SARS-CoV-2 vaccines — the biggest medical research project of the 21st century

Drishya Kurup[1] and Matthias J Schnell[1,2]

SARS-CoV-2 has been detected in more than 141 million people and caused more than 3 million deaths worldwide. To reduce the additional loss of millions of lives until natural immunity is reached, researchers have focused on the only known method to stop the COVID-19 pandemic: vaccines. The pandemic has propelled high-speed vaccine development, some based on novel technology previously not utilized in the vaccine field. The new technology opens new possibilities and comes with challenges because the long-term performance of the new platforms is unknown. Here we review the current leading vaccine candidates against COVID-19 and outline the advantages and disadvantages as well as the unknowns of each candidate.

Addresses
[1] Department of Microbiology and Immunology, Thomas Jefferson University, Philadelphia, PA, United States
[2] Jefferson Vaccine Center, Thomas Jefferson University, Philadelphia, PA, United States

Corresponding author:
Schnell, Matthias J (Matthias.Schnell@jefferson.edu)

Introduction

Clean water and vaccines have saved more human lives than any other human invention [1•]. The importance of vaccines has been highlighted since the emergence in December 2019 of the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, brought daily life to a standstill globally. SARS-CoV-2 is a highly transmissible and pathogenic virus that can cause coronavirus disease 2019 (COVID-19), leading to severe, life-threatening respiratory pathologies and lung injuries [2]. As of February 27, 2021, 113 million people had been infected, with 2.5 million deaths worldwide [3••]. Global efforts to end the current pandemic hinge on necessary travel restrictions and precautions and, in the long run, require control by mass vaccinations, a strategy previously used to prevent diseases like smallpox and polio successfully [4].

SARS-CoV-2 spike protein gains entry into human cells by binding to the human angiotensin-converting enzyme 2 (ACE2) [5]. Receptor binding and membrane fusion activity have been attributed to the S1 and S2 subunits of the trimeric spike protein. The S1 subunit contains the receptor-binding domain (RBD) that binds to the ACE2 receptor. Antibodies that bind to the spike protein, especially to its receptor-binding domain (RBD) and the N-terminal domain (NTD), prevent its attachment to the host cell and neutralize the virus [6]. Virus neutralizing antibody (VNA) is likely to be an essential correlate of protection [7]. In addition to antibodies, natural infection with SARS-CoV-2 triggers a Th1-biased response with strong spike protein-specific CD4+ T cells and fewer CD8+ T cells [8,9]. A recent study has suggested a high degree of heterogeneity in the magnitude of adaptive immune responses in SARS-CoV-2 infected persons [10]. The memory B cells and CD4+ T cell responses were measurable in greater than 90% of subjects for more than five months after infection [10]. The same study also indicated that antibodies against SARS-CoV-2 S, RBD, and neutralizing antibodies declined moderately over eight months, raising concerns for long-term protection and herd immunity post-infection [11••,12,13].

Previous research on other pathogenic betacoronaviruses like SARS-CoV and MERS-CoV, and lessons learned from the human immune response to natural infection, helped identify the spike protein as an antigenic target for SARS-CoV-2 vaccine development. Therefore, most vaccines in pre-clinical and clinical trials have utilized the spike protein as their target antigen. Here we discuss the advantages and disadvantages of the lead candidates currently approved for mass vaccination and the other advanced candidates in phase 3 trials. Many features of these vaccines are not yet known based on their relatively short time of use. Some information is provided on preprint servers without peer-review and press releases from the companies. With more than 73 vaccines in clinical and 182 vaccines in pre-clinical development, we focus our opinions on the current front runners that may profoundly affect global health. This review aims to caution readers to refer to peer-reviewed journals for vaccine information without endorsing any of these novel vaccines and provide an unbiased evaluation.

