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

Eduardo Massad , Ronald H. Behrens ,
Marcelo N. Burattini , Francisco A. B. Coutinho

London School of Hygiene and Tropical Diseases, U.K.

School of Medicine, University of Sao Paulo
Brazil

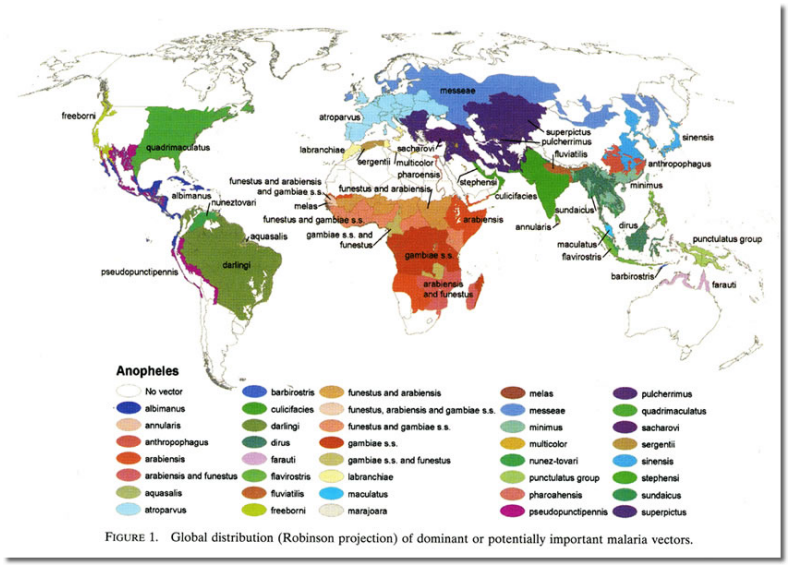


FIGURE 1. Global distribution (Robinson projection) of dominant or potentially important malaria vectors.

Ross's Threshold Theorem for Malaria

1. The amount of malaria in a locality tends towards a fixed limit determined by the number of malaria-bearing mosquitoes;
2. If the number of malaria-bearing Anophelines is below a certain figure, that limit will be zero.

$$m = 1 - \frac{40}{a}$$

R_0 for vector-borne infection can be understood as the number of secondary human (vetors) cases generated by one infected human (vector) in an entirely susceptible human (vector) population through the mosquito vectors (humans).

m = density of mosquitoes as related to humans
a = mosquitoes daily biting rate
b = probability of infection from mosquitoes to humans
c = probability of infection from humans to mosquitoes
μ = mosquitoes mortaility rate
τ = extrinsic incubation period
$e^{-\mu\tau}$ = probability that the mosquitoes survive through the extrinsic incubation period
γ = humans recovery rate from infection

$$R_0 = \frac{ma^2cbe^{-\mu\tau}}{\mu\gamma}$$

Effective inoculation rate

Force of infection = per capita rate of new infections per time unit

$$h = mabs = \frac{ma^2byce^{-\mu\tau}}{\mu}$$

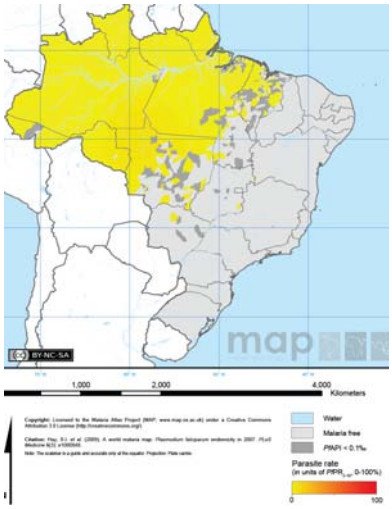
$$h = b(1 - e^{-Cy})$$

Risk of malaria

Probability of aquiring malaria in a given time period

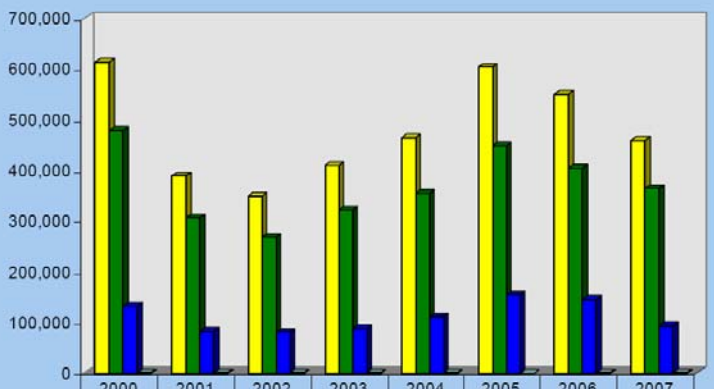
$$RM = 1 - e^{-ht}$$

The spatial distribution of *Plasmodium falciparum* malaria endemicity in Brazil



Pan American Health Organization
Regional Office of the World Health Organization

