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*SCHISTOSOMIASIS TRANSMISSION*

Timestep [1 month] *t*

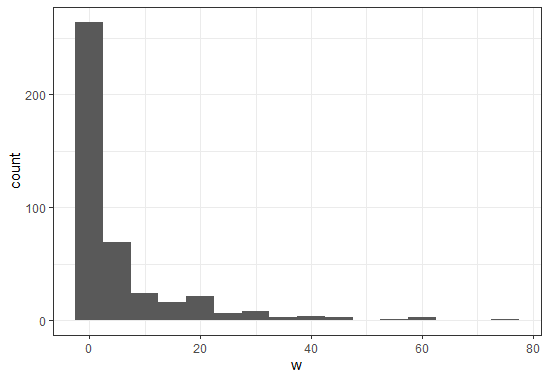
Human hosts *i = 1, …, N*

**INITIAL POPULATION**

Population is initialised as the following:

* Initial age distribution based on Uganda lifetables (upper histogram). SAC are about 31% of the population.
* Initial worm distribution in the population (lower histogram)





* Individuals are assigned with sex and individual susceptibility to infection (described below)

In the sections below, all the quantities reported with the subscript *i* refer to the *i-th* individual in the simulated population.

At each timestep *t* the following events occur in the same order as described here*:*

**DEMOGRAPHY**

At each time step, births, deaths, aging and migration define the demography, according to **birth rates**, **death probabilities** and **crude net migration rate** publicly available for Sub-Saharan Africa. The parameters related to the African demography describe an expanding population, displayed in the graph below where no infection is simulated. Ten stochastic seeds (grey lines) with the mean (black line) are displayed for a simulation of T=200 years.



**Births**

The number of **births** for the current month *t*is determined by a Poisson drawn with a rate given as:

where

is the crude **annual** birth rate for Uganda (per **1000** individuals)

is the population size at timestep *t*

The population is updated with *# births* new individuals, assigned with age=0 and worm load=0. Sex and individual susceptibility are also drawn as described in the next section.

**Deaths**

Each month individuals can dye according to an age- and sex- specific **death probability** available from the WHO Demography App for Sub-Saharan Africa.

In case of **death,** the individual is removed from the population.

**Migration**

The number of individuals migrating in the time step is drawn from a Poisson with

where

represents the **net** migration rate (per **1000** individuals)

Only individuals between 5 and 55 years old are assumed eligible for migration.

**Discussion point:** not constant population size. Migration is not enough to balance the positive population growth.

I had explored this aspect using two different methods (**these options are discarded at the moment**):

1. **The reaper.**

The number of **births** for the current month *t*is determined by a Poisson drawn with a rate given as:

where

is the crude **annual** birth rate for Sub-Saharan Africa (per **1000** individuals)

is the population size at timestep *t*

The population is updated with *#births* new individuals, assigned with age=0 and worm load=0. Sex and individual susceptibility are also assigned as described in the next section.

Each month individuals can dye according to an age- and sex- specific **death probability** available from the WHO Demography App for Sub-Saharan Africa.

In case of **death,** the individual is removed from the population.

**Updating age and population quantities:**

After births and deaths occurred, individual age is (monthly) incremented and population size, number of SAC and cumulative exposure accordingly updated.

The reaper (used in WORMSIM) occurs annually and all the times that the population size exceeds a given maximum value, the population is reduced of 10%. This mechanism **preserves the age distribution over time**, but the population dynamics are totally dependent on the chosen input value.

To produce the plot below I am using the reaper mechanism with a max population of 700 individuals. Ten stochastic seeds (grey lines) with the mean (black line) are displayed.

**Population size over time**

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1. **Replacing dead individuals**

Each month individuals can dye according to an age- and sex- specific **death probability** available from the WHO Demography App for Sub-Saharan Africa.

In case of **death,** the individual is removed from the population and replaced by a new born: the age is set to zero, the sex re-assigned and the parasitological quantities reset. This mechanism **keeps constant the population size** (to the same value as the initial population), but it **does not preserve the age distribution over time**, since the births are not defined by an actual birth rate.

The two histograms below compare the **age** distribution for the initial population given a Sub-Saharan Africa demography (left panel) and the age distribution at the end of the simulation (500 years) (right panel), assuming only birth/death events and no transmission of the disease.



**INFECTION DYNAMICS**

**EXPOSURE to infection**

**Force of infection acting on individual *i* : number of new juvenile worms acquired [jw1]**

are considered juveniles and not able yet to reproduce

*cloud* = number of cercariae in the reservoir

*zeta =* overall exposure rate (it mainly drives transmission --> the level of true prevalence)

= age-specific contact (exposure) rates. It could be either step-wise or linear interpolation. It corresponds now to a moderate adult burden setting, according to Toor J., *et al.* (2018).



: level of aggregation of worms in the population, including individual propensities to infection. It has a range in Graham (2021). It affects the prevalence of high intensities of infection.

individual susceptibility to infection. It is assigned at birth and lasts lifelong.

**WORMS**

New acquired juvenile worms are not paired and they will pass through three maturation phases (, , ). The total **pre-patent period** is assumed to be 3 months.

Juvenile worms at stage 3 (*jw3)* are considered mature and patent to pair. Worms that will not pair do not survive to the next month.

