Trypanosoma evansi as a Major Cause of Animal Trypanosomiasis: A Comprehensive Review

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Abstract

Trypanosomiasis caused by *Trypanosoma evansi* is a major protozoan illness that affects animals worldwide. It is also referred to as "surra" and affects a variety if wild and domestic animals such as sheep, cattle, goats, dogs, buffaloes, pigs, elephants, amongst others. In preparing this review, relevant scientific articles were searched on PubMed, SCOPUS, and Web of Science databases using the keyword "*Trypanosoma evansi* AND animals". *T. evansi* are carried by a vast number of hematophagous flies and are found in the extracellular and internal fluids of certain hosts. Trypanosomosis is mostly characterized by anemia, and the degree of anemia can typically be used as a gauge for the disease's severity. Trypanosomiasis compromises the host animal's immune system and its diagnosis is dependent on a number of factors such as thorough clinical examination, suitable sample collection, sample size, suitable diagnostic test performance, and logical interpretation of test results. The clinical manifestations of trypanosomiasis vary widely in both appearance and severity, ranging from neurological disturbances and skin plaques to vaginal enlargement. Hematophagous biting flies, including *Tabanus*, *Haematopota*, *Glossina*, *Chrysops*, *Lyperosia*, *Stomoxys*, and *Hippobusca* flies, contribute to the spread of trypanosomiasis. Four medications are primarily used to treat trypanosomiasis: quinapyramine, karetin, diminazene aceturate (Berenil), and melarsomine (cymelarsan). An efficient vaccination program is an additional technique for managing infectious diseases in addition to treatment. The most important step in curtailing the spread of trypanosomiasis caused by *T. evansi* is to stop its transmission by flies via physical and chemical methods.

Keywords: fly, diseases, parasitemia, *Trypanosoma*, trypanosomiasis

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INTRODUCTION

Trypanosomiasis caused by *Trypanosoma evansi*, also referred to as "Surra", is a protozoan illness that affects animals worldwide, including camels, goats, buffalo, horses, donkeys, mules, sheep, pigs, cats, cattle, and dogs (Kim *et al*., 2023). *Trypanosoma* is a genus of unicellular

extracellular flagellate protozoan that belong to the Trypanosomatidae family that cause this disease (Chau *et al*., 2016). This organism comes from the words "trypano" which means borer and "soma" which means body (Langousis and Hill, 2014). The capacity of trypanosomes to periodically change the major glycoproteins on their surface results in the recurrence of parasitemia (Aresta-Branco *et al*., 2019). The degree of its clinical impact is contingent upon vulnerability of the host.

Trypanosoma infections are known to be transmitted by various hematophagous flies genera, including *Stomoxys*, *Tabanus*, *Glossina*, and *Haematopota* (Lendzele *et al*., 2022). This parasite can live in reservoirs such as camels, goats, buffalo, horses, sheep, pigs, cats, cattle, and dogs. Severe infections are primarily seen in camels, horses, cattle, and buffalo (Aregawi *et al*., 2019). *T. evansi* has broad range with regards to geographic location (Dario *et al*., 2021). For instance, camels are the primary hosts throughout Africa and the Middle East (Sazmand *et al*., 2019). In contrast, the most prevalent infections in Asia are seen in buffalo and elephants, particularly in the Philippines, Thailand, and India (Kim *et al*., 2023; Kengradomkij *et al*., 2025). The vampire bat species *Desmodus rotundus* is a common vector and host in South America (Quiroga *et al*., 2022). Conversely, *T. evansi* infections afflict deer, wild boar, and rodents in Australia and Europe (Keatley *et al*., 2020; Magri *et al*., 2021). The variety of hosts offers *T. evansi* a great chance to grow and spread throughout the world.

Trypanosomiasis due to *T. evansi* can present with either acute and chronic clinical symptoms. Infected animals (such as cattle, buffaloes, sheep, goats, dogs, and pigs) that exhibit the acute form of the disease, experience fever, starvation, edema, and ultimately die. In contrast, the chronic form of the disease is characterized by increasing weight loss, intermittent high fever, generalized muscular atrophy, pale mucous membranes, and occasionally, abdominal edema (Abdel-Rady, 2008). Trypanosomiasis-affected animals may also smell sweet because of an increase in urine ketones (Getahun *et al*., 2022). The disease's chronic form is the most prevalent because it is most often linked to an infection that results from immune suppression caused by a *Trypanosoma* infection (Boushaki *et al*., 2019). Treatment guidelines and chemotherapeutic control tactics are based on data regarding the region's trypanosomiasis risk and trypanocidal drug resistance prevalence (Kasozi *et al*., 2022). The successful treatment of trypanocidal drugs and the detection of parasites both depend on the sensitivity and specificity of the diagnostic technique employed.

The illness has a major financial impact, but it is impossible to calculate the exact costs because there are inadequate epidemiological statistics and it is difficult to gather sufficient data in underdeveloped nations (Snijders *et al*., 2021). This causes enormous economic crises and catastrophic losses in underdeveloped nations, with effects that may double those of developed nations. This illness outbreak puts millions of cows, buffalo, horses, and camels in danger of dying worldwide with significant economic losses, especially with regards to reduced productivity. Trypanosomiasis's effects on animals can lower the predicted profit yield from livestock production by as much as 30% of net income (Abro *et al*., 2021). *Trypanosoma evansi* is the primary cause of trypanosomiasis among all pathogenic Trypanosoma species since it has the largest host range and geographic distribution worldwide (Kim *et al*., 2023).

The spread of trypanosomiasis is a global health concern that might be lethal if proper diagnosis and treatment are delayed. The aim of writing this review is to comprehensively explain the etiology, history, life cycle, epidemiology, pathogenesis, immune response, diagnosis, clinical symptoms, transmission, risk factors, economic impact, treatment, vaccination, and control of trypanosomiasis. We searched relevant scientific articles on PubMed, SCOPUS, and Web of Science databases using the keyword "*Trypanosoma evansi* AND animals" in the preparation of this review. A total of 139 articles which reported relevant information such as etiology, pathogenesis, epidemiology, diagnosis, clinical symptoms, treatment, and control of *T.*

evansi infections in animals were selected, downloaded, and reviewed. Comprehending the general overview of trypanosomiasis is important for executing efficacious control strategies.

