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# Safety and Efficacy of COVID-19 Vaccines in Special Populations

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**Abstract**
Coronavirus disease 2019 (COVID-19), is a pandemic that resulted in extreme human and economic losses. A higher incidence of morbidity and mortality to COVID-19 was demonstrated in a special population. Factors that impact the disease severity include old age, obesity, pregnancy, diabetes mellitus, cancer, and immunosuppressive drugs. Fortunately, several COVID-19 vaccines were developed such as Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, and Johnson & Johnson among others. These vaccines have shown good efficacy and safety profiles in the general population, but serious rare adverse effects were reported related to specific vaccines. Several studies are undergoing to test the efficacy in special populations. Reduced efficacy or delayed immunological response to COVID-19 vaccines were suggested for patients with autoimmune disorders or organ transplant patients, especially those receiving certain medications such as rituximab. There is a concern about organ rejection in organ transplant patients. Despite these facts, there is an agreement among health care providers to consider prioritization of the above-mentioned groups for receiving vaccinations with the same precautions followed for the general population. It is recommended to ongoing studies determine the efficacy and safety of COVID-19 vaccines in patients with comorbidities based on clinical data.
**Keywords:** COVID-19, SARS-CoV-2, Johnson & Johnson's, Pfizer, Moderna, vaccine

## COVID 19 Vaccines

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by a highly infectious respiratory tract virus (SARS-CoV-2). It has resulted in significant human and economic loss. More than 207 million cases had been confirmed as of August 16, 2021, with more than 4.36 million verified deaths.[1] By the end of 2020, several vaccines had become available for use in different parts of the world.[2] Most vaccines for COVID-19 aimed to achieve an adequate immune response to the virus's distinctive spike protein.[3] These vaccines are being developed using various techniques, which include the inactivated or attenuated virus, viral protein subunits. Viral vectors, and RNA encoding viral spike protein.[4,5]

This noncomprehensive review provides a simplified overview of the efficacy and safety of the most extensively used COVID-19 vaccines in special populations. The review faces limited restricted search on data provided in the English language. Vaccine subtypes, their development, ranking efficacy and safety in the general population werepresented in several reviews.[6-8] The safety and efficacy of COVID-19 vaccines in children and adolescents were also reviewed.[9] The RCTs on BNY162b2 showed that the efficacy of the vaccine in children and adolescents was 100%.[10] Regarding safety, 38 cases of myopericarditis due to BNY162b2 were described in 2 reports, of which 93% occurred after the second dose, 90% occurred in males, [11, 12]. The estimated incidence of myopericarditis was 0.008% in adolescents 16–17 years of age and 0.01% in those aged 12–15 years.[12] A brief description of the most used Covid 19 vaccines is provided in the next section.

### *Pfizer–BioNTech COVID-19 vaccine (BNT162b2)*

It is an mRNA-based COVID-19 vaccine developed by BioNTech, (Germany) in collaboration with Pfizer (USA).[13] It is a lipid nanoparticle encapsulating nucleoside-modified mRNA-expressing spike protein of SARS-CoV-2.[14] The Phase III results indicated an overall efficacy of 95% in the general population after two doses separated by 21 weeks.[15]

For immunocompromised individuals e.g. organ transplant patients, a lower vaccine efficacy after a single dose was reported.[16] It was reported to be safe and effective in delivering protection to pregnant and nursing women.[17] Its overall effectiveness (7–56 d) after the second dose in pregnant women was reported as 96%.[18]

The efficacy was about 100% in adolescents, but the incidence of myocarditis and pericarditis was likely to be higher in young adults.[9] It was reported that patients with β-cell Non-Hodgkin lymphoma treated with an anti-CD20 antibody are unlikely to achieve humoral response to BNT162b2 mRNA COVID-19 vaccine.[7]

### *Moderna (mRNA-1273)*

It was developed by the Moderna pharmaceutical company and approved for use in individualsabove the age of twelve. It is intended to be given in two doses or three for immunocompromised patients. Each dose is 0.5 mL administered by intramuscular injections spaced at least 28 days apart.[19] It consists of a lipid nanoparticle (LNP) containing nucleoside-modified messenger RNA (modRNA), which encodes the SARS-CoV-2 virus's perfusion stabilized spike (S) protein, as well as an

S1-S2 cleavage site with a transmembrane component. The presence of the S-2P antigen on its surface permits it to enter the host cell. The RNA is then transferred into host cells, where the SARS-CoV-2 S antigens are expressed. It provides antibody response to SARS-CoV-2 S antigens.[20,21] In the general population, it showed an overall efficacy of 95% against symptomatic COVID-19.[15,22] The efficacy of two doses against infection with the delta variant was 87.9% in those aged 18–64 years, but lower (75.2%) in the elderly > 65 year.[23]

