Immunogenicity, efficacy and safety of COVID-19 vaccines: an update of data published by 31 December 2021

Authors

Kun Xu[1,2], Chunxiang Fan[3], Yuxuan Han[4], Lianpan Dai[2,4,5] and George F. Gao[4,5]

Affiliations

[1]Research Network of Immunity and Health (RNIH), Beijing Institutes of Life Science, Chinese Academy of Sciences, Beijing 100101, China

[2]Key Laboratory of Tropical Translational Medicine of Ministry of Education, School of Tropical Medicine and Laboratory Medicine, The First Affiliated Hospital, Hainan Medical University, Hainan 571199, China

[3]National Immunization Programme, Chinese Center for Diseases Control and Prevention, Beijing 100050, China

[4]Savaid Medical School, University of Chinese Academy of Sciences, Beijing 101408, China

[5]CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China

Correspondence to: G. F. Gao; E-mail: gaof@im.ac.cn

Abstract

The unprecedented coronavirus disease 2019 (COVID-19) pandemic has caused a disaster for public health in the last 2 years, without any sign of an ending. Various vaccines were developed rapidly as soon as the outbreak occurred. Clinical trials demonstrated the reactogenicity, immunogenicity and protection efficacy in humans, and some of the vaccines have been approved for clinical use. However, waves of infections such as the recently circulating Omicron variant still occur. Newly emerging variants, especially the variants of concern, and waning humoral responses pose serious challenges to the control of the COVID-19 pandemic. Previously, we summarized the humoral and cellular immunity, safety profiles and protection efficacy of COVID-19 vaccines with clinical data published by 21 May 2021. In this review, we summarize and update the published clinical data of COVID-19 vaccines and candidates up to December 31, 2021.

Keywords: antibody, SARS-CoV-2, vaccine effectiveness, vaccine efficacy, cellular immune response

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented disaster for humans (1). To control and prevent the disease and reduce transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, vaccine development was rapidly initiated worldwide, using different targets and platforms (2-4). After the proof-of-concept and pre-clinical studies, clinical studies (Phase 1, 2 and 3) were conducted for vaccine safety and efficacy evaluation in humans.

Previously, we summarized the COVID-19 vaccine development progress up to May 2021, including the humoral and cellular immunity and safety of COVID-19 vaccines from published articles (5). Table 1 summarizes the protection efficacy in Phase 3 clinical trials and effectiveness in the real world studies for preventing COVID-19 about some of those vaccines and Table 2 summarizes findings from some newer vaccines. To date, 331 COVID-19 vaccine candidates have been developed, and 30 of them have been approved for use in at least one country or region worldwide under authorization (Fig. 1). Although large-scale vaccination campaigns were continued, new SARS-CoV-2 variants emerged, circulated and caused breakthrough infections. A waning humoral immune response to COVID-19 vaccines was observed and boost doses were administered. Therefore, we have updated the progress of the COVID-19 vaccines and candidates up to December 31, 2021 in this review.

mRNA vaccines

BNT162b2 (Comirnaty) is an mRNA vaccine expressing a prefusion-stabilized spike protein (S protein) with K986P and V987P substitutions (S-2P protein). Vaccination with BNT162b2 in adults induces innate and adaptive immune responses (6). Anti-viral polyfunctional and long-lived CD4 and CD8 T cells with T helper type 1 (Th1) polarization are induced (6-9). Two doses of BNT162b2 induce strong humoral immune responses in children, adolescents, younger adults and older adults (10-12). Six months after the second dose of the BNT162b2 vaccination, levels of receptor-binding domain (RBD)-binding antibodies and neutralizing-antibodies (NAbs) substantially decrease, especially among people aged 65 years or older (13,14). Therefore, a third dose can be administered to boost the antiviral immune response. The reports revealed that at 1 month after dose 3, NAb geometric mean titers (GMTs) against the prototype virus increased to more than 5–7 times as high as the GMTs at 1 month after dose 2. In addition, the breadth of neutralized SARS-CoV-2 variants also increased with dose 3 (15,16).

Immune responses induced by BNT162b2 against SARS-CoV-2 variants have been previously reported (5). The Omicron variant, defined as a new Variant of Concern (VOC) in late 2021, began to circulate globally and showed the highest resistance to NAbs induced by infection with ancestral SARS-CoV-2 (prototype and D614G) and by licensed COVID-19 vaccine immunization, including BNT162b2 (NAb GMT reduction of 22-fold compared with D614G) (17). Beta and Gamma VOCs also extensively escape NAbs induced by BNT162b2 in humans (18-21). In addition, Delta, Kappa, Epsilon and Iota variants show slight or moderate escape from BNT162b2-elicited NAbs (22-27). However, T cell-mediated immunity elicited by BNT162b2 was not affected by mutations in SARS-CoV-2 variants, such as Alpha and Beta VOCs (28).

The results of Phase 3 clinical trials of BNT162b2 revealed that vaccine efficacies against symptomatic COVID-19 and severe disease were 91.3% and 96.7%, respectively, after 6 months of follow-up (29) (Table 1). The effectiveness of two-doses of BNT162b2 in the real-world have been reported as follows: i) 91% and 96% against symptomatic COVID-19 infection and severe outcomes (hospitalization and death) respectively, in Canada (30); ii) 91.3% against COVID-19 in New York, USA (31); iii) 83.3% and 90.6% against SARS-CoV-2 infection and COVID-19-related mortality, respectively, in Hungary (32); iv) 83% against Alpha VOC infection in Italy (33); v) 93.7% and 88.0% against symptomatic disease caused by the Alpha and Delta VOCs, respectively, in the UK (34); vi) 90% against death from the Delta VOC in Scotland (35); and vii) 51.9% and 93.4% against Delta VOC infection and Delta-induced severe, critical or fetal disease, respectively (36) and 89.5% and 75.0% against infection with the Alpha and Beta VOCs, respectively, in Qatar (37).

In addition, the decline in BNT162b2 vaccine effectiveness against SARS-CoV-2 infection between 1 month and 5 months after the second-dose vaccination was observed in other studies in the USA and Qatar, probably because of waning neutralizing antibody titers over time. However, the effectiveness of BNT162b2 against hospital admissions for severe disease was high until 6 months after vaccination (38-40). By analyzing the viral loads of breakthrough infections in Israel, it was found that the viral loads were lower in vaccinees who received single or full doses of BNT162b2 than those in unvaccinated individuals. This effect began to decline 2 months post vaccination and even vanished at 6 months or longer, as did vaccine effectiveness (41-43). The booster vaccine dose could restore the effect of BNT162b2 on reducing viral loads in breakthrough infections and significantly enhance the effectiveness against COVID-19-related hospitalization, severe disease and death (41,42,44).

Another mRNA vaccine, mRNA-1273 (SpikeVax) contains mRNA expressing the S-2P protein. Vaccine mRNA-1273 induces strong humoral and specific T-cell responses in adolescents, younger adults and older adults (45,46). Robust and rapid polyfunctional CD4 T cell generation, a gradual CD8 T-cell response and a durable T cell memory induced by mRNA-1273 have been observed (47-49). In addition, T cells of vaccinees effectively recognize variants, including Alpha, Beta, Gamma and Epsilon (50). Comprehensive analysis of neutralization of SARS-CoV-2 variants by plasma revealed that lineages with E484K and N501Y/T mutations were greatly reduced, followed by lineages with L452R (27).The NAb activity of sera from mRNA-1273 recipients against the prototype D614G virus decreased at 6 months post vaccination, and NAb titers against Beta, Gamma and Delta VOCs were low and even undetectable (13,51-53). A third dose of mRNA-1273 at 6 months induced increased NAb activity against the prototype virus and key VOCs and Variants of Interest (VOIs) (52).

The final analysis of Phase 3 clinical trials of mRNA-1273 revealed that the vaccine efficacies in preventing symptomatic COVID-19, severe disease and asymptomatic infection were 93.2%, 98.2% and 63.0%, respectively (54) (Table 1). The effectiveness of two doses of mRNA-1273 in the real world was reported as follows: i) 94% and 96% against symptomatic COVID-19 infection and severe outcomes (hospitalization and death), respectively, in Ontario, Canada (30); ii) 88.7% and 93.6% against SARS-CoV-2 infection and COVID-19-related mortality, respectively, in Hungary (32); iii) 73.1% and 96.1% against any Delta VOC infection and Delta-induced severe, critical or fetal disease, respectively, in Qatar (36); and iv) 86.7% and 97.5% against infection or hospital admission with the Delta

VOC, respectively, and the effectiveness against Delta VOC infection declined from 94.1% on Day 14–60 to 80.0% on Day 151–180 post vaccination in Southern California, USA (55).

CVnCoV is an mRNA vaccine candidate, developed by CureVac AG, Germany. It contains nucleotides without chemical modification, encapsulated in lipid nanoparticles (LNP), and also expresses the S-2P protein (56). The Phase 1 trial compared the immunogenicity of 2, 4, 6, 8 and 12 μg doses of CVnCoV and found that the humoral immune responses induced by CVnCoV were dosage-dependent (56). In addition, two doses of CVnCoV (12 μg) elicited similar RBD and S protein-binding IgG GMT levels and lower NAb GMT level in participants than those of human convalescent sera (HCS) (56). The results of a Phase 3 trial showed that two doses of CVnCoV (12 μg), 28 days apart, provided 48.2% and 70.7% protection efficacy against symptomatic COVID-19 and moderate-to-severe COVID-19, respectively (57) (Table 2). CVnCoV had an acceptable safety profile (56,57). Because of the emergence of SARS-CoV-2 variants and the other reasons, CureVac ceased the further development of CVnCoV candidate and focused on the next-generation vaccine candidates (57).

Adenovirus-based vaccines

AZD1222 (Vaxzevria) is a recombinant chimpanzee-adenovirus into which the gene encoding the SARS-CoV-2 full-length S protein was inserted and two doses were administered. Several new studies on the immunogenicity of AZD1222 have been published recently. A third dose (boost dose) of the AZD1222 vaccine elicited higher antibody titers and boosted T-cell responses (58). Although the NAb GMTs in AZD1222-elicited human sera were lower against the Delta VOC than against the prototype SARS-CoV-2, the levels of vaccine-induced CD4 and CD8 T-cell responses were similar to those against Delta and prototype viruses (59). After immunization with two doses of AZD1222, broad CD4 and CD8 T-cell coverage across the S protein was elicited, with polyfunctional Th1-dominated T-cell responses (60).

The Phase 3 clinical trials in the USA, Chile and Peru showed that the overall estimated vaccine efficacy against symptomatic COVID-19 was 74.0%, and vaccine efficacy for preventing SARS-CoV-2 infection was 64.3% (61) (Table 1). Another Phase 3 trial in Brazil found that AZD-1222 vaccine efficacy was 69% against any symptomatic COVID-19 caused by the Zeta (P.2) variant and 64% against the Gamma VOC with fewer disease cases (62).

In the real world, the effectiveness of two doses of the AZD-1222 vaccine was as follows: i) 71.5% and 88.3% against SARS-CoV-2 infection and COVID-19-related mortality, respectively, in Hungary (32); ii) 74.5% and 67.0% against symptomatic disease caused by the Alpha and Delta VOCs, respectively, in the UK (34); iii) 91% against death from the Delta VOC in Scotland (35); and iv) 63.1% and 81.5% against virus infection and preventing moderate-to-severe COVID-19 during the delta VOC surge in India (59). In addition, at 2–3 and 18–19 weeks after the second dose of AZD-1222, vaccine effectiveness decreased from 83.7% to 63.7% in Scotland when the Delta VOC was the most widespread one and from 86.4% to 42.2% in Brazil when the Gamma VOC was common (63).

Ad26.COV2.S was designed as a single administration of recombinant type 26 adenovirus expressing the SARS-CoV-2 S-2P protein in addition to two mutations at the furin cleavage site (R682S and R685G). Ad26.COV2.S induces durable humoral and cellular immune

responses for at least 8 months post vaccination (13,64). In particular, the expansion of NAb breadth against SARS-CoV-2 variants over this time period has been observed (13). The median pseudovirus NAb titers induced by Ad26.COV2.S were 5.0-fold and 3.3-fold lower against the Beta and Gamma VOCs, respectively, compared with the prototype virus (WA1/2020) (65). The vaccine elicited CD8 and CD4 T-cell responses and the central and effector memory responses were comparable among the prototype virus and Alpha, Beta, Gamma and Epsilon variants (65).

Ad26.COV2.S protected against moderate to severe-critical COVID-19 with an efficacy of 66.9% in multi-center Phase 3 clinical trials, at least 14 days after vaccination (66) (Table 1). In the real world, the vaccine effectiveness of Ad26.COV2.S against SARS-CoV-2 infection in the USA was 73.6% (67). Recently, a decline in effectiveness against laboratory-confirmed COVID-19 was observed, possibly caused by waning immunity and circulating of Delta VOC (31).

Ad5-nCoV (Convidecia) is a recombinant human type 5 adenovirus expressing the SARS-CoV-2 full-length S protein. Previous reports on the results of Phase 1 and Phase 2 trials showed that a single dose of Ad5-nCoV administered intramuscularly induced specific humoral and cellular immune responses (68,69). Another Phase 1 trial was conducted to evaluate the safety, tolerability and immunogenicity of aerosolized Ad5-nCoV in adults. The immune responses induced by an intramuscular injection, aerosol inhalation or intramuscular injection prime followed by an aerosol inhalation boost were compared. The results indicated that aerosolized Ad5-nCoV was well tolerated, and two doses of aerosolized Ad5-nCoV elicited similar levels of NAb response to one dose of intramuscular injection. Priming by intramuscular injection and boosting by inhalation, which were separated by 28 days, induced stronger IgG and NAb responses than single-dose intramuscular injection and two-dose inhalation (70).

Recently, the final efficacy analysis of single-dose Ad5-nCoV (intramuscular administration) in Phase 3 was released, with 63.7% and 57.5% protection against symptomatic COVID-19 at 14 and 28 days or more post vaccination, respectively (71) (Table 1).

Gam-COVID-Vac (Sputnik V) is a two-dose vaccine regimen with a recombinant adenovirus 26 prime and a recombinant adenovirus 5 boost, both carrying the gene for the SARS-CoV-2 S protein. The kinetics of antibodies induced by Gam-COVID-Vac up to 6 months after immunization in Argentina were analyzed and it was found that anti-RBD titers began to decrease between 28 and 60 days post vaccination, remained stable between 60 and 90 days post vaccination, and decreased to a low level at 180 days post vaccination, with 31% of sera positive for anti-RBD antibody (72). The Gam-COVID-Vac-elicited sera neutralized the Alpha VOC with a similar level compared with the prototype but the Beta VOC partially escaped with a GMT reduction of 6.1-fold compared with the prototype (73). In addition, reduced neutralizing activities against the Gamma VOC compared with the prototype virus were observed (74).

In Phase 3 clinical trials, Gam-COVID-Vac provided 91.6% prevention efficacy against COVID-19 21 days after the first dose (Table 1). In Hungary, the effectiveness of Gam-COVID-Vac against SARS-CoV-2 infection and COVID-19-related mortality was 85.7% and 97.5%, respectively (32). In addition, the first dose of Gam-COVID-Vac could confer 78.6%

and 84.8% effectiveness for preventing SARS-CoV-2 infection and COVID-19-related death, respectively, in 60–79-year-old vaccinees as conducted in Argentina (75). Because of the shortage in the supply of vaccines, Sputnik Light was developed with a single-dose immunization of a recombinant adenovirus type 26 vector expressing the SARS-CoV-2 S protein. The results of the Phase1/2 trial reported that Sputnik Light induced IFN-γ release from T cells, RBD-specific IgG and NAb production, with a GMT lower than that in a panel of convalescent plasma (76).

