Advancements in Parasitic Vaccinology: Novel Approaches and Technologies

AUTHORS DETAIL

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Abstract

Parasitic diseases continue to burden health and economies in developing countries, especially in low- and middle-income nations. Immunology and molecular biology have made tremendous strides in vaccine development against parasitic diseases, but their slow development has been largely hindered by the complexity of the parasite life cycle, immune evasion strategies, and antigenic diversity. Traditional approaches to vaccine development, which include live attenuated, inactivated, and subunit vaccines, have shown promise but are limited in terms of effectiveness, safety, and even scalability. New innovations within the context of vaccinology change the landscape that defines how vaccines are prepared against parasites. The advancement of genomics and proteomics as well as the reverse vaccinology and synthetic biology platforms enables the selection of novel antigens with the aim of optimizing vaccine construction. New platforms, such as mRNA-based vaccines, have emerged with better immune-generating and specificity-focused approaches in vaccine development and improved nanotechnology-based drug delivery mechanisms. Problems facing a lack of adequate, temporary immune responses have been handled with new adjuvant technologies and immunomodulating approaches. However, issues related to the cost and access of vaccines remain among under-resourced settings where they are needed the most. Multidisciplinary research, in collaboration with international health organizations, as well as the public and private sectors' partnership, have played an important role in these developments and will continue to be so. This chapter highlights the progress achieved in developing vaccines against parasitic infections. The focus of this chapter is on technological innovation and a holistic approach for the better control of parasitic diseases, thus reducing their burden globally and improving health equity.

Keywords: Vaccine development, Antigen discovery, Reverse vaccinology, mRNA vaccines, Nanotechnology

1. Introduction

Parasitic diseases of animals are one of the significant public health issues because of their potential to be zoonotic. The agents causing such diseases are varied, from protozoa to helminths. These pathogens are indirectly and directly transmitted through contaminated water or fecal matter (Pal et al., 2023; Khatoon, 2024). Many serious diseases are reportedly caused by zoonotic parasites, such as *Toxoplasma gondii*, *Echinococcus* spp., and *Giardia*, in human beings (Gómez-Muñoz, 2021; Pal et al., 2023). This situation is further exacerbated by the socioeconomic factors which increases the prevalence of these parasites by inadequacies in sanitation and veterinary service in under developed countries (Colley, 2008; Pal et al., 2023). In addition, the life cycles of parasites, usually involving multiple hosts and vectors, adding to the complexity of control measures. This complexity requires a multidisciplinary approach to alleviate their pathological effects on both animal and human health (Colley, 2008; Aebischer et al., 2018). One of the major causes of morbidity in the world, especially in developing countries, are parasitic infections. These infections interfere with the metabolic functions of the host and alter their immune response.

This alteration worsens the severity of comorbid conditions like cancer and metabolic disorders. Therefore, more research on these infections need to be carried out, in relation to comorbidities and their therapeutic application (Oliveira et al., 2022). Protozoan parasites, mainly *Giardia lamblia* and *Entamoeba histolytica*. are the leading cause of gastrointestinal diseases that have long-term health consequences like malnutrition (Beiting and John, 2022). Vaccination should be initiated to prevent parasitic infections that together lead to immense morbidity and economic losses around the world, especially in underdeveloped areas.

With complex life cycles and mechanisms of immune evasion, it becomes difficult to develop vaccines against the parasites, thereby leading to the shortage of useful vaccines, particularly against helminths and protozoans (Tizard, 2021; Ridi, 2022). These vaccines have effectively shown efficacy as well as the ability to lower the parasite burden within the livestock, including coccidiosis and *Theileria* spp. Nevertheless, the vast majority of vaccines do not eradicate all the parasites entirely (Florin-Christensen, 2021; Tizard, 2021). The development of such vaccines is critical for boosting animal productivity and further bolstering food security alongside minimizing the dangers to humans by zoonotic infections (Kalkal et al., 2020; Florin-Christensen, 2021). Advances in understanding parasite biology and innovative vaccine technologies are important for developing effective and sustainable solutions to the diseases that plague the tropical areas, including these neglected tropical diseases (Kato, 2020).

