Decision support for malaria-control programmes – a system dynamics model

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Although malaria claims millions of casualties every year there are hardly any recent efforts to model its epidemiology in order to support decision-makers of malaria-control programmes. There have been ample attempts to develop analytical models during the era of WHO malaria eradication programmes (1950–1970), but none of them was detailed enough to honour the high complexity arising from the interdependencies of the environment, the parasite, vector and host system. This paper presents a multi-group system dynamics model of the spread of malaria in an African country. Epidemiological details are included so that the impact of several intervention programmes can be simulated and analysed. The model's basic structure is fully described and some examples of the simulations are presented. It becomes obvious that detailed multi-group system dynamics models are valuable to assess the effectiveness and efficiency of anti-malaria campaigns.

Keywords: epidemiological model, health care policy and management, malaria, system dynamics, strategic decision support

1. Introduction

The first mathematical model of epidemiological processes was developed by Sir Ronald Ross about 100 years ago in order to predict the spread of malaria [28,29]. This parasitosis has always caused more morbidity and mortality than any other infectious disease. It is estimated that about 300–500 million infections and 2–4 million deaths are due to malaria every year [9]. The Organisation of African Union estimates that the direct and indirect costs of malaria in Africa alone are more than 3600 million US$ every year [1]. The high morbidity and mortality as well as the high complexity of the infection cycle call for mathematical modelling. Thus, the first simple model of Ross was followed by several other analytical models [4–6,12,19,23,26], mainly using differential equations or Markov chains to predict the spread of the disease. The majority of these models was developed in the late fifties or sixties while the World Health Organisation (WHO) pursued the malaria-eradication programmes. The mathematical models predicted that malaria could be eradicated world-wide by fighting the anopheles mosquito. Unfortunately, the ecological system was so complex that these programmes failed in tropical countries. WHO had to accept that malaria will persist or even increase in the tropics. Mathematical modelling of malaria transmission was buried together with the malaria-eradication programme in the early seventies.

The development of computers has changed the prospects of mathematical modelling and the presentation of these models [11,14,25,34] completely and makes it necessary to consider again the usefulness of mathematical modelling for decision-makers of malaria-control programmes. The older models could only reflect a few components of the ecological and epidemiological system, as more details would lead to highly complex systems of equations which could not be solved at that time. Therefore, Bailey [5] concludes his analysis of several epidemiological models (Ross–Macdonald, Dietz–Molineaux–Thomas, Dutertre, Nasell and Bekessy–Moineaux–Storey): "These applications are not always well founded. Sometimes the mathematics used does not represent the model intended. On other occasions a factor will turn out to differ by at least an order of magnitude from a value assigned to it to be on the safe side" (p. 188). And later: "Formulae may be chosen for practical application because they are easy to use or are simply traditional, and not because they correctly reflect the assumption of the investigator" (p. 188). Seeing the computational capabilities of the time when these models were developed it is no wonder that model-builders had to pay more attention to computability than epidemiological reality and the way in which models are represented and communicated.

Today system dynamics models [8,13] consist of thousands of interdependent equations and can be easily computed with a PC. Bailey sees the future of epidemiological modelling in these simulations: "One extremely promising tool in the OR armamentarium is the approach implied by the term 'system dynamics' " (p. 193). And therefore, malaria models based on system dynamics "could be of prime practical importance for the control of malaria,. . ." (p. 193).

However, the failure of the older models to predict the spread of malaria makes malariologists very suspicious against any kind of mathematical modelling. Whereas there are quite a number of excellent models to forecast the AIDS

epidemic [17,27] and OR-magazines dedicate special issues to this topic [18], there are only few recent attempts to model the spread of malaria [3], although malaria claims many more victims than AIDS! The following model was developed in order to support decision-makers of malaria-control programmes. In addition, it is our target to demonstrate the usefulness of system dynamics models for malariologists and other epidemiologists. We are aware of the fact that this model can only be a first step, the concrete application in a particular situation must follow. Therefore, we would like to invite malariologists and management science to improve our mathematical model and suggest practical applications.

2. Model

The mathematical model – as presented in the appendix – follows the infection cycle consisting of agent (*Plasmodium falciparum* parasite), vector (*Anopheles gambiae* mosquito) and host (human being). In addition the ecological system of the anopheles is simulated. The interdependent equations of the ecological, infectious and human system cannot be analysed independently as there are several feed-back loops, e.g., the number of infectious human beings determines the number of infections of anopheles which itself determines the number of infections of humans (figure 1). These loops are dynamic and it were systems of that kind which caused Forrester to develop this particular branch of Operations Research called "system dynamics" [8,13] which was used for this malaria model. It is solved as a discrete simulation with time intervals of one day ($\Delta t = 1$). Parameters were either taken from malaria literature [1,2,7,9,28] or derived by a two-stage Delphi procedure involving several German malariologists. The process of calibration could build on experiences with a system dynamics model of the AIDS-epidemic in Tanzania undergone by the author previously [17]. Meanwhile he used to live for several years in Tanzania, and therefore the model is mainly suited for this country; however, its findings can easily be applied to other African countries.

As the spread of malaria depends on the habitat of the anopheles vector, the model has to simulate the ecological system. The model-population lives in two separate regions. Region 1 (300 m altitude) is characterised by constantly high malaria (holoendemic), region 2 (1500 m altitude) by periodically fluctuating malaria (epidemic). Temperature and precipitation depend on the altitude and rain seasons. It is assumed that in both regions 15th of January has the highest, 15th of August the lowest temperature. It is assumed that the average temperature declines by 0.5 °C [24] with an increase of altitude by 100 m, i.e., the temperature in region 2 is 6 °C lower than in region 1. Precipitation differs from this pattern because the inner tropics have a major and a minor rain season. The model assumes the peak of the long rains on 15th of April and the peak of the short rains on 15th of October. Region 2 receives 1.5 times more rain than region 1, as usually higher altitudes receive more precipitation.

