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CHEMOTHERAPY RESISTANCE STATUS OF COMMON HUMAN PATHOGENIC PROTOZOA

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Abstract. Protozoal infections exert significant health, community, and economic impact globally, primarily in tropical and subtropical regions. Due to the absence or inefficacy of vaccines for deadly protozoal illnesses, chemotherapy is a primary means for preventing such diseases. Growing drug resistance, rising cross-resistance, and a lack of new agents with novel modes of action all significantly reduce the effectiveness of current antiprotozoal treatments. Society seems to be ignorant of the extent and repercussions of drug resistance associated with anti-infective agents, even though it is a reality. Evidence suggests that reduced drug uptake, reshaped drug targets, genetic modifications resulting in loss of drug activity, and decreased drug export from parasites contribute to resistance development. Recently, there has been a significant gain in our understanding of drug resistance by isolating and characterizing genes and proteins associated with resistance. This fact has also paved the way for the discovery of potential new drugs. This review focuses on drug resistance in the most common vector and foodborne human-recovered parasites.

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Keywords: bloodborne parasites, foodborne parasites, parasite drug resistance, parasite treatment, protozoa

1. Introduction

Protozoan infections continue to pose a significant global health challenge, particularly in regions with limited access to medical resources. These parasitic infections are quite common, especially in less wealthy nations, causing illnesses ranging from mild to severe impairment and mortality. Previous records show a significant influence on the emergence and spread of infections in high-income countries, and this pattern is likely to continue (Steverding 2020). Vector-borne *Plasmodium* spp., *Leishmania* spp., *Trypanosoma* spp., and foodborne *Toxoplasma* spp., *Entamoeba* spp., and *Giardia* spp. are among the prevalent protozoans that pose a continuous threat to human life (Fig. 1). Across historical records and other current investigations, they have ranked among the most frequently recovered parasites (Gibb *et al*. 2015; Naghavi *et al*. 2024). The absence of safe and affordable medications and effective vaccines for preventing and treating human protozoan infections has further contributed to the significant impact of these parasites and the diseases they cause. The emergence of drug resistance (DR) in parasites progressively challenges the efficacy of existing medications. Therefore, the need for novel antiparasitic medications motivates research efforts worldwide, spurring the development of innovative approaches to ensure the continuous discovery of promising drugs. This review will provide an update on the possible key elements associated with DR in commonly encountered parasites.

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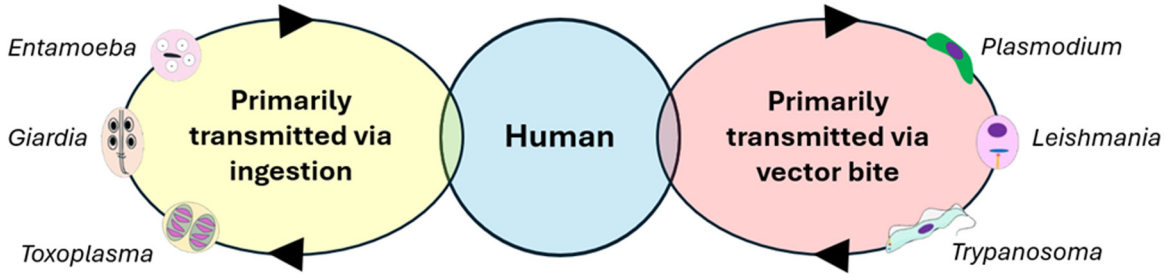

Fig. 1. The link between humans and six parasitic genera. *Plasmodium*, *Leishmania*, and *Trypanosoma* are transferred to humans mainly through the bite of an infected vector, while *Toxoplasma*, *Giardia*, and *Entamoeba* are transmitted via ingestion.

2. *Plasmodium* overview

Among all human parasites, those belonging to the genus *Plasmodium* are responsible for the devastating malaria disease and are the most lethal. Malaria continues to be a significant public health issue in the majority of tropical regions. According to the 2023 World Malaria Report, global estimates for 2022 indicated over 200,000,000 cases and 608,000 fatalities. Nigeria, the Democratic Republic of Congo (DRC), and Uganda have the highest reported incidence of malaria cases among African countries, totalling over 100,000,000 cases combined. Five *Plasmodium* species, namely *P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi* are responsible for the etiology of this medical condition. Infections caused by *P. falciparum* and *P. vivax* account for the vast majority of cases, with the most serious symptoms and the highest rates of DR (WHO 2023). The *Plasmodium* parasite's life cycle is intricate, involving a succession between their vector *Anopheles* mosquito host and their human host (CDC 2024a). These apicomplexan parasites adjust their structure and metabolic requirements to suit the various environments found in their diverse hosts. The different shifting forms of each species are helpful in species laboratory identification. Depending on its developmental stage, it can reside within or outside cells particularly during transmission and between infection cycles. Most *Plasmodium* parasites reside in the host's liver or red blood cells, shielded from host defenses, posing a significant obstacle to developing effective vaccinations (Rénia and Goh 2016). Malaria may not exhibit any diagnostic clinical characteristics; however, certain patients may develop classical periodic febrile paroxysms that occur every 48 or 72 hours as a part of uncomplicated malaria situations. Moreover, *P. vivax* and *P. ovale* during the liver stage can form dormant structures responsible for the disease's recurrence (Balaji et al. 2020). Pregnant women are as vulnerable as many people are, and so they are considered high-risk, as well as young children, HIV+, and immunocompromised individuals. Delays in treatment or delayed treatment responses may result in life-threatening consequences for the patient, such as organ dysfunction or failure; such clinical signs are referred to as severe malaria, usually caused by *P. falciparum*. One of the main reasons why *P. falciparum* infection is so dangerous and often fatal is that the parasites can hide in the tiny blood vessels of several organs, including the brain, causing cerebral malaria (Moreira *et al.* 2025). The course of malaria treatment depends mainly on the availability and efficacy of antimalarial chemotherpy.

2.1. *Plasmodium* treatment and resistance

For thousands of years, people have used the bark, roots, and leaves of plants such as the bark of the cinchona tree, which contains quinine (QN) as remedies for malaria (Noronha *et al.* 2020). However, the extraction and employment of their active components as pharmaceutical drugs did not occur until the last century (Semedo *et al.* 2021). Throughout malaria treatment history, pharmacological research derived the most field appreciated compound, chloroquine (CQ), from QN (Berberian 1947). Incomplete patient compliance exposed *Plasmodium* parasites to intense drug selection pressure, leading them to develop resistance mechanisms (Waithera *et al.* 2023). In addition to vector control, emerging antimalarial resistance is one of the current obstacles to malaria prevention. Some of the available anti-malaria drug arsenals include QN, CQ, mefloquine (MQ), halofantrine (HF), lumefantrine (LF), quinacrine, sulfadoxine-pyrimethamine (SP), atovaquone (AQ), proguanil (PR), primaquine (PRQ), amodiaquine (ADQ), piperaquine (PPQ), clindamycin, doxycycline, tetracycline, tafenoquine (TFQ), artemisinin (ART), artesunate (ARN), artemether (ARM), and other ART derivatives (Meshnick and Dobson 2001; Tse *et al.* 2019). Moreover, with the emergence of resistance to CQ, researchers initiated investigations on CQ resistance (CQR) in the 1960s, which led to the adoption of MQ and HF, two more drugs that met a similar fate to CQ in the 1980s (Amelo and Makonnen 2021). A genetic-cross experiment revealed that the membrane transport protein PfCRT (*P. falciparum* CQ resistance transporter) is essential for CQR and localizes to the food vacuole (FV), where hemoglobin is degraded (Fidock

et al. 2000). Researchers have investigated the protein for its ability to transport numerous synthetic compounds. Still, they have not yet identified the physiological substrate. PvCRT, the homolog of PfCRT in *P. vivax*, is not believed to be connected to CQR, whereas PfCRT in *falciparum* is (Marques *et al*. 2014). Instead, PvMDR1 (*P. vivax* multidrug resistance protein 1), a homolog of human p-glycoprotein, is the suggested implicated gene (Schousboe *et al*. 2015). The ABC (ATP binding cassette) transporter PfMDR1 in *P. falciparum*, located on the FV membrane, is also believed to influence CQR (Reed *et al*. 2000). Mutations in the PfMDR1 gene (N86Y) and the PfCRT gene (K76T and A220S, respectively) confer substantial resistance to CQ (Nsobya *et al*. 2007). In addition to CQR, mutant PfCRT was suggested to confer resistance to PPQ and ADQ, while PfMDR1 to MQ, ART, and QN (Wicht *et al*. 2020). These and other changes impact the relative abundance of parasite populations by conferring fitness costs (Pulcini *et al*. 2015). The K76T substitution in PfCRT exhibits notable regional variability across Africa, with particularly high frequencies observed in Ethiopia (91.6%) and Mali (72.9%), compared to lower frequencies in DRC (26%) and non-African nations like India (78%) and Turkey (12.1%) (Patel *et al*. 2017; Hassen *et al*. 2022; Avcı *et al*. 2024; Baina *et al*. 2024; Dama *et al*. 2024). Meanwhile, the N86Y mutant in the PfMDR1 gene shows significant geographic variation as well: it occurs at 6.8% in DRC and 10.2% in Niger and rises dramatically to 78.4% in Oceania (Issa *et al*. 2022; Moss *et al*. 2022; Baina *et al*. 2024). Remarkably, CQ-sensitive strains have returned to countries like Ghana and Cote d'Ivoire after switching to ART-based combination therapy (ACT) instead of CQ for some years. This fact has raised the possibility of CQ returning to the field as it used to be (Asare *et al*. 2021). Furthermore, the parasite expresses PfMRP1, an ABC transporter located on membrane-bound vesicles and its plasma membrane. This protein promotes the transport of organic anionic substrates, such as oxidized glutathione, sulfate conjugates, and drugs. Two mutations in the PfMRP1 locus at positions Y191H and A437S were identified as being associated with resistance to QN and CQ (Gil and Fançony 2021). Although CQR remains a persistent issue, CQ is currently employed to treat uncomplicated CQ-sensitive (CQS) malaria caused by any of the five human pathogenic *Plasmodium* species (CDC 2024b). Some compounds, such as SP, stop the production of folate by blocking enzymes called *P. falciparum* dihydropteroate synthase (PfDHPS) and dihydrofolate reductase-thymidylate synthase (PfDHFR-TS). Biochemical and genetic investigations of *P. falciparum* reveal that mutations in these genes diminish the drug sensitivity of antifolates (Pacheco *et al*. 2020). When the S108N mutation is present, other changes in the inhibitor binding region of PfDHFR, like A16V, N51I, C59R, and I164L, make antifolate resistance even worse. *P. falciparum's* resistance to cycloguanil is linked to the PfDHFR double mutations A16V and S108T (Staines *et al*. 2018). In Thailand and other Southeast Asian regions, *P. vivax* is naturally resistant to sulfadoxine and has obtained resistance to pyrimethamine (Imwong *et al*. 2001). In a study, SP treatment failure occurred in over 50% of *P. vivax* patients due to mutations in PfDHFR and PfDHFR-TS homologs in *P. vivax* PvDHPS and PvDHFR-TS, which are reserved with mutations described to cause resistance in *P. falciparum*, suggesting a possible association (Tjitra *et al*. 2002). AQ is a mitochondrial electron transport inhibitor that disrupts parasite respiration by binding to cytochrome b (cyt-b) and inhibiting ubiquinol oxidation. *P. falciparum* isolates with a single mutation in the Pfcyt-b gene, specifically in the Y268N/S/C codon, exhibited AQ resistance (Staines *et al*. 2018). It is usually combined with PR (Malarone™) for uncomplicated malaria caused by *P. falciparum*. Moreover, ARTs have been documented to bind to many parasite proteins and influence various cellular and organellar processes. Once activated, the carbon-centred radical of the heme drug accelerates the production of additional cytotoxic reactive oxygen species (ROS) through a cluster bomb-like effect, ultimately leading to cell death (O'Neill *et al*. 2010). The first-line treatment for malaria, known as ACTs, has been widely used since the early 2000s (CDC 2024b). It is based on the idea of combining two drugs, one with a shorter half-life (such as ART or an ART derivative) and one with a longer one (such as a quinolone). ACTs are most frequently administered in the following combinations: (ARM + LF), (ARN + MQ), (ARN + AM), and (dihydroartemisinin + PPQ) (Pluijm *et al*. 2021; CDC 2024b). Whole-genome sequencing of an ART-resistant parasite linked the *P. falciparum* Kelch 13 (K13) to ART resistance mutations in both clinical and field isolates of *P. falciparum* (Xie *et al*. 2020). The C580Y mutation in K13 has been strongly linked to reduced susceptibility to artemisinin-based treatments, with a particularly high prevalence in Southeast Asia, notably within the Greater Mekong Subregion, including Cambodia, Myanmar, and Thailand, where it occurs in 35.5% of cases (Takala-Harrison *et al*. 2015; Yoshida *et al*. 2021). In contrast, the K189T mutation in K13 is the dominant variant in Africa, with a prevalence of 22.8% (Hung *et al*. 2024). On the other hand, *in vitro* investigations have shown a probable link between a Y976F mutation in the PvMDR1 gene and resistance to ARN and MQ; however, additional clinical trials are necessary to understand this association fully (Cowell and Winzeler 2019). Moreover, mutations in the Na^+/H^+ exchanger gene Pfnhe-1 have been reported to confer resistance to QN, but this is still a debatable matter of research (Andriantsoanirina *et al*. 2013). For relapse prevention because of *P. vivax* and