BRAZIL: Malaria Morbidity, 2000-2007



	2000	2001	2002	2003	2004	2005	2006	2007
No. of Cases	613,241	388,303	348,259	408,821	464,602	603,026	549,184	458,041
P. vivax	478,212	306,396	267,245	320,360	354,080	448,017	403,122	363,830
P. falciparum & mixed	131,616	81,333	80,188	88,163	110,305	154,835	145,827	93,160
P. malariae	932	574	826	298	217	174	235	235 *

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. Cases fell between 1992 to 2002 from 572,000 to 349,873 All cases laboratory confirmed, and 19% in 2007 were *P. falciparum*.

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.

- deterministic version of the model to describe the malaria dynamics at the resident population level.
- stochastic version (the equations of the probe) to describe the risk (probability of contracting malaria) for an individual traveler visiting the region.

The Model

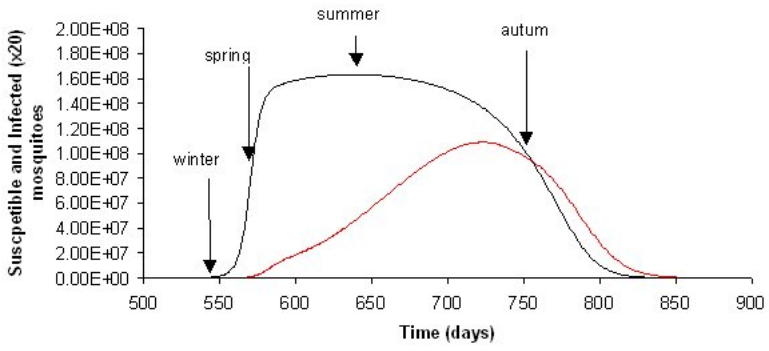
Model's parameters			
Parameter	Biological interpretation	Value	Source
a	Mosquitoes' biting rate	$0.3\ days^{-1}$	[24]*
a'	Mosquitoes' biting rate in the probe	Poisson (0.3)	Assumed
b	Probability of infection to humans	$8.8\times10^{-2}\ days^{-1}$	[25]
b'	Probability of infection to humans in the probe	Normal (0.088, 0.017)	Assumed
c	Probability of infection to mosquitoes	$8.7\times10^{-2}\ days^{-1}$	Fitted+
μ_H	Humans' mortality rate	$3.9\times10^{-5}\ days^{-1}$	[26]
γ	Recovery rate	$5.5\times10^{-3}\ days^{-1}$	[27]
ξ	Loss of immunity	$3.3\times10^{-2}\ days^{-1}$	[28]
α	Malaria's mortality rate	$1.0\times10^{-2}\ days^{-1}$	[29]
r_H	Humans' reproductive rate	$8\ days^{-1}$	[26]
K_H	Humans' carrying capacity	1.6×10^{7}	[26]
μ_M	Mosquitoes' mortality rate	$1.0\times10^{-1}\ days^{-1}$	[30]
τ	Extrinsic incubation period	$7\ days$	[27]
r_M	Mosquitoes' reproductive rate	$4\ days^{-1}$	[24]
K_M	Mosquitoes' carrying capacity	$2.0\times10^{8}\ days^{-1}$	Fitted+
c_s	Seasonality factor	$7.0\times10^{-2}\ days^{-1}$	Fitted+
d_s	Seasonality factor	$5.3\times10^{-2}\ days^{-1}$	Fitted+
f	Frequency of seasonality	$2.7\times10^{-3}\ days^{-1}$	Fitted+

*Estimated as the inverse of the gonothophic cycle duration.

+Fitted to reproduce the observed prevalence of falciparum malaria in the area.

