Modeling directly transmitted infections considering age-structured contact rate and vaccination

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Summary

- Introduction
- Model formulation with vaccination
- Analysis of the model
- Examples
- Numerical results
- Conclusion

Introduction

Directly transmitted infections

- Known as childhood infection
- Examples – measles, mumps, rubella, chickenpox, smallpox
- Vaccination resulted in eradication or control of these infections
- One of the main features of directly transmitted infections – the risk of infection depending on age
- The infection is influenced by the contact among individuals
- The contact between susceptible and infecctious individuals depends on the age
- In general, these infections result in lifelong immunity

Vaccination

- Availability of efficient and efficacy vaccine
- Vaccination of early aged children
- The goal is the eradication of infection
- Paradigm – vaccination increases the average age of the infection
- Rubella – avoiding Congenital Rubella Syndrome (CRS)
- Rubella – incidence of CRS can increase with vaccination
- Rubella – vaccine does not result in CRS (two doses of vaccine in order to avoid CRS are not necessary)

Model formulation with vaccination

Variables and parameters

Variables (age-specific, a, at time t):

- $X(a,t)$ – susceptibles
- $H(a,t)$ – exposed
- $Y(a,t)$ – infectious
- $Z(a,t)$ – recovered
- Notice – the number is the sum over all ages

Parameters (per-capita):

- μ – natural mortality rate
- σ – incubating rate
- γ – infectious or recovery rate
- $\nu\,(a)$ – vaccination rate
- $\beta\,(a,a')$ – contact rate
- $\lambda\,(a,t)$ – incidence rate (force of infection)

Dynamical system

- System of partial differential equations

$$\begin{cases} \frac{\partial}{\partial t}X(a,t) + \frac{\partial}{\partial a}X(a,t) &= -\left[\lambda(a,t) + \nu(a) + \mu\right] X(a,t) \\ \frac{\partial}{\partial t}H(a,t) + \frac{\partial}{\partial a}H(a,t) &= \lambda(a,t)\, X(a,t) - (\mu+\sigma)\, H(a,t) \\ \frac{\partial}{\partial t}Y(a,t) + \frac{\partial}{\partial a}Y(a,t) &= \sigma H(a,t) - (\mu+\gamma)\, Y(a,t) \\ \frac{\partial}{\partial t}Z(a,t) + \frac{\partial}{\partial a}Z(a,t) &= \nu(a)\, X(a,t) + \gamma Y(a,t) - \mu Z(a,t) \end{cases}$$

- The force of infection

$$\lambda(a,t) = \int_0^L \beta(a,a')\, Y(a',t)\, da'$$

- Recovered individuals are decoupled – $Z(a,t)$

Initial and boundary conditions

- Initial conditions ($t = 0$): $X(a,0) = X_0(a)$, $H(a,0) = H_0(a)$ and $Y(a,0) = Y_0(a)$ are steady state solution before introduction of vaccine, $\nu(a) = 0$

$$\begin{cases} \frac{d}{da}X_0(a) &= -\left[\lambda_0(a) + \mu\right] X_0(a) \\ \frac{d}{da}H_0(a) &= \lambda_0(a)X_0(a) - (\sigma + \mu)\, H_0(a) \\ \frac{d}{da}Y_0(a) &= \sigma H_0(a) - (\gamma + \mu)\, Y_0(a) \end{cases}$$

- Boundary conditions ($a = 0$): $X(0,t) = X_a$, $H(0,t) = 0$ and $Y(0,t) = 0$
  - ▷ X_a is new born rate
  - ▷ neither maternal antibodies nor placent infection
- Boundary conditions ($a \to \infty$): age distributions satisfy these boundary conditions – $X(\infty,t) = 0$, $H(\infty,t) = 0$ and $Y(\infty,t) = 0$

