ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 6, Issue – 4, July – 2021 , Page No. : 61 - 73

Fighting COVID 19, One Shot at a Time

[1]Apurva Bansal, MBBS student, Amrita Institute of Medical Sciences, Kochi, Kerala, India.

[2]Ashvin Rajeev Pillai, MBBS student, Amrita Institute of Medical Sciences, Kochi, Kerala, India.

Corresponding Author: Apurva Bansal, MBBS student, Amrita Institute of Medical Sciences, Kochi, Kerala, India.

Citation this Article: Apurva Bansal, Ashvin Rajeev Pillai, "Fighting COVID 19, One Shot at a Time", IJMSIR- July - 2021, Vol – 6, Issue - 4, P. No. 61 – 73.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Close to 2 years old now, the SARS-Cov-2 virus has caused havoc worldwide causing close to 3.4 million deaths Healthcare systems have become overburdened with COVID-19 cases, countries have re-imposed lockdowns and the only solution expected for this is a vaccine. We have compiled data from published research papers and news articles, the hurdles faced in the distribution of vaccines and where can we fill in the gaps to be prepared for pandemic of this scale in the future. With the Pfizer-BioNtech and Moderna mRNA vaccines showing high efficacy, they seem to be the frontrunners in the vaccine race but face challenges due to their extremely low storage temperatures. The AstraZeneca-Oxford vaccine with an efficacy of 70% has an upper hand in terms of logistics because it just requires 2-8°C temperature. With many vaccines being launched, the challenge that now lies ahead is the supply-chain vulnerabilities for which the world wasn't prepared. In a country like India, where ultra-low temperature cold chain infrastructure hasn't had much investment, vaccines with refrigerator storage temperatures offer an opportunity for higher rural penetrance and faster outreach. CoWIN is the site launched by the government for easy outreach of the vaccines throughout the country. Coordination of different components of the supply-chain from airports to primary health centres is key in the successful implementation of a vaccine. As of 20th May, 2021, 1.4 billion vaccine doses have been administered in India.

Keywords: COVID-19, vaccine, supply-chain, temperature, cold-chain.

Introduction

The first case of Covid-19 disease was reported on 21st December, 2019 in Wuhan, China [1]. The SARS-CoV-2 virus spread rapidly around the world and on 11th March, 2020, the WHO pronounced the world to be suffering from a COVID-19 pandemic [2]. As of 20th May, 2021 there had been more than 164 million cases of the disease detected and more than 3.4 million deaths worldwide. 1.4 billion Vaccine doses have been administered in India [3].

COVID-19 affects the respiratory system primarily with the patients varying from asymptomatic or mild rhinorrhoea to patients suffering from ARDS and death [4]. The patients commonly present with fever, cough, myalgia, fatigue and dyspnoea at the onset of the disease [5, 6]. Other less common symptoms such as headache, diarrhea, abdominal pain, hemoptysis, vomiting, nausea, anosmia, ageusia, urticaria, myocarditis etc. are also seen [7, 8, 9]. Most of the asymptomatic patients are younger [10] and most of the patients who require Intensive Care Unit (ICU) admission due to severe complications are of the older age group with most having underlying co-morbidities [11].

SARS-CoV-2 virus is a member of the coronavirus family infecting humans and similar to others such as SARS-CoV and MERS-CoV [12]. The case-mortality ratio of the Covid-19 varies around the world, ranging from 1.5% to 9.4% per 100,000 population in the 20 worst affected countries [13]. Even though the case-mortality ratio of covid-19 is less than the SARS-CoV and MERS-CoV, the death toll due to SARS-CoV-2 is exponentially higher than SARS-CoV and MERS-CoV combined [14].

Common modes of transmission for SARS-CoV-2 is via respiratory droplets during face to face exposure, via contact surface spread and airborne transmission [15,16]. Doubts persist in the scientific community about the latter [17]. It is important to adhere to the WHO guidelines for prevention of transmission of Covid-19 [18].

Recently, Remdesivir was shown to have some positive effect in the management of the affected patients [19]. With therapeutics unable to decrease the high mortality, the only way to end this pandemic now, seems to be with the help of vaccines.

Material and Methods

This review was focused on the logistics of vaccine supply in India. For an in-depth analysis of the various Covid-19 vaccines and their possible distribution strategies in India, we conducted an intensive search of Google scholar and PubMed, along with a manual search on google. Articles in medical journals and news reporting regarding the topic were referred for writing this article.

