# Outline


Introduction

- The rabies puzzle
- Digression: heterogeneity and $\mathcal{R}_0$

Life-history evolution

- Space
- Digression: burnout

A simple model

- Burnout again!

Conclusion

# Modeling the evolution of within-host reproductive rates in pathogens

- New Directions in Probabilistic Models of Evolution
- Simons Institute

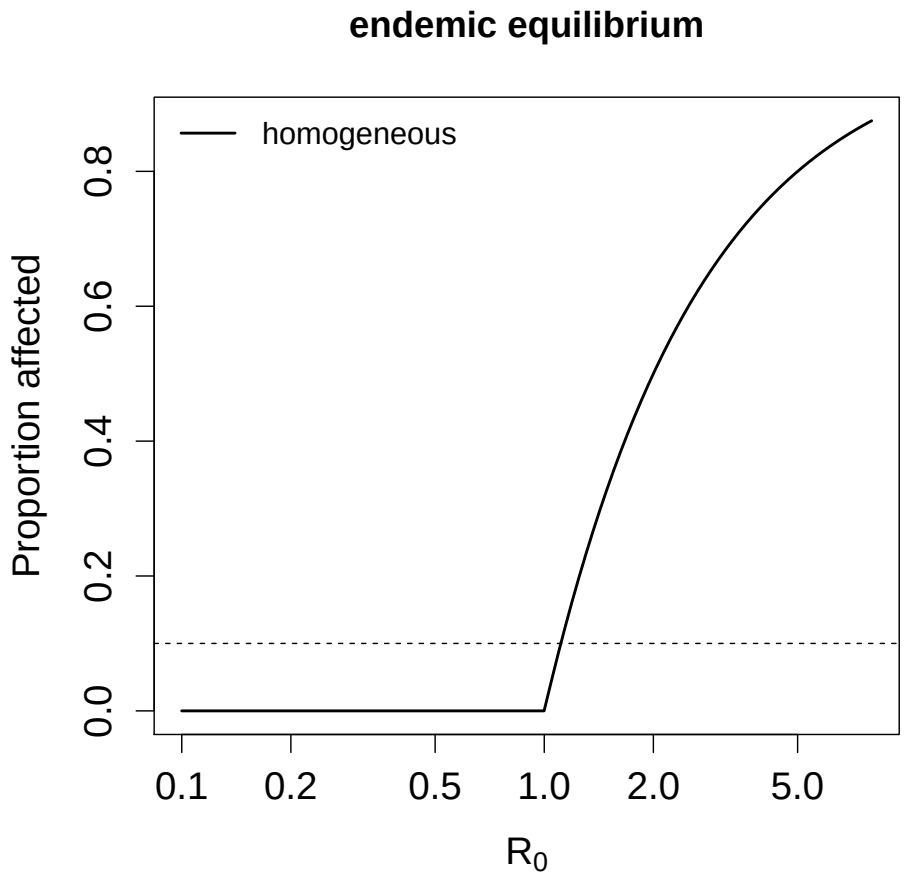

- Jonathan Dushoff
- McMaster University

# Collaborators

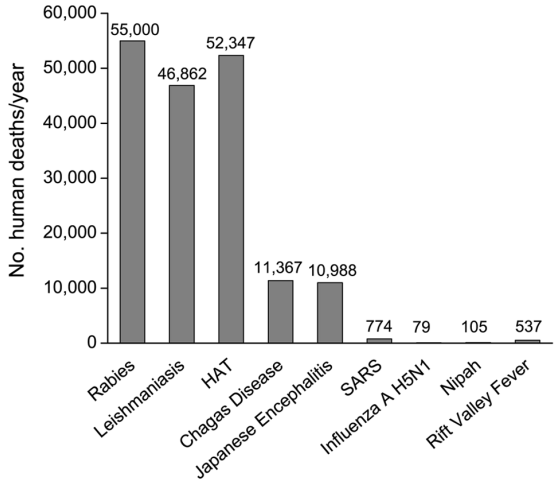
- Tallulah Andrews
- David Earn
  - David Earn lab
- Juliet Pulliam
- Katie Hampson
- Lee Worden and WorkingWiki

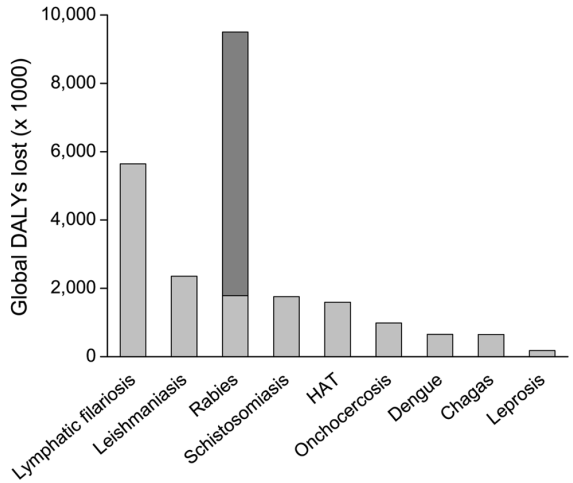
# The basic reproductive number

- $\mathcal{R}_0 = \beta D$ is the mean *potential* number of new infections created by an infectious individual
- $\mathcal{R}_e = \beta DS/N$ is the mean *realized* number



# The rabies puzzle

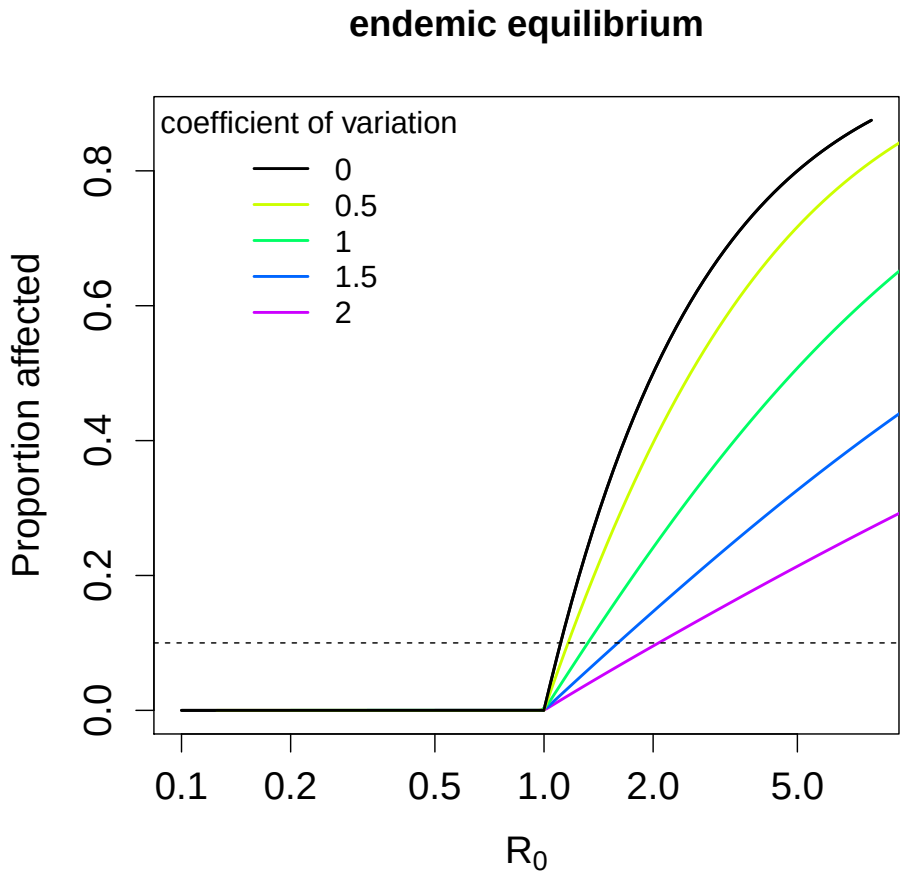



# $\mathcal{R}_0$ estimates for rabies

| Site | $R_0$ | 95% Confidence Interval | Months (weeks) |
|---|---|---|---|
| Tokyo, Japan [43] | 1.05 | 1.04–1.06 | 29 |
| Kanagawa, Japan [44] | 1.09 | 1.02–1.17 | 8 |
| Perak, Malaysia [45] | 1.12 | 0.99–1.27 | 6 |
| Israel [46] | 1.12 | 1.07–1.19 | 9 |
| Ngorongoro District, Tanzania (Figure 3B) | 1.14 (1.10) | 0.94–1.32 (0.98–1.23) | 13 (52) |
| Serengeti District, Tanzania (Figure 3B) | 1.19 (1.18) | 1.12–1.41 (1.08–1.29) | 11 (44) |
| Lima-Callau, Peru [47] | 1.19 | 1.03–1.38 | 8 |
| Tokyo, Japan [44] | 1.25 | 1.14–1.37 | 4 |
| Hong Kong [48] | 1.27 | 1.02–1.60 | 8 |
| Central New York, USA [49] | 1.32 | 1.25–1.40 | 11 |
| Central Java, Indonesia [50] | 1.49 (1.63) | 1.23–1.80 (1.32–2.02) | 4 (15) |
| Selangor, Malaysia [45] | 1.62 | 1.48–1.82 | 11 |
| Hermosillo, Mexico [28] | 1.68 | 1.52–1.91 | 11 |
| Memphis, USA (<10% coverage) [51] | 1.69 (1.80) | 1.33–2.17 (1.44–2.23) | 3 (11) |
| Sultan Hamad, Kenya (~24% coverage) [52] | 1.72 (1.85) | 1.34–2.18 (1.03–2.92) | 4 (14) |

The exponential growth rates of the epidemics were estimated by fitting exponential curves to monthly time series of rabies incidence and converted to e
distribution from the contact tracing data in Tanzania (see Materials and Methods). Estimates based on weekly data are shown in parentheses. The estim
growth, the year of the epidemic onset, and a description of the epidemic setting (where available) are listed. For populations that were partially vaccina
dividing by the proportion of vaccinated animals at the onset of the outbreak. Our estimates show that $R_0$ for canine rabies is inherently low throughc
doi:10.1371/journal.pbio.1000053.t002

