Module 6:
Introduction to Stochastic Epidemic Models with Inference

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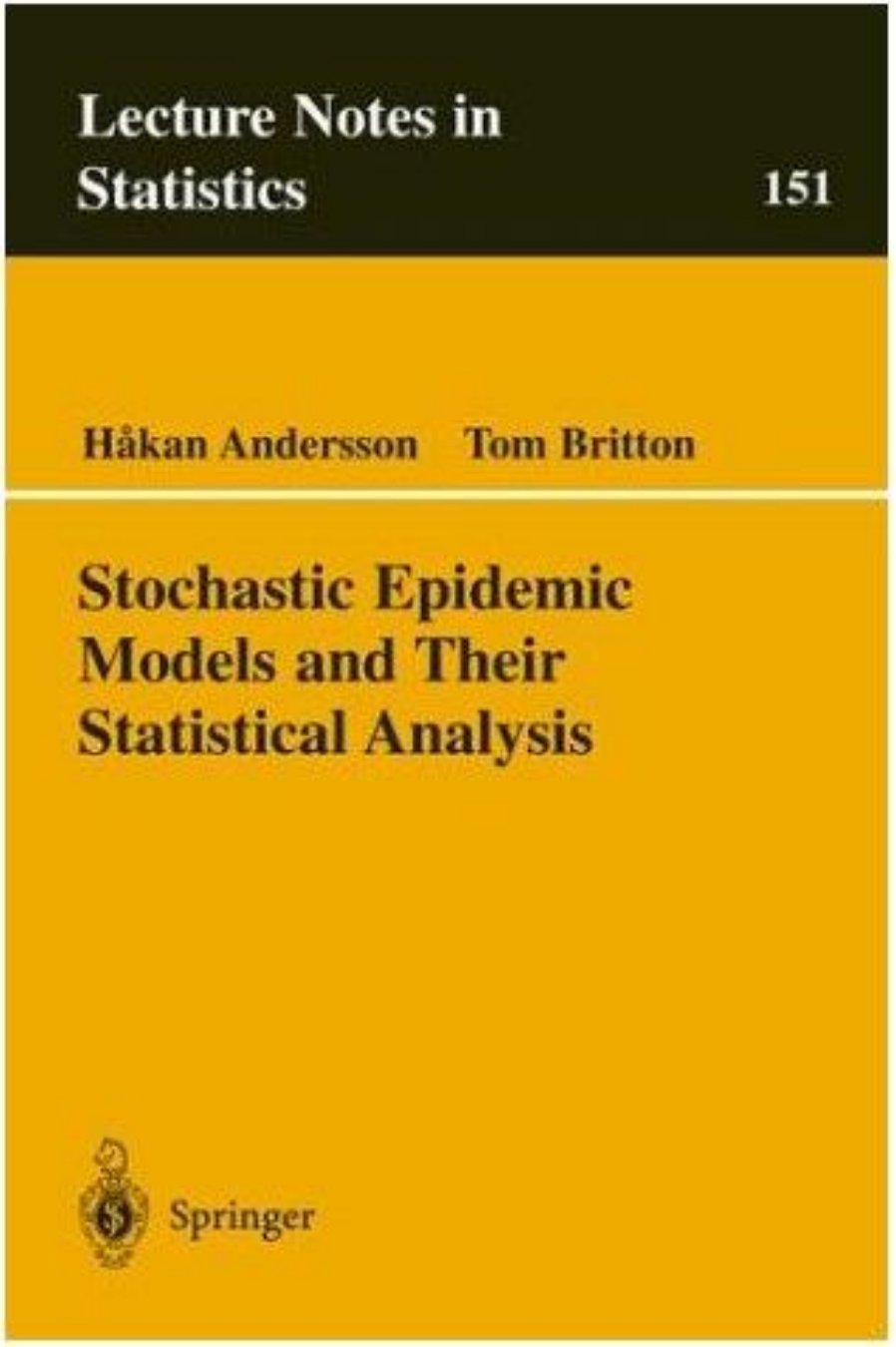
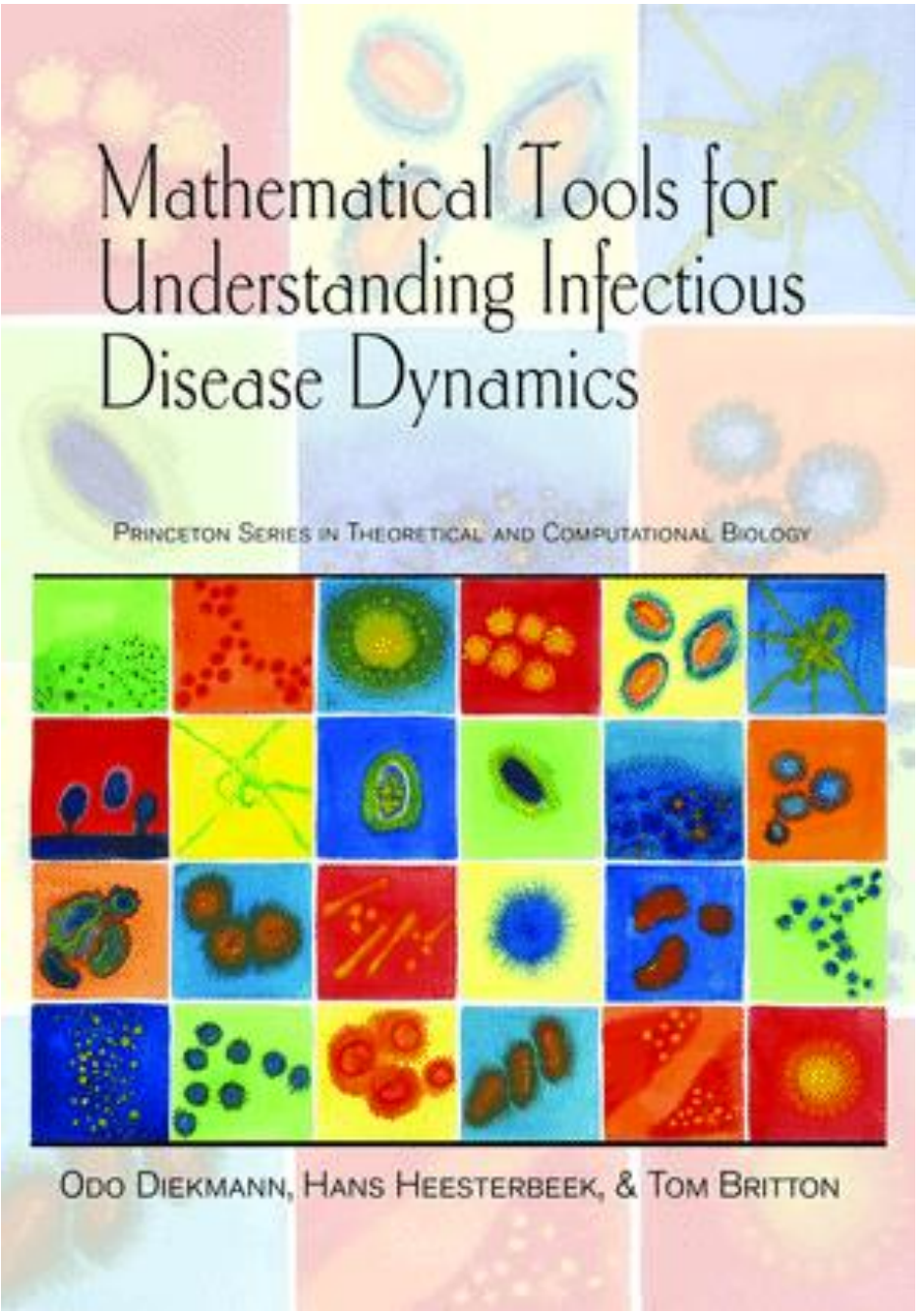
Philosophy of this course (i.e., Reductionist statements)

- Analytic work on the transmission and control of infectious diseases depends on an understanding of epidemic theory
- A technical understanding of the underlying non-linear, stochastic dynamics of infectious disease transmission is the basis for this understanding
  - This almost always involves non-linear functions for the interaction of $\boldsymbol{x}$ susceptible and $\boldsymbol{y}$ infected people at time *t*.
- This technical understanding leads to sound inferential structures for estimation of governing parameters and functions

Some Books of Interest for This Course





CENTER FOR INFERENCE & DYNAMICS OF INFECTIOUS DISEASES

UF UNIVERSITY of FLORIDA

csquid CENTER FOR STATISTICS & QUANTITATIVE INFECTIOUS DISEASES

Stockholm University

Statistics for Biology and Health

M. Elizabeth Halloran • Ira M. Longini, Jr. • Claudio J. Struchiner

Design and Analysis of Vaccine Studies

Widespread immunization has many different kinds of effects in individuals and populations, including in the unvaccinated individuals. The challenge is in understanding and estimating all of these effects. This book presents a unified conceptual framework of the different effects of vaccination at the individual and at the population level. The book covers many different vaccine effects, including vaccine efficacy for susceptibility, for disease, for post-infection outcomes, and for infectiousness. The book includes methods for evaluating indirect, total and overall effects of vaccination programs in populations. Topics include household studies, evaluating correlates of immune protection, and applications of casual inference. Material on concepts of infectious disease epidemiology, transmission models, casual inference, and vaccines provides background for the reader. This is the first book to present vaccine evaluation in this comprehensive conceptual framework.