Structure of SARS-CoV-2

In order to understand the mechanism of action of the vaccine, it is important to understand the structure of virus. The coronavirus are spherical, enveloped viruses, with a helical nucleocapsid and surface projections [20]. The large, single-stranded, positive-sense RNA strand encodes 4 main structural proteins: Membrane (M) protein, Surface (S) protein, Nucleocapsid (N) protein, Envelope (E) protein [21]. Studies have shown that among the structural proteins, S protein is the only significant SARS-CoV-2 neutralizing and protective antigen and thus it is of much interest for vaccine development against SARS-CoV-2 [22]. The coronaviruses use S protein homotrimers for attachment and fusion of the virus to the host cell membranes. The S protein is consists of S1 subunit containing receptor binding domain (RBD) and S2 subunit is responsible for membrane fusion and entry into the host cell [23].

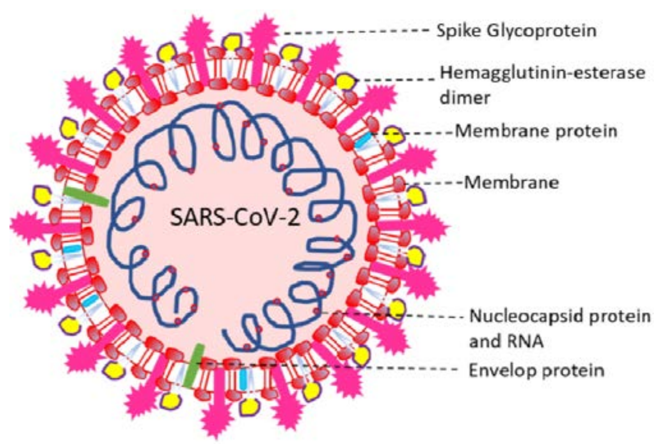

Figure 1: Structure of SARS-CoV-2 virus [21]

Vaccinations for SARS-CoV-2

According to previous studies on SARS-CoV-1, the receptor binding domain (RBD), of the S1 protein of the coronaviridae, is the most important area for research for vaccines as it has a highly potent neutralizing antibodies response [24]. While the vaccines were able to help in protection from an infection of the virus on giving a challenge dose, they did not provide sterilizing immunity. In some cases, vaccination in the mice models led to increased complications [25]. There was also the issue of waning of the immunity against the virus after some time, leading to the possibility of re-infection [26].

Another observation made for SARS-CoV-1 and SARS-CoV-2, is that elderly are affected more severely than those in the young. For Influenza vaccines, it was observed that higher titres of neutralizing antibodies were required to provide immunity to people above 65 years of age as compared to younger people [27]. This issue will be required to be addressed for SARS-CoV-2 vaccines due to the exponentially higher mortality rates of the virus in the elderly.

The vaccines currently in the final phases of development against the SARS-CoV-2 virus are discussed briefly here.

A. Nucleic acid vaccines

Recombinant DNA/RNA vaccines uses cloned DNA/RNA plasmid that sequence the immunogenic proteins for the pathogen, grown in a suitable eukaryotic host and purified. These purified plasmid nucleic acids are then directly inoculated to the patient and they cause production of the immunogenic protein on expression of the plasmid by the host cells [28, 29].

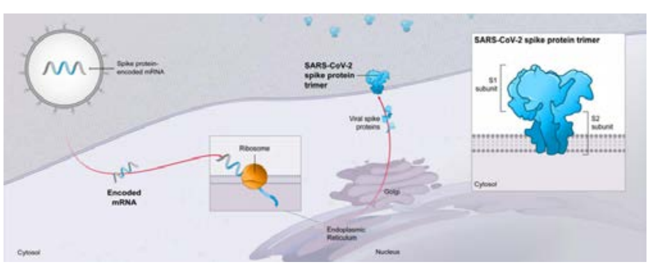

Figure 2: mRNA-1273 encodes for the full-length Spike Protein in the Pre-fusion [30]

a. Pfizer-BioNTech BNT162b2

The mRNA vaccine candidate’s had an efficacy of 95%. The vaccine schedule consists of 2 doses, to be taken 28 days apart. The vaccine is to be stored at -70°C temperature, and once thawed, can be kept at refrigerator temperature for a maximum of 3 days, before it becomes unusable. No serious side effects have been reported. [31, 32, 33].

b. Moderna mRNA-1273 Vaccine

The vaccine’s efficacy is reported to be 94.5% few days after the second dose. The vaccine schedule consists of 2 doses, given 28 days apart. The vaccine can be stored in a conventional freezer at the temperature of -20°C for up to 6 months and once thawed, it can be kept in a standard refrigerator for up to 30 days. No serious side effects have been reported. [34, 35, 36, 37].

