Malaria Module

Table of Contents

[Summary 2](#_Toc14967047)

[Individual Properties managed by this module 2](#_Toc14967048)

[Malaria natural history 3](#_Toc14967049)

[Simulating the occurrence of new malaria infections 3](#_Toc14967050)

[Children aged under 15 years 3](#_Toc14967051)

[Pregnant women 3](#_Toc14967052)

[Disability weights 3](#_Toc14967053)

[Mortality 4](#_Toc14967054)

[Initialising the simulation 5](#_Toc14967055)

[Malaria prevalence in 2010 5](#_Toc14967056)

[Coverage of interventions at baseline 5](#_Toc14967057)

[Health system interactions 5](#_Toc14967058)

[Malaria prevention 7](#_Toc14967059)

[Malaria testing 7](#_Toc14967060)

[Malaria treatment 7](#_Toc14967061)

[Health system links to other diseases 8](#_Toc14967062)

[Main limitations 8](#_Toc14967063)

[References 10](#_Toc14967064)

# Summary

The malaria module updates the individual properties each month related to malaria status, malaria treatment and malaria preventive measures. Malaria is widely endemic throughout Malawi with the highest risk occurring in the more humid low-lying regions and during the rainy season beginning in November each year.(Mathanga, Walker et al. 2012) An estimated 4 million cases occur every year with the majority of severe illness reported in children under the age of 5 and pregnant women.[Malaria Indicator Survey 2017] The majority of infections are caused by *Plasmodium falciparum*, with *P. malariae* and *P.* *ovale* accounting for < 9% of infections in children aged 6-59 months.[Malawi MIS 2017]

The incidence of asymptomatic, clinical and severe malaria for children (under 15 years) and pregnant women is informed by the Malaria Modelling Research Group (Imperial College London) estimates and spatial distribution by the Malaria Atlas Project (Oxford University). Interventions against malaria focus on prevention, using long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), seasonal malaria chemoprevention (SMC) and preventing malaria in pregnancy using intermittent preventive therapy (IPTp). Recommended treatment for uncomplicated malaria is with artemisinin-based combination therapy (ACTs) rather than monotherapy in order to delay the emergence of resistance. Estimates of intervention coverage are derived from the Malaria Modelling Research Group and the National Malaria Program in Malawi. The effects of interventions on clinical cases of malaria are based on intervention simulations performed by the Malaria Modelling Research Group and are linked via a statistical model to the transmission intensity in every district in each month of the year.

# Individual Properties managed by this module

Table 1. Individual properties managed by the malaria module.

|  |  |  |
| --- | --- | --- |
| Property | Description | Values |
| ml\_inf | Malaria infection status (positive parasitaemia) | True / False |
| ml\_date\_inf | Date most recent malaria infection | date |
| ml\_specific\_symptoms | Level of symptoms due to malaria | Categorical: asymptomatic, clinical, severe |
| ml\_unified\_symptom\_code | Level of symptoms on the standardised scale | Categorical: 0,1,2,3,4 |
| ml\_tx | currently on anti-malarial treatment | True / False |
| ml\_itn | If person sleeps under an insecticide-treated bednet | True / False |
| ml\_irs | If household has used indoor residual spraying | True / False |
| ml\_ipt | if pregnant, has had IPTp2+ or IPTp3 during this pregnancy | True / False |
| ml\_date\_ipt | date of last dose of IPTp | Date |
| ml\_chemo | if infant, currently using seasonal chemoprophylaxis | True / False |
| ml\_inf\_preg | Number of previously infected pregnancies | Integer |

