An Examination of Malaria, African Trypanosomiasis, and American Trypanosomiasis: Blood-borne Parasitic Infections Spread through Vector Transmission

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Honors 401/402

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April 28, 2021

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Introduction

Neglected tropical diseases (NTDs), which often impact poor, rural areas, are known to impair both physical and cognitive development, contribute to mother and child illness and death, exacerbate the difficulty of farming, and limit workplace productivity. The CDC states that NTDs, which include various parasitic, viral, and bacterial diseases, affect more than one billion people globally. Both American Trypanosomiasis and African Trypanosomiasis are considered NTDs, resulting in approximately 60,000 - 510,000 combined deaths per year. In order for NTDs to be eradicated, stronger education and prevention programs are needed. While malaria is not considered a NTD, it can be included in the diseases that need a more aggressive approach due to it causing over 400,000 deaths per year - most of which are children (CDC, 2021).

Through vector transmission, certain blood-borne parasites have the ability to infiltrate and infect both the human circulatory and lymphatic system. Although treatments and preventative plans are already in place or available for many countries, the contraction of blood-borne parasitic infections continues to concern health officials across the globe. If a more proactive preventative care plan is created and enforced within a community, then the incidence of blood-borne parasitic infections will decrease; therefore, raising awareness and education toward these infections is the first step needed in lowering these cases.

The purpose of this paper is to examine the similarities and differences between three blood-borne parasites, including (but not limited to) mode of transmission, geographical location, groups most susceptible, physiology, symptoms, diagnosis, and treatments. Highlighting possible connections for future research dealing with innovative prevention/protection plans and potential medical treatments for these blood-borne parasitic infections will be discussed.

Malaria

History

Before thy feet I fall
Lord, who made high my fate
For in the mighty small
Thou showd'st the mighty great.

- *Ronald Ross*

Ronald Ross, recipient of the Nobel prize for physiology and medicine in 1902, wrote this particular verse on August 21, 1897. The "mighty small" was referring to the mosquito's protozoan parasite and the "mighty great" to the mechanism of malaria. Ross wrote this piece the day after he observed pigmented granules, similar to those found in the blood of malaria victims (**Fig 1**), in the stomach wall of an *Anopheles* mosquito. These pigments were later determined to be the cause of malaria, the *Plasmodium falciparum* or *Plasmodium vivax* parasites (Heilbron and Bynum, 1998).

During all early periods of history - especially in great wars - there were more casualties caused by diseases than by injuries. Disease spread rapidly among the large crowds of soldiers whose wounds were not properly cleaned and dressed, lived in cramped spaces with insufficient water supplies, used dirty restrooms, and ate inadequate diets. Things changed dramatically with the increasing modernity of war in the 20th century. World War I was the first modern war in which the ratio of casualties caused by injuries vs disease was inverted. This is believed to be due to bacteriological and serological research which offered effective vaccines against typhoid fever and diphtheria, along with the development of quinine for the treatment of malaria; however, malaria still persists today (Lederberg, 2000; Eckart, 1999).

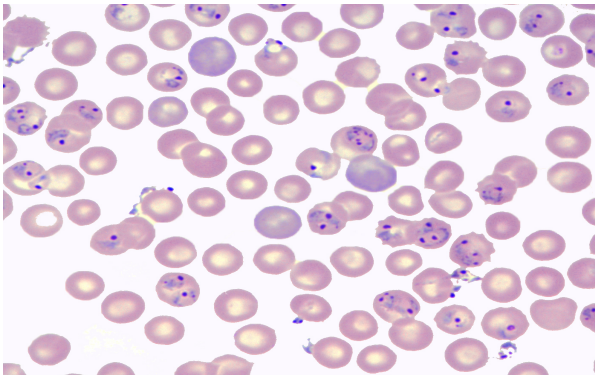

Figure 1. *Plasmodium* parasites in red blood cells. The malaria parasites can be seen as pigmented (purple) granules both within and outside red blood cells (pink).
(Figure Credit: HHMI*)

*See Glossary

Geographical Location

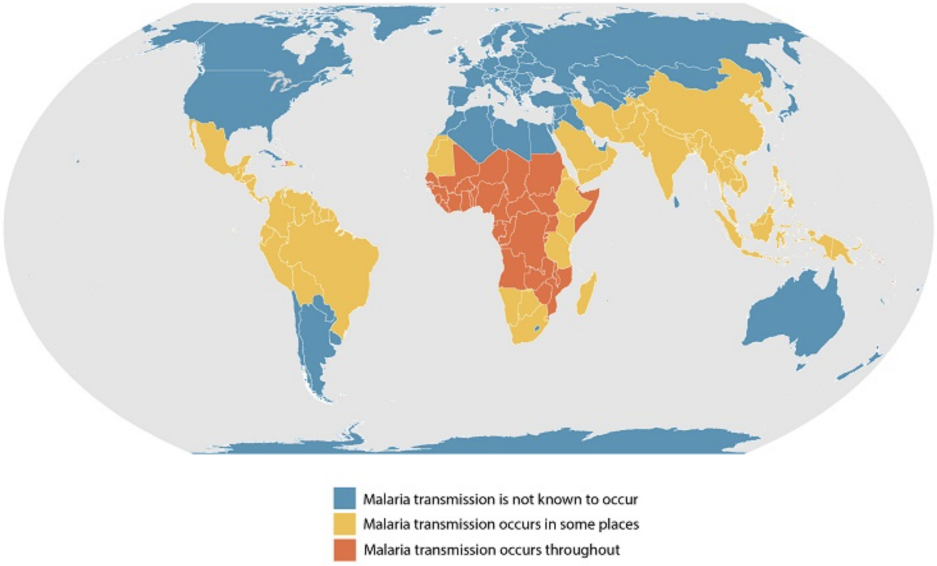

Figure 2. Global malaria transmission (2020)**.** This map depicts the approximate locations of malaria transmission around the world.
(Figure Credit: CDC*)

Malaria is becoming increasingly transported throughout Africa. It is transmitted in tropical and subtropical areas including sub-Saharan Africa and southern Asia; however, parts of Oceania and Africa south of the Sahara have the highest rate of transmission (**Fig 2**) (CDC, 2021).

Mode of Transmission

Malaria is transmitted through the bite of an infected *Anopheles* mosquito, making this a vector-borne disease. This disease is present in 108 countries that are inhabited by roughly 3 billion people. In 2010, there were an estimated 216 million cases and 655,000 deaths (Cotter et al., 2013). More than 85% of malaria cases and over 90% of malaria deaths occur in sub-Saharan Africa, mainly in children younger than 5 years old (CDC, 2021).

While most transmission consists of local mosquito exposure, another growing concern is “airport” malaria. Malaria caused by infected mosquitoes that are transferred quickly by aircraft from a malaria-endemic country to a non-endemic country is known as "airport" malaria. If the local conditions allow, they can bite the local population, infecting them with malaria (CDC, 2021).

It is also important to note that approximately 150 cases of congenital malaria occur each year. This is when infected pregnant mothers transmit parasites to their child either transplacentally or perinatally (Jabbarzare et al., 2020).

Parasite Life Cycle

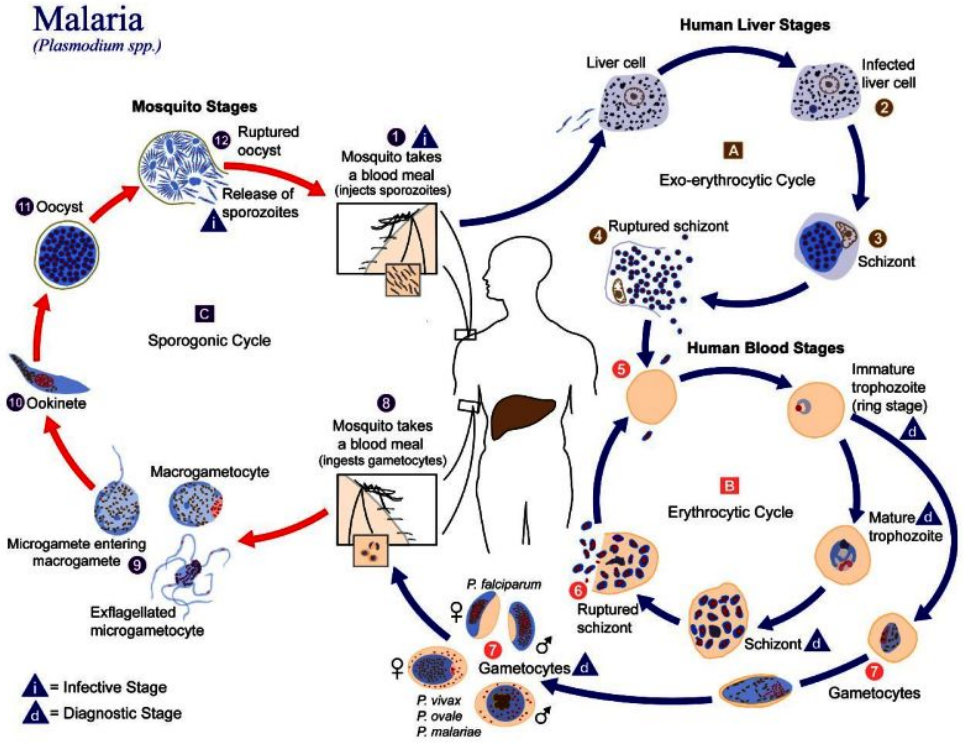

Figure 3. *Plasmodium* parasite life cycle.
(Figure Credit: CDC*)

Two hosts are involved in the malaria parasite life cycle (**Fig 3**). A malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host during a blood meal **(1)**. Sporozoites (infective agents) infect liver cells **(2)**, mature into schizonts **(3)**, and then rupture, releasing merozoites **(4)**. (It's worth noting that a dormant stage in *P. vivax* and *P. ovale* can remain in the liver [if left untreated] and cause relapses by entering the bloodstream weeks or even years later.) After initial replication in the liver (exo-erythrocytic schizogony **[A]**), the parasites proliferate asexually in the erythrocytes (erythrocytic schizogony **[B]**). Merozoites then infect red blood cells **(5)**. The trophozoites in the ring stage develop into schizonts, which rupture and release merozoites **(6)**. Some parasites differentiate into gametocytes, which are a part of the sexual erythrocytic stages **(7)**. The clinical manifestations of the disease are caused by blood stage parasites. An *Anopheles* mosquito consumes male (microgametocytes) and female (macrogametocytes) gametocytes during a blood meal **(8)**. The sporogonic cycle **[C]** describes the parasites' replication in the mosquito. The microgametes enter the macrogametes in the mosquito's gut, resulting in zygotes **(9)**. The zygotes become motile and elongated (ookinetes) **(10)** and infiltrate the mosquito's midgut wall, where they grow into oocysts **(11)**. The oocysts expand, burst, and release sporozoites **(12)**, which invade the salivary glands of the mosquito. The malaria life cycle is perpetuated by injecting sporozoites **(1)** into a new human host (CDC, 2021).

Physiology

The immune response to *P. falciparum* and *P. vivax* is still poorly understood and highly complex. Although antibodies and T cells can control parasite growth in model systems, natural immunity to malaria in regions of high endemicity takes several years to develop. Variation and polymorphism of antibody target antigens are known to impede immune responses, but these factors alone cannot account for the slow acquisition of immunity (Good et al., 2005).

Cell-mediated responses can effectively monitor parasite growth in human and animal model systems, however these responses are controlled by parasite load via direct effects on dendritic cells and, ultimately, T and B cell function. In addition, a high parasite load is linked to pathology, and cell-mediated responses play a significant role in host damage (Good et al., 2005).

The acquisition of cerebral malaria, anemia, weight loss, and respiratory failure have all been linked to inflammatory cytokines. Rapid parasite clearance, efficient modulation of anti-parasite inflammatory effects, and the ultimate production of a range of antibodies effective against different strains are all required for parasite immunity (Moncunill et al., 2013; Knox et al., 2016).

Signs and Symptoms

Malaria is often the most common cause of fever in endemic areas. Malaria begins with non-specific symptoms such as malaise, headache, exhaustion, muscle aches, and abdominal pain, often followed by an irregular fever. Nausea, vomiting, and orthostatic hypotension are all common symptoms of malaria. Generalized seizures are only associated with *falciparum* malaria and may be followed by coma (cerebral malaria). Other than a fever, moderate anemia, and a palpable spleen, most patients with uncomplicated infections have few irregular physical findings. The liver can enlarge in children under the age of five, while mild jaundice is more common in adults. Recurrent infections cause chronic anemia and splenomegaly in young children living in areas where transmission is constant. The symptoms of severe *falciparum* malaria vary according to age. Children are more likely to develop severe anemia and hypoglycemia, while adults are more likely to develop acute pulmonary edema, acute kidney injury, and jaundice; coma and acidosis occur in all age groups. Although the correlation between parasite density and prognosis for *falciparum* malaria is highly variable, when parasitemia reaches 2%, the mortality rises. Studies have shown that uncomplicated *falciparum* malaria has a mortality rate of around 0.1% when treated promptly with approved antimalarial drugs (White et al., 2014).

