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A mathematical model for evaluating the role of trypanocide treatment of cattle in the epidemiology and control of *Trypanosoma brucei rhodesiense* and *T. b. gambiense* sleeping sickness in Uganda

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ABSTRACT

Background: Human and animal African trypanosomiases impose a large economic and health burden in their endemic regions. Large strides have been made in the control of human African trypanosomiasis (HAT), yet these efforts have largely focused on the non-zoonotic form of the disease. Using a mathematical model with a 10 year time horizon, we demonstrate the role of the cattle treatment with trypanocides in the epidemiology of zoonotic and non-zoonotic HAT in Uganda, and its potential implications on elimination and eradication of the disease.

Methodology/principal findings: We created two compartmental, deterministic models, each comprised of three sub-models: humans, the tsetse fly vector (*Glossina fuscipes fuscipes*), and cattle. We applied these models to two HAT foci in Uganda: the gambiense (chronic, non-zoonotic) form in the Northern Region, and the rhodesiense (acute, zoonotic) form in the Eastern Region. Parameters were derived from prior literature or assumed. In both foci we assumed *G. fuscipes fuscipes* expresses zoophilic biting behavior.

With trypanocide treatment of cattle administered every 3 months, treatment in stage I (representing engagement in active or passive surveillance) had a larger impact on HAT burden than cattle treatment coverage. However increasing cattle treatment coverage allowed for further reduction in prevalence in both foci. Using these model parameters, our estimated R_0 suggests humans cannot alone sustain the HAT epidemic in Uganda.

Conclusions/significance: Even in the absence of zoonotic transmission, loss of a preferred tsetse host species can affect HAT risk. Thus One Health strategies which integrate HAT and animal African trypanosomiasis control may improve the timeliness and sustainability of gHAT and rHAT elimination and eradication in Uganda. Furthermore, such strategies reduce the burden of a high-morbidity livestock disease of economic importance.

Abbreviations: HAT, human African trypanosomiasis; AAT, animal African trypanosomiasis; AT, the African trypanosomiases (AAT and HAT); gHAT, gambiense HAT; rHAT, rhodesiense HAT.

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1. Introduction

Throughout sub-Saharan Africa, the trypanosomiases cause focal epidemics of high mortality in both humans and livestock. With nearly four thousand cases reported in 2014 (Franco et al., 2017), human African trypanosomiasis (HAT) results in an estimated annual loss of over 500,000 Disability Adjusted Life Years (Murray et al., 2012). Combined with economic losses due to animal African trypanosomiases (AAT), the annual cost of the African trypanosomiases has been estimated to exceed US$1 billion (Kristjanson et al., 1999).

In the past 15 years, national sleeping sickness control programs and international efforts have succeeded in driving down the number of new HAT cases reported. Due to this success, the World Health Organization's Strategic and Technical Advisor Group for Neglected Tropical Diseases has targeted elimination of the chronic form (caused by *Trypanosoma brucei gambiense*, gHAT) as a public health problem by 2020, and eradication or zero disease incidence by 2030 (Holmes, 2014).

However, gHAT elimination and eradication are threatened by the uncertain role of animal reservoirs (Büscher et al., 2018) and recent mathematical modeling efforts to confirm or rule-out an this reservoir have had mixed results (Funk et al., 2013; Rock et al., 2017). Furthermore, eradication is considered impossible for the acute form (*T. b. rhodesiense*, rHAT) due to its domestic and wild animal reservoirs. Finally, there is general consensus on the importance of proportion of bloodmeals taken from humans to the success of elimination efforts (Davis et al., 2011; Rogers, 1988).

Control efforts that include both humans and domestic animals may thus have greater efficacy for both gHAT and rHAT control than those that target humans alone. Furthermore, such efforts also contribute to the control of AAT, a production-limiting disease of cattle and a major constraint to the development of crop-livestock agricultural systems (Diall et al., 2017). A One Health approach to control of the African trypanosomiases (AT), in which AAT and HAT control are coordinated, may therefore maintain donor and community engagement as gHAT elimination nears and cases decline, and furthermore maintain control following elimination and thereby prevent re-emergence (Simo and Rayaisse, 2015).

