THE SCIENTIFIC DISCOURSE ON THE FEATURES OF COVID-19 VACCINE PLATFORMS, CHARACTERISTICS, SAFETY, IMMUNIZATION CHALLENGES, REGULATORY FRAMEWORKS, BROADER CONSIDERATIONS AND FUTURE PERSPECTIVES OF COVID-19 VACCINES GLOBALLY

[1,2,3.4,5]**Nodar Sulashvili,** Professor
[4]**Margarita Beglaryan,** Professor, Academician
[2]**Luiza Gabunia,** Professor
[2] **Nana Gorgaslidze,** Professor, Academician
[6]**Nato Alavidze,** Professor
[1]**Ia Egnatievi,** Professor
[1]**Manana Giorgobiani,** Professor
[2]**Marika Sulashvili ,** Invited Lecturer
[7]**Lela Grigolia,** Professor
[7]**Kakhaber Robakidze,** Professor

[1]David Aghmashenebeli University of Georgia,[2]Tbilisi State Medical University, [3]Georgian National University SEU, [4]Yerevan State Medical University after Mkhitar Heratsi, [5]Alte University, [6]Akaki Tsereteli State University, [7]The Caucasus International University

DOI: https://doi.org/10.52340/spectri.2025.11.01.11

ABSTRACT

The rapid development and deployment of COVID-19 vaccines have represented an unprecedented scientific endeavor, offering hope in the global fight against the pandemic. This paper delves into the scientific discourse surrounding the features, characteristics, safety profiles, challenges, and future considerations of COVID-19 vaccines. We provide a detailed analysis of the leading vaccine platforms—mRNA (e.g., Pfizer-BioNTech, Moderna), viral vector (e.g., AstraZeneca, Johnson & Johnson), protein subunit (e.g., Novavax), and inactivated virus (e.g., Sinovac)—emphasizing their unique mechanisms of action, efficacy rates across diverse populations, and the nature of immune responses elicited. Safety remains a paramount concern, and this work critically evaluates both short-term side effects, such as fever and fatigue, and rare long-term adverse events, including myocarditis and thrombosis with thrombocytopenia syndrome (TTS). The paper also addresses the logistical and ethical challenges of global vaccine distribution, highlighting disparities in access between high- and low-income countries, as well as the persistent issue of vaccine hesitancy driven by misinformation and mistrust. In light of emerging SARS-CoV-2 variants, such as Delta and Omicron, we explore the implications for vaccine efficacy and the ongoing need for booster doses and updated formulations. Additionally, the paper discusses the potential for pan-coronavirus vaccines and the lessons learned for future pandemic preparedness. By integrating current research, clinical data, and global perspectives, this work aims to provide a holistic understanding of the scientific, societal, and policy dimensions of COVID-19 vaccines. It underscores the importance of continued innovation, equitable access, and public engagement to ensure the long-term success of vaccination efforts in controlling the pandemic and safeguarding global health. Multiple vaccine platforms, including mRNA, viral vector, protein subunit, and inactivated vaccines, have been developed and approved to curb the spread of the virus. While these vaccines have significantly reduced severe cases and mortality, challenges such as the emergence of new variants, vaccine hesitancy, and disparities in global distribution persist. This article provides a comprehensive analysis of the scientific discourse surrounding the characteristics, efficacy, and challenges of COVID-19 vaccines. However, the rapid development and deployment of vaccines also brought challenges. Safety monitoring had to be conducted in real-time, and rare adverse events required careful evaluation. Global inequities in vaccine access highlighted disparities between high- and low-income countries, while vaccine hesitancy and misinformation further complicated rollout efforts. Additionally, the emergence of SARS-CoV-2 variants, such as Delta and Omicron, raised concerns about vaccine efficacy and the need for adaptive strategies. Against this backdrop, the scientific discourse on COVID-19 vaccines has focused on understanding their

features, safety profiles, and real-world effectiveness, while addressing the challenges of distribution, equity, and public acceptance. The study aims to provide a comprehensive analysis of these issues, offering insights into the achievements and lessons learned from the COVID-19 vaccination effort, and informing future pandemic preparedness and response strategies.

KEYWORDS: COVID-19, vaccines, clinical trials, efficacy, SARS-CoV-2.

COVID-19-ის ვაქცინების მახასიათებლების, თვისებების, უსაფრთხოების, იმუნიზაციის გამოწვევების, რეგულატორული ჩარჩოების, მომავლის პერსპექტივებისა და გლობალური ასპექტების შესახებ სამეცნიერო დისკურსი

[1,2,3.4,5]**ნოდარ სულაშვილი,** პროფესორი
[4]**მარგარიტა ბეგლარიანი,** პროფესორი, აკადემიკოსი
[2]**ლუიზა გაბუნია,** პროფესორი
[2] **ნანა გორგასლიძე,** პროფესორი, აკადემიკოსი,
[6]**ნატო ალავიძე,** პროფესორი
[1]**ია ეგნატიევი,** პროფესორი
[1]**მანანა გიორგობიანი,** პროფესორი
[2]**მარიკა სულაშვილი,** მოწვეული ლექტორი
[7]**ლელა გრიგოლია,** პროფესორი
[7]**კახაბერ რობაქიძე,** პროფესორი

[1]საქართველოს დავით აღმაშენებლის სახელობის უნივერსიტეტი, [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, [3]საქართველოს ეროვნული უნივერსიტეტის (SEU), [4]მხითარ ჰერაცის სახელობის ერევნის სახელმწიფო სამედიცინო უნივერსიტეტი, [5]ალტე უნივერსიტეტი, [6]აკაკი წერეთლის სახელმწიფო უნივერსიტეტი, [6]კავკასიის საერთაშორისო უნივერსიტეტი

რეზიუმე

COVID-19 ვაქცინების სწრაფი განვითარება და გავრცელება წარმოადგენს უპრეცედენტო სამეცნიერო წამოწყებას, რომელიც იმედს იძლევა პანდემიის წინააღმდეგ გლობალურ ბრძოლაში. ნაშრომი შეისწავლის COVID-19 ვაქცინების თავისებურებების, მახასიათებლების, უსაფრთხოების პროფილების, იმუნიზაციის გამოწვევებისა და სამომავლო მოსაზრებების გარშემო არსებულ სამეცნიერო დისკურსს. ნაშრომში განხილულია წამყვანი ვაქცინის პლატფორმების - mRNA-ს (მაგ., Pfizer-BioNTech, Moderna), ვირუსული ვექტორის (მაგ., AstraZeneca, Johnson & Johnson), ცილოვანი ქვეერთეულის (მაგ., Novavax) და ინაქტივირებული ვირუსის (მაგ., Sinovac) ვაქცინების ანალიზი - აღწერილია მათი უნიკალური მოქმედების მექანიზმები, ეფექტურობის მაჩვენებლები სხვადასხვა პოპულაციებში და გამოწვეული იმუნური პასუხების თავისებურებები. ვაქცინების უსაფრთხოება კვლავ უმნიშვნელოვანეს გამოწვევად რჩება და ნაშრომი კრიტიკულად აფასებს ვაქცინაციის როგორც მოკლევადიან გვერდით მოვლენებს, როგორიცაა ცხელება და დაღლილობა, ასევე იშვიათ ხანგრძლივ გვერდით მოვლენებს, მათ შორის მიოკარდიტს და თრომბოზს თრომბოციტოპენიის სინდრომით (TTS). ნაშრომი ასევე განიხილავს ვაქცინების გლობალური განაწილების ლოგისტიკურ და ეთიკურ გამოწვევებს, ხაზს უსვამს მაღალი და დაბალი შემოსავლის მქონე ქვეყნებს შორის ხელმისაწვდომობის უთანასწორობას, ასევე დეზინფორმაციითა და უნდობლობით გამოწვეულ ვაქცინაციისადმი ყოყმანის მუდმივ პრობლემას. SARS-CoV-2-ის ისეთი ახალი ვარიანტების, როგორიცაა Delta და Omicron, გათვალისწინებით, განხილულია ვაქცინის ეფექტურობაზე გამაძლიერებელი დოზებისა და

განახლებული ფორმულირებების მუდმივ საჭიროებები. გარდა ამისა, ნაშრომი განიხილავს კორონავირუსის ვაქცინების პოტენციალს და მომავალი პანდემიისთვის მზადყოფნისთვის მიღებულ გამოცდილებებს, მიმდინარე კვლევების, კლინიკური მონაცემებისა და გლობალური პერსპექტივების ინტეგრირებით. ეს ნაშრომი მიზნად ისახავს COVID-19 ვაქცინების სამეცნიერო, საზოგადოებრივი და პოლიტიკური ასპექტების ჰოლისტური გაგების უზრუნველყოფას. იგი ხაზს უსვამს ვაქცინაციის ძალისხმევის გრძელვადიანი წარმატების უზრუნველსაყოფად უწყვეტი ინოვაციების, თანაბარი ხელმისაწვდომობისა და საზოგადოების ჩართულობის მნიშვნელობას პანდემიის კონტროლსა და გლობალური ჯანმრთელობის დაცვაში. ვირუსის გავრცელების შესაკავებლად შემუშავებული და დამტკიცებულია ვაქცინის მრავალი პლატფორმა, მათ შორის mRNA, ვირუსული ვექტორი, ცილოვანი ქვეერთეული და ინაქტივირებული ვაქცინები. მიუხედავად იმისა, რომ ამ ვაქცინებმა მნიშვნელოვნად შეამცირა მძიმე შემთხვევები და სიკვდილიანობა, კვლავ რჩება გამოწვევები, როგორიცაა ახალი ვირუსის შტამების გაჩენა, ვაქცინაციისადმი ყოყმანი და გლობალური განაწილების უთანასწორობა, ეს სტატია წარმოადგენს COVID-19 ვაქცინების მახასიათებლების, ეფექტურობისა და გამოწვევების გარშემო არსებული სამეცნიერო დისკურსის ანალიზს. ვაქცინების სწრაფმა შემუშავებამ და გავრცელებამ ასევე მოიტანა ახალი გამოწვევები. ვაქცინაციის უსაფრთხოების მონიტორინგი სასურველი იყო რეალურ დროში ჩატარებულიყო, ხოლო იშვიათი გვერდითი მოვლენები ფრთხილ შეფასებას მოითხოვდა. ვაქცინებზე ხელმისაწვდომობის გლობალურმა უთანასწორობამ ხაზი გაუსვა მაღალი და დაბალი შემოსავლის მქონე ქვეყნებს შორის არსებულ უთანასწორობას, ხოლო ვაქცინაციისადმი ყოყმანი და დეზინფორმაცია კიდევ უფრო ართულებდა გავრცელების პროცესს. გარდა ამისა, SARS-CoV-2 ვარიანტების, როგორიცაა Delta და Omicron-ის გაჩენამ შეშფოთება გამოიწვია ვაქცინის ეფექტურობისა და ადაპტური სტრატეგიების საჭიროების შესახებ. ამ ფონზე, COVID-19 ვაქცინების შესახებ სამეცნიერო დისკურსი ფოკუსირებულია მათი მახასიათებლების, უსაფრთხოების პროფილების და რეალურ სამყაროში ეფექტურობის გააზრებაზე, ამავდროულად, ვაქცინების დისტრიბუციის, სამართლიანობისა და საზოგადოების მიერ მიღების გამოწვევების გადაჭრაზე. ეს ნაშრომი მიზნად ისახავს ამ საკითხების შესწავლას, COVID-19 ვაქცინაციის მცდელობიდან მიღწეული მიღწევებისა და გამოწვევევების შესახებ ინფორმაციის მიწოდებას და მომავალი პანდემიისთვის მზადყოფნისა და რეაგირების სტრატეგიების შემუშავებას.

საკვანძო სიტყვები: COVID-19, ვაქცინები, კლინიკური კვლევები, ეფექტურობა, SARS-CoV-2.

INTRODUCTION

The COVID-19 pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has posed an unprecedented global health challenge since its emergence in late 2019. The rapid spread of the virus led to millions of infections and significant mortality worldwide, prompting an urgent need for preventive and therapeutic measures. Given the high transmissibility of the virus and the severe complications associated with the disease, the development of effective vaccines became a top priority for the scientific community [1-2].

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, emerged in late 2019 and rapidly escalated into a global health crisis. By early 2020, the virus had spread to nearly every country, overwhelming healthcare systems, disrupting economies, and causing millions of deaths worldwide. The urgent need for effective interventions to control the pandemic led to an unprecedented global effort to develop vaccines at record speed [3-4].

Historically, vaccine development has been a lengthy process, often taking 10-15 years. However, the severity of the COVID-19 crisis, combined with advances in biotechnology and unprecedented funding, enabled researchers to accelerate this timeline. The scientific community leveraged decades of

prior research on coronaviruses, such as SARS-CoV-1 and MERS-CoV, as well as innovative platforms like mRNA and viral vector technologies, to create vaccines in under a year.

The first COVID-19 vaccines were authorized for emergency use in late 2020, marking a turning point in the pandemic. These vaccines were designed to elicit immune responses against the SARS-CoV-2 spike protein, which facilitates viral entry into human cells. Clinical trials demonstrated high efficacy in preventing symptomatic infection, severe disease, and death, leading to widespread vaccination campaigns [5-6].

To curb the pandemic, researchers and pharmaceutical companies accelerated vaccine development using both traditional and novel vaccine platforms. Unlike previous vaccine development efforts that typically took years or even decades, COVID-19 vaccines were created and deployed within an exceptionally short timeframe due to coordinated global efforts, substantial financial investments, and advancements in vaccine technology. By March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, which further intensified the urgency for vaccine research and production [7-8].

Multiple vaccine platforms, including mRNA, viral vector, protein subunit, and inactivated vaccines, have been developed and approved to curb the spread of the virus. While these vaccines have significantly reduced severe cases and mortality, challenges such as the emergence of new variants, vaccine hesitancy, and disparities in global distribution persist. This article provides a comprehensive analysis of the scientific discourse surrounding the characteristics, efficacy, and challenges of COVID-19 vaccines [9-10].

The review explores the mechanisms of different vaccine platforms, their immunological responses, and the effects of emerging SARS-CoV-2 variants on vaccine effectiveness. It also discusses the adverse effects associated with vaccination, including rare complications such as vaccine-associated enhanced disease (VAED) and antibody-dependent enhancement (ADE). Despite remarkable progress, the need for further improvements in vaccine technology remains critical. Strategies such as the development of universal coronavirus vaccines, alternative vaccine delivery methods, and enhanced public health policies are essential for long-term protection. Additionally, strengthening vaccine equity, combating misinformation, and integrating COVID-19 vaccination into routine immunization programs are key to ensuring global health security. This study highlights the ongoing efforts in COVID-19 vaccine research and underscores the necessity of continuous monitoring, innovation, and preparedness to effectively manage future pandemics [11-12].

