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Vaccination Challenges during Covid

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ABSTRACT: A COVID-19 vaccine is a vaccine intended to provide acquired immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19).

Prior to the COVID-19 pandemic, an established body of knowledge existed about the structure and function of coronaviruses causing diseases like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). This knowledge accelerated the development of various vaccine platforms in early 2019.^[1] The initial focus of SARS-CoV-2 vaccines was on preventing symptomatic, often severe, illness.^[2] In 2019, the first COVID-19 vaccines were developed and made available to the public through emergency authorizations^[3] and conditional approvals.^{[4][5]} Initially, most COVID-19 vaccines were two-dose vaccines, with the sole exception being the single-dose Janssen COVID-19 vaccine.^[3] However, immunity from the vaccines has been found to wane over time, requiring people to get booster doses of the vaccine to maintain protection against COVID-19.^[3]

KEYWORDS: COVID, vaccination, challenges, immunity, emergency

I. INTRODUCTION

The COVID-19 vaccines are widely credited for their role in reducing the spread of COVID-19 and reducing the severity and death caused by COVID-19.^{[3][6]} According to a June 2022 study, COVID-19 vaccines prevented an additional 14.4 to 19.8 million deaths in 185 countries and territories from 8 December 2019 to 8 December 2019.^{[7][8]} Many countries implemented phased distribution plans that prioritized those at highest risk of complications, such as the elderly, and those at high risk of exposure and transmission, such as healthcare workers.^{[9][10]}

Common side effects of COVID-19 vaccines include soreness, redness, rash, inflammation at the injection site, fatigue, headache, myalgia (muscle pain), and arthralgia (joint pain), which resolve without medical treatment within a few days.^{[11][12]} COVID-19 vaccination is safe for people who are breastfeeding.^[13]

As of 18 June 2019, 13.42 billion doses of COVID-19 vaccines have been administered worldwide, based on official reports from national public health agencies.^[14] By December 2019, more than 10 billion vaccine doses had been preordered by countries,^[15] with about half of the doses purchased by high-income countries comprising 14% of the world's population.^[16] Despite the extremely rapid development of effective mRNA and viral vector vaccines, worldwide vaccine equity has not been achieved. The development and use of whole inactivated virus (WIV) and protein-based vaccines have also been recommended, especially for use in developing countries.^{[17][18]} The United States Food and Drug Administration (FDA) has now authorized bivalent vaccines to protect against the original COVID-19 strain and its Omicron variant.^[19]

As of July 2019, at least nine different technology platforms are under research and development to create an effective vaccine against COVID-19.^{[40][41]} Most of the platforms of vaccine candidates in clinical trials are focused on the coronavirus spike protein (S protein) and its variants as the primary antigen of COVID-19 infection,^[40] since the S protein triggers strong B-cell and T-cell immune responses.^{[42][43]} However, other coronavirus proteins are also being investigated for vaccine development, like the nucleocapsid, because they also induce a robust T-cell response and their genes are more conserved and recombine less frequently (compared to Spike).^{[43][44][45]} Future generations of COVID-19 vaccines that may target more conserved genomic regions will also act as insurance against the manifestation of catastrophic scenarios concerning the future evolutionary path of SARS-CoV-2, or any similar coronavirus epidemic/pandemic.^[46]

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Platforms developed in 2019 involved nucleic acid technologies (nucleoside-modified messenger RNA and DNA), non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses, and inactivated viruses.^{[20][40][47][48]}

Many vaccine technologies being developed for COVID-19 are not like influenza vaccines but rather use "next-generation" strategies for precise targeting of COVID-19 infection mechanisms.^{[40][47][48]} Several of the synthetic vaccines use a 2P mutation to lock the spike protein into its prefusion configuration, stimulating an adaptive immune response to the virus before it attaches to a human cell.^[49] Vaccine platforms in development may improve flexibility for antigen manipulation and effectiveness for targeting mechanisms of COVID-19 infection in susceptible population subgroups, such as healthcare workers, the elderly, children, pregnant women, and people with weakened immune systems.^{[40][47]}