In 1988, D.J. Rogers modeled the effect of sudden loss of a preferred animal host on HAT infection rate, finding an initial increase followed by a later decline (Rogers, 1988). Thus, in addition to the arguments for a One Health approach to AT control immediately above (Simo and Rayaisse, 2015), aversion of cattle losses to AAT may have a direct effect on HAT burden. Since Rogers's work, subsequent authors have modeled the role of animal reservoirs for gHAT (Funk et al., 2013; Rock et al., 2017; Pandey et al., 2015) and the effect of cattle treatment with trypanocides and insecticides on rHAT and AAT (Hargrove et al., 2012). Furthermore, field studies have demonstrated the effectiveness of insecticide treated cattle for vector control in a gHAT focus (Bauer et al., 1995). However, we are aware of no prior efforts to model the effect of cattle treatment with trypanocides ("cattle treatment")—a mainstay of farmer-based control activities, in particular in areas where effective vector control efforts are lacking (Meyer et al., 2016)— on gHAT control, nor to compare this effect across gHAT vs. rHAT foci in which the tsetse fly vector expresses zoophilic behavior. In rHAT foci, this effect captures the role of cattle as a disease reservoir and preferred tsetse host species ("zooprophylaxis"). Conversely, in gHAT foci this captures the role of zooprophylaxis alone.

Separately, we built one three-species model for each of two HAT foci in Uganda: the gHAT focus in Northern Uganda, and the rHAT focus in Eastern Uganda (Franco et al., 2017; "World Health Organization, 2000–2014, Mapping the distribution of human African trypanosomiasis: Uganda"). We assumed cattle are the only animal reservoir for rHAT and that there are no animal reservoirs for gHAT, and in each focus we modeled the effect of cattle treatment with low versus high probability of care seeking in stage I (representing active or passive surveillance in the gHAT focus and passive surveillance only in the rHAT focus). We assumed a single vector species, *Glossina fuscipes fuscipes* (Cecchi et al., 2015). Finally, as the goal of this model was to explore the effect of AAT control in cattle on HAT burden given zoophilic vector behavior—rather than propose a particular control strategy—we assumed no vector control efforts were implemented.

2. Methods

2.1. Model structure

In each focus, we divided a compartmental, deterministic model into three sub-models, one per species (Fig. 1). For humans and oxen a susceptible-exposed-infected-recovered (SEIR) structure was used for both models. Infected flies do not recover.

We assumed human infection was *T. b. rhodesiense* in the Eastern Region and *T. b. gambiense* in the Northern Region. We did not explicitly model cattle and fly infection type, that is infected cattle and infected flies were not stratified by trypanosome species. AAT is caused by *T. brucei* s.l., *T. congolense*, and *T. vivax*; only the rhodesiense subspecies of *T. brucei* s.l. is zoonotic, and clinical manifestations are most severe with *T. vivax* and *T. congolense* (Connor, 1994). We allowed flies in both models to be infected only on their first feeding: pupae are non-susceptible, as are non-teneral (fed) flies. This reflects the teneral effect of *T. brucei* s.l., which does not occur in *T. congolense* and *T. vivax* (Rogers, 1988). In the Northern Region, we allowed humans to be infected only by flies that took their first bite from a human (Appendix A). In the Eastern Region, we allowed humans to be infected by flies that took their first bite from a human, or by flies that took their first bite from a bovid, scaled by the probability that bovid is infected by *T. b. rhodesiense* (Appendix A). In both models we did not consider the source of the fly's first bloodmeal in the force of infection, implying co-infection between *T. brucei* s.l. and other cattle-infective trypanosome species can occur. However we assumed the gHAT and rHAT foci are distinct and that no migration of humans, flies, or cattle occurs between the two foci, and thus no human co-infection with gHAT and rHAT was modeled.

