Annals of Phytomedicine 13(2): 7-22, 2024

DOI: http://dx.doi.org/10.54085/ap.2024.13.2.2

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

SARS-CoV-2 variants and vaccines: Efficacy, side effects and clinical evidences

Zeenath Banu*, Pidigam Saidaiah, Unaiza Khan***, A. Geetha****, Shiba Khan***** and Adnan A. Khan********

** Department of Pharmacology, RBVRR Women's College of Pharmacy, Hyderabad-500027, Telangana State, India*

*** Department of Genetics and Plant Breeding, College of Horticulture, Sri Konda Laxman Telangana State Horticultural University, Mojerla 509387, Wanaparthy District, Telangana State, India*

**** Liver Transplant Anaesthetist and Critical Care Specialist, Marengo Asia Hospital, Sector 16, Faridabad-121002, Haryana, India*

***** Department of Crop Physiology, College of Agriculture, Professor Jayashankar Telangana State Agricultural University, Rajendranagar Hyderabad-500030, Telangana State, India*

****** Speciality Doctor, Royal Lancaster Infirmary Hospital, Ashton Road, Lancaster LA1 4RP, United Kingdom*

******* Division of Nephrology and Hypertension, Department of Medicine, University of California, San Diego-92121, USA*

Article Info

Article history

Received 13 July 2024

Revised 29 August 2024

Accepted 30 August 2024

Published Online 30 December 2024

Keywords

SARS-CoV-2

COVID-19

Variants

Vaccines

Efficacy

Side effects

Clinical evidence

Abstract

The global challenge posed by the SARS-CoV-2 pandemic has been unprecedented due to the rapid evolution of the virus, resulting in the emergence of variants that complicate control measures. The presented review offers a thorough examination of the relationship between SARS-CoV-2 variants and the effectiveness of vaccines, as well as a detailed evaluation of vaccine safety. The analysis focuses on significant variants such as Alpha, Beta, Gamma, Delta, and Omicron, each characterized by specific mutations that contribute to increased transmissibility, immune evasion, or pathogenicity. Of particular, mutations like D614G and more than 30 alterations in the spike protein observed in Omicron. Initially, various vaccine technologies, including mRNA and inactivated virus platforms, demonstrated considerable efficacy (60-90%) against early virus strains. However, the effectiveness of vaccines has been notably reduced against symptomatic infection with variants like Beta and Omicron. This decline is supported by real-world data, for example, the Pfizer-BioNTech vaccine showed a decrease in efficacy from 89.5% against Alpha to 75% against Beta. Despite this decline, the vaccines continue to provide robust protection (over 90%) against severe disease, even with the Omicron variant. Extensive clinical trials and post-market surveillance have consistently reaffirmed the safety of vaccines. Mild side effects are commonly reported, while severe adverse events are uncommon. For instance, thrombosis with thrombocytopenia syndrome occurs in 1-7 cases per million doses of adenoviral vector vaccines. Despite these isolated incidents, overwhelming evidence supports the conclusion that the advantages of vaccination far surpass the associated risks. This review consolidates the current understanding of SARS-CoV-2 variants, vaccine effectiveness against these variants, and the safety profiles of the vaccines. It offers crucial insights for healthcare professionals and policymakers to effectively manage the changing landscape of the ongoing pandemic.

1. Introduction

The onset of the COVID-19 pandemic, initiated by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has had a profound global impact since its emergence towards the end of 2019. As of August 2023, the virus has affected hundreds of millions of individuals and led to over 6 million fatalities worldwide, placing substantial pressure on healthcare systems, economies, and societal frameworks (WHO, 2023). The rapid evolution of the virus, resulting in multiple variants, has further complicated the international response to this critical situation. SARS-CoV-2, a single-stranded RNA virus belonging to the Coronaviridae family, possesses an enveloped, positive-sense structure. Its notable ability to mutate and adapt is primarily fueled by its error-prone RNA-dependent RNA polymerase, which lacks proofreading mechanisms (Pachetti *et al*., 2020). While replicating within host cells, the virus accumulates mutations, some of which enhances its transmissibility, ability to evade the immune system or disease-causing potential. The appearance of variants has significantly impacted the course of the pandemic. The D614G mutation in the spike protein, which became predominant globally by June 2020, increased the virus's fitness without significantly altering the severity of the illness (Korber *et al*., 2020). Subsequently, variants of concern (VOCs) surfaced, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529 and its sub-lineages) (CDC, 2023). Each variant exhibits a distinct mutational profile, particularly in the receptor-binding domain (RBD) and N-terminal domains (NTD) of the spike proteins, which are crucial for entering host cells and are the primary targets for neutralizing antibodies. The Delta variant, initially identified in India in December 2020, became the dominant strain globally by mid-2021. It was approximately 60% more transmissible than the Alpha variant and was linked to increased disease severity and hospitalization rates (Twohig *et al*., 2022). The emergence of the Omicron variant in November 2021 brought about

Corresponding author: Dr. Adnan A. Khan

Division of Nephrology and Hypertension, Department of Medicine, University of California, San Diego-92121, USA

E-mail: ukaaz@yahoo.com

Tel.: +19137300090

significant changes to the landscape. Omicron, characterized by over 30 mutations in the spike protein, displayed unprecedented transmissibility roughly 70% higher than that of Delta and notable immune evasion properties.

Vaccination has played a pivotal role in managing the global health crisis. Various vaccine technologies emerged within a short timeframe after the virus's genetic decoding, such as mRNA, viral vector, protein subunit, and inactivated virus platforms. These vaccines were developed building upon extensive scientific groundwork, notably advancements in mRNA research following previous viral outbreaks like SARS and MERS (Kariko *et al*., 2005; Pardi *et al*., 2018). Clinical trials showcased remarkable efficacy rates of these vaccines against the initial strain of the virus and its early mutations. Pfizer-BioNTech and Moderna's mRNA vaccines, for instance, demonstrated efficacy exceeding 90% in averting symptomatic illness, while viral vector and protein subunit vaccines displayed efficacy levels ranging from 60% to 90% (Baden *et al*., 2021; Polack *et al*., 2020; Voysey *et al*., 2021). Nonetheless, the presence of immune-evading variants like Beta, Gamma, and Omicron posed substantial challenges to the effectiveness of these vaccines. Observations from real-world studies have offered valuable insights into the performance of vaccines against these variants. For instance, a study conducted in Qatar revealed that the effectiveness of the Pfizer-BioNTech vaccine dropped from 89.5% against the Alpha variant to 75% against Beta (Abu-Raddad *et al*., 2021). During the surge of the Delta variant, the efficacy of vaccines in preventing symptomatic infection decreased from over 90% to approximately 65-70% for mRNA vaccines, though protection against severe illness remained high at over 90% (Lopez Bernal *et al*., 2021). The emergence of the Omicron variant has further emphasized the influence of viral evolution on vaccine efficacy, with its numerous mutations in critical antigenic regions substantially reducing the neutralization capacity of vaccine-induced antibodies. Research has indicated that two doses of mRNA vaccines provide only 30-40% defence against symptomatic Omicron infection, which rises to 70-75% following a booster dose (Andrew *et al*., 2022). Despite these challenges, the vaccines persist in offering robust protection (exceeding 90%) against severe illness, hospitalization, and mortality, even in cases of Omicron infection (Collie *et al*., 2022). The safety profile of COVID-19 vaccines has been subject to thorough examination both during clinical trials and post-marketing surveillance. Common side effects typically include mild to moderate symptoms like pain at the injection site, fatigue, headache, myalgia, and fever, which usually resolve within a short period. These reactions are indicative of the immune response elicited by the vaccine and not the actual COVID-19 infection. Uncommon yet severe adverse events have been identified through rigorous monitoring (CDC, 2023). The AstraZeneca and Johnson & Johnson vaccines, for instance, have been associated with exceedingly rare instances (approximately 1-7 per million doses) of thrombosis with thrombocytopenia syndrome (TTS), prompting some countries to favour mRNA vaccines (Schultz *et al*., 2021). Specifically, mRNA vaccines, especially in young males post the second dose, have been linked to rare cases (around 1-5 per 100,000) of myocarditis or pericarditis, with most cases being mild and responsive to treatment (Mevorach *et al.,* 2021). Despite these isolated occurrences, overwhelming evidence supports the notion that the advantages of vaccination far outweigh the potential risks, particularly in light of the significantly higher rates of cardiovascular complications stemming from COVID-19 itself.

As the virus undergoes continual evolution, the landscape of vaccines is adjusting accordingly. Producers have created boosters tailored to specific variants, such as the bivalent mRNA vaccines designed to address both the original strain and the Omicron subvariants. These modified formulations seek to enhance immune defence against existing and potential forthcoming variants (Chalkias *et al*., 2022). Furthermore, there is on-going research on universal coronavirus vaccines that focus on conserved epitopes shared among various coronaviruses, offering optimism for broader and more enduring protection (Cohen, 2023). This comprehensive review delves into the primary SARS-CoV-2 variants, their influence on vaccine effectiveness, the clinical data supporting vaccine efficacy, and the intricate safety characteristics of diverse vaccine platforms. Through a synthesis of recent studies, our objective is to furnish healthcare professionals, policymakers, and the general populace with a lucid, evidence-based comprehension of our present status and future trajectories in this dynamic and critical confrontation.

2. Epidemiology of SARS-CoV-2

The SARS-CoV-2 virus, first discovered in China, is responsible for inducing the COVID-19 illness, which can result in severe health complications and fatalities (Lu *et al*., 2020; Ji *et al*., 2020). Initially, there were suspicions surrounding the involvement of the Huanan seafood market in the initial dissemination of the virus, yet the precise source and natural host(s) remains ambiguous (Ji *et al*., 2020). It is worth mentioning that the primary confirmed case had no association with the aforementioned market (Huang *et al*., 2020). The predominant mode of transmission is through respiratory droplets and proximity, with asymptomatic individuals also capable of transmitting the virus (Xu *et al*., 2020; Lipsitch *et al*., 2020). An alternative route of potential transmission is through aerosol exposure within enclosed environments. Despite the virus being detectable in urine, faeces, and tears, there have been no documented infections originating from these bodily fluids (Lu *et al*., 2020; Li *et al*., 2020). The population at large appears to be susceptible to contracting the virus, with an estimated basic reproduction number (R0) of 3.77 (Wu *et al*., 2020). China has implemented effective preventive strategies, including the implementation of city-wide lockdowns and quarantine measures, resulting in a reduction in this transmission rate (Lu *et al*., 2020; Benvenuto *et al*., 2020; Li *et al*., 2020). To date, there have been 2,354,474 confirmed cases worldwide, with the majority of patients falling within the age bracket of 30 to 79 years, and a median age of 47 (Guan *et al*., 2020). Males make up 58.1% of the reported cases. A significant proportion of cases (81%) exhibit mild symptoms, while 14% are classified as severe and the overall mortality rate stand at 2.3%. Among a subset of 1,099 confirmed cases, 1.9% had a documented history of wildlife exposure (Guan *et al*., 2020). Within China, 43.9% of cases were identified in Wuhan, with 72.3% of other cases being linked to travel to or contact with individuals from Wuhan. Furthermore, 23.7% of patients presented with underlying health conditions such as hypertension, diabetes, cerebrovascular ailments, or cancer. The median duration of the incubation period is reported to be 4 days. Healthcare workers account for 3.5% of all infections, with over 3,400 cases primarily concentrated in Hubei Province and 15 documented fatalities among medical personnel (Bai *et al*., 2020).

