

Review

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Review

Schistosoma Vaccine Development: A Comprehensive Review of Progress, Challenges, and Future Directions

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Abstract

Schistosomiasis is a neglected tropical disease caused by parasitic trematodes of the genus *Schistosoma*, which affect millions of people globally. It poses a substantial public health challenge, particularly in low- and middle-income countries, most of which are in sub-Saharan Africa, where defecating and urinating in or near freshwater bodies is prevalent. Despite decades of control efforts, including mass drug administration, reinfection by the parasites remains a common occurrence, with a vaccine being viewed as a crucial tool for sustainable control and the ultimate elimination of the disease. Recent advancements in vaccine development, particularly through the Vaccine Against Schistosomiasis in Africa initiative, offer hope for the development of an anti-schistosomiasis vaccine soon. Several vaccine candidates, including Glutathione S-transferase, Sm-TSP-2, Sm14, and Sm-p80, are currently being explored. Sm-p80, *S. mansoni* calcium-activated neutral protease, and calpain are involved in tegmental maintenance, and promising safety and immunogenicity results have been obtained in Phase 1b trials conducted in a couple of African countries, paving the way for Phase 2a trials. These efforts, supported by global regulatory engagement and partnerships, aim to streamline the approval of anti-schistosomiasis vaccines and ensure equitable access; however, they are not without challenges. This review, therefore, explores the current state of schistosomiasis vaccine development, highlighting key scientific, regulatory, and logistical gains made toward a viable and impactful vaccine solution against the disease.

Keywords: schistosomiasis; schistosoma; vaccine; recombinant; clinical trials; antibodies; cytokines

1. Introduction

Schistosomiasis affects over 250 million people globally, primarily in sub-Saharan Africa, Asia, and South America (WHO, 2024). The disease is transmitted through contact with freshwater containing cercariae released by infected snails, which secrete proteolytic enzymes that breach the skin's barrier defenses to enable cercariae to penetrate the skin of a person wading in the water leading to chronic infections with liver, intestines, and urogenital tract pathology depending on the species involved: *S. hematobium* (urogenital disease), *S. mansoni*, and *S. japonicum* (hepatic/intestinal forms), with each presenting distinct epidemiological and pathological profiles (WHO, 2024). Morbidity stems from granulomatous inflammation around eggs trapped in tissues, leading to hepatic fibrosis (Zhou et al., 2024; Torrico et al., 2025), hematuria and bladder cancer (Smith-Togobo et al., 2023), infertility in both sexes (Bowers et al., 2025; Abdel-Naser et al., 2019), and increased susceptibility to human immunodeficiency (Colley et al., 2014).

In males, factors such as genital ductal system obstruction, testicular tissue damage, decreased libido, prostatic infestation, hormonal imbalance, and associated erectile dysfunction may lead to infertility (Abdel-Naser et al., 2019). Similarly, female genital schistosomiasis is linked to adverse reproductive outcomes, including ectopic pregnancy and miscarriage (Ajanga et al., 2006). Pregnant women with schistosomiasis face additional risks, such as placental inflammation, nutrient malabsorption, and anemia. This anemia is exacerbated by iron loss through egg shedding and

inflammatory cytokines that stimulate hepcidin, reducing iron availability for red blood cell production. These mechanisms compound chronic blood loss and nutritional deficiencies, significantly affecting maternal and fetal health (Leir et al., 2019).

Other helminths, notably hookworms (*Ancylostoma duodenale* and *Necator americanus*), contribute to iron-deficiency anemia by attaching to the intestinal mucosa and consuming the blood of the host. Heavy infections can cause substantial daily blood loss, leading to severe anemia if left untreated (Mengist et al., 2017).

Current control strategies rely heavily on mass drug administration (MDA) of praziquantel. Despite its effectiveness against adult worms, it does not prevent reinfection (King & Bertsch, 2015), necessitating repeated treatment. Moreover, chemotherapy cannot interrupt transmission, and concerns about potential drug resistance (Doenhoff et al., 2009) underscore the urgent need for a vaccine. A vaccine that induces long-term protection could be a game-changer in control strategies aimed at reducing disease transmission and facilitating its elimination.

Therefore, vaccine development for schistosomiasis has been a long-standing goal, urged by evidence of acquired immunity in endemic populations and experimental models (Hotez et al., 2016). Several vaccine candidates have progressed to clinical trials, and novel platforms such as messenger ribonucleic acid (mRNA) and extracellular vesicle-based vaccines are being explored. However, the complexity of the parasite life cycle, immune evasion strategies, and limited funding present significant challenges. Therefore, this review provides an overview of the immunological basis for *Schistosoma* vaccine development, historical and current vaccine candidates, clinical trial outcomes, and future directions in *Schistosoma*/Schistosomiasis vaccine research.

2. Immunological Basis for Vaccine Development

Experimental studies in non-permissive hosts, such as rats and rhesus macaques, have demonstrated robust immune responses capable of eliminating schistosomes before they mature (Wilson et al., 2008). In humans, the immune response to schistosome infection is dynamic and complex, involving innate and adaptive components of the immune system, with specific immunity starting a couple of weeks after the initial infection (Driciru et al., 2025). This acquired, non-sterile immunity, especially against reinfection, develops slowly over several years, with older individuals showing reduced worm burdens and egg outputs (Mutapi et al., 2011).

Therefore, protective immunity encompasses both humoral and cellular responses, including IgG-mediated antibody-dependent cytotoxicity and balanced Th1 and Th2 cytokine levels. However, schistosomes employ immune evasion strategies, such as tegumental renewal and immunomodulatory molecules (e.g., IL-10 induction), to complicate the effectiveness of the immune response and vaccine design (Driciru et al., 2021).

Protective Immunity

Cell-mediated immunity: Upon cercarial penetration of the skin while wading through infested water, the host mounts an innate immune response involving dendritic cells, macrophages, and neutrophils (Houlder et al., 2023). This is followed by the activation of the adaptive immunity component of the immune system, particularly CD4⁺ T cells, a few weeks later (Driciru et al., 2025). Early infection elicits a Th1-type response, characterized by IFN- γ , TNF- α , interleukin-1 (IL-1), IL-2, and IL-6 (Costain et al., 2022; Zheng et al., 2020; Hiatt RA et al., 1979), with an IL-17-producing CD4⁺ T-cell population secreting IL-23, IL-1, and IL-17, which are linked to the severe form of the disease (Shainheit et al., 2011). However, these polarizations shift to a Th2-dominated profile, marked by regulatory T cell (Treg) activation and increased secretion of IL-4, IL-5, IL-10, and IL-13 during worm maturation and the beginning of egg production (Costain et al., 2022; Zheng et al., 2020; Maizels et al., 2004). Th2 response dominance in response to soluble egg antigens is associated not only with granuloma formation or schistosome egg trapping in tissues, fibrosis, and organ damage, especially in the liver and intestines, but also contributes to parasite clearance (Pearce & MacDonald, 2002; Costain et al., 2018; Hams et al., 2013). Cytokines as IL-13, though, help granuloma formation, aid in

transporting eggs to the intestinal or bladder lumen for excretion (McManus et al., 2020). Interleukin-5 promotes eosinophil proliferation with IL-4/IL-13 immunoglobulin class switch to IgE production, both of which are vital in targeting helminths (Araújo et al., 2004), including trematodes, *Schistosoma* spp.

Antibody-mediated immunity: IgG and IgE antibodies target surface and secreted antigens, and enzymes such as glutathione S-transferase (GST) and fatty acid-binding proteins (FABPs) are particularly important (Capron et al., 2001; Capron et al., 2025) in conferring protection against disease in the human host. This is marked by reductions in worm burden, egg excretion, and reinfection, and sets in after multiple exposures or incomplete treatment (Butterworth & Hagan 1987; Dunne & Cooke 2005). This specific immunity is associated with elevated levels of antigen-specific IgE, IgG1, and peripheral blood eosinophilia and is more evident after puberty (Wilkins et al, 1987; Rihet et al., 1991; Dunne & Cooke, 2005). These insights guided the selection of antigens (Table 1) for vaccine development, focusing on molecules involved in parasite survival, immune evasion, and host-parasite interactions.

The complex and dynamic immune process is characterized by distinct phases that correspond to the developmental stages of the parasite and the host’s attempt to control both the infection and its associated pathology. The following table outlines the key stages of infection and the dominant immune responses in each phase:

Table 1. Mediators of stage-specific immune responses to *Schistosoma* spp.