Diagnosis

The gold standard for diagnosis is the examination of both thick and thin blood film microscopy. Simple, sensitive, and specific antibody-based rapid diagnostic tests that recognize species specific proteins PfHRP2 (*Plasmodium falciparum* histidine-rich proteins 2), pan-malaria/species-specific lactate dehydrogenase, or aldolase antigens in finger-prick blood are now routinely used. PfHRP2-based tests (which determine the concentration of these circulating glycoproteins) can test positive for weeks after an acute infection which limits their usefulness in high-transmission areas (Ho et al., 2014). However, these tests can be used to diagnose severe malaria in patients who have cleared peripheral parasitemia after taking artemisinin (lactone used to treat *falciparum* malaria) due to the test remaining strongly positive. For the diagnosis of *falciparum* malaria, PfHRP2-based rapid diagnostic tests are as reliable as routine microscopy due to the positive correlation between protein and parasite concentration (Ho et al., 2014; Ravaoarisoa et al., 2010). While sensitivity is poor for *P. vivax* densities less than 200/L, the new-generation tests, which are based on the detection of plasmodium lactate dehydrogenase, are considered effective at diagnosing both *falciparum* and *vivax* infections. Aldolase-based tests are considered less sensitive, especially for non-*falciparum* species such as *P. vivax*. Rapid diagnostic tests are particularly useful in epidemic investigations due to their simplicity and speed. They are, however, costly and do not measure parasitemia (White et al., 2014).

Treatments

Malaria vaccines have required a significant amount of time, effort, and money to produce. The most advanced vaccine in development is the RTS,S subunit vaccine, which targets *P. falciparum*'s circumsporozoite protein, boosted by the potent ASO adjuvant. The findings of a major multicenter study of RTS,S in infants (aged 6-12 weeks) at first immunization (deployed as a monthly dose for three months) showed strong safety but only moderate efficacy, with only 30% protection against clinical malaria and 26% protection against severe malaria within 12 months of last dose. Previously reported results in slightly older children (aged 5-17 months) were better, with 55% protection against all *falciparum* malaria and 35% protection against severe malaria up to 14 months after vaccination (Agyekum, 2012; White et al., 2014). The quest for an efficacious vaccine continues. One clinical trial conducted recently examined a PfSPZ (*Plasmodium falciparum* and sporozoites) vaccine (designed to target sporozoites) that protected over 80% of the volunteers (Zenklusen et al., 2018).

Other treatments for malaria include oral drugs such as amodiaquine plus sulfadoxine-pyrimethamine (AQ + SP), chloroquine, hydroxychloroquine, artemisinin combination, and doxycycline. Doxycycline is one of the cheapest malaria drugs available and is highly effective at killing the asexual, erythrocytic stages of the malaria parasite; however, it is not recommended for children under the age of 12 and women who are pregnant (White et al., 2014).

Drug Resistance in Parasite

During the rainy season (July to November) when malaria usually ravages the population, ~1.2 million healthy children across western Africa (Mali, Togo, Chad, Niger, Nigeria, and Senegal) receive antimalarial drugs. The countries' governments deploy this intervention, known as seasonal malaria chemoprevention (SMC) (AQ + SP), through financial support from the United States, the United Nations, and Doctors Without Borders (also known as Médecins sans Frontières) (Maxmen, 2013). Although SMC is quick and easy to dispense and protects ~75% of those who take it (WHO, 2012), scientists fully expect SMC to encourage widespread drug resistance. No one knows when, exactly, but drug resistance could develop in as little as five years from now (Maraka et al., 2020).

Antimalarial oral drug prevention is not new: travelers regularly take them while traveling to endemic countries; however, those living in malaria-endemic areas have long been advised to avoid taking drugs prophylactically in order to prevent the development of drug resistant *Plasmodium falciparum* and/or *vivax* (Maxmen, 2013). The current areas of greatest concern are western Cambodia and the Thailand-Myanmar border, where artemisinin-resistant *P. falciparum* have emerged. Resistance to both chloroquine and sulfadoxine-pyrimethamine emerged in this region previously; as a result, these resistance genes spread to Africa, leading to millions of deaths in both instances. After artemisinin combination treatment, artemisinin-resistant parasites are gradually removed from the bloodstream. With parasite clearance times beginning to exceed 3 days, treatment failure has become increasingly common. The use of artemisinin combinations containing various drugs (such as amodiaquine, sulfadoxine-pyrimethamine, and, to a lesser extent, mefloquine) are limited due to the development of drug-resistant malaria (White et al., 2014).

Despite increasing *P. vivax* resistance, chloroquine is still commonly used to treat non-*falciparum* malaria, excluding Indonesia and Papua New Guinea, where highly resistant *P. vivax* is common. *P. vivax* and *P. falciparum* often co-infect in Asia, and subsequent *P. vivax* infection occurs in up to 50% of patients treated for *falciparum* malaria in parts of Southeast Asia. Artemisinin combination treatment appears to be the most appropriate first-line treatment for all human malarias due to the increasing resistance to chloroquine in *P. vivax*, the potential for misdiagnosis and eventual inadvertent use of chloroquine to treat *falciparum* malaria, and operational advantages (White et al., 2014).

Gender, Pregnancy, and Age

Several studies have shown a significant adult male bias in clinical malaria. A striking and common epidemiological shift in countries focused on the elimination of malaria is the increasing proportions of adults and men among all malaria cases. This shift is connected to the proportionally increased importance of occupational and behavioral factors outside the home that put these groups in contact with infective vectors. These adult men act as parasite reservoirs, with many infections carried asymptomatically and with low parasite densities, and have been reported as the source of infection for seasonal outbreaks and epidemics (Naidoo et al., 2011; Tomaszunas, 1998).

Every year, about 25 million pregnancies in sub-Saharan Africa are at risk of malaria infection. Morbidity and mortality related to malaria is very common in pregnant women and children less than five years of age. Malaria during pregnancy is responsible for 10,000 maternal deaths annually and is associated with increased risk of miscarriage, stillbirth, fetal growth restriction, preterm deliveries, low birth weight (LBW) and infant mortality. According to the Centers for Disease Control and Prevention (CDC), pregnant women lose some of their immunity and are prone to malaria infection because of the changes in women's immune systems during pregnancy and the presence of placenta with new places for parasites to bind (Goshu and Yitayew, 2019).

Although global morbidity and mortality have decreased substantially, malaria still kills roughly 2,000 people per day, most of which are children in Africa (White et al., 2014). Although the burden of malaria among children of school-going age has been largely overshadowed by the huge burden among children younger than 5, a recent review has shown that teenagers (10–19 years), who live in areas susceptible to seasonal malaria, sometimes encounter clinical episodes more often. Globally, malaria is a common cause of death in adolescence, accounting for 7.4% of deaths from all causes (Lalloo et al., 2007). Malaria also widely contributes to school absenteeism and poor academic achievement, accounting for 3–8% of all reasons for absenteeism. Thus, schoolchildren should be educated to cope with malaria. Additionally, schoolchildren could not be just recipients of malaria education but also health change agents; children can convey the knowledge and skills that they acquire at school to the community, thus increasing general community awareness about malaria (Cairns et al., 2020; Nonaka et al., 2012).

Socioeconomic Background

Similarly to NTDs, those who belong to poor and rural communities are the most at-risk group for contracting this disease.

In tribal Indian communities, for example, culturally specific beliefs pertaining to which practitioners to consult about health complications affect healthcare seeking behavior. According to Vijayakumar et al. (2009), tribal communities in Eastern India sought traditional healers first for treatment of malaria symptoms. A study conducted in the Gadchiroli district (one of the poorest districts in India) suggested that local tribal people do not allow insecticide spraying in all rooms of the home, particularly where household altars to deities are located - rendering the insecticide program ineffective. Literacy rates are also low among tribal populations with many not speaking the dominant language of the region. Because tribal children often drop out of school during their third or fourth year and "relapse into virtual illiteracy," educational materials presented by community health workers (CHWs) (who do not speak tribal languages) are not always clear and comprehensible (Sundararajan et al., 2013).

Prevention Plan

In many countries where malaria is prevalent, the general public has little to no knowledge of the disease. It has been reported that many families living in rural communities in Nigeria, Ethiopia, and Bangladesh are unaware of how malaria is transmitted. This lack of awareness is often linked to ineffective preventive measures among local community members, which can lead to an increased risk of infection. People who understand little about the linkage between malaria and mosquito bites are more likely not to use a bed net as illustrated in Ghana, Tanzania, and India. Moreover, people who do not know about the cause of malaria are more likely to have malaria as illustrated in Tanzania and Zimbabwe. A lack of knowledge regarding malaria symptoms and treatment can cause delays in health care seeking from trained health professionals (Cotter et al., 2013; Sundararajan et al., 2013).

While there are many preventative measures and treatments in place and being developed, the ultimate goal of programs should focus on malaria education. This malaria education should be geared for all ages with increased efforts made in schools, communities, and households.

African Trypanosomiasis

History

Since the beginning of the 20th century, Human African Trypanosomiasis (HAT) has killed millions of people. African Trypanosomiasis, which is a vector-borne protozoan disease caused by parasites of the *Trypanosoma brucei* (*T. brucei*) species (**Fig 4**), has caused devastating epidemics. These epidemics have occurred in, among other places, Uganda, Democratic Republic of the Congo, Cameroon, and other western African countries. Today, the disease is rare compared to the more than 38,000 cases presented in 1998 (Kohler and Kohler, 2002); however, HAT is still considered a neglected tropical disease (NTD). Cases have been reported from more than 20 countries in Africa, where the disease causes substantial morbidity among the affected rural populations and continues to pose the threat of severe epidemics. Historically, deadly epidemics have followed periods when the disease seemed controlled (**Fig 5**); therefore, having a better understanding of this neglected disease could prove useful in the development of proactive measures and to ensure the public does not become complacent (Zimmer, 2001).

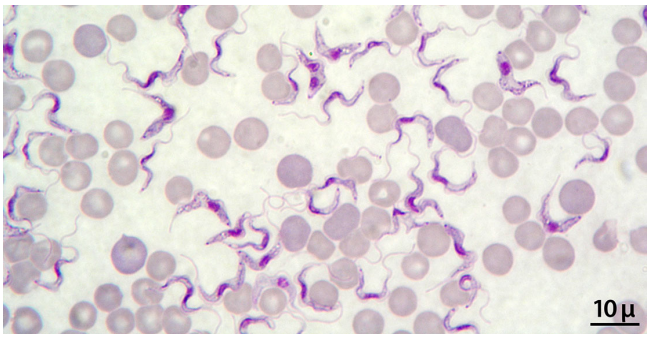

Figure 4. *Trypanosoma brucei* parasite in the blood. The parasite (purple) can be seen surrounding red blood cells (pink).
(Figure Credit: ITMA*)

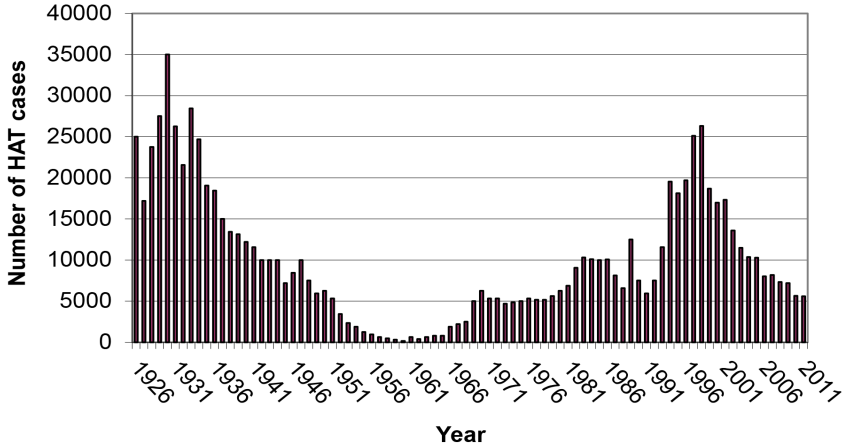

Figure 5. Trends in the number of global Human African Trypanosomiasis cases per year. This graph shows a sudden spike following a period where the disease seemed controlled.
(Figure Credit: PLOS*)

Geographical Location

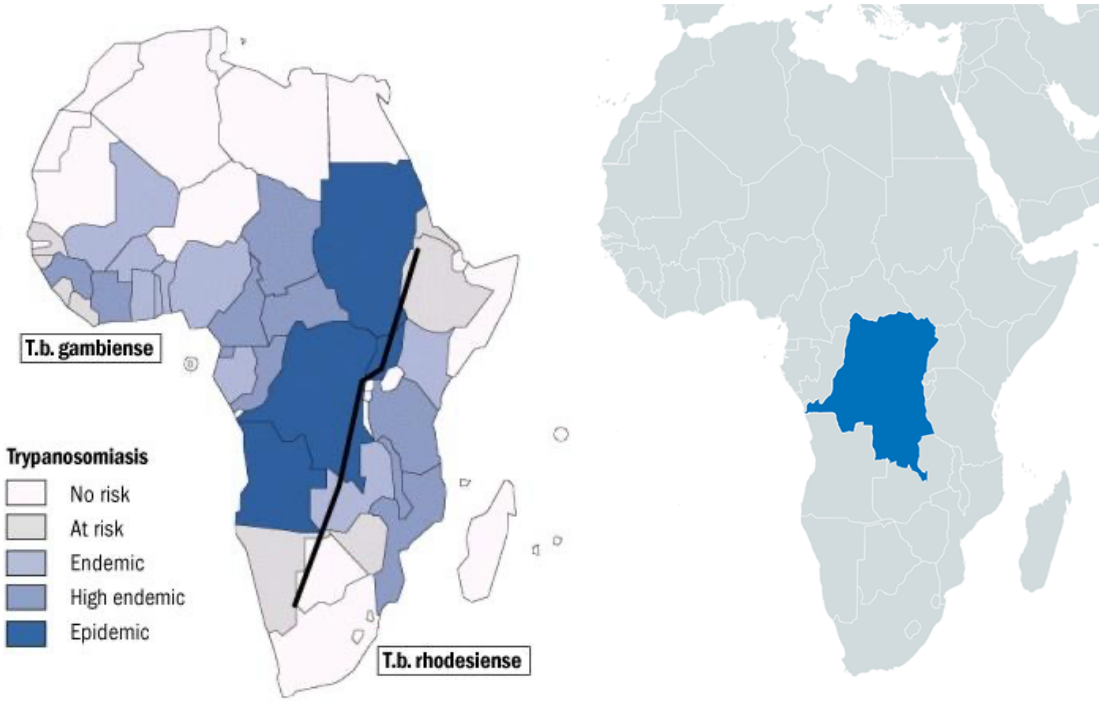

Figure 6. Maps of Africa detailing Trypanosomiasis risk level (left) and the Democratic Republic of the Congo (right). The risk levels of regions associated with either *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiense* can be seen separated by the black line. In the Democratic Republic of the Congo, as in other regions, the number of Trypanosomiasis (*gambiense*) cases has reached epidemic proportions.
(Figure Credits: WHO* and UNHCR* respectively)

This disease is usually found in rural areas with habitats suitable for the tsetse fly vector and frequent human–tsetse contact; as a result, it is estimated that approximately 8.5 million people live in areas that are at a moderate to severe risk of infection (CDC, 2021).