This book is intended for colleagues and students in statistics, biostatistics, epidemiology, and infectious diseases. Most essential concepts are described in simple language accessible to epidemiologists, followed by technical material accessible to statisticians.

Elizabeth Halloran and Ira Longini are professors of biostatistics at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle. Claudio Struchiner is professor of epidemiology and biostatistics at the Brazilian School of Public Health of the Oswaldo Cruz Foundation in Rio de Janeiro. The authors are prominent researchers in the area. Halloran and Struchiner developed the study designs for dependent happenings to delineate indirect, total, and overall effects. Halloran has made contributions at the interface of epidemiological methods, causal inference, and transmission dynamics. Longini works in the area of stochastic processes applied to epidemiological infectious disease problems, specializing in the mathematical and statistical theory of epidemics. Struchiner has contributed to understanding the role of transmission in interpreting vaccine effects.

EPIDEMIOLOGY

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Struchiner

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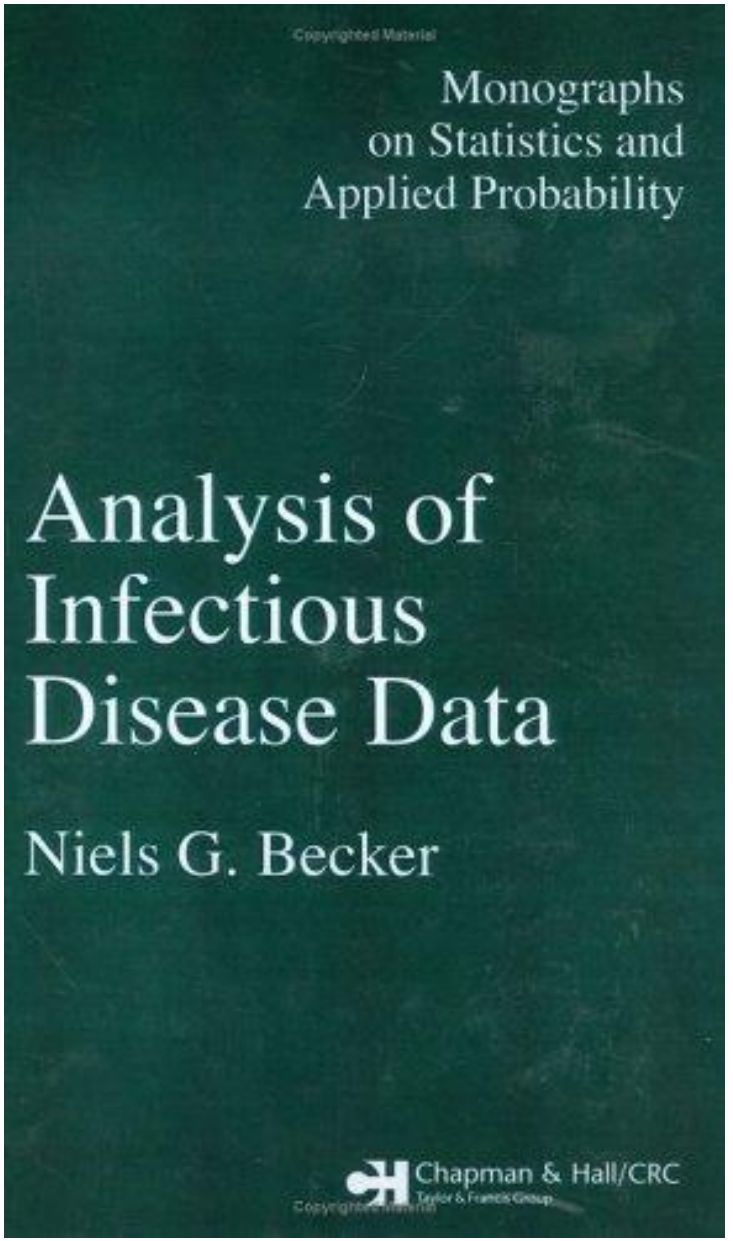
The Mathematical Theory of Infectious Diseases
and its Applications

Norman T. J. Bailey, M.A., D.Sc.
Unit of Health Statistical Methodology, World Health Organization, Geneva. Formerly Professor of Biomathematics, Cornell University Graduate School of Medical Sciences, and Member of the Sloan-Kettering Institute for Cancer Research

Second edition

CHARLES GRIFFIN & COMPANY LTD
London and High Wycombe



1975, 1st addition 1957

Inference on infectious diseases modules in addition to this one

- **Module 4**: MCMC I for Infectious Diseases, July 11 – 13
- **Module 7**: Simulation-based Inference for Epidemiological Dynamics, July 16 – 18
- **Module 9**: Statistics and Modeling with Novel Data Streams, July 16 – 18
- **Module 10**: MCMC II for Infectious Diseases, July 18 – 20
- **Module 14**: Spatial Statistics in Epidemiology and Public Health, July 23 – 25

Lectures

July 11:

1. Introduction to stochastic epidemic models; notation, properties, examples, IL, TB
2. Important properties: R_0, growth rate, generation intervals, etc., TB

July 12:

3. Inference on stochastic epidemic models, TB
4. Stochastic models for arboviruses, IL
5. Modeling using networks and other heterogeneities, TB
6. Different models for vaccine mechanisms, IL

Lectures

July 13:

7. Inference for small groups such as households, IL
8. Inference for large groups such as cities, TB
9. Study designs for evaluating vaccine efficacy, IL
10. Cluster randomized vaccine trials for emerging infectious disease epidemics: The case of ring vaccination for Ebola, IL

Some Infectious Diseases Under Study

- Influenza
- Novel Coronavirus, SARS-CoV, MERS-CoV
- Ebola and other filoviruses
- Cholera, Typhoid, Rotavirus
- Dengue, Zika, Chikungunya
- Lassa, Nipah, plague
- HIV
- Others, polio, pertussis, hand-foot-and-mouth (EV71)
- Agent X

World Health Organization

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A research and development Blueprint for action to prevent epidemics

Sharing biological samples and data during public health emergencies

WHO is developing a web-based tool to facilitate equitable sample and data sharing during public health emergencies. This document is now released for comments. It discusses in detail the possible approaches that can be used to share samples and benefits on the same footing, and provides concrete, real world examples of how these can be embedded in an MTA. Go to public consultation page

Read more on biological smaples and data sharing

Go to public consultation page

http://www.who.int/blueprint/en/

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Revised list of priority diseases, January 2017

- Arenaviral hemorrhagic fevers (including Lassa Fever)
- Crimean Congo Haemorrhagic Fever (CCHF)
- Filoviral diseases (including Ebola and Marburg)
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
- Other highly pathogenic coronaviral diseases (such as Severe Acute Respiratory Syndrome, (SARS))
- Nipah and related henipaviral diseases
- Rift Valley Fever (RVF)
- Severe Fever with Thrombocytopenia Syndrome (SFTS)
- Zika
- Disease X *

