

# Malaria Elimination Trials and Simulations



Lisa J White

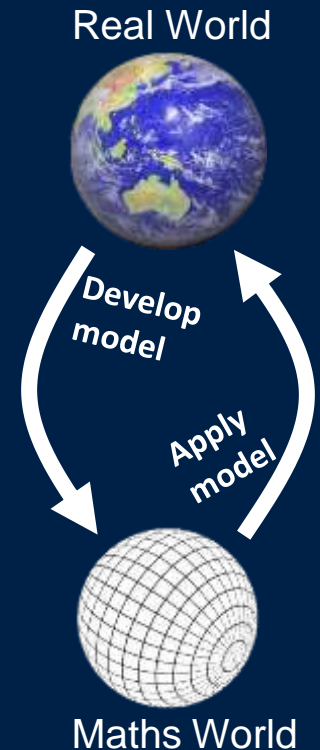
Oxford Modelling for Global Health (OMGH)

Big Data Institute, Nuffield Department of Medicine

University of Oxford

# A mathematical model...

- is a description of a system or multiple interacting systems using mathematics
- can be used to answer “what if” questions about the system
- can be simple or complex
- has many limitations:
  - Simple models have more limitations in biology but are faster to write and run with small data
  - Complex models have more detail but are slower to write and run and demand large sets of data



**World Health Organization  
Global Technical Strategy for Malaria  
2016-2030**

***Pillar 1***

**Ensure universal access to  
malaria prevention, diagnosis  
and treatment**

***Pillar 2***

**Accelerate efforts towards  
elimination and attainment of  
malaria-free status**

***Pillar 3***

**Transform malaria surveillance  
into a core intervention**

***Supporting  
Element 1***

**Harnessing Innovation & Expanding Research**

***Supporting  
Element 2***

**Strengthening the Enabling Environment**

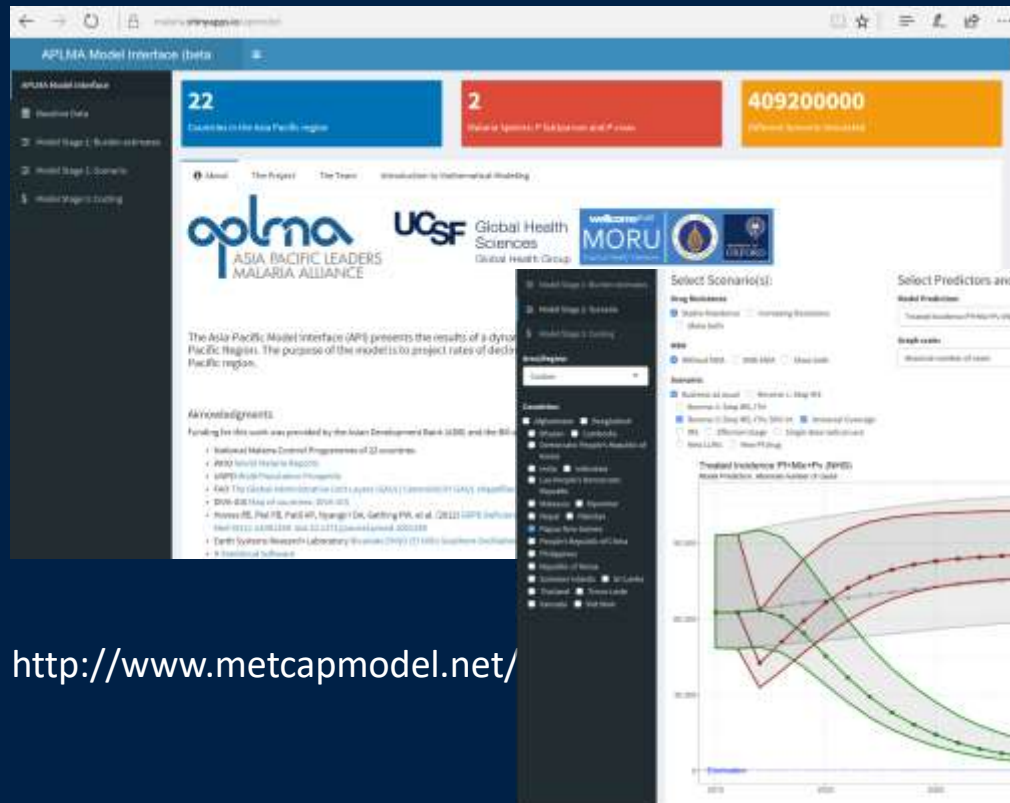
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# METCAP: Malaria Elimination Transmission and Costing in the Asia-Pacific



<http://www.metcapmodel.net/>



Dr Sheetal Silal, UCT

# Model Equations

$$\frac{dS}{dt} = \mu P(t) - \mu S - \Lambda(t)S + \omega R$$

$$\frac{dI_n}{dt} = -\mu I_n + p_{en}(1 - p_s)\Lambda(t)S - r_n I_n + r_a I_n - (1 - p_{rn})(1 - p_r)\Lambda(t)I_n - p_r \Lambda(t)I_n + p_{rn}(1 - p_r)p_{rel}\nu L$$

$$\frac{dI_a}{dt} = -\mu I_a + (1 - p_{an})(1 - p_s)\Lambda(t)S + (1 - p_{sev})r_c I_c - r_a I_a + (1 - p_{rn})(1 - p_r)\Lambda(t)I_n - p_r \Lambda(t)I_n + (1 - p_{rn})(1 - p_r)\Lambda(t)(R + H) + pt f(1 - pt f c)r_i(T_o + T_v + T_h)$$

$$\frac{dI_c}{dt} = -\mu I_c + (1 - \tau)p_s \Lambda(t)S + (1 - \tau_{sev})(1 - \theta_1)r_s I_s - (1 - p_{sev})r_c I_c - p_{sev}r_c I_c + p_r(1 - \tau)\Lambda(t)(I_n + I_a + R + H) + pt f(pt f c)(1 - pt f tr)r_i(T_o + T_v + T_h)$$

$$\frac{dI_s}{dt} = -\mu I_s - (1 - \tau_{sev})r_s I_s - \tau_{sev}r_Q I_a + p_{sev}r_c I_c$$

$$\frac{dT_o}{dt} = -\mu T_o + \tau_o p_s \Lambda(t)S - (1 - pt f)r_i T_o + p_r \tau_o \Lambda(t)(I_n + I_a + R + H)$$

$$\frac{dT_v}{dt} = -\mu T_v + \tau_v p_s \Lambda(t)S - (1 - pt f)r_i T_v + p_r \tau_v \Lambda(t)(I_n + I_a + R + H)$$

$$\frac{dT_h}{dt} = -\mu T_h + \tau_h p_s \Lambda(t)S - (1 - pt f)r_i T_h + p_r \tau_h \Lambda(t)(I_n + I_a + R + H) + pt f(pt f c)(pt f tr)r_i(T_o + T_v + T_h)$$

$$\frac{dR}{dt} = -\mu R + r_n I_n - \Lambda(t)R - \omega R + \chi H$$

$$\frac{dH}{dt} = -\mu H + (1 - pt f)r_i(T_o + T_v + T_h) + \tau_{sev}(1 - \theta_2)r_Q I_s - \Lambda(t)H - \chi H$$

$$\frac{dS}{dt} = \mu P(t) - \mu S - \Lambda(t)S + \omega R + \kappa L$$

$$\frac{dI_n}{dt} = -\mu I_n + p_{en}(1 - p_s)\Lambda(t)S - r_n I_n + r_a I_n - (1 - p_{rn})(1 - p_r)\Lambda(t)I_n - p_r \Lambda(t)I_n + p_{rn}(1 - p_r)p_{rel}\nu L + p_{rn}(1 - p_r)\Lambda(t)(R + L)$$

$$\frac{dI_a}{dt} = -\mu I_a + (1 - p_{an})(1 - p_s)\Lambda(t)S + (1 - p_{sev})r_c I_c - r_a I_a + (1 - p_{rn})(1 - p_r)\Lambda(t)I_n - p_r \Lambda(t)I_n + (1 - p_{rn})(1 - p_r)p_{rel}\nu L + (1 - p_{rn})(1 - p_r)\Lambda(t)(R + L) + p_{rf}(1 - pt f c)r_i(T_o + T_v + T_h + T_{oGD} + T_{vGD} + T_{hGD})$$

$$\frac{dI_c}{dt} = -\mu I_c + (1 - \tau)p_s \Lambda(t)S + (1 - \tau_{sev})(1 - \theta_1)r_s I_s - (1 - p_{sev})r_c I_c + p_r(1 - \tau)\Lambda(t)I_n - p_{sev}r_c I_c + p_r(1 - \tau)\Lambda(t)I_n + p_r(1 - \tau)p_{rel}\nu L + p_r(1 - \tau)\Lambda(t)(R + L) + p_{rf}(1 - pt f tr)(pt f c)r_i(T_o + T_v + T_h + T_{oGD} + T_{vGD} + T_{hGD})$$

$$\frac{dI_s}{dt} = -\mu I_s - (1 - \tau_{sev})r_s I_s - \tau_{sev}r_Q I_a + p_{sev}r_c I_c$$

$$\frac{dT_o}{dt} = -\mu T_o + (1 - p_{gd})\tau_o p_s \Lambda(t)S - (1 - p_{rf})r_i T_o + (1 - p_{gd})p_r \tau_o \Lambda(t)(I_n + I_a + R + L) + (1 - p_{gd})p_r \tau_o p_{rel}\nu L$$

$$\frac{dT_v}{dt} = -\mu T_v + (1 - p_{gd})\tau_v p_s \Lambda(t)S - (1 - p_{rf})r_i T_v + (1 - p_{gd})p_r \tau_v \Lambda(t)(I_n + I_a + R + L) + (1 - p_{gd})p_r \tau_v p_{rel}\nu L$$

$$\frac{dT_h}{dt} = -\mu T_h + (1 - p_{gd})\tau_h p_s \Lambda(t)S - (1 - p_{rf})r_i T_h + (1 - p_{gd})p_r \tau_h \Lambda(t)(I_n + I_a + R + L) + (1 - p_{gd})p_r \tau_h p_{rel}\nu L + p_{rf}(pt f tr)(pt f c)r_i(T_o + T_v + T_h)$$

$$\frac{dT_{oGD}}{dt} = -\mu T_{oGD} + p_{gd}\tau_o p_s \Lambda(t)S - (1 - p_{rf})r_i T_{oGD} + p_{gd}p_r \tau_o \Lambda(t)(I_n + I_a + R + L) + p_{gd}p_r \tau_o p_{rel}\nu L$$

