Modeling the risk-benefit of chemoprophylaxis for travelers to areas with stable malaria transmission

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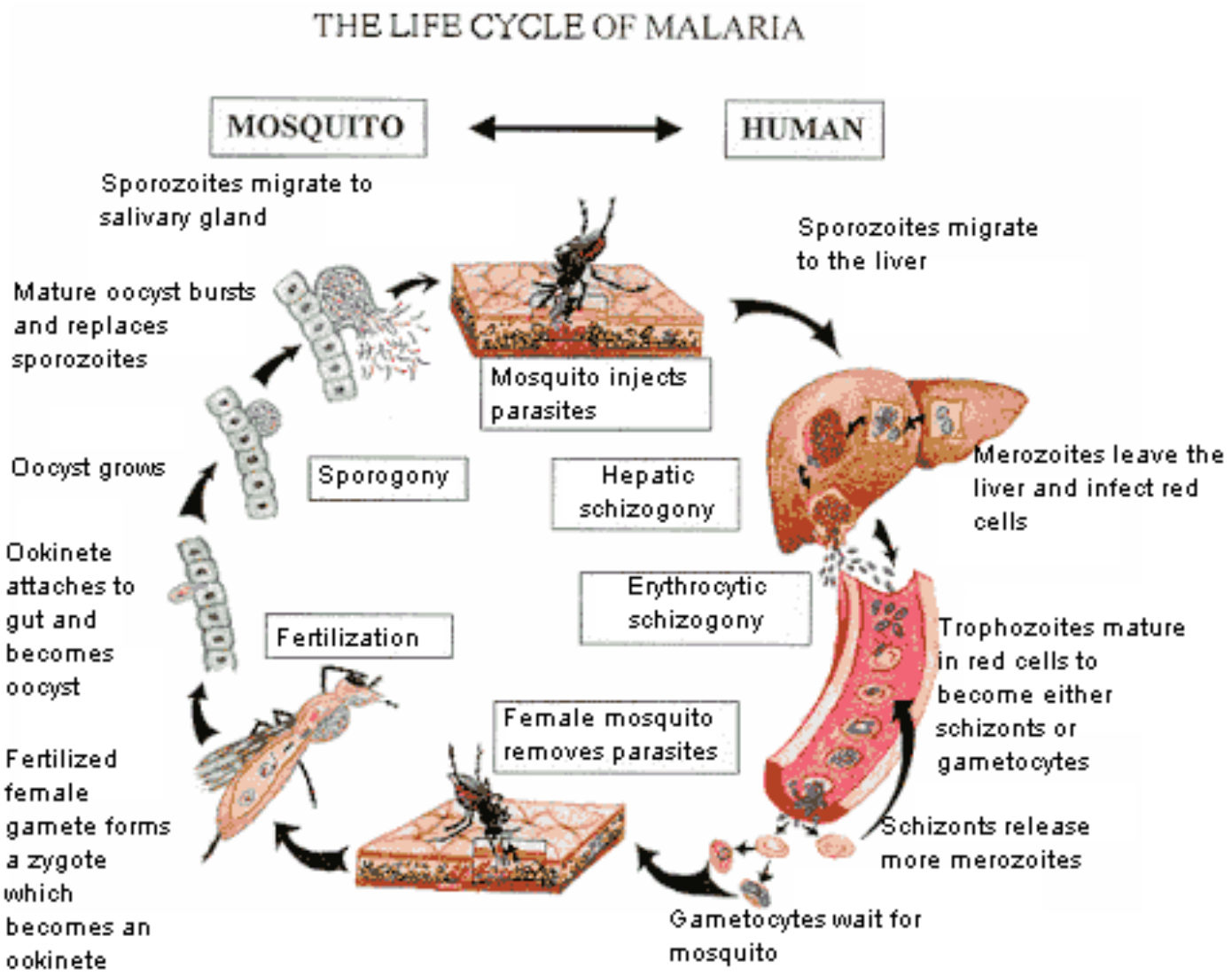
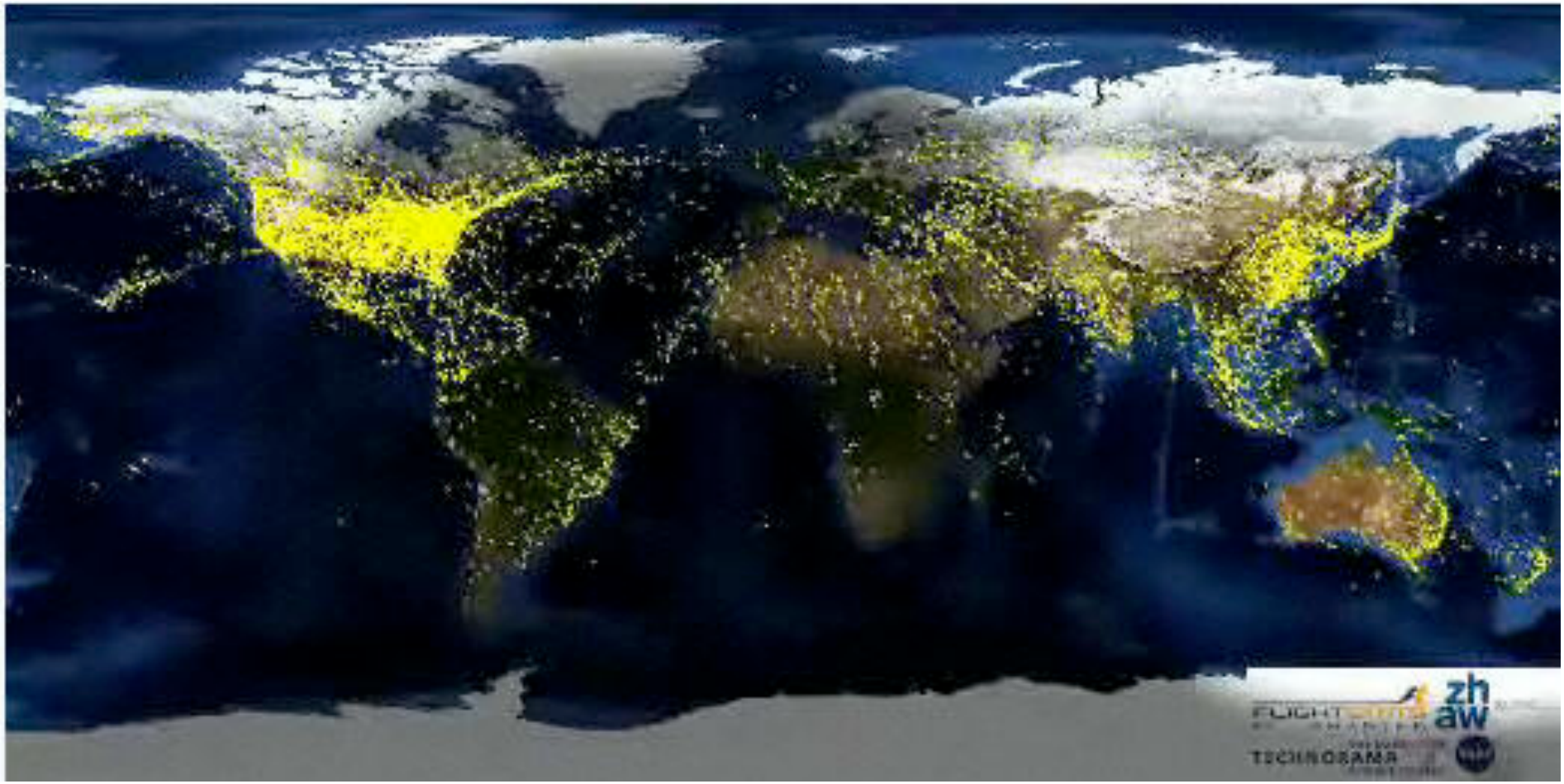
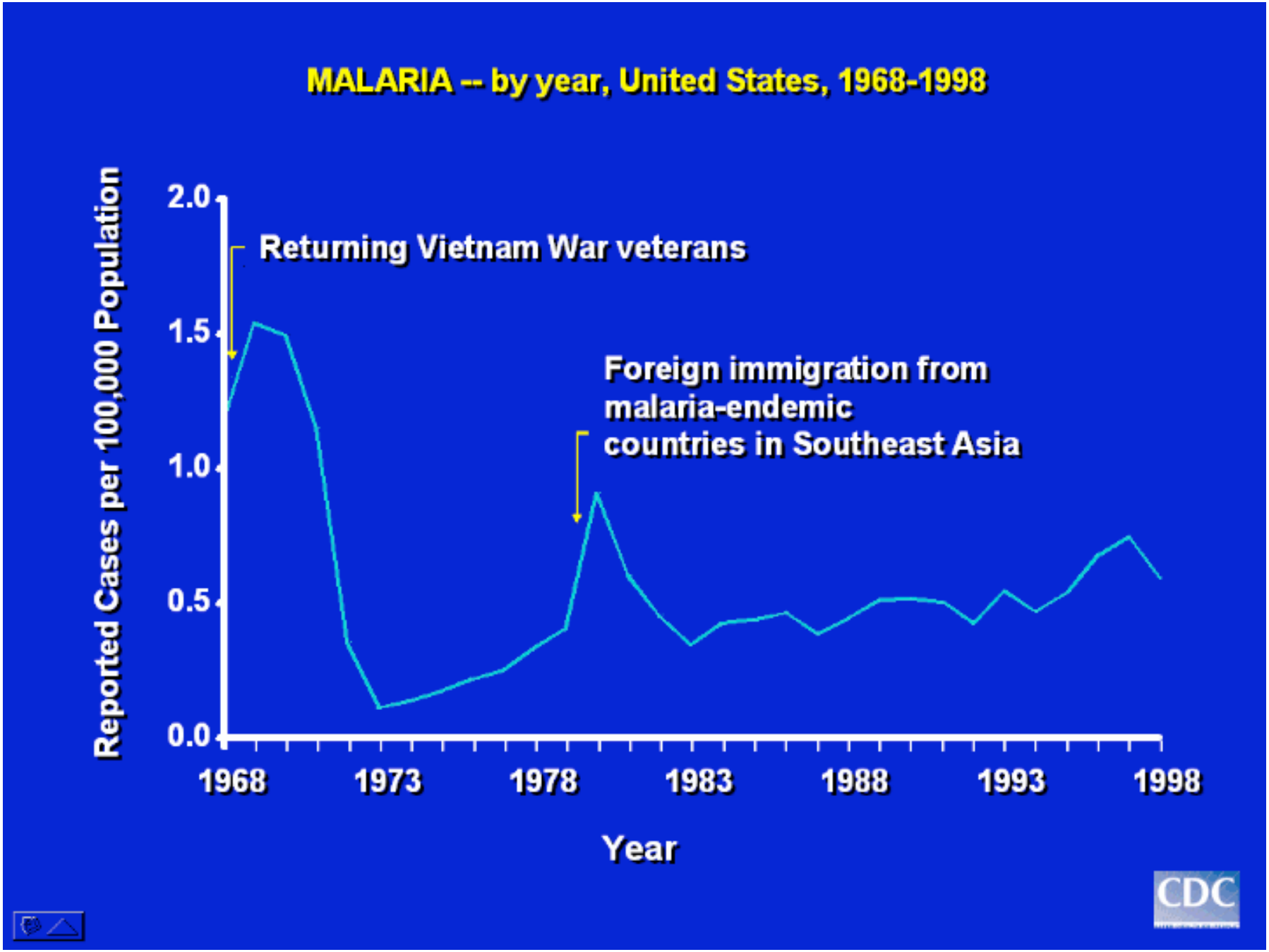
How long can a visitor to a malaria endemic area remain safely free of chemoprophylaxis ?