R&D BLUEPRINT

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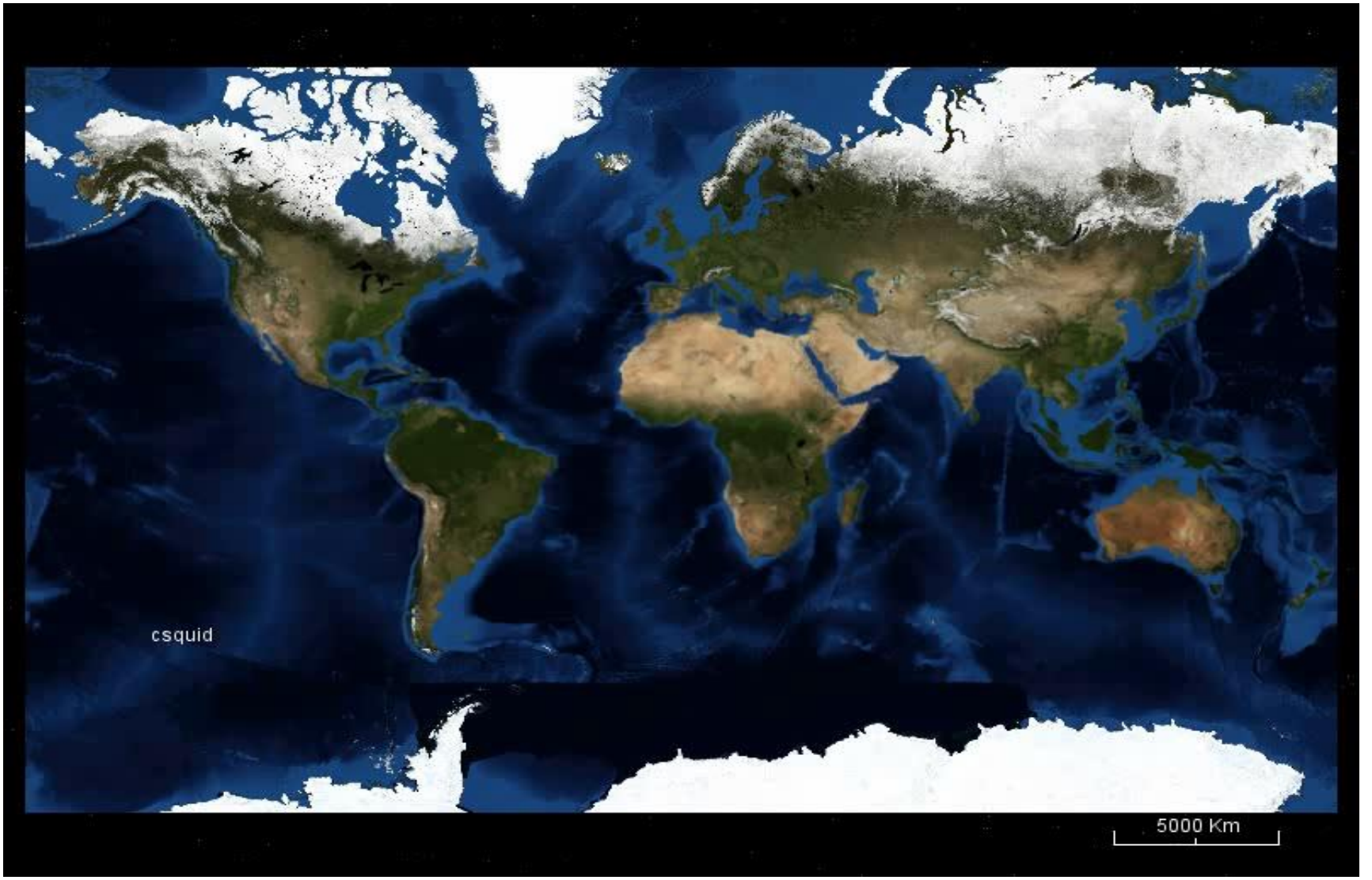
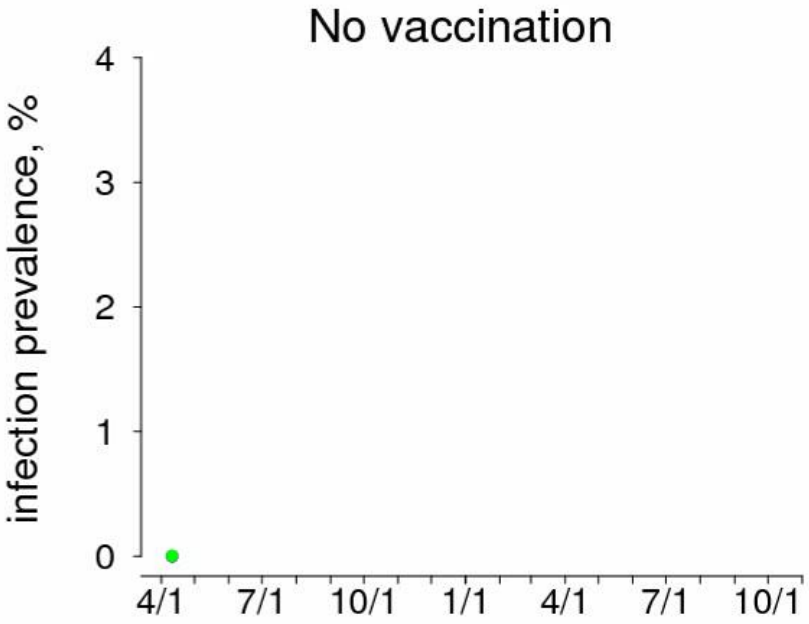
Some Examples