RESULTS AND DISCUSSION

Etiology

T. evansi is a member of the Trypanozoon subgenus of the *Trypanosoma* genus (Salivarian) (Misra *et al*., 2016). The traits of a slender Trypanozoon parasite are seen in fresh blood samples: thin posterior extremity, free flagellum, active movement that results in limited displacement in the microscope field, a highly visible undulating membrane that "traps" light (light may appear to be captured at one end of the parasite and moved to the other end for release), and small size in comparison to *Trypanosoma theileri* but large in comparison to *T. congolense* (Desquesnes *et al*., 2013).

T. evansi is consistently described as a tiny, monomorphic trypomastigote parasite when seen in thin smears stained with Giemsa (Misra *et al*., 2016). There are a few isolated reports of short forms in this species which are thoroughly examined before concluding that the polymorphism of *T. evansi* is an irregular occurrence that happens occasionally (Hoare, 1964). In contrast to *T. brucei*, this parasite primarily exhibits slender forms (long free flagellum and thin posterior end with small subterminal kinetoplast) and some intermediate forms (shorter free flagellum and posterior end with almost terminal kinetoplast) (Figure 1).

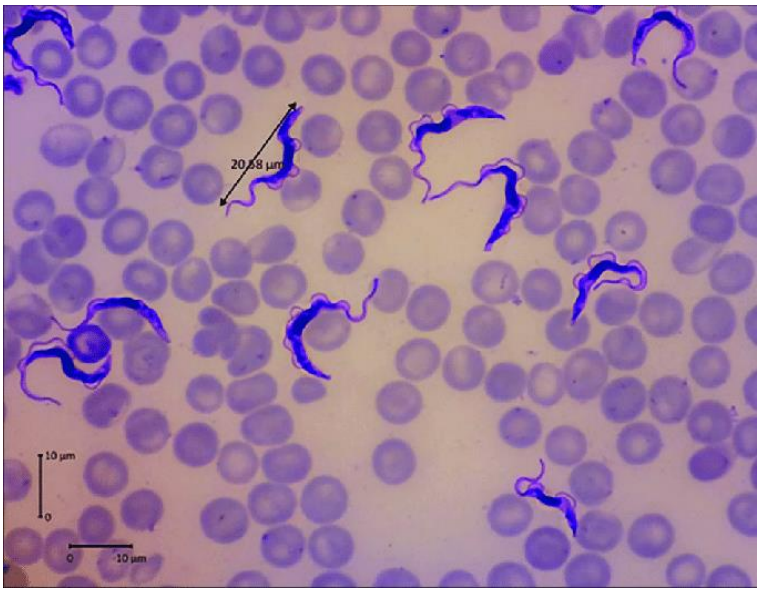

Figure 1. *T. evansi* morphology under a light microscope using Giemsa staining (original 400×) (Nuryady *et al*., 2019).

T. evansi parasites have an average length of 24 ± 4 µm (minimum 15 µm, maximum 33 µm), and there is no discernible correlation between strain, host, or even geographic origin (Desquesnes *et al*., 2013). Similarly, dyskinetoplastic (or even akinetoplastic) strains are no longer thought to be different from *T. evansi*, and morphological studies based on the absence of kinetoplasts in population proportions ranging from 0% (*T. equinum*) to 100% or intermediate (*T. venezuelense*) have not produced significant differences. Lastly, historical and contemporary observations indicate that the size and shape of *T. evansi* blood forms are more or less determined by the host's immunological response and the parasite's development environment than by genetic traits (Tejero *et al*., 2008). Of note, in certain instances, truncated parasite forms were seen. These forms can be difficult to identify in blood smears because, as was the case in recent cases in Spain, truncated parasites can look like *T. vivax*, but *T. vivax* has

larger kinetoplasts than *T. evansi* (Tamarit *et al*., 2010). *T. evansi* exhibits the thin morphology and morphometry of the Trypanozoon subgenus, with very little variation and no traits that make it a species.

History

The British veterinarian Griffith Evans identified *T. evansi*, the first pathogenic mammalian trypanosoma, in 1880 from diseased camels and other similar animals in the Dera Ismail Khan district of Punjab (Desquesnes *et al*., 2013). The tsetse fly is assumed to be the source of *T. evansi*, which is thought to have descended from *T. brucei*. However, the lack of the upper loop of kinetoplastic mitochondrial DNA has prevented *T. evansi* from undergoing cyclical development in the tsetse fly (Kamidi *et al*., 2017). This hemoparasite-caused illness originated in Africa and has since expanded from the Arabian Peninsula to a large region spanning from Iran to Indonesia (Sawitri *et al*., 2019). Its current geographic range extends from the northern region of Africa through Southeast Asia and the Middle East (Fetene *et al*., 2021).

