Epidemiology of Trypanosomiasis in Wildlife—Implications for Humans at the Wildlife Interface in Africa

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While both human and animal trypanosomiasis continue to present as major human and animal public health constraints globally, detailed analyses of trypanosome wildlife reservoir hosts remain sparse. African animal trypanosomiasis (AAT) affects both livestock and wildlife carrying a significant risk of spillover and cross-transmission of species and strains between populations. Increased human activity together with pressure on land resources is increasing wildlife–livestock–human infections. Increasing proximity between human settlements and grazing lands to wildlife reserves and game parks only serves to exacerbate zoonotic risk. Communities living and maintaining livestock on the fringes of wildlife-rich ecosystems require to have in place methods of vector control for prevention of AAT transmission and for the treatment of their livestock. Major Trypanosoma spp. include Trypanosoma brucei rhodesiense, Trypanosoma brucei gambiense, and Trypanosoma cruzi, pathogenic for humans, and Trypanosoma vivax, Trypanosoma congolense, Trypanosoma evansi, Trypanosoma brucei brucei, Trypanosoma dionisi, Trypanosoma thomsoni, Trypanosoma elephantis, Trypanosoma vegrandis, Trypanosoma copemani, Trypanosoma irwini, Trypanosoma copemani, Trypanosoma gilletti, Trypanosoma theileri, Trypanosoma godfreyi, Trypanosoma simiae, and Trypanosoma (Megatrypanum) pestanai. Wildlife hosts are important for the transmission of human diseases, and their role in the epidemiology of AAT should be addressed.
INTRODUCTION

The African and American trypanosomiases present significant global health challenge in human, domesticated animal, and wildlife communities. Spillover of parasites from wildlife to domestic livestock and humans and from domestic animal species to wildlife compromises health (1, 2). Most trypanosome infections in wildlife do not cause obvious damage to their host (3, 4), but some wildlife species are highly susceptible to trypanosome infections, including Rattus nativitatis and Macleay's rats (Rattus macleari) (5).

Trypanosoma are primarily transmitted by vectors (6) within which they undergo complex development cycles. Trypanosomes, which develop in the posterior section of the digestive tract in insects, are called stercorarian, for example, Trypanosoma cruzi the causal agent of Chagas disease, common in Latin America (7). Salivarian trypanosomes develop in the anterior part of the insect gut tract and include the causal agents of African animal trypanosomiasis (AAT) or nagana and for human African trypanosomiasis (HAT) caused by Trypanosoma brucei rhodesiense and Trypanosoma brucei gambiense that are present across Sub-Saharan Africa (8).

Animal trypanosomiasis is endemic in tropical regions of Africa, parts of Asia, and South America (9). T. brucei s.l., Trypanosoma congolense, Trypanosoma simiae, and Trypanosoma uniforme are transmitted within the tsetse belts of Africa and cannot be transmitted by mechanical vectors (9). T. vivax and Trypanosoma evansi can be transmitted mechanically and occur within and outside tsetse fly-infested zones (10).

EPIDEMIOLOGY OF ANIMAL TRYPA NOSOMIASIS

Trypanosomiasis is one of the most important diseases affecting livestock, equines, and dogs within the Sub-Saharan region (11, 12). Cross transmission of parasites between livestock and wildlife hosts has been reported, especially in areas in close proximity to game parks and wildlife reserves. Wildlife species can survive within the tsetse belts across the Sub-Saharan region, despite being reservoir hosts for multiple species of trypanosome. The high prevalence of trypanosomiasis within protected areas traditionally has rendered these areas unattractive for livestock keeping and agricultural production (13).

Phylogenetic analysis shows a remarkable complexity of trypanosome species, subspecies, and strains in tsetse flies, human, domestic, and wildlife hosts. Examining the trypanosome species circulating within an ecosystem is a key to identifying the wildlife reservoirs of infection and transmission parameters to other animal hosts, including livestock within the ecosystem (3). Understanding the various trypanosome species harbored in wildlife hosts can guide preventive and control measures of trypanosomiasis in communities living at the livestock–wildlife interface. A wide variety of trypanosome species are circulating among wildlife hosts including T. brucei s.l., T. congolense, T. simiae, T. godfreyi, and T. theileri (3).

