HAT

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Contents

1 Introduction

Human African Trypanosomiasis (HAT), which is fatal if left untreated, continues to present a serious health risk to humans in vast regions of Sub-Saharan Africa. It is caused by two sub-species of the protozoan parasite *Trypanosoma brucei* (*T.b.*), and is transmitted by tsetse flies. The sub-species, *T.b. gambiense*, is responsible for the majority of reported cases of HAT, and is transmitted by tsetse flies. Over the last decade, expanded control efforts have led to a decline in the number of new HAT cases, spurring the WHO to include *T.b. gambiense* HAT on its roadmap for 2020 elimination.

To inform implementation of WHO's elimination goal, it is imperative to understand the likelihood of whether the control interventions are sufficient and, if not what other complementary strategies would synergistically facilitate achieving the 2020 target.

We developed a mathematical model for Gambian HAT to evaluate vector control as well as screen and treat strategies. We will calibrate our model

to data from various "foci of infection" such that they vary in terms of transmission intensity or/and ecological settings. Currently, we are trying to use data from Boffa, Guinea which is classified as "medium transmission intensity" foci and where livestock play a limited role in HAT transmission cycle.

A brief introduction to various aspects of Gambian HAT and tsetse fly follows:

1.1 Gambian HAT

Gambian HAT is caused by *T.b.gambiense* and transmitted by the *Palpalis*-group species of tsetse, particularly subspecies of *Glossina fuscipes* and *Glossina palpalis*. This group of tsetse is commonly known as **riverine tsetse** and generally infest relatively humid habitats fringing the rivers, lake shores and wetlands of West and Central Africa.

The disease progress over several years from the initial symptoms of fever, headaches and lymphadenopathy (Stage I) through neuropsychiatric disorders (Stage II) and sleep disturbance (hence the name) and in most cases death.

1.2 Tsetse fly

In contrast to other vectors like mosquitoes, blackflies and sandflies, both sexes of tsetse rely exclusively on blood for all their nutritional needs. Tsetse become infected after feeding on an infected host. The trypanosomes undergo a complex process of maturation in the fly and after a period of about 20-40 days the infective forms appear in the salivary glands of the fly which, thereafter remains potentially infective to any humans it bites. Most flies are inherently refractory to infection and even those that are not refractory to infection are most susceptible during their first blood meal.

Tsetse have an unusual form of reproduction, termed adenotrophic viviparity, in which the larva develops within the female. From the age of about 6 days, adult females produce a single egg which matures in the uterus for about 7-12 days, the duration being dependent of temperature. A single mature third-stage larva is deposited by the female on loose soil and it burrows into the ground and pupates. The time to deposition for subsequent larvae is shorter than for the first offspring and the time between offspring decreases with increasing temperature. A mature adult fly emerges 20-40 days after deposition and this pupal duration also decreases with increasing temperature. This resultant low rate of reproduction is only sustainable because of relatively long life span of tsetse flies.

- ***Mortality***: In one field study, female mortality was about 10% per day in newly emerged flies, fell to about 2% by age 10 days, increasing slowly thereafter. The pattern was similar for male but mortality increased much more rapidly with age. The changes relate to low-fat levels and poorly developed flight musculature in newly emerged flies, resulting in the double difficulty of needing to find and feed on a host rapidly but with a limited flight capacity. Accordingly, many young tsetse flies either die of starvation, or by attempting to feed off high-risk hosts such as humans. Those that do feed successfully build up energy reserves and flight muscles, and subsequent mortality declines. Increased mortality in older flies is associated with increased wing wear resulting in diminished flight capacity. Adult mortality also increases with temperature and may be up to six times as high in the hot part of the year as in the cool part.