Analysis of the model

Steady state, $t \to \infty$

$$\begin{cases} X_\infty(a) &= X_b e^{-[\mu a+\Lambda(a)+N(a)]} \\ H_\infty(a) &= X_b e^{-(\mu+\sigma)a} \int_0^a e^{\sigma\zeta-N(\zeta)} \lambda_\infty(\zeta) e^{-\Lambda(\zeta)} d\zeta \\ Y_\infty(a) &= X_b e^{-(\mu+\gamma)a} \int_0^a \sigma e^{(\gamma-\sigma)s} ds \int_0^s e^{\sigma\zeta-N(\zeta)} \lambda_\infty(\zeta) e^{-\Lambda(\zeta)} d\zeta \end{cases}$$

resulting for the force of infection

$$\lambda_\infty(a) = \int_0^L B(a,\zeta) \times M\left(\zeta, \lambda_\infty\left(\zeta\right), \nu\left(\zeta\right)\right) \times \lambda_\infty(\zeta) d\zeta$$

where
$\Lambda(\zeta) = \int_0^\zeta \lambda_\infty(s) ds, N(\zeta) = \int_0^\zeta \nu(s) ds, M\left(\zeta, \lambda\left(\zeta\right), \nu\left(\zeta\right)\right) = e^{-\int_0^\zeta [\lambda(s)+\nu(s)] ds}$
and $B\left(a,\zeta\right) = \sigma X_b e^{-N(\zeta)} \int_\zeta^L e^{-\sigma(s-\zeta)} e^{\gamma s} \left[\int_s^L \beta\left(a,a'\right) e^{-(\mu+\gamma)a'} da'\right] ds$

Existence Theorem

Existence Theorem. The operator $T : C[0, L] \to C[0, L]$ described by the equation

$$Tu(a) = \int_0^L B(a, \zeta) M(\zeta, u(\zeta), \nu(\zeta)) u(\zeta) d\zeta$$

is such that if the spectral radius $r(T'(0)) \leq 1$, the only solution of equation

$$\lambda(a) = \int_0^L B(a, \zeta) M(\zeta, \lambda(\zeta), \nu(\zeta)) \lambda(\zeta) d\zeta$$

is the trivial solution; otherwise, if $r(T'(0)) > 1$, there is at least one non-trivial positive solution for this equation

Proof: C. H. Dezotti and H. M. Yang, *Proceedings of Biomat 2010*, 106 (2011)

Uniqueness Theorem. Let us consider the function

$D(a,s) = e^{\gamma s} G(a,s)$, with $G(a,s) = \int_s^L \beta(a,a')\, e^{-(\mu+\gamma)a'}\, da'$

decreasing in s for each a and the operator $T : C[0,L] \to C[0,L]$ defined in the previous theorem. If $r(T'(0)) > 1$, then the equation

$$\lambda(a) = \int_0^L B(a,\zeta)\, e^{-\Lambda(\zeta)} \lambda(\zeta)\, d\zeta,$$

where $\Lambda(\zeta) = \int_0^\zeta \lambda(s)\, ds$, has a unique non-zero solution which can be attained by successive approximations,

$$\lambda_n = T\lambda_{n-1}, n = 1, 2, \cdots,$$

and is independent of the initial approximation λ_0, $\lambda_0 \neq 0$

Proof: H. M. Yang and C. H. Dezotti, *Proceedings of Biomat 2013*, submitted

Lower and upper bounds for R_0

Lower and upper bounds for R_0. Let us consider the linear operator on Banach space $C[0,L]$ with cone $C[0,L]^+$ given by

$$T'(0)\,h(a) = \int_0^L B(a,\zeta)\,h(\zeta)\,d\zeta,$$

where $B(a,\zeta)$ was previously defined. Then

$$R_\nu^l = \inf_{a\in[0,L]} \int_0^L B(a,\zeta)\,d\zeta \leq r\left(T'(0)\right) \leq \sup_{a\in[0,L]} \int_0^L B(a,\zeta)\,d\zeta = R_\nu^u,$$

where $r(T'(0)) = R_0$

Proof: H. M. Yang and C. H. Dezotti, *Proceedings of Biomat 2013*, submitted

Stability of the trivial solution

Stability of the trivial solution. Let $x(a,t)$, $h(a,t)$ and $y(a,t)$ be small perturbations from the equilibrium $(X_\infty(a), H_\infty(a)$ and $Y_\infty(a)$

$$\begin{cases} X(a,t) &= X_\infty(a) + x(a,t) \\ H(a,t) &= H_\infty(a) + h(a,t) \\ Y(a,t) &= Y_\infty(a) + y(a,t) \end{cases}$$

giving rise a small perturbation on the force of infection

$$\lambda(a,t) = \lambda_\infty(a) + l(a,t)$$

Stability Theorem. If $r(T'(0)) \leq 1$, then the trivial equilibrium is locally stable. If $r(T'(0)) > 1$, then the trivial equilibrium is locally unstable

