

Review



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The Role of COVID-19 Vaccination for Patients With Atherosclerotic Cardiovascular Disease in the Upcoming Endemic Era

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ABSTRACT

COVID-19 vaccination has played a pivotal role in coping with the COVID-19 pandemic by providing a powerful tool to curb the spread of the virus, reduce severe illness and hospitalizations, and ultimately save lives and facilitate a return to normal daily routines. As COVID-19 vaccination has become more widespread and more individuals have recovered from the infection, COVID-19 has entered an endemic disease phase. This phase is characterized by a less severe and more stable pattern of infection within certain regions, similar to the predictability of seasonal influenza. In this endemic era, COVID-19 vaccines may appear to be less important, and many people are reluctant to receive COVID-19 vaccination for various reasons, including the fear of adverse events. However, COVID-19 remains a major public health problem, in that the incidence rate of new COVID-19 infections is still high and the morbidity and mortality in high-risk populations are substantial. Therefore, the role of COVID-19 vaccines in protecting high-risk individuals is crucial, and ongoing research and surveillance are imperative to refine vaccination recommendations in the ever-changing landscape of the COVID-19 endemic era. This review explores the role of COVID-19 vaccination in the upcoming COVID-19 endemic era.

Keywords: COVID-19; Vaccine; Endemic disease

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has had a profound and far-reaching impact on nearly every aspect of human life, including health, social, and economic domains.^{1,6} The officially reported number of COVID-19-related deaths, as shown on the World Health Organization COVID-19 Dashboard, has approached nearly 7 million to date. In response to the risks posed by COVID-19, various vaccines have been developed, with messenger RNA (mRNA) vaccines becoming the most widely used. However, the success of these vaccines has been accompanied by unexpected adverse events, which have posed challenges to their widespread acceptance.^{7,10} Despite these unexpected adverse events, COVID-19 vaccination continues to play a pivotal role in coping with the COVID-19 pandemic by providing a powerful tool to curb the spread of the virus, reduce severe illness and hospitalizations, and ultimately save lives and facilitate a return to normal daily routines.

With the widespread use of COVID-19 vaccines and an increasing number of individuals recovering from the infection, COVID-19 has entered an endemic phase. This phase is characterized by less severe and more stable patterns of disease within specific regions, similar to the predictability of seasonal influenza.^{11,12} Consequently, vaccination policies for COVID-19 have been updated in most countries around the world. In this endemic era, the perceived importance of COVID-19 vaccines appears to have diminished, with people becoming less eager or more hesitant to receive the vaccine due to various concerns, including fear of adverse events. Nonetheless, COVID-19 remains a significant public health issue, as the incidence of new infections remains high and the morbidity and mortality among high-risk populations are still substantial. Therefore, the role of COVID-19 vaccines in protecting high-risk individuals is vital, and continued research and surveillance are essential to adapt vaccination recommendations to the dynamic context of the COVID-19 endemic era.

This review discusses the benefits and drawbacks of COVID-19 vaccines during the COVID-19 pandemic and explores the role of COVID-19 vaccination in the upcoming COVID-19 endemic era.

ROLE OF COVID-19 VACCINATION IN THE PANDEMIC ERA

COVID-19 vaccination has played a pivotal role in the ongoing battle against the COVID-19 pandemic. The roles of COVID-19 vaccination in the pandemic era are summarized in **Table 1**.

The primary functions of COVID-19 vaccination are prevention, protection, and mitigation of the disease. First and foremost, COVID-19 vaccination has prevented new COVID-19 cases by building immunity in individuals, reducing the spread of the virus within communities, and ultimately limiting transmission.^{13,14} Furthermore, COVID-19 vaccines have played a critical role in protecting vulnerable groups, such as the elderly and those with underlying comorbidities, from severe illness and death.^{15,16} COVID-19 vaccination also has contributed to achieving herd immunity, which is essential for ending the pandemic. Additionally, COVID-19 vaccination has supported economic recovery by reducing the strain on the healthcare system, allowing businesses to reopen, and eventually aiding in the gradual return to normal life. The global role of vaccination cannot be overstated, as it has helped to control the pandemic on an international scale, reduced the emergence of new variants, and strengthened public health efforts. Despite challenges and concerns, vaccination remains a crucial tool in navigating these unprecedented times.

