CDM CMM
Centre for Disease Modelling
Centre de la modélisation des maladies

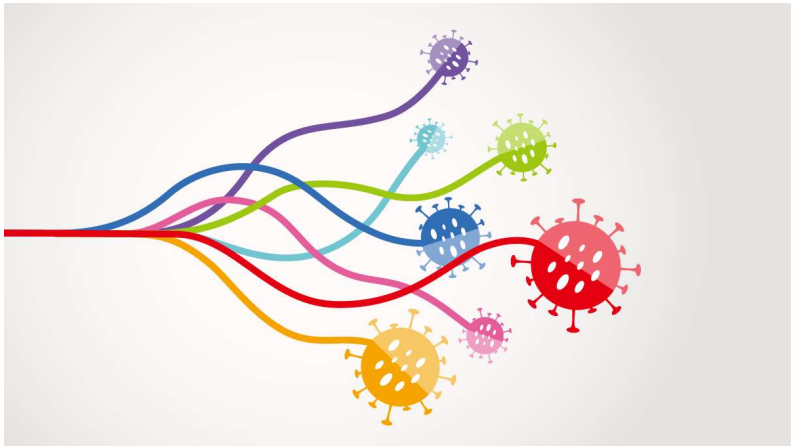
YORK UNIVERSITÉ UNIVERSITY
redefine THE POSSIBLE.

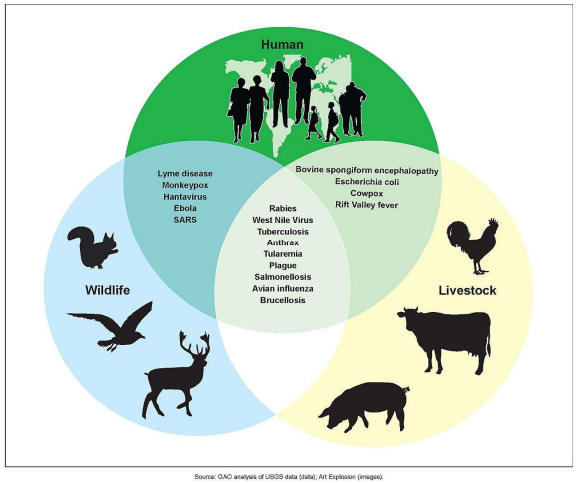
Multi-Pathogen / Multi-Host Models

Keeling and Rohani Book

Lecture Syllabus

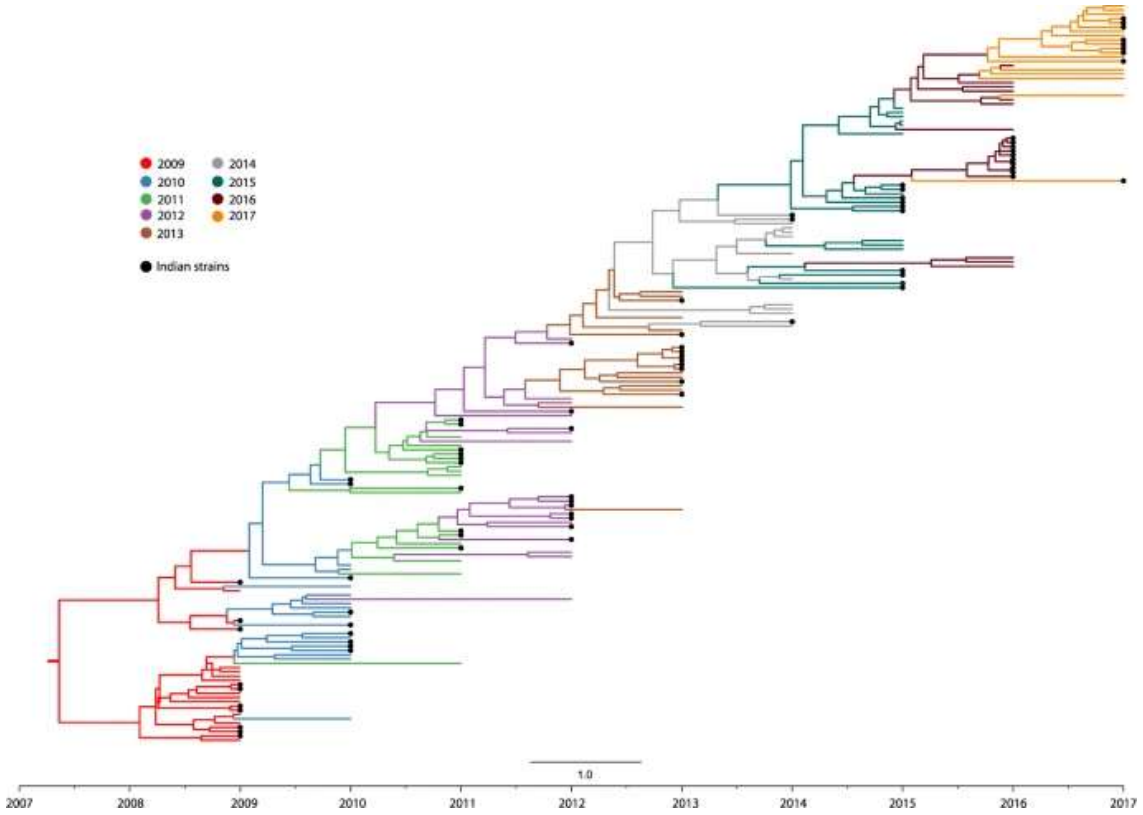
- Consider
  - Multiple infectious diseases (or strains) spreading through one host species
  - A single infectious disease that can be transmitted between different species





Multiple infectious diseases (or strains) spreading through one host species

- Examples
  - Influenza, meningitis, COVID-19, malaria, dengue
- Strain structure
- Must consider effects of cross-immunity over longer timespans



https://www.nature.com/articles/s41598-019-51097-w Phylogenetic tree of H1N1 influenza A virus from Indian and global strains reported from 2009 till 2017 with branches colored by year of isolation

Model with Cross-Immunity

$$\frac{dN_{SS}}{dt} = \nu - \beta_1 N_{SS} I_1 - \beta_2 N_{SS} I_2 - \mu N_{SS}$$

$$\frac{dN_{IS}}{dt} = \beta_1 N_{SS} I_1 - \gamma_1 N_{IS} - \mu N_{IS},$$

$$\frac{dN_{RS}}{dt} = \gamma_1 N_{IS} - \alpha_2 \beta_2 N_{RS} I_2 - \mu N_{RS},$$