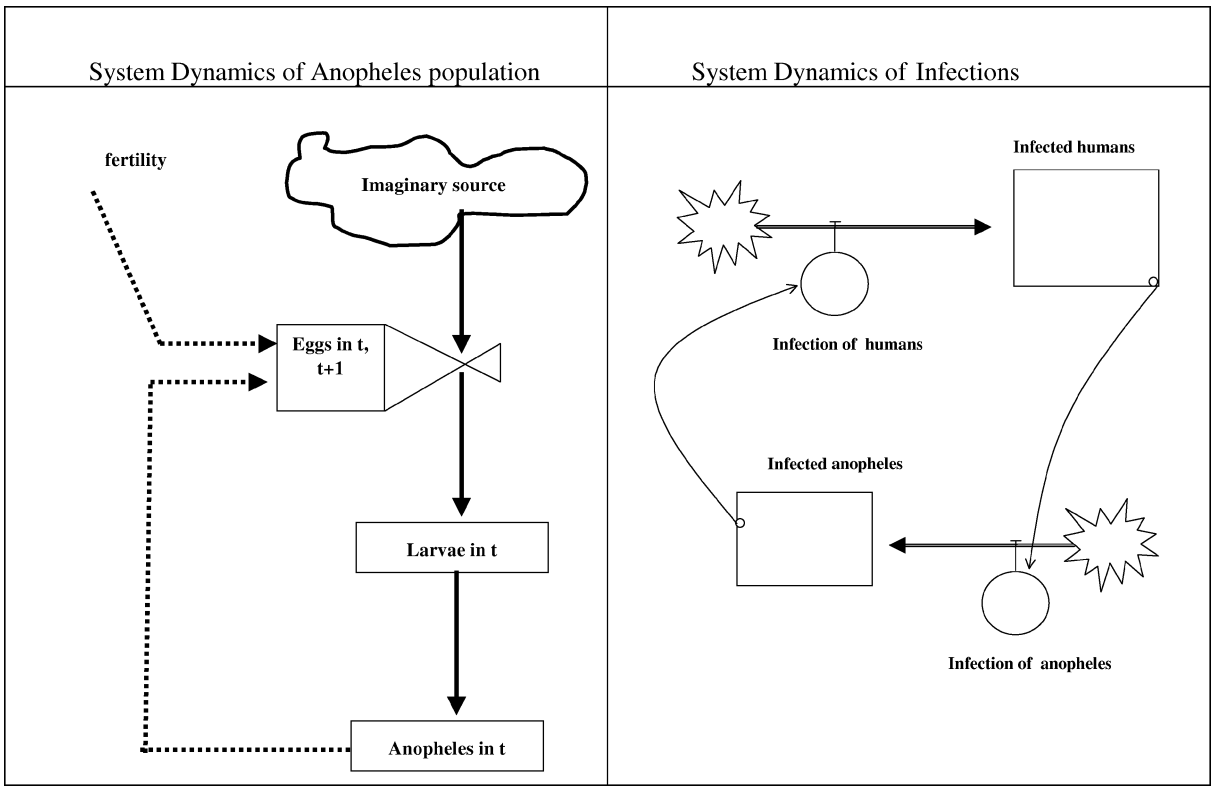

Figure 1.

Precipitation determines the size of the pools which can be used as habitat of anopheles larvae. The model assumes that the pool consists of the precipitation of the last 10 days, i.e., the suitable breeding-ground for anopheles is fluctuating with rain seasons.

The model analyses the ecology of *Anopheles g.*, the most prominent malaria vector in Africa. In order to be able to lay eggs anopheles have to have a bloodmeal which is – on average – sufficient for 300 eggs. Afterwards they need new blood. The larvae mature in the water, but this period depends on the temperature. The model allows for natural mortality of larvae and anopheles as well as mortality due to larvicides, insecticides (in-door and out-door spraying) and drainage of pools.

An anopheles is infected if it bites an infectious human being. The number of newly infected anopheles depends on the number of non-infected mosquitoes, the number of infectious human beings and the application of bed-nets preventing mosquitoes from biting humans. Multiple infections with booster-effects are not considered. After the infection the plasmodium matures in the anopheles. This period depends on the temperature, i.e., the warmer it is, the faster the plasmodium matures.

The model simulates the demographic system of the two populations (fertility, natural ageing, mortality and mobility between region 1 and 2). A non-infected human being is infected if he is bitten by an infectious anopheles; however, only a small percentage (medical infectiosity) of them will indeed be infected. An infected human being develops malaria after – on average – 12 days. At that stage he will become infectious. It is assumed that this period does not depend on air temperature. A certain percentage of those developing malaria die, others recover and build up semi-immunity which reduces medical infectiosity and mortality risk. This semi-immunity is lost if no re-infections occur at least every six months.

3. Simulations

The high number of compartments and interdependencies makes the solution of differential equations impossible. Therefore, the interdependent model was formulated and programmed with Turbo Pascal 6.0 as a system dynamics simulation on a Pentium 166. The validity of variables is a major problem of all system dynamics models. For the simulations of the malaria model several variables had to be calibrated. However, as real data of malaria in developing countries is more available [1,2,7,9,28] than for some other diseases this process was successful. All conclusions drawn from the model are based on "most likely" parameters and are supported by sensitivity analysis.