Table 1. The roles of COVID-19 vaccination in the pandemic era

Role of COVID-19 vaccination	Description
Preventing COVID-19	Vaccination significantly reduces the risk of contracting COVID-19. It provides protection against symptomatic and severe illness.
Reducing transmission	Vaccinated individuals are less likely to transmit the virus to others, helping to slow the spread of COVID-19 within communities.
Preventing severe complications	Vaccination lowers the risk of severe outcomes, including hospitalization, ICU admission, and death among those who do contract the virus.
Protecting vulnerable populations	Vaccination offers crucial protection for individuals at higher risk, such as older adults, individuals with underlying health conditions, and healthcare workers.
Contributing to herd immunity	Widespread vaccination helps establish herd immunity, reducing the overall transmission of the virus and protecting those who cannot be vaccinated.
Economic recovery	Vaccination is key to reopening economies by reducing the burden on healthcare systems and allowing a return to normal activities and business operations.
Global health	Vaccination is a crucial tool in controlling the pandemic worldwide, preventing the emergence of new variants and supporting global public health efforts.

COVID-19, coronavirus disease 2019; ICU, intensive care unit

DRAWBACKS OF COVID-19 VACCINES: ADVERSE EVENTS

Despite the numerous benefits of COVID-19 vaccination as described above, it is important to carefully consider its use in light of potential expected or unexpected adverse events. The risks and adverse events associated with different types of COVID-19 vaccines are summarized in **Table 2**.

Common side effects include pain, swelling, or redness at the injection site, as well as fatigue, headache, muscle pain, chills, fever, and nausea. Typically, these symptoms resolve within a few days and are indicative of the body building protection against the virus.⁷

While most adverse events associated with COVID-19 vaccines are mild, there have been some rare but more serious incidents linked to specific vaccines. For instance, rare cases of myocarditis and pericarditis, with an incidence rate of 1.4–5.0 per 100,000 vaccinated individuals, have been observed, particularly in younger males following mRNA vaccines such as BNT162b2 and mRNA-1273.^{17,19} In addition, extremely rare instances of blood clotting disorders have been reported. These include vaccine-induced immune thrombotic thrombocytopenia, occurring at a rate of 1–2 per 100,000 vaccinated persons,²⁰ cerebral venous sinus thrombosis, with 3.6 cases per 1 million vaccinated persons,²¹ and venous thromboembolism with or without thrombocytopenia.²² These events have been associated with certain viral vector vaccines, including ChAdOx-1S and Ad26.COV2.S.

RISKS VERSUS BENEFITS OF COVID-19 VACCINATION

Considering the research that has been conducted to date, it is important to emphasize that the risk of severe adverse events from COVID-19 vaccination is extremely low, especially when compared to the risk of severe illness, hospitalization, and death from COVID-19 infection. The benefits of vaccination in preventing COVID-19 and its complications far outweigh the

Table 2. Risks or AEs of COVID-19 vaccines

Type of COVID-19 vaccine	Common AEs	Rare/severe AEs	Special considerations
mRNA vaccines (e.g., BNT162b2, mRNA-1273)	Pain, swelling, or redness at the injection site, fatigue, headache, myalgia, fever/chills	Myocarditis and pericarditis (rare, more common in younger males) Anaphylaxis (very rare)	Most side effects are mild and short-lived. Myocarditis and pericarditis cases have been reported but are generally mild and self-limiting.
Viral vector vaccines (e.g., ChAdOx-1S, Ad26.COV2.S)	Pain, swelling, or redness at the injection site, fatigue, nausea, headache, myalgia, fever/chills	Blood clotting disorders (very rare) GBS (rare, particularly with Ad26.COV2.S)	Blood clotting disorders, such as VITT, CVST, and VTE have been reported with certain viral vector vaccines but are extremely rare. The risks are often outweighed by the benefits, especially in regions with high COVID-19 transmission rates.
Protein subunit vaccines (e.g., NVA-CoV2373)	Pain, swelling, or redness at the injection site, fatigue, headache, myalgia, fever/chills	AEs are generally mild and self-limiting.	Data on protein subunit vaccines are still being gathered, but early results indicate favorable safety profiles.
Inactivated vaccines (e.g., BBIBP-CorV, CoronaVac, BBV152)	Pain, swelling, or redness at the injection site, fatigue, headache, myalgia, fever/chills	AEs are generally mild and self-limiting.	Inactivated vaccines have a long history of use, and their safety profiles are well established.
Special considerations	Vaccine-specific AEs may vary, and recommendations for specific populations may differ	The benefits of vaccination often outweigh the risks, especially in reducing the risk of severe COVID-19 and its complications.	

*A Korean nationwide study suggested the possibility of severe cases of COVID-19 vaccine-related myocarditis, including fulminant myocarditis or death. AE, adverse event; COVID-19, coronavirus disease 2019; GBS, Guillain-Barré syndrome; VITT, vaccine-induced immune thrombotic thrombocytopenia; CVST, cerebral venous sinus thrombosis; VTE, venous thromboembolism.

risks. COVID-19 vaccination remains a critical tool in controlling the spread of the virus, protecting vulnerable populations, and bringing the pandemic to an end. Individuals are encouraged to consult with healthcare providers for personalized guidance on COVID-19 vaccination, taking into account their health status and risk factors.