- ***Abundance and distribution***: Tsetse populations are able to persist at remarkably low densities. Obtaining reliable estimates of absolute densities of tsetse for sparse populations is difficult, but it seems likely that they can survive at densities of 1 tsetse/km^2 or less, while maximum densities seems to be in order of 10,000 tsetse/km^2. Tsetse are

highly mobile, moving up to 1 km per day. For the more typical habitats of riverine tsetse, flies are confined to the vegetation fringing rivers and lakes and hence displacement is largely along river margins and lake shores. The important consequence of the high mobility of tsetse is that populations of tsetse are seldom isolated and hence migration of tsetse into and out of an HAT focus is the norm.

- ***Feeling interval***: Male and females are obligate blood feeders obtaining meals at 2-5 day intervals. The blood meal provides all of the fly's requirements for energy, water and growth, including production of larvae. Hence for tsetse, it imperative to find and feed on a host regularly to avoid starvation. The defensive behavior of hosts and predatory insects (e.g. Asilidae (robber or assassin flies) and Bembicidae (a family of wasps)) in the host vicinity also pose a risk to feeding tsetse.

- ***Host selection***: Tsetse use a combination of olfactory and visual cues to locate their hosts. In general savannah tsetse feed on Suidae and Bovidae, particularly warthog and buffalo in wilderness area and cattle where they are present. Humans are rarely bitten by savannah tsetse; odours and visual stimuli produced by humans are repellant and those who do bite humans tend to be young and/or in an advanced stage of starvation. Riverine tsetse have broader range of hosts which can include primates, Suidae, Bovidae and reptiles, particularly the Nile monitor lizard. Humans are not repellent to riverine tsetse and as a consequence, humans can form an important part of their diet.

1.3 Trypanosome biology

The latent period between initial inoculation of *T.brucei* and a mammalian host becoming infectious is about 7-14 days. The duration of subsequent infection ranges between several months and years and is strongly right-skewed with some cases persisting for many years without morbidity or death. The mean duration for stage I is 17 months and for stage II is 16 months. Severe illness and/or hospitalization during stage II may effectively remove the human host from the population of hosts by preventing contact with tsetse flies, in which case the mean duration of infectiousness would be 17 months.

The probability of a fly being infected depends not only on the levels of parasitaemia in the host but also the age, nutritional condition, sex and species of the fly itself. The 'teneral effect'. Newly emerged unfed tsetse ('teneral' flies) that are typically less than 3 days old are much more susceptible to infection with subspecies of *T.brucei* at their first blood meal than

older flies.

1.4 Control for Gambian HAT

Due to the absence of a vaccine, intervention strategies against HAT rely on vector control and on active and passive case detection followed by treatment. These two strategies were initially effective, and the disease was nearly eradicated in the early 1960s. However, a collapse of surveillance and control activities int he endemic countries, often due to periods of political instability, led to progressive re-emergence of the disease since early 1990s.

Since the resurgence of HAT, expanded control activities has facilitated an overall decline in the number of new cases of HAT being reported to WHO annually. The achievements of the past 20 years have been realized almost exclusively through active case detection and treatment. Screening of the population is based on the use of Card Agglutination Test for Trypanosomiasis followed by staging of positive cases through examination of the cerebrospinal fluid which involves a lumbar puncture.

Currently, the drugs used to treat Gambian HAT are **pentamidine** for stage I and **nifurtimox-eflornithine** combination therapy for stage II. While vector control has not been an important part of efforts against Gambian sleeping sickness, the recent development of cost-effective methods to control riverine tsetse suggests that tsetse control will form an important part of efforts to eliminate Gambian HAT in the future.

1.5 Usefulness of HAT models

The few models of HAT that exist suggest that elimination of HAT will not require killing the last fly or finding and treating the last case. Rather, reducing the mean infectious period of humans through case detection and treatment, and reducing the longevity and density of tsetse flies through vector control may eliminate transmission. There are many questions that HAT models can be used to answer:

- What percentage of a human population needs to be screened and treated to eliminate a focus of Gambian HAT transmission ?
- At what frequency should such a screen and treat program be repeated ?
- What deduction in the density and longevity of tsetse flies is required to eliminate transmission of HAT ?