Stage of Infection	Dominant Immune Response	Immune Components	Reference
Initial invasion & larval migration	Mixed/innate and early Th1 response	Neutrophils, macrophages, basal IFN- γ , TNF	(Costain et al., 2022; Zheng et al., 2020)
Acute Phase (Egg production)	Dominant Th2 and granuloma formation	Th2 cells (IL-4, IL-5, IL-13), eosinophils, IgE, granuloma formation.	Costain et al., 2022 (Molehin 2020; Zheng et al., 2020)
Chronic phase	Regulation and modulated immunity	Tregs (IL-10), Bregs, IgG4, exhausted T cell phenotypes	(Costain et al., 2022; Molehin 2020; Zheng et al., 2020)

The table outlines the specific immune response associated with each stage of the *Schistosoma* parasite and the key components of the immune system involved in the responses.

3. Historical and Experimental Vaccine Approaches

3.1. Radiation-Attenuated Cercariae

One of the earliest and most informative approaches to *Schistosoma* vaccine development involved the use of radiation-attenuated cercariae, the snail stage of the parasites with proteolytic enzymes that infect the human host through penetration of the skin while the host wades through slow-flowing freshwater bodies infested with them. These live parasites, rendered non-infective through gamma irradiation, elicit a protective immune response in animal models, particularly in mice and non-human primates (Bickle, 2009). This protective immunity, involving the stimulation of robust cell-mediated and humoral responses, is achieved through the activation and expansion of CD4⁺ T cells and the production of specific immunoglobulins against the parasite. However, despite their efficacy, radiation-attenuated vaccines are impractical for human use because of safety concerns, production complexity, and regulatory hurdles. Nonetheless, they provide critical insights into the types of immune responses required for protection and help identify key antigens for subunit vaccine development (Wilson et al., 2016).

3.2. Recombinant Antigen-Based Vaccines

Recombinant deoxyribonucleic acid (DNA) technology has enabled the production and purification of *Schistosoma* antigens, allowing for safer and more targeted vaccine strategies. The cloning and expression of *Schistosoma* antigens in bacterial, yeast, and mammalian systems are ongoing. Some of these antigens with demonstrable immunogenicity and partial protection in animal models have progressed to human clinical trials (Hotez et al., 2016; Molehin et al., 2022), including:

- (a) *Schistosoma mansoni* Fatty Acid-Binding Protein (Sm14): A fatty acid-binding protein involved in lipid metabolism in *S. mansoni*.
- (b) *Schistosoma mansoni* Tetraspanin-2 (Sm-TSP-2): A tetraspanin protein located on the integument of *S. mansoni*.
- (c) *Schistosoma mansoni* calpain (Sm-p80): A calpain-like protease implicated in immune evasion from *S. mansoni*.
- (d) *Schistosoma hematobium* 28-kDa Glutathione S-Transferase (Sh28GST): A detoxification enzyme by *S. hematobium*.

3.3. Extracellular Vesicle-Based Vaccines

Recent studies have explored the use of extracellular vesicles secreted by *Schistosoma* spp. as vaccine candidates. Extracellular vesicles contain a rich cargo of proteins, lipids, and RNAs that reflect the biology of the parasite and can modulate host immune responses (Sotillo et al., 2017). Immunization with extracellular vesicles or extracellular vesicle-derived antigens has shown promise in murine models, inducing both humoral and cellular responses, marked by enhanced IFN- γ and antibody responses (Sotillo et al., 2017; Mossallam et al., 2021). Extracellular vesicle-based vaccines offer numerous advantages, including multivalent antigen presentation and potential adjuvant effects, although standardization and scalability remain challenges for clinical application.

4. Leading Vaccine Candidates in Clinical Trials

Several *Schistosoma* vaccine candidates have advanced to clinical evaluation, marking significant progress in this field. The most prominent examples are as below.

4.1. *Rsh28gst* (*Schistosoma hematobium* 28-Kda Glutathione S-Transferase)

Developed by the Institut Pasteur and its collaborators, *Schistosoma hematobium* 28-kDa Glutathione S-Transferase (rSh28GST) targets glutathione S-transferase, a detoxification enzyme crucial for the survival of the parasite. It is designed to elicit antibody responses that can inhibit the enzymatic activity of glutathione S-transferase, which involves conjugating glutathione to toxic compounds of endogenous and exogenous origin to increase their solubility and facilitate their expulsion to help prevent oxidative stress and drug effects. Preclinical studies have demonstrated its ability to reduce worm burden and egg output in animal models (Capron et al., 2005). Phase I and II trials conducted in Senegal and France revealed its safety and immunogenic nature, eliciting IgG and IgE responses without adverse hypersensitivity reactions. This humoral immune response was largely confirmed in a Phase 3 clinical trial when IgG1, IgG2, and IgG4 production was observed, in addition to inhibition of the enzymatic activity of rSh28GST by sera from the vaccinees (Driguez et al., 2016; Riveau et al., 2018). Although the efficacy in preventing infection was modest, rSh28GST may reduce pathology and transmission, making it a candidate for integration with MDA programs.

4.2. *Sm14* (*Schistosoma Mansoni* Fatty Acid-Binding Protein)

Schistosoma mansoni Fatty Acid-Binding Protein (Sm14) is a well-characterized and important member of the fatty acid-binding proteins (FABPs) of *Schistosoma mansoni* that facilitates lipid uptake, transport, and compartmentalization within the parasite. The parasite is unable to synthesize long-chain fatty acids and therefore depends on the host for its growth and development; hence,

FABPs, including Sm14, are crucial for the growth and development of the parasite. Sm14, adjuvanted with a Toll-like receptor 4 agonist glucopyranosyl lipid adjuvant-stable emulsion (GLA-SE), displays good immunogenicity, eliciting strong immune responses, including cellular and humoral immune responses, in animal studies (Tendler et al., 2015). The antibodies produced bind to Sm14 of the parasite to starve it of essential nutrients and kill it. The cellular immune response induced by Sm14/GLA-SE demonstrated a balanced Th1/Th2 response. The Sm14/GLA-SE vaccination reduced worm burden and egg viability and protected against *S. mansoni* and *Fasciola hepatica*, making it very attractive for use in both human and veterinary vaccines (Tendler et al., 2015).

4.3. Sm-Tsp-2 (*Schistosoma Mansoni* Tetraspanin-2)

Schistosoma mansoni Tetraspanin-2 (Sm-TSP-2) is a 9-kDa surface antigen based on the extracellular domain of a unique *S. mansoni* tetraspanin protein. It is expressed on the surface of the juvenile stage of the parasite, schistosomula, and adult worm, which the parasite uses to survive in the bloodstream. This surface-exposed protein plays a role in tegument integrity and complexing with host ligands, potentially including major histocompatibility complex (MHC) molecules, to evade the host immune system (Tran et al., 2006). It was identified through proteomic analysis of the surface of the parasite and has shown strong immunogenicity in mice and rhesus macaques (Tran et al., 2006), eliciting antibodies that interfere with the proper formation and maturation of the schistosome tegument, as well as the interaction between tegument and host ligands, making the parasite vulnerable to immune responses (Tran et al., 2006). A recombinant version of Sm-TSP-2 formulated with the GLA-SE adjuvant entered Phase I trials in Australia and the United States, with the results demonstrating good safety and humoral antibody responses. Vaccination of adults with Sm-TSP-2/Alhydrogel (aluminum hydroxide gel) in an area of ongoing *S. mansoni* transmission was safe, minimally reactogenic, and elicited significant IgG and IgG subclass responses (Diemert et al., 2023) needed for immunity against the parasite.

4.4. Sm-P80 (*Schistosoma Mansoni* Calpain)

Calpain, a proteolytic protein involved in membrane biosynthesis, consists of a catalytic and regulatory subunit. The large subunit, *Schistosoma mansoni* Calpain (Sm-p80), changes to a membrane-bound status through calcium-activated auto-proteolysis by the small subunit, which is involved in tegument remodeling and immune modulation. Sm-p80 helps *Schistosoma* evade immune responses through its tegument renewal process, constantly evading the immune response by remodeling the parasite membrane. The Sm-p80 recombinant protein elicits a response from a combination of T-helper (Th)1, Th2, and Th17 cells, marked by the release of interleukin (IL)-2, IL-4, IL-10, IL-18, IL-21, IL-22, interferon- γ , IgA, IgM, and IgG and its subclasses IgG1 and IgG2 responses, leading to the development of immunity that is both highly protective and long-lasting in preclinical trials (Zhang et al., 2018; Zhang et al., 2010; Karmakar et al., 2014). Sm-p80 is formulated as a DNA vaccine or as a recombinant protein with adjuvants and is a strong candidate for multivalent vaccines. Together with Sm-CatB, it has consistently achieved >90% efficacy in animal models, whereas most other candidates fall below 60% (Houlder et al., 2025).

5. Preclinical Vaccine Candidates

Numerous *Schistosoma* vaccine candidates have reached clinical trials, and several others are still in preclinical development, with many showing promise in animal models to offer insights into novel mechanisms of protection.

