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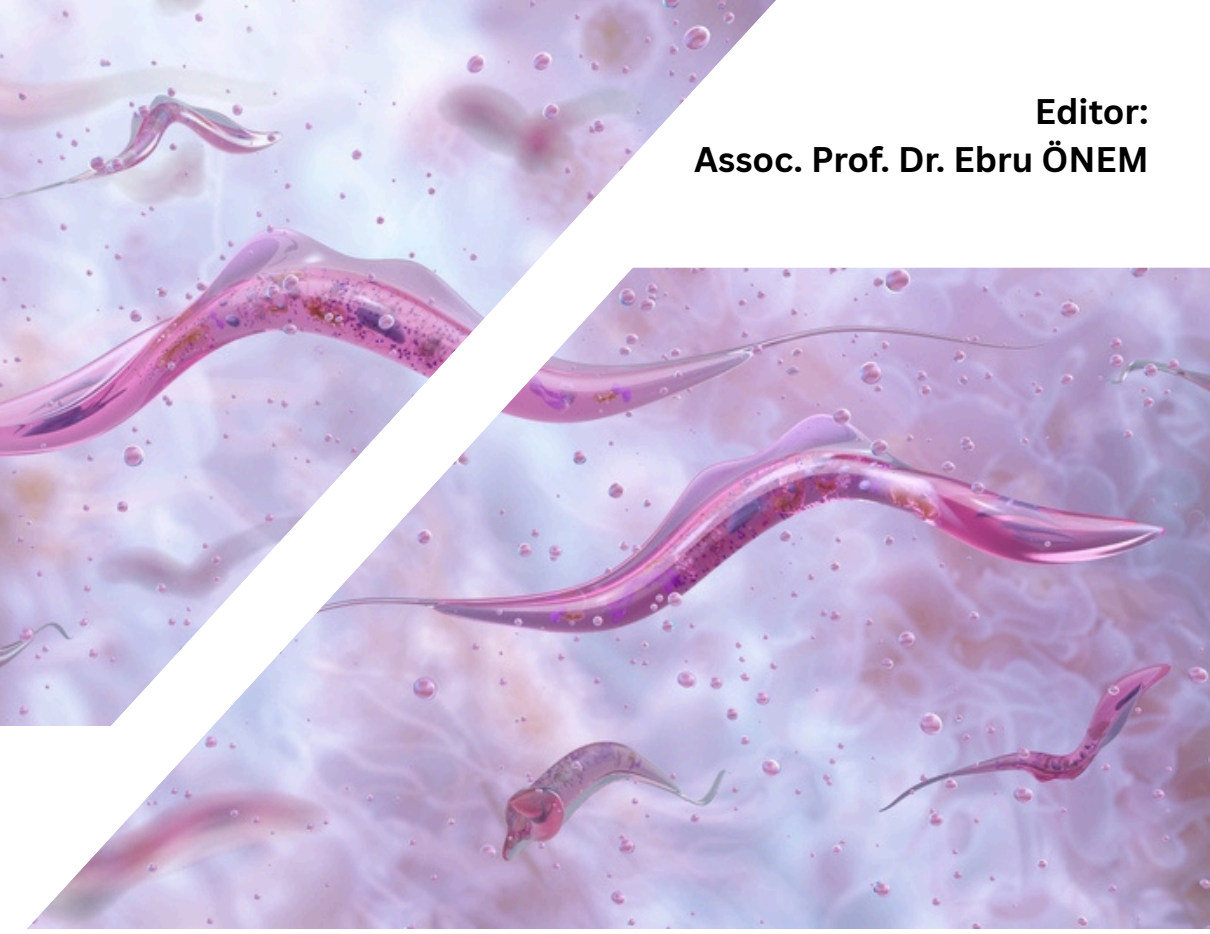

IMMUNITY AND PATHOGENESIS IN PARASITIC INFECTIONS: MOLECULAR BASIS AND APPLICATIONS

Bashar IBRAHIM

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PREFACE

Parasitic infections represent complex biological interactions that have significant implications for global health and economic conditions. Therefore, a deeper understanding of parasitology is urgently needed, as these infections contribute substantially to morbidity, mortality, and development challenges, particularly in low- and middle-income countries. Advances in molecular biology, immunology, and genomics have revolutionized our understanding of parasite pathogenesis, host interactions, and immune evasion mechanisms.

This book offers a contemporary overview of the multifaceted field of parasitology. It begins by examining how parasites manipulate host cells at the molecular level, then delves into host immunity, distinguishing between protective and pathological responses, and the tactics employed by parasites to evade these immune defenses. A central focus is on antiparasitic resistance, highlighting its molecular determinants and emerging therapeutic strategies. Additional coverage includes the details of Neglected Tropical Diseases (NTDs), the complexities of host-parasite-microbiota interactions, and the current status of vaccine research and development for parasites.

Authored by experts in the field, this volume serves as a crucial resource for researchers, clinicians, specialists, and advanced students. It provides a comprehensive and contemporary perspective, integrating molecular and immunological foundations with epidemiological threats and control strategies. Ultimately, this work aims to enhance the understanding and management of parasitic infections.

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Chapter 1

Molecular Pathogenesis of Parasitic Infections: Host Cell Manipulation and Immune Escape Mechanisms

Abstract

Parasitic infections are a major threat to global health, and understanding the molecular pathogenesis mechanisms underlying these diseases is crucial for developing effective control strategies. This chapter examines in detail how parasites manipulate host cells (through strategies such as cytoskeletal rearrangement, use of endocytosis/phagocytosis, modulation of cell surface receptors and signaling pathways) and how they evade the host immune system (through sophisticated mechanisms such as antigenic variation (examples of *Trypanosoma*, *Plasmodium*), immunosuppression, and immune tolerance induction). The role of modern molecular tools such as genomics, proteomics, and CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) in elucidating these complex host-parasite interactions is emphasized, and the implications of the information obtained on diagnostic methods, new treatment, vaccine development studies, and public health policies are discussed. Future research is expected to open new horizons in combating parasitic infections by focusing on areas such as systems biology approaches and the use of immune escape mechanisms as therapeutic targets.

Keywords: Parasitic Infections, Molecular Pathogenesis, Host-Parasite Interactions, Host Cell Manipulation, Immune Evasion

1. Introduction

Parasitic infections have a devastating impact on global public health, particularly in developing countries in tropical and subtropical regions. Infectious diseases such as malaria, schistosomiasis, leishmaniasis, trypanosomiasis, and different helminth infections have affected millions of people, leading to high morbidity and mortality with substantial socio-economic losses. The complexity of these infections and the challenging control necessitates a detailed insight into the biological mechanisms involved (Kaminsky et al., 2025).

The molecular mechanism of parasite pathogenesis is defined as molecular pathogenesis. Parasites enter host cells using surface receptors and hijack metabolic processes to establish a suitable living environment. Chronic pathogens use a spectrum of strategies, including antigenic variation and immunosuppression. It is backed by modern Technologies like genomics, proteomics, and CRISPR. This knowledge is of crucial importance for the discovery of new diagnostic tools, targeted therapies, and vaccines (Azeez et al., 2024).

Host-parasite interactions are among the most widespread and ecologically decisive interactions in the biosphere. In short, these relationships are relationships in which a single organism uses the resources of another organism for its own survival and reproductive success, usually to the detriment of the host. As a result of evolutionary processes spanning millions of years, a co-evolutionary dynamic shaped by mutual selection pressures has formed between parasites and their hosts. This process can be thought of as a kind of "evolutionary dialogue," in which both parties continually develop adaptations. Parasites evolve to exploit their hosts more effectively and evade host defenses, while hosts evolve to improve their ability to recognize, tolerate, or destroy the parasites. This is based on genetic and phenotypic diversity that determines both the infectivity and virulence characteristics of the parasites and the resistance and tolerance abilities of the hosts (Solomon et al., 2015; Wells et al., 2022).

Parasites have developed highly complex and specialized strategies in the evolutionary process to survive and reproduce by effectively exploiting the biological resources of host organisms (nutrients, shelter, metabolic pathways). The diversity of these strategies varies according to the species of the parasite, its life cycle, and its specific interaction with the host. At the molecular level, parasites use various virulence factors such as specialized surface proteins (adhesins) that ensure adhesion and entry into host cells, enzymes that degrade host tissues or make nutrients accessible (proteases, lipases), secretory molecules that suppress or direct the host immune response (immunomodulators), and effector proteins that alter the functioning of host cells to their advantage to

successfully carry out infection. In parallel, they have evolved sophisticated immune escape mechanisms such as molecular mimicry, antigenic variation that constantly changes surface antigens, intracellular life protected from immune surveillance, or the formation of dormant forms such as cysts/spores resistant to adverse conditions to avoid recognition and elimination by the host immune system. This integrated set of molecular and cellular strategies enables the parasite to successfully colonize within the host, replicate, and ultimately spread to new hosts (Bartošová-Sojková et al., 2024; Trejo-Meléndez et al., 2024).

To combat the ever-present risk of parasitic colonization, host organisms have a formidable, complex, and multilayered arsenal of defense mechanisms that prevent, regulate, or resolve parasitic infection. These defenses are classically categorized into innate and adaptive immunity. Innate immunity, which constitutes the first line of defense against infection involves physical barriers (skin, mucosa), chemical barriers (gastric acid, lysozyme), phagocytic cells (macrophages, neutrophils), and nonspecific factors with mechanisms such as pattern recognition receptors (PRRs) which recognize parasite-specific molecular patterns (PAMPs). (Chulanetra et al., 2021).

The innate immune system is quickly engaged during infection and usually activates the adaptive immune response. As diverse in antigen recognition specificity as the adaptive immune response is, it also utilizes only two main cellular types: B lymphocytes, which are responsible for antibody production, and T lymphocytes, which engage in cellular immunity and help regulate other immune responses. T lymphocytes can recognize specific parasite antigens. This system can also form immunological memory so that the response is stronger and quicker when the organism is infected again. Host defenses are primarily aimed at directly killing parasites, preventing their replication , or reducing the damage they cause (R. Wang et al., 2024).

Host-parasite relationships are characterized by a continuous cycle of adaptation and counter-adaptation, a dynamic known as the "evolutionary arms race." When parasites develop novel exploitation or evasion tactics (like new virulence factors or antigenic variants), they impose selection pressure favoring resistant hosts. Conversely, effective host defenses drive the selection of parasites capable of overcoming them. This reciprocal pressure leads to ongoing genetic changes in both populations. Molecularly, this arms race manifests as rapid evolution in parasite virulence genes (via mechanisms such as point mutation, gene duplication, and horizontal gene transfer) and high diversity or rapid evolution in host immune genes (e.g., MHC, antibody, and PRR genes). This molecular tug-of-war fundamentally shapes the specific and dynamic nature of the interaction (Hill et al., 2020; Jdeed et al., 2025).

Gaining a detailed understanding of the molecular mechanisms underpinning host-parasite interactions, such as the structure and function of parasite virulence factors, how host immune receptors recognize parasite molecules, associated signaling pathways, and effector responses, is essential for clarifying the critical factors that dictate the course and outcome of an infection (de Castro Neto et al., 2021). The delicate balance within these interactions profoundly influences the result. For instance, while a robust host immune response might completely clear the parasite (achieving sterilizing immunity), effective evasion mechanisms by the parasite or an inadequate host response can lead to chronic infection. In some scenarios, an excessive or misdirected immune reaction can trigger immunopathology, where the host sustains more damage from its response than from the parasite itself, potentially causing acute disease. Ultimately, the equilibrium between the parasite's virulence level and the host's capacity for resistance and tolerance determines where the infection outcome falls along a spectrum, ranging from asymptomatic carriage to severe illness or even death. Therefore, deciphering these molecular engagements is fundamentally important for grasping the pathogenesis of infectious diseases, developing novel diagnostic methods, and designing innovative therapeutic interventions (like drugs or vaccines) that target parasite strategies or bolster host immunity (Deroost et al., 2016; Romero-Cordero et al., 2021).

2. Host Cell Manipulation Strategies of Parasites

Parasites employ a diverse repertoire of sophisticated strategies to manipulate host cellular biology, thereby facilitating their survival, reproduction, and dissemination within the host organism. While the specific tactics utilized are contingent upon whether the parasite maintains an intracellular or extracellular existence, the fundamental objectives commonly converge on securing essential nutrients, circumventing or actively suppressing host immunological defenses, and establishing an environment permissive for successful replication (Oke et al., 2024).

2.1. Strategies of Intracellular Parasites: Reprogramming the Host Cell

A fundamental requirement for the lifecycle completion of obligate or facultative intracellular parasites, such as *Plasmodium, Toxoplasma, Leishmania*, and *Trypanosoma cruzi*, is the sophisticated manipulation of their host cells. Through profound and subtle alterations to host biology, these pathogens secure environments conducive to their survival, replicate within designated cytoplasmic or vacuolar compartments, and ultimately escape the host immune system (Horta et al., 2020)

2.1.1. Cytoskeleton Manipulation and Cell Entry

Parasitic manipulation frequently centers on controlling the host cell cytoskeleton, specifically the dynamics of actin filaments and microtubules. Utilizing a sophisticated array of effector proteins secreted from specialized organelles like the Apicomplexan rhoptries and micronemes, parasites actively redirect host cytoskeletal polymerization, depolymerization, cross-linking, and motor protein engagement (Seo et al., 2022). Preventing fusion of the parasitophorous vacuole (PV) with host degradative pathways is paramount for intracellular parasite survival. This protection is achieved through extensive cytoskeletal remodeling, primarily involving actin polymerization, which governs multiple critical processes, including active host cell invasion and parasite motility within and between cells. The 'moving junction' (MJ) utilized by *Toxoplasma gondii* during invasion exemplifies this interplay. Formed at the interface between parasite and host membranes via secreted parasite proteins and host receptors, the MJ orchestrates parasite entry while simultaneously isolating the developing PV from the host endomembrane network, thus blocking access to lysosomes. The formation and function of the MJ, and consequently parasite survival, are therefore entirely contingent upon finely tuned actin dynamics (Ferrel et al., 2023) (Table 1).

Table 1: Molecular Mechanisms in Host Cell Manipulation and Immune Evasion by Parasites

Topic	Description
Host Cytoskeleton Manipulation	Parasites secrete effector proteins that control the dynamics of actin filaments and microtubules, directing cytoskeletal polymerization, depolymerization, cross-linking, and interactions with motor proteins.
Specialized Secretory Organelles	Organelles found in Apicomplexa, such as rhoptries and micronemes, secrete sophisticated effector proteins to manipulate the host cytoskeleton.
Host Cell Invasion	Parasites reorganize the host cytoskeleton during active entry into the host cell. For example, *Toxoplasma gondii* forms the "moving junction" structure.
Motility	Cytoskeleton manipulation is crucial for parasite movement, both intracellularly and intercellularly.
Parasitophorous Vacuole (PV)	The parasite forms a PV within the host cell and avoids destruction by preventing its fusion with the host's lysosomal pathway.
Toxoplasma gondii Example	The parasite facilitates cell entry by forming the moving junction and ensures the differentiation of the PV membrane from the host endomembrane system.
Actin Polymerization	Parasite invasion and survival processes rely on the precise regulation of actin polymerization.

2.1.2. Exploitation of Endocytosis/Phagocytosis Pathways and Parasitophorous Vacuole Modification

The mechanisms by which intracellular parasites gain entry into host cells are varied, though many involve the exploitation or imitation of inherent host cellular processes such as endocytosis and phagocytosis. Leishmania promastigotes, for instance, are taken up by their principal host macrophages through phagocytosis (Nandan et al., 2024). Subsequently, these parasites actively interfere with the phagosome maturation cascade. Intracellular pathogens employ various strategies to survive within host phagosomes, commonly including the attenuation of phagosomal acidification, the inhibition of fusion with lysosomes, and the modification of the phagosomal membrane's protein and lipid composition. In contrast to these evasion tactics, certain *Leishmania* species possess distinct adaptations that confer intrinsic resistance to the harsh environment of the mature phagolysosome itself (Duque, 2018). *Plasmodium* parasites utilize a different paradigm, initiating invasion through specific molecular interactions. Sporozoite entry into hepatocytes and merozoite entry into erythrocytes are both driven by high-affinity binding events occurring between distinct parasite surface ligands and corresponding host cell receptors. This binding event orchestrates host membrane invagination, culminating in the parasite residing within a parasitophorous vacuole (PV). This structure establishes a protective intracellular niche, sequestering the parasite from host cytosolic factors and enabling its developmental program. Critically, the function of the Parasitophorous Vacuole (PV) is not limited to passive retention but to create an active biological interface. Parasites remodel the PV membrane by integrating their transmembrane proteins, thereby controlling the acquisition of vital host-derived nutrients and lipids, facilitating waste removal, and ultimately tailoring the vacuolar compartment to meet their metabolic and developmental demands (Ferrel et al., 2023; Segireddy et al., 2024) (Table2).

Table 2: Entry of Intracellular Parasites into Host Cells and Parasitophorous Vacuole Mechanisms

Topic	Description
Host Cell Entry Mechanisms	Parasites gain entry into host cells by mimicking or exploiting host endocytic and phagocytic pathways.
Leishmania promastigotes	Phagocytosed by macrophages; however, the parasite inhibits phagosome maturation, limits pH reduction, delays or prevents fusion with lysosomes, and alters membrane composition.
Phagolysosomal Adaptation	Some *Leishmania* species have developed adaptations enabling them to withstand the harsh conditions of the acidified phagolysosomal environment.
Plasmodium Entry Mechanisms	Sporozoites invade hepatocytes, and merozoites invade erythrocytes through specific molecular interactions between host cell receptors and parasite surface ligands.
Parasitophorous Vacuole (PV)	A specialized niche formed by the parasite within the host cell, separating the parasite from the host cytoplasm. The PV is modified by parasite-derived proteins and functions in nutrient acquisition and waste egress.
Dynamic Function of the PV	The PV is not a static structure; the parasite actively remodels the PV membrane according to its needs, facilitating molecular exchange between the parasite and the host cell.

2.2. Interaction Strategies of Extracellular Parasites with Hosts

2.2.1. Surface Interactions and Immune Escape Mechanisms

Extracellular parasites, which do not actively invade host cells, must establish intricate molecular dialogues with the host organism to sustain their life cycles. Organisms such as *Trypanosoma brucei*, the causative agent of sleeping sickness, or various helminths reside within host tissues, the bloodstream, or other bodily fluids, employing sophisticated strategies at the host-parasite interface. Foremost among these are adhesion mechanisms enabling attachment to the host; parasites utilize specific ligands expressed on their surfaces to bind host cell surface receptors or components of the extracellular matrix, thereby securing their physical position and resisting mechanical dislodgement (Qadeer et al., 2024). Critically, extracellular parasites face constant pressure from the host immune system, driving the evolution of diverse molecular mechanisms to evade immune recognition and elimination. These strategies encompass molecular mimicry (displaying surface antigens resembling host molecules), antigenic variation (periodically switching surface antigens to elude the adaptive immune response, classically exemplified by the Variant Surface Glycoprotein (VSG) system of *T. brucei*), secretion of immunomodulatory or immunosuppressive molecules, and even self-camouflage through the acquisition of host proteins onto their surfaces.

Collectively, these adaptations promote the parasite's long-term survival within the host environment (Moreno et al., 2019) (Table 3).

Table 3: Interaction Mechanisms of Extracellular Parasites with the Host and Immune Escape

Topic	Description
Characteristics of Extracellular Parasites	Parasites that do not actively invade host cells establish complex molecular dialogues with the host organism to sustain their life cycles.
Adhesion Mechanisms	Parasites establish physical anchorage by binding via specific surface ligands to host cell receptors or extracellular matrix components, thereby resisting mechanical clearance.
Molecular Mimicry	Facilitates immune evasion through the production of surface antigens that mimic host molecules.
Antigenic Variation	Parasites evade immune recognition by periodically altering their surface antigens. The Variant Surface Glycoprotein (VSG) system of *Trypanosoma brucei* exemplifies this strategy.
Immunosuppression	Extracellular parasites secrete molecules that suppress or modulate the host immune system.
Camouflage Mechanisms	Parasites camouflage themselves by coating their surfaces with host proteins.
Long-term Survival Strategies	These mechanisms enable extracellular parasites to persist long-term within the host organism and effectively neutralize immune threats.

2.2.2. Modulation of Cellular Signaling Pathways by Secreted Molecules

Parasites, encompassing extracellular and intracellular forms, actively modulate their host environment through mechanisms extending beyond mere surface contact to include the secretion of a diverse repertoire of bioactive molecules, collectively termed the secretome. This secretome serves as a critical interface, mediating communication with and enabling the parasite to manipulate the host system (Tritten et al., 2018). The secretome contains enzymes, metabolites, vesicles (like exosomes), and particularly important effector proteins. These effectors target host cell functions, often by interacting with surface receptors or entering the cell to modulate key intracellular signaling pathways. The outcomes are critical for parasite success; for example, apoptosis modulation can involve inhibiting death in host cells while inducing it in immune cells (e.g., T lymphocytes, macrophages). Core signaling pathways like Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor kappa B (NF-κB) which regulate inflammation, stress, survival, and proliferation, are also frequently manipulated. Through such targeted interference, parasites can alter inflammatory responses, hinder immune cell activation, and reprogram host cell

metabolism and proliferation to favor their persistence. Ultimately, these sophisticated molecular interactions enable parasites to thrive within the host (Zhang et al., 2024) (Table 4).

Table 4: Mechanisms of Host Cell Manipulation and Immune System Modulation by Parasites

Topic	Description
Secretome and Bioactive Molecules	Parasites manipulate host cells by secreting enzymes (e.g., proteases, glycosidases), metabolites, exosomes, and effector proteins.
Host Cell Surface Interactions	Effector molecules bind to host cell receptors or are internalized, targeting intracellular signaling pathways.
Apoptosis Modulation	Parasite secretions can inhibit apoptosis in host cells while triggering it in immune cells (e.g., T lymphocytes, macrophages), thereby suppressing the immune response.
Manipulation of Signaling Pathways	Pathways involved in cellular stress, inflammation, and survival, such as MAPK and NF-κB, are frequently targeted by parasite effectors.
Alteration of the Inflammatory Response	Parasites suppress pro-inflammatory cytokine production or promote anti-inflammatory responses, thereby inhibiting immune system activation.
Reprogramming of Host Cell Metabolism	Parasites reorganize host cell metabolism and proliferation to suit their own needs.
Parasite Survival Strategies	These molecular interactions enable the parasite to persist long-term within the host environment.

3. Immune Escape Mechanisms

3.1. Antigenic Variation

Antigenic variation is a critical immune escape mechanism that allows parasites to change their surface antigens to evade the host adaptive immune system, particularly antibody-mediated responses. This strategy often works through antigenic switching, where different antigenic variants from a large family of genes are expressed sequentially or stochastically. Alternatively, some parasites cover their surfaces with host-derived molecules to hide from immune recognition through antigenic masking. This constant change in surface antigens renders the host's immunological memory for specific antigens dysfunctional, allowing the parasite to persist in the host and sustain chronic infections (Florini et al., 2022). The best-studied examples of antigenic variation include *Trypanosoma brucei*, the causative agent of African sleeping sickness, and Plasmodium falciparum, the causative agent of malaria. *T. brucei* has a repertoire of hundreds of genes that encode proteins called Variant Surface Glycoproteins (VSGs) that cover the entire cell surface; the parasite actively expresses only one

of these genes and activates a different VSG gene at regular intervals to neutralize the existing antibody response. A similar strategy is used by *P. falciparum*. This parasite has a large var gene family that encodes the PfEMP1 (*P. falciparum* erythrocyte membrane protein 1) protein family, which it transports to the surface of infected erythrocytes. The alternating expression of different var genes allows the parasite to evade antibodies and mediates its adhesion to the capillary endothelium of infected erythrocytes (cytoadherence), creating antigenic diversity that plays a critical role in pathogenesis (Obado et al., 2016).

