Evolution of pathogens: a within-host approach

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Outline

1. Introduction
   - evolution of virulence

2. Evolution of infectious diseases
   - a “within-host” approach
   - changing model details
   - imperfect vaccines

3. Conclusions
   - implications for immuno-epidemiology

4. Appendix I
   - heterogeneity
   - details
   - vaccines

5. Appendix II
   - modelling mortality
$R_0$ equals the average number of secondary infections causes by an infected host introduced into a wholly susceptible population.
Once a pathogen has emerged \( (R_0 > 1) \), the important question is whether it is going to evolve to be benign or virulent.

The evolution of pathogens is generally considered in terms of the basic reproductive number \( R_0 \).

- Pathogens evolve to maximize \( R_0 \) (i.e., their total transmission).
- Pathogens evolve their virulence, defined as the reduction in host fitness due to infection with the pathogen.
- In models, virulence is measured by host mortality rate or case mortality.

Anderson and May (1982); Bremermann and Thieme (1989)
The basic reproductive number $R_0$

For directly transmitted diseases

$$R_0 = \frac{\beta N}{\alpha + d + \nu} \times \frac{1}{\alpha + d + \nu} = \frac{\beta(\alpha)N}{\alpha + d + \nu(\alpha)}$$

Anderson and May (1982)
Introduced virus strain: 1950

Fenner and Fantini (1999);

virulence was measured in laboratory (standard) rabbits.
Virus prevalence: 1952

Fenner and Fantini (1999);

virulence was measured in laboratory (standard) rabbits.
Virus prevalence: 1970

Case mortality > 0.99

Case mortality ≈ 0.23

Fenner and Fantini (1999);

Virulence was measured in laboratory (standard) rabbits.
Virus prevalence: 1984

Fenner and Fantini (1999);

virulence was measured in laboratory (standard) rabbits.
Trade-offs for the myxoma virus infection of rabbits

\[ \alpha^* = 0.0400183 \]

Fenner et al. 1956; Mead-Briggs et al. 1975; Anderson and May 1982
Within-host dynamics of pathogens

- Parasite
- Immune response

Transmission: $u_P$

- $r_P$
- $hXP$
- $sP_X/k+P$

$a$ “within-host” approach
Dynamics of the pathogen and the immune response

\[ \dot{P} = rP - hPX, \]
\[ P = 0, \text{ if } P(t) \geq D, \]
\[ \dot{X} = \frac{sXP}{k + P}, \]
\[ l(r) = \int_0^\Delta P(t) \, dt. \]

- Pathogen kills the host if it reaches a lethal density \( D \);
- There is no transmission from a dead host;
- Pathogens evolve to maximize their total transmission.

\( P \) – pathogen, \( X \) – immune response, \( l \) – total transmission, \( \Delta \) – duration of infection.

Parameters: \( P(0) = 1, X(0) = 1, h = 10^{-3}, k = 10^3, s = 1, D = 10^9, r = 2.08. \)

Antia et al. 1994
Dynamics of the pathogen and the immune response

\[
\begin{align*}
\dot{P} &= rP - hPX, \\
P &= 0, \text{ if } P(t) \geq D, \\
\dot{X} &= \frac{sXP}{k + P}, \\
l(r) &= u \int_0^\Delta P(t) \, dt.
\end{align*}
\]

- $P$ – pathogen, $X$ – immune response, $l$ – total transmission, $\Delta$ – duration of infection.

Parameters: $P(0) = 1, X(0) = 1, h = 10^{-3}, k = 10^3, s = 1, D = 10^9, r = 2.08$. 

Antia et al. 1994
a “within-host” approach

Total transmission of pathogens

where total transmission

\[ l(r) = \int_0^\Delta P(t) \, dt. \]
Stochastic heterogeneity in $r$

average growth rate

$\bar{r}$
Stochastic heterogeneity in $r$

average growth rate

$\bar{r}$

host 1

$\bar{r} + \Delta r_1$
Stochastic heterogeneity in $\bar{r}$

average growth rate

$\bar{r}$

host 1

$\bar{r} + \Delta r_1$

host 2

$\bar{r} - \Delta r_2$
Stochastic heterogeneity in $\bar{r}$

average growth rate

$\bar{r}$

host 1

$\bar{r} + \Delta r_1$

host 2

$\bar{r} - \Delta r_2$

... 