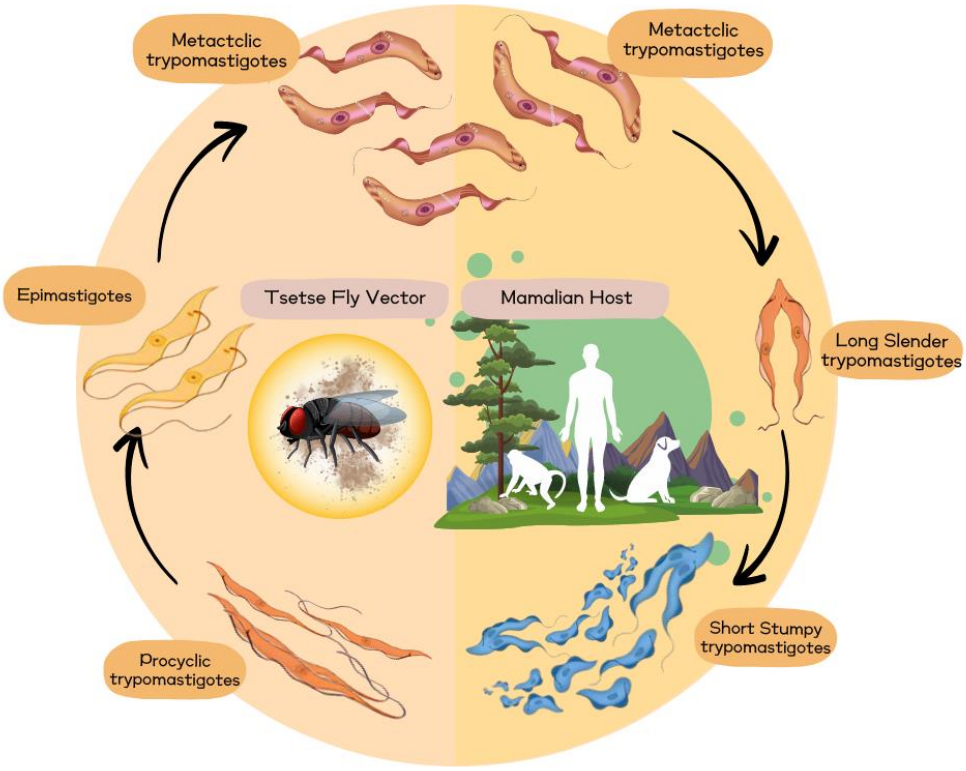

Figure 2. *T. evansi* life cycle: Developmental progression and vector-mammalian host transmission mechanisms.

Trypanosomiasis in animals and humans has a long history in India, with records extending back to the eighth century BC (Steverding, 2008). It is prevalent in nearly all nations where the ideal conditions (such as savanna, forests, and areas near waterbodies like rivers and streams) exist for the fly vector to reproduce. Spanish conquistadors are said to have carried the illness to Latin America, where vampire bats (*Desmodus rotundus*) played a role in the infection's spread (Quiroga *et al*., 2022). There have also been reports of *T. evansi* infections in France and Spain (Tamarit *et al*., 2010). It is only via early detection and management that *T. evansi* can be completely removed from a given area. *T. evansi* cannot be eradicated once it has reached enzootic levels, probably because large domestic and wild reservoirs exist, it can spread silently through healthy carriers, and it can transmit using nonspecific mechanical vectors found all over the world (Behour *et al*., 2019).

Life Cycle

T. evansi are carried by a vast number of hematophagous flies and are found in the extracellular and internal fluids of certain hosts. The life cycle of *T. evansi* is intricate, and the vector for transmission is through the tsetse fly (Geiger *et al*., 2018). It involves further development between the vector and mammalian host in several stages. Indeed, Figure 2 hereafter depicts the commencement of the life cycle when a tsetse fly ingests long slender trypomastigotes in the infected bloodstream of a mammal. These trypomastigotes finally differentiate into the short stumpy trypomastigote stage, specialized for survival within the fly vector (Silvester *et al*., 2017a; Geiger *et al*., 2018). Insects that feed on blood are the ones that cause its mechanical transmission. The complex life cycle of *T. evansi* includes cell division, proliferation, and differentiation (Matthews, 2005). It is crucial for the parasite to be able to control its cell cycle in order to produce many divisions in order to infect both hosts and vectors (Wheeler *et al*., 2019). The thin-stage cells that are circulating in the mammalian host's blood eventually reach large quantities and change into stump-stage cells, which have entered the cell cycle and are unable to proliferate (Silvester *et al*., 2017a). The stumpy stage is thought to be the only one that can successfully transfer the vector. It carries out two crucial tasks: it controls the host's parasite load and acts as a bridge between the parasite and host loads (Choi *et al*., 2024).

This parasite can travel across a variety of bodily fluids, the placenta, and the circulatory system, which includes the lymphatic and cerebral fluids (Pereira *et al*., 2019). The brain and central nervous system (CNS) are the most commonly affected organs by parasite diseases, which spread from fluids to tissues (Mogk *et al*., 2017). The parasite, known as a trypomastigote, starts to travel to the midgut of the vector insect as soon as the fly starts consuming blood, though, at which point the activities taking place inside the vector become visible for the first time (Schuster *et al*., 2017). The trypomastigotes proliferate and travel via the esophagus and hypopharynx after exiting the midgut, eventually arriving at the salivary glands (Franco *et al*., 2014). This parasite has many strains that are infectious and non-contagious. They have the capacity to develop into extremely harmful metacyclic forms (Martín-Escolano *et al*., 2022).

The flies can absorb more blood with each meal by storing the contaminated blood in the plant for a short while, or it can be immediately transmitted to the midgut (Telleria *et al*., 2014). Trypanosomes pass through the midgut and proceed to the proliferative procyclic stage (Alfituri *et al*., 2020). The parasite has to move through the peritrophic matrix after becoming implanted in the midgut (Aksoy, 2019). This barrier keeps the surrounding midgut tissue and the blood meal apart. According to theory, parasites accomplish this by swimming through the endotrophic space and into the proventriculus, which is the site of the development of the peritrophic matrix. From there, they can enter the ectotrophic area (Schuster *et al*., 2021).

Epidemiology

Even though trypanosomiasis is commonly known as African trypanosomiasis, some trypanosomiases can infect people outside of Africa (Kasozi *et al*., 2022; Lobo *et al*., 2019). Trypanosomiasis is caused by *T. evansi*, which is found not only in Africa but also in Central and South America, the Middle East, and Asia (Chau *et al*., 2016). Trypanosomiasis has a wide range of hosts, with the primary host species changing depending on the geographical location. The camel is the most significant mammal in Africa, especially in areas of East Africa and beyond the northernmost limits of the fly belt, whereas the horse is the most impacted in Central and South America (Eyob and Matios, 2013). A greater range of hosts are involved in Asia, such as Bactrian camels and dromedaries, cattle, buffalo, horses, and pigs (Desquesnes *et al*., 2013). Contrast this with findings from South America and Africa, where there is scant data indicating that domestic livestock other than horses and camels are clinically impacted by or infected with *T. evansi* (Roy *et al*., 2010).