THE LIFE CYCLE OF MALARIA
MOSQUITO
HUMAN
Sporozoites migrate to salivary gland
Mature oocyst bursts and replaces sporozoites
Oocyst grows
Sporogony
Ookinete attaches to gut and becomes oocyst
Fertilization
Fertilized female gamete forms a zygote which becomes an ookinete
Mosquito injects parasites
Sporozoites migrate to the liver
Hepatic schizogony
Merozoites leave the liver and infect red cells
Erythrocytic schizogony
Trophozoites mature in red cells to become either schizonts or gametocytes
Schizonts release more merozoites
Gametocytes wait for mosquito
Female mosquito removes parasites




MALARIA -- by year, United States, 1968-1998
Reported Cases per 100,000 Population
2.0
1.5
1.0
0.5
0.0
Returning Vietnam War veterans
Foreign immigration from malaria-endemic countries in Southeast Asia
1968
1973
1978
1983
1988
1993
1998
Year
CDC

Region	Cases	At Risk (Millions)	RR	95% CI of RR
Very low risk areas*	83	1766.9	1	0.7-1.4
Caribbean	9	50.5	3.8	1.9-7.5
North Africa	10	30.8	6.9	3.6-13.3
South America	17	43.8	8.3	4.9-13.9
South-East Asia	64	118.8	11.5	8.3-15.9
Central America	24	13.5	37.8	24.0-59.6
South Asia	45	17.8	53.8	37.4-77.4
Oceania	31	8.6	76.7	50.8-115.9
Sub-Saharan Africa	514	52.7	207.6	164.7-261.8

In 2007 Brazil reported approximately 50% of the total number of the malaria cases in the Americas. Ninety-nine percent of those cases were from the Legal Amazon, where 10% to 15% of the population of Brazil population live. Case numbers fell between 1992 to 2002 from 572,000 to 349,873, with around 16.5% of all the slides examined resulted positive for malaria. A rebound occurred between 2003 to 2007 with number of cases peaking at 607,000 in 2005 and 458,041 cases in 2007. All reported malaria cases were confirmed by laboratory analysis, and 19% in 2007 were *P. falciparum*.

Low risk - antimalarials not usually advised

High risk - antimalarials usually advised.

Surrounding countries with malaria risk

This map is only intended as a guide since mosquitoes do not respect boundaries and the risk areas shown may not be exact.

Click on an icon below for additional country information

Regional Information

Major Airports

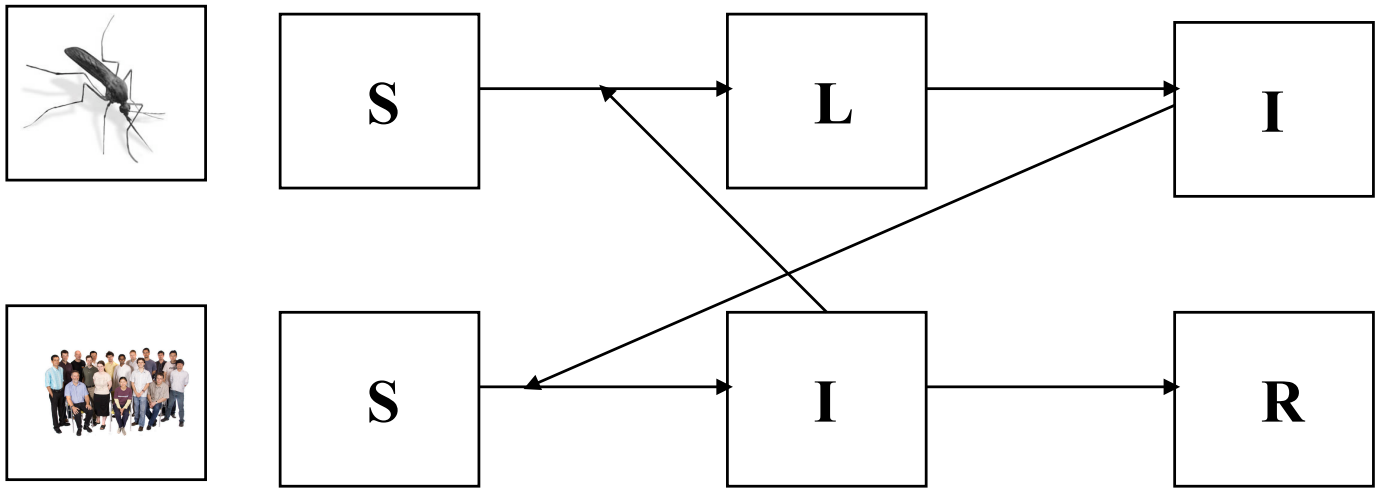
Major Railways

The average burden of malaria over the last decade has been approximately 600,000 cases per year, with a prevalence of falciparum around 20% . WHO estimated the total numbers of malaria cases in 2006 as approximately 1.4 million .