B. Viral Vector Vaccines

Viral vector vaccines use laboratory generated, chimeric viruses that can be replicating or non-replicating, attenuated or inactivated viral vectors which have been spliced with the genes coding for the immunogenic proteins of the target pathogen [38, 39, 40].

a. Oxford-AstraZeneca AZD1222

It uses a chimpanzee non-replicating DNA based adenovirus viral vector with the genetic sequence of the Spike (S) protein. The interim efficacy report for phase III trials shows that the vaccine has 62% efficacy with 2 standard doses, one month apart and efficacy of 90% when half dose vaccine followed by standard dose regimen after 28 days, with an overall efficacy of 70%. The vaccine can be stored at refrigerator temperature (2°C-8°C). There are reports from some countries of blood clotting in under-40 yrs who were vaccinated with the same [33, 41, 42, 43].

b. Gamaleya Centre's Sputnik V

Sputnik V is a heterologous, non-replicating adenovirus viral vector vaccine containing recombinant adenovirus type 26 (rAd26) vector and recombinant adenovirus type 5 (rAd5) vector. It was the first approved SARS-CoV-2 vaccine in the world. The interim efficacy report of the vaccine is reported to be 92%.The vaccine is a freeze-dried vaccine, to be stored at -18°C. [44, 45, 46].

c. CanSinoBIO'sAd5-CoV

AD5-CoV was the first Chinese vaccine in development by the CanSino Biologics and the Academy of Military Medical Services, China. It uses non-replicating Ad5 Adenovirus vector. Only one intramuscular dose induced a significant immune response. No significant side effects were seen. The vaccine efficacy is 90.98% in preventing severe cases. [47, 48, 49].

d. Johnson and Johnson's JNJ-78436735

The vaccine is based on non-replicating Ad26 Adenovirus viral vector. The vaccine is one of the few Covid-19 vaccines that has a one dose regimen. It is estimated to remain stable at around -20°C for 2 years and at 2°C-8°C for around 3 months [50, 51, 52, 53].

C. Inactivated viral vaccines

Inactivated viral vaccines are prepared by cultivation in a suitable medium. After which, these pathogens are inactivated by using 2 methods: either by chemical or physical methods, or combination of both. When injected into the body, they stimulate active immunity [54].

a. Bharat Biotech's Covaxin

Bharat Biotech, in collaboration with ICMR and National Institute of Virology, are developing India's first endogenous Covid-19 vaccine, with alum as its adjuvant. The vaccine regimen consists of 2 doses intramuscularly, 28 days apart. The vaccine has 78% efficacy with very mild to moderate side effects [55, 56, 57].

b. Sinopharm's Covid-19 vaccine

Sinopharm is currently working on 2 vaccines, in collaboration with Wuhan Institute of Biological Products and Beijing Institute of Biological Products. For the vaccine with Wuhan Institute of Biological Products, it was observed that dose regimen with 2 intramuscular doses, 21 days apart was found to be the most efficacious. There were mild side effects. The vaccine produced with Beijing Institute of Biological Products has a 2 dose intramuscular regimen, with very few adverse effects. The vaccine has been said to show high efficacy [58, 59, 60].

c. SinoVac's CoronaVac

CoronaVac is an inactivated vaccine with alum adjuvant. The dose regimen is 2 intramuscular doses, taken 28 days apart. Reports showed about 67% efficacy against symptomatic infection. It has mild to moderate side effects. The vaccine can be kept at refrigerator temperature for up to 3 years [61, 62].

D. Protein subunit Vaccines

Protein subunit vaccines are formed by isolation of the immunogenic proteins of the pathogen. In SARS-CoV-2 the proteins used are S protein or the receptor binding domain [63].

a. Nvavax's NVX-CoV2373

NVX-CoV2373 is a full-length stable, pre-fused S protein chain with Matrix M protein as adjuvant. It is given in 2 intramuscular doses, 28 days apart. The vaccine showed no serious adverse effects. It has to be stored at normal refrigerator (2°C-8°C) temperature [63, 64, 65].

Vaccine Hesitancy

Even with highly efficacious vaccines, another challenge that mass vaccination may face is the scepticism present among many people, including some healthcare workers, regarding the speed of the scientific trials of these vaccines, which may have compromised their safety [66]. To increase the confidence of the public in the vaccines, it is necessary for regulatory bodies and vaccine developers, to have complete transparency and try to clear all the uncertainties surrounding the COVID 19 vaccines in the public's mind [67].

Logistics of Covid 19 Vaccination

Logistical factors conducted internationally during roll out of a COVID-19 vaccine may include: sharing of supllier audits, visibility and traceability by barcodes for each vaccine vial, sharing of chain of custody for a vaccine vial from manufacturer to the individual being vaccinated, new packaging and delivery technologies, use of vaccine temperature monitoring tools, temperature stability testing and assurance, stockpiling, coordination of supplies within each country (personal protective equipment, syringes, needles, rubber stoppers, diluents, refrigeration fuel or power sources and waste-handling among others), technology and the environmental impacts in each country [68][69][70].

