Review Paper

Safety, Acceptance, and Hesitancy of COVID-19 Vaccines Among High-risk Sub-populations: A Narrative Review

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ABSTRACT

To end the new COVID-19 pandemic, most of the world's population needs to be immune to the virus, protecting individuals from infection, and ultimately ensuring herd immunity at the population level. A variety of COVID-19 vaccines have been developed worldwide for adults and children over the age of 12 years, and the effectiveness of the vaccine in preventing symptomatic diseases and hospitalization is being studied. One of the major obstacles to COVID-19 vaccination that has emerged along with the global immunization program is vaccine hesitation or disapproval. The World Health Organization (WHO) has reported vaccine hesitation as one of the 10 global health threats of 2019. This is also related to COVID-19.

The present review, explore the current evidence on COVID-19 vaccination platforms and vaccination efficacy, safety, and adverse effects among strategic sub-populations, including elderly people, people with chronic disease (diabetes, cancer), pregnant and lactating women, children, youth, and vaccination willingness or hesitancy among the target population.

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Introduction

On February 11, 2020, World Health Organization (WHO) announced a state of emergency on the novel coronavirus, COVID-19. The disease was identified in Hubei Province, Wuhan City, China in late December 2019 and spread to 213 countries on June 16, 2020, and then worldwide [1, 2]. Globally, until June 11, 2022, there have been 539,909,004 confirmed cases of COVID-19, including 6,330,207 deaths [3]. Due to the many similarities between the virus and the severe acute respiratory syndrome (SARS) virus, the International Committee on Taxonomy of Viruses (ICVT) called it SARS-CoV-2 [2, 4].

Strategy

We conducted a systematic search of PubMed, Embase, Web of Science, and Scopus from December 2019 to October 2021, to find out the COVID-19 vaccination among children, adolescents, pregnant women, lactating women, and the elderly. The search strategy combines the keywords "(vaccination or vaccine) and (COVID-19 or COVID-19 virus disease or 2019-nCoV infection or coronavirus disease-19 or SARS coronavirus 2 infection or SARS-CoV-2 infection or COVID-19 pandemic) and (child or children or kid or kids or preschool child or children, preschool or preschool children or infant or adolescents or ado-lescence or teens or teen or teenagers or teenager or pregnant women or pregnant woman or woman, pregnant or women, pregnant or adult or elderly)", in the title and abstract, following the search guidelines for each database. Two authors used the search strategy to identify relevant studies and screen all titles or abstracts of the identified studies. The full texts of the relevant studies will be reviewed by two independent reviewers. The reference lists of the retrieved articles were searched for future studies.

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) virology

COVID-19 is an enveloped virus with a genome size between 26 and 32 kb. It is one of the largest viruses with a ribonucleic acid (RNA) genome. These viruses resemble the crown of the sun, which is characteristic of coronaviruses [5]. The virus has the hardest and most stable envelope in the coronavirus family and SARS-CoV-2 seems to be more resistant to body fluids and the environment than SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-Cov) [6].

The genome of this virus has four open reading frames to encode the viral proteins, including nucleocapsid proteins (NP), spike proteins (SP), envelope proteins (EP), as well as membrane proteins (MP) [7]. Nucleocapsid proteins (NP) (molecular weight 180 kDa) have two domains and involves in virus replication. This protein composes of many viral phosphoproteins produced during infection and providing high immunogenicity. Serum and urine samples can be detected during the first two weeks of the disease which lead to the diagnosis of the virus [6]. Spike protein is a major glycoprotein (molecular weight 180 kDa) that has two separate subunits called S1 and S2. SP of SARS-CoV-2 penetrates the cells by the host cell surface angioten-sin-converting enzyme 2 (ACE2) receptor [8]. Spike antigen plays a key role in vaccine production. Antibodies against this an-tigen, especially the second receptor, play a protective role in disease [5, 7]. Envelope protein (EP) is another type of structur-al protein involving viral practicle assembly and release as well as viral pathogenicity [7]. Membrane proteins (MP) or anti-gene M have three domains which are located between the membranes and form the virus and bind to the nucleocapsid [6].