P. ovale liver stages, either PRQ or a newer drug called TFQ is used. While some studies indicate the effectiveness of a single dose of TFQ against *P. vivax*, testing on patients with blood disorders or young children remains to be done, necessitating further research (Rodrigo *et al.* 2020). A summary of the medications to be administered to malaria-infected patients is illustrated in Table I. The table illustrates the 1st line of common malaria treatment regimens based on the Centers for Disease Control and Prevention (CDC) guidelines and displays the status of DR (CDC 2024b). Researchers are currently investigating, testing, or inventing various potential vaccines against malaria.

2.2. *Plasmodium* vaccines

On October 6, 2021, the World Health Organization (WHO) recommended RTS,S/AS01 (Mosquirix™), a malaria vaccine developed by GlaxoSmithKline Biologicals, for broad usage. The sporozoite surface protein (CSP) is the basis of the subunit vaccine RTS,S/AS01. The vaccine comprises CSP fused with hepatitis B surface antigen (HBsAg) and other virus-like particles of extra HBsAg that have not been fused (Hammershaimb and Berry 2024). The WHO recommended RTS,S/AS01 for children aged 5 months and older living in regions with moderate to high malaria transmission. Currently, available malaria vaccines reduce the risk of uncomplicated malaria by approximately 40%, severe malaria by approximately 30%, and mortality by approximately 13% (WHO 2023). The CDC recommends administering malaria medicines in conjunction with other control measures.

3. *Leishmania* overview

The obligate intracellular parasite *Leishmania* is the primary cause of leishmaniasis, predominantly transmitted by sand fly vectors. In both the Old and New Worlds, this parasite, a member of the Trypanosomatidae family, causes skin, mucous membrane, and internal organ diseases. Multiple subspecies of leishmaniasis cause the complex disease with many symptoms. The disease has spread to many parts of the world, including Asia, Africa, Central and South America, and the Middle East. The WHO anticipates approximately one million new cases annually, impacting 12,000,000 individuals globally (WHO 2024a). Poverty, migration, hunger, lack of personal hygiene, and an impaired immune system are all contributors to the development of leishmaniasis. The amastigotes (diagnostic stage of *Leishmania*) undergo proliferation within specific host immune cells, such as macrophages, and then spread to several tissues in the body, eliciting diverse immunological responses. Visceral leishmaniasis (VL) is a life-threatening systemic infection that affects the internal organs and can lead to fatalities during epidemics. Several species, including *L. donovani*, *L. infantum*, and *L. chagasi* cause it. In countries such as India, Bangladesh, and Nepal, these species are responsible for an estimated three hundred thousand to five hundred thousand cases of VL globally each year (Perry *et al.* 2013). Mucocutaneous leishmaniasis (MCL) is a clinical manifestation associated with several *Leishmania* species, including *L. braziliensis*, *L. amazonensis*, and *L. panamensis*. MCL is characterized by visible physical disfigurement resulting from mucosal involvement. It has been reported that 9% of cases in Brazil and 2.3% of cases in France present with mucosal involvement (Camuset *et al.* 2007; Faucher *et al.* 2011). Cutaneous leishmaniasis (CL) is generally considered a non-lethal, self-limiting skin infection. However, it can lead to significant, stigmatizing skin lesions. The disease is caused by several *Leishmania* species, including *L. major*, *L. tropica*, and *L. aethiopica*, which are endemic in regions such as Yemen and Ethiopia, with reported prevalence rates of 29.4% and 22.4%, respectively (Bisetegn *et al.* 2020; Mann *et al.* 2021; Alshahethi *et al.* 2024). Animal reservoirs such as dogs and rodents affect the control efforts by maintaining the parasite's survival (Tripathi and Nailwal 2021). Human treatment has depended on chemotherapy since the early 1920s due to the absence of an effective vaccine. Although vaccines for dogs have been developed, there is still ongoing debate regarding their effectiveness (Sasidharan and Saudagar 2021).

3.1. *Leishmania* treatment and resistance

There are only a handful of anti-*Leishmania* drugs available, and they all have serious drawbacks such as toxicity, expensive manufacturing costs, and low efficiency. Sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®) are two examples of the several pentavalent antimonials (Sb^V) that are available as systemic therapy. Amphotericin B (AMB), pentamidine (PMD), fluconazole (FLZ), and miltefosine (MT) are additional compounds that are currently in use. Sb^V compounds are typically used in many countries as the first-line treatment (Herwaldt and Berman 1992). In Latin America, Sb^vs represent the gold standard for CL treatment (Mann *et al.* 2021). Several regions have seen the emergence of resistance in the past few years, including India, Europe, the Middle East, and South America (Wijnant *et al.* 2022). The resistance pathway is not clear yet. However, several ABC transporters, such as ABCI4 and ABCG2, were thought to contribute to drug efflux mechanisms (Ponte-Sucre *et al.* 2017). It was also suggested that MRP1 in Sb^v-resistant *L. donovani* strains reduces drug accumulation by reduc-

ing drug import functions (Mukherjee *et al*. 2007). The aquaglyceroporin (AQP1) transporter is another potential factor in Sb^V resistance; its inactivation may decrease Sb^V absorption, and AQP1 mutations may increase resistance (Potvin *et al*. 2020). The ergosterol antagonist AMB is utilized in regions where Sb^V treatment is hindered by resistance (Pinart *et al*. 2020). No resistance has been reported except in laboratory-pressured isolates that showed mutations in CYP51, SC5D, and SMT (Pountain *et al*. 2019). Moreover, an oral medication known as MT is thought to block *Leishmania* parasites' phospholipid metabolism. MT resistance has been found in both *in vitro* and *in vivo* tests in *L. donovani* when the MT translocation pathway has mutations or deletions (Carnielli *et al*. 2019). Experimentally induced mutations in the *L. donovani* MT transporter (LdMT) and LdRos3 have been reported to affect drug transport (Srivastava *et al.* 2017). Another suggested resistance mechanism to MT is reduced drug accumulation by overexpression of ABCB4, ABCG4, and ABCG6 (Pérez-Victoria *et al*. 2011). Moreover, another drug that has shown promise against both CL and VL is paromomycin (PMM), which has a cure rate of up to 80%. The widespread application of PMM in VL treatment is challenged by the relatively high post-treatment relapse rates, which call for proper implementation and monitoring of the development of resistance (Sosa *et al.* 2019). The underlying causes of resistance and the specific mutations responsible remain largely unresolved and require further investigation. Table II summarizes the status of *Leishmania* treatment and DR status in general.

4. *Toxoplasma* overview

The apicomplexan intracellular parasite known as *Toxoplasma gondii* (*T. gondii*), the agent responsible for toxoplasmosis, is an intracellular parasite that infects humans and a broad range of animals. The three transmissible stages of *T. gondii* are as follows: the fast-replicating tachyzoites (involved in the acute phase of infection), which are found in clusters or clones; the slow-replicating bradyzoites (involved in the chronic phase of infection), which are found in tissue cysts, and the sporozoites, which are found in oocysts (Black and Boothroyd 2000). The parasite can be acquired through ingesting tissue cysts through raw or uncooked meat or consuming contaminated water, food, fruits, and vegetation, with mature oocysts usually originating from feline feces. It can also be transplacental, passing from the mother to the fetus via the congenital pathway. Transmission through blood transfusion (tachyzoites) and organ transplantation (bradyzoites) have been reported as well. *T. gondii* can transition between tachyzoites and bradyzoites within the host, adding complexity to its life cycle. *T. gondii* cysts may develop in various organs, such as the brain, eyes, liver, lungs, heart, kidneys, and skeletal muscles. The parasites are exclusively capable of sexual breeding in felines, which is why they are regarded as the definitive host (CDC 2024c). The parasite infection remains asymptomatic or manifests as moderate symptoms similar to the flu in most immunocompetent individuals and is often self-limiting. That said, in individuals with immunological deficiencies, relatively severe pathology may develop, including encephalitis, myocarditis, hepatitis, pneumonia, and eye disease. Suppose a mother contracts *T. gondii* while she is pregnant; in that case, her unborn child may suffer from congenital toxoplasmosis, a condition characterized by severe neurological deficits, retinal lesions, or even stillbirth or miscarriage (Johnson 1990). According to estimates, congenital toxoplasmosis imposes a staggering annual disease burden of 1.20 million DALYs (disability-adjusted life years), with 190,100 new cases reported globally each year (Torgerson and Mastroiacovo 2013). These figures are alarming when considering the wide-ranging impact of the disease. The *T. gondii* antibody prevalence remains relatively low in the United States at approximately 11.14%. However, in regions such as Europe, Central, and South America, the infection rate soars to an astonishing 30–90% of the population (Dubey and Jones 2008; Minbaeva *et al*. 2013; Jones *et al*. 2018; Dubey 2021). Even more concerning is the finding from a recent study on pregnant women in Africa, where the seroprevalence of *T. gondii* reached 42.89%. Countries like Ethiopia, Tanzania, Nigeria, and Morocco, where the study was conducted, reflect some of the highest infection rates globally (Gelaw *et al*. 2024).

