International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 1180-1198 www.ijprajournal.com ISSN: 2249-7781

A Review on COVID19 Vaccines Around the World

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Submitted: 15-12-2021 Accepted: 31-12-2021

ABSTRACT: This review provides using WHO's data and CAS-curated data, this provides a comprehensive review on COVID-19 vaccine around the world percept the COVID-19 situation also represents a picture of public health impact, pathophysiology, and clinical manifestations, diagnosis, case management, emergency response, and preparedness.Coronavirus disease 2019 (COVID-19) originated in the city of Wuhan, Hubei Province, Central China, and has spread quickly to 72 countries.The COVID-19, caused by a novel coronavirus, was declared as a global pandemic by WHO. Globally, as of 5:09pm CEST, 14 December 2021, there have been 270,031,622 confirmed cases of COVID-19, including 5,310,502 deaths,reported to WHO. In December 2019, many pneumonia cases that were clustered in Wuhan city were reported for the source to have shown Huanan Seafood Market as the origin. The first case of the COVID-19 epidemic was discovered with unexplained pneumonia on December 12, 2019, and 27 viral pneumonia cases with seven being severe, were officially announced on December 31,2019. This review will focus on the nine vaccines that have received emergency vaccination licenses from health organizations in vaccine-producing countries the vaccines are as follows Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 Vaccine, Pfizer-BioNTech COVID-19 Vaccine, Moderna COVID-19 Vaccine, Oxford/AstraZeneca COVID-19 vaccine,Sinovac-CoronaVac COVID-19 vaccine, Sputnik V COVID -19 vaccine, Covaxin (BBV 152), Novavax COVID-19 vaccine (NVX-CoV2373,Sinopharm. In addition to reviewing the different vaccines, this review also explains vaccine development, vaccine types, vaccine platforms, vaccine mechanism of action,vaccine doses,vaccine side effects.

KEYWORDS:COVID19,Vaccine,Pandemic, WHO, COVAXIN

I. INTRODUCTION:

Coronaviruses (CoVs) belong to the subfamily Orthocoronavirinae in the family Coronaviridae. There are four genera in the Orthocoronavirinae subfamily. They are as follows:

- Alpha- coronavirus (α-CoV)
- Betacoronavirus (β-CoV)
- Gammacoronavirus (γ-CoV)
- Deltacoronavirus (δ-CoV)

The coronavirus (CoV) genome is an enveloped,positive-sense,Single-stranded RNA with a size differing between 26kb and 32kb. It is the largest genome of known RNA viruses. Theα and β- CoV genera are known for infecting mammals while δ and γ-CoV infect birds. [1] The coronavirus can be observed under an electron microscope as it possesses a crown-like appearance. Primarily human type coronavirus is linked with minor clinical symptoms. Simultaneously,the World Health Organisation(WHO) has conducted studies as well as lab research for the identification of a new strain of CoV, named COVID-19. On the other way,the International Committee on Taxonomy of Viruses referred to the disease-causing virus as the SARS-CoV-2 virus.[2]

History of CoV-related diseases in humans:

Human coronaviruses (HCoVs) were first reported in the mid-1960 when two species were isolated from a person with the common cold: HCoV -229E and HCoV–OC43. From the time,seven different types of CoVs had been detected from humans,out of the three are appeared to be highly pathogenic,and all suggested to be originated from bats:the Middle East respiratory syndrome coronavirus(MERS-CoV), severe acute respiratory syndrome coronavirus(SARS-CoV), and SARS CoV-2[34]. The first time, CoV wreaked global havoc in 2002 when SARS-CoV caused a severe acute respiratory syndrome and spread likea highly pandemic disease.It first

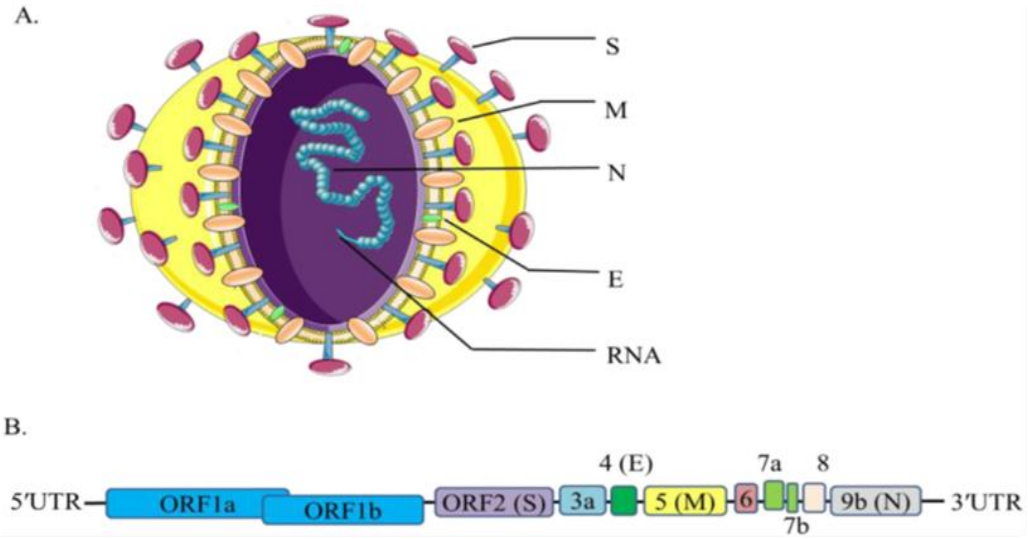
International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 1180-1198 www.ijprajournal.com ISSN: 2249-7781

appeared as a human pathogen in the Guangdong province of southern China in 2002.Later, it spread to 26 countries and resulted in more than 8000 cases and 774 deaths in 2003.World Health Organisation declared the end of this outbreak in July 2003.Another respiratory syndrome outbreak similar to that of SARS-CoVarise in June 2012 in Saudi Arabia and was named MERS-CoV.[3, 28]

The first case of COVID-19:

According to a retrospective study, the onset of the first known case belongsto 8 December 2019.[4,26]On December 31,2019, China had informed the World Health Organisation (WHO) regarding pneumoniacases of unknown etiology which was detected in Wuhan city,[25] Hubei province of China.[32]From December 31,2019, to January 3, 2020, a total of 44 patients with pneumonia of unknown etiology were reported to WHO by the national authorities in China. At that time the causative agent has not been identified The cases which were initially identified had a history of relation to the Huanan Seafood wholesale Market.[5]The cause of this infectious disease was identified as a natural virus of an animal origin with a huge infection possibility. It was detected that the geographical source of this virus was Huanan South China Seafood Market,[30]but the exact animal source of the CoV was unknown. Now it is thought that this virus came from bats as their primary host s then it passed through one or more intermediate hosts,possibly including pangolins,to infect human beings.International Committee on Taxonomy of Viruses (ICTV) announced SARS-CoV-2 as the name for the new virus on February 11,2020,because of its genetic similarities of the virus with the CoV responsible for the outbreak of 2003. And by following guiding principles which were previously developed with the world organization for Animal Health (OIE) and the Food and Agriculture Organization (FAO)of the United Nations,WHO named the disease “COVID-19” and it was announced as a Global Pandemic on March 11, 2020.[3,22,23]

Structure of SARS-CoV-2:



Structure and genome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

There are four structural proteins as follows: spike (S) surface glycoprotein (purple); membrane (M) protein (orange); nucleocapsid (N) protein (blue); and envelope (E) protein (green). Genomic RNA is shown encased in the N protein. (B) The SARS- CoV-2 genome is arranged in the order of 5-replicase (ORF1a/b)–structural proteins [spike (S)–envelope (E)–membrane (M)–nucleocapsid (N)]

