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AN OVERVIEW OF THE COVID-19 PANDEMIC, SARS-COV-2 VIROLOGY, VACCINES, AND VARIANTS

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Abstract

The infectious disease responsible for the worldwide epidemic is coronavirus virus 2019 (COVID-19), due to the novel severe respiratory disorder coronavirus 2 (SARS-CoV-2), initially found in Wuhan, China. Rapid global expansion of COVID-19 had disastrous effects on societal structures, economics, and healthcare systems. Many methods, such as public health initiatives and therapeutic therapies, have been used to lower morbidity and mortality (Huang et al., 2020). The strongest promising strategy for avoiding SARS-CoV-2 infection and limiting its spread among these is the creation of potent vaccinations. Extensive clinical studies have demonstrated the safety and efficacy of numerous vaccinations, significantly lowering the risk of infection and the severity of illness. However, issues about the efficacy of the vaccination have been raised by the appearance of novel SARS-CoV-2 variants with alterations that allow immune evasion.

Introduction

The bacterial pneumonia outbreak that started in China's Hubei Province in December 2019 swiftly spread to nearby areas and sparked concerns about public health globally (World Health Organization [WHO], 2020). The 2002–2003 serious acute respiratory disorder outbreak was shown to be caused by a new coronavirus that shared around 80% of its genome with SARS-CoV (Zhou et al., 2020). On February 11, 2020, the World Health Organization (WHO) formally termed the virus causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), following the designation of the related sickness as coronavirus disease 2019 (COVID-19) (WHO, 2020).

Since it first appeared, SARS-CoV-2 has generated previously unheard-of worldwide health crises that have had a significant impact on public health systems, economies, cultures, and political institutions all over the world (Nicola et al., 2020). The best method for lowering serious illness and death from viral infections has been shown to be vaccination (Polack et al., 2020). In response, more than 200 vaccine concepts were developed; several of these were promptly authorised by authorities and disseminated globally (WHO, 2022). As of December 2022, the WHO had issued the Emergency Use List (EUL) for eleven COVID-19 vaccines, comprising the messenger RNA (mRNA), protein subunit, an adenoviral vector, and vaccines that were inactivated (WHO, 2022).

Nearly 7 million deaths and over 770,000,000 confirmed COVID-19 infections have been reported globally by September 2023 (WHO, 2023). More than thirteen billion doses of the vaccine have been given globally, and more than 70% of people have received more than one shot (WHO, 2023). Many low-income nations still have poor immunisation rates despite these

Frontier in Medical & Health Research

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developments (Our World in Data, 2023). Therefore, this review covers COVID-19 vaccine production and vaccine implementation issues, the impact of viral variations on vaccination efficacy, and continuing clinical research to improve treatment and prevention measures (Harvey et al., 2021; WHO, 2023).

Etiology of coronavirus

Human coronaviruses were discovered in 1965 as a result of a child's nasal discharge from an ordinary cold (Tyrrell and Bynoe, 1965). According to Fehr and Perlman (2015), coronaviruses are enclosed, unsegmented, positive-sense, single-stranded RNA viruses that range in diameter from 60 to 140 nm. Their characteristic spike-like surface projections that resemble crowns are the source of the word "coronavirus" (Almeida et al., 1968). Humans, bats, birds, and reptiles are among the many hosts that coronaviruses (CoVs), which belong to the family Coronaviridae within the genus Nidovirales, infect (Cui et al., 2019). Torovirinae and Coronavirinae are the two subfamilies that make up this family (International Committee for Terminology of Viruses [ICTV], 2020).

The four genera comprising the Coronavirinae subfamily are alpha coronavirus, beta coronavirus, gamma coronavirus and deltacoronavirus (ICTV, 2020). Alphacoronaviruses and betacoronaviruses are predominantly human viral infections, while these viruses and deltacoronaviruses are predominantly associated with birds (Woo et al., 2012). Alphacoronaviruses usually cause moderate or asymptomatic infections, whilst betacoronaviruses are often linked to serious illness (Paules et al., 2020).

According to Cui et al. (2019), there are 7 known coronaviruses of humans thus far (HCoVs): HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, MERS-CoV, and the two known strains of coronavirus (SARS and the more recent one called Coronavirus 19). SARS-CoV, MERS, and specifically now, the current one (SARS-CoV-2) are species of the beta coronavirus species and cause severe respiratory illnesses with a high mortality rate, but the other 4 viruses are usually associated with minor upper respiratory tract infections (Paules et al., 2020). About 2% of persons are asymptomatic carriers of coronaviruses, which are thought to be responsible for five to ten percent of major respiratory disorders (van der Hoek, 2007).