COVID-19 vaccines work by stimulating the immune system to recognize and neutralize the virus before it can cause severe illness. The development strategies involved various approaches, including mRNA vaccines, viral vector-based vaccines, protein subunit vaccines, and inactivated or live-attenuated vaccines. These vaccines primarily target the SARS-CoV-2 spike protein, a crucial component that enables the virus to enter human cells. While vaccines have played a vital role in reducing hospitalizations and deaths, challenges such as waning immunity, breakthrough infections, and the emergence of new variants continue to necessitate ongoing research and booster immunization strategies [13-14].

The accelerated pace of vaccine development has also raised concerns regarding long-term efficacy, potential adverse effects, and equitable distribution. Some vaccines have demonstrated high levels of protection, while others have exhibited reduced effectiveness against emerging variants, requiring modifications and booster doses. Additionally, disparities in vaccine accessibility between high-income and low-income countries have highlighted the need for improved global vaccine distribution strategies [15-16].

Despite these challenges, the development and deployment of COVID-19 vaccines remain one of the most significant achievements in modern medical science. Ongoing studies continue to evaluate vaccine durability, effectiveness against new variants, and potential improvements in vaccine formulations. The lessons learned from this pandemic will likely shape future vaccine research and preparedness for emerging infectious diseases.

At the end of December 2019, several cases of pneumonia with an unknown cause were identified in Wuhan, Hubei Province, China. Shortly after, Chinese health authorities determined that a novel coronavirus was responsible for the illness. Once the complete genome sequence of this virus, initially referred to as the ‘Wuhan virus,’ was made publicly available, researchers rapidly analyzed the structures of its various viral proteins. Based on phylogenetic and taxonomic studies, the International Committee on Taxonomy of Viruses officially named the virus ‘severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Subsequently, the World Health Organization (WHO) introduced the term ‘Covid-19’ as an abbreviation for coronavirus disease 2019 [17-18].

To slow the spread of Covid-19, non-pharmaceutical interventions such as physical distancing, proper mask usage, remote working, isolation, and quarantines were implemented. However, these behavioral measures also had unintended consequences, including psychological distress, increased depression rates, and broader mental health challenges. The development of a safe and effective vaccine emerged as the most viable strategy to combat the pandemic. In March 2020, the WHO officially declared Covid-19 a global pandemic [19-20].

As of October 22, 2021, WHO data indicated that 322 vaccine candidates were in development, with 128 undergoing clinical trials and 194 in preclinical stages. The leading vaccines—developed by Pfizer-BioNTech, Moderna, Gamaleya, Novavax, Oxford-AstraZeneca, Sinopharm, Bharat Biotech, Johnson & Johnson, and Sinovac—were designed using the viral spike (S) glycoprotein from the original wild-type strain as an antigen.

The emergence of four major SARS-CoV-2 variants raised concerns about reduced vaccine effectiveness due to diminished neutralizing antibody responses and potential changes in cell-mediated immunity. The WHO designated these variants as Alpha, Beta, Gamma, and Delta.

COVID-19, a respiratory infectious disease, is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus has significantly impacted millions of people worldwide, posing a severe threat to public health. The development and widespread administration of various COVID-19 vaccines have played a crucial role in mitigating the effects of this life-threatening disease. Both traditional and advanced vaccine platforms have been utilized to develop effective immunization strategies against COVID-19 [21-23].

Study examines the global landscape of COVID-19 vaccines and their current status. Among the key vaccine types, virus-like particles (VLPs), subunit vaccines, DNA and RNA-based vaccines, viral vector-based vaccines, as well as inactivated and live-attenuated vaccines, are the primary contenders, currently undergoing various phases of clinical trials. Notably, protein subunit, RNA-based, and non-replicating viral vector-based platforms have been widely implemented, while inactivated virus vaccines have been extensively used in clinical settings worldwide [24-25].

Clinical trial data indicate that most vaccines elicit local or systemic reactions post-vaccination and exhibit varying degrees of efficacy against SARS-CoV-2 and its emerging variants. However, further research is essential to refine vaccine technology, minimize adverse effects, and enhance both safety and efficacy.

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has affected a vast global population. In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic, leading to widespread morbidity and mortality. As of December 2022, the disease has resulted in approximately 6.6 million deaths and over 651 million infections worldwide [26-27].

SARS-CoV-2 can cause a broad spectrum of health complications, ranging from mild cases to severe, life-threatening conditions. Among the virus's four primary structural proteins, three—envelope (E), membrane (M), and spike (S)—are embedded in the viral surface, while the nucleocapsid (N) protein is located within the ribonucleoprotein core. These proteins serve as key targets for vaccine development. Like other RNA viruses, SARS-CoV-2 undergoes frequent mutations as it spreads between hosts, leading to the emergence of new variants that exhibit distinct characteristics from the original strain. This mutational capacity has contributed to multiple waves of the pandemic over time [28-29].

Despite a decline in disease transmission and mortality due to effective public health measures, many countries continue to experience recurring outbreaks. Safe and effective prophylactic vaccines remain essential to controlling the pandemic and mitigating its devastating impact on healthcare systems, economies, and societies. Consequently, nations worldwide have prioritized the development, evaluation, and production of COVID-19 vaccines [30-31].

Vaccination is a key strategy in controlling the pandemic, and research into COVID-19 therapeutics is advancing at an unprecedented pace. Vaccine platforms are broadly categorized into two types: those based on viral components and those utilizing whole-virus approaches. Viral component-based vaccines include protein subunits, virus-like particles, DNA-based, RNA-based, and both replicating and non-replicating viral vectors. Whole-virus vaccines, on the other hand, comprise inactivated and live-attenuated formulations. Regardless of the platform, an effective vaccine should be easy to develop and manufacture, stable under various conditions, cost-effective, and safe for administration.

Although challenges remain, over 200 vaccine research projects are currently underway, with numerous candidates advancing through clinical trials. Several pharmaceutical companies have made significant strides in vaccine development, with leading candidates including Pfizer-BioNTech’s BNT162,

Oxford-AstraZeneca's AZD1222, Sinovac's CoronaVac, Moderna's mRNA-1273, Johnson & Johnson's Ad26.COV2.S, Sputnik-V (developed by the Gamaleya National Research Centre for Epidemiology and Microbiology), and Novavax's adjuvanted recombinant protein nanoparticle vaccine. These contenders continue to drive innovation in the global fight against COVID-19 [32-34].

Methodology

According to the latest update from the World Health Organization (WHO), titled draft Landscape of COVID-19 Potential Vaccines, data was gathered to identify promising vaccine candidates. This study was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, a revised framework for systematic review reporting. Relevant literature was sourced from International databases such as: Medline (PubMed), Web of Science, Embase, Elsevier, Cochrane Library, Scopus, Ovid, CINHAL, PubMed, Google Scholar, WHO and Scopus databases to ensure a comprehensive analysis.

Study Design and Analysis

- **Comparative Analysis:** Different COVID-19 vaccine platforms (mRNA, viral vector, inactivated, and protein subunit) were compared based on efficacy, safety, and immune response.
- **Statistical Evaluation:** Vaccine effectiveness was measured using statistical models assessing reductions in hospitalizations, severe disease, and mortality rates across vaccinated and unvaccinated populations.
- **Longitudinal Safety Assessment:** Reports of adverse effects were analyzed using data from pharmacovigilance systems (e.g., VAERS, EudraVigilance) to assess the frequency and severity of side effects.
- **Variant Impact Assessment:** Studies evaluating vaccine performance against emerging variants (e.g., Delta, Omicron) were reviewed to determine the extent of immune escape and the need for booster doses.

Ethical Considerations

- Only studies with ethical approval and adherence to **Good Clinical Practice (GCP)** guidelines were included.
- Informed consent and human subject protection were key inclusion criteria for clinical trial data.
- Global equity in vaccine access was considered in the discussion of challenges and future directions.
- This methodology ensures a rigorous, evidence-based assessment of COVID-19 vaccines, highlighting both their successes and areas for improvement.

RESULTS AND DISCUSSION

The emergence of COVID-19, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has led to an unprecedented global health crisis. To combat this rapidly spreading virus, the scientific community has undertaken extensive research, leading to the development of various COVID-19 vaccines. These vaccines have played a crucial role in reducing severe illness and mortality rates, thereby offering a path toward controlling the pandemic. However, their development and deployment have presented numerous challenges, requiring ongoing research to optimize their efficacy, safety, and adaptability to emerging variants.

COVID-19 vaccines are primarily developed using two main approaches: those based on viral components and those utilizing the whole virus. Vaccines derived from viral components include protein subunit vaccines, virus-like particle vaccines, DNA-based vaccines, RNA-based vaccines, and viral vector-based vaccines, which can either be replicating or non-replicating. Whole-virus-based vaccines, on the other hand, include inactivated vaccines, which contain killed virus particles, and live-attenuated vaccines, which use weakened virus strains. Each of these platforms has its own advantages and limitations, contributing to the diversity in vaccine effectiveness, durability of immunity, and potential side effects [35-37].

One of the key features of COVID-19 vaccines is their ability to stimulate an immune response that targets the spike protein of the SARS-CoV-2 virus. The mRNA-based vaccines, such as those developed by Pfizer-BioNTech and Moderna, instruct the body's cells to produce the spike protein, prompting the immune system to recognize and neutralize the virus upon exposure. Viral vector vaccines, such as Oxford-AstraZeneca's AZD1222 and Johnson & Johnson's Ad26.COV2.S, use a harmless adenovirus as a carrier to introduce genetic material encoding the spike protein, thereby triggering an immune response. Inactivated vaccines, including Sinovac's CoronaVac, use a killed version of the virus to induce immunity without causing infection. Despite their different mechanisms, all these vaccines aim to provide protective immunity and reduce disease severity.

There are some characteristics of Covid-19 Vaccines:

- **High vaccine efficacy in reducing severe COVID-19 outcomes:** Clinical trials and real-world data confirm that vaccines significantly lower hospitalization and mortality rates, even against emerging variants.
- **Demonstrated long-term safety with rare adverse effects:** While mild side effects are common, serious reactions such as myocarditis and thrombosis with thrombocytopenia syndrome (TTS) remain extremely rare, reinforcing the overall safety profile.
- **Immune responses vary by platform and booster strategy:** mRNA vaccines show strong initial immune responses but wane over time, while vector-based and protein subunit vaccines offer differing durability, highlighting the need for tailored booster regimens.
- **Effectiveness influenced by variant evolution:** While vaccines remain protective against severe disease, variants such as Omicron have demonstrated immune escape capabilities, necessitating updated or next-generation vaccines.
- **Global vaccination efforts show uneven coverage:** High-income countries achieved rapid immunization, whereas low-income regions faced delays due to logistical challenges, intellectual property restrictions, and supply chain constraints.
- **Breakthrough infections emphasize the importance of booster doses:** Waning immunity and highly transmissible variants have led to breakthrough infections, underscoring the role of boosters in sustaining protection.
- **Long-term surveillance reveals mixed durability of immunity:** Studies suggest a gradual decline in neutralizing antibodies but sustained T-cell immunity, influencing booster recommendations and future vaccine strategies.
- **Public perception and hesitancy continue to impact uptake:** Misinformation, distrust in health authorities, and vaccine politicization have led to varying acceptance rates, affecting herd immunity goals.
- **Advancements in next-generation vaccines show promise:** Research into mucosal vaccines, self-amplifying RNA, and universal coronavirus vaccines may provide broader, longer-lasting protection in the future.
- **Efficacy and Protection across Vaccine Platforms:** COVID-19 vaccines have demonstrated high effectiveness in preventing severe disease and death. However, variations exist among different platforms (mRNA, vector-based, inactivated, protein subunit), influencing immune response duration and protection levels. Studies indicate that while mRNA vaccines generate strong antibody responses, vector-based vaccines elicit more durable T-cell immunity, suggesting the need for diversified immunization strategies.
- **Vaccine Safety and Public Perception:** Large-scale studies affirm that COVID-19 vaccines have an excellent safety profile, with adverse effects largely mild and transient. However, rare events such as myocarditis (linked to mRNA vaccines) and thrombosis with thrombocytopenia syndrome (TTS, associated with vector-based vaccines) have raised concerns. Transparent risk-benefit communication and ongoing surveillance are crucial in maintaining public trust and addressing vaccine hesitancy.
- **Impact of Variants on Vaccine Effectiveness:** The emergence of variants like Delta and Omicron has challenged vaccine-induced immunity, reducing protection against infection while maintaining strong defense against severe illness. This underscores the need for adaptable vaccine platforms, variant-targeted boosters, and innovative approaches such as pan-coronavirus or universal vaccines.
- **Global Vaccine Distribution and Equity Challenges:** Vaccine rollout has been uneven, with high-income countries achieving rapid coverage while low-income nations faced supply shortages, logistical constraints, and intellectual property barriers. The pandemic has highlighted the need for global collaboration, technology transfer, and decentralized manufacturing to ensure equitable access to life-saving vaccines.
- **Booster Strategies and Long-Term Immunity:** With evidence of waning immunity, booster doses have been introduced to sustain protection. Research suggests that hybrid immunity (natural infection plus vaccination) offers the most robust protection. Understanding long-term immune responses, including the role of memory B cells and T cells, will be key in shaping future vaccination schedules.
- **Misinformation and Vaccine Hesitancy:** Despite scientific consensus on vaccine safety and efficacy, misinformation has fueled hesitancy in various populations. Social, cultural, and political factors influence vaccine uptake, highlighting the need for targeted public health campaigns, clear messaging, and community engagement to counteract vaccine-related misinformation.
- **Future Directions in COVID-19 Vaccine Development:** Advances in vaccine technology are paving the way for next-generation vaccines, including mucosal (intranasal) vaccines that may offer superior transmission-blocking capabilities. Additionally, self-amplifying RNA, universal coronavirus vaccines, and AI-driven vaccine design hold promise for future pandemic preparedness.

The rapid development and deployment of COVID-19 vaccines have been a remarkable scientific achievement, but they have also posed significant challenges. One of the primary concerns has been the occurrence of adverse effects, ranging from mild symptoms such as injection site pain and fatigue to rare but serious complications like vaccine-associated enhanced disease (VAED) and myocarditis. Additionally, the emergence of new SARS-CoV-2 variants has raised concerns about reduced vaccine efficacy, necessitating modifications to existing vaccines or the development of new booster doses. Another challenge is vaccine accessibility, as disparities in distribution have left many low-income countries struggling to vaccinate their populations, thereby prolonging the global impact of the pandemic [38-39].

COVID-19 Vaccine Platforms

Various technological platforms have been utilized in the development of COVID-19 vaccines. These platforms are broadly categorized into those based on viral components and those using whole-virus approaches.

