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REVIEW

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Recent developments in SARS-CoV-2 vaccines: A systematic review of the current studies

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Abstract

Designing and manufacturing efficient vaccines against coronavirus disease 2019 (COVID-19) is a major objective. In this systematic review, we aimed to evaluate the most important vaccines under construction worldwide, their efficiencies and clinical results in healthy individuals and in those with specific underlying diseases. We conducted a comprehensive search in PubMed, Scopus, EMBASE, and Web of Sciences by 1 December 2021 to identify published research studies. The inclusion criteria were publications that evaluated the immune responses and safety of COVID-19 vaccines in healthy individuals and in those with pre-existing diseases. We also searched the VAERS database to estimate the incidence of adverse events of special interest (AESI) post COVID-19 vaccination. Almost all investigated vaccines were well tolerated and developed good levels of both humoural and cellular responses. A protective and efficient humoural immune response develops after the second or third dose of vaccine and a longer interval (about 28 days) between the first and second injections of vaccine could induce higher antibody responses. The vaccines were less immunogenic in immunocompromised patients, particularly those with haematological malignancies. In addition, we found that venous and arterial thrombotic events, Bell's palsy, and myocarditis/pericarditis were the most common AESI. The results showed the potency of the SARS-CoV-2 vaccines to protect subjects against disease. The provision of further effective and safe vaccines is necessary in order to reach a high coverage of immunisation programs across the globe and to provide protection against infection itself.

KEYWORDS
COVID-19, efficacy, immune system, immunogenicity, SARS-CoV-2, vaccine

Abbreviations: AEs, adverse events; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; CAMS, Chinese Academy of Medical Sciences; IFNγ, interferon gamma; IL, interleukin; MMR, measles, mumps and rubella; MERS-CoV, Middle East respiratory syndrome coronavirus; nAbs, neutralising antibodies; rAd26, recombinant adenovirus type 26; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumour necrosis factor; VLP, virus-like particle.

Mona Sadeghalvad and Amir Hossein Mansourabadi contributed equally to the manuscript.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is probably the most challenging disease of the current century, which has had irreversible effects on public health since 2 December019.[1] The present epidemic of COVID-19 is the third well-known spill over of an animal coronavirus onto humans in the last two decades, which has led to a major worrying pandemic worldwide.[2] The speed of transmission of SARS-CoV-2 and the daily increase in the number of confirmed cases is much faster than the other members of the SARS family.[3] At the time of writing this review article, this outbreak has spread to almost all countries and territories and has infected at least 262 million people so far and killed more than five million individuals globally.[4]

Although transmission reduction strategies, including social-distancing, which are performed in almost all countries, have prevented individuals from being affected, these strategies will paradoxically leave them unprotected from SARS-CoV-2 and thus vulnerable to infection.[5] In the meantime, health-care workers, elderlies, and those with a defect or suppressed immune systems are at particularly high risk.[6] Therefore, the best way to control this pandemic is to create an effective and useful vaccine.

SARS-CoV-2 contains four major structural proteins, used in vaccine design (Figure 1). The general consensus is that the world will not return to its pre-pandemic status until effective and safe vaccines become available and a global vaccination programme is successfully implemented.

Inactivated vaccines have received a lot of attention because they can elicit immune responses similar to those that occur against the virus particles.[7] These types of vaccines contain whole virus particles without replicating potential due to a lack of live genetic material. These vaccines are prepared by using virus inactivation approaches such as using chemical agents (e.g. formaldehyde, phenol, glutaraldehyde), radiation (e.g. ultra violet (UV), X-ray, or gamma irradiation), or by physical methods (e.g. heat, pressure, or pH).[7]

Nucleic acid-based vaccines are new types of vaccines, that include RNA vaccines.[8] These types of vaccines include an mRNA strand coding for a specific antigen. They can be transcribed into a viral protein once they are delivered into human cells. To trigger an immune response, the viral protein could be presented on the cell surface where it is recognised by immune system components.[8] RNA-based vaccines have been previously studied for viral infections such as influenza, rabies, and cytomegalovirus (CMV).[8]

Two main types of viral vector-based vaccines have been identified.[9] Non-replicating vector vaccines just produce the vaccine antigen, and they are unable to produce new viral particles. Replicating vector vaccines could produce new viral particles and also enable to infect cells. Current developed viral vector vaccines for SARS-CoV-2 are non-replicating viral vectors.[9]

Prior attempts for development of vaccines against other Coronaviruses such as SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), revealed that spike (S) proteins are appropriate targets for developing the SARS-CoV-2 subunit vaccines.[10] S protein contains two subunits, S1 and S2, which mediate receptor binding and membrane fusion, respectively. Subunit S1 consists of RBD that can stimulate tissue tropism of viruses as well as induction of neutralising antibodies (nAbs).[10]

Virus-like particles (VLPs) are artificially produced nanoparticles composed of a subset of viral components that roughly resemble the structure, size, and surface composition of natural viruses which accounts for their robust immunogenicity and induction of both antibody and cellular immune responses.[11] Different expression systems, including mammalian cell lines, bacteria, insect cell lines, yeast, and plant cells, have been used to construct VLPs.[12] Due to a lack of core genetic material, VLPs are non-infectious which suggests them as a safer vaccine platform compared to several others, as well as makes them a safe and relevant model in performing molecular virus studies under biosafety level (BSL)-2 conditions without biosafety protection. Besides being safe and efficacious, VLP vaccines also have the advantages of multivalency, inhaled vaccination potential, self-adjuvant property, scalable manufacturing, and easily maintainable temperatures in the supply chain.[13] Human papillomavirus (HPV) and hepatitis B vaccines are of well-known and commercially available FDA-approved VLP vaccines[14] and many more types of VLP vaccine targeting other diseases, including COVID-19, are currently being developed.

In this systematic review, we have evaluated the most important vaccines under construction worldwide, their efficacy and safety in healthy individuals and those with underlying diseases of interest.

2 | METHODS

This systematic review was prepared according to the Preferred Reporting Items for systematic review and Meta-Analysis (PRISMA) 2020 checklist (Table S1).[15]

2.1 | Search strategy

A comprehensive search strategy was performed in PubMed, Scopus, EMBASE, and Web of Sciences by 1 December 2021 to identify published publications regarding the immune response and safety of COVID-19 vaccines in healthy individuals and those with underlying diseases. The search keywords are available in the supplementary data, Table S2.

2.2 | Study eligibility criteria

Title and abstract screening were performed by two authors using the predefined inclusion criteria and excluded duplicate publications. Disagreement was resolved through discussion with two more authors.

To be eligible, studies had to meet the following criteria:

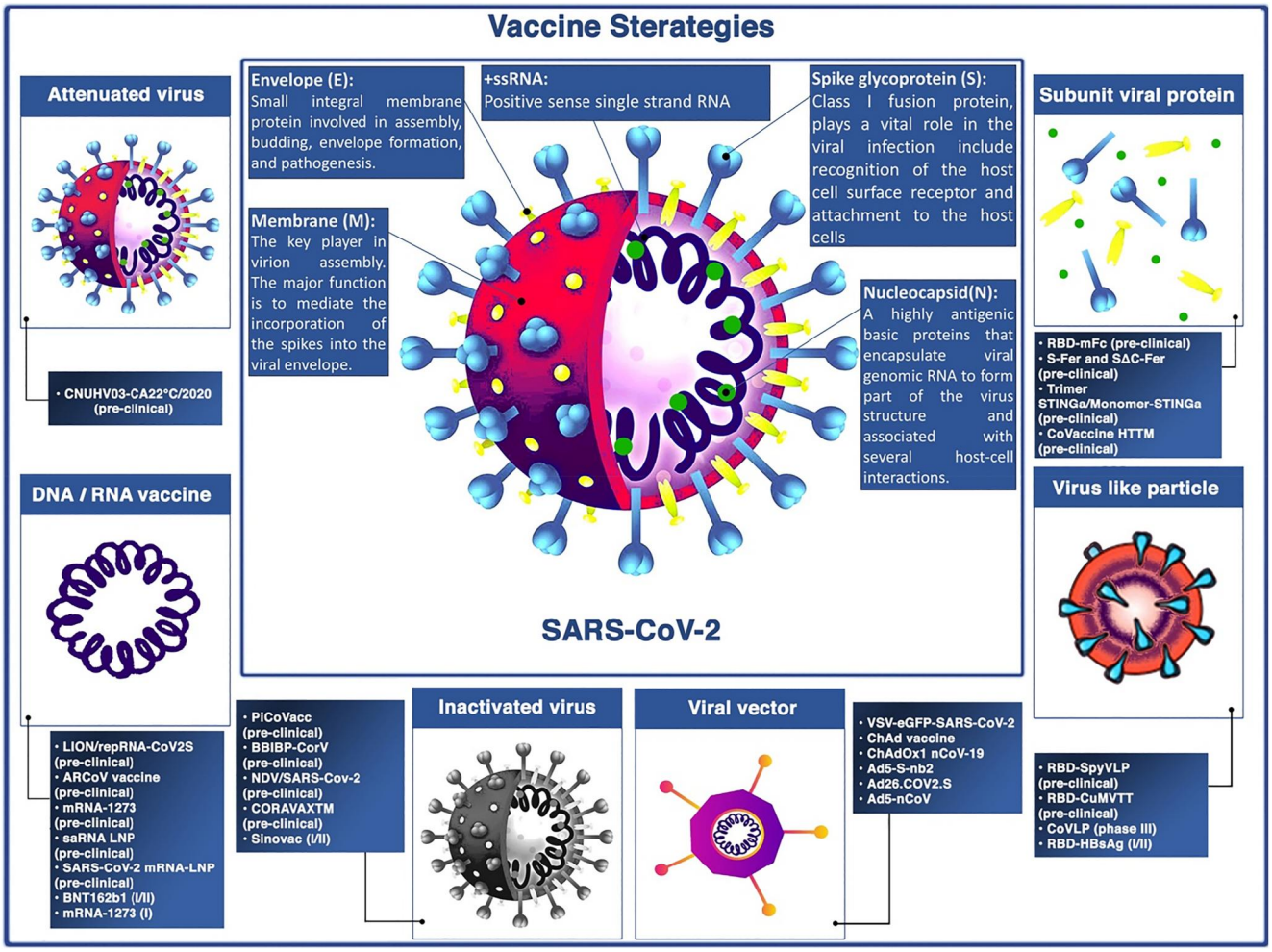

FIGURE 1 SARS-CoV-2 major structural proteins and summary of strategy types for COVID-19 vaccine designing

(1) Clinical trials assessing the immunogenicity, safety, and efficacy of COVID-19 vaccines that published their results.
(2) Publications assessing the immunogenicity and safety of COVID-19 vaccines in participants with underlying disorders.

Meanwhile, trials were excluded directly, if:

(1) Received any types of therapies except SARS-CoV-2 vaccines.
(2) Received vaccines against other types of coronaviruses except SARS-CoV-2.
(3) Review articles, systematic reviews, hypothesis articles, abstracts, case reports, case series, and bioinformatics assessments.

2.3 | Study quality assessment and data extraction

The quality of each publication was independently evaluated by two authors according to the PRISMA checklist. The full text of relevant studies was reviewed by three authors for evaluating the eligibility according to the inclusion and exclusion criteria. The following items were extracted from the included studies: first author's name, publication date, name of vaccine and the manufacture, number of participants, health status, schedule and dose of the vaccine received, immunogenicity, safety, and efficacy.

2.4 | Analysing the incidence of adverse events of special interest post COVID-19 vaccination in the USA

We utilised the data from the Vaccine Adverse Event Reporting System (VAERS) framework, which is a national post marketing spontaneous surveillance programme for vaccine safety.[16] Symptoms of adverse events (AEs) in VAERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA), which is a highly validated and standardised terminology.[17] In order to estimate the incidence of some commonly reported adverse events of special interest post COVID-19 immunisation with three vaccines (i.e. Pfizer-BioNTech, Moderna, and Johnson & Johnson's Janssen), which have been authorised for emergency use in the USA, we searched the VAERS as of 22 November 2021. The number of reported venous and arterial thrombotic events, Bell's palsy,

myocarditis/pericarditis, anaphylaxis, Guillian-Barre syndrome, and transverse myelitis cases who received at least one dose of vaccine, were retrieved from the VAERSE database along with demographic information of the cases.

3 | RESULTS

3.1 | Immunogenicity, safety, and efficacy of SARS-CoV-2 vaccines

By 1 Dec 2021 from an initial screen of 132 identified studies, 88 studies provided clinical outcome data on the use of SARS-CoV-2 vaccines in healthy subjects. These results include inactivated vaccines (n = 15), RNA vaccines (n = 13), vector-based vaccines (n = 16), and subunit vaccines (n = 10; Figure 2). Totally, 6,831,932 healthy subjects were enroled in these studies. Besides, 34 publications were also found which evaluated the immunogenicity and safety of COVID-19 vaccines in individuals with underlying diseases. The characteristics of the included clinical studies, including the study type, clinical phase, country, route/schedule of the vaccination, days of injections, immunogenicity of the vaccines (humoural and cellular immune responses), efficacy, and related AEs are summarised in Table 1.

3.1.1 | Inactivated whole virus vaccines

A total of 15 studies were identified that provided clinical outcomes as well as vaccine immunogenicity and efficacy on the use of SARS-CoV-2 inactivated vaccines in healthy subjects.[18–32] Two studies[22,26] were in the phase I trial, five studies[25,28–31] in the phase I/II trial, three studies in the phase II trial,[19,21,32] and five studies in the phase III trial.[18,20,23,24,27]

The reports of phase I and II trials of an inactivated SARS-CoV-2 vaccine (CoronaVac) developed by Sinovac Biotech in China showed that the nAbs and specific IgG antibodies were increased at 14 and 28 days after two-dose vaccination with either 6 μg or 3 μg formulations and that the higher increase in antibody titres was observed in 6 μg group.[31,32] For adults aged 60 years or older, the seroconversion rate for nAbs reached 99% in 6 μg group 28 days post second immunisation.[28] A phase III trial of the vaccine was conducted in three countries (Turkey, Indonesia, and Chile). The overall vaccine efficacy ranged from 65.3% to 83.5%, and the vaccine was efficient in preventing hospitalisation by 87.5%–100%. Pain at the injection site was the most common local AE, while fatigue and myalgia were frequently reported systemic AEs.[23,24,27]

Similar results were found by the phase I/II trial of two inactivated SARS-CoV-2 vaccines (WIV04 and HB02 strains) developed by Sinopharm's vaccine-making unit. The results of both phases showed that high levels of nAbs and specific IgG antibodies could be developed after two injections by 21 or 28 days intervals compared with a shorter interval schedule (14 days interval).[29,30] The phase 3 trial that was conducted in the United Arab Emirates and Bahrain reported the overall vaccine efficacy to be 64% for the vaccine based on the WIV04 strain and 73.5% for the HB02 strain, which could completely prevent hospitalisation.[18] The most reported injection site AE was pain, and the highest rate of systemic AEs was for fever and headache.

The results of the phases I and II trials of the inactivated vaccine developed by Institute of Medical Biology (IMB) and the Chinese Academy of Medical Sciences (CAMS) reported that two injections of vaccine at day D0/D14 or D0/D28 induced high levels of nAbs, anti-N, and anti-S antibodies that were higher in the medium dose group with a 14-days interval for phase I trial.[26] However, the antibody titres were higher in the high dose group with a 28-days interval schedule for the phase II trial.[19] The most common injection side AE was pain, which was mild and self-limiting. Slight fatigue and fever were the most systemic AEs.

Three phases of another inactivated vaccine (BBV152) developed by Bharat Biotech in collaboration with the Indian Council of Medical Research were completely conducted in India. In phase 1 with a 14-day interval schedule, the seroconversion rate was higher for the 6 μg group with Algel-IMDG, while in phase 2 that the doses were 28 days apart, the 3 μg group with Algel-IMDG were seroconverted at higher rates. Both 3 μg and 6 μg regimens elicited detectable CD4+ and CD8+ T-cell responses.[21,22] The overall efficacy of vaccine in phase 3 trial was 77.8% and it was 65.2% for B.1.617.2 variant.[20] The most commonly reported local and systemic AEs were pain at the injection site and fever in addition to headache, in descending order of frequency.

The last inactivated vaccine (KCONVAC) was developed by Shenzhen Kangtai Biological Products and Beijing Minhai Biotechnology in China and its findings from phase I/II trials have been published. It revealed that a 5 μg regimen group with 28-day intervals elicited higher antibody titres than that of 10 μg groups with 14-day intervals. The vaccine induced a moderate T-cell response with higher rates of detection of interleukin (IL)-2 than interferon (IFN)-γ, post second dose injection.[25] Pain at inoculation site and fatigue were highly reported AEs.

3.1.2 | Nucleic acid-based vaccines

A total of 13 studies were identified that provided clinical outcomes as well as vaccine immunogenicity and efficacy of SARS-CoV-2 RNA vaccines in healthy subjects. Five studies[33–37] were in the phase I trial, two studies in the phase I/II trial,[38,39] one study in the phase II trial,[40] two studies in the phase II/III trial,[41,42] and three studies in phase III trial.[43–45] The mRNA coding for the S-protein of SARS-CoV-2 was the most common antigen in these trials.