The model is used to answer the following questions:

- Can there be an equilibrium between man and malaria?
- What is the impact of rain seasons on the disease diffusion?
- What are the costs and benefits of in-door-spraying programmes?
- What are the costs and benefits of out-door-spraying programmes?
- Is it possible to eradicate the anopheles by the use of larvicides and drainage of pools?
- What is the long-term impact of impregnated bed-nets?
- How high must the efficacy of a vaccine be in order to eradicate malaria?
- What is the impact of global warming on malaria?
- What is the impact of migration on malaria?

The simulations give useful answers to these questions. This is demonstrated for a particularly difficult issue: the use of impregnated bed-nets. Obviously, the use of bed-nets with repellents prevents mosquitoes from biting the sleeping human being because anopheles bite only after sunset. This is in particular important for young children who can be kept under the net during the whole night. Therefore, several short-term studies proved that bed-nets are an effective means of preventing malaria [2,7,10,15,16, 20]. On the other hand, if young children are not bitten by mosquitoes they will never acquire semi-immunity and thus morbidity and mortality will be just transferred to later years of life where it is not possible to be under the net for the whole night [21,31–33]. The result might be a disastrous malaria epidemic in 10 to 15 years.

Most physicians and epidemiologists argue that one must indeed wait for 10–15 years until this question can be answered. Seeing that meanwhile millions might die, the mathematical model can give an early insight. The model assumes that all children of age $a = 1$ are perfectly protected against bites (variable $V_{r,1} = 0$). Figures 2 and 3 show the number of infections and deaths under this condition. The curve titled "Standard" represents the development of malaria cases if no bed-net programmes are launched. The "25 years" curve shows the development if a bed-net programme is working for 25 years, the "5-years" curve if the programme is withdrawn after the fifth year.

The consequent use of bed-nets by infants does definitely have a positive effect on malaria incidence and mortality. This decline is due to different causes: First of all, no more infants are infected. This will lead to a lower prevalence of plasmodia in anopheles mosquitoes which will result in a lower risk of being infected for older children and adults. Therefore, the prevalence of malaria will decrease. However, the impact is greatest in the first few years of the programme. Older children and adults will lose their semi-immunity and thus become vulnerable for infections. Although the risk of one mosquito-bite being infectious is less, the decreased semi-immunity will result in a higher risk of infection and mortality. Therefore, short-term studies give a completely wrong picture of the real effectiveness of bed-nets. After a period of 2–3 years the number of infections and deaths starts growing again. This increase is

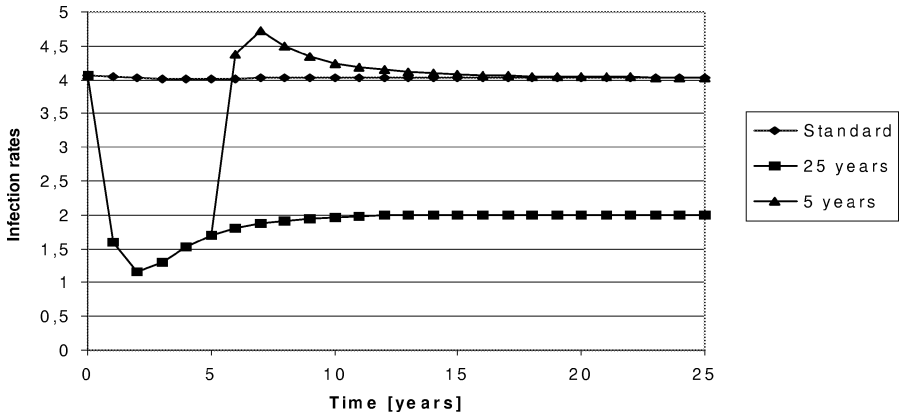

Figure 2. Infection rates and bed-net programmes, region 1.

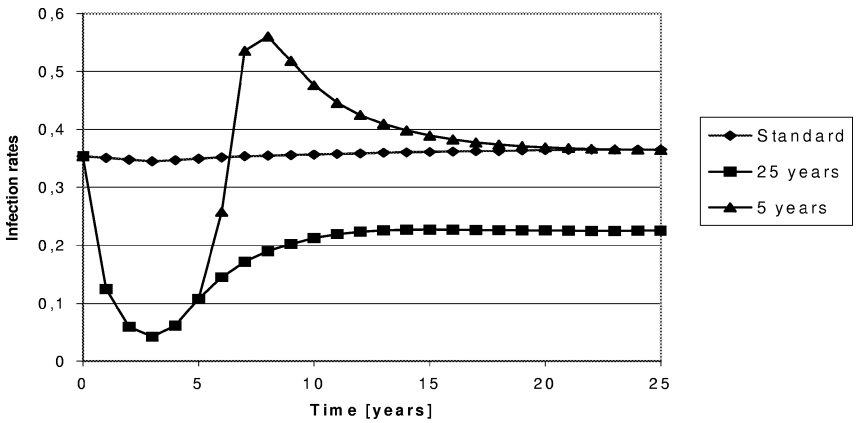

Figure 3. Infection rates and bed-net programmes, region 2.

greatest in region 2 as the number of infectious bites is so high in region 1 that even older children and adults can still acquire semi-immunity. In region 2, however, the loss of semi-immunity cannot be made good. Thus, after 25 years the number of infections with bed-net programmes is 72.41% of the number without any programme, whereas in region 1 only 61.91% of the infections occur. In both regions the number of infections and deaths of older children and adults ($a = 2, 3, 4$) is higher than without bed-net programmes. Therefore, the protection of infants has negative effects on the health of adults.

