

**CONCEPT OF VACCINE DEVELOPMENT AND UPDATES
ON ADVERSE EFFECTS OF COVID-19 VACCINATION**

ABSTRACT

Coronavirus disease-2019 (COVID-19) is an outbreak on a scale unseen in modern human history. And over two years after the outbreak began, there are 271 million reported fatalities and more than 5.32 million mortalities globally. Vaccination has been the most successful medical intervention in the last century to minimize mortality and suffering due to infectious illnesses. Only the discovery and dissemination of an effective vaccine will probably result at the end of this pandemic. Tremendous attempts have also been made to develop secure and convenient vaccinations. Vaccination is an efficient method of preventing viral illness, stopping its spread, and developing protective immunity. Improved understanding of protective immunity and significant advances in gene editing has enabled the development of a wide range of novel vaccines by manipulating sugars, RNA, proteins, and DNA. The development of attenuated mutants, the expression of prospective antigens in live vectors, and the purifying and direct production of antigens in novel systems have all greatly enhanced vaccination science. Several researchers have been working to assess the effectiveness and toxicity of potential vaccinations against new COVID-19. Furthermore, it is critical to assess the impact of immunization on the severity of illness. Vaccination is currently the most efficient method of regulating animal and human viral illnesses, either by avoiding fatality or lowering suffering.

Keywords: SARS-CoV-2; Vaccine; Vaccine ADRs; Vaccine Platform;

INTRODUCTION

Vaccination's origins seem to be lost over history, described as an apparent endeavor to utilize part or all of a bacterial virus to safeguard against that microorganism. Vaccination most likely evolved from homeopathic ideas about little quantities of illness guarding against

major disease, which were empirically validated by consumption of minute amounts of toxin to avoid deadly deliberate poisoning of rulers by competitors (1). When Koch, Merieux, Pasteur, and Ramon discovered the germ hypothesis and created vaccinations relying on inactivated (killed) or live-attenuated pathogens and toxins, the vaccination golden era began (toxoids). In infants, these immunizations protected against tuberculosis (TB), tetanus, rabies, pertussis, and diphtheria (2,3). The Food and Drug Administration's (FDA) wide definition of vaccination effectiveness includes two critical variables. To begin, vaccinations should be capable of preventing viral spreading from infected to vulnerable individuals. Secondly, it ought to be beneficial in slowing the progression of the disease while also reducing the need for critical care services. The FDA has established a minimum effectiveness criterion of 50% for the vaccination (4).

The novel CoV-19 (nCoV-19) outbreak has created a serious worldwide hazard. The causal pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was originally found in early December 2019 in Wuhan, China, and has since been designated as COVID-19 by the World Health Organization (WHO) (5,6). Since many nations continue to combat new CoV-19 illnesses, vaccine production has been intensified to build protection against the virus and cease transmission. Figure 1 depicts the typical vaccine development cycle, which is lengthy and laborious. Recent developments in SARS-CoV-2 vaccine development have shown that research innovations are cumulative, drawing on prior knowledge. This enables the unprecedented pace with which the SARS-CoV-2 vaccinations have been manufactured. Vaccines are biological products that give active acquired immunity to a specific infectious illness. They accomplish this by inducing an immune reaction to an antigen, which is a chemical located in the virus (7). The effectiveness of vaccinations in combating the CoV-19 outbreak is determined by several criteria, including their efficacy, how quickly they are developed, licensed, and supplied, protection against new variations, and the number of people immunized. Several health agencies are attempting to ensure that authorized CoV-19 vaccinations are as efficient as possible to have the most impact on the COVID-19 outbreak. A vaccination is an important weapon in the fight against CoV disease, and deploying the tools we now have has several saving and population health advantages (8). The S protein is the primary target for CoV-19 vaccine production, intending to elicit virus-neutralizing antibodies (NAbs) as immunological correlates to vaccination protection (9).

The rapid release of viable vaccinations in the United States (US) and other nations with substantial SARS-CoV-2 infections would be a significant step toward preventing the

worldwide epidemic. Nevertheless, using a non-effective vaccination may aggravate the outbreak since social approval of vaccination may reduce the adoption of other control strategies. As a result, we require a rapid and convenient assessment of the effectiveness of CoV-19 vaccinations based on clinically meaningful outcomes (10). Despite potential vaccine research advances, the timescale for public access is currently unexplained, needing proper safety screening and thorough demonstration of efficacy. This is exacerbated more by the fact that a large number of CoV clinical features essential to vaccination efforts remain unknown, and vaccine production and distribution challenges, such as proper storage/transportation, could further hinder diffusion (11).

Several trials have been carried out all over the world to assess the effectiveness and toxicity of experimental vaccinations against SARS-CoV-2. Interim findings from many large-scale phases 3 randomized, observer-blinded, placebo-controlled clinical studies have shown high efficacy, considerably beyond the FDA and WHO requirements of 50% symptomatic illness reduction. However, those studies have just been running for a few weeks, and the information they possess thus yet can only speak to short-term efficacy (12). Since there is limited effective vaccination, the creation of a safe and effective COVID-19 vaccination, which is critical for disease prevention, has piqued the interest of the entire world. SARS-CoV-2 vaccines were created quickly and demonstrated excellent efficacy in various randomized clinical trials (RCTs) and observational studies (13).

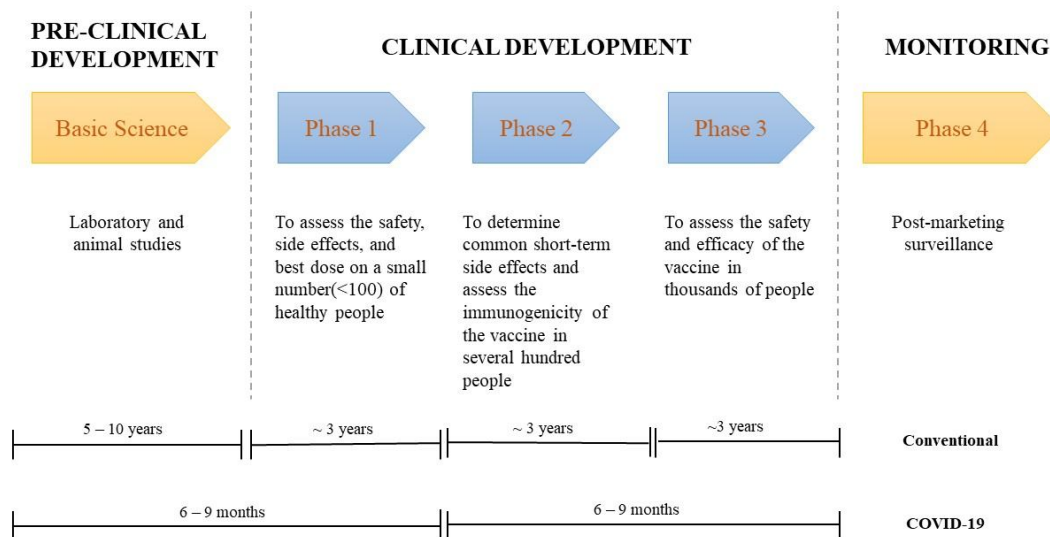


Figure 1. COVID-19 vaccine development versus traditional vaccine development.

COVID-19 VACCINE DEVELOPMENT

So far, vaccine development has been a lengthy process that normally takes 10-15 years, as seen in Figure 1. The fastest vaccination to be produced and licensed for use was for mumps, which took about 5 years. As a result, developing a vaccine for SARS-CoV-2 in 12–24 months is a concern. The initial stage of vaccine development is an exploration step that involves basic laboratory bench research and computer modelling to uncover natural or synthetic antigens that might be employed as a vaccine candidate, perhaps preventing or curing the disease. The second step consists of pre-clinical investigations, which include cell-culture or tissue-culture systems as well as animal trials to examine the security of the potential vaccine as well as its immunogenicity, or capacity to elicit an immune reaction. After efficacy in the above steps, human clinical trials begin, to evaluate the safety and immunogenicity in small groups, then large groups, through three phases, as detailed below (14–16).

Phase 1 - Safety: The vaccine was introduced to people for the very first time at this phase. As a secondary consequence, the vaccination of a limited group of healthy and immunocompetent persons to test for safety, optimum dosage, and the immunological reaction was done (17).

Phase 2 - Expanded Safety: The vaccine is administered to hundreds of patients, who are divided into population characteristics. These, once again, test for efficacy, optimal dose, and duration between dosages, as well as immunological response as a secondary consequence (18).