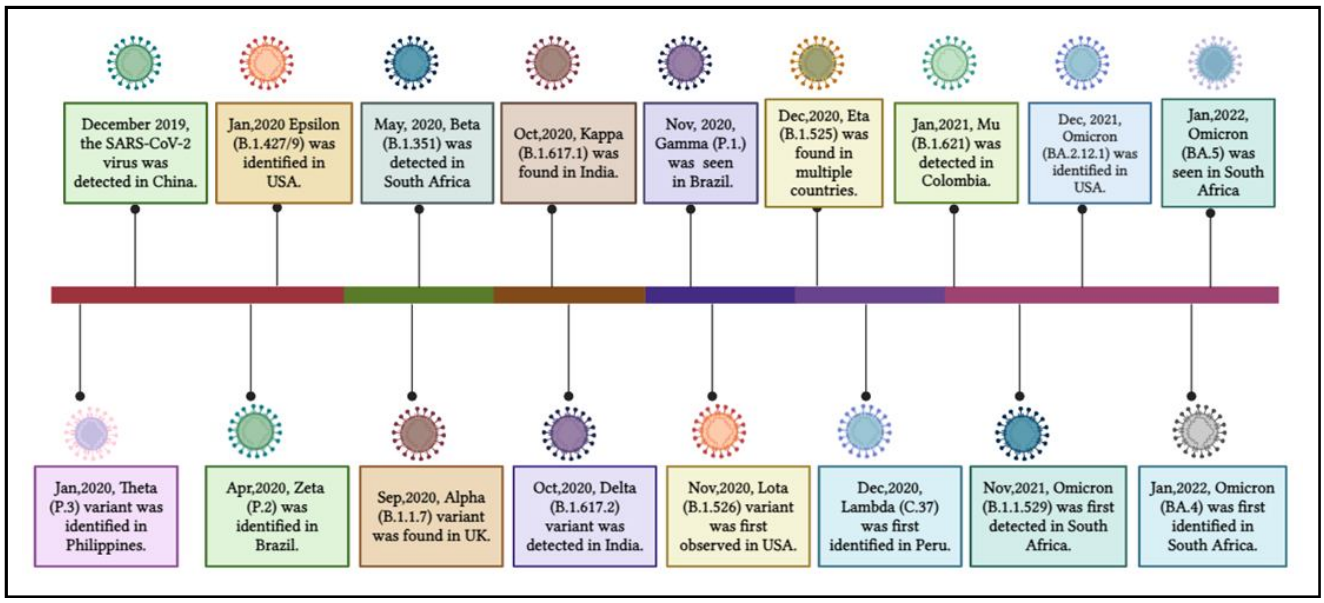

Figure 1: A Schematic timeline illustrating the onset of the COVID-19 pandemic and the development of different SARS-CoV-2 variants.

3. SARS-CoV-2 variants and their characteristics

During the COVID-19 pandemic's duration, numerous iterations of SARS-CoV-2 have surfaced. These iterations are categorized according to genetic alterations that impact their characteristics, such as transmissibility, severity of illness, and efficacy of vaccines. Entities in the healthcare sector, such as the World Health Organization (WHO), classify these iterations into clusters like variants of concern (VOCs) and variants of interest (VOIs). Presented below are some of the primary iterations that have been recognized (Table 1 and Figure 1).

3.1 Alpha variant (B.1.1.7)

In the autumn of 2020, a genetically distinct variant of SARS-CoV-2, namely B.1.1.7 or the Alpha variant, was identified by the United Kingdom. This particular variant harbours a total of 17 mutations (Rambaut *et al*., 2020), consisting of 14 non-synonymous point mutations and 3 deletions, with a noteworthy nine mutations occurring in the Spike (S) protein (Tian *et al*., 2021), a critical element for the virus's entry into host cells (Davies *et al*., 2021). Significant mutations within the Alpha variant include N501Y, which enhances its binding to the ACE2 receptor (Starr *et al*., 2020), P681H, associated with an increase in transmissibility (Peacock *et al*., 2021), and the H69/V70 deletion, linked to immune evasion (Meng *et al*., 2021). The Alpha variant is marked by increased mortality rates, elevated transmissibility, and a potential for more severe clinical outcomes (Bian *et al*., 2021; Cai *et al*., 2021). Nevertheless, its impact on the efficacy of emergency use authorization (EUA) monoclonal antibody therapies is minimal, and it shows only a slight decrease in neutralization by convalescent and post-vaccination sera (Collier *et al*., 2021; Edara *et al*., 2021; Shen *et al*., 2021; Wang *et al*., 2021; Wu *et al*., 2021). Studies suggest that this variant is 30-50% more transmissible than the original strain and was responsible for 66% of COVID-19 cases in the United States before the emergence of the Delta variant as the predominant strain (Paul*et al*., 2021).

3.2 Beta variant (B.1.351)

The Beta variant, known as B.1.351, originated in Nelson Mandela Bay, Eastern Cape Province, South Africa, displaying a total of 21 mutations with a focus on nine within the Spike (S) protein that enhances its affinity for human cells (Karim, 2020, Callaway, 2021). Despite sharing some mutations with the Alpha variant (B.1.1.7), these variants emerged separately, with the notable E484K mutation in the receptor-binding domain (RBD) of the S protein aiding the virus in evading neutralizing antibodies (Weisblum *et al*., 2020; Yi *et al*., 2020; Jangra *et al*., 2021). Studies conducted in early 2021 indicated a decrease in the neutralizing activity of antibodies from individuals immunized with Pfizer/BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccines against the Beta variant compared to the original strain (Greaney *et al*., 2021; Cele *et al*., 2021). The Beta variant has been correlated with increased transmissibility, possibly increased severity, and increased rates of hospitalization (Meng *et al*., 2021; Wang *et al*., 2021).

3.3 Gamma variant (P.1)

In January 2021, a pair of novel COVID-19 strains was recognized in Brazil, denoted as P.1 (Gamma variant) and P.2 (Zeta variant). Despite exhibiting certain mutations with other variants, they originated separately. The P.1 mutation, also known as the Gamma variant, was initially observed in four travellers from Brazil upon their arrival in Tokyo (Fujino *et al*., 2021). This particular variant showcases 17 distinctive amino acid alterations, with 10 manifesting within the spike (S) protein (Faria *et al*., 2021). Noteworthy mutations within P.1 encompass N501Y, K417N, and E484K, akin to those found in the Alpha and Beta variants. These mutations heighten the virus's affinity for binding to the human ACE2 receptor, thus amplifying both transmissibility and the likelihood of immune evasion (Sabino *et al*., 2021). The emergence of P.1 resulted in widespread infection in Manaus, Brazil, although it was absent in samples obtained from March to November 2020. This variant has been associated with cases of reinfection and a marginal decline in vaccine efficacy, primarily

due to the E484K mutation, which possesses the capability to evade neutralizing antibodies from convalescent plasma. Conversely, the P.2 variant, also referred to as the Zeta variant, is characterized by the presence of the E484K mutation. Nevertheless, this variant is presently either undetectable or present at exceedingly low levels in several nations (Voloch *et al*., 2021).

3.4 Epsilon variant (B.1.427)

After 2020, a novel SARS-CoV-2 mutation emerged in California, encompassing two distinct lineages, namely B.1.427 and B.1.429 (Deng *et al*., 2021; Mc Callum *et al*., 2021; Tchesnokova *et al*., 2021). These lineages exhibit a commonality of three mutations (W152C, S13I, and L452R) within the ACE2-binding site of the spike protein, yet they differ in additional mutations that are either synonymous or non-synonymous (Peng *et al*., 2022). Studies conducted by the academic institution of the University of California unveiled that this particular variant displays a reduced susceptibility by a factor of four towards neutralizing antibodies derived from convalescent individuals of COVID-19. Moreover, it manifests a twofold increase in resistance against antibodies generated by vaccination with either the Moderna (mRNA-1273) or Pfizer/BioNTech (BNT162b2) vaccines (Peng *et al*., 2022).

3.5 Eta variant (B.1.525)

In December 2020, the B.1.525 variant was identified in Nigeria and the UK. This particular variant exhibits several genetic alterations in common with the B.1.1.7 lineage, including mutations like E484K, and deletions “H69/V70 and “144 within the N-terminal domain (NTD) of the spike (S) protein, collectively leading to enhanced transmissibility of SARS-CoV-2 (59 Public Health England). What distinguishes the B.1.525 variant is its distinctive mutations in the S protein Q677H, Q52R, A67V, and F888L potentially enhancing its capacity to efficiently bind to human cells (Ozer *et al*., 2022).

3.6 Lota variant (B.1.526)

In October 2021, the emergence of the B.1.526 variant of SARS-CoV-2 was documented within the confines of New York City (Annavajhala *et al*., 2021; Lasek-Nesselquist *et al*., 2021; West *et al*., 2021). This particular variant showcases mutations at positions D614G and A701V in the spike (S) protein, along with the emergence of numerous novel point mutations (Zhou *et al*., 2021). The presence of the E484K mutation, a characteristic shared with the Iota variant, has been observed to drastically reduce the efficacy of neutralizing antibodies and vaccine sera. An alternative iteration of the B.1.526 variant harbours the S477N mutation, potentially enhancing its binding affinity to the ACE2 receptor (Zhou *et al*., 2021).

3.7 Delta variant (B.1.617)

Lineage B.1.617 of SARS-CoV-2 was initially identified in Maharashtra, India, in October 2020 (Ministry of Health and Family Welfare, 2022) and swiftly disseminated to numerous nations, encompassing three distinct sublineages: B.1.617.1, B.1.617.2, and B.1.617.3. By May 2021, the B.1.617.2 sub lineage (Delta variant) received classification as a variant of concern (VOC) owing to its comparable transmissibility to the Alpha variant (Public Health England, 2021). Within B.1.617.2, mutations in the spike (S) protein, particularly L452R, and E484Q in the receptor-binding domain (RBD), are observed, facilitating evasion of neutralizing antibodies (Mlcochova *et al*., 2021; Liu *et al*., 2022; Yadav *et al*., 2022). This specific variant represents the initial instance, where these two mutations conjoin. Preliminary data indicates that B.1.617.2/Delta might elevate the probability of hospitalization in contrast to the B.1.1.7/Alpha variant (Sheikh *et al*., 2021). Recent investigations also underscore the significance of the P681R mutation in B.1.617.2/Delta in augmenting its pathogenicity. As outlined by the CDC and diverse scholarly inquiries, these variant exhibits potential resistance to certain emergency use authorization (EUA) monoclonal antibody therapies and slightly diminished sensitivity to antibodies produced through immunizations (Saito *et al*., 2022).

3.8 Mu variant (B.1.621)

The Mu variant (B.1.621) of SARS-CoV-2 was classified as a variant of interest by the World Health Organization on August 30, 2021, after its initial detection in Colombia in January 2021. This particular variant harbours a total of eight mutations within the spike (S) protein, namely T95I, YY144-145TSN, R346K, E484K, N501Y, D614G, P681H, and D950N. Several of these mutations, such as E484K (also identified in the Beta and Gamma variants), P681H and N501Y (shared with the Alpha variant), and D950N (shared with the Delta variant), have the potential to reduce the efficacy of antibodies produced through natural infection or vaccination against SARS-CoV-2. Recent studies indicate that the Mu variant displays a considerably higher level of resistance around 12.4 times against antibodies from individuals recovering from COVID-19 who were infected early in the pandemic compared to the original virus (Miteva *et al*., 2023). Moreover, it demonstrates significant resistance to antibodies generated through natural infection and the BNT162b2 mRNA vaccine. It is imperative to engage in ongoing surveillance of the Mu variant due to its assortment of mutations that suggest possible attributes for evading immune responses (Miteva *et al*., 2023).

3.9 Omicron variant (B.1.1.529)

The Omicron variant (B.1.1.529) was first identified in South Africa (Botswana) in November 2021 and was classified as a variant of concern (VOC) by the WHO. It contains over 30 mutations in the spike (S) protein, some of which are also found in earlier variants like Alpha, Beta, Gamma, and Delta. Additional mutations in the envelope, membrane, and nucleocapsid proteins give Omicron improved abilities to spread, attach to cells, and evade antibodies. Initially, the variant was classified into three lineages (BA.1, BA.2, and BA.3), and by mid-2022, two more lineages (BA.4 and BA.5) had been identified (Miteva *et al*., 2023). BA.1 and BA.2 have 21 mutations in common in the S protein, while BA.4 and BA.5 resemble BA.2 but with an additional deletion. The BA.1 subvariant shares mutations with previous VOCs, indicating the potential for genetic recombination. Research comparing Omicron and the Delta variant suggests that Omicron is more easily transmitted and has a greater ability to bypass immunity, making people more susceptible to infection even if they are vaccinated. The effectiveness of vaccinations against Omicron increases notably with a third dose or booster, leading to efficacy rates of more than 70 % (Miteva *et al*., 2023).

