intro to infectious disease modeling

Vittoria Colizza

INSERM & UPMC
Paris, France

ISI Foundation,
Turin, Italy

Inserm
Institut national
de la santé et de la recherche médicale

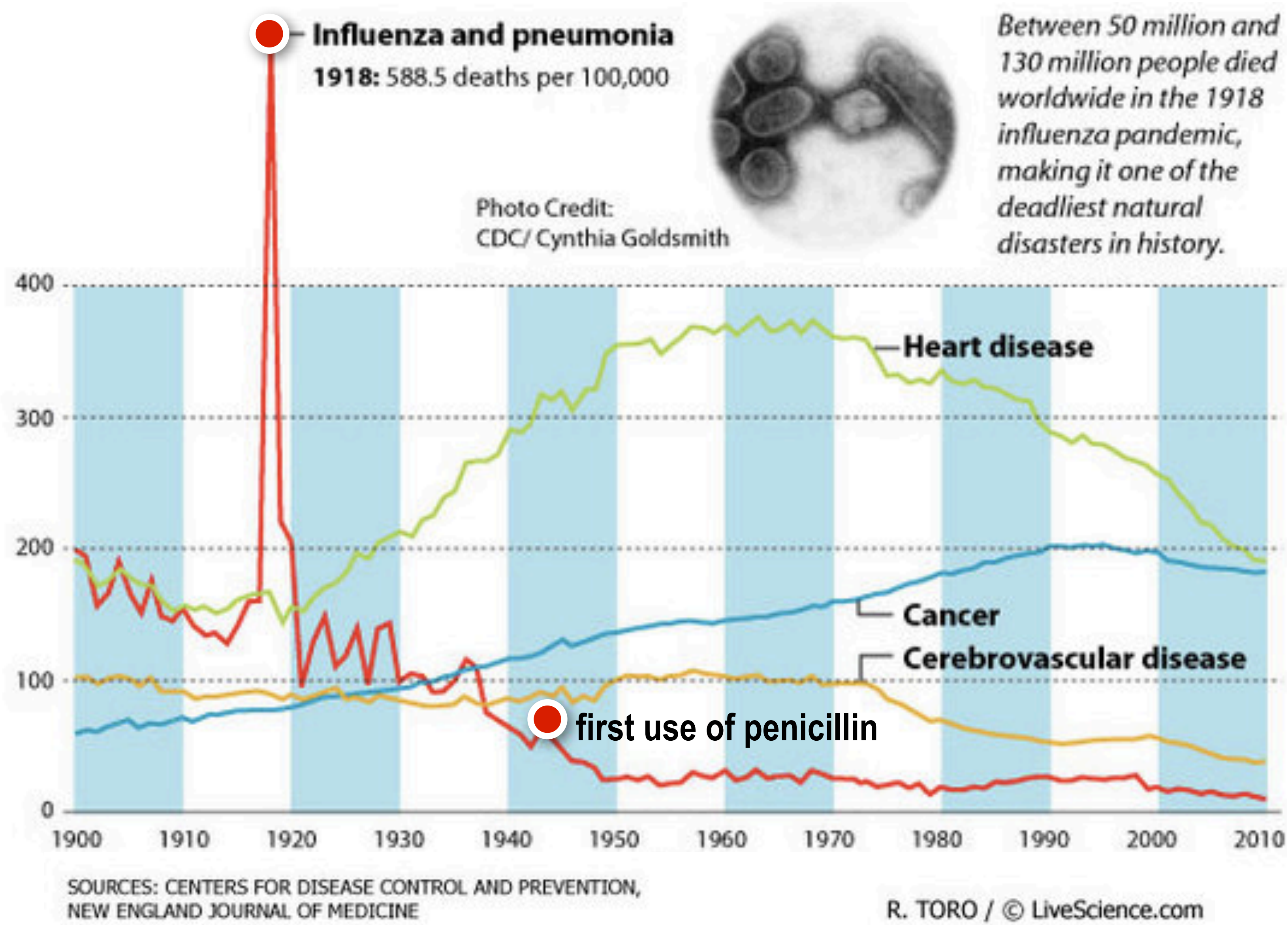
UPMC
PARIS UNIVERSITAS

infectious diseases

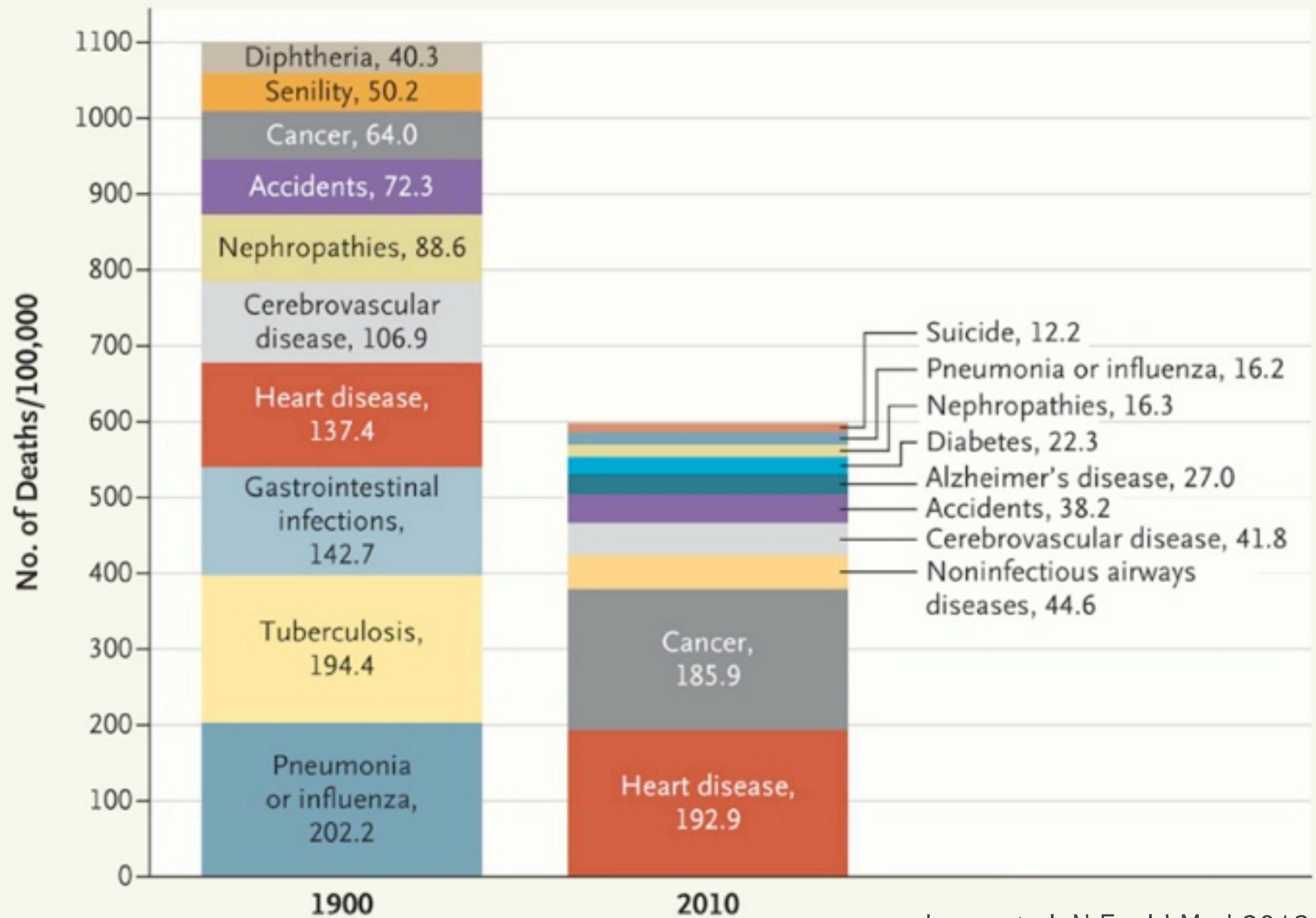
- some background
- principles, notation, classification
- modeling (I): homogeneous mixing
- modeling (II): contact networks
- modeling (III): space
- surveillance
- applications to H1N1 pdm

infectious diseases: some background

mortality

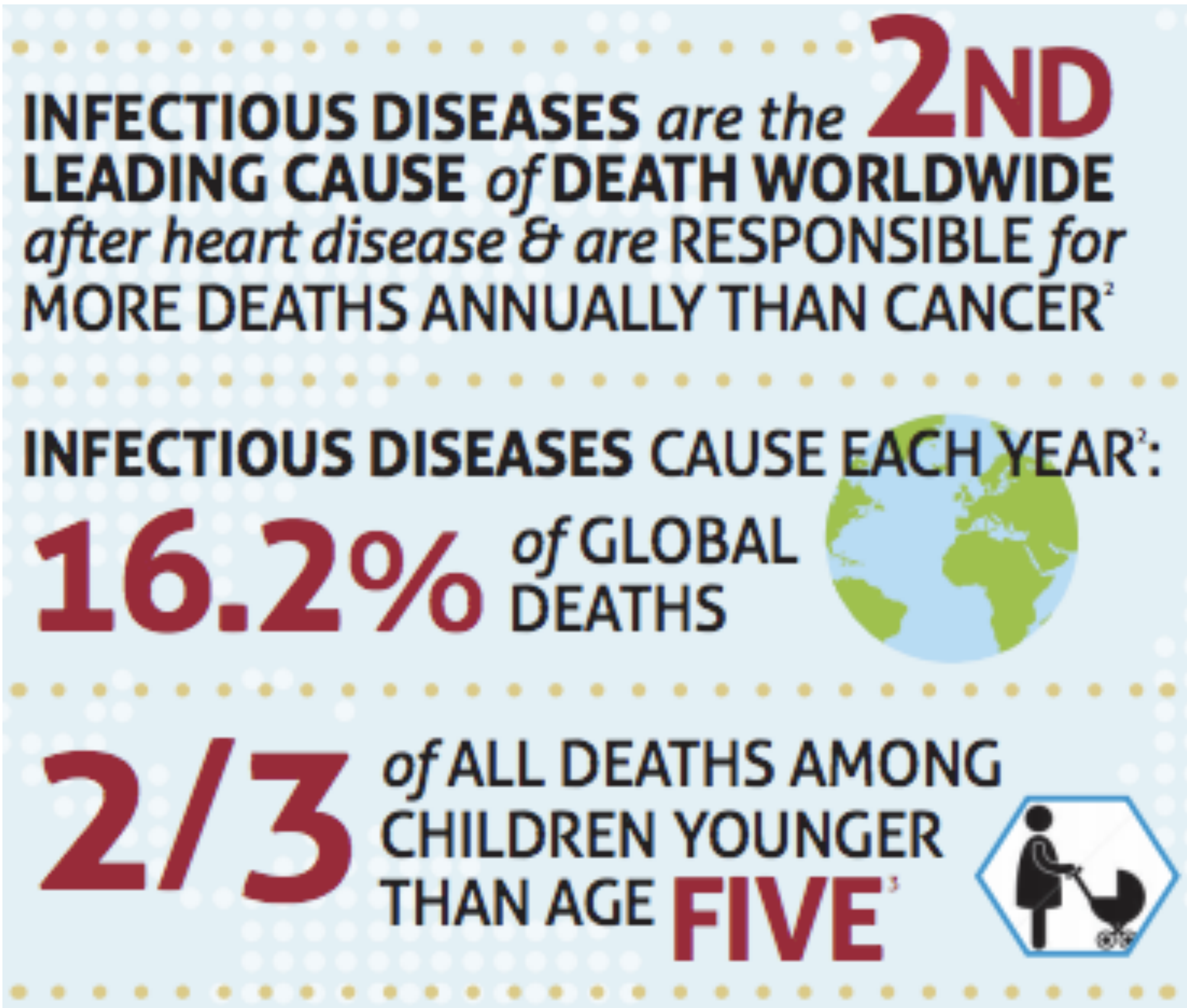

Influenza and pneumonia
1918: 588.5 deaths per 100,000
Photo Credit:
CDC/ Cynthia Goldsmith
Between 50 million and 130 million people died worldwide in the 1918 influenza pandemic, making it one of the deadliest natural disasters in history.
Heart disease
Cancer
Cerebrovascular disease
first use of penicillin
400
300
200
100
0
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
SOURCES: CENTERS FOR DISEASE CONTROL AND PREVENTION,
NEW ENGLAND JOURNAL OF MEDICINE
R. TORO / © LiveScience.com

10 leading causes of death (US)