mRNA-based vaccines

On December 11–18, 2020, the first two COVID-19 vaccines received emergency use approval for mass vaccinations in the US; BNT162b1 was developed by Pfizer and mRNA-1273 by Moderna and both were mRNA-based vaccines [14–16]. These vaccines use a lipid-based delivery platform and an almost identical antigen, a pre-fusion stabilized SARS-CoV-2 spike protein-encoding mRNA. The vaccines differ in their proprietary lipid delivery platform and the amount of antigen used (30 μg for Pfizer and 100 μg for Moderna). A recent phase 3 study with both vaccines indicated that both bestowed an exceptionally high protection level of about 95% in preventing symptomatic COVID-19 disease and 100% prevention of severe COVID-19 disease [15,16]. The mRNA vaccines also induced a robust CD4 cytokine response involving type 1 helper T (Th1) cells among participants [17,18]. While the clinical results are outstanding, the stability of this protective immune response beyond four months is unknown, and little is known about whether this new platform can provide long-term immunity [19]. The presence of CD4+ memory T cells in humans vaccinated with the Pfizer vaccine suggests a supportive memory phenotype [17]. The mRNA vaccine's primary drawback is the adverse effects induced one day following vaccination, which is more prominent after the second shot. Further studies need to be performed to verify the safety of additional boosters with this platform in case of waning immune responses or emerging new virus variants. These adverse effects may be either due to the antigen used or the delivery platform. If the adverse effect is caused by the delivery vehicles, further use of such vaccines for boosting or other pathogen vaccines would be concerning. An additional drawback of the mRNA vaccines is the strict low-temperature storage requirement, making large stockpiling almost impossible and disqualifying these vaccines for most of the world population. In summary, mRNA has been developed rapidly and proven to be a highly efficient vaccine for the developed world during the pandemic. Safety and efficacy studies are pending in children below 16–18 years, pregnant women, and immunocompromised individuals. The cost and temperature sensitivity significantly affect the feasibility of use for containing the COVID-19 pandemic worldwide.

Replication-incompetent adenoviruses

The Oxford-AstraZeneca-developed vaccine, referred to as *AZD1222* or *ChAdOx1 nCoV-19* or the Oxford vaccine, is based on a replication-incompetent chimpanzee-based simian adenovirus (Ad) vector containing the full-length codon-optimized coding sequence of SARS-CoV-2 spike protein along with a tissue plasminogen activator (tPA) leader sequence [20,21]. Unlike human adenoviral vectors like Ad5 or Ad26, the use of viruses naturally not present in the human population avoids the concern of pre-existing vector-based immunity. Safety, immunogenicity, and efficacy data support a two-dose regime, boosting binding antibodies after the second dose [22–25]. Interestingly, the two-dose regime did not boost the neutralizing titers after the second dose [24]. However, live viral vectors induce vector antibodies that might prevent multiple boosting with this platform. Heterologous prime-boost with Adenovirus prime and a Poxvirus boost have previously shown to be more effective in boosting titers than homologous prime-boost strategies [26,27]. Therefore, the Oxford vaccine might serve more like a single-shot vaccine in terms of immunogenicity. The Oxford vaccine's initial publication showed that in a UK trial, two immunizations with a low dose (LD) prime and a standard dose (SD) boost could provide efficacy of up to 90% and an efficacy of 62.1% in the SD/SD cohort. In contrast, interim safety and efficacy data for ChAdOx1 nCoV-19 evaluated in four trials across three continents (Brazil, South Africa, and the UK) showed vaccine efficacy of 70.4% after two SD doses and protection of 64.1% after one SD dose against symptomatic disease [23]. There have been significant concerns with the ChAdOx1 nCoV-19 trials. The safety study was performed with the administration of a pain reliever before vaccination; the efficacy study yielded substantially lower efficacy in the SD/SD cohort; and, lastly, there have been reports of serious adverse events [25,28]. A recent study showed that a single dose provided an efficacy of 76%, and increasing the time interval between the first and the second dose to 12 weeks enhanced efficacy to 82.4% [29]. Additionally, the single dose induces a Th1-biased T cell and antibody response in humans [30]. Although the efficacy is lower than the mRNA vaccines, especially in older adults, the vaccine's stability at fridge temperature makes it a feasible candidate as a worldwide vaccine [24]. In late December 2020-early January 2021, the Oxford vaccine received emergency use approval in the UK and India (commercial name-COVISHIELD™), and on January 29, 2021, it received emergency approval from the European Union (EU).