Proof: H. M. Yang and C. H. Dezotti, *Proceedings of Biomat 2013*, submitted

Examples

Example 1

Example 1. Vaccination $\nu(a)$ and contact $\beta(a, a')$ rates given by

$$\begin{cases} \nu(a) = \nu\theta(a - a_1)\,\theta(a_2 - a) \\ \beta(a, a') = \beta\delta(a - a') \end{cases}$$

where the Heaviside function is $\theta(x) = 1$, if $x \geq 0$, otherwise, 0; and the Dirac delta function is $\delta(x) = \infty$, if $x = 0$, otherwise, 0.
A non-linear homogeneous Volterra integral equation of second type arises $\lambda(a) = \int_0^a B(a, \zeta)\, e^{-\int_0^\zeta \lambda(s)ds} \lambda(\zeta)\, d\zeta$, where the kernel is

$$B(a, \zeta) = \begin{cases} \frac{\beta\sigma X_b}{\gamma - \sigma} e^{-\mu a} \left[e^{-\sigma(a-\zeta)} - e^{-\gamma(a-\zeta)} \right], & if \quad \zeta \leq a \\ 0, & if \quad a < \zeta \end{cases}$$

There is a unique solution $\lambda \equiv 0$, showing that the ages of contact must be relaxed to occur the transmission

Example 2

Example 2. Vaccination $\nu(a)$ and contact $\beta(a, a')$ rates given by

$$\begin{cases} \nu(a) = \nu\theta(a - a_1)\,\theta(a_2 - a) \\ \beta(a, a') = \beta e^{-c_1 a} e^{-c_2 a'} \end{cases}$$

resulting in $R_\nu^l = R_\nu^u = R_\nu$, with

$$R_\nu = R_0 \left\{ 1 - \frac{\nu e^{-(\mu + c_1 + c_2)a_1}}{\mu + \nu + c_1 + c_2} \left[1 - e^{-(\mu + \nu + c_1 + c_2)(a_2 - a_1)} \right] \right\},$$

where the basic reproduction number R_0 is

$$R_0 = \frac{\beta \sigma X_b}{(\mu + c_1 + c_2)(\mu + \gamma + c_2)(\mu + \sigma + c_2)}$$

Example 3

Example 3. Vaccination $\nu(a)$ and contact $\beta(a, a')$ rates given by

$$\begin{cases} \nu(a) = \nu\theta(a - a_1)\,\theta(a_2 - a) \\ \beta(a, a') = \beta \end{cases}$$

a special case of example 2, with $c_1 = c_2 = 0$, resulting in

$$R_\nu = R_0 \left\{ 1 - \frac{\nu}{\mu + \nu} e^{-\mu a_1} \left[1 - e^{-(\mu+\nu)(a_2 - a_1)} \right] \right\},$$

where the basic reproduction number R_0 is

$$R_0 = \frac{\beta\sigma X_b}{\mu(\mu + \gamma)(\mu + \sigma)}$$

See: H. M. Yang, *Appl. Math. Comput.* **122 (1)**, 27 (2001)

Example 4

Example 4. Vaccination $\nu(a)$ and contact $\beta(a, a')$ rates given by

$$\begin{cases} \nu(a) = \nu\theta(a - a_1)\,\theta(a_2 - a) \\ \beta(a, a') = \beta_0 \times \frac{b_3}{b_2\Gamma(b_1+1)} \times \frac{\left(\frac{a}{b_2}\right)^{b_1} e^{-\frac{a}{b_2}}}{2-e^{-b_3 a}} \times e^{-b_3|a-a'|} \end{cases}$$

where $\Gamma(x)$ is the gamma function, β_0 (dimension of $time$) is the period of exposure encompassing the infectivity of virus, b_1 is the average number of potentially infective contacts, b_2 (dimension of $time$) is the togetherness period, and b_3 is the infective contact rate (dimension of $time^{-1}$)

Note: $\beta(a, a')$ does not satisfy $\beta(a, a') > 0$ for all $a, a' \in [0, L]$, except for $a = a' = 0$ where $\beta(a, a') = 0$