Vaccines are characteristically labile during temperature variations, requiring cold chain management throughout the whole supply chain, typically at temperatures of 2–8°C (36–46°F)[70]. With several novel vaccine technologies, there are new hurdles for cold chain system management, with some vaccines that are stable while frozen but unstable to heat, while others shouldn't be frozen, and some are stable across temperatures [71]. Damage caused due to freezing and inadequate training of personnel within the local vaccination process are major concerns [72]. During a situation where more than one COVID-19 vaccine is approved, the vaccine cold chain may need to be inclusive of these temperature sensitivities across different regions with variable climate conditions and native resources for maintenance of temperature [71]. Inactivated vaccines may be transported using current cold chain systems, while CoronaVac doesn't need to be frozen [73][74].

mRNA vaccine technologies could be even more difficult to manufacture at scale and control degradation, requiring ultracold storage and transport [75]. For instance, Moderna's vaccine candidate requires cold chain management just above freezing temperatures (-20°C) with limited storage duration, but the one being developed by BioNTech-Pfizer requires storage at -70°C (-94°F) or colder throughout deployment until vaccination [76][77].

After the vaccine vial is punctured for administering a dose, it's viable for about six hours, then it should be discarded, which needs attentive local management of cold storage and vaccination processes [78][79]. Because there'll be an acute shortage of the COVID-19 vaccine during early roll out stages, the vaccination staff will need to take measures to avoid spoilage and wastage, which usually are the maximum amount, as 30% of the availability [78][79]. The cold chain has further hurdles to face within the sort of the local transportation for the vaccines in rural areas, like by motorcycle, mules or drones, the necessity for booster doses, use of diluents, and access to the vulnerable section of the population, like frontline healthcare workers and the elderly [78][80]

Currently the Government of India has setup an online platform named "CoWIN" online platform for the people to register themselves and book a slot in a nearby Government PHC or General hospital or privately run hospital to get their vaccination. The gap between the two Covishield doses should be increased to 12 to 16 weeks from the existing 6-8 weeks, the National Expert Group on Vaccine Administration for Covid-19 (NEGVAC), headed by Niti Aayog member (health) VK Paul has suggested [81].

Distribution networks in India have operations mainly via four government medical store depots in Karnal, Chennai, Mumbai and Kolkata, which procure vaccines from the manufacturers. Approximately 53 state vaccine stores get their supplies from either these Government medical store depots or directly from the manufacturers.[82]

The Indian vaccine supply chain consists of enter ice rooms, deep freezers and ice lined refrigerators at the state level, of which the enter ice rooms have a storage capacity of 13440L. Within the peripheral units, the modalities are cold box, vaccine carriers and day carriers of which cold boxes can carry up to 30 vaccines and day carriers can carry up to 6 vaccines. There is an urgent need to complete the cold chain inventory within the lowest levels and their functional status. The inventory updating is to be done at regular intervals (initially quarterly, then monthly). Review and reconciliation of the cold chain devices must be finished validation and realistic projection of cold chain space need at different levels.

The WHO has implemented an "Effective Vaccine Management" strategy which is inclusive of constructing priorities to equip the national and subnational personnel and facilities for vaccine distribution, including trained staff to handle time and temperature-sensitive vaccines, robust monitoring capabilities to ensure optimal vaccine storage and transport, temperature-controlled facilities and equipment, traceability and security. [83]

The Serum Institute of India in Pune plans to produce at least one billion vaccine doses, with half the doses reserved for India [84].

In India, with a population of 1.3 billion people, it may not be feasible to vaccinate every individual, but this may not also be necessary. To achieve herd immunity, only 70% of the population needs to be vaccinated. Excluding under 10 years old children and pregnant women, around 700 million individuals will need to be vaccinated. With such a large vaccination target, it will be prudent to use more than one vaccine, and to track who all have been vaccinated, India may need to use systems such Aadhar-linked vaccine batch numbers. There may be the problem of the funding for such a massive vaccine drive, for which the centre and the states may have to combine funds. It will also be essential to be very clear, depending on each state's population, positive cases and Covid deaths, the amount of vaccines that will be allocated to the state. The final distribution of the vaccines depending on the priority groups will be done by the states [85].

Conclusion

While there are many vaccine candidates around the world currently in research, it will take quite a few years to understand which vaccine will actually be practical to reach the common man. The key to a global success is in the simplicity of technology and cost effectiveness. There is an urgent need to complete the cold chain inventory in the least levels and their functional status. Review and reconciliation of the cold chain devices must be validated and realistic projections of cold chain space are vital[73]. ASHA workers, AYUSH practitioners, anganwadi workers and allied health professionals should be mobilized for faster outreach. In the absence of a truly effective drug, we will likely need to follow the social distancing and hygiene precautions for the foreseeable future [86].