Hosts and Species of Trypanosomes

Apart from T. cruzi, present in South America, and T. theileri, present worldwide, trypanosomes infect a large number of wild and domestic ungulate species (6). Infection in the wildlife is influenced by species and habitat (12). Wildlife hosts for trypanosomiasis are numerous and include antelope species, warthogs (Phacochoerus aethiopicus), elephants (Loxodonta africana), hippopotamus (Hippopotamus amphibius), lions, hyenas, jackals, caracals, and wild ruminants (14–16). Trypanosome species commonly found in wildlife species include T. vivax, T. brucei s.l., T. congolense, and T. evansi (14). T. vivax, a pathogen affecting cattle, has been identified in waterbucks and giraffes, but the strains of T. vivax in these two host species were unique (3). Multiple wildlife hosts carry the human-infective zoonotic trypanosome strain T. b. rhodesiense, including bushbucks (Tragelaphus scriptus), impala (Aepyceros melampus), lion (Panthera leo), zebra (Equus...
including biting flies of the Tabanidae family (horse flies) as well as mechanical transmission through tsetse and alternative vectors \( T. evansi \) as Stomoxys species. \( \text{(serve as reservoirs for AAT and HAT (Kasozi et al. Trypanosomes in Wildlife)} \)

Transmission to Wildlife
Transmission of trypanosome species is generally by biting vectors including Tsetse flies, Tabanids, Stomoxys, Heematopota, and Hippobosca \((15, 30, 31)\). Infection in carnivores is additionally from consumption of infected meat as documented in the Felidae and Canidae \((31, 32)\). Desmodus rotundus (Vampire bats) also transmit trypanosomiasis \((32)\). Trypanosomes engage in two patterns of transmissions: Cyclical transmission in which trypanosomes undergo active multiplication within the vectors (tsetse flies) as is common for \( T. congolense \), \( T. simiae \), \( T. vivax \), \( T. brucei \), and the human infective trypanosome species \( T. rhodesiense \) and \( T. gambiense \); and mechanical transmission through tsetse and alternative vectors including biting flies of the Tabanidae family (horse flies) as well as Stomoxys species. \( T. evansi \) and \( T. vivax \) can be mechanically transmitted \((33)\).

Distribution of Reservoir Hosts
Preservation of natural resources including game parks and game reserves has led to an expansion of wildlife populations that serve as reservoirs for AAT and HAT \((34)\). Human encroachment on the game parks and forests has increased AAT transmission between wildlife and domestic livestock, due to increased tsetse–human and tsetse–livestock contacts \((34)\). The distribution of host populations within these areas determine vector and parasite survival. Wildlife hosts including monkeys and warthogs live in less restrictive habitats, unattactive to poachers with limited trophy hunting leading to increased reservoir host multiplication rates. They are widely distributed in the ecological environment and are favorable reservoirs for multiple trypanosome species due to their availability to vectors. Crocodiles and hippopotamuses are limited to specific habitats, limiting access of vectors.

Distribution of Tsetse Flies
Trypanosomiasis affects one-third of Africa’s land mass \((35–37)\). Tsetse are found across most of West, Eastern, Central, and Southern Africa \((38)\). The different species and subspecies of tsetse are shown in Table 2. Tsetse populations require moderate temperatures \((23–25°C)\), high relative humidity \((75–90%)\) with weak saturation deficit and shade \((47–49)\). Temperatures above 34.1°C limit survival of tsetse and trypanosomes \((35)\).

Food Source—Activity and Migration
Differences in wildlife food sources, particularly for wild bovinae, influence their exposure to trypanosomiasis. Among ruminant wildlife hosts, browsers are more at risk of trypanosomiasis compared with grazers; semi-browsers are moderately susceptible. Eland, Waterbuck, Kudu, and Bushbuck are more heavily infected, associated with their preference for inhabiting thickets during tsetse feeding hours, predisposing them to more bites \((13, 18)\).

Diurnal wildlife hosts have more susceptible to trypanosome infection compared with the nocturnal species. Warthogs are most active in the morning and late afternoon and show high infection rates for trypanosomiasis in correlation to vector feeding hours \((20)\). Lions are more infected in areas of high tsetse challenge than low challenge \((50)\). The movement of large numbers of animals within wildlife ecosystems also influences infection. Animals will migrate in the dry season toward water sources that are also tsetse habitats \((20)\).

Pathogenesis of Trypanosomosis
Trypanosome infection leads to erythrophagocytosis and heme catabolism resulting in iron accumulation in tissues and hyperbilirubinemia, liver dysfunction, and multiple organ failure \((51)\). At necropsy, atrophy of body fats, pulmonary edema, hepatomegaly, lymphadenopathy, and hemorrhages are observed. Trypanosomes are found in tissues and body organs, and enlarged periarteriolar sheaths have been observed in wildlife \((52)\).

Clinical Signs
Trypanosomiasis is a chronic progressive disease, and clinical signs may become obvious in advanced stages of the disease \((53)\). Bovines affected by \( T. vivax \) present with severe anemia, lethargy, photophobia, lacrimation, and inappetence \((17, 54, 55)\); pyrexia fluctuates with the fluctuating parasitemia. Leukopenia, thrombocytopenia, and degenerative and inflammatory lesions are observed in most organs \((56)\). Body condition scores deteriorates gradually, and animals are dehydrated and debilitated before death. Superficial lymph nodes are enlarged and conspicuous. Corneal opacity may be observed with lacrimation \((57)\). Young animals are stunted even with proper feeding, and productivity is impaired by abortions \((32, 38)\). Animals may show localized or generalized edema \((58)\). Except for \( T. equiperdum \), other Trypanosoma species include similar clinical signs, but variations in intensity may happen in the various species. \( Trypanosoma brucei \) s.l infection shows limited clinical signs in bovines of indigenous species but is highly pathogenic in exotic species \((59)\).

