Predicting and Controlling Future Zika Outbreaks

Eduardo Massad
School of Applied Mathematics
Fundacao Getulio Vargas
Brazil

Insert Logo of partner authoring

eduardo.massad@fgv.br

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Preparedness Latin American Network
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Has Zika burnt itself out in Brazil/Latin America?

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Will Zika resurge in the foreseeable future?

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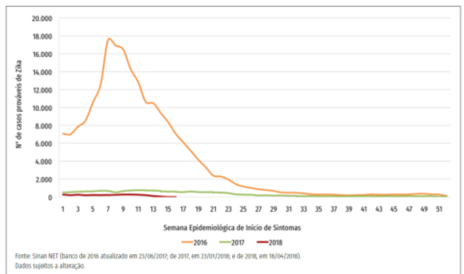
Reported numbers of Zika 2016-2018



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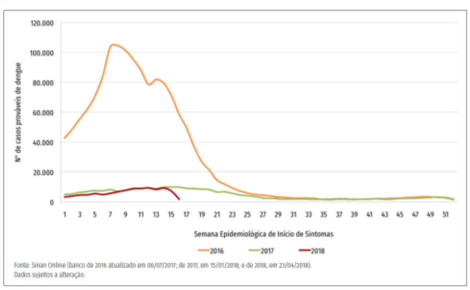
Reported numbers of Dengue 2016-2018



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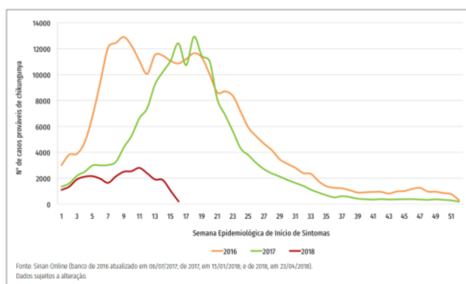
Reported numbers of Chikungunya 2016-2018



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Cases of Zika, Chik and Dengue, Brazil

	2016	2017	2018
Zika	170535	10286	2985
Chik	135030	86568	29675
Dengue	1.18E+06	128730	101863

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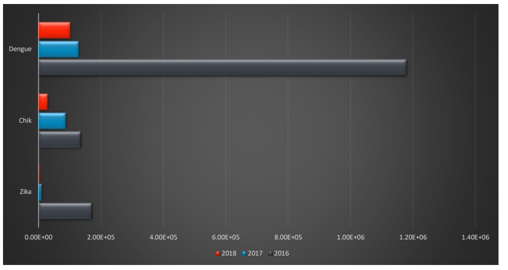
Cases of Zika, Chik and Dengue, Brazil



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Travellers from French Polynesia to Brazil

Table 1. Number of travellers departing French Polynesian airports with final destinations in Brazilian cities between December 2013 and February 2014

Departure Month	Departure Year	Destination City	Total Number
December	2013	Sao Paulo	20
December	2013	Rio de Janeiro	14
December	2013	Recife	11
December	2013	Porto Alegre	5
December	2013	Florianopolis	4
December	2013	Curitiba	4
January	2014	Sao Paulo	18
January	2014	Sao Paulo	16
January	2014	Goiania	9
January	2014	Rio de Janeiro	9
January	2014	Curitiba	8
January	2014	Vitoria	7
January	2014	Fortaleza	2
January	2014	Rio de Janeiro	2
January	2014	Salvador	2
February	2014	Sao Paulo	20
February	2014	Porto Alegre	10
February	2014	Rio de Janeiro	9
February	2014	Curitiba	6
February	2014	Sao Paulo	4
February	2014	Uberlandia	2

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ZIKV Infected Travellers Arriving in Brazil

Table 2. Individual risk of ZIKV infection in French Polynesia and the expected number of ZIKV infections exported to Brazil via travellers on commercial flights between December 2013 and February 2014