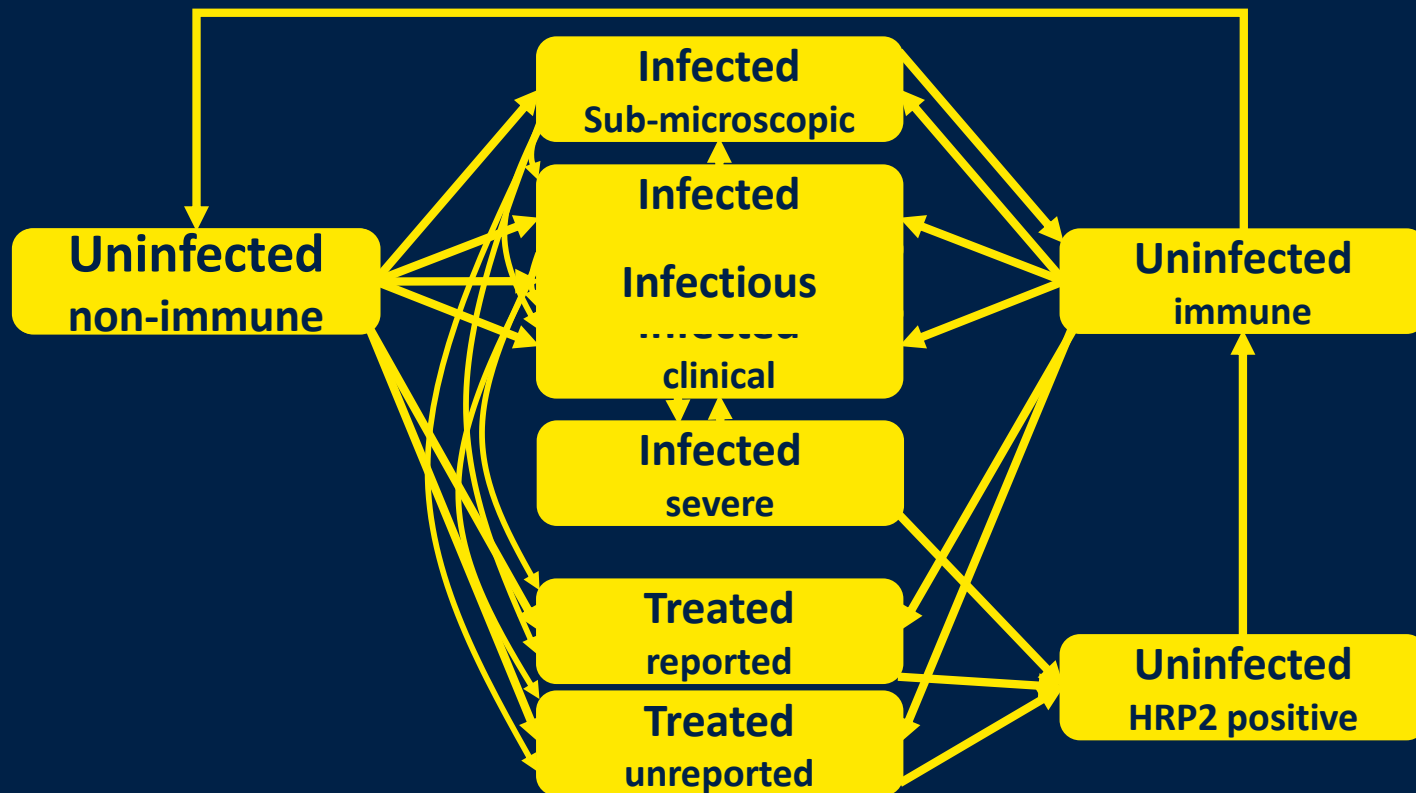
$$\frac{dT_{vGD}}{dt} = -\mu T_{vGD} + p_{gd}\tau_v p_s \Lambda(t)S - (1 - p_{rf})r_i T_{vGD} + p_{gd}p_r \tau_v \Lambda(t)(I_n + I_a + R + L) + p_{gd}p_r \tau_v p_{rel}\nu L$$

$$\frac{dT_{hGD}}{dt} = -\mu T_{hGD} + p_{gd}\tau_h p_s \Lambda(t)S - (1 - p_{rf})r_i T_{hGD} + p_{gd}p_r \tau_h \Lambda(t)(I_n + I_a + R + L) + p_{gd}p_r \tau_h p_{rel}\nu L + p_{rf}(pt f tr)(pt f c)r_i(T_{oGD} + T_{vGD} + T_{hGD})$$

$$\frac{dR}{dt} = -\mu R + (1 - p_h)(1 - p_{rf})r_i(T_o + T_v + T_h + T_{oGD} + T_{vGD} + T_{hGD}) + (1 - p_h)\tau_{sev}(1 - \theta_2)r_Q I_s + r_n I_n - \Lambda(t)R - \omega R$$

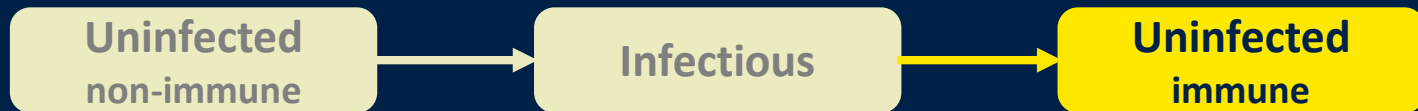
$$\frac{dL}{dt} = -\mu L + p_h(1 - p_{rf})r_i(T_o + T_v + T_h + T_{oGD} + T_{vGD} + T_{hGD}) + p_h\tau_{sev}(1 - \theta_2)r_Q I_s - p_{rel}\nu L - \Lambda(t)L - \kappa L$$