Diagnosis of Trypanosomiasis
Trypanosomiasis is characterized by the intermittent presence of parasites in the blood and intermittent fever \((54)\). Parasitological examinations are relatively sensitive during the acute phase...
of the disease. Wet blood film examination is used to detect the presence of motile trypanomastigotes but has low sensitivity. Blood is taken from the tail or ear veins (55). Fluorescence microscopy can improve sensitivity for thin and thick smears (60). Parasitic concentration by centrifugation and examination of the buffy coat is more sensitive than the wet and thick smears (61). Dark ground or phase-contrast microscopy increases sensitivity at low parasitemia (62). Anion exchange chromatography is also sometimes deployed for detecting low parasitemia (54, 63, 64).

Molecular tests and serological tests are more sensitive than the usual parasitological tests for *Trypanosoma* (3, 63–68). Common serological tests include CFT, ELISA, and IFAT, while the common molecular tests are PCR, LOOP/LAMP, and LFA.

### TABLE 1 | Trypanosome species and taxonomy of wildlife hosts.

| Taxonomic group | Wildlife host (scientific name) | Trypanosome species | References |
|-----------------|---------------------------------|---------------------|------------|
| Bovidae         | Waterbuck (*Kobus ellipsoypyrnus*) | *T. vivax*, *T. congolense*, *T. brucei*, *T. evansi* | (12) |
| Giraffidae      | Giraffe (*Giraffa camelopardalis*) | *T. vivax*, *T. evansi*, *T. brucei* | (12) |
| Bovidae         | African buffalo (*Syncerus caffer*) | *T. b. rhodesiense*, *T. congolense*, *T. brucei* | (12) |
|                 | Bushbuck (*Tragelaphus scriptus*) | *T. b. rhodesiense*, *T. congolense*, *T. vivax*, *T. evansi* | (12) |
|                 | Greater kudu (*Tragelaphus strepsiceros*) | *T. congolense*, *T. vivax* | (12) |
|                 | Red lechwe (*Kobus leche*) | *T. theileri* | (18) |
|                 | Hartebeest (*Alcelaphus buselaphus*) | *T. godfreyi*, *T. brucei*, *T. godfreyi* | (18) |
|                 | Sable antelope (*Hippotragus niger*) | *T. brucei*, *T. theileri* | (18) |
|                 | African buffalo (*Syncerus caffer*) | *T. theileri*, *T. godfreyi* | (18) |
|                 | Eland (*Taurotragus derbianus*) | *T. vivax*, *T. congolense*, *T. brucei* | (12) |
|                 | Impala (*Aepyceros melampus*) | *T. godfreyi*, *T. brucei* | (18) |
| Elephantidae    | Elephant (*Loxodonta africana*) | *T. vivax*, *T. congolense*, *T. evansi*, *T. elephantis* | (19) |
| Hippopotamidae  | Hippopotamus (*Hippopotamus amphibiws*) | *T. vivax*, *T. brucei*, *T. evansi*, *T. congolense* | (20) |
| Suidae          | Warthog (*Phacochoerus africanus*) | *T. brucei*, *T. vivax*, *T. congolense*, *T. evansi* | (20) |
|                 | Warthog (*Phacocoerus africanus*) | *T. godfreyi*, *T. brucei*, *T. simiae* | (18) |
|                 | Feral pig (*Sus scrofa*) | *T. evansi* and *T. cruzi* | (21) |
| Pantherinae     | *Panthera leo* | *T. brucei*, *T. evansi*, *T. congolense*, *T. congolense* | (12, 19) |
| Equidae         | Leopard (*Panthera pardus*) | *T. brucei*, *T. congolense*, *T. evansi* | (12) |
| Cephalophinae   | Zebra (*Equus quagga boehmii*) | *T. b. rhodesiense* | (12) |
| Aepycerotinae   | Common duiker (*Sylvicapra grimmia*) | *T. b. rhodesiense*, *T. vivax*, *T. congolense* | (12) |
| Rhinocerotidae  | Impala (*Aepyceros melampus*) | *T. b. rhodesiense*, *T. congolense*, *T. evansi* | (20) |
| Alcephinae      | Rhino (*Dicerorhinus bicornis*) | *T. brucei* | (20) |
| Hyaenidae       | Wildebeest (*Connochaetes taurinus cooksonii*) | *T. brucei*, *T. congolense*, *T. vivax* | (20) |
| Hyaenidae       | Hartbeest (*Alcephalus busephalus*) | *T. evansi*, *T. brucei* | (20) |
| Cercopithecinae | Hyena (*Hyena hyena*) | *T. evansi*, *T. congolense* | (12) |
| Cercopithecinae | Vervet monkey (*Cercopithecus aethiops*) | *T. gambiensis* | (12) |
| Crocidolidae    | Baboon (*Papio cynocephalus*) | *T. congolense* | (12) |
| Crocodylidae    | Crocodile (*Crocodylus niloticus*) | *T. vivax* | (12) |
| Hipppotraginae  | Roan antelope (*Hippotragus equinus*) | *T. vivax*, *T. congolense* | (12) |
| Pteropodidae    | Megabat/fruit bat (*Chiroptera*) | *Trypanosoma brucei*, *T. cruzi* | (22, 23) |
| Phalangeridae   | Brushtail possum (*Trichosurus vulpecula*) | *Trypanosoma brucei*, *T. cruzi* | (22, 23) |
| Muridae         | Brush-tailed rabbit-rat (*Conilurus penicillatus*) | *Trypanosoma brucei*, *T. cruzi* | (22, 23) |
| Potoroidae      | Brush-tailed bettong (*Bettongia penicillata*) | *T. evansi*, *T. congolense*, *T. vivax* | (24) |
| Dasyuridae      | Northern quoll (*Dasyurus hallucatus*) | *Trypanosoma brucei*, *T. cruzi* | (5) |
| Peramelidae     | Northern brown bandicoot (*Isoodon macrourus*) | *Trypanosoma brucei*, *T. cruzi* | (5) |
| Phascolarctidae | Koalas (*Phascolarctos cinereus*) | *Trypanosoma brucei*, *T. congolense*, *T. evansi* | (25) |
| Cervidae        | Marsh deer (*Blastocerus dichotomus*) | *T. gillettii* | (25) |
| Canidae         | African wild dog (*Lycaon pictus*) | *Trypanosoma brucei*, *T. congolense*, *T. evansi* | (26) |
| Potoroidae      | Boodie (*Bettongia lesueurii*) | *Trypanosoma brucei*, *T. congolense*, *T. evansi* | (26) |
| Tayassuidae     | White-lipped peccary (*Tayassu pecari*) | *Trypanosoma brucei*, *T. congolense*, *T. evansi* | (26) |
| Mustelidae      | Wild European badger (*Meles meles*) | *Trypanosoma brucei*, *T. congolense*, *T. evansi* | (26) |
| Meliphagidae    | Regent honeyeater (*Anthochaera phrygia*) | *Trypanosoma thomastobactefri* | (29) |
Low-flow assay (LFA) is cheaper with 96.3% sensitivity and 93.9% specificity (69). Approved tests for AAT are shown in Table 3.

