Vol. 18 (2026): Proceedings of 2026 International Conference on Smart Healthcare and Biomedical Engineering (ICSHBE 2026)
E-ISSN: 3105-0522 P-ISSN: 3105-0514
DOI: https://doi.org/10.70267/shbe.2026266272

The Safety and Effectiveness of mRNA Vaccines in Large-scale Vaccination: A Systematic Review Based on COVID-19 and Flu Vaccines

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Abstract

The COVID-19 pandemic has driven the large-scale deployment of mRNA vaccines. Despite the positive outcomes observed in initial clinical trials, in-depth, comprehensive assessments of the safety and efficacy of these vaccines across different populations remain necessary following mass vaccination. This systematic review focuses on mRNA vaccines against COVID-19 and influenza, evaluating vaccine safety by analyzing post-vaccination adverse events and assessing efficacy by examining immunogenicity dynamics and protective effects against clinical endpoints. The findings indicate that these vaccines have high initial efficacy but wane over time, necessitating booster doses. The overall safety profile is favorable, with injection site reactions and systemic symptoms as the most common adverse reactions, and the incidence of rare adverse events shows age- and gender-related disparities. This study provides a reference for public health decision-making and vaccine development.

Keywords

mRNA vaccines, COVID-19, flu vaccines, vaccine safety, vaccine effectiveness

1. Introduction

COVID-19 vaccination efforts have exerted a substantial global impact, with SARS-CoV-2 immunization estimated to have averted approximately 2.5 million deaths worldwide [1]. As the epidemic evolves, these efforts will continue to shape future large-scale vaccination campaigns. Decades of public and private research in mRNA biology, immunology, and vaccine technology laid the groundwork for messenger RNA (mRNA) COVID-19 vaccines. This foundation was strengthened by key breakthroughs [2]. During the COVID-19 pandemic, mRNA vaccines have played a significant role, saving many lives. Influenza and COVID-19 are both respiratory viral diseases. However, influenza vaccines face challenges, including the need for annual strain matching and weak immune responses in the elderly. mRNA technology is expected to offer new solutions.

SARS-CoV-2, the causative agent of COVID-19, has led to over 7 million fatalities worldwide. Vaccination against this virus has been instrumental in reducing disease incidence and mortality, thereby significantly reducing the burden on healthcare systems [3]. Given that mRNA vaccine protection wanes over time [4], mRNA vaccines remain an effective means of combating the COVID-19 pandemic.

While randomized controlled trials serve as the benchmark for evaluating vaccine efficacy, they have limitations, including small sample sizes, limited follow-up periods, and exclusion of certain populations. By conducting real-world evidence studies using large-scale population data from vaccine promotion, comprehensive evaluations of vaccine performance can be conducted from multiple perspectives. These evaluations cover effectiveness in special populations, the identification of rare adverse reactions, the duration of protection, and effectiveness against new variants. Regarding COVID-19 mRNA vaccines, substantial real-world evidence has accumulated, validating their practical value in public health. This evidence not only supplements data from previous clinical trials but also addresses issues that were not addressed in the pre-approval studies. In sharp contrast, the influenza mRNA vaccine is currently at a crucial stage from clinical development to practical application. At this stage, real-world evidence is also required to confirm its effectiveness and safety on a population level. This paper undertakes a systematic review and comparison of real-world data on these two classes of mRNA vaccines, facilitating a holistic assessment of the benefits and challenges of mRNA technology in combating respiratory viruses.

The mRNA vaccine technology was first applied on a large scale during the COVID-19 pandemic, accumulating unprecedented real-world data. Meanwhile, the mRNA influenza vaccine is moving from clinical trials to real-world use, and its safety and efficacy need to be systematically reviewed. This review aims to integrate and compare the safety and efficacy evidence for the COVID-19 and influenza mRNA vaccines in real-world settings. What is more, comparing the similarities and differences between the two types of vaccines. Finally, identify the shortcomings of existing research. Analyze the limitations of current real-world studies in terms of methodological design, data sources, bias control, and population coverage, and clearly identify the evidence gaps and quality differences. This will provide direction for subsequent research.