Table 1: Comprehensive overview of SARS-CoV-2 variants (Tatsi *et al.*, 2021; WHO, 2023; CDC, 2023; ECDC, 2023)

Variant	Lineage	Mutations	First identified	Key characteristics
Alpha	B.1.1.7	N501Y, D614G	UK, Sep 2020	Increased transmissibility
Beta	B.1.351	E484, K417N, N501Y	South Africa, May 2020	Reduced vaccine effectiveness
Gamma	P.1	E484K, K417T, N501Y	Brazil, Nov 2020	Increased transmissibility and potential reinfection
Delta	B.1.617.2	L452R, T478K, D614G	India, Oct 2020	Highly transmissible, severe disease
Omicron	B.1.1.529	G339D, S371L, S373P, S375F, T478K, E484A, N501Y, D614G, P681H.	Multiple countries, Nov-2021	Highly transmissible, immune escape
Lambda	C.37	G75V, T76I, L452Q, F490S, D614G, T859N	Peru, Dec 2020	Potential increased transmissibility
Mu	B.1.621	E484K, N501Y, P681H	Colombia, Jan 2021	Potentially reduced vaccine effectiveness
Omicron BA.1	B.1.1.529.1	N501Y, P681H, K417N, E484A	Multiple countries, Nov 2021	Immune escape spread globally
Omicron BA.2	B.1.1.529.2	L452Q, D405N	Multiple countries, Dec 2021	More contagious than the BA.1 variant.
Omicron BA.4/ BA.5	B.1.1.529. 4/5	L452R, F486V	Multiple countries, 2022	Immunity evasion, worldwide prevalence
Omicron XBB.1.5	XBB.1.5	F486P, S486S	Multiple countries, Oct 2022	Highly contagious, capable of evading immunity.
Omicron XBB.1.16	XBB.1.16	F486P, S486P	Multiple countries, Dec 2022	Enhanced transmissible, evasion of immunity.
Epsilon	B.1.427 B.1.429	S13I, W152C, L452R	United States of America, Mar 2020	Increase in transmissibility and a decrease in resistance to antibodies from convalescent serum
Zeta	P.2	E484K, D614G	Brazil, Apr 2020	There is no resistance to antibodies from convalescent serum, but there is an increase in resistance to bamlanivimab
Eta	B.1.525	E484, F888L	Multiple countries, Dec 2020	There is an increase in the resistance to antibodies from convalescent serum.
Theta	P.3	D614G, H1101Y, E1092K, V1176F	Philippines, Jan 2021	The resistance to antibodies is increased, compared to that observed in the B.1. 351 variant.
Iota	B.1.526	L5F, T95I, D253G, E484K, D614G and A701V.	United States of America, Nov 2020	There is a decrease in resistance to antibodies from convalescent serum and monoclonal antibodies
Kappa	B.1.617.1	L452R, E484Q, P681R, D614G, T95I, Q1071H	India, Oct 2020	There is a lower susceptibility to antibodies from COVID-19 patients' serum compared to the P.3 and B.1.351 variants.
EG.5	XBB.1.9.2	Q52H	China, Feb 2023	-
BA.2.86[$]	BA.2	Mutations relative to BA.2	Israel and Denmark, July 2023	-
JN.1[#]	-	BA.2.86 + S: L455S	United States of America, Aug 2023	-
JN.1.7	-	-	Oct 2023	-
KP.2	-	-	Jan 2024	-
KP.3	-	-	Feb 2024	-
JN.1.18	-	-	Nov 2024	-

4. Mechanism and impact of SARS CoV-2 variants

The infection mechanism of SARS-CoV-2 hinges on the interaction between the spike protein and the ACE2 receptor, which is vital for the virus to enter host cells. Mutations occurring in the spike protein, particularly within the receptor-binding domain (RBD), play a critical role as they have the potential to enhance the virus's ability to bind effectively, prompting significant concerns. One notable mutation, N501Y, found in the Alpha, Beta, and Gamma variants, amplifies the virus's capacity to attach to ACE2, consequently increasing its infectivity. Despite initial reports indicating that the Alpha variant did not elevate the risk of hospitalization, subsequent research revealed a spike in mortality rates by as much as 61% and a rise in the severity of the disease. The presence of the P681H mutation in the Alpha variant, located near the furin cleavage site, further facilitates transmission. Furthermore, the ÄH69/V70 mutation has been observed to enhance viral infectivity in laboratory settings (Figure 2) (Mistry *et al*., 2022).

In comparison to the Alpha variant, the Beta variant exhibits a higher number of mutations in the spike protein. Computational analyses focusing on the interactions between RBD and ACE2 suggest that while mutations like K417T and E484K may decrease the binding affinity, the N501Y mutation significantly strengthens it, ultimately enhancing the transmissibility of the Beta variant. In South Africa, the Beta variant quickly became dominant; correlating with a more severe second wave of infections and increased mortality rates (Mistry *et al*., 2022).

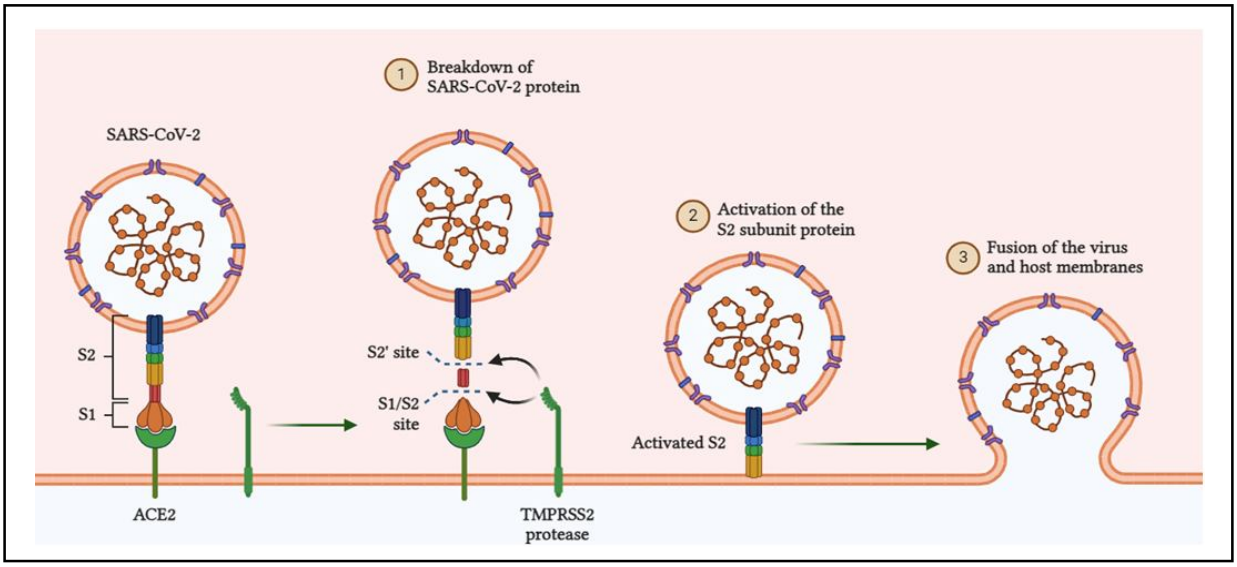

Figure 2: Mechanism of SARS-CoV-2 entry, replication, and immune response activation.

In Brazil, the Gamma variant, characterized by 17 amino acid modifications, initiated a significant outbreak, displaying heightened transmissibility and increased severity, particularly affecting the younger population. Gamma notably raised the fatality rate in comparison to previous outbreaks. The Delta variant, first identified in India, rapidly spread globally due to its elevated transmissibility, attributed to the mutations L452R and P681R. Delta replaced the Beta variant in South Africa and the Alpha variant in the UK, linked to increased rates of hospitalization and more severe disease (Alinejad *et al*., 2022).

Omicron, discovered in late 2021 in South Africa, quickly became the dominant variant, outpacing Delta. Initial findings suggested that Omicron led to milder disease compared to Delta. The ongoing evolution of SARS-CoV-2 involves a multitude of mutations that enhance both transmission and severity, underscoring the need for continuous research to comprehensively grasp these alterations and their consequences (Alinejad *et al*., 2022).

5. Efficacy of vaccines against each SARS-CoV-2 variant

The global distribution of COVID-19 vaccines has coincided with the emergence of various SARS-CoV-2 variants, necessitating continuous research to assess vaccine efficacy across an evolving viral landscape. From the original Wuhan-Hu-1 strain to variants like Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2), and more recently the Omicron family (B.1.1.529 and its sub-lineages such as BA.4, BA.5, and XBB.1.5), each mutation has challenged vaccine performance. This has highlighted the complex interactions between immune evasion, different vaccine technologies, and the significant role of booster doses in maintaining immunity (Table 2 and Figure 3) (Tao *et al*., 2021).

5.1 Original variant

Initially, the focus of COVID-19 vaccine trials was on the original SARS-CoV-2 strain to establish benchmarks for efficacy. The BNT162b2 vaccine from Pfizer-BioNTech displayed a 95% efficacy rate against symptomatic disease (Polack *et al*., 2020), while Moderna's mRNA-1273 vaccine exhibited a 94.1% efficacy (Baden *et al*., 2021). The Oxford-AstraZeneca vaccine, known as ChAdOx1 nCoV-19, demonstrated a 70.4% efficacy rate, which varied based on dosing schedules (Voysey *et al*., 2021), whereas Johnson & Johnson's Ad26 COV2.S vaccine achieved a global efficacy of 66% against moderate to severe disease (Sadoff *et al*., 2021). These results were largely supported by real-world studies, such as the study in Israel where the BNT162b2 vaccine was found to be 92% effective against documented infections and 87% effective against hospitalizations based on the research (Dagan *et al*., 2021).

5.2 Alpha variant (B.1.1.7)

As new variants like the Alpha (B.1.1.7) from the UK emerged, vaccines generally maintained a high level of efficacy. The ChAdOx1 nCoV-19 vaccine showed a 74.6% effectiveness against symptomatic Alpha variant (Emary *et al*., 2021), while the BNT162b2 vaccine demonstrated 93.7% effectiveness against the Alpha variant (Bernal *et al*., 2021).

5.3 Beta variant (B.1.351)

However, challenges arose with the Beta (B.1.351) variant from South Africa due to its ability to evade immune responses. The ChAdOx1 nCoV-19 vaccine faced difficulties in protecting against mild-to-moderate COVID-19 in the presence of the Beta variant, as highlighted in the study by Madhi *et al*., 2021, whereas the BNT162b2 vaccine showed a 75% efficacy rate in Qatar as per Abu-Raddad *et al*., 2021. In contrast, Moderna's vaccine demonstrated high effectiveness with a 96.4% efficacy rate against the Beta variant (Chemaitelly *et al*., 2021).

5.4 Gamma variant (P.1)

Gamma (P.1) originating from Brazil demonstrated the potential for immune evasion. The CoronaVac vaccine exhibited a 42% efficacy rate against symptomatic Gamma infection, as reported by Hitchings *et al*., 2021. Conversely, mRNA vaccines displayed an efficacy of over 80% in Canada (Fabiani*et al*., 2022).

5.5 Delta variant (B.1.617.2)

The Delta variant (B.1.617.2) emerged as the predominant strain globally, characterized by its high transmissibility. Studies in Scotland by Sheikh *et al*., 2021 revealed that BNT162b2 exhibited 92% effectiveness against Delta, while in England, (Bernal *et al*., 2021) reported 88% effectiveness. Concerns were raised regarding declining immunity amidst the surge of the Delta variant.

Table 2: The effectiveness of the SARS-CoV-2 vaccines and their ability to protect against variants (Miteva *et al*., 2023; Singh *et al*., 2021)

Vaccine (Manufacturer)	Type of vaccine	% effectiveness against infection	% effectiveness against variants of concern and severe disease
BNT162b2 (Pfizer-BioNTech)	mRNA	78-95%	Alpha-95%; Beta-95%; Delta-94%; Omicron-72% (initial vaccination); 90% (with booster)
m-RNA-1273 (Moderna)	mRNA	84-94.1%	Alpha, Beta, and Delta variants show 97% efficacy, while the Omicron variant shows 73% efficacy after the initial vaccination series and 90% efficacy following a booster dose.
AZD1222 (AstraZeneca)	Viral vector	75-80.7%	The alpha variant has an efficacy of 94%, Beta variant data is not available, the Delta variant shows 92% efficacy, and the Omicron variant has 71% efficacy after the primary vaccination series.
Ad26.COV-2-S (Janssen)	Viral vector	66-72%	86% for the Alpha variant, 76% for both the Beta and Delta variants, and 57% for the Omicron variant.
CoronaVac (Sinovac Biotech)	Inactivated virus	51-91%	50% for the Alpha variant, with no reported data for the Beta, Delta, and Omicron variants.
NVX-CoV2373 (Novavax)	Protein subunit	86-93%	89% for the Alpha variant, 86% for the Beta variant, with no reported data for the Delta variant, and 65% for the Omicron variant.
BBIB-CorV (Sinopharm)	Inactivated virus	68-93%	73% for the Alpha variant, with no reported data for the Beta and Delta variants, and 65% for the Omicron variant.
WIBP-CorV (Sinopharm)	Inactivated virus	73%	The efficacy range for preventing hospitalization and mortality is 94% to 98.6%.
Covaxin(Bharat Biotech)	Viral vector	78%	93% efficacy against the delta variant.
Sputnik V (Gamaleya)	Viral vector	92%	85.7% for the Alpha variant, 81% for the Beta variant, and 85.9% for both the Delta and Omicron variants. For those who received more than two or three doses, the efficacy increased to 87.6% and 97.0%, respectively.
Convidecia(CanSino Biologics)	Viral vector	58-64%	The efficacy range against severe COVID-19 is between 92% and 96%.
COVIFENZ (GSK)	Adjuvanted plant-based COVID-19	71%	Not reported.