Jones et al, N Engl J Med 2012

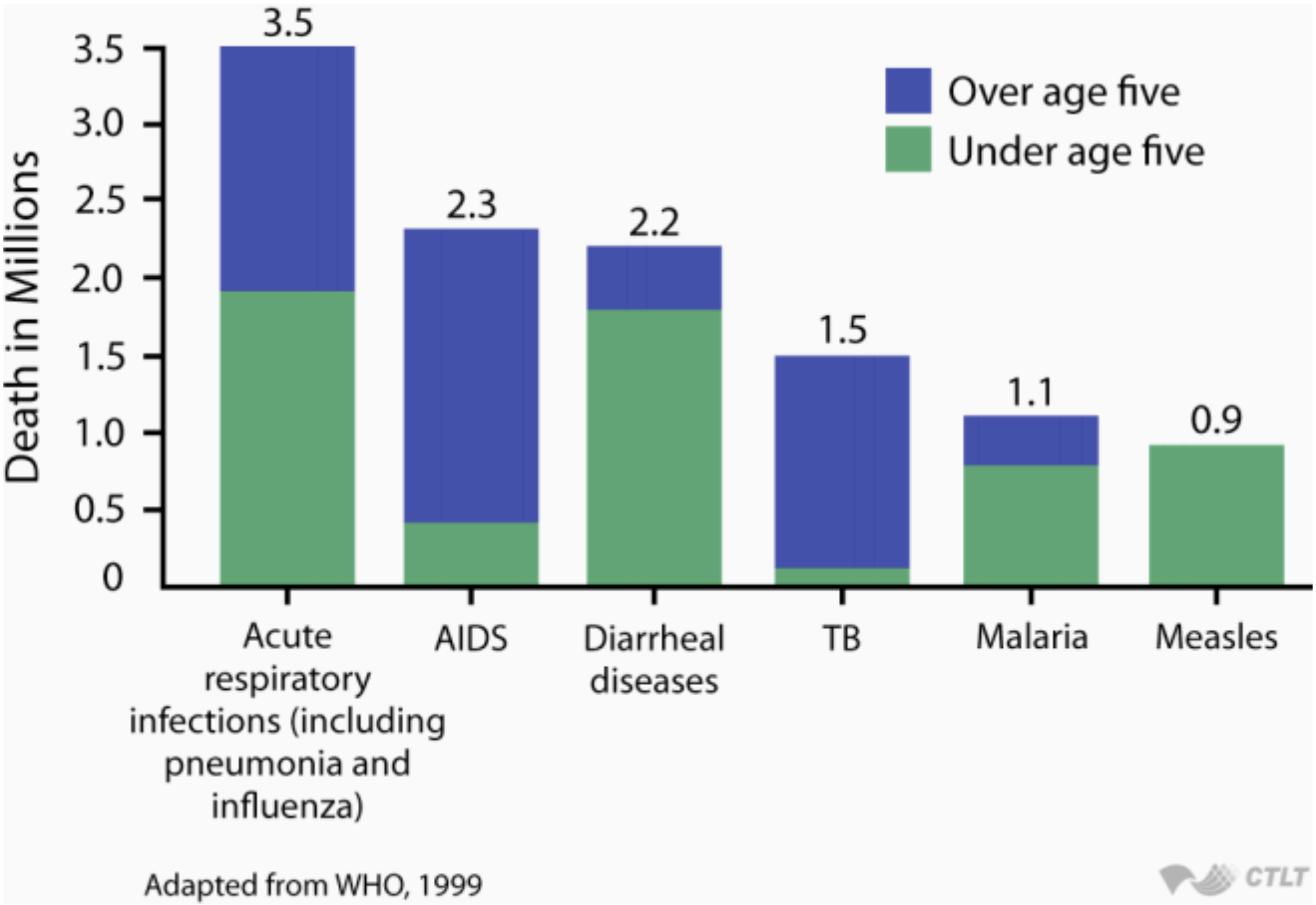
infectious disease impact worldwide



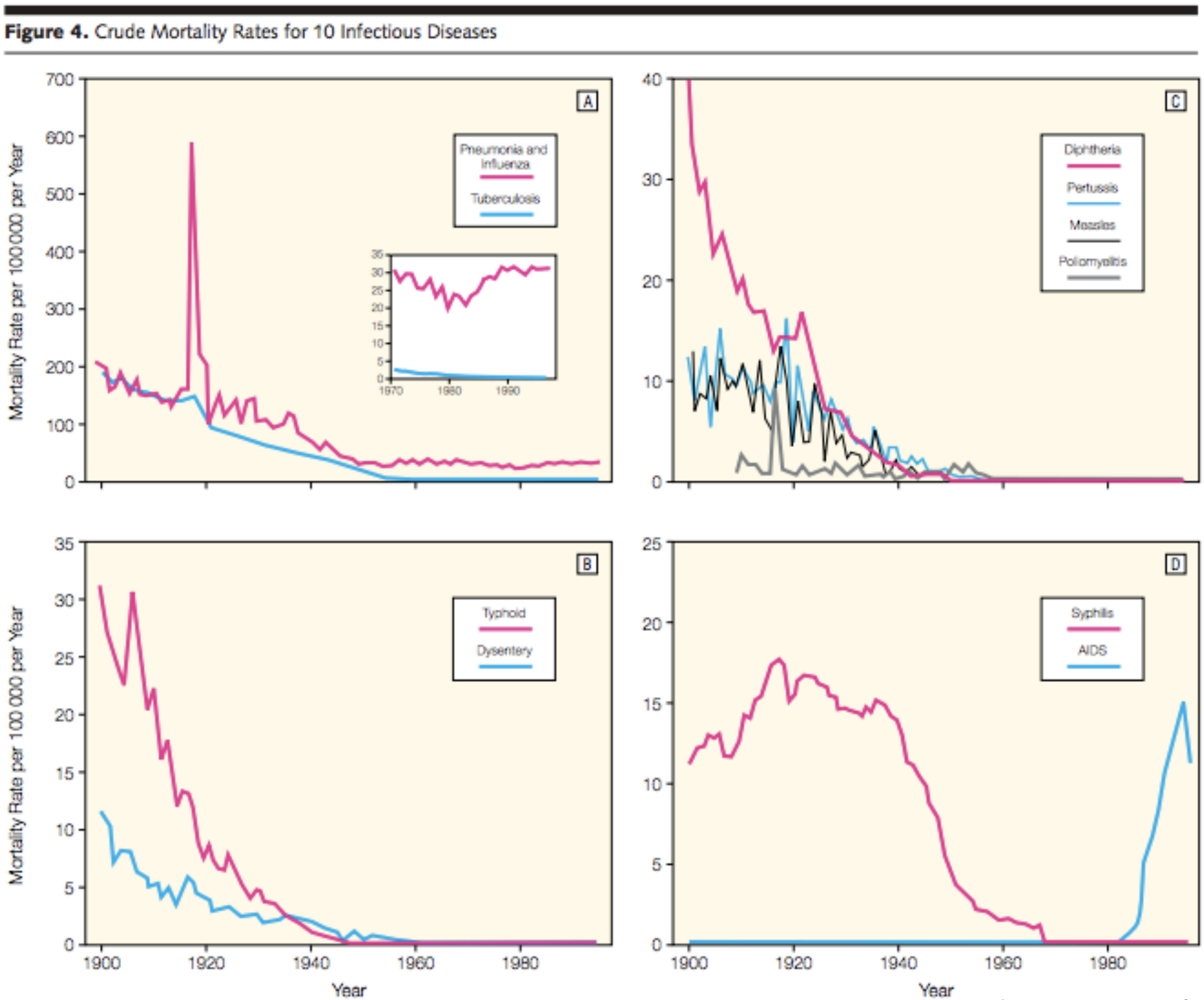
WHO, www.bcm.edu/molvir/id

NIH, www.nih.gov/about/
discovery/infectious diseases/

infectious disease impact worldwide

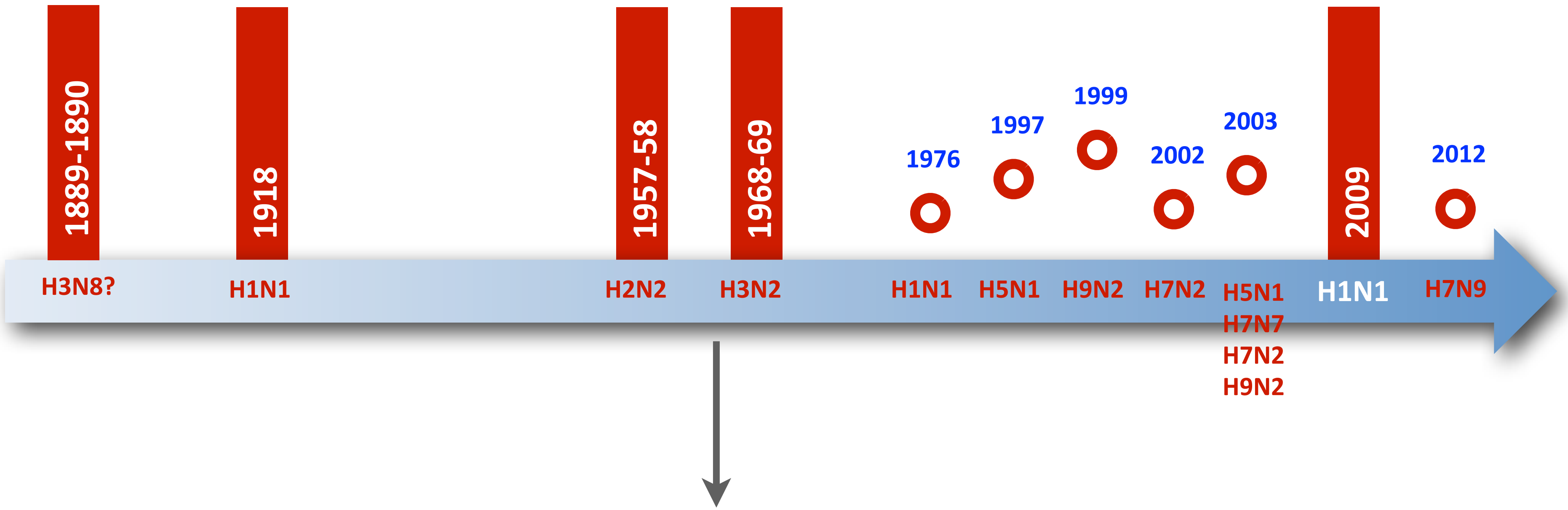


infectious disease mortality (US)



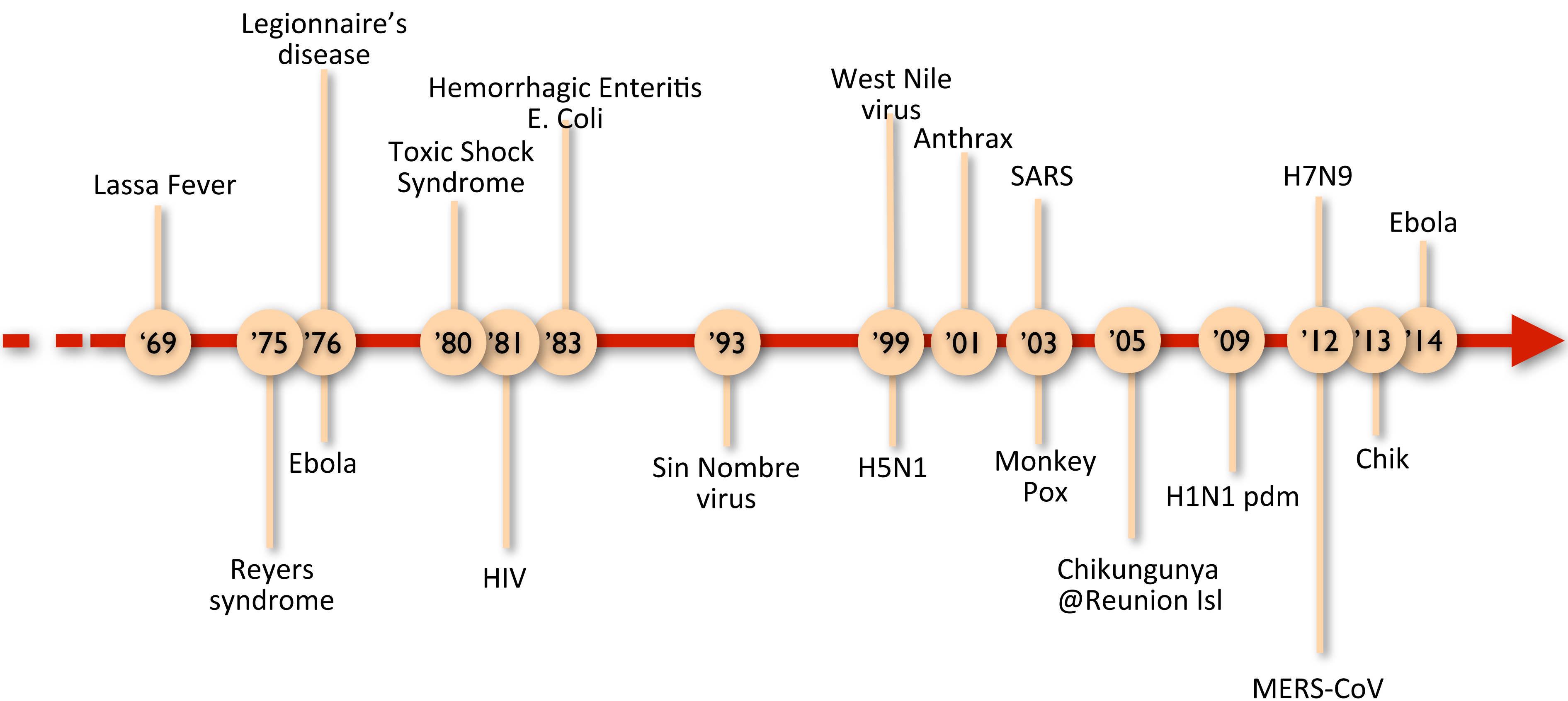
Armstrong et al, J Am Med Ass, 1999

brief history of flu



"because infectious diseases have been
largely controlled in the US,
we can now close
the book on infectious diseases"
US Surgeon General 1967

some recent epidemics of EID



some recent epidemics of EID

HIV-related infectious diseases

1. *pneumocystis carinii* pneumonia
2. tuberculosis
3. mycobacterium-avium complex
4. Kaposi's sarcoma
5. HSV-2
6. cryptosporidium
7. microsporidium
8. *cryptococcus neoformans*
9. *penicillium marneffei*
10. disseminated salmonella
11. bacillary angiomatosis
12. HPV
13. ...