Protein subunit vaccines

ZF2001 (ZIFIVAX) is a protein subunit vaccine jointly developed by us and Anhui Zhifei Longcom Biopharmaceutical Co., Ltd. ZF2001 contains the SARS-CoV-2 tandem-repeat dimeric RBD protein, which showed higher immunogenicity than monomeric RBD protein, and the aluminum hydroxide adjuvant (77). In the Phase 1 and 2 clinical trials, we demonstrated that ZF2001 induced robust humoral immune responses and balanced cellular immune responses in humans, with low reactogenicity (78). In addition, we also found that the ZF2001-elicited sera efficiently neutralize the SARS-CoV-2 variants with a range of GMT reduction folds between 1.1 and 2.1 for Beta, Gamma, Epsilon, Eta, Kappa and Delta variants, demonstrated by pseudotyped-virus neutralization assays (79). Humoral immune responses in ZF2001 vaccines exhibit higher tolerance to Beta VOC than convalescents do, because the induced anti-RBD NAbs display a high diversity and are unaffected by the N-terminal domain (NTD) of the S protein mutations, characterized by neutralization assays of plasma and high-throughput single-cell VDJ sequencing of peripheral blood mononuclear cells (PBMCs) from vaccinees and convalescents (80).

Following the circulating of Omicron VOC, we tested the ZF2001-clicited human sera and found that three doses of ZF2001 administration with a long interval (4-6-month) between the second and third doses elicited higher NAb levels against the Omicron VOC than those with a short interval (less than 2-month) (81). The NAb GMTs against the Omicron VOC were 3.1 and 10.6 folds lower than those against the prototype in the recipients with long interval and short interval vaccination, respectively (81). Therefore, a boost strategy with an extended interval would be beneficial for enhanced and broad humoral immune responses against SARS-CoV-2 variants, including Omicron. In addition, recently, we released the data of Phase 3 clinical trials, which showed that ZF2001 conferred efficacies in preventing symptomatic and severe-to-critical COVID-19 of 81.4% and 92.9%, respectively, with short-term (~50 days) follow-up, and of 75.7% and 87.6% respectively, with long-term (6 months) follow-up (Table 1). The vaccine efficacies preventing Alpha and Delta VOCs were 92.7% and 81.4% in the short-term follow-up, and 88.3% and 76.1% in the long-term follow-up, respectively (82).

NVX-CoV2373 (Nuvaxovid) is composed of a trimeric full-length S-2P protein with another three mutations at the furin cleavage site (R682Q, R683Q and R685Q), adjuvanted with Matrix-M1 (83). A Phase 2 trial found that a two-dose regimen of 5-μg NVX-CoV2373 was immunogenic and well tolerated in both younger and older adults, with serum neutralization GMTs exceeding those seen in a panel of HCS (84). In Phase 3 clinical trials, two 5-μg doses of NVX-CoV2373 provided 90.4% efficacy protection against COVID-19 in the USA and Mexico, in which most cases were caused by VOCs and VOIs (largely Alpha) (85)

(Table 1). Another study in South Africa showed that the efficacy of the NVX-CoV2373 vaccine was 60.1% in HIV-negative participants during circulation of the Beta VOC in South Africa (86). In the UK, 89.7% protection was observed, with an efficacy of 86.3% against the Alpha VOC (87).

Seasonal influenza epidemics occur globally. An annual influenza vaccination is recommended for prevention in many countries. This continued large-scale COVID-19 vaccination campaign will certainly coincide with the influenza vaccination. A sub-study was conducted in the UK to evaluate the safety, immunogenicity and efficacy of NVX-CoV2373 co-administered with licensed seasonal influenza vaccines. The results showed that the incidence of adverse events was low and balanced between the co-administration group and the NVX-CoV2373-alone group. Although a reduction in antibody responses to the NVX-CoV2373 vaccine was observed in the co-administration groups, the NVX-CoV2373 vaccine efficacy in the sub-study was 87.5%, similar to the efficacy in the main study (88).

Another recombinant COVID-19 vaccine developed by West China Hospital of Sichuan University, China (89) (Table 2) contains the SARS-CoV-2 RBD protein and has an aluminum hydroxide adjuvant. Both this RBD immunogen and the previously described spike immunogen used in the NVX-CoV2373 vaccine were grown in Sf9 cells. The results of Phase 1 and 2 trials showed that the levels of humoral immune responses induced by this vaccine were highest in the participants receiving three doses (0, 14, 28 days) at a high dose (40 μg) among all the groups (90). In addition, cellular immune responses (IFN-γ release) could be elicited by this vaccine and the magnitude was highest in the 14 days after the last immunization. The most common adverse reactions were pain, fatigue, cough, sore throat, fever and headache, which were mild or moderate in severity (90). The results of Phase 1 and 2 trials demonstrated that this vaccine is safe and immunogenic in humans with three doses of administration (90).

MVC-COV1901 vaccine, developed by Medigen Vaccine Biologics Corporation, Taiwan, China, contains the S protein ectodomain with two proline substitutions at residues 986 and 987, a “GSAS” substitution at residues 682–-685 to abolish the furin cleavage site and a T4 fibritin trimerization motif; it is adjuvated by aluminum hydroxide and CpG 1018 (91,92).

MVC-COV1901 has a good safety profile in Phase 1 and 2 clinical trials (91,92). Two doses of 15 μg and 25 μg MVC-COV1901 vaccine both induced higher NAb levels than those of a panel of HCS (91). In the antibody titration assays, The World Health Organization (WHO) reference standard National Institute for Biological Standards and Control (NIBSC) was used to convert the NAb and binding-antibody GMTs to international units (IUs)/ml and binding-antibody units (BAUs)/ml, respectively (92). To confront the SARS-CoV-2 variants, the NAb activity against a pseudovirus with Beta VOC S protein declined significantly, compared with the prototype S protein pseudovirus (93). In addition, enzyme-linked immunospot (ELISpot) assays showed that MVC-COV1901 vaccine elicited IFN-γ-producing cells, but minimal IL-4-producing cells (91) (Table 2).

The Sclamp subunit vaccine contains the prefusion S ectodomain, replaces the furin cleavage site 680–690 with a glycine–serine–glycine linker, trimerized by a molecular clamp sequence from human immunodeficiency virus 1 (HIV-1) glycoprotein 41 (gp41) and is adjuvanted by MF59; it was developed by University of Queensland and CSL Limited, Australia (94). The results of a Phase 1 trial showed that Sclamp was well tolerated with

similar frequencies of adverse events to the placebo group (94). Two doses of Sclamp vaccine induced strong antigen-specific polyfunctional CD4 T-cell responses and NAb responses. The NAb GMTs were at similar levels among the 5, 15 and 45 μg groups (94) (Table 2). However, humoral responses against HIV-1 gp41 were elicited by the Sclamp vaccine, which could be detected by commonly used HIV diagnostic tests, posing the potential to impact existing HIV screening programmes. Therefore, studies are ongoing with alternative trimerization domains to ameliorate this response (94).

FINLAY-FR-1 and FINLAY-FR-1A contain a recombinant SARS-CoV-2 dimeric RBD protein adjuvanted by aluminum hydroxide (FINLAY-FR-1A) or adjuvanted by the outer membrane vesicles from *Neisseria meningitidis* group B (OMVs) plus aluminum hydroxide (FINLAY-FR-1); they were developed by Finlay Vaccine Institute and Centre of Molecular Immunology, Cuba (95). The recombinant dimeric RBD protein has two copies of the RBD protein (amino acid residues 319–541 with a poly-histidine fusion tag at its C-terminus) connected by a Cys538–Cys538 interchain disulphide bridge (95).

The NAb GMT induced by three doses of FINLAY-FR-1 (50 μg) was higher than those of FINLAY-FR-1A (25 and 50 μg), indicating that OMVs improved the immune response induced by the dimeric RBD protein (Table 2). The adverse events reported by participants who received FINLAY-FR-1 vaccine were higher than those reported by FINLAY-FR-1A vaccine, though serious adverse events were not found (95). Another study demonstrated that a booster dose of FINLAY-FR-1A (50 μg) to COVID-19 convalescents enhanced the magnitudes of NAb titers and cellular immune responses (96). These results of Phase 1 trials showed that both FINLAY-FR-1 and FINLAY-FR-1A were safe and immunogenic, and the addition of OMVs adjuvant increased the NAb responses (95,96).

Inactivated virus vaccines

BBIBP-CorV (Covilo) is an inactivated whole virus, adjuvanted with aluminum hydroxide. BBIBP-CorV is safe, well tolerated and immunogenic in participants aged 3–17, 18–59 and ≥ 60 years (97,98). The results of the Phase 3 trial showed that BBIBP-CorV conferred 78.1% protection against COVID-19 (99). The effectiveness of BBIBP-CorV against SARS-CoV-2 infection and COVID-19-related mortality in Hungary was 68.7% and 87.8%, respectively (32) (Table 1).

CoronaVac is composed of an inactivated virus and an aluminum hydroxide adjuvant. A study in Chile demonstrated that immunization with CoronaVac in a 0–14 day schedule induced IFN-γ-producing cellular responses and generation of NAbs with higher titers in participants aged 18–59 years than in adults aged ≥ 60 years (100). In addition, a Phase 1/2 clinical trial of CoronaVac conducted in China showed that two doses of CoronaVac were well tolerated and induced humoral responses in children and adolescents aged 3–17 years (101). However, vaccine-elicited circulating NAb titers declined substantially six months after the second dose.

To reduce the decrease in antibody levels after vaccination, a third dose was administered (102). Recently, the results showed that a third dose of CoronaVac in adults administered 8 months after the second dose effectively induced a remarkable increase in antibody levels (102). Specially, in the group of recipients received 3 μg CoronaVac, which is the licensed

formulation, with a 0-28 days-8 months schedule, the induced NAb GMTs were 45.9, 6.8 (slightly below the seropositive cutoff) and 143.1 at 28 days after the second dose, 6 months after the second dose and 28 days after the third dose, respectively. (102). The immune responses induced by CoronaVac against variants were evaluated and showed that 50% pseudovirus-neutralization titers in sera collected 14 days after the second dose decreased by 1.51-, 1.25-, 3.92-, 4.03- and 5.27-fold for Alpha, Epsilon, Gamma, Iota and Beta, respectively, compared with NAb levels against wild-type S pseudovirus (103). For the currently emerging and circulating Omicron VOC, all 25 tested sera samples from CoronaVac-vaccinees, with neutralization activity against the prototype virus, could not neutralize the Omicron VOC (104). Although SARS-CoV-2 variants (especially Beta, Gamma and Omicron) escape vaccine-elicited NAbs, the elicited IFN-γ-secreting T cells exhibit similar responses to the prototype and VOCs of SARS-CoV-2 (105,106).

Phase 3 clinical trials revealed that vaccine efficacy against symptomatic COVID-19 was 83.5% in Turkey (107) (Table 1). In the real world, two doses of CoronaVac immunization were associated with 46.8% protection against symptomatic COVID-19 in older adults (≥ 70 years old) in the setting of widespread transmission of the Gamma VOC in Brazil (108). The effectiveness of vaccine CoronaVac was 65.9% for the prevention of COVID-19 analyzed in a cohort that included approximately 10 million persons in Chile (109). In addition, the overall effectiveness of two-dose BBIBP-CorV and CoronaVac during the outbreak of the Delta VOC in May 2021 in Guangzhou, China was 59.0% against COVID-19 and 70.2% against moderate disease (110).

BBV152 (Covaxin) is another inactivated virus vaccine with a toll-like receptor 7 (TLR7)/TLR8 agonist molecule adsorbed to alum (Algel-IMDG) adjuvant. Following the two-dose schedule vaccination, both antibody responses and cellular immune responses were activated (111), as well as innate immune responses, characterized by profound changes in plasma cytokine and chemokine levels (112). In the Phase 3 trial, two doses of immunization with BBV152 were immunogenic and conferred efficacies of 77.8% and 63.6% in preventing symptomatic COVID-19 and asymptomatic infections, respectively (113) (Table 1).

QazCovid-in vaccine contains inactivated whole-virion and an aluminum hydroxide adjuvant; it was developed by the Research Institute for Biological Safety Problems, Kazakhstan (114). The results of Phase 1 and 2 trials showed that this vaccine was safe and well-tolerated in adults aged from 18 to 70 years and caused predominantly mild adverse events. Two doses of QazCovid-in vaccine (5 μg) promoted pronounced humoral immune responses, with higher antibody titers in young participants aged 18-49 years than in participants aged ≥50 years. In addition, multifunctional cellular responses (induction of IFN-α, IFN-γ, TNF-α, IL-4 and IL-6) were elicited (114) (Table 2).

DNA vaccine

A DNA vaccine, ZyCoV-D, expresses full-length S protein and was developed by Zydus Cadila, India (115). ZyCoV-D was administered with three doses through the intradermal route via a needle or needle-free injection system (NFIS) by the Pharmajet Tropis® device. The NAb GMT level induced in the NFIS 2 mg group was the highest among needle 1/2 mg

and NFIS 1/2 mg groups, similar to a panel of HCS (Table 2). In addition, cellular responses (IFN-γ production) were induced (115). Further Phase 2 and 3 studies are ongoing.

Sequential heterologous immunization

In order to mitigate intermittent COVID-19 vaccine supply shortages and enhance safety and immunogenicity, heterologous COVID-19 vaccine regimens have been studied. Compared with the two doses of AZD1222 immunization, AZD1222-prime and BNT162b2-boost induced significantly higher frequencies of S-specific T cells and higher titers of NAbs against prototype, Alpha, Beta, Gamma and Delta VOCs (116-120).

A real-world study in Denmark showed that the vaccine effectiveness of heterologous immunization with AZD1222 and an mRNA vaccine (BNT162b2 or mRNA-1273) against SARS-CoV-2 infection was 88% 14 days after the second dose and onwards (121). Two doses of inactivated virus vaccine followed by a third boost dose of AZD1222 or BNT162b2 were studied and showed that the NAb titers in recipients significantly increased after the boost immunization (122-124). In addition, heterologous immunization with two doses of inactivated virus vaccine and a third dose of subunit protein vaccine ZF2001 induced higher generation of NAbs against prototype virus and variants than three doses of inactivated virus vaccine (125,126).

Safety and AEFI

Following the large-scale COVID-19 vaccine inoculation campaign, several rare adverse events have been reported, including myocarditis, thrombotic thrombocytopenia and others.

The occurrence of myocarditis was rare and mainly observed in the vaccinees receiving the mRNA COVID-19 vaccines within the first week, especially after the second dose, in which case it usually resolves within days or weeks. After the second-dose immunization of COVID-19 mRNA vaccines in the USA, the myocarditis reporting rates were 40.6 and 2.4 cases per million doses in males aged 12−29 and ≥30 years, respectively, and 4.2 and 1.0 cases per million doses in females aged 12−29 and ≥30 years, respectively. It was highest in males aged 12−17 years, with 62.8 cases per million doses (127-130).

One explanation for myocarditis following mRNA vaccine immunization is that the human immune system detects exogenetic mRNA as an antigen and activates inflammatory cascades and immunologic pathways, which may contribute to the development of myocarditis as a systemic reaction in certain individuals. Another explanation is the cross-reaction between the anti-S-protein antibodies and self-antigens. In addition, sex hormone differences may contribute to the male predominance in myocarditis cases (131).

The benefits of using mRNA COVID-19 vaccines under the Food and Drugs Administration (FDA) Emergency Use Authorization (EUA) clearly outweigh the risks in all populations, including adolescents and young adults, for the following reasons: i) the occurrence ratio of myocarditis after an mRNA vaccine vaccination is more than 100-fold lower than that caused by COVID-19, and the mRNA vaccines protect vaccinees against COVID-19; and ii) the mRNA vaccine-related myocarditis is generally mild or moderate, but

the symptoms of COVID-19-related myocarditis are much more severe and the risks of hospitalization and death associated with COVID-19 are much greater (130,131).

