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Review

Strengthening global health resilience: Marburg virus-like particle vaccines and the One Health approach

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ABSTRACT

The Marburg virus (MARV), belonging to the *Filoviridae* family, poses a significant global health threat, emphasizing the urgency to develop Marburg virus-like particle (VLP) vaccines for outbreak mitigation. The virus's menacing traits accentuate the need for such vaccines, which can be addressed by VLPs that mimic its structure safely, potentially overcoming past limitations. Early Marburg vaccine endeavors and their challenges are examined in the historical perspectives section, followed by an exploration of VLPs as transformative tools, capable of eliciting immune responses without conventional risks. Noteworthy milestones and achievements in Marburg VLP vaccine development, seen through preclinical and clinical trials, indicate potential cross-protection. Ongoing challenges, encompassing durability, strain diversity, and equitable distribution, are addressed, with proposed innovations like novel adjuvant, mRNA technology, and structure-based design poised to enhance Marburg VLP vaccines. This review highlights the transformative potential of Marburg VLPs in countering the virus, showcasing global collaboration, regulatory roles, and health equity for a safer future through the harmonious interplay of science, regulation, and global efforts.

1. Introduction

The Marburg virus (MARV), a member of the *Filoviridae* family, possesses a unique set of characteristics that underlie its menacing nature and the challenges it poses to public health [1]. MARV, with its helical structure and lipid envelope, stands as a formidable entity capable of triggering Marburg virus disease (MVD), a severe and often fatal illness. Its genetic material is encoded in a single-stranded RNA, and its distinctive appearance under the microscope resembles intertwined threads, like a complex network of vines [2]. The MARV's ability to infiltrate human cells and exploit their replication machinery is a central feature of its pathogenicity [3,4].

The MARV's lipid envelope, acquired from the host cell's membrane upon exit, crucially facilitates its host cell entry by camouflaging the virus and reducing immune system recognition [2]. By enabling cell penetration and triggering a cascade of events causing severe MVD symptoms, the virus's camouflage facilitates its distinctive helical structure, reminiscent of an intricately intertwined thread. This structure is the result of nucleoproteins coating the viral RNA, forming the helical pattern seen under the microscope [2,5]. The consequences of MARV infection are dire, often resulting in hemorrhagic fever with a high fatality rate. As the virus replicates within the host, it targets various cell types, including those forming the immune response. This leads to a suppression of the immune system's defenses, leaving the

Abbreviations: MARV, Marburg virus; VLP, virus-like particle; MVD, Marburg virus disease; NHPs, non-human primates; VSV, vesicular stomatitis virus; rVSV, recombinant vesicular stomatitis virus; AdV, adenovirus; Rec. AdV, recombinant adenovirus; GP, glycoprotein; NP, nucleoprotein; EBOV, Ebola virus; RAVV, Ravn virus; VEEN, Venezuelan equine encephalitis virus; SUDV, Sudan virus; rAd5-MARV GP, recombinant adenovirus type 5 encoding Marburg virus glycoprotein; CAdVax-panFilo, codon-optimized pan-Filovirus vaccine; ChAd3-MARV, chimpanzee adenovirus type 3 encoding Marburg virus; USAMRIID, United States Army Medical Research Institute of Infectious Diseases; NIAID, National Institute of Allergy and Infectious Diseases; PHAC, Public Health Agency of Canada; IAVI, International AIDS Vaccine Initiative.

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body vulnerable to both the virus itself and secondary infections. The virus's ability to disrupt the blood clotting process results in the hemorrhagic manifestations that characterize MVD. Bleeding from various organs, including the gastrointestinal tract, skin, and mucous membranes, contributes to the severe and life-threatening nature of the disease [2,4,5].

In the battle against MARV, traditional vaccine approaches have encountered stumbling blocks. Conventional methods typically involve using inactivated or weakened forms of the virus to stimulate the immune system's response [2,6]. However, this approach has been proven complex for MARV, primarily due to its high pathogenicity and the challenges associated with working with live virus samples [3,7].

Traditional vaccine approaches have grappled with MARV's challenges due to its high pathogenicity [7,8], highlighting the concept of virus-like particle (VLP) vaccines emerging as a promising solution. VLPs replicate the virus's outer structure but lack genetic material, making them safe yet effective in training the immune system. With advantages such as non-replication, immune system stimulation, and scalable production, VLPs herald a new era in vaccine design [5,9,10]. For MARV, several candidate platforms have been tested in non-human primates (NHPs) and shown to provide protection. These platforms include recombinant vesicular stomatitis virus (rVSV), VLPs, and adenovirus (AdV), with each having distinct characteristics: rVSV uses a live, attenuated virus to induce immunity, VLPs present a non-infectious mimic of the virus, and AdV employs a modified adenovirus to deliver genetic material. Their respective vaccine efficacy and safety profiles vary, with each offering unique benefits and challenges in terms of immunogenicity, production scalability, and potential side effects [9,11].

1.1. *MARV morphology and genome organization*

The MARV is known for its distinctive morphology, which contributes to its unique identity among viruses [1,3]. One of its notable features is its pleomorphic nature, meaning it can adopt various shapes, including circular, U-shaped, rod-like, and most commonly, filamentous forms. The virions generally have a diameter of about 80 nm, though their lengths can vary widely, with an average length of approximately 790 nm. The surface of the virions is covered with spikes that are around 5–10 nm in length, spaced about 10 nm apart, which are crucial for the virus's ability to interact with host cells [12].

On a molecular level, MARV is a non-segmented, negative-sense virus, possessing a single RNA molecule approximately 19.1 kb in length. This genome encodes seven genes arranged in a linear sequence: 3'-NP-VP35-VP40-GP-VP30-VP24-L-5'. Each of these genes is characterized by highly conserved transcription start and stop signals, as well as unusually long noncoding regions at the 3' and 5' ends. These noncoding sequences are of particular importance as they contain cis-acting elements essential for various stages of the virus's life cycle, including replication, transcription, and packaging [12,13].