3.2. Immunosuppression

Parasites enhance their chances of survival by actively suppressing various components of the host's immune system, a process known as immunosuppression. This suppression can involve directly inhibiting the functions of essential immune cells, such as T cells, B cells, macrophages, and dendritic cells, or inducing apoptosis in these cells. Molecules secreted by parasites or present on their surface can hinder the activation, proliferation, antigen-presenting capacity, or cytotoxic effects of immune cells (Elmahallawy et al., 2021).

For instance, in certain helminth infections, the alternative activation of macrophages (known as M2 polarization) can suppress the classical activation (M1) that is typically effective against parasites. A key mechanism of immunosuppression is the modulation of cytokine production. Parasites may influence host cells by reducing the production of pro-inflammatory cytokines (like IFN-γ and TNF-α) while simultaneously increasing the production of anti-inflammatory or regulatory cytokines (such as IL-10 and TGF-β). This imbalance leads to a suppression of Th1-type immune responses against the parasite, creating an immune environment that allows the parasite to persist more easily or go unchecked (Bruschi et al., 2022).

For example, elevated levels of IL-10 are linked to the persistence of parasites in chronic conditions such as *Leishmaniasis* and *Schistosomiasis* (Camelo et al., 2023).

3.3. Immune Tolerance

Some parasites modulate the host immune system to prevent an effective immune response rather than actively suppressing it. This leads to the development of a state of tolerance in which the immune system perceives parasite antigens as “harmless” or “non-invasive.” This process may also trigger the induction or expansion of tolerogenic immune cell populations, such as regulatory T cells (Treg). Molecular mimicry the resemblance of parasite antigens

to host molecules, may lead the immune system to recognize the parasite as "self," thus preventing an immune attack. These successful immune tolerance mechanisms often result in chronic parasitic infections. Although the host cannot eliminate the parasite, the parasite can persist for long periods without killing the host, allowing it time to reproduce and infect new hosts (McManus et al., 2023).

During chronic infections, a low-level, controlled inflammatory response may develop; this typically keeps the parasite load in check without eliminating it. Many helminth infections, such as those caused by filarial nematodes and schistosomes, exhibit distinct immune tolerance mechanisms (Gazzinelli-Guimaraes et al., 2024).

4. Molecular Tools and Techniques

High-throughput "omics" technologies, including genomics and proteomics, have revolutionized our understanding of parasite disease at the molecular level. For example, by sequencing the genomes of these parasites, researchers can identify important virulence factors as well as potential drug targets and families of genes that lead to immune evasion, including the var genes, which have been implicated in malaria, and the VSG genes that encode for the surface antigen of the *T. brucei* parasite. Examples include RNA sequencing (RNA-seq) based transcriptomic analyses, which show altered gene expression profiles at certain points of the infectious cycle or in certain hosts. Moreover, mass spectrometry-based proteomic approaches have allowed for the identification of effector proteins from parasites (the secretome) as well as proteins involved in host–pathogen interactions. Such integrated approaches enable an extensive characterization of the molecular components that underlie pathogenesis (Al-Malki, 2025).

Gene editing technologies, particularly the CRISPR-Cas9 system, have greatly enhanced the study of functional genetics in parasitology. This technology enables researchers to precisely knock out, modify, or tag specific genes within parasite genomes. Scientists can directly investigate the roles of candidate genes in various processes, such as parasite invasion, intracellular survival, host cell manipulation, and immune evasion. In addition to CRISPR, other gene-silencing techniques, like RNA interference (RNAi), are used in certain parasite systems. These tools are crucial for understanding the underlying molecular mechanisms (Ebrahimi et al., 2023).

Appropriate model organisms are crucial for the exploration of host-parasite interactions. In vitro models enable studies of parasite interaction with specific cell types under controlled conditions, such as macrophages, erythrocytes, and hepatocytes. But when it comes to studying pathogenesis in the context of the

host immune system and its overall physiology, in vivo animal models, usually mice, but sometimes hamsters or primates, are essential. Transgenic mouse models (e.g., mice deficient in certain immune cells or cytokines) are especially useful for investigating the contributions of specific elements of the host immune response during infection (Otun et al., 2024) (Table 5).

Table 5: Modern Technological Approaches and Models in Understanding the Molecular Pathogenesis of Parasites

Topic	Description
Omics Approaches	Genomic and proteomic analyses, following parasite genome sequencing, identify virulence factors, potential drug targets, and immune evasion gene families (e.g., *var* genes, VSG genes).
Transcriptomics and RNA-seq	Reveal changes in gene expression profiles during different stages of infection.
Proteomic and Secretome Analyses	Used to identify effector proteins secreted by the parasite and proteins present at the host-parasite interaction interface.
CRISPR-Cas9 Technology	Gene editing enables the direct testing of molecular mechanisms through gene deletion (knock-out), expression reduction (knock-down), and specific genetic modifications within the parasite genome.
RNAi Techniques	Gene silencing methods are effective for elucidating molecular mechanisms, particularly in certain amenable parasite systems.
In Vitro Models	Utilized for studying controlled parasite interactions with specific cell types, such as macrophages, erythrocytes, and hepatocytes.
In Vivo Animal Models	Employed to investigate parasitic pathogenesis within the context of a complete immune system and physiology, using models like mice, hamsters, and non-human primates.
Genetically Modified Mouse Models	Mouse models deficient in specific immune cells or cytokines allow for the investigation of the immune response's role during the infection process.

5. Clinical and Public Health Perspectives

Recent studies on molecular pathogenesis have significantly enhanced the diagnosis of parasitic infections. In addition to traditional microscopic techniques, various nucleic acid-based molecular tests have been developed. Notable advancements include polymerase chain reaction (PCR), quantitative PCR (qPCR), and loop-mediated isothermal amplification (LAMP). These methods offer greater sensitivity and specificity for detecting low parasite loads and enable differentiation between species or subspecies. They can also identify genetic markers associated with drug resistance. Furthermore, molecular data are being used to create immunoassays that detect either parasite antigens or host antibodies (Alsharksi et al., 2024).

A thorough understanding of molecular pathogenesis is essential for developing new and more effective therapeutic strategies and vaccines. A key objective is to identify metabolic pathways, mechanisms of cell invasion, and immune escape factors that are critical for the survival of parasites, as these can serve as potential drug targets. For instance, drug development studies have focused on the metabolic pathways within the apicoplast organelle of *Plasmodium* and the glycolysis enzymes of *Trypanosoma*. Additionally, researchers are evaluating surface antigens and secreted proteins that may trigger protective immune responses against these parasites as potential vaccine candidates. However, challenges such as antigenic variation significantly hinder progress in vaccine development (Molina-Franky et al., 2022).

Understanding parasitic infections at the molecular level is essential for shaping global health policies and prevention strategies. For example, molecular epidemiology studies utilize this knowledge to track the genetic diversity of parasite populations, map their geographical distribution, and monitor the emergence and spread of drug resistance. These insights are vital for evaluating the effectiveness of existing control programs, such as mass drug administration and vector control initiatives, and for strategically allocating resources to areas with the highest burden or risk (Nelson et al., 2019).

Furthermore, examining the molecular interactions between hosts, parasites, and vectors offers significant potential for developing innovative intervention strategies. This could lead to advancements in vector control technologies, such as gene drive techniques, or to new methods aimed at blocking transmission pathways altogether (Parres-Mercader et al., 2023).

6. Future Perspectives: New Horizons in the Investigation of Host-Parasite Interactions

6.1. Technological Advances and Systems Biology Integration

Research in molecular pathogenesis is constantly evolving, significantly driven by rapid advancements in high-throughput technologies. Moving beyond traditional reductionist approaches, systems biology provides a powerful framework for understanding the complex networks involved in host-parasite interactions. This new perspective requires the integration of various "omic" data layers, including genomics (DNA sequencing and variations), transcriptomics (gene expression profiles), proteomics (protein abundance, modifications, and interactions), and metabolomics (metabolite profiles) (Fan et al., 2025).

By synthesizing these multi-omic datasets through computational modeling, researchers aim to create a dynamic and comprehensive view of cellular and molecular processes during infection. This approach helps clarify causal

relationships and identify potential biomarkers and therapeutic targets. Importantly, such integrative analyses can reveal emergent properties and intricate regulatory networks that may remain hidden when examining individual components in isolation (X. Wang et al., 2023).

6.2. Discovery of Heterogeneity at Single Cell Resolution and New Research Areas

A significant technological advancement that is transforming our understanding of host-parasite interactions is single-cell RNA sequencing (scRNA-seq) and related single-cell analytical methods. These techniques reveal the cellular diversity that traditional bulk analyses often overlook, as the latter provide only averaged profiles. During an infection, there is notable diversity within the parasite population, which manifests as subpopulations with distinct developmental stages, metabolic states, or virulence profiles. Additionally, there is variation among host cells, including different and dynamic responses from various immune cell types, as well as between infected and bystander cells. scRNA-seq allows researchers to map this complex heterogeneity at an unprecedented level of detail, identify rare cell populations, and determine the roles of specific cell types in influencing the overall infection outcome (Lin et al., 2020).

Moreover, an important new area of research is focusing on the interactions between parasites and not only their hosts but also the microbial communities (the parasite microbiome) and viruses (the parasite virome) they carry either internally or on their surfaces. These endosymbiotic or associated microorganisms are increasingly recognized for their potential to influence parasite virulence, metabolism, and the host immune response (González et al., 2021).

6.3. The Necessity of Interdisciplinary Collaboration and Advanced Model Systems

Addressing the inherent multi-layered complexity of host-parasite interactions encompassing genetic, cellular, immunological, ecological, and evolutionary dimensions mandates research strategies that transcend the confines of individual disciplines, making robust interdisciplinary collaboration among parasitologists, immunologists, cell biologists, geneticists, bioinformaticians, and epidemiologists indispensable for substantial progress in this field. (White et al., 2022). The synergistic integration of knowledge and methodologies from these diverse specialties enables the formulation and rigorous testing of more comprehensive hypotheses, yet bridging the gap between laboratory observations

and physiological or clinical reality concurrently necessitates the adoption of more sophisticated model systems, given that traditional cell cultures and standard animal models frequently fail to adequately recapitulate the intricacies of human infections. concluding, the development and utilization of advanced in vivo and ex vivo platforms such as "humanized" mouse models incorporating human immune system components or three-dimensional organoid cultures designed to emulate the structural and functional attributes of specific organs are critically important for advancing translational research; Furthermore, these models offer invaluable systems for interrogating parasite behavior within distinct anatomical niches and for dissecting the modulation of host-parasite dynamics by extrinsic factors like nutritional status and concurrent infections (Duque-Correa et al., 2020; Suhito et al., 2025; Xiang et al., 2024).

6.4. Using Immune Escape Mechanisms as Therapeutic Targets

Understanding the sophisticated and diverse mechanisms that parasites use to evade the host immune system is crucial for grasping pathogenesis and identifying promising targets for new therapeutic strategies. Traditional antiparasitic drugs typically focus on disrupting basic metabolic pathways or essential functions of the parasite. However, targeting immune escape mechanisms offers a novel approach to intervention (Mustafa, 2024).

For instance, inhibiting molecular switches that control antigenic variation, such as epigenetic regulators or DNA recombination enzymes, can help parasites maintain their surface antigens, allowing for better recognition by the immune system. Additionally, neutralizing immunosuppressive molecules secreted by the parasite, using specific antibodies or small molecule inhibitors, or pharmacologically disrupting the parasite's ability to induce immune tolerance, may enhance the effectiveness of the host's innate defense mechanisms (Chandley et al., 2023).

These methods, often referred to as "host-directed therapies," focus on boosting the host's immune response or weakening the parasite's defenses rather than directly killing the parasite. Such strategies could provide valuable alternatives, especially in cases where resistance to existing drugs is common, or they could serve as adjuvants to improve the effectiveness of vaccines. Future research is anticipated to further uncover the molecular details of these immune escape pathways and translate this understanding into rational drug design (Kaufmann et al., 2018).

Conclusion

A comprehensive understanding of the sophisticated molecular mechanisms underlying parasite pathogenesis, particularly those mediating immune evasion, is imperative for the development of effective next-generation therapeutic strategies. While conventional antiparasitic interventions primarily target essential parasite metabolic pathways or vital functions, a focus on disrupting immune escape mechanisms presents a novel and promising therapeutic paradigm. Specifically, strategies aimed at inhibiting the molecular regulators of antigenic variation such as epigenetic factors or DNA recombination enzymes, could potentially maintain parasite antigen presentation, thereby facilitating enhanced recognition and clearance by the host immune system. Concurrently, the neutralization of parasite-secreted immunosuppressive molecules via targeted antibodies or small-molecule inhibitors, or the pharmacological interference with parasite-induced immune tolerance, represents viable approaches to bolster the host's intrinsic defense capabilities.

These methodologies, often conceptualized as "host-directed therapies," prioritize the potentiation of host immunity or the debilitation of parasite defenses over direct parasiticidal action. Such approaches hold significant potential as valuable alternatives or adjuncts, particularly in addressing the challenge of emerging drug resistance, and may serve to augment the efficacy of existing or future vaccine platforms.

Future research needs to focus on understanding the intricate molecular details of how parasites evade the immune system. Translating this understanding into practical drug design is crucial for developing the new and innovative treatments required to tackle the major global health problem of parasitic diseases.

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Chapter 2

Immune Response to Parasites: Protection, Pathology, and Immunomodulation Mechanisms

Abstract

Parasites, encompassing protozoa and helminths, exhibit complex interactions with the host immune system. Protective immunity requires tailored responses. İnterferon-gamma (IFN-γ)-mediated T helper 1 (Th1) immunity, involving macrophage and Cytotoxic T lymphocytes (CTL) activation, targets intracellular protozoa, whereas Interleukins (IL-4/IL-5/IL-13)-driven T helper 2 (Th2) responses, characterized by Immunoglobulin E (IgE), eosinophils, and mast cells, are crucial against helminths. However, these powerful immune reactions often lead to immunopathology, including excessive inflammation, granuloma-induced fibrosis (as in schistosomiasis), or autoimmunity (as in Chagas disease). To persist, parasites utilize sophisticated evasion tactics such as antigenic variation and intracellular residence. Critically, they modulate host immunity through secreted/excreted products (ESPs). These molecules can hinder antigen presentation, suppress Th1 responses, and promote immunosuppressive regulatory T cells (Tregs) and cytokines like IL-10 and Transforming growth factor-beta (TGF-β), tilting the immune balance in their favor. This dynamic interplay highlights an evolutionary equilibrium between host defense, immune-mediated pathology, and parasite escape. Understanding these intricate host-parasite relationships is essential for the rational design of effective vaccines and therapeutic strategies to combat parasitic diseases worldwide.

Keywords: Host-parasite interactions, Parasite immunology, Immune response, Immunomodulation, Antigenic variation

1. Introduction

Parasitic infections, which are caused by a heterogeneous population of eukaryotic organisms, from simple unicellular protozoa to complex multicellular helminths, constitute a huge global public health problem. These infections are largely affecting socioeconomically disadvantaged populations, especially in tropical and subtropical areas. Hundreds of millions of people worldwide are plagued by diseases such as malaria, Schistosomiasis, Leishmaniasis, *Trypanosomiasis*, and numerous helminth infections, resulting in considerable morbidity and mortality and major economic losses. The ability of these parasites to act as effective pathogens is mainly due to the set of complex adaptations these parasites evolved after millions of years of co-evolution with their hosts (Branda et al., 2025; Papagni et al., 2023).

Parasites exhibit extensive evolutionary adaptations resulting in remarkable biological diversity, encompassing significant variations in size, cellular organization, and surface molecular composition. Many possess intricate life cycles characterized by multiple hosts and distinct developmental stages, occupying specific locations within and outside host cells. This profound biological heterogeneity presents substantial challenges to the host immune system, hindering effective recognition, control, and elimination of these pathogens. Consequently, the nature of the immunological challenge is fundamentally dictated by the specific parasite type. For instance, the host immune system confronts vastly different hurdles when responding to a microscopic, intracellular protozoan employing evasion tactics versus a large, multicellular, tissue-migrating helminth potentially reaching several meters in length. Effective host defense, therefore, necessitates the deployment of distinct and highly adapted immunological strategies tailored to the particular parasitic threat (Kolářová et al., 2022).

The interaction between a host and its parasite is a dynamic and ongoing struggle characterized by continuous adaptations from both parties. This interplay involves the host and the parasite evolving strategies in response to each other's changes. On one side, the host has complex innate and adaptive immune defense mechanisms designed to limit or eliminate the parasitic invader. On the other side, the parasite employs sophisticated strategies to evade, subvert, or actively suppress these host defenses, which helps ensure its survival, replication, and successful transmission to new hosts. Ultimately, these reciprocal engagements significantly influence the nature and effectiveness of the immune response mounted against the parasite (Choi et al., 2024; Penczykowski et al., 2016). In this scenario, the immune response to parasitic disease frequently reflects a careful equilibrium that can yield three interrelated consequences.

The first outcome is protective immunity, which is beneficial to the host by either diminishing the parasite burden or eliminating the infection. The second consequence, counterintuitively, is immunopathology. Here, the immune response becomes maladaptive, trying to kill the parasite but causing collateral damage to the host's cells. This may aggravate the clinical manifestations and signs of the disease. The third comprises the array of immunomodulatory and evasion strategies used by parasites to manipulate the directionalities of the host immune system in their favor. These strategies enable the parasites to escape immune recognition and counteraction of the defenses of the host (Al-Qahtani et al., 2024; Deroost et al., 2016).

The three central aspects of host-parasite interaction involving protective immunity, immunopathology, and parasite-driven immunomodulation must be understood. These components create an ecological whole, where each element constantly affects and is affected by the others. *Schistosomiasis* is a paradigmatic instance of this complex interdependence. In this disease, granulomas that surround and wall off the eggs trapped in host tissues initially protect the host by containing the infection. In contrast, the chronic presence of these granulomas may lead to fibrotic pathology and significant organ damage, demonstrating the ability of the immune response to shift from a beneficial to a deleterious presence during chronic infection (Jutzeler et al., 2024). A strong Th1 immune response is essential for controlling parasites in leishmaniasis, but an excessive or poorly regulated response can lead to increased tissue damage. Additionally, the production of IL-10 induced by the parasite adds another layer of complexity, as this cytokine helps to manage immunopathology while also allowing the parasite to persist and cause chronic infection. This situation underscores the delicate and sometimes contradictory balance of the immune system that ultimately determines the outcome of parasitic infections (Costa-Da-silva et al., 2022; Volpedo et al., 2021).

This chapter explores the complex and multifaceted nature of parasite immunology. We will start by outlining the basic mechanisms of the innate and adaptive immune responses, including their cellular and humoral components, cytokine networks, and effector molecules. These mechanisms are mobilized by the host against various types of parasites, such as protozoa and helminths, and play crucial protective roles.

Next, we will examine how the immune response can become harmful to the host, focusing on the mechanisms that lead to immunopathology. This includes excessive inflammation, granuloma formation, fibrosis, autoimmunity, and allergic reactions, along with their manifestations in specific parasitic diseases. A thorough comprehension of these intricate interactions at the molecular and

cellular levels is paramount. It not only deepens our fundamental understanding of immunology and parasitology but also provides the essential foundation for designing more effective vaccines, developing novel immunotherapeutic strategies, and establishing sustainable control programs to combat these pervasive and often devastating diseases.

2. Natural and Cellular Basis of Protective Immune Responses

The evolutionary success of parasites largely depends on their ability to overcome or manipulate the complex and constantly adapting defense mechanisms of the host's immune system. In response, hosts have developed intricate defenses against these microbial threats, which involve the coordinated efforts of both the innate and adaptive immune systems. The nature and effectiveness of these immune responses are influenced by several factors, including the biological characteristics of the parasite (such as whether it is a protozoan or a helminth), its stage in the life cycle, its specific location within the host (whether intracellular or extracellular), and the molecular details of its interactions with the host (Dimitriu et al., 2020).

2.1. The Critical Role of Innate Immunity in Early Detection and Response Initiation

When a host first encounters a parasite, the innate immune system, which serves as the first line of defense, responds quickly. This initial immune response involves various types of cells, including those in the epithelial barrier, tissue-resident macrophages, dendritic cells (DCs), mast cells, and circulating neutrophils. These cells utilize specialized sensors known as Pattern Recognition Receptors (PRRs) to identify either specific molecular patterns associated with the parasites (known as Pathogen-Associated Molecular Patterns, or PAMPs) or internal signals that indicate tissue damage within the host (known as Damage-Associated Molecular Patterns, or DAMPs) (Maizels et al., 2018). The innate immune system PAMPs are specific to parasites. For instance, lipophosphoglycans (LPG) and glycoinositol phospholipids (GIPL) from *Leishmania* species are examples of these structures. Additionally, glycosylphosphatidylinositol (GPI) anchors and surface mucins from Trypanosoma cruzi are also recognized as PAMPs. Furthermore, GPIs and hemozoin, which are derived from the digestion of hemoglobin by Plasmodium falciparum, can stimulate the immune response. Other important PAMPs include chitin, glycan structures, ESPs, and nucleic acids, particularly CpG DNA, originating from helminths.

The interaction between PAMPs and PRRs triggers intracellular signaling cascades, leading to the activation of transcription factors such as NF-κB, AP-1, MAPK, and IRF. These processes are facilitated by adaptor proteins like MyD88 and TRIF (Assis et al., 2012; Ghosh et al., 2014; Karaś et al., 2019).

This process triggers the production and release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, and IL-12. It also stimulates the release of chemokines such as CXCL8/IL-8, CCL2/MCP-1, and CCL5/RANTES, which guide the migration of leukocytes. Certain cells, particularly DCs, can generate strong Type I interferon responses (IFN-α/β) when exposed to specific PAMPs (Li et al., 2023). These early mediators initiate local signs of inflammation, including vasodilation, increased vascular permeability, and leukocyte extravasation, while attracting phagocytic cells like neutrophils and monocytes to the site of infection (Karaś et al., 2019).

Macrophages engulf small protozoa and debris from parasites through a process known as phagocytosis. Inside the phagolysosomal compartment, they utilize powerful microbicidal molecules to eliminate these pathogens. These include reactive oxygen species (ROS), such as superoxide anions and hydrogen peroxide, produced by the enzyme NADPH oxidase (NOX2), as well as reactive nitrogen species (RNS), like nitric oxide (NO), synthesized from L-arginine by inducible nitric oxide synthase (iNOS/NOS2). However, many intracellular parasites have developed resistance mechanisms to evade these destructive processes. In addition to phagocytosis, neutrophils adopt a different strategy to combat larger or aggregated parasites. They release their chromatin DNA, which combines with histones and antimicrobial proteins from degranulation (e.g., elastase, cathepsin G, and myeloperoxidase) to form structures known as Neutrophil Extracellular Traps (NETs) through a process called NETosis. These NETs physically ensnare parasites, restricting their movement while simultaneously delivering high concentrations of toxic molecules directly to the targeted pathogens (Herb et al., 2021).

The decrease in MHC class I expression or an increase in stress ligands, such as MICA/B, in infected cells triggers the activation of natural killer (NK) cells. Once activated, NK cells induce apoptosis in target cells through cytotoxicity by secreting perforin and granzymes. They are also a significant early source of IFN-γ, which is crucial for the Th1 polarization of adaptive immunity.