- How long must interventions be applied to eliminate a focus ?
- Why is HAT not more widespread, and will movement of reservoir hosts, tsetse or infected humans cause it to spread ?
- How does HAT persist at the low levels of prevalence that have been measured in humans and tsetse flies ?

2 Data

2.1 Available data

- Plot of prevalence data
- Age Distribution of HAT
- Summary of Data
- Survey Results
- Between 1997-2009
- Disease Stages
- Some other data from papers

NOTE:

1. Before 2008, no medical survey by mass screening was performed in the area and all HAT cases were diagnosed passively in that period.
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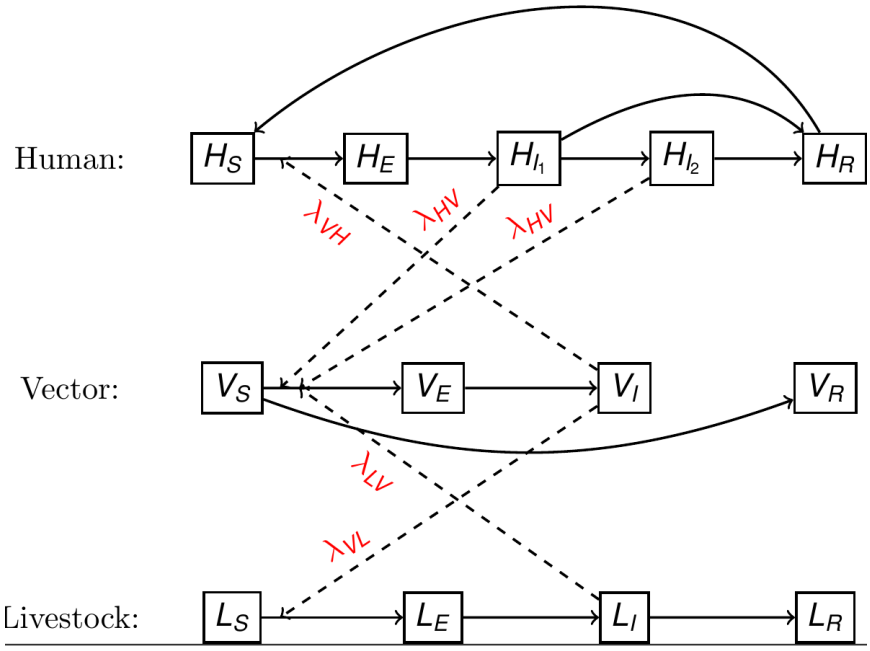
3. In 2008 and 2010 medical surveys were organized by mass screening but only in selected villages (where new cases had been passively diagnosed in the previous years).
4. In 2012 and 2013, all villages from the area were included in the surveys.

3 Model

We constructed a three-species SEIR differential-equation model for *T.b.gambiense* trypanosome infection among tsetse, humans and livestocks based on previous work Rogers. The population of each species: tsetse (V), humans (H) and livestocks (L) is divided into 4 states: susceptible (V_S, H_S, L_S), exposed (V_E, H_E, L_E), infectious (V_I, H_{I_1}, H_{I_2} L_I) and recovered (V_R, H_R, L_R) respectively.



- **Tsetse Dynamics:** Susceptible tsetse can only become infected during their first blood meal, which they take with rates a_H and a_L on humans and livestocks respectively. Tsetse do not become infected, if they do not become infected during a period of time $(1/\sigma_V)$ immediately after emergence. After an incubation period of $1/\tau_V$, tsetse become infectious and do not recover and finally die.
  Birth and death rate: We take birth rate for tsetse (B_V) to be constant, whereas the death rate to be increasing quadratic to measure the effect of intra-species competition on death rate:

$$\mu_V = \mu_{V_0}(1 + \mu_{V_1} V)$$

  where μ_{V_0} is the death rate in the absence of intra-species competition, while μ_{V_1} measures the effect of intra-species competition on

death rate. **Note: Is this assumption alright ? Specially when vector control needs to be measured.** *We need some sense of vector population for foci*

- **Vector Control**: The vector control methods to be considered are:
  - *Traps, Insecticide*
  - *Sterilized male release*

  How do we model these ?

