRNA]-1273 and it was developed by Moderna, an American company [15, 16]. The results of phase I showed that protective antibodies were developed in forty-five volunteers. The optimal dose, as well as the effectiveness of the vaccine, were also decided during the first phase [15]. 30,000 participants were involved in the third phase of testing and the vaccine showed safety for three months [17, 18]. The efficacy of this vaccine was 94.1% and it was approved by the Food and Drug Administration [FDA] in the United States for emergency use on December 17, 2020 [17].

2.1. Pfizer and BioNTech

Another RNA-based vaccine, BNT162b2 was developed by Pfizer and BioNtech [19]. In the third phase, thirty thousand healthy participants were treated, and the efficacy of the vaccine was 95%. The level of efficacy was the same in people of different racial groups, different ages, and individuals with diabetes. Canada, Mexico, and the United States have approved BNT162b2 for emergency uses due to the positive results from the third trial [20]. Frequent fatigue, muscle aches, and fever were reported due to this vaccine there were four adverse cases and six deaths as a result of this vaccinee, though none of the deaths were attributed to this vaccine [19, 21].

2.2. Non-replicating Viral Vector Vaccines

2.2.1. Ad5-nCoV

Beijing Institute of Biotechnology and CanSino Biological Inc developed Ad5-nCoV, which is a non-replicating viral vector-based vaccine [21]. This vaccine utilizes Ad5 adenovirus to incorporate the genes of SARS-CoV-2 into the body of humans. In the first phase, three different doses were tested on a trial base. The better tolerated among these doses were low and medium, while high doses resulted in fatigue, joint pain, and high fever, which is the result of a high reactive profile [21]. After that, low and moderate doses were evaluated in phase II. Vaccines with low doses provided better immunogenicity and protection results [21]. Ad5-nCoV was approved by the Chinese Central Military Commission (CMC) for military use only on 25 June 2020 [22].

2.2.2. AstraZeneca

The Oxford Jenner Institute, The University of Oxford, and AstraZeneca made a collaborative effort and developed a COVID-19 vaccine (AZD1222). During trial phase I and II, there were no serious adverse cases were reported [23]. In the third phase of trials, the vaccine was tested on almost 30,000 people in different countries of the world, including South Africa, the United States, the UK as well as Brazil [24]. According to the results of phase III, which were recently published, the efficiency of this vaccine is 90% [25].

2.2.3. Sputnik V

Another non-replicating vaccine, Sputnik V, was also developed by Gamaleya Research Institute of Epidemiology and Microbiology. Sputnik V was approved by the Russian government [26]. The results of phase III in which more than 40,000 people participated, showed more than 90% efficacy against SARS-CoV-2 [27].

2.3. Inactivated Virus Vaccine

2.3.1. Sinovac

CoronaVac is an inactivated virus vaccine made by a pharmaceutical company in China, Sinovac. In this vaccine, aluminum adjuvants are used [28]. In the 1st and 2nd phase of trials, 743 volunteers were vaccinated and there were no adverse cases. On July 03, 2020, this vaccine received approval to proceed to the third phase [29].

Table 1 Efficiency of different COVID-19 vaccines candidates

Candidates for Vaccines	Vaccine Type	Clinical Phase	Efficacy	Reference
Pfizer/BioNTech	mRNA	Phase 3	95%	[19]
Moderna	mRNA	Phase 3	94.1%	[17]
AstraZeneca	Adenovirus based	Phase 3	90%	[25]
Sputnik V	Adenovirus based	Phase 3	91.4%	[27]
Ad5-nCoV	Adenovirus based	Phase 3	65.7%	[30]
Sinovac	Inactivated Virus	Phase 3	50.4%	[31]

2.4. Protein-Based Vaccines

2.4.1. Novavax

Novavax developed a protein-based vaccine which is in the III phase of testing. This vaccine contains an adjuvant in a few groups which has resulted in an increased immune response [32]. Institute of Microbiology, Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutical from China have also developed a protein-based vaccine that has entered phase III of trials [10, 33].