The estimated population exposed to malaria that is not resident of the Amazon region is around half a million visitors per year.

This study was designed to use a mathematical model to estimate the risk of acquiring falciparum malaria for travelers to the endemic regions of Brazil.

The Model


S
L
I
S
I
R

Models' variables	
S'_H	Human susceptible individuals in the "probe"
I'_H	Human infected individuals in the "probe"
R'_H	Human recovered individuals in the "probe"
S_H	Human susceptible individuals in the resident population
I_H	Human infected individuals in the resident population
R_H	Human recovered individuals in the resident population
S_M	Susceptible mosquitoes
L_M	Latent mosquitoes
I_M	Infected mosquitoes

Parameter	Biological interpretation
a	Mosquitoes' biting rate
a'	Mosquitoes' biting rate in the probe
b	Probability of infection to humans
b'	Probability of infection to humans in the probe
c	Probability of infection to mosquitoes
μ_H	Humans' mortality rate
γ	Recovery rate
σ	Loss of immunity
α	Malaria's mortality rate
r_H	Humans' reproductive rate
κ_H	Humans' carrying capacity
μ_M	Mosquitoes' mortality rate
τ	Extrinsic incubation period
r_M	Mosquitoes' reproductive rate
κ_M	Mosquitoes' carrying capacity
c_S	Seasonality factor
d_S	Seasonality factor
f	Frequency of seasonality

$$
\begin{aligned}
\frac{dS_H}{dt} &= -abI_M\frac{S_H}{N_H} - \mu_H S_H + \sigma_H R_H + r_H N_H\left(1-\frac{N_H}{\kappa_H}\right)\\
\frac{dI_H}{dt} &= abI_M\frac{S_H}{N_H} - \left(\mu_H + \gamma_H + \alpha_H\right)I_H\\
\frac{dR_H}{dt} &= \gamma_H I_H - \mu_H R_H - \sigma_H R_H\\
\frac{dS_M}{dt} &= -\mu_M S_M - acS_M\frac{(I_H + I_H^{'})}{N_H}\\
&\quad + r_M N_M\left(1-\frac{N_M}{\kappa_M}\right)\left[c_s - d_s sin\left(2\pi ft\right)\right]\\
\frac{dL_M}{dt} &= acS_M\frac{(I_H + I_H^{'})}{N_H}\\
&\quad - e^{-\mu_M\tau}acS_M\left(t-\tau\right)\frac{\left[I_H\left(t-\tau\right)+I_H^{'}\left(t-\tau\right)\right]}{N_H\left(t-\tau\right)} - \mu_M L_M\\
\frac{dI_M}{dt} &= e^{-\mu_M\tau}acS_M\left(t-\tau\right)\frac{\left[I_H\left(t-\tau\right)+I_H^{'}\left(t-\tau\right)\right]}{N_H\left(t-\tau\right)} - \mu_M I_M
\end{aligned}
\tag{1}
$$

The evolution equations for the probe cohort are:

$$\begin{aligned}
\frac{dS'_H}{dt} &= (-a'b'I_M \frac{S'_H}{N_H} - \mu_H S'_H)\theta(t-t_0) \\
\frac{dI'_H}{dt} &= (a'b'I_M \frac{S'_H}{N_H} - (\mu_H + \gamma_H + \alpha_H)I'_H)\theta(t-t_0) \qquad (2) \\
\frac{dR'_H}{dt} &= (\gamma_H I'_H - \mu_H R'_H - \sigma_H R'_H)\theta(t-t_0)
\end{aligned}$$