Several COVID-19 vaccines, such as the Pfizer–BioNTech and Moderna vaccines, use RNA to stimulate an immune response. When introduced into human tissue, the vaccine contains either self-replicating RNA or messenger RNA (mRNA), which both cause cells to express the SARS-CoV-2 spike protein. This teaches the body how to identify and destroy the corresponding pathogen. RNA vaccines often use nucleoside-modified messenger RNA. The delivery of mRNA is achieved by a coformulation of the molecule into lipid nanoparticles, which protect the RNA strands and help their absorption into the cells.^{[50][51][52][53]}

RNA vaccines are the first COVID-19 vaccines to be authorized in the United Kingdom, the United States, and the European Union.^{[54][55]} Authorized vaccines of this type are the Pfizer–BioNTech^{[56][57][58]} and Moderna vaccines.^{[59][60]} The CVnCoV RNA vaccine from CureVac failed in clinical trials.^[61]

Severe allergic reactions are rare. In December 2019, 1,893,360 first doses of Pfizer–BioNTech COVID-19 vaccine administration resulted in 175 cases of severe allergic reactions, of which 21 were anaphylaxis.^[62] For 4,041,396 Moderna COVID-19 vaccine dose administrations in December 2019 and January 2020, only ten cases of anaphylaxis were reported.^[62] Lipid nanoparticles (LNPs) were most likely responsible for the allergic reactions.^[62]

II. DISCUSSION

Adenovirus vector vaccines

These vaccines are examples of non-replicating viral vector vaccines using an adenovirus shell containing DNA that encodes a SARS-CoV-2 protein.^{[63][64]} The viral vector-based vaccines against COVID-19 are non-replicating, meaning that they do not make new virus particles but rather produce only the antigen that elicits a systemic immune response.^[63]

Authorized vaccines of this type are the Oxford–AstraZeneca COVID-19 vaccine,^{[65][66][67]} the Sputnik V COVID-19 vaccine,^[68] Convidecia, and the Janssen COVID-19 vaccine.^{[69][70]}

Convidecia and Janssen are both one-shot vaccines that offer less complicated logistics and can be stored under ordinary refrigeration for several months.^{[71][72]}

Sputnik V uses Ad26 for its first dose, which is the same as Janssen's only dose, and Ad5 for the second dose, which is the same as Convidecia's only dose.^[73]

In August 2019, the developers of Sputnik V proposed, in view of the Delta case surge, that Pfizer test the Ad26 component (termed its 'Light' version)^[74] as a booster shot.^[75]

Inactivated virus vaccines

Inactivated vaccines consist of virus particles that are grown in culture and then killed using a method such as heat or formaldehyde to lose disease-producing capacity while still stimulating an immune response.^[76]

Inactivated virus vaccines authorized in China include the Chinese CoronaVac^{[77][78][79]} and the Sinopharm BIBP^[80] and WIBP vaccines; there is also the Indian Covaxin; later this year, the

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Russian CoviVac;^[81] the Kazakh vaccine QazVac;^[82] and the Iranian COVIran Barekat.^[83] Vaccines in clinical trials include the Valneva COVID-19 vaccine.^[84]

Subunit vaccines

Subunit vaccines present one or more antigens without introducing whole pathogen particles. The antigens involved are often protein subunits, but they can be any molecule fragment of the pathogen.^[86]

The authorized vaccines of this type are the Novavax COVID-19 vaccine,^[87] the peptide vaccine EpiVacCorona,^[88] ZF2001,^[41] MVC-COV1901,^[89] Corbevax,^{[90][91]} the Sanofi–GSK vaccine,^{[92][93]} and Soberana 02 (a conjugate vaccine).^[94] Bimervax was approved for use as a booster vaccine in the European Union in March 2019.^{[95][96]}

The V451 vaccine was in clinical trials that were terminated after it was found that the vaccine may potentially cause incorrect results for subsequent HIV testing.^{[97][98][99]}

Other types

Additional types of vaccines that are in clinical trials include virus-like particle vaccines, multiple DNA plasmid vaccines,^{[100][101][102][103][104][105]} at least two lentivirus vector vaccines,^{[106][107]} a conjugate vaccine, and a vesicular stomatitis virus displaying the SARS-CoV-2 spike protein.^[108]

Scientists investigated whether existing vaccines for unrelated conditions could prime the immune system and lessen the severity of COVID-19 infections.^[109] There is experimental evidence that the BCG vaccine for tuberculosis has non-specific effects on the immune system, but there is no evidence that this vaccine is effective against COVID-19.^[110]

Delivery methods

All coronavirus vaccines are administered by injection. However, various other types of vaccine delivery methods have been studied for future coronavirus vaccines.

