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Narrative Review

ADVANCEMENTS IN MARBURG VIRUS VACCINE DEVELOPMENT: UNRAVELLING RECENT FINDINGS. A NARRATIVE REVIEW.

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ABSTRACT.

Marburg Virus Disease (MVD) is a lethal single-stranded RNA virus transmitted by Egyptian rousette bats, causing 12 surges in Sub-Saharan Africa, including a recent outbreak in Tanzania in 2023. With a fatality rate of approximately 90%, no approved vaccines currently exist. Ongoing research explores potential candidates, such as a recombinant vesicular stomatitis virus (VSV)-based vaccine and MVA-BN-Filo, aiming to combat this deadly infection. The objective of this review is to comprehensively examine Marburg virus vaccines, exploring various candidates and their development stages, efficacy in non-human primates and human studies, and challenges faced in the development process. Various vaccines are under development, including Ad26, Ad5, viral vector, and DNA vaccines. Promising candidates like Ad26.Filo and ChAd3-MARV have emerged. Additionally, VLP-based, DNA plasmid and rVSV-based vaccines are discussed, highlighting their effectiveness and challenges in development, such as limited information, gene expression issues, and outbreak control measures. The implications for future research and clinical practice/policy development are significant. Marburg virus vaccine development shows promise in mitigating the threat posed by this deadly pathogen. Despite complex challenges, advancements in vaccine candidates offer hope. Continued research and development may lead to the successful prevention of major Marburg virus outbreaks. Ongoing clinical trials indicate potential breakthroughs in a short period, contributing to public health protection.

***Keywords**: Epidemiology, Hemorrhagic fever, Diagnosis, Outbreaks, Vaccines, Prevention and control, Marburg virus, African countries, Lethal*
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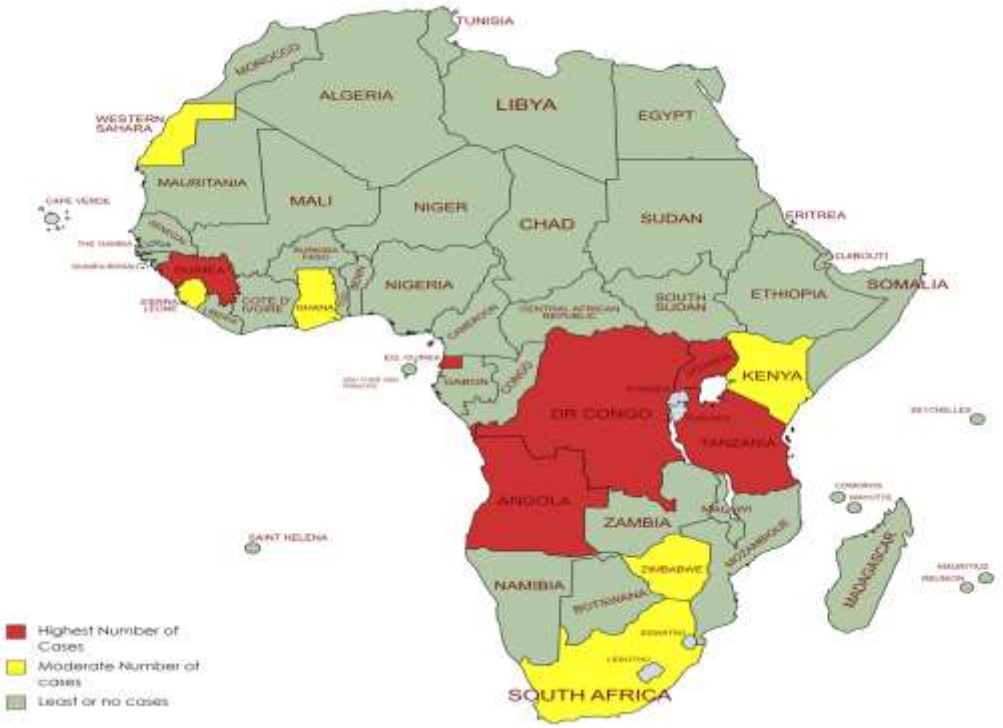
INTRODUCTION.

Marburg Virus is a single-stranded RNA virus, and a particularly lethal member of the filovirus family, causing life-threatening hemorrhagic fever. Initially, it was found to be transmitted to humans from bats, with Egyptian rousette bats acting as natural reservoirs. [1] Wirsiy FS et al. developed a SPIN (Socio-environmental context, Possible transmission routes, Informing and guiding public health action, needs in terms of control measures) framework, a comprehensive approach to comprehending and addressing outbreaks of a specific disease. The key elements of this framework include social context, possible transmission paths and determinants, informing and leading actions, and requirements of public health in terms of control measures. Individual features are part of the socio-environmental setting (such as demographic, socio-economic and cultural, health-seeking behaviors), environmental factors which are further divided into immediate social environment i.e. family (Parents and siblings), and peers, hunting and mining as means of subsistence and the institutional environment i.e. community (norms and values), school settings, religious settings (church, mosque, religious bodies), health and laboratory systems and the policies and regulations that directly or indirectly affect disease control efforts (such as healthcare infrastructure, surveillance systems, or public health campaigns). The element of "Possible Transmission Routes and Determinants" focuses on understanding the

different ways in which MVD (Marburg Virus Disease) can be transmitted. It considers each of the two wildlife-to-human transmissions. Interhuman transmission primarily occurs through direct contact with body fluids and blood of diseased people, typically within domestic or healthcare settings where preventive infection measures may be inadequate. The virus enters blood or lymph vessels infecting macrophages, dendritic cells, and monophages through exposed mucosa or abraded skin. [2] The possible transmission route from wildlife (fruit bats, monkeys/apes) to humans is bushmeat consumption and its state when being eaten, acquisition of meat- through hunting, picking dead animals in the forest for consumption, carrying out laboratory work or research activities involving samples taken from suspected animal cases for investigation of MVD and other infections. Another element of SPIN, educating the public and directing its actions, reiterates the importance of information gained from the first two elements, namely socio-environmental settings and channels of spread to inform and guide community health intervention which involve identification of exemplary procedures and safety precautions that can effectively prevent and manage MVD outbreaks. This could include measures such as surveillance systems, early detection and diagnosis, isolation and quarantine protocols, treatment strategies, vaccination campaigns, health education, and community engagement. The element of "Needs in Terms of Control Measures" within the SPIN framework focuses on understanding the specific requirements and obstacles involved in implementing the identified interventions and control measures. It considers the context-specific factors, available resources, and necessary capabilities to successfully execute these measures. This includes factors such as the quality of healthcare infrastructure, the presence of skilled personnel, the opportunity to use essential medical supplies and equipment, the level of community acceptance and participation, and the coordination among various stakeholders engaged in disease control efforts to avoid the number of deaths. [1,2] **(Figure 1)**

Fig 1| Spatial Representation of Marburg Virus Cases: Geographic Distribution.