# Digression: heterogeneity and $\mathcal{R}_0$



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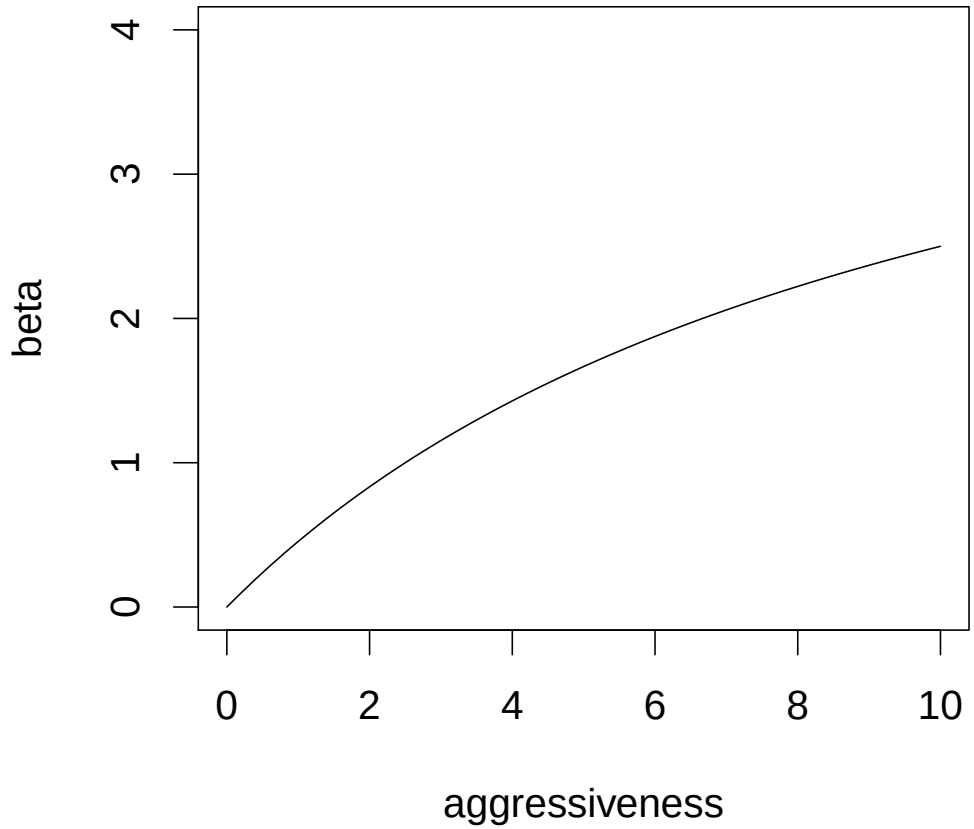
# The commensal theory