Phases I/II trials conducted by Pfizer/BioNtech in the USA reported the safety, tolerability, and immunogenicity data of BNT162b1, an mRNA vaccine, among 45 healthy adults. An increased concentration of RBD-binding IgG was reported on day 21 after the

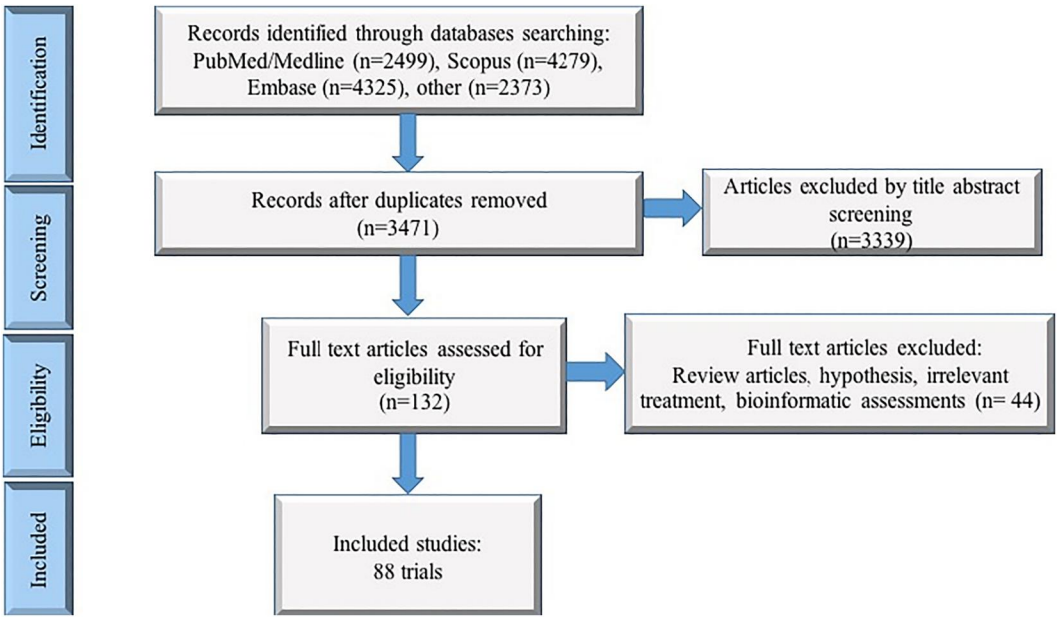

FIGURE 2 Flow diagram of study selection

first dose, which substantially increased on day 7 after the second dose injection. SARS-CoV-2 neutralisation antibodies were increased at day 28 (i.e. 7 days after the second dose).[39]

In order to evaluate the potency and safety of BNT162b1 and BNT162b2, a phase I trial was applied in two age groups including 18–55- and 65–85-years' old subjects in the USA by Pfizer/BioNTech. Although antigen-binding IgG and virus-neutralising responses were boosted by the second dose (highest titre on day 28 or 35) in both the younger adults and the older adults, the older ones had lower levels of antibodies than the younger ones.[36] In older adults, BNT162b2 was related to a lower incidence and severity of systemic adverse events than BNT162b1. Similar results were obtained from a phase 1 trial that was conducted in China to evaluate the potency and safety of the BNT162b1 vaccine.[35] In general, the most reported local AE was pain, and the most common systemic AEs were fever, fatigue, and headache, which followed a dose-dependent trend with the highest incidence in the 30 μg group. In addition, older participants represented a higher incidence of AEs than younger adults.

Cellular immune responses against BNT162b1 were assessed in a phase I/II trial in Germany.[38] On day 29, IFNγ was produced by a large fraction of RBD-specific CD8+ and CD4+ T cells. The rates of CD4+ and CD8+ T cell response were lower in low dose groups compared with high dose groups. Higher serum nAbs were achieved 7 days after the booster dose. Although RBD-binding IgG had increased in a dose-dependent manner 21 days after the first dose and showed the booster response 7 days after the second dose (i.e. day 29 and day 43), the titres decreased after day 43 (except for the low dose group).[38]

After selection of BNT162b2 for further advancement to safety and efficacy evaluation, a phase II/III trial was conducted in a multicenter setting for participants aged 16 or older.[41] The overall efficacy was estimated to be 95%. The efficacy of the vaccine in adolescent recipients was assessed in another phase III trial, and it was found that the vaccine was 100% efficient regardless of whether the recipient had a previous history of SARS-CoV-2.[45] Moreover, a phase III investigation has revealed that the vaccine efficacy dropped to 91.1% within a period of 6 months after receiving the first dose. In terms of assessing the efficacy of vaccines against variants of concern, BNT162b2 showed 100% protection against the B.1.351 variant.[42]

Phases I and II trials of mRNA-1273 vaccine developed by Moderna in the USA showed both humoural and cellular immune responses induction post-vaccination. Two doses of vaccine with 28-day intervals schedule induced high levels of binding IgG antibody and neutralising antibody, CD4 T-cell (TNF, IL-2, IFNγ production), and CD8 T-cell responses which were increased in a dose dependent manner, with 100 μg regimen showed the highest seroconversion rate. Furthermore, the immune response was more potent in younger recipients and higher reactogenicity was also reported in this group of participants. Pain at the site of injection together with fatigue, headache, and myalgia were the most often reported local and systemic AEs, in a descending order in frequency.[33,37,40]

Two phase III trials of mRNA-1273 vaccines were undertaken in the USA and reported an overall vaccine efficacy of 93.2% and 94.1%. Both trials have come to the conclusion that the vaccine was 100% efficient in preventing severe COVID-19 and death.[43,44]

Another published finding of an RNA vaccine was related to the phase I trial of the CVnCoV vaccine, which was carried out in Germany and Belgium. A dose-dependent increase in antibody response and the incidence of AEs was noted. Meanwhile, 100% of participants seroconverted to anti-S IgG, while 83% seroconverted to nAbs in the 12 μg group, 2 weeks after second inoculation.[34]

TABLE 1 Immunogenicity, safety, and efficacy of COVID-19 vaccines reported in recent clinical trials

Study ID	Vaccine type or name/ developed by	Study type	Route	Phase/ country	Groups/ Doses			Schedule	NP	Humoral immune response	Cellular immune response	Vaccine efficacy	Adverse events (AE)	Ref
Inactivated vaccines														
Xia et al.	Inactivated vaccine (WIV04 strain)/ developed by Wuhan Institute of Biological Products (Sinopharm)	Randomized/ double-blind/ placebo-controlled	IM	I/II/ China	4 groups (phase I) (18-59)	2.5 μg		D0, D28, D56	24	In phase I, at day 14 after 2 injections, the highest titer of nAbs and specific IgG were seen in low dose group. In phase 2, the highest titer of nAbs and specific IgG were seen in groups who received vaccine at D0, D21.	N/A	N/A	Within 7 days after vaccination: -most common injection site AE: pain -most reported systemic AEs: fever -no serious AEs were noted	(29)
						5 μg		D0, D28, D56	24					
						10 μg		D0, D28, D56	24					
						Alum adjuvant only		D0, D28, D56	24					
					4 groups (phase II) (18-59 years)	5 μ		D0, D14	84					
						Alum adjuvant only		D0, D14	28					
						5 μg		D0, D21	84					
						Alum adjuvant only		D0, D21	28					
Xia et al.	Inactivated vaccine, BBIBP-CorV (HB02 strain)/ Beijing Institute of Biological Products (Sinopharm)	Randomized/ double-blind/ placebo-controlled	IM	I/II/ China	8 groups (phase I)	18-59 years	2 μg	D0, D28	24	Seroconversion rates reached 100% in all three cohorts on day 28. nAbs was detected in 100% of participants on day 42 after the second inoculation. The nAb titers was significantly higher in two dose schedules, than one dose after 28 days.	N/A	N/A	Within 7 days after vaccination: -most common injection site AE: pain. [In 18–59 years' group, swelling, itch, were also seen. In ≥ 60 group, induration was also seen. (increased with dose)]. -most reported systemic AEs: fever (18-59 years), In ≥ 60 years' group, fever and fatigue were reported in the 8 μg dose group and headache, diarrhea, joint pain were reported in 4 μg group.	(30)
							4 μg	D0, D28	24					
							8 μg	D0, D28	24					
							Placebo	D0, D21	24					
						≥ 60 years	2 μg	D0, D28	23					
							4 μg	D0, D28	24					
							8 μg	D0, D28	23					
							Placebo	D0, D28	23					
					5 groups (phase II) (18-59 years)	8 μg		D0	84					
						4 μg		D0, D14	84					
						4 μg		D0, D21	84					
						4 μg		D0, D28	84					
						Placebo		For all groups	112					
Kaabi et al.	Inactivated SARS-CoV-2 vaccine/ Wuhan Institute of Biological Products and the Beijing Institute of Biological Products	Randomized/ double-blind	IM	III/ United Arab Emirates and Bahrain	3 groups (>18 years)	WIV04 (5 μg/dose)		D0, D21	13 459	N/A	N/A	At least 14 days after the second dose: -symptomatic infection: 83.5% -hospitalozation: 100% -symptomatic and asymptomatic infection: WIV04: 64.0% HB02: 73.5% The seroconversion rate: WIV04: 99.3% HB02: 100.0% alum-only: 2.3%	Within 7 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache -serious adverse events occurred with similar rates in the 3 groups. -most AEs were mild in severity (grade 1 or 2) and were transient	(18)
						HB02 (4 μg/dose)		D0, D21	13 465					
						Alum only		D0, D21	13 458					
Zhan	Inactivated	Randomize/	IM	I/II/	8 groups	3 μg		D0, D14	24	In phase 1, nAbs on day 14	N/A	N/A	within 28 days after	(31)

g et al.	vaccine, CoronaVac/ developed by Sinovac	double-blind/ placebo-controlled		China	(phase I) (18-59 years)	Placebo	D0, D14	12	after vaccination were higher in 6 μg group than 3 μg. nAbs at day 28, were higher in 6μg than 3 μg group. In phase 2, nAbs at day 14 and 28 were higher in 6 μg group.			vaccination: -most reported injection site AEs: pain -most reported systemic AEs: Fatigue	
						6μg	D0, D14	24					
						Placebo	D0, D14	12					
						3 μg	D0, D28	24					
						Placebo	D0, D28	12					
						6μg	D0, D28	24					
						Placebo	D0, D28	12					
					6 groups (phase II) (18-59 years)	6 μg	D0, D14	120					
						3 μg	D0, D14	120					
						Placebo	D0, D14	60					
						6 μg	D0, D28	120					
						3 μg	D0, D28	120					
						Placebo	D0, D28	60					
Zhang et al.	Inactivated vaccine, CoronaVac/ developed by Sinovac	Randomized/ double-blind/ placebo-controlled	IM	II/ China	3 groups (18-59 years)	3 μg	D0, D14	120	Specific IgG antibodies and nAbs were increased at 14 and 28 days after two-dose vaccination. longer interval (28 days) between the first and second injections produced higher antibody responses.	N/A	N/A	within 72 hours after vaccination: -most reported injection site AEs: pain -most reported AEs resolved within 72 hours after vaccine administration	(32)
						6 μg	D0, D14	120					
						Placebo	D0, D14	60					
Wu et al.	Inactivated vaccine, CoronaVac/ developed by Sinovac	Randomized/ double-blind/ placebo-controlled	IM	I/ II/ China	4 groups (phase I) (>60 years)	3 μg	D0, D28	24	In phase I, the seroconversion rate was 95.7% and 100% in 6 μg and 3 μg group, respectively, 28 days after the second dose. In phase II, the seroconversion rate was 99.0%, 98%, and 90.7% in 6, 3, and 1.5 μg group, respectively, 28 days after the second dose.	N/A	N/A	Within 28 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fever -a slightly higher incidence of headache and mucocutaneous eruption was observed in the 6 μg group. -All adverse reactions were either mild or moderate in severity.	(28)
						Placebo	D0, D28	12					
						6 μg	D0, D28	24					
						Placebo	D0, D28	12					
					4 groups/ (phase II) (>60 years)	1.5	D0, D28	100					
						3 μg	D0, D28	100					
						6 μg	D0, D28	99					
						Placebo	D0, D28	50					
Tanriove et al.	Inactivated vaccine, CoronaVac/ developed by Sinovac	Randomize/ double-blind/ placebo-controlled	IM	III/ Turkey	3 groups (18-59 years)	CoronaVac (3 μg vaccine)	D0, D14	6 646	89·7% vaccine recipients and 4·4% placebo recipients were seropositive for RBD-specific total antibody. Seropositivity decreased with increasing age in women and men.	N/A	At least 14 days after the second dose: -symptomatic infection: 83.5% -hospitalozation: 100%	Within 7 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fatigue, myalgia, and chills -adverse events resolved in a median of 1 day -two severe AEs were occurred among vaccinated group.	(27)
						Placebo	D0, D14	3 568					
Fadlyana et al.	Inactivated vaccine, CoronaVac/ developed by Sinovac	Randomized/ observer-blind/ placebo-controlled	IM	III/ Indonesia	2 groups (18-59)	CoronaVac	D0, D14	798	14 days after second dose vaccination, the seroconversion rate for IgG and nAb were 97.48% and 87.5%, respectively.	N/A	At least 14 days after the second dose: Overall: 65.3%	Within 7 days after second dose vaccination: -most common injection site AE: pain -most reported systematic AE: myalgia -AEs were more common after the first dose	(23)
						Placebo	D0, D14	804					
Jara et al.	Inactivated vaccine,	Prospective national cohort	IM	III/ Chile	3 groups (>16)	CoronaVac (two dose)	D0, D28	4 173 574	N/A	N/A	Overall: -partially immunized: 15.5%	N/A	(24)

	CoronaVac/ developed by Sinovac					CoronaVac (one dose)	D0, D28	542 418			-fully immunized: 65.9% Hospitalization: -partially immunized: 37.4% -fully immunized: 87.5% ICU admission: -partially immunized: 44.7% -fully immunized: 90.3% Confirmed death: -partially immunized: 45.7% -fully immunized: 86.3%		
						No vaccine	D0, D28	5 471 728					
Pan et al.	Inactivated vaccine, KCONVAC/ Shenzhen Kangtai Biological Products and Beijing Minhai Biotechnolog, China	Randomized/ double-blind/ placebo-controlled	IM	I/II/ China	4 groups (phase I) (8-59 years)	5 mg	D0, D14	24	Almost 85% to 100% of participants seroconverted for nAbs or RBD-IgG antibody by 14- and 28-days post administration of the second dose. After two dose vaccination, significant elevation of nAbs or RBD-IgG was observed as compared to baseline titers. 0/28 regimen showed a higher immune response than that did 0/14 regimen after receiving two 5 mg vaccine doses.	The vaccine induced a moderate T-cell response, with 57% and 63% of participants in the 5- and 10-mg vaccine groups showed positive IFNγ-ELISpot responses at 14 days after administration of the second dose, respectively. Serum IL-2 was detected in majority of participants at 14 or 28 days after administration of the second dose.	N/A	Within 28 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fatigue -All the AEs were grade 1 or 2 in intensity.	(25)
						Placebo	D0, D14	6					
						10 mg	D0, D14	24					
						Placebo	D0, D14	6					
					6 groups (phase II) (18-59 years)	5 mg	D0, D14	100					
						10 mg	D0, D14	100					
						Placebo	D0, D14	50					
						5 mg	D0, D28	100					
						10 mg	D0, D28	100					
						Placebo	D0, D28	50					
Pu et al.	Inactivated vaccine/ developed by Medical Biology (IMB), Chinese Academy of Medical Sciences (CAMS)	randomized/ double-blinded/ placebo-controlled	IM	I/ China	8 groups (18–59 years)	Low dose (50 EU)	D0, D14	24	For both 0, 14 and 0, 28 schedule the medium dose vaccination showed the highest seroconversion rate. Antibodies against the S protein, N protein and virion increased significantly after second dose for both schedules.	Cytotoxic T lymphocyte (CTL) responses against the S protein, N protein and virion increased significantly for both schedules. Genes related to T and B cell activation were upregulated by 40% and 25%, respectively, at day 7 after the booster inoculation.	N/A	Within 7 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fatigue -low dose vaccination with 14 days apart and medium dose vaccination with 28 days apart represented the highest rate of AEs. -No severe adverse reactions were observed within 28 days.	(26)
						Medium dose (100 EU)	D0, D14	24					
						High dose (150 EU)	D0, D14	24					
						Placebo	D0, D14	24					
						Low dose (50 EU)	D0, D28	24					
						Medium dose (100 EU)	D0, D28	24					
						High dose (150 EU)	D0, D28	24					
						Placebo	D0, D28	23					
Che et al.	Inactivated vaccine/ developed by Medical Biology (IMB), Chinese Academy of Medical Sciences (CAMS)	Randomized/ double-blind/ placebo-controlled	IM	II/ China	6 groups (18-59 years)	100 EU viral antigen	D0, D14	150	nAbs, anti-N and anti-S antibodies were increased at day 14 and 28 compared with placebo group and was higher in high dose group.	N/A	N/A	Within 28 days after vaccination: -most reported injection site AEs: pain itching and redness -most reported systemic AEs: slight fatigue and fever	(19)
						150 EU viral antigen	D0, D14	150					
						Placebo	D0, D14	75					
						100 EU viral antigen	D0, D28	150					
						150 EU viral antigen	D0, D28	150					
						Placebo	D0, D28	75					
Ella et al.	Inactivated vaccine, BBV152/ Bharat Biotech in collaboration with the Indian Council of Medical Research	Double-blind/ randomize	IM	I/ India	4 groups (18–55 years)	3 µg with Algel-IMDG group	D0, D14	100	GMTs to all epitopes (spike protein, RBD, and nucleocapsid protein) increased rapidly after the administration of both doses. Seroconversion rates were 87·9% in the 3 µg with Algel-IMDG group, 91·9% in the 6 µg with Algel-IMDG group, and 82·8% in the 6 µg with Algel group.	Both the Algel-IMDG groups elicited CD3+, CD4+, and CD8+ T-cell responses that were reflected in the IFN-γ production. There was a minimal detection of less than 0·5% of CD3+, CD4+, and CD8+ T-cell responses in the 6 µg with Algel group and the Algel only group.	N/A	Within 7 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache, fatigue, fever -Solicited adverse events were more frequent after the first dose. -All adverse events were mild or moderate in severity and resolved within 24 h of onset.	(22)
						6 µg with Algel-IMDG	D0, D14	100					
						6 µg with Algel	D0, D14	100					
						Algel only	D0, D14	75					