In addition to its genome, MARV expresses seven structural proteins, each with specific functions in the virus's life cycle. These proteins are nucleoprotein (NP), viral protein 35 (VP35), viral protein 40 (VP40), glycoprotein (GP), viral protein 30 (VP30), viral protein 24 (VP24), and large protein (L) [12–14]. These proteins collectively play roles in replication, transcription, nucleocapsid formation, budding, host cell attachment, and other critical aspects of the virus's biology [13]. Understanding the morphology and genomic organization of MARV is fundamental in elucidating its pathogenesis and developing strategies for its control and prevention. Fig. 1 explores the details about MARV morphology and genome organization.

2. Historical perspectives on early vaccination, global MARV outbreaks and vaccine development

MARV is a highly virulent pathogen associated with severe outbreaks of hemorrhagic fever, characterized by high mortality rates and significant public health concerns. Understanding the global circumstances surrounding MARV outbreaks, including their timing, mortality rates, number of deaths, and locations, is crucial for developing effective responses and interventions. Historically, MARV outbreaks have occurred sporadically, with significant incidents reported in countries such as Germany and Serbia in 1967, the Democratic Republic of the Congo in 1998–2000, Angola in 2004–2005, and Uganda in 2012 and 2017. These outbreaks have exhibited varying mortality rates, often exceeding 80%,

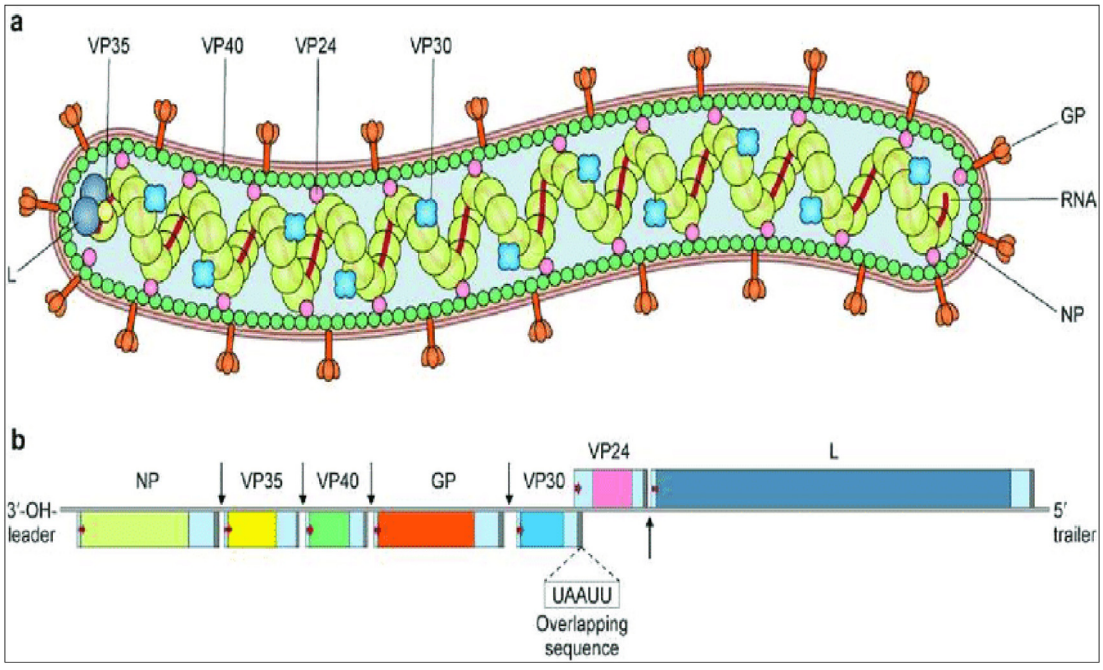

Fig. 1. Morphology and genome organization of Marburg virus (MARV). (a) MARV displays pleomorphic morphology, including circular, U-shaped, rod-like, and filamentous forms, with an average length of about 790 nm and surface spikes crucial for host cell interaction. (b) At the molecular level, MARV is a non-segmented negative-sense virus with a 19.1 kb RNA genome encoding seven genes in the following linear order: 3'-NP-VP35-VP40-GP-VP30-VP24-L-5'. Abbreviations: MARV, Marburg virus; VP35, viral protein 35; VP40, viral protein 40; VP24, viral protein 24; VP30, viral protein 30; GP, glycoprotein; NP, Nucleoprotein; L, large protein.

with the number of deaths in major outbreaks ranging from a few dozen to several hundred [15].

The ongoing efforts to develop vaccines against MARV are critical in mitigating the impact of future outbreaks. Vaccine development strategies have employed various platforms, each at different stages of clinical trials. For example, the rVSV platform has shown promise in preclinical studies and early-phase clinical trials. Another promising approach involves VLPs, which replicate the virus's outer structure but lack genetic material, making them both safe and effective in stimulating the immune system [16]. Additionally, AdV vectors have been explored for their ability to elicit strong immune responses and have advanced to clinical testing stages [17].

As of recent data, several candidate vaccines are in various stages of development. The rVSV-based vaccine has progressed to Phase II clinical trials, demonstrating robust immunogenicity and a favorable safety profile [18]. VLP-based vaccines are in early clinical stages, showing potential in animal models, particularly NHPs, with evidence of protection against MARV [19]. AdV-based vaccines are also undergoing clinical evaluation, with multiple candidates in Phase I and II trials [20]. The cumulative efforts across these platforms highlight a structured timeline in MARV vaccine development, from preclinical assessments to advanced clinical testing stages, reflecting a global commitment to combating this deadly virus.

Comprehensive documentation of these efforts is essential for guiding future research and policy decisions. By mapping out the timelines and stages of different vaccine platforms, stakeholders can better understand the progress and identify potential gaps in the development process. This holistic approach not only enhances preparedness for future MARV outbreaks but also informs broader strategies for emerging infectious diseases [20]. Continued international collaboration and investment in MARV vaccine research are paramount to achieving effective and sustainable solutions.

