German Journal of Veterinary Research

eISSN:2703-1322

Review

A review on current knowledge of major zoonotic protozoan diseases affecting farm and pet animals

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Article History:
Received: 09-Jun-2021
Accepted: 04-Jul-2021
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Abstract

Given the high importance of animal uses for human beings, avoidance of contact with animals is far from straightforward, even if there is a risk of zoonotic diseases. Animal products or byproducts are essential sources of food for humans. Also, there are large numbers of companion animals worldwide which are important for the soundness of mental health for the owners. Understanding of the disease in animals is of paramount importance to control and prevent transmission to humans. Zoonotic protozoan parasites, including malaria, babesiosis, trypanosomiasis, toxoplasmosis and cryptosporidiosis, can cause severe infections to humans, and some of them can drastically affect both economy and society. Impacts of such infections are aggravated when asymptomatic animals being in contact with susceptible individuals, including infants, pregnant women or immunocompromised people. Malaria, babesiosis and trypanosomiasis are vector-borne diseases that cause hemolytic anemia and high fever. Toxoplasmosis is a congenitally transmitted infection characterized by abortion and congenital abnormalities in infected persons and animals. Cryptosporidiosis is a highly contagious disease affecting humans and various animal species, and diarrhea is the main clinical form. These infections are globally distributed and affect various demographics. However, awareness of these often neglected diseases in almost all countries and communities is required to protect animals, owners, and customers. Thus, this review is aimed to provide the recent and current knowledge on transmission, epidemiology and control of some protozoan diseases of zoonotic importance.

Keywords: Malaria, *Babesia*, *Trypanosoma*, Toxoplasmosis, Cryptosporidiosis

Citation: Abdelbaky, H. H., Umeda, K., Nguyen, T., Mohamed, A. E. A. and Fereig, R. M. 2021. A review on current knowledge of major zoonotic protozoan diseases affecting farm and pet animals. Ger. J. Vet. Res. 1 (2): 61-76. https://doi.org/10.51585/gjvr.2021.2.0021

Introduction

Except for malaria, almost all protozoan diseases are extremely neglected even in highly advanced countries and among well-educated communities. These diseases constitute a significant health burden for animals or humans because of the problematic situation of vaccine or drug-based control. Malaria is considered a major global health problem and constitutes an enormous hazard on humanity because of financial and social harms. Malaria is transmitted through biting of humans by infected mosquitoes and threatens all people particularly children, pregnant women, and immunocompromised individuals. Many *Plasmodium* species can cause infection in humans, including *P. falciparum*, *P. vivax*, *P. malaria*, *P. ovale* and *P. knowlesi* (Greenwood et al., 2008; Collins, 2012). Human babesiosis is caused mainly by *Babesia microti* or *B. divergens* via tick biting, resulting in health problems in immunocompromised individuals. Due to high transmission, health hazards, and extensive emergence of drug resistance, malaria and babesiosis possess potential risks to human health. Brain dysfunction is the most severe form of malaria. However, the mechanism of cerebral malaria is still unknown (Renia et al., 2012; Schiess et al., 2020).

Trypanosoma is an economically important unicellular and flagellated protozoan parasite group belonging to the class *Kinetoplastea* (Moreira et al., 2004; Gibson, 2016). Most of these parasites are transmitted to humans or animals via blood-sucking invertebrates. Trypanosomes can infect a wide range of hosts and induce various diseases, including fatal human diseases such as sleeping sickness caused by *Trypanosoma brucei* and Chagas disease caused by *T. cruzi*. In ad-