Another replication-incompetent adenovirus vectored COVID-19 vaccine, *Ad26.COV2.S*, developed by Johnson and Johnson (J&J) received emergency approval on February 26, 2021. The single-shot J&J vaccine, which encodes a full-length and pre-fusion stabilized SARS-CoV-2 spike protein, was 66% effective at preventing moderate to severe COVID-19 and 85% protective against the most severe symptoms [31,32]. Interestingly, the phase 1–2a results reported milder adverse effects after the boost, contrary to the mRNA vaccines, suggesting that such side-effects are more likely based on delivery vehicles than the antigen. However, the lower side effects in the second round of immunization suggest a less efficient viral replication due to vector-directed immunity, raising questions on the booster capabilities of this platform. Detectable, lower CD8+ T-cell responses were reported in older adults, but the importance of CD8+ T cells in protection against SARS-CoV-2

is unknown. One significant advantage of the Ad26. COV2.S is the initial relatively potent VNA against SARS-CoV-2 after one immunization, suggesting its use as a single-shot vaccine [32]. Although extensive phase 3 studies are needed to confirm the single-shot vaccine's efficacy, efficacy is lower with around 65% protection [33]. Compared to mRNA vaccines, the Ad26 might be less efficient in the over 65 age group, who generally have reduced immune responses. In that regard, the mRNA vaccines elicit a different response, with higher side effects after the second injections but better efficacy in the older population (93–94%). mRNA-based vaccines are highly immunogenic, causing the highest adverse effects, with still unknown long-term impact. Of note, a single inoculation with the Ad26. COV2.S induced higher VNA titers than a single inoculation with mRNA vaccines but lower VNA titers than the two inoculations with mRNA vaccines. Similar to the mRNA-based vaccine, Ad26.COV2.S also induces a strong Th1 biased immune response [33]. Although a two-dose regime's efficacy is currently being evaluated, previous research using an Ad26 based vaccine against the Ebola virus required boosting with an unrelated viral vector (Modified Vaccinia Ankara) to achieve improved efficacy [34•].

Gam-COVID-Vac or *Sputnik V* is a combined vector vaccine based on two replication-deficient rAd26 and rAd5 viral vectors that carry the gene SARS-CoV-2 full-length glycoprotein S (rAd26-S and rAd5-S). It was the first vaccine in the world to receive approval (in Russia) in August 2020 and received sharp criticism. rAd26-S and rAd5-S are administered intramuscularly separately with a 21-day interval, intended to overcome any pre-existing adenovirus immunity in the population. Immunogenicity data shows the absence of neutralizing antibodies until the boost on day 21 [35]. Although the Sputnik V reports substantially lower neutralizing titers than the mRNA, Oxford, or the Ad26.COV2.S vaccines, the trial reports an efficacy of 91.6% against COVID-19 [36]. Similar protection was also extended to adults older than 60 years of age. Since the reported efficacy does not align with the neutralizing titers, the efficacy seen may be due to country-specific lock-down restrictions. More extensive cohort studies may be required in other countries to verify the efficacy results. Lastly, the Sputnik V vaccine has a significant advantage in that it can be lyophilized without affecting immunogenicity, circumventing the need for continuous cold-chain storage.

In summary, all three replication-deficient adenovirus-based vaccines have been shown to be beneficial in people under 65, with a more significant advantage seen with the single-shot Ad26.COV2.S vaccine. Additionally, the adenovirus vaccine has not yet proven long-term immunity in humans.

Subunit protein-based vaccine

NVX-CoV2373, a nanoparticle vaccine developed by Novavax, is composed of trimeric prefusion stabilized full-length SARS-CoV-2 spike glycoproteins and the saponin-based Matrix-M1 adjuvant [37]. The safety and immunogenicity study reported a dramatic boost in binding and neutralizing titers in the adjuvanted groups after the second immunization. More importantly, neutralizing antibody responses after the second vaccination in the adjuvanted groups exceeded values seen in symptomatic COVID-19 outpatients as well as convalescent serum from hospitalized patients with COVID-19. The T cell responses, binding, and neutralizing antibody responses were similar in the 5 μg and 25 μg NVX-CoV2373 Matrix-M1 adjuvanted groups, highlighting the benefit of the adjuvant in antigen-dose sparing [38]. The nanoparticle platform has the advantage of safety data on more than 14 000 participants in various vaccine trials, including children, pregnant women, older adults, and more than 4300 participants exposed to Matrix-M1 adjuvant, from 5 months to 85 years of age. The safety profile and stability of the vaccine and adjuvant at fridge temperatures make NVX-CoV2373 a promising candidate.