# The tradeoff theory

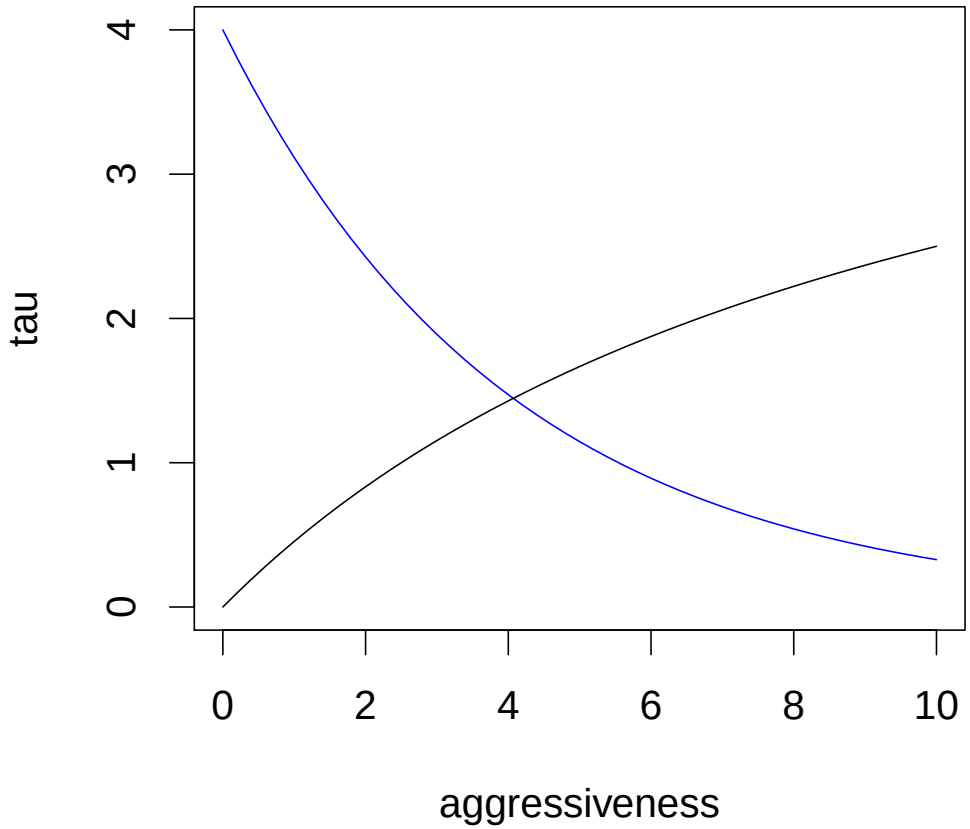
Susceptibles as a resource

- Clearance = death
- Immune = dead

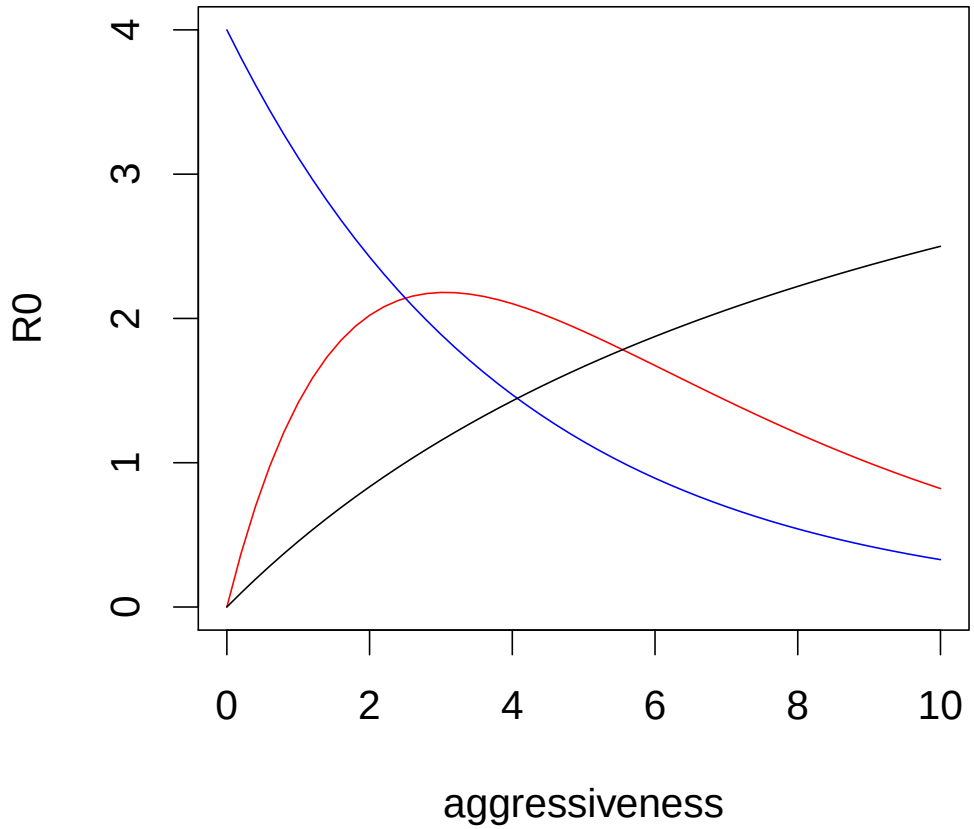
# Tradeoff



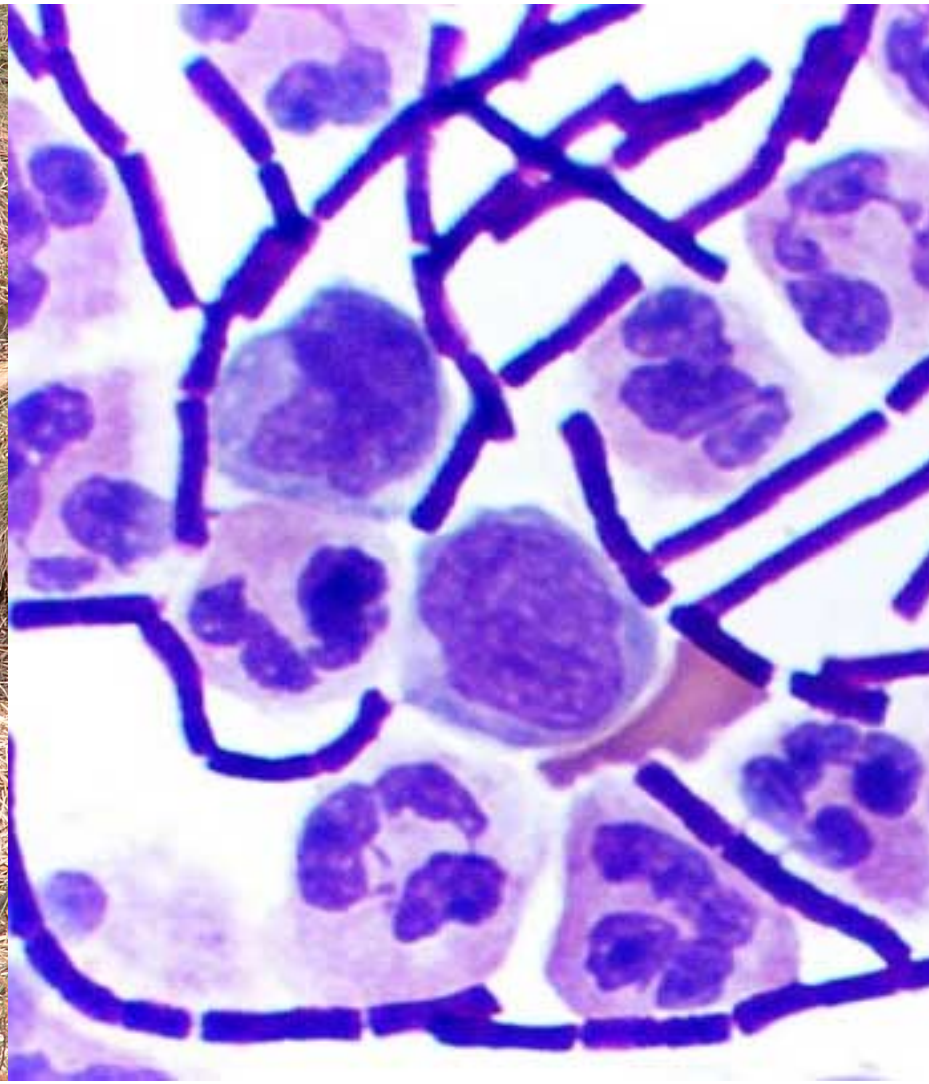
# Tradeoff



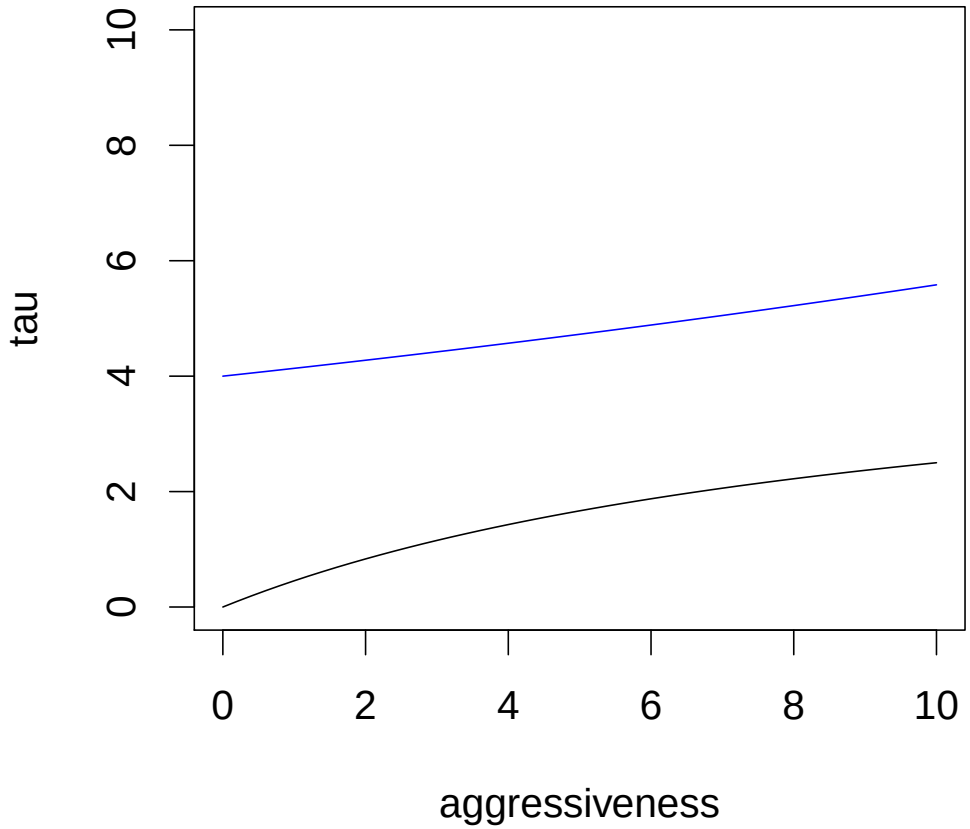
# Tradeoff



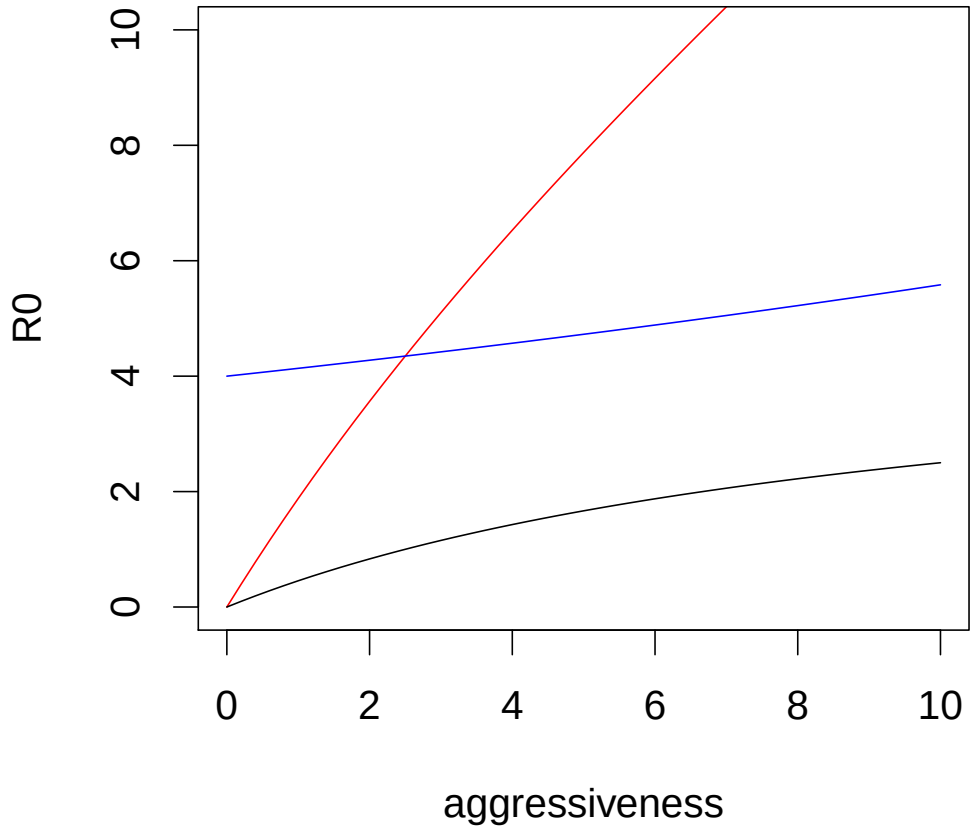
# Micro-predators



# No tradeoff



# No tradeoff



# Modeling assumptions

# Self-limiting pathogens

PNAS PNAS PNAS PNAS

## Emergent trade-offs and selection for outbreak frequency in spatial epidemics

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Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved October 27, 2004 (received for review August 4, 2004)

**Nonspatial theory on pathogen evolution generally predicts selection for maximal number of secondary infections, constrained only by supposed physiological trade-offs between pathogen infectiousness and virulence. Spread of diseases in human populations can, however, exhibit large scale patterns, underlining the need for spatially explicit approaches to pathogen evolution. Here, we show, in a spatial model where all pathogen traits are allowed to evolve independently, that evolutionary trajectories follow a single relationship between transmission and clearance. This trade-off relation is an emergent system property, as opposed to being a property of pathogen physiology, and maximizes outbreak frequency instead of the number of secondary infections. We conclude that spatial pattern formation in contact networks can act to link infectiousness and clearance during pathogen evolution in the absence of any physiological trade-off. Selection for outbreak frequency offers an explanation for the evolution of pathogens that cause mild but frequent infections.**

evolution | pathogen | spatial model | spatial patterns

Current theory on pathogen evolution places much emphasis on physiological (or life-history) trade-offs that relate virulence, infectiousness, mode of transmission, and immune clearance (1–6). These trade-offs, motivated by a supposed functional link between two (or more) traits, specify that evolutionary improvements in one trait are necessarily accompanied by a decline in another (7, 8). One of the most commonly made trade-off assumptions is that increased production of transmission stages causes increased host mortality and thereby shortens the infection period (9). Where traits can evolve independently, nonspatial theory typically predicts selection for maximal transmissibility and infection period, thus maximizing the number of secondary infections (i.e., the number of new infections an infected host causes). It is commonly held, however, that the benefits of increased transmission and the associated penalties of virulence and shorter infection are balanced so that the number of secondary infections is maximized at intermediate transmissibility and virulence (2). In simple nonspatial models, this evolutionary maximization corresponds to selection for maximal basic reproductive ratio $R_0$ (10), i.e., the expected number of secondary infections in an unexposed population [but note that this result depends on absence of multiple infections (5) and vertical transmission (11, 12)]. The current popularity of trade-offs in studies of pathogen evolution stems from the fact that they provide a possible explanation for selection for intermediate virulence and transmissibility (8), and that they can be used to predict pathogen evolution in response to human interventions such as the use of imperfect vaccines (4) or improved hygiene (13). However, the exact shape (and even existence) of trade-offs is unknown for many diseases (14).

A growing body of work reports on the role of spatial pattern formation on evolutionary processes (3, 6, 15–21). Recent studies have shown large-scale spatiotemporal patterns in measles (22) and dengue fever (23). Existing theoretical work on pathogen evolution and spatial pattern formation has focused on a model in which local colonization of "empty spaces" by susceptible hosts plays a central role (3, 6, 19–21). Pathogen lethality in this model leads to host patchiness, and too aggressive pathogens will die out because they cause local extinction of hosts (19). In this manner, spatial processes can lead to limitations in the evolution of transmissibility, but the evolutionary attractor is close to host extinction. Furthermore, local clustering of infections (so-called self-shading) reduces the effective infection rate (20). This effect of spatial patterns makes trade-off optimization in spatial populations less straightforward than in their nonspatial counterparts. Although theoretically appealing, the patchiness that dominates this model depends heavily on local birth of hosts into empty spaces, which does not seem representative for, e.g., human populations. Moreover, for the persistence mechanism proposed by this model to work, the infection process and host reproduction must operate on similar timescales. This implicit assumption does not hold for a large number of pathogen–host systems. Our aim is to examine how spatial selection processes determine pathogen evolution in the absence of the dominant role of virulence, host demographics, and physiological trade-offs.