Reported common adverse events include the following (%,): injection site tenderness/pain (92), swelling (14.7), redness (10.0), fever (15.5), fatigue (70.0), headache (64.7), muscle pain (61.5), chills (45.4), joint pain (46.4), swollen lymph nodes (1.1), nausea/vomiting (23.0), hypersensitivity (1.5). Serious side effects were reported as 1%, and a few cases of Bell's palsy (0.1%) were also documented.[22]

At 28 days after the second dose of vaccination poor or suboptimal antibodies response was observed in cancer patients under chemotherapy. However, antibodies raise significantly after the 2nd dose (compared to that after the 1st dose). These findings suggest the value of the 3rd boosting dose of the vaccine in cancer patients.[24]

The efficacy of the vaccine after the first dose was lower among patients with decompensated (50.3%) compared with compensated cirrhosis (66.8%). After the second dose, there was a 78.6% reduction in COVID-19 infections and 100% reduction in COVID-19-related hospitalization.[25] Most dialysis patients showed adequate antibody response after two doses of BNT162b2 or mRNA-1273 vaccines.[26]

In vaccinated pregnant women, the rate of adverse events (in both the mother and the fetus) was comparable to that in non-immunized pregnant women.[27]

### *Oxford–AstraZeneca COVID-19 vaccine (AZD122) ChAdOx1-S*

It is a viral vector (modified chimpanzee adenovirus ChAdOx1) vaccine for the prevention of COVID-19. It was developed by Oxford University in collaboration with AstraZeneca.[28,29] Early investigations conducted in 2020 showed that the vaccine efficacy was 76.0% in preventing symptomatic COVID-19, starting from 22 days after the first dose and up to 81.3% after the second dose.[30] A study in Scotland revealed thatafter the second dose the vaccine was 81% effective against the alpha variant, and 61% against the delta variant.[31] An interim analysis of randomized controlled trials in Brazil, South Africa, and the UK have documented an overall efficacy of 70·4%.[32] A meta-analysis suggested equivalent effectiveness of BNT162b2 and ChAdOx1 COVID-19 vaccine against SARS-CoV-2 infection and COVID-19 related morbidity and mortality.[33]

Moreover, common adverse effects in vaccinated individualswere as follow: local reaction at the injection site, soreness, headache, and lethargy.[34] Systemic reactions were observed in (86%) of 18–55 y group, but lower (77%) in 56–69 y, and (65%) in the 70 y or older age group. It was concluded that this vaccine is likely better tolerated in older adults.[35]

Concerning serious adverse events, there are reports of vaccine-induced immune thrombotic thrombocytopenia (VITT).[36] According to the "European Medicine Agency's Pharma covigilance Risk Assessment Committee," 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis were reported among the 34 million individuals who received the AstraZeneca COVID-19 vaccine. The majority of these casesoccurred within the first two weeks following vaccination in women under the age of 60.[34] An early study in the UK documented that the estimated rate of thrombotic thrombocytopenia syndrome (TTS) within 14 days of the first dose of the vaccine was 8·1 per million vaccines.[37]

Details of CVST, related venous infarct and hemorrhagic stroke, arterial infarct, intracerebral hemorrhage (ICH) and VITT following the AstraZeneca COVID-19 vaccination were discussed by a meta-analysis. In this context, 41 cases were presented (36 CVST, 4 infarctions, and 1 ICH). Sixteen of the 36 patients with CVST experienced an ICHand/or a subarachnoid hemorrhage (SAH), of which 18 cases (44%) died.[38] Rare cases of the multisystem inflammatory syndrome[39] and Guillain-Barré syndrome (GBS) were also reported.[40]

At 120 vaccination centers in Mumbai, India, as of April 13th 2021, the total adverse effects following immunization (AEFIs) was reported as (93.53 %), of which 3.87% were moderate, 3.87% were severe, and 2.58% were serious.[41] An Australian risk-benefit analysis for individuals < 60 years suggested that the risk of the AZD1222 vaccination may exceed the benefits in younger individuals who are at low risk of serious COVID-19.[42]

In individuals with HIV, the ChAdOx1 vaccination was demonstrated to elicit protection and a safety profile similar to those without HIV. This investigation, recommends vaccination for those patients on antiretroviral therapy (ART).[43]

