Review Article

A Comprehensive Review on Various Aspects of SARS-CoV-2 (COVID-19) Vaccines

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Abstract

This is a comprehensive review based on the published papers in the field of COVID-19 vaccines and vaccination. Many efforts have been made to develop vaccines to combat this pandemic. Since December 2020, more than 200 vaccines have been tested in various research stages and in clinical trials on humans, of which eight vaccines reached phase four clinical trials in humans and approved by FDA and EUA. After the Pfizer–BioNTech vaccine that had the highest efficacy (95%), the efficacy of the other vaccines are as follows: Moderna 94.5%, Sputnik V 91%, Novavax 89.7%, Sinopharm 79.3%, Oxford/AstraZenaca 70.4%, Johnson and Johnson 66.9%, and Sinovac 50.7%. At present, protein-based vaccines, with 35% of all available COVID-19 vaccines, are the most common technique in the vaccine production, and then there are vaccines of non-replicating viral vector (13.3%), mRNA1 (12.1%), DNA (10.2%), replicating viral vector (9.8%), and inactivated vaccines (8.2%). The most frequently recognized adverse effects within 7 days of each vaccine dose involved fever, fatigue, headache, chill, and myalgia. The mRNA-based vaccines were associated with a higher occurrence of local side effects (78.3 vs. 70.4%; Sig. = 0.064), whereas the viral vector-based vaccine was associated with a higher prevalence of systemic side effects (87.2 vs. 61%; Sig. < 0.001). Based on the evidence and articles in the field of vaccination, AstraZeneca-Oxford and Sinopharm vaccines reported the highest and lowest side effects, respectively. Because of being emerging, pathogenicity, and high infectivity of COVID-19, vaccination against the disease to prevent its incident rate and decrease the prevalence rate is recommended immediately. Being informed of various aspects of the existing vaccines such as efficacy, effectiveness, safety, etc.can accelerate to make effective and useful choices and consequently have a vaccinated community against the epidemic.

Keywords: *Comprehensive review, COVID-19, efficacy, safety, vaccination, vaccines*

Introduction

A review on COVID-19 and the role of vaccination in controlling the spread of the disease

At the beginning of the New Year 2020 in Wuhan, China, an outbreak of an unknown pneumonia with unusual symptoms led to the discovery and introduction of a new type of coronavirus with a scientific name of Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV-2) that led to the development of an acute viral respiratory disease called coronavirus disease 2019 (COVID-19).

After the rapid spread of the disease and its transfer across the borders of different countries as well as continents, it became a terrible pandemic, insofar as that for the sixth time on January 20, 2020, the World Health Organization (WHO) declared COVID-19 the cause of a public health emergency worldwide.[1] The emergence of this disease once again showed the power of infectious pathogens in endangering the health of people and society, and it was noted that communicable diseases should never be neglected.[2] For the third time in a row (SARS 2003, Middle East Respiratory Syndrome [MERS] 2012, and COVID-19 2019), in the last two decades, pandemics caused by coronaviruses have taken the world by surprise and challenged the health care systems of different countries.[3,4]

Coronaviruses are a large family of viruses that are a subset of Coronaviridae.[4] The family members of these coated viruses are the single-stranded ribonucleic acid (RNA) genome with positive polarity.[4] The Alpha and Beta coronaviruses (β-CoV and

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α-CoV) can infect mammals, whereas Gamma and Delta coronaviruses (γ-CoV and δ-CoV) primarily infect birds. Epidemiological and phlebogenic analyzes have identified the main host of this virus as bats and the intermediate host as animals that facilitate the transmission of the virus from bats to humans, such as pangolins (Manis javanica) and anteaters, but in this regard, no certainty has been reached yet.[1,5]

COVID-19 infection covers a huge range of symptoms, including fever, chills, cough, shortness of breath, chest pain, sore throat, nausea, loss of appetite, diarrhea, vomiting, headache, dizziness, arthritis, fatigue, malaise, loss of odor and taste, decreased renal function, pneumonia, runny nose, conjunctival congestion of the eyes, bruising of the lips and face and other lung, cardiovascular, cerebral, renal, hepatic, and other gastrointestinal sufferings.[6] Based on the findings of meta-analysis studies, the mean of case fatality rate (95%CI: 2.40, 2.98), basic reproduction number (R_0) (95% CI: 2.25, 3.13), incubation period (95%CI: 5.9–7.1), and serial interval (95%CI: 4.9–5.5) of COVID-19 were estimated to be 2.69, 2.67, 6.5, and 5.2 days, respectively.[7,8]