host $i$

$\bar{r} \pm \Delta r_i$
Stochastic heterogeneity in $\bar{r}$

\[ f(r, \bar{r}) = \frac{\bar{r}/\sigma^2}{\Gamma(\bar{r}^2/\sigma^2)} \left( \frac{\bar{r}r}{\sigma^2} \right)^{\frac{\bar{r}^2}{\sigma^2} - 1} \times \exp \left[ -\frac{\bar{r}r}{\sigma^2} \right], \]

\[ L(\bar{r}) = \int_{0}^{\infty} l(r) f(r, \bar{r}) dr. \]
Optimal growth rate and total transmission

\[ L(r) = \int_0^\infty l(r, x) f(x) \, dx. \]

where \( f(x) \) is given by a gamma distribution of \( r \) with standard deviation \( \sigma \).
a "within-host" approach

Changes in virulence

\[ M(\bar{r}) = \int_{r^*}^{\infty} f(r, \bar{r}) dr \]
a “within-host” approach

Changes in virulence

\[ M(\overline{r}) = \int_{r^*}^{\infty} f(r, \overline{r}) dr \]

\[ LD_{50}(\overline{r}) = P_0 : \int_{r^*[P_0]}^{\infty} f(r, \overline{r}) dr = 0.5 \]
Estimating epidemiological parameters and trade-offs

\[
\hat{\beta}(r) = \frac{l(r)}{\Delta(r)}
\]

\[
\beta(\bar{r}) = \int_{0}^{\infty} \hat{\beta}(r) f(r, \bar{r}) \, dr
\]
Estimating epidemiological parameters and trade-offs

\[ \hat{\beta}(r) = \frac{l(r)}{\Delta(r)} \]

\[ \beta(\bar{r}) = \int_{0}^{\infty} \hat{\beta}(r) f(r, \bar{r}) \, dr \]

\[ \alpha(\bar{r}) = \int_{0}^{\infty} \frac{m(r)}{\Delta(r)} f(r, \bar{r}) \, dr \]

\[ \nu(\bar{r}) = \int_{0}^{\infty} \frac{1 - m(r)}{\Delta(r)} f(r, \bar{r}) \, dr \]

where \( m(r) \) is the probability of host’s death following infection.
Trade-offs emerging from the within-host dynamics

To myxoma trade-offs

Ganusov et al 2002
Within-host and between host dynamics of pathogens are inherently linked.

Trade-offs for the myxoma virus infection can be originated from simple properties of the within-host dynamics.

- **but**: other explanations may work too.

Prediction on the evolution of pathogen virulence may depend on the definition of virulence used.

Ganusov et al. 2002; Gilchrist and Sasaki 2002; André et al. 2003; André and Gandon (2006); Ganusov and Antia 2003, 2006
Can virulence be predicted from a single factor?

Table 1  Mortality associated with parasites transmitted with and without vectors

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Without vectors</th>
<th>With vectors</th>
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</thead>
<tbody>
<tr>
<td>&gt;1%</td>
<td>Kuru</td>
<td>Yellow fever virus</td>
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<tr>
<td></td>
<td>Yersinia</td>
<td>B. bacillusformis</td>
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<td></td>
<td>Corynebacterium diphtheriae</td>
<td>R. prowazekii</td>
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<tr>
<td></td>
<td>Mycobacterium tuberculosis (35)</td>
<td>B. recurrentis</td>
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<td></td>
<td>Treponema pallidum</td>
<td>Leishmania donovani</td>
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<td></td>
<td></td>
<td>Plasmodium falciparum</td>
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<td></td>
<td></td>
<td>P. malariae (57)</td>
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<td></td>
<td></td>
<td>P. vivax (47)</td>
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<tr>
<td></td>
<td></td>
<td>Treponosoma crusi</td>
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<tr>
<td></td>
<td></td>
<td>T. brucel</td>
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<tr>
<td>&lt;1%</td>
<td>Adenovirus</td>
<td>Chikungunya</td>
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<tr>
<td></td>
<td>Coronavirus</td>
<td>Dengue (41)</td>
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<tr>
<td></td>
<td>Cytomegalovirus</td>
<td>O'nyong-nyong</td>
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<td></td>
<td>Epstein-Barr</td>
<td>Oropouche</td>
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<td></td>
<td>Herpes simplex</td>
<td>Phlebovirus fever virus</td>
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<td></td>
<td>Influenza</td>
<td>Reoherpes virus</td>
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<td></td>
<td>Mumps</td>
<td>Plasmodium ovale</td>
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<tr>
<td></td>
<td>Papillomavirus</td>
<td>Leishmania tropica</td>
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<tr>
<td></td>
<td>Parainfluenza</td>
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<td>Respiratory syncytial virus</td>
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<td></td>
<td>Rhinovirus</td>
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<td></td>
<td>Rubella</td>
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<td></td>
<td>Rubella (23)</td>
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<td></td>
<td>Varicella-zoster</td>
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<tr>
<td></td>
<td>Bordetella parapertussis</td>
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<tr>
<td></td>
<td>B. pertussis (18)</td>
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<tr>
<td></td>
<td>Brunhamella catarrhalis</td>
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<td></td>
<td>Cataynomycobacterium granuloma</td>
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<td>Chlamydia trachomatis</td>
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<td>Gardnerella vaginalis</td>
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<td>Hemophilus ducreyi</td>
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<td>H. influenzae (90)</td>
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<tr>
<td></td>
<td>Hemophilus spp. (104)</td>
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<td></td>
<td>Moraxella spp. (88)</td>
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<td></td>
<td>Mycobacterium leprae (1)</td>
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<td></td>
<td>Mycoplasma hominis</td>
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<td></td>
<td>M. pneumoniae (64)</td>
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<tr>
<td></td>
<td>Neisseria gonorrhoea</td>
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<tr>
<td></td>
<td>N. meningitides (8)</td>
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<tr>
<td></td>
<td>Neisseria spp. (88)</td>
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<tr>
<td></td>
<td>Staphylococcus aureus</td>
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<td></td>
<td>S. epidermidis</td>
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<tr>
<td></td>
<td>S. saprophyticus</td>
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</tr>
</tbody>
</table>