$$\frac{dN_{SI}}{dt} = \beta_2 N_{SS} I_2 - \gamma_2 N_{SI} - \mu N_{SI},$$

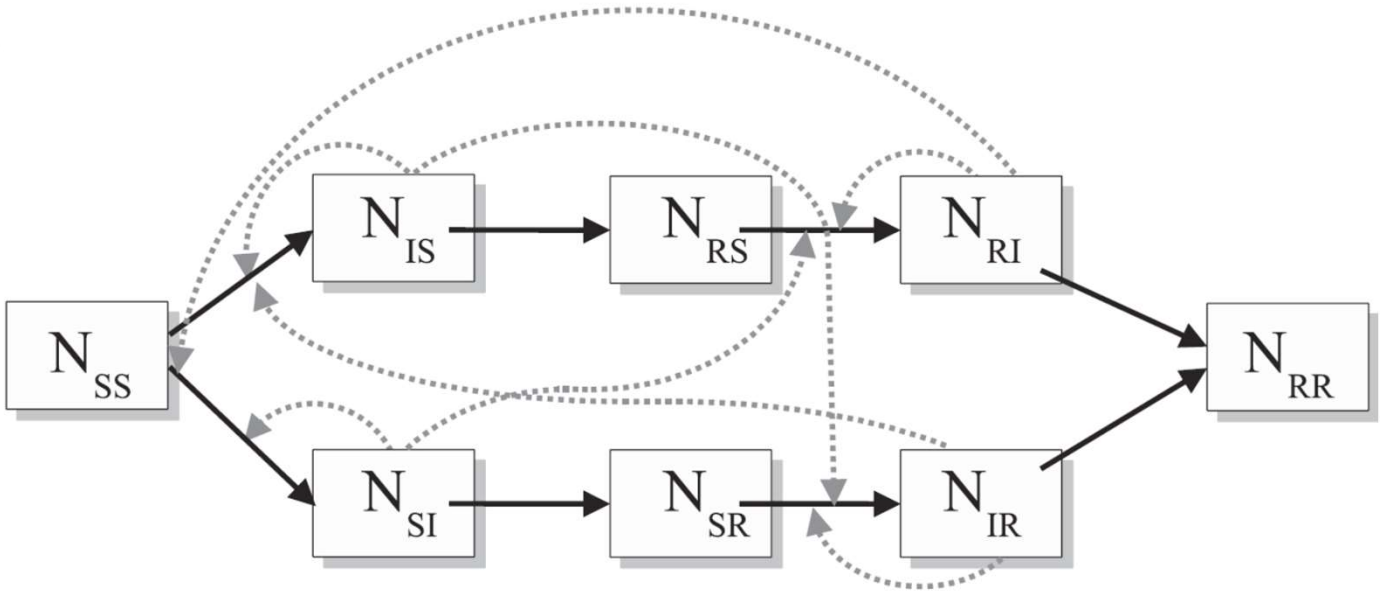
$$\frac{dN_{RI}}{dt} = \alpha_2 \beta_2 N_{RS} I_2 - \gamma_2 N_{RI} - \mu N_{RI},$$

$$\frac{dN_{SR}}{dt} = \gamma_1 N_{IS} - \alpha_1 \beta_1 N_{SR} I_1 - \mu N_{RS},$$

$$\frac{dN_{IR}}{dt} = \alpha_1 \beta_1 N_{SR} I_1 - \gamma_1 N_{IR} - \mu N_{IR},$$

$$\frac{dN_{RR}}{dt} = \gamma_1 N_{IR} + \gamma_2 N_{RI} - \mu N_{RR},$$

$$I_1 = N_{IS} + a_1 N_{IR}, \qquad I_2 = N_{SI} + a_2 N_{RI}$$



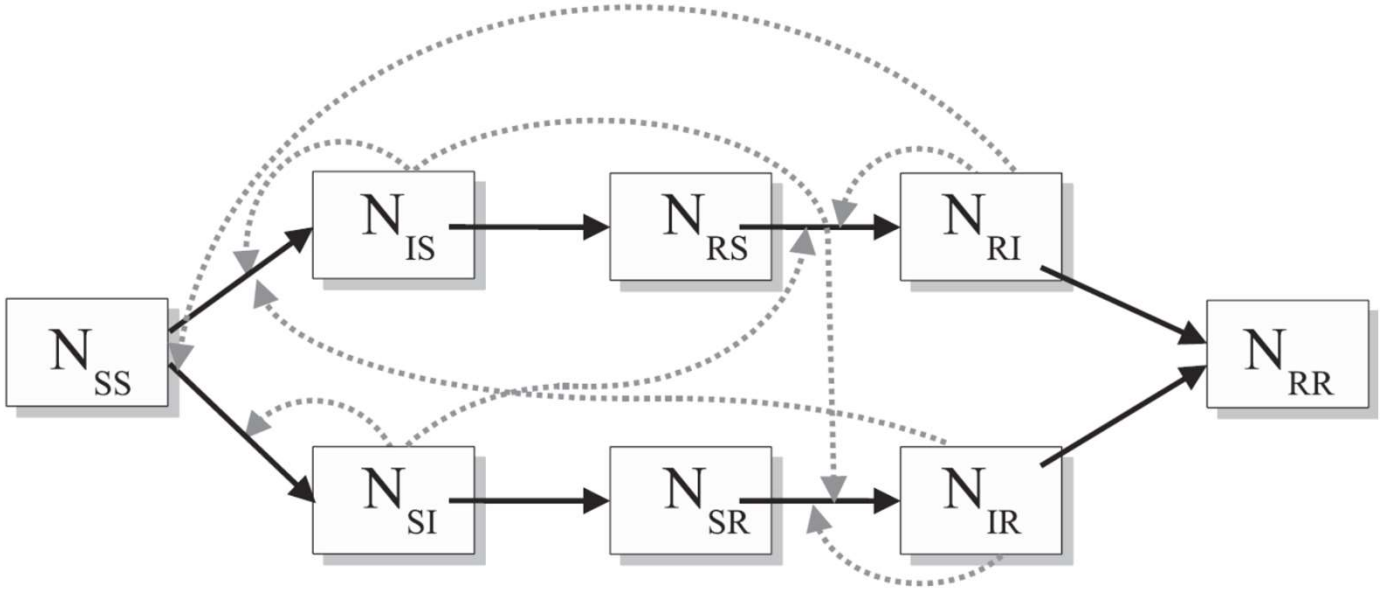
- ν, μ – birth, death
- $\beta_{1,2}$ – infection
- $\alpha_{1,2}$ – susceptibility reduction
- $a_{1,2}$ – transmission reduction
- $\gamma_{1,2}$ – recovery

- N_{ij} – popn in disease class i for strain 1 and j for strain 2 where i,j=S,I,R

I would also modify recovery rate depending on infection history

Assumptions

- Can't be infected by both strains at the same time (Innate immunity, but could revise model to allow this)
- Recovery rate is not affected by previous



- ν, μ – birth, death
- $\beta_{1,2}$ – infection
- $\alpha_{1,2}$ – susceptibility reduction
- $a_{1,2}$ – transmission reduction
- $\gamma_{1,2}$ – recovery

- N_{ij} – popn in disease class i for strain 1 and j for strain 2 where i,j=S,I,R

I would also modify recovery rate depending on infection history

Reproduction Numbers and Invasion

- If only have one strain, we can reduce the system and see that $R_0^1 = \frac{\beta_1}{\gamma_1+\mu}$ $R_0^2 = \frac{\beta_2}{\gamma_2+\mu}$
- Suppose that one strain has already infected the population and the population has reached equilibrium, then

$$N_{SS}^* = \frac{\gamma_1+\mu}{\beta_1}, \quad N_{IS}^* = \frac{\mu}{\gamma_1+\mu} - \frac{\mu}{\beta_1}, \quad N_{RS}^* = \frac{\gamma_1}{\gamma_1+\mu} - \frac{\gamma_1}{\beta_1}$$

and

$$\frac{dI_2}{dt} = \frac{dN_{SI}}{dt} + \frac{a_2 dN_{RI}}{dt} = \ \ldots \ = \beta_2\left[\frac{1}{R^1} - \frac{1}{R^2}\right] I_2 + \frac{a_2\alpha_2\gamma_1}{\gamma_1+\mu}\left(1 - \frac{1}{R^1}\right) I_2$$

$\frac{dI_2}{dt} > 0$ when $R_0^2 > R_0^1 > 1$ (where $R_0^1 > 1$ is given since strain 1 infected the population), or if cross immunity ($a_2\alpha_2$) is sufficiently high enough for the second term to dominate