COVID-19 vaccine platforms

It is essential to discover and inject an effective vaccine to prevent COVID-19 as a highly contagious emerging infectious dis-ease [1]. To combat this pandemic, more than 40 countries have attempted to manufacture and develop vaccines since De-cember 2020, and more than 200 COVID-19 vaccines were developed [9-11]. As of January 5, 2022, 30 vaccines were in phase 1 clinical trials (to test safety and toxicity) and 18 vaccines were in phase 2 (to test expanded safety trials). 34 vaccines were in phase 3 (to test efficacy and effectiveness among a larger population), 19 vaccines were approved for limited use, 9 vac-cines were approved by the food and drug administration (FDA) for full use, and 10 vaccines are abundant and out of produc-tion and supply (vaccines were abandoned after trial) [12].

Vaccines are based on multiple platforms, including live-attenuated viruses, inactivated viruses, virus-like particles (VLPs), protein subunits, DNA, RNA, and viral-vector vaccines. Table 1 describes the advantages and disadvantages of each vaccine platform [6-14]. Live attenuated vaccines at similar doses can provide effective and long-term safety compared to inactivated virus vaccines. These vaccines stimulate both humoral and cellular immune systems [2, 6, 9-11]. Currently, protein-based vaccines are the most commonly developed vaccines, accounting for 35% of all available SARS-CoV-2

Table 1. Advantages and disadvantages of vaccine platforms

Vaccine Platform	Advantages	Disadvantages
Live attenuated virus	Strong immune responses No adjuvant required Cost-effective	Biosafety issue Risk of reversion to virulence Time-consuming development
Inactivated virus	Stable and no risk of reversion Strong antibody response Cost-effective	Biosafety issue Usually requires adjuvants Weak cellular immune response
Virus-like particle (VLP)	No risk of infection and reversion Fewer side effects Good antibody response	Complicated manufacturing process Requires adjuvants High cost
Recombinant protein subunit	No risk of infection and reversion Fewer side effects Easy antigen modification	Low immunogenicity Requires adjuvants High cost
DNA	Rapid development and production Stable at room temperature High reducibility	Low immunogenicity Requires a delivery device (electroporator or jet-injector)
mRNA	Cell-free Rapid development and production Good immunogenicity	Unstable High cost Requires low temperature storage
Viral-vectored	Strong immune responses Various viral vectors Large-scalable	Pre-existing immunity against the vector

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vaccines, followed by vaccines of non-replicating viral vector (13.3%), messenger ribonucleic acid (mRNA1) (12.1%), DNA (10.2%), replicating viral vector (9.8%), and inactivated vaccines (8.2%) [11]. According to a meta-analysis, the local and systemic side effects of the SARS-CoV-2 vaccine in protein subunit vaccines (33.0% vs 22.3%), inactivated vaccines (23.7% Vs 21.0%), and DNA vaccines (39.5% vs 29.3%), are significantly lower than non-replicating vector vaccines (55.9% vs 66.3%), RNA vaccines (89.4% vs 83.3%), and virus-like particle vaccines (100.0% vs 78.9%) [14]. Table 2 presents the characteristics of vaccines approved by the FDA and emergency use authorization (EUA) [1, 9-11].

Vaccination among sub-populations

Vaccination is a step to end the epidemic and return to normal life. From the start of the pandemic to January 3, 2022, more than 9,195 billion doses have been administered worldwide. More than half of the world's population (about 60%) has been vaccinated with at least one dose of the COVID-19 vaccine, 51% have received two doses of the vaccine, and 6.8% have received an additional dose. The top 10 countries with the highest immunization rates are United Arab Emirates (>99%), Bru-nei (93%), Cuba (92%), Chile (91%), Mainland China (90%), and Portugal (89%), Malta (88%), Cambodia (86%), South Korea (86%), Argentina (85%).

Vaccination is a critical tool for reducing hospitalization and mortality [15]. Evidence suggests that approved CO-VID-19 vac-cines are safe and effective for adult people [16-19]. Few and sparse data are available on the vaccination of children, preg-nant and lactating women, the elderly, and people with pre-existing medical conditions and illnesses [20]. There are concerns about the efficacy, safety, and side effects of vaccination in people under the age of 18 years [21]. Studies are ongoing to evaluate vaccination against COVID-19 in individuals under the age of 18 years, but both the FDA and EUA have already sought approval for use [20]. Because pregnant and lactating women were not included in the primary vaccine studies, in-formation on the efficacy and safety of vaccines among this group is limited [22]. Immune senescence decreases response to vaccines in the elderly [15].