  1. Traps and Insecticide techniques will decrease the current population of tsetse in a foci, that can be captured in model by decreasing population of tsetse.
  2. Other way to capture this could be from biting rate. So, using traps and insecticides lead to lower population density of tsetse which in turn results into less exposure of tsetse to humans and lowering the chances of bites.
  3. For Sterilized male release technique, effects will be bit delayed.
  4. Pupae stage (Is it important ?)
  5. Seasonality in Tsetse population, Mobility of Tsetse vectors.

- **Human Dynamics:** Humans become infected when bitten by an infected tsetse with probability β_{H}, incubate for a period of $1/\tau_{\mathrm{H}}$, and then are stage I infectious. Without treatment individuals in stage I progress to stage II after a duration of $1/\gamma_{\mathrm{H}_1}$ and dies after a duration of $1/\gamma_{\mathrm{H}_2}$ if left untreated in stage II. We assume that only tsetse become infected only after biting stage I infectious individuals as stage II infectious are severely ill at home or hospital and thus hardly come in contact with tsetse.

- **Human Treatment:** Case detection and treatment still remains one of the primary methods of controlling gambiense HAT. The case detection is conducted by active case-finding through mobile teams or when patients visit health structures (passive case finding). In our model, the rate at which an infectious individual in any stage receive treatment depends on efficacy and coverage of treatment. The coverage of treatment at stages I and II is defined by parameters ϕ_1 and ϕ_2 as

$$\phi_i = P_i P_{i+/D} P_{iT/+}$$

where for i = 1, 2, P_i is the probability that a stage i patient gets a CATT test, $P_{i+/D}$ is sensitivity of the diagnostic tests that is the probability that a stage i patient gets a positive CATT test and a positive parasitology test, and $P_{iT/+}$ is the probability that a stage i patient gets treatment after getting positive CATT test and a positive parasitology test.
A stage I patient remains in stage I and later progresses to stage II in case of treatment failure. Similarly, treatment failure in stage II results into patient either remaining stage II infectious and later dying due to the disease or dying due to the side effects of the stage II treatment with a rate of p_2.

- **Livestock Dynamics:** Livestocks are modeled similar to humans, but only one infectious class is considered. Livestock can become infected after being bitten by an infected tsetse with probability β_L, incubate infection for a period of $1/\text{tau}_L$ and are infectious for a period of $1/\gamma_L$ and then immune for a period of $1/\delta_L$. Few concerns regarding Livestock modeling/dynamics:
  - Do Livestock die from AAT/nagna ?
  - Are we only treating Livestock as reservoir ? Then, do we need full dynamics ? *Not important for Boffa.*

3.1 Model Equations

- *Tsetse* :

$$\begin{aligned}
\frac{\mathrm{d}V_S}{dt} &= B_V V - (a_H + a_L + \sigma_V + \mu_V)V_S, \\
\frac{dV_E}{dt} &= (a_H\lambda_{VH} + a_L\lambda_{VL})V_S - (\tau_V + \mu_V)V_E, \\
\frac{dV_I}{dt} &= \tau_V V_E - \mu_V V_I, \\
\frac{dV_R}{dt} &= [a_H(1-\lambda_{VH}) + a_L(1-\lambda_{VL}) + \sigma_V]V_S - \mu_V V_R,
\end{aligned} \tag{1}$$