Additionally, the complement system serves as an essential humoral component of innate immunity against parasites. It can be activated through three pathways: the alternative pathway, which involves the spontaneous hydrolysis and amplification of C3 by specific structures on the parasite surface; the lectin pathway, which occurs when Mannose Binding Lectin (MBL) or ficolins bind to

mannose or other sugars on the parasite surface; and the classical pathway, which involves subsequent antibody responses. The central component of the activation cascade is the cleavage of C3 into two fragments: C3a and C3b. C3b plays a vital role in facilitating phagocytosis, particularly through complement receptors CR1 and CR3 located on macrophages and neutrophils. It does this by covalently binding to the surface of parasites, a process known as opsonization. Later in the cascade, the formation of the C5b-9 complex, also known as the Membrane Attack Complex (MAC), can lead to direct lysis of certain parasites, including specific forms of *Trypanosomes* and helminth larvae. Meanwhile, C3a and C5a, known as anaphylatoxins, serve as potent chemoattractants. They degranulate mast cells and basophils, triggering the release of inflammatory mediators such as histamine and leukotrienes. This reaction increases vascular permeability and enhances the influx of inflammatory cells. These rapid and diverse mechanisms of innate immunity aim to limit the parasite load, although they often do not suffice for complete elimination. A critical function of innate immunity is to shape the type and strength of the adaptive immune response. This adaptive response is more specific and persistent, and it is influenced by the cytokines produced by innate immunity, such as IL-12, IL-6, TNF-α, and Type I interferons, as well as through antigen presentation, particularly by mature DCs (Chen et al., 2024; Duan et al., 2019; Herb et al., 2021; Wang et al., 2024).

2.2. Development of Specificity, Memory and Effector Mechanisms of Acquired Immunity

Innate immune cells, particularly DCs, play a crucial role in processing parasite antigens. They present these antigens on MHC class II molecules for exogenous antigens and on MHC class I molecules for endogenous antigens, either through cross-presentation or direct infection. This presentation occurs in secondary lymphoid organs, such as lymph nodes and the spleen, where naïve T lymphocytes (CD4+ or CD8+) reside. For T cells to become activated, two key signals are required. The first signal is the specific interaction between the T cell receptor (TCR) and the peptide-MHC complex. The second signal comes from the interaction of costimulatory molecules (CD80/B7.1 and CD86/B7.2) on the antigen-presenting cell (APC) with CD28 on the T cell. Additionally, the presence of cytokines secreted by APCs provides a third important signal for the activation of T lymphocytes (Nakayama, 2015).

The combination of these signals triggers clonal proliferation and differentiation of antigen-specific T cells into specific effector phenotypes. The profile of the T cell response (Th1, Th2, Th17, Treg, etc.) depends largely on the type of parasite (intracellular vs. extracellular), the microenvironment in which

the infection is established, and especially on the cytokine profile produced by DCs in response to PAMPs sensed by PRRs (e.g. IL-12 → Th1; IL-4 presence → Th2; IL-6, TGF-β, IL-23 → Th17). The interplay of these signals initiates the clonal proliferation and differentiation of antigen-specific T cells into various effector phenotypes. The type of T cell response (such as Th1, Th2, Th17, or Treg) is primarily influenced by the nature of the parasite (whether it is intracellular or extracellular), the microenvironment where the infection occurs, and particularly by the cytokine profile produced by DCs in response to PAMPs detected by PRRs. For example, IL-12 promotes Th1 differentiation, the presence of IL-4 favors Th2, and a combination of IL-6, TGF-β, and IL-23 drives Th17 responses (Morales-Primo et al., 2024).

2.2.1. Type 1 (Th1) Immune Response

It plays a central role in protection against protozoal parasites that replicate within macrophages (e.g. *Leishmania major*, *Toxoplasma gondii*, *Trypanosoma cruzi*) or other host cells (e.g. *Plasmodium* sporozoites in hepatocytes, *Plasmodium* merozoites in part in erythrocytes). IL-12 produced by DCs and macrophages and IFN-γ released by NK cells and early activated T cells direct the differentiation of naïve CD4+ T cells to a Th1 phenotype by expressing the transcription factor T-bet. IFN-γ, the prototypical cytokine of Th1 cells, has multiple functions in parasite elimination. IL-12, produced by DCs and macrophages, plays a central role in the body's defense against protozoal parasites that replicate within macrophages (such as *Leishmania* major, *T. gondii*, and *T. cruzi*) or other host cells (like *Plasmodium* sporozoites in hepatocytes and *Plasmodium* merozoites in erythrocytes). The interaction between IL-12 and IFN-γ, released by NK cells and early activated T cells, guides the differentiation of naïve CD4+ T cells into a Th1 phenotype by promoting the expression of the transcription factor T-bet. IFN-γ, recognized as the prototypical cytokine of Th1 cells, has several important functions in the elimination of parasites (Schanz et al., 2024).

2.2.2. Macrophage Activation (Classical Activation/M1 Polarization

It significantly boosts the expression and activity of inducible nitric oxide synthase (iNOS) and NADPH oxidase in infected macrophages. This increase maximizes the production of reactive nitrogen species (RNS) and reactive oxygen species (ROS), enhancing the microbicidal capacity of the macrophages. Additionally, it promotes the fusion of phagosomes and lysosomes, thereby improving the antigen-presenting capacity of macrophages by elevating the expression of MHC class II and costimulatory molecules (Herb et al., 2021).

2.2.3. CD40-CD40L Interaction

Th1 cells express a molecule known as CD40 Ligand (CD40L) on their surface. When this ligand interacts with the CD40 receptor on the macrophage surface, it synergizes with IFN-γ signaling, further enhancing macrophage activation and the production of IL-12. This interaction is also crucial for activating B cells and promoting subsequent antibody production (Díaz et al., 2021) Fig 1.

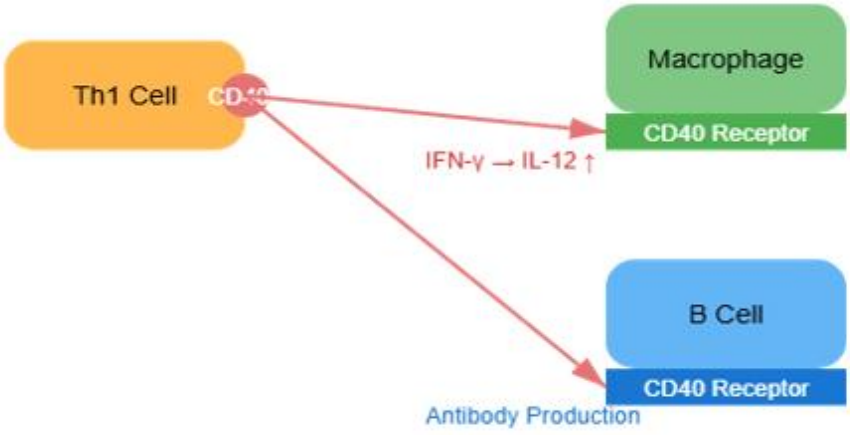

Figure 1: The Role of Th1 Cells in Immune Response

2.2.4. Support of CD8+ Cytotoxic T Lymphocyte (CTL) Responses

IFN-γ is a crucial signal for the differentiation, proliferation, and effector functions of CTLs. CTLs are activated when they recognize parasite peptides presented by MHC class I molecules on the surface of infected host cells through their TCRs. Once activated, CTLs induce apoptosis in the target cells to eliminate the intracellular reservoir of parasites. They accomplish this killing process in two main ways: first, by secreting perforin, which is stored in their cytoplasmic granules and creates pores in the cell membrane; and second, by releasing granzymes, which are serine proteases that activate caspases and trigger apoptosis. Alternatively, CTLs can directly signal apoptosis by interacting with Fas Ligand (FasL) on their surface and the Fas (CD95) receptor on the target cell. This cytotoxic mechanism is essential for controlling infections, particularly those caused by *Plasmodium* during the liver stage and *Toxoplasma* (Garnier et al., 2022) Fig 2

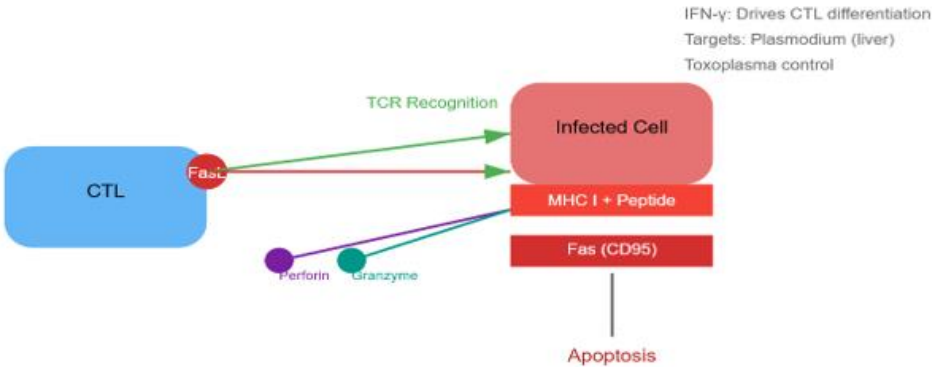

Figure 2: Role of CTL in Cellular Immunity

2.2.5. Antibody Class Change

Th1 responses direct immunoglobulin class switching of B cells, particularly to IgG subclasses (IgG1 and IgG3 in humans; IgG2a and IgG2c in mice), which are effective for opsonization and Antibody-Dependent Cellular Cytotoxicity (ADCC) and are good complement activators (Lunding, 2021).

2.3. Type 2 (Th2) Immune Response: Collective and Physical Defense Against Extracellular Helminths

The Th2 immune response is specifically developed to combat multicellular parasitic worms, known as helminths, which include nematodes, trematodes, and cestodes. These organisms typically reside in various tissues such as the intestinal lumen, blood vessels, lymphatics, and subcutaneous tissue. Due to their larger size, they cannot be effectively eliminated by phagocytosis. Naïve CD4+ T cells differentiate into the Th2 phenotype by expressing the transcription factor GATA3. This process is influenced by alarmins, signaling molecules such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, that are released from epithelial cells when they are stimulated or damaged by helminths or their secreted excretory-secretory (ES) products. Some subsets of dendritic cells are also involved, likely activated in the presence of IL-4. During the initial stages of the Th2 response, group 2 innate lymphoid cells (ILC2s) play a crucial role. These cells respond directly to tissue damage or alarmins and are an important source of Th2 cytokines, including IL-4, IL-5, IL-9, and IL-13. The key cytokines produced by Th2 cells coordinate a variety of effector mechanisms to combat helminth infections (Lunding, 2021; Ogulur et al., 2025).

2.3.1. IL-4 and IL-13

These two cytokines are structurally and functionally similar and utilize different components of the same receptor complex, specifically Type I and Type II IL-4 receptors. They regulate immunoglobulin class switching in B cells, directing the production of IgE as well as the IgG1 subclass in mice and the IgG4 subclass in humans. IgE antibodies bind to the high-affinity Fc receptor, FcεRI, found on mast cells, basophils, and activated eosinophils (Bernstein et al., 2023). When parasite antigens cross-link the IgE antibodies bound to these cells, it triggers rapid degranulation. This process releases various mediators, which include vasoactive amines (such as histamine), lipid mediators (including leukotrienes C4, D4, and E4, as well as prostaglandin D2), proteases (like tryptase and chymase), chemokines, and cytokines (such as TNF-α, IL-4, IL-5, and IL-13) (Parente et al., 2023). Mediators play a crucial role in the inflammatory response by initiating a series of physiological changes. These changes include the dilation of blood vessels (vasodilation), increased vascular permeability, contraction of smooth muscles in structures such as the bronchi and intestines (bronchoconstriction and increased intestinal peristalsis), and stimulation of mucus secretion. These effects aid in the migration of inflammatory cells, primarily eosinophils, to the affected tissue through processes known as chemotaxis and extravasation. Specifically, these mediators are instrumental in the physical expulsion of parasites by promoting increased fluid secretion and enhancing intestinal motility to defend against intestinal helminths. Additionally, the cytokine IL-13 boosts mucus production by increasing the number and maturity (hyperplasia and differentiation) of mucus-producing goblet cells. IL-13 also helps prevent parasite adhesion to the intestinal mucosa by accelerating the turnover rate of epithelial cells (Inclan-Rico et al., 2022) Table 1.

Table 1: IL-4/IL-13 Functions in IgE Responses and Parasite Immunity

Features	Description
Cytokine Characteristics	Structurally and functionally similar; utilize components of the same receptor complex (Type I and Type II IL-4 receptors).
Effect on B Cells	Drive immunoglobulin class switching to IgE and IgG1 (mouse) / IgG4 (human).
IgE Antibody Function	Binds to the high-affinity Fc receptor (FcεRI) on mast cells, basophils, and activated eosinophils.
Cell Activation Trigger	Cross-linking of cell-bound IgE by parasite antigens triggers rapid degranulation of these cells (mast cells, basophils, eosinophils).
Released Mediators	Vasoactive amines (histamine), lipid mediators (Leukotrienes C4, D4, E4; Prostaglandin D2), proteases (tryptase, chymase), chemokines, and cytokines (TNF-α, IL-4, IL-5, IL-13).
Physiological Effects	Vasodilation, increased vascular permeability, smooth muscle contraction (bronchoconstriction, increased intestinal peristalsis), stimulation of mucus secretion.
Inflammatory-Cell Recruitment	Facilitate chemotaxis and extravasation of inflammatory cells (especially eosinophils) into the tissue.
Role in Intestinal Parasite Defense	Contribute to physical expulsion of helminths by promoting increased fluid secretion and intestinal motility.
Specific-IL-13 Functions	Enhances mucus production (via goblet cell hyperplasia and differentiation); increases epithelial cell turnover, hindering parasite adhesion.

2.3.2. IL-5

The process strongly stimulates the production of eosinophils (hematopoiesis), including their differentiation, release, migration into tissues (induced by chemokines such as eotaxins/CCL11), and survival/activation from the bone marrow. Eosinophils are a characteristic type of immune cell involved in helminth infections. They adhere to the surface of helminth larvae that are coated with IgE or IgG antibodies through FcεRI or Fcγ receptors. Once attached, eosinophils discharge their cytotoxic granules, which contain Major Basic Protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil neurotoxin (EDN), onto the parasite's surface (tegument/cuticle) in a process known as antibody-dependent cellular cytotoxicity (ADCC). These proteins are highly toxic to the parasite and can damage its surface structures (Ehrens et al., 2022).

2.3.4. IL-9

IL-9 plays several important roles in the immune system, particularly in type 2 immune responses and mucosal immunity. One of its most well-known functions is to significantly promote the growth, survival, and activation of mast

cells. This enhancement allows mast cells to degranulate and release potent inflammatory mediators, which are essential during allergic reactions and in defending against certain parasites, especially helminths.

In addition to its effects on mast cells, IL-9 also significantly influences the function of other key lymphocyte populations involved in type 2 responses, such as innate lymphoid cells type 2 (ILC2s) and Th2 cells. It often amplifies their cytokine production and effector capabilities. Furthermore, IL-9 contributes to barrier defense mechanisms by directly stimulating intestinal epithelial cells, which increases the production and secretion of mucus. This mucus forms a crucial physical barrier that helps trap and expel pathogens within the gut lümen (Bick et al., 2024).

2.3.5. Alternative Macrophage Activation (M2 Polarization)

IL-4 and IL-13 promote the transformation of macrophages into an "alternatively activated" or M2 phenotype. These M2 macrophages exhibit high levels of Arginase-1 (Arg1), which converts L-arginine into urea and ornithine, competing with inducible Nitric Oxide Synthase (iNOS). As a result, M2 macrophages have a lower capacity to kill microbes and secrete immunosuppressive and regulatory cytokines such as IL-10 and TGF-β. They also produce molecules involved in tissue repair and remodeling, including fibronectin, collagen precursors, and metalloproteinases. The role of M2 macrophages in the Th2 immune response is complex. On one hand, they help contain parasites, particularly established larvae or eggs, by forming a capsule around them and assisting in tissue repair. On the other hand, their secretion of IL-10 and TGF-β can lead to local immunosuppression and suppression of the Th1 response, which may allow the parasite to persist in a chronic state (Inclan-Rico et al., 2022; Parente et al., 2023).

2.4. Roles of Other T Cell Subsets and B Cells

2.4.1. Th17 Cells

They secrete cytokines such as IL-17A, IL-17F, and IL-22. IL-17, in particular, strongly induces neutrophil chemotaxis and activation by stimulating the release of granulocyte colony-stimulating factor (G-CSF) and CXCL8. IL-22 acts on epithelial cells to enhance their barrier functions by increasing the production of antimicrobial peptides and repairing tight junctions. The role of Th17 responses in parasitic infections varies depending on the type of parasite and the stage of infection. Th17 responses have been shown to contribute to some protozoal infections, such as certain forms of mucocutaneous *leishmaniasis*, and to certain helminth infections, providing early protection against *Trichuris muris*

and contributing to egg granuloma pathology in *Schistosoma* infections. Overall, Th17 responses are generally more critical in responses to bacterial and fungal infections (Huangfu et al., 2023).

2.4.2. Regulatory T Cells (Tregs)

The cells primarily express the transcription factor Foxp3 and fall into two categories: naturally occurring thymic regulatory T cells (nTreg) and peripherally induced regulatory T cells (iTreg). Regulatory T cells (Tregs) are essential negative regulators that help prevent excessive immune responses and the development of autoimmune diseases. Their main mechanisms of action include the secretion of immunosuppressive cytokines such as IL-10 and TGF-β. They also reduce IL-2 levels by expressing the high-affinity IL-2 receptor (CD25), and they inhibit costimulatory molecules on antigen-presenting cells (APCs) through CTLA-4. Furthermore, Tregs modulate metabolic pathways, including adenosine production. In cases of chronic parasitic infections, particularly helminthiasis, Treg populations are often found to expand and become activated. This expansion helps to limit immunopathological damage to host tissues. However, it also suppresses Th1 and Th2 protective effector responses against the parasite. This suppression significantly contributes to the long-term survival of the parasite and the establishment of chronic infection (Ge et al., 2024).

2.4.3. B Cells and Antibodies

B lymphocytes are fundamental to the humoral immune response against parasitic infections. These cells are responsible for producing antibodies that are specific to parasitic antigens. Effective antibody production and isotype switching often depend on signals from T lymphocytes, particularly T follicular helper (Tfh) cells found in germinal centers. The antibodies produced by B lymphocytes contribute to various protective mechanisms against parasites (Ritzau-Jost et al., 2021).

2.4.3.1.Neutralization

Antibodies can prevent the adhesion or invasion of parasites into host cells through a neutralization mechanism. A specific example is the blocking of the entry of merozoite forms of the *Plasmodium* genus parasite into erythrocytes by antibodies (Chandley et al., 2023).

2.4.3.2.Optionization

The process of opsonization occurs when antibodies bind to parasites or infected cells. This binding enhances target recognition and promotes

phagocytosis (cellular engulfment) by phagocytic cells like macrophages and neutrophils through Fcγ receptors (Lee et al., 2020).

2.4.3.3.Complement Activation

The activation of the complement system is a significant outcome of antibody-mediated responses. Specifically, IgM and certain subclasses of IgG, such as IgG1 and IgG3 in humans, initiate the classical complement pathway. This activation can lead to the direct lysis, or disintegration, of the target parasite's cell membrane, or it can enhance opsonization by complement proteins, making the target more recognizable for immune clearance (Berentsen, 2015).

2.4.3.4. Antibody Dependent Cellular Cytotoxicity (ADCC)

IgG antibodies play a crucial role in directing NK cells to infected cells through the FcγRIII/CD16 receptor, prompting the NK cells to eliminate those infected cells. In contrast, IgE antibodies guide eosinophils, macrophages, and platelets to target helminth larvae, triggering these immune cells to release their granule contents, which is part of the Th2 response. The effectiveness of the antibody response varies based on the life stage and location of the parasite. It is generally more effective against extracellular forms of parasites that are present in the bloodstream or tissue fluid. However, the response is limited against intracellular parasites and cyst forms. Additionally, it’s important to note that parasites can evade antibody responses through mechanisms such as antigenic variation (Forthal et al., 2018).

2.5. Immunopathology in Parasitic Infections

Immune responses to parasitic infections are crucial for defending the host, but when these responses become excessive, uncontrolled, or misdirected, they can lead to immunopathological mechanisms that cause significant damage to the host's tissues. The symptoms associated with many parasitic diseases and the resulting health issues (morbidity) often stem from these inappropriate immune responses rather than direct harm caused by the parasite itself. The nature and severity of the observed immunopathology can vary based on factors specific to the host, including genetic makeup, nutritional status, and pre-existing infections, as well as characteristics of the parasite, such as its type and density in the host (Shivahare et al., 2023).

2.5.1. Pathology Associated with Excessive Inflammatory Responses and Cytokine Storm

During acute infections or specific pathological conditions, there can be an excessive and uncontrolled release of pro-inflammatory cytokines, particularly mediators like TNF-α, IFN-γ, IL-1β, IL-6, and IL-12. This excessive cytokine release can lead to a severe immunological response known as a "cytokine storm." Such a storm can result in widespread tissue damage, organ dysfunction, and potentially fatal outcomes (Riyaz Tramboo et al., 2024).

2.5.2. Cerebral Malaria

One of the most severe complications of *P. falciparum* infection is cerebral malaria. This condition occurs when infected red blood cells adhere to the brain's capillary endothelium through adhesion molecules, such as PfEMP1, expressed by the parasite. This adhesion leads to local ischemia and damage to the endothelium. As a result, immune cells, including monocytes, macrophages, and T cells, infiltrate the affected area. These immune cells release high levels of cytokines, such as TNF-α, IFN-γ, and Lymphotoxin-α (LT-α). The release of these cytokines disrupts the integrity of the blood-brain barrier, increases vascular permeability, and results in microhemorrhages, brain edema, neuronal damage, and apoptosis. These effects can lead to severe outcomes such as coma, convulsions, and neurological complications (Akide Ndunge et al., 2022).

2.5.3. Late Stage of African Trypanosomiasis (Sleeping Sickness)

The meningoencephalitic phase of African Sleeping Sickness is marked by the invasion of the central nervous system (CNS) by the parasites *T. brucei gambiense* or *T. brucei rhodesiense*, which cross the blood-brain barrier. Once in the brain parenchyma, these parasites activate T lymphocytes, primarily Th1-type T cells, as well as astrocytes and microglia, which are the brain’s resident macrophages. These activated cells produce high levels of pro-inflammatory cytokines, particularly IFN-γ and TNF-α. This chronic neuroinflammation is a fundamental pathological mechanism that leads to demyelination, neuronal damage, and the characteristic neuropsychiatric symptoms of the disease, including sleep disturbances, personality changes, motor and sensory dysfunction, and progressive encephalopathy (Kennedy, 2004).

2.5.4. Acute Chagas Disease

During the early (acute) phase of *T. cruzi* infection, particularly in children or immunocompromised individuals, high levels of parasitemia can lead to severe systemic inflammation. The parasite intensely invades heart muscle cells

(cardiomyocytes), triggering a strong inflammatory response mediated by cytokines such as IFN-γ and TNF-α. These cytokines are released by macrophages, Th1-type helper T cells, and CTL. This immune response can result in serious cardiac complications, including acute myocarditis and potentially heart failure. Additionally, involvement of the central nervous system, such as meningitis or encephalitis, has been reported during this stage (Macaluso et al., 2023; Olivo-Freites et al., 2023) Fig. 3.