The rapid transmission of the virus has posed a major challenge to WHO, and in less than a month, from a limited outbreak in Wuhan, China, it has become a major pandemic in the world.[6] Usually, the primary ways of transmitting the virus include close person-to-person transmission, transmission through respiratory droplets during coughing and sneezing, transmission through aerosols, transmission by touching surfaces and contact with infected objects, and fomites transmission.[6,9] In this disease, dealing with virus to infectiousness (latent period) may be shorter than the incubation period, which is very important subject for vaccination and transmission dynamics.[10] To diagnose the disease, cumulative radiological, laboratory, clinical, and epidemiological evidence is required.[11]

Coronavirus pandemic is a propagated (progressive source) epidemic that matches to the pathogenic model of the epidemiological triangle that emphasizes the interaction of three factors, including host, pathogen and environment; therefore, one of the most important activities and health actions to break the virus transmission chain is to promote the individuals' immune system in response to the virus and broad and continuous vaccination of people at risk of the disease.[6]

Currently, a great deal of information has been sent to the general public, especially the experts in medical and health sciences, who play the main role in suppressing this emerging pandemic, and studying all of them in this golden time will be impossible and confusing. In these situations, systematic review studies will be very valuable because of the aggregation of information and summarizing scientific resources in various fields and the transfer of useful scientific messages in a short period of time. Therefore, this study tries to promote the knowledge related to vaccination and available vaccines by reviewing various information resources about COVID-19 to gain more familiarity with the full details of different vaccines, such as efficacy, effectiveness, safety, platform, developer, target antigen, country of origin, storage, dose, number and type of injection, vaccination, and vaccine development, in addition to providing an appropriate resource for decision making in the field of COVID-19 vaccination.

Materials and Methods

Study design

The study was a comprehensive review based on the published papers in the field of COVID-19 vaccines and vaccination.

Information collection techniques

Data collection tool was a researcher-made checklist for writing the articles details (author name, place, time, and main results). The search process was performed to identify the published studies by a completely independent five-member team. After reviewing the full text and carrying out the quality assessment by the researchers, the articles that met the inclusion criteria were reviewed and the required information was extracted. Inclusion criteria included 1) the articles that were in the field of COVID-19 vaccination, 2) there was no confounders or selection or measurement bias in the results of the study, 3) the articles that have obtained the required scores of the clinical trials (Consolidated Standards of Reporting Trials), and review articles (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklists. Exclusion criteria included articles that 1) are similar articles found by researchers or articles that have been published several times (multiple publication bias) by various journals or research centers (multicenter studies), 2) had only an abstract and no full text access, 3) short reports and letters to the editor, and 4) published in BioRxiv and Medrxiv databases before being peer reviewed. To reduce the selection bias in the selection of the articles, database bias, publication bias, citation bias, reporting bias, and language bias were considered so that all published articles that have been indexed in credible indexing databases and published in global reliable websites were included in the study without considering their sample size, language, significant or non-significant results, and number of citations after the quality evaluation phase.

Search strategies and searched databases for identification of studies

Using keywords "COVID-19, 2019-nCoV, SARS-CoV-2, Coronavirus 2019 Vaccine, Vaccination, Effectiveness, Immunogenicity, Virology, Safety, Moderna (mRNA-1273), Pfizer/BioNTech (BNT-162b2), Oxford/AstraZeneca (AZD-1222), Gamaleya Research Institutes (Gam-COVID-Vac), Sputnik V, Janssen Pharmaceutical

Companies (Ad26.COV2.5), Sinopharm (BBIBP-CorV), Sinovac Life Sciences (CoronaVac), Novavax (NVX-CoV2373), Covaxin (BBV152 A, B, and C), Bharat Biotech," the search for retrieving documents until October 24, 2021 was done in the scientific databases of "Web of Science," "PubMed," "Scopus," "Google Scholar," and "Embase" in addition to the journals with a special issue allocated to this disease in the sub-category of "Science Direct," "BMJ," "JAMA," "Oxford," and "The Lancet." Reliable websites, such as WHO, Centers for Disease Control and Prevention, and Worldometer, were also used to receive the latest statistics and information. Search was performed using operators of "AND," "OR," and "NOT."

A total of 132 different articles were retrieved, 38 articles of which were similar or their results were reported and repeated in other journals. Finally, after reviewing the full text of 94 remaining articles and doing quality assessment phase based on inclusion and exclusion criteria, 45 articles were eligible for inclusion in the study and the necessary information was extracted from them.

