Acta Scientific Microbiology (ISSN: 2581-3226)

Volume 9 Issue 8 August 2026

Review Article

Immunotherapy as an Emerging Strategy in Parasitic Disease Control and Elimination

Evelyn Orevaoghene Onosakponome[1]* and Ikpeama Roseanne Adah[2]

[1]Department of Medical Microbiology and Parasitology, Federal University Otuoke, Bayelsa State, Nigeria

[2]Department of Medical Laboratory Science, PAMO University of Medical Sciences Port Harcourt, Rivers State, Nigeria

***Corresponding Author:** Evelyn Orevaoghene Onosakponome, Department of Medical Microbiology and Parasitology, Federal University Otuoke, Bayelsa State.

DOI: 10.31080/ASMI.2026.09.1616

Received: June 15, 2026

Published: July 22, 2026

Abstract

Parasitic diseases constitute a significant global health burden, affecting over two billion individuals and contributing substantially to morbidity, mortality, and economic loss in resource-limited settings. Traditional control strategies including mass drug administration, chemotherapy, and vector control have achieved measurable success in disease reduction but increasingly confront critical limitations: the emergence of drug-resistant parasite strains, insecticide-resistant vector populations, and crucially, the absence of durable host immunity following treatment. Immunotherapy approaches, including vaccination, monoclonal antibody therapies, and immune modulation strategies, offer a fundamentally different mechanism by which to address parasitic infection through enhancement of host-mediated parasite elimination and establishment of sustained immunological protection. Recent clinical advances, particularly the World Health Organization approval and real-world implementation of RTS,S/AS01 (Mosquirix) and R21/Matrix-M malaria vaccines, demonstrate proof-of-concept for immunotherapeutic approaches in endemic populations. This narrative review systematically examines the current evidence base for immunotherapy in parasitic disease control, analysing vaccine development strategies, monoclonal antibody approaches, immune modulation mechanisms, and the parasite-derived immune evasion strategies that constrain immunotherapeutic efficacy. Integration of immunotherapy with conventional public health strategies, supported by technological advances in recombinant antigen production, nanoparticle delivery systems, and artificial intelligence-assisted vaccine design, provides a viable pathway toward sustainable global parasite elimination.

Keywords: Immune Evasion; Immunotherapy; Neglected Tropical Diseases; Parasitic Disease Control; Vaccine Development

Introduction

Parasitic diseases remain among the most prevalent infectious conditions globally, with over two billion individuals at risk of infection and approximately one billion experiencing active disease across tropical and subtropical regions [1,2]. The epidemiological significance of parasitic infections is particularly evident in their concentration within low-income and lower-middle-income countries where the disease burden is highest; malaria alone causes approximately 249 million infections annually, with sub-Saharan Africa accounting for approximately 94% of cases and deaths [2]. Within this region, Nigeria bears an extraordinary burden, accounting for roughly 27% of global malaria cases and

deaths, thereby positioning it as the country with the highest parasite disease burden globally [2]. Schistosomiasis represents a second major parasitic threat, affecting approximately 240 million individuals with chronic infection of the liver, intestinal tract, and urinary system [1]. Lymphatic filariasis, caused by *Wuchereria bancrofti* and transmitted through mosquito vectors, chronically damages lymphatic system architecture in over 120 million individuals, resulting in permanent disability through elephantiasis and hydrocele [3]. Soil-transmitted helminthiasis, including infections with *Ascaris lumbricoides*, hookworms, and *Trichuris trichiura*, represents the most widespread parasitic infection, affecting approximately 1.5 billion individuals globally, with particular concentration among school-aged children in endemic regions [1]. These infections disproportionately affect the poorest populations, contributing to malnutrition, educational deficits, reduced economic productivity, and perpetuation of poverty cycles, characteristics that have led to their designation as neglected tropical diseases [4].