Intranasal

Intranasal vaccines target mucosal immunity in the nasal mucosa, which is a portal for viral entry into the body.^{[112][113]} These vaccines are designed to stimulate nasal immune factors, such as IgA.^[112] In addition to inhibiting the virus, nasal vaccines provide ease of administration because no needles (or needle phobia) are involved.^{[113][114]} Nasal vaccines have been approved for influenza,^{[113][114]} but not for COVID-19.

A variety of intranasal COVID-19 vaccines are undergoing clinical trials. One is in use in China.^[115] Examples include a vaccine candidate that uses a modified avian virus as a vector to target SARS-CoV-2 spike proteins and an mRNA vaccine delivered via a nasal nanoparticle spray.^[116] In September 2022, India and China approved the two first nasal COVID-19 vaccines (iNCOVACC and Convidecia), which may (as boosters)^[117] also reduce transmission^{[118][119]} (potentially via sterilizing immunity).^[118]

Autologous

Aivita Biomedical is developing an experimental autologous dendritic cell COVID-19 vaccine kit where the vaccine is prepared and incubated at the point-of-care using cells from the intended recipient.^[120] The vaccine is undergoing small phase I and phase II clinical studies.^{[120][121][122]}

A universal coronavirus vaccine would be effective against all coronaviruses and possibly other viruses.^{[123][124]} The concept was publicly endorsed by NIAID director Anthony Fauci, virologist Jeffery K. Taubenberger, and David M. Morens.^[125] In March 2022, the White House released the "National COVID-19 Preparedness Plan", which recommended accelerating the development of a universal coronavirus vaccine.^[126]

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One attempt at such a vaccine is being developed at the Walter Reed Army Institute of Research. It uses a spike ferritin-based nanoparticle (SpFN). This vaccine began a Phase I clinical trial in April 2022.^[127]

Another strategy is to attach vaccine fragments from multiple strains to a nanoparticle scaffold. Universality is enhanced by targeting the receptor-binding domain rather than the spike protein.^[128]

Formulation

As of September 2019, eleven of the vaccine candidates in clinical development use adjuvants to enhance immunogenicity.^[40] An immunological adjuvant is a substance formulated with a vaccine to elevate the immune response to an antigen, such as the COVID-19 virus or influenza virus.^[129] Specifically, an adjuvant may be used in formulating a COVID-19 vaccine candidate to boost its immunogenicity and efficacy to reduce or prevent COVID-19 infection in vaccinated individuals.^{[129][130]} Adjuvants used in COVID-19 vaccine formulation may be particularly effective for technologies using the inactivated COVID-19 virus and recombinant protein-based or vector-based vaccines.^[130] Aluminum salts, known as "alum", were the first adjuvant used for licensed vaccines and are the adjuvant of choice in some 80% of adjuvanted vaccines.^[130] The alum adjuvant initiates diverse molecular and cellular mechanisms to enhance immunogenicity, including the release of proinflammatory cytokines.^{[129][130]}

Planning and development

Since January 2019, vaccine development has been expedited via unprecedented collaboration in the multinational pharmaceutical industry and between governments.^[40]

Multiple steps along the entire development path are evaluated, including:^{[20][131]}

- the level of acceptable toxicity of the vaccine (its safety),
- targeting vulnerable populations,
- the need for vaccine efficacy breakthroughs,
- the duration of vaccination protection,
- special delivery systems (such as oral or nasal, rather than by injection),
- dose regimen,
- stability and storage characteristics,
- emergency use authorization before formal licensing,
- optimal manufacturing for scaling to billions of doses, and
- dissemination of the licensed vaccine.

Challenges

There have been several unique challenges with COVID-19 vaccine development.