Created with mapchart.net

The symptoms of the Marburg virus depend on the day of the incubation period. The incubation timeframe of the Marburg virus ranges between three to twenty days (usually 5 to 10 days), and aspects like the dosage of infection and the mode of transmission possibly influence it. The progression of MVD is divided into 3 phases which depend on the outcomes of the disease: an early dissemination stage, a stage of early involvement of organs, and a subsequent stage encompassing either late organ manifestation or a convalescent period. The initial dissemination phase is the onset of Marburg virus infection characterized by generic flu-like symptoms that typically last from day one to four. These symptoms include high fever (usually ranging from 39-40°C), severe headache, chills, muscle pain, fatigue, and

general discomfort. This is followed by a rapid deterioration in many patients, marked by gastrointestinal issues such as loss of appetite, abdominal pain, nausea, vomiting, and watery diarrhea. Around the fourth or fifth day, patients may develop an enanthem (mucous membrane rash), dysphagia, and throat inflammation. A distinct maculopapular rash serves as an early distinguishing feature of filovirus infection. Other common symptoms include swelling of lymph nodes, decreased white blood cells, and platelet count. In the early organ phase of Marburg virus infection (days 5 to 13), initial symptoms may persist, accompanied by a high fever.

Neurological symptoms like irritability, encephalitis, and confusion may occur. Patients may also experience dyspnea and abnormal vascular permeability (conjunctival injection and edema), and over 75% of patients develop clear hemorrhagic indications, for example bleeding in mucous membranes, gastrointestinal tract, and skin. Not all patients show hemorrhagic symptoms, so the term "hemorrhagic fevers" is currently discouraged. The pancreas, kidney, and liver are just a few of the impacted organs with elevated levels of liver enzymes, such as SGPT (Serum glutamic pyruvic transaminase) and SGOT (Serum Glutamic Oxalo-acetic Transaminase) observed in most medical cases. Commencing from day 13 and beyond, the advanced stages of MVD yield either one of the possible consequences: patients may yield to the illness or embark on an extended phase of recovery. During this phase, individuals may display preagonal symptoms such as restlessness, confusion, obtundation, convulsions, severe dehydration leading to compromised circulation, metabolic imbalances, widespread coagulopathy, failure of multiple organs, shock, and coma. Death commonly occurs 8-16 days after symptoms initiate, primarily due to shock and multiorgan failure. Survivors undergo a protracted convalescence period marked by myalgia, fatigue, profuse perspiration, skin peeling at rash sites, partial memory loss, and heightened vulnerability to secondary infections. The late stages of MVD, from day 13 onwards, entail these characteristic manifestations. [3]

In August 1967, the Marburg virus first occurred in laboratory personnel in Frankfurt and Marburg, Germany, and Belgrade, Serbia, from an unknown source of infection. Later, the infection source was identified as African green monkeys *(Chlorocebus aethiops)* that had been brought from Uganda and distributed to all these places. The virus was named after the city of Marburg, where it was initially discovered. [3] There have been around 12 surges of Marburg Virus Disease in Sub-Saharan African countries, the most recent in Tanzania in 2023. (Table 1)

Table 1: Summary of the initial outbreaks of Marburg Virus indicating years, number of cases, death, fatality rate, and situation. [35, 36]

Outbreak Number	Country	Year	Cases	Death	Case Fatality Rate	Situation
1	Germany and Serbia	1968	31	7	23%	Concurrently, outbreaks occurred among laboratory workers who had been handling African green monkeys imported from Uganda. Apart from the initially reported 31 cases, an additional primary case was retrospectively diagnosed through serological analysis.
2	South Africa	1978	3	1	33%	A man with a recent travel history to Zimbabwe was admitted to hospital in South Africa. The infection spread from the man to his traveling companion and a nurse at the hospital. The man died, but both women were given vigorous supportive treatment and eventually recovered.
3	Kenya	1980	2	1	50%	The individual had recently traveled, including a visit to Kitum Cave in Mount Elgon National Park, Kenya. Despite receiving specialized care in Nairobi, the male patient passed away. Subsequently, a doctor who participated in resuscitation efforts developed symptoms nine days later but ultimately recovered.
4	Kenya	1987	1	1	100%	A 15-year-old boy from Denmark was admitted to the hospital after experiencing headaches, malaise, fever, and vomiting for three days. He had visited Kitum Cave in Mount Elgon National Park nine days before the onset of symptoms. Despite receiving aggressive supportive therapy, the patient succumbed to the illness on the 11th day. No additional cases were identified.

Table 2: Outbreaks of Marburg Virus from 1990-2010 indicating years, number of cases, death, fatality rate, and situation. [35, 36]

Country	Year	Cases	Deaths	Fatality Rate	Summary
Russia	1990	1	1	100%	Laboratory Contamination
Democratic Republic of the Congo	2000	154	128	83%	The majority of cases were observed among young male workers at a gold mine located in Durba, situated in the northeastern region of the country, identified as the outbreak's epicenter. Subsequent cases were identified in the nearby village of Watsa.
Angola	2004	252	227	90%	The outbreak is thought to have originated in Uige Province in October 2004. The majority of cases identified in other provinces have been directly associated with the outbreak in Uige.
United States of America ex Uganda	2008	1	0	0%	In January 2008, a U.S. traveler who had returned from Uganda developed an illness four days after arrival, leading to hospitalization. After discharge, the patient fully recovered. Subsequently, retrospective diagnosis confirmed the presence of Marburg virus infection.
Netherland ex Uganda	2008	1	1	100%	A 40-year-old Dutch woman, who had recently traveled to Uganda, was hospitalized in the Netherlands. The initial symptoms of fever and chills appeared three days before admission, leading to a swift clinical decline. Unfortunately, the woman passed away on the 10th day of the illness.

Table 3: Outbreaks of Marburg Virus indicating years, number of cases, death, fatality rate, and the situation in Uganda. [35, 36]

Country	Year	Cases	Deaths	Fatality Rate	Summary
Uganda	2007	4	1	25%	A small outbreak occurred, involving four cases among young males employed in a mine. As of now, no further cases have been identified.
Uganda	2012	15	4	27%	CDC/UVRI testing revealed the occurrence of a Marburg virus disease outbreak spanning three weeks in the districts of Kabale, Ibanda, Mbarara, and Kampala.
Uganda	2014	1	1	100%	In summary, a single confirmed case (resulting in a fatality) was identified, and 197 contacts were monitored for three weeks. Among these contacts, eight individuals exhibited symptoms resembling Marburg, yet all tested negative at the Uganda Virus Research Institute with assistance from the CDC.
Uganda	2017	4	3	75%	A blood sample collected in Kween District, Eastern Uganda, yielded a positive result for the Marburg virus. Within 24 hours of confirmation, prompt measures for outbreak response were initiated. The outbreak was confined to a family cluster, with no further transmission observed beyond the four related cases.