Animal reservoirs were the source of the pathogens which are responsible for the outbreaks of the coronaviruses: CoV (SARS) in 2002, MERS-CoV in 2012 and CoV-2 (SARS) in 2019, which caused serious outbreaks with a negative impact on the human population (2007) and the general population (Zhou et al., 2020). Among these, the virus that caused the global disease called 'SARS-CoV-2' has had the largest worldwide impact, which has threatened human health by causing the 'Covid-19' pandemic (World Health Organisation [WHO], 2020).

Spike protein's function in the development of SARS-CoV-2 infection

Spike protein's function in the development of the formation of a new member of the beta coronavirus family – Covid-19 – the connection with the domain spike protein is not yet very clear. Nucleotide positive-sense, single-stranded RNA genome that is capped at 5' and altered at 3' (Kim et al., 2020). Non-structural peptide amino acids (NSPs), structural components of protein particles, accessory proteins, and a number of open reading frame (ORF) amino acids are all encoded by its genome (Wu et al., 2020). Some of the amino acids produced by the ORF parts that are crucial for viral replication and transcription are papain-like enzyme (PLpro), RNA-independent synthesis of RNA, and primary protease (3CLpro) (Harcourt et al., 2020). Snijder et al. (2016) state that the genome of virus growth, host mRNA degradation, transmembrane remodelling, protein synthesis and RNA modification are dependent on NSP3, NSP9, NSP10, NSP12, NSP13, NSP15 and NSP16.

One of the technically important proteins (nucleocapsid (N) protein) has a high degree of similarity in sequence with the viruses of the coronaviruses of the human respiratory system and is involved in both reproduction (viral) and immunological activation (Chang et al., 2014). The most essential factor which affects the viral

Frontier in Medical & Health Research

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pathogenesis is, however, the spike (S) protein. This transmembrane glycoprotein facilitates viral adhesion, separation of plasma membranes, and entry into host cells by binding to the ACE2 (angiotensin-converting enzyme 2 receptor) (Hoffmann et al., 2020).

S1 and S2 are the two subunits that comprise the spike protein (Walls et al., 2020). The ACE2 interaction is induced by the S1 subunit binding to receptor regions (RBD) and the N-terminal region (NTD), which are targets for neutralising immunological responses and the production of the vaccines (Lan et al., 2020). The fusing of the viral and the host cell membranes is mediated by the S2 subunit (Wrapp et al., 2020). Host proteases like transmembrane protein protease containing serine 2 (TMPRSS2) facilitate the entry of the virus by triggering the spike protein after contact with the receptor (Hoffmann et al., 2020). The host exocytosis route creates and releases new virions after the release, replication and translation of viral RNA within the host cell (V'kovski et al., 2021).

Symptoms of SARS-CoV-2 viral infection

SARS-CoV-2 can directly or indirectly attack the lungs, brain, immune system, and heart besides the major target organ, the respiratory tract (Gupta et al., 2020). The clinical symptoms that can be induced by the coronavirus disease (COVID-19) range widely from mild, undiagnosed disease to serious disease characterised by sudden respiratory failure and death (Guan et al., 2020). Fatigue, migraine, cough and fever & shortness of breath are typical symptoms that resemble those belonging to the winter flu (Huang et al., 2020). Additional symptoms include bleeding, diarrhoea, vomiting, myalgia & sputum production, which may be manifested in more severe instances (Zhou et al., 2020). Patients should seek medical attention immediately if they have severe symptoms, such as breathing problems and chest pain, as well as a decreased voice or movement [WHO, 2021].

Clinical diagnosis of SARS-CoV-2 infection

Accurate and rapid detection of the coronavirus is crucial for prevention of the pandemic as well as for people with the coronavirus in large groups (Corman et al., 2020). Antigen tests, which detect viral proteins, such as nucleocapsid or spike protein; genetic tests, such as RT-PCR, that detect the viral RNA; and tests for serology, that identify antigens that are viral or the immune response that is created during present or past infections, are the three main diagnostic test classifications (Peeling et al., 2020).

Despite lesser sensitivity than molecular techniques, the rapid antigen tests are beneficial for point-of-care screening because of their excellent specificity and low to high sensitivity, especially in people with elevated viral loads during the first week of symptoms (Mak et al., 2020). Serological test methods such as ELIAs, CLIAs and IFAs identify the presence of the immunoglobulin G and immunoglobulin M (IgG and IgM) antibodies that are specific for the spike and mitochondrial proteins in order to identify current or previous infections (Long et al., 2020). In either laboratory or non-laboratory settings, these diagnostic methods can be done with little training; however, the nature of the population, when a sample is collected, the quality of the specimen, the proficiency of the operator, and the proper interpretation of the result all influence the accuracy of the test (Peeling et al., 2020).

