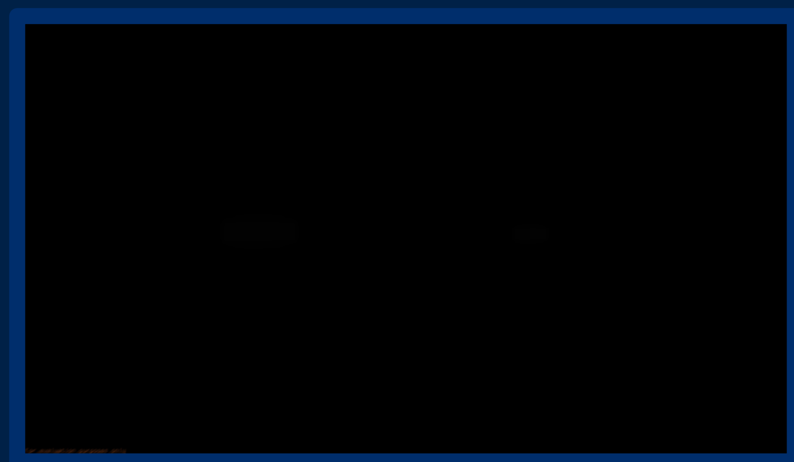
Malaria Elimination Trials and Simulations



Lisa J White
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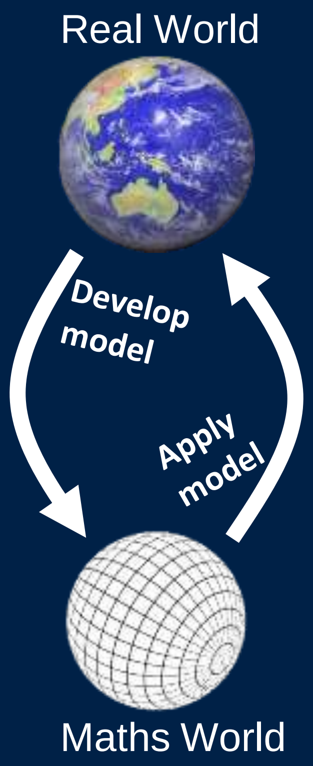
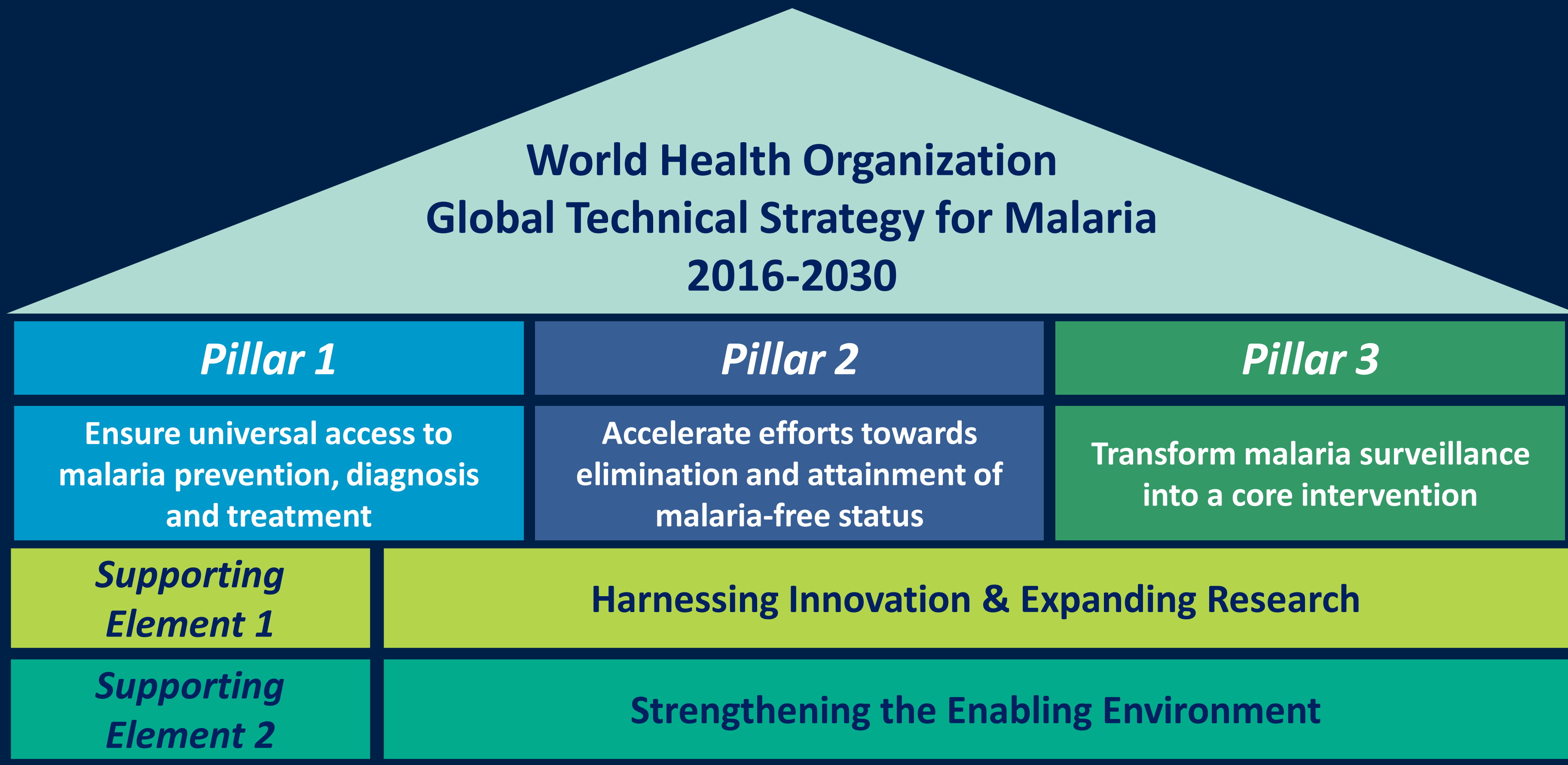
University of Oxford

A mathematical model…

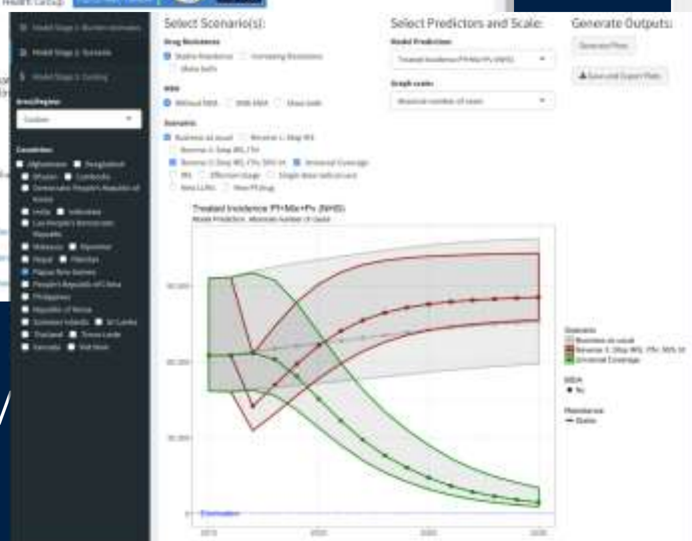
- is a description of a system or multiple interacting systems using mathematics
- can be used to answer “what if” questions about the system
- can be simple or complex
- has many limitations:
  - Simple models have more limitations in biology but are faster to write and run with small data
  - Complex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

Pillar 1	*Pillar 2*
Ensure universal access to malaria prevention, diagnosis and treatment	**Accelerate efforts towards elimination and attainment of malaria-free status**

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



http://www.metcapmodel.net/

Dr Sheetal Silal, UCT

Model Equations

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

$$\frac{dI_n}{dt} = -\mu I_n + p_{sn}(1-p_s)\Lambda(t)S - r_n I_n + r_a I_a - (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_n + p_{rn}(1-p_r)\Lambda(t)(R+H)$$

$$\frac{dI_a}{dt} = -\mu I_a + (1-p_{sn})(1-p_s)\Lambda(t)S + (1-p_{sev})r_c I_c - r_a I_a + (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_a + (1-p_{rn})(1-p_r)\Lambda(t)(R+H) + ptf(1-ptfc)r_1(T_o+T_v+T_h)$$

$$\frac{dI_c}{dt} = -\mu I_c + (1-\tau)p_s\Lambda(t)S + (1-\tau_{sev})(1-\theta_1)r_s I_s - (1-p_{sev})r_c I_c - p_{sev}r_c I_c + p_r(1-\tau)\Lambda(t)(I_n+I_a+R+H) + ptf(ptfc)(1-ptftr)r_t(T_o+T_v+T_h)$$

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

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

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

$$\frac{dT_h}{dt} = -\mu T_h + \tau_h p_s\Lambda(t)S - (1-ptf)r_t T_h + p_r\tau_h\Lambda(t)(I_n+I_a+R+H) + ptf(ptfc)(ptftr)r_1(T_o+T_v+T_h)$$

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

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

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

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

$$\frac{dI_a}{dt} = -\mu I_a + (1-p_{sn})(1-p_s)\Lambda(t)S + (1-p_{sev})r_c I_c - r_a I_a + (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_a + (1-p_{rn})(1-p_r)p_{rel}\nu L + (1-p_{rn})(1-p_r)\Lambda(t)(R+L) + p_{tf}(1-ptfc)r_1(T_o+T_v+T_h+T_{oGD}+T_{vGD}+T_{hGD})$$

$$\frac{dI_c}{dt} = -\mu I_c + (1-\tau)p_s\Lambda(t)S + (1-\tau_{sev})(1-\theta_1)r_s I_s - (1-p_{sev})r_c I_c + p_r(1-\tau)\Lambda(t)I_a - p_{sev}r_c I_c + p_r(1-\tau)\Lambda(t)I_n + p_r(1-\tau)p_{rel}\nu L + p_r(1-\tau)\Lambda(t)(R+L) + p_{tf}(1-ptftr)(ptfc)r_t(T_o+T_v+T_h+T_{oGD}+T_{vGD}+T_{hGD})$$

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

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

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

$$\frac{dT_h}{dt} = -\mu T_h + (1-p_{gd})\tau_h p_s\Lambda(t)S - (1-p_{tf})r_t T_h + (1-p_{gd})p_r\tau_h\Lambda(t)(I_n+I_a+R+L) + (1-p_{gd})p_r\tau_h p_{rel}\nu L + p_{tf}(ptftr)(ptfc)r_t(T_o+T_v+T_h)$$