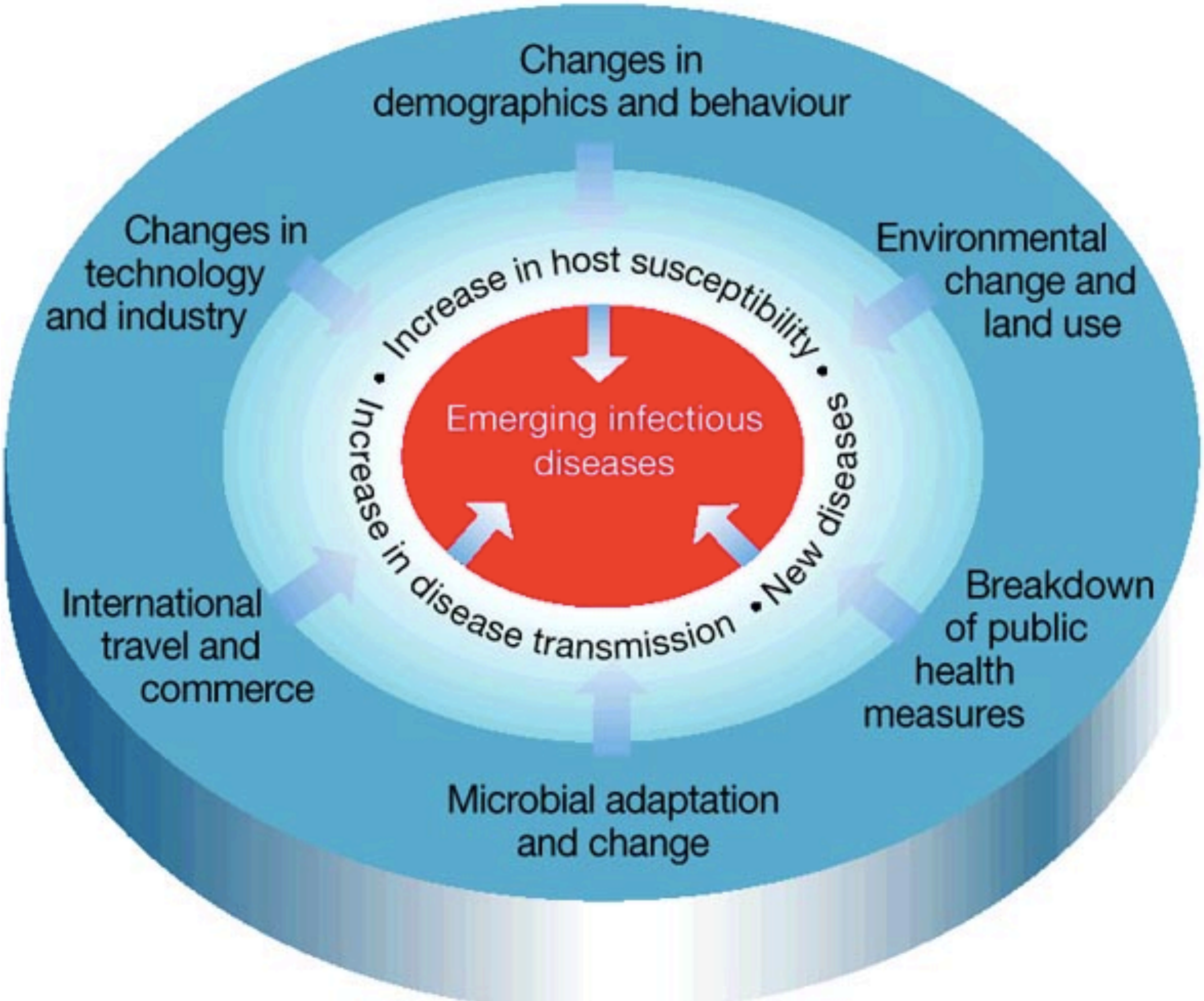
non-HIV-related infectious diseases

1. SARS
2. influenza (H5N1, H1N1, H7N9, ...)
3. West Nile disease
4. variant CJD disease
5. monkeypox
6. Ebola and Marburg viruses
7. Dengue
8. Hanta virus
9. *E. coli*
10. antibiotic resistant microbes
11. Anthrax
12. Chikungunya
13. MERS-CoV
14. ...

main factors leading to EID

- HIV
- population growth
- speed and ease of travel
- rural vs. urban
- climate change
- increased antibiotic use in humans and animals
- relocation of animals
- population aging
- human-animal contact

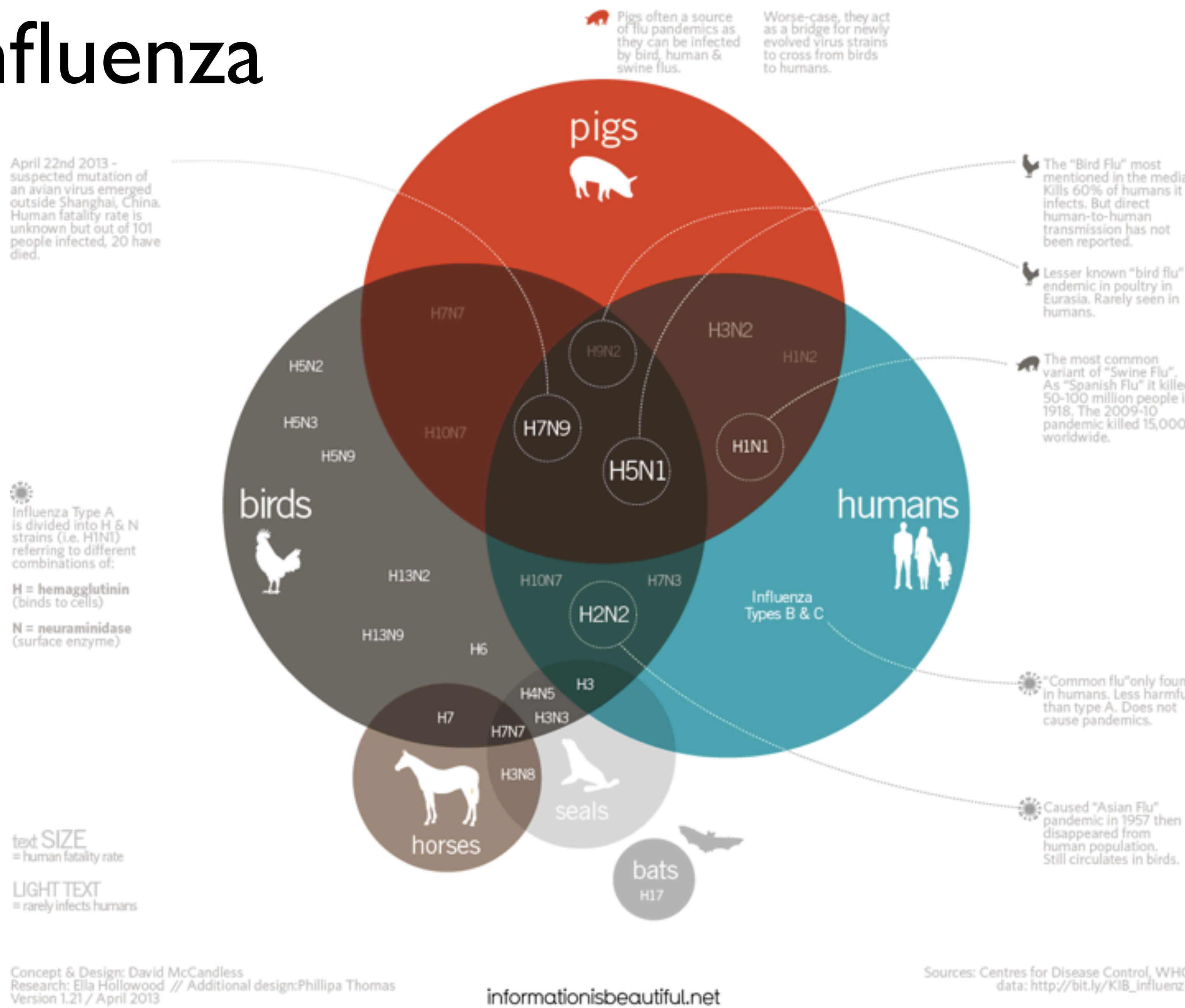
main factors leading to EID



>50% human pathogens from animals

disease	animal
HIV	primates
influenza	*many!* [originally derived from avian flu viruses]
ebola	primates
marburg	primates
hanta virus	deer mouse
arena virus	rodents
variant CJD	cattle
cryptosporidia	cattle
hendra virus	fruit bats
nipah virus	pigs, fruit bats
SARS	bats
monkey dogs	prairie dogs
MERS-CoV	camels?

influenza



Pigs often a source of flu pandemics as they can be infected by bird, human & swine flus.
Worse-case, they act as a bridge for newly evolved virus strains to cross from birds to humans.
pigs
April 22nd 2013 - suspected mutation of an avian virus emerged outside Shanghai, China. Human fatality rate is unknown but out of 101 people infected, 20 have died.
The "Bird Flu" most mentioned in the media. Kills 60% of humans it infects. But direct human-to-human transmission has not been reported.
Lesser known "bird flu" endemic in poultry in Eurasia. Rarely seen in humans.
H7N7
H9N2
H3N2
H1N2
H5N2
H5N3
H5N9
H10N7
H7N9
H5N1
H1N1
The most common variant of "Swine Flu". As "Spanish Flu" it killed 50-100 million people in 1918. The 2009-10 pandemic killed 15,000 worldwide.
birds
humans
Influenza Type A is divided into H & N strains (i.e. H1N1) referring to different combinations of:
H = hemagglutinin (binds to cells)
N = neuraminidase (surface enzyme)
H13N2
H10N7
H7N3
H2N2
Influenza Types B & C
H13N9
H6
H3
H4N5
H3N3
H7
H7N7
H3N8
"Common flu" only found in humans. Less harmful than type A. Does not cause pandemics.
seals
horses
bats
H17
Caused "Asian Flu" pandemic in 1957 then disappeared from human population. Still circulates in birds.
text SIZE = human fatality rate
LIGHT TEXT = rarely infects humans
Concept & Design: David McCandless
Research: Ella Hollowood // Additional design: Phillipa Thomas
Version 1.21 / April 2013
informationisbeautiful.net
Sources: Centres for Disease Control, WHO
data: http://bit.ly/KIB_influenza

reservoirs of IDs

human

animal

soil

water

reservoirs of IDs

human

- HIV
- Hepathitis B virus
- Syphillis
- Gonorrhea
- Typhoid fever
- Herpes simplex virus
- ...

animal

soil

water

reservoirs of IDs

human

- HIV
- Hepathitis B virus
- Syphillis
- Gonorrhea
- Typhoid fever
- Herpes simplex virus
- ...

animal

- rabies
- MERS-CoV
- influenza
- brucellosis
- anthrax
- ...

soil

water

reservoirs of IDs

human

- HIV
- Hepathitis B virus
- Syphillis
- Gonorrhea
- Typhoid fever
- Herpes simplex virus
- ...

animal

- rabies
- MERS-CoV
- influenza
- brucellosis
- anthrax
- ...

soil

- tetanus
- botulism
- ...

water

reservoirs of IDs

human

- HIV
- Hepathitis B virus
- Syphillis
- Gonorrhea
- Typhoid fever
- Herpes simplex virus
- ...

animal

- rabies
- MERS-CoV
- influenza
- brucellosis
- anthrax
- ...

soil

- tetanus
- botulism
- ...

water

- Legionnaires' disease
- ...

infectious diseases: some notation & classification

example: 3 pathogens

influenza

- ...
- ...
- ...

HIV

- ...
- ...
- ...

tuberculosis

- ...
- ...
- ...

classification of the disease?

IDs: a biological point of view

viruses

bacteria

fungi

parasites

IDs: a biological point of view

viruses

- HIV
- influenza
- SARS, MERS-CoV
- chikungunya
- ...

bacteria

fungi

parasites

IDs: a biological point of view

viruses

- HIV
- influenza
- SARS, MERS-CoV
- chikungunya
- ...

bacteria

- tuberculosis
- pneumonia
- salmonella
- tetanus
- typhoid fever
- ...

fungi

parasites

IDs: a biological point of view

viruses

- HIV
- influenza
- SARS, MERS-CoV
- chikungunya
- ...

bacteria

- tuberculosis
- pneumonia
- salmonella
- tetanus
- typhoid fever
- ...

fungi

parasites

- malaria
- toxoplasmosis
- scabies
- ...

IDs: a biological point of view

viruses

- HIV
- influenza
- SARS, MERS-CoV
- chikungunya
- ...

bacteria

- tuberculosis
- pneumonia
- salmonella
- tetanus
- typhoid fever
- ...

fungi

- *Pneumocystis* pneumonia
- cryptococcal meningitis
- candidiasis
- ...

parasites

- malaria
- toxoplasmosis
- scabies
- ...

IDs: a clinician point of view

clinical symptoms

respiratory diseases	diarrheal diseases
cutaneous infection	central nervous system infection
fever of undet. origin	septicemic diseases

IDs: an epidemiologist point of view

transmission

contact

- direct
- indirect (fomites, body secretions, ...)