The analysis shows that bed-net programmes have disastrous consequences if they are not sustained. A mosquito-net can easily tear and the impregnation will be ineffective if it is not re-done at least twice a year. Therefore, the number of infections increases dramatically if programmes are not continued. Infants will be bitten and infected. Children could not acquire semi-immunity and are thus highly vulnerable. In region 1 semi-immunity returns faster than in region 2, as the number of mosquitoes and consequently the number of bites is much higher than in region 2. Therefore, after the bed-net programme has been withdrawn, the number of infections and deaths in region 2 will be significantly higher than without any programme. In the third year after the programme was stopped there are 62.45% more infections than without any programme. Therefore, health interventions call for long-term commitment, otherwise they have contrary effects.

A survey in Tanzania showed that the costs of a suitable bed-net can be estimated as 12 US$ and the annual costs of impregnation are 1 US$ (two impregnations per year). Assuming that a mosquito-net will have to be replaced after three years, the annual costs per impregnated bed-net can be estimated at 5 US$. Furthermore, our own surveys in Tanzanian hospitals and dispensaries showed that the costs per average malaria patient are 3.70 US$ for the entire treatment. In region 1 the present value of the difference between the direct and indirect costs of malaria and the costs of the bed-net programme is positive for any discounting factor, i.e., bed-net programmes are efficient investments in health. In region 2 sensible discounting factors ($<$30%) lead to negative present values. Therefore, it is not efficient to finance bed-net programmes in region 2. It becomes obvious that health policy decisions must take the geographic situation into account.

The costs per life saved differ between 96.54 US$ (region 1, 10% discounting rate) and 1,097.84 US$ (region 2, 0% discounting rate). Thus, the results of the simulation make it possible to compare the investment in malaria control programmes with other health investments. It seems that anti-malaria campaigns are highly efficient in comparison to other programmes.

4. Summary

Mathematical modelling of epidemiological processes is a powerful tool which has hardly been utilised by physicians and biologists. This is mainly due to the fact that the traditional bio-mathematical models could only reflect a very limited aspect of the complex reality and consequently failed to serve as decision-support for epidemiologists. System dynamics models have the capability to overcome these difficulties and open the door to a new era of mathematical modelling in epidemiology. 100 years after Ross developed the first malaria model it is overdue that the time-, cost- and risk-saving advantages of these models are utilised in malariology. The armamentarium of Operations Research offers the foundation for epidemiological forecasting and economic analysis of curative and preventive health care programmes and should be used for other complex ecological systems consisting of agent, vector and host. Thus, this paper calls for an intensified co-operation between Operations Research and biology/medicine. OR specialist must focus on developing models with graphical interfaces easily accessible for practioners. At the same time, public health planners, administrators and managers of intervention programmes should be trained in management science so that they are relieved from believing what mathematicians tell them, but they are personally involved in the development and application of system dynamics models. Seeing that Schools of Public Health are improving their syllabi in this sense and that modern computer models are very user-friendly, there is a great possibility to develop realistic epidemiological models based on system dynamics for other diseases.

Appendix. Model

Ecological system

The model defines two regions:

$$r = \begin{cases} 1 & \text{300 m altitude,} \\ 2 & \text{1500 m altitude.} \end{cases}$$

Temperature and precipitation depend on the altitude and rain seasons.

$$\text{temperature}_{d,1} = \begin{cases} T\_\text{min} + \frac{T\_\text{max} - T\_\text{min}}{180} * (d + 135) & \text{for } 1 \leqslant d < 45, \\ T\_\text{max} + \frac{T\_\text{max} - T\_\text{min}}{180} * (d - 45) & \text{for } 45 \leqslant d < 225, \\ T\_\text{min} + \frac{T\_\text{max} - T\_\text{min}}{180} * (d - 225) & \text{for } 225 \leqslant d \leqslant 360, \end{cases}$$

with

T_min	minimum temperature in region 1 (15 August) [°C],
T_max	maximum temperature in region 1 (15 February) [°C],
d	day (360 days per year),
$\text{temperature}_{d,1}$	temperature on day d in region 1 [°C].

T_min and T_max are symmetrically distributed around the average, i.e.,

$$T\_\text{min} = T\_\text{av}^* \left(1 - \tfrac{T\_\text{var}}{100}\right),$$
$$T\_\text{max} = T\_\text{av}^* \left(1 + \tfrac{T\_\text{var}}{100}\right)$$

with

T_av	annual average temperature in region 1 [°C],
T_var	maximum variation of temperature in region 1 [%].

It is assumed that the average temperature declines by 0.5 °C [24] with an increase of altitude by 100 m, i.e.,

$$\text{temperature}_{d,2} = \text{temperature}_{d,1} - 6.$$

Precipitation differs from this pattern because the inner tropics have a major and a minor rain season. This is modelled for region 1 as follows:

$$\text{prec}_{d,1} = \begin{cases} N\_\text{max}\,2 - \frac{N\_\text{max}\,2 - N\_\text{min}\,1}{90} * (d + 75) & \text{for } 1 \leqslant d < 15, \\ N\_\text{min}\,1 + \frac{N\_\text{max}\,1 - N\_\text{min}\,1}{90} * (d - 15) & \text{for } 15 \leqslant d < 105, \\ N\_\text{max}\,1 - \frac{N\_\text{max}\,1 - N\_\text{min}\,2}{90} * (d - 105) & \text{for } 105 \leqslant d < 195, \\ N\_\text{min}\,2 + \frac{N\_\text{max}\,2 - N\_\text{min}\,2}{90} * (d - 195) & \text{for } 195 \leqslant d \leqslant 285, \\ N\_\text{max}\,2 - \frac{N\_\text{max}\,2 - N\_\text{min}\,1}{90} * (d - 285) & \text{for } 285 \leqslant d < 360 \end{cases}$$