Week	Individual Probability of Infection	Expected Number of Travellers Infected with ZIKV
02/December/2013	0.0979584	3
09/December/2013	0.114501	2
16/December/2013	0.121446	1
23/December/2013	0.11955	0
30/December/2013	0.112717	4
07/January/2014	0.100661	2
14/January/2014	0.0845351	1
21/January/2014	0.068227	0
28/January/2014	0.0532315	2
04/February/2014	0.0407119	1
11/February/2014	0.0312288	0
18/February/2014	0.0227581	0
25/February/2014	0.0166078	1
Total		18

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Theoretical R_0 in Brazilian Cities

Table 3. Estimated Basic Reproduction number $R_{0\text{-}ZIKV}$ for the selected Brazilian cities

	Expected number of ZIKV infected travelers							
	Rio de Janeiro	**São Paulo**	**Recife**	**Fortaleza**	**Salvador**	**Goiania**	**Vitoria**	**Total**
Dec/2013	2	2	1	0	0	0	0	**5**
Jan/201414	1	3	0	0	0	1	1	**6**
Feb/2014	0	1	0	0	0	0	0	**1**
Total	3	6	1	0	0	1	1	**12**
$R_{0\text{-}ZIKV}$	**1.4**	**2.15**	**1.31**	**1.45**	**1.6**	**1.46**	**1.4**	

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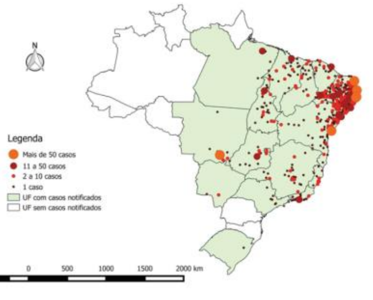
ZIKV Cases in Brazil, 2015



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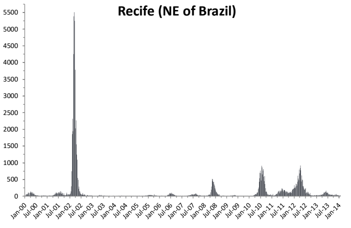
Dengue in Recife 2002



150,000 infections
AR = 13%
R_0 = 1.15

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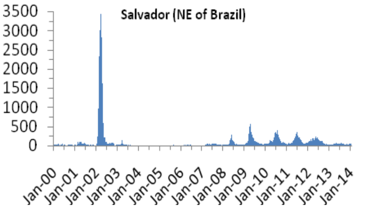
Dengue in Salvador 2002



117,000 infections
AR = 5%
R_0 = 1.05

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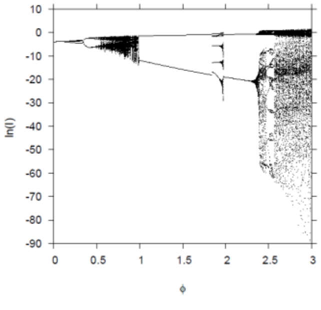
The Chaotic Dynamics of Dengue



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For vector-borne infections

$$R(t) = \frac{ma^2bce^{-\mu_M\tau}}{\mu_M(\mu_H+\gamma_H+\alpha_H)}\frac{S(t)}{N(t)}$$

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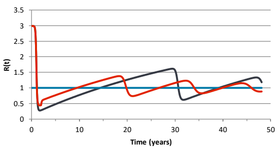
Effective Reproductive Number $R(t)$

$$R(t) = \frac{ma^2bce^{-\mu_M\tau}}{\mu_M(\mu_H+\gamma_H+\alpha_H)}\frac{S_H(t)}{N_H(t)}$$