## *Plasmodium falciparum*



Building an malaria model  
 Individuals may become infected with malaria,

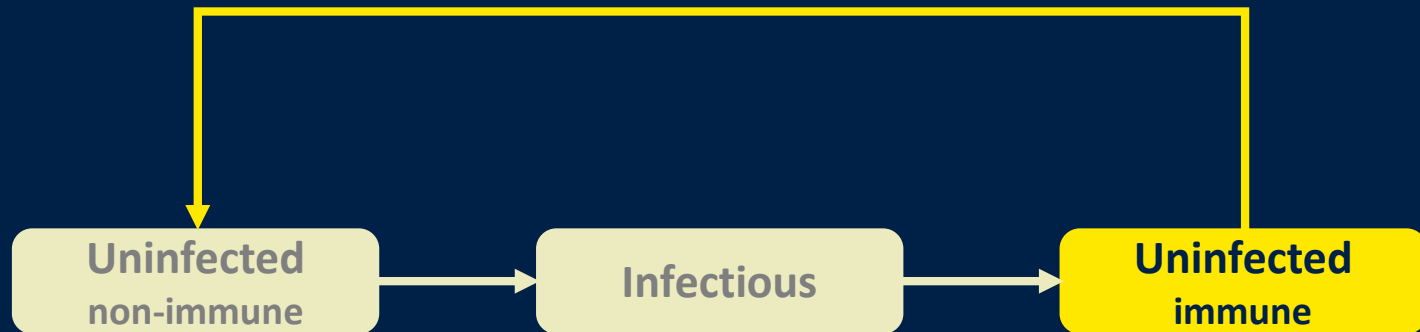
## *Plasmodium falciparum*



recover naturally and develop immunity

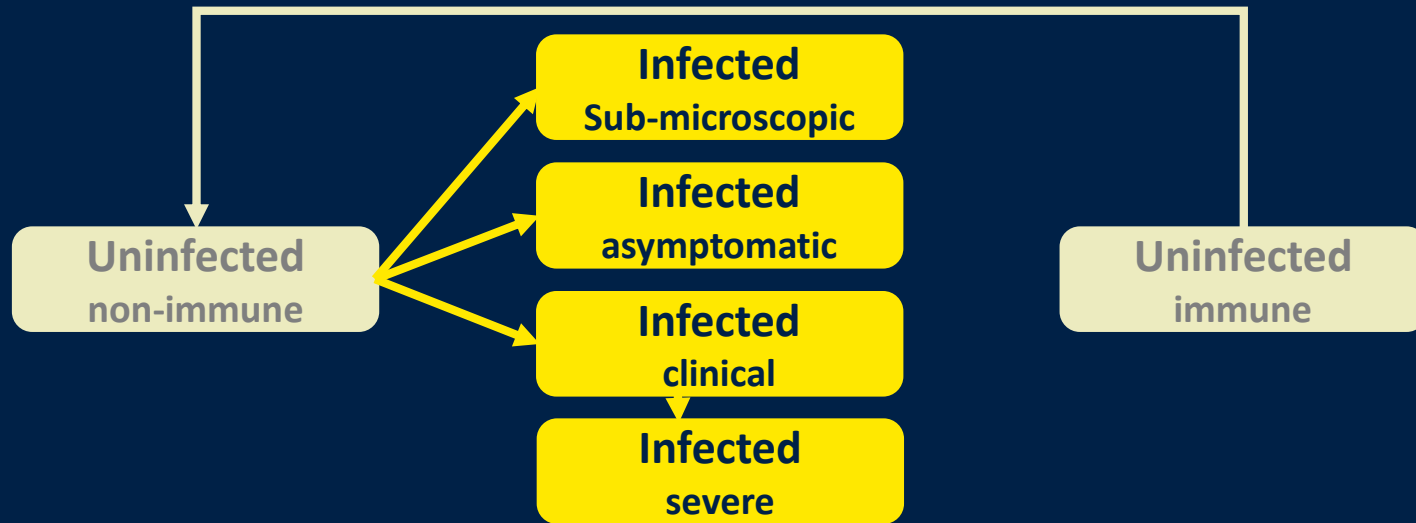


## *Plasmodium falciparum*



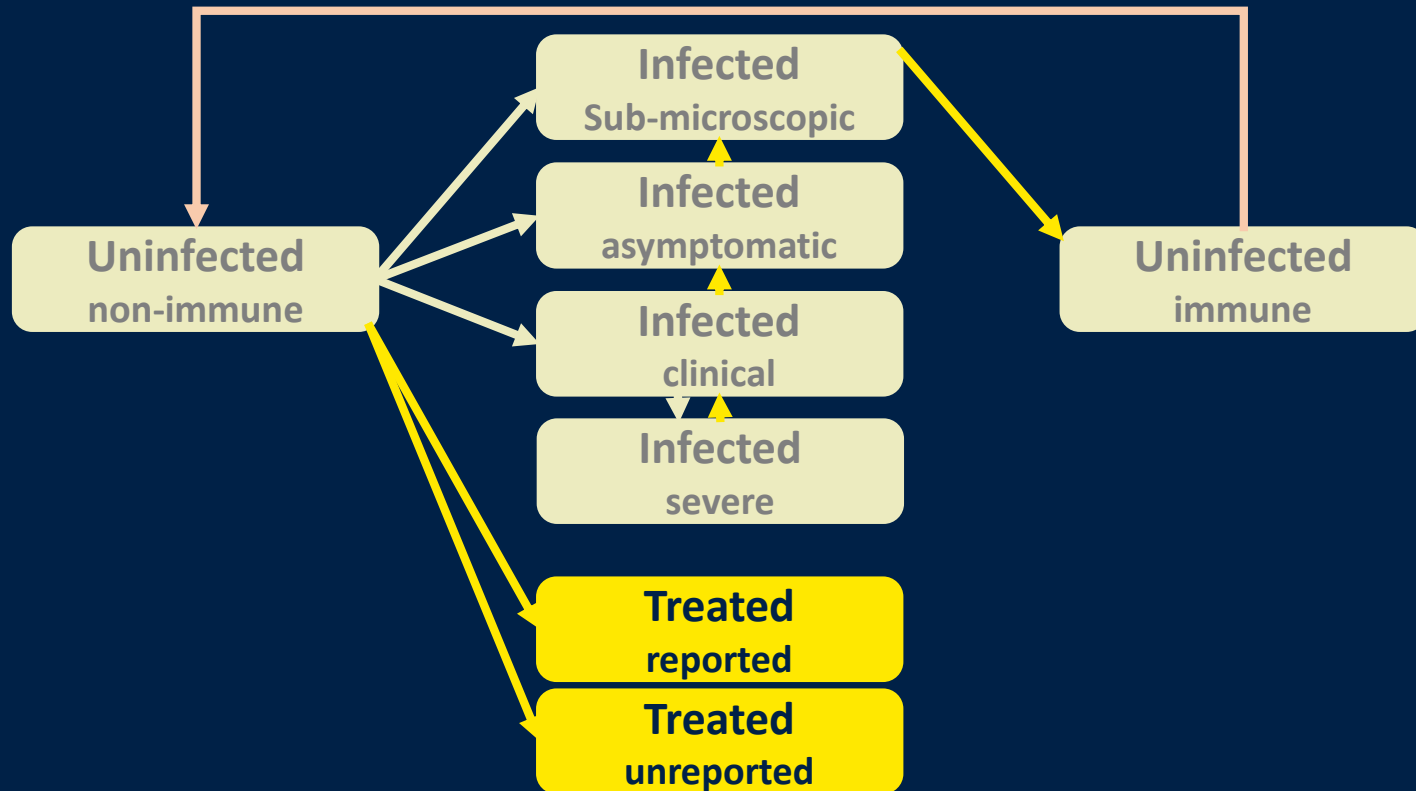
immunity may be lost over time

## *Plasmodium falciparum*



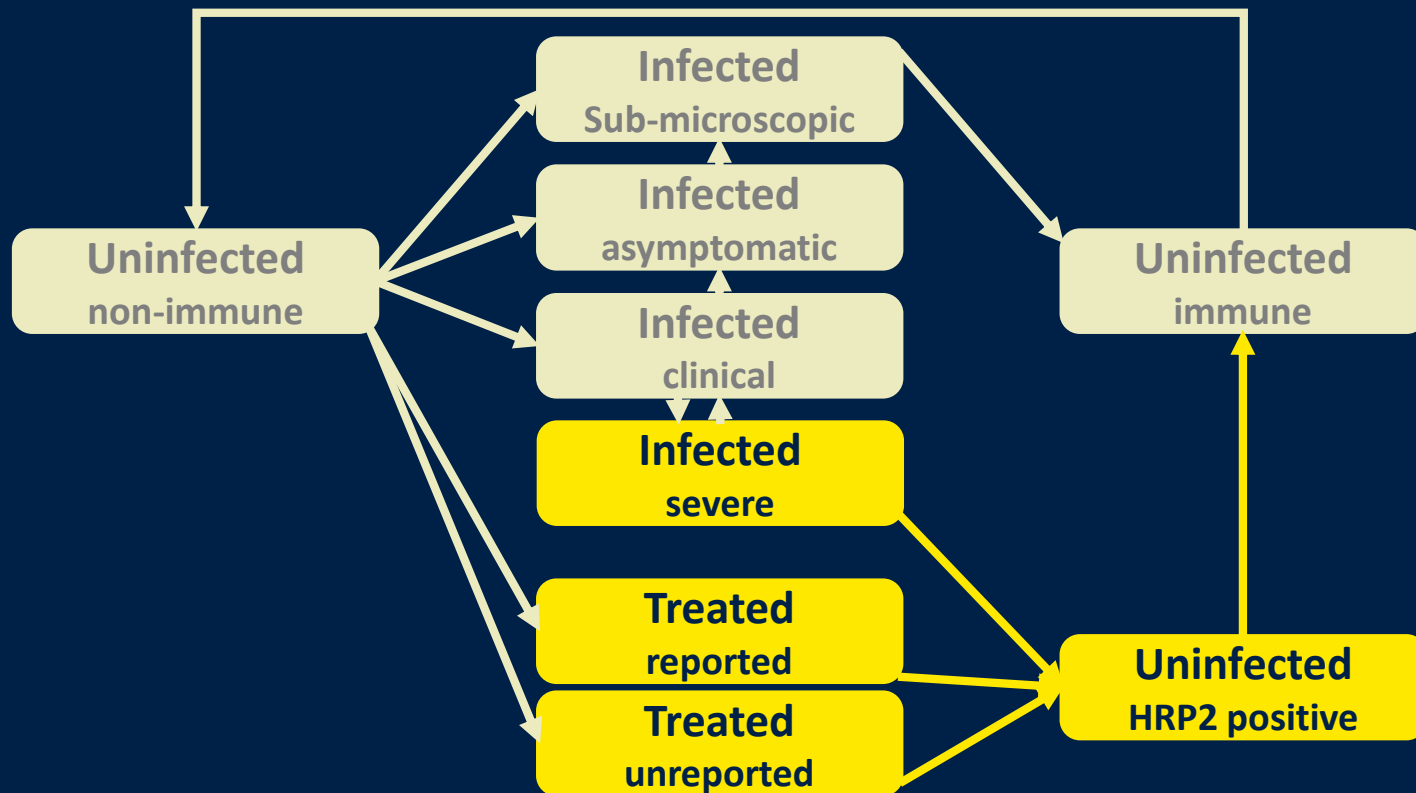
infections have different levels of severity