Inactivated SARS-COV-2

Three safety and immunogenicity Phase 1/2 studies have been conducted by different companies (Sinopharm, Sinovac, and Bharat Biotech) utilizing the inactivated SARS-CoV-2 virus adjuvanted aluminum hydroxide [39–41]. All three studies followed a prime-boost regime and reported a significant increase in binding and neutralizing antibodies after the second immunization. The advantage of the inactivated vaccine platform is the relatively lower adverse events reported compared to mRNA or the Oxford vaccines, multiple boosting capability, and the excellent safety and immunogenicity profile in older adults [40]. The Sinopharm and Sinovac vaccines have received emergency use approval in China and UAE, and the Bharat Biotech vaccine has received emergency use approval in India.

Vaccines and SARS-CoV-2 variants: outlook

The rapidly spreading SARS-Cov-2 virus has led to rapid progress in vaccine development. Widespread whole genome sequencing (WGS) efforts have allowed researchers to track the spread of different lineages globally. Some mutations have emerged that appear to be advantageous to the virus by providing fitness and facilitating the faster spread of particular lineages, such as the recently described variant of concern 202012/01 (B.1.1.7) lineage in the UK. The emergence of variants of SARS-CoV-2 has raised concerns about the ability of the approved vaccines to neutralize the variants [42••]. A lentivirus-based pseudovirion assay with the UK variant showed that human sera from Pfizer, Moderna, and Novavax vaccinated individuals remained sensitive to

neutralization, with moderately reduced levels in comparison to wild-type virus [43]. Meanwhile, the South African (SA) variant emerged with several mutations in the spike protein, specifically RBD, that cause a dramatic reduction in convalescent serum neutralizing titers. A recent study has shown a small reduction, but preserved neutralization, in sera from Pfizer BNT162b2 vaccine individuals [44]. Sera from individuals vaccinated with the Moderna and Pfizer mRNA vaccine showed a small but significant reduction in neutralizing potential against the variants, with the most profound effect seen with the RBD mutation of E484K seen in the SARS-CoV-2 SA variant [45]. A preprint publication has reported that the two-dose regimen of ChAdOx1-nCoV19 did not protect against mild-moderate COVID-19 caused by the SA variant (B.1.351) [46]. The Ad26.COV2.S also reportedly reduced efficacy of 57% in the SA trials [47]. These results suggest that all vaccines may need to be periodically updated to maintain efficacy.

The emergence of variants has highlighted the importance of conducting clinical trials in several countries in order to account for variants and health and economic status while assessing efficacy. The Novavax NVX-CoV2373 study found that vaccine efficacy was 89% in the UK and 60% in South Africa [48]. The J&J Ad26. COV2.S study found that efficacy was 72% in the US, 66% in Brazil, and 57% in South Africa [47]. The rise of variants may be attributed to the intrinsic nature of RNA viruses to evolve, as well as the geographic spread of the virus leading to distinct variants. The emergence of the variant B.1.1.7 in the United Kingdom was first detected in September 2020 and is now the most predominant form of SARS CoV-2 in the US. The SA variant called B.1.351, which was detected in January 2021 may have the ability to re-infect people who have recovered from earlier versions of the SARS CoV-2 infections, in addition to being somewhat resistant to some of the coronavirus vaccines in development as seen by the reduced neutralizing potential in comparison to the parental and the UK strain [45,46]. The deficit in worldwide vaccine coverage coinciding with the widespread prevalence of the SARS CoV-2 may have been a contributing factor for the rise of these variants.

The lack of vaccines for children, pregnant women, and immunocompromised individuals poses a significant risk to the population. With the rise of fast-spreading and more infectious variants and asymptomatic individuals being 75% as infectious as symptomatic COVID-19 patients, the pandemic is more difficult to control [49]. WHO has provided the following recommendation concerning the new variants: (1) governments should make increased efforts to prevent the spread of the variants; (2) manufacturers should be prepared to adjust to the SARS-CoV-2 viral evolution to potentially provide future booster shots; (3) trials should be designed to allow any

changes in efficacy to be assessed; (4) genomic surveillance should be enhanced; (5) high-risk groups worldwide should receive priority vaccination (6) Governments and donors support the COVAX initiative in order to ensure equitable access and delivery of vaccines [50]. The slow vaccine rollout in the US and UK and the struggle of low-income and middle-income countries to obtain even a minimum number of vaccine doses along with widespread vaccine hesitancy have significantly hampered the control of SARS-CoV-2. Despite these barriers, on-going studies demonstrating the efficacy of current vaccines against the variants gives us a fighting chance for controlling the pandemic and holds the promise of saving countless lives.