- *Human* :

$$
\begin{aligned}
\frac{dH_S}{dt} &= B_H H + \delta_H H_R - a_H \beta_H V_I \frac{H_S}{H} - \mu_H H_S, \\
\frac{dH_E}{dt} &= a_H \beta_H V_I \frac{H_S}{H} - [\tau_H H_E + \mu_H] H_E, \\
\frac{dH_{I_1}}{dt} &= \tau_H H_E + [-\phi_1 \epsilon_1 - (1-\phi_1)\gamma_{H1} - \mu_H] H_{I1}, \\
\frac{dH_{I_2}}{dt} &= (1-\phi_1)\gamma_{H1} H_{I1} + [-\phi_2 \epsilon_2 - (1-\phi_2)\gamma_{H2} - \phi_2(1-\epsilon_2)p_2 - \mu_H] H_{I2}, \\
\frac{dH_R}{dt} &= \phi_1 \epsilon_1 H_{I1} + \phi_2 \epsilon_2 H_{I2} - (\delta_H + \mu_H) H_R,
\end{aligned}
\tag{2}
$$

- *Livestock* :

$$
\begin{aligned}
\frac{dL_S}{dt} &= \delta_L L_R - a_L \beta_L V_I \frac{L_S}{L}, \\
\frac{dL_E}{dt} &= a_L \beta_L V_I \frac{L_S}{L} - \tau_L L_E, \\
\frac{dL_I}{dt} &= \tau_L L_E - \gamma_L L_I, \\
\frac{dL_R}{dt} &= \gamma_L L_I - \delta_L L_R.
\end{aligned}
\tag{3}
$$

The probabilities of a susceptible tsetse becoming infected from a blood meal from humans and animal hosts repectively are

$$
\begin{aligned}
\lambda_{VH} &= \beta_{VH} \frac{H_{I_1} + \kappa H_{I_2}}{H}, \\
\lambda_{VL} &= \beta_{VL} \frac{L_I}{L}.
\end{aligned}
\tag{4}
$$

where β_{VH} and β_{VL} are transimission probabilities from human to tsetse and animal hosts to tsetse respectively and κ is 0 or 1 depending on our belief about whether individuals in stage II contribute to transmission or not.

The total population sizes are given by $V = V_S + V_E + V_I + V_R$ for tsetse, $H = H_S + H_E + H_I + H_R$ for humans and $L = L_S + L_E + L_I + L_R$ for animal hosts. The model parameters and their estimates used from literature that are used in simulations are in the table below.

3.2 Model Parameters

- Tsetse

Parameter	Definition	Value	Interval	Reference

- Human

Parameter	Definition	Value	Interval	Reference

- Livestock

Parameter	Definition	Value	Interval	Reference

- Transmission

Parameter	Definition	Value	Interval	Reference

- Control

Parameter	Definition	Value	Interval	Reference

4 Notes

- Modeling population changes of tsetse:
  - *Birth and death models:*
    In Rogers (1990) and Rogers et al. (1994), they estimated birth rates from ambient temperatures and overall density-independent mortalities from observed changes in the population. The important result of this approach was that it was always found essential, for population stability, to include density-dependent mortality in the model.
    Hargrove & Williams (1998) modeled adult tsetse mortality to be a linear function of maximum temperature whose coefficients were estimated by the optimized simulation procedure. Results from this study supports indications from other work of the overriding importance of temperature in controlling the density-independent growth rates of tsetse populations.
  - *Models including migration:*
    Williams et al. (1992) assumed diffusive movement and logistic growth, making no assumption about the mode of operation of the density-dependent processes, except that they applied only to

the birth and death processes, not to dispersal rates. In simple terms, it was assumed that each population has a characteristic carrying capacity and that the growth rate slows as this level is approached. This approach has been used by Hargrove (2000) to model the re-invasion of areas cleared of tsetse and by Hargrove et al. (2000) to model the use of insecticide-treated livestock as a method of tsetse control. It could be used for modeling observed changes in natural tsetse population, both natural and as a consequence of human intervention.

- Ask Bruno about people who did not participate in surveys to take into account any sampling biased.
- Email to contact people in Belgium working in DRC for data.