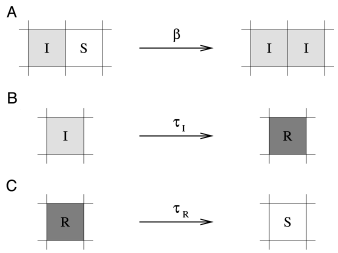


**Fig. 1.** Representation of processes in the contact network model. (*A*) Infection. Infected hosts (I) can infect susceptible (S) neighbors with infection rate $\beta$. The total probability of infection is $1 - e^{i\beta\Delta t}$, where $i$ is the number of infected neighbors. (*B*) Acquisition of resistance. Hosts are infectious for a fixed period $\tau_I$, after which they become resistant (R). (*C*) Loss of resistance. After a fixed period $\tau_R$, resistant hosts once again become susceptible.

### Methods

We developed a spatial susceptible-infected-resistant (SIRS) model for disease dynamics (24), using a grid-structured contact network (25, 26). In the model (see Fig. 1), hosts can be susceptible (S), infected (I), or resistant (R). Infected hosts can

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*W.M.v.B. and M.C.B. contributed equally to this work.

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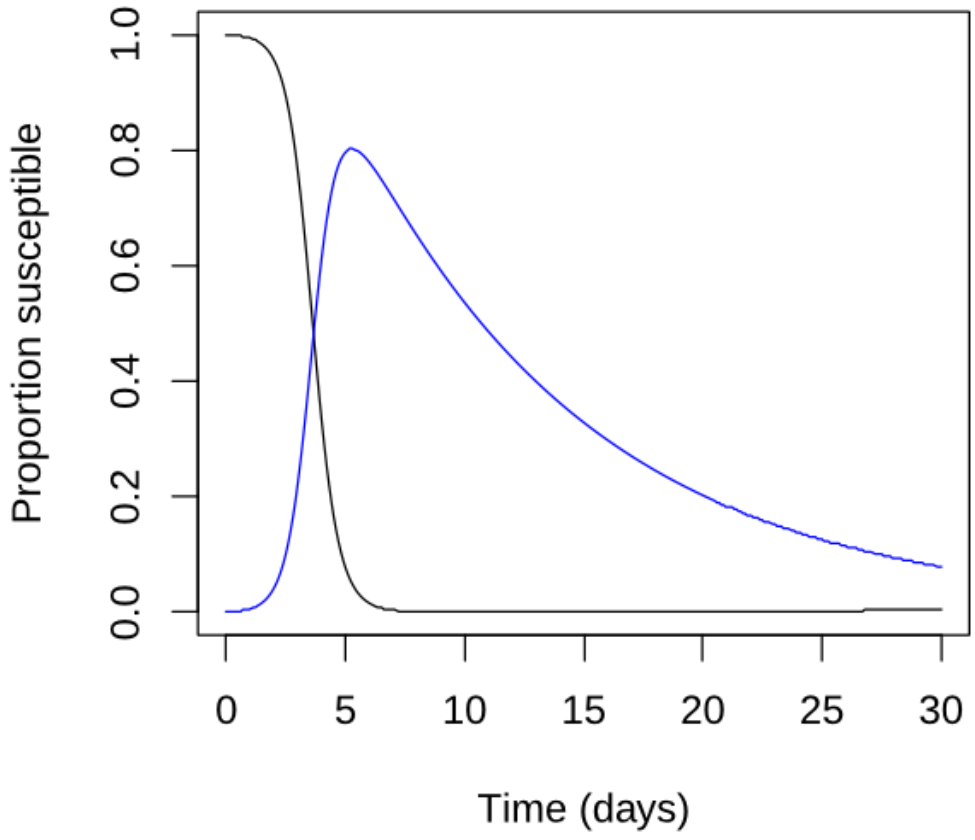
www.pnas.org/cgi/doi/10.1073/pnas.0405682101

# Digression: burnout



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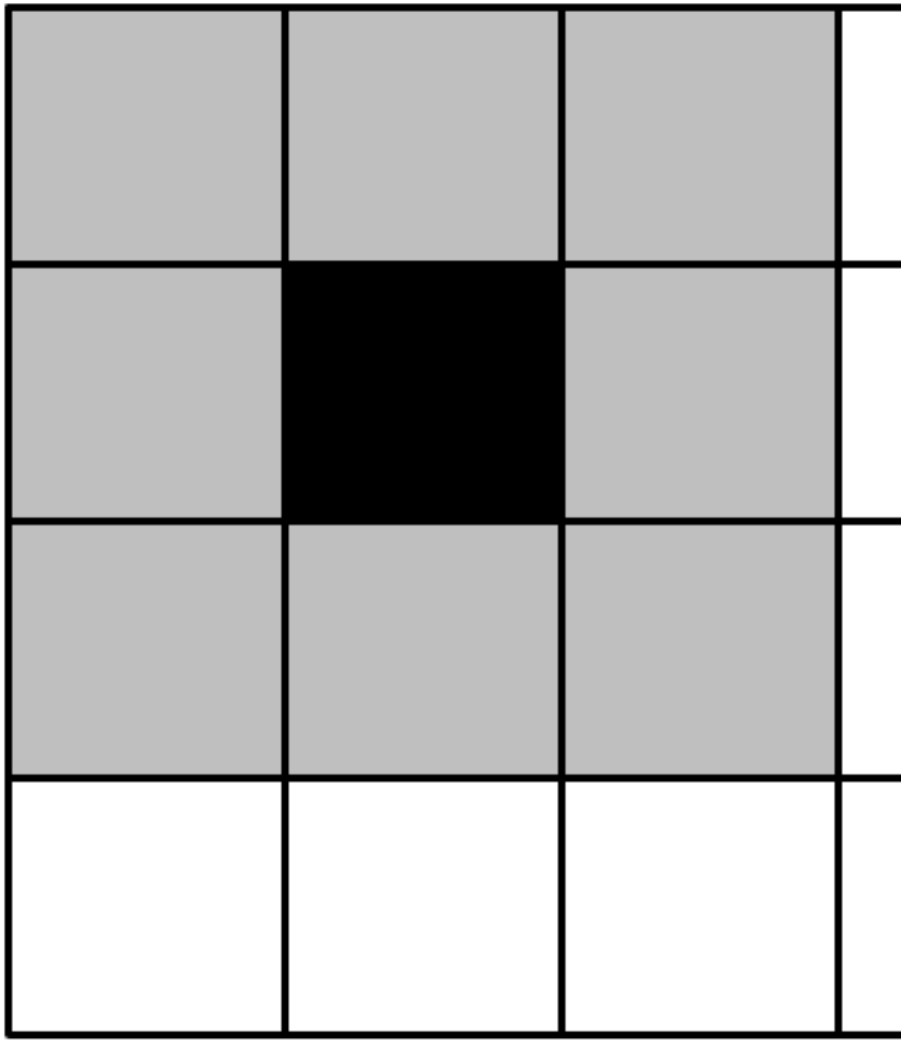
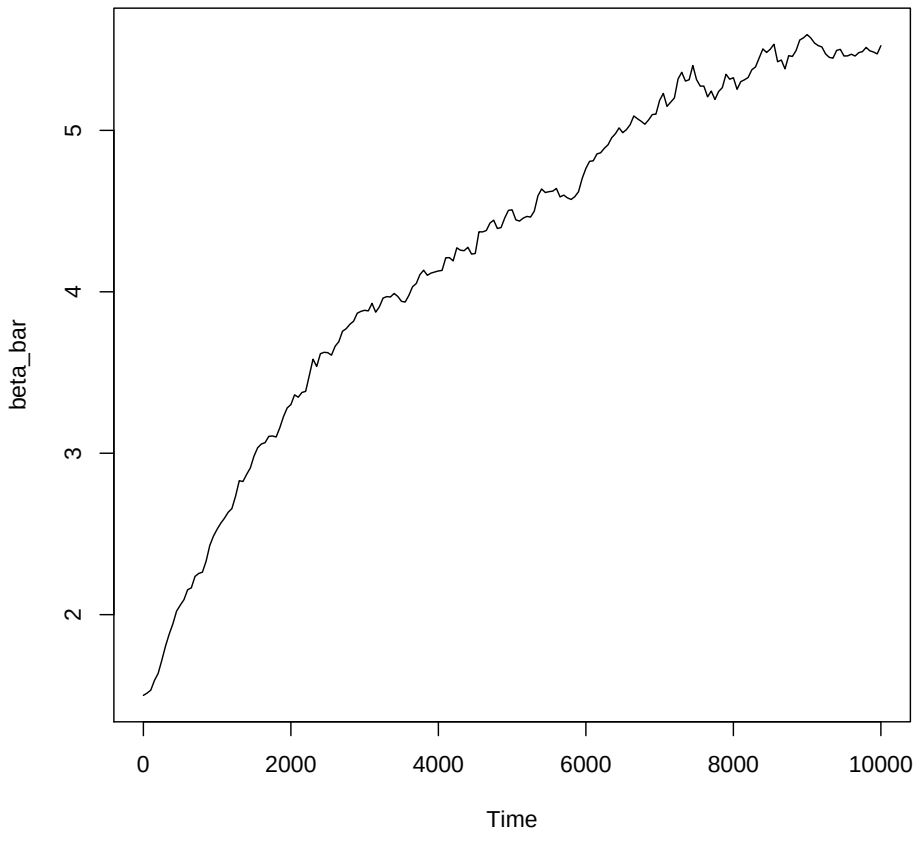
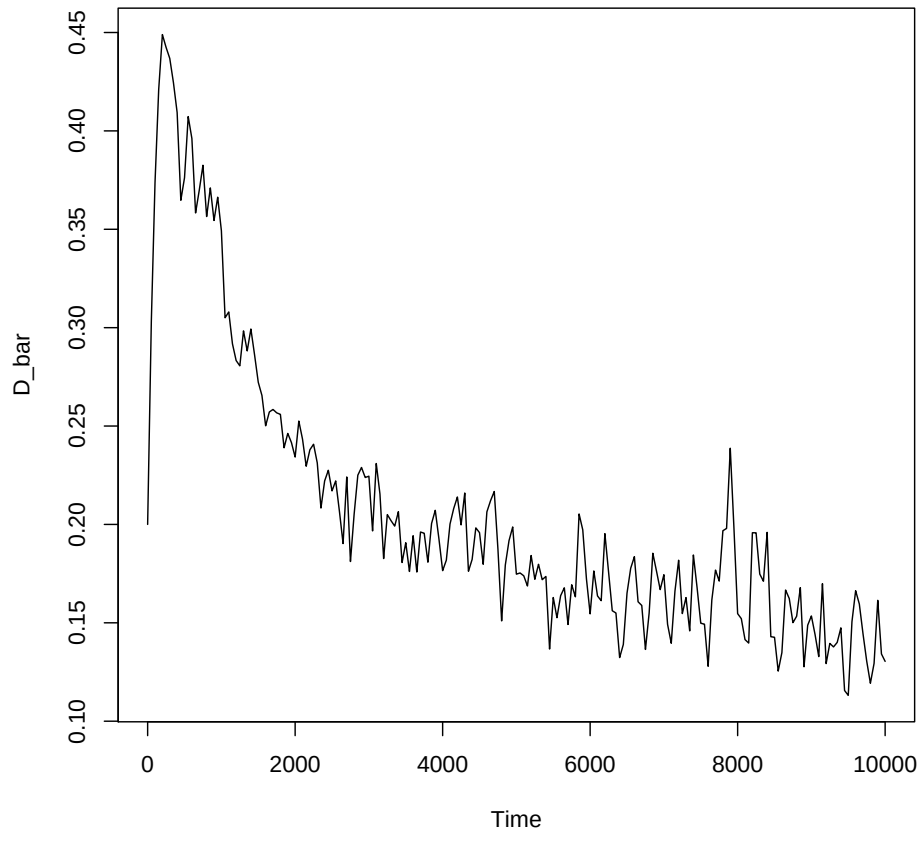
# A simple model