Table 4: Overview of the last five years of Marburg Virus Outbreaks. [35, 36]

Country	Year	Cases	Death	Death Rate	Summary
Guinea	2021	1	1	100%	The Guinean Ministry of Health reported and confirmed a single case of a patient diagnosed posthumously. Following the monitoring of over 170 high-risk contacts for 21 days, no additional cases were confirmed.
Ghana	2022	3	2	75%	On July 7, 2022, a fatal suspected case of Marburg virus disease (MVD) was identified in Ghana's Ashanti region. Ghana's national laboratory initially detected it through PCR, later confirmed at the Institut Pasteur in Dakar, Senegal—the first MVD case in Ghana. Two more family members were confirmed with MVD. No further cases were found beyond the family cluster, and the outbreak concluded in September.
Tanzania	2023	8	5	63%	On March 21, 2023, Tanzania declared its first Marburg Virus Disease (MVD) outbreak. By May 31, nine cases were reported in Bukoba district, Kagera region. Of the eight confirmed cases, three recovered, and six resulted in death (67% Case Fatality Rate), primarily affecting males aged 1 to 59. The outbreak concluded on June 2, 2023, 42 days after the last potential exposure, with six cases being relatives of the index case and two being healthcare workers.
Equatorial Guniea	2023	29	27	93%	Equatorial Guinea declared a Marburg Virus Disease outbreak on February 13, 2023, following suspected viral hemorrhagic fever deaths. By June 8, the outbreak, which affected five districts across four provinces, concluded after 17 confirmed and 23 probable cases, resulting in 12 deaths (75% Case Fatality Rate), with the last confirmed case discharged on April 26.

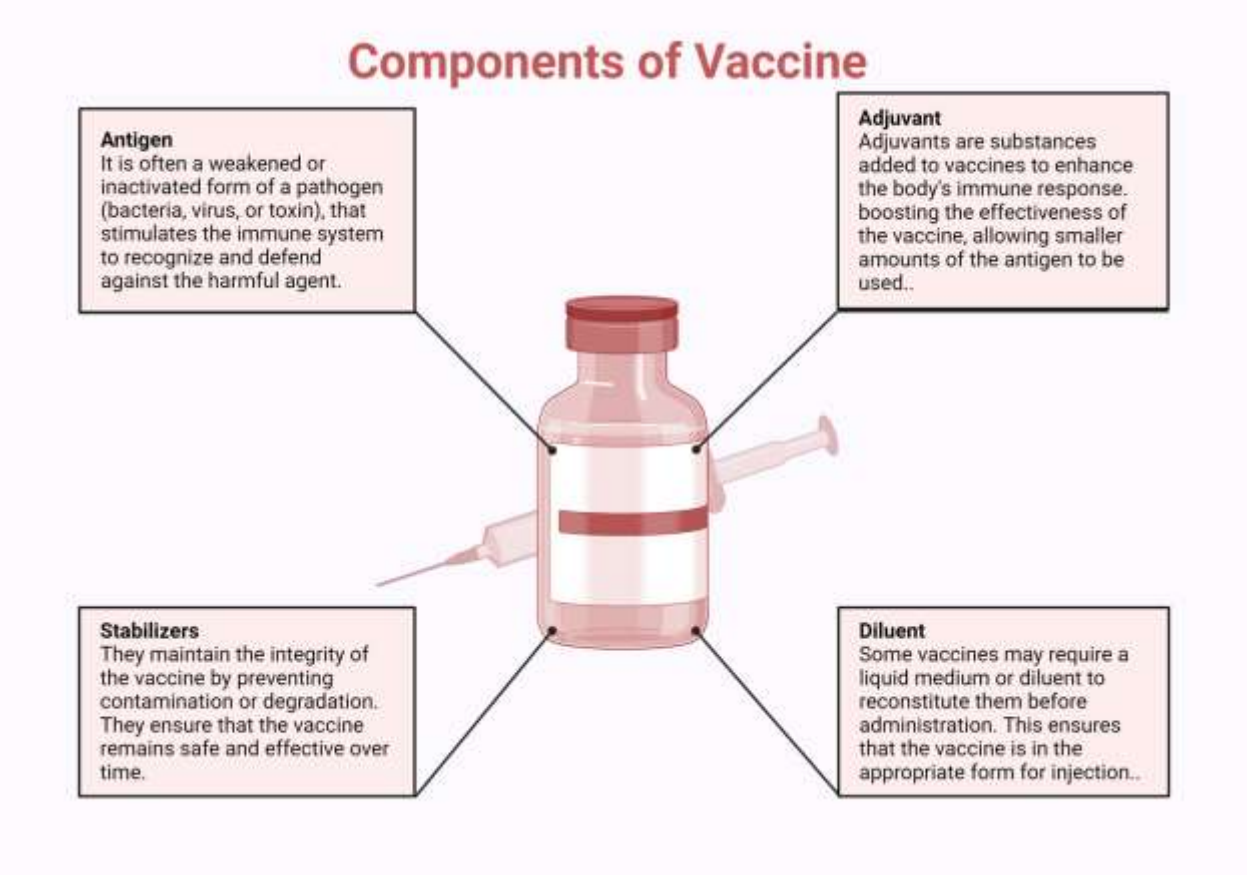
The WHO classified the Marburg Virus as a level 4 biohazard, highlighting the crucial need for effective and safe treatment options. [4] Initially, the Marburg virus was considered less dangerous than its well-known family member, Ebola, as it exhibited a lower fatality rate. However, in the recent outbreak, the fatality rate of the Marburg virus was found to be approximately 90%, rendering it as deadly as Ebola [5] Despite the significant impact of filovirus hemorrhagic fever (FHF) on human health, it remains one of the neglected infectious diseases when compared to widespread illnesses such as malaria or AIDS, which have a high number of cases each year. Given the classification of the Marburg virus as a Biohazard level 4 pathogen, one might anticipate the availability of vaccines for prevention. However, there are yet to be verified vaccines or specific therapies for the treatment of Marburg virus infections. Consequently, these pathogens necessitate handling within maximum containment labs and are categorized as select agents, emphasizing the need for approved vaccines against the virus. [6] The challenges in developing a vaccine for the Marburg virus are a complex endeavor; however, DNA vector-based vaccines, while promising, have faced limitations in terms of their effectiveness when tested on primates. This is largely due to issues with gene expression and targeting specific cells. The World Health Organization (WHO) expresses skepticism about the feasibility of successful trials due to the potential for outbreak control measures, such as quarantine, to halt the outbreak before a vaccine can be widely administered. Additionally, there might not be a sufficient number of cases during a trial to accurately determine the vaccine's efficacy.

