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Review Article

Current Status and Prospects for Development of a Vaccine against African Trypanosoma: A Review

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Abstract: ***Background*:** African trypanosomiasis, a disease caused by *Trypanosoma brucei*, remains a significant health challenge in sub-Saharan Africa, particularly in rural communities with limited healthcare access. Despite control efforts, the disease persists due to the parasite's complex immune evasion mechanisms, including antigenic variation and destruction of the host's humoral immune response. Current treatments face limitations, and the development of an effective vaccine is stalled by the parasite's genetic diversity and insufficient research funding. ***Objective*:** This review aimed to compile recent advancements in vaccine development against African trypanosomiasis, evaluate potential vaccine candidates, and identify challenges and future directions for developing an effective vaccine. ***Method*:** We adopted the PRISMA protocol to guide our systematic literature on Medline/PubMed and Google Scholar databases, focusing on studies published between 2005 and April 2025. ***Results*:** The findings revealed several encouraging approaches to vaccine development against African trypanosomiasis. DNA vaccines targeting specific parasite proteins have demonstrated partial protection in animal studies, stimulating immune responses that delay disease progression. The *T. brucei* membrane surface protein B (Tbmsp-b) gene was cloned into a pVAX-1 plasmid and administered into a BALB/c mice model, conferring partial protection. Similarly, DNA plasmid encoding an invariant surface glycoprotein (ISG) of *T. brucei* provided partial protection against T. brucei in the BALB/c mice model. Plasmid DNA containing the 5′-terminal region of the *T. brucei brucei* trans-sialidase (nTSA) gene also provided partial protection in BALB/c mice. Innovative computer-designed vaccines, which combine multiple *T. brucei* epitopes, showed particular promise against the parasite's variability in terms of antigenicity. Finally, another promising approach involves the application of virus-like particles (VLPs) as vaccine adjuvants which presents an approach for incorporating protozoan antigens into vaccines targeting *T. brucei*. ***Conclusion*:** While DNA vaccines, Multi-Epitope Vaccines, and VLP-based vaccines show promise, further research is needed to optimize their efficacy. A combined approach integrating multiple antigens and synergistic immune responses may offer the best solution for developing an effective vaccine against African trypanosomiasis. Addressing funding gaps and advancing clinical trials are critical to achieving this goal.

Keywords: "Trypanosoma", "African Trypanosomiasis", "Trypanosoma Vaccine", "Vaccine" "Vaccine Candidates".

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1.0 INTRODUCTION

Human African trypanosomiasis (HAT) is a neglected tropical disease that is caused by flagellated parasites of the genus *Trypanosoma* and species Brucei, primarily *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* [1, 2]. Infection with *rhodesiense* is zoonotic, with occasional infection of humans. Humans are the main reservoir for the *gambiense* and play a key role in the transmission cycle of the disease [3]. The parasitic infection almost invariably progresses to death unless treated [4]. HAT was endemic in 36 sub-Saharan African countries where

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the transmitting vector, tsetse flies, are found, but sustained and concerted control actions by national governments and international organizations have significantly reduced the number of new cases and paved the way for the elimination target by 2030 [5]. Despite these recent successes, the disease is still endemic in parts of sub-Saharan Africa, where it is a considerable burden on rural communities, notably in central Africa [1-4]. The intricate relationship between poverty and African trypanosomiasis exacerbates its impact, as it predominantly affects marginalized populations in remote rural areas, where healthcare access is limited. Furthermore, the seemingly neglect of research and development for treatments is evident, stemming from pharmaceutical companies' hesitance to invest in products for neglected tropical diseases due to low profitability and high research and development costs [6].

Trypanosomes use a combination of several independent mechanisms to avoid clearance by the humoral immune system. First, perpetuated antigenic variation of the surface coat (variant surface glycoprotein) allows them to escape antibody-mediated elimination [7]. Secondly, when antibodies bind to the coat, they are efficiently transported toward the endocytosis pathway, where they are removed from the coat proteins. Finally, trypanosomes engage in the active destruction of the mammalian humoral immune response [8].