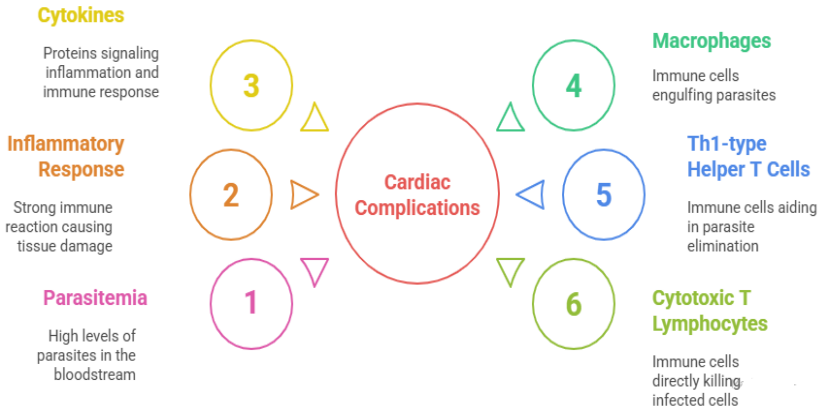

Figure3. Factors Leading to Cardiac Complications in Acute Chagas Disease

2.5.5. Acute *Schistosomiasis* (Katayama Fever)

Acute *Schistosomiasis*, also known as Katayama Fever, is a clinical syndrome similar to serum sickness that typically occurs a few weeks after the initial infection with *Schistosoma species,* particularly *Schistosoma japonicum* and *Schistosoma mansoni*. This syndrome emerges when the parasites reach their adult form within the host and begin laying eggs. The pathogenesis of acute *Schistosomiasis* involves a systemic hypersensitivity reaction, which is triggered by immune complexes formed as the host's immune system responds to egg antigens released into the bloodstream. It is believed that early Th1/Th17-type cellular immune responses may also play a role in this reaction. Clinically, acute Schistosomiasis is characterized by systemic symptoms such as fever, urticaria (hives), angioedema (swelling), muscle pain (myalgia), non-productive cough (dry cough), and diarrhea. Laboratory findings often show marked eosinophilia (an elevated number of eosinophils) as well as lymphadenopathy (swollen lymph nodes) and hepatosplenomegaly (enlargement of the liver and spleen) that can be detected during a physical examination. While acute Schistosomiasis typically

resolves on its own, it can lead to serious complications in some cases (Biber et al., 2022; Ross et al., 2007) Fig 4.

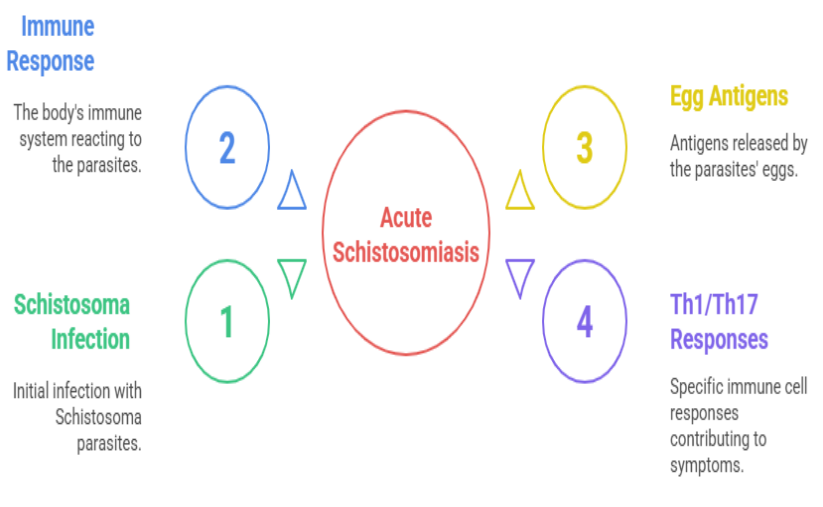

Figure 4. Pathogenesis of Acute Schistosomiasis

2.6. Granuloma Formation, Chronic Inflammation, and Fibrosis-Associated Organ Damage

The immune system forms organized cellular structures known as granulomas to limit and isolate large or resistant parasites, larvae, or especially the eggs left in tissues by helminths that cannot be cleared through phagocytosis. Initially, granulomas serve as a protective mechanism; however, as infection becomes chronic, they can become a primary source of pathology. Granulomas are comprised of activated macrophages (epithelioid cells and multinucleated giant cells) clustered around antigenic stimuli, along with lymphocytes (Th1, Th2, Th17, Treg), eosinophils, neutrophils, fibroblasts, and other cells. The cytokines, chemokines, and growth factors released by cells within the granuloma trigger a sustained inflammatory response and stimulate the production and accumulation of extracellular matrix (ECM) components, particularly collagen. This process ultimately leads to fibrosis, which is characterized by the formation of scar tissue (Vacca et al., 2022).

2.6.1. *Schistosomiasis*

Schistosomiasis can lead to significant long-term health issues primarily due to the accumulation of parasite eggs in organs such as the liver or bladder. When these foreign eggs settle in the body, the immune system responds by forming inflammatory nodules known as granulomas around them. Over time, this results

in the development of scar tissue (fibrosis) in the affected areas. The substances secreted by the eggs activate a specific part of the immune system, particularly the Th2 branch. Chemical messengers like IL-4 and IL-13 prompt immune cells, such as macrophages, to contribute to healing and scarring, while also stimulating fibroblasts to produce collagen, the main component of scar tissue (Mawa et al., 2021).

If the immune response intensifies in the liver, it can lead to severe scarring, known as periportal fibrosis, around the portal vein, which is the main blood vessel in the liver. This scarring can obstruct blood flow within the liver and cause increased pressure in the portal vascular system, resulting in portal hypertension. Consequently, the spleen may enlarge (splenomegaly), fluid could accumulate in the abdominal cavity (ascites), and life-threatening complications may develop, such as dilation and bleeding of the veins in the esophagus (esophageal variceal bleeding) (Manzella et al., 2008).

In cases where the issue arises in the urinary tract, granulomas, scarring, and calcifications forming in the bladder wall can impede the flow of urine from the kidneys to the bladder. This obstruction can lead to kidney swelling (hydronephrosis) and may eventually result in impaired kidney function or kidney failure. Additionally, the ongoing inflammation and deterioration of cell structure in the bladder significantly increase the risk of developing bladder cancer, particularly the squamous cell carcinoma type (Sah et al., 2015) Fig. 5.

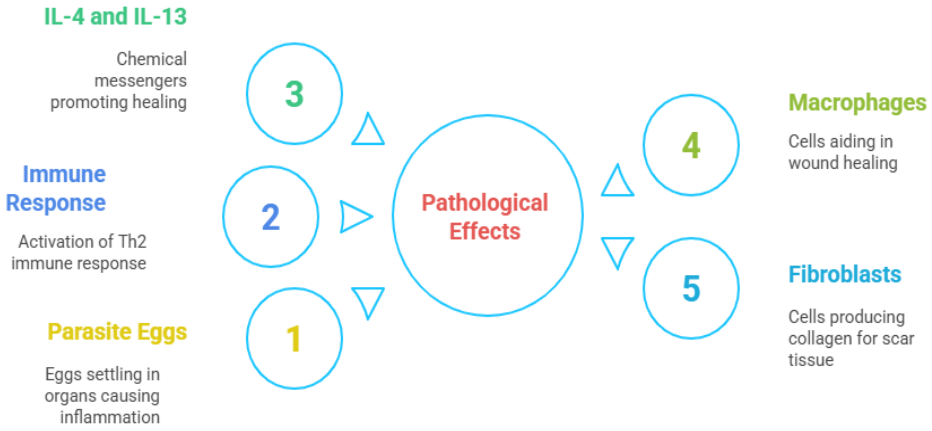

Figure 5. Pathological Effects of Schistosomiasis

2.6.2. Lymphatic Filariasis

Adult forms of filarial nematodes, particularly the species *Wuchereria bancrofti* and *Brugia malayi*, are found in the human lymphatic system, specifically in lymph vessels and lymph nodes. The presence of these parasites can lead to chronic inflammation of the lymph vessels (lymphangitis) and lymph nodes (lymphadenitis). However, a more significant factor in the progression of chronic disease is the host's immune response to dead or dying adult parasites. This response triggers granulomatous reactions and subsequent fibrotic processes around the remnants of the parasites, resulting in structural damage and obstruction in the lymph vessels. As a consequence, lymphatic drainage becomes impaired. Over the years, this progressive lymphatic insufficiency can result in the development of massive, often irreversible lymphedema in the affected areas of the body, particularly in the lower extremities and genital region. The most advanced stage of this condition is known as elephantiasis, which is characterized by severe skin thickening (hyperkeratosis) and hardening (induration), in addition to significant lymphedema (Rajamanickam et al., 2025; Setegn et al., 2024) Fig 6.

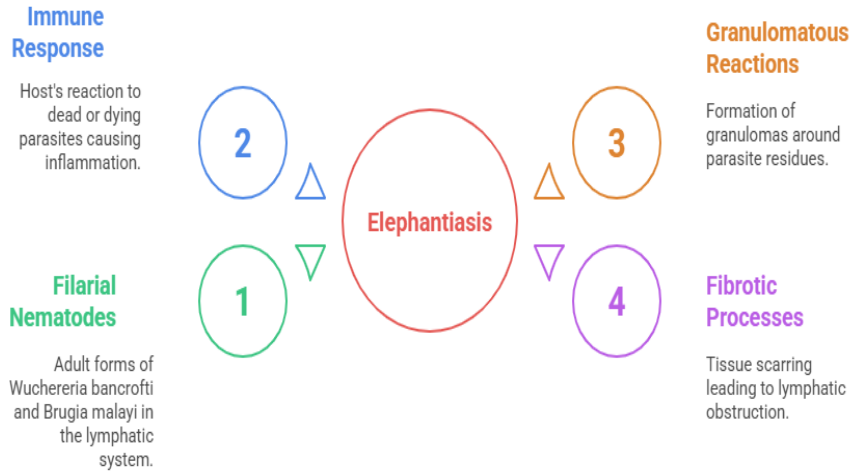

Figure 6. Factors Leading to Elephantiasis

2.6.3. Visceral Leishmaniasis (Kala-azar)

Visceral leishmaniasis is a systemic infection caused by the intracellular protozoan parasite *L. donovani or L. infantum.* These parasites multiply within host macrophages and lead to widespread infiltration of the organs in the reticuloendothelial system, primarily the liver, spleen, and bone marrow. The persistent presence of the parasites triggers a chronic inflammatory response in these organs. This response, while not always well-organized, includes

granulomatous reactions and significant macrophage hyperplasia, resulting in notable hepatosplenomegaly. Bone marrow infiltration and dysfunction often lead to hypersplenism, which is characterized by pancytopenia, anemia, leukopenia, and thrombocytopenia. Another critical consequence of visceral leishmaniasis is the suppression of the host's overall immune response, making individuals more susceptible to secondary bacterial infections and other opportunistic infections. In advanced cases, fibrotic changes may also occur as a result of chronic inflammation (Costa et al., 2023) Table 2.

Table 2. Features of Visceral Leishmaniasis (Kala-azar)

Features	Description
Type of Disease	Systemic infection
Causative Agent	*Leishmania donovani* or *L. infantum* (Protozoan parasites)
Basic Mechanism	Obligate intracellular multiplication of parasites within host macrophages
Target System/Organs	Reticuloendothelial system (primarily Liver, Spleen, Bone Marrow)
Pathological Process	Widespread infiltration of target organs by these infected cells; Chronic inflammatory response triggered by parasite persistence (granulomas, macrophage hyperplasia)
Main Clinical Findings	Clinically massive hepatosplenomegaly (Enlargement of liver and spleen)
Bone Marrow Effects	Infiltration and dysfunction; Contribution of hypersplenism
Hematological Consequences	Pancytopenia (manifested by Anemia, Leukopenia, Thrombocytopenia)
Effect on Immune System	Suppression of the host's general immune response
Consequences of Immunosuppression	Increased susceptibility to secondary bacterial or other opportunistic infections
Advanced Stage Sequelae	Fibrotic changes may develop as a sequela of chronic inflammation (in advanced cases)

2.6.4. Onchocerciasis (River Blindness)

The basic mechanism behind onchocerciasis involves severe inflammatory reactions triggered by microfilariae, the microscopic larvae of the *Onchocerca volvulus* parasite, when they die in the skin and eye tissues. In the skin, this condition presents as chronic dermatitis (skin inflammation), intense itching, thickening and coarsening of the skin (lichenification), thinning of the skin (atrophy), and regional pigment loss (depigmentation), which can be described as "leopard skin." When the eyes are involved, the situation becomes more serious, as microfilariae can invade vital structures of the eye, including the cornea (the clear front layer of the eye), the anterior chamber (the space between the cornea and the iris), the iris (the colored part of the eye), the retina (the layer

that enables vision), and the optic nerve (which transmits visual information to the brain). The death of microfilariae in these delicate tissues results in various eye conditions, such as punctate keratitis (small inflammatory dots on the cornea), sclerosing keratitis (progressive clouding and hardening of the cornea), iridocyclitis (inflammation of the iris and nearby structures), chorioretinitis (inflammation of the retina and underlying vascular layer), and optic atrophy (damage to the optic nerve). These eye pathologies accumulate over time, leading to progressive vision loss and, ultimately, blindness, a condition known as river blindness. The development of these damaging processes is believed to involve different response mechanisms of the immune system, known as Th2 and Th1/Th17, as well as certain molecules released by Wolbachia, a symbiotic bacterium that resides within the parasite (Frallonardo et al., 2022; Katawa et al., 2015), Fig. 7.

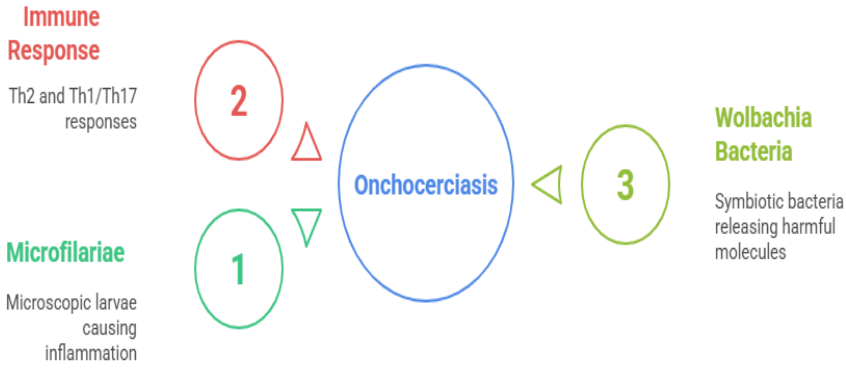

Figure 7. Factors Leading to Onchocerciasis

3. Immune Complex Deposition and Associated Vasculitis/Nephritis

Immune complexes (ICs) are formed when soluble parasite antigens in the bloodstream interact with antibodies produced by the host, particularly IgM and IgG classes. These complexes can play a significant role in disease progression. Under certain immunological conditions, such as when there is an excess of antigens or antibodies, or when the body's normal mechanisms for clearing these complexes are insufficient, ICs can accumulate in the walls of small blood vessels. This accumulation is especially noticeable in areas like the basement membranes of the renal glomeruli and the synovial membranes of the joints (Tenaglia et al., 2023).

Accumulation of immune complexes (ICs) in tissues strongly activates the classical pathway of the complement system. This activation results in the production of pro-inflammatory anaphylatoxins, such as C3a and C5a, as well as

the formation of the membrane attack complex (MAC), which can lead to cell damage. C5a, in particular, is a powerful chemotactic factor that attracts and activates neutrophils to the site of accumulation. Once neutrophils arrive at the site, they bind to the immune complexes through Fc receptors on their surface. This binding triggers the degranulation of neutrophils, releasing cytotoxic molecules, including lysosomal enzymes and reactive oxygen species (ROS), into the surrounding tissue. Consequently, this sequence of events causes localized tissue damage and results in a Type III hypersensitivity reaction. Clinically, this may manifest as vasculitis (inflammation of blood vessels), glomerulonephritis (inflammation of the kidneys), or arthritis (inflammation of the joints) (Kulkarni et al., 2024) Table 3.

Table 3. Mechanism of Immune Complex Deposition and Associated Vasculitis/Nephritis

Component / Process	Mechanism / Description	Key Mediators / Sites / Outcomes
Immune Complex (IC) Formation	Interaction between circulating soluble parasite antigens and host-produced antibodies.	Soluble parasite antigens, Host antibodies (esp. IgM, IgG)
IC Deposition	Accumulation of ICs in small blood vessel walls, favoured by antigen/antibody excess or inadequate physiological clearance.	Sites: Renal glomerular basement membranes, synovial membranes (Tenaglia et al., 2023)
Complement Activation	Deposited ICs trigger the classical pathway of the complement system.	Classical complement pathway components
Generation of Inflammatory Mediators	Complement activation leads to the formation of pro-inflammatory molecules and cell-damaging complexes. C5a acts as a potent chemoattractant.	Anaphylatoxins (C3a, C5a), Membrane Attack Complex (MAC)
Neutrophil Recruitment & Activation	C5a attracts neutrophils to the site of IC deposition. Neutrophils bind to deposited ICs via surface Fc receptors, triggering activation.	C5a (chemotaxis), Neutrophils, Fc receptors
Effector Phase / Tissue Damage	Activated neutrophils degranulate, releasing cytotoxic molecules into the surrounding tissue.	Lysosomal enzymes, Reactive Oxygen Species (ROS)
Pathological Outcome	The cascade results in localized tissue damage, characterized as a Type III hypersensitivity reaction, leading to inflammation of affected tissues.	Clinical Manifestations: Vasculitis, Glomerulonephritis, Arthritis; Type III Hypersensitivity

4. Malaria-Associated Nephropathy

Quartan malarial nephropathy is a specific type of immune complex-mediated glomerulonephritis that is linked to chronic infection with *P. malariae*. The pathogenesis of this condition primarily involves the deposition of immune complexes (IC) in the subendothelial and mesangial areas of the glomerular capillary wall. These immune complex deposits activate the complement system, resulting in a local inflammatory response and subsequent progressive glomerulosclerosis. Clinically, quartan malarial nephropathy presents as a persistent nephrotic syndrome that typically does not respond well to standard therapies. It is important to differentiate this condition from the more common transient acute kidney injury associated with *P. falciparum* infections, which usually occur due to acute tubular necrosis or acute glomerulonephritis (Gentile et al., 2019).

5. *Schistosomiasis*-Associated Glomerulonephritis

In some patients with chronic infections caused by *S. mansoni* or *S. japonicum*, particularly those with the hepatosplenic form of the disease, various types of glomerulonephritis may develop. This includes mesangioproliferative, membranoproliferative, and focal segmental glomerulosclerosis. These conditions can arise from the accumulation of immune complexes (ICs) formed by circulating parasite antigens, such as egg or adult antigens, in the glomeruli. As a result, patients may experience proteinuria or nephrotic syndrome (Liao et al., 2022).

6. Triggering or Exacerbation of Autoimmunity

During parasitic infections, autoimmune reactions may occur when the host's immune system mistakenly attacks its tissues while responding to parasite antigens. Potential mechanisms underlying this phenomenon include (Chulanetra et al., 2021).

6. 1. Molecular Mimicry

If structural similarities exist between parasite antigens and host proteins, T cell or antibody responses against the parasite may also react to these similar host molecules (Martins et al., 2023).

6.2. Bystander Activation

During a parasite infection, the inflammatory environment can cause APCs, especially DCs, to become nonspecifically activated. As a result, they may present self-antigens that the immune system usually tolerates. This activation

can lead to the stimulation of previously anergic or naive autoreactive T cells. Additionally, released cytokines may facilitate this process (Kim et al., 2019).

6.3. Epitope Spreading

Damage to host tissues caused by parasite infections or related inflammation can expose proteins that are typically hidden from the immune system, known as cryptic epitopes. When the immune system reacts to and develops a response towards these newly exposed self-antigens, the process is referred to as cryptogenic epitope spreading. This phenomenon results in the immune response initially targeting the pathogen and expanding to also include the host's tissue structures (Lekki-Jóźwiak et al., 2024).

6.4. Chronic Chagas Cardiomyopathy and Mega Syndromes

Autoimmunity is believed to play a significant role in the development of megaesophagus and megacolon in patients with dilated cardiomyopathy, cardiac conduction disorders, and gastrointestinal denervation seen in the chronic phase of Chagas disease. Research has demonstrated that immune responses to T. cruzi antigens, such as the B13 protein and cruzipain, can cross-react with cardiac muscle proteins, including myosin, laminin, and neuronal proteins in the ganglia of the autonomic nervous system. This process is complex, involving both direct damage caused by the parasite and immune-mediated mechanisms (Medina-Rincón et al., 2021).

7. Allergic Type Hypersensitivity Reactions

Helminth infections typically trigger a strong Th2 polarization of the immune system. This polarization results in increased production of IgE antibodies, primarily driven by the cytokines IL-4 and IL-13. Additionally, it leads to significant activation of eosinophils and mast cells through the action of IL-5. This specialized immunological environment makes the host particularly vulnerable to allergic responses known as Type I hypersensitivity reactions. These allergic reactions are characterized by the IgE-mediated degranulation of mast cells and the release of vasoactive amines such as histamine, which typically occurs upon subsequent exposure to the same parasite antigens or during certain stages of the parasite’s life cycle (Ayelign et al., 2020).

7.1. Tropical Pulmonary Eosinophilia (TPE)

In some individuals with lymphatic filariasis, there is an exaggerated inflammatory response mediated by IgE and eosinophils to microfilariae trapped in the lung capillaries. This condition is characterized by nighttime asthma-like

symptoms, which include coughing, wheezing, and shortness of breath, as well as fever, weight loss, very high blood eosinophil counts (greater than 3000/mm³), and elevated total IgE levels. A chest X-ray typically reveals widespread reticulonodular infiltrates. If left untreated, this condition can progress to chronic lung disease and fibrosis (Joanna V, 2019).

7.2. Löffler Syndrome

This condition is a transient syndrome that occurs during the migration of certain helminth larvae, such as Ascaris lumbricoides and hookworms (*Necator americanus* and *Ancylostoma duodenale*), from the lungs as part of their life cycle. It is characterized by migratory pulmonary infiltrates in the lungs, along with symptoms like cough, fever, and significant blood eosinophilia. Typically, this syndrome is mild and resolves on its own (Caldrer et al., 2022).

7.3. Anaphylaxis

Systemic anaphylaxis is a rare but life-threatening emergency that can occur due to the sudden and widespread degranulation of mast cells. This may happen in specific situations, such as when hydatid cysts caused by *Echinococcus granulosus* rupture, often due to trauma or surgery. It can also result from mass exposure to certain helminths, such as Ascaris. Symptoms of systemic anaphylaxis include widespread urticaria (hives), angioedema (swelling), bronchospasm (tightening of the airways), hypotension (low blood pressure), and circulatory collapse (Khaled et al., 2021).

8. Conclusion

The immunological interaction between host and parasite is one of the most complex and dynamic areas of biology. This interaction involves a continuous competition of adaptation and counter-adaptation, shaped by millions of years of co-evolution. He host immune system utilizes a complex array of innate and adaptive defenses to recognize, control, and ultimately eliminate parasitic pathogens. This multifaceted response is illustrated by key immunological concepts, such as the polarization of T helper cells into Th1 or Th2 subsets. These subsets orchestrate distinct mechanisms tailored to address different types of parasitic threats. At the same time, parasites have developed sophisticated strategies to evade and modulate the host's immune response, ensuring their survival and promoting their spread. These strategies vary in complexity; some are relatively simple, like antigenic variation or hiding from the immune system, while others involve intricate molecular mechanisms that actively suppress,

disrupt, or manipulate components of the host immune response for their advantage.