Model with Fully Protective Immunity

$$\frac{dN_{SS}}{dt} = \nu - \beta_1 N_{SS} I_1 - \beta_2 N_{SS} I_2 - \mu N_{SS}$$

$$\frac{dN_{IS}}{dt} = \beta_1 N_{SS} I_1 - \gamma_1 N_{IS} - \mu N_{IS},$$

$$\frac{dN_{RS}}{dt} = \gamma_1 N_{IS} - \alpha_2 \beta_2 N_{RS} I_2 - \mu N_{RS},$$

$$\frac{dN_{SI}}{dt} = \beta_2 N_{SS} I_2 - \gamma_2 N_{SI} - \mu N_{SI},$$

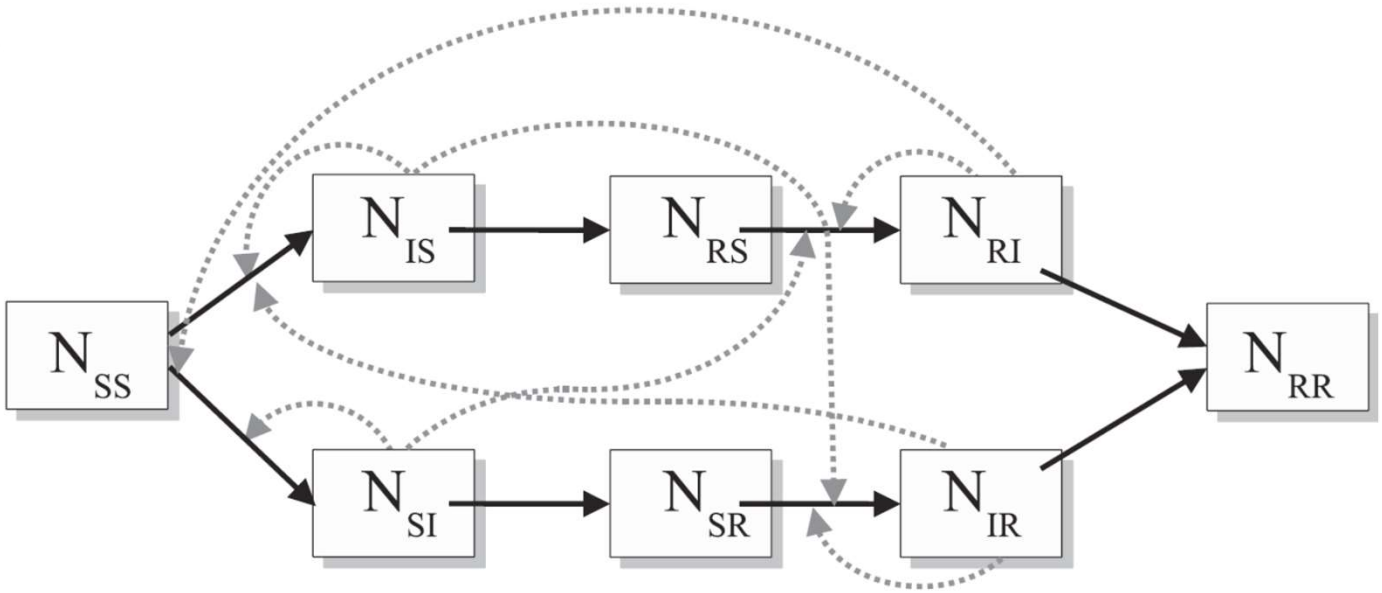
$$\frac{dN_{RI}}{dt} = \alpha_2 \beta_2 N_{RS} I_2 - \gamma_2 N_{RI} - \mu N_{RI},$$

$$\frac{dN_{SR}}{dt} = \gamma_1 N_{IS} - \alpha_1 \beta_1 N_{SR} I_1 - \mu N_{RS},$$

$$\frac{dN_{IR}}{dt} = \alpha_1 \beta_1 N_{SR} I_1 - \gamma_1 N_{IR} - \mu N_{IR},$$

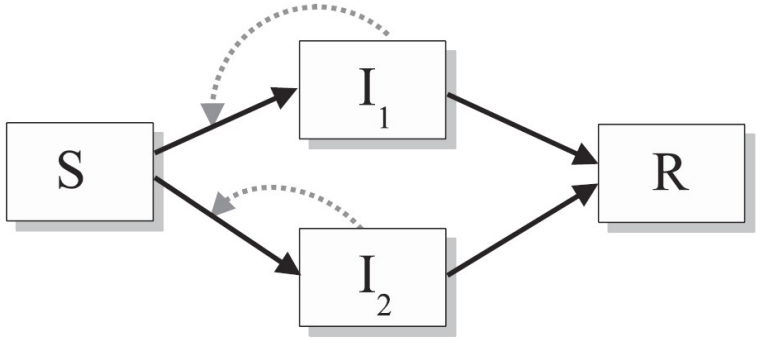
$$\frac{dN_{RR}}{dt} = \gamma_1 N_{IR} + \gamma_2 N_{RI} - \mu N_{RR},$$

$$I_1 = N_{IS} + a_1 N_{IR}, \qquad I_2 = N_{SI} + a_2 N_{RI}$$

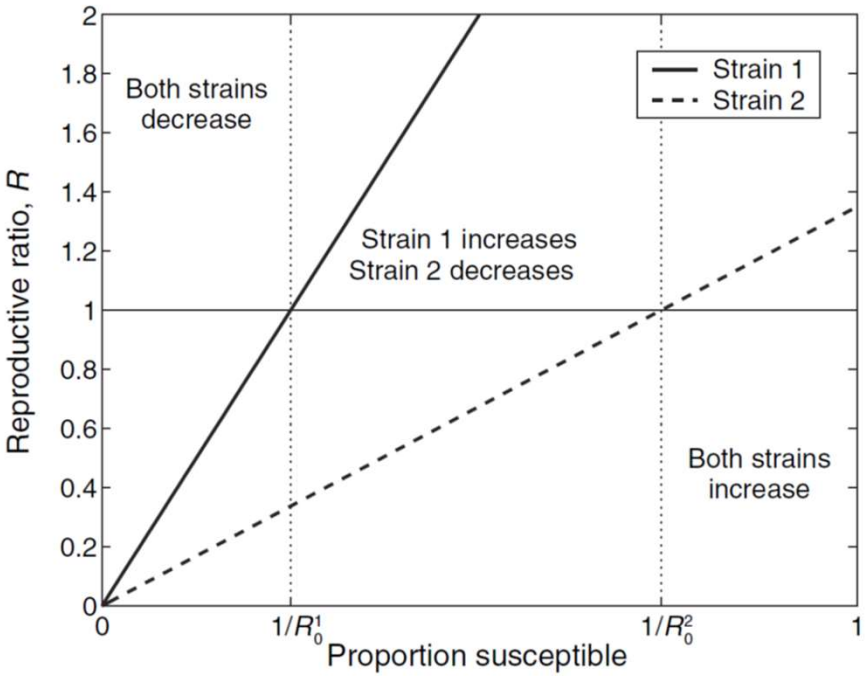


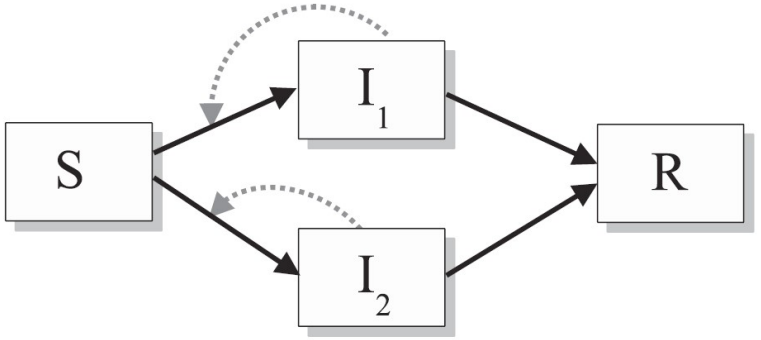
- If $\alpha_1, \alpha_2 = 0$, this model becomes

where $S = N_{SS}$, $I_1 = N_{IS}, I_2 = N_{SI}$,



Model with Fully Protective Immunity





Only one strain will exist, the one with the largest reproduction number

Figure 4.2. The reproductive ratio, $R = S \times R_0$, of two competing strains that offer complete cross-immunity. When the level of susceptibles is low the prevalence of both strains decreases, whereas when a high proportion are susceptible both strains can increase, although this will eventually lead to a decrease in the proportion susceptible, changing the dynamics. In the intermediate region, only strain 1 can increase with the weaker strain 2 being driven to extinction. ($\beta_1 = 4$, $\beta_2 = 1.35$, $\gamma_1 + \mu = \gamma_2 + \mu = 1$, $m_1 = m_2 = 0$.)

