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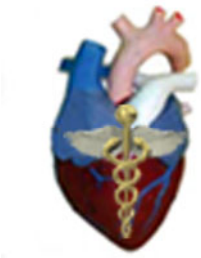

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EDITORIAL

COVID-19 Vaccines: Cardiovascular Perspectives

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Abstract

The accelerated development of COVID-19 vaccines has ushered in new hope for the beginning of the end of this unprecedented pandemic with the heaviest toll on global health and economy. The goal of vaccination is to achieve "herd immunity" which helps interrupt the chain of transmission with the threshold of such immunity estimated at 60-70%. There are four main types of COVID-19 vaccines: messenger RNA (mRNA); viral vector; protein-based; and whole virus. mRNA vaccines and most of the COVID-19 vaccines are using various versions of the spike (S) protein as their vaccine antigen component, while a few vaccines employ the whole virion. Local reactions and mild symptoms are the most common adverse reactions to vaccination; however, *anaphylaxis* is a potentially life-threatening adverse effect and needs to be monitored and promptly managed. Deaths with temporal association with vaccination have also been reported, but not causally linked to vaccination. Thrombotic events have also been reported, particularly with two brands, and have caused alarm but apparently remain extremely rare, nevertheless authorities remain watchful. One is considered fully vaccinated for COVID-19 ≥2 weeks after one has received the last dose. Unfortunately, new strains of COVID-19 are emerging fast, for which the current vaccines may be less effective. Thus, it is still crucial to continue wearing facemasks, apply hand washing, and social distancing in order to slow viral spread and to protect everybody from infection. Several unknowns still remain about COVID-19 vaccines that relate to the safety and efficacy of the vaccines in "special" populations, the degree and duration that these vaccines protect against infection and transmission. and possible long-term adverse effects of vaccination, not yet encountered in phase 3 trials. ***Rhythmos 2021;16(2): 22-33***.

Key Words: COVID-19; SARS-CoV-2; COVID vaccines; herd immunity; mRNA vaccine; vaccine associated enhanced disease

Abbreviations: CDC = Centers for Disease Control; COVID-19 = corona virus disease 2019; CVD = cardiovascular disease; EMA = European Medicines Agency; FDA = Food and Drug Administration; mRNA = messenger RNA; VAED = vaccine-associated enhanced disease; VLPs = virus-like particles

Introduction

The corona virus disease 2019 (COVID-19) pandemic has plagued the world for over a year now causing global disarray, misery and suffering with a heavy toll in morbidity and mortality, [1-4] with over 136 million cases globally, and deaths approaching 3 million in 192 countries (https://coronavirus.jhu.edu/map.html). Thus, the emergence of COVID-19 vaccines,[5, 6] already introduced into 169 countries (https://view-hub.org/covid-19/?set=current-vaccine-intro-status&group=vaccine-introduction&category=covid), can only be seen as light at the end of the tunnel offering a strong beacon of hope. Most of the vaccines have targeted the surface spike (S) glycoprotein of SARS-CoV-2 and achieved a ~85-95% reduction in the risk of symptomatic COVID-19. [5]

The goal of vaccination of the public against any infectious disease is to achieve "*herd immunity*" which helps interrupt the chain of transmission. For SARS-CoV-2 causing COVID-19 infection, the herd immunity threshold is estimated at 60-70%, although this may vary significantly in different environments and populations;[7, 8] herd immunity is achieved either via vaccinations or prior exposure to the virus.[8] However, obstacles have emerged in achieving the suggested threshold, that include the appearance of new variants of the virus and the delay in having vaccinations available for children.[8]

In an unprecedented and historical scientific race and acceleration of research efforts, effective COVID-19 vaccines were developed within 11 months.[5, 6] There are 87 COVID-19 vaccines in clinical development and 186 in pre-clinical development (www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines); a few have already made it into the clinical arena. These include the Pfizer-BioNTech COVID-19 vaccine, the Moderna COVID-19 vaccine, the Janssen COVID-19 vaccine and the AstraZeneca COVID-19 vaccine. The first 3 vaccines have been authorized by the U.S. Food and Drug Administration (FDA) for emergency use, while all four have been provided with conditional marketing authorization by the European Medicines Agency (EMA); several other vaccines are at different stages of development by manufacturers and assessment by Authorities (**Table 1**).[6, 9-17] The EMA is currently evaluating 3 additional vaccines: CVnCoV by CureVac (Tuebingen, Germany), NVX-CoV2373 by Novavax (US), and Sputnik V or Gam-COVID-Vac by Gamaleya (Russia).