Vaccines against protozoan parasites, including pathogens such as those causing coccidiosis, babesiosis, and theileriosis, have been developed; however, several vaccines have failed as the complex biology and various mechanisms of immune evasion developed by these pathogens make vaccination problematic (Patra et al., 2017; Tizard, 2021). For example, *Theileria* and *Babesia* are apicomplexan parasites, and creating a vaccine against them is tricky due to poor understanding regarding pathogenesis associated with them (Florin-Christensen, 2021). On the other hand, helminthic vaccines against lungworms and *Hemonchus* appears promising but its main aim is to reduce parasitic burdens rather than to eradicate them (Tizard, 2021). However, progress in the development of parasitic vaccines is still hindered by challenges including antigenic variability and problems associated with growing most targeted parasites under laboratory conditions (Knox, 2006). Thus, although progress exists, the quest for practical vaccines remains largely hindered by major obstacles (Sacks et al., 2016).

2. Current State of Parasitic Vaccinology

Parasitic diseases, such as malaria, schistosomiasis, and leishmaniasis, are among the major parasitic diseases that have a direct impact on global health and are mainly prevalent in developing countries. Malaria, caused by *Plasmodium* spp., leads to acute infections and high mortality rates in children, despite the efficacy of treatments and ongoing vaccination trials, including the R21/Matrix-M Vaccine, which has shown encouraging results (Siddiqui et al., 2023). Schistosomiasis caused by *Schistosoma* spp. has affected millions in terms of malnutrition and cognitive impairments, which is treated with praziquantel as the drug of choice; however, drug resistance is emerging, and so there is an urgent need for effective vaccines (Molehin et al., 2022). The second most lethal parasitic disease, Leishmaniasis, causes extreme morbidity and socio-economic burdens; however, clear-cut vaccines are vague, mainly because of the complexity in development and production (Volpedo et al., 2021). Overall, the lack of effective vaccines for these diseases underscores the necessity for innovative approaches in parasitic vaccinology (McManus, 2020; Koger-Pease et al., 2023).

The current parasitic vaccines face various challenges mainly because of the complex life cycle of parasites, the ease with which parasites escape their host's immune mechanisms, and the difficulties encountered during the identification of a vaccine target. The conventional methodologies used in the production of vaccines have not faired well with these complexities that always lead to inefficient immunological responses and expensive processes of production (You et al., 2023). For example, although extracellular vesicles of parasites have been proven to be promising as vaccine carriers, their use in clinical practices is not widespread, mainly because the interactions between them and the host-parasite dynamics are yet to be fully understood (Alfandari et al., 2023). The concept of trained immunity is an interesting approach for enhancing innate immunity against pathogens, but this method suffers from the biological nature of parasites. It has been established that the complex nature of parasites explains how they are resistant to certain treatment measures (Zhu et al., 2023). Currently, the entire aquaculture sector comprises merely a single commercially available vaccine targeting sea lice, as this is the least represented group of effective alternatives towards aquatic parasites (Shivam et al., 2021). Several factors also pose a challenge for developing vaccines against *Toxoplasma gondii* which are; potent immune response towards the diverse host species, and choice of antigens and complex methods of antigen delivery (Mévélec et al., 2020).

3. Traditional Methodss

A. Live attenuated vaccines: Live attenuated vaccines (LAVs) is a traditional and still evolving method to prevent parasitic infections caused by protozoan parasites, such as *Leishmania* and *Trypanosoma*. LAVs utilize weakened versions of the disease-causing agent. Therefore, they cause excellent immune responses without creating any pathological disease that can

ensure long-term immunity against the diseases including cutaneous leishmaniasis and Chagas disease (Rooholamini et al., 2024). With the advancements in genetic engineering tools such as CRISPR/Cas-based tools, site-specific modification of these vaccines can now be done to integrate them into the genome of the pathogen involved to make them safer and more effective (Rooholamini et al., 2024). For instance, recombinant *Leishmania* major expressing *Trypanosoma cruzi* antigens provided protective immunity against Chagas disease, making LAVs flexible platforms for vaccine development. Other than that, practical application of LAVs in the veterinary medicine area, such as bovine babesiosis, shows that these vaccines induce effective immune responses in the native environment (Álvarez-Martínez et al., 2022).