Model with No Cross-Immunity

$$\frac{dN_{SS}}{dt} = \nu - \beta_1 N_{SS} I_1 - \beta_2 N_{SS} I_2 - \mu N_{SS}$$

$$\frac{dN_{IS}}{dt} = \beta_1 N_{SS} I_1 - \gamma_1 N_{IS} - \mu N_{IS},$$

$$\frac{dN_{RS}}{dt} = \gamma_1 N_{IS} - \alpha_2 \beta_2 N_{RS} I_2 - \mu N_{RS},$$

$$\frac{dN_{SI}}{dt} = \beta_2 N_{SS} I_2 - \gamma_2 N_{SI} - \mu N_{SI},$$

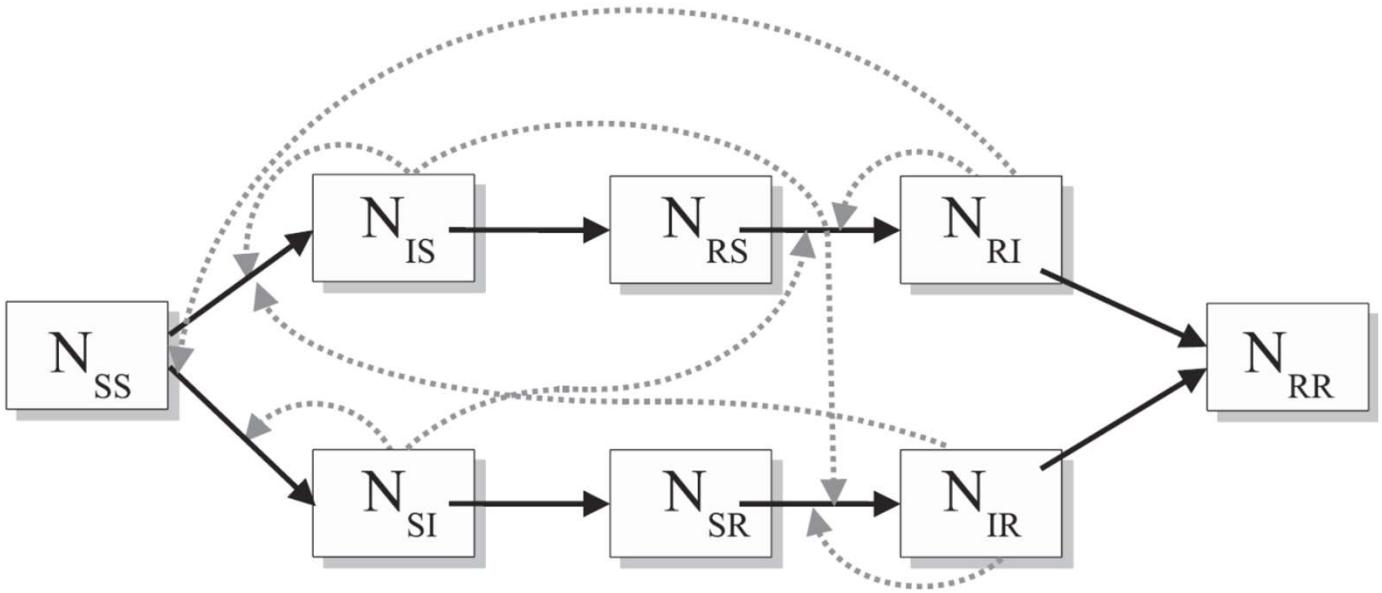
$$\frac{dN_{RI}}{dt} = \alpha_2 \beta_2 N_{RS} I_2 - \gamma_2 N_{RI} - \mu N_{RI},$$

$$\frac{dN_{SR}}{dt} = \gamma_1 N_{IS} - \alpha_1 \beta_1 N_{SR} I_1 - \mu N_{RS},$$

$$\frac{dN_{IR}}{dt} = \alpha_1 \beta_1 N_{SR} I_1 - \gamma_1 N_{IR} - \mu N_{IR},$$

$$\frac{dN_{RR}}{dt} = \gamma_1 N_{IR} + \gamma_2 N_{RI} - \mu N_{RR},$$

$$I_1 = N_{IS} + a_1 N_{IR}, \qquad I_2 = N_{SI} + a_2 N_{RI}$$



- If $\alpha_1, \alpha_2 = 1$
- Still assumes that someone can't be infected by both strains at the same time
  - Innate immune system is ramped up, so this is totally feasible
  - BUT, we can modify the model to allow for co-infection

Model with Increased Susceptibility

- SIS model
- Can be the case for sexually transmitted infections
  - Infection with one STI can increase susceptibility for another

$$\frac{dN_{SS}}{dt} = -\beta_1 N_{SS} I_1 - \beta_2 N_{SS} I_2 + \gamma_1 N_{IS} + \gamma_2 N_{SI} + \gamma_3 N_{II},$$

$$\frac{dN_{IS}}{dt} = \beta_1 N_{SS} I_1 - \gamma_1 N_{IS} - \widehat{\beta}_2 N_{IS} I_2,$$

$$\frac{dN_{SI}}{dt} = \beta_2 N_{SS} I_2 - \gamma_2 N_{SI} - \widehat{\beta}_1 N_{SI} I_1,$$

$$\frac{dN_{II}}{dt} = \widehat{\beta}_1 N_{SI} I_1 + \widehat{\beta}_2 N_{IS} I_2 - \gamma_3 N_{II},$$

$$I_1 = N_{IS} + N_{II}, \qquad I_2 = N_{SI} + N_{II}.$$

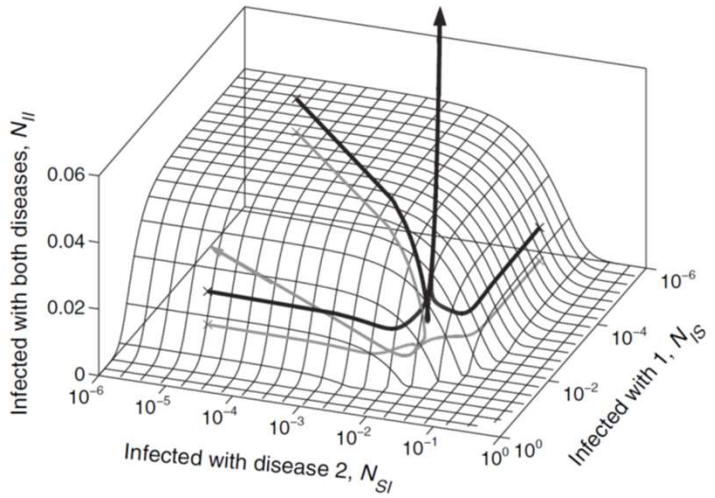


Figure 4.7. Example of six trajectories from the enhanced susceptibility model, equation (4.5), clearly demonstrating the Allee effect. The surface separating persistence from extinction is also shown as a mesh. Gray orbits start just below the surface and lead to extinction, whereas black orbits start just above the surface and tend to a fixed point with a high prevalence of both infections. ($\gamma_1 = \gamma_2 = \gamma_3 = 1$, $\beta_1 = 0.9$, $\beta_2 = 0.85$, $\widehat{\beta}_1 = 8$, $\widehat{\beta}_2 = 7$.)