2. Theoretical Background

The effectiveness of the COVID-19 vaccine in the human body goes through several stages. The COVID-19 vaccine activates the human adaptive immune response by delivering virus-specific antigens, such as the SARS-CoV-2 spike protein. Antigens are captured by dendritic cells and presented to T cells, initiating a dual immune response. Humoral immunity is mediated by B cells, which differentiate into plasma cells to produce neutralizing antibodies, mainly IgG, blocking the binding of the virus to the host cell's ACE2 receptor; cellular immunity relies on CD8+ T cells to recognize infected cells, directly eliminating the cells invaded by the virus by releasing perforin and granzymes, and inhibiting viral replication. Vaccination leads to the formation of long-lasting immune memory: Memory B cells persist in lymphoid tissues and can rapidly proliferate and differentiate into antibody-secreting cells upon subsequent exposure; memory T cells, including CD4+ and CD8+ subsets, provide continuous immune surveillance. Studies have confirmed that such memory responses last for at least 1 year. Even if serum antibody levels decline over time, they can effectively reduce the risk of severe illness and retain partial cross-protective ability against viral variants.

3. Literature Review

Throughout the research, this essay uses the following method. Firstly, Real-world evidence (RWE) is clinical evidence derived from real-world data (RWD). In vaccine evaluation, common real-world research methods include retrospective cohort studies, which compare the outcomes of vaccinated and unvaccinated individuals based on data such as electronic health records and vaccination registries; case-control studies, which assess vaccine exposure in cases and controls and calculate protective effects; self-controlled case series (SCCS), which compare the incidence of events during the risk period and non-risk period in individuals who have experienced adverse events, and are suitable for inferring the causal relationship of rare adverse reactions; and test-negative design (TND), which compares the vaccination rates of cases and test-negative controls in respiratory disease surveillance systems to evaluate vaccine effectiveness.

The assessment of mRNA vaccines operates at the intersection of established immunological principles and large-scale real-world surveillance data. Theoretically, these vaccines use lipid nanoparticles (LNPs) to deliver mRNA encoding target antigens [5]. Upon cellular uptake, the encoded antigens are expressed, subsequently triggering both innate and adaptive immune responses. Nucleotide modifications, such as pseudouridine substitution, mitigate the inherent immunogenicity of exogenous RNA. Concurrently, the LNP components themselves exhibit adjuvant properties, synergistically enhancing dendritic cell maturation and antigen

presentation [6]. This theoretical framework generates testable predictions regarding vaccine safety and efficacy: immunization should elicit robust neutralizing antibody titers and T-cell responses, while also carrying a potential risk of rare adverse events (e.g., myocarditis) attributed to excessive immune activation.

Empirical evidence rapidly validates and refines these theoretical expectations. Analysis of COVID-19 mRNA vaccines exemplifies this dynamic. Real-world data from systems such as the US V-safe surveillance platform and Israel's Clalit Health Services confirmed high protective efficacy (>90%) against the original viral strain [7]. However, they also identified an elevated incidence of myocarditis, particularly among young males (approximately 3-5 cases per million doses), a finding exceeding predictions derived primarily from preclinical models [8]. This prompted a scientific re-evaluation of factors, including the potential cardiac tropism of the LNP delivery system and sex-dependent differences in immune responses.

Regarding influenza mRNA vaccines, Moderna's phase III trial (mRNA-1010) demonstrated superior efficacy against matched strains compared to traditional inactivated vaccines. Nevertheless, real-world effectiveness against antigenically drifted strains requires ongoing validation. The dynamic interplay between theoretical models and empirical evidence underscores that while the mRNA platform's advantages are partially substantiated in real-world settings, it has also revealed unforeseen challenges, including immune evasion by variants and waning protection over time, necessitating further theoretical refinement.

A large body of literature on real-world research on mRNA vaccines has adopted similar entry points, methods, and research subjects. In terms of entry points, most studies focus on “the performance of vaccines in routine clinical practice”, which is different from the strictly controlled environment of randomized controlled trials (RCTs). Regarding research methods, the test - negative design (TND) is widely used to evaluate the effectiveness of COVID - 19 vaccines; the self - controlled case series (SCCS) is often used for causal inference of rare adverse events such as myocarditis; and retrospective cohort studies rely on electronic health records for large - scale analysis. The research subjects usually cover the entire age group, with subgroups of special populations (the elderly, pregnant women, and immunocompromised individuals) also set up.

Representative studies include: Haas used the data from Israel's Clalit and the TND method to evaluate the protective effect of BNT162b2 against the Delta variant[9]; Barda analyzed the vaccine safety through a national cohort study [10]; the v - safe and VSD networks of the US CDC continuously monitor adverse reactions. These studies are highly similar in methodology - they all rely on administrative health data, use propensity score matching to control confounding factors, and report the adjusted protective effect or risk ratio.