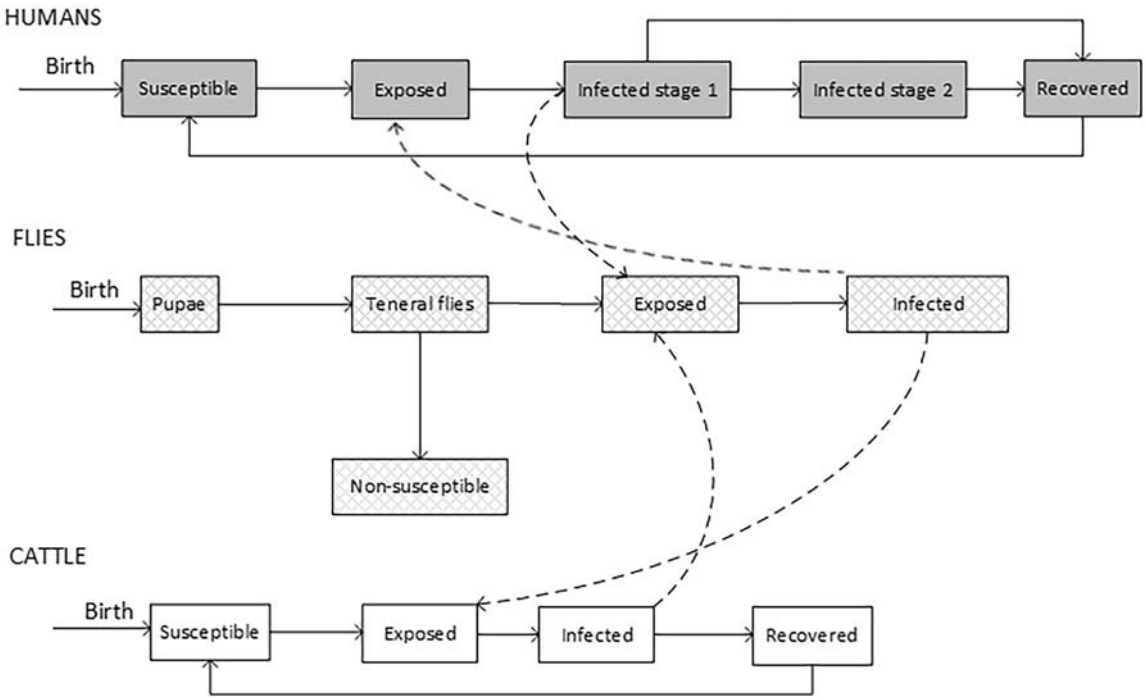

Fig. 1. Model structure. Compartmental deterministic model of the African trypanosomiases.

We assumed trypanocidal treatment of cattle influenced both duration of disease and probability of recovery but did not alter the force of infection, thereby modeling a therapeutic effect rather than a prophylactic effect on AAT (Appendix A). We did not directly model any other trypanosomiasis reservoirs, however our choice of parameters allowed tsetse flies to feed on hosts other than cattle or humans (Appendix B).

Equations for both models are provided in Appendix A. We used R v3.2.2 (R Core Team, 2015) to construct this model and produce all figures. We ran simulations with a one day time step for a time horizon of 10 years. R code used to build and run the models is contained in Appendix E.

2.2. Model parameterization and assumptions

We largely derived baseline parameters from published literature, with several assumed parameters. Parameter values and sources are detailed in Appendix B. Our sources for baseline prevalence data for humans and cattle were: 2002 case reports for humans (Franco et al., 2017), and data from a study conducted in 2008–2009 for cattle (Selby et al., 2013).

HAT and AAT are both transmitted by the tsetse fly, *Glossina* spp. Members of the Palpalis or "riverine" subgenus are the predominant vectors of gHAT. While members of the Morsitans or "savannah" sub-genus are the predominant vectors of rHAT and AAT (Pandey et al., 2015) in general, in Eastern Uganda *G. fuscipes fuscipes* (Palpalis subgenus) is the predominant vector species (Cecchi et al., 2015). Thus, our parameterization assumes *G. fuscipes fuscipes* is the vector in both foci.

Our assumed baseline parameters for both models include the probability a given stage I human case seeks care (=0.10), probability of cattle treatment (=0), frequency of cattle treatment (every 3 months), and fly:human ratio (=2). We set the cattle population as stable by setting cattle mortality rate equal to birth rate. We assumed tsetse fly mortality and birth rates do not change, implying no vector control efforts were implemented: no traps or targets, no insecticide-treated livestock, and no sterile male insect releases. For all models (baseline and sensitivity analyses), at time 0 we assumed all infected humans were stage I, all flies were teneral, infected cattle were dictated by prevalence parameters (Appendix B), and no humans or cattle were in the exposed or recovered compartments.