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The Ross-Macdonald Model

Humans

$$\frac{dS_H}{dt} = -abI_M\frac{S_H}{N_H} + \mu_H(N_H - S_H)$$

$$\frac{dI_H}{dt} = abI_M\frac{S_H}{N_H} - (\mu_H + \gamma_H)I_H$$

$$\frac{dR_H}{dt} = \gamma_H I_H - \mu_H R_H$$

Mosquitoes

$$\frac{dS_M}{dt} = -acS_M\frac{I_H}{N_H} + \mu_M(L_M + I_M) + \frac{dN_M}{dt}$$

$$\frac{dL_M}{dt} = acS_M\frac{I_H}{N_H} - \gamma_M L_M - \mu_M L_M$$

$$\frac{dI_M}{dt} = \gamma_M L_M - \mu_M I_M$$

$$N_H = S_H + I_H + R_H$$
$$N_M = S_M + L_M + I_M$$

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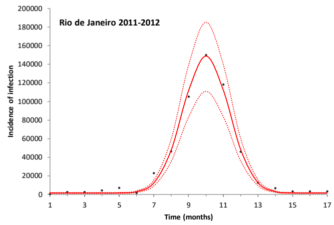
Fitting Dengue Incidence



Incidence

$$Incidence_{DENV}(t) = c_1 \exp\left[-\frac{(t-c_2)^2}{c_3}\right] + c_4$$

$$Incidence(t) = \lambda(t) S_H(t) = ab\frac{I_M(t)}{N_H} S_H(t)$$

Susceptible, Latent and Infected Mosquitoes

$$I_M(t) = \frac{Incidence_{DENV}(t) N_H(t)}{abS_H(t)}$$

$$L_M(t) = \frac{1}{\gamma_M}\left[\frac{d}{dt} I_M(t) + \mu_M I_M(t)\right]$$

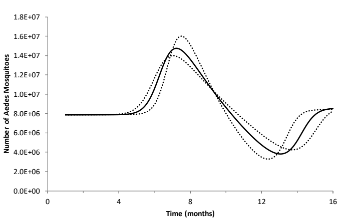
$$S_M(t) = \frac{N_H}{acI_H(t)}\left[\frac{d}{dt} L_M(t) + (\mu_M + \gamma_M) L_M(t)\right]$$

Total Number of Mosquitoes

$$N_M = S_M(t) + L_M(t) + I_M(t)$$

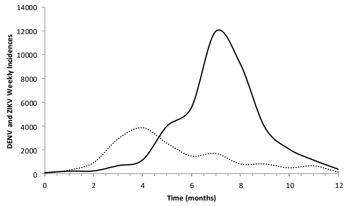
$$\frac{dN_M(t)}{dt} = \frac{dS_M(t)}{dt} + \frac{dL_M(t)}{dt} + \frac{dI_M(t)}{dt}$$

Mosquitoes' Seasonality



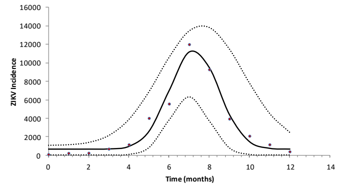
Predicting Zika resurgence in the foreseeable future

ZIKV (continuous line) and Dengue (dotted line) Salvador 2015



Fitting ZIKV Incidence Salvador 2015

$$Incidence_{ZIKV}(t) = c_1 \exp\left[-\frac{(t-c_2)^2}{c_3}\right] + c_4$$



Number of Aedes mosquitoes Salvador 2015

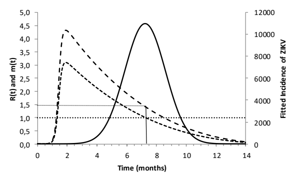
$$Incidence_{ZIKV}(t) = c_1 \exp\left[-\frac{(t-c_2)^2}{c_3}\right] + c_4$$

$$I_M(t) = \frac{Incidence_{ZIKV}(t) N_H(t)}{abS_H(t)}$$

$$L_M(t) = \frac{1}{\gamma_M}\left[\frac{d}{dt} I_M(t) + \mu_M I_M(t)\right]$$

$$S_M(t) = \frac{N_H}{acI_H(t)}\left[\frac{d}{dt} L_M(t) + (\mu_M + \gamma_M) L_M(t)\right]$$