Transmission of the Covid-19 Pandemic

Animal-to-human transmission of the virus (SARS-CoV-2)

Understanding the source and routes of transmission of the novel coronavirus (SARS-CoV-19) is necessary in order to stop future outbreaks (Zhou et al. 2020). Palm civets were first thought to be a possible reservoir during the earlier SARS-CoV pandemic, but further research revealed that civets were probably intermediate hosts who picked up the virus from different creatures (Guan et al., 2003). Since horseshoe bats have been found to harbour many SARS-like coronaviruses, it has been suggested that bats are the main natural source of SARS-CoV (Li et al., 2005).

Scientists postulated an identical zoonotic origin for SARS-CoV-2 due to structural & genetic similarity between both forms of SARS-CoV

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

(Andersen et al., 2020). Early findings connected possible transmission incidents to animals sold at Wuhan, China's Huanan seafood market (Wu et al., 2020). According to phylogenetic analyses, bat-associated coronavirus BatCoV RaTG13 and SARS-CoV-2 have over 96% genome-wide similarity, indicating that bats are the most likely natural source (Zhou et al., 2020). Further research, such as codon use analysis, confirmed that bats are the primary reservoir of the SARS-CoV-2 virus (Wang et al., 2020).

Since direct bat-to-person transmission is thought to be uncommon, an intermediary host may be involved (Zhang et al., 2020). Because coronaviruses discovered in pangolins have a significant degree of similarity to SARS-CoV-2, particularly in the receptor-binding domain of the spike protein, monkeys have been designated as a potential alternate species (Xiao et al., 2020). Although the exact intermediate host has not yet been determined, comparative genomic studies suggest that SARS-CoV-2 may have arisen through fusion among bat and monkey coronaviruses prior to infecting humans (Lam et al., 2020).

Human-to-human spread

Coronaviruses primarily spread through human-to-human contact, touch, and meeting (World Health Organisation [WHO], 2021). The main source of infection is breathing in an infected environment or coming into contact with an infected person's respiratory secretions. Others can absorb the bigger droplets that may come into direct contact with the mucus layer of the throat, nose, and eyes; smaller respiratory aerosols or droplets produced when sneezing, coughing, and speaking can be absorbed by others (Jayaweera et al., 2020). Coronavirus can also be transferred or spread when people touch dirty surfaces and this dirt (van Doremalen et al., 2020). Variants of SARS-CoV-2

Similar to other RNA-based viruses, that of the novel coronavirus (SARS-CoV-2) is genetically complex and undergo frequent mutations and recombination, creating strains that are different from its original form (Korber et al., 2020). During the epidemic of coronavirus (SARS-CoV-2) infection, a number of mutations of the virus were identified throughout the world. Coronaviruses are relatively more physically stable than several RNA viruses thanks to a mechanism of sequencing carried out by a disordered protein called nsp14 with exonuclease activity viruses. Mutations accrue through time, but more slowly than with viruses, e.g., HIV-1 or influenza A virus (Smith et al., 2020).

Early genomic analysis, including work by Korber and colleagues using GISAID sequence data, identified the D614G change in the protein to produce spikes. This mutation was quickly found to be the dominant type around the world because of its enhanced transmissibility (Korber et al., 2020). Other mutations have arisen due to episodes of zoonotic transmission, such as that of the virus caused by the coronavirus in the case of mink in Denmark (Oude Munnink et al., 2021). Ongoing genomic surveillance has identified several changes throughout the genome of the virus, which is called the 'SARS-CoV-2' genome. Although changes outside of the spiked area can have a substantial impact on the virulence and actions of the virus, variations are often classified based on mutations to the spike protein (Harvey et al., 2021).

These genetic changes may impact viral generation, cell tropism, transmission, illness severity, treatment susceptibility & immune evasion (Plante et al., 2021). In response to the increasing number of variants, the World Health Organisation (WHO) classified the variants of the virus (SARS-CoV-2) as Variants Under Monitoring (VUMs), Variants of Attention (VOIs) and Variants of Concern (VOCs) in late 2020 (World Health Organisation [WHO], 2021).

Alpha/UK type (B.1.1.7 or 20I/501Y.V1)

The Alpha variation (B.1.1.7), also referred to as 20I/501Y.V1 or GRY, was the first type of the coronavirus to be identified as a variation of concern (VOC). After being identified in the southern region of Britain in autumn 2020, this soon became the most prevalent strain globally (Volz et al., 2021). On December 18, 2020, the World Health Organization gave it the name of Alpha. Alpha has around 17 mutations, some of which are present in the spike protein. These

Frontier in Medical & Health Research

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include losses H69/V70 and Y144 and N501Y, D614G & P681H. Because it makes the spike protein stickier to the person's ACE2 receptor, the N501Y mutation is particularly important, as it makes viral entry better into host cells (Davies et al., 2021). Despite this, vaccines continued to show good efficacy, with the Oxford-AstraZeneca vaccine showing around 70% efficacy and the Pfizer-BioNTech vaccine showing around 89.5% efficacy after two doses. Continuing viral evolution has also resulted in rare recombinant forms, e.g., XE and "Deltacron", and other Omicron sub-lineages.