for

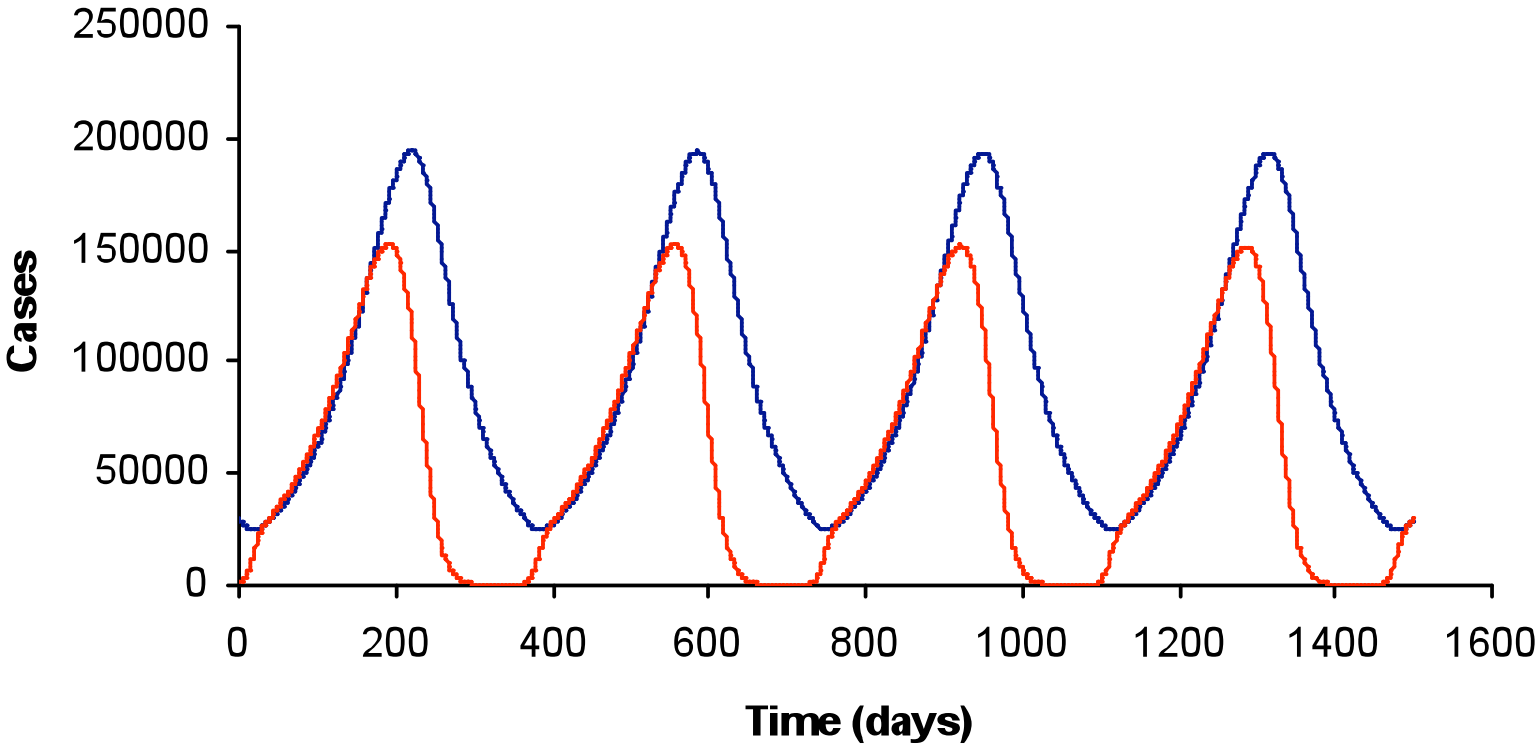
$$a' = POISSON(0.3)$$

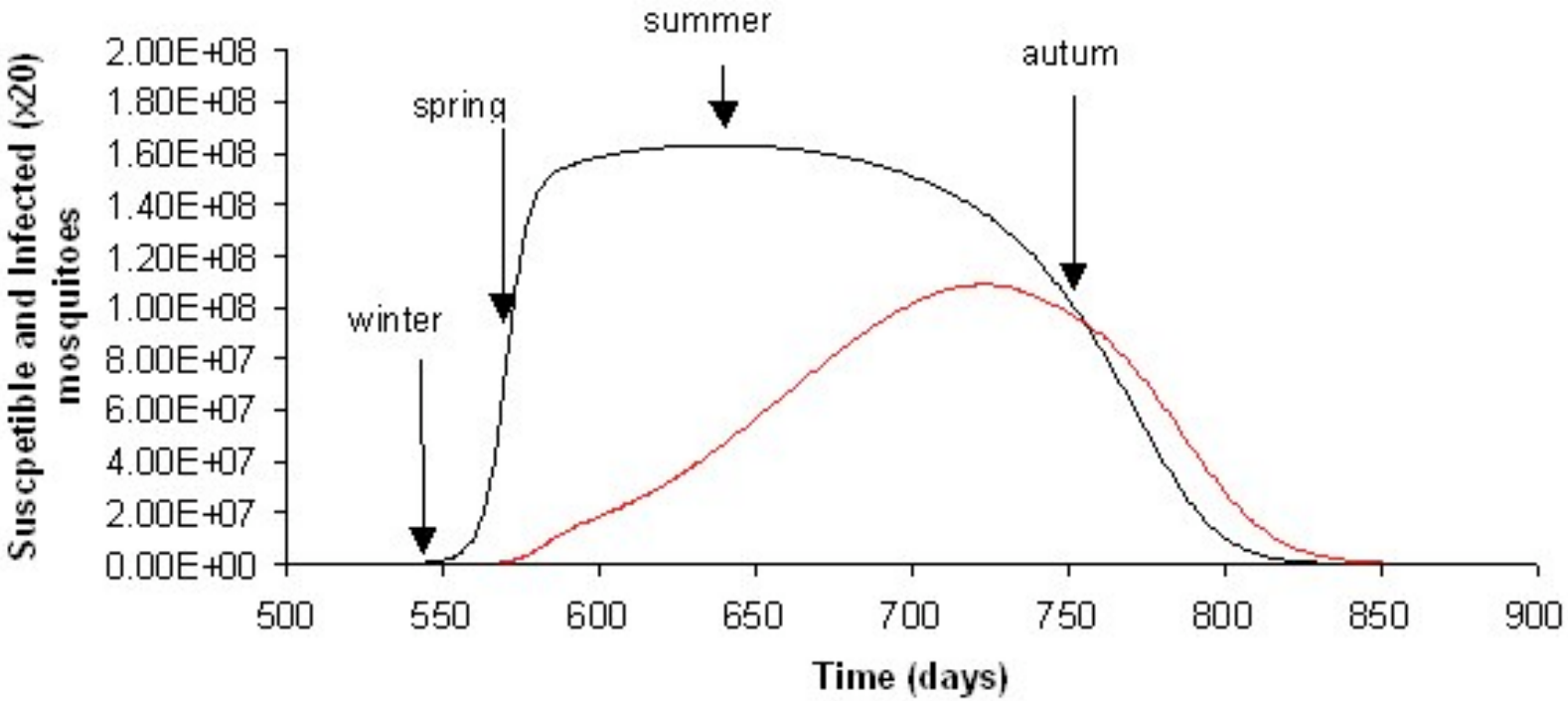
$$b' = NORMAL(0.088, 0.017)$$

$$\begin{aligned} N_H^{'} &= S_H^{'} + I_H^{'} + R_H^{'} \\ N_H &= N_H^{'} + S_H + I_H + R_H \\ N_M &= S_M + L_M + I_M \end{aligned} \tag{3}$$

and is the Heaviside function.

$$n_{falc.} = \int_{t=1}^{365} abI_M(t) \frac{S_H(t)}{N_H(t)} dt = 250{,}000$$


250000
200000
150000
100000
50000
0
Cases
0
200
400
600
800
1000
1200
1400
1600
Time (days)

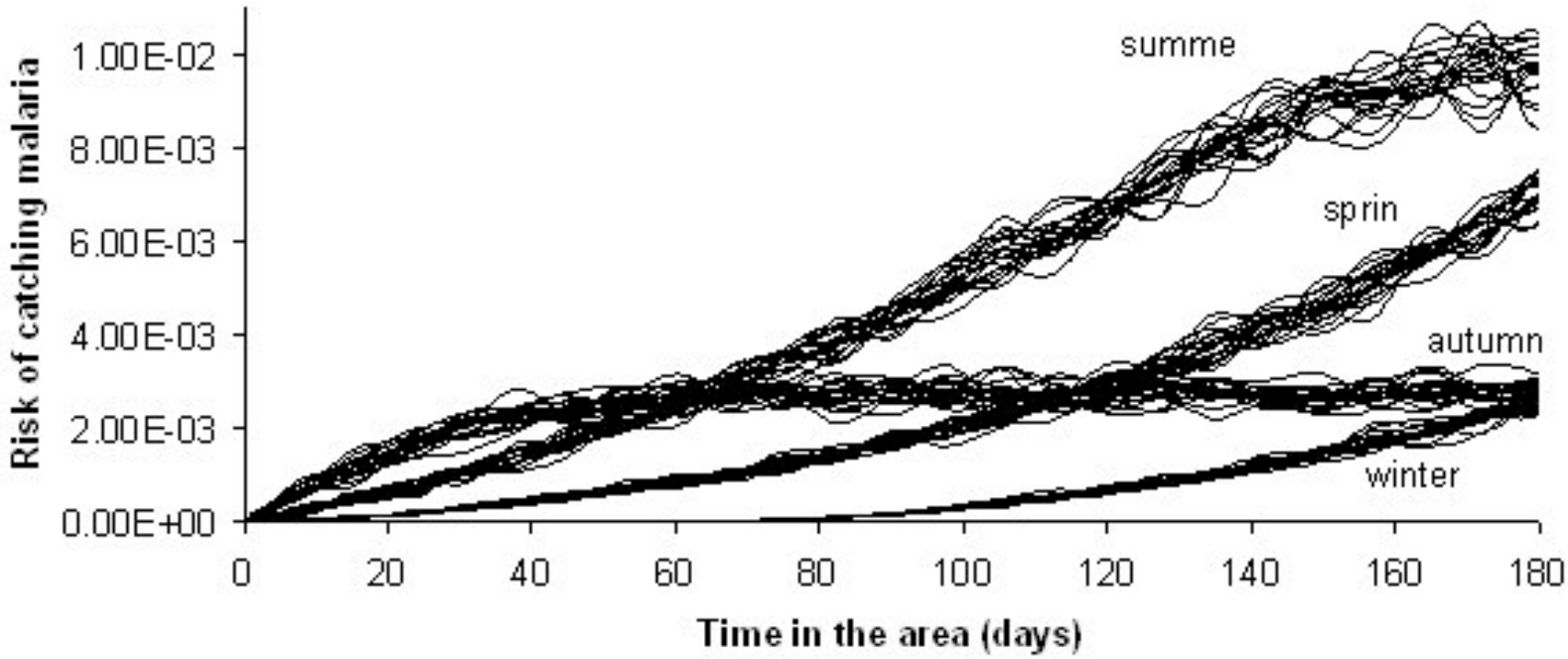

summer
autum
spring
winter
2.00E+08
1.80E+08
1.60E+08
1.40E+08
1.20E+08
1.00E+08
8.00E+07
6.00E+07
4.00E+07
2.00E+07
0.00E+00
Suscpetible and Infected (x20) mosquitoes
500
550
600
650
700
750
800
850
900
Time (days)

Estimating the risk of malaria

$$\pi_{mal} = \frac{\int_0^{\infty} S'_H(t) h_{mal}(t) dt}{N'_H(0)}$$

$$h_{mal}(t) = a'b'_{mal} \frac{I_M(t)}{N_H(t)}$$

$$\pi_{mal}^{travelers} = \frac{\int_{\Omega}^{\Omega+\omega} S'_H(t) h_{mal}(t) dt}{N'_H(\Omega)}$$


Risk of catching malaria
1.00E-02
8.00E-03
6.00E-03
4.00E-03
2.00E-03
0.00E+00
0
20
40
60
80
100
120
140
160
180
Time in the area (days)
summe
sprin
autumn
winter

Sensitivity analysis

$$\Delta\pi = \sum_i \frac{\partial \pi}{\partial Par_i} \times \Delta Par_i$$

$$\frac{\Delta\pi}{\pi} = \sum_i Par_i \frac{\partial \pi}{\partial Par_i} \times \frac{\Delta Par_i}{Par_i} \times \frac{1}{\pi}$$

Sensitivity of the model to each of the parameters (Par) in different periods of the year. The analysis assumes a 1% variation in the value of each parameter and the risk was calculated for 30 days of permanence.