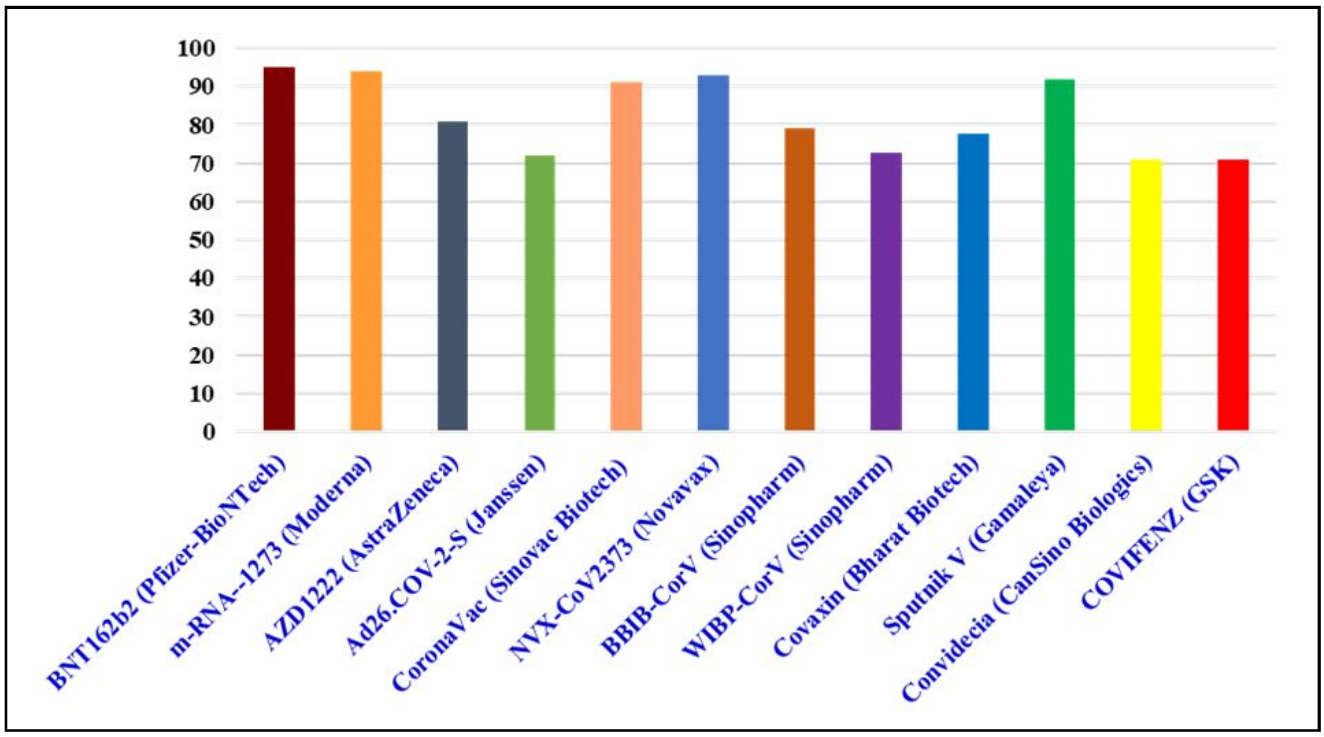

Figure 3: Effectiveness of the leading COVID-19 vaccines against SARS-CoV-2 infection, derived from multiple studies conducted during 2021 and 2022.

5.6 Omicron variant (B.1.1.529)

The emergence of the Omicron variant (B.1.1.529) presented significant hurdles due to its numerous mutations. Initially, a minimal level of protection was observed with two doses of BNT162b2 or ChAdOx1 nCoV-19 against symptomatic Omicron disease; however, subsequent booster doses enhanced efficacy, as demonstrated by Andrew *et al*., 2022. Despite a decrease in protection against infection, vaccines continued to offer substantial defence against severe outcomes, as indicated by Collie *et al*., 2022. The administration of booster doses became crucial, with studies showing that three doses of mRNA vaccines provided 67% effectiveness against Omicron, as reported by Accorsi *et al*., 2022. Bivalent boosters designed to target Omicron spike proteins exhibited improved efficacy against newer subvariants, as evidenced by Qu *et al*., 2023.

5.7 Omicron sub lineage XBB.1.5

The emergence of the Omicron sublineage XBB.1.5 was characterized by heightened transmissibility and evasion of the immune system. Supplementary safeguarding against symptomatic XBB/XBB.1.5-linked infection was provided by bivalent mRNA boosters as reported by Link-Gelles *et al*., 2023.

The long-term effectiveness of vaccines is critical for treating infectious diseases. Understanding the longevity of vaccine-induced immunity and the possible need for future booster doses is critical for pandemic control and public health interventions. Vaccination activates B cells and T cells, which produce antibodies and help identify and eliminate infectious cells. This combination response is necessary for long-term immunity (Polack *et al*., 2020; Baden *et al*., 2021). Early research on SARS-CoV-2 vaccines indicated significant immune responses, with high antibody levels lasting for the first six months after vaccination (Polack *et al*., 2020; Baden *et al*., 2021). However, antibody levels normally decrease with time, potentially impairing the vaccine's efficacy to prevent infection and serious complications. According to studies, antibody levels might drop considerably within a few months of vaccination. Despite this decline, vaccines continue to provide significant protection against severe illness, hospitalization, and death, especially in the months immediately following vaccination (Vashishtha *et al*., 2024). T cells help to maintain long-term immunity by identifying and responding to infected cells, and their responses are typically more persistent than antibodies (Deng *et al*., 2022). T cell-mediated immunity has been proven to last for long periods, giving continuous protection against severe disease (Merad *et al*., 2022).

Vaccines initially exhibited high efficacy against the original SARS-CoV-2 strain and early variations (Polack *et al*., 2020; Baden *et al*., 2021). However, newer variations, such as Delta and Omicron, have demonstrated varying levels of resistance to vaccine-induced immunity, resulting in lower efficacy in infection prevention but continuing protection against catastrophic outcomes (Plante *et al*., 2021; Garcia-Beltran *et al*., 2014). Breakthrough infections, in which vaccinated people get COVID-19, have increased due to diminishing immunity and the advent of novel variations (Sun *et al*., 2022). Nonetheless, vaccinated people have milder symptoms and lower rates of hospitalization and mortality than unvaccinated people, demonstrating vaccines' efficacy in preventing severe disease (Pilishvili *et al*., 2021).

Booster doses aim to restore and extend immunity by increasing antibody levels and improving the immunological response to variations (Li and Luo, 2022). Boosters have been shown to effectively restore high levels of protection, particularly in older people and

those with impaired immune systems. CDC and WHO recommend booster doses based on ongoing efficacy evaluations and new findings. As the virus changes and immunity weakens, more booster doses may be required to maintain high levels of protection. Periodic boosters or updated vaccines may be needed to address emerging variations and maintain protection (Liu *et al*., 2022). To regulate the virus's developing features and maintain long-term protection, public health interventions should include booster campaigns and potentially improved vaccines (Slaoui and Hepburn, 2020).

6. The effect of vaccine uncertainty on the success of SARS-CoV-2 immunization efforts

Vaccine uncertainty, defined as the unwillingness or resistance to receive vaccinations despite their availability, presents a significant obstacle to the success of vaccination campaigns against SARS-CoV-2. This uncertainty impedes the attainment of herd immunity, prolongs the duration of the pandemic, and contributes to avoidable instances of sickness and mortality. The mitigation of vaccine uncertainty stands as a critical factor in achieving positive public health outcomes.

6.1 Diminished vaccination rates

Vaccine uncertainty results in decreased levels of vaccination coverage, hindering the realization of herd immunity thresholds. To achieve herd immunity against COVID-19, 70-85% of the population must receive immunization, depending on the strain (Randolph and Barreiro, 2020). The presence of vaccine uncertainty complicates the process of reaching these objectives, leaving a substantial portion of the population susceptible to infection.

6.2 Prolonged persistence of the pandemic

Inadequate vaccination coverage facilitates the ongoing transmission of the virus within communities, leading to persistent waves of infection. This perpetuates the pandemic's duration, engendering enduring societal, economic, and healthcare obstacles (Anderson *et al*., 2020).

6.3 Emergence and dissemination of mutations

Low vaccination rates produce chances for the virus to undergo mutations and adaptations, resulting in the development of variants characterized by increased transmissibility or partial resistance to vaccines. This situation complicates endeavours aimed at pandemic management and may necessitate modifications to the existing vaccines (Plante *et al*., 2021).

6.4 Increased burden on the healthcare sector

Vaccine uncertainty can culminate in heightened incidences of severe illness and hospitalizations, particularly among vulnerable demographics. This increases stress on healthcare systems, which may become overwhelmed during spikes in infections, impacting the overall quality of healthcare provision (Ranney *et al*., 2020).

6.5 Economic and societal consequences

The enduring circumstances of the pandemic resulting from low vaccine uptake can trigger far-reaching economic and social consequences. Ongoing constraints, lockdowns, and disruptions to daily life have repercussions on economies, mental well-being, and societal welfare (Cutler and Summers, 2020).

7. Approaches to combat vaccine uncertainty

Effectively addressing vaccine uncertainty necessitates a holistic approach that integrates elements of education, communication, and policy endeavours. Public education and awareness play a crucial role in disseminating transparent and comprehensive information regarding the advantages and risks associated with vaccination (Dube *et al*., 2015). Educational Campaigns, for instance, can be initiated by public health entities to elucidate the mechanism of vaccines, their safety profile, and their significance in averting morbidity and mortality. Engaging with communities is equally vital as collaborating with key stakeholders, healthcare professionals, and influencers can foster trust and combat the dissemination of misinformation (Larson *et al*., 2016).

Combatting misinformation, particularly in the context of COVID-19 vaccines, requires concerted efforts to counter the widespread dissemination of false information across various social media and digital platforms. Strategies such as Fact-Checking Initiatives, involving partnerships with social media platforms to identify and eradicate misleading content, and public endorsements by reputable figures in the healthcare sector and communities can effectively debunk misinformation (Roozenbeek *et al*., 2020).

Involving healthcare providers in addressing vaccine hesitancy is paramount, considering their standing as credible sources of vaccine-related information. Encouraging healthcare professionals to initiate dialogues with patients, addressing their queries and apprehensions, as well as providing unequivocal recommendations advocating for vaccination as a safe and efficacious method to prevent COVID-19 are instrumental in this regard (Puri *et al*., 2020).

Furthermore, the implementation of policy measures by governments and organizations can significantly enhance vaccination rates (Opel *et al*., 2013). Measures like vaccine mandates targeting specific cohorts, such as healthcare personnel, can bolster coverage rates and shield vulnerable populations. Incentives, including financial rewards or additional privileges like travel or event participation, can serve as motivational factors for individuals to embrace vaccination. Moreover, enhancing Accessibility through initiatives like mobile vaccination clinics, extended operational hours, and workplace vaccination schemes can alleviate barriers to vaccine uptake (Edwards *et al*., 2016).

The role of achieving herd immunity in controlling the pandemic cannot be overstated, with vaccine hesitancy being a pivotal factor in attaining the requisite vaccination thresholds. sustaining high vaccination coverage is imperative for achieving herd immunity, necessitating a substantial proportion of the population to be immunized to disrupt virus transmission (Gostin *et al*., 2021). This effort is vital in safeguarding vulnerable groups unable to receive vaccines due to medical conditions or inadequate immune responses. Additionally, by preventing outbreaks and community transmission, herd immunity facilitates a return to normalcy and diminishes the necessity for stringent public health interventions (Brewer *et al*., 2017).

