On adverse events of mRNA vaccine - mechanisms, risks and management

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1. Introduction

Artificial active immunization has traditionally relied on vaccines using inactivated pathogens or protein subunits, which face scalability challenges during pandemics. mRNA vaccine technology offers rapid antigen design and scalable production, enabling accelerated deployment during the COVID-19 crisis. While mRNA platforms represent a transformative advancement, their emergency use revealed safety concerns linked to immunogenicity risks in genetically susceptible individuals. This review categorizes adverse events (AEs) into three mechanistic domains: individual susceptibility (e.g., sex-specific responses), delivery system components (e.g., LNP-induced inflammation), and mRNA design. By integrating these insights, we aim to inform targeted strategies for next-generation vaccine optimization.

2. Methods & Results

In our study, we conducted preliminary screening using the search term "mRNA vaccine adverse" in the abstract, title, and keyword fields across the Science Direct, PubMed, Springer Link, and Web of Science databases, with the publication date range set from January 2019 to April 2025. The preliminary screening criteria included articles spanning all years and reports of AEs from various global agencies such as EudraVigilance in Europe, VAERS in the United States, and CANVA in Canada.

Overview of mRNA Vaccine Candidates, Clinical Trial Stages, and Advantages, for Targeted Pathogens

Pathogen	Clinical Trial Phase	Advantages	References
Ebola fever	Pre-clinical	Demonstrates the ability to induce durable antibody responses and T-cell immunity against key Ebola glycoproteins in animal models, with potential for rapid deployment during outbreaks. mRNA vaccines against EBOV elicited robust expression of IFN-γ and IL-2 by CD8+ and CD4+ T-cells	[115, 135]
Lassa fever	Pre-clinical	Induces robust neutralizing antibody responses targeting the Lassa virus glycoprotein and elicits cross-reactive immunity across multiple strains in preclinical studies	[116, 117]
HIV	I	Successfully elicits broadly neutralizing antibodies and CD8+ T-cell responses targeting conserved regions of the virus, with early results showing promise for overcoming strain variability	[118, 119]
Chikungunya	I	Safe and well-tolerated; induces high titers of neutralizing antibodies that correlate with protection and show durability up to 12 months post-vaccination in early trials	[120–122]
Zika	II	Nucleoside-modified mRNA-LNP demonstrates rapid and robust induction of neutralizing antibodies that protect against Zika virus challenge in animal models and provide cross-protection with related flaviviruses in humans	[123–126]
Influenza A & B	II	Achieves strain-specific antibody responses and significant cross-reactivity across different influenza strains; offers the potential for universal flu vaccine development	[75, 84, 127, 128]
Respiratory syncytial virus (RSV)	III	83.7% effective in a late-stage trial at preventing at least two symptoms of the cold-like disease caused by the virus in adults aged 60 years and over	[129, 130]
SARS-CoV-2	IV	Highly effective (up to 95% efficacy in preventing symptomatic COVID-19); robust cellular and humoral responses, with significant protection against severe disease and hospitalizations	[85, 131–134]

Adverse Event Profiles by Organ Systems

- Cardiovascular : myocarditis , thrombosis
- Neurological: headaches, Bell's palsy, functional disorders
- Mucocutaneous: urticaria, vitiligo, injection-site reactions
- Inflammatory : thyroiditis , IgA nephropathy , multisystem inflammation

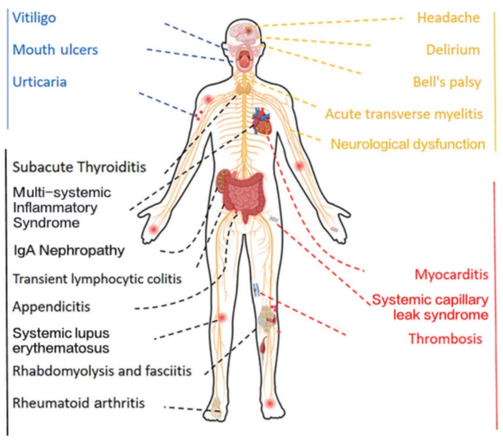
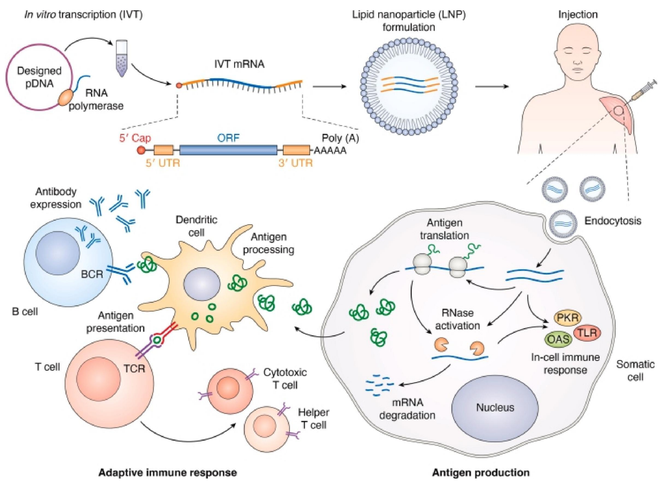


Fig. 1. AEs map of Human body distribution. Different colors in the figure represent different AEs categories by system and organs. Red represents cardiovascular AEs, yellow represents neurological AEs, blue represents mucocutaneous and connective tissue disorders, and black represents inflammatory AEs. The dashed guide line indicates the affected area of Aes.