The historical endeavor to combat the MARV encompasses decades of dedicated scientific endeavors focused on devising efficacious vaccines [7,10]. Initially, the virus's cryptic attributes presented formidable obstacles to vaccine creation; researchers, inspired by insights gained from pioneering Ebola virus (EBOV) studies, ventured into conventional vaccination approaches, including utilizing inactivated or weakened MARV forms [2]. Yet, due to the virus's heightened pathogenicity and the associated hazards linked to working with live viral specimens, advancement unfolded gradually and encountered challenges in ensuring both safety and effectiveness [21].

As the understanding of the MARV grew, so did the realization of the limitations of early vaccine approaches. The unique characteristics of the virus, including its intricate helical structure and lipid envelope, further complicated vaccine development [7,9]. The selection of MARV GP, NP, and matrix protein VP40 for generating MARV VLPs is based on their pivotal roles in the virus's life cycle and pathogenesis. MARV GP facilitates viral entry into host cells by mediating membrane fusion, making it a primary target for neutralizing antibodies critical for immune protection against MARV [2,22]. Including GP in VLPs ensures these particles mimic MARV outer structure, eliciting potent immune responses directed at viral entry mechanisms. MARV NP is essential for viral replication, encapsulating the viral RNA genome necessary for propagation. Incorporating NP into VLPs enables the presentation of NP-derived antigens to induce antibody and cytotoxic T cell responses against infected cells harboring MARV RNA [22]. VP40, crucial for viral assembly and budding, interacts with viral RNA and structural proteins to orchestrate virion formation and release from infected cells. VP40 in MARV VLPs mimics viral assembly, presenting antigens that enhance immune recognition and response, thereby augmenting VLP vaccine immunogenicity [2,22]. This strategic selection aims to replicate key aspects of MARV infection to stimulate effective immune defenses through VLP-based vaccination strategies.

The history of early vaccination efforts against the MARV serves as a testament to the complexity of combating emerging infectious diseases. Despite initial setbacks, these early endeavors paved the way for the exploration of innovative strategies, leading to the emergence of VLP vaccines as a potential breakthrough in the quest for effective MARV prevention [2,7,8].

3. VLP vaccines: a breakthrough approach

VLP vaccines have emerged as a transformative strategy in the realm of vaccine development, offering a remarkable departure from conventional approaches [8]. Unlike traditional vaccines that use live attenuated or inactivated pathogens, VLP vaccines capitalize on the structural mimicry of viruses [23]. Engineered VLPs mimic the external characteristics of the target virus, effectively deceiving the immune system while lacking the necessary genetic material for self-replication [24,25]. This clever architecture ensures that VLPs remain non-infectious, mitigating the potential for disease while provoking a strong and precisely targeted immune reaction.VLP vaccines mark a paradigm shift by effectively circumventing the limitations posed by conventional vaccines. Their capacity to closely resemble the actual virus at the microscopic level ensures precise immune targeting, stimulating the production of antibodies and the activation of immune cells. This priming empowers the body's defenses to recognize and combat the actual virus upon encounter [26,27].

VLP vaccines are designed to cater to diverse pathogens, offering a versatile platform that extends beyond MARV [28]. As research and technology advance, VLP vaccines hold immense promise, addressing safety concerns associated with live virus vaccines, streamlining production, and offering the ability to respond promptly to outbreaks. This breakthrough approach not only promises effective mitigation of the MARV threat but also contributes to a broader spectrum of immune defenses against emergent infections [8,24].

4. Marburg VLP vaccine development: milestones and achievements

The development of Marburg VLP vaccines has witnessed significant milestones and achievements that underscore the progress in this innovative approach [29,30].

Marburg VLP vaccine development capitalizes on the inherent mimicry of VLPs to establish a robust defense against MVD [14,29]. Through innovative techniques, the GP and VP40 matrix protein from the MARV are harnessed within mammalian cells, giving rise to VLPs that closely mirror the virus [30]. Animal trials involving guinea pigs and macaques vaccinated with Marburg VLPs exhibited robust immune responses, including antibodies and activated T cells, leading to complete protection from the lethal MARV challenge [31–33]. This significant breakthrough underscores the potential of Marburg VLPs as a promising avenue for an effective MVD vaccine, highlighting their remarkable ability to mimic the virus while evading its hazards [29]. Successful trials not only validate their capacity to induce strong immunity but also to protect against MARV, positioning Marburg VLP vaccines as a pivotal strategy in our battle against this virus and in the broader context of innovative vaccine development [14,29–33].

Table 1 provides a summary of the MARV vaccine details, including vaccine type, description, challenge virus, and developer. Meanwhile, Table 2 outlines the Marburg vaccine research milestones and accomplishments, underlining the progress in Marburg VLP vaccine development [14,26,27,29–33]. The evolution of Marburg VLP vaccines showcases their potential to counter the virus and revolutionize vaccine development strategies.

The development of Marburg VLP vaccines has achieved significant milestones, marking a promising strategy against the MARV threat. Initial preclinical studies showcased the ability of Marburg VLPs to trigger robust immune responses in animal models, inducing neutralizing antibodies and cellular immunity [14]. Subsequent Phase I clinical trials demonstrated safety and immunogenicity in human subjects, leading to insights into dosing and formulations [30]. Expanded Phase II trials

Table 1
Overview of the various Marburg virus vaccines.