with

$N\_\min 1$	minimum precipitation, major dry season (15 January) [mm],
$N\_\max 1$	maximum precipitation, major rain season (15 April) [mm],
$N\_\min 2$	minimum precipitation, minor dry season (15 July) [mm],
$N\_\max 2$	maximum precipitation, minor rain season (15 October) [mm],
d	day,
$\text{prec}_{d,1}$	precipitation on day d in region 1 [mm]

with

$$N\_\min 1 = \frac{N\_\text{total}}{360} * \left(1 - \frac{N\_\text{var}}{100}\right),$$
$$N\_\max 1 = \frac{N\_\text{total}}{360} * \left(1 + \frac{N\_\text{var}}{100}\right),$$
$$N\_\min 2 = \frac{N\_\text{total}}{360} * \left(1 - \frac{N\_\text{var}}{200}\right),$$
$$N\_\max 2 = \frac{N\_\text{total}}{360} * \left(1 + \frac{N\_\text{var}}{200}\right)$$

with

N_total	annual precipitation in region 1 [mm],
N_var	maximum variation of precipitation in region 1 [%].

It is assumed that region 2 receives 1.5 times more rain than region 1, as usually higher altitudes receive more precipitation:

$$\text{prec}_{d,2} = 1.5 * \text{prec}_{d,1}.$$

Precipitation determines the size of the pools which can be used as habitat of anopheles larvae. The model assumes that the pool consists of the precipitation of the last 10 days, i.e.,

$$P_{r,d} = \left[20\text{m}^2 + s\_\text{par} * \sum_{k=1}^{10} \text{prec}_{d-k+1}\right]$$

with

$\text{prec}_t = \text{prec}_{360+t}$	for $t \leqslant 0$,
$P_{r,d}$	size of pool $[\text{m}]^2$ on day d,
s_par	parametric constant $[\text{m}^2/\text{mm\_of\_rainfall}]$.

The parametric constant is used as a calibration variable in order to stabilise the mosquito population.

Vector system

The model analyses the ecology of *Anopheles gambiae*. The following variables are defined:

$L_{r,u,d}$	larvae in region r of age u [days] on simulation day d,
r	region, $r = \begin{cases} 1 & \text{region 1: 300 m altitude,} \\ 2 & \text{region 2: 1500 m altitude,} \end{cases}$
u	age of larvae, $u = 1 \ldots 20$,
$A_{r,v,b,d}$	adult anopheles in region r in infection status v, b days after the last blood meal on simulation day d,
v	infection status, $v = \begin{cases} 1 & \text{not infected,} \\ 2 & \text{infected, but not infectious,} \\ 3 & \text{infectious,} \end{cases}$
b	days since last blood meal, $b = 0, \ldots, 9$,
$M_{i,r,a,s,z,d}$	human beings with immunity status i in region r of age a with health status s with z infections on day d,
i	immunity status, $i = \begin{cases} 1 & \text{not immune,} \\ 2 & \text{immune,} \end{cases}$
r	region, $r = \begin{cases} 1 & \text{300 m altitude,} \\ 2 & \text{1500 m altitude,} \end{cases}$

a age, $a = \begin{cases} 1 & 0 \leqslant \text{age} < 5 \text{ years}, \\ 2 & 5 \leqslant \text{age} < 12 \text{ years}, \\ 3 & 12 \leqslant \text{age} < 43 \text{ years}, \\ 4 & 43 \leqslant \text{age} < 80 \text{ years}, \end{cases}$

s health status, $s = \begin{cases} 1 & \text{not infected}, \\ 2 & \text{incubation period}, \\ 3 & \text{sickness}, \end{cases}$

z number of infections survived,

d day in year, $d = 1 \ldots 360$,

$S\_M_{i,r,a,s,z,d}$ number of bites suffered by human beings with immunity status i in region r with age a, with health status s and z infections on day d,

$S\_A_{r,v,d}$ number of bites by anopheles in region r and infection status v on day d.

Anopheles lay eggs on the third, sixth and ninth day after their bloodmeal. Afterwards they need new blood. Therefore, the number of new larvae is calculated as:

$$L_{r,1,d} = 100 * \sum_{v=1}^{3} \{A_{r,v,3,d} + A_{r,v,6,d} + A_{r,v,9,d}\} \quad \text{with daily ageing, i.e.,}$$

$$A_{r,v,b+1,d+1} = A_{r,v,b,d} \quad \text{for } b = 1 \ldots 8,$$

$$A_{r,v,0,d+1} = A_{r,v,0,d} + A_{r,v,9,d} - S\_A_{r,v,d},$$

$$A_{r,v,1,d} = S\_A_{r,v,d}.$$

The time which larvae need to mature depends on the temperature. If the temperature is below 15 °C larvae will die. The maturation period was approximated as a negative-exponential equation.

$$L_{r,u+1,d+1} = \begin{cases} L_{r,u,d} & \text{for temperature}_{d,r} \geqslant 20 \text{ and } u = 1 \ldots (R\_L_r - 1), \\ L_{r,u+1,d} & \text{for } 15 \leqslant \text{temperature}_{d,r}(r) < 20 \text{ and } u = 1 \ldots (R\_L_r - 1), \\ 0 & 15 > \text{temperature}_{d,r}, \end{cases}$$

$$\Delta A\_\text{birth}_{r,1,0,d+1} = -\Delta L\_\text{mature}_{r,R\_L_r,d+1} = \begin{cases} L_{r,R\_L_r,d} & \text{for temperature}_{d,r} \geqslant 20, \\ 0 & \text{else} \end{cases}$$

with

R_L_r maturation period of larvae in region r [days],

$R\_L_r = \max\{6;\ \text{round}\,(134.9 * e^{-0.095 * \text{temperature}_{d,r}})\}$,

$\Delta A\_\text{birth}_{r,v,b,d}$ change of number of anopheles due to maturing larvae,

$\Delta L\_\text{mature}_{r,u,d}$ change of larvae due to maturation.