Studied by numerical simulations

See: H. M. Yang, *Math. Compt. Model.* **29 (8)**, 39 (1999)
H. M. Yang, *Math. Compt. Model.* **29 (7)**, 11 (1999)

numerical results

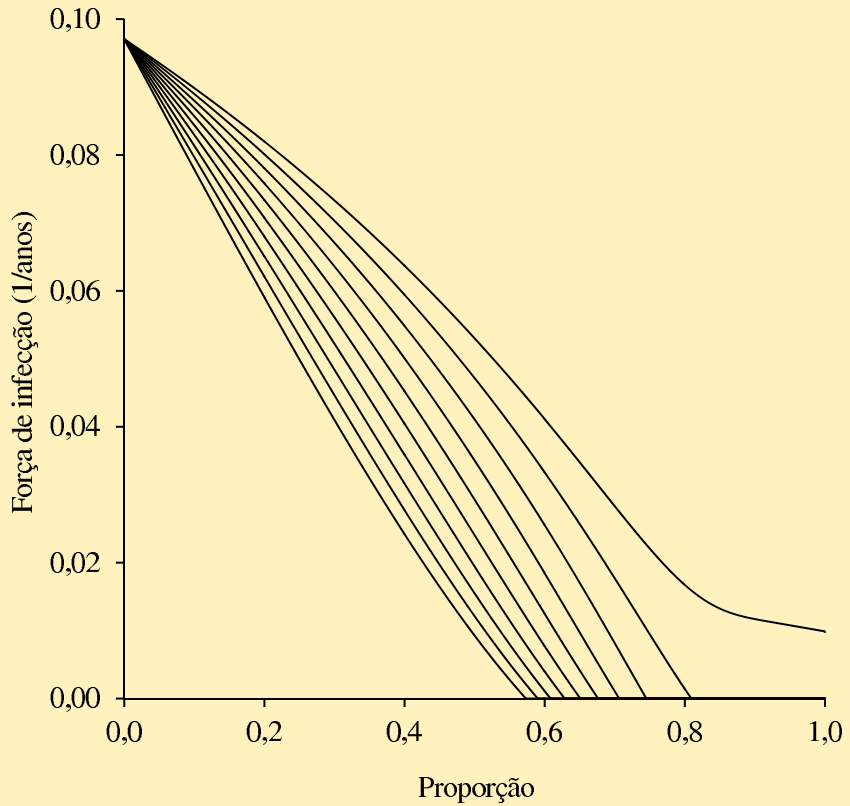
Constant contact rate – Example 3

- Seroprevalence from city in Brazil
- Estimation of the force of infection – $\lambda(a)$

- $\lambda(a)$ – estimation of $\beta(a, a')$
- Average age of infection – $a_0 = 7.41\ years$
- Age-dependent simulations

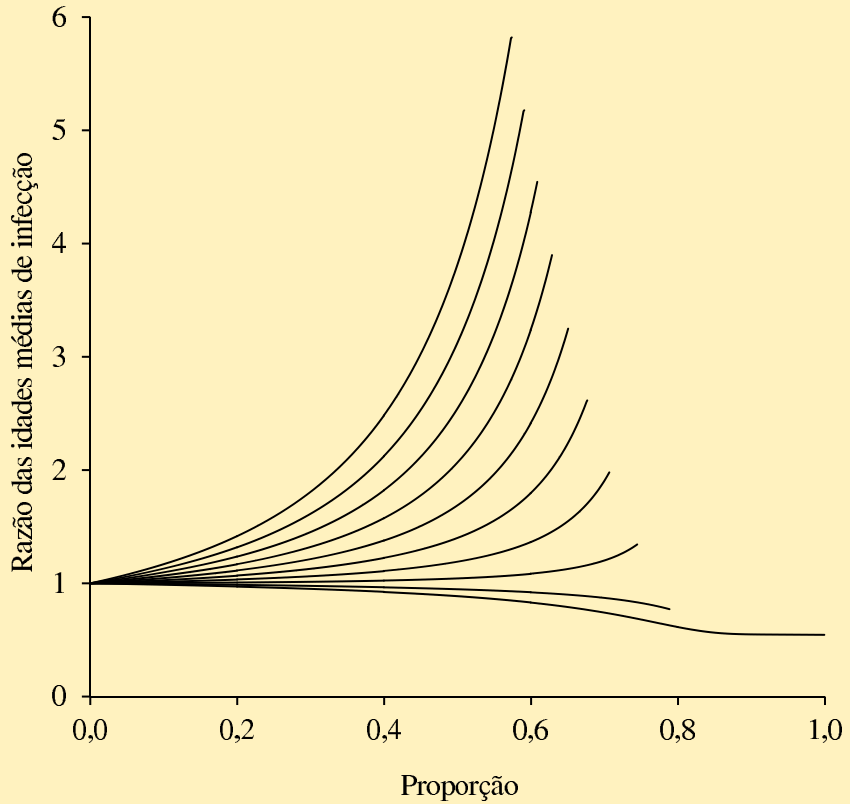
- $\lambda(a)$ – calculation of mean value λ_m
- λ_m – estimation of mean value β_m
- Average force of infection – $\lambda_0 = 0.097\ years^{-1}$
- Average age of infection – $a_0 = 8.77\ years^{-1}$
- Age-independent simulations

