Essentials of Aggregate System Dynamics Infectious Disease Models

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Mathematical Models Link Together Diverse Factors

Typical Factors Included

- Infection
  - Mixing & Transmission
  - Development & loss of immunity – both individual and collective
  - Natural history (often multi-stage progression)
  - Recovery
- Birth & Migration
- Aging & Mortality
- Intervention impact

Sometimes Included

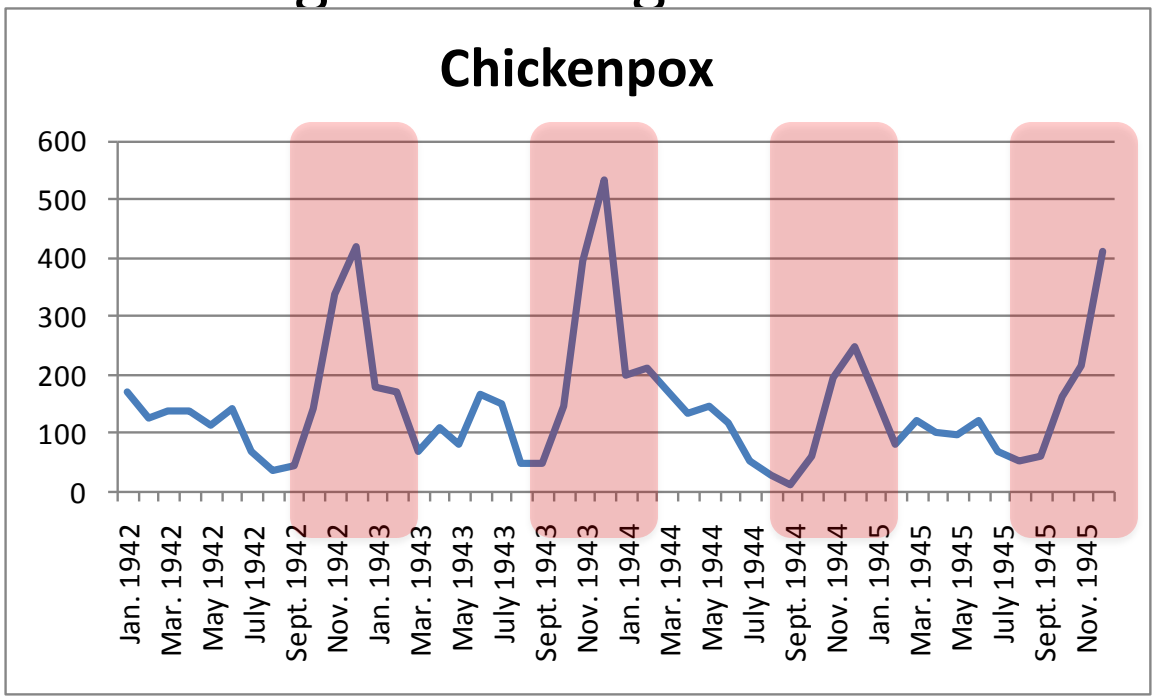
- Preferential mixing
- Variability in contacts
- Strain competition & cross-immunity
- Quality of life change
- Health services interaction
- Local perception
- Changes in behavior, attitude
- Immune response

Emergent Characteristics of Infectious Diseases Models

- Instability
- Nonlinearity
- Tipping points
- Oscillations
- Multiple fixed points/equilibria
  - “Endemic” equilibrium
  - Disease free equilibrium

Instability

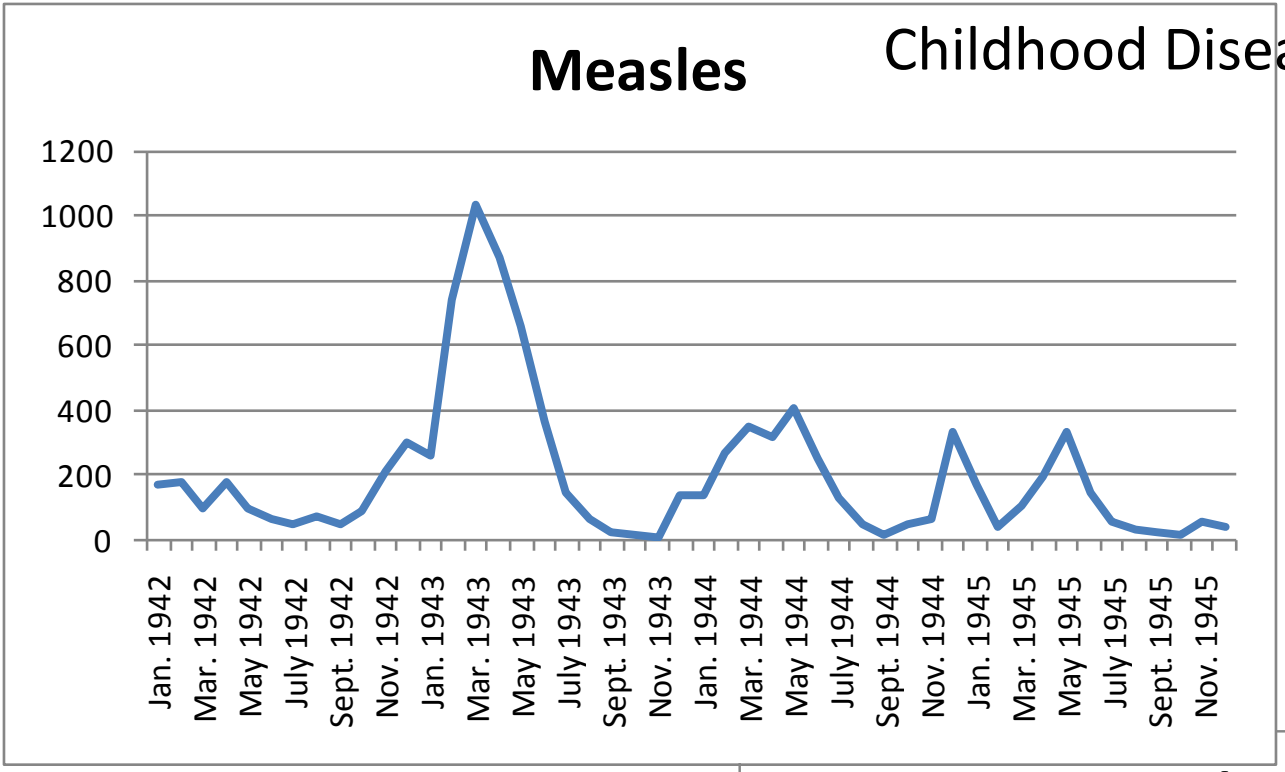
- Slight perturbation (e.g. arrival of infectious person on a plane) can cause big change in results
  - Contrast with “goal seeking” behaviour

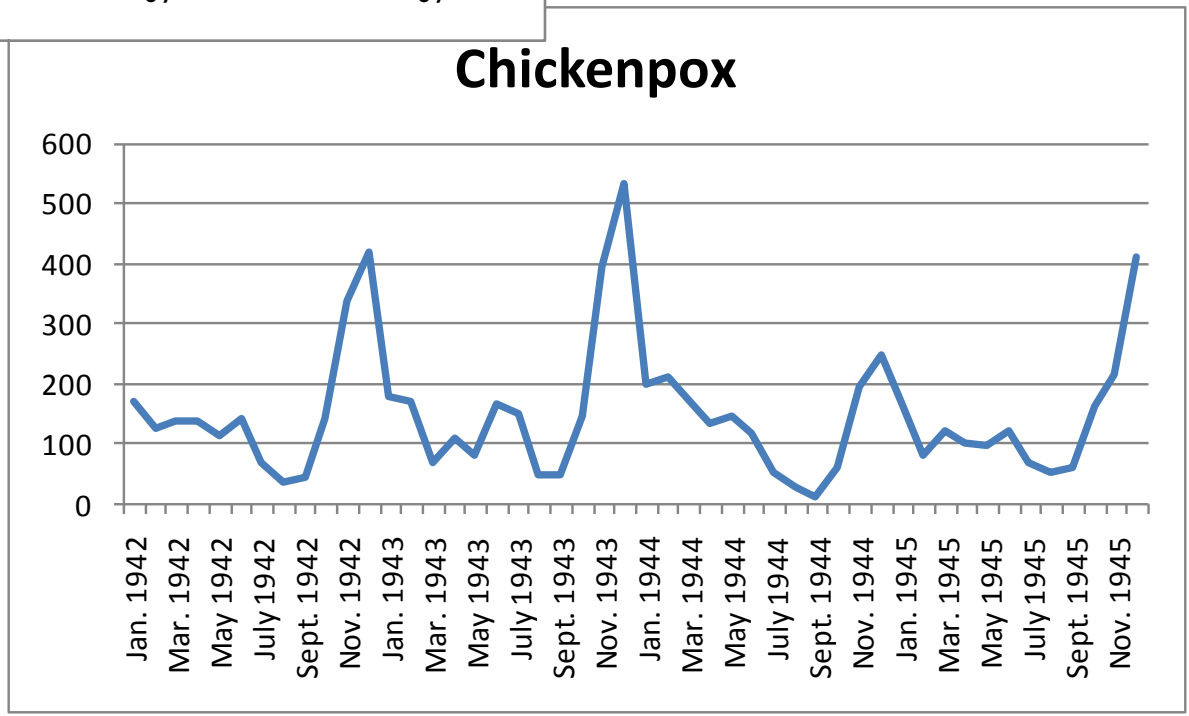


Oscillations & Delays

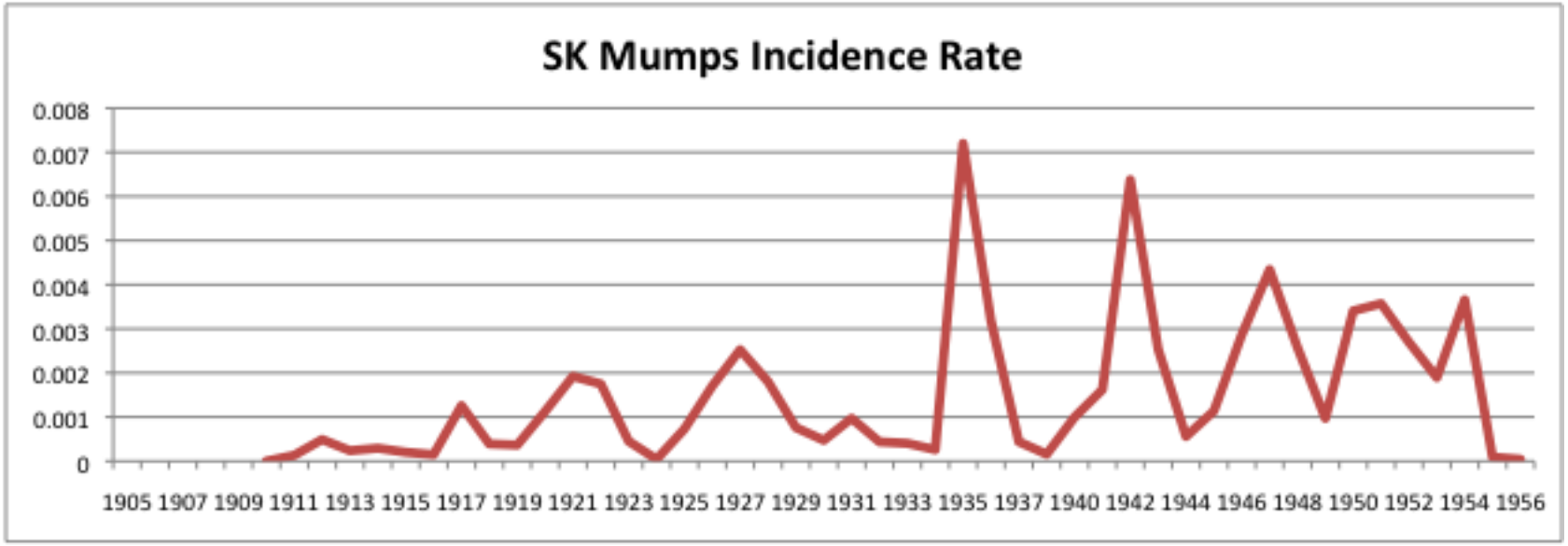
- The oscillations reflect negative feedback loops with delays
- These delays reflect “stock and flow” considerations and specific thresholds dictating whether net flow is positive or negative
  - Stock & Flow: Stock continues to deplete as long as outflow exceeds inflow, rise as inflow>outflow
    - The stock may stay reasonably high long after inflow is low!
  - Key threshold R*: When # of individuals being infected by a single infective = 1
    - This is the threshold at which outflows=inflows

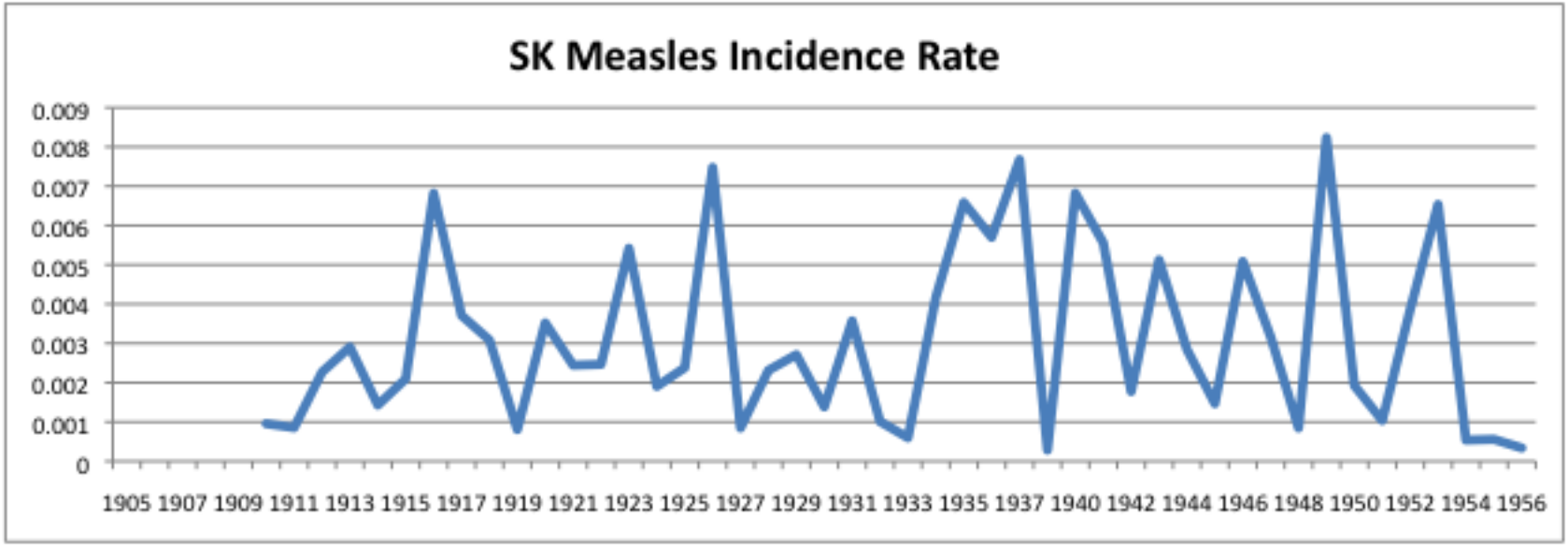
Childhood Diseases in Saskatchewan

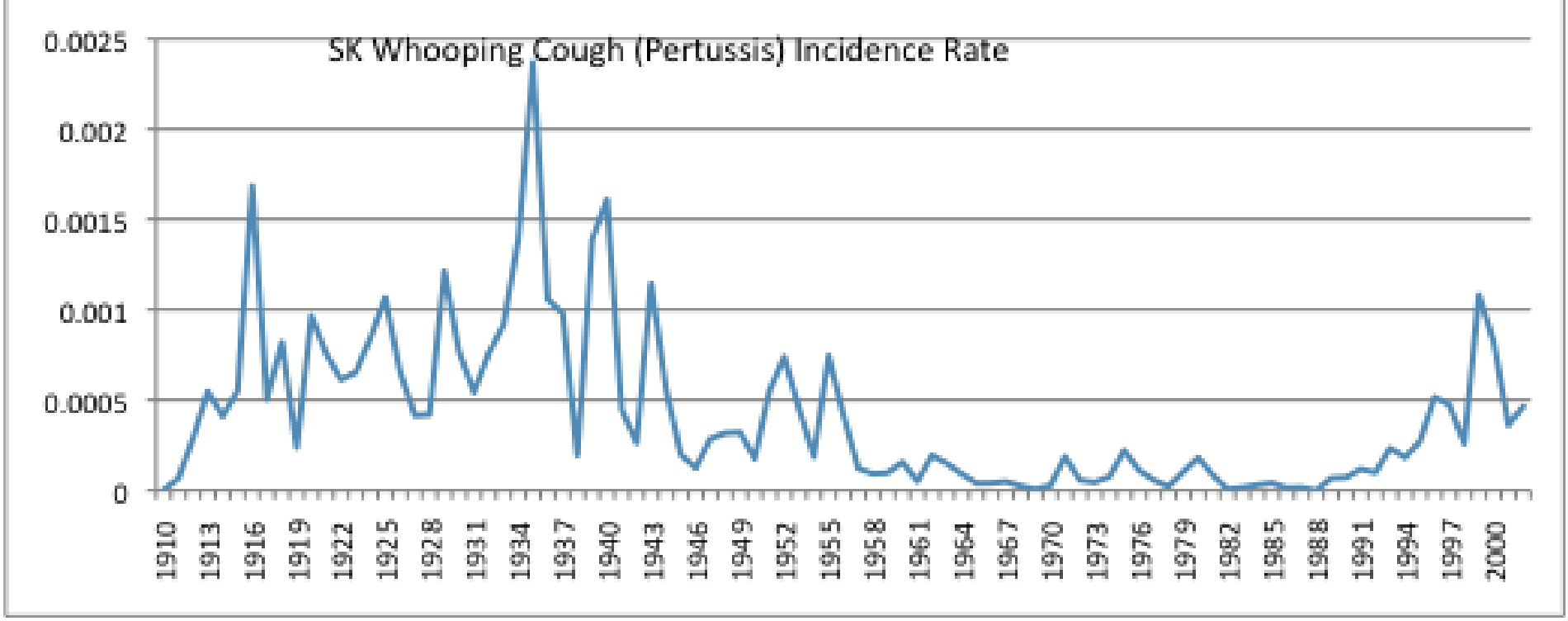




Saskatchewan Childhood Diseases






SK Whooping Cough (Pertussis) Incidence Rate
0.0025
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0.0015
0.001
0.0005
0
1910
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1922
1925
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1931
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1937
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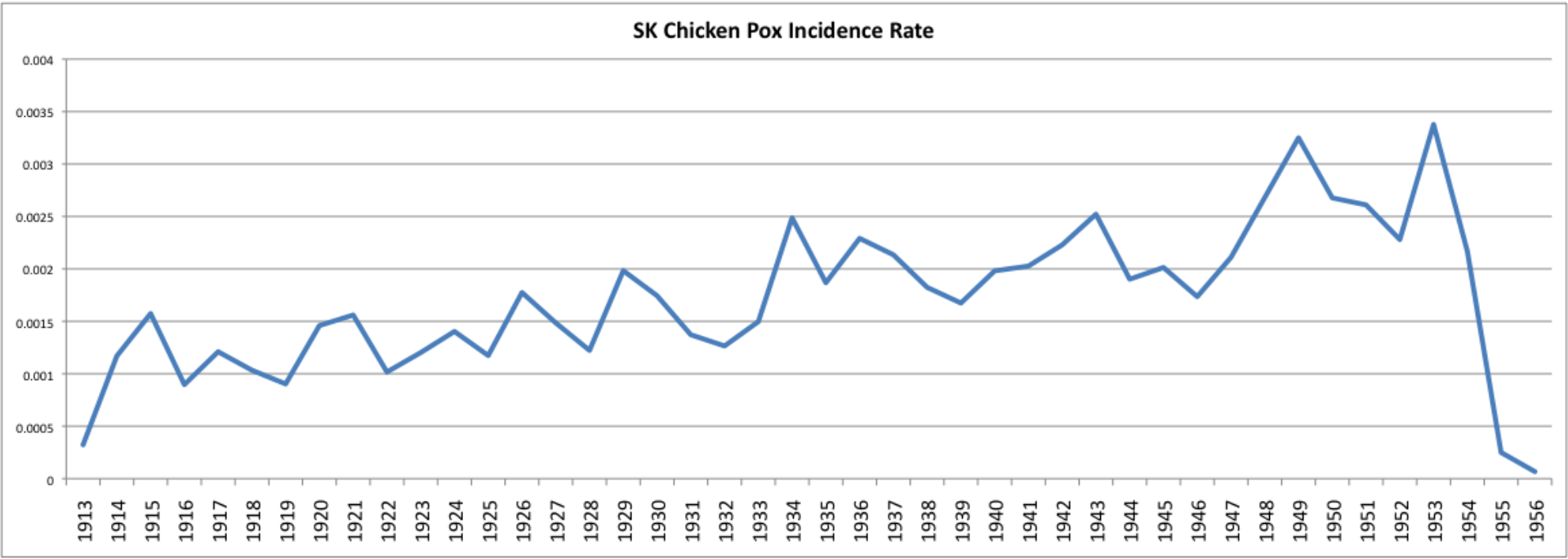
SK Chicken Pox Incidence Rate
0.004
0.0035
0.003
0.0025
0.002
0.0015
0.001
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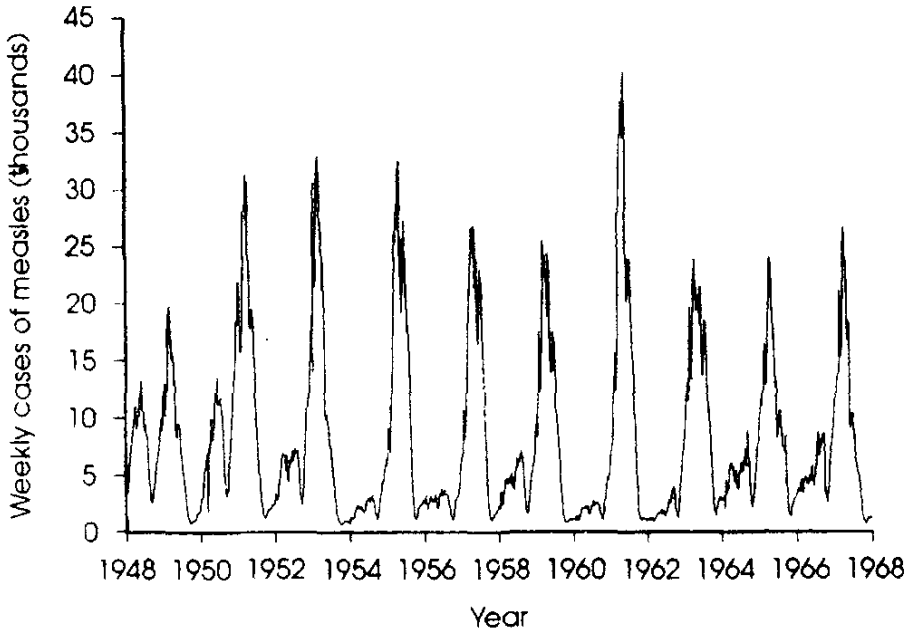


Fig. 6.3. Weekly case notifications of measles in England and Wales for the period 1948 to 1968 prior to the introduction of mass vaccination.

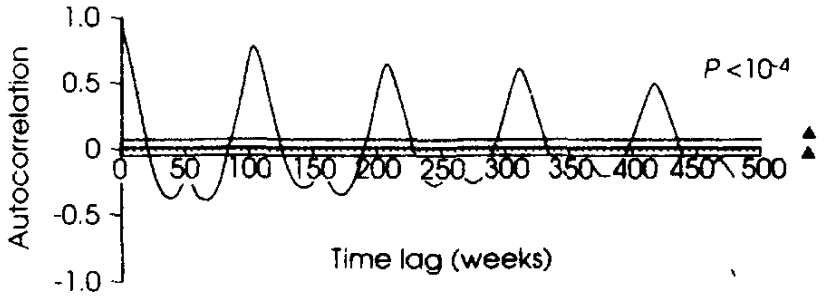


Fig. 6.4. Correlogram of weekly measles reports for England and Wales, 1948–68. Here, and in subsequent correlograms, the solid triangles indicate the 95 per cent confidence limits for the zero correlogram from a completely random series, and p is the probability that such data could generate the observed correlogram (see Appendix in Anderson *et al.* (1984)).