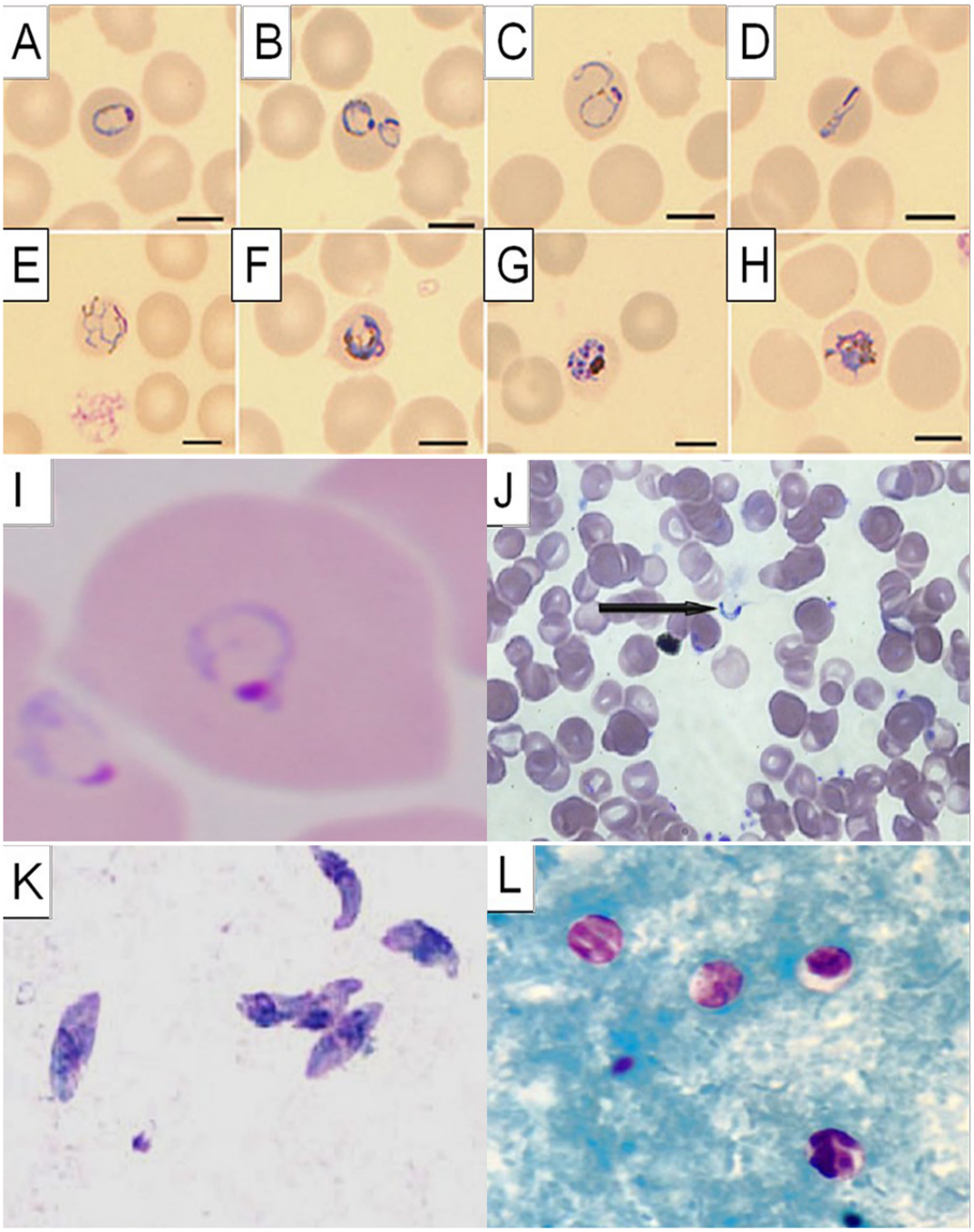

Figure 1: Microscopical examination of selected protozoan parasites. (A-H) *Plasmodium knowlesi* in a thin blood smear stained with Giemsa stain. Trophozoites (A-F), a schizont (G), and a gametocyte (H). Scale bars= 5μm (Modified from van Hellemond et al. (2009)). (I) Giemsa stained thin blood films showing *Babesia microti* trophozoites stage as ring forms in RBCs (Modified from Vannier and Krause (2012)). (J) *Trypanosoma cruzi* trypomastigote in the patient's blood smear stained with Wright Giemsa stain (Taken from Alarcón et al. (2016)). (K) *Toxoplasma gondii* tachyzoites. Tachyzoites are typically crescent shaped with a prominent, centrally placed nucleus (Taken from CDC, https://www.cdc.gov/dpdx/toxoplasmosis/index.html). (L) *Cryptosporidium parvum* oocysts stained by modified acid fast stain (taken from CDC, https://www.cdc.gov/dpdx/cryptosporidiosis/index.html).

dition, many trypanosomes, particularly *T. vivax*, *T. evanasi*, *T. congolense* and *T. equiperdum*, can infect a wide range of animal hosts and induce severe economic losses (Hamilton et al., 2004).

Toxoplasmosis is a worldwide zoonotic disease caused by the obligatory intracellular protozoan parasite *Toxoplasma gondii*. Approximately a third of the human population is positive for *T. gondii* specific antibodies worldwide (Halonen and Weiss, 2013). Moreover, specific anti-*T. gondii* antibodies were recorded in many animal species, including marine mammals globally, including Arctic and Antarctic areas. The disease induces substantial economic losses in the livestock industry because of the abortions in pregnant ewes and sows, neonatal mortalities and culling of infected and contact animals. Up to date, there are no commercial safe, effective and broad spectral vaccines or drugs for prevention or treatment of toxoplasmosis in animals or humans, albeit numerous research trials (van de Velde et al., 2016).

Cryptosporidium is a cosmopolitan intracellular protozoan parasite invading most vertebrate animals, including humans. In numerous estimates, *Cryptosporidium* species are responsible for more than the half number of waterborne outbreaks of the parasitic origin globally (Efstratiou et al., 2017). In addition to its zoonotic importance, *C. parvum* is the major cause of diarrhea among cattle calves, inducing severe weight loss and death. The infection occurs via ingestion of food or water contaminated with oocysts (Current and Garcia, 1991). Currently, there is no commercially available potent and safe vaccine or drug against *Cryptosporidium*. Thus, the efficient diagnosis would be the potential control measure of cryptosporidiosis. However, the diagnosis of cryptosporidiosis is still suboptimal and requires the development of more specialized tests (Checkley et al., 2015). Figure 1 shows the characteristic microscopical features of *Plasmodium*, *Babesia*, *Trypanosoma*, *T. gondii* and *C. parvum* parasites. In addition, a summary of pathogen, host, route of transmission, clinical picture and control measure are summarized in Table 1.

Malaria

General background

Malaria remains a subversive parasitic disease in tropical and sub-tropical countries, causing 600,000 deaths and 200 million cases annually. Human malaria is caused by multiple species of protozoan parasite *Plasmodium*, of which *Plasmodium falciparum* is the most virulent and responsible for the majority of human deaths. The high morbidity and mortality caused by *P. falciparum* parasites are linked only to intraerythrocytic cycles. The disease is transmitted via a bite from an infected female *Anopheles* mosquito, which introduces the organisms from its saliva into a person's blood vessels. In the blood, the parasites targeted the liver for full development. Malaria causes symptoms that typically include fever and malaise, and in severe cases, can progress to coma or death, particularly in young children less than 5 years old (Smith and Styczynski, 2018).

Lately, several reports have described human malaria caused by *P. knowlesi*, which usually infects macaque monkeys. Hundreds of human cases have been reported from Malaysia, and several cases have been reported from other Southeast Asian countries. Like other *Plasmodium* species, *P. knowlesi* has a life cycle that requires infection of both a mosquito and a warm-blooded host. While the natural warm-blooded hosts of *P. knowlesi* are likely various Old World monkeys, humans can be infected by *P. knowlesi* if infected mosquitoes feed upon them. *P. knowlesi* is closely related to the human parasite *P. vivax* and other *Plasmodium* species that infect non-human primates. Humans infected with *P. knowlesi* can develop either uncomplicated or severe malaria similar to that caused by *P. falciparum*.

Diagnosis of *P. knowlesi* infection is challenging as *P. knowlesi* very closely resembles other species that infect humans. Treatment is similar that for other types of malaria, with chloroquine or artemisinin combination therapy typically recommended. *P. knowlesi*-associated malaria is an emerging disease previously thought to be rare in humans but increasingly recognized as a major health burden in Southeast Asia. *P. knowlesi* was first described as a distinct species and a potential cause of human malaria in 1932. It was briefly used in the early 20th century to cause fever as a treatment for neurosyphilis. In the mid-20th century, *P. knowlesi* became popular as a tool for studying *Plasmodium* biology and was used for basic research, vaccine research and drug development. *P. knowlesi* is still used as a laboratory model for malaria, as it readily infects the model primate, the rhesus macaque and can be grown in cell culture in human or macaque blood (Collins, 2012; Chin et al., 2020).