The Size of the SARS-Cov2 genome is 30kb encodes a large, non-structural polyprotein (ORF1a/b)which is further proteolytically cleaved to form 15/16 proteins 4 structural proteins, and 5 accessory proteins(ORF3a, ORF6, ORF7, ORF8, and ORF9).The four structural proteins consist of

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 1180-1198 www.ijprajournal.com ISSN: 2249-7781

the spike (S) surface glycoprotein,the membrane (M) protein, the envelope (E) protein, and the nucleocapsid (N) protein which is required for SARS-CoV-2 assembly and infection.The spike surface glycoprotein plays important role in the attachment of it to host cells and then it can be cleaved by host proteases into an N-terminal S1subunit and the membrane-bound C-terminal S2region.Perfusion trimer can be destabilized by binding of S-1 subunit to host receptor,this leading to Shedding of S-1 Subunit and transition of S-2 subunit into a highly stable perfusion conformation.To engage a host receptor, the receptor-binding domain (RBD) of the S-1 subunit undergoes hinge-like conforminants of receptor binding.These two states of S1 subunit can be described as "down confirmation and "up confirmation".In which the former represents an inaccessible state of receptor and the latter correlates to accessible state and hence by understanding the structure and function of spike protein can be helpful to develop monoclonal antibody drugs and also guide for design and development of vaccines.[1,24,35]

Etiology and pathogenesis COVID-19:

SARS-CoV-2 is the seventh member of the CoVs family which infects humans.Four humanCoVs (HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1) can cause a wide range of upper respiratory tract infections (common cold), while SARS-CoV and MERS-CoV are responsible for atypical pneumonia.The causes of different infection sites are likely related to the presence of dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2) (35)in the lower respiratory tract, which are the major human receptors for the surface spike (S) glycoprotein of MERS-CoV.The pathogenesis of SARS- CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure. [4]

The causes of different infection sites are likely related to the presence of dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2) in the lower respiratory tract, which is the major human receptors for the surface spike (S) glycoprotein of MERS-CoVand SARS-CoV, respectively.The genetic sequence of SARS-CoV-2 is ≥70% similar to that SARS-CoV, and SARS-CoV-2 having the capability of using the same cell entry receptor (ACE2) as SARS-CoV to infect humans, on the other hand, there are more differences in the key S proteins that the viruses use to interact with host cells. SARS-CoV-2 spike binds to human ACE2 with approximately 10–20-fold higher affinity than the SARS-CoV spike, making it easier to spread from human to human.Upon entry into alveolar epithelial cells, SARS-CoV-2 replicates fast and triggers a strong immune response, resulting in cytokine storm syndromes and pulmonary tissue damage.Cytokine storm syndromes are also called hypercytokinaemia, are a group of disorders characterized by the uncontrolled production of pro-inflammatory cytokines and these are important causes of acute respiratory distress syndrome (ARDS) and also multiple organ failure.Analysis of the first 99 confirmed cases of SARS-CoV-2 infection reported that cytokine storm syndromes occurred in patients with severe COVID-19 in which 17 patients (17%) had ARDS, among whom 11 (11%) deteriorated within a short period and died of multiple organ failure. In addition, the numbers of total T-cells, CD4 + T-cells, and CD8 + T-cells are decreased in patients with SARS-CoV-2 infection, and the surviving T-cells are functionally exhausted,suggesting a decreased immune function in SARS-CoV-2-infected patients.Acute respiratory distress syndrome decreased immune function, and secondary infection further damages respiratory failure.[1]

Transmission:

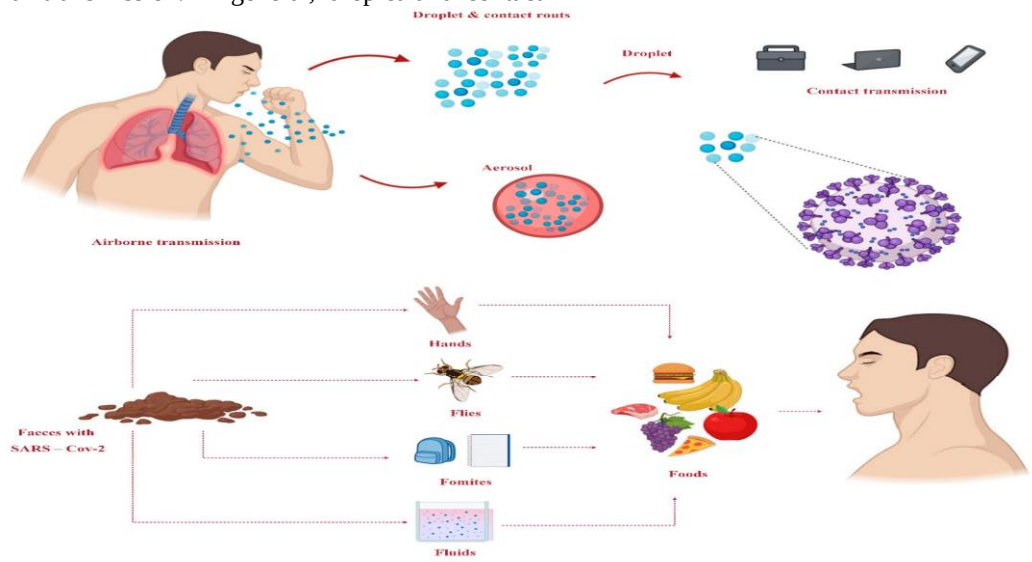
COVID-19 can be transmitted from direct exposure to infected animals, human to human, and environmental contamination.At the first, the initial cases of COVID-19 are related to direct contact with infected animals.Also, the virus can spread from one person to another and this is considered as the main form of transmission as spreading occurs from the release of respiratory droplets,mainly through coughing. Hence, close contact with an individual can result in transmission.And also, the virus can spread by touching contaminated surfaces. This happens when it touches these surfaces and then transfers the virus to mucous membranes in the upper parts of the body, especially the mouth, eyes, or nose.It implies that the virus remains active on surfaces that individuals are definitelyto touch daily. Environmental contamination is more likely to be a possible source of infection in environments where there is heavy viral contamination, mainly in an infected person's household. [2]

Transmission Routes:

Due to the lack of specific treatment and preventing the disease's outbreak, knowing the

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 6 Nov-Dec 2021, pp: 1180-1198 www.ijprajournal.com ISSN: 2249-7781

transmission methods can reduce the disease's occurrence. Routes of transmission are through contaminated surfaces as well as airborne, fecal-oral transmission. In general, droplet and contact route, airborne transmission, and fecal and oral have been identified to transmit the SARS-CoV-2 virus.



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Schematic representation of SARS-CoV-2 Transmission Routes

Droplet and contact routs:

The main routes of transmission of the COVID-19 virus are respiratory droplets and close contact. Generally, the transmission of the COVID-19 virus through droplets and contact can be done in two ways: [1] direct contact with infected people and [2] indirect contact with surfaces used by an infected person. If the infected person does not observe the social distance (1 m) can make a healthy person sick through coughing or sneezing, the virus entering the mucous membranes of the mouth or nose, or the Conjunctiva (eyes).

Airborne transmission:

Transmission of the virus through airborne particles is one of the main transmission routes of COVID-19 disease. According to published research, if the suspended particles remain in the air for a long time, then they will spread the virus.Also, World Health Organization stated that the virus could also be spread through aerosols in poorly ventilated indoors. In closed environments (ICU rooms), airborne droplets or suspended particles in the air may infect the lungs when large doses of aerosols are inhaled.