## *Plasmodium falciparum*



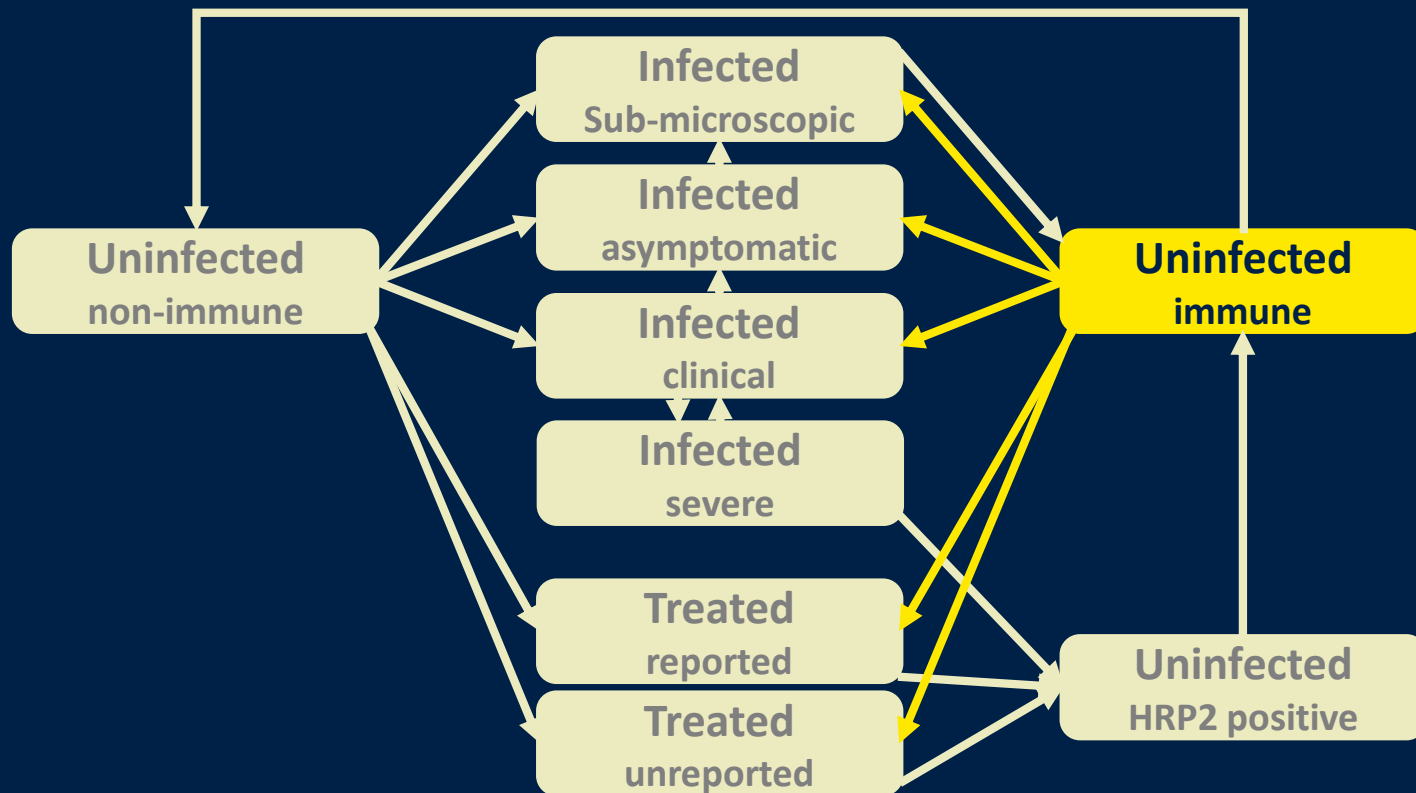
some infections are treated, others recover naturally

## *Plasmodium falciparum*



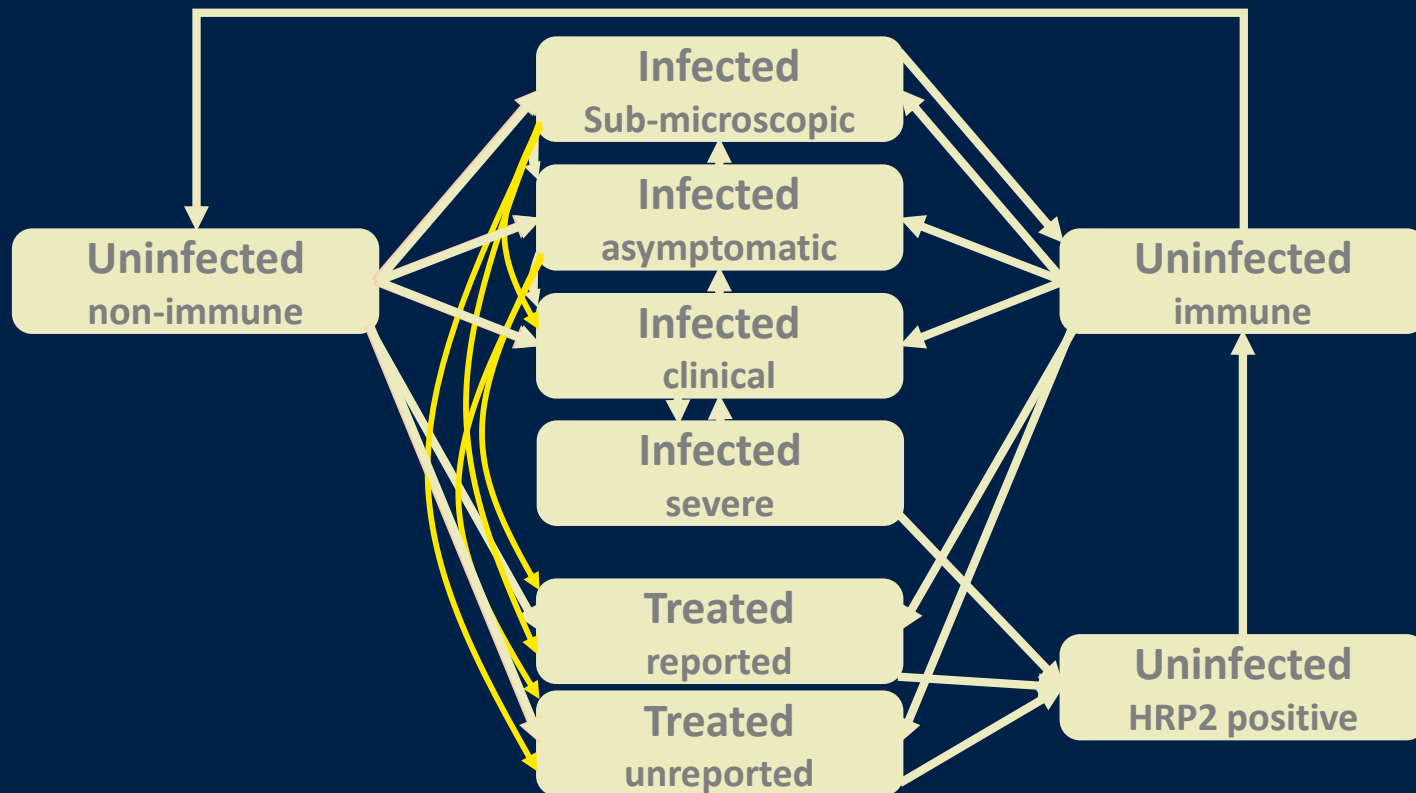
people can still test positive for after successful treatment

## *Plasmodium falciparum*



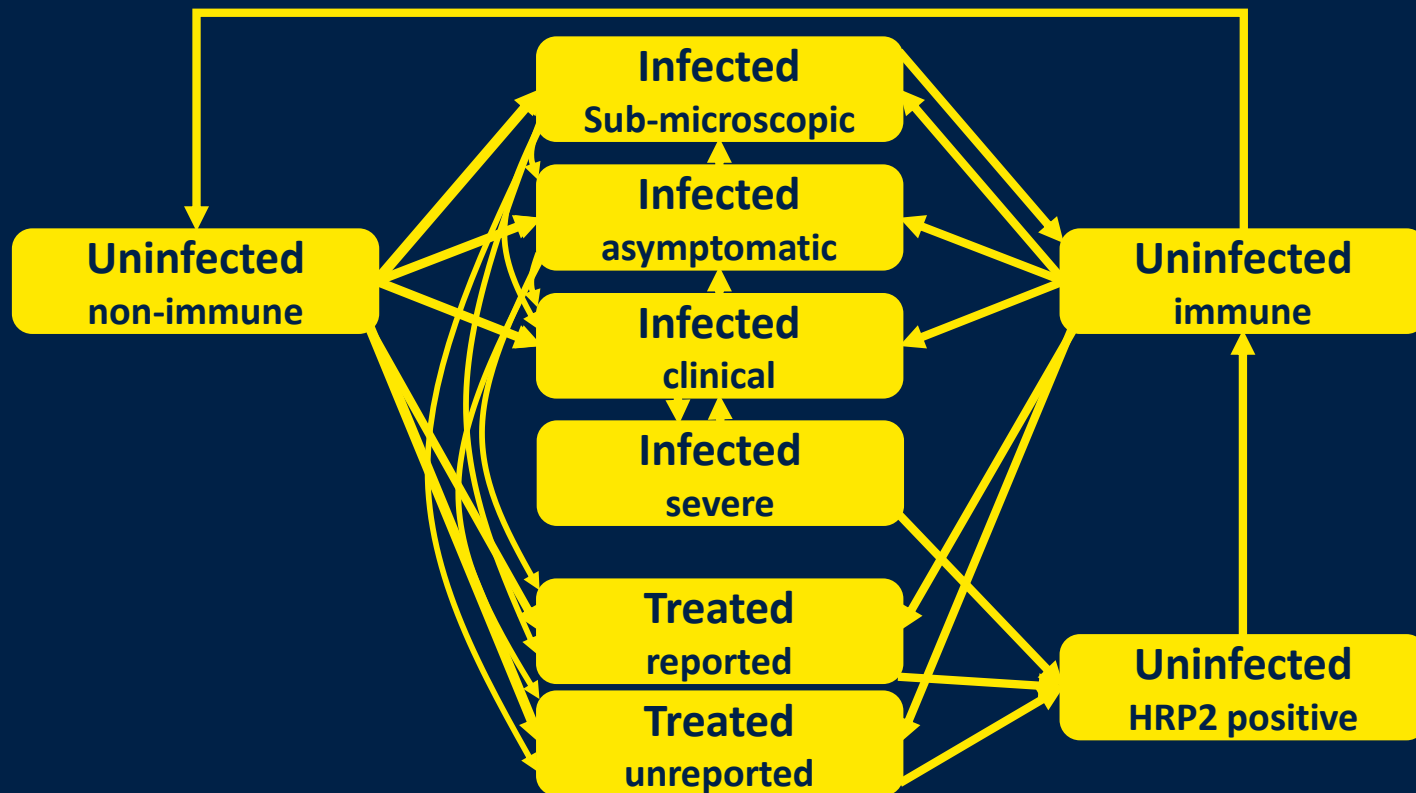
immune people get infected, but are less likely to have symptoms