# Malaria natural history

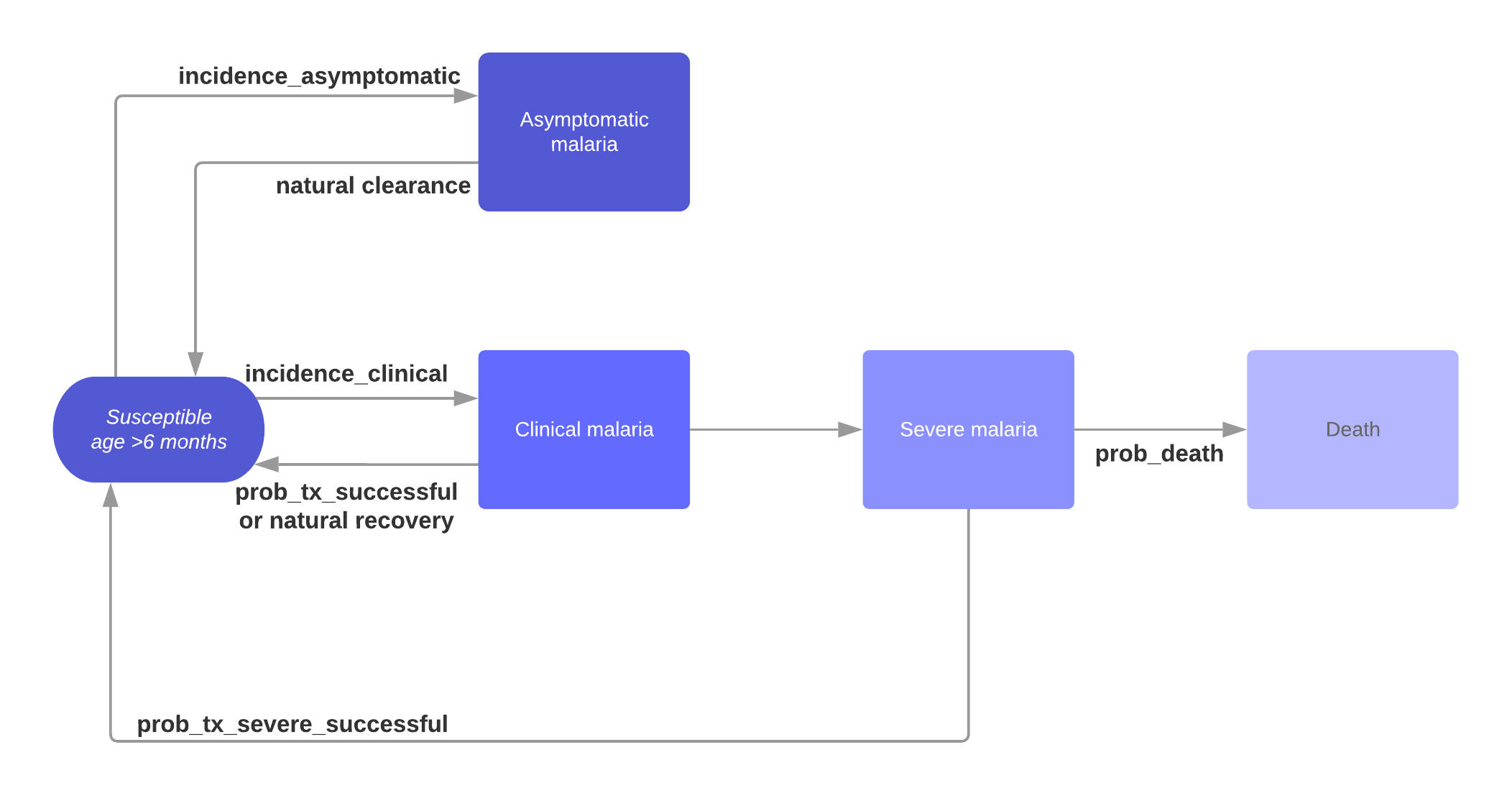


Figure 1. Structure of malaria natural history model.