Thrombosis with thrombocytopenia syndrome is a rare but potentially fatal complication that occurs after vaccination with COVID-19 vaccines, particularly AZD1222 and Ad26.COV2.S. (132-136). The incidence of vaccine-induced immune thrombotic thrombocytopenia (VITT) is 14.9 cases per million vaccinees after the first or unknown dose and 1.8 cases per million vaccinees after the second dose (137).

Antibodies against platelet factor 4 (PF4) and low platelet levels were observed in patients with VITT. Immune complexes are formed with these anti-PF4 antibodies and bind to platelet FcγRIIa receptors, consequently activating platelets and the coagulation system (138,139).

The link between vaccination with COVID-19 vaccines and the formation of anti-PF4 antibodies is a critical focus. One explanation is that PF4 interacts with adenoviral vectors or other vaccine components (such as culture cell-derived proteins), becoming immunogenic and triggering the formation of autoantibodies against PF4 (138,140). In addition, the possibility of cross-reactivity between anti-PF4 antibodies and SARS-CoV-2 S protein was excluded (141). The exact mechanism has yet to be determined.

Conclusions and perspectives

The published clinical trials data show that most of the COVID-19 vaccines and candidates are safe, with a very low incidence of rare adverse events, and they are immunogenic and confer substantial protection against COVID-19, including that caused by SARS-CoV-2 variants. However, following the ongoing COVID-19 vaccine immunization campaigns, adverse events — especially rare adverse events with low incidence and vaccine effectiveness in the real world — should be monitored continuously, which will provide valuable advice for policy making.

Although high immunization coverage has been achieved in some countries, the uneven distribution of COVID-19 vaccines has led to limited access to vaccines and low vaccination coverage rates in some countries. In the era of globalization, solidarity and cooperation are necessary to control the unprecedented COVID-19 pandemic. In addition to increasing the supply of vaccines to countries with low vaccination coverage, immunization strategies could be optimized to build an effective immune barrier rapidly. These include: i) increasing the coverage of single-dose immunization, because the high seroconversion rate after a single dose in naive participants could benefit the prevention of COVID-19 and delay the administration of the second dose to increase the number of people vaccinated (142-144); ii) an extended vaccine interval, which contributes to higher antibody levels compared with those vaccinated with standard or short intervals, as well as vaccine efficacies (58,81,145,146); and iii) sequential heterogeneous vaccination.

Currently, decreased vaccine effectiveness has been observed. One major factor is the newly emerging and circulating SARS-CoV-2 variants, particularly the Omicron VOC, which are resistant to the immune responses induced by COVID-19 vaccines. The other is the waning of antibody responses, especially half a year after the last dose of vaccination, and NAb titers were correlated with vaccine protection efficacy (147). Therefore, boost

immunization is performed to overcome the decline in vaccine effectiveness. Meanwhile, the development of vaccines with the advantages of broad cross-reactivity to SARS-CoV-2 variants and the induction of mucosal immune responses will contribute to higher efficacy in boosting immunization.

Funding

This work is supported by the National Key R&D Program of China (2020YFA0907100), the National Natural Science Foundation of China (NSFC) (82041048 and 81991494), a grant from the Bill & Melinda Gates Foundation (INV-027420), the Chinese Academy of Sciences (YSBR-010), and the intramural special grant for SARS-CoV-2 research from the Chinese Academy of Sciences. L.D. is supported by the Excellent Young Scientist Program from NSFC (82122031) and Youth Innovation Promotion Association of the CAS (2018113).

Conflicts of interest statement: K.X., L.D. and G.F.G. are listed in the patent as the inventors of the RBD-dimer as coronavirus vaccines. All other authors declare no competing interests.

References

1 Tan, W., Zhao, X., Ma, X., Wang, W., Niu, P., Xu, W., Gao, G. F., and Wu, G. 2020. A novel coronavirus genome identified in a cluster of pneumonia cases - Wuhan, China 2019-2020. *China CDC Wkly* 2:61.

2 Gao, G. F. 2021. Science-based COVID-19 vaccine development. *Natl Sci Rev* 8:nwab193.

3 Dai, L. and Gao, G. F. 2021. Viral targets for vaccines against COVID-19. *Nat Rev Immunol* 21:73.

4 Stenseth, N. C., Dharmarajan, G., Li, R., Shi, Z. L., Yang, R., and Gao, G. F. 2021. Lessons learnt from the COVID-19 pandemic. *Front Public Health* 9:694705.

5 Xu, K., Dai, L., and Gao, G. F. 2021. Humoral and cellular immunity and the safety of COVID-19 vaccines: a summary of data published by 21 May 2021. *Int Immunol* 33:529.

6 Arunachalam, P. S., Scott, M. K. D., Hagan, T., Li, C., Feng, Y., Wimmers, F., Grigoryan, L., Trisal, M., Edara, V. V., Lai, L., Chang, S. E., Feng, A., Dhingra, S., Shah, M., Lee, A. S., Chinthrajah, S., Sindher, S. B., Mallajosyula, V., Gao, F., Sigal, N., Kowli, S., Gupta, S., Pellegrini, K., Tharp, G., Maysel-Auslender, S., Hamilton, S., Aoued, H., Hrusovsky, K., Roskey, M., Bosinger, S. E., Maecker, H. T., Boyd, S. D., Davis, M. M., Utz, P. J., Suthar, M. S., Khatri, P., Nadeau, K. C., and Pulendran, B. 2021. Systems vaccinology of the BNT162b2 mRNA vaccine in humans. *Nature* 596:410.

7 Guerrera, G., Picozza, M., D'Orso, S., Placido, R., Pirronello, M., Verdiani, A., Termine, A., Fabrizio, C., Giannessi, F., Sambucci, M., Balice, M. P., Caltagirone, C., Salvia, A., Rossini, A., Battistini, L., and Borsellino, G. 2021. BNT162b2 vaccination induces durable SARS-CoV-2-specific T cells with a stem cell memory phenotype. *Sci Immunol* 6:eabl5344.

8 Oberhardt, V., Luxenburger, H., Kemming, J., Schulien, I., Ciminski, K., Giese, S., Csernalabics, B., Lang-Meli, J., Janowska, I., Staniek, J., Wild, K., Basho, K., Marinescu, M. S., Fuchs, J., Topfstedt, F., Janda, A., Sogukpinar, O., Hilger, H., Stete, K., Emmerich, F., Bengsch, B., Waller, C. F., Rieg, S., Sagar, Boettler, T., Zoldan, K., Kochs, G., Schwemmle, M., Rizzi, M., Thimme, R., Neumann-Haefelin, C., and Hofmann, M. 2021. Rapid and stable mobilization of CD8(+) T cells by SARS-CoV-2 mRNA vaccine. *Nature* 597:268.

9 Sahin, U., Muik, A., Vogler, I., Derhovanessian, E., Kranz, L. M., Vormehr, M., Quandt, J., Bidmon, N., Ulges, A., Baum, A., Pascal, K. E., Maurus, D., Brachtendorf, S., Lorks, V., Sikorski, J., Koch, P., Hilker, R., Becker, D., Eller, A. K., Grutzner, J., Tonigold, M., Boesler, C., Rosenbaum, C., Heesen, L., Kuhnle, M. C., Poran, A., Dong, J. Z., Luxemburger, U., Kemmer-Bruck, A., Langer, D., Bexon, M., Bolte, S., Palanche, T., Schultz, A., Baumann, S., Mahiny, A. J., Boros, G., Reinholz, J., Szabo, G. T., Kariko, K., Shi, P. Y., Fontes-Garfias, C., Perez, J. L., Cutler, M., Cooper, D., Kyratsous, C. A., Dormitzer, P. R., Jansen, K. U., and Tureci, O. 2021. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. *Nature* 595:572.

10 Frenck, R. W., Jr., Klein, N. P., Kitchin, N., Gurtman, A., Absalon, J., Lockhart, S., Perez, J. L., Walter, E. B., Senders, S., Bailey, R., Swanson, K. A., Ma, H., Xu, X., Koury, K., Kalina, W. V., Cooper, D., Jennings, T., Brandon, D. M., Thomas, S. J., Tureci, O., Tresnan, D. B., Mather, S., Dormitzer, P. R., Sahin, U., Jansen, K. U., Gruber, W. C.; The C4591001 Clinical Trial Group. 2021. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med* 385:239.

11 Walter, E. B., Talaat, K. R., Sabharwal, C., Gurtman, A., Lockhart, S., Paulsen, G. C., Barnett, E. D., Munoz, F. M., Maldonado, Y., Pahud, B. A., Domachowske, J. B., Simoes, E. A. F., Sarwar, U. N., Kitchin, N., Cunliffe, L., Rojo, P., Kuchar, E., Ramet, M., Munjal, I., Perez, J. L., Frenck, R. W., Jr., Lagkadinou, E., Swanson, K. A., Ma, H., Xu, X., Koury, K., Mather, S., Belanger, T. J., Cooper, D., Tureci, O., Dormitzer, P. R., Sahin, U., Jansen, K. U., Gruber, W. C., and the C4591007 Clinical Trial Group. 2022. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N Engl J Med* 386:35.

12 Wei, J., Stoesser, N., Matthews, P. C., Ayoubkhani, D., Studley, R., Bell, I., Bell, J. I., Newton, J. N., Farrar, J., Diamond, I., Rourke, E., Howarth, A., Marsden, B. D., Hoosdally, S., Jones, E. Y., Stuart, D. I., Crook, D. W., Peto, T. E. A., Pouwels, K. B., Eyre, D. W., Walker, A. S.; The COVID-19 Infection Survey Team. 2021. Antibody responses to SARS-CoV-2 vaccines in 45,965 adults from the general population of the United Kingdom. *Nat Microbiol* 6:1140.

13 Collier, A. Y., Yu, J., McMahan, K., Liu, J., Chandrashekar, A., Maron, J. S., Atyeo, C., Martinez, D. R., Ansel, J. L., Aguayo, R., Rowe, M., Jacob-Dolan, C., Sellers, D., Barrett, J., Ahmad, K., Anioke, T., VanWyk, H., Gardner, S., Powers, O., Bondzie, E. A., Wan, H., Baric, R. S., Alter, G., Hacker, M. R., and Barouch, D. H. 2021. Differential kinetics of immune responses elicited by Covid-19 vaccines. *N Engl J Med* 385:2010.

14 Levin, E. G., Lustig, Y., Cohen, C., Fluss, R., Indenbaum, V., Amit, S., Doolman, R., Asraf, K., Mendelson, E., Ziv, A., Rubin, C., Freedman, L., Kreiss, Y., and Regev-Yochay, G. 2021. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *N Engl J Med* 385:e84.

15 Falsey, A. R., Frenck, R. W., Jr., Walsh, E. E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Bailey, R., Swanson, K. A., Xu, X., Koury, K., Kalina, W., Cooper, D., Zou, J., Xie, X., Xia, H., Tureci, O., Lagkadinou, E., Tompkins, K. R., Shi, P. Y., Jansen, K. U., Sahin, U., Dormitzer, P. R., and Gruber, W. C. 2021. SARS-CoV-2 neutralization with BNT162b2 vaccine dose 3. *N Engl J Med* 385:1627.

16 Nemet, I., Kliker, L., Lustig, Y., Zuckerman, N., Erster, O., Cohen, C., Kreiss, Y., Alroy-Preis, S., Regev-

Yochay, G., Mendelson, E., and Mandelboim, M. 2022. Third BNT162b2 vaccination neutralization of SARS-CoV-2 Omicron infection. *N Engl J Med*. 386:492.

17 Cele, S., Jackson, L., Khoury, D. S., Khan, K., Moyo-Gwete, T., Tegally, H., San, J. E., Cromer, D., Scheepers, C., Amoako, D. G., Karim, F., Bernstein, M., Lustig, G., Archary, D., Smith, M., Ganga, Y., Jule, Z., Reedoy, K., Hwa, S. H., Giandhari, J., Blackburn, J. M., Gosnell, B. I., Abdool Karim, S. S., Hanekom, W., Ngs, S. A., Team, C.-K., von Gottberg, A., Bhiman, J. N., Lessells, R. J., Moosa, M. S., Davenport, M. P., de Oliveira, T., Moore, P. L., and Sigal, A. 2021. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature* 602:654.

18 Bates, T. A., Leier, H. C., Lyski, Z. L., McBride, S. K., Coulter, F. J., Weinstein, J. B., Goodman, J. R., Lu, Z., Siegel, S. A. R., Sullivan, P., Strnad, M., Brunton, A. E., Lee, D. X., Adey, A. C., Bimber, B. N., O'Roak, B. J., Curlin, M. E., Messer, W. B., and Tafesse, F. G. 2021. Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum. *Nat Commun* 12:5135.

19 Jalkanen, P., Kolehmainen, P., Hakkinen, H. K., Huttunen, M., Tahtinen, P. A., Lundberg, R., Maljanen, S., Reinholm, A., Tauriainen, S., Pakkanen, S. H., Levonen, I., Nousiainen, A., Miller, T., Valimaa, H., Ivaska, L., Pasternack, A., Naves, R., Ritvos, O., Osterlund, P., Kuivanen, S., Smura, T., Hepojoki, J., Vapalahti, O., Lempainen, J., Kakkola, L., Kantele, A., and Julkunen, I. 2021. COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants. *Nat Commun* 12:3991.

20 Wang, P., Nair, M. S., Liu, L., Iketani, S., Luo, Y., Guo, Y., Wang, M., Yu, J., Zhang, B., Kwong, P. D., Graham, B. S., Mascola, J. R., Chang, J. Y., Yin, M. T., Sobieszczyk, M., Kyratsous, C. A., Shapiro, L., Sheng, Z., Huang, Y., and Ho, D. D. 2021. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 593:130.

21 Garcia-Beltran, W. F., Lam, E. C., St Denis, K., Nitido, A. D., Garcia, Z. H., Hauser, B. M., Feldman, J., Pavlovic, M. N., Gregory, D. J., Poznansky, M. C., Sigal, A., Schmidt, A. G., Iafrate, A. J., Naranbhai, V., and Balazs, A. B. 2021. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *Cell* 184:2372.

22 Wall, E. C., Wu, M., Harvey, R., Kelly, G., Warchal, S., Sawyer, C., Daniels, R., Hobson, P., Hatipoglu, E., Ngai, Y., Hussain, S., Nicod, J., Goldstone, R., Ambrose, K., Hindmarsh, S., Beale, R., Riddell, A., Gamblin, S., Howell, M., Kassiotis, G., Libri, V., Williams, B., Swanton, C., Gandhi, S., and Bauer, D. L. 2021. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *Lancet* 397:2331.

23 Mlcochova, P., Kemp, S. A., Dhar, M. S., Papa, G., Meng, B., Ferreira, I., Datir, R., Collier, D. A., Albecka, A., Singh, S., Pandey, R., Brown, J., Zhou, J., Goonawardane, N., Mishra, S., Whittaker, C., Mellan, T., Marwal, R., Datta, M., Sengupta, S., Ponnusamy, K., Radhakrishnan, V. S., Abdullahi, A., Charles, O., Chattopadhyay, P., Devi, P., Caputo, D., Peacock, T., Wattal, C., Goel, N., Satwik, A., Vaishya, R., Agarwal, M.; The Indian, SARS-CoV-2 Genomics Consortium (INSACOG); The Genotype to Phenotype Japan (G2P-Japan) Consortium; The CITIID-NIHR BioResource COVID-19 Collaboration; Mavousian, A., Lee, J. H., Bassi, J., Silacci-Fegni, C., Saliba, C., Pinto, D., Irie, T., Yoshida, I., Hamilton, W. L., Sato, K., Bhatt, S., Flaxman, S., James, L. C., Corti, D., Piccoli, L., Barclay, W. S., Rakshit, P., Agrawal, A., and Gupta, R. K. 2021. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. *Nature* 599:114.

24 Liu, J., Liu, Y., Xia, H., Zou, J., Weaver, S. C., Swanson, K. A., Cai, H., Cutler, M., Cooper, D., Muik, A., Jansen, K. U., Sahin, U., Xie, X., Dormitzer, P. R., and Shi, P. Y. 2021. BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. *Nature* 596:273.