Types of Vaccines

There are four main types of COVID-19 vaccine: messenger RNA (mRNA); viral vector; protein-based; and whole virus (**Table 1**). mRNA vaccines are made from strands of genetic material that code for a protein on the virus that elicits an immune response. Most of the COVID-19 vaccines are using various versions of the spike (S) protein as their vaccine antigen component, while a few vaccines employ the whole virion (entire virus particle).[18] The full-length spike (S) glycoprotein or receptor binding domain (RBD) of the virion can prevent host and virus interaction by inducing neutralizing antibodies and thus it is considered as the most important vaccine target antigen.

Thus, several types of COVID vaccines have been developed or are in development (**Table 1**), including:

- *RNA and DNA vaccines*, an innovative approach that uses genetically engineered RNA or DNA to generate the S protein that induces an immune response. The mRNA vaccines introduce mRNA into cells, usually via a lipid nanoparticle. Similarly, DNA-based vaccines introduce the DNA coding for the SARS-CoV-2 S protein into cells using viral vectors, leading cells to produce spike proteins.
- *Viral vector vaccines*, which use a safe virus that cannot cause disease but serves as a platform to produce coronavirus proteins to generate an immune response.
- *Protein-based vaccines*, which use harmless fragments of proteins or spike protein shells that mimic the COVID-19 virus to safely generate an immune response.
- *Inactivated or weakened (attenuated) virus vaccines*, which use a form of the virus that has been inactivated or weakened so it does not cause disease, but still generates an immune response

RNA vaccines.

The messenger RNA (mRNA) vaccines are being used for the first time in this pandemic. The COVID-19 mRNA vaccines consist of synthetic mRNA strands encoding the full-length S protein, packaged in lipid nanoparticles to deliver mRNA to cells. [19] A major advantage of the mRNA approach is that the S protein is produced by the host cells as it would be in case of a natural infection with the virus. Vaccinating against the full-length S protein, rather than only one of its components, is expected to lead to an improved response which will be less affected when the virus undergoes genetic changes. To date, there are three mRNA vaccines available, Comirnaty or BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna) and Zorecimeran or CVnCoV (CureVac) (**Table 1**).

DNA Vaccines

DNA-based vaccines are non-infectious and non-replicating, they confer long-term immunogenicity to the host.[18, 20] They consist of gene or fragments of it, encoding