Result

Virology of SARS-CoV-2 and vaccine development

Pathogen of SARS-CoV-2 is a coated virus with a genome of the RNA of 29.8 kb in length. The genome of this virus has 14 Open Reading Frames that encode 27 proteins, including the nucleocapsid protein (NP), spike protein (SP), envelope protein (EP), and membrane protein (MP).[12] NP plays a key role in virus replication and identification, SP in immunogenicity, EP in the assembly, release, and pathogenicity, and MP in virus formation. The presence of SP in the SARS-CoV-2 is one of the most important structural features of the virus that helps in the production of vaccines, which has been considered by many scientists and companies. Spike is a major target antigen for COVID-19 vaccines. SP of SARS-CoV-2 directly attaches to the receptor of angiotensin-converting enzyme 2 (ACE2) of the surface area of the host cell and plays a key role in binding to the cell surface area receptor, which facilitates the entry of the virus into the cell and its replication. In fact, the novel coronavirus, SARS-CoV-2, uses ACE2 as a receptor to enter the cell.[13] ACE2 receptor is abundant in human alveolar epithelial cells, which is why the lungs are one of the most vulnerable organs in the body when the coronavirus SARS-CoV-2 enters. The high binding affinity to receptors may facilitate the virus entry to the lung cells and lead to more individual transmission through direct or indirect contact with respiratory droplets of infected patients by COVID-19.

COVID-19 vaccination

Vaccine preparation and development to treat COVID-19 seem to prevent the death of many people in this century. With the introduction of the first vaccine by a German–American company called Pfizer–BioNTech in December 2020, 11 months after the diagnosis of the first case infected of COVID-19, the scientists were able to complete a multi-year process of producing a new vaccine in less than a year and this brought more hope to save a person's life and coming back to the routine life.[14,15] Until May 8, 2022, 11,647,236,583 doses of COVID-19 vaccine have been injected of which 67% of the world's population has received at least one dose and 61% have been fully vaccinated. United Arab Emirate (99%), Portugal (93%), Chile (92%), Cuba (91%), Malta (91%), Qatar (90%), Singapore (89%), Cambodia (88%), Spain (87%), and Uruguay (86%) had the highest vaccination coverage.[16] So far, various technologies have been developed all over the world for the production of vaccines against SARS-CoV-2. These vaccines include the following: Nucleic acid-based vaccines (DNA or RNA), viral-vectored vaccines (non-replicating vector vaccines or replicating vector vaccines), inactivated virus or live-attenuated virus vaccines, and protein-based vaccines (protein subunit or virus-like particle (VLP).[17] From December 2020, more than 200 COVID-19 vaccine candidates are being developed on several different platforms, and there are at least eight types of coronavirus vaccines that have received emergency licenses and have been widely used.[15] Many efforts have been made to develop vaccines to combat this pandemic and more than 200 vaccines have been tested in various phases of research and clinical trials since December 2020, of which eight vaccines have reached phase four clinical trials and have been approved by reliable organizations, such as Food and Drug Administration (FDA) and Emergency Use Authorization (EUA).[13,18] Until May 8, 2022, 34 vaccines in phase one clinical trials (vaccines testing safety and dosage), 28 vaccines in phase one-two (combined trials), 20 vaccines in phase two (vaccines in expanded safety trials), nine vaccines in phase two-three (combined trials), 20 vaccines in phase three (vaccines in large-scale efficacy tests), 15 allowed vaccines with limited use (vaccines in early or limited use), nine approved vaccines by FDA (vaccines approved for full use), and five vaccines were abounded and suspended in production and supply (vaccines abandoned after trials).[17,18] More than 40 countries have attempted to produce and develop vaccine and could introduce 232 COVID-19 candidate vaccines.[13,19] At this time, protein-based vaccines, with 35% of all available COVID-19 vaccines, are the most common vaccine with this production technique; thereafter, there are the vaccines of non-replicating viral vector (13.3%), mRNA1 (12.1%), DNA (10.2%), replicating viral vector (9.8%), and inactivated vaccines (8.2%).[19] In a meta-analysis study, the local and systemic reactions of COVID-19 vaccines belonged to RNA (89.4%, 83.3%), non-replicating vector (55.9%, 66.3%), and VLP (100.0%, 78.9%); and significantly higher than inactivated (23.7%, 21.0%), protein subunit (33.0%, 22.3%), and DNA vaccines (39.5%, 29.3%).[20]

Details of vaccines approved by FDA and EUA

Pfizer/BioNTech (BNT-162b2) vaccine

Pfizer/BioNTech was the first anti-COVID-19 vaccine that showed promising effective data. This vaccine is based on mRNA that induces cells to respond to the SP of SARS-CoV-2 virus for immune response. The vaccine's mRNA is capped in lipid nanoparticles (LNPs) that help it in delivering to human cells and also act as an adjuvant to boost the immune response.[21] The target antigen of the vaccine was S protein with 2P (K986P and V987P).[18]