Nonlinearity (in state variables)

- Effect of multiple policies non-additive
- Doubling investment does not yield doubling of results
- Leads to
  - Multiple basins of tracking (equilibrium)

Multiple Equilibria & Tipping Points

- Separate basins of attraction have qualitatively different behaviour
  - Oscillations
  - Endemic equilibrium
  - Disease-free equilibrium

Equilibria

- Disease free
  - No infectives in population
  - Entire population is susceptible
- Endemic
  - Steady-state equilibrium produced by spread of illness
  - Assumption is often that children get exposed when young

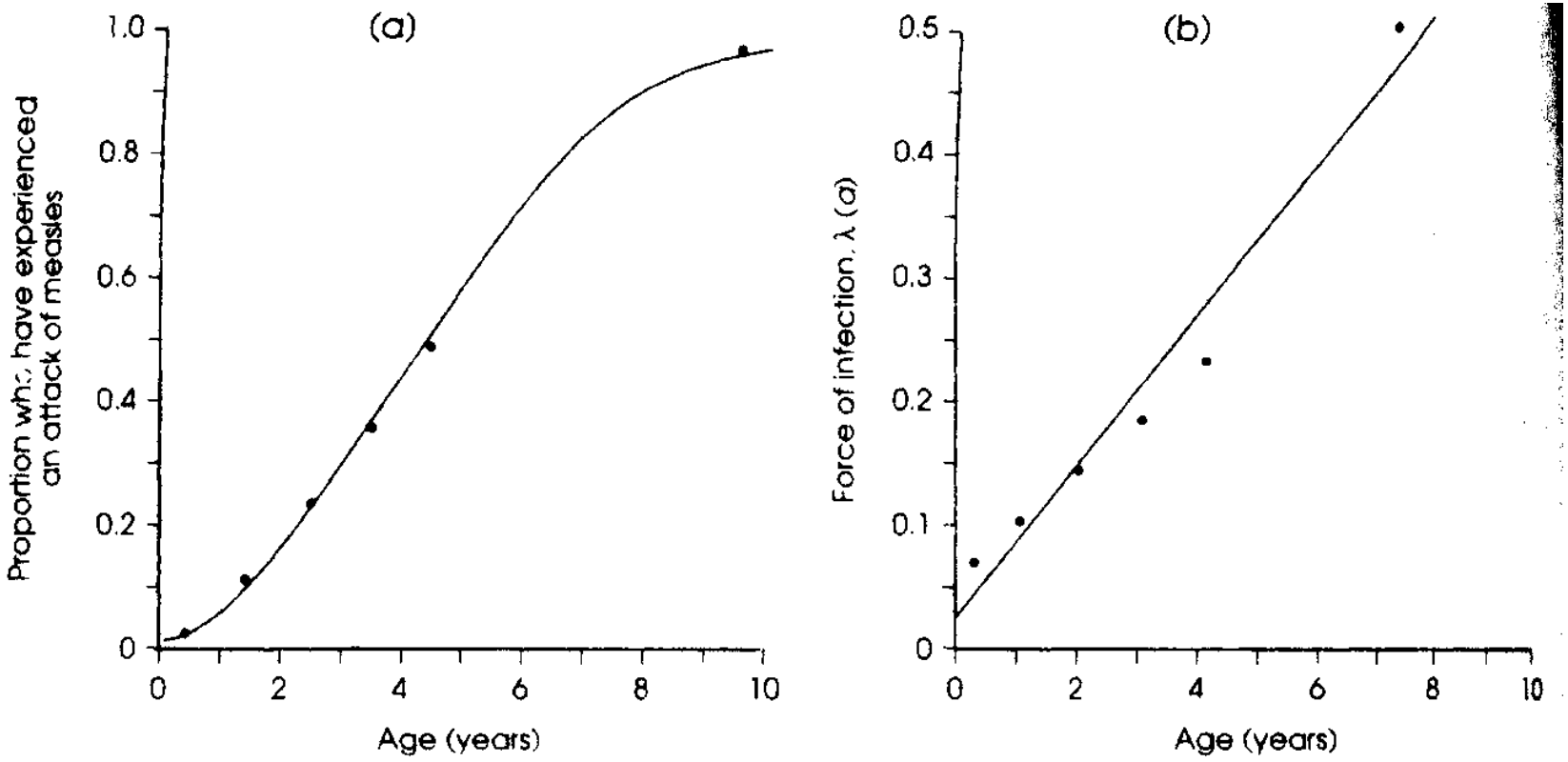
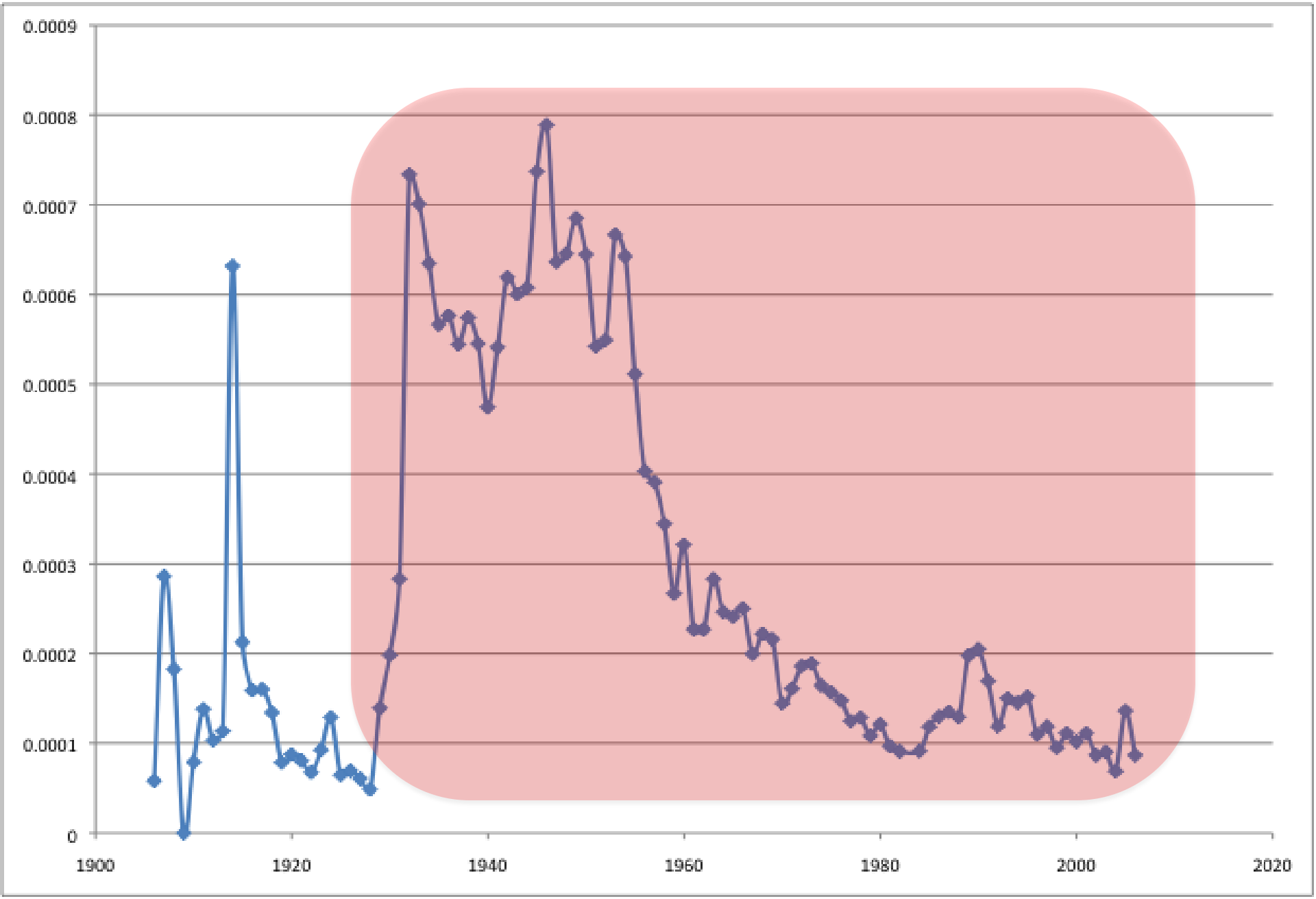


Fig. 5.14. Measles. (a) Proportion of children who had experienced an attack of measles at various ages in England and Wales in 1958 (based on case notification records). Dots, observed values; full curve, predictions of a simple catalytic model with age-dependent rates of infection (see text). (b) The age dependency in the rate or force of infection $\lambda(a)$. Dots, calculated values; full curve, best-fit linear model of the form $\lambda(a) = m + va$, where $m = 0.0178$ and $v = 0.063$ ($r^2 = 0.96$).

TB In SK


0.0009
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0.0007
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0.0002
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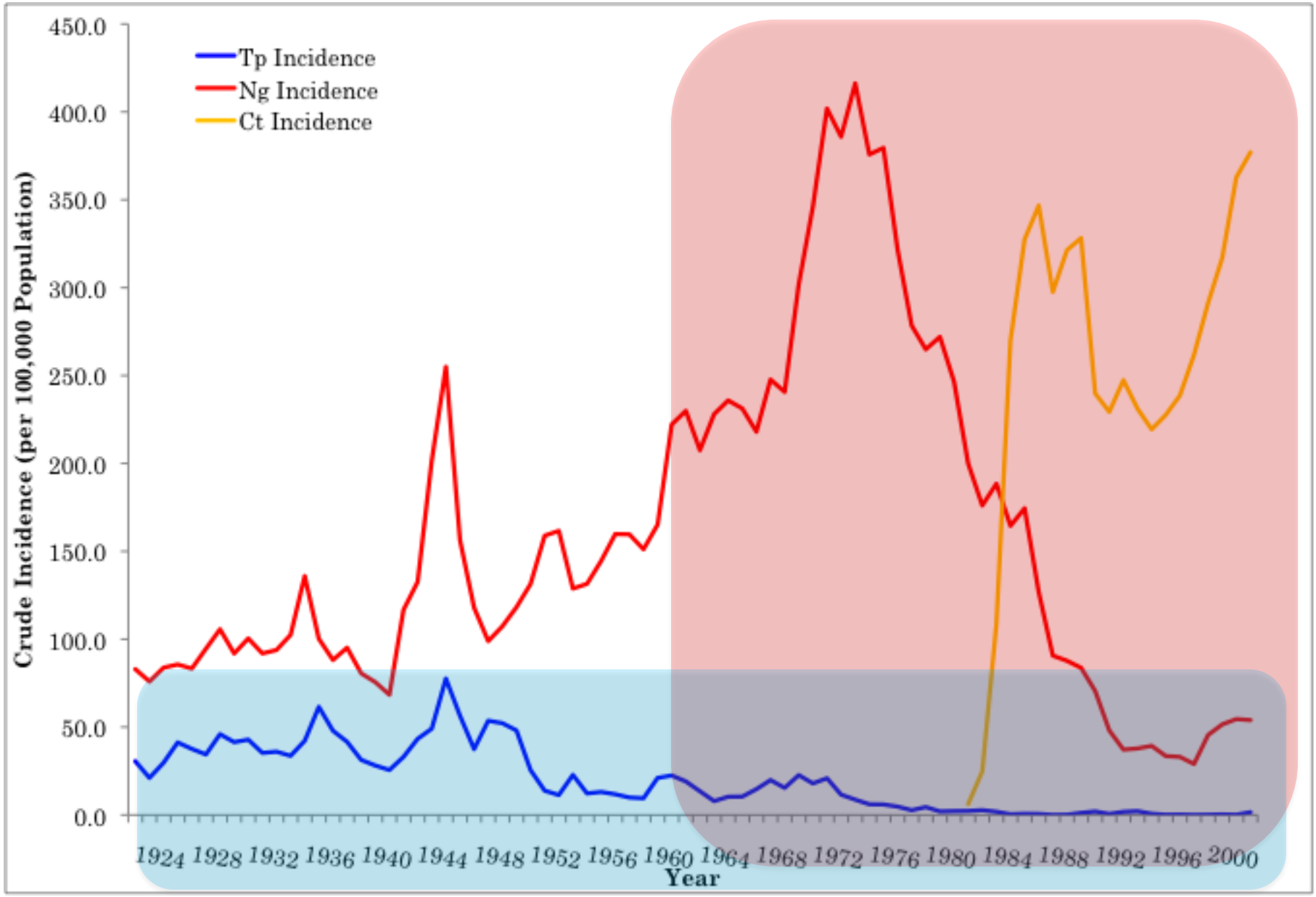
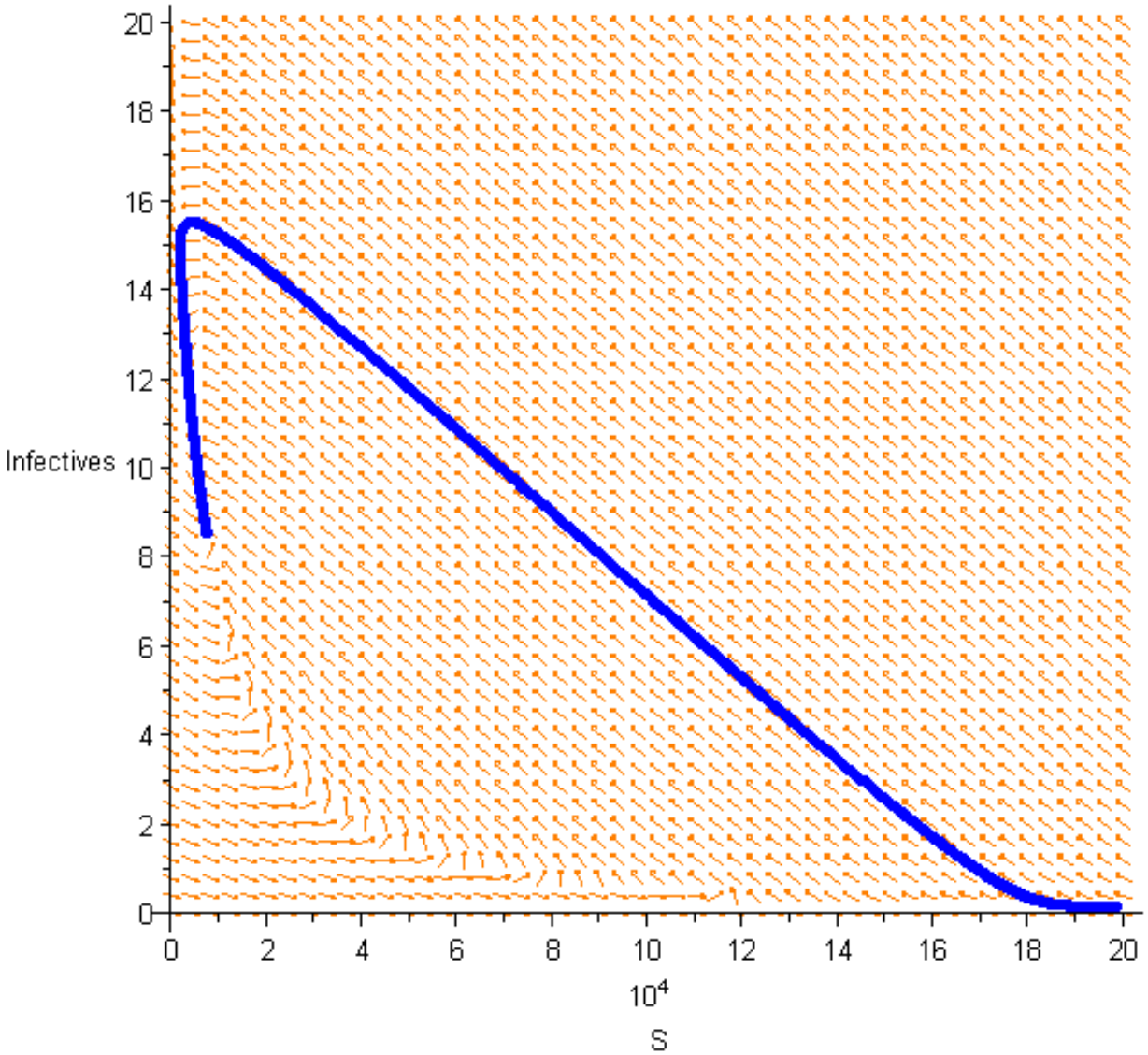
0
1900
1920
1940
1960
1980
2000
2020

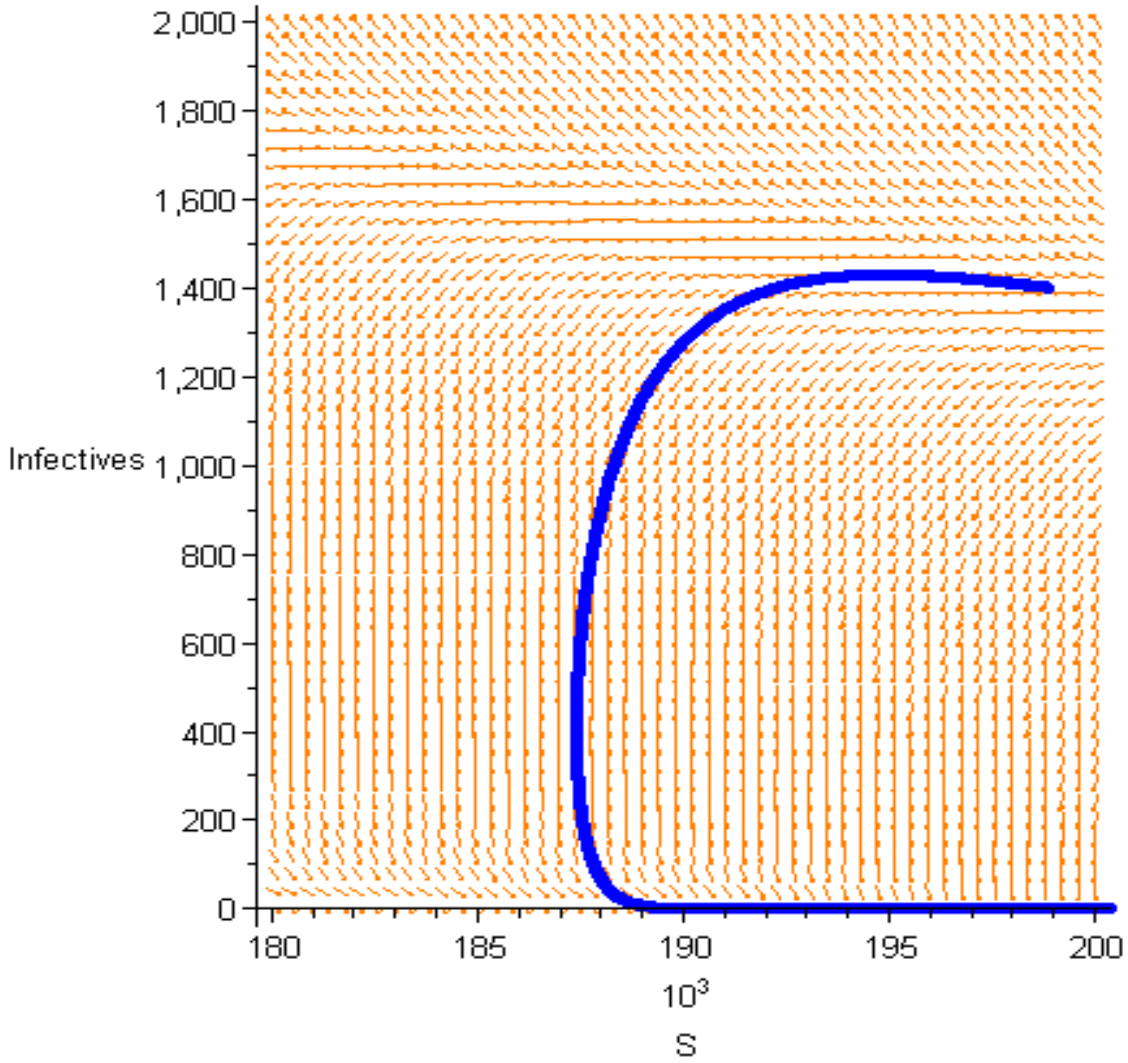
Example: STIs



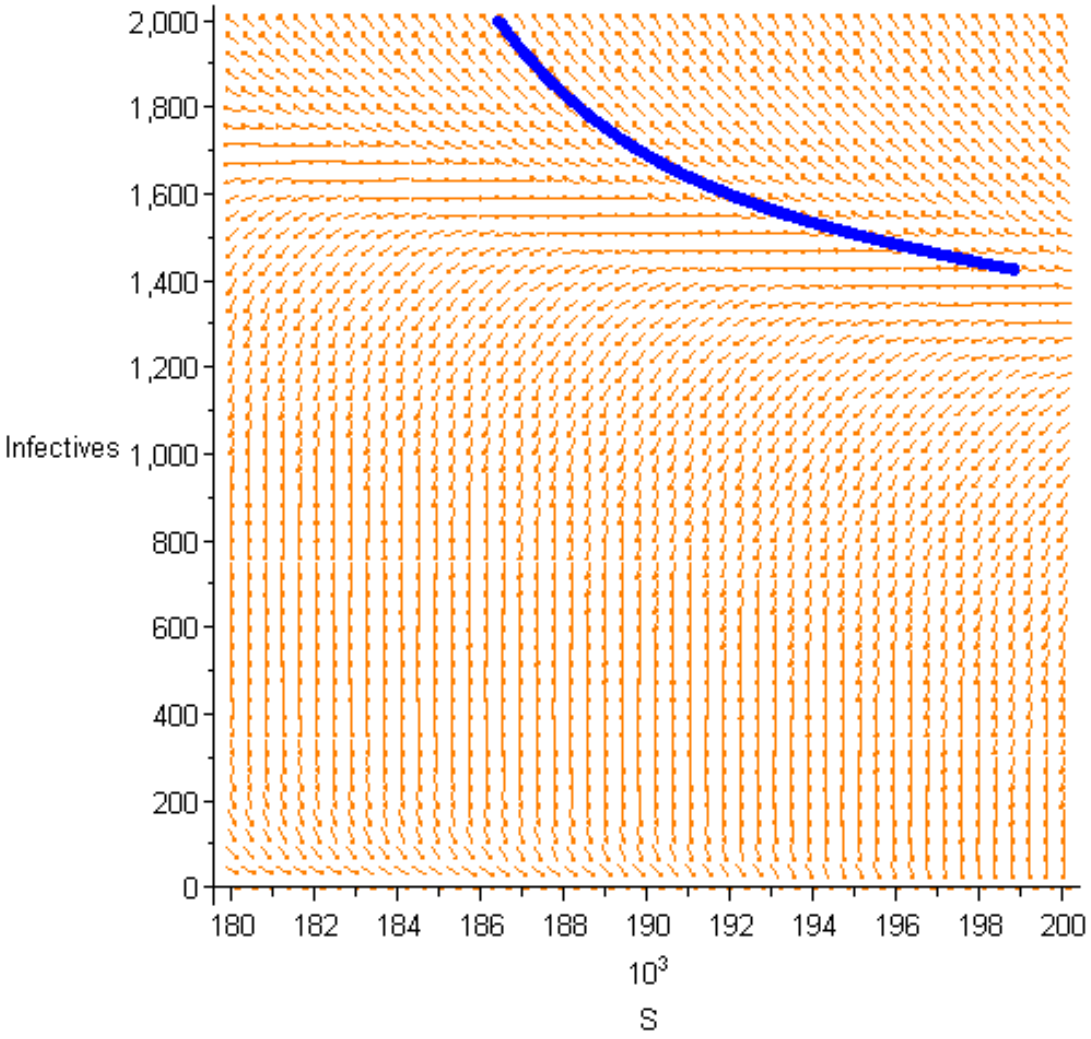
$R_0 < 1$: 200 HC Workers, $I_0 = 1425$



$R_0 < 1$: 200 HC Workers, $I_0 = 1400$

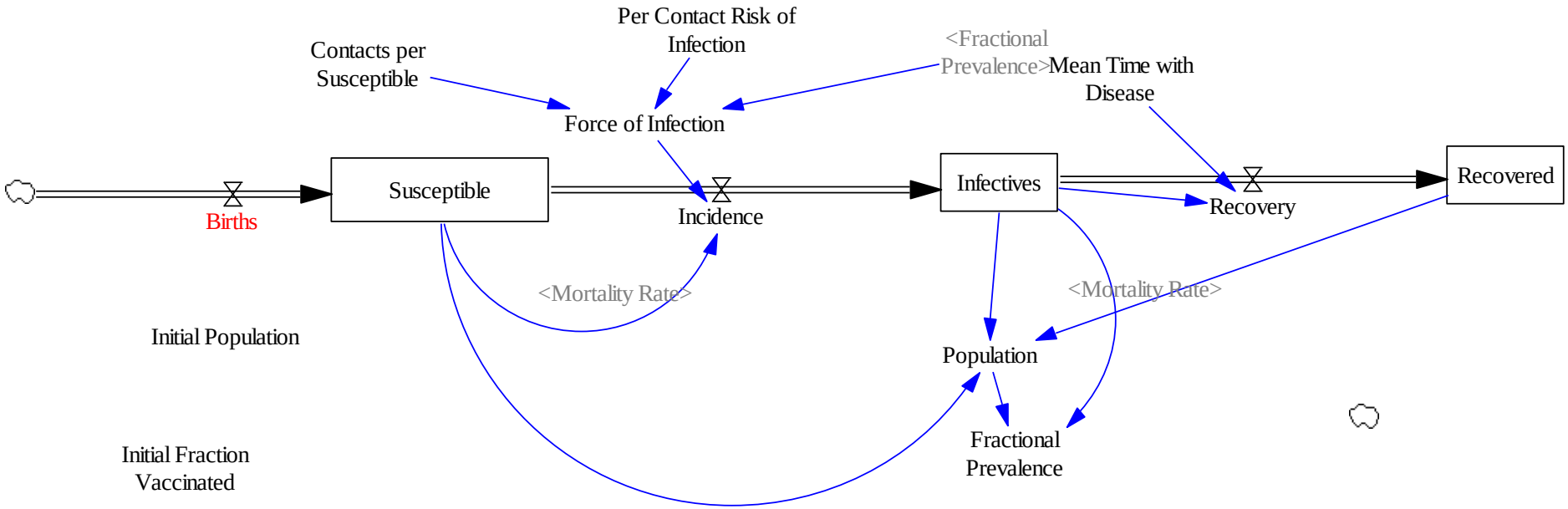


$R_0 < 1$: 200 HC Workers, $I_0 = 1425$



Kendrick-McKermack Model

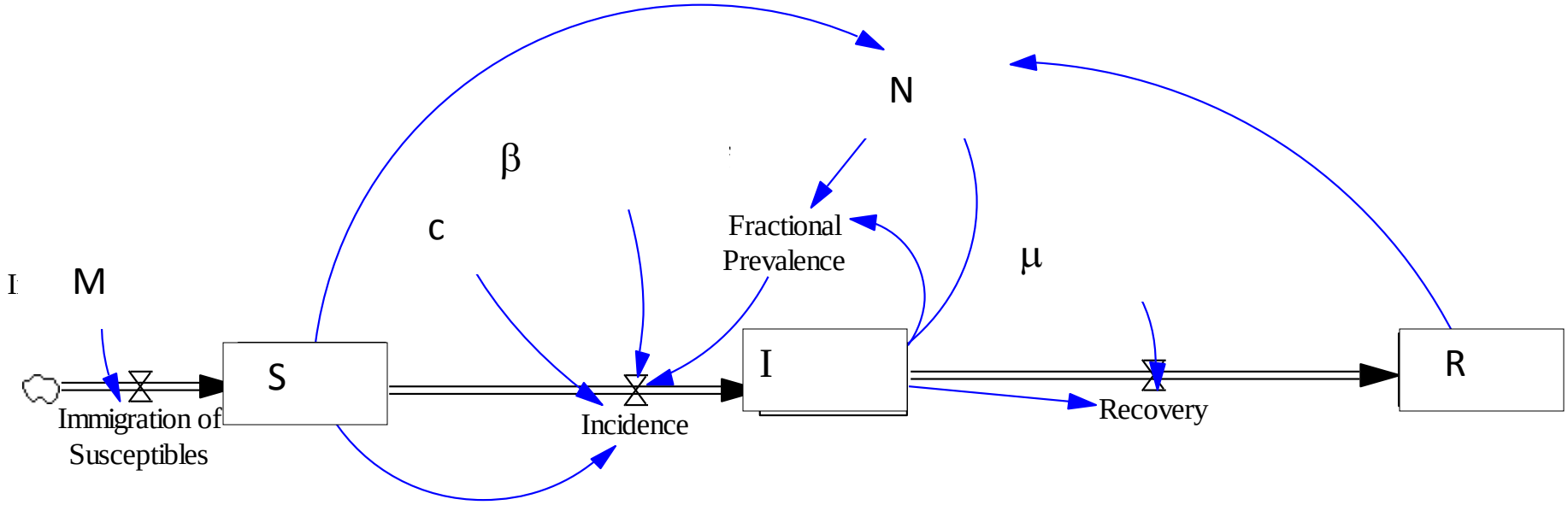
- Partitioning the population into 3 broad categories:
  - Susceptible (S)
  - Infectious (I)
  - Removed (R)


Per Contact Risk of Infection
Contacts per Susceptible
<Fractional Prevalence>
Mean Time with Disease
Force of Infection
Susceptible
Infectives
Recovered
Births
Incidence
Recovery
<Mortality Rate>
<Mortality Rate>
Initial Population
Population
Initial Fraction Vaccinated
Fractional Prevalence

Shorthand for Key Quantities for Infectious Disease Models: Stocks

- *I* (or *Y*): Total number of infectives in population
  - This could be just one stock, or the sum of many stocks in the model (e.g. the sum of separate stocks for asymptomatic infectives and symptomatic infectives)
- N: Total size of population
  - This will typically be the sum of all the stocks of people
- S (or *X*): Number of susceptible individuals

Mathematical Notation



Key Quantities for Infectious Disease Models: Parameters

- Contacts per susceptible per unit time: c
  - e.g. 20 contacts per month
  - This is the number of contacts a given susceptible will have with *anyone*

- Per-infective-with-susceptible-contact transmission probability: β
  - This is the per-contact likelihood that the pathogen will be transmitted from an infective to a susceptible with whom they come into a single contact.