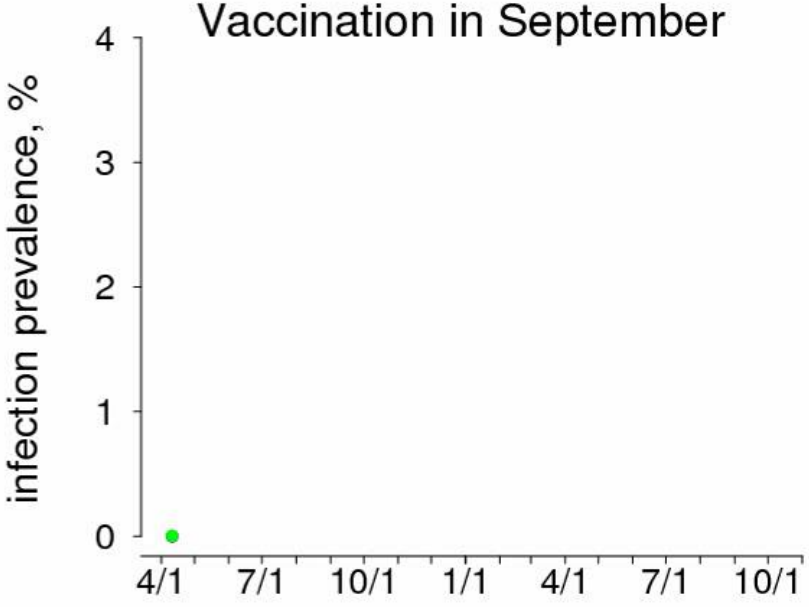
Pandemic H1N1, 2009-2010

Stochastic, Compartmental, Patch



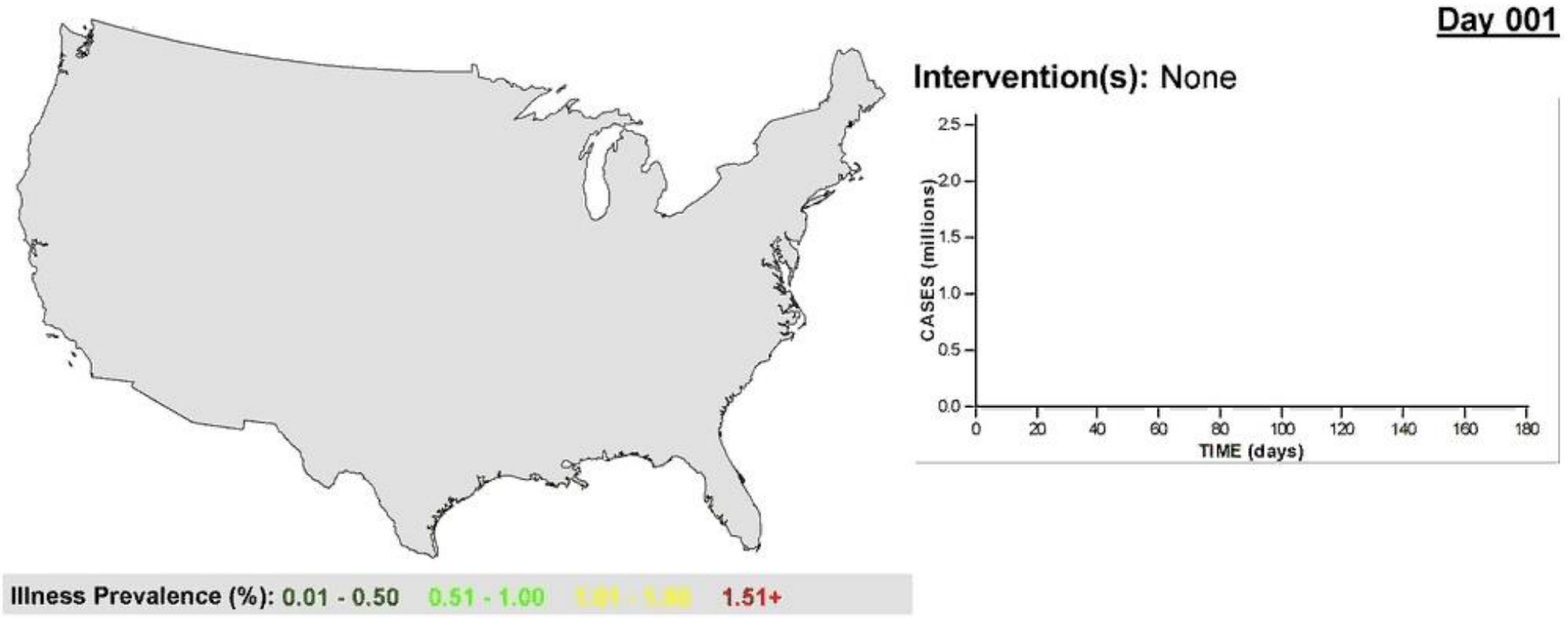
Pandemic H1N1 With Vaccination



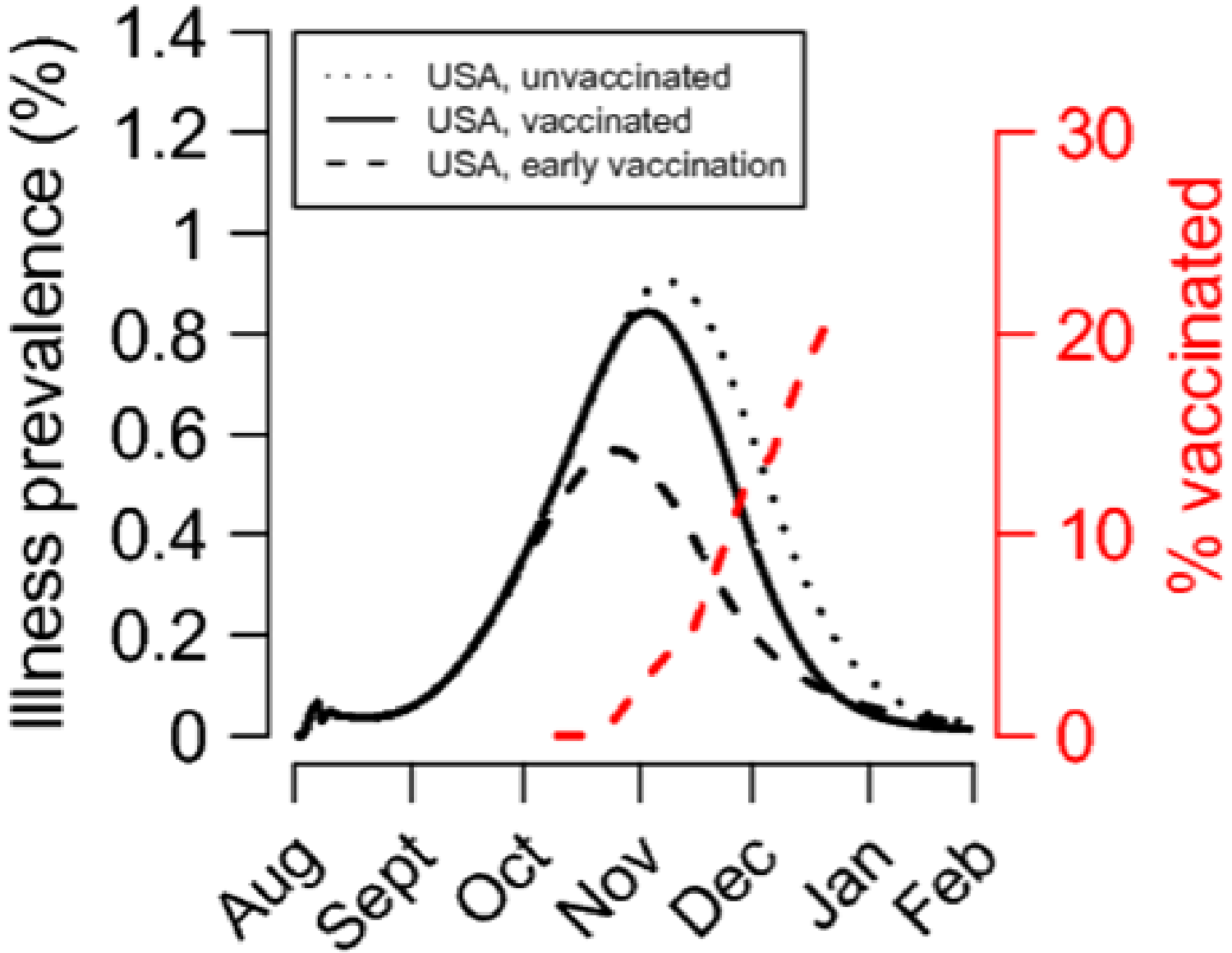


Spread the within US

Agent-based, RF

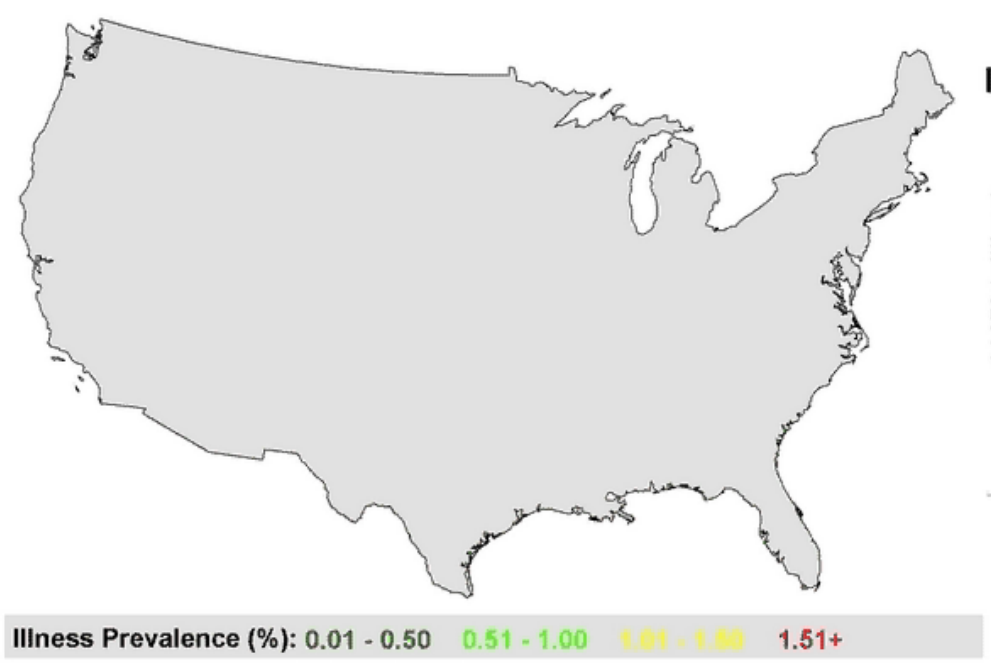