The vaccine at a dose of 30 μg is recommended for people older than 12 years. The Pfizer/BioNTech vaccine stability is at –70°C and can be stored for up to 10 days in the mentioned condition. To store for more than 10 days, a much lower temperature is required.[22] This vaccine as a series of two doses of 0.3 mL is administrated intramuscularly to deltoid muscle at least 21 days apart. The vaccine production was a multinational collaboration between Pfizer (USA) and BioNTech (Germany) companies.[19] Phases three and four trial size was 43,998 (age +12). Participants included in safety set were 22,752 individuals and vaccine effectiveness has been recorded 95%.[19,20]

In the study by Hind *et al*.,[23] potential adverse effects of three vaccines, including Sinopharm, AstraZeneca-Oxford, and Pfizer–BioNTech, were assessed. According to the results of this study, the side effects of Pfizer–BioNTech vaccine after injection were the following: fever (40.6%), fatigue (48.2%), headache (26.2%), chill (7.9%), myalgia (31.9%), nausea and vomiting (2.7%), cough (3.9%), shortness of breath (2.3%), loss of smell and taste sense (0.7%), injection site reaction (66.9%), diarrhea (0.7%), hypotension (0.3%), tachycardia (0.3%), and allergic reaction (0.7%).

mRNA-1273 (Moderna) vaccine

Moderna is an mRNA-based vaccine enclosed in LNPs that encode SP of SARS-CoV-2.[24] The target antigen of the vaccine was S protein with 2P (K986P and V987P).[18] The vaccine is given as a sterile liquid with a concentration of 0.2 mg/mL that is injected into the deltoid muscle in two doses. Injections are done at 28 days intervals, in the same arm, in a volume of 0.5 mL containing 100 μg mRNA-1273.

The vaccine does not require dilution prior to administration and the doses can be in syringes up to 8 h of room temperature between 2° and 8°C. Moderna can be stored up to 6 months at –20°C, although it is expected to be stable up to 30 days at the normal temperature of refrigerator (2–8°C).[25] The vaccine is recommended for all individuals from 19 to 95 years of age.[19,20] This vaccine has been made in Boston, USA.[19]

Phases three and four trial size was 3,000 (12 to <18) and 30,420 (age +18), respectively, and participants included in safety set were 15,208 individuals, and vaccine effectiveness has been recorded 94.1%.[19,20]

The most frequently recognized adverse effects within 7 days of each vaccine dose involved headache, myalgia, and fatigue; however, the rates of Electronic Health Records (EHR) record for each side effect were particularly low in comparison to those derived from active solicitation during clinical trials. Severe measures involving facial paralysis, anaphylaxis, and cerebral venous sinus thrombosis were rare and happened at alike occurrences in vaccinated and unvaccinated individuals. Severe adverse effects are rare among individuals receiving BNT162b2 or mRNA-1273. This investigation of vaccine-related adverse effects from more than 1.2 million EHR summaries of more than 130,000 persons confirms the safety and permissibility of the FDA-authorized mRNA COVID-19 vaccines in practice.[26]

AZD-1222 (Oxford/AstraZeneca) vaccine

Oxford/AstraZeneca is of particular importance because it requires no cold chain management at very low temperatures and at 2–8°C is well kept. This vaccine is more cost effective than other approved COVID-19 vaccines, such as Pfizer and Modern; therefore, it is more feasible to distribute the vaccine for global use, especially in limited resources.[24] It belongs to replication-deficient viral vector vaccine categories. The vaccine uses a new technology that is based on the chimpanzee adenovirus vector (ChAdOx) to encode the immune response of the production of SP related to SARS-CoV-2, and for the importance of this issue, at each injectable dose, there are 5×10^{10} viral particle.[27,28] Unlike Moderna and Pfizer, which encode the subunit of SP, the Oxford/AstraZeneca vaccine specifically encodes the complete SP.[28] Target antigen of the vaccine was S protein.[18]

The vaccine in two doses of 0.5 mL is administrated intramuscularly into the deltoid muscle with 28 days interval. The vaccine has been made by The Jenner Institute in the University of Oxford.[19]

Phases three and four trial size was 12,390 (age +18) and participants included in safety set were 12,021 individuals and vaccine effectiveness has been recorded 70.4%.[19,20]

In the study by Hind *et al*.,[23] potential adverse effects of AstraZeneca–Oxford vaccine after injection comprising fever (48.4%), fatigue (64.9%), headache (48%), chill (28%), myalgia (54.2%), nausea and vomiting (10.3%), cough (4.5%), shortness of breath (4.1%), loss of smell and taste sense (2%), injection site reaction (54.2%), diarrhea (0.5%), hypotension (0.0%), tachycardia (0.1%), and allergic reaction (0.1%).