Model Accounting for Many Strains

- Model with n strains has 2n equations

$$\frac{dS_i}{dt} = \nu - \sum_j \beta_j c_{ij} S_i I_j - \mu S_i,$$

$$\frac{dI_i}{dt} = \beta_i S_i I_i - \gamma_i I_i - \mu I_i,$$

- where $0 \leq c_{ij} \leq 1$ changes susceptibility, and $c_{ii} = 1$
- Note: susceptibility classes are not mutually exclusive
- Gog/Grenfell: strains on 1D line

$$c_{ij} = \exp(-A[i-j]^2)$$

Model with 4 Strains

- S_i, P_i, R_i are total, partial, not at all susceptible to strain I
- λ_i - force of infection of strain I
- c_{ij} is 1 if i, j are neighboring strains, but 0 otherwise
- $a < 1, \quad \alpha = 1, \beta_i = \beta$

$$\frac{dS_i}{dt} = \mu - S_i \sum_j c_{ij}\lambda_j - \mu S_i,$$

$$\frac{dP_i}{dt} = S_i \sum_{j \neq i} c_{ij}\lambda_j - \beta P_i I_i - \mu P_i,$$

$$\frac{dR_i}{dt} = (S_i + P_i)\lambda_i - \mu R_i,$$

$$\frac{d\lambda_i}{dt} = [S_i + a P_i]\lambda_i - \gamma I_i - \mu I_i,$$

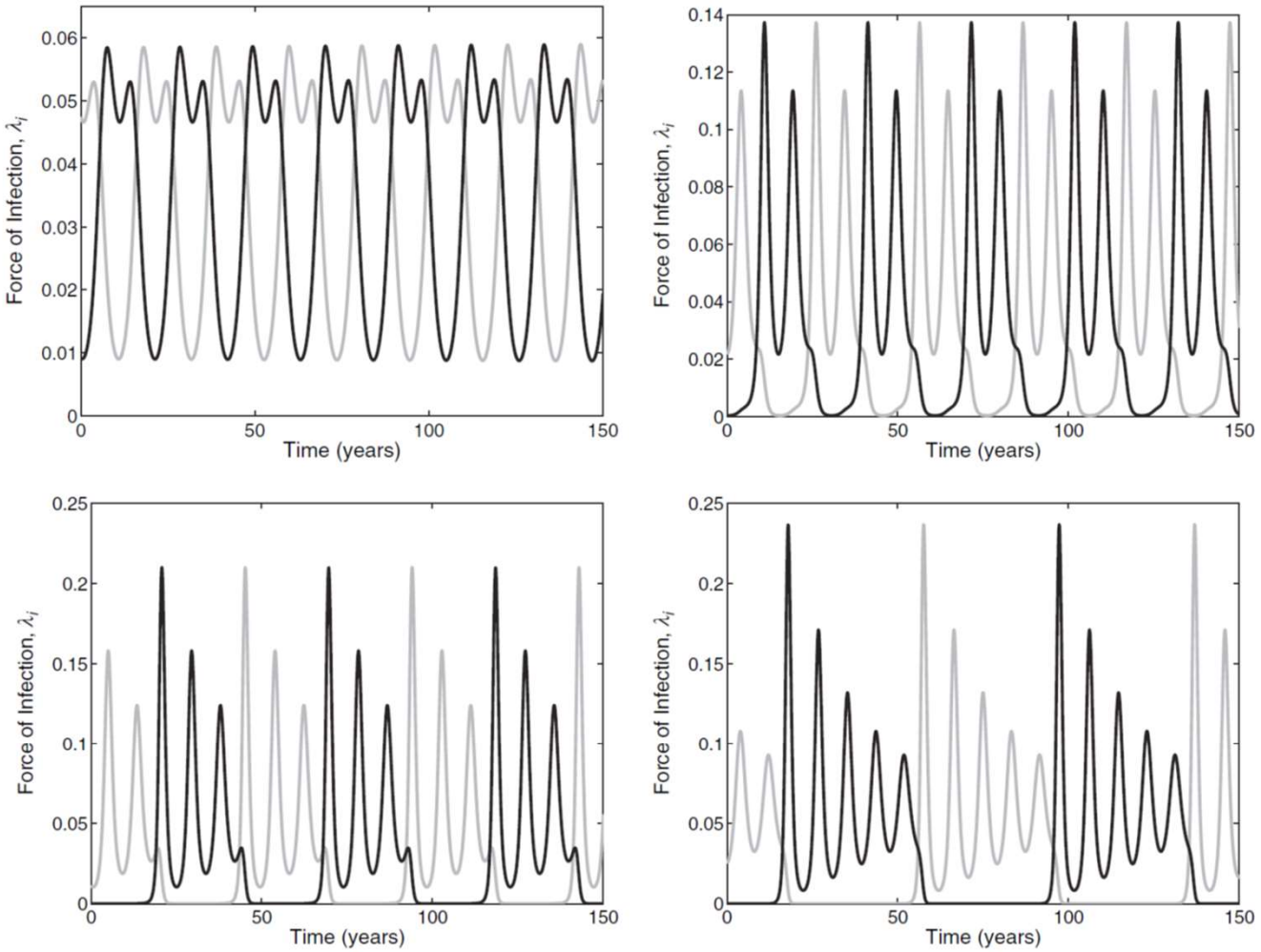


Figure 4.9. The dynamics of strains 1 and 2 of a four-strain system as typified by the force of infection for each strain, λ_i. The level of cross-immunity, a, increases from top left to bottom right ($a = 0.55, 0.6, 0.65, 0.7$). ($\mu = 0.02$ per year, $\gamma = 10$ per year ($1/\gamma = 36.5$ days), $\beta = 40$ per year, hence $R_0 = 4$.)

Multiple Hosts

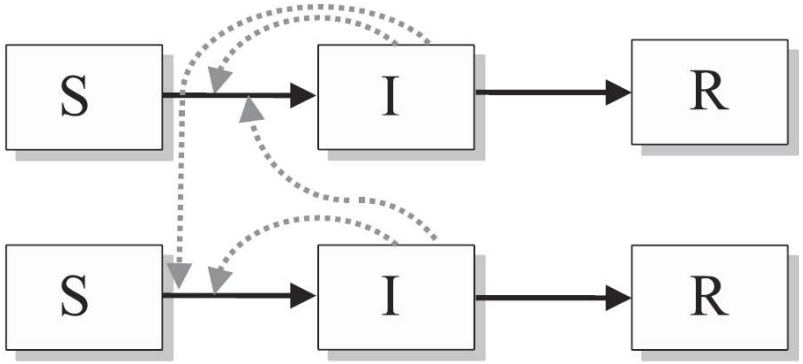
- One disease can infect different hosts
  - MERS-CoV, SARS-1, SARS-CoV-2 (COVID-19), influenzas, West Nile virus, Foot-and-Mouth Disease (i.e., sheep, cattle)

- Consider
  - Directly transmitted diseases
  - Vector-borne disease

- Zoonoses (directly transmitted and vector-borne transmission)

Shared Hosts

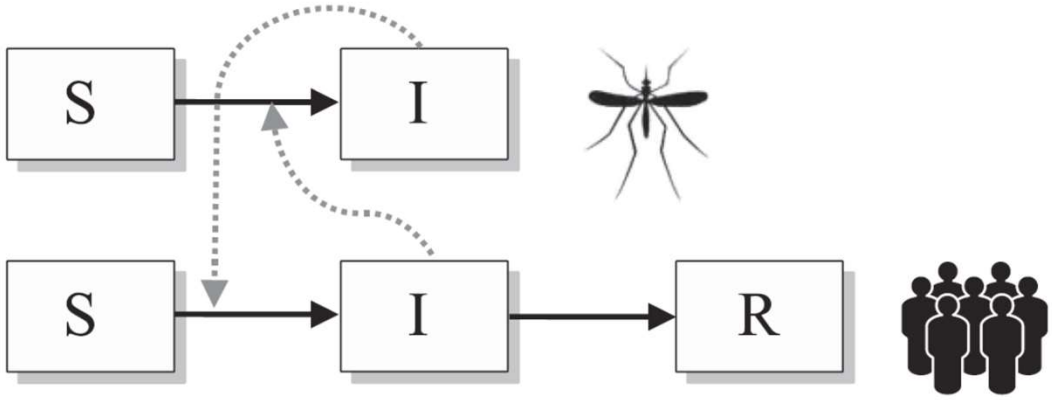
$$\frac{dX_A}{dt} = \nu_A - X_A(\beta_{AA}Y_A + \beta_{AB}Y_B) - \mu_A X_A,$$
$$\frac{dY_A}{dt} = X_A(\beta_{AA}Y_A + \beta_{AB}Y_B) - \gamma_A Y_A - \mu_A Y_A,$$
$$\frac{dX_B}{dt} = \nu_B - X_B(\beta_{BA}Y_A + \beta_{BB}Y_B) - \mu_B X_B,$$
$$\frac{dY_B}{dt} = X_B(\beta_{BA}Y_A + \beta_{BB}Y_B) - \gamma_B Y_B - \mu_B Y_B.$$