airborne

- small-particle aerosols

vector

- anthropods

food/water

IDs: an epidemiologist point of view

pathogen's properties

infectivity

pathogenicity

virulence

IDs: an epidemiologist point of view

pathogen's properties

infectivity

- propensity for transmission

pathogenicity

virulence

IDs: an epidemiologist point of view

pathogen’s properties

infectivity

- propensity for transmission

pathogenicity

- propensity to cause disease or clinical symptoms

virulence

IDs: an epidemiologist point of view

pathogen's properties

infectivity

- propensity for transmission

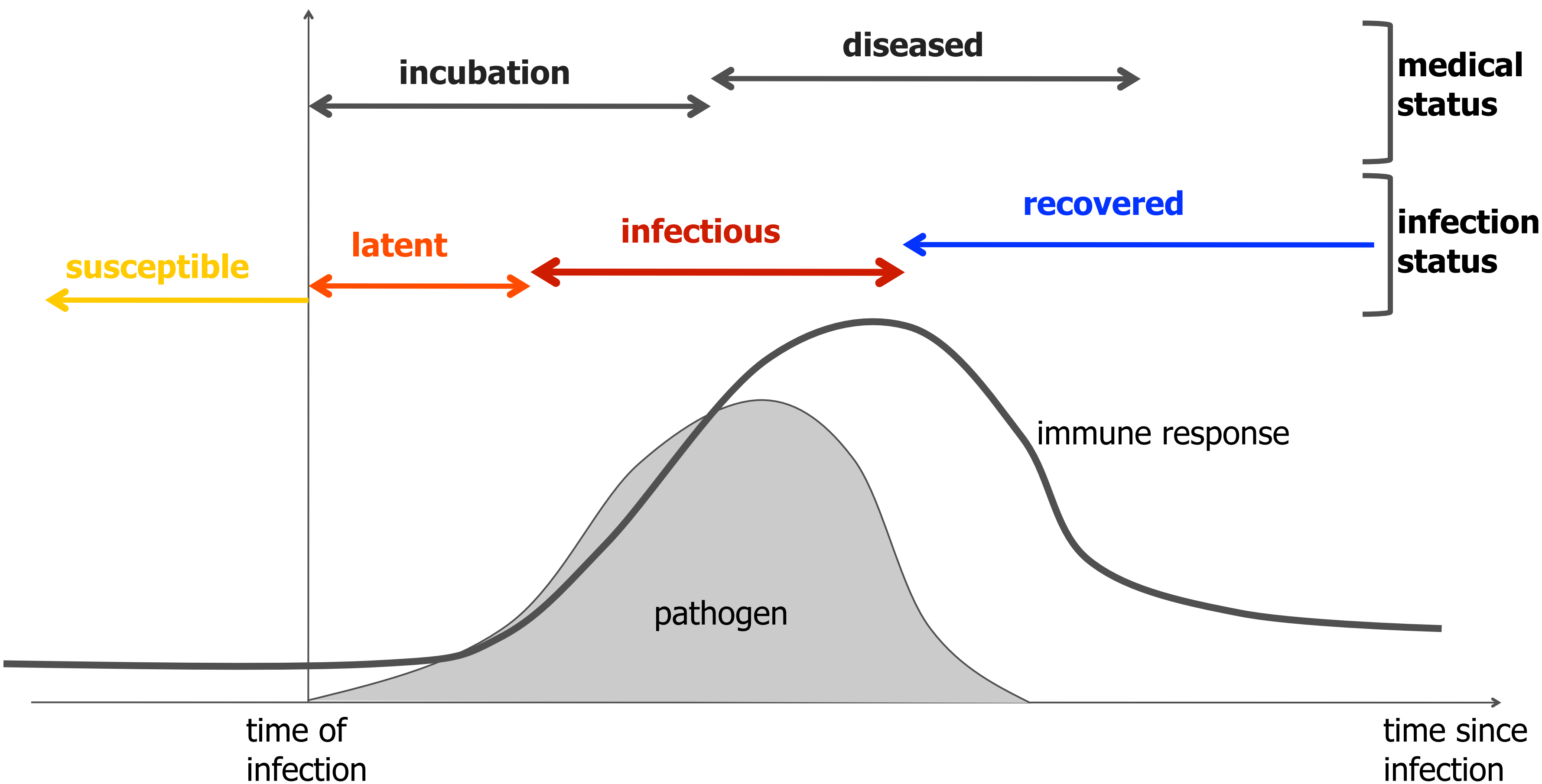
pathogenicity

- propensity to cause disease or clinical symptoms

virulence

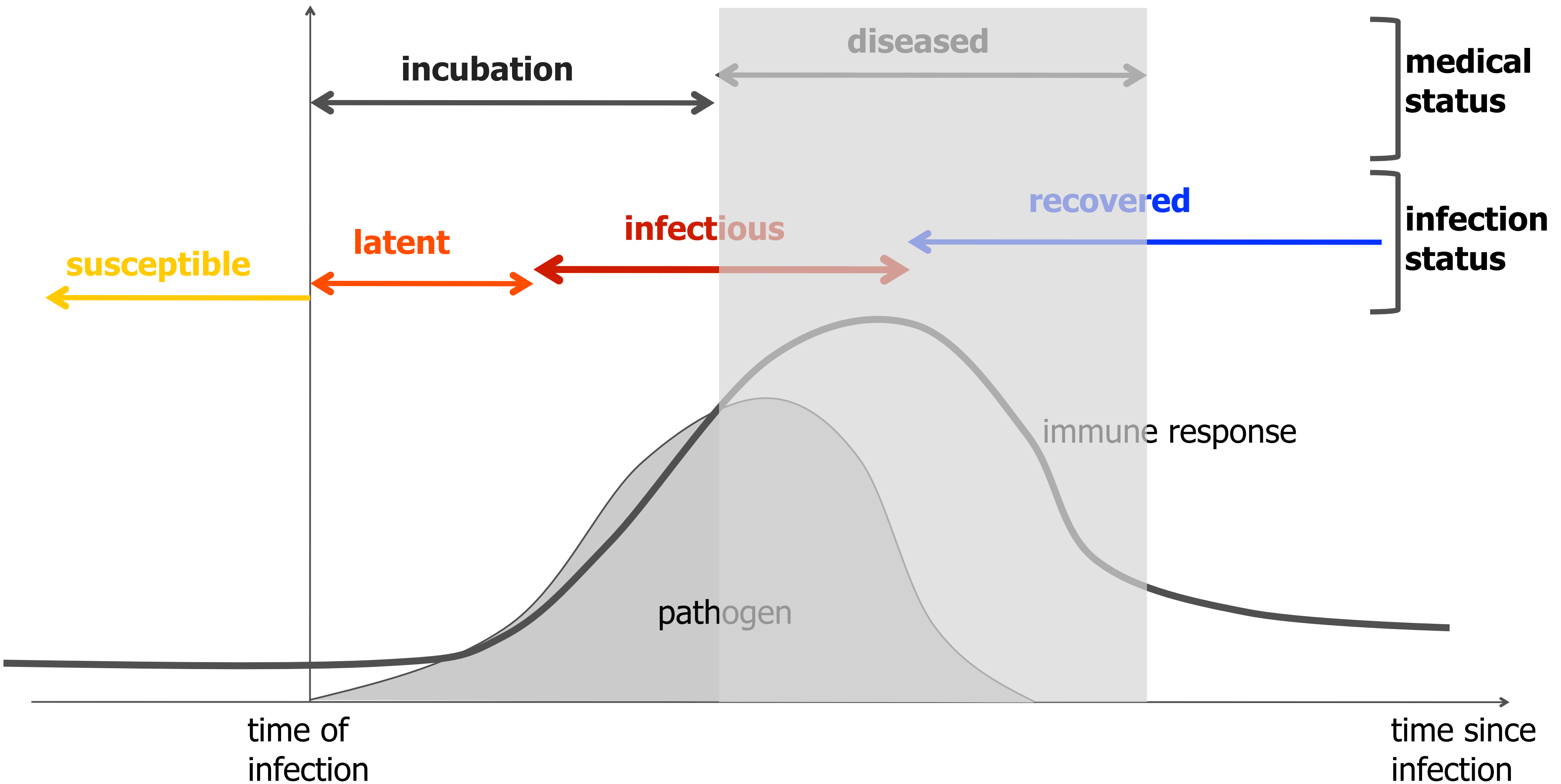
- propensity to cause severe disease

epidemiologist *vs.* clinician point of view



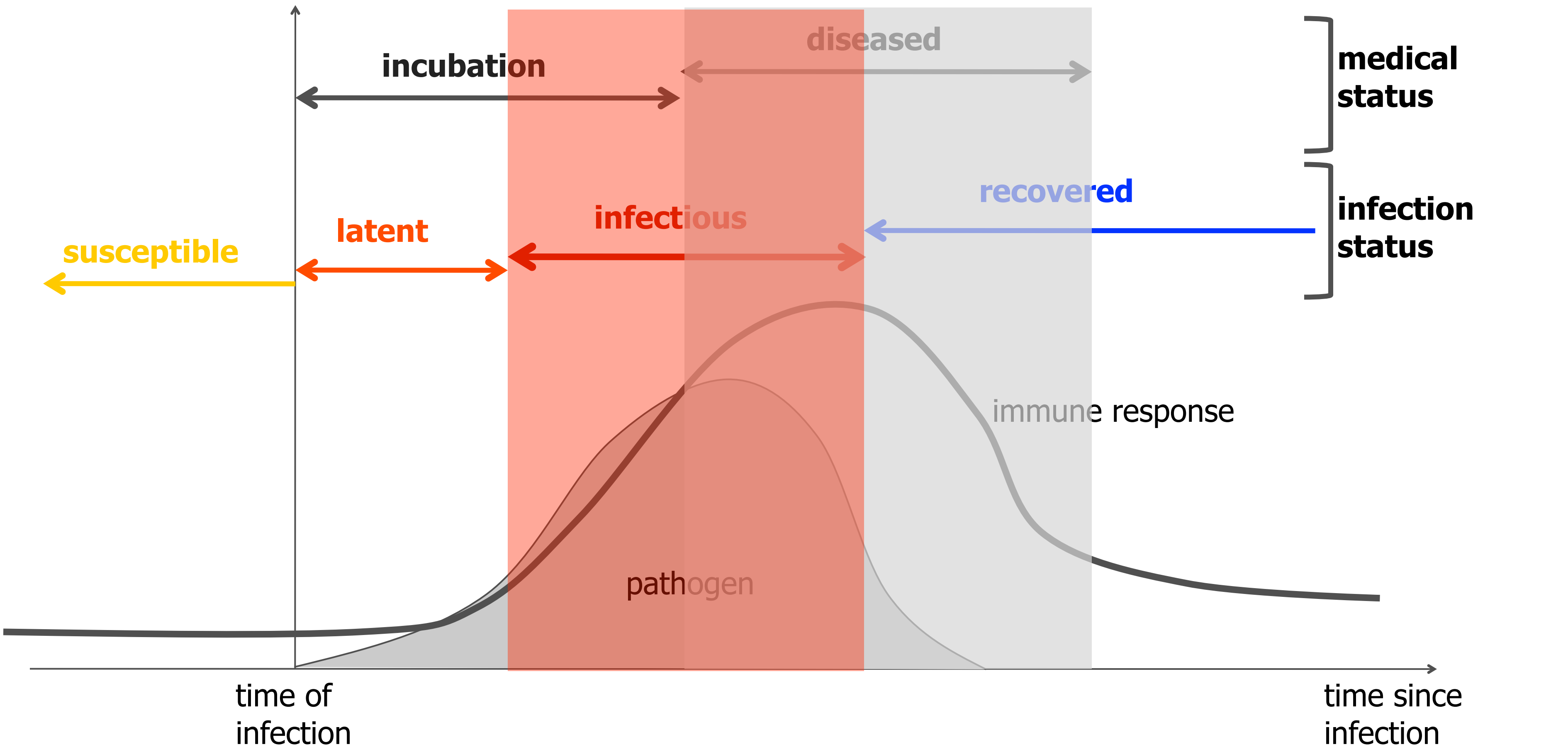
adapted from: Keeling & Rohani, Modeling Infectious Diseases (2008)

epidemiologist *vs.* clinician point of view



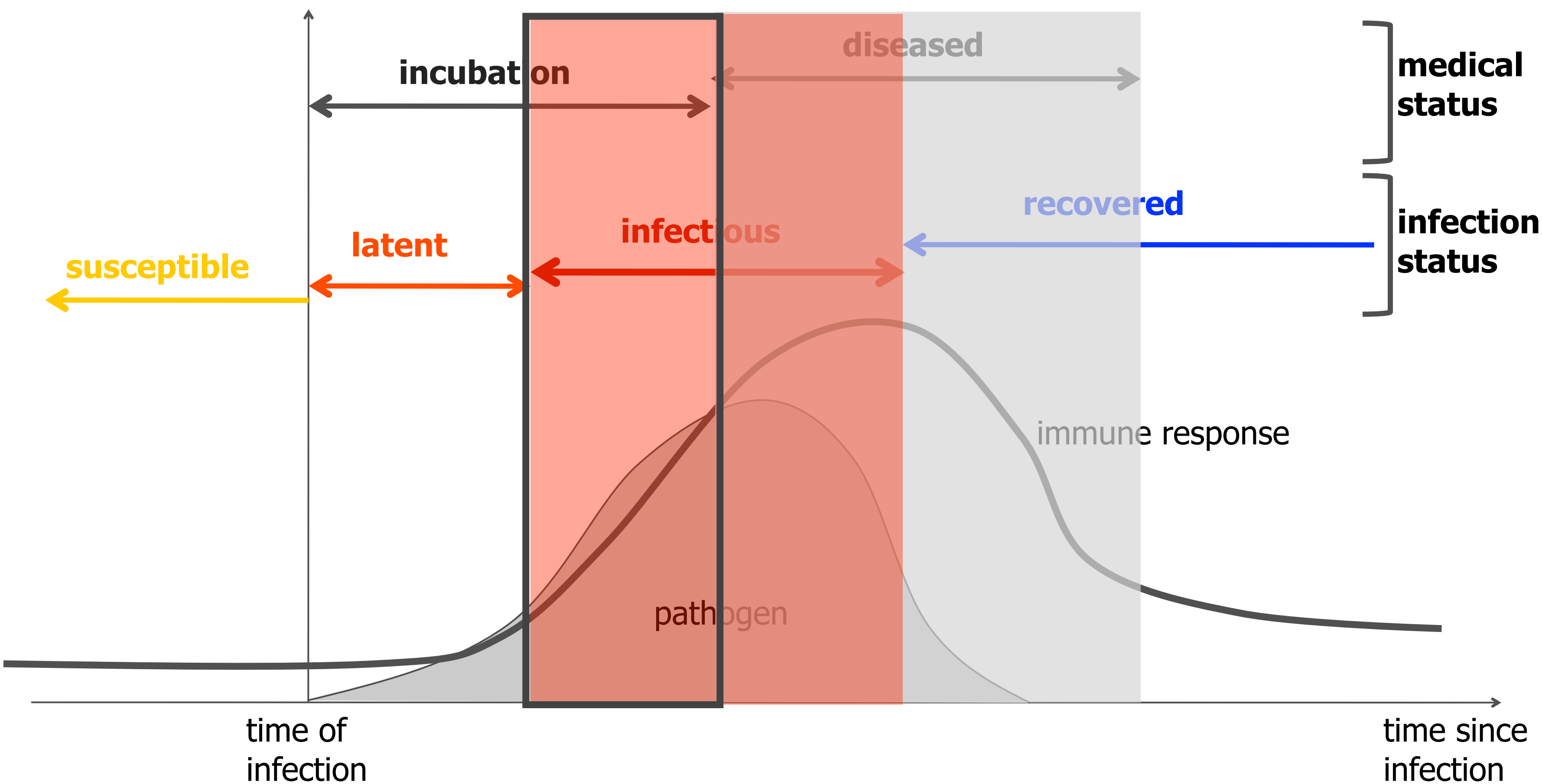
adapted from: Keeling & Rohani, Modeling Infectious Diseases (2008)

