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1 **Transmission Dynamics of Rhodesian Sleeping Sickness at the Interface of Wildlife and**
2 **Livestock Areas**

3
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10
11 **Key words**

12 Rhodesian human African trypanosomiasis, wildlife/livestock interface, wilderness areas,
13 animal reservoirs, tsetse, mathematical models

14
15 **Abstract**

16 Many wilderness areas of east and southern Africa are foci for Rhodesian sleeping sickness,
17 a fatal zoonotic disease caused by trypanosomes transmitted by tsetse flies. Although
18 transmission in these foci is traditionally driven by wildlife reservoirs, rising human and
19 livestock populations may increase the role of livestock in transmission cycles. Deciphering
20 transmission dynamics at wildlife and livestock interface areas is key to developing
21 appropriate control. Data are lacking for key parameters, including host distributions, tsetse
22 density and mortality rates, and the relative roles of livestock and wildlife as hosts in
23 fragmented habitats, limiting the development of meaningful models to assist in the
24 assessment and implementation of control strategies.

1 **Rhodesian Sleeping Sickness: A Disease in Decline?**

2 Human African trypanosomiasis (HAT or sleeping sickness) caused by trypanosomes
3 transmitted by tsetse flies, is targeted by the World Health Organisation (WHO) for
4 elimination by 2020
5 (http://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf). This goal
6 is qualified as 'elimination as a public health problem', defined as an annual incidence of
7 less than 1 case per 10 000 population, and less than 2000 cases reported globally each year
8 [1]. Two forms of HAT, Gambian HAT (g-HAT) found in west and central Africa and
9 Rhodesian HAT (r-HAT) found in east and southern Africa, differ in epidemiology and
10 control. Although good progress is being made in controlling g-HAT through mass screening
11 and treatment of affected people with trypanocidal drugs, long term elimination of r-HAT is
12 considered to be unfeasible due to the existence of animal reservoirs.

13
14 HAT is caused by subspecies of *Trypanosoma brucei*. The pathogen for g-HAT, *T. b.*
15 *gambiense*, is transmitted by 'riverine' species of tsetse such as *Glossina palpalis* and *G.*
16 *fuscipes*. The disease is generally considered to be an anthroponosis with no important
17 non-human hosts. r-HAT is caused by *T. b. rhodesiense* transmitted largely – but not
18 exclusively - by 'savannah' species of tsetse such as *G. morsitans* and *G. pallidipes*. r-HAT is
19 a zoonosis, with livestock and wild mammals such as warthog, buffalo and bushbuck acting
20 as reservoir hosts. A third subspecies, *T. b. brucei*, is morphologically identical but does not
21 cause disease in man. The different epidemiology of the two human pathogens reflects their
22 genetics. *T. b. rhodesiense* is essentially a variant of *T. b. brucei*, but carries a single gene
23 (Serum Resistance Associated; SRA) [2] that confers the ability to infect humans [3]. In
24 contrast, *T. b. gambiense* is genetically distinct from both *T. b. brucei* and *T. b. rhodesiense*,
25 is clonal and evidence suggests it to be reproductively isolated [4–7]. A key feature of HAT is
26 its focal nature. It tends to be reported in specific areas which appear to remain consistent
27 over time.

28
29 Although the number of r-HAT cases reported globally has declined in the last 15 years
30 (Figure 1A), this trend is driven to a great extent by the reduction in cases in south-eastern
31 Uganda, where outbreaks associated with civil unrest and livestock-dominated transmission
32 have gradually been brought under control (Figure 1B). Reported cases in Tanzania have

1 also declined. In contrast, in Malawi and Zambia, reported case numbers have been
2 relatively consistent over the last decade (Figure 1B). In addition, the data illustrated in
3 Figure 1 are likely an underestimate. Many r-HAT foci are in remote areas; a lack of
4 diagnostic facilities and awareness of HAT are frequently reported around foci [8,9] and
5 under-detection of cases is a recognised problem [10]. Small numbers of cases are also
6 regularly diagnosed in non-endemic countries, serving to highlight transmission which may
7 not be reliably detected [11]. Many r-HAT foci have been linked to devastating outbreaks in
8 the past, and more recent outbreaks, although smaller in magnitude, suggest this risk is still
9 present [12–14].