A small study in Japan indicated a lower response in the elderly after two doses of AZD1222. Neutralizing antibody responses were predicated as 67.5%, 60.3%, and 50.0% ofvaccinated individuals aged between 18–55, 56-69, and => 70 Y, respectively. No vaccine-related serious adverse events or deaths were reported.[44] A 51-year-old woman had pancreas allograft rejection after receiving the ChAdOx1 vaccine.[45] Rare cases of the acute hyperglycemic crisis were reported in diabetic patients 3–5 weeks following the first dose of the vaccine.[46]

### *Janssen COVID-19 vaccine (Ad26.COV2.S)*

Ad26.COV2.S is a replication-ineffective human adenovirus type 26 (Ad26) vector that expresses a pre-fusion stabilized SARS-CoV-2 spike protein (Wuhan 2019 strain, which is similar to the WA1/2020 strain's).[47-51] In the phase III trial in the US, Brazil, and South Africa, by day 28 after vaccination, a single dose of Ad26.COV2.S provided 72%, 68%, and 64% protection against moderate to severe COVID-19 respectively. In this trial, Ad26.COV2.S provided robust protective efficacy against a few SARS-CoV-2 variants, with 95% of sequenced viruses from confirmed COVID-19 cases in South Africa being the B.1.351 variant.[52] In another study on day 71 following vaccination, Ad26.COV2.S generated median pseudovirus neutralizing antibody titers which were 5.0-fold and 3.3-fold lower against the B.1.351 and P.1 SARS-CoV-2 variants, respectively, compared to that against WA1/2020 strain. However, similar CD8 and CD4 T cell responses, including central and effector memory responses were recognized against all tested SARS-CoV-2 variants.[53]

Rare Guillain-Barré syndrome cases (GBS) were reported after Ad26.COV2.S vaccine. The estimated incidence per million of vaccinated individuals were 6.2 for females and 7.8 for males.[7]

### Covaxin (BBV152)

Covaxin (BBV152) was developed by Bharat Biotech and the Council of Medical Research (India). It is an inactivated whole virion SARS-CoV-2 vaccine, formulated with a toll-like receptor 7/8 agonist (TLR7/8) molecule adsorbed to alum (Algel-IMDG). The TLR7/8 adjuvant formulation specifically boosted SARS-CoV-2 lymphocyte as well as Th1 driven antibody responses.[54]

A randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trial was conducted in India on adults (age ≥18 years) who were healthy or had stable chronic medical conditions. The study demonstrated, the overall efficacy of 78%. Efficacy and safety were also confirmed in children. Currently, limited data are available to predicate its safety and efficacy in immunocompromised patients, patients with cancer or pregnant women.[55,56]

The common adverse effects after vaccination were as follow: injection site pain (5%), headache (3%), fatigue (3%), fever (9%), nausea or vomiting (2%).[57]

### Corona Vac, SinoVac

It is an inactivated virus COVID-19 vaccine developed by the Chinese company SinoVac Biotech. It was developed by culturing SARS-CoV-2 CN2 strain to replicate in Vero Cell, immediately harvesting, isolating, and inactivating the grown strain with B-propiolactone.[58,59]

Vaccine efficacy in the general population, detailed efficacy and safety of Corona Vac can be retrieved in these publications.[59,60,61] Phase 3 trials were carried out in Brazil,[62] Turkey,[63] and Indonesia. The reported vaccination efficacy values (VE) in the general population ranged from about 51% in a Brazilian trial, 65% in Indonesian trial, and 84% in a Turkish trial.[61]

The following provides an example of reported adverse effects: incidence per 100,000: anaphylaxis (121); seizures (36), Bell's palsy (28), thromboembolic events (16), and Guillain-Barre syndrome (4).[61] Rare adverse events such as serious cutaneous and allergic reactions, nephrotic syndrome, optic neuritis and subacute thyroiditis, bell's palsy, bronchial asthma was also reported.[64-73]

In Brazil, good efficacy of this vaccine was observed in the elderly. After two doses of the vaccine, better protection ratios were obtained, with an attributable protection ratio of 99.2%.[74] In the phase 2 study, a limited number of children (186) 3–17 years were enrolled, and sero conversion was observed in 97% in the low dose vaccine group (1.5 micrograms) and 100% in higher dose vaccine group (3 micrograms). No serious adverse effects were documented.[75] However, up to our current knowledge, guidelines did not recommend its use in children.[61]