Control strategies of malaria causative agents are based primarily on chemotherapy, peculiarly using artemisinin derivatives or combining it with other antimalaria drugs to decrease the risk of drug resistance. Vaccination is another preventive control strategy that is used to minimize the hazards and severity of *Plasmodium* infections. Several attempts and research studies were and still applied to develop highly effective and safe vaccines against malaria parasites, but most ended with failure, while others achieved limited success. The Circumsporozoite Protein (CSP and RTS,S) based vaccines from the pre-erythrocytic stage are now widely used in immunization against malaria infections. Further vaccine candidates are required to establish a more potent, safe and cheap preventive strategy. Mosquito control via insecticides as picaridin or using mosquito net also may be a helpful strategy in reducing the malaria infections especially in the endemic areas (Arora et al., 2021; Fornace et al., 2021; Wimberly et al., 2021).

Recent aspects for diagnosis and control

Malaria is a devastating global health problem affecting millions of people and claiming hundreds of thousands

Table 1: Summary of pathogen, host, transmission, main signs and control measures for major zoonotic protozoan diseases.

Disease	Pathogen	Host (including human)	Transmission	Main signs	Available control
Malaria	*P. knowlesi*	Monkeys	Infected mosquitoes biting	Fever, anemia and high mortalities	Treatment by chloroquine or artemisinin combination Vaccination by CSP and RTS vaccines.
Babesiosis	*B. microti* *B. divergens*	Rodents (*B. microti*) Rodents and cattle (*B. divergens*)	Infected tick biting	Fever followed by anemia or self recovery	Treatment by the combination of atovaquone and azithromycin
Trypanosomiasis	*T. cruzi* *T. brucei*	Dogs (*T. cruzi*) cattle (*T. brucei*)	Biting by infected flies and insects	Fever, anemia, coma and high mortalities	Treatment by suramin or fexinidazole
Toxoplasmosis	*T. gondii*	Cat as definitive host Sheep, goat, pigs as intermediate hosts	Ingestion of oocysts shed from cat feces or tissue cysts in raw meat	Abortion, foetal anomalies, behavioral changes	No effective and safe treatment or vaccines
Cryptosporidiosis	*C. parvum*	Cattle	Ingestion of oocysts from contaminated food, water or accidentally	Diarrhea and malnutrition	No effective and safe treatment and vaccines

of lives every year. Current antimalarial chemotherapies are severely compromised because of the emerged resistance in many endemic countries. Therefore, there is an urgent need for the development of more effective control and preventive strategies. The development of novel and effective therapies by mimicking the body's own natural defenses led to the clearance of the parasites may be the future trend for malaria control. Macrophages are known to play a key role in combating infections and clearing the pathogens via phagocytosis. Identifying the host effective molecules secreted during phagocytosis and developing synthetic analogs with therapeutic potential may be an effective strategy for malaria control (Terkawi et al., 2017). International organizations such as WHO, UNICEF, FAO, international banks, and multinational incorporations are integrated in fighting malaria through synchronizing efforts, setting up strategies, and supporting funds for implementing the designed control plans. Governmental and non-governmental organizations (NGOs) have a crucial role in combating malaria infections by integrating malaria control programs into general health promotion planning, changing control strategy from vertical to a horizontal one, and spreading public awareness regarding malaria hazards and control measures.

Babesiosis

General background

Human babesiosis is a tick-borne disease caused by the protozoan parasite *Babesia* species, and it is encountered as an emerging infectious disease in the USA, particularly in the northeast and the upper midwest, but it is also recorded in other parts of the world. The most common cases of the disease reported in the USA attributed to *B. microti* and a lesser extent to *B. duncani* and *B. divergens*. While the main etiologies in other parts of the world are *B. divergens*, *B. microti*-like organism and *Babesia* spp. KO1 strain in Europe, Japan and South Korea, respectively. The predominant transmission route of babesiosis among people is via the bite of infected tick vectors, especially *Ixodes scapularis* for *B. microti* in the USA and *I. ricinus* for *B. duncani*, B. duncan*i type and B. divergens* like parasites in Europe. Other routes of infection like transplacental transmission and blood transfusion were also recorded in a few cases.

The disease is reported throughout the year but mostly from early summer to late fall (Krause et al., 2007; Vannier and Krause, 2012; Lobo et al., 2020; Chan et al., 2021). A previous report revealed the detection of *B. microti* and *B. divergens* in rodents which may act as a reservoir host for human infection (Hamsikova et al., 2016). In addition to human infection, *B. divergens*, transmitted by the tick *I. ricinus*, and is considered the most common cause of bovine babesiosis in northern Europe. It is also playing a role as a zoonotic pathogen (Springer et al., 2020). *Babesia* is a heterogenous pathogen that needs two hosts to complete its life cycle. Sexual stage develops in the tick vectors where it develops from gametocytes in the gut to sporoblasts that remain in salivary gland until delivered in the blood of vertebrate host as sporozoites that

attached to erythrocyte by binding to glycosaminoglycans and sialoglycoprotein to complete its developmental stage inducing their pathogenicity.

The infection may be subclinical, clinical or fatal and these depend on the immune status of the host and type of *Babesia* species. The symptomatically infected person usually suffers from a high fever that may reach 40°C with related symptoms as chills, sweating, malaise, fatigue, myalgia and arthralgia. These may be accompanied by splenomegaly, hepatomegaly, pharyngeal erythema or fatal complications as thrombosis and tissue anoxia. The laboratory findings of the disease are those related to anemia, such as low packed cell volume (PCV), hemoglobin (Hb) level, red blood cell (RBC) count as well ashaptoglobin level and blood platelets, while there is elevation in reticulocyte count and lactate dehydrogenase (LDH) level in the blood. The spleen plays a crucial role in protection from babesiosis by dual roles; firstly by clearance of bloodstream from the infected erythrocytes and secondly by synchronizing the immune responses. Interferon (IFN)-γ produced from CD4+ T cells and natural killer (NK) cells is the most vital weapon responsible for killing *Babesia* species by stimulating macrophages and antibodies production by B cells.

The severity of babesiosis is attributed to a disruption in the erythrocyte membrane and through aggravated stimulation to the host immune response resulting in high production of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. The babesiosis can be diagnosed through numerous protocols and study of the case history where the history of tick biting or visiting endemic areas or contact with infected people is highly helpful information for diagnosing babesiosis (Yokoyama et al., 2006; Terkawi et al., 2015). Microscopical examination of thin blood film stained by Giemsa or Wright stain is the basic test for detection of babesiosis as it is a rapid, easy and accurate method, where organisms appear mainly in a paired pear-shaped objects in the erythrocytes, it may also be arranged in different numbers as tetrad and forms as a ring or cross-like patterns. Conventional and real-time polymerase chain reactions (PCR) are also sensitive and specific tools for detecting babesiosis.