8. Future therapies and vaccination regimens

The current global health crisis caused by the COVID-19 pandemic has stimulated significant advancements in the field of therapeutics and immunizations against SARS-CoV-2. Researchers and pharma-

ceutical entities worldwide are actively engaged in exploring diverse strategies to augment treatment options and optimize vaccine regimens aimed at combating this newly identified coronavirus (WHO, 2021).

8.1 Antiviral medications

Antiviral drugs designed to target SARS-CoV-2 are intended to impede viral replication and mitigate the severity of the disease (Krammer, 2021). Recent progress includes the development of Molnupiravir, an oral antiviral agent that exhibits promise in reducing viral replication and expediting recovery during initial clinical studies by inducing mutations in viral RNA (FDA, 2021). Another example is Paxlovid (Nirmatrelvir/Ritonavir), an emergency-approved combination of protease inhibitors that disrupt viral replication by blocking the main protease enzyme. Ongoing investigations are focused on refining dosage regimens, exploring combined therapies, and identifying novel targets to enhance the effectiveness of treatments against emerging viral variants (Krammer, 2021).

8.2 Monoclonal antibodies (mAbs)

Monoclonal antibodies have emerged as targeted therapeutic options for COVID-19, especially for individuals at high risk. Notable developments in this area include the authorization of Sotrovimab for emergency usage, demonstrating efficacy against prevalent variants such as Delta and Omicron (FDA, 2021). Additionally, the cocktail therapy Casirivimab and Imdevimab (REGEN-COV) has proven effective in reducing hospitalizations and mortality rates among high-risk patients (Krammer, 2021). Future strategies are aimed at enhancing mAb efficacy against evolving viral strains and investigating the feasibility of long-lasting formulations to provide extended protection.

8.3 Next-generation vaccines

Progress in vaccine development is striving to enhance efficacy, longevity, and ease of administration (Krammer, 2021). Current initiatives are concentrated on various aspects such as advancements in mRNA vaccines by Pfizer-BioNTech and Moderna, investigating modified mRNA sequences and booster strategies to bolster immunity against variants like Delta and Omicron (CDC, 2022). Furthermore, efforts in optimizing dosages and enhancing immune response durability are ongoing for vector vaccines from AstraZeneca/Oxford and Johnson & Johnson (CDC, 2022). Other endeavours include the advancement of protein subunit vaccines by Novavax and other entities to ensure safety and scalability (FDA, 2021).

Initiatives are in progress to develop universal vaccines that offer broad protection against multiple coronaviruses, encompassing potential future variants of SARS-CoV-2 (WHO, 2021). These vaccines are designed to target conserved regions of viral proteins to induce enduring immunity and prepare for forthcoming global health emergencies.

8.4 Plant-based vaccines

Plant-based vaccines for SARS-CoV-2 are an innovative approach to combating COVID-19. One notable example is Covifenz, developed by the Canadian biopharmaceutical company Medicago. This vaccine uses virus-like particles that mimic the SARS-CoV-2 spike protein, which is grown in a plant related to tobacco, *Nicotiana benthamiana*. Another interesting development is the exploration of oral vaccines using plants like lettuce. Researchers have been working on expressing the SARS-CoV-2 Receptor Binding Domain (RBD) in various edible plants to create an oral vaccine (Monique *et al.,* 2021). These plant-based vaccines offer several advantages, including potentially lower production costs, ease of scalability, and reduced risk of contamination with human pathogens.

9. Side effects of SARS-CoV-2 vaccines

The global COVID-19 vaccination drive has played a critical role in managing the pandemic. As millions of people worldwide receive these vaccines, understanding their side effects and clinical effectiveness is crucial for making informed public health decisions and developing effective vaccination strategies (Figure 4).

9.1 Common side effects

Various COVID-19 vaccines, such as mRNA vaccines (Pfizer-BioNTech and Moderna), viral vector vaccines (AstraZeneca/Oxford, Johnson & Johnson), and protein subunit vaccines (Novavax), have been associated with a range of side effects. These commonly include

Local reactions

Pain, redness, and swelling at the injection site, usually resolve within a few days.

Systemic symptoms

Fever, fatigue, headache, muscle pain, and chills are frequent systemic reactions that generally appear within the first few days after vaccination.

Rare severe reactions

Serious adverse events like anaphylaxis are extremely rare, occurring at a rate of about 2 to 5 cases per million doses administered (CDC, 2023).

9.2 Specific adverse events

Recent findings have highlighted several specific adverse events associated with different types of vaccines

Heart inflammation (Myocarditis)

Conditions like myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the outer lining of the heart) have been observed mainly in younger males, typically within a few days after the second dose of mRNA vaccines (Heymans and Cooper, 2022).

Thrombosis and Thrombocytopenia

This rare but serious condition, known as thrombosis with thrombocytopenia syndrome (TTS), has been associated with adenovirus vector vaccines like AstraZeneca and Johnson & Johnson (CDC, 2023).

Guillain-Barré Syndrome (GBS)

There have been reports of this rare neurological disorder in recipients of the Johnson & Johnson vaccine, although a definitive causal link has not been established (CDC, 2023).

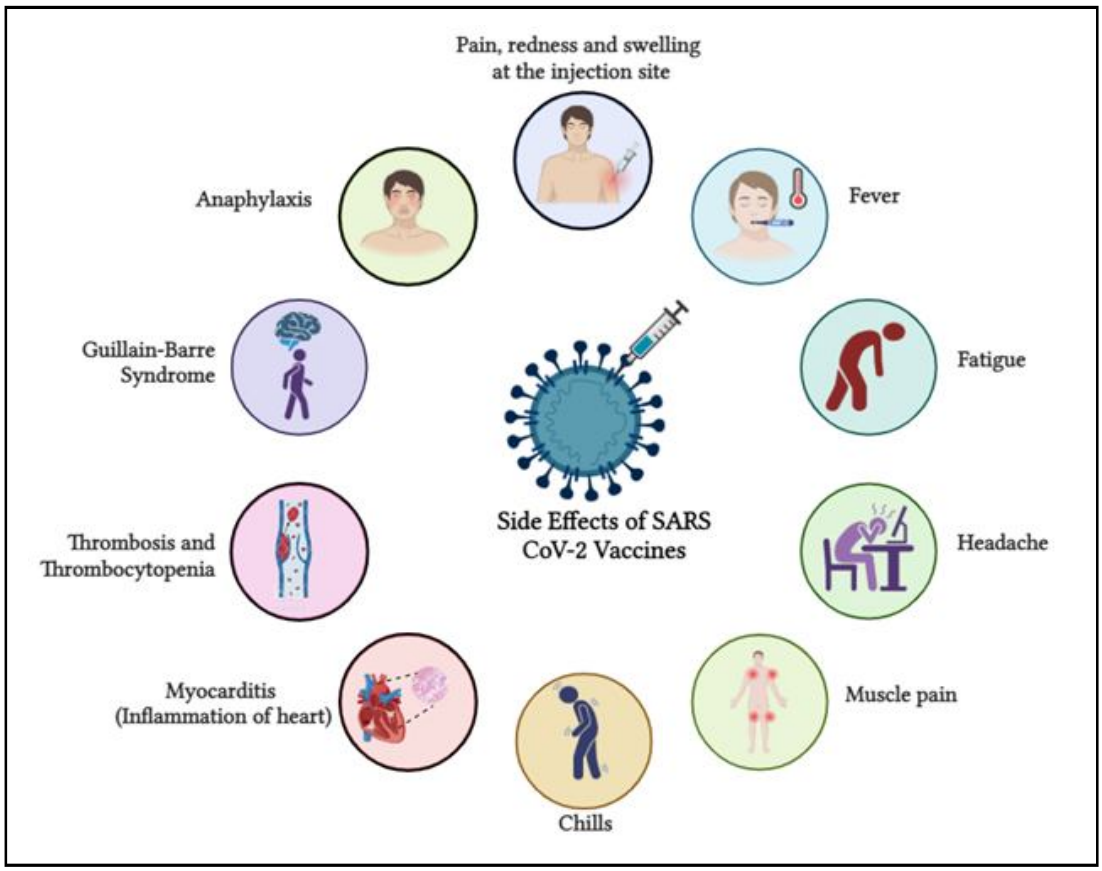

Figure 4: Adverse effects of SARS-CoV-2 vaccines.

10. Clinical evidence of vaccine efficacy

Extensive clinical trials and real-world studies have demonstrated the effectiveness of COVID-19 vaccines in preventing COVID-19 and its severe outcomes:

10.1 Pfizer/BioNTech vaccine

Clinical trials of the Pfizer/BioNTech vaccine revealed the most prevalent adverse effects to include pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, and fever (Pfizer/BioNTech, 2020). The vaccine has exhibited notable efficacy, boasting a 95% success rate in the prevention of symptomatic COVID-19 (Polack, 2020). A study released in The Lancet in May 2022 detailed an overall efficacy of 91.3% against the Omicron variant (Tartof, 2022). Furthermore, a recent publication in The New England Journal of Medicine in March 2023 indicated that the Pfizer vaccine displayed a 69% effectiveness in averting hospitalization due to the Omicron variant in children aged 5-11 years (Walter *et al*., 2022).

10.2 Moderna vaccine

In the case of the Moderna vaccine, clinical trials highlighted the most common side effects as pain at the injection site, fatigue, headache, muscle pain, joint pain, and chills (Moderna, 2020). The vaccine has proven to be highly effective, with a recorded efficacy rate of 94.1% in preventing symptomatic COVID-19 (Baden, 2021). A study published in the New England Journal of Medicine in December 2022 reported a 93.3% efficacy against severe COVID-19 stemming from the Omicron variant (CDC, 2023). Additionally, a recent study published in JAMA network open in April 2023 suggested that the Moderna vaccine conferred 96% protection against COVID-19 hospitalization in adults aged 18-64 years (CDC, 2023).

10.3 Johnson & Johnson vaccine

Regarding the Johnson & Johnson vaccine, clinical trials identified the most common side effects as pain at the very injection site, headache, fatigue, muscle pain, nausea, and fever. The vaccine has demonstrated an efficacy rate of 66.3% in preventing moderate to severe COVID-19. A study published in the Journal of Medical Virology in February 2023 indicated that the Johnson & Johnson vaccine provided 85% protection against severe COVID-19 resulting from the Omicron variant (Livingston *et al*., 2021).

11. Considerations of vaccines

Continuous safety monitoring is crucial for identifying and assessing vaccine-related adverse events. Systems such as the vaccine adverse event reporting system (VAERS) in the United States and similar programs worldwide provide ongoing surveillance and a rapid response to emerging safety concerns.

11.1 Special populations and considerations

Ongoing research is focusing on the safety and efficacy of vaccines in specific populations, including pregnant women, children, and immunocompromised individuals. Early studies suggest that vaccines are safe and effective across these groups, although specific recommendations may vary.

COVID-19 vaccines have shown robust efficacy in preventing infections and reducing disease severity, supported by extensive clinical evidence from trials and real-world studies. While common side effects are generally mild and transient, rare adverse events are closely monitored through rigorous safety surveillance systems. Continued research and surveillance are essential to optimize vaccine strategies, including booster doses, and to ensure equitable access to effective vaccines globally.

11.2 Challenges and considerations

The development and implementation of SARS-CoV-2 vaccines have played a crucial role in controlling the COVID-19 outbreak, although they present notable obstacles and factors to consider. One key issue is the constant emergence of new strains, like Delta and Omicron that could potentially weaken the effectiveness of existing vaccines. Studies suggest that while initial vaccines offered robust protection against the original virus strain, their efficiency may diminish with new variants, leading to the need for booster shots and potentially new vaccine formulas. This ongoing evolution of the virus necessitates a flexible and adaptable approach to vaccine development and distribution.

Furthermore, vaccine adverse effects represent a significant area of concern. Common reactions, such as soreness at the injection site, tiredness, and headaches, are generally mild and short-lived. Nevertheless, uncommon but severe side effects, such as myocarditis-particularly in young males after mRNA vaccines and thrombosis with thrombocytopenia syndrome (TTS) linked to adenoviral vector vaccines like AstraZeneca and Johnson & Johnson, demand careful monitoring and investigation. The identification and management of these rare yet serious side effects are crucial for upholding public trust in vaccination programs.

Clinical data strongly underpins the effectiveness of vaccines. Both mRNA and viral vector vaccines have demonstrated high success rates in preventing symptomatic COVID-19 and severe consequences, including hospitalizations and fatalities. Nevertheless, the varying performance of vaccines against distinct variants highlights the necessity for continuous research and surveillance. Real-world investigations consistently validate the efficacy of vaccines across various demographics and in the face of emerging strains, underscoring the pivotal role of booster shots in maintaining elevated immunity levels.