Fitted ZIKV Incidence(continuous line), mosquitoes' density (gross dotted line) and effective reproduction number (fine dotted line), Salvador 2015



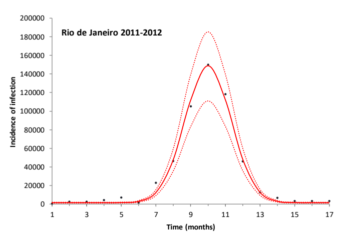
m_{crit} (t) ~ 1.5

Critical density of mosquitões, m_{crit}

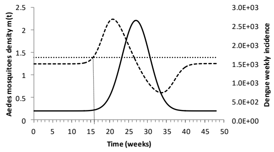
$$m_{crit} = \frac{N_H}{S_H(t_{crit})}\kappa,$$

$$\kappa = \frac{\mu_M(\mu_H + \gamma_H)(\mu_M + \gamma_M)}{a^2 bc\gamma_M}$$

Fitting Dengue Incidence Rio de Janeiro - 2011/12



Incidence and Density of Aedes mosquitoes



15.64 (14.16 - 16.52)

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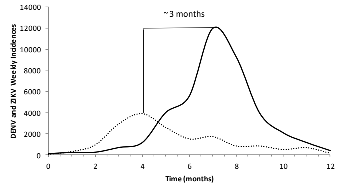
Timeline Gap Between ZIKV and Dengue Salvador 2015



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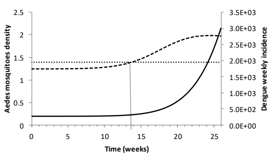
Incidence and Density of Aedes mosquitoes in the first 25 weeks



13.68 (11.52 - 15.84)

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Sexual Transmission

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Basic Reproduction Number of Sexual Transmission

$$R_0 = n\beta c T$$

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Number of Sexual Partners

$$n \equiv \frac{\langle i^2 \rangle}{\langle i \rangle}$$

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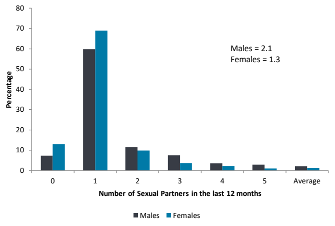
Brazilians sexual behaviour



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Brazilians sexual behaviour

	Males	Fem
0	7.2	12.9
1	59.8	69
2	11.6	9.8
3	7.5	3.7
4	3.5	2.2
5	2.9	0.9
m	2.1	1.3
σ^2	22	26

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Mean Number of sexual partners

$$n \equiv 2.1 + \frac{22}{2.1} = 10.4$$

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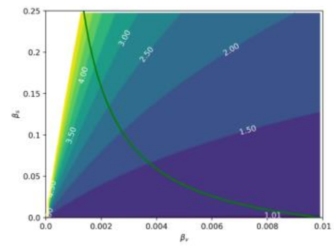
Attack rates ratios of females and males



Ratio ARW/ARM for a range of βs and βv values. The green line represents $R_0 = 1$, i.e. the epidemic threshold. Any point to the right of this curve, has R0 > 1. It is worth noticing that the reported excess cases reported for Zika in women are possible both during epidemics and off-season.

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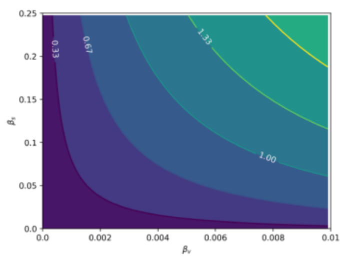
R_0 and relative transmission intensities – sexual vs vectorial



R_0 as a function of the relative intensities of sexual (βs) and vectorial (βv) transmissions. The R0 values are already adjusted for the heterogeneity in sexual contact rates.