												-6 µg with Algel-IMDG group represented the highest frequency of AEs, followed by 3 µg with Algel-IMDG, 6 µg with Algel group, and Algel-only group.	
Ella et al.	Inactivated vaccine, BBV152/ Bharat Biotech in collaboration with the Indian Council of Medical Research	Double-blind/ randomized	IM	II/ India	2 groups (12–65 years)	3 µg with Algel-IMDG group	D0, D28	190	The GMT at day 56 was significantly higher in the 6 µg group than in the 3 µg group, and was not significantly different to the GMT observed in convalescent serum collected from patients who had recovered from COVID-19. The seroconversion rate at day 56 was 92.9% in 3 µg group and 98.3% in 6 µg group.	The 3 µg and 6 µg formulations elicited T-cell responses that were biased to a Th1 phenotype at day 42. A significant increase in the levels of Th1 cytokines, IFNγ, IL-2, and TNFα was observed on day 56 compared with day 0.	N/A	Within 7 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fever -No association between the dose of vaccine and the number of adverse events was observed. -Most adverse events were mild and resolved within 24 h of onset. -33% of unsolicited adverse events were reported to be related to the vaccine.	(21)
						6 µg with AIgel-IMDG group	D0, D28	190					
Ella et al.	Inactivated vaccine, BBV152/ Bharat Biotech in collaboration with the Indian Council of Medical Research	Double-blind/ randomized	IM	III/ India	2 groups (18-98 years)	BBV152	D0, D28	12 221	N/A	N/A	Efficacy at least 14 days after the second dose: Overall: 77.8% Symptomatic infection: 93.4% Asymptomatic infection: 63.6% B.1.617.2 variant: 65.2% 18-59 years: 79.4% >60: 67.8%	Within 7 days after second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache, pyrexia, fatigue -Incidence of solicited AEs was lower after the second dose. -Only 12·4% of participants reporting any solicited AE after vaccine or placebo. -There were similar rates of solicited, unsolicited, and serious AEs and AEs of special interest in vaccine and placebo groups.	(20)
						Placebo	D0, D28	12 198					
RNA-vaccines													
Walsh et al.	RNA-vaccine BNT162b1 and BNT162b2 / developed by Pfizer/ BioNTech	Placebo-controlled/ observer-blinded/ randomized	IM	I/ USA	BNT162B1 6 groups(18-55 years)	Placebo	D0	12	The highest nAbs were measured in samples obtained on day 28 or on day 35. Antigen-binding IgG and nAbs were boosted by the second dose in both the younger adults and the older adults. The levels of antibodies were lower in older age group. Higher doses appeared to elicit somewhat higher antibody responses.	Strong cell-mediated immune responses (Th1-biased CD4+ and CD8+) elicited by BNT162b1 have been reported in the German trial.	N/A	Within 7 days after vaccination: - most common injection site AE: pain (more frequent after the second dose). -most reported systemic AEs: Fever and chills -BNT162b2 was associated with a lower incidence and severity of systemic reactions than BNT162b1, particularly in older adults.	(36)
						Placebo	D0, D21	9					
						BNT162b1 10µg	D0, D21	12					
						BNT162b1 20µg	D0, D21	12					
						BNT162b1 30µg	D0, D21	12					
						BNT162b1 100µg	D0	12					
					BNT162B1 4 groups (65-85 years)	Placebo	D0, D21	9					
						BNT162b1 10µg	D0, D21	12					
						BNT162b1 20µg	D0, D21	12					
						BNT162b1 30µg	D0, D21	12					
					BNT162B2 6 groups(18-55 years)	Placebo	D0, D21	9					
						BNT162b2 10µg	D0, D21	12					
						BNT162b2 20µg	D0, D21	12					
						BNT162b2 30µg	D0, D21	12					
					BNT162B2 6 groups(65-	Placebo	D0, D21	9					
						BNT162b2 10µg	D0, D21	12					

					85 years)	BNT162b2 20μg	D0, D21	12					
						BNT162b2 30μg	D0, D21	12					
Li et al.	RNA-vaccine BNT162b1/ developed by Pfizer/ BioNTech	Randomized/ double-blind/ placebo-controlled	IM	I/China	3 Groups (18-55 years)	10 μg BNT162b1	D0, D21	24	-The highest titers of nAbs were seen 21 days after the second dose for both young and old participants. -The older participants represented lower peak nAb response than younger adults. -30 μg dose elicited higher nAb response than 10 μg dose. -In addition to nAbs, BNT162b1 induced high levels of S1-binding and RBD-binding IgG GMTs after the prime–boost regimen.	-The vaccine elicited robust IFN-γ T cell responses for both younger and older participants. -Older participants showed lower geometric mean IFN-γ+ spot counts than younger adults.	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fever, headache, and fatigue -AEs were dose-dependent and were more observed in the 30 μg dose group. -AEs were mostly transient and mild to moderate -soliated AEs were more common in younger adults than older participants.	(35)
						30 μg BNT162b1	D0, D21	24					
						Placebo	D0, D21	24					
					3 Groups (65-85 years)	10 μg BNT162b1	D0, D21	24					
						30 μg BNT162b1	D0, D21	24					
						Placebo	D0, D21	24					
Mulligan et al.	RNA vaccine/ BNT162b1/ developed by Pfizer/ BioNTech	Placebo-controlled/ observer-blinded/ randomized	IM	I/II/ USA	4 groups (18-55 years)	Placebo	D0, D21	9 (3 for each group)	RBD-binding IgGs were detected at 21 days after the first dose, and increased 7 days after the second dose given at day 21. nAbs were measurable after a single vaccination at day 21 for all dose levels and increased at day 28.	N/A	N/A	Within 7 days after vaccination: - most common injection site AE: pain - most reported systemic AEs in both BNT162b1 and placebo groups: fatigue and headache. - most reported systemic AEs in BNT162b1 group: chills, muscle pain and joint pain. Systemic AEs increased with dose level.	(39)
						BNT162b1 10 μg	D0, D21	12					
						BNT162b1 30 μg	D0, D21	12					
						BNT162b1 100 μg	D0	12					
Sahin et al.	RNA-vaccine BNT162b1/developed by Pfizer/ BioNTech	non-randomized/ open-label	IM	I/II/ Germany	5 groups (18-55 years)	BNT162b1 1 μg	D0, D21	12	21 days after the priming dose, RBD-binding IgG had increased in a dose-dependent manner 7 days after second dose (day 29) and day 43. Higher serum-nAbs were achieved 7 days after the booster dose. On day 43 (21 days after the boost), nAbs and RBD-binding antibody decreased (with the exception of the 1 μg dose group).	At day 29, Interferon-γ was produced by a large fraction of RBD-specific CD8+ and CD4+ T cells. at 1 μg BNT162b1 the rates of CD4+ and CD8+ T cell response were lower than for the other doses.	N/A	Within 7 days after vaccination: - most common injection site AE: pain and tenderness ((dose-dependent, more pronounced after the boost dose). -most reported systemic AEs: fever, chills, headache, muscle pain, joint pain, injection site pain, and tenderness.	(38)
						BNT162b1 10 μg	D0, D21	12					
						BNT162b1 30μg	D0, D21	12					
						BNT162b1 50 μg	D0, D21	12					
						BNT162b1 60 μg	D0	12					
Polack et al.	RNA-vaccine BNT162b2/ developed by Pfizer/ BioNTech	placebo-controlled, observer-blinded-randomized	IM	II/III/ Global	2 groups (≥ 16 years)	30 μg BNT162b2	D0, D21	18 860	N/A	N/A	Efficacy at least 7 days after the second dose: Overall: 95% Without and those with history of COVID-19: 94.6% >55 years old: 93.7% 16-55 years old: 95.6% Male sex: 96.4% Female sex: 93.7%	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fatigue and headache -AEs were less common among >55 age group. -systemic and local AEs occurred more often after the second dose.	(41)
						placebo	D0, D21	18 846					
Frenck et al.	RNA-vaccine BNT162b2/ developed by Pfizer/ BioNTech	placebo-controlled/ observer-blinded/ randomized	IM	III/USA	2 Groups (12-15 years)	Placebo	D0, D21	1 129	One month after the second dose, the geometric mean ratio of BNT162b2 nAb titer in 12-15 age group to that in 16-25 age group was 1.76, indicating a greater response in adolescent as compared to	N/A	Efficacy at least 7 days after the second dose: -Efficacy among those who did not have previous history of SARS-CoV-2 infection: 100% - Efficacy regardless of whether having previous	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fatigue, headache, and chills -systemic AEs were more mild after fist dose and it was more	(45)
						30 μg BNT162b2	D0, D21	1 131					

					2 Groups (16-25 years)	Placebo	D0, D21	1 807	young adults. Geometric mean fold rise from baseline to 1 month after dose 2 substantially increased for both age groups, however the value was higher among 12-15 age group.		history of SARS-CoV-2 infection: 100%	moderate after second dose. -use of antipyretic medications was more common after second dose. -there were no vaccine related serious adverse events and few overall severe adverse events were reported.	
						30 μg BNT162b2	D0, D21	1 803					
Thomas et al.	RNA-vaccine BNT162b2/ developed by Pfizer/ BioNTech	placebo-controlled/ observer-blinded/ randomized	IM	II/ III/ global	2 groups (≥16 years)	Placebo	D0, D21	20 794	N/A	N/A	**Within 6 months after the first dose:** Without history of COVID-19: 91.3% With or without history of COVID-19:91.1% Severe infection: 96.7% 16-17 years old: 100% >75 years old: 96.2% >4 months after receipt of second dose: 83.7% >2 months after receipt of second dose: 90.1% B.1.351 variant: 100%	-most reported injection site AEs: pain -most reported systemic AEs: fatigue -the same frequency of AEs was reported among those with and without history of SARS-CoV-2 infection, with similar severity. -Recipients with evidence of previous infection reported systemic AEs more often after receipt of the first dose, and those without evidence reported systemic events more often after second dose.	(42)
						30 μg BNT162b2	D0, D21	20 334					
Jackson et al.	RNA-vaccine mRNA-1273/ developed by Moderna/NIAID	open-label	IM	I/ USA	3 groups (18-55 years)	mRNA-1273, 25 μg	D0, D28	15	29-days post-vaccination, binding antibody IgG nAbs had increased in a dose-dependent manner On day 57, Ab titers were increased. the higher responses in the 100-μg and 250-μg groups were similar in magnitude.	The 25-μg and 100-μg doses elicited CD4 T-cell responses (TNF, IL-2, IFN). CD8 T-cell responses were detected after the second vaccination in the 100-μg dose group	N/A	Within 7 days after vaccination: -most common injection site AE: pain -most reported systemic AEs: fatigue, chills, headache, myalgia -Systemic AEs were more common after the second vaccination, particularly with the highest dose	(37)
						mRNA-1273, 100 μg	D0, D28	15					
						mRNA-1273, 250 μg	D0, D28	15					
Anderson et al.	RNA-vaccine mRNA-1273/ developed by Moderna/NIAID	Randomized/ observer-blind/ placebo-controlled	IM	I/ USA	2 groups (56-70 years)	mRNA-1273, 25 μg	D0, D28	10	By day 57, anti–S-2P GMT was higher in ≥71 age group as compared to 56-70 group for both 25 and 100 doses. After second vaccination, nAbs was detected in all participants through multiple methods. Binding and neutralizing antibodies were above the median titers of donated convalescent serum.	Vaccine elicited strong CD4 response involving Th1, while Th2 response was minimal. CD8 T-cell responses were observed at low levels after the second vaccination among all participants.	N/A	Within 7 days after second dose vaccination: -most common injection site AE: pain -most reported systemic AEs: fatigue, headache, and myalgia -AEs were more reported after second dose. -while systemic AEs occurred more frequently in 56-70 age group, local AEs had higher frequency among ≥71 age group.	(33)
						mRNA-1273, 100 μg	D0, D28	10					
					2 groups (≥71 years)	mRNA-1273, 25 μg	D0, D28	10					
						mRNA-1273, 100 μg	D0, D28	10					
Chu et al.	RNA-vaccine mRNA-1273/ developed by Moderna/NIAID	Randomized/ observer-blind/ placebo-controlled	IM	II/ USA	3 groups (18-55 years)	mRNA-1273, 50 μg	D0, D28	100	-Anti SARS-CoV-2 spike binding and neutralizing Ab levels increased substantially by 14 days after the second vaccination with higher GMT for younger adults and dose of 100 μg. - 100% seroconversion rate was observed for both younger and older cohorts, 14 and 28 days after the second vaccination with 50 μg or 100 μg dose.	N/A	N/A	Within 7 days after second dose vaccination: -most common injection site AE: pain -most reported systemic AEs: headache, fatigue -Systemic AEs occurred more frequently after the second vaccination, particularly with 100 μg dose. -AEs was more common and longer in younger adults as compared to older ones.8-The majority of AEs were mild and moderate in severity, an8 no deaths or serious AEs were	(40)
						mRNA-1273, 100 μg	D0, D28	100					
						Placebo	D0, D28	100					
					3 groups (>55 years)	mRNA-1273, 50 μg	D0, D28	100					
						mRNA-1273, 100 μg	D0, D28	100					
						Placebo	D0, D28	100					

												reported8	
Baden et al.	RNA-vaccine mRNA-1273/ developed by Moderna/NIAID	Randomized/ observer-blind/ placebo-controlled	IM	III/USA	2 groups (≥ 18 years)	mRNA-1273, 100 µg	D0, D28	15210	N/A	N/A	Efficacy at least 14 days after the second dose: Overall: 94.1% >65 years: 86.4% Male: 95.4% Female: 93.1% White ethnic group: 93.2% Prevention of severe covid-19: 100%	Within 7 days after second dose vaccination: -most common injection site AE: pain -most reported systemic AEs: fatigue, headache, and myalgia -grade 3 AEs were more reported after the second dose	(43)
						Placebo	D0, D28	15210					
El Sahly et al.	RNA-vaccine mRNA-1273/ developed by Moderna/NIAID	Randomized/ observer-blind/ placebo-controlled	IM	III/USA	2 groups (≥ 18 years)	mRNA-1273, 100 µg	D0, D28	15209	N/A	N/A	Efficacy at least 14 days after the second dose: Overall: 93.2% Severe disease: 98.2% Death: 100% Asymptomatic infection: 63% >75 years old: 100% HIV infected: 100%	N/A	(44)
						Placebo	D0, D28	15206					
Kremsner et al.	RNA vaccine, CVnCoV, CureVac N.V., Tübingen, Germany	Randomized/ observer-blinded/ placebo-controlled	IM	I/ Germany and Belgium	6 groups (18-60 years)	2 µg	D0, D28	47	Dosage-dependent increases in anti-S IgG together with nAbs were evident in all groups 2 weeks after the second dose. 100% of participants seroconverted to S-protein, and 83% seroconverted for nAbs in the 12µg group.	N/A	N/A	No vaccine-related serious AEs were reported. A doe-dependent increasing in frequency and severity of solicited systemic AEs, and to a lesser extent local AEs was observed. AEs were mainly mild or moderate and transient in duration.	(34)
						4 µg	D0, D28	48					
						6 µg	D0, D28	46					
						8 µg	D0, D28	44					
						12 µg	D0, D28	28					
						Placebo	D0, D28	32					
Vector vaccines/ Recombinant vaccines													
Folegatti et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ Single blind	IM	I/II/ UK	1 group (phase I) (18-55 years)	5×10^{10} vp	D0, D28	10	Anti-spike IgG responses peaked at day 28. Anti-spike IgG were increased following booster dose.	Spike-specific T-cell peaked on day 14 and maintained up to day 56. A boost in cellular responses was not observed following the second ChAdOx1 nCoV-19 dose.	N/A	Within 28 days after vaccination: - most common injection site AE: pain and tenderness - most reported systemic AEs: fatigue and headache.	(54)
					2 group (phase II) (18-55 years)	Control vaccine	D0	534					
						5×10^{10} vp	D0	543					
Barrett et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ Single blind	IM	I/ II/ UK	2 groups (18-55 years)	Initial standard dose of ChAdOx1 nCoV-19+ standard dose boost	D0, D56	20	At day 14 post second dose, there were no significant different between anti-spike and anti-RBD IgG antibody titers in 56d and 28d interval groups, however, those who received lower boost dose represented lower antibody titers than standard dose boost group. Anti-spike antibody dependent neutrophil and monocyte phagocytosis, complement deposition, and NK cell activation were induced by the first dose and significantly rose to higher levels after second dose, with larger trend in 56d interval	At day 28 post second dose, Spike-specific T cell responses were not significantly different between 28d and 56d interval groups.	N/A	Within 7 days after second dose vaccination: - most common injection site AE: pain and tenderness - most reported systemic AEs: fatigue, headache, and chills. -overall, booster dose result in lower local and systemic reactogenicity than the first dose. -half dose boost had lower AEs than the standard dose boost.	(48)
						Initial standard dose of ChAdOx1 nCoV-19+dose-sparing half-dose boost	D0, D56	32					