All these findings emphasize the urgent need to address toxoplasmosis as a critical public health issue, with significant consequences for both morbidity and mortality worldwide. The data also paints a stark picture of the disease's disproportionate burden in certain regions, calling for targeted interventions to mitigate its impact. Treatment of *T. gondii* depends on the administration of drugs due to the lack of an effective vaccine, but many studies are optimistic.

4.1. *Toxoplasma* treatment and resistance

Anti-toxoplasma medications primarily target the folate pathway, an enzyme complex including the dihydrofolate reductase (DHFR) and the dihydropteroate synthetase (DHPS). This complex is involved in DNA synthesis (Lapinskas and Ben-Harari 2019). It is noteworthy to mention that no medication available today can eliminate *T. gondii* tissue cysts from the infected host; instead, they remain dormant within the host as long as the immune system is robust enough to

prevent the cysts from reactivating and becoming tachyzoites (Konstantinovic *et al*. 2019). Spiramycin (SPI) is the preferred treatment for acute *T. gondii* infection during pregnancy (at least for the 1st trimester) due to the potential for PYR to result in congenital abnormalities (Bogacz 1954). In cases when fetal toxoplasmosis is identified beyond week 16 of gestation, the treatment is typically substituted with PYR and sulfadiazine (SDZ) because SPI has trouble crossing the placenta barrier (Robert-Gangneux *et al*. 2011). Regrettably, there are significant adverse effects associated with the combination. Both PYR and SDZ suppress the DNA synthesis in tachyzoites of *T. gondii* and may have a similar impact on specific host organs, even bone marrow. Hence, incorporating folinic acid (FA) into the drug combination can prevent these negative consequences, which are restored when the medication is stopped, as seen in previous studies (Prusa *et al*. 2015). Various combinations are being investigated to find a better treatment option with fewer adverse effects since treatment failure has been linked to either DR, malabsorption, or intolerance of the current combination (Silva *et al*. 2017). Clarithromycin, cotrimoxazole, AQ, dapsone, and azithromycin are other medications used to treat toxoplasmosis. However, these treatments do not work against the bradyzoites form (Dunay *et al*. 2018). Because of the lack of conclusive evidence from *in vitro* research, identifying genes imparting resistance to PYR and SDZ is an area of dispute (Meneceur *et al*. 2008; Doliwa *et al*. 2013). However, treating clinical toxoplasmosis with AQ is possible if SPI is unavailable (SA Maternal & Neonatal Clinical Network 2015). Like *P. falciparum*, AQ kills *Toxoplasma* at its chronic bradyzoite stage by blocking the mitochondrial electron transport chain. Evidence suggests that AQ binds to the Qo domain of cyt-b, hence targeting the *Toxoplasma* cyt-bc1 enzyme (Alday *et al.* 2017). Significant mutational alterations in M129L and I254L on the Qo domain are thought to be responsible for *T. gondii's* resistance to AQ. However, this theory has not been validated by further research (McFadden *et al.* 2000). Furthermore, the treatment of immunocompromised individuals is based on the same medications used to treat congenital toxoplasmosis, demonstrating how limited our existing ammunition is and emphasizing the importance of searching and testing for more and safer compounds (Hajj *et al*. 2021). Table III summarizes the status of *T. gondii's* standard treatment and DR status in general.

5. African *Trypanosoma* overview

The African sleeping sickness kinetoplastids parasites, *Trypanosoma brucei* (*T.b.*), are human African trypanosomiasis (HAT) causative agents. The blood-sucking tsetse fly of the *Glossina* species transmits HAT to humans and animals through its bite. The two hemoflagellate sub-species, *T.b. gambiense* (*T.b.g*) and *T.b. rhodesiense* (*T.b.r*), are the causative agents of HAT in rural regions of sub-Saharan Africa (Büscher *et al*. 2017). HAT prevalence correlates with the vector distribution, which lives near plants and sources of water. The predominant cause of infections in West and Central Africa is *T.b.g*, which is endemic in 24 countries (CDC 2024d). In recent reports, DRC and Côte d'Ivoire reported a prevalence of 0.3% and 0.06%, respectively (Koné *et al*. 2021; Franco *et al*. 2024). The decline in cases is credited to the hard work of national control programs and other agencies that aided the WHO mission (WHO 2020). In Eastern and Southern Africa, *T.b.r* infects humans but also domestic and wildlife species. Identifying HAT at the early stages can be challenging because the significant symptoms might take months or even years to manifest, depending on the sub-species. Infections caused by *T.b.r* are acute, whereas infections caused by *T.b.g* are chronic (CDC 2024d). The first stage of HAT symptoms includes headaches, fever, and joint discomfort caused by parasites proliferating in the circulation and lymphatic system, commonly known as the hemolymphatic phase. The second stage of the disease is characterized by severe neurological abnormalities, such as meningoencephalitis, caused by parasites crossing the blood-brain barrier (BBB) to the central nervous system, and, if left untreated, it can lead to death. Recently, the implementation of control measures and eradication efforts by the WHO and other organizations has decreased the overall impact of the diseases (WHO 2020). The severity of the illness dictates the course of treatment. No vaccine is available for human use yet.

5.1. African *Trypanosoma* treatment and resistance

Several anti-trypanosomal drugs are available to use in clinics, including PMD, suramin (SUR), melarsoprol (Mel^b), eflornithine (EFL), fexinidazole (FXZ), and nifurtimox (NFX). PMD is a drug administered to treat the initial phase of the illness caused by *T.b.g* (Bouteille *et al*. 2003). There are several routes via which the medication enters parasite cells. Partial transport is facilitated by the aminopurine transporter P2, also known as *T.b.* aminopurine transporter 1 (TbAT1). This has been demonstrated by observing reduced sensitivity to PMD when the TbAT1 gene is knocked out and partial suppression of PMD transport by adenine, an established substrate of TbAT1 (de Koning *et al*. 2004). In 2001, the presence of two additional channels, a high-affinity PMD transporter (HAPT1) and a low-affinity PMD transporter (LAPT1), were identified, which facilitated the majority of PMD transport (Bridges *et al.* 2007). The synthesis of DNA and RNA is believed to be inhibited

by PMD, which interferes with nuclear mechanisms (Sands *et al*. 1985). It is reported that PMD resistance in HAT results from the loss of TbAT1 function (Matovu *et al*. 2003). Even with PMD resistance, treatment effectiveness is over 93% (WHO 2024b). If PMD is not available to treat the initial stage of *T.b.g,* FXZ is recommended (CDC 2024d). Also, NECT (NFX/EFL Combination Therapy), a therapy created in 2009, works just as well at treating *gambiense* types of disease in Central and West African countries. It is considered much safer for patients and is usually used for second-stage *gambiense* disease (CDC 2024d). Moreover, since the 1920s, SUR has been employed as the primary therapy for the hemolymphatic early phases of HAT caused by *T.b.r* (Zoltner *et al*. 2020). Research indicates that it is conveyed by the invariant surface glycoprotein 75 (ISG75) and the major facilitator superfamily transporter (MFST). SUR interacts synergistically with the second-stage medicines EFL, NFX, and Mel^{b} (Makarov *et al*. 2023). By contrast, PMD's action is inhibited by SUR (Guimaraes and Lourie 1951). Apart from having a half-life of around 44–54 days and being in use for nearly a century, there have been no instances of SUR resistance in human pathogenic trypanosomes (Babokhov *et al*. 2013). Moreover, Mel^{b} is an organic medicine containing melaminophenyl arsenic. It was developed in the late 1940s as a treatment for second-stage HAT because of its capacity to cross the BBB. It continues to be the primary treatment for second-stage *T.b.r* infection (Nok 2003). TbAT1, as well as aquaglyceroporin 2 (AQP2), are suggested as the transporters responsible for the selective uptake of Mel^{b} by the parasite (Graf *et al*. 2013). Research indicates that each of TbAT1 and TbAQP2 have significant involvement in the transport of Mel^{b} and PMD (Ungogo *et al*. 2022). Furthermore, Mel^{b} and PMD cross-resistance (MPXR) are two of the most distinct patterns from *T.b.* DR research (Munday *et al*. 2015). This phenomenon has since been linked to the decreased uptake of these two drugs from MPXR *Trypanosoma* cells, which may result from genetic modifications or the loss of essential transporter proteins (Munday *et al*. 2014). Table IV summarizes the status of *T.b.* current treatment and DR status in general.

6. *Giardia* overview

Giardia lamblia (G. lamblia), also known as *G. intestinalis* or *G. duodenalis*, is a flagellate enteric protozoan parasite that thrives in low-oxygen environments. Approximately 200,000,000 individuals in Asia, Africa, and Latin America experience symptomatic giardiasis, with around 500,000 new cases reported each year, despite the existence of current programs for surveillance (Certad *et al*. 2017). A recent study identified a prevalence rate of 6.8% in India (Ghosal *et al*. 2023). Additionally, a pooled prevalence of 18.3% was observed among children across several African countries, including Niger and Cameroon (Kalavani *et al*. 2024). Giardiasis is spread by ingesting its cyst stage, which is achieved primarily through the fecal-oral route. It can be transmitted directly from person to person, indirectly through food or water, or zoonotically from animal to human or animal to animal. The trophozoite, the active feeding stage, is responsible for the destruction of the enterocytes, the loss of the brush boundary of the epithelial cells of the intestine, the shortening of microvilli, and the alteration of epithelial barrier function, all of which contribute to the human disease (Allain *et al*. 2017). The majority of the time, a *Giardia* infection resolves on its own. Still, if it gets worse, it can cause a variety of symptoms, including malabsorption and weight loss, and in cases of chronic disease, gas, bloating, steatorrhea, nausea, and vomiting (Cernikova *et al*. 2018). Veterinary studies using phylogenetic analysis identified eight *G. lamblia* assemblages from A to H (Monis *et al*. 2009). Even though assemblages A and B have been demonstrated to infect humans, controversy remains (Zajaczkowski *et al.* 2021). Although *Giardia* vaccines are commercially available for animals like cats and dogs, not humans, their efficacy results remain debated and unclear.