Constant contact rate – Example 3



The force of infection after vaccination varying proportion vaccinated. The vaccinated intervals (fixing 1 age interval) are (curves from bottom to top): $[1, 2]$, $[2, 3]$, $[3, 4]$, $[4, 5]$, $[5, 6]$, $[6, 7]$, $[7, 8]$, $[8, 9]$, $[9, 10]$, and $[10, 11]$
The last age interval does not eradicate infection

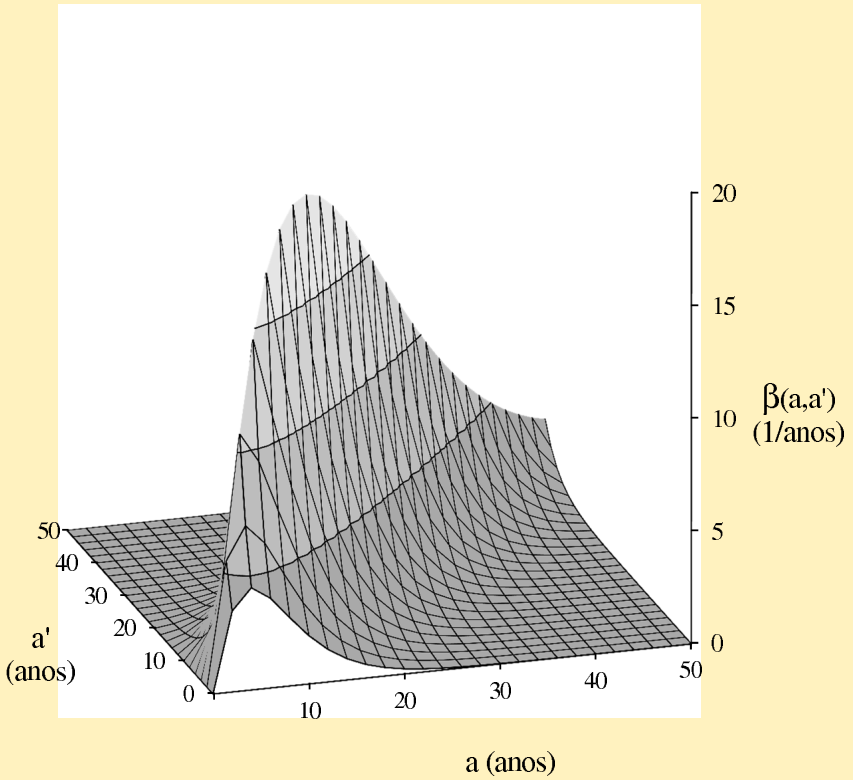
Constant contact rate – Example 3



The ratio between average age of infection after and before vaccination varying proportion vaccinated. The vaccinated intervals (fixing 1 age interval) are (curves from top to bottom): $[1, 2]$, $[2, 3]$, $[3, 4]$, $[4, 5]$, $[5, 6]$, $[6, 7]$, $[7, 8]$, $[8, 9]$, $[9, 10]$, and $[10, 11]$