Fecal and oral:

As mentioned, gastrointestinal symptoms are a common symptom of COVID-19 disease. Some patients with SARS-CoV-2 have the RNA virus in their stools. Recent research has shown that SARS-CoV-2 in fecal samples from patients with COVID-19 can be another way of transmitting the virus. This transmission can occur through contact with food and contaminated water with fecalsecretions Zhanget al. reported that the molecular diagnostic value of COVID-19 in a stool sample was equivalent to that of an oropharyngeal swab.[6]

Symptoms:

The effect of COVID-19 may vary from person to person, and it may be from mild to moderate with an incubation period of 6 to 41 days (median of 14 days). The manifestation of multiple COVID-19 symptoms, as well as the duration of incubation time, depends on age groups, health conditions, and exposure times. Old age people and patients with immunosuppressed disorders are the most susceptible to the infection. On average, symptoms appear in 5 days after exposure.[11,3]Symptoms of COVID-19 disease differ from patient to patient. Sometimes it may be asymptomatic. Typically, in the early stages of COVID-19 infection, the most common infection symptoms can be fever, dry cough, and tiredness. Less common symptoms are nausea or vomiting, muscle or joint pain, sore throat, loss of sense of smell or taste or both, nasal congestion, conjunctivitis, headache, different types of skin rashes, diarrhea, shivering, and dizziness. In the

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disease's progression stages, the patient will face severe shortness of breath, decreased blood oxygen (hypoxia), destruction of the lungs, and several organs dysfunction. More severe and rare neurological complications of COVID-19 disease. Figure 5 demonstrates the common symptoms of COVID-19.[6]

Diagnosis:[33]

Because of the lack of definitive curative treatment for this disease, the most effective solution after preventing and controlling is the timely diagnosis of the disease and isolating the illnesses. There are several ways to diagnose the disease early, such as the RT-PCR method, CT-Scan, Serological antibody blood test, and Artificial intelligence.WHO recommends the first screen for more common causes of respiratory illness. If a negative result is found, the sample should be sent to a referral laboratory for SARS-CoV-2 detection.[31]

RT-PCR Method:

One of the most important ways to detect the SARS-CoV-2 virus in upper and lower respiratory specimens is the Real-Time Reverse Transcriptase (RT)–PCR Diagnostic Panel. The basis of the PCR iscopying the RNA and DNA structure of the sample,which can diagnose infectious origin and various genetic and blood diseases Below figure demonstrates COVID-19 diagnostic testing through real-time RT-PCR. As shown in Figure 9, there are five necessary steps to perform the test: sample collection, RNA extraction, RT-qPCR set up, and test results, all of which can be customized to explain both this and other RT-qPCR diagnostic protocols. The steps for performing the RT-qPCR test are as follow;

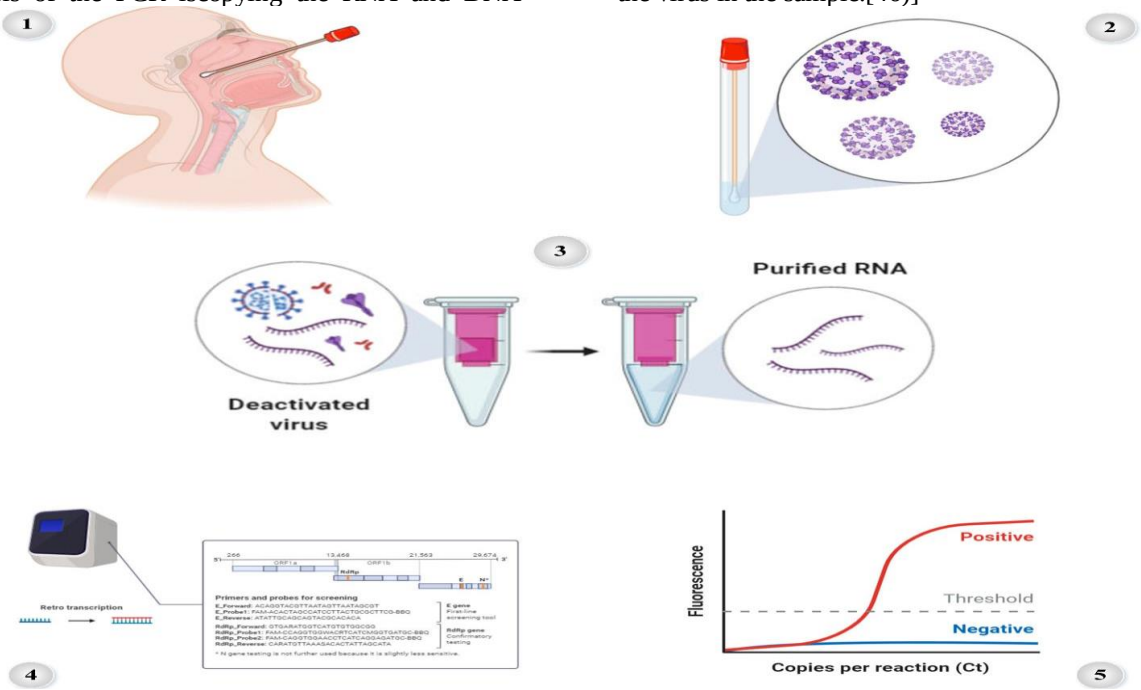
Nasopharyngeal swab <15 min: Cotton swab is inserted into the nostril to absorb sections. Collected specimen 0–72 h specimen is stored at 2–8◦C for up to 72 h or proceed to RNA extraction.

RNA extraction ~45 min purified RNA is extracted from the deactivated virus.

RT-qPCR, ~1 h per primer, set purified RNA is reverse transcribed to cDNA and amplified by qPCR.

Test results real-time positive SARS-CoV-2 patients cross the threshold line within 40.00 cycles (<40.00 Ct).

This method aims to detect the nucleic acid present in the nasal swab sampling or the respiratory tract using the PCR process in real-time. It is confirmed based on the reproduction function and sequence of the virus in the sample.[46)]



The Protocol template COVId-19 diagnostic testing through real-time RT-PCR

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(1)Nasopharyngeal swab (2) Collected specimen, (3) RNA extraction, (4) purified RNA, and (5) Test results real-time

CT-Scan:

Computed tomography (CT) is a suitable diagnostic method that sheds light on several stages of disease diagnosis and development. One way to look at the morphological patterns of lung lesions associated with COVID-19 is through chest scans such as X-rays and computed tomography (CT) scans. It should be noted that the accuracy of diagnosis depends heavily on specialists. In the early stages of the epidemic in any country, the use of CT imaging methods was more critical than RT-PCR due to the lack of RT-PCR technology or the lack of kits and diagnostic equipment suitable for accurate sampling. In addition, CT images are a valuable tool to help physicians identify internal structures and examine their shape, size, density, and texture.Moreover, CT imaging can help to reveal the abnormalities caused by COVID 19. [46]

The Serological Antibody Blood Test:

Serology testing is a diagnostic method for detecting antibody-mediated immune responses against infectious agents. The European Center for Disease Control and Prevention (ECDC) has approved the COVID-19 serological test for epidemiological and monitoring purposes only because it does not detect the early stages of infection The use of serological tests with low prevalence is not appropriate because this method is likely to have false-positive results compared to the actual positive.

The steps for performing a serology test shown in Figure are as follows :

(1) Sample loading: add a drop of blood or serum in the sample well (S).

(2) Buffer loading: add dilution phosphate saline buffer to sample well.