European Medicines Agency described other blood clots related to thrombocytopenia, involving arterial thromboses and splanchnic vein thrombosis, after administration of the

AstraZeneca vaccine. A case report of Guillain − Barre syndrome followed the administration of the first dose of the ChAdOx1 vaccine.[29]

Vaccine Sputnik V (Gam-COVID-Vac)

The vaccine also known as Gamaleya Research Institutes (Gam-COVID-Vac) uses recombinant adenovirus from the heterologous approach using adenoviruses 26 and 5 (rAd5 and rAd26 prime-boost) as a carrier of SP, responsible for causing SARS. It should be considered that the adenovirus used in the vaccine cannot be reproduced but in two doses sufficiently provides DNA of SP to obtain an immune response.[30] The vaccine is in the category of non-replicating viral vector vaccines and its target antigen was S protein.[18]

In this vaccine, two different serotypes for two doses are administered intramuscularly at intervals of 21 days in people more than 18 years old, which is a distinctive feature of this vaccine from other vaccines that use the same substances for each dose.[31]

The first dose vials are in blue color and the second dose vials are in red color. The dosage in each dose of vaccine is half a milliliter. The vaccine vials should always be at a temperature less than –20°C before injection into the individuals.[30] Factors such as low cost and ease of maintenance (no need for very low temperatures) are the advantages of the vaccine, which has led to its use in countries that do not have sufficient cooling facilities.[32] This vaccine has been made in Russia by Gamaleya Research Institute.[19]

Phases three and four trial size was 33,758 (age +18) and participants included in safety set were 16,427 individuals and vaccine effectiveness has been recorded 91.6%.[19,20]

First-dose adverse events following immunization (AEFIs) rate was 53.3% (systemic reactions at 42.2%), whereas second-dose AEFI rate was 66.8% (systemic reactions at 50.4%) (n = 1,288). The most common signs were local pain, asthenia, headache, and joint pain. Albeit preliminary, reports suggest that Sputnik V has a high acceptability profile in the people aged 60 years in terms of short-term AEFIs.[33]

Beijing Institute of Biological Products/Sinopharm (BBIBP-CorV)

Sinopharm vaccine contains a hydroxy-aluminum compound of inactivated Coronavirus SARS-CoV-2, which stimulates the immune system to produce antibodies that bind to the surface SP of the virus. Hydroxy-aluminum activates the pre-inflammatory mechanisms of the immune system by secreting high levels of interleukin1-beta and interleukin18 derivatives. The vaccine belongs to the category of inactivated vaccine and its target antigen is whole pathogen.[18]

The vaccine is kept at the refrigerator temperature of 2–8°C. The vaccine is in a single-dose vial. Each vial contains 0.5 mL of vaccine and it is an intramuscular injection.[34,35] The injection spot is in the deltoid muscle, in the outer upper-third of the arm. For adequate safety, the vaccine should be given twice in 21 days interval. The type of the vaccine in the first and second injections is exactly the same and does not differ. The easy storage requirements of this vaccine have made it very accessible, especially for areas with poor equipment supply.[35] This vaccine is made in China in BBIBP and Sinopharm.[19]

Phases three and four trial size was 3,000 (age + 18) and participants included in safety set were 13,555 individuals and vaccine effectiveness has been recorded 79.3%.[19,20]

In the study by Hind *et al*.,[23] potential adverse effects of Sinopharm vaccine after injection were fever (37.8%), fatigue (40.9%), headache (33.3%), chill (19.6%), myalgia (36.3%), nausea and vomiting (10.6%), cough (7.5%), shortness of breath (3%), loss of smell and taste sense (3%), and injection site reaction (54.5%). But no complications, such as diarrhea, hypotension, tachycardia, and allergic reaction, were observed.

Janssen Pharmaceutical Companies (Ad26.COV2.5)

The vaccine is known as Johnson and Johnson vaccine and uses adenovirus 26 (Ad26) that is the most common cause of respiratory infections. In this adenovirus, DNA was modified in such a way that produces an important part of the viral particles of SARS-CoV-2 to which the body reacts appropriately immune response. Adenoviruses that transfer the related genes of SARS-CoV-2 cannot be reproduced; therefore, it does not cause infection. Because this system is based on DNA molecules, does not require super-cold storage and is easy to distribute.[36]

This vaccine is in non-replicating viral vector adenovirus categories and its target antigen was SP with 2P (K986P and V987P) and two mutations at furin cleavage site (R682S and R685G).[20] In a study in the USA, the effectiveness of the vaccine has been reported to be 77% that this amount is less in comparison with the performance of Moderna and Pfizer with 99% and 88%, respectively.[37] Vaccine Janssen Ad26.CoV2 is administrated intramuscularly as a single dose and half milliliters.[37] The vaccine is kept at 2–8°C in a normal refrigerator. This vaccine has been made in USA by Johnson and Johnson Institute.[19] Phases three and four trial size was 44,325 (age +18) and participants included in safety set were 21,895 individuals and vaccine effectiveness has been recorded 66%.[19,20]

After the administration of the Johnson and Johnson vaccine, a case of thrombocytopenia, elevated D-dimers, and pulmonary emboli was found. The event of thrombosis with thrombocytopenia syndrome was connected to adenovirus vector vaccines, such as ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and AD26.