2.3. Sensitivity analyses

We conducted several sensitivity analyses to explore the importance of cattle treatment and care seeking in stage I, in the absence of vector control. First, we set coverage levels of cattle treatment with trypanocides to 0% (base case), 50%, and 75%, without changing the frequency of treatment. Next, to evaluate sensitivity of both models to varying rates of both stage I care seeking and cattle treatment, we modeled scenarios defined by all combinations of care seeking probabilities of 10%, 30%, and 50%, and cattle treatment coverage of 0%, 50%, and 75%.

3. Results

In the base model, the epidemic curve (incident cases) was a unimodal function over the 10 years it was modeled, with the area under the curve being slightly lower for rHAT than gHAT (Fig. 2a).

Peak incidence was similar for both rHAT than gHAT, while peak prevalence was higher and later for gHAT than rHAT (Fig. 2b). Far more deaths were predicted to be due to rHAT than gHAT (Fig. 2c). The size of the recovered compartment (both rHAT and gHAT cases) was far smaller than the infected compartment throughout the modeled period (Fig. 2d).

3.1. Sensitivity analyses

With stage I care seeking probability fixed at 10%, peak gHAT prevalence was highly sensitive to varying cattle treatment coverage. Unexpectedly, this effect was non-monotonic. Conversely, peak rHAT and AAT prevalences were not appreciably affected by cattle treatment coverage. The most dramatic impact of higher levels of cattle treatment is on the overall cattle population, declining markedly at lower levels of treatment of cattle but being relatively stable otherwise (Fig. 3c). The impact of stage I care seeking was found to be relatively greater than that of cattle treatment in both foci, however within a given stage I care seeking scenario, cattle treatment achieved greater case reductions than stage I care seeking alone (Fig. 3d); all of these effects were monotonic.

4. Discussion

Stage I care seeking, representing active and passive surveillance in the gHAT focus and passive surveillance in the rHAT focus, had a greater effect on overall HAT cases than cattle treatment. However, we found that cattle treatment allowed for further reduction in HAT cases beyond that achieved by increasing stage I care seeking, for instance by increasing active surveillance coverage or passive surveillance capacity. As we assumed fly mortality is fixed, this effect must be through changes in proportion of bloodmeals taken from humans following the loss of cattle to AAT. Consistent with the findings of previous authors, in foci in which the fly:human density ratio is equal to 2 (Appendix B) the estimated R_0 suggests humans alone cannot sustain either the rHAT or gHAT epidemic in Uganda (Appendix C).

Several non-intuitive findings of our model warrant discussion. First, in the absence of cattle treatment, nearly all cattle died. In reality, trypanocide and insecticide treatment is likely higher than that assumed in the base case (0%) (Fyfe et al., 2017; Hamill et al., 2017). Second, the effect of cattle treatment on gHAT was non-monotonic when the probability of human case detection via in stage I is 10% but not at 30% or 50%, and cattle treatment had little effect on AAT prevalence. These findings reflect the small effect of cattle treatment on duration of infection (Appendices A and B), and are largely resolved when the frequency cattle treatment is set to monthly (Appendix D; a slight non-monotonic effect persists for gHAT). Thus the loss of a preferred host species appears to have a non-linear effect on gHAT burden: when the probability of detection in stage I was low, gHAT burden was highest if the population of the preferred host species was maintained, second highest when this population suffered marked losses, and lowest when the this population incurred moderate losses. Rogers hypothesized that eradication of a preferred animal host species would result in an initial increase in human cases as flies must now feed on human hosts, followed by a decrease due to increased tsetse death (Rogers, 1988). As we assumed fly mortality is fixed, no such decrease will be captured in our model. Finally, while peak rHAT incidence was close to peak gHAT incidence, peak rHAT prevalence was far lower than peak gHAT prevalence due to the higher case fatality and shorter disease duration of rHAT vs. gHAT (Appendices B and C). Thus, estimates of disease burden based on cross-sectional data are likely to underestimate the burden of rHAT relative to gHAT.

Of note, we parameterized the cattle sub-model equivalently for both regions. This implies that the dynamics of AAT are equivalent in both foci, and underestimates true AAT burden by ignoring the absence of a teneral effect for *T. congolense* and *T. vivax*.