TRANSITION FROM COVID-19 PANDEMIC TO ENDEMIC AND VICE VERSA

After COVID-19 was first recognized in December 2019, the WHO officially declared COVID-19 to be a pandemic on March 11, 2020, due to its rapid and extensive global spread. The pandemic has led to widespread illness, hospitalizations, and fatalities, resulting in significant public health and socioeconomic challenges. Efforts to combat the pandemic have included vaccination campaigns, public health measures such as social distancing and mask-wearing, and international cooperation to curb the virus's transmission.

With the widespread use of COVID-19 vaccines and an increasing number of individuals recovering from the infection, COVID-19 has transitioned into an endemic phase. Endemicity refers to a situation in which the disease is consistently present and maintained at a relatively stable level in a specific geographic area or population over an extended period.^{11,12} In an endemic state, the virus that causes COVID-19 continues to circulate among the population, leading to sporadic cases or occasional outbreaks, but it does not necessarily result in widespread, uncontrolled transmission or large-scale epidemics.

However, it is important to keep in mind that COVID-19, when endemic in a particular area or population, can change and potentially flare up, leading to the possibility of a pandemic re-occurring under certain circumstances. The transition from an endemic state to a pandemic can occur if the disease acquires new characteristics that allow it to spread more easily, if there are significant changes in the population's immunity, or if the disease adapts in a way that makes it more transmissible or virulent. It is important to note that the transition from endemic to pandemic is not guaranteed, and public health measures, surveillance, and vaccine strategies play critical roles in preventing and mitigating that possibility. Vigilance and proactive measures are essential to manage and control infectious diseases such as COVID-19. Public health organizations and governments monitor the situation closely and adjust strategies as needed to reduce the risk of a pandemic resurgence.

THE NEED FOR COVID-19 VACCINATION IN THE ENDEMIC ERA

COVID-19 vaccination remains necessary in the endemic era for several reasons.

First, the incidence of COVID-19 is still high, with considerable mortality, even though the pandemic is over. The Korea Disease Control and Prevention Agency (KDCA) reported in its official monitoring for December 2023 that Korea is experiencing approximately 6,000–7,000 new COVID-19 cases each week. Moreover, the Korean Statistics Office's 2022 data indicates that COVID-19 is now the third leading cause of death among Koreans. Consequently, vaccination against COVID-19 continues to be crucial in preventing the disease and its complications.

Second, COVID-19 infection in high-risk populations is associated with death or severe illness. The most frequently reported underlying conditions in the high-risk population for COVID-19 infection include old age (age >60 years), cardiovascular disease (CVD), diabetes, chronic lung disease, chronic kidney disease, or immunocompromised conditions.²³ Hospitalization rates are known to be six times higher and death rates 12 times higher for COVID-19 patients with these high-risk conditions. Therefore, although not mandatory for the entire population, COVID-19 vaccination is considered essential for these high-risk groups.

Third, while COVID-19 may become endemic, there is still the potential for localized outbreaks or spikes in cases resulting in an epidemic or pandemic. High vaccination rates can help prevent these outbreaks and minimize their impact.

Fourth, COVID-19 vaccination can prevent or slow the emergence of new variants of the virus by reducing transmission.²⁴ Some variants have shown resistance to immunity from previous infection or vaccination; therefore, minimizing transmission is important.

Fifth, keeping COVID-19 cases at manageable levels through vaccination helps prevent healthcare systems from being overwhelmed, ensuring that hospitals and medical resources are available for those in need.

Sixth, some individuals experience long-term health effects (long COVID) even after recovering from the acute phase of COVID-19 infection. The long-term risk of incident CVD was found to be substantially higher in COVID-19 survivors than in non-COVID-19 controls in a retrospective large cohort study from the United States. Clinicians should pay careful attention to the cardiovascular (CV) health of individuals with a history of COVID-19 in the long term.²⁵ COVID-19 vaccination can reduce the risk of infection and potential long-term health consequences.²⁶

Seventh, the emergence of new COVID-19 variants and the potential for waning immunity necessitate booster doses or updated vaccines during the endemic phase. A recent large population-based study found that vaccination with bivalent BA.4-5 or BA.1 mRNA booster vaccines as a fourth dose was associated with reduced rates of COVID-19-related hospital admissions and deaths among adults aged 50 years and older.²⁷ The study reported no significant difference in the protection provided by the bivalent BA.4-5 and BA.1 boosters when directly compared. These findings strongly support the use of updated bivalent COVID-19 mRNA vaccines to combat COVID-19 variants and their associated complications. In Korea, these updated bivalent mRNA vaccines are available and are being used for booster vaccinations.