A particularly striking aspect of the struggle against parasitic diseases is the inherent dilemma of the immune response: the very mechanisms essential for protection can also lead to immunopathology, causing significant damage to host tissues. In many instances, excessive inflammation, fibrotic processes, and autoimmune reactions contribute more to the morbidity and mortality associated with parasitic infections than the direct impact of the parasites themselves. Parasites possess the ability to subtly manipulate the immune system, particularly through the induction of regulatory T cells (Tregs) and the activation of suppressive pathways like IL-10 and TGF-β. This manipulation plays a crucial role in establishing chronic infections, potentially creating a general state of immunosuppression in the host. As a result, the host becomes more vulnerable to secondary infections and the efficacy of vaccines may be reduced. Understanding the complexities of parasite immunology is not only biologically interesting but also crucial for global health. To develop effective vaccine strategies that provide strong protection while minimizing harmful immune responses, we must also create innovative therapeutic approaches, such as immunomodulatory treatments, to counteract the immune evasion tactics employed by parasites. Moreover, enhancing the effectiveness of existing control programs relies on our understanding of the molecular and cellular intricacies of the host-parasite interaction. Future research in this field will shed light on these issues and open new possibilities in our fight against the devastating diseases that impact millions of people.

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Chapter 3

Antiparasitic Resistance: Molecular Basis, Epidemiological Threats, and New Therapeutic Strategies

Abstract

Resistance to antiparasitic drugs is a major global health threat that endangers the control of parasitic diseases, including malaria and helminthiases. Resistance emerges from a range of molecular mechanisms, including mutations in drug target proteins of the parasites (e.g., *Plasmodium falciparum* Chloroquine Resistance Transporter (*P. falciparum* Chloroquine Resistance Transporter; PfCRT, β-tubulin), amplification of transporters that efflux drugs (e.g., *P. falciparum* Mutlidrug Resistance Protein 1; PfMDR1), alterations in drug metabolism, or increased number of resistance genes (e.g., Kelch protein propeller domain containing gene; K13 and artemisinin resistance). The rapid spread of resistance is driven by factors as diverse as the kinds and volumes of drugs being used (drug pressure), the parasitic biology, and the mobility of infected hosts. Dealing with this threat needs multi-pronged efforts. Risk-based drug administration and optimal dosing; development of drugs with new mechanisms of action (e.g., Artemisinin-Based Combination Therapies for Malaria; ACTs) for combination therapies to delay resistance; and rational drug administration. In addition, vector control (as with malaria), the development of better diagnostic methods, the development of new vaccines, and robust surveillance systems to monitor the spread of resistance must be factored in. Interdisciplinary collaboration and a "One Health" approach are essential for mitigating this growing threat, despite challenges like inadequate funding and the complexity of parasites.

Key words: Antiparasitic Resistance, Molecular Mechanisms, Epidemiology, Combination Therapy, Treatment Strategies, Global Health

1. Introduction

Parasitic infections have significantly impacted global health and well-being throughout human history. Diseases such as malaria, schistosomiasis, sleeping sickness (African trypanosomiasis), Chagas disease (American trypanosomiasis), Leishmaniasis, Filariasis, and soil-borne helminthiases pose a threat to billions of people and numerous animals living in low- and middle-income countries, particularly in tropical and subtropical regions. These infections hinder the socioeconomic development of individuals and societies not only by directly causing high morbidity (disease burden) and mortality (death) rates but also through indirect effects such as anemia, malnutrition, and delays in cognitive development. Additionally, they result in significant economic losses in the agricultural and livestock sectors (Garrido-Cardenas et al., 2022; Kaminsky et al., 2025).

Since the mid-20th century, antiparasitic drugs have significantly changed the fight against devastating diseases, owing to advancements in chemical synthesis and the discovery of natural products. Medications such as chloroquine, praziquantel, ivermectin, benzimidazoles, and artemisinin and its derivatives have saved millions of lives. These drugs are essential tools for disease control and have even contributed to achieving elimination goals in certain regions. They are invaluable for reducing parasite loads, treating individual cases, and controlling epidemics through mass drug administration (MDA) programs. Their success is largely attributed to their affordability, ease of use, and high effectiveness (Cox, 2002; Le et al., 2024).

The emergence and global spread of resistance to antiparasitic drugs is becoming a serious crisis that threatens significant advancements in treatment and control. This situation parallels the alarming rise in antibiotic resistance (Picot et al., 2022). Resistance occurs when a parasite population can survive and reproduce despite standard doses of medication that previously eliminated or inhibited its growth. This resistance can lead to treatment failures, disease resurgence, increased transmission, and the necessity to use more expensive and potentially more toxic alternative treatments. Ultimately, these challenges jeopardize the sustainability of control programs. Notable examples of this issue include the widespread resistance to chloroquine and sulfadoxine-pyrimethamine in *P. falciparum*, as well as the more recent resistance to artemisinin derivatives, which originated in Southeast Asia and poses a threat to Africa. Resistance to drugs like benzimidazole and ivermectin is becoming more common in helminths that affect livestock and humans (Takala-Harrison et al., 2015). Therefore, gaining a deeper understanding of antiparasitic resistance is one of the most urgent priorities on today's global health agenda (Giannelli et al., 2024).

This chapter aims to thoroughly explore the complex issue of antiparasitic resistance. First, we will examine the molecular mechanisms that contribute to this

resistance, including genetic changes and biochemical pathways. Understanding these mechanisms is essential for developing molecular markers to detect resistance and for identifying new drug targets.mSecond, we will discuss the dynamics of epidemiology, focusing on how resistance develops in specific geographic areas. We will consider factors such as drug pressure, parasite biology, host characteristics, and human mobility, all of which can accelerate the spread of resistance. This knowledge serves as the foundation for designing effective surveillance and control strategies. Finally, we will explore new approaches to combat this growing threat, which include discovering and developing new drugs, employing combination therapies to maintain the effectiveness of existing drugs, promoting the rational use of medications, improving diagnostic methods, and integrating alternative or complementary strategies such as vector control.

2. Molecular Basis of Antiparasitic Resistance

The increasing threat of antiparasitic drug resistance to global health and agriculture. It happens when specific populations of parasites persist and replicate despite the fact that they are treated with lethal therapeutic doses of drugs that were once effective against them. This multifactorial phenomenon results from spontaneous or experimentally induced genetic alterations in the parasite genome (substitutions, deletions, amplifications, or chromosomal rearrangements). These mutations are selected for and disseminated within the population due to the extraordinary pressure exerted by drug exposure (Oliveira et al., 2024).

The mechanisms of resistance are varied at the molecular level. These can include changes in the target molecule of the drug, frequently an enzyme or receptor, causing a reduced binding affinity with the drug. Other mechanisms include impaired uptake pathways such as the disruption of carrier proteins, or overexpression of efflux pumps (e.g. ABC transporters) to excrete drug away from the cell, an enhanced ability of the parasite to metabolize drug into inert or less-toxic forms, and the emergence of new enzymatic systems that bypass the inhibited enzyme(s) in the drug's target pathway (Hajiagha et al., 2023).

Emergence and spread of drug resistance is thereby promoted by a range of factors, such as incomplete doses of medication, improper treatment duration, mass prophylactic treatment, non-compliance and spread of resistant parasites between hosts. This scenario greatly reduces the activity of current treatment options, aggravates infection control programs, and indicates the critical need for the design of effective antiparasitic agents (Wale et al., 2017).

2.1. Target Molecule Modification

Target molecule modification is one of the most common mechanisms of antiparasite resistance. In this process, the parasite alters the structure of a critical protein, usually an enzyme or a structural component, affected by the drug through genetic changes, particularly point mutations. These mutations can significantly reduce or completely block the drug's binding affinity by changing amino acids at the drug's binding site on the target protein or by disrupting the overall shape of the protein, thereby eliminating the drug's efficacy (Oliveira et al., 2024). When the drug is administered, parasites with these mutations can survive, multiply, and dominate the population. Specific mutations in the Dihydrofolate Reductase/Dihydropteroate Synthase (DHFR/DHPS) enzymes, targeted by antifolates in malaria, or in the β-tubulin protein, targeted by benzimidazoles in nematodes, are classic examples of this mechanism. These mutations have led to widespread treatment failures (Pacheco et al., 2020).

Ex 1. Antiparasitic resistance mechanisms observed in *P. falciparum* are closely linked to specific genetic mutations. Chloroquine resistance, in particular, is caused by mutations in the gene that encodes the *P. falciparum* chloroquine resistance transporter (PfCRT). These mutations lead to a reduced accumulation of chloroquine in the parasite's food vacuole. Similarly, resistance to the combination of sulfadoxine and pyrimethamine is determined by point mutations in the dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) genes, which play a crucial role in folate metabolism (Singh Sidhu et al., 2002).

Ex 2. Benzimidazole resistance observed in nematodes, such as those affecting albendazole and mebendazole, is often attributed to specific point mutations in the gene that encodes the β-tubulin protein, the primary target of these drugs. Commonly reported mutations include: a change from phenylalanine to tyrosine at codon 200 (F200Y), a change from glutamic acid to alanine at codon 198 (E198A), and a change from phenylalanine to tyrosine at codon 167 (F167Y). These mutations impede the binding of benzimidazoles to β-tubulin, leading to a resistance phenotype (Emery-Corbin et al., 2021).

2.2. Increased Drug Flow (Efflux)

Parasites can enhance the expression of carrier proteins, such as ATP-binding cassette (ABC) transporters and P-glycoproteins, found in the cell membrane. These proteins actively pump drugs out of the cell. Furthermore, parasites may acquire mutations that modify the activity of these proteins. Consequently, the concentration of the drug inside the cell may fall below the effective level (de Santana et al., 2025).

Ex. In *P. falciparum*, an increased copy number or specific mutations in the PfMDR1 gene (*P. falciparum* multidrug resistance protein 1) have been linked to

resistance against certain drugs, including mefloquine and artemisinin. Additionally, the overexpression of ABC transporters in *Leishmania* species plays a role in developing resistance to antimonial compounds and miltefosine (de Santana et al., 2025).

2.3. Alteration of the Metabolism or Activation of the Drug

Some antiparasitic drugs are prodrugs, meaning they require metabolic activation within the parasite to become effective. Parasites can develop resistance to these drugs through mutations or alterations in the expression of genes responsible for the enzymes involved in these activation pathways. Additionally, they might enhance detoxification processes that deactivate the drug (Bahreini et al., 2025).

Ex. One of the key mechanisms behind drug resistance in parasites is the disruption of drug transport into the cell or the activation of metabolic processes. For instance, resistance to arsenical compounds, such as melarsoprol, which are used to treat African trypanosomiasis, is primarily linked to loss-of-function mutations in specific membrane transporters. One such transporter is the P2 aminopurine transporter, which is responsible for facilitating drug intake into the parasite cell. When this transporter is compromised, the intracellular concentration of the drug decreases, leading to resistance. Similarly, the effectiveness of nitroimidazole antiparasitics, like benznidazole, relies on their conversion to cytotoxic forms by nitroreductase enzymes within the parasite. Any alterations in the genes that encode these enzymes, or reductions in their expression levels, can result in insufficient activation of the drug, ultimately contributing to a resistance phenotype (de Koning, 2020; Fairlamb et al., 2018).

2.4. Gene Amplification or Copy Number Variations (CNV)

Parasites can increase the number of copies of genes associated with drug resistance, such as target genes and efflux pump genes, to enhance the expression of these genes and counteract the effects of medications (Osei et al., 2018).

Ex. Gene copy number variations (CNVs) play a significant role in the development of antiparasitic resistance in *P. falciparum*. Specifically, increased copy numbers in the promoter region of the GTP cyclohydrolase I (GCH1) gene may promote the selection of mutations in the dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) genes. These genes are the primary mechanisms of resistance to antifolate drugs and may enhance the fitness of parasites carrying these mutations. Additionally, amplification of the *P. falciparum* multidrug resistance 1 (PfMDR1) gene has been linked to reduced susceptibility to various antimalarial agents (Osei et al., 2018).

2.5. Stress Response and Epigenetic Changes

Parasites can develop temporary or permanent resistance to drugs under stressful conditions, such as exposure to medications. This adaptation occurs through changes in gene expression, which are influenced by epigenetic mechanisms like DNA methylation and histone modifications. These mechanisms are believed to contribute to an early decrease in susceptibility to artemisinins. Specifically, mutations in the K13 (Kelch 13) gene of *P falciparum* result in a delayed response to artemisinin-derived drugs. This is due to either a reduction in the activation of artemisinin or alterations in the parasite's stress response during its ring stage. These developments pose a significant threat to the effectiveness of artemisinin-based combination therapies (ACTs) (Xie et al., 2020).

Resistance mechanisms typically work in combination rather than in isolation, resulting in higher levels of drug resistance or even multiple drug resistance. Therefore, understanding the molecular basis of these resistance mechanisms is essential. This knowledge will facilitate the development of molecular markers for effective monitoring of resistance and help identify new therapeutic targets (Tanner et al., 2025).

3. Epidemiology and Spread of Resistance

The epidemiology of antiparasitic resistance is a complex process influenced by both the intensity and duration of parasite exposure to drugs, known as drug pressure. Additionally, intrinsic factors such as the genetic makeup of the parasite, its mutation rate, reproductive strategies (either sexual or asexual), and the biological fitness cost associated with resistance play crucial roles. This selection process is particularly intensified by situations that lead to suboptimal drug exposure, including incorrect dosages, counterfeit drugs, and non-adherence to treatment regimens. Moreover, environmental pressures arising from veterinary drug use introduce a "One Health" dimension. Individual factors, such as host immunity, along with environmental conditions like climate change, also impact transmission dynamics and the selection of resistance. However, the primary driver of the rapid geographical spread of resistant strains is increased human and animal mobility, resulting from travel, trade, and migration. This spread often originates in specific "hot spots" and occurs on a global scale. Operational and health system shortcomings, such as inadequate diagnostic capacity, failure to adhere to treatment guidelines, and insufficient surveillance systems, compound these challenges. As a result, resistance emerges and spreads, ultimately threatening the effectiveness of existing treatment options (Pramanik et al., 2019; Whitlock et al., 2021).

3.1. Drug Pressure

The primary factor contributing to the emergence of resistance to antiparasitic drugs is the type and intensity of drug exposure. Widespread, continuous, uncontrolled, or suboptimal drug use can eliminate susceptible parasite populations while creating strong selection pressure. This process triggers the selection and spread of naturally occurring or spontaneously emerging resistant mutants within the population. In this context, Mass Drug Administration (MDA) programs, which aim to reduce parasite burden, especially in endemic regions, can achieve significant public health gains. However, these programs may jeopardize long-term control efforts by accelerating the spread of resistant genotypes unless they are carefully planned and managed according to epidemiological and pharmacological principles. Additionally, non-adherence to treatment and the use of poor-quality or counterfeit drugs can result in suboptimal drug concentrations, leading to the development of resistance (Thu et al., 2017).

3.2. Parasite Biology

The genetic diversity of a parasite, along with its mutation rate, reproductive capacity (either through sexual or asexual reproduction), and population size, plays a significant role in the emergence and spread of resistant alleles. Parasites that reproduce quickly and can undergo genetic recombination, such as *P. falciparum*, can acquire and disseminate resistance more rapidly (Kamiya et al., 2022).

3.3. Host and Environmental Factors

The effectiveness of antiparasitic drugs and the subsequent development of resistance are influenced not only by the interactions between the drugs and parasites but also by a complex set of host-specific biological factors and environmental conditions. For instance, a host's immune system strength, nutritional status, and the presence of other infections can significantly impact treatment outcomes. These factors can also affect selection pressures on resistant parasites by influencing how drugs are processed and their effects on the body. Additionally, large-scale environmental changes, such as climate change, can modify the distribution and population dynamics of vectors and intermediate hosts. This alteration can facilitate the spread of both parasites and their resistant strains to new ecological areas and regions, thereby expanding the scope of the resistance issue (Liao et al., 2024; Morales et al., 2024).

3.4. Human and Animal Mobility

The migration and travel of infected hosts, whether human or animal, as well as their vectors, play a crucial role in the geographic spread of resistant parasite strains. This mobility enables resistant genotypes to be rapidly transported and established in areas where they were previously absent, complicating global control efforts. A clear illustration of this phenomenon's epidemiological significance can be seen in the historical spread of chloroquine resistance and, more recently, artemisinin resistance in *P. falciparum*. These resistances originated in Southeast Asia and have spread to the African continent, underscoring the critical influence of human and vector mobility in the dissemination of antiparasitic resistance (Wilson, 2020).

3.5. Operational Factors

Effective management of antiparasitic resistance largely depends on the strength and functionality of health systems. Key factors include the availability and quality of diagnostic facilities, the efficiency of pharmaceutical supply chains, and the coverage and sensitivity of epidemiological surveillance systems. These elements are crucial for the early detection, monitoring, and control of resistant strains. Inadequate surveillance activities can allow resistance to spread undetected across geographical areas, leading to an increase in prevalence. This situation compromises the effectiveness of existing treatment regimens and poses serious threats to public health (Oliveira et al., 2024). The epidemiology of resistance often exhibits a dynamic pattern, with the emergence of resistance occurring in specific geographic "hotspots" before spreading to neighboring regions and continents. Molecular surveillance, which involves screening for genetic markers associated with resistance, and phenotypic testing, which measures the in vitro or in vivo drug susceptibility of parasites, are essential tools for monitoring resistance and guiding control strategies (Ndiaye et al., 2021).

4. Strategies to Combat Antiparasitic Resistance

The increasing and serious threat posed by antiparasitic resistance to global public health highlights the inadequacy of one-dimensional or piecemeal approaches to this complex issue. The evolution and spread of resistance are influenced by several interacting factors, including drug selection pressures, host characteristics, parasite genetics, environmental changes, the mobility of humans and animals, and the capacity of health systems. Given this multifactorial nature, it is essential to design and implement comprehensive and integrated control strategies. These strategies should effectively combine various approaches, such as drug development and rational use, enhanced diagnostic capabilities,

strengthened surveillance systems, vector control, and potentially vaccine development, to successfully control and manage resistance (Ahmed et al., 2024).

4.1. New Drug Development

The growing issue of antiparasitic resistance poses a serious threat to the effectiveness of current treatments. Therefore, discovering and developing new drugs that operate through different mechanisms is of strategic importance. This process involves identifying new drug targets based on the biology of parasites, using high-throughput screening techniques to assess large chemical libraries, and applying rational drug design principles. However, the development of new antiparasitic agents is faced with significant challenges due to the biological complexity of parasites and identifying suitable targets. This makes the process often lengthy, costly, and fraught with a high risk of failure. Despite these hurdles, the development of next-generation drug candidates such as KAE609 (Cipoglitazar) and KAF156 (Ganaplacide) for malaria and emodepside for helminth infections offers promising potential in combating resistance (Schmitt et al., 2022).

4.2. Combination Therapies

One of the fundamental strategies used to delay the development of antiparasitic resistance and enhance treatment efficacy is the use of combination therapies. This approach involves administering two or more drugs that target different biochemical pathways or have different mechanisms of action at the same time. The rationale behind this method is to eliminate parasites that have developed resistance to one drug with the other active agents in the combination. Additionally, it significantly reduces the likelihood that multiple independent resistance mutations will occur and be selected simultaneously within a single parasite strain (Dhorda et al., 2021).

Ex. Artemisinin-based combination therapies (ACTs) have become the global standard for treating malaria caused by Plasmodium falciparum. However, the emergence of resistance to the artemisinin partner drug, or both drugs in the combination, poses a threat to the effectiveness of ACTs. Additionally, combination therapies, such as albendazole plus ivermectin and praziquantel plus ivermectin, are being explored for the treatment of helminth infections and are used in certain cases. The success of these combination therapies relies on the pharmacokinetic and pharmacodynamic compatibility of the drugs involved, as well as factors like cost and ease of administration (Rasmussen et al., 2022; Sulik et al., 2023).

5. Alternative and Complementary Strategies

5.1. Rational Drug Use and Dose Optimization

Artemisinin-based combination therapies (ACTs) are widely regarded as the global gold standard for treating uncomplicated malaria caused by Plasmodium falciparum. However, the long-term effectiveness of this approach is significantly threatened by the emergence and spread of parasite resistance, particularly to partner drugs associated with artemisinin derivatives. In some endemic areas, there is also growing resistance to artemisinins themselves, which jeopardizes the therapeutic lifespan of ACTs (Onita et al., 2025). Similarly, combination therapies are actively being researched and, in some cases, programmatically implemented for other important parasitic infections, such as helminthiases. For instance, albendazole and ivermectin are used for soil-transmitted helminths or lymphatic filariasis, while praziquantel and ivermectin are explored for conditions like schistosomiasis. The goal of these combination treatments is to broaden their effectiveness, improve treatment success, and slow down the development of resistance (Chai et al., 2021). The clinical and public health success of these combination regimens for both malaria and other parasitic infections relies heavily on the compatibility of the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the combined drugs. This means that the drugs should interact in a synergistic or at least additive manner, avoiding antagonism and ensuring adequate and simultaneous exposure to the drugs against the targeted parasite stages. Additionally, practical factors such as the overall cost of treatment, simplicity of administration protocols, and compatibility with existing health systems play a crucial role in the success of these therapies (Griffin et al., 2016).

5.2. Integration with Vector Control

Sustainable management and elimination of vector-borne diseases, such as Malaria, *Leishmaniasis*, and *Trypanosomiasis*, require a coordinated approach that combines chemotherapy with vector control strategies. The systematic implementation of measures like insecticide-treated bed nets (ITNs), indoor residual spraying (IRS), larval source management, and new vector intervention tools currently in development can significantly reduce the intensity of parasite transmission. This reduction is achieved by decreasing vector population density and lowering the rates of human-vector contact (or bite rates). In turn, this decline in transmission intensity can reduce the selection pressure for antiparasitic drug resistance, as it alleviates the need for antiparasitic drugs and thus lowers drug pressure at the population level. However, the effectiveness of vector control methods is increasingly undermined by the growing issue of insecticide resistance in target vector populations. This situation underscores the necessity for careful

implementation of integrated vector management (IVM) and insecticide resistance management (IRM) strategies (Kalitsilo et al., 2025; Tizifa et al., 2018).

5.3. Development and Use of Diagnostic Methods

To ensure the rational use of antiparasitic drugs and reduce the selection pressure for resistance, it is critical to have access to effective and reliable diagnostic tools. For instance, rapid diagnostic tests (RDTs), which have become widely used in malaria control, confirm true cases of infection and ensure that only those patients receive treatment. This approach helps avoid unnecessary drug exposure. Additionally, advancements in molecular diagnostic technologies enable the early and accurate detection of parasite strains with specific genetic markers associated with resistance. This capability allows for evidence-based adjustments to treatment regimens at both individual and population levels, preventing ineffective treatments and proactively managing the spread of resistant infections. Ultimately, this improves clinical outcomes and provides valuable data for strategies aimed at controlling resistance (Mortazavi et al., 2025).

5.4.Vaccine Development

The development of effective vaccines that offer protective immunity against parasitic diseases is a promising strategic goal. Achieving this could reduce long-term reliance on chemotherapeutic agents and lessen the selection pressure that leads to antiparasitic drug resistance. A significant advancement in this field is the RTS, S/AS01 vaccine, the first developed to combat Plasmodium falciparum malaria. This vaccine has undergone pilot applications. However, its partial protection and declining efficacy over time underscore the need for ongoing research and development of new-generation malaria vaccines that can provide greater immunogenicity and long-lasting protection. While vaccine development efforts are also underway for other major parasitic infections, such as schistosomiasis, leishmaniasis, and trypanosomiasis, these initiatives encounter significant challenges. These challenges stem from the biological characteristics of the parasites, including their complex life cycles, antigenic diversity, and advanced mechanisms that allow them to evade the host immune system (De Albuquerque Luna et al., 2020; Laurens, 2019).