Immunofluorescence antibody test (IFAT) is considered the standard assay for detecting IgM and IgG antibodies specific for *Babesia* species. Laboratory animal inoculation as hamster by the blood of a suspected person is very helpful and confirmatory in diagnosing babesiosis, where the organisms appear in the blood after 2 to 4 weeks of inoculation. Combined diagnostic tests, especially PCR and IFAT, are highly recommended as confirmatory tests. The anti-babesial drug of choice combines atovaquone and azithromycin, especially in mild to moderate cases of immunocompetent patients. Other drug combinations, including clindamycin and quinine used in severe babesiosis, but worries are rising because of their effects on cardiac functions.

The preventive protocol for human babesiosis should include personal, environmental and community aspects. The personal preventive measures include self-protection by personal hygiene, wearing protective cloth, avoiding endemic areas and contact with infected people, animals, and suspicious places. Applying preventive measures related to the environment includes eradicating ticks by insecticides and eliminating thatches and grass nests that may be used as a habitat for ticks and other hosts. The community role includes increasing public awareness about the risks of human babesiosis and applying screening tests for babesiosis on the soundness of blood donors.

Recent aspects for diagnosis and control

Human babesiosis is one of the most severe tick-borne diseases, in which tick vectors play a crucial role in its spreading, so particular interest could be focused on the tick as an important stage for control of the disease. Although many diagnostic protocols are applied to detect human babesiosis, more sensitive, accurate, and applicable field tests are needed. More researches and studies are required to develop vaccines for human babesiosis that may help in minimizing the disease incidence and severity. Current anti-babesial chemotherapies are severely compromised because of the emerging resistance in many endemic countries.

Therefore, there is an urgent need for the development of more effective control and preventive strategies. The accurate epidemiological studies and surveys provide us with valuable data that is considered the cornerstone in developing novel control policies, including vaccination or chemotherapy. Microsatellite and other recent molecular epidemiological tools enabled us to easily and efficiently determine and monitor the infection aspects, including species and strain variability and demeanor. Microsatellites are extensively used because they can be readily amplified by PCR and their capacity to screen a large amount of allelic variation at each locus. On the other hand, some limitations in these tools should be overcome, represented in time-consuming factors and the inability to distinguish primary infection from re-activated infection.

Trypanosomiasis

General background

Trypanosomes are a hemo-protozoan parasite belonging to the subkingdom Protozoa, class *Kinetoplastea*, and genus *Trypanosoma* (Moreira et al., 2004; Gibson, 2016). Among more than twenty *Trypanosoma* species, only a few of them are pathogenic to humans and animals. Trypanosome infections in humans include Chagas disease/American trypanosomiasis caused by *T. cruzi* in South America and sleeping sickness/human African trypanosomiasis (HAT) caused by *T. brucei*, which is classified into three subspecies: *T. b. brucei*, *T. b. gambiense* and *T. b. rhodesiense*, where the latter two (*T. brucei* rhodesiense and *T. b. gambiense*) are known to be zoonotic parasites infecting human and livestock animals in Africa (Deborggraeve et al.,

2008). In addition to human infection, dogs are considered reservoir hosts and kissing bugs as vectors for *T. cruzi* (Barbabosa-Pliego et al., 2011).

Rarely, *T. b. brucei* infects humans, but it causes animal African trypanosomiasis (AAT) and *T. vivax*, *T. congolense* and *T. evansi* in cattle buffaloes, camels and horses not only in Africa but also in Central and South America, the Middle East, and Asia. *T. equiperdum* is pathogenic to equines and *T. suis* to swine. Based on the transmission route, trypanosomes are divided into two main groups: stercoraria and salivaria. The group stercoraria includes *T. cruzi*, which develops in the hindgut of the invertebrate vector and transmits disease via feces. Other pathogenic trypanosomes belong to the salivaria group, which never pass to the intestinal tract. Rather, they develop in the midgut and then migrate to the salivary gland of the vector to transmit disease through a vector bite. This review paper will only focus on salivarian trypanosomes (African trypanosomes).

The African trypanosomes are eukaryotic cells. They have two genomes, one within the nucleus and the other in a single mitochondrion, namely kinetoplast. The nuclear genome is of relatively low complexity, with 80% are megabase (1Mb) chromosomes, carrying most of the genes involved with the basic functions of the parasites. Kinetoplast DNA (kDNA) is present in a network of interlocked circular DNA, consisting of minicircles and maxicircles. Minicircles encode guide RNA that modifies the maxicircle transcripts, known as RNA editing (Shaw, 2004; Maudlin, 2006). Since the first genomic sequencing project on *T. brucei* was published in 2005, assemblies of other African trypanosome genomes have been generated, with the latest *T. evansi* and *T. equiperdum* (Berriman et al., 2005; Carnes et al., 2015; Matthews, 2015; Hebert et al., 2017; Davaasuren et al., 2019). The genomic database provides more evidences and insights to broaden our understanding of trypanosome biology.

African trypanosomes developed excellent strategies to adapt to the environment. They require a cyclical development inside a vector (tsetse fly) to complete their lifecycle. For that reason, the epidemiological distribution of trypanosomiasis is tightly linked with the tsetse fly habitat, called tsetse belt in sub-Saharan Africa. However, two trypanosome species *T. evansi* and *T. equiperdum* are exceptional. Molecular and parasitological studies of the two species support the hypothesis that they derived from *T. brucei* which loss their kDNA. Depletion of kDNA does not affect their kinetoplast structure but blocks *T. evansi* and *T. equiperdum* in the bloodstream form (Lai et al., 2008). To adapt to partially (*T. equiperdum*) or, completely (*T. evansi*) loss of the maxicircles, which essential for the development of procyclic trypomastigotes in tsetse fly, the parasites changed their transmission mode from biological to a mechanical one. *T. evansi* infection is transmitted mechanically by biting flies; and *T. equiperdum* through coitus.

The transmission is independent of tsetse fly, allowing the disease to spread outside the African continent. Analysis of the *T. evansi* genomic database revealed that several procyclin-associated genes (PAGs) were disrupted or not found, suggesting a selective loss of function in the absence of the insect life-cycle stage. It also confirmed a mutation in the γ subunit of ATP synthase, enabling the parasite to compensate for the lack of the A6 subunit due to the loss of the A6-specific gRNAs, thus allowing survival (Carnes et al., 2015). Being exposed to the host immune system throughout their life cycle, extracellular trypanosomes use antigenic variations by the mean of variant surface glycoprotein coat (VSG) to evade the host immune response. Noted that salivarian trypanosomes are only trypanosomes that express VSG. There are more than 2,500 VGS genes and pseudogenes; all are located at subtelomeric regions in the trypanosome genome (Jackson et al., 2012; Saha et al., 2020).