6.1. *Giardia* treatment and resistance

Metronidazole (MTZ), albendazole (ALB), and tinidazole (TNZ) are the most commonly prescribed drugs for giardiasis treatment (CDC 2024e). MTZ monotherapy and ALB have shown effectiveness in most cases, but there have been reported cases of treatment failure (Krakovka *et al*. 2022). Although the precise process by which MTZ kills anaerobic microbes is still unresolved, a potential explanation is that it disrupts their double-strand DNA. The compound is also thought to inhibit the function of thioredoxin reductase, a redox enzyme, in *G. lamblia* by targeting its disulfide reductase activity. These mechanisms induce severe oxidative stress (Riches *et al*. 2020). The reduced cellular concentrations of pyruvate, ferredoxin oxidoreductase and downregulation of ferredoxin pathways in *G. lamblia* are believed to contribute to its resistance to MTZ. Resistance leads to decreased MTZ uptake into the protozoa lumen due to the low-redox-potential anaerobic metabolism. The proportion of treatment failures attributable to actual resistance is unknown (Adam 2021). ALB affects β-tubulin, which is a cytoskeleton subunit. The resistance to ALB is believed to be caused by changes in the cytoskeleton of *G. lamblia*, specifically in the ROD domain of the β-tubulin structure (Lagunas-Rangel *et al*. 2021). Alternatively, other research suggests an efflux mechanism where an ABC-C1 actively transports less ALB, resulting

in a lower ALB concentration (Ángeles-Arvizu *et al.* 2021). Another theory for ALB resistance is to reduce ROS generated by ALB by activating an antioxidant response (Argüello-García *et al.* 2015). Table V summarizes the general treatment and DR status of *Giardia*.

7. *Entamoeba* overview

Amebiasis is a condition induced by unicellular intestinal parasites of the *Entamoeba* genus. In humans, the estimated prevalence of *Entamoeba* infection is 3.55%, making it the third most prevalent parasitic disease associated with mortality on a global scale (Cui *et al.* 2019). Numerous species of the genus *Entamoeba*, including *E. histolytica*, *E. dispar*, *E. hartmanni*, *E. moshkovskii,* and *E. coli,* are known to parasitize the human intestine. Despite its long-held reputation as the sole pathogenic *Entamoeba* species, *E. histolytica* is indistinguishable in appearance from *E. dispar* and *E. moshkovskii*. So, even under a microscope, it's difficult to tell them apart (Singh *et al.* 2009). To contract amebiasis, one must drink water or consume food contaminated with the parasite's infectious cysts. After the parasite excystation, they either colonize the large intestine symptomlessly (which happens in most cases) or cause bloody diarrhea. The trophozoites can become virulent and invasive, causing amebic dysentery and migrating through the portal veins to the liver, damaging the hepatocellular layer. Ulcers that resemble colonic flasks are diagnostic for *E. histolytica* (Tharmaratnam *et al.* 2020). *E. histolytica* infections display significant regional variation in prevalence across the globe. In Asia, India is recognized as one of the countries with the highest burden, with prevalence rates ranging from 3% to 23% (Gupta *et al.* 2022). In Africa, particularly in Ethiopia, a notable 19.8% prevalence rate has been reported (Roro *et al.* 2022). Similarly, a study involving 30 countries in the Americas estimated an overall prevalence of 9%, with 22 countries showing varying infection rates (Servián *et al.* 2022). These regional differences highlight the widespread nature of *E. histolytica* infections and the need for focused public health strategies. Chemotherapy is the only therapeutic option for amoebiasis since no vaccination is currently available for humans.

7.1. *Entamoeba* treatment and resistance

Although several medications are available to treat amoebiasis, MTZ has long been considered the gold standard for *E. histolytica*. It has been well-established that it is safe and effective against amoebiasis (CDC 2019). Thus far, there has been no evidence of resistance from *E. histolytica*. Other systems, including bacteria such as *E. coli*, suggest the drug exerts its effects through DNA damage and oxidative stress. However, the *in vitro* mechanisms of resistance and the existence of resistant clones have yet to be fully established (Jackson *et al.* 1984). A recent investigation found that treating clinical isolates with MTZ increased their IC^{50} (Singh *et al.* 2023). Moreover, like MTZ, TNZ is a second-generation nitroimidazole that acts on several protozoa. In addition to effectively eliminating amoebiasis, its greater half-life (12 to 14 hours vs. 8 hours) makes it possible to shorten the duration of treatment (Sawyer *et al.* 1976). Table VI summarizes the current *Entamoeba* treatment status.

Table I. *Plasmodium* species treatment and possible resistance proteins summary

Plasmodium
Uncomplicated malaria by CQS *P. vivax, P. ovale, P. malariae, P. knowlesi,* and *P. falciparum*
CQ phosphate; is also the drug of choice for pregnant women
Uncomplicated malaria by CQR *P. falciparum*, *P. vivax*, and *P. ovale*
An ACT combination such as ARM-LF; is also the drug of choice for pregnant women
Anti-relapse treatment *P. vivax* and *P. ovale*
PRQ phosphate or TFQ; Anti-relapse is risky during pregnancy
Complicated malaria regardless of the species or drug susceptibility
Administer intravenous ARN
Possible proteins involved in resistance
P. vivax: PvMDRI (CQ, ARN, and MQ), PvDFHR-TS, and PvDHPS (SP)
P. falciparum: PfCRT (CQ, PPQ, ADQ), PfMDRI (CQ, QN, ART, and MQ), PfMRPI (CQ and QN), PfK13 (ART), Pfcytb (AQ), Pfnhe-1 (QN), PfDHPS, and PfDHFR-TS (SP)
Available human vaccine
RTS,S/AS01 (Mosquirix™) by GlaxoSmithKline Biologicals

Sources: Fidock et al. 2000; Reed et al. 2000; Tjitra et al. 2002; Nsobya et al. 2007; O'Neill et al. 2010; Andriantsoanirina et al. 2013; Schousboe et al. 2015; Pacheco et al. 2020; Wicht et al. 2020; Gil and Fançony 2021; CDC 2024a; Hammershaimb and Berry 2024

Table II. *Leishmania* treatment and possible resistance proteins summary

Leishmania
Compounds usually used for treatment
Sb^V, AMB, PMD, FLZ or MT
Possible proteins involved in resistance
- Sb^V: gene products of ABCI4, ABCG2, MRP1 and AQP1 - MT: gene products of LdMT gene and LdRos, and ABCB4, ABCG4, and ABCG6 - AMB: gene products of CYP51, SC5D, and SMT
Available human vaccine
No human vaccine is available

Sources: Herwaldt and Berman 1992; Mukherjee et al. 2007; Pérez-Victoria et al. 2011; Ponte-Sucre et al. 2017; Srivastava et al. 2017; Pountain et al. 2019; Potvin et al. 2020

Table III. *Toxoplasma* treatment and possible resistance proteins summary

Toxoplasma
Commonly used compounds for treatment
- If fetal illness was negative: SPI (in some cases AQ) - If fetal illness was positive: PYR + SDZ + FA
Proteins involved in resistance
AQ: *Toxoplasma* cyt-bc1
Available human vaccine
No human vaccine is available

Sources: Bogacz 1954; McFadden et al. 2000; Robert-Gangneux et al. 2011; Prusa et al. 2015; SA Maternal & Neonatal Clinical Network 2015; Alday et al. 2017; Lapinskas and Ben-Harari 2019

Table IV. African *Trypanosoma* treatment and possible resistance proteins summary

African *Trypanosoma*
Commonly used compounds for treatment
T.b.g: 1st stage: PMD or FXZ 2nd stage: NECT or FXZ *T.b.r.* 1st stage: SUR 2nd stage: Mel[b]
Possible proteins involved in resistance
PMD and Mel[b]: TbAT1 and TbAQP2
Available human vaccine
No human vaccine is available

Sources: Bouteille et al. 2003; Nok 2003; Munday et al. 2015; Zoltner et al. 2020; CDC 2024b

Table V. *Giardia* treatment and possible resistance proteins summary

Giardia
Commonly used compounds for treatment
MTZ, ALB or TNZ
Possible proteins involved in resistance
ALB: ROD domain of the β-tubulin and ABC-C1
Available human vaccine
No human vaccine is available

Sources: Argüello-García et al. 2015; Ángeles-Arvizu et al. 2021; Lagunas-Rangel et al. 2021; CDC 2024c

Table VI. *Entamoeba* treatment and possible resistance proteins summary

Entamoeba
Commonly used compounds for treatment
MTZ or TNZ
Proteins involved in resistance
No clear evidence yet
Available human vaccine
No human vaccine is available

Sources: Sawyer et al. 1976; CDC 2019

8. Perspective

The unavoidable global issue of DR in parasitic microorganisms has impeded progress in human health over the past 50 years. This review investigated six pathogenic human parasites and determined that at least two (*Giardia* and *Entamoeba*) did not develop resistance to their current first-line chemo treatments (or at least it is not clear if it is yet). At the same time, the rest have varying degrees of resistance, and some

suspected resistance pathways were identified. There appears to be a proportional relationship between the level of resistance in a system (which stems from the proportion of people suffering from it) and the amount of effort, money, and human power invested in developing novel therapeutics, effective vaccines, and fast and reliable diagnostics, as seen in the case of *Plasmodium* compared to the others. Unfortunately, the bulk of these diseases and resistance occur in less developed countries, and as such, it necessitates the support of developed nations in disease elimination for sustainable living. Moreover, to get a cure and stop protozoans from getting resistant, everyone must do their bit, especially patients who must take their medicine exactly as prescribed. Managing vectors can reduce the strain on chemotherapy treatments for protozoans transmitted by vectors. Using insecticide-coated bed nets, insecticide spray, and improved home construction and fortification can prevent arthropod-transmitted parasites from succumbing to drug pressure selection, as recommended by the WHO. Furthermore, administering treatment as a single dose, similar to certain medications for bacterial urinary tract infections like Fosfomycin (Monural), would benefit the field (Keating 2013). This approach would prevent drug misuse, provide the prescribed dose in a single shot, and would help to monitor DR. Also, the gut microbiome has the potential to be a novel approach to fighting enteric parasites, provided that we have a comprehensive understanding of the interactions and behaviors between parasites and the microbiome (Sharpton *et al*. 2020). Not only humans but also animals are treated using a variety of antiparasitic treatments to treat the same parasites and non-parasitic agents. MTZ is well established in many reports as a treatment for some protozoan diseases, including amoebiasis, giardiasis, and other parasites and pathogenic bacteria. Dogs with giardiasis are also treated with MTZ (Ciuca *et al*. 2021). Examining the library of accessible, efficient medications for various systems and testing them on some of the most prevalent ailments caused by new pathogens would be helpful; these medications would serve as a great alternative if the current ones were ineffective. Hence, to maintain successful, cost-effective, and sustainable control of protozoal diseases, key sectors must work together within the "one health" strategy (Kaplan *et al*. 2009). The WHO, UN Environment Programme, Food and Agriculture Organization of the United Nations, and World Organisation for Animal Health recently launched the "One Health joint plan of action (2022–2026)" to implement strategies on the various forms of life on the planet to prevent health risks and enhance the quality of life. This initiative is based on the fact that our lives are inextricably linked, whether directly or indirectly. However, it is crucial to closely monitor the execution of field plans to assess the effectiveness of the chosen method and develop more efficient strategies. Previously, it was believed that developing a vaccine for parasites was unrealistic. Nevertheless, the WHO approval of the first malaria vaccine in 2021 has renewed optimism that chemotherapy is not the sole viable option for combating malaria and potentially other parasitic diseases. Various institutions are currently developing vaccines to reduce infection rates and improve life sustainability.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