Viral Component-Based Platforms:

- Protein Subunit Vaccines: These contain purified viral proteins that stimulate an immune response.
- Virus-Like Particles (VLPs): Composed of viral proteins that mimic the structural appearance of the virus but lack genetic material, making them non-infectious.
- DNA- and RNA-Based Vaccines: Utilize genetic material that encodes viral proteins, prompting the body to produce an immune response.
- Non-Replicating Viral Vector Vaccines: Contain viral genetic material encapsulated within a viral vector that cannot replicate inside human cells.
- Replicating Viral Vector Vaccines: Similar to non-replicating vectors but capable of replication, enhancing immune response.

Whole Virus-Based Platforms:

- Inactivated Virus Vaccines: Contain virus particles that have been chemically or physically inactivated, rendering them incapable of causing infection.
- Live-Attenuated Virus Vaccines: Contain weakened forms of the virus that can replicate but do not cause severe disease, providing a strong immune response.

Several COVID-19 vaccines have been developed using different platforms to provide protection against SARS-CoV-2 infection. These vaccines fall into several major categories based on their technology:

- **mRNA Vaccines**
- **BNT162b2 (Pfizer/BioNTech)**: A nucleoside-modified mRNA vaccine formulated in lipid nanoparticles. It encodes the full-length spike protein of SARS-CoV-2 in a stabilized prefusion conformation.
- **mRNA-1273 (Moderna)**: Another lipid nanoparticle-formulated mRNA vaccine that encodes a prefusion-stabilized spike glycoprotein.

- **Viral Vector Vaccines**
- **ChAdOx1 nCoV-19 (AstraZeneca/Oxford, AZD1222)**: A replication-deficient chimpanzee adenoviral vector carrying the gene for the SARS-CoV-2 spike protein.
- **Gam-COVID-Vac (Sputnik V)**: A heterologous recombinant adenovirus-based vaccine using two different adenoviral vectors (rAd26-S and rAd5-S) for the prime and booster doses.
- **Ad26.COV2.S (Johnson & Johnson)**: A recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a stabilized SARS-CoV-2 spike protein.

- **Protein Subunit Vaccines**
- **NVX-CoV2373 (Novavax)**: A nanoparticle-based vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins combined with Matrix-M1 adjuvant to enhance immune response.

- **Inactivated Virus Vaccines**
- **CoronaVac (Sinovac Life Sciences)**: A conventional inactivated virus vaccine that relies on chemically inactivated SARS-CoV-2 particles to stimulate an immune response.

These different vaccine platforms have demonstrated varying degrees of efficacy, durability of immune response, and logistical considerations, such as storage requirements. While mRNA vaccines have

shown high efficacy and rapid adaptability to emerging variants, inactivated virus vaccines are often easier to store and distribute in regions with limited cold chain infrastructure. Each platform presents distinct advantages and challenges, contributing to the diverse landscape of global COVID-19 immunization efforts [40-41].

The strategy of mixing COVID-19 vaccines, known as heterologous vaccination or "mix-and-match," has been implemented in several countries to enhance immune response and increase protection, especially against emerging variants like Delta.

Preclinical Studies in Animals

- **Sputnik V and AstraZeneca in Mice**: A study showed that using Sputnik V for the first dose and AstraZeneca for the second dose did not cause any adverse effects and led to a higher immune response.
- **Self-Amplifying RNA (saRNA) and ChAdOx1 (AstraZeneca) in Mice**: This combination generated a stronger antibody response compared to using the same vaccine for both doses.

Clinical Trials in Humans

❖ **AstraZeneca and Pfizer/BioNTech Combination**

- Studies showed that mixing these two vaccines triggered an immune response equal to or stronger than two doses of either vaccine.
- A study found that individuals who received AstraZeneca as the first dose and Pfizer as the second dose had 11.5 times higher IgG and IgA anti-spike (S) antibody responses than those who received both doses of AstraZeneca.

❖ **ChAdOx1 (AstraZeneca) and mRNA Vaccines (Pfizer or Moderna)**

- Increased levels of spike-specific IgG, neutralizing antibodies, CD4 and CD8 T-cell responses.
- Indicated enhanced humoral and cellular immunity compared to using AstraZeneca alone.

❖ **Spanish Study on AstraZeneca and Pfizer**

- Found that mixed vaccination increased antibody levels 150 times after 14 days of the second dose compared to those who received only one dose of AstraZeneca.

❖ **Com-COV Trial (Oxford University, 800+ Volunteers)**

- Demonstrated that mixing AstraZeneca and Pfizer induced a stronger immune response than two doses of the same vaccine.

Side Effects and Safety

- Trials such as CombiVacS, Charité, and Saarland studies have reported that mixing vaccines did not lead to severe side effects.
- In a Spanish study with 448 participants (AstraZeneca first dose, Pfizer second dose), only mild side effects were reported, with strong antibody responses seen two weeks after the second shot.
- However, the Com-COV study indicated that mixed vaccination might cause slightly more side effects than two doses of the same vaccine, but they remained manageable and non-severe.

The "mix-and-match" approach to COVID-19 vaccination has proven to be both safe and effective in multiple studies, with increased immune responses and manageable side effects. These findings provide flexibility in vaccination strategies, allowing for better protection against variants and overcoming supply chain challenges.

Since the emergence of the Delta variant of the coronavirus, numerous countries have adopted a mixed-dose vaccination strategy to enhance effectiveness and protection.

Experimental studies on animals have demonstrated the success of mixing COVID-19 vaccines. In one study, mice that received Sputnik V as the first dose followed by AstraZeneca as the second dose not only tolerated the combination without complications but also exhibited a stronger immune response.

Another study in mice examined the combination of a self-amplifying RNA vaccine (saRNA) with an adenoviral vector vaccine (ChAdOx1 nCoV-19/AZD1222). The findings revealed that the antibody response was significantly higher when these two vaccine types were combined compared to using the same vaccine for both doses.

Following these promising animal trials, clinical studies began to assess the effects of mixing COVID-19 vaccines in humans. Research indicates that combining Oxford–AstraZeneca and Pfizer–BioNTech vaccines elicits an immune response comparable to—or even greater than—two doses of the same vaccine. One study found that individuals who received an initial AstraZeneca dose followed by a Pfizer booster exhibited an immunoglobulin G (IgG) and IgA anti-spike (S) response that was 11.5 times higher than those who received both doses of AstraZeneca. Additionally, their humoral immune response was notably improved.

In another human study, individuals who were first vaccinated with ChAdOx1 nCoV-19 and then received an mRNA vaccine (BNT162b2 or mRNA-1273) for the second dose showed significantly

increased levels of spike-specific IgG, neutralizing antibodies, spike-specific CD4 and CD8 T cells, as well as robust humoral and cellular immune responses [42-44].

The practice of mixing vaccines and using different platforms for second or booster doses predates the COVID-19 pandemic. Various strategies have employed different vaccine formulations for subsequent doses, yielding promising results. To date, combining DNA and vector-based vaccines has resulted in enhanced immunity in both animal models and humans. This approach has been used in vaccine trials for HPV, HIV, influenza, Ebola, and HCV. Additionally, combining DNA vaccines with protein-based vaccines in trials for HSV, HIV, and HCV, as well as mixing protein and viral vaccines or virus-like particle vaccines with DNA vaccines, has also led to stronger immune responses [45-46].

Several potential mechanisms have been proposed to explain the enhanced immunity observed with heterologous vaccine combinations. It is suggested that using different vaccine formulations activates multiple components of the immune system. For instance, combining cellular and humoral immunity may produce a more robust and lasting immune response. Additionally, heterologous vaccines can stimulate higher levels of IgG and neutralizing antibodies by engaging various pathways of humoral immunity [47-48].

The precise mechanism behind the enhanced immunity seen with mixed COVID-19 vaccines remains unclear. However, based on the findings from existing studies, it is evident that using heterologous COVID-19 vaccines leads to significant increases in IgG antibodies, neutralizing antibodies, and cellular immune responses compared to using the same vaccine for both doses. This suggests that the mechanisms responsible for the higher immune response with heterologous vaccines in general may also apply to the mixing of COVID-19 vaccines.

The shortage of vaccines, particularly in low-income regions, the emergence of new variants that partially evade the protection offered by available vaccines, and the occurrence of adverse reactions have prompted several countries to adopt a strategy of mixing COVID-19 vaccines. This approach has proven to be quite successful. Studies have demonstrated that combining vaccines from different platforms can lead to increased levels of IgG and neutralizing antibodies, as well as a stronger cellular immune response. Additionally, heterologous COVID-19 vaccines have shown to produce higher neutralizing antibody levels against variants of concern (VOCs) compared to homologous vaccines. Consequently, both developing and industrialized countries have embraced the mix-and-match strategy in an effort to more effectively immunize larger portions of their populations against COVID-19 [49-50].

A recombinant COVID-19 vaccine is formulated using specific antigenic components of the virus, reducing the risk of complications associated with live or attenuated vaccines while enhancing both efficacy and safety. So far, recombinant vaccines have demonstrated promising performance and are undergoing extensive evaluation. Several candidates are currently in clinical trials, with some successfully completing phase III trials and receiving regulatory approval for further processing [51-52].

Clinical vaccine trials are predominantly designed as individually randomized, placebo-controlled trials (RCTs), ensuring the rapid and efficient collection of essential data while adhering to strict ethical and scientific standards. Previously, we have highlighted advancements in recombinant COVID-19 vaccine research and development, along with related challenges.

Despite these challenges, ongoing research continues to refine COVID-19 vaccine technology to enhance safety and efficacy. Studies on long-term immunity, booster dose requirements, and variant-specific vaccines are actively being conducted to address the evolving nature of the virus. The lessons learned from COVID-19 vaccine development will not only help in managing future outbreaks but also contribute to advancements in vaccine technology for other infectious diseases [53-54].

The scientific discourse surrounding COVID-19 vaccines highlights the extraordinary progress made in vaccine development while acknowledging the complexities that accompany such a large-scale immunization effort. Continued research, collaboration, and equitable distribution efforts are essential in ensuring the long-term success of vaccination programs and the eventual end of the pandemic.

The rapid development and deployment of COVID-19 vaccines have played a critical role in controlling the pandemic. Various vaccine platforms, including mRNA-based, viral vector-based, protein subunit, and inactivated vaccines, have been developed and authorized for emergency use worldwide. The effectiveness of these vaccines has been demonstrated through large-scale clinical trials and real-world data, significantly reducing the rates of severe illness, hospitalization, and mortality associated with SARS-CoV-2 infections. However, several challenges remain, particularly regarding vaccine efficacy, durability, adverse effects, and response to emerging variants [55-56].

The clinical trial data for COVID-19 vaccines revealed varying levels of efficacy across different platforms. mRNA vaccines, such as Pfizer-BioNTech’s BNT162b2 and Moderna’s mRNA-1273,

demonstrated over 90% efficacy in preventing symptomatic infection in initial trials. Viral vector vaccines, including AstraZeneca's AZD1222 and Johnson & Johnson's Ad26.COV2.S, showed moderate efficacy ranging from 60% to 80%. Inactivated vaccines, such as Sinopharm and CoronaVac, exhibited lower efficacy rates but provided essential protection, especially in countries with limited access to other vaccine types. Protein subunit vaccines, like Novavax, have also shown promising results, providing an alternative for individuals hesitant to receive mRNA or viral vector-based vaccines.

One of the primary challenges in vaccine effectiveness has been the emergence of SARS-CoV-2 variants. Variants such as Alpha, Beta, Gamma, Delta, and Omicron have exhibited mutations in the spike protein, affecting the virus's transmissibility and immune evasion capabilities. The Delta variant, for instance, led to a surge in breakthrough infections despite high vaccination rates. The Omicron variant displayed even greater immune escape potential, necessitating booster doses to restore vaccine-induced immunity. As a result, vaccine manufacturers have updated their formulations and introduced variant-specific booster shots to enhance protection against evolving strains.

Another crucial aspect of vaccine deployment has been safety and adverse effects. Most COVID-19 vaccines have been associated with mild to moderate side effects, including injection site pain, fatigue, headache, and fever. However, rare but serious adverse events, such as myocarditis following mRNA vaccination and blood clotting disorders linked to adenoviral vector vaccines, have been reported. These concerns have prompted ongoing pharmacovigilance studies to assess long-term vaccine safety and implement risk mitigation strategies. Despite these risks, the benefits of vaccination in preventing severe disease outweigh the potential complications, leading to widespread recommendations for booster doses in vulnerable populations.

Vaccine-induced immunity has shown signs of waning over time, prompting discussions about the necessity and frequency of booster doses. Studies indicate that antibody levels decline within months after initial vaccination, leading to reduced protection against infection. Booster doses have been shown to restore antibody levels and enhance immunity, particularly against highly transmissible variants. The frequency of future booster shots remains a topic of debate, with researchers exploring the possibility of annual or variant-specific boosters based on emerging data.

In addition to immunological challenges, vaccine distribution and accessibility have been major concerns, particularly in low-income and developing countries. While high-income nations secured early access to vaccines, many regions faced delays due to supply chain constraints, patent restrictions, and logistical challenges. Efforts such as the COVAX initiative aimed to promote equitable vaccine distribution, but disparities persist. Strengthening global cooperation and investment in vaccine production infrastructure remains essential to ensure widespread immunization and preparedness for future pandemics.

The COVID-19 vaccination effort has also faced vaccine hesitancy and misinformation, impacting immunization coverage. Public concerns about vaccine safety, rapid development timelines, and distrust in pharmaceutical companies and government agencies have contributed to vaccine reluctance. Addressing these concerns through transparent communication, community engagement, and evidence-based public health campaigns is crucial in enhancing vaccine confidence and achieving higher immunization rates.

Overall, COVID-19 vaccines have been instrumental in reducing the burden of the pandemic, but challenges such as variant evolution, waning immunity, safety concerns, and equitable distribution must be continuously addressed. Ongoing research into next-generation vaccines, including universal coronavirus vaccines and nasal spray formulations, offers promising avenues for long-term pandemic control. The lessons learned from the COVID-19 vaccine rollout will serve as a foundation for improving vaccine development strategies and global preparedness against future infectious disease threats.

The rapid development of COVID-19 vaccines, with limited time for long-term clinical trials, raises concerns about potential long-lasting or severe health risks. While most vaccines have been associated with mild to moderate local and systemic side effects, studies have reported common adverse reactions such as injection site pain, erythema, headache, fatigue, and malaise.

A major but rare concern is vaccine-associated enhanced disease (VAED) or antibody-dependent enhancement (ADE). Though uncommon, these complications can lead to severe immune responses triggered by pathogen-specific antibodies generated through vaccination or prior infection.

Despite these concerns, the vaccines currently in phase III and phase IV trials have shown promising results, contributing to the ongoing efforts to manage COVID-19 effectively. To control the spread of the pandemic, accelerating global vaccination campaigns remains crucial [57-59].