Intuition Behind Common Terms

- I/N: The Fraction of population members (or, by assumption, contacts!) that are infective
  - Important: Simplest models assume that this is also the fraction of a given susceptible's contacts that are infective! Many sophisticated models relax this assumption
- c(I/N): Number of *infectives* that come into contact with a susceptible in a given unit time
- c(I/N)β: "Force of infection": *Likelihood a given susceptible will be infected per unit time*
  - The idea is that if a given susceptible comes into contact with c(I/N) infectives per unit time, and if each such contact gives β likelihood of transmission of infection, then that susceptible has roughly a total likelihood of c(I/N) β of getting infected per unit time (e.g. month)

Key Term: Flow Rate of New Infections

- This is the key form of the equation in many infectious disease models
- Total # of susceptibles infected per unit time

  # of Susceptibles * "Likelihood" a given susceptible will be infected per unit time = S*("*Force of Infection*") =S(c(I/N)β)

  – Note that this is a term that multiplies both S and I !
    - This is much different than the purely linear terms on which we have previously focused
  – "Likelihood" is actually a likelihood density (e.g. can be >1 – indicating that mean time to infection is <1)

Another Useful View of this Flow

- Recall: Total # of susceptibles infected per unit time = # of Susceptibles * "Likelihood" a given susceptible will be infected per unit time = S*("*Force of Infection*") = S(c(I/N)β)
- The above can also be phrased as the following:S(c(I/N)β)=I(c(S/N)β)=I(c*f*β)= # of Infectives * Mean # susceptibles infected per unit time by each infective
- This implies that as # of susceptibles falls=># of susceptibles surrounding each infective falls=>the rate of new infections falls ("Less fuel for the fire" leads to a smaller burning rate

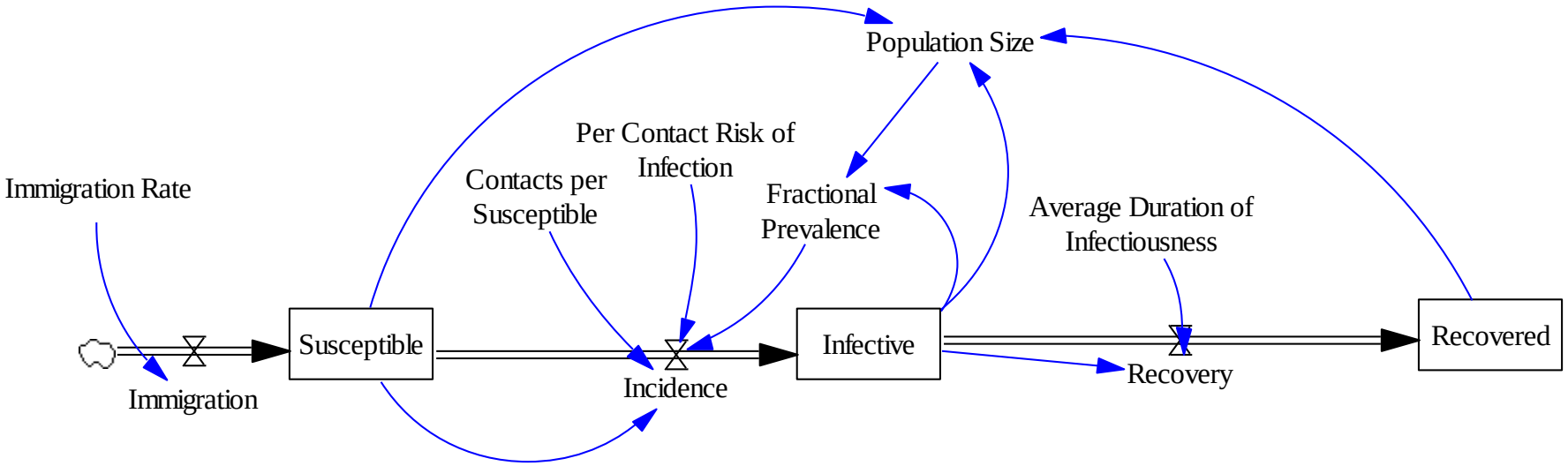
A Critical Throttle on Infection Spread: Fraction Susceptible (*f*)

- The fraction susceptible (here, S/N) is a key quantity limiting the spread of infection in a population
  - Recognizing its importance, we give this name *f* to the fraction of the population that issusceptible

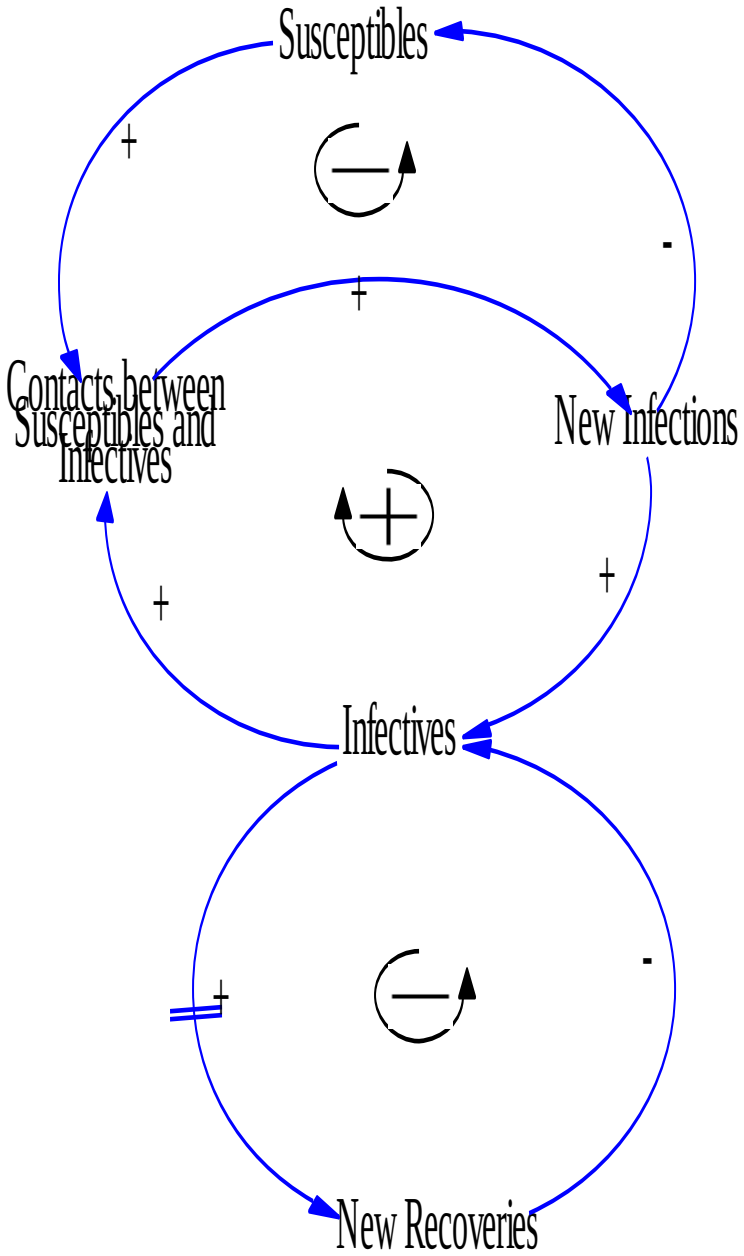
The Importance of Susceptible Fraction

- Recall: Total # of susceptibles infected per unit time = # of Susceptibles * "Likelihood" a given susceptible will be infected per unit time = S*("*Force of Infection*") = S(c(I/N)β)
- The above can also be phrased as the following:S(c(I/N)β)=I(c(S/N)β)=# of Infectives * *Average # susceptibles infected per unit time by each infective*
- This implies that as Fraction of susceptibles falls=>Fraction of susceptibles surrounding each infective falls=>the rate of new infections falls ("Less fuel for the fire" leads to a smaller burning rate)

Basic Model Structure



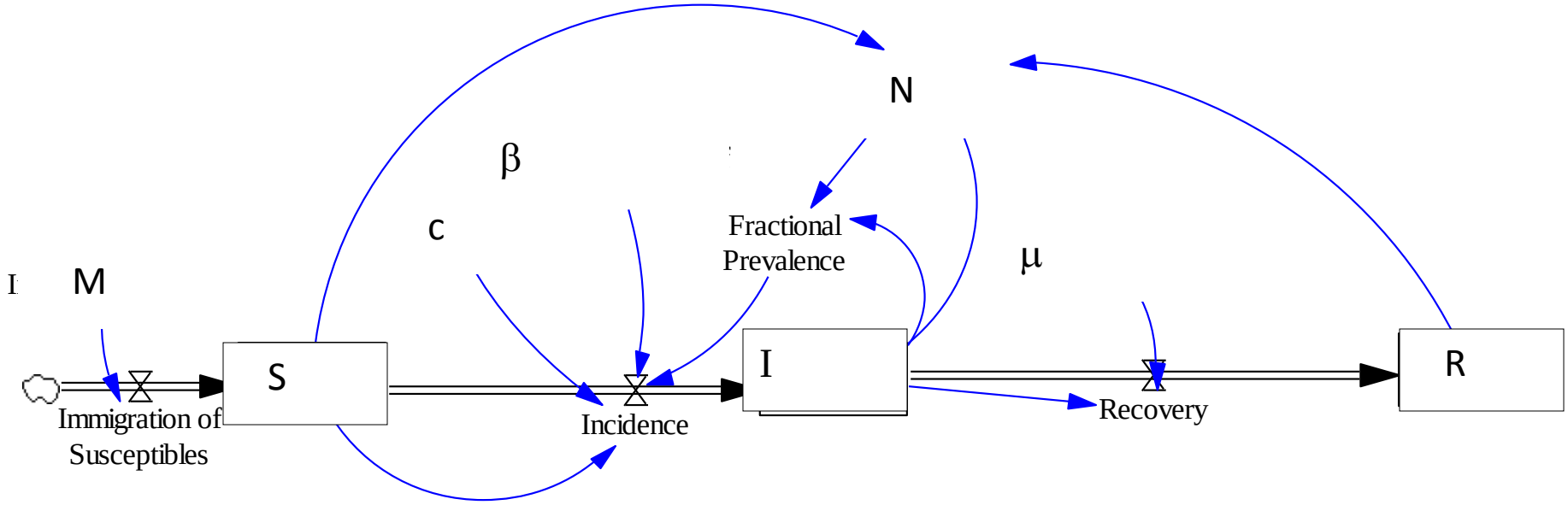
Associated Feedbacks



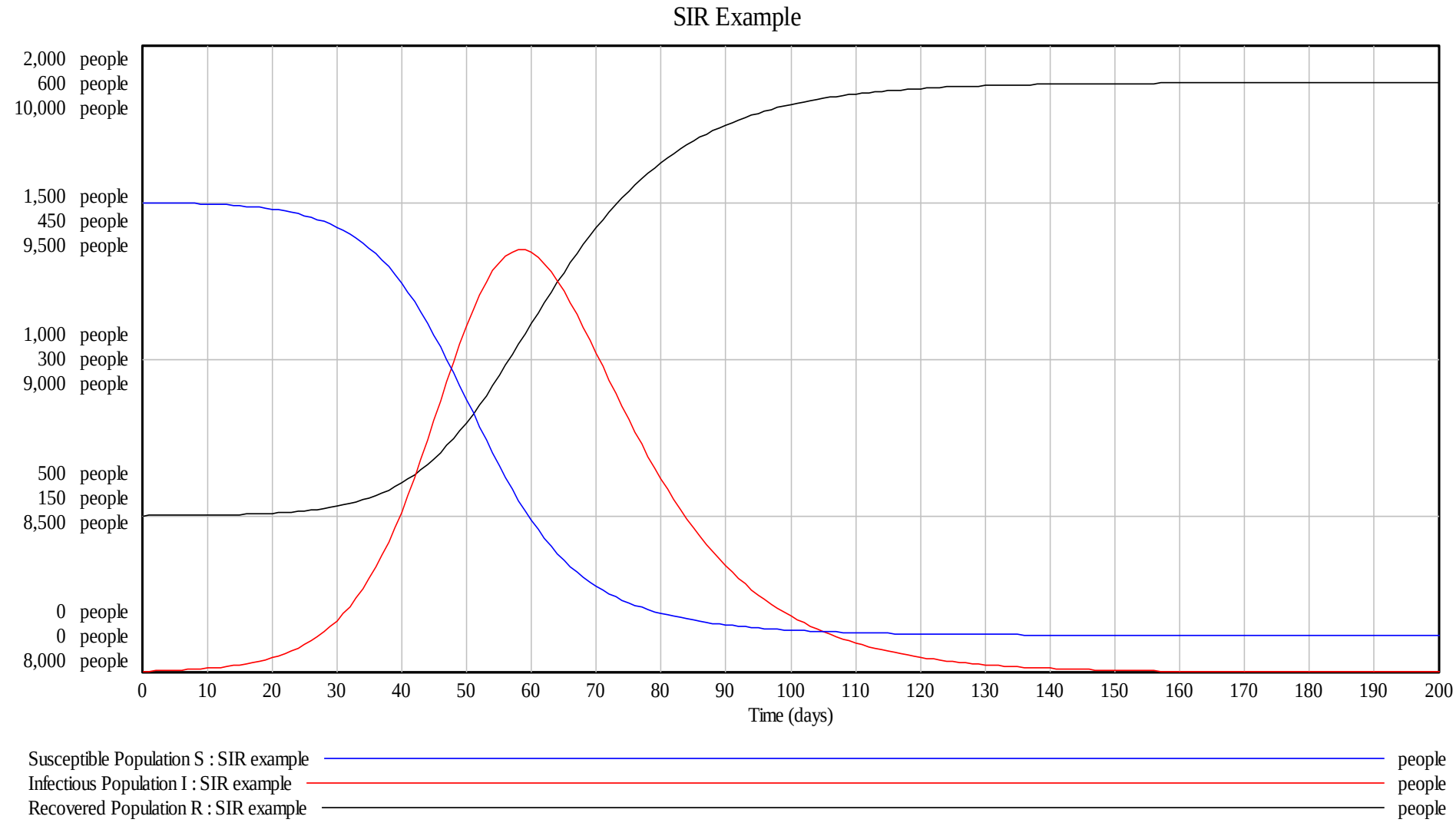
Recall: Our model

- Set
  - c=10 (people/month)
  - β=0.04 (4% chance of transmission per S-I contact)
  - μ=10
  - Birth and death rate=0
  - Initial infectives=1, other 1000 susceptible

Mathematical Notation



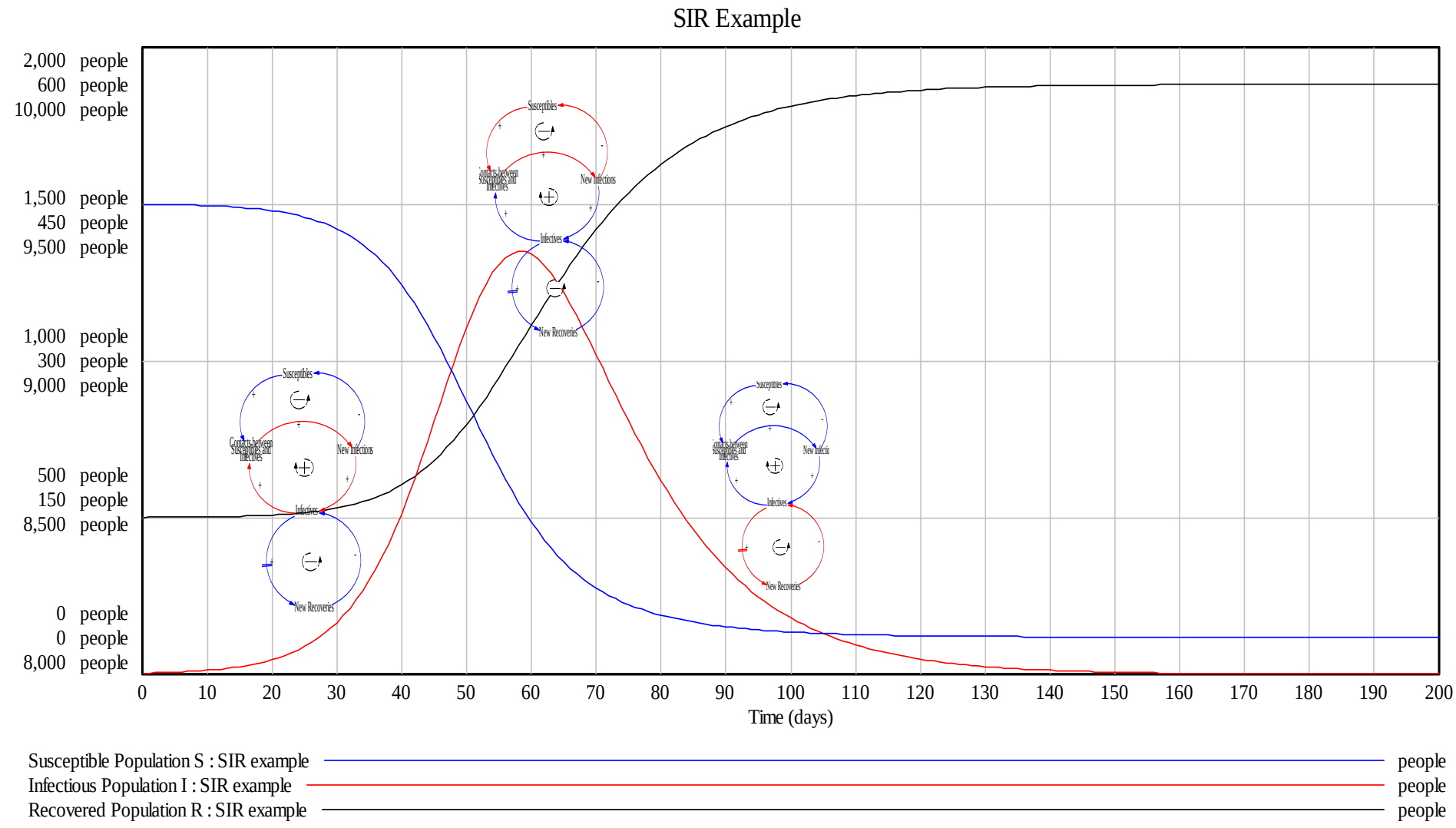
Example Dynamics of SIR Model (No Births or Deaths)



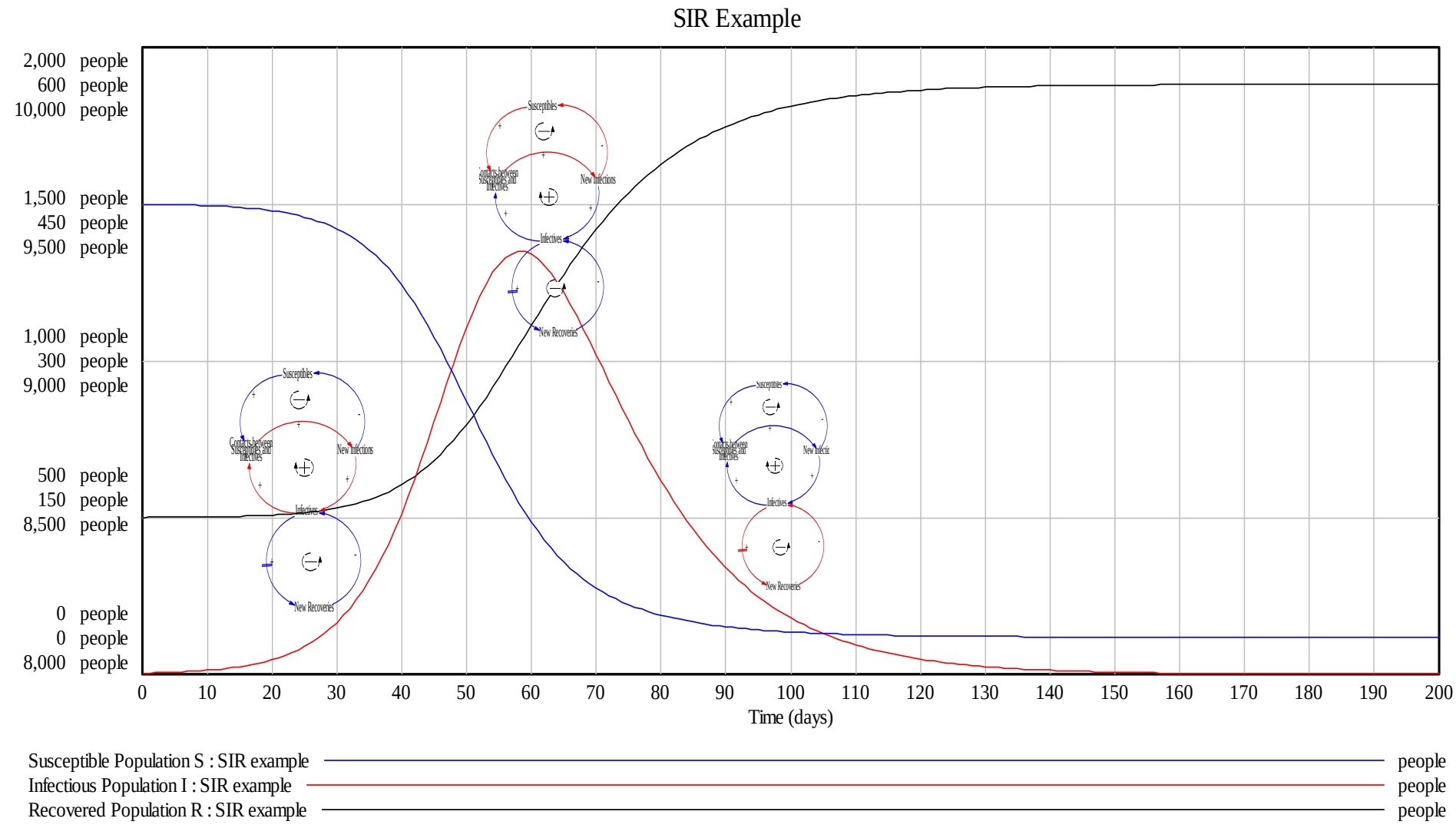
Explaining the Stock & Flow Dynamics: Infectives&Susceptibles

- Initially
  - Each infective infects $c(S/N)\beta \approx c\beta$ people on average for each time unit – the maximum possible rate
  - The rate of recoveries is 0
- In short term
  - # Infectives grows (quickly)=> rate of infection rises quickly
    - (Positive feedback!)
  - Susceptibles starts to decline, but still high enough that each infective is surrounded overwhelmingly by susceptibles, so efficient at transmitting
- Over time, more infectives, and fewer Susceptibles
  - Fewer S around each I =>Rate of infections per I declines
  - Many infectives start recovering => slower rise to I
- "Tipping point": # of infectives plateaus
  - Rate of infections = Rate of recoveries
  - Each infective infects exactly one "replacement" before recovering
- In longer term, declining # of infectives&susceptibles=> Lower & lower rate of new infections (negative feedback!)
- Change in I dominated by recoveries => goal seeking to 0 (negative feedback!)

Case 1: Outbreak



Shifting Feedback Dominance

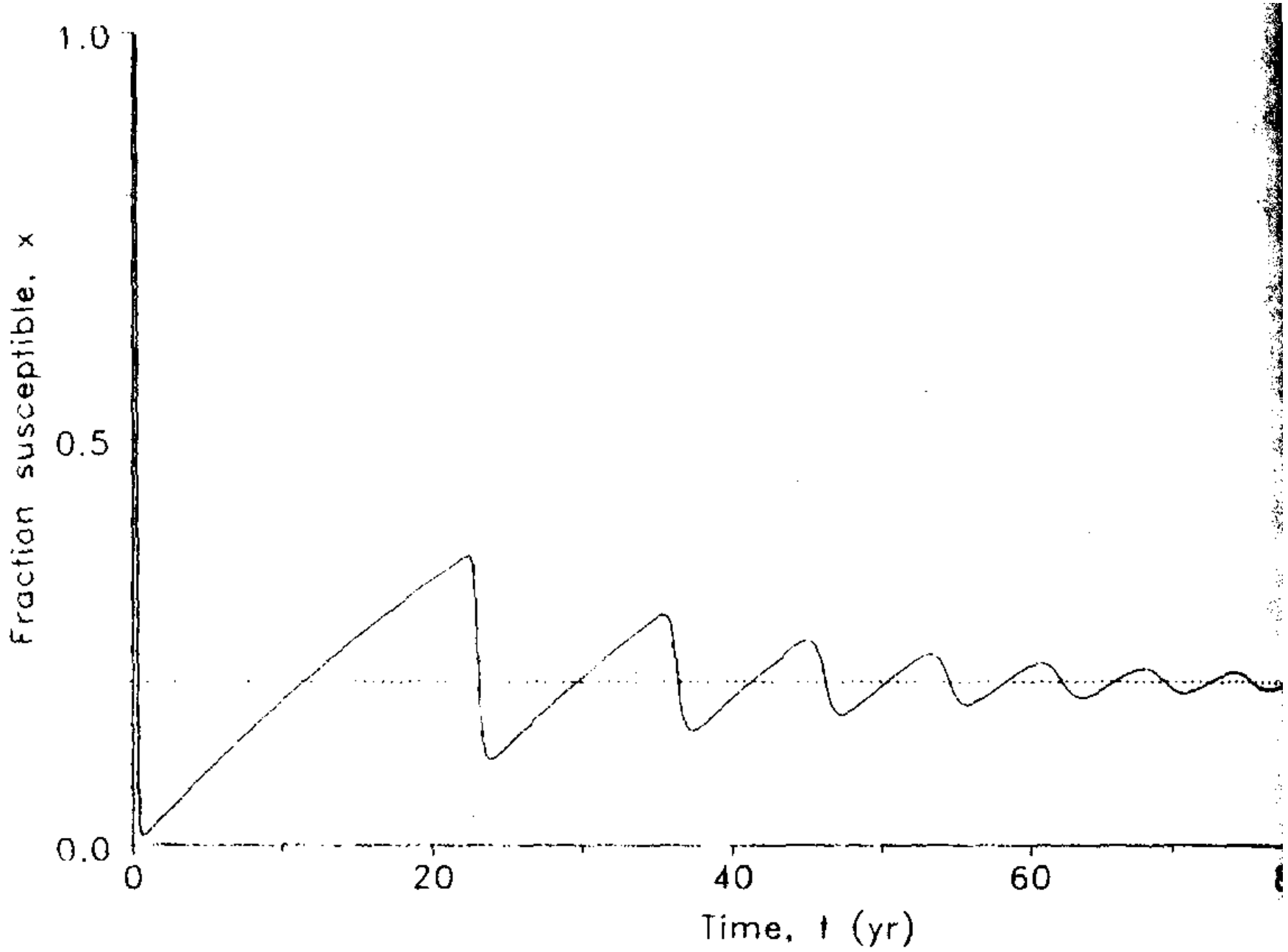


Introducing Births & Deaths

- Consider the introduction of birth & death changes the behaviour
- Why would this affect things?
- How would it make it a difference?

Table 6.1 Inter-epidemic period, T, of some common infections (from Anderson and May 1985c) and theoretical predictions of the period (eqn (6.15))

Infection	Inter-epidemic period, T, (years) (observed)	Geographical location and time period	Average age at infection, A	Latent plus infectious period, $D + D'$, (days)	Inter-epidemic period, T, (years) (calculated)
Measles	2	England and Wales, 1948–68	4–5	12	2
	2	Aberdeen, Scotland, 1883–1902	4–5		2
	2	Baltimore, USA, 1900–27	4–5		2
	2	Paris, France, 1880–1910	4–5		2
	1	Yaounde, Cameroun, 1968–75	2		1–2
	1	Ilesha, Nigeria, 1958–61	2		1–2
Rubella	3.5	Manchester, UK, 1916–83	11	18	4–5
	3.5	Glasgow, Scotland, 1929–64	11		4–5
Parvovirus (HPV)	3–5	England and Wales, 1960–80	?	?	
Mumps	3	England and Wales, 1948–82	6–7	16–26	3
	2–4	Baltimore, USA, 1928–73	8–9		3–4
Poliomyelitis	3–5	England and Wales, 1948–65	11–12	15–23	4–5
Echovirus (type II)	5	England and Wales, 1965–82	?	?	–
Smallpox	5	India, 1868–1948	12	10–14	4–5
Chickenpox	2–4	New York City, USA, 1928–72	6–8	18–23	3–4
	2–4	Glasgow, Scotland, 1929–72	6–8		3–4
Coxsackie virus (type B2)	2–3	England and Wales, 1967–82	?	?	
Scarlet fever	3–6	England and Wales, 1897–1978	10–14	15–20	4–5
Diphtheria	4–6	England and Wales, 1897–1979	11	16–20	4–5
Pertussis	3–4	England and Wales, 1948–85	4–5	27	3–4
Mycoplasma pneumoniae	4	England and Wales, 1970–82	?	?	