Beta/South Africa variant (B.1.351 or 20H/501Y.V2)

The 2nd wave of COVID-19 infections in South Africa was caused by the Beta variation (B.1.351), commonly referred to as 501Y.V2, which was initially identified there in May 2020 (Tegally et al., 2021). The WHO classed it as a VOC and labelled it as Beta on December 18, 2020. Nine significant spike protein mutations, such as K417N, E484K, and N501Y, are present in beta and improve binding affinity to the ACE2 human receptor while decreasing antibody neutralisation (Cele et al., 2021). The Pfizer-BioNTech vaccine exhibited about 75% protection against Beta, Novavax 60% in Africa and 86% in the UK, and the Oxford-AstraZeneca vaccine only 10%.

Gamma (P.1 or 20J/501Y.V3)/Brazilian variant

A notable second wave in the area was caused by the Gamma variation (P.1), also known as 20J/501Y.V3, which was initially discovered in Manaus, Brazil, in December 2020 (Faria et al., 2021). In January 2021, it was found in passengers arriving in Japan from Brazil. K417T, E484K, N501Y, & D614G are among the 12 spike protein mutations found in Gamma, which originated from the B.1.1.28 lineage. These alterations increase the likelihood of reinfection, immune evasion, and transmissibility. Compared to other circulating variations in Brazil, gamma was found to be 1.7 to 2.4 times more transmissible, with some studies showing a 2.2-fold increase. The AstraZeneca-Oxford and Pfizer-BioNTech vaccines demonstrated about 50% efficacy against Gamma, Moderna about 61%, and CoronaVac between 37% and 59% efficacy when compared to earlier strains.

Delta variant (B.1.617.2 or GK)

The Delta variation (B.1.617.2), also referred to as GK, was first discovered in October 2020 in the Indian state of Maharashtra. It was responsible for a devastating 2nd wave of COVID-19 illnesses in the nation (Cherian et al., 2021). The WHO designated it as a VOC on May 11, 2021. Delta was found in more than 169 different nations and quickly rose to prominence as the most common strain worldwide. Ten important spike protein mutations, such as L452R, T478K, and P681R, increase viral propagation and immune evasion, making it roughly 60% more transmissible than the Alpha form. The effectiveness of the vaccine against Delta was relatively diminished: after two doses, Pfizer-BioNTech and AstraZeneca demonstrated about 88% and 60% efficacy, respectively, compared to 93% & 66% efficacy against Alpha.

Omicron (B.1.1.529)

On November 26, 2021, the World Health Organisation (WHO) classified the Omicron variation (B.1.1.529) as a variation of Concern (VOC), shortly after it was discovered in South Africa (WHO, 2021). Omicron is made up of several closely related sub-lineages, such as BA.1, BA.1.1, BA.2, and BA.3. It has about thirty spike protein mutations, many of which are common to earlier variations, including Alpha, Beta, Gamma & Delta. (Viana et al., 2022).

Mutations that improve binding to the body's ACE2 receptor are responsible for Omicron's strong transmissibility. Although N501Y and K417N lead to both enhanced infectivity and immune evasion, mutations like K417N, E484A, and Q493R decrease antibody neutralisation, allowing immunological escape (Cao et al., 2022). According to epidemiological research, Omicron spreads 2.7 to 3.7 times more quickly than the Delta version. According to medical information from the US and other nations, Omicron infections are typically linked to milder disease and lower hospitalisation rates than Delta

Frontier in Medical & Health Research

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infections, despite their higher transmissibility (Wolter et al., 2022).

The Pfizer-BioNTech vaccine, in particular, is less effective against Omicron when administered according to the conventional two-dose regimen. Booster dosages enhance defense against infection and serious illness by dramatically raising neutralizing antibody levels (Andrews et al., 2022). Ongoing viral evolution has also produced rare recombinant forms, such as XE and "Deltacron", as well as other Omicron sub-lineages. These genetic changes continue to impact immune evasion, spread, disease severity, diagnostic accuracy, and vaccination efficacy, making public health management challenging.

Three SARS-CoV-2 Infection Waves

These variations, which arise from genetic mutations, have often called into doubt the effectiveness of vaccination efforts, healthcare initiatives, and containment strategies, making handling a pandemic more challenging.

The virus rapidly spread around the world following the first infections of coronavirus in China in the final month of 2019 (Zhu et al., 2020). By March of 2020, the first wave of the virus had spread worldwide, and almost every region was affected. Seasonal factors resulted in a delayed influence in the southern hemisphere. Africa had relatively low numbers of cases and deaths due to its young population and past exposure to outbreaks of infectious diseases such as Ebola (Nkengasong & Mankoula, 2020). The first wave caused major disruption to the world economy, social institutions, and healthcare systems, which resulted in decreased productivity, increased unemployment, and a host of other social issues. Experts were warning that subsequent waves might be more destructive.