# Deriving the baseline case incidence

The baseline incidences of asymptomatic, clinical and severe malaria cases in the absence of any interventions were obtained from Malaria Modelling Research Group’s malaria transmission model which incorporates the full dynamics of *P. falciparum* parasite transmission between humans and mosquitoes along with age and exposure-dependent immunity functions.(Griffin, Hollingsworth et al. 2010) Through using this transmission model, we are able to incorporate many of the complex features of their model, such as the seasonality of malaria, the decay of maternal immunity of the first six months of a child’s life and the acquired immunity gained through exposure to malaria parasites which is in turn dependent on transmission intensity.

The impact of each intervention (LLINs and IRS) on incidence is variable depending on the transmission intensity in each district. The Malaria Modelling Research Group produced a set of incidence rates for every age and sex in each district in Malawi related to coverage of both interventions between 0-70%. From these lookup tables, we can use survey data to find the reported intervention coverage in each district for each month up to 2018 and derive the incidence rates distributed by age and sex (data shared from Oxford University BDI, Mike Thorn).

# Simulating the occurrence of new malaria infections

To simulate new cases of clinical malaria each month, we randomly sample uninfected individuals with probability equal to the per capita incidence rate of clinical malaria by age, sex and district. Likewise, we randomly sample individuals with probabilities equal to the incidence rates of asymptomatic and severe malaria to assign these infection states. The expected incidence rates vary throughout the year, reflecting the seasonal nature of malaria transmission.

We assume that the duration of both treated and untreated symptomatic clinical disease is 5 days and the rates of parasite clearance are 1/21 days with treatment, 1/195 days with untreated clinical malaria and 1/110 days for untreated sub-patent (asymptomatic) infections.(Filipe, Riley et al. 2007, Walker, Griffin et al. 2016, Winskill, Slater et al. 2017)

There are risk factors which predispose certain individuals to malaria infection, such as poorly constructed housing, poor sanitation, wealth quintile and distance to nearest water body which are currently not captured in this approach. In future, the allocation of infections could be weighted by the relative risks of the individual based on their characteristics. This would enable us to simulate clustering of cases and repeated infections in high-risk groups.

Case fatality rates

Reported case fatality rates are highly variable and are conditional on age-dependent immunity, transmission setting and the availability and timing of treatment. Estimates for Malawi have been reported in both a community and hospital setting (case-fatality rate 15% and 5% respectively for severe malaria) although these rates are not stratified by age and may include pregnant women.(Camponovo, Bever et al. 2017) Other estimates range from 9% in children treated in hospitals to 21% in adults (Mozambique) and 60.9% in children under 5 years, 17.6% in children aged 5-14 years and 49.3% in adults (Western Kenya).(Hendriksen, Ferro et al. 2012, Kapesa, Kweka et al. 2018) Modelled estimates using the estimated incidence of hospitalised severe malaria in each age group resulted in a case fatality rate of 21.5%.(Griffin, Bhatt et al. 2016)

We use the community mortality rates reported for Malawi (15% case fatality rate) with an adjustment applied to match the reported numbers of malaria deaths over time.

Symptoms of malaria

Four symptoms are assigned to all individuals with clinical malaria infections: fever, headache, vomiting and stomach-ache. For those with severe malaria infections, six additional symptoms are randomly sampled and assigned with an age-dependent probability (Table 2). The presence of these symptoms drives the healthcare-seeking behaviour of children and adults through a statistical model informed by IHS data in Malawi (see document Healthcare-Seeking Behaviour).

Table . Symptoms of severe malaria

|  |  |  |
| --- | --- | --- |
| Symptom | Age 0-5 years | Age ≥5 years |
| Jaundice | 0.05 – 0.1 | 0.1 – 0.6 |
| Acidosis | 0.4 – 0.45 | 0.45 – 0.6 |
| Coma or convulsions | 0.3 – 0.4 | 0.38 – 0.45 |
| Renal failure | 0.05 – 0.15 | 0.1 – 0.5 |
| Anaemia | 0.4 – 0.5 | 0.1 – 0.45 |
| Shock | 0.05 – 0.15 | 0.1 – 0.2 |

Source: (World Health Organization 2014)