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

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

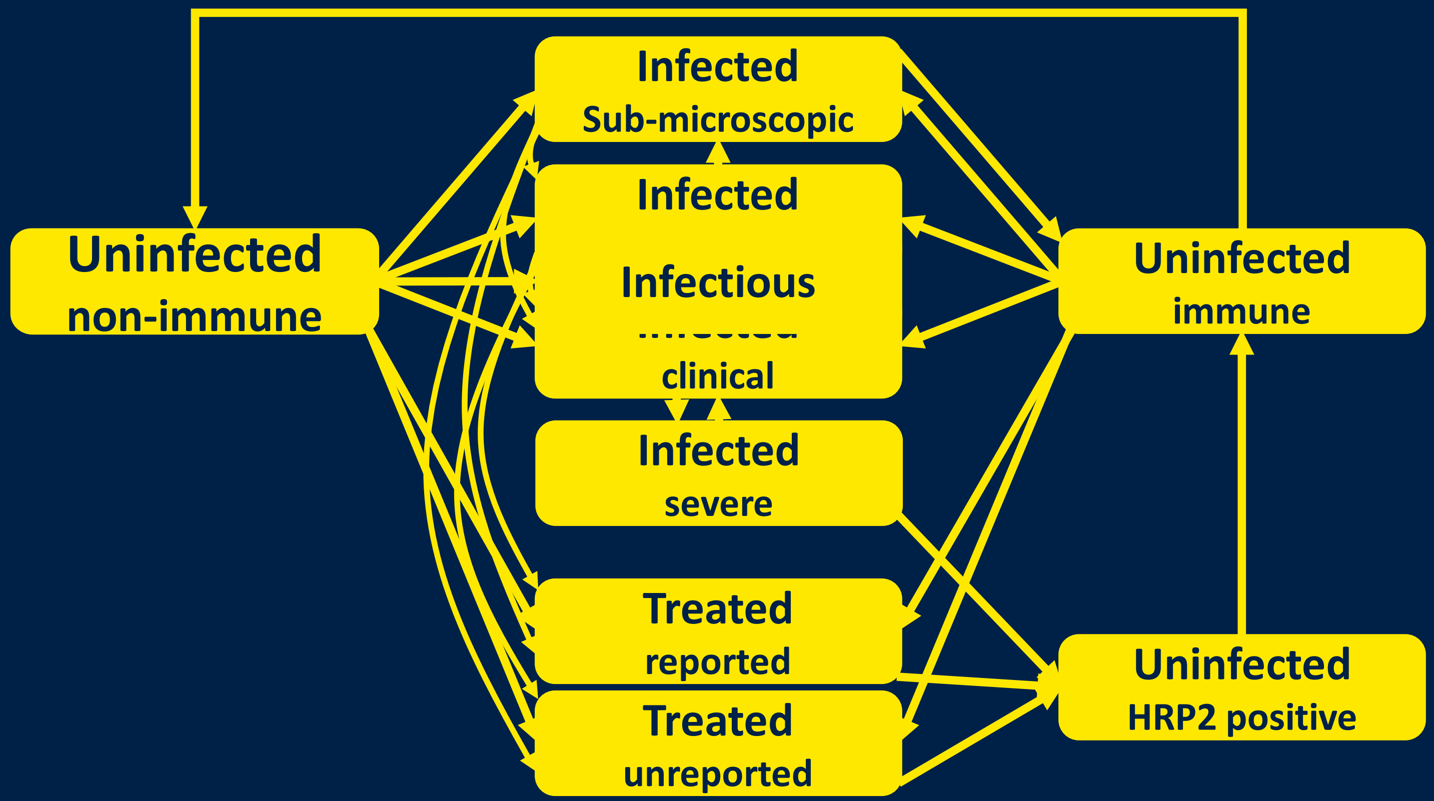
$$\frac{dT_{hGD}}{dt} = -\mu T_{hGD} + p_{gd}\tau_h p_s\Lambda(t)S - (1-p_{tf})r_t T_{hGD} + p_{gd}p_r\tau_h\Lambda(t)(I_n+I_a+R+L) + p_{gd}p_r\tau_h p_{rel}\nu L + p_{tf}(ptftr)(ptfc)r_t(T_{oGD}+T_{vGD}+T_{hGD})$$