The vulnerable, such as the elderly, immuno compromised, and those with co-morbidities for example patients with ILD, particularly those of advanced age, have increased odds of severe disease and death from COVID-19 [87] should be given priority along with frontline healthcare workers.

A mass vaccination campaign for an infectious disease outbreak is a complicated enterprise that requires balancing different strategies for allocation, administration, distribution, access, monitoring and other considerations. Each infectious disease outbreak differs in terms of its clinical characteristics, epidemiology and impact across various populations [88]. Equitable health care service delivery is central to achieving success worldwide.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine. 2020 Jan 24.
2. WHO DG. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. 2020 [cited 2020Dec8]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
3. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) [Internet]. ArcGIS Dashboards. 2020 [cited 2020Dec8]. Available from: https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html
4. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: The current state of play. Paediatric respiratory reviews. 2020 Sep 1;35:43-9.
5. Song Y, Liu P, Shi XL, Chu YL, Zhang J, Xia J, Gao XZ, Qu T, Wang MY. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut. 2020 Jun 1;69(6):1143-4.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020 Apr 30;382(18):1708-20.
7. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. Journal of the European Academy of Dermatology and Venereology. 2020 Mar 26.
8. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini G, Antinori S. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clinical Infectious Diseases. 2020 Mar 26.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.
10. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin JI. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. International journal of infectious diseases. 2020 Sep 1;98:180-6.

11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020 Mar 17;323(11):1061-9
12. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nature Reviews Microbiology. 2019 Mar;17(3):181-92.
13. Mortality Analyses [Internet]. Johns Hopkins Coronavirus Resource Center. 2020 [cited 2020Dec8]. Available from: https://coronavirus.jhu.edu/data/mortality
14. Giwa AL, Desai A. Novel coronavirus COVID-19: an overview for emergency clinicians. Emerg Med Pract. 2020 Feb 27;22(2 Suppl 2):1-21
15. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. Jama. 2020 Aug 25;324(8):782-93.
16. Morawska L, Milton DK. It is time to address airborne transmission of COVID-19. Clin Infect Dis. 2020 Jul 6;6:ciaa939.
17. Lewis D. Is the coronavirus airborne? Experts can't agree. Nature. 2020 Apr 9;580(7802):175
18. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public
19. Beigel JH, Tomashek KM, Dodd LE. Remdesivir for the Treatment of Covid-19—Final Report.[published online October 8, 2020]. N Engl J Med. doi.;10..
20. Goldsmith CS, Tatti KM, Ksiazek TG, Rollin PE, Comer JA, Lee WW, Rota PA, Bankamp B, Bellini WJ, Zaki SR. Ultrastructural characterization of SARS coronavirus. Emerging infectious diseases. 2004 Feb;10(2):320.
21. Boopathi S, Poma AB, Kolandaivel P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. Journal of Biomolecular Structure and Dynamics. 2020 Apr 29:1-0.
22. Buchholz UJ, Bukreyev A, Yang L, Lamirande EW, Murphy BR, Subbarao K, Collins PL. Contributions of the structural proteins of severe acute respiratory syndrome coronavirus to protective immunity. Proceedings of the National Academy of Sciences. 2004 Jun 29;101(26):9804-9.
23. Walls AC, Tortorici MA, Bosch BJ, Frenz B, Rottier PJ, DiMaio F, Rey FA, Veesler D. Cryo-electron microscopy structure of a coronavirus spike glycoprotein trimer. Nature. 2016 Mar;531(7592):114-7.
24. Zhu X, Liu Q, Du L, Lu L, Jiang S. Receptor-binding domain as a target for developing SARS vaccines. Journal of thoracic disease. 2013 Aug;5(Suppl 2):S142.
25. Roper RL, Rehm KE. SARS vaccines: where are we?. Expert review of vaccines. 2009 Jul 1;8(7):887-98.
26. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. Epidemiology & Infection. 1990 Oct;105(2):435-46.
27. Benoit A, Beran J, Devaster JM, Esen M, Launay O, Leroux-Roels G, McElhaney JE, Oostvogels L, van Essen GA, Gaglani M, Jackson LA. Hemagglutination inhibition antibody titers as a correlate of protection against seasonal A/H3N2

influenza disease. InOpen forum infectious diseases 2015 Apr 1 (Vol. 2, No. 2, p. ofv067). Oxford University Press.

