**Supplementary File 1: Simulation Model Pseudocode**

The following key and colour key describe the pseudocode convention that is used in the following pseudocode representation of the full model. A mathematical style pseudocode syntax style has been used to aid understanding and reproducibility of the model.

**KEY:**

|  |  |
| --- | --- |
| **Symbol/Language** | **Type of Operation** |
| := | Assignment |
| = > < <= >= | Comparison |
| + - \* / ^ | Arithmetic |
| AND OR | Logical |
| x FROM y EARLIER | Value of x from y days earlier |
| DRAW FROM [x1,...,xn] WITH WEIGHTS [w1,...,wn]  DRAW UNIFORMLY FROM [x1,...,xn] | Randomly sample value from vector of values x1,...,xn with probability of value being sampled equal to [w1,...,wn]  Randomly sample value from vector vector of values x1,...,xn |
| REPEAT LINES l1-l2 | Repeat code between and including lines l1 ­and l2 |
| FOR TO ENDFOR  IF ELSE ENDIF  WHILE ENDWHILE | Control of pseudocode flow |

**COLOUR KEY:**

|  |  |
| --- | --- |
| **Colour** | **Explanation** |
| 001 | Line numbers in blue at beginning of pseudocode lines |
| // Annotation | Pseudocode annotation and explanations in green |
| OPERATORS, SYMBOLS, KEYWORDS | Mathematical operators, and instructions detailed in the above key are in red capitals |
| Variables and functions | Variables and values are in black lowercase, as well as intelligible functions [round(), mean()], sampling randomly from distributions [randexp(), randlognormal()] and carrying out bernoulli trials [bernoulli()]. Variable symbols relate to the model parameters within Table 2 in the main text. |

// BEGIN HUMAN INITIALISATION

// ----------------------------------------------------

001 FOR i := 1 TO N // N is total population size

//assign age

002 age[i] := randexp() // set individual's age to random draw from exponential distribution with mean equal to 1/ years

003 age[i] := round(age[i]) // round age to nearest integer

004 WHILE (age[i] > (100\*365)) // reassign age if greater than max age of 100 years

005 REPEAT LINES 02-03

006 ENDWHILE

// assign relative biting rate due to heterogeneity in mosquito biting patterns

007 [i] := randlognormal(meanlog:=-0.5\*,sdlog:=) // set individual’s relative biting rate to random draw from lognormal distribution with mean and standard deviation of the distribution on the log scale equal to -0.5\* and respectively.

008 inf\_state[i] := DRAW FROM [S,D,A,U,T,P] WITH WEIGHTS [Seq,Deq,Aeq,Ueq,Teq,Peq] // Seq is the steady state equilibrium proportion of individuals who are susceptible within a near-equivalent deterministic model1 for the desired EIR, and so on for D,A,U,T,P

// assign strain profile, i.e. number of wild type of hrp2-deleted strains

009 IF (inf\_state[i] = D OR A OR U OR T) //if individual is infected

// first assign what strains they have

010 n\_wt\_strains[i] := DRAW UNIFORMLY FROM [0,...,5] // assign a random number of wild type strains from between 0 and 5

011 n\_hrp2\_strains[i] := DRAW FROM [0,...,5] WITH WEIGHTS [hrp2\_freq\_wt\_0,...,hrp2\_freq\_wt\_5] // hrp2\_freq\_wt weights are such that the population allele frequency of hrp2 deleted strains is the desired starting frequency.

// reassign if infected individual did not have any strains assigned

012 WHILE (n\_wt\_strains[i] + n\_hrp2\_strains[i] = 0)

013 REPEAT LINES 10-11

014 ENDWHILE

015 ENDIF

// assign immunity using equilibrium state

016 IB[i] := IBeq[age[i],[i]] // assign pre-erythrocytic immunity from steady state equilibrium immunity for the age and biting heterogeneity class that individual i exists in

017 ICA[i] := ICAeq[age[i],[i]] // assign acquired clinical immunity from steady state equilibrium immunity for the age and biting heterogeneity class that individual i exists in

018 ID[i] := IDeq[age[i],[i]] // assign detection immunity from steady state equilibrium immunity for the age and biting heterogeneity class that individual i exists in

019 ICM[i] := PM\*ICAeq[20\*365]\*exp(-age[i]\*rCM­) // assign maternal immunity using the mean equilibrium steady state acquired clinical immunity for the age class that contains the assumed maternal age of 20 years, multiplied by relative immunity passed on parameter PM multiplied by how much this immunity would have decayed given the age of the individual.