5.1. Sm23 (*Schistosoma Mansoni* 23-Kda Integral Membrane Protein)

Schistosoma mansoni 23-kDa integral membrane protein (Sm23) is a cysteine-rich, hydrophobic membrane protein expressed widely in schistosome life stages, adult tegument, and several tissues (Da'dara et al., 2001; Da'dara et al., 2002; Gaugitsch, 1991) and on mammalian hematopoietic or tumor

cells (Köster & Strand, 1994). It is involved in nutrient uptake and immune evasion. Immunization with recombinant Sm23 has demonstrated partial protection in mice, reducing the worm burden and egg production (Da'dara et al., 2001; Da'dara et al., 2002). Its tegument localization makes it accessible to host antibodies and could be included in multivalent vaccine formulations.

5.2. Sm29 (*Schistosoma Mansoni* 29 Kilodalton (Kda) Protein)

The *Schistosoma mansoni* 29-kilodalton (kDa) protein (Sm29) is another tegumental protein that has shown strong immunogenicity and protective efficacy in murine models, particularly when formulated with alum or CpG (Cardoso et al., 2008). Sm29, identified through proteomic analysis, is highly recognized by IgG1 and IgG3 antibodies from naturally exposed, schistosomiasis-resistant individuals. It induces both Th1 and Th2 responses to confer resistance in mice when vaccinated using the recombinant form and may complement other antigens in combination vaccines (Cardoso et al., 2008).

5.3. Paramyosin

Paramyosin, a complement-interacting molecule, is expressed in *Trichinella spiralis* and other helminths and plays a role in immune modulation. It binds complement components, such as C1q, C8, and C9, thereby inhibiting membrane attack complex formation on the parasite, preventing complement-mediated lysis, and helping the parasite evade host defenses (Zhang et al., 2001). Vaccination with paramyosin has led to significant reductions in worm burden in animal studies, and its immunomodulatory properties make it a candidate for developing therapeutic vaccines.

5.4. Cathepsins and Proteases

Schistosoma-specific proteolytic enzymes, such as cathepsins B and L, are essential for nutrient digestion, enabling *Schistosoma* to feed on host blood by digesting proteins such as hemoglobin. These enzymes are also involved in the development and invasion of a host by parasites. We also demonstrated that a schistosome cysteine protease, *S. mansoni* cathepsin B1 (SmCB1, Sm-CatB), which is secreted from the gut of the parasite, is targeted by IgE (de Oliveira Fraga et al., 2010), contributing significantly to the Th2 CD4⁺ T cell response during early infection which not only limits the pathology associated with the Th17 response but also contributes to the chronicity of the disease (de Oliveira Fraga et al., 2010). Administration of *S. mansoni* cathepsin B1 (SmCB1) or *S. mansoni* cathepsin L3 (SmCL3) led to a Th2-type immune environment that is harmful to the development of *S. mansoni* larvae, ultimately resulting in a drastic reduction in worm burden and liver egg counts (Tallima et al., 2017). Immunization with recombinant cathepsins protected mice, and the conservation of these schistosome-secreted enzymes across species and other helminths (Robinson et al., 2008) enhances their potential as broad-spectrum vaccine candidates.

5.5. Extracellular Vesicle Proteins

Proteomic analysis of *Schistosoma*-derived extracellular vesicles has identified several novel antigens, including tetraspanins, heat shock proteins, and enzymes. These proteins are involved in host-parasite communication and immune modulation. In murine models, vaccination with extracellular vesicles (EVs) or EV-derived proteins has shown promise, stimulating the need for further research to enhance their delivery and immunogenicity (Sotillo et al., 2017).

Table 2. Vaccine candidates, mechanisms of action and immunological correlates of protection.

Vaccine Name	Type	Target Species	Mechanism/Target Antigen	Clinical Trial Phase	Key Notes	Immunologic Correlates	Reference
Sm-p80 (SchistoShield®)	Recombinant protein vaccine	<i>Schistosoma mansoni</i>	Calpain (tegumental maintenance)	Phase 1 (USA); Phase 1b (Africa); Phase 2 planned	Safe; strong IgG response; >90% worm burden reduction in non-human primate models	High IgG1/IgG3 titers; IFN- γ and TNF- α secretion; mixed Th1/Th2 profile	Jackson et al., 2025; Kim et al., 2024
Sm14	Recombinant protein vaccine	<i>Schistosoma mansoni</i>	Fatty acid-binding protein (FABP)	Phase 1 (Brazil); Phase 2a (Senegal); Phase 2b (Children)	Safe; strong IgG response; ongoing efficacy evaluation	IgG1 and IgG3 predominance; IL-4 and IL-13 upregulation; eosinophilia	Ly et al., 2025; Tendler et al., 2017; Chen, 2024
Sm-TSP-2	Recombinant protein vaccine	<i>Schistosoma mansoni</i>	Tetraspanin (tegument integrity)	Phase 1b (Brazil); Phase 2 (Uganda); Phase 3	Safe; significant IgG and IgG subclass responses; Partial protection; mixed efficacy results.	IgG1 and IgG4 responses; Th2 cytokines (IL-5, IL-13); moderate IFN- γ	Diemert et al., 2023
Sh28GST (Bilhvax)	Recombinant protein vaccine	<i>Schistosoma haematobium</i>	Glutathione S-transferase (GST)	Phase 3 (Senegal)	Immunogenic; failed to significantly delay recurrence	IgG and IgE responses; IL-4 and IL-10 elevation; granuloma modulation	Riveau et al., 2018
EV-based Vaccines	Extracellular vesicle-based vaccine	<i>Schistosoma</i> spp.	Extracellular vesicle proteins (e.g., tetraspanins, GST)	Preclinical (murine models)	Up to 93% reduction in hepatic egg counts; strong IFN- γ and antibody responses	Mixed Th1/Th2 response; IgG and IgE elevation; dendritic cell activation	Mossalla et al., 2021; Kuipers et al., 2025
Sm23	Recombinant protein vaccine	<i>Schistosoma mansoni</i>	Tegumental tetraspanin	Preclinical	Surface-exposed antigen; promising in murine models	IgG1/IgG2a; IFN- γ , TNF- α (Th1 bias)	Mekonnen et al., 2020

Sm29	Recombinant protein vaccine	<i>Schistosoma mansoni</i>	Tegumental membrane protein	Preclinical	50–60% worm burden reduction in mice	High IgG1/IgG2a; IFN- γ , IL-12 (Th1 dominant)	Cardoso et al., 2008; Alves et al., 2018
Paramyosin	Recombinant protein vaccine	<i>Schistosoma japonicum</i> , <i>S. mansoni</i>	Muscle structural protein	Preclinical	Significant worm burden reduction. Cross-species potential; tested in bovine models.	IgG and IgE responses; complement inhibition	Al-Naseri et al., 2021
Cathepsins (Sm-CatB, Sm-CatL)	Recombinant protein vaccine	<i>Schistosoma mansoni</i>	Cysteine proteases (gut digestion)	Preclinical	Sm-CatB achieved >90% efficacy in NHP models	IgG1, IgG3; IL-4, IL-13; mixed Th1/Th2	Houlder et al., 2025
mRNA/DNA vaccines	Nucleic acid-based vaccine	<i>Schistosoma mansoni</i>	Encodes Sm-p80, Sm14, or multi-antigen construct	Preclinical (concept stage)	Rapid design; potential for multi-antigen delivery	Expected Th1/Th2 balanced response; IFN- γ , IgG subclasses	Molehin et al., 2022

NHP: Non-human primate. Sm-p80 is currently the most advanced candidate, with strong preclinical efficacy and promising Phase 1/1b safety and immunogenicity data; Sm14 and Sm-TSP-2 are progressing through Phase 2 trials in endemic regions, targeting both adults and children; Sh28GST (Billhvax) reached Phase 3 but failed to meet efficacy endpoints, highlighting challenges in translating immunogenicity into protection and or use of the most appropriate adjuvant and route of administration while extracellular vesicle-based approaches are emerging as next-generation platforms, offering multivalent antigen presentation and intrinsic adjuvant properties.

6. Challenges in Schistosoma Vaccine Development

Despite significant progress, Schistosoma vaccine development faces several scientific, logistical, and regulatory challenges.