The animals primarily affected by this illness are horses, donkeys, mules, camels, dogs, and cats

(Eyob and Matios, 2013). More vulnerable than sheep and goats, which are likewise more vulnerable than cattle and pigs, are camels, horses, dogs, and Asian elephants (Misra *et al*., 2016). When used as experimental hosts, rats and mice are especially vulnerable to *T. evansi* infections (Da Silva *et al*., 2011). It's been proposed that reservoirs of infection in animals are not significant for *T. evansi*, in contrast to fly-borne trypanosomiasis, though it's likely that South American coati and capybara are exceptions to this rule (Herrera *et al*., 2002). *T. evansi* has spread to regions of Africa north of the Sahara desert, the Soviet Union, China, Indonesia, Pakistan, India, the Philippines, Madagascar, Mauritius, and South and Central America due to its potential to be spread by bloodsucking insects other than Glossina (Gao *et al*., 2020). Infections continue to spread to Australia, North America, and South West Africa (Kasozi *et al*., 2022). High infection rates, which can reach 30 to 100%, are typically associated with the introduction of parasites into new locations (Ponte-Sucre, 2016). Insects carry trypanosomes, and their continued life is dependent on vector dynamics. Trypanosomiasis induced by *T. evansi* affects most camels and is mechanically and independently spread by flies (Selim *et al*., 2022). In most herds, the disease is endemic, and the parasite *T. evansi* is present anywhere animals are housed (Sawitri *et al*., 2019).

Pathogenesis

The earliest clinical sign of *T. evansi* infection in any host is the development of a chancre on a fly bite which is a swelling of the skin where the trypanosomes first proliferate (Ponte-Sucre, 2016). This first replication not only facilitates the establishment of infection but also marks the beginning of interactions between the host immune system and trypanosomes (Pereira *et al*., 2019). Trypanosoma enters the bloodstream after chancre development, causing fever (Aksoy *et al*., 2017). When the temperature drops, parasitemia may peak for four to six days before declining again (Misra *et al*., 2016). Trypanosomosis pathology is mostly characterized by anemia, and the degree of anemia can typically be used as a gauge for the disease's severity (Stijlemans *et al*., 2018). Large amounts of red blood cells (RBCs) are eliminated from the bloodstream by hematoma lymph nodes, the bone marrow, and the spleen's mononuclear phagocytic system (MPS) cells when an individual has parasitemia (Boada-Sucre *et al*., 2016). The packed cell volume (PCV) drops to below 25% or even up to 10% when a significant amount of red blood cells are removed (Farikou *et al*., 2023). As a result, the animal develops anemia, dullness, anorexia, lethargicness, eye discharge, and loss of body condition.

Anemia is the primary culprit in advanced stages, while there may be other factors as well. Nevertheless, the primary functional defect resulting from continuous anemic tissue anoxia, which lowers tissue pH and damages blood vessels, is anoxic conditions, regardless of the source of anemia (Pereira *et al*., 2019). The obvious symptoms include increased cardiac output brought on by elevated heart rate and stroke volume as well as shortened circulation times (Elliott *et al*., 2013). According to reports, the central nervous system is particularly vulnerable to anoxia, which can lead to the development of cerebral anoxia (Chuenkova and Pereiraperrin, 2010). Upon postmortem, the carcasses of animals afflicted with trypanosomiasis are typically pale, emaciated, and occasionally skinny (Njiru *et al*., 2004). At the incision, the lymph nodes are swollen and enlarged. Ascites, hydropericardium, and hydrothorax are present (Williams *et al*., 2009). The spleen enlarges in acute cases and atrophy occurs in chronic situations; however, these changes are not thought to be pathognomonic for a particular disease (Deleeuw *et al*., 2019).

It is established that *T. evansi* belongs to the *T. brucei* group, which is known to favor the connective tissue of the host in order to break down collagen connections and eliminate the fibroblasts that create and preserve collagen (Wei *et al*., 2021). Large volumes of cytoplasmic and mitochondrial enzymes are considered to be released into the serum as a result of the disruption of the host's connective tissue and

vascular damage brought on by the *T. brucei* group, further inflicting tissue damage (Pereira *et al*., 2019). High-temperature fevers could be brought on by the harmful metabolites that deceased Trypanosoma generate (Ponte-Sucre, 2016). Moreover, a considerable reduction in albumin levels may also contribute to the edema observed in various body areas based on the chronic stage, causing modifications in blood osmotic pressure (Soeters *et al*., 2019).

Immune Response

The illness trypanosomiasis compromises the host animal's immune system. The host's immune system is meant to defend it against infections, but occasionally it can get overworked, react improperly, or produce an immunological-mediated illness that manifests clinically (Chaplin, 2010). Rarely are circulating trypanosomes observed in patients with chronic illnesses, and research has not demonstrated a connection between the degree of parasitemia and the degree of inflammation (Morrison *et al*., 2023). This might happen as a result of the immune system attacking self-antigens and parasites. The parasite may accomplish this by inflammatory responses, tissue damage, or molecular mimicry, which releases tissue proteins and promotes the production of self-antigens (Bonney *et al*., 2011).

Pure extracellular parasite *T. evansi* may live, proliferate, and undergo differentiation in the extracellular fluid of mammals, including the hostile vascular milieu (Phongphaew *et al*., 2023). As a result, these parasites are always up against different immune system defenses, from innate to adaptive. It has been demonstrated that trypanosomal DNA, among other chemicals, may be released from dead trypanosomes and cause macrophages to release pro-inflammatory chemicals like Tumor Necrosis Factor Alpha (TNF-α), IL-6, IL-1, IL-10, and Nitric Oxide (NO) (Stijlemans *et al*., 2022). Through the damaging effects of TNF-α and NO on both host cells and parasites, the host immune system's initial response helps regulate the first peak of parasitemia (Stijlemans *et al*., 2018).

As archetypal extracellular parasites, these pathogens evade antibody (Ab) recognition by varying their primary exposed membrane surface glycoproteins (also known as variable surface glycoproteins, or VSGs) sporadically (Stijlemans *et al*., 2016). This subtle mechanism of antigenic variation allows the pathogens to elude humoral immunity. Only directly activated B cells have the IL-6 receptor, which is released by activated macrophages and increases IgM and IgG antibodies (Somoza *et al*., 2022).