In the blood stream form, VSGs have expressed exclusively from blood stream form VSG expression sites (B-ESs). Although there are multiple B-ESs, only one is fully active at a time, presenting a single type of VSG on the cell surface. When a certain surface antigen is recognized and suppressed by the host immune system, trypanosome switches it to a different one. VSG switching has two major pathways: in situ switching and DNA recombination. In situ switching occurs at the transcriptional level, where the originally active ES is silenced while another silent ES is switched to active. DNA recombination-mediated pathway involves telomere exchange, either in crossover or conversion type. Many studies showed that trypanosomes use DNA recombination-mediated pathways, particularly gene conversion type the most (Morrison et al., 2009; Saha et al., 2020).

HAT threatens millions of people in 36 countries in Sub-Saharan Africa (WHO, 2021). Many of the affected populations live in remote rural areas with limited access to adequate health systems. In addition, displacement of population, war and poverty are key factors that facilitate disease transmission. The disease is fatal without treatment. There are two forms of the disease which are caused by two *T. brucei* subspecies: chronic infection caused by *T. b. gambiense* accounts for 95% of reported cases, and acute infection caused by *T. b. rhodesiense* represents under 5% of reported cases. *T. b. rhodesiense* infection leads to death within 6 months (Büscher et al., 2017). There have been several epidemics of HAT in Africa over the 20th century: one between 1896 and 1906, one in 1920, and the most recent epidemic started in 1970 and lasted until the late 1990s. In the 21st century, 2,804 cases were reported to WHO in 2015 and dropped to 992 cases in 2019. The disease should be treated as soon as possible by fexinidazole in the acute or chronic stage or by suramin in the early stage (WHO, 2021). Exported HAT cases are reported from all continents, with most cases being *T. b. rhodesiense* disease in tourists who have visited national parks and game reserves in Tanzania, but also in Kenya, Malawi, Uganda, Zambia and

Zimbabwe. Exported cases of *T. b. gambiense* disease are rarer and include migrants, refugees, and long-term expatriates (Büscher et al., 2017).

AAT is the most economically important livestock disease of Africa. Although trypanosomes can infect all domesticated animals: pigs, goats, sheep, horses and dogs, the disease affects cattle in which the disease is usually chronic (OIE, 2021). Some may slowly recover but usually relapse when stressed. The most important clinical sign is nonregenerative anemia, and the most common reason animals are unable to function normally. When the tsetse challenge is high, morbidity is usually also high. All species of trypanosomes will eventually cause death in their hosts unless treated. According to Tesfaye et al. (2012), cattle mortality due to trypanosomiasis was 4.4%, and 50.9% of farmers rank draught loss as the most important impact of trypanosomes in Ethiopia.

Musa et al. (2006) reported that 60% of cattle owners reported trypanosomiasis cases and accounted for 48.5% of all reported treatments given to cattle in central Sudan. The cost for trypanosomiasis in cattle production was calculated on mortality, fertility and milk, and treatment. Removing animal trypanosomiasis would bring maximum benefit to livestock keepers in Eastern Africa, the maximum amount to nearly USD 2.5 billion (Shaw et al., 2014). Three trypanosome species: T. vivax, *T. evansi*, and *T. equiperdum*, can be transmitted mechanically by biting flies, and thus, is also found in parts of Africa free of tsetse flies, and parts of Central and South America and Caribbean, Asia, Middle East and part of Europe. Camel raising in Africa and buffalo production in Asia are severely affected by *T. evansi* infection (surra).

Recent aspects for diagnosis and control

In the absence of a vaccine, control of African trypanosomiasis depends on diagnosis, treatment and to a lesser extent, vector control. Since HAT has significantly reduced (85% reduction in cases reported in the past 16 years), WHO targeted the elimination of the disease by 2020; and stop the transmission by 2030. In the current elimination context, the most effective control strategy is case finding and treatment, which reduces the human reservoir and thus decreases *T. brucei* transmission. On the other hand, the domestic and wild animals can be *T. brucei* reservoirs (Vourchakbe et al., 2020; Chimera et al., 2021; WHO, 2021). Testing of animals, including tsetse flies, could become part of the disease control program.

Standard diagnostic tests for trypanosomiasis suggested by OIE can be found in the OIE manual of diagnostic tests and vaccines for terrestrial animals (OIE, 2021). Control of surra can be difficult as there is no vector specificity and a wide range of hosts. Control of *T. equiperdum* infection depends on compulsory notification and slaughter of infected animals, movement control enforced by legislation in most countries, and good hygiene at assisted mating is also essential. Pharmaceutical therapy is not recommended because animals may improve clinically but remain carriers of the parasite.

Toxoplasmosis

General background

Toxoplasmosis is caused by an obligate intracellular parasite *Toxoplasma gondii* that is distributed worldwide and can infect virtually any warm-blooded animals. It is estimated that about one-third of the world's human population is infected with latent toxoplasmosis, and the seroprevalence varies from 1% to >90% according to countries (Halonen and Weiss, 2013; Flegr et al., 2014). Despite the existence of a sexual phase in the life cycle, the population of *T. gondii* is unusually highly clonal, with only three predominant lineages (Types I, II, and III) widespread in North America and Europe (Khan et al., 2006).

There are basically three infectious stages of *T. gondii*: sporozoites, tachyzoites and bradyzoites (Dubey et al., 1998). Sexual reproduction of the parasite occurs only within the definitive feline hosts, such as domestic cats. All other hosts are intermediate hosts in which only asexual reproduction can occur. Feline hosts can be infected with *T. gondii*, e.g., by consuming the meat of infected intermediate hosts, such as mice. After passing through the stomach, the parasite reaches the small intestine of the felid and infects the epithelial cells (Dubey, 2009). In the epithelial cells of the small intestine, the parasite reproduces both asexually (schizogony) and sexually (gametogony) and eventually produces unsporulated oocysts. They are shed in feces and persist in the environment to mature into sporulated oocysts. Mature oocysts containing sporozoites are transmitted to other hosts through the inadvertent ingestion of contaminated soil, water, and plant materials (Attias et al., 2020).