- $X_{A,B}, Y_{A,B}$ - fraction of population A,B that is susceptible or infected with the disease
- $\nu_{A,B}, \mu_{A,B}$ - birth and death rates of different populations
- β_{ij} - transmission rate between indivs in popn $i, j \, \epsilon \{A, B\}$
- $\gamma_{A,B}$ - different popns have different recovery rates (humans vs camels for MERS)

Vectored Transmission

- Lyme disease, West Nile Virus, Malaria, etc



$$\frac{dX_H}{dt} = \nu_H - rT_{HM}Y_M X_H - \mu_H X_H,$$
$$\frac{dY_H}{dt} = rT_{HM}Y_M X_H - \mu_H Y_H - \gamma_H Y_H,$$
$$\frac{dX_M}{dt} = \nu_M - rT_{MH}Y_H X_M - \mu_M X_M,$$
$$\frac{dY_M}{dt} = rT_{MH}Y_H X_M - \mu_M Y_M,$$

$r = \frac{b}{N_H}$, The number of bites per unit time

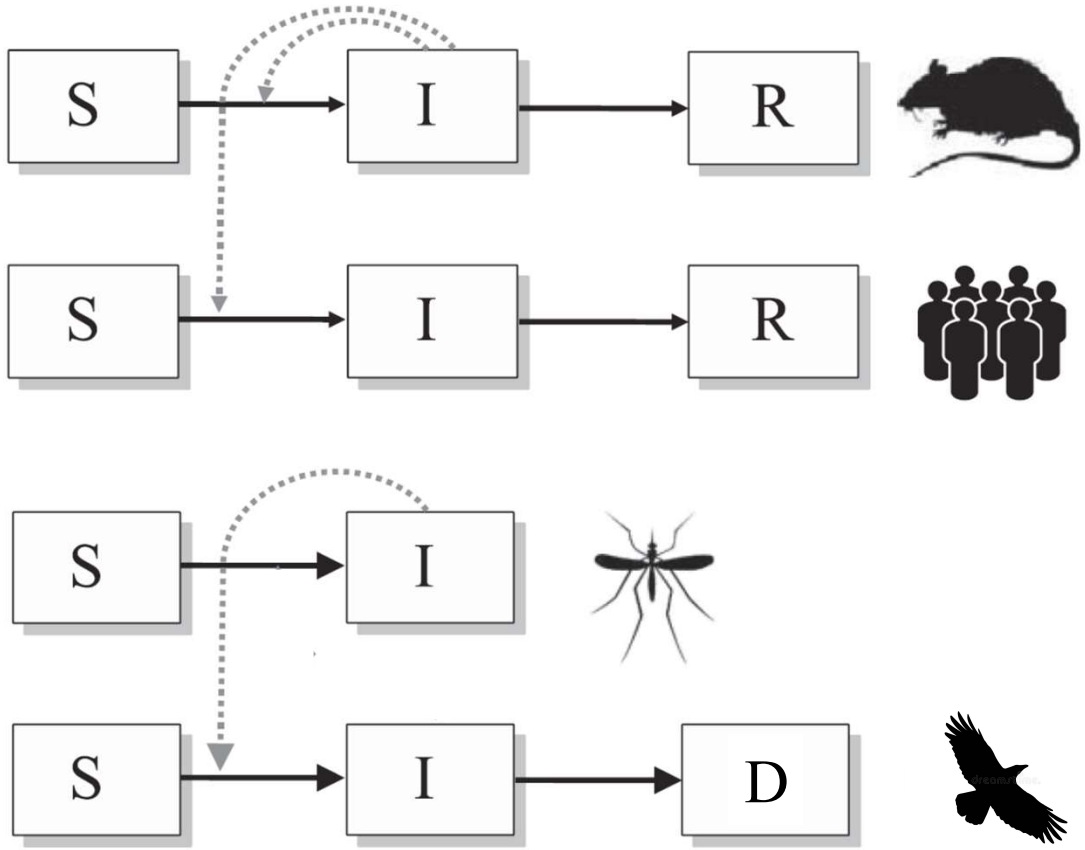
$$\boldsymbol{\beta} = \begin{pmatrix} 0 & rT_{HM} \\ rT_{MH} & 0 \end{pmatrix}$$

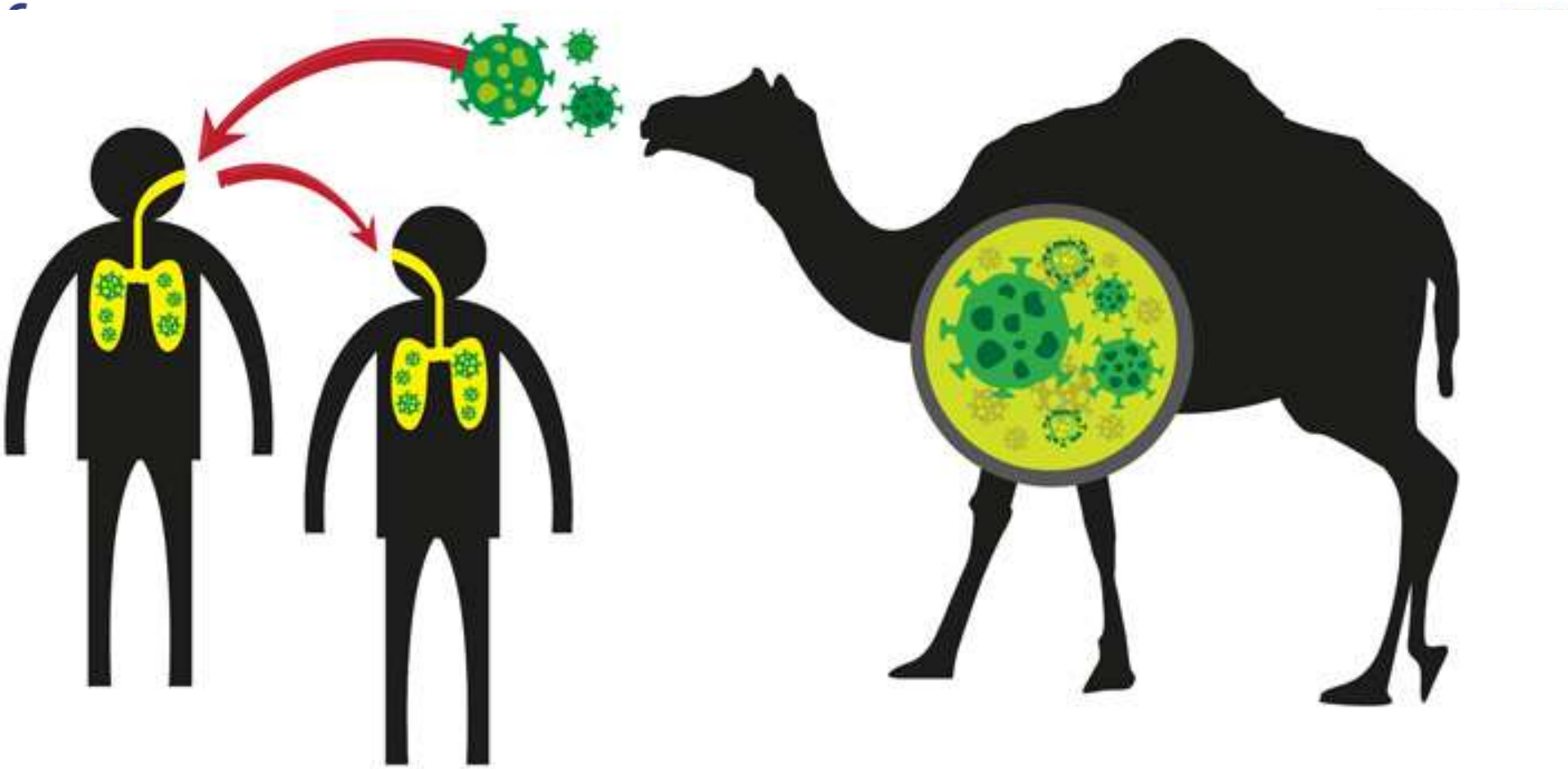
$$R_0 = \frac{b^2 T_{HM} T_{MH} N_M}{\mu_M(\gamma_H + \mu_H)N_H}$$