25 Liu, Y., Liu, J., Xia, H., Zhang, X., Zou, J., Fontes-Garfias, C. R., Weaver, S. C., Swanson, K. A., Cai, H., Sarkar, R., Chen, W., Cutler, M., Cooper, D., Muik, A., Sahin, U., Jansen, K. U., Xie, X., Dormitzer, P. R., and Shi, P. Y. 2021. BNT162b2-elicited neutralization against new SARS-CoV-2 spike variants. *N Engl J Med* 385:472.

26 McCallum, M., Bassi, J., De Marco, A., Chen, A., Walls, A. C., Di Iulio, J., Tortorici, M. A., Navarro, M. J., Silacci-Fregni, C., Saliba, C., Sprouse, K. R., Agostini, M., Pinto, D., Culap, K., Bianchi, S., Jaconi, S., Cameroni, E., Bowen, J. E., Tilles, S. W., Pizzuto, M. S., Guastalla, S. B., Bona, G., Pellanda, A. F., Garzoni, C., Van Voorhis, W. C., Rosen, L. E., Snell, G., Telenti, A., Virgin, H. W., Piccoli, L., Corti, D., and Veesler, D. 2021. SARS-CoV-2 immune evasion by the B.1.427/B.1.429 variant of concern. *Science* 373:648.

27 Lucas, C., Vogels, C. B. F., Yildirim, I., Rothman, J. E., Lu, P., Monteiro, V., Gehlhausen, J. R., Campbell, M., Silva, J., Tabachnikova, A., Peña-Hernandez, M. A., Muenker, M. C., Breban, M. I., Fauver, J. R., Mohanty, S., Huang, J., Shaw, A. C., Ko, A. I., Omer, S. B., Grubaugh, N. D., and Iwasaki, A. 2021. Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity. *Nature* 600:523.

28 Geers, D., Shamier, M. C., Bogers, S., den Hartog, G., Gommers, L., Nieuwkoop, N. N., Schmitz, K. S., Rijsbergen, L. C., van Osch, J. A. T., Dijkhuizen, E., Smits, G., Comvalius, A., van Mourik, D., Caniels, T. G., van Gils, M. J., Sanders, R. W., Oude Munnink, B. B., Molenkamp, R., de Jager, H. J., Haagmans, B. L., de Swart, R. L., Koopmans, M. P. G., van Binnendijk, R. S., de Vries, R. D., and GeurtsvanKessel, C. H. 2021. SARS-CoV-2 variants of concern partially escape humoral but not T-cell responses in COVID-19 convalescent donors and vaccinees. *Sci Immunol* 6:sciimmunol.abj1750.

29 Thomas, S. J., Moreira, E. D., Jr., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Perez Marc, G., Polack, F. P., Zerbini, C., Bailey, R., Swanson, K. A., Xu, X., Roychoudhury, S., Koury, K., Bouguermouh, S., Kalina, W. V., Cooper, D., Frenck, R. W., Jr., Hammitt, L. L., Tureci, O., Nell, H.,

Schaefer, A., Unal, S., Yang, Q., Liberator, P., Tresnan, D. B., Mather, S., Dormitzer, P. R., Sahin, U., Gruber, W. C., Jansen, K. U.; The C4591001 Clinical Trial Group. 2021. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med* 385:1761.

30 Chung, H., He, S., Nasreen, S., Sundaram, M. E., Buchan, S. A., Wilson, S. E., Chen, B., Calzavara, A., Fell, D. B., Austin, P. C., Wilson, K., Schwartz, K. L., Brown, K. A., Gubbay, J. B., Basta, N. E., Mahmud, S. M., Righolt, C. H., Svenson, L. W., MacDonald, S. E., Janjua, N. Z., Tadrous, M., and Kwong, J. C. 2021. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe Covid-19 outcomes in Ontario, Canada: test negative design study. *BMJ* 374:n1943.

31 Rosenberg, E. S., Dorabawila, V., Easton, D., Bauer, U. E., Kumar, J., Hoen, R., Hoefer, D., Wu, M., Lutterloh, E., Conroy, M. B., Greene, D., and Zucker, H. A. 2021. Covid-19 vaccine effectiveness in New York State. *N Engl J Med* 386:116.

32 Voko, Z., Kiss, Z., Surjan, G., Surjan, O., Barcza, Z., Palyi, B., Formanek-Balku, E., Molnar, G. A., Herczeg, R., Gyenesei, A., Miseta, A., Kollar, L., Wittmann, I., Muller, C., and Kasler, M. 2021. Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary-the HUN-VE study. *Clin Microbiol Infect* 28:398.

33 Rovida, F., Cassaniti, I., Paolucci, S., Percivalle, E., Sarasini, A., Piralla, A., Giardina, F., Sammartino, J. C., Ferrari, A., Bergami, F., Muzzi, A., Novelli, V., Meloni, A., Cutti, S., Grugnetti, A. M., Grugnetti, G., Rona, C., Daglio, M., Marena, C., Triarico, A., Lilleri, D., and Baldanti, F. 2021. SARS-CoV-2 vaccine breakthrough infections with the alpha variant are asymptomatic or mildly symptomatic among health care workers. *Nat Commun* 12:6032.

34 Lopez Bernal, J., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., Stowe, J., Tessier, E., Groves, N., Dabrera, G., Myers, R., Campbell, C. N. J., Amirthalingam, G., Edmunds, M., Zambon, M., Brown, K. E., Hopkins, S., Chand, M., and Ramsay, M. 2021. Effectiveness of Covid-19 vaccines against the B.1.617.2 (Delta) variant. *N Engl J Med* 385:585.

35 Sheikh, A., Robertson, C., and Taylor, B. 2021. BNT162b2 and ChAdOx1 nCoV-19 vaccine effectiveness against death from the Delta variant. *N Engl J Med* 385:2195.

36 Tang, P., Hasan, M. R., Chemaitelly, H., Yassine, H. M., Benslimane, F. M., Al Khatib, H. A., AlMukdad, S., Coyle, P., Ayoub, H. H., Al Kanaani, Z., Al Kuwari, E., Jeremijenko, A., Kaleeckal, A. H., Latif, A. N., Shaik, R. M., Abdul Rahim, H. F., Nasrallah, G. K., Al Kuwari, M. G., Al Romaihi, H. E., Butt, A. A., Al-Thani, M. H., Al Khal, A., Bertollini, R., and Abu-Raddad, L. J. 2021. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat Med* 27:2136.

37 Abu-Raddad, L. J., Chemaitelly, H., Butt, A. A.; The National Study Group for COVID-19 Vaccination. 2021. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. *N Engl J Med* 385:187.

38 Pilishvili, T., Gierke, R., Fleming-Dutra, K. E., Farrar, J. L., Mohr, N. M., Talan, D. A., Krishnadasan, A., Harland, K. K., Smithline, H. A., Hou, P. C., Lee, L. C., Lim, S. C., Moran, G. J., Krebs, E., Steele, M. T., Beiser, D. G., Faine, B., Haran, J. P., Nandi, U., Schrading, W. A., Chinnock, B., Henning, D. J., Lovecchio, F., Lee, J., Barter, D., Brackney, M., Fridkin, S. K., Marceaux-Galli, K., Lim, S., Phipps, E. C., Dumyati, G., Pierce, R., Markus, T. M., Anderson, D. J., Debes, A. K., Lin, M. Y., Mayer, J., Kwon, J. H., Safdar, N., Fischer, M., Singleton, R., Chea, N., Magill, S. S., Verani, J. R., and Schrag, S. J. 2021. Effectiveness of mRNA Covid-19 vaccine among U.S. health care personnel. *N Engl J Med* 385:e90.

39 Chemaitelly, H., Tang, P., Hasan, M. R., AlMukdad, S., Yassine, H. M., Benslimane, F. M., Al Khatib, H. A., Coyle, P., Ayoub, H. H., Al Kanaani, Z., Al Kuwari, E., Jeremijenko, A., Kaleeckal, A. H., Latif, A. N., Shaik, R. M., Abdul Rahim, H. F., Nasrallah, G. K., Al Kuwari, M. G., Al Romaihi, H. E., Butt, A. A., Al-Thani, M. H., Al Khal, A., Bertollini, R., and Abu-Raddad, L. J. 2021. Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *N Engl J Med* 385:e83.

40 Tartof, S. Y., Slezak, J. M., Fischer, H., Hong, V., Ackerson, B. K., Ranasinghe, O. N., Frankland, T. B., Ogun, O. A., Zamparo, J. M., Gray, S., Valluri, S. R., Pan, K., Angulo, F. J., Jodar, L., and McLaughlin, J. M. 2021. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 398:1407.

41 Levine-Tiefenbrun, M., Yelin, I., Alapi, H., Katz, R., Herzel, E., Kuint, J., Chodick, G., Gazit, S., Patalon, T., and Kishony, R. 2021. Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. *Nat Med* 27:2108.

42 Levine-Tiefenbrun, M., Yelin, I., Katz, R., Herzel, E., Golan, Z., Schreiber, L., Wolf, T., Nadler, V., Ben-Tov, A., Kuint, J., Gazit, S., Patalon, T., Chodick, G., and Kishony, R. 2021. Initial report of decreased SARS-CoV-2 viral load after inoculation with the BNT162b2 vaccine. *Nat Med* 27:790.

43 Goldberg, Y., Mandel, M., Bar-On, Y. M., Bodenheimer, O., Freedman, L., Haas, E. J., Milo, R., Alroy-Preis, S., Ash, N., and Huppert, A. 2021. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med* 385:e85.

44 Barda, N., Dagan, N., Cohen, C., Hernan, M. A., Lipsitch, M., Kohane, I. S., Reis, B. Y., and Balicer, R. D. 2021. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *Lancet* 398:2093.

45 Ali, K., Berman, G., Zhou, H., Deng, W., Faughnan, V., Coronado-Voges, M., Ding, B., Dooley, J., Girard, B., Hillebrand, W., Pajon, R., Miller, J. M., Leav, B., and McPhee, R. 2021. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med* 385:2241.

46 Anderson, E. J., Rouphael, N. G., Widge, A. T., Jackson, L. A., Roberts, P. C., Makhene, M., Chappell, J.

D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A. B., Flach, B., Lin, B. C., Doria-Rose, N. A., O'Dell, S., Schmidt, S. D., Corbett, K. S., Swanson, P. A., 2nd, Padilla, M., Neuzil, K. M., Bennett, H., Leav, B., Makowski, M., Albert, J., Cross, K., Edara, V. V., Floyd, K., Suthar, M. S., Martinez, D. R., Baric, R., Buchanan, W., Luke, C. J., Phadke, V. K., Rostad, C. A., Ledgerwood, J. E., Graham, B. S., and Beigel, J. H. 2020. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med* 383:2427.

47 Sureshchandra, S., Lewis, S. A., Doratt, B. M., Jankeel, A., Coimbra Ibraim, I., and Messaoudi, I. 2021. Single-cell profiling of T and B cell repertoires following SARS-CoV-2 mRNA vaccine. *JCI Insight* 6:e153201.

48 Mateus, J., Dan, J. M., Zhang, Z., Rydyznski Moderbacher, C., Lammers, M., Goodwin, B., Sette, A., Crotty, S., and Weiskopf, D. 2021. Low-dose mRNA-1273 COVID-19 vaccine generates durable memory enhanced by cross-reactive T cells. *Science* 374:eabj9853.

49 Painter, M. M., Mathew, D., Goel, R. R., Apostolidis, S. A., Pattekar, A., Kuthuru, O., Baxter, A. E., Herati, R. S., Oldridge, D. A., Gouma, S., Hicks, P., Dysinger, S., Lundgreen, K. A., Kuri-Cervantes, L., Adamski, S., Hicks, A., Korte, S., Giles, J. R., Weirick, M. E., McAllister, C. M., Dougherty, J., Long, S., D'Andrea, K., Hamilton, J. T., Betts, M. R., Bates, P., Hensley, S. E., Grifoni, A., Weiskopf, D., Sette, A., Greenplate, A. R., and Wherry, E. J. 2021. Rapid induction of antigen-specific CD4(+) T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination. *Immunity* 54:2133.

50 Tarke, A., Sidney, J., Methot, N., Yu, E. D., Zhang, Y., Dan, J. M., Goodwin, B., Rubiro, P., Sutherland, A., Wang, E., Frazier, A., Ramirez, S. I., Rawlings, S. A., Smith, D. M., da Silva Antunes, R., Peters, B., Scheuermann, R. H., Weiskopf, D., Crotty, S., Grifoni, A., and Sette, A. 2021. Impact of SARS-CoV-2 variants on the total CD4(+) and CD8(+) T cell reactivity in infected or vaccinated individuals. *Cell Rep Med* 2:100355.

51 Tré-Hardy, M., Cupaiolo, R., Wilmet, A., Antoine-Moussiaux, T., Della Vecchia, A., Horeanga, A., Papleux, E., Vekemans, M., Beukinga, I., and Blairon, L. 2021. Immunogenicity of mRNA-1273 COVID vaccine after 6 months surveillance in health care workers; a third dose is necessary. *J Infect* 83:559.

52 Choi, A., Koch, M., Wu, K., Chu, L., Ma, L., Hill, A., Nunna, N., Huang, W., Oestreicher, J., Colpitts, T., Bennett, H., Legault, H., Paila, Y., Nestorova, B., Ding, B., Montefiori, D., Pajon, R., Miller, J. M., Leav, B., Carfi, A., McPhee, R., and Edwards, D. K. 2021. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. *Nat Med* 27:2025.

53 Pegu, A., O'Connell, S. E., Schmidt, S. D., O'Dell, S., Talana, C. A., et al. 2021. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. *Science* 373:1372.

54 El Sahly, H. M., Baden, L. R., Essink, B., Doblecki-Lewis, S., Martin, J. M., Anderson, E. J., Campbell, T. B., Clark, J., Jackson, L. A., Fichtenbaum, C. J., Zervos, M., Rankin, B., Eder, F., Feldman, G., Kennelly, C., Han-Conrad, L., Levin, M., Neuzil, K. M., Corey, L., Gilbert, P., Janes, H., Follmann, D., Marovich, M., Polakowski, L., Mascola, J. R., Ledgerwood, J. E., Graham, B. S., August, A., Clouting, H., Deng, W., Han, S., Leav, B., Manzo, D., Pajon, R., Schödel, F., Tomassini, J. E., Zhou, H., and Miller, J. 2021. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med* 385:1774.

55 Bruxvoort, K. J., Sy, L. S., Qian, L., Ackerson, B. K., Luo, Y., Lee, G. S., Tian, Y., Florea, A., Aragones, M., Tubert, J. E., Takhar, H. S., Ku, J. H., Paila, Y. D., Talarico, C. A., and Tseng, H. F. 2021. Effectiveness of mRNA-1273 against delta, mu, and other emerging variants of SARS-CoV-2: test negative case-control study. *BMJ* 375:e068848.

56 Kremsner, P. G., Mann, P., Kroidl, A., Leroux-Roels, I., Schindler, C., Gabor, J. J., Schunk, M., Leroux-Roels, G., Bosch, J. J., Fendel, R., Kreidenweiss, A., Velavan, T. P., Fotin-Mleczek, M., Mueller, S. O., Quintini, G., Schonborn-Kellenberger, O., Vahrenhorst, D., Verstraeten, T., Alves de Mesquita, M., Walz, L., Wolz, O. O., Oostvogels, L.; The CV-NCOV-001 Study Group. 2021. Safety and immunogenicity of an mRNA-lipid nanoparticle vaccine candidate against SARS-CoV-2 : A phase 1 randomized clinical trial. *Wien Klin Wochenschr* 133:931.