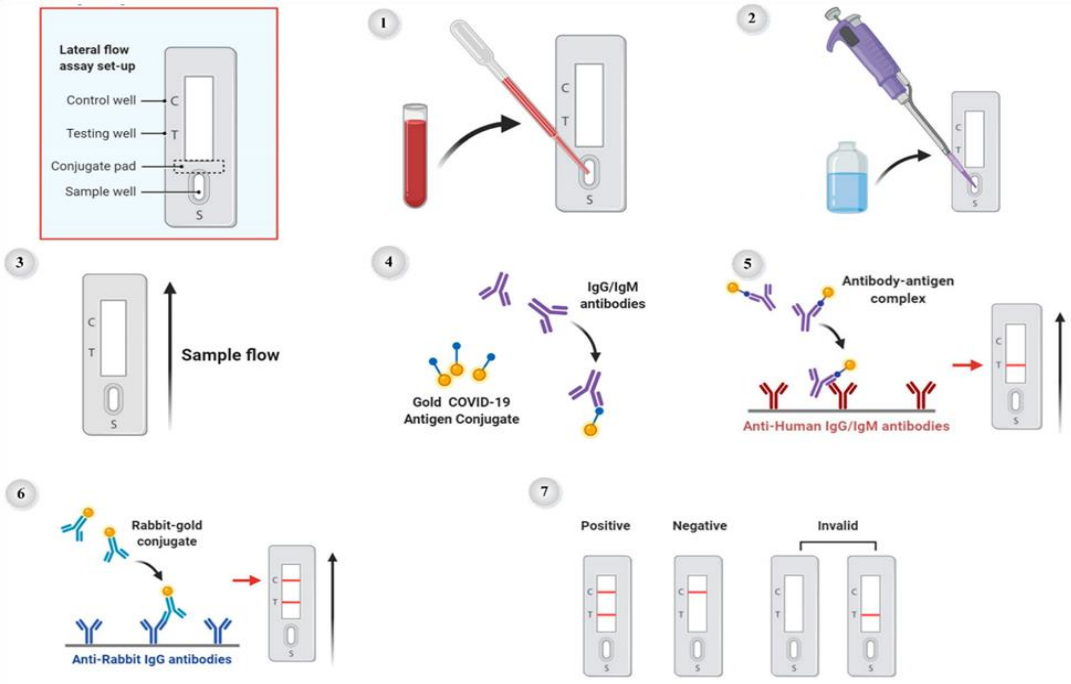
(3) Sample incubation: capillary action moves sample across lateral flow test.

(4) Antibody-antigen recognition: antibodies with specificity for COVID-19 bind to gold COVID-19-antigen conjugates in the conjugate pad.

(5) COVID-19 antibody detection: sample enters testingwell (T), and COVID-19 antibody-antigen complex binds to immobilized anti-human lgG/IgM antibodies.

(6) Control antibody detection: rabbit antibody-gold conjugate binds to immobilized anti-rabbit lgG antibodies.

(7) Interpreting results: Positive: one strip each in C well and T well, Negative = one strip in C well. [6,27]



Schematic of serological testing steps

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Treatment:

Determine the treatment site according to the condition of the patient.According to the severity of a patient's symptoms and the medical resources available in a region, different treatment sites may be selected to observe and isolate patients. The specific classification, from Chinese guidelines,is as follows

Asymptomatic cases: Asymptomatic cases are cases that have not been confirmed and should not be considered as new cases. The main treatment for this measure is centralized quarantine for 14 days and further monitoring by the local Public Health Department. If these cases are in home isolation, household members should stay in a different room, or if this is not possible, maintain a distance of at least 1 meter from the quarantined person

Suspected cases: After permission, patients who have the ability to self-care, age ≤ 65 years old, without primary diseases like respiratory diseases, cardiovascular diseases, and mental health issues, should go to a health care facility voluntarily

Mild cases: They are treated in a mobile cabin hospital if available or at home, if hospitalization is not possible due to the heavy burden on the health care system.The clinical symptoms of these cases are mild and there is no pneumonia manifested on chest imaging. Patients should stay in bed, which is the principle for treatment of mild COVID-19 cases.

Severe/critically ill cases:Patients who are initially diagnosed as critically ill should be admitted into the Intensive Care Unit (ICU) immediately for treatment.Severe cases have severe respiratory symptoms such as shortness of breath, a decrease of oxygen levels, and a decrease of PaO2/FiO2. The general treatment principles for these cases are active prevention and treatment of complications, prevention of secondary infections while treating basic diseases, and organ function support treatment promptly.If respiratory distress and/or hypoxemia cannot be relieved, high-flow nasal cannula oxygen therapy or noninvasive ventilation should be used.[7,27]

Epidemiology:

All ages are at risk of getting the illness. This is because the ailment is transmitted through large droplets that result from coughing and sneezing by symptomatic individuals.[2]In December 2019, many pneumonia cases that were clustered in Wuhan city [30]were reported for the source have shown Huanan Seafood Market as the origin. The first case of the COVID-19 epidemic was discovered with unexplained pneumonia on December 12, 2019, and 27 viral pneumonia cases with seven being severe, were officially announced on December 31, 2019.On January 22, 2020, novel CoV has been declared be originated from wild bats and belonged to Group 2 of beta-coronavirus that contains Severe Acute Respiratory Syndrome Associated Coronavirus (SARS-CoV).Although COVID-19 and SARS-CoV belong to the same beta corona virüs subgroup[8,28]

Covid cases worldwide:Globally, as of 5:02pm CET, 14 December 2021, there have been 270,031,622 confirmed cases of COVID-19, including 5,310,502 deaths, reported to WHO

No of vaccinated pepole:

As of 12 December 2021, a total of 8,200,642,671 vaccine doses have been administered. [9,21]

Different Vaccines in COVID -19 Virus :

How do vaccines work?[9]

Germs are all around us, both in our environment and in our bodies. When a person is susceptible and they encounter a harmful organism, it can lead to disease and death.

The body has many ways of defending itself against pathogens (disease-causing organisms). Skin, mucus, and cilia (microscopic hairs that move debris away from the lungs) all work as physical barriers to prevent pathogens from entering the body in the first place.

When a pathogen does infect the body, our body's defenses, called the immune system, are triggered and the pathogen is attacked and destroyed, or overcome

The body's natural response:

A pathogen is a bacterium, virus, parasite, or fungus that can cause disease within the body. Each pathogen is made up of several subparts, usually unique to that specific pathogen and the disease it causes. The subpart of a pathogen that causes the formation of antibodies is called an antigen. The antibodies produced in response to the pathogen's antigen are an important part of the immune system. You can consider antibodies as the soldiers in your body's defense system. Each antibody, or soldier, in our system, is trained to recognize one

(1) Sample loading, (2) Buffer loading, (3) Sample incubation, (4) Antibody-antigen recognition, (5) COVID-19 antibody detection, (6) Control antibody detection and (7) Interpreting results: Positive (Reprinted from "COVID-19 Serologic Diagnostic Test through Antibody Detection

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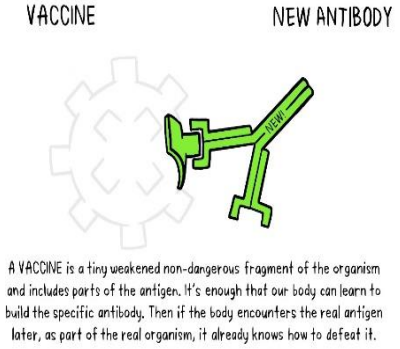
specific antigen. We have thousands of different antibodies in our bodies. When the human body is exposed to an antigen for the first time, it takes time for the immune system to respond and produce antibodies specific to that antigen. In the meantime, the person is susceptible to becoming ill. Once the antigen-specific antibodies are produced, they work with the rest of the immune system to destroy the pathogen and stop the disease. Antibodies to one pathogen generally don't protect against another pathogen except when two pathogens are very similar to each other, like cousins. Once the body produces antibodies in its primary response to an antigen, it also creates antibody-producing memory cells, which remain alive even after the pathogen is defeated by the antibodies. If the body is exposed to the same pathogen more than once, the antibody response is much faster and more effective than the first time around because the memory cells are at the ready to pump out antibodies against that antigen.