epidemiologist *vs.* clinician point of view



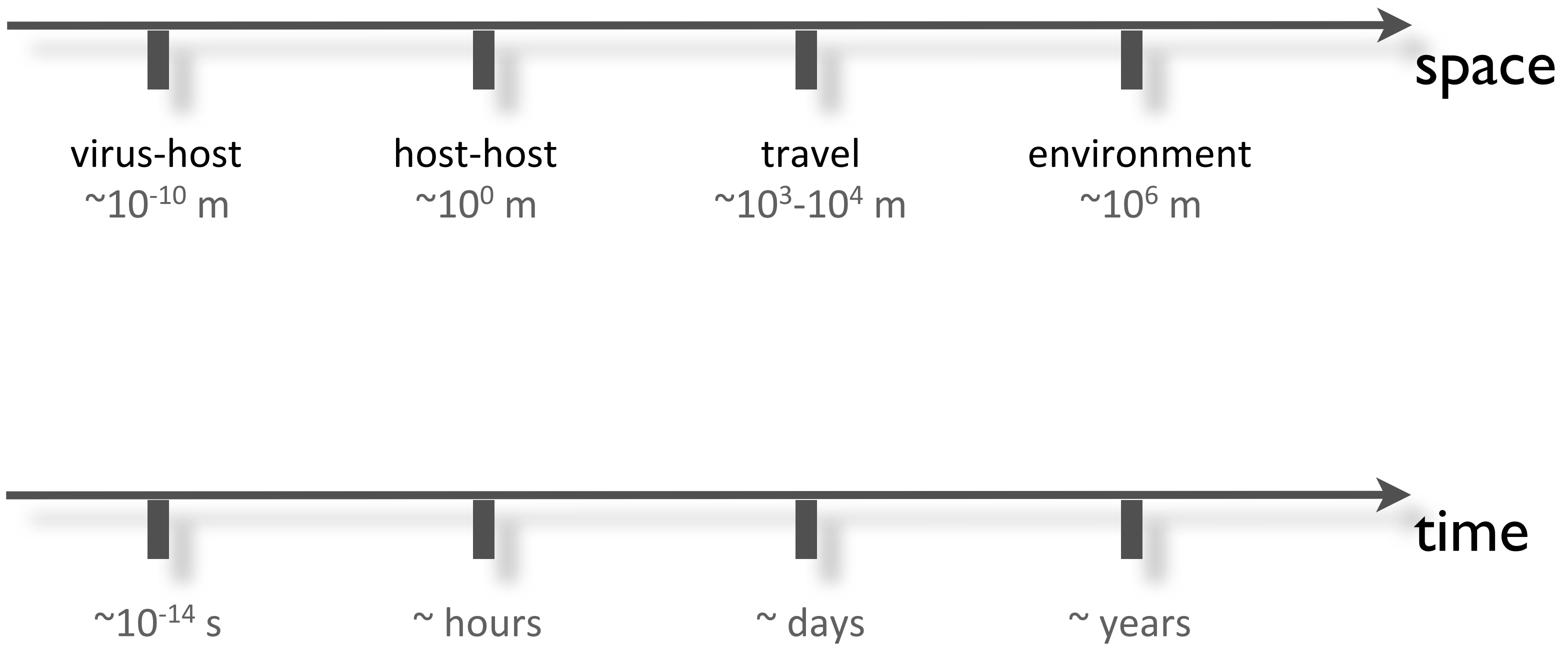
adapted from: Keeling & Rohani, Modeling Infectious Diseases (2008)

epidemiologist *vs.* clinician point of view



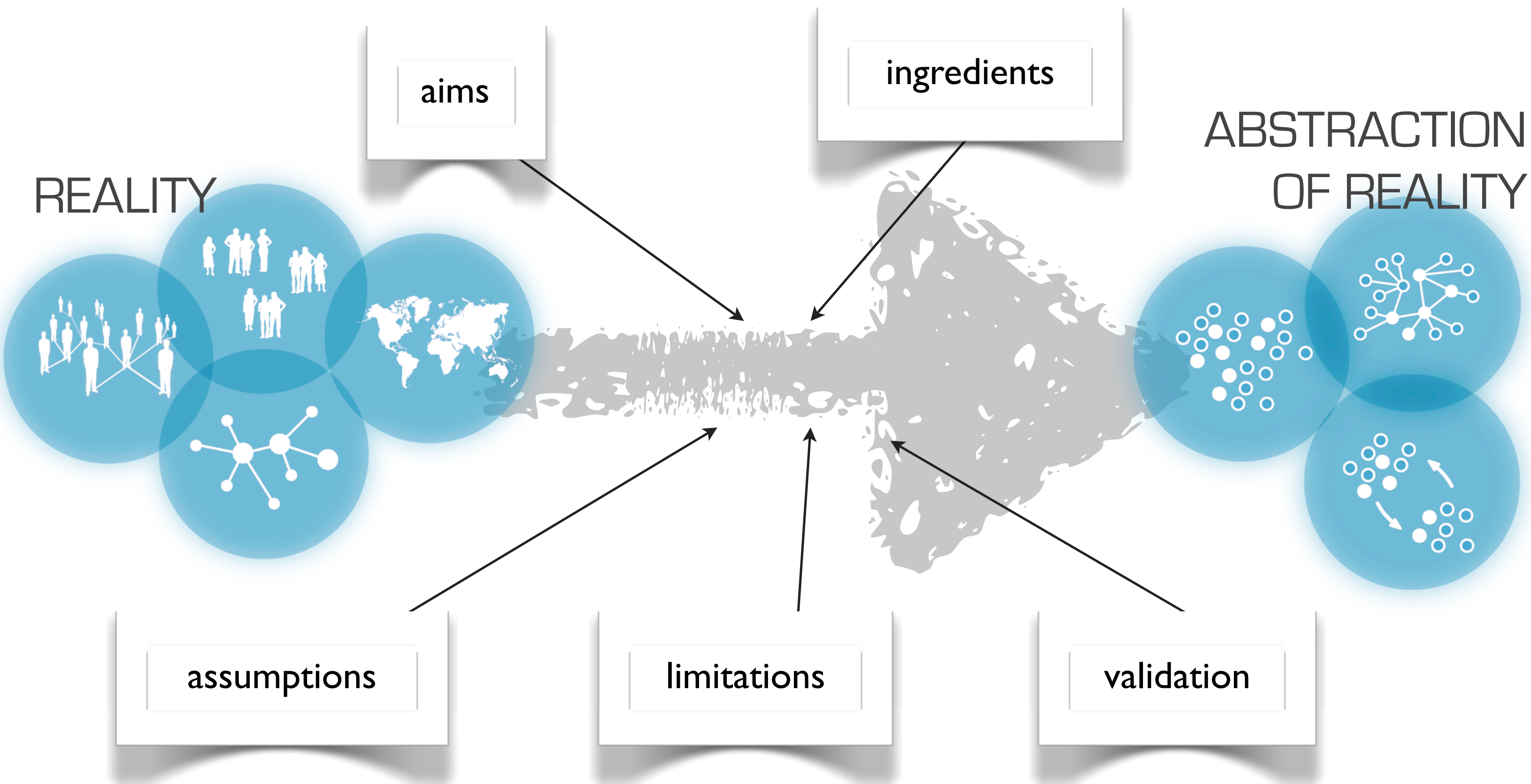
adapted from: Keeling & Rohani, Modeling Infectious Diseases (2008)

scales


space
virus-host
~10^-10 m
host-host
~10^0 m
travel
~10^3-10^4 m
environment
~10^6 m
time
~10^-14 s
~ hours
~ days
~ years

infectious diseases: simple models

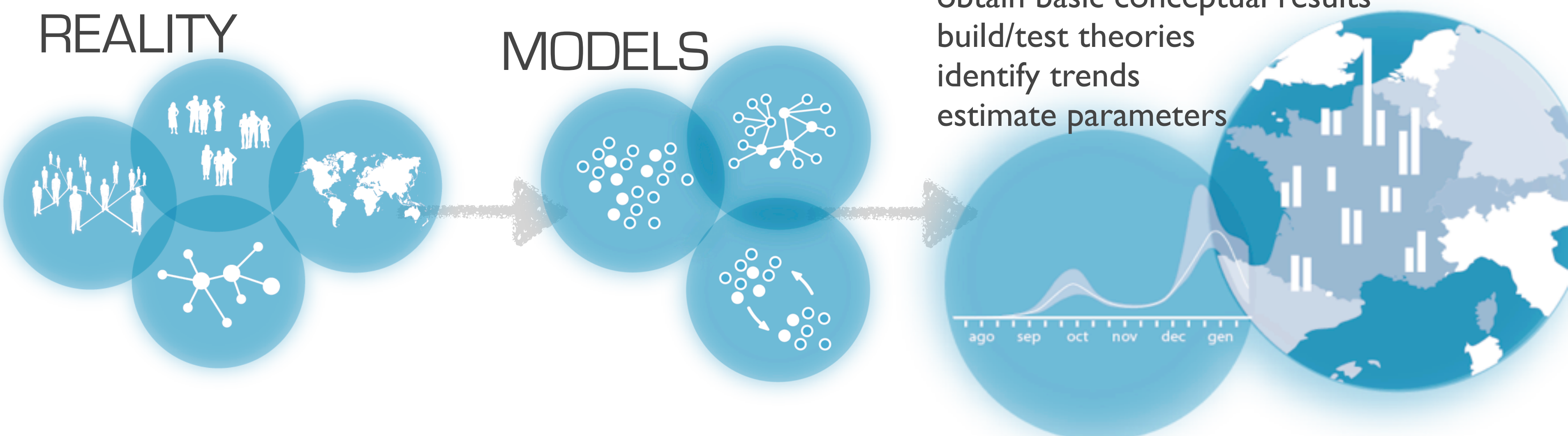
dynamical modeling 101



aims

UNDERSTAND

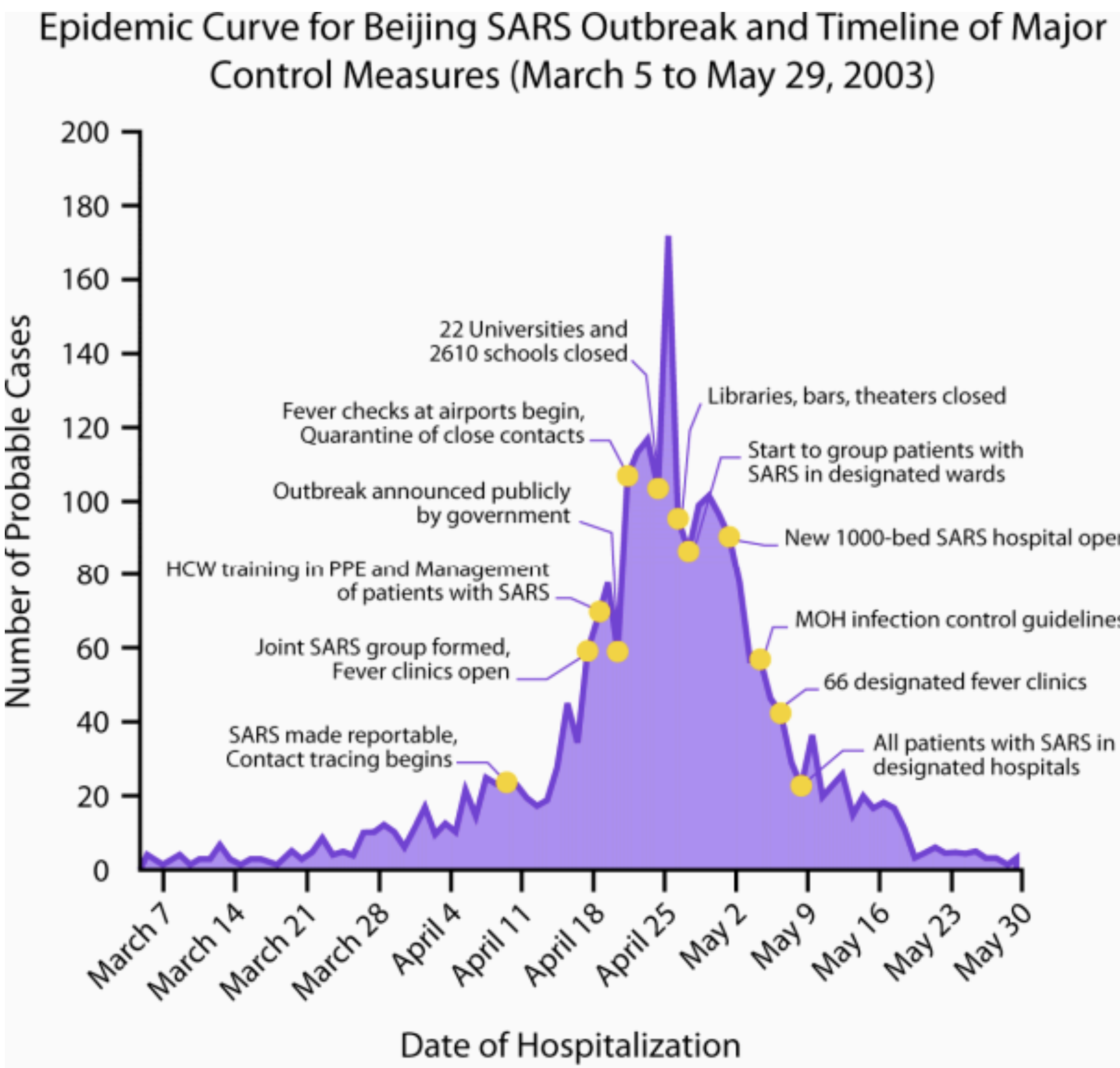
identify key mechanisms
obtain basic conceptual results
build/test theories
identify trends
estimate parameters



PREPARE/PREDICT

explore scenarios
test/evaluate/compare interventions
answer specific questions
provide forecasts (?)

population level



example: modeling 3 pathogens

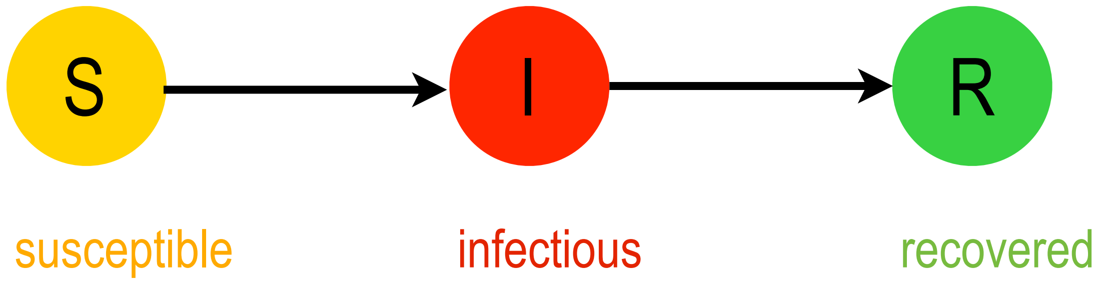
influenza
- ...
- ...
- ...