B. Inactivated Vaccines: Inactivated vaccines are a traditional form of parasitic vaccination that may offer a safer alternative choice than live attenuated vaccines for conferring immunity. For instance, the radiation-inactivated *Salmonella enterica* serovar *Gallinarum* vaccine was demonstrated to have a higher level of humoral immunity than formalin-inactivated vaccines, and it has been indicated that the method applied during inactivation highly impacts the performance of the vaccine (Ji et al., 2021). Progress on anthelminthic vaccines is also gradually being developed as a potentially viable strategy in the control of soil-transmitted helminths, which brings some challenges, including identifying appropriate antigens and needing to surpass immune evasion mechanisms used by the parasites (Zawawi and Else, 2020). An example is controlled antigen presentation and protective immunity through inactivated vaccine with whole-cell inactivated vaccines, such as ETVAX, which is a vaccine against enterotoxigenic *Escherichia coli* (Walker and Bourgeois, 2023). Although inactivated vaccines will not closely mimic the immune responses elicited by live vaccines, improvements in the formulation of inactivated vaccines and the delivery mechanisms that are likely to enhance their efficacy against many parasitic infections (Criado et al., 2024).

C. Subunit Vaccines: Subunit vaccines hold great promise as a traditional method of parasitic immunization, at a time when drug resistance is increasing and there is a need for long-lasting immunity. A study by Onile et al. (2020) shows the development of multiepitope subunit vaccine that specifically targets various kinds of parasites, including *Toxoplasma gondii*, as well as schistosomes, with immunoinformatic improvement in both antigenicity and immunogenicity yet safe for use in human beings. The researchers are still working on subunit vaccines targeting gastrointestinal nematodes and soil-transmitted helminths. These challenges are brought about by the anthelmintic resistance, and absolutely required for these parasites are the effective immune responses (Matthews et al., 2016; Noon and Aroian, 2017). Thirdly, the described subunit vaccines for leishmaniasis show how recombinant techniques can produce an effective immunogen that can be scaled up for use (Duthie and Reed, 2014).

D. Challenges and Limitations of Traditional Approaches: Traditional parasitic vaccination strategies face many challenges and limitations. The major challenge is the antigenic variation and polymorphism shown by parasites, which makes it hard to identify consistent vaccine targets. For instance, in malaria, the ability of the parasite to change its surface proteins enables it to avoid immune responses. Further complexities are added to the development of immunizations by immune non-responsiveness to certain antigens and maternal immunity (Good et al., 2004). Antiparasitic drugs have brought drug-resistant strains along with themselves, making vaccination efficacy an issue in eradicating the disease (Knox and Redmond, 2006; Morrison and Tomley, 2016). Logistical issues, such as continuous medication administration in cases of rapidly reproducing parasites, further exemplify the shortcomings of present control measures (Morrison and Tomley, 2016). Other significant barriers to developing prophylactic vaccines, particularly for livestock and poultry, include financial and technical limitations (Al-Khalaifa and Al-Nasser, 2018).

4. Novel Approaches in Parasitic Vaccinology

The approaches that have been used and include many strategies, as mentioned below, have significantly enhanced recent advances in vaccine development against parasitic infections:

A. Genomic and Proteomic Approaches: Genomic and proteomic methodologies have significantly allowed the development of vaccines for parasitic disease through strategies such as reverse vaccinology, proteogenomics, and immunopeptidomics. Such approaches enable the determination of potential vaccine antigens based on the whole genome and proteome exploration and analysis. This facilitate the detection of immunodominant epitopes that can be made available for inclusion into the vaccine design (Islam et al., 2022; Albaqami et al., 2024; Bhattacharjee et al., 2024). For example, the combination of molecular dynamics simulations and docking studies has been used to evaluate the binding affinities of vaccine candidates with immune receptors, thereby improving their immunogenic potential (Islam et al., 2022; Albaqami et al., 2024). Systems biology incorporated in the development of vaccines might enable an all-encompassing understanding of host immune responses to improve the design of informed vaccines targeted at protozoan and helminth parasites (Daga et al., 2022; Tomazic et al., 2022). It supports fast-moving vaccine development along with resolving all the issues and safety as well as concerns

related to efficacy of the vaccines that involve conventional procedures of production in tandem with it (Tomazic et al., 2022; Bhattacharjee et al., 2024).