Phase 3 - Efficacy: It is accomplished by administering vaccines to thousands of individuals to measure efficacy, tolerability, and toxicity. Finally, the data is analyzed and assessed before being submitted for clearance to regulatory agencies (19).

After completion of the first 3 phases of clinical trials, in which their efficacy and toxicity were to find out. It moves to phase 4 (20):

a. Examine and Approval: Normally, regulatory organizations such as the FDA in the US or the European Medicines Agency (EMA) in the European Union (EU) must discuss the findings of clinical studies and determine if the vaccine is suitable for authorization.

b. Manufacturing and Post-Marketing Surveillance: This is conducted after the vaccine has been released to the public and is checked for overall efficacy in the community. They also document any negative side effects that may occur when the vaccine is widely used.

TYPES OF VACCINE

Vaccines are one of the most cost-effective and hence critical healthcare programs (21). There are currently 136 vaccine candidates in clinical trials and 194 candidates in pre-clinical research against SARS-CoV-2 across the world. The platforms are classified as 'conventional' techniques (inactivated or live-virus vaccinations), platforms that have lately resulted in licensed vaccines (recombinant protein vaccines and vectored vaccines), and platforms that have yet to produce a licensed vaccine (RNA and DNA vaccines) (Table 1) (22–24).

Table 1. Vaccine Platforms and Their Potential Benefits and Drawbacks (25–27).

Vaccine platform	Antigen	Advantages	Disadvantages	Existing Vaccine examples
DNA	S protein	Fast to produce. Scalable. Non-infectious. Reusable platform. Stable at room temperature. High safety.	May need special delivery devices. Cytotoxic and humoral immunity, the titers remain low. Insertion of foreign DNA into the host genome may cause abnormalities in the cell. May induce the antibody production against itself.	N.A.
Inactivated	Whole virion	Broad antigenic profile. Easy to prepare. Safe.	Reduced immune response. Requirement for biosafety facilities. Lower purity. Require the booster shots to maintain the immunity. Furthermore, large amounts of viruses need to be handled and the integrity of the immunogenic particles must be maintained.	Hepatitis A Polio (IPV) Rabies Influenza

Live-attenuated	Whole virion	<p>Strong and long-lasting immune response.</p> <p>Broad antigenic profile.</p> <p>Rapid development.</p> <p>Less adverse effects.</p> <p>Induce a high immune response.</p>	<p>The potential risk of disease.</p> <p>Requirement for biosafety facilities.</p> <p>Requires extensive accessory testing to establish safety and efficacy.</p> <p>There is a probability of nucleotide substitution during viral replication, resulting in the creation of recombinants postvaccination.</p>	<p>Smallpox</p> <p>Tuberculosis (BCG)</p> <p>Measles</p> <p>Polio (OPV)</p>
RNA	S protein	<p>Fast to produce.</p> <p>Non-infectious.</p> <p>No genome integration risk.</p> <p>Reusable platform.</p> <p>Stimulates strong T cell response.</p> <p>Simple formulations</p> <p>Easy to design.</p> <p>The higher degree of adaptability.</p>	<p>Need extremely low temperatures for storage and transportation.</p> <p>Need special delivery systems.</p> <p>Safety issues with reactogenicity have been reported for various RNA based vaccines.</p> <p>Shows instability.</p>	COVID-19 (EUA)
Nonreplicating viral vector	S protein	<p>Fast to produce.</p> <p>Reusable platform.</p> <p>Strong in both cell- and antibody-mediated immune responses.</p>	<p>Pre-existing immunity against the vector.</p> <p>Risk of adverse reactions.</p>	N.A.
Protein subunit	S protein	<p>Non-infectious.</p> <p>Targeting key antigens.</p>	<p>Limited capability in inducing cell-mediated immunity.</p> <p>The adjuvant is often needed.</p> <p>Induce an immune response.</p> <p>Memory for future</p>	<p>Hepatitis B (HBV)</p> <p>DTP (diphtheria, tetanus, and pertussis)</p>

Replicating viral vector	S protein	Fast to produce. Lower doses/single dose. Reusable platform. Strong in both cell- and antibody-mediated immune response. Less infectious.	Pre-existing immunity against the vector. Risk of adverse reactions.	responses is doubtful. Ebola (EUA)
Virus-Like Particle	S protein	Non-infectious. Broad antigenic profile. Induces high cellular and humoral immune responses.	Limited immunogenicity. Lower purity.	Hepatitis B (HBV) Papillomavirus (HPV)

Conventional Whole Virus Vaccines

Conventional vaccine development techniques, while incredibly efficient in tackling highly infectious illnesses like measles, need vast quantities of viruses or bacteria that can survive for weeks. These germs are then used as the essential component of a vaccine, known as an antigen, which alerts the human immune system that certain foreign organisms have infiltrated the body and must be destroyed. Traditional vaccine development procedures offer the benefit of becoming recognized and well-studied, but these vaccines may take longer to produce (28).

- Inactivated vaccines

When a novel pathogen appears, such as CoV-19, due to a lack of knowledge of pathophysiology and therefore a long time to produce efficient therapies, the speedy and easy creation of a vaccine against the developing infectious illness is critical. As a result, because we have expertise with numerous commercial inactivated vaccines against other viral infections, the traditional technique of employing inactivated, cell-culture-based viruses is likely to be the quickest and easiest option for CoV vaccine development. Inactivated vaccinations may keep the S protein in its natural shape. Several investigations have shown that vaccinations based on complete, inactivated CoV elicit significant levels of Nab in animal models (29).

Over the last 70 years, inactivated vaccine platforms have been frequently employed. Inactivated vaccines are created by inactivating viruses using chemicals, ultraviolet light, and heat. The inactivation of the bacterium results in a safe vaccination, especially for immunocompromised individuals. These vaccinations, however, produce a lower immune response than live vaccines and require additional booster doses. These inactivated vaccines take longer to develop because the virus must be cultivated in the lab before being inactivated. Several inactivated SARS-CoV-2 vaccine candidates are now in clinical studies, with a few more in preclinical testing (30).

- Live attenuated vaccines

Live-attenuated vaccinations (LAVs), which have a long history of effectiveness, such as smallpox and polio vaccinations, are analogous to natural infections in that they produce a wide variety of environmental viral antigens over a lengthy amount of time and are frequently more immunogenic than non-replicating vaccines (29). LAVs have been used to combat infectious diseases such as yellow fever, mumps, measles, rubella, polio, and chickenpox. The S protein is encoded by the highly attenuated modified vaccinia virus Ankara, recombinant adeno-associated virus, or an attenuated parainfluenza virus (31).

Recombinant Viral Protein-Based Vaccines

The transmission of one or more genes encoding a target antigen within an unrelated, manufactured virus is referred to as viral vector technology. The viral vector might be either replication-competent or replication-incompetent. The recombinant vesicular stomatitis virus-Zaire Ebola virus (rVSV-ZEBOV) vaccine is presently the only vector vaccine approved and licensed for clinical application, and it is only developed and used in restricted quantities (32).

- Protein Subunit Vaccines

The struggle against the SARS-CoV-2 outbreak is far from over, and the discovery of safe and effective vaccinations, as well as their mass production, is urgently needed. Although the rate at which vaccines are presently being produced around the world demonstrates the importance of this endeavor, the reality that certain vaccines failed to stop infection in humans despite showing promising results in pre-clinical studies, and that others have been linked to complications are all warning signs that there is little to no room for error. Extensive long-term studies that effectively prove that vaccinations are safe are critical to ensuring that the impact is low. Furthermore, the person should have long-term protection

against SARS-CoV-2 following vaccination. This is critical since COVID-19 has been demonstrated to have a rather significant reinfection capability, in which a person experiences signs after catching the virus again, albeit in a much weaker form. As a result, the immunizations protection should extend for several months, if not years (33).

- **Virus-like Particle Vaccines**

Virus-like particles (VLPs) are a type of protein vaccination that consists of entirely artificial nanoparticles that mimic viruses. VLPs are composed of part or all of the proteins that make up the viral capsid, instead of a single protein. They are comparable to live attenuated or inactivated vaccines in that they can elicit powerful cellular and humoral immune responses with no chance of reversal since they contain no viral genetic material. They have been evaluated for a variety of diseases, and preclinical SARS-CoV-1-VLPs. VLP Nanoparticles are protein particles that self-assemble and are not always produced from viral capsid proteins (34).

