Section A-Research paper

An Overview about COVID-19 Vaccinations

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Abstract

Background: The WHO has a list of more than 200 COVID-19 vaccines that are in development. High hopes exist for preventive COVID-19 vaccinations that are successful.3 Vaccines that passed phase III clinical studies and were shown to be safe and efficacious could be available in 2021. A number of vaccines, including Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2, have received commercial approval. Both humoral and cellular immunity must be taken into account in the development of the COVID-19 vaccines. Additionally, as COVID-19 is mostly transmitted through touch with the respiratory system, more focus should be placed on the function of mucosal immunity in avoiding viral infections. Four structural proteins are present in the virus.

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The first types of coronaviruses (CoV) were discovered in mid 1960s and has in the past years caused viral outbreaks all over the world. The name is adapted from their characteristic surface crown-like spikes. Normally CoVs circulate in animals, such as camels, cats, pangolin, snakes, and bats, and have the ability to be transmitted between animals and humans. **(1)**

Five varieties of CoVs have been identified in contemporary medical history, three of which have caused viral epidemics. First found in the mid-1960s, HCoV-OC43 and HCoV-229E were demonstrated to cause the common cold but seldom infections of the lower respiratory tract. **(2)**

More recently, two new human coronaviruses have been identified: HCoV-HKU1 was recovered from a 71-year-old man with fever and cough, and HCoV-NL63 was isolated from a seven-month-old baby. **(3)**

The massive spike protein molecules that are found on the viral surface and give the virions a crown-like form gave the coronavirus family its name; coronavirus genomes are the biggest among RNA viruses. Alpha, beta, and gamma are the three major genera that make up this family. Seven viruses from this family are now known to cause human infection; these include the alpha genus's NL63 and 229E, and the beta genus's OC43, HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2. According to the International Committee on Taxonomy of Viruses, SARS-CoV is a positivestranded RNA virus that belongs to the family Coronaviridae, order Nidovirales, genus Betacoronavirus, and lineage B. **(4)**

MERS-CoV was the first betacoronavirus lineage C member identified as a "novel coronavirus" with a genomic size of 30,119 nucleotides, although belonging to the same family, order, and genus as SARS-CoV. Ten proteins are encoded by the MERS-CoV genome. Two replicase polyproteins (ORF1ab and ORF1a), four structural proteins (E, N, S, and M), and four nonstructural proteins (ORFs 3, 4a, 4b, and 5) make up the ten proteins in question. **(5)**

There are accessory protein genes scattered between the structural protein genes in addition to the rep and structural genes, which may affect the host innate immune response in infected animals. **(6)**

Most MERS cases had prior interaction with dromedary camels, unlike the SARS cases. The MERS-CoV isolates were discovered to be quite common in camels from the Middle East, Africa, and Asia. The MERS-CoV isolates were virtually identical to those recovered from people. **(7)**

Several different zoonotic viruses cause acute respiratory tract infections in western and developing countries. Annually, there are an estimated one billion zoonotic positive cases every year, and up to millions of deaths yearly. **(8)**

Coronaviruses are identified as a zoonotic virus-containing single stranded RNA, that transmit infection between people and vertebrate animals and is found throughout this world. The three big coronaviruses that have caused fatal consequences have started twice in China and once in middle east. **(8)**

SARS-CoV-2 in human and betacoronaviruses in bats are proven until date to be the most closely related, but the intermediate host leading to transmission in humans is still unknown. **(9)**

To survive the mammal immune system, SARS viruses develops virulence factors that manipulate and suppress the immune system. SARS-CoV-2 has developed postponement and hindrance of IFN mediated production of neutralizing antibodies. **(10)**

