Summary:
Modelling timelines to elimination of sleeping sickness in the DRC accounting for possible cryptic human and animal transmission

Maryam Aliee[1,2], Ronald E Crump[1,2], Samuel A Sutherland[1,3], Ching-I Huang[1,2], Emily H Crowley[1,2], Simon E F Spencer[1,4], Matt J Keeling[1,2,5], Chansy Shampa[6], Erick Mwamba Miaka[6], Kat S Rock[1,2]

[1] Zeeman Institute for System Biology and Infectious Disease Epidemiology Research, The University of Warwick, Coventry, U.K.
[2] Mathematics Institute, The University of Warwick, Coventry, U.K.
[3] Warwick Medical School, The University of Warwick, Coventry, U.K.
[4] The Department of Statistics, The University of Warwick, Coventry, U.K.
[5] The School of Life Sciences, The University of Warwick, Coventry, U.K.
[6] PNLTHA, Kinshasa, D.R.C.

Abstract

Sleeping sickness (*gambiense* human African trypanosomiasis, gHAT) is a vector-borne disease targeted for global elimination of transmission (EoT) by 2030. There are, however, unknowns that have the potential to hinder the achievement and measurement of this goal. These include asymptomatic gHAT infections (inclusive of the potential to self-cure or harbour skin-only infections) and whether gHAT infection in animals can contribute to the transmission cycle in humans. Using modelling we explore how cryptic (undetected) transmission impacts the monitoring of progress towards as well as the achievement of the EoT goal. We have developed gHAT models that include either asymptomatic or animal transmission, and compare these to a baseline gHAT model without either of these transmission routes, to explore the potential role of cryptic infections on the EoT goal. Each model was independently calibrated using available historic human case data for 2000–2020 (obtained from the World Health Organization's HAT Atlas) which includes routine data from active and passive screening for five different health zones in the Democratic Republic of the Congo (DRC).

Our results suggest that to match past case data, we have similar estimated numbers of new human infections between model variants, although they are slightly higher in the models with cryptic infections. We simulated the continuation of screen-confirm-and-treat interventions and found that forward projections from the animal and asymptomatic transmission models produced lower probabilities of EoT than the baseline model. Simulation of a (as yet to be available) screen-and-treat strategy found that removing a parasitological confirmation step was predicted to have a more noticeable benefit to transmission reduction under the asymptomatic model compared to the others. Our simulations suggest vector control could greatly impact all transmission routes in all models, although this resource-intensive intervention should be carefully prioritised.

Introduction

In this article, we take three different model variants for transmission of *gambiense* human African trypanosomiasis (gHAT) and fit them to longitudinal data (2000–2020) for five endemic health zones of the Democratic Republic of the Congo (DRC). We use the fits to make projections and assess the probability of reaching elimination of transmission (EoT) in each health zone under different strategies for each model variant.

Statistical methods were used to incorporate information from the most informative health zones for the asymptomatic human infection model into the analysis of less informative health zones, under the assumption that the parameters associated with the asymptomatic human infection model are biological parameters that would be expected not to differ between health zones.

The statistical evidence was estimated for each model variant in each health zone, this indicates which model variant has the most statistical support. Using this information we created "ensemble" model predictions which capture our uncertainty around 1. cryptic infections and 2. epidemiological components of transmission needed to parameterise the model.

Methods

In this study, we used three previously developed variants of the Warwick gHAT model [2, 3, 1]. These are described below:

- *The baseline gHAT model* – no animal or asymptomatic transmission routes
- *The animal transmission model* – includes animals that can acquire and transmit infection to and from tsetse. The baseline and asymptomatic models consider animals as dead-end hosts that do not contribute to the transmission cycle of gHAT.
- *The asymptomatic transmission model* – includes asymptomatic human infections which may or may not be detectable in the blood through parasitology, and have the potential to self-cure without treatment. The baseline and animal models can also include asymptomatic infections but under those models, asymptomatic infections are always assumed to have the potential to be detected (based on diagnostic test sensitivity) and will eventually develop into symptomatic infections if not treated.

All models include low-risk and high-risk humans and capture systematic non-participation in active screening of high-risk groups in the population and take into account previous improvements in medical, diagnostic and control systems, in the same way as described in previous work [2].