The predominant IgM response and minimal IgG production are the hallmarks of polyclonal B cell activation brought on by *T. evansi* infection (Baral, 2010). Stijlemans *et al*. (2016) postulated that because IgM is larger than IgG, it may be more difficult to penetrate tissues where Trypanosoma multiplies. This could result in persistent infection because of the presence of a tissue reservoir while halting the parasite's unchecked development. IgG levels cannot be found until after parasitemia, although IgM can be seen during parasitemia. Thus, it seems that the primary mechanism for eliminating infected VAT is an IgM response, even if during infection, both IgM and IgG responses to variable surface glycoprotein (VSG) take place (Magez *et al*., 2008). The parasite is opsonized by antibodies directed against particular surface epitopes of the exposed VSG layer, and immune complexes are effectively phagocytosed and eliminated by macrophages, mostly in the liver (Magez *et al*., 2020). Complement-deficient mice infected with *T. evansi* manage consecutive waves of parasitemia as effectively as complement-competent strains, suggesting a role for complement-mediated lysis in parasite clearance that cannot be verified (Sari *et al*., 2015).

There have been reports of elevated IgM during both acute and chronic *T. evansi* infections, yet this is not protective because the majority of antibodies are autoantibodies (Nguyen *et al*., 2021). Both the spleen and lymph nodes are extremely reactive during the acute stage of the illness. This could account for the generalized hyperplasia of lymphoid tissue that characterizes *T. evansi* infections, while in the

later stages, the immune system experiences a loss of lymphoid cells (Dargantes *et al*., 2005).

Diagnosis

Trypanosomiasis diagnosis is dependent on a number of factors, including a thorough clinical examination, suitable sample collection, sample size, suitable diagnostic test performance, and logical interpretation of test results. In situations when trypanosomiasis is highly prevalent, a number of tests with a low diagnostic sensitivity might be enough. Microscopic analysis of the lymph nodes that aspirate blood or the cerebrospinal fluid (CSF) from infected animals can be used to make a parasitological diagnosis (Lumbala *et al*., 2018). In order to prevent trypanosomes in blood samples from immobilizing and lysing, samples should be checked as soon as feasible. Generally, compared to a venipuncture, a blood sample obtained at the tip of the ear yields more parasites (Setiawan *et al*., 2021). Collected blood samples should be stored in an ice bag away from sunlight because trypanosomes is quickly damaged by sunlight (Chappuis *et al*., 2005). To create a moist blood smear, a drop of blood (about 2 - 5 μL) is placed on a sanitized glass slide and covered with a cover slip to eliminate any air bubbles. Afterwards, under 400x magnification, the sample will be inspected using an aperture condenser, phase contrast, or interference contrast to ensure proper visualization (22 × 22 mm) (Morais *et al*., 2022).

The blood smear technique is the most widely used test for trypanosomiasis, despite having a very low detection capability of 10,000 parasites in 200 tiny fields (Bouteille and Buguet, 2012). *T. brucei* positives sprint across the microscopic field, but *T. congolense* parasites move slowly (Silvester *et al*., 2017b). Microscopic inspection increases the detection of these parasites, enabling a conclusive diagnosis. Whenever there are trypanosomes in the blood, the surrounding erythrocytes' movement usually draws notice. Blood samples should be taken every other day to check for peak parasitemia when parasites are easily detectable due to changes in parasitemia (Costa *et al*., 2022). With the use of a hemolytic agent like sodium dodecyl sulfate (SDS), red blood cell lysis can be performed prior to analysis, greatly increasing the sensitivity of this approach (Biéler *et al*., 2012).

Immune system proteins and antibodies produced in response to infections can be found using serological techniques. The diagnostic test RoTat 1.2 looks for antibodies in serum that point to a Type A infection with *T. evansi* (Desquesnes *et al*., 2022). These tests consist of the Enzyme Linked Immunosorbent Test (ELISA/*T. evansi*), the Latex Agglutination Test (LATEX/*T. evansi*), and the Card Agglutination Test (CATT/*T. evansi*) (Tran *et al*., 2009). The antigen type variants (VAT) are identified by vector surface glycoproteins (VSGs), which are highly immunogenic and induce host antibody responses for opsonization, agglutination, and trypanolytic activity (Kim *et al*., 2023). The *T. evansi*-specific antibodies present in the host's blood can be found using the quick and straightforward agglutination test CATT/*T. evansi* (Reck *et al*., 2021).

Genes present in *Trypanosoma* are detected molecularly using Polymerase Chain Reaction (PCR). Numerous genes are utilized in the diagnosis of *Trypanosoma*, such as ESAG6/7 and TBR1/2 (Witola *et al*., 2005; Suprihati *et al*., 2022). The Trypanozoon subspecies, which includes *T. brucei*, *T. equiperdum*, and *T. evansi*, include this multicopy gene. TBR is involved in antigenic variation, and the transferrin receptor complex is encoded by ESAG (Young *et al*., 2008). TBR1/2 primers often exhibited greater sensitivity than ESAG6/7 primers (Pruvot *et al*., 2010). Since ribosomal RNA (rRNA) genes are highly conserved and enable the differentiation of closely related trypanosome species, they are also typically utilized. The *Trypanosoma* rRNA contains the internal transcribed spacer (ITS) region, which is bordered by highly conserved portions that can be used to construct primers (Dollet *et al*., 2012). Additionally, PCR primers can be created so that every species yields a distinct PCR amplicon length.

Clinical Symptoms

Clinical symptoms of trypanosomiasis due to *T. evansi* can differ greatly in appearance and intensity. Clincal symtoms could also be

infuluenced by the state of the diet and environmental stress. The signs of this condition might vary and include neurological issues, skin plaques, and vaginal enlargement (Claes *et al*., 2005). The onset of clinical symptoms might take weeks or months, and they frequently wax and wane with relapses that are almost definitely brought on by stress (Mudji *et al*., 2020). This could occur multiple times before the animal passes away or seems to recover. This disease is thought to have a case fatality rate of more than 50 % to almost 100 % if left untreated or without prompt appropriate treatment (Kennedy, 2004; Abera *et al*., 2024).