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

5

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

Plasmodium falciparum



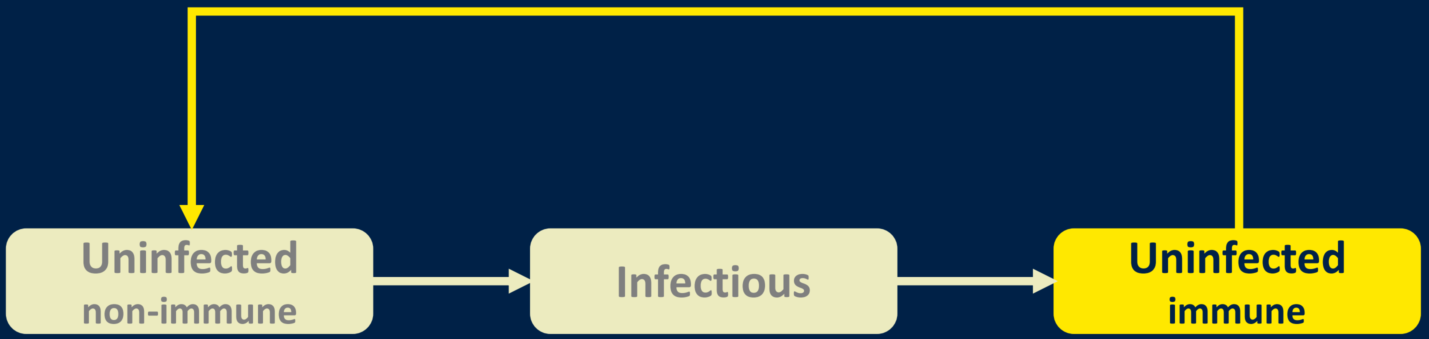
Building a malaria model…

individuals may become infected with malaria,

Plasmodium falciparum

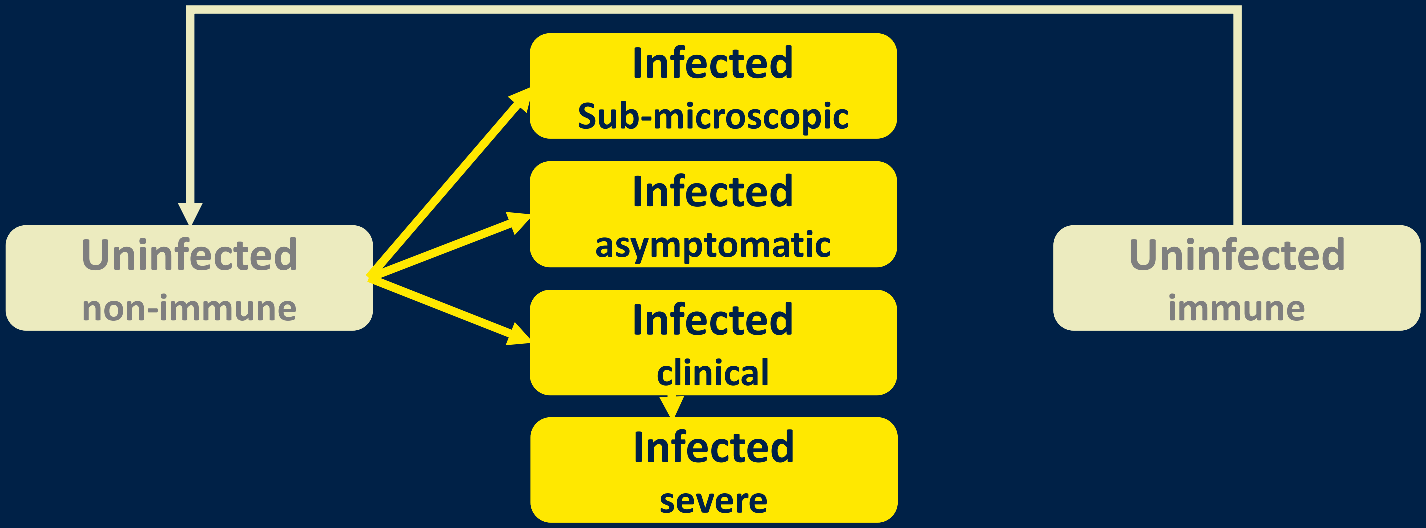
recover naturally and develop immunity

Plasmodium falciparum



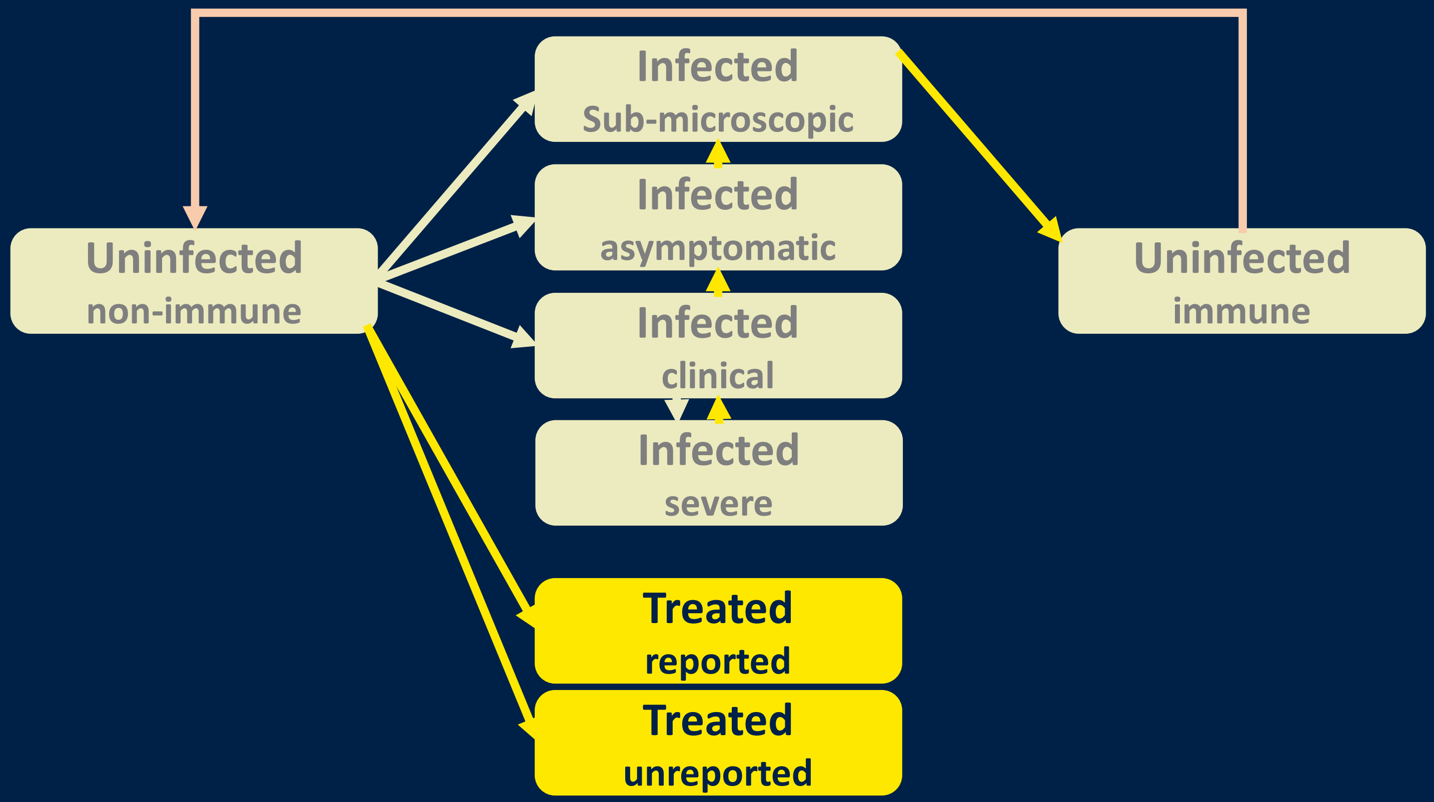
immunity may be lost over time

Plasmodium falciparum



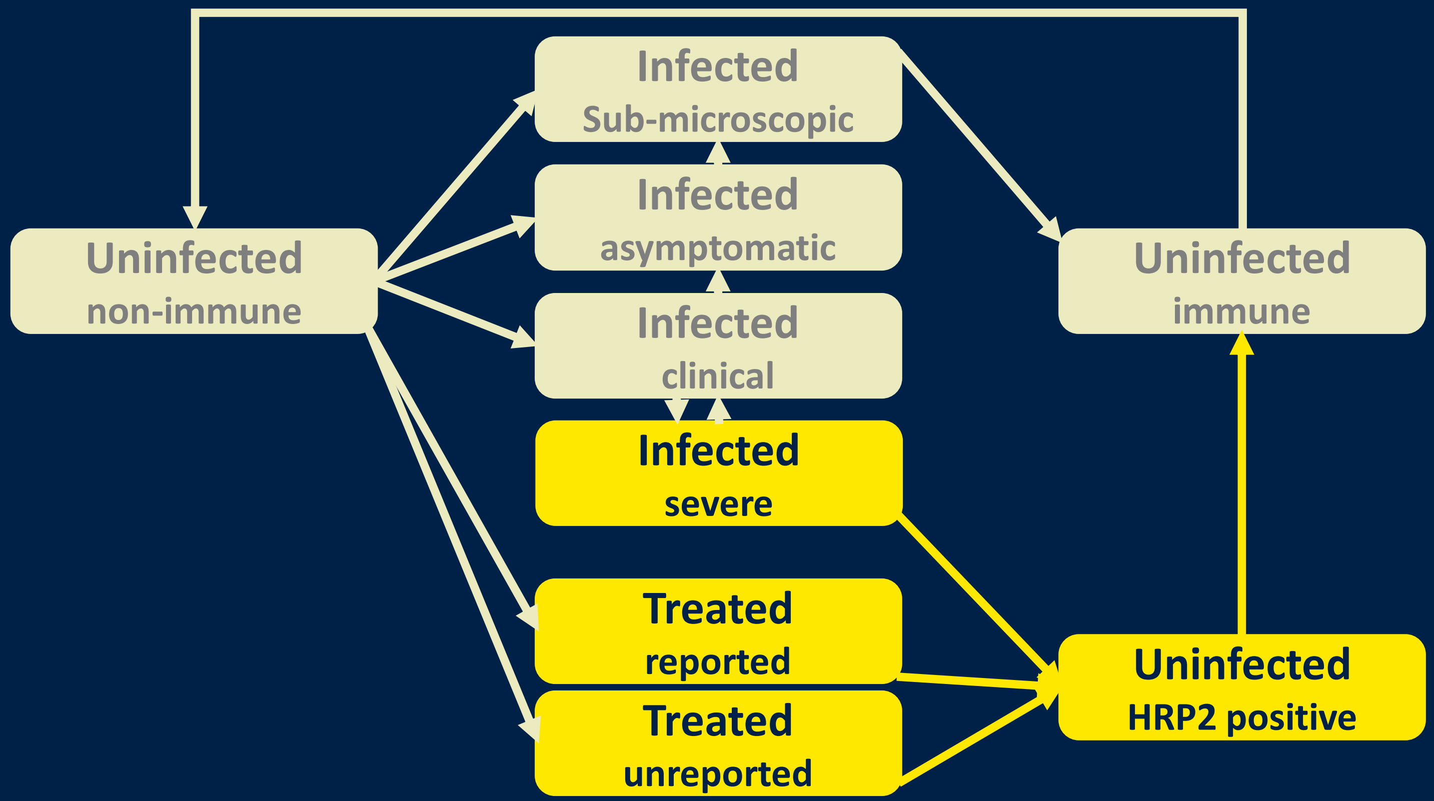
infections have different levels of severity

Plasmodium falciparum



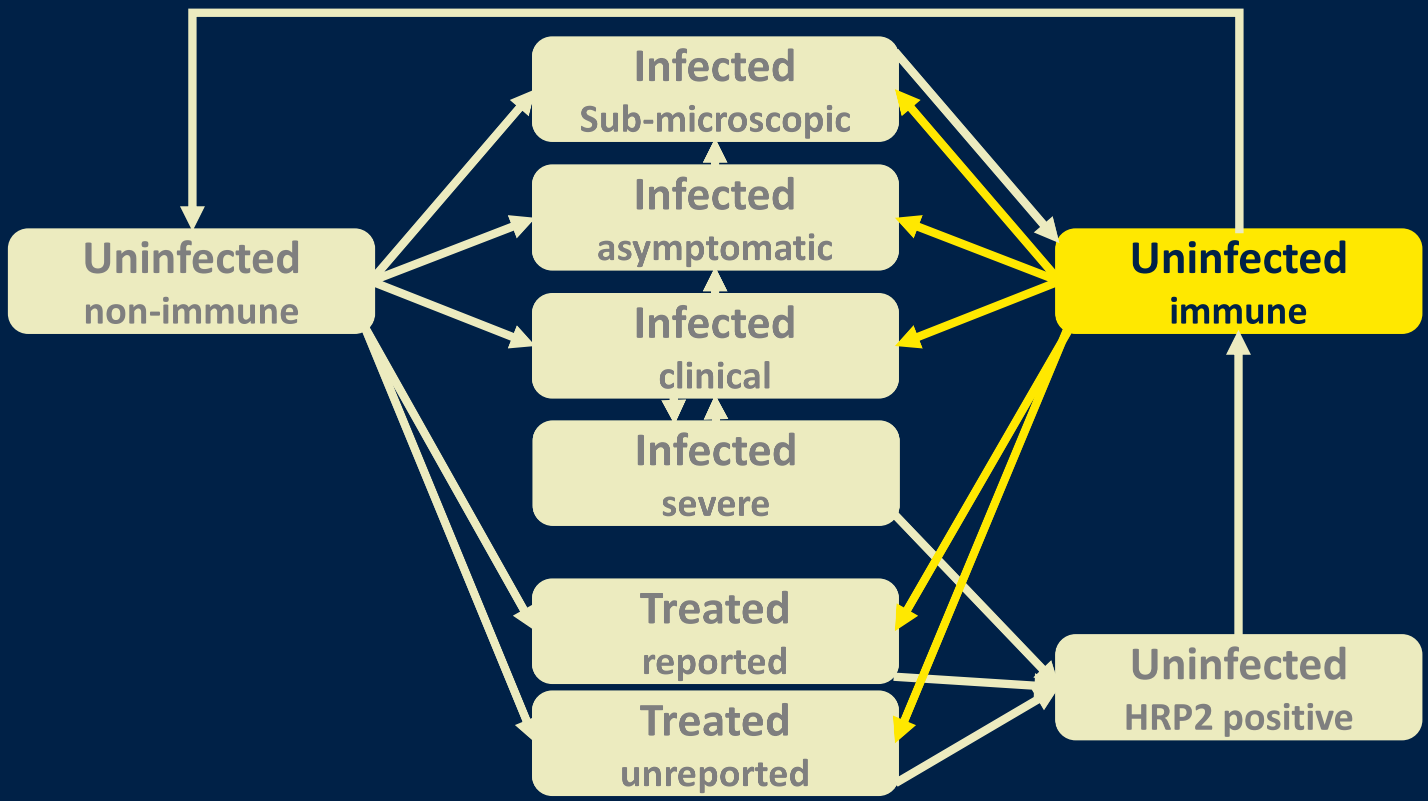
some infections are treated, others recover naturally

Plasmodium falciparum



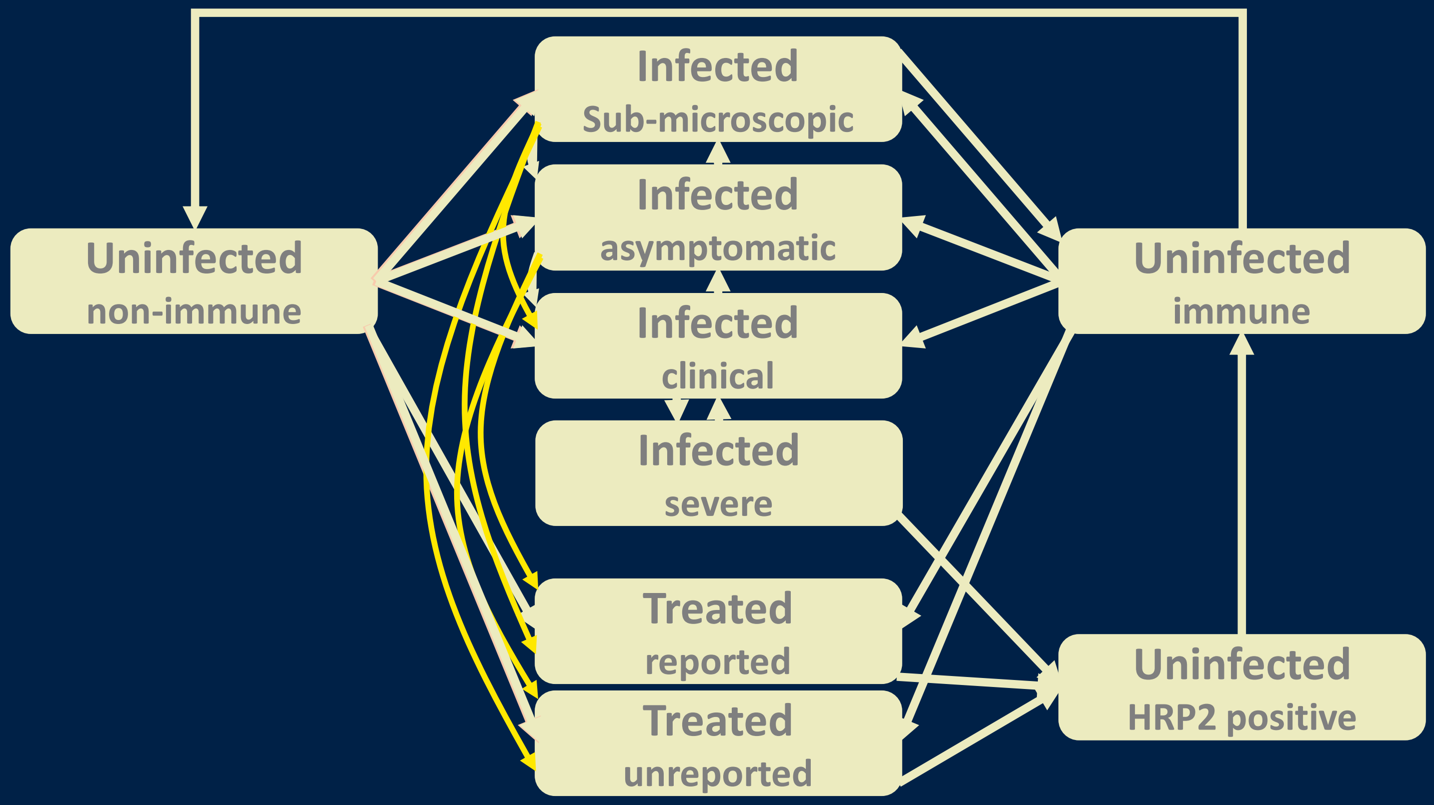
people can still test positive for after successful treatment