The epidemiology of the disease is mediated by the interaction of the parasite (trypanosome) with the vectors (tsetse flies), as well as with the human and animal hosts within a particular environment. Related to these interactions, the disease is confined in spatially limited areas called "foci", which are located in Sub-Saharan Africa, mainly in remote rural areas. The risk of contracting HAT is, therefore, determined by the possibility of contact of a human being with an infected tsetse fly [3]. Epidemics of HAT were described at the beginning of the 20th century; intensive activities were set up to confront the disease, and it was brought under control in the 1960s, with fewer than 5,000 cases reported in the whole continent. The disease resurged at the end of the 1990s. Renewed efforts from endemic countries, cooperate agencies, and nongovernmental organizations led by the World Health Organization succeeded in raising awareness and resources, while reinforcing national programs, reversing the trend of the cases reported, and bringing the disease under control again [3]. The control of African trypanosomiasis depends on the detection and treatment of positively diagnosed cases, the treatment of economically important animals, and efforts to control the insect vectors [8]. This is impeded by many throwbacks such as the drugs' limited effectiveness, complex dosing, drug resistance, and lack of an efficacious vaccine regimen. Despite more than a century of research and investigations, the development of a vaccine for HAT is still not achieved due to the complex nature of the parasite [1].

Considering the growing number of cases and the complex nature and mechanisms of *T. brucei*, conscious efforts to develop an effective vaccine against African trypanosomiasis, have gained momentum [9]. Detecting antigens and methodologies with a high potential for antibody formation is the main focus of vaccine development efforts. This is motivated by the assertion that the main defense against extracellular trypanosomes should be the generation of B cell-mediated antibodies [10]. Promising vaccine candidates have entered different phases of research as a result of recent developments in immunology. According to research on novel vaccine formulations, a novel strategy that incorporates antigens may improve immune responses, therefore, raising the effectiveness of possible vaccinations. Moreover, because nano-biotechnology increases bioavailability and decreases toxicity, two critical factors in the treatment of neglected diseases like HAT and its application in vaccine delivery systems have demonstrated considerable promise [9]. Developing effective vaccines against African Trypanosomiasis is faced with challenges that hinder progress and a vaccine breakthrough. One major challenge is the complex nature of the *Trypanosoma* parasite, which exhibits antigenic variations and complicates the identification of stable vaccine targets [1]. However, new-generation vaccinations with improved antigenicity and safety have been made possible by advancements in computational modeling. A multi-epitope vaccination (MEV) that is made from a group of antigenic peptides is one of these novel strategies. An MEV vaccine can stimulate both humoral and cellular immune responses as well as prevent possible allergenic reactions.

Pharmaceutical corporations tend to target more lucrative areas of study which makes the lack of funding and investment in research on neglected tropical diseases even more problematic [11, 12]. These are mostly demonstrated by the low funding allocated to research and development for illnesses that primarily impact sub-Saharan Africans [13]. Financial barriers are still significant even if product development agreements have been formed to sponsor vaccination research. Innovative financial mechanisms that could sustain long-term expenditures in vaccine development such as public-private partnerships tailored for neglected diseases, should address these financial obstacles [14].

This review compiles the most recent information on the development of vaccines against African *Trypanosoma*, highlights important developments, and pinpoints pertinent issues and potential paths forward. The review also provides a thorough summary of the advancements made in the identification and testing of possible vaccine candidates, as well as the underlying immunological mechanisms, by analyzing the potential vaccine candidates.

2.0 METHODOLOGY

2.1 Search Strategy

This study was carried out in accordance with the Cochrane library guidelines and is described in line with the PRISMA statement for reporting systematic reviews. A thorough literature search was performed in Medline/PubMed and Google Scholar databases. The search phrases included were "Trypanosoma", "African trypanosomiasis", "Trypanosoma vaccine", "vaccine" "vaccine candidates," and "immunization". These search terms were applied to the Boolean search strings “OR” and “AND” to maximize the recovery of articles.