We fit to human case data from 2000–2020 in five health zones of the DRC – Bominenge, Budjala and Mbaya in the former Equateur province, and Bagata and Mosango in the former Bandundu province – chosen to reflect a range of prevalence settings. After fitting we assessed the impact that the different model assumptions made on our EoT model predictions under different intervention strategies. To do this we used our stochastic model which also captures chance events like local elimination. Intervention strategies are outlined below:

1. Mean active screening (*Mean AS*) strategy represents the continuation of screen-confirm-and-treat active and passive screening interventions, using the mean level of active screening coverage for 2016–2020 for each health zone.
2. Mean screen-and-treat (*Mean S&T*) strategy represents the continuation of screening, but in active screening, we assume that serologically positive people will be treated with acoziborole without parasitological confirmation from 2028 (screen-and-treat). We assume that post-hoc confirmation would still be performed (e.g. using Trypanolysis) for case reporting.

3. Mean active screening and vector control (*Mean AS + VC*) strategy which is the same as (1) but inclusive of vector control beginning in 2024, where VC has not already begun, which reduces tsetse populations by 80% after 1 year.

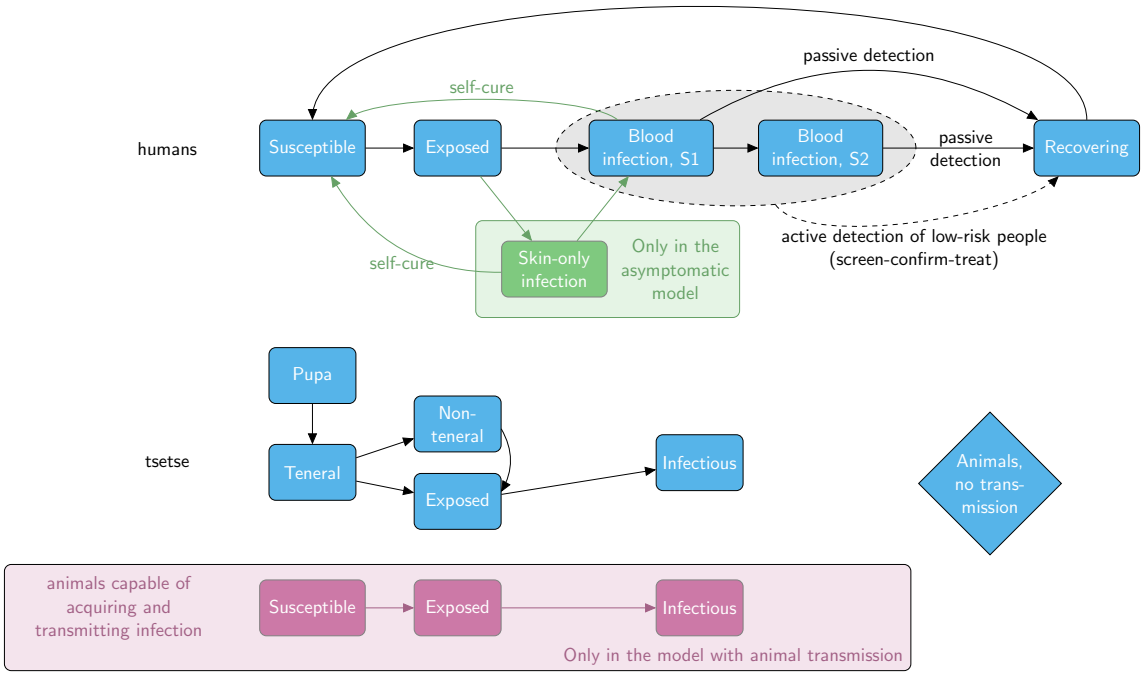

Figure 1: **Model diagrams** Schematic for the three model variants considered in this study. Blue components form the baseline model and are also included in the other two model variants. The pink boxes and arrows are only found in the animal model and the green boxes and arrows are only in the asymptomatic model variant. Births, deaths and transmission pathways are not shown to aid readability. Arrows relating to disease/infection progression are shown. The grey oval and dashed lines indicate infection classes assumed to be detectable using a traditional screen-confirm-treat approach in active screening (although some infections still may be missed due to imperfect diagnostic sensitivity).