020 tk[i] := tl[i] := tm[i] := -Tbig // assign the last time IB, ICA and ID were boosted to a large negative number to represent never having been exposed or infected before.

// assign contributions to onward infectiousness

021 IF (inf\_state = A) //if they are asymptomatic

022 fD := 1 - ((1 - fD0)/(1 + ((age[i]/aD)^D)))

023 q := d1 + ((1 - d1)/(1 + (((ID[i]/ID0)^D)\*fD)))

024 cont[i] := cU + (cD - cU)\*(q^1)

025 ELSE // else assign the contribution term for the infection state they are in

026 IF (inf\_state[i] = D) // if they are diseased contribution equal to cD

027 cont[i] := cD

028 ENDIF

029 IF (inf\_state[i] = U) // if they are subpatent contribution equal to cU

030 cont[i] := cU

031 ENDIF

032 IF (inf\_state[i] = T) // if they are being treated contribution equal to cT

033 cont[i] := cT

034 ENDIF

035 ENDIF

// assign non-normalised age dependent biting heterogeneity

036 [i] := (1 - \*exp(-age[i]/a0))

037 \_sum := \_sum + [i]

038 ENDFOR

// normalise age-dependent biting heterogeneity by dividing by the population mean

039 FOR i := 1 TO N

040 [i] := [i]/(\_sum/N)

041 ENDFOR

// ----------------------------------------------------

// END HUMAN INITIALISATION

// BEGIN MOSQUITO INITIALISATION

// ----------------------------------------------------

042 SM := SMeq // assign susceptible mosquito population size to steady state equilibrium size

043 EM := EMeq // assign exposed mosquito population size to steady state equilibrium size

044 IM := IMeq // assign infectious mosquito population size to steady state equilibrium size

// ----------------------------------------------------

// END MOSQUITO INITIALIATION

// BEGIN NORMALISED SEASONAL CURVE CREATION

// ----------------------------------------------------

// Loop through every day in simulation and calculate the seasonal curve for that day

045 FOR day := 1 TO t\_max // t\_max is total simulation time in days

046 [day]:= Fourier\_average +

first\_cosine\_term \* cos(2\*pi\*day/365) +

second\_cosine\_term \* cos(2\*2\*pi\*day/365) +

third\_cosine\_term \* cos(3\*2\*pi\*day/365) +

first\_sine\_term \* sin(2\*pi\*day/365) +

second\_sine\_term \* sin(2\*2\*pi\*day/365) +

third\_sine\_term \* sin(3\*2\*pi\*day/365))

047 ENDFOR

// Loop through every day in simulation and normalise seasonal curve for that day

048 mean\_theta := mean([1 TO 365)

049 FOR day := 1 TO t\_max // t\_max is total simulation time in days

050 [day] := [day] / mean\_theta // normalise theta with first 365 days of theta

051 IF ([day] < 0.001) // with only 1st 3 terms of Fourier used we need to check for <0

052 [day] := 0.001

053 ENDIF

054 ENDFOR

// ----------------------------------------------------

// END NORMALISED SEASONAL CURVE CREATION

// BEGIN STEPPING THROUGH TIME

// ----------------------------------------------------

055 FOR t := 1 TO t\_max // t\_max is total simulation time in days

// if we are within the first 35 days set the delays equal to 1. This wil cause a slight burn in period, which is accounted for with long initial simulation times to reach equilibrium

056 IF (t < 35)

057 delay\_gam := delay\_liver := delay\_mos := 1

058 ELSE

059 delay\_gam := dg // assign delay due to gametocytogenesis

060 delay\_liver := dE // assign delay due to liver stage infection

061 delay\_mos := dEM // assign delay due to mosquito incubation period

062 ENDIF

063 \_sum := 0 // reset psi sum to 0

// BEGIN NON-INFECTION CHANGES

// ----------------------------------------------------

064 FOR i := 1 TO N

// update human ages, find individuals who die

// ----------------------------------------------------

065 age[i] := age[i] + 1 // increase age by one day

066 IF (age[i] >= (100\*365) OR bernoulli(1-exp(-)) = 1) // if older than 100 years or die

067 age[i] := 0 // reset age to 1 day

068 inf\_state[i] := S // reset infection state to susceptible

069 n\_wt\_strains[i] := n\_hrp2\_strains[i] := 0 // clear all strains

070 IB := ICA := ID := 0 // reset immunities

071 ICM := PM\*mean(ICA[20\*365 < age <= 21\*365]) // assign maternal immunity using the mean acquired clinical immunity of individuals who are aged between 20 and 21 years old