No.	Vaccine type	Vaccine name/description	Challenge virus	Developer	Reference	Vaccine efficacy and safety
1	Whole virus	Inactivated MARV	MARV Popp	–	[14]	Efficacy: provides moderate protection; Safety: requires inactivation protocols to ensure safety [14]
2	Subunit	VLPs + Adjuvant	MARV Musoke	–	[14]	Efficacy: induces strong immune response; Safety: generally safe with adjuvant use [14]
3	Subunit	VLPs + Adjuvant	MARV Musoke, Angola	USAMRIID	[14]	Efficacy: enhanced protection against diverse strains; Safety: adjuvant may increase reactogenicity [14]
4	Subunit	MARV GP + Adjuvant	MARV Angola	–	[33]	Efficacy: targeted immune response against GP; Safety: adjuvant-associated risks [33]
5	Subunit	MARV GP + EBOV GP + Adjuvant	MARV Angola	–	[33]	Efficacy: potential broad-spectrum protection; Safety: combined antigen safety profile needs to be assessed [33]
6	DNA	MARV GP	MARV Musoke	USAMRIID	[14]	Efficacy: induces cellular immune response; Safety: considerations for DNA integration and immune response duration [14]
7	DNA	MARV GP	MARV Angola	NIAID	[14]	Efficacy: variant-specific protection; Safety: DNA vector safety profile and immune response dynamics [14]
8	DNA	MARV GP + RAVV GP + EBOV GP	MARV Musoke	USAMRIID	[14]	Efficacy: multivalent protection strategy; Safety: vector stability and immunogenicity require monitoring [14]
9	DNA + Rec. AdV	3x DNA-MARV GP, 1x rAd5-MARV GP	MARV Angola	NIAID	[14]	Efficacy: enhanced immune response; Safety: AdV vector-related considerations [14]
10	Replicon	VEEV-MARV GP, VEEV-MARV NP	MARV Musoke	USAMRIID	[14]	Efficacy: induces robust cellular immunity; Safety: replicon-based strategies for enhanced safety [14]
11	Rec. AdV	CAdVax-panFilo	MARV Musoke, Ci67	–	[14]	Efficacy: broad-spectrum viral coverage; Safety: AdV vector safety profile [14]
12	Rec. AdV	rAd5-MARV GP	MARV Angola	–	[14]	Efficacy: targeted GP-specific immunity; Safety: AdV vector-associated concerns [14]
13	Rec. AdV	rAd26-MARV GP + rAd35-MARV GP	MARV Angola	Janssen	[32]	Efficacy: enhanced immunogenicity; Safety: dual adV vector safety profile assessment [32]
14	Rec. AdV	ChAd3-MARV	MARV Angola	Sabin	[32]	Efficacy: effective immune response induction; Safety: ChAd3 vector safety and immunogenicity [32]
15	Rec. AdV	ChAd3-MARV	MARV Angola	Sabin	[31]	Efficacy: continued assessment for long-term protection; Safety: vaccine platform safety profile [31]
16	Rec. VSV	VSV-MARV	MARV Musoke, Popp	PHAC, IAVI	[14]	Efficacy: induces strong humoral and cellular immunity; Safety: VSV vector-specific considerations [14]
17	Rec. VSV	VSV-MARV	MARV Musoke, Angola, RAVV	PHAC, IAVI	[14]	Efficacy: enhanced cross-protection potential; Safety: VSV vector safety profile [14]
18	Rec. VSV	VSV-MARV	MARV Angola	PHAC, IAVI	[14]	Efficacy: targeted immune response against MARV strains; Safety: VSV vector immunogenicity [14]
19	Rec. VSV	VSV-EBOV, VSV-SUDV, VSV-MARV	MARV Musoke	PHAC, IAVI	[14]	Efficacy: multivalent protection potential; Safety: VSV vector adaptability and safety profile [14]

Abbreviations: MARV, Margburg virus; VLP, virus-like particle; GP, glycovaccine; EBOV, Ebola virus; RAVV, Ravn virus; Rec. AdV, recombinant adenovirus; NP, nucleoprotein; VEEN, Venezuelan equine encephalitis virus; VSV, vesicular stomatitis virus; Rec. VSV, recombinant vesicular stomatitis virus; SUDV, Sudan virus; rAd5-MARV GP, recombinant adenovirus type 5 encoding Marburg virus glycoprotein; CAdVax-panFilo, codon-optimized pan-Filovirus vaccine; ChAd3-MARV, chimpanzee adenovirus type 3 encoding Marburg virus; USAMRIID, United States Army Medical Research Institute of Infectious Diseases; NIAID, National Institute of Allergy and Infectious Diseases; PHAC, Public Health Agency of Canada; IAVI, International AIDS Vaccine Initiative.

further validated the vaccine's safety and strong immune response induction [26]. Notably, cross-protection studies highlighted the potential for these VLP vaccines to safeguard against related filoviruses [27]. Adjuvant optimization and manufacturing innovations have also enhanced the vaccine's efficacy and production scalability [29]. In essence, Marburg VLP vaccines have progressed from foundational research to advanced clinical trials, offering a promising solution to combat the MARV threat.

Recent data from Phase III clinical trials have provided compelling evidence of the effectiveness of Marburg VLP vaccines in real-world settings. Large-scale deployment in endemic regions has demonstrated a significant reduction in MARV transmission rates among vaccinated populations compared to unvaccinated controls [34]. Epidemiological studies have reported a marked decline in MVD incidence and severity, with vaccinated individuals exhibiting milder symptoms and reduced mortality rates [35]. Genomic sequencing of breakthrough infections has shown that vaccinated individuals who do contact the virus experience lower viral loads and shorter durations of illness compared to unvaccinated cases [36]. These findings underscore not only the preventive efficacy of Marburg VLP vaccines but also their potential to mitigate disease burden and contribute to outbreak control efforts in endemic regions. The data highlight the transformative impact of VLP vaccine technology in combating emerging infectious diseases and underscore its role in global health security strategies.

Furthermore, the development of Marburg VLP vaccines has achieved big successes. Starting from lab tests on animals, these vaccines have shown they can make the body's immune system strong against the MARV [31]. They went on to be tested in people in different stages, and the results showed they are safe and can help the body fight the virus [32]. Researchers are still working to make the vaccines even better by improving some parts and studying how they can protect against related viruses [33]. The progress made so far gives us hope that these vaccines could be an effective way to fight the MARV in the future.