57 Kremsner, P. G., Ahuad Guerrero, R. A., Arana-Arri, E., Aroca Martinez, G. J., Bonten, M., et al. 2022. Efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate in ten countries in Europe and Latin America (HERALD): a randomised, observer-blinded, placebo-controlled, phase 2b/3 trial. *Lancet Infect Dis* 22:329.

58 Flaxman, A., Marchevsky, N. G., Jenkin, D., Aboagye, J., Aley, P. K., et al. 2021. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). *Lancet* 398:981.

59 Thiruvengadam, R., Awasthi, A., Medigeshi, G., Bhattacharya, S., Mani, S., Sivasubbu, S., Shrivastava, T., Samal, S., Rathna Murugesan, D., Koundinya Desiraju, B., Kshetrapal, P., Pandey, R., Scaria, V., Kumar Malik, P., Taneja, J., Binayke, A., Vohra, T., Zaheer, A., Rathore, D., Ahmad Khan, N., Shaman, H., Ahmed, S., Kumar, R., Deshpande, S., Subramani, C., Wadhwa, N., Gupta, N., Pandey, A. K., Bhattacharya, J., Agrawal, A., Vrati, S., Bhatnagar, S., and Garg, P. K. 2021. Effectiveness of ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 infection during the delta (B.1.617.2) variant surge in India: a test-negative, case-control study and a mechanistic study of post-vaccination immune responses. *Lancet Infect Dis* 22:473.

60 Swanson, P. A., 2nd, Padilla, M., Hoyland, W., McGlinchey, K., Fields, P. A., Bibi, S., Faust, S. N., McDermott, A. B., Lambe, T., Pollard, A. J., Durham, N. M., and Kelly, E. J. 2021. AZD1222/ChAdOx1

nCoV-19 vaccination induces a polyfunctional spike protein-specific T(H)1 response with a diverse TCR repertoire. *Sci Transl Med* 13:eabj7211.

61 Falsey, A. R., Sobieszczyk, M. E., Hirsch, I., Sproule, S., Robb, M. L., Corey, L., Neuzil, K. M., Hahn, W., Hunt, J., Mulligan, M. J., McEvoy, C., DeJesus, E., Hassman, M., Little, S. J., Pahud, B. A., Durbin, A., Pickrell, P., Daar, E. S., Bush, L., Solis, J., Carr, Q. O., Oyedele, T., Buchbinder, S., Cowden, J., Vargas, S. L., Guerreros Benavides, A., Call, R., Keefer, M. C., Kirkpatrick, B. D., Pullman, J., Tong, T., Brewinski Isaacs, M., Benkeser, D., Janes, H. E., Nason, M. C., Green, J. A., Kelly, E. J., Maaske, J., Mueller, N., Shoemaker, K., Takas, T., Marshall, R. P., Pangalos, M. N., Villafana, T., Gonzalez-Lopez, A.; The AstraZeneca AZD1222 Clinical Study Group. 2021. Phase 3 safety and efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 vaccine. *N Engl J Med* 385:2348.

62 Clemens, S. A. C., Folegatti, P. M., Emary, K. R. W., Weckx, L. Y., Ratcliff, J., Bibi, S., De Almeida Mendes, A. V., Milan, E. P., Pittella, A., Schwarzbold, A. V., Sprinz, E., Aley, P. K., Bonsall, D., Fraser, C., Fuskova, M., Gilbert, S. C., Jenkin, D., Kelly, S., Kerridge, S., Lambe, T., Marchevsky, N. G., Mujadidi, Y. F., Plested, E., Ramasamy, M. N., Simmonds, P., Golubchik, T., Voysey, M., Pollard, A. J.; The AMPHEUS Project & Oxford COVID Vaccine Trial Team. 2021. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 lineages circulating in Brazil. *Nat Commun* 12:5861.

63 Katikireddi, S. V., Cerqueira-Silva, T., Vasileiou, E., Robertson, C., Amele, S., Pan, J., Taylor, B., Boaventura, V., Werneck, G. L., Flores-Ortiz, R., Agrawal, U., Docherty, A. B., McCowan, C., McMenamin, J., Moore, E., Ritchie, L. D., Rudan, I., Shah, S. A., Shi, T., Simpson, C. R., Barreto, M. L., Oliveira, V. d. A., Barral-Netto, M., and Sheikh, A. 2021. Two-dose ChAdOx1 nCoV-19 vaccine protection against COVID-19 hospital admissions and deaths over time: a retrospective, population-based cohort study in Scotland and Brazil. *Lancet* 399:25.

64 Barouch, D. H., Stephenson, K. E., Sadoff, J., Yu, J., Chang, A., Gebre, M., McMahan, K., Liu, J., Chandrashekar, A., Patel, S., Le Gars, M., de Groot, A. M., Heerwegh, D., Struyf, F., Douoguih, M., van Hoof, J., and Schuitemaker, H. 2021. Durable humoral and cellular immune responses 8 months after Ad26.COV2.S vaccination. *N Engl J Med* 385:951.

65 Alter, G., Yu, J., Liu, J., Chandrashekar, A., Borducchi, E. N., Tostanoski, L. H., McMahan, K., Jacob-Dolan, C., Martinez, D. R., Chang, A., Anioke, T., Lifton, M., Nkolola, J., Stephenson, K. E., Atyeo, C., Shin, S., Fields, P., Kaplan, I., Robins, H., Amanat, F., Krammer, F., Baric, R. S., Le Gars, M., Sadoff, J., de Groot, A. M., Heerwegh, D., Struyf, F., Douoguih, M., van Hoof, J., Schuitemaker, H., and Barouch, D. H. 2021. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. *Nature* 596:268.

66 Sadoff, J., Gray, G., Vandebosch, A., Cardenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P. A., Truyers, C., Fennema, H., Spiessens, B., Offergeld, K., Scheper, G., Taylor, K. L., Robb, M. L., Treanor, J., Barouch, D. H., Stoddard, J., Ryser, M. F., Marovich, M. A., Neuzil, K. M., Corey, L., Cauwenberghs, N., Tanner, T., Hardt, K., Ruiz-Guinazu, J., Le Gars, M., Schuitemaker, H., Van Hoof, J., Struyf, F., Douoguih, M., and the ENSEMBLE Study Group. 2021. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 384:2187.

67 Corchado-Garcia, J., Zemmour, D., Hughes, T., Bandi, H., Cristea-Platon, T., Lenehan, P., Pawlowski, C., Bade, S., O'Horo, J. C., Gores, G. J., Williams, A. W., Badley, A. D., Halamka, J., Virk, A., Swift, M. D., Wagner, T., and Soundararajan, V. 2021. Analysis of the effectiveness of the Ad26.COV2.S adenoviral vector vaccine for preventing COVID-19. *JAMA Netw Open* 4:e2132540.

68 Zhu, F.-C., Li, Y.-H., Guan, X.-H., Hou, L.-H., Wang, W.-J., Li, J.-X., Wu, S.-P., Wang, B.-S., Wang, Z., Wang, L., Jia, S.-Y., Jiang, H.-D., Wang, L., Jiang, T., Hu, Y., Gou, J.-B., Xu, S.-B., Xu, J.-J., Wang, X.-W., Wang, W., and Chen, W. 2020. 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* 395:1845.

69 Zhu, F.-C., Guan, X.-H., Li, Y.-H., Huang, J.-Y., Jiang, T., Hou, L.-H., Li, J.-X., Yang, B.-F., Wang, L., Wang, W.-J., Wu, S.-P., Wang, Z., Wu, X.-H., Xu, J.-J., Zhang, Z., Jia, S.-Y., Wang, B.-S., Hu, Y., Liu, J.-J., Zhang, J., Qian, X.-A., Li, Q., Pan, H.-X., Jiang, H.-D., Deng, P., Gou, J.-B., Wang, X.-W., Wang, X.-H., and Chen, W. 2020. 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. *Lancet* 396:479.

70 Wu, S., Huang, J., Zhang, Z., Wu, J., Zhang, J., Hu, H., Zhu, T., Zhang, J., Luo, L., Fan, P., Wang, B., Chen, C., Chen, Y., Song, X., Wang, Y., Si, W., Sun, T., Wang, X., Hou, L., and Chen, W. 2021. Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: preliminary report of an open-label and randomised phase 1 clinical trial. *Lancet Infect Dis* 21:1654.

71 Halperin, S. A., Ye, L., MacKinnon-Cameron, D., Smith, B., Cahn, P. E., Ruiz-Palacios, G. M., Ikram, A., Lanas, F., Lourdes Guerrero, M., Muñoz Navarro, S. R., Sued, O., Lioznov, D. A., Dzutseva, V., Parveen, G., Zhu, F., Leppan, L., Langley, J. M., Barreto, L., Gou, J., Zhu, T., Mao, H., Gagnon, L., Tran, S.-P., Khan, S. T., Becerra Aquino, A. G., Saldaña Montemayor, E. E., Rivera Martínez, N. E., Bohórquez López, V. C., Simón Campos, J. A., Pineda Cárdenas, F. d. J., Chen, W., Hou, L., Zhang, Z., Corral, G., López, E., Teijeiro, R., Alzogaray, M. F., Zaidman, C., Lopardo, G., Goecke, B., Feijooó Seoane, R. M., Mahmood, S. F., Khan, E. A., Akram, J., Abbas, S., Salahuddin, N., Rozhkova, E., and Zubkova, T. 2021. Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: an

international, multicentre, randomised, double-blinded, placebo-controlled phase 3 trial. *Lancet* 399:237.

72 Chahla, R. E., Tomas-Grau, R. H., Cazorla, S. I., Ploper, D., Vera Pingitore, E., López, M. A., Aznar, P., Alcorta, M. E., Vélez, E., Stagnetto, A., Ávila, C. L., Maldonado-Galdeano, C., Socias, S. B., Heinze, D., Navarro, S. A., Llapur, C. J., Costa, D., Flores, I., Edelstein, A., Kowdle, S., Perandones, C., Lee, B., Apfelbaum, G., Mostoslavsky, R., Mostoslavsky, G., Perdigón, G., and Chehín, R. N. 2022. Long-term analysis of antibodies elicited by SPUTNIK V: A prospective cohort study in Tucumán, Argentina. *Lancet Reg Health Am* 6:100123.

73 Ikegame, S., Siddiquey, M. N. A., Hung, C. T., Haas, G., Brambilla, L., Oguntuyo, K. Y., Kowdle, S., Chiu, H. P., Stevens, C. S., Vilardo, A. E., Edelstein, A., Perandones, C., Kamil, J. P., and Lee, B. 2021. Neutralizing activity of Sputnik V vaccine sera against SARS-CoV-2 variants. *Nat Commun* 12:4598.

74 Blanco, S., Salome Konigheim, B., Diaz, A., Spinsanti, L., Javier Aguilar, J., Elisa Rivarola, M., Beranek, M., Collino, C.; MinSalCba Working Group; Fcm-Unc Working Group; Diaz, M., Gabriela Barbas, M., Mangeaud, A., and Veronica Gallego, S. 2021. Evaluation of the Gam-COVID-Vac and vaccine-induced neutralizing response against SARS-CoV-2 lineage P.1 variant in an Argentinean cohort. *Vaccine* 40:811.

75 Gonzalez, S., Olszevicki, S., Salazar, M., Calabria, A., Regairaz, L., Marin, L., Campos, P., Varela, T., Martinez, V. V. G., Ceriani, L., Garcia, E., Kreplak, N., Pifano, M., Estenssoro, E., and Marsico, F. 2021. Effectiveness of the first component of Gam-COVID-Vac (Sputnik V) on reduction of SARS-CoV-2 confirmed infections, hospitalisations and mortality in patients aged 60-79: a retrospective cohort study in Argentina. *EClinicalMedicine* 40:101126.

76 Tukhvatulin, A. I., Dolzhikova, I. V., Shcheblyakov, D. V., Zubkova, O. V., Dzharullaeva, A. S., Kovyrshina, A. V., Lubenets, N. L., Grousova, D. M., Erokhova, A. S., Botikov, A. G., Izhaeva, F. M., Popova, O., Ozharovskaia, T. A., Esmagambetov, I. B., Favorskaya, I. A., Zrelkin, D. I., Voronina, D. V., Shcherbinin, D. N., Semikhin, A. S., Simakova, Y. V., Tokarskaya, E. A., Shmarov, M. M., Nikitenko, N. A., Gushchin, V. A., Smolyarchuk, E. A., Zubkova, T. G., Zakharov, K. A., Vasilyuk, V. B., Borisevich, S. V., Naroditsky, B. S., Logunov, D. Y., and Gintsburg, A. L. 2021. An open, non-randomised, phase 1/2 trial on the safety, tolerability, and immunogenicity of single-dose vaccine "Sputnik Light" for prevention of coronavirus infection in healthy adults. *Lancet Reg Health Eur* 11:100241.

77 Dai, L., Zheng, T., Xu, K., Han, Y., Xu, L., Huang, E., An, Y., Cheng, Y., Li, S., Liu, M., Yang, M., Li, Y., Cheng, H., Yuan, Y., Zhang, W., Ke, C., Wong, G., Qi, J., Qin, C., Yan, J., and Gao, G. F. 2020. A universal design of betacoronavirus vaccines against COVID-19, MERS, and SARS. *Cell* 182:722.

78 Yang, S., Li, Y., Dai, L., Wang, J., He, P., Li, C., Fang, X., Wang, C., Zhao, X., Huang, E., Wu, C., Zhong, Z., Wang, F., Duan, X., Tian, S., Wu, L., Liu, Y., Luo, Y., Chen, Z., Li, F., Li, J., Yu, X., Ren, H., Liu, L., Meng, S., Yan, J., Hu, Z., Gao, L., and Gao, G. F. 2021. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. *Lancet Infect Dis* 21:1107.

79 Zhao, X., Zheng, A., Li, D., Zhang, R., Sun, H., Wang, Q., Gao, G. F., Han, P., and Dai, L. 2021. Neutralisation of ZF2001-elicited antisera to SARS-CoV-2 variants. *Lancet Microbe* 2:e494.

80 Cao, Y., Yisimayi, A., Bai, Y., Huang, W., Li, X., Zhang, Z., Yuan, T., An, R., Wang, J., Xiao, T., Du, S., Ma, W., Song, L., Li, Y., Li, X., Song, W., Wu, J., Liu, S., Li, X., Zhang, Y., Su, B., Guo, X., Wei, Y., Gao, C., Zhang, N., Zhang, Y., Dou, Y., Xu, X., Shi, R., Lu, B., Jin, R., Ma, Y., Qin, C., Wang, Y., Feng, Y., Xiao, J., and Xie, X. S. 2021. Humoral immune response to circulating SARS-CoV-2 variants elicited by inactivated and RBD-subunit vaccines. *Cell Res.* 31:732.

81 Zhao, X., Li, D., Ruan, W., Chen, Z., Zhang, R., Zheng, A., Qiao, S., Zheng, X., Zhao, Y., Dai, L., Han, P., and Gao, G. F. 2022. Effects of a prolonged booster interval on neutralization of Omicron variant. *N Engl J Med* 386:894.

82 Dai, L., Gao, L., Tao, L., Hadinegoro, S. R., Erkin, M., Ying, Z., He, P., Girsang, R. T., Vergara, H., Akram, J., Satari, H. I., Khaliq, T., Sughra, U., Celi, A. P., Li, F., Li, Y., Jiang, Z., Dalimova, D., Tuychiev, J., Turdikulova, S., Ikram, A., Flores Lastra, N., Ding, F., Suhardono, M., Fadlyana, E., Yan, J., Hu, Z., Li, C., Abdurakhmonov, I. Y., Gao, G. F.; The ZF2001 Global Trial Group. 2022. Efficacy and safety of the RBD-dimer-based Covid-19 vaccine ZF2001 in adults. *N Engl J Med*. DOI:10.1056/NEJMoa2202261

83 Keech, C., Albert, G., Cho, I., Robertson, A., Reed, P., Neal, S., Plested, J. S., Zhu, M., Cloney-Clark, S., Zhou, H., Smith, G., Patel, N., Frieman, M. B., Haupt, R. E., Logue, J., McGrath, M., Weston, S., Piedra, P. A., Desai, C., Callahan, K., Lewis, M., Price-Abbott, P., Formica, N., Shinde, V., Fries, L., Lickliter, J. D., Griffin, P., Wilkinson, B., and Glenn, G. M. 2020. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. *N Engl J Med* 383:2320.