COVID-19 vaccines in children and teenagers

Center for disease controls (CDC) and FDA authorized Pfizer-BioNTech in children aged 5 years and older. Mass

Table 2. Characteristics of the vaccines approved by FDA and EUA

Platform	Developer (Product Name)	Target Antigen	Country of Origin	Effectiveness, (%)	Dose, Number, Interval, Injection Route	Phase 3 and 4 Trial Size
mRNA [8, 9, 11, 89]	Pfizer/BioNTech (BNT-162b2)	S protein with 2P (K986P and V987P)	Multinational	95	0.3 mL, 2 shots, 21 days apart, Intramuscular	43,998 (age >12)
	Moderna (mRNA-1273)	S protein with 2P (K986P and V987P)	USA	94.5	0.5 mL, 2 shots, 28 days apart, Intramuscular	30,420 (age >18); 3,000 (12≤18)
Viral-vectored [8, 11, 90, 91]	Oxford/AstraZenaca (AZD-1222)	S protein	UK	70.4	0.5 mL, 2 shots, 4-12 weeks apart, Intramuscular	12,390 (age >18)
	Sputnik V (Gam-COVID-Vac)	S protein	Russia	91	0.5 mL, 2 shots, 3 weeks apart, Intramuscular	33,758 (age >18)
	Janssen pharmaceutical companies (Ad26.COV2.5)	S protein with 2P (K986P and V987P) and 2 mutations at furin cleavage site (R682S and R685G)	Australia	66.9	0.5 mL, Single dose, intramuscular, A booster dose (0.5 mL) may be administered at least 2 months after primary vaccination	44,325 (age 18+)
Inactivated virus [11, 91]	Beijing institute of biological products/sinopharm (BBIBP-CorV)	Whole pathogen	China	79.3	0.5 mL, 2 shots, 3 weeks apart, Intramuscular	3,000 (age >18)
	Sinovac life sciences (CoronaVac)	Whole pathogen	China	50.7	0.5 mL, 2 shots, 2 weeks apart, Intramuscular	12,688 (age >18)
Recombinant protein subunit [9, 11]	Novavax (NVX-CoV2373)	S protein with 2P (K986P and V987P) and 3 mutations at furin cleavage site (R682Q, R683Q and R685Q)	USA	89.7	0.5 mL, 2 shots, 3 weeks apart, Intramuscular	30,000 (age >18)

vaccinations for this age group have been initiated in several countries [23]. According to the WHO's strategic advisory group of experts (SAGE), the Pfizer/BioNTech vaccine is appropriate for use in children older than 12 years. According to WHO, more evidence is needed on the use of other COVID-19 vaccines in children to make global recommendations for children vaccination [3].

Randomized phase 2-3 trials are conducted to evaluate the safety and efficacy of two doses of 10 mcg of Pfizer's BioNTech vaccine in children aged 6 months to 11 years who are given at 21-day intervals. Survey results for children aged 5 to 11 years have been released, but results for children under the age of 5 years have not yet been released. This study showed that the Pfizer-BioNTech vaccination regimen was safe, immunogenic, and effective for children aged 5 to 11 years, and had no serious adverse events [24].

In a randomized clinical trial (RCT) of the Pfizer-BioNTech vaccine, injection site pain was the most common side effect and no death was reported. Other commonly reported adverse events were fever, headache, and fatigue [25, 27]. In the Pfizer-BioNTech mass vaccination of children aged 12 to 15 years in Israel, no serious adverse events were observed [27]. Adverse reactions associated with mRNA-based COVID-19 vaccines such as the Pfizer-BioNTech have been reported in the United States. Follow-up of reported cases of myocardial inflammation is underway [28]. Pfizer-BioNTech RCTs show that vaccine efficacy against COVID-19 in children and adolescents is 100% (95% CI: 75.3-100). This result supports the use of a dose of 3.0 µg in two immunization schedules in children and adolescents [25].