2.5. Threats

Eight healthcare workers experienced serious allergic reactions after receiving both mRNA-based vaccines, but the scientists speculated that these serious allergic reactions may be related to anyone from polyethylene glycol or lipid-based nanoparticles in the vaccines, which are used to prolong their lifespan [34-36]. BioNTech/Pfizer, AstraZeneca, and Moderna were approved by the European Union. On the 2nd day of vaccination, two adverse but resolved events of anaphylaxis were reported [37].

Complacency, misinformation, and lack of confidence can also lead to vaccine hesitancy, which is listed in the top ten threats to world health by the World Health Organization [38-40]. Some side effects such as tiredness, chills, joint pain, fever, swelling at the injection site, a state of being unwell, headache, and swelling of lymph nodes were also reported by using the approved vaccines against COVID-19 [41].

Almost 1.89 million doses of the BioNTech/Pfizer vaccine were given in the US till 23 December 2020. Of these, 0.2% of adverse cases were reported and the reports of these events were sent to the Vaccine Adverse Event Reporting System for further analysis [42]. A major concern that can lead to the ineffectiveness of vaccines is political pressure by governments to speed up the process of development of a vaccine. As a result of such a situation, the public may feel hesitant to accept the future vaccine [43].

2.6. Challenges

Historical and early studies on the coronavirus family, which includes SARS, Middle East Respiratory Syndrome [MERS], and SARS-CoV-2, indicate that infection does not provide long-term immunity [33, 44]. If long-term immunity is not achieved, only healthcare workers and vulnerable people can be protected by a vaccine by decreasing the quantity of the virus that a vaccinated individual produces and eliminates [45]. Previously, the use of adjuvants to improve long-lasting memory has been shown and in medical trials, the vaccine candidates have already used adjuvants [46].

One of the biggest challenges in making millions of vaccines quickly is to promote manufacturing, as the infrastructure will vary depending on the type of vaccine [47]. Combining the phases to speed up the vaccine development includes trials in small groups. It is a major concern because when the vaccine is declared for public use, it may cause severe side effects in a large population that were not previously seen in small groups [48].

Although it is unclear whether these vaccines will actually work, some countries have already secured millions of doses of vaccines from different pharmaceutical companies [49]. With many uncertainties, rapid mass production is also a big challenge to overcome the demand for vaccines against an epidemic disease [43].

It is also an important challenge that the vaccine may have limited efficacy against the virus as a result of mutations in the viral genome [50, 51]. Previous studies show that nucleic acid-based platforms like deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) could not develop an effective vaccine for diseases of human beings, and it remains to be seen how messenger RNA vaccine will be made successfully. This is because the lipid nanoparticles are sensitive to temperature and may show difficulty in increasing the production of vaccines [52].

2.7. World Responses

Different responses were received by a variety of respondents. A study was conducted to check the acceptance of a vaccine against COVID-19, in which 13,426 participants from 19 countries participated. According to this study, 71.5 percent of individuals agreed to get an effective vaccine against COVID-19 while 48.1 percent of people responded that they would take the vaccine on their employer recommendations [53].

Another survey was conducted before the approval of the Pfizer vaccine in the UK. According to this, 51 percent of individuals agreed to be vaccinated against COVID-19. Among the countries where the survey was conducted, half of the French people (from those who participated in the survey) were unwilling to be vaccinated, while 65 percent of the British people (from those who participated in the survey) were most likely to agree [54].

An online survey was conducted in China in which 2058 people participated. Out of these, 91.3% of individuals agreed to be vaccinated against COVID-19 of which 52.2% participants wanted to be vaccinated quickly while the remaining responded that they would get vaccinated after the confirmation of vaccine safety [55].