Ewald 1983
Changing pathogen transmissibility

\[ \xi(P) \]

linear
saturated
exponential

Ganusov and Antia 2003
Changing pathogen transmissibility

- Linear
- Saturated
- Exponential

Ganusov and Antia 2003
Changing mechanism of pathogenesis

\[ P(0) = 1, \ R(0) = R_0 = 10^4, \ X(0) = 1, \ h = 10^{-3}, \ k = 10^3, \ s = 1, \ R_d = 3.25 \times 10^3, \ c = 10^3, \]
\[ y = 10^5, \ d = 0.05. \] Heterogeneity is modelled by a normal distribution of \( r \).
Changing mechanism of pathogenesis

\[ P(0) = 1, R(0) = R_0 = 10^4, X(0) = 1, h = 10^{-3}, k = 10^3, s = 1, R_d = 3.25 \times 10^3, c = 10^3, \]
\[ y = 10^5, d = 0.05. \] Heterogeneity is modelled by a normal distribution of \( r \).
Details do matter!

- Changing the structure of the model may dramatically affect the optimal level of virulence.
- It seems unlikely that a single factor can determine virulence of diverse pathogens.
Vaccines and pathogen evolution

- Escape from vaccines
Vaccines and pathogen evolution

- Escape from vaccines
- Evolution of pathogen virulence in response to vaccination

Imperfect vaccines and the evolution of pathogen virulence

Sylvain Gandon*,†, Margaret J. Mackinnon*,†, Sean Nee* & Andrew F. Read*

NATURE | VOL 414 | 13 DECEMBER 2001 | www.nature.com
Imperfect vaccines and evolution of pathogens

- Epidemiological approach and $R_0$

\[ R_0[\alpha^*, \alpha] = \frac{\beta^*(\hat{x} + \sigma\hat{y})}{d + \alpha^* + \nu^* + \sigma\beta\hat{y}} \]

where $^*$ and $\hat{\cdot}$ denote mutant and resident, and $\sigma$ is superinfection parameter.
Imperfect vaccines and evolution of pathogens

- **Epidemiological approach and** $R_0$

\[ R_0[\alpha^*, \alpha] = \frac{\beta^*(\hat{x} + \sigma \hat{y})}{d + \alpha^* + \nu^* + \sigma \beta \hat{y}} \]

where $\ast$ and $\hat{\cdot}$ denote mutant and resident, and $\sigma$ is superinfection parameter.