5. Current challenges and limitations

While Marburg VLP vaccines hold promise, several challenges and limitations persist in the realm of both MARV infection and vaccine development [37]. An exploration of these issues sheds light on the complexities that researchers and healthcare professionals face [38]. Table 3 explores in detail the current challenges and limitations of MARV infection and vaccine development. The journey of developing Marburg VLP vaccines encounters hurdles such as limited human trials, potential side effects, and the need for long-lasting immunity, all while accommodating the diverse strains of the MARV [39,40]. Overcoming challenges in manufacturing scalability and swift distribution during outbreaks is crucial [11]. Additionally, comprehensive studies are imperative to confirm cross-protection across strains [38]. Tackling these complexities is vital to propel the Marburg VLP vaccine advancement and effectively combat the multifaceted challenges posed by the MARV. Collaboration among researchers, policymakers, and healthcare experts remains key to surmounting these barriers and mitigating the public health impact of the virus [37].

Assessing the value of any vaccine involves a thorough consideration of its benefits and potential drawbacks. While initial safety testing may indicate promising results, ongoing monitoring is essential to detect rare adverse events or long-term effects that may not have been evident in early trials [41]. Variability in vaccine efficacy across different populations and in response to emerging virus variants also necessitates continuous evaluation to optimize deployment strategies [42]. Logistical challenges, such as specific storage requirements and distribution complexities, can hinder widespread implementation, particularly in resource-limited settings [12]. Furthermore, understanding vaccine immunogenicity in special populations, including elderly individuals and immunocompromised patients, requires targeted research to ensure

Table 2
Overview of MARV VLP vaccine development [14,29,31].

Vaccine name	Company name	Development phase	Antigens included	Current status	Vaccine efficacy and safety
Marburg VLP Vaccine	Various (Research)	Preclinical	MARV VP40, GP, NP	Research and development	Efficacy: demonstrates potential in preclinical models; Safety: requires further testing for immunogenicity and safety profile refinement
mVLP MARV-Musoke Vaccine	Non-human primate studies	Preclinical	MARV-Musoke VP40, GP, NP	Tested in non-human primates	Efficacy: induces immune response in non-human primates; Safety: initial safety profile in animal models, ongoing assessment for potential adverse effects
mVLP MARV-Ravn Vaccine	Non-human primate studies	Preclinical	MARV-Ravn VP40, GP, NP	Tested in non-human primates	Efficacy: promising immune response in preclinical studies; Safety: evaluated for safety parameters in non-human primates, continued safety monitoring needed
mVLP MARV-Ci67 Vaccine	Non-human primate studies	Preclinical	MARV-Ci67 VP40, GP, NP	Tested in non-human primates	Efficacy: elicits immune response specific to MARV-Ci67; Safety: initial safety profile in non-human primates, ongoing safety evaluations for potential risks

Abbreviations: MARV, Margburg virus; VLP, virus-like particle; mVLP, Marburg VLP; GP, glycoprotein; NP, nucleoprotein.

Table 3
Challenges and limitations in MARV infection and vaccine development [11,37,39].

Challenge/Limitation	Description
Limited human trials	Few human trials were conducted, hindering thorough assessment of the vaccine's safety and effectiveness
Adverse effects	Mild adverse effects are seen in clinical trials, raising concerns for larger population safety
Long-term potection	Uncertain duration of vaccine-induced immunity, more research is needed for long-term effectiveness
Variability of Marburg strains	Diverse Marburg strains complicate universal vaccine design to cover all strains
Manufacturing scalability	Scaling up production of Marburg VLP vaccines remains challenging despite progress
Limited resources in outbreaks	Deploying vaccines during outbreaks faces logistical hurdles, impacting containment efforts
Cross-protection validation	Promising cross-protection potential, but further studies are required for conclusive evidence

adequate protection [42]. Addressing public concerns, misinformation, and vaccine hesitancy is crucial for fostering acceptance and maximizing the effectiveness of vaccination programs [43]. Therefore, a comprehensive assessment of these factors is vital to determine whether the benefits of a vaccine outweigh its potential drawbacks, thereby informing effective promotion strategies.

Choosing VLPs as a platform for MARV vaccines offers distinct advantages over other methods such as rVSV and AdVs, particularly in NHP models. VLPs are non-infectious and safer due to their lack of genetic material, reducing the risk of vaccine-related disease [29]. They mimic the native virus structure effectively, eliciting robust immune responses including antibodies and T cells crucial for MARV protection [30]. VLPs are stable, scalable for mass production, and potentially provide cross-protection against related viruses within the *Filoviridae* family [27]. In contrast, live viral vectors like rVSV and AdVs may pose safety concerns, such as vaccine-associated disease and immune interference from pre-existing immunity [26]. Their production is more complex, requiring stringent biosafety measures and potentially higher costs. Thus, while each approach has merits, VLPs emerge as a safer, immunogenic, and scalable option for advancing MARV vaccine development, particularly in NHP studies and future clinical trials.

6. Cutting-edge approaches and future directions

The landscape of MARV prevention is advancing with cutting-edge approaches that hold promise for enhancing the efficacy and reach of vaccines. Novel strategies are being explored to address existing challenges and elevate the potential of Marburg VLP vaccines. Cutting-edge approaches and future directions in MARV vaccine development are discussed below.

6.1. Incorporation of advanced adjuvants

Researchers are investigating the integration of innovative adjuvants to enhance the immune response elicited by Marburg VLP vaccines. Adjuvants, such as immune-stimulating compounds, can amplify the body's immune reactions, potentially leading to more robust and enduring protection. This approach aims to further strengthen the vaccine's efficacy, particularly in populations with weaker immune responses [44–46].

6.2. mRNA technology

The emergence of mRNA technology has opened new avenues for Marburg vaccine development. Leveraging the mRNA platform, researchers can design and produce VLP vaccines with precision, facilitating rapid adaptation to evolving virus strains. mRNA vaccines have succeeded against other diseases, offering a potential breakthrough for MARV prevention [47,48].