In comparison to SARSCoV-1, SARS-CoV-2 has an evolutionary gain of Furin cleavage site (FCS) on the S protein. Infection caused by this virus can be spread with contact/droplet, airborne, and fomite transmission, along with other methods of transmission. Contact and droplet transmission is spread with respiratory droplets through coughs, sneezes, and talks with infected people. Touching contaminated surfaces and then eyes, nose or mouth, can lead to fomite transmission. Fomite of liable SARS-CoV-2 virus or RNA analyzed with RT-PCR has shown that SARSCoV-2 can be found on these surfaces for hours to days, depending on the environment (humidity and temperature). **(11)**

Additionally, the scant and insufficient information suggests that although highly unlikely, maternal-fetal transmission of SARS-CoV-2 is possibly conceivable. Recent studies revealed that SARS-CoV-2 was found in stools, along with its nucleocapsid protein, which was found in gastrointestinal tissues. Live SARS-CoV-2 was also grown from stools. It should be noted that SARSCoV-2 might also be found in sputum, urine, blood/serum, ocular surface, saliva, and aerosol.. **(12)**

The WHO has a list of more than 200 COVID-19 vaccines that are in development. High hopes exist for preventive COVID-19 vaccinations that are successful.3 Vaccines that passed phase III clinical studies and were shown to be safe and efficacious could be available in 2021. A number of vaccines, including Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2, have received commercial approval. **(13)**

Both humoral and cellular immunity must be taken into account in the development of the COVID-19 vaccines. Additionally, as COVID-19 is mostly transmitted through touch with the respiratory system, more focus should be placed on the function of mucosal immunity in avoiding viral infections. Four structural proteins are present in the virus. **(13)**

They are Nucleocapsid (N) protein, Spike (S) protein, Envelope (E) protein, and Membrane/Matrix protein. S1 and S2 are the two divisions of the S protein. Cells are infected by the virus when the S protein attaches to certain receptors. This process can be stopped and the virus invasion prevented by the neutralizing antibody directed against the S protein. **(14)**

The most crucial target antigen for vaccine development is S protein because it has the ability to efficiently boost T-cell immunity. It has also been demonstrated that N and M proteins may stimulate the body to develop a powerful cellular immunological response. **(14)**

For a respiratory virus that binds to angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 is rare. Almost all organs, but particularly the lungs, intestines, and brain, may express ACE2. Because of this, SARS-CoV-2 has a wider biological distribution than the majority of respiratory viruses and may cause significant harm outside the respiratory system. The genitourinary system, digestive system, circulatory system, and central nervous system are all negatively impacted. **(15)**

A number of different alterations in symptoms, including dyspnea, headaches, diarrhea, venous thromboembolism, and elevated blood pressure, are brought on by the ubiquitous distribution of ACE2

receptors. To facilitate infection, the S protein interacts to ACE2 on cells. While the S2 subunit encourages viral fusion with cells to start infection, the S1 subunit, which has the receptor-binding domain (RBD), is in charge of initial attachment to the host cells via the ACE2 receptor. As it is anticipated that antibodies attaching to the proper epitope on the S protein may be neutralizing and impede intercellular viral propagation, the S protein is frequently the target of vaccines. **(16)**

A total of 13,375,580,553 doses of various vaccines have been administered by May 2023 worldwide. **(8)**

Types of Vaccines

DNA Vaccines

Similar to viral infections, DNA vaccines may enter cells and produce target antigens by using the host protein translation machinery. It can simultaneously trigger cellular and humoral immune responses since it is an endogenous immunogen. Given the benefits of nucleic acid vaccinations, safety is increased by the fact that DNA vaccines do not require live viruses. In order to produce antigen proteins in host cells and trigger immune responses to prevent illness, DNA vaccines incorporate genes encoding foreign antigens onto plasmids containing eukaryotic expression elements before directly injecting the plasmids into people or animals. **(17)**

Plasmid DNA can be created very easily, and the double-strand DNA molecules are more durable than viral counterparts and can be freeze-dried for long-term preservation. The DNA vaccine immunization technique restricts its use. After vaccination, the vaccine is primarily dispersed in the intercellular space, therefore the immune response is significantly diminished since only a very little quantity of vaccine can enter the cell to make protein immunogen. The poor transfection effectiveness of the plasmid DNA vaccine, which necessitates transfection methods, is the key deterrent. For instance, the COVID-19 vaccine candidate from Inovio, INO-4800, employs the CELLECTRA portable electroporation equipment. **(18)**