Larvae and anopheles die due to natural or artificial causes, such as larvicides, insecticides or drainage of pools. The natural mortality of larvae and anopheles is given as:

$\Delta L\_\text{mortal}_{r,u,d} = -L_{r,u,d} * m\_l_r$,

m_l_r natural mortality rate of larvae in region r per day,

$\Delta L\_\text{mortal}_{r,u,d}$ change of larvae due to death,

$\Delta A\_\text{mortal}_{r,v,b,d} = -A_{r,v,b,d} * m\_a_r$,

m_a_r natural mortality of adult anopheles in region r per day,

$\Delta A\_\text{mortal}_{r,v,b,d}$ change of anopheles due to death.

The following equations allow the use of larvicides and insecticides:

$\Delta L\_\text{lar}_{r,u,d} = -L_{r,u,d} * t\_l_r$,

t_l_r share of pools treated with larvicides,

$\Delta L\_\text{lar}_{r,u,d}$ change of larvae due to larvicides,

$\Delta A\_\text{indoor}_{r,v,0,d} = -A_{r,v,0,d} * t\_i_r$,

$$t\_i_r = \begin{cases} 0.4 & \text{if } \frac{\text{Budget\_Indoor}_r}{\text{Pop}_{r,d}} > 11.33 \text{ [US\$/capita]}, \\ 0.4 * \frac{\text{Budget\_Indoor}_r}{11.33 * \text{Pop}_{r,d}} & \text{else}, \end{cases}$$

$\Delta A\_\text{indoor}_{r,v,b,d}$ change of anopheles due to in-door-spraying,

t_i_r share of mosquitos killed by in-door-spraying in region r,
Budget_Indoor_r budget for in-door-spraying in region r [US$],
$\text{Pop}_{r,d}$ population in region r on day d, i.e.,

$$\text{Pop}_{r,d} = \sum_{i=1}^{2}\sum_{a=1}^{4}\sum_{s=1}^{3}\sum_{z=0}^{20} M_{i,r,a,s,z,d},$$

$$\Delta A\_\text{out}_{r,v,b,d} = -A_{r,v,b,d} * t\_o_r \quad \text{for } b = 1\ldots 9,$$

$\Delta A\_\text{out}_{r,v,b,d}$ change of anopheles due to out-door-spraying,
t_o_r share of the environment treated with out-door-spraying in region r.

The drainage shall have the following consequences:

$$\Delta P_{r,d} = -(P_{r,d} - 20) * t\_p_r,$$
$$P_{r,d} = P_{r,d} + \Delta P_r,$$

t_p_r reduction of pools by drainage,

$$\Delta L\_\text{drain}_{r,u,d} = L_{r,u,d} - \frac{L_{r,u,d}}{\sum_{k=1}^{20} L_{r,k,d}} * \min\left\{\sum_{k=1}^{20} L_{r,k,d};\ 500000 * P_r\right\},$$

$\Delta L\_\text{drain}_{r,u,d}$ change of larvae due to drainage.

The number of bites suffered by human beings of a certain compartment depends on the risk of being bitten and the number of mosquitoes, i.e.,

$$S\_M_{i,r,a,s,z,d} = \frac{V_{r,a} * M_{i,r,a,s,z,d}}{\text{Pop\_un}_r} * \min\left\{\sum_{v=1}^{3} A_{r,v,0,d};\ 30 * \text{Pop\_un}_r\right\}$$

with

$V_{r,a}$ share of population in region r and age a not protected against mosquitos,
Pop_un_r unprotected population in region r, i.e.,

$$\text{Pop\_un}_r = \sum_{k=1}^{2}\sum_{j=1}^{4}\sum_{l=1}^{3}\sum_{w=0}^{20} V_{r,j} * M_{k,r,j,l,w,d}.$$

Accordingly, the number of bites by anopheles of a certain compartment is given as:

$$S\_A_{r,v,d} = \frac{A_{r,v,0,d}}{\sum_{k=1}^{3} A_{r,k,0,d}} * \min\left\{\sum_{k=1}^{3} A_{r,k,0,d};\ 30 * \text{Pop\_un}_r\right\}.$$

An anopheles is newly infected if she bites an infectious human being, i.e.,

$$\Delta A\_\text{inf}_{r,2,1,d} = -\Delta A\_\text{inf}_{r,1,0,d} = S\_A_{r,1,d} * \frac{\sum_{i=1}^{2}\sum_{a=1}^{4}\sum_{z=0}^{20} V_{r,a} * M_{i,r,3,a,z,d}}{\text{Pop\_un}_r},$$

$\Delta A\_\text{inf}_{r,v,b,d}$ change of anopheles due to infection.