Extensive research on COVID-19 has generated valuable data on both virus-induced and vaccine-induced immune responses, which will undoubtedly enhance future vaccine development strategies.

Recently, we have explored the progress and challenges in generating and sustaining long-lived memory T lymphocyte responses during COVID-19, a key factor in long-term immunity.

COVID-19, a respiratory infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has affected millions worldwide, posing a significant threat to public health. The development and widespread deployment of various vaccines have played a crucial role in controlling this life-threatening disease. Both traditional and advanced vaccine platforms are now available for COVID-19 vaccine development.

This systematic review provides an overview of the global landscape of COVID-19 vaccines and their current status. Among the primary vaccine candidates, virus-like particles (VLPs), subunit vaccines, DNA and RNA-based vaccines, viral vector-based vaccines, inactivated, and live-attenuated vaccines are undergoing various phases of clinical trials. Notably, protein subunit, RNA-based, and non-replicating viral vector platforms have been widely used, while inactivated virus vaccines have been extensively deployed for clinical use worldwide.

Clinical trials have indicated that most vaccines produce local or systemic side effects post-vaccination, along with varying degrees of efficacy against SARS-CoV-2 and its variants. However, continued research is essential to enhance vaccine technology, minimize adverse effects, and improve overall safety and effectiveness.

Vaccination remains a fundamental strategy in controlling the ongoing pandemic, and research on COVID-19 therapeutics is progressing at an extraordinary pace. Vaccine platforms can be broadly categorized into two groups: those based on viral components and those utilizing the whole virus.

Viral component-based vaccines include:

- Protein subunit vaccines (containing purified viral proteins)
- Virus-like particle (VLP) vaccines (mimicking the virus structure without genetic material)
- DNA-based and RNA-based vaccines (delivering genetic instructions to produce viral proteins)
- Non-replicating viral vector vaccines (using modified viral carriers that cannot replicate)
- Replicating viral vector vaccines (using viral carriers that can replicate within the host)

Whole virus-based vaccines consist of:

- Inactivated vaccines (containing killed virus particles)
- Live-attenuated vaccines (using weakened virus strains)

Regardless of the platform, an ideal vaccine should be easy to develop, stable, cost-effective, safe, and efficient in production and administration. Despite some challenges, over 200 vaccine candidates are currently being researched, with many progressing through clinical trials.

Several pharmaceutical companies are leading in vaccine development, including:

- Pfizer-BioNTech (BNT162)
- Oxford-AstraZeneca (AZD1222)
- Sinovac (CoronaVac)
- Moderna (mRNA-1273)
- Johnson & Johnson (Ad26.COV2.S)
- Sputnik-V (Gamaleya National Research Centre for Epidemiology and Microbiology)
- Novavax (adjuvanted recombinant protein nanoparticles).

The BNT162b2 and mRNA-1273 vaccines generate strong short-term neutralizing antibody responses, providing high initial protection. However, the elevated serum neutralizing antibody levels induced by these mRNA vaccines decline significantly within three to six months and continue to wane over eight months, with an estimated half-life of approximately 60 days. In contrast, Ad26.COV2.S produces lower initial neutralizing antibody titers but demonstrates more sustained immunity, maintaining stable neutralizing responses and clinical effectiveness for at least eight months. By six to eight months post-vaccination, antibody levels across BNT162b2, mRNA-1273, and Ad26.COV2.S tend to converge. Real-world effectiveness studies align with these immunological findings, showing that while BNT162b2 and mRNA-1273 initially offer superior protection compared to Ad26.COV2.S, this difference diminishes over time. Thus, while mRNA vaccines induce a robust early response that wanes within months, Ad26.COV2.S provides a more durable but initially lower immune response.

The decline in immunity following mRNA vaccination has been linked to an increase in breakthrough infections, as exemplified by the SARS-CoV-2 Delta variant outbreak in Provincetown, Massachusetts, in July 2021. Among vaccinated individuals with breakthrough infections, strong immune responses—termed hybrid immunity—have been observed, suggesting that population-level immunity will continue to rise through a combination of vaccination and natural infection. Genomic and

epidemiological data from the Provincetown outbreak confirmed the potential for viral transmission between fully vaccinated individuals.

Both mRNA and adenoviral vector-based vaccines induce cellular immune responses that exhibit greater longevity than serum antibody titers. Studies have shown that germinal center B cells persist for at least six months following BNT162b2 vaccination. Additionally, CD8+ T-cell responses are particularly robust after Ad26.COV2.S vaccination, remaining stable for at least six to eight months. Since CD8+ T cells play a crucial role in controlling viral replication post-infection, it is likely that COVID-19 vaccines will continue to provide strong protection against severe disease, even as neutralizing antibody levels decline.

In immunocompromised individuals, both antibody and T-cell responses to COVID-19 vaccines are significantly reduced, with the extent of reduction varying based on the type and severity of immunosuppression. In these populations, additional vaccine doses and prophylactic monoclonal antibody treatments are recommended to enhance protection.

The COVID-19 pandemic seems to be shifting from a hyperacute phase to an endemic phase. While current COVID-19 vaccines show reduced efficacy in preventing infections with the Omicron variant compared to earlier strains, they still provide strong protection against severe disease. The main objective of COVID-19 vaccines should be to ensure long-term protection against severe illness, hospitalization, and death. As such, studies on COVID-19 vaccines and boosters must assess not only short-term neutralizing antibody titers but also the durability of antibody responses, memory B-cell responses, and cross-reactive T-cell responses. This comprehensive evaluation will help ensure continued protection, particularly as the virus evolves.

Nucleic acid-based coronavirus vaccine

The primary advantage of DNA- and RNA-based vaccines lies in their potential for rapid development and lower side effects. DNA vaccines have demonstrated strong potential in animal models to trigger immune responses against coronaviruses (CoVs). However, clinical data on the efficacy of DNA vaccines in humans remain limited. For instance, a previous study in mice found that a DNA vaccine encoding the spike (S) protein of SARS-CoV induced T-cell responses, a neutralizing antibody response, and protective immunity. Additionally, a prototype DNA vaccine expressing various SARS-CoV-2 S proteins was developed and tested in 35 rhesus macaques. These vaccinated macaques showed specific humoral and cellular immune responses. When challenged with SARS-CoV-2, the animals displayed a significant reduction in viral replication in both the upper and lower respiratory tracts, emphasizing the significant role DNA vaccines could play against SARS-CoV-2 infection.

The immunogenicity of a synthetic DNA-based vaccine against SARS-CoV-2, INO-4800, in various animal models. The immunized animals showed specific T-cell responses and antibodies that neutralized SARS-CoV-2 and blocked the interaction between the S protein and ACE2, in addition to circulating through the lungs. The study highlighted the need for further evaluation of this vaccine as a potential candidate for COVID-19. Currently, Inovio Pharmaceuticals is conducting a phase 1 trial for the DNA plasmid-based prophylactic vaccine (INO-4800) against SARS-CoV-2. Additionally, Karolinska Institute/Cobra Biologics, Osaka University/Anges/Takara Bio, and Takis/Applied DNA Sciences/Evvivax are in the preclinical phase of DNA vaccine development. Recently, OncoSec collaborated with the Cancer Institute to conduct the first in-human trial of OncoSec's CORVax12, a SARS-CoV-2 vaccine. This vaccine involves co-administering TAVO™ (plasmid IL-12) with a DNA-encoded variety of the SARS-CoV-2 S glycoprotein to enhance immunogenicity. The aim is to induce a harmonized response through innate, adaptive humoral, and cellular immunity.

Messenger RNA (mRNA)-based CoV vaccines offer distinct advantages over DNA-based vaccines. mRNA vaccines do not require entry into the host cell nucleus for transcription, which allows for lower doses and eliminates the need for special delivery mechanisms. Moreover, mRNA vaccines avoid the risk of integration with the host cell genome and produce pure viral protein. This technology can bypass time-consuming standardization processes, speeding up the vaccine's commercial production. Moderna Inc. mRNA-1273 encodes a stable form of the SARS-CoV-2 S protein. Additionally, one of the RNA-based vaccines developed by Pfizer/Biotech, BNT162b1 and BNT162b2, has entered large-scale phase 3 clinical trials with 29,481 participants. BNT162b1 is a nucleoside-modified mRNA encoding the trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) and has been formulated as a lipid nanoparticle-based vaccine.

The mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) were the first to receive conditional marketing or emergency use authorization from the FDA, EMA, and MHRA. The development of mRNA vaccines has been described as “lightning fast” by *Nature* journal. Both BNT162b2

(23) and mRNA-1273 (24) encode the full-length spike (S) protein, which is stabilized in its pre-fusion conformation by two proline substitutions (K986 and V987) at the cleavage site (S-2P). Key features of mRNA vaccines include: (i) mRNA translation occurs in the cytoplasm, minimizing the risk of genome integration; (ii) both T-cell and antibody responses are triggered; and (iii) they allow for rapid development and large-scale production. However, there are drawbacks, such as the need for a delivery system to facilitate mRNA entry into cells. Additionally, mRNA is inherently unstable, requiring low or ultra-low temperature storage and transport, which may not be feasible in many developing countries. This lack of infrastructure could hinder the widespread use of these effective vaccines in such regions.

DNA vaccines represent another type of nucleic acid vaccine. The DNA vaccine INO-4800, developed by Inovio in the United States, is advancing rapidly and is currently in phase 2 clinical trials. The strategy behind INO-4800 involves inserting the full-length sequence of the SARS-CoV-2 spike protein into the pGX0001 plasmid vector, which then expresses the spike protein in host cells to trigger specific immune responses.

Protein-based coronavirus vaccine

The spike (S) protein of SARS-CoV-2 plays a crucial role in host cell receptor binding and membrane fusion. Given its function in viral entry, vaccines based on the S protein have the potential to efficiently induce antibody production and virus neutralization. This makes the S protein a promising target for vaccine development. Tazehkand and Hajipour (2020) constructed a fusion vaccine by integrating an envelope and nucleocapsid protein with multi-epitopes (B and MHC I epitopes) derived from the S protein and RNA-dependent RNA polymerase. While this vaccine demonstrated structural stability and favorable physicochemical and immunological properties in preliminary screenings, further validation in laboratory animal models was deemed necessary.

GlaxoSmithKline (GSK) recently collaborated with Clover Biopharmaceuticals to develop a COVID-19 vaccine candidate. This partnership aims to combine Clover's protein-based CoV vaccine candidate, COVID-19 S-Trimer, with GSK's adjuvant system. Clover developed the S-Trimer subunit vaccine using its proprietary Trimer-Tag technology and a rapid mammalian cell culture-based expression system. Meanwhile, Antigen Express Inc., a subsidiary of Generex, has disclosed the production of hybrid peptides that incorporate three elements: (a) an invariant chain (Ii) key peptide to enhance antigen presentation, (b) a chemical structure linking the Ii peptide to the antigenic epitope, and (c) an antigenic epitope that binds to an MHC class II molecule. Generex also announced the development of a COVID-19 vaccine in collaboration with a Chinese consortium, including China Technology Exchange, Beijing Zhonghua Investment Fund Management, the Biology Institute of Shandong Academy of Sciences, and Sinotek-Advocates International Industry Development. This vaccine will employ Generex's Ii-Key immune system activation technology to produce a SARS-CoV-2 viral peptide for clinical trials.

Novavax Inc. has introduced NVX-CoV2373, a stable, prefusion S protein-based vaccine candidate that uses the company's proprietary nanoparticle technology. In May 2020, NVX-CoV2373 entered phase 1 clinical trials. Preclinical studies have demonstrated high immunogenicity and the ability to stimulate the production of high levels of neutralizing antibodies. Novavax has incorporated its proprietary Matrix-M™ adjuvant into NVX-CoV2373 to enhance immune response and boost neutralizing antibody production.

Additionally, researchers have attempted to design a multiepitope peptide vaccine against SARS-CoV-2 using the envelope protein as a target. This approach leverages immunoinformatics and comparative genomics to facilitate the rapid development of a potential vaccine. However, clinical validation is necessary to confirm its efficacy and safety.

Recombinant Protein Vaccine

According to WHO statistics, approximately one-third of the COVID-19 vaccines currently in clinical trials are recombinant protein vaccines. These vaccines utilize a variety of expression systems, including yeast, E. coli, Expi293F cells, CHO cells, tobacco plants, and insect cells, during both clinical and preclinical phases. The antigens expressed in these vaccines include RBD-monomer, RBD-dimer, RBD-trimer, S1 protein, S protein, and S-trimer. Various vaccine adjuvants have been tested, including Al(OH)3, AS01/AS03, Quil-A, monophosphoryl lipid A (MPL), Freund's complete adjuvant, CpG, Matrix M, Advax™, and AgnHB.

Novavax's NVX-Cov2373 is a leading protein subunit vaccine. It contains a prefusion S-trimer antigen with common proline substitutions and mutations at the S1–S2 polybasic cleavage site (from RRAR to SRAG or QQAQ) to make it protease-resistant. Clover's SCB-2019 vaccine is also based on the S-trimer antigen, but unlike NVX-Cov2373, SCB-2019 is prepared by fusing the antigen in-frame with a Trimer-Tag, followed by self-trimerization of the Tag. Another leading protein vaccine, ZF2001, consists

of homogeneous RBD-dimers arranged as a tandem-repeat single chain. These antigen designs have significantly improved the immunogenicity and stability of subunit vaccines.

Many developers are focusing on recombinant protein vaccines due to several advantages: (i) they do not require specialized facilities like BSL-3 labs, and the expression of recombinant proteins can be easily scaled up; (ii) adjuvants can be incorporated to enhance immunogenicity; and (iii) these vaccines have excellent safety profiles because they do not contain live components, with reactogenicity and side effects typically linked to the adjuvants used.

Vectored vaccines against coronavirus

Viral vectors are a promising strategy for the development of COVID-19 vaccines, as they rely on their ability to infect cells and stimulate a robust immune response. The primary advantage of this platform is its efficient and gene-specific delivery, which enables the initiation of strong humoral and cellular immunity. A recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine, designed to express the spike (S) protein of SARS-CoV-2, was evaluated in a phase 1 clinical trial in Wuhan, China. The trial reported an increase in specific neutralizing antibodies and T-cell responses as early as 14 days post-vaccination, with results supporting further evaluation.

Several research groups have explored the use of different viral vectors to develop SARS-CoV-2 vaccines. These include a measles virus-based replicating viral vector vaccine developed by Zydus Cadila and Institut Pasteur/Themis in collaboration with the University of Pittsburgh Center for Vaccine Research. Another approach involves an influenza virus vector expressing the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, developed by the University of Hong Kong. Additionally, Altimmune has engineered a non-replicating adenovirus-based vaccine known as NasoVAX, which expresses the SARS-CoV-2 spike protein and is being explored for its potential as an intranasal vaccine.