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Outbreak Vaccine

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The Model

$$\frac{dN_H(t)}{dt} = r_H\left[1-\frac{N_H(t)}{K_H}\right]\left[S_H(t)+R_H(t)+gI_H(t)\right]-\mu_H N_H(t)$$

$$\frac{dS_H(t)}{dt} = -abI_M(t)\frac{S_H(t)}{N_H(t)} - \mu_H S_H(t) + r_H\left[1-\frac{N_H(t)}{K_H}\right]\left[S_H(t)+R_H(t)+gI_H(t)\right]- -\upsilon S_H(t)\theta(t-t_0)\theta(t_1-t)$$

$$\frac{dI_H(t)}{dt} = abI_M(t)\frac{S_H(t)}{N_H(t)} - (\mu_H+\gamma_H)I_H(t)$$

$$\frac{dR_H(t)}{dt} = \gamma_H I_H(t) - \mu_H R_H(t)$$

$$\frac{dV_H(t)}{dt} = \upsilon S_H(t)\theta(t-t_0)\theta(t_1-t) - \mu_H V_H(t)$$

$$\frac{dB_H(t)}{dt} = r_H\left[1-\frac{N_H(t)}{K_H}\right]\left[(1-g)I_H(t)\right] - p\sigma B_H(t) - (1-p)\gamma_H B_H(t)$$

$$\frac{dR_B(t)}{dt} = (1-p)\gamma_H B_H(t) - \mu_H R_B(t)$$

$$\frac{dM_H(t)}{dt} = p\sigma B_H(t) - (\mu_H+\alpha_H)M_H(t)$$

$$\frac{dS_M(t)}{dt} = -acS_M(t)\frac{\left[I_H(t)+I_H^T(t)\right]}{N_H(t)} + \mu_M\left[L_M(t)+I_M(t)\right] + \frac{dN_M}{dt}$$

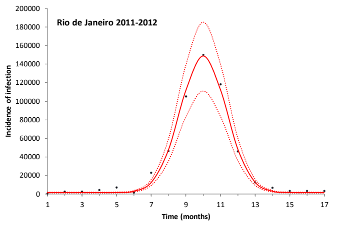
$$\frac{dL_M(t)}{dt} = acS_M(t)\frac{\left[I_H(t)+I_H^T(t)\right]}{N_H(t)} - (\mu_M+\gamma_M)L_M(t)$$

$$\frac{dI_M(t)}{dt} = \gamma_M L_M(t) - \mu_M I_M(t)$$

$$I_H^T(t) = I_H^T(0)\exp\left[-(\mu_H+\gamma_H+\alpha_H)(t-t_x)\right]\theta(t-t_x)$$

$$N_M(t) = S_M(t)+L_M(t)+I_M(t)$$

Fitting Dengue Incidence



Number of Aedes Mosquitoes

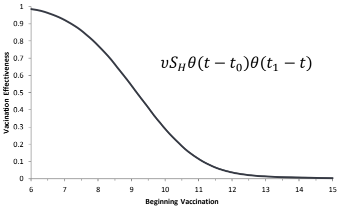
$$Incidence_{ZIKV}(t) = c_1\exp\left[-\frac{(t-c_2)^2}{c_3}\right]+c_4$$

$$I_M(t) = \frac{Incidence_{ZIKV}(t)N_H(t)}{abS_H(t)}$$

$$L_M(t) = \frac{1}{\gamma_M}\left[\frac{d}{dt}I_M(t)+\mu_M I_M(t)\right]$$

$$S_M(t) = \frac{N_H}{acI_H(t)}\left[\frac{d}{dt}L_M(t)+(\mu_M+\gamma_M)L_M(t)\right]$$

