Epidemiology and Infection

Evaluating the impact of two training interventions to improve diagnosis and case-management of malaria and pneumonia in Uganda

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**Supplementary Material**

**Recovery rate and rate out of emergency**

Recovery rate applies to individuals with non-severe symptomatic disease.

The general recovery term considers two cases: those reporting to the clinic and those who do not report. For the ones who do not report, they may use traditional medicine or may recover naturally. There is evidence that shows that some individuals clear their infection

without treatment [1, 2]. We assume that untreated symptomatic infections are cleared in 180 days [3-5].

For individuals reporting to the clinic, they may be tested or assessed, diagnosed, prescribed appropriate or inappropriate medication and they may receive or not receive the medication. We make the assumption that all those who receive appropriate medication recover and only 80% of those who receive inappropriate medication recover and that those who do not receive medication, use tradition medicine or recover naturally.

For the recovery rate of malaria,$ r\_{M}$ we did not consider the tested term, and for the recovery term for pneumonia, $r\_{P}$ we did not consider the assessment term. This is because most individuals presenting with fever are presumed to be having malaria and are given malaria medication. Similarly, most individuals presenting with cough are presumed to have pneumonia and are given antibiotics.

Rate out of emergency applies to individuals in severe disease class. It depends on the

proportion of individuals triaged, those that are prescribed and receive

appropriate medication. Patients with severe disease may die within hours or days [6].

It is documented that individuals and children hospitalized with severe malaria or severe pneumonia die within 24 to 48 hours [6-10].

We take the duration of being an emergency case to be 2 days if one is to recover. Supplementary Figure S1 shows the general framework for the recovery term.



Supplementary Figure S1: Framework for general recovery term - assessed is for pneumonia and tested is for malaria

The six terms making up the average recovery term, *r* are given as:

 $r\_{1}= $proportion reporting to clinic \* proportion assessed/tested \* proportion with appropriate prescription \* proportion that receive medication \* (1/duration of symptomatic disease with appropriate medication).

 $r\_{2}=$ proportion reporting to clinic \* proportion assessed/tested \* proportion with appropriate prescription \* (1-proportion that receive medication) \* (1/duration of symptomatic disease with no medication).

 $r\_{3}$=proportion reporting to clinic \* proportion assessed/tested \* (1-proportion with appropriate prescription) \* proportion that receive medication \* (1/duration of symptomatic disease with inappropriate medication).

$r\_{4}=$ proportion reporting to clinic \* proportion assessed/tested \* (1-proportion with appropriate prescription) \* (1-proportion that receive medication) \* (1/duration of symptomatic disease with no medication).

 $r\_{5}=$ proportion reporting to clinic \* proportion not assessed/not tested \* (1/duration of symptomatic disease with no medication).

$r\_{6}=$ proportion not reporting to clinic \*(1/duration of symptomatic disease with no medication)

$$r=r\_{1}+r\_{2}+r\_{3}+r\_{4}+r\_{5}+r\_{6}$$

$r$ gives the general recovery term and for the recovery term for malaria $r\_{M}$ and pneumonia, $r\_{P}$, we do not consider the assessment or tested term. Thus $r\_{5}$ term disappears and $r\_{M }$and $r\_{P} $will only contain five terms, $r\_{1}, r\_{2}, r\_{3}, r\_{4}$ and $r\_{6}$.

The rate out of emergency is defined as:

$=$ proportion reporting to clinic \* proportion triaged \*

proportion with appropriate treatment \* (1/duration as a treated emergency case).

**Demographical, epidemiological and programmatic parameters**

We use Ugandan demographical data because the population under study is located in Uganda and it is representative of the whole country [11].We also use epidemiological data to get parameters.

**Demography**

We use Ugandan demographical data because the population under study is located in Uganda and it is representative of the whole country [11]. Uganda has one of the highest birth rates [12].

In the 2000/2001 census, it was 47.3 per 1000 [13] and in the recent 2005/2006 census it was 41 per 1000 [14].

Uganda also has a young population with approximately 50% of its

population being under 15 years of age [15]. Therefore, a model

with a density dependent birth term and realistic aging rates would

represent its demography well. It would show a population growing

exponentially which is representative of Uganda's population for the last

two decades up-to-date. However, when disease dynamics are incorporated,

using such a model would also show an exponential growth in the number of

disease cases. This presents problems when one seeks to study the dynamics

of disease at steady state and impact of interventions for a short period of

time. One needs to deal with things such as: having an appropriate age

structure, having a relatively constant number of cases and finding

realistic parameter values.