Three stages characterize the disease's progression: genital lesions in stage 1, skin signs in stage 2, and nerve signals in stage 3 (MacLean *et al*., 2012). In male animals, the glans penis and foreskin area show the earliest indications of edema. Enlargements can occur in the scrotum, ventral abdomen, chest, and perineum (Guiton and Drevet, 2023). There may be vesicles or boils on the genitalia, and when they heal, they could leave permanent scars. The place where the male animal's penis is continuously tugged and delayed might become inflamed with orchitis (Sivajothi and Reddy, 2019). Animals are susceptible to paraphimosis (Kasozi *et al*., 2022). Mares has a mucopurulent discharge and vaginitis (Yasine *et al*., 2019). The vulva swells, and this swelling might spread to the mammary glands and the ventral portion of the stomach along the perineum (Suganuma *et al*., 2016). Signs of pain and vulvitis or vaginitis with polyuria may be observed. Pigmentation may develop in the udder, perineum, and genital area (Gizaw *et al*., 2017). More virulent strains may cause abortions.

Skin indications, sometimes referred to as the urticaria stage, are typified by the skin eruption of distinct, elevated, spherical, or oval-shaped patches known as "plaques" (Barrett and Croft, 2012). Edema patches, sometimes known as "Silver Dollar Plaques", can develop on the skin, particularly on the neck, shoulders, ribs, and thighs (Gizaw *et al*., 2017). They can measure up to 5-8 cm in diameter and 1 cm thick. These symptoms are usually pathognomonic and linger for three to seven days. The last stage, known as the paralysis stage, is typified by nervous system disruptions. These symptoms start off as restlessness and a propensity to switch one leg for the other, then progress to increasing weakness and coordination, and ultimately culminate in death and paralysis, particularly in the rear legs (Adebiyi *et al*., 2021). More symptoms include emaciation, conjunctivitis, keratitis, intermittent fever, and progressive anemia manifested by pallor of the mucous membranes surrounding the eyes and mouth (Desquesnes *et al*., 2013).

Transmission

Hematophagous biting flies, including *Tabanus*, *Haematopota*, *Glossina*, *Chrysops*, *Lyperosia*, *Stomoxys*, and *Hippobusca* flies, contribute to the spread of *T. evansi* in animals such as cattle, buffalo, antelopes, pigs, as well as rodents (Hairani *et al*., 2023). Efficiency of transmission is influenced by the level of parasitemia, the severity of the fly attack, and the time between two feedings in a row (Van Den Abbeele *et al*., 2010). A high density of insect vectors is connected with trypanosomiasis epidemics in certain locations, which peak during the rainy and post-rainy seasons (Franco *et al*., 2014). There are four possible modes of transmission: oral, iatrogenic, vertical, and horizontal. Carnivorous animals can also become infected after eating infected tissue when the oral mucosa is damaged (Giordani *et al*., 2016). There is also a chance that *Trypanosoma* can be sexually transmitted (Biteau *et al*., 2016). Investigations on the possibility of *T. evansi* transmission by leeches, particularly Asian buffalo leeches, are necessary (Su *et al*., 2022). In certain instances, trypanosomiasis has also been documented to spread vertically or transplacentally (Lindner and Priotto, 2010). In Latin America, the vampire bat (*Desmodus rotundus*) serves as a host, reservoir, and biological vector for parasites, allowing *T. evansi* to spread from bite to bite or vice versa (Austen and Barbosa, 2021). These bats can also infect cattle since they are persistent vectors that can infect their hosts for extended periods of time. A recent study evaluated the potential of a previously identified antitrypanosomal nucleoside called 3’-deoxytubercidin, as a

therapeutic candidate in combating *T. evansi* using mouse models (Ilbeigi *et al*., 2025). In this study, mice that were previously infected with *T. evansi* were subsequently treated by administering 3'-deoxytubercidin intraperitoneally once daily for five consecutive days at a dosage of 6.25 mg/kg. This *in vivo* treatment resulted in a successful cure of all *T. evansi*-infected mice without any form of toxicity (Ilbeigi *et al*., 2025). This intriguing successful treatment result which was confirmed by both microscopic examination and quantitative PCR techniques, further highlighting its potential in improving trypanosomiasis disease management in affected regions.

Risk Factor

Important risk factors for trypanosomiasis include stress conditions, young age, immunocompromised individuals, housing facilities, farming, hunting, herding cattle, and other activities such as tourism and migration to regions endemic with hematophagous biting flies. Some animals may recover from a *T. evansi* infection on their own, whereas other animals may experience the disease at different phases. The duration of time between the onset of clinical symptoms and the initial infection in trypanosomiasis varies greatly, but often falls between 5 and 60 days, but longer times (such as 3 months) have been reported (Biteau *et al*., 2016). Typically, the time span between infection and the emergence of parasites in the bloodstream is under 14 days. The initial dosage of infection (equal to the number of bites by infectious insects) and stress are risk factors that affect the incubation time (Giordani *et al*., 2016). In more vulnerable animals, stress arises during the end of pregnancy and the early stages of nursing (Malafaia and Talvani, 2011; Firdausy *et al*., 2025). Stress-producing infectious infections, such as helminthosis, can exacerbate the disease's severity (Cortes-Serra *et al*., 2022). *Trypanosoma* tolerance can also be reduced due to low nutritional levels or when the animal must move to find water and pasture in the dry season (Pathak, 2009).

Animals of all ages are susceptible to trypanosomiasis, although adult animals are more likely to contract the disease immediately after weaning (Saldanha *et al*., 2024). The rainy season typically sees an increase in fly vector populations (*Tabanids*, *Hippoboscids*, and *Stomoxys*), as the wet climate is conducive to reproduction and the spread of new illnesses (Hairani *et al*., 2023). These flies also like to congregate around rivers and wetlands, where herders typically bring their cattle during the dry season (Okello *et al*., 2023). The challenge, or the quantity of vector fly bites an animal sustains in a specific period of time determines the extent of the *Trypanosoma* infection risk. In contrast to cyclically transmitted trypanosomes, *T. evansi* has evolved to a fully mechanical and non-cyclical form of transmission via blood-sucking insects other than tsetse, and it infects a greater variety of animal hosts (Choi *et al*., 2024).