Sallam [56] reviewed various publications about the perception of society about COVID-19 vaccination in various countries and found that in the case of the general public, Ecuador, Malaysia, Indonesia, and China were the countries

with the highest COVID-19 acceptance rate while acceptance rates were lowest in countries like France (58.9%), USA (56.9%), Poland (56.3%), Russia (54.9%), Italy (53.7%), Jordan (28.4%) and Kuwait 23.6%). Various surveys of doctors and nurses revealed that vaccine acceptance was lowest in Congo (27.7%) and highest in Israel (78.1%). The lowest rates for accepting COVID-19 vaccination were found in Africa, Russia, the Middle East, and most of the European countries that showed that in order to build the trust of the general public as well as medical workers, it is necessary to address the hesitation of COVID-19 vaccination.

3. Conclusion

Although it was not an easy task, some pharmaceutical companies have developed vaccines that are more than 90% effective against SARS-CoV-2. Vaccines against COVID-19 cause some common side effects, but misinformation and lack of confidence are the main reasons why people feel hesitant about being vaccinated. In the end, still approved vaccines by the FDA are facing many challenges, including manufacturing on a large scale and distribution of vaccines across different countries of the world.

Compliance with ethical standards

Disclosure of conflict of interest

All the authors (Muhammad Shoaib, Ahmad Waheed, Muhammad Wajid, Hafiza Urwa, Tehmina Khan, Muhammad Saleem Khan, Muhammad Waseem Aslam, Shabbir Ahmad, Kamran Jafar, Hasnain Akmal, Muhammad Iqbal Mahmood, and Samrina Shamim) declare that they have no conflict of interest.

References

[1] Commission WMH. Wuhan Municipal Health Commission briefing on the pneumonia epidemic situation. Wuhan, China: Municipal Health Commission; 2019.

[2] Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? The lancet infectious diseases. 2020; 20(5): e102-e7.

[3] Worldometer. Coronavirus Cases [Internet]. 2021 [cited 2021 Feb 16]. Available from: https://www.worldometers.info/coronavirus/

[4] Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. 2020; 581(7807): 215-20.

[5] Callaway E. The race for coronavirus vaccines: a graphical guide. Nature. 2020; 580(7805): 576-7.

[6] Jain S, Batra H, Yadav P, Chand S. COVID-19 Vaccines Currently under Preclinical and Clinical Studies, and Associated Antiviral Immune Response. Vaccines (Basel). 2020; 8(4): 649.

[7] FDA. FDA Takes Additional Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for Second COVID-19 Vaccine [Internet]. Food and Drug Administration: 2020 [cited 2021 Feb 16]. Available from: https://www.fda.gov/news-events/press-announcements/fda-takes-additional-action-fight-against-covid-19-issuing-emergency-use-authorization-second-covid

[8] Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020; 584(7821): 457-62.

[9] Sempowski GD, Saunders KO, Acharya P, Wiehe KJ, Haynes BF. Pandemic Preparedness: Developing Vaccines and Therapeutic Antibodies For COVID-19. Cell. 2020; 181(7): 1458-63.

[10] Mellet J, Pepper M. A COVID-19 vaccine: big strides come with big challenges. 2021; 9: 39. Vaccines. 2021; 9(1): 39.

[11] Salvatori G, Luberto L, Maffei M, Aurisicchio L, Roscilli G, Palombo F, et al. SARS-CoV-2 SPIKE PROTEIN: an optimal immunological target for vaccines. J Transl Med. 2020; 18(1): 222.

[12] Ledford H, Cyranoski D, Van Noorden R. The UK has approved a COVID vaccine-here's what scientists now want to know. Nature. 2020; 588(7837): 205-6.

[13] Greenwood B. The contribution of vaccination to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci. 2014; 369(1645): 20130433.

[14] Thi EP, Mire CE, Lee AC, Geisbert JB, Zhou JZ, Agans KN, et al. Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected nonhuman primates. Nature. 2015; 521(7552): 362-5.

[15] Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. New England Journal of Medicine. 2020; 383: 1920-31.