6.1. Biological and Immunological Complexity

The development of an effective schistosomiasis vaccine faces significant biological challenges due to the complex life cycle of the parasite. Schistosomes are sophisticated multicellular organisms with multiple developmental stages, each expressing distinct antigenic profiles as the eggs hatch into miracidia, infect the snail intermediate host, and transform from cercariae to schistosomula, adult worms, and egg-laying pairs (Driciru et al., 2021) in the human host. This biological complexity means that each stage, either in an animal or a human host, has different proteins that are expressed, making the identification of optimal vaccine targets particularly challenging. Furthermore, schistosomes have evolved sophisticated immune evasion mechanisms that enable their long-term survival in human hosts, including molecular mimicry, surface membrane biogenesis, and induction of regulatory immune responses (Jackson et al., 2025; Driciru et al., 2021). Unlike viruses or bacteria, parasites such as schistosomes are genetically complex organisms with extensive genetic diversity,

creating additional hurdles in the development of broadly protective vaccines across different species and geographical strains. The ability of the parasite to modulate host immunity through Treg/IL-10-mediated immune suppression in chronically infected populations further complicates vaccine development, as Treg/IL-10 may impede robust vaccine-induced immune responses in endemic settings (Driciru et al., 2021), especially in parasite-exposed populations.

6.2. Antigen Selection, Standardization, and Pre-Clinical to Clinical Translation

The transition from promising pre-clinical results to effective human vaccines has been hampered by inconsistent study designs and model limitations in these studies. A recent scoping review of pre-clinical schistosomiasis vaccine studies revealed that 141 candidate antigens have been tested in the past three decades, with most antigens evaluated only once and only three (Sm-CatB, Sm-p80, and Sm-14) tested more than 20 times (Houlder et al., 2025). The median protective efficacy against worm burden in these studies was approximately 35%, with only ten antigens achieving over 60% efficacy and only two (Sm-p80 and Sm-CatB) exceeding 90% protection (Houlder et al., 2025). The large variations in the observed efficacy with all repeatedly tested antigens may be traced to differing formulations and study designs, thereby making direct comparison of vaccine targets extremely challenging (Houlder et al., 2025). Another sad aspect is the heavy reliance on murine models, which have an apparent ceiling of 40-50% protection and low maturation rates of penetrating cercariae (about 32% in the case of *S. mansoni*), unlike natural hosts, where maturation is more than 90% (Siddiqui & Siddiqui 2017). This has led to calls for greater use of non-human primate models, particularly baboons, which better mimic human immune responses and clinical disease manifestations, to serve as a more relevant bridge to human trials (Siddiqui & Siddiqui, 2017).

However, identifying antigens that are both protective and safe is challenging. Many candidates elicit strong immune responses but fail to provide significant protection in humans. Moreover, standardizing antigen production, purification, and formulation for clinical use requires substantial investments and technical expertise (Driguez et al., 2016).

6.3. Clinical Development and Implementation Hurdles

Advancing promising *Schistosoma* vaccine candidates through clinical trials presents unique challenges related to target populations and their integration with existing control programs. Individuals in endemic areas often have pre-existing exposure to schistosomes, resulting in modified immune backgrounds that may interfere with vaccine responses (Driciru et al., 2021). Furthermore, co-infections with other pathogens, such as malaria, soil-transmitted helminths, and various bacterial and viral infections in schistosomiasis-endemic regions, can leave a life-long immunological imprint on the human host that may interfere with vaccine immunogenicity (Driciru et al 2021). The need to co-administer vaccines with praziquantel through existing MDA programs introduces another layer of complexity, as praziquantel treatment induces both transient and long-term immunomodulatory effects due to tegument destruction, worm killing, and subsequent contact of worm antigens to the host immune system (Driciru et al., 2021).

6.4. Immunological Complexity

Schistosomes have evolved sophisticated mechanisms to evade host immunity, including antigen masking, immune modulation, and molecular mimicry. The complex life cycle of the parasite, which involves multiple developmental stages with distinct antigenic profiles, complicates vaccine design (Hotez et al., 2016). In addition, chronic infection promotes the expansion of regulatory T cells (Tregs) and alternatively activated macrophages (M2), producing potent immunosuppressive cytokines such as IL-10 and transforming growth factor beta (TGF- β), to dampen effector responses (Licá et al., 2023) of the host. IgG4 antibodies that compete with protective IgE for antigen binding and inhibit eosinophil-mediated killing are also induced. Granulomatous responses to trapped eggs exacerbate tissue damage while diverting immunity from other parasite stages.

Risk of hypersensitivity. Some *Schistosoma* antigens, particularly those associated with IgE responses, pose a risk of hypersensitivity reactions, a dysregulated immune response, especially in endemic populations with prior exposure to the parasite. Vaccine formulations must, therefore, balance immunogenicity with safety, avoiding exacerbation of allergic or unnecessary inflammatory responses (Capron et al., 2005) by employing some of the suggestions in Table 3.

6.5. Limited Funding and Infrastructure

Schistosomiasis primarily affects low-income regions, mostly in Africa, Latin America, and Southeast Asia (WHO 2024), and vaccine development has historically received limited funding compared to other infectious diseases. Conducting large-scale clinical trials requires robust infrastructure, ethical oversight, and community engagement, which are often lacking in endemic areas (King & Bertsch, 2015).

6.6. Regulatory and Logistical Barriers

Navigating regulatory pathways for neglected tropical disease vaccines is complex, particularly for novel platforms such as DNA or mRNA vaccines. Ensuring cold chain logistics, manufacturing scalability, and integration with existing health systems are critical for successful deployment (Tendler et al., 2015).

7. Future Directions

The path toward an effective *Schistosoma* vaccine is promising but requires strategic innovation and collaboration. Several key areas are emerging as priorities for future research and development (Table 4), including:

7.1. Overcoming the Effect of Immune Evasion

The parasite has multiple evasion mechanisms, like molecular mimicry, so targeting several angles simultaneously by using a multi-stage and multi-species cocktail of antigens rather than a single recombinant protein is likely necessary to achieve a successful vaccine. Additionally, the use of modern and potent adjuvants like TLR agonists may be crucial in stimulating a strong and persistent immune response, particularly for generating high titers of protective antibodies with recombinant proteins (Table 3). There is also a need to focus on the vulnerable stages of the parasite. Adult worms are largely impervious, but not necessarily the migrating larval stages in the lungs, so targeting these stages may be more successful, particularly as some successful animal models work by "arming" the lungs with effector T-cells that block further larval migration (Wilson R. A. 2023).

Table 3. Immune evasion mechanism and vaccine design.

Evasion Mechanism	Immunological Consequence	Vaccine Design Countermeasure
Tegument shedding	Antibody clearance	Employ conserved internal antigens
Incorporation of host antigens	Reduced immunorecognition	Target non-host-like epitopes
Treg/IL-10 induction	Suppressed effector T-cell responses	Incorporate TLR agonists (e.g., GLA-SE)
IgG4 blocking antibodies	Inhibition of ADCC	Enhance IgG3/IgE balance with adjuvants
Stage-specific antigens	Immune escape during maturation	Multivalent vaccines targeting multiple stages

The table shows some of the immune mechanisms by which the parasite may escape the effect of control, with suggestions on how to possibly overcome them, including inhibition of antibody-dependent cytotoxicity (ADCC).

7.2. Integration with mass drug administration (MDA)

Vaccines may not replace chemotherapy in the short-term deployment against Schistosomiasis, but must complement MDA programs to reduce reinfection and transmission. Per modeling studies, combining vaccination with praziquantel treatment could accelerate the disease elimination efforts, especially in high-transmission areas, rather than either of the two being used alone (King & Bertsch, 2015; Collyer et al., 2019). Vaccine deployment strategies must, therefore, consider timing, coverage, and community engagement to maximize impact, as these factors affect not only efficacy but also vaccine uptake hesitancy, which may then influence herd immunity and hence elimination.

7.3. Novel Vaccine Platforms

Advances in vaccine technology offer new opportunities for Schistosoma vaccine development. Such advances in vaccine platforms, including mRNA technologies that proved successful during the COVID-19 pandemic, offer promising avenues for schistosomiasis vaccine development (Gandvi et al., 2025). mRNA vaccines, proven effective in COVID-19, allow rapid antigen design and scalable production. Studies of DNA vaccines encoding Schistosoma proteins, as being explored in Sm-p80 development, have shown immunogenicity in animal models and may offer long-term protection (Hotez et al., 2021), and this could be extended to other antigens or molecules. Nanoparticle and liposome-based delivery systems can enhance antigen stability and immune targeting. These platforms have the potential to overcome limitations of traditional protein-based vaccines and facilitate multivalent formulations to target several biological pathways of the parasite simultaneously.

7.4. Multivalent and Pan-Schistosome Vaccines

Given the diversity of human Schistosoma species, with the major ones being *S. mansoni*, *S. hematobium*, and *S. japonicum*, developing vaccines that confer cross-species protection is essential. Computational approaches continue to evolve, enabling more sophisticated antigen selection and multi-epitope vaccine design (Gandvi et al., 2025). Leveraging on this to combine antigens from different species, life stages, or epitopes may improve efficacy and broaden coverage (Tendler et al., 2015).