**TRYPANOSOMES IN WILDLIFE**

The majority of trypanosome species require multiple obligatory hosts to complete their life cycles (heteroxenous), and the transmission of the parasites is mainly via hematophagous invertebrate vectors (2, 88). Trypanosomes are found in blood and tissues; blood-borne protozoan trypanosomes (Trypanosoma vегrandis) have been identified in wild animals including, but not limited to, the northern brown bandicoot (Isodon macrourus), common brushtail possum (Trichosurus vulpecula), northern quoll (Dasyurus hallucatus), and brush-tailed rabbit-rat (Conilurus penicillatus) (5). Trypanosoma cruzi, Trypanosoma dionisii, and an insect trypanosome (Blastocrithidia) have been found to infect bats and other mammalian wildlife in Europe and South America (22). Bats, possums, and rats act as reservoirs of trypanosomes for domestic and wild animals, as well as humans (5, 22). *T. cruzi* (Chagas) has been identified in kidney tissue, heart muscle, and blood, urine, and peritoneal fluid of wild spp. including foxes, opossums, raccoons, and striped skunks (89, 90), and parasites can be transmitted from animal-to-animal by contamination of animal wounds with blood, urine, and peritoneal fluid (89, 90).

**Trypanosome–Host Relationships**

Hosts are classified according to their role as a definitive host [if the mature sexual stage(s) of the parasite occurs within them] or intermediate hosts when the more mature sexual stages of the parasite only aid part of the life cycle (91). Transfer (paratenic) hosts are not vital for the completion of parasitic development cycles but maintain the parasite before it reaches the obligatory/definitive host (92, 93). Invertebrates (vectors) acting as hosts and carriers of parasites facilitate the completion of parasitic life cycles by transmitting parasites (94–96).