B. Reverse Vaccinology and Epitope Mapping: Reverse vaccinology, together with epitope mapping, is the state of the art in parasitic vaccinology. It will be promising approaches to build vaccines against complex parasitic infections. Reverse vaccinology applies genomic and proteomic information in order to postulate vaccine antigens without the requirement to culture pathogens, a technique particularly useful for highly infectious or difficult-to-culture organisms (Mulatu et al., 2023). This approach has been applied to the parasite *Plasmodium falciparum*, where machine learning algorithms have been used for the prediction of vaccine candidate antigens. These ML algorithms utilized the proteomic, structural, and immunological datasets which served as a basis for antigen identification in the context of different pathogens (Chou et al., 2024). Similarly, the use of reverse vaccinology in combination with immunoinformatics for the development of a multi-epitope subunit vaccine for the parasite *Naegleria fowleri*. The designed epitopes was aimed to elicit responses from both T-cells and B-cells, thereby facilitating comprehensive immune activation (Sarfraz et al., 2023). In the case of *Leishmania donovani*, reverse vaccinology has facilitated the creation of a chimeric vaccine. It covers extensive population and have significant potential for inducing an immune response, as evidenced by research involving molecular docking and simulations (Dikhit & Sen, 2023).

C. Synthetic biology and genetic engineering: Synthetic biology and genetic engineering are greatly transforming the vaccinology of parasitic infections because they make it feasible to design novel vaccines against complex protozoan and helminth parasites. In conjunction with systems biology methodologies, new advances in sequencing technologies have made it possible to identify new antigens and the strategic design of vaccines, particularly for the Apicomplexan parasite *Plasmodium falciparum*, and a few promising candidates were derived from genetically attenuated parasites (GAPs). Gaps that have been developed through gene deletions, have appeared to be safe and immunogenic through clinical trials conducted on human volunteers suggesting a possible role in preventing malaria (Goswami et al., 2019; Murphy et al., 2022). Moreover, the latest advancements in genetic engineering technologies that encompass CRISPR/Cas9 and RNA interference transform the functional characterization of the proteins of the parasites, which could lead to new findings in helminth vaccine and therapeutic targets (Lalawmpuii and Lalrinkima, 2023). All these techniques highlight the deeper importance of synthetic biology in eradicating the world menace from parasitic infections (Tomazic et al., 2022).

D. Nanotechnology and vaccine delivery systems: Nanotechnology represents an emerging revolutionary trend within the field of parasitic vaccinology primarily via complex delivery mechanisms of vaccines. Diverse forms of nanoparticle, which include solid lipid nanoparticles (SLNs), liposomes, as well as virus-like particles (VLPs) ensure improved vaccine efficacy since these enhance antigen stability along with targeting immune cells or influence immune responses (Tiwari et al., 2023; Rashidi et al., 2024). The VLP-based malaria vaccine showed a considerable improvement in antibody responses compared to the conventional formulations (Ren et al., 2023). Additionally, nanoparticles allow for the controlled release and targeted delivery of antigens and overcome the issues traditional vaccines face, including poor bioavailability and rapid clearance (Jahanmahin and Borji, 2023). The application of nanotechnology in vaccine development not only enhances the immunogenicity but has the potential to be more effective at preventive measures against parasitic diseases. This opens up avenues for future advancements (Tiwari et al., 2023; Rashidi et al., 2024).

E. Adjuvants and immune-enhancing strategies: Adjuvants and immunoenhancing methods have greatly enhanced parasitic vaccinology; mainly, these enhances the profile of vaccines both in efficacy and safety. One such adjuvant is the novel non-inflammatory nucleic acid adjuvant called ARNAX. ARNAX activates Toll-like receptor 3 and, as a result, enables an improved cross-presentation of antigens while eliciting relatively small inflammatory responses (Seya et al., 2022). In addition, the D-peptide D-15800 has been shown to exhibit synergistic properties that enhance immunity when combined with TLR9 agonists to help in the generation of important cytokines, including IL-12 and IFN-α (Agrez et al., 2024). The inclusion of nanotechnology in vaccine formulations enhances the physicochemical properties of adjuvants, thus enhancing both innate and adaptive immune responses against powerful pathogens. Secondly, anti-CD200 and anti-CD300a as adjuvants have been found to have profoundly improved cell-mediated immunity to confer resistance against pathogenic *Leishmania* parasites. Thus, both classical and novel adjuvant approaches are possible to be utilized in the development of vaccines (Tiwari et al., 2023).