The conventional paradigm for parasitic disease control has emphasised external chemical and vector-based interventions. Artemisinin-based combination therapies have achieved substantial reductions in malaria mortality since their introduction, with artemisinin now considered one of the most important antimalarial agents available [5]. Complementary approaches including praziquantel for schistosomiasis, albendazole for soil-transmitted helminths, and ivermectin for lymphatic filariasis form the backbone of global mass drug administration programmes [3]. Vector control strategies, particularly insecticide-treated mosquito nets (ITNs) and indoor residual spraying (IRS), have demonstrated substantial effectiveness in malaria transmission interruption [2]. Despite these achievements, conventional control strategies confront increasingly severe limitations that constrain their capacity to achieve disease elimination. Drug resistance has emerged as a persistent threat; artemisinin-resistant *Plasmodium falciparum* strains now prevalent in Southeast Asia compromise treatment efficacy in affected populations [5]. Insecticide resistance among mosquito vectors continues to expand geographically and temporally, undermining vector control effectiveness [1]. More fundamentally, these conventional approaches lack the biological capacity to establish durable immunity; individuals treated successfully with chemotherapy in endemic settings typically acquire new infections within weeks to months of treatment cessation due to persistent environmental exposure and the absence of host-mediated protection [4]. This reinfection pattern reflects a core limitation of conventional approaches: they manage existing infections without preventing acquisition of new parasites from the environment.

Immunotherapy represents a conceptually distinct approach to parasitic disease control, one grounded in enhancement of host immune capacity rather than direct parasite targeting. Defined as medical strategies designed to stimulate, enhance, or regulate host immune responses to achieve effective parasite elimination and sustained protection, immunotherapy operates through activation of adaptive and innate immune mechanisms that generate lasting immunological memory [6]. This mechanistic distinction from conventional chemotherapy is fundamental: whereas chemotherapy provides temporary parasite clearance lasting only as long as drug concentrations remain therapeutically relevant, immunotherapy establishes immunological memory through T cell and B cell responses that persist for years or decades following initial vaccination [7]. This review systematically examines the emerging evidence base for immunotherapy in parasitic disease control and elimination, focusing on five core objectives. First, the review delineates the major parasitic diseases targeted by immunotherapeutic interventions, with particular emphasis on those causing the highest global disease burden and mortality. Second, the review explains the mechanistic pathways through which conventional parasitic disease control operates and identifies the specific biological and epidemiological limitations that constrain their effectiveness. Third, the review describes the conceptual and mechanistic foundations of immunotherapeutic approaches in parasitology, examining both the theoretical basis for immune-mediated parasite control and the specific immune pathways activated by distinct immunotherapy modalities. Fourth, the review comprehensively examines the major immunotherapy strategies currently in clinical development or deployment, including vaccine platforms, monoclonal antibody approaches, and immune modulation strategies, analysing their mechanisms, clinical evidence, and implementation feasibility. Fifth, the review evaluates parasite-derived immune evasion mechanisms that constrain immunotherapeutic efficacy, examining antigenic variation, intracellular survival strategies, and parasite-induced immune suppression. Sixth, the review compares and contrasts traditional control methods with immunotherapy across multiple

operational, biological, and economic dimensions. Finally, the review examines current technological advances, identifies critical research and implementation challenges, and proposes future directions for parasitological immunotherapy. The ultimate purpose of this examination is to establish whether immunotherapy represents a viable and sustainable alternative or complement to conventional parasitic disease control strategies capable of supporting movement toward global parasite elimination.

Parasitic diseases and global disease burden

Understanding the epidemiology and disease burden of parasitic infections provides essential context for evaluating the potential impact of immunotherapeutic interventions. Malaria, caused by *Plasmodium* species transmitted through the bite of infected female *Anopheles* mosquitoes, remains the most lethal parasitic infection in humans [8]. *Plasmodium falciparum*, the most virulent malaria parasite species, causes approximately 608,000 deaths annually, with young children under five years of age accounting for the vast majority of fatalities [2]. The parasite's pathogenesis involves initial infection of hepatocytes, where parasites undergo initial replication before release into the bloodstream and invasion of red blood cells, leading to mechanical obstruction of microvasculature, oxidative damage, and immune-mediated tissue injury [8]. Severe malaria manifestations include cerebral malaria, severe anaemia, acute kidney injury, and metabolic acidosis, each contributing to the high mortality observed, particularly in young children lacking acquired immunity [2].