There are two subspecies of African sleeping sickness: *gambiense* and *rhodesiense* (**Table 1**). *Gambiense* sleeping sickness (~98% of cases) has been reported in 15 countries in western and central Africa; whereas, *rhodesiense* (~2% of cases) sleeping sickness has been reported in 7 countries in eastern and southern Africa (**Fig 6**). In 2018, roughly 68% of sleeping sickness cases were reported in the Democratic Republic of the Congo (DRC), making this a hotspot (**Fig 6**) (CDC, 2021).

Mode of Transmission

The tsetse flies (**Fig 7**) that transmit this vector-borne disease are found in rural areas in endemic countries. They have been found in 36 African countries and, depending on the species of fly, inhabit forests, savannas, and areas of dense vegetation along rivers and waterholes (CDC, 2021). Travelers to urban areas in endemic countries are at minimal risk; however, transmission has been observed in some urban settings in the past. In areas where the disease is present, most tsetse flies are not infected with the parasite that causes African Trypanosomiasis; as a result, the risk of infection increases with the frequency an individual has been bitten (WHO, 2020). Those most likely to be exposed to *T. brucei* infections are hunters and villagers with infected cattle herds (**Fig 8**). Rarely, *T. b. gambiense* may be acquired congenitally (through transplacental or perinatal transmission) if the mother is infected during pregnancy. Tourists and others working in or visiting game parks may also be at risk if they spend long periods of time in rural areas where the disease is present (Lindner and Priotto, 2010). Since the tsetse flies that transmit this disease are only found in endemic countries within Africa, the disease cannot be contracted outside of the African continent.

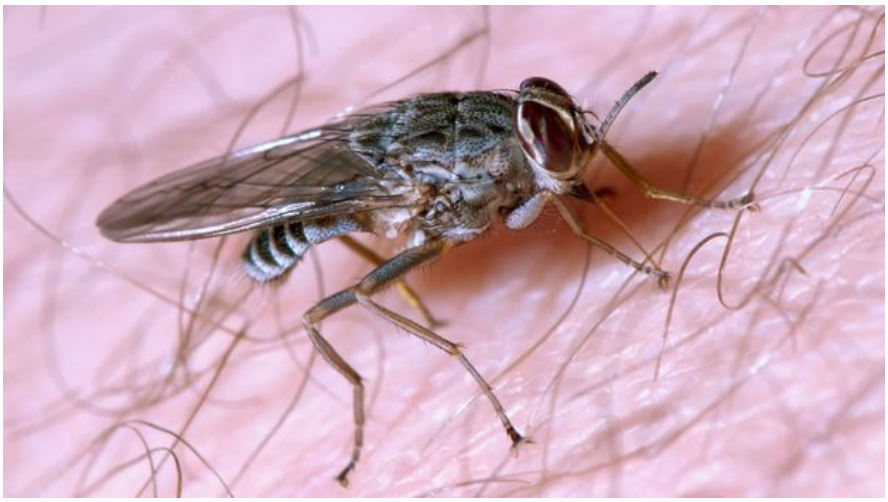

Figure 7. *Glossina* (Tsetse fly) vector. The tsetse fly has landed for a blood meal. (Figure Credit: ITMA*)

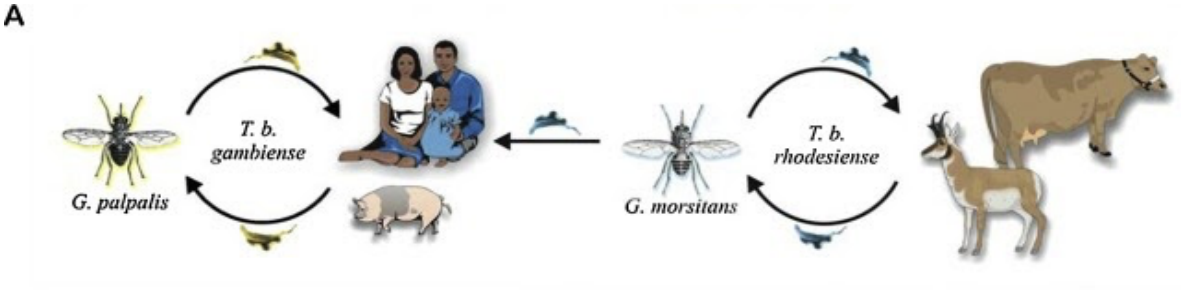

Figure 8. Transmission of the two types of African Trypanosomiasis. *Trypanosoma brucei gambiense* is transmitted to humans and mammals via the *Glossina palpalis* tsetse fly; whereas, *Trypanosoma brucei rhodesiense* is transmitted via the *Glossina morsitans* tsetse fly. (Figure Credit: ITMA*)

Parasite Life Cycle

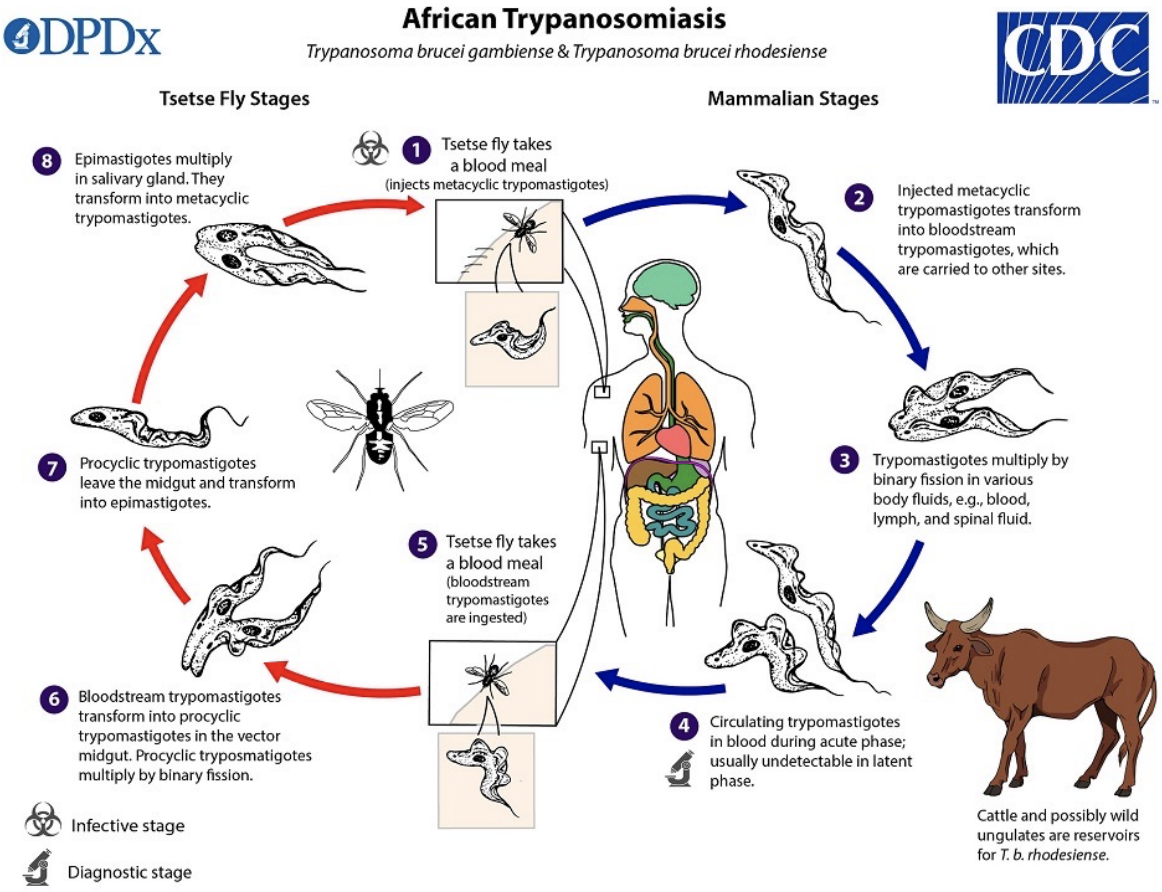

Figure 9. *Trypanosoma brucei* parasite life cycle.
(Figure Credit: CDC*)

An infected tsetse fly (genus *Glossina*) injects metacyclic trypomastigotes into skin tissue during a blood meal on the mammalian host (**Fig 9**). The parasites infiltrate the lymphatic system followed by the bloodstream **(1)**. The metacyclic trypomastigotes differentiate into bloodstream trypomastigotes **(2)** within the host, are then transported to other parts of the body, enter other body fluids (e.g., lymph, spinal fluid), and continue replication by binary fission **(3)**. Extracellular stages reflect the entire life cycle of African trypanosomes. When a tsetse fly feeds on the blood of an infected mammalian host, it becomes infected with bloodstream trypomastigotes **(4)**, **(5)**. The parasites develop into procyclic trypomastigotes in the midgut of the fly, multiply by binary fission **(6)**, exit the midgut, and differentiate into epimastigotes **(7)**. The epimastigotes enter the salivary glands of the fly and continue to multiply through binary fission, resulting in metacyclic trypomastigotes **(8)**. The cycle takes approximately 3 weeks to complete within the fly (CDC, 2021).

Physiology

The immunopathology of HAT remains poorly understood and most of our understanding comes from experimental *T. brucei* infections in mice, which also serve as a model for vaccine development (Lejon et al., 2014). African trypanosomes evade the host's immune attack by covering their entire surface with a dense coat of about five million copies of a single antigen termed variant surface glycoprotein (VSG) that is periodically changed (**Fig 10**). This mechanism of antigenic variation allows a portion of the parasite population to avoid being destroyed by immune mechanisms mediated by serum antibodies and to repopulate the host (Magez et al., 2020; Torrecilhas et al., 2020).

Resistance of *T. brucei rhodesiense* to lysis by normal human serum is conferred by a gene that encodes a truncated form of VSG which is termed serum resistance-associated protein (SRA). Expression of this gene is necessary and sufficient to confer resistance to human serum. The SRA is an atypical VSG devoid of surface loops - the part of the molecule that is exposed to the host immune system on the surface of trypanosomes. It has been shown that SRA is a lysosomal protein (although not found in a lysosome) and the N-terminal α-helical region of SRA is responsible for resistance to human serum (Cayla et al., 2019; Oli et al., 2006).

Gambiense sleeping sickness is believed to be associated with a relevant increase (early-on) in memory T and B cells in the peripheral blood, in particular T-independent memory B-cells (Lejon et al., 2014).