A phase 2 clinical trial study of coronaVac's was safe and elicited a humoral response in children and adolescents aged 3 to 17 years. The results of this study support the use of a dose of 3.0 µg in two immunization regimens [29]. The phase 3 clinical trial of CoronaVac was conducted only in adults and no information is found on the phase clinical trial of 3 CoronaVac in children and adolescents. Other CoronaVac RCTs have not evaluated the efficacy of the vaccine. China is preparing to give mass vaccinations to children younger than 12 years [30].

ZyCoV-D is another vaccine approved by the Indian Pharmaceutical Regulatory Authority for emergency use in people younger than 12 years. Children aged 2 to 6 years participated in a clinical trial of covaxin [31]. In addition to ZyCoV-D, other vaccines are in clinical trials, but the results of these RCTs have not been published.

AstraZeneca is another COVID-19 vaccine, and clinical trials of this vaccine in adolescence have been discontinued due to ra-re but severe vaccine-induced thrombosis and thrombocytopenia syndrome in young adults after the first dose [32].

COVID-19 vaccines in pregnancy and breastfeeding

Evidence of the safety and efficacy of COVID-19 vaccination during pregnancy and lactation is limited, but increasing. No ev-idence shows that the COVID-19 vaccine causes infertility problems [33]. To evaluate the safety of the Pfizer-BioNTech, Moderna, Jonssen & Jonssen vaccines in animals, studies were conducted by the FDA that found no side effects [22]. In a co-hort study, vaccinated pregnant women showed a strong antibody response, but unvaccinated pregnant women were nega-tive [34]. Another cohort study was conducted on 30 pregnant, 16 lactating, and 57 neither pregnant nor lactating women who received the mRNA-1273 (Moderna) or BioNTech (BNT)162b2 (Pfizer-BioNTech) COVID-19 vaccines. Twenty-two preg-nant women with SARS-CoV-2 infection and six unvaccinated non-pregnant women showed that the COVID-19 mRNA vaccine was immunogenic in pregnant women. Vaccine-induced antibodies are transported in infant umbilical cord blood and breast milk. Pregnant and lactating women are also safe with the COVID-19 mRNA vaccine against the SARS-CoV-2 variants [35]. A cross-sectional study of healthcare workers evaluated the side effects of 38 pregnant women (20 of whom were vaccinated with the Pfizer-BioNTech vaccine and the remaining 18 were vaccinated with the Moderna vaccine, of whom 81.58% received both doses of mRNA vaccines). The side effects of pregnant women were similar to those of non-pregnant women vaccinated with the mRNA vaccine immediately or early after vaccination, and each was life-threatening [36]. Other vaccines, such as the recombinant vaccine (Novavax), are considered safe during pregnancy due to their non-replicating nature. However, the spe-cial saponin-based adjuvants used in these vaccines may have safety issues and, currently, no data exist on pregnant women [37]. A prospective observational study investigated the pregnancy complications of the Pfizer-BioNTech vaccine BNT162b2 and found a similar rate of complications between vaccinated and unvaccinated pregnant women. It is also effective in pre-venting COVID-19 infection and has no serious adverse events [38]. Another study showed that a strong maternal humoral response was effectively transmitted to the fetus [39]. One study reported that pregnant women vaccinated with the BNT162b2 vaccine had no safety concerns and no short-term obstetric and neonatal sequelae

[40]. A prospective cohort study was conducted on 14 lactating and 10 non-lactating women vaccinated with BNT162b2 Pfizer-BioNTech. No difference was observed in post-vaccination side effects among these women. The most common side effect was myalgia. Moreover, this study reported positive IgM, IgA, and IgG antibodies among vaccinated women. Low levels of antibodies, especially 42.9% IgG, have been observed in the breast milk of lactating women [41].

Concerning the effects of vaccination on breastfeeding, a study in 4,445 breastfeeding mothers with COVID-19 vaccination (BNT162b2 [Pfizer-BioNTech] and Moderna vaccine) reported discontinuous breastfeeding. The most common side effects of the mother were pain at the injection site, malaise, and headache [42].