Leishmaniasis, caused by *Leishmania* parasites transmitted by infected sandflies, presents three major clinical forms: visceral leishmaniasis, cutaneous leishmaniasis, and mucocutaneous leishmaniasis [6]. The parasite survives and replicates within host macrophages through inhibition of phagolysosomal fusion and production of anti-inflammatory mediators, establishing chronic infection that persists unless antimicrobial immunity is generated [8]. Approximately 1 billion individuals inhabit leishmaniasis-endemic regions across Africa, Asia, and South America, placing them at risk of transmission [3]. Schistosomiasis, caused by *Schistosoma* species acquired through direct contact with contaminated freshwater, affects approximately 240 million individuals, with substantial concentration in sub-Saharan Africa [1]. The parasite's pathogenesis involves adult worm egg production within hepatic and mesenteric blood vessels, with chronic tissue inflammation leading to progressive fibrosis and organ dysfunction [9]. Lymphatic filariasis, caused by *Wuchereria bancrofti* and transmitted via mosquito vectors, chronically damages lymphatic vessels and nodes, resulting in permanent disability in over 120 million individuals [3]. Soil-transmitted helminthiasis, encompassing *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura* infections, affects approximately 1.5 billion individuals, with the highest burden concentrated in school-aged children [1]. These infections collectively contribute to anemia, malnutrition, and cognitive deficits, with particularly severe consequences for child development and educational attainment.

Limitations of conventional parasitic disease control

Conventional parasitic disease control strategies operate through two primary mechanisms: direct parasite targeting via chemotherapy and interruption of transmission through vector control. Artemisinin-based combination therapies, first-line agents for malaria treatment, rapidly clear parasitemia and achieve clinical cure in the majority of treated patients [5]. Praziquantel, the standard treatment for schistosomiasis, achieves cure rates exceeding 80% when administered at appropriate dosage [1]. Albendazole and ivermectin effectively eliminate soil-transmitted helminths and *Wuchereria bancrofti* respectively [3]. Vector control strategies, particularly ITNs and IRS, have demonstrated substantial effectiveness in reducing malaria transmission intensity in multiple endemic regions [2]. Despite these documented successes, conventional approaches increasingly confront critical limitations that constrain their capacity to achieve sustained disease control or elimination.

Drug resistance has emerged as a persistent and expanding threat to chemotherapeutic efficacy. Artemisinin-resistant *Plasmodium falciparum* strains, first identified in Cambodia, have now spread across Southeast Asia and threaten further geographic expansion [5]. Resistance is typically characterised by delayed parasite clearance from peripheral blood, and whilst mortality remains low, reduced drug efficacy creates potential for therapeutic failure, selection of resistant parasites, and loss of treatment efficacy [5]. Insecticide resistance among *Anopheles* vectors has similarly expanded; resistance to pyrethroids, the class of insecticides most commonly employed in ITNs, is now documented in the majority of countries with active malaria transmission [2]. Concomitant resistance to multiple insecticide classes, known as multiple

resistance, increasingly compromises vector control effectiveness. Beyond resistance, chemotherapy lacks the biological capacity to prevent reinfection. Parasites persist in the environment, and individuals in endemic regions experience rapid reinfection following successful treatment; the absence of treatment-induced immunity means individuals remain as susceptible to new infections as before treatment [4]. This reinfection pattern creates a fundamental epidemiological constraint: chemotherapy requires indefinite, repeated administration to maintain disease control, imposing substantial logistical and financial burdens on resource-limited health systems.

The immune mechanisms underlying naturally acquired immunity to parasites are only partially understood, yet available evidence suggests that durable, protective immunity develops slowly and incompletely. In malaria, acquired immunity develops gradually over years of repeated exposure, and protection remains incomplete even among long-term residents of highly endemic regions; some degree of parasitemia may persist despite apparent clinical immunity [10]. This pattern contrasts sharply with immunity to other infectious diseases such as measles or polio, where vaccination generates sterilising immunity preventing infection establishment entirely. The partial nature of acquired malaria immunity reflects parasite-derived immune evasion strategies that are discussed subsequently. For schistosomiasis and soil-transmitted helminthiasis, repeated exposure generates partial protection, but reinfection readily occurs following treatment [9]. Conventional control strategies, by targeting parasites directly rather than enhancing host immunity, fail to leverage or accelerate the development of protective immunity. This mechanistic limitation; the inability to generate durable, sustained host immunity, represents perhaps the most fundamental constraint on conventional approaches.

Immunotherapy: Mechanisms and theoretical foundations

Immunotherapy operates fundamentally differently from conventional chemotherapy by enhancing host immune responses to achieve parasite elimination and establish lasting immunological protection. Two primary mechanisms underlie immunotherapeutic approaches: active immunity, wherein vaccination exposes the host to parasite antigens to generate adaptive immune responses and immunological memory, and passive immunity, wherein preformed antibodies are administered directly to provide immediate parasite-targeted effects without requiring host immune activation [6]. Active immunity approaches align most closely with vaccination strategies currently demonstrating greatest clinical promise, and thus this review emphasises active immunotherapy throughout.