84 Formica, N., Mallory, R., Albert, G., Robinson, M., Plested, J. S., Cho, I., Robertson, A., Dubovsky, F., Glenn, G. M., and nCo, V. S. G. 2021. Different dose regimens of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373) in younger and older adults: A phase 2 randomized placebo-controlled trial. *PLoS Med* 18:e1003769.

85 Dunkle, L. M., Kotloff, K. L., Gay, C. L., Anez, G., Adelglass, J. M., Barrat Hernandez, A. Q., Harper, W. L., Duncanson, D. M., McArthur, M. A., Florescu, D. F., McClelland, R. S., Garcia-Fragoso, V., Riesenberg, R. A., Musante, D. B., Fried, D. L., Safirstein, B. E., McKenzie, M., Jeanfreau, R. J., Kingsley, J. K., Henderson, J. A., Lane, D. C., Ruiz-Palacios, G. M., Corey, L., Neuzil, K. M., Coombs, R. W., Greninger, A. L., Hutter, J., Ake, J. A., Smith, K., Woo, W., Cho, I., Glenn, G. M., Dubovsky, F.; The 2019nCoV-301 Study Group. 2021. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. *N Engl J Med* 386:531.

86 Shinde, V., Bhikha, S., Hoosain, Z., Archary, M., Bhorat, Q., Fairlie, L., Lalloo, U., Masilela, M. S. L., Moodley, D., Hanley, S., Fouche, L., Louw, C., Tameris, M., Singh, N., Goga, A., Dheda, K., Grobbelaar, C., Kruger, G., Carrim-Ganey, N., Baillie, V., de Oliveira, T., Lombard Koen, A., Lombaard, J. J., Mngqibisa, R., Bhorat, A. E., Benade, G., Lalloo, N., Pitsi, A., Vollgraaff, P. L., Luabeya, A., Esmail, A., Petrick, F. G., Oommen-Jose, A., Foulkes, S., Ahmed, K., Thombrayil, A., Fries, L., Cloney-Clark, S., Zhu, M., Bennett, C., Albert, G., Faust, E., Plested, J. S., Robertson, A., Neal, S., Cho, I., Glenn, G. M., Dubovsky, F., Madhi, S. A.; The 2019nCoV-501 Study Group. 2021. Efficacy of NVX-CoV2373 Covid-19 vaccine against the B.1.351 variant. *N Engl J Med* 384:1899.

87 Heath, P. T., Galiza, E. P., Baxter, D. N., Boffito, M., Browne, D., Burns, F., Chadwick, D. R., Clark, R., Cosgrove, C., Galloway, J., Goodman, A. L., Heer, A., Higham, A., Iyengar, S., Jamal, A., Jeanes, C., Kalra, P. A., Kyriakidou, C., McAuley, D. F., Meyrick, A., Minassian, A. M., Minton, J., Moore, P., Munsoor, I., Nicholls, H., Osanlou, O., Packham, J., Pretswell, C. H., San Francisco Ramos, A., Saralaya, D., Sheridan, R. P., Smith, R., Soiza, R. L., Swift, P. A., Thomson, E. C., Turner, J., Viljoen, M. E., Albert, G., Cho, I., Dubovsky, F., Glenn, G., Rivers, J., Robertson, A., Smith, K., Toback, S.; The 2019nCoV-302 Study Group . 2021. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med* 385:1172.

88 Toback, S., Galiza, E., Cosgrove, C., Galloway, J., Goodman, A. L., et al. 2021. Safety, immunogenicity, and efficacy of a COVID-19 vaccine (NVX-CoV2373) co-administered with seasonal influenza vaccines: an exploratory substudy of a randomised, observer-blinded, placebo-controlled, phase 3 trial. *Lancet Respir Med* 10:167.

89 Yang, J., Wang, W., Chen, Z., Lu, S., Yang, F., Bi, Z., Bao, L., Mo, F., Li, X., Huang, Y., Hong, W., Yang, Y., Zhao, Y., Ye, F., Lin, S., Deng, W., Chen, H., Lei, H., Zhang, Z., Luo, M., Gao, H., Zheng, Y., Gong, Y., Jiang, X., Xu, Y., Lv, Q., Li, D., Wang, M., Li, F., Wang, S., Wang, G., Yu, P., Qu, Y., Yang, L., Deng, H., Tong, A., Li, J., Wang, Z., Yang, J., Shen, G., Zhao, Z., Li, Y., Luo, J., Liu, H., Yu, W., Yang, M., Xu, J., Wang, J., Li, H., Wang, H., Kuang, D., Lin, P., Hu, Z., Guo, W., Cheng, W., He, Y., Song, X., Chen, C., Xue, Z., Yao, S., Chen, L., Ma, X., Chen, S., Gou, M., Huang, W., Wang, Y., Fan, C., Tian, Z., Shi, M., Wang, F. S., Dai, L., Wu, M., Li, G., Wang, G., Peng, Y., Qian, Z., Huang, C., Lau, J. Y., Yang, Z., Wei, Y., Cen, X., Peng, X., Qin, C., Zhang, K., Lu, G., and Wei, X. 2020. A vaccine targeting the RBD of the S protein of SARS-CoV-2 induces protective immunity. *Nature* 586:572.

90 Meng, F. Y., Gao, F., Jia, S. Y., Wu, X. H., Li, J. X., Guo, X. L., Zhang, J. L., Cui, B. P., Wu, Z. M., Wei, M. W., Ma, Z. L., Peng, H. L., Pan, H. X., Fan, L., Zhang, J., Wan, J. Q., Zhu, Z. K., Wang, X. W., and Zhu, F. C. 2021. Safety and immunogenicity of a recombinant COVID-19 vaccine (Sf9 cells) in healthy population aged 18 years or older: two single-center, randomised, double-blind, placebo-controlled, phase 1 and phase 2 trials. *Signal Transduct Target Ther* 6:271.

91 Hsieh, S. M., Liu, W. D., Huang, Y. S., Lin, Y. J., Hsieh, E. F., Lian, W. C., Chen, C., Janssen, R., Shih, S. R., Huang, C. G., Tai, I. C., and Chang, S. C. 2021. Safety and immunogenicity of a recombinant stabilized prefusion SARS-CoV-2 spike protein vaccine (MVC-COV1901) adjuvanted with CpG 1018 and aluminum hydroxide in healthy adults: a Phase 1, dose-escalation study. *EClinicalMedicine* 38:100989.

92 Hsieh, S.-M., Liu, M.-C., Chen, Y.-H., Lee, W.-S., Hwang, S.-J., Cheng, S.-H., Ko, W.-C., Hwang, K.-P., Wang, N.-C., Lee, Y.-L., Lin, Y.-L., Shih, S.-R., Huang, C.-G., Liao, C.-C., Liang, J.-J., Chang, C.-S., Chen, C., Lien, C. E., Tai, I. C., and Lin, T.-Y. 2021. Safety and immunogenicity of CpG 1018 and aluminium hydroxide-adjuvanted SARS-CoV-2 S-2P protein vaccine MVC-COV1901: interim results of a large-scale, double-blind, randomised, placebo-controlled phase 2 trial in Taiwan. *Lancet Respir Med* 9:1396.

93 Lien, C. E., Kuo, T. Y., Lin, Y. J., Lian, W. C., Lin, M. Y., Liu, L. T., Cheng, J., Chou, Y. C., and Chen, C. 2021. Evaluating the neutralizing ability of a CpG-adjuvanted S-2P subunit vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern. *Clin Infect Dis*. DOI:10.1093/cid/ciab711

94 Chappell, K. J., Mordant, F. L., Li, Z., Wijesundara, D. K., Ellenberg, P., Lackenby, J. A., Cheung, S. T. M., Modhiran, N., Avumegah, M. S., Henderson, C. L., Hoger, K., Griffin, P., Bennet, J., Hensen, L., Zhang, W., Nguyen, T. H. O., Marrero-Hernandez, S., Selva, K. J., Chung, A. W., Tran, M. H., Tapley, P., Barnes, J., Reading, P. C., Nicholson, S., Corby, S., Holgate, T., Wines, B. D., Hogarth, P. M., Kedzierska, K., Purcell, D. F. J., Ranasinghe, C., Subbarao, K., Watterson, D., Young, P. R., and Munro, T. P. 2021. Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: a randomised, double-blind, placebo-controlled, phase 1 trial. *Lancet Infect Dis* 21:1383.

95 Perez-Rodriguez, S., de la Caridad Rodriguez-Gonzalez, M., Ochoa-Azze, R., Climent-Ruiz, Y., Alberto Gonzalez-Delgado, C., Paredes-Moreno, B., Valenzuela-Silva, C., Rodriguez-Noda, L., Perez-Nicado, R., Gonzalez-Mugica, R., Martinez-Perez, M., Sanchez-Ramirez, B., Hernandez-Garcia, T., Diaz-Machado, A., Tamayo-Rodriguez, M., Martin-Trujillo, A., Rubino-Moreno, J., Suarez-Batista, A., Dubed-Echevarria, M., Teresa Perez-Guevara, M., Amoroto-Roig, M., Chappi-Estevez, Y., Bergado-Baez, G., Pi-Estopinan, F., Chen, G. W., Valdes-Balbin, Y., Garcia-Rivera, D., and Verez-Bencomo, V. 2022. A randomized, double-blind Phase I clinical trial of two recombinant dimeric RBD COVID-19 vaccine candidates: safety, reactogenicity and immunogenicity. *Vaccine* 40:2068.

96 Chang-Monteagudo, A., Ochoa-Azze, R., Climent-Ruiz, Y., Macías-Abraham, C., Rodríguez-Noda, L., Valenzuela-Silva, C., Sánchez-Ramírez, B., Perez-Nicado, R., Hernández-García, T., Orosa-Vázquez, I., Díaz-Hernández, M., García-García, M., Jerez-Barceló, Y., Triana-Marrero, Y., Ruiz-Villegas, L.,

Rodríguez-Prieto, L. D., Puga-Gómez, R., Guerra-Chaviano, P. P., Zúñiga-Rosales, Y., Marcheco-Teruel, B., Rodríguez-Acosta, M., Noa-Romero, E., Enríquez-Puertas, J., Porto-González, D., Fernández-Medina, O., Valdés-Zayas, A., Chen, G. W., Herrera-Martínez, L., Valdés-Balbín, Y., García-Rivera, D., and Verez-Bencomo, V. 2021. A single dose of SARS-CoV-2 FINLAY-FR-1A vaccine enhances neutralization response in COVID-19 convalescents, with a very good safety profile: An open-label phase 1 clinical trial. *Lancet Reg Health Am* 4:100079.

97 Xia, S., Zhang, Y., Wang, Y., Wang, H., Yang, Y., Gao, G. F., Tan, W., Wu, G., Xu, M., Lou, Z., Huang, W., Xu, W., Huang, B., Wang, W., Zhang, W., Li, N., Xie, Z., Zhu, X., Ding, L., You, W., Zhao, Y., Zhao, J., Huang, L., Shi, X., Yang, Y., Xu, G., Wang, W., Liu, P., Ma, M., Qiao, Y., Zhao, S., Chai, J., Li, Q., Fu, H., Xu, Y., Zheng, X., Guo, W., and Yang, X. 2021. Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: a randomised, double-blind, controlled, phase 1/2 trial. *Lancet Infect Dis* 22:196.

98 Xia, S., Zhang, Y., Wang, Y., Wang, H., Yang, Y., Gao, G. F., Tan, W., Wu, G., Xu, M., Lou, Z., Huang, W., Xu, W., Huang, B., Wang, H., Wang, W., Zhang, W., Li, N., Xie, Z., Ding, L., You, W., Zhao, Y., Yang, X., Liu, Y., Wang, Q., Huang, L., Yang, Y., Xu, G., Luo, B., Wang, W., Liu, P., Guo, W., and Yang, X. 2020. 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* 21:39.

99 Al Kaabi, N., Zhang, Y., Xia, S., Yang, Y., Al Qahtani, M. M., Abdulrazzaq, N., Al Nusair, M., Hassany, M., Jawad, J. S., Abdalla, J., Hussein, S. E., Al Mazrouei, S. K., Al Karam, M., Li, X., Yang, X., Wang, W., Lai, B., Chen, W., Huang, S., Wang, Q., Yang, T., Liu, Y., Ma, R., Hussain, Z. M., Khan, T., Saifuddin Fasihuddin, M., You, W., Xie, Z., Zhao, Y., Jiang, Z., Zhao, G., Zhang, Y., Mahmoud, S., ElTantawy, I., Xiao, P., Koshy, A., Zaher, W. A., Wang, H., Duan, K., Pan, A., and Yang, X. 2021. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. *JAMA* 326:35.

100 Bueno, S. M., Abarca, K., Gonzalez, P. A., Galvez, N. M. S., Soto, J. A., Duarte, L. F., Schultz, B. M., Pacheco, G. A., Gonzalez, L. A., Vazquez, Y., Rios, M., Melo-Gonzalez, F., Rivera-Perez, D., Iturriaga, C., Urzua, M., Dominguez, A., Andrade, C. A., Berrios, R. V., Canedo-Marroquin, G., Covian, C., Moreno-Tapia, D., Saavedra, F., Vallejos, O. P., Donato, P., Espinoza, P., Fuentes, D., Gonzalez, M., Guzman, P., Munoz-Venturelli, P., Perez, C. M., Potin, M., Rojas, A., Fasce, R., Fernandez, J., Mora, J., Ramirez, E., Gaete-Argel, A., Oyarzun-Arrau, A., Valiente-Echeverria, F., Soto-Rifo, R., Weiskopf, D., Sette, A., Zeng, G., Meng, W., Gonzalez-Aramundiz, J. V., Kalergis, A. M.; CoronaVac03CL Study Group. 2021. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine in a subgroup of healthy adults in Chile. *Clin Infect Dis*. DOI:10.1093/cid/ciab823

101 Han, B., Song, Y., Li, C., Yang, W., Ma, Q., Jiang, Z., Li, M., Lian, X., Jiao, W., Wang, L., Shu, Q., Wu, Z., Zhao, Y., Li, Q., and Gao, Q. 2021. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 21:1645.

102 Zeng, G., Wu, Q., Pan, H., Li, M., Yang, J., Wang, L., Wu, Z., Jiang, D., Deng, X., Chu, K., Zheng, W., Wang, L., Lu, W., Han, B., Zhao, Y., Zhu, F., Yu, H., and Yin, W. 2021. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. *Lancet Infect Dis* 22:483.

103 Chen, Y., Shen, H., Huang, R., Tong, X., and Wu, C. 2021. Serum neutralising activity against SARS-CoV-2 variants elicited by CoronaVac. *Lancet Infect Dis* 21:1071.

104 Lu, L., Mok, B. W., Chen, L. L., Chan, J. M., Tsang, O. T., Lam, B. H., Chuang, V. W., Chu, A. W., Chan, W. M., Ip, J. D., Chan, B. P., Zhang, R., Yip, C. C., Cheng, V. C., Chan, K. H., Jin, D. Y., Hung, I. F., Yuen, K. Y., Chen, H., and To, K. K. 2021. Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. *Clin Infect Dis*. DOI:10.1093/cid/ciab1041

105 Melo-Gonzalez, F., Soto, J. A., Gonzalez, L. A., Fernandez, J., Duarte, L. F., Schultz, B. M., Galvez, N. M. S., Pacheco, G. A., Rios, M., Vazquez, Y., Rivera-Perez, D., Moreno-Tapia, D., Iturriaga, C., Vallejos, O. P., Berrios-Rojas, R. V., Hoppe-Elsholz, G., Urzua, M., Bruneau, N., Fasce, R. A., Mora, J., Grifoni, A., Sette, A., Weiskopf, D., Zeng, G., Meng, W., Gonzalez-Aramundiz, J. V., Gonzalez, P. A., Abarca, K., Ramirez, E., Kalergis, A. M., and Bueno, S. M. 2021. Recognition of variants of concern by antibodies and T cells induced by a SARS-CoV-2 inactivated vaccine. *Front Immunol* 12:747830.