This model has several limitations, mostly arising from our decision to opt for a simple, interpretable model, and from limitations in available data. Despite the focal nature of HAT epidemics—implying a strong spatial structure—we did not model any spatial heterogeneity within the regional foci (Cecchi et al., 2009). Similarly, we did not model any temporal—seasonal or secular—dynamics for either AAT or HAT. Furthermore, we assumed that there is no animal reservoir of *T. b. gambiense*, and no non-cattle reservoirs for *T. b. rhodesiense*. While there is evidence that pigs may be a reservoir for *T. b. gambiense* (Büscher et al., 2018), and the reservoir role of other domestic and wild animals is well-established for *T. b. rhodesiense*, these simplifications allow for a more interpretable model, and do not unduly interfere with the goal of our model: to explore the effect of a One Health approach to AT control on HAT burden. We allowed tsetse to feed on hosts other than humans or cattle, however our parameterization for the probability a fly's first bloodmeal was taken from a human versus a bovid ignores the presence of other hosts (Appendix A, Section 2). Previous authors have demonstrated that model findings may not be robust to violations of these assumptions (Hargrove et al., 2012; Pandey et al., 2015). Due to limitations in available data, we assumed several parameters—including transmission probabilities and treatment-seeking behaviors—are equivalent across the two foci.

Finally, previous authors have clearly demonstrated the superiority of cattle treatment with insecticides over trypanocides for the control of rHAT, with treatment coverage required to reach $R_0 < 1$ depending on proportion of bloodmeals taken from cattle, wild animal reservoirs, and non-reservoir wild animals (Hargrove et al., 2012; Kajunguri, 2013). As our model did not investigate insecticide treatment of cattle, it provides no evidence to contradict these earlier models. While we know of no previous models have that explored the role of trypanocide treatment of cattle on gHAT control, it is reasonable to hypothesize that insecticide