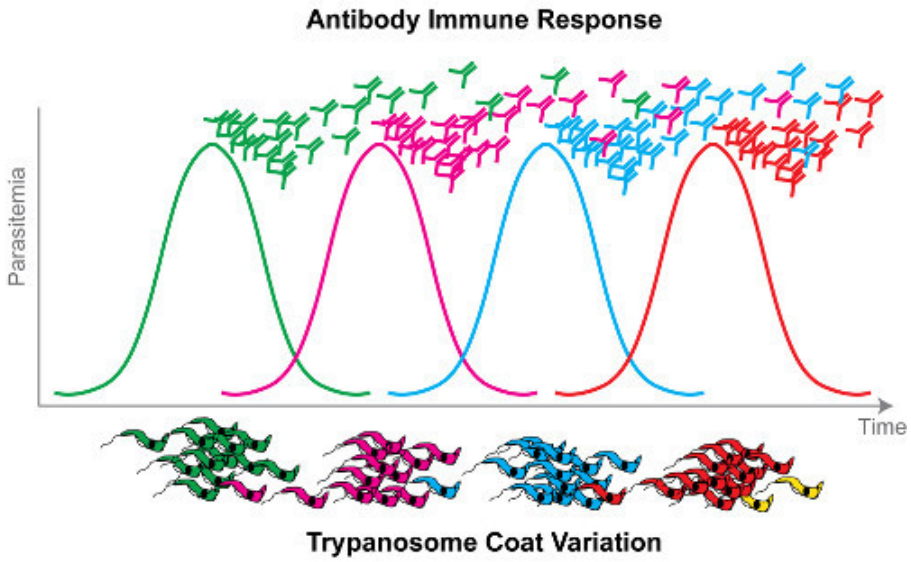

Figure 10. Antibody response to VSG coat changes. As parasitemia levels increase, the human immune system produces antibodies in response to the parasites. The VSG coat on the parasite changes as antibody production begins, allowing the parasites to escape destruction and repopulate. This cycle repeats as new antibodies are produced.
(Figure Credit: George Washington University)

Signs and Symptoms

The infection progresses in two stages: a hemolymphatic stage and a meningoencephalitic stage (after the trypanosomes reach the central nervous system). Many of the signs and symptoms are similar in both stages, making it impossible to distinguish between them based on clinical features alone. Within 2-14 days of being bitten by an infected tsetse fly, the development of a trypanosomal chancre (**Fig 11**) at the site of inoculation may precede first-stage symptoms (this is most commonly seen with *T. b. rhodesiense*, rarely with *T. b. gambiense*; however, chancres have been observed with *T. b. gambiense* in travelers from non-endemic countries). The first stage of *T. b. rhodesiense* includes nonspecific, generalized symptoms that appear 1–3 weeks after the tsetse fly bite; the incubation period for *T. b. gambiense* is less well defined, but the disease progresses more slowly than *T. b. rhodesiense*. Headache, malaise, exhaustion, nausea, pruritus, and arthralgia are common first-stage symptoms in both forms of sleeping sickness. Hepatosplenomegaly, weight loss, and sporadic fevers lasting 1-7 days can also be included in first-stage symptoms. Lymphadenopathy, mostly posterior cervical (although axillary, inguinal, and epitrochlear lymphadenopathy have been recorded), may also occur during the hemolymphatic stage. In *T. b. gambiense* infections, the posterior triangle cervical lymphadenopathy known as "Winterbottom's sign" (**Fig 11**) is commonly seen (CDC, 2021).

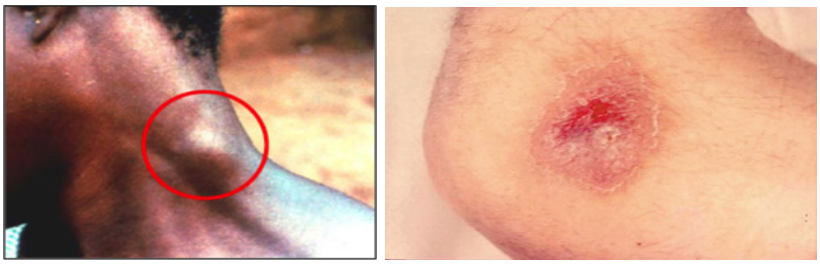

Figure 11. Winterbottom's sign (left) and trypanosomal chancre (right)
(Figure Credits: SD* and The Lancet respectively)

After an average of 300–500 days, *T. b. gambiense* infection progresses to the second stage; whereas, *T. b. rhodesiense* infection progresses to the second stage after an estimated 21–60 days. The second-stage is determined for both forms of disease by examining the cerebrospinal fluid (CSF) for the presence of trypomastigotes. In addition to first-stage symptoms and signs, the invasion of the central nervous system by trypomastigotes triggers a range of neuropsychiatric symptoms for second-stage disease. With daytime somnolence, nocturnal insomnia, and sudden urges to sleep, the sleep/wake cycle is reversed, hence the common name "African sleeping sickness". The patient may also experience mental (seizures, anxiety, mania, confusion, hallucinations, apathy, delirium, aggression), motor (gait disturbances, tremor, abnormal reflexes, ataxia, motor weakness, speech disturbances), and sensory (anesthesia, hyperesthesia, visual problems, pruritus, paresthesia) signs and symptoms. When compared to *T. b. gambiense*, *T. b. rhodesiense* is more likely to cause endocrine disorders such as adrenal insufficiency, thyroid dysfunction, and hypogonadism; furthermore, cardiac implications, such as myocarditis, have been documented to be more severe. It is important to note that sleeping sickness is fatal if left untreated (CDC, 2021; Brun et al., 2010).

Diagnosis

In the early stage of either type of sleeping sickness, misdiagnosis is common. If left untreated, parasites in the brain's pia mater can cross the blood-brain barrier and infect the central nervous system, resulting in advanced sleeping sickness (DNDi, 2021).

Early diagnosis is challenging due to the non-specific nature of the signs and symptoms in the early stages, as well as the insensitivity of diagnostic tests. The presence of the parasite in any body fluid must be confirmed for diagnosis. Since parasitemia levels are normally low and can vary, it may be difficult to detect trypomastigotes in routine blood smears for *T. b. gambiense* infections. Light-microscopic detection of the parasite in a lymph node aspirate (usually, from a posterior cervical node) is the traditional approach for diagnosing *T. b. gambiense* infection; however, blood can be tested using various concentration methods and serial tests (centrifugation followed by buffy coat examination, microhematocrit centrifugation technique, or mini-anion exchange centrifugation technique) (CDC, 2021; Johns Hopkins Medicine, 2021).

Serologic testing for *T. b. gambiense* is only used as a screening tool, the parasite must be observed under a microscope for a conclusive diagnosis. The HAT Sero-K-SeT and the SD Bioline HAT 2.0 are two rapid diagnostic tests recently developed for *T. b. gambiense* infections that are now being utilized in endemic countries. These rapid tests are better suited for passive screening and surveillance in endemic countries where electricity and laboratory equipment are scarce (CDC, 2021; Gjini, 2017).

Parasitemia is normally higher in *T. b. rhodesiense* than in *T. b. gambiense* with symptomatic patients usually having detectable parasites in the blood. In addition to bone marrow aspirates, parasites can also be seen in chancre or other bodily fluids. There is currently no reliable serologic testing for *T. b. rhodesiense*, therefore microscopic examination of the parasite is the only way to obtain a definitive diagnosis (CDC, 2021; Gjini, 2017).

Clinical staging (i.e., assessment of neurological infection) for both *T. b. rhodesiense* and *T. b. gambiense* infections is determined through microscopic analysis of CSF (obtained via lumbar puncture) by observing and quantifying trypomastigotes (motile) and white blood cells (WBCs). Patients with less than five WBCs/μL and no trypomastigotes are in the first stage of infection, whereas those with more than five WBCs/μL or motile trypomastigotes are in the second stage. CSF testing is performed after a parasitological diagnosis has been made by microscopic examination of blood, lymph node aspirates, chancre fluid, bone marrow, or if there are signs of infection that would warrant a lumbar puncture (such as clinical signs and symptoms or strong serologic suspicion). Isolation of the parasite by inoculation of rats or mice is a sensitive diagnostic tool used in cases where false negatives are suspected; however, this method is restricted to *T. b. rhodesiense* infections (CDC, 2021; Gjini, 2017).

Treatments

Pentamidine, which was developed in 1937 (**Fig 12**), is the recommended drug for first stage *T. b. gambiense* infection and is continuously used today (CDC, 2021). Treatments for stage 2 of this disease prior to 2009 were either toxic or difficult to administer, such as the arsenic derivative melarsoprol that was developed in 1949 (**Fig 12**). Melarsoprol is no longer used to treat *gambiense* sleeping sickness due to it killing up to 5% of those who take it; however, it is still the only available drug used to treat advanced *rhodesiense* sleeping sickness. NECT (Nifurtimox-eflornithine combination therapy), was introduced in 2009 as the first new treatment for sleeping sickness in over two decades; however, this form of therapy requires specialized clinical staff (**Fig 12**). At the end of 2018, the European Medicines Agency (EMA) recommended fexinidazole (a 10-day all-oral medication) for the treatment of both stages of *gambiense* sleeping sickness (DNDi, 2021; Molyneux et al., 2017).

NECT has been provided free of charge in all countries with recent sleeping sickness cases. The World Health Organization (WHO) provides NECT free of charge to countries with recent infections via drug donations by pharmaceutical companies such as Sanofi and Bayer. In 2019, Sanofi began donating supplies of fexinidazole to countries in need as well (WHO, 2020).

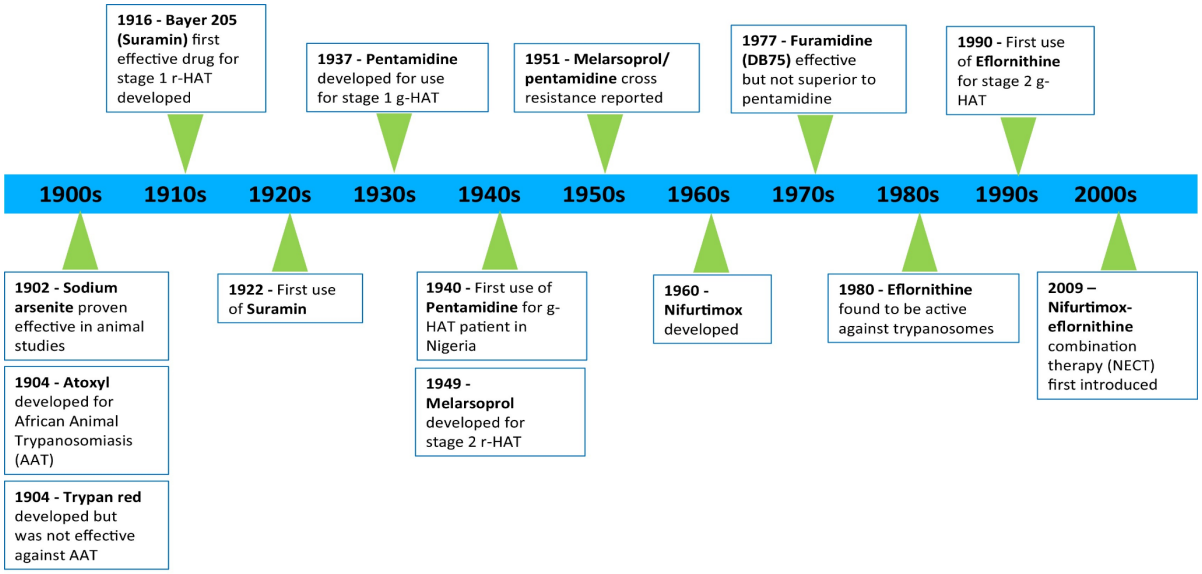

Figure 12. Timeline of African Trypanosomiasis drug development. Although not listed, fexinidazole was recommended in 2018 to treat both stages of *gambiense* sleeping sickness. (Figure Credits: TP*)

Depending on the type of infection (*T. b. gambiense* or *T. b. rhodesiense*) and the disease stage, specific drugs and treatments will be used to treat those diagnosed. Patients should be closely monitored for 24 months after treatment to ensure that they do not relapse. If symptoms recur, an analysis of body fluids (including CSF) will be required in order to detect motile trypanosomes (CDC, 2021).

Drug Resistance in Parasite

Mutations in the genome of *T. brucei gambiense* (such as aquaporin 2 which is responsible for drug uptake in the parasite) have been observed that confer resistance to melarsoprol and pentamidine (**Fig 13**). A new analysis of HAT cases from the Democratic Republic of the Congo found that patients treated with melarsoprol had a high incidence of relapse. This was due to parasite regrowth with gene mutations being potentially responsible for the drug resistance (Richardson et al., 2016).