									and standard dose boost groups.				
Ramasamy et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ Single blind	IM	II/III/ UK	A	18-55 years	$2{\cdot}2\times10^{10}$ vp	D0,D28	50	In participants who received two doses of vaccine, median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts. Also, no significant differences were seen in anti-spike IgG and nAb titres between low-dose and standard-dose vaccine recipients. nAbs titers after a boost dose were similar across all age groups. Anti-spike IgG and nAbs titers peaked on day 42.	T-cell responses peaked at day 14 after a single standard dose of ChAdOx1 nCoV-19	N/A	Within 7 days after vaccination: - most common injection site AE: pain - most reported systemic AEs: fever, muscle ache, headache. AEs were less common in older adults (aged ≥56 years)	(57)
							Control vaccine	D0,D28	50					
						56-69 years	$2{\cdot}2\times10^{10}$ vp	D0,D28	30					
							Control vaccine	D0,D28	10					
							$2{\cdot}2\times10^{10}$ vp	D0	30					
							Control vaccine	One dose	10					
						≥ 70 years	$2{\cdot}2\times10^{10}$ vp	D0,D28	50					
							Control vaccine	D0,D28	10					
							$2{\cdot}2\times10^{10}$ vp	D0	50					
							Control vaccine	D0	10					
					B	18-55 years	$3{\cdot}5–6{\cdot}5\times10^{1}$ vp	D0,D28	50					
							Control vaccine	D0,D28	50					
						56-69 years	$3{\cdot}5–6{\cdot}5\times10^{1}$ vp	D0,D28	30					
							Control vaccine	D0,D28	10					
							$3{\cdot}5–6{\cdot}5\times10^{1}$ vp	D0	30					
							Control vaccine	One dose	10					
						≥ 70 years	$3{\cdot}5–6{\cdot}5\times10^{1}$ vp	D0,D28	50					
							Control vaccine	D0,D28	10					
							$3{\cdot}5–6{\cdot}5\times10^{1}$ vp	D0	50					
							Control vaccine	D0	10					
Voysey et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ blinded	IM	II/ III	3 groups (18-55 years)		COV002 (UK; LD/SD; 2×10^{10} and 5×10^{10})	8 weeks apart	2741	N/A	N/A	Efficacy at least 14 days after the second dose: -overall: 70.4% -SD/SD: 62.1% -LD/SD: 90.0%	There were two cases of COVID-19 related hospitalization in vaccinated group, both less than 21 days after the first dose.	(58)
							COV002 (UK; SD/SD; 5×10^{10} and 5×10^{10})	28 days apart	4807					
							COV003 (Brazil; all SD/SD; 2×10^{10} and 5×10^{10})	12 weeks apart	4088					
Clemens et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ blinded	IM	III/ Brazil/ P.1 variant	2 groups (≥ 18 years)		ChAdOx1 nCoV-19 ($3.5–6.5\times10^{10}$ viral particles)	4-12 weeks apart	4772	N/A	N/A	symptomatic infection: P.2: 68.7% P.1: 63.6% hospitalization: 95% severe infection or death: 100%	N/A	(59)
							Control vaccine	4-12 weeks apart	4661					
Emary et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ single-blind	IM	II/ III/ UK/ B.1.1.7 variant	2 groups (≥ 18 years)		ChAdOx1 nCoV-19	N/A	4244	N/A	N/A	Overall: B.1.1.7: 61.7% Symptomatic infection: B.1.1.7: 70.4% Asymptomatic infection: B.1.1.7: 28.9%	N/A	(56)
							Control vaccine	N/A	4290					

Madhi et al.	Adenovirus-vectored vaccine (ChAdOx1 nCoV-19)/ developed by University of Oxford/ AstraZeneca	Randomized/ double-blind/ placebo-controlled	IM	1b–2/ South Africa/ B.1.351	2 groups (16-65 years)	5×10^{10} viral particles	D0, D(21 to 35)	1011	-46% of vaccine recipients without evidence of previous SARS-CoV-2 infection showed no neutralization activity against an RBD triple-mutant pseudovirus (containing K417N, E484K, and N501Y variants), and 85% had no neutralization activity against B.1.351 pseudovirus. -28 days after second dose, the sera from vaccine recipients showed the highest neutralization activity for variant of South Africa and the least for variant of Brazil.	N/A	Efficacy at least 14 days after the second dose: -Mild-to-moderate illness in seronegative recipient at baseline: 21.9% -Mild-to-moderate illness associated with B.1.351 variant in seronegative recipient at baseline: 10.4% -Mild-to-moderate illness regardless of baseline serostatus: 10.6%	-General disorders and administration site conditions were comparable between vaccine and placebo group. -The only serious adverse event attributed to the ChAdOx1 nCoV-19 vaccine was a body temperature above 40°C after the first dose.	(51)
						Placebo	D0, D(21 to 35)	1010					
Logunov et al.	Recombinant adenovirus rAd26 and rAd5/ developed by N F Gamaleya National Research Centre for Epidemiology and Microbiology	Open-label/ non-randomized	IM	I/II/ Russia	2 groups (phase I) (18-60 years)	rAd26	D0	9	RBD-specific IgGs were detected at day 14 (especially in rAd26-S group). During phase II, SARS-CoV-2 RBD-specific IgGs were detected on day 14 (after priming with rAd26-S).	Cell-mediated responses (interferon-γ production or lymphoproliferation) were detected in all participants at day 28	N/A	Within 28 and 42 days after vaccination in phase I and II, respectively: - most common injection site AE: pain - most reported systemic AEs: hyperthermia, headache, asthenia, and muscle and joint pain. -no serious AEs were detected.	(50)
						rAd5	D0	9					
					1 group (phase II) (18-60 years)	rAd26 (D0) + rAd5 (D21)	D0,D21	20					
Logunov et al.	Recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac/(Sputnik V)/ developed by N F Gamaleya National Research Centre for Epidemiology and Microbiology	Randomised/ double-blind/ placebo-controlled	IM	III/ Russia	2 groups (≥ 18 years)	Vaccine rAd26/rAd5	D0, D21	14964	42 days after the first dose, the seroconversion rate of RBD-specific IgG and nAb was 98·25% and 95·83% for vaccine group while it was 14·91% and 7·14% for the placebo group, respectively. The 18–30 years age group had a significantly higher GMT than the other age groups.	28 days after first dose, all participants in the vaccine group had significantly higher levels of IFN-γ as compared with the day of administration.	Efficacy at least 7 days after the second dose: 91·1% Efficacy at the day of second dose: Overall: 91·6% Male: 94·2% Female: 87·5% Older than 60: 91·8% Moderate or severe cases: 100% Rates of disease onset were similar for the vaccine and placebo groups until about 16–18 days after dose 1, after which, early onset of protection led to the number of cases in the vaccine group increasing much more slowly than in the placebo group.	The most common adverse events were flu-like illness, injection site reactions, headache, and asthenia. None of the serious adverse events and death were considered associated with vaccination.	(60)
						Placebo	D0, D21	4902					
Zhu et al.	Recombinant adenovirus Ad5 vectored COVID-19 vaccine/ developed by Beijing Institute of Biotechnology	open-label/ non-randomized	IM	I/ China	3 Groups (18-60 years)	5×10^{10} VP/ 0.5 mL	D0	36	IgG and nAbs increased significantly at day 14, and peaked 28-days post-vaccination.	Specific T-cell response peaked at day 14 post-vaccination. Increased level of IL-2, IFN-γ and TNF-α from T cells at day 14.	N/A	Within 14 days after vaccination: -most common injection site AE: pain -most reported systematic AE: fever, fatigue, headache, and muscle pain. -No serious AEs was noted within 28-days post-vaccination.	(47)
						1×10^{11} VP/ mL	D0	36					
						$1{\cdot}5\times10^{11}$ VP/ 1.5 mL	D0	36					
Zhu	Recombinant	Randomized/	IM	II/ China	3 groups (≥	Placebo	D0	126	RBD-specific Abs detected at	IFNγ responses were	N/A	Within 14 days after	(55)

et al.	adenovirus Ad5 vectored COVID-19 vaccine/ developed by Beijing Institute of Biotechnology	double-blind/ placebo-controlled			18 years)	1×10^{11} VP/ mL	D0	253	day 14 and peaked at day 28 post-vaccination Increased nAbs was detected in both of the groups at day 28 post-vaccination, however, the seroconversion rate was 59% in 1×10^{11} group and 47% in 5×10^{5} group.	developed at day 28 post vaccination		vaccination: -most common injection site AE: pain -most reported systemic AEs: fatigue, fever, and headache.	
						5×10^{5} VP/ mL	D0	129					
Stephenson et al.	Ad26.COV2.S/ developed by Johnson & Johnson	Randomized/ double-blind/ placebo-controlled	IM	I/ USA	5 groups (18 to 55 years)	Ad26.COV2.S 5×10^{10} viral particles	D0, D57	5	-By days 57, 100% of vaccine recipients showed nAbs as well as S- and RBD-specific binding antibodies. -The boost immunization increased binding antibody titers by a mean of 2.56-fold and neutralizing antibody titers by a mean of 4.62-fold on day 71. -A variety of antibody subclasses, Fc receptor binding properties, and antiviral functions were induced.	-IFN-γ were observed in 65% of vaccine recipients by day 15 and in 84% of vaccine recipients by day 71. -CD4+ and CD8+ T-cell responses were induced.	N/A	N/A	(46)
						Ad26.COV2.S 5×10^{10} viral particles	D0, D57 (placebo)	5					
						Ad26.COV2.S 1×10^{11} viral particles	D0, D57	5					
						Ad26.COV2.S 1×10^{11} viral particles	D0, D57 (placebo)	5					
						Placebo	D0, D57	5					
Sadoff et al.	Ad26.COV2.S/ developed by Johnson & Johnson	Randomized/ double-blind/ placebo-controlled	IM	1–2a/ Belgium and the United States	3 groups (18-55 years)	Ad26.COV2.S 5×10^{10} viral particles (low dose)	D0, D57	162	nAbs were detected in 90% or more of all participants on day 29 after the first vaccine dose, regardless of vaccine dose or age group. nAb titers reached 100% by day 57 after the first dose with a further increase in titers in younger cohort. Titers remained stable until day 71	On day 14, 76 to 83% of the younger participants and 60 to 67% of older ones had a detectable CD4+ T-cell responses with predominance of type 1 helper T cells. CD8+ T-cell responses were detected in all participants but it was lower in older participants.	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache, fatigue, and myalgia -systemic AEs was more prevalent among younger adults and after the high dose. -reactogenicity was lower after the second dose	(53)
						Ad26.COV2.S 1×10^{11} viral particles (high dose)	D0, D57	158					
						Placebo	D0, D57	82					
					3 groups (>65 years)	Ad26.COV2.S 5×10^{10} viral particles (low dose)	D0, D57	161					
						Ad26.COV2.S 1×10^{11} viral particles (high dose)	D0, D57	161					
						Placebo	D0, D57	81					
Sadoff et al.	Ad26.COV2.S/ developed by Johnson & Johnson	Randomized/ double-blind/ placebo-controlled	IM	III/ Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States	2 groups (18-59 years)	Ad26.COV2.S 5×10^{10} viral particle	Single dose	19,630	N/A	N/A	Efficacy at least 14 days after the second dose: **Worldwide;** -Moderate to severe–critical Covid-19: 66.3% -Severe–critical Covid-19: 76.3% **South Africa (B.1.351 variant);** -Moderate to severe–critical Covid-19: 52.0% -Severe–critical Covid-19: 73.1% Efficacy at least 28 days after the second dose: **Worldwide;** -Moderate to severe–critical Covid-19: 65.5% -Severe–critical Covid-19: 83.5% **South Africa (B.1.351**	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache, fatigue, and myalgia -more AEs were reported by participants 18 to 59 years of age than by those 60 years of age or older. -Venous thromboembolic events were reported for 11 participants in the vaccine group vs. 3 in the placebo group. -seizure occurred in 4 participants in the vaccine group vs. 1 in the placebo group and tinnitus in 6 vs. 0.	(61)
						Placebo	Single dose	19,691					

											variant); -Moderate to severe–critical Covid-19: 64.0% -Severe–critical Covid-19: 81.7%		
Meng et al.	Baculovirus vectored recombinant vaccine (Sf9 cells) / developed by West China Hospital of Sichuan University	Randomised/ double-blind/ placebo controlled	IM	I/ II/ China	Phase 1	18-55 years	Low dose	D0, D28	24	28 days after the last dose, high dose group showed the highest binding Ab titers for both adult and older participants. Seroconversion of anti-RBD antibodies was noted in 96-99% of adults and 78-80% of elderlies for the high dose group (0, 14, 28 days). Seroconversion of nAbs was noted in 96-100% of adults and 73-78% of elderlies for the high dose group (0, 14, 28 days).	The positive rate of IFN-γ peaked at 14 days after the last dose vaccination, with 50% in low dose group (0, 28 days), 88% in high dose group (0, 28 days), 88% in high dose group (0, 14, 28 days) for adults. The corresponding results in the elderly group were 61%, 83%, 72%, respectively.	N/A	Within 7 days after second dose vaccination: -most common injection site AE: pain -most reported systematic AE: phase I: fatigue, cough, sore throat phase II: Cough, fever, headache -All AEs were mild or moderate in severity. -No significant difference was observed in the incidences of AEs among groups, in both trials.	(52)
							Placebo	D0, D28	8				
							High dose	D0, D28	24				
							Placebo	D0, D28	8				
							High dose	D0, D14, D28	24				
							Placebo	D0, D14, D28	8				
						>56 years	Low dose	D0, D28	18				
							Placebo	D0, D28	6				
							High dose	D0, D28	18				
							Placebo	D0, D28	6				
							High dose	D0, D14, D28	18				
							Placebo	D0, D14, D28	6				
					Phase 2	18-55 years	Low dose	D0, D21	100				
							Placebo	D0, D21	20				
							High dose	D0, D21	100				
							Placebo	D0, D21	20				
							Low dose	D0, D14, D28	100				
							Placebo	D0, D14, D28	20				
							High dose	D0, D14, D28	100				
							Placebo	D0, D14, D28	20				
						>56 years	Low dose	D0, D21	100				
							Placebo	D0, D21	20				
							High dose	D0, D21	100				
							Placebo	D0, D21	20				
							Low dose	D0, D14, D28	100				
							Placebo	D0, D14, D28	20				
							High dose	D0, D14, D28	99				
							Placebo	D0, D14, D28	20				
Goepfert et al.	Baculovirus vectored recombinant Vaccine (CoV2 preS dTM)/ developed by Sanofi Pasteur	Randomized/ double-blind	IM	I/ II/ USA	6 groups (18-49 years)		Low dose+AF03	D0, D21	17	nAb titers were higher in AF03-adjuvanted group, while binding Ab titers were higher in AS03-adjuvanted group, 36 days post vaccination. Antibody response were more potent in younger participants. In day 36, seroconversion rate of nAbs was 88% and 71% in the high dose plus AS03 and AF03 groups, respectively. In day 36, all groups with adjuvant were seroconverted for binding antibody.	Increasing in IFN-γ, IL-2, and TNFα cytokines from pre-vaccination to days 22 and 36 tended to be more robust than were the increases for IL-4, IL-5, and IL-13, especially in the AS03-adjuvanted groups.	N/A	Within 7 days after second dose vaccination: -most common injection site AE: pain -most reported systematic AE: myalgia, headache, and malaise -systemic and local AEs were more common after the second dose. -local and systemic AEs occurred more frequently after AS03 and AF03 adjuvant group, respectively. -less frequent AEs were reported in elderlies.	(49)
							Low dose+AS03	D0, D21	53				
							High dose+AF03	D0, D21	17				
							High dose+AS03	D0, D21	54				
							High dose	D0, D21	17				
							Placebo	D0, D21	18				
					5 groups (≥50 years)		Low dose+AF03	D0, D21	10				
							Low dose+AS03	D0, D21	28				
							High dose+AF03	D0, D21	10				
							High dose+AS03	D0, D21	31				
							High dose	D0, D21	11				
Keech et al.	NVX-CoV2373/ developed by Novavax	Randomized/ observer-blinded/ placebo-controlled	IM	I/ Australia	5 groups (18-59 years)		Placebo	D0, D21	23	Only the results of phase I were published. In phase I, on day 35, the two-dose 5μg NVXCoV2373/Matrix-M1 vaccine induced potent anti-spike IgG and nAbs that exceeded responses in convalescent serum from mostly symptomatic Covid-19	In phase I, 7 days after the second vaccination (day 28), adjuvanted regimens induced a strong Th1 bias, reflected in IFN-γ, IL-2, and TNF-α production following spike protein stimulation. Th2 responses (as measured by IL-5 and IL-13 cytokines) were minimal.	N/A	Within 35 days after vaccination: -most reported injection site AEs: pain and tenderness -most reported systemic AEs: joint pain and fatigue -AEs was more common with adjuvant. -Second vaccinations induced greater local and systemic	(65)
							25 μg without Matrix-M	D0, D21	25				
							5 μg + 50 μg Matrix-M	D0, D21	29				
							25 μg + 50 μg Matrix-M	D0, D21	28				
							25 μg +50 μg Matrix-M	D0	26				