7.5. Standardized Efficacy Metrics

Establishing reliable correlates of protection and efficacy endpoints for schistosomiasis vaccine trials remains a major challenge. Current expert recommendations for an effective vaccine include achieving at least a 75% reduction in worm burden and egg excretion; however, accurately measuring these parameters in humans is complex and requires advanced diagnostic tools (Driciru et al., 2021; Siddiqui & Siddiqui, 2017). Moreover, ensuring cross-stage and cross-species protection adds another layer of difficulty.

There is no consensus on standardized parameters or methods for evaluating vaccine performance in non-human primate challenge studies or human trials. Parasitological outcomes, such as egg output and hatching rates, are commonly used as surrogate markers for worm burden, but these indicators do not always correlate with clinical outcomes. Direct determination of worm burden is only feasible in animal models through portal perfusion, while in humans, fecal egg counts and circulating antigen levels serve as proxies. The sensitivity and reliability of these surrogates, as well as their correlation with actual worm burden, require further validation.

Future clinical trials should incorporate additional indicators—such as biomarkers of morbidity, transmission potential, and long-term immunity—to provide a more comprehensive assessment of vaccine impact (Driguez et al., 2016).

7.6. Strengthening Research Capacity in Endemic Regions

Building local capacity for vaccine research, clinical trials, and manufacturing is critical. Partnerships between academic institutions, governments, and global health organizations may promote infrastructure development, training, and technology transfer, with community involvement and ethical oversight in vaccine development being essential for successful vaccine implementation.

Some of the factors to be considered, actions to be taken, rationales behind them, and metrics to look for in strengthening vaccine research and developing capacity in developing countries are summarized in Table 4 below.

Table 4. Strengthening Schistosoma Vaccine Research and Development of Capacity.

Area	What/Actions	Why / Rationale	Metrics
Local needs assessment to lay the foundation	Mapping existing institutions, laboratories, clinical trial experience, regulatory/ethics capacity, human resources, cold-chain and animal facilities, surveillance data, and community engagement structures that are needed. Implementing regular assessment using surveys and site visits to identify gaps and prepare a budget.	Recent assessments show needs vary significantly by country and region, so targeted capacity building must be based on local gaps.	Completed gap analysis and budget, and number of priority areas identified (TDR, 2024; Nakanjako et al., 2025).
Human resource development	Providing MSc/PhD scholarships in vaccinology, immunology, clinical trials, biostatistics, regulatory science, and GCP. Offering short courses in immune assays (ELISA, Luminex, Flow Cytometry, and ELISPOT), culture models, biobanking, bioinformatics, and GMP. Establishing twinning programs with global vaccine institutions. Create structured career pathways.	Tying scholarships to local institutions retains talent. Successful partnerships accelerate skills transfer and are a cornerstone of effective capacity strengthening.	Number of trained professionals, number of twinning partnerships, and retention rates (TDR, 2024; Nakanjako et al., 2025).
Core laboratory and clinical trial Infrastructure	Equipping basic laboratories (PCR, cold storage), securing access to specialized animal facilities, and building GCP-trained clinical trial units with data management and cold-chain facilities. Strengthening national regulatory authorities and ethics committees.	Regular site meetings and auditing Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) checklist items, ensuring international standards compliance	Number of sites meeting GCP/GLP standards and operational biobanking facilities. (TDR, 2024).
Sustainable financing	Providing seed funding for early-stage research. Advocating for dedicated national research budget lines. Pursuing multilateral, donor, and industry funding. Encouraging cost-sharing among institutions.	Early funding drives innovation, and diversifying financing and domestic investment ensures sustainability.	Ratio of domestic to external funding/research budget; multi-year grants secured (TDR, 2024).

Regional hubs and networks	Establishing regional R&D hubs. Creating networks for sample sharing, standard operating procedure harmonization, multicenter trials, and pooled procurement.	Leverage economies of scale and concentrate expertise.	Number of countries participating in the hub and sample testing turnaround time across the network (TDR, 2024).
Regulatory and manufacturing pathways	Strengthen national regulatory agencies. Harmonizing processes through regional frameworks and the WHO prequalification. Developing fill-and-finish capacity or partner with manufacturers. Train ethics committees.	Streamlining processes is critical.	Time to regulatory approval for a clinical trial protocol and the existence of GMP agreements (TDR, 2024).
Surveillance and data systems	Updating prevalence and intensity maps, adopting standardized endpoints for trials, and investing in electronic data capture and LIMS.	High-quality prevalence data is essential for choosing clinical trial sites, and using standardized endpoints facilitates pooling analyses across trials.	Updated prevalence maps; number of sites using standardized endpoints (Nakanjako et al., 2025).
Community engagement	Co-designing protocols with local communities, conducting acceptability studies, and risk communication integrate insights on helminth-vaccine interactions.	Engaging communities early ensures ethical conduct and improves vaccine uptake.	Community engagement scores and enrollment and retention rates (Nakanjako et al., 2025).
Translational research and product development	Advance candidates from preclinical testing to early-phase trials. Support formulation, adjuvant testing, and delivery optimization. Strengthening academia-industry-regulator linkages.	Ensures that built capacity is actively applied to advance vaccine candidates through the development pipeline.	Number of candidates advancing through development stages.

The table outlines a strategic framework for building sustainable local capacity for Schistosomiasis vaccine research and development, from initial assessment to translational research. LMICs: Low- and middle-income countries; GCP: Good Clinical Practice; R&D: Research and development; GMP: Good Manufacturing Practice; PCR: Polymerase chain reactions; ELISA: enzyme-linked immunosorbent assay.

8. Conclusions

In conclusion, schistosomiasis remains a persistent global health challenge, particularly in sub-Saharan Africa, Asia, and Latin America. While praziquantel has been instrumental in controlling morbidity, it does not prevent reinfection or transmission. Vaccine development offers a sustainable and long-term solution, and when achieved, will represent a major advancement in global efforts to control and eliminate this neglected tropical disease. Even though significant progress has been made

in understanding host-parasite immunology and identifying protective antigens with numerous vaccine candidates, Sm14, Sm-TSP-2, and Sh28GST are demonstrating safety and immunogenicity. Novel platforms like mRNA and EV-based vaccines are expanding the horizon in the effort to develop an efficacious *Schistosoma* vaccine. Major hurdles related to the biological complexity of the parasite, translational gaps between animal models and human applications, and implementation challenges in endemic settings, however, remain. The future success of schistosomiasis vaccines depends to some extent on collaborative efforts across multiple sectors, including continued scientific innovation to identify novel antigens, functionally relevant targets, and delivery platforms, strategic integration with existing control programs like mass drug administration, and sustainable manufacturing and distribution avenues that safeguard access for affected populations in low-resource settings. The lessons from decades of schistosomiasis vaccine research not only advance the specific goal of controlling this disease but also contribute valuable knowledge to the broader field of parasitology and vaccine science. With sustained commitment and strategic investment, an effective schistosomiasis vaccine can become a reality within the foreseeable future, representing a critical tool for eliminating schistosomiasis as a public health problem sooner than later.

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References

- WHO. (2024). Schistosomiasis and soil-transmitted helminthiasis: Progress report 2023. *Weekly Epidemiological Record*, 99(48), 707–717.
- Zhou, X., Xue, Q., Wu, C., Li, X., Wang, Y., Dai, Y., Xiong, C., Zhang, Y., Xu, Y., Liu, X., & Huang, Y. (2025). A novel combination therapy with Uridine and Praziquantel effectively alleviates schistosomiasis-induced hepatic fibrosis through promoting adipogenic differentiation. *PLoS pathogens*, 21(8), e1013403. <https://doi.org/10.1371/journal.ppat.1013403>
- Torrico, J. C., & Gregorio, G. E. V. (2025). Hepatosplenic Schistosomiasis Presenting as Melena in an Adolescent Filipino Male: A Case Report and Literature Review. *Acta medica Philippina*, 59(5), 92–98. <https://doi.org/10.47895/amp.vi0.9817>
- Smith-Togobo, C., Mprah, R., Yeboah, E. A., Anyidoho, H. K., Asigbe, D., Afernorfe, J. K., Ayro, F., & Duedu, K. O. (2023). Detection of cytological abnormalities in urothelial cells from individuals previously exposed or currently infected with *Schistosoma haematobium*. *PloS one*, 18(3), e0278202. <https://doi.org/10.1371/journal.pone.0278202>
- Orish, V. N., Kaba, G., Dah, A. K., Maalman, R. S., Amoh, M., Appiah-Kubi, A., Azanu, W., Adzah, D., Nyonator, W. R., Kumi, M. B., Awutey-Hinidza, D. S., Atachie, I., Ahiaku, P., Kwadzokpui, P. K., Fatau, A. A., Smith-Togobo, C., Yong, T. S., Cho, Y. S., Morhe, E. S. K., Kim, S. Y., ... Gyapong, M. (2025). The burden of visually diagnosed female genital schistosomiasis among women with infertility in the Volta Region of Ghana. *Tropical medicine and health*, 53(1), 31. <https://doi.org/10.1186/s41182-024-00660-x>
- Bowers, S. F., Sonnet, F., & Downs, J. A. (2025). Schistosomiasis: a neglected cause of infertility in females and males. *Current opinion in infectious diseases*, 38(5), 385–391. <https://doi.org/10.1097/QCO.0000000000001127>
- Colley, D. G., Bustinduy, A. L., Secor, W. E., & King, C. H. (2014). Human schistosomiasis. *Lancet (London, England)*, 383(9936), 2253–2264. [https://doi.org/10.1016/S0140-6736\(13\)61949-2](https://doi.org/10.1016/S0140-6736(13)61949-2)
- Kołodziej, P., Szostakowska, B., Lass, A., Sulima, M., Sikorska, K., Kocki, J., Krupski, W., Starownik, D., Bojar, P., Szumiło, J., Kasztelan-Szczerbińska, B., Cichoż-Lach, H., Bogucki, J., Szymańska, M., Fota-Markowska, H., & Bogucka-Kocka, A. (2024). Chronic intestinal schistosomiasis caused by co-infection with