106 Souza, W. M., Amorim, M. R., Sesti-Costa, R., Coimbra, L. D., Brunetti, N. S., Toledo-Teixeira, D. A., de Souza, G. F., Muraro, S. P., Parise, P. L., Barbosa, P. P., Bispo-dos-Santos, K., Mofatto, L. S., Simeoni, C. L., Claro, I. M., Duarte, A. S. S., Coletti, T. M., Zangirolami, A. B., Costa-Lima, C., Gomes, A. B. S. P., Buscaratti, L. I., Sales, F. C., Costa, V. A., Franco, L. A. M., Candido, D. S., Pybus, O. G., de Jesus, J. G., Silva, C. A. M., Ramundo, M. S., Ferreira, G. M., Pinho, M. C., Souza, L. M., Rocha, E. C., Andrade, P. S., Crispim, M. A. E., Maktura, G. C., Manuli, E. R., Santos, M. N. N., Camilo, C. C., Angerami, R. N., Moretti, M. L., Spilki, F. R., Arns, C. W., Addas-Carvalho, M., Benites, B. D., Vinolo, M. A. R., Mori, M. A. S., Gaburo, N., Dye, C., Marques-Souza, H., Marques, R. E., Farias, A. S., Diamond, M. S., Faria, N. R., Sabino, E. C., Granja, F., and Proença-Módena, J. L. 2021. Neutralisation of SARS-CoV-2 lineage P.1 by antibodies elicited through natural SARS-CoV-2 infection or vaccination with an inactivated SARS-CoV-2 vaccine: an immunological study. *Lancet Microbe* 2:E527.

107 Tanriover, M. D., Doğanay, H. L., Akova, M., Güner, H. R., Azap, A., Akhan, S., Köse, Ş., Erdinç, F. Ş., Akalın, E. H., Tabak, Ö. F., Pullukçu, H., Batum, Ö., Şimşek Yavuz, S., Turhan, Ö., Yıldırmak, M. T.,

Köksal, İ., Taşova, Y., Korten, V., Yılmaz, G., Çelen, M. K., Altın, S., Çelik, İ., Bayındır, Y., Karaoğlan, İ., Yılmaz, A., Özkul, A., Gür, H., Unal, S., Kayaaslan, B., Hasanoğlu, İ., Dalkıran, A., Aydos, Ö., Çınar, G., Akdemir-Kalkan, İ., İnkaya, A. Ç., Aydin, M., Çakir, H., Yıldız, J., Kocabıyık, Ö., Arslan, S., Nallı, B., Demir, Ö., Singil, S., Ataman-Hatipoğlu, Ç., Tuncer-Ertem, G., Kınıklı, S., Önal, U., Mete, B., Dalgan, G., Taşbakan, M., Yamazhan, T., Kömürcüoğlu, B., Yalnız, E., Benli, A., Keskin-Sarıtaş, Ç., Ertosun, M. G., Özkan, Ö., Emre, S., Arıca, S., Kuşçu, F., Candevir, A., Ertürk-Şengel, B., Ayvaz, F., Aksoy, F., Mermutluoğlu, Ç., Demir, Y., Günlüoğlu, G., Tural-Önür, S., Kılıç-Toker, A., Eren, E., Otlu, B., Mete, A. Ö., Koçak, K., Ateş, H., Koca-Kalkan, İ., and Aksu, K. 2021. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 398:213.

108 Ranzani, O. T., Hitchings, M. D. T., Dorion, M., D'Agostini, T. L., de Paula, R. C., de Paula, O. F. P., Villela, E. F. M., Torres, M. S. S., de Oliveira, S. B., Schulz, W., Almiron, M., Said, R., de Oliveira, R. D., Vieira da Silva, P., de Araujo, W. N., Gorinchteyn, J. C., Andrews, J. R., Cummings, D. A. T., Ko, A. I., and Croda, J. 2021. Effectiveness of the CoronaVac vaccine in older adults during a Gamma variant associated epidemic of Covid-19 in Brazil: test negative case-control study. *BMJ* 374:n2015.

109 Jara, A., Undurraga, E. A., Gonzalez, C., Paredes, F., Fontecilla, T., Jara, G., Pizarro, A., Acevedo, J., Leo, K., Leon, F., Sans, C., Leighton, P., Suarez, P., Garcia-Escorza, H., and Araos, R. 2021. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. *N Engl J Med* 385:875.

110 Li, X. N., Huang, Y., Wang, W., Jing, Q. L., Zhang, C. H., Qin, P. Z., Guan, W. J., Gan, L., Li, Y. L., Liu, W. H., Dong, H., Miao, Y. T., Fan, S. J., Zhang, Z. B., Zhang, D. M., and Zhong, N. S. 2021. Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta variant infection in Guangzhou: a test-negative case-control real-world study. *Emerg Microbes Infect* 10:1751.

111 Ella, R., Reddy, S., Jogdand, H., Sarangi, V., Ganneru, B., Prasad, S., Das, D., Raju, D., Praturi, U., Sapkal, G., Yadav, P., Reddy, P., Verma, S., Singh, C., Redkar, S. V., Gillurkar, C. S., Kushwaha, J. S., Mohapatra, S., Bhate, A., Rai, S., Panda, S., Abraham, P., Gupta, N., Ella, K., Bhargava, B., and Vadrevu, K. M. 2021. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. *Lancet Infect Dis* 21:950.

112 Kumar, N. P., Banurekha, V. V., C, P. G., Nancy, A., Padmapriyadarsini, C., Mary, A. S., Devi, K. R. U., Murhekar, M., and Babu, S. 2021. Prime-boost vaccination with Covaxin/BBV152 induces heightened systemic cytokine and chemokine responses. *Front Immunol* 12:752397.

113 Ella, R., Reddy, S., Blackwelder, W., Potdar, V., Yadav, P., et al. 2021. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet* 398:2173.

114 Zakarya, K., Kutumbetov, L., Orynbayev, M., Abduraimov, Y., Sultankulova, K., Kassenov, M., Sarsenbayeva, G., Kulmagambetov, I., Davlyatshin, T., Sergeeva, M., Stukova, M., and Khairullin, B. 2021. Safety and immunogenicity of a QazCovid-in(R) inactivated whole-virion vaccine against COVID-19 in healthy adults: a single-centre, randomised, single-blind, placebo-controlled phase 1 and an open-label phase 2 clinical trials with a 6 months follow-up in Kazakhstan. *EClinicalMedicine* 39:101078.

115 Momin, T., Kansagra, K., Patel, H., Sharma, S., Sharma, B., Patel, J., Mittal, R., Sanmukhani, J., Maithal, K., Dey, A., Chandra, H., Rajanathan, C. T., Pericherla, H. P., Kumar, P., Narkhede, A., and Parmar, D. 2021. Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India. *EClinicalMedicine* 38:101020.

116 Barros-Martins, J., Hammerschmidt, S. I., Cossmann, A., Odak, I., Stankov, M. V., Morillas Ramos, G., Dopfer-Jablonka, A., Heidemann, A., Ritter, C., Friedrichsen, M., Schultze-Florey, C., Ravens, I., Willenzon, S., Bubke, A., Ristenpart, J., Janssen, A., Ssebyatika, G., Bernhardt, G., Munch, J., Hoffmann, M., Pohlmann, S., Krey, T., Bosnjak, B., Forster, R., and Behrens, G. M. N. 2021. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. *Nat Med* 27:1525.

117 Schmidt, T., Klemis, V., Schub, D., Mihm, J., Hielscher, F., Marx, S., Abu-Omar, A., Ziegler, L., Guckelmus, C., Urschel, R., Schneitler, S., Becker, S. L., Gartner, B. C., Sester, U., and Sester, M. 2021. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. *Nat Med* 27:1530.

118 Liu, X., Shaw, R. H., Stuart, A. S. V., Greenland, M., Aley, P. K., Andrews, N. J., Cameron, J. C., Charlton, S., Clutterbuck, E. A., Collins, A. M., Dinesh, T., England, A., Faust, S. N., Ferreira, D. M., Finn, A., Green, C. A., Hallis, B., Heath, P. T., Hill, H., Lambe, T., Lazarus, R., Libri, V., Long, F., Mujadidi, Y. F., Plested, E. L., Provstgaard-Morys, S., Ramasamy, M. N., Ramsay, M., Read, R. C., Robinson, H., Singh, N., Turner, D. P. J., Turner, P. J., Walker, L. L., White, R., Nguyen-Van-Tam, J. S., Snape, M. D., Munro, A. P. S., Bartholomew, J., Presland, L., Horswill, S., Warren, S., Varkonyi-Clifford, S., Saich, S., Adams, K., Ricamara, M., Turner, N., Yee Ting, N. Y., Whittley, S., Rampling, T., Desai, A., Brown, C. H., Qureshi, E., Gokani, K., Naker, K., Kellett Wright, J. K., Williams, R. L., Riaz, T., Penciu, F. D., Di Maso, C., Howe, E. G., Vichos, I., Ghulam Farooq, M., Noristani, R., Yao, X. L., Oldfield, N. J., Hammersley, D., Belton, S., Royal, S., San Francisco Ramos, A., Hultin, C., Galiza, E. P., Shiham, F., Solórzano, C., Sainsbury, H., Davies, K., Ambrose, P., Hitchins, L., Baker, N., Leung, S., Fothergill, R., Godwin, K., Buttigieg, K., Shaik, I., Brown, P., Knight, C., Lall, P., and Allen, L. 2021. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored

and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. *Lancet* 398:856.

119 Hillus, D., Schwarz, T., Tober-Lau, P., Vanshylla, K., Hastor, H., Thibeault, C., Jentzsch, S., Helbig, E. T., Lippert, L. J., Tscheak, P., Schmidt, M. L., Riege, J., Solarek, A., von Kalle, C., Dang-Heine, C., Gruell, H., Kopankiewicz, P., Suttorp, N., Drosten, C., Bias, H., Seybold, J., Klein, F., Kurth, F., Corman, V. M., Sander, L. E., Al-Rim, B., Bardtke, L., Beheim-Schwarzbach, J. I., Behn, K., Bergfeld, L., Bethke, N., Bleicker, T., Briesemeister, D., Brumhard, S., Conrad, C., Dieckmann, S., Frey, D., Gabelich, J.-A., Georg, P., Gläser, U., Hasler, L., Hetey, A., Hiller, A. L., Horn, A., Hülso, C., Kegel, L., Koch, W., Krannich, A., Kroneberg, P., Lisy, M., Mackeldanz, P., Maeß, B., Münn, F., Olk, N., Peiser, C., Pohl, K., Hermel, A., Rönnefarth, M., Rubisch, C., Sanchez Rezza, A., Schellenberger, I., Schenkel, V., Schlesinger, J., Schmidt, S., Schwanitz, G., Sinnigen, A.-S., Stubbemann, P., Tesch, J., Treue, D., Wendisch, D., and Zvorc, S. 2021. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. *Lancet Respir Med* 9:1255.

120 Behrens, G. M., Cossmann, A., Stankov, M. V., Nehlmeier, I., Kempf, A., Hoffmann, M., and Pohlmann, S. 2021. SARS-CoV-2 delta variant neutralisation after heterologous ChAdOx1-S/BNT162b2 vaccination. *Lancet* 398:1041.

121 Gram, M. A., Nielsen, J., Schelde, A. B., Nielsen, K. F., Moustsen-Helms, I. R., Sorensen, A. K. B., Valentiner-Branth, P., and Emborg, H. D. 2021. Vaccine effectiveness against SARS-CoV-2 infection, hospitalization, and death when combining a first dose ChAdOx1 vaccine with a subsequent mRNA vaccine in Denmark: A nationwide population-based cohort study. *PLoS Med* 18:e1003874.

122 Yorsaeng, R., Suntronwong, N., Phowatthanasathian, H., Assawakosri, S., Kanokudom, S., Thongmee, T., Vichaiwattana, P., Auphimai, C., Wongsrisang, L., Srimuan, D., Thatsanatorn, T., Klinfueng, S., Sudhinaraset, N., Wanlapakorn, N., and Poovorawan, Y. 2021. Immunogenicity of a third dose viral-vectored COVID-19 vaccine after receiving two-dose inactivated vaccines in healthy adults. *Vaccine* 40:524.

123 Moghnieh, R., Mekdashi, R., El-Hassan, S., Abdallah, D., Jisr, T., Bader, M., Jizi, I., Sayegh, M. H., and Rahman Bizri, A. 2021. Immunogenicity and reactogenicity of BNT162b2 booster in BBIBP-CorV-vaccinated individuals compared with homologous BNT162b2 vaccination: Results of a pilot prospective cohort study from Lebanon. *Vaccine* 39:6713.

124 Intapiboon, P., Seepathomnarong, P., Ongarj, J., Surasombatpattana, S., Uppanisakorn, S., Mahasirimongkol, S., Sawaengdee, W., Phumiamorn, S., Sapsutthipas, S., Sangsupawanich, P., Chusri, S., and Pinpathomrat, N. 2021. Immunogenicity and safety of an intradermal BNT162b2 mRNA vaccine booster after two doses of inactivated SARS-CoV-2 vaccine in healthy population. *Vaccines (Basel)* 9:1375.

125 Ai, J., Zhang, H., Zhang, Y., Lin, K., Zhang, Y., Wu, J., Wan, Y., Huang, Y., Song, J., Fu, Z., Wang, H., Guo, J., Jiang, N., Fan, M., Zhou, Y., Zhao, Y., Zhang, Q., Liu, Q., Lv, J., Li, P., Qiu, C., and Zhang, W. 2021. Omicron variant showed lower neutralizing sensitivity than other SARS-CoV-2 variants to immune sera elicited by vaccines after boost. *Emerg Microbes Infect* 11:1.

126 Cao, Y., Hao, X., Wang, X., Wu, Q., Song, R., Zhao, D., Song, W., Wang, Y., Yisimayi, A., Wang, W., Zhang, W., Du, J., Yu, H., Xie, X. S., and Jin, R. 2021. Humoral immunogenicity and reactogenicity of CoronaVac or ZF2001 booster after two doses of inactivated vaccine. *Cell Res.* 32:107.

127 Chua, G. T., Kwan, M. Y. W., Chui, C. S. L., Smith, R. D., Cheung, E. C., Tian, T., Leung, M. T. Y., Tsao, S. S. L., Kan, E., Ng, W. K. C., Man Chan, V. C., Tai, S. M., Yu, T. C., Lee, K. P., Wong, J. S. C., Lin, Y. K., Shek, C. C., Leung, A. S. Y., Chow, C. K., Li, K. W., Ma, J., Fung, W. Y., Lee, D., Ng, M. Y., Wong, W. H. S., Tsang, H. W., Kwok, J., Leung, D., Chung, K. L., Chow, C. B., Chan, G. C. F., Leung, W. H., To, K. K. W., Yuen, K. Y., Lau, Y. L., Wong, I. C. K., and Ip, P. 2021. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following Comirnaty vaccination. *Clin Infect Dis*. DOI:10.1093/cid/ciab989

128 Mevorach, D., Anis, E., Cedar, N., Bromberg, M., Haas, E. J., Nadir, E., Olsha-Castell, S., Arad, D., Hasin, T., Levi, N., Asleh, R., Amir, O., Meir, K., Cohen, D., Dichtiar, R., Novick, D., Hershkovitz, Y., Dagan, R., Leitersdorf, I., Ben-Ami, R., Miskin, I., Saliba, W., Muhsen, K., Levi, Y., Green, M. S., Keinan-Boker, L., and Alroy-Preis, S. 2021. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med* 385:2140.