Simulated Mass Vaccination in US



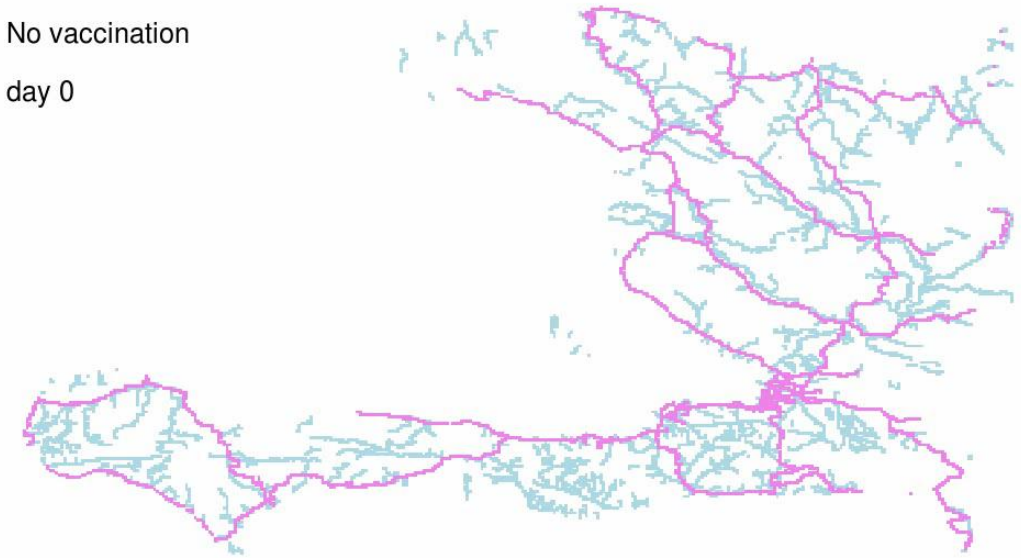
What Could Have Been Done

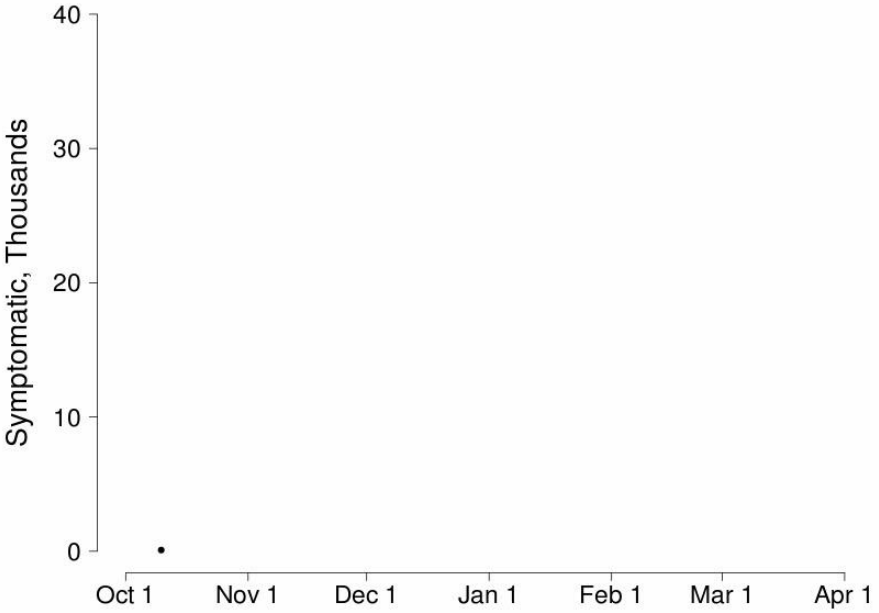
Agent-based, RF

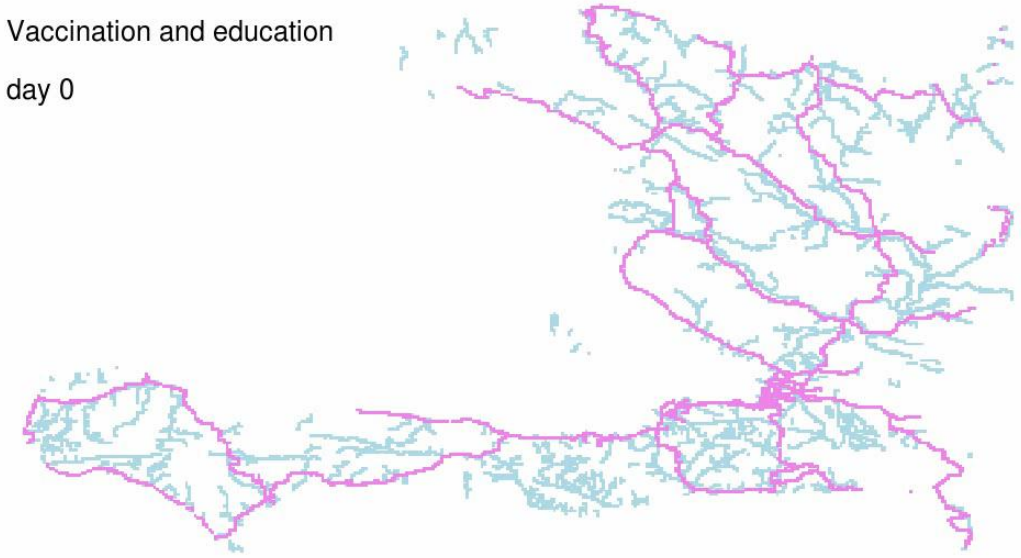


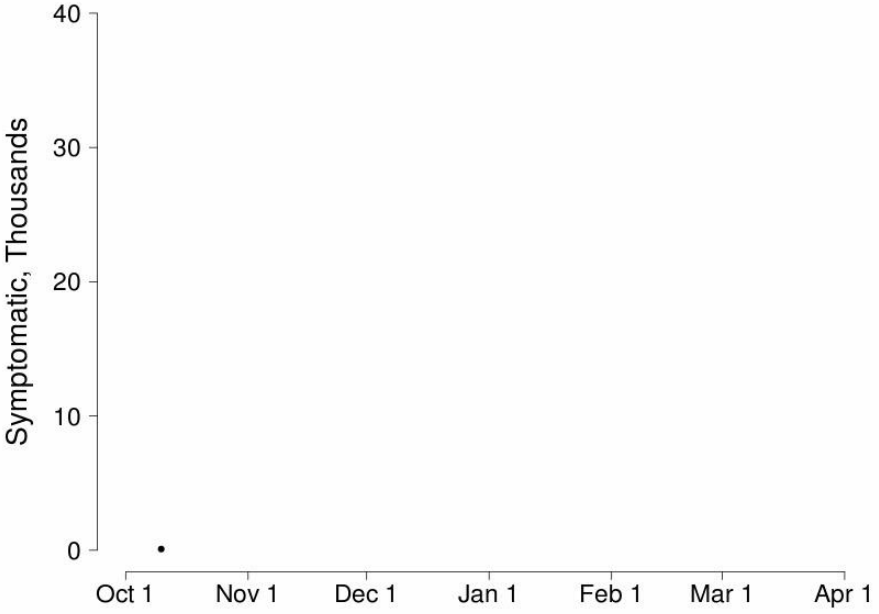
Cholera Epidemic in Haiti with Reactive Vaccination,

