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Advances in Bivalent Hemorrhagic Fever with Renal Syndrome Vaccine Development

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ABSTRACT

Hemorrhagic fever with renal syndrome (HFRS), caused by hantaviruses of the Orthohantavirus genus, is a zoonotic disease with significant morbidity and mortality, particularly in Asia and Europe. Vaccination remains the most effective strategy for HFRS prevention. This review summarizes recent advances in bivalent HFRS vaccine development, focusing on improved immunogenicity, safety, and manufacturing technologies. We discuss the evolution of vaccine platforms, including inactivated, recombinant, and virus-like particle (VLP) vaccines, as well as emerging strategies such as mRNA and nanoparticle-based approaches. Challenges in global vaccine accessibility and future directions for HFRS vaccine research are also highlighted.

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Abbreviations: HFRS, Hemorrhagic Fever with Renal Syndrome; VLP, Virus-Like Particle; HTNV, Hantaan Virus; SEOV, Seoul Virus

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Introduction

HFRS, a severe viral disease transmitted primarily by rodents, is endemic in regions with high rodent populations, including China, Korea, Russia, and parts of Europe. The disease is caused by hantaviruses, with Hantaan virus (HTNV) and Seoul virus (SEOV) being the most common pathogens in Asia. Vaccination has been a cornerstone of HFRS control, particularly in endemic areas. Traditional inactivated vaccines have demonstrated efficacy but face limitations in immunogenicity, production scalability, and global accessibility. Recent advances in vaccine technology have paved the way for the development of next-generation bivalent HFRS vaccines, offering improved protection and broader applicability [1,2].

1. Technical route for the development of hemorrhagic fever vaccines

1.1 Inactivated Vaccines

Inactivated HFRS vaccines, first developed in the 1980s, remain the primary preventive measure in endemic regions, particularly in China. These vaccines are produced by culturing hantavirus in cell lines (e.g., Vero cells) and inactivating the virus with formalin or β-propiolactone. While effective, inactivated vaccines have limitations, including the need for multiple doses, potential safety concerns related to residual viral components, and challenges in scaling production to meet global demand [3].

1.2 Recombinant Protein Vaccines

Recombinant protein vaccines represent a significant advancement in HFRS vaccine development. These vaccines utilize viral surface glycoproteins (Gn and Gc) expressed in heterologous systems (e.g., yeast, insect cells, or mammalian cells) to elicit neutralizing antibodies. Recombinant vaccines offer improved safety profiles and simplified production processes compared to inactivated vaccines. However, challenges remain in achieving consistent immunogenicity and cross-protection against multiple hantavirus strains [4].

1.3 Virus-Like Particle (VLP) Vaccines

VLP vaccines mimic the structure of native viruses without containing viral genetic material, offering a safe and immunogenic alternative. VLPs are produced by expressing viral structural proteins in host cells, which self-assemble into virus-like particles. Recent studies have demonstrated the potential of VLP-based HFRS vaccines to induce robust humoral and cellular immune responses, with promising results in preclinical and early clinical trials [5].

2. Recent Advances in Bivalent HFRS Vaccines

2.1 Bivalent Inactivated Vaccines

Bivalent inactivated vaccines targeting both HTNV and SEOV have been developed to address the co-circulation of these viruses in endemic regions. These vaccines combine

inactivated HTNV and SEOV antigens, providing broader protection compared to monovalent vaccines. Recent clinical trials have demonstrated high efficacy and safety, with seroconversion rates exceeding 90% in vaccinated individuals [6].

2.2 Recombinant Bivalent Vaccines

Recombinant bivalent vaccines have been designed to express Gn and Gc glycoproteins from both HTNV and SEOV in a single formulation. Advances in protein engineering and adjuvant development have enhanced the immunogenicity of these vaccines, with studies showing robust neutralizing antibody responses against both viral strains. The use of novel adjuvants, such as aluminum hydroxide and oil-in-water emulsions, has further improved vaccine efficacy [7].

2.3 mRNA and Nanoparticle-Based Vaccines

Emerging technologies, including mRNA and nanoparticle-based vaccines, hold promise for HFRS prevention. mRNA vaccines, which encode viral antigens, have demonstrated rapid development and scalability, as demonstrated by their success in COVID-19 vaccine development. Nanoparticle-based vaccines, which mimic viral structures, have shown potential to induce strong immune responses with fewer doses. While still in early stages of development, these platforms offer exciting opportunities for next-generation HFRS vaccines [8].

3.Challenges in HFRS Vaccine Development and Global Accessibility

About the vaccine efficacy against diverse Strains, Hantaviruses exhibit significant genetic diversity, posing challenges for vaccine design. Ensuring cross-protection against multiple hantavirus strains remains a critical goal for bivalent and multivalent vaccines [9].

About the manufacturing and distribution, The production of HFRS vaccines, particularly those requiring cell culture systems, is resource-intensive and may limit global accessibility. Developing cost-effective and scalable manufacturing processes is essential for expanding vaccine coverage in endemic regions [10].

About the public health infrastructure,In many endemic regions, limited public health infrastructure and vaccine distribution networks hinder the implementation of vaccination programs. Strengthening healthcare systems and increasing public awareness are critical for maximizing vaccine impact [11].

4. Outlook of HFRS Vaccine

Bivalent HFRS vaccines represent a significant advancement in the prevention of this zoonotic disease. Recent progress in vaccine technology has improved immuno-genicity, safety, and scalability, offering hope for broader vaccine coverage in endemic regions. However, challenges remain in ensuring cross-protection against diverse

hantavirus strains and improving global vaccine accessibility. Continued research and innovation, coupled with global collaboration, will be critical for achieving the goal of HFRS eradication.

Future research should focus on developing multivalent vaccines that target additional hantavirus species, such as Puumala virus (PUUV) and Dobrava virus (DOBV), which are prevalent in Europe and other regions [12].

Exploring novel vaccine platforms, including mRNA, DNA, and viral vector-based vaccines, could lead to the development of more effective and easily producible HFRS vaccines [13].

Enhancing international collaboration and research efforts is essential for addressing the global burden of HFRS. Establishing global surveillance systems and sharing data on hantavirus epidemiology and vaccine efficacy will support the development of next-generation vaccines [14].

Competing interests

The authors declare all financial and non-financial competing interests.

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