Table 1. Types of COVID-19 Vaccines

Vaccine Type	Developer/ Manufacturer	Age	Dosing	Studies	Approval	Comments
RNA						--Expressing the COVID-19 spike glycoprotein --mRNA used to produce antigenic proteins of the pathogenic virus / Noninfectious --Possible adverse reaction in those with autoimmune disease / Can elicit an unintended, albeit minimized, immune response --Storage: -70 ºC for 6 mo/2–8 ºC for 5 d
BNT162b2 / Comirnaty®	Pfizer/BioNTech	≥12 y	2 IM doses of 30 µg, 3 w apart	C4591001 (NCT04368728) [10]	FDA/EMA	A lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored full-length spike protein
mRNA-1273	Moderna	≥18 y	2 IM doses of 100 mg, 4 w apart	COVE (NCT04470427) [11]	FDA/EMA	A lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein Storage: -20 ºC for 6 mo/2–8 ºC for 30 d /RT for 12 h
CVnCoV / Zorecimeran	CureVac N.V. / Novartis / Bayer / GSK	≥18 y	2 IM doses of 100 mg, 4 w apart	NCT04652102	--	Uses a lipid nanoparticle-formulated, non-modified, more natural mRNA less affected by hydrolysis, enabling storage at 5 °C (41 °F) / encodes the prefusion stabilized full-length spike protein
DNA						DNA plasmid that contains genes which code for antigenic proteins of the pathogenic virus / Noninfectious
INO-4800	INOVIO, U.S.	≥18 y	2 ID doses 4 w apart	NCT04336410 [12]	--	Contains the plasmid pGX9501, which encodes for the entire length of the Spike protein / Stable at room temperature for >1 year / Phase II/III trials
ZyCoV-D	Zydus Cadila	18-60 y	2 IM doses, 4 w apart	CTRI/2021/03/032051	India	A DNA vaccine platform using non-replicating and non-integrating plasmids carrying the gene of interest
Viral Vector / Spike Protein						These vaccines express spike protein from adenovirus vector platforms
ChAdOx1 nCoV-19 or AZD1222 / Vaxzevria	AstraZeneca/ Oxford	≥18 y	2 IM doses of 5 x 1010 viral particles, 4 w apart	NCT04324606, NCT04400838, NCT04444674 [13]	UK, EMA	Non-replicating (chimpanzee) adenovirus engineered to express spike protein / Storage: 2–8 ºC for 6 months
Gam-COVID-Vac / Sputnik V	Gamaleya Research Institute	≥18 y	Two IM doses, 3 w apart	NCT04530396 [21]	Russia/+57 countries	A viral 2-vector vaccine based on 2 human adenoviruses (adenovirus type 26 & 5) containing the gene that encodes the full-length spike protein
Protein-based (Spike protein)						Probably the most immunogenic / using transgenic plants as producers of spike protein could allow production of large quantities at low cost
JNJ-78436735 / Ad26.COV2-S	Janssen (J&J)	≥18 y	One IM dose of 5 x 1010 viral particles	COV1001 (NCT04436276) [14] ENSEMBLE (NCT04505722)	FDA/EMA	--Modified adenovirus containing the gene for the spike protein --Storage: 2–8 ºC
NVX-CoV2373	Novavax, Inc, US	≥18 y	Two IM doses, 3 w apart	PREVENT-19, Phase 3 trial (NCT04611802)	--	The purified protein is encoded by the genetic sequence of the S protein, produced in insect cells / It can neither cause COVID-19 nor can it replicate/Stable at 2-8°C/NVX-CoV2373 was created using recombinant nanoparticle technology and is adjuvanted with Novavax' patented saponin-based Matrix-M™ to enhance the immune response and stimulate high levels of neutralizing antibodies

Convidicea (Ad5-nCoV)	CanSinoBIO Biologics Inc., China	≥18 y	One IM dose	CTII-nCoV (NCT04341389)* [15] & NCT04526990 †	China, Hungary, Mexico, Pakistan	--The replication-defective adenovirus type 5 is used as the vector to express spike protein / --The vaccine is stored and transported at 2-8°C
Inactivated / Weakened (Live attenuated) virus						--**Inactivated**: can still be recognized by the immune system but is unable to reproduce / Weaker immune response than a live attenuated vaccine; requires periodic booster shots / Risk of vaccine-enhanced disease (VAED) --**Live attenuated**: Closest to natural infection / Induces a CD8 T cell and T-dependent antibody response to confer long-term immunity / Not suitable for immunocompromised or pregnant pts / Risk of infection in immunocompromised patients
CoronaVac	Sinovac Biotech, China	≥18 y	2 IM doses 2 w apart	NCT04352608 [16] / PROFISCOV (NCT04456595) [17]	China, Brazil	Inactivated virus / Phase III trial / Transported and stored at 2–8 °C
BBIBP-CorV (Vero Cell)	Sinopharm, China	≥18 y	2 IM doses 3/4 w apart	NCT04560881	China, Nepal, UAE	Inactivated virus / Phase III trials
COVAXIN (BBV152)	Bharat Biotech, India	≥12 y	2 IM doses, 4 w apart	NCT04641481 [22]	India	Inactivated virus/vaccine adjuvant: Alhydroxiquim-II /Phase III trial/no need for sub-zero storage, stable at 2-8ºC
Covi-Vac	Codegenix Inc, NY / Serum Institute of India	≥18 y	One intranasal dose	NCT04619628	--	Attenuated virus / Intranasal vaccine / Phase I trial
CoviVac	Chumakov Centre	18-60 y	2 IM doses 2 w apart	NCT04830800	Russia	Inactivated virus / Transported and stored at 2-8 ºC