Trypanosomes can infect many hosts, transmitted by hematophagous insect vectors mainly the tsetse fly and triatomid kissing bugs (subfamily: Reduviidae) (13, 97). Salivarian trypanosomes, *Trypanosoma brucei*, *T. rhodesiense*,

**Table 2** | Tsetse species, geographical distribution, and wildlife spp. affected by trypanosomiasis.

| Subgenus       | Glossina species | Glossina subspecies | Country                           | Wildlife animal spp.                  | References |
|----------------|------------------|---------------------|-----------------------------------|---------------------------------------|------------|
| *Nemorhina*    | *G. palpalis*    |                     | Nigeria, Angola Camerooon, etc.    | Bushbuck, primates, warthogs           | (36)       |
| G. tachinoides | G. p. palpalis   |                     | Nigeria                           | Baboons, monkeys, chimps               | (37)       |
| G. gambiæsis   | G. f. fuscipes   |                     | Gambia, Senegal, Republic of Guinea | Baboons, monkeys, chimps               | (39, 40)   |
| G. tachinoides | G. f. martini    |                     | Uganda, Tanzania, DRC             | Buffaloes                             | (41)       |
| G. tachinoides | G. f. quanzensis |                     | Uganda, Tanzania                  | Buffaloes, antelopes                  | (42)       |
| G. pallicera   | G. p. pallicera  |                     | Cameroon, Ivory coast, Liberia     | Antelopes                             | (43–45)    |
| G. pallipes    | G. p. newsteadi  |                     | DRC                               | Lions, leopards                       | (46)       |
| G. pallipes    |                   |                     | Nigeria, Ghana, Cameroon          | Buffaloes, lions, buffaloes           | (46)       |
| G. calagineae  |                   |                     | Nigeria, Congo Brazaville         | Cheetah, lions, leopards              | (46)       |
| G. m. morsitans| G. m. morsitans  |                     | Nigeria, Uganda, Tanzania, Zambie | Buffaloes, rhinoceros, antelopes      | (46)       |
| G. m. submorsitans | G. m. submorsitans |                   | Uganda, Tanzania                  | Buffaloes, bushbuck, antelopes        | (46)       |
| G. m. centralis |                   |                     | Uganda, Tanzania                  | Buffaloes, bushbucks, antelopes       | (46)       |
| G. swynnertonii|                   |                     | Nigeria, Congo Brazaville         | Lions, cheetahs                        | (46)       |
| G. longipalpis |                   |                     | Ivory Coast, Senegal, Mali         | Buffaloes, lions                       | (46)       |
| G. pallipes    |                   |                     | Ethiopia, DRC, Uganda, Kenya,      | Buffaloes, lions, antelopes           | (46)       |
| G. austeni     |                   |                     | Zambia, Tanzania, Mozambique      | Bushbucks, antelopes, lions            | (46)       |
| G. vanhooft    |                   |                     | DRC                               | Lions                                 | (46)       |
| G. tabaniformis|                   |                     | Nigeria, DRC                       | Buffaloes, lions                       | (46)       |
| G. sevrini     |                   |                     | DRC                               | Lions, bushbucks                      | (46)       |
| G. schwezeti   |                   |                     | Togo, Congo Brazaville             | Wild ruminants                         | (46)       |
| G. nigrofuscus |                   |                     | Ivory Coast, Nigeria, CAR, DRC     | Elephants, lions, monkeys              | (46)       |
| G. nashi       |                   |                     | Cameroon, Nigeria, Togo            | Monkeys, baboons, wild cats            | (46)       |
| G. medicorum   |                   |                     | Ghana, Gambia                      | Lions, buffaloes                       | (46)       |
| G. longipennis |                   |                     | Tanzania, Sudan, Kenya             | Antelopes, bushbuck, lions             | (46)       |
| G. hanningtoni |                   |                     | Nigeria, Cameroon, Gambia          | Buffaloes, buffaloes                   | (46)       |
| G. fuscipennis |                   |                     | CAR, DRC Cameroon                  | Lions, buffaloes                       | (46)       |
| G. brevipalpis |                   |                     | Kenya, DRC, Tanzania               | Buffaloes, antelopes                   | (46)       |
T. equiperdum, T. vivax, and T. congolense are transmitted in tsetse fly (Glossina spp.) saliva to the host spp. Hosts are as follows: T. brucei s.l. (domestic mammals and humans), T. vivax (ruminants, horses, and camels), T. equiperdum (equines), T. simiae (pigs), and T. congolense (dogs and cats) causing T. evansi (domestic mammals), and other numerous wildlife hosts such as monkeys, guinea pigs, rabbits, rats, etc., are also affected (91, 98). Stercorian trypanosomes are transmitted through the fecal matter of the insects (Triatomaíneae, e.g., Triatoma infestans) to host skin where they gain access to tissues. Other vectors of transmission for stercorians include Tabanid flies, stable flies, Glossina tsetse fly (Glossina m. m. marinkellei, T. m. dionisi, T. m. blommersae, Trypanosoma evansi, Trypanosoma vivax, and Trypanosoma rangeli) (94, 95, 98, 99). Among wildlife, T. cruzi is found in armadillos, dogs, possums, foxes, bats, raccoons, and striped skunks (5, 22, 89, 90). In addition, T. melophagium and T. theileri are found in Europe infecting cattle, buffaloes, and antelopes (98).