A significant hurdle lies in the scarcity of information. Since the Marburg virus has no approved vaccine or cure, research is confined to a few highly secure laboratories worldwide. Various vaccine types are under development, with viral vector and DNA vaccines displaying promise in safeguarding rodents and nonhuman primates. To create an effective vaccine, insights from multiple outbreaks are imperative. Identifying the most susceptible individuals is crucial for prioritized vaccination, encompassing research lab personnel, those with heightened occupational exposure

risks like miners, and individuals residing in areas prone to endemic outbreaks. Overcoming these challenges is paramount for developing a successful Marburg virus vaccine. [7]

The main components of vaccines include protein antigens that stimulate immune responses for protection against infectious diseases. While the primary focus is on protein antigens, vaccines developed to combat bacterial infections, such as those caused by Streptococcus pneumoniae, have also utilized polysaccharide antigens since the late 1980s. Clinical trials assess vaccine effectiveness by correlating immune responses to vaccine antigens with clinical outcomes, such as preventing infection or reducing disease severity. In addition to antigens, vaccines may contain preservatives, emulsifiers (like polysorbate 80), stabilizers (such as gelatine or sorbitol), and trace components from the manufacturing process. These trace components, including antibiotics, egg or yeast proteins, latex, formaldehyde, and acidity regulators, are carefully monitored to ensure the safety and efficacy of vaccines, with no known health risks unless there are specific allergy concerns. [8] **(Figure 2)**

Fig 2| Components of Vaccine. (Created with BioRender.com)



Several potential vaccines for the Marburg virus are undergoing trials; in animal models, a recombinant vesicular stomatitis virus (VSV)-based vaccine manifesting the Marburg virus glycoprotein (VSV-MARV) provided rapid protection against Marburg virus disease (MVD) [9] Another investigational vaccine MVA-BN-Filo, incorporating antigens from the pair, Marburg and Ebola viruses [10] Currently, a phase 3 trial is in progress to measure the efficiency of the MVA-BN-Filo vaccine against the Ebola virus, while its effectiveness against the Marburg virus (MARV) has yet to be evaluated. In addition to preventive vaccines, researchers are now focusing on the development of post-exposure therapies for Marburg virus disease (MVD). These include the exploration of small-molecule antivirals and MARV-specific monoclonal antibodies (mABs) as potential treatments. In a non-human primate model, researchers have investigated the mixture of an antiviral drug (remdesivir) and monoclonal antibody (MR186-YTE) for their effectiveness against Marburg virus disease.[11] We will now review the ongoing development of vaccines to combat the Marburg virus, as explored in the study titled "Unraveling Recent Clinical Findings, Challenges, and Novel Methodologies." This review delves into recent clinical discoveries, the obstacles faced, and

innovative approaches employed in the quest for effective treatments.

METHODOLOGY.

Commencing with a traditional literature review, our objective was to comprehensively explore recent developments in Marburg virus vaccine development and unravel key findings. Opting for a structured approach, we defined review concepts, established inclusion and exclusion criteria, and adhered to a systematic plan for study selection. The subsequent sections elaborate on these methods, elucidating the systematic organization of information gleaned from various articles.

Search Strategy.

The search strategy for this narrative review centered on identifying literature about advancements in Marburg virus vaccine development. The search strategy for this review included the use of keywords “Marbug Virus” “MVD” and “Hemorrhagic Fever” for the concept of Marburg virus and “Vaccine” Vaccine development” “Vaccine Efficacy’, “Vaccine Safety” for the concept of vaccines. These specific keywords related to the Marburg virus, vaccine candidates, and recent breakthroughs were chosen. We executed searches across prominent databases, including PubMed, Google Scholar, and ScienceDirect. A table outlines the comprehensive list of keywords and databases utilized, ensuring transparency in our literature search approach. (Table 5)

Table 5: Search Strategy.

Concept	Database	Keywords
Marburg Virus	Pubmed, Google Scholar, and Science Direct	Marburg Virus, Marburg hemorrhagic fever, hemorrhagic fever, MARV, filovirus, Marburg virus disease, Marburg infection, Marburg outbreak, Marburg transmission
Vaccine	Pubmed, Google Scholar, and Science Direct	vaccination, vaccine development, vaccine candidates, viral vaccines, hemorrhagic fever vaccines filovirus vaccines, immunization, vaccine research, vaccine efficacy, vaccine safety, vaccine clinical trials, vaccine response, vaccine production, novel vaccines, emerging infectious disease vaccines

Study Selection.

To gather relevant information on recent advancements in Marburg virus vaccine development, a meticulous study selection process was undertaken. Extensive database searches were followed by the elimination of duplicate entries. Titles and abstracts were scrutinized to ensure alignment with the scope of our review. Full articles were then thoroughly assessed for relevance, with inaccessible full texts excluded. This rigorous approach aimed to include studies with accessible content, preserving the integrity of our narrative review. The selected articles were extensively read to extract essential details and illuminate recent findings in Marburg virus vaccine development.

Exclusion and Inclusion Criteria.

Articles included in the review met criteria ensuring linguistic consistency (English language) and relevance to recent developments in Marburg virus vaccine research. Exclusion criteria encompassed articles unrelated to vaccine development, correspondence, perspectives, conference abstracts, editorials, and news items. Stringent criteria were applied to focus on articles directly contributing to the narrative review on advancements in Marburg virus vaccine development.

Data Extraction and Narration.

Data extraction focused on key aspects such as vaccine candidates, breakthroughs, challenges, and recent findings in Marburg virus vaccine development. Extracted information was then organized into thematic categories, allowing for a cohesive narrative that unraveled the current landscape of advancements in Marburg virus vaccine research.

RESULTS.

In our results, we found five potential vaccines for Marburg Virus, namely: Adenovirus (AD) 26. Filo vaccine, Chimpanzee adenovirus 3 (ChAd3)-MARV vaccine,

MARV Virus like Particles (mVLPs), DNA-GP vaccines, rVSV-MARV-GP.

1. Adenovirus (AD) 26. Filo vaccine.

Adenovirus (Ad) 26 vectors have extensively undergone investigations as potential vaccine candidates against various contagious diseases. Adenoviruses are classified into numerous serotypes, with over seventy human serotypes identified and classified into 7 species (A to G) based on their genetic resemblance. Ad26, belonging to species D, has been utilized to develop two authorized vaccines: Zabdeno, in combination with Mubea, for preventing the Ebola virus disease, and Ad26.COV2.S which prevents COVID-19. Other adenovirus vectors, such as Ad5 and ChADOx 1, have also been employed in the formation of COVID-19 vaccines in various countries. Furthermore, various Ad types are currently being explored as potential candidates for creating vaccines targeting HIV, RSV, malaria, and other diseases. Pre-existing immunity to adenoviral vectors, particularly to the same type utilized in a vaccine, can potentially impact the delivery of vaccine-encoded antigens or lead to the removal of cells expressing the vaccine's immunogen. This could reduce the vaccine's effectiveness. Pre-existing immunity may arise from earlier exposure to natural adenoviruses or prior vaccination with the same Ad vector.Ad5, belonging to species C, is highly prevalent and induces robust anti-vector responses in individuals, proving vaccines based on Ad5 to be unsatisfactory for widespread use. On the other hand, Ad35, Ad26, and Ad48, belonging to species B and D, have less natural seroprevalence and low levels of antibody titers in previously exposed individuals. As a result, Ad26 is considered an appealing choice for vaccine development. Clinical studies using Janssen's Ad26-based vaccines for RSV, Ebola, COVID-19, and HIV have not shown any significant negative impact of naturally occurring neutralizing antibodies (Nabs) against the wild-type Ad26 virus on the immune responses induced by these vaccines. When there is the occurrence of vaccine-induced anti-Ad26 vector Nabs, the immunological responses that are specified to the vaccine's targeted antigen are enhanced when the Ad26-based vaccine containing the same genetic material is administered repeatedly. In summary, the presence of pre-existing neutralizing antibodies against the Ad26 virus does not appear to hinder the effectiveness of Ad26-based vaccines in generating strong immune responses against the targeted antigens. Instead, subsequent doses of the Ad26-based vaccine can enhance the immune responses to the specific antigens encoded by the vaccine when these neutralizing antibodies are already present due to prior exposure to Ad26 or related vaccines. [12]