- **Both virulence** $\alpha$ **and transmissibility** $\beta$ **are reduced in vaccinated hosts.**

\[
\alpha_V = (1 - r_2)(1 - r_4)\alpha_U, \\
\beta_V = (1 - r_3)\beta_U[(1 - r_2)\alpha_U],
\]

where $r_2$, $r_3$, and $r_4$ are the efficacies of vaccines blocking replication, transmission and virulence, respectively.
Imperfect vaccines and evolution of pathogens

- **Epidemiological approach and** $R_0$

  $$R_0[\alpha^*, \alpha] = \frac{\beta^*(\hat{x} + \sigma\hat{y})}{d + \alpha^* + \nu^* + \sigma\beta\hat{y}}$$

  where $*$ and $\hat{\cdot}$ denote mutant and resident, and $\sigma$ is superinfection parameter.

- **Both virulence $\alpha$ and transmissibility $\beta$ are reduced in vaccinated hosts.**

  $$\alpha_V = (1 - r_2)(1 - r_4)\alpha_U,$$
  $$\beta_V = (1 - r_3)\beta_U[(1 - r_2)\alpha_U],$$

  where $r_2$, $r_3$, and $r_4$ are the efficacies of vaccines blocking replication, transmission and virulence, respectively.

- **Vaccination does not affect trade-offs** $\beta = \beta(\alpha)$ and $\nu = \nu(\alpha)$. 

Gandon et al. 2001
Imperfect vaccines: Gandon et al. conclusions

- Anti-growth and anti-virulence vaccines are expected to select for pathogens with high virulence.
- Anti-transmission vaccines are expected to select for pathogens with low virulence.

Gandon et al. 2001
Within-host approach
imperfect vaccines

Model

- response $X_1$ reduces the rate of expansion of the pathogen population within the host;
- response $X_2$ reduces the rate of pathogen transmission from infected hosts.

\[
\begin{align*}
\dot{P} &= (r - h_1X_1)P, \\
\dot{X}_i &= \frac{sX_iP}{k + P}, \quad i = 1, 2, \\
l(r) &= \int_0^\Delta \frac{P(t)dt}{1 + h_2X_2(t)}.
\end{align*}
\]

Vaccination results in an increase in the number of pathogen-specific immune cells (precursor numbers) existing prior to infection.

Ganusov and Antia 2006
imperfect vaccines

Within-host dynamics: anti-growth vaccines

\[ P(0) = 1, \ h_1 = 10^{-3}, \ h_2 = 10^{-4}, \ k = 10^3, \ s = 1, \ D = 10^9, \ r = 2.08, \] pathogen density is multiplied by \( 10^{-9} \), the immune response densities are multiplied by \( 4 \times 10^{-6} \).
imperfect vaccines

Transmission and virulence: anti-growth vaccines
imperfect vaccines

Within-host dynamics: anti-transmission vaccines

![Graph showing within-host dynamics](image)
imperfect vaccines

Transmission/virulence: anti-transmission vaccines

---

Graph showing the percentage of maximal transmission (% maximal transmission) against the growth rate (r) for different values of heterogeneity (σ) and vaccination status (unvacc, vaccinated). The graphs illustrate the impact of heterogeneity and vaccination on the transmission rate of a disease.
For anti-growth vaccines, the precursor number increases from $X_{10} = 1$ to $X_{10} = 2$ (bold red lines) or to $X_{10} = 10$ (plain red lines). For anti-transmission vaccines, the precursor number increases from $X_{20} = 0$ to $X_{20} = 10$ (bold blue lines).
**Do results depend on the model?**

In these models, the difference arises due to different description of pathogenesis and as the result, due to high ES virulence in unvaccinated hosts in the right panel (at $p = 0$).

Ganusov and Antia 2006; André and Gandon 2006
Implications for epidemiology

- Epidemiological models can include the within-host dynamics:

\[
\frac{dS(t)}{dt} = \lambda - dS(t) - h(t)S(t),
\]

\[
\frac{\partial I(t, \tau)}{\partial t} + \frac{\partial I(t, \tau)}{\partial \tau} = -(d + \alpha(\tau) + \nu(\tau))I(t, \tau),
\]

\[
\frac{dR(t)}{dt} = \int_0^t I(t, \tau)\nu(\tau)\,d\tau - dR(t),
\]

\[
I(t, 0) = h(t)S(t) = S(t)\int_0^t I(t, \tau)\beta(\tau)\,d\tau.
\]

- Future studies may investigate the role of mutation, co- and super-infection in determining evolution of pathogens using within-host models.

André and Gandon 2006
Predictions on the evolution of pathogens may depend on the model used as well on the model parameters, and therefore, building of proper models requires better understanding of the biology of pathogen-host interactions.