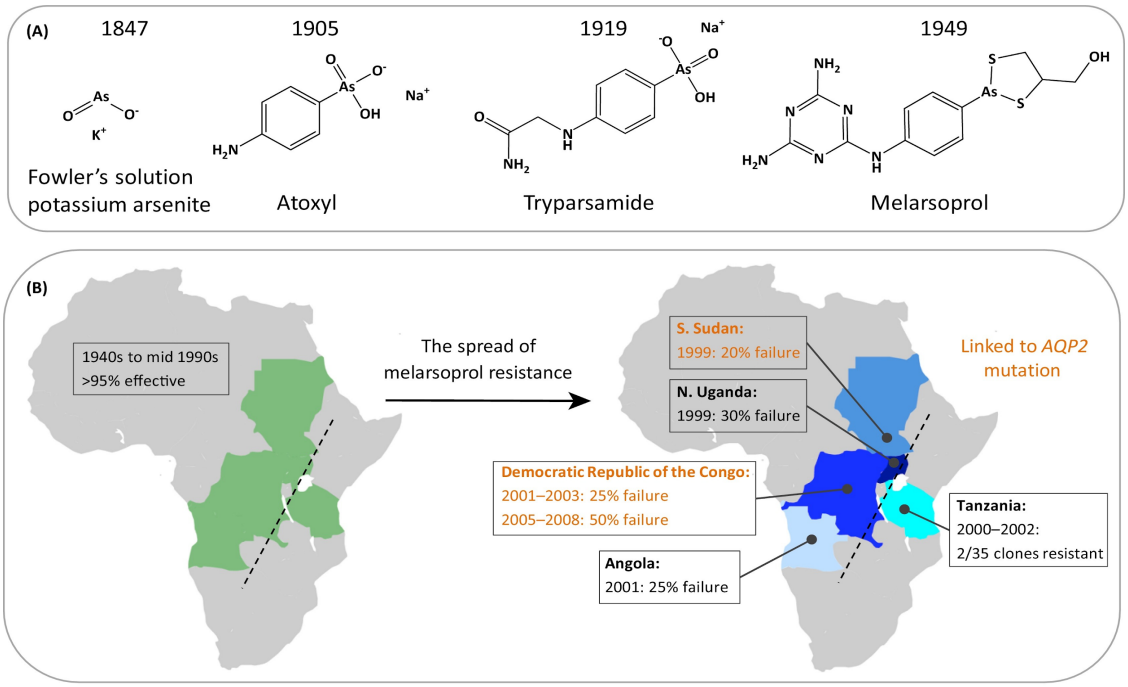

Figure 13. Melarsoprol drug resistance. The development of melarsoprol-resistant *Trypanosoma brucei* parasites over the last few decades. Gene mutations linked to aquaporin 2 (AQP2) have been observed in both Sudan and the Democratic Republic of the Congo.
(Figure Credit: TP*)

Gender, Pregnancy, and Age

All age groups and both sexes are at risk; however, prevalence is higher in adults, and sex distribution varies due to occupational and behavioral factors outside the home such as hunting and fishing (predominantly male activities) or water fetching and small-crop growing (predominantly female activities) (Büscher et al., 2017). Rarely, *T. b. gambiense* may be acquired congenitally (through transplacental or perinatal transmission) if the mother is infected during pregnancy (Lindner and Priotto, 2010).

Socioeconomic Background

Extreme poverty has been linked to areas with increased sleeping sickness cases as illustrated in the Democratic Republic of the Congo (DRC), the second-poorest country in the world, which has approximately 20,000 new HAT cases per year (Büscher et al., 2017).

Prevention Plan

There is currently no vaccine or drug available for the prevention of African Trypanosomiasis; therefore, the main preventative measures in place are to minimize contact with tsetse flies. In endemic countries, local residents are usually conscious of highly infested areas to avoid (CDC, 2021). Other helpful measures include (CDC, 2021):

1) Proper clothing. Wearing medium-weight, long-sleeved clothes in neutral tones that match the surrounding environment can help prevent tsetse bites. Bright or dark colors often attract tsetse flies, which are capable of biting through light-weight clothes.
2) Inspecting vehicles. Tsetse flies are drawn to the motion and dust associated with moving vehicles; therefore, inspecting vehicles before entering could protect against being bitten.
3) Avoiding bushes. During the hottest part of the day, tsetse flies are less active; however, they will bite if disturbed so avoiding plants (such as bushes) is key.
4) Using insect repellent. It's worth noting that insect repellent has not been proven to work well against tsetse flies. This measure is to prevent other bug bites that can cause illness (such as malaria).

Case finding (both active and passive), treatment (of reported cases), and vector management (to reduce the tsetse population) are the three main strategies in place for eliminating *gambiense* sleeping sickness. Since *T. b. rhodesiense* has a large variety of animal hosts (and ultimately a greater chance of zoonosis), reducing the reservoir of infection is much more difficult. As a result, complete interruption of *rhodesiense* sleeping sickness transmission is not believed to be achievable. Currently, the primary strategy in place for *rhodesiense* sleeping sickness are vector control programs; however, a multisectoral approach (animal health and resource management) is critical for minimizing transmission rates (Gjini, 2017; CDC, 2021).

Table 1. *Gambiense* and *Rhodesiense* Sleeping Sickness Comparison

Disease	West African Trypanosomiasis	East African Trypanosomiasis
Parasite	*T. brucei gambiense*	*T. brucei rhodesiense*
Distribution	West and Central Africa	East and South Africa
Presentation	Fever, Headache, Progressive Mental Status Changes	Fever, Headache +/- Myocarditis
Time of symptom onset post infection	Months - Years	~1-3 Weeks
Posterior Cervical Lymphadenopathy	Characteristic	Absent
Chancre	Absent	Characteristic
Time of death if left untreated	~3 Years	~3 Months
Parasitemia	Uncommon/Low	Common/High
Available serological test	Yes	No
Vector	Riverine Tsetse Fly	Savanna Tsetse Fly
Reservoir in Cattle/Wild Animals	No	Yes
Treatment for Acute Stage	1. Pentamidine 2. Suramin 3. Fexinidazole	1. Pentamidine 2. Suramin
Treatment for Chronic Stage	1. NECT (Nifurtimox-eflornithine combination therapy) 2. Fexinidazole	1. Melarsoprol
Disease Burden in Africa	~1,000 new cases per year ~98% of HAT cases	~100 new cases per year ~2% of HAT cases
Occurrence in Travellers	Very rare among travelers, occasionally among immigrants	Occasionally among travelers to safari parks

American Trypanosomiasis

History

American Trypanosomiasis - Chagas' Disease - which affects more than 8 million people in South America, is a neglected tropical disease (NTD). Chagas' Disease, caused by the flagellated protozoan *Trypanosoma cruzi* (*T. cruzi*) (**Fig 14**), is a major public health problem that kills over 10,000 people per year. It was initially restricted to Latin America, but it is now expanding globally due to increased travel (Madeira et al., 2021). Chagas' disease afflicted man as early as 9000 years ago, according to findings from paleoparasitology studies that recovered *T. cruzi* DNA from human mummies. Notably, the first recorded case of Chagas' disease might have preceded Carlos Chagas' discovery; Charles Darwin quite possibly contracted *T. cruzi* infection during his expedition to South America in 1835, as suggested by his vivid description of contact with the triatomine bug, and by some of his symptoms later in life. Chagas' disease is transmitted to humans, more than 150 species of domestic animals (dogs, cats, and guinea pigs), and wild mammals (rodents, marsupials, and armadillos). Despite the fact that there are more than 130 species of triatomine bugs, only a few are competent *T. cruzi* vectors. The 3 most prominent vector species that transmit *T. cruzi* to humans are *Triatoma infestans*, *Rhodnius prolixus*, and *Triatoma dimidiata*; historically, *T. infestans* (**Fig 14**) has been the most prominent vector across South America and is known to be the primary vector in sub-Amazonian endemic regions (Rassi et al., 2010; CDC, 2019).

Figure 14. *Triatoma infestans* (left) and *Trypanosoma cruzi* in the blood (right). *Triatoma infestans* can grow up to 3cm in length and have brown and orange coloration. These insects transmit *Trypanosoma cruzi* parasites (pink) that infiltrate the host's immune system. These parasites may or may not be found during a routine blood smear.
(Figure Credits: TVP* and AHA* respectively)

Geographical Location

People living with Chagas' disease can be found all over the world, however the disease is only transmitted by triatomine bugs in the Americas. The majority of people who contract Chagas' disease live in rural areas of Mexico, Central America, and South America (**Fig 15**). Due to a lack of vectors, vector-borne transmission does not occur in the Caribbean (such as Puerto Rico and Cuba). Due to increased population movements, rare cases of Chagas' disease have been recorded in the United States, Canada, Europe, Japan, and Australia (**Fig 16**) (Montgomery et al., 2016; CDC, 2019).

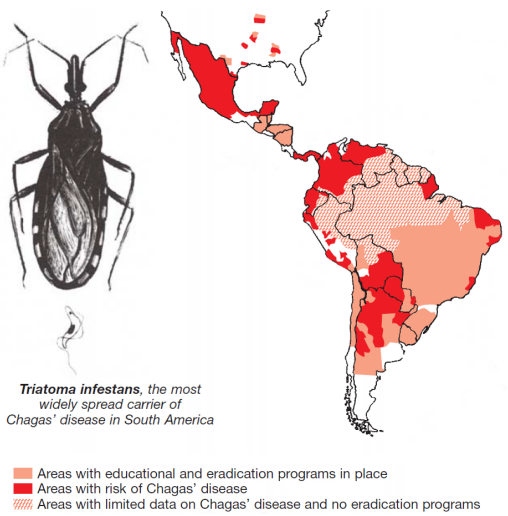

Figure 15. Geographical location of Chagas' disease. Chagas' disease is endemic to Central and South America; however, other countries are now at risk of *Trypanosoma cruzi* infections.
(Figure Credits: IAMAT*)

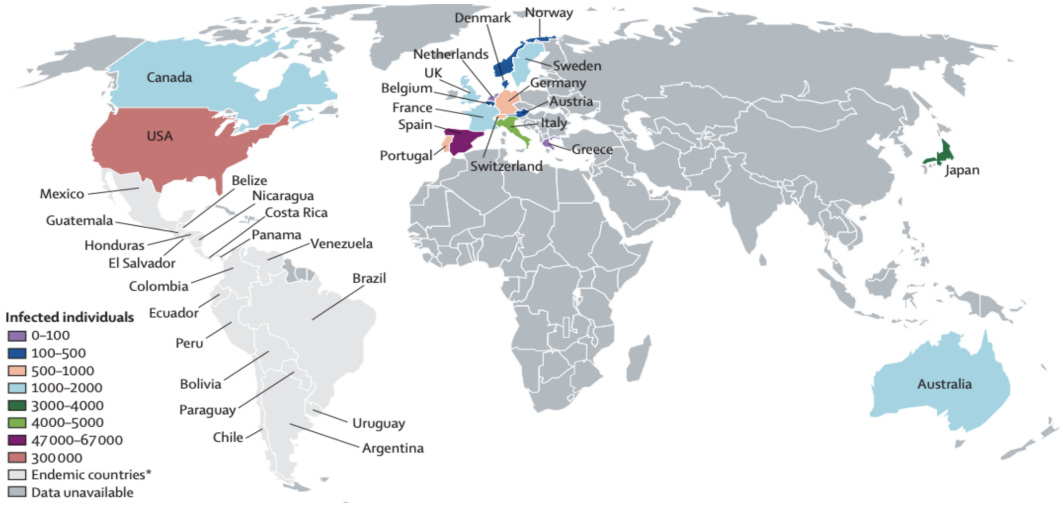

Figure 16. Incidence of American Trypanosomiasis cases worldwide. It is important to note the countries bordering endemic regions (such as the United States) have a higher risk of outbreaks if the environment allows for vector survival.
(Figure Credit: The Lancet)

Mode of Transmission

In areas where Chagas' disease is common, the main mode of transmission is triatomine bugs. These blood-sucking insects become infected with *T. cruzi* after biting an infected animal or person. Once infected, the parasites are passed through the feces of the bug, often after a blood meal. During the day, these insects can be found in roofs and crevices of homes made out of clay, adobe, straw, and palm thatch. The bugs emerge at night, while the occupants are sleeping, and are known to bite the faces (**Fig 17**) of individuals, earning them the nickname "kissing bugs". The bugs then defecate on the victim after their blood meal; as a result, the victim can then become infected if *T. cruzi* parasites in the bug's feces enter the body through mucous membranes or breaks/cuts in the skin. The unsuspecting victim may accidentally rub or scratch the feces into the bite wound, mouth, and/or eyes - leading to infection (**Fig 18**) (CDC, 2019).

As is true for all protozoan diseases, people can also become infected through: congenital transmission, blood transfusions, organ transplantation, and/or the consumption of uncooked food that is contaminated with feces from infected vectors (CDC, 2019).