Results

For each health zone, the inferred level of new human infections each year is very similar between models although there is a little more variance for the animal and asymptomatic models. When we project forwards and compute the expected probability of EoT under any strategy we find that the baseline model always has the highest probability, the ordering of the next most optimistic model variant depends on the health zone. This pattern is clear in Mosango, but less so in some of the other health zones where the outcomes for different model variants are very close. With the *Mean AS + VC* strategy, there is a great impact on transmission arising from any source and therefore there is a high predicted probability of EoT within a few years following implementation. With the *Mean S&T* strategy there is negligible impact on transmission dynamics for the baseline and animal models as screening without confirmation enables a few more people to be identified who might have tested false negative based on parasitology, but this difference is small. For the asymptomatic model, we

assume that more individuals might test serologically positive but might never be confirmed through parasitological visualisation and therefore there is a small but noticeable improvement in the predicted probability of EoT under the screen-and-treat approach. In this summary, we show results for the Mosango health zone but qualitatively similar results are obtained for the other four health zones. We emphasise that acoziborole is expected to have other benefits such as ease of implementation which are not directly captured in our transmission model outputs here.

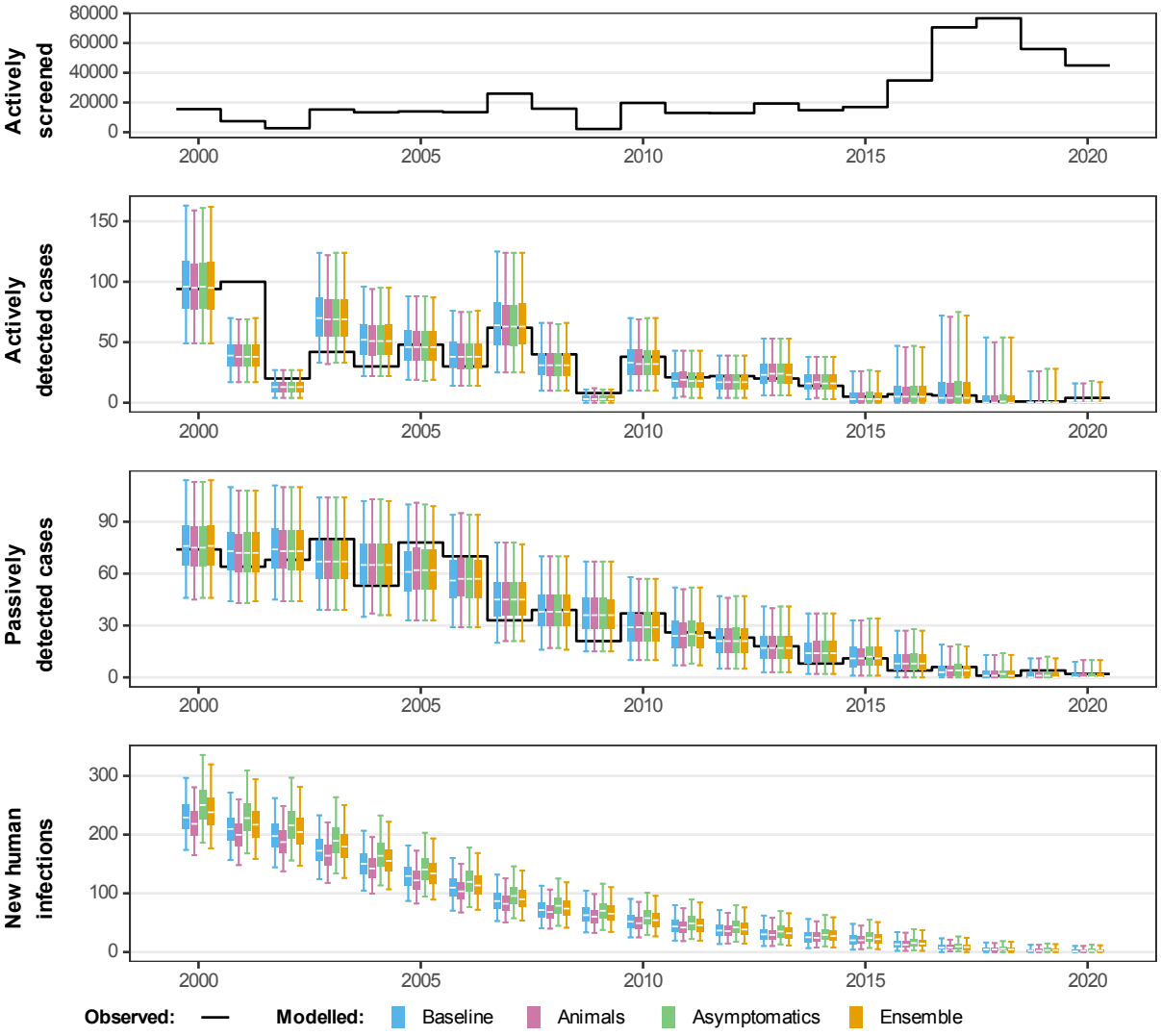

Figure 2: **Comparison of fits in Mosango** using the stochastic model. Blue, pink, green and orange box and whisker plots show the baseline, animal transmission, asymptomatic and ensemble model fits, respectively. The central line of each box is the median, the box is the 50% credible interval (CI) and the whiskers show the 95% CI. Case data are shown as a black line. New infections are estimated through the model fit, however, there is no way to directly observe this so there are no corresponding observational data.