Economic Impact

The economic losses due to trypanosomiasis are quite high, and treatment is cost effective. According to recent estimates based on bioeconomic infectious disease models, a Philippine community with 80 buffalo, 40 cattle, 200 pigs, 150 goats/sheep, and 15 horses that are moderately to severely impacted by trypanosomosis may lose up to US$158,000 annually. However, it has been proven that the same village can earn the same amount of money if treatment is used (Dobson *et al*., 2009). Trypanosomiasis is very endemic in Mindanao, Philippines, and a 4-year field survey yielded a vast amount of data that were used to create the model. Comparatively, prior estimates of the country's annual losses from trypanosomiasis in the Philippines were barely US$0.1 million (Manuel, 1998). In contrast to the present data, which is based on losses from poor reproduction, diagnosis, treatment expenses, and replacement costs, previous estimates were based solely on limited mortality data that was provided to the government. However, because a number of factors were overlooked, current estimates of the financial losses caused by trypanosomiasis may still be too low: losses as a result of decreased

milk production, weight loss, carcass quality, and selling prices. Animals with *T. evansi* infections sell for extremely cheap prices (30–50% less) in Mindanao (Desquesnes *et al*., 2013). The significant financial losses resulting from *T. evansi* infections in endemic regions significantly affect impoverished livestock producers and their families, who rely on these animals for both agricultural pursuits and revenue (Benaissa *et al*., 2020). Low-income marginal farmers face an additional financial strain due to the requirement to import replacement stock from other sources.

Trypanosomiasis-related economic losses can be prevented by putting into practice efficient control strategies and approaches. The most cost-effective treatment option in the trypanosomosis endemic Pantanal region of Brazil, where the livestock industry is significant and horses are utilized for grazing livestock, has been found to be monitoring and treating horses with diminazene aceturate for a year. This approach results in a total net loss of more than US $2 million annually (Silva *et al*., 1995). Nevertheless, this approach makes the implausible assumption that the medication is 100% effective against *T. evansi*, particularly in regions where drug resistance is present. Similar to the Philippines, the best course of action for combating trypanosomiasis is to treat all affected animals specifically with very effective medications (such as melarsomine dihydrochloride) all year long (Giordani *et al*., 2016). It is also financially possible to treat all cattle species in a community in bulk, twice a year; however, this may lead to drug resistance in *T. evansi* isolates.

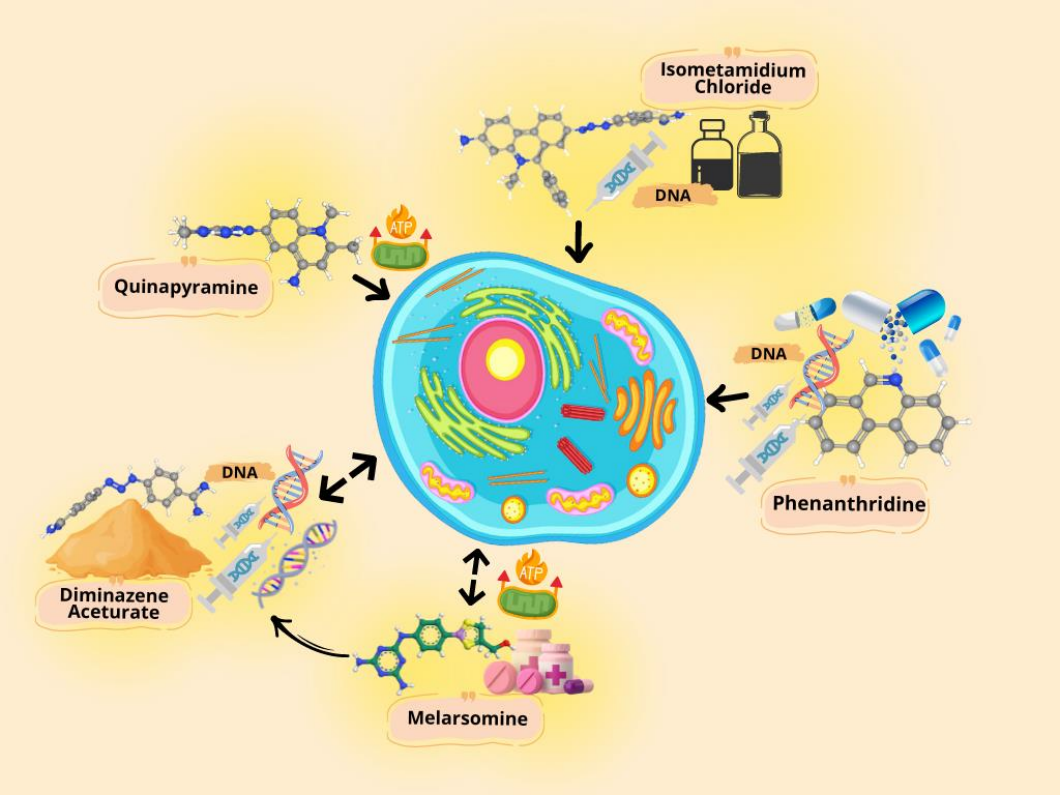

Figure 3. Molecular mechanism of action of drugs primarily used to treat trypanosomiasis.

Treatment

Animal infections with *Trypanosoma* can be lethal if left untreated (Carvalho *et al*., 2018). The primary means of controlling infection is chemotherapy; however, the effectiveness of the available treatments is limited, they are hazardous, and resistant *Trypanosoma* strains are starting to arise (Lewis *et al*., 2015). *T. evansi* requires different therapy because it is resistant to the majority of prescribed medications (Mdachi *et al*., 2023). Drugs used to treat trypanosomiasis have significant side effects, and the parasites develop resistance to the medications (Venturelli *et al*., 2022).