The Second Wave

After a period of fewer cases during the summer, the second wave started in mid-to-late 2020, when public complacency (Chen et al., 2021). Similar to other seasonal respiratory infections, Covid-19 reappeared during the winter season and was more serious than the first wave in many countries. Certain localities experienced a rise in hospitalisation, hospital admissions to intensive care units and death rates. Several governments turned their attention from strict containment measures to protection of economic activities, which led to an increase in transmission of the virus. Among the most affected countries were France, Brazil, India and the United Kingdom. Research found that it was not the vacation gatherings that were the main cause of this wave but the lack of implementation of healthcare laws (Bollyky et al., 2020).

The Third wave

During the 3rd wave, which broke out worldwide after December 2020, the highly contagious Alpha (B.1.1.7) type was able to spread quickly (Volz et al., 2021). This wave was caused by a combination of changes in the virus and more interpersonal contacts in the absence of suitable controls. Reinfections also contributed to an upsurge in instances. To prevent further waves, vaccination coverage will need to be accelerated, and adherence to public health precautions, such as using a mask, hand hygiene, social distancing and public awareness campaigns, will need to be strengthened. The third wave showed the need for a combined approach of vaccination and non-pharmaceutical methods for preventing the spread of viruses (Taleghani & Taghizadeh-Hesary, 2021).

Vaccines platform for SARS-CoV-2 exposure

Since the SARS-CoV-2 virus spreads more swiftly than other viruses and poses a major threat to public health, strict isolation measures were the primary focus of early containment efforts (World Health Organisation [WHO], 2020). Lockdowns, social segregation, and travel restrictions were implemented in many countries. These measures significantly disrupted society and the economy, even if they were successful in reducing the spread of the virus. This demonstrated how urgently safe and efficient immunisations are needed. As a result, scientists from all over the world expedited the creation of COVID-19 vaccines on various platforms; as a result, a number of vaccines have been approved or are undergoing clinical development in nations like the US, Europe, the UK, India, and China. (Thanh Le et al., 2020).

Frontier in Medical & Health Research

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Vaccines for Protein subunit

Because they use certain fragments of protein (antigens) to trigger an immune response, protein subunit vaccines are thought to be safer than whole-pathogen vaccines (Krammer, 2020). Adjuvants are needed to boost immune responses in these vaccines, which are usually made utilising recombinant DNA technology. The spike (S) glucose protein and its subunits, S1 and S2, including the receptor-binding domain (RBD), are frequently employed as target antigens for SARS-CoV-2 in order to elicit neutralising antibodies. Although they may need adjuvants and several booster doses to produce long-lasting immunity, protein subunit vaccines often have good safety profiles and are reasonably priced (Poland et al., 2020).

Novavax (NVX-CoV2373)

The protein-based subunit vaccine NVX-CoV2373 was created by Novavax and the Coalition for Innovation in Epidemic Preparedness (CEPI). It is made with a baculovirus–insect gene expression technique and includes the saponin-derived Matrix-M adjuvant together with a full-length translational SARS-CoV-2 spike protein (Keech et al., 2020). Clinical trials demonstrated robust T-cell and antigen responses.UK trials reported around 90% efficacy, whereas phase 3 trials demonstrated about 96% efficacy against symptoms of COVID-19, including substantial defence against the Alpha (B.1.1.7) form.

EpiVacCorona

The protein that makes up the subunit vaccine EpiVacCorona was created by the VECTOR Institute. It is a hybrid construct made up of three biologically synthesised peptides that are derived from the spike protein of SARS-CoV-2. Adults 18 years of age and older receive it intramuscularly in two administrations spaced seven days apart. Strong immunity, safety, and the capacity to elicit neutralising immune responses were all shown in phase 1/2 investigations (Kozlov, 2021).

ZF2001 (Anhui Zhifei)

Anhui Zhifei Longcom worked with the Academy of Army Medicine in China to create the ZF2001 vaccine. It has an alum adjuvant and a dimeric form of the spike red blood cell protein. Three intramuscular doses of the vaccine are given at intervals of four weeks. Research has demonstrated that ZF2001 demonstrates significant immunogenicity along with favourable tolerability in human trials while maintaining neutralising effectiveness against several SARS-CoV-2 variants, especially Beta, Gamma, & Delta (Yang et al., 2021).

mRNA Vaccines

Messenger RNA coding viral antigens is delivered into host cells via mRNA vaccines using lipid nanoparticles. The mRNA is converted into antigenic proteins in the cytoplasm, which trigger defensive immunological reactions (Pardi et al., 2018). This platform is regarded as non-infectious, non-integrating, highly immunogenic, safe, and quickly deployable. Because the messenger RNA (mRNA) is broken down after translation, long-term genetic hazards are prevented. The most popular mRNA vaccines against COVID-19 are Moderna Pharmaceuticals (mRNA-1273) and Pfizer-BioNTech (BNT162b2).