Optimum moment, t_0, to inroduce the vaccine

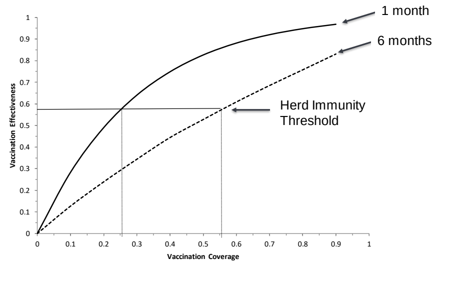


Definition of Vaccine Efficacy

$$Efficacy = 1 - \frac{Cases_{after}}{Cases_{before}}$$

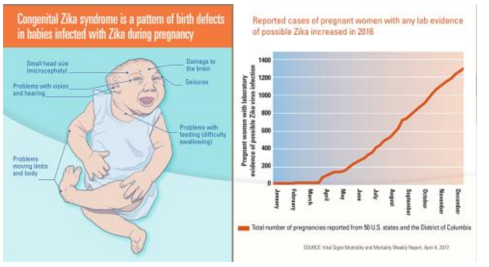
$$Cases = \int_0^\infty abI_M(t)\frac{S_H(t)}{N(t)}dt$$

Optimum Duration of the Campaign

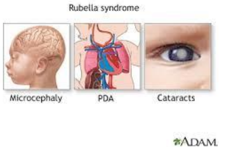


Routine Vaccine

Congenital Zika Syndrome



Congenital Rubella Syndrome



Lifetime Expected Risk of Infection

The sum over all ages of the product of the force of infection (per capita incidence rate, λ(a), timed the seroconvertion rate, C(a), times the disease's "undesirability", R(a), times the probability of infected chidren not seroconverting.

Lifetime Expected Risk of Infection

The sum over all ages of the product of the force of infection (per capita incidence rate, λ(a), timed the seroconvertion rate, C(a), times the disease's "undesirability", R(a), times the probability of infected chidren not seroconverting.

$$E = \int_0^\infty \lambda(a)C(a)R(a)\exp\left[-\int_0^a \lambda(a)C(a')da'\right]da$$

Lifetime Expected Risk of Infection

$$E = \int_0^\infty \lambda(a)C(a)R(a)\exp\left[-\int_0^a \lambda(a)C(a')da'\right]da$$

Lifetime Expected Risk of Infection

Force of Infection (Incidence)

$$E = \int_0^\infty \lambda(a) C(a) R(a) \exp\left[-\int_0^a \lambda(a) C(a') da' \right] da$$

Lifetime Expected Risk of Infection

Seroconversion Rate of the Vaccine ("Taking")

$$E = \int_0^\infty \lambda(a) C(a) R(a) \exp\left[-\int_0^a \lambda(a) C(a') da' \right] da$$

Lifetime Expected Risk of Infection

"Undesirability" of the infection (with age)

$$E = \int_0^\infty \lambda(a) C(a) R(a) \exp\left[-\int_0^a \lambda(a) C(a') da' \right] da$$

Lifetime Expected Risk of Infection

Probability of of infected chidren not seroconverting.

$$E = \int_0^\infty \lambda(a) C(a) R(a) \exp\left[-\int_0^a \lambda(a) C(a') da' \right] da$$

Seroprevalence of Infection

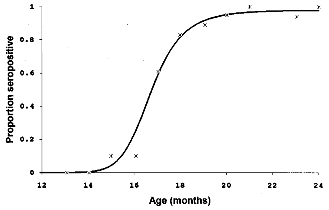


FIGURE 4 *Seroprofile obtained between 12 and 24 months of age (stars), fitted to a logistic function (line), showing the seroconversion attributed to the routine vaccination programme*

Calculating the Force of Infection

$$\lambda(a) = \frac{\left[-dS^+(a) \right] / da}{\left[1 - S^+(a) \right]}$$

Average Age of First Infection

$$\overline{A}_{1st} = \frac{\int_0^\infty a\lambda(a)S_H(a)da}{\int_0^\infty \lambda(a)S_H(a)da} \approx \frac{1}{\overline{\lambda}}$$

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"Typical" form of the Force of Infection

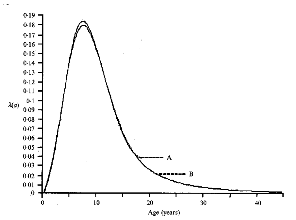

Fig. 5. Age-dependent force of infection, $\lambda(a)$, estimated by catalytic methods (curve A) through the equation, described in [11], [17]:

$$\lambda(a) = \frac{[-dS^+(a)]/da}{[1-S^+(a)]}$$

where $S^+(a)$ is the age-dependent proportion of seropositives, as compared with that estimated by applying equation (15) (curve B).