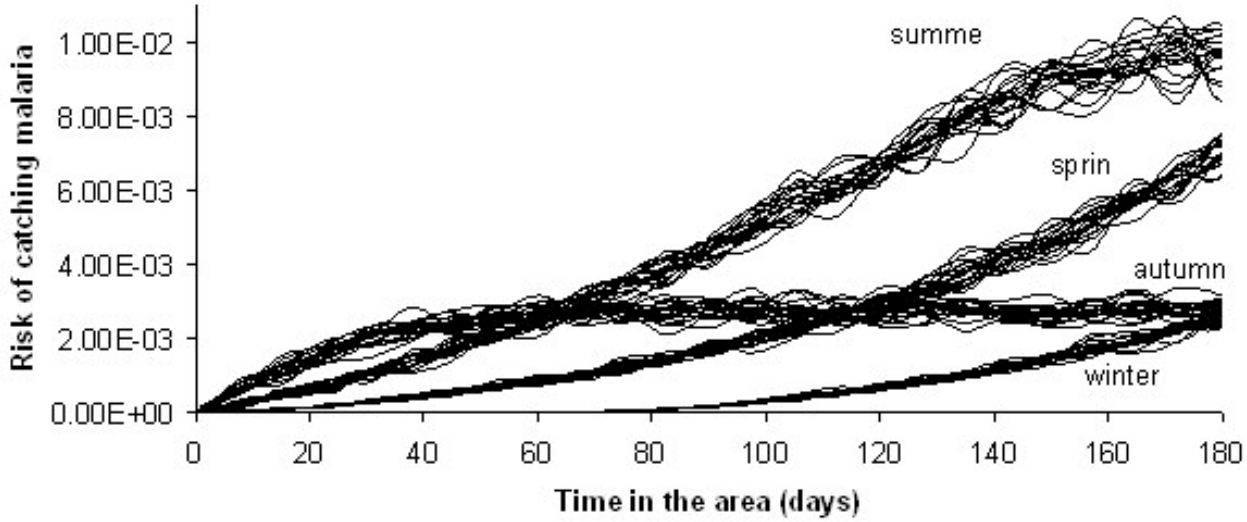
	Winter		Spring		Summer		Autumn	
π	0.0000026		0.000265		0.001008		0.001961	
Par	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)
a	0.0000914	10.5	0.00966	10.81	0.044383	13.21	0.114948	17.58
b	0.0001556	5.22	0.01628	5.39	0.0753904	6.58	0.195216	8.76
c	0.0004556	5.20	0.001642	5.39	0.0761103	6.57	0.197145	8.75
μ_H	- 0.0010232	0.015	-0.13629	0.021	-0.560427	0.021	-1.24269	0.025
γ	- 0.0010051	1.92	-0.131761	2.48	-0.548329	2.72	-1.22159	3.11
σ	0.0000072	0.091	0.000734	0.0912	0.0.0027967	0.0915	0.0054288	0.0913
α	- 0.0010004	3.83	-0.13155	4.96	-0.547397	5.43	-1.21920	6.21
r_H	0	0	-3.75×10^{-09}	0.000113	0	0	-2.98×10^{-0}	0.000122
κ_H	9.98×10^{-13}	6.09	1.04×10^{-10}	6.27	-4.83×10^{-10}	7.67	-1.17×10^{-09}	9.57
μ_M	-0.000585	22.27	-0.0463206	17.45	-0.173717	17.23	-0.43966	22.41
τ	- 0.0000012	3.34	-0.000166	4.38	-0.000734	5.09	-0.001826	6.51
r_M	0.0000045	6.99	0.00063081	9.51	0.0018048	7.16	0.00416124	8.48
κ_M	6.56×10^{-14}	4.99	6.87×10^{-12}	5.17	3.20×10^{-11}	6.36	8.37×10^{-11}	8.53

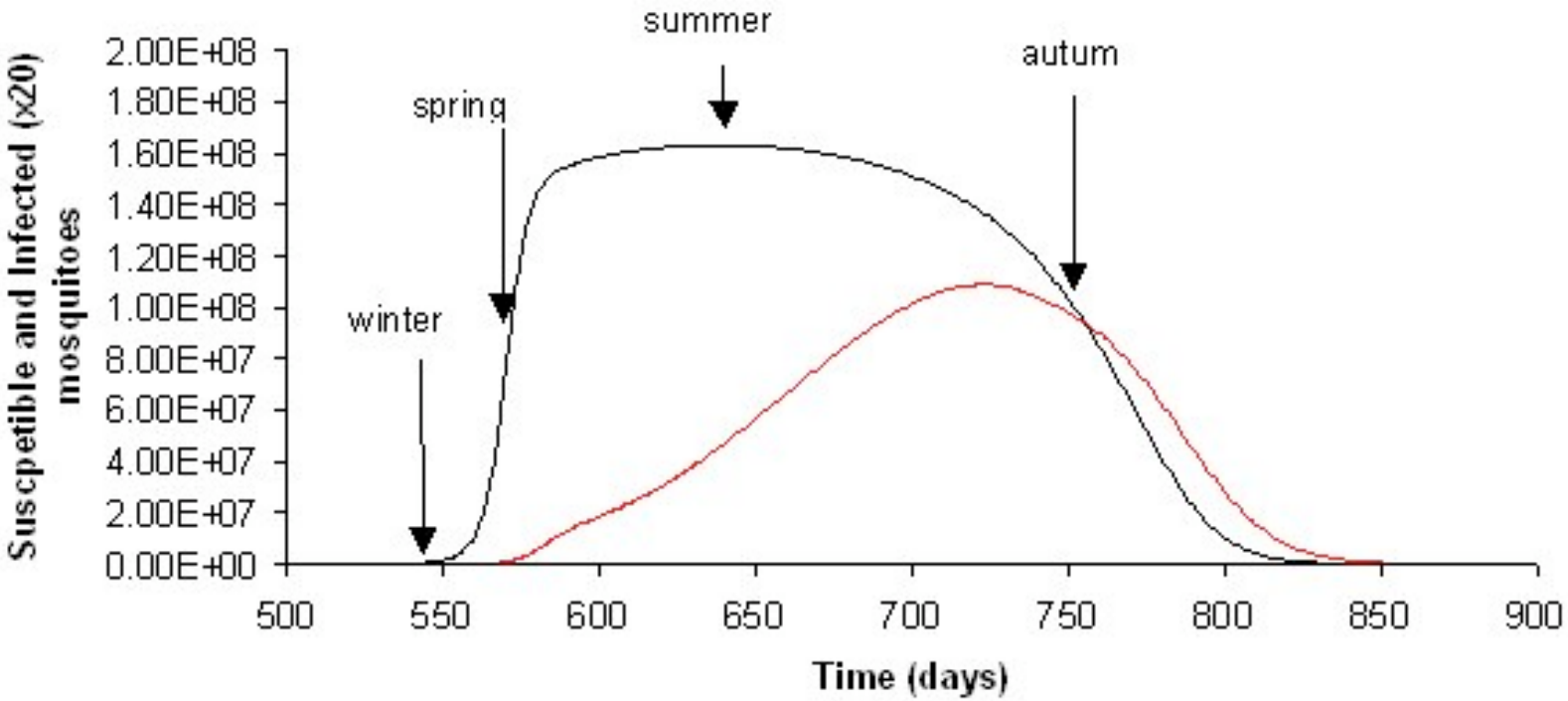
Average risk of malaria acquisition (with confidence intervals) for travelers who remain 30 days in the area.