Conflict of interest statement
M.J.S. and D.K. are coinventors of the patent application 'Coronavirus disease (COVID-19) vaccine'.

Acknowledgements

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Andre FE, Booy R, Bock HL *et al.*: **Vaccination greatly reduces**
•   **disease, disability, death and inequity worldwide**. *Bull World Health Organ* 2008, **86**:140-146.
A comprehensive review of the biology of coronaviruses.

2. V'Kovski P, Kratzel A, Steiner S, Stalder H, Thiel V: **Coronavirus biology and replication: implications for SARS-CoV-2**. *Nat Rev Microbiol* 2021, **19**:155-170.

3. *World Health Organization Coronavirus Disease (COVID-19)*
•• *Dashboard*. 2021 . . [Accessed on 26 February 2021] *https:// covid19.who.int/*.
This is the link to the newest information of the WHO on the current cases of Covid- 19 and vaccine information.

4. Mosby K: In *Immunology for Pharmacy*. Edited by Flaherty DK. 2012. Chapter 25 - Vaccine-Preventable Disease.

5. Hu B, Guo H, Zhou P, Shi ZL: **Characteristics of SARS-CoV-2 and COVID-19**. *Nat Rev Microbiol* 2021, **19**:141-154.

6. Krammer F: **SARS-CoV-2 vaccines in development**. *Nature* 2020, **586**:516-527.

7. Lau EHY, Tsang OTY, Hui DSC *et al.*: **Neutralizing antibody titres in SARS-CoV-2 infections**. *Nat Commun* 2021, **12**:63.

8. Grifoni A, Weiskopf D, Ramirez SI *et al.*: **Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals**. *Cell* 2020, **181**:1489-1501 e15.

9. Poland GA, Ovsyannikova IG, Kennedy RB: **SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates**. *Lancet* 2020, **396**:1595-1606.

10. Dan JM, Mateus J, Kato Y et al.: **Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection**. *Science* 2021, **371**.

11. Seow J, Graham C, Merrick B et al.: **Longitudinal observation
•• and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans**. *Nat Microbiol* 2020, **5**:1598-1607.
This paper addresses the concerns of weaning antibody responses after natural infection with SARS-CoV-2.

12. Self WH, Tenforde MW, Stubblefield WB et al.: **Decline in SARS-CoV-2 antibodies after mild infection among frontline health care personnel in a multistate hospital network - 12 states, April–August 2020**. *MMWR Morb Mortal Wkly Rep* 2020, **69**:1762-1766.

13. Robbiani DF, Gaebler C, Muecksch F et al.: **Convergent antibody responses to SARS-CoV-2 in convalescent individuals**. *Nature* 2020, **584**:437-442.

14. Jackson LA, Anderson EJ, Rouphael NG et al.: **An mRNA vaccine against SARS-CoV-2 - preliminary report**. *N Engl J Med* 2020, **383**:1920-1931.

15. Polack FP, Thomas SJ, Kitchin N et al.: **Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine**. *N Engl J Med* 2020, **383**:2603-2615.

16. Baden LR, El Sahly HM, Essink B et al.: **Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine**. *N Engl J Med* 2021, **384**:403-416.

17. Sahin U, Muik A, Derhovanessian E et al.: **COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses**. *Nature* 2020, **586**:594-599.

18. Anderson EJ, Rouphael NG, Widge AT et al.: **Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults**. *N Engl J Med* 2020, **383**:2427-2438.

19. Widge AT, Rouphael NG, Jackson LA et al.: **Durability of responses after SARS-CoV-2 mRNA-1273 vaccination**. *N Engl J Med* 2021, **384**:80-82.

20. van Doremalen N, Lambe T, Spencer A et al.: **ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques**. *Nature* 2020, **586**:578-582.

21. Watanabe Y, Mendonca L, Allen ER et al.: **Native-like SARS-CoV-2 spike glycoprotein expressed by ChAdOx1 nCoV-19/AZD1222 vaccine**. *bioRxiv* 2021.

22. Barrett JR, Belij-Rammerstorfer S, Dold C et al.: **Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses**. *Nat Med* 2021, **27**:279-288.

23. Voysey M, Clemens SAC, Madhi SA 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**:99-111.

24. Ramasamy MN, Minassian AM, Ewer KJ et al.: **Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial**. *Lancet* 2021, **396**:1979-1993.