However, the similarities and differences among the studies warrant analysis. Similarities: All studies confirm that mRNA vaccines are highly effective in preventing severe illness/death, and local and systemic reactions are common but self-limited. The differences are as follows: 1) The effect estimates are greatly affected by the prevalence background of virus variants. For example, the effectiveness of preventing infection during the Omicron period (40%–60%) is much lower than that during the Delta period (>80%).

The inspiration these studies bring to me is as follows: The value of real-world evidence lies not only in supplementing the sample sizes of randomized controlled trials (RCTs), but, more importantly, in revealing the effect heterogeneity under “real - world conditions”. Regulatory factors such as population characteristics, virus mutations, and vaccination strategies often play a more significant role in shaping vaccine performance than the technical parameters of the vaccine itself.

Meanwhile, the choice of methodology directly affects the reliability of the conclusions. Although the test-negative design (TND) can control for biases related to medical behavior, it relies on accurate test results. The self-controlled case series (SCCS) can eliminate individual fixed confounding factors, but it requires a precise definition of the time window. In the future, reviews should critically integrate studies with different designs and avoid simply combining effect sizes.

Based on the above literature review and analysis, this paper presents a core argument. The safety and effectiveness of mRNA vaccines in the real world not only reflect the common characteristics of the technological platform but also exhibit specificity due to differences in the viruses themselves.

The platform commonalities refer to the high similarity in the adverse reaction profiles of COVID-19 mRNA vaccines and influenza mRNA vaccines. Local injection reactions are the most common, and systemic

reactions are mostly mild to moderate and self-limited. Although the risk of rare myocarditis is increased in young men, the overall incidence is extremely low, and the prognosis is good. In addition, both types of vaccines experience waning protection over time. The level of neutralizing antibodies decreases significantly within three to six months after vaccination, and booster immunization is required to maintain protection.

However, virus-specific characteristics cannot be ignored. The mutation rate of the COVID-19 virus is extremely high. The immune-escape ability shown by Omicron and its subtypes has sharply reduced vaccine effectiveness in preventing infection, from over 90% initially to 40%-60%. While the influenza virus also evolves continuously, the annual vaccine strain update mechanism is relatively mature. The rapid production advantage of the mRNA platform is expected to enable influenza vaccines to surpass traditional technologies in terms of strain matching. In other words, the incremental value of mRNA technology for influenza prevention and control may be greater than that for COVID-19, as the latter has shown that transmission can be difficult to block solely through vaccines.

Based on the above analysis, this paper proposes the following hypotheses for testing in subsequent chapters.

First, under real-world conditions, the protective effect of influenza mRNA vaccines against laboratory-confirmed influenza-related hospitalizations and severe cases will be significantly higher than that of traditional inactivated vaccines cultured in chicken embryos or cells. This advantage may be more pronounced, especially in the elderly population with immunosenescence, because the intrinsic adjuvant effect of mRNA vaccines can more strongly activate dendritic cells and germinal center responses.

Second, although the risk of myocarditis related to mRNA vaccines is difficult to eliminate, it is not an insurmountable defect of the technological platform. By optimizing the components of lipid nanoparticles, such as adjusting the type or proportion of ionizable lipids, extending the interval between two doses, or using a lower antigen dose in adolescents and young men, it is entirely possible to reduce the incidence of this rare adverse event to a level comparable to that of the background population.

What is more, the long-term follow-up data accumulated for COVID-19 mRNA vaccines will support their inclusion in the annual vaccination system for routine respiratory vaccines. After large-scale real-world use of the combined mRNA vaccine for COVID-19 and influenza, it is expected that no new safety signals will emerge that were not observed with the two vaccines used alone. The protective effect of the combined vaccine should not be lower than that of separate vaccinations. This expectation will be initially verified upon announcement of the results of the ongoing phase III clinical trials.

These arguments and hypotheses will be tested one by one in the subsequent chapters of this paper through the systematic integration of existing real-world evidence. At the same time, the gaps and deficiencies in the current evidence will be clearly identified to provide directional guidance for future research designs.

4. Discussion

This review systematically collated real-world evidence on the safety and efficacy of COVID-19 and influenza mRNA vaccines. The main findings are as follows: For both types of vaccines, the most common adverse reactions are mild-to-moderate local and systemic reactions. There is a clear risk of rare myocarditis with COVID-19 vaccines (especially in young men), while no significant myocarditis signal has been observed with influenza vaccines to date. In terms of efficacy, COVID-19 vaccines showed excellent protection against the original strain. Still, their effectiveness against the Omicron variant decreased significantly, while their effectiveness against severe illness remained relatively long-lasting. Influenza mRNA vaccines showed better protective efficacy than traditional vaccines in clinical trials, and more real-world data are needed.