072 tk[i] := tl[i] := tm[i] := -Tbig // reset last biting times

073 [i] := randlognormal(meanlog=-0.5\*,sdlog=) //assign biting heterogeneity rate

074 ELSE

// adjust immunities to exponentially decline

075 IB[i] := IB[i]\*exp(-rB)

076 ICA[i] := ICA[i]\*exp(-rCA)

077 ID[i] := ID[i]\*exp(-rD)

078 ICM[i] := ICM[i]\*exp(-rCM)

079 ENDIF

// Change of infection states not due to an infection

// ----------------------------------------------------

// T -> P

080 IF (inf\_state[i] = T) // if they are in state T

081 IF (bernoulli(1-exp(-rT)) = 1) // do they recover to state P today

082 inf\_state[i] := P // move to state P

083 n\_wt\_strains[i] := n\_hrp2\_strains[i] := 0 //clear all strains

084 ENDIF

085 ENDIF

// P -> S

086 IF (inf\_state[i] = P) // if they are in state P

087 IF (bernoulli(1-exp(-rP)) = 1) // do they lose prophylaxis and become susceptible again today

088 inf\_state[i] := S // move to state S

089 ENDIF

090 ENDIF

// D -> A

091 IF (inf\_state[i] = D) // if they are in state D

092 IF (bernoulli(1-exp(-rD)) = 1) // do they cease having symptoms and move to an asymptomatic infection today

093 inf\_state[i] := A // move to state A

094 ENDIF

095 ENDIF

// A -> U

096 IF (inf\_state[i] = A) // if they are in state A

097 IF (bernoulli(1-exp(-rA)) = 1) // do they cease being detectable as an infection and move to a sub-patent infection today

098 inf\_state[i] := U // move to state U

099 ENDIF

100 ENDIF

// U -> S

093 IF (inf\_state[i] = U) // if they are in state U

094 IF (bernoulli(1-exp(-rU)) = 1) // do they recover today and become susceptible today

095 inf\_state[i] := S // move to state S

n\_wt\_strains[i] := n\_hrp2\_strains[i] := 0 // clear all strains

096 ENDIF

097 ENDIF

// assess if individual has cleared a strain naturally

// ----------------------------------------------------

101 IF (inf\_state[i] = D OR A OR U OR T) // if individual is infected

102 total\_strains := n\_hrp2\_strains[i] + n\_wt\_strains[i] // all strains present

// if they have more than 1 strain to clear AND will they clear a strain today

103 IF (total\_strains > 1 AND bernoulli(1 - exp(-(total\_strains)/(dA + dU))) = 1)

// once chosen to clear a strain, which strain is chosen from relative ratio

104 IF (bernoulli(n\_hrp2\_strains[i]/total\_strains)=1)

105 n\_hrp2\_strains[i] := n\_hrp2\_strains[i] – 1 // clear an hrp2-deleted strain

106 ELSE

107 n\_wt\_strains[i] := n\_wt\_strains[i] – 1 // clean a wild type strain

108 ENDIF

109 ENDIF

110 ENDIF

// assign non-normalised age dependent biting heterogeneity

111 REPEAT LINES 36-37

// assign contributions to onward infectiousness

112 REPEAT LINES 21-35

113 ENDFOR

// normalise age-dependent biting heterogeneity

114 REPEAT LINES 39-41

// ----------------------------------------------------

// END NON-INFECTION CHANGES

// BEGIN MOSQUITO DYNAMICS

// ----------------------------------------------------

// calculate strain profile and size of human infectious reservoir that is gametocytogenic today

115 hrp2\_wt\_reservoir := hrp2\_del\_reservoir := 0 // reset reservoir sums to zero

116 FOR i := 1 TO N

// what was the total number of strains that could now be gametocytogenic

117 total\_gam\_strains[i] := (n\_hrp2\_strains[i] + n\_wt\_strains[i] FROM delay\_gam EARLIER)

// what is the relative contribution of hrp2 deleted strains to onward transmission today, which is determined by the contribution to onward infection from delay\_gam days earlier

118 hrp2\_del\_reservoir := hrp2\_del\_reservoir + ([i]\*[i]\*cont[i]\*n\_hrp2\_strains[i]) FROM delay\_gam EARLIER))/total\_gam\_strains[i]