Active vaccination generates protective immunity through two distinct mechanisms. First, vaccines generate adaptive immune responses through activation of both T lymphocyte and B lymphocyte populations. T cells, specifically CD4+ T helper cells and CD8+ cytotoxic T cells, recognise parasite-derived antigens presented on major histocompatibility complex molecules and become activated to proliferate and differentiate into effector cells capable of mediating parasite destruction [10]. CD4+ T cells differentiate into specialised subsets, including T helper 1 (Th1) cells that produce interferon-gamma and interleukin-2, promoting activation of macrophages and enhancement of intracellular parasite killing, and regulatory T cells that produce anti-inflammatory mediators including interleukin-10 (IL-10) [8]. B cells recognise native parasite antigens and, upon appropriate T cell help, differentiate into plasma cells that produce high-affinity antibodies specific for parasite targets. These antibodies mediate parasite destruction through multiple mechanisms: opsonisation enhancing phagocyte-mediated killing, complement activation driving complement-mediated lysis, and antibody-dependent cellular cytotoxicity involving natural killer cells and other effector cells [10]. Critically, B cells also generate long-lived memory cells that persist in lymphoid tissues and bone marrow, capable of rapid reactivation upon antigen re-exposure to generate secondary immune responses of greater magnitude and affinity maturation than primary responses [7].

Second, vaccines establish immunological memory that persists for years or decades following initial vaccination. This memory response represents the mechanistic basis for durable protection: upon re-exposure to parasites, existing memory T cells and B cells become reactivated rapidly, generating accelerated effector responses that achieve parasite clearance before clinical disease develops [7]. The capacity of memory responses to prevent infection establishment or limit parasitemia to subclinical levels represents the biological distinction between vaccination and chemotherapy. Whereas chemotherapy requires continuous, repeated administration to maintain therapeutic drug levels, vaccination establishes a state of readiness within

the immune system that persists indefinitely in the absence of antigen re-exposure. This mechanistic distinction has profound epidemiological consequences: vaccination once administered offers potential for lifelong protection, whereas chemotherapy requires perpetual administration. The establishment of immunological memory through vaccination thus provides the biological basis for sustainable disease control capable of supporting movement toward disease elimination.

Beyond parasite destruction, immunotherapy addresses immune dysfunction caused by parasitic infections themselves. Many parasites have evolved sophisticated strategies to actively suppress host immunity, allowing chronic infection despite ongoing immune responses [9]. Schistosomiasis parasites, for example, produce excretory-secretory products that promote differentiation of T cells toward the immunoregulatory phenotype, leading to skewing of immune responses away from T helper 1 (Th1)-mediated destruction and toward T helper 2 (Th2) and regulatory T cell phenotypes characterised by production of anti-inflammatory mediators including IL-10 [9]. Intracellular parasites including *Leishmania* likewise produce anti-inflammatory mediators that redirect macrophage activation toward tissue repair rather than antimicrobial activity [8]. Immunomodulatory agents designed to reverse parasite-induced immune suppression, through blocking regulatory T cell differentiation, antagonising IL-10 signalling, or promoting Th1 differentiation, can restore effective host-mediated immunity. Combination approaches integrating immune modulation with vaccination or monoclonal antibodies thus address multiple levels of immune dysfunction simultaneously.

Immunotherapy Strategies: Current evidence and clinical development

Vaccine development and clinical implementation

Vaccination represents the most clinically advanced and promising immunotherapy approach for parasitic disease control. The approval and real-world implementation of RTS,S/AS01 (Mosquirix) and R21/Matrix-M malaria vaccines constitute the most significant recent advances in parasitological immunotherapy, providing proof-of-concept for the feasibility of generating protective immunity against parasitic pathogens. The RTS,S/AS01 vaccine, developed through two decades of research and clinical evaluation, was first approved by the European Medicines Agency in 2015 and subsequently by the World Health Organization in 2021 for deployment in endemic regions [11]. Phase 3 clinical trials of RTS,S/AS01 demonstrated approximately 36.3% efficacy against clinical malaria and 26.9% efficacy against severe malaria over a 3.5-year follow-up period, with efficacy declining over time [11]. The R21/Matrix-M vaccine, developed through collaboration between the University of Oxford and the Serum Institute of India, demonstrated approximately 75% efficacy against clinical malaria in its first year of follow-up during phase 3 trials, achieving the World Health Organization's original efficacy threshold and demonstrating superior manufacturing scalability compared to RTS,S/AS01 [11]. Both vaccines have received World Health Organization prequalification and are currently deployed within national immunisation programmes across sub-Saharan Africa.