HIV
- ...
- ...
- ...

tuberculosis
- ...
- ...
- ...

ingredients? assumptions?

simple compartmental models



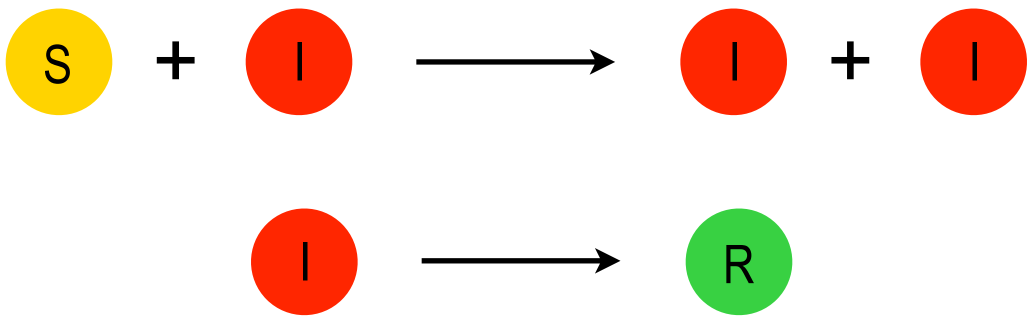
direct transmission

we neglect:

- age
- gender
- health
- job
- severity of disease
- environment
- social status
- latency
- susceptibility
- ...

basic epidemic theory

chemical reactions

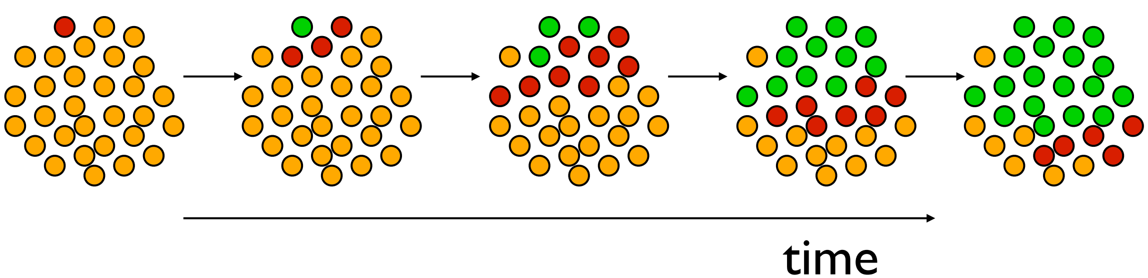


$$\frac{dS}{dt} = -\beta S \frac{I}{N}$$

$$\frac{dI}{dt} = \beta S \frac{I}{N} - \mu I$$

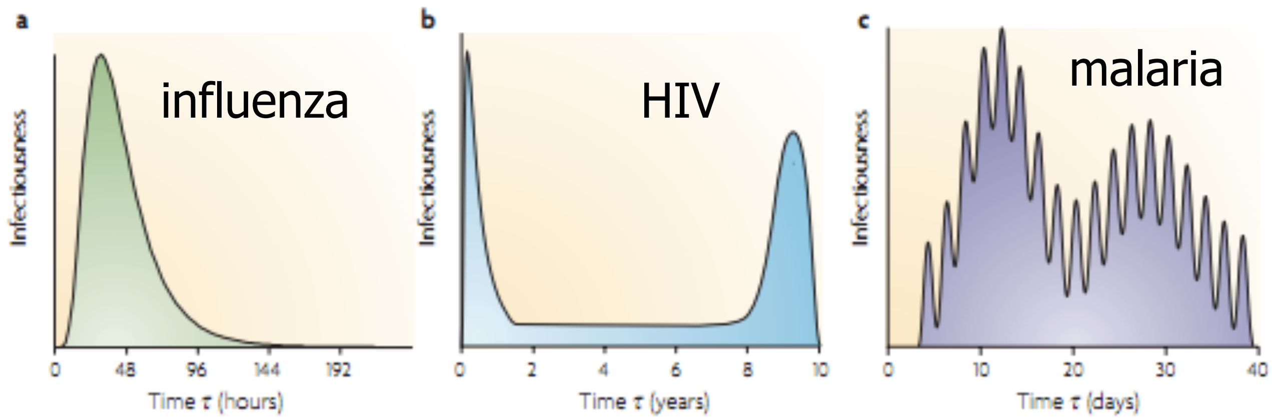
$$\frac{dR}{dt} = \mu I$$

homogeneous mixing

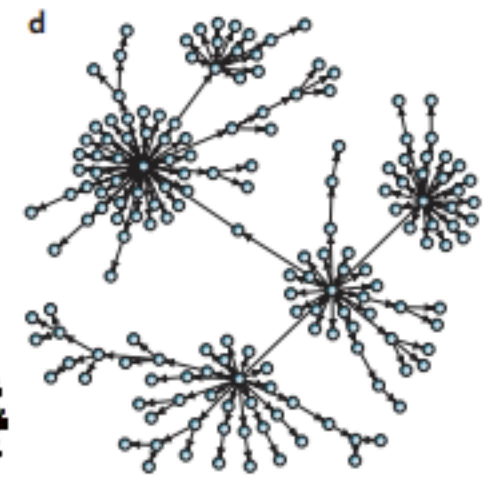


infectiousness β

- **biological infectiousness:** related to pathogen’s life cycle, host’s immune system, interaction with drugs



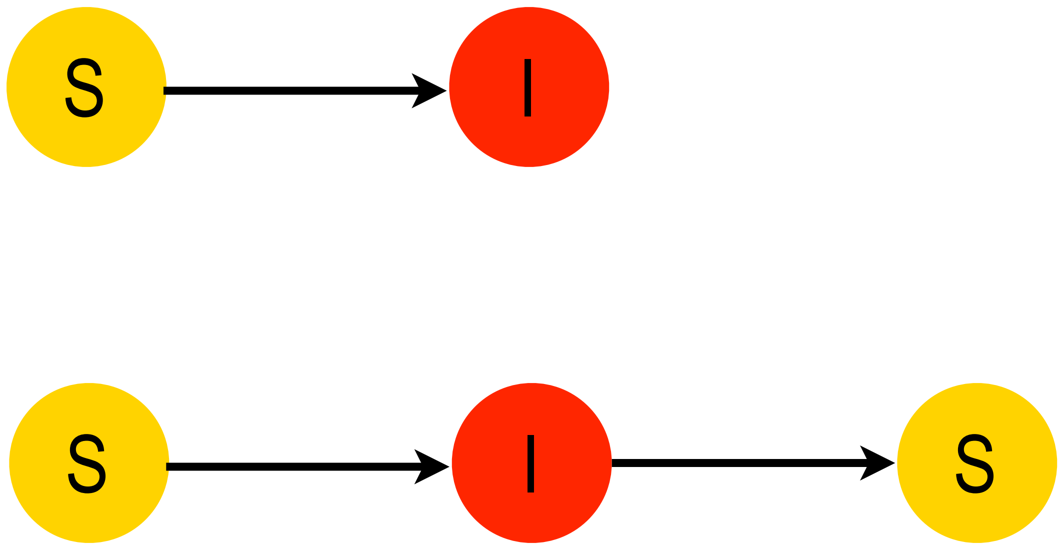
Grassly & Fraser, Nat Rev Microbiol (2008)



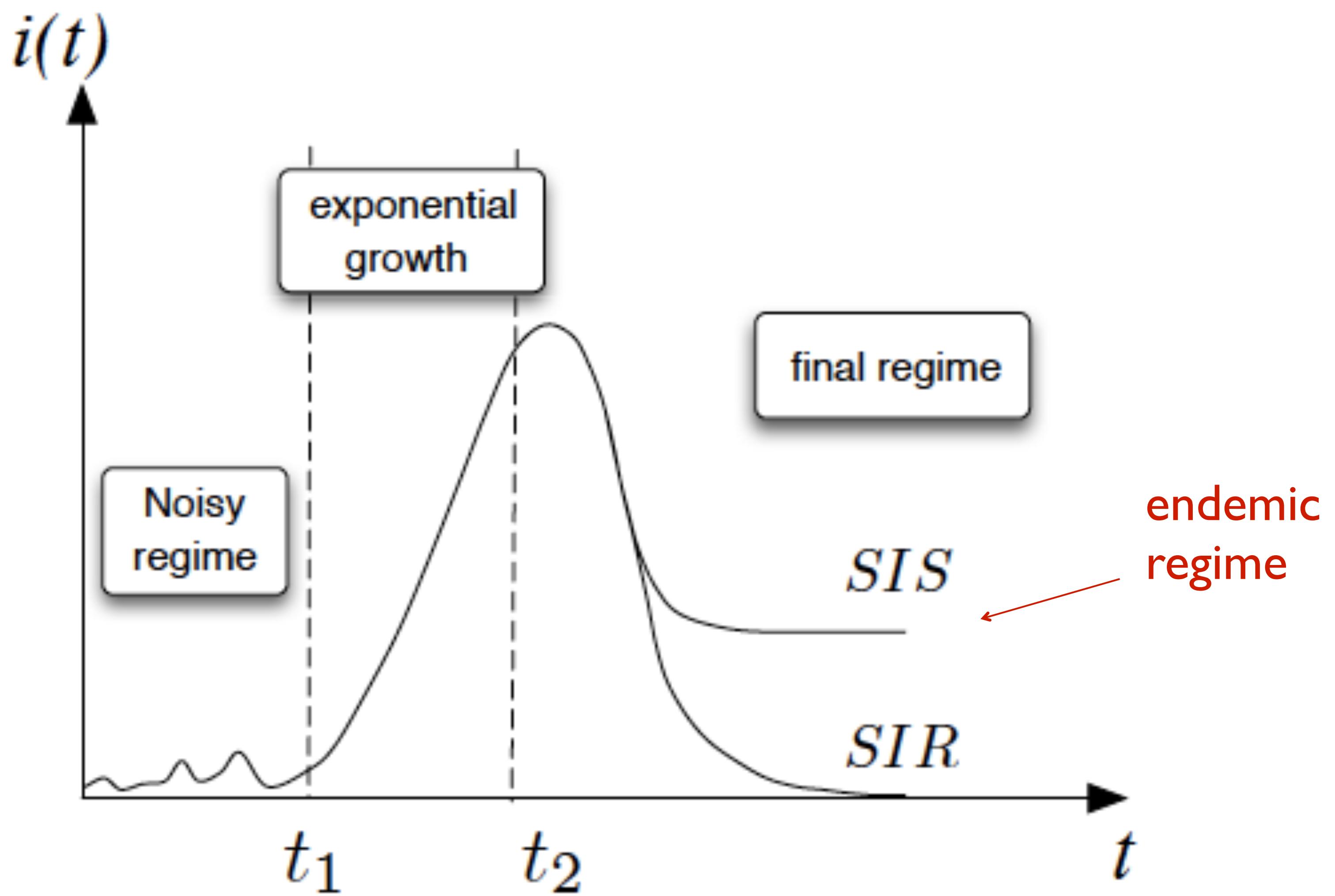
- **behavioral infectiousness:** related to the contact pattern of an infected individual

- **environmental infectiousness:** related to the location and environment of an infected individual, e.g. climatic and seasonal variations

some basic variants



at population level



SIR model: basic questions

- how do we define a growing epidemics versus one that goes extinct?
- how strong does a virus need to be to propagate?