Other factors may further complicate the picture: within-host evolution of pathogens, co- and super-infection, locality of transmission, host evolution, etc.
Acknowledgements

- Rustom Antia and Carl Bergstrom
- Theoretical Biology group at Utrecht University
- Marie Curie Incoming International Fellowship (Framework Programme 6)
Testing model predictions?

- Higher levels of (host) heterogeneity select for more virulent pathogens.
  - High mutation rate of Neisseria meningitidis helps escaping immune response.
  - Malaria (P. falciparum) infecting resistant adults and nonimmune infants.
- Transmission-blocking vaccines may select for more rapidly growing pathogens
  - ?
- Testing both predictions in serial passage experiments?
Coevolution of the myxoma virus and rabbits
Coevolution of the myxoma virus and rabbits
Heterogeneity

heterogeneity in other parameters

heterogeneity = \sigma / \text{mean}.
Changing pathogen transmissibility

Heterogeneity \((CV = \sigma / D)\) is modelled by a gamma distribution of the lethal density \(D\).
Dynamics of the pathogen, resource and the immune response

\[ \dot{P} = \frac{rPR}{c + R} - hPX, \]
\[ \dot{R} = d(R_0 - R) - y^{-1} \frac{rPR}{c + R}, \]
\[ \dot{X} = \frac{sXP}{k + P}, \]

\( P \) – pathogen, \( R \) – resource, \( X \) – immune response.

Parameters: \( P(0) = 1, R(0) = R_0 = 10^4, X(0) = 1, h = 10^{-3}, k = 10^3, s = 1, R_d = 2.7 \times 10^3, \)
\( c = 10^3, y = 10^5, d = 0, r = 2.08. \)
Heterogeneity \((CV = \sigma / R_d)\) is modelled by a gamma distribution in the minimal resource density \(R_d\).

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P(0) = 1, \ R(0) = R_0 = 10^4, \ X(0) = 1, \ h = 10^{-3}, \ k = 10^3, \ s = 1, \ R_d = 2.7 \times 10^3, \ c = 10^3, \ y = 10^5, \ d = 0.
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Changing mechanism of pathogenesis

Heterogeneity \((CV = \sigma / R_d)\) is modelled by a gamma distribution in the minimal resource density \(R_d\).

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\]
Changes in trade-offs with vaccination

ANTI-GROWTH

ANTI-TRANSMISSION
Changes in $R_0$ with vaccination

- Trade-offs do change with vaccination although changes may be small at low efficacy of vaccines (small increase in $X_{10}$ and $X_{20}$).
- Anti-transmission vaccines may select for more virulent pathogens.
Virulence in unvaccinated and vaccinated hosts

The relationship between virulence of a pathogen with a fixed growth rate $r$ in vaccinated $\alpha_V$ and unvaccinated $\alpha_U$ hosts is nonlinear.

Note that in the study by Gandon et al. 2001, $\alpha_V = (1 - r_2)(1 - r_4)\alpha_U$. 
Total transmission vs. $r$

$p = 0.1$

$p = 0.5$

$\left(1-p\right)L_u$

$pL_v$
Total transmission and virulence vs vaccine efficacy

![Graph showing the relationship between transmission, virulence, and vaccine efficacy.](image)
Two stages

\[ X_1 \]
Immune response

\[ X_2 \]
Immune response

\[ P_1 \]
Pathogen

\[ P_2 \]
Pathogen

replication

transmission

vaccines
Pathogenesis and transmission

- The probability of host survival $S(t)$ until time $t$ is the solution of

$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

where $\pi(r, P)$ is the rate of host’s death due to pathogen.
Pathogenesis and transmission

The probability of host survival $S(t)$ until time $t$ is the solution of

$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

where $\pi(r, P)$ is the rate of host’s death due to pathogen.

$$\pi[r, P] = \lim_{n \to \infty} (P/D)^n$$
Pathogenesis and transmission

- The probability of host survival $S(t)$ until time $t$ is the solution of

$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

where $\pi(r, P)$ is the rate of host’s death due to pathogen.

- The total transmission of the pathogen during the infection is

$$l = \int_0^\Delta \zeta[P(t)]S(t)\,dt$$

where $\zeta(P)$ is the rate of pathogen transmission.
Pathogenesis and transmission

- The probability of host survival $S(t)$ until time $t$ is the solution of
  \[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]
  where $\pi(r, P)$ is the rate of host’s death due to pathogen.