Viral Vector Vaccines

Along with conventional vaccinations, viral vectors are frequently utilized, in which the genome of one virus has been utilized to convey the antigen of some other pathogen, allowing the creation of a virus production platform technology. These technologies are now accessible for large-scale vaccine manufacturing. The disadvantages of such vaccines have included a wide range of purifying procedures, as well as the necessity for accurate validation of the quality and viral function (35).

- **Nonreplicating Viral Vector Vaccines**

An unconnected virus, such as measles or adenovirus, is genetically modified to express the desired gene. These are regarded as safe but necessitate boosting dosages to develop long-term protection. These vaccinations have not yet been approved for use. Ad5-nCoV by CanSino Biological Inc./Beijing Institute of Biotechnology is one example of a COVID-19 vaccine, as is ChAdOx-nCoV-19 by the University of Oxford (36).

- **Replicating Viral Vector Vaccines**

Viral vector vaccines employ replication-deficient viruses that have been genetically modified to produce the antigen of relevance in the host genome. HIV, TB, malaria, and the Ebola virus all have replication-incompetent adenoviruses. This vaccination strategy has had varying degrees of effectiveness, which is frequently hampered by pre-existing immunity to

the adenovirus vector. Using adenoviruses against which there is little pre-existing immunity in the US and EU, two vaccines have shown early promise: adenovirus serotype 26 vector vaccine (Ad26.CoV2.S; Johnson & Johnson) and chimp adenovirus vector vaccine (ChAdOx; AstraZeneca). Both appear to be effective in avoiding CoV-19 - related hospitalization and mortality, although their effectiveness in reducing clinical illness, especially disease induced by the new COVID-19 variants, varies (37).

Nucleic Acid Vaccines

Nucleic acid therapies have developed as possible replacements for traditional vaccination techniques. In 1990, the first reporting of effective use of in-vitro transcribed (IVT) mRNA in animals was reported, when reporter gene mRNAs were injected into mice and protein synthesis was identified (38).

- DNA vaccines

In the last few decades, the functionality of synthetic DNA technology has evolved tremendously. A mixture of developments in DNA delivery into cells, enhanced tolerability, and numerous iterations in genetic designs and compositions have resulted in a more powerful and effective vaccine framework with several characteristics essential for quick vaccine development and implementation against epidemics (39). DNA technology is safe and more resilient in theory than traditional vaccination techniques. Plasmids are non-living and nonreplicating, therefore there is no chance of illness reversal or opportunistic infections. Research into merging various vaccination systems with DNA, improved ways of administration, and novel molecular adjuvants is presently ongoing (40). In contrast to most vaccinations that target humoral immunity, they boost the cellular immune response. This sort of vaccine formulation has promise for successful viral hepatitis or viral pathology prevention due to its great antigenic diversity. Although it avoids the entrance of a live viral strain into the organism, this sort of vaccination may pose carcinogenic hazards by integrating DNA into the host cell's chromosomes or by suppressing tumor suppressor genes (41).

- RNA vaccines

The field of mRNA vaccines expanded in 2000 with the introduction of a novel vaccine strategy that allowed the delivery of naked mRNA by intradermal injection (42). mRNA has emerged as a viable tool for treating in the realms of vaccine production and protein replacement treatment as a result of significant technological progress and research

expenditure over the last decade. The use of mRNA provides several advantages over subunit, inactivated, and live attenuated viral vaccines, as well as DNA-based vaccines. First, there is no chance of infection or insertional mutagenesis since mRNA is a non-infectious, non-integrating platform. Furthermore, mRNA is destroyed by natural physiological processes, and its in-vivo half-life may be controlled by a variety of changes and delivery mechanisms. To improve the safety record, the mRNA's intrinsic immunogenicity can be reduced. Second, in terms of effectiveness, certain changes make mRNA more stable and translatable. By forming mRNA into carrier molecules, which enable fast absorption and expression in the cytoplasm, effective in vivo administration may be accomplished. Because mRNA is the smallest genetic vector, anti-vector immunity is minimized, and mRNA vaccines may be given frequently. Third, because of the high yields of in vitro transcription processes, mRNA vaccines have the promise of quick, low-cost, and scalable manufacture (43–45).

Following successful clinical studies, two CoV-19 mRNA vaccines (from Biontech/Pfizer and Moderna) were recently approved in several nations (US and EU) and are now in general use. Lipid nanoparticles (LNPs) are used to administer both vaccines. These vaccines, which include 30g and 100g RNA, must be stored at -70°C (Biontech) or -20°C (Moderna) due to their instability. According to statistics from phase 3 clinical studies, infection prevention rates after two injections were as high as 95 percent and 94.1 percent, respectively, with manageable side effects (46).

VACCINES FOR COVID-19 BY DIFFERENT COUNTRIES

- **University of Oxford/AstraZeneca, UK**

Oxford/AstraZeneca

The Oxford-AstraZeneca vaccine is built on a replication-deficient Chimpanzee Adenovirus vector (ChAdOx1) carrying a codon-optimized S protein. Efficacy data from a blinded, randomized, controlled trial conducted in the United Kingdom (UK) and Brazil, in which the control group received meningococcal vaccination, revealed AZD1222 vaccine efficacy of 62.1 percent in the standard dose scheme (two standard doses, 28 days apart), but 90 percent

efficacy in the low dose scheme (one low dose followed by a standard dose, 28 days apart). Immunocompromised volunteers were not included in the experiment, and only a small number of senior people (over 65) were represented, sparking a controversy about the demographic for the EMA conditional marketing authorization. At the time of writing, certain European nations (ENs) have temporarily halted its usage as a precautionary measure due to reports of unusual blood coagulation issues among recipients of this vaccine. However, the WHO and the EMA believe that the advantages of the AZD1222 vaccine exceed the dangers, and hence recommend that immunizations continue (47).

Following reports of thromboembolic events, some with fatal consequences, among patients who had received this vaccine, several ENs suspended immunization against COVID-19 with the ChAdOx1 nCoV-19 (AZD1222) vaccine from Oxford-AstraZeneca in early and mid-March 2021. On March 18, 2021, the EMA ruled that "benefits still exceed the risks despite suspected relationship to uncommon blood clots with low blood platelets" concerning the Oxford-AstraZeneca CoV-19 vaccine. This prompted some ENs to quickly resume immunization with the Oxford-AstraZeneca COVID-19 vaccine, while others – notably Denmark – elected to wait for additional investigation into the potential link between the vaccine and incidents of thromboembolism (48).

- **Moderna/NIAID, USA**

mRNA-1273

Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), within the National Institutes of Health (NIH), developed mRNA-1273, an LNPs – encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein, fairly soon after the SARS-CoV-2 genetic sequence was established in January 2020. The mRNA-1273 vaccine protected animals in challenging studies and showed promising efficacy and immunogenicity in early-stage human research (49). The pre-fusion S protein is encoded by this lipid nanoparticle encapsulated mRNA vaccine. In Phase III randomized, placebo-controlled trial conducted in 99 centers in the US, people at high risk of CoV-19 infection or its comorbidities were given two intramuscular (IM) doses or placebo 28 days apart, and the vaccine was found to be 94.1 percent effective at preventing COVID-19. Hypersensitivity responses were recorded in 1.5 percent and 1.1 percent of individuals in the vaccination and placebo groups, respectively, with three cases of Bell's palsy in the vaccine group and one case in the placebo group (50). The COVID-19 vaccine mRNA-1273 exhibited strong Nab

titers and has been demonstrated to be extremely effective in avoiding symptomatic CoV-19 illness (51). After a median follow-up of 64 days, the phase 3 study of mRNA-1273 demonstrated 94.1 percent vaccine effectiveness against Covid-19, with tolerable safety and adverse effect characteristics (52).

- **BioNTech SE and Pfizer Inc., USA**

BNT162b2

Following the licensing of the Pfizer-BioNTech mRNA vaccine, BNT162b2, for emergency use on December 8, 2020, the UK became the first nation to begin a covid-19 immunization campaign (53). According to the preliminary results, BNT162b2 has potential effectiveness of greater than 90%. This vaccine is made up of a lipid-enclosed, nucleoside-modified mRNA that encodes the conformation of a mutant COVID-19 spike protein (54). BNT162b2 vaccination should be injected IM at a dose of 0.3 mL containing 30 g nucleoside-modified mRNA in two doses separated by 21 days. The BNT162b2 vaccination was 95% effective against SARS-CoV-2. This effectiveness might be attained at least 7 days following administration of the second dosage. Furthermore, it has been stated that after the first dose, and effectiveness of 52% would be obtained. The FDA confirmed the EUA for Pfizer/BioNTech vaccine to prevent COVID-19 in people aged 15 and up in December 2020 (55). This vaccination stimulates the body's immune response to neutralize the virus, which is reliant on the S protein for entrance via the Angiotensin-Converting Enzyme 2 (ACE2) receptor on type 2 alveolar cells [108]. The BNT162b2 and mRNA-1273 vaccines, which employ mRNA technology, were linked with the best effectiveness in avoiding symptomatic COVID-19 when evaluated to the other vaccinations, according to Rotshild (56).