The CDC has established the v-safe COVID-19 vaccine pregnancy registry to record all adverse events of these vaccines dur-ing this period [33]. A study on BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccine reactiongenicity on the day after vaccination of pregnant women show that 70% of adverse events are non-specific pregnancy and 29.9% are related to pregnancy or newborns [43].

Vaccines in elderly people

In a multi-state network of fully and partially vaccinated US hospitals among adults older than 65 years, Pfizer-BioNTech and Moderna vaccines were effective against COVID-19 hospitalization in 94% (95% confidence interval [CI]=49%–99%) and 64% (95% confidence interval [CI]=28%–82%), respectively [44]. A cohort study linked the electronic health registries of 1,409,831 Portuguese aged 65-79 and 470,520 aged 80 and over to examine the efficacy of the mRNA vaccine against hospi-talization and death due to COVID-19. Vaccine efficacy for hospitalization for ages 65-79 years and older than 80 years was 94% and 82%, and for mortality in these two age groups was 96% and 81% [45]. The efficacy of the mRNA vaccine for hospi-talization associated with COVID-19 in immunocompromised elderly people aged 65 years and older who received two doses was reported to be 87% [46]. A total of 7280 laboratory-confirmed COVID-19 were evaluated in the United States who were vaccinated with Pfizer BioNTech and Moderna and Janssen vaccines aged 65-74 years. The effectiveness against COVID-19-related hospitalization was 96% for Pfizer BioNTech, 96% for Moderna, and 84% for Janssen vaccine products. The feature in adults aged 75 years was 91% for Pfizer-BioNTech, 96% for Moderna, and 85% for Janssen vaccine products [47].

In a randomized phase 2/3 clinical trials in adults aged 55-69 and 70 years and older who received one or two doses of the ChAdOx1 nCoV-19 vaccine (AstraZeneca), all side effects were mild and moderate and no serious side effects occurred. Pain and tenderness of the injection site were the most common local side effects, and fatigue, headache, fever, and myalgia were the most common systemic side effects. All side effects were mild in patients who received the second dose. This study showed that the AstraZeneca vaccine was safe and well-tolerated, and older people had a lower reactogenicity index than younger people. The low-dose vaccine was less reactogenic than the standard-dose vaccine in all participants [48].

Several studies have shown neutralizing antibody responses in older adults using other vaccine platforms, including two mRNA vaccines (Moderna and Pfizer-BioNTech, USA), adenovirus type-5 vectored vaccine (CanSino Biological/Beijing Institute of Biotechnology, China), and chimpanzee adenovirus-vectored vaccine (AstraZeneca, UK) [15]. According to a cohort study of 45,965 adults without previous infection with COVID-19 who received either the SARS-CoV-2 vaccine ChAdOx1 (AstraZeneca) or BNT162b2 (Pfizer-BioNTech), serum conversion rate and the quantitative antibody level after a single dose were low for the elderly, especially those over the age of 60. Antibody levels increased faster and reached higher levels with a single dose of Pfizer-BioNTech compared to a single dose of AstraZeneca, but decreased after a single dose of Pfizer-BioNTech in the el-derly. After two doses of vaccination, the response was high in all age groups [49].

According to an observational study in Chile, the adjusted effectiveness of CoronaVac in people over the age of 60 years at least 14 days after the second dose was 66.6% [50]. The results of a randomized clinical trial of the CoronaVac vaccine in people older than 60 years showed that CoronaVac is safe and well tolerated in the elderly. The optimal dose was 3 µg [15]. A case-control study measured the efficacy of the CoronaVac vaccine in adults aged 70 years and older, with effectiveness of 46.8% for symptomatic COVID-19 at least 14 days after the second dose, and 55.5% for preventing hospitalization, and 61.2% for deaths [51].

A randomized phase 3 clinical trial assessed the safety and efficacy of a double-dose NVX-CoV2373 vaccine (Novavax) in adults aged 18-64 years and 65 years and older. The results of this study showed that the 5 µg dose of the Novavax vaccine was 89.7% effective. The most common local side effects were tenderness or

pain at the injection site, and the most common systemic side effects were headache, muscle pain, and fatigue after the first and second doses. Local and systemic adverse events were reported more frequently in younger people (18-64 years) than in older participants (65 years and older). The incidence of serious adverse events was low, similar to the vaccine and placebo groups [52].