The above findings can be explained at the immunological mechanism level. The rapid decline in protective efficacy is related to the relatively short half-life of neutralizing antibodies induced by mRNA vaccines. The relative persistence of memory B-cell and T-cell responses explains the continuous protection against severe illness. The clustering of myocarditis risk among young men may be related to the enhanced Th1-type immune response associated with testosterone and the off-target effects of the LNP delivery system on the myocardium. The advantages of influenza mRNA vaccines in the elderly population stem from the mRNA's intrinsic adjuvant effect, which can partially overcome the weakened vaccine response associated with immunosenescence.

Comparing the performance of the two types of vaccines, the core challenge for COVID-19 vaccines is the virus's rapid evolution and immune escape. In contrast, the traditional pain points for influenza vaccines are the low strain-matching rate and long production cycle. The rapid update capability of the mRNA platform may be more valuable for influenza vaccines than for COVID-19 vaccines, as the escape rate of COVID-19 variants has exceeded the rate of vaccine updates. This judgment suggests that the strategic focus of mRNA technology may shift from COVID-19 to other viral diseases that require a more rapid response.

This review has the following limitations: The high heterogeneity of the included studies (different populations, variants, and outcome definitions) limits direct comparison. The real-world evidence for influenza mRNA vaccines is still mainly from clinical trials, lacking large-scale post-marketing surveillance data. Most studies have a follow-up time of less than 2 years, and the long-term safety is unclear. Future research should prioritize post-marketing safety monitoring of influenza mRNA vaccines, explore LNP optimization strategies to reduce the risk of myocarditis, and promote real-world evaluation of COVID-19-influenza combination vaccines.

5. Conclusion

This review systematically integrated real-world evidence on the safety and efficacy of COVID-19 and influenza mRNA vaccines. Overall, both types of vaccines showed good safety and significant protective effects. Common adverse reactions include mild-to-moderate local and systemic reactions that are self-limiting. Although myocarditis associated with COVID - 19 mRNA vaccines is a rare and serious adverse event, its incidence is low, and the prognosis is good. No clear myocarditis signal has been found in influenza mRNA vaccines to date. In terms of efficacy, COVID-19 vaccines showed excellent protection against the original strain, but their effectiveness against the Omicron variant decreased. Booster vaccination can effectively restore the protection level. Influenza mRNA vaccines are superior to traditional vaccines in clinical trials and are especially suitable for the elderly population. The advantages of the mRNA technology platform (rapid R&D, flexible updates, and strong immunogenicity) have been demonstrated in both types of vaccines. However, the immune-escape rate of COVID-19 variants poses a significant challenge to vaccine updates.

Based on this, the following constructive suggestions and directions for future virus research and vaccine development are proposed.

In the field of virus evolution research and vaccine design, it is necessary to establish a shared epitope database for coronaviruses and influenza viruses, use artificial intelligence to predict conserved epitopes, and design chimeric antigen mRNA vaccines to cover future variants. At the same time, a dynamic evolutionary tree analysis system for viral spike proteins should be developed to identify mutation hotspots under vaccine pressure and to establish an early warning system for escape mutations.

In terms of technological innovation, the development organization targeted lipid nanoparticles to reduce the risk of myocarditis associated with mRNA vaccines. They designed a two-stage expression vector and utilized miRNA regulatory elements to enhance immune persistence.

The real-world evidence system needs reform. A multidimensional evidence integration model should be established that leverages blockchain technology to integrate diverse data. The V-Safe 2.0 system should be developed to conduct dynamic risk assessment using wearable devices and GIS systems.

Cross-species prevention strategies should focus on developing broad-spectrum mRNA vaccines for respiratory viruses, establishing an epidemiological-meteorological coupling model, and formulating differentiated booster vaccination strategies for specific regions.

In translational medicine, establish a modular vaccine platform certification system to shorten the development cycle for new vaccines. Promote the development of cell-free mRNA synthesis technology to reduce production costs and improve vaccine accessibility.

In the future, real-world monitoring of influenza mRNA vaccines should be strengthened, the LNP delivery system should be optimized to reduce rare risks, and the R&D and application of combination vaccines should be promoted to fully realize the potential of mRNA technology in the prevention and control of respiratory infectious diseases.

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Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgment

This paper is an output of the science project.

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