To sum up, the challenges presented by SARS-CoV-2 variants and the importance of monitoring and managing vaccine side effects call for a comprehensive strategy. Persistent research, adaptable vaccine approaches, and robust safety surveillance mechanisms are indispensable for upholding the sustained efficacy of vaccines and public trust in vaccination campaigns. International cooperation and investment in public health infrastructure are indispensable for surmounting these challenges and effectively addressing the pandemic.

12. Future perspective

Future prospects for SARS-CoV-2 variants and vaccines encompass several critical areas impacting ongoing research and public health strategies. The emergence of novel variants such as Delta and Omicron has prompted a significant emphasis on the development of adaptable vaccine formulations capable of precisely targeting evolving viral strains while retaining robust efficacy. Studies are also aimed at elucidating the mechanisms by which current vaccines trigger immune responses against different variants and exploring novel vaccine technologies to achieve broader and more enduring protection. Ensuring fair global distribution and effective vaccine rollout remains essential for addressing inequalities in access and achieving high vaccination coverage. Continuous monitoring of vaccine safety and efficacy, particularly for uncommon adverse events, is imperative to maintain public confidence in vaccination initiatives. Extended investigations are required to evaluate the longevity of vaccine-induced immunity and assess the necessity for booster shots. Additionally, forthcoming research will scrutinize the effectiveness of vaccines in specific populations such as immunocompromised individuals and children, guiding tailored vaccination approaches. It is imperative to address these future prospects to mitigate the impact of the pandemic and advance international endeavours in the fight against COVID-19.

13. Conclusion

In conclusion, to address the complexities presented by SARS-CoV-2 variants and vaccines, a comprehensive approach is required that integrates scientific progress, global collaboration, and equitable distribution. The role of vaccines in the fight against the COVID-19 pandemic has been significant. However, obstacles such as the appearance of new variants and adverse effects of vaccines underscore the continuous necessity for research and alertness. While vaccines have demonstrated their effectiveness in reducing severe illness and fatalities, their capacity to counter evolving variants might require modifications like booster doses and updated compositions. It is imperative to consistently monitor the safety and efficacy of vaccines to maintain public trust and enhance vaccination strategies. Moving forward, overcoming these challenges demands persistent investment in public health infrastructure, strong surveillance systems, and inclusive scientific inquiries to effectively address COVID-19 and prepare for future health emergencies.

Acknowledgements

The authors acknowledge all authors of the original articles cited in this review.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abu-Raddad, L.J.; Chemaitelly, H. and Butt, A.A. (2021). Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 Variants. N. Engl. J. Med., **385**(2):187-189.

Accorsi, E.K.; Britton, A.; Fleming-Dutra, K.E.; Smith, Z.R.; Shang, N.; Derado, G.; Miller, J.; Schrag, S.J. and Verani, J.R. (2022). Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA, **327**(7):639-651.

Alinejad, T.; Zareh, D.; Hao, Z., Zhou, T. and Chen, C.S. (2022). SARS-CoV-2 Mutation Mechanism, Features, and Future Perspective. Curr. Top. SARS-CoV-2/COVID-19-Two Years After., IntechOpen.

Anderson, R.M.; Vegvari, C.; Truscott, J. and Collyer, B.S. (2020). Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. The Lancet, **396**(10263):1614-1616.

Andrews, N.; Stowe, J.; Kirsebom, F.; Toffa, S.; Rickeard, T.; Gallagher, E.; Gower, C.; Kall, M.; Groves, N.; O'Connell, A.M. and Simons, D., (2022). Covid-19 vaccine effectiveness against the Omicron (B. 1.1. 529) variant. N. Engl. J. Med., **386**(16):1532-1546.

Annavajhala, M.K.; Mohri, H.; Wang, P.; Nair, M.; Zucker, J.E.; Sheng, Z.; Gomez-Simmonds, A.; Kelley, A.L.; Tagliavia, M.; Huang, Y. and Bedford, T. (2021). Emergence and expansion of the SARS-CoV-2 variant B. 1.526 identified in New York. MedRxiv.

Baden, L.R.; El Sahly, H.M.; Essink, B.; Kotloff, K.; Frey, S.; Novak, R.; Diemert, D.; Spector, S.A.; Rouphael, N.; Creech, C.B. and McGettigan, J. (2021). Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N. Engl. J. Med., **384**(5):403-416.

Bai, Y.X.; Xu, Y.H.; Wang, X.; Sun, C.; Guo, Y.; Qiu, S. and Ma, K.W. (2020). Advances in SARS-CoV-2: a systematic review. Eur. Rev. Med. Pharmacol. Sci., **24**(17).

Benvenuto, D.; Giovanetti, M.; Ciccozzi, A.; Spoto, S.; Angeletti, S. and Ciccozzi, M. (2020). The 2019 new coronavirus epidemic: evidence for virus evolution. J. Med. Virol., **92**(4):455-459.

Bernal, J.L.; Andrews, N.; Gower, C.; Gallagher, E.; Simmons, R.; Thelwall, S.; Stowe, J.; Tessier, E.; Groves, N.; Dabrera, G. and Myers, R. (2021). Effectiveness of Covid-19 vaccines against the B. 1.617. 2 (Delta) variant. Engl. J. Med.

Bernal, J.L.; Andrews, N.; Gower, C.; Robertson, C.; Stowe, J.; Tessier, E.; Simmons, R.; Cottrell, S.; Roberts, R.; O'Doherty, M. and Brown, K. (2021). Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on COVID-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. BMJ, **373**(1088):1088.

Bian, L.; Gao, F.; Zhang, J.; He, Q.; Mao, Q.; Xu, M. and Liang, Z. (2021). Effects of SARS-CoV-2 variants on vaccine efficacy and response strategies. Expert. Rev. Vaccines., **20**(4):365-373.

Brewer, N.T.; Chapman, G.B.; Rothman, A.J.; Leask, J. and Kempe, A. (2017). Increasing vaccination: Putting psychological science into action. Psychol. Sci. Public Interest, **18**(3):149-207.

Cai, Y.; Zhang, J.; Xiao, T.; Lavine, C.L.; Rawson, S.; Peng, H.; Zhu, H.; Anand, K.; Tong, P.; Gautam, A. and Lu, S. (2021). Structural basis for enhanced infectivity and immune evasion of SARS-CoV-2 variants. Science, **373**(6555):642-648.

Callaway, E. (2021). Could new COVID variants undermine vaccines? Labs scramble to find out. Nature, **589**(7841):177-179.

CDC. (2022). *COVID-19 Vaccines for Children and Teens*. Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/vaccines/vaccine-safety-children-teens.html.

CDC. (2023). Possible Side Effects After Getting a COVID-19 Vaccine. Centers for Disease Control and Prevention.

CDC. (2023). SARS-CoV-2 Variant Classifications and Definitions. Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html.

CDC. (2023). Selected Adverse Events Reported after COVID-19 Vaccination. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.

CDC. (2023). Omicron Subvariants. https://www.cdc.gov/coronavirus/2019-ncov/variants/index.html.

Cele, S.; Gazy, I.; Jackson, L.; Hwa, S.H.; Tegally, H.; Lustig, G.; Giandhari, J.; Pillay, S.; Wilkinson, E.; Naidoo, Y. and Karim, F. (2021). Escape of SARS-CoV-2 501Y. V2 from neutralization by convalescent plasma. Nature, **593**(7857):142-146.

Chalkias, S.; Harper, C.; Vrbicky, K.; Walsh, S.R.; Essink, B.; Brosz, A.; McGhee, N.; Tomassini, J.E.; Chen, X.; Chang, Y. and Sutherland, A. (2022). A bivalent omicron-containing booster vaccine against Covid-19. N. Engl. J. Med., **387**(14):1279-1291.

Chemaitelly, H.; Yassine, H.M.; Benslimane, F.M.; Al Khatib, H.A.; Tang, P.; Hasan, M.R.; Malek, J.A.; Coyle, P.; Ayoub, H.H.; Al Kanaani, Z. and Al Kuwari, E. (2021). mRNA-1273 COVID-19 vaccine effectiveness against the B. 1.1.7 and B.1.351 variants and severe COVID-19 disease in Qatar. Nat. Med., **27**(9):1614-1621.

Cohen, J. (2023). The race for a pan-coronavirus vaccine. Science. https://www.science.org/content/article/why-efforts-make-better-more-universal-coronavirus-vaccines-are-struggling.

Collie, S.; Champion, J.; Moultrie, H.; Bekker, L.G. and Gray, G. (2022). Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. N. Engl. J. Med., **386**(5):494-496.

Collier, D.A.; De Marco, A.; Ferreira, I.A.; Meng, B.; Datir, R.P.; Walls, A.C.; Kemp, S.A.; Bassi, J.; Pinto, D.; Silacci-Fregni, C. and Bianchi, S. (2021). Sensitivity of SARS-CoV-2 B. 1.1. 7 to mRNA vaccine-elicited antibodies. Nature, **593**(7857):136-141.

Cutler, D.M. and Summers, L.H. (2020). The COVID-19 pandemic and the $16 trillion virus. Jama, **324**(15):1495-1496.

Dagan, N.; Barda, N.; Kepten, E.; Miron, O.; Perchik, S.; Katz, M.A.; Hernán, M.A.; Lipsitch, M.; Reis, B. and Balicer, R.D. (2021). BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. N. Engl. J. Med., **384**(15):1412-1423.

Davies, N.G.; Abbott, S.; Barnard, R.C.; Jarvis, C.I.; Kucharski, A.J.; Munday, J.D.; Pearson, C.A.; Russell, T.W.; Tully, D.C.; Washburne, A.D. and Wenseleers, T. (2021). Estimated transmissibility and impact of SARS-CoV-2 lineage B. 1.1. 7 in England. Science, **372**(6538):3055.

Deng, X.; Garcia-Knight, M.A.; Khalid, M.M.; Servellita, V.; Wang, C.; Morris, M.K.; Sotomayor-González, A.; Glasner, D.R.; Reyes, K.R.; Gliwa, A.S. and Reddy, N.P. (2021). Transmission, infectivity, and neutralization of a spike L452R SARS-CoV-2 variant. Cell, **184**(13):3426-3437.

Deng, X.; Terunuma, H. and Nieda, M. (2022). Exploring the utility of NK cells in COVID-19. Biomed., **10**(5):1002.

Dubé, E.; Gagnon, D. and MacDonald, N.E. (2015). Strategies intended to address vaccine hesitancy: Review of published reviews. Vaccine, **33**(34):4191-4203.

Edara, V.V.; Floyd, K.; Lai, L.; Gardner, M.; Hudson, W.; Piantadosi, A.; Waggoner, J.J.; Babiker, A.; Ahmed, R.; Xie, X. and Lokugamage, K. (2021). Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. MedRxiv, 2021-02.

Emary, K.R.; Golubchik, T.; Aley, P.K.; Ariani, C.V.; Angus, B.; Bibi, S.; Blane, B.; Bonsall, D.; Cicconi, P.; Charlton, S. and Clutterbuck, E.A. (2021). Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B. 1.1. 7): an exploratory analysis of a randomised controlled trial. The Lancet, **397**(10282):1351-1362.

ECDC. (2023). ECDC classifies XBB. 1.5-like lineages with the amino acid change F456L as variants of interest following an increase in SARS-CoV-2 transmission in EU/EEA countries and abroad.https://www.ecdc.europa.eu/en/news-events/ecdc-classifies-xbb15-lineages-amino-acid-change-f456l-variants-interest-following.

Edwards, K.M.; Hackell, J.M.; Committee on Infectious Diseases, The Committee on Practice and Ambulatory Medicine, Byington, C.L.; Maldonado, Y.A.; Barnett, E.D.; Davies, H.D.; Edwards, K.M.; Lynfield, R.; Munoz, F.M. and Nolt, D. (2016). Countering vaccine hesitancy. Pediatrics, **138**(3):2016-2146.

Fabiani, M.; Puopolo, M.; Morciano, C.; Spuri, M.; Alegiani, S.S.; Filia, A.; D'Ancona, F.; Del Manso, M.; Riccardo, F.; Tallon, M. and Proietti, V. (2022). Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe COVID-19 during predominant circulation of the delta variant in Italy: retrospective cohort study. BMJ, 376.