5.5. Surveillance and Monitoring

Effective management of antiparasitic resistance requires the establishment and maintenance of robust surveillance systems. These systems are designed to systematically monitor the geographic spread, prevalence, and underlying molecular mechanisms of resistant phenotypes. The data collected from these systems is

essential for creating evidence-based treatment policies and control strategies at both national and international levels. In this context, it is crucial to conduct regular screening for molecular markers associated with resistance (genotypic surveillance) and to carry out periodic Therapeutic Effectiveness Studies (TES), which evaluate the clinical efficacy of drugs (phenotypic surveillance). Together, these approaches provide a comprehensive understanding of the resistance situation and guide intervention decisions (Oliveira et al., 2024; Uddin et al., 2021).

6. Challenges and Future Perspectives

Addressing antiparasitic resistance presents significant challenges. One major issue is the lack of sustainable funding for research and development (R&D), which impedes the creation of new drugs and tools, particularly for neglected tropical diseases. Additionally, the complexity of parasite biology and the variety of resistance mechanisms complicate the search for universal solutions. Socioeconomic factorssuch as poverty, weaknesses in health systems, and political instability further accelerate the spread of resistance and reduce the effectiveness of control programs (Rao et al., 2023).

In the future, successfully combating resistance will rely on interdisciplinary collaboration among various professionals, including parasitologists, molecular biologists, clinicians, epidemiologists, pharmacologists, social scientists, and health policymakers. A “One Health” approach is essential, as it acknowledges the interconnectedness of human health, animal health, and environmental health, while also considering how the use of antiparasitics in veterinary and agricultural medicine affects human health. “Omics” technologies, such as genomics, transcriptomics, and proteomics, will provide deeper insights into resistance mechanisms and help identify new targets for intervention. Additionally, artificial intelligence and machine learning are expected to play an increasingly significant role in drug discovery and in modeling the spread of resistance. It is crucial to evaluate and implement the effectiveness of resistance management strategies, such as drug rotation and mosaic practices (Elshobary et al., 2025; Smith et al., 2015).

7. Conclusion

Antiparasitic resistance is a significant and growing global threat that could reverse decades of progress in controlling parasitic diseases. It is crucial to understand the molecular basis of this resistance, monitor its spread epidemiologically, and develop comprehensive strategies to combat it. To effectively address this issue, a multifaceted approach is necessary. This includes discovering new drugs, utilizing existing medications rationally, implementing combination therapies, controlling vectors, improving diagnostics, developing

vaccines, and establishing strong surveillance systems. This challenge is not solely a scientific and technical issue; it also requires sustained financial support, political commitment, and global cooperation. Successfully combating antiparasitic resistance is essential to protect the health of millions of people and animals and to ensure global health security.

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Chapter 4

Parasites of Neglected Tropical Diseases (NTDs): Biology, Socioeconomic Impact, and Elimination Objectives

Abstract

Neglected Tropical Diseases (NTDs) are a group of infectious diseases that primarily affect billions of people around the world, especially in impoverished and marginalized communities. Many of these diseases are caused by parasites that have complex life cycles. This chapter gives an overview of the most prevalent of the parasitic NTDs, including *Schistosomiasis*, *Leishmaniasis*, Chagas Disease, and Human African *Trypanosomiasis* (Sleeping Sickness). It covers aspects of parasite biology, host-pathogen interactions, and the bidirectional linkage between these diseases and poverty." It also explored social determinants of health and the challenges and successes in reaching global elimination targets. Reducing the burden of NTDs is essential for achieving global health objectives, as well as for alleviating poverty and promoting sustainable development.

Keywords: Neglected Tropical Diseases, *Schistosomiasis*, *Leishmania*, Chagas Disease, Human African *Trypanosomiasis*, Poverty, Global Health

1. Introduction

There are about 20 infectious diseases that are considered NTDs by the World Health Organization (WHO). These diseases predominantly impact impoverished populations worldwide, especially in tropical and subtropical areas. NTDs are described as a "heterogeneous group" because they are highly diverse in their origin, routes of transmission, and clinical manifestations. The commonality among these diseases is that they are strongly correlated with socioeconomic conditions such as poverty, poor sanitation, lack of clean drinking water, and limited access to health care (CA et al., 2024). The term "neglected" refers to a group of diseases for several important and interconnected reasons. Mainly, these conditions are consistently overshadowed by more prominent diseases such as HIV/AIDS, tuberculosis, and malaria in terms of global health policy focus and funding. As a result, research and development (R&D) efforts aimed at finding new treatments, diagnostic tools, and vaccines for these diseases suffer from significant underfunding. This lack of investment is largely due to the economic reality that the populations most affected by these diseases typically have low purchasing power, which means they do not represent a commercially profitable market for pharmaceutical companies. Consequently, this reduces the financial incentives for innovation in this area (Aerts et al., 2017).

The causes of infectious tropical diseases (ITD) are notably diverse, encompassing microorganisms from various biological classes. This group includes a range of infections caused by viruses (such as dengue fever and rabies), bacteria (including leprosy, trachoma, and Buruli ulcer), and fungi (like mycetoma). This variety in causative agents necessitates distinct and specific strategies for the prevention, diagnosis, and treatment of each disease (Freile-Pelegrín et al., 2019).

Among the groups of pathogens involved in NTDs, parasites represent an important subgroup due to their endemicity and the large morbid burden they cause. This means parasitic diseases are a top priority. These pathogens can be broadly classified into two groups: Protozoa, unicellular eukaryotes that cause a range of debilitating human diseases such as Chagas disease, *leishmaniasis*, and human African *Trypanosomiasis* (sleeping sickness), and helminths, multicellular proteinaceous parasitic worms responsible for diseases such as *Schistosomiasis*, lymphatic filariasis, and soil-transmitted helminthiases.

A comprehensive understanding of the unique biological traits and epidemiological trends associated with these protozoan and helminthic infections is essential for addressing the complex public health challenges they present and for developing effective control and elimination strategies (R Haque, 2007; Kaminsky et al., 2025)

NTDs, especially those caused by parasites, have a significant negative impact on individuals and communities. These diseases typically do not present with immediate, severe symptoms. Instead, they gradually lead to chronic health issues and disabilities that can last for many years. As a result, NTDs contribute substantially to long-term illness and a decreased quality of life (Branda et al., 2025; Papagni et al., 2023).

This chapter examines four major parasitic neglected tropical diseases NTDs that pose a threat to billions of people worldwide and serve as a significant public health concern: *Schistosomiasis*, *Leishmaniasis*, Chagas Disease (*American Trypanosomiasis*), and *Human African Trypanosomiasis* (HAT or Sleeping Sickness). These diseases were selected due to their prevalence and the variety of parasite species they encompass (helminths and protozoa), as well as their different transmission routes (waterborne and vector-borne) and clinical manifestations.

This chapter aims to analyze the parasitological and biological aspects of these diseases, along with their socioeconomic implications. It will explore the complex life cycles of the parasites and their mechanisms of disease development. Additionally, the strong connection between these diseases and social determinants, such as poverty, inadequate sanitation, unsafe water sources, poor housing conditions, and lack of access to healthcare services, will be emphasized.

2. *Schistosomiasis* (Bilharziasis)

2.1. *Schistosoma* Life Cycle and Biological Characteristics

Schistosomiasis is a parasitic infection caused by blood flukes (trematodes) belonging to the genus Schistosoma, which is part of the class Trematoda. The primary species responsible for disease in humans are *Schistosoma haematobium*, which causes urinary schistosomiasis, and *Schistosoma mansoni* and *Schistosoma japonicum*, which lead to intestinal and hepatosplenic schistosomiasis, respectively.

The life cycle of these parasites is complex and involves two hosts. Specific freshwater snails serve as mandatory intermediate hosts, while humans, and in some cases other mammals, act as definitive (final) hosts. The process begins when the parasite eggs, released into freshwater through the feces or urine of infected definitive hosts, hatch under appropriate environmental conditions and release free-swimming ciliated larvae known as miracidia. Larvae of certain species actively infect specific snail intermediate hosts by following chemical signals. Inside the snail's tissues, the miracidia transform into sporocysts, which multiply significantly through asexual reproduction. Eventually, these sporocysts

develop into thousands of infectious larval forms called cercariae, which have forked tails. The cercariae are released from the snail into the water and can penetrate the skin of humans in contact with it. Once the Schistosomula (the larval form that enters through the skin) enters the bloodstream, it first migrates to the lungs and then travels to the intrahepatic portal vein branches of the liver via the systemic circulation, where it matures into adult male and female worms. The mature worm pairs reside in the lumen of either the mesenteric venules (for *S. mansoni* and *S. japonicum*) or the venous plexuses surrounding the bladder (for *S. haematobium*), depending on the species. Mated female worms continuously produce eggs throughout their lives. The pathogenesis of schistosomiasis is driven by an intense T-cell-mediated immunological response to these eggs. Because the eggs cannot be transported by the host's circulatory system, they become trapped in tissues such as the liver, intestinal wall, or bladder. This immune response leads to tissue damage, fibrosis, and chronic complications associated with the disease (Freile-Pelegrín et al., 2019; Kaminsky et al., 2025; Nelwan, 2019; Zaghloul et al., 2020) (Fig.1, Fig2)

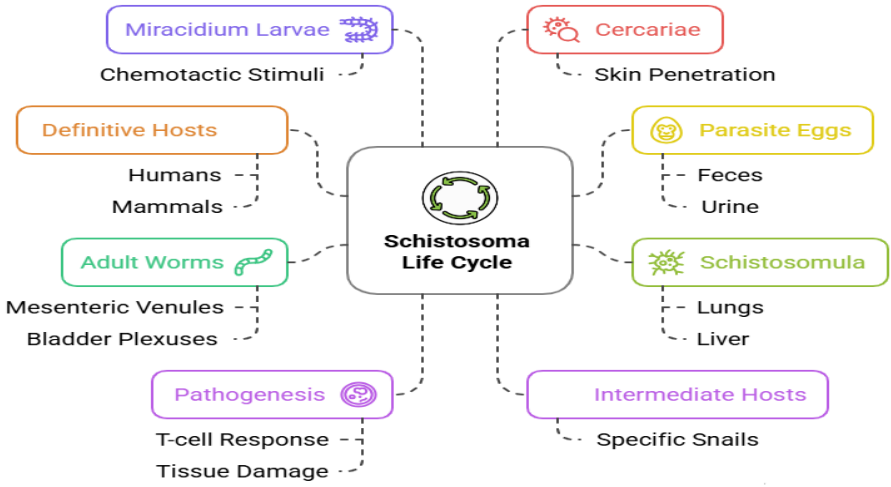

Figure 1: Life Cycle of Schistosoma Species

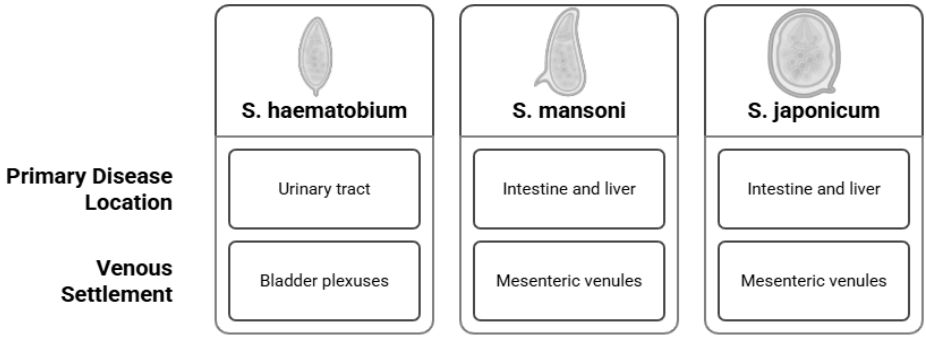

Figure 2: Schistosomiasis Comparison by Species

2.2. Socioeconomic Impact and Social Determinants

Schistosomiasis primarily affects rural and impoverished communities that lack access to safe drinking water and adequate sanitation. The main risk factor for transmission is contact with contaminated water during activities such as agriculture, fishing, and collecting water for domestic use. Chronic infection can result in anemia, stunted growth, and cognitive developmental disorders in children (Yamey et al., 2024). In adults, schistosomiasis can lead to organ damage, including liver fibrosis, portal hypertension, and an increased risk of bladder cancer. Additionally, it can reduce labor productivity and cause fertility issues. This disease perpetuates the cycle of poverty: poverty increases exposure to risk factors, while the health problems and economic losses associated with the disease further entrench poverty (Abdelghani et al., 2020).

2.3. Elimination Objectives and Challenges

The foundation of schistosomiasis control is mass drug treatment (MDT), which involves the periodic administration of praziquantel to at-risk populations. This primary strategy is complemented by additional interventions such as controlling snail populations, intermediate hosts of the parasite, improving the safe water supply, enhancing sanitation and hygiene (WASH) conditions, and providing community-based health education. The main goal of this comprehensive approach is to reduce morbidity by decreasing the burden of the disease and its associated complications. In the long term, the aim is to achieve the elimination of the disease by completely interrupting its transmission in areas where conditions are conducive to such efforts. However, these control and elimination initiatives face several significant challenges. Key obstacles include the financial and logistical sustainability of MDT programs, the potential development of drug resistance to praziquantel, and high reinfection rates,

particularly in regions with inadequate WASH conditions. Additionally, concerns regarding the environmental impact, cost-effectiveness, and sustainability of snail control methods, as well as the limited sensitivity of current diagnostic techniques, especially in detecting low-density infections, complicate efforts. Operational difficulties in effectively integrating all these various intervention components (MDT, WASH, snail control, and education) in the field further hinder progress towards achieving these targets (Chanhanga et al., 2023; Li et al., 2019).

3. *Leishmaniasis*

3.1. *Leishmania* Life Cycle and Biological Characteristics

Leishmaniasis refers to a group of complex vector-borne diseases caused by protozoan parasites belonging to the genus *Leishmania*, which is part of the family *Trypanosomatidae*. The transmission of these parasites occurs when infected female *Phlebotomine sandflies*, specifically from the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World, inject the infectious promastigote stage into a vertebrate host during their feeding process. The life cycle of the parasite is digenetic, meaning it alternates between development within the sandfly vector and a vertebrate host. This dual life cycle is essential for the parasite's propagation and the continuation of the disease (Costa-Da-silva et al., 2022). In the digestive system of the sandfly, the parasite multiplies in the form of extracellular, motile, and flagellated promastigotes. It then differentiates into infective metacyclic promastigotes. When the sandfly bites a mammalian host (such as humans or various reservoir animals), the parasite settles and multiplies within phagocytic cells, particularly in macrophages, transforming into intracellular, non-motile, and non-flagellated amastigotes. Clinically, *Leishmaniasis* can present a wide spectrum of symptoms depending on the infecting Leishmania species (over 20 pathogenic species exist) and the host's immunological response. The disease is classified into three main forms (Elmahallawy et al., 2021). Cutaneous leishmaniasis (CL) is the most common form and is characterized by localized papules, nodules, or ulcers on the skin. CL often heals spontaneously; however, it can leave scars or become a chronic condition. Mucocutaneous *Leishmaniasis* (MCL), caused primarily by species of the Viannia subgenus, particularly in the New World, can occur years after the initial skin lesion. It leads to severe, progressive, and destructive lesions in the nasopharyngeal and oral mucosa, resulting in deformities. Visceral leishmaniasis (VL), also known as "kala-azar," this form is mainly caused by *L. donovani* and *L. infantum* species. VL leads to a systemic infection, and if left untreated, it typically results in symptoms such as fever, weight loss, significant enlargement

of the liver and spleen (hepatosplenomegaly), decreased blood cell counts (pancytopenia), and elevated levels of antibodies (hypergammaglobulinemia). Without treatment, VL is usually fatal (Volpedo et al., 2021). The development, symptoms, and outlook of the disease can differ significantly based on the genetic and biological traits of the parasite, as well as the type and effectiveness of the host's immune response. This response can be either protective, driven by Th1 cells, or harmful, influenced by Th2 cells (Volpedo et al., 2021) (Fig3, Fig.4).

Characteristic	Cutaneous Leishmaniasis	Mucocutaneous Leishmaniasis	Visceral Leishmaniasis
Primary Location	Skin	Mucous membranes	Systemic
Severity	Mild to moderate	Severe	Severe
Common Species	Various	Viannia subgenus	L. donovani & L. infantum
Symptoms	Papules, nodules, ulcers	Nasopharyngeal lesions	Fever, weight loss, organ enlargement

Figure 3: Leishmania Forms Comparison

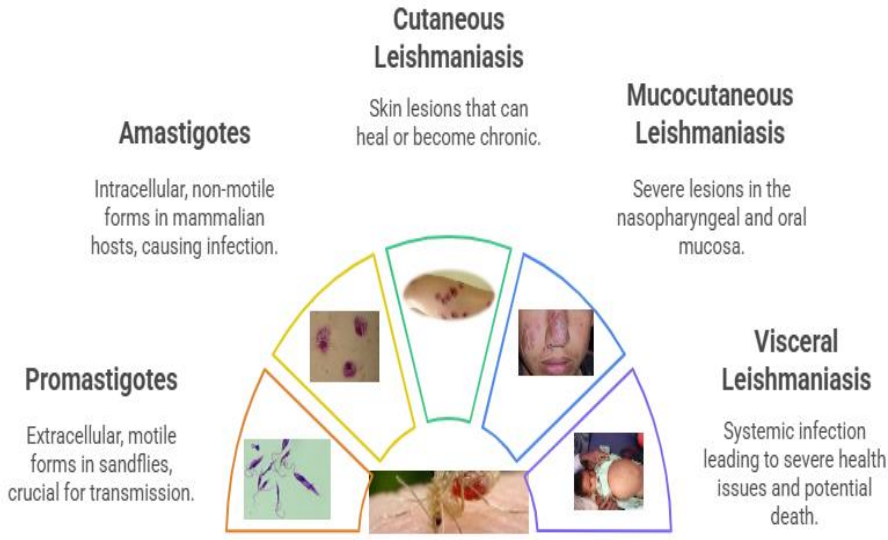

Figure 4: Life Cycle and Clinical Forms of Leishmaniasis

3.2. Socioeconomic Impact and Social Determinants

Leishmaniasis is often linked to several factors, including poverty, inadequate housing, which serves as a breeding ground for sandflies, malnutrition that weakens the immune system, deforestation, urbanization, and climate change. The cutaneous form of the disease can lead to disfiguring lesions that can result in social isolation and psychological issues. On the other hand, the visceral form is almost always fatal if left untreated, posing a significant threat to children and individuals co-infected with HIV. Treatment for leishmaniasis can be lengthy, costly, and toxic, creating a substantial economic burden for poor families (Monge-Maillo et al., 2025; Gómez-Bravo et al., 2024).

3.3. Elimination Objectives and Challenges

The elimination of Visceral *Leishmaniasis* in South Asia, aiming to reduce its incidence below a specific threshold, is a crucial global objective, and notable progress has been achieved in this endeavor(Rijal et al., 2019). Control strategies include early diagnosis and rapid treatment, vector control (insecticide-treated bed nets, environmental spraying), reservoir host control (e.g., dogs), and social mobilization. Challenges include the emergence of drug-resistant Leishmania strains, lack of effective and safe vaccines, limitations of diagnostic testing (especially in field conditions), sustainability of vector control, disruption of control programs in conflict and instability zones, and management of complications such as Post-Kala-Azar Dermal *Leishmaniasis* (PKDL) (Bamorovat et al., 2024).

4. Chagas Disease (American Trypanosomiasis)

4.1. Trypanosoma Life Cycle and Biological Characteristics

Chagas disease, also known as *American trypanosomiasis*, is a potentially life-threatening zoonosis caused by the protozoan parasite *T. cruzi*, which is transmitted by a vector (Gómez-Bravo et al., 2024). The main way this disease is transmitted is through contamination with the feces of blood-sucking insects from the Triatominae subfamily (*Hemiptera: Reduviidae*), commonly referred to as "kissing bugs" or "*vinchuca*" (Beatty et al., 2020). Transmission of *T. cruzi*, the etiologic agent of Chagas disease, is mainly via a vector (via an insect, usually a triatomine bug, which, after the blood meal from an infected mammalian host, including humans and animal reservoirs, defecates in the wound) Following a meal, the insect usually defecates during or right after the blood feast. The feces contain infective metacyclic trypomastigotes that gain entrance via the bite wound, cutaneous lesions, or microlesions of the skin or adjacent mucosal surfaces, including the conjunctiva. The host often brings this about by scratching

or rubbing the area. Besides this main vectorial route of infection, *T. cruzi* can also enter the human body through multiple non-vectorial pathways. This happens through transfusion of contaminated blood or blood products, organ transplantation from infected donors, or oral ingestion of raw or undercooked food and beverages (ex, acai or sugarcane juice) that harbor the parasite. In addition, the parasite can infect the fetus via transplacental passage, giving rise to congenital Chagas disease (Schaub, 2024).

After entering the host, parasites in the trypomastigote form circulate freely in the blood and actively invade various nucleated cells, primarily targeting cardiac muscle cells (cardiomyocytes), smooth muscle cells, and cells in the central and peripheral nervous systems (neurons and glial cells). Within the cytoplasm of these cells, the parasites transform into a non-flagellate, replicative amastigote form, where they multiply rapidly by binary fission. This process eventually fills the host cell, causing it to rupture. The parasites then redifferentiate back into the trypomastigote form and are released into the bloodstream. This release allows the parasites to infect new cells or continue their life cycle by being taken up by a blood-sucking triatomine vector. This cyclical process underpins the pathogenesis of both the acute and chronic phases of the disease (Useche et al., 2022) (Fig.5).

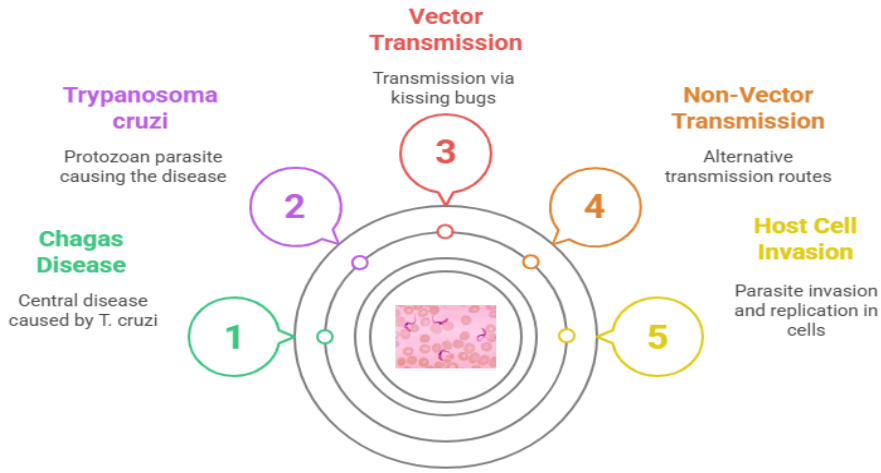

Figure 5: Chagas Disease: Agent, Modes of Transmission and Cell Invasion

4.2. Socioeconomic Impact and Social Determinants

Chagas disease is primarily found in rural and impoverished communities across Latin America. Poor-quality housing, characterized by adobe walls and thatched roofs with cracks that provide hiding spots for the triatomine bug (the

vector that transmits the disease), creates an ideal environment for infection. Chagas disease progresses through two phases: an acute phase that is often asymptomatic and a chronic phase that can develop after several years. The chronic phase may lead to serious complications, including heart failure, arrhythmias, megaesophagus (enlargement of the esophagus), and megacolon. These long-term effects can impair patients' ability to work, place a significant burden on healthcare systems, and reduce life expectancy. Additionally, due to migration, Chagas disease has emerged as a public health concern in non-Latin American countries, including the USA, various European nations, and Japan (Melo et al., 2020).