- The total transmission of the pathogen during the infection is
  \[ l = \int_0^\Delta \zeta[P(t)]S(t) \, dt \]
  where $\zeta(P)$ is the rate of pathogen transmission.
Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_0^\Delta \zeta[r, P(t)]S(t) \, dt \]
Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_0^\Delta \zeta[P(t)]S(t) \, dt \]

- Consider a particular case when \( \pi \sim P^n \) and \( \zeta \sim P \):
Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_0^\Delta \zeta[P(t)]S(t) \, dt \]

- Consider a particular case when \( \pi \sim P^n \) and \( \zeta \sim P \):

\[ \pi(r, P) = \left[ \frac{P}{D} \right]^n \]
Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_0^\Delta \zeta[P(t)]S(t) \, dt \]

- Consider a particular case when \( \pi \sim P^n \) and \( \zeta \sim P \):

\[ \pi(r, P) = \left[ \frac{P}{D} \right]^2 \]
Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_{0}^{\Delta} \zeta[P(t)]S(t) \, dt \]

- Consider a particular case when \( \pi \sim P^n \) and \( \zeta \sim P \):

\[ \pi(r, P) = \left[ \frac{P}{D} \right]^5 \]
Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_0^\Delta \zeta[P(t)]S(t)\,dt \]

- Consider a particular case when \( \pi \sim P^n \) and \( \zeta \sim P \):

\[ \pi(r, P) = \left( \frac{P}{D} \right)^{10} \]
Back to a more general “stochastic” approach: II

- Basic formulas

\[
\dot{S}(t) = -\pi[r, P(t)]S(t)
\]

\[
l(r) = \int_{0}^{\Delta} P(t)S(t) \, dt
\]

\[
M(r) = 1 - S(\Delta)
\]

- Traditionally, stochastic host survival is modelled differently, \( \pi = \lambda r^m P \).

Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.
Back to a more general “stochastic” approach: II

- **Basic formulas**

  \[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

  \[ l(r) = \int_0^\Delta P(t)S(t) \, dt \]

  \[ M(r) = 1 - S(\Delta) \]

- **Traditionally, stochastic host survival is modelled differently,** \( \pi = \lambda r^m P \).

  \[ \pi(r, P) = \lambda r^{-1} P \]

Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.
Back to a more general “stochastic” approach: II

- **Basic formulas**

\[
\dot{S}(t) = -\pi [r, P(t)] S(t)
\]

\[
l(r) = \int_0^\Delta P(t) S(t) \, dt
\]

\[
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Back to a more general “stochastic” approach: II

- **Basic formulas**

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_{0}^{\Delta} P(t)S(t) \, dt \]

\[ M(r) = 1 - S(\Delta) \]

- **Traditionally, stochastic host survival is modelled differently**, \( \pi = \lambda r^m P \).

\[ \pi(r, P) = \lambda r^2 P \]
Back to a more general “stochastic” approach: II

- Basic formulas

\[ \dot{S}(t) = -\pi[r, P(t)]S(t) \]

\[ l(r) = \int_0^\Delta P(t)S(t) \, dt \]

\[ M(r) = 1 - S(\Delta) \]

- Traditionally, stochastic host survival is modelled differently, \( \pi = \lambda r^m P \).

\[ \pi(r, P) = \lambda r^{5} P \]

Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.
Back to a more general “stochastic” approach: II

- **Basic formulas**

  \[
  \dot{S}(t) = -\pi[r, P(t)]S(t)
  \]

  \[
  l(r) = \int_0^\Delta P(t)S(t)\,dt
  \]

  \[
  M(r) = 1 - S(\Delta)
  \]

- Traditionally, stochastic host survival is modelled differently, \( \pi = \lambda r^m P \).

  \[
  \pi(r, P) = \lambda r^{10} P
  \]

Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.
Summary

- Even in simple “within-host” models, a variety of methods exist to describe pathogenesis.
- Moderate levels of virulence (case mortality) can evolve if rate of pathogenesis $\pi \sim P^n$.
- When $\pi \sim r^m P$, saturation in the transmission rate may help to reduce the case mortality.
Introducing heterogeneity in parameters

- For a parameter $X$, $f(x) \, dx$ is the probability that during a given infection, the parameter $X$ will be in the range $(x, x + dx)$.

- Then total transmission of the pathogen with the growth rate $r$ in a heterogeneous population is calculated as

$$L(r) = \int_{0}^{\infty} l(r, x) \, f(x) \, dx.$$

- Thus, such heterogeneity may arise due to stochasticity in pathogen-host interactions.

- We illustrate the results with heterogeneity in the growth rate $r$ described by a gamma distribution.