[16] Phase IAPI. Data for INO-4800 Vaccine for COVID-19. 2020.

[17] Moderna I. Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization [Internet]. Moderna Inc.: 2020 [cited 2021 Feb 16]. Available from: https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-primary-efficacy-analysis-phase-3-cove-study

[18] Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med. 2021; 384(1): 80-2.

[19] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020; 383(27): 2603-15.

[20] FDA. FDA Takes Key Action in Fight Against COVID-19 By Issuing Emergency Use Authorization for First COVID-19 Vaccine [Internet]. Food and Drug Administration: 2020 [cited 2021 Feb 16]. Available from: https://www.fda.gov/news-events/press-announcements/fda-takes-key-action-fight-against-covid-19-issuing-emergency-use-authorization-first-covid-19

[21] Zhu FC, Li YH, Guan XH, Hou LH, Wang WJ, Li JX, et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet. 2020; 395(10240): 1845-54.

[22] Staff R. CanSino's COVID-19 vaccine candidate approved for military use in China [Internet]. 2020 [cited 2021 Feb 16]. Available from: https://www.reuters.com/article/us-health-coronavirus-china-vaccine/cansinos-covid-19-vaccine-candidate-approved-for-military-use-in-china-idUSKBN2400DZ#:${\sim%20}$:text=China's%20Central%20Military%20Commission%20approved,of%20Military%20Science%20(AMS)

[23] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020; 396(10249): 467-78.

[24] Oxford. Trial of Oxford COVID-19 vaccine starts in Brazil [Internet]. 2020 [cited 2021 Feb 16]. Available from: https://www.research.ox.ac.uk/Article/2020-06-28-trial-of-oxford-covid-19-vaccine-starts-in-brazil

[25] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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. 2021; 397(10269): 99-111.

[26] Burki TK. The Russian vaccine for COVID-19. The Lancet Respiratory Medicine. 2020; 8(11): e85-e6.

[27] Sputnik. Clinical trials [Internet]. 2020 [cited 2021 Feb 16]. Available from: https://sputnikvaccine.com/about-vaccine/clinical-trials/

[28] Palacios R, Patiño EG, de Oliveira Piorelli R, Conde MTRP, Batista AP, Zeng G, et al. Double-Blind, Randomized, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of treating Healthcare Professionals with the Adsorbed COVID-19 (Inactivated) Vaccine Manufactured by Sinovac–PROFISCOV: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020; 21(1): 1-3.

[29] Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020; 369(6499): 77-81.

[30] Peshimam GN, Farooq U. CanSinoBIO's COVID-19 vaccine 65.7% effective in global trials, Pakistan official says [Internet]. Reuters: 2021 [cited 2021 Mar 8]. Available from: https://www.reuters.com/article/us-health-coronavirus-vaccine-pakistan/cansinobios-covid-19-vaccine-657-effective-in-global-trials-pakistan-official-says-idUSKBN2A81N0

[31] Mcgregor G. Why did the efficacy of China's top vaccine drop from 78% to 50%? [Internet]. Fortune: 2021 [cited 2021 Mar 5]. Available from: https://fortune.com/2021/01/13/sinovac-vaccine-efficacy-rate-drop/

[32] Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. New England Journal of Medicine. 2020; 383(24): 2320-32.

[33] Dai L, Zheng T, Xu K, Han Y, Xu L, Huang E, et al. A Universal Design of Betacoronavirus Vaccines against COVID-19, MERS, and SARS. Cell. 2020; 182(3): 722-33 e11.

[34] Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med. 2021; 384(7): 643-9.