Faria, N.R.; Mellan, T.A.; Whittaker, C.; Claro, I.M.; Candido, D.D.S.; Mishra, S.; Crispim, M.A.; Sales, F.C.; Hawryluk, I.; McCrone, J.T. and Hulswit, R.J. (2021). Genomics and epidemiology of the P. 1 SARS-CoV-2 lineage in Manaus, Brazil. Science, **372**(6544):815-821.

FDA. (2021). Investigational COVID-19 Convalescent Plasma. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-covid-19-convalescent plasma#:~:text=Most%20recently%2C%20FDA%20revised %20the,the%20outpatient %20or% 20inpatient%20setting.

Fujino, T.; Nomoto, H.; Kutsuna, S.; Ujiie, M.; Suzuki, T.; Sato, R.; Fujimoto, T.; Kuroda, M.; Wakita, T. and Ohmagari, N. (2021). Novel SARS-CoV-2 variant in travelers from Brazil to Japan. Emerg. Infect. Dis., **27**(4):1243.

Garcia-Beltran, W.F.; Lam, E.C.; Denis, K.S.; Nitido, A.D.; Garcia, Z.H.; Hauser, B.M.; Feldman, J.; Pavlovic, M.N.; Gregory, D.J.; Poznansky, M.C. and Sigal, A. (2014). Circulating SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. *medRxiv*.

Gostin, L.O.; Salmon, D.A. and Larson, H.J. (2021). Mandating COVID-19 vaccines. JAMA, **325**(6):532-533.

Greaney, A.J.; Loes, A.N.; Crawford, K.H.; Starr, T.N.; Malone, K.D.; Chu, H.Y. and Bloom, J.D. (2021). Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell. Host Microbe., **29**(3):463-476.

Guan, W.J.; Ni, Z.Y.; Hu, Y.; Liang, W.H.; Ou, C.Q.; He, J.X.; Liu, L.; Shan, H.; Lei, C.L.; Hui, D.S. and Du, B. (2020). Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med., **382**(18):1708-1720.

Heymans, S. and Cooper, L.T. (2022). Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. Nat. Rev. Cardiol., **19**(2):75-77.

Hitchings, M.D.; Ranzani, O.T.; Torres, M.S.S.; de Oliveira, S.B.; Almiron, M.; Said, R.; Borg, R.; Schulz, W.L.; de Oliveira, R.D.; da Silva, P.V. and de Castro, D.B. (2021). Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am, **1**.

Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X. and Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, **395**(10223):497-506.

Jangra, S.; Ye, C.; Rathnasinghe, R.; Stadlbauer, D.; Krammer, F.; Simon, V.; Martinez-Sobrido, L.; Garcia-Sastre, A.; Schotsaert, M. and PVI Study Group. (2021). The E484K mutation in the SARS-CoV-2 spike protein reduces but does not abolish neutralizing activity of human convalescent and post-vaccination sera. MedRxiv.

Ji, W.; Wang, W.; Zhao, X.; Zai, J. and Li, X. (2020). Cross species transmission of the newly identified coronavirus 2019 nCoV. J Med Viro., **92**(4):433-440.

Karikó, K.; Buckstein, M.; Ni, H. and Weissman, D. (2005). Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. Immunity, **23**(2):165-175.

Karim, S.S.A. (2020). The 2nd Covid-19 wave in South Africa: transmissibility & a 501.V2 variant. CAPRISA.

Korber, B.; Fischer, W.M.; Gnanakaran, S.; Yoon, H.; Theiler, J.; Abfalterer, W.; Hengartner, N.; Giorgi, E.E.; Bhattacharya, T.; Foley, B. and Hastie, K.M. (2020). Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell, **182**(4):812-827.

Krammer, F. (2021). SARS-CoV-2 vaccines in development. *Nature,* **586**(7830):516-527.

Larson, H.J.; De Figueiredo, A.; Xiahong, Z., Schulz, W.S.; Verger, P.; Johnston, I.G.; Cook, A.R. and Jones, N.S. (2016). The state of vaccine confidence 2016: global insights through a 67-country survey. EbioMed., **12**:.295-301.

Lasek-Nesselquist, E.; Lapierre, P.; Schneider, E.; George, K.S. and Pata, J. (2021). The localized rise of a B. 1.526 SARS-CoV-2 variant containing an E484K mutation in New York State. MedRxiv, 2021-02.

Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K.S.; Lau, E.H.; Wong, J.Y. and Xing, X. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N. Engl. J. Med., **382**(13):1199-1207.

Li, T. and Luo, K.Q. (2022). Recipients of COVID-19 vaccines face challenges of SARS-CoV-2 variants. Int. J. Biol. Sci., **18**(12):4642.

Li, X.; Zai, J.; Wang, X. and Li, Y. (2020). Potential of large "first generation" human to human transmission of 2019 nCoV. J. Med. Virol., **92**(4):448-454.

Link-Gelles, R. (2023). Early Estimates of bivalent mRNA booster dose vaccine effectiveness in preventing symptomatic SARS-CoV-2 infection attributable to Omicron BA. 5–and XBB/XBB. 1.5–related sublineages among immunocompetent adults—Increasing Community Access to Testing Program, United States, December 2022-January 2023. MMWR, 72.

Lipsitch, M.; Swerdlow, D.L. and Finelli, L. (2020). Defining the epidemiology of COVID-19: studies needed. N Engl J Med., **382**(13):1194-1196.

Liu, Y.; Liu, J.; Johnson, B.A.; Xia, H.; Ku, Z.; Schindewolf, C.; Widen, S.G.; An, Z.; Weaver, S.C.; Menachery, V.D. and Xie, X. (2022). Delta spike P681R mutation enhances SARS-CoV-2 fitness over Alpha variant. Cell. Rep., **39**(7).

Livingston, E.H.; Malani, P.N. and Creech, C.B. (2021). The Johnson & Johnson Vaccine for COVID-19. JAMA, **325**(15):1575-1575.

Lopez Bernal, J.; Andrews, N.; Gower, C.; Gallagher, E.; Simmons, R.; Thelwall, S.; Stowe, J.; Tessier, E.; Groves, N.; Dabrera, G. and Myers, R. (2021). Effectiveness of Covid-19 vaccines against the B. 1.617. 2 (Delta) variant. N. Engl. J. Med., **385**(7):585-594.

Lu, C.W.; Liu, X.F. and Jia, Z.F. (2020). 2019-nCoV transmission through the ocular surface must not be ignored. Lancet, **395**(10224):39.

Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N. and Bi, Y. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, **395**(10224):565-574.

Madhi, S.A.; Baillie, V.; Cutland, C.L.; Voysey, M.; Koen, A.L.; Fairlie, L.; Padayachee, S.D.; Dheda, K.; Barnabas, S.L.; Bhorat, Q.E. and Briner, C. (2021). Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B. 1.351 variant. N. Engl. J. Med., **384**(20):1885-1898.

McCallum, M.; De Marco, A.; Lempp, F.A.; Tortorici, M.A.; Pinto, D.; Walls, A.C.; Beltramello, M.; Chen, A.; Liu, Z.; Zatta, F. and Zepeda, S. (2021). N-terminal domain antigenic mapping reveals a site of vulnerability for SARS-CoV-2. Cell, **184**(9):2332-2347.

Meng, B.; Kemp, S.A.; Papa, G.; Datir, R.; Ferreira, I.A.; Marelli, S.; Harvey, W.T.; Lytras, S.; Mohamed, A.; Gallo, G. and Thakur, N. (2021). Recurrent emergence of SARS-CoV-2 spike deletion H69/V70 and its role in the Alpha variant B. 1.1. 7. Cell. Rep., **35**(13).

Merad, M.; Blish, C.A.; Sallusto, F. and Iwasaki, A. (2022). The immunology and immunopathology of COVID-19. Sci., **375**(6585):1122-1127.

Mevorach, D.; Anis, E.; Cedar, N.; Bromberg, M.; Haas, E.J.; Nadir, E.; Olsha-Castell, S.; Arad, D.; Hasin, T.; Levi, N. and Asleh, R. (2021). Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N. Engl. J. Med., **385**(23):2140-2149.

Ministry of Health and Family Welfare. (2022). Genome Sequencing by INSACOG Shows Variants of Concern and a Novel Variant in India. Available online: https://pib.gov.in/Press ReleaseI framePage. aspx?PRID=1707177 (accessed on 4 October 2022).

Mistry, P.; Barmania, F.; Mellet, J.; Peta, K.; Strydom, A.; Viljoen, I.M.; James, W.; Gordon, S. and Pepper, M.S. (2022). SARS-CoV-2 variants, vaccines, and host immunity. Front. Immunol., **12**:809244.

Miteva, D.; Kitanova, M.; Batselova, H.; Lazova, S.; Chervenkov, L.; Peshevska-Sekulovska, M.; Sekulovski, M.; Gulinac, M.; Vasilev, G.V.; Tomov, L. and Velikova, T. (2023). The end or a New Era of development of SARS-CoV-2 virus: Genetic variants responsible for severe COVID-19 and clinical efficacy of the most commonly used vaccines in clinical practice. Vaccines, **11**(7):1181.

Mlcochova, P.; Kemp, S.; Dhar, M.S.; Papa, G.; Meng, B.; Mishra, S.; Whittaker, C.; Mellan, T.; Ferreira, I.; Datir, R. and Collier, D.A. (2021). SARS-CoV-2 B. 1.617. 2 Delta variant replication, sensitivity to neutralising antibodies and vaccine breakthrough.

Moderna. (2020). COVE Study: Evaluating the Safety and Efficacy of an mRNA Vaccine Candidate against COVID-19. https://www.moder natx.com/cove-study.

Monique Power, Taha Azad, John C. Bell, Allyson M MacLean bioRxiv. 2021. Plant-based expression of SARS-CoV-2 antigen for use in an oral vaccine. doi: https://doi.org/10.1101/2021.12.07.471131.

Opel, D.J.; Mangione-Smith, R.; Taylor, J.A.; Korfiatis, C.; Wiese, C.; Catz, S. and Martin, D.P. (2011). Development of a survey to identify vaccine-hesitant parents: The parent attitudes about childhood vaccines survey. Hum Vaccine, **7**(4):419-425.

Ozer, E.A.; Simons, L.M.; Adewumi, O.M.; Fowotade, A.A.; Omoruyi, E.C.; Adeniji, J.A.; Olayinka, O.A; Dean, T.J.; Zayas, J.; Bhimalli, P.P. and Ash, M.K. (2022). Multiple expansions of globally uncommon SARS-CoV-2 lineages in Nigeria. Nat. Commun., **13**(1):688.

Pachetti, M.; Marini, B.; Benedetti, F.; Giudici, F.; Mauro, E.; Storici, P.; Masciovecchio, C.; Angeletti, S.; Ciccozzi, M.; Gallo, R.C. and Zella, D. (2020). Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. J. Transl. Med., **18**:1-9.

Pardi, N.; Hogan, M.J.; Porter, F.W. and Weissman, D. (2018). mRNA vaccines-A new era in vaccinology. Nat. Rev. Drug Discov., **17**(4):261-279.

Paul, P. (2021). Genomic surveillance for SARS-CoV-2 variants circulating in the United States, December 2020–May 2021. MMWR. Morbidity and mortality weekly report, 70.

Peacock, T.P.; Goldhill, D.H.; Zhou, J.; Baillon, L.; Frise, R.; Swann, O.C.; Kugathasan, R.; Penn, R.; Brown, J.C.; Sanchez-David, R.Y. and Braga, L. (2021). The furin cleavage site in the SARS-CoV-2 spike protein is required for transmission in ferrets. Nat. Microbiol., **6**(7):899-909.

Peng, J.; Liu, J.; Mann, S.A.; Mitchell, A.M.; Laurie, M.T.; Sunshine, S.; Pilarowski, G.; Ayscue, P.; Kistler, A.; Vanaerschot, M. and Li, L.M. (2022). Estimation of secondary household attack rates for emergent spike L452R severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants detected by genomic surveillance at a community-based testing site in San Francisco. Clin. Infect. Dis., **74**(1):32-39.

Pfizer/BioNTech. (2020). A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. https:// www.pfizer.com/science/coronavirus/vaccine.

Pilishvili, T.; Gierke, R.; Fleming-Dutra, K.E.; Farrar, J.L.; Mohr, N.M.; Talan, D.A.; Krishnadasan, A.; Harland, K.K.; Smithline, H.A.; Hou, P.C. and Lee, L.C. (2021). Effectiveness of mRNA Covid-19 vaccine among US health care personnel. N. Engl. J. Med., **385**(25):90.