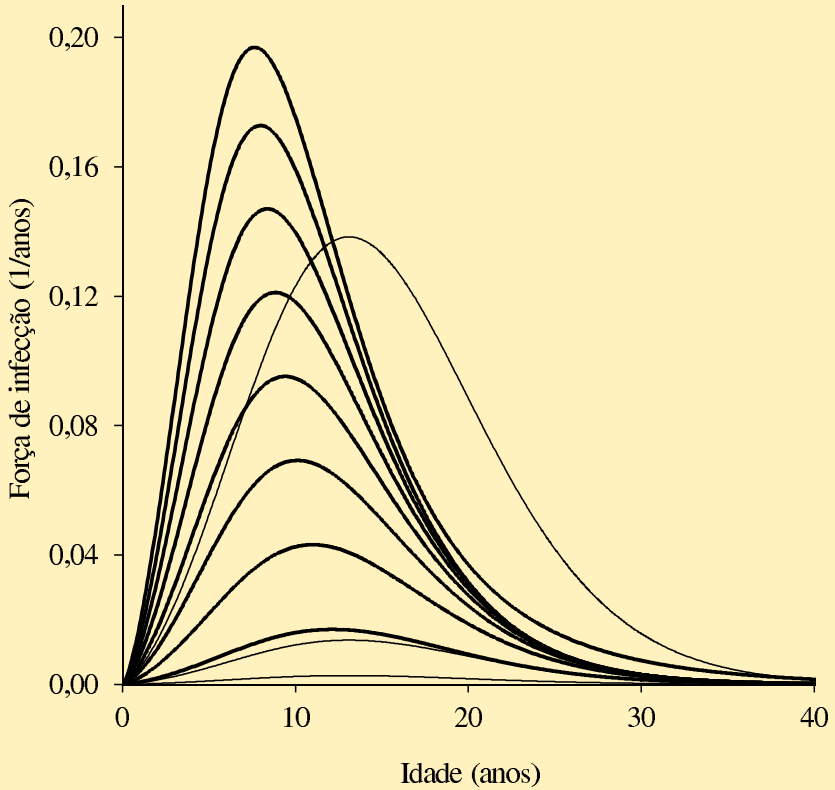
The average age of infection always increases with vaccination

Age-structured contact rate – Example 4



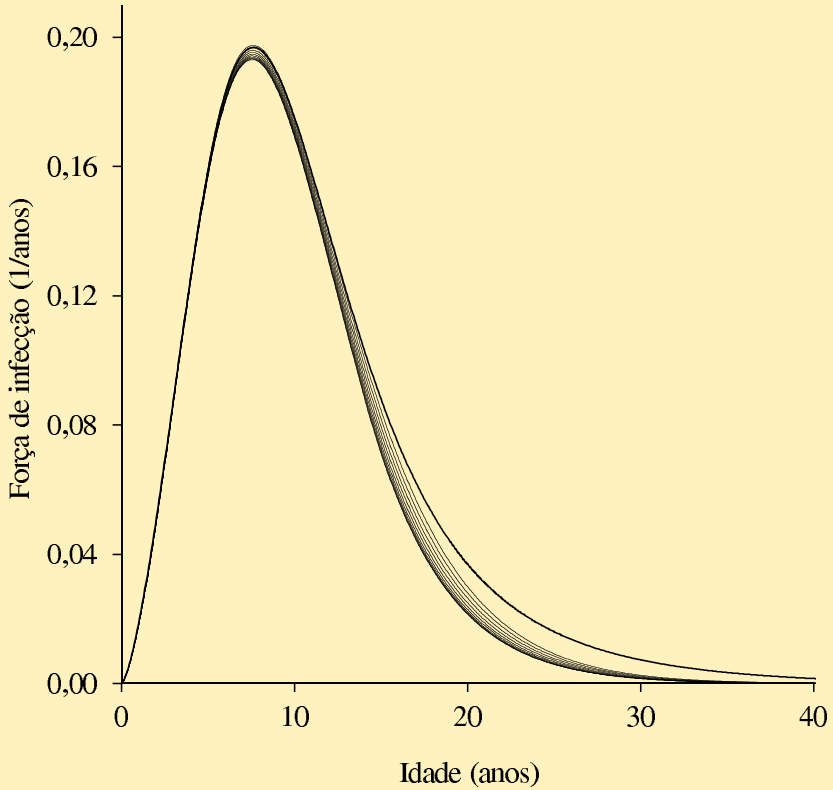
The estimated age-structured contact rate $\beta(a, a')$