Vaccination among people with underlying medical conditions

The CDC and the American Diabetes Association (ADA) support the prioritization of vaccinations for diabetics to decrease the risk of infection in these people [53].

Studies have shown that diabetes is a chronic disease that weakens the immune system, especially in uncontrolled diabetic patients with low HgbA (A1c) and or irregular blood glucose levels [54]. In contrast, another study showed that diabetes and hyperglycemia did not affect the kinetics and persistence of the neutralizing antibody responses to the COVID-19 vaccine. This result shows that vaccination should be prioritized for diabetics [55].

In diabetic patients compared to non-diabetic patients, antibody timing and titers were slightly different, adaptive, and un-affected by glucose rate. The increased severity and mortality of COVID-19 respiratory disease observed in patients with hy-perglycemia was not the result of an abnormal humoral immune response to COVID-19. Receptor-binding domain (RBD) im-munoglobulin positivity is associated with a significant protective effect, enabling cautious expectations regarding the effica-cy of future vaccines against COVID-19 in diabetic patients [56].

It is still unclear whether diabetes changes the immunity to the vaccine. An Italian study of 150 participants reported that the presence of diabetes and hyperglycemia did not affect the kinetics, persistence, or production of neutralizing antibodies [55]. Protective immunity lasted for at least 6 months throughout the study, at the same rate as non-diabetic patients [56]. However, other studies on BNT162b2 (Pfizer-BioNTech) have shown that type 2 diabetes reduces the effectiveness of the vaccine by 0.73 compared to non-diabetic patients [57]. Therefore, we must seriously follow the standard precautions rec-ommended by WHO. Maintaining proper glycemic control for diabetics and prioritizing vaccination of diabetics is one of the crucial recommendations [58].

Patients with cancer are at increased risk of coronavirus disease and related serious complications, especially those receiv-ing active treatment, patients with multiple conditions, and the elderly [59]. Although current data on the protection and efficacy of approved coronavirus vaccines in cancer patients, especially those receiving active treatment, are limited, given the high risk of complications and death, benefits may outweigh the complications and side effects associated with coronavirus vaccine [60].

Cancer patients can be vaccinated, but some studies have found exceptions. Cancer patients receiving or have recently re-ceived radiation therapy, chemotherapy, targeted therapy, stem cell transplantation, or immunosuppressive therapy should not be vaccinated with the COVID-19 vaccines. However, patients who recover, do not require treatment in a short period, and do not have active cancer should be considered for a vaccination with an approved vaccine [61].

In a meta-analysis study of 281 cancer patients with solid tumors, the rate of anti-S antibody response after scheduled complete vaccination with the coronavirus vaccine was promising (≥90%). The antibody response to the coronavirus vaccine was low in 340 patients with hematological malignancies. However, this meta-analysis showed that coronavirus vaccines are efficient, safe, and should be prioritized for cancer patients. However, cancer patients who have already been vaccinated should continue to wear masks to maintain distance and hand hygiene [62].

Studies have shown that the leading coronavirus vaccines are safe and at least partially effective in cancer patients. This is consistent with the CDC's recommendation for immunocompromised people, and recent guidelines and recommendations from the Cancer Immunotherapy Association, the European medical oncology association, the American association for can-cer research (AACR) COVID-19, and the cancer working group. Recently the COVID-19 vaccination advisory committee of the national comprehensive cancer network. (NCCN) issued coronavirus vaccine recommendations [63].

Few studies advised healthcare providers to vaccinate cancer patients, even for those with active disease or receiving anti-cancer treatment [64]. The results of some studies have shown that nano-based vaccines can reduce vaccination side effects and improve efficacy, depending on the unique ability of nanomaterials to generate important immunomodulatory activity. This is especially true for people with altered immune respons-

es, such as cancer patients and other immunocompromised patients [65].

Acceptance of COVID-19 vaccination

Vaccine hesitation or rejection is one of the most challenging issues related to COVID-19 vaccination that has evolved along with the global immunization program. This is defined as "delayed acceptance or refusal of vaccinations despite the availabil-ity of vaccination services" [66].