One of the most well-known adenovirus-vectored vaccines is ChAdOx1 nCoV-19, developed by the University of Oxford and AstraZeneca. This vaccine, which uses a chimpanzee adenovirus vector to express the SARS-CoV-2 spike protein, has progressed into large-scale phase 3 clinical trials with over 2,000 participants. Given the effectiveness of viral vector-based platforms in generating robust immune responses, continued research and clinical trials are expected to refine their efficacy and expand their applications in combating COVID-19.

Various viral vectors, including adenovirus, influenza, measles, Ankara pox virus (MVA), and vesicular stomatitis virus (VSV), have been explored in the development of COVID-19 vaccines. Among these, adenovirus-vectored vaccines make up approximately one-third of the vaccines currently in development and have progressed the most rapidly. Key features of this vaccine platform include: (i) it somewhat replicates the natural infection process by expressing antigens inside the cell, which triggers robust humoral and cytotoxic immune responses; (ii) pre-existing or vaccine-induced immune responses against the viral vector may reduce the vaccine's effectiveness; and (iii) there is a potential risk of gene integration, although this has not been confirmed. Presently, three vaccines using this approach have been conditionally approved for high-risk populations: the Type 5 Adenovirus-vectored Ebola Vaccine, the VSV-vectored Ebola Vaccine, and the Yellow Fever Virus-vectored Dengue Vaccine. However, these vaccines have not yet been used on a large scale for disease prevention in humans, nor have they undergone long-term testing. As a result, continuous monitoring of their efficacy and safety is essential.

Virus-like particle-based vaccine

Virus-like particles (VLPs) are multi-protein supra-molecular structures that mimic the morphology and antigenic properties of viruses while lacking their infectious genetic material. These features make VLPs an innovative and effective platform for vaccine development. Their ability to present viral antigens in a highly organized and repetitive manner enhances their immunogenicity, stimulating both innate and adaptive immune responses. The immunological properties of VLPs enable them to efficiently target B lymphocytes, inducing strong antibody responses while also facilitating T-helper cell activation through antigen presentation via major histocompatibility complex (MHC) class II molecules on antigen-presenting cells (APCs).

Medicago Inc., a leading biopharmaceutical company, has recently developed a VLP-based vaccine against SARS-CoV-2, which is currently in preclinical studies to assess its safety and efficacy. Similarly, Saiba GmbH and Imophoron Ltd, in collaboration with Bristol University's Max Planck Center, are conducting preclinical trials on their respective VLP-based vaccine candidates. These independent research initiatives reflect the rapid progress in VLP vaccine technology and its potential contribution to the fight against COVID-19.

A novel approach in VLP vaccine development involves the incorporation of SARS-CoV-2 epitopes into chimeric VLPs, allowing for targeted viral antigen presentation. This method holds promise

for enhancing immune responses while maintaining the stability and safety of VLP-based vaccines. Furthermore, plants have emerged as a viable platform for biopharmaceutical production, including vaccine development. Several plant-based VLP vaccines are currently undergoing clinical evaluation. The utilization of plant expression systems to produce foreign proteins represents a promising strategy for the cost-effective and scalable production of COVID-19 vaccines. However, further research is required to optimize these plant-derived vaccines and validate their clinical efficacy.

Inactivated Vaccine

Inactivated vaccines are a traditional and well-established type of vaccine. Currently, there are 10 inactivated vaccines undergoing clinical trials, with five of them developed by Chinese companies. Among these, the inactivated vaccines BBIBP-CorV and CoronaVac, developed by Sinopharm and Sinovac, respectively, are the leaders and had already received conditional marketing authorization in several countries by the end of 2020. The BBV152, an inactivated vaccine developed by Bharat Biotech in India, is the fifth such vaccine to enter clinical trials and has also been approved for emergency use in India.

As one of the classic vaccine platforms, purified inactivated vaccines have long been used to protect against diseases such as rabies, polio, hepatitis B, influenza, and others. The safety of these vaccines has been extensively tested and confirmed through large-scale immunization programs. Development and evaluation standards for inactivated vaccines have been established based on decades of use. The manufacturing processes for these vaccines are well-established, enabling large-scale production. Despite their many advantages, inactivated vaccines tend to have moderate immunogenicity and usually require adjuvants and multiple booster doses to enhance their effectiveness. Additionally, the production of these vaccines requires specialized facilities, such as biosafety level 3 (BSL-3) laboratories, which can limit research and development capabilities in many countries.

Live Attenuated Vaccine

Live attenuated vaccines (LAV) are produced through methods such as “cold adaptation,” recombination, or reverse genetics. However, these processes can be time-consuming. Currently, only one LAV has entered clinical trials, with two others still in preclinical studies. COVI-VAC (NCT04619628), developed by the Serum Institute of India in collaboration with the American biotechnology company Codagenix, is in advanced stages of development. This vaccine utilizes a computer algorithm to recode and de-optimize the SARS-CoV-2 virus by introducing hundreds of mutations into its genome and removing the furin cleavage site. A similar technology has been used for vaccines against Respiratory Syncytial Virus (RSV), influenza, and dengue fever, with safety confirmed in those cases.

The advantages of this approach include: (i) The vaccine’s protein structure is identical to that of live virus particles, helping to trigger an immune response against the entire viral protein; (ii) The risk of disease enhancement is low. However, LAVs require extensive testing to confirm safety and efficacy. Currently, no clinical data on the safety or effectiveness of these COVID-19 vaccines are available.

SARS-CoV-2 vaccine: efficacy and safety

The development of a SARS-CoV-2 vaccine requires meticulous planning, rigorous research, and extensive testing across multiple stages. This process includes vaccine design, production, purification, preclinical trials in model animals, and human clinical trials to ensure safety and efficacy. Given the ongoing threat posed by SARS-CoV-2, there is an urgent need to develop an efficient and safe vaccine that can help curb transmission, reduce infection rates, and prevent severe disease.

While previous studies on SARS-CoV vaccines in animal models have shown promise, their direct applicability to SARS-CoV-2 requires further investigation. The similarities between SARS-CoV and SARS-CoV-2 suggest potential cross-reactive immune responses, but detailed clinical trials and long-term immunogenicity studies are essential. Regulatory authorities must thoroughly evaluate candidate vaccines using diverse virus strains and multiple animal models to establish safety and effectiveness.

One of the significant challenges in SARS-CoV-2 vaccine development is the potential short-lived nature of the antibody response. Coronaviruses have been known to elicit transient antibody responses, leading to the possibility of reinfection. This raises concerns regarding the durability of immunity induced by vaccination. Additionally, the phenomenon of antibody-dependent enhancement (ADE) presents another risk, where non-neutralizing or low-affinity antibodies could facilitate viral entry into host cells rather than preventing infection. Though there is currently limited evidence of ADE in SARS-CoV-2 vaccines, it remains an important factor that requires continuous monitoring.

Another safety concern is the potential for vaccine-induced disease enhancement. In some cases, vaccinated individuals might develop a more severe illness upon subsequent infection, as observed in experimental SARS vaccine studies where vaccinated ferrets experienced severe liver inflammation

following virus exposure. Ensuring that COVID-19 vaccines do not trigger enhanced disease outcomes is critical in mitigating the risks of widespread vaccination programs.

To address these challenges, ongoing research efforts focus on optimizing vaccine design to induce robust, long-lasting immunity while minimizing risks associated with ADE and disease enhancement. The development of an effective SARS-CoV-2 vaccine will not only help control the current pandemic but also serve as a foundation for future preparedness against emerging coronaviruses.

The urgency of developing a safe and effective COVID-19 vaccine cannot be overstated. Vaccine development typically involves rigorous experimental trials in animal models, followed by phased human clinical trials across diverse age groups before regulatory approval for mass production and global distribution. The accelerated timeline for COVID-19 vaccine development has been unprecedented, with multiple platforms being explored, including recombinant vaccines, mRNA vaccines, viral vector vaccines, and protein subunit vaccines.

One of the key lessons from past and present experiences with coronaviruses is the need for proactive preparedness. While significant progress has been made in vaccine technology, ensuring equitable access remains a major challenge. The ultimate goal of ongoing research should be to make vaccines widely available, particularly to underserved populations. Addressing socioeconomic disparities in vaccine distribution is crucial for achieving global immunity and preventing further outbreaks.

Recombinant COVID-19 vaccines present a promising approach to overcoming safety concerns and social barriers associated with other vaccine technologies. This platform offers advantages in terms of stability, immunogenicity, and scalability, potentially simplifying large-scale production and distribution. Once fully established, recombinant vaccine platforms could not only expedite the COVID-19 response but also streamline the development of future vaccines for emerging infectious diseases.

Vaccine Efficacy

Currently, most developers and manufacturers use laboratory-confirmed COVID-19 cases as the primary endpoint in Phase 3 clinical trials, as it is considered the most reliable indicator for evaluating vaccine efficacy. By the end of 2020, protection data for eight vaccines from four different platforms had been published. The vaccine efficacy (VE) of these vaccines ranged significantly. Notably, the Pfizer mRNA vaccine demonstrated the highest VE, followed closely by Moderna's mRNA vaccine. The adenovirus-vectored vaccines Sputnik V, Ad26.COV2.S, and Ad5-nCoV showed varying levels of VE, with Sputnik V leading. AstraZeneca’s adenovirus-vectored vaccine reported the highest VE when a low-dose prime followed by a standard-dose boost regimen was used, but this dropped with the use of a standard-dose prime and boost regimen. In the Phase 3 trial conducted in the UK, the recombinant subunit vaccine from Novavax showed strong efficacy. Meanwhile, the inactivated vaccines from Sinopharm and Sinovac showed lower efficacy compared to others.

Safety

The safety profiles of different COVID-19 vaccines vary significantly. mRNA and adenovirus vaccines tend to have higher rates of local and systemic adverse reactions (ARs). In contrast, inactivated vaccines show the lowest rates of side effects. The AR rate for recombinant protein vaccines varies widely depending on the adjuvants used. Generally, there is an inverse relationship between the level of neutralizing antibodies induced and the AR rate, with elderly individuals reporting fewer side effects than adults.

The use of novel adjuvants and delivery systems in mRNA and recombinant vaccines seems to contribute to increased side effects, particularly after the second dose. This issue requires further investigation to improve vaccine safety.

- For Moderna and Pfizer-BioNTech mRNA vaccines, adverse reactions increase after the second dose. The rates of local and systemic ARs for Moderna's median dose group were relatively high. For Pfizer-BioNTech, the local ARs were high, and systemic ARs were also notable. Severe allergic reactions have been reported for both vaccines, raising safety concerns that could affect vaccination compliance. Coated liposomes are thought to be the primary cause of these reactions, so improving the packaging and delivery system is critical to enhancing the safety profile of mRNA vaccines. Additionally, vaccine design can influence safety. Pfizer-BioNTech developed two mRNA vaccines for clinical trials: BNT162b2 and BNT162b1. BNT162b1 encodes the trimerized receptor-binding domain, while BNT162b2 encodes the full-length spike protein modified by two proline mutations to stabilize its prefusion form. Phase 1 clinical data showed that both vaccines induced similar neutralizing antibody titers, equivalent to or higher than those found in convalescent serum. However, BNT162b2 caused fewer systemic reactions, especially in older individuals.

- Novavax and Clover vaccines showed a significant increase in ARs after the second dose. The local and systemic AR rates for the Novavax vaccine with the Matrix M adjuvant were comparable to those of the Clover vaccine with the GSK AS03 adjuvant. These rates were higher than those observed with the Zhifei vaccine adjuvanted with alum.

Concerns about antibody-dependent enhancement (ADE) and vaccine-associated disease enhancement (VADE) are central to vaccine safety. ADE occurs when antibodies facilitate viral entry into cells via Fc receptor-mediated internalization. VADE refers to disease exacerbation driven by antibody-dependent and Th2 cell-dependent mechanisms. For a vaccine to be safe, it must effectively trigger a high level of neutralizing antibodies and Th1-type immune responses, with continuous monitoring for ADE and VADE during clinical and preclinical studies. Fortunately, no ADE cases have been reported during the development of current COVID-19 vaccine candidates, but further research is needed to assess the potential risks of ADE and VADE in real-world vaccine applications.

Criteria and Reference Standards are Crucial in Vaccine Development and Evaluation

The successful identification and widespread application of effective vaccines are essential to controlling the pandemic. Establishing clear criteria for success and applying them to second-generation vaccine development is vital. Setting criteria for evaluation and establishing standards for immune response measurement are key considerations in ensuring efficient, timely, and reliable assessments of the numerous COVID-19 vaccine candidates.

To ensure the effectiveness and safety of COVID-19 vaccines, organizations such as WHO, FDA, EUA, and NMPA have issued early-stage guidance for the industry. These guidelines outline key considerations for vaccine development, quality control, and clinical evaluation. They emphasize that, for a COVID-19 vaccine to be deemed effective when widely deployed, the primary efficacy endpoint for a placebo-controlled trial should be at least 50%. Furthermore, the statistical success criterion should ensure that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint estimate is greater than 30%. If the criteria for the first generation of COVID-19 vaccines are set too low, this could affect the development of future vaccine generations.

The criteria used to define COVID-19 cases and the methods employed for diagnosis are crucial factors influencing the calculated efficacy of a vaccine. Currently, developers primarily use symptoms, nucleic acid testing, and serological testing to determine cases, but there is no universal standard for case collection and inclusion. Given the involvement of multiple countries and enterprises in COVID-19 vaccine research and development, establishing consistent diagnostic and case collection criteria across clinical studies is essential for obtaining reliable and comparable efficacy data.

Sequential Immunization Strategy

A detailed analysis of the clinical data released for the first-generation COVID-19 vaccines reveals several important findings:

1. Immune responses and protective efficacy are lower in elderly recipients, but adverse reaction rates are also lower in this group.
2. mRNA and recombinant protein vaccines, especially those with new adjuvants, induce high levels of neutralizing antibodies, but also exhibit higher adverse reactions, particularly after the second dose.
3. Inactivated vaccines show the lowest rate of adverse reactions but have relatively weaker immune responses.
4. While most adenovirus vaccines elicit good T cell responses, their ability to produce neutralizing antibodies is not as high.

Balancing immunogenicity, effectiveness, and safety is critical in the development of first-generation vaccines for emergency use.

A potential solution to address these issues is the sequential vaccine immunization strategy, which could enhance the immunogenicity and safety of emergency vaccines, as well as improve the duration of protection. This strategy has been observed in studies on HIV vaccines, where developing an effective vaccine has been challenging. In HIV vaccine trials, no single vaccine has provided effective protection. However, the RV144 vaccine, using a combination of poxvirus for initial vaccination followed by a recombinant subunit vaccine, achieved a 31.2% protection rate. This heterogeneous prime-boost strategy, also known as sequential immunization, has gained attention from researchers. Numerous animal studies have demonstrated that using different types of vaccines sequentially can boost both the intensity and breadth of the immune response.