Plasmodium falciparum



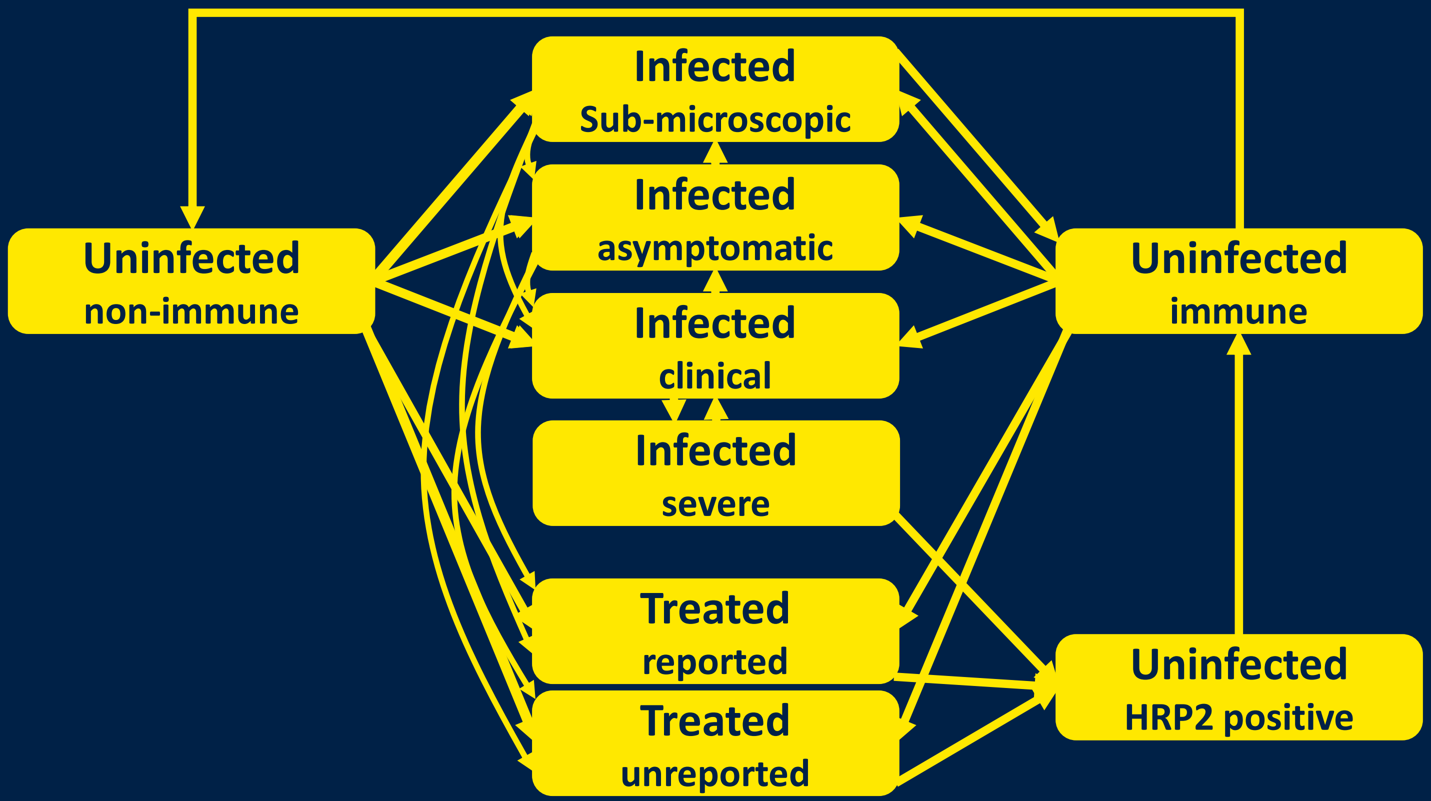
immune people get infected, but are less likely to have symptoms

Plasmodium falciparum

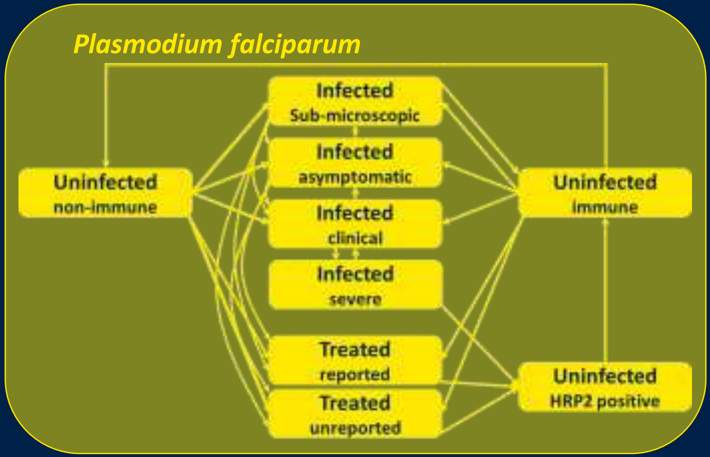


more than one infection at the same time (superinfection)