## *Plasmodium falciparum*

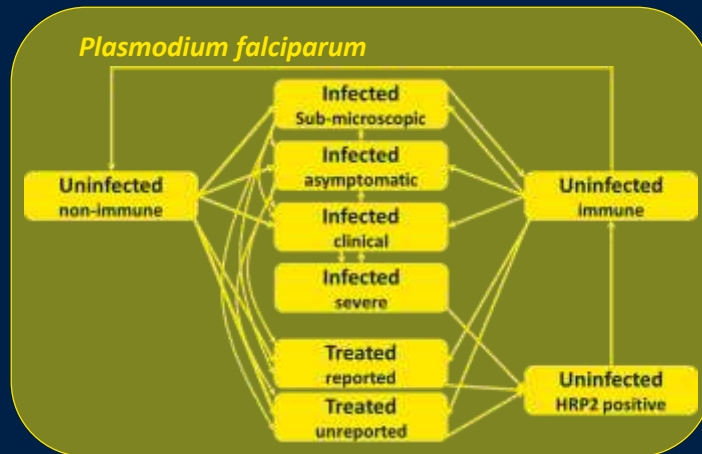


more than one infection at the same time (superinfection)

## *Plasmodium falciparum*



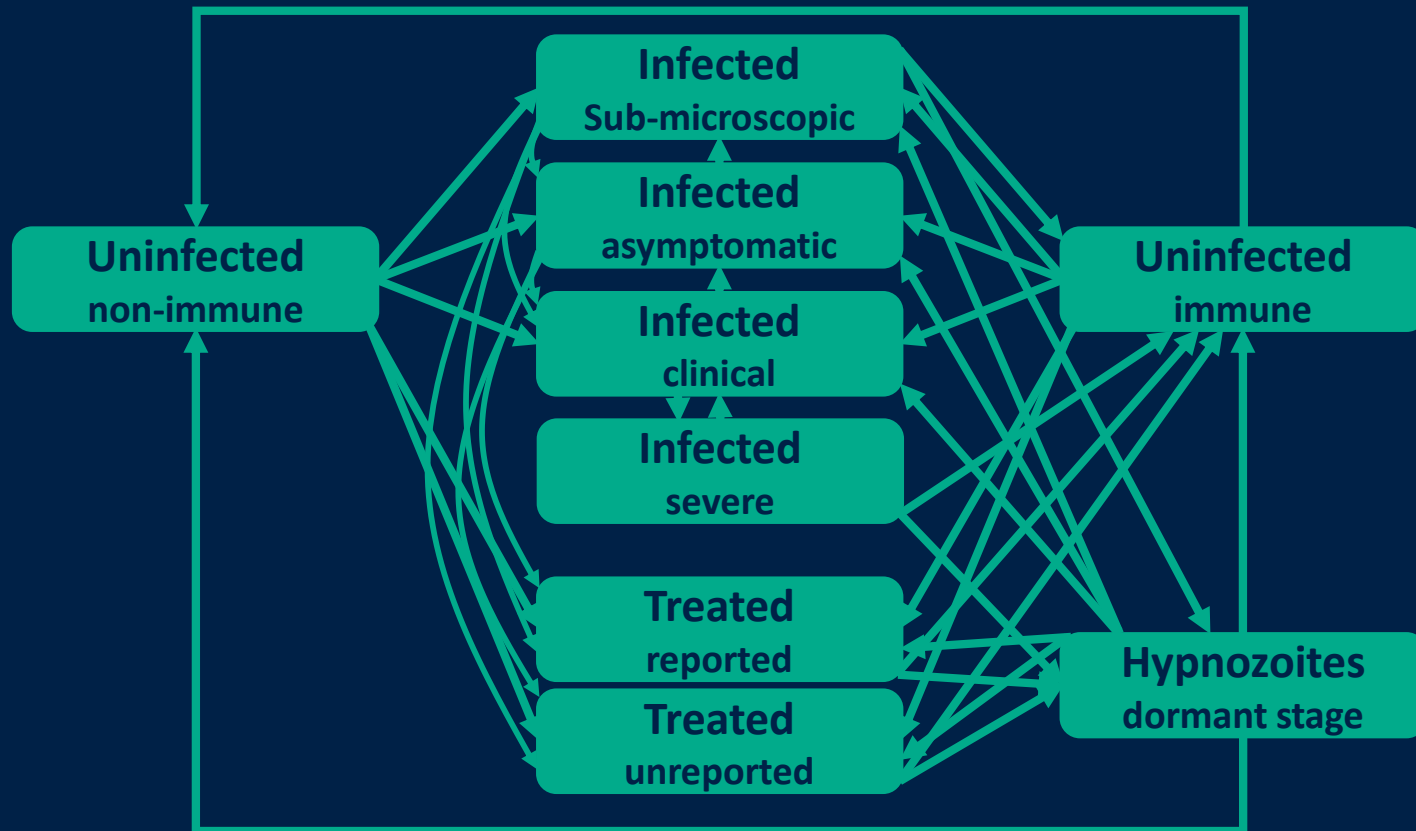
the model combines all these processes in one framework