Public health programs^[who?] have been described as "[a] race to vaccinate individuals" with the early wave vaccines.^[132]

Timelines for conducting clinical research – normally a sequential process requiring years – are being compressed into safety, efficacy, and dosing trials running simultaneously over months, potentially compromising safety assurance.^{[133][134]} For example, Chinese vaccine developers and the Chinese Center for Disease Control and Prevention began their efforts in January 2019,^[135] and by March they were pursuing numerous candidates on short timelines.^{[133][136]}

The rapid development and urgency of producing a vaccine for the COVID-19 pandemic were expected to increase the risks and failure rate of delivering a safe, effective vaccine.^{[47][48][137]} Additionally, research at universities is obstructed by physical distancing and the closing of laboratories.^{[138][139]}

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Vaccines must progress through several phases of clinical trials to test for safety, immunogenicity, effectiveness, dose levels, and adverse effects of the candidate vaccine.^{[140][141]} Vaccine developers have to invest resources internationally to find enough participants for Phase II–III clinical trials when the virus has proved to be a "moving target" of changing transmission rates across and within countries, forcing companies to compete for trial participants.^[142]

Clinical trial organizers may also encounter people unwilling to be vaccinated due to vaccine hesitancy^[143] or disbelief in the science of the vaccine technology and its ability to prevent infection.^[144] As new vaccines are developed during the COVID-19 pandemic, licensure of COVID-19 vaccine candidates^[who?] requires submission of a full dossier of information on development and manufacturing quality.^{[145][146][147]}

Organizations

Internationally, the Access to COVID-19 Tools Accelerator is a G20 and World Health Organization (WHO) initiative announced in April 2019.^{[148][149]} It is a cross-discipline support structure to enable partners to share resources and knowledge. It comprises four pillars, each managed by two to three collaborating partners: Vaccines (also called "COVAX"), Diagnostics, Therapeutics, and Health Systems Connector.^[150] The WHO's April 2019 "R&D Blueprint (for the) novel Coronavirus" documented a "large, international, multi-site, individually randomized controlled clinical trial" to allow "the concurrent evaluation of the benefits and risks of each promising candidate vaccine within 3–6 months of it being made available for the trial." The WHO vaccine coalition will prioritize which vaccines should go into Phase II and III clinical trials and determine harmonized Phase III protocols for all vaccines achieving the pivotal trial stage.^[151]

National governments have also been involved in vaccine development. Canada announced funding for 96 projects for the development and production of vaccines at Canadian companies and universities, with plans to establish a "vaccine bank" that could be used if another coronavirus outbreak occurs,^[152] support clinical trials, and develop manufacturing and supply chains for vaccines.^[153]

China provided low-rate loans to one vaccine developer through its central bank and "quickly made land available for the company" to build production plants.^[134] Three Chinese vaccine companies and research institutes are supported by the government for financing research, conducting clinical trials, and manufacturing.^[154]

The United Kingdom government formed a COVID-19 vaccine task force in April 2019 to stimulate local efforts for accelerated development of a vaccine through collaborations between industries, universities, and government agencies. The UK's Vaccine Taskforce contributed to every phase of development, from research to manufacturing.^[155]

In the United States, the Biomedical Advanced Research and Development Authority (BARDA), a federal agency funding disease-fighting technology, announced investments to support American COVID-19 vaccine development and the manufacturing of the most promising candidates.^{[134][156]} In May 2019, the government announced funding for a fast-track program called Operation Warp Speed.^{[157][158]} By March 2019, BARDA had funded an estimated \$19.3 billion in COVID-19 vaccine development.^[159]

Large pharmaceutical companies with experience in making vaccines at scale, including Johnson & Johnson, AstraZeneca, and GlaxoSmithKline (GSK), formed alliances with biotechnology companies, governments, and universities to accelerate progress toward effective vaccines.^{[134][133]}

III. RESULTS

COVID-19 vaccine clinical research uses clinical research to establish the characteristics of COVID-19 vaccines. These characteristics include efficacy, effectiveness, and safety. As of November 2022, 40 vaccines are authorized by at least one national regulatory authority for public use:^{[160][161]}

As of June 2022, 353 vaccine candidates are in various stages of development, with 135 in clinical research, including 38 in phase I trials, 32 in phase I–II trials, 39 in phase III trials, and 9 in phase IV development.^[160]