- Square grid (8 neighbors)
- $\tau$ and $D$ can evolve *freely*

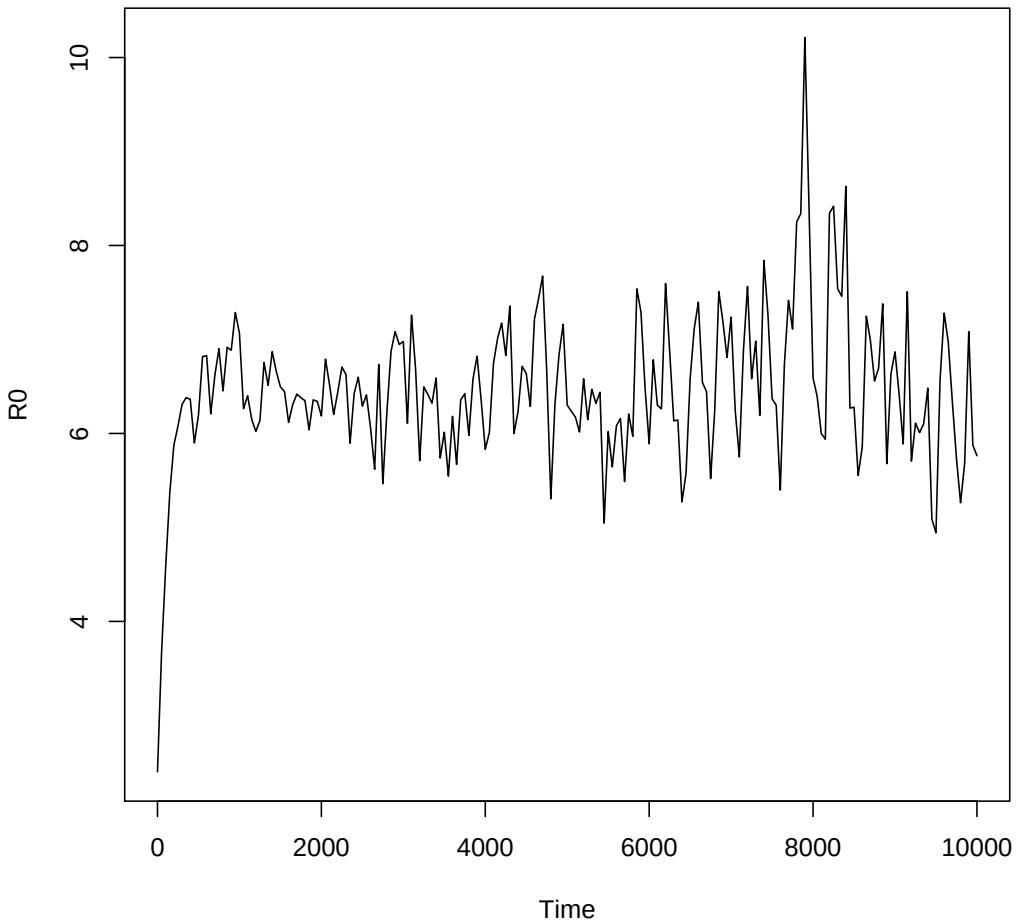


# Fixed time course



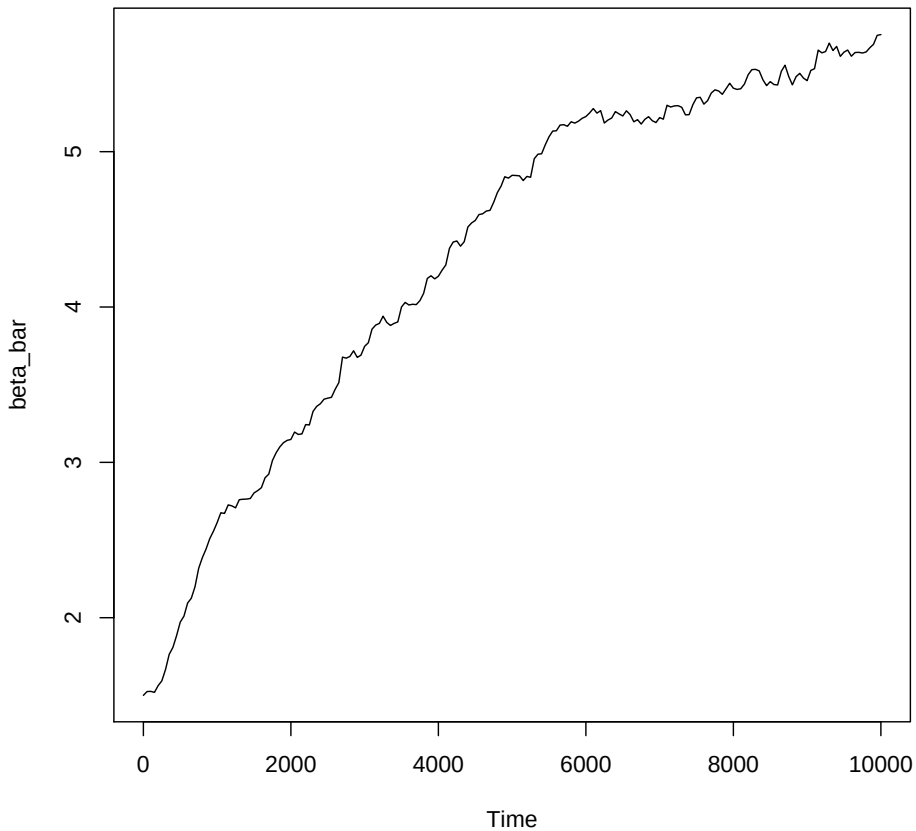
# Fixed time course

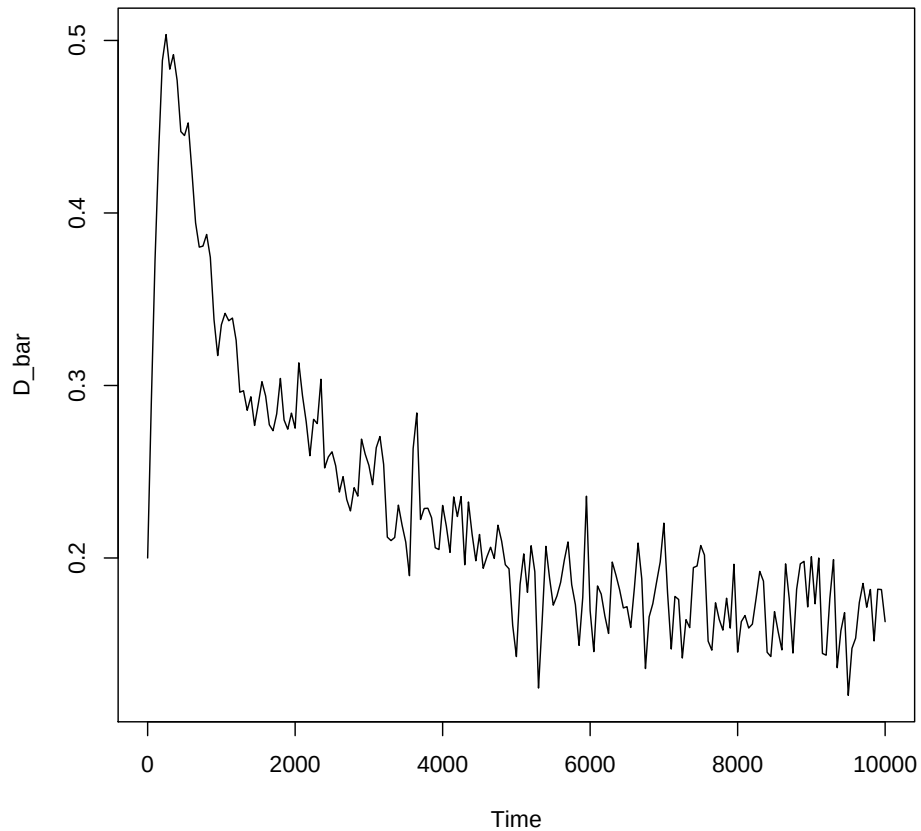


# Fixed time course

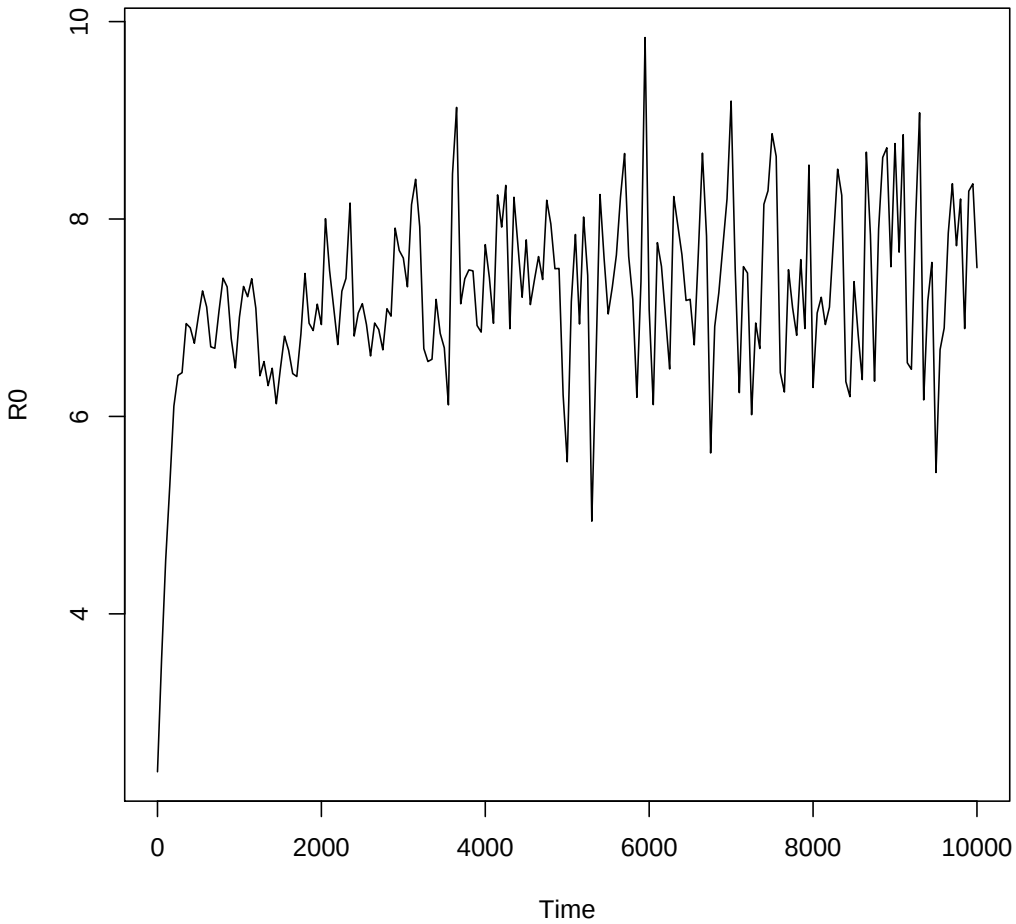
- Movie