10

11 Three types of r-HAT focus have been characterised according to the dominant reservoir
12 host species: wilderness foci where wildlife-dominated transmission is associated with
13 natural protected areas; livestock-dominated foci where cattle have replaced wild species as
14 the non-human reservoir; and foci where both wildlife and livestock are present [15].
15 However, many of the foci regarded as wilderness foci are also inhabited by increasing
16 densities of people and livestock (for example in Serengeti, Tanzania, and Luangwa, Zambia
17 [16; Basic data for Livestock and Fisheries Sectors 2013, United Republic of Tanzania
18 Ministry of Livestock and Fisheries Development [www.mifugouvuvu.go.tz/wp-](http://www.mifugouvuvu.go.tz/wp-content/uploads/2014/12/DRAFT-ONE-_Basic-Data-1.pdf)
19 [content/uploads/2014/12/DRAFT-ONE-_Basic-Data-1.pdf](http://www.mifugouvuvu.go.tz/wp-content/uploads/2014/12/DRAFT-ONE-_Basic-Data-1.pdf); J. Mubanga, PhD thesis,
20 University of Edinburgh, 2008]) and transmission associated with both wildlife and livestock
21 hosts is arguably more common than is widely recognised. r-HAT transmission – particularly
22 in wildlife/livestock foci - is complex due to the involvement of multiple host and vector
23 species within heterogeneous and often fragmented landscapes.

24

25 Mathematical models can be powerful tools for understanding transmission dynamics and
26 assisting in disentangling such complexity. Recent reviews of the mathematical modelling
27 literature for mosquito and tsetse-borne pathogens have highlighted gaps with respect to
28 incorporating heterogeneity into model structures - variation which is likely to be required
29 to understand and predict invasion and transmission dynamics of such pathogens [17,18]. In
30 this paper we therefore review the current literature concerning the transmission ecology of
31 r-HAT at the wildlife-livestock interface by focusing upon core parameters in mathematical
32 models of trypanosome transmission [18]. These parameters are summarised in Figure 2,

1 alongside potential impacts of increasing human and livestock density and changing land
2 use patterns. It is anticipated that this review will stimulate efforts to integrate empirical
3 and quantitative approaches to better understand the variation in r-HAT transmission
4 observed across ecological contexts. We consider examples from four foci: Serengeti in
5 Tanzania, Luangwa Valley in Zambia, Rumphi in Malawi, and Ugala River/Moyowosi in
6 western Tanzania (Table 1, Figure 3).

7

8 **Host Factors that Affect the Transmission of *T. b. rhodesiense***

9 The abundance and distribution of animal host species, and their respective competence as
10 hosts for trypanosomes, are key factors affecting transmission of *T. b. rhodesiense*.

11 Serengeti in Tanzania, Luangwa Valley in Zambia, and Rumphi in Malawi are all examples of
12 foci where wildlife populations within protected areas maintain infection (Table 1). At the
13 other end of the spectrum, in south-east and central Uganda and western Kenya, cattle
14 have replaced wild species as the non-human reservoir of *T. b. rhodesiense*. Transmission in
15 areas where both wild hosts and livestock are present is less well understood. Although
16 Western Tanzania is often described as a focus where transmission is maintained by both
17 wildlife and livestock [15] (Table 1), the presence of increasing livestock populations in so-
18 called ‘wilderness foci’ suggests that livestock are also likely to be important in transmission
19 in these areas.

20

21 *Host competence*

22 Host competence reflects a combination of the susceptibility of the host when bitten by an
23 infected vector, the ability of the pathogen to persist in the host, and the likelihood that the
24 host infects a feeding susceptible vector [19]. A large number of wildlife host species are
25 competent for *T. brucei* s.l., and wildlife hosts form a reservoir community that can maintain
26 transmission (discussed in Box 1). Of the few experimental studies available comparing wild
27 and domestic hosts, the proportion of susceptible tsetse that developed a mature *T. brucei*
28 infection after feeding on an infected host was approximately 16% in susceptible cattle
29 breeds, compared to 8% in buffalo, 10% in eland and 12% in waterbuck [20]. Although these
30 figures were based on single host animals, the pattern is consistent with the parasitaemia
31 patterns seen in cattle and wild hosts. After the initial acute phase of infection, cattle
32 infected with *T. brucei* s.l. tend to show low parasitaemia, which is present for extended

1 periods but only intermittently detectable [21,22]. Wild bovids show even fewer patent
2 parasitaemic waves, and lower overall parasitaemia [20,23,24].