ν_m, μ_m can vary with climate. Same with r

Zoonoses

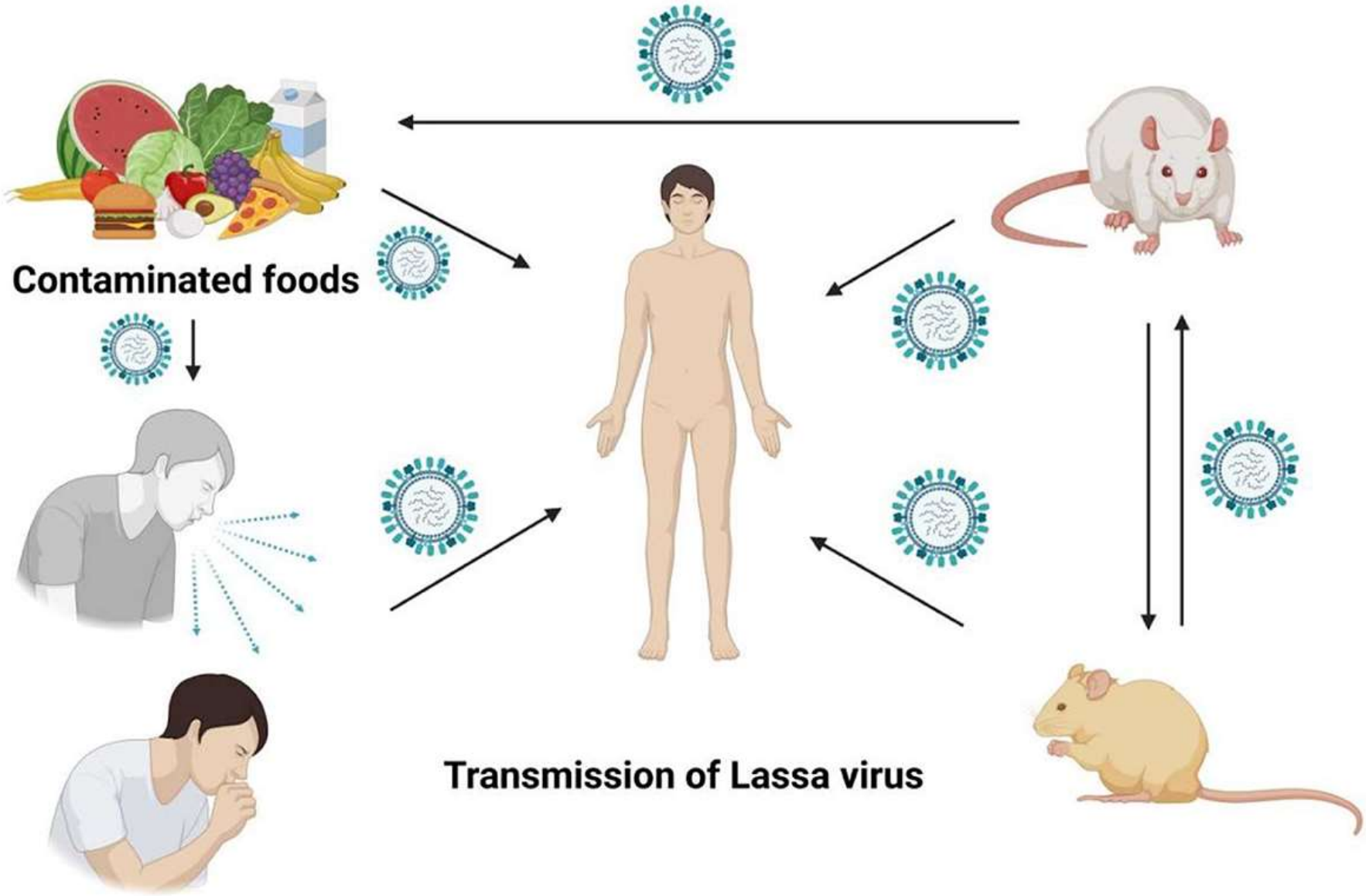
- One host-type is main reservoir
- Other host-type contributes very little to overall transmission
- Examples:
  - Rabies, MERS-CoV Lassa Fever, Hantavirus
  - WNV is a vector-borne zoonoses for birds (D, dead birds)





MERS-COV

Middle East Respiratory Syndrome


Contaminated foods
Transmission of Lassa virus

Dengue fever

A potentially lethal disease that affects two million people worldwide annually

- First recognised in the Philippines and Thailand in the 1950s
- Reported incidents have increased 30-fold in the last 50 years
- Prevention and control solely depend on mosquito control measures

Transmitted through bites of the female Aedes aegypti mosquito

The virus

- Severe flu-like illness that affects infants, young children and adults
- No specific treatment, but early detection and access to medical care can lower fatality rates

- Up to 100 million people a year contract the disease
- Estimated 500,000 people with severe dengue require hospitalisation each year
- Dengue kills up to 20,000 people annually

Four distinct but **related viruses** cause dengue

A
B
C
D

Recovery from one gives lifelong **immunity** to that particular strain

A
A

A second infection by one of the different strains can lead to dengue haemorrhagic fever (DHV), which has a 2.5% mortality rate