# Variable time course (sdlog=0.2)

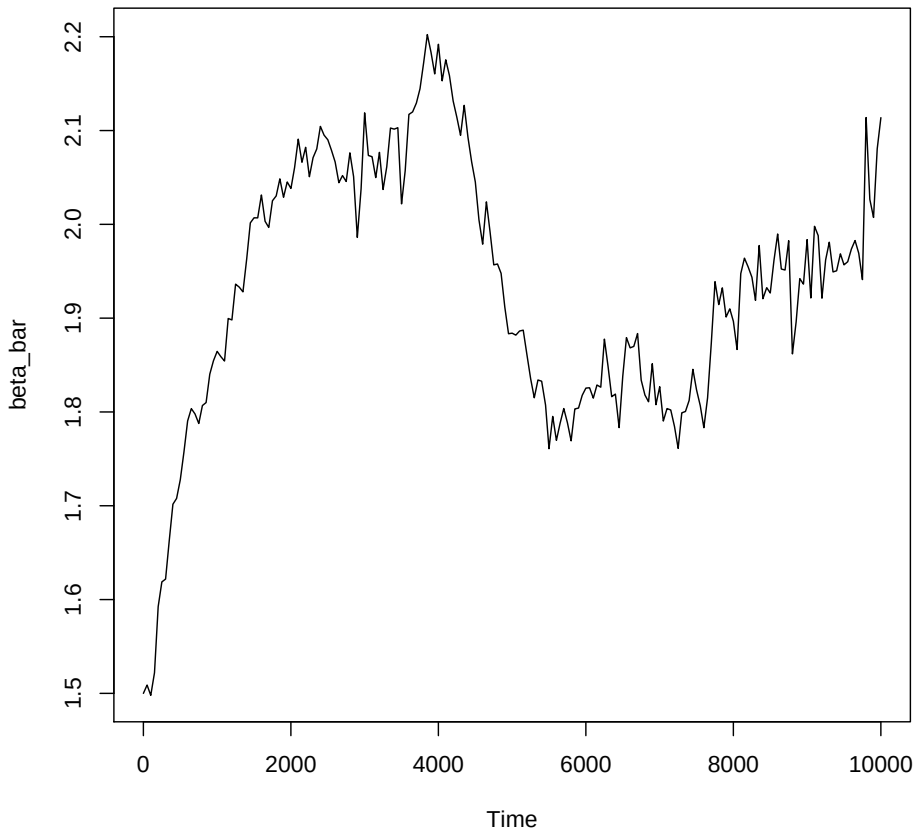


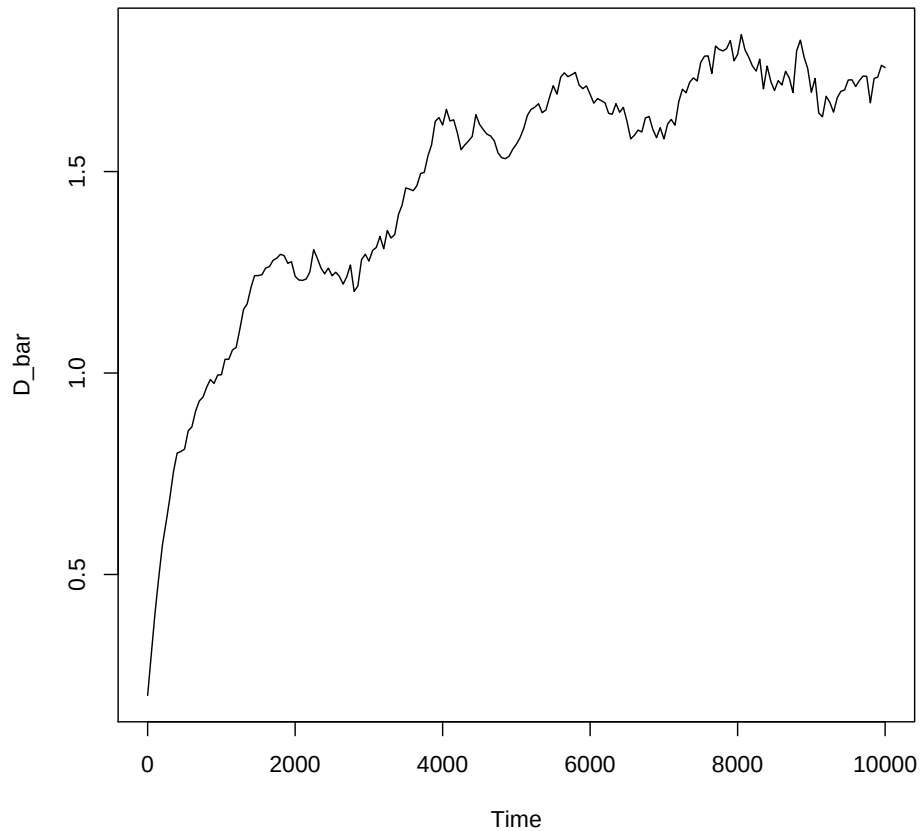



# Sdlog = 0.2

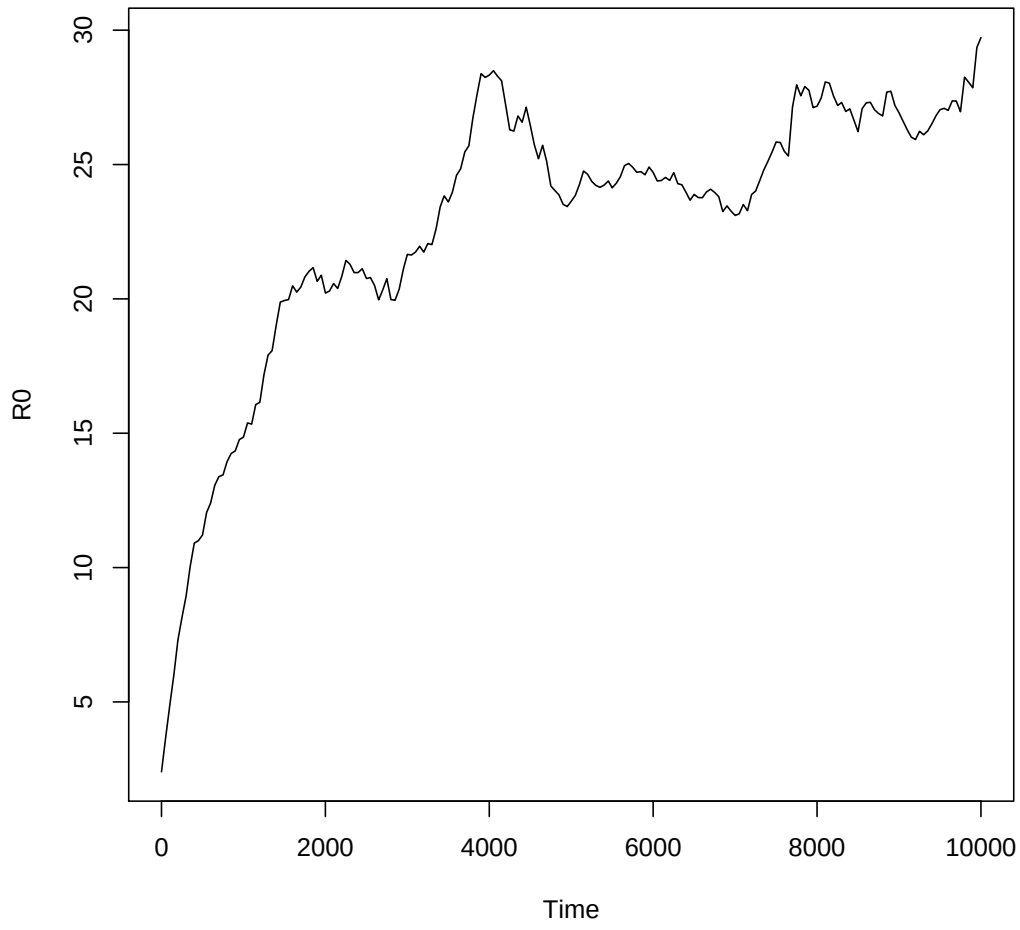


# Variable time course (sdlog=0.5)

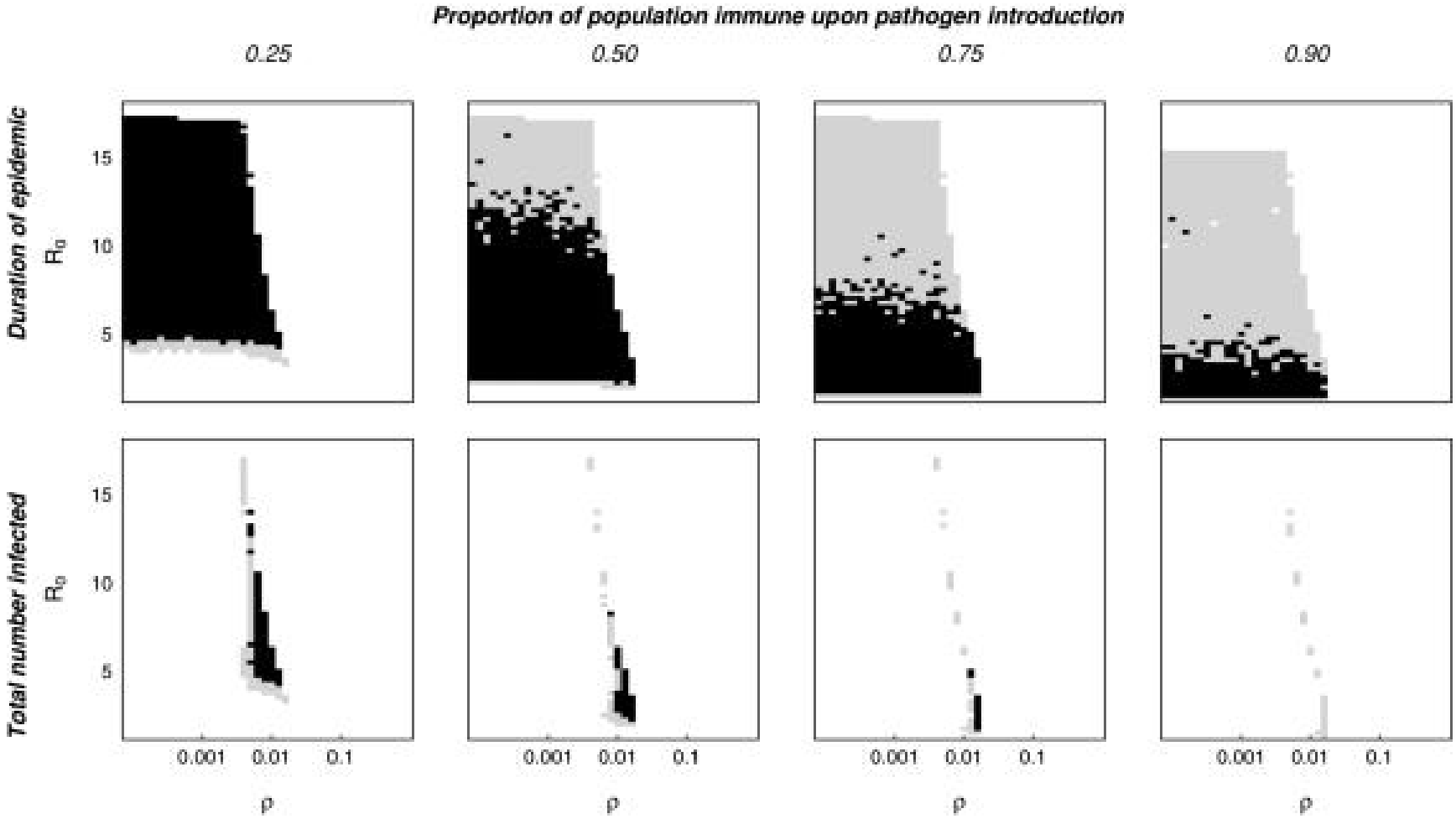


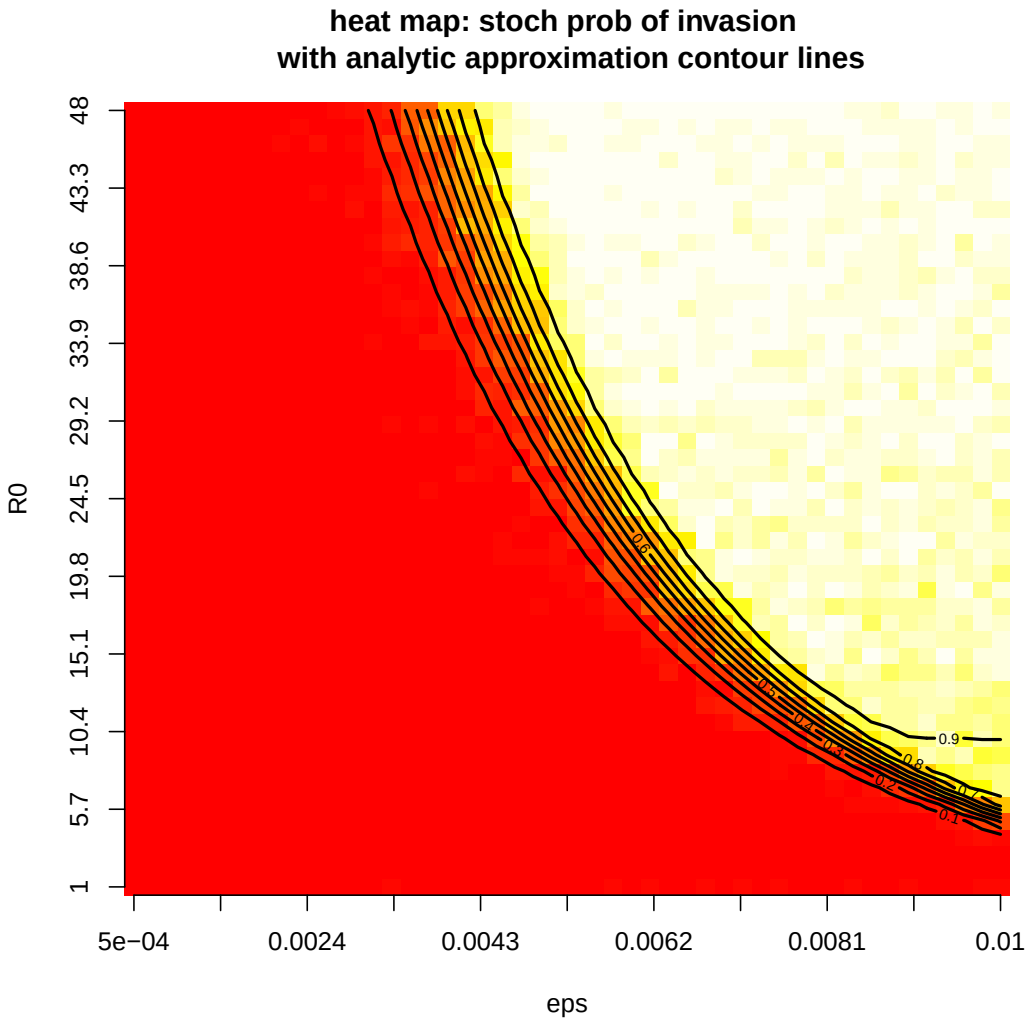