3 4 *T. brucei* s.l. prevalence in hosts

5 Prevalence in host species is influenced by host competence, but also depends on the
6 exposure of hosts to infected tsetse. As such, prevalence alone cannot indicate the
7 importance of a species as a reservoir host. However, it is often the only measure that is
8 available to provide some information about the roles of different host species. *T. brucei* s.l.
9 is observed in many wildlife species, with prevalence variable by species (Box 1). In Uganda,
10 where cattle transmission predominates, cattle show a prevalence of *T. brucei* s.l. of 20-27%
11 in high prevalence villages [25] and up to 17.5% at markets by PCR [26]. Although small
12 ruminants can also be infected with *T. brucei* s.l., the very low prevalence found in sheep
13 and goats suggest they are less important than cattle in maintaining transmission [27].
14 Cattle living in and around wilderness areas are also frequently infected with *T. brucei* s.l.,
15 although the data available are insufficient to explore differences between foci. Around
16 Serengeti National Park, 6% of cattle carried *T. brucei* s.l. by PCR, and 30% by loop-mediated
17 isothermal amplification (LAMP), and around Luangwa Valley in Zambia 1% by PCR and 25%
18 by LAMP were reported [14,28,29; J. Mubanga, PhD thesis, University of Edinburgh, 2008]
19 (Table 1). Combined with higher host competence in cattle compared to wild bovids, this
20 suggests that cattle may be important in r-HAT transmission around wilderness areas.

21 22 *Abundance, distribution and species composition of animal hosts*

23 Given the variability in competence between host species, r-HAT risk is influenced by the
24 species present. In south-eastern Uganda, where livestock transmission dominates, a large
25 cattle population combines with a low density of wildlife. Since *T. brucei* s.l. is usually
26 asymptomatic or causes only mild clinical signs in cattle [27], movements of apparently
27 healthy cattle have been responsible for introducing disease into new areas in Uganda
28 [30,31]. At the other extreme, many r-HAT foci are located in protected wilderness areas
29 where the density and diversity of wildlife species are high, and often well characterised
30 (Table 1).

1 There are fewer data available on the abundance and species composition of hosts in
2 wildlife/livestock interface areas. Wildlife populations are less well monitored outside
3 protected areas and the degree to which wildlife species are found in more fragmented
4 areas varies by location and wildlife species [32]. For instance, to the west of the Serengeti
5 National Park, elephant and impala are more common within farming areas than other
6 species such as buffalo (Goodman, P.S. 2014. Large herbivore population estimates for the
7 Grumeti Reserves – August 2014, Grumeti Fund, Sasakwa, Serengeti District, Tanzania,
8 unpublished report). Bushbuck also survive well in human-dominated landscapes [33] and
9 are competent hosts for *T. brucei* s.l. (Box 1). The presence of bushbuck and other
10 competent species in farming areas may serve to bring trypanosomes into regions where
11 cattle and human densities are high and thus contribute to linking wildlife-livestock
12 transmission cycles. Although savannah tsetse inside protected areas do not frequently
13 feed on bushbuck [34], the absence of preferred hosts such as buffalo in farming areas
14 might increase the proportion of bloodmeals taken from bushbuck and therefore disease
15 risk. Currently not enough is known about the competence of other wild host species to
16 accurately identify how host distributions in fragmented areas might affect risk.

17
18 Countries such as Tanzania, Zambia and Malawi are undergoing rapid human population
19 expansion, and around protected areas increasing human and livestock densities are
20 common [16]. Some boundary areas show disproportionately higher population increases,
21 as illustrated to the west of Serengeti National Park in Tanzania where demand for land for
22 cultivation and grazing is leading to high rates of immigration [16,35]. In this area, the
23 density of cattle around the protected areas is now very high (Fig. 3), having undergone
24 substantial increases in the last two decades (Basic data for Livestock and Fisheries Sectors
25 2013, United Republic of Tanzania Ministry of Livestock and Fisheries Development
26 www.mifugouvuvu.go.tz/wp-content/uploads/2014/12/DRAFT-ONE-_Basic-Data-1.pdf)
27 (Table 1). Increasing human and livestock density around protected areas has also been
28 reported in Eastern Province of Zambia where immigration to find more fertile land is
29 common (J. Mubanga, PhD thesis, University of Edinburgh, 2008). Historically, the presence
30 of tsetse-transmitted trypanosomes pathogenic to cattle has acted as a disincentive to
31 grazing in protected areas. However, to the west of Serengeti the availability of

1 trypanocides and insecticides appears to have reduced this barrier; cattle incursions into
2 protected areas are likely to bring both people and livestock in contact with tsetse.