6.3. Structure-based vaccine design

Advances in understanding the detailed structure of the MARV at the atomic level guide the design of vaccines with unparalleled specificity. This approach allows researchers to target critical regions on the virus's surface, eliciting targeted immune responses. By focusing on these vulnerable sites, researchers aim to enhance the vaccine's ability to neutralize the virus and confer lasting protection [46,48].

6.4. Broad-spectrum protection

Efforts to design vaccines that confer broad-spectrum protection against multiple filoviruses, including Marburg and Ebola, are gaining momentum. This approach capitalizes on shared features among these viruses, potentially yielding vaccines that guard against a range of threats. As research progresses, the prospect of a single vaccine capable of addressing multiple filovirus infections could revolutionize outbreak responses [44,45].

The horizon of MARV vaccine development shines with cutting-edge approaches poised to revolutionize the field. The integration of novel adjuvants holds the promise of enhancing vaccine-induced immune responses, potentially leading to more robust and persistent protection [44–46]. Leveraging the remarkable success of mRNA technology in the

realm of COVID-19 vaccines, researchers are exploring its application to Marburg VLP vaccines, opening doors to safer and more adaptive vaccine platforms [47,48]. Furthermore, capitalizing on structural insights into the MARV allows for the precise tailoring of vaccine candidates, maximizing immune recognition and enabling cross-protection against various strains [46,48]. As these groundbreaking strategies continue to be explored and refined, the future of MARV prevention grows brighter, offering hope for a more effective and comprehensive defense against this formidable pathogen.

7. Regulatory and global health considerations

The advancement of Marburg VLP vaccines hinges not only on scientific breakthroughs but also on robust regulatory frameworks and comprehensive global health considerations [49,50]. Regulatory agencies play a pivotal role in ensuring the safety, efficacy, and quality of vaccines [51]. Collaborative efforts among international regulatory bodies are essential to streamline the approval process and facilitate timely access to vaccines, particularly during outbreaks [49]. These agencies also contribute to establishing standardized guidelines for vaccine manufacturing, clinical trials, and post-marketing surveillance, reinforcing public trust in vaccine development [49,50].

Beyond regulatory aspects, global health considerations encompass equitable vaccine distribution, access, and affordability [52]. Ensuring that Marburg VLP vaccines reach vulnerable populations in endemic regions is vital [52,53]. Collaborations between governments, non-governmental organizations, and vaccine manufacturers can pave the way for equitable vaccine allocation, bolstered by initiatives like COVAX [52]. Additionally, reinforcing healthcare infrastructure in these regions is crucial to effectively administer vaccines and respond to outbreaks [51]. A harmonized global effort is necessary to address regulatory challenges and global health considerations, ensuring that Marburg VLP vaccines are a cornerstone in defending against this viral threat.

The safety testing mentioned in the article indicates that the vaccine has shown positive results in initial population tests. However, specific details about the representativeness of the test population, global applicability, and suitability for special populations are crucial considerations in vaccine development. Representative testing populations ensure that the vaccine's safety and efficacy data reflect diverse demographics, including age groups, ethnicities, and geographical locations [42]. This diversity is essential for assessing how well the vaccine performs across different populations and environments, thereby informing its potential global use.

Global applicability involves evaluating factors such as storage requirements, distribution logistics, and scalability of production to ensure the vaccine can be effectively deployed in various healthcare settings worldwide [15]. Additionally, assessing the vaccine's suitability for special populations, including pregnant women, immunocompromised individuals, and those with underlying health conditions, is critical. These groups may have specific safety concerns or immune responses that require tailored studies to determine the vaccine's efficacy and safety [12].

8. Conclusion

MARV's intricate helical structure and lipid envelope pose formidable challenges to public health. VLP vaccines have emerged as a transformative solution, mimicking the virus's external traits without genetic material to induce potent immunity. From animal studies to advanced clinical trials, Marburg VLP vaccines exhibit robust immune responses and cross-protection potential against related viruses. However, hurdles persist, including limited human trials, potential side effects, and the need for durable immunity. Overcoming manufacturing scalability and ensuring swift distribution during outbreaks is essential. Collaborative efforts among researchers, policymakers, and healthcare experts are crucial to surmount these challenges and contain the virus's impact. Innovative strategies, like advanced adjuvants, mRNA technology, and structural design, offer promising avenues for enhancing vaccine efficacy. Regulatory collaboration and global health initiatives must complement scientific advancements for comprehensive MARV prevention, fostering a brighter future of improved global health security.

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CRediT authorship contribution statement

Ram Bahadur Khadka: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Khimdhoj Karki:** Writing – review & editing. **Jitendra Pandey:** Writing – review & editing. **Rabin Gyawali:** Validation, Resources. **Gautam Prasad Chaudhary:** Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.soh.2024.100076.