This means that if the person is exposed to the dangerous pathogen in the future, their immune system will be able to respond immediately, protecting against disease.

How do vaccines help?

Vaccines contain weakened or inactive parts of a particular organism (antigen) that trigger an immune response within the body. Newer vaccines contain the blueprint for producing antigens rather than the antigen itself. Regardless of whether the vaccine is made up of the antigen itself or the blueprint so that the body will produce the antigen, this weakened version will not cause the disease in the person receiving the vaccine, but it will prompt their immune system to respond much as it would have on its first reaction to the actual pathogen.

Some vaccines require multiple doses, given weeks or months apart. This is sometimes needed to allow for the production of long-lived antibodies and the development of memory cells. In this way, the body is trained to fight the specific disease-causing organism, building up the memory of the pathogen to rapidly fight it if and when exposed in the future**.**



Vaccines development :

What are the ingredients in a vaccine?

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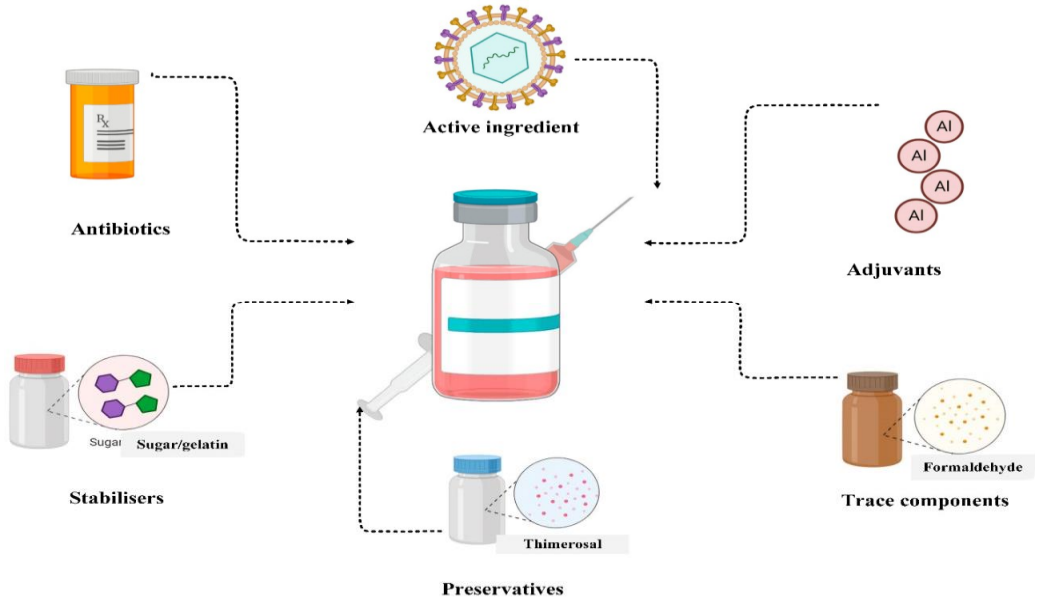
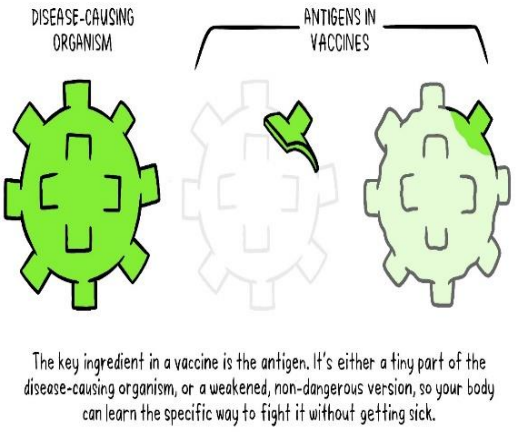


Common components / Ingredients of Vaccines

Vaccines contain tiny fragments of the disease-causing organism or the blueprints for making the tiny fragments. They also contain other ingredients to keep the vaccine safe and effective. These latter ingredients are included in most vaccines and have been used for decades in billions of doses of vaccines.Each vaccine component serves a specific purpose, and each ingredient is tested in the manufacturing process. All ingredients are tested for safety.

Antigen:

All vaccines contain an active component (the antigen) that generates an immune response, or the blueprint for making the active component. The antigen may be a small part of the disease-causing organism, like a protein or sugar, or it may be the whole organism in a weakened or inactive form.



Preservatives:

Preservatives prevent the vaccine from becoming contaminated once the vial has been opened if it will be used for vaccinating more than one person. Some vaccines don't have preservatives because they are stored in one-dose vials and are discarded after the single dose is administered. The most commonly used preservative is 2-phenoxyethanol. It has been used for many years in several vaccines, is used in a

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range of baby care products, and is safe for use in vaccines, as it has little toxicity in humans.

Stabilizers:

Stabilizers prevent chemical reactions from occurring within the vaccine and keep the vaccine components from sticking to the vaccine vial.

Stabilizers can be sugars (lactose, sucrose), amino acids (glycine), gelatin, and proteins (recombinant human albumin, derived from yeast).

Surfactants:

Surfactants keep all the ingredients in the vaccine blended. They prevent settling and clumping of elements that are in the liquid form of the vaccine. They are also often used in foods like ice cream.

Residuals:

Residuals are tiny amounts of various substances used during the manufacturing or production of vaccines that are not active ingredients in the completed vaccine. Substances will vary depending on the manufacturing process used and may include egg proteins, yeast, or antibiotics. Residual traces of these substances which may be present in a vaccine are in such small quantities that they need to be measured as parts per million or parts per billion.

Diluent:

A diluent is a liquid used to dilute a vaccine to the correct concentration immediately before use. The most commonly used diluent is sterile water.

Adjuvant:

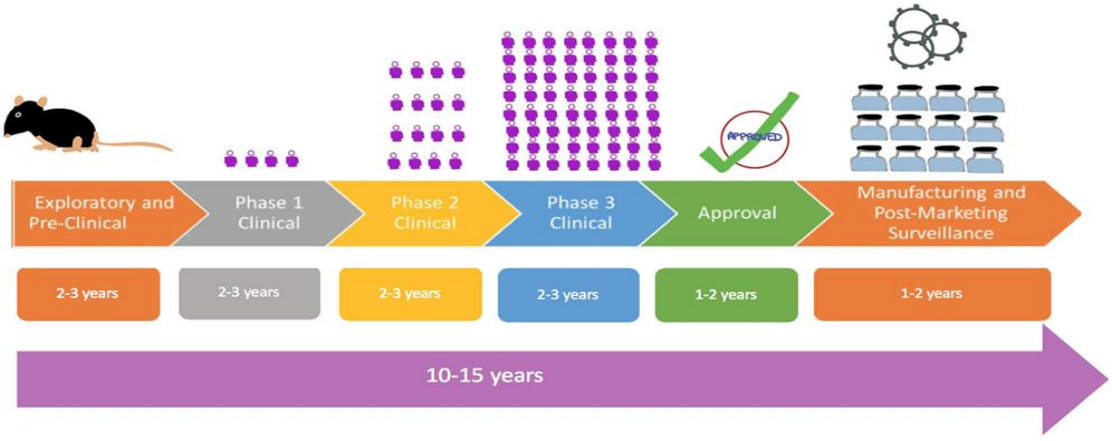
Some vaccines also contain adjuvants. An adjuvant improves the immune response to the vaccine, sometimes by keeping the vaccine at the injection site for a little longer or by stimulating local immune cells.