Agent-based, RF



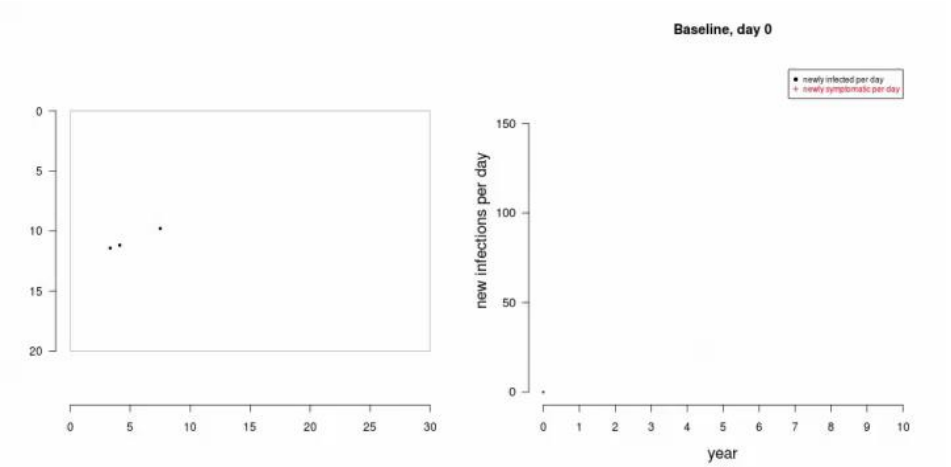


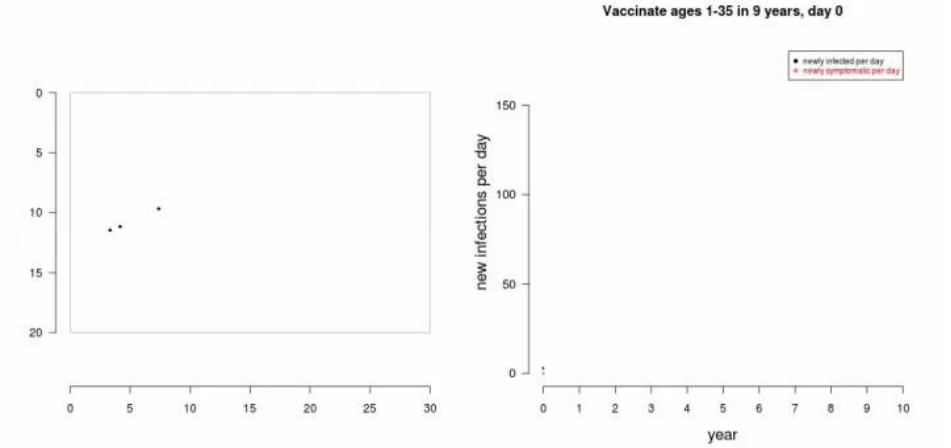


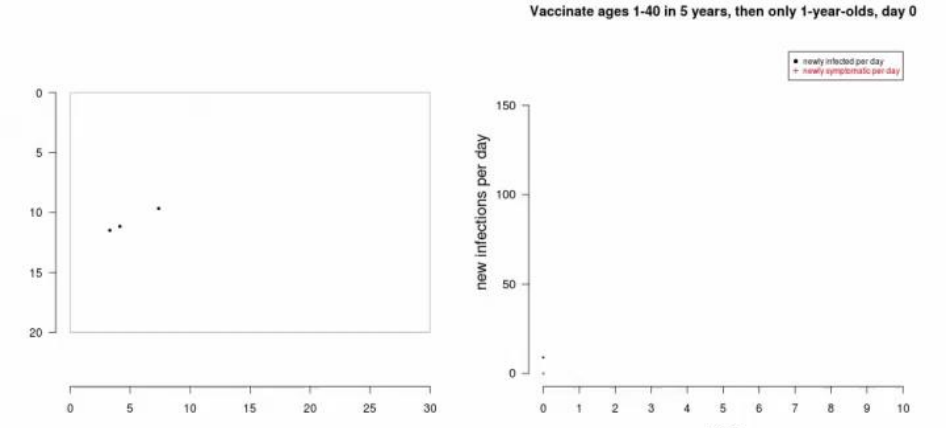


Dengue Vaccines in Thailand

Agent-based, RF



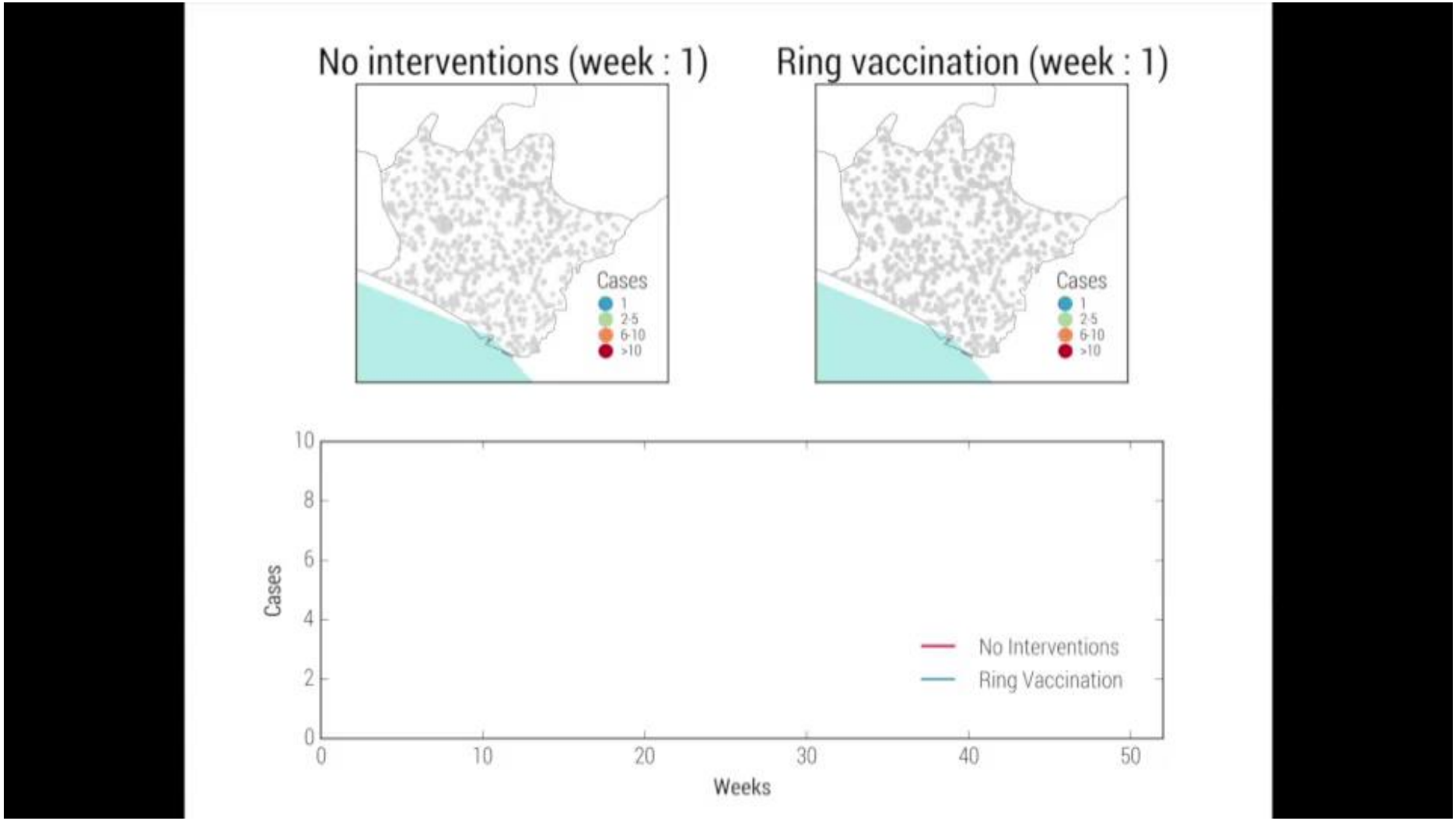




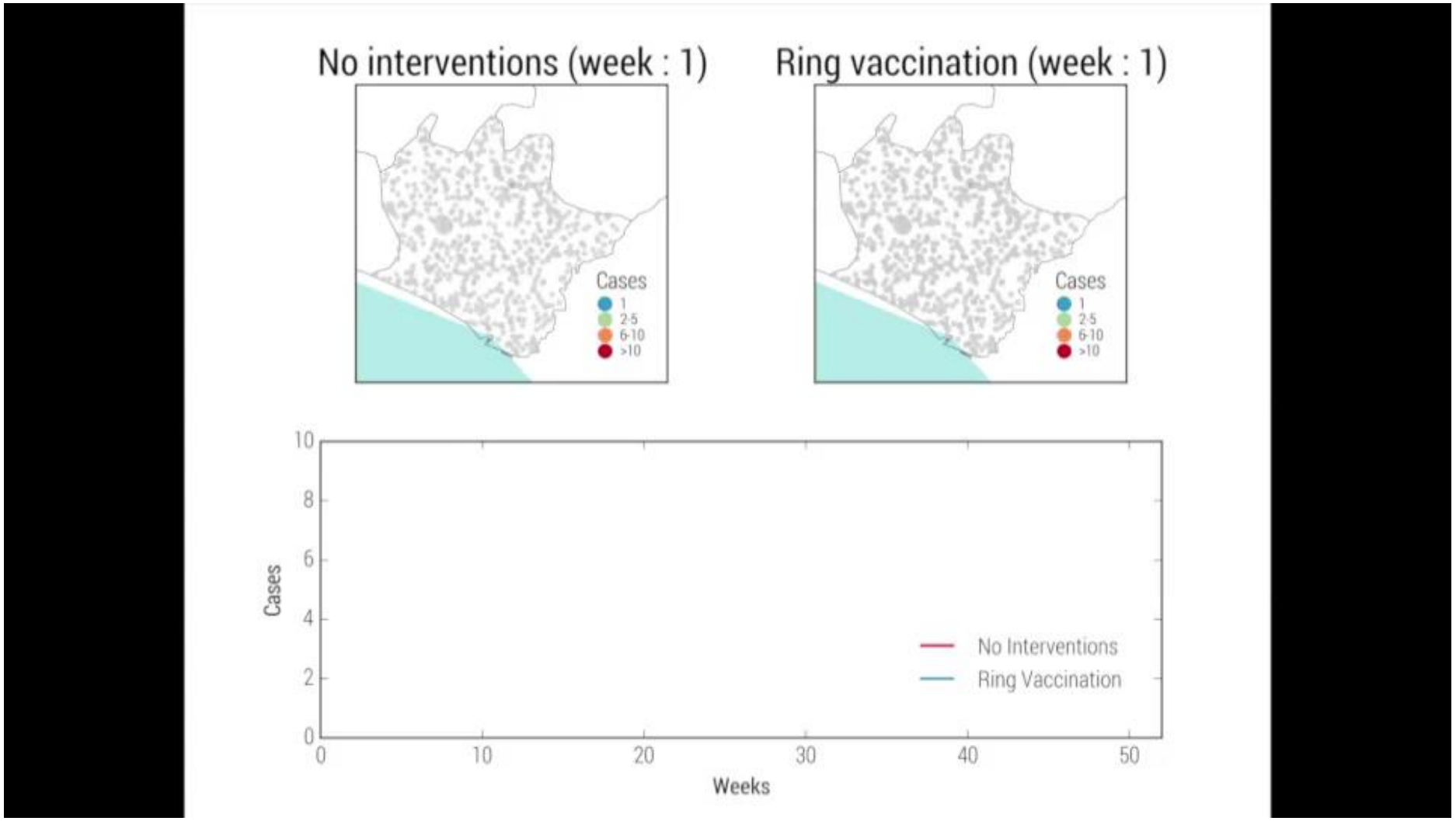
Ebola vaccine trials

- Phase III Ebola ring vaccination efficacy trial in Guinea – VSV vaccine estimated to have 100% efficacy.
- Stochastic transmission models have been used to help estimate vaccine efficacy and effectiveness
- Ring vaccination is used to eliminate Ebola in human populations, e.g., smallpox eradication

Ring vaccination contained



Ring vaccination not contained



To lecture 1

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L1, Introduction to stochastic epidemic models

Tom Britton

July, 2018

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Stochastic models

Mathematical models describes some feature in a *simplified way*

The discrepancy between model and reality may be contained in "random part" in model

Very important in small populations

Stochastic models enable uncertainty estimates (i.e. standard errors) when estimating parameters

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Background

We want to model the spread of transmittable disease in a community of individuals

At a given time-point an individual may be *Susceptible*, infected but not yet infectious (*Latent* or *Exposed*), *Infectious*, or recovered and immune (*Removed*)

Different class of epidemic models: SIR, SEIR, SIS, SIRS, ...

Main focus: SIR (childhood diseases, STDs, influenza, ...)

Short term outbreak vs endemic situation

Simplification for short term: fixed population, no waning immunity

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Notation

Some notation to be used

- $n = \#$ individuals ($n(t)$ if varying over time)
- $S(t) = \#$ "susceptibles" (susceptible individuals) at time t
- $I(t) = \#$ "infectives" (infectious individuals) at time t
- $R(t) = \#$ "removeds" (removed individuals) at time t
- $T =$ the time when the epidemic stops
- Z $(= R(T) - 1) = \#$ infected during the epidemic (excluding index case). Possible values: 0,1,...,$n - 1$.

We start with the simplest situation: all individuals are "identical" (with respect to disease spreading) and all pairs of individuals have contact at equal rates.

Homogeneous community that mixes uniformly

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The Reed-Frost stochastic epidemic model

Short term outbreak (fixed community), homogeneous community, uniform mixing

An epidemic model (Reed-Frost, 1928)

- Assume 1 index case (externally infected) the rest $n-1$ susceptible
- Anyone who gets infected infects other susceptibles independently with prob p and then recovers
- A recovered individual plays no further role in epidemic

The index case infects a random number ($\text{Bin}(n-1,p)$) of individuals, they in turn infect an additional random number, and so on. Once no new individuals are infected the epidemic stops

Think in "generations"

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Exercise 1

Suppose $n = 3$ (one index case and 2 susceptibles) and $p = 0.2$

Possible values for Z: 0,1,2.