### Development of Resistance

Trypanotolerance can enable the regulation of parasite levels in the blood (parasitemia) and body tissues. Resistance in wildlife species has been associated with serum xanthine oxidase and catalase and other trypanolytic molecules (108, 109). Stress can affect trypanotolerance in wildlife (71). Trypanotolerance has been investigated in mice and cattle, although these have differences in immune response, i.e., more pronounced B-cell activation in mice than in cattle (50). In cattle, antibody (IgG and IgM) and complement activity against parasitic VSGs leads to protection (110), through antigenic neutralization and IL-4 production (111) (Figure 1).

In Cape buffalo, resistance has been associated with non-specific trypanocidal activity in serum, which helps to lower the parasitemia following action of xanthine oxidase (XO), which generates reactive oxygen species (ROS). Since trypanosomes cannot metabolize XO, this cripples parasitic binding and endocytosis (111), trypanosomes are starved of ATP, and death follows (Figure 1). An increase in catalase activity is associated with increased parasitemia (112). Some wildlife spp., including the black rhinoceros have significant deficiencies for ATP, catalase, and glycolysis enzymes (conditions that favor trypanosome parasitemia) leading to adaptive evolutionary changes, which help to protect the animals against the parasites (113).
Wild animals show varying levels of trypanotolerance; the Thomson’s gazelle, dikdik, blue forest duiker, jackal, bat-eared fox, ant bear, hyrax, serval, and monkey are all susceptible to *T. rhodesiense* and *T. brucei*, whereas the common duiker, eland, bohor reedbuck, spotted hyena, oribi, bushbuck, impala, warthog, bushpig, porcupine, and baboon are considered resistant (or less susceptible) to *T. b. rhodesiense* and *T. brucei* infection (114, 115). Animals most susceptible are usually found in areas of high tsetse challenge, while those least susceptible (resistant) animals within the population may have acquired resistance through low exposure and challenge over time (116).

The clinical course of trypanosomiasis has been examined in native African buffalo (*Syncerus caffer*), oryxes (*Oryx beisa*), eland (*Taurotragus oryx*), and waterbuck (*Kobus defassa*) following infection with *T. congolense*, *T. vivax*, or *T. brucei*. These animals showed resistance in the form of negligible parasitemia
and minimal anemia (115). Wild and domestic animals have been observed to develop resistance to trypanosomiasis after being subjected to prolonged continuous trypanosome infections (117, 118), and as previously mentioned, indigenous bovines are resistant to T. brucei within endemic foci in Uganda (114, 115).

TRYPANOSOMIASIS AT THE WILDLIFE, DOMESTIC ANIMAL INTERFACE

Diversity of Trypanosomes in Wildlife

Multiple Trypanosoma species and genotypes contribute to a large reservoir of parasite diversity. This presents major problems in the management of trypanosomiasis at the wildlife–domestic animal interface, with the risk of virulent strains emerging that impact both wildlife and domestic populations (5). A review of Australian animal trypanosomes found a huge variety of parasites: T. pteropi, T. thylacis, T. hippo sideri, T. binneyi, T. irwini, T. copemani, T. gilletti, T. vegr andis, T. lewisi, T. melophagium, T. theleri, T. nabiasi, T. evansi, T. cruzi, T. pteropi, T. hippo sideri, T. binneyi, T. thylacis, T. copemani, T. Irwin, and T. gilleti. Such biodiversity may have negative impacts on the wildlife and national parks, and is associated with biosecurity concerns (88, 119). Newly identified genotypes of wildlife animals include Trypanosoma vegr andis G6 and T. vegr andis G3 (5). Furthermore, a study in bats found three Trypanosoma spp. (T. cruzi, T. dionisi, and Blastocrithidia spp.) (22) demonstrating the great diversity in several wildlife species.

Infection at the Wildlife, Domestic Animal Interface

Climate change, population pressure, and incentives to end poverty through farming have forced humans to encroach into land previously occupied by wildlife (108, 120). Human encroachment in protected zones runs the risk of parasite transmission from wildlife to domestic animals and zoonotic transmission (108, 109, 121). Synanthropic zoonotic infections are spread from livestock to humans, and exoanthropic infections are spread by wildlife and feral animals to humans—contributing to the increasing gene pool of anthropones (98). The cross-species (interspecies) transmission, also known as host jump or spillover, means the potential of an external parasite to invade a new host and infect them to ultimately spread to the whole population of the new host. About 63% of host jumps are responsible for interspecies diseases (109, 122, 123).