EMA = European Medicines Agency; FDA = (US) Food and Drug Administration; ID = intradermal; IM = intramuscular; VAED = vaccine-associated enhanced disease
* Phase 2 ; † Phase 3

immunogenic antigens delivered to the host's cell nuclei by using DNA plasmids as a vector; the *S protein is the immunogen in all DNA vaccines*. They have the ability to induce both humoral and cellular immune responses. Other advantages, compared to traditional vaccines, relate to induction of broad immune responses without any risk of replicating microorganisms; efficient large-scale, low-cost producibility; high storage stability; construction of a vector encoding different antigens in a single vaccine. Currently, there are 4 COVID-19 vaccine candidates in clinical evaluation and 14 in preclinical evaluation stage developed using the DNA platform.[18]

Viral vectors

Based on their ability to replicate in the host cell, viral (commonly adenoviral) vectors can be replicating and non-replicating recombinant vectors. These vectors deliver the viral genome encoding the gene of interest. The vaccine-generated longevity of the immune response depends on the type of viral vector that is employed. Adenoviruses are the most utilized and advanced viral vectors developed for SARS-CoV-2 vaccines.[23] Vaccines based on viral vectors include the AstraZeneca/Oxford vaccine and the Russian Sputnik V vaccine (**Table 1**)

Protein-Based Vaccines

Virus-Like Particles (VLPs). These are protein multimers which mimic a structure of real virus but lack genetic material and therefore are non-infectious; they are recognized by the immune system in the same way as the original virus is recognized and thus act by activating B- and T-cell immune responses.[24] *E. coli* is the most common bacterial host cell for VLP production. However, VLP formulations because of their poor immunogenicity generally need adjuvants. Currently, there are 3 COVID-19 vaccine candidates developed as VLPs in clinical evaluation

(CoVLP, Medicago/GSK, NCT04636697; RBD SARS-CoV-2 HBsAg VLP, SpyBiotech, ACTRN12620000817943; VBI-2902a, VBI Vaccines Inc, NCT04773665) and 15 COVID-19 vaccine candidates in preclinical evaluation.

Recombinant Protein Based Vaccine. As mentioned, the S protein is the primary source of all major vaccine antigen targets to date. The S-protein is made up of two subunits, S1 and S2; within the S1 subunit, a distinct receptor-binding domain (RBD) and within it, a distinct receptor-binding motif (RBM), is responsible for the initial docking of the virus to angiotensin converting enzyme 2. There are full-length S-protein based vaccines (e.g., the NVX-CoV2372 produced by Novavax), RBD-based vaccines, and multi-epitope vaccines. These vaccines are non-replicating and lack any of the infectious components of a viral particle, and are considered a safer approach compared to vaccines derived from live attenuated viruses. There are currently at least 16 vaccines based on recombinant protein antigens in clinic studies, and 56 in pre-clinical testing.[25] For the production of recombinant proteins, a variety of expression platforms are currently available, including microbial systems, such as *E. coli* and various yeasts, as well as insect cells, mammalian cells, and even plants. *E. coli* is the least expensive choice for protein production, while mammalian cells are the most expensive option. [25] ***Plant based vaccines***, being capable of producing edible vaccines, can be easily available globally to the needy population. Importantly, to enhance the immune response and allow for antigen dose sparing, most protein-based COVID-19 vaccines are formulated in combination with adjuvants (immunostimulants), e.g., aluminum salts, saponin, oil-in-water emulsion, etc.

Whole Virion Vaccines

Inactivated or weakened virus vaccines use a form of the virus that has been inactivated or weakened so it does not cause infection, but still generates an immune response. [22]

Adverse Effects

Allergic reactions, including ***anaphylaxis***, have been reported.[26] Anaphylaxis can be life-threatening leading to asphyxiation, cardiovascular collapse, and death; it requires prompt recognition and treatment with epinephrine The incidence of anaphylaxis associated with the Comirnaty® vaccine (Pfizer SARS-CoV-2 mRNA vaccine) seems to be ~10-fold higher compared to that reported with all previous vaccines, at about 1 in 100,000 vs 1 in 1,000,000. [27] The UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the US Centers for Disease Control and prevention (CDC) recommend exclusion from vaccination with the Pfizer– BioNTech or Moderna mRNA vaccines of any person with a history of a severe or immediate (within 4 hours) allergic reaction associated with any of the vaccine components, including polyethylene glycol (PEG) and PEG derivatives such as polysorbates. [27, 28]