CoV2·S (Johnson and Johnson), raising worries. For the AstraZeneca and Johnson and Johnson COVID-19 vaccines, the filler polysorbate 80, also identified as Tween 80, has been occupied in the allergic reactions.[29]

Covaxin (BBV152 A, B, and C)

The vaccine is also known as Bharat Biotech and is categorized in inactivated corona vaccine that uses of a complete viral particle of SARS-CoV-2 including RNA surrounded by a protein shell but modified in such a way that it cannot reproduce (Whole-Virion Inactivated).

The vaccine belongs to the inactivated corona vaccine and its target antigen is whole pathogen.[18] The vaccine is ready to be injected in liquid form and is administrated muscularly with 0.5 cc in the deltoid region.[38] The injection should be in two doses with 4–6 weeks apart. The vials contain 10 doses that should be used less than 6 h when they were opened and kept in 2–8°C.[39] The vaccine is licensed by EUA in India by Indian Council of Medical Research but it has not yet been approved for mass injection worldwide.[19] This vaccine has been made in India by Bharat Biotech Institute.[19]

Phases three and four trial size was 25,800 (age +18) and participants included in safety set were 190 individuals and vaccine effectiveness has been recorded 81%.[19,20,40]

The ache at the injection site (17 (5%)), headache (13 (3%)), fatigue (11 (3%)), fever (nine (2%)), and nausea or vomiting (seven (2%)) were prevalent; Mild (43 (69%) of 62) or moderate (19 (31%)) were also common after the first dose, with only one severe case reported in the 6 μg with Algel group.[41]

No large-scale adverse reactions have been reported so far supporting the notion that it is generally safe.[42]

Novavax (NVX-CoV2373)

Novavax vaccine consists of 5 μg of recombinant nanoparticles of SP plus 5 μg of Matrix-M adjuvant. The vaccine is categorized in Protein subunit vaccines and its target antigen was S protein with 2P (K986P and V987P) and three mutations at furin cleavage site (R682Q, R683Q, and R685Q).[18] Novavax should be taken in two doses of 5 mL intramuscular injection with 21 days intervals.[43] The vaccine is kept in a normal refrigerator at 2–8°C (36–46°F) and, therefore, is suitable for poor and developing countries.[44]

The test of the third phase of the NVX-CoV2373 Novavax vaccine was conducted in the UK with 15,000 participants of whom 27% were over 65 years old. Unlike other vaccines, such as AstraZeneca, this vaccine has been tested on a large number of elderly populations; this means that regarding the fact that the older age group is at higher risk of severe consequences of infection by COVID-19 but they will gain more immunity after receiving this vaccine. This vaccine has been made in the USA by Novavax Company.[19] Phases three and four trial size was 30,000 (age +18) and participants included in safety set were 257 individuals and vaccine effectiveness has been recorded 89.7%.[19,20]

These events took place more commonly among NVX-CoV2373 recipients than among placebo ones (any local adverse event (AE), 58.0% and 21.1%, respectively, after dose 1 and 78.9% and 21.7% after dose 2; any systemic AE, 47.7% and 40.0%, respectively, after dose 1 and 69.5% and 35.9% after dose 2). No safety concerns related to vaccination were observed.

NVX-CoV2373 is a new adjuvanted recombinant protein vaccine that can be added to the portfolio of vaccines that are safe and highly defensive against existing SARS-CoV-2 strains and that has a satisfactory side-effect profile.[45]

Sinovac Life Sciences (CoronaVac)

Sinovac is an inactivated vaccine and uses the inactivated viruses of the SARS-CoV-2 virus; therefore, it cannot reproduce; but SP keeps an intact surface to stimulate the immune system to produce antibodies to protect the body against the live virus. This vaccine belongs to the inactivated vaccines and its target antigen was whole pathogen.[18] The vaccine injection is in two doses of 0.5 mL with muscle intake that is recommended between 14 and 28 days intervals.[46]

The vaccine is kept in the refrigerator temperature at 2–8°C. The vaccine has been made in China by the Sinovac Company.[19] Phase three and four trial size was 12,688 (age +18) and participants included in safety set were 6,958 individuals and vaccine effectiveness has been recorded 50.7%.[19,20]

CoronaVac was well tolerated and safe and induced humoral replies in children and adolescents aged 3–17 years. Safe in adults and older adults and insufficient data available for pregnant women.[47]

The various characteristics of the approved vaccines by FDA and EUA are summarized in Table 1.