The electrodes and the vaccination will both be inserted intradermally. The cell membrane is then split apart by an electric pulse, allowing the plasmid to enter the cells. While using a well-established device may enable a quick start in clinical trials, it also introduces new challenges for widespread immunization. Although nucleic acid vaccines can successfully elicit systemic immune responses, their immunogenicity is poor and it is difficult to elicit mucosal immune responses. Although there have been a few animal DNA vaccines on the market, no human DNA vaccine has yet to receive commercial approval. Better immunological effects can be achieved by combining vaccinations. **(18)**

mRNA Vaccines

MRNA vaccines are potentially safer than DNA vaccinations since they don't need to reach the nucleus to cause the expression of the target antigens. mRNA vaccines have been created quickly in recent years. Although the phase I clinical assessment of the mRNA vaccines for the rabies virus and influenza virus is complete, the immunological impact is not sufficient because to a disproportionately high incidence of headaches, exhaustion, and adverse effects such muscular discomfort. Within a year, the immunological protection brought on by the vaccination gradually diminished, and there was no sign of a cellular immune response. Therefore, it is essential to further enhance the immunological effectiveness and long-term defense of mRNA vaccines. **(19)**

There isn't an mRNA vaccination available right now. The development and study of mRNA vaccine research, however, has been ongoing. The study and development of COVID-19 mRNA vaccines has been promptly started by several universities both domestically and overseas. A phase I clinical trial for the mRNA vaccine has been spearheaded by the National Institute of Allergy and Infectious Diseases (NIAID) and Moderna. The prefusion form of the S antigen, including a transmembrane anchor and the full S1-S2 cleavage site, is uniquely encoded by the Moderna vaccine, mRNA-1273. **(20)**

Non-replicating Viral Vector Vaccines

Adenovirus (Ad) is one of the most researched viral vector choices and is now utilized by CanSino, Oxford/AstraZeneca, and others.

Common cold viruses having a double-stranded DNA genome are called adenoviruses. Ad type 5 (Ad5) is being used by CanSino, and the vaccine is known as Ad5-nCoV.The SARS-CoV-2 full-length S protein can be encoded for by 22 Ad5-nCoV. The tissue plasminogen activator signal peptide and this gene, which is derived from the Wuhan-Hu-1 sequence of SARS-CoV-2, were cloned into the E1- and E3-deleted Ad5 vector. This vaccine's efficiency is rather good, but a drawback is that persons who have infectious viruses with recessive ancestry may not benefit from it. **(16)**

Inactivated Vaccines

The most traditional type of vaccination is an inactivated vaccine. They are simple to manufacture and effectively elicit humoral immune responses. They are frequently the first option for newly emerging infectious illnesses. Three inactivation techniques, including formaldehyde, -propiolactone, and UV light, are primarily used to produce inactivated vaccines. Mice, hamsters, ferrets, and monkeys can all create high-titer neutralizing antibodies in response to the inactivated SARS and MERS vaccinations. Phase I clinical studies of the SARS-inactivated vaccine have shown that it is safe for use in people and can stimulate the formation of neutralizing antibodies. However, inactivated vaccinations often only induce a modest T-cell immune response. Inactivated vaccines for SARS and MERS cannot successfully induce the body to create cellular immunological responses, according to earlier research. **(21)**

Despite the production of large titers of serum neutralizing antibodies, the protective effect is also not met. According to several research, mice's lungs can have pathological allergic responses after receiving the MERS-inactivated vaccination. **(22)**

The SARS-CoV-2 vaccine (Vero cells) is now being utilized. Additionally, the operation of large concentrations of live viruses is necessary for the manufacturing of vaccines, which presents a small biological safety risk. **(13)**