Several European countries, like Denmark, Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, and Latvia, suspended use of the Oxford-AstraZeneca covid-19 vaccine as a precautionary move after reports of ***thrombotic events*** and several deaths temporally related to vaccination.[29, 30] The reports include multiple thromboses (with concurrent thrombocytopenia) in the form of disseminated intravascular coagulation (DIC), deep venous thrombosis, pulmonary embolism, and cerebral venous sinus thrombosis.[30-32]

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT). It has been suggested to name this novel entity of venous and arterial thromboses associated with thrombocytopenia as VITT to avoid confusion with heparin-induced thrombocytopenia (HIT) to which it clinically resembles.[31, 32] On April 7, 2021, EMA's safety committee (Pharmacovigilance Risk Assessment Committee-PRAC) announced that unusual thrombosis with thrombocytopenia occurring within 2 weeks of vaccination should be listed as very rare side effects of Vaxzevria (AstraZeneca COVID-19 Vaccine) (www.ema.europa.eu/en/ news/ astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood). This adverse effect of thrombosis occurred in unusual sites such as cerebral venous sinus thrombosis and splanchnic vein thrombosis as well as arterial thrombosis. Most of the cases reported so far have occurred in women <60 years. Most cases occurred within 2 weeks of the

first vaccine dose. A total of 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis were reported in the EU drug safety database (EudraVigilance) as of 4 April 2021, 18 of which were fatal. About 34 million people had been vaccinated in the EU and UK by that date.

One plausible explanation for the combination of thrombosis and thrombocytopenia is an immune response, leading to a condition similar to heparin induced thrombocytopenia (HIT). The Agency recommends that one should seek urgent medical attention immediately if one develops any of the following symptoms in the weeks after vaccination: shortness of breath; chest pain; leg swelling; persistent abdominal pain; neurological symptoms, such as severe and persistent headaches or blurred vision; tiny blood spots under the skin (purpuric rash) beyond the site of the injection.

Just recently, a similar situation arose with the Johnson & Johnson (Janssen) vaccine. As of April 12, 2021, more than 6.8 million doses of this vaccine had been administered in the U.S. and 6 cases of unusual thromboses were reported and scrutinized by the CDC and FDA (www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine). In these cases, cerebral venous sinus thrombosis (CVST) was seen in combination with thrombocytopenia. All 6 cases occurred among women aged 18-48, and symptoms occurred 6-13 days after vaccination. Treatment of this specific type of blood clot is different from the treatment that might typically be administered, whereby heparin may be risky, and alternative treatments need to be given (HIT-like scenario).

Investigators report minimal risk of severe ***neurological disorders*** after vaccination (e.g., transverse myelitis, Bell's palsy, Guillain-Barré syndrome-GBS, acute disseminated encephalomyelitis); however, this does not suggest a causal link with the vaccination; nevertheless, the risk of long-time effect still needs to be monitored.[33] The most common neurological symptoms may include headache, dizziness, muscle spasms, myalgia, and paresthesias, as transient effects of the vaccination. Rare cases of tremor, diplopia, tinnitus, dysphonia, seizures, and reactivation of herpes zoster have also been reported. Authorities maintain that to date, there has not been a signal suggesting higher rates of neurological disease associated with the COVID-19 vaccines and assert that the benefits of COVID-19 vaccination far outweigh the risks of a neurological complication. [34]

The US Center for Disease Control (CDC) conducted descriptive analyses of safety data from the first month of vaccination (December 14, 2020-January 13, 2021) with use of the two vaccines, Pfizer-BioNTech COVID-19 vaccine on December 11, 2020, and for the Moderna COVID-19 vaccine on December 18, 2020.[35] During this period, 13,794,904 vaccine doses were administered, the Vaccine Adverse Event Reporting System (VAERS) received and processed 6,994 reports of adverse events after vaccination; 6,354 (90.8%) were classified as nonserious and 640 (9.2%) as serious. The symptoms most frequently reported to VAERS were headache (22.4%), fatigue (16.5%), and dizziness (16.5%). A total of 113 deaths were reported to VAERS, including 78 (65%) among long-term care facility residents; available information did not suggest any causal relationship between COVID-19 vaccination and death. Rare cases of anaphylaxis after receipt of both vaccines were reported (4.5 reported cases per million doses administered). Among persons who received the Pfizer-BioNTech vaccine, reactions reported were more frequent after receipt of the second dose than after the first.