Figure 17. Mode of transmission for Chagas' disease. The triatomine bug bites the face of a sleeping victim and then defecates near the bite wound.
(Figure Credit: IAMAT*)

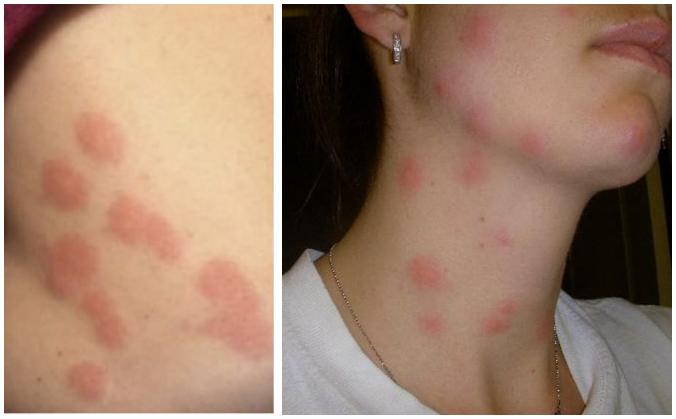

Figure 18. Triatomine bug bite. The triatomine bug can leave large, red welts after feeding.
(Figure Credits: AJM* and ER* respectively)

Parasite Life Cycle

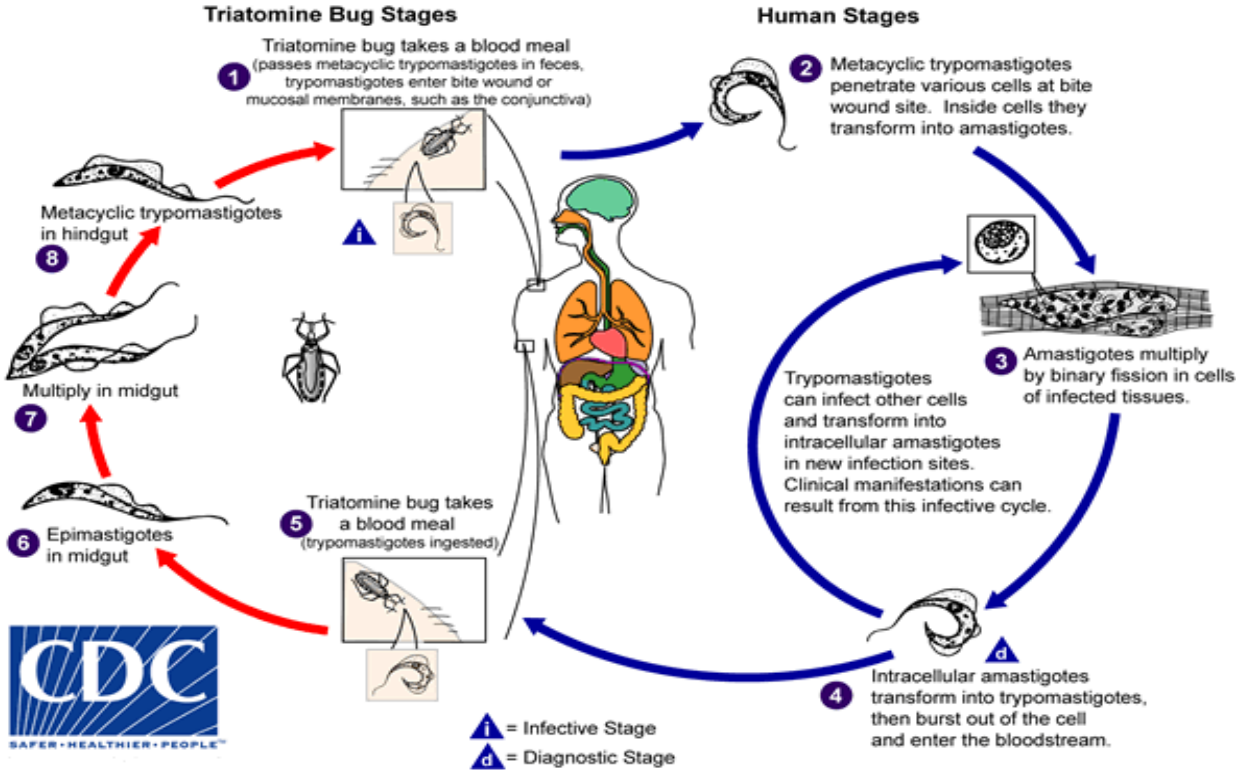

Figure 19. *Trypanosoma cruzi* parasite life cycle.
(Figure Credit: CDC*)

A blood meal is taken by an infected triatomine "kissing bug" vector which then releases metacyclic trypomastigotes within its feces near the bite wound (**Fig 19**). The trypomastigotes can invade the host through openings such as cuts or intact mucosal membranes **(1)**. The trypomastigotes invade cells near the inoculation site within the host, where they differentiate into intracellular amastigotes **(2)** and multiply by binary fission **(3)**. The amastigotes then revert back to trypomastigotes, which are then released as bloodstream trypomastigotes into the host's circulation **(4)**. Circulating trypomastigotes infect a large variety of cells and tissues, transforming into intracellular amastigotes at new infection sites. This infective cycle can lead to clinical manifestations. Unlike the African trypanosomes, the trypomastigotes in the bloodstream do not replicate. Only when the parasites invade another cell or are swallowed by the vector does replication resume. The "kissing bug" then becomes infected after ingesting circulating parasites from their blood meal **(5)**. In the midgut of the vector, the ingested trypomastigotes differentiate into epimastigotes **(6)** and multiply **(7)**. The parasites then differentiate in the hindgut into metacyclic trypomastigotes **(8)** (CDC, 2019).

Physiology

T. cruzi replicates in the cytoplasm of a variety of cells in mammalian hosts, including macrophages, fibroblasts, skeletal and heart muscle cells, and endothelial cells. *T. cruzi* trypomastigotes (which can survive lysosomal fusion) enter host cells and use a low pH-dependent lytic protein to disrupt the parasitophorous vacuole, allowing them to escape into the cytosol. Infected cells release trypomastigotes, which can infect neighboring cells or spread to other organs via the blood and lymph. The infiltration and destruction of host cells is the first known manifestation of *T. cruzi* infection-related tissue damage (Andrade and Andrews, 2004). There is ample evidence that the most severe forms of the disease are defined by damage to vital tissues generally framed by inflammation; as a result, this strongly suggests that *T. cruzi* and damaged tissue brings about the recruitment of inflammatory cells. During acute infection, parasite levels in the bloodstream are the highest, due to increased trypomastigotes entering the bloodstream; whereas, during chronic infection, the parasite levels in the bloodstream are extremely low due to amastigotes residing in various tissues - this is known as nesting (**Fig 20**) (Rassi et al., 2010; Fernandes and Andrews, 2012).

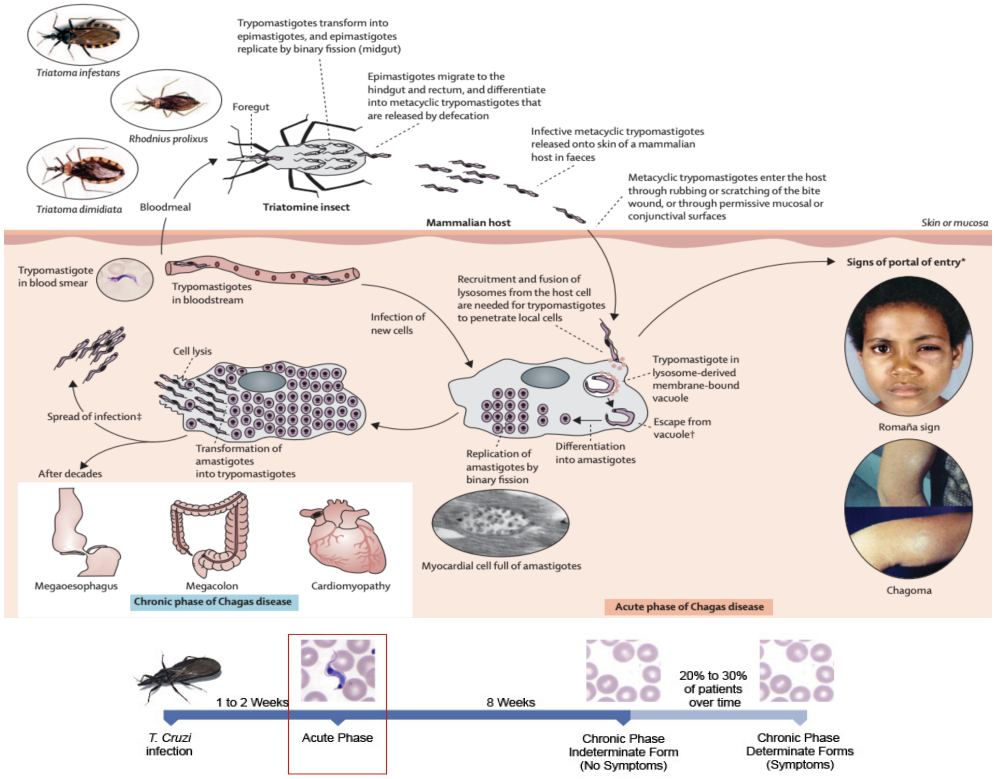

Figure 20. *Trypanosoma cruzi* infection. After defecating on the unsuspecting victim, the parasite enters the body via a cut or mucosal membrane. A romana or chagoma are both signs of entry and can be seen at the inoculation site. The parasites are capable of evading destruction by the host and replicate in various tissue types. Parasite growth in certain tissues can lead to chronic Chagas' with complications dealing with the esophagus, colon, and/or heart. Parasites are normally only seen in blood smears during the acute phase (red box).
(Figure Credits: The Lancet [top] and CDC* [bottom])

Signs and Symptoms

Acute

Acute Chagas' infection is asymptomatic ~95% of the time, which is likely due to the low parasitic load. When symptoms occur they include: prolonged fever; malaise; enlargement of the liver, spleen, and lymph nodes; subcutaneous edema (localized or generalized); and, in the particular case of vector-borne transmission, the signs of portal of entry of *T. cruzi* through the skin (Chagoma) or via the ocular mucous membranes (Romana) (PAHO, 2020).

Chronic

The clinical outcome of the chronic phase of Chagas' disease ranges from the absence of signs and symptoms of disease (indeterminate form) to severe illness and premature death. Clinical manifestations during the chronic phase are classified as either cardiac, digestive, or a combination (cardio-digestive). These manifestations are linked to the pathological involvement of the heart, esophagus, colon, or a combination of these organs (Wang et al., 2021; Menezes et al., 2011; Hidron et al., 2010).

Cardiac

The cardiac form of chronic Chagas' disease is the most dangerous yet common manifestation. It can cause conduction system abnormalities, thromboembolism, abnormal heart beats (bradyarrhythmias or tachyarrhythmias), apical aneurysms, heart failure, and death in ~20-30% of chronic patients (Rassi et al., 2010).

Digestive

The digestive form is seen almost exclusively south of the Amazon basin (mainly in Argentina, Brazil, Chile, and Bolivia), and is rare in northern South America, Central America, and Mexico. This geographical distribution is probably due to differences in parasite strains. Gastrointestinal dysfunction (mainly megaesophagus, megacolon, or both) develops in about 10-15% of chronically infected patients (Rassi et al., 2010).

Cardio-digestive

The cardio-digestive form of chronic Chagas' disease is characterized by the combination of heart disease with megaesophagus or megacolon (possibly both). Megaesophagus normally develops before colon and heart disease in most countries; however, due to a lack of adequate research, the exact prevalence is unknown for the cardio-digestive form (Rassi et al., 2010).

Diagnosis

Acute

For all patients, the diagnosis of acute infection is solely dependent on the microscopic examination of trypomastigotes in the blood (**Fig 21**). Because of its heightened sensitivity and small amount of blood required, microhematocrit is the method of choice for detecting congenital infection and is highly recommended for all babies (Rassi et al., 2010).

Chronic

Due to low parasitemia levels during the chronic phase, the detection of IgG antibodies (**Fig 21**) against *T. cruzi* antigens must be confirmed using at least two serological methods (ELISA, indirect immunofluorescence, or indirect hemagglutination). Because of the need for specialized laboratory facilities, low standardization, and possible DNA cross-contamination, PCR is not used for routine diagnosis; however, because of its high sensitivity, PCR can be used for diagnosis confirmation in cases of inconclusive serology (Rassi et al., 2010; Duarte et al., 2014).

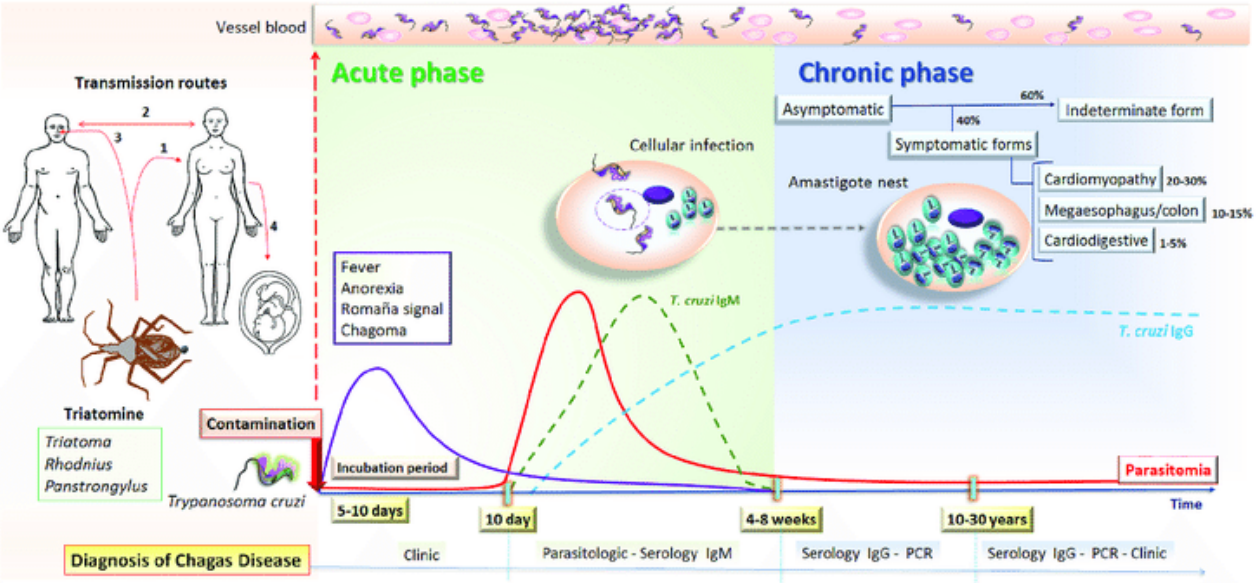

Figure 21. Chagas' disease diagnosis. The diagnosis of Chagas' disease is based on either parasite examination in the blood or the detection of IgG antibodies. Parasites are easily detectable in the blood for acute Chagas' due to parasite levels remaining high. Serological tests are required for the diagnosis of chronic Chagas' due to low parasitemia in the blood. (Figure Credit: RG*)

Treatments

Antitrypanosomal medication is recommended for all American Trypanosomiasis cases except for patients (18 years or older) with chronic Chagas' disease. Antitrypanosomal medication is generally recommended for all adults aged 19-50 years who do not have advanced Chagas' heart disease or any other chronic form. These medications are not usually prescribed during pregnancy and in patients who experience extreme renal or hepatic complications (Rassi et al., 2010; CDC, 2019).