Discussion

COVID-19 pandemic is definitely one of the most important challenges to measure the efficacy and effectiveness of the health care system in different countries around the world. The latest statistics on the worldwide incidence, mortality, and recovery of COVID-19 in May 8, 2021 was updated by Worldometer website shows that the total number of the cases, recovered, and deaths were 517,370,745, 472,147,192, and 6,276,658, respectively; the highest number of the cases have been seen in the United States of America, India, Brazil, Britain, and Russia, respectively, but the number of the cases per one million people have been reported in Seychelles, Montenegro, Andorra, Gibraltar, and Georgia, respectively.

Table 1: Characteristics of the approved vaccines by FDA and EUA[13,18,19,40,48,49]

Platform	Name of the Vaccine	Made in	Target antigen	Dose	Number	Phase 3 and 4 trial size	Efficacy (%)	Potential Adverse Effects
Inactivated virus	Beijing Institute of Biological Products/ Sinopharm (BBIBP-CorV)	China	Whole pathogen	Two separate doses of 0.5 mL	The second dose should be administered 3 weeks after the first dose	3,000 (age 18+)	79.3	Fever (37.8%), fatigue (40.9%), headache (33.3%), chill (19.6%), myalgia (36.3%), nausea and vomiting (10.6%), cough (7.5%), shortness of breath (3%), loss of smell and taste sense (3%),injection site reaction (54.5%)
	Sinovac Life Sciences (CoronaVac)	China	Whole pathogen	Two separate doses of 0.5 mL	The second dose should be administered 2 weeks after the first dose	12,688 (age 18+)	50.7	Well-tolerated and safe and induced humoral responses in children and adolescents aged 3-17 years. Safe in adults and older adults, and insufficient data for pregnant women
mRNA	Pfizer/BioNTech (BNT-162b2)	Multinational	S protein with 2P (K986P and V987P)	Each dose contains 30 µg (0.3 mL)	2 shots, given 21 days apart	43,998 (age 12+)	95	Fever (40.6%), fatigue (48.2%), headache (26.2%), chill (7.9%), myalgia (31.9%), nausea and vomiting (2.7%),cough (3.9%), shortness of breath (2.3%), loss of smell and taste sense (0.7%), injection site reaction (66.9%), diarrhea (0.7%), hypotension (0.3%), tachycardia (0.3%),allergic reaction (0.7%)
	Moderna (mRNA-1273)	USA	S protein with 2P (K986P and V987P)	Each dose contains 50 µg (0.5 mL)	2 shots, given 28 days apart	30,420 (age 18+); 3,000 (12 to <18)	94.5	Headache myalgia fatigue
Recombinant protein subunit	Novavax (NVX-CoV2373)	USA	S protein with 2P (K986P and V987P) and 3 mutations at furin cleavage site (R682Q, R683Q and R685Q)	Two separate doses of 0.5 mL	The second dose should be administered 3 weeks after the first dose	30,000 (age 18+)	89.7	Local adverse event, 58.0% and 21.1%, after dose 1 and 78.9% and 21.7% after dose 2; any systemic adverse event, 47.7% and 40.0%, respectively, after dose 1 and 69.5% and 35.9% after dose 2

Contd...

Table 1: Contd...

Platform	Name of the Vaccine	Made in	Target antigen	Dose	Number	Phase 3 and 4 trial size	Efficacy (%)	Potential Adverse Effects
Viral-vectored	Oxford/ AstraZenaca (AZD-1222)	UK	S protein	Two separate doses of 0.5 mL	The second dose should be administered between 4 and 12 weeks after the first dose.	12,390 (age 18+)	70.4	Fever (48.4%) fatigue (64.9%), headache (48%), chill (28%), myalgia (54.2%), nausea and vomiting (10.3%), cough (4.5%), shortness of breath (4.1%), loss of smell and taste sense (2%), injection site reaction (54.2%), diarrhea (0.5%), hypotension (0.0%), tachycardia (0.1%),allergic reaction (0.1%)
	Sputnik V (Gam-COVID-Vac)	Russia	S protein	first component I at a dose of 0.5 mL, then after 3 weeks component II at a dose of 0.5 mL.	3 weeks component II at a dose of 0.5 mL.	33,758 (age 18+)	91	First dose AEFIs (53.3%) (systemic reactions at 42.2%); Second dose AEFI (66.8%) (systemic reactions at 50.4%) n = 1,288 Most common signs: Local pain, asthenia, headache, joint pain
	Janssen Pharmaceutical Companies (Ad26. COV2.5)	Australia	S protein with 2P (K986P and V987P) and 2 mutations at furin cleavage site (R682S and R685G)	single dose of 0.5 mL	booster dose (0.5 mL) may be administered at least 2 months after primary vaccination	44,325 (age 18+)	66.9	A case of thrombocytopenia, elevated D dimers, pulmonary emboli

FDA=Food and Drug Administration, EUA=emergency use authorization

Coronavirus pandemic is a propagated (progressive source) epidemic that matches to the pathogenic model of the epidemiological triangle that emphasizes the interaction of three factors, including host, pathogen, and environment; therefore, one of the most important activities and health actions to break the virus transmission chain is to promote the individuals' immune system in response to the virus and broad and continuous vaccination of people at risk of the disease.