Regarding these two vaccines (Pfizer-BioNTech and Moderna), allergic symptoms have been reported for both vaccines.[36] The COVID-19 vaccines can cause mild adverse effects after the first or second doses, including pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain, and can also rarely cause anaphylactic shock. The occurrence of adverse effects is reported to be lower in the Pfizer/BioNTech vaccine compared to the Moderna vaccine. However, for the Pfizer–BioNTech vaccine, which has been in use longer than the Moderna vaccine and therefore has generated more data, side effects increase with the second dose.[37]

Preliminary data from clinical trials of the adenovirus-based Sputnik V vaccine in Russia suggest its most common side effects include flu-like symptoms and injection-site reactions.[21]

With regard to allergies, some researchers suspect polyethylene glycol (PEG) as the anaphylaxis-causing agent in the mRNA vaccines (Moderna and Pfizer–BioNTech vaccines).[37] Vaccines that do not use PEG, such as the vaccine from Johnson & Johnson, which also uses an adenovirus to trigger immunity to the coronavirus - might be a way to vaccinate people with a sensitivity to the polymer.

For the vaccines of Pfizer/BioNTech and Oxford University/AstraZeneca, the MHRA reported that the overwhelming majority of adverse reports relate to injection-site reactions (sore arm for example) and generalized symptoms such as 'flu-like' illness, headache, chills, fatigue (tiredness), nausea (feeling sick), fever, dizziness, weakness, aching muscles, and rapid heartbeat. Generally, these happen shortly after the vaccination and are not associated with more serious or lasting illness (www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/ coronavirus-vaccine-summary-of-yellow-card-reporting).

Regarding ***thromboembolic events***, until the 24th of March 2021, the MHRA had received 22 reports of cerebral venous sinus thrombosis (CVST) and 8 reports of other thrombosis events with low platelets, out of a total of 18.1 million doses of COVID-19 Vaccine AstraZeneca given by that date. There were no reports for the Pfizer/BioNTech vaccine.

Deaths

Several deaths have been reported temporally associated to COVID-19 vaccination.[38, 39] However, to date, investigations into the causes of these deaths have remained inconclusive whether the vaccination has been causative.

Authorities in Norway are conducting thorough investigation into 23 deaths of patients shortly after receiving the Pfizer BioNTec *vaccine*.[38] For 13 of the deaths, authorities concluded that common adverse reactions of mRNA vaccines, such as fever, nausea, and diarrhea, may have contributed to fatal outcomes in some of the frail patients.

According to the British Regulatory Agency of Medicines and Health Care Products (MHRA), up to and including 24 March, MHRA has received 22 reports of cerebral venous sinus thrombosis (CVST) and 8 reports of other thrombosis events with low platelets, out of a total of 18.1 million doses of COVID-19 Vaccine AstraZeneca given by that date.[39] There were no reports for the Pfizer/BioNTech vaccine. The MHRA had received 246 UK spontaneous adverse reactions associated with anaphylaxis or anaphylactoid reactions with the Pfizer/BioNTech COVID-19 vaccine and 390 reports with the AstraZeneca vaccine.

Importantly, the MHRA has received 283 UK reports of suspected adverse reactions to the Pfizer/BioNTech vaccine in which the patient died shortly after vaccination, 421 reports for the Oxford University/AstraZeneca vaccine and 9 where the brand of vaccine was unspecified (www.gov.uk/ government/publications/ coronavirus-covid-19-vaccine-adverse-reactions /coronavirus-vaccine-summary-of-yellow-card-reporting).[39] The majority of these reports were in elderly people or people with underlying illness. However, the Agency indicated that usage of the AstraZeneca has increased rapidly and as such, so has reporting of fatal events with a temporal association with vaccination, however, "this does not indicate a link between vaccination and the fatalities reported".

According to CDC, >145 million doses of COVID-19 vaccines were administered in the US during the period from December 14, 2020, through March 29, 2021; during this period, VAERS received 2,509 reports of death (0.0017%) among people who received a COVID-19 vaccine. In the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/ vaccines/safety/adverse-events.html), it is reported that there is no evidence that vaccination contributed to patient deaths after review of available clinical information including death certificates, autopsy, and medical records.