									patients.			reactogenicity.	
Formica et al.	NVX-CoV2373/ developed by Novavax	Randomized/ observer-blinded/ placebo-controlled	IM	II/ Australia and USA	5 groups (18-84 years)	Placebo/ placebo	D0, D21	255	Anti-S IgG titers were similar for both 2-dose regimens of 5-μg and 25-μg, and the seroconversion rate was 98% and 100% respectively. Seroconversion rate of nAb was 100% for both dose active vaccines. Anti-S IgG and nAb titers were higher for younger participants.	N/A	N/A	Within 7 days after vaccination: -most reported injection site AEs: tenderness and pain -most reported systemic AEs: myalgia, fatigue, and headache The frequency of AEs were higher among younger participants.	(63)
						5 μg/ 5 μg	D0, D21	258					
						5 μg/ placebo	D0, D21	256					
						25 μg/ 25 μg	D0, D21	259					
						25 μg/ placebo	D0, D21	255					
Heath et al.	NVX-CoV2373/ developed by Novavax	Randomized/ observer-blinded/ placebo-controlled	IM	III/ UK	2 groups (18-84 years)	Placebo	D0, D21	7019	N/A	N/A	Efficacy at least 7 days after the second dose: -overall: 89.7% -18 to <65 year: 89.8% -≥65 to 84 year: 88.9% -White race: 90.7% -B.1.1.7 variant: 86.3% -Non-B.1.1.7 variants: 96.4%	Within 7 days after vaccination: -most reported injection site AEs: pain and tenderness -most reported systemic AEs: muscle pain, fatigue, and headache -second vaccinations induced greater local and systemic reactogenicity. -moderate and severe AEs was more common after second dose injection.	(64)
						5 μg NVX-CoV2373	D0, D21	7020					
Shinde et al.	NVX-CoV2373/ developed by Novavax	Randomized/ observer-blinded/ placebo-controlled	IM	IIa-b/ South Africa/ B.1.351 variant	2 groups (18-84 years)	Placebo	D0, D21	1327	N/A	N/A	Efficacy at least 7 days after the second dose: -seronegative at baseline: 49.4% -seropositive at baseline: 52.6% -HIV negative participants: 57.7%	Within 7 days after vaccination: -most reported injection site AEs: pain and tenderness -most reported systemic AEs: muscle pain, fatigue, and headache -seropositive participants showed higher local AEs after each dose, as compared to seronegative ones. -moderate and severe AEs was more common after second dose injection.	(67)
						5 μg NVX-CoV2373	D0, D21	1357					
Richmond et al.	Protein subunit vaccine/ SCB-2019/ developed by QEII Medical Centre (Perth, WA, Australia)	Randomised/ double-blind/ placebo-controlled	IM	I/ Australia	10 groups (18-75 years)	30 μg SCB-2019 with no adjuvant	D0, D21	9	By day 22, none of the participants who received two dose of vaccination formulated with adjuvant were seroconverted. By day 36 and 50, nearly all participants receiving adjuvanted vaccines were seroconverted while a little or no response to nonadjuvanted SCB-2019 was seen. For all vaccine groups, GMTs were lower in the equivalent older adults. Dose-dependent increases in antibodies were observed in both adjuvanted SCB-2019, but these responses were higher in magnitude for AS03 adjuvant groups.	Assessment of Th-1-biased cell-mediated immune responses specific to the SARS-CoV-2 S-protein were recorded in both adjuvanted vaccine groups with increases in IFN-γ and IL-2-positive CD4+T-cells after the first dose, which further increased after the second dose. There were no cell-mediated immune responses with non-adjuvanted SCB-2019.	N/A	After second dose vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache, fatigue, and myalgia No unsolicited adverse events were causally related to vaccination. The frequency and severity of adverse events increased after the second dose. SCB-2019 + AS03 formulation represented the highest rate of AEs. Younger adults reported local and systemic adverse events more frequently than did older adults after the first dose, but incidence was similar in the two age groups after the second dose.	(66)
						30 μg SCB-2019 with AS03 adjuvant	D0, D21	8					
						30 μg SCB-2019 CpG/Alum adjuvant	D0, D21	8					
						9 μg SCB-2019 with no adjuvant	D0, D21	8					
						9 μg SCB-2019 with AS03 adjuvant	D0, D21	8					
						9 μg SCB-2019 CpG/Alum adjuvant	D0, D21	8					
						3 μg SCB-2019 with no adjuvant	D0, D21	8					
						3 μg SCB-2019 with AS03 adjuvant	D0, D21	8					
						3 μg SCB-2019 CpG/Alum adjuvant	D0, D21	8					
						Placebo	D0, D21	18					

Zhang et al.	Recombinant fusion protein vaccine (V-01)/ developed by the Institute of Biophysics, Chinese Academy of Sciences, and Livzon Bio Inc. China	Randomized/ double-blind/ placebo-controlled	IM	I/ China	4 groups (18-59 years)	10 µg	D0, D21	24	The nAb titers peaked at day 35 or day 49. Seroconversion rates of nAbs were mostly below 70% at day 21 and were above 95% in all vaccinated groups at day 49. The seroconversion rates of RBD-binding antibody were above 90% at day 21 and were 100% in vaccinated groups at day 49.	N/A	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain and pruritus -most reported systemic AEs: fever, anorexia, muscle pain, and headache -No significant differences of overall AEs within 30 days across vaccine groups and placebo groups was observed. - All the AEs were mild or moderate in severity.	(70)
						25 µg	D0, D21	24					
						50 µg	D0, D21	24					
						Placebo	D0, D21	18					
					4 groups (≥ 60 years)	10 µg	D0, D21	24					
						25 µg	D0, D21	24					
						50 µg	D0, D21	24					
						Placebo	D0, D21	18					
Shu et al.	Recombinant fusion protein vaccine (V-01)/ developed by the Institute of Biophysics, Chinese Academy of Sciences, and Livzon Bio Inc. China	Randomized/ double-blind/ placebo-controlled	IM	II/ China	5 groups (18-59 years)	50 µg	D0	120	the levels of nAbs peaked at day 35 and remained high, although slightly declined, at day 49. At day 49, the seroconversion rate of nAbs were 98.3% for 10 µg group and 99.2% for 25 µg group in younger adults. 50 µg single dose group has remarkably lower seroconversion rate. Overall, GMT were lower in older participants.	N/A	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: fever, headache, and muscle pain -AEs were milder in participants aged ≥60 than those aged 18 to 59 years. -The majority of the local and systemic AEs was mild or moderate. - overall rate of AEs within 30 days of immunization was higher in the two-dose, 10 mg V-01 group than that in the two-dose, 25 mg V-01 group of young adults.	(68)
						Placebo	D0	40					
						10 µg	D0, D21	120					
						25 µg	D0, D21	120					
						Placebo	D0, D21	40					
					5 groups (≥ 60 years)	50 µg	D0	120					
						Placebo	D0	40					
						10 µg	D0, D21	120					
						25 µg	D0, D21	120					
						Placebo	D0, D21	40					
Chappell et al.	Recombinant sclamp antigen vaccine/ developed by CSIRO Manufacturing, Clayton, VIC, Australia	Randomized/ double-blind/ placebo-controlled	IM	I/ Australia	5 groups (18-55 years)	Placebo	D0, D29	24	99% seroconversion rate was reported 57 days after any concentration of two dose vaccines and it was 13% for the single dose group. No difference was observed between dosing groups for antibody responses.	Spike specific CD4+ T cell responses including Th1 and Th2 produced cytokines were elevated in all vaccinated groups at day 15. No CD8+ T cell responses were noted.	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain and tenderness -most reported systemic AEs: headache, fatigue, and malaise -no serious AEs was reported.	(62)
						5 µg	D0, D29	24					
						15 µg	D0, D29	24					
						45 µg	D0, D29	24					
						45 µg	D0	24					
Yang et al.	recombinant protein subunit vaccine (ZF2001)/ developed by Institute of Microbiology, Chinese Academy of Sciences, and Anhui Zhifei Longcom Biopharmaceutica	Randomized/ double-blind/ placebo-controlled	IM	I/ II/ China	3 groups (18-59 years)	Placebo	D0, D30, D60	10	At day 30 after the second dose, 93% of 25 µg group and 94% of 50 µg group were seroconverted for nAbs, while 7 days after the third dose, seroconversion rate reached 100%. Seroconversion rate in phase 2 after 14 days post third vaccination was 97-99% in 25 µg group and 93-97% in 50 µg group for nAbs and binding antibodies, respectively.	25 µg and 50 µg doses elicited moderate levels of both Th1 (IFNγ and IL-2) and Th2 (IL-4 and IL-5) cytokine production after the immunisations.	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain, redness, and itch -most reported systemic AEs: cough, fever, headache, and fatigue	(69)
						25 µg	D0, D30, D60	20					
						50 µg	D0, D30, D60	20					
					6 groups (18-59 years)	Placebo	D0, D30	150					
						25 µg	D0, D30	150					
						50 µg	D0, D30	150					
						Placebo	D0, D30, D60	150					
						25 µg	D0, D30, D60	150					
						50 µg	D0, D30, D60	150					
Virus-like particle vaccine													

Ward et al.	Coronavirus-Like Particle COVID-19 Vaccine/ developed by Medicago	Observer-blinded/ randomized	IM	I/ Canada	9 groups (18-55 years)	CoVLP (3.75 μg) Unadjuvanted	D0, D21	20	unadjuvanted CoVLP elicited no detectable antibody response after each dose. nAb titers increased significantly with both adjuvants, however, CoVLP+AS03 was more potent in eliciting nAbs as compared to CoVLP+CpG10118. After the second dose, 100% of participants receiving AS03-adjuvanted formulation seroconverted regardless of the CoVLP dose level.	The IFN-γ and IL-4 responses to the CoVLP + AS03 formulation at all dose levels were 10-50 fold higher than those observed in the unadjuvanted group while CoVLP + CpG10118 response was approximately 5 fold higher than the unadjuvanted groups for IFN-γ and similar or reduced for IL-4.	N/A	Within 7 days after vaccination: -most reported injection site AEs: pain -most reported systemic AEs: headache and fatigue -both adjuvants increased the rate of reported AEs -AEs were mostly mild to moderate, however, more moderate AEs were reported after the second dose.	(137)
						CoVLP (3.75 μg)+ CpG	D0, D21	20					
						CoVLP (3.75 μg)+ AS03	D0, D21	20					
						CoVLP (7.5 μg) Unadjuvanted	D0, D21	20					
						CoVLP (7.5 μg)+ CpG	D0, D21	20					
						CoVLP (7.5 μg)+ AS03	D0, D21	20					
						CoVLP (15 μg) Unadjuvanted	D0, D21	20					
						CoVLP (15 μg)+ CpG	D0, D21	20					
						CoVLP (15 μg)+ AS03	D0, D21	20					

Note: In this table, the study type, clinical phase, groups, immune responses, and adverse events related to current vaccines including inactivated vaccines, RNA-vaccines, Vector-based, recombinant, subunit, and virus-like particle vaccines were separately addressed.

Abbreviations: Ab, antibody; AE, adverse event; IFNγ, Interferon gamma; IM, intra-muscular; nAbs, neutralising antibodies; NP, number of participants; RBD, receptor binding domain; S, SARS-CoV-2 spike protein; VP, viral particle.

3.1.3 | Vector-based SARS-CoV-2 vaccines

A total of 16 studies were identified that provided clinical outcomes as well as vaccine immunogenicity and efficacy on the use of vector-based SARS-CoV-2 vaccines in healthy subjects. Two studies were in phase I trial,[46,47] seven studies in phase I/II trial,[48–54] one study in phase II trial,[55] three studies in phase II/III trial,[56–58] and three studies in phase III trial.[59–61]

In a phase I/II trial by Folegatti et al.[54] in the UK, the immune response and reactogenicity of the ChAdOx1 nCoV-19 (COV001) vaccine were evaluated. Spike-specific T-cell and anti-spike IgG responses peaked on day 14 and day 28, respectively. Anti-spike IgG responses were increased following the booster dose. Also, neutralising activity was seen in all participants after the second dose. Pain and tenderness, fatigue, and headache were the most commonly reported injection site and systemic reactions, respectively. Moreover, another phase I/II trial of the ChAdOx1 nCoV-19 vaccine was tested in order to compare the immunogenicity and safety of standard dose or half dose booster vaccination. It was demonstrated that a half-dose boost elicited lower immune responses with lower induction of AEs.[48] Results of phase II/III ChAdOx1 nCoV-19 vaccine in the UK, aiming to investigate the effects of two different doses of vaccine in three age groups, showed no significant variations in anti-spike IgG and nAb titres between low-dose and standard-dose vaccine recipients. Besides, within a week post second vaccination, older adults showed a lower incidence of AEs as compared to younger counterparts.[57]

The overall vaccine efficacy was 70.4%, with a higher efficacy as 90% in the low dose prime vaccine regimen than 62.1% in standard dose prime vaccine regimen. Notably, three trials were conducted later in order to examine the efficacy of the vaccine against different types of SARS-CoV-2 variants. It has been estimated that ChAdOx1 nCoV-19 is 63.6% efficient against the P.1 variant, 61.7% against the B.1.1.7 variant, and only 10.6% against the B.1.351 variant.[51,56,59]

In a phase I/II trial, a heterologous COVID-19 vaccine (Gam-COVID-Vac or Sputnik V) consisting of a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the spike glycoprotein gene of SARS-CoV-2, was tested in Russia. SARS-CoV-2 RBD-specific IgGs were detected on day 14 after the last immunisation in all participants. Cell-mediated responses (IFNγ production or lymphoproliferation) were detected in all participants on day 28.[50] The phase III of the vaccine showed that the seroconversion rate for RBD-specific IgG and nAbs was 98.25% and 95.83%, respectively. Also, the trial reported 91.1% overall efficacy for the vaccine that could protect individuals against moderate or severe forms of COVID-19 completely.[60] Common local AEs was pain at the injection site and headache and asthenia were frequently reported systemic AEs.

In other two clinical trials conducted in Belgium and the USA, the safety and potency of the Ad26 vectored COVID-19 vaccine (Ad26.COV2.S) developed by Johnson & Johnson were tested in phase I/II trials. The vaccine induced acceptable titres of nAbs and

T-cell responses after the second dose of vaccine.[46,53] The worldwide efficacy analysis of the Ad26.COV2.S vaccine in a single dose manner estimated 66.3% protection against moderate to severe forms of the disease and 73.1% against severe to critical form. In addition, the vaccine was 52% efficient in preventing B.1.351 variant infection.[61] Pain at the site of injection together with headache, fatigue, and myalgia are considered the most commonly reported AEs.

In addition, in a first-in-human phase I trial conducted by Zhu et al. in China, the safety and immunogenicity of the Ad5 vectored COVID-19 vaccine developed by Beijing Institute of Biotechnology (Beijing, China) and CanSino Biologics (Tianjin, China) were tested in healthy adults.[47] A single intramuscular (IM) injection of the vaccine was tested in a dose-escalation manner, including three viral particle doses in phase I and two viral particle doses in phase II.[55] Antibody responses against RBD were detected from day 14, in all three groups and peaked at day 28. Produced IFNγ from CD4+ and CD8+ T cells was reported at day 14 and 28 post vaccination. In addition to the injection site pain as a frequent local AE, fever, fatigue, and headache were the most reported systemic AEs, with a higher incidence in the greater viral particle group.

Apart from adenoviral vectored vaccines, two other phase I/II trials utilised baculovirus as a vaccine vector.[49,52] The first trial, which was carried out in China, reported that the seroconversion rate of nAbs was 96%–100% in adults and 73%–78% in the elderly for the high dose group with triple injections.[52] The latter trial evaluated the immune response of the vaccine with two different adjuvants. It found that 36 days after vaccination, nAb titres were higher in the AF03-adjuvanted group, while binding Ab titres were higher in the AS03-adjuvanted group, with full seroconversion of all participants receiving the vaccine plus adjuvant. Furthermore, local and systemic AEs occurred more frequently after AS03 and AF03-adjuvanted groups, respectively.[49]

3.1.4 | SARS-CoV-2 Subunit vaccines

A total of nine studies were identified that provided clinical outcomes as well as vaccine immunogenicity and efficacy on the use of vector-based SARS-CoV-2 vaccines in healthy subjects.[62–70] Four studies were in phase I trials,[62,65,66,70] one in phase I/II trial,[69] three in phase II trials,[63,67,68] and one in phase III trial.[64]

NVX-CoV2373, a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine, contains purified coronavirus spike (S) protein (named SARS-CoV-2 rS) adjuvanted with Novavax's patented saponin-based Matrix-M. The results of the phase I trial, which was conducted in Australia, showed that two-doses of 5-μg adjuvanted regimen elicited robust anti-spike IgG and nAbs, which were numerically (4-6 and 4-fold, respectively) superior to those seen in human convalescent sera. Increased Th1 responses were reported at day 28 post vaccination.[65] The phase II trial assessed the immunogenicity and safety of the NVX-CoV2373 vaccine in two different dose regimens as a single or double inoculation in healthy adults. No difference was observed in terms of anti-S IgG titres for both 2-dose regimens of 5-μg and 25-μg, and the seroconversion rate was 98% and 100%, respectively. Anti-S IgG and nAb titres were higher for younger participants, with a higher frequency of AEs in this age group.[63] The result of the safety analysis revealed more severe AEs after the second dose injection. Findings of the NVX-CoV2373 phase III trial noted an overall vaccine efficacy of 89.7% that dropped to 86.3% against the B.1.1.7 variant.[64] In terms of protecting against the B.1.351 variant, vaccine performed less effectively, such that the efficacy was 49.4% in the baseline seronegative group and 52.6% in the baseline seropositive group.[67]

Phases I and II trials of a recombinant COVID-19 vaccine (V-01) containing fusion protein of the SARS-CoV-2 were conducted in China. Levels of nAb titres peaked 2 weeks after the second dose and remained high, although slightly declined, 4 weeks later. Almost all vaccinated participants developed RBD-binding antibodies and nAb responses after the boost dose, with lower immunogenicity in single dose group. Vaccine related AEs were milder in older recipients and those who received higher dose regimens. In addition to pain as the most recorded local AE, fever, headache, and muscle pain were accounted as frequently reported systemic AEs.[68,70]