BioNTech-Pfizer COVID-19 Vaccine (BNT162b2)

Lipid nanoparticles are used to administer the BNT162b2 vaccine, which encodes the whole SARS-CoV-2 spike protein. Around ninety-five percent efficacy against COVID-19 infection symptoms was shown in clinical trials (Polack et al., 2020). After two doses, the vaccine retains strong efficacy across several age groups and offers good protection against several variations, notably Alpha, Beta, Gamma, & Delta.

Moderna mRNA-1273 Vaccine

The whole spike protein is also encoded by the Moderna mRNA-1273 vaccine. Approximately 94% efficacy against COVID-19 symptoms was found in phase III trials (Baden et al., 2021). It provides strong defense against the Alpha, Beta, Delta, and Gamma forms, even though its efficacy diminishes over time and is diminished against the Omicron variation, underscoring the significance of booster doses to preserve immunity.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

CureVac Vaccine (CVnCoV)

The whole spike protein is encoded using unaltered mRNA in the CureVac CVnCoV vaccine. Phase 2b/3 trials showed significant protection against severe illness, hospitalization, and mortality but showed limited effectiveness against symptomatic infection. The safety profile of the vaccine was validated by phase I studies (Türeci et al., 2021).

Vaccines Based on DNA

DNA vaccines use plasmid DNA to transfer proteins encoding antigens from viruses into host cells, especially antigen-presenting cells. The host cell machinery generates antigenic proteins once within the nucleus, which trigger humoral and cell-mediated defences (Kutzler & Weiner, 2008). Plasmid uptake is frequently improved by electroporation, which momentarily opens holes in the cell membrane. DNA vaccines are rather simple to produce, stable, inexpensive, and non-infectious. However, their effectiveness may be limited by the need for nuclear entrance, and the DNA vector itself may be the target of immunological reactions (Modjarrad et al., 2019).

INO-4800 Vaccine

The INO-4800 vaccine, which contains the SARS-CoV-2 spike protein, was created by Inovio Pharmaceuticals. To increase DNA uptake, it is injected intradermally utilizing the CELLECTRA electroporation apparatus. INO-4800 can be used as a primary & booster vaccination because clinical trials have shown that it is safe, tolerated well, and able to elicit both T-cell and antibody-induced immune responses (Smith et al., 2021).

ZyCoV-D Vaccine

The first DNA vaccination approved for use in humans is ZyCoV-D, created by Zydus Cadila. It is a DNA plasmid that encodes the spike protein from SARS-CoV-2 and is authorised for use in people 12 years of age and older. An important turning point in the advancement of genetic vaccine technology was reached when clinical trials showed a good safety profile & an efficacy of roughly 66 per cent against symptomatic COVID-19 (Mallapaty, 2021).

Whole-Virus Inactivated Vaccines

Vaccines against inactivated viruses are created by treating the entire virus with heat, radiation, or chemicals to make it non-infectious. The immune system detects the virus and triggers an immunological response even though it is unable to reproduce or spread illness (Minor, 2015). Established vaccinations against illnesses like polio, rabies, influenza, and hepatitis A are based on this strategy. Although inactivated vaccinations are generally safe, their response to infection is typically less than that of vaccines that are alive; therefore, they frequently need adjuvants and several booster doses to produce adequate immunity (WHO, 2020). Inactivated vaccine platforms provide the basis for a sizable fraction of the SARS-CoV-2 vaccine candidates entering clinical testing.

CoronaVac (Sinovac)

Sinovac created the CoronaVac vaccine, which is an ineffective COVID-19 vaccine made from SARS-CoV-2 grown in Vero cells. Different levels of effectiveness against COVID-19 symptoms were shown in clinical trials conducted in Argentina, Turkey, and Indonesia. Although neutralising antibody responses against certain variations, including Beta, Delta & Omicron, were decreased, the vaccination demonstrated robust protection against severe illness (Palacios et al., 2021). CoronaVac still offers significant protection against hospitalisation and mortality despite this decline in effectiveness against new strains.

Covaxin (BBV152)

The complete inactivated SARS-CoV-2 vaccine Covaxin was created by Bharat Biotech in India using a strain of the virus that was isolated locally. Strong neutralising antibody responses were seen in early clinical trials, and these responses lasted for several months after immunisation. Phase III trials demonstrated excellent efficacy against COVID-19 symptoms and total protection against severe disease, confirming its safety and capacity to elicit both humoral and cell-driven immune responses (Ella et al., 2021). Although there is less protection against asymptomatic infection,

Frontier in Medical & Health Research

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Covaxin has shown efficacy against variations like Alpha, Beta, and Delta.