If a non-infected anopheles bites a non-infectious human being merely the blood-status b is increased, i.e.,

$$\Delta A\_\text{inf}_{r,1,1,d} = -\Delta A\_\text{inf}_{r,1,0,d} = S\_A_{r,1,d} * \left\{1 - \frac{\sum_{i=1}^{2}\sum_{a=1}^{4}\sum_{z=0}^{20} V_{r,a} * M_{i,r,3,a,z,d}}{\text{Pop\_un}_r}\right\}.$$

Multiple infections with booster-effects are not considered, i.e.,

$$\Delta A\_\text{inf}_{r,v,1,d} = -\Delta A\_\text{inf}_{r,v,0,d} = S\_A_{r,v,d} \quad \text{for } v = 2, 3.$$

After the infection the plasmodium matures in the anopheles. This period depends on the temperature, i.e.,

$$\text{Incubat\_}A_r = \begin{cases} \max[5;\ 270 * \mathrm{e}^{-0.11 * \text{temperature}_{d,r}}] & \text{for temperature}_{d,r} \geqslant 16, \\ \infty & \text{else,} \end{cases}$$

$$\Delta A\_\text{incu}_{r,3,b,d} = -\Delta A\_\text{incu}_{r,2,b,d} = \frac{A_{r,2,b,d}}{\text{Inkubat\_}A_r}$$

with

$\text{Incubat\_}A_r$ incubation period in anopheles [days],
$\Delta A\text{\_incu}_{r,v,b,d}$ change of anopheles due to incubation.

Finally, every day the number of larvae and anopheles has to adjusted, i.e.,

$$A_{r,v,b,d+1} = A_{r,v,b,d} + \Delta A\text{\_birth}_{r,v,b,d} + \Delta A\text{\_mortal}_{r,v,b,d} + \Delta A\text{\_indoor}_{r,v,b,d} + \Delta A\text{\_out}_{r,v,b,d} + \Delta A\text{\_inf}_{r,v,b,d} + \Delta A\text{\_incu}_{r,v,b,d},$$
$$L_{r,u,d+1} = L_{r,u,d} + \Delta L\text{\_mature}_{r,u,d} + \Delta L\text{\_mortal}_{r,u,d} + \Delta L\text{\_lar}_{r,u,d} + \Delta L\text{\_drain}_{r,u,d}.$$

Human beings

The model assumes a natural crude birth rate of 5%.

$$\Delta M\text{\_birth}_{1,r,1,1,0,d} = \frac{0.05}{360} * \sum_{i=1}^{2}\sum_{a=1}^{4}\sum_{s=1}^{3}\sum_{z=0}^{20} M_{i,r,a,s,z,d},$$

$\Delta M\text{\_birth}_{i,r,a,s,z,d}$ change of M due to birth.

The population is structured in four age sets:

- $a = 1$ $0 \leqslant$ age $<$ 5 years,
- $a = 2$ $5 \leqslant$ age $<$ 12 years,
- $a = 3$ $12 \leqslant$ age $<$ 43 years,
- $a = 4$ age $\geqslant$ 43 years.

Every day a share is taken from class a and transferred to class $a + 1$. In order to account for exponential growth, the following formula is applied:

$$-\Delta M\text{\_age}_{i,r,a,s,z,d} = +\Delta M\text{\_age}_{i,r,a+1,s,z,d} = M_{i,r,a,s,z,d} * \frac{m_a}{1-(1-m_a)^{n_a+1}} * (1-m_a)^{n_a}$$

with

$\Delta M\text{\_age}_{i,r,a,s,z,d}$ change of M due to ageing,
m_a mortality in age a,
n_a time interval of age set a [days].

The natural mortality is considered as follows:

$$\text{Mor\_}N_{i,r,1,s,z,d} = \frac{1}{22500} * M_{i,r,1,s,z,d},$$
$$\text{Mor\_}N_{i,r,2,s,z,d} = \frac{1}{84000} * M_{i,r,2,s,z,d},$$
$$\text{Mor\_}N_{i,r,3,s,z,d} = \frac{1}{56575} * M_{i,r,3,s,z,d},$$
$$\text{Mor\_}N_{i,r,4,s,z,d} = \frac{1}{13320} * M_{i,r,4,s,z,d},$$
$$\Delta M_{i,r,a,s,z,d} = -\text{Mor\_}N_{i,r,a,s,z,d}$$

with

$\text{Mor\_}N_{i,r,4,s,z,d}$ natural mortality.

Every day a certain share migrates to the other region.

$$\Delta M\text{\_mig1}_{i,2,a,s,z,d} = -\Delta M\text{\_mig1}_{i,1,a,s,z,d} = \frac{\text{mig}_{1,2}}{360} * M_{i,1,a,s,z,d},$$
$$\Delta M\text{\_mig1}_{i,1,a,s,z,d} = -\Delta M\text{\_mig1}_{i,2,a,s,z,d} = \frac{\text{mig}_{2,1}}{360} * M_{i,2,a,s,z,d} \quad \text{for every day,}$$

$\Delta M\text{\_mig1}_{i,r,a,s,z,d}$ change of M due to normal migration,
$\text{mig}_{k,l}$ share of population migrating regularly from region k to region 1.

However, strong (government-induced) moves are possible as well (once per year):

$$\Delta M\text{\_mig2}_{i,2,a,s,z,d} = -\Delta M\text{\_mig2}_{i,1,a,s,z,d} = \text{mig\_spec}_{1,2} * M_{i,1,a,s,z,d},$$
$$\Delta M\text{\_mig2}_{i,1,a,s,z,d} = -\Delta M\text{\_mig2}_{i,2,a,s,z,d} = \text{mig\_spec}_{2,1} * M_{i,2,a,s,z,d},$$

$\text{mig\_spec}_{k.l}$ special (unique) migration from region k to region 1,
$\Delta M\text{\_mig2}_{i,r,a,s,z,d}$ change of M due to special migration.