Ad26.Filo consists of three non-replicative recombinant vaccines based on Ad26, combined in a 1:1:1 proportion. These three vaccines are Ad26.MARV, Ad26.ZEBOV and Ad26.SUDV, which encodes the glycoproteins (GPs) of MARV, EBOV, and SUDV, respectively. [13]

The adenoviral vector vaccines and heterologous adenovirus vector / MVA vector vaccines have been tested in non-human primate (NHP) and human studies. Two trials were conducted to evaluate this vaccine strategy, one in humans and one in NHPs. During these trials, the vaccines utilized adenoviral vectors that expressed filovirus glycoprotein(s). The options for vaccination included either Ad.26 ZEBOV alone or a combination of Ad.26 ZEBOV + Ad35 ZEBOV. Additionally, a separate vaccination involved the MVA-Bn-Filo construct. The MVA vector included glycoproteins from Sudan virus, Tai Forest virus, Ebola virus, and Marburg virus. Both trials demonstrated the efficacy and antigenicity of the non-identical regimen in NHPs. The vaccines were found to be safe in both humans and NHPs. The presence of cross-reactivity towards the filovirus glycoproteins was detected. In a human clinical trial, a phase 1 study conducted by Milligan and colleagues explored the effectiveness of a vaccine utilizing MARV glycoprotein in combination with a human adenovirus 26 vector. Additionally, this method was augmented by MVA-Bn-Filo, which incorporates a modified vaccinia Ankara vector containing glycoproteins sourced from the Sudan virus, Ebola virus, Tai Forest, and Marburg Virus nucleoproteins. Notably, no severe adverse effects were linked to this vaccine strategy, and all participants exhibited detectable IgG response to the Ebola virus at both 21 days after vaccination and 8 months later. However, the study did not present specific immunogenicity outcomes related to the Marburg virus, the study only recorded reactions to the Ebola virus component of the vaccine. [14,15]

Recently, Janssen developed an adenovirus (Ad)-based vaccine utilizing an Ad26 vector that encodes the MARV Angola GP. This vaccination approach is built upon the EBOV prime/boost vaccine Zabdeno/Mvabea (Ad26-ZEBOV/MVA-BN-filo), which has been approved by the European Medicines Agency (EMA). In preclinical trials for Marburg virus disease (MVD), the prime-boost vaccination with Ad26-MARV/Ad35-MARV demonstrated protection against MARV-Angola and elicited durable antibody responses. The vaccine has progressed to phase 1 clinical trials in the United States, where its immunogenicity as a single-dose vaccine is being evaluated. Additionally, the study aims to investigate the potential benefits of a booster vaccination using the EMA-approved vector Mvabea (MVA-BN-Filo) or another adenovirus-vectored filovirus vaccine. [16, 17]

The selection of Adenovirus vectors (Ad.26 and Ad.35) and the MVA vector for these studies stemmed from their established history of safety and effectiveness in numerous vaccine and clinical trial implementations. The use of these vectors in the heterologous regimen showed promising results in terms of efficacy and immune response in both animal and human studies. [14, 15]

2. Chimpanzee adenovirus 3 (ChAd3)-MARV vaccine.

The vaccine candidate, ChAd3-MARV, is composed of DP ChAd3 Marburg Angola with the lot number (LN) RL20-0006 and is an aseptic, adjuvanted-free, neutralized, water-

based solution. A specific formulation buffer is used to fill single-dose vials with the ChAd3-Marburg (LN RL20-0004) drug substance, constituting the ChAd3-MARV vaccine with each ampoule containing a vaccine volume of 1.2 ± 0.1 mL, with a total concentration of 8.21 × 1010 virus particles (vp) per milliliter. The ChAd3-MARV vaccine and its formulation with A195 Light buffer. The researchers observed data suggesting that the vaccine has the potential to induce T-cell responses, which are important for cellular immunity. It is also anticipated that the same vaccine formulation can induce both humoral (antibody-based) and cellular immunity. The probability is based on previous findings from studies involving similar vaccines that use the ChAd3 platform in both non-human primates (NHPs) and humans, which showed that these vaccines can stimulate both types of immune responses effectively. In summary, the researchers believe that the ChAd3-MARV vaccine in the A195 Light formulation can potentially activate a robust immune response, involving both antibodies and T cells, which could be beneficial in protecting against the target disease. [18]

To endorse, back, or substantiate the authorization of the chimpanzee adenovirus 3 (ChAd3)-MARV vaccine, which had already undergone phase 1 trials. The ChAd3 vector used in the vaccine is nonreplicating and has been proven to be protected in human subjects. In the study, it was demonstrated that the vaccine protected a consistently fatal opponent with the Marburg virus (MARV) strain Angola. The defensive immune mechanism conferred by the vaccine was observed within just 7 days after vaccination and remained effective for at least one year after vaccination. The study identified antigen-specific antibodies as a crucial immune correlation associated with protection in the acute challenge model, along the amount of these antibodies was found to predict protection against MARV. Results show that the single-shot ChAd3-MARV vaccines effectively produced a protective immunological response that was not only quick but also long-lasting. The presence of a specific correlate of immune protection reinforces the potential of the vaccine for further advanced clinical development, supporting its potential approval for widespread use to combat Marburg virus infection. [19]

In a recent study by MJ et al. in response to the emergence of the Marburg virus as a significant threat, a critical phase 1 clinical trial was conducted. This study aimed to address the urgent need for a vaccine against the virus, particularly emphasized by its recent outbreak in Ghana. Healthy adults were enlisted as participants, and they received a single dose of the vaccine, which utilized an innovative approach involving a chimpanzee adenovirus type 3 vector. The main emphasis of the trial was to assess the safety and efficacy of this vaccine candidate. The trial was carried out at the renowned Walter Reed Army Institute of Research Clinical Trials Center in the USA by the Sabin Vaccine Institute. During the trial period, researchers meticulously monitored and evaluated the vaccine's impact on the participants. Promisingly, the vaccine demonstrated a robust safety profile, with no severe adverse effects reported among the participants. This finding is of paramount importance when considering the potential for broader vaccine deployment. Furthermore, the vaccine elicited strong immune responses within the participants, a key indicator of its efficacy. Particularly noteworthy was the production of antibodies targeting the Marburg virus glycoprotein, a pivotal component for neutralizing the virus and preventing infection. Even more impressive was the duration of these immune responses. The antibodies remained at significant levels even 48 weeks after the initial vaccination, suggesting the potential for long-lasting protection against the virus. The trial's success represents a substantial leap forward in our ability to combat Marburg virus outbreaks. By showcasing the vaccine's safety, efficacy, and ability to induce enduring immune responses, this study lays a solid foundation for further research and development in the fight against this emerging and potentially deadly pathogen. [17, 20]