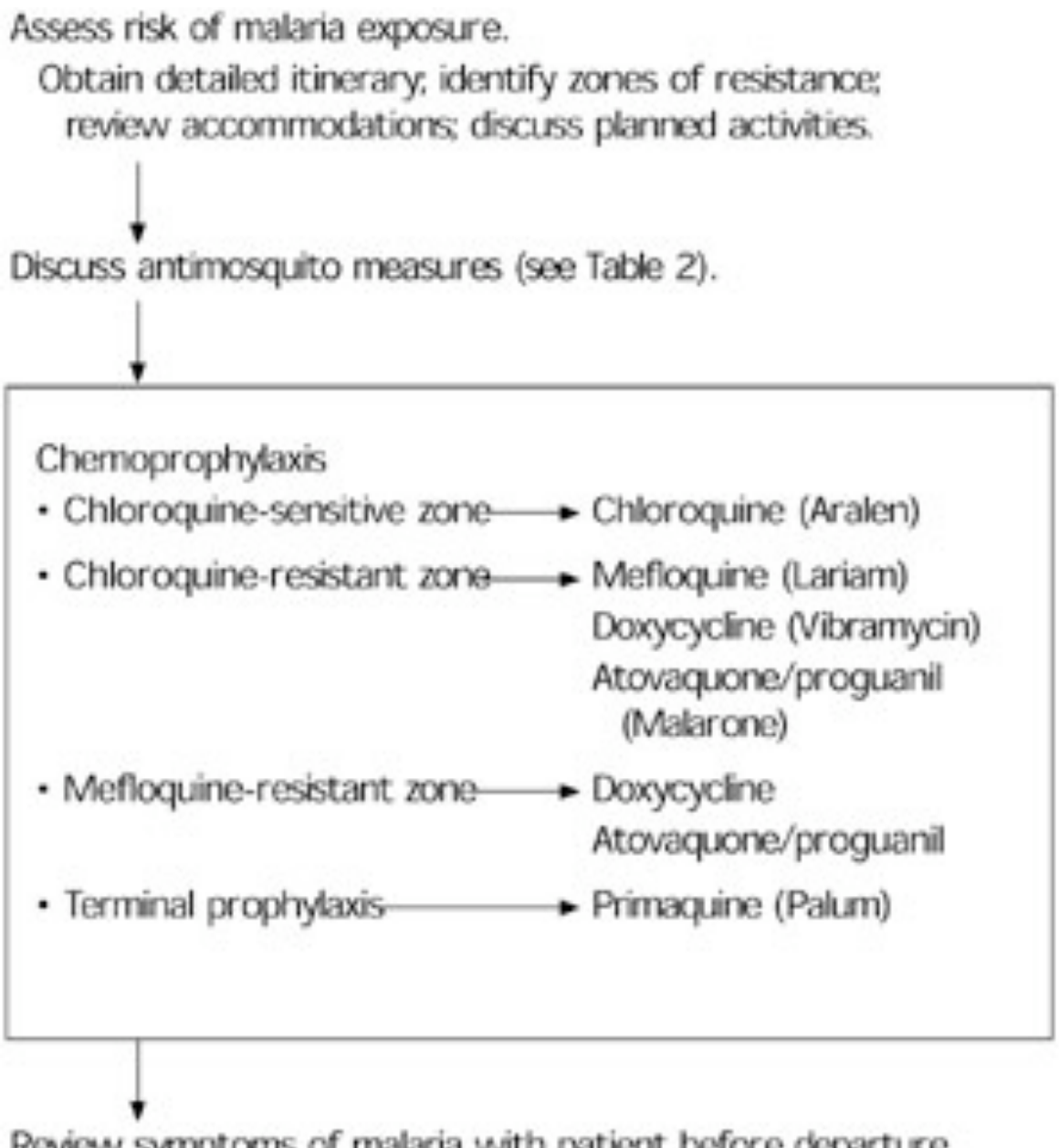
	Winter	Spring	Summer	Autumn
$\bar{\pi}$	2.60×10^{-6}	2.66×10^{-4}	1.01×10^{-3}	1.96×10^{-3}
C.I.(95%)	2.10×10^{-8}	1.96×10^{-6}	6.64×10^{-6}	1.25×10^{-5}
± Relative error (%)	0.81	0.74	0.66	0.64

It should be noted that for an individual who remains 1 year in the area, this risk equals to $1.10 \times 10^{-2} \pm 2.75 \times 10^{-5}$, that is, a relative error of ± 0.25%. This figure should be compared with the malaria incidence observed in residents of the Amazon region of 1.16×10^{-2} per person-year.

A traveler arriving in summer (Dec-Feb) and exposed for 120 days has at least a ten-fold higher risk of infection than a traveler, who arrive in the winter (June-Aug) for a visit of the same duration. We also confirm that the risk increases nonlinearly with time, but this again varies by season of exposure.




summer
autum
spring
winter
2.00E+08
1.80E+08
1.60E+08
1.40E+08
1.20E+08
1.00E+08
8.00E+07
6.00E+07
4.00E+07
2.00E+07
0.00E+00
Suscpetible and Infected (x20) mosquitoes
500
550
600
650
700
750
800
850
900
Time (days)


Assess risk of malaria exposure.
Obtain detailed itinerary; identify zones of resistance; review accommodations; discuss planned activities.
Discuss antimosquito measures (see Table 2).
Chemoprophylaxis
• Chloroquine-sensitive zone → Chloroquine (Aralen)
• Chloroquine-resistant zone → Mefloquine (Lariam)
Doxycycline (Vibramycin)
Atovaquone/proguanil (Malarone)
• Mefloquine-resistant zone → Doxycycline
Atovaquone/proguanil
• Terminal prophylaxis → Primaquine (Palum)
Review symptoms of malaria with patient before departure.

Cost analysis

Let us define the following:

Pd = probability of taking chemoprophylasis (constant)

e = effectiveness of chemoprophylaxis in preventing malaria (increases with time taking drugs)

Pae = probability of having adverse events due to chemoprophylaxis (increases with time taking drugs)

PM = probability of catching malaria (increases with time remaining in the endemic area)

CM = costs of catching malaria (increases with *PM*)

Cnc = costs of avoiding chemoprophylaxis (constant)

Cc = costs of chemoprophylaxix (increases with time taking drugs)

Cae = costs of adverse events (increases with time taking drugs)

With this, it is possible to define the following possibilities:

Non-treated individuals who catch malaria = (1-*Pd*)*PM*

Non-treated individuals who do not catch malaria = (1-*Pd*)(1-*PM*)

Treated individuals who are protected from malaria = *ePdPae*

Treated individuals who catch malaria = (1-e)PdPaePM

Treated individuals who do not catch malaria = (1-e)PdPae(1-*PM*)

Total cost of chemoprophylaxis, C_T

$$C_T = (C_c + \mathrm{C_{ae}})\mathrm{eP_dP_{ae}} + (C_c + C_{ae} + \mathrm{C_M})(1\text{-e})\mathrm{P_dP_{ae}P_M}$$
$$+ (C_c + \mathrm{C_{ae}})(1\text{-e})\mathrm{P_dP_{ae}}(1\text{-}P_M)$$

Total cost of avoiding chemoprophylaxis, C_{NT}

$$C_{NT} = (C_M + \mathrm{C_{nc}})(1 - P_d)\, P_M + \mathrm{C_{nc}}(1 - \mathrm{P_d})(1 - P_M)$$

Cost's parameters (arbitrary units)