28. Deering RP, Kommareddy S, Ulmer JB, Brito LA, Geall AJ. Nucleic acid vaccines: prospects for non-viral delivery of mRNA vaccines. Expert opinion on drug delivery. 2014 Jun 1;11(6):885-99.
29. Robinson HL. Nucleic acid vaccines: an overview. Vaccine. 1997 Jun 1;15(8):785-7.
30. Miller JM. mRNA-1273 clinical development program.
31. Mahase E. Covid-19: Pfizer and BioNTech submit vaccine for US authorisation.
32. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D, Brachtendorf S. COVID-19 vaccine BNT162b1 elicits human antibody and TH 1 T cell responses. Nature. 2020 Oct;586(7830):594-9.
33. Walsh EE, Frenck Jr RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, Lockhart S, Neuzil K, Mulligan MJ, Bailey R, Swanson KA. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. New England Journal of Medicine. 2020 Oct 14.
34. Mahase E. Covid-19: Vaccine candidate may be more than 90% effective, interim results indicate.
35. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott AB. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. New England Journal of Medicine. 2020 Sep 29.
36. Jackson LA, Anderson EJ, Rouphael NG, Roberts PC, Makhene M, Coler RN, McCullough MP, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ. An mRNA vaccine against SARS-CoV-2—preliminary report. New England Journal of Medicine. 2020 Nov 12;383(20):1920-31.
37. Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, Flach B, O'Connell S, Bock KW, Minai M, Nagata BM. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. New England Journal of Medicine. 2020 Oct 15;383(16):1544-55.
38. Condit RC, Kim D, Robertson JS, Excler JL, Gurwith M, Monath TP, Pavlakis G, Fast PE, Smith J, Smith ER, Chen RT. The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of viral vector vaccines. Vaccine. 2020 Nov 17;38(49):7708-15.
39. de Vries RD, Rimmelzwaan GF. Viral vector-based influenza vaccines. Human vaccines & immunotherapeutics. 2016 Nov 1;12(11):2881-901.
40. Ura T, Okuda K, Shimada M. Developments in viral vector-based vaccines. Vaccines. 2014 Sep;2(3):624-41.
41. Mode D, Stockholm LC. AstraZeneca: COVID-19 vaccine AZD1222 showed robust immune responses in all participants in Phase I/II trial.
42. Mahase E. Covid-19: Oxford vaccine is up to 90% effective, interim analysis indicates.
43. Mahase E. Covid-19: UK government asks regulator to assess Oxford vaccine as questions are raised over interim data.

44. Balakrishnan VS. The arrival of Sputnik V. The Lancet Infectious Diseases. 2020 Oct 1;20(10):1128.
45. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, Grousova DM, Erokhova AS, Kovyrshina AV, Botikov AG, Izhaeva FM. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. The Lancet. 2020 Sep 26;396(10255):887-97.
46. Chappell, B. (2021, February 2). Russia's Sputnik Vaccine Is Reported To Be 92% Effective Against COVID-19. NPR. https://www.npr.org/sections/coronavirus-live-updates/2021/02/02/963166648/russias-sputnik-vaccine-is-reported-to-be-92-effective-against-covid-19.
47. Ahamad S, Branch S, Harrelson S, Hussain MK, Saquib M, Khan S. Primed for global coronavirus pandemic: Emerging research and clinical outcome. European Journal of Medicinal Chemistry. 2020 Sep 19:112862.
48. Peshimam, G. N., & Farooq, U. (2021, February 8). CanSinoBIO's COVID-19 vaccine 65.7% effective in global trials, Pakistan official says. Reuters. https://www.reuters.com/article/us-health-coronavirus-vaccine-pakistan-idUSKBN2A81N0.
49. Zhu FC, Guan XH, Li YH, Huang JY, Jiang T, Hou LH, Li JX, Yang BF, Wang L, Wang WJ, Wu SP. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. 2020 Aug 15;396(10249):479-88.
50. Ad5-nCoV Vaccine [Internet]. Precision Vaccinations. 2020 [cited 2020Dec8]. Available from: https://www.precisionvaccinations.com/vaccines/ad5-ncov-vaccine
51. Janssen Vaccines & Prevention B.V. A Randomized, Double-blind, Placebo-controlled Phase 3 Study to Assess the Efficacy and Safety of Ad26.COV2.S for the Prevention of SARS-CoV-2-mediated COVID-19 in Adults Aged 18 Years and Older [Internet]. Janssen Vaccines & Prevention B.V. Clinical Protocol. 2020 [cited 2020]. Available from: https://www.jnj.com/coronavirus/covid-19-phase-3-study-clinical-protocol
52. Johnson & Johnson. Johnson & Johnson Prepares to Resume Phase 3 ENSEMBLE Trial of its Janssen COVID-19 Vaccine Candidate in the U.S. [Internet]. Johnson & Johnson Content Lab U.S. 2020 [cited 2020Dec8]. Available from: https://www.jnj.com/our-company/johnson-johnson-prepares-to-resume-phase-3-ensemble-trial-of-its-janssen-covid-19-vaccine-candidate-in-the-us
53. Cohen J. Vaccine designers take first shots at COVID-19 [Internet]. Science. American Association for the Advancement of Science; 2020 [cited 2020Dec8]. Available from: https://science.sciencemag.org/content/368/6486/14.full
54. Sanders B, Koldijk M, Schuitemaker H. Inactivated viral vaccines. InVaccine analysis: Strategies, principles, and control 2015 (pp. 45-80). Springer, Berlin, Heidelberg.