[35] Firger J, Caldwell T. Third Alaskan health care worker has allergic reaction to Covid-19 vaccine [Internet]. 2020 [cited 2021 Feb 16]. Available from: https://edition.cnn.com/2020/12/18/health/alaska-third-allergic-reaction-vaccine/index.html

[36] Vrieze JD. Suspicions grow that nanoparticles in Pfizer's COVID-19 vaccine trigger rare allergic reactions [Internet]. 2020 [cited 2021 Feb 16]. Available from: https://www.sciencemag.org/news/2020/12/suspicions-grow-nanoparticles-pfizer-s-covid-19-vaccine-trigger-rare-allergic-reactions

[37] Sokolowska M, Eiwegger T, Ollert M, Torres MJ, Barber D, Del Giacco S, et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. Allergy. 2021.

[38] de Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. Lancet. 2020; 396(10255): 898-908.

[39] Mills M, Rahal C, Brazel D, Yan J, Gieysztor S. COVID-19 vaccine deployment: Behaviour, ethics, misinformation and policy strategies. London: The Royal Society The British Academy. 2020.

[40] Massey PM. Where do US adults who do not use the internet get health information? Examining digital health information disparities from 2008 to 2013. Journal of health communication. 2016; 21(1): 118-24.

[41] Pfizer. Fact sheet for recipients and caregivers: Emergency Use Authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19) in individuals 16 years of age and older [Internet]. Pfizer Inc., New York, NY 10017: 2021 [cited 2021 Feb 17]. Available from: https://www.fda.gov/media/144414/download

[42] McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018; 141(2): 463-72.

[43] Jiang S. Don't rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees. Nature. 2020; 579(7799): 321-.

[44] Liu A, Wang W, Zhao X, Zhou X, Yang D, Lu M, et al. Disappearance of antibodies to SARS-CoV-2 in a-COVID-19 patient after recovery. Clinical Microbiology Infection. 2020; 26(12): 1703-5.

[45] Branswell H. The world needs Covid-19 vaccines. It may also be overestimating their power [Internet]. 2020 [cited 2021 Feb16]. Available from: https://www.statnews.com/2020/05/22/the-world-needs-covid-19-vaccines-it-may-also-be-overestimating-their-power/

[46] Davis CW, Jackson KJ, McCausland MM, Darce J, Chang C, Linderman SL, et al. Influenza vaccine–induced human bone marrow plasma cells decline within a year after vaccination. Science. 2020; 370(6513): 237-41.

[47] Khamsi R. If a coronavirus vaccine arrives, can the world make enough? Nature. 2020; 580(7805): 578-80.

[48] Span P. Older adults may be left out of some COVID-19 trials. The New York Times. 2020.

[49] Sarah K. The U.S. Commits to Buying Millions of Vaccine Doses. Why That's Unusual [Internet]. 2020 [cited 2020 Feb 24]. Available from: https://www.nytimes.com/2020/07/22/upshot/vaccine-coronavirus-government-purchase.html

[50] Malik YS, Kumar N, Sircar S, Kaushik R, Bhat S, Dhama K, et al. Coronavirus Disease Pandemic (COVID-19): Challenges and a Global Perspective. Pathogens. 2020; 9(7): 519.

[51] Kault DA. Superspreaders help covid-19 elimination. MedRXiv. 2020.

[52] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. New England Journal of Medicine. 2020; 382(21): 1969-73.

[53] Lazarus JV, Ratzan SC, Palayew A, Gostin LO, Larson HJ, Rabin K, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med. 2021; 27(2): 225-8.

[54] Alford J. Under half of people currently willing to get COVID-19 vaccine, survey suggests [Internet]. Imperial College London: 2020 [cited 2021 Feb 17]. Available from: https://www.imperial.ac.uk/news/210393/under-half-people-currently-willing-covid-19/

[55] Wang J, Jing R, Lai X, Zhang H, Lyu Y, Knoll MD, et al. Acceptance of COVID-19 Vaccination during the COVID-19 Pandemic in China. Vaccines (Basel). 2020; 8(3): 482.

[56] Sallam M. COVID-19 Vaccine Hesitancy Worldwide: A Concise Systematic Review of Vaccine Acceptance Rates. Vaccines (Basel). 2021; 9(2): 160.