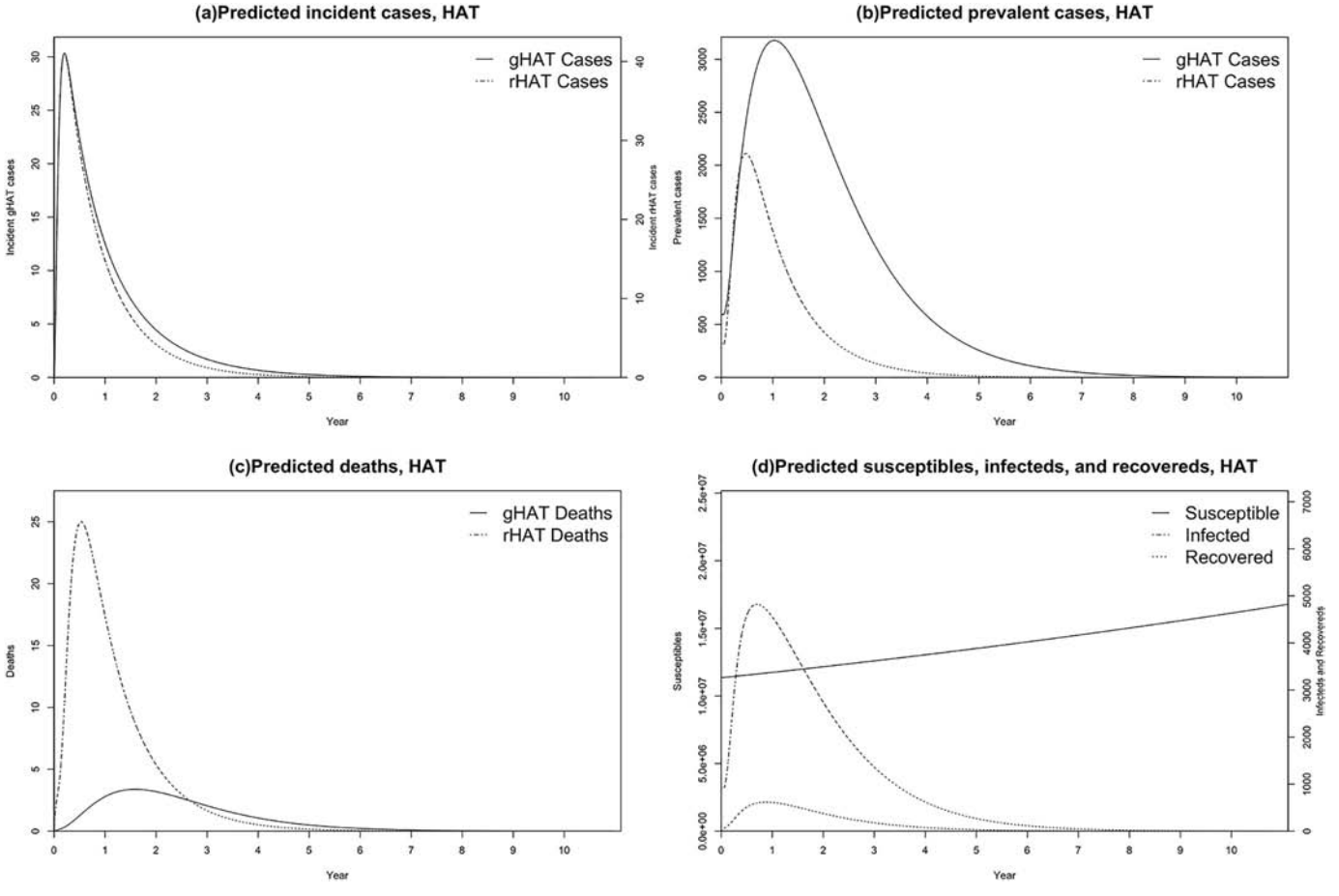

Fig. 2. Base model predictions. Predicted incident cases (a), predicted prevalent cases (b), and predicted deaths (c) due to rHAT and gHAT. Predicted sizes of the susceptible, infected (total HAT) and recovered compartments in the human sub-model across both foci (d).