$P(Z = 0)$? For this to happen the index can't infect anyone

$P(Z = 1)$? For this to happen the index must infect EXACTLY one AND this individual cannot infect anyone further

$P(Z = 2)$? Either the index infects exactly one AND this individual infects the last one, OR the index infects both

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Exercise 1

Suppose $n = 3$ (one index case and 2 susceptibles) and $p = 0.2$

Possible values for Z: 0,1,2.

$P(Z = 0)$? For this to happen the index can't infect anyone

$P(Z = 1)$? For this to happen the index must infect EXACTLY one AND this individual cannot infect anyone further

$P(Z = 2)$? Either the index infects exactly one AND this individual infects the last one, OR the index infects both

$P(Z = 0) = (1 - p)^2 = 0.64$
$P(Z = 1) = \binom{2}{1} p(1 - p) \times (1 - p) = 0.256$
$P(Z = 2) = \binom{2}{1} p(1 - p) \times p + p^2 = 0.104$
or ... $P(Z = 2) = 1 - P(Z = 0) - P(Z = 1)$

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What about larger communities?

General n, think in "generations"

Epidemic chains: $i \to 3 \to 2 \to 0$: the index infects 3, they infect 2 and these infect no further and the epidemic stops

$$P(Z = 0) = P(i \to 0) = (1-p)^{n-1}$$

$$P(Z = 1) = P(i \to 1 \to 0) = \binom{n-1}{1} p^1 (1-p)^{n-2} \times (1-p)^{n-2}$$

$$P(Z = 2) = P(i \to 2 \to 0) + P(i \to 1 \to 1 \to 0) = \ldots$$

$$P(Z = 3) = P(i \to 3 \to 0) + P(i \to 2 \to 1 \to 0) + P(i \to 1 \to 2 \to 0) + P(i \to 1 \to 1 \to 1 \to 0) = \ldots$$

$P_n(Z = z)$ gets very complicated when $n \geq 10$ and $z \geq 5$.

Underlying reason for the complication: individuals' outcome are **dependent**! (As opposed to other deseases)

What to do then?

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Approximations when n large

When n large then often p (=per individual transmission probability) is small.

Expected number of infectious contacts: $(n-1)p \approx np =: R_0$

R_0 = basic reproduction number

Next page: Histogram of final outbreak sizes from 10 000 simulations in a community of $n = 1000$ individuals (both $R_0 < 1$ and $R_0 > 1$)

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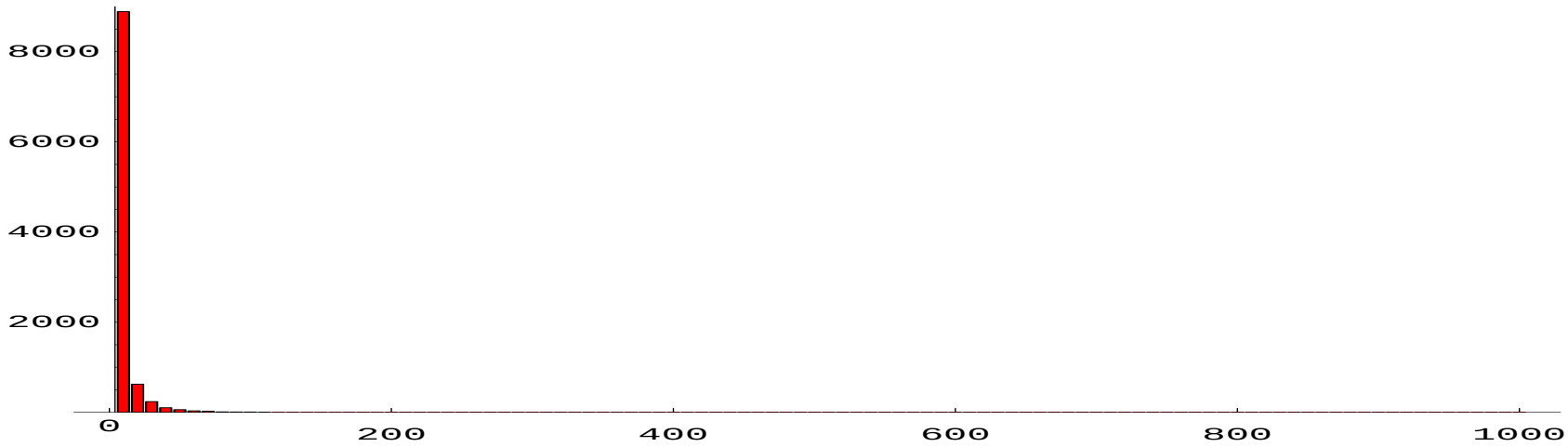
Histogram of final size: $R_0 = 0.8$



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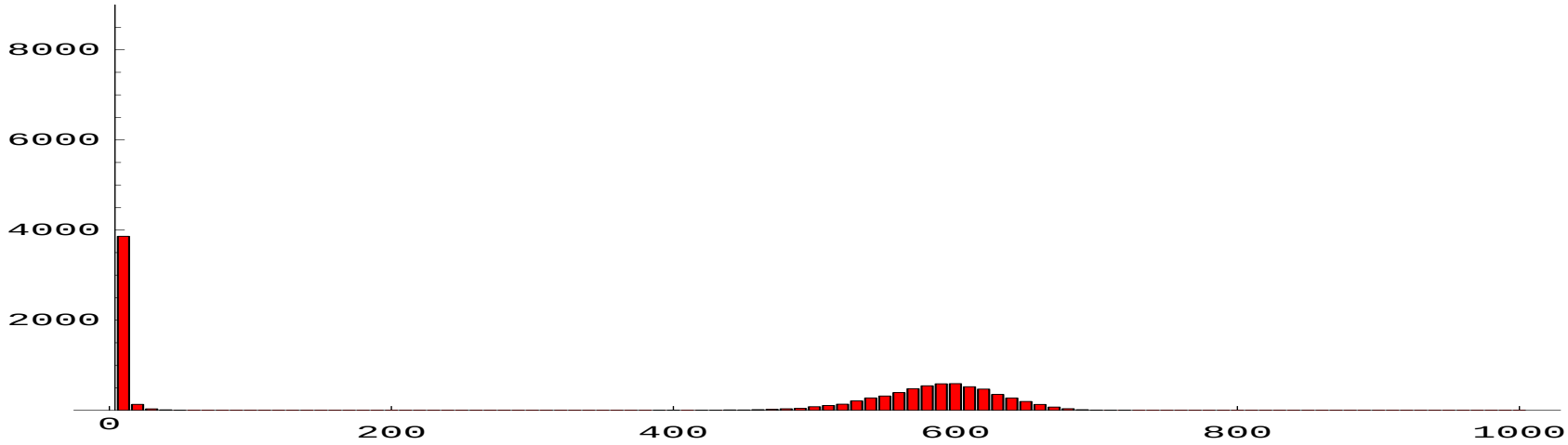
Histogram of final size: $R_0 = 1.5$



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An approximation for the final size

$R_0 = 1$ is "threshold value"

We now derive an equation for τ heuristically (recall $p = R_0/n$)

Assume n large and let $\tau = Z/n =$ final *fraction* infected

$$
\begin{aligned}
1 - \tau &= \text{proportion not infected} && (1)\\
&\approx \text{ probability not get infected} && (2)\\
&= \text{prob to escape inf from all infected} && (3)\\
&= (1-p)^Z && (4)\\
&= \left(1 - \frac{R_0}{n}\right)^{n\tau} && (5)\\
&\approx e^{-R_0\tau} \qquad \text{(using that } (1-x/n)^n \approx e^{-x}\text{)} && (6)
\end{aligned}
$$

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Approximation for final size

τ should hence (approximately) solve

$$1 - \tau = e^{-R_0 \tau}$$

There are two solutions: $\tau = 0$ and (if $R_0 > 1$): $\tau = \tau^\star > 0$.

Exercise 2 Compute τ^* numerically when $R_0 = 1.5$, 3 and 6.