Plasmodium falciparum

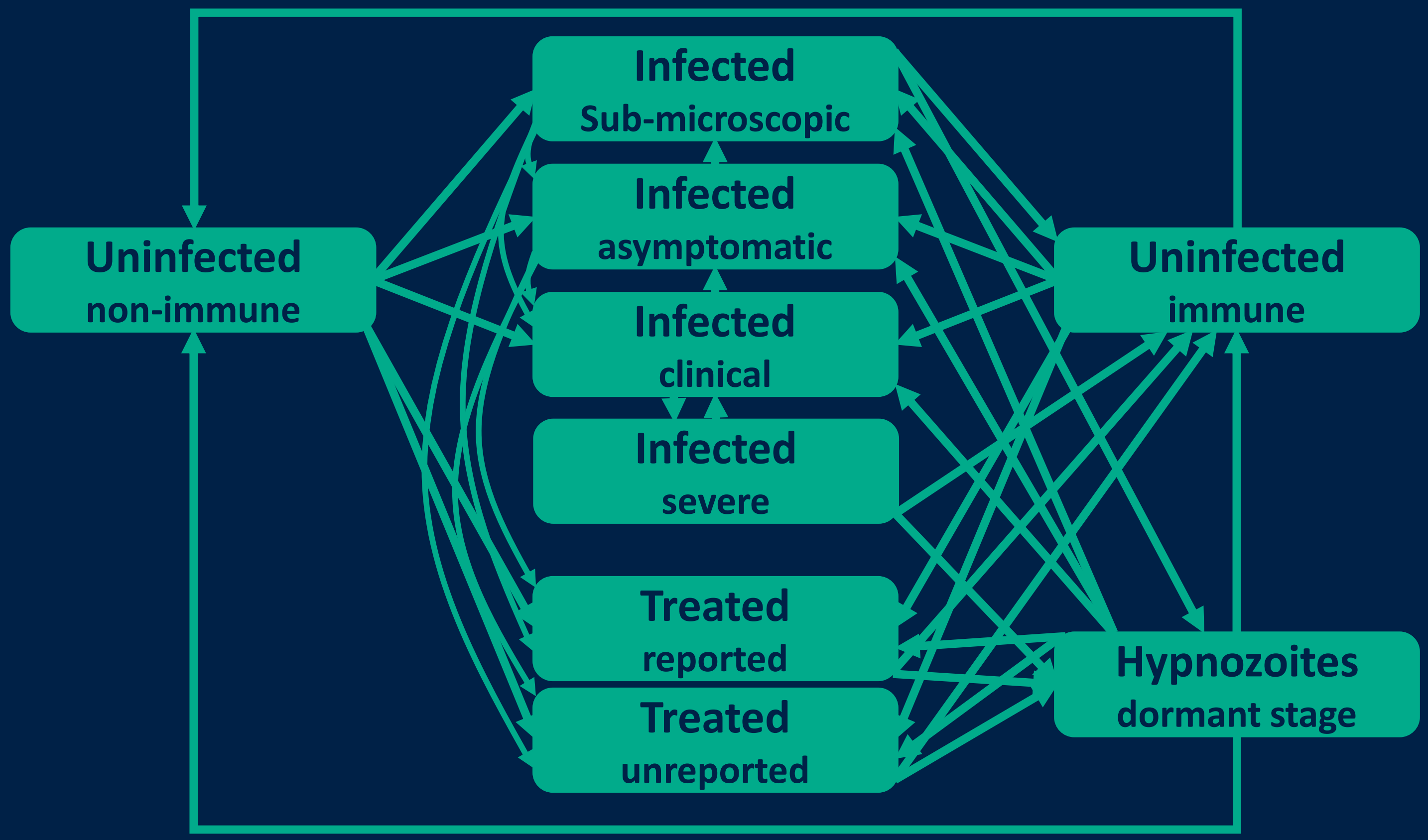


the model combines all these processes in one framework



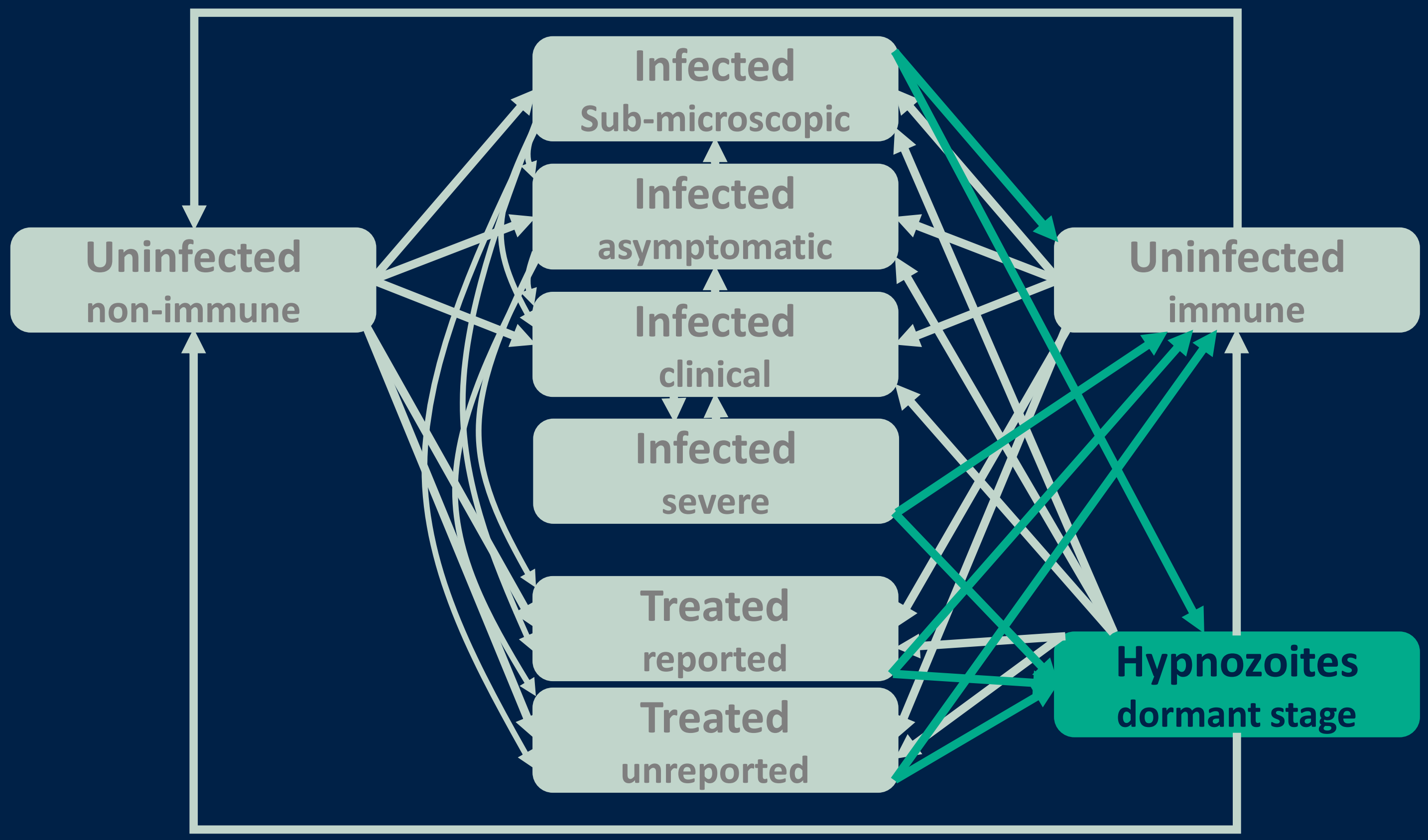
but the Asia-Pacific has two major malaria species

Plasmodium vivax



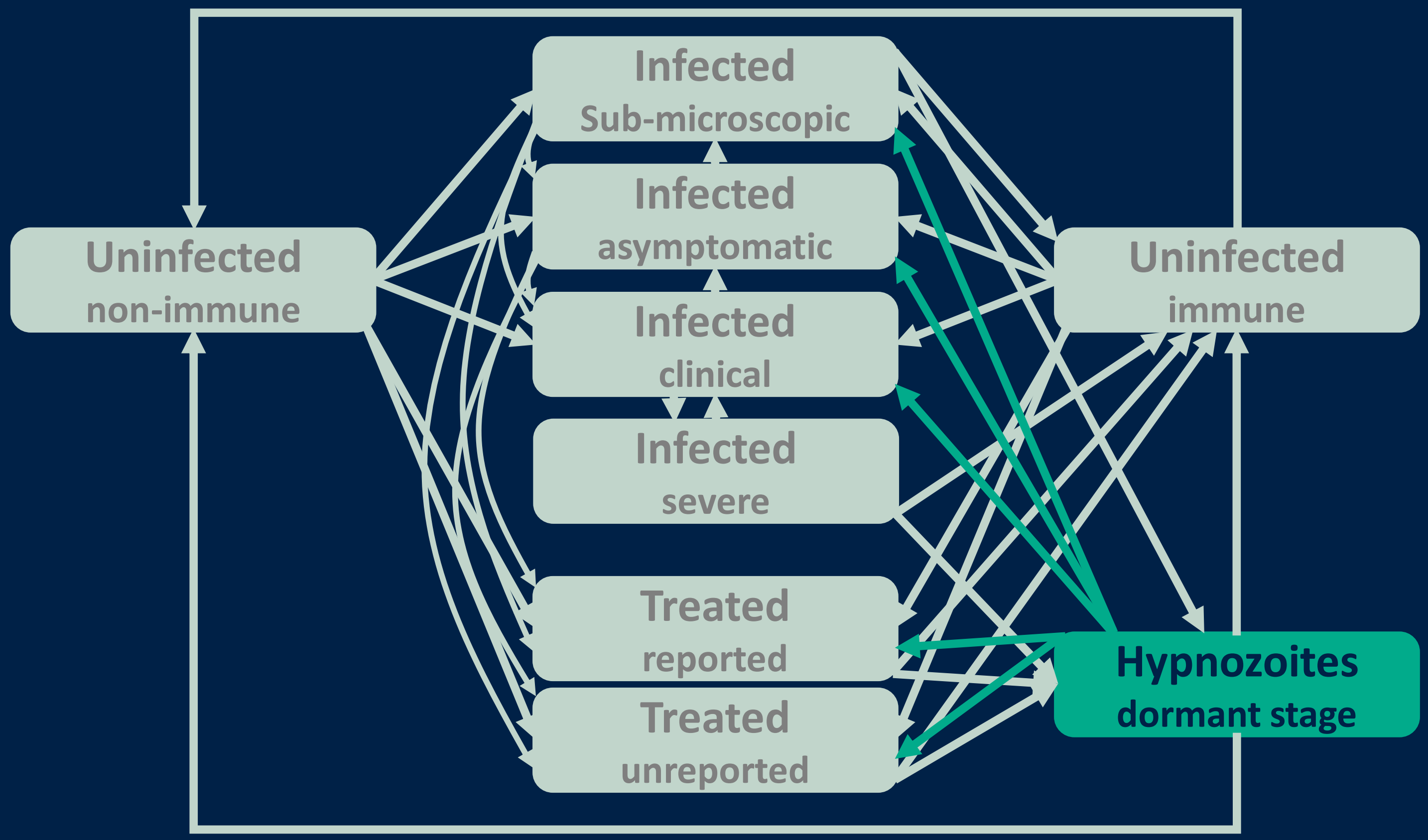
The model for *P. vivax* is different from the model for *P. falciparum*

Plasmodium vivax

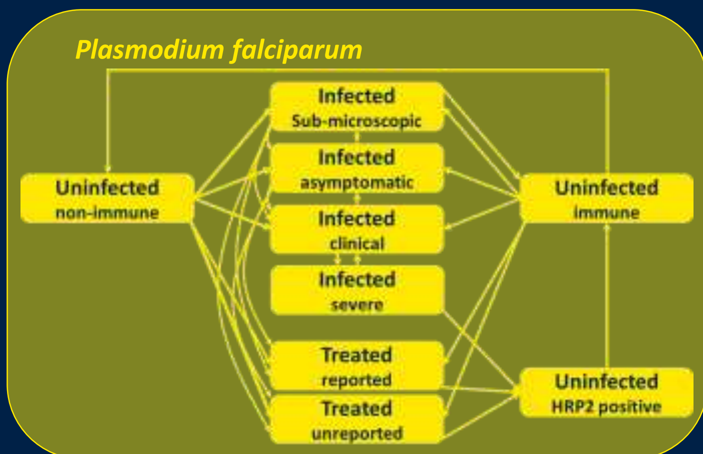


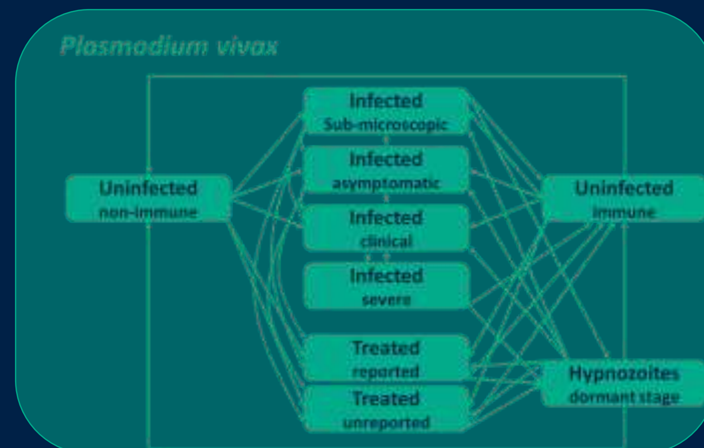
recovery may result in the dormant stage (hypnozoites)