The adjuvant may be a tiny amount of aluminium salts (like aluminium phosphate, aluminium hydroxide, or potassium aluminium sulphate). Aluminium has been shown not to cause any long-term health problems, and humans ingest aluminium regularly through eating and drinking.

How are vaccines developed?

The development of a new vaccine has been a long process that can take 10 to 15 years. The fastest vaccine that has been developed and approved for use is for mumps, which took approximately 5 years. Hence, it is a challenge to develop a vaccine against COVID-19 in 12–24 months. The first phase of vaccine development is an exploratory stage involving basic laboratory bench research and computational modeling to identify natural or synthetic antigens that can be used as a vaccine candidate which might help prevent or treat a disease.[18,45]

The second stage consists of preclinical studies which might help prevent or treat a disease., which involve cell-culture or tissue-culture systems and trials on an animal model to assess the safety of the candidate vaccine and its immunogenicity, or ability to provoke an immune response. Once safety, immunogenicity, and efficacy are demonstrated on animals then, progress is made to human clinical trials which test for safety and immunogenicity in small groups than large groups over 3 phases, as given below.



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The traditional process of vaccine development:

Phase 1 - Safety:

Phase 1 is the first stage where the vaccine is administered to humans. The vaccine is given to a small number of healthy and immunocompetent individuals to primarily test for safety, appropriate dose, and to check for immune response, as a secondary effect.

Phase 2 - Expanded Safety:

In Phase 2 the vaccine is given to hundreds of people split into different groups by demographics (example: elderly vs. young). These again test primarily for safety, appropriate dosage, and the interval between doses and check for immune response, as a secondary effect. This phase serves to confirmthe vaccine is safe and immunogenic and also determines the appropriate dose to be used in Phase 3 trials.

Phase 3 - Efficacy:

Phase 3 is a large-scale trial where the vaccine is given to thousands of people to evaluate efficacy Vaccine efficacy (VE) is defined as the percentage by which the rate of disease incidence is reduced in vaccinated groups as compared to placebo. At this phase Incidence of disease impacts the sample size. In the case of a low incidence of disease in the population, large sample size will be needed to adequately determine vaccine efficacy. After the completion of human clinical trials, the safety and clinical efficacy have been determined, then the vaccine will move to:

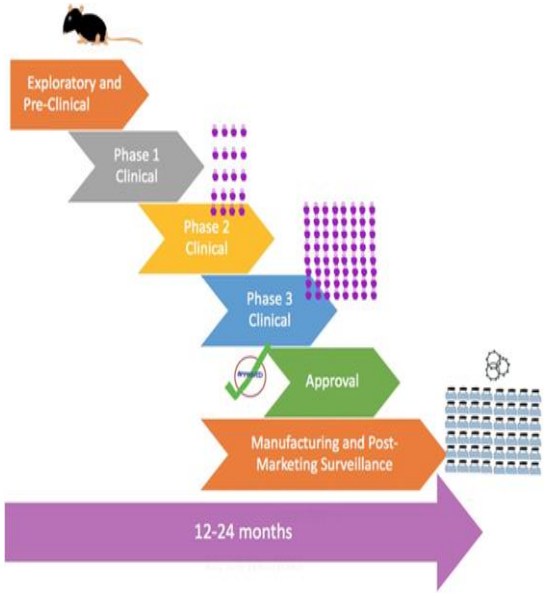
• Review and Approval:

Generally, regulatory bodies, such as the Food and Drug Administration (FDA) of the USA, or the European Medicines Agency in the EU, must review the results from clinical trials and decide if the vaccine is fit to be approved. As this process can take a duration from 1 to 2 years, vaccines may be approved for emergency use in a pandemic.

• Manufacturing and Post-Marketing Surveillance:

Manufacturing and Post-Marketing Surveillance is done after the vaccine is marketed for public use and monitored for general effectiveness within the population. They also record adverse effects that might be experienced after the vaccine is adopted for widespread use

The pandemonium caused by the COVID-19 pandemic and the urgent need for an effective vaccine globally, vaccine development can be accelerated by combining phases, as shown by Figure 2. An example would be combining Phases 1 and 2 to test for safety in hundreds of people directly.And hence vaccines also do not go through the full approval process and may instead be approved for emergency use for a quick release for use by the most vulnerable group.[10]



Flowchart showing accelerated process of vaccine development: in a pandemic with combined phases, pre-approval, and rapid large-scale manufacturing. The symbol is a representation of the number of human subjects in trials.

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Types of COVID-19 vaccines :

There are three main approaches to designing a vaccine. Their differences lie in whether they use a whole virus or bacterium; just the parts of the germ that triggers the immune system; or just the genetic material that provides the instructions for making specific proteins and not the whole virus.

The whole-microbe approach:

Inactivated vaccine

Inactivated vaccine platforms have been widely used over the past 70 years. Inactivated vaccines are produced by inactivating the viruses with chemicals, UV light, and heat. Inactivation of the organism makes a safe vaccine[44]

The first way to make a vaccine is to take the disease-carrying virus or bacterium, or one very similar to it, and inactivate or kill it using chemicals, heat, or radiation. This approach usestechnology that's been proven to work in people this is the way the flu and polio vaccines are made and vaccines can be manufactured on a reasonable scale.However, it requires special laboratory facilities to grow the virus or bacterium safely, can have a relatively long production time, and will likely require two or three doses to be administered.[39,9]Inactivated pathogen vaccines use a dead form of the pathogen, thus ensuring a better safety profile than live attenuated vaccines.[49]

Live-attenuated vaccine

Live-attenuated vaccines (LAV) controlled several infections disease outbreaks like yellow fever, mumps, measles, rubella, polio, and chickenpox.[44] A live-attenuated vaccine uses a living but weakened version of the virus or one that's very similar. The measles, mumps, and rubella (MMR) vaccine and the chickenpox and shingles vaccine are examples of this type of vaccine. This approach uses similar technology to the inactivated vaccine and can be manufactured at scale. However, vaccines like this may not be suitable for people with compromised immune systems.[35]

Viral vector vaccine

This type of vaccine uses a safe virus to deliver specific sub-parts – called proteins – of the germ of interest so that it can trigger an immune response without causing disease. To do this, the instructions for making particular parts of the pathogen of interest are inserted into a safe virus. The safe virus then serves as a platform or vector to deliver the protein into the body. The protein triggers the immune response. The Ebola vaccine is a viral vector vaccine and this type can be developed rapidly.[9]

A subunit vaccine is one that only uses the very specific parts (the subunits) of a virus or bacterium that the immune system needs to recognize. It doesn't contain the whole microbe or uses a safe virus as a vector. The subunits may beproteins or sugars. Most of the vaccines on thechildhood schedule are subunit vaccines, protecting people from diseases such as whooping cough, tetanus, diphtheria, and meningococcal meningitis.