Regarding immunocompromised patients, Corona Vac's immunogenicity and safety were evaluated in a cohort study of 910 adult patients with autoimmune rheumatic disorders (ARD) and 182 age- and sex-frequency matched healthy adults in a phase 4 prospective controlled experiments. At day 69, patients with ARD had significantly lower anti-SARS-CoV-2 IgG seroconversion (70.4 vs. 95.5%) and low rneutralizing antibodies (Nab) (56.3 vs. 79.3%). These data suggesting lower efficacy of the vaccines in those population.[76] Another study showed similar findings and suggested that Patients with immune-mediated illness and being 60 years or older are independently linked with lower antibody response.[77]

CoronaVac vaccine immunogenicity and safety were evaluated in 47 cancer patients receiving active systemic therapy. Four weeks following the second dosage of the vaccine, more than half of the patient (63.8%) exhibited immunogenicity. The rate of seropositivity was 59.5% in those who received at least one cytotoxic medication, and 100% in those who received monoclonal antibodies and immunotherapy; however, immunogenicity was related to the patients' age.[75]

### Sinopharm COVID-19 Vaccine (BBIBP-CorV)

BBIBP-CorV, or BIBP vaccine, is an inactivated virus COVID-19 vaccine developed by Sinopharm's (Beijing Institute of Biological Products).[78] A sample of the WT virus (HB02 strain) was cultivated in Vero cells, isolated, and chemically inactivated by β-propiolactone, then mixed with an aluminum-based adjuvant. It completed Phase III trials in several countries with over 60,000 participants.[79] An interim analysis of the phase 3 study (38,206 participants were randomized to receive the one of the following vaccines SARS-CoV-2 WIV04 (5 μg/dose; $n$ = 13,459) (vaccine subtype 1); HB02 (4 μg/dose; $n$ = 13,465) (Vaccine subtype 2) or aluminum hydroxide (alum)–only (control) ($n$ = 13,458). All participants received 2 intramuscular injections 21 days apart. The vaccine efficacy compared was 72.8% for the 1st vaccine and 78.1% for the 2nd subtype. Serious adverse events were rare and similar in the 3 groups (WIV04: [0.5%]; HB02: [0.4%]; alum-only: [0.6%]).[80] Local reactions at the injection site, fatigue, and headache were the most prevalent post 1st dose adverse effects. Pain at the immunization site, fatigue, lethargy, headache, and tenderness were the most common post 2nd dose side effects in both groups. Two serious adverse events were possibly linked to the vaccine, serious nausea and a rare neurological disorder known as acute disseminated encephalomyelitis.[28] One participant with a diagnosis of thrombus was identified in the Phase 3 trial, in the BBIBP-CorV group. All acute allergic reactions were Grade 1 and 2 in the BBIBP-CorV group.[81]

Regarding Children and adolescents, participants aged 3–17 years, the inactivated COVID-19 vaccination BBIBP-CorV was shown to be safe and well-tolerated. After two doses, BBIBP-CorV elicited strong humoral responses against SARS-CoV-2 infection.[78,82]

The elderly group showed a similar safety profile compared to younger adults, but with lower reactogenicity in older adults. In clinical trials, no serious adverse effects occurred in adults ≥60 years in the vaccine group.[81]

### Sputnik V (Gam-COVID-Vac)

The Gamaleya Research Institute of Epidemiology and Microbiology in Russia produced Sputnik V (Gam-COVID-Vac), which is an adenovirus viral vector vaccine for COVID-19. The Russian Ministry of Health has registered it on August 11th 2020.[83] The vaccine uses similar technology to the Oxford AstraZeneca vaccine; however, it follows a prime and then boosts regime. The two shots use different vectors, the first is rAd26 and the second is rAd5 while both carry the gene for the full SARS-CoV-2 spike protein.[84]

The findings of Phase III trials have shown that the two-dose regime of the vaccine was generally well tolerated with no associated serious adverse events and similar efficacy in those aged over and under 60. It was tested at 25 hospitals and polyclinics in Moscow. The clinical trial indicated an overall

efficacy of 91.6%.[84] A study among health workers in Argentina observed that 94% of naïve individuals generate spike-specific IgG antibodies 21 days after receiving the first dose of the vaccine.[85] However, the early approval provoked criticism among scientists.[86,87]

The most reported adverse events in phase III clinical trial were grade 1 [94%] (0.3% of participants in the vaccine group and (0.4%) of participants in the placebo group. Four fatalities were recorded (less than 0.1%) in the vaccination group and one (less than 0.1%) in the placebo group; however, none of which were thought to be attributable to the vaccine.[84] Moreover, in Iranian research, 3,236 vaccinated health workers self-reported the following side effects: discomfort at the injection site (50.9%), body pain (43.9%), headache (35.7%), fever (32.9%), joint pain (30.3%), chills (29.8%), and tiredness (20.3%).[88]