1.0
0.5
0.0
Fraction susceptible, x
0
20
40
60
Time, t (yr)

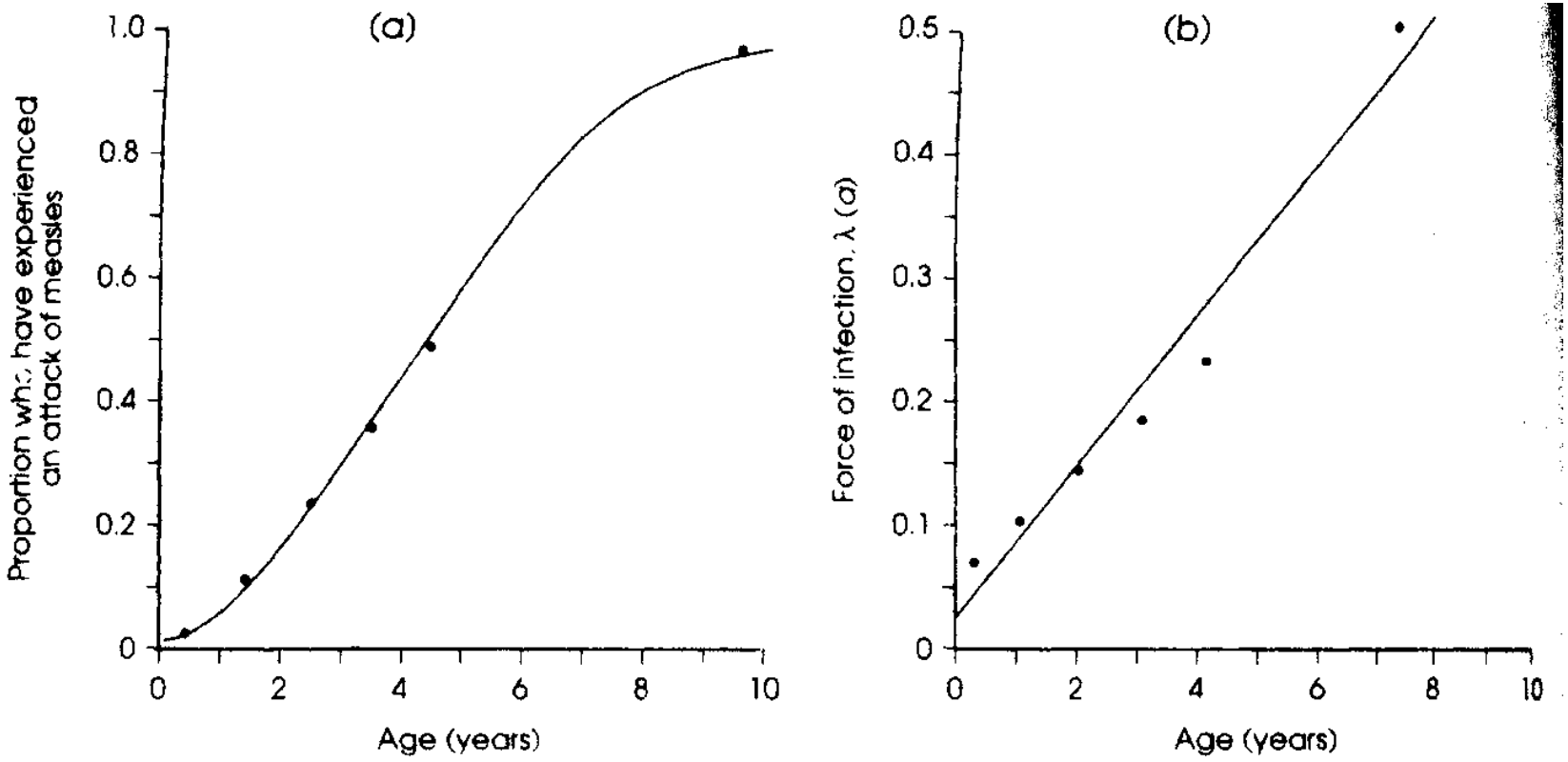


Fig. 5.14. Measles. (a) Proportion of children who had experienced an attack of measles at various ages in England and Wales in 1958 (based on case notification records). Dots, observed values; full curve, predictions of a simple catalytic model with age-dependent rates of infection (see text). (b) The age dependency in the rate or force of infection $\lambda(a)$. Dots, calculated values; full curve, best-fit linear model of the form $\lambda(a) = m + va$, where $m = 0.0178$ and $v = 0.063$ ($r^2 = 0.96$).

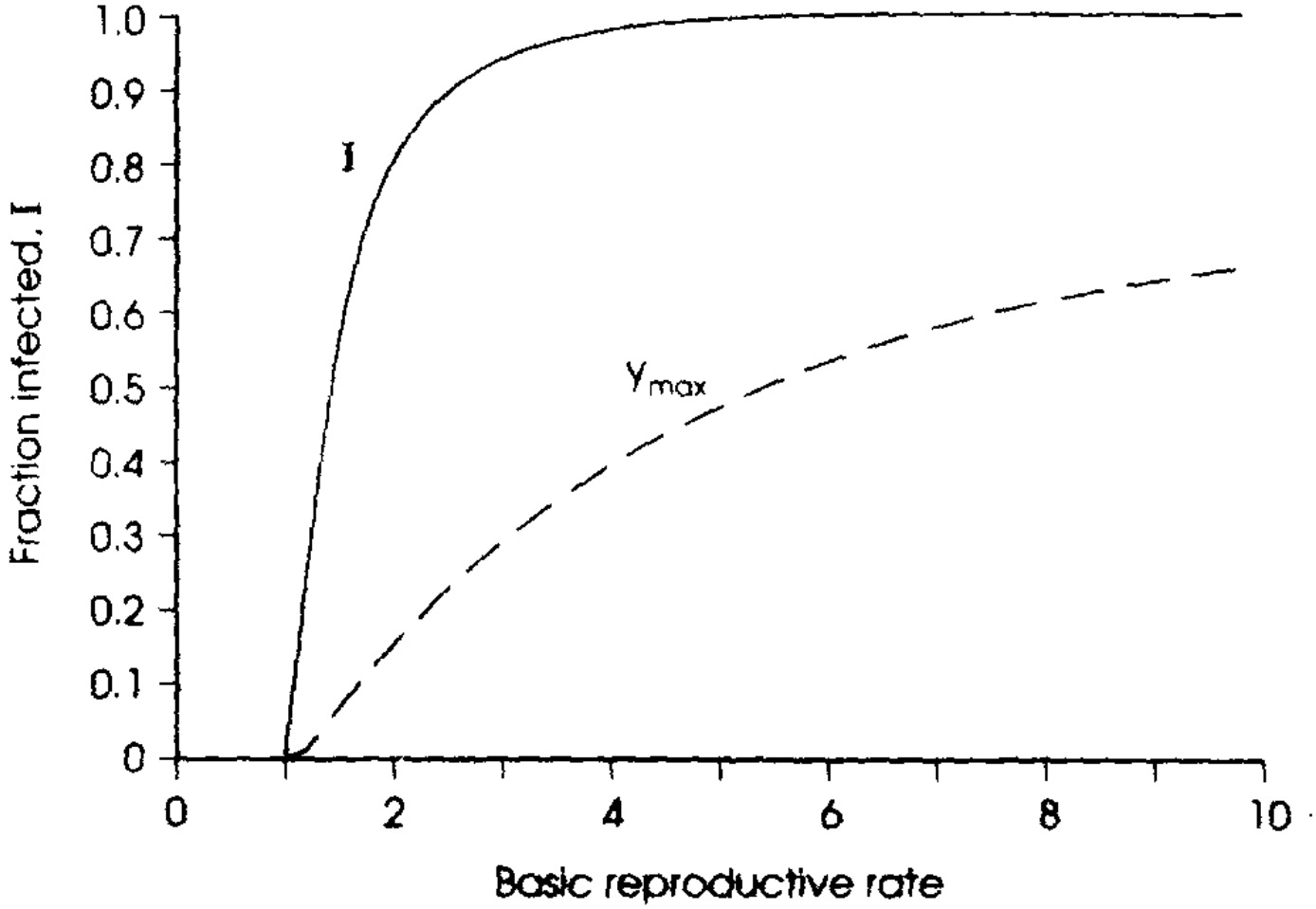


Fig. 6.2. The peak fraction infected, y_{max}, and the fraction ever infected, I, plotted as functions of R_0 (see text and eqns (6.20) and (6.21)).

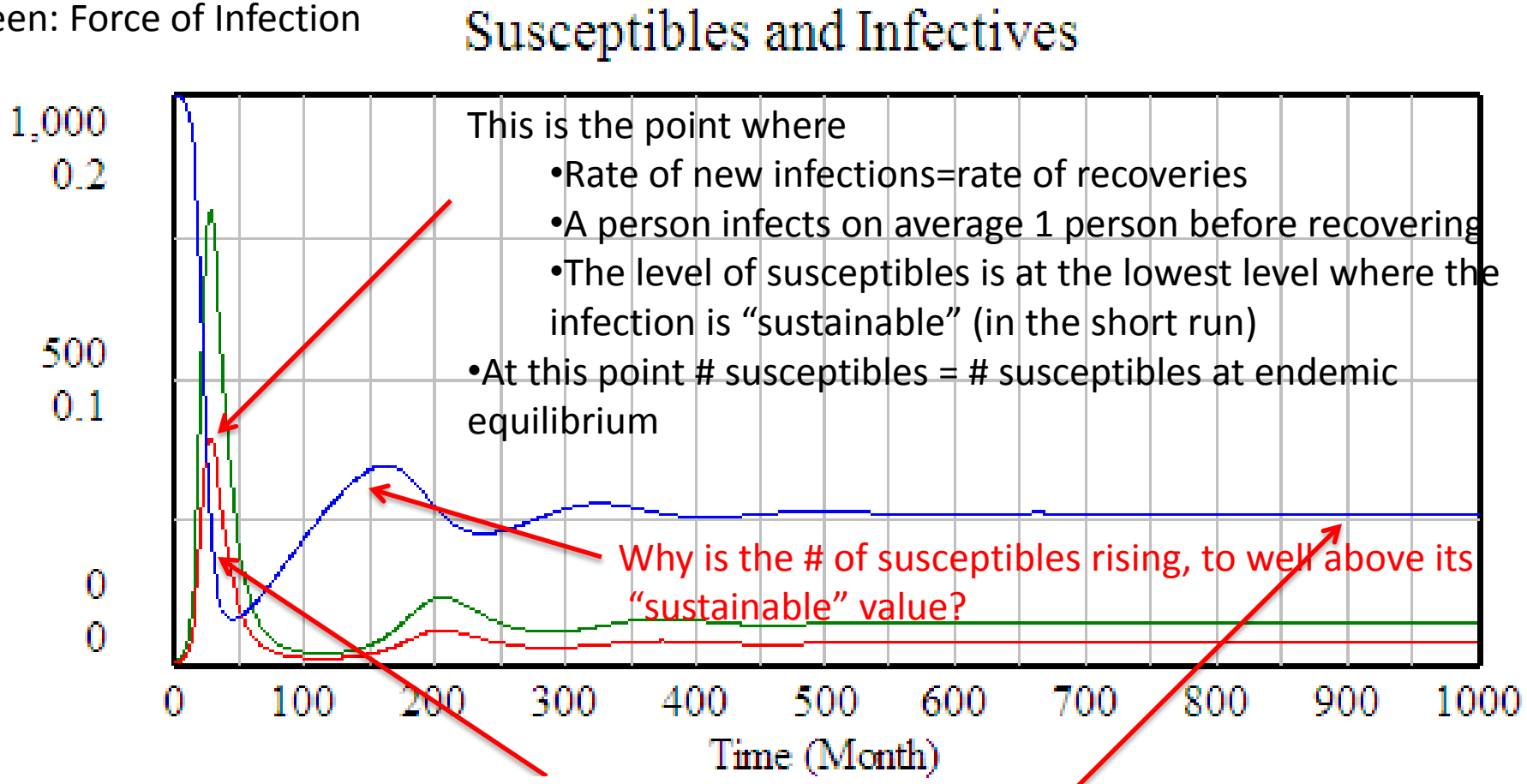
Table 4.1 Estimated values of the basic reproductive rate, R_0, for various infections (data from Anderson (1982*b*), Anderson and May (1982*d*, 1985*c*, 1988), Anderson *et al.* (1988), Nokes and Anderson (1988)).

Infection	Geographical location	Time period	R_0
Measles	Cirencester, England	1947–50	13–14
	England and Wales	1950–68	16–18
	Kansas, USA	1918–21	5–6
	Ontario, Canada	1912–13	11–12
	Willesden, England	1912–13	11–12
	Ghana	1960–8	14–15
	Eastern Nigeria	1960–8	16–17
Pertussis	England and Wales	1944–78	16–18
	Maryland, USA	1943	16–17
	Ontario, Canada	1912–13	10–11
Chicken pox	Maryland, USA	1913–17	7–8
	New Jersey, USA	1912–21	7–8
	Baltimore, USA	1943	10–11
	England and Wales	1944–68	10–12
Diphtheria	New York, USA	1918–19	4–5
	Maryland, USA	1908–17	4–5
Scarlet fever	Maryland, USA	1908–17	7–8
	New York, USA	1918–19	5–6
	Pennsylvania, USA	1910–16	6–7
Mumps	Baltimore, USA	1943	7–8
	England and Wales	1960–80	11–14
	Netherlands	1970–80	11–14
Rubella	England and Wales	1960–70	6–7
	West Germany	1970–7	6–7
	Czechoslovakia	1970–7	8–9
	Poland	1970–7	11–12
	Gambia	1976	15–16
Poliomyelitis	USA	1955	5–6
	Netherlands	1960	6–7
Human Immunodeficiency Virus (Type I)	England and Wales (male homosexuals)	1981–5	2–5
	Nairobi, Kenya (female prostitutes)	1981–5	11–12
	Kampala, Uganda	1985–7	10–11

Delays

- For a while after infectives start declining (i.e. susceptibles are below sustainable endemic value), they still deplete susceptibles sufficiently for susceptibles to decline
- For a while after susceptibles are rising (until susceptibles=endemic value), infectives will still decline
- For a while after infectives start rising, births > # of infections =>susceptibles will rise to a peak well above endemic level

Blue: # Susceptible
Red: # infective
Green: Force of Infection



This is the point where
- Rate of new infections=rate of recoveries
- A person infects on average 1 person before recovering
- The level of susceptibles is at the lowest level where the infection is "sustainable" (in the short run)

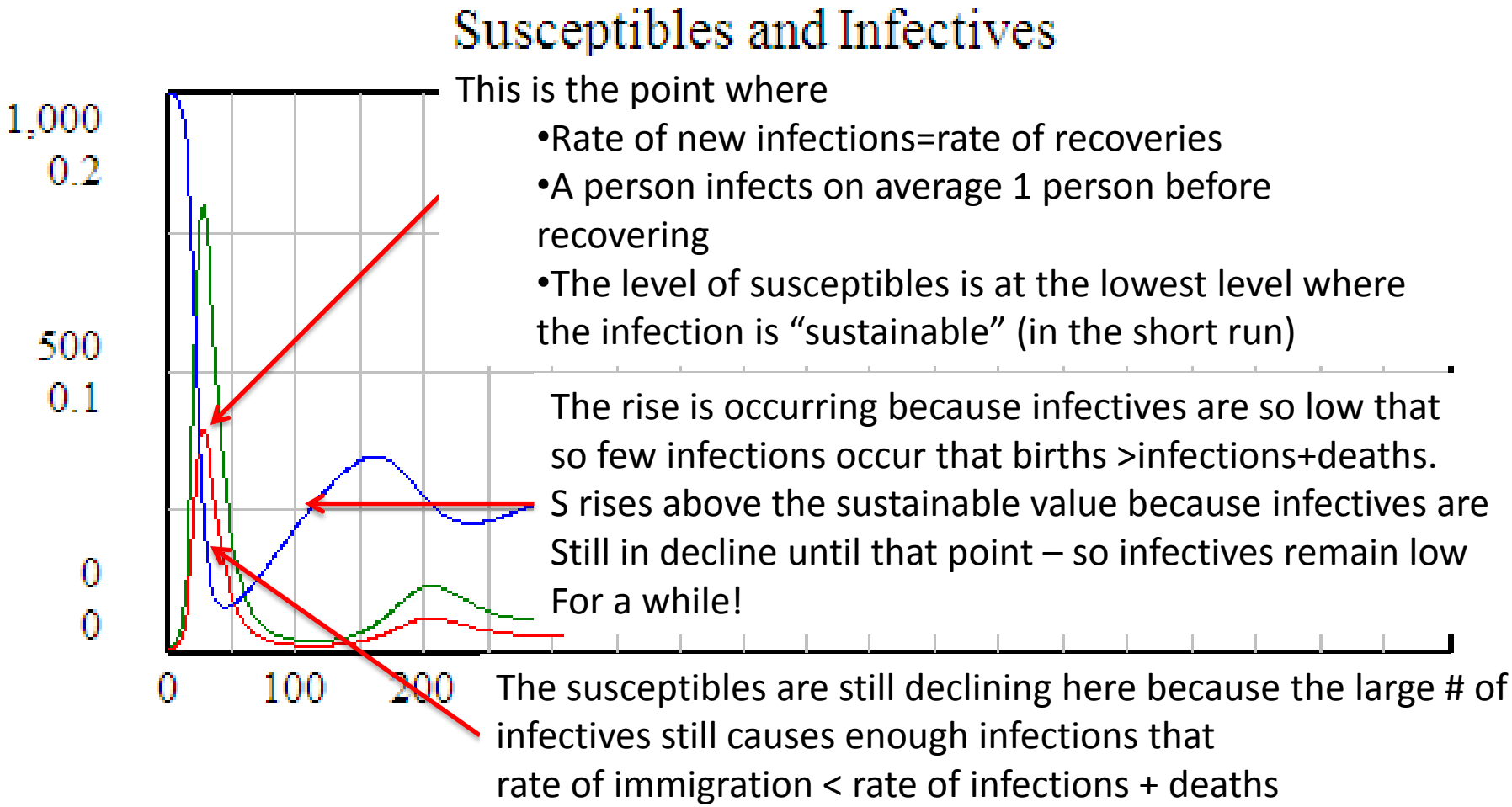
- At this point # susceptibles = # susceptibles at endemic equilibrium

Why is the # of susceptibles rising, to well above its "sustainable" value?

Why is the # of susceptibles still declining?

This fraction of susceptibles at endemic equilibrium is the minimum "sustainable" value of susceptible – i.e. the value where the properties above hold.

- Above this fraction of susceptibles, the # infected will rise
- Below this fraction of susceptibles, the # infected will fall



This is the point where

- Rate of new infections=rate of recoveries
- A person infects on average 1 person before recovering
- The level of susceptibles is at the lowest level where the infection is "sustainable" (in the short run)

The rise is occurring because infectives are so low that so few infections occur that births >infections+deaths. S rises above the sustainable value because infectives are Still in decline until that point – so infectives remain low For a while!

The susceptibles are still declining here because the large # of infectives still causes enough infections that rate of immigration < rate of infections + deaths

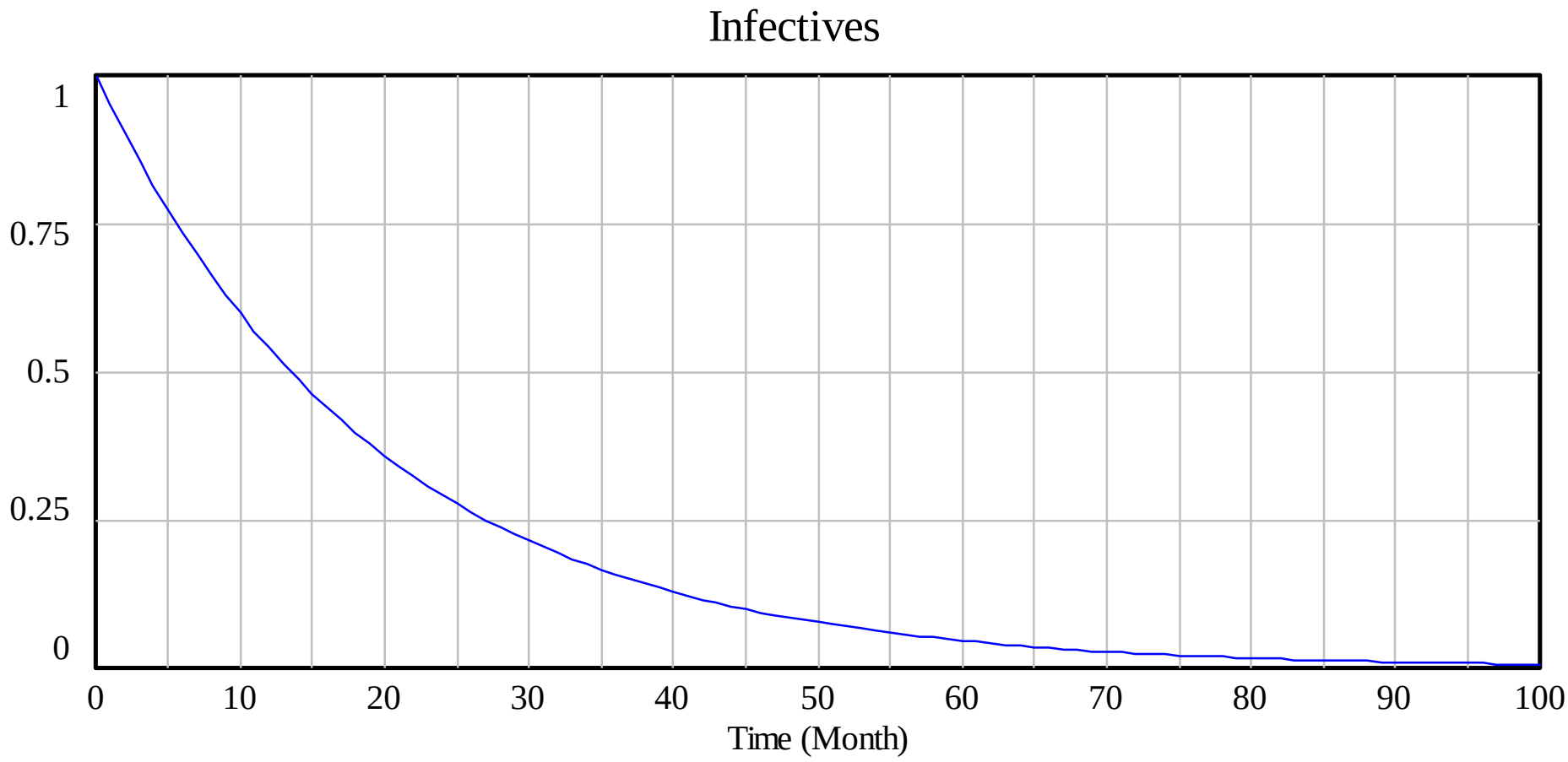
Equilibrium Behaviour

- With Births & Deaths, the system can approach an “endemic equilibrium” where the infection stays circulating in the population – but in balance
- The balance is such that (simultaneously)
  - The rate of new infections = The rate of immigration
    - Otherwise # of susceptibles would be changing!
  - The rate of new infections = the rate of recovery
    - Otherwise # of infectives would be changing!