129 Witberg, G., Barda, N., Hoss, S., Richter, I., Wiessman, M., Aviv, Y., Grinberg, T., Auster, O., Dagan, N., Balicer, R. D., and Kornowski, R. 2021. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med* 385:2132.

130 Gargano, J. W., Wallace, M., Hadler, S. C., Langley, G., Su, J. R., Oster, M. E., Broder, K. R., Gee, J., Weintraub, E., Shimabukuro, T., Scobie, H. M., Moulia, D., Markowitz, L. E., Wharton, M., McNally, V. V., Romero, J. R., Talbot, H. K., Lee, G. M., Daley, M. F., and Oliver, S. E. 2021. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep* 70:977.

131 Bozkurt, B., Kamat, I., and Hotez, P. J. 2021. Myocarditis with COVID-19 mRNA vaccines. *Circulation* 144:471.

132 Schultz, N. H., Sørvoll, I. H., Michelsen, A. E., Munthe, L. A., Lund-Johansen, F., Ahlen, M. T., Wiedmann, M., Aamodt, A. H., Skattør, T. H., Tjønnfjord, G. E., and Holme, P. A. 2021. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 384:2124.

133 Scully, M., Singh, D., Lown, R., Poles, A., Solomon, T., Levi, M., Goldblatt, D., Kotoucek, P., Thomas, W., and Lester, W. 2021. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 384:2202.
134 Muir, K. L., Kallam, A., Koepsell, S. A., and Gundabolu, K. 2021. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. *N Engl J Med* 384:1964.
135 Sangli, S., Virani, A., Cheronis, N., Vannatter, B., Minich, C., Noronha, S., Bhagavatula, R., Speredelozzi, D., Sareen, M., and Kaplan, R. B. 2021. Thrombosis with thrombocytopenia after the messenger RNA-1273 vaccine. *Ann Intern Med* 174:1480.
136 Hippisley-Cox, J., Patone, M., Mei, X. W., Saatci, D., Dixon, S., Khunti, K., Zaccardi, F., Watkinson, P., Shankar-Hari, M., Doidge, J., Harrison, D. A., Griffin, S. J., Sheikh, A., and Coupland, C. A. C. 2021. Risk of thrombocytopenia and thromboembolism after Covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. *BMJ* 374:n1931.
137 Pavord, S., Hunt, B. J., Horner, D., Bewley, S., and Karpusheff, J. 2021. Vaccine induced immune thrombocytopenia and thrombosis: summary of NICE guidance. *BMJ* 375:n2195.
138 Kelton, J. G., Arnold, D. M., and Nazy, I. 2021. Lessons from vaccine-induced immune thrombotic thrombocytopenia. *Nat Rev Immunol* 21:753.
139 Huynh, A., Kelton, J. G., Arnold, D. M., Daka, M., and Nazy, I. 2021. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. *Nature* 596:565.
140 Greinacher, A., Selleng, K., Palankar, R., Wesche, J., Handtke, S., Wolff, M., Aurich, K., Lalk, M., Methling, K., Völker, U., Hentschker, C., Michalik, S., Steil, L., Reder, A., Schönborn, L., Beer, M., Franzke, K., Büttner, A., Fehse, B., Stavrou, E. X., Rangaswamy, C., Mailer, R. K., Englert, H., Frye, M., Thiele, T., Kochanek, S., Krutzke, L., Siegerist, F., Endlich, N., Warkentin, T. E., and Renné, T. 2021. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. *Blood* 138:2256.
141 Greinacher, A., Selleng, K., Mayerle, J., Palankar, R., Wesche, J., Reiche, S., Aebischer, A., Warkentin, T. E., Muenchhoff, M., Hellmuth, J. C., Keppler, O. T., Duerschmied, D., Lother, A., Rieg, S., Gawaz, M. P., Mueller, K. A. L., Scheer, C. S., Napp, M., Hahnenkamp, K., Lucchese, G., Vogelgesang, A., Flöel, A., Lovreglio, P., Stufano, A., Marschalek, R., and Thiele, T. 2021. Anti-platelet factor 4 antibodies causing VITT do not cross-react with SARS-CoV-2 spike protein. *Blood* 138:1269.
142 Tauzin, A., Nayrac, M., Benlarbi, M., Gong, S. Y., Gasser, R., Beaudoin-Bussieres, G., Brassard, N., Laumaea, A., Vezina, D., Prevost, J., Anand, S. P., Bourassa, C., Gendron-Lepage, G., Medjahed, H., Goyette, G., Niessl, J., Tastet, O., Gokool, L., Morrisseau, C., Arlotto, P., Stamatatos, L., McGuire, A. T., Larochelle, C., Uchil, P., Lu, M., Mothes, W., De Serres, G., Moreira, S., Roger, M., Richard, J., Martel-Laferriere, V., Duerr, R., Tremblay, C., Kaufmann, D. E., and Finzi, A. 2021. A single dose of the SARS-CoV-2 vaccine BNT162b2 elicits Fc-mediated antibody effector functions and T cell responses. *Cell Host Microbe* 29:1137.
143 Shrotri, M., Krutikov, M., Palmer, T., Giddings, R., Azmi, B., Subbarao, S., Fuller, C., Irwin-Singer, A., Davies, D., Tut, G., Lopez Bernal, J., Moss, P., Hayward, A., Copas, A., and Shallcross, L. 2021. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of long-term care facilities in England (VIVALDI): a prospective cohort study. *The Lancet Infectious Diseases* 21:1529.
144 Lopez Bernal, J., Andrews, N., Gower, C., Robertson, C., Stowe, J., Tessier, E., Simmons, R., Cottrell, S., Roberts, R., O'Doherty, M., Brown, K., Cameron, C., Stockton, D., McMenamin, J., and Ramsay, M. 2021. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on Covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 373:n1088.
145 Amirthalingam, G., Bernal, J. L., Andrews, N. J., Whitaker, H., Gower, C., Stowe, J., Tessier, E., Subbarao, S., Ireland, G., Baawuah, F., Linley, E., Warrener, L., O'Brien, M., Whillock, C., Moss, P., Ladhani, S. N., Brown, K. E., and Ramsay, M. E. 2021. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England. *Nat Commun* 12:7217.
146 Payne, R. P., Longet, S., Austin, J. A., Skelly, D. T., Dejnirattisai, W., Adele, S., Meardon, N., Faustini, S., Al-Taei, S., Moore, S. C., Tipton, T., Hering, L. M., Angyal, A., Brown, R., Nicols, A. R., Gillson, N., Dobson, S. L., Amini, A., Supasa, P., Cross, A., Bridges-Webb, A., Reyes, L. S., Linder, A., Sandhar, G., Kilby, J. A., Tyerman, J. K., Altmann, T., Hornsby, H., Whitham, R., Phillips, E., Malone, T., Hargreaves, A., Shields, A., Saei, A., Foulkes, S., Stafford, L., Johnson, S., Wootton, D. G., Conlon, C. P., Jeffery, K., Matthews, P. C., Frater, J., Deeks, A. S., Pollard, A. J., Brown, A., Rowland-Jones, S. L., Mongkolsapaya, J., Barnes, E., Hopkins, S., Hall, V., Dold, C., Duncan, C. J. A., Richter, A., Carroll, M., Screaton, G., de Silva, T. I., Turtle, L., Klenerman, P., Dunachie, S.; The Pitch Consortium. 2021. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. *Cell* 184:5699.
147 Feng, S., Phillips, D. J., White, T., Sayal, H., Aley, P. K., Bibi, S., Dold, C., Fuskova, M., Gilbert, S. C., Hirsch, I., Humphries, H. E., Jepson, B., Kelly, E. J., Plested, E., Shoemaker, K., Thomas, K. M., Vekemans, J., Villafana, T. L., Lambe, T., Pollard, A. J., Voysey, M.; Oxford COVID Vaccine Trial Group. 2021. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* 27:2032.
148 Logunov, D. Y., Dolzhikova, I. V., Shcheblyakov, D. V., Tukhvatulin, A. I., Zubkova, O. V., Dzharullaeva, A. S., Kovyrshina, A. V., Lubenets, N. L., Grousova, D. M., Erokhova, A. S., Botikov, A. G., Izhaeva, F. M., Popova, O., Ozharovskaya, T. A., Esmagambetov, I. B., Favorskaya, I. A., Zrelkin, D. I., Voronina, D. V., Shcherbinin, D. N., Semikhin, A. S., Simakova, Y. V., Tokarskaya, E. A., Egorova, D. A., Shmarov, M.

M., Nikitenko, N. A., Gushchin, V. A., Smolyarchuk, E. A., Zyryanov, S. K., Borisevich, S. V., Naroditsky, B. S., and Gintsburg, A. L. 2021. 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* 397:671.

149 Desai, D., Khan, A. R., Soneja, M., Mittal, A., Naik, S., Kodan, P., Mandal, A., Maher, G. T., Kumar, R., Agarwal, A., Gowda, N. R., H, V., Kumar, P., Pandey, S., Pandey, R. M., Kumar, A., Ray, A., Jorwal, P., Nischal, N., Choudhary, A., Brijwal, M., Madan, K., Lodha, R., Sinha, S., Dar, L., Wig, N., and Guleria, R. 2021. Effectiveness of an inactivated virus-based SARS-CoV-2 vaccine, BBV152, in India: a test-negative, case-control study. *Lancet Infect Dis* 22:349.

Table 1. Updated results of the efficacy and effectiveness in preventing COVID-19 of early vaccines.

Vacci1ne	Efficacy in preventing COVID-19 in Phase 3 clinical trials	Effectiveness in preventing COVID-19 in real-world	References
BNT162b2 (Comirnaty)	91.3% (symptomatic) 96.7% (severe)	USA: 91.3% (symptomatic) Canada: 91% (symptomatic); 96% (hospitalization/death) Hungary: 83.3% (infection); 90.6% (death) UK: 93.7% (symptomatic caused by Alpha); 88.0% (symptomatic caused by Delta); 90% (death caused by Delta in Scotland) Italy: 83% (infection caused by Alpha) Qatar: 51.9% (infection); 93.4% (severe/critical/fetal disease caused by Delta)	(29-34,35,36)
mRNA-1273 (SpikeVax)	63.0% (infection) 93.2% (symptomatic) 98.2% (severe)	Canada: 94% (symptomatic); 96% (hospitalization/death) Hungary: 88.7% (infection); 93.6% (death) USA: 86.7% (infection); 97.5% (hospitalization caused by Delta) Qatar: 73.1% (infection); 96.1% (severe/critical/fetal caused by Delta)	(30,32,36,54,55)
AZD1222 (Vaxzevria)	74.0% (symptomatic)[1] 100% (severe or critical symptomatic)	UK: 74.5% (symptomatic COVID-19 caused by Alpha); 67.0% (symptomatic COVID-19 caused by Delta); 91% (death caused by Delta in Scotland) Hungary: 71.5% (infection); 88.3% (death) India[1]: 63.1% (infection); 81·5% (moderate-to-severe)	(32,34,35,59,61)
Ad26.COV2.S	66.9% (symptomatic) 76.7% (severe–critical)	USA: 73.6%[2] (infection) 86.6%[3] (symptomatic)	(31,66,67)
Ad5-nCoV (Convidecia)	57.5% (symptomatic) 91.7% (severe)	NA	(71)
Gam-COVID-Vac (Sputnik V)	91.6% (symptomatic) 100% (moderate or severe)	Hungary: 85.7% (infection); 97.5% (death)	(32,148)
ZF2001 (ZIFIVAX)	Short-term (~50 days) follow-up: 81.4% (symptomatic) 92.9% (severe–critical) Long-term (6 months) follow-up: 75.7% (symptomatic) 87.6% (severe–critical)	NA	(82)
NVX-CoV2373 (Nuvaxovid)	US and Mexico[4]: 90.4% (symptomatic); 100% (moderate-to-severe) South Africa[5]: 60.1% (symptomatic) UK[4]: 89.7% (symptomatic)	NA	(85-87)
BBIBP-CorV (Covilo)	78.1% (symptomatic)	Hungary: 68.7% (infection); 87.8% (death)	(32,99)
CoronaVac	83.5%[6] (symptomatic)	Brazil[7]: 46.8% (symptomatic); 55.5% (hospital admission); 61.2% (death) Chile: 65.9% (symptomatic); 87.5% (hospitalization); 86.3% (death)	(107-109)
BBV152 (Covaxin)	63·6% (asymptomatic infection) 77.8% (symptomatic) 93.4% (severe)	India: 50% (symptomatic)[1]	(113,149)

[1]In the setting of widespread transmission of Delta VOC.

[2]Arizona, Iowa, Minnesota, Florida, and Wisconsin.

[3]New York State.

[4]In the setting of widespread transmission of the Alpha VOC.

[5]Largely caused by Beta VOC.

[6]The interim efficacy results of phase 3 clinical trial in Turkey.

[7]In the setting of widespread transmission of the Gamma VOC.

NA, not applicable.

Table 2. Features of recent vaccines and candidates against COVID-19.

Vaccine	Platform	Developer	Formulation	NAb level in humans	Cellular responses in humans	Efficacy	References
Recombinant COVID-19 vaccine	Protein subunit (Sf9 cells)	West China Hospital of Sichuan University, China	RBD protein + aluminum hydroxide adjuvant	Induction of NAb in humans and no comparison with HCS	Induction of IFN-γ^+ T-cell responses	NA	(90)
MVC-COV1901	Protein subunit (CHO cells)	Medigen Vaccine Biologics Corporation, Taiwan, China	S protein with two proline substitutions (K986P and V987P), 682-685 "GSAS" substitution at the furin cleavage site and T4 fibritin trimerization motif + aluminum hydroxide and CpG 1018 adjuvants	Higher GMT levels than HCS in 15 μg and 25 μg groups	Induction of IFN-γ^+ T-cell responses	NA	(91,92)
Sclamp	Protein subunit (CHO cells)	University of Queensland and CSL Limited, Australia	Prefusion trimeric S protein with molecular clamp domain from HIV-1 gp41 protein + MF59 adjuvant	Similar titers among 5, 15 and 45 μg groups, and generally similar to HCS	Predominantly Th1 phenotype	NA	(94)
FINLAY-FR-1 (SOBERANA 01) and FINLAY-FR-1A (SOBERANA Plus)	Protein subunit (CHO cells)	Finlay Vaccine Institute and Centre of Molecular Immunology, Cuba	Dimeric RBD protein with Cys538–Cys538 interchain disulphide bridge + OMVs and aluminum hydroxide adjuvants (for FINLAY-FR-1) or aluminum hydroxide adjuvant (for FINLAY-FR-1A)	Higher GMT level than HCS in FINLAY-FR-1 (50 μg) group; Lower GMT levels than HCS in FINLAY-FR-1A (25 and 50 μg) groups	NA in naïve participants	NA	(95)
CVnCoV	mRNA	CureVac AG, Germany	LNP-mRNA expressing full-length S protein with two proline substitutions (K986P and V987P)	Generally lower GMT levels for all dose groups than HCS	NA	48.2% overall vaccine efficacy against symptomatic COVID-19	(56,57)
ZyCoV-D	DNA	Zydus Cadila, India	DNA plasmid expressing full-length S protein	Generally similar (NFIS 2 mg group) to or lower (NFIS 1 mg and Needle 1/2 mg groups) than HCS	Induction of IFN-γ^+ cellular responses	NA	(115)
QazCovid-in	Inactivated virus	Research Institute for Biological Safety Problems, Kazakhstan	Inactivated whole virus + aluminum hydroxide adjuvant	Induction of NAb in humans and no comparison with HCS	Induction of IFN-α^+, IFN-γ^+, TNF-α^+, IL-4^+ and IL-6^+ T-cell responses	NA	(114)

NA, not appplicable.

Figure legend

Fig. 1. The 30 authorized COVID-19 vaccines.