Real-world effectiveness data from cluster-randomised implementation studies provide evidence of these vaccines' impact in endemic populations. An evaluation of RTS,S/AS01 implementation across Ghana, Kenya, and Malawi within the Malaria Vaccine Implementation Programme documented a 13% reduction in all-cause childhood mortality among vaccinated cohorts relative to unvaccinated controls [11]. More recent real-world data from implementation in Ghana, Kenya, and Malawi published in 2024 demonstrated a 32% reduction in severe malaria admissions and 9% reduction in all-cause mortality over one year of follow-up [12]. These reductions in childhood mortality represent the most significant outcome measure, demonstrating that vaccination not only reduces malaria incidence and severe disease but also prevents fatal infections. The feasibility of integrating malaria vaccines into existing routine immunisation programmes, demonstrated through successful implementation in multiple endemic countries, establishes the operational viability of vaccination as a public health intervention.

Vaccine development for other parasitic diseases remains at earlier developmental stages. For schistosomiasis, research has advanced candidate antigens including Sm14 and Sm-TSP-2 through clinical development phases [1]. Early-phase human clinical trials of Sm14 antigen formulated with the GLA-SE adjuvant have demonstrated safety and immunogenicity profiles supporting progression to phase 2b efficacy trials [1]. Recombinant antigen technology, wherein isolated parasite antigens are produced in

laboratory expression systems such as insect cells or mammalian cells, enables generation of safer vaccine candidates compared to historical whole-organism approaches whilst maintaining immunogenicity [13]. Nanoparticle-based vaccine delivery platforms further enhance immunogenicity by improving vaccine stability, enabling precise co-delivery of multiple antigens and immunostimulatory adjuvants, and amplifying downstream immune responses through particle-induced activation of pattern recognition receptors [14]. Viral-vectored vaccines employing chimpanzee adenovirus platforms have been explored for malaria and leishmaniasis, leveraging established recombinant vaccine technologies to deliver parasite antigens within a replication-incompetent viral vector [15].

Despite these advances, vaccine development confronts substantial biological and logistical challenges. Parasites display extensive antigenic variation; *Plasmodium falciparum* expresses a large repertoire of variant surface antigens encoded by approximately 60 distinct var genes, allowing continuous immune evasion through switching of expressed var gene variants [16]. Antigenic diversity both between parasite strains and within individual parasites creates a moving target for vaccine design; a vaccine targeting one var gene variant may prove ineffective against parasites expressing different variants. Parasites display complex, multi-stage life cycles; malaria parasites exist as sporozoites in mosquito saliva, pre-erythrocytic stages in hepatocytes, erythrocytic stages in blood, and sexual stages in mosquitoes, each representing potential vaccine targets but requiring distinct immune mechanisms for optimal control. Natural infections typically generate weak or short-lived immune memory against parasites, creating a vaccine design challenge: vaccines must generate immunity exceeding that generated by natural infection. Vaccine development timelines remain lengthy, typically 10-20 years from antigen identification to approval, and development costs are substantial, creating barriers for vaccines targeting diseases affecting primarily impoverished populations [6]. These challenges have driven development of multi-antigen and multi-stage vaccine approaches simultaneously targeting multiple parasite forms and developmental stages, reducing likelihood that parasites evade all vaccine-induced immunity through single-antigen variation.

Monoclonal antibody therapies

Monoclonal antibodies (mAbs) represent a second major immunotherapeutic approach. These laboratory-synthesised antibodies, generated through isolation of individual B cell clones or through recombinant technologies, provide extreme specificity for parasite-derived antigens. Therapeutic mechanisms of monoclonal antibodies targeting parasites include direct parasite neutralisation, prevention of parasite attachment to host cells, and enhancement of complement-mediated or antibody-dependent cellular cytotoxicity-mediated parasite destruction [6]. Antibodies against *Plasmodium falciparum* blood-stage and sporozoite-stage antigens have demonstrated promising results in phase 1 and phase 2 clinical trials, with documented neutralisation of parasite invasion and enhancement of parasite clearance [6]. Monoclonal antibody-based therapies against various *Leishmania* species have been explored as alternatives to traditional chemotherapy, with laboratory studies demonstrating that antibodies targeting *Leishmania* surface antigens effectively prevent parasite attachment to macrophages and accelerate parasite clearance without generating toxic host reactions [6]. The advantages of monoclonal antibody approaches include extreme specificity for parasite targets, potential for minimal off-target effects on host tissues, and established manufacturing capacity for recombinant antibody production. Limitations include substantial production costs, requirement for repeated administration to maintain therapeutic antibody concentrations, and potential for parasite selection of antibody-escape variants. These constraints suggest that monoclonal antibodies will optimally serve roles in combination with other immunotherapy modalities rather than as monotherapy.