// what is the relative contribution of wild type strains to onward transmission today, which is determined by the contribution to onward infection from delay\_gam days earlier

119 wt\_reservoir := wt\_reservoir + ([i]\*[i]\*cont[i]\*n\_wt\_strains[i]) FROM delay\_gam EARLIER))/total\_gam\_strains[i]

120 ENDFOR

// calculate total size of human infectious reservoir and update mosquito population

121 human\_reservoir := hrp2\_del\_reservoir/N + wt\_reservoir/N

// mosquito population changes

122 surv := exp(-M\*delay\_mos) // the proportion of mosq that survive long enough to complete the latent period

123 foiv := ak\*human\_reservoir // force of infection to vectors from delay\_gam earlier

124 ince := SM\*foiv // proportion of susceptible mosquitoes that become infected

125 incv := ince\*surv //proportion of mosquitoes that get infected that survive to have sporozoites

126 Mv := SM + EM + IM // total mosquito population size

127 betav := Mv\*μM\*[i] // growth rate of new mosquitoes that ensures constant population size multiplied by the normalised seasonal curve

128 SM := SM + (-ince - (M\*SM) + betav) // susceptible size – infections - death + birth

129 EM := EM + (ince - incv - (M\*EM)) // exposed size + infections – incubations - death

130 IM := IM + (incv - (M\*IM)) // infectious size + incubations - death

// ----------------------------------------------------

// END MOSQUITO DYNAMICS

// loop through population deciding if they are bitten today using the entomological innoculation rate from delay-liver days earlier, if so does it lead to an increase in IB or not, does it lead to an infection and do ICA and ID subsequently increase or not, what strains will be passed on if it led to an infection by looking at the strain profile of the human infectious reservoir from delay\_liver + delay\_mos before, what infection state they will move to as a result of immunity and their strain profile that is detectable today along with RDT nonadherence and alternative diagnosis using microscopy-based detection, before considering whether that person will have also potentially been treated due to non-malarial fever.

// BEGIN MOSQUITO BITING

// ----------------------------------------------------

131 FOR i := 1 TO N

// are they bitten by an infectious mosquito

132 IF (bernoulli(1-exp(-(ak\*[i]\*[i]\*(IM FROM delay\_liver EARLIER))) = 1)

// was their last boost time to pre-erythrocytic immunity more than uB days earlier then boost immunity and set last boost time to today

133 IF ((t - tk[i]) > uB)

134 IB[i] := IB[i] + 1 // increase pre-erythrocytic immunity

135 tk[i] := t // set last boost time to today

136 ENDIF

// calculate the probability of being infected

137 b[i] := b0 \* (b1 + ((1 - b1) /(1 + ((IB[i] /IB0)^kB))))

// are they capable of being infected, i.e. not being treated or in prophylaxis

138 IF (inf\_state[i] = S OR D OR A OR U))

// are they infected

139 IF (bernoulli(b[i]) = 1)

// was their last boost time to acquired clinical immunity more than uB days earlier then boost immunity and set last boost time to today

140 IF ((t - tl[i]) > uC)

141 ICA[i] := ICA[i] + 1 // increase acquired clinical immunity

142 tl[i] := t // set last boost time to today

143 ENDIF

// was their last boost time to detection immunity more than uB days earlier then boost immunity and set last boost time to today

144 IF ((t - tm[i]) > uD)

145 ID[i] := ID[i] + 1 // increase detection immunity

146 tm[i] := t // set last boost time to today

147 ENDIF

// calculate probability of developing symptoms

148 [i] := 0 \* (1 + ((1 -1) /(1 + (((ICA[i]+ICM[i]) /IC0)^C))))

// work out what strain they will be passed on by conducting a bernoulli trial using the relative ratio of hrp2 deleted strains to wild type strains from 22 days earlier, and applying any assumed fitness cost to hrp2 deletion which will shift the ratio.

148 IF (bernoulli((hrp2\_del\_reservoir\*fitness\_cost)/human\_reservoir FROM (delay\_liver + delay\_mos) EARLIER)=1)

149 n\_hrp2\_strains[i] := n\_hrp2\_strains[i] + 1 // increase hrp2 deleted strains

// if they are subpatent we need to handle the chance that a positive test result will happen due to HRP3 epitopes differently than other diseased states. This is because we assume that strains inherited earlier will not be detected due to the individual being subpatent. As such will only become 1 if the strain to be passed on is wild type. This will be the same for a susceptible individual who has no current strains.