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

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



Estimating the risk of malaria

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

force of infection of malaria $h_{mal}(t)$

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

probability of infection $\pi_{mal}^{travelers}$

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

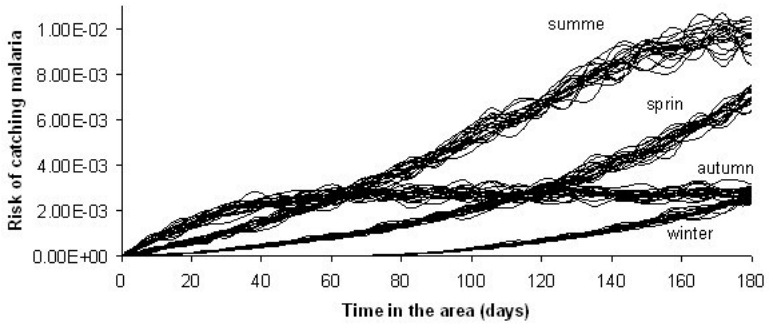
Table 1. Models' variables

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

Table 2. Model's parameters

Parameter	Biological interpretation	Value	Source
a	Mosquitoes' biting rate	0.3 $days^{-1}$	[24]*
a'	Mosquitoes' biting rate in the probe	Poisson (0.3)	Assumed
b	Probability of infection to humans	8.8×10^{-2} $days^{-1}$	[25]
b'	Probability of infection to humans in the probe	Normal (0.088, 0.017)	Assumed
c	Probability of infection to mosquitoes	8.7×10^{-2} $days^{-1}$	Fitted+
μ_H	Humans' mortality rate	3.9×10^{-5} $days^{-1}$	[26]
γ	Recovery rate	5.5×10^{-3} $days^{-1}$	[27]
σ	Loss of immunity	3.3×10^{-2} $days^{-1}$	[28]
α	Malaria's mortality rate	1.0×10^{-2} $days^{-1}$	[29]
r_H	Humans' reproductive rate	8 $days^{-1}$	[26]
N_H	Humans' carrying capacity	1.6×10^{7}	[26]
μ_M	Mosquitoes' mortality rate	1.0×10^{-1} $days^{-1}$	[30]
τ	Extrinsic incubation period	7 $days$	[27]
r_M	Mosquitoes' reproductive rate	4 $days^{-1}$	[24]
N_M	Mosquitoes' carrying capacity	2.0×10^{8} $days^{-1}$	Fitted+
c_s	Seasonality factor	7.0×10^{-2} $days^{-1}$	Fitted+
d_s	Seasonality factor	5.3×10^{-2} $days^{-1}$	Fitted+
f	Frequency of seasonality	2.7×10^{-3} $days^{-1}$	Fitted+

*Estimated as the inverse of the gonothophic cycle duration.
+Fitted to reproduce the observed prevalence of falciparum malaria in the area.



Sensitivity analysis

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

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

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

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

1:6,666 prob. of infection within 3 months of arrival

1:6,666 prob. of infection within 1 week of arrival

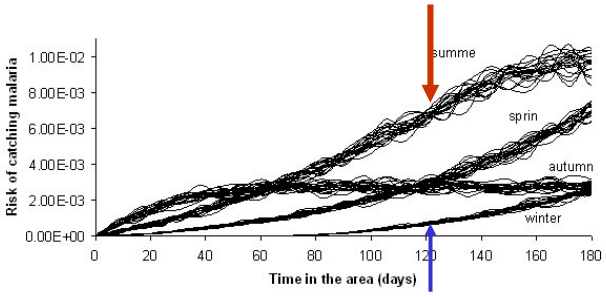
Sensitivity of the model to each of the parameters (Par) in different periods of the year. The analysis assumes a 1% variation in the value of each parameter and the risk was calculated for 30 days of permanence.

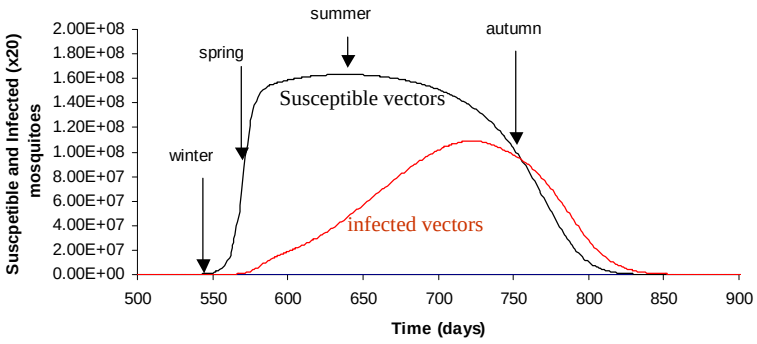
	Winter		Spring		Summer		Autumn	
π	0.0000026		0.000265		0.001008		0.001961	
Par	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)	$\frac{\partial \pi}{\partial Par}$	± Relative error (%)
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^{-8}	0.000122
K_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
K_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

Model risk for1 year exposure = $1.10 \times 10^{-2} \pm 0.25\%$.
Observed malaria incidence in Amazon residents = 1.16×10^{-2} per person-year.