Oral tablets benznidazole and nifurtimox are the only available drugs shown to be effective against Chagas' disease. Benznidazole, which is an antiparasitic belonging to the nitroimidazole family, produces radical species capable of disrupting the parasite's cellular machinery and DNA. This medication is often used as first-line treatment due to it having one of the best efficacy profiles. Nifurtimox, when taken in conjunction with benznidazole, is capable of inhibiting parasite replication by breaking down parasite DNA (Rassi et al., 2010; CDC, 2019).

Drug Resistance in Parasite

Benznidazole has been used to treat chronic *T. cruzi* infections for ~50 years; however, in recent clinical trials, treatment failures are becoming increasingly reported with non-curative results ranging from 6%-50%. The antifungal drug posaconazole has recently shown promising results that accentuated the need for the replacement of benznidazole. In a recent study conducted in 2020, the cure rates for mice infected with *T. cruzi* parasites were much higher for posaconazole (90%) when compared to benznidazole (76%) (Calvet et al., 2020). Evidence of cross-resistance with nifurtimox, the prolonged treatment period (60-90 days), and toxic side effects are all problematic factors associated with benznidazole that support the need for new drug treatments (Campos et al., 2017) .

Gender, Pregnancy, and Age

Studies have indicated that the group most at risk for becoming infected by *T. cruzi* are males between the ages of 25 and 49 years old (Bern et al., 2011). It is possible that the acquisition of the disease is strongly related to occupational activities (such as farming or mining) since the incidence is significantly different (up to three times lower) for females in the same age group (WHO, 2020; Vlassoff, 2017).

Congenital transmission occurs through chorionic villi where the trypomastigotes from an infected mother are capable of entering the fetal bloodstream (**Fig 22**) (Fretes and Kemmerling, 2012). During childbirth, the baby is at an increased risk of becoming infected with trypomastigotes, if not already infected, while exiting the birth canal. Breastfeeding is considered safe, even if the mother is infected with *T. cruzi* parasites; however, if nipples become cracked or start to bleed, the mother should pump and discard the milk until the nipples are healed (Fretes and Kemmerling, 2012; CDC, 2019).

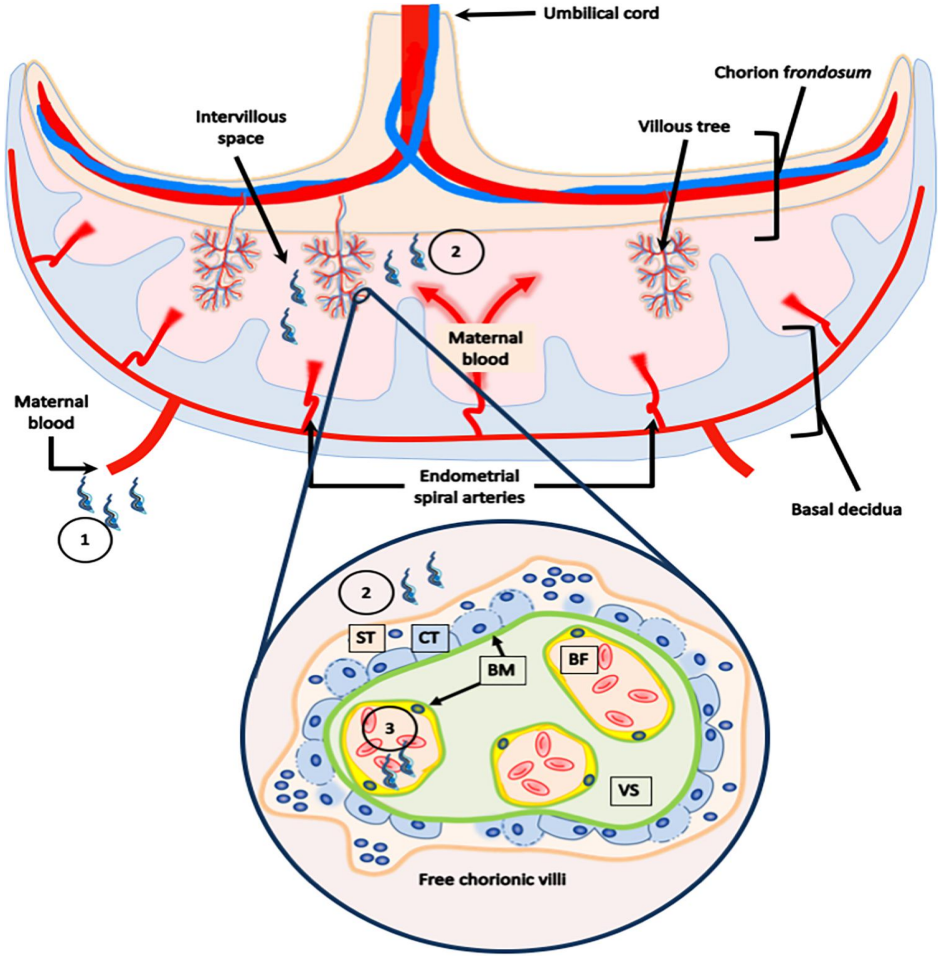

Figure 22. Congenital transmission of Chagas' disease. *Trypanosoma cruzi* in maternal blood (1) are capable of entering fetal circulation via chorionic villi (2).
(Figure Credit: FM*)

Socioeconomic Background

Low incidences have been reported in Mexico City and the surrounding urban area. This could be related to the habitat decrease of triatomines and better socioeconomic environments compared to the endemic areas in the southern part of the country (**Fig 23**). The countries of Brazil and Argentina experience the greatest number of infections, averaging around 1.5 million cases each (WHO, 2020).

The economic impact (including annual and lifetime health-care costs, disability-adjusted life-years, and total costs) associated with Chagas' disease is more than $7 billion per year, a figure exceeding the total global costs linked to rotavirus ($2 billion), cervical cancer ($4.7 billion), and Lyme disease ($2.5 billion); therefore, decreasing the disease burden that results from this infection could greatly impact the socioeconomic status of those living in rural areas (Lee et al., 2013).

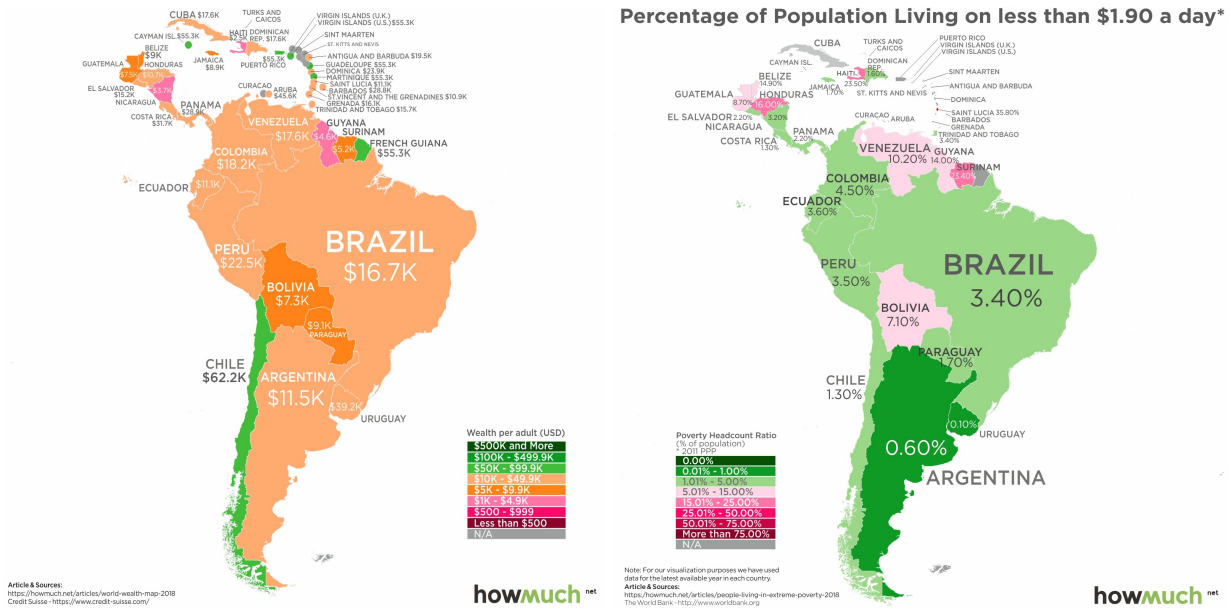

Figure 23. Wealth map of Latin America (left) and percentage of people living in extreme poverty (right). Both Brazil and Argentina experience the largest number of *Trypanosoma cruzi* infections.

(Figure Credits: HM*)

Prevention Plan

Since no vaccine is available, the focus of primary prevention has relied on vector control and prevention of transmission from non-vectorial mechanisms. Compulsory screening of blood donors and continuous application of insecticides in infested houses have resulted in a significant reduction in the burden of Chagas' disease. These measures are supported by continuous health education, community participation, improved housing, and epidemiological surveillance; however, this neglected disease is far from conquered (**Fig 24**). The continued risk of vector-borne transmission in endemic areas, resurgence of vector-borne transmission in once controlled regions, and the emergence of Chagas' disease in non-endemic countries are all geographical challenges associated with this disease; similarly, local micro-epidemics, congenital transmission, and blood/organ transfusions also pose potential challenges for future control efforts. In various regions across Latin America, attempts to eradicate triatomine bugs (referred to as vector control programs) have been effective at halting vector-borne transmission of the disease; therefore, this type of prevention should be considered in other regions (Rassi et al., 2010).

Exposure to *T. cruzi* summary

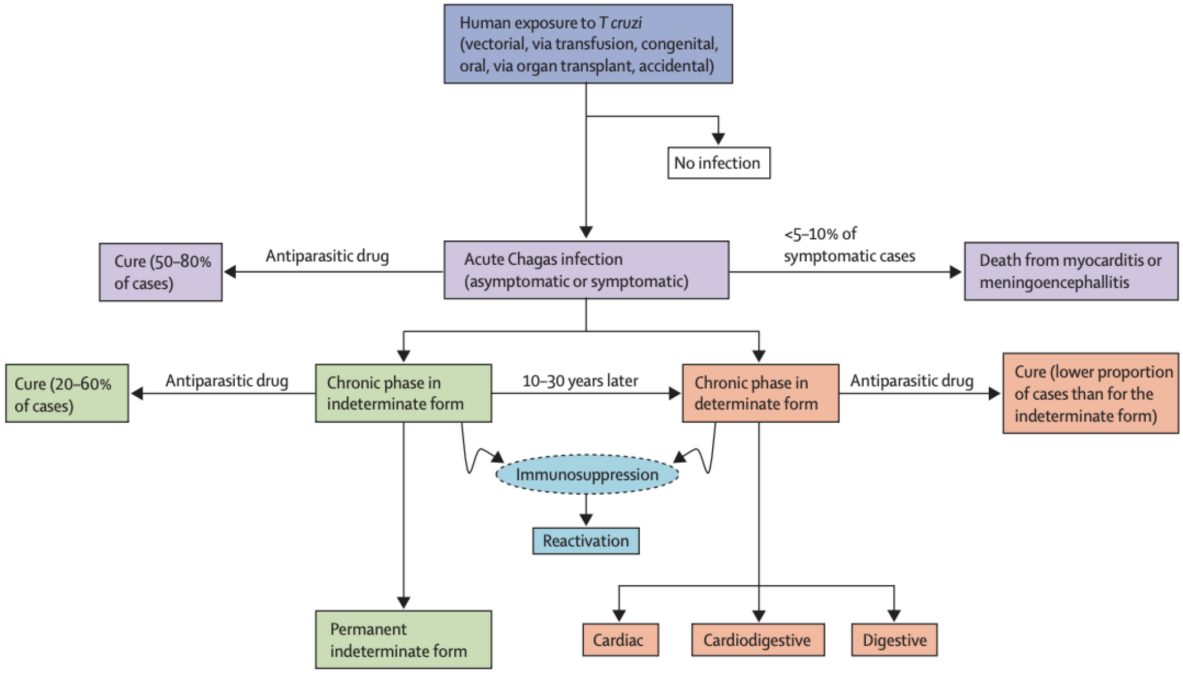

Figure 24. Chagas' disease summary. This chart depicts the duration, challenges, and outcomes associated with a *Trypanosoma cruzi* infection. In order to decrease the burden of this disease, vector control programs are crucial.
(Figure Credit: The Lancet)

Conclusion

In conclusion, NTDs including African trypanosomiasis and American trypanosomiasis, along with other diseases such as malaria, should warrant further research and education programs. The need to combat these diseases has only grown in the last year due to the shift of research going toward the global Coronavirus pandemic. It is crucial to not let the progress made in the last few decades slip away due to these diseases being placed on the back-burner in both funding and research. Future efforts to raise awareness are needed in order for everyone to keep fighting these invisible predators.