but the Asia-Pacific has two major malaria species

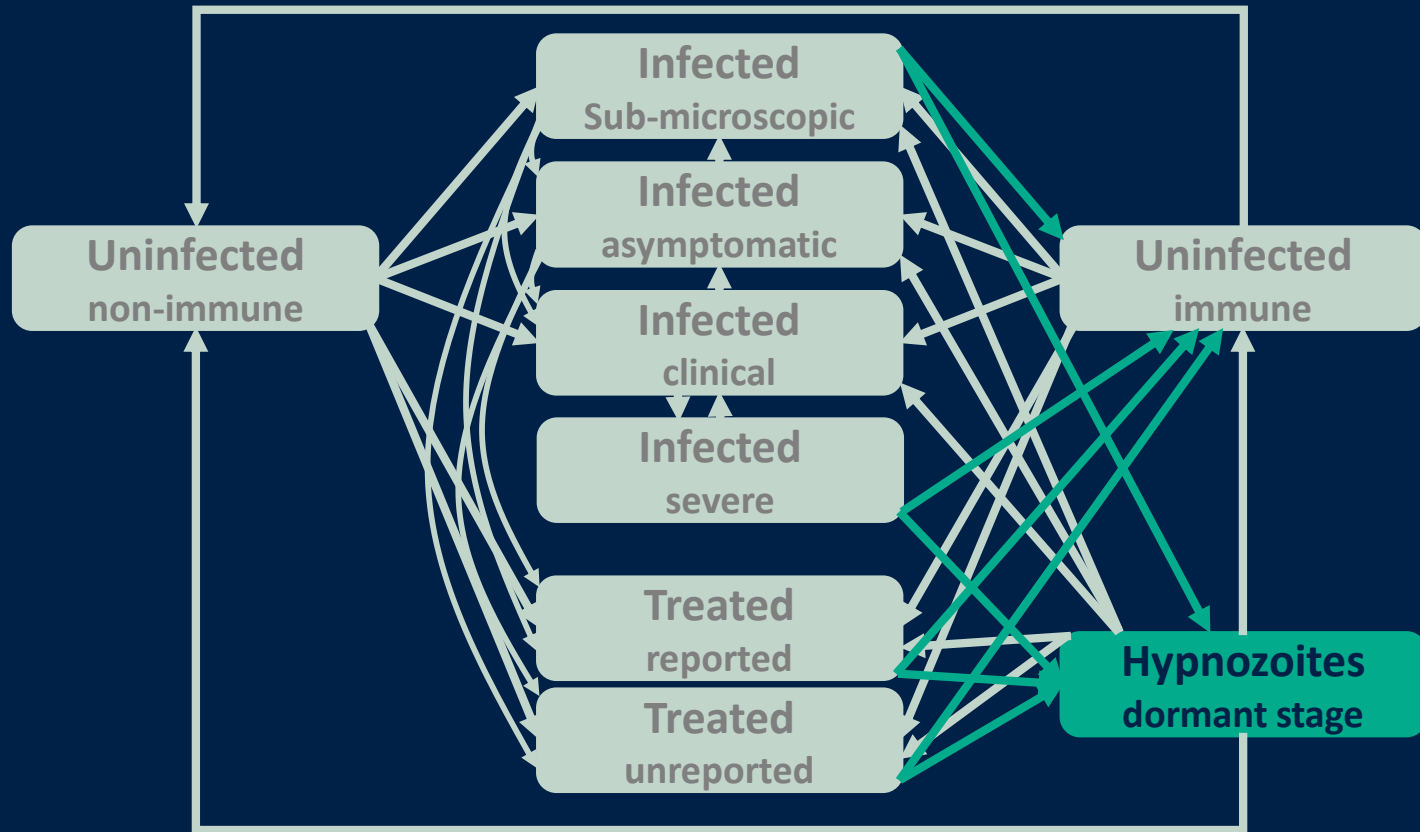


## *Plasmodium vivax*



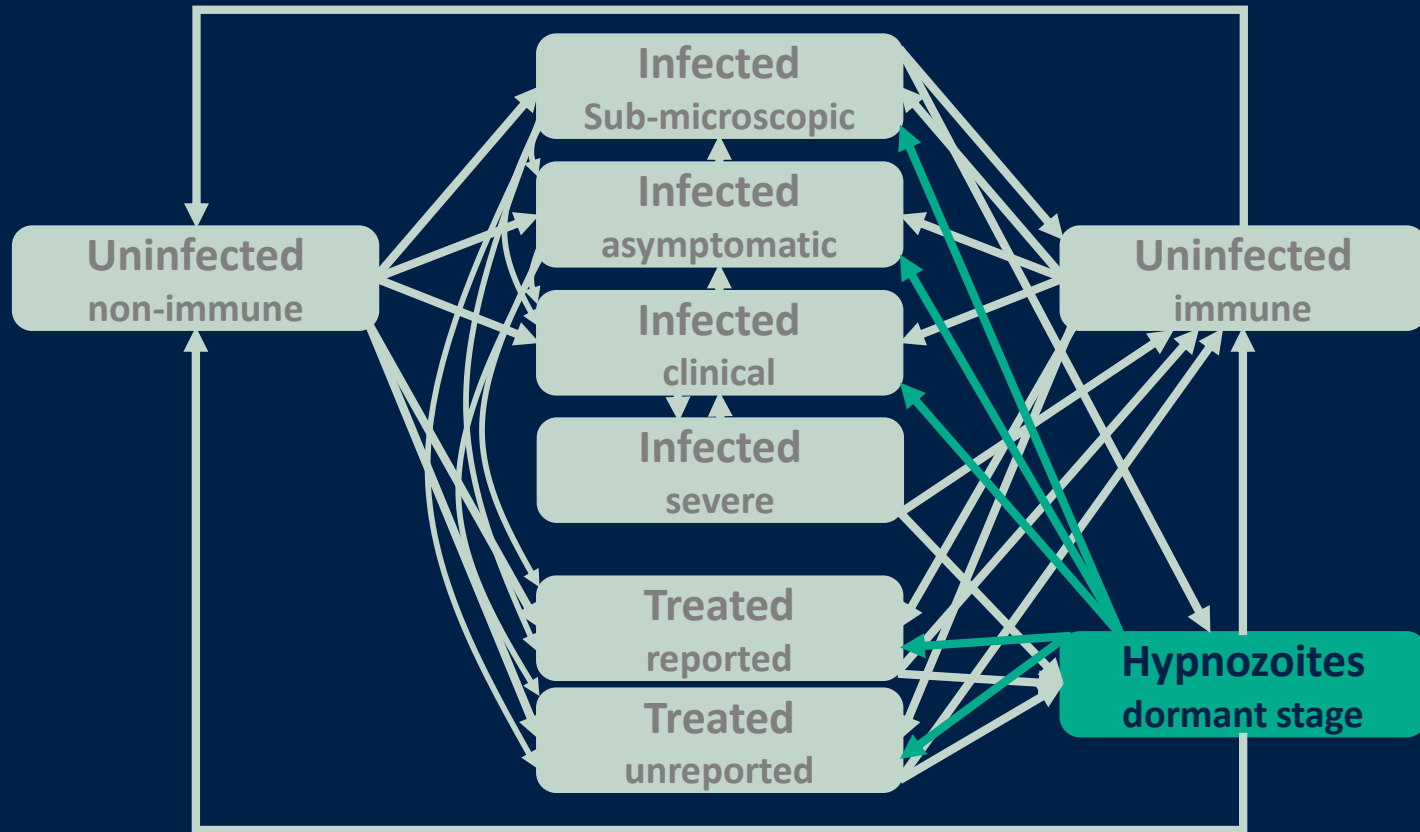
The model for *P. vivax* is different from the model for *P. falciparum*

## *Plasmodium vivax*

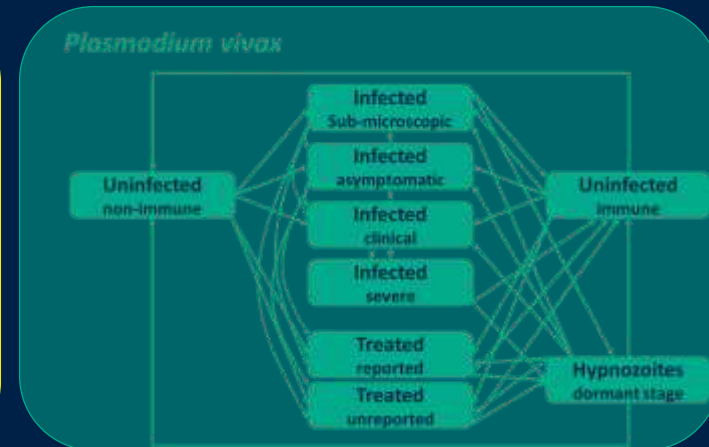
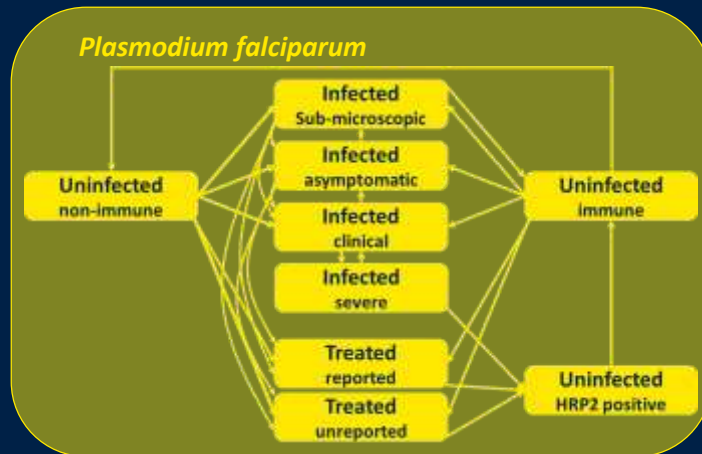


recovery may result in the dormant stage (hypnozoites)

## *Plasmodium vivax*



hypnozoites are a source of relapse months after the initial infection



the transmission and control of both species is simultaneous

*Plasmodium falciparum*

*Plasmodium vivax*

the species interact

# Building a spatial model

- Start with the geographic scope and define the sub-population or “patch”



# Building a spatial model

- Include data on population distribution by patches



# Building a spatial model

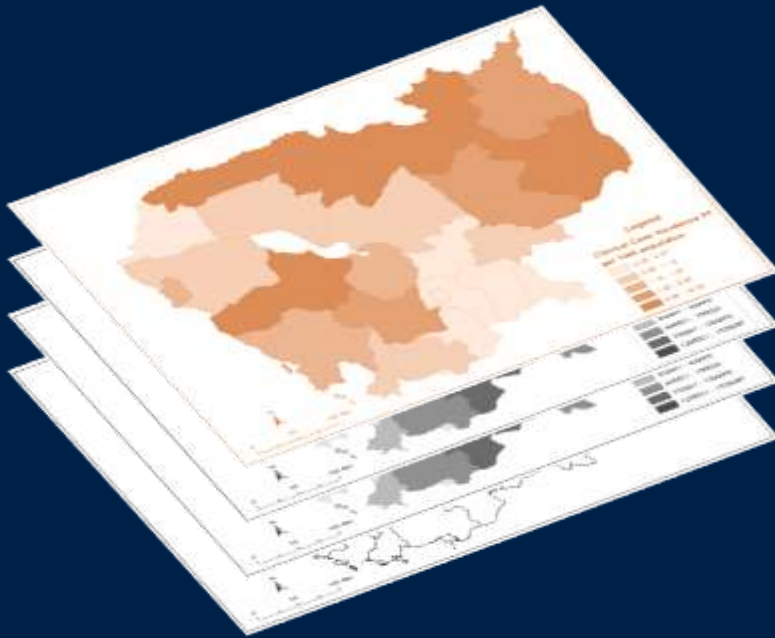
- Include some assumptions or data on connectivity between patches