3

4 Changes in the relative densities of cattle may have different impacts on transmission to
5 humans, depending upon context. The proximity of cattle to their owners, especially in
6 traditional livestock production systems, may act as a bridge to human infection – this
7 seems to be the case with r-HAT in Uganda where recent epidemics have been strongly
8 linked with livestock and riverine tsetse. However, livestock might have a zooprophylactic
9 effect protecting people from being bitten. There is some evidence that livestock protect
10 their owners from infection. A combination of the upright shape [36] and natural odours
11 [37] of humans repels savannah species of tsetse. On the other hand, the size, shape and
12 odour of livestock, particularly cattle, are attractive to tsetse [36]. Hence even in areas
13 where tsetse are abundant, few humans are bitten by tsetse if they are close to livestock: a
14 study in a national park in Zimbabwe found that the catch of tsetse landing on a human
15 walking through tsetse-infested woodland was reduced by >95% if he was accompanied by
16 an ox [38].

17

18 **Vector factors that affect transmission of r-HAT**

19 In south-eastern Uganda, *G. fuscipes fuscipes*, a riverine species of tsetse, is responsible for
20 transmission of *T. b. rhodesiense*. Riverine tsetse such as *G. f. fuscipes* feed on a wide range
21 of hosts, including humans and cattle [39], and can persist in areas with high densities of
22 people [40]. However, in most other r-HAT foci, *T. b. rhodesiense* is vectored by savannah
23 species, such as *G. morsitans spp.*, *G. swynnertoni* and *G. pallidipes*.

24

25 *Vector competence*

26 Vector competence, the innate ability of a vector to acquire, maintain and transmit a
27 pathogen, varies with tsetse species, as well as other intrinsic (e.g., sex) and extrinsic factors
28 (e.g., environmental temperature and nutritional status) [41]. Low prevalence of mature *T.*
29 *brucei* s.l. is common in tsetse, reflecting the general refractoriness of tsetse to
30 trypanosome infection and maturation [reviewed by 42]. Experimental infections suggest
31 that *G. morsitans* has higher vector competence than *G. pallidipes* (0 to 2.7% of *G. pallidipes*
32 became infected after feeding on hosts infected with two different strains of *T. brucei*

1 *brucei*, compared to 9.3 to 18.4% of *G. morsitans centralis*) [43]. Although both *G. pallidipes*
2 and *G. morsitans spp.* are found in r-HAT foci, they vary in abundance and their relative
3 importance as vectors is likely to also depend on their host feeding patterns, as well as
4 inherent vector competence.

5

6 *Abundance, distribution and mortality*

7 On a regional scale, a general reduction in investment in large scale tsetse control since the
8 1980s [44] has been balanced against loss of tsetse habitat for agricultural expansion [45–
9 48]. This has led to an overall decline in habitat suitable for tsetse. However, protected
10 areas and their surroundings form islands that can sustain populations of savannah tsetse–
11 *G. morsitans*, *G. swynnertoni* and *G. pallidipes* [45,49]. These areas are often surrounded by
12 significant land use change [16], and fragmented tsetse habitat [48,50], but habitat
13 distribution varies from hard borders where land use changes quickly (for example in
14 Rumphi, Malawi [51] and Western Serengeti, Tanzania) to more gradual gradients in land
15 use and tsetse habitat (as seen in Luangwa Valley, Zambia [48,50]).