- Schistosoma intercalatum* and *Schistosoma mansoni*. The Lancet. Infectious diseases, 24(3), e196–e205. [https://doi.org/10.1016/S1473-3099\(23\)00486-3](https://doi.org/10.1016/S1473-3099(23)00486-3)
- Ajanga, A., Lwambo, N. J., Blair, L., Nyandindi, U., Fenwick, A., & Brooker, S. (2006). *Schistosoma mansoni* in pregnancy and associations with anaemia in northwest Tanzania. Transactions of the Royal Society of Tropical Medicine and Hygiene, 100(1), 59–63. <https://doi.org/10.1016/j.trstmh.2005.06.024>
- Leir, S. A., Foot, O., Jeyaratnam, D., & Whyte, M. B. (2019). Schistosomiasis and associated iron-deficiency anaemia presenting decades after immigration from sub-Saharan Africa. BMJ case reports, 12(4), e227564. <https://doi.org/10.1136/bcr-2018-227564>
- Mengist, H. M., Zewdie, O., & Belew, A. (2017). Intestinal helminthic infection and anemia among pregnant women attending ante-natal care (ANC) in East Wollega, Oromia, Ethiopia. BMC research notes, 10(1), 440. <https://doi.org/10.1186/s13104-017-2770-y>
- King, C. H., & Bertsch, D. (2015). Historical perspective: snail control to prevent schistosomiasis. PLoS neglected tropical diseases, 9(4), e0003657. <https://doi.org/10.1371/journal.pntd.0003657>
- Doenhoff, M. J., Hagan, P., Cioli, D., Southgate, V., Pica-Mattoccia, L., Botros, S., Coles, G., Tchuem Tchuenté, L. A., Mbaye, A., & Engels, D. (2009). Praziquantel: its use in control of schistosomiasis in sub-Saharan Africa and current research needs. Parasitology, 136(13), 1825–1835. <https://doi.org/10.1017/S0031182009000493>
- Hotez, P. J., Strych, U., Lustigman, S., & Bottazzi, M. E. (2016). Human anthelmintic vaccines: Rationale and challenges. Vaccine, 34(30), 3549–3555. <https://doi.org/10.1016/j.vaccine.2016.03.112>
- Wilson, R. A., Langermans, J. A., van Dam, G. J., Vervenne, R. A., Hall, S. L., Borges, W. C., Dillon, G. P., Thomas, A. W., & Coulson, P. S. (2008). Elimination of *Schistosoma mansoni* Adult Worms by Rhesus Macaques: Basis for a Therapeutic Vaccine?. PLoS neglected tropical diseases, 2(9), e290. <https://doi.org/10.1371/journal.pntd.0000290>
- Driciru, E., Koopman, J. P. R., Steenbergen, S., Sonnet, F., Stam, K. A., Bes-Roeleveld, L., Iliopoulou, E., Janse, J. J., Sijtsma, J., Nambuya, I., Hilt, S. T., König, M., Kruize, Y., Casacuberta-Partal, M., Egesa, M., van Dam, G. J., Corstjens, P. L. A. M., van Lieshout, L., Mpairwe, H., MacDonald, A. S., ... Houlder, E. L. (2025). T cell responses in repeated controlled human schistosome infection compared to natural exposure. Nature communications, 16(1), 6827. <https://doi.org/10.1038/s41467-025-62144-8>
- Mutapi, F., Imai, N., Nausch, N., Bourke, C. D., Rujeni, N., Mitchell, K. M., Midzi, N., Woolhouse, M. E., Maizels, R. M., & Mduluzza, T. (2011). Schistosome infection intensity is inversely related to auto-reactive antibody levels. PloS one, 6(5), e19149. <https://doi.org/10.1371/journal.pone.0019149>
- Driciru, E., Koopman, J. P. R., Cose, S., Siddiqui, A. A., Yazdanbakhsh, M., Elliott, A. M., & Roestenberg, M. (2021). Immunological Considerations for *Schistosoma* Vaccine Development: Transitioning to Endemic Settings. Frontiers in immunology, 12, 635985. <https://doi.org/10.3389/fimmu.2021.635985>
- Costain, A. H., Phythian-Adams, A. T., Colombo, S. A. P., Marley, A. K., Owusu, C., Cook, P. C., Brown, S. L., Webb, L. M., Lundie, R. J., Smits, H. H., Berriman, M., & MacDonald, A. S. (2022). Dynamics of Host Immune Response Development During *Schistosoma mansoni* Infection. Frontiers in immunology, 13, 906338. <https://doi.org/10.3389/fimmu.2022.906338>
- Houlder, E. L., Costain, A. H., Nambuya, I., Brown, S. L., Koopman, J. P. R., Langenberg, M. C. C., Janse, J. J., Hoogerwerf, M. A., Ridley, A. J. L., Forde-Thomas, J. E., Colombo, S. A. P., Winkel, B. M. F., Galdon, A. A., Hoffmann, K. F., Cook, P. C., Roestenberg, M., Mpairwe, H., & MacDonald, A. S. (2023). Pulmonary inflammation promoted by type-2 dendritic cells is a feature of human and murine schistosomiasis. Nature communications, 14(1), 1863. <https://doi.org/10.1038/s41467-023-37502-z>
- Driciru, E., Koopman, J. P. R., Steenbergen, S., Sonnet, F., Stam, K. A., Bes-Roeleveld, L., Iliopoulou, E., Janse, J. J., Sijtsma, J., Nambuya, I., Hilt, S. T., König, M., Kruize, Y., Casacuberta-Partal, M., Egesa, M., van Dam, G. J., Corstjens, P. L. A. M., van Lieshout, L., Mpairwe, H., MacDonald, A. S., ... Houlder, E. L. (2025). T cell responses in repeated controlled human schistosome infection compared to natural exposure. Nature communications, 16(1), 6827. <https://doi.org/10.1038/s41467-025-62144-8>
- Zheng, B., Zhang, J., Chen, H., Nie, H., Miller, H., Gong, Q., & Liu, C. (2020). T Lymphocyte-Mediated Liver Immunopathology of Schistosomiasis. Frontiers in immunology, 11, 61. <https://doi.org/10.3389/fimmu.2020.00061>