### Pregnant women

Malaria in pregnancy is defined as having a prevalent infection at the time of becoming pregnant or acquiring an infection during the pregnancy. Malaria in pregnancy results in parasites being sequestered in the placenta (placental infection) and is associated with a number of maternal and foetal adverse effects, such as maternal anaemia, impaired foetal development, low birth weight and stillbirth. The adverse outcomes due to malaria in pregnancy are applied through the pregnancy module, which applies the risk of stillbirth, preterm birth and maternal anaemia for any pregnant women with an existing or incident malaria infection (odds ratio 1.81. 3.08 and 1.45 respectively).

### HIV and malaria

Studies describing the effect of HIV on malaria have shown highly variable results, with some reporting increased risk of clinical or severe malaria while others, particularly early studies, report no differences.(Flateau, Le Loup et al. 2011) Currently, HIV is not included as a risk factor for either infection or severity of disease. There is also no evidence for impaired response to antimalarial treatment in children or adults with HIV.

Pregnant women

A meta-analysis of HIV and malaria co-infection in pregnant women showed a consistently higher risk of placental and peripheral malaria, higher prevalence of severe anaemia and poorer birth outcomes than in HIV-negative women.(Ter Kuile, Parise et al. 2004) Here we apply an odds ratio for neonatal death in infants born to mothers with both placental malaria and HIV of 4.5 compared with mothers with malaria infection only.(Bloland, Wirima et al. 1995). This risk is applied through the pregnancy module.

# Disability weights

Currently we consider three malaria states; asymptomatic, clinical and severe which relate to the DALY weights presented below. Anaemia is a common outcome associated with malaria, particularly in young children and pregnant women. This will be modelled as a population-level risk of anaemia, with risk factors including malaria, helminth infection and malnutrition.

Table 3. DALY weights associated with malaria infection.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Code** | **Sequela** | **Health state name** | **Description** | **DALY** | **lower** | **upper** |
| 213 | Severe malaria | Infectious disease, acute episode, severe | has a high fever and pain, and feels very weak, which causes great difficulty with daily activities. | 0.133 | 0.088 | 0.19 |
| 218 | Moderate malaria with mild anemia | Infectious disease, acute episode, moderate, with mild anemia | combined DW:   1. has a fever and aches, and feels weak, which causes some difficulty with daily activities 2. feels slightly tired and weak at times, but this does not interfere with normal daily activities. | 0.054 | 0.034 | 0.079 |
| 236 | Asymptomatic malaria parasitemia (PfPR) | Asymptomatic | -- | 0 | -- | -- |

# Health system interactions

### Malaria prevention

Long-lasting insecticide-treated bednets and indoor residual spraying

District-level estimates of annual coverage of LLINs and IRS are derived from the Malaria Atlas Project (Big Data Institute, University of Oxford). These coverage estimates are used to derive the expected incidence of malaria for every age-group through a complex mathematical model developed by the Malaria Team at Imperial College London. The efficacy of both interventions used in combination is a non-linear function which describes the probability of an infected mosquito feeding on a human host and the subsequent risks of malaria transmission.

Seasonal malaria chemoprophylaxis

Seasonal malaria chemoprophylaxis (SMC) comprising Sulfadoxine / Pyrimethamine and Amodiaquine is available to children between 6 months and 5 years of age in the peak season of malaria transmission. A three-course regimen is administered to children between November and April of each year in high transmission districts only. SMC given to an infected child acts in the same manner as treatment for diagnosed clinical disease, i.e. infected children will have a probability of successful treatment with SMC dependent on the class of drug. Non-ACTs have a 75% success rate for clearing an infection and ACTs have a 95% success rate.(Okell, Cairns et al. 2014) For those not infected when receiving SMC, they will have a period of 30 days of drug-dependent partial protection from infection.(Griffin, Bhatt et al. 2016)

Intermittent preventive therapy for pregnant women

Each dose of Sulfadoxine / Pyrimethamine (SP) used for intermittent preventive therapy for pregnant women clears both asymptomatic and symptomatic infections and provides up to six weeks of post-treatment prophylaxis preventing further infection.(White 2005) Pregnant women in Malawi are recommended to receive at least three doses of SP given four weeks apart after the first trimester of pregnancy during each scheduled antenatal care visit. SP is contraindicated for women receiving cotrimoxazole.