SPECIAL CONSIDERATIONS: VACCINE-RELATED MYOCARDITIS

COVID-19 mRNA vaccines, such as BNT162b2 and mRNA-1273, have been linked to a rare side effect known as myocarditis, which involves inflammation of the heart muscle. Reports of myocarditis, primarily among adolescents and young adult males, have most frequently occurred after the second dose of the vaccine. However, it is crucial to note that these instances are extremely rare when weighed against the overall benefits of vaccination. The majority of studies on COVID-19 vaccine-related myocarditis (VRM) indicate that it is typically mild and self-limiting, often resolving with little to no medical intervention.^{17,18} The

benefits of COVID-19 vaccination in preventing severe disease, hospitalization, and death far outweigh the risks of myocarditis, particularly when considering the heightened risk of cardiovascular complications following a natural COVID-19 infection.²⁸

A recent nationwide study in Korea involving 44,276,704 vaccinated individuals has been published.¹⁹ The findings align with previous research on COVID-19 VRM, showing it to be extremely rare, associated with mRNA vaccines, and primarily affecting young males. However, this study identified several notable differences in the clinical presentation and characteristics of VRM compared to earlier reports. Most significantly, the study found that severe VRM, including cases requiring extracorporeal membrane oxygenation or resulting in death, was uncommon. Furthermore, the study reported that 8 out of 21 deaths were due to sudden cardiac death (SCD) linked to VRM, confirmed by autopsy. All SCD cases associated with vaccine-related myocarditis occurred in individuals under 45 years old who had received mRNA vaccines. The findings from this study suggest that the administration of COVID-19 mRNA vaccines in younger individuals without clear high-risk factors should be approached with caution. Additionally, the potential for SCD as a serious complication of COVID-19 vaccination warrants close monitoring, particularly in those aged under 45 years.

SPECIAL CONSIDERATIONS: COVID-19 VACCINATION IN ATHEROSCLEROTIC CVD

Adverse events related to COVID-19, such as death or hospitalization, are known to increase not only in individuals with pre-existing atherosclerotic cardiovascular disease (ASCVD),^{23,29} but also in individuals with CV risk factors.^{30,31} Renal disease, diabetes, hypertension, smoking history, and current smoking status were identified as risk factors for higher mortality and severe COVID-19 in the study by Harrison et al.³⁰ Given that many of the risk factors associated with adverse COVID-19 outcomes are potentially modifiable, the researchers suggested that primary and secondary prevention strategies targeting cardiovascular risk factors could improve outcomes for individuals following a COVID-19 infection. A recent population-based cohort study in England showed that individuals without pre-existing CVD but with elevated CV risk were more likely to experience severe COVID-19 outcomes, including deaths, intensive care unit admissions, or hospitalizations. Therefore, the authors recommended that individuals with elevated cardiovascular risk should be considered an important target for COVID-19 prevention and management strategies. Similarly, a nationwide epidemiological study in Korea confirmed that cardiovascular risk factors were significant predictors of severe COVID-19.³² Therefore, it is recommended that individuals with pre-existing ASCVD or risk factors for ASCVD should be considered a high-risk group for severe COVID-19, and vaccination against COVID-19 is strongly advised for this high-risk population.

CURRENT RECOMMENDATION FOR COVID-19 VACCINATION IN KOREA

The KDCA formulates vaccination policies by considering the prevalent strains and the extent of COVID-19 infection in the population during the vaccine rollout. The most recent “23-'24 Seasonal COVID-19 Vaccination Implementation Plan” has been developed with an emphasis on preventing severe illness and fatalities, particularly among high-risk

groups that carry a relatively high disease burden. In line with this, the KDCA has strongly recommended COVID-19 vaccination for individuals aged 65 and older, those aged 12–64 with immunodeficiency, and people in high-risk settings, such as those who are hospitalized, institutionalized, or staff members in these environments. Vaccination is also available to individuals aged 12 and above who are not considered high-risk, should they choose to be vaccinated. For the COVID-19 vaccination campaign in Korea, two types of mRNA vaccines based on the XBB.1.5 variant (Pfizer and Moderna) and one XBB.1.5-based recombinant gene vaccine (Novavax) are currently in use.

CONCLUSION

Considering the high incidence rate, significant fatality rate, and the issue of long COVID (including cardiovascular events), COVID-19 remains a global health threat. Although there have been reports of severe adverse events following COVID-19 vaccination, it is crucial to note that the likelihood of these events is exceedingly low, particularly when compared to the risks of severe illness, hospitalization, and death associated with COVID-19 infection. The protective benefits of vaccination in preventing COVID-19 and its complications overwhelmingly outweigh these risks. The latest COVID-19 vaccines, including mRNA vaccines, have been updated to combat new variants and are effective in preventing infection, severe illness, death, and long-term cardiovascular complications. Therefore, in the post-pandemic or endemic era, COVID-19 vaccination remains essential, especially for individuals with high-risk conditions such as ASCVD.

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