Plante, J.A.; Mitchell, B.M.; Plante, K.S.; Debbink, K.; Weaver, S.C. and Menachery, V.D. (2021). The variant gambit: COVID-19's next move. Cell Host Microbe., **29**(4):508-515.

Polack, F.P.; Thomas, S.J.; Kitchin, N.; Absalon, J.; Gurtman, A.; Lockhart, S.; Perez, J.L.; Pérez Marc, G.; Moreira, E.D.; Zerbini, C. and Bailey, R. (2020). Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N. Engl. J. Med., **383**(27):2603-2615.

Public Health England (PHE). (2021). Risk assessment for SARS-CoV-2 variant: Delta (VOC-21APR-02, B.1.617.2). Available online:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/991135/3_June_ 2021_ Risk_ assessment_for_SARS-CoV-2_variant_DELTA.pdf (accessed on 3 June 2021).

Public Health England. (2022). SARS-CoV-2 Variants of Concern and Variants under Investigation in England: Technical Briefing 10. Available online:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/98 4274/Variants_of_ Concern_ VOC_Technical_Briefing_10_England.pdf (accessed on 4 October 2022).

Puri, N.; Coomes, E. A.; Haghbayan, H. and Gunaratne, K. (2020). Social media and vaccine hesitancy: New updates for the era of COVID-19 and globalized infectious diseases. Hum. Vaccin. Immunother., **16**(11):2586-2593.

Qu, P.; Evans, J.P.; Faraone, J.N.; Zheng, Y.M.; Carlin, C.; Anghelina, M.; Stevens, P.; Fernandez, S.; Jones, D.; Lozanski, G. and Panchal, A. (2023). Enhanced neutralization resistance of SARS-CoV-2 omicron subvariants BQ. 1, BQ. 1.1, BA. 4.6, BF. 7, and BA. 2.75. 2. Cell Host Microbe, **31**(1):9-17.

Rambaut, A.; Holmes, E.C.; O'Toole, Á.; Hill, V.; McCrone, J.T.; Ruis, C.; du Plessis, L. and Pybus, O.G. (2020). A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. Nat. Microbiol., **5**(11):1403-1407.

Randolph, H.E. and Barreiro, L.B. (2020). Herd immunity: understanding COVID-19. Immunity, **52**(5):737-741.

Ranney, M.L.; Griffeth, V. and Jha, A.K. (2020). Critical supply shortages-the need for ventilators and personal protective equipment during the Covid-19 pandemic. N. Engl. J. Med., **382**(18):41.

Roozenbeek, J.; Schneider, C.R.; Dryhurst, S.; Kerr, J.; Freeman, A.L.; Recchia, G.; Van Der Bles, A.M. and Van Der Linden, S. (2020). Susceptibility to misinformation about COVID-19 around the world. R. Soc. Open Sci., **7**(10):201199.

Sabino, E.C.; Buss, L.F.; Carvalho, M.P.; Prete, C.A.; Crispim, M.A.; Fraiji, N.A.; Pereira, R.H.; Parag, K.V.; da Silva Peixoto, P.; Kraemer, M.U. and Oikawa, M.K. (2021). Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet, **397**(10273):452-455.

Sadoff, J.; Gray, G.; Vandebosch, A.; Cárdenas, V.; Shukarev, G.; Grinsztejn, B.; Goepfert, P.A.; Truyers, C.; Fennema, H.; Spiessens, B. and Offergeld, K. (2021). Safety and efficacy of single-dose Ad26. COV2. S vaccine against Covid-19. N. Engl. J. Med., **384**(23):2187-2201.

Saito, A.; Irie, T.; Suzuki, R.; Maemura, T.; Nasser, H.; Uriu, K.; Kosugi, Y.; Shirakawa, K.; Sadamasu, K.; Kimura, I. and Ito, J. (2022). Enhanced fusogenicity and pathogenicity of SARS-CoV-2 Delta P681R mutation. Nature, **602**(7896):300-306.

Schultz, N.H.; Sørvoll, I.H.; Michelsen, A.E.; Munthe, L.A.; Lund-Johansen, F.; Ahlen, M.T.; Wiedmann, M.; Aamodt, A.H.; Skattør, T.H.; Tjønnfjord, G.E. and Holme, P.A. (2021). Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N. Engl. J. Med., **384**(22):2124-2130.

Sheikh, A.; McMenamin, J.; Taylor, B. and Robertson, C. (2021). SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet, **397**(10293):2461-2462.

Shen, X.; Tang, H.; McDanal, C.; Wagh, K.; Fischer, W.; Theiler, J.; Yoon, H.; Li, D.; Haynes, B.F.; Sanders, K.O. and Gnanakaran, S. (2021). SARS-CoV-2 variant B. 1.1. 7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines. Cell Host Microbe., **29**(4):529-539.

Singh, D.D.; Parveen, A. and Yadav, D.K. (2021). SARS-CoV-2: emergence of new variants and effectiveness of vaccines. Front. Cell. Infect. Microbiol., **11**:777212.

Slaoui, M. and Hepburn, M. (2020). Developing safe and effective Covid vaccines-Operation Warp Speed's strategy and approach. N. Engl. J. Med., **383**(18):1701-1703.

Starr, T.N.; Greaney, A.J.; Hilton, S.K.; Ellis, D.; Crawford, K.H.; Dingens, A.S.; Navarro, M.J.; Bowen, J.E.; Tortorici, M.A.; Walls, A.C. and King, N.P. (2020). Deep mutational scanning of the SARS-CoV-2 receptor binding domain reveals constraints on folding and ACE2 binding. Cell, **182**(5):1295-1310.

Sun, J.; Zheng, Q.; Madhira, V.; Olex, A.L.; Anzalone, A.J.; Vinson, A.; Singh, J.A.; French, E.; Abraham, A.G; Mathew, J. and Safdar, N. (2022). Association between immune dysfunction and COVID-19 breakthrough infection after SARS-CoV-2 vaccination in the US. JAMA Intern. Med., **182**(2):153-162.

Tao, K.; Tzou, P.L.; Nouhin, J.; Gupta, R.K.; de Oliveira, T.; Kosakovsky Pond, S.L.; Fera, D. and Shafer, R.W. (2021). The biological and clinical significance of emerging SARS-CoV-2 variants. Nat. Rev. Genet., **22**(12):757-773.

Tartof, S.Y.; Slezak, J.M.; Fischer, H.; Hong, V.; Ackerson, B.K.; Ranasinghe, O.N.; Frankland, T.B.; Ogun, O.A.; Zamparo, J.M.; Gray, S. and Valluri, S.R. (2021). Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. The Lancet, **398**(10309):1407-1416.

Tatsi, E.B.; Filippatos, F. and Michos, A. (2021). SARS-CoV-2 variants and effectiveness of vaccines: a review of current evidence. Epidemiol. Infect., **149**:237.

Tchesnokova, V.; Kulasekara, H.; Larson, L.; Bowers, V.; Rechkina, E.; Kisiela, D.; Sledneva, Y.; Choudhury, D.; Maslova, I.; Deng, K. and Kutumbaka, K. (2021). Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. J. Clin. Microbiol., **59**(11):10-1128.

Tian, F.; Tong, B.; Sun, L.; Shi, S.; Zheng, B.; Wang, Z.; Dong, X. and Zheng, P. (2021). N501Y mutation of spike protein in SARS-CoV-2 strengthens its binding to receptor ACE2. Elife, **10**:69091.

Twohig, K.A.; Nyberg, T.; Zaidi, A.; Thelwall, S.; Sinnathamby, M.A.; Aliabadi, S.; Seaman, S.R.; Harris, R.J.; Hope, R.; Lopez-Bernal, J. and Gallagher, E. (2022). Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B. 1.617. 2) compared with alpha (B. 1.1. 7) variants of concern: a cohort study. Lancet Infect. Dis., **22**(1):35-42.

Vashishtha, V.M. and Kumar, P. (2024). The durability of vaccine-induced protection: An overview. Expert Rev. Vaccines., **23**(1):389-408.

Voloch, C.M.; da Silva Francisco Jr, R.; de Almeida, L.G; Cardoso, C.C.; Brustolini, O.J.; Gerber, A.L.; Guimarães, A.P.D.C.; Mariani, D.; da Costa, R.M.; Ferreira Jr, O.C. and Covid19-UFRJ Workgroup. (2021). Genomic characterization of a novel SARS-CoV-2 lineage from Rio de Janeiro, Brazil. J. Virol., **95**(10):10-1128.

Voysey, M.; Clemens, S.A.C.; Madhi, S.A.; Weckx, L.Y.; Folegatti, P.M.; Aley, P.K.; Angus, B.; Baillie, V.L.; Barnabas, S.L.; Bhorat, Q.E. and Bibi, S. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. The Lancet, **397**(10269):99-111.

Walter, E.B.; Talaat, K.R.; Sabharwal, C.; Gurtman, A.; Lockhart, S.; Paulsen, G.C.; Barnett, E.D.; Muñoz, F.M.; Maldonado, Y.; Pahud, B.A. and Domachowske, J.B. (2022). Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N.Engl. J. Med.*, **386**(1):35-46.

Wang, P.; Nair, M.S.; Liu, L.; Iketani, S.; Luo, Y.; Guo, Y.; Wang, M.; Yu, J.; Zhang, B.; Kwong, P.D. and Graham, B.S. (2021). Antibody resistance of SARS-CoV-2 variants B. 1.351 and B. 1.1. 7. Nature, **593**(7857):130-135.

Weisblum, Y.; Schmidt, F.; Zhang, F.; DaSilva, J.; Poston, D.; Lorenzi, J.C.; Muecksch, F.; Rutkowska, M.; Hoffmann, H.H.; Michailidis, E. and Gaebler, C. (2020). Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife, **9**:61312.

West, A.P.; Barnes, C.O.; Yang, Z. and Bjorkman, P.J. (2021). SARS-CoV-2 lineage B. 1.526 emerging in the New York region detected by software utility created to query the spike mutational landscape. BioRxiv.

WHO. (2021). *Therapeutics and COVID-19*. Retrieved https://www.who.int/teams/health-care-readiness/covid-19/therapeutics.

WHO. (2024). Tracking SARS-CoV-2 variants. https://www.who.int/activities/tracking-SARS-CoV-2-variants.

WHO. (2023). World Health Organization COVID-19 Dashboard.

WHO (2023). XBB.1.5Updated Rapid Risk Assessment. https://www.who.int/docs/default-source/coronaviruse/25012023xbb.1.pdf?sfvrsn=c3956081_1.

Wu, J.T.; Leung, K. and Leung, G.M. (2020). Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: A modelling study. Lancet, **395**(10225):689-697.

Wu, K.; Werner, A.P.; Moliva, J.I.; Koch, M.; Choi, A.; Stewart-Jones, G.B.; Bennett, H.; Boyoglu-Barnum, S.; Shi, W.; Graham, B.S. and Carfi, A. (2021). mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. BioRxiv, 2021-01.

Xu, Z.; Li, S.; Tian, S.; Li, H. and Kong, L.Q. (2020). Full spectrum of COVID-19 severity still being depicted. Lancet, **395**(10228):947-948.

Yadav, P.D.; Sapkal, G.N.; Abraham, P.; Ella, R.; Deshpande, G; Patil, D.Y.; Nyayanit, D.A.; Gupta, N.; Sahay, R.R.; Shete, A.M. and Panda, S. (2022). Neutralization of variant under investigation B. 1.617. 1 with sera of BBV152 vaccinees. Clin. Infect. Dis., **74**(2):366-368.

Yi, C.; Sun, X.; Ye, J.; Ding, L.; Liu, M.; Yang, Z.; Lu, X.; Zhang, Y.; Ma, L.; Gu, W. and Qu, A. (2020). Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies. Cell. Mol. Immunol., **17**(6):621-630.

Zhou, B.; Thao, T.T.N.; Hoffmann, D.; Taddeo, A.; Ebert, N.; Labroussaa, F.; Pohlmann, A.; King, J.; Steiner, S.; Kelly, J.N. and Portmann, J. (2021). SARS-CoV-2 spike D614G change enhances replication and transmission. Nature, **592**(7852):122-127.

Citation **Zeenath Banu, Pidigam Saidaiah, Unaiza Khan, A. Geetha, Shiba Khan and Adnan A. Khan (2024). SARS-CoV-2 variants and vaccines: Efficacy, side effects and clinical evidences. Ann. Phytomed., 13(2):7-22. http://dx.doi.org/10.54085/ap.2024.13.2.2.**