- Maizels, R. M., Balic, A., Gomez-Escobar, N., Nair, M., Taylor, M. D., & Allen, J. E. (2004). Helminth parasites--masters of regulation. *Immunological reviews*, 201, 89–116. <https://doi.org/10.1111/j.0105-2896.2004.00191.x>
- Pearce, E. J., & MacDonald, A. S. (2002). The immunobiology of schistosomiasis. *Nature Reviews. Immunology*, 2(7), 499–511. <https://doi.org/10.1038/nri843>
- Costain, A. H., MacDonald, A. S., & Smits, H. H. (2018). Schistosome Egg Migration: Mechanisms, Pathogenesis, and Host Immune Responses. *Frontiers in immunology*, 9, 3042. <https://doi.org/10.3389/fimmu.2018.03042>
- Hams, E., Aviello, G., & Fallon, P. G. (2013). The schistosome granuloma: friend or foe?. *Frontiers in immunology*, 4, 89. <https://doi.org/10.3389/fimmu.2013.00089>
- McManus, D. P., Bergquist, R., Cai, P., Ranasinghe, S., Tebeje, B. M., & You, H. (2020). Schistosomiasis-from immunopathology to vaccines. *Seminars in immunopathology*, 42(3), 355–371. <https://doi.org/10.1007/s00281-020-00789-x>
- Araújo, M. I., Hoppe, B. S., Medeiros, M., Jr, & Carvalho, E. M. (2004). Schistosoma mansoni infection modulates the immune response against allergic and auto-immune diseases. *Memorias do Instituto Oswaldo Cruz*, 99(5 Suppl 1), 27–32. <https://doi.org/10.1590/s0074-02762004000900005>
- Molehin A. J. (2020). Current Understanding of Immunity Against Schistosomiasis: Impact on Vaccine and Drug Development. *Research and reports in tropical medicine*, 11, 119–128. <https://doi.org/10.2147/RRTM.S274518>
- Capron, A., Capron, M., Dombrowicz, D., & Riveau, G. (2001). Vaccine strategies against schistosomiasis: from concepts to clinical trials. *International archives of allergy and immunology*, 124(1-3), 9–15. <https://doi.org/10.1159/000053656>
- Capron, A., Riveau, G., Capron, M., & Trottein, F. (2005). Schistosomes: the road from host-parasite interactions to vaccines in clinical trials. *Trends in parasitology*, 21(3), 143–149. <https://doi.org/10.1016/j.pt.2005.01.003>
- Butterworth, A. E., & Hagan, P. (1987). Immunity in human schistosomiasis. *Parasitology today (Personal ed.)*, 3(1), 11–16. [https://doi.org/10.1016/0169-4758\(87\)90091-3](https://doi.org/10.1016/0169-4758(87)90091-3)
- Dunne, D. W., & Cooke, A. (2005). A worm's eye view of the immune system: consequences for evolution of human autoimmune disease. *Nature reviews. Immunology*, 5(5), 420–426. <https://doi.org/10.1038/nri1601>
- Wilkins, H. A., Blumenthal, U. J., Hagan, P., Hayes, R. J., & Tulloch, S. (1987). Resistance to reinfection after treatment of urinary schistosomiasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 81(1), 29–35. [https://doi.org/10.1016/0035-9203\(87\)90273-2](https://doi.org/10.1016/0035-9203(87)90273-2)
- Rihet, P., Demeure, C. E., Bourgois, A., Prata, A., & Dessein, A. J. (1991). Evidence for an association between human resistance to Schistosoma mansoni and high anti-larval IgE levels. *European journal of immunology*, 21(11), 2679–2686. <https://doi.org/10.1002/eji.1830211106>
- Bickle Q. D. (2009). Radiation-attenuated schistosome vaccination--a brief historical perspective. *Parasitology*, 136(12), 1621–1632. <https://doi.org/10.1017/S0031182009005848>
- Wilson, R. A., Li, X. H., & Castro-Borges, W. (2016). Do schistosome vaccine trials in mice have an intrinsic flaw that generates spurious protection data?. *Parasites & vectors*, 9, 89. <https://doi.org/10.1186/s13071-016-1369-9>
- Molehin, A. J., McManus, D. P., & You, H. (2022). Vaccines for Human Schistosomiasis: Recent Progress, New Developments and Future Prospects. *International journal of molecular sciences*, 23(4), 2255. <https://doi.org/10.3390/ijms23042255>
- Sotillo, J., Doolan, D., & Loukas, A. (2017). Recent advances in proteomic applications for schistosomiasis research: potential clinical impact. *Expert review of proteomics*, 14(2), 171–183. <https://doi.org/10.1080/14789450.2017.1271327>
- Mossallam, S. F., Abou-El-Naga, I. F., Abdel Bary, A., Elmorsy, E. A., & Diab, R. G. (2021). Schistosoma mansoni egg-derived extracellular vesicles: A promising vaccine candidate against murine schistosomiasis. *PLoS neglected tropical diseases*, 15(10), e0009866. <https://doi.org/10.1371/journal.pntd.0009866>
- Riveau, G., Schacht, A. M., Dompnier, J. P., Deplanque, D., Seck, M., Waucquier, N., Senghor, S., Delcroix-Genete, D., Hermann, E., Idris-Khodja, N., Levy-Marchal, C., Capron, M., & Capron, A. (2018). Safety and efficacy of the rSh28GST urinary schistosomiasis vaccine: A phase 3 randomized, controlled trial in Senegalese children. *PLoS neglected tropical diseases*, 12(12), e0006968. <https://doi.org/10.1371/journal.pntd.0006968>

- Tendler, M., Almeida, M., & Simpson, A. (2015). Development of the Brazilian Anti Schistosomiasis Vaccine Based on the Recombinant Fatty Acid Binding Protein Sm14 Plus GLA-SE Adjuvant. *Frontiers in immunology*, 6, 218. <https://doi.org/10.3389/fimmu.2015.00218>
- Tran, M. H., Pearson, M. S., Bethony, J. M., Smyth, D. J., Jones, M. K., Duke, M., Don, T. A., McManus, D. P., Correa-Oliveira, R., & Loukas, A. (2006). Tetraspanins on the surface of *Schistosoma mansoni* are protective antigens against schistosomiasis. *Nature medicine*, 12(7), 835–840. <https://doi.org/10.1038/nm1430>
- Diemert, D. J., Correa-Oliveira, R., Fraga, C. G., Talles, F., Silva, M. R., Patel, S. M., Galbiati, S., Kennedy, J. K., Lundeen, J. S., Gazzinelli, M. F., Li, G., Hoeweler, L., Deye, G. A., Bottazzi, M. E., Hotez, P. J., El Sahly, H. M., Keitel, W. A., Bethony, J., & Atmar, R. L. (2023). A randomized, controlled Phase 1b trial of the Sm-TSP-2 Vaccine for intestinal schistosomiasis in healthy Brazilian adults living in an endemic area. *PLoS neglected tropical diseases*, 17(3), e0011236. <https://doi.org/10.1371/journal.pntd.0011236>
- Zhang, W., Ahmad, G., Molehin, A. J., Torben, W., Le, L., Kim, E., Lazarus, S., Siddiqui, A. J., Carter, D., & Siddiqui, A. A. (2018). *Schistosoma mansoni* antigen Sm-p80: prophylactic efficacy using TLR4 agonist vaccine adjuvant glucopyranosyl lipid A-Alum in murine and non-human primate models. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research*, 66(8), 1124–1132. <https://doi.org/10.1136/jim-2018-000786>
- Zhang, W., Ahmad, G., Torben, W., Noor, Z., Le, L., Damian, R. T., Wolf, R. F., White, G. L., Chavez-Suarez, M., Podesta, R. B., Kennedy, R. C., & Siddiqui, A. A. (2010). Sm-p80-based DNA vaccine provides baboons with levels of protection against *Schistosoma mansoni* infection comparable to those achieved by the irradiated cercarial vaccine. *The Journal of Infectious Diseases*, 201(7), 1105–1112. <https://doi.org/10.1086/651147>
- Karmakar, S., Zhang, W., Ahmad, G., Torben, W., Alam, M. U., Le, L., Damian, R. T., Wolf, R. F., White, G. L., Carey, D. W., Carter, D., Reed, S. G., & Siddiqui, A. A. (2014). Use of an Sm-p80-based therapeutic vaccine to kill established adult schistosome parasites in chronically infected baboons. *The Journal of infectious diseases*, 209(12), 1929–1940. <https://doi.org/10.1093/infdis/jiu031>
- Houlder, E. L., da Silva, L. F., van Diepen, A., Amaral, M. S., Wilson, R. A., Hokke, C. H., Roestenberg, M., & Bakker, W. A. M. (2025). Pre-clinical studies of *Schistosoma mansoni* vaccines: A scoping review. *PLoS neglected tropical diseases*, 19(6), e0012956. <https://doi.org/10.1371/journal.pntd.0012956>
- Da'dara, A. A., Skelly, P. J., Wang, M. M., & Harn, D. A. (2001). Immunization with plasmid DNA encoding the integral membrane protein, Sm23, elicits a protective immune response against schistosome infection in mice. *Vaccine*, 20(3-4), 359–369. [https://doi.org/10.1016/s0264-410x\(01\)00374-7](https://doi.org/10.1016/s0264-410x(01)00374-7)
- Da'dara, A. A., Skelly, P. J., Fatakawala, M., Visovatti, S., Eriksson, E., & Harn, D. A. (2002). Comparative efficacy of the *Schistosoma mansoni* nucleic acid vaccine, Sm23, following microseeding or gene gun delivery. *Parasite immunology*, 24(4), 179–187. <https://doi.org/10.1046/j.1365-3024.2002.00453.x>
- Gaugitsch, H. W., Hofer, E., Huber, N. E., Schnabl, E., & Baumruker, T. (1991). A new superfamily of lymphoid and melanoma cell proteins with extensive homology to *Schistosoma mansoni* antigen Sm23. *European journal of immunology*, 21(2), 377–383. <https://doi.org/10.1002/eji.1830210219>
- Cardoso, F. C., Macedo, G. C., Gava, E., Kitten, G. T., Mati, V. L., de Melo, A. L., Caliari, M. V., Almeida, G. T., Venancio, T. M., Verjovski-Almeida, S., & Oliveira, S. C. (2008). *Schistosoma mansoni* tegument protein Sm29 is able to induce a Th1-type of immune response and protection against parasite infection. *PLoS neglected tropical diseases*, 2(10), e308. <https://doi.org/10.1371/journal.pntd.0000308>
- de Oliveira Fraga, L. A., Lamb, E. W., Moreno, E. C., Chatterjee, M., Dvořák, J., Delcroix, M., Sajid, M., Caffrey, C. R., & Davies, S. J. (2010). Rapid induction of IgE responses to a worm cysteine protease during murine pre-patent schistosome infection. *BMC immunology*, 11, 56. <https://doi.org/10.1186/1471-2172-11-56>
- Robinson, M. W., Dalton, J. P., & Donnelly, S. (2008). Helminth pathogen cathepsin proteases: it's a family affair. *Trends in biochemical sciences*, 33(12), 601–608. <https://doi.org/10.1016/j.tibs.2008.09.001>
- Jackson, L. A., Coler, R. N., Deye, G. A., Carter, D., Gray, S. A., Pecor, T., Davis, J., Larsen, S. E., Posavad, C. M., Cox, C., Watanabe, A., Lundeen, J. S., Gill, R., Kalyanasundaram, A., & Siddiqui, A. A. (2025). Safety and immunogenicity of the Sm-p80 GLA-SE schistosomiasis vaccine. *NPJ vaccines*, 10(1), 247. <https://doi.org/10.1038/s41541-025-01261-3>