1. Adam R.D.: *Giardia duodenalis*: Biology and Pathogenesis. *Clinical Microbiology Reviews*. **34**(4), e00024-19 (2021) doi:10.1128/CMR.00024-19
2. Alday P.H., Bruzual I., Nilsen A., Pou S., Winter R., Ben Mamoun C., Riscoe M.K., Doggett J.S.: Genetic Evidence for Cytochrome b Qi Site Inhibition by 4(1H)-Quinolone-3-Diarylethers and Antimycin in *Toxoplasma gondii*. *Antimicrob Agents Chemother*. **61**(2) e01866-16 (2017) doi:10.1128/AAC.01866-16
3. Allain T., Amat C.B., Motta J.P., Manko A., Buret A.G.: Interactions of *Giardia* sp. with the intestinal barrier: Epithelium, mucus, and microbiota. *Tissue Barriers*. **5**(1), e1274354 (2017) doi:10.1080/21688370.2016.1274354
4. Alshahethi M.A., Al-Hadheq A.A., Edrees W.H., Abdullah Q.Y., Al-Awar M.S.: Cutaneous leishmaniasis among attending hospitals and health centers in amran governorate, yemen. *Electronic Journal of University of Aden for Basic and Applied Sciences*. **5**(3) 269–276 (2024) doi:10.47372/ejua-ba.2024.3.373
5. Amelo W. and Makonnen E.: Efforts Made to Eliminate Drug-Resistant Malaria and Its Challenges. *BioMed Research International*. **2021**(1), 5539544 (2021) doi:10.1155/2021/5539544
6. Andriantsoanirina V., Khim N., Ratsimbasoa A., Witkowski B., Benedet C., Canier L., Bouchier C., Tichit M., Durand R., Ménard D.: *Plasmodium falciparum* Na+/H+ Exchanger (pfnhe-1) Genetic Polymorphism in Indian Ocean Malaria-Endemic Areas. *The American Journal of Tropical Medicine and Hygiene*. **88**(1), 37 (2013) doi:10.4269/ajtmh.2012.12-0359
7. Ángeles-Arvizu A., Enriquez-Flores S., Jiménez-Gutiérrez A., Pérez-Rangel A., Luna-Arias J.P., Castillo-Romero A., Hernández J.M., León-Avila G.: MDR1 protein (ABC-C1) Over Expression in *Giardia Intestinalis* Incubated with Albendazole and Nitazoxanide. *Acta Parasit*. **66**(4) 1158–1166 (2021) doi:10.1007/s11686-021-00385-5
8. Argüello-García R., Cruz-Soto M., González-Trejo R., Paz-Maldonado L.M.T., Bazán-Tejeda M.L., Mendoza-Hernández G., Ortega-Pierres G.: An antioxidant response is involved in resistance of *Giardia duodenalis* to albendazole. *Front Microbiol*. **6**, 286 (2015) doi:10.3389/fmicb.2015.00286

9. Asare K.K., Africa J., Mbata J., Opoku Y.K.: The emergence of chloroquine-sensitive *Plasmodium falciparum* is influenced by selected communities in some parts of the Central Region of Ghana. *Malar. J.* **20**(1) 447 (2021) doi:10.1186/s12936-021-03985-8
10. Avcı K.D., Karakuş M., Kart Yaşar K.: Molecular survey of pfmdr-1, pfcrt, and pfk13 gene mutations among patients returning from *Plasmodium falciparum* endemic areas to Turkey. *Malar J*. **23**(1) 286 (2024) doi:10.1186/s12936-024-05107-6.
11. Babokhov P., Sanyaolu A.O., Oyibo W.A., Fagbenro-Beyioku A.F., Iriemenam N.C.: A current analysis of chemotherapy strategies for the treatment of human African trypanosomiasis. *Pathogens and Global Health*. **107**(5) 242–252 (2013) doi:10.1179/2047773213Y.0000000105
12. Baina M.T., Djontu J.C., Mbama Ntabi J.D., Mfoutou Mapanguy C.C., Lissom A., Vouvoungui C.J., Boumpoutou R.K., Mouanga A.M., Nguimbi E., Ntoumi F.: Polymorphisms in the Pfcrt, Pfmdr1, and Pfk13 genes of *Plasmodium falciparum* isolates from southern Brazzaville, Republic of Congo. *Sci Rep*. **14**(1), 27988 (2024) doi:10.1038/s41598-024-78670-2
13. Balaji S.N., Deshmukh R., Trivedi V.: Severe malaria: Biology, clinical manifestation, pathogenesis and consequences. *Journal of Vector Borne Diseases*. **57**(1) 1 (2020) doi:10.4103/0972-9062.308793
14. Berberian D.A.: Treatment and prophylaxis of malaria with aralen. *J Palest Arab Med Assoc*. **2**(6) 143–151 (1947)
15. Bisetegn H., Zeleke A.J., Gadisa E., Shumie G., Damte D., Fenta T., Behaksra S., Bayih A.G.: Clinical, parasitological and molecular profiles of Cutaneous Leishmaniasis and its associated factors among clinically suspected patients attending Borumeda Hospital, North-East Ethiopia. *PLoS Negl Trop Dis*. **14**(8) e0008507 (2020) doi:10.1371/journal.pntd.0008507
16. Black M.W. and Boothroyd J.C.: Lytic Cycle of *Toxoplasma gondii*. *Microbiol Mol Biol Rev*. **64**(3) 607–623 (2000) doi: 10.1128/MMBR.64.3.607-623.2000
17. Bogacz J.: 1954. [Comparative effect of various synthetic agents and various antibiotics, including spiramycin, on *Toxoplasma*]. *Bull Soc Pathol Exot Filiales*. **47**(6) 903–915
18. Bouteille B., Oukem O., Bisser S., Dumas M.: Treatment perspectives for human African trypanosomiasis. *Fundamental & Clinical Pharmacology*. **17**(2) 171–181 (2003) doi:10.1046/j.1472-8206.2003.00167.x
19. Bridges D.J., Gould M.K., Nerima B., Mäser P., Burchmore R.J.S., Koning H.P.: Loss of the High-Affinity Pentamidine Transporter Is Responsible for High Levels of Cross-Resistance between Arsenical and Diamidine Drugs in African Trypanosomes. *Mol Pharmacol*. **71**(4) 1098–1108 (2007) doi:10.1124/mol.106.031351
20. Büscher P., Cecchi G., Jamonneau V., Priotto G.: Human African trypanosomiasis. *Lancet*. **390**(10110) 2397–2409 (2017) doi:10.1016/S0140-6736(17)31510-6
21. Camuset G., Remy V., Hansmann Y., Christmann D., Gomes de Albuquerque C., Sena Casseb G.A.: [Mucocutaneous leishmaniasis in Brazilian Amazonia]. *Med Mal Infect*. **37**(6) 343–346 (2007) doi:10.1016/j.medmal.2007.03.012.
22. Carnielli J.B.T., Monti-Rocha R., Costa D.L., Molina Sesana A., Pansini L.N.N., Segatto M., Mottram J.C., Costa C.H.N., Carvalho S.F.G., Dietze R.: Natural Resistance of *Leishmania infantum* to miltefosine Contributes to the Low Efficacy in the Treatment of Visceral Leishmaniasis in Brazil. *Am J Trop Med Hyg*. **101**(4) 789–794 (2019) doi:10.4269/ajtmh.18-0949
23. CDC. 2019. CDC – DPDx – Amebiasis. https://www.cdc.gov/dpdx/amebiasis/index.html. [accessed 2024 Aug 27]
24. CDC. 2024a. CDC – DPDx – Malaria. https://www.cdc.gov/dpdx/malaria/index.html. [accessed 2024 Aug 26]
25. CDC. 2024b. Appendix A: Malaria in the United States: Treatment Tables. Malaria. https://www.cdc.gov/malaria/hcp/clinical-guidance/malaria-treatment-tables.html. [accessed 2024 Sep 7]
26. CDC. 2024c. About Toxoplasmosis. Toxoplasmosis. https://www.cdc.gov/toxoplasmosis/about/index.html. [accessed 2024 Sep 15]
27. CDC. 2024d. Clinical Care of Human African Trypanosomiasis. Sleeping Sickness (African Trypanosomiasis). https://www.cdc.gov/sleeping-sickness/hcp/clinical-care/index.html [accessed 2024 Sep 9]
28. CDC. 2024e. Patient Care for *Giardia* Infection. *Giardia*. https://www.cdc.gov/giardia/hcp/clinical-care/index.html. [accessed 2024 Sep 15]
29. Cernikova L., Faso C., Hehl A.B.: Five facts about *Giardia lamblia*. *PLOS Pathogens*. **14**(9) e1007250 (2018) doi:10.1371/journal.ppat.1007250
30. Certad G., Viscogliosi E., Chabé M., Cacciò S.M.: Pathogenic Mechanisms of *Cryptosporidium* and *Giardia*. *Trends in Parasitology*. **33**(7) 561–576 (2017) doi:10.1016/j.pt.2017.02.006
31. Ciuca L., Pepe P., Bosco A., Caccio S.M., Maurelli M.P., Sannella A.R., Vismarra A., Cringoli G., Kramer L., Rinaldi L., *et al.* Effectiveness of Fenbendazole and Metronidazole Against *Giardia* Infection in Dogs Monitored for 50-Days in Home-Conditions. *Front Vet Sci*. **8** 626424 (2021) doi:10.3389/fvets.2021.626424
32. Cowell A.N., Winzeler E.A.: The genomic architecture of antimalarial drug resistance. *Brief Funct Genomics*. **18**(5) 314–328 (2019) doi:10.1093/bfgp/elz008
33. Cui Z., Li J., Chen Y., Zhang L.: Molecular epidemiology, evolution, and phylogeny of *Entamoeba* spp. *Infection, Genetics and Evolution*. **75**, 104018 (2019) doi:10.1016/j.meegid.2019.104018
34. Dama S., Diakite B., Dinkorma O.T., Niangaly A., Kone A.K., Dara A., Kone A., Bamadio A., Kodio A., Doumbia D., *et al.*: Dynamics of Pfcrt K76T and Pfmdr1N86Y fifteen years after the withdrawal of chloroquine in Mali. *AJPME*. **2**(1), 0–0 (2024) doi:10.35995/ajpme2010004
35. Doliwa C., Escotte-Binet S., Aubert D., Sauvage V., Velard F., Schmid A., Villena I.: Sulfadiazine resistance in Toxoplasma gondii: no involvement of overexpression or polymorphisms in genes of therapeutic targets and ABC transporters. *Parasite*. **20**, 19 (2013) doi:10.1051/parasite/2013020
36. Dubey J.P.: Toxoplasmosis of Animals and Humans. 3rd ed. Boca Raton: CRC Press. (2021)
37. Dubey J.P. and Jones J.L.: *Toxoplasma gondii* infection in humans and animals in the United States. *Int J Parasitol*. **38**(11) 1257–1278 (2008) doi:10.1016/j.ijpara.2008.03.007
38. Dunay I.R., Gajurel K., Dhakal R., Liesenfeld O., Montoya J.G.: Treatment of Toxoplasmosis: Historical Perspective, Animal Models, and Current Clinical Practice. *Clin Microbiol Rev*. **31**(4), e00057-17 (2018) doi:10.1128/CMR.00057-17
39. Faucher B., Pomares C., Fourcade S., Benyamine A., Marty P., Pratlong L., Faraut F., Mary C., Piarroux R., Dedet J.P., *et al.*: Mucosal *Leishmania infantum* leishmaniasis: specific pattern in a multicentre survey and historical cases. *J Infect*. **63**(1), 76–82 (2011) doi:10.1016/j.jinf.2011.03.012
40. Reed D.A., Nomura T., Talley A.K., Cooper R.A., Dzekunov S.M., Ferdig M.T., Ursos L.M., Sidhu A.B., Naudé B., Deitsch K.W., *et al.*: Mutations in the *P. falciparum* digestive vacuole transmembrane protein PfCRT and evidence for their role in chloroquine resistance. *Mol Cell*. **6**(4), 861–871 (2000) doi:10.1016/s1097-2765(05)00077-8