2.2 Inclusion and Exclusion Criteria

To provide a thorough review of potential vaccine candidates against African trypanosomiasis, the inclusion criteria made sure that only the most recent and relevant studies were taken into account. Relevant publications from 2005 to March 2025 were considered for the review. Additionally, only English-language publications were included to prevent possible errors in interpretation. Research publications that addressed vaccine candidates for African Trypanosoma were the main focus of the review.

Articles published before 2005 were not included to maintain the review’s focus on relatively current advancements in African trypanosome vaccine development. Moreover, papers written in languages other than English were also excluded. Editorials, commentaries, and opinion pieces that do not have original research data were not included. Also, systematic reviews were excluded. To preserve the review's specificity, studies on parasites other than African *Trypanosoma* or its vaccine candidates unrelated to this context were also excluded. To guarantee the accuracy and legitimacy of the data in this review, non-peer-reviewed sources were also excluded.

2.3 Data Extraction

Data were extracted from the selected articles, including vaccine type, immunogenicity and efficacy, safety, and study design. The quality of the studies was assessed using the Cochrane risk-of-bias tool.

3.0 RESULTS

3.1 Articles Identification, Screening, Eligibility, and Inclusion

As shown in Figure 1, a total of 361 articles were retrieved from Medline/PubMed and Google Scholar databases. Out of these, 180 articles (49.9%) were assessed using the text of the title and abstract after the removal of duplicates. Following the screening of titles and abstracts, 141 articles were excluded due to their irrelevance to the subject matter. Finally, 39 articles were assessed for eligibility per the inclusion criteria, of which 14 were review articles, 11 were duplicates and 8 did not follow the study protocol and hence were excluded. 6 articles were eventually found to fulfill the selection criteria, hence included in this review.