In a small study with 18 participating health workers, the researchers discovered that (83%) of Sputnik V recipients' infants (1–6 yr) suffered from fever and chills for 1–2 days after their parents' immunization, which can be linked to an Adenovirus infection.[89]

In Argentina, retrospective cohort research was carried out where the first dose of Gam-COVID-Vac was given to 40,387 elderly (60–79 yr). Vaccine efficacy for avoiding laboratory-confirmed illnesses was 78.6%, and for preventing hospitalizations and fatalities was 87.6% and 84.8%, respectively.[90]

The Gam-COVID-Vac vaccine was well tolerated, with no grade 3–5 side effects recorded in 112 patients with metastatic genitourinary cancer. Two COVID-19 cases (1.8%) were verified in the vaccination group after a median follow-up of 6.2 months.[91]

A non-comprehensive summary of characteristics, safety and potentially serious adverse effects of some authorized vaccines are presented in Tables 1–2.

In the following paragraphs, we will attempt to summarize the currently available (October 2021) guidelines, recommendations relevant to the efficacy and safety of vaccines against COVID-19 in special populations.

## Efficacy and Safety in Special Population

### *Autoimmune diseases and allergy*

Rituximab has been linked to a reduced serological response to the SARS-CoV-2 vaccine in rheumatoid arthritis patients.[95] Immune responses against the SARS-CoV-2 (BioNTech/Pfizer) one-shot was studied in patients with immune-mediated inflammatory diseases including spondyl arthritis, inflammatory bowel disease, psoriasis, and rheumatoid

Table 1. **Characteristics of examples of leading Covid-19 vaccines**[92,93]

| Company | BioNTech. GmbH | ModernaTX, Inc. | Janssen Inc | AstraZeneca Canada Inc. |
|---|---|---|---|---|
| Code name | (BNT162b2) | mRNA-1273 | Ad26.COV2.S [recombinant] | ChAdOx1-S [recombinant] |
| Type | mRNA-based | mRNA-based | Viral victor | Viral victor |
| Authorized age | ≥5 years | ≥12 years | ≥18 years | ≥18 years |
| Dosing Schedule | 2 doses, at least 21 days apart | 2 doses, 4 weeks apart | | |
| Storage | –90° to –60°C protected from light | –25 to –15°C | +2 to +8°C | +2 to +8°C |
| Vaccine efficacy (VE) | 95 %, 7 days after the 2nd dose | 94.1%, 2 weeks after the second dose | 85.4%, 28 days after vaccination against severe/critical COVID-19 | 62.1%, 2 weeks after the second dose |
| Elderly >65 yr | Similar to adults | Slightly lower, 86.4% | Consistent efficacy | |
| Pregnancy | Preferred in view of current data | | | |
| Adverse events of special interest (AESI) | Myocarditis/pericarditis, Bell's palsy and anaphylaxis | | Guillain-Barré syndrome (GBS), thrombosis with thrombocytopenia syndrome (TTS) including VITT, capillary leak syndrome (CLS), venous thromboembolism (VTE), immune thrombocytopenia (ITP) and anaphylaxis | |

Table 2. **Serious adverse events (SAE) of some authorized vaccines**[94]

| SAE | Incidence | Notes |
|---|---|---|
| Anaphylaxis after | 2–5/million | All vaccines |
| Thrombosis (TTS)* | 36 per 12 million doses | J & J/Janssen COVID-19 vaccination Women < 50 year |
| | 1 case/306 million doses | mRNA COVID-19 vaccination |
| Myocarditis and pericarditis | 393 confirmed cases (FDA) | Most cases mRNA COVID-19 vaccination; male adolescents (18–30) |
| Report of deaths* | 5,479 reported deaths (0.0017%), 318 million doses | December 14, 2020, through June 21, 2021, VAERS**, all vaccines |

*a plausible causal relationship between the vaccine and death was confirmed only for a limited number of cases received J & J/Janssen COVID-19 Vaccine due to thrombosis with thrombocytopenia syndrome (TTS). **VAERS: vaccine adverse event reporting system.

arthritis. Those patients were maintained on pharmacotherapy that included methotrexate, glucocorticoids, TNF inhibitors, IL-inhibitors, and JAK inhibitors among others. Overall responses were delayed and reduced in patients compared with controls.[96]