Another protein subunit vaccine (SCB-2019) was developed by QEII Medical Centre in Australia and tested in a phase I trial by Richmond et al.[66] They demonstrated that nearly all participants in vaccine group formulated with adjuvant were seroconverted while a little or no antibody response to non-adjuvanted SCB-2019 was seen. Likewise, IFN-γ and IL-2-positive CD4+T-cells were increased in adjuvanted groups with no cell-mediated immune response for non-adjuvanted group. Considering the safety profile of the vaccine, the frequency and severity of AEs increased after the second dose, with a predominance of pain at the injection site, headache, and fatigue.[66]

Immunisation with a recombinant vaccine developed by Chappell et al., which comprises a trimeric glycosylated SARS-CoV-2 spike glycoprotein ectodomain, induced an effective antibody response in all immunised individuals with a booster dose, 4 weeks after the second vaccination, with no difference in antibody titres in dosing groups. Besides, the number of CD4+ T cells was found to be increased in all vaccine-treated groups, and no CD8+ T cell responses were detected. Investigating the vaccine safety profile, none of the AEs were serious.[62]

ZF2001, as a SARS-CoV-2 subunit vaccine, developed by the Institute of Microbiology in China. Triple dose regimens in the phase I/II trial showed a robust induction of both neutralising and binding antibodies and that higher titres were elicited in low dose group of 25 μg. In addition, the vaccine was able to evoke a moderated level of both Th1 (IFNγ and IL-2) and Th2 (IL-4 and IL-5) cytokine production. Within a week after immunisation, pain,

redness, and itching were more probable local AEs, while cough, fever, and headache were considered to be highly reported systemic AEs.[69]

3.1.5 | SARS-CoV-2 virus-like particle (VLP) vaccines

One VLP-based COVID-19 vaccine candidate was produced by Medicago.[71] The immunogenicity results of the Phase I trial of Medicago's COVID-19 vaccine candidate, which is a plant-derived Coronavirus Virus-Like Particle (CoVLP), demonstrated that CoVLP alone elicits weak humoural but modest cellular responses while adjuvanted formulations (GSK pandemic adjuvant (AS03), and Dynavax's CpG 1018™) have the potential to improve anti-spike IgG and nAbs as well as IFNγ and IL4 responses. There were no serious solicited local and systemic AEs and pain was the most commonly reported injection site reaction. Their findings suggest that the CoVLP (3.75 μg)+AS03 regimen could be considered for further clinical assessment.[71]

3.2 | Immunogenicity and safety of COVID-19 vaccines in patients with underlying diseases of interest

A total of 34 studies have assessed the immunogenicity and/or safety of COVID-19 vaccines in patients with different underlying disorders or specific conditions such as malignancies (i.e. solid tumours and haematological malignancies),[72–80] transplant recipients,[81–93] individuals on dialysis,[85,94–99] inflammatory rheumatic diseases,[100–102] inborn errors of immunity,[103] immune-mediated inflammatory diseases,[104] and pregnant or lactating women.[105] All studies evaluated the effects of mRNA COVID-19 vaccines (i.e. BNT162b2 and mRNA-1273 COVID-19 vaccines) except for two studies that also assessed the COVID-19 adenovirus platform (i.e. ChAdOx1/nCoV-19)[96,106] (Table 2).

In general, immunocompromised patients, such as organ transplantation patients and those suffering from cancers, particularly haematological malignancies, developed lower levels of immune response to COVID-19 vaccines. A study that only included participants with multiple myeloma showed that previous SARS-CoV-2 infection led to a significantly higher SARS-CoV-2 spike-binding IgG antibody levels than non-infected patients ($p < 0.001$).[75] Also, treatment with anti-CD38 agents was associated with antibody production among these patients (odds ratio (OR): 4.25; $p = 0.005$).[75] In another study on adolescents and young adults with cancer, 90% developed seroconversion 1 month after vaccination, while it was 80% 3 weeks following vaccination.[79] Among recipients of allogenic stem cell transplantation compared with controls, there was a significantly lower rate of seroconversion following the first dose of the BNT162b2 COVID-19 vaccine (55% vs. 100%; $p < 0.001$)[82] (Table 2). Examining whether COVID-19 vaccines are immunogenic enough in pregnant and lactating women, a recent study revealed that binding, neutralising, and functional non-neutralising antibody responses as well as CD4+ and CD8+ T-cell responses were present at an optimal level in this population. Binding and neutralising antibodies were also observed in infant cord blood and breast milk.[105]

The most common local and systemic adverse events in patients with different underlying diseases of interest who received COVID-19 vaccines were pain at the injection site and fatigue, respectively.[77,89,91,95,99,101] Other reactions like myalgia, arthralgia, headache, fever, and gastrointestinal disturbances were also reported, but none of them were serious or life-threatening[78,89,101] (Table 2).

3.3 | Incidence of AESI post COVID-19 vaccination in the USA

As of 22 November 2021, 262.23 million doses of Pfizer/Biotech, 172.32 million doses of Moderna, and 16.44 doses of Janssen vaccines were administrated in the USA.[107] Overall, the AESI was more likely to occur after receiving the Janssen vaccine. Venous and arterial thrombotic events, Bell's palsy, and myocarditis/pericarditis were more common post immunisation. Although venous and arterial thrombotic events, Bell's palsy, Guillian-Barre syndrome, and transverse myelitis were often reported in 65–79 age group, myocarditis/pericarditis and anaphylaxis were reported frequently in 18–29 age group and 30–39 age group, respectively. Unlike other AESI, the occurrence of myocarditis/pericarditis, and anaphylaxis followed a sex distribution pattern which mostly involved males. Table 3 summarises the comparative frequency of the AESI per million doses of the three vaccines, together with the frequency and rate of these events stratified by age and sex groups.

4 | COVID-19 VACCINES AND OMICRON VARIANT

A new SARS-CoV-2 variant named Omicron (B.1.1.529), has been announced by WHO as a variant of concern on 26 November 2021. This newly emerged variant showed 32 amino acid alterations in the spike protein, which included three deletions and one insertion. As previously discussed, currently available COVID-19 vaccines mostly target the S protein. The variant's ability to evade current vaccines may be considerably enhanced as a result of these changes.[108,109]

However, research is currently underway into the effect of COVID-19 vaccines on Omicron prevention. Viruses undergo continual mutations as they spread throughout time. This can lead to the emergence of novel varieties, such as the SARS-CoV-2 Omicron variant. The spike protein of Omicron has a lot of mutations, which makes it easier for it to attach to cells and infect them. As a result, Omicron is easier to disseminate and generates more infections than prior virus variants. COVID-19 vaccines are

TABLE 2 The immunogenicity and safety of COVID-19 vaccines in individuals with specific underlying disorders

First author (Reference)	Country	Underlying disease	Study design	Vaccine type and dose	Time point of analysis after vaccine dose	Number of participants	Age (years)	Sex	Vaccine immunogenicity	Vaccine safety	Reference
Hematological malignancies											
Maneikis et al.	Lithuania	Hematological malignancies	Prospective cohort	BNT162b2; first and second dose	0–10 days before the first dose; on the day of second dose; 7 to 21 days after the second dose	Cases (n=857); Controls (n=67)	Controls: (Median: 40 [IQR: 32-53]) Cases: (Median: 65 [IQR: 54-72])	Female: 509 Male: 416	Anti-S1 IgG antibody responses after two vaccine doses: cases: 6961 AU/mL [IQR 1292–20672] Controls: 21395 AU/mL [14831–33553]; p<0.0001	N/A	(72)
Van Oekelen et al.	USA	Multiple myeloma	Prospective cohort	BNT162b2 (69.1%); mRNA-1273 (27.2%); Unknown (3.8%); first and second dose	>10 days after the second dose	N= 260	Patients with detectable anti-spike IgG antibody (Median [range]: 69 [38-93]); Patients with undetectable anti-spike IgG antibody (Median [range]: 70 [43-86])	Female: 109 Male: 151	Of the fully immunized multiple myeloma patients, 84.2% (219/260) mounted measurable SARS-CoV-2 spike-binding IgG antibody levels. Antibody levels in the 38 fully vaccinated multiple myeloma patients with prior reported COVID-19 infections were 10 times higher than those of multiple myeloma patients that were naive at the time of vaccination (median for COVID-19 survivors: 801 AU/mL [range: 0–7,882 AU/mL] versus median for COVID-19 naive MM patients: 68.5 AU/mL [range: 0–3,174 AU/mL], p<0.001).	N/A	(75)
Harrington et al.	UK	Chronic myeloid leukemia	Cohort	BNT162b2; first dose	Safety was assessed by 2-weekly telephone calls. Efficacy was assessed 3 weeks after the first vaccine injection.	N= 16	Mean [SD]: 45.6 [14.9]	Female: 4 Male: 12	Anti-Spike IgG was detected in 14/16 (87.5%). All developed a neutralizing antibody response (i.e. serum dilution that inhibits 50% infection). T-cell response was seen in 14/15 (93.3%) of patients. Polyfunctional responses seen in 12/15 (80%) patients.	Localized inflammation (56.3%) Transient flu-like illness (23.5%)	(76)
Harrington et al.	UK	Myeloproliferative neoplasms (e.g. essential thrombocythemia, myelofibrosis, and polycythaemia vera)	Cohort study	BNT162b2; first dose	Efficacy: Median of 21 days (IQR 21–21) following first injection Safety: 7 days after administration	N= 21	Mean [SD]: 55.0 [10.7]	Female: 14 Male: 7	A positive anti-S IgG was seen in 76.1% of patients following vaccination. The median anti-S IgG EC50 amongst positive samples was 239 (IQR 25–4544). Positive neutralizing antibodies were detected in 85.7% of patients, with a median ID50 of 457 (IQR 150.3–2622). High (>501) neutralizing titers were observed in 42.9% of patients.	The vaccine was safe and generally well tolerated with 57.1% patients reporting localized inflammation and 47.6% of patients reporting systemic side effects including flu-like illness, fatigue and gastrointestinal symptoms, following injection.	(77)
Solid tumors											
Fong et al.	Italy	Solid tumors in previously infected patents (Cases: 63%; Controls: 63.6%) Hematological malignancies in previously infected patients (Cases:	Retrospective cohort	BNT162b2; first and second dose	At week three after the first dose	RT-PCR confirmed (n=74); seropositive Patients (n= 15); Controls (n= 154)	Seropositive: (Median[range]: 62 [28-86]); Seronegative: (Median[range]: 68 [31-85])	Female: 118 Male: 125	After first dose: increasing seropositive patients to 81 of 89 (91.0%; S-IgG median value 15,927 AU/mL, range: 0-40,000) seroconversion in CoV-negative patients in 94 of 154 (61.0%; median S-IgG value 101.2 AU/mL, range: 0-38,727) After second dose: increasing seropositive patients to 86/89 (96.6%) seroconversion in CoV-negative patients in 132 of 154 (85.7%)	N/A	(73)

		37%; Controls: 36.4%)									
Addeo et al.	USA and Switzerland	Solid tumors (n= 106) Hematological malignancies (n= 25)	Prospective cohort	mRNA-1273 (n= 93), BNT162b2 (n= 38); first and second dose	Three weeks after first dose of BNT162b2 and 4 weeks after first dose of mRNA-1273 and at 3 weeks after second dose of mRNA-1273 or 4 weeks after second dose of BNT162b2	N= 131	Median [IQR]: 63 [55-69]	Female: 59 Male: 72	94% of participants achieved seroconversion after receipt of two vaccine doses. Seroconversion rate after the first dose was significantly lower than after the second dose ($p<0.001$). 6% did not develop any antibodies after two doses.	N/A	(74)
Revon-Riviere et al.	France	≥16 year-old patients under treatment for a solid tumors or within 6 months after treatment	Retrospective analysis	mRNA-BNT162b2; second dose	Before first administration, before second administration and one month after the second administration of the vaccine.	N= 13	Mean [SD]: 67.6 [14.8]	Female: 2 Male: 10	All patients but 1 had pre-vaccination negative serology; 7 of 10 patients tested had positive serology before second vaccine injection, and 9 of 10 patients had positive serology one month after the second injection.	Five patients did not report any side effects after the first injection and 4 after the second injection. Main local symptom: injection-site pain (6 and 2 patients after the first and second dose). Main systemic reaction: Fatigue (2 and 5 patients after the first and second dose).	(79)
Monin et al.	UK	Patients with solid cancer (n= 95); patients with hematological cancer (n= 56)	Prospective observational study	BNT162b2; second dose	Before vaccination and at 3 weeks and 5 weeks after the first vaccination. 21 days after vaccination for evaluation of vaccine boosting on seroconversion	Patients with cancer (n= 151); healthy controls (n= 54)	Patients with cancer (Median [IQR]: 73.0 [64.5-79.5]); healthy controls (Median [IQR]: 40.5 [31.3-50.0])	Female: 99 Male: 106	The proportion of positive anti-S IgG titers were 94%, 38%, and 18% in controls, patients with solid cancers, and patients with hematological malignancies, respectively. 95% of patients with solid cancer, 100% of healthy controls, and 60% of patients with hematological cancers who received second dose were seropositive, compared with 30%, 86%, and 11%, respectively, who did not receive a boost.	No toxicities were reported in 54% of patients with cancer following the first dose and in 71% of patients with cancer following the second dose. No toxicities were reported in 38% of healthy controls after the first dose and in 31% after the second dose. Injection-site pain was the most commonly reported local reaction (35% of patients with cancer; 48% of healthy controls). No vaccine-related deaths were reported.	(92)
Transplant patients											
Schramm et al.	Germany	Transplant patients [1–3 years post heart (n= 42), lung (n= 7), or heart–lung (n= 1)]	Prospective cohort	BNT162b2; first and second dose	Pre-vaccination, 21 days after the first vaccine dose and 21 days after the second vaccine dose	Transplant patients (n=50); Healthy staff members (n=50)	Transplant patients: (Mean [SD]: 50 [10]); Healthy staff members: (Mean [SD]: 47 [10])	Female: 18 Male: 32	**IgG response** After first dose: All but one control subject had anti-SARS-CoV-2 IgG titers above the cut-off value of 7.1 BAU/ml After second dose: anti-SARS-CoV-2 IgG titers increased in all individuals **nAb response** After first dose: a positive immunization effect (cut-off ≥ 20% inhibition) in 82% of control and no patient in the case group After second dose: Inhibitory capacity in all controls. No significant increase in inhibitory capacity of cases. **T-cell response**	N/A	(81)

									Lower IFN-γ response to spike antigens of SARS-CoV-2 peptides in cases than controls (median: 0.031 vs. 0.512; p<0.0001).		
Chevallier et al.	France	Individuals receiving allogeneic hematopoietic stem cell transplant	Prospective cohort	BNT162b2; first dose	At the time of the second injection	Case: 94 Controls: 24	Median [range]: 57 [20-75]	Female: 45 Male: 67	55% rate of seroconversion in allotransplanted patients compared to 100% for the controls (p<0.001).	Any reaction: Cases (45/94 (47.8%)) Controls (16/24 (66.6%)) None of the participants required medical attention after the vaccination.	(82)
Narasimhan et al.	USA	Lung-transplant recipients	Cohort	mRNA-1273 (34%) and BNT162b2 (66%); two-dose regime	Median time of 17.5 days after two-dose of BNT162b2 Median time of 19 days after two-dose of mRNA-1273	Spike-specific IgG antibody positive: n= 18 Spike-specific IgG antibody negative: n= 55	Median [IQR]: 65 [53.5-69.5]	Female: 26 Male: 47	18/73 of SARS-CoV-2 uninfected-lung transplant patients generated a positive spike-IgG response (36% of mRNA-1273 and 19% of BNT162b2 recipients). Transplant-recipient patients elicited a significantly lesser median spike-specific IgG response (1.7 AU/mL, 95% CI: 0.6–7.5 AU/mL) compared to non-transplanted, uninfected naïve subjects (14,209 AU/mL, 95% CI: 11,261–18,836 AU/mL; p<0.0001).	N/A	(83)
Malinis et al.	USA	Solid organ transplant recipients (388 kidney, 105 liver, 50 heart, 14 combined organ transplants)	Retrospective, observational study	BNT162b2 (n= 324); mRNA-1273 (n= 206); Ad26.CoV2.S (n= 27); first and second dose	NA	N= 557	Median [range]: 62 [16-91]	Female: 208 Male: 349	Six of 98 (6.12%) receiving one dose developed SARS-CoV-2 infection. Positive SARS-CoV-2 NAAT ≥14 days postvaccine series completion, occurred in 3 of 459 (0.65%).	N/A	(84)
Danthu et al.	France	Kidney transplant recipients and hemodialysis patients	Retrospective observational study	BNT162b2; first dose	0, 14, 28, 36, and 58 days after the first dose.	Patients undergoing hemodialysis (n= 78), kidney transplant recipients (n= 74), healthy controls (n= 7)	Patients undergoing hemodialysis (Mean [SD]: 73.5 [12.8]); kidney transplant recipients (Mean [SD]: 64.8 [11.5]), healthy controls (Mean [SD]: 51.6 [6.8])	Female: 65 Male: 94	In controls, antibodies were detected at a positive level (>13 AU/ml) at day 14 post injection. It increased progressively to peak at day 36 (1082AU/ml; [IQR]: 735.0–1662.0). Patients undergoing hemodialysis had lower titers that peaked at day 58 (276AU/ml; IQR, 83.4–526.0). A positive antibody level was detected in only three transplant recipients at day 36.	N/A	(85)
Miele et al.	Italy	Solid organ transplant recipients	Cohort	BNT162b2; second dose	At least 15 days after the administration of the second dose	Solid organ transplant recipients (n=16); immunocompetent subjects (n= 23)	Solid organ transplant recipients (Mean [SD]: 57 [15.9]); immunocompetent subjects (Mean [SD]: 44 [7.2])	Female: 16 Male: 23	All immunocompetents resulted positive for anti-SARS-CoV2 IgG, but only 6/16 solid organ transplant recipients (37%) had positive serology showing besides a much lower mean titer of antiviral antibodies of 87.32 UA/ml versus 233 UA/ml in immunocompetents. Humoral response was significantly lower in Solid organ transplant recipients than in immunocompetents (p<.0001).	N/A	(86)
Chenxi Song et al.	USA	Kidney transplant recipients	Cross-sectional	BNT162b2 (n= 5); mRNA-1273 (n= 2); second dose	Follow-up from vaccine completion to COVID-19 diagnosis (Median: 33 days)	N= 7	Mean [SD]: 63.0 [11.0]	Female: 2 Male: 5	3/7 patients had detectable Sars-CoV-2 spike IgG antibody, while 2/7 had both spike and nucleocapsid protein IgG at the time of COVID-19 diagnosis.	4/7 were hospitalized, however only 2 developed severe COVID-19 symptoms requiring supplemental oxygenation, redemsivir and dexamethasone.	(87)