4.3. Elimination Objectives and Challenges

The primary goals are to interrupt both vector-borne and transfusion-related transmission, as well as to reduce congenital transmission. Strategies to achieve these include vector control measures such as household spraying and improving housing conditions. Screening in blood banks; testing pregnant women; treating infected newborns, and managing chronic phase patients (particularly children and young adults) with antiparasitic therapy. However, there are challenges to these efforts. These include the limited effectiveness of treatments for chronic phase disease, potential side effects of medications, maintaining sustainable vector control (especially due to the risk of reinfestation from the sylvatic cycle), the adaptation of vectors to urban environments, the need for standardized and accessible diagnostic tests, a lack of awareness caused by the disease's silent nature, and difficulties in integrating these strategies into health systems (da Gama et al., 2025; Hernández-Flores et al., 2025).

5. Human African Trypanosomiasis (HAT or Sleeping Sickness)

5.1. Biology and Life Cycle

Human African *Trypanosomiasis* (HAT), commonly known as Sleeping Sickness, is a complex parasitic infection caused by different subspecies of the protozoan T. brucei. It is transmitted by the tsetse fly (genus *Glossina*) and can be fatal if left untreated. The disease presents in two distinct forms. The *T. b. gambiense* form, which accounts for over 90% of cases, is primarily found in West and Central Africa and is characterized by a chronic, slow progression. The *T. b. rhodesiense* form occurs in East and Southern Africa and presents as an acute, rapidly progressing zoonotic disease, with various wild and domestic animals serving as the main reservoir hosts (Rock et al., 2015). The transmission cycle of the infection starts when a night fly, after feeding on the blood of an infected mammalian host (which can be either a human or an animal), acquires

the bloodstream trypomastigote forms of the parasite. The parasite then undergoes a complex developmental process and multiplies in the fly's digestive tract and salivary glands, transforming into the infectious metacyclic trypomastigote form. When an infected fly bites a healthy human, it injects these infectious forms into the skin along with its saliva (Papagni et al., 2023). In humans, the disease generally has two stages. The first stage is the early hemolymphatic stage. In this phase, the parasites are in the blood, lymph fluid, and lymph nodes. Symptoms include fever, headache, arthralgia, and marked lymphadenopathy, particularly in the posterior cervical region (Winterbottom's sign). The late stage, referred to as the meningoencephalitic stage, is the second stage. The parasites make their way into the blood-brain barrier and central nervous system (CNS) in this phase. This can cause sleep disturbances, including sleepiness during the day (and excessive at night), confusion, behavioral changes, disturbances of the senses, and motor coordination disturbances like ataxia. Severe neurological and psychiatric symptoms can develop, ending in coma and death if untreated (Buguet et al., 2014). Tablo 1.

Table 1: Basic Features of Human African Trypanosomiasis (HAT)

Features	Information
Disease	Human African Trypanosomiasis (HAT) / Sleeping Sickness
Agent	*Trypanosoma brucei* subspecies
Vector	Tsetse fly (*Glossina*)
Transmission	Tsetse fly bite
Outcome	Generally fatal if untreated
Forms	*Trypanosoma brucei gambiense* : West/Central Africa, >90% cases, chronic. *Trypanosoma brucei rhodesiense*: E/S Africa, acute, zoonotic.
Stages	Stage 1 (Hemolymphatic): Blood/lymph; fever, lymphadenopathy. Stage 2 (Meningoencephalitic): CNS invasion; neurological symptoms (incl. sleep disturbance), lethal.

5.2. Socioeconomic Impact and Social Determinants

HAT affects communities involved in agriculture, fishing, and animal husbandry, particularly in the most remote and impoverished rural areas of Sub-Saharan Africa. This disease leads to significant economic losses at both the individual and societal levels. Individuals may experience a loss of labor and incur treatment costs, while communities face reduced agricultural production and limitations in animal husbandry due to animal trypanosomiasis. Additionally, conflict, instability, and displacement can disrupt control programs, increasing the likelihood of disease outbreaks (Kikwai et al., 2022).

5.3. Elimination Objectives and Challenges

Eliminating HAT as a public health issue, specifically to stop its transmission, is a global target (Ortiz-Martínez et al., 2023). In recent years, significant progress has been made toward achieving this goal, with case numbers dropping to historically low levels. The strategies implemented include both active and passive case screening, early diagnosis and treatment, and control measures targeting the tsetse fly vector. Innovations such as simpler diagnostic tests and safer, single-dose oral therapy with fexinidazole, especially for *T. b. gambiense*, have bolstered elimination efforts (Mulenga et al., 2019). Challenges include the remoteness and accessibility of disease-infected areas, the sustainability of surveillance systems (interest and resources may decline as cases decrease), the zoonotic nature of *T. b. rhodesiense* (which requires control of animal reservoirs), potential drug resistance, and the continuity of surveillance after elimination (Jamabo et al., 2023).

6. Socioeconomic Impact and the Poverty Cycle

Parasitic NTDs represent a significant obstacle to development due to their high rates of morbidity and mortality, as well as the lasting socioeconomic damage they inflict, particularly in low-income communities. A vicious cycle exists between these diseases and poverty, as they reinforce and exacerbate one another. Poverty-related factors, such as inadequate sanitation, lack of access to clean water, substandard housing that increases exposure to disease vectors, malnutrition, and limited access to healthcare services, make individuals more susceptible to parasitic infections. Conditions like soil-transmitted helminthiases, schistosomiasis, lymphatic filariasis, Chagas disease, and leishmaniasis notably increase the risk of infection in these vulnerable populations (Branda et al., 2025). While poverty creates an environment conducive to the spread of NTDs, these diseases also contribute to the ongoing cycle of poverty.

Chronic diseases caused by parasitic infections, such as anemia, malnutrition, cognitive developmental delays (especially in children), blindness, physical deformities, and disabilities, significantly contribute to deepening poverty through various interconnected mechanisms. First, infected individuals often experience reduced labor capacity and overall productivity, resulting in significant income losses, especially among populations reliant on agriculture or physical labor. Second, frequent occurrences of NTDs in childhood lead to decreased school attendance and impaired learning abilities, limiting long-term educational attainment and economic potential. Third, the costs associated with diagnostics, treatment, and rehabilitation create financial strain on already limited household and national budgets, potentially pushing families further into poverty

due to catastrophic health expenditures. Additionally, visible physical deformities resulting from diseases like lymphatic filariasis or cutaneous leishmaniasis can lead to social stigma, preventing affected individuals from fully participating in social and economic life. Finally, the ongoing burden of these diseases on health systems in endemic regions drains scarce resources, disrupting other essential health services and development-oriented investments. This, in turn, reinforces the cycle of poverty, perpetuating it across generations (Branda et al., 2025; Ocholaid et al., 2021).

6.1. Healthcare Expenditures

The financial costs associated with the diagnosis and treatment of parasitic NTDs can create a significant and often unsustainable economic burden on resource-poor households, especially when infections are chronic or recurrent. These costs encompass both direct expenses, such as those for diagnostic methods (e.g., microscopy, serology, molecular testing) and medications, as well as indirect costs, including transportation to health centers and lost wages during treatment. Such financial demands place significant strain on the already limited budgets of low-income families. Often, these costs escalate to the point of "catastrophic health expenditure," as defined by the World Health Organization, forcing families to forgo other necessities like food and education. This situation not only deepens their existing poverty but also hinders their ability to escape the cycle of poverty (Branda et al., 2025; Lee et al., 2015).

6.2. Workforce Loss and Productivity Decrease

Chronic health issues caused by parasitic NTDs have a significant negative impact on individuals' economic productivity and potential for development. Conditions such as schistosomiasis and Chagas disease can lead to persistent pain, widespread anemia, and progressive damage to vital organs, including the liver, spleen, heart, and bladder. Furthermore, diseases like lymphatic *Filariasis* and *Onchocerciasis* can result in permanent disabilities, while certain helminth infections are linked to cognitive developmental disorders. These health issues severely restrict adults' ability to work consistently and earn an income. For especially vulnerable children, these conditions can interfere with school attendance, impair concentration, and disrupt the learning process. As a consequence, many children fall behind in their education, which ultimately lowers their long-term educational attainment. This diminished education affects their future earning potential and overall socioeconomic status. (Chaparro et al., 2019).

6.3. Stigma and Social Exclusion

Some parasitic NTDs can lead to physical disfigurement, particularly through persistent and visible skin lesions caused by cutaneous Leishmaniasis or marked limb swelling, known as lymphedema or elephantiasis, resulting from advanced lymphatic filariasis. These physical changes often lead to severe social stigma and isolation for those affected, preventing them from fully participating in social life. This isolation significantly hinders their access to basic life opportunities, such as marriage and stable employment (McCollum et al., 2024).

6.4. Agricultural and Animal Production Losses

The economic impacts of Parasitic NTDs extend beyond direct effects on human health. They also undermine basic livelihoods. For instance, HAT and its associated animal disease, *Trypanosomiasis* (nagana), severely affect the livestock sector by decreasing animal populations and reducing meat, milk, and labor yields. Similarly, diseases like *Schistosomiasis*, which are common among agricultural workers engaged in water-based activities, significantly diminish agricultural productivity by impairing the physical capabilities of individuals. When we consider these various socioeconomic effects together, it becomes evident that parasitic NTDs contribute to the cycle of intergenerational poverty. They trap individuals, families, and communities in a "poverty trap" characterized by poor health, low educational attainment, reduced productivity, and increased healthcare costs. Therefore, addressing these diseases comprehensively is not only a critical public health intervention but also an essential development strategy for achieving sustainable development goals (Branda et al., 2025; Ocholaid et al., 2021).

7. The Main Strategies Used

7.1. Preventive Chemotherapy (Mass Drug Therapy- KIT)

Preventive chemotherapy (PC), or mass drug administration (MDA), is an important public health intervention used to control and eliminate specific NTDs, most notably *Schistosomiasis*, Lymphatic *Filariasis* (LF), Soil-Transmitted Helminthiases (STH), and bacterial Trachoma. This population-based treatment approach entails delivering deworming treatment systematically to all individuals, or targeted sub-groups (for example, school-age children for soil-transmitted helminths and *Schistosomiasis*), living in at-risk areas. The intervention consists of specific antiparasitic or antibiotic drugs, designed to be safe, effective, and provided in single doses given in repeated intervals (usually annual), regardless of individual infection status. The underlying aim of this strategy is to prevent disease burden by lowering the population-wide parasite or

bacterial burden. It also seeks to contribute to the end of these diseases in the long run by interrupting transmission (Hoefle-Bénard et al., 2024).

7.2. Intensive Disease Management

Intensified disease management (IDM) is defined as a key approach to control NTDs, particularly those for which Mass Drug Distribution (MDA) is not appropriate or sufficient. This strategy focuses on the detection and treatment of individual cases to reduce disease transmission and manage morbidity. The key components of IDM include both passive case finding, where patients present with symptoms to health care facilities, and active screening by health care teams in at-risk communities to detect asymptomatic or early-stage cases. Detected cases must be diagnosed early using reliable diagnostic methods to prevent disease progression and potential complications. Once diagnosed, prompt and appropriate treatment protocols with effective drugs must be initiated to halt the course of the disease, reduce mortality and break the chain of transmission; This approach is particularly applicable to NTDs, that require complex diagnostic and therapeutic processes or where individual case management is essential for disease control, such as HAT various forms of *Leishmaniasis* and Chagas disease (Mitjà et al., 2017).

7.3. Vector Control

Vector control consists of strategies aimed at reducing the population of arthropod vectors or minimizing human exposure to them, as these vectors are crucial in the transmission of parasitic NTDs. The interventions employed in vector control encompass: 1. Spraying insecticides that effectively target specific vectors, either indoors or outdoors (known as residual spraying). 2. Using insecticide-impregnated bed nets to protect sleep. 3. Setting up various types of traps and bait stations designed to attract, capture, or kill vectors. 4. Implementing environmental management strategies to eliminate or modify areas where vectors breed, rest, or seek shelter, such as water bodies, cracks in buildings, and certain types of vegetation (Shaw et al., 2019).

7.4. Safe Water, Sanitation and Hygiene (WASH)

Improving water, sanitation, and hygiene (WASH) conditions is a crucial strategy for preventing the spread of parasitic NTDs, particularly waterborne diseases such as schistosomiasis and soil-borne diseases like soil-transmitted helminthiases (STH). Ensuring continuous access to safe drinking water, establishing appropriate sanitation facilities for the hygienic disposal of human and animal feces, and promoting basic hygiene practices, such as handwashing,

can significantly reduce the burden of these diseases. This is achieved by interrupting the life cycle of parasites and minimizing human exposure to their infectious forms. However, effective implementation and sustainability of these comprehensive infrastructure and behavior change initiatives cannot be accomplished by the health sector alone. Therefore, an intersectoral approach is essential, requiring strong collaboration and coordination among various public and private organizations, including those in health, water and sanitation, education, environment, and local governments. This integrated approach not only complements other control strategies but also addresses the key environmental and socioeconomic factors that contribute to these diseases. It is vital for achieving long-term, sustainable control and elimination goals (Campbell et al., 2018).

7.5. Veterinary Public Health

Effective management of animal reservoirs is crucial for controlling zoonotic NDDs, particularly those where these reservoirs play a significant role in maintaining infection and transmitting diseases to humans. This is particularly important for diseases such as acute human African *Trypanosomiasis*, caused by *T brucei rhodesiense*, where both wild and domestic animals serve as primary reservoirs. Another example is some forms of leishmaniasis, such as visceral leishmaniasis, for which dogs are significant reservoirs of *L. infantum*. Management strategies for animal reservoirs may involve detecting and treating infected animals (when feasible), controlling or reducing reservoir populations (like rodent control), implementing measures to minimize contact between animals and vectors or humans (such as using insecticidal collars on dogs), and conducting surveillance activities to monitor the prevalence and distribution of the parasite in animal populations. These interventions are essential components of the "One Health" approach, which integrates human, animal, and environmental health, and they complement other strategies for the sustainable control and elimination of zoonotic infectious diseases (Crump et al., 2022; Matovu et al., 2020).

8. Achievements

International collaboration, raising funds, and the combination of controlling strategies have led to tremendous success in the worldwide fight against NTDs since the turn of the millennium. Among the best examples is the *Dracunculiasis* (Guinea Worm) eradication program, now on the brink of complete eradication thanks to intensified surveillance, effective case management, and efforts to provide safe water. Likewise, with MDA programs and other complementary

interventions, *Lymphatic Filariasis* (Elephantiasis) and Onchocerciasis (River Blindness) have been eliminated as public health problems in most endemic countries. There has been a >90% reduction in cases of HAT due to increased case detection, diagnosis, effective treatment, and vector control measures. The SAFE strategy (operating field, antibiotics, highly hygienic face, area improvement) has greatly reduced the population vulnerable to blindness due to trachoma. *Visceral Leishmaniasis* (Kala-azar) elimination targets in the South Asian region are being addressed using integrated vector management, rapid diagnostic tests, and effective drug regimens. These successes have shown that sustained and multi-faceted work on NTDs works, and that such diseases can be controlled and even eliminated (Rumunu JP., 2008).

9. Challenges

There are still significant and multifaceted obstacles to fully achieving the goals of control and elimination for NTDs. Among these challenges, chronic underfunding is a major issue, as it is critical for sustaining NTD programs. This emphasizes the urgent need for long-term and predictable financial resources (Weng et al., 2020). Additionally, the limitations of current therapeutic and diagnostic tools present a significant barrier. For many NTDs, there is a notable lack of more effective, safer, and easy-to-administer drugs, as well as sensitive, rapid, and field-compatible diagnostic tests that can detect infection at an early stage or with low parasite loads. Ideally, preventive vaccines are also needed. Moreover, the increasing development of drug resistance poses a threat to progress in this area (Yamin et al., 2023). In many endemic countries, existing health systems are weak due to inadequate infrastructure, insufficient human resources, and logistical challenges. These issues hinder the effective implementation of surveillance, case management, treatment distribution, and control measures, making it difficult to successfully integrate these interventions into primary health care platforms (Branda et al., 2025; Gyapong et al., 2010). Moreover, the concentration of NTDs in geographically remote, hard-to-reach, and socioeconomically disadvantaged areas, alongside factors like ongoing conflict, political instability, or mass migration, can significantly disrupt access to health services and control programs (Kelly-Hope et al., 2021; Ocholaid et al., 2021). Inadequate coordination and cooperation among sectors like Water, Sanitation, and Hygiene (WASH), education, and agriculture, which are essential for disease prevention, undermine comprehensive interventions that address the main factors contributing to diseases (Bose et al., 2024). The potential for climate change to impact the epidemiology and transmission patterns of diseases presents new and complex challenges for future control strategies. This impact can occur

in unpredictable ways by affecting the geographic distribution, population dynamics, and life cycles of vectors (such as flies and beetles) and intermediate hosts (like snails) (Cable et al., 2017). As disease incidence and prevalence decrease due to successful control programs, it becomes more challenging and expensive to maintain the necessary focus, technical expertise, and funding required for effective surveillance systems. This is essential to detect any remaining low-level transmission and to prevent a resurgence of the disease during the post-elimination phase (Baker et al., 2010; Branda et al., 2025).

10. Conclusion and Future Perspectives

NTDs persist as critical focal points within global health and development frameworks, attributable to their intricate biological characteristics, epidemiological association with poverty, and the substantial morbidity they inflict. Exemplified by conditions such as *Schistosomiasis, Leishmaniasis*, Chagas Disease, and HAT , these infections highlight both the profound challenges and the pressing necessity associated with their control and elimination. Addressing this requires not only augmented investment in research and development (R&D) to generate novel and improved tools, including enhanced diagnostics, therapeutics, and vaccines, but also the optimized implementation and deployment of existing strategies, such as effective drug administration and vector control measures.

Future success depends on sustained political will and financial commitment, integrated and multi-sectoral approaches that include non-health sectors (WASH, education, agriculture), strengthening of health systems by integrating NTDs control into primary care, sustained and focused research, and active participation of affected communities in all processes. These multi-faceted efforts will not only improve the health and quality of life of millions of people but will also make significant contributions to breaking the cycle of poverty, achieving global health equity, and achieving the Sustainable Development Goals (SDGs). Ending the neglect of ITHs is therefore a global responsibility**.**

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Chapter 5

Host-Parasite-Microbiota Interactions: The Triangle of Health and Disease

Abstract

The traditional understanding of host-pathogen interactions is evolving with the recognition of the crucial role that resident microbial communities, particularly the gut microbiota, play during infections. This chapter examines the complex interactions among the host, parasites, and microbiota. We discuss how microbiota can provide protection and prevent colonization through various mechanisms, including competition for resources and the production of inhibitory metabolites. They also play a role in modulating the host immune system, influencing factors such as barrier integrity, antimicrobial peptide production, immunoglobulin A (IgA) levels, and the balance of T-helper cells. Additionally, we explore how parasites can directly or indirectly alter the microbiota. This alteration can occur through niche modification or the consumption/inhibition of bacteria, often leading to a state of dysbiosis. These intricate interactions have significant implications for susceptibility to parasitic infections, disease severity, the risk of co-infections, chronic inflammation, and responses to treatment. A better understanding of this "Triangle of Health and Disease" enhances our insight into the pathogenesis of parasitic diseases and opens up new possibilities for microbiota-targeted therapeutic strategies, such as probiotics, prebiotics, or fecal microbiota transplantation.

Anahtar Kelimeler: Konak-Parazit Etkileşimleri, Mikrobiyota, İmmünomodülasyon Kolonizasyon Direnci, Disbiyozis

1. Introduction

Traditional approaches to studying infectious diseases have primarily concentrated on the binary interactions between host and pathogen. Although this method has resulted in substantial progress in uncovering the mechanisms of disease development and the fundamental dynamics of immune responses, recent findings, especially over the past two decades, have shown that this perspective is incomplete. It fails to capture the much more complex biological reality of these interactions (Lu et al., 2025). Recent advancements in high-throughput sequencing technologies and bioinformatics analyses have shown that host organisms are composed not only of their cells but also of complex ecological communities known as microbiota. These communities consist of trillions of microorganisms, including bacteria, archaea, viruses, fungi, and protists, that have co-evolved with their hosts. While microbial communities inhabit various areas of the body, such as the skin, mouth, respiratory tract, and urogenital system, the gut microbiota is particularly significant. It functions almost like a central organ, exerting profound systemic effects on host physiology, metabolism, nutrition, and the development and functioning of the immune system. This is largely due to its vast numerical density, approximately 10^{14} microorganisms and its genetic diversity, which surpasses that of the human genome by more than 100 times (Aggarwal et al., 2023).

The fundamental approaches in infection biology and immunology are currently undergoing a significant transformation. It is now recognized that the outcome of an infection is influenced not only by direct interactions between the host and the pathogen, but also by the microbial ecosystem surrounding these interactions. This new understanding is leading to a major shift in the field of parasitology. While parasitic infections caused by eukaryotic pathogens such as protozoa and helminths remain a considerable burden on global public health, there is growing scientific evidence that the course and severity (pathogenesis) of these infections, as well as the host's immune responses, can be significantly influenced by the resident microbiota of the host (Carlsson et al., 2024; McCoy et al., 2024).

This chapter explores the complex and dynamic interactions among the host, parasite, and microbiota. It emphasizes that these relationships are bidirectional, with each component actively influencing the others.

2. The Role of Microbiota in Defense Against Parasitic Infections

The gut microbiota acts as an essential barrier against parasites due to its high compositional density and taxonomic diversity (Fang et al., 2024).

2.1. Colonization Resistance (Competition and Exclusion)

The host microbiota, especially the resident commensal bacteria found in the gut, play a crucial role in defending against parasitic infections through a mechanism known as “colonization resistance.” This resistance is achieved in two main ways: first, by the direct competition between beneficial bacteria and pathogenic parasites for limited nutrients and attachment sites on the intestinal surface; and second, by the production of substances by these commensal bacteria that are harmful to the parasites or inhibit their growth. These protective substances include various metabolites, such as short-chain fatty acids (SCFAs), like butyrate, bacteriocins, and hydrogen sulfide (H_2S). For instance, secondary bile acids produced by certain Clostridium species have been shown to suppress the active (trophozoite) form of the intestinal protozoan Entamoeba histolytica, highlighting the importance of gut microbiota in parasite resistance (Kamel et al., 2024; Soylu et al., 2025).

2.2. Modulation of the Immune System

The microbiota plays a vital role in regulating the development and function of both the innate and adaptive immune systems in the host. A healthy microbial composition maintains immune balance by preserving the integrity of the intestinal epithelial barrier, stimulating the production of antimicrobial peptides such as defensins and REG3γ, and aiding in the maturation of mucosal IgA responses. Moreover, the microbiota can influence the nature of specific host immune responses to parasitic infections by affecting the differentiation and balance of T helper (Th) cell subsets (e.g., Th1, Th2, Th17, Treg). For instance, certain commensal bacterial species or their metabolites can enhance Th1 responses, which are effective against protozoan parasites, while also regulating Th2 responses that are crucial in helminth infections. Therefore, disruptions in microbial composition, known as dysbiosis, can disturb this delicate immunological balance, increasing the host's susceptibility to parasitic infections (Grondin et al., 2024) Fig.1

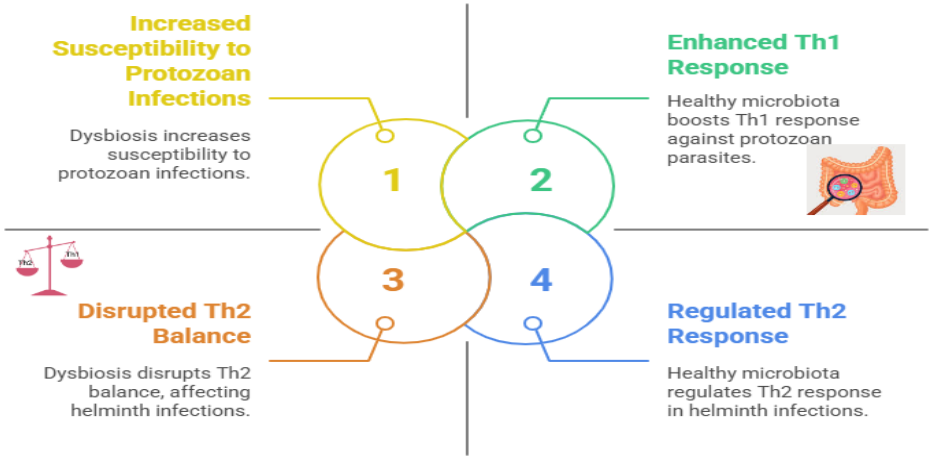

Figure 1: Microbiota's Influence on Immune Responses

2.3. Direct Antiparasitic Effects

Some members of the microbiota or their products may directly kill or inhibit the growth of parasites. For example, there is both in vitro and in vivo evidence that certain lactobacilli reduce the proliferation and virulence of *Giardia intestinalis* (Al-Rashidi et al., 2024).