# Sdlog = 0.5



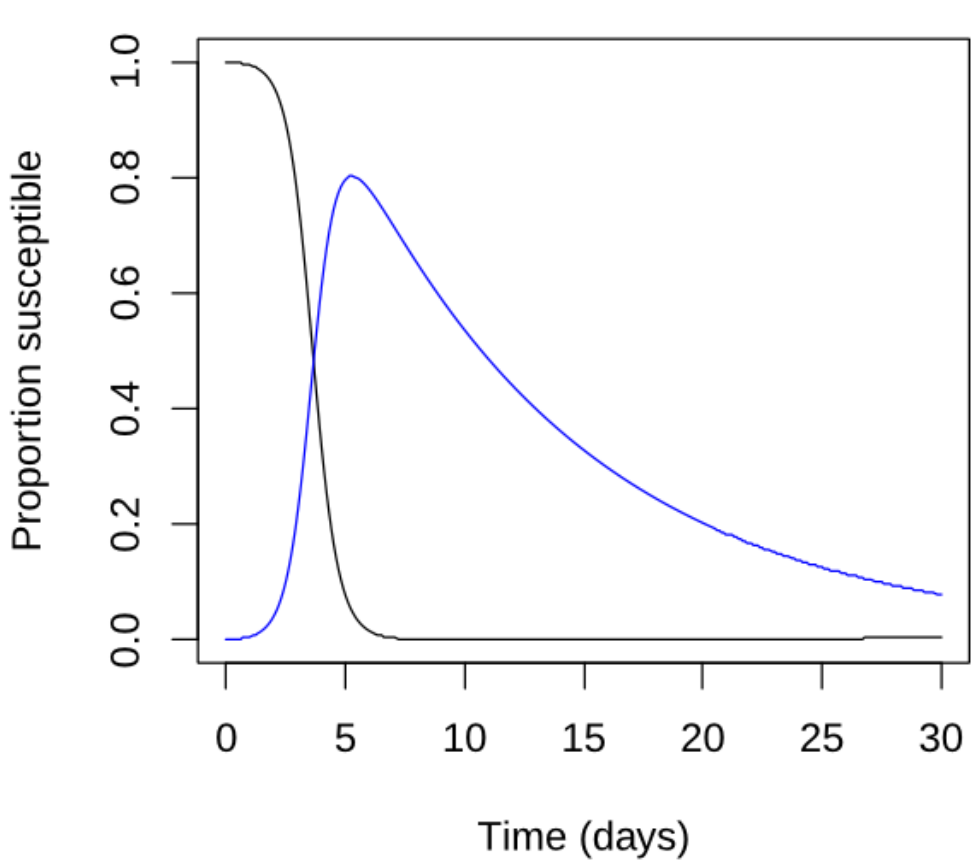
# The conventional wisdom

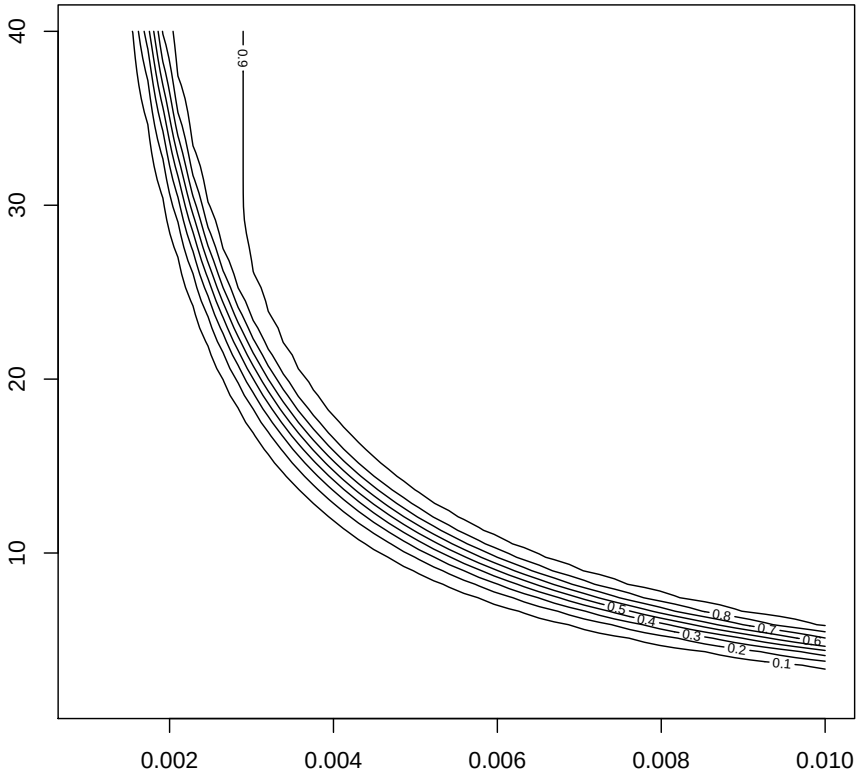


# Some simpler simulations

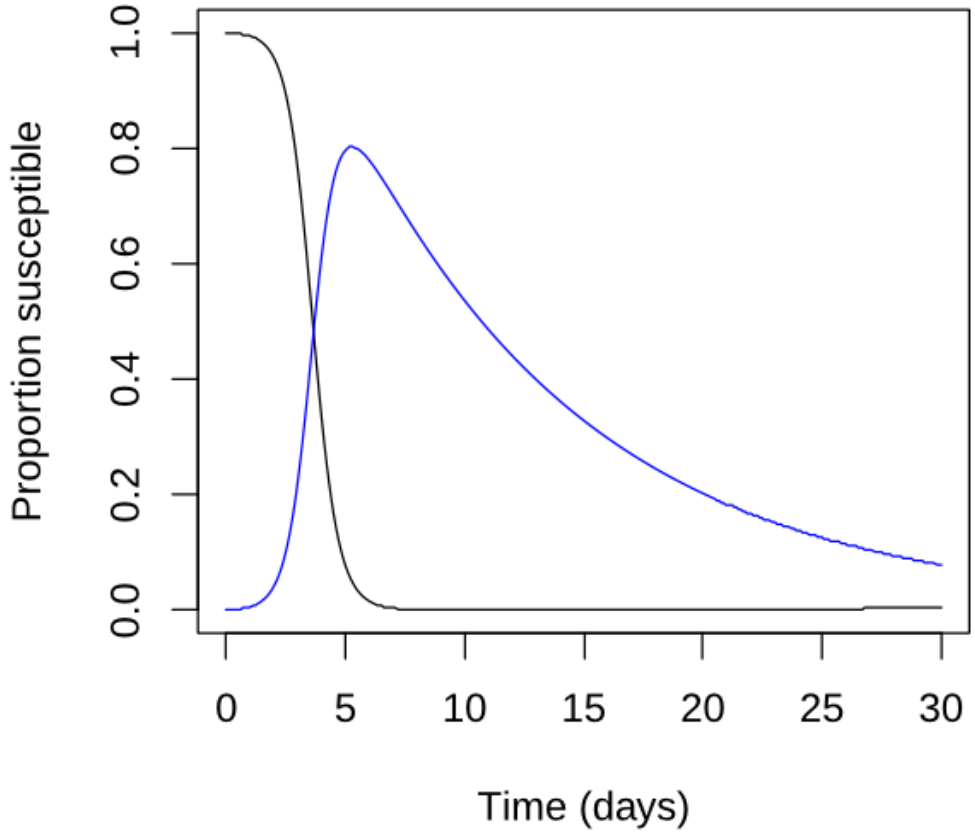


# An approximation



# Modeling assumptions



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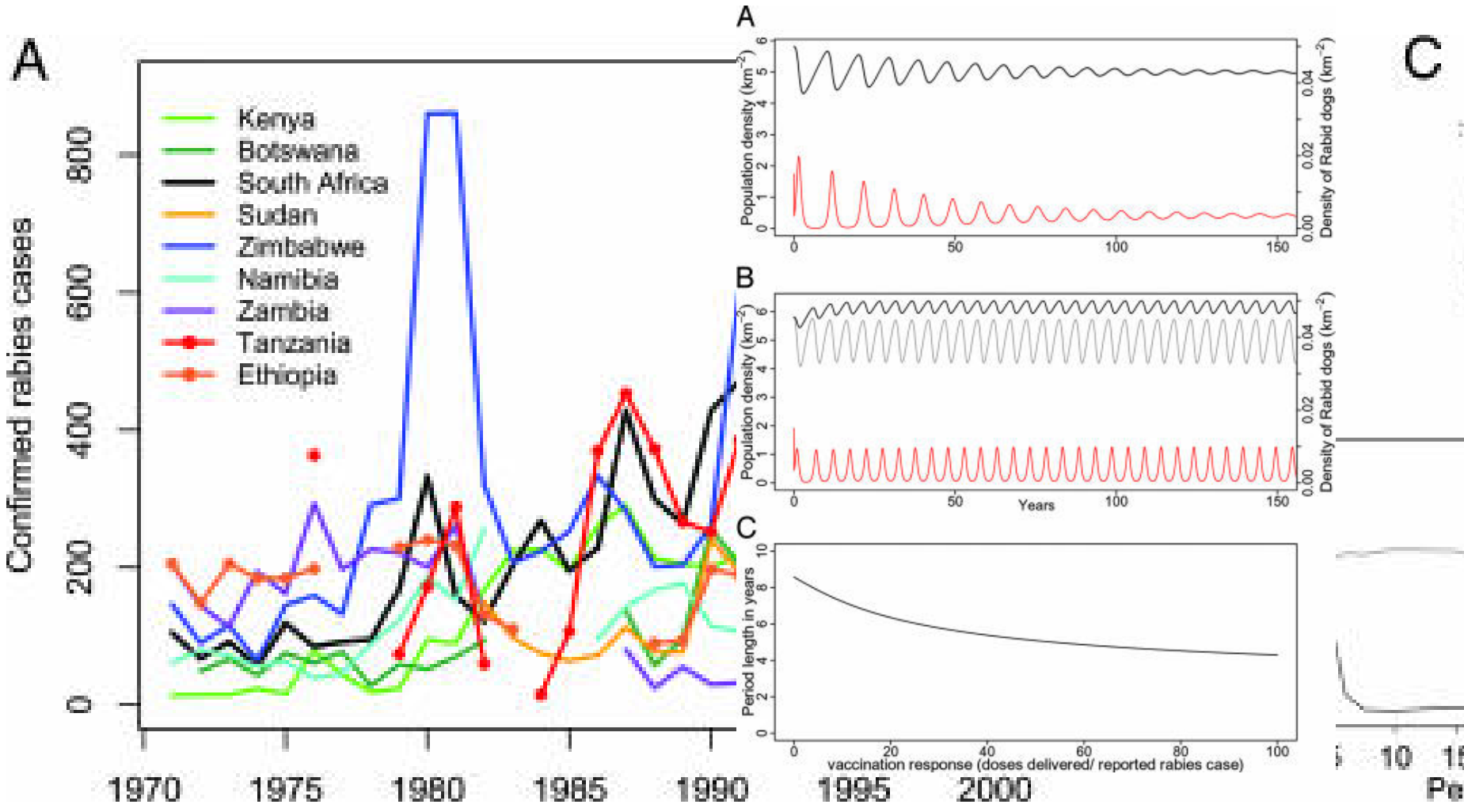
A
Confirmed rabies cases
0
200
400
600
800
1970
1975
1980
1985
1990
1995
2000
Kenya
Botswana
South Africa
Sudan
Zimbabwe
Namibia
Zambia
Tanzania
Ethiopia
A
Population density (km$^{-2}$)
Density of Rabid dogs (km$^{-2}$)
B
Years
C
Period length in years
vaccination response (doses delivered/ reported rabies case)
C