Transmitted parasites are transformed into tachyzoites, a rapid growth stage during initial acute infection (Black and Boothroyd, 2000). Tachyzoites can infect any nucleated cells and disseminate throughout the body, but most of them are eliminated within a few weeks by the host immune response primarily mediated by IFN-γ (Halonen and Weiss, 2013). After the acute infection, tachyzoites differentiate into bradyzoites, an encysted slower replicating form, and eventually establish a latent chronic infection (Skariah et al., 2010). The cysts are found predominantly in the central nervous system and muscle tissue and persist for the lifetime of the host (Weiss and Kim, 2000). After ingested with host tissue, cysts are ruptured and release bradyzoites in the digestive tract. These bradyzoites infect the epithelium of the intestinal lumen, where they differentiate back to the tachyzoite stage, thereby completing the asexual cycle (Black and Boothroyd, 2000).

Transmission routes of the parasite are the following: (i) ingestion of soil, water, fruits or vegetables contaminated with oocysts; (ii) consumption of uncooked or undercooked meat containing tissue cysts; (iii) transplacental transmission from the mother; (iv) direct transmission of tachyzoites through a blood transfusion or laboratory accident; (v) organ transplantation, where the organs may contain cysts or

tachyzoites (Attias et al., 2020). Infections with toxoplasmosis usually cause no obvious symptoms in most healthy adults, while some develop a mild flu-like disease. Unless immunosuppression occurs and the parasite reactivates, people usually remain asymptomatic and are believed to remain infected for life. However, there are researches reporting effects of chronic *T. gondii* infection on reaction time, the tendency for accidents, behavior and mental illness (Flegr, 2007; Dubey and Jones, 2008).

In immunocompromised individuals, such as patients with acquired immune deficiency syndrome (AIDS) and transplant recipients in immunosuppressive therapy, toxoplasmosis may cause severe clinical diseases through reactivation and uncontrolled parasite replication. This can cause damage to the brain (encephalitis) or the eyes (necrotizing retinochoroiditis). Moreover, if a woman receives her first exposure to *T. gondii* while pregnant, the developing fetus can be congenitally infected. Congenital toxoplasmosis is associated with fetal death and abortion and can also cause chorioretinitis, hydrocephalus, or intracranial calcifications (Jones et al., 2001).

T. gondii infections may also be pathogenic to livestock. While pigs, cattle and poultry rarely develop clinical signs after infection with *T. gondii*, small ruminants such as sheep and goats are highly susceptible to infections, and the parasite is considered a major cause of their reproductive losses worldwide (Stelzer et al., 2019). *T. gondii* infections in livestock cause economic losses to farmers and affect human health through consumption of meat. In pet animals, clinical cases of toxoplasmosis are much more frequent in cats than in dogs. The disease in dogs is mostly linked to immunosuppression and the absence of vaccination against canine distemper virus (CDV). Cases of toxoplasmosis in dogs include neurological disease and cutaneous manifestations. In cats, clinical toxoplasmosis is more severe in congenitally infected kittens, which frequently develop hepatitis or cholangiohepatitis, pneumonia, and encephalitis. In adults, unspecific clinical signs can be observed, and the disease may be rapidly fatal with severe respiratory or neurological signs (Calero-Bernal and Gennari, 2019).

Recent aspects for diagnosis and control

Clinical signs of toxoplasmosis are generally nonspecific and are not sufficiently characteristic for a definite diagnosis. Diagnosis of toxoplasmosis is made by biological, serological, histological, or molecular methods. *T. gondii* may be detected in blood, amniotic fluid, or cerebrospinal fluid by PCR (Switaj et al., 2005). As a direct demonstration of the *T. gondii* parasite is often difficult, several diagnostic methods have also been established, including the most commonly used serological assays: (i) the Sabin-Feldman dye test (DT) that utilizes complementation of live tachyzoite incubation with patient serum; (ii) agglutination tests including direct or modified agglutination test (DAT/MAT), indirect hemagglutination test (IHA), and latex agglutination test (LAT); (iii) indirect immunofluorescent test (IFAT) in which fluorescent-labeled anti-human IgG or IgM antibodies detect the specific antigen-antibody interaction from diluted serum specimens with killed tachyzoites; (iv) enzyme-linked immunosorbent assays (ELISA) typically consisting of a solid phase antigen or antibody, enzyme-labeled antigen or antibody, and a substrate for the enzyme reaction; (v) immunochromatographic tests (ICT), a rapid lateral flow test intended to detect the presence or absence of the target analyte; (vi) the western blotting which shows the reaction of sera with *T. gondii* antigen (Hill and Dubey, 2002; Ybanez et al., 2020).

Despite continuous and successful efforts to improve diagnosis, available options for toxoplasmosis chemotherapy are so far limited. The main target of anti-*Toxoplasma* drugs is the folate pathway, involved in DNA synthesis with the dihydrofolate reductase (DHFR) and dihydropteroate synthetase (DHPS) enzymes. Pyrimethamine and trimethoprim are two major drugs in treating acute toxoplasmosis, and both acts on parasite DHFR, but are unable to distinguish it from the enzyme of the human host. Taken alone, they are not powerful enough. Thus they must be associated in combination regimens with sulfonamides such as sulfadiazine which block DHPS. Therefore, current treatment regimens have side effects due to myelotoxicity and require discontinued therapy or induce lack of compliance. Women infected during pregnancy are generally offered spiramycin, a potent macrolide antibiotic that concentrates in the placenta, making it an ideal preliminary treatment option for preventing congenital infection.

Unfortunately, spiramycin is ineffective for treating an established fetal infection since it barely crosses the placental barrier. Clindamycin, azithromycin and atovaquone are also alternative treatments when other drugs cannot be used. Most of all, no current drug can eliminate latent toxoplasmosis from the infected host as the antibiotics do not reach the encysted bradyzoites in sufficient concentration (Konstantinovic et al., 2019). Regarding vaccination, recently, vaccine development against *T. gondii* infections has shown a tremendous advance at the research level only, while no success in veterinary field and applications. Previously, only one live attenuated vaccine was used and induced a limited decrease in abortions and fetal losses in pregnant ewes. Many researchers have investigated numerous classes of vaccines, including live attenuated, vectors based, and recombinant subunit vaccines (Fereig et al., 2018a).