Three Mechanistic Axes of Aes

1) Host Susceptibility
- Sex-specific immunity (testosterone - linked sST2 elevation and myocarditis risk in males)
- Age-related immune dysregulation
- Genetic predisposition and autoimmune backgrounds
- Life style and racial/ ethnic factors influencing immune variation



2) Delivery System Interactions
- Lipid nano particle (LNP)-induced inflammation and bio distribution-related toxicity
- PEG-associated hypersensitivity
- Local vs systemic innate immune activation
- Off-target tissue exposure (e.g. liver, cardiovascular system)

3) mRNA Molecular Design
- dsRNA impurities and uncapped transcripts triggering PRR signaling
- Molecular mimicry between viral antigens and human proteins
- Codon optimization and nucleoside modification affecting immune responses
- Translational efficiency vs reactogenicity balance

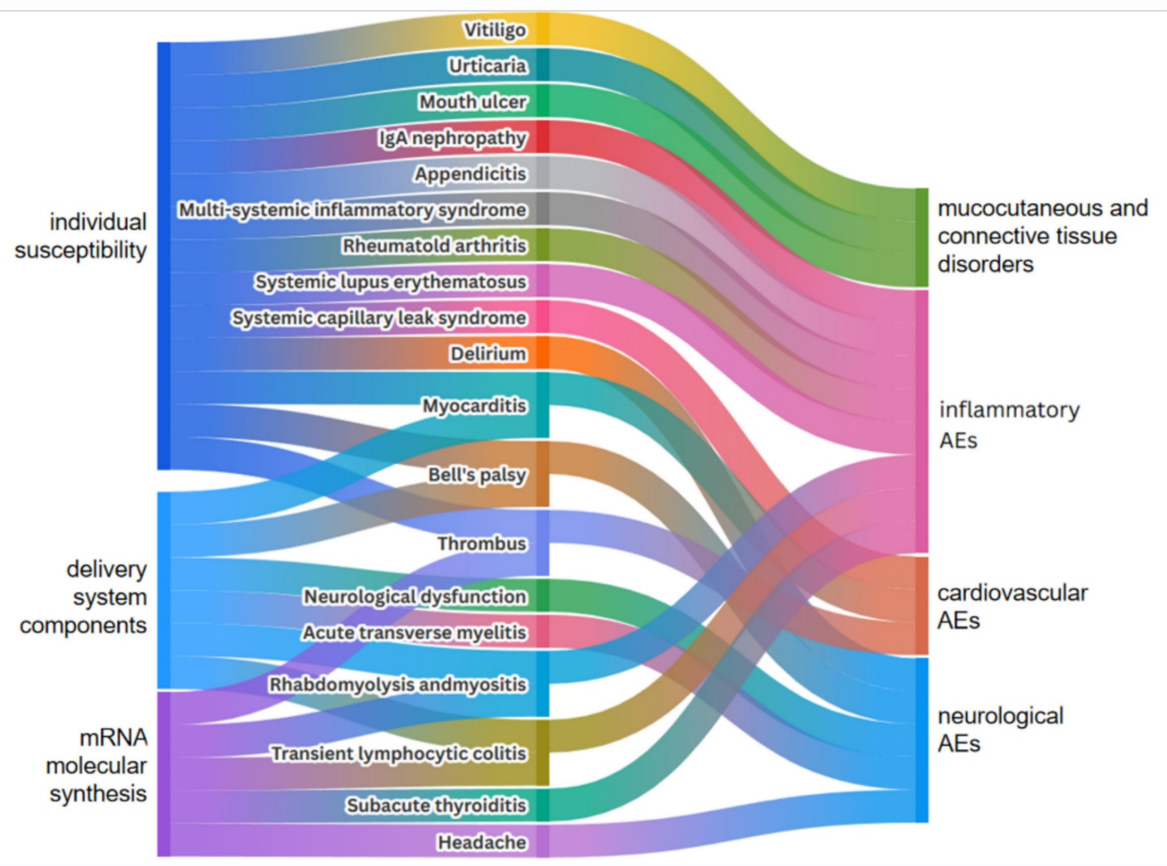


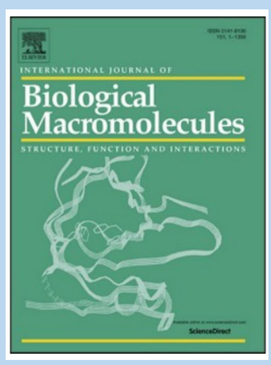
Fig. 2. Sankey diagram of mechanisms, AEs and human tissues. The relationships among AEs, inducing factors of mRNA vaccines, and the clinic categories, are elucidated though the connections.

Mechanism-Driven Optimization Roadmap

- Improve IVT purity and reduce dsRNA contaminants
- Engineer biodegradable, tissue-targeted lipid vectors
- Tune adjuvanticity to avoid overactivation of innate immunity
- Develop biomarkers for pre-vaccination risk stratification
- Design population-adapted dosing regimens
- Expand real-world safety monitoring networks

3. Conclusion

Although adverse events (AEs) from mRNA vaccines are rare, they require close monitoring due to potential health impacts and the risk of undermining public confidence, which can contribute to vaccine hesitancy. At the same time, these AEs drive innovation in mRNA vaccine technology, with mechanisms such as molecular mimicry, direct neurotoxicity, and aberrant immune responses. Overall, despite occasional AEs, vaccination remains the most effective way to prevent disease, achieve herd immunity, and control pandemics, making continued research on AEs essential for maintaining public trust and vaccination success.



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