Transmission zones

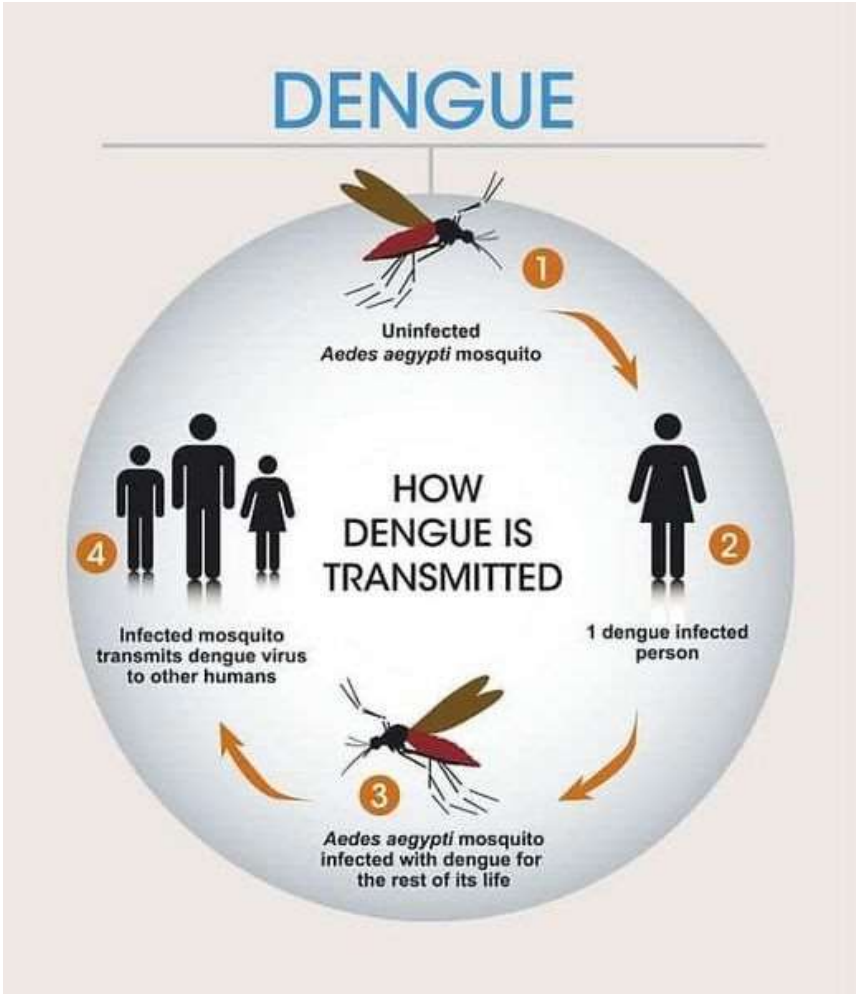
Found in tropical and sub-tropical areas worldwide, predominantly in urban and semi-urban areas

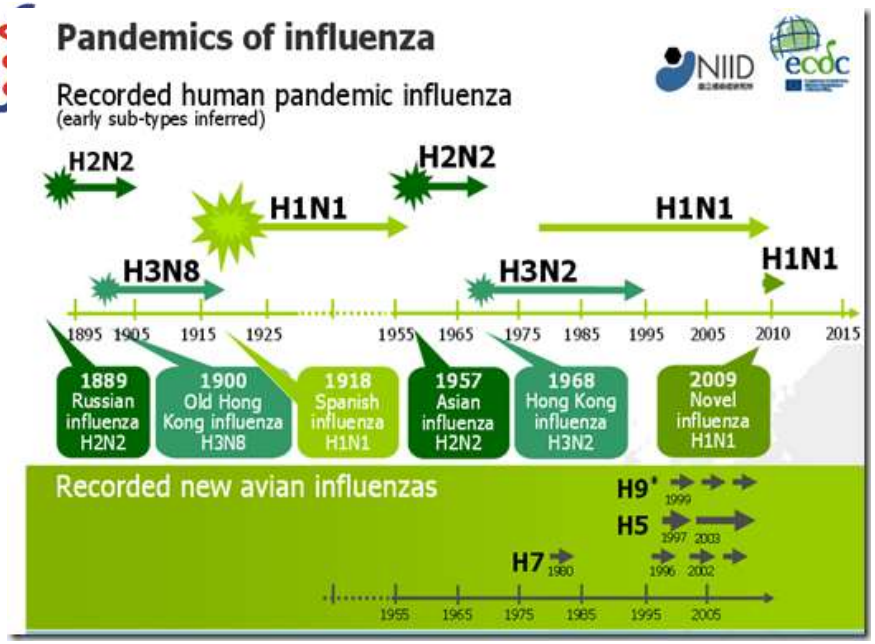
2.5 billion people are potentially at risk

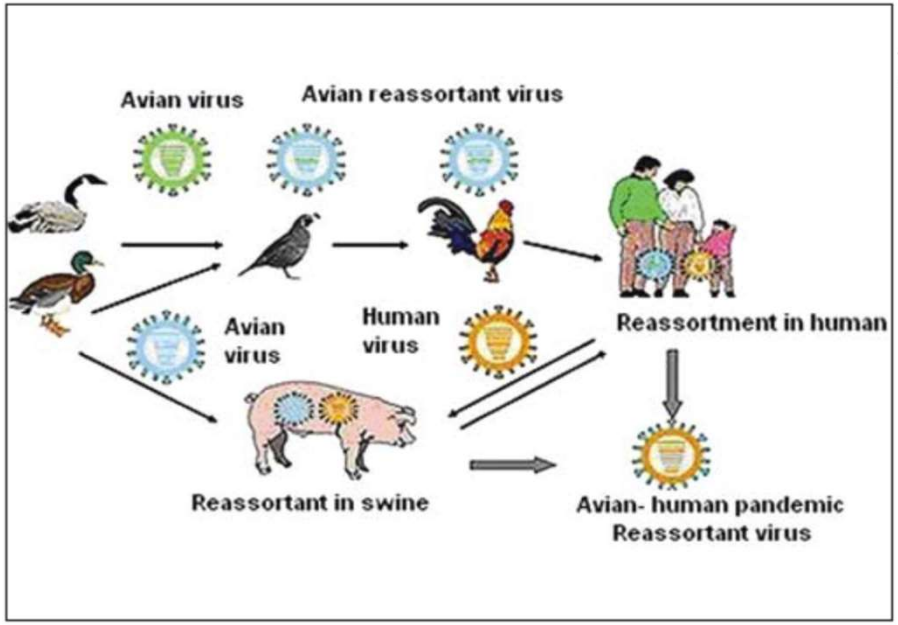
Southeast Asia and the Western Pacific are the most seriously affected areas

Source: WHO/CDC/Stanford University/India Ministry of Health & Family Welfare

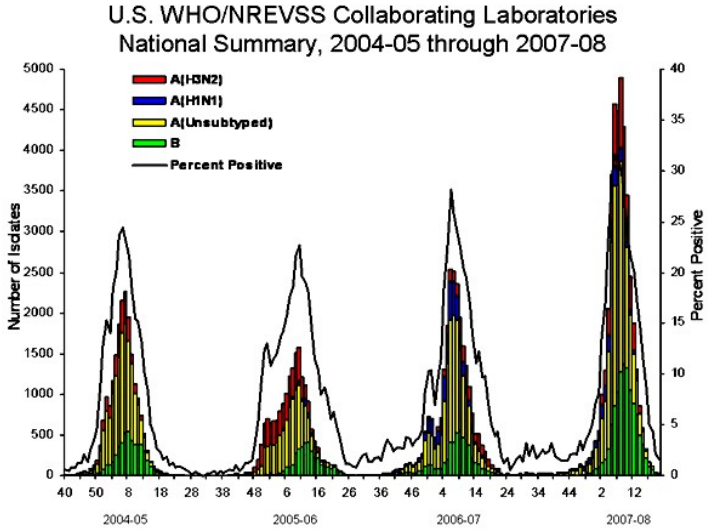
AFP




Pandemics of influenza
Recorded human pandemic influenza
(early sub-types inferred)
H2N2
H1N1
H2N2
H1N1
H3N8
H3N2
H1N1
1895 1905 1915 1925 1955 1965 1975 1985 1995 2005 2010 2015
1889 Russian influenza H2N2
1900 Old Hong Kong influenza H3N8
1918 Spanish influenza H1N1
1957 Asian influenza H2N2
1968 Hong Kong influenza H3N2
2009 Novel influenza H1N1
Recorded new avian influenzas
H9' 1999
H5 1997 2003
H7 1980
1996 2002
1955 1965 1975 1985 1995 2005


Avian virus
Avian reassortant virus
Avian virus
Human virus
Reassortment in human
Reassortant in swine
Avian- human pandemic Reassortant virus


REMEMBER THE 3 W'S
to protect yourself and others this season:
WASH your hands
WEAR your mask
WATCH your distance
GET YOUR FLU SHOT


U.S. WHO/NREVSS Collaborating Laboratories
National Summary, 2004-05 through 2007-08
A(H3N2)
A(H1N1)
A(Unsubtyped)
B
Percent Positive
Number of Isolates
Percent Positive
2004-05
2005-06
2006-07
2007-08