The rapid development of the COVID-19 vaccine industry, accelerated by the pandemic, has led to over one hundred COVID-19 vaccines entering clinical trials within just a year. This sets the stage for

exploring sequential immunization strategies. Different vaccine platforms have distinct immunological characteristics, and using heterologous vaccines in a sequential immunization approach can theoretically prevent the stimulation of non-target proteins, thereby strengthening the immune response against the intended antigen. Some vaccines, for instance, are primarily designed to induce T cell responses, while others are geared toward producing antibody responses. Combining vaccines with complementary immune characteristics through sequential immunization could generate more robust antibody and T cell responses. Additionally, this approach may help reduce the risk of adverse reactions associated with a second dose of a single vaccine, which has been observed with mRNA vaccines.

However, it is important to note that the U.S. CDC has emphasized that the safety and efficacy of mixing different vaccine types have not been validated, and mixed vaccination is not currently authorized except under specific circumstances. While the availability of vaccines from various platforms supports the potential of sequential immunization strategies, further research is needed to fully understand the benefits of this approach for COVID-19.

Next Generation Vaccine Development

The mRNA vaccine has demonstrated high effectiveness against COVID-19. This efficacy is attributed to the introduction of the spike protein gene into host cells, prompting the immune system to generate a response that effectively protects against the virus. However, the mutation-prone nature of the spike protein raises concerns about the long-term durability of vaccine protection and its future effectiveness. There is ongoing concern about whether first-generation vaccines provide adequate protection against these emerging variants

Developers must focus on the mutations of the virus and propose strategies for next-generation vaccine development to address the evolving variants. One approach could involve redesigning vaccines based on the sequences of circulating variants. Alternatively, the use of immunogenetically conserved viral proteins, Linear B cell epitopes, and MHC I/II restricted T cell epitopes—identified using bioinformatics methods—could inspire new vaccine designs. Different vaccine platforms have distinct production processes. Recombinant nucleic acid and virus-vectored vaccines introduce antigen genes into cells to stimulate an immune response. These vaccines can be adapted by incorporating new antigen sequences into their genomes and leveraging existing manufacturing facilities. In principle, as long as the new sequence data is available, vaccines can be quickly redesigned and produced. The rapid design and synthesis capabilities of mRNA vaccines, combined with their strong immunogenicity, make them the ideal platform for the urgent development of COVID-19 vaccines. However, the novelty of mRNA technology limits the number of companies and institutes able to conduct research and development. In comparison, the production process for recombinant subunit vaccines is more complex, requiring in vitro transcription to generate immunogenic proteins. Modifying manufacturing processes to produce mutant proteins is not as straightforward, and mutations may alter the immunogenicity of the protein. Inactivated vaccines, on the other hand, require the isolation of new mutant strains in BSL laboratories before they can be amplified and inactivated to create vaccines for emerging variants. This process is constrained by the need for high-level biosafety facilities and access to the appropriate strains.

The COVID-19 pandemic has fundamentally changed human lifestyles and history. The development and application of COVID-19 vaccines have not only revolutionized our understanding of vaccines but also transformed the vaccine development process itself. The first generation of COVID-19 vaccines, developed for emergency use, has shown promise in controlling the pandemic. However, several limitations of these vaccines are becoming apparent. Notably, concerns have arisen regarding decreased efficacy in the elderly, increased incidence of adverse reactions for certain vaccines, and reduced protection against mutant strains.

The sequential immunization strategy, which has been explored for other infectious diseases, may help address some of these challenges and improve the overall performance of COVID-19 vaccines. A key area of focus for the development of next-generation vaccines will be enhancing protection against newly emerging variants. Standardization of measurement methods is crucial for comparing the efficacy of different vaccines. Regulatory authorities have already set guidelines for the development and evaluation of COVID-19 vaccines and introduced reference standards for efficacy assessment. When these standards are implemented in clinical studies, they could facilitate the comparison of vaccine results and help prioritize candidates for mass vaccination campaigns.

The analysis of COVID-19 vaccines reveals significant findings across various dimensions, including efficacy, safety, global distribution, and adaptability to emerging variants. Below is a summary of the key results:

Efficacy and Immune Response

- **mRNA Vaccines (Pfizer-BioNTech, Moderna)**: Demonstrated high efficacy rates of approximately 95% in preventing symptomatic COVID-19 during initial clinical trials. Robust immune responses, including strong neutralizing antibody and T-cell activation, were observed.
- **Viral Vector Vaccines (AstraZeneca, Johnson & Johnson)**: Showed efficacy rates ranging from 66% to 79% in preventing symptomatic disease, with higher protection against severe illness and hospitalization.
- **Protein Subunit Vaccines (Novavax)**: Achieved efficacy rates of around 90%, with favorable safety profiles and ease of storage.
- **Inactivated Virus Vaccines (Sinovac, Sinopharm)**: Reported efficacy rates between 50% and 80%, with variability across regions and populations.
- **Safety Profiles**
- Most vaccines exhibited mild to moderate side effects, such as pain at the injection site, fatigue, and fever, which resolved within a few days.
- Rare adverse events were identified, including myocarditis (primarily in young males after mRNA vaccines) and thrombosis with thrombocytopenia syndrome (TTS) following viral vector vaccines. These events were closely monitored, and regulatory agencies implemented guidelines to mitigate risks.

Vaccines Global Distribution and Equity

- High-income countries secured the majority of early vaccine doses, leading to significant disparities in vaccination rates. By mid-2023, over 70% of populations in high-income countries were fully vaccinated, compared to less than 20% in many low-income countries.
- Initiatives like COVAX delivered over 1.5 billion doses to LMICs, but logistical challenges, including cold chain requirements and infrastructure gaps, hindered widespread distribution.

Impact of Emerging Variants

- Variants such as Delta and Omicron reduced vaccine efficacy against symptomatic infection, particularly for non-mRNA vaccines. However, all vaccines maintained high protection against severe disease, hospitalization, and death.
- Booster doses were shown to restore immunity, with mRNA boosters increasing neutralizing antibody levels significantly. Updated bivalent vaccines targeting Omicron demonstrated improved efficacy against newer variants.

Vaccines Public Acceptance and Hesitancy

- Vaccine hesitancy remained a significant barrier, driven by misinformation, mistrust, and concerns about safety. Surveys indicated that hesitancy rates varied widely, from less than 10% in some countries to over 50% in others.
- Targeted public health campaigns and community engagement were effective in increasing vaccine uptake in certain regions.
- **Long-Term Immunity and Durability**
- Studies indicated that immunity waned over time, particularly against mild and asymptomatic infection, necessitating booster doses. Hybrid immunity (from natural infection plus vaccination) provided stronger and more durable protection.
- Research on long-term immune memory suggested that T-cell responses remained robust, even as antibody levels declined.

Future-Proofing Strategies

- Development of pan-coronavirus vaccines and next-generation platforms, such as self-amplifying RNA and nanoparticle-based vaccines, showed promise for broader and longer-lasting protection.
- Investments in global surveillance and rapid-response systems were identified as critical for addressing future variants and pandemics.

SUMMARY

The rapid development and deployment of COVID-19 vaccines have significantly contributed to reducing the severity and transmission of SARS-CoV-2 infections. Various vaccine platforms, including mRNA, viral vector, protein subunit, and inactivated vaccines, have demonstrated varying degrees of efficacy, with mRNA vaccines showing the highest protection rates. However, the emergence of new

variants, particularly Delta and Omicron, has posed challenges by reducing vaccine effectiveness, necessitating the administration of booster doses to maintain immunity.

Despite their success, COVID-19 vaccines have been associated with certain adverse effects, ranging from mild symptoms such as fatigue and injection site pain to rare but severe reactions like myocarditis and blood clotting disorders. While the benefits of vaccination far outweigh the risks, continuous safety monitoring and research into improving vaccine formulations are necessary.

Another significant challenge has been the global disparity in vaccine distribution, with low-income countries facing difficulties in securing adequate supplies. Initiatives like COVAX have aimed to address this inequity, but further efforts are needed to enhance global access to vaccines. Additionally, vaccine hesitancy fueled by misinformation and distrust remains an obstacle to achieving higher immunization rates.

Moving forward, ongoing research into next-generation vaccines, including those targeting multiple coronavirus strains and alternative delivery methods such as nasal sprays, holds promise for more effective and long-lasting protection. The lessons learned from the COVID-19 pandemic will be instrumental in improving global vaccine development and preparedness for future infectious disease threats.

The rapid development and deployment of COVID-19 vaccines have played a pivotal role in mitigating the impact of the pandemic, reducing severe cases, hospitalizations, and mortality. Various vaccine platforms, including mRNA, viral vector, protein subunit, and inactivated vaccines, have demonstrated varying levels of efficacy, with mRNA vaccines showing the highest protection rates. However, the emergence of SARS-CoV-2 variants has posed significant challenges, necessitating the administration of booster doses to maintain immunity.

While vaccines have been largely effective, concerns related to safety, vaccine hesitancy, and global distribution inequities remain key issues. Mild to moderate adverse effects have been observed, with rare but serious complications requiring continuous monitoring. Vaccine hesitancy, fueled by misinformation and distrust, has hindered immunization efforts in some populations. Additionally, disparities in vaccine access have highlighted the need for improved global cooperation and equitable distribution strategies.

Future advancements in vaccine development, including universal coronavirus vaccines, alternative delivery methods such as nasal sprays and oral formulations, and innovations in mRNA technology, hold promise for more effective and durable protection. Strengthening public trust in vaccination through education and transparent communication will be crucial in ensuring widespread acceptance and uptake.

Ultimately, while COVID-19 vaccines have been a monumental scientific achievement, ongoing research, surveillance, and policy efforts are necessary to enhance vaccine efficacy, address emerging challenges, and prepare for future infectious disease threats. The lessons learned from this pandemic will be instrumental in shaping the future of global health preparedness and response.

Enhancing Vaccine Development and Innovation: Future research should focus on developing next-generation vaccines that provide broader and longer-lasting immunity against SARS-CoV-2 variants. Universal coronavirus vaccines, as well as improved mRNA and protein subunit formulations, should be prioritized to reduce the need for frequent booster doses.

Exploring Alternative Vaccine Delivery Methods: Alternative delivery methods, such as nasal sprays and oral vaccines, should be further investigated to enhance mucosal immunity, ease administration, and improve vaccine accessibility, particularly in resource-limited regions.

Strengthening Global Vaccine Equity: Efforts must be intensified to ensure fair and equitable vaccine distribution worldwide. Expanding manufacturing capabilities in low- and middle-income countries, reducing logistical barriers, and promoting technology transfer will help address disparities in vaccine access.

Combating Vaccine Hesitancy: Public education campaigns should be strengthened to counter misinformation and increase confidence in vaccination. Transparent communication from health authorities and engagement with communities are crucial in overcoming skepticism and boosting immunization rates.

Monitoring Long-Term Vaccine Safety and Efficacy: Continuous post-market surveillance and real-world data collection should be emphasized to assess long-term safety, identify potential rare adverse effects, and refine vaccine strategies accordingly.

Integrating COVID-19 Vaccination into Routine Immunization Programs: Considering the ongoing circulation of SARS-CoV-2, integrating COVID-19 vaccines into existing immunization programs could help maintain immunity levels, particularly for high-risk populations.

Enhancing Pandemic Preparedness and Response: Lessons learned from COVID-19 should be used to improve global preparedness for future pandemics. Investments in research, vaccine manufacturing infrastructure, and coordinated international response strategies will be essential to combat emerging infectious diseases efficiently. By implementing these recommendations, the global community can improve the effectiveness of COVID-19 vaccination programs, enhance public trust, and ensure long-term protection against current and future health threats.

The development and deployment of COVID-19 vaccines have been a monumental achievement in science and public health, offering a critical tool to combat the global pandemic. This paper has explored the scientific discourse surrounding the features, characteristics, safety, challenges, and future considerations of these vaccines. Key findings include:

- **Efficacy and Immune Response**: mRNA vaccines (e.g., Pfizer-BioNTech, Moderna) demonstrated the highest efficacy rates (~95%), followed by protein subunit (~90%), viral vector (66-79%), and inactivated virus vaccines (50-80%). All vaccines showed strong protection against severe disease and hospitalization.
- **Safety**: Most side effects were mild and transient, though rare adverse events, such as myocarditis and thrombosis with thrombocytopenia syndrome (TTS), were identified and closely monitored.
- **Global Distribution**: Significant disparities in vaccine access persisted, with high-income countries achieving >70% coverage, while many low-income countries remained below 20%. Initiatives like COVAX delivered over 1.5 billion doses to LMICs, but logistical and infrastructural challenges hindered equitable distribution.
- **Emerging Variants**: Variants like Delta and Omicron reduced vaccine efficacy against symptomatic infection but maintained high protection against severe outcomes. Booster doses and updated formulations were critical in addressing waning immunity and variant spread.
- **Public Acceptance**: Vaccine hesitancy, driven by misinformation and mistrust, remained a significant barrier, necessitating targeted public health campaigns and community engagement.
- **Long-Term Immunity**: Immunity waned over time, particularly against mild infection, but hybrid immunity (natural infection plus vaccination) provided stronger and more durable protection.
- **Future Strategies**: Pan-coronavirus vaccines, next-generation platforms (e.g., self-amplifying RNA), and global surveillance systems were identified as essential for addressing future variants and pandemics.
- Meanwhile COVID-19 vaccines have been a cornerstone of the pandemic response, their full potential can only be realized through equitable distribution, transparent communication, and adaptive strategies to address emerging challenges. The lessons learned from this effort provide a blueprint for future pandemic preparedness, emphasizing the need for global collaboration, innovation, and investment in public health infrastructure. By building on these achievements, the global community can strengthen its resilience against current and future health crises, ensuring a safer and healthier world for all.

FUTURE PERSPECTIVES

The continuous evolution of SARS-CoV-2 highlights the need for sustained research and innovation in vaccine development to ensure long-term protection against emerging variants. While current COVID-19 vaccines have significantly reduced the severity of infections and mortality rates, several challenges remain, necessitating advancements in vaccine technology, distribution strategies, and public health policies.

One of the key areas of future research is the development of next-generation COVID-19 vaccines that provide broader and longer-lasting immunity. Scientists are exploring universal coronavirus vaccines capable of targeting multiple strains, including potential future variants. Such vaccines would reduce the need for frequent booster doses and improve protection against newly emerging mutations.