41. Franco J.R., Priotto G., Paone M., Cecchi G., Ebeja A.K., Simarro P.P., Sankara D., Metwally S.B.A., Argaw D.D.: The elimination of human African trypanosomiasis: Monitoring progress towards the 2021–2030 WHO road map targets. *PLOS Neglected Tropical Diseases* **18**(4), e0012111 (2024) doi:10.1371/journal.pntd.0012111
42. Gelaw Y.M., Dagnew G.W., Alene G.D., Gangneux J.P., Robert-Gangneux F.: Tox*oplasma gond*ii seroprevalence among pregnant women in Africa: A systematic review and meta-analysis. *PLOS Neglected Tropical Diseases*. **18**(5), e0012198 (2024) doi:10.1371/journal.pntd.0012198
43. Ghosal A., Sardar S.K., Haldar T., Maruf M., Saito-Nakano Y., Dutta S., Nozaki T., Ganguly S.: Genotyping and epidemiological distribution of diarrhea-causing isolates of *Giardia duodenali*s in southeastern part of West Bengal, India. *Parasitol Res*. **122**(11), 2567–2584 (2023) doi:10.1007/s00436-023-07956-7.44
44. Gibb H., Devleesschauwer B., Bolger P.M., Wu F., Ezendam J., Cliff J., Zeilmaker M., Verger P., Pitt J., Baines J., *et al.* World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins, 2010: a data synthesis. *F1000Res*. **4**, 1393 (2015) doi:10.12688/f1000research.7340.1
45. Gil J.P. and Fançony C.: *Plasmodium falciparum* Multidrug Resistance Proteins (pfMRPs). *Front Pharmacol*. **12** (2021) doi:10.3389/fphar.2021.759422 [accessed 2024 Aug 31] https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.759422/full
46. Keating G.M.: Fosfomycin trometamol: A review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria. *Drugs*. **73**, 1951–1966 (2013) https://doi.org/10.1007/s40265-013-0143-y
47. Graf F.E., Ludin P., Wenzler T., Kaiser M., Brun R., Pyana P.P., Büscher P., Koning H.P. de, Horn D., Mäser P.: Aquaporin 2 Mutations in *Trypanosoma brucei gambiense* Field Isolates Correlate with Decreased Susceptibility to Pentamidine and Melarsoprol. *PLOS Neglected Tropical Diseases*. **7**(10), e2475 (2013) doi:10.1371/journal.pntd.0002475
48. Guimaraes J.L., Lourie E.M.: The inhibition of some pharmacological actions of pentamidine by suramin. *British Journal of Pharmacology and Chemotherapy*. **6**(3), 514 (1951) doi:10.1111/j.1476-5381.1951.tb00663.x
49. Gupta P., Singh K., Balodhi A., Jain K., Deeba F., Salam N.: Prevalence of Amoebiasis and Associated Complications in India: A Systematic Review. *Acta Parasitologica*. **67** (2022) doi:10.1007/s11686-022-00547-z.
50. Hajj R.E., Tawk L., Itani S., Hamie M., Ezzeddine J., El Sabban M., El Hajj H.: Toxoplasmosis: Current and Emerging Parasite Druggable Targets. *Microorganisms*. **9**(12), 2531 (2021) doi:10.3390/microorganisms9122531
51. Hammershaimb E.A. and Berry A.A.: Pre-erythrocytic malaria vaccines: RTS,S, R21, and beyond. *Expert Review of Vaccines*. **23**(1), 49–52 (2024) doi:10.1080/14760584.2023.2292204
52. Hassen J., Alemayehu G.S., Dinka H., Golassa L.: High prevalence of Pfcrt 76T and Pfmdr1 N86 genotypes in malaria infected patients attending health facilities in East Shewa zone, Oromia Regional State, Ethiopia. *Malaria Journal*. **21**(1), 286 (2022) doi:10.1186/s12936-022-04304-5
53. Herwaldt B.L., Berman J.D.: Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg*. **46**(3), 296–306 (1992) doi:10.4269/ajtmh.1992.46.296
54. Hung D.T., Tran L., Tam D.N.H., Elshafei G., Cuong N.T.K., Ha N.X., Khader S.A.E., Le Quang L., Shaikhkhalil H.W., Abdallfatah A., *et al.*: The prevalence of Pfk13 polymorphism in malaria patients treated with artemisinin-based therapy: a systematic review and meta-analysis. *Parasitol Res*. **123**(5), 209 (2024) doi:10.1007/s00436-024-08203-3
55. Imwong M., Pukrittakayamee S., Looareesuwan S., Pasvol G., Poirreiz J., White N.J., Snounou G.: Association of Genetic Mutations in *Plasmodium vivax* dhfr with Resistance to Sulfadoxine-Pyrimethamine: Geographical and Clinical Correlates. *Antimicrobial Agents and Chemotherapy*. **45**(11), 3122–3127 (2001) doi:10.1128/aac.45.11.3122-3127.2001
56. Issa I., Lamine M.M., Hubert V., Ilagouma A., Adehossi E., Mahamadou A., Lobo N.F., Sarr D., Shollenberger L.M., Sandrine H., *et al.* Prevalence of Mutations in the Pfdhfr, Pfdhps, and Pfmdr1 Genes of Malarial Parasites Isolated from Symptomatic Patients in Dogondoutchi, Niger. *Tropical Medicine and Infectious Disease*. **7**(8), 155 (2022) doi:10.3390/tropicalmed7080155
57. Jackson D., Salem A., Coombs G.H.: The *in-vitro* activity of metronidazole against strains of *Escherichia coli* with impaired DNA repair systems. *Journal of Antimicrobial Chemotherapy*. **13**(3), 227–236 (1984) doi:10.1093/jac/13.3.227
58. Johnson A.M.: *Toxoplasma*: Biology, Pathology, Immunology, and Treatment. In: Coccidiosis of Man and Domestic Animals. *CRC Press*. 34 p. (1990)
59. Jones J.L., Kruszon-Moran D., Elder S., Rivera H.N., Press C., Montoya J.G., McQuillan G.M.: *Toxoplasma gondii* Infection in the United States. *Am J Trop Med Hyg*. **98**(2), 551–557 (2018) doi:10.4269/ajtmh.17-0677
60. Kalavani S, Matin S., Rahmanian V., Meshkin A., Bahadori Mazidi B., Taghipour A., Abdoli A.: Prevalence of *Giardia duodenalis* among African children: A systematic review and meta-analysis. *Parasite Epidemiology and Control*. **26**, e00365 (2024) doi:10.1016/j.parepi.2024.e00365
61. Kaplan B., Kahn L.H., Monath T.P., Woodall J.: "ONE HEALTH" and parasitology. *Parasites & Vectors*. **2**(1), 36 (2009) doi:10.1186/1756-3305-2-36
62. Koné M., Kaba D., Kaboré J., Thomas L.F., Falzon L.C., Koffi M., Kouamé C.M., Ahouty B., Compaoré C.F.A., N'Gouan E.K., *et al.*: Passive surveillance of human African trypanosomiasis in Côte d'Ivoire: Understanding prevalence, clinical symptoms and signs, and diagnostic test characteristics. *PLOS Neglected Tropical Diseases*. **15**(8) e0009656 (2021) doi:10.1371/journal.pntd.0009656
63. de Koning H.P., Anderson L.F., Stewart M., Burchmore R.J.S., Wallace L.J.M., Barrett M.P.: The Trypanocide Diminazene Aceturate Is Accumulated Predominantly through the TbAT1 Purine Transporter: Additional Insights on Diamidine Resistance in African Trypanosomes. *Antimicrobial Agents and Chemotherapy*. **48**(5), 1515–1519 (2004) doi:10.1128/aac.48.5.1515-1519.2004
64. Konstantinovic N, Guegan H, Stäjner T, Belaz S, Robert-Gangneux F. 2019. Treatment of toxoplasmosis: Current options and future perspectives. Food and Waterborne Parasitology. 15:e00036. doi:10.1016/j.fawpar.2019.e00036.
65. Krakovka S., Ribacke U., Miyamoto Y., Eckmann L., Svärd S.: Characterization of Metronidazole-Resistant *Giardia intestinalis* Lines by Comparative Transcriptomics and Proteomics. *Front Microbiol*. **13** (2022) doi:10.3389/fmicb.2022.834008 [accessed 2024 Aug 27] https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2022.834008/full
66. Lagunas-Rangel F.A., Yee J., Bermúdez-Cruz R.M.: An update on cell division of *Giardia duodenalis* trophozoites. *Microbiological Research*. **250**, 126807 (2021) doi:10.1016/j.micres.2021.126807
67. Lapinskas P.J. and Ben-Harari R.R.: Perspective on current and emerging drugs in the treatment of acute and chronic toxoplasmosis. *Postgraduate Medicine*. **131**(8), 589–596 (2019) doi:10.1080/00325481.2019.1655258