Two doses of IPTp reduces the risk of incident placental malaria (relative risk [RR], 0.48; 95% CI, 0.35-0.68), low birth weight (RR, 0.71; 95% CI, 0.55-0.92), and anaemia (RR, 0.90; 95% CI, 0.81-0.99). We apply this as a reduction in the incidence of new infections each month in pregnant women, lasting up to six weeks following the final dose.

**Pregnant women with HIV**

**Daily cotrimoxazole is recommended for all pregnant women with HIV as an alternative to IPTp.** For pregnant women with HIV, the only studies we found reported the effect of cotrimoxazole compared with intermittent preventive therapy for pregnant women (IPTp). The estimated odds ratio for malaria in pregnant women on cotrimoxazole was 0.35 (0.20 – 0.60) and 0.43 (0.19 – 0.97) compared with those on IPTp.(Kapito-Tembo, Meshnick et al. 2011, Dow, Kayira et al. 2013) We therefore assume the same incidence rate ratio for pregnant women with HIV taking cotrimoxazole as in other adults with HIV (IRR=0.31).

Cotrimoxazole

**Cotrimoxazole is given alongside ART for individuals infected with HIV. The incidence rate ratio for clinical and severe malaria in HIV-infected individuals receiving both ART and cotrimoxazole compared with no intervention was 0.08 (95% CI 0.04 – 0.17).(Mermin, Ekwaru et al. 2006) We apply this as a reduction in the probability of a clinical malaria episode each month (derived from the look-up table) that the person is on treatment. The effect of ART and cotrimoxazole is assumed to be consistent across all age-groups.**

### Malaria testing

WHO recommends that case management of malaria must be preceded by a confirmatory diagnostic test such as microscopy or malaria rapid diagnostic tests (RDTs). The National Malaria Policy in Malawi recommends the use of RDTs across all facilities with microscopy testing reserved for severe malaria cases. The majority of RDTs used across sub-Saharan Africa target *P. falciparum* histidine-rich protein 2 *Pf*HRP2 in the peripheral blood, however the clinical sensitivity of these tests depends on the population parasite density which in is driven by the transmission intensity.

The sensitivity of RDTs in Malawi was 90-92% depending on the test manufacturer although specificity was low (39 – 68%).(Chinkhumba, Skarbinski et al. 2010) An extensive meta-analysis reported the sensitivity of *Pf*HRP2 RDT in endemic areas was 95.0% (95% CI 93.5 – 96.2%) and specificity was 95.2% (93.4 – 99.4%), although this test does have the disadvantage of detecting recently treated or self-cleared infections for several weeks afterwards.(Abba, Deeks et al. 2011) We assume a sensitivity of 95% for RDTs and specificity of 100% for malaria parasitaemia. In pregnant women, the sensitivity of RDTs falls to 81%.(Kattenberg, Ochodo et al. 2011)

### Malaria treatment

The treatment options for uncomplicated and complicated (severe) malaria are detailed in Table 4. We currently don’t include second line anti-malarials. Treatment is given following confirmation of parasitaemia using a RDT.