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Impact of Vaccination on λ(a)

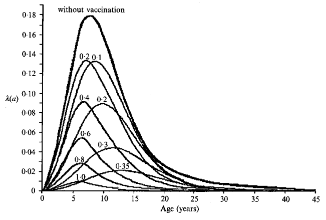

Fig. 6. Impact of two alternative vaccination strategies on the force of infection. The set of curves under that without vaccination represents the force of infection after the vaccination between 1 and 2 years of age (right curves labelled with coverage proportions 0·1–0·35), and between 7 and 8 years of age (left curves labelled with coverage proportions 0·2–1·0).

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Fertility curve as a proxy for R(a)

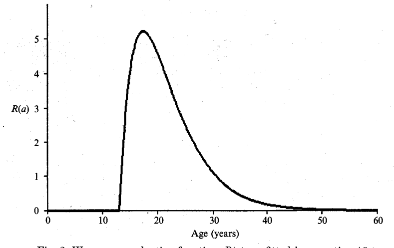

Fig. 2. Women reproductive function, $R(a)$, as fitted by equation 16 to demographic data from the State of São Paulo, Brazil.

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Optimum Age to Vaccinate

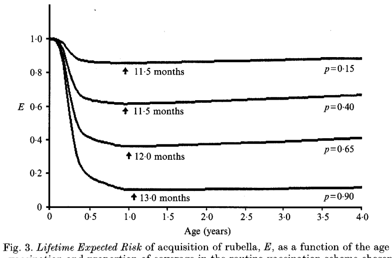

Fig. 3. *Lifetime Expected Risk* of acquisition of rubella, E, as a function of the age of vaccination and proportion of coverage in the routine vaccination scheme chosen.

ZikaPLAN

Relative Impact on Congenital Syndrome

The ratio of the number of congenital syndrome cases after vaccination over the the number of congenital syndrome Cases before vaccination.

$$\rho = \frac{\int_0^a r_p(a')\lambda_p(a')S_p(a')da'}{\int_0^a r_b(a')\lambda_b(a')S_b(a')da'} da$$

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Relative Impact on Congenital Syndrome

Incidence of CS in Infected Pregnant Women Before Vaccination

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Relative Impact on Congenital Syndrome

Incidence of CS in Infected Pregnant Women Before Vaccination

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Incidence of CS in Infected Pregnant Women After Vaccination

Relative Impact on Congenital Syndrome

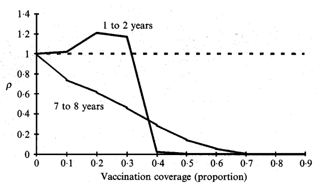

Fig. 8. Relative number of cases of CRS after vaccination as compared with before vaccination as a function of coverage proportions. Broken line denoting 1 indicates no effect of intervention, whilst continuous lines represent the impact of vaccination between 1 and 2 years of age, as compared with vaccination between 7 and 8 years of age. It can be noted that, for low coverages, the latter strategy is more effective. On the other hand, for high coverages, the former strategy has a greater impact on the CRS incidence.

Impact of Vaccination on CRS

TABLE 4 *Reported number of cases of congenital rubella syndrome*

	1992	1993	1994
Confirmed	16	1	0
Suspected	13	5	0
Discarded	18	8	1
Total	48	15	1

"Prediction is very difficult, especially about the future"

Niels Bohr