Questions

Several questions remain to be answered. They relate to: several serious and/or fatal events recorded after vaccination, whether they are caused by the vaccine itself, as they are

temporally related to the vaccine; possible long-term adverse effects; safety and efficacy of vaccination in pregnant women and children; efficacy of vaccines in variant/mutant viral strains; duration of immunity and need for (?annual) booster shots

Vaccine Prioritization

Vaccine prioritization is recommended for several population groups and patient categories (**Table 2**). Prioritization is also advised for several cardiac patients with cardiovascular (CV) risk factors and CV disease (CVD) who are at variable risk for adverse outcomes should they contract the COVID-19 virus:[40]

- Patients with more advanced CVD, such as patients with poorly controlled hypertension, or insulin-dependent, complicated, or poorly controlled diabetes
- Patients with morbid obesity vs overweight
- Patients with high-risk or symptomatic atherosclerotic CVD, including coronary (CAD) or peripheral artery disease (PAD) have a higher risk compared with asymptomatic or fully revascularized patients.
- Patients with cardiac arrhythmias, such as those with atrial fibrillation or flutter who have heavy arrhythmic load and those ventricular arrhythmias (VT/VF) fitted with an implantable cardioverter defibrillator (ICD) device or receiving antiarrhythmic drugs
- Among patients with heart failure, those with worse functional status (i.e., NYHA class III/IV) and those requiring recent hospitalization or an urgent visit for worsening heart failure compared with those patients who are well-compensated on medical therapy and infrequently hospitalized
- Patients with heart failure who are being considered for or are already listed for a heart transplant
- Patients with a history of a heart transplant should be considered higher risk, given their immunosuppressed status, especially those in the immediate postoperative state and at the highest intensity of immunosuppression.
- Although there are less data in the pulmonary hypertension (PH) population, patients with moderate-severe PH should be considered higher risk, especially those who are decompensated and being considered or listed for lung transplant.
- Patients with adult congenital heart disease (ACHD) with advanced physiological stage, indicating more advanced disease, should be prioritized.

Table 2. Prioritization of COVID-19 Vaccination Allocation [40]

Overall Risk	CV Risk
Increased exposure risk (e.g., health care personnel)	Recent hospitalization for CVD/PHTN (III/IV)/CHD (C/D)
Advanced age	CAD/HF (III/IV; C/D)/PAD
Increased non-CV risk	Morbid obesity/≥2 CV risk factors/Poorly controlled IDDM
Increased CV risk	High burden VTAs/PHTN (I/II)/ CHD (A/B)
Health care accessibility issues	CAD (revascularized)/HF (I/II; B/C) / PAD (revascularized)
Socioeconomic groups	Obesity/Poorly controlled HTN/ IDDM
	Overweight/HTN/NIDDM

CAD = coronary artery disease; CHD = congenital heart disease; CV = cardiovascular; CVD = cardiovascular disease; HF = heart failure; HTN = hypertension; IDDM = insulin-dependent diabetes; NIDDM = non-insulin dependent diabetes; PAD = peripheral artery disease; PHTN = pulmonary hypertension; VTAs = ventricular tachyarrhythmias

Travel Advisory and Public Health Recommendations for Fully Vaccinated People

A person is considered fully vaccinated for COVID-19 ≥2 weeks after one has received the second dose in a 2-dose series (Pfizer-BioNTech or Moderna), or ≥2 weeks after one has received a single-dose vaccine (Johnson and Johnson (J&J)/Janssen). Fully vaccinated people can resume domestic travel and do not need to get tested before or after travel or self-quarantine after travel. Fully vaccinated people do not need to get tested before leaving their country (unless required by the destination) or self-quarantine after arriving back to their home country. See Table 3 for additional recommendations.

Table 3. Guidance for Fully Vaccinated Individuals

- Can visit with other fully vaccinated individuals or unvaccinated individuals at low risk for severe COVID-19 infection from single household indoors without physical distancing or wearing a mask
- No need for quarantine and testing following a known exposure if asymptomatic

- Can resume domestic travel / No need for testing before or after travel or self-quarantine after travel
- Can forego testing before leaving the country for international travel (unless required by the destination) / No need for self-quarantine after arriving back home
- Should continue taking precautions in public by wearing a mask and physical distancing
- Should wear masks and adhere to physical distancing and to other prevention measures when visiting with unvaccinated people who are at increased risk for severe COVID-19 disease or when visiting with unvaccinated people from multiple households
- Should avoid medium- and large-sized in-person gatherings
- Should get tested if experiencing COVID-19 symptoms
- Should follow guidance issued by individual employers