|  |  |
| --- | --- |
| Age | Treatment |
| Uncomplicated – 1st line |  |
| Adults | Malaria test kit (RDT) |
|  | Lumefantrine 120mg/Artemether 20mg, 30x18\_540\_CMST |
|  | Paracetamol 500mg\_1000\_CMST |
| Children 0-5 years | Malaria test kit (RDT) |
|  | Lumefantrine 120mg/Artemether 20mg, 30x18\_540\_CMST |
|  | Paracetamol syrup 120mg/5ml\_0.0119047619047619\_CMST |
| Children 5-15 years | Malaria test kit (RDT) |
|  | Lumefantrine 120mg/Artemether 20mg, 30x18\_540\_CMST |
|  | Paracetamol syrup 120mg/5ml\_0.0119047619047619\_CMST |
| First trimester - uncomplicated | Quinine sulphate 300mg\_1000\_CMST |
|  | Clindamycin, tabcap, 300 mg |
|  | Paracetamol 500mg\_1000\_CMST |
| Second trimester - uncomplicated | Lumefantrine 120mg/Artemether 20mg, 30x18\_540\_CMST |
|  | Paracetamol 500mg\_1000\_CMST |
|  |  |
| Complicated (severe) |  |
| Adults | Injectable artesunate |
| Children | Injectable artesunate |
| Pregnant women | Quinine dihydrochloride 300mg/ml, 2ml\_each\_CMST |
|  | Quinine sulphate 300mg\_1000\_CMST |
|  | Clindamycin, tabcap, 300 mg |
|  | Dextrose (glucose) 5%, 1000ml\_each\_CMST |

Table . Treatment options for malaria

### Main limitations

Immunity functions are a key determinant for describing malaria risk in an endemic setting. Due to the complexity of the immunity functions needed to accurately model malaria incidence, we rely on the outputs from the Malaria Modelling Group who incorporate these functions within their host-vector model. As children age, the likelihood that they will have clinical malaria decreases as a function of past exposure. Rather than track each infection in each child and moderate their propensity for future infections, we apply a changing risk by age across the population. It is possible therefore, that we may assign repeated clinical malaria episodes to children who should be immune or assign asymptomatic infections to those who have never had a malaria infection before.

The probability of low birth weight is assumed to be homogenous across the stages of maternal infection (acute versus chronic or past) although acute infection at the time of delivery is unlikely to cause low birth weight. The duration of chronic infection is dependent on maternal immunity, developed through past infected pregnancies. Incorporating a gravidity-dependent duration of chronic infection with low birth weight proportionately related to this may improve the predictions of the model. Likewise adjusting the risk of low birth weight by the timing of infection may improve the model estimates.

At first infected pregnancy, the duration of the chronic stage is 100 days, falling to less than 10 days by the fourth infected pregnancy. Assuming the same clearance rates for all untreated pregnant women may result in over-estimating the prevalence for this subgroup.

Treatment will also have a small impact on the transmission intensity (along with LLINs and IRS) and hence the incidence rates by reducing the duration of parasitaemia, but this is not included this in the development of the incidence rates by intervention coverage levels.

Table 5. Description of parameters and proposed values.

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Proposed value | Description | Sources and notes |
|  |  |  |  |
| inc\_asym  inc\_clin  inc\_sev | lookup table | Incidence of malaria (asymptomatic, clinical and severe) | By age group, sex, month/year and district  Informed by Malaria Modelling Group estimates |
| sensitivity\_rdt | 0.95 | Sensitivity of rapid diagnostic test in diagnosing malaria parasitaemia | (Abba, Deeks et al. 2011) |
| cfr | 0.15 | case fatality rate for all ages | (Camponovo, Bever et al. 2017) |
| dur\_asym | 110 | Duration (days) of parasitaemia in asymptomatic infections | 110 (95% CI 87,131)  (Walker, Griffin et al. 2016) |
| dur\_clin | 14 | Duration (days) of clinical symptoms in clinical (non-severe) malaria | assumption |
| dur\_clin\_para | 195 | Duration (days) of parasitaemia in clinical infections | (Winskill, Slater et al. 2017) |

### Sample model outputs

Published estimates show more than ≥75% of malaria infections are asymptomatic [Bousema, Nature 2014]

The gap between PfPR and clinical prevalence will be the prevalence of asymptomatic infection: ~85% in this example.

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