PAHO estimated incidence of 75 malaria cases per 1000 (7.5×10^{-2}) inhabitants per year. As we are estimating only the cases of falciparum malaria, which represent about one third of the total malaria cases, the total expected malaria cases for this region is about 3.3×10^{-2} inhabitants per year.

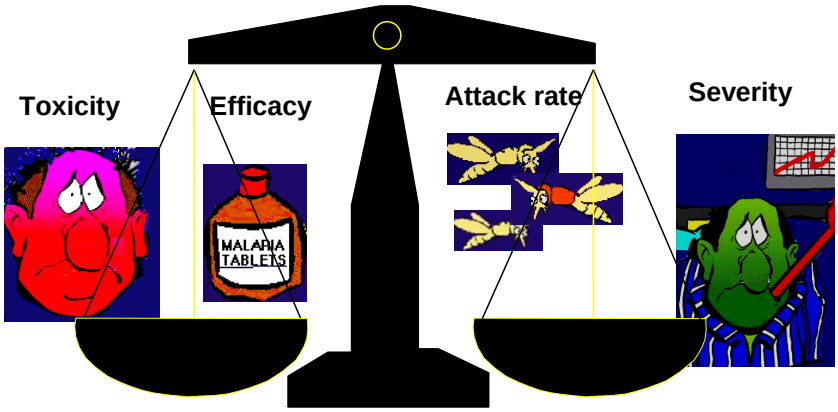
A traveler arriving in summer (Dec-Feb) and exposed for 120 days has at least a ten-fold higher risk of infection than a traveler, who arrive in the winter (June-Aug) for a visit of the same duration. We also confirm that the risk increases nonlinearly with time, but this again varies by season of exposure.





Definition of the seasons as related to the fluctuations on the susceptible mosquitoes populations (black line). The infected mosquitoes (red line) amplified 20 times.

Cost : Benefit Assessment for Malaria chemoprophylaxis



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

$C_T = (C_c + C_{ae}) e P_d P_{ae} + (C_c + C_{ae} + C_M)(1-e) P_d P_{ae} P_M$

$\Rightarrow C_c + C_{ae})(1-e) P_d P_{ae} (1-P_M)$

Total cost of avoiding chemoprophylaxis, C_{NT}

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

Cost's parameters (arbitrary units)