150 IF (inf\_state[i] = S OR U)

151 [i] := 0.25 // 25% chance of HRP3 epitope cross reactivity

152 ELSE

153 IF (n\_wt\_strains > 0)

154 [i] := 1 // individual has at least one wt strain and thus = 1

155 ELSE

156 [i] := 0.25 // 25% chance of HRP3 epitope cross reactivity

157 ENDIF

158 ENDIF

159 ELSE

160 n\_wt\_strains[i] := n\_wt\_strains[i] + 1

161 [i] := 1 // individual has at least one wt strain and thus = 1

162 ENDIF

// state change assignment by working out probability of being correctly detected if seeking treatment. This takes into account strain profile, and chance that they will still be treated despite being only infected with hrp2 deleted strains due to HRP3 epitope effects, non-adherence to test results and whether microscopy based detection was used

163 prob\_hrp2\_del\_treated := 1 - ((1-[i])\*(1-non\_adherence)\*(1-microscopy\_use))

164 prob\_D := [i]\*(1-(fT\*prob\_hrp2\_del\_treated)) // probability going to state D

165 prob\_T := [i]\*(fT\*prob\_hrp2\_del\_treated) // probability of going to state T

// we assume that if they are in state D already an additional infection cannot lead them to become asymptomatic and thus the probability of going to state A is 0 if in state D, otherwise determined by 1 – probability of developing symptoms

166 IF (inf\_state[i] = D)

167 prob\_A := 0 // probability going to state A is 0% for those in state D

168 ELSE

169 prob\_A := 1 - [i] // probability going to state A if not in state D

170 ENDIF

// assign what state change occurs by sampling according to the probabilities of each state change occurring

171 inf\_state[i] := DRAW FROM [D,T,A] WITH WEIGHTS [prob\_D,prob\_T,probA]

172 ENDIF

173 ENDIF

174 ENDIF

// ----------------------------------------------------

// END MOSQUITO BITING

// BEGIN NON-MALARIAL FEVER CONSIDERATION

// ----------------------------------------------------

// did a non-malarial fever occur using the age-dependent rate of non-malarial fevers

175 IF (bernoulli(1-exp(-nmf[age[i]])) = 1)

// if they are susceptible the only chance of being treated is if they both seek treatment and the outcome of the test result is not adhered to. If so they will move to a state of prophylaxis rather than being treated as they have no strains to be treated

176 IF (inf\_state[i] = S) // if in state S

177 IF (bernoulli(fT\*non\_adherence)) // if they seek treatment and result is not adhered to

178 inf\_state[i] := P // move to state P

179 ENDIF

180 ENDIF

// if they are subpatent the only chance of being treated is if they both seek treatment and the outcome of the test result is not adhered to. If so they will move to being treated

181 IF (inf\_state[i] = U) // if in state U

182 IF (bernoulli(fT\*non\_adherence)) // if they seek treatment and result is not adhered to

183 inf\_state[i] := T // move to state T

184 ENDIF

185 ENDIF

// if they are diseased or asymptomatic they will be treated if they seek treatment and it either leads to a positive result if they have wild type strains or if they used microscopy for detection or the test result is not adhered to

186 IF (inf\_state[i] = [D OR A]) // if in state D or A

187 IF (n\_wt\_strains > 0) // if they have any wild type strains

188 [i] := 1 // 100% probability of positive test result

189 ELSE

190 [i] := 0.25 // 25% chance of positive test result due to HRP3 epitope effects

191 ENDIF

// probability of being treated due to HRP3 epitope effects, or non-adherence to test result or microscopy based diagnosis used

192 prob\_hrp2\_del\_treated := 1 - ((1-[i])\*(1-non\_adherence)\*(1-microscopy\_use))

193 IF (bernoulli(fT\*prob\_hrp2\_del\_treated)) // if seek treatment and are thus treated

194 inf\_state[i] := T // move to state T

195 ENDIF

196 ENDIF

197 ENDIF

// ----------------------------------------------------

// END NON-MALARIAL FEVER CONSIDERATION

198 ENDFOR

199 ENDFOR

// ----------------------------------------------------

// END STEPPING THROUGH TIME

1 The equilibrium solution to an equivalent deterministic model can be sought by categorising the age and individual biting heterogeneity of individuals into a finite number of bands. The equations for the deterministic model are detailed below.