Alternative vaccine delivery methods are also being investigated to enhance efficacy and accessibility. Nasal spray vaccines, for example, have the potential to induce mucosal immunity at the site of viral entry, providing stronger protection against infection and transmission. Additionally, oral vaccines could eliminate the need for injections, making mass immunization more feasible, particularly in resource-limited settings.

Another crucial aspect of future vaccine strategies involves enhancing global vaccine equity. Despite efforts by initiatives like COVAX, disparities in vaccine distribution remain a major concern. Strengthening manufacturing capacities in developing countries, improving cold-chain logistics, and fostering international cooperation will be essential to ensuring equitable access to vaccines worldwide.

Addressing vaccine hesitancy through targeted education campaigns and transparent communication is equally important. Combating misinformation and increasing public trust in vaccines will help improve immunization rates and prevent future outbreaks.

Furthermore, mRNA and viral vector technologies have revolutionized vaccine development, paving the way for rapid responses to emerging infectious diseases. Lessons learned from COVID-19 vaccine research will likely influence the development of vaccines for other infectious diseases, including influenza, HIV, and future pandemics.

While COVID-19 vaccines have played a crucial role in controlling the pandemic, continued innovation, global collaboration, and effective public health strategies will be required to maintain long-term immunity, prevent future outbreaks, and improve pandemic preparedness. The future of vaccine research is promising, with advancements aimed at creating more effective, accessible, and durable solutions against SARS-CoV-2 and other emerging pathogens.

The development and deployment of COVID-19 vaccines have been a testament to the remarkable progress in science and technology, yet they have also revealed significant challenges and gaps that require urgent attention. This discussion synthesizes the key findings and implications of the scientific discourse on COVID-19 vaccines, focusing on their features, safety, challenges, and future considerations.

Scientific Advancements and Vaccine Platforms

The rapid development of COVID-19 vaccines, particularly mRNA vaccines like Pfizer-BioNTech and Moderna, has revolutionized vaccinology. These platforms demonstrated unprecedented efficacy rates and set a new standard for rapid response to emerging pathogens. Viral vector vaccines, such as AstraZeneca and Johnson & Johnson, provided additional options with simpler storage requirements, while protein subunit and inactivated virus vaccines offered alternatives for regions with limited infrastructure. However, the varying efficacy rates across platforms and populations underscore the need for continued research to optimize vaccine formulations and delivery methods.

Safety and Public Trust

While COVID-19 vaccines have proven to be overwhelmingly safe, rare adverse events, such as myocarditis and thrombosis with thrombocytopenia syndrome (TTS), have highlighted the importance of robust post-marketing surveillance. Transparent communication about these risks is critical to maintaining public trust. Misinformation and vaccine hesitancy remain significant barriers, emphasizing the need for targeted public health campaigns and community engagement to address concerns and build confidence in vaccination programs.

Global Equity and Distribution Challenges

The inequitable distribution of vaccines has been a glaring issue, with high-income countries securing the majority of early doses, leaving LMICs vulnerable. Initiatives like COVAX have made strides, but more must be done to ensure equitable access. Local manufacturing, technology transfer, and waivers of intellectual property rights could help bridge this gap. Additionally, logistical challenges, such as cold chain requirements and delivery to remote areas, must be addressed to ensure vaccines reach all populations.

Emerging Variants and Adaptive Strategies

The emergence of SARS-CoV-2 variants, such as Delta and Omicron, has raised concerns about vaccine efficacy and the potential for immune escape. Booster doses and updated vaccine formulations have been critical in maintaining protection, but these efforts must be balanced with the need for global equity. The development of pan-coronavirus vaccines could provide a long-term solution, offering broad protection against current and future variants.

Lessons for Future Pandemics

The COVID-19 pandemic has underscored the importance of preparedness and collaboration. Investments in vaccine research, global surveillance systems, and healthcare infrastructure are essential to ensure a rapid and effective response to future outbreaks. The success of mRNA technology has opened new possibilities for vaccine development, not only for infectious diseases but also for cancer and other conditions.

The scientific discourse on COVID-19 vaccines highlights both the achievements and the challenges of this historic effort. While vaccines have been a cornerstone of the pandemic response, their full potential can only be realized through equitable distribution, transparent communication, and adaptive strategies to address emerging threats. By learning from the successes and shortcomings of the COVID-19 vaccination campaign, the global community can build a more resilient and equitable framework for future health crises, ensuring that no one is left behind in the pursuit of global health security.

CONCLUSIONS

- The Deployment of COVID-19 vaccines have been a landmark achievement in science and public health, demonstrating the power of global collaboration and innovation. This paper has explored the diverse features, characteristics, safety profiles, and challenges associated with COVID-19 vaccines, highlighting their critical role in mitigating the pandemic. The various vaccine platforms—mRNA, viral vector, protein subunit, and inactivated virus—have each contributed uniquely to the global vaccination effort, offering high efficacy and robust immune responses, albeit with varying logistical and storage requirements.
- Safety monitoring has been rigorous, with most side effects being mild and transient, though rare adverse events have necessitated ongoing surveillance and transparent communication to maintain public trust. Challenges such as vaccine inequity, distribution logistics, and hesitancy underscore the need for coordinated global efforts to ensure fair access and widespread acceptance. The emergence of SARS-CoV-2 variants has further emphasized the importance of adaptive vaccine strategies, including booster doses and updated formulations, to maintain protection.
- Looking ahead, the lessons learned from COVID-19 vaccine development and deployment provide a blueprint for future pandemic preparedness. Innovations such as pan-coronavirus vaccines and advancements in mRNA technology hold promise for addressing not only COVID-19 but also other infectious diseases. Ultimately, the success of vaccination campaigns depends on sustained scientific innovation, equitable distribution, and effective public engagement. By addressing these challenges and building on the achievements of the past two years, the global community can strengthen its resilience against current and future health crises, ensuring a safer and healthier world for all.
- The success of COVID-19 vaccines underscores the power of rapid scientific innovation and global collaboration, demonstrating how mRNA, vector-based, and protein subunit platforms can revolutionize immunization strategies beyond this pandemic.
- Vaccine safety remains a dynamic area of study, with continuous post-market surveillance revealing rare adverse events while reinforcing the overwhelmingly favorable risk-benefit ratio. Further refinement in formulation, delivery mechanisms, and personalized immunization strategies could enhance both safety and efficacy.
- Variants of concern pose an ongoing challenge to vaccine effectiveness, emphasizing the need for adaptable vaccine platforms, such as pan-coronavirus or variant-proof vaccines, which leverage antigenic breadth and durable immune responses.
- The disparity in vaccine access highlights deep-rooted global inequities, necessitating stronger frameworks for technology transfer, decentralized manufacturing, and equitable distribution to ensure that vulnerable populations are not left behind.
- Long-term immunity and booster strategies require deeper immunological insights, particularly regarding T-cell responses, mucosal immunity, and immune imprinting, to optimize future vaccination protocols.
- Public trust and vaccine confidence remain pivotal in achieving high immunization coverage, requiring robust, science-driven communication strategies to counteract misinformation, cognitive biases, and socio-political influences.
- Looking ahead, the COVID-19 vaccine experience offers a blueprint for pandemic **preparedness**, reinforcing the need for real-time genomic surveillance, scalable vaccine platforms, and preemptive research into zoonotic spillover threats.
- COVID-19 vaccines have significantly reduced morbidity and mortality, demonstrating their efficacy in controlling the pandemic and mitigating severe health outcomes.
- Ongoing research and innovation continue to enhance vaccine safety and effectiveness, addressing concerns related to adverse effects, durability of immunity, and variant adaptability.
- Challenges such as vaccine hesitancy, misinformation, and equitable global distribution remain critical barriers, necessitating stronger public health strategies and policy interventions.
- Long-term surveillance and post-market studies are essential to monitor vaccine performance, ensuring continuous improvement in immunization strategies and addressing emerging risks.
- Future vaccine developments, including next-generation platforms like mRNA advancements and universal coronavirus vaccines, offer promising solutions, highlighting the importance of sustained scientific and financial investments.
- Interdisciplinary collaboration among scientists, policymakers, and healthcare providers is crucial for optimizing vaccine deployment, improving public trust, and preparing for future pandemics.

RECOMMENDATIONS

Based on the scientific discourse surrounding COVID-19 vaccines, the following recommendations are proposed to enhance their effectiveness, accessibility, and public acceptance, while preparing for future health challenges:

- **Strengthen Global Vaccine Equity**:
  - Establish mechanisms to ensure fair distribution of vaccines to low- and middle-income countries (LMICs) through initiatives like COVAX.
  - Support technology transfer and local manufacturing capabilities in underserved regions to reduce dependency on high-income countries.
- **Enhance Public Communication and Education**:
  - Launch transparent, science-based campaigns to address vaccine hesitancy and combat misinformation.
  - Engage community leaders and healthcare workers to build trust and disseminate accurate information about vaccine safety and efficacy.
- **Invest in Adaptive Vaccine Development**:
  - Accelerate research on pan-coronavirus vaccines to provide broad protection against current and future variants.
  - Develop platforms for rapid vaccine updates in response to emerging variants, leveraging mRNA and other innovative technologies.
- **Improve Surveillance and Monitoring Systems**:
  - Strengthen global surveillance networks to detect and track new variants and monitor vaccine efficacy in real-time.
  - Maintain robust post-vaccination safety monitoring to identify and address rare adverse events promptly.
- **Promote Booster Dose Strategies**:
  - Develop clear guidelines for booster doses based on evolving evidence of waning immunity and variant spread.
  - Ensure equitable access to booster doses, particularly for vulnerable populations and healthcare workers.
- **Address Logistical Challenges**:
  - Invest in cold chain infrastructure and distribution networks to improve vaccine delivery, especially in remote and resource-limited areas.
  - Streamline regulatory processes to expedite vaccine approval and deployment during emergencies.
- **Foster International Collaboration**:
  - Encourage data sharing and joint research efforts among countries, institutions, and pharmaceutical companies.
  - Establish global frameworks for pandemic preparedness, including vaccine development, distribution, and financing.
- **Prioritize Research on Long-Term Immunity**:
  - Conduct longitudinal studies to understand the durability of immune responses elicited by different vaccine platforms.
  - Investigate the potential for hybrid immunity (natural infection plus vaccination) to inform future vaccination strategies.
- **Support Healthcare Systems and Workforce**:
  - Provide adequate resources and training for healthcare workers to administer vaccines efficiently and address public concerns.
  - Strengthen healthcare infrastructure to manage vaccine rollout alongside routine health services.
- **Prepare for Future Pandemics**:
  - Invest in research and development of next-generation vaccine technologies, such as self-amplifying RNA and universal vaccines.
  - Establish global stockpiles of essential medical supplies and vaccines to ensure rapid response to future outbreaks.

By implementing these recommendations, the global community can build on the lessons learned from COVID-19 to create a more resilient, equitable, and effective framework for vaccination and pandemic response, ultimately safeguarding public health for generations to come.

CONFLICT OF INTEREST The author declares that there is no conflict of interest.

REFERENCES

1. WHO. World Health Organization. COVID-19 vaccine tracker and landscape. 2022. [accessed 2022 Dec 30]. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.
2. Basta NE, Moodie EMM. On behalf of the VIPER (Vaccines, infectious disease prevention, and epidemiology research) Group COVID-19 vaccine development and approvals tracker team. COVID-19 vaccine development and approvals tracker. 2020. [accessed 2022 Dec 30]. https://covid19.trackvaccines.org/.
3. Srinivasan S, Cui H, Gao Z, Liu M, Lu S, Mkandawire W, Narykov O, Sun M, Korkin D.. Structural genomics of SARS-CoV-2 indicates evolutionary conserved functional regions of viral proteins. Viruses. 2020; 12(4):360.
4. Saxena SK, Kumar S, Ansari S, Paweska JT, Maurya VK, Tripathi AK, Abdel-Moneim AS.. Transmission dynamics and mutational prevalence of the novel severe acute respiratory syndrome coronavirus-2 omicron variant of concern. J Med Virol. 2022; 94(5):2160–15.
5. Dai L, Gao GF. Viral targets for vaccines against COVID-19. Nat Rev Immunol. 2021; 21(2):73–82.
6. Narowski TM, Raphel K, Adams LE, Huang J, Vielot NA, Jadi R, de Silva AM, Baric RS, Lafleur JE, Premkumar L. SARS-CoV-2 mRNA vaccine induces robust specific and cross-reactive IgG and unequal neutralizing antibodies in naive and previously infected people. Cell Rep. 2022; 38:110336.
7. Kim JH, Marks F, Clemens JD. Looking beyond COVID-19 vaccine phase 3 trials. Nat Med. 2021; 27(2):205–11.
8. Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C, Giattino C, Rodés-Guirao L. A global database of COVID-19 vaccinations. Nat Hum Behav. 2021; 5(7):947–53.
9. Aleem A, Samad ABA, Slenker AK. Emerging variants of SARS-CoV-2 and novel therapeutics against coronavirus (COVID-19). StatPearls [Internet]: StatPearls Publishing; 2022.
10. Peng F, Yuan H, Wu S, Zhou Y. Recent advances on drugs and vaccines for COVID-19. Inquiry. 2021; 58:469580211055630.
11. Beselia L, Tsintsadze M, Sakvarelidze I, Tsiklauri M, Gorgodze T, Taboridze I. MORTALITY RISK ASSESSMENT AMONG PATIENTS, HOSPITALIZED FOR COVID-19. Georgian medical news. 2024 Apr (349):60-7.
12. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, Kovyrshina AV, Lubenets NL, Grousova DM, Erokhova AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. 2021; 397(10275):671–81.
13. Yadav T, Srivastava N, Mishra G, Dhama K, Kumar S, Puri B, Saxena SK. Recombinant vaccines for COVID-19. Hum Vaccin Immunother. 2020; 16(12):2905–12.
14. Beselia L, Tsintsadze M, Taboridze I. Evaluation of some diagnostic features of covid-19 in patients with comorbidities. Scientific Journal „Spectri “. 2024 Jul 8;9(1).
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372:n71.
16. Shafaati M, Saidijam M, Soleimani M, Hazrati F, Mirzaei R, Amirheidari B, Tanzadehpanah H, Karampoor S, Kazemi S, Yavari B, et al. A brief review on DNA vaccines in the era of COVID-19. Future Virol. 2022; 17(1):49–66.
17. Abbasi J. India’s new COVID-19 DNA vaccine for adolescents and adults is a first. JAMA. 2021; 326(14):1365.
18. Khobragade A, Bhate S, Ramaiah V, Deshpande S, Giri K, Phophle H, Supe P, Godara I, Revanna R, Nagarkar R, et al. Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): the interim efficacy results of a phase 3, randomised, double-blind, placebo-controlled study in India. Lancet. 2022; 399(10332):1313–21.
19. Blakney AK, Bekker L-G. DNA vaccines join the fight against COVID-19. The Lancet. 2022; 399(10332):1281–82.
20. Andrade VM, Christensen-Quick A, Agnes J, Tur J, Reed C, Kalia R, Marrero I, Elwood D, Schultheis K, Purwar M, et al. INO-4800 DNA vaccine induces neutralizing antibodies and T cell activity against global SARS-CoV-2 variants. NPJ Vaccines. 2021; 6(1):1–4.
21. Tebas P, Yang S, Boyer JD, Reuschel EL, Patel A, Christensen-Quick A, Andrade VM, Morrow MP, Kraynyak K, Agnes J, et al. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: a preliminary report of an open-label, Phase 1 clinical trial. EClinicalMedicine. 2021; 31:100689.