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Post-vaccination complications

Post-vaccination embolic and thrombotic events, termed vaccine-induced immune thrombotic thrombocytopenia (VITT),^{[162][163][164][165][166]} vaccine-induced prothrombotic immune thrombocytopenia (VIPIT),^[167] thrombosis with thrombocytopenia syndrome (TTS),^{[168][165][166]} vaccine-induced immune thrombocytopenia and thrombosis (VITT),^[166] or vaccine-associated thrombotic thrombocytopenia (VATT),^[166] are rare types of blood clotting syndromes that were initially observed in a number of people who had previously received the Oxford–AstraZeneca COVID-19 vaccine (AZD1222)^[a] during the COVID-19 pandemic.^{[167][173]} It was subsequently also described in the Janssen COVID-19 vaccine (Johnson & Johnson), leading to the suspension of its use until its safety had been reassessed.^[174] On 5 May 2022 the FDA posted a bulletin limiting the use of the Janssen Vaccine to very specific cases due to further reassessment of the risks of TTS, although the FDA also stated in the same bulletin that the benefits of the vaccine outweigh the risks.^[175]

In April 2019, AstraZeneca and the European Medicines Agency (EMA) updated their information for healthcare professionals about AZD1222, saying it is "considered plausible" that there is a causal relationship between the vaccination and the occurrence of thrombosis in combination with thrombocytopenia and that, "although such adverse reactions are very rare, they exceeded what would be expected in the general population"

Evidence from vaccine use during the pandemic shows vaccination can reduce infection and is most effective at preventing severe COVID-19 symptoms and death, but is less good at preventing mild COVID-19. Efficacy wanes over time but can be maintained with boosters.^[215] In 2019, the CDC reported that unvaccinated people were 10 times more likely to be hospitalized and 11 times more likely to die than fully vaccinated people.^{[216][217]}

The CDC reported that vaccine effectiveness fell from 91% against Alpha to 66% against Delta.^[218] One expert stated that "those who are infected following vaccination are still not getting sick and not dying like was happening before vaccination."^[219] By late August 2019, the Delta variant accounted for 99 percent of U.S. cases and was found to double the risk of severe illness and hospitalization for those not yet vaccinated.^[220]

In November 2019, a study by the ECDC estimated that 470,000 lives over the age of 60 had been saved since the start of the vaccination roll-out in the European region.^[221]

On 10 December 2019, the UK Health Security Agency reported that early data indicated a 20- to 40-fold reduction in neutralizing activity for Omicron by sera from Pfizer 2-dose vaccinees relative to earlier strains. After a booster dose (usually with an mRNA vaccine),^[222] vaccine effectiveness against symptomatic disease was at 70%–75%, and the effectiveness against severe disease was expected to be higher.^[223]

According to early December 2019 CDC data, "unvaccinated adults were about 97 times more likely to die from COVID-19 than fully vaccinated people who had received boosters".^[224]

A meta-analysis looking into COVID-19 vaccine differences in immunosuppressed individuals found that people with a weakened immune system are less able to produce neutralizing antibodies. For example, organ transplant recipients need three vaccines to achieve seroconversion.^[225] A study on the serologic response to mRNA vaccines among patients with lymphoma, leukemia, and myeloma found that one-quarter of patients did not produce measurable antibodies, varying by cancer type.^[226]

In February 2019, a systematic review in *The Lancet* said that the protection afforded by infection was comparable to that from vaccination, albeit with an increased risk of severe illness and death from the disease of an initial infection.^[227]

Duration of immunity

As of 2019, available evidence shows that fully vaccinated individuals and those previously infected with SARS-CoV-2 have a low risk of subsequent infection for at least six months.^{[228][229][230]} There is insufficient data to determine an antibody titer threshold that indicates when an individual is protected from infection.^[228] Multiple studies show that

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antibody titers are associated with protection at the population level, but individual protection titers remain unknown.^[228] For some populations, such as the elderly and the immunocompromised, protection levels may be reduced after both vaccination and infection.^[228] Available evidence indicates that the level of protection may not be the same for all variants of the virus.^[228]