Tipping Point

- Now try setting transmission rate β to 0.005

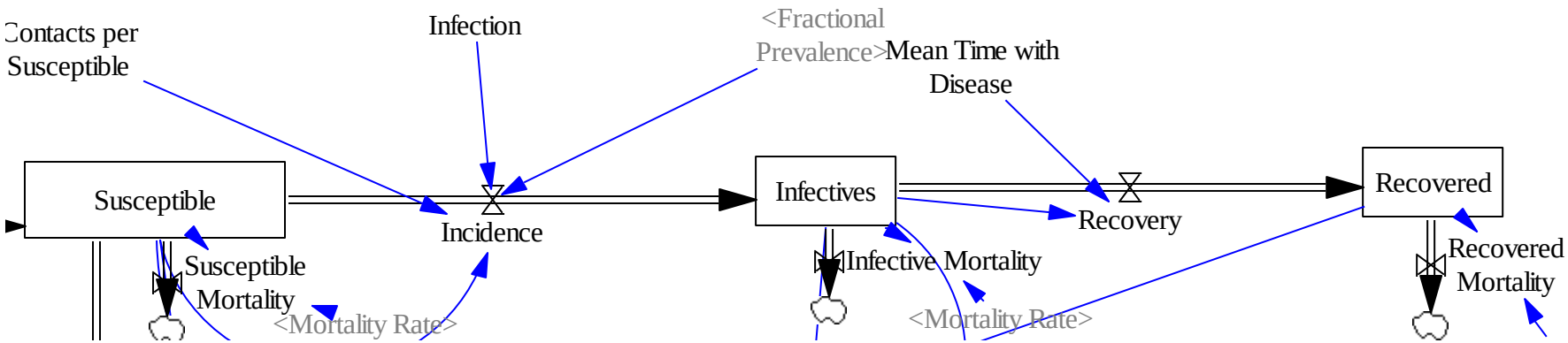
Case 2: Infection declines immediately



Recall: Closed Population (No Birth & Death)

- Infection always dies out in the population
- Some infections will take longer to die out
- There is a “tipping point” between two cases
  - # of people infected declines out immediately
  - Infection causes an outbreak before the infection dies down (# of people infected rises and then falls)

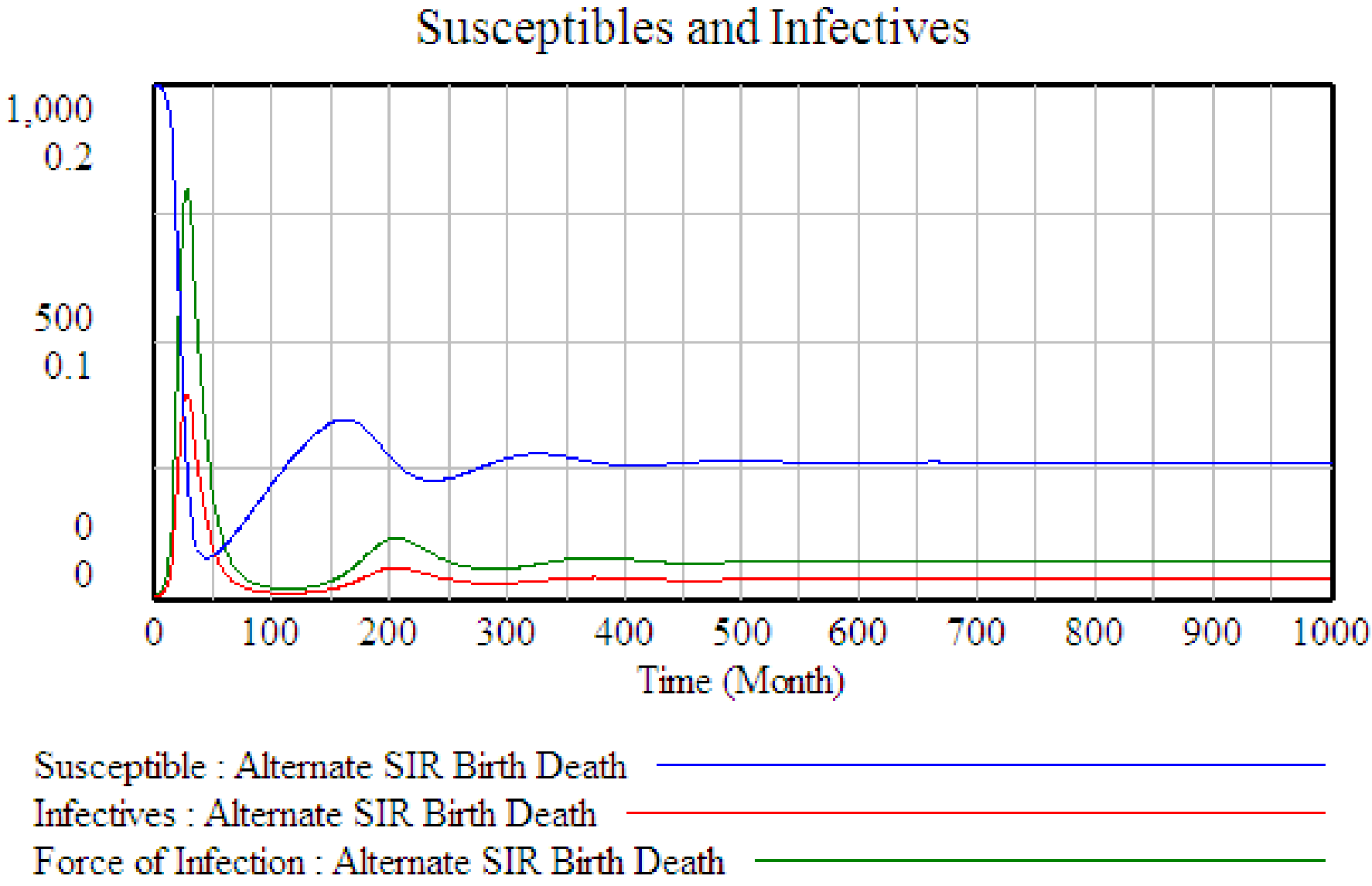
Recall: Simple Model Incorporating Population Turnover



Recall: Our model

- Set
  - c=10 (people/month)
  - β=0.04 (4% chance of transmission per S-I contact)
  - μ=10
  - Birth and death rate=0.02
  - Initial infectives=1, other 1000 susceptible

Here, the Infection Can Remain (Endemic)



Damped Oscillatory Behavior

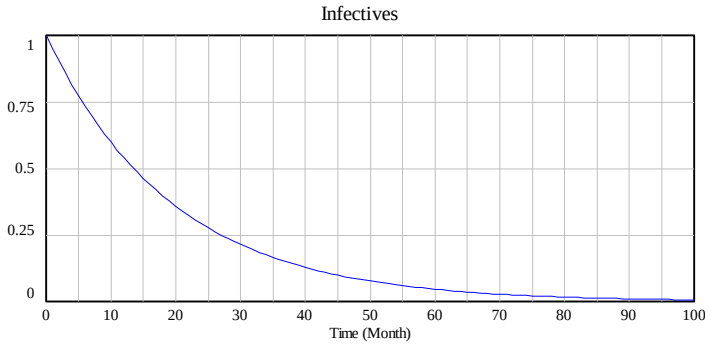
- Modify model to have births and deaths, with an annual birth-and-death rate
- Set Model/Settings/Final Time to 1000 (long time frame)
- In “Synthesim” (“Running man”) mode, set Birth/death rates
  - 0.02
  - 0.05
  - 0.07
  - 0.01
  - 0.001

Exploring the Tipping Point

- Now try setting transmission rate β to 0.005

Infection Extinction

- As for the case with a closed population, an open population has two cases
  - Infection dies out immediately



  - Outbreak: Infection takes off
    - Here – in contrast to the case for a closed population – the infection will typically go to an endemic equilibrium

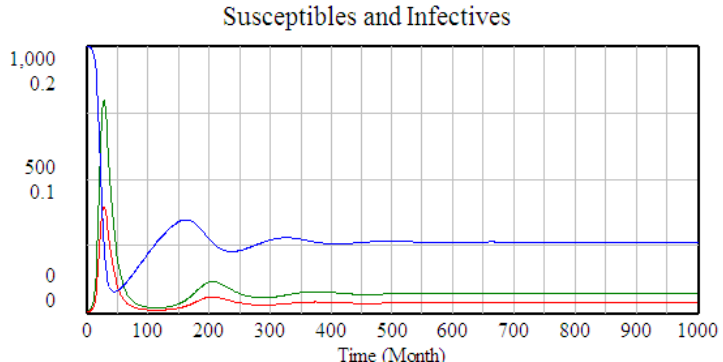
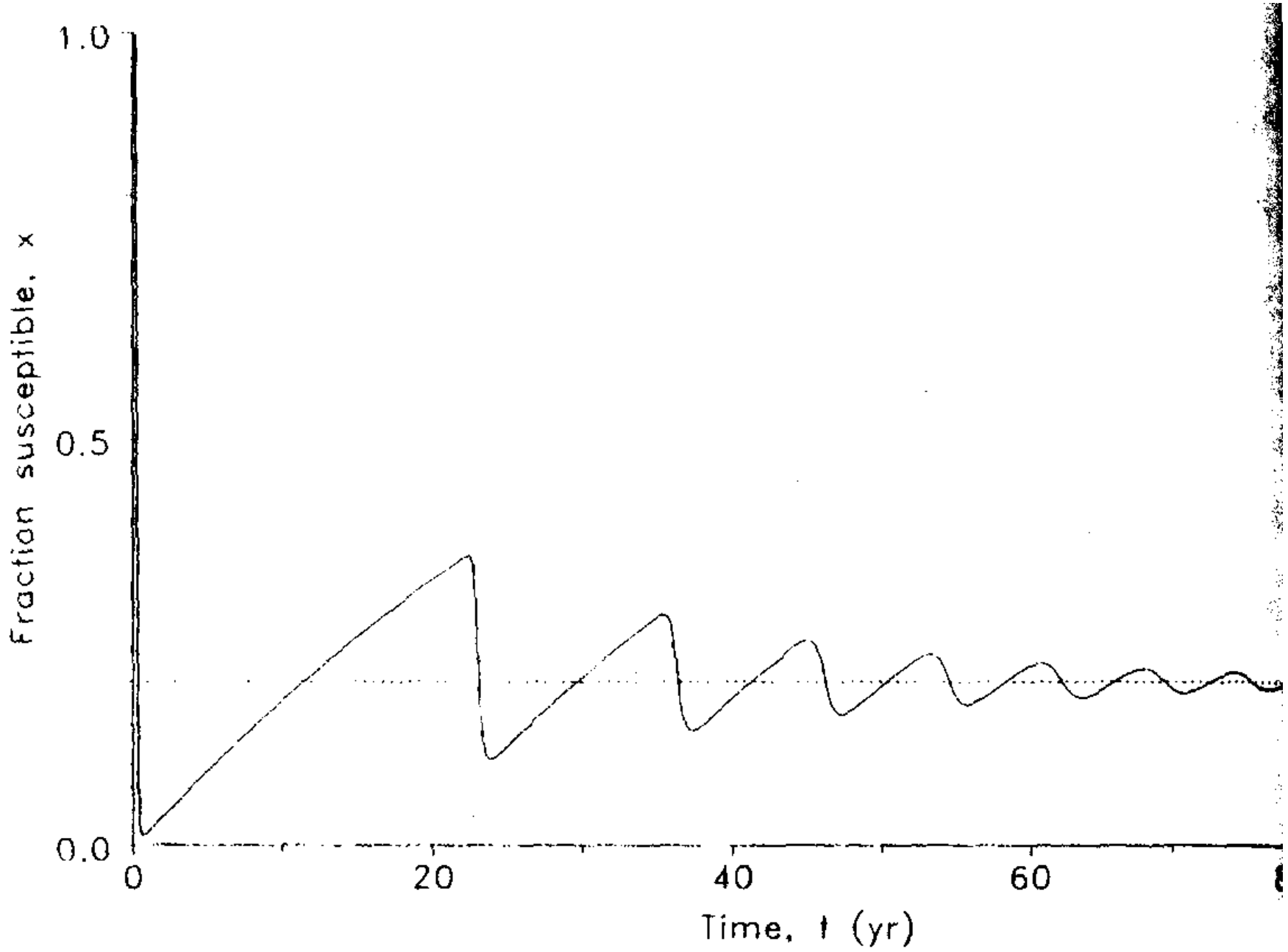


Table 6.1 Inter-epidemic period, T, of some common infections (from Anderson and May 1985c) and theoretical predictions of the period (eqn (6.15))

Infection	Inter-epidemic period, T, (years) (observed)	Geographical location and time period	Average age at infection, A	Latent plus infectious period, $D + D'$, (days)	Inter-epidemic period, T, (years) (calculated)
Measles	2	England and Wales, 1948–68	4–5	12	2
	2	Aberdeen, Scotland, 1883–1902	4–5		2
	2	Baltimore, USA, 1900–27	4–5		2
	2	Paris, France, 1880–1910	4–5		2
	1	Yaounde, Cameroun, 1968–75	2		1–2
	1	Ilesha, Nigeria, 1958–61	2		1–2
Rubella	3.5	Manchester, UK, 1916–83	11	18	4–5
	3.5	Glasgow, Scotland, 1929–64	11		4–5
Parvovirus (HPV)	3–5	England and Wales, 1960–80	?	?	
Mumps	3	England and Wales, 1948–82	6–7	16–26	3
	2–4	Baltimore, USA, 1928–73	8–9		3–4
Poliomyelitis	3–5	England and Wales, 1948–65	11–12	15–23	4–5
Echovirus (type II)	5	England and Wales, 1965–82	?	?	–
Smallpox	5	India, 1868–1948	12	10–14	4–5
Chickenpox	2–4	New York City, USA, 1928–72	6–8	18–23	3–4
	2–4	Glasgow, Scotland, 1929–72	6–8		3–4
Coxsackie virus (type B2)	2–3	England and Wales, 1967–82	?	?	
Scarlet fever	3–6	England and Wales, 1897–1978	10–14	15–20	4–5
Diphtheria	4–6	England and Wales, 1897–1979	11	16–20	4–5
Pertussis	3–4	England and Wales, 1948–85	4–5	27	3–4
Mycoplasma pneumoniae	4	England and Wales, 1970–82	?	?	


1.0
0.5
0.0
Fraction susceptible, x
0
20
40
60
Time, t (yr)

Typically, in Endemic Equilibrium, the Uninfected Fraction of the Population (S/N) is the Young

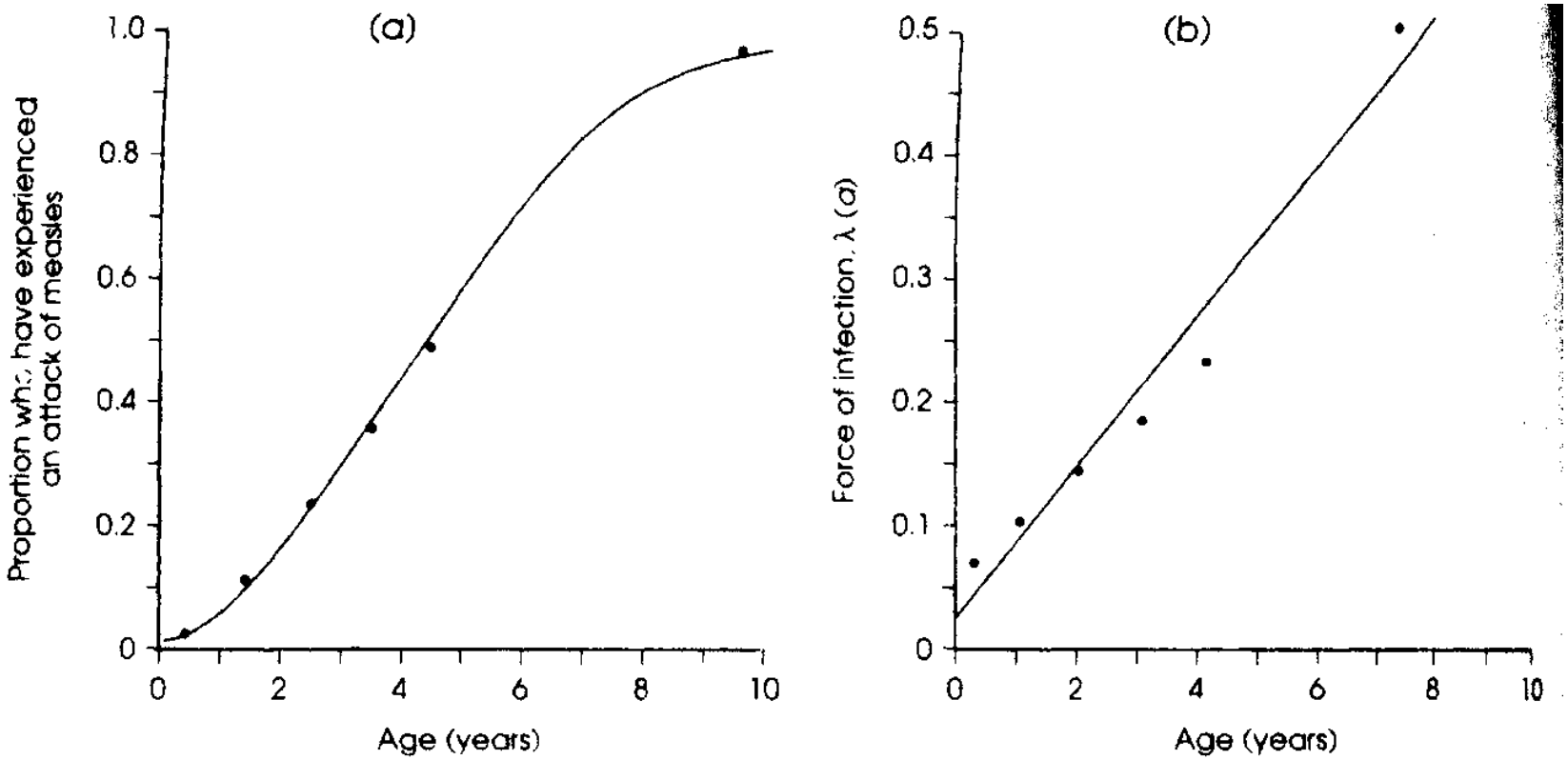


Fig. 5.14. Measles. (a) Proportion of children who had experienced an attack of measles at various ages in England and Wales in 1958 (based on case notification records). Dots, observed values; full curve, predictions of a simple catalytic model with age-dependent rates of infection (see text). (b) The age dependency in the rate or force of infection $\lambda(a)$. Dots, calculated values; full curve, best-fit linear model of the form $\lambda(a) = m + va$, where $m = 0.0178$ and $v = 0.063$ ($r^2 = 0.96$).

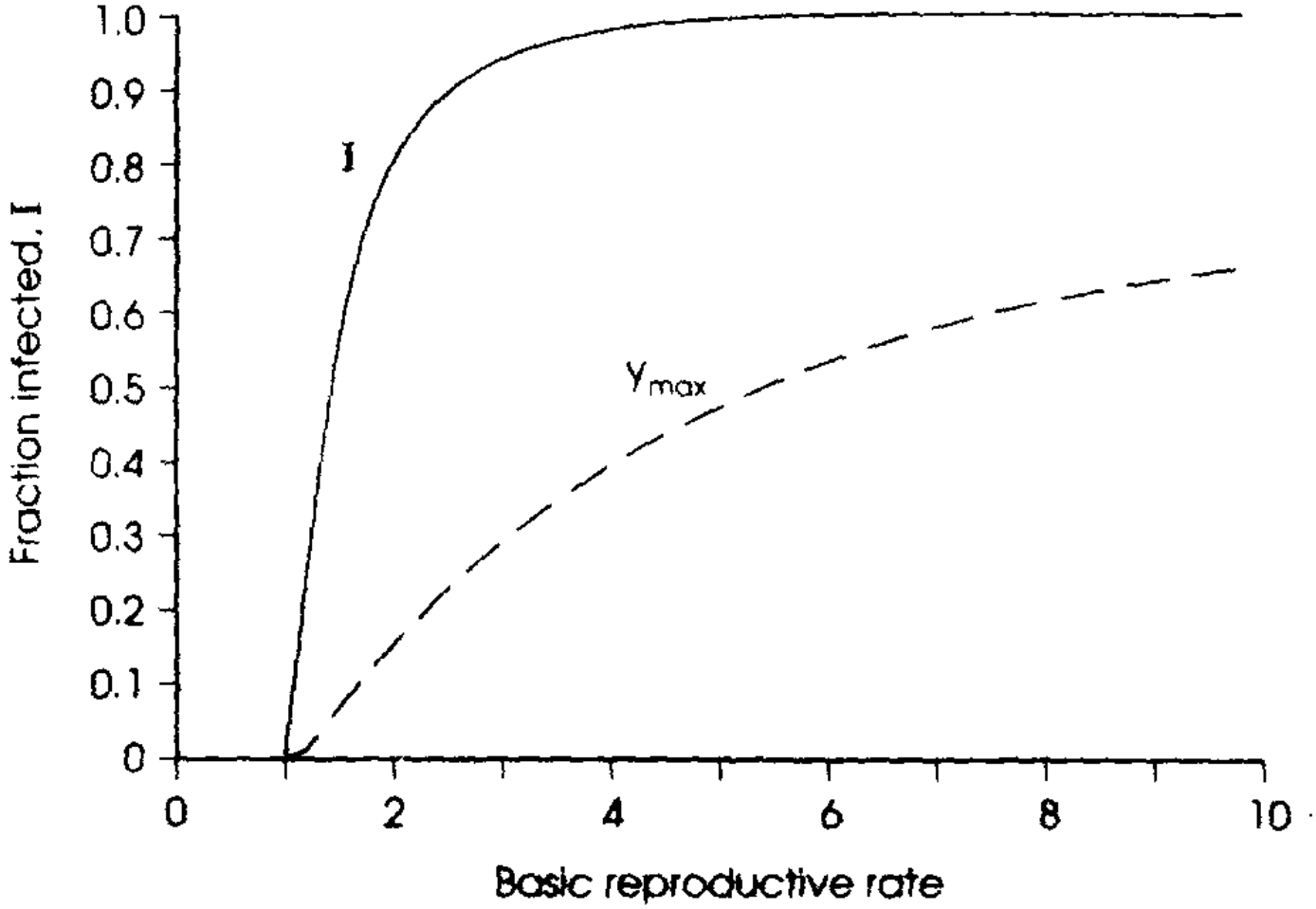


Fig. 6.2. The peak fraction infected, y_{max}, and the fraction ever infected, I, plotted as functions of R_0 (see text and eqns (6.20) and (6.21)).

Table 4.1 Estimated values of the basic reproductive rate, R_0, for various infections (data from Anderson (1982*b*), Anderson and May (1982*d*, 1985*c*, 1988), Anderson *et al.* (1988), Nokes and Anderson (1988)).

Infection	Geographical location	Time period	R_0
Measles	Cirencester, England	1947–50	13–14
	England and Wales	1950–68	16–18
	Kansas, USA	1918–21	5–6
	Ontario, Canada	1912–13	11–12
	Willesden, England	1912–13	11–12
	Ghana	1960–8	14–15
	Eastern Nigeria	1960–8	16–17
Pertussis	England and Wales	1944–78	16–18
	Maryland, USA	1943	16–17
	Ontario, Canada	1912–13	10–11
Chicken pox	Maryland, USA	1913–17	7–8
	New Jersey, USA	1912–21	7–8
	Baltimore, USA	1943	10–11
	England and Wales	1944–68	10–12
Diphtheria	New York, USA	1918–19	4–5
	Maryland, USA	1908–17	4–5
Scarlet fever	Maryland, USA	1908–17	7–8
	New York, USA	1918–19	5–6
	Pennsylvania, USA	1910–16	6–7
Mumps	Baltimore, USA	1943	7–8
	England and Wales	1960–80	11–14
	Netherlands	1970–80	11–14
Rubella	England and Wales	1960–70	6–7
	West Germany	1970–7	6–7
	Czechoslovakia	1970–7	8–9
	Poland	1970–7	11–12
	Gambia	1976	15–16
Poliomyelitis	USA	1955	5–6
	Netherlands	1960	6–7
Human Immunodeficiency Virus (Type I)	England and Wales (male homosexuals)	1981–5	2–5
	Nairobi, Kenya (female prostitutes)	1981–5	11–12
	Kampala, Uganda	1985–7	10–11

Delays

- For a while after infectives start declining (i.e. susceptibles are below sustainable endemic value), they still deplete susceptibles sufficiently for susceptibles to decline
- For a while after susceptibles are rising (until susceptibles=endemic value), infectives will still decline
- For a while after infectives start rising, births > # of infections =>susceptibles will rise to a peak well above endemic level

Infection

- Recall: For this model, a given infective infects $c(S/N)\beta$ others per time unit
  - This goes up as the number of susceptibles rises
- Questions
  - If the mean time a person is infective is μ, how many people does that infective infect before recovering?
  - With the same assumption, how many people would that infective infect if everyone else is susceptible?
  - Under what conditions would there be more infections after their recovery than before?

Fundamental Quantities

- We have just discovered the values of 2 famous epidemiological quantities for our model
  - Effective Reproductive Number: R_*
  - Basic Reproductive Number: R_0

Effective Reproductive Number: R_*

- Number of individuals infected by an 'index' infective in the current epidemological context
- Depends on
  - Contact number
  - Transmission probability
  - Length of time infected
  - # (Fraction) of Susceptibles
- Affects
  - Whether infection spreads
    - If $R_* > 1$, # of cases will rise, If $R_* < 1$, # of cases will fall
      - Alternative formulation: Largest real eigenvalue <> 0
  - Endemic Rate

Basic Reproduction Number: R_0

- Number of individuals infected by an 'index' infective *in an otherwise disease-free equilibrium*
  - This is just R_* at disease-free equilibrium all (other) people in the population are susceptible other than the index infective
- Depends on
  - Contact number
  - Transmission probability
  - Length of time infected
- Affects
  - Whether infection spreads
    - If $R_0 > 1$, Epidemic Takes off, If $R_0 < 1$, Epidemic dies out
      - Alternative formulation: Largest real eigenvalue <> 0
    - Initial infection rise $\propto$ exp(t*(R0-1)/D)
  - Endemic Rate

Basic Reproductive Number R_0

- If contact patterns & infection duration remain unchanged and if fraction f of the population is **susceptible**, then mean # of individuals infected by an infective over the course of their infection is $f*R_0$
- In endemic equilibrium: Inflow=Outflow $\Rightarrow (S/N)\cdot R_0=1$
  - Every infective infects a "replacement" infective to keep equilibrium
  - Just enough of the population is susceptible to allow this replacement
  - The higher the R_0, the lower the fraction of susceptibles in equilibrium!
    - *Generally some* susceptibles remain: At some point in epidemic, susceptibles will get so low that can't spread

Our model

- Set
  - c=10 (people/month)
  - β=0.04 (4% chance of transmission per S-I contact)
  - μ=10
  - Birth and death rate= 0
  - Initial infectives=1, other 1000 susceptible
- What is R_0?
- What should we expect to see ?

Thresholds

- R_*
  - Too low # susceptibles => R* < 1: # of infectives declining
  - Too high # susceptibles => R* > 1: # of infectives rising
- R_0
  - R_0>1: Infection is introduced from outside will cause outbreak
  - R_0<1: “Herd immunity”: infection is introduced from outside will die out (may spread to small number before disappearing, but in unsustainable way)
    - **This is what we try to achieve by control programs, vaccination, etc.**
- Outflow from susceptibles (infections) is determined by the # of Infectives

Equilibrium Behaviour

- With Births & Deaths, the system can approach an “endemic equilibrium” where the infection stays circulating in the population – but in balance
- The balance is such that (simultaneously)
  - The rate of new infections = The rate of immigration
    - Otherwise # of susceptibles would be changing!
  - The rate of new infections = the rate of recovery
    - Otherwise # of infectives would be changing!