16

17 Although there are limited data, savannah tsetse do not appear to survive well outside
18 protected areas. In Malawi, 15 times more *G. m. morsitans* were caught inside the
19 Nkhotakota Game Reserve than in suitable habitat – predicted from satellite imagery –
20 outside the reserve (when numbers caught were adjusted by trapping effort). This
21 difference was attributed to human activity, destruction of tsetse habitat and low density of
22 hosts [49]. In Zambia, fly-round catches of *G. m. morsitans* were from four to 280 times
23 higher in natural habitats compared with natural habitats fragmented by agriculture [48,50].
24 Catches of tsetse from traps and fly-rounds will be affected by sampling biases and may not
25 reflect the true population densities [36]. Nonetheless, the consistent finding that apparent
26 numbers of tsetse outside protected areas are much reduced suggests that savannah tsetse
27 are largely restricted to relatively undisturbed habitat. Savannah tsetse are intolerant of
28 high temperatures and low humidity [52]. The reduced numbers of trees and bushes in
29 farming areas that provide the necessary shade and high humidity for tsetse seems an
30 obvious explanation why they do not persist outside protected areas. However, farming
31 areas often comprise a mosaic of crop field, pastures and relic savannah and woodland and
32 hence the essential microclimates are likely to be present. A better understanding of the

1 habitat requirements of savannah tsetse would assist in predicting areas where populations
2 may be sustained outside protected areas.

3

4 Disease risk is not only influenced by tsetse abundance. Mweempwa [50] reported that
5 although apparent abundance decreased in more fragmented habitats in Zambia, the flies
6 present were more likely to be older. Tsetse age is important in HAT risk because flies take
7 around 18 days to develop a mature transmissible *T. b. rhodesiense* infection [53]; older fly
8 populations therefore present a higher risk of transmitting HAT to people. Mweempwa *et al.*
9 found that the most fragmented site showed the highest mature infection rate, although
10 the entomological inoculation rate (an estimate of disease risk which takes into account fly
11 abundance as well as infection rates) was highest in the least fragmented site [50].

12

13 *Host selection*

14 In south-eastern Uganda, cattle are the most important host of *G. fuscipes fuscipes*
15 providing ~50% of bloodmeals [54]. The only remaining important wild host of tsetse in the
16 area is the Nile monitor lizard, which rarely carries *T. brucei*. In wilderness areas savannah
17 tsetse have preferred hosts (particularly warthog, buffalo, giraffe and elephant [39]) but
18 they are able to feed on a wide range of wildlife species. Although savannah flies are known
19 to feed on both livestock and wildlife hosts [34,55], few studies have looked specifically at
20 feeding patterns in areas where both are present. At two sites in Kenya where both wildlife
21 and livestock were present, Bett *et al.* reported that 16% of *G. pallidipes* feeds identified at
22 Nguruman and 58% at Nkineji came from livestock, with the rest from wildlife [56] but the
23 absence of data on the relative abundance of wildlife and livestock at these two sites makes
24 it difficult to draw more general conclusions about tsetse choice. The likelihood that
25 tsetse will feed on a particular species is driven by a number of factors. Experimental studies
26 suggest the numbers of tsetse attracted to and landing on a host are related to mass: larger
27 hosts attract more tsetse [36,57,58]. The probability that tsetse attracted to a host take a
28 meal seems to be largely controlled by host defensive behaviour [59]. Impala and warthog
29 are of comparable size but the high rates of defensive behaviour displayed by the former
30 probably explains why it is rarely identified in bloodmeals [34]. It appears that tsetse rarely
31 feed on impala or other antelope species (gazelle, wildebeest) despite their
32 abundance. Similarly, amongst domestic livestock species, goats display high rates of

1 defensive behaviour [59] and hence are relatively rare as hosts [34], whilst adult cattle
2 display low rates of defensive behaviour [59,60]. In conclusion, cattle, with their large size
3 and relatively low rates of defensive behaviour, make particularly good hosts.

4 5 **Understanding Transmission in a Changing Environment**

6 Reviewing the data available on r-HAT at wildlife/livestock interface areas highlights several
7 key aspects where a lack of data prevents a full understanding of the transmission
8 dynamics. In particular, host distributions, vector abundance and mortality around
9 protected areas and the role of livestock as hosts in savannah tsetse systems, are all key
10 aspects that are currently lacking in data. The land use change associated with increasing
11 human and livestock densities may lead to declining tsetse populations outside protected
12 areas, but there is a risk that this fragmented habitat may actually increase r-HAT risk, at
13 least in the shorter term, through altered dynamics of tsetse and host populations. Although
14 the paucity of comparable data limits detailed comparisons, there is considerable
15 heterogeneity in some parameters between foci. For example the density of cattle around
16 Serengeti in Tanzania is considerably higher than in foci in Zambia and Malawi, and may
17 indicate that there is a spectrum of livestock involvement. The lack of published data on
18 some foci, for example Ugala River/Moyowosi in western Tanzania (Table 1), identifies the
19 need to focus research not only on well-known protected areas.