On next page is a plot of final size as function of R_0

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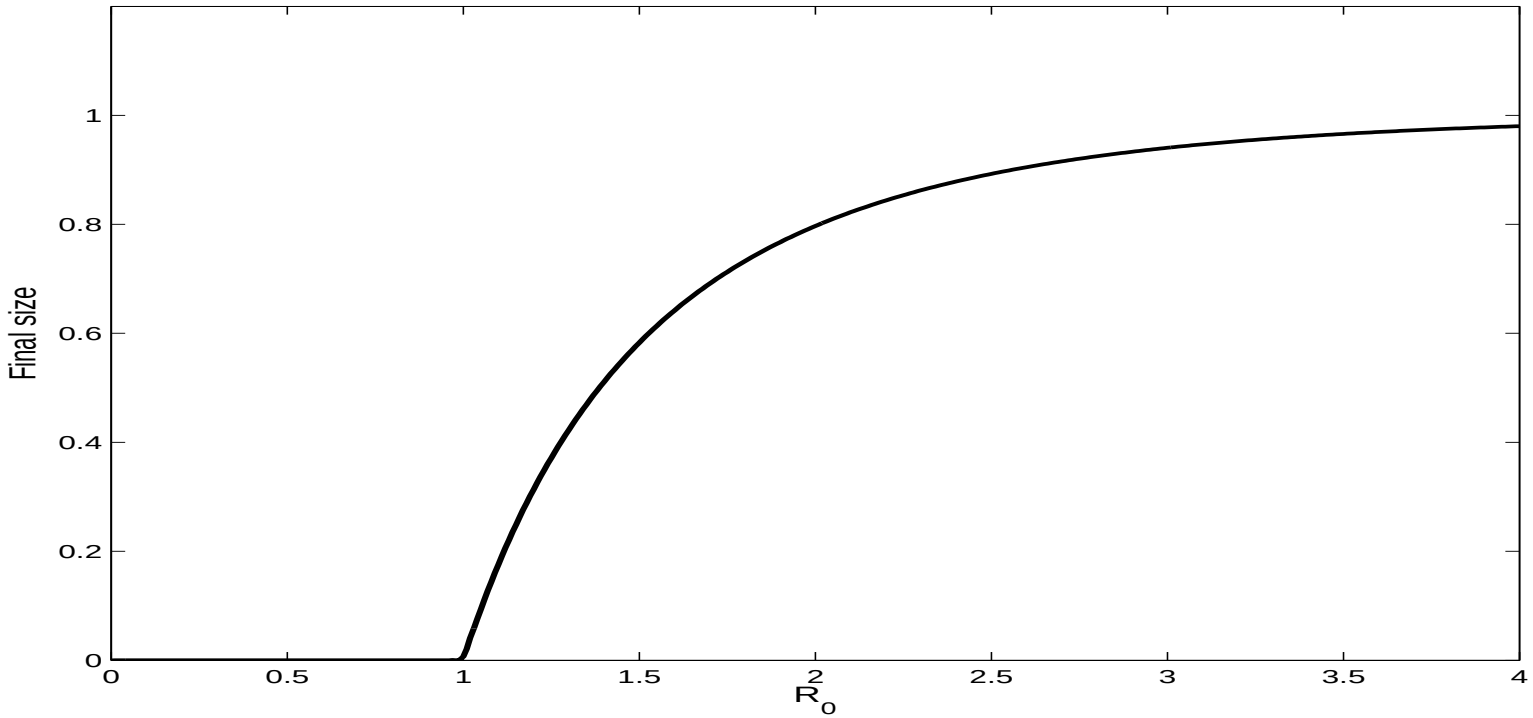
Plot of final outbreak size as function of R_0



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Approximation, cont'd

Seen from simulations: strong dichotomy: minor outbreak – major outbreak

$P(\text{major outbreak}) = 1 - P(\text{minor outbreak})$ can be determined using *branching process* theory

For Reed-Frost model: $P(\text{major outbreak}) = \tau^*$!!!

Normal distribution for major outbreak:

$$\sqrt{n}\left(\frac{Z}{n} - \tau^*\right) \approx Normal(0, \sigma^2)$$

σ^2 depends on model parameters

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What about epidemic over time?

A related stochastic epidemic model (the "General stochastic epidemic") can be defined in continuous time:

- During the infectious period an individual has "infectious contacts" randomly in time at the average rate β, each time individual is chosen randomly
- A susceptible who receives an infectious contact becomes infectious and remains so for a exponentially distributed time with mean ν (other contacts have no effect)

$R_0 =$ expected number of infectious contacts $= \beta\nu$

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What about epidemic over time?

When n is large the process $(S(t)/n, I(t)/n)$ is close to deterministic limit $(s(t), i(t))$ which solves differential system

$$s'(t) = -\beta s(t) i(t) \tag{7}$$

$$i'(t) = \beta s(t) i(t) - \frac{1}{\nu} i(t) \tag{8}$$

$$r'(t) = \frac{1}{\nu} i(t) \tag{9}$$

Next page: plot of $I(t)/n$ for one (typical) simulated epidemic and deterministic limit $i(t)$, for a few different n

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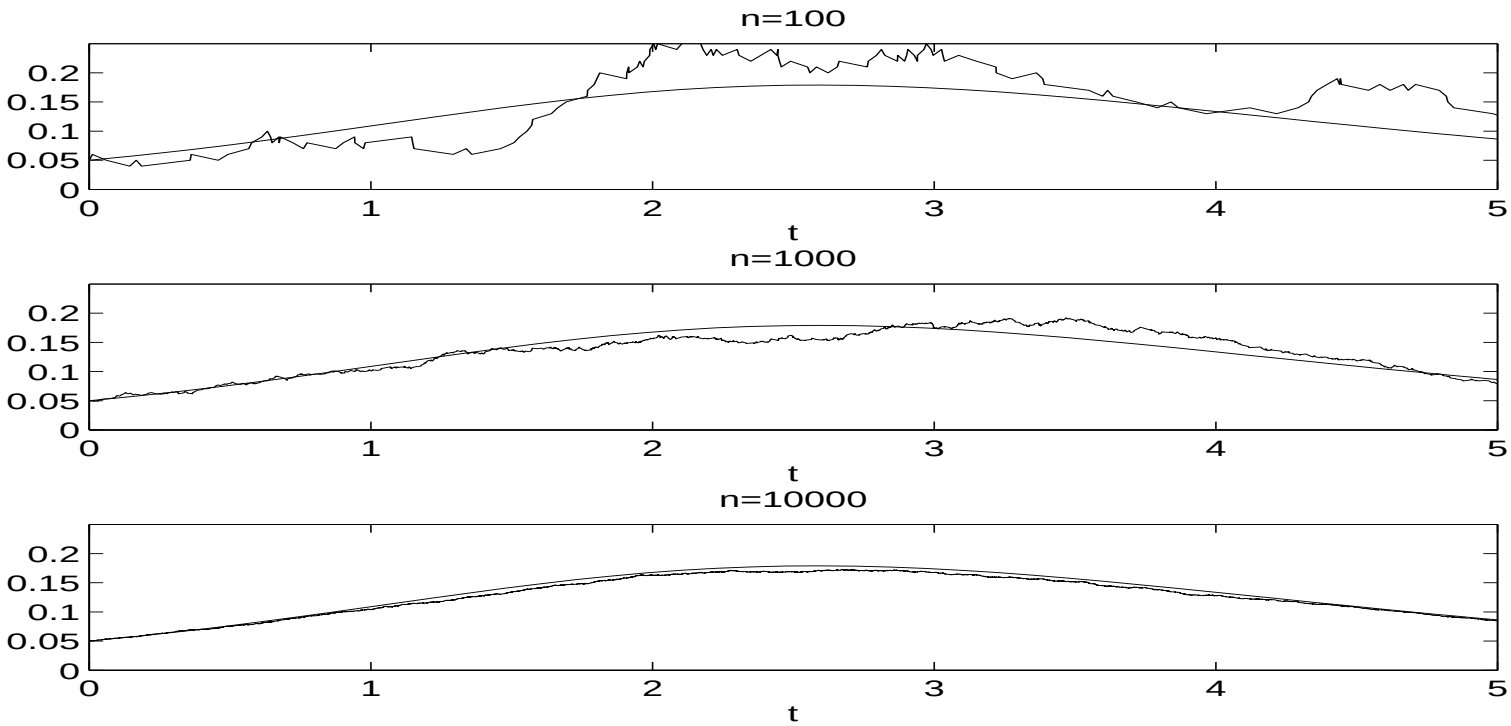
Plots of simulated stochastic epidemic and deterministic curve



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Summary

Exact distribution of Z (final size) is complicated

When n large two things may happen:

- either very few get infected ($Z/n \approx 0$), or
- a close to deterministic fraction $Z/n \approx \tau^*$ get infected

$R_0 = np = \beta\nu =$ expected number of infections by one individual during his/her infectious period

Second scenario only possible if $R_0 > 1$

$P(\text{major outbreak}) = \tau^*$ for Reed-Frost model

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Extensions

Random infectious force (e.g. length of infectious period): affects P(outbreak) but hardly final size τ

Latent period: big effect on timing of epidemic peak and duration of epidemic but no effect on final size (unless control measures are initiated)

More than one index case: big effect on P(outbreak) but negligible effect on final size τ in large outbreak

Exercise 3. If infectious period deterministic then P(major outbreak)$= \tau^*$. If infectious period is exponentially distributed then P(major outbreak)$= 1 - 1/R_0$. Compute the latter probability for $R_0 = 1.5$, 3 and 6 and compare with Reed-Frost model.

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Extensions

Initial fraction of immunes. If there is a fraction r of initially immunes the same methodology can be used. The difference is that R_0 is replaced by $R_0(1-r)$ since initially only the fraction $(1-r)$ is susceptible. The final fraction infected *among the initally susceptible* then solves

$$1 - \tau = e^{-R_0(1-r)\tau}$$

Major outbreak possible only if $R_0(1-r) > 1$

Exercise 4. Compute τ^* if initially only 50% were susceptible (and 50% were immune), for $R_0 = 1.5$, 3 and 6.

Exercise 5. What are the *overall* fractions infected during outbreak in later case?