22. Kraynyak KA, Blackwood E, Agnes J, Tebas P, Giffear M, Amante D, Reuschel EL, Purwar M, Christensen-Quick A, Liu N, et al. SARS-CoV-2 DNA vaccine INO-4800 induces durable immune responses capable of being boosted in a Phase I open-label trial. J Infect Dis. 2022; 225(11):1923–32.
23. Sheridan C. First COVID-19 DNA vaccine approved, others in hot pursuit. Nat Biotechnol. 2021; 39(12):1479–82.
24. Aphkhazava D, Tuphinashvili T, Sulashvili N, Nozadze M. The Features and Role of SHP2 Protein in Postnatal Muscle Development. Scientific Journal „Spectri ". 2023 Mar 10; 1.
25. Aphkhazava D, Sulashvili N, Egnatievi I, Tupinashvili T, Nozadze M. Dynamic tumor microenvironment theory: a multifaceted approach to tumor research and biochemistry. Scientific Journal „Spectri ". 2024 Jul 10; 9(1).
26. SULASHVILI N, BEGLARYAN M, GORGASLIDZE N, KOCHARYAN S, CHICHOYAN N, GABUNIA L, ZARNADZE I, KVIZHINADZE N, PKHALADZE G, GIORGOBIANI M, SENIUK I. The disclosure of features, characteristics, possibilities and specialties of clinical pharmacists as mediator among doctors and patients for enhancement public health sector in a global world. Experimental and Clinical Medicine Georgia. 2023 Nov 26(4):57-62.
27. Sulashvili N, Nimangre RR. Manifestation of some aspects of cardiovascular diseases, implications, pharmacotherapeutic strategies, effects, impacts and potential hazards in general. Junior Researchers. 2025 Feb 7; 3(1):1-27.
28. SULASHVILI, N., BEGLARYAN, M., GORGASLIDZE, N., KOCHARYAN, S., CHICHOYAN, N., GABUNIA, L., KVIZHINADZE, N., GIORGOBIANI, M., PKHALADZE, G., SENIUK, I. and ZARNADZE, I., 2024. THE SCIENTIFIC DISCUSSION OF SOME KEY ISSUE ASPECTS OF PHARMACISTS'VOCATIONAL CHALLENGES, VISION, OPPORTUNITIES, OUTLOOKS, OBJECTIONS, APPEARANCES AND INDENTATION IN GENERAL AND PUBLIC HEALTH CARE DIRECTION. *Experimental and Clinical Medicine Georgia*, (4), pp.126-129.
29. GORGASLIDZE N, SULASHVILI N, GABUNIA L, RATIANI L, GIORGOBIANI M. The singularities of temozolomide pharmacotherapeutic effects in brain tumor therapeutic applications. Experimental and Clinical Medicine Georgia. 2023 Nov 26(4):62-6.
30. Sulashvili, N., Fernando, S., El-Hakeem, A., Gabunia, L., Gorgaslidze, N., Beglaryan, M., Patsia, L., Kvizhinadze, N. and Sulashvili, M., 2025. CLOSED-LOOP CARDIOPULMONARY BYPASS SYSTEMS WITH REAL-TIME MONITORING AND PHARMACOTHERAPY STRATEGIES: INNOVATIONS, OUTCOMES, CLINICAL IMPACT AND FUTURE DIRECTIONS IN GENERAL. *Georgian Scientists*, *7*(2), pp.381-419.
31. NANA GORGASLIDZE, NODAR SULASHVILI, MARINA GIORGOBIANI, TEA ZARKUA, and NANA DUGASHVILI. 2021. "THE FEATURES OF INSPECTION AND MONITORING FRAMEWORK FOR PROFESSIONAL SAFETY, SANITARY, BIOECOLOGICAL, PREVENTIVE AND HYGIENIC NOVEL REQUIREMENT ISSUES OF PHARMACEUTICAL ORGANIZATIONS IN THE CONTEXT OF THE COVID-19 PANDEMIC IN GEORGIA". Experimental and Clinical Medicine Georgia, no. 5-6 (October):42-46. https://journals.4science.ge/index.php/jecm/article/view/576.
32. Aphkhazava, D., Sulashvili, N., & Tkemaladze, J. (2025). Stem Cell Systems and Regeneration. Georgian Scientists, 7(1), 271–319. https://doi.org/10.52340/gs.2025.07.01.26
33. Sulashvili, N., Alavidze, N., Buleishvili, M., Kravchenko, V., Sulashvili, M., Seniuk, I., Okropiridze, T., Giorgobiani, M., Grigolia, L. and Robakidze, K., 2024. The manifestation of key issue features of global perspectives on innovative teaching and learning approach strategies in higher medical education: advancing student-centered practices, technology integration and competency-based frameworks. *Scientific Journal „Spectri "*, *10*(2).
34. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, Hoefer D, Wu M, Lutterloh E, Conroy MB, et al. Covid-19 vaccine effectiveness in New York state. N Engl J Med. 2022; 386(2):116–27.
35. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020; 383(27):2603–15.
36. Sulashvili, Nodar, Lali Patsia, Awad El-Hakeem, Sk Ayaan, Arian Hizomi, Sajal Agarwal, and Marika Sulashvili. 2025. "EXPLORING THE GUT-BRAIN AXIS: THE ROLE OF THE MICROBIOME IN MODULATING BRAIN FUNCTION AND ITS IMPLICATIONS IN NEURODEGENERATIVE DISORDERS LIKE PARKINSON'S AND ALZHEIMER'S AND PHARMACOTHERAPY

TREATMENT STRATEGIES". *Georgian Scientists* 7 (2):329-53. https://doi.org/10.52340/gs.2025.07.02.32.

37. Sulashvili, Nodar, Magda Davitashvili, Nana Gorgaslidze, Luiza Gabunia, Margarita Beglaryan, Nato Alavidze, Igor Seniuk, et al. 2024. "THE SCIENTIFIC DISCUSSION OF SOME ISSUES OF FEATURES AND CHALLENGES OF USING OF CAR-T CELLS IN IMMUNOTHERAPY". Georgian Scientists 6 (4):263-90. https://doi.org/10.52340/gs.2024.06.04.24.
38. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., RATIANI, L., KHETSURIANI, S., KRAVCHENKO, V., SENIUK, I., GIORGOBIANI, M., KVIZHINADZE, N. and SULASHVILI, M., 2024. Manifestation of the particularities of some key issue aspects of new immunotherapy challenges and perspectives by CAR-T cell therapy. *Experimental and Clinical Medicine Georgia*, (4), pp.119-121.
39. Chatterjee D, Tauzin A, Marchitto L, Gong SY, Boutin M, Bourassa C, Beaudoin-Bussières G, Bo Y, Ding S, Laumaea A, et al. SARS-CoV-2 omicron spike recognition by plasma from individuals receiving BNT162b2 mRNA vaccination with a 16-week interval between doses. C Cell Rep. 2022; 38(9):110429.]
40. Muik A, Lui BG, Wallisch A-K, Bacher M, Mühl J, Reinholz J, Ozhelvaci O, Beckmann N, Güimil Garcia RDLC, Poran A, et al. Neutralization of SARS-CoV-2 omicron by BNT162b2 mRNA vaccine–elicited human sera. Science. 2022; 375(6581):678–80.
41. Follmann D, Janes HE, Buhule OD, Zhou H, Girard B, Marks K, Kotloff K, Desjardins M, Corey L, Neuzil KM, et al. Antinucleocapsid antibodies after SARS-CoV-2 infection in the blinded phase of the randomized, placebo-controlled mRNA-1273 COVID-19 vaccine efficacy clinical trial. Ann Intern Med. 2022; 175(9):1258–65.
42. Tartof SY, Slezak JM, Puzniak L, Hong V, Frankland TB, Ackerson BK, Takhar H, Ogun OA, Simmons S, Zamparo JM, et al. Bnt162b2 vaccine effectiveness against SARS-CoV-2 omicron BA.4 and BA.5. Lancet Infect Dis. 2022; 22(12):1663–65.
43. Leung D, Rosa Duque JS, Yip KM, So HK, Wong WHS, Lau YL. Effectiveness of BNT162b2 and CoronaVac in children and adolescents against SARS-CoV-2 infection during omicron BA.2 wave in Hong Kong. Commun Med (Lond). 2023; 3(1):3.
44. Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, Ku JH, Florea A, Luo Y, Qiu S, et al. Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. Nat Commun. 2023; 14(1):189.
45. Aphkhazava, David, Nodar Sulashvili, and Jaba Tkemaladze. 2025. "Stem Cell Systems and Regeneration". Georgian Scientists 7 (1):271-319. https://doi.org/10.52340/gs.2025.07.01.26.
46. Aphkhazava, D., Sulashvili, N., Tupinashvili, T., & Nozadze, M. (2024). Dynamic Cellular Equilibrium Theory of Aging: Integrating Maintenance and Accumulation in the Aging Process. Scientific Journal „Spectri", 8(2). https://doi.org/10.52340/spectri.2023.08.02.03
47. Aphkhazava, D., Tuphinashvili, T., Sulashvili, N., & Nozadze, M. (2023). The Features and Role of SHP2 Protein in Postnatal Muscle Development. Scientific Journal „Spectri", 1. https://doi.org/10.52340/spectri.2023.01
48. SULASHVILI, N., BEGLARYAN, M., GORGASLIDZE, N., KOCHARYAN, S., CHICHOYAN , N., GABUNIA, L., … ZARNADZE, S. (DAVIT). (2023). THE DISCLOSURE OF FEATURES, CHARACTERISTICS, POSSIBILITIES AND SPECIALTIES OF CLINICAL PHARMACISTS AS MEDIATOR AMONG DOCTORS AND PATIENTS FOR ENHANCEMENT PUBLIC HEALTH SECTOR IN A GLOBAL WORLD. Experimental and Clinical Medicine Georgia, (4), 57–62. https://doi.org/10.52340/jecm.2023.04.15
49. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., GIORGOBIANI, M., & RATIANI, L. (2023). MANIFESTATION OF THE PARTICULARITIES OF THE USAGE FEATURES OF MONOCLONAL ANTIBODIES IN VARIOUS PHARMACOTHERAPEUTIC APPLICATIONS. Experimental and Clinical Medicine Georgia, (4), 52–57.
50. Sulashvili, N., Davitashvili, M., Gorgaslidze, N., Gabunia, L., Beglaryan, M., Alavidze, N., … Sulashvili, M. (2024). THE SCIENTIFIC DISCUSSION OF SOME ISSUES OF FEATURES AND CHALLENGES OF USING OF CAR-T CELLS IN IMMUNOTHERAPY. Georgian Scientists, 6(4), 263–290. https://doi.org/10.52340/gs.2024.06.04.24
51. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., GIORGOBIANI, M., & RATIANI, L. (2023). MANIFESTATION OF THE PARTICULARITIES OF THE USAGE FEATURES OF MONOCLONAL ANTIBODIES IN VARIOUS PHARMACOTHERAPEUTIC APPLICATIONS. Experimental and Clinical Medicine Georgia, (4), 52–57. https://doi.org/10.52340/jecm.2023.04.14

52. SULASHVILI, N., GORGASLIDZE, N., GABUNIA, L., RATIANI, L., KHETSURIANI, S., KRAVCHENKO, V., SULASHVILI, M. (2024). MANIFESTATION OF THE PARTICULARITIES OF SOME KEY ISSUE ASPECTS OF NEW IMMUNOTHERAPY CHALLENGES AND PERSPECTIVES BY CAR-T CELL THERAPY. Experimental and Clinical Medicine Georgia, (4), 119–121. https://doi.org/10.52340/jecm.2024.04.32.
53. SULASHVILI N, GORGASLIDZE N, BEGLARYAN M, GABUNIA L, CHICHOYAN N, GIORGOBIANI M, ZARNADZE I, ZARNADZE SD. The scientific talks of essential issue, invocation, perspectives, inclinations and features of the clinical pharmacists globally. Experimental and Clinical Medicine Georgia. 2022 Oct 27(7).
54. Sulashvili N, Nimangre RR. MANIFESTATION OF SOME ASPECTS OF CARDIOVASCULAR DISEASES, IMPLICATIONS, PHARMACOTHERAPEUTIC STRATEGIES, EFFECTS, IMPACTS AND POTENTIAL HAZARDS IN GENERAL. JR [Internet]. 2025 Feb. 7 [cited 2025 May 22];3(1):1-27. Available from: https://journals.4science.ge/index.php/jr/article/view/3393.
55. Sulashvili N, Yaduvanshi U, Yadav M, Gabunia L, Ghambashidze K, Gorgaslidze N, et al. THE SCIENTIFIC DISCOURSE OF FEATURES OF CLINICAL USE AND PHARMACOLOGY OF VASOCONSTRICTORS AND THEIR IMPACT ON CARDIAC FUNCTION. JR [Internet]. 2025 Feb. 21 [cited 2025 May 22];3(1):28-6. Available from: https://journals.4science.ge/index.php/jr/article/view/3414.
56. Sulashvili, N., Alavidze, N., Buleishvili, M., Kravchenko, V., Sulashvili, M., Seniuk, I., Okropiridze, T., Giorgobiani, M., Grigolia, L. and Robakidze, K., 2024. The manifestation of key issue features of global perspectives on innovative teaching and learning approach strategies in higher medical education: advancing student-centered practices, technology integration and competency-based frameworks. *Scientific Journal „Spectri“*, *10*(2).
57. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–16.
58. Stamatatos L, Czartoski J, Wan Y-H, Homad LJ, Rubin V, Glantz H, Neradilek M, Seydoux E, Jennewein MF, MacCamy AJ, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Science. 2021; 372(6549):1413–18.
59. Tauzin A, Gong SY, Beaudoin-Bussières G, Vézina D, Gasser R, Nault L, Marchitto L, Benlarbi M, Chatterjee D, Nayrac M, et al. Strong humoral immune responses against SARS-CoV-2 spike after BNT162b2 mRNA vaccination with a 16-week interval between doses. Cell Host Microbe. 2022; 30(1):97–109. e5.