References

[1] S. Akash, T.B. Emran, H. Chopra, K. Dhama, Re-emerging of marburg virus: warning about its virulence and potential impact on world's health, Int. J. Surg. 109 (2) (2023) 165–166.
[2] M.A. Islam, S.S. Adeiza, M.R. Amin, F.H. Kaifa, J.M. Lorenzo, P. Bhattacharya, et al., A bibliometric study on Marburg virus research with prevention and control strategies, Front. Trop. Dis. 3 (2023) 1068364.
[3] A. Amara, J. Mercer, Viral apoptotic mimicry, Nat. Rev. Microbiol. 13 (8) (2015) 461–469.
[4] K. Cheng, Q. Guo, S. Gu, H. Wu, C. Li, Deadly Marburg virus outbreak received sustained attention: what can we learn from the existing studies? Int. J. Surg. 109 (8) (2023) 2539–2541.
[5] F. Scarpa, L. Bazzani, M. Giovanetti, A. Ciccozzi, F. Benedetti, D. Zella, et al., Update on the phylodynamic and genetic variability of marburg virus, Viruses 15 (8) (2023) 1721.
[6] S. Sahoo, R.K. Narang, A. Singh, The marburg virus outbreak in west africa, Curr. Drug Targets 24 (5) (2023) 380–381.
[7] Y. Mashkoor, F. Rafique, A. Zubair, Recurrent Marburg virus disease outbreaks from 1967 to 2022: a perspective on challenges imposed and future implications, Asian Pac. J. Tropical Med. 15 (9) (2022) 385–386.
[8] M.P. Manohar, V.J. Lee, E.U. Odunukwe, P.K. Singh, B.S. Mpofu, C. Oxley, Advancements in Marburg (MARV) virus vaccine research with its recent reemergence in Equatorial Guinea and Tanzania: a scoping review, Cureus 15 (7) (2023) e42014.
[9] W. Zhu, G. Liu, W. Cao, S. He, A. Leung, U. Ströher, et al., A cloned recombinant vesicular stomatitis virus-vectored Marburg vaccine, PHV01, protects Guinea pigs from lethal Marburg virus disease, Vaccines 10 (7) (2022) 1004.
[10] R.W. Cross, I.M. Longini, S. Becker, K. Bok, D. Boucher, M.W. Carroll, et al., An introduction to the Marburg virus vaccine consortium, MARVAC, PLoS Pathog. 18 (10) (2022) e1010805.
[11] X. Jiang, Z. Fan, S. Li, H. Yin, A review on zoonotic pathogens associated with non-human primates: understanding the potential threats to humans, Microorganisms 11 (2) (2023) 246.
[12] K. Brauburger, A.J. Hume, E. Mühlberger, J. Olejnik, Forty-five years of Marburg virus research, Viruses 4 (10) (2012) 1878–1927, https://doi.org/10.3390/v4101878.