Equilibria

- Disease free
  - No infectives in population
  - Entire population is susceptible
- Endemic
  - Steady-state equilibrium produced by spread of illness
  - Assumption is often that children get exposed when young
- The stability of the these equilibria (whether the system departs from them when perturbed) depends on the parameter values
  - For the disease-free equilibrium on R_0

Vaccination

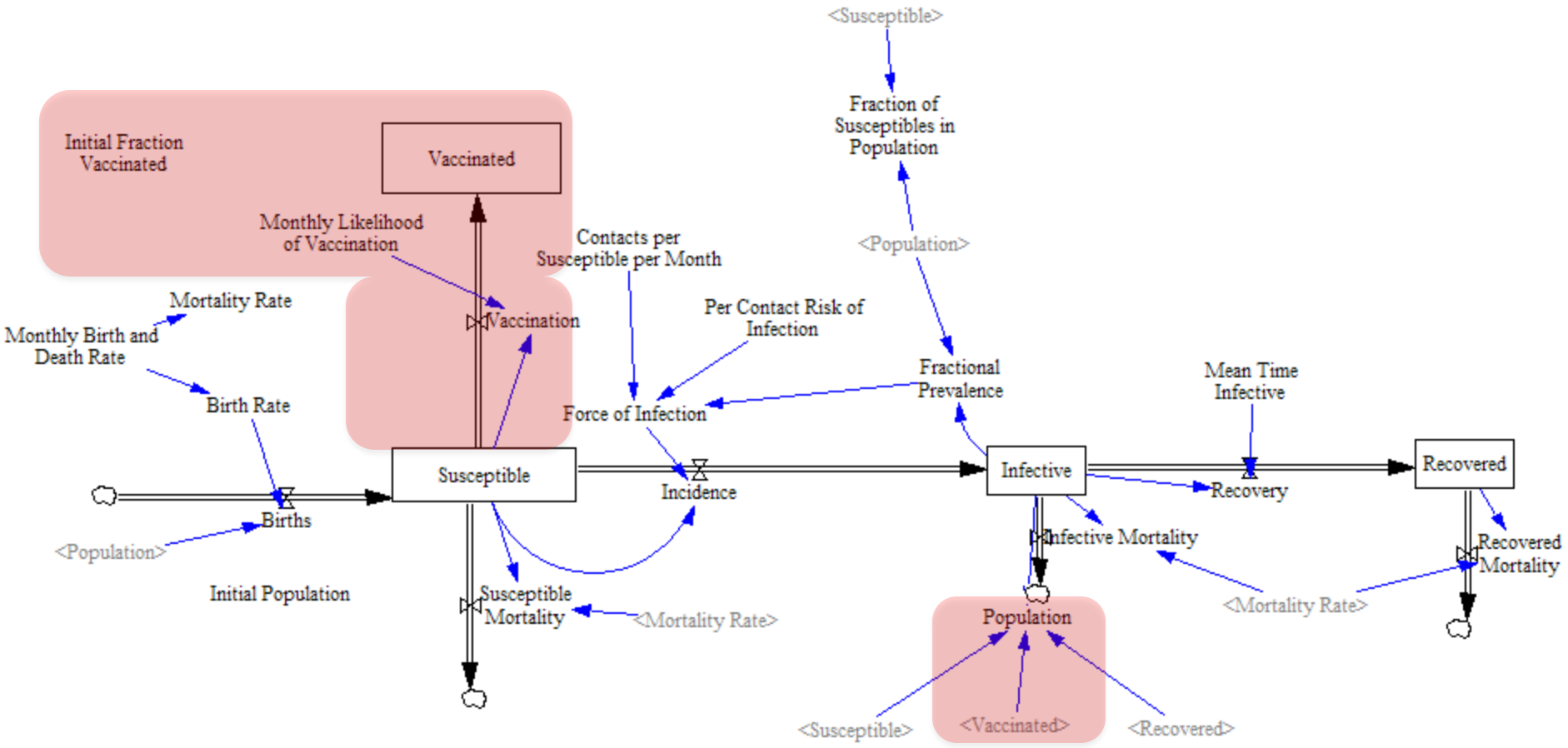
Adding Vaccination Stock

- Add a
  - “Vaccinated” stock
  - A constant called “Monthly Likelihood of Vaccination”
  - “Vaccination” flow between the “Susceptible” and “Vaccinated” stocks
    - The rate is the stock times the constant above
- Set initial population to be divided between 2 stocks
  - Susceptible
  - Vaccinated
- Incorporate “Vaccinated” in population calculation

Additional Settings

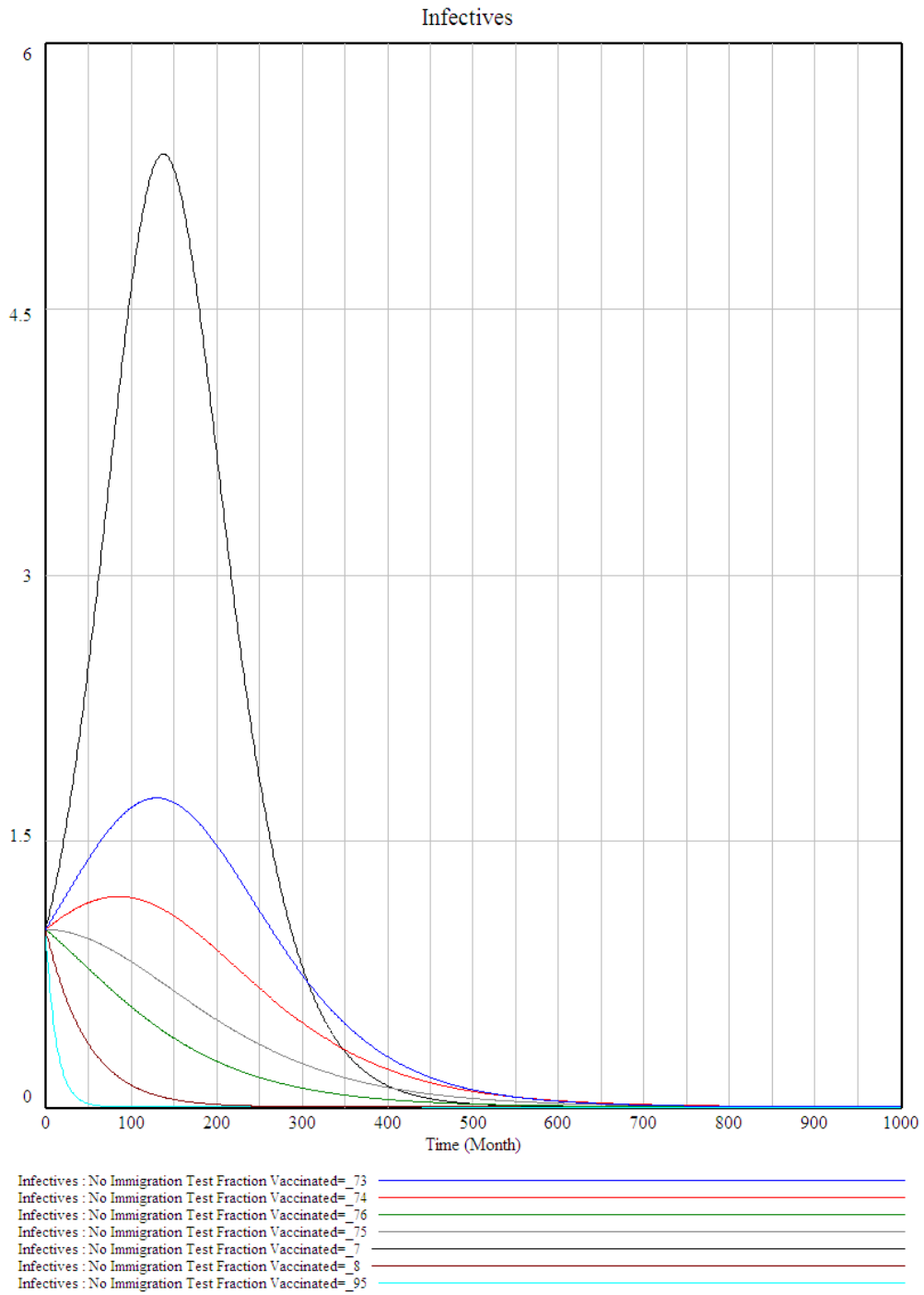
- c= 10
- Beta=.04
- Duration of infection = 10
- Birth & Death Rate=0

Adding Stock



Experiment with Different Initial Vaccinated Fractions

- Fractions = 0.25, 0.50, 0.6, 0.7, 0.8


Infectives
6
4.5
3
1.5
0
0
100
200
300
400
500
600
700
800
900
1000
Time (Month)
Infectives : No Immigration Test Fraction Vaccinated=_73
Infectives : No Immigration Test Fraction Vaccinated=_74
Infectives : No Immigration Test Fraction Vaccinated=_76
Infectives : No Immigration Test Fraction Vaccinated=_75
Infectives : No Immigration Test Fraction Vaccinated=_7
Infectives : No Immigration Test Fraction Vaccinated=_8
Infectives : No Immigration Test Fraction Vaccinated=_95

Recall: Thresholds

- R*
  - Too low # susceptibles => R* < 1: # of infectives declining
  - Too high # susceptibles => R* > 1: # of infectives rising
- Outflow from susceptibles (infections) is determined by the # of Infectives
- Delays:
  - For a while after infectives start declining, they still deplete susceptibles sufficiently for susceptibles to decline
  - For a while after infectives start rising, the # of infections is insufficient for susceptibles to decline

Effective Reproductive Number: R_*

- Number of individuals infected by an 'index' infective in the current epidemiological context
- Depends on
  - Contact number
  - Transmission probability
  - Length of time infected
  - # (Fraction) of Susceptibles
- Affects
  - Whether infection spreads
    - If $R_* > 1$, # of cases will rise, If $R_* < 1$, # of cases will fall
      - Alternative formulation: Largest real eigenvalue <> 0
  - Endemic Rate

Basic Reproduction Number: R_0

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      - Alternative formulation: Largest real eigenvalue <> 0
    - Initial infection rise $\propto$ exp(t*(R0-1)/D)
  - Endemic Rate

Recall: A Critical Throttle on Infection Spread: Fraction Susceptible (*f*)

- The fraction susceptible (here, S/N) is a key quantity limiting the spread of infection in a population
  - Recognizing its importance, we give this name *f* to the fraction of the population that issusceptible
- If contact patterns & infection duration remain unchanged and, then mean # of individuals infected by an infective over the course of their infection is $f*R_0$

Recall: Endemic Equilibrium

- Inflow=Outflow $\Rightarrow (S/N)\cdot R_0 = f\cdot R_0 = 1$
  - Every infective infects a "replacement" infective to keep equilibrium
  - Just enough of the population is susceptible to allow this replacement
- The higher the R_0, the lower the fraction of susceptibles in equilibrium!
  - *Generally some* susceptibles remain: At some point in epidemic, susceptibles will get so low that can't spread

Critical Immunization Threshold

- Consider an index infective arriving in a "worst case" scenario when noone else in the population is infective or recovered from the illness
  - In this case, that infective is most "efficient" in spreading
- The goal of vaccination is keep the fraction susceptible low enough that infection cannot establish itself even in this worst case
  - We do this by administering vaccines that makes a person (often temporarily) immune to infection
- We say that a population whose *f* is low enough that it is resistant to establishment of infection exhibits "herd immunity"

Critical Immunization Threshold

- Vaccination seeks to lower *f* such that $f^*R_0<1$
- *Worst case: Suppose we have a population that is divided into immunized (vaccinated) and susceptible*
  - Let q_c be the critical fraction immunized to stop infection
  - *Then* $f=1-q_c$, $f^*R_0<1 \Rightarrow (1-q_c)^*R_0<1 \Rightarrow q_c>1-(1/R_0)$
- So if $R_0 = 4$ (as in our example), $q_c=0.75$*(i.e. 75% of population must be immunized – just as we saw!)*

Infectious Disease Models 5 -- Vaccination

CMPT 858

Nathaniel Osgood

3-30-2010

Equilibrium Behaviour

- With Births & Deaths, the system can approach an “endemic equilibrium” where the infection stays circulating in the population – but in balance
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- Incorporate “Vaccinated” in population calculation

Additional Settings

- c= 10
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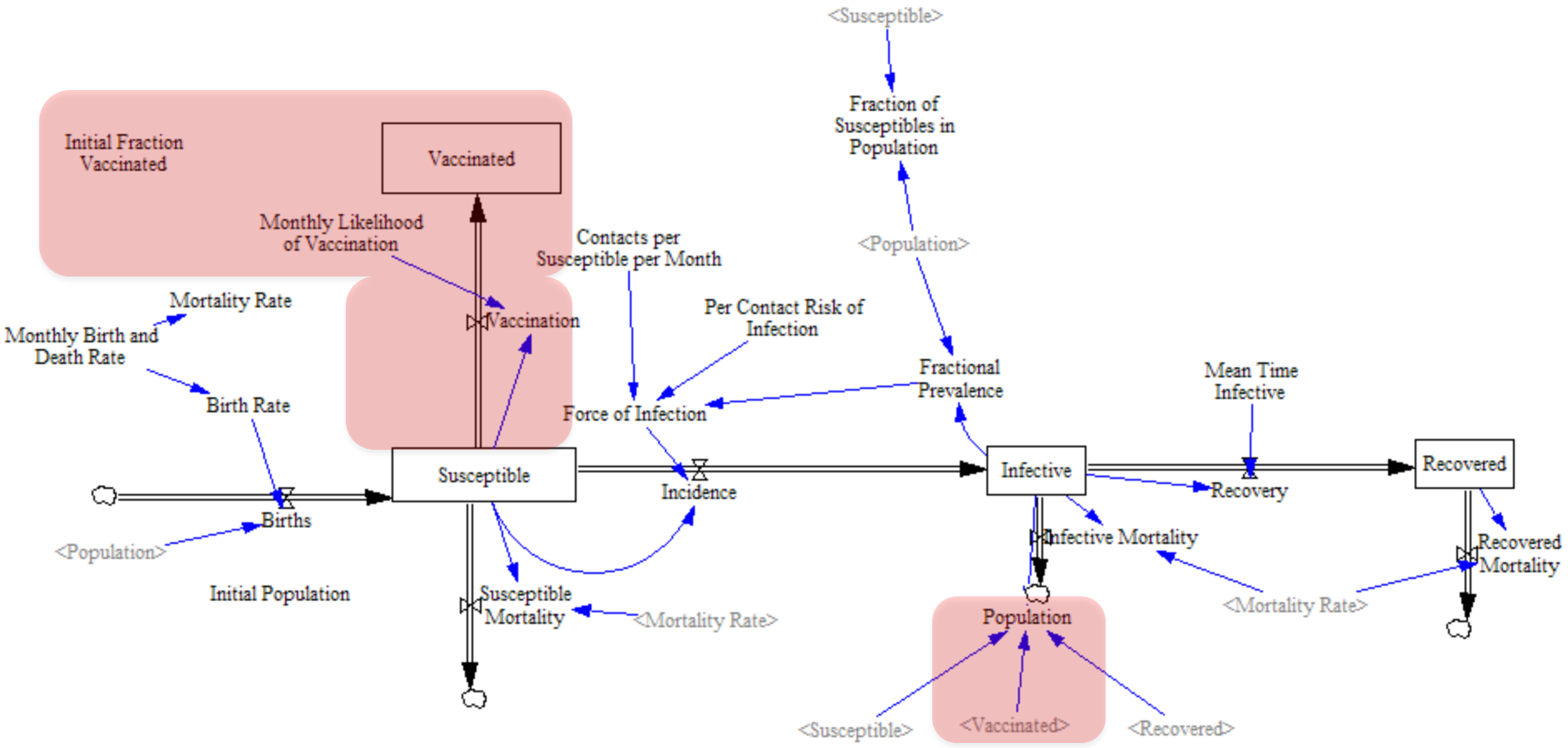
- Duration of infection = 10
- Birth & Death Rate=0

Adding Stock



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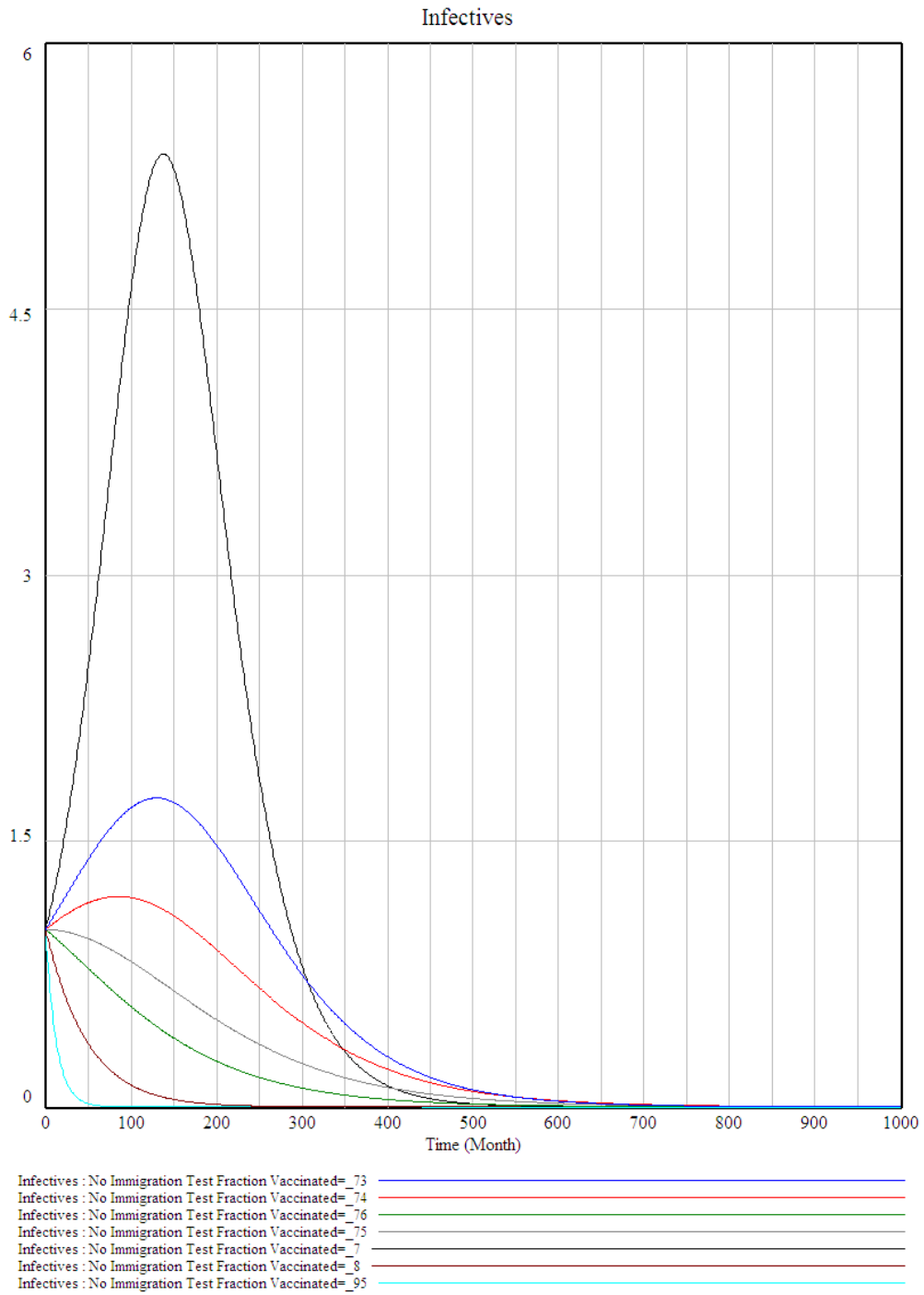
Infectives
6
4.5
3
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Infectives : No Immigration Test Fraction Vaccinated=_74
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Infectives : No Immigration Test Fraction Vaccinated=_75
Infectives : No Immigration Test Fraction Vaccinated=_7
Infectives : No Immigration Test Fraction Vaccinated=_8
Infectives : No Immigration Test Fraction Vaccinated=_95

Critical Immunization Threshold

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- So if $R_0 = 4$ (as in our example), $q_c=0.75$*(i.e. 75% of population must be immunized – just as we saw!)*

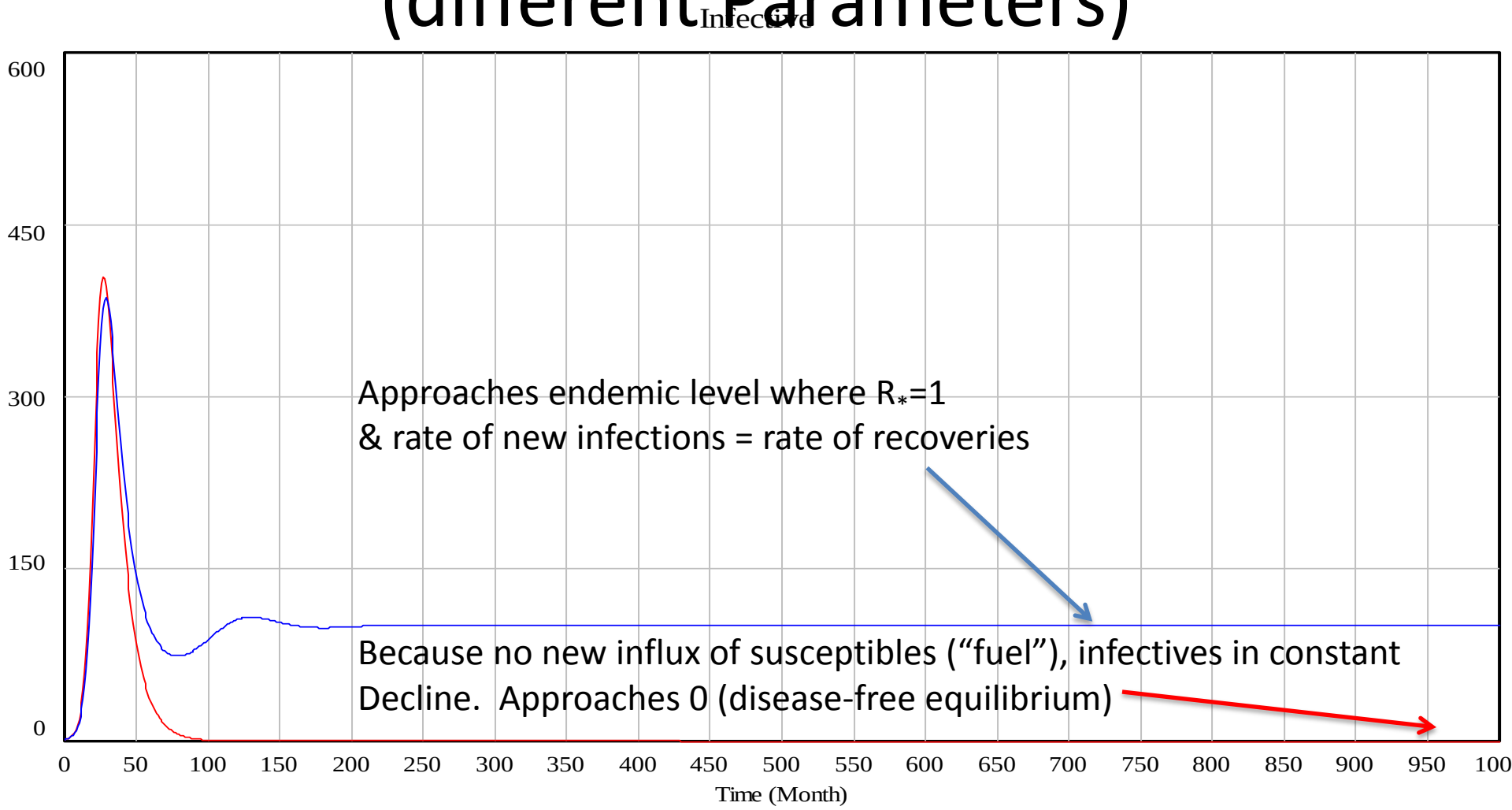
Intervention Impact on an Open Population

Nathaniel Osgood

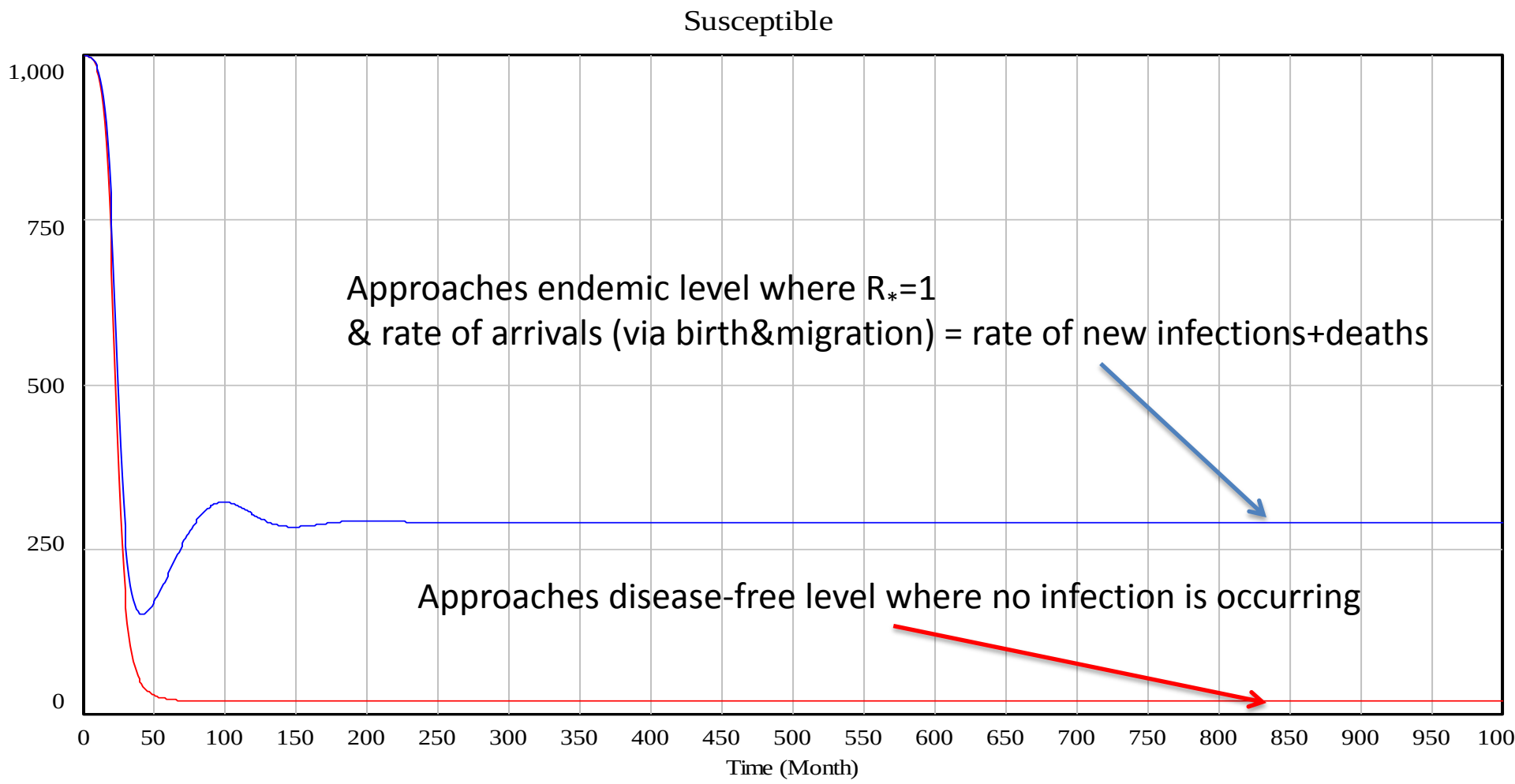
Open/Closed Population

	Case	Does Epidemic Occur?	Steady-state	
			Fraction infective	**Fraction susceptible**
Open Population	$R_0>1$	Yes	Such that Infection rate=Recovery rate	$1/R_0$
	$R_0<1$	No	0	1
Closed Population	$R_0>1$	Yes	0	<1 (often <<1) but >0
	$R_0<1$	No	0	≈1

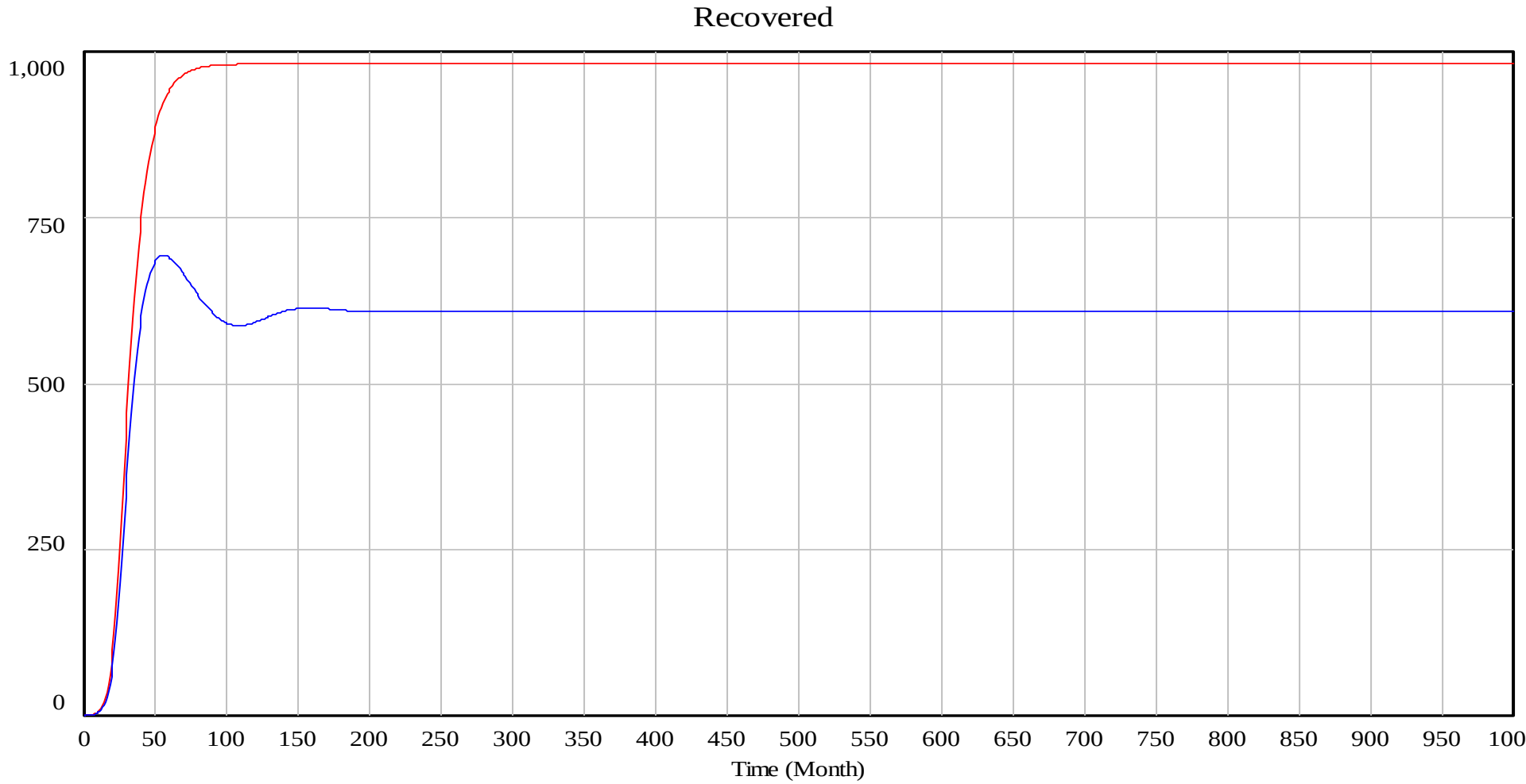
Effects of An Open Population (different Parameters)