The genetic approach (nucleic acid vaccine)

One of the recent trends in vaccine development is the development of nucleic acid platforms that encode pathogen antigens.[49].Unlike vaccine approaches that use either a weakened or dead whole microbe or parts of one, a nucleic acid vaccine just uses a section of genetic material that provides the instructions for specific proteins, not the whole microbe. DNA and RNA are the instructions our cells use to make proteins. In our cells, DNA is first turned into messenger RNA, which is then used as the blueprint to make specific proteins.A nucleic acid vaccine delivers a specific set of instructions to our cells, either as DNA or mRNA, for them to make the specific protein that we want our immune system to recognize and respond to. The nucleic acid approach is a new way of developing vaccines. Before the COVID-19 pandemic, none had yet been through the full approvals process for use in humans, though some DNA vaccines, including for particular cancers, were undergoing human trials. Because of the pandemic, research in this area has progressed very fast and some mRNA vaccines for COVID-19 are getting emergency use authorization, which means they can now be given to people beyond using them only in clinical trials.[9]

Vaccine for COVID-19:

1)Johnson & Johnson's Janssen (J&J/Janssen) COVID-19 Vaccine:[12]

- Name of vaccine :JNJ-78436735
- Manufacturer: Janssen Pharmaceuticals Companies of Johnson & Johnson.
- Emergency use authorization:February 27, 2021[14]
- Type of vaccine:Viral Vector
- Number of Shots: 1 shot[16)]

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- Route of administration:Shot in the muscle of the upper arm.
- Recommanded dose: one dose (0.5 ml) [9]
- Mechanism of action:The vaccine uses Jansen's AdVac and PER.C6 technologies to develop the JNJ-78436735 vaccine (Johnson & Johnson, 2020). The vaccine is a recombinant vector vaccine that uses a human adenoviral vector to express the COVID-19 spike protein within cells. It introduces a piece of DNA from SARS-CoV-2 into the common cold-causing adenovirus that has been genetically changed so that it can't replicate in the body[11].The J&J/Janssen COVID-19 Vaccine was 66.3% effective in clinical trials (efficacy) at preventing laboratory-confirmed COVID-19 infection in people who received the vaccine and had no evidence of being previously infected. People had the most protection 2 weeks after getting vaccinated.In the clinical trials, the vaccine had high efficacy at preventing hospitalization and death in people who did get sick. No one who got COVID-19 at least 4 weeks after receiving the J&J/Janssen COVID-19 Vaccine had to be hospitalized.CDC will continue to provide updates as we learn more about how well the J&J/Janssen COVID-19 Vaccine works in real-world conditions[12]
- Possible Side Effects
- Side effects that have been reported with the Janssen COVID-19 Vaccine include:
  - Injection site reactions: pain, redness of the skin, and swelling.
  - General side effects: headache, feeling very tired, muscle aches, nausea, and fever.
  - Swollen lymph nodes.
  - Unusual feeling in the skin (such as tingling or a crawling feeling) (paresthesia), decreased feeling
  - or sensitivity, especially in the skin (hypoesthesia).
  - Persistent ringing in the ears (tinnitus).
  - Diarrhea, vomiting[14]

2)Pfizer-BioNTech COVID-19 Vaccine:

- Name: BNT162b2
- Manufacturer: Pfizer, Inc., and BioNTech
- Emergency use authorization: WHO listed the Pfizer/BioNTech vaccine for emergency use on 31 December 2020.
- Type of Vaccine: mRNA[48]
- Number of Shots: 2 shots, 21 days apart.Moderately to severely immunocompromised people should get an additional shot (3rd dose) at least 28 days after their 2nd shot. Other groups of people are recommended to get a booster shot at least 6 months after getting their 2nd shot.
- Route of administration: Shot in the muscle of the upper arm
- Mechanism of action:Just like mRNA-1273, BNT162b2 is an mRNA vaccine that passes instructions to human cells that do not make spike proteins on their own. The cells read the mRNA instructions of the BNT162b2 vaccine and instruct it to produce the spike protein responsible for triggering the immune system to initiate defensive responses against SARS-CoV-2.[11].Based on evidence from clinical trials in people 16 years and older, the Pfizer-BioNTech (COMIRNATY) vaccine was 95% effective at preventing laboratory-confirmed infection with the virus that causes COVID-19 in people who received two doses and had no evidence of being previously infected. In clinical trials, the Pfizer-BioNTech vaccine wasalso highly effective at preventing laboratory-confirmed COVID-19 infection in adolescents 12–15 years old, and the immune response in people 12–15 years old was at least as strong as the immune response in people 16–25 years old. The vaccine was also highly effective in clinical trials at preventing COVID-19 among people of diverse age, sex, race, and ethnicity categories and among people with underlying medical conditions.[38] Evidence shows mRNA COVID-19 vaccines offer similar protection in real-world conditions as they have in clinical trial settings reducing the risk of COVID-19, including severe illness by 90% or more, among people who are fully vaccinated.[12]
- Possible Side Effects
  - In the arm where you got the shot:
  - Pain
  - Redness
  - Swelling
  - Throughout the rest of your body:
  - Tiredness
  - Headache
  - Muscle pain
  - Chills
  - Fever
  - Nausea

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These side effects happen within a day or two of getting the vaccine. They are normal signs that your body is building protection and should go away within a few days.[12]

3)Moderna COVID-19 Vaccine:

- Name: mRNA-1273
- Manufacturer: ModernaTX, Inc.
- Emergency use authorization: December 18, 2020[45]
- Type of Vaccine: mRNA
- Number of Shots: 2 shots, 28 days apart,Some immunocompromised people should get 3 shots.
- Route of administration: Shot in the muscle of the upper arm.[36]
- Mechanism of action:

Moderna's mRNA-1273 vaccine is an mRNA vaccine which is essentially strands of mRNA carrying instructions for the cell guiding it on how to produce a spike protein that is distinct to SARS-CoV-2 which then stimulates the immune response/produces antibodies to fight the virus. mRNA-1273 encodes for the full-length spike (S) protein of SARS-CoV-2,modified to introduce 2 proline residues to stabilize the S protein (S2P) in a prefusion conformation. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies that prevent infection.[11].Based on evidence from clinical trials, in people aged 18 years and older, the Moderna vaccine was 94.1% effective at preventing laboratory-confirmed COVID-19 infection in people who received two doses and had no evidence of being previously infected[37].The vaccine was also highly effective in clinical trials at preventing COVID-19 among people of diverse age, sex, race, and ethnicity categories and among people with underlying medical conditions.CDC will continue to provide updates as we learn more about how well the Moderna vaccine works in real-world conditions.[12]

- Common vaccine side effects may include:
  - Symptoms at the injection site, such as
  - redness
  - soreness
  - swelling
  - Flu-like symptoms, such as:
  - chills
  - fatigue
  - joint pain
  - headache
  - mild fever
  - Rare vaccine side effects
  - Rare reactions that have been reported and confirmed after taking an mRNA vaccine are:
  - Myocarditis and pericarditis
  - Bell's palsy (facial paralysis
  - muscle aches[36]

4)Oxford/AstraZeneca COVID-19 vaccine:[9]

- Name of Vaccine: AZD1222
- Manufacturer:Two versions of the vaccine – produced by AstraZeneca-SKBio (Republic of Korea) and the Serum Institute of India(Covishield).
- Effective Date:15 February 2021[9]
- Type of vaccine:Viral vector[15]
- Number of Shots: 2 shots.
- Route of administration: Intramuscular (IM) injection only.[13]
- Mechanism of action:

Consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein;nCoV-19) gene. AZD1222 uses a replication-deficient chimpanzee adenovirus as a vector. It has within it an encoded genetic sequence of SARS-CoV-2 and works by instructing cells to produce the spike protein of COVID-19 that triggers the immune response that prepares the body against future attacks of the virus.[11].

- Possible side effects/Adverse reactions:
  - The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination.[13].