The incubation period of plasmodium in the human body is a constant, i.e., every day a certain number of infected human beings develop malaria.

$$\Delta M\_\text{inc}_{i,r,a,3,z,d} = -\Delta M\_\text{inc}_{i,r,a,2,z,d} = M_{i,r,a,2,z,d} * \frac{1}{\text{Inku}\_M},$$

$\Delta M\_\text{inc}_{i,r,a,s,z,d}$ change of M due to incubation.

Malaria-related mortality is expressed as:

$$M\_M_{i,r,a,d} = -\Delta M\_\text{mal}_{i,r,a,3,z,d} = \frac{WS\_m\_m_{i,a,h}}{d\_m_{i,h}} * M_{i,r,a,3,z,d},$$

$$G_{i,r,a,s,z,d} = (1 - WS\_m\_m_{r,a,h}) * \frac{M_{i,r,a,3,z,d}}{d\_m_{i,h}}$$

with

$M\_M_{i,r,a,d}$	malaria deaths on day d,
$\Delta M\_\text{mal}_{i,r,a,3,z,d}$	change of M due to malaria related death,
$G_{i,r,a,s,z,d}$	recoverers on day d,
$WS\_m\_m_{i,a,h}$	probability to die from malaria, immune status i, age a, treatment h,
$d\_m_{i,h}$	sickness periode [days].

The number of new infected human beings is calculated as:

$$\begin{aligned} F_{i,r,a,z,d} &= \Delta M\_\text{inf}_{i,r,a,2,z,d} = -\Delta M\_\text{inf}_{i,r,a,1,z,d} \\ &= \frac{A_{r,3,0,d}}{\sum_{v=1}^{3} A_{r,v,0,d}} * \min\{M_{i,r,a,1,z,d};\ S\_M_{i,r,a,1,z,d}\} * \left\{1 - (1 - q_{i,a,z})^{\frac{S\_M_{i,r,a,1,z,d}}{M_{i,r,a,1,z,d}}}\right\} \end{aligned}$$

with

$F_{i,r,a,z,d}$	new infections,
$q_{i,a,z}$	medical infectiosity of human beings with immunity status i, age a and z infections,
$\Delta M\_\text{inf}_{i,r,a,s,z,d}$	change of M due to infections.

After several infections semi-immunity can be achieved which reduces the medical infectiosity and the mortality risk. Therefore, the number of infections is counted when a human being recovers:

$$\begin{aligned} &\Delta M\_\text{hea}_{1,r,a,1,z+1,d} = -\Delta M\_\text{hea}_{1,r,a,3,z,d} = G_{1,r,a,z,d} \quad \text{for } z = 0 \ldots 19;\ a = 1,2,3,4, \\ &\Delta M\_\text{hea}_{2,r,a,1,20,d} = -\Delta M\_\text{hea}_{1,r,a,3,20} = G_{1,r,a,20,d} \quad \text{for } a = 2,3,4, \\ &\Delta M\_\text{hea}_{1,r,1,1,20,d} = -\Delta M\_\text{hea}_{1,r,1,3,20,d} = G_{1,r,1,20,d}, \\ &\Delta M\_\text{hea}_{2,r,a,1,20,d} = -\Delta M\_\text{hea}_{2,r,a,3,20,d} = G_{2,r,a,20,d}, \\ &\Delta M\_\text{hea}_{i,r,a,s,z,d} \quad \text{change of } M \text{ due to recovery.} \end{aligned}$$

However, semi-immunity is lost if no re-infections occur at least every six months. Therefore, the probability to be bitten by at least one infectious mosquito is calculated and used to determine the number of people loosing semi-immunity on day d:

$$\Delta M\_\text{im}_{1,r,a,1,20,d} = -\Delta M\_\text{im}_{2,r,a,1,20,d} = \tfrac{1}{180} * M_{2,r,a,1,20,d} * \prod_{k=1}^{180} \{1 - f_{2,r,a,20,(d-k)}\},$$

$\Delta M\_\text{im}_{i,r,a,s,z,d}$ change of M due to immunity change

with

$$f_{i,r,a,z,d} = 1 - \left[\frac{\sum_{l=1}^{2} A_{r,l,0,d}}{\sum_{k=1}^{3} A_{r,k,0,d}}\right]^{\frac{S\_M_{i,r,a,1,z,d}}{M_{i,r,a,1,z,d}}}.$$

Those who were not yet semi-immune fall behind in their struggle to obtain semi-immunity, i.e.,

$$\Delta M\_\text{im}_{1,r,a,s,z-1,d} = -\Delta M\_\text{im}_{1,r,a,s,z,d} = \tfrac{1}{180} * M_{1,r,a,s,z,d} * \prod_{k=1}^{180} \{1 - f_{1,r,a,s,z,(d-k)}\}$$

for $z = 1 \ldots 20$.

Finally, all changes are reflected in M:

$$M_{i,r,a,s,z,d+1} = M_{i,r,a,s,z,d} + \Delta M\_\text{birth}_{i,r,a,s,z,d} + \Delta M\_\text{age}_{i,r,a,s,z,d} + \Delta M\_\text{mig1}_{i,r,a,s,z,d} + \Delta M\_\text{mig2}_{i,r,a,s,z,d} + \Delta M\_\text{inf2}_{i,r,a,s,z,d} + \Delta M\_\text{mal}_{i,r,a,s,z,d} + \Delta M\_\text{hea}_{i,r,a,s,z,d}.$$

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