55. Bharat Biotech – COVAXIN™ [Internet]. GEN. 2020 [cited 2020Dec8]. Available from: https://www.genengnews.com/covid-19-candidates/bharat-biotech-covaxin/
56. Kay, C. (2021). Bloomberg.com. Homegrown Indian Covid Vaccine Already in Use Shows 78% Efficacy. https://www.bloomberg.com/news/articles/2021-04-21/homegrown-indian-covid-vaccine-already-in-use-shows-78-efficacy.
57. Bharat Biotech. COVAXINTM - India's First indigenous COVID-19 Vaccine [Internet]. Bharat Biotech-Vaccines & Bio-Therapeutics Manufacturer in India. 2020 [cited 2020Dec8]. Available from: https://www.bharatbiotech.com/covaxin.html
58. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Frontiers in Immunology. 2020 Oct 14;11:2413.
59. Reuters. China's Sinopharm says data 'better than expected' from it's COVID vaccine trial [Internet]. mint. 2020 [cited 2020Dec8]. Available from: https://www.livemint.com/companies/news/china-s-sinopharm-says-data-better-than-expected-from-it-s-covid-vaccine-trial-11605100199684.html
60. France-Presse A. Almost A Million People Inoculated With Chinese Sinopharm Covid Vaccine [Internet]. NDTV.com. 2020 [cited 2020Dec8]. Available from: https://www.ndtv.com/world-news/almost-a-million-people-inoculated-with-chinese-sinopharm-covid-19-vaccine-2327811
61. Sherwood, D. (2021). Game changer: Chile hails Sinovac's 67% effectiveness in study. https://news.yahoo.com/chinas-sinovac-covid-19-vaccine-133324288.html.
62. CoronaVac [Internet]. Wikipedia. Wikimedia Foundation; 2020 [cited 2020Dec8]. Available from: https://en.wikipedia.org/wiki/CoronaVac
63. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, Plested JS, Zhu M, Cloney-Clark S, Zhou H, Smith G. Phase 1–2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. New England Journal of Medicine. 2020 Sep 2.
64. Guebre-Xabier M, Patel N, Tian JH, Zhou B, Maciejewski S, Lam K, Portnoff AD, Massare MJ, Frieman MB, Piedra PA, Ellingsworth L. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. Vaccine. 2020 Nov 25;38(50):7892-6.
65. Tian JH, Patel N, Haupt R, Zhou H, Weston S, Hammond H, Lague J, Portnoff AD, Norton J, Guebre-Xabier M, Zhou B. SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 elicits immunogenicity in baboons and protection in mice. BioRxiv. 2020 Jan 1.
66. Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrachi M, Zigron A, Srouji S, Sela E. Vaccine hesitancy: the next challenge in the fight against COVID-19. European journal of epidemiology. 2020 Aug;35(8):775-9.
67. The COVID vaccine challenges that lie ahead [Internet]. Nature News. Nature Publishing Group; 2020 [cited 2020Dec8]. Available from: https://www.nature.com/articles/d41586-020-03334-w
68. Shukla P. Blockchain's potential role in the history-making plan to deliver the COVID-19 vaccine [Internet]. World Economic Forum. 2020 [cited 2020Dec7]. Available from:

https://www.weforum.org/agenda/2020/07/blockchain-role-in-distributing-covid-19-vaccine-could-make-history/