# Building a spatial model

- Include surveillance data on spatial heterogeneity in transmission

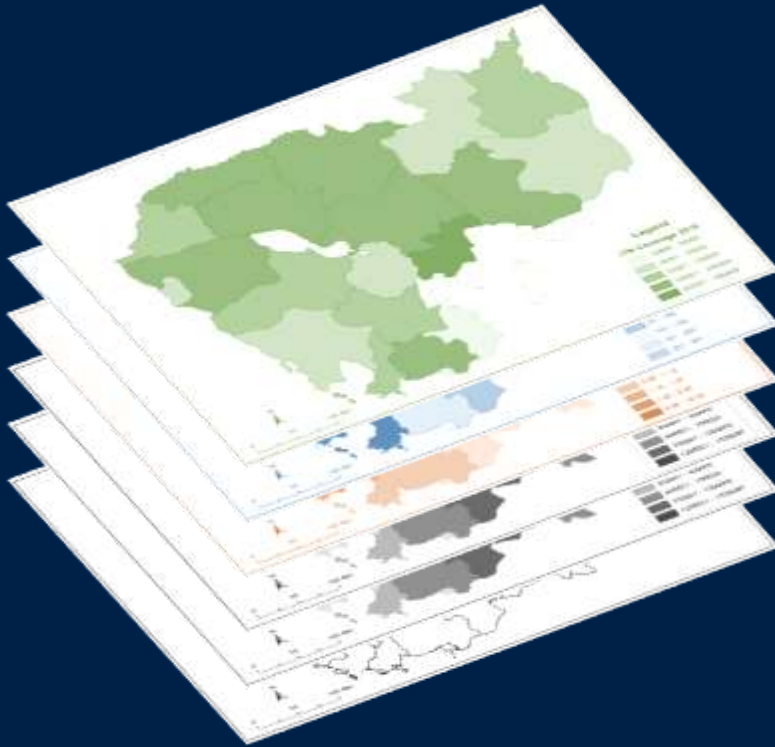


# Building a spatial model

- Include data on historical and planned clinical case management



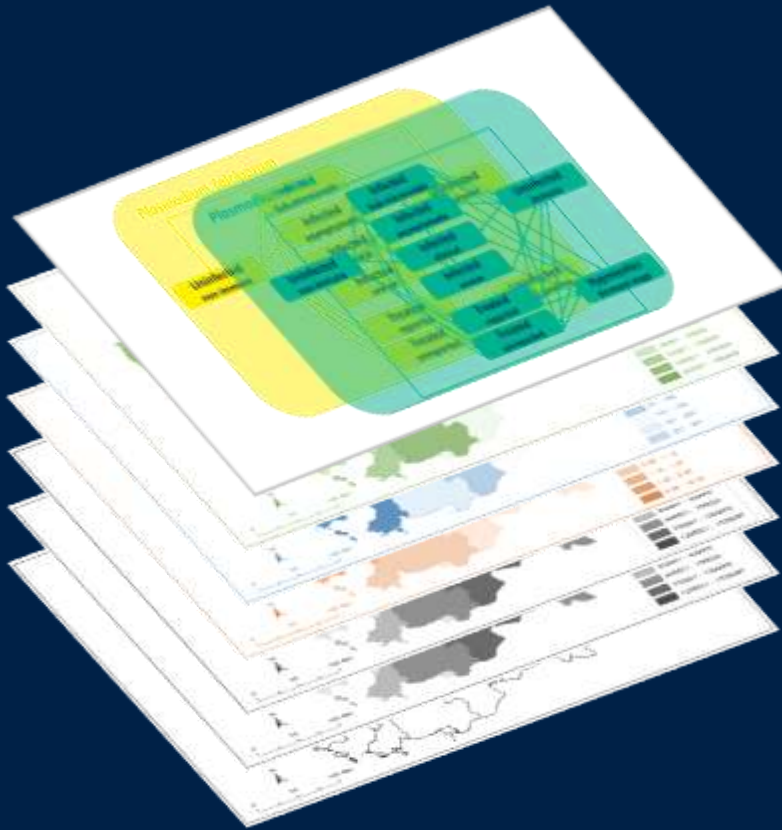
# Building a spatial model



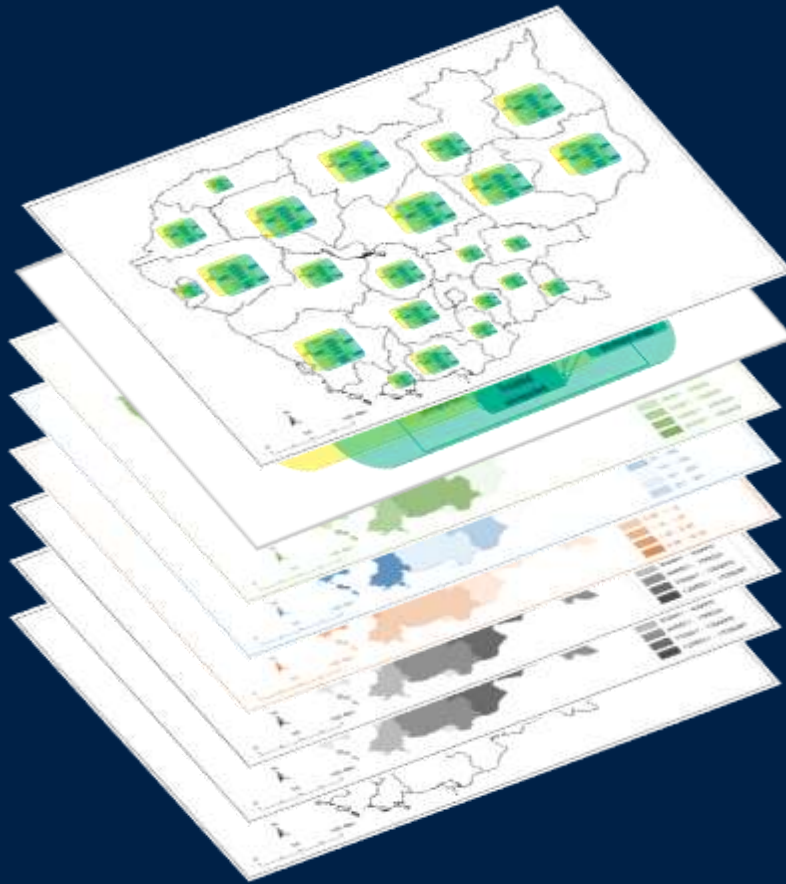
- Include data on historical and planned vector control

# Building a spatial model

- Create a model



# Building a spatial model



- Replicate the compartmental model for each patch
- link the submodels using connectivity assumption or data
- Include the historical intervention data
- Fit the model to surveillance data
- Include costs

# ~1000 lines of code

```
107 # 3=Is: infected asymptomatic
108 # 4=Ic: infected clinical
109 # 5=Is: infected severe
110 # 6=To: treated unrecorded
111 # 7=Tr: treated VWA
112 # 8=Tr: treated HIV
113 # 9=S: uninfected immune
114 # 10=M: uninfected and HRP2 positive
115 #
116 lshumpop<-1:10
117
118 # =====
119 # define indices
120 # =====
121 varind<-matrix(0,nrow=B,ncol=N)
122 trairnd<-matrix(0,nrow=A,ncol=N)
123 for (n in 1:N){
124   for (b in 1:B){
125     varind[b,n]<-(n-1)*B+b
126   }
127   for (a in 1:A){
128     trairnd[a,n]<-(n-1)*A+a
129   }
130 }
131
132 # =====
133 # define transitions
134 # =====
135 # first transition is given without index
136 transitions<-ssa.maketrans(V,rbind(varind[4,1],+1)) # birth was patch 1
137 for (n in 1:N){
138   #Alternate formulation of transitions matrix (used in epimodel function)
139   transitions2<-NULL
140   for (i in 1:length(transitions)){
141     transitions2<-rbind(transitions2,cbind(as.integer(names(transitions[[i]]))[[1]],as.integer(names(transitions[[i]]))[[2]],transitions[[i]][1],transitions[[i]][2]))
142   }
143   row.names(transitions2)<-NULL
144   transitionsiul<-transitions2[,1]
145   transitionsiul2<-transitions2[,2]
146   transitionsiv1<-transitions2[,3]
147   transitionsiv2<-transitions2[,4]
148 }
149
150 # =====
151 # Set the parameters
152 # =====
153 pars = list(
154   # Mosquitoes
155   Pmax=4000*seq_len(N)/seq_len(N), # the maximum populations of mosquitoes in each patch
156   delta_m=365.25/14, # death rate of mosquitoes
157 )
```

# Estimate the cost of future interventions

Introduction Interventions Baseline Personnel Travel Consumable Programme cost Training Monitoring and supervision Equipment Incentive Epidemiological studies Optional Extra Download data

### Demographic characteristics

Total number of villages: 10

Average population in a village: 1000

### Programme assumption

Length of programme (months): 12

### Mass drug administration

Percentage of villages that are offered MDA activity: 100

Number of mass drug administration rounds in a year: 1

Average population coverage for mass drug administration in a round (%): 100

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### Potential interventions

- ☒ Mass drug administration
  - ☐ Mass screening and treatment
  - ☐ Mass vaccination
  - ☐ Mass drug administration + mass vaccination
  - ☐ Mass screening and treatment + mass vaccination
- ☐ Training
- ☐ Monitoring
- ☐ Program management

### Existing interventions

- ☐ Community Engagement
  - ☐ Community Health Worker
  - ☐ Distribution of insecticide treated bed nets
  - ☐ Epidemiological studies

### Targeting strategy for mass malaria interventions

- ☒ Targeting using qPCR method
- ☐ Targeting based on surveillance system
- ☐ Full mass interventions in all villages without screening

### Results

Name	Staff	Travel	Consumable	Program	Equipment	Incentive	Total
Mass drug administration activity	87,484	14,368	12,370	8,544	000	3,204	121,667
Community engagement activity	73,828	11,443	884	4,272	54	16,374	106,308
Identifying hotspot villages	24,138	5,728	10,270	2,593	117	306	51,128
Community health worker programme	0	0	0	0	0	0	0
Distribution of insecticide treated bed nets	0	0	0	0	0	0	0
Epidemiological studies	0	0	0	0	0	0	0
Extra	0	0	0	0	0	0	0
<b>Total program cost</b>	<b>185,128</b>	<b>36,573</b>	<b>31,332</b>	<b>15,379</b>	<b>771</b>	<b>19,944</b>	<b>289,128</b>