Plasmodium vivax

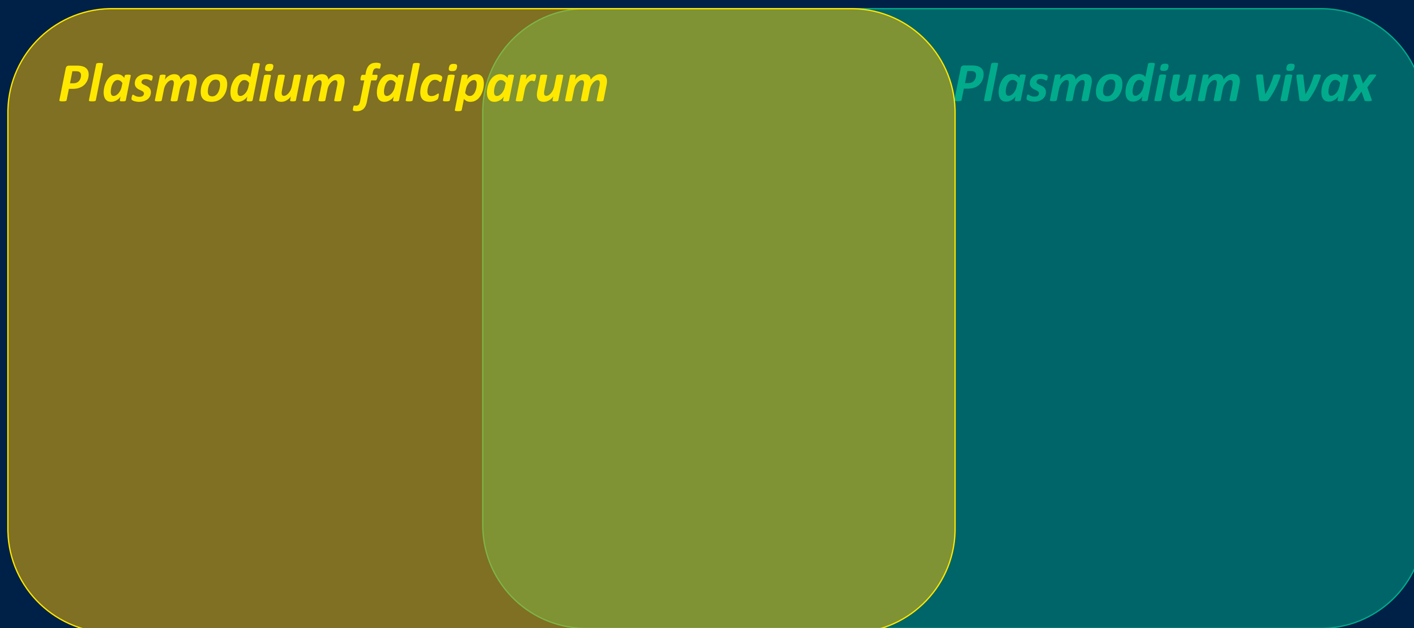


hypnozoites are a source of relapse months after the initial infection





the transmission and control of both species is simultaneous

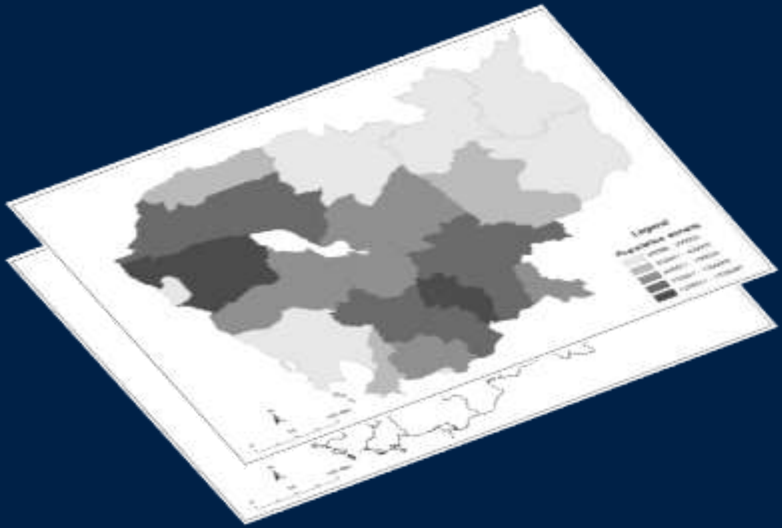


the species interact

Building a spatial model

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

Building a spatial model

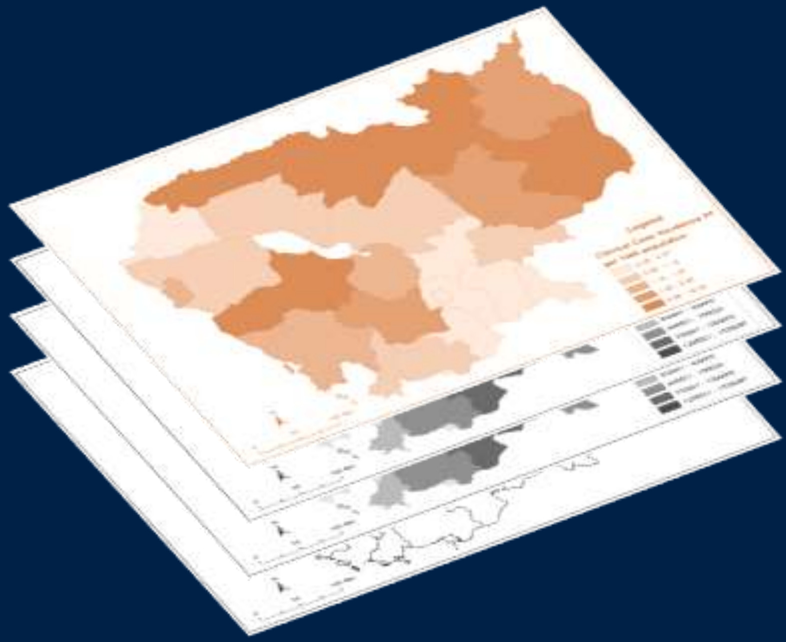


- Include data on population distribution by patches

Building a spatial model

- Include some assumptions or data on connectivity between patches

Building a spatial model

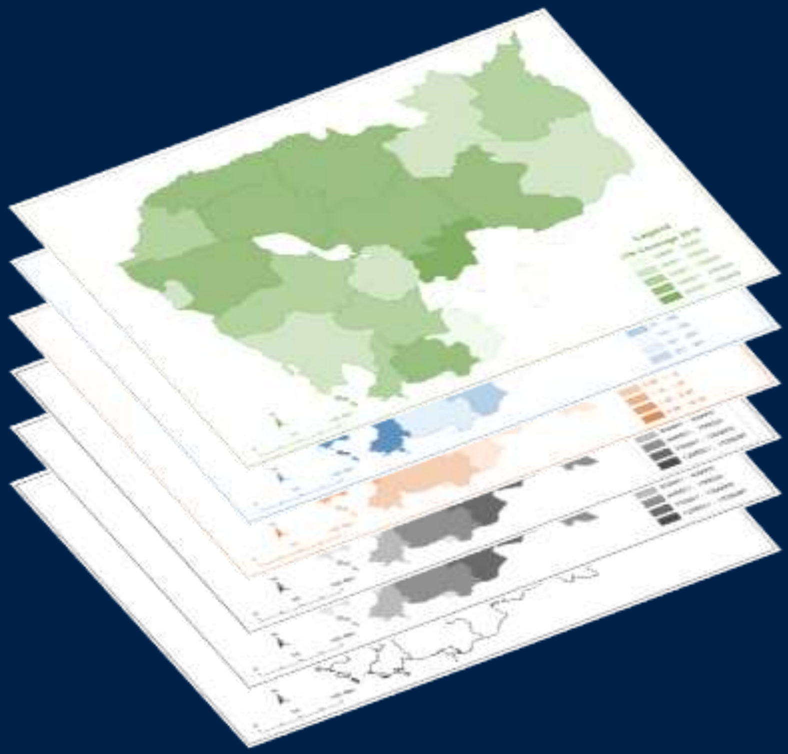


- Include surveillance data on spatial heterogeneity in transmission

Building a spatial model

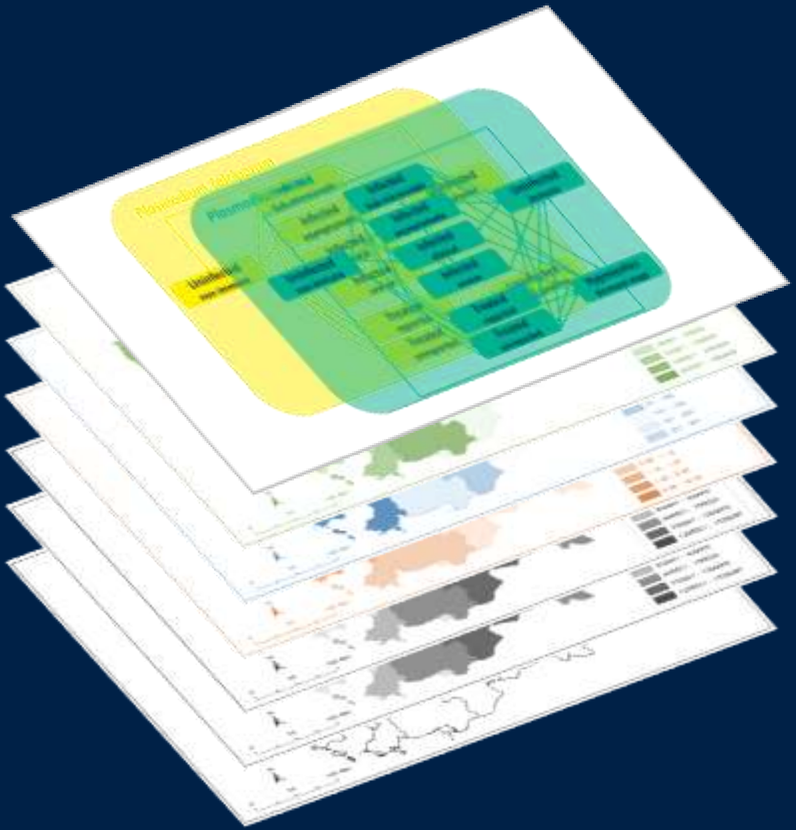
- Include data on historical and planned clinical case management

Building a spatial model



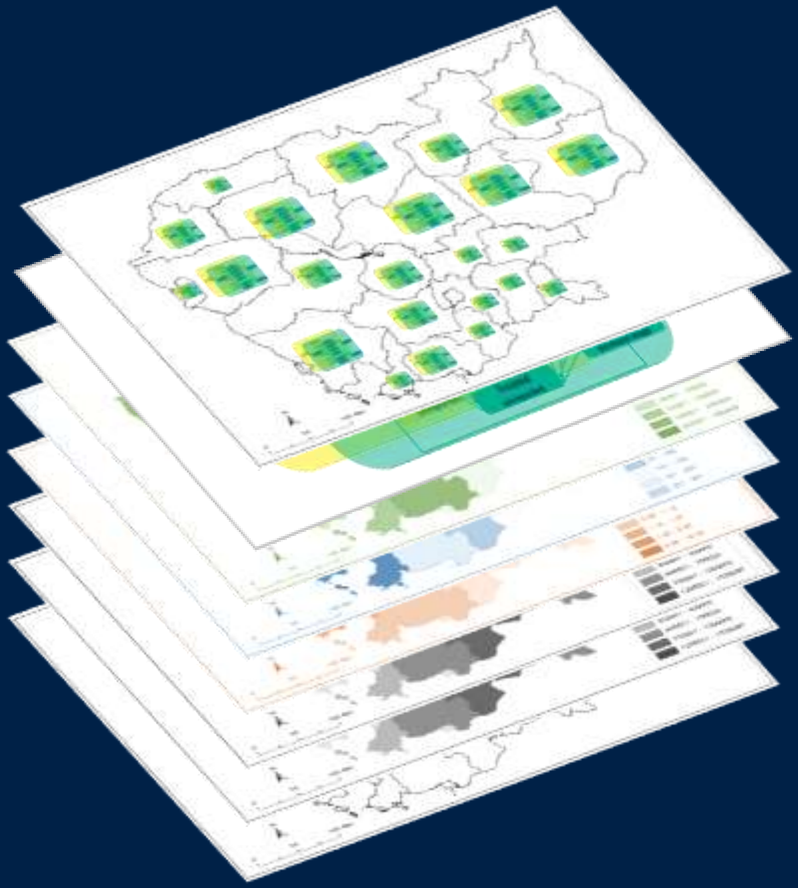
- Include data on historical and planned vector control