3. Effects of Parasites on Host Microbiota

Microbiota and parasites reciprocally interact with each other; they co-evolve over time. Additionally, parasites can actively influence the composition and metabolic functions of their host's microbiome. Conversely, the changes induced by parasites in the host microbiota can significantly affect the progression of the infection, the host's immune status, the severity of the disease, and potentially the risk of chronic conditions (Mezouar et al., 2018).

3.1. Direct Interactions and Environmental Modification

Intestinal parasites can significantly alter the composition of the microbiome by changing the local environment in which they reside. They may damage the mucosal layer or increase mucus production, leading to conditions that might be unfavorable for some bacterial species while promoting the growth of others. Additionally, parasites can directly consume commensal bacteria as a nutrient source or actively influence microbial balance by secreting specific molecules that either inhibit or stimulate bacterial growth. For example, infection with *Giardia* has been shown to cause considerable dysbiosis in the intestinal

microbiota, particularly resulting in a marked decrease in anaerobic bacterial populations (Grondin et al., 2024).

3.2. Indirect Effects Through Manipulation of the Immune Response

Parasites frequently influence the immune response of the host to endure. Many helminth infections, for example, lead to a strong Type 2 immune response that induces the activation of Th2 cells as well as the production of cytokines, including IL-4, IL-5, IL-13, and Immunoglobulin E (IgE). It is also known that regulatory T cells (Tregs) are activated in this immune environment, and Tregs indirectly regulate the composition of host microbiota. Type 2 cytokines can enhance the expansion of some bacterial populations (e.g., Clostridiales) while inhibiting others through modulation of epithelial cell function and mucus production. This suggests that immune modulation mediated by parasites can indirectly target the microbiota and may influence dysbiosis (Al-Rashidi et al., 2024; Grondin et al., 2024) Fig2.

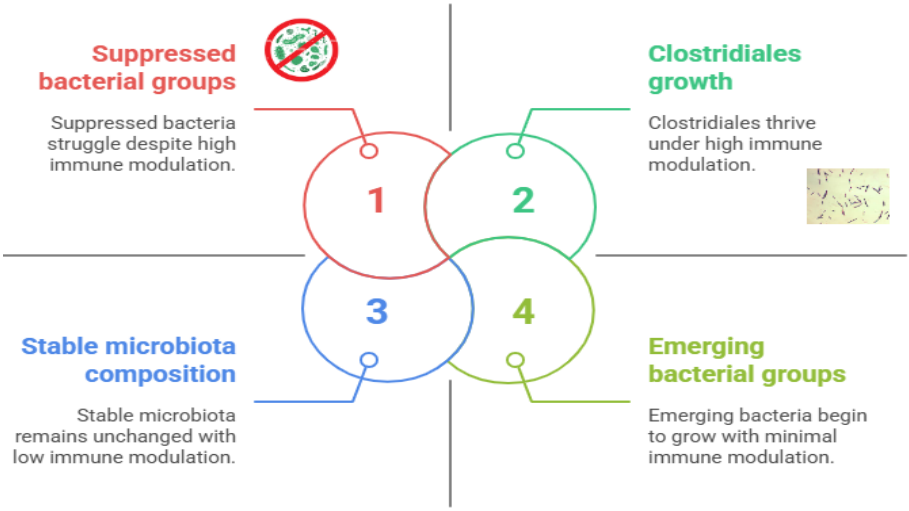

Figure 2: Parasite-Induced Immune Modulation and Microbiota Composition

3.3. Metabolic Changes

Parasitic infections can greatly impact the metabolic activities of both the host and its associated microbial community. For instance, when a parasite directly consumes nutrients or when an infection leads to malabsorption by the host, it can change the composition and availability of nutrient substrates within the intestinal lumen. These changes directly influence microbial metabolic pathways,

ultimately resulting in a remodeling of the microbiota's composition and structure (Grondin et al., 2024; Klimczak et al., 2024).

4. Results of the Triple Interaction: Balance of Health and Disease

The complex interactions among the host, parasite, and microbiota play a crucial role in determining the pathogenesis, severity, and outcome of infections. This interconnected network significantly influences the course of disease by affecting various biological processes, including the modulation of immune responses and changes in metabolism (Grondin et al., 2024; Pandiyan et al., 2019).

4.1. Infection Susceptibility and Severity

The initial state of the host's microbiota, its taxonomic composition and diversity, plays a crucial role in determining how susceptible or resistant the host is to parasitic infections. A dysbiotic microbial profile can increase the host's vulnerability to infection, potentially due to reduced colonization resistance and impaired immune responses. Additionally, during the later stages of infection, the parasite may further disrupt the microbiota composition, which can worsen pathological processes, increase disease severity, and increase the likelihood of chronic infection (Alloo et al., 2022).

4.2. Co-infections and Secondary Complications

Changes in microbiota and immune modulation resulting from parasite infections can increase the host's susceptibility to other pathogens, such as bacteria and viruses, or may lead to opportunistic infections. For instance, it is well established that the Type 2 immune response triggered by helminth infections can suppress Type 1 responses, which are crucial for protection against certain bacterial infections (Allen et al., 2014; Al-Rashidi et al., 2024).

4.3. Chronic Inflammation and Long-Term Effects

Chronic immune activation and dysbiosis resulting from interactions between parasites and the microbiota have the potential to influence not only the acute progression of infections but also long-term health outcomes. Research is actively exploring their possible connections to the development of chronic conditions such as inflammatory bowel disease (IBD), metabolic syndrome, and autoimmune diseases. In this context, the immunomodulatory functions of helminths and their ability to modulate the microbiota, as examined within the framework of the "Hygiene Hypothesis," emerge as a promising therapeutic

strategy for preventing or treating these chronic inflammatory diseases (Garcia-Bonete et al., 2023; Ianiro et al., 2022).

4.4. Treatment Responses

The composition of the host microbiota can influence the effectiveness and metabolic profiles of administered antiparasitic drugs. Conversely, antiparasitic treatment regimens, especially those combined with broad-spectrum antibiotics, may disrupt the microbial balance, leading to dysbiosis. This disruption can delay recovery after treatment and increase the risk of recurrent infections (Dahiya et al., 2023).

5. Therapeutic Perspectives and Future Directions

Understanding the intricate interactions among the host, parasite, and microbiota is essential for the thoughtful design and development of new targeted therapeutic strategies. This knowledge will enhance the management of parasitic diseases and pave the way for promising new approaches in the field (Bhat et al., 2025).

5.1. Microbiota Modulation

Targeted manipulation of the microbiota is emerging as a potential therapeutic strategy for treating parasitic infections. In this context, researchers are investigating the use of probiotics (beneficial microorganisms), prebiotics (substances that promote the growth of beneficial microorganisms), and synbiotics (a combination of both) to enhance the host's resistance to infection or to complement existing treatments. Additionally, Fecal Microbiota Transplantation (FMT), which has proven effective, particularly in recurrent dysbiotic conditions such as *Clostridioides difficile* infection, is also being evaluated as a potential intervention for managing parasitic infections, especially in cases that are resistant or have relapsed (Cheng et al., 2019; Mukherjee et al., 2018).

5.2. Targeted Therapies

Understanding how parasites manipulate microbiota and how microbiota affect parasites will aid in the rational design and development of new drugs or therapeutic interventions targeting these biological interactions (Fang et al., 2024).

5.3. Challenges and Future Research

This area of research is fast-moving, but important methodological and conceptual gaps persist. A prominent problem is the high interindividual heterogeneity of the human microbiota and possible confounding factors, including genetic predisposition, dietary habits, and environmental exposure. These factors complicate the derived causal relationships establishment and interpretation. Thus, additional studies are warranted to elucidate these causal relationships and the potential host-parasite microbiota host axis molecular mechanisms. Longitudinal cohort studies and multi-omic technologies, including metagenomics, metatranscriptomics, metabolomics, and proteomics, integrated with complex in vivo models, can enable this. Additionally, the systemic effects of parasite (such as *Plasmodium*, *Trypanosoma*, and *Leishmania*) interactions with host microbiota represent an emerging research direction, to deepen our understanding of these parasites that colonize sites other than the intestine and highlight how the understanding of the role of host microbiota might provide new venues for treatment (Kamel et al., 2024; Scotti et al., 2017).

6. Conclusion

Research on host-parasite-microbiota interactions is a novel and rapidly growing frontier in infection biology. Inclusion of the microbiota in the host-pathogen model is a paradigm shift in our understanding of the pathogenesis, host susceptibility, disease progression, and response to therapy of parasitic infections. The microbiota can also confer protection against parasites by processes such as colonization resistance and immune modulation. It is also possible that parasites can manipulate the microbiota to their benefit, indicating the complexity and significance of these three-way interactions. A more profound understanding of this "Health and Disease Triangle" will be fundamental to devising new strategies for the prevention, diagnosis, and treatment of parasitic diseases in the coming years

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Chapter 6

Parasite Vaccines: Challenges, Advances and Future Perspectives

Abstract

Developing vaccines for parasites is a highly challenging process due to the complex biology of these organisms, their various immune escape mechanisms, and our limited understanding of the host immune response. This section outlines the main challenges in creating parasite vaccines, including parasite biology, antigenic diversity, immune evasion, and the lack of known immunological determinants for protection. Significant progress has been made in this field, exemplified by the first malaria vaccine, RTS, S/AS01, and advances in vaccine platforms and antigen discovery strategies. Future perspectives in the field include the use of systems biology approaches, mRNA technology, structural vaccinology, and the development of transmission-blocking vaccines. Despite the existing challenges, technological innovations and a growing basic scientific understanding offer hope for the future development of more effective parasite vaccines.

Keywords: Parasite Vaccines, Immunology, Vaccine Development, Challenges and Advances, Future Perspectives

1. Introduction

Parasitic infections represent a significant burden of illness and death globally. These diseases disproportionately affect resource-limited communities, particularly in tropical and subtropical areas, negatively impacting individual health and socioeconomic development (Štrkolcová et al., 2024). Current control strategies for parasitic diseases include chemotherapy (drug therapy), vector control measures such as mosquito nets and insecticides, and improved sanitation. However, the effectiveness of these methods can be limited by the emergence of drug resistance, changes in vector behavior, and sustainability issues. In this context, vaccines that offer long-term protection and have the potential to significantly reduce the disease burden are considered essential tools in the fight against parasitic diseases (Huijben et al., 2018). Developing effective vaccines against parasites is inherently more complex and challenging compared to the creation of successful vaccines for viral and bacterial diseases. This complexity arises from the unique biological and immunological characteristics of parasites ((El-Moamly et al., 2023). This chapter aims to provide a comprehensive review of the primary obstacles faced in the development of parasite vaccines, the significant achievements made thus far, and the innovative approaches anticipated for the future.

2. Main Challenges of Parasite Vaccine Development

The challenges in developing vaccines against parasites are multifaceted and arise from both the intrinsic biology of the parasite and the complex interactions it establishes with the host (Tomazic et al., 2022).

2.1. Biological Complexity of Parasites

The significant structural complexity and larger genomic structure of parasites, particularly protozoa and helminths, pose considerable challenges for vaccine development. Unlike bacteria and viruses, these parasites have thousands of genes and protein-coding capabilities, which complicate the vaccination process. Additionally, their intricate life cycles, often involving multiple hosts and various developmental stages, such as sporozoites, merozoites, and gametocytes in *Plasmodium species*, present different antigenic profiles at each stage. This variability creates a major obstacle, making it very difficult to devise a single vaccine formulation that is effective throughout the entire life cycle of the parasite (Carey et al., 2022).

2.2. Antigenic Diversity and Variation

A significant challenge in developing vaccines for parasites is the substantial variation in antigens exhibited by many parasite species. This variation can occur in two ways: parasites can actively modify their surface antigens during infection (known as antigenic variation), and there can be considerable genetic differences in key antigens among parasite strains from different geographic regions (referred to as polymorphism). While antigenic variation enables parasites to evade the host immune response, antigenic variation and polymorphism greatly limit the protective effectiveness of vaccines designed based on specific antigen structures. This makes it extremely difficult to create a universal vaccine that can provide broad protection against different strains of parasites (Pollard et al., 2021).

2.3. Mechanisms to Escape the Host Immune Response

Parasites have developed a variety of sophisticated strategies to avoid elimination and protection from the host's immune system. These strategies include hiding inside host cells (as seen in pathogens like Leishmania and Plasmodium), secreting molecules that suppress the immune response, directly altering the functions of host immune cells, inducing immune tolerance by mimicking host proteins, and camouflaging their surface antigens with molecules derived from the host. These diverse immune evasion mechanisms significantly hinder both the successful activation and effector functions of protective immune responses that vaccines aim to induce. This represents a fundamental challenge in the rational design and development of effective vaccines against parasites (Chulanetra et al., 2021).

2.4. Lack of Immunological Correlates of Protection

For many parasitic diseases, the specific immunological mechanisms that protect against natural infection or vaccination, such as specific antibody levels or T cell responses, are not fully understood. This lack of knowledge regarding these "markers of protection" complicates the assessment of vaccine candidates' efficacy in laboratories and early clinical trials, as well as the design of effective vaccines (Panzner et al., 2021).

2.5. Technical and Logistical Challenges

Some parasites are challenging or even impossible to culture in vitro, which creates obstacles for antigen production and fundamental research. Additionally, the absence of suitable animal models that accurately replicate human diseases restricts the preclinical evaluation of vaccine candidates. Furthermore, developed vaccines must address practical challenges, including low production costs and minimal cold chain requirements, particularly in resource-limited regions (Kiani et al., 2022).

3. Current Advances and Strategies in Parasite Vaccine Development

Despite these challenges, significant progress has been made in the field of parasite vaccines:

3.1. Identification of Target Antigens

Recent advancements in "omics" technologies, including genomics, transcriptomics, and proteomics, have significantly accelerated and improved the process of identifying potential vaccine antigens. These antigens are molecules from the parasite that can be recognized by the immune system. One innovative approach, known as reverse vaccinology, starts by predicting potential antigens based on the parasite's genome. The targets typically consist of proteins located on the parasite's surface or those that it utilizes to invade host cells. An example of such antigens includes the circumsporozoite protein (CSP) for malaria and Apical Membrane Antigen 1 (AMA1) (Ciubotariu et al., 2024).

3.2. Vaccine Platforms

Different vaccine types and technologies are being tested for parasite vaccines:

3.2.1. Attenuated or Inactivated Whole Organism Vaccines

Using the entire parasite in vaccine development has the potential to stimulate a strong immune response due to the diverse range of antigens it offers. However, this approach comes with significant challenges related to the state of the parasite used. For example, live attenuated parasites may pose safety risks, such as the possibility of reverting to virulence or causing disease in immunocompromised individuals. Additionally, the mass production of inactivated parasites while preserving their antigenic integrity presents technical difficulties. An example of this vaccine strategy is the radiation-attenuated malaria sporozoites, which have been clinically investigated (You et al., 2023) (Fig.1).

3.2.2. Subunit Vaccines

Subunit vaccines consist of specific proteins or peptides derived from a parasite. These components are either purified or produced using recombinant DNA technology and are designed to stimulate an immune response rather than using the entire parasite. This approach typically provides a higher safety profile compared to whole parasite vaccines. However, because the immunogenicity of these purified or recombinant antigens is often insufficient on their own, it is usually necessary to incorporate adjuvant agents that enhance the immune response into the formulation to achieve an adequate protective effect. A notable example of this type of vaccine is

the RTS, S malaria vaccine currently being used in clinical settings. (Karakavuk et al., 2022; Laurens, 2019) (Fig.1).

3.2.3. Nucleic Acid Vaccines (DNA and mRNA)

Nucleic acid-based vaccines represent an innovative approach by delivering genetic material, either plasmid DNA or messenger RNA (mRNA), that encodes specific parasite antigens directly to the host. When the host cells take up this genetic material, they process it through cellular mechanisms, such as transcription and translation, which leads to the production of the relevant antigens in vivo. This process ensures that the antigens are effectively recognized by the host's immune system, thereby stimulating the targeted immune response (Kisakova et al., 2023). In particular, mRNA technology has gained significant attention due to its rapid development potential and the clinical successes seen during the COVID-19 pandemic. This technology holds considerable promise for vaccine development against parasites with complex life cycles (Chaudhary et al., 2021; You et al., 2023) (Fig.1).

3.2.4. Viral Vector Vaccines

Viral vector vaccines are a type of vaccine that uses a modified, harmless virus (known as a vector) to deliver genetic material encoding the target parasite antigen. These vectors are typically incapable of replication or have been weakened to ensure safety. Once the vector virus infects the host cells, it transfers the gene encoding the parasite antigen into those cells. The host cells then use their own transcription and translation processes to produce the antigen, which stimulates the immune system to respond effectively (Ewer et al., 2015; Rauch et al., 2018) (Fig1.)

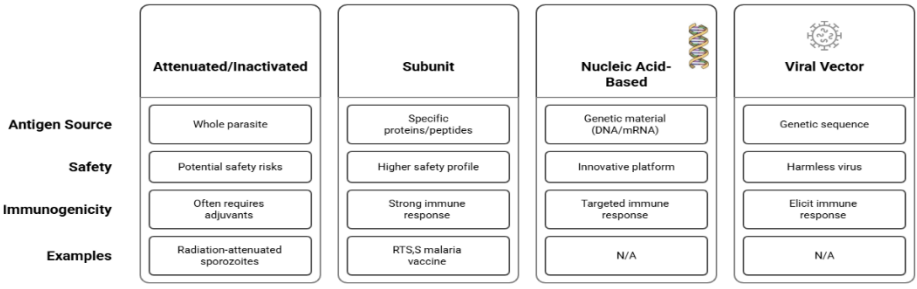

Figure 1: Vaccine Platform Comparison

3.3. Adjuvants and Strengthening the Immune Response

Protective immunity against parasites often requires a robust combination of both antibody (B cell) and cellular (T cell, particularly Th1 type) responses. Some vaccine platforms, like subunit vaccines, may not generate a strong enough or the appropriate type of immune response on their own. Therefore, developing new and more effective adjuvants that enhance and direct the immune response is crucial. An example of success in this area is the AS01 adjuvant used in the RTS, S vaccine (Gustifante et al., 2025).

3.4. Important Vaccine Candidates and Achievements

The most significant achievement in malaria prevention is the RTS, S/AS01 vaccine (Mosquirix™), which is the first malaria vaccine recommended for use by the World Health Organization (WHO). This vaccine targets the CSP protein in the sporozoite stage of the Plasmodium falciparum parasite and has demonstrated partial effectiveness in reducing the incidence of clinical malaria cases and severe malaria, especially in young children. Additionally, there are other vaccine candidates currently in development or undergoing clinical trials for diseases such as *Leishmaniasis*, *Schistosomiasis,* and hookworm infections. However, vaccines for parasites other than RTS, S have not yet been widely implemented (Laurens, 2019; Nadeem et al., 2022).

4. Future Perspectives and Innovative Approaches

Research on parasite vaccines is advancing rapidly due to the integration of advanced technologies and innovative strategies, shaping future perspectives and potential breakthroughs in the field (Weerarathna et al., 2024).

4.1. Systems Biology and Multi-Omics Approaches

The integrated analysis of genomic, transcriptomic, proteomic, and metabolomic data within the field of systems biology is being utilized to gain a more comprehensive understanding of host-parasite interactions and the mechanisms that protect the immune system. These methods could help identify new and more effective vaccine targets, as well as discover markers of protection (Nikulkova et al., 2024).

4.2. Structural Vaccinology

Understanding the three-dimensional (3D) structures of parasite antigens at high resolution allows for their rational design. This ensures optimal recognition by the immune system and promotes strong neutralizing antibody responses. This

approach, known as “structure-based vaccine design,” facilitates the precise targeting of immune responses (Kennedy et al., 2020).

4.3. mRNA Technology and Other New Platforms

The speed, flexibility, and potential to elicit strong T-cell responses of mRNA vaccine platforms also show great promise for developing parasite vaccines. Other next-generation platforms, such as nanoparticle-based vaccines and self-replicating RNA vaccines, are under investigation (Versteeg et al., 2019).

4.4. Multi-Stage and Multi-Antigen Vaccines

Vaccines that target various stages of the parasite's life cycle, either multi-stage or multi-antigen, have the potential to offer broader and more long-lasting protection than single-target vaccines (Veiga et al., 2023).

4.5. Transmission-Blocking Vaccines (TBs)

Transmission-blocking vaccines (TBVs) are designed to prevent the transmission of parasites through their vectors, such as Anopheles mosquitoes, rather than directly protecting the host from disease. The primary goal of this approach is to aid in efforts to eliminate diseases by interrupting or significantly reducing the spread of the parasite within the population. TBVs work by allowing the vector to receive specific antibodies from the bloodstream of a vaccinated individual when it takes a blood meal. These antibodies neutralize or block the sexual and later asexual developmental stages of the parasite in the vector's digestive tract. By doing this, TBVs disrupt the life cycle of the parasite and prevent the transmission of infectious forms to other individuals (Patel et al., 2021).

4.6. Therapeutic Vaccines

Prophylactic vaccines are intended to prevent infections; therapeutic vaccines, on the other hand, are intended to support treatment for existing infections or chronic infections. These vaccines operate by acting on the immüne system to decrease the pathogen load or by inducing modulation of immune responses that cause the disease symptoms. Therapeutic vaccine strategies are actively being researched, particularly for parasitic diseases known to induce chronic infections, such as chronic Chagas disease and *Leishmaniasis* (Pinazo et al., 2024).

4.7. Integrated Control Strategies

Future strategies for controlling parasitic diseases are expected to rely on a combination of methods that work together, integrating vaccines with existing

medications, managing vector populations (vector control), and implementing broader public health initiatives. Rather than considering vaccines as a standalone solution, this integrated approach will offer a more effective pathway to achieving sustainable control and potential elimination of these diseases, given the complex biology and transmission dynamics of parasites (Wang et al., 2023).

5. Conclusion

The development of vaccines for parasites is a complex process filled with scientific and technical challenges. The unique biological properties of parasites, their intricate interactions with the host immune system, and the incomplete understanding of the immunological basis for protection have hindered progress in this area. However, significant milestones, such as the development and availability of the RTS, S malaria vaccine, demonstrate that these challenges can be overcome.

Recent technological advancements in genomics, structural biology, and new vaccine platforms, particularly mRNA technology, are reinvigorating parasite vaccine research. In the future, we expect to see the development of more effective and broad-spectrum parasite vaccines through systematic approaches, rational design strategies, and innovative platforms. Achieving this goal will require sustained investment, interdisciplinary collaboration, and a commitment to advancing global health equity while reducing the burden of these devastating diseases that affect millions of people.

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