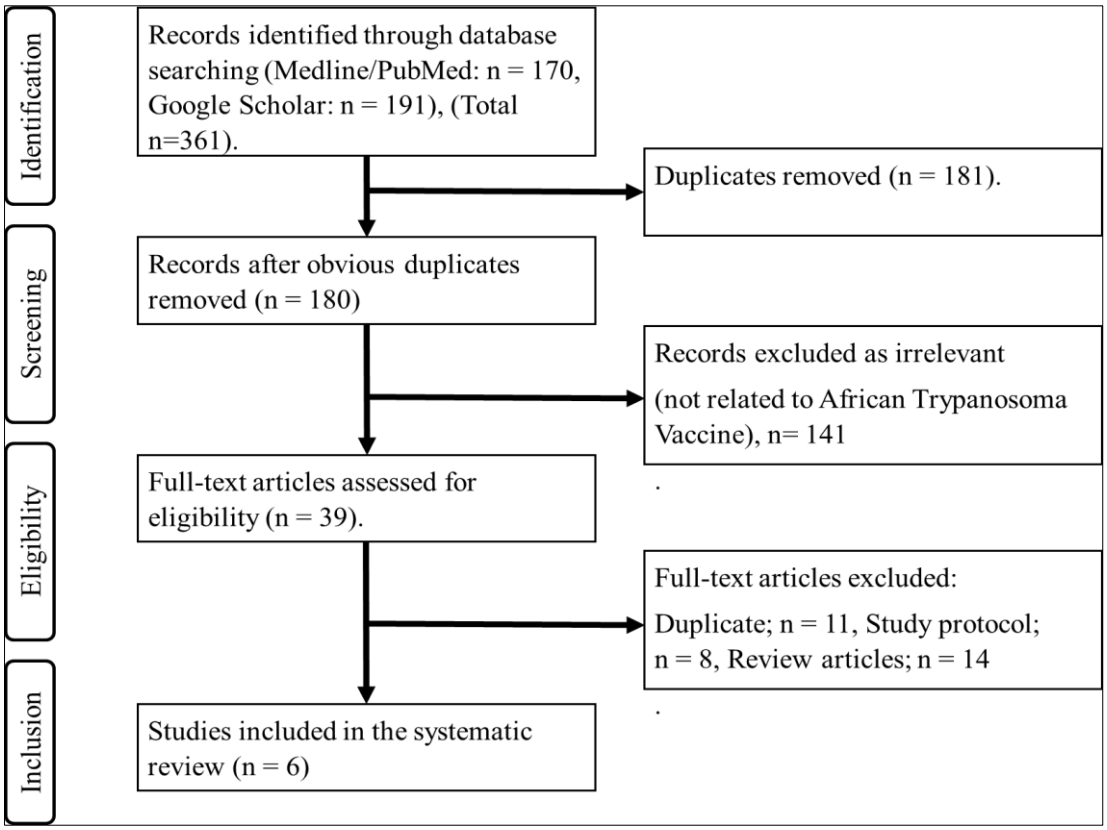

Figure 1: A simplified PRISMA diagram indicating the article identification, screening, eligibility and inclusion criteria

3.2 Findings from the Reviewed Articles

Because of the intricate nature of the African *Trypanosoma* parasite, developing a vaccine to combat it remains difficult even after more than a century of studies [1]. The process of mediating antigenic diversity through VSG release and surface localization is one method of vaccine development. The parasite can survive in its host owing to this crucial stage. A likely effective vaccine target is the gene Tbmsp-b that codes for molecules that mediate such processes. The vaccine designed was able to confer the immunized mice partial protection [5].

Using a DNA vaccine model to evaluate the effectiveness of immunization in mice infected with *Trypanosoma brucei brucei* is another potential approach. BALB/c mice administered with a single dose of a DNA plasmid encoding an invariant surface glycoprotein (ISG) from the parasite's bloodstream stage showed partial protection against a deadly *T. b. brucei* assault [15].

Similarly, BALB/c mice that received a single 100 µg dose of a plasmid DNA containing the 5′-terminal portion of *T. brucei brucei* trans-sialidase (nTSA) gene produced IgG antibodies. These antibodies identified the recombinant nTSA protein and interacted with protein extracts from *T. brucei* and provided partial immunity to the experimental mice [16].

Furthermore, a novel approach to vaccine development by employing multi-epitope vaccines (MEVs), which are composed of specific antigenic peptides has been investigated. Although they offer partial protection, MEVs minimize allergic hazards while increasing antigenicity and safety by inducing humoral and cellular immune responses [1-17].

The application of virus-like particles (VLPs) as vaccine adjuvants presents a promising approach for incorporating protozoan antigens into vaccines targeting *Trypanosoma brucei*. The parasite's immune evasion strategies and important antigens involved in host-parasite interactions have been studied and in order to create and test new vaccines, the immunostimulatory properties of VLPs may be essential [18].

Table 1: Potential Vaccine Candidates for African Trypanosomiasis

#	Vaccine Candidate	Model	Immunological Outcome	Reference
1	DNA vaccine (pVAX-1- Tbmsp-b)	Mice	Partial protection	[5]
2	DNA plasmid encoding ISG	Mice	Partial protection	[15]
3	Plasmid DNA encoding nTSA gene	Mice	Partial Protection	[16]
4	Multi-epitope vaccine	Computational	Partial protection	[1, 17]
5	Trypanosomatids antigens with virus-like particles (VLPs)	Computational	Partial protection	[18]

4.0 DISCUSSION

One promising approach to vaccine development is targeting vital parasite components that support the functions of variable surface glycoproteins (VSGs). The main surface protease, B (MSP-B) of *Trypanosoma brucei* is one such possibility. It is essential for removing old VSGs so that new ones can be expressed, which is an important immune evasion strategy. A DNA vaccine candidate was designed by cloning the Tbmsp-b gene onto a pVAX-1 plasmid. Comparing immunosuppressed mice to controls, the former showed significantly higher levels of IgG and γ-IFN, decreased parasitemia (by 75% and 51.2% in the first and fifth weeks post-infection, respectively), and increased life by up to 22 days. These results show MSP-B's potential as an antigen for African trypanosomiasis vaccines by suggesting that MSP-B-based DNA vaccinations may provide susceptible BALB/c mice with some protection against *T. b. brucei* (Federe strain) [5].