- Kim, J., Davis, J., Lee, J., Cho, S. N., Yang, K., Yang, J., Bae, S., Son, J., Kim, B., Whittington, D., Siddiqui, A. A., Carter, D., & Gray, S. A. (2024). An assessment of a GMP schistosomiasis vaccine (SchistoShield®). *Frontiers in tropical diseases*, 5, 1404943. <https://doi.org/10.3389/fitd.2024.1404943>
- Ly, A. T., Diop, D., Diop, M., Schacht, A. M., Mbengue, A., Diagne, R., Guisse, M., Dompnier, J. P., Messias, C., Coler, R. N., Ramos, C. R., Tendeng, J. N., Ndiaye, S., Marroquin-Quelopana, M., de Carvalho Parra, J., Dos Santos, T., Sirianni Dos Santos Almeida, M., Mendes-da-Cruz, D. A., Reed, S., Savino, W., ... Tendler, M. (2025). The Sm14+GLA-SE Recombinant Vaccine Against *Schistosoma mansoni* and *S. haematobium* in Adults and School Children: Phase II Clinical Trials in West Africa. *Vaccines*, 13(3), 316. <https://doi.org/10.3390/vaccines13030316>
- Kuipers, M. E., Ozir-Fazalalikhani, A., Haeblerlein, S., Driessen, N. N., de Korne, C. M., Mes, L., Hensbergen, P. J., Nolte-'t Hoen, E. N. M., Hokke, C. H., & Smits, H. H. (2025). Extracellular Vesicles From *Schistosoma mansoni* Adult Worms Stimulate IL-10 Release by B Cells. *Parasite immunology*, 47(9), e70023. <https://doi.org/10.1111/pim.70023>
- Mekonnen, G. G., Tedla, B. A., Pickering, D., Becker, L., Wang, L., Zhan, B., Bottazzi, M. E., Loukas, A., Sotillo, J., & Pearson, M. S. (2020). *Schistosoma haematobium* Extracellular Vesicle Proteins Confer Protection in a Heterologous Model of Schistosomiasis. *Vaccines*, 8(3), 416. <https://doi.org/10.3390/vaccines8030416>
- Al-Naseri, A., Al-Absi, S., El Ridi, R., & Mahana, N. (2021). A comprehensive and critical overview of schistosomiasis vaccine candidates. *Journal of parasitic diseases : official organ of the Indian Society for Parasitology*, 45(2), 557–580. <https://doi.org/10.1007/s12639-021-01387-w>
- Molehin, A. J., McManus, D. P., & You, H. (2022). Vaccines for Human Schistosomiasis: Recent Progress, New Developments and Future Prospects. *International journal of molecular sciences*, 23(4), 2255. <https://doi.org/10.3390/ijms23042255>
- Siddiqui, A. A., & Siddiqui, S. Z. (2017). Sm-p80-Based Schistosomiasis Vaccine: Preparation for Human Clinical Trials. *Trends in parasitology*, 33(3), 194–201. <https://doi.org/10.1016/j.pt.2016.10.010>
- Driguez, P., McWilliam, H. E., Gaze, S., Piedrafita, D., Pearson, M. S., Nakajima, R., Duke, M., Trieu, A., Doolan, D. L., Cardoso, F. C., Jasinkas, A., Gobert, G. N., Felgner, P. L., Loukas, A., Meeusen, E., & McManus, D. P. (2016). Specific humoral response of hosts with variable schistosomiasis susceptibility. *Immunology and cell biology*, 94(1), 52–65. <https://doi.org/10.1038/icb.2015.61>
- Licá, I. C. L., Frazão, G. C. C. G., Nogueira, R. A., Lira, M. G. S., Dos Santos, V. A. F., Rodrigues, J. G. M., Miranda, G. S., Carvalho, R. C., Silva, L. A., Guerra, R. N. M., & Nascimento, F. R. F. (2023). Immunological mechanisms involved in macrophage activation and polarization in schistosomiasis. *Parasitology*, 150(5), 401–415. <https://doi.org/10.1017/S0031182023000021>
- Collyer, B. S., Turner, H. C., Hollingsworth, T. D., & Keeling, M. J. (2019). Vaccination or mass drug administration against schistosomiasis: a hypothetical cost-effectiveness modelling comparison. *Parasites & vectors*, 12(1), 499. <https://doi.org/10.1186/s13071-019-3749-4>
- Gandvi, D., Jyotishi, C., Patel, M., & Gupta, R. (2025). In silico design of a multi-epitope pan vaccine targeting *Schistosoma* species. *Genomics & informatics*, 23(1), 21. <https://doi.org/10.1186/s44342-025-00053-4>
- Hiatt RA, Sotomayor ZR, Sanchez G, Zambrana M, Knight WB. Factors in the pathogenesis of acute schistosomiasis mansoni. *J Infect Dis*. (1979) 139:659–66. doi: 10.1093/infdis/139.6.659
- Tallima H, Dvorak J, Kareem S, Abou El Dahab M, Abdel Aziz N, Dalton JP, et al. Protective immune responses against *Schistosoma mansoni* infection by immunization with functionally active gut-derived cysteine peptidases alone and in combination with glyceraldehyde 3-phosphate dehydrogenase. *PLoS Negl Trop Dis*. (2017) 11:e0005443. doi: 10.1371/journal.pntd.0005443
- Shainheit MG, Lasocki KW, Finger E, Larkin BM, Smith PM, Sharpe AH, et al. The pathogenic Th17 cell response to major schistosome egg antigen is sequentially dependent on IL-23 and IL-1 beta. *J Immunol*. (2011) 187:5328–35. doi: 10.4049/jimmunol.1101445
- Wilson R. A. (2023). Models of Protective Immunity against Schistosomes: Implications for Vaccine Development. *Pathogens (Basel, Switzerland)*, 12(10), 1215. <https://doi.org/10.3390/pathogens12101215>

- Köster, B., & Strand, M. (1994). Schistosoma mansoni: Sm23 is a transmembrane protein that also contains a glycosylphosphatidylinositol anchor. Archives of biochemistry and biophysics, 310(1), 108–117. <https://doi.org/10.1006/abbi.1994.1146>
- Nakanjako, D., Egesa, M., Byakwaga, H., Tolo, C. U., Byaruhanga, A. M., Beinamaryo, P., Banturaki, G., Nakiyingi, L., Ocama, P., Kanya, M. R., & Elliott, A. M. (2025). Identification of training needs in schistosomiasis research to build capacity for schistosomiasis control in Uganda. Tropical medicine & international health : TM & IH, 30(4), 314–321. <https://doi.org/10.1111/tmi.14098>
- TDR (2024). Annual report 2023: building the science of solutions. Geneva: World Health Organization.

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