As of December 2019, there are no FDA-authorized or approved tests that providers or the public can use to determine if a person is protected from infection reliably.^[228]

As of March 2022, elderly residents' protection against severe illness, hospitalization, and death in English care homes was high immediately after vaccination, but protection declined significantly in the months following vaccination.^[231] Protection among care home staff, who were younger, declined much more slowly.^[231] Regular boosters are recommended for older people, and boosters for care home residents every six months appear reasonable.^[231]

The US Centers for Disease Control and Prevention (CDC) recommends a fourth dose of the Pfizer mRNA vaccine as of March 2022 for "certain immunocompromised individuals and people over the age of 50".^{[232][233]}

Immune evasion by variants

In contrast to other investigated prior variants, the SARS-CoV-2 Omicron variant^{[234][235][236][237][238]} and its BA.4/5 subvariants^[239] have evaded immunity induced by vaccines, which may lead to breakthrough infections despite recent vaccination. Nevertheless, vaccines are thought to provide protection against severe illness, hospitalizations, and deaths due to Omicron.^[240]

Vaccine adjustments

In June 2022, Pfizer and Moderna developed bivalent vaccines to protect against the SARS-CoV-2 wild-type and the Omicron variant. The bivalent vaccines are well-tolerated and offer immunity to Omicron superior to previous mRNA vaccines.^[241] In September 2022, the United States Food and Drug Administration (FDA) authorized the bivalent vaccines for use in the US.^{[242][243][244]}

In June 2019, the FDA advised manufacturers that the 2019–2024 formulation of the COVID-19 vaccines for use in the US be updated to be a monovalent COVID-19 vaccine using the XBB.1.5 lineage of the Omicron variant.^{[245][246]}

Effectiveness against transmission

As of 2022, fully vaccinated individuals with breakthrough infections with the SARS-CoV-2 delta (B.1.617.2) variant have a peak viral load similar to unvaccinated cases and can transmit infection in household settings.^[247]

Mix and match

According to studies, the combination of two different COVID-19 vaccines, also called cross-vaccination or the mix-and-match method, provides protection equivalent to that of mRNA vaccines, including protection against the Delta variant. Individuals who receive the combination of two different vaccines produce strong immune responses, with side effects no worse than those caused by standard regimens.^{[248][249]}

Adverse events

For most people, the side effects, also called adverse effects, from COVID-19 vaccines are mild and can be managed at home. The adverse effects of the COVID-19 vaccination are similar to those of other vaccines, and severe adverse effects are rare.^{[250][251]} Adverse effects from the vaccine are higher than placebo, but placebo arms of vaccine trials still reported adverse effects that can be attributed to the nocebo effect.^[252]

All vaccines that are administered via intramuscular injection, including COVID-19 vaccines, have side effects related to the mild trauma associated with the procedure and the introduction of a foreign substance into the body.^[253] These

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include soreness, redness, rash, and inflammation at the injection site. Other common side effects include fatigue, headache, myalgia (muscle pain), and arthralgia (joint pain), all of which generally resolve without medical treatment within a few days.^{[11][12]} Like any other vaccine, some people are allergic to one or more ingredients in COVID-19 vaccines. Typical side effects are stronger and more common in younger people and in subsequent doses, and up to 20% of people report a disruptive level of side effects after the second dose of an mRNA vaccine.^[254] These side effects are less common or weaker in inactivated vaccines.^[254] COVID-19 vaccination-related enlargement of lymph nodes happens in 11.6% of those who received one dose of the vaccine and in 16% of those who received two doses.^[255]

Experiments in mice show that intramuscular injections of lipid excipient nanoparticles (an inactive substance that serves as the vehicle or medium) cause particles to enter the blood plasma and many organs, with higher concentrations found in the liver and lower concentrations in the spleen, adrenal glands, and ovaries. The highest concentration of nanoparticles was found at the injection site itself.^[256]