With all these considered, we use a model with a constant number of births and we use a birth rate of 41 per 1000.

For mortality, we calculated natural death rates using population numbers from Spectrum

(DemProj) [16] with default Uganda country data. Probabilities

of dying in different age groups in the years 2009 to 2011 were obtained

(Number of deaths within an age group in a particular year/Population of age

group in that year). Using these probabilities, the rates of death for the

years under consideration were calculated using formulas in

[17, 18]. We took the average death rates and these were given

as $µ\_{1}=$ 0.026, $µ\_{2}= $0.004 and $µ\_{3}= $0.008 for the [0,5), [5,14) and [14,50) age groups

respectively.

Choice of aging rates is also important. The simple aging rate would be given as

(1/duration of time spent in a particular age group) which applies

if the age distribution is exponential. In the case of Uganda, it isn't. Thus in accordance to our choice of using a model with a constant number of births, we calculate aging rates that give the appropriate age structure of Uganda as 19% for [0,5), 27% for [5,14) and 54% for [14,50) [15] and also maintain a constant population. Our aging rates are given as $η\_{1}=$ 0.19 for out of [0,5), $η\_{2}=$ 0.13 for out of [5,14) and $η\_{3}=$ 0.057 for out of [14,50).

**Infection terms**

The infection term of malaria is calculated using two terms, the probability of transmission of

malaria from mosquito to human, $p\_{vh}$ or the probability of

transmission of malaria from human to mosquito, $p\_{hv }$and the mosquito

biting rate. That is $β\_{vh}= a\_{b}p\_{vh} $and $β\_{hv}= a\_{b}p\_{hv}$.

In [19], $p\_{vh}$ ranges from 0.01 to 0.2 and $p\_{hv }$ is given as

from 0.2 to 0.5 [20-23]. We estimated the probabilities of transmission of malaria for the different age groups. The mosquito biting rate is given as 0.3 per day [20-23].

For pneumonia, the infection rate is calculated from the probability of acquistion of pneumonia.

In [24], the probability of acquisition of different serotypes of

*S. pneumoniae* in young children ranged from 0.00007 to 0.0059

per day and this gives a range of rates from 0.025 to 2.16 per year.

The infection rates we used in our model were estimated. The estimates are based on individuals who report to the clinics and may not be directly comparable to the population-based estimates.

**Rate into emergency and reactivation rate**

The rate of progressing to severe disease depends on the time taken before

one becomes an emergency case. It may differ in different individuals

depending on their immunity to the disease. Individuals who have not been

exposed to malaria before may develop severe disease in 3 to 30 days

after infection if not treated, yet it might take 14 days even months for

those who have been exposed to malaria [6]. The rates into

emergency, for both malaria ($α\_{M\_{j}}) $and pneumonia ($α\_{P\_{j}}$), for the age groups [0,5), [5,14) and [14,50) were estimated and their values are given in the main article.

Individuals with malaria infection may develop symptomatic malaria after

infection or they may stay with the infection and reactivate it later. In

[6], it may take months and even years before malaria infection

is reactivated and it might be due to the individuals immunity being

compromised by other infections. We estimated the reactivation rates for malaria, $ϑ\_{M\_{j}}$for the

age groups [0,5), [5,14) and [14,50) and their values are given in the main article.

For pneumonia, it is mostly children under five years of age who become emergency cases.

Children may develop severe pneumonia in 3 to 7 days [25]. We also estimated the rate into emergency for pneumonia disease for the three age groups and these values are given in the main article.

The rates of reactivation, $ϑ\_{P\_{j}}$ of asymptomatic pneumonia have also been estimated.

**Disease induced death rates**

Our model's assumption is that deaths due to malaria and pneumonia occur only in

the severe class and that individuals with non-severe symptomatic malaria or non-severe pneumonia just experience natural death as the susceptible individuals (fully susceptible

and asymptomatic individuals).

For individuals who are untreated, the average duration that they spend in the severe disease class is unknown.