Those individuals should be vaccinated against COVID-19, ideally while their disease activity is under control. Antibody responses to vaccines do not appear to be affected by low-level immunosuppression. Vaccinations should be administered before the start of any biological DMARDs. Patients using rituximab should be vaccinated at least 4 weeks before or 6 months after treatment. Because tofacitinib can lower antibody responses, especially when combined with methotrexate, it has been suggested that stopping it before vaccination and restarting it after 14 days can be a beneficial approach. Vaccinations can be scheduled in a variety of ways to ensure effectiveness.[97] Practical guidelines for optimal safety of vaccination of patients with immunological disorders were suggested by J. Peter.[98]

## Benign blood disorders

Individuals with a history of blood clots, or certain thrombophilic disease, may be at increased risk of a very rare immune-mediated thrombosis induced by some authorized vaccines.[99]

Vaccines can be given safely for most patients maintained on anticoagulant medication, after applying certain precautions.For example, a fine needle gauge (23–25) is recommended for vaccination followed by an intense pressure applied to the injection site without scratching for at least two minutes.[100] Patients with other hematological disorders such as sickle cell disease, thalassemia, and rare hereditary anemia, should be vaccinated against COVID-19, Patients on warfarin with a supra therapeutic international normalized ratio (INR) should wait until their INR is below 4.[101]

## Cancer patients

A study was conducted in one chronic lymphocytic leukemia (CLL) patient (stage O untreated) to demonstrate the safety and efficacy of the BNT162b2 mRNA vaccine. It documented the capability of two doses of the vaccine to generate humoral and cellular response against COVID-19 but to a lower extent than that in matched age healthy volunteers.[102] In patients with myelo proliferative neoplasms ($n$ = 21), a single dose of Pfizer-BNT162b2 mRNA vaccine resulted in a high frequency of neutralizing antibodies and poly functional T-cell responses. Also, the vaccine was safe and generally well-tolerated.[103]

In patients with CLL, an observation study evaluated humoral immune responses to the BNT162b2 mRNA COVID-19 vaccination and compared them to responses in age-matched healthy control volunteers. Patients received two vaccination doses, 21 days apart. The study enrolled 52 CLL patients and a similar number of sex- and age-matched healthy control participants. It demonstrated that CLL patients had a significantly lower response rate (52%) compared to the control. Patients who achieved clinical remission following treatment had the highest response rate (79.2%), followed by treatment-naive patients (55.2%) and patients who were receiving treatment at the time of vaccination (16.0%). Response rates were low in patients treated with Bruton's tyrosine kinase inhibitors or Veneto lax anti-CD20 antibody (16.0% and 13.6%, respectively). None of the patients who had been exposed to anti-CD20 antibodies (e.g. rituximab) 12 months before immunization had a positive antibody response.[104] A possible explanation of these results, is that the immune system may be compromised by the persistent B-cell depletion caused by rituximab, which is maybe the mechanism of action of anti-CD20 antibodies in antibody-mediated autoimmune diseases.[105]

A group of researchers examined 44 consecutive patients with CLL who received two doses of mRNA vaccine (BNT162b2 or mRNA-1273) and tested for anti-SARS-CoV-2 S1/S2 antibodies. The results have predicted that vaccination in patients with CLL may not provide the efficacy seen in healthy individuals. Patients receiving Bruton Tyrosine Kinase inhibitor at the time of vaccination or who have received anti-CD20 monoclonal antibody within 1 year showed very poor vaccine efficacy in a prospective study.[106] The immune response of the BNT162b2 mRNA vaccine in multiple myeloma patients was significantly lower, particularly in those on anti-CD38-based treatment.[107]

A comprehensive review indicated that no safety concerns specific to patients with cancer receiving mRNA vaccine was anticipated. Certain chemotherapy can inhibit immune responses to the vaccine. In conclusion, the benefits of vaccination in most cancer patients are likely to outweigh the risks.[108]

The updated guideline Infectious Diseases Working Organization (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) recommended the vaccination of patients with cancer against COVID-19 especially those active disease.[109] The Australian and New Zealand guidelines stated that patients with hematological malignancies and some benign hematological illnesses should have accelerated access to COVID-19 vaccinations.[110]

French oncology societies (GCO, TNCD, UNICANCER) recommends that patients with cancer who are undergoing treatment or who had therapy less than three years ago should be vaccinated, as well as their families.[111]