Cryptosporidiosis

General background

Cryptosporidiosis is as an important zoonotic disease caused by many *Cryptosporidium* species and infects many animal species (Chalmers and Katzer, 2013). *Cryptosporidium* was first identified as a cause of diarrhea in calves in 1971 (Panciera et al., 1971), and afterward, it has been recorded as a second leading cause of diarrhea worldwide (de Graaf et al., 1999). Among numerous already recognized *Cryptosporidium* species,

C. parvum, which infects primarily cattle and humans and *C. hominis* infecting humans are acquiring considerable concerns (Rose et al., 2002).

Only one host is enough for completion of *Cryptosporidium* life cycle. The infection is triggered by swallowing of oocysts in contaminated food or water or through direct contact with infected humans, animals, or contaminated utensils or environment (Rose, 1997). The infective oocysts are highly resistant to environmental factors such as harsh temperatures and humidity (Ramirez et al., 2004). In the small intestine, the excystation of oocysts occurs, and the sporozoites are freed to infect the cells and develop into trophozoites. Then, some parasites develop to type I meront, which liberates merozoites that reproduce sexually and can reinfect the neighboring cells. Other parasites develop into type II meront, which releases merozoites that reproduce sexually by producing micro or macrogamonts that undergo further development resulting in microgametes or macrogametes, respectively. Finally, later stages are responsible for fertilization and formation of zygotes which develop into oocysts. Thin-walled oocysts can induce reinfection of the host, or thick-walled oocysts are excreted in feces and act as a major source of infection (Current and Garcia, 1991).

Cryptosporidium (*C.*) *parvum* has special importance among all other *Cryptosporidium* species because of its zoonotic character, worldwide distribution and wide range of host affection (Chalmers and Katzer, 2013). In regard to the veterinary sector, *C. parvum* induces severe hazards because of clinical infection in cattle, sheep and goats. In humans, *C. parvum* and *C. hominis* are the predominantly recognized species in clinical cases of cryptosporidiosis (Morgan-Ryan et al., 2002). In case of severe infection, the disease may cause serious consequences such as persistence for a long time, dissemination to several organs, end by death (Denkinger et al., 2008; Mor et al., 2010). Profuse water diarrhea is the major clinical sign induced by *Cryptosporidium* infections and responsible for most of recorded health hazards and economic losses because of the resultant dehydration, electrolyte imbalance and malnourishment (Klein et al., 2008).

In humans, following the Rotavirus, infections with *C. parvum* and *C. hominis* are the second leading cause of moderate-to-severe diarrhea in 0–11 month-old infants and the third most common in 12–23 month-old toddlers in Sub-Saharan Africa and South Asia (Kotloff et al., 2013). Chronic cryptosporidiosis is accompanied with malnutrition, poor growth and impaired cognitive functions in young children in developing countries (Guerrant et al., 1999; Korpe et al., 2016). Moreover, around 202,000 deaths are attributable to cryptosporidiosis among children younger than 2 years old in Sub-Saharan Africa, India, Pakistan, Bangladesh, Afghanistan and Nepal (Sow et al., 2016). Similarly, in developed countries, cryptosporidiosis is considered a significant health concern because of recording numerous waterborne outbreaks caused by the contamination with *C. parvum* or *C. hominis* oocysts of drinking or recreational water (Chalmers, 2012; Efstratiou et al., 2017).

In case of immunocompetent individuals, the integrity of intestinal epithelial cells (IECs) plays an essential role during *Cryptosporidium* infections, which acts as a natural mechanical and functional barrier to prevent the infection (Laurent and Lacroix-Lamande, 2017). Also, secreted mucous, chemokines, cytokines and antimicrobial peptides (AMPs) existed in the intestinal lumen, submucosa and bloodstream are vital in combating cryptosporidial infection at an early stage. Many pattern recognition receptors as toll-like receptors (TLRs) as TLR2, 4, 5 and 9 have been found as essential immune effectors for killing and elimination of the parasites (Barrier et al., 2006; Costa et al., 2011; O'Hara et al., 2011; Lantier et al., 2014; Perez-Cordon et al., 2014). In addition, infection with *Cryptosporidium* spp. activates the MyD88 and nuclear factor (NF)-κB signaling pathway to induce the production of human β-defensin 2 for clearance of parasites (Chen et al., 2005). IECs secrete cytokines and chemokines such as IL-8, CCL2, CXCL10 (Laurent et al., 1997; Auray et al., 2007; Pantenburg et al., 2008). AMPs like β-defensins secreted from IECs also reduce the sporozoites efficiency in the intestinal lumen (Carryn et al., 2012). Immediately after infection, the immune effectors cells such as macrophage, dendritic cells and natural killer cells participate effectively via secreting IFN-γ to eliminate *C. parvum* infection (McDonald et al., 2013). IL-12 and IL-18 were reported to control *C. parvum* infection through the feedback mechanism with IFN-γ (Urban et al., 1996; Choudhry et al., 2012). Nitric oxide (NO) is another effector participating in *C. parvum* elimination and decreases oocyst shedding (Leitch and He, 1994; Nordone and Gookin, 2010).

Recent aspects for diagnosis and control

As mentioned earlier in most protozoan diseases, at this moment, there is no commercially available potent and safe vaccine or drug against *Cryptosporidium*. Early diagnosis is considered a potential control measure of cryptosporidiosis. However, diagnosis of cryptosporidiosis is still defective and requires the development of more potent tests (Checkley et al., 2015). Although the microscopical finding of oocysts in feces is easy and inexpensive, it is an inaccurate and insensitive method. Detecting the parasite DNA by PCR or secreted antigens in stool via IFAT or ICT is more specific, but it has a short lifetime after infection and needs special equipment and qualified technicians.

Additionally, the screening of specific antibodies is still in a primitive stage, and scanty reports have achieved some progress. As a screening study, numerous previously reported *C. parvum* antigens (P23, P2, GP15, and GP60) were examined by ELISA. P23 followed by GP15 exhibited the superior diagnostic ability against cattle sera from farms with the history of *C. parvum* infection (Ichikawa-Seki et al., 2019). The ICT is a valuable diagnostic tool because of its rapid detection and use in the field and remote areas. We also developed the first ICT that can detect specific anti-