SIR model: early stage

new infections loss of infectiousness

$$\frac{dI}{dt} = \lambda\langle k\rangle S\frac{I}{N} - \mu I$$

average #contacts

$$\beta = \lambda\langle k\rangle$$

per-contact transmissibility

$$i = I/N$$

prevalence

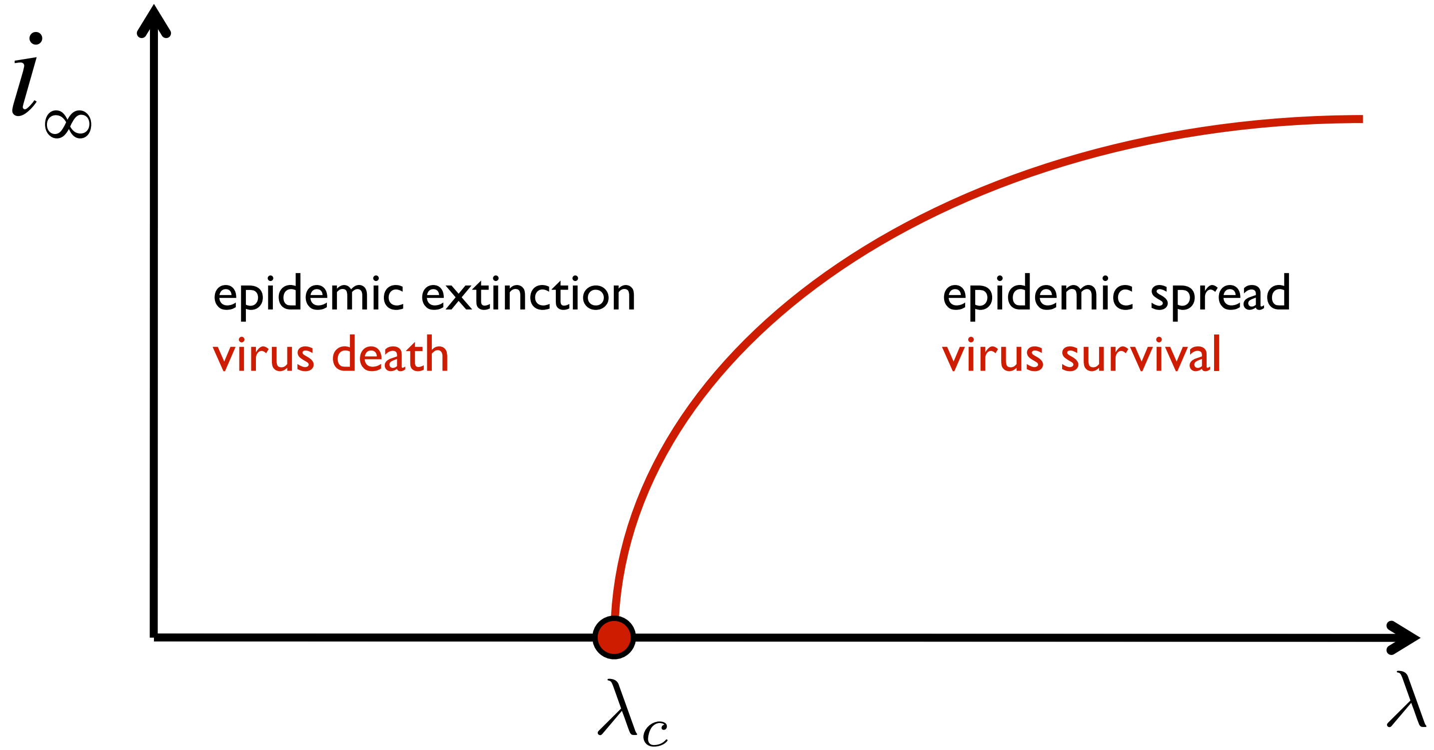
$$\frac{di}{dt} = \lambda\langle k\rangle s i - \mu i \simeq \lambda\langle k\rangle i - \mu i > 0 \Leftrightarrow \lambda\langle k\rangle - \mu > 0$$

$s \simeq 1$

$$\frac{di}{dt} > 0 \quad \Leftrightarrow \quad \boxed{\lambda > \lambda_c = \mu/\langle k\rangle}$$

epidemic threshold

epidemic threshold



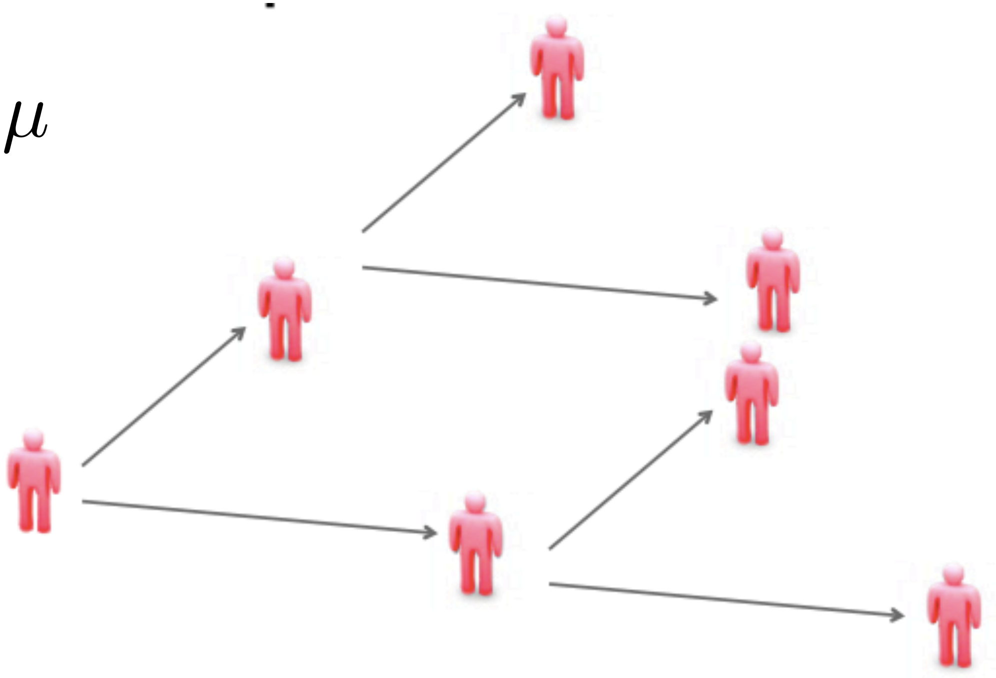
- very general result (SI, SIS, SEIR, ...)
- related to the reproductive number

reproductive number

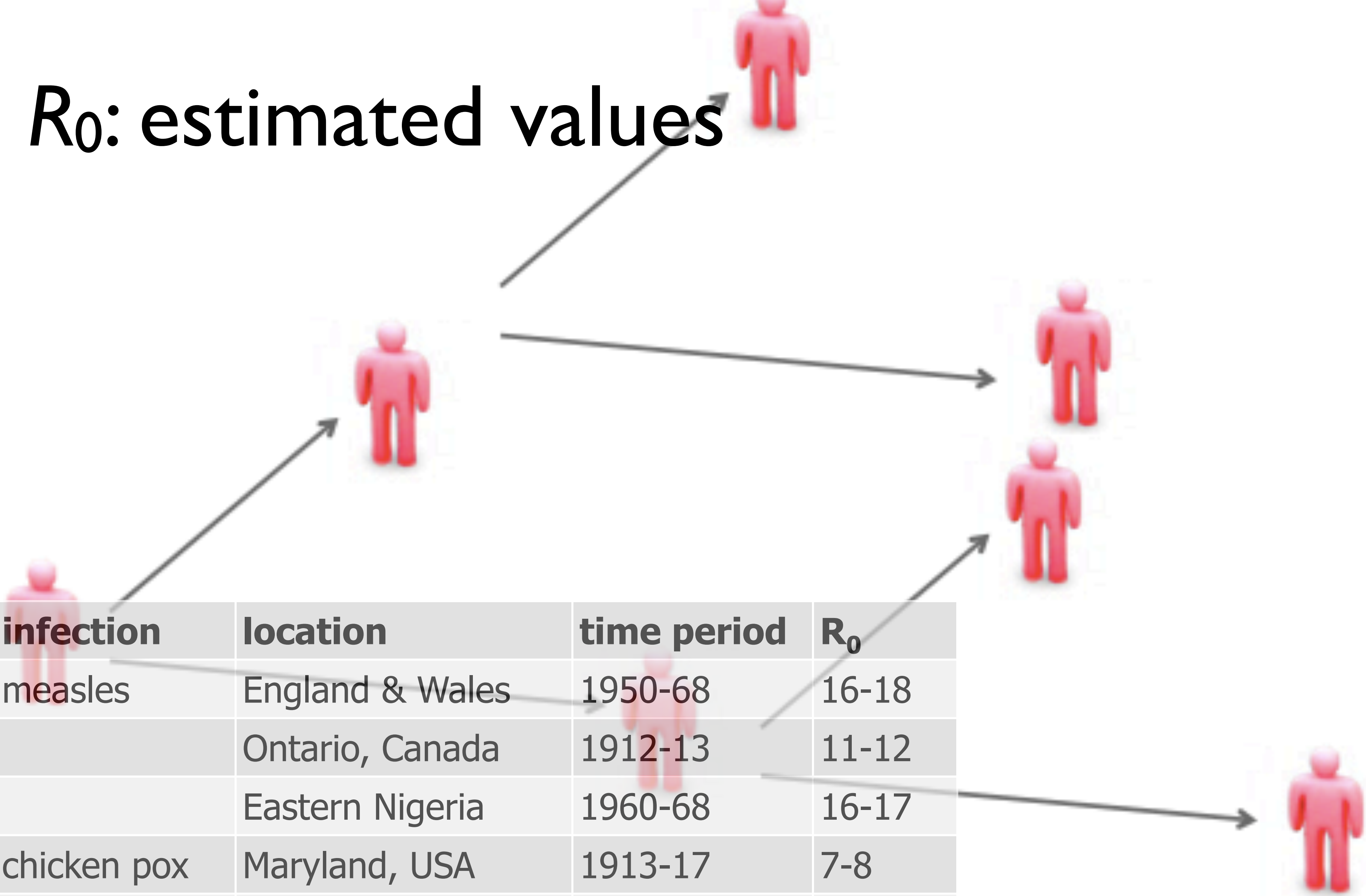
R_0 is the average number of individuals infected directly by an infected individuals during his infectious period in a fully susceptible population.

$$\lambda > \lambda_c \quad \Leftrightarrow \quad \lambda \langle k \rangle > \mu$$

$$\boxed{R_0 = \frac{\lambda \langle k \rangle}{\mu} > 1}$$



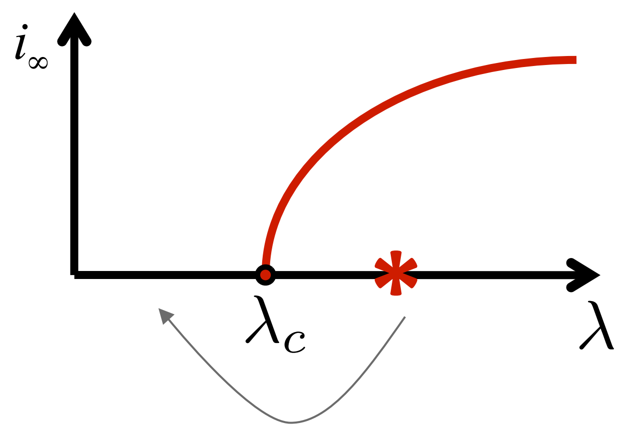
R_0: estimated values



infection	location	time period	R_0
measles	England & Wales	1950-68	16-18
	Ontario, Canada	1912-13	11-12
	Eastern Nigeria	1960-68	16-17
chicken pox	Maryland, USA	1913-17	7-8
	Baltimore, USA	1943	10-11
pertussis	England & Wales	1944-78	16-18

epidemic threshold & health policy

if $\quad R_0 = \dfrac{\lambda \langle k \rangle}{\mu} > 1$ what can we do to stop/prevent an epidemic outbreak ?



we want to effectively reduce the epidemic below the threshold...

again on the definition of R_0

R_0 is the average number of individuals infected directly by an infected individuals during his infectious period in a fully susceptible population.

what if the population is not fully susceptible??

again on the definition of R_0

R_0 is the average number of individuals infected directly by an infected individuals during his infectious period in a fully susceptible population.

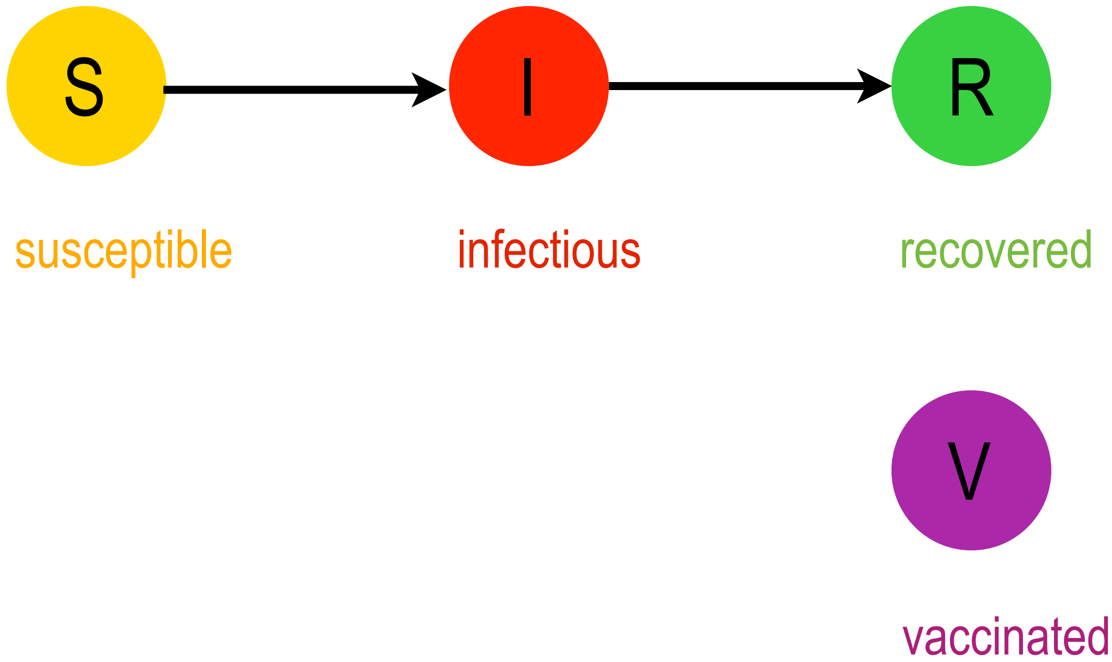
what if the population is not fully susceptible??

...for example... *vaccination*

a certain fraction of the population is vaccinated and therefore immune to the disease

- additional compartment: vaccinated

SIS epidemic with vaccination



$$N = S(t) + I(t) + R(t) + V \;\rightarrow\; S(t) = N - I(t) - R(t) - V$$

SIR epidemic with vaccination

$$\frac{di}{dt} = \lambda\langle k\rangle(1-v)i - \mu i\,,\;\; v = \frac{V}{N}$$

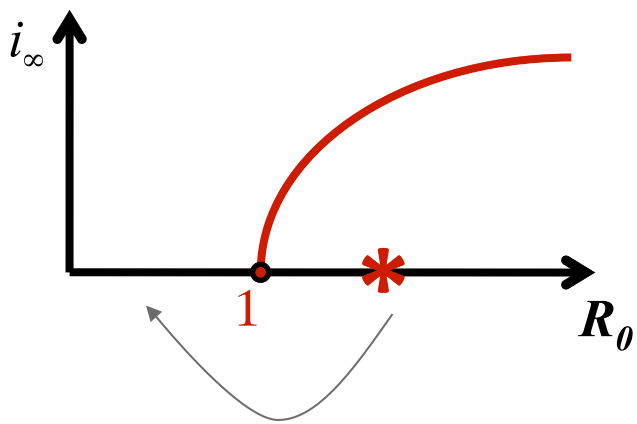
$$\frac{di}{dt} > 0 \Leftrightarrow \lambda(1-v) - \frac{\mu}{\langle k\rangle} > 0$$

$$\boxed{\lambda(1-v)} - \lambda_c > 0$$

$$\lambda \Rightarrow \lambda(1-v)$$

$$R_0^{'} = R_0(1-v) < R_0$$

immunization threshold



condition to prevent/control an epidemic outbreak ?