$Cc = 10$ units

$Cae = 10$ units

$e = 0.9$

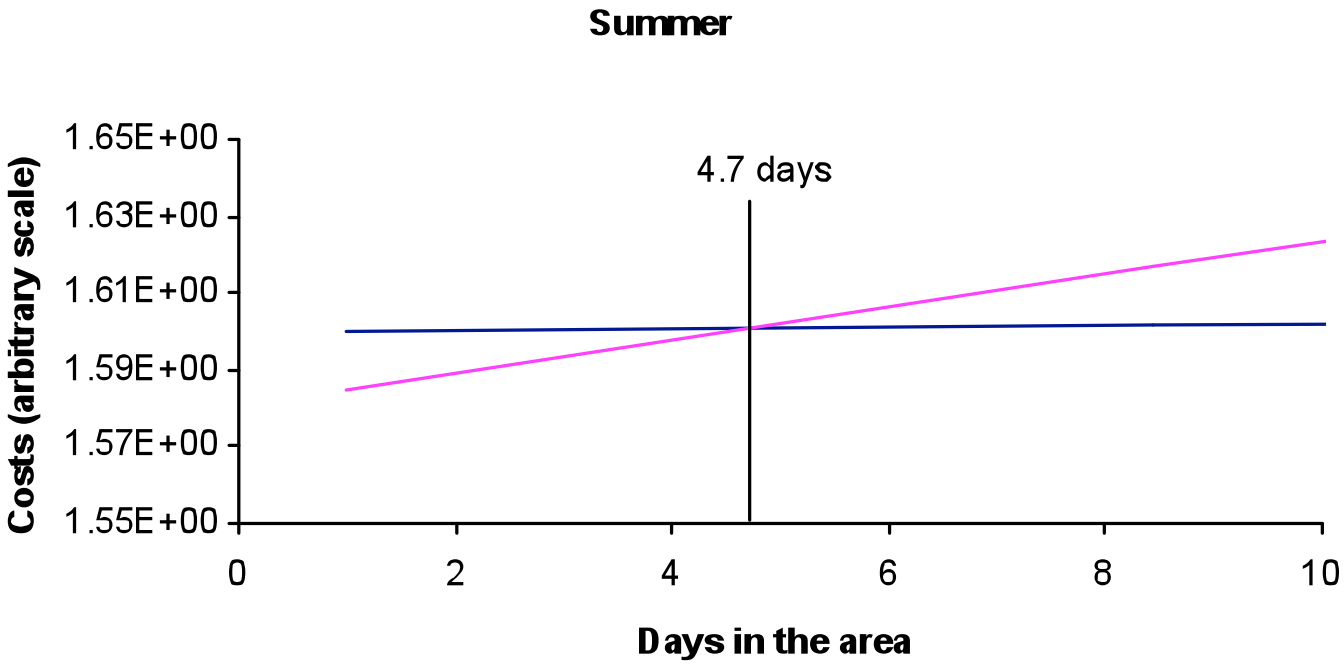
$Pd = 0.8$

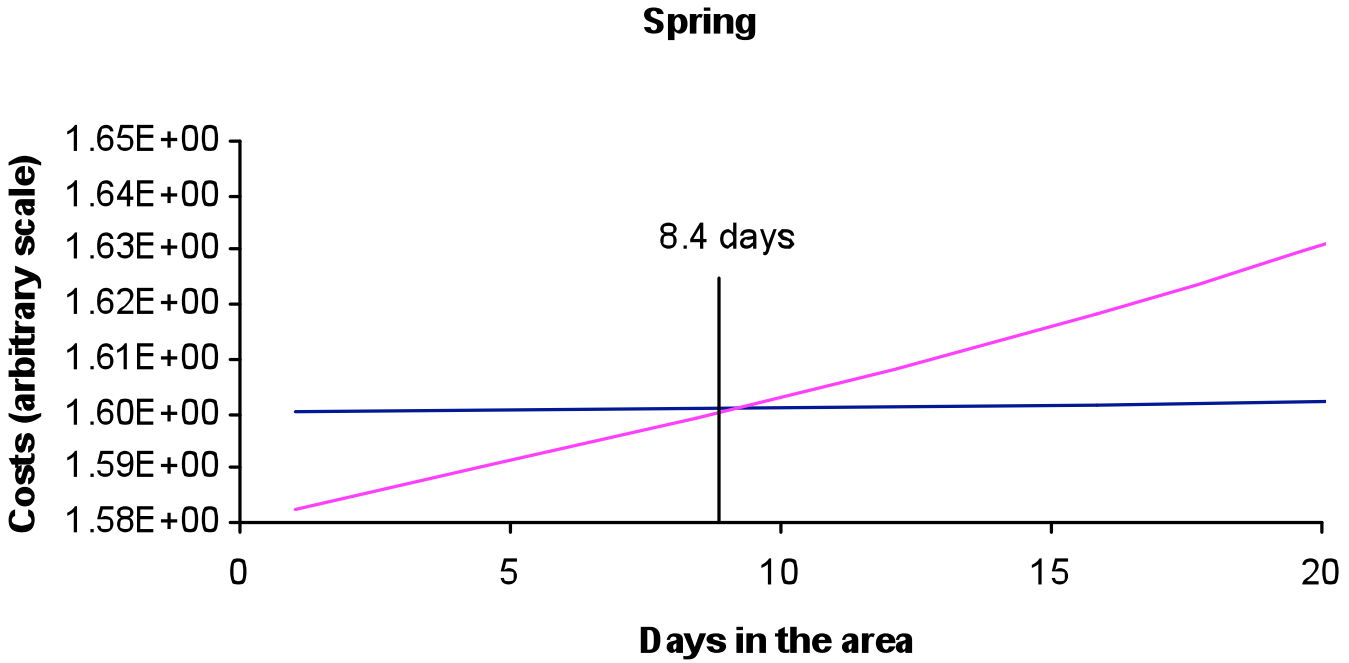
$Pae = 0.1$

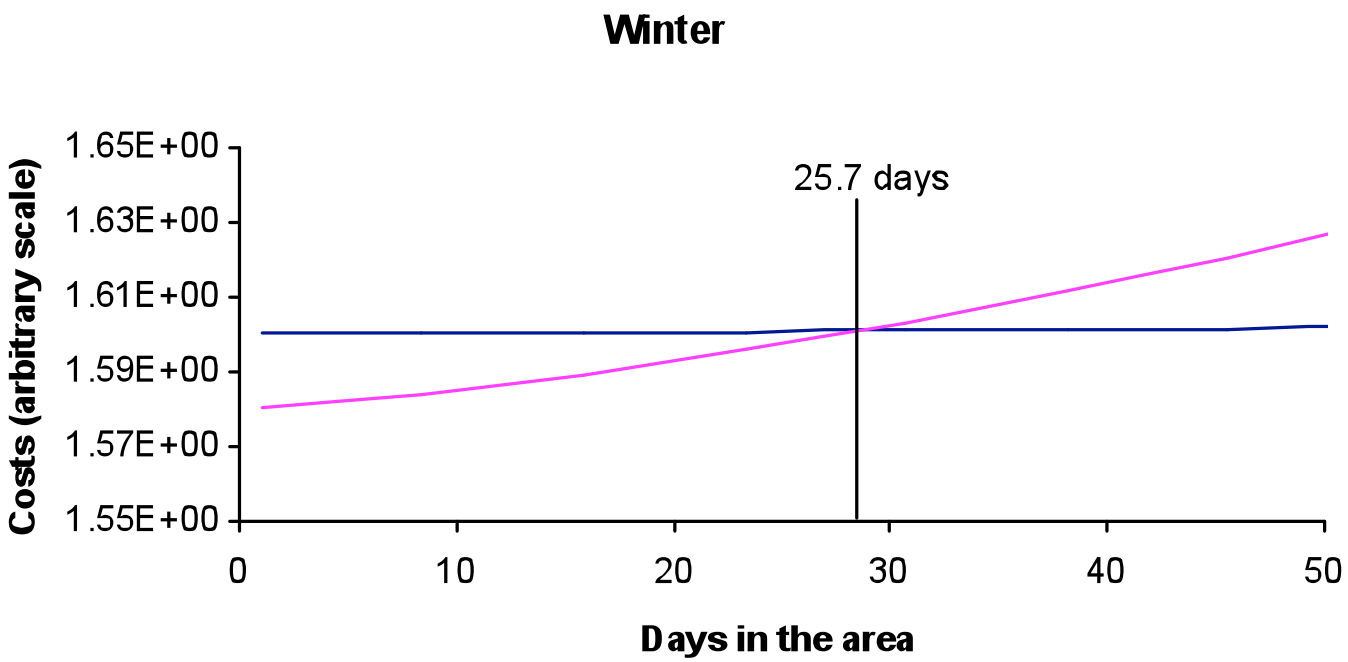
$CM = 175$ units

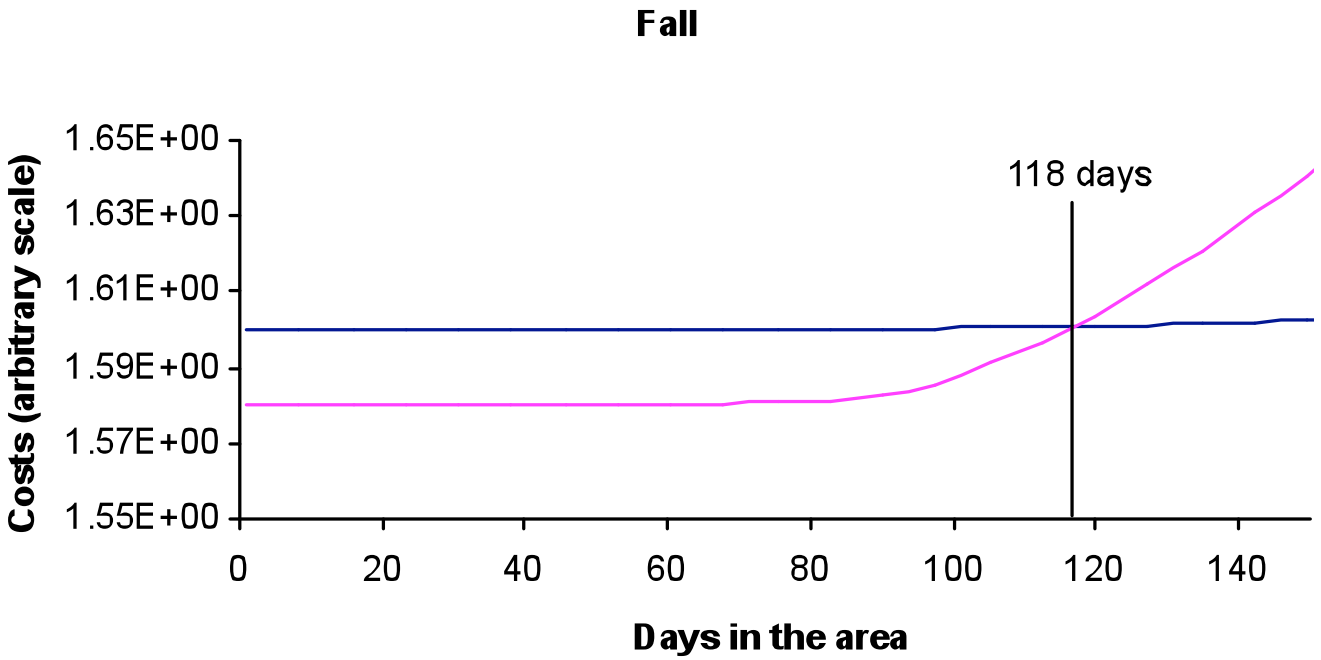
$CNC = 7.9$ units

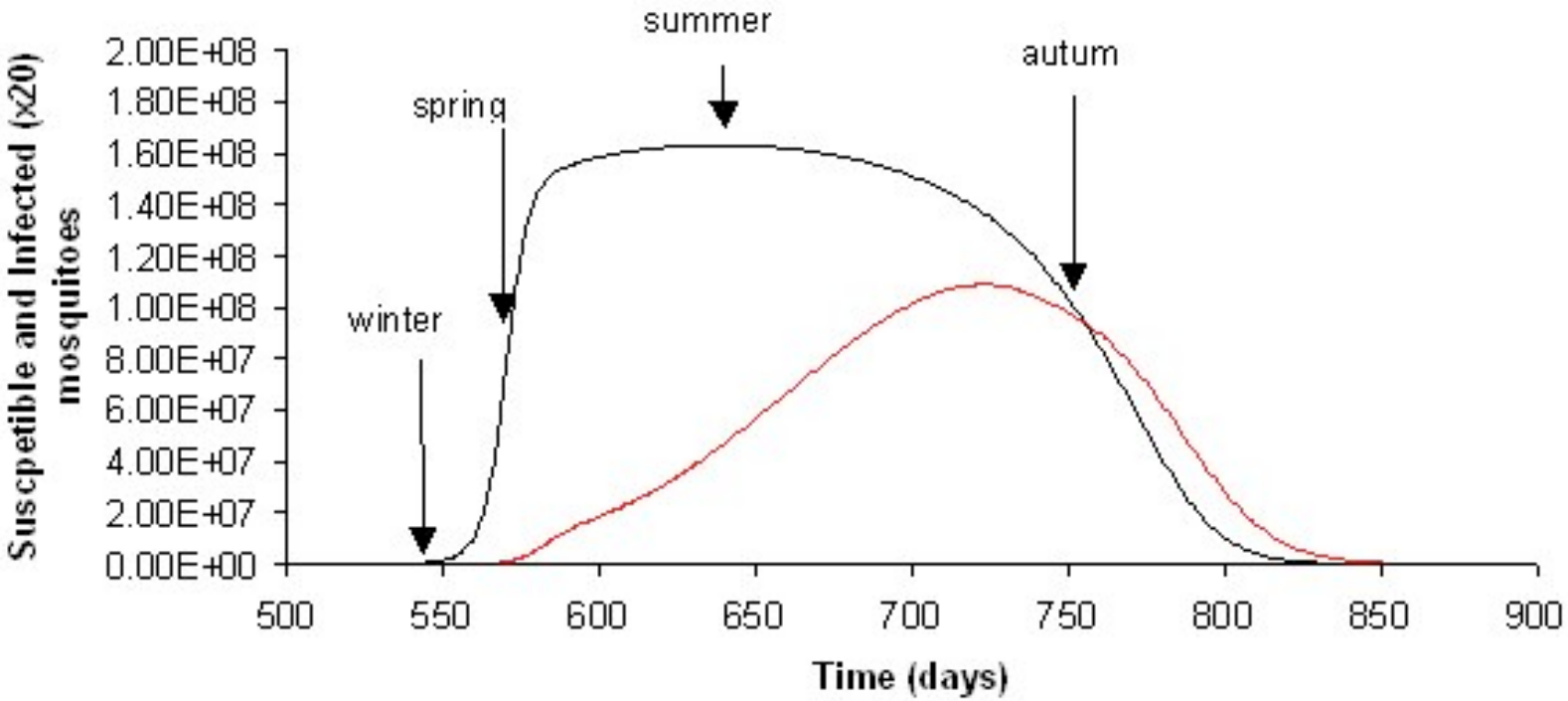
$PM =$ variable


Summer
Costs (arbitrary scale)
1.65E+00
1.63E+00
1.61E+00
1.59E+00
1.57E+00
1.55E+00
4.7 days
0
2
4
6
8
10
Days in the area


Spring
Costs (arbitrary scale)
1.65E+00
1.64E+00
1.63E+00
1.62E+00
1.61E+00
1.60E+00
1.59E+00
1.58E+00
8.4 days
0
5
10
15
20
Days in the area


Winter
Costs (arbitrary scale)
1.65E+00