Havlin et al.	Czech Republic	Lung transplant recipients	Cohort study	BNT162b2; first and second dose	SARS-CoV-2 spike IgG detection: immediately before 1st dose or 2nd dose; 1 week after 2nd dose; 4-6 weeks after 2nd dose SARS-CoV-2 spike specific T cell response detection: 9 weeks after 2nd dose	Vaccinated lung transparent recipients (n= 48) Post-COVID lung transplant recipients (n= 33)	Vaccinated lung transparent recipients (Mean [SD]: 52.1 [14.3]) Post-COVID lung transplant recipients (Mean [SD]: 51.6 [15.5])	Female: 33 Male: 48	None of the vaccines tested after two doses of the mRNA BNT162b2 vaccine developed anti-SARS-CoV-2 IgG, while 85% patients presented an antibody response after SARS-CoV-2 infection. SARS-CoV-2 specific T-cells was detected in 4 out of 12 tested patients.	N/A	(88)
Itzhaki Ben Zadok et al.	Israel	Heart transplant recipients	Prospective single-centre cohort study	BNT162b2; second dose	At days 21–26 and days 35–40 after the first vaccine dose	N= 42	Median [IQR]: 61 [44-69]	Female: 7 Male: 35	15% demonstrated the presence of positive S-IgG antibody titers in response to the first vaccine dose [geometric mean titers: 90 (IQR 54–229) AU/mL]. 49% induced S-IgG antibodies in response to either the first or the full two-dose vaccine schedule [geometric mean titers: 426 (IQR 106–884) AU/mL].	Pain at the injection site (71%), Redness (5%), Fatigue (14%), Myalgia (10%), Arthralgia (12%), Headache (5%), and Systemic fever (2%)	(89)
Korth et al.	Germany	Renal transplant recipients	Cohort	BNT162b2; second dose	3 days after the second dose	Renal transplant recipients (n= 23); healthy controls (n= 23)	Renal transplant recipients (Mean [SD]: 57.7 [13.5]); healthy controls (Mean [SD]: 44.4 [9.2])	Female: 26 Male: 20	Only 5 of 23 (22%) renal transplant recipients were tested positive for SARS-CoV-2 IgG antibodies after the second dose of vaccine. All 23 (100%) controls were tested positive for antibodies after the second dose. The mean SARS-CoV-2 IgG titer was 50.9 (SD: 138.7) and 727.7 (SD: 151.3) AU/mL in cases and controls, respectively.	N/A	(90)
Rabinowich et al.	Israel	Liver transplant recipients	Cohort	BNT162b2; second dose	Mean time period between administration of the vaccinations and antibody testing after the second dose was 14.8 (SD: 3.2) days in cases and 15.8 (SD: 2.9) days in controls.	Liver transplant recipients (n= 80); healthy controls (n= 25)	Liver transplant recipients (Mean [SD]: 60.1 [12.8); healthy controls (Mean [SD]: 52.7 [11.5])	Female: 41 Male: 64	Immunogenicity among liver transplant recipients was significantly lower with positive serology in only 47.5% ($p < 0.001$). Antibody titer was also significantly lower in this group (mean 95.41 AU/ml vs. 200.5 AU/ml in controls, $p < 0.001$).	Injection site reactions occurred in 60.5% of cases and 71% of controls following the first dose. It occurred in 53.5% of cases and 71% of controls following second dose. The frequency of systemic events was 19.7% and 28% among cases and controls, respectively. The most common systemic side effects were fatigue, headache, and myalgia.	(91)
Hemodialysis patients											
Broseta et al.	Spain	Hemodialysis patients	Observational prospective multicenter cohort study	BNT162b2 (n= 324); mRNA-1273 (n= 206); Ad26.CoV2.S (n= 27); first and second dose	3 weeks after completing vaccination.	N= 175	Mean [SD]: 70.9 [15.0]	Female: 57 Male: 118	97.7% of patients who were seronegative at baseline developed a response (humoral, cellular, or both) 95.4% of these patients seroconverted, while 62% of those tested for cellular immunity had a positive response.	N/A	(94)
Longlune et al.	France	Patients on hemodialysis (n=85) or peritoneal dialysis (n= 24)	Prospective cohort	BNT162b2; second (n=97) or third (n=5) dose	One-month follow-up after the second and third doses	N= 112	Mean [SD]: 64.0 [14.0]	Female: 35 Male: 77	The seroconversion rate after the first dose was 21.25%. The seroconversion rate after the second dose was 84.1%. Overall, anti-SARS-CoV-2 antibodies were detected in 90.2% of patients. The seroconversion rate after two or three doses was 89.6%.	No serious adverse events were reported by patients who received the vaccine.	(95)

										There were fatigue (n=15), myalgia (n=15) and low fever (n=7) within the first 24 hours.	
Lesny et al.	Germany	Patients on hemodialysis or peritoneal dialysis	Multicenter prospective observational pilot study	BNT162b2 and ChAdOx1 nCoV-19; first dose	Time from first vaccination to sampling was 14 days for hemodialysis patients, 17.5 days for peritoneal dialysis patients and 14 days for staff.	Hemodialysis patients (n= 23), peritoneal dialysis patients (n= 4) and healthy staff (n= 14)	Patients on hemodialysis (Median [IQR]: 64 [61-83]); peritoneal dialysis (Median [range]: 60 [52-79]); and healthy staff (Median [range]: 54 [35-56])	Female: 25 Male: 16	Vaccination responder rates (i.e. SARS-CoV-2 spike IgG levels ≥ 50 AU/mL) were 17.4% (4/23) in hemodialysis patients, 100% (4/4) in peritoneal dialysis patients and 57.1% (8/14) in controls (Hemodialysis vs. Peritoneal dialysis: p=0.004, Hemodialysis vs. controls: p=0.027). IgM spike levels were 0.86 (0.03–7.46) and Nucleocapsid-protein Index levels were 3.0 (1.4–6.0) in hemodialysis patients.	N/A	(96)
Simon et al.	Austria	Hemodialysis patients	Prospective cohort study	BNT162b2; second dose	21 days after the second dose	Hemodialysis patients (n= 81); healthy controls (n= 80)	Hemodialysis patients (Mean [range]: 67 [34-86]); healthy controls (Mean [range]: 49 [29-65])	Female: 60 Male: 101	The hemodialysis patients had significantly lower anti-SARS-CoV-2 S antibody titers than the control patients (Median: 171 U/ml vs. 2,500 U/ml). 27% of hemodialysis patients did not develop a protective antibody titer (i.e., >29 U/ml)	No grade-4 adverse events (emergency department visit or hospitalization) were reported in either group. The control group reported significantly more local adverse events (first dose: p=0.006; second dose: p<0.0001) and more systemic adverse events after both vaccine doses (first dose: p=0.0005; second dose: p<0.0001) compared to the dialysis group.	(97)
Jahn et al.	Germany	Patients on hemodialysis	Cohort	BNT162b2; second dose	Patients on hemodialysis (Median [IQR]: 17.0 [15.0-18.0]); healthy controls (Median [IQR]: 13.0 [13.0-13.0]) days	Patients on hemodialysis (n= 72); healthy controls (n= 16)	Patients on hemodialysis (Median [IQR]: 68.0 [60.0-77.0]); healthy controls (Median [IQR]: 45.5 [41.2-54.7])	Female: 40 Male: 48	93% of patients on hemodialysis were tested positive for SARS-CoV-2 IgG after vaccination. The median antibody titer in all hemodialysis patients was 366.5 AU/mL (IQR: 89.6-606.0). Median antibody titer was 800.0AU/mL (IQR: 520.5-800.0) in controls. Antibody titers were detected in all tested controls.	Only mild localized pain at the injection-site was frequently reported by the hemodialysis patients	(93)
Agha et al.	USA	Hematological malignancies	Cohort	mRNA-1273 (n=43); BNT162b2 (n=34); second dose	Median [IQR]: 23 [16-31] days	N= 77	Median [IQR]: 71 [65-77]	Female: 32 Male: 45	31/67 patients (46.3%) had a negative antibody result after vaccination. Patients with CLL were significantly less likely to develop SARS-CoV-2 antibodies compared to patients with other hematological malignancies (23.1% (3/13) versus 58 61.1% (33/54), respectively, p = 0.01).	N/A	(80)
Grupper et al.	Israel	Patients on maintenance hemodialysis	Cohort	BNT162b2; second dose	Median of 30 days after receipt of the second dose	Patients on maintenance hemodialysis (n= 56); healthy controls (n= 95)	Hemodialysis patient (Mean [SD]: 74.0 [11.0); healthy controls (Mean [SD]: 57.0 [9.0])	Female: 83 Male: 68	100% of subjects in the control group developed an antibody response compared with 96% positive responders in the dialysis group. The IgG levels in the dialysis group (median, 2900; IQR: 1128–5651) were significantly lower than in the control group (median, 7401; IQR: 3687–15471; p<0.001).	N/A	(98)
Zitt et al.	Austria	Patients on hemodialysis	Observational study	mRNA-BNT162b2; first and second dose	Safety: At every dialysis session during the first post-vaccination week after the first and second vaccine dose. Efficacy: Four weeks after vaccination	N= 50	Mean [SD]: 67.6 [14.8]	Female: 16 Male: 34	42% of the patients developed a positive antibody response with an anti-SARS-CoV-2 spike IgG median (IQR) of 20.0 (11.7, 51.0) BAU/mL. 97.9% were seropositive with a concentration of 1075 (290.8, 1735) BAU/mL.	Local reaction: Pain at the injection site was the most commonly reported local reaction (mild degree in 38% after first dose; 29.2%, 2.1%, and 2.1% had mild, moderate, and severe after the second dose). Systemic reaction: Diarrhea (4% mild, 4% moderate) and fatigue (8% mild) were the most frequent after the first injection.	(99)

Other diseases											
Rubbert-Roth et al.	Switzerland	Rheumatoid arthritis	Non-andomized, prospective, observational trial	mRNA-1273 (n= 9), BNT162b2 (n= 64); first and second dose	Baseline, 3 weeks after the first vaccination, and 2 weeks after the second vaccination.	Case: 53 Control: 20	Case (Mean [SD]: 64.6 [11.5]) Controls (Mean [SD]: 44.8 [13.9])	Female: 43 Male: 30	Vaccine-induced antibody titers to SARS-CoV-2 S1 protein were significantly lower in patients with rheumatoid arthritis 3 weeks after the first vaccination (median 0.4 U/mL, IQR 0.4–2.13) and 2 weeks after the second vaccination (657 U/mL, IQR 188–2500) than in the control group (3 weeks after first vaccination: 99.2 U/mL, IQR 24.8–172; 2 weeks after second vaccination: 2500 U/mL, IQR 2500–2500)	N/A	(100)
Hagin et al.	Israel	Inborn errors of immunity	Cohort	BNT162b2; two dose	2 weeks after recovery from COVID-19 (i.e. 10 days following a positive SARS-CoV-2 RT-PCR test and no symptoms for at least 3 days) in convalescent donors; 2 weeks after the second vaccine dose for others	N= 26	Mean [SD]: 48.5 [14.3]	Female: 15 Male: 11	18 developed specific antibody response 19 showed S-peptide–specific T-cell response.	9 patients reported injection site pain following the first dose 3 patients reported fever following second dose One patient with CVID reported unilateral axillary lymphadenopathy that lasted 5 days. None of the patients reported long-lasting adverse effects.	(103)
Braun-Moscovici et al.	Israel	Inflammatory rheumatic diseases	Cohort	BNT162b2; first and second dose	4–6 weeks after receiving the second dose of vaccine	N= 264	Mean [SD]: 57.6 [13.2]	Female: 201 Male: 63	227 patients (86%) mounted IgG Ab against SARS-CoV-2 (mean (SD) 5830.8 (8937) AU/mL) and 37 patients (14%) did not. 52% of anti-CD20-treated patients did not develop a significant humoral response. The IgG Ab titers were significantly higher in the vaccinated patients compared with the recovered COVID-19 patients with inflammatory rheumatic diseases (mean (SD) 6764.27 (9291.61) AU/mL, median 3058 AU/mL vs. mean (SD) 2044.8 (4944.8), median 480 AU/mL, $p<0.05$).	There were minor side effects, including local pain, redness or swelling at injection site (58%), fatigue (30%), muscle sore (12%), headache (20%), low grade fever (3%).	(101)
Collier et al.	USA	Pregnant and lactating women	Prospective cohort study	BNT162b2 and mRNA-1273; second dose	Non-pregnant women: 21 days (IQR, 17-27 days) after the second vaccine dose Pregnant women: 21 days (IQR, 14-36 days) Lactating women: 26 days (IQR, 19-31 days)	Vaccinated (n= 103); Unvaccinated (n= 28)	Range: 18-45	Female: 131 Male: 0	Binding, neutralizing, and functional non-neutralizing antibody responses as well as CD4 and CD8 T-cell responses were present in pregnant, lactating, and nonpregnant women following vaccination. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. Binding and neutralizing antibody titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, but T-cell responses were preserved against viral variants.	Fever was reported in 27 nonpregnant (52%), 4 pregnant (14%), and 7 lactating (44%) women	(105)
Haberman et al.	USA	Patients with immune-mediated inflammatory diseases (IMIDs) on methotrexate treatment	Cohort	BNT162b2; second dose	IMIDs on methotrexate (Median [IQR]: 34.6 [21-73]); IMIDs with no methotrexate (Median [IQR]: 32.5 [25-45]; healthy controls (Median [IQR]: 29 [23-44]) days post prime dose	Patients with immune-mediated inflammatory diseases (n= 51); controls (n=26)	IMIDs on methotrexate (Median [IQR]: 63.2 [22-77]); IMIDs with no methotrexate (Median [IQR]: 49.1 [29-79]; healthy controls (Median [IQR]: 49.2 [28-74])	Female: 52 Male: 25	Of the healthy participants, 25 (96.1%) of 26 demonstrated adequate humoral immune response. Patients with IMID not on methotrexate achieved a similar rate of high antibody titers (24/26, 92.3%), whereas those on methotrexate had a lower rate of humoral response (18/25, 72.0%).	N/A	(104)

Waissengrin et al.	Israel	Patients with cancer treated with immune-checkpoint inhibitors	Cohort	BNT162b2; second dose	17–21 days after the first dose and at a median of 19 days (IQR: 12–31) after the second dose.	N= 134	Median [range]: 72 [29-93]	Female: 61 Male: 73	N/A	Fatigue (34%), headache (16%), muscle pain (34%), fever (10%), chills (10%), flu like symptoms (2.2%), gastrointestinal disturbance (10%). None of the reported side-effects required admission to hospital or any other special intervention.	(78)
Geisen et al.	Germany	Patients with chronic inflammatory diseases (CID) (e.g. psoriatic arthritis, rheumatoid arthritis, mixed connective tissue diseases, spondyloarthropathy, sarcoidosis, giant cell vasculitis, Crohn's disease; systemic lupus erythematous, and myositis)	Cohort	BNT162b2 and mRNA-1273; first and second dose	On day 0, the day of secondary immunisation and day 7 after secondary immunisation. Side effects were monitored 14 days after secondary vaccination.	Patients with chronic inflammatory diseases (n= 26); healthy controls (n= 42)	Patients with chronic inflammatory disease (Mean [SD]: 50.5 [15.8]); healthy controls (Mean [SD]: 37.5 [13.4])	Female: 46 Male: 22	Anti-SARS-CoV-2 antibodies as well as neutralizing activity could be detected in all study participants. IgG titers were significantly lower in patients as compared with controls (2053 BAU/mL ±1218 vs 2685±1102).	Mild systemic side effects such as fatigue and myalgia were more frequent in the CID patient cohort relative to healthy controls (53.8% vs 43.2% and 42.3% vs 31.6%). There were no fever in cases vs. 13.5% in controls.	(102)

Note: Studies assessing the immunogenicity of vaccines in patients with underlying disease are reviewed separately in this table.