Sinopharm Vaccine (BBIBP-CorV)

Vero cell cultures are used for the production of the inactivated SARS-CoV-2 vaccine referred to as Sinopharm BBIBP-CorV. Its safety and tolerance were verified by phase one and two trials. Significant defense against symptomatic COVID-19, along with significant effectiveness in preventing intermediate to severe disease, is shown by clinical trials in phase III and real-world research. Phase 3 studies are currently underway in a number of Asian, African, and European nations (Xia et al., 2021).

COVID-19 vaccination using a viral vector

By introducing DNA encoding the spike protein from SARS-CoV-2 into host cells via a safe, replication-competent, and replication-incompetent viral vector, viral vector vaccines trigger both humoral and cellular immune responses (Sadoff et al., 2021; Logunov et al., 2021). Unrelated to SARS-CoV-2, adenoviruses are frequently employed as vectors to promote cytotoxic T-cell activation, which helps eradicate infected cells. The spike protein is produced by host cells upon vaccination, which causes T-cell responses and neutralising antibodies to eliminate infected cells. AstraZeneca–Oxford (ChAdOx1 nCoV-19/AZD1222), the Sputnik V vaccine (Gam-COVID-Vac), Janssen-Ad26.COV2.S & Convidecia (AD5-nCoV) are among the viruses that carry COVID-19 vaccines that have been produced.

Oxford-AstraZeneca (ChAdOx1 nCoV-19/AZD1222)

A non-replicating chimpanzee virus (adenovirus) vector is used in the Oxford–AstraZeneca vaccine to transfer the spike protein gene. Over 60,000 patients in several countries participated in clinical trials that showed a total effectiveness of 70.4% against symptoms of COVID-19, rising to 81.3 percent when two doses were given at a considerable interval. It was found to be 74.5% and 67% effective against the Alpha & Delta strains, respectively (Voysey et al., 2021).

Sputnik V (Gam-COVID-Vac)

The fifth Sputnik is a heterogeneous adenoviral vector vaccine that uses rAd5 for the second dose and rAd26 for the first. With an effectiveness of 91.6 percent to 92.2 percent against symptomatic COVID-19, phase III trials showed significant neutralization versus B.1.1.7 (Alpha), Delta, and additional variations (Logunov et al., 2021).

Janssen-Ad26.COV2.S

As much as 85 percent immunity to severe COVID-19 and 66 percent efficacy against symptoms of infection were demonstrated by the single-dose Jansen Ad26.COV2.S vaccine. Alpha was 77% effective against variations, Gamma was 50–90%, Delta was 42%, and Omicron was 60% effective as well (Sadoff et al., 2021).

Convidecia (AD5-nCoV)

Convidecia, also known as AD5-nCoV, is a one-time-use adenovirus type-5 vector vaccine that boosts humoral and cellular immunity. Phase III trials showed 65–66% efficacy against COVID-19 symptoms and 90 to 100 per cent efficacy against serious illness (Zhu et al., 2020).

While efficacy may vary according to circulating variations, viral vector vaccines generally show substantial immunity, ease of preservation and dissemination, and significant defence against symptomatic and severe COVID-19 (Folegatti et al., 2020).

Vaccine with live attenuation

In order to produce robust and long-lasting viral and cellular immune responses, live-attenuated vaccinations (LAVs) are created from viruses that have been reduced or made less virulent (Minor, 2015). LAVs provide strong protection without the requirement for adjuvants by successfully simulating natural infection. However, these vaccinations are typically not advised for immunocompromised people, the elderly, or neonates due to the possibility of reversion to a severe form (Pulendran & Ahmed, 2011). Using deoptimisation technology, Coda Gen Biotech Inc. is currently working with the Blood Institute of India to create COVI-VAC, a living-attenuated COVID-19 vaccine. Furthermore, an influenza-

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only LAV with a deleted NS1 gene has been created by the University of Hong Kong's School of Medicine.

Virus-like particle-based vaccine

The structural viral proteins that make up virus-like particle (VLP) vaccines self-assemble into nanoparticles that resemble the genuine virus but are missing genetic material, rendering them non-replicative and non-infectious (Grgacic & Anderson, 2006). Low-containment facilities can make VLP vaccines without the need for live virus or inactive procedures. B-cell receptors are effectively engaged by their repeated antigenic surfaces, resulting in strong antibody responses. VLP vaccines mainly target the spike (S) protein of SARS-CoV-2, specifically the receptor-binding domain (RBD), which is essential for viral entry and neutralisation. Clinical trials are underway for five of the nine VLP-based COVID-19 vaccines. Notably, the Netherlands' Central Committee on Investigations Involving Human Beings (CCMO) has approved the ABNCoV2 virus VLP vaccine for clinical testing within the framework of the PREVENT-nCoV project (AdaptVac, 2022).