- **Janssen Pharmaceuticals, USA**

JNJ-78436735 (Johnson & Johnson's)

This is a non-replicating recombinant human adenovirus (Ad) 26 that carries the full-length SARS-CoV-2 S protein, which promotes an antibody response against SARS-CoV-2 infection. Antibody directed against the S protein reduces SARS-CoV-2 viral invasion in type 2 alveolar cells of the lungs, lowering infection severity and morbidity (57,58). Previously, the Johnson & Johnson (J&J) vaccine produced antibodies against SARS-CoV-2 in 90% of persons who got it after the first dosage. The number of antibodies was higher in individuals

who received two doses of the vaccination. According to data given by Johnson & Johnson, one dose of vaccine was 66% effective in avoiding moderate to severe COVID-19 and 100% effective in preventing COVID-19–related hospitalization and mortality. In the tests of this vaccination, no one had a severe allergic reaction, and the vaccine's adverse effects were identical to that of previous immunizations, with 9 percent of volunteers experiencing fever. There did not show up to be any more significant consequences as a result of the immunization (59).

- **Novavax, Inc., USA**

Novavax

Novavax's (US biotechnology corporation) NVX-CoV2373 vaccine contains the full-length SARS CoV-2 spike protein component in glycosylated form. Proline substitutions assist retain the prefusion structure; mutations at the S1/S2 cleavage region shield the spike protein from proteolytic destruction. Except for a slight variation in the S1 subunit and typical interactions between both the spike trimers, the structure of this synthetic spike protein is extremely similar to that of the wild protein. NVX-CoV2373 was originally tested on macaques (*Macaca fascicularis*) that were inoculated with the vaccine and then challenged intranasally and intratracheally with the natural virus (60). According to early results from clinical studies, the SARS-CoV-2 vaccine NVX-CoV2373 is 95.6 percent effective against the original strain of SARS-CoV-2 but also gives protection against the subsequent variants B.1.1.7 (85.6 percent) and B.1.351 (60 percent). Novavax investors' expectations were restored as recently as November 2021, when NVX-CoV2373 gained emergency use authorization in Indonesia and the Philippines, and regulatory filings were finalized in Australia, Canada, New Zealand, and the EU, and India, as well as with WHO (61).

- **Gamaleya Research Institute, Russia**

Sputnik V

The vaccine, also known as Gam-COVID-Vac, employs a heterologous two-dose virus-vector adenovirus method, with Ad26 and Ad5 serving as vectors for the production of the Gamaleya Research Institute's SARS-CoV-2 spike protein (62,63). The vaccine makers reported the findings of a phase III study in February, claiming that it is 91.6 percent effective at avoiding symptomatic COVID-19 infection and 100 percent effective at preventing serious conditions (64). It drew criticism from the scientific community throughout its early stages of

development since Russia accorded its official registration before the phase 3 effectiveness study had even commenced. Despite this, the vaccination has been demonstrated to be 91.6 percent efficacious and has been licensed in at minimum 26 nations. The Russian Direct Investment Fund has sold approximately 327 million doses of Sputnik V to 22 nations, the majority of which are low- and middle-income countries (LMICs), including India, Vietnam, Uzbekistan, and Mexico, Nepal, Egypt, Argentina, Venezuela, and Brazil (65).

- **Sinovac Biotech, China**

CoronaVac

Sinovac, a biopharmaceutical company, manufactures CoronaVac, an inactivated vaccine candidate (Beijing, China). SARSCoV2 virus (CN2 strain) was isolated, grown in Vero cells, chemically inactivated with propiolactone, and combined with alum adjuvant (66). In a Phase 3 study done in Brazil, the CoronaVac was reported to be 50.4 percent effective against all symptomatic sickness and 78 percent effective against mild to severe conditions (67). It has been authorized by 32 nations and jurisdictions and is being used in mass vaccination programmes in low- and middle-income countries, many of which are having covid-19 outbreaks as a result of the development of the SARS-CoV-2 subtypes (68). Although phase 3 clinical trial results are being aggregated in China, Hong Kong, Indonesia, Brazil, Chile, Philippines, and Turkey, the WHO has approved CoronaVac, an inactivated virus vaccine against SARS-CoV-2, for emergency use in several countries, including three the world's six most populated—Brazil, China, and Turkey—which are critical for world dominance of this ailment (69).

- **Wuhan Institute of Biological Products/Sinopharm, China**

Sinopharm

Sinopharm BBIBPCorV is an inactivated vaccine candidate developed by the Beijing Institute of Biological Products of Sinopharm (China). A sample of the WT virus (HB02 strain) was grown in Vero cells, then chemically inactivated using propiolactone before being combined with an aluminum-based adjuvant. The vaccination showed 78.1 percent effectiveness against symptomatic Covid19 infections, according to an interim review of the phase 3 research. A study of 282 Sri Lankans who received the vaccine formulation revealed

a tenfold drop in NAb titers against Beta and a 1.38-fold reduction against Delta when compared to the reference strain (70,71). Although Sinopharm/BBIBP-CoV is the primary vaccine used in many Asian and Middle Eastern nations, evidence of its effectiveness in distinct nations and for different variations is scarce. Furthermore, evidence is scarce on the durability of antibody and T cell responses in fully vaccinated people (72).

- **CanSino Biological Inc./Beijing Institute of Biotechnology, China**

Convidecia

Ad5-nCoV is a single-shot virus-vector vaccine produced by CanSino Biologics and the People's Liberation Army that is the third Chinese vaccine in the international marketplace. Over 70 million vaccine doses have been supplied to LMICs, including Mexico and Pakistan, which sponsored phase 3 effectiveness studies of the vaccine and demonstrated 65.7 percent immunity against symptomatic illnesses (65). Ad5-nCoV was created using the same method that was utilized to create the world's first Ebola vaccine. The vaccine, like AZD1222, employs a weakened Ad to convey genetic instructions regarding SARS-CoV-2 to cells, causing them to make the spike protein, which stimulates an immune response in which SARS-CoV-2 specific antibodies are created (73).

- **Bharat Biotech International Limited, India**

Covaxin

BBV152, commonly known as Covaxin, is a whole virion inactivated SARS-CoV-2 vaccine based on Vero cells is an indigenous COVID-19 vaccine developed by Bharat Biotech in conjunction with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV) (74). It is the first alum-imidazoquinoline adjuvanted vaccination to be authorized for widespread use made up of a toll-like receptor 7/8 agonist molecule (75). The vaccination is given in the form of two intramuscular injections of 6g of inactivated virus, four weeks apart. Recently published phase 3 results showed effectiveness against symptomatic infection of up to 78 percent, severe illness effectiveness of 93.4 percent, and asymptomatic disease effectiveness of 63.6 percent. Despite its worldwide distribution and ability to provide clinically substantial protection, there is minimal data on the mechanism of immunity and immunological response features created by BBV152 (76). The vaccine is identical to CoronaVac in that it employs a fully infective SARS-CoV-2 viral particle made

up of RNA enclosed by a protein shell, but it has been changed such that it cannot multiply (77). According to new research, Covaxin can successfully destroy the recently discovered B.1.1.7 SARS-CoV-2 strain (UK variant) (78).