Building a spatial model



- Create a model

Building a spatial model

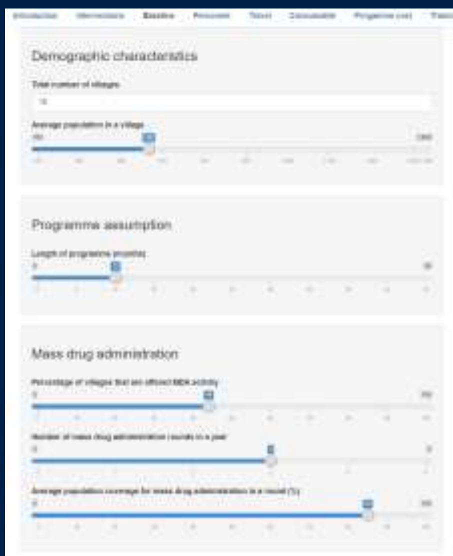


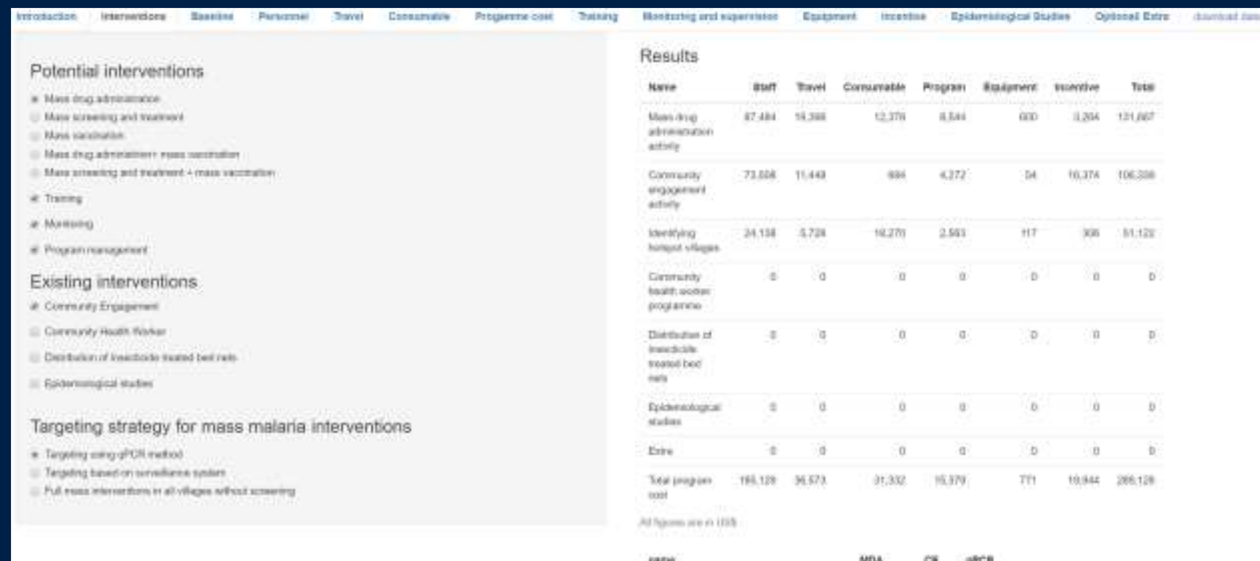
- Replicate the compartmental model for each patch
- link the submodels using connectivity assumption or data
- Include the historical intervention data
- Fit the model to surveillance data
- Include costs

~1000 lines of code

```
# 4=Ic: infected clinical
# 5=Is: infected severe
# 6=To: treated unrecorded
# 7=Tv: treated VMW
# 8=Th: treated HIS
# 9=R: uninfected immune
# 10=H: uninfected and HRP2 positive
#
lshumpop<-1:10

# ******************************************************************************** #
# define indices
# ******************************************************************************** #
varind<-matrix(0,nrow=B,ncol=N)
traind<-matrix(0,nrow=A,ncol=N)
for (n in 1:N){
  for (b in 1:B){
    varind[b,n]<-(n-1)*B+b
  }
  for (a in 1:A){
    traind[a,n]<-(n-1)*A+a
  }
}

# ******************************************************************************** #
# define transitions
# ******************************************************************************** #
# first transition is given without index
transitions =ssa.maketrans(V,rbind(varind[4,1], +1)) # birth mos patch 1
for (n in 1:N){...}
#Alternate formulation of transitions matrix (used in epimodel function)
transitions2<-NULL
for (i in 1: length(transitions)){
  transitions2<-rbind(transitions2,cbind(as.integer(names(transitions[[i]]))[1],as.integer(names(transitions[[i]]))[2], transitions[[i]][1], transitions[[i]][2]))
}
row.names(transitions2)<-NULL
transitionsiu1<-transitions2[,1]
transitionsiu2<-transitions2[,2]
transitionsiv1<-transitions2[,3]
transitionsiv2<-transitions2[,4]


# ******************************************************************************** #
# Set the parameters
# ******************************************************************************** #
pars = list(
  # Mosquitoes
  Pmax=40000*seq_len(N)/seq_len(N), # the maximum populations of mosquitoes in each patch
  delta_m=365.25/14, # death rate of mosquitoes
```

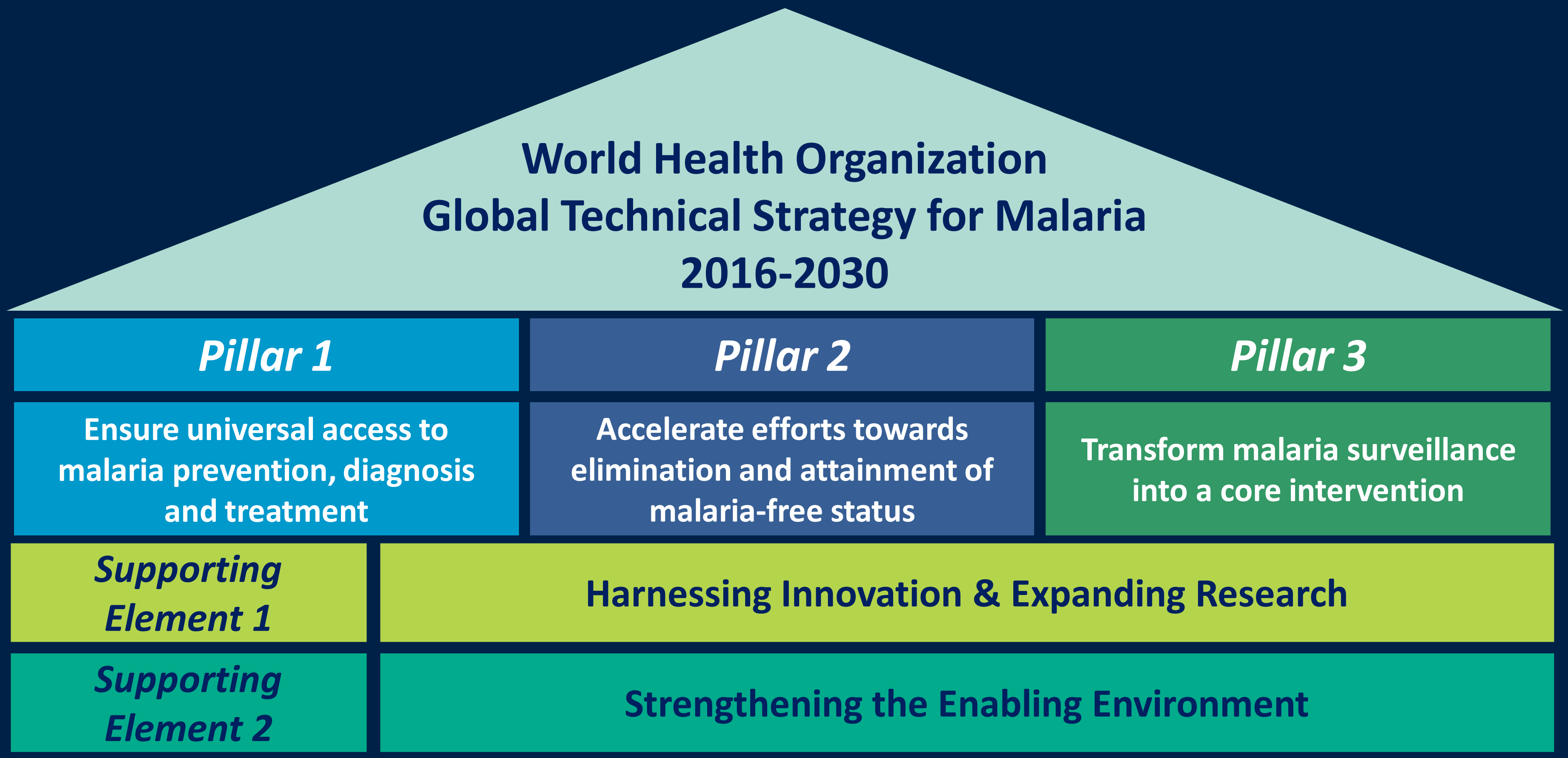
Estimate the cost of future interventions