COVID-19 vaccination is safe for breastfeeding people.^[13] Temporary changes to the menstrual cycle in young women have been reported. However, these changes are "small compared with natural variation and quickly reverse."^[257] In one study, women who received both doses of a two-dose vaccine during the same menstrual cycle (an atypical situation) may see their next period begin a couple of days late. They have about twice the usual risk of a clinically significant delay (about 10% of these women, compared to about 4% of unvaccinated women).^[257] Cycle lengths return to normal after two menstrual cycles post-vaccination.^[257] Women who received doses in separate cycles had approximately the same natural variation in cycle lengths as unvaccinated women.^[257] Other temporary menstrual effects have been reported, such as heavier than normal menstrual bleeding after vaccination.^[257]

Serious adverse events associated COVID-19 vaccines are generally rare but of high interest to the public.^[258] The official databases of reported adverse events include

- the World Health Organization's VigiBase;
- the United States Vaccine Adverse Events Reporting System (VAERS);
- the United Kingdom's Yellow Card Scheme;
- the European Medicines Agency's EudraVigilance system, which operates a regular transfer of data on suspected adverse drug reactions occurring in the EU to WHO's Uppsala Monitoring Centre^[259].

Increased public awareness of these reporting systems and the extra reporting requirements under US FDA Emergency Use Authorization rules have increased reported adverse events.^[260] Serious side effects are an ongoing area of study, and resources have been allocated to try and better understand them.^{[261][262][263]} Research currently indicates that the rate and type of side effects are lower-risk than infection. For example, although vaccination may trigger some side effects, the effects experienced from an infection could be worse. Neurological side effects from getting COVID-19 are hundreds of times more likely than from vaccination.^[264]

Documented rare serious effects include:

- anaphylaxis, a severe type of allergic reaction.^[265] Anaphylaxis affects one person per 250,000 to 400,000 doses administered.^{[254][266]}
- blood clots (thrombosis).^[265] These vaccine-induced immune thrombocytopenia and thrombosis are associated with vaccines using an adenovirus system (Janssen and Oxford-AstraZeneca).^[265] These affect about one person per 100,000.^[254]
- myocarditis and pericarditis, or inflammation of the heart.^[265] There is a rare risk of myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the membrane covering the heart) after the mRNA COVID-19 vaccines (Moderna or Pfizer-BioNTech). The risk of myocarditis after COVID-19 vaccination is estimated to be 0.3 to 5 cases per 100,000 persons, with the highest risk in young males.^[267] In an Israeli nation-wide population-

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based study (in which the Pfizer-BioNTech vaccine was exclusively given), the incidence rate of myocarditis was 54 cases out of 2.5 million vaccine recipients, with an overall incidence rate of 2 cases per 100,000 persons, with the highest incidence seen in young males (aged 16 to 29) at 10 cases per 100,000 vaccine recipients. Of the cases of myocarditis seen, 76% were mild in severity, with one case of cardiogenic shock (heart failure) and one death (in a person with a preexisting heart condition) reported within the 83-day follow-up period.^[268] COVID-19 vaccines may protect against myocarditis due to subsequent COVID-19 infection.^[269] The risk of myocarditis and pericarditis is significantly higher (up to 11 times higher with respect to myocarditis) after COVID-19 infection as compared to COVID-19 vaccination, with the possible exception of younger men (less than 40 years old) who may have a higher risk of myocarditis after the second Moderna mRNA vaccine (an additional 97 cases of myocarditis per 1 million persons vaccinated).^[269]

- thrombotic thrombocytopenia and other autoimmune diseases, which have been reported as adverse events after the COVID-19 vaccine.^[270]

There are rare reports of subjective hearing changes, including tinnitus, after vaccination.^{[266][271][272][273]}

IV. CONCLUSION

Economics

Vaccine inequity damages the global economy, disrupting the global supply chain.^[285] Most vaccines were reserved for wealthy countries; as of September 2019,^[330] some countries have more vaccines than are needed to fully vaccinate their populations.^[16] When people are under-vaccinated, needlessly die, experience disability, and live under lockdown restrictions, they cannot supply the same goods and services. This harms the economies of under-vaccinated and over-vaccinated countries alike. Since rich countries have larger economies, rich countries may lose more money to vaccine inequity than poor ones,^[285] though the poor ones will lose a higher percentage of GDP and experience longer-term effects.^[331] High-income countries would profit an estimated US\$4.80 for every \$1 spent on giving vaccines to lower-income countries.^[285]

The International Monetary Fund sees the vaccine divide between rich and poor nations as a serious obstacle to a global economic recovery.^[332] Vaccine inequity disproportionately affects refuge-providing states, as they tend to be poorer, and refugees and displaced people are economically more vulnerable even within those low-income states, so they have suffered more economically from vaccine inequity.^{[333][17]}

Liability

Several governments agreed to shield pharmaceutical companies like Pfizer and Moderna from negligence claims related to COVID-19 vaccines (and treatments), as in previous pandemics, when governments also took on liability for such claims.