Table 2 . COVID-19 vaccines in human clinical trials Phase 3 in India (as of mid-December 2021)

Vaccine	Sponsor	Study Type	Location Of Phase 3 Trials	Clinical Trial Registration
BCG VACCINE	Tuberculosis Research Centre, India	Interventional	Tamil Nadu, India	NCT04475302
BBV152	Bharat Biotech International Limited, India	Interventional	Haryana, India	NCT04641481
MONOVALENT AND BIVALENT RECOMBINANT PROTEIN VACCINES	Sanofi Pasteur, France	Interventional	Rajasthan, India. Uttar Pradesh, India. Odisha, India. Tamil Nadu, India. Hyderabad, India. Gujarat, India. Karnataka, India.	NCT04904549
GAM-COVID-VAC	Dr. Reddy's Laboratories Limited	Interventional	Uttar Pradesh, India. Hyderabad, India. Gujarat, India. Delhi, India. Maharashtra, India. West Bengal, India. Pondicherry, India. Rajasthan, India.	NCT04640233
COVAXIN	Bharat Biotech International Limited	Interventional	Rajasthan, India. Andhra Pradesh, India. Telangana, India. Uttar Pradesh, India. Bihar, India. Karnataka, India.	NCT04918797

AD26.COV2.S	Janssen	Interventional	Maharashtra, India.	NCT050070
	Vaccines &		Hyderabad, India.	
	Prevention B.V.,		Maharashtra, India.	
	Netherlands		Gujarat, India.	
			Tamil Nadu, India.	80

SAFETY CONSIDERATIONS

Vaccines have been by far the most successful technique for preventing viral illnesses throughout the last generation. Although most vaccinations are harmless; articular disorders (arthritis), cerebral illnesses (multiple sclerosis, Guillain-Barre syndrome (GBS)), and other autoimmune diseases have been recorded as adverse effects (79).

Given the critical need for CoV-19 vaccinations, thorough safety information gathering is still essential before and throughout the broad use of these vaccinations. The introduction of vaccination without proper safety evaluation may be harmful. This situation would erode community hope for new COVID-19 vaccinations while also jeopardizing the acceptance of many other existing vaccines. This threat may be highly pertinent for LMICs, where increased vaccination protection has been associated with lower infant death over the last 30 years and where concerted international investment has been required to reduce vaccine-preventable illnesses such as polio. Whereas childhood vaccination programs statuses are fairly similar throughout territories, too little is recognized about adult vaccination toxicity profile in LMICs, which may have elevated incidence of chronic parasitic infections, cytomegalovirus infection, hepatitis B, HIV infection, and TB (80).

Historically, post-marketing vaccination efficacy evaluations have depended on the voluntarily reporting of adverse events (AE) by health care providers, vaccinated patients, and caretakers. Although there is a growing desire for comprehensive pharmacovigilance programs (PvP) that use regular screening instead of passively monitoring, only a small number of high-income nations have been able to build such programs so far (81).

ADVERSE EVENTS WITH COVID VACCINES

Nearly all CoV vaccinations induce typical AE such as injection site discomfort and swelling, fever, cold, tiredness, muscle aches, vomiting, sore muscles, and headaches. Furthermore, certain side effects seen during clinical studies are particular to individual vaccinations, such as neutropenia with the AstraZeneca/Oxford vaccine, heart palpitations with the Sputnik V vaccine, and vomiting with the CanSino vaccine. Nonetheless, the results of several clinical

studies with COVID-19 vaccinations revealed that the vaccinations were well-tolerated and had a positive safety background. This has aided in the massive assessment of COVID-19 vaccines in continuing phase III studies, as well as emergency use permission by regulatory authorities in the majority of nations (82).

A rare, recently found illness known as thrombosis with thrombocytopenia syndrome (TTS) has not been documented in conjunction with any other viral vector vaccination yet, linked to two viral vector vaccines, AZD1222 and Ad26.COV2.S (Janssen; Johnson & Johnson). This uncommon immune-mediated illness is characterized by thrombosis in various places, and also with TTS. Myocarditis has recently been observed in adults and adolescents who got an mRNA COVID-19 vaccination (BNT162b2 or mRNA-1273) in the US and Israel at greater rates (83).

An in vitro investigation found that the ChAdOx1 nCoV-19 vaccination gave appropriate safeguards against the novel B.1.1.7 variation, with 70.4 percent (95 percent) safety in symptomatic patients of the B.1.1.7 variant relative to 81.5 percent protection in non-B.1.17 variations. Another research found that a two-dose regimen of the Pfizer/BioNTech BNT162b2 vaccination generated Nab against both the UK and South African versions. Two doses of the ChA-dOx1 nCoV-19 vaccine, on the other hand, were ineffective against mild-to-moderate COVID-19 symptoms produced by the South African B.1.351 strain. The effectiveness of mRNA vaccines, notably Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273), against the UK and South African variants was severely decreased. As a result, the already licensed vaccines should be evaluated further, and the expected continuous appearance of new SARS-CoV-2 variants should be watched (84).

The following serious AE have been reported in grownups: anaphylaxis (2.5-4.8 cases per million dose levels among grownups) and myocarditis (6-27 cases per million) for mRNA vaccines; thrombosis with thrombocytopenia syndrome for the Janssen vaccine (three cases per million) and AstraZeneca vaccine (two cases per million) for the Janssen vaccine; and GBS (7.8 cases per million). Capillary leak syndrome has also been discovered as a probable side effect of AZD1222, and the multisystem inflammatory syndrome is being investigated (85).

According to Hind et al., the most commonly occurred AEs were tiredness, injection site responses, fever, muscle aches, headache, and shivering. Adverse responses to the Covid-19 vaccination occurred in over 80% of vaccine recipients; however, the majority of symptoms were mild to moderate in intensity and may be endured (86).

According to Qutaiba et al., Pfizer, AstraZeneca, and Sinopharm vaccines were deemed to be acceptable based on the finding of mild to moderate postvaccination clinical manifestations. After the first and second doses, the Sinopharm vaccination had a lower incidence of negative effects than the Pfizer and AstraZeneca. The side effects of the Sinopharm vaccine varied from 1.18 percent anosmia to 27.06 percent headache. Unusual negative effects should be closely watched to establish if they are connected to the immunization or not (87).

The most prevalent AEs of the Sputnik V, AZD-1222, and Covaxin vaccines among Birjand (Iran) healthcare professionals, according to Zare et al., were injection site discomfort, muscular pain, tiredness, fever and chills, and headache. These findings were in line with clinical research conducted by vaccine producers. The incidence of adverse effects was more in females than in males overall, but the association was stronger in the case of Sputnik V. Adverse reactions were also inversely connected to age, with older adults being less prone to have post-vaccination issues (88).

According to Haya et al., the most common AEs for the three vaccines manufactured by Pfizer, AstraZeneca, and Sinopharm were local, such as discomfort, and swelling at the site of injection. AstraZeneca vaccination caused the most musculoskeletal discomfort, fever, shivers, exhaustion, headache, abdominal discomfort, and anxiety, followed by the Pfizer vaccine and Sinopharm vaccine. Females were more likely than males to have complaints after getting the COVID-19 vaccination (89).

According to Abanoub et al., 95.2 percent of individuals had at least one AE following CoV-19 immunization using mRNA-based vaccines. Injection site discomfort was the most prevalent AE (91.8 percent), followed by tiredness (62.5 percent), headache (36.4 percent), and muscular soreness (34.9 percent) (90). These adverse effects normally subside after a few days and are an indication that your immune system is functioning properly (91).

Abdulaziz et al. studied the brief AEs of CoV-19 vaccines licensed for use in Saudi Arabia, as well as vaccines from Oxford-AstraZeneca and Pfizer-BioNTech. We discovered that the majority of individuals experienced exhaustion, soreness at the injection site, fever, and headache and that these symptoms were more prevalent after the second dosage of vaccinations. Furthermore, owing to the negative effects of immunizations, only a few people are required to consult a doctor or be hospitalized. When compared to the Pfizer-BioNTech vaccine, fatigue and fever were strongly related to Oxford-AstraZeneca (92).

Only 3 studies documented anaphylactic shock as AE of CoV-19 vaccines: (1) one case out of 84 vaccine cases for the inactivated vaccine; (2) one case out of 2063 vaccinated for the adenovirus-based vaccine; and (3) one case out of 15,181 in the vaccine group and one case out of 15,170 in the placebo group for the mRNA-based vaccine. A total of 37 blood clots, including 22 cases of pulmonary embolus and 5 cases of deep vein thrombosis, have been recorded for the Oxford-AstraZeneca vaccination among 17 million persons in the EU and the UK (93).

Overall, 88.1 percent of the German healthcare professionals in Klugar et al., study experienced at least one AE after receiving the CoV-19 immunization. The mRNA-based vaccinations had a greater incidence of local adverse effects, but the viral vector-based vaccine had a high incidence of systemic adverse reactions. Females and younger age groups had a higher risk of AE after either mRNA-based or viral vector-based immunizations. The most frequent local AE was injection site discomfort, while the most common systemic AE was fatigue, muscular soreness, malaise, chills, and joint pain (94).