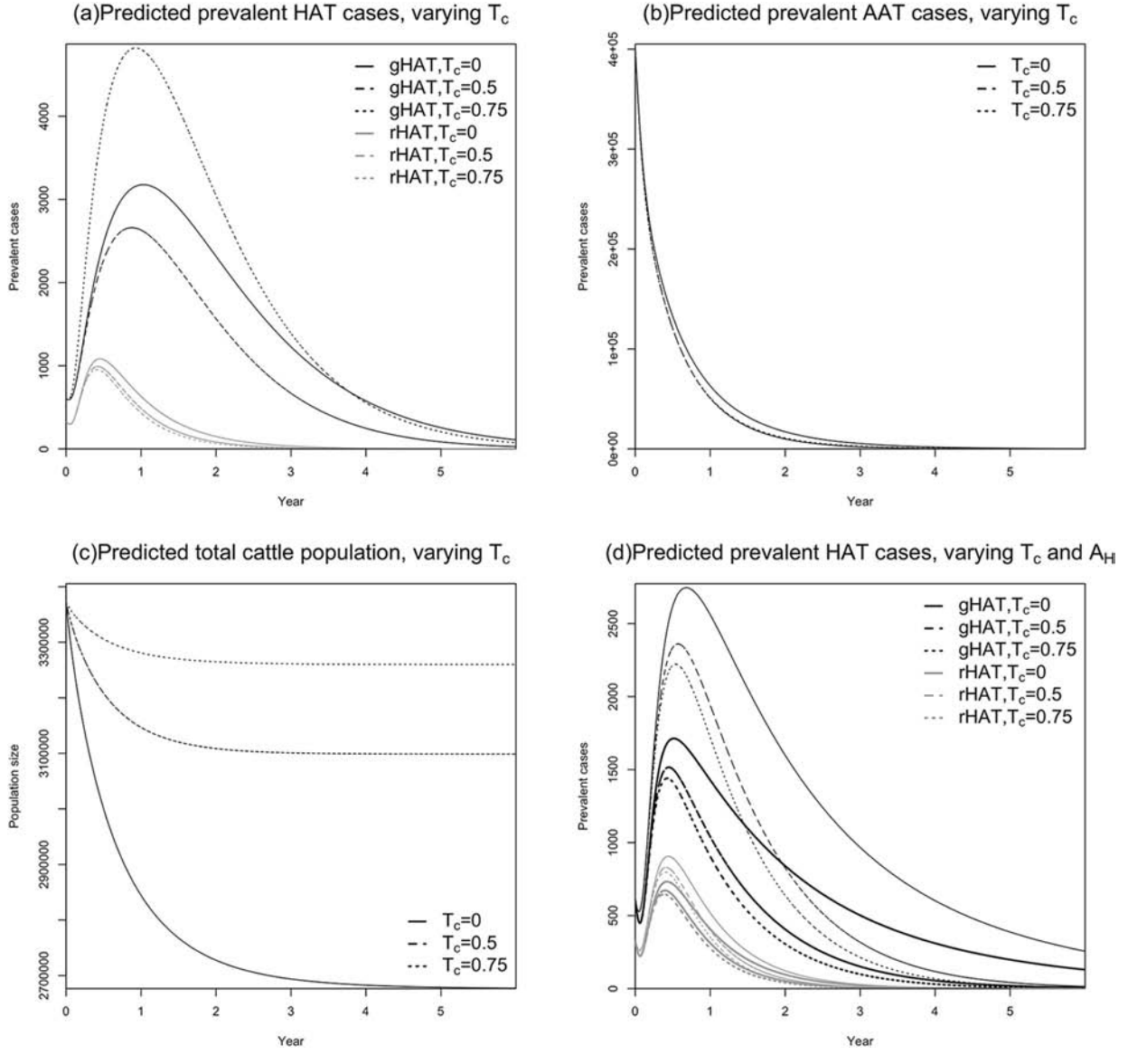

Fig. 3. Predicted outcomes under varying cattle treatment and human surveillance conditions (years 0–5). Predicted prevalent rHAT and gHAT cases (a), prevalent AAT cases (b), and total cattle population (c), under varying cattle treatment coverage but assuming 10% probability of stage I care seeking among humans. (d) Predicted prevalent gHAT and rHAT cases under varying cattle treatment coverage (solid vs. dashed lines) and varying care seeking probabilities (thin = 30%, bold = 50%).

treatment, a method of vector control, would be preferred in this setting as well. Thus, when programmatic goals target HAT control alone, per current evidence insecticide treatment of cattle should always be preferred to trypanocide treatment.

Despite these limitations, this model adds to the existing body of evidence suggesting that the eradication of both forms of HAT may be aided by cattle treatment, and that sustained and timely elimination of gHAT may require consideration of non-human host population dynamics. While our model is the first—to our knowledge—to study trypanocide treatment of cattle in gHAT foci, we note that monitor lizards play an identical role in Hargrove et al.'s (2012) model to that of cattle in our gHAT model. These authors did not study the effect of monitor lizard population dynamics on rHAT risk, however they speculated that the distribution of rHAT may reflect that of monitor lizards. Our model provides evidence that indeed, distribution of a preferred tsetse host species influences HAT risk, regardless of whether that host is a trypanosomiasis reservoir. Furthermore, our work presents a novel approach to modeling HAT that could readily be extended to include additional tsetse host species, more refined modeling of bovine AAT, and vector control.

5. Conclusion

While large gains have been made in recent decades in the control of human African trypanosomiasis, transmission has been sustained at isolated foci (Checchi et al., 2008), and mathematical models suggest that elimination cannot be achieved or maintained without control of non-human reservoirs. Our findings suggest that in even in the absence of animal reservoirs, interventions that reduce losses in non-human tsetse fly hosts may hasten elimination of gHAT. Furthermore, control of AAT implies control of nagana, improving productivity and longevity of cattle in endemic areas. Finally, integrating AAT control—of which trypanocide treatment is a mainstay—with HAT control may maintain donor and community interest in HAT control close to and following eradication, ensuring eradication is both successful and sustained (Simo and Rayaisse, 2015). Pending future study of its cost effectiveness, and despite its inferiority to insecticide treatment for HAT control, our model suggests the addition of trypanocide treatment of cattle to existing control strategies in both rHAT and gHAT endemic areas may optimize effectiveness of HAT control, promote economic growth, and improve animal welfare.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parepi.2019.e00106.

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Declarations of interest

None.

Data statement

This work relies only on data derived from previously published literature.

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