[13] D.M. Emperador, L.T. Mazzola, B.W. Trainor, A. Chua, C. Kelly-Cirino, Diagnostics for filovirus detection: impact of recent outbreaks on the diagnostic landscape, BMJ Global Health 4 (Suppl 2) (2019) e001112.
[14] P. Reynolds, A. Marzi, Ebola and Marburg virus vaccines, Virus Gene. 53 (2017) 501–515.
[15] Centers for Disease Control and Prevention, Marburg hemorrhagic fever outbreaks, 2022. https://www.cdc.gov/vhf/marburg/outbreaks/index.html. (Accessed 4 April 2024).
[16] B. Beall, M.C. McEllistrem, R.E. Gertz Jr., D.J. Boxrud, J.M. Besser, L.H. Harrison, et al., Emergence of a Novel Penicillin-Nonsusceptible, Invasive Serotype 35B Clone of Streptococcus pneumoniae within the United States, J. Infect. Dis. 186 (1) (2002) 118–122.
[17] D. Vandenheuvel, R. Lavigne, H. Brüssow, Bacteriophage therapy: advances in formulation strategies and human clinical trials, Annu. Rev. Virol. 2 (1) (2015) 599–618.
[18] L.F. Dantas, J.F. Marchesi, I.T. Peres, S. Hamacher, F.A. Bozza, R.A. QuintanoNeira, Public hospitalizations for stroke in Brazil from 2009 to 2016, PLoS One 14 (3) (2019) e0213837.
[19] C. Woolsey, R.W. Cross, K.N. Agans, V. Borisevich, D.J. Deer, J.B. Geisbert, et al., A highly attenuated Vesiculovax vaccine rapidly protects nonhuman primates against lethal Marburg virus challenge, PLoS Negl. Trop. Dis. 16 (5) (2022) e0010433.
[20] E. Suder, W. Furuyama, H. Feldmann, A. Marzi, E. de Wit, The vesicular stomatitis virus-based Ebola virus vaccine: from concept to clinical trials, Hum. Vaccines Immunother. 14 (9) (2018) 2107–2113.
[21] C.L. Finch, C. Martinez, E. Leffel, M.H. Skiadopoulos, A. Hacker, B. Mwesigwa, et al., Vaccine licensure in the absence of human efficacy data, Vaccines 10 (3) (2022) 368.
[22] S. Chakraborty, D. Chandran, R.K. Mohapatra, M. Alagawany, M.I. Yatoo, M.A. Islam, et al., Marburg virus disease – a mini-review, J. Exp. Biol. Agric. Sci. 10 (4) (2022) 689–696.
[23] B. Perdiguero, P. Pérez, L. Marcos-Villar, G. Albericio, D. Astorgano, E. Álvarez, et al., Highly attenuated poxvirus-based vaccines against emerging viral diseases, J. Mol. Biol. 435 (15) (2023) 168173.
[24] L. Widerspick, J.F. Steffen, D. Tappe, C. Muñoz-Fontela, Animal model alternatives in filovirus and bornavirus research, Viruses 15 (1) (2023) 158.
[25] C. Diot, G. Cosentino, M.A. Rameix-Welti, Ribonucleoprotein transport in negative strand RNA viruses, Biol. Cell. 115 (1) (2023) 2200059.
[26] E.B. Struble, J.M. Rawson, T. Stantchev, D. Scott, M.A. Shapiro, Uses and challenges of antiviral polyclonal and monoclonal antibody therapies, Pharmaceutics 15 (5) (2023) 1538.
[27] R. Nwalozie, B.A. Nnokam, R.A. Ikpeama, Ebola virus disease (Evd): Nigeria perspective, J. Appl. Health Sci. Med. 3 (1) (2023) 1–9.
[28] S. Wang, B. Liang, W. Wang, L. Li, N. Feng, Y. Zhao, et al., Viral vectored vaccines: design, development, preventive and therapeutic applications in human diseases, Signal Transduct. Targeted Ther. 8 (1) (2023) 149.
[29] I.M. Longini, Y. Yang, T.R. Fleming, C. Muñoz-Fontela, R. Wang, S.S. Ellenberg, et al., A platform trial design for preventive vaccines against Marburg virus and other emerging infectious disease threats, Clin. Trials 19 (6) (2022) 647–654.
[30] S. Malik, S. Kishore, S. Nag, A. Dhasmana, S. Preetam, O. Mitra, et al., Ebola virus disease vaccines: development, current perspectives & challenges, Vaccines 11 (2) (2023) 268.
[31] R. Hunegnaw, A. Honko, L. Wang, D. Carr, T. Murray, W. Shi, et al., Rapid and durable protection against Marburg virus with a single-shot Chad3-MARV GP vaccine, bioRxiv 25 (2021), 2021-12.
[32] B. Callendret, J. Vellinga, K. Wunderlich, A. Rodriguez, R. Steigerwald, U. Dirmeier, et al., A prophylactic multivalent vaccine against different filovirus species is immunogenic and provides protection from lethal infections with Ebolavirus and Marburgvirus species in non-human primates, PLoS One 13 (2) (2018) e0192312.
[33] A.T. Lehrer, E. Chuang, M. Namekar, C.A. Williams, T.A. Wong, M.M. Lieberman, et al., Recombinant protein filovirus vaccines protect cynomolgus macaques from Ebola, Sudan, and Marburg viruses, Front. Immunol. 12 (2021) 703986.
[34] Spring Conference, NHSDC - from Data to Difference, 2023. https://www.nhsdc.org/. (Accessed 24 April 2024).
[35] Healthy Developments, WHS 2023: is it time to re-think outbreak response teams, 2023. https://health.bmz.de/events/whs-2023-is-it-time-to-re-think-outbreak-response-teams/. (Accessed 7 June 2024).
[36] European Centre for Disease Prevention and Control, Factsheet about Marburg Virus Disease, 2022. https://www.ecdc.europa.eu/en/infectious-disease-topics/ebola-virus-disease/facts/factsheet-about-marburg-virus-disease. (Accessed 11 July 2024).
[37] K. Lundstrom, Application of viral vectors for vaccine development with a special emphasis on COVID-19, Viruses 12 (11) (2020) 1324, https://doi.org/10.3390/v12111324.
[38] R. Gyawali, K.D. Karki, R. Bhandari, B. Neupane, R.R. Kafle, D. Pant, et al., Corona viruses: diagnostic approaches for COVID-19, J. Exp. Biol. Agric. Sci. 8 (2020) S09–S20, https://doi.org/10.18006/2020.8(Spl-1-SARS-CoV-2).S09.S20.
[39] M. Yıldız, A. Tanimowo, M. Monti, M.S. Yıldırım, R.B. Khadka, A.H. Sbaih, et al., Individuals' coronavirus disease knowledge levels: a cross-sectional survey in eleven countries, J. Clin. Med. Kaz. 18 (2) (2021) 8–13, https://doi.org/10.23950/jcmk/9710.
[40] R. Bahadur Khadka, R. Bhandari, R. Gyawali, B. Neupane, D. Pant, Epidemiology and pathogenesis of coronavirus disease (Covid-19), Nov, Res. Microbiol. J. 4 (2) (2020) 675–687, https://doi.org/10.21608/nrmj.2020.84016.
[41] Z.L. Rand, D.P. Carpenter, A.S. Kesselheim, A. Bhaskar, J.J. Darrow, W.B. Feldman, Securing the trustworthiness of the FDA to build public trust in vaccines, Hastings Cent. Rep. 53 (2023) S60–S68.
[42] WHO, WHO results report 2020-2021, 2021. https://www.who.int/about/accountability/results/who-results-report-2020-2021. (Accessed 19 May 2024).
[43] R.R. Chiu, K. Burkhart, J. Florian, K. Ford, M.I. Garcia, D.G. Strauss, New science, drug regulation, and emergent public health issues: The work of FDA's division of applied regulatory science, Front. Med. 9 (2023) 1109541.
[44] D. Yang, RNA viruses: host gene responses to infections, World Scientific (2009) 1–167.
[45] K.J. Olival, D.T. Hayman, Filoviruses in bats: current knowledge and future directions, Viruses 6 (4) (2014) 1759–1788.
[46] S. Bhattacharyya, N. Mulherkar, K. Chandran, Endocytic pathways involved in filovirus entry: advances, implications and future directions, Viruses 4 (12) (2012) 3647–3664.
[47] V. Latorre, F. Mattenberger, R. Geller, Chaperoning the Mononegavirales: current knowledge and future directions, Viruses 10 (12) (2018) 699.
[48] G. Simmons, P. Zmora, S. Gierer, A. Heurich, S. Pöhlmann, Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research, Antivir. Res. 100 (3) (2013) 605–614.
[49] J.K. Andrus, X. Aguilera, O. Oliva, S. Aldighieri, Global health security and the international health regulations, BMC Publ. Health 10 (2010) 1–4.
[50] A. Timen, M.P. Koopmans, A.C. Vossen, G.J. van Doornum, S. Günther, F. Van den Berkmortel, et al., Response to imported case of Marburg hemorrhagic fever, The Netherlands, Emerg. Infect. Dis. 15 (8) (2009) 1171.
[51] D.L. Heymann, L. Chen, K. Takemi, D.P. Fidler, J.W. Tappero, M.J. Thomas, et al., Global health security: the wider lessons from the west African Ebola virus disease epidemic, Lancet 385 (9980) (2015) 1884–1901.
[52] R.C. Reuben, S.A. Abunike, Marburg virus disease: the paradox of Nigeria's preparedness and priority effects in co-epidemics, Bull. Natl. Res. Cent. 47 (1) (2023) 10.
[53] G.P. Chaudhary, R.B. Khadka, A. Lamichhane, B. Dhakal, N. Das, N.S. Tharu, et al., Impact of COVID-19 pandemic on learning status of student in Nepal, J. Educ. Health Promot. 11 (1) (2022) 314.