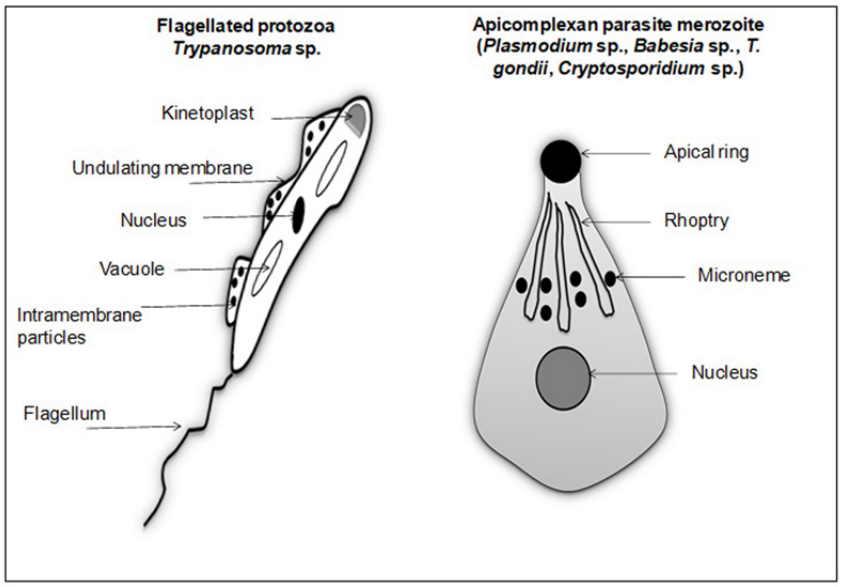

Figure 2: Diagram and main cellular features of flagellated *Trypanosoma* (left side) and merozoite of apicomplexan parasites (right side).

bodies against *C. parvum* (Fereig et al., 2018c). In our ICTs, the previously reported antigens GP15 or P23 were used to detect relevant antibodies. Both ICTs could differentiate between positive and negative control sera and exhibited good performance in sampled field cattle.

A deep understanding of adaptive immune response against *Cryptosporidium* spp. is the key factor for successful vaccine development. As an intracellular pathogen, the cell-mediated immune response is critical for resistance against *Cryptosporidium* spp. infection. T cell subsets are the key immune effector cells playing interactive pathways to achieve the complete resolution of parasite infection. CD4+ T cell is critical in controlling *Cryptosporidium* species in response to acute infection (Fayer and Xiao, 2007). In addition, CD8+ T cell is also has a role in protection against infection with *Cryptosporidium* parasites, albeit to a lower extent than CD4+ T cell (Kvac et al., 2011).

Previous vaccination studies have reported successful vaccine antigens and approaches against *Cryptosporidium* spp., albeit no commercially available one. Adequate immunogenicity (reactivity with effector immune cells and molecules) and antigenicity (ability to generate specific antibodies) are essential properties for vaccine antigen possessing protective efficacy against cryptosporidiosis (Fereig et al., 2018a). A complementary role for IL-12 and IFN-γ has been reported resulting in stimulation of further T helper (Th) 1 cell and secretion of abundant IFN- and IgG2, and differentiation of CD8+ T cell. Also, IL-4 induces differentiation of a number of CD4+ T cells to Th2 cells, which produce additional IL-4, IL-10 and IgG1. IFN-γ has a negative feedback on Th2 cells and a similar effect for IL-4 and IL-10 against Th1 (Ludington and Ward, 2015; Lemieux et al., 2017), creating a status of immunological balance between.

In addition, previous studies have reported the protective role of antibody-based immunity against *Cryptosporidium* spp. in mouse, cattle and human models. Paramount rise in specific IgG, IgM and IgA antibodies was observed following cryptosporidial infection. However, these antibodies could not prevent the adverse effect of the disease (Kassa et al., 1991; Allison et al., 2011; Borad et al., 2012). Furthermore, a protective effect of antibodies was observed when the newly born animals were passively immunized with already prepared antibodies in colostrum or hyperimmune sera whatever before or shortly after infection (Tatalick and Perryman, 1995; Perryman et al., 1999; Wang et al., 2003).

Concluding remarks

Public health and veterinary sectors are adversely affected by protozoan parasitic infection. Numerous protozoan parasites are reported to be deadly for humans and all kinds of animals. Apicomplexan parasites, including *Plasmodium* spp., *T. gondii*, *Babesia* spp., and Cryptosporidium spp., are derived initially from high varieties of animals leading to severe financial losses not only for individuals but also for governments and enterprises. Similarly, trypanosomes are inducing a group of serious diseases in various animal species.

In addition, most of these parasites are inducing health hazards in humans, especially in immunocompromised persons including infants, the elderly, pregnant women and people suffering from chronic and debilitating diseases. Because of high mortalities in humans induced by malaria and trypanosomiasis and drastic economic losses caused by most of the diseases mentioned above, such infections also negatively impact humanity and social relationships. Most of these protozoan infections cannot be efficiently eliminated by vaccines or drugs. In addition, diagnostic performances of currently available tools are still far from

perfection. Rapid and accurate detection tools of such diseases, such as point of care tests or on-site detection tools, will greatly improve the control policies and reduce the hazards on human health or animal production. Indeed, this approach has significantly succeeded in reducing the hazards of toxoplasmosis and cryptosporidiosis on humans or animals because of minimizing the risk of environmental contamination by oocysts.

Regarding vector-borne diseases such as malaria, babesiosis and trypanosomiasis, special interests should be directed to control the transmitting vectors. The development of blocking vaccines that disrupt the parasite cycle in invertebrate hosts is a recent trend that needs additional researches to evaluate the efficacy. Targeting main and specific cell organelles that produce proteins involved in invasion, multiplication, and manipulation of host immunity is a highly promising approach for developing potent antigens for diagnosis or vaccination against such parasites.

Moreover, disruption of these cellular compartments or inhibition of their secreted proteins via some inhibitors will be useful for drug development. Targeting micronemes and rhoptries in apicomplexan parasites and kinetoplast in trypanosomes are highly encouraging to develop control strategies (Figure 2). These hypotheses had already been demonstrated in our previous literature reviews on different protozoan parasites (Fereig and Nishikawa, 2016; Fereig et al., 2018a,b; Fereig and Nishikawa, 2020). Increasing public awareness and focusing the research on zoonotic protozoan infections will significantly improve the quality of life if accomplished by developing potent diagnostic tools, drugs and vaccines.

Article Information

Funding. This research received no extrnal fund.

Acknowledgments. Authors are thankful to the staff of the National Research Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine, Japan, and the Department of Animal Medicine, Faculty of Veterinary Medicine, South Valley University, Qena, Egypt for their help to achieve this study.

Author Contributions. H.H.A., R.M.F. developed the concept for the review. All authors wrote the manuscript and original draft preparation and read and approved the final manuscript.

Conflict of Interest.The authors declare no conflict of interest.

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