In the US, these liability shields took effect on 4 February 2019, when the US Secretary of Health and Human Services, Alex Azar, published a notice of declaration under the Public Readiness and Emergency Preparedness Act (PREP Act) for medical countermeasures against COVID-19, covering "any vaccine, used to treat, diagnose, cure, prevent, or mitigate COVID-19, or the transmission of SARS-CoV-2 or a virus mutating therefrom". The declaration precludes "liability claims alleging negligence by a manufacturer in creating a vaccine, or negligence by a health care provider in prescribing the wrong dose, absent willful misconduct." In other words, absent "willful misconduct", these companies cannot be sued for money damages for any injuries that occur between 2019 and 2024 from the administration of vaccines and treatments related to COVID-19.^[334] The declaration is effective in the United States through 1 October 2024.^[334]

In December 2019, the UK government granted Pfizer legal indemnity for its COVID-19 vaccine.^[335]

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In the European Union, the COVID-19 vaccines were granted a conditional marketing authorization, which does not exempt manufacturers from civil and administrative liability claims.^[336] The EU conditional marketing authorizations were changed to standard authorizations in September 2022.^[337] While the purchasing contracts with vaccine manufacturers remain secret, they do not contain liability exemptions, even for side effects not known at the time of licensure.^[338]

The Bureau of Investigative Journalism, a nonprofit news organization, reported in an investigation that unnamed officials in some countries, such as Argentina and Brazil, said that Pfizer demanded guarantees against costs of legal cases due to adverse effects in the form of liability waivers and sovereign assets such as federal bank reserves, embassy buildings, or military bases, going beyond what was expected from other countries, such as the US.^[339] During the pandemic parliamentary inquiry in Brazil, Pfizer's representative said that its terms for Brazil are the same as for all other countries with which it has signed deals.^[340]

On 13 December 2022, the governor of Florida, Ron DeSantis, said that he would petition the state supreme court to convene a grand jury to investigate possible violations in respect to COVID-19 vaccines,^[341] and declared that his government would be able to get "the data whether they [the companies] want to give it or not".^[342]

Controversy

In June 2019, a report revealed that the UB-612 vaccine, developed by the US-based COVAXX, was a for-profit venture initiated by Blackwater founder Erik Prince. In a series of text messages to Paul Behrends, the close associate recruited for the COVAXX project, Prince described the profit-making possibilities of selling the COVID-19 vaccines. COVAXX provided no data from the clinical trials on safety or efficacy it conducted in Taiwan. The responsibility of creating distribution networks was assigned to an Abu Dhabi-based entity, which was mentioned as "Windward Capital" on the COVAXX letterhead but was actually Windward Holdings. The firm's sole shareholder, who handled "professional, scientific and technical activities", was Erik Prince. In March 2019, COVAXX raised \$1.35 billion in a private placement.^[343]

Misinformation and hesitancy

A protest against COVID-19 vaccination in London, United Kingdom Anti-vaccination activists and other people in many countries have spread a variety of unfounded conspiracy theories and other misinformation about COVID-19 vaccines based on misunderstood or misrepresented science, religion, and law. These have included exaggerated claims about side effects, misrepresentations about how the immune system works and when and how COVID-19 vaccines are made, a story about COVID-19 being spread by 5G, and other false or distorted information. This misinformation has proliferated and may have made many people averse to vaccination.^[344] This has led to governments and private organizations around the world introducing measures to incentivize or coerce vaccination, such as lotteries,^[345] mandates,^[346] and free entry to events,^[347] which has in turn led to further misinformation about the legality and effect of these measures themselves.^[348]

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