5)Sinovac-CoronaVac COVID-19 vaccine:

- Name of Vaccine: Corona Vac
- Manufacturer:Sinovac. Biotech Ltd [44]
- Type of vaccine:Inactivated virus[15]
- Number of shots: 2[16]
- Route of administration:intramuscularly into the deltoid muscle[9]
- Mechanism of action:

CoronaVac is an inactivated vaccine where the specific virus is contained with heat or chemicals and its dead cells introduced to the subject's body. The immune system then learns from the dead antigens how to deal with live versions of it should the subject happen to get infected with the virus in the future. In

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CoronaVac's case, the coronavirus was inactivated with beta-propiolactone and contained inactivated SARS-CoV-2 of course.[11]

- Side effect :
  - Injection site pain
  - Soreness
  - fatigue
  - diarrhea
  - muscle weakness
  - itching
  - swelling
  - inflammation
  - raised bumps

6)Sputnik V COVID -19 vaccine:

- Name of vaccine:Gam-COVID-Vac(Sputnik V).
- Manufacturer:Gamaleya National Research Center for Epidemiology and Microbiology(Russia)
- Type of vaccine:Viral vector
- Number of shots:2[50]
- Mechanism of action:

Sputnik V is a two-adenoviral vector vaccine that gets gene encoding of SARS-CoV-2 S protein added into each vector (Clinical Trials, 2020). During the first vaccination, the initial gene-containing vector (rAd26) which carries instructions on SARS-CoV-2 S protein gets into the cells which after synthesis triggers an immune response. Another vector (rAd5) is introduced to the body through second vaccination which boosts the immune response and provides long-term immunity.

- Side effects:

An interim analysis of phase 3 clinical trial data, published in The LancetTrusted Source in February 2021, reports on the efficacy and safety of the vaccine. Based on the data, the most common side effects were:

- flu-like illness
- headache
- fatigue
- injection-site reactions

These side effects are similar to those of the Pfizer, Moderna, and Johnson & Johnson COVID-19 vaccines, as noted by the Centers for Disease Control and Prevention (CDC).[40]

7)Covaxin (BBV 152):

- Name of vaccine: Covaxin
- Manufacturer:Bharat Biotech
- Type of vaccine:Inactivated virus
- Number of shots:2[50]
- Mechanism of action :

BBV 152 is a whole-viron inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule (IMDG) adsorbed to alum (Algel).Previous animal studies showed acceptable safety profiles, humoral and cell-mediated responses. Phase 2 trials showed good reactogenicity, safety profile, and enhanced humoral and cell-mediated immune responses when participants received a higher dose (6 g) of Algel-IMDG formulation. In the phase 2 trial, the GMT at day 56 was significantly higher in the 6 g group (197.0, 95% CI 155.6–249.4) compared with the 3 g group (100.9, 95% CI 74.7–137.4, p = 0.0041). Seroconversion rates were 92.9% (95% CI 88.2–96.2) in the 3 age group and 98.3% (95% CI 95.1–99.6) in the 6 g group. The Algel-IMDG formulation elicited T-cell responses biased to a Th1 phenotype at day 42,with no significant difference in causing local or systemic adverse reactions between the 3 g and the 6 g groups. No serious adverse events were reported in the study. Protective efficacy was not reported.[16]

- Side Effect:Side effects that have been reported with the Bharat Biotech COVID-19 (COVAXIN) include:
  - Injectionsite pain/ Swelling / Redness/ Itching
  - Headache
  - Fever
  - Malaise/bodyache
  - Nausea
  - Vomiting
  - Rashes(20)

8)Novavax COVID-19 vaccine (NVCoV2373):

- Name of vaccine:NVX-CoV2373[50]
- Manufacture:Novavax, Inc (US)[47]
- Type of vaccine:Protein subunit
- Number of shots:2[15]
- Mechanism of action

The vaccine combines spike proteins into a knucklebone-shaped nanoparticle that can be injected along with its proprietary Matrix-M adjuvant which has demonstrated a potent and well-tolerated effect by stimulating the entry of antigen-presenting cells into the injection site and enhancing antigenpresentation in local lymph nodes, boosting immune Response.[11]

  - Side effects :
  - Injection site pain and tenderness,
  - fatigue,
  - muscle pain was the most commonly reported side effect.[42]

9)Sinopharm:

- Name of vaccine:BBIBP-CorV

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- Manufacture:Sinopharm ½ (China)
- Type of vaccine:Inactivated virus
- Number of shots:2[15]
- Mechanism of action:

This vaccine is being developed by a Chinese state-owned company called Sinopharm. It is an inactivated vaccine that gets introduced into the body as a dead copy of SARS-CoV-2. Its dead antigens are then used to produce antibodies that prime the immunity system against future attacks by the virus.[11].

- Side effect:Prevalence of general side effects after the first dose of the Sinopharm COVID-19 vaccination
  - Normal pain at the vaccination site
  - Severe pain at the vaccination site
  - Tenderness
  - Redness
  - Headache
  - Fatigue
  - Nausea
  - Diarrhea
  - Cough
  - Allergy
  - Muscle pain
  - Abdominal pain
  - Back pain
  - Lethargy[41]

Future Perspective:

The destructive impact of COVID-19 has catalyzed the extraordinary development of vaccines and vaccine technologies in the fight against this pandemic.The COVID-19 outbreak is proving to be an unprecedented disaster, especially in the most addicted countries including China, Italy, Iran, and the USA in all aspects, especially health, social and economic.Within one year of the outbreak of this disease, many COVID-19 vaccines progressed, and more than 70 vaccines have proceeded into clinical trials. A few of these have obtained conditional approval, and more hold the promise to gain such approval.Many vaccines under development use traditional approaches, several innovative technologies, such as mRNA vaccines, and nonreplicating adenovirus vaccinesDespite such remarkable progress in COVID-19 vaccine development, many issues remain to be addressed. Although clinical trial data have shown that the COVID-19 vaccines approved so far can expose immunity with a high degree of efficacy, it is not yet known how strong the immunity will be.A recently published study examining multiple components of adaptive immunity in COVID-19 infection cases indicated that SARS-CoV-2 immunity may last at least 8 months.On the other hand, a matching study predicts decay of neutralization titer over the first 250 days after immunization with seven conditionally approved vaccines. More long-term studies of immune responses following vaccination will be needed to provide a more conclusive answer.[17]

II. CONCLUSION:

This review provides using WHO's data and CAS-curated data, which provides a comprehensive review on COVID-19 vaccine around the world[17]. The COVID-19 pandemic has challenged the world not just in global health but also the global psychosocial and economic health.[18]. There is a rapidly growing body of literature on this topic and hopefully,this will help. Only once this pandemic ends, one will be able to assess the health, social and economic impact of this global disaster and we should be able to learn lessons especially in terms of public and global health for any future similar pandemic.The prevalence of COVID-19 had been identified as a global health emergency. According to the WHO Globally, as of 5:09pm CEST, 20 October 2021, there have been 241,411,380 confirmed cases of COVID-19, including 4,912,112 deaths.Fortunately, due to researchers' and pharmaceutical companies'efforts, many effective vaccines to prevent the prevalence of this deadly disease have been approved by the World Health Organization.After the results drawn from phase 3 trials of the various vaccines against SARS-CoV-2, it can be concluded that very helpful interventions have been developed to fight the Coronavirus pandemic. At this rate, the world will not only have one vaccine but a dozen full of them. In addition to the positive results, research from the whole vaccine development operation will provide very useful insights in future quests for a vaccine.The COVID-19 vaccines in clinical trials have all shown promising immunogenicity with varying degrees of protective efficacy and an acceptable safety profile. A second dose immunization gives a more robust immune response in all vaccines. The immunological outcome in the elderly is poorer than in the younger recipients. Further exploration of immunization schedulesis required, such as more frequent vaccinations or higher dosage in each injection. Grade 3 or above side effects are not common in the clinical trials to date.

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