## Cardiovascular disease

The American Heart Association declared that authorized vaccines are safe for adults who have or have had cardiovascular disease and that their efficacy is similar to that observed in the general population. Patients with heart problems were included in the COVID-19 vaccine studies, and the vaccine had no major side effects in these patients. However, patients with severe heart disease and unstable angina may experience mild fever and flu-like symptoms due to the vaccine. However, these effects are not serious and respond well to symptomatic treatment. Patients with heart disease may become critically ill in the presence of a severe allergic reaction. On the other hand, there are no reported interactions between the vaccine and medications prescribed for cardiac diseases. In conclusion, the advantages of vaccination in patients with cardiovascular diseases significantly outweigh the potential risk.[112] Similar recommendations were provided by a published report of the American College of Cardiology.[113] Moreover, the American Heart Association confirms that patients with cardiovascular diseases have priority in receiving vaccines against the coronavirus.[114]

### Diabetic patients

Regarding immunogenicity, efficacy, and effectiveness of immunization in diabetic patients, the clinical data are limited. Previous vaccinations showed variable results.[115]

A small study suggested that SARS-CoV-2 antibody response may be impaired in diabetic patients.[116] However, other studies reported that humoral immune response against SARS-CoV-2 in diabetic patients was like non-diabetic patients.[117,118]

More than 3,000 individuals with diabetes were part of the clinical trial for the Pfizer vaccine, and the Moderna vaccine included 2,875 individuals with diabetes in its clinical trial. Both trials observed the vaccine to be safe and effective.[119,120] In summary, no specific safety concerns were reported regarding these authorized vaccines in diabetic patients in the USA.[121] As with any vaccine, the coronavirus vaccine may cause elevated blood glucose levels.[122]

### Hepatic disease

Innate and humoral immune deficits are well-recognized characteristics in patients with severe liver disease, this phenomenon is called cirrhosis-associated immune dysfunction. For example, in individuals with cirrhosis, rates of sero conversion soon after hepatitis B virus vaccination, as well as the durability of humoral immunity after pneumococcal and influenza vaccination, are all significantly reduced. Patients with cirrhosis have reduced immune responses to SARS-CoV-2 vaccination as well. Regarding the safety of the vaccines, neither the Oxford–AstraZeneca ChAdOx1-nCoV-19 nor the Pfizer–BioNTech COVID-19 vaccine (BNT162b2) represents a particular safety concern for these patients.[123] Although autoimmune hepatitis could occur as a rare complication of COVID-19 vaccines.[124]

Regardless of limited data onthe safety and efficacy of covid19 vaccines in patients with liver diseases, guidelines of several organizations have recommended that patients with chronic liver disease and liver transplant recipients can be encouraged to get vaccinated.[125-128]

### Solid-organ transplant (SOT) recipients

Theoretical concern exists regarding the safety of the COVID-19 vaccine in SOT patients, which include the potential of enhanced inflammatory response due to mRNA based vaccines,[129] or activation of the adenovirus vector in immunocompromised patients.[130] However, currently approved COVID-19 vaccines that are based on replication-deficient adenovirus vectors or mRNA are not contraindicated in SOT patients. Their advantages likely outweigh the expected risks provided that the standard precautions are taken.[130-133] Furthermore, guidelines for optimal use of COVID-19 vaccines in SOT recipients are available.[134,135]

The effectiveness of COVID-19 vaccines is likely to be reduced in Solid organ transplant patients.[136-139] It has been shown that kidney transplant recipients show limited early antibody response after the first dose of the COVID-19 vaccine.[136]

Few studies were conducted to evaluate the short-term safety and efficacy of COVID-19 vaccines in SOT patients.[140] A study reported that only 17% of transplant recipients who received a single dose of SARS-CoV-2 vaccination generated detectable anti-spike antibodies compared to 100% of healthy participants, but after two doses, the response was about 54%.[16,141] A small retrospective study reported the failure of COVID-19 vaccination in transplant patients to effectively protect them from being infected and suffering serious complications.[142] In another study that included 658 SOT recipients who received two doses of the Pfizer–BioNTech COVID-19 vaccine (BNT162b2) COVID-19 vaccine, 46% had no detectable antibodies against the virus proteins after 29 days following the second dose of the vaccine.[143]

Use of antimetabolites (e.g., mycophenolate mofetil, and azathioprine) and a shorter time since transplantation was associated with a higher rate of nonresponse. In reports of transplant recipients who received the third dose of mRNA vaccines, seroconversion rates were higher after the additional dose, although approximately 30 to 50% remained seronegative.[144,145]

### Children & adolescents

BNTb162b (Pfizer COVID-19 vaccine) is authorized for children 5 years or older (ref) andadolescents aged 12 through 15 years based on evidence that efficacy, immunogenicity, and the adverse effect profile in this population are comparable to those in older individuals.[146]