Live attenuated Vaccines

Through a point mutation or the deletion of a critical viral protein, the live attenuated vaccination lessens the pathogenicity of the virus while leaving its immunogenicity and capacity for reproduction unaffected. This vaccination program has excellent immunogenicity, may produce long-lasting systemic immunity as well as mucosal immune response. Yellow fever, smallpox, measles, polio, mumps, rubella, and chickenpox are among the diseases for which live attenuated vaccinations have been available. The SARS live attenuated vaccine will regain its virulence with repeated passage in cells or animals, indicating a higher biological safety risk for the vaccination plan. **(23)**

This approach is not currently advised for the COVID-19 vaccine development since there is not enough proof to guarantee that live attenuated vaccines won't regain strength. **(13)**

Subunit Vaccines

The safest vaccinations are subunit vaccines, which are made of pure recombinant proteins. Several subunit vaccinations, such as those for hepatitis B, hepatitis E, and human papillomavirus, are now available. Nasal or oral vaccination can also trigger a mucosal immune response, more effectively preventing the virus from spreading via the respiratory system. SARS and MERS subunit vaccines can create high-titer neutralizing antibodies in animals. The studies also demonstrate that mucosal immunization has superior protective effectiveness than intramuscular injection. **(24)**

Subunit vaccines, on the other hand, cannot be delivered by MHC-I and cannot successfully create sensitized cytotoxic T lymphocytes (CTL) since they are non-endogenous antigens. The subunit vaccination for COVID-19 is most effective when administered in concert with other platform vaccines because of the crucial role that cellular immunity plays in eradicating coronavirus infections. To stimulate mucosal immune responses, it is advised to include nasal and oral mucosal vaccination methods. **(25)**

Trained Immunity-Based Vaccines

Vaccines based on trained immunity can stimulate the adaptive immune system and offer defense against a specific infection. Bacille Calmette-Guerin (BCG), a TB vaccine, is now undergoing clinical review, which will take time to verify, and can generate trained immunity against COVID-19. The BCG vaccination has special difficulties even if it is effective against COVID-19. That is to say, the BCG vaccine production standards will differ from nation to nation, and it is unclear if certain quality criteria are necessary to give protection against COVID-19. **(26)**

Adverse Reactions of Vaccines

The immunization might cause side effects like fever, redness, edema, and muscular discomfort. A list of desired and most fundamental needs, such as vaccination safety and efficacy, is included in the strategic goals of the COVID-19 vaccine roadmap created by the WHO. Safety and reactogenicity sufficient to provide a highly favorable benefit/risk profile in the context of the observed vaccine efficacy and only mild, transient related to adverse vaccination events without serious adverse events are the desired criteria for safety and reactogenicity. **(27)**

The most fundamental criteria for safety/reactogenicity include that the advantages of vaccinations outweigh any possible risks to your health. In the context of the reported vaccination effectiveness and immunogenicity, the long-term outcomes were a safety that is sufficient to give extremely favorable benefits/risk characteristics. There were no significant adverse reactions following immunization. The protective efficacy in the general population must be at least 70%, and the same is true for the elderly, according to the desired parameters for effectiveness. If the therapy is meant to prevent an epidemic, the preventive effect must start within two weeks and persist at least a year. The population's protective effect must be at least roughly 50% for at least six months as one of the bare minimum standards. **(27)**

Clinical Trials and Efficacy Evaluation

It was crucial to take safety into account during the research and development of the COVID-19 vaccine. The majority of the target populations for preventative vaccinations are healthy people, and ensuring their safety throughout vaccine research and clinical trials is of utmost importance. For the purpose of directing vaccine development and clinical trials, the State Drug Administration has released the "Notice on the Guidelines for the Classification of Adverse Events in Clinical Trials of Preventive Vaccines" and other pertinent rules. In the past, there has been an upsurge in antibody-dependent infection with the discovery of inactivated measles vaccinations and respiratory syncytial virus vaccines.