68. Makarov A., Began J., Mautone I.C., Pinto E., Ferguson L., Zoltner M., Zoll S., Field M.C.: The role of invariant surface glycoprotein 75 in xenobiotic acquisition by African trypanosomes. *Microb Cell*. **10**(2), 18–35 (2023) doi:10.15698/mic2023.02.790
69. Mann S., Frasca K., Scherrer S., Henao-Martínez A.F., Newman S., Ramanan P., Suarez J.A.: A Review of Leishmaniasis: Current Knowledge and Future Directions. *Curr Trop Med Rep*. **8**(2), 121–132 (2021) doi:10.1007/s40475-021-00232-7
70. Marques M.M., Costa M.R.F., Santana Filho F.S., Vieira J.L.F., Nascimento M.T.S., Brasil L.W., Nogueira F., Silveira H., Reyes-Lecca R.C., Monteiro W.M., *et al*.: *Plasmodium vivax* Chloroquine Resistance and Anemia in the Western Brazilian Amazon. *Antimicrobial Agents and Chemotherapy*. **58**(1), 342–347 (2014) doi:10.1128/aac.02279-12
71. Matovu E., Stewart M.L., Geiser F., Brun R., Mäser P., Wallace L.J.M., Burchmore R.J., Enyaru J.C.K., Barrett M.P., Kaminsky R., *et al*.: Mechanisms of Arsenical and Diamidine Uptake and Resistance in *Trypanosoma brucei*. *Eukaryotic Cell*. **2**(5), 1003–1008 (2003) doi:10.1128/ec.2.5.1003-1008.2003
72. McFadden D.C., Tomavo S., Berry E.A., Boothroyd J.C.: Characterization of cytochrome *b* from *Toxoplasma gondii* and Qo domain mutations as a mechanism of atovaquone-resistance. *Molecular and Biochemical Parasitology*. **108**(1), 1–12 (2000) doi:10.1016/S0166-6851(00)00184-5
73. Meneceur P., Bouldouyre M.A., Aubert D., Villena I., Menotti J., Sauvage V., Garin J.F., Derouin F.: *In Vitro* Susceptibility of Various Genotypic Strains of *Toxoplasma gondii* to Pyrimethamine, Sulfadiazine, and Atovaquone. *Antimicrob Agents Chemother*. **52**(4), 1269–1277 (2008) doi:10.1128/AAC.01203-07
74. Meshnick S.R. and Dobson M.J.: The History of Antimalarial Drugs. In: Rosenthal PJ, editor. Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery. *Totowa, NJ: Humana Press*. p. 15–25 (2001) [accessed 2024 Sep 7] https://doi.org/10.1007/978-1-59259-111-4_2
75. Minbaeva G., Schweiger A., Bodosheva A., Kuttubaev O., Hehl A.B., Tanner I., Ziadinov I., Torgerson P.R., Deplazes P.: Toxoplasma gondii infection in Kyrgyzstan: seroprevalence, risk factor analysis, and estimate of congenital and AIDS-related toxoplasmosis. *PLoS Negl Trop Dis*. **7**(2), e2043 (2013) doi:10.1371/journal.pntd.0002043
76. Monis P.T., Caccio S.M., Thompson R.C.A.: Variation in *Giardia*: towards a taxonomic revision of the genus. *Trends in Parasitology*. **25**(2), 93–100 (2009) doi:10.1016/j.pt.2008.11.006
77. Moreira E.T. de S., Castro Faria Neto H.C. de, Reis P.A.: Chapter 17 – Cerebral malaria: Understanding the parasite pathogenesis in the brain. In: De Quevedo JL, Barichello T, Hasbun R, Dal-Pizzol F, editors. Neurobiology of Infectious Diseases. Academic Press. (Neurobiology of Disease). p. 291–304 (2025)
78. Moss S., Mańko E., Krishna S., Campino S., Clark T.G., Last A.: How has mass drug administration with dihydroartemisinin-piperaquine impacted molecular markers of drug resistance? A systematic review. *Malar J*. **21**(1), 186 (2022) doi:10.1186/s12936-022-04181-y
79. Mukherjee A., Padmanabhan P.K., Singh S., Roy G., Girard I., Chatterjee M., Ouellette M., Madhubala R.: Role of ABC transporter MRPA, γ-glutamylcysteine synthetase and ornithine decarboxylase in natural antimony-resistant isolates of *Leishmania donovani*. *Journal of Antimicrobial Chemotherapy*. **59**(2), 204–211 (2007) doi:10.1093/jac/dkl494
80. Munday J.C., Eze A.A., Baker N., Glover L., Clucas C., Aguinaga Andrés D., Natto M.J., Teka I.A., McDonald J., Lee R.S., *et al*. *Trypanosoma brucei* aquaglyceroporin 2 is a high-affinity transporter for pentamidine and melaminophenyl arsenic drugs and the main genetic determinant of resistance to these drugs. *Journal of Antimicrobial Chemotherapy*. **69**(3), 651–663 (2014) doi:10.1093/jac/dkt442
81. Munday J.C., Settimo L., de Koning H.P.: Transport proteins determine drug sensitivity and resistance in a protozoan parasite, *Trypanosoma brucei*. *Front Pharmacol*. **6** (2015) doi:10.3389/fphar.2015.00032
82. Naghavi M., Mestrovic T., Gray A., Hayoon A.G., Swetschinski L.R., Aguilar G.R., Weaver N.D., Ikuta K.S., Chung E., Wool E.E., *et al*.: Global burden associated with 85 pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Infectious Diseases*. **24**(8), 868–895 (2024) doi:10.1016/S1473-3099(24)00158-0
83. Nok A.J.: Arsenicals (melarsoprol), pentamidine and suramin in the treatment of human African trypanosomiasis. *Parasitol Res*. **90**(1), 71–79 (2003) doi:10.1007/s00436-002-0799-9
84. Noronha M., Pawar V., Prajapati A., Subramanian R.B.: A literature review on traditional herbal medicines for malaria. *South African Journal of Botany*. **128** 292–303 (2020) doi:10.1016/j.sajb.2019.11.017
85. Nsobya S.L., Dokomajilar C., Joloba M., Dorsey G., Rosenthal P.J.: Resistance-Mediating *Plasmodium falciparum* pfcrt and pfmdr1 Alleles after Treatment with Artesunate-Amodiaquine in Uganda. *Antimicrobial Agents and Chemotherapy*. **51**(8), 3023–3025 (2007) doi:10.1128/aac.00012-07
86. O'Neill P.M., Barton V.E., Ward S.A.: The molecular mechanism of action of artemisinin-the debate continues. *Molecules*. **15**(3), 1705–1721 (2010) doi:10.3390/molecules15031705
87. Pacheco M.A., Schneider K.A., Cheng Q., Munde E.O., Ndege C., Onyango C., Raballah E., Anyona S.B., Ouma C., Perkins D.J., *et al*. Changes in the frequencies of *Plasmodium falciparum* dhps and dhfr drug-resistant mutations in children from Western Kenya from 2005 to 2018: the rise of Pfdhps S436H. *Malar J*. **19**(1), 378 (2020) doi:10.1186/s12936-020-03454-8
88. Patel P., Bharti P.K., Bansal D., Ali N.A., Raman R.K., Mohapatra P.K., Sehgal R., Mahanta J., Sultan A.A., Singh N.: Prevalence of mutations linked to antimalarial resistance in *Plasmodium falciparum* from Chhattisgarh, Central India: A malaria elimination point of view. *Sci Rep*. **7**(1), 16690 (2017) doi:10.1038/s41598-017-16866-5
89. Pérez-Victoria J.M., Bavchvarov B.I., Torrecillas I.R., Martínez-García M., López-Martín C., Campillo M., Castanys S., Gamarro F.: Sitamaquine overcomes ABC-mediated resistance to miltefosine and antimony in *Leishmania*. *Antimicrob Agents Chemother*. **55**(8), 3838–3844 (2011) doi:10.1128/AAC.00065-11
90. Perry D., Dixon K., Garlapati R., Gendernalik A., Poché D., Poché R.: Visceral Leishmaniasis Prevalence and Associated Risk Factors in the Saran District of Bihar, India, from 2009 to July of 2011. *Am J Trop Med Hyg*. **88**(4), 778–784 (2013) doi:10.4269/ajtmh.12-0442
91. Pinart M., Rueda J.R., Romero G.A., Pinzón-Flórez C.E., Osorio-Arango K., Silveira Maia-Elkhoury A.N., Reveiz L., Elias V.M., Tweed J.A.: Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database Syst Rev*. **2020**(8), CD004834 92020) doi:10.1002/14651858.CD004834.pub3
92. Pluijm R.W. van der, Amaratunga C., Dhorda M., Dondorp A.M.: Triple Artemisinin-Based Combination Therapies for Malaria – A New Paradigm? *Trends in Parasitology* **37**(1), 15–24 (2021) doi:10.1016/j.pt.2020.09.011
93. Ponte-Sucre A., Gamarro F., Dujardin J.C., Barrett M.P., López-Vélez R., García-Hernández R., Pountain A.W., Mwenechanya R., Papadopoulou B.: Drug resistance and treatment failure in leishmaniasis: A 21st century challenge. *PLOS Neglected Tropical Diseases* **11**(12), e0006052 (2017) doi:10.1371/journal.pntd.0006052
94. Potvin J.E., Leprohon P., Queffeulou M., Sundar S., Ouellette M.: Mutations in an Aquaglyceroporin as a Proven Marker of Antimony Clinical Resistance in the Parasite *Leishmania donovani*. *Clin Infect Dis*. **72**(10), e526–e532 (2020) doi:10.1093/cid/ciaa1236