5. The Role of Emerging Technologies in Parasitic Vaccinology

This advancement in new emerging technologies is transforming parasitic vaccinology and is thus providing state-of-the-art solutions for highly complex problems associated with the infection caused by parasites. Some of the important technologies include CRISPR-Cas9, mRNA vaccines, and advanced mechanisms of delivery. These all technologies play significant roles in improving vaccine efficiency, designing novel formulations for vaccines, and studying aspects of immune responses.

i) Adjuvants and Delivery Systems: Adjuvants are those agents that enhance the host's immune response to a particular antigen. For the field of parasitic vaccinology, using adjuvants along with advanced delivery systems like LNPs has been quite promising. One good example is the use of lipid nanoparticles (LNPs) in mRNA vaccines, where it enables the stabilization and efficient delivery of mRNA that leads to strong immune responses against a range of pathogens, including parasites (You et al., 2023; Wu et al., 2024). The other technique is electroporation, which has been used as a method that increases DNA uptake from vaccines and greatly enhances the immunopotentiation of such vaccines (Brisse et al., 2020).
ii) Nanotechnology in the Delivery of Vaccines: Nanotechnology greatly contributes to the delivery of vaccines as it enables efficient targeted transport of vaccine components. Nanoparticles, involved in antigen and adjuvant encapsulation, make it possible for controlled release, and high stability is facilitated. mRNA vaccines have most benefited from this technology in which LNP has particularly contributed to shielding the mRNA against degradation, and it encouraged uptake within cells. Nanocarriers may enhance the bioavailability of vaccine components and enable the distribution of these within the organism (Ghattas et al., 2021; Wu et al., 2024).
iii) Synthetic Biology in Vaccine Development: Synthetic biology is revolutionizing vaccine development through the provision of synthetic biologists with the capability of engineering novel antigens and streamlining their expression. CRISPR-Cas9 has made it possible to carry out precise modifications within the genomes of parasites for the discovery of novel targets for vaccines. Synthetic DNA vaccines have also been designed that evoke high levels of immunity against many pathogens, including those causing parasitic infections. The synthetic approaches can be rapidly used to address emerging threats and may eventually lead to more effective vaccines (Ghattas et al., 2021).
iv) Advanced imaging techniques in the analysis of immune responses: The advanced imaging technologies are equally important in analyzing the immune responses that vaccines trigger. Techniques such as intra-vital microscopy allow researchers to view, in real time, the interaction of immune cells within living organisms. It helps us understand more clearly how vaccines produces the immunity against parasites and allows the scientists to identify potential changes in the formulation of a vaccine (Brisse et al., 2020).
v) *The Role of Genomics and Bioinformatics in Identifcation of the Vaccine Candidate:* Genomics and bioinformatics are critical methodologies for the identification of potential vaccine candidates for parasitic infections. High-throughput sequencing allows the detailed analysis of a parasite genome, thus ensuring the identification of potential antigens that vaccines can target (Tomazic et al., 2022). In addition, the use of bioinformatics tools helps in the analysis of large datasets generated from genomic studies, which allows researchers to rank candidates based on their immunogenic potential and their relevance to disease pathophysiology (You et al., 2023).
vi). Role of Immune Informatics in Designing Parasitic Vaccines: This merger of immunology with computational biology comes in handy for the rationally designed vaccines. The fact is that, employing knowledge about immune responses as well as features of the pathogens, scientists can determine which antigens are supposed to more probably provide protective immunity (You et al., 2023).

6. Conclusion

Parasitic diseases are considered as major public health and economic burden, particularly in low-income (developing) and middle-income countries. The complex parasite life cycles, immune evasion, and antigenic diversity have hindered the development of vaccine. Traditional vaccines—live attenuated, inactivated, or subunit—face technical and immunological challenges. Emerging approaches, including genomics, proteomics, reverse vaccinology, nanotechnology, CRISPR-Cas9, and mRNA technology, offer the promising solutions. However, affordability, accessibility, and implementation in resource-limited settings remain critical barriers. A multidisciplinary approach, involving public-private partnerships and global health organizations, is essential to translate advancements into practical solutions. Sustainable control and eradication of parasitic diseases require integrating scientific innovations with socio-economic strategies and policy-driven actions.

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