Therefore, it is important to consider if COVID-19 vaccines would result in comparable immunopathological responses while researching them. We need to make long-term safety observations. Although the Food and Drug Administration (FDA) of the United States suggests that the COVID-19 endpoint be defined as virologically confirmed SARS-CoV-2 infection accompanied by one or more of 11 Symptoms, trialists have the freedom to choose particular symptoms and severities to trigger virologic testing. It is crucial to establish a standard COVID-19 endpoint that can be used uniformly across trials in order to assist both the interpretation of the data and the meta-analyses of the trials. **(28)**

It is crucial to employ a consistent set of clinical endpoints for assessing vaccination effectiveness across all trials in order to carry out a unified and thorough assessment of benefits and hazards and to enable the analysis of the immune-surrogate endpoint using aggregated data. In any event, any vaccination effectiveness study should consider COVID-19 and severe COVID-19 as significant independent clinical outcomes. **(13)**

In order to get useful information to assess long-term defense against these two endpoints, notably the severe COVID-19, all participants should be properly followed up. For reliable vaccination effectiveness quantification, more endpoint counts are required. The capacity to assess vaccine effectiveness against the asymptomatic infection endpoint should be incorporated in trial designs given that the reduction in the incidence of symptomatic SARS-CoV-2 infections brought on by vaccination may be accompanied by a shift towards more asymptomatic illnesses. **(13)**

Vaccine Application

Preventative vaccinations will manage the value of vaccinations in avoiding illness and mortality from infectious illnesses supports COVID-19. Even if there is no longer a shortage of vaccines, people's reluctance to get vaccines continues to be a significant impediment. **(29)**

At the University of Texas Southwestern Medical Centre, first-line medical personnel, 234 of the 8,969 unvaccinated workers (2.61%) and just 4 of the 8,121 vaccinated employees (0.05%) were infected. A comparable study conducted in California likewise produced similar findings. **(30)**

Even while the B.1.1.7 variant suddenly increased (see up to 80% of cases) in a hospital in Jerusalem, among the medical personnel who had two doses of the vaccine, the frequency of new COVID-19 cases had considerably dropped. These statistics demonstrate that vaccinations had substantially shielded front-line healthcare providers in dangerous situations. As a result, vaccination plays a crucial role in the effort to avoid epidemics worldwide. **(31)**

Travel Immunization

Both entrance and exit personnel should be the objective of executing the immunization plan, and close contacts of entrance people should be employed as vaccines if the epidemic situation is properly handled and the future epidemic scenario is primarily imported. **(13)**

Post-Exposure Immunization

Close contacts of confirmed COVID-19 cases may be considered for post-exposure immunization if it is determined that the COVID-19 vaccine has the effect of preventing or reducing the illness symptoms in the exposed people. In order to demonstrate the scientific validity of post-exposure vaccination, it is thus vital to assess the protective impact of COVID-19 vaccinations, particularly vaccines generated using innovative technology. **(13)**

Pre-Exposure Immunization

Pre-immune prophylaxis measures should be taken by people who may be exposed to COVID-19 patients or high-risk diseases, such as medical professionals in fever clinics, COVID-19 pathogen testing workers, contact persons from COVID-19 endemic countries, etc. **(13)**

Emergency Immunization

An emergency immunization plan for the populace in the epidemic area can be thought of in the case of a COVID-19 epidemic, presuming that the COVID-19 vaccine's emergency immunization impact is confirmed. Thus, in the early stages of vaccine development.

It is crucial for marketers to evaluate the impact of emergency immunization, particularly the adoption of the ring immunization approach.

Because COVID-19 is contagious across the population, it differs from the H1N1 pandemic in addition to the four immunization techniques mentioned above. The objectives and immunization techniques for mass pandemic vaccination are determined by thorough assessment of protection goals, decreasing mortality and cluster outbreaks, and vaccine supply in batches. **(32)**

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