Cc = 10 units

Cae = 10 units

e = 0.9

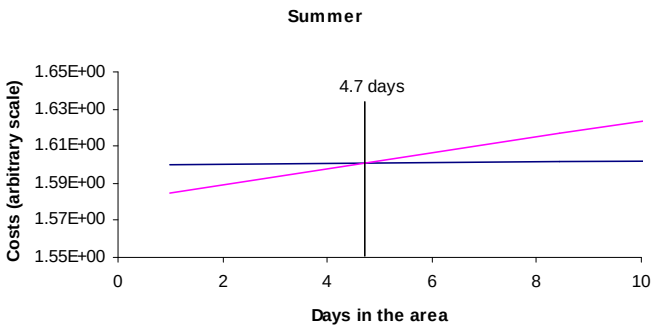
Pd = 0.8

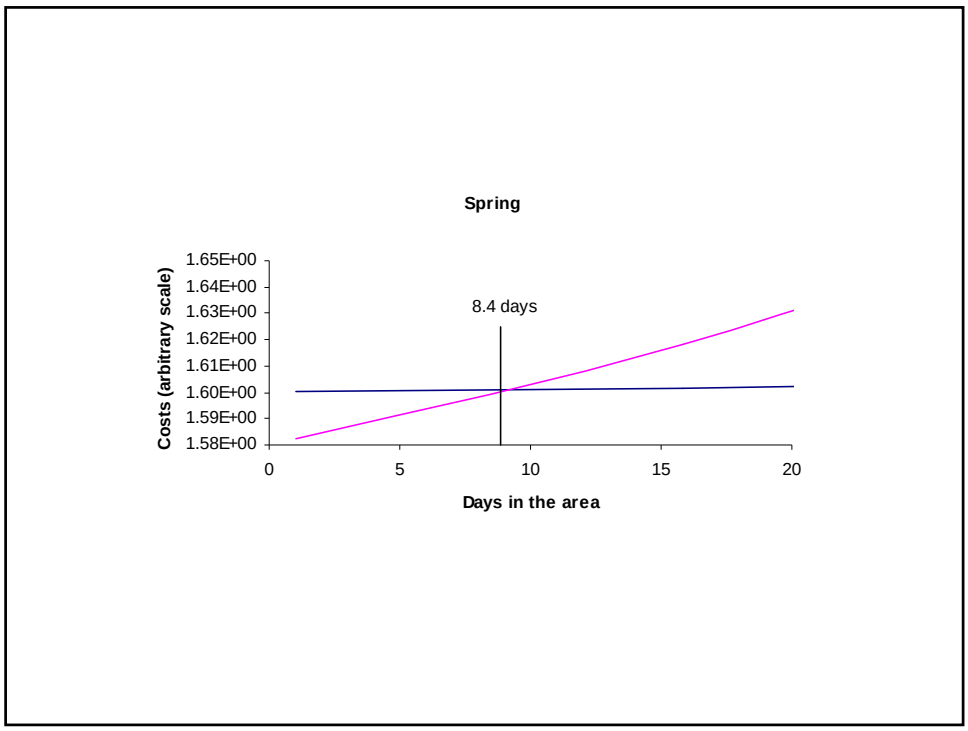
Pae = 0.1

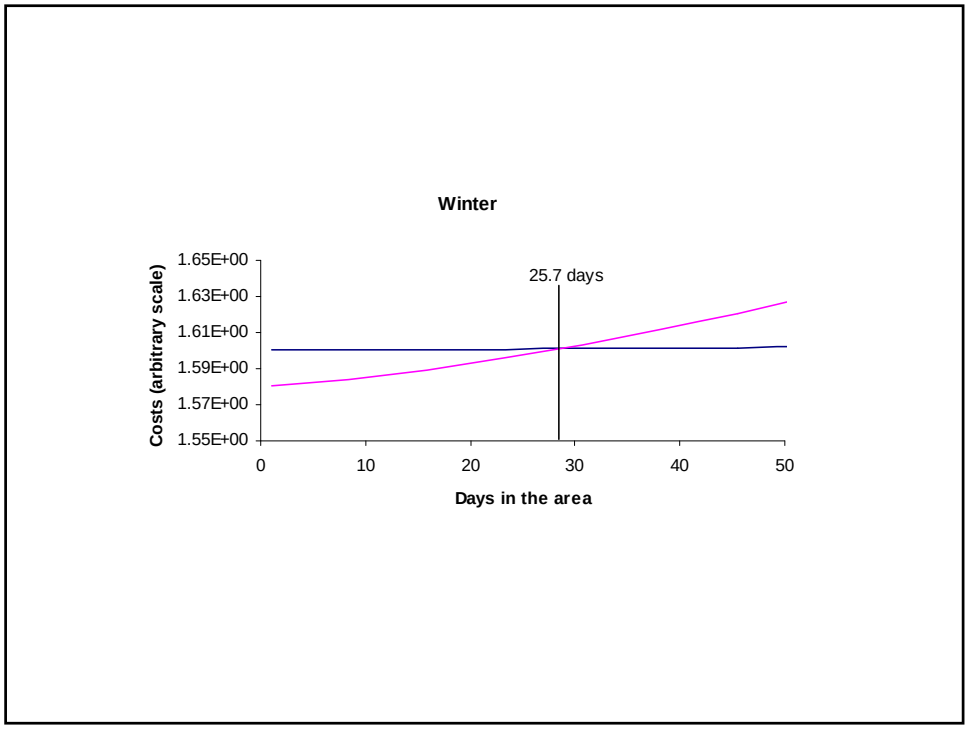
CM = 175 units

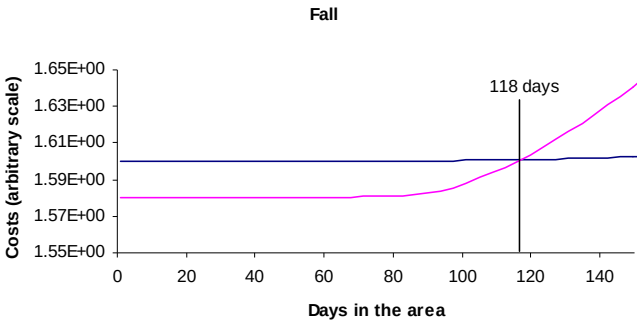
CNC = 7.9 units

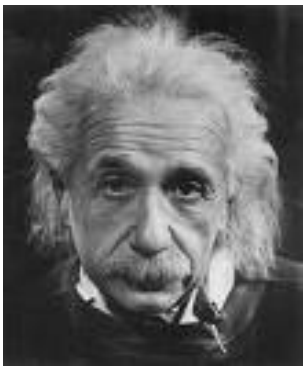
PM = variable




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


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





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

Albert Einstein