### Elderly

There is theoretical concern regarding decreased immunogenicity with advanced age; however, vaccination strategies such as adjuvants, and vaccines that specifically target the aged immune system were suggested to enhance the efficacy of vaccines in the elderly.[147]

Although further research is needed, preliminary data of phase 1 dose-escalation trials of the Moderna, mRNA-1273 vaccination found that effective antibody responses were equivalent in three age groups (18–55, 56–70, and 71 and older). The measured antibody titers suggested that mRNA vaccinations in the elderly have adequate efficacy.[148,149] AstraZeneca's ChAdOx1 nCoV-19 vaccine (AZD1222) also showed promising efficacy in older adults.[150]

Few publications addressed special safety concerns; for example, a study by Norwegian authorities declared that the Pfizer-BioNTech vaccine was possibly responsible for 10 deaths among 30,000 elders.[151]

In preliminary research, 55 deaths were observed, with a COVID-19 vaccine fatality rate of 8.2 per million population. A total of 37 fatalities were reported among residents of long-term care facilities, with a mortality rate of 53.4 per million. The authors of the mentioned study concluded that the advantages of COVID-19 vaccines outweigh the dangers in elder populations, and their data do not justify policies that prevent older individuals from receiving vaccinations.[152]

### Obesity

Obesity can be defined as a body mass index (BMI) of ≥ 30 kg/m$^2$. Pfizer-BioNTech vaccine efficacy (after the second dose) was about 95% in obese and normal individuals.[153] Individuals with severe obesity (BMI ≥ 40 kg/m$^2$) were included in Moderna studies where overall efficacy (after the second dose) was 94.1%, and 91.2% in those with severe obesity.[22,154] A post hoc analysis similarly demonstrated comparable efficacy in obese participants with no high-risk comorbidity.[154]

### *Pregnant and lactating women*

Data on the safety of COVID-19 vaccines in pregnant individuals are limited but emerging.[155,156] A study revealed that COVID-19 vaccine-specific titers of antibodies after receiving the vaccines were comparable, albeit slightly lower, between pregnant and lactating women compared to non-pregnant control.[157] A multicenter study showed that the antenatal Pfizer-BioNTech mRNA vaccine induced a robust maternal humoral response that effectively transfers to the fetus, supporting the role of vaccination during pregnancy.[158] Vaccinated pregnant and breastfeeding women had immune responses comparable to non-pregnant controls, and greater antibody titers were observed than those seen after SARS-CoV-2 infection during pregnancy according to prospective cohort research from two academic institutes. Moreover, after maternal vaccination, vaccine-generated antibodies were found in umbilical cord blood and breast milk.[159]

Currently approved vaccines in the USA are unlikely to pose specific risks for pregnant women, the fetus, or breastfeeding newborns.[160] Up until June 2021, preclinical and observational clinical studies suggest that the risks of the maternal COVID-19 outweigh the undocumented and hypothetical risks of the COVID-19 vaccines given during pregnancy.[161,162] As of the end of May 2021, in the CDC's v-safe post-vaccination health system, about 120,000 pregnancies were reported. Although no specific safety signals have been found, vaccine safety is still being monitored.[163] Furthermore, unproven accusations that COVID-19 vaccinations cause infertility, have been discredited scientifically.[164-166]

## Conclusions and Recommendations

The immunogenicity of COVID-19 vaccines appears to be lower in some immunocompromised individuals compared with the general population, and vaccine efficacy is uncertain. These conditions include active use of chemotherapy for cancer, hematologic malignancies, hematopoietic stem cell or solid organ transplant, untreated HIV infection with CD4 cell count <200 cells/μL, and use of immunosuppressive medications (e.g., mycophenolate mofetil; rituximab; and prednisone >20 mg/day for >14 days).[104,143,146,167-170] Any concern related to vaccination of specific immunocompromised populations is discussed in detail elsewhere.[146,167] One case of pancreatic rejection was associated with vaccines raising concern of the safety of risk of vaccines in organ transplant patients.

As for other populations such as cardiac patients, pulmonary diseases, diabetes, the elderly, pregnant women, etc., it is expected that the effectiveness of vaccines is similar to that in the general population. Also, these conditions do not constitute an absolute contraindication to receiving vaccinations. It is encouraged that these patients discuss their health status and receive advice from the doctors who follow their cases before receiving vaccinations.

### Conflicts of Interest

There are no conflicts of interest.

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