Utilizing the ChAd3 platform, Sabin's single-dose investigational Marburg vaccine has demonstrated promise in Phase 1 clinical and non-clinical studies, exhibiting safety and eliciting rapid, robust immune responses. The Sabin Vaccine Institute has initiated a Phase 2 clinical trial for this vaccine against the lethal Marburg virus. Administered to healthy volunteers at Makerere University Walter Reed Project (MUWRP) in Kampala, Uganda, on October 19, 2023, the Phase 2 trial aims to further assess safety and immunogenicity among a larger participant cohort. This randomized, placebo-controlled, double-blind study involves concealing whether participants receive the vaccine or a placebo until the trial concludes, minimizing experimental bias. The trial spans a full year, monitoring participants across different age groups, including younger (18-50 years) and older (51-70 years) individuals. Interim results are anticipated next year. In addition to ongoing trials in Uganda and Kenya, Sabin intends to conduct a similar Phase 2 clinical trial for Marburg in the United States. (21)

3. MARV Virus Like Particles (mVLPs).

One of the promising approaches for the development of the Marburg vaccine is the use of VLPs which are non-infectious particles with no viral genome that mimic the structure of the virus. Successful Virus-Like Particle (VLP)-based vaccines, which have achieved significant success and widespread acceptance are briefly introduced in combination with the latest findings from clinical trials. [22] VLPs in the field of vaccines have emerged to be a potential framework for a vast set of viral pathogens comprising both enveloped and nonenveloped viruses. For MARV VLP vaccines, a pair of non-human primate infection studies and one study aiming to analyze immunological reaction to the vaccine. In the challenge studies of Dye et al. and Swenson et al., the entire group of 22 vaccinated animals survived. In the study of Dye. et matrix protein 40, nucleoprotein, and Marburg glycoprotein were utilized in the vaccine, which was found to be 100% productive in saving all 13 non-human primates from the disease. Animals in the adjuvant-treated control group unveiled noticeable symptoms of the

Marburg disease and had to be euthanized. Conversely, in the study of Swenson et al. in which the NHPs were injected subcutaneously (1000 Plaque Forming Units), all 3 out of 3 controls died. [12,22] In all the 3 mentioned studies, binding antibodies were raised, but the study of Weiwei et al. observed neutralizing antibody effects. In addition, only this study recorded induced responses of T-cells upon vaccination, showing elicited levels of interleukin 4 and interferon-gamma indicating that T helper 2 and T helper 1 both were activated which is an indication of adaptive immunity activation. According to the results, all 3 animals showed significant elevation of concentration of IGg against the glycoprotein of MARV [24]

4. DNA-GP Vaccines.

The genetic content and selection of vector delivery have an impact on the durability and antigenicity of genetically modified vaccines. DNA vectors have been demonstrated to be an effective vaccine combination that can demonstrate efficacy when mixed with a prime-boost regimen of rRNA or viral vectors, but there has been limited comparison between the various types of vaccines in primates due to possible cell targeting and suboptimal gene expression. In this research, different vaccination strategies were assessed to gauge their efficacy in providing immune defense against lethal infection caused by the Angola Marburg Virus (MARV). These approaches involved the utilization of DNA plasmids engineered to enhance antigen expression, as well as recombinant adenovirus (rAd) vectors, all carrying the glycoprotein (GP) gene from MARV. The evaluated vaccines included DNA plasmid vaccines, such as single-modality rAd5-GP and DNA-GP-only vaccines, as well as a heterologous DNA-GP/rAd5-GP prime-boost regimen. Remarkably, all vaccinated participants survived even after exposure to a lethal dose of MARV Angola, indicating the promising effectiveness of these vaccination methods. Humoral responses were induced by these vaccines as compared to when induced following a solitary inoculation with rAd5-GP, strong cellular immune responses were elicited, involving both CD8(+) and CD4(+) T-cells. Significantly, the immune response demonstrated a prominent bias toward CD4(+) T-cell activation specifically targeted at the MARV GP antigen. Vaccination schedules incorporating rAd-GP, with either a booster or administered alone, demonstrated notable cellular responses characterized by a prevalence of CD8(+) T-cell activity. Among the different vaccine groups, a significant CD8(+) T-cell subset dominance was observed, characterized by cells exhibiting a functional phenotype with both gamma interferon (IFN-gamma) and tumor necrosis factor-alpha (TNF- alpha) double-positive properties. Interestingly, when this CD4(+) T-cell dominance was observed, there was either an absence of clinical symptoms or a low frequency of such symptoms. This finding indicates that both the functional phenotype and magnitude of CD8(+) T cells play a vital role in determining vaccine efficacy versus MARV Angola infection. [25]

Under the research conducted by Grant Klein et al. Cynomolgus macaques received vaccinations through an intramuscular route, using distinct DNA plasmids that expressed the glycoprotein (GP) genes of either the Marburg virus (MARV) or Ebola virus (EBOV). Additionally, a combination vaccine containing codon-optimized glycoprotein DNA for Sudan virus, EBOV, Ravn virus, and MARV was also administered to a group of macaques. The immune responses of the vaccinated macaques were assessed using various assays. The results showed that individual vaccines for EBOV or MARV elicited slightly higher IgG responses when assessed by ELISA compared to the combination vaccines. Nevertheless, upon evaluation using pseudovirion neutralization and IFN-γ ELISpot assays, no noteworthy variations in immune responses were observed between the macaques who received individual vaccines and those who received combination vaccines. These results suggest that both types of vaccines elicited comparable immune responses. Furthermore, both the MARV vaccine and the mixed vaccine (containing multiple GP genes) were effective in protecting the macaques from lethal MARV challenge with the majority of animals surviving in both groups. On the contrary, a greater percentage of vaccinated macaques who received the EBOV vaccine alone demonstrated survival following a lethal EBOV challenge in comparison to those administered with the mixed vaccine. Notably, the surviving macaques exhibited notably higher pre-challenge neutralizing antibody titers when compared to those that did not survive the EBOV challenge. These findings suggest that the combination vaccine, while effective against MARV, may not be as efficacious as the individual EBOV vaccine in conferring immunity against lethal EBOV inoculation. The difference in neutralizing antibody titers between survivors and non-survivors indicates that the level of pre-existing immunity might play a role in determining the outcome of EBOV infection in vaccinated macaques. Additional research is essential to comprehend the elements that impact vaccine effectiveness and immune responses in the context of various viral challenges. [26]