COVID-19 Variants

The B.1.1.7 variant, first identified in the U.K. where it has become the dominant variant, confers higher transmission, potentially increased virulence.[41] The B.1.351 or South African variant has more consequential changes to the spike glycoprotein than B.1.1.7, and also is associated with increased transmissibility.[42] Importantly, B1.351, but not B.1.1.7, may increase the risk of infection in immunized individuals.[43] The P.1 variant has recently emerged in Brazil in a high transmission setting and also has several consequential changes in the spike protein, with 3 mutations within the receptor binding domain.[44] A novel variant of concern, CAL.20C (B.1.427/ B.1.429), was initially detected in California, however, it is currently spreading throughout the US and ~30 additional countries. [45]

Vaccines will likely perform differently against increasingly heterologous strains. As the pandemic continues, new strains with mutations in the S protein are emerging with variable response to vaccination challenging vaccine efficacy and probably requiring changes in the vaccines already available in order to fight these more transmissible variants. [46]

Unknowns

Several unknowns still remain about vaccines against COVID-19 infection. They relate to the safety and efficacy of the vaccines in "special" populations, such as children, pregnant women, patients with underlying diseases, and those receiving drugs that might affect the immune response to a vaccine.

Unknown is the duration of protection provided by these vaccines and their long-term efficacy.[47] A most important unknown relates to the degree to which these vaccines protect against infection and transmission. It is critical to continue to reinforce the public health measures of social distancing, handwashing, and masking until the current outbreak is under control.

Finally, a theoretical concern relates to possible long-term adverse effects of vaccination, not yet encountered in phase 3 trials.[48] Because of the significant sequence homology between SARS-CoV-2 and SARS-CoV, there arises the potential for antibody-dependent enhancement (ADE), seen in vitro where viral entry or replication is enhanced in the presence of vaccine-induced antibody, and the potential for vaccine-associated enhanced disease (VAED).[49] This might result in enhanced infection or increase in 'severe' infections in vaccinated individuals who are infected by the homologous coronavirus. With both ADE and VAED, the effect of waning antibody titers after vaccination (or after infection) and potential safety signals is unknown. With regards to CV manifestations of VAED, one may encounter tachycardia, blood pressure changes, acute cardiac injury, myocarditis, heart failure, vasculitis, and cardiogenic shock.[49]

Another potential concern comes from multi-system inflammatory syndrome in children (MIS-C) who are infected with COVID-19; some have warned that the occurrence of MIS-C should be carefully monitored after COVID-19 vaccination becomes widespread. [50]

Conclusion

COVID-19 infection may have dreaded and fatal complications.[2] Accelerated progress in the field of vaccination has come into fruition and several types of vaccines are already available to the public (**Table 1**).

There are 4 main types of COVID-19 vaccines: mRNA; viral vector; protein-based; and whole virus. Most of the COVID-19 vaccines are using various versions of the spike (S) protein as their vaccine antigen component. Local reactions and mild symptoms are the most common adverse reactions to vaccination; however, *anaphylaxis* is a potentially life-threatening adverse effect and needs to be monitored and promptly managed. Deaths with temporal association with vaccination have also been reported, but not definitely and causally linked to vaccination. However, unusual cases of venous and arterial thromboses have recently alarmed the Authorities and the public, particularly with two brands (Vaxzevria and JNJ-78436735), and some vaccination programs have been halted, while provisional recommendations have been issued.

One is considered fully vaccinated for COVID-19 ≥2 weeks after one has received the last dose. Herd immunity to COVID-19 transmission and infection will be likely achieved when ~60-70% of the population is vaccinated.[5,10] However, new strains of COVID-19 are emerging fast, for which the current vaccines may be less effective. Thus, it remains crucial to continue wearing facemasks, apply hand washing, and social distancing in order to slow viral spread and to protect ourselves and everybody else from infection.

Several unknowns still remain about COVID-19 vaccines that relate to the safety and efficacy of the vaccines in "special" populations, the degree and duration that these vaccines protect against infection and transmission and possible long-term adverse effects of vaccination, not yet encountered in phase 3 trials.

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