COVID-19 pandemic in Japan

In February 2021, a statewide vaccination effort utilising BioNTech-Pfizer, Moderna, and AstraZeneca-Oxford vaccines was initiated after Japan confirmed its initial COVID-19 case in the first half of 2020 (Saito et al., 2021). Early outbreak discovery, prompt care for serious infections, and public adherence to preventative measures were the main goals of the government's cluster-based containment approach. Like seasonal influenza, covid-

Category 5 infectious diseases were categorised as category 5 infectious diseases in May 2023. Despite this revision, from surveillance data, it was evident that there was a steady increase in cases in most of the age groups in 2023, partly because of the continued spread of Omicron sub-variants, reinforcing the need for continued surveillance and awareness about public health (National Institute of Infectious Disorders [NIID], 2023).

Plasmid-based nasal COVID-19 vaccine

Nasal vaccines provide a number of benefits, such as being simple to administer, causing little discomfort, and allowing for self-administration under minimum supervision from physicians (van Riet et al., 2012). Nasal vaccines activate both mucosal and system immune responses, in contrast to intramuscular vaccines, which mainly elicit systemic immunity. Since SARS-CoV-2 is mostly spread by airborne particles (<5 millimetres) that enter via the nasal channel, focusing on the upper respiratory system is especially crucial (Sungnak et al., 2020). The first line of immunological defence is the nasal and oral mucosa, which contains cilia, secretory antibodies, and antibacterial components. Therefore, nasal vaccinations offer immediate protection at the first points of viral entry, whereas intramuscular vaccinations could not sufficiently cover.

Building on earlier work with plasmid-derived gene treatments and cancer vaccines, the clinic's molecular biology department produced a viral DNA-derived COVID-19 vaccine for intramuscular administration. Antigen-presenting cells and cytokines originating from helper T and killer T (NKT) cells stimulate the synthesis of secretory IgA after mucosal vaccination, which is essential for mucosal neutralisation (Czerkinsky et al., 2011). The vaccine uses an optimised cytomegalovirus (CMV) promoter that codes for the SARS-CoV-2 spike protein, a crucial modulator of virus entry via ACE2 receptors, to guarantee high-level expression. The NCBI Genomic database provided the spike sequence of the gene (MN908947.3). Both humoral and cell immune systems are triggered by the nasal DNA vaccine, offering complete protection both systemically and at the mucosal surfaces.

Intranasal COVID-19 vaccination delivery method

Using clinical-grade components and techniques, we developed a nasal vaccination administration method that is currently in use. The components are shown, and the main filling body is a single millilitre NIPRO Japan syringe.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Challenges and future perspectives

Vaccine efficacy is seriously impaired by the continual emergence of immune-evasive mutations in the circulating human coronavirus (SARS-CoV-2). Spike protein mutations can reduce the protection provided by vaccines and enhance viral transmissibility, such as in the hospital setting, as well as prevent antibody detection (Harvey et al., 2021). These changes raise the question of how long immunity lasts, especially in light of the recorded cases of reinfection. Despite no confirmation for the spread of the novel coronavirus or the lack of confirmation of its link to the development of this virus, it is still considered when developing vaccines (Tirado & Yoon, 2003).

The lengthy and expensive vaccine development process and the exclusion of the disadvantaged population from early clinical trials and vaccination hesitancy induced by false information and lack of public confidence are additional obstacles (Puri et al., 2020).

Future immunisation strategies should have a high priority to conduct genomic surveillance, work on clinical research, and update vaccines regularly so as to maintain vaccine efficacy against new variants (Krammer, 2020). Improvement of adjuvants, multi-epitope vaccination formulations and booster doses are some of the improvements which could enhance immunological persistence and reduce immune escape. In addition to offering flexibility in antigen design, nucleic acids as vaccine platforms may help resolve issues of safety, such as the potential to experience ADE.

To accelerate vaccine research and ensure fair distribution, international collaboration between public health organisations, businesses and academics is necessary. Sustained investment in immunisation infrastructure, disease monitoring, public health awareness and measures that are not pharmaceutical, such as wearing masks and social distancing, will be required to control the spread of the virus and mitigate the impact of future variations in the virus (WHO, 2022).

Conclusion

Despite the introduction of many highly effective vaccinations in some countries, COVID-19 remains a major global danger (Polack et al., 2020; Baden et al., 2021). To combat future waves of SARS-CoV-2, nations, public health authorities, doctors, and researchers continue to make significant investments in the development of effective vaccines, treatments, and tactics. The present epidemic keeps causing significant morbidity and mortality due to the emergence of novel virus strains with greater transmissibility and immune escape, highlighting the need for continuous advancements in vaccine effect and protection (Harvey et al., 2021; Krammer, 2020). Continuous vaccination programmes, genomic surveillance, high-throughput analysis of viral genomes, and adherence to pharmaceutical substitutes, including mask use, hand hygiene, and social isolation are all necessary to prevent the spread of viruses and facilitate the early discovery of novel variants.

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