20
21 Of particular concern is that a shift from wildlife- to cattle-dominated transmission may
22 increase the overall reservoir potential and potentially increase HAT risk: cattle are known
23 to carry human pathogenic trypanosomes, there is some evidence that they have higher
24 host competence than wild bovinds, and they are particularly good hosts for tsetse. Since the
25 drivers for epidemic spread are complex, it is not clear whether increasing involvement of
26 cattle in r-HAT cycles could also increase the risk of epidemic spread, or movement of
27 disease to new areas as has happened in south-eastern Uganda, although the role of
28 riverine tsetse in Uganda undoubtedly plays a role in the spread of r-HAT in farming areas in
29 this focus.

30
31 Quantifying the relative contribution of livestock and wildlife species in mixed-transmission
32 settings is not easy. The gold standard of reservoir identification is observation of

1 decreasing disease in the target population following either (i) the control of infection in the
2 putative reservoir species, or (ii) prevention of contact between the reservoir species and
3 the target population [61], but realistically in foci with low r-HAT incidence it is not feasible
4 to assess interventions in this way. As recently highlighted by Viana et al., [62], integration
5 of multiple methodologies and data sources, for example using mathematic models, are
6 likely to be needed to improve understanding of the reservoir dynamics. Even when the
7 current limitations of significant data gaps are overcome, the complexity of these disease
8 systems mean that model outputs require careful interpretation in order to develop
9 meaningful control strategies. This emphasizes the need to understand transmission better
10 at a scale relevant to control at the wildlife-livestock interface; although control measures
11 aimed at wildlife are not feasible, interventions aimed at cattle could provide an effective
12 option for control in areas where both wildlife and cattle are present.

13

14 **R-HAT control in wildlife/livestock interface areas**

15 Since humans are not part of the reservoir of r-HAT except perhaps in an epidemic situation,
16 the mass screening programs that have been effective against g-HAT are not appropriate for
17 r-HAT. Control of r-HAT in protected areas has been achieved through various methods of
18 vector control, for example a combination of aerial spraying and odour-baited targets was
19 used to eliminate tsetse and trypanosomiasis from the Okavango Delta of Botswana [63],
20 but the costs of control on this scale are usually prohibitive.

21

22 While the elimination of r-HAT seems unlikely, a better understanding of transmission
23 dynamics in specific foci would allow control to be targeted more effectively. Insecticide-
24 treated cattle are the most cost-effective method of vector control where sufficient cattle
25 are present [64] but this approach requires that cattle form at least 10% of the diet of tsetse
26 for transmission of HAT to be interrupted [65]. In practice, a minimum density of around 10
27 cattle/km² [66] distributed relatively evenly [67] can provide effective control. In foci where
28 livestock are at a sufficient density, such as Serengeti in Tanzania, insecticide treated cattle
29 could provide a cost-effective means of containing r-HAT, depending on the extent of r-HAT
30 transmission outside the protected areas. Cattle-based interventions to control r-HAT will
31 also impact on diseases of veterinary importance, particularly tsetse and tick-borne diseases
32 affecting livestock in the boundary areas. However, the lack of understanding about

1 transmission in r-HAT foci is currently limiting development of effective control, and it is not
2 feasible to assess the likely effectiveness of potential control options without better data to
3 parameterise models of transmission in these areas.

4

5 **Concluding Remarks**

6 Rhodesian HAT is unlikely to be eliminated completely from wilderness areas due to the role
7 of animal hosts. Although there is a perception that r-HAT transmission in wilderness foci is
8 decreasing, there is little evidence to support this. In fact, a number of features of r-HAT in
9 interface areas could actually lead to an increase in disease risk. The potential involvement
10 of livestock, the effect of habitat fragmentation on tsetse and host population dynamics,
11 and the risk of increasing tsetse-human-livestock contact suggest an ongoing risk for r-HAT
12 transmission. This review highlights substantial gaps in our understanding of transmission in
13 wilderness areas (see Outstanding Questions box). Improved prediction and more targeted
14 control of Rhodesian HAT outbreaks will not be possible unless these gaps are addressed.