After a probable relationship between uncommon blood clots and the COVID19 vaccination produced by Oxford–AstraZeneca was discovered in April 2021, the EMA advised caution. A week afterward, US regulators suggested that the administration of the vaccine developed by J&J, be temporarily halted due to alleged cases of unexpected blood clots, even though the number of cases reported was only 6 out of 7 million. As a result of this action, J&J has temporarily halted the delivery of its vaccine to certain nations. These judgments have a far-reaching influence. As a result, several nations have opted to limit the use of the AstraZeneca vaccine to particular audiences, limiting the vaccination's delivery, as well as some nations, such as Denmark, have discontinued using it entirely. All of this is adding to the misunderstanding, although authorities and academics have said categorically that the vaccine's advantages greatly outweigh the drawbacks it causes. One source of this perplexity is the insufficient, unfiltered, and erratic real-time data accessible to everyone on the planet (95).

VACCINATION GIVEN GENDER DIFFERENCE

Preliminary results on COVID-19 vaccinations available to Alessia et al. reveal possible sex-related variations in potency (96). Numerous genetic, immunological, hormonal, and environmental variables fluctuate among males and females, contributing to sex- and gender-

specific vaccination effects and reactions, according to an in vitro investigation of humans and animals (Table 3). Women respond to illnesses more vigorously and produce more antibodies as a result of the disease and immunization. In women, a stronger immune response may result in a higher risk of autoimmune illness and a higher ability to resist infections. According to preliminary research, females produce more specific subtypes of antibodies (IgGs) than males following SARS-CoV-2 infection (97).

Females have a higher humoral and cell-mediated immune function to antigenic stimulation, vaccination, and infections than men do. Females consistently have greater basal levels of immunoglobulin (Ig) and antibody responsiveness to infections and vaccinations than males, in both young and old people (98). As a result, the effectiveness of vaccinations indicated for adults is typically higher in women than for men (99).

Table 3. Gender response to vaccines.

Gender	Efficacy	Reasons
Male	Low	High levels of Testosterone
Female	High	Immunological, hormonal, genetic, and microbiome differences of Steroid hormones.

An increasing body of research suggests that pregnant women are at a greater risk of the cause of death and disability from CoV-19, including an increased risk of respiratory failure requiring admission to critical care and mechanical ventilation, when compared to age-matched non-pregnant women. COVID-19 has also been linked to a higher risk of miscarriage (100). According to Agustin et al., based on available data, there appear to be no obvious safety issues associated with COVID-19 vaccinations, their components, or the technology platforms employed for pregnant women. Because pregnant women are at a higher risk of severe outcomes, it is prudent to investigate COVID-19 immunization (101).

More research and long-term population-level monitoring are urgently urged to improve the safety aspect of COVID-19 vaccinations. This should include important contributions to vaccine safety surveillance equipment, improved surveillance of early COVID-19 vaccine recipients and passive surveillance, standardized reporting and pharmacovigilance mechanisms, hospital-based systems to assess vaccine-specific antibody correlates, and cross-reactivity to other strains. All reports of potential severe reactions should be examined, and

red flags should be analyzed as soon as possible, to enable the deployment of suitable risk-mitigation strategies and the updating of the benefit/risk ratio of vaccination (102).

While vaccination can help protect individual patients and those around them, a huge proportion of the population has to be inoculated and safeguarded for transmission can be significantly decreased. No vaccination is known to be 100 percent effective, and a vaccine that protects against clinical disease development may not protect against transmission to others. Furthermore, the lifetime of naturally existing immunity to infections with SARS-CoV-2 is uncertain and may decline over time. As a result, the length of immunity provided by new COVID-19 vaccinations is uncertain. SARS-CoV-2 will be a continued worry for these factors, even when vaccinations become accessible. Effective public health precautions, such as social distance, restricting the extent of meetings, and wearing a mask, will be required for minimum few years (103).

CONCLUSION

As the outbreak continues, the efficiency of the vaccinations will be studied further, and more information will become accessible. Presently, while developing a safer vaccination policy, the adjuvant, the technique of vaccinations, the age and gender of vaccinees, and the level of pre-existing resistance should be taken into account. Growing international procedures are urgently needed to ease the development, financing, manufacturing, and fair distribution of COVID-19 vaccines. Managing the epidemic necessitates worldwide collaboration.

The struggle against the SARS-CoV-2 virus is far from over, and the discovery of secure and reliable vaccinations, and also their mass production, is urgently needed. But even though the rate during which vaccines are indeed being produced around the world demonstrates the severity of the effort, the reality that certain vaccines failed to stop infection in humans despite showing impressive outcomes in pre-clinical research findings, and that many have been linked to complications are all warning signs that there is little to no room for error. Various vaccinations with extremely high effectiveness have been generated present which is used globally. AstraZeneca, BBIBP-CorV, BioNTech, Novavax, Pfizer, and Sputnik V vaccines with satisfactory effectiveness include the most often used SARS CoV-2 vaccines.

ABBREVIATIONS

1. COVID19 - Coronavirus Disease 2019
2. TB – Tuberculosis

3. FDA - Food and Drug Administration
4. nCoV-19 - Novel CoV-19
5. SARSCoV2 - Severe Acute Respiratory Syndrome Coronavirus 2
6. WHO - World Health Organization
7. nAb - Neutralising Antibody
8. US - United States
9. RCTs - Randomised Clinical Trials
10. EMA - European Medicines Agency
11. EU - European Union
12. LAV - Live-attenuated Vaccinations
13. rVSV-ZEBOV - Recombinant Vesicular Stomatitis Virus-Zaire Ebola virus
14. VLP - Virus-like Particle
15. IVT - In-Vitro Transcribed
16. LNP - Lipid Nanoparticles
17. EN - European Nations
18. ChAdOx1 - Chimpanzee Adenovirus vector
19. UK - United Kingdom
20. NIAID - National Institute of Allergy and Infectious Diseases
21. IM – Intramuscular
22. J&J - Johnson & Johnson
23. ACE2 - Angiotensin-Converting Enzyme 2
24. Ad – Adenovirus
25. LMIC - Low-and Middle-Income Countries
26. ICMR - Indian Council of Medical Research
27. GBS - Guillain-Barre Syndrome
28. AE - Adverse Effects
29. PvP - Pharmacovigilance Programs
30. TTS - Thrombocytopenia Syndrome

REFERENCES

1. Plotkin SA. Vaccines: past, present and future. *Nature medicine*. 2005;11(4 Suppl):S5.
2. Delany I, Rappuoli R, de Gregorio E. Vaccines for the 21st century. *EMBO molecular medicine*. 2014;6(6):708–20.

3. Rappuoli R, Mandl CW, Black S, de Gregorio E. Vaccines for the twenty-first century society. *Nature Reviews Immunology*. 2011;11(12):865–72.
4. Abbas S, Abbas B, Amir S, Wajahat M. Evaluation of adverse effects with COVID-19 vaccination in Pakistan. *Pakistan Journal of Medical Sciences*. 2021;37(7):1959.
5. Li Q, Lu H. Latest updates on COVID-19 vaccines. *Bioscience trends*. 2021;14(6):463–6.
6. Hussain MS, Sharma P, Dhanjal DS, Khurana N, Vyas M, Sharma N, et al. Nanotechnology based advanced therapeutic strategies for targeting interleukins in chronic respiratory diseases. *Chemico-Biological Interactions*. 2021;348:109637.
7. Ndwandwe D, Wiysonge CS. COVID-19 vaccines. *Current opinion in immunology*. 2021;71:111–6.
8. Tavilani A, Abbasi E, Kian Ara F, Darini A, Asefy Z. COVID-19 vaccines: Current evidence and considerations. *Metabolism Open*. 2021;12:100124.
9. Wu SC. Progress and Concept for COVID-19 Vaccine Development. *Biotechnology journal*. 2020;15(6).
10. Lin D-Y, Zeng D, Mehrotra D v, Corey L, Gilbert PB. Evaluating the Efficacy of Coronavirus Disease 2019 Vaccines. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2021;73(8):1540–4.
11. Gupta R, Morain SR. Ethical allocation of future COVID-19 vaccines. *Journal of Medical Ethics*. 2021;47(3):137–41.
12. Zeng B, Gao L, Zhou Q, Yu K, Sun F. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: a systematic review and meta-analysis. *medRxiv*. 2021;21264048.
13. Lin D-Y, Zeng D, Gilbert PB. Evaluating the Long-Term Efficacy of COVID-19 Vaccines. *medRxiv*. 2021;
14. Sharma O, Sultan AA, Ding H, Triggle CR. A Review of the Progress and Challenges of Developing a Vaccine for COVID-19. *Frontiers in immunology*. 2020;11.
15. Orloff J, Douglas F, Pinheiro J, Levinson S, Branson M, Chaturvedi P, et al. The future of drug development: advancing clinical trial design. *Nature reviews Drug discovery*. 2009;8(12):949–57.