The Kibuuka et al. study conducted a clinical trial involving human participants, enrolling a total of 108 individuals between November 2, 2009, and April 15, 2010. The chief aim was to assess the reliability and immune response effectiveness of two vaccines designed to target both Ebola and Marburg viruses. Every participant received a minimum of one study injection, and 100 individuals successfully adhered to the injection regimen. The research evaluated the capacity of these vaccines to be tolerated and the resulting antibody and T-cell responses. The research revealed that the vaccines were effectively tolerated, and there were no notable variations in reactions, whether local or systemic, among the different groups. Both vaccines induced targeted antibody and T-cell reactions against the glycoproteins of Ebola and Marburg viruses. Notably, there were no notable dissimilarities in immune responses when the vaccines were administered separately or together. In the group of MAR vaccines: 31% of participants exhibited an immune reaction in the form of antibodies to the Marburg glycoprotein while

52% of participants exhibited a T-cell response to the same glycoprotein. These findings hold importance as they mark the inaugural Marburg or Ebola vaccine trial held in Africa. The study showcases the favorable tolerance and capability of both vaccines to trigger immune responses, including antibodies and T-cells tailored to the specific glycoproteins, whether administered individually or in combination. [27]

The VRC 206 study assessed DNA vaccines containing wild-type glycoproteins (GPs) from Ebola Virus and Marburg Virus in humans. Given through intramuscular injection at intervals of 0, 4, and 8 weeks, followed by a booster shot at or after week 32, the vaccines demonstrated safety and good tolerability. By week 12, 80% of subjects showed positive immune responses, as indicated by enzyme-linked immunosorbent assay results. Notably, the fourth vaccine dose further amplified these responses. The study's findings suggest the potential for inducing protective immunity against these viruses using wild-type GP antigens in vaccine development. [28]

5. rVSV-MARV-GP.

In nine NHP trials investigating VSV-vectored Marburg vaccines (totaling 104 animals), studies were diverse, including post-exposure prophylaxis, neurovirulence assessment, and efficacy in the Marburg challenge (8 studies). Across 8 challenge studies in non-human primates (NHP), VSV vaccines demonstrated noteworthy effectiveness, achieving 100% efficacy in 6 of these studies. Different dosing methods were employed in these trials, targeting both the Angola and Musoke variants of the virus. [14]

In a study by Mire et al. six *Cynomolgus macaques* were vaccinated with rVSV-MARV-GP, and after 14 months, the animals were challenged with the virus, showing no sign of the disease which demonstrated the presence of anti-MARV GP Ig G antibodies during the period before the infection, hence this vaccine provided complete protection against the infection of MARV. [29]

Mire et al. assessed the presence of neurovirulence symptoms in *Cynomolgus macaques* following vaccination with recombinant VSV (Vesicular Stomatitis Vector) vaccines targeting Marburg and Ebola. They introduced a parent vector (rVSV-wt) and vehicle control groups. Out of 21 animals, two out of three subjects vaccinated with rVSV-wt exhibited pronounced neurological symptoms. Conversely, animals vaccinated with the vehicle control group, rVSV-MARV-GP, or rVSV-EBOV-GP manifested no indications, thus supporting the safety of this vaccine for potential human usage. [30]

In the study conducted by Geisbert et al., non-human primates were subjected to aerosol challenge with Marburg and Ebola viruses. Remarkably, all of the monkeys that were vaccinated with VSV vector vaccines demonstrated survival, while in the control group, all the monkeys succumbed to the infections. These compelling findings underscore the significant efficacy of VSV vector vaccines in protecting deadly aerosolized exposures to Ebola and Marburg viruses in non-human primate models. [31]

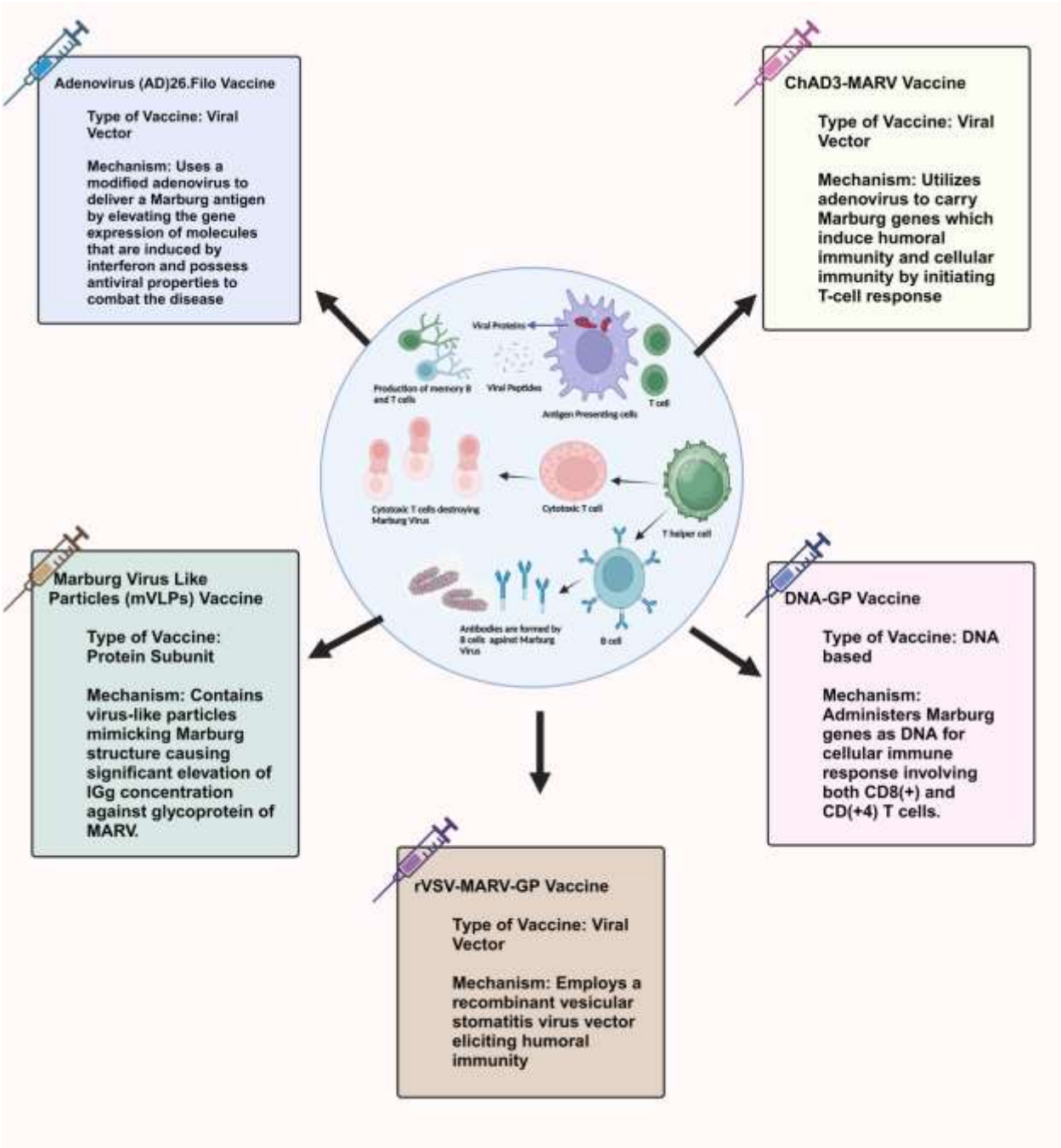
In post-exposure immunity against the Marburg virus, three studies proved the efficacy of the VSV vector vaccine. In the study by Daddario-Dicaprio et.al, all three monkeys that were infected with the highly deadly dose of the virus survived for eighty days after being administered by the rVSV MARV vector while all the control animals succumbed till day 12. [32]