Immune modulation strategies

Immune modulation strategies employ cytokine therapies and immune checkpoint inhibition to enhance parasite-directed immune responses. Cytokine therapy utilises exogenous administration of recombinant signalling proteins, particularly interferon-gamma (IFN-gamma) and interleukins including IL-12 and IL-2, to activate macrophages and promote T helper 1 (Th1)-mediated immune responses [1]. These cytokines activate macrophages to produce reactive oxygen and nitrogen species capable of killing intracellular parasites, and promote differentiation of CD4+ T cells toward the Th1 phenotype, producing IFN-gamma and driving

sustained antimicrobial immunity [1]. CD4+ and CD8+ T-cell activation enhancement strategies aim to amplify intracellular killing of parasites such as *Leishmania* and *Plasmodium* species that survive within host cells through inhibition of intracellular degradation pathways [8]. Immunomodulatory agents designed to reverse parasite-induced immune suppression block regulatory T cell activity or antagonise IL-10-mediated anti-inflammatory responses, restoring effective host capacity to clear chronic, embedded parasite burdens [1]. Experimental studies have demonstrated that these agents, when employed in combination with vaccination or monoclonal antibodies, generate synergistic improvements in parasite clearance beyond those achieved by single modalities [1].

Parasite immune evasion and constraints on immunotherapy

The remarkable capacity of parasites to establish chronic infections despite ongoing host immune responses reflects the evolution of elaborate immune evasion mechanisms. *Plasmodium falciparum* employs antigenic variation through expression of variant surface antigens (PfEMP1) encoded by a diverse family of var genes, each encoding proteins with distinct antigenic properties; by sequentially switching the expressed var gene, parasites change their surface antigenic profile faster than host antibodies can respond, enabling continuous evasion of antibody-mediated clearance [16]. This mechanism explains the gradual development of immunity in naturally exposed populations; only through accumulated exposure to many parasite variants over years of repeated infection does an individual acquire antibodies spanning sufficient antigenic diversity to provide partial protection [10].

Intracellular parasites including *Leishmania* establish chronic infection within host macrophages through multiple mechanisms. The parasite inhibits phagolysosomal fusion, the normal degradative pathway through which macrophages destroy ingested pathogens, thereby allowing parasite survival within the macrophage cytoplasm [8]. *Leishmania* simultaneously produces anti-inflammatory mediators including prostaglandins and anti-inflammatory cytokines, directing macrophage activation toward the alternatively activated, immunoregulatory phenotype rather than the classically activated, antimicrobial phenotype [8]. Schistosomiasis parasites employ distinct evasion mechanisms related to their multicellular complexity. Schistosomiasis parasites secrete immunomodulatory molecules that skew host immunity toward the immunotolerant Th2 and regulatory T cell phenotype, promoting production of anti-inflammatory cytokines including IL-10 and transforming growth factor-beta [9]. Additional evasion mechanisms documented across parasitic pathogens include molecular mimicry, wherein parasites express host-like antigens avoiding immune recognition; antigenic shedding, wherein excess surface antigens are released to overwhelm antibody responses; and direct alteration of host immune signalling pathways to block effector T cell responses.

These parasite immune evasion strategies pose substantial challenges for vaccine development and deployment. Antigenic variation rapidly reduces vaccine effectiveness over time, necessitating either periodic revaccination or development of pan-reactive vaccines capable of recognising conserved epitopes across multiple variant forms [1]. The immunogenic challenge of helminthic parasites differs from protozoans; whilst antigenic variation operates in protozoans, helminthic parasites further employ active immune suppression through production of immunomodulatory molecules [9]. Multi-antigen and multi-stage vaccine approaches attempt to overcome single-antigen evasion by simultaneously targeting multiple parasite components and life-cycle stages, reducing likelihood that parasites escape all vaccine-induced immunity through variation of a single antigen.