25. Folegatti PM, Ewer KJ, Aley PK 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**:467-478.

26. Folegatti PM, Bellamy D, Roberts R et al.: **Safety and immunogenicity of a novel recombinant simian adenovirus ChAdOx2 as a vectored vaccine**. *Vaccines (Basel)* 2019, **7**.

27. Stylianou E, Griffiths KL, Poyntz HC et al.: **Improvement of BCG protective efficacy with a novel chimpanzee adenovirus and a modified vaccinia Ankara virus both expressing Ag85A**. *Vaccine* 2015, **33**:6800-6808.

28. Knoll MD, Wonodi C: **Oxford-AstraZeneca COVID-19 vaccine efficacy**. *Lancet* 2021, **397**:72-74.

29. Voysey M, Costa Clemens SA, Madhi SA et al.: **Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials**. *Lancet* 2021.

30. Ewer KJ, Barrett JR, Belij-Rammerstorfer S et al.: **T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial**. *Nat Med* 2021, **27**:270-278.

31. Bos R, Rutten L, van der Lubbe JEM et al.: **Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 spike immunogen induces potent humoral and cellular immune responses**. *NPJ Vaccines* 2020, **5**:91.

32. Sadoff J, Le Gars M, Shukarev G et al.: **Interim results of a phase 1-2a trial of Ad26.COV2.S Covid-19 vaccine**. *N Engl J Med* 2021.

33. COVID-19 Vaccine Ad26.COV2.S: **Janssen Biotech, Inc. Sponsor Briefing Document.** *Vaccines and Related Biological Products Advisory Committee Meeting*. https://www.fda.gov/media/146219/download. [26 FEBRUARY 2021].

34. Pollard AJ, Launay O, Lelievre JD et al.: **Safety and
• immunogenicity of a two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in adults in Europe (EBOVAC2): a randomised, observer-blind, participant-blind, placebo-controlled, phase 2 trial**. *Lancet Infect Dis* 2020.
This publication addresses the need of another viral vector for boosting after priming with an adenoviral vector.

35. Logunov DY, Dolzhikova IV, Zubkova OV et al.: **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**. *Lancet* 2020, **396**:887-897.

36. Logunov DY, Dolzhikova IV, Shcheblyakov DV et al.: **Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia**. *Lancet* 2021, **397**:671-681.

37. Tian JH, Patel N, Haupt R et al.: **SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice**. *Nat Commun* 2021, **12**:372.

38. Keech C, Albert G, Cho I et al.: **Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine**. *N Engl J Med* 2020, **383**:2320-2332.

39. Ella R, Vadrevu KM, Jogdand H et al.: **Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial**. *Lancet Infect Dis* 2021.

40. Xia S, Zhang Y, Wang Y et al.: **Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial**. *Lancet Infect Dis* 2021, **21**:39-51.

41. Zhang Y, Zeng G, Pan H et al.: **Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial**. *Lancet Infect Dis* 2021, **21**:181-192.

42. Williams TC, Burgers WA: **SARS-CoV-2 evolution and vaccines:
•• cause for concern?** *Lancet Respir Med* 2021.
This review analyzes the current knowledge of SARS-CoV-2 evolution and its possible effects on the efficacy of vaccine.

43. Shen X, Tang H, McDanal C et al.: **SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines**. *bioRxiv* 2021.

44. Xie X, Liu Y, Liu J et al.: **Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera**. *Nat Med* 2021.

45. Wang Z, Schmidt F, Weisblum Y *et al.*: **mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants**. *Nature* 2021.

46. Madhi SA, Baillie V, Cutland CL *et al.*: **Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa**. *medRxiv* 2021. 2021.02.10.21251247.

47. *Johnson & Johnson Announces Single-shot Janssen Covid-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 Ensemble Trial*. Johnson & Johnson; 2021. Posted January 29, 2021. https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial. [Accessed 2 March 2021].

48. *Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial*. 2021 . , January 28 In: *https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3*.

49. Johansson MA, Quandelacy TM, Kada S *et al.*: **SARS-CoV-2 transmission from people without COVID-19 symptoms**. *JAMA Netw Open* 2021, **4**:e2035057.

50. *COVAX Statement on New Variants of SARS-CoV-2*. 2021. Posted on 8 February 2021. https://www.who.int/news/item/08-02-2021-covax-statement-on-new-variants-of-sars-cov-2. [Accessed on 2 March 2021].