Abbreviations: CID, chronic inflammatory diseases; CLL, chronic lymphocytic leukaemia; CVID, common variable immunodeficiency; IFNγ, Interferon gamma; IMIDs, immune-mediated inflammatory diseases; nAbs, neutralising antibodies; RT-PCR, real time polymerase chain reaction.

being studied to see how well they protect against Omicron and other variants. To this end, studies are being conducted to investigate the humoural and cellular immunity induced by COVID-19 vaccines against the Omicron variant. The current studies discovered evidence that existing vaccinations could induce cellular immunity against Omicron. In a study by Tarke A et al., T cell responses against COVID-19 variants in vaccinated people were assessed. To this end, samples from 96 people who had gotten one of four vaccines (Pfizer-BioNTech, Moderna, Johnson & Johnson/Janssen, or Novavax) were examined. Six months after immunisation, they found significantly fewer memory B cells and neutralising antibodies in people's blood. Unlike antibodies, T cell responses from the vaccinations detected all variations, including Delta and Omicron. When compared to early variants, 84% of CD4+ (helper) T cell responses and 85% of CD8 + (killer) T cell responses to Omicron remained the same 6 months after immunisation.[110]

Another study by Liu J et al., examined samples from 47 people vaccinated with Johnson & Johnson or Pfizer-BioNTech vaccines. These people showed robust T cell responses against Delta and Omicron variants following final vaccination.[111] Accordingly, Omicron was found to evade antibody neutralisation by the Pfizer–BioNTech vaccine in the live-virus neutralisation experiments.[112] In addition, the effectiveness of the BNT162b2 vaccine has also been reported in preventing the hospitalisation of patients with the Omicron variant in South Africa.[113] Another study by Muik A et al, showed that three doses of the BNT162b2 could increase Omicron-neutralising titres, suggesting probable protection against Omicron-mediated COVID-19.[114] These data could provide evidence that current vaccines have the potency to induce potent cellular immunity but low antibody responses to the SARS-CoV-2 Omicron variant.

5 | DISCUSSION

The newly emerged coronavirus, SARS-CoV-2, and the associated disease, COVID-19, have become a worldwide pandemic with a considerable rate of mortality and morbidity.[1] According to the World Health Organization (WHO), global dissemination of SARS-CoV-2 may continue until there is a high level of population immunity around the world. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus that belongs to the family of coronaviruses.[2] For a superior understanding of the SARS-CoV-2, great research has been performed, and different strategies have been established with the aim of developing safe drugs and efficient vaccines.[115] According to our extensive search, a variety of COVID-19 vaccines are being evaluated in different stages of clinical trials globally and will be authorised or approved only if they make it substantially less likely that we will get COVID-19. According to the WHO reports, some of these vaccines have been approved for use in some countries (Table 4).

TABLE 3 Adverse event of special interest post vaccination in the USA

	Venous and arterial thrombotic events	Bell's palsy	Myocarditis/pericarditis	Anaphylaxis	Guillian-Barre syndrome	Transverse myelitis
Vaccine manufacture						
Pfizer/BioNtech						
n	2997	2457	1984	1076	307	84
Per million dose	11.43	9.37	7.57	4.1	1.17	0.32
Moderna						
n	2338	1856	1056	684	224	67
Per million dose	13.57	10.77	6.13	3.97	1.3	0.39
Johnson & Johnson's Janssen						
n	1695	417	134	112	203	26
Per million dose	103.1	25.35	8.15	6.81	12.35	1.58
Sex						
Male						
n	2845	1949	2186	1504	365	74
%	41.55	41.83	69.91	83.6	51.19	41.57
Female						
n	4002	2710	941	295	348	104
%	58.45	58.17	30.1	16.4	48.81	58.43
Age						
<18						
n	54	36	493	19	11	1
%	0.85	1.93	23.68	6.79	3.25	0.61
18–29						
n	336	125	742	41	20	14
%	5.28	6.72	35.64	14.64	5.92	8.54
30–39						
n	847	259	322	62	24	31
%	13.31	13.92	15.47	22.14	7.10	18.90
40–49						
n	1146	352	172	43	55	27
%	18.01	18.91	8.26	15.36	16.27	16.46
50–59						
n	1236	394	139	42	79	28
%	19.42	21.17	6.68	15	23.37	17.07
60–64						
n	668	199	55	25	42	18
%	10.5	10.69	2.64	8.93	12.43	10.98
65–79						

(Continues)

TABLE 3 (Continued)

	Venous and arterial thrombotic events	Bell's palsy	Myocarditis/pericarditis	Anaphylaxis	Guillian-Barre syndrome	Transverse myelitis
n	1574	401	140	40	87	37
%	24.74	21.55	6.72	14.29	25.74	22.56
>80						
n	502	95	19	8	20	8
%	7.9	5.10	0.91	2.86	5.92	4.88

TABLE 4 Eight approved SARS-CoV-2 vaccines by December 2021

Vaccine name	Type	Developer	Number of countries approved the vaccine	Number of trials
BNT162b2	RNA vaccine	Pfizer/BioNTech	112	46 trials in 21 countries
mRNA1273	RNA vaccine	Moderna	78	33 trials in 8 countries
Ad26.COV2.S	Vector-based	Johnson & Johnson	85	16 trials in 18 countries
AZD1222	Vector-based	Oxford AstraZeneca	127	50 trials in 23 countries
Covishield	Vector-based	Oxford AstraZeneca formulation	47	2 trials in 1 country
Covaxin	Inactivated vaccine	Bharat Biotech	12	7 trials in 1 country
BBIBP-CorV	Inactivated vaccine	Sinopharm-Beijing	72	19 trials in 10 countries
CoronaVac	Inactivated vaccine	Sinovac	46	26 trials in 8 countries

SARS-CoV-2 consists of sixteen non-structural proteins, namely nsp1 to nsp16, and four structural proteins that form the main structure of the virus.[116] Among these structural and non-structural proteins, the S protein is located on the surface of SARS-CoV-2 and binds to human angiotensin-converting enzyme 2 (hACE2), which plays a critical role in the virulence of the virus[117,118] and elicits effective cellular and humoural immune responses.[119,120] S protein (especially RBD) is considered as an important target for SARS-CoV-2 vaccines.[121] On the other hand, the titres of neutralising antibodies and the levels of anti-RBD IgG, and RBD-specific IgG titres were significantly correlated with each other.[122,123] Therefore, RBD is considered a promising target for SARS-CoV-2 vaccines.

To provide an effective immune response to immunisation, it is necessary to stimulate both the innate and adaptive immune systems (Figure 3).[124] Humoural and cellular immune responses induced by SARS-CoV-2 vaccines have been reported mostly by the titters of RBD-specific IgG, neutralising antibodies, and the levels of T cell cytokines, especially IFNγ after vaccination (Table 1).

Whole inactivated vaccines have been used effectively for immunisation against several viral diseases such as influenza, poliovirus, hepatitis A, SARS, and rabies.[125–127] Several advantages have made them popular, including rapid and easy production processes, high stability, strong immune responses, usability in immunodeficient subjects, and no risk for virus activation.[125] Humoural immunity and production of nAbs against virus antigens, especially S proteins of SARS-CoV-2, are the main immune responses against inactivated vaccines. Antibody titres against these types of vaccines diminish with time after the first vaccination. Therefore, a protective and efficient humoural immune response develops after the second or third dose of vaccine mixed with adjuvants, resulting in "boost" antibody titres.[29,128] In accordance with this, it has been shown that a longer interval (about 28 days) between the first and second injections of vaccine could induce higher antibody responses in humans and animal models.[32,129,130] Although a low dose of vaccine after two or three boosters can elicit an efficient immune response, participants who received high dose of inactivated vaccine had higher levels of nAbs and specific IgG antibodies in their sera.[19] In addition to considering the interval time, using appropriate adjuvants would also be an inevitable factor in eliciting robust immune responses. NDV/SARS-CoV-2, an inactivated SARS-CoV-2 vaccine induced the highest titre of S-specific Ab in BALB/c mice when administered with R-DOTAP as an adjuvant compared with using Addavax.[131] Of note, the frequent adjuvant which used in human trials is aluminium hydroxide ($Al(OH)_3$).[19,29]

In contrast to the inactivated vaccines, which needed several booster doses and an adjuvanted formulation, the protective immunity against live-attenuated vaccines could be developed after a single, small dose of vaccine. The main concern about these vaccines is the possibility of a reversion of virus pathogenicity. In addition, these types of vaccines cannot be used in immunocompromised persons.[132] Live-attenuated SARS-CoV-2 vaccines are currently being tested in pre-clinical studies.[133] Some trials have been registered to evaluate the efficacy of live-attenuated SARS-CoV-2 vaccines in

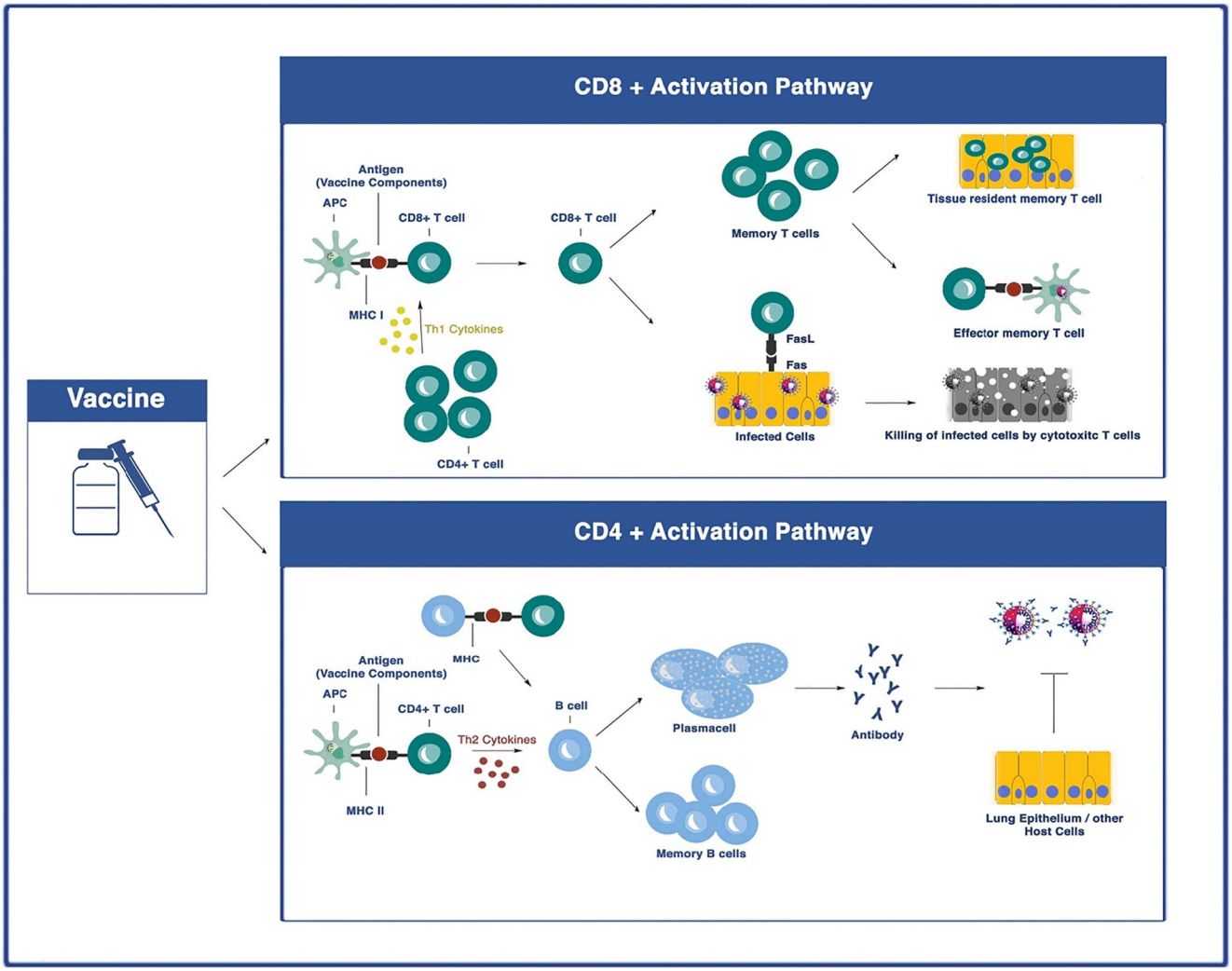

FIGURE 3 Vaccine-induced immune responses. Antigen-presenting cells (APCs) including dendritic cells (DC) can process and present vaccine antigens to both CD4+ and CD8+ T cells. CD4+ T cells that activated by SARS-CoV-2 vaccine antigens presented by APCs can production Th2 cytokines which help B cells to differentiate into plasma cells and memory B cells. The activated B cells can produce neutralising antibodies (nAbs). CD8+ T cells can be activated by Th1 cytokines and acquire the ability to attack and lysis the SARS-CoV-2 infected cells

healthy subjects (NCT04475081 and NCT04619628), but there are no published results yet.

Although subunit vaccines are safer than whole virus vaccines, these proteins are less immunogenic in the absence of other viral components. Therefore, subunit vaccines often require higher doses, booster schedule, and concomitant administration of adjuvants to enhance antigen-specific immunity.[134] Phases I and II results of NVX-CoV2373 developed by Novavax showed that two injection (D0,D21) of vaccine with adjuvant (Matrix-M) could elevate humoural and cellular immune responses including high anti-spike IgG and nAbs, and Th1 responses in adults, with an overall efficacy of 89.7%.[65] These studies showed that the efficacy and immunogenicity of the subunit vaccine greatly depend on how the subunit protein is presented to immune cells, co-administration with adjuvants, adjuvant type, etc.

Nucleic acid-based immunisation has emerged as a promising alternative to conventional vaccine approaches to protection against SARS-CoV-2. Virus particles are not used in the process of nucleic acid-based vaccine production, so they are non-infectious vaccines. Besides, the RNA strand could not integrate into the host genome, which is made of DNA, and it degrades when the protein is made. Importantly, production process of these vaccines is cost-efficient and could be produced rapidly[8] and both cellular and humoural immune responses could be elicited by them. These advantages make them popular among conventional approaches, although it should be noted that these vaccines would need to be maintained frozen, which could affect vaccine distribution. Their immunogenicity and efficacy have been evaluated in several pre-clinical and clinical studies. BNT162b2 developed by Pfizer and mRNA-1273 developed by Moderna as human RNA vaccines could elicit a potent immune

response against SARS-CoV-2. Although efficient immunity was shown to be induced after a single dose of some RNA vaccines such as mRNA1273 and mRNA-LNP in pre-clinical studies[135,136] but booster schedule effectively induced both humoural and cellular immunity in human adults.[36–38]

Most clinical trials of SARS-CoV-2 RNA vaccines showed durable immunogenicity until about 28 days post-vaccination.[36,38,39] mRNA-1273 developed by Moderna/NIAD showed increased levels of antibody titres even on day 57 post-vaccination.[37] BNT162b1 developed by Pfizer/BioNTech showed decreased levels of nAbs and RBD-binding antibodies on day 43 (21 days after the boost) in most vaccinated groups (with the exception of the 1 μg dose group),[38] while it seems that RNA vaccines could be considered as potential immunisation approaches against SARS-CoV-2. In addition, these vaccine platforms showed a high efficacy against the most recent emerged infectious variants.[42]

Viral vector-based vaccines can increase immunogenicity without an adjuvant and elicit a strong cytotoxic T lymphocyte (CTL) response to eliminate virus-infected cells. Several types of vectors have been used in order to deliver genetic code for antigens (e.g. the gene for spike protein) into human cells. Among them, adenoviruses are widely used as viral-vectors due to their high transduction efficacy and high level of transgene expression.[9] Besides, a single dose of SARS-CoV-2 vaccine elicited both humoural and cellular immune responses in healthy adults.[47,50,54,55] As several studies show, the efficacy of vaccines could be affected by several factors. Selecting an appropriate antigen is an important factor for inducing a potent immune response.

As patients with pre-existing diseases, particularly immunocompromised ones, were not enroled in the main trials, the efficacy and safety of COVID-19 vaccines have yet to be clarified. These patients are at a high risk of mortality due to the effects of SARS-CoV-2 and the ineffectiveness of the vaccines, both due to immunosuppression status related to the therapeutic agents they receive and the underlying condition. Future trials should be guided towards adjusting the dose and time interval of administering vaccines for these patients to efficiently respond to immunisation.

Although approximately no serious AEs were reported in clinical trials of COVID-19 vaccines, some rare events following public mass administrations have been reported in recent publications. Using the VAERS database, we demonstrated that venous and arterial thrombotic events, bell's palsy, and myocarditis/pericarditis were commonly reported AESI post immunisation. Therefore, it seems that follow-up surveillance after a recipient of the COVID-19 vaccine must be strengthened in order to prevent the occurrence or manage the condition at the earliest possible time. Furthermore, assigning several programs across the world to gather the characteristics, clinical presentation, progress, and outcomes of individuals affected by the AESI post administration of COVID-19 vaccination would be necessary to provide clinicians with the most optimal way of treating patients and inform the expert advisory body regarding COVID-19 vaccination.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Nima Rezaei directed the project. Mona Sadeghalvad, Amir Hossein Mansourabadi and Nima Rezaei designed research. Data extraction performed by Mona Sadeghalvad, Amir Hossein Mansourabadi, Masoomeh Masoomikarimi, Masoumeh Alimohammadi, Maryam Noori, and Seyed Aria Nejadghaderi, The paper was draughted by Mona Sadeghalvad, Amir Hossein Mansourabadi, Masoomeh Masoomikarimi, Masoumeh Alimohammadi, Maryam Noori, and Seyed Aria Nejadghaderi. Nima Rezaei did critical revision of the paper. All the authors contributed to protocol development, read and finally approved the paper.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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