Effects of An Open Population



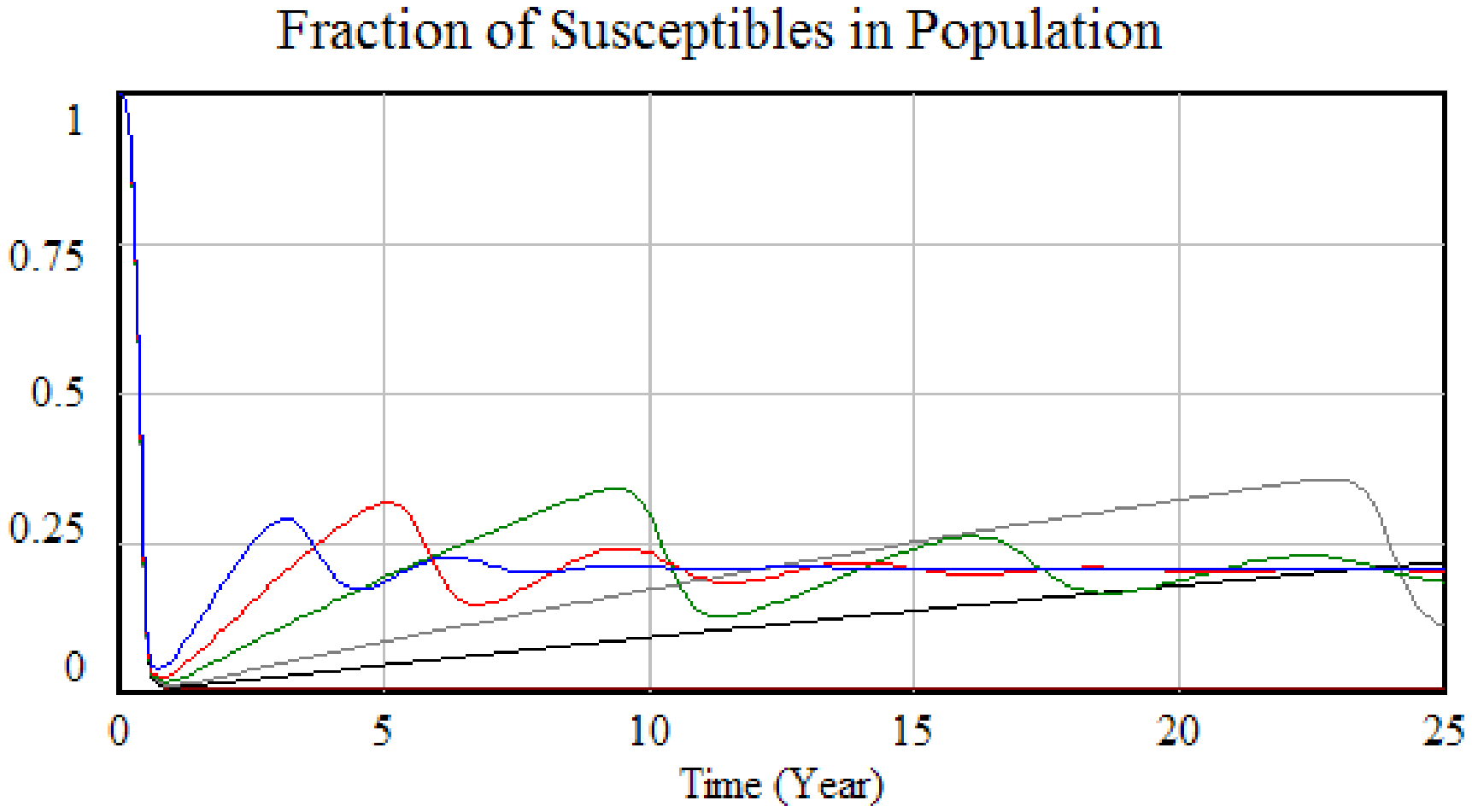
Recovereds


Recovered
1,000
750
500
250
0
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950
100
Time (Month)
Recovered : Baseline 2% Annual Turnover
Recovered : Baseline Closed Population

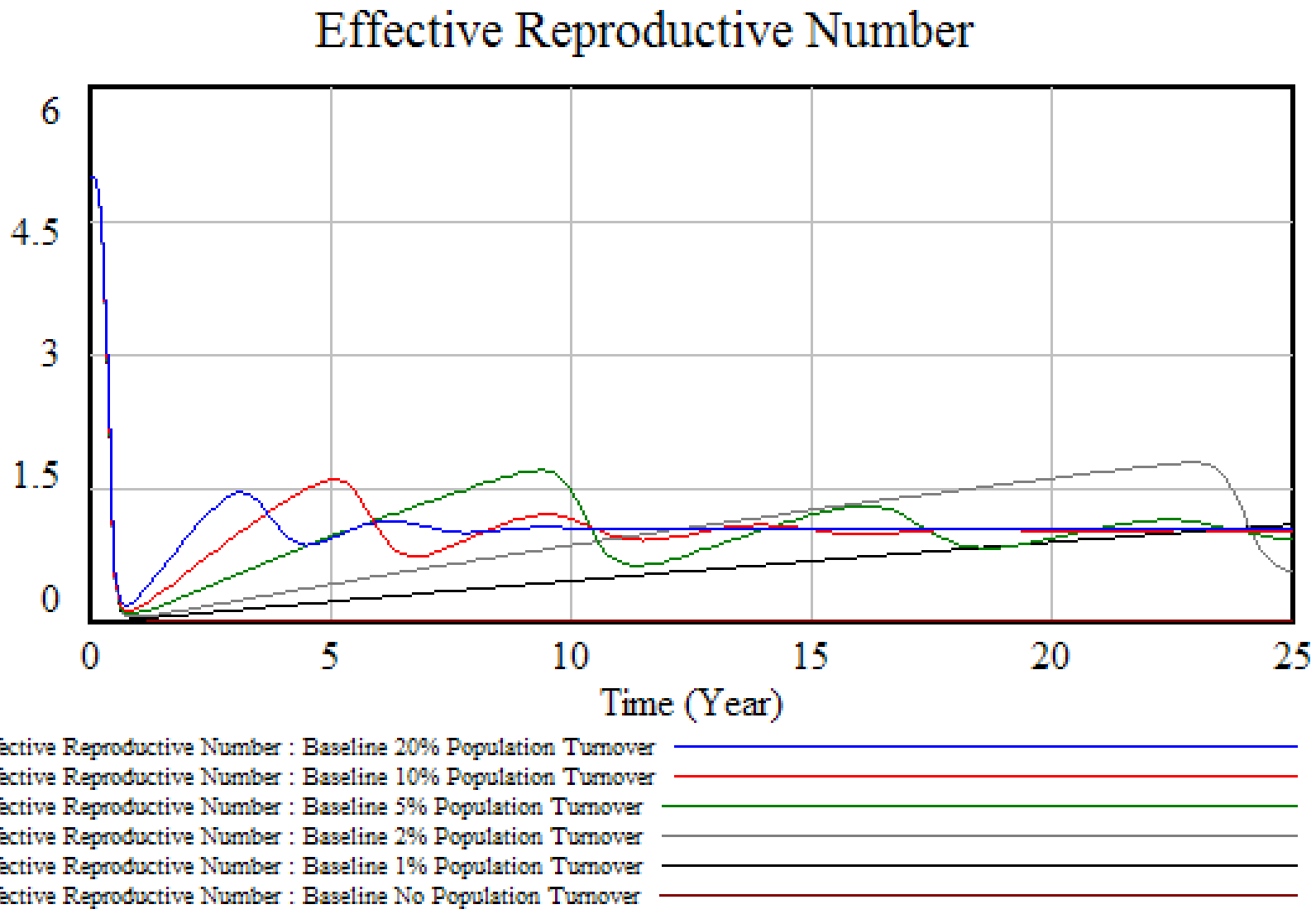
Impact of Turnover

- The greater the turnover rate, the greater the fraction of susceptibles in the population => the greater the endemic rate of infection

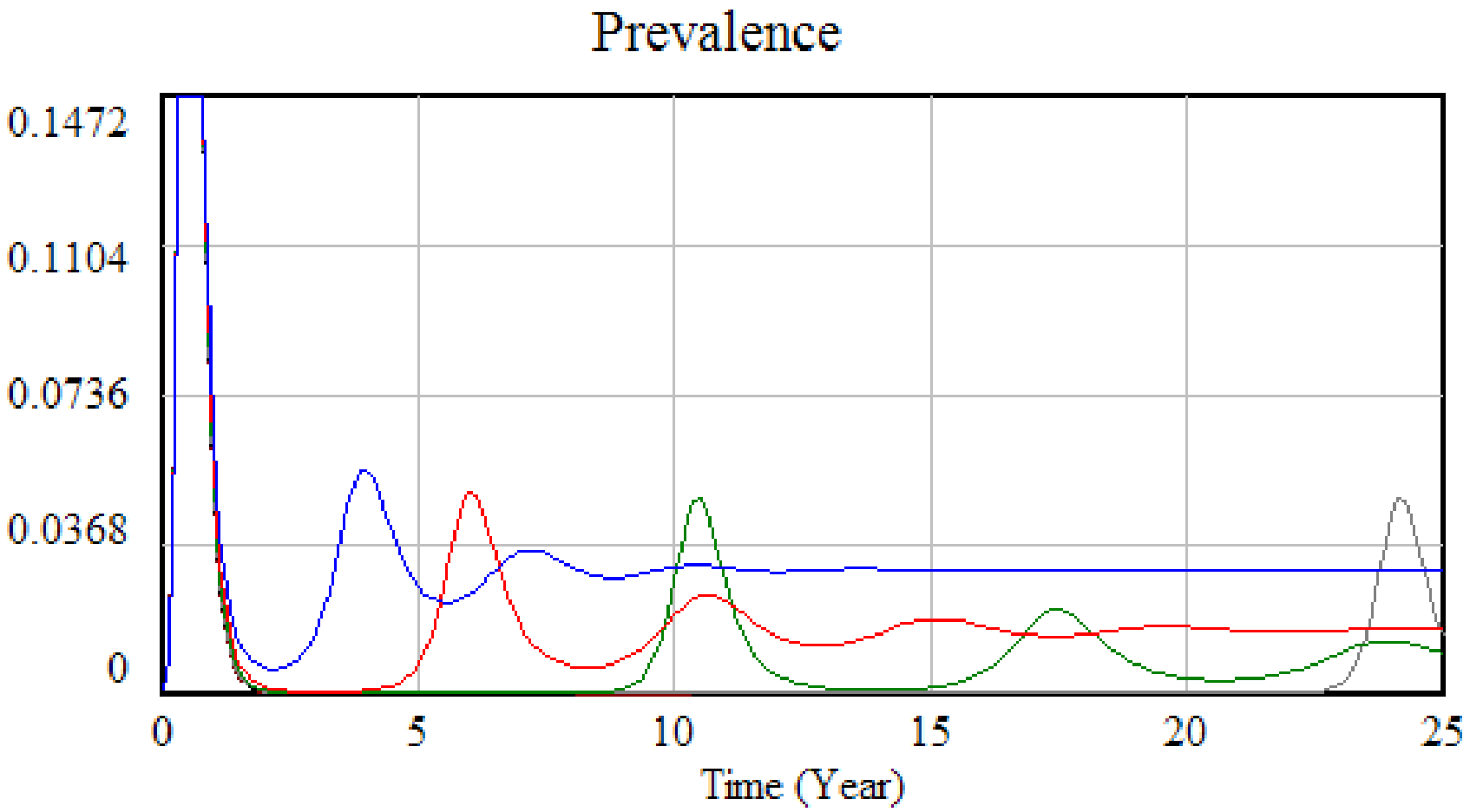
Fraction of Susceptibles



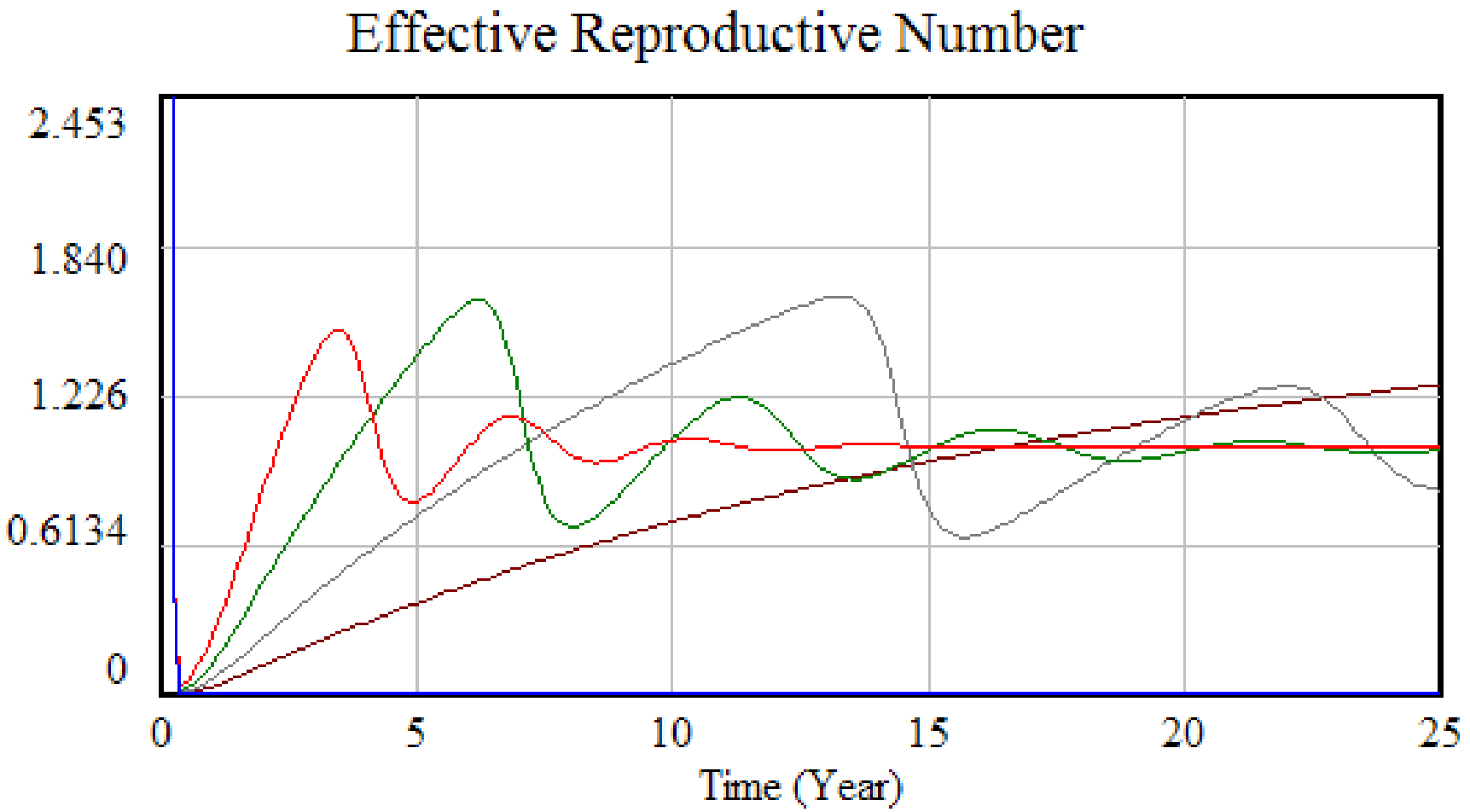
Effective Reproductive Number



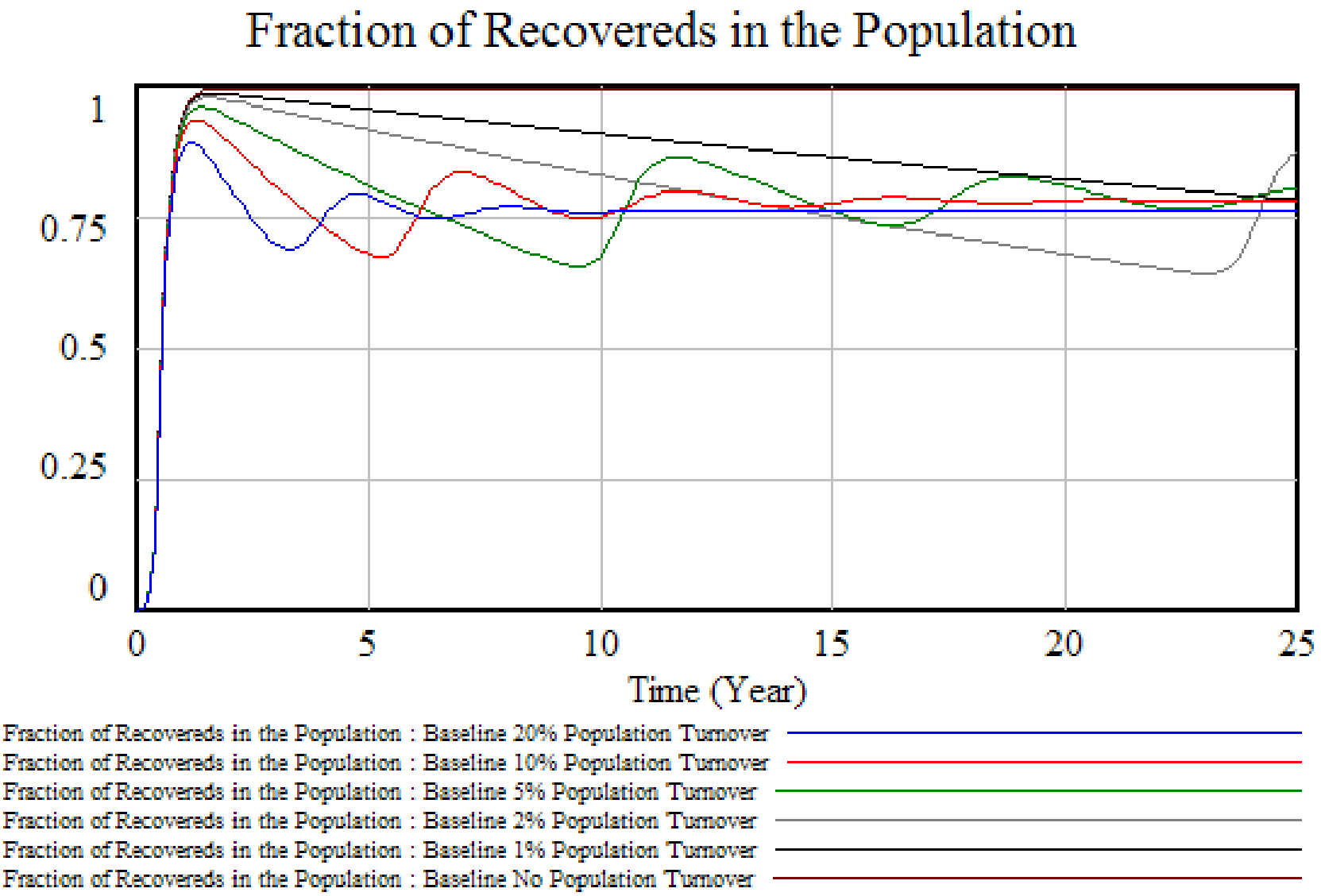
Prevalence


Prevalence
0.1472
0.1104
0.0736
0.0368
0
0
5
10
15
20
25
Time (Year)
Prevalence : Baseline 20% Population Turnover
Prevalence : Baseline 10% Population Turnover
Prevalence : Baseline 5% Population Turnover
Prevalence : Baseline 2% Population Turnover
Prevalence : Baseline 1% Population Turnover
Prevalence : Baseline No Population Turnover

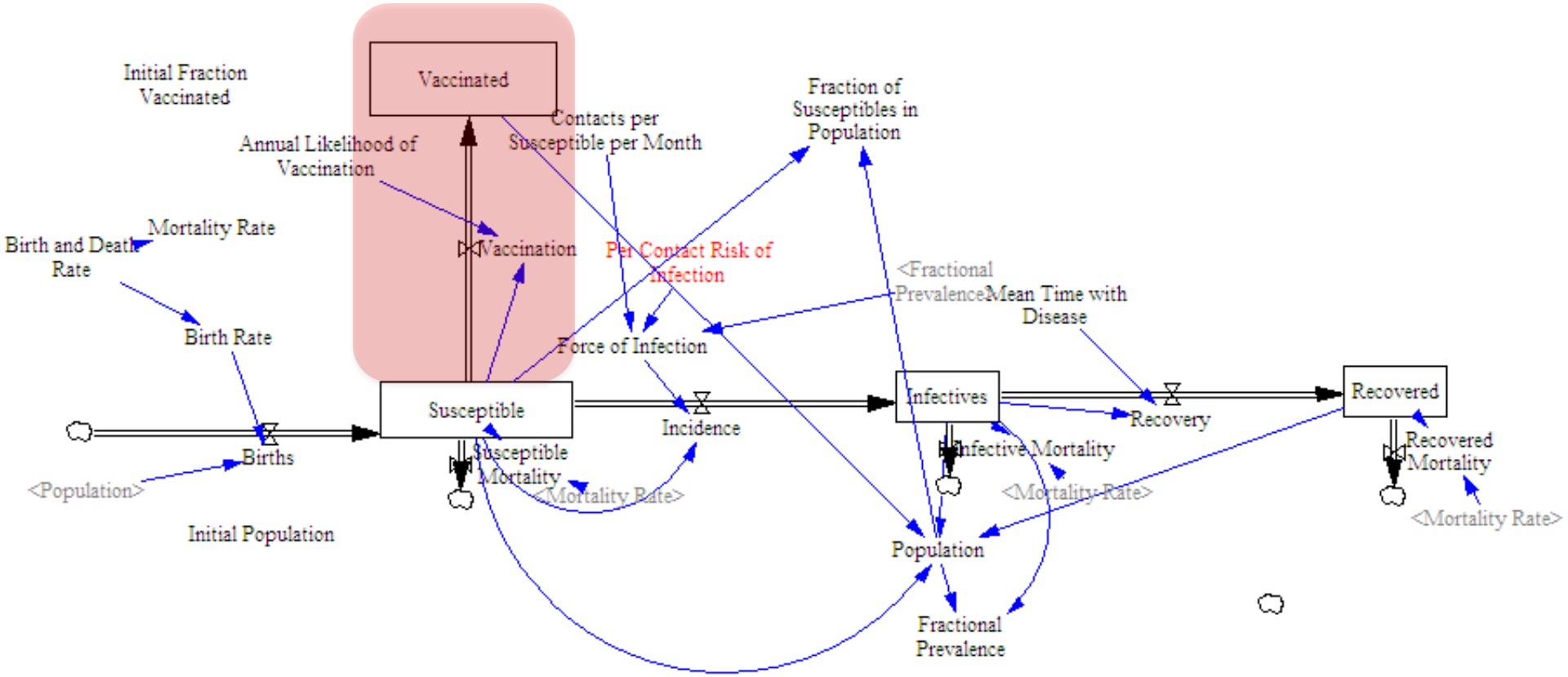
R_*


Effective Reproductive Number
2.453
1.840
1.226
0.6134
0
0
5
10
15
20
25
Time (Year)
Effective Reproductive Number : Baseline Closed Population
Effective Reproductive Number : Baseline 8% Population Turnover
Effective Reproductive Number : Baseline 4% Population Turnover
Effective Reproductive Number : Baseline 2% Population Turnover
Effective Reproductive Number : Baseline 32% Population Turnover
Effective Reproductive Number : Baseline 1% Population Turnover