95. Pountain A.W., Weidt S.K., Regnault C., Bates P.A., Donachie A.M., Dickens N.J., Barrett M.P.: Genomic instability at the locus of sterol C24-methyltransferase promotes amphotericin B resistance in *Leishmania* parasites. *PLoS Negl Trop Dis*. **13**(2), e0007052 (2019) doi:10.1371/journal.pntd.0007052
96. Prusa A.R., Kasper D.C., Pollak A., Olischar M., Gleiss A., Hayde M.: Amniocentesis for the detection of congenital toxoplasmosis: results from the nationwide Austrian prenatal screening program. *Clinical Microbiology and Infection*. **21**(2), 191.e1-191.e8 (2015) doi:10.1016/j.cmi.2014.09.018
97. Pulcini S., Staines H.M., Lee A.H., Shafik S.H., Bouyer G., Moore C.M., Daley D.A., Hoke M.J., Altenhofen L.M., Painter H.J., *et al.*: Mutations in the *Plasmodium falciparum* chloroquine resistance transporter, PfCRT, enlarge the parasite's food vacuole and alter drug sensitivities. *Sci Rep*. **5**(1), 14552 (2015) doi:10.1038/srep14552
98. Reed M.B., Saliba K.J., Caruana S.R., Kirk K., Cowman A.F.: Pgh1 modulates sensitivity and resistance to multiple antimalarials in *Plasmodium falciparum*. *Nature*. **403**(6772), 906–909 (2000) doi:10.1038/35002615
99. Rénia L. and Goh Y.S.: Malaria Parasites: The Great Escape. *Front Immunol*. **7** (2016) doi:10.3389/fimmu.2016.00463
100. Riches A., Hart C.J.S., Trenholme K.R., Skinner-Adams T.S.: Anti-*Giardia* Drug Discovery: Current Status and Gut Feelings. *J Med Chem*. **63**(22), 13330–13354 (2020) doi:10.1021/acs.jmedchem.0c00910
101. Robert-Gangneux F., Murat J.B., Fricker-Hidalgo H., Brenier-Pinchart M.P., Gangneux J.P., Pelloux H.: The placenta: a main role in congenital toxoplasmosis? *Trends Parasitol*. **27**(12), 530–536 (2011) doi:10.1016/j.pt.2011.09.005
102. Rodrigo C., Rajapakse S., Fernando D.: Tafenoquine for preventing relapse in people with *Plasmodium vivax* malaria. *Cochrane Database Syst Rev.* **2020**(9), CD010458 (2020) doi:10.1002/14651858.CD010458.pub3
103. Roro G.B., Eriso F., Al-Hazimi A.M., Kuddus M., Singh S.C., Upadhye V., Hajare S.T.: Prevalence and associated risk factors of *Entamoeba histolytica* infection among school children from three primary schools in Arsi Town, West Zone, Ethiopia. *J Parasit Dis*. **46**(3), 776–784 (2022) doi:10.1007/s12639-022-01495-1
104. SA Maternal & Neonatal Clinical Network. South Australian Perinatal Practice Guidelines toxoplasmosis in pregnancy. (2015)
105. Sands M., Kron M.A., Brown R.B.: Pentamidine: A Review. *Reviews of Infectious Diseases*. **7**(5), 625–6344 (1985) doi:10.1093/clinids/7.5.625
106. Sasidharan S. and Saudagar P.: Leishmaniasis: where are we and where are we heading? *Parasitol Res*. **120**(5), 1541–1554 (2021) doi:10.1007/s00436-021-07139-2
107. Sawyer P.R., Brogden R.N., Pinder R.M., Speight T.M., Avery G.S.: Tinidazole: a review of its antiprotozoal activity and therapeutic efficacy. *Drugs*. **11**(6), 423–440 (1976) doi:10.2165/00003495-197611060-00003
108. Schousboe M.L., Ranjitkar S., Rajakaruna R.S., Amerasinghe P.H., Morales F., Pearce R., Ord R., Leslie T., Rowland M., Gadalla N.B, *et al.* Multiple Origins of Mutations in the mdr1 Gene-A Putative Marker of Chloroquine Resistance in *P. vivax*. *PLOS Neglected Tropical Diseases*. **9**(11), e0004196 (2015) doi:10.1371/journal.pntd.0004196
109. Semedo M.G., Pereira A.L., Pita J.R.: The influence of German science on Cinchona and quinine research in Portugal in the second half of the 19th century. *Pharmazie*. **76**(8), 396–402 (2021) doi:10.1691/ph.2021.1050
110. Servián A., Helman E., Iglesias M. del R., Panti-May J.A., Zonta M.L., Navone G.T.: Prevalence of Human Intestinal *Entamoeba* spp. in the Americas: A Systematic Review and Meta-Analysis 1990-2022. *Pathogens*. **11**(11), 1365 (2022) doi:10.3390/pathogens11111365
111. Sharpton T.J., Combrink L., Arnold H.K., Gaulke C.A., Kent M.: Harnessing the Gut Microbiome in the Fight against Anthelmintic Drug Resistance. Curr Opin Microbiol. **53**, 26–34 (2020) doi:10.1016/j.mib.2020.01.017
112. Silva L.A., Reis-Cunha J.L., Bartholomeu D.C., Vítor R.W.A.: Genetic Polymorphisms and Phenotypic Profiles of Sulfadiazine-Resistant and Sensitive *Toxoplasma gondii* Isolates Obtained from Newborns with Congenital Toxoplasmosis in Minas Gerais, Brazil. *PLOS ONE* **12**(1), e0170689 (2017) doi:10.1371/journal.pone.0170689
113. Singh A., Banerjee T., Shukla S.K., Upadhyay S., Verma A.: Creep in nitroimidazole inhibitory concentration among the *Entamoeba histolytica* isolates causing amoebic liver abscess and screening of andrographolide as a repurposing drug. *Sci Rep*. **13**(1), 12192 (2023) doi:10.1038/s41598-023-39382-1
114. Singh A., Houpt E., Petri W.A.: Rapid Diagnosis of Intestinal Parasitic Protozoa, with a Focus on Entamoeba histolytica. *Interdisciplinary Perspectives on Infectious Diseases* **2009**(1), 547090 (2009) doi:10.1155/2009/547090
115. Sosa N., Pascale J.M., Jiménez A.I., Norwood J.A., Kreishman-Detrick M., Weina P.J., Lawrence K., McCarthy W.F., Adams R.C., Scott C., *et al.* Topical paromomycin for New World cutaneous leishmaniasis. *PLoS Negl Trop Dis*. **13**(5), e0007253 (2019) doi:10.1371/journal.pntd.0007253
116. Srivastava S., Mishra J., Gupta A.K., Singh A., Shankar P., Singh S.: Laboratory confirmed miltefosine resistant cases of visceral leishmaniasis from India. *Parasit Vectors*. **10**, 49 (2017) doi:10.1186/s13071-017-1969-z
117. Staines H.M., Burrow R.., Teo B.H.Y., Chis Ster I., Kremsner P.G., Krishna S.: Clinical implications of *Plasmodium* resistance to atovaquone/proguanil: a systematic review and meta-analysis. *J Antimicrob Chemother*. **73**(3), 581–595 (2018) doi:10.1093/jac/dkx431
118. Steverding D.: The spreading of parasites by human migratory activities. *Virulence*. **11**(1), 1177–1191 (2020) doi:10.1080/21505594.2020.1809963
119. Takala-Harrison S., Jacob C.G., Arze C., Cummings M.P., Silva J.C., Dondorp A.M., Fukuda M.M., Hien T.T., Mayxay M., Noedl H., *et al.* Independent emergence of artemisinin resistance mutations among *Plasmodium falciparum* in Southeast Asia. *J Infect Dis*. **211**(5), 670–679 (2015) doi:10.1093/infdis/jiu491
120. Tharmaratnam T., Kumanan T., Iskandar M.A., D'Urzo K., Gopee-Ramanan P., Loganathan M., Tabobondung T., Tabobondung T.A., Sivagurunathan S., Patel M., *et al. Entamoeba histolytica* and amoebic liver abscess in northern Sri Lanka: a public health problem. *Trop Med Health*. **48**(1), 2 (2020) doi:10.1186/s41182-020-0193-2
121. Tjitra E., Baker J., Suprianto S., Cheng Q., Anstey N.M.: Therapeutic Efficacies of Artesunate-Sulfadoxine-Pyrimethamine and Chloroquine-Sulfadoxine-Pyrimethamine in *Vivax* Malaria Pilot Studies: Relationship to *Plasmodium vivax* dhfr Mutations. *Antimicrob Agents Chemother*. **46**(12), 3947–3953 (2002) doi:10.1128/AAC.46.12.3947-3953.2002
122. Torgerson P.R. and Mastroiacovo P.: The global burden of congenital toxoplasmosis: a systematic review. *Bull World Health Organ*. **91**(7), 501–508 (2013) doi:10.2471/BLT.12.111732
123. Tripathi L.K., Nailwal T.K.: Chapter 1 – Leishmaniasis: an overview of evolution, classification, distribution, and historical aspects of parasite and its vector. In: Samant M, Chandra Pandey S, editors. Pathogenesis, Treatment and Prevention of Leishmaniasis. Academic Press. p. 1–25 (2021) https://www.sciencedirect.com/science/article/pii/B9780128228005000044

124. Tse E.G., Korsik M., Todd M.H.: The past, present and future of antimalarial medicines. *Malaria Journal*. **18**(1), 93 (2019) doi:10.1186/s12936-019-2724-z
125. Ungogo M.A., Campagnaro G.D., Alghamdi A.H., Natto M.J., de Koning H.P.: Differences in Transporters Rather than Drug argets Are the Principal Determinants of the Different Innate Sensitivities of *Trypanosoma* congolense and Trypanozoon Subgenus Trypanosomes to Diamidines and Melaminophenyl Arsenicals. *International Journal of Molecular Sciences* **23**(5), 2844 (2022) doi:10.3390/ijms23052844
126. Waithera M.W., Sifuna M.W., Kimani S.K., Takei M.:. Drug selection pressure and fitness cost for artemether-resistant *Plasmodium berghei* ANKA parasites in vivo. *International Journal of Antimicrobial Agents* **62**(6), 107012 (2023) doi:10.1016/j.ijantimicag.2023.107012
127. WHO. 2020. Sustained decline in sleeping sickness cases puts elimination within reach. [accessed 2024 Oct 4]. https://www.who.int/news/item/23-06-2020-sustained-decline-in-sleeping-sickness-cases-puts-elimination-within-reach.
128. Wicht K.J., Mok S., Fidock D.A.: Molecular Mechanisms of Drug Resistance in *Plasmodium falciparum* Malaria. *Annual Review of Microbiology*. **74**, 431–454 (2020) doi:10.1146/annurev-micro-020518-115546
129. Wijnant G.J, Dumetz F., Dirkx L., Bulté D., Cuypers B., Van Bocxlaer K., Hendrickx S.: Tackling Drug Resistance and Other Causes of Treatment Failure in Leishmaniasis. *Front Trop Dis*. **3** (2022) doi:10.3389/fitd.2022.837460
130. WHO. 2024a. Leishmaniasis. [accessed 2024 Aug 26]. https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.
131. WHO. 2024b. Guidelines for the treatment of human African trypanosomiasis.[accessed 2024 Sep 3]. https://www.who.int/publications/i/item/9789240096035.
132. WHO. 2023. World Malaria Report 2023. [accessed 2024 Aug 26]. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023.
133. Xie S.C., Ralph S.A., Tilley L.:. K13, the Cytostome, and Artemisinin Resistance. *Trends Parasitol*. **36**(6), 533–544 (2020) doi:10.1016/j.pt.2020.03.006
134. Yoshida N., Yamauchi M., Morikawa R., Hombhanje F., Mita T.: Increase in the proportion of *Plasmodium falciparum* with kelch13 C580Y mutation and decline in pfcrt and pfmdr1 mutant alleles in Papua New Guinea. *Malar J*. **20**(1), 410 (2021) doi:10.1186/s12936-021-03933-6
135. Zajaczkowski P., Lee R., Fletcher-Lartey S.M., Alexander K., Mahimbo A., Stark D., Ellis J.T.: The controversies surrounding *Giardia intestinalis* assemblages A and B. *Current Research in Parasitology & Vector-Borne Diseases* **1**, 100055 (2021) doi:10.1016/j.crpvbd.2021.100055
136. Zoltner M., Campagnaro G.D., Taleva G., Burrell A., Cerone M., Leung K.F., Achcar F., Horn D., Vaughan S., Gadelha C., e*t al.* Suramin exposure alters cellular metabolism and mitochondrial energy production in African trypanosomes. *Journal of Biological Chemistry*. **295**(24), 8331–8347 (2020) doi:10.1074/jbc.RA120.012355