In a similar vein, it has been demonstrated in experimental models of African Trypanosoma (BALB/c mice) that DNA vaccines containing the invariant surface glycoprotein (ISG) antigen produce humoral immunity and partial protection. Th1-mediated immunity may be crucial for protection, as evidenced by the immune response's tilt toward a Th1 profile, which was marked by increased IgG anti-trypanosome antibodies [15].

It has been demonstrated in another study that intramuscular immunization of BALB/c mice with a plasmid DNA encoding the N-terminal portion of *T. brucei* trans-sialidase (nTSA) produced IgG antibodies that could bind to both recombinant nTSA and parasite protein extracts. Significantly, 60% of the vaccinated mice showed no signs of illness, indicating that TSA is a promising candidate for vaccine development [16].

With recent developments in computational biology and omics data, which have completely changed the vaccine design process, the designing of multi-epitope vaccines with improved antigenicity and safety have been made possible using conserved putative membrane proteins from *T. b. gambiense*, the main agent of human African trypanosomiasis in West and Central Africa [1]. Structural stability, antigenicity, non-toxicity, and the ability to interact with important immunological receptors were all anticipated for the 402-amino acid construct; MEV. This MEV is positioned as a good option for HAT vaccine development since immune simulations revealed significant immunogenicity and

long-lasting memory responses. It is established that computational methods enable the development of customized vaccinations that target a variety of Trypanosoma species, potentially overcoming host immune response heterogeneity [17]. An ideal MEV should have epitopes that induce helper T cells, B cells and cytotoxic T cells in order to produce holistic immunity [19]. Moreover, it is established that combining several antigens into a single vaccination may improve results in animal models and possibly in people by utilizing synergistic immune responses throughout the stages of the parasite life cycle [11].

Vaccinations regimen based on virus-like particles have drawn interest because of their ability to mimic real illnesses and produce potent and long-lasting immune responses. Multiple antigens of trypanosomes can be shown by VLPs, increasing defense against different strains. For conditions like African trypanosomiasis, where strong T-helper responses are crucial, their natural adjuvant qualities further boost immunological activation and induce humoral and cell-mediated immunity [18]. VLP-based vaccines are still not well understood in trypanosomiasis, despite their potential. Although studies have been conducted on leishmaniasis [20, 21], and Chagas disease [22], their use in African trypanosomiasis has not yet been studied.

5.0 LIMITATIONS

There were inadequacy relevant publications on vaccine candidates against African trypanosoma; a neglected tropical disease. The capacity of this review to evaluate the real applicability of the vaccine candidates is limited by the lack of current, high-quality studies, particularly clinical trials. This is caused by temporal bias as well as the intrinsic difficulties of neglected tropical diseases research funding and publications. The generalizability of the findings of this review is hampered by gaps in geographical and strain-specific research.

6.0 CONCLUSION

Several approaches are being used to further the creation of an efficient vaccination to prevent African trypanosomiasis. Although they require optimization, DNA vaccines like pVAX-1-TBMSp-b, DNA plasmids encoding ISG, and plasmids encoding the nTSA gene are intriguing options. Partial protection is also offered by focusing on important parasite compounds, which emphasizes the necessity for optimization. The heterogeneity of parasites is a hurdle to peptide-based vaccines; nevertheless, by combining conserved epitopes, computational designs of Multi-Epitope Vaccines provide a route to widespread immunity. Although there is little study on African trypanosomiasis, VLP vaccines, which mimic natural infections and enhance immune responses, have great potential. To create effective and long-lasting vaccines against this illness, a combination strategy that incorporates several antigens and makes use of synergistic immune responses is essential, as is additional research on MEVs and VLPs.

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