Fraction Recovered

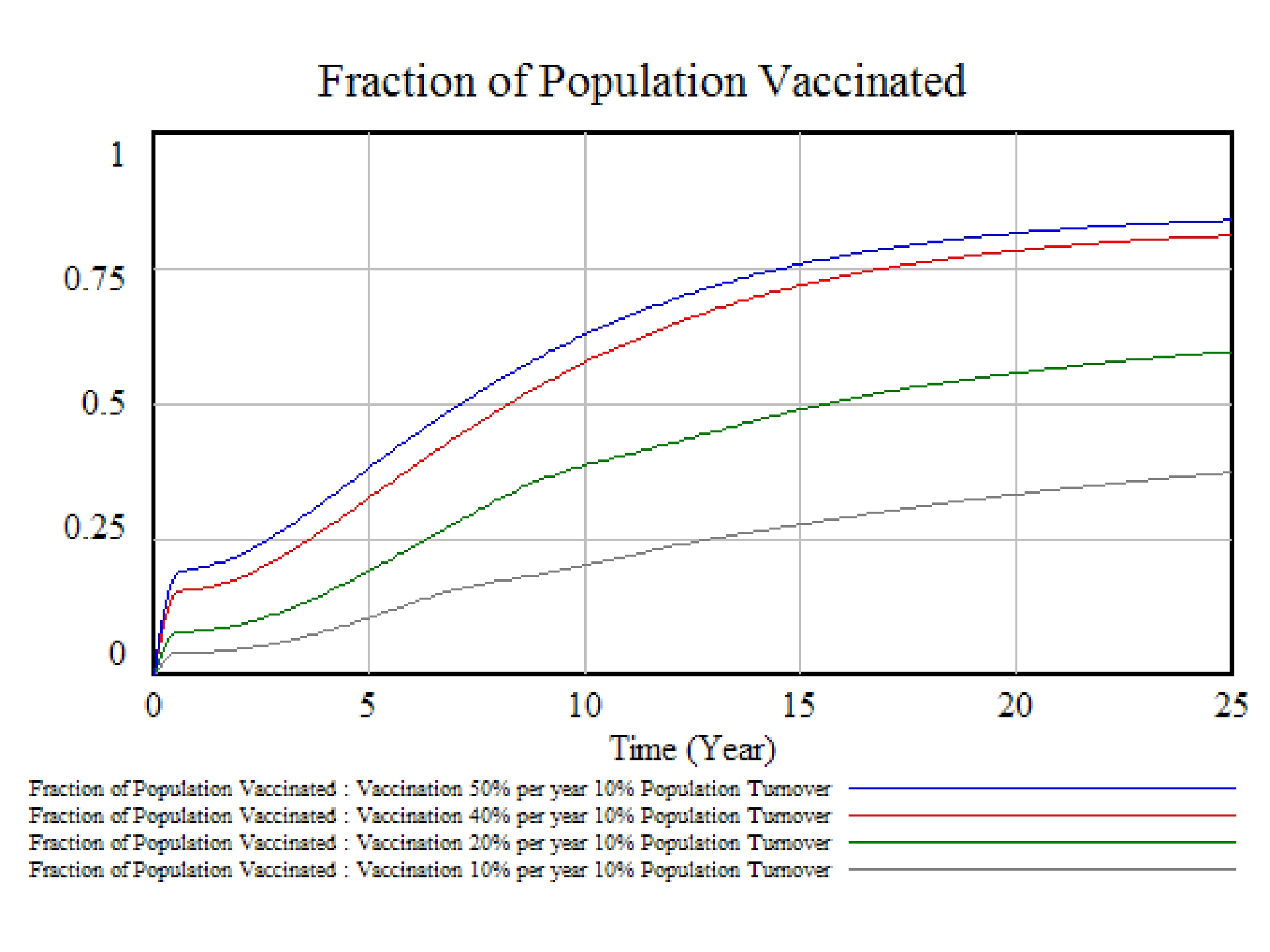


Adding Ongoing Vaccination Process

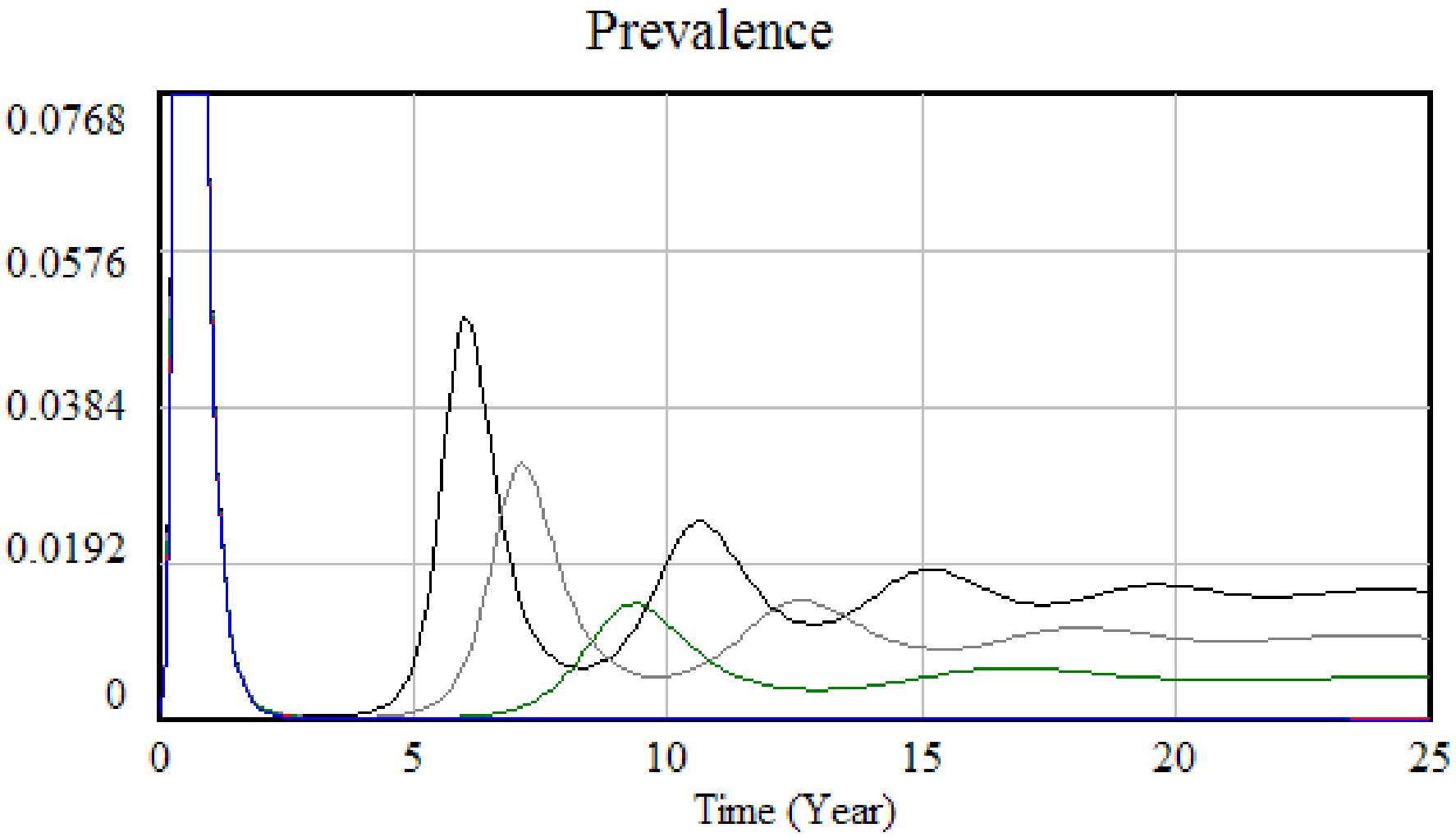


Simulating Introduction of Vaccination for a Childhood Infection in an Open Population

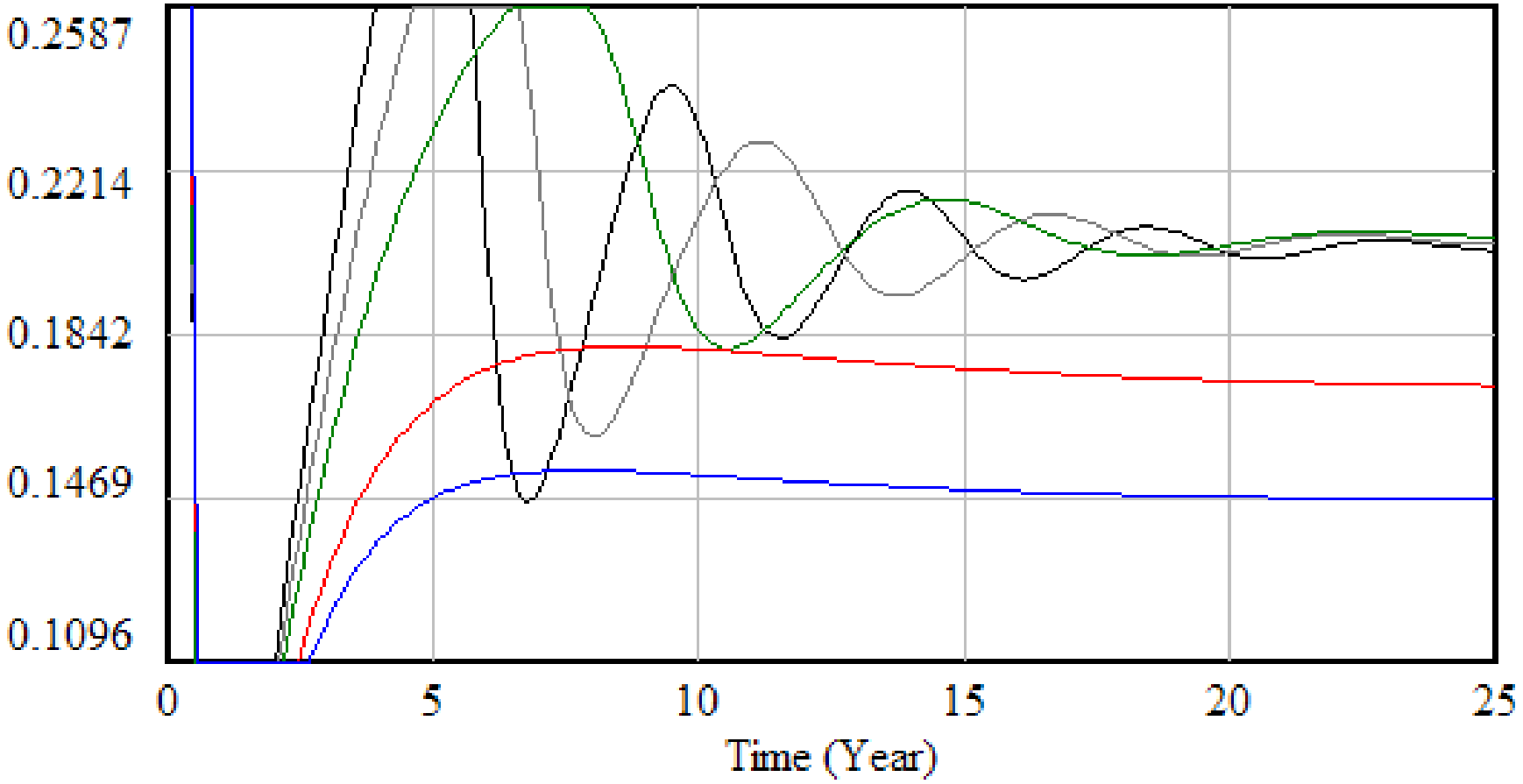
- c = 500
- Beta = 0.05
- Duration of infection = .25
- Initial Fraction Vaccinated = 0
- Monthly birth & death rate = 10% per year
  (focusing on children 0-10 years of age)
- Questions
  - What is R_0?
  - What level of susceptibles is required to sustain the infection
  - What is the critical vaccination fraction?


Fraction of Population Vaccinated
1
0.75
0.5
0.25
0
0
5
10
15
20
25
Time (Year)
Fraction of Population Vaccinated : Vaccination 50% per year 10% Population Turnover
Fraction of Population Vaccinated : Vaccination 40% per year 10% Population Turnover
Fraction of Population Vaccinated : Vaccination 20% per year 10% Population Turnover
Fraction of Population Vaccinated : Vaccination 10% per year 10% Population Turnover

What Rate of Vaccination Eliminates?

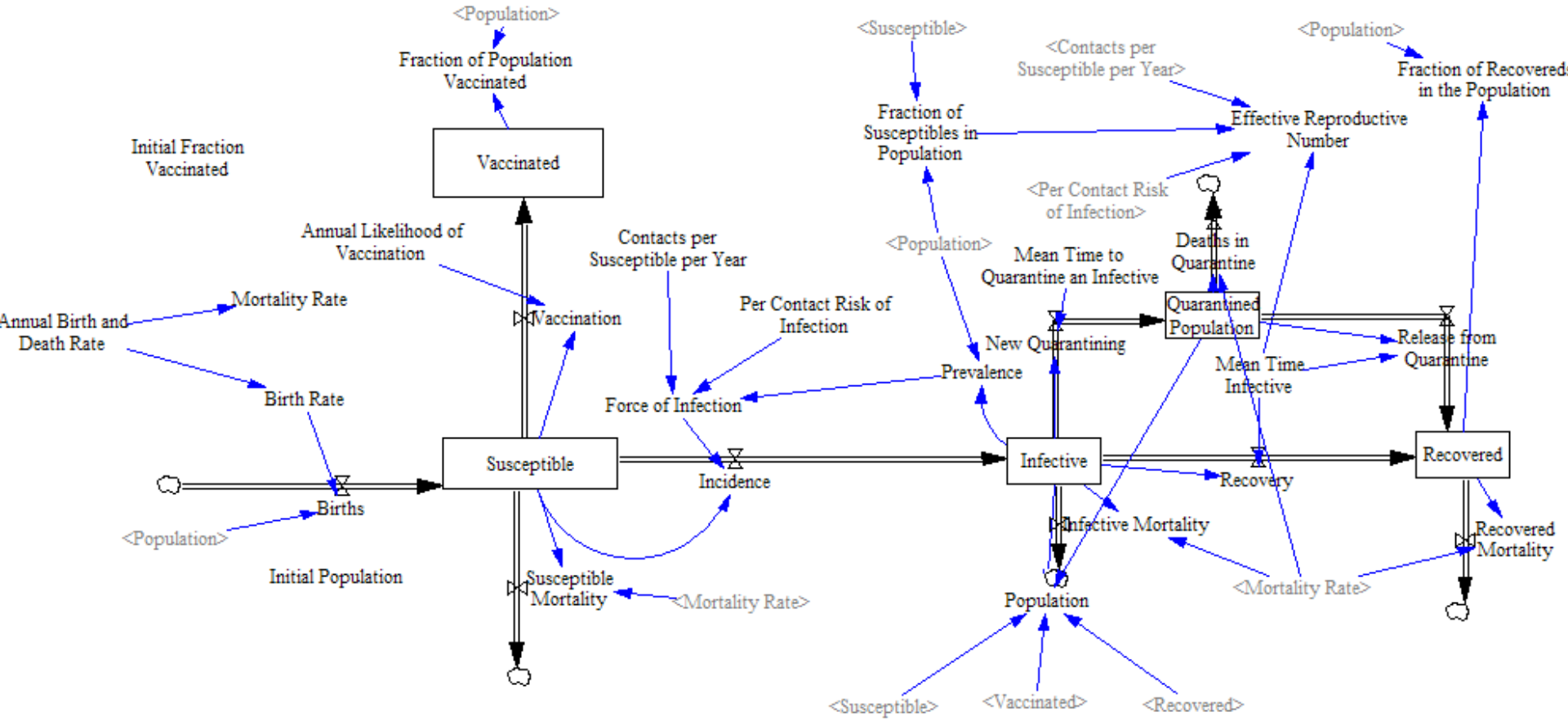


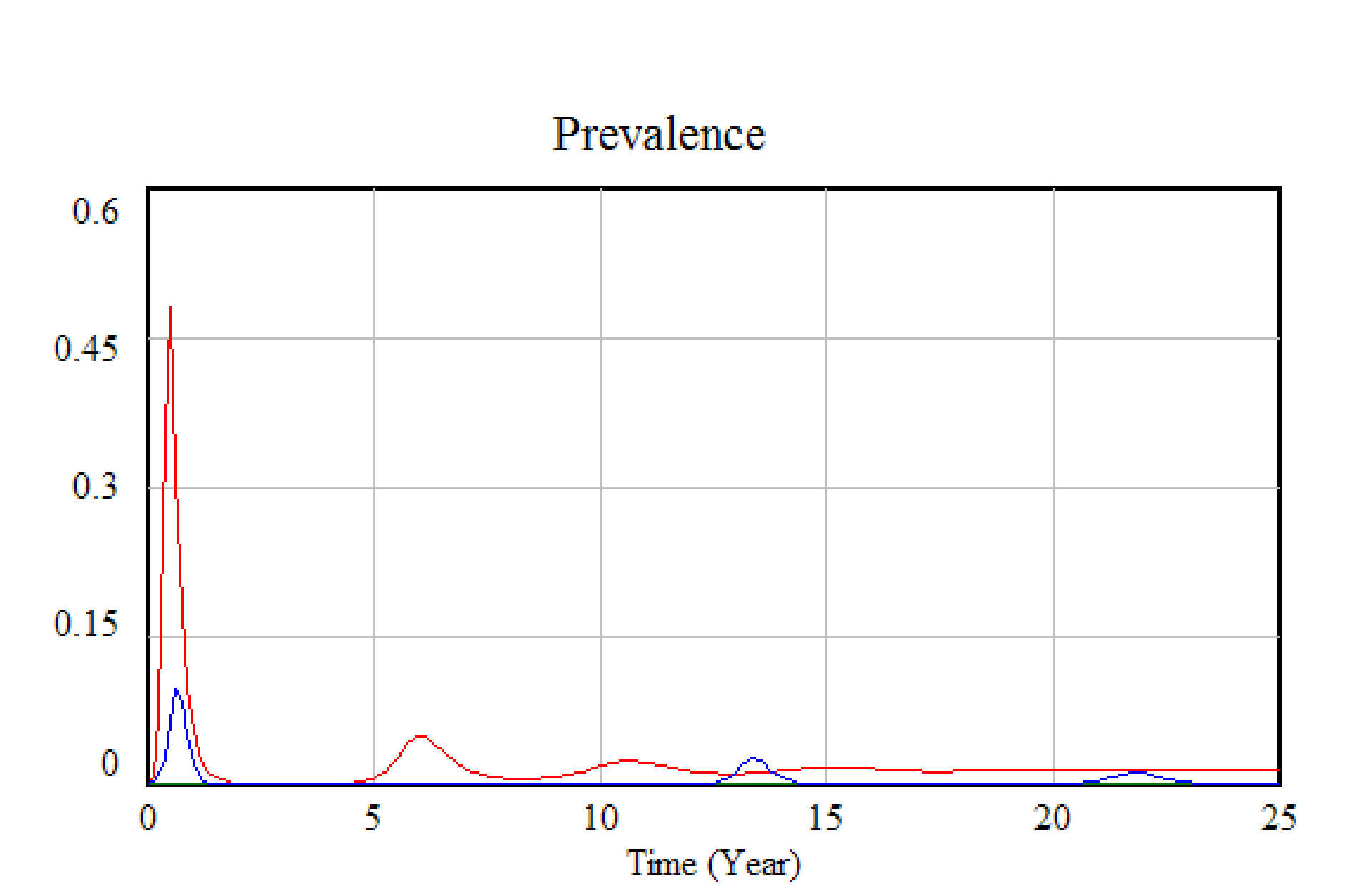
Fraction of Susceptibles in Population

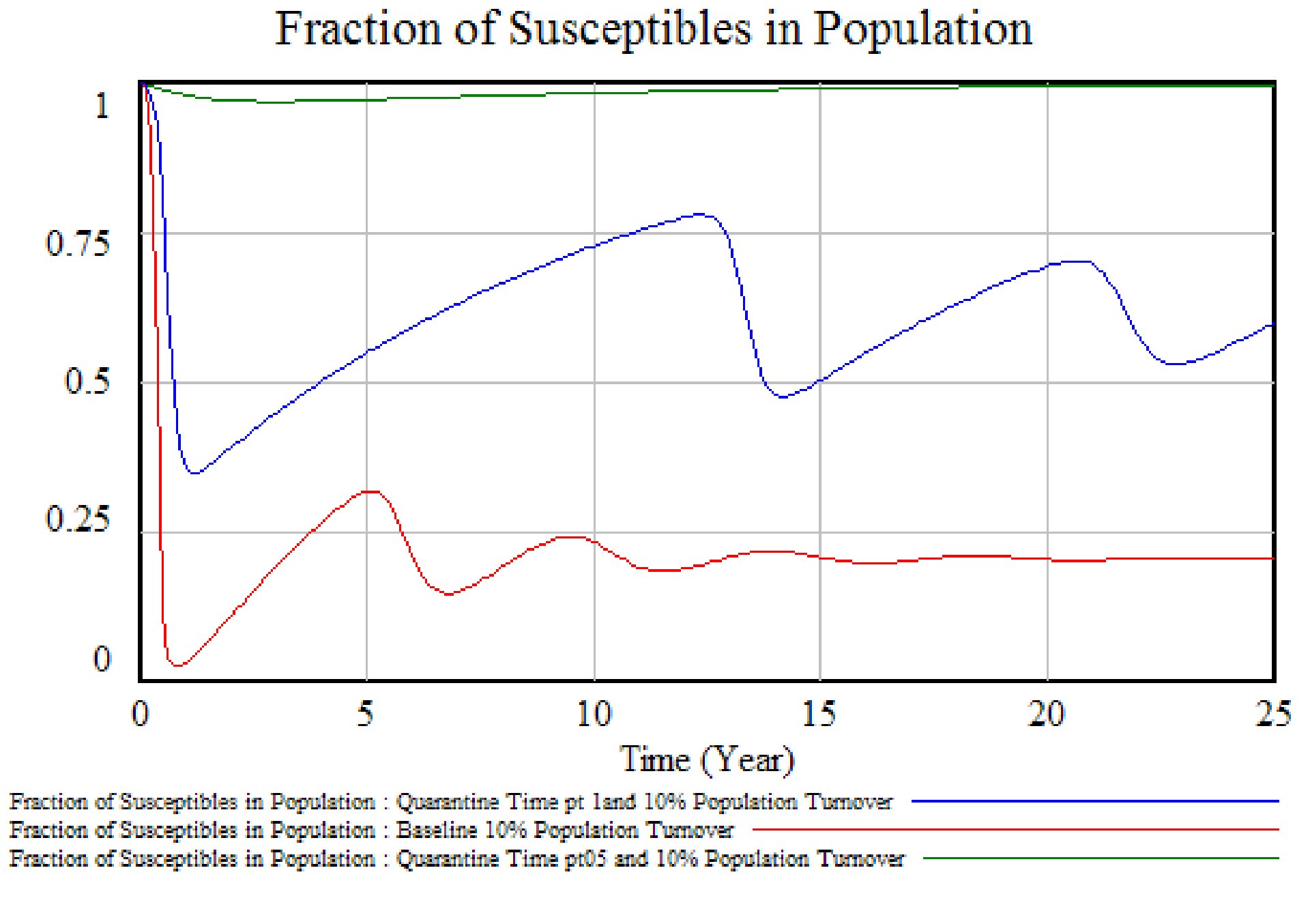


Fraction of Susceptibles in Population : Vaccination 50% per year 10% Population Turnover
Fraction of Susceptibles in Population : Vaccination 40% per year 10% Population Turnover
Fraction of Susceptibles in Population : Vaccination 20% per year 10% Population Turnover
Fraction of Susceptibles in Population : Vaccination 10% per year 10% Population Turnover
Fraction of Susceptibles in Population : Baseline 10% Population Turnover

Representing Quarantine




Prevalence
0.6
0.45
0.3
0.15
0
0
5
10
15
20
25
Time (Year)
Prevalence : Quarantine Time pt 1and 10% Population Turnover
Prevalence : Baseline 10% Population Turnover
Prevalence : Quarantine Time pt05 and 10% Population Turnover


Fraction of Susceptibles in Population
1
0.75
0.5
0.25
0
0
5
10
15
20
25
Time (Year)
Fraction of Susceptibles in Population : Quarantine Time pt 1and 10% Population Turnover
Fraction of Susceptibles in Population : Baseline 10% Population Turnover
Fraction of Susceptibles in Population : Quarantine Time pt05 and 10% Population Turnover

Endemic Situations

- In an endemic context, infection remains circulating in the population
- The common assumption here is that
  - The susceptible portion of the population will be children
  - At some point in their life trajectory (at an average age of acquiring infection A), individuals will be exposed to the infection & develop immunity

Table 6.1 Inter-epidemic period, T, of some common infections (from Anderson and May 1985c) and theoretical predictions of the period (eqn (6.15))

Infection	Inter-epidemic period, T, (years) (observed)	Geographical location and time period	Average age at infection, A	Latent plus infectious period, $D + D'$, (days)	Inter-epidemic period, T, (years) (calculated)
Measles	2	England and Wales, 1948–68	4–5	12	2
	2	Aberdeen, Scotland, 1883–1902	4–5		2
	2	Baltimore, USA, 1900–27	4–5		2
	2	Paris, France, 1880–1910	4–5		2
	1	Yaounde, Cameroun, 1968–75	2		1–2
	1	Ilesha, Nigeria, 1958–61	2		1–2
Rubella	3.5	Manchester, UK, 1916–83	11	18	4–5
	3.5	Glasgow, Scotland, 1929–64	11		4–5
Parvovirus (HPV)	3–5	England and Wales, 1960–80	?	?	
Mumps	3	England and Wales, 1948–82	6–7	16–26	3
	2–4	Baltimore, USA, 1928–73	8–9		3–4
Poliomyelitis	3–5	England and Wales, 1948–65	11–12	15–23	4–5
Echovirus (type II)	5	England and Wales, 1965–82	?	?	–
Smallpox	5	India, 1868–1948	12	10–14	4–5
Chickenpox	2–4	New York City, USA, 1928–72	6–8	18–23	3–4
	2–4	Glasgow, Scotland, 1929–72	6–8		3–4
Coxsackie virus (type B2)	2–3	England and Wales, 1967–82	?	?	
Scarlet fever	3–6	England and Wales, 1897–1978	10–14	15–20	4–5
Diphtheria	4–6	England and Wales, 1897–1979	11	16–20	4–5
Pertussis	3–4	England and Wales, 1948–85	4–5	27	3–4
Mycoplasma pneumoniae	4	England and Wales, 1970–82	?	?	

Age of Exposure & Reproductive Constant

- Cf a "natural" (non-immunized) constant size population where all die at same age and where
  - Mean Age at death L
  - Mean Age of exposure A (i.e. we assume those above A are exposed)
- Fraction susceptible is S/N = A/L (i.e. proportion of population below age A)
- Recall for our (and many but not *all* other) models: $R^*=(S/N)R_0=1 \Rightarrow S/N=1/R_0$
- Thus

$$A/L = 1/R_0 \Rightarrow L/A = R_0$$

  - This tells us that the larger the R_0, the earlier in life individuals become infected

Incompletely Immunized Population

- Suppose we have *q* fraction of population immunized ($q<q_c$)
- Suppose we have fraction *f* susceptible
- Fraction of the population currently or previously *infected* is 1-q-f
  - If we assume (as previously) that everyone lives until L and is infected at age A, then fraction 1-A/L has been infected
  - So $1-A/L= 1-q-f \Rightarrow A = L(q+f)$
    - This can be much higher than for the natural population
      - This higher age of infection can cause major problems, due to waning of childhood defenses
    - i.e. incomplete immunization leads to older mean age ofexposure

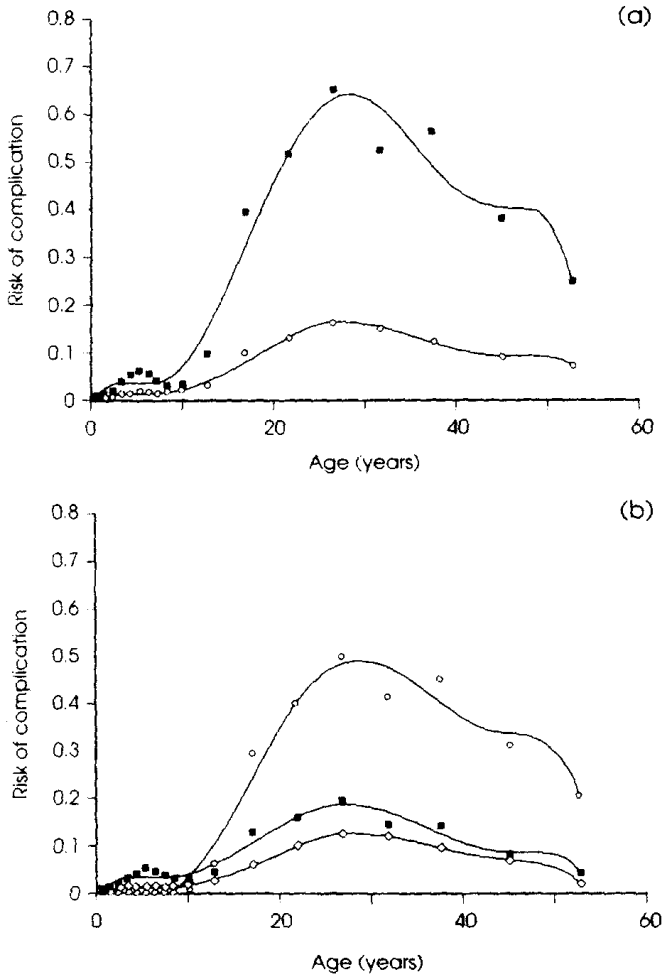


Fig. 5.19. The age- and sex-dependent risk of serious complications arising from infection by the mumps virus. The points represent the proportion of cases of mumps, admitted to hospitals in England and Wales in 1958–9, that presented with complications (data from RCGP (1974)), adjusted to mirror the proportion of the total number of cases of mumps in each age class (see text for further details). The recorded risk values denote relative as opposed to absolute changes with respect to age. Full curves, best-fit polynomials of the form $m(a) = b_0 + b_1a + b_2a^2 + b_3a^3 + b_4a \cdots b_na^n$. (a) solid squares, males, and open circles, females, denote the total relative risk of complications. (b) Complications divided into the risk of meningitis and/or encephalitis in males (solid squares) and females (open diamonds), and the risk of orchitis in males (open circles). Parameter values as defined in Anderson *et al.* (1987*a*).