Comparative analysis: Traditional control versus immunotherapy

Traditional and immunotherapeutic approaches differ fundamentally across multiple operational, biological, and epidemiological dimensions. Regarding mechanism of action, traditional chemotherapy and vector control intervene externally, applying chemical or physical parasite control measures external to the host immune system. Immunotherapy conversely trains the body's own defence systems to eliminate parasites and establish lasting protection. With respect to duration of protection, chemotherapy offers only temporary coverage lasting as long as drug levels remain therapeutically relevant in blood and tissues; immunity induced by vaccination provides sustained protection through immunological memory persisting years or decades following initial vaccination. Drug and insecticide resistance represents a critical failure point for conventional methods; parasites and vectors continuously evolve resistance through

selective pressure of repeated drug exposure and the capacity of microorganisms to undergo genetic changes conferring survival at high drug concentrations. Immunotherapy strategies generally carry lower resistance risk because they activate multiple immune mechanisms simultaneously, making single-mutation escape less feasible; parasites would require simultaneous mutations conferring resistance to multiple immune effector mechanisms, an event of substantially lower probability than single-mutation resistance to a single drug target [17].

Reinfection patterns diverge markedly between approaches. Chemotherapy provides immediate symptom relief and parasite clearance but offers no protection against reinfection; individuals in endemic settings typically reacquire infections within weeks or months. Vaccination maintains protective immunity that reduces both infection frequency and severity upon reinfection, gradually decreasing transmission intensity within vaccinated populations. Economic considerations favour different approaches depending on timeframe examined. Chemotherapy and vector control require lower initial investment but demand continuous, indefinite funding for repeated drug purchases and vector control campaigns. Vaccination demands substantial upfront research, development, and manufacturing investment but establishes potentially permanent protection within vaccinated cohorts. Sustainability metrics similarly diverge; traditional interventions require perpetual logistical implementation and cycling, whilst vaccination's sustainability improves with time as vaccination coverage expands and infection pressure decreases community-wide. Specificity and off-target effects differ; chemical therapies and vector control employ broad-spectrum approaches that sometimes cause unintended ecological damage or adverse host effects, whilst immunotherapy targets specific parasite antigens or life stages with minimal off-target impact on host physiology.

Technological advances and current implementation status

Multiple technological advances are currently accelerating immunotherapy development and deployment. The R21/Matrix-M vaccine demonstrates superior manufacturing scalability compared to the earlier RTS,S/AS01 vaccine, enabling production of vaccine doses at substantially lower cost and with greater logistical feasibility, thereby improving viability of broad African deployment [11]. Recombinant DNA and protein technologies enable production of isolated parasite antigens in laboratory expression systems, generating safer vaccine candidates compared to historical whole-organism approaches whilst maintaining antigenicity [13]. Viral-vectored vaccines employing chimpanzee adenovirus platforms leverage established recombinant vaccine platforms to deliver parasite antigens within replication-incompetent viral vectors [15]. Nanoparticle-based delivery systems improve vaccine stability during storage and transport, critically important for deployment in settings with limited cold-chain infrastructure, and enable precise co-delivery of multiple antigens and adjuvants, addressing parasite antigenic diversity through simultaneous exposure to multiple immune targets [14]. Artificial intelligence and machine learning approaches accelerate the vaccine discovery-to-candidate pipeline through rapid identification of immunogenic parasite antigens, prediction of major histocompatibility complex-binding epitopes, and computational optimisation of adjuvant formulations, substantially shortening development timelines relative to traditional laboratory-based approaches.

Research priorities and future directions

The most promising path forward integrates immunotherapy with conventional public health approaches rather than treating them as competing strategies. Combination therapy approaches are currently being investigated in clinical trials to determine whether pairing immunotherapy with standard chemotherapy improves parasite elimination rates and reduces post-treatment reinfection relative to either modality alone. Multi-antigen vaccines targeting multiple parasite developmental stages simultaneously are under development to overcome single-antigen immune evasion and generate broader, more durable protection. Artificial intelligence-assisted vaccine design and machine learning platforms are expected to further accelerate vaccine discovery and epitope prediction, shortening timelines from antigen identification to active clinical candidates. Because many parasitic diseases display zoonotic characteristics, a One Health integration framework binding together human, animal, and environmental health sectors will strengthen international surveillance and control programmes. Global elimination of neglected tropical diseases ultimately requires sustained international partnerships, equitable vaccine access, increased research funding directed toward diseases affecting impoverished populations, and formal integration of immunotherapy into national health programmes across all endemic countries.