15

16

17

1 **Box 1- Understanding transmission of *T. b. rhodesiense* in wildlife hosts**

2 In sylvatic transmission cycles, a large number of wildlife species form a reservoir
3 community. Both *T. brucei* s.l. and *T. b. rhodesiense* have been identified in a wide range of
4 species, [for example 14,68–73]. The prevalence varies greatly between species. Species
5 such as bushbuck and reedbuck are consistently reported to show high prevalence with *T.*
6 *brucei* s.l. (18% to 100% [14,68]), and carnivore species such as lions and hyaena are also
7 frequently infected (16-64% [14,69,71,72,74]). In contrast, many species, including warthog,
8 buffalo, and many antelope, have been identified to carry *T. brucei* s.l. but with low
9 prevalence [68,70,71,73,75,76].

10
11 The importance of different species in *T. brucei* s.l. transmission depends on a host's
12 competence, and the likelihood that the host will be fed on by a tsetse. Generally, wildlife
13 species are considered to control trypanosome infections well, suggesting competence
14 should be low, but this may not be true for all species: in historic experimental infection
15 studies, warthog and buffalo generally showed low parasitaemia for a few weeks, but
16 species such as reedbuck, bushbuck and Thomson's gazelle were reported to be easy to
17 infect, to show high parasitaemia for several months, and to infect feeding tsetse regularly
18 [23,77,78].

19
20 *G. morsitans* spp. and *G. swynnertoni* feed particularly on warthog [34], leading to
21 speculation that warthog might be particularly important in transmission. In contrast,
22 bushbuck, reedbuck and other antelope species are rarely fed on [39]. However, it is
23 possible that the role of species such as reedbuck and bushbuck has been underestimated,
24 with their high prevalence and high infectivity potentially driving transmission. These
25 relationships are unlikely to be quantified without developing transmission models, but this
26 is limited by a lack of robust data. The dynamics of transmission in wildlife are undoubtedly
27 important in the persistence of r-HAT foci. Without understanding the relative role of
28 different wildlife species, and their relationship to environmental factors, it is unlikely it will
29 be possible to understand how foci are maintained within wilderness area, and in particular
30 identify the drivers that might lead to r-HAT outbreaks.

31 **Table 1. Summary of Key Parameters for Four Exemplar Foci of Rhodesian Human African Trypanosomiasis**

	Serengeti, Tanzania	Ref.	Luangwa Valley, Zambia	Ref.	Rumphi, Malawi	Ref.	Ugala River/Moyowosi, Tanzania	Ref.
Protected areas	Serengeti NP ^a , Ikorongo, Grumeti and Maswa GRs ^b , wildlife management areas	^u	North Luangwa NP, South Luangwa NP, Luambe NP, Lukusuzi NP, game management areas	^u	Vwaza Marsh WR ^c and Nyika NP	^u	Moyowosi GR, Kigozi GR, Ugala River GR, wildlife management areas	^u
Presence of wildlife	Very high density and diversity of wildlife within PA ^d . Low density outside PA, variable by species.	[79] ^v	High density and diversity of wildlife within PA.	[80, 81]	High diversity within PA.	^w	High density and diversity of wildlife present within PA. Lower densities outside PA, variable by species.	[82,83].
Trypanosomes in wildlife	<i>T. brucei</i> s.l. and <i>T. b. rhodesiense</i> commonly reported.	[14, 84].	<i>T. brucei</i> s.l. and <i>T. b. rhodesiense</i> commonly reported.	[68, 85]	No data.		No data.	
Presence of livestock	Increasing cattle density, cattle population in Mara region estimated at 1.1 million in 2002/2003 and 1.7 million in 2007/2008. Livestock present close to PA at increasing density.	^x	Historically very few livestock within the valley, increasing density towards plateau, high density on plateau (11 cattle/km ²). Cattle density currently increasing in mid Luangwa valley.	[80, 86] ^y	Cattle density generally low in Malawi (Figure 3). Distribution relative to PA unknown.	[87]	Livestock present around PA (Figure 3). High livestock numbers, agricultural expansion and overgrazing reported in the wider ecosystem.	[87–89]
Trypanosomes of <i>T. brucei</i> s.l. in cattle	29/518 <i>T. brucei</i> s.l., 6/518 <i>T. b. rhodesiense</i> in cattle around PA by PCR. <i>T. brucei</i> s.l. reported in 1/148 and 45/148 in cattle around PA by PCR and LAMP respectively.	[14, 29]	6/649 by PCR towards plateau. 2/241 and 48/195 reported by PCR and LAMP respectively in cattle.	[28] ^y	<i>T. brucei</i> s.l. identified in 1 out of 481 cattle in Rumphi district.	[90]	134/865 cattle reported positive for <i>T. brucei</i> s.l. on ITS PCR from Ugala ecosystem but location details not provided.	^z
Tsetse distribution	Widespread <i>G. swynnertoni</i> and <i>G. pallidipes</i> in PA, small populations <i>G. brevipalpis</i> in PA. Tsetse appears to be low outside PA but little published data.	[91–93].	<i>G. pallidipes</i> , <i>G. morsitans morsitans</i> , <i>G. brevipalpis</i> widespread in PA. Increasing fragmentation and decreasing tsetse density towards the plateau.	[48, 50] 14	<i>G. morsitans</i> , <i>G. pallidipes</i> , predominantly confined to PA.	[51, 90]	Tsetse populations reported close to villages. <i>G. morsitans</i> present.	[9,45]