Sensitivity, specificity, positive predictive value, and negative predictive value are very important indicators in epidemiology and accurate diagnosis of the disease. The higher the value of these indicators, the higher the strength of the tests in distinguishing between sick and healthy people.[50,51] But COVID-19 laboratory tests have not yet reached the level of certainty, which will subsequently increase the number of false positives and negatives in the society.

In this emergency situation, the incidence and subsequent prevalence of disease and mortality are increasing exponentially; therefore, the categories of detection, rapid diagnosis, and treatment of patients and, most importantly, prevention of the new cases using vaccination are very important.

Until October 16, 2021, 6,637,457,407 doses of vaccine have been injected, of which 49% of the world's population have received at least one dose and 37% have been fully vaccinated. United Arab Emirate (97%), Portugal (87%), Chile (86%), Cuba (85%), Malta (84%), Qatar (83%), Singapore (82%), Cambodia (81%), Spain (80%), and Uruguay (80%) had the highest vaccination coverage.

The Pfizer–BioNTech COVID-19 vaccine was the first vaccine against COVID-19, which in December 2020, 11 months after the registration of the first case of COVID_19, showed promising information about the prevention of the disease (95% efficacy). After the Pfizer–BioNTech vaccine that had the highest efficacy (95%), the efficacy of the other vaccines are as follows: Moderna 94.5%, Sputnik V 91%, Novavax 89.7%, Sinopharm 79.3%, Oxford/AstraZenaca 70.4%, Johnson and Johnson 66.9% and Sinovac 50.7%.

Nowadays, the slogan "Prevention is better than cure" must be obeyed and turned into action more than ever, because no definitive antiviral drug has been approved for the treatment of COVID-19. Therefore, injecting effective vaccines along with observing the health protocols, such as social distancing, use of masks and gloves, frequent hand

washing, disinfection of the surfaces, avoidance of close and direct contact with infected individuals, absence from gatherings, quarantine and isolation of the patients, etc., are considered as the most important health actions in epidemic conditions.

The signs most commonly stated after vaccination were fatigue (79%), local pain in the injection site (77.4%), malaise (73%), and body pain (71.1%).[52]

Young-aged contributors, females, participants with history of COVID-19 infection, and those with comorbid diseases were statistically significant risk factors for having adverse reactions post AstraZeneca vaccination; fatigue, injection site reactions, fever, myalgia, headache, and chills were the most stated side effects. Mild to moderate side effects were more frequently described with the Oxford-AstraZeneca vaccine. Sinopharm vaccine was documented as the least effective vaccine.[23]

The mRNA-based vaccines were associated with a higher occurrence of local side effects (78.3 vs. 70.4%; Sig. = 0.064), whereas the viral vector-based vaccine was associated with a higher prevalence of systemic side effects (87.2 vs. 61%; Sig. < 0.001).[53]

The study by Linyi *et al*. entitled "Safety of Global SARS-CoV-2 Vaccines, A Meta-Analysis" showed that the occurrence rate of AEs was 20.05–94.48%. The incidence rate of vascular events increased after viral vector vaccination, whereas decreased after mRNA vaccination. Viral vector vaccine had a higher AE rate in comparison to mRNA vaccines and inactivated vaccines. In most circumstances, the incidence of AEs was higher in older people, female, and after the second dose. Viral vector vaccine had a higher risk of leading to thrombosis events.[54]

However, the risk of severe AEs or even death was low. Cumulatively, more than 100,000 persons took part in these studies, both common local and systemic adverse reactions are dose dependent and ranging from mild to moderate and depends on the age of the persons.[41]

Conclusions

Human society very soon comprehends the fears, anxieties, and unintended consequences of the emerging and pernicious virus, so that the relentless efforts of various organizations all over the world to develop the effective COVID-19 vaccine will reduce the prevalence of the disease and promoting the individuals' health in the community. Accelerating production of the vaccines to control the epidemic, reducing the burden of disease, and the prevention of new cases and deaths by COVID-19 are essential; the cause of the disease is a viral pathogen that can be transmitted directly or indirectly, and the vaccine is very effective in cutting the chain of transmission. The health care systems in different countries should be strengthened and satisfied to administer any one of the different approved vaccines of COVID-19 to the people.

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Conflicts of interest

There are no conflicts of interest.

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