Conclusion

Immunotherapy represents a transformative frontier in parasitic disease control and elimination. Traditional approaches including chemotherapy, mass drug administration, and vector control remain essential immediate interventions. Yet these methods increasingly confront mounting limitations from drug and insecticide resistance, high reinfection rates in endemic populations, and fundamentally, an inability to establish lasting immunity. Immunotherapy addresses these gaps through vaccines, monoclonal antibodies, and cytokine therapies that establish sustained, durable parasite protection. World Health Organization approval and real-world implementation of RTS,S/AS01 and R21/Matrix-M malaria vaccines have provided definitive proof-of-concept, demonstrating both clinical efficacy and operational feasibility in resource-limited endemic settings. Parallel clinical development of vaccines targeting schistosomiasis, leishmaniasis, and helminthic infections, combined with advances in monoclonal antibody and immunomodulatory therapies, collectively demonstrate the breadth of immunotherapy's potential.

Challenges certainly remain. Parasite immune evasion through antigenic variation, multi-stage life cycles, and active immune suppression mechanisms creates substantial design obstacles. Host variability in immune responses, limited research funding for neglected diseases, and requirements for extensive safety evaluation before population deployment collectively slow progress. Current technological advances in recombinant antigen production, nanoparticle delivery systems, and artificial intelligence-assisted vaccine design demonstrate accelerating progress in addressing these barriers. Integration of immunotherapy with conventional public health approaches, supported by robust international funding, cross-border collaboration, and One Health frameworks encompassing human, animal, and environmental health sectors, provides a viable pathway toward permanent global elimination of parasitic diseases. The evidence reviewed herein establishes that immunotherapy is not merely a supplementary addition to conventional parasitic disease control, but rather a foundational component of any sustainable strategy capable of supporting movement toward global parasite elimination.

Bibliography

1. Hotez PJ and Kamath A. "Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden". *PLOS Neglected Tropical Diseases* 3.8 (2009): e412.

2. World Health Organization. "World malaria report 2025". Geneva: WHO; (2025).

3. World Health Organization. "Neglected tropical diseases: key facts and data". Geneva: WHO; (2024).

4. Hotez PJ., *et al*. "Control of neglected tropical diseases". *The New England Journal of Medicine* 357.10 (2007): 1018-1027.

5. World Health Organization. "Malaria vaccine: WHO position paper May 2024". *Weekly Epidemiological Record* 99.19 (2024): 225-248.

6. Modjarrad K and Chamanian M. "Therapeutic vaccines for parasitic diseases". *Expert Reviews Vaccines* 9.2 (2010): 109-24.

7. Slifka MK and Ahmed R. "Long-lived plasma cells: a mechanism for maintaining persistent antibody production". *Current Opinion on Immunology* 10.3 (1998): 252-258.

8. Miller LH., *et al*. "The pathogenic basis of malaria". *Nature* 415.6872 (2002): 673-679.

9. Pearce EJ and MacDonald AS. "The immunobiology of schistosomiasis". *Nature Reviews Immunology* 2.7 (2002): 499-511.

10. Kurtovic L., *et al*. "The role of antibodies and complement in naturally acquired immunity to Plasmodium falciparum malaria". *Immunology Review* 293.1 (2018): 214-230.

11. Ogieuhi IJ., *et al*. "A narrative review of the RTS,S/AS01 malaria vaccine and its implementation in Africa to reduce the global malaria burden". *Discovery Public Health* 21.1 (2024): 152.

12. Asante KP., *et al*. "Feasibility, safety, and impact of the RTS,S/AS01E malaria vaccine when implemented through national immunisation programmes: evaluation of cluster-randomised introduction of the vaccine in Ghana, Kenya, and Malawi". *Lancet* 403.10437 (2024): 1660-70.

13. Radosevic K., *et al*. "Recombinant malaria vaccines: current status and perspectives". *Expert Reviews Vaccines* 12.12 (2013): 1459-1477.

14. Smith TG and Loukas A. "Protease inhibitors and vaccines for ecto- and endoparasitic arthropods and worms". *Trends in Parasitology* 32.12 (2016): 945-955.

15. Reyes-Sandoval A and Bachmann MO. "Recombinant viral vaccines for malaria". *Human Vaccine Immunotherapy* 9.11 (2013): 2217-2225.

16. Haldar K and Uyetake L. "The malaria parasite's evasion of innate immunity". *Current Opinion on Immunology* 28 (2014): 92-99.

17. Rasco JM., *et al*. "Drug-resistant parasitic infections: mechanisms and implications". *Tropical Medicine and Infectious Disease* 5.3 (2020): 118.