Human cases	Cases in local population within PA and close to PA boundary. Cases diagnosed in NEC ^e from within PA (30 cases 2000-2010).	[11, 94]	HAT cases reported from this area (2000-2009). Seven cases reported in NEC from South Luangwa (2000-2010).	[11]	163 cases in Rumphi district 2000-2006; 97% of these from within 5km of Vwaza GR boundary. Two cases reported in NEC from Vwaza (2000-2010).	[11, 95]	Numerous HAT cases reported in this area (2000-2009). Two cases reported in NEC from Moyowosi GR (2000-2010).	[11,94]
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33 ^a NP, National Park; ^b GR, game reserve; ^c WR, wildlife reserve; ^d PA, protected area; ^e NEC, non-endemic countries;

34 ^u United Nations List of Protected Areas (<http://www.protectedplanet.net/>, accessed 03/05/16); ^v Goodman, P.S. 2014. Large herbivore
35 population estimates for the Grumeti Reserves – August 2014. Grumeti Fund, Sasakwa, Serengeti District, Tanzania, unpublished report; ^w

36 <http://www.nyika-vwaza-trust.org/Articles/Mammals.pdf>; ^x Basic data for Livestock and Fisheries Sectors 2013, United Republic of Tanzania

37 Ministry of Livestock and Fisheries Development [www.mifugouvuvuvi.go.tz/wp-content/uploads/2014/12/DRAFT-ONE- Basic-Data-1.pdf](http://www.mifugouvuvuvi.go.tz/wp-content/uploads/2014/12/DRAFT-ONE-Basic-Data-1.pdf),

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43 **Figure 1. Rhodesian Human African Trypanosomiasis Cases Reported Between 1990 and**
44 **2014.** The number of Rhodesian human African trypanosomiasis (r-HAT) cases reported is
45 shown for A) all countries, and B) Malawi, Tanzania, Uganda and Zambia. Data from the
46 World Health Organisation (WHO)
47 (http://www.who.int/gho/neglected_diseases/human_african_trypanosomiasis/en/). Note
48 different scale for individual country graphs.

49

50 **Figure 2. Factors Influencing Transmission of Rhodesian Human African Trypanosomiasis.**
51 Key parameters describing hosts, vectors and human risk are listed in grey boxes, alongside
52 potential effects of increasing human and livestock density and changing land use patterns.

53

54 **Figure 3. Distribution of Cases, Cattle and Protected Areas in Rhodesian Human African**
55 **Trypanosomiasis Foci.** A) Cases of human African trypanosomiasis in eastern and
56 southeastern Africa. Boxes (solid line) show four exemplar foci of Rhodesian human African
57 trypanosomiasis. In addition, a dashed line box indicates livestock-dominated transmission
58 focus in south-eastern and central Uganda. Reproduced from [94]. B) Detailed maps of the
59 four exemplar foci highlighted in A, illustrating the density of cattle in 2010 (data from the
60 Gridded Livestock of the World [96]), and protected areas boundaries (from United Nations
61 List of Protected Areas <http://www.protectedplanet.net/>). Protected areas shown include
62 national parks (NP), game reserves (GR), wildlife reserves (WR), game management areas
63 (GMA), wildlife management areas (WMA) and Ngorongoro Conservation Area (NCA).

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