Endemic zones are created by encroaching on places of game parks. This has caused a wildlife and livestock interface, and development of the trypanosome parasite reservoirs (117). Wildlife is often implicated as the reservoir of parasites especially trypanosomes (37, 124, 125). It is common for the high incidences of trypanosomiasis in the wildlife to spillover to the domestic cycle in the tsetse fly-infested zones (71). Domestic animals pose a risk to wildlife, particularly the great apes, especially if the domestic carriers are present, for example, cattle and dogs (32).

Infection with T. b. rhodesiense is common in communities living proximal to, or that are dependent on, wildlife or eco tourism (126, 127). In the Luangwa Valley, Zambia, considerable efforts are made to keep domestic animals away from the national park, for biosecurity of livestock keepers, the national parks, and game conservancies (128). In Zambia, HAT infections have been associated with young children attending school and older women demonstrating in the homestead (129, 130).

A study in Australia failed to find T. cruzi and T. evansi in native domestic and wildlife animals; however, a spillover for exotic Trypanosoma spp. was expected that would affect humans, domestic, and wild animals (88). Wildlife (Glyoms laticeps, Thrichomys pachyurus, and Oecomys marmorae) can be reservoir hosts for Trypanosoma spp., e.g., T. evansi and T. cruzi that could infect humans and other wildlife populations without affecting the rodent spp. (131).

Factors That Could Influence Trypanosomiasis Epidemiology in Wildlife Areas

Host species that are widely distributed and with fewer restrictions on habitat have proved to be of more importance to trypanosome diversity due to their unlimited breeding potential and less risk for poaching and trophy hunting. Such hosts include warthogs, bushbucks, kudus, buffaloes, and giraffes (20). More habitat-restricted host species have minimal contribution to the epidemiology of trypanosomiasis in wildlife communities due to their relative safety from trypanosome vectors like Glossina and Tabanids, e.g., crocodiles and hippopotamus.

Differences in feeding patterns of the trypanosome hosts influence the distribution of trypanosomiasis in wildlife areas. Certain preferences maintained by certain hosts like bovines (bushbuck, waterbuck, eland, kudu, etc.) to bushy areas and thickets have predisposed them to higher exposure rates to tsetse and other biting flies, intensifying the spread of trypanosomes (20). Trypanosome diversity among the host species has facilitated the cross-transmission of various trypanosome strains and variants among the hosts, increasing infection rates among wildlife communities at both clinical and subclinical levels. For example, the discovery of three different variants of T. vivax in three different host species including a buffalo, a waterbuck, and a giraffe not similar to any published strain, demonstrating genetic diversity, provides insights on pathogen epidemiology (3).

Furthermore, the introduction of new host species from a different geographical location into a wildlife reserve can greatly influence the trypanosome species diversity in a wildlife community. This way, new variants and species of trypanosomes are spread from one host to another by tsetse and other biting flies, resulting in devastating effects on wildlife health and livestock health in the area, for example, the discovery of T. melophagium, T. nabasi, T. theleri, and T. evansi in Australia following the introduction of various mammals into their wildlife populations, which had a great impact on the native marsupials (9).
Wildlife Encroachment and the Epidemiology of Trypanosomiasis

Encroachment to wildlife and the increasing human and livestock density as well as the altered patterns in land use are key parameters that govern the transmission of trypanosomes (132). It is expected that understanding how the encroachment to wildlife affects the epidemiology of trypanosomes will inspire practical approaches to improve the understanding of epidemiological characteristics of trypanosome transmission in the context of ecological factors. Encroachment to wilderness areas of Africa increases the epidemiology of trypanosomes, hence, increasing the transmission of HAT. Primarily, wildlife are trypanosome reservoirs; however, growing human and livestock numbers around or in wildlife areas increase the significance of livestock in the transmission cycles thereby increasing the epidemiology of trypanosomes pertinent to human health (132).

Understanding undercurrents associated with the transmission of trypanosomes and in relationship with the encroachment of livestock and humans to wildlife areas are vital to developing robust control measures. This would help identify important parameters on host distributions, tsetse populations, epidemiology of trypanosomes, infection and mortality rates, the significance of livestock, humans, and livestock as hosts in wildlife areas, hence, promoting the progress of models to help in the evaluation and application of control measures (132). Parameters that determine the dynamics in encroachment levels to wildlife areas such as protected area, wildlife density, livestock density, human density, and location according to space and time, would help determine the foci of HAT. This is important since increased human and livestock populations and their distribution may lead to land-use pattern changes in fragmented tsetse habitats, and this inevitably affects the distribution of wildlife species. These ultimately result in increased tsetse abundance and distribution, host selection, and tsetse mortality, which are indicators of increased vector competence (132). Host population density is a key factor in determining the dynamics of tsetse populations, i.e., a decline in host density through encroachment to wildlife areas influences tsetse population changes in space and time. This, in turn, influences the transmission of trypanosomes, and although low host density decreases trypanosome transmission as a consequence of tsetse mortality, the low host density may also be associated with an increased level of trypanosome transmission arising from the hungrier flies that bite humans through increased host-seeking efficiency of tsetse flies (133).