There is very little literature on severe disease in untreated individuals. In [6], it is said that death from severe disease may occur within hours or days. In [26], it is stated that the probability of dying from severe malaria in untreated cases is 73% for low transmission settings and it is 60% for high to medium transmission settings. It is also stated that the probability of dying from a severe illness requiring antibiotics ranges from 28% to 68%. However, there is no time frame mentioned. In [27], the calculated death rate for children under five years of age in emergency ranged from 0.421 to 0.794 per month before the intervention on emergency care. In [28], the calculated death rate was 0.066 per month before the intervention. Thus the values of disease induced death rates that we use are chosen in reference to the ones in [27, 28].

The death rates for severe cases of malaria, pneumonia are given as:

$µ\_{M\_{1}}=0.028$, $µ\_{M\_{2}}= $0.109, $µ\_{M\_{3}}= $0.0107,

$µ\_{P\_{1}}= $0.302, $µ\_{P\_{2}}= $0.759, $µ\_{P\_{3}}= $0.117.

It is important to note that the death rate for individuals with malaria-pneumonia coinfection

is higher than for individuals with either one of the diseases.

In [29], the case fatality ratio of severe malaria cases who also

had bacteraemia was 22.0% yet that of severe malaria cases only was 4%

and in [30], the case fatality for children with severe pneumonia

and clinical malaria was 14% and that for clinical malaria alone was 9%.

Thus there is a 2 to 5 fold increase in mortality if there is bacteraemia

(pneumonia) present in children with severe malaria [29-31]. In our model simulations, we use a 3 fold increase in mortality for individuals with severe coinfection.

**Calibrating the model**

**Human and mosquito population**

The product of the ratio of mosquitoes to humans and average number of

humans bitten by one mosquito per year gives the number of mosquito

bites per human per year. Multiplying this with the sporozoite index

gives the number of infective bites per person per year.

In equation terms and in relation to our model, the EIR is given as $a\_{2}\frac{I\_{v}}{N\_{v}}\frac{N\_{v}}{N}$, where $a\_{2}$ is the mosquito biting rate given per year. $\frac{I\_{v}}{N\_{v} }$ is the sporozoite rate and $\frac{N\_{v}}{N}$ is the mosquito to human ratio.

In Uganda, about 70% of the regions have an EIR > 100 per year and about 20%

have an EIR >10 per year and the other 10% have an EIR >1 per year [32, 33]. The sporozoite rate ranges from 1% to 20% [19, 34-37].

We use an EIR of approximately 130 per year, mosquito biting rate of 109.4 per year and a sporozoite rate of 19% to give a ratio of mosquito to humans.

Multiplying this ratio with the human population (\approx 36000) gives us the population of mosquitoes at the site of 224946.

Note that the sporozoite rate of 19% is the fitted value that we get with

the malaria cases and it is the average considering all the available months

of data. However, we use a sporozoite rate of 5% for initial conditions

so as to capture the low malaria values at baseline. Thus our initial

conditions for the model are:

$$S\_{1}\left(0\right)=6605, P\_{1}\left(0\right)=20, M\_{1}=109, C\_{1}\left(0\right)=6, E\_{1}\left(0\right)=100$$

$$S\_{2}\left(0\right)=9604, P\_{2}\left(0\right)=6, M\_{2}=78, C\_{2}\left(0\right)=0, E\_{2}\left(0\right)=32$$

$$S\_{3}\left(0\right)=19251, P\_{3}\left(0\right)=28, M\_{3}=111, C\_{3}\left(0\right)=1, E\_{3}\left(0\right)=49$$

$$S\_{v}\left(0\right)=213699, I\_{v}\left(0\right)=11247$$

**Fitting baseline malaria data, mosquito birth rate**

Malaria is seasonal with a peak in the June of the first year and July

of the second year and these months correspond to the rainy season in

Uganda. To capture this dynamics, we use a time dependent mosquito birth

rate since it is known that the number of mosquitoes increases during the

rainy season due to the availability of stagnant pools of water for breeding

of mosquitoes. Individuals in the population have asymptomatic malaria

infection and thus high numbers of mosquitoes lead to an increase in malaria

transmission which in turn translates into disease and explains the peak in

the number of malaria cases that is seen at health facilities [38-40].

Supplementary Figure S2 gives the mosquito births function



Supplementary Figure S2: Number of Mosquito births

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