The rate has been evaluated in many studies from different countries. Based on the results of a scoping review, vaccination hesitation in various countries is 10%-57% [67]. Another systematic review and meta-analysis results report 66% vaccine acceptance worldwide [68].

The determinants of vaccination acceptance or delay have also been evaluated in many studies. Therefore, it is a multifacto-rial characteristic that includes vaccine characteristics (efficacy and side effects), information sources, health and social ine-quality, socioeconomic status, and religious beliefs. The results are not similar in different countries or nations. Most studies have shown that vaccine acceptance is higher in people with higher education, while in Japan, it is higher in people with less education. One of the critical determinants of hesitation in vaccination against COVID-19 is the timing and duration of the vaccination program. Studies have shown that the rate was high in the first few months of vaccination and decreased over time as the program continued. The rapid development of the COVID-19 vaccine is believed to be the main reason for hesita-tion in vaccination [67, 69-71].

The above admission rate is for the general population. The rate and its determinants do not appear to be similar between individuals in different age groups and different health conditions. Some high-risk populations, such as children and adoles-cents, the elderly, pregnant and lactating women, and people with cancer and other underlying illnesses, are evaluated for vaccination acceptance.

Vaccination acceptance has been reported to be higher in the elderly than in adults. Older people appear to have greater concerns and perceived threats than younger people [72, 73].

In individuals with underlying diseases, the reported results are not similar. In some populations, the acceptance rate of pa-tients in this subgroup was low [74]. In some others, such as Japanese patients, the rate was high [75]. Low acceptance rates for obese patients with a body mass index (BMI) are reported greater than 40 [74].

More than 50% of cancer patients believe that vaccination could prevent COVID-19 infection, but are also worried about the side effects of vaccination [76]. Based on the available data, physicians' recommendations may raise their awareness of vac-cination preparation [77]. A study on cancer patients in South Korea found this percentage at 66% [77]. Hesitation rates for cancer, chronic lung disease, and autoimmune disease have been reported to be 13.4%, 17.8%, and 19.4%, respectively [78].

One of the critical determinants of vaccination acceptance in patients with the underlying disorder is regular influenza vac-cination. It plays a positive and predictive role in the acceptance of COVID-19 vaccination [78].

In children and adolescents, the most important determinant that can affect vaccination acceptance is parental motivation toward vaccination [79, 80]. The parents may be reluctant to vaccinate their children, primarily due to long-term side effects and concerns about vaccine safety. Parents are more hesitant to vaccinate younger children than adolescents, and mothers have less willingness to vaccinate their children than fathers [80, 81].

The acceptance rate between 30% (Romania and Turkey)–89% (China) was reported in different countries The rate was also high in children and adolescents from Latin America and the Caribbean (92.2%) [82]. Results of a systematic review study reported an acceptance rate of 57% for children [83].

The acceptance rate ranges from 30% (in Romania and Turkey) to 89% (in China) in various countries [82-84]. This rate is higher in children and adolescents in Latin America and the Caribbean (92.2%) [85]. The results of a systematic review study report the acceptance rate of children at 57% [86].

Pregnant and lactating women are another high-risk and challenging group in this area. Survey results from 16 countries found that the acceptance rate of pregnant women is lower. This rate was higher for pregnant women in India and the Philip-pines than in Australia, the United States, and Russia [84]. In a study in the United States, willingness for COVID-19 vaccina-tion was as follows, 76.2% of non-pregnant women, 55.2% of lactating women, and 44.3% of pregnant women [85].

The vaccination acceptance rate seems to be low in developing countries. In Turkey, the rates for pregnant and lactating women were 37% and 33% [86, 87]. The results of another meta-analysis showed that Africa had the lowest acceptance rate at 19% [88].

Since the COVID-19 vaccination rate is not similar by country/region, disease, or age group, the determinants of vaccination hesitation also differed in the regions and subpopulations surveyed. As with all groups and populations, the critical determi-nant is the public increased knowledge and confidence regarding the safety, efficacy, and potential complications of vaccina-tion. It is recommended to reduce false information in this regard by developing more practical health education programs that utilize both national and international facilities.

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Compliance with ethical guidelines

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Authors contributions

All authors equally contributed to preparing this article.

Conflicts of interest

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