INFECTION CONTROL AT THE WILDLIFE–LIVESTOCK–HUMAN INTERFACE

While communities fail to understand the value of wildlife ecosystems, continued wildlife–human conflict presents an increased risk of infection spillover to humans (18, 118, 134, 135). Game parks, the natural habitats for tsetse species, pose risks to livestock and human populations (136, 137), and parasitic infestations among the livestock and humans equally pose a risk to wildlife. Wildlife reservoirs make approaches of trypanosomosis control at the wildlife–livestock–human interface more complicated (30, 31). There is a need to limit the interaction between livestock and wildlife by preventing encroachment into wildlife-protected zones. Mitigation of risk to prevent trypanosome (and other) infections circulating among livestock and wildlife demands a holistic One Health approach (108, 138, 139). Top–down, approaches, shooting games and radical bush clearing, and insecticide spraying in protected zones are neither practical nor acceptable (140). Stakeholder and community-derived solutions are likely to be sustainable options to explore. Approaches to infection control require to be nuanced in these zones, with communication, education, and interventions embedded within the affected communities. Integrated insect control approaches including the use of insecticide-impregnated targets can protect livestock and game (141). Application of insecticides to cattle, using livestock as live baits, can offer sustainable solutions (138, 142, 143); however, challenges remain on the sustainability of this approach especially in low–middle income countries (LMICs). Insecticides are a reliable method for tsetse control and can be improved by deploying an integrated insecticide approach (139, 141). Routine prophylaxis among livestock can protect livestock and offer collateral benefits for humans and wildlife (144, 145). There is also a need to limit the interaction between livestock and wildlife by stopping encroaching on gazetted wildlife zones to lower the trypanosome prevalence in domesticated livestock (108).

Animal and Human Health for the Environment and Development (AHEAD), launched in 2003, comprises a One Health team of socioeconomic scientists, ecobiologists, veterinarians, agriculturalists, wildlife, and public health specialists that address issues at the wildlife, human, and domestic livestock interface. This includes efforts to monitor parasitic diversity in wildlife species to assist in the strengthening of disease surveillance in LMICs (146). Management and communication with regard to wildlife is key to the One Health approach; in pastoral communities, retaliatory persecution through poisonings of predatory wildlife continues to challenge conservation efforts (147). Conflicts associated with competition for natural resources between livestock-keeping communities and wildlife can be mitigated by a combination of communication and control strategies to promote peaceful coexistence of wildlife and humans as promoted by AHEAD.

Management of Spillover of Trypanosomiasis Among the Human–Wildlife Areas

Communities in the wildlife zones sometimes agree on coexistence with wildlife and the creation of buffer zones (148). However, the coexistence of human communities and wildlife poses risks of outbreaks of various zoonoses (149). In the gazetted wildlife zones, there should be no mixing of domestic animals with wild trypanosomiasis reservoirs. Proper fencing can be used to control the spillover in wildlife borders (150) as part of the integrated trypanosomiasis control strategy. Restrictive models need to be developed by engaging the communities
CONCLUSION

Trypanosomiasis continues to be a major global challenge, particularly so at the wildlife–domestic livestock interface. Multiple wildlife species serve as maintenance hosts promoting infections at the livestock–wildlife interface. There is a high risk of infection spillover from game parks and conservation areas where parasites and vectors are concentrated in high numbers, and domestic livestock pose risks to wildlife-protected species. The basis of trypanotolerance in wildlife species is not well-understood. The wide genetic diversity exhibited by Trypanosoma spp. is a challenge, both exacerbating the risk of increased virulence and making the development of a vaccine unlikely. One Health strategies that are community and environmentally friendly are needed to support stakeholders to mitigate risk. There is a need to strengthen trypanosomiasis research, particularly in LMICs, especially at the human–domestic–wildlife interface to prevent cross-species infection.

AUTHOR CONTRIBUTIONS

KIK and SCW conceptualized the study, designed the study, and analyzed and interpreted the data. KIK, GZ, FS, BB, KJA, KM, HNN, LA, DO, PB, JJO, SI, WM, DPN, GESB, LOO, TS, MA, LO, and SCW collected the data. KIK wrote initial draft while SCW critically reviewed it for intellectual content. All authors approved the manuscript for publication and remain in agreement on all aspects of the work.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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