A random portion of *jw3* is assigned male sex. The rest of the basket are female worms.

**Mature worms are paired [wp] and considered as infective units for the rest of the transmission cycle. Paired worms can produce eggs.**

**Discussion point:** probability of insemination. For now I assume all pairs reproduce.

number of worm pairs, are computed as the minimum between male and female worms in the group *jw3.* This means that we consider the all the possible couples are formed.

, expected egg load

: number of male mature worms for human host *i*

: number of female mature worms for human host *i*

: number of detected eggs from human host *i*

: fecundity of female worms in eggs/worm pair. Range studied in De Vlas (1992). It has effect on the shape/slope of the bounce backs.

**Discussion point:** correct definition of . When is it defined as eggs/worm pair and when as eggs/worm pair/slide ? Does this parameter account for accumulation of eggs?

: aggregation parameter for detected egg counts. It drives the discrepancy between true prevalence and egg-based prevalence. De Vlas (1992) takes into account quantity of stool and repeated sample to quantify it.

**CONTRIBUTION to the reservoir**

**Individual contributions []**

**CONTROL**

*(****MDA* assumptions*: 75% coverage, 80% efficacy, annual to pre-SAC and SAC, 10 years)***

If *t* is the time of MDA:

If age of individual *i* is in the target population: with the input **coverage**, the total amount of (**adult) worms** of that individual is **reduced** of a portion equal to the drug efficacy.

**WORM PAIRS are updated for the next month:**

The worm pairs formed in the current month are added. A portion of worm pairs do not survive to the next time step, according to the assumption of exponential survival of worms.

*:* 1 - survival probability of worms from the previous month

: lifespan of an adult worm in the human host [years]

**RESERVOIR/CLOUD**

**Assumption 1:** snails are not explicitly modelled yet, but a **general cloud** with the two larval stages is included.

The amount of miracidae **[m\_in]** entering the reservoir at time *t* is given by:

We assume miracidiae infect snails and spend 1 month within the intermediate host. We also express the relationship between the burdens of miracidiae and cercariae as a hyperbolic saturation function. This could account for saturation of susceptible snails. Thus, the amount of cercariae in the reservoir **[cloud]** at time *t* is further updated with:

Where

: is the number of miracidiae released in the reservoir at time *t-1.*

is the number of cercariae produced for each miracidia, in absence of density-dependence. It drives the initial slope of the function.

: is the saturation level for cercariae production. It defines the maximum plateau of the function.

We assume particles not infecting humans do not survive in the cloud to the next month. The amount of particles in the cloud is used at next time step to determine the rate of new worms acquisition and the cycle can restart.

**Assumption 2:** snails are explicitly modelled via a compartmental SEI model, where the amount of miracidiae excreted by human hosts drive the FOI on the snails and the outcome of cercariae shed by infected snails will increase and update the infective cloud.

The model dynamics are described by the following system of ODEs.

The variables represent:

* S(t): burden snails **susceptibles** to miracidiae infection
* E(t): burden of **exposed** snails. They have been invaded by miracidiae, but larvae are not patent yet, so snails do not shed cercariae at this stage.

**Discussion point:** 1. Should the mortality of exposed snails be higher due to infection? 2. Is there evidence for portion of exposed snails to naturally recover and solve infection without moving to the infective stage?

* I(t): **infected** snails. They shed patent cercariae and contribute to the central cloud.

Parameters:

, is the birth rate for snails, according to a logistic growth due to competition for resources. Only S and E contribute to reproduction of snails, because infection from miracidiae produce infertility in snails. maximum reproduction rate. N = S+E+I, total population of snails. *k =* carrying capacity for the logistic growth.

, is the natural mortality rate for snails

, is the force of infection from humans to snails. c = exposure rate for snails. This could also be a calibrating parameter. probability of a successful invasion for a single miracidia getting in contact with the snail. It is for now computed from a Poisson such as P(x=1)=0.8\*exp(-0.8) using the infection rate from Anderson & May (1991). However, I would consider it a calibrating parameter as well. (*Or look for data about!*)

, is the infection rate. = the maturation period of miracidiae within the snail.

, is the additional mortality due to infection.

TO DO:

* Use the outcome in terms od cercariae to define the FOI from snails to humans.
* Combine different time steps (monthly for human population dynamics, daily for snail population dynamics.

**OUTCOMES**

**Prevalence timelines**

1. True prevalence: presence of at least 1 adult worm
2. Egg-based prevalence: portion of population detected with at least 1 egg
3. Egg-based prevalence in SAC: portion of SAC detected with at least 1 egg
4. Prevalence of high intensity of infections: portion of population detected with >400 epg



**Fig 3.** Prevalence timelines from a simulation of T=200 years. α=0.28, =0.9 to account for portion of miracidiae dying or not infecting snails, . Ten stochastic seeds (light lines) with the mean (dark line) are displayed. MDA for 30 years is included.

With this version of the model, the amount of particles in the reservoir has an upper bound defined by the *b* parameter and the prevalence goes to the equilibrium. I think it may be difficult to properly estimate *b.* The figure suggests that assumption of saturation of particles in the reservoir mitigates the effect of MDA on the prevalence of infection, with respect to what is observed in **Fig 2**.