"But if they're so successful, why haven't parasites taken over the world? The answer is simple: they have. We just haven't noticed. That's because successful parasites don't kill us; they become part of us, making us perform all the work to keep them alive and help them reproduce."

- Daniel Suarez (2009)

Glossary

Definitions provided by Merriam-Webster* and Mayoclinic**

A

Adjuvant* - enhancing the effectiveness of medical treatment

Adrenal Insufficiency** - when the adrenal glands do not produce enough hormones

Afflicted* - grievously affected or troubled (as by a disease)

AHA - American Heart Association

AJM - American Journal of Medicine

Aldolase* - a crystalline enzyme that occurs widely in living systems and catalyzes reversibly the cleavage of a phosphorylated fructose into triose sugars

Amastigote* - the nonmotile, parasitic form in the life cycle of some protozoans that usually develops in the cells of vertebrate hosts and occurs as a minute, ovoid or spherical body with a prominent, rod-shaped kinetoplast and a rudimentary, internal flagellum arising from a basal body

Anemia* - a condition in which the blood is deficient in red blood cells, in hemoglobin, or in total volume

Anesthesia* - loss of sensation with or without loss of consciousness

Anion Exchange* - a chemical process in which anions are exchanged or removed

Antibody* - any of a large number of proteins of high molecular weight that are produced normally by specialized B cells after stimulation by an antigen and act specifically against the antigen in an immune response, that are produced abnormally by some cancer cells, and that typically consist of four subunits including two heavy chains and two light chains

Antigen* - any substance (such as an immunogen or a hapten) foreign to the body that evokes an immune response either alone or after forming a complex with a larger molecule (such as a protein) and that is capable of binding with a product (such as an antibody or T cell) of the immune response

Apathy* - lack of feeling or emotion

Apical Aneurysm** - a ballooned and weakened area in an artery found at an apex

Arthralgia* - pain in one or more joints

Aspirate* - to remove (something such as blood) by suction

Asymptomatic* - not causing, marked by, or presenting with signs or symptoms of infection, illness, or disease

Ataxia* - an inability to coordinate voluntary muscular movements that is symptomatic of some central nervous system disorders and injuries and not due to muscle weakness

Axillary* - of, relating to, or located near the armpit

B

B Cells* - any of the lymphocytes that have antigen-binding antibody molecules on the surface, that comprise the antibody-secreting plasma cells when mature, and that in mammals differentiate in the bone marrow

Binary Fission* - reproduction of a cell by division into two approximately equal parts

Biomass* - the amount of living matter (as in a unit area or volume of habitat)

Blood-borne* - carried or transmitted by the blood

Bloodstream Trypomastigote** - the morphological form of trypanosomatids found in the blood

Bradyarrhythmias** - a slow heart rate (<60 bpm)

C

CDC - Centers for Disease Control and Prevention

Centrifugation* - the process of centrifuging

Centrifuge* - a machine using centrifugal force for separating substances of different densities, for removing moisture, or for simulating gravitational effects

Chagoma* - a swelling resembling a tumor that appears at the site of infection in Chagas' disease

Chancre* - a primary sore or ulcer at the site of entry of a pathogen

Circulatory System* - the system of blood, blood vessels, lymphatics, and heart concerned with the circulation of the blood and lymph

Circumsporozoite Protein** - a major surface protein of the infective sporozoite

Congenital* - acquired during development in the uterus and not through heredity

Conjunctiva* - the mucous membrane that lines the inner surface of the eyelids and is continued over the forepart of the eyeball

Cytokine* - any of a class of immunoregulatory proteins (such as interleukin or interferon) that are secreted by cells especially of the immune system

Cytoplasm* - the organized complex of inorganic and organic substances external to the nuclear membrane of a cell and including the cytosol and membrane-bound organelles

Cytosol* - the fluid portion of the cytoplasm exclusive of organelles and membranes

D

Dehydrogenase* - an enzyme that accelerates the removal of hydrogen from metabolites and its transfer to other substances

Deity* - a god or goddess

Dendritic Cells** - A special type of immune cell that is found in tissues, such as the skin, and boosts immune responses by showing antigens on its surface to other cells of the immune system

Disseminate* - to disperse throughout

E

Efficacy* - the power to produce an effect

ELISA* - (enzyme-linked immunosorbent assay) an in vitro method for quantifying an antigen or antibody concentration in which the test material is immobilized on a surface and exposed either to a complex of an enzyme linked to an antibody specific for the antigen or an enzyme linked to an antigen specific for the antibody followed by reaction of the enzyme with a substrate to yield a colored product corresponding to the concentration of the test material

Endemic* - restricted or peculiar to a locality or region

Endocrine* - producing secretions that are distributed in the body by way of the bloodstream

Epidemiology* - a branch of medical science that deals with the incidence, distribution, and control of disease in a population

Epimastigote** - a stage in the life cycle of certain trypanosomatids wherein the unicellular organism has a flagellum along the length of its cell body

Epitrochlear* - the medial epicondyle at the distal end of the humerus

ER - Elite Readers

Erythrocyte* - red blood cell

Extracellular* - situated or occurring outside a cell or the cells of the body

F

Fibroblast* - a connective-tissue cell of mesenchymal origin that secretes proteins and especially molecular collagen from which the extracellular fibrillar matrix of connective tissue forms

Flagella* - a long tapering process that projects singly or in groups from a cell and is the primary organ of motion of many microorganisms

FM - Frontiers in Microbiology

G

Gait* - a manner of walking or moving on foot

Gametocyte* - a cell (as of a protozoan causing malaria) that divides to produce gametes

H

Hemolymph* - the circulatory fluid of various invertebrate animals that is functionally comparable to the blood and lymph of vertebrates

Hepatic* - of, relating to, affecting, associated with, supplying, or draining the liver

Hepatomegaly* - enlargement of the liver

Hepatosplenomegaly* - coincident enlargement of the liver and spleen

HHMI - Howard Hughes Medical Institute

HM - HowMuch

Hyperesthesia* - unusual or pathological sensitivity of the skin or of a particular sense

Hypoglycemia* - abnormal decrease of sugar in the blood

Hypogonadism* - functional incompetence of the gonads especially in the male with subnormal or impaired production of hormones and germ cells

I

IAMAT - International Association for Medical Assistance to Travellers

IgG Antibodies** - the most common antibody that is found in blood and other body fluids that protects against bacterial and viral infections.

Immunopathology* - a branch of medicine that deals with immune responses associated with disease

Incidence* - rate of occurrence or influence

Indeterminate* - not leading to a definite end or result

Indirect Hemagglutination** - passive agglutination in which erythrocytes, usually modified by mild treatment with tannic acid or other chemicals, are used to adsorb soluble antigen onto their surface, and which then agglutinate in the presence of antiserum specific for the adsorbed antigen

Indirect Immunofluorescence** - a technique used in laboratories to detect circulating autoantibodies in patient serum

Inguinal* - of, relating to, or situated in the region of the groin or in either of the lowest lateral regions of the abdomen

Inoculation* - the introduction of a pathogen or antigen into a living organism to stimulate the production of antibodies

Insecticide* - an agent that destroys one or more species of insects

Insomnia* - prolonged and usually abnormal inability to get enough sleep especially due to trouble falling asleep or staying asleep

ITMA - Institute of Tropical Medicine Antwerp

Intracellular* - existing, occurring, or functioning within a cell

J

Jaundice* - yellowish pigmentation of the skin, tissues, and body fluids caused by the deposition of bile pigments

K

L

Lymphadenopathy* - abnormal enlargement of the lymph nodes

Lymphatic System* - the part of the circulatory system that is concerned especially with scavenging fluids and proteins which have escaped from cells and tissues and returning them to the blood, with the phagocytic removal of cellular debris and foreign material, and with the immune response and that consists especially of lymphoid tissue, lymph, and lymph-transporting vessels

Lysis* - a process of disintegration or dissolution (as of cells)

Lysosomal Fusion** - direct fusion of the phagosome to the lysosome that is essential for intracellular killing of microorganisms

Lytic Protein* - productive of or effecting lysis (as of cells) through proteins

M

Macrophage* - a phagocytic tissue cell of the immune system that may be fixed or freely motile, is derived from a monocyte, functions in the destruction of foreign antigens (such as bacteria and viruses), and serves as an antigen-presenting cell

Malaise* - an indefinite feeling of debility or lack of health often indicative of or accompanying the onset of an illness

Megacolon* - extreme dilation of the colon that may be congenital or acquired

Megaesophagus* - dilation and hypertrophy of the lower portion of the esophagus

Meningoencephalitis* - inflammation of the brain and meninges

Metacyclic Trypomastigote* - broad and stocky, produced in an intermediate host, and infective for the definitive host

Microhematocrit* - a procedure for determining the ratio of the volume of packed red blood cells to the volume of whole blood by centrifuging a minute quantity of blood in a capillary tube coated with heparin

Microscopy* - the use of or investigation with a microscope

Morbidity* - the incidence of disease

Mortality* - the number of deaths in a population during a given time or place

Myocarditis* - inflammation of the middle muscular layer of the heart wall

N

O

Oocyst* - a sporozoan zygote undergoing sporogenous development

Orthostatic Hypotension** - a form of low blood pressure that happens when standing up from sitting or lying down

P

Paleoparasitology** - the study of parasites from the past

Parasitemia* - a condition in which parasites are present in the blood —used especially to indicate the presence of parasites without clinical symptoms

Parasitophorous Vacuole** - allows the parasite to develop while protected from the phagolysosomes of the host cell

Paresthesia* - a sensation of pricking, tingling, or creeping on the skin that has no objective cause

Pathology* - the study of the essential nature of diseases and especially of the structural and functional changes produced by them

PCR* - (polymerase chain reaction) an in vitro technique for rapidly synthesizing large quantities of a given DNA segment that involves separating the DNA into its two complementary strands, using DNA polymerase to synthesize two-stranded DNA from each single strand, and repeating the process

Perinatal* - occurring in, concerned with, or being in the period around the time of birth

Pia Mater* - the innermost layer of the meninges covering the brain and spinal cord

PLOS - Public Library of Science

Polymorphism* - the quality or state of existing in or assuming different forms

Posterior* - situated behind

Prevalence* - the percentage of a population that is affected with a particular disease at a given time

Procyclic Trypomastigote** - A form of a trypanosome (at the beginning of its life cycle) that lives in the midgut of its host

Prophylaxis* - measures designed to preserve health (as of an individual or of society) and prevent the spread of disease

Protozoan* - any of a phylum or subkingdom (Protozoa) of chiefly motile and heterotrophic unicellular protists (such as amoebas, trypanosomes, sporozoans, and paramecia) that are represented in almost every kind of habitat and include some pathogenic parasites of humans and domestic animals

Pruritus* - to have an itch

Pulmonary Edema* - abnormal accumulation of fluid in the lungs

Q

R

Renal* - of, relating to, involving, or located in the region of the kidneys

Reservoir* - a host organism in which an infectious agent (such as a bacterium or virus) that is pathogenic for some other species lives and multiplies typically without damaging the host

RG - ResearchGate

Romana** - swelling of the eyelid

S

Schizogony* - asexual reproduction by multiple segmentation characteristic of sporozoans (such as the malaria parasite)

Schizont* - a multinucleated sporozoan that reproduces by schizogony

SD - ScienceDirect

Sensitivity** - the ability of a test to correctly identify patients with a disease

Serum* - the clear, yellowish fluid that remains from blood plasma after clotting factors (such as fibrinogen and prothrombin) have been removed by clot formation

Socioeconomic* - of, relating to, or involving a combination of social and economic factors

Somnolence* - the quality or state of being drowsy

Specificity** - the ability of a test to correctly identify people without the disease

Splenomegaly* - abnormal enlargement of the spleen

Sporozoite* - a usually motile infective form of some sporozoans that is a product of sporogony and initiates an asexual cycle in the new host

Standardization* - to bring into conformity with a standard especially in order to assure consistency and regularity

Subcutaneous Edema** - abnormal accumulation of fluid under the skin

T

Tachyarrhythmias* - arrhythmia characterized by a rapid irregular heartbeat

T Cells* - any of several lymphocytes (such as a helper T cell) that differentiate in the thymus, possess highly specific cell-surface antigen receptors, and include some that control the initiation or suppression of cell-mediated and humoral immunity (as by the regulation of T and B cell maturation and proliferation) and others that lyse antigen-bearing cells

Thromboembolism* - the blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation

TP - Trends in Parasitology

Transmission* - to cause or allow to spread

Transplacental* - passing through or occurring by way of the placenta

Trophozoite* - a protozoan of a vegetative form as distinguished from one of a reproductive or resting form

Trypomastigote* - any flagellate of the family Trypanosomatidae that has the typical form of a mature blood trypanosome

TVP - Today's Veterinary Practice

U

UNHCR - United Nations High Commissioner for Refugees

V

Vacuole* - a cavity or vesicle in the cytoplasm of a cell usually containing fluid

Vector* - an organism (such as an insect) that transmits a pathogen from one organism or source to another

W

WHO - World Health Organization

X

Y

Z

Zoonosis* - an infection or disease that is transmissible from animals to humans under natural conditions

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Conclusion

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