Five FDA-approved medications such as quinapyramine, isometamidium chloride, phenanthridine, diminazene aceturate, and melarsomine are primarily used to treat trypanosomiasis. Taken together, their mechanism is described in Figure 3. Quinapyramine interferes with the metabolism of *T. evansi* by inhibiting DNA synthesis and suppressing the activity of mitochondrial ribosomes to produce energy and replication; as a result, the cell dies. Isometamidium chloride acts in the interference of kinetoplast DNA replication and transcription beside interfering with reproduction, leading to cell death. Phenanthridine binds with the interference of DNA and RNA synthesis with further damage to both the nuclear and mitochondrial genetic material on the kinetoplast DNA, leading to the death of the parasite. Diminazene aceturate acts by interfering with DNA and RNA replication in the kinetoplast, thereby affecting genetic replication and transcription. However, toxic side effects regarding animals may be produced. Melarsomine binds to sulfhydryl groups of important energy-producing enzymes, which will result in their inactivation. Additionally, the depletion of ATP will bring about the death of the parasite, especially the drug-resistant isolates (Kasozi *et al*., 2022). Drug resistance concerns have led to the introduction of melarsomine, also known as cymelarsen, as a treatment for trypanosomiasis (Baker *et al*., 2013). Previously, animals infected with *T. evansi* have been treated with suramin and quinapyramine (Dargantes *et al*., 2021). Most medications, including homidium bromide, are too toxic for animals to utilize as a cure, as is the case with diminazene aceturate (Kasozi *et al*., 2022). Pets with *T. evansi* infections are frequently treated with diminazene aceturate, yet this might be harmful to the host (Da Silva *et al*., 2009).

Vaccination

An efficient vaccination program is an additional technique for managing infectious diseases in addition to treatment. Due to antigenic changes of the trypanosome surface layer, all traditional anti-parasitic vaccination attempts for trypanosomiasis that have been made to date using dominant surface proteins have failed (La Greca and Magez, 2011). Consequently, several immunization approaches are required. A different strategy to vaccination has involved the use of various parasite molecules. Variable surface glycoproteins (VSG) containing glycosylphosphatid linositol (GPI) have been identified as one of the primary parasite components generating the inflammatory response linked to infection (Moreno *et al*., 2019). This data was utilized in one study to assess GPI-based immunization as a substitute approach with possible anti-disease effects (Munir *et al*., 2023). GPI delivered before to infection has been demonstrated to improve control of parasitemia and extend the survival of infected mice by using liposomes as a slow delivery mechanism (Bossard *et al*., 2021). This experiment effectively decreased anemia, acidosis, weight loss, and liver damage in *T. evansi* infection models; this decrease in pathology was linked to decreased TNF production, elevated IL-10 levels, and the expression of alternatively activated macrophages. T cell-dependent B cell activation is caused by CD4/Th cells activating and secreting IL-4, IL-10, and IL-13 in response to elevated IL-10 levels (Tao *et al*., 2011).

Control

The first and most important step in stopping the spread of trypanosomiasis is to stop the transmission of flies via physical and chemical methods. Physical methods include clearing undergrowth in ditches and water bodies, managing manure, avoiding animal grazing in direct sunlight, managing dung in dense piles (which helps kill *Stomoxys* and *Liperosia* larvae), and routinely removing manure and damp bedding (von Wissmann *et al*., 2011). In the meanwhile, chemical fly management methods such as dipping or spraying insecticides on animals during fly season and putting kerosene on waterbodies to stop *Tabanus* flies from sliding into them are used (Okello *et al*., 2021). Large-scale insecticide spraying program to kill *Tabanus* flies and other biting flies (Mihok, 2002).

Furthermore, international animal trade regulation is required to prevent the introduction of diseased animals into areas that are not affected (Desquesnes *et al*., 2013). International trade between diseased and uninfected nations should be subject to quarantine. This entails a quarantine of four weeks at the farms that import and export (Austen and Barbosa, 2021). An animal must come from an uninfected farm in an unsuspected location, test negative for trypanosomiasis twice at intervals of three to four weeks during each quarantine, and demonstrate these results in order to be qualified for trade (Thuita *et al*., 2008).

A farm is considered a non-suspect area if there have been no reports of trypanosomiasis in the previous three years within a 30 km radius of the farm (Desquesnes *et al*., 2013). Only animals with negative trypanosomiasis test results and those originating from non-infected farms situated in non-suspicious areas are permitted access into non-infected farms (Desquesnes *et al*., 2022). If two tests for trypanosomiasis are negative for every species of animal on a farm within a three-month period, the farm is considered uninfected (Latif *et al*., 2019). In order to preserve the farm's non-infected status, trypanosomiasis negative tests every ten to twelve months are required for every species of animal (Ilboudo *et al*., 2023).

CONCLUSION

Trypanosomiasis, caused by *Trypanosoma evansi*, is a protozoan illness that affects arrays of domestic and wild animals worldwide with significant public health challenges. The spread of trypanosomiasis is a global health concern that might be lethal if proper diagnosis and treatment are delayed. Animal infections with *T. evansi* can be lethal. Case fatality rate of almost 100 % has been reported for trypanosomiasis, especially if left untreated or without prompt appropriate treatment. Clinical symptoms of trypanosomosis due to *Trypanosoma evansi* might vary and could include neurological issues, skin plaques, and vaginal enlargement. Importantly, hematophagous biting flies have been recognized to contribute in its spread. More challenging is its economic impact as it could drastically reduce the productivity of livestock which are mostly used as food sources. Identified risk factors for trypanosomiasis include stress conditions, young age, immunocompromised individuals, housing facilities, farming, hunting, herding cattle, and other activities such as tourism and migration to regions endemic with hematophagous biting flies. The most important step in curtailing the spread of trypanosomiasis is to control the transmission of flies via physical and chemical methods. The integration of advanced molecular techniques such as whole-genome sequencing, multiplex PCR, and immunochromatographic tests in the diagnosis of *T. evansi*, especially in routine livestock health management systems and the prioritization of research directed at sustainable vector (hematophagous biting flies) control strategies will be critical in curtailing the burden of *T. evansi* and safeguarding global livestock productivity. Additionally, collaborative efforts between government agencies and veterinarians, cross-border collaborations, and strict quarantine protocols will be impactful in curtailing the risk of trypanosomiasis transmission and curtail its impact on livestock productivity, including farmers' livelihoods.

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AUTHORS' CONTRIBUTIONS

ML served as the principal investigator and conceptor of the study. SHW, ARK, and MAA contributed to study design, methodology

development, and data acquisition. HAH, WPL, and MKJK were responsible for fieldwork, sample collection, and primary data processing. SW, SRA, and BWKW supported data validation, literature review, and interpretation of findings. IF, SMY, and IBM performed statistical analysis, data visualization, and contributed to manuscript drafting. AP, SA, and KAF assisted in critical review, editing, and refinement of the manuscript. RZA and DAAK contributed to formatting, reference management, and final proofreading. All authors reviewed, revised, and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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