All figures are in US\$

Name	MDA	CE	qPCR
Cost per village in one round	10072.29	1667.34	5090.22
Cost per person reached in one round	21.94	11.62	11.30
Cost per person treated in one round	25.32	11.62	113.03

Name	CHW	ITN
Cost per village in one year	0.00	0.00
Cost per person reached in one year	3.00	0.00

<https://costingapp.shinyapps.io/costingtool/>

Dr Shwe Sin Kyaw, MORU



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### ***Pillar 3***

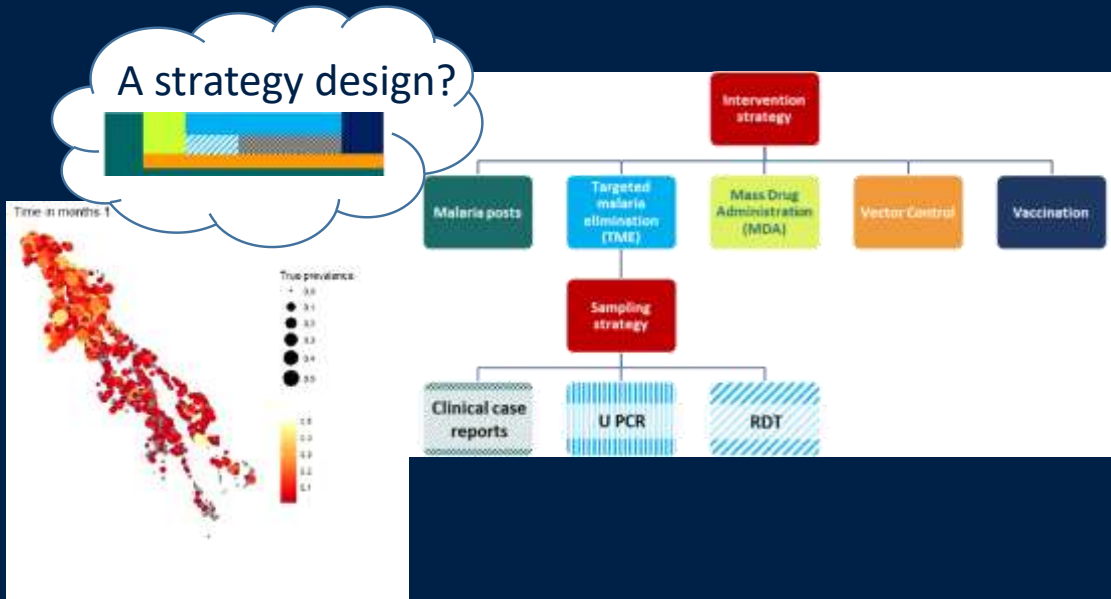
**Transform malaria surveillance  
into a core intervention**

# Smartphones for Community Health in Rural Cambodia



Pengby Ngor, CNM

A strategy design?



Dr Ricardo Aguas, MORU



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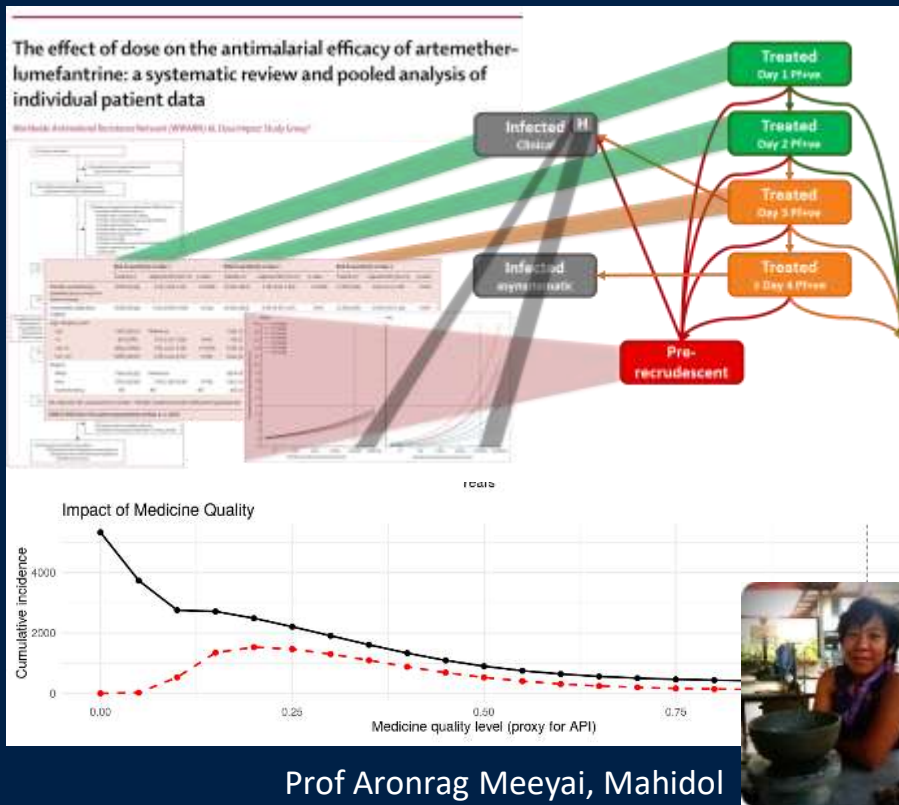
**Harnessing Innovation & Expanding Research**

***Supporting  
Element 2***

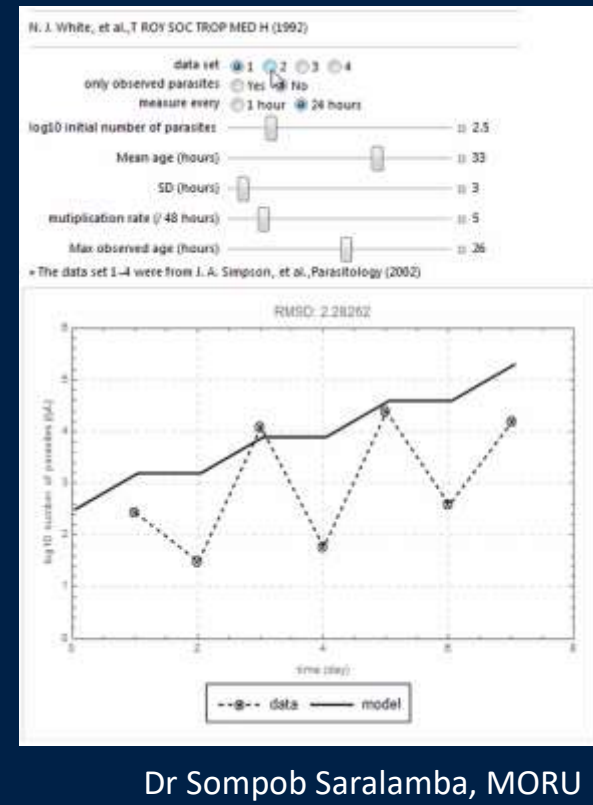
**Strengthening the Enabling Environment**

**Harnessing Innovation & Expanding Research**

# Medicine quality



# Within-host models



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*Supporting  
Element 2*

Strengthening the Enabling Environment

# Which is faster?

- 1 modeller learns 5 cultures and health systems?

OR

- 5 people learn modelling?

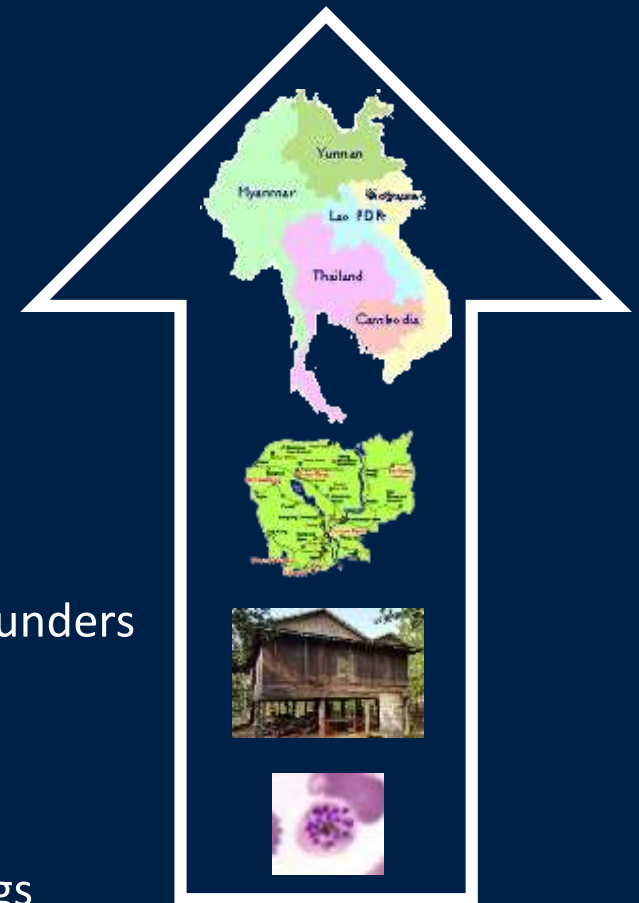


# Individual and institutional capacity building in modelling



# Conclusions

- Research
  - Understanding the context
  - Developing the best methods
  - Economic features
- Communication
  - Stakeholders, collaborators, policymakers, funders
  - Participatory modelling
  - User-friendly tools and interfaces
- Training
  - Modellers leading groups in endemic settings
  - Modellers providing training to stakeholders



# Acknowledgements

- Mahidol Oxford Tropical Medicine Research Unit
  - Mathematical and Economic Modelling group
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  - Ben Burgess



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- Work funded by
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# Any questions?