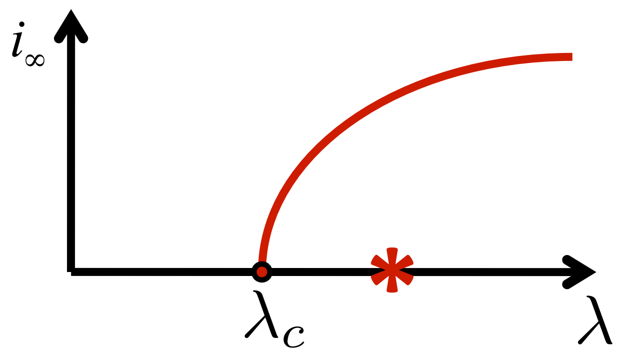
v_c such that $R_0' < 1$ $\Rightarrow$ $R_0' = R_0(1-v) < 1$

$$\boxed{v > v_c = \frac{R_0 - 1}{R_0}}$$

fraction of the population to be vaccinated to prevent/control the outbreak

simple epidemic models: *summary*

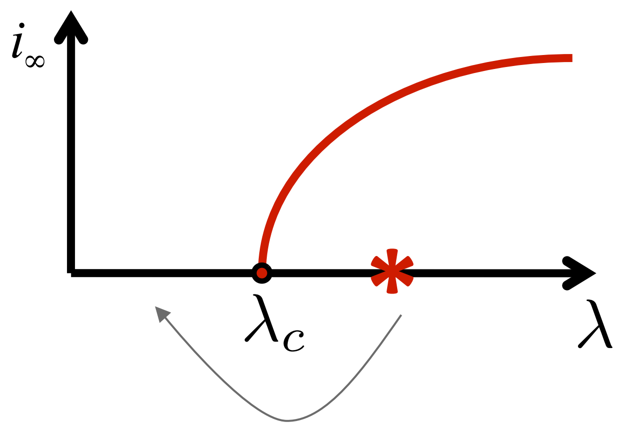
homogeneous mixing



epidemic threshold:

active phase i.e. virus spreads only if

$$\lambda > \lambda_c = \mu \langle k \rangle^{-1}$$

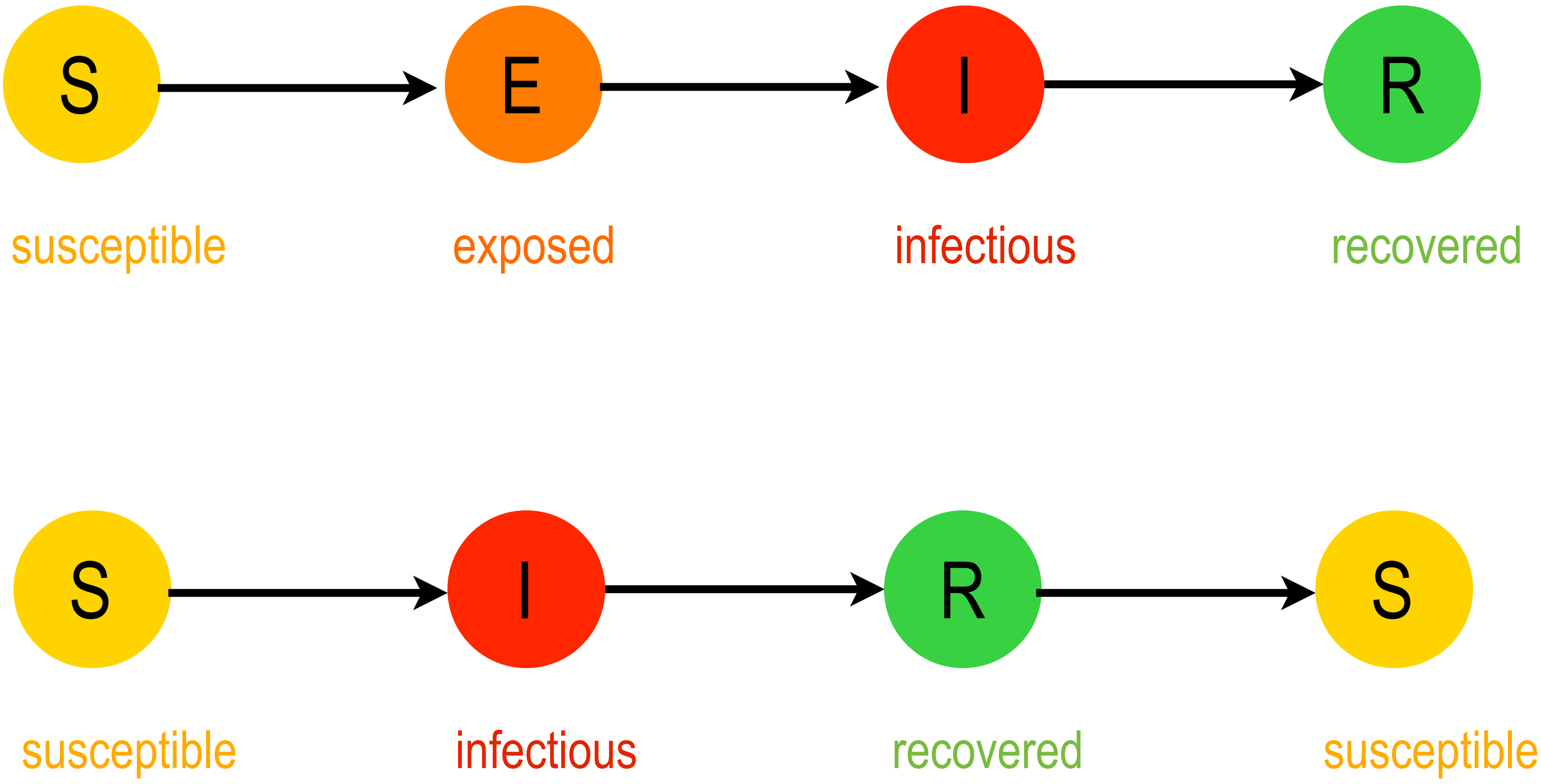


immunization threshold:

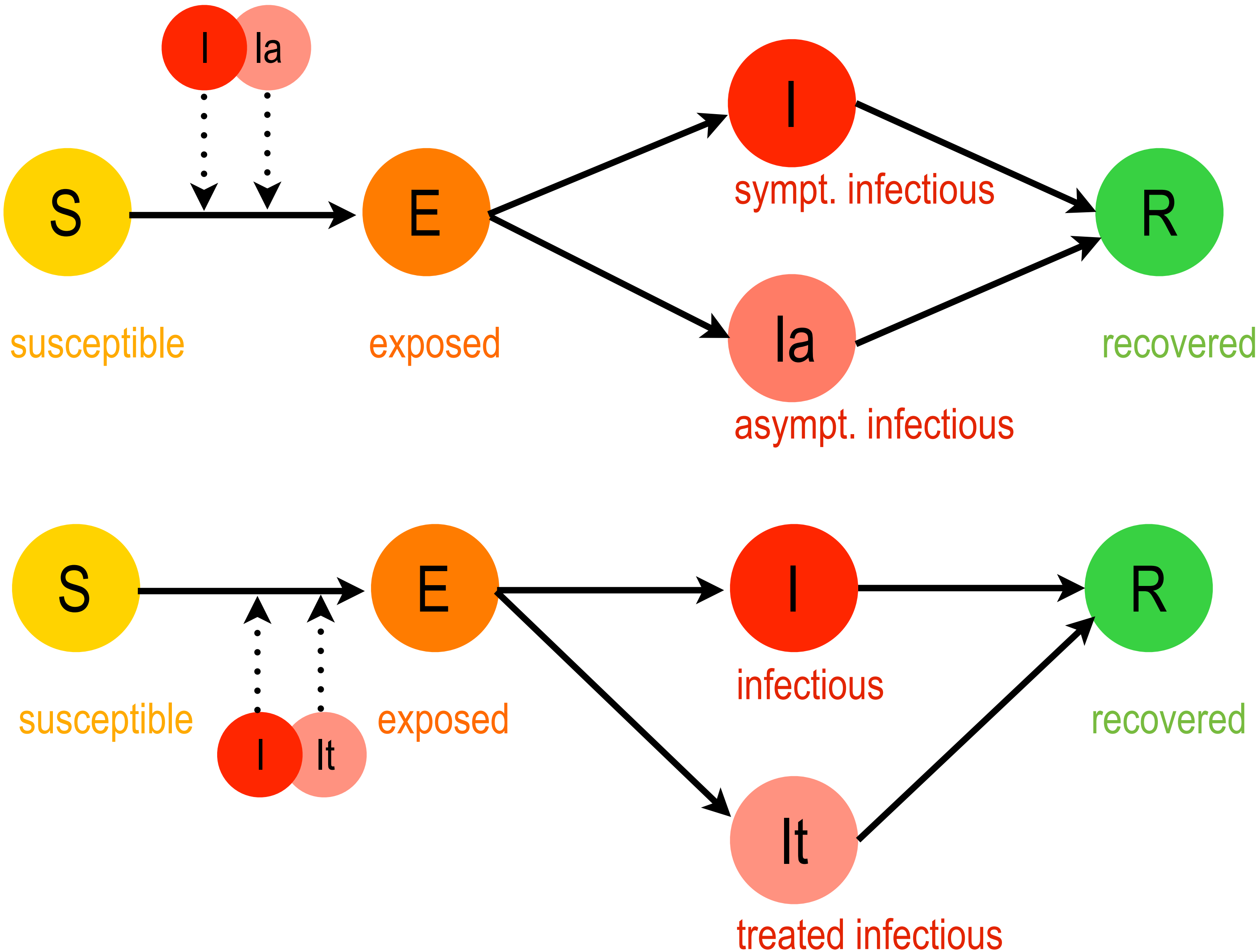
epidemic is stopped if

$$v > v_c = \frac{R_0 - 1}{R_0}$$

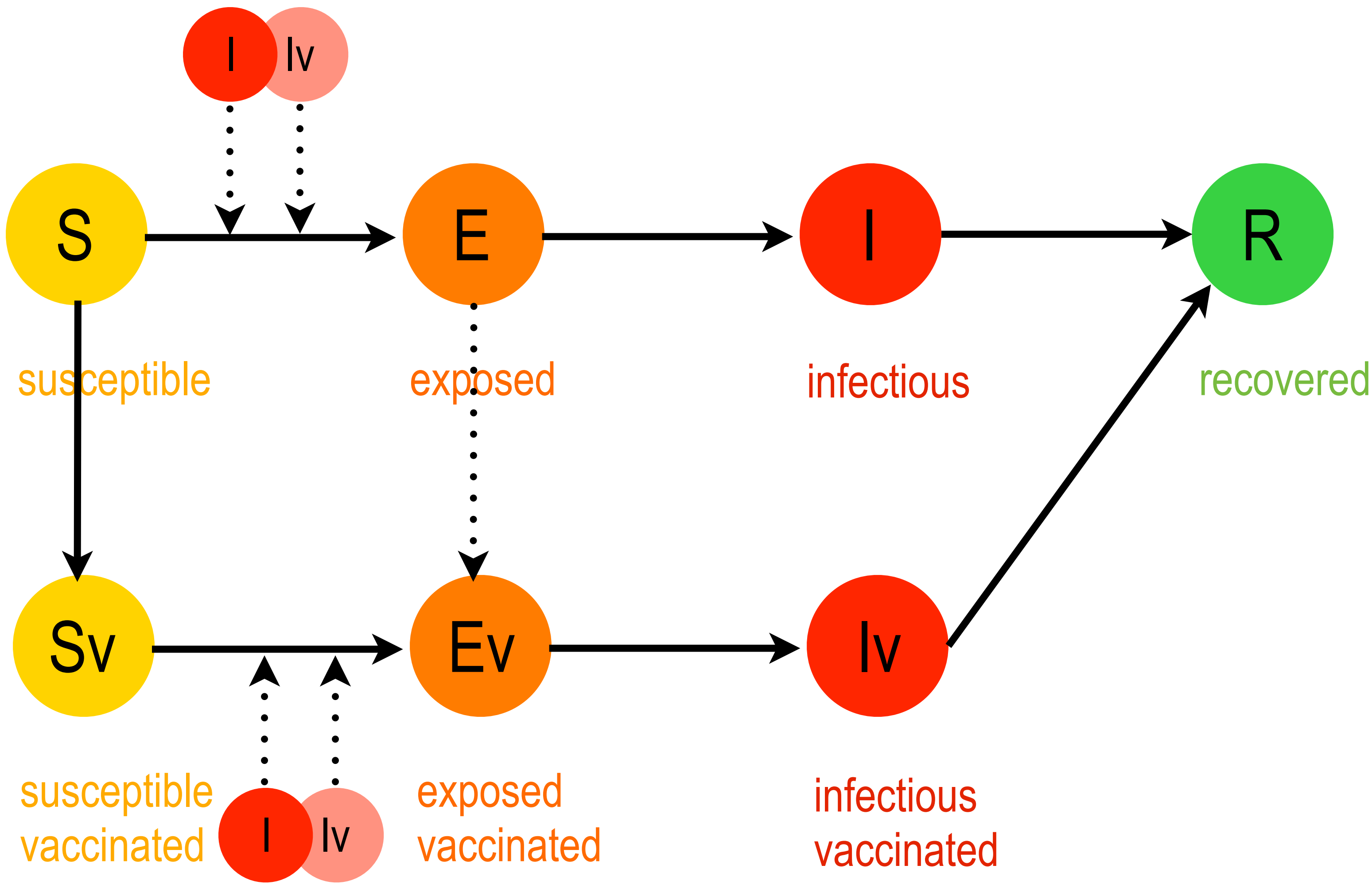
going beyond (1): additional stages



going beyond (1): additional stages



going beyond (1): additional stages