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

Dr Shwe Sin Kyaw, MORU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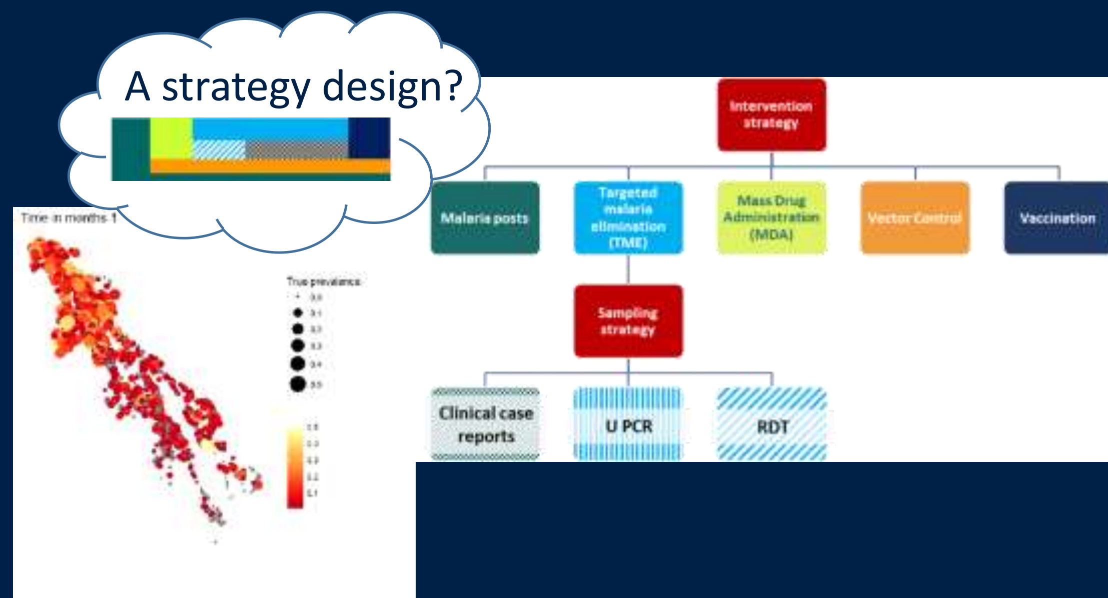
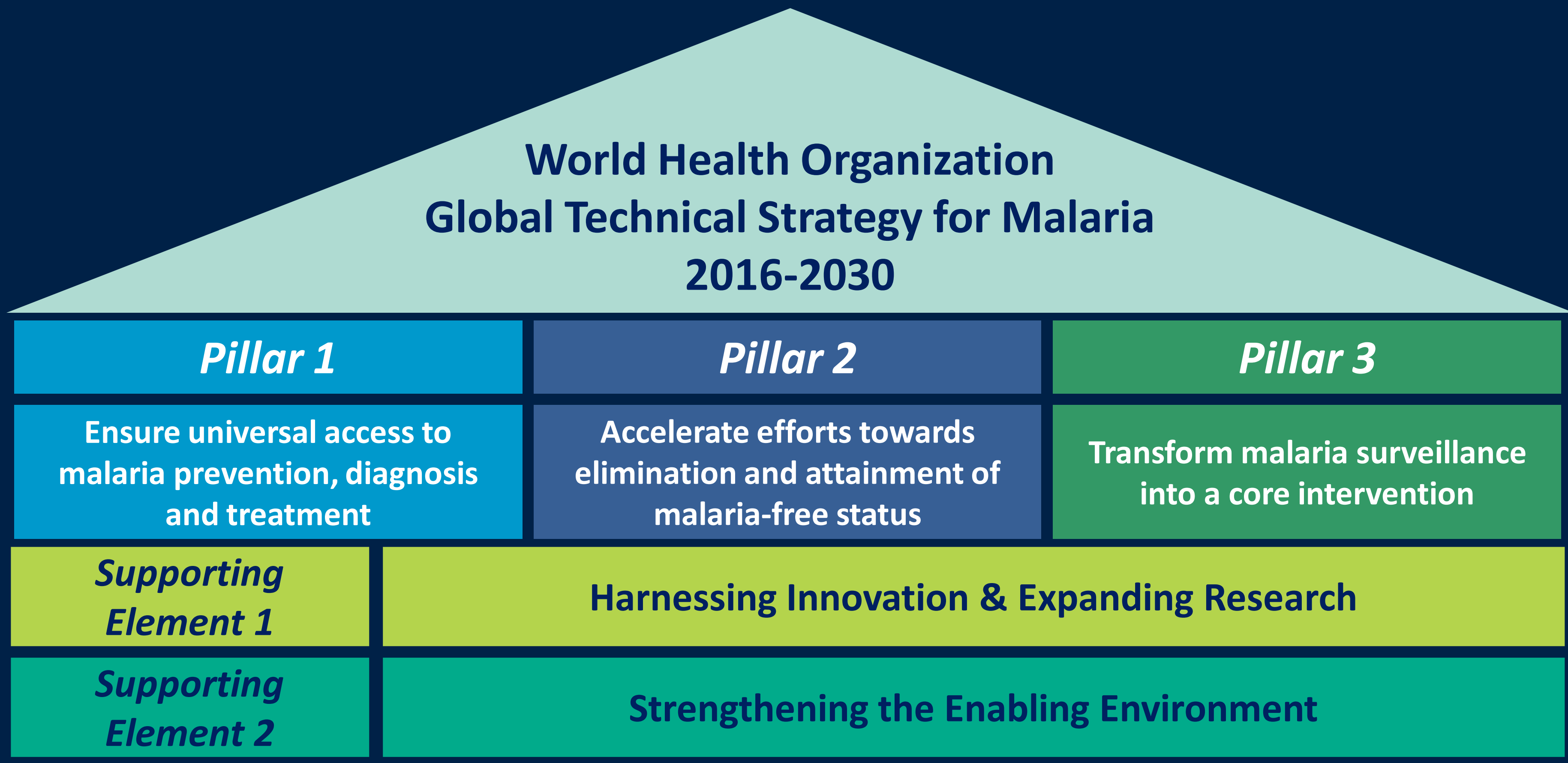
Transform malaria surveillance into a core intervention

Smartphones for Community Health in Rural Cambodia

Pengby Ngor, CNM



Dr Ricardo Aguas, MORU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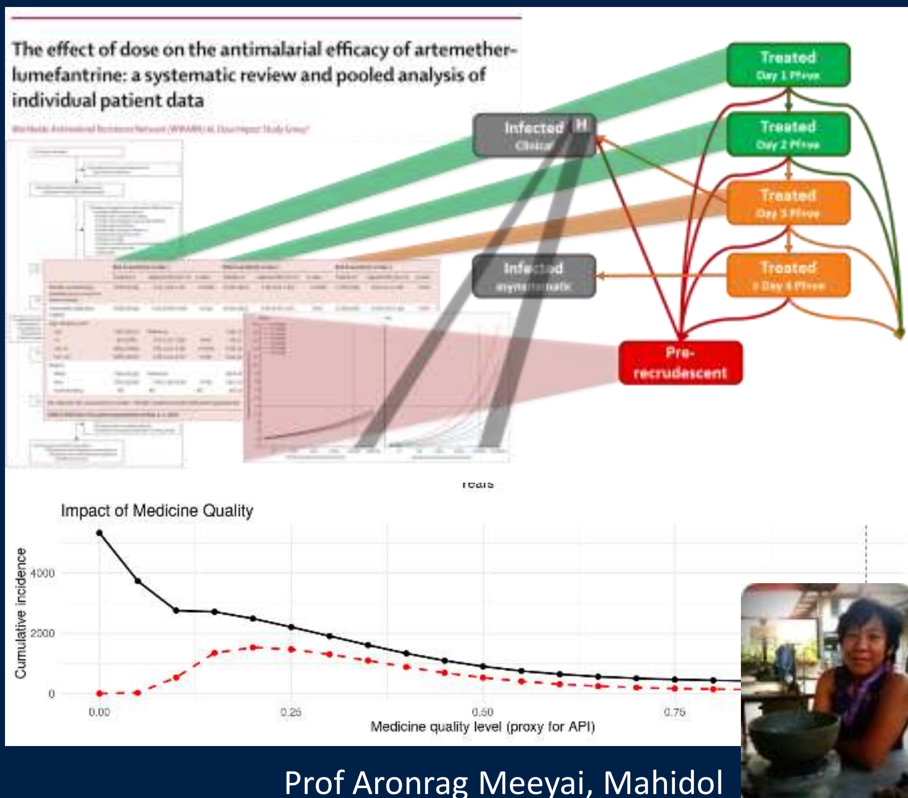
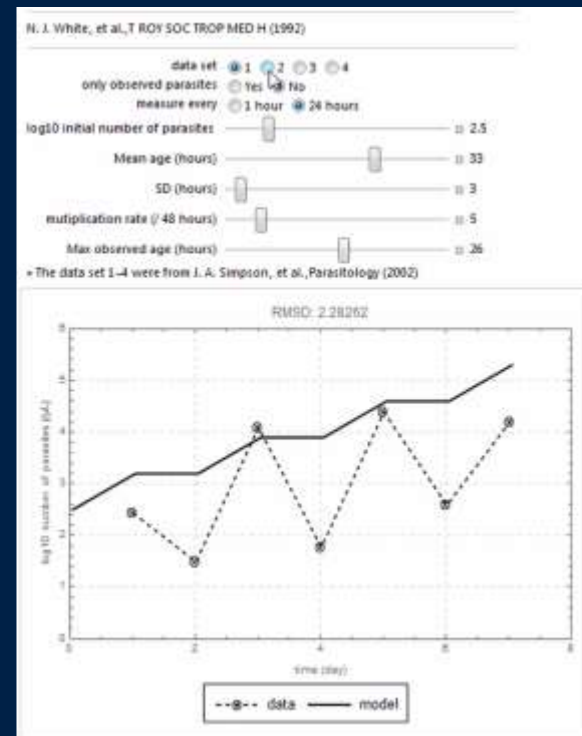
Harnessing Innovation & Expanding Research

Medicine quality

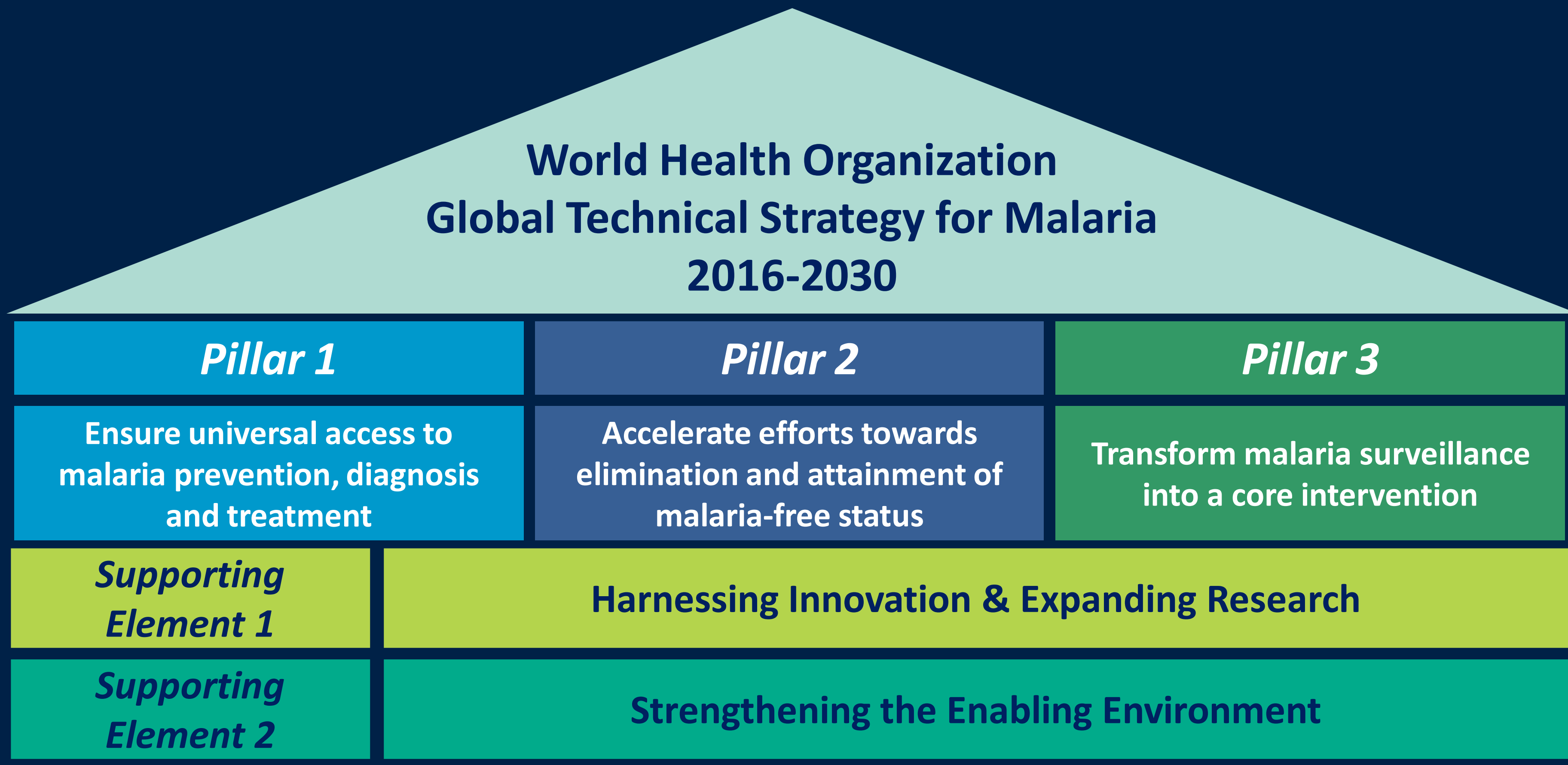


Prof Aronrag Meeyai, Mahidol

Within-host models



Dr Sompob Saralamba, MORU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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
    - Arjen M Dondorp
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    - Nicholas P J Day
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Any questions?