Another study that experimented on post-infection therapy for the Marburg virus showed that the rVSV-based vaccine conferred protection to Rhesus monkeys from the Marburg virus when delivered within 20–30 minutes post-infection. Subsequent administration at 24 hours led to 5 out of 6 monkeys being protected, but this rate decreased to 2 out of 6 animals when given after 48 hours. [33]

In a study by Woolsey et al. the rVSV vaccine carrying the glycoprotein from the Marburg virus (MARV) the variant of Musoke provided complete protection for macaques against Ravn virus and two MARV variants when administered as either a preventive vaccine or a postexposure treatment. However, when tested against the more virulent MARV variant Angola, with the treatment given 20-30 minutes after exposure, the efficacy reduced significantly, resulting in a survival rate of only 25% in high-dose exposure and 60-75% in low-dose exposure. This diminished effectiveness is likely due to the faster disease progression of the variant of Angola compared to the variant of Musoke. [34]

These five mentioned vaccines exhibit promise in combating the Marburg virus. Notably, each vaccine employs distinct mechanisms of action and falls into different categories, emphasizing the importance of varied approaches in advancing to further testing stages. This diversity in modes of action and vaccine types underscores their significance in comprehensive evaluations for potential effectiveness against the Marburg virus**. (Figure 3)**

Fig 3| Marburg Virus Vaccines Mechanisms and Delivery.



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DISCUSSION:

The development of vaccines for Marburg virus (MARV) presents a critical component of our preparedness against this highly contagious and deadly pathogen. Several vaccine approaches have been explored, each with its unique strengths and considerations. In this discussion, we will delve into the key findings from various studies and vaccine candidates, drawing from your provided references.

Adenovirus-based vaccines, particularly Ad26.Filo has shown significant promise in the fight against the Marburg virus. Ad26 vectors, belonging to Ad species D, have been harnessed to develop vaccines targeting MARV. The vaccine combines Ad26.MARV, Ad26.ZEBOV, and Ad26.SUDV, each encoding glycoproteins for different

filoviruses. Clinical trials involving Ad26-based vaccines have demonstrated their safety and efficacy in both non-human primates (NHPs) and humans. The presence of pre-existing neutralizing antibodies against Ad26 does not appear to hinder the effectiveness of these vaccines. Instead, subsequent doses of the Ad26-based vaccine can enhance immune responses, providing a promising avenue for vaccine development [12-15].

Chimpanzee adenovirus 3 (ChAd3)-MARV vaccines have also been investigated. These vaccines have shown the potential to induce robust immune responses, including both humoral and cellular immunity. Studies on NHPs and humans have highlighted their safety and effectiveness in protecting against Marburg virus infection. These findings are significant, particularly in the context of recent Marburg virus outbreaks [18-20].

Marburg Virus-Like Particles (mVLPs) represent another promising approach. VLP-based vaccines have demonstrated significant success against MARV in NHPs. These studies indicate that mVLP vaccines can effectively induce binding antibodies, neutralizing antibody effects, and T-cell responses, all crucial components of adaptive immunity [22-24].

DNA-GP vaccines have been explored with positive results. These vaccines have shown effectiveness in protecting against lethal MARV infection, inducing both humoral and cellular immune responses. The balance between CD4(+) and CD8(+) T-cell activation appears to be a critical factor in vaccine efficacy [25, 26].

The rVSV-MARV-GP vaccine has demonstrated high efficacy in various NHP trials. These studies have shown remarkable effectiveness against the Marburg virus, with the vaccine conferring protection even when administered after viral exposure. The presence of pre-existing immunity and the choice of viral variant can influence vaccine effectiveness, indicating the importance of tailored approaches [29-34].

In short, the development of Marburg virus vaccines is a dynamic field with multiple promising candidates. Each vaccine approach, whether based on adenoviruses, chimpanzee adenoviruses, VLPs, DNA, or rVSV vectors, has its unique strengths and considerations. The successful outcomes of preclinical and clinical trials suggest that a multi-pronged approach to vaccine development, potentially incorporating different strategies, could be crucial in our efforts to combat this deadly pathogen. Furthermore, understanding the role of pre-existing immunity and tailoring vaccines to specific viral variants is essential in achieving optimal protection. These findings pave the way for further research and development in our quest to prepare for and respond to Marburg virus outbreaks.

CONCLUSION.

In conclusion, the Marburg Virus (MARV) is a deadly RNA virus from the family of filovirus known for inducing severe and life-threatening hemorrhagic fever. It was initially transmitted to humans from Egyptian rousette bats, acting as natural reservoirs. To comprehensively address MARV outbreaks, the SPIN framework considers social context, possible transmission paths, and determinants, guiding public health actions for disease control. MARV infection presents three phases, each with distinct symptoms and outcomes. Significant endeavors have been made to address MARV, resulting in the advancement of promising vaccines and therapeutic approaches. Notably, Adenovirus (Ad)26. Filo vaccine and ChAd3-MARV vaccine have shown promise in animal and human studies. The Ad26.Filo vaccine uses Ad26 vectors encoding glycoproteins from EBOV, SUDV, and MARV, demonstrating efficacy and safety. Additionally, Marburg Virus Like Particles (mVLPs) have emerged as a promising approach, to protecting vaccinated animals. Additionally, DNA-GP vaccines have proven to be efficacious, eliciting robust cell-based immune responses characterized by a CD8(+) T-cell dominance in response to MARV. VSV-vectored vaccines demonstrate encouraging results in NHP trials against the Marburg virus, but efficacy varies with different variants, necessitating further investigation.

However, despite advancements, MARV remains a neglected infectious disease, emphasizing the need for approved vaccines and therapies. The ongoing research and clinical trials offer hope for the development of effective vaccines to combat this deadly virus. The findings from these studies contribute to the continuous efforts to improve our understanding of MARV and enhance our capacity to respond to potential outbreaks.

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LIST OF ABBREVIATIONS.

MVD: Marburg Virus Disease
EVD: Ebola Virus Disease
FHF: Filovirus hemorrhagic fever
HIV: Human Immunodeficiency Virus
RSV: Recombinant Stomatitis Virus
SUDV: Sudan Virus

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Conceptualization: [Amna Zaheer]; Literature Search: [Amna Zaheer, Daniyah Zehra Hussain]; Writing - original draft preparation: [Amna Zaheer]; Writing - review and editing: [Ahmad, Akhtar, Daniyah Zehra Hussain]; Supervision: [Ahmad Akhtar]

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