Age-structured contact rate – Example 4



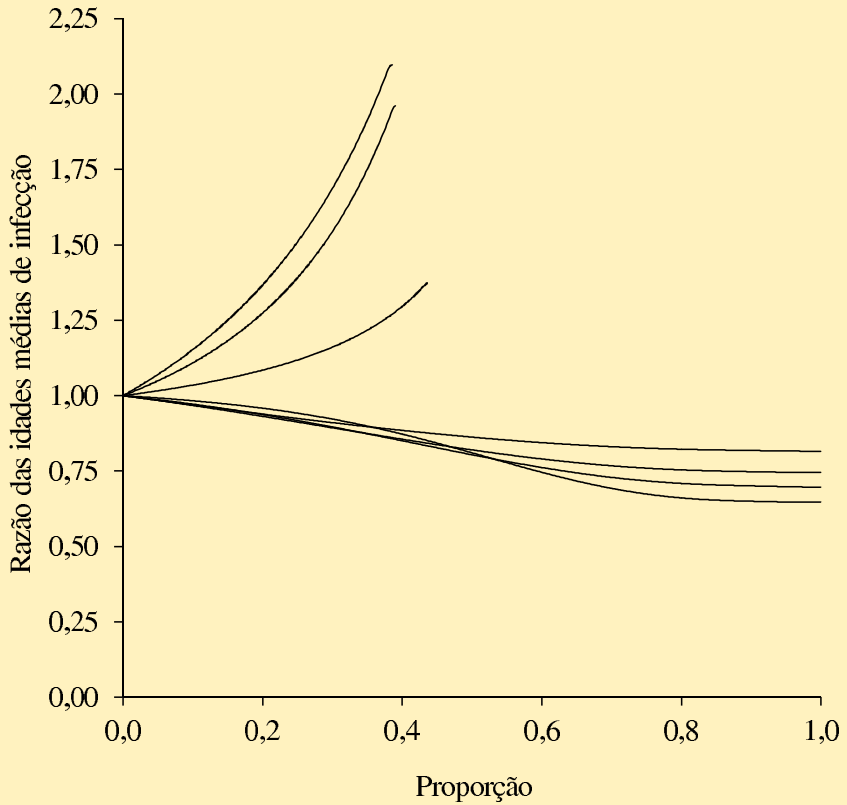
The age-structured force of infection $\lambda(a)$ when vaccinating 1 year age interval $[1, 2]$ for diffferent proportions of vaccination (%): 0, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 (curves from top to bottom)
Three thin curves must be multiplied by 5×10^{-8}

Age-structured contact rate – Example 4



The age-structured force of infection $\lambda(a)$ when vaccinating 1 year age interval $[14, 15]$ for diffferent proportions of vaccination $(\%)$:0, 110, 20, 30, 40, 50, 60, 70, 80, 90 and 100 (curves from top to bottom)

Age-structured contact rate – Example 4



The ratio between average age of infection after and before vaccination varying proportion vaccinated. The vaccinated intervals are (curves from top to bottom): $[1, 2]$, $[3, 4]$, $[5, 6]$, $[7, 8]$, $[8, 9]$, $[9, 10]$, and $[11, 12]$
The average age of infection increases for three first age intervals, while decreases for last four intervals

Conclusion

Conclusion

- Basic reproduction number and spectral radius – $R_0 = r\left(T'\left(0\right)\right)$
- $R_0 < 1$ – Trivial equilibrium (eradication of disease) is stable
- $R_0 > 1$ – Trivial equilibrium (eradication of disease) is unstable, and a unique non-trivial equilibrium (epidemics) arises
- Age-structured vaccination rate $\nu(a) = \nu\theta\left(a - a_1\right)\theta\left(a_2 - a\right)$ – paradigm is valid when earlier aged children are vaccinated. When higher aged children are vaccinated, the average age of infection decreases with vaccination
- Constant contact rate β – The lower bound of age interval vaccinated is around $10\ years$
- Age-structured contact rate $\beta(a, a')$ – The lower bound of age interval vaccinated is around $7\ years$

Thank You

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