1.63E+00
1.61E+00
1.59E+00
1.57E+00
1.55E+00
25.7 days
0
10
20
30
40
50
Days in the area


Fall
1.65E+00
1.63E+00
1.61E+00
1.59E+00
1.57E+00
1.55E+00
Costs (arbitrary scale)
118 days
0
20
40
60
80
100
120
140
Days in the area


summer
autum
spring
winter
2.00E+08
1.80E+08
1.60E+08
1.40E+08
1.20E+08
1.00E+08
8.00E+07
6.00E+07
4.00E+07
2.00E+07
0.00E+00
Suscpetible and Infected (x20) mosquitoes
500
550
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850
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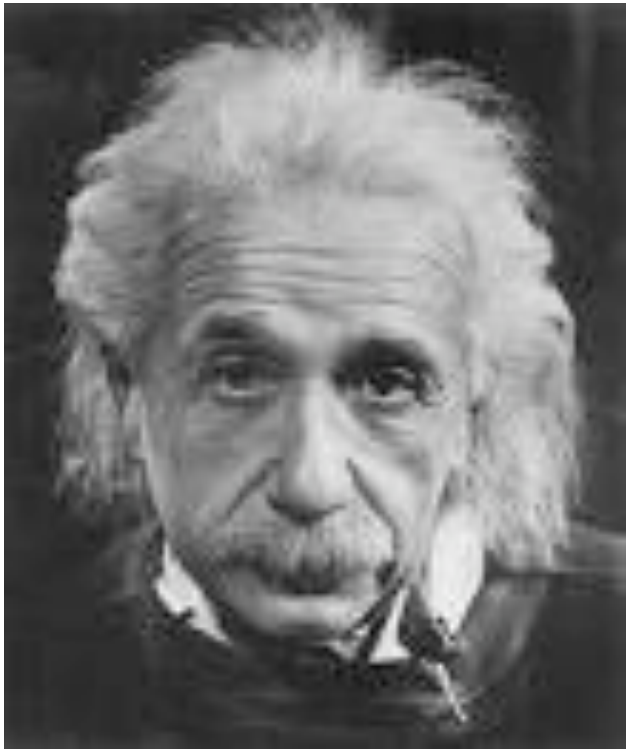
Time (days)



All models are wrong; some models are useful...

Albert Einstein