69. Jarrett S, Yang L, Pagliusi S. Roadmap for strengthening the vaccine supply chain in emerging countries: Manufacturers' perspectives. Vaccine: X. 2020 Aug 7;5:100068.
70. Lloyd J, Cheyne J. The origins of the vaccine cold chain and a glimpse of the future. Vaccine. 2017 Apr 19;35(17):2115-20..
71. Kartoglu U, Milstien J. Tools and approaches to ensure quality of vaccines throughout the cold chain. Expert review of vaccines. 2014 Jul 1;13(7):843-54.
72. Hanson CM, George AM, Sawadogo A, Schreiber B. Is freezing in the vaccine cold chain an ongoing issue? A literature review. Vaccine. 2017 Apr 19;35(17):2127-33.
73. Howard J. There are clear frontrunners in the COVID-19 vaccine race - but getting it to a clinic is a challenge in itself [Internet]. 2020 [cited 2020Dec7]. Available from: https://www.abc.net.au/news/2020-10-25/the-logistics-of-lab-to-jab-covid-19-vaccine/12808914
74. Time24.news. CoronaVac: Doses will come from China on nine flights and can... [Internet]. AlKhaleej Today. AlKhaleej Today; 2020 [cited 2020Dec7]. Available from: https://alkhaleejtoday.co/international/5246732/CoronaVac-Doses-will-come-from-China-on-nine-flights-and-can.html
75. Vaccines Use Bizarre Stuff. We Need a Supply Chain Now. [Internet]. Bloomberg.com. Bloomberg; [cited 2020Dec7]. Available from: https://www.bloomberg.com/opinion/articles/2020-08-18/a-resilient-covid-19-vaccine-supply-chain-starts-now
76. Blankenship K. Pfizer, Moderna's coronavirus shot rollouts could freeze up, experts say, citing cold-storage needs [Internet]. FiercePharma. 2020 [cited 2020Dec7]. Available from: https://www.fiercepharma.com/manufacturing/pfizer-moderna-s-covid-19-shot-rollouts-could-be-ice-as-analysts-question-cold
77. O’Donnell C. Why Pfizer's ultra-cold COVID-19 vaccine will not be at the local pharmacy any time soon [Internet]. Reuters. Thomson Reuters; 2020 [cited 2020Dec7]. Available from: https://de.reuters.com/article/us-health-coronavirus-vaccines-distribut/why-pfizers-ultra-cold-covid-19-vaccine-will-not-be-at-the-local-pharmacy-any-time-soon-idUSKBN27P2VI
78. Gates B. What you need to know about the COVID-19 vaccine [Internet]. gatesnotes.com. [cited 2020Dec7]. Available from: https://www.gatesnotes.com/Health/What-you-need-to-know-about-the-COVID-19-vaccine
79. Weise E. 'Mind-bogglingly complex': Here's what we know about how COVID-19 vaccine will be distributed when it's approved [Internet]. USA Today. Gannett Satellite Information Network; 2020 [cited 2020Dec7]. Available from: https://www.usatoday.com/story/news/health/2020/09/06/covid-vaccine-complex-distribution-supply-chain-follow-approval/5712053002/
80. UNICEF to lead procurement and supply of COVID-19 vaccines in world's largest and fastest ever operation of its kind [Internet]. UNICEF. 2020 [cited 2020Dec7]. Available from: https://www.unicef.org/press-releases/unicef-lead-

procurement-and-supply-covid-19-vaccines-worlds-largest-and-fastest-ever

81. Thacker T. Expert panel recommends increasing gap between two Covishield doses to 12-16 weeks [Internet]. Economic Times. 2021 [cited 2021 May 17].
82. Tauseef Shahidi NR. India's vaccine distribution challenge, explained in five charts [Internet]. mint. 2020 [cited 2020Dec7]. Available from: https://www.livemint.com/news/india/india-s-vaccine-distribution-challenge-explained-in-five-charts-11607106132744.html
83. Effective Vaccine Management (EVM) Initiative:Vaccine Management Handbook" [Internet]. 2020 [cited 2020Dec7]. Available from: https://www.who.int/immunization/programmes_systems/supply_chain/evm/en/index5.html
84. Callaway E. The unequal scramble for coronavirus vaccines-by the numbers. Nature. 2020 Aug;584(7822):506-7.
85. Ahluwalia M. How India can crack the vaccine challenge [Internet]. mint. 2020 [cited 2020Dec8]. Available from: https://www.livemint.com/news/india/how-india-can-crack-the-vaccine-challenge-11607361801770.html
86. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. Frontiers in Immunology. 2020 Oct 14;11:2413.
87. Esposito AJ, Menon AA, Ghosh AJ, Putman RK, Fredenburgh LE, El-Chemaly SY, Goldberg HJ, Baron RM, Hunninghake GM, Doyle TJ. Increased Odds of Death for Patients with Interstitial Lung Disease and COVID-19: A Case-Control Study. American Journal of Respiratory and Critical Care Medicine. 2020 Sep 8(ja).
88. Gayle H, Foege W, Brown L, Kahn B. Framework for equitable allocation of COVID-19 vaccine. The National Academy, DC. Press, Washington 2020 Oct 2;10:25917.