16. Kumar A, Dowling WE, Román RG, Chaudhari A, Gurry C, Le TT, et al. Status Report on COVID-19 Vaccines Development. *Current infectious disease reports*. 2021;23(6).
17. Fletcher HA, Voss G, Casimiro D, Neyrolles O, Williams A, Kaufmann SHE, et al. Progress and challenges in TB vaccine development. *F1000Research*. 2018;7.
18. Chugh T. Timelines of COVID-19 vaccines. *Current Medicine Research and Practice*. 2020;10(4):137.
19. Cunningham AL, Garçon N, Leo O, Friedland LR, Strugnell R, Laupèze B, et al. Vaccine development: From concept to early clinical testing. *Vaccine*. 2016;34(52):6655–64.
20. Kaufmann SHE, Juliana McElrath M, Lewis DJM, del Giudice G. Challenges and responses in human vaccine development. *Current Opinion in Immunology*. 2014;28(1):18–26.
21. Hussain MS, Mohit, Pamma P, Kumari B. Treatment modalities of the covid-19 pandemic through repurposed drugs and status of vaccines. *International Journal of Applied Pharmaceutics*. 2021;13(2):48–58.
22. Krammer F. SARS-CoV-2 vaccines in development. *Nature*. 2020;586(7830):516–27.
23. Iwasaki A, Omer SB. Why and How Vaccines Work. *Cell*. 2020;183(2):290–5.
24. Soltani S, Zandi M, Shiri Aghbash P, Rezaei M, Mohammadzadeh N, Afsharifar A, et al. A review of COVID-19 vaccines and major considerations for diabetic patients. *Biotechnology and applied biochemistry*. 2020.
25. Li Y, Tenchov R, Smoot J, Liu C, Watkins S, Zhou Q. A Comprehensive Review of the Global Efforts on COVID-19 Vaccine Development. *ACS Central Science*. 2021;7(4):512–33.
26. Chung JY, Thone MN, Kwon YJ. COVID-19 vaccines: The status and perspectives in delivery points of view. *Advanced drug delivery reviews*. 2021;170:1–25.
27. Kaur SP, Gupta V. COVID-19 Vaccine: A comprehensive status report. *Virus research*. 2020;288.
28. McIntyre P, Joo YJ, Chiu C, Flanagan K, Macartney K. COVID-19 vaccines - are we there yet? *Australian prescriber*. 2021;44(1):19–25.
29. Zhao J, Zhao S, Ou J, Zhang J, Lan W, Guan W, et al. COVID-19: Coronavirus Vaccine Development Updates. *Frontiers in immunology*. 2020;11.

30. Belete TM. Review on Up-to-Date Status of Candidate Vaccines for COVID-19 Disease. *Infection and Drug Resistance*. 2021;14:151.
31. Dai X, Xiong Y, Li N, Jian C. Vaccine Types. *Vaccines - the History and Future*. 2019.
32. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: The current state of play. *Paediatric respiratory reviews*. 2020;35:43–9.
33. Ye T, Zhong Z, García-Sastre A, Schotsaert M, de Geest BG. Current Status of COVID-19 (Pre)Clinical Vaccine Development. *Angewandte Chemie*. 2020;132(43):19045–57.
34. Tregoning JS, Brown ES, Cheeseman HM, Flight KE, Higham SL, Lemm NM, et al. Vaccines for COVID-19. *Clinical and experimental immunology*. 2020;202(2):162–92.
35. Calina D, Docea AO, Petrakis D, Egorov AM, Ishmukhametov AA, Gabibov AG, et al. Towards effective COVID-19 vaccines: Updates, perspectives and challenges (Review). *International journal of molecular medicine*. 2020;46(1):3–16.
36. Kashte S, Gulbake A, El-Amin SF, Gupta A. COVID-19 vaccines: rapid development, implications, challenges and future prospects. *Human cell*. 2021;34(3):711–33.
37. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. *JAMA*. 2021;325(13):1318–20.
38. Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, et al. Direct gene transfer into mouse muscle in vivo. *Science (New York, NY)*. 1990;247(4949 Pt 1):1465–8.
39. Gary EN, Weiner DB. DNA vaccines: prime time is now. *Current Opinion in Immunology*. 2020 Aug 1;65:21–7.
40. Ferraro B, Morrow MP, Hutnick NA, Shin TH, Lucke CE, Weiner DB. Clinical Applications of DNA Vaccines: Current Progress. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2011;53(3):296.
41. Calina D, Sarkar C, Arsene AL, Salehi B, Docea AO, Mondal M, et al. Recent advances, approaches and challenges in targeting pathways for potential COVID-19 vaccines development. *Immunologic Research*. 2020;68(6):1.
42. Schlake T, Thess A, Fotin-Mleczek M, Kallen KJ. Developing mRNA-vaccine technologies. *RNA Biology*. 2012;9(11):1319.
43. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines — a new era in vaccinology. *Nature Reviews Drug Discovery* 2018;17(4):261–79.

44. Fathizadeh H, Afshar S, Masoudi MR, Gholizadeh P, Asgharzadeh M, Ganbarov K, et al. SARS-CoV-2 (Covid-19) vaccines structure, mechanisms and effectiveness: A review. *International journal of biological macromolecules*. 2021;188:740–50.
45. Dai L, Gao GF. Viral targets for vaccines against COVID-19. *Nature Reviews Immunology* 2020 21:2. 2020;21(2):73–82.
46. Heinz FX, Stiasny K. Profiles of current COVID-19 vaccines. *Wiener klinische Wochenschrift*. 2021;133(7–8):271–83.
47. Peiffer-Smadja N, Rozencwajg S, Kherabi Y, Yazdanpanah Y, Montravers P. COVID-19 vaccines: A race against time. *Anaesthesia, critical care & pain medicine*. 2021;40(2).
48. Med D, Sønderskov KM, Dinesen PT, Dinesen Østergaard S. Sustained COVID-19 vaccine willingness after safety concerns over the Oxford-AstraZeneca vaccine. *Danish Medical Journal*. 2021;68(5):3210292.
49. Baden LR, el Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine*. 2021;384(5):403–16.
50. Khuroo MS, Khuroo M, Khuroo MS, Sofi AA, Khuroo NS. COVID-19 Vaccines: A Race Against Time in the Middle of Death and Devastation! *Journal of clinical and experimental hepatology*. 2020;10(6):610–21.
51. Wu K, Werner AP, Koch M, Choi A, Narayanan E, Stewart-Jones GBE, et al. Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine. *New England Journal of Medicine*. 2021;384(15):1468–70.
52. el Sahly HM, Baden LR, Essink B, Doblecki-Lewis S, Martin JM, Anderson EJ, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. *New England Journal of Medicine*. 2021;385(19):1774–85.
53. Bernal JL, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ*. 2021;373.
54. Zieneldien T, Kim J, Cao J, Cao C. COVID-19 Vaccines: Current Conditions and Future Prospects. *Biology*. 2021;10(10):960.

55. Ghasemiyeh P, Mohammadi-Samani S, Firouzabadi N, Dehshahri A, Vazin A. A focused review on technologies, mechanisms, safety, and efficacy of available COVID-19 vaccines. *International immunopharmacology*. 2021;100.
56. Rotshild V, Hirsh-Racah B, Miskin I, Muszkat M, Matok I. Comparing the clinical efficacy of COVID-19 vaccines: a systematic review and network meta-analysis. *Scientific Reports*. 2021;11(1):1–9.
57. Forni G, Mantovani A, Forni G, Mantovani A, Moretta L, Rappuoli R, et al. COVID-19 vaccines: where we stand and challenges ahead. *Cell Death & Differentiation*. 2021;28(2):626–39.
58. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COVS.2 Vaccine against Covid-19. *New England Journal of Medicine*. 2021;384(23):2187–201.
59. Livingston EH, Malani PN, Creech CB. The Johnson & Johnson Vaccine for COVID-19. *JAMA*. 2021;325(15):1575–1575.
60. Prüß BM. Current State of the First COVID-19 Vaccines. *Vaccines*. 2021;9(1):1–12.
61. Tinari S, Riva C. Covid-19: Whatever happened to the Novavax vaccine? *BMJ*. 2021;375:n2965.
62. Jones I, Roy P. Sputnik V COVID-19 vaccine candidate appears safe and effective. *Lancet*. 2021;397(10275):642–3.
63. Cazzola M, Rogliani P, Mazzeo F, Matera MG. Controversy surrounding the Sputnik V vaccine. *Respiratory medicine*. 2021;187.
64. Nogrady B. Mounting evidence suggests Sputnik COVID vaccine is safe and effective. *Nature*. 2021;595(7867):339–40.
65. Choi EM. COVID-19 vaccines for low- and middle-income countries. *Transactions of The Royal Society of Tropical Medicine and Hygiene*. 2021;115(5):447–56.
66. Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*. 2020;369(6499):77–81.

67. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos J do P, Tilli Reis Pessoa Conde M, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. SSRN Electronic Journal. 2021.
68. Ranzani OT, Hitchings MDT, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. *BMJ*. 2021;374.
69. Medeiros-Ribeiro AC, Aikawa NE, Saad CGS, Yuki EFN, Pedrosa T, Fusco SRG, et al. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. *Nature Medicine*. 2021;27(10):1744–51.
70. Jeewandara C, Aberathna IS, Pushpakumara PD, Kamaladasa A, Guruge D, Jayathilaka D, et al. Antibody and T cell responses to Sinopharm/BBIBP-CorV in naïve and previously infected individuals in Sri Lanka. *medRxiv*. 2021;21260621.
71. Hadj Hassine I. Covid-19 vaccines and variants of concern: A review. *Reviews in medical virology*. 2021.
72. Jeewandara C, Aberathna IS, Pushpakumara PD, Kamaladasa A, Guruge D, Wijesinghe A, et al. Persistence of antibody and T cell responses to the Sinopharm/BBIBP-CorV vaccine in Sri Lankan individuals. *medRxiv : the preprint server for health sciences*. 2021.
73. Zahid MN, Moosa MS, Perna S, Buti E bin. A review on COVID-19 vaccines: stages of clinical trials, mode of actions and efficacy. 2021;28(1):225–33.
74. Darbar S, Agarwal S, Saha S. COVID19 Vaccine: COVAXIN ® -India's First Indigenous Effective Weapon to Fight against Coronavirus (A Review). *Parana Journal of Science and Education*. 2021;7(3):1–9.
75. Ella R, Reddy S, Jogdand H, Sarangi V, Ganneru B, Prasad S, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. *The Lancet Infectious Diseases*. 2021;21(7):950–61.
76. Vikkurthi R, Ansari A, Pai AR, Jha SN, Sachan S, Pandit S, et al. Inactivated virus vaccine BBV152/Covaxin elicits robust cellular immune memory to SARS-CoV-2 and variants of concern. *medRxiv*. 2021;11.14.21266294.
77. Thiagarajan K. What do we know about India's Covaxin vaccine? *BMJ*. 2021;373.

78. Sharun K, Dhama K. India's role in COVID-19 vaccine diplomacy. *Journal of Travel Medicine*. 2021;28(7).
79. Maleki A, Look-Why S, Manhapra A, Foster CS. COVID-19 Recombinant mRNA Vaccines and Serious Ocular Inflammatory Side Effects: Real or Coincidence? *Journal of ophthalmic & vision research*. 2021;16(3):490–501.
80. Koff WC, Schenkelberg T, Williams T, Baric RS, Adrian McDermott, Cameron CM, et al. Development and deployment of COVID-19 vaccines for those most vulnerable. *Science translational medicine*. 2021;13(579).
81. Riad A, Schünemann H, Attia S, Peričić TP, Žuljević MF, Jürisson M, et al. COVID-19 Vaccines Safety Tracking (CoVaST): Protocol of a Multi-Center Prospective Cohort Study for Active Surveillance of COVID-19 Vaccines' Side Effects. *International journal of environmental research and public health*. 2021;18(15).
82. Shrestha S, Khatri J, Shakya S, Danekhu K, Khatiwada AP, Sah R, et al. Adverse events related to COVID-19 vaccines: the need to strengthen pharmacovigilance monitoring systems. *Drugs & therapy perspectives: for rational drug selection and use*. 2021;37(8):376–82.
83. Sharma K, Koirala A, Nicolopoulos K, Chiu C, Wood N, Britton PN. Vaccines for COVID-19: Where do we stand in 2021? *Paediatric Respiratory Reviews*. 2021;39:22–31.
84. Nagy A, Alhatlani B. An overview of current COVID-19 vaccine platforms. *Computational and structural biotechnology journal*. 2021;19:2508–17.
85. Fiolet T, Kherabi Y, MacDonald C-J, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2021.
86. Almufly HB, Mohammed SA, Abdullah AM, Merza MA. Potential adverse effects of COVID19 vaccines among Iraqi population; a comparison between the three available vaccines in Iraq; a retrospective cross-sectional study. *Diabetes & metabolic syndrome*. 2021;15(5).
87. al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al. Safety of COVID-19 vaccines. *Journal of medical virology*. 2021;93(12):6588–94.

88. Zare H, Rezapour H, Mahmoodzadeh S, Fereidouni M. Prevalence of COVID-19 vaccines (Sputnik V, AZD-1222, and Covaxin) side effects among healthcare workers in Birjand city, Iran. *International immunopharmacology*. 2021;101.
89. Omeish H, Najadat A, Al-Azzam S, Tarabin N, Abu Hameed A, Al-Gallab N, et al. Reported COVID-19 vaccines side effects among Jordanian population: a cross sectional study. *Human vaccines & immunotherapeutics*. 2021.
90. Riad A, Pokorná A, Klugarová J, Antalová N, Kantorová L, Koščík M, et al. Side Effects of mRNA-Based COVID-19 Vaccines among Young Adults (18-30 Years Old): An Independent Post-Marketing Study. *Pharmaceuticals*. 2021;14(10).
91. Hartert T v., Sockrider M. What Are COVID-19 Vaccines? *American journal of respiratory and critical care medicine*. 2021;203(9):22–3.
92. Alhazmi A, Alamer E, Daws D, Hakami M, Darraj M, Abdelwahab S, et al. Evaluation of Side Effects Associated with COVID-19 Vaccines in Saudi Arabia. *Vaccines*. 2021;9(6).
93. Pormohammad A, Zarei M, Ghorbani S, Mohammadi M, Razizadeh MH, Turner DL, et al. Efficacy and Safety of COVID-19 Vaccines: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Vaccines*. 2021;9(5).
94. Klugar M, Riad A, Mekhemar M, Conrad J, Buchbender M, Howaldt HP, et al. Side Effects of mRNA-Based and Viral Vector-Based COVID-19 Vaccines among German Healthcare Workers. *Biology*. 2021;10(8).
95. Ahmed S, Khan S, Imran I, al Mughairbi F, Sheikh FS, Hussain J, et al. Vaccine Development against COVID-19: Study from Pre-Clinical Phases to Clinical Trials and Global Use. *Vaccines*. 2021;9(8).
96. Bignucolo A, Scarabel L, Mezzalira S, Polesel J, Cecchin E, Toffoli G. Sex Disparities in Efficacy in COVID-19 Vaccines: A Systematic Review and Meta-Analysis. *Vaccines*. 2021;9(8):825.
97. ElBagoury M, Tolba MM, Nasser HA, Jabbar A, Elagouz AM, Aktham Y, et al. The find of COVID-19 vaccine: Challenges and opportunities. *Journal of infection and public health*. 2021;14(3):389–416.
98. Fink AL, Klein SL. Sex and Gender Impact Immune Responses to Vaccines Among the Elderly. *Physiology*. 2015;30(6):408–16.

99. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nature Reviews Immunology* 2008 8:9. 2008;8(9):737–44.
100. Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. *Lancet*. 2020;396(10252):e22.
101. Ciapponi A, Bardach A, Mazzoni A, Alconada T, Anderson SA, Argento FJ, et al. Safety of components and platforms of COVID-19 vaccines considered for use in pregnancy: A rapid review. *Vaccine*. 2021;39(40):5891–908.
102. Wu Q, Dudley MZ, Chen X, Bai X, Dong K, Zhuang T, et al. Evaluation of the safety profile of COVID-19 vaccines: a rapid review. *BMC Medicine*. 2021;19(1):1–16.
103. Goodman JL, Grabenstein JD, Braun MM. Answering Key Questions About COVID-19 Vaccines. *JAMA*. 2020;324(20):2027–8.