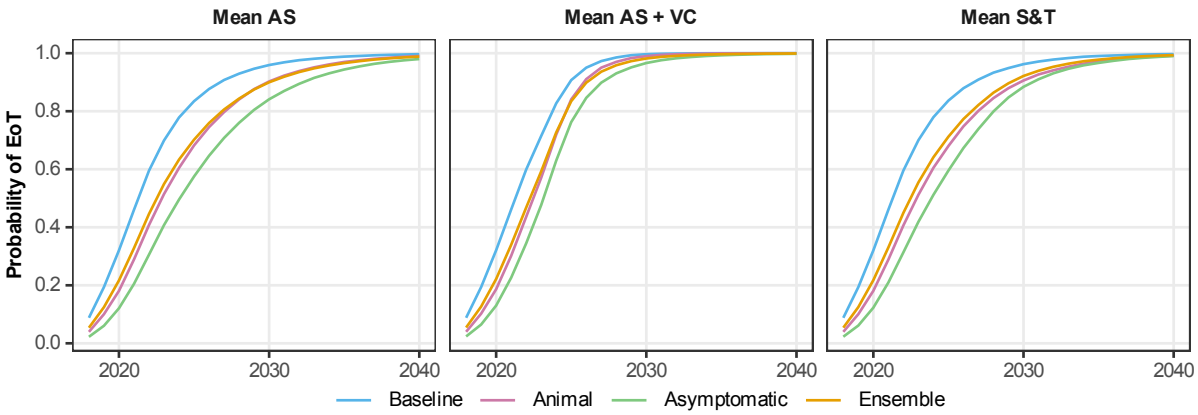

Figure 3: **Comparing elimination of transmission (EoT) in Mosango health zone**, under each model variant and under three different strategies. The blue, pink, green and orange curves represent the models' estimated probability of EoT by each year, calculated by taking the number of realisations where there are no new infections to humans in or after that year until the end of the simulation and diving by the total number of realisations. For the second strategy with vector control (VC), we assume this novel intervention begins in 2024, and for the third strategy using screen-and-treat (S&T) we assume this novel intervention begins in 2028.

Conclusion

Whilst recent evidence suggests that some people can harbour *gambiense* trypanosomes in the skin and have undetectable blood parasitemia, the modelling work presented here suggests that such infections do not play a large role in transmission, if any. We cannot rule out some level of asymptomatic transmission but we expect the impact of this on elimination targets to be relatively small. Likewise, there is some small predicted delay to elimination if we simulate animal transmission in the model, however, in these five health zones of the DRC, it appears relatively unlikely that non-human animals are contributing to transmission.

If there is some asymptomatic transmission, a screen-and-treat strategy with a safer new drug would be expected to be more beneficial compared to if there is no asymptomatic transmission. For infections arising from asymptomatics, non-human animals or people not participating in screening, vector control could help to reduce transmission quickly although it should be coupled with suitable detection and treatment and vector control will not be necessary in all settings.

In the future, we would also like to explore the impact of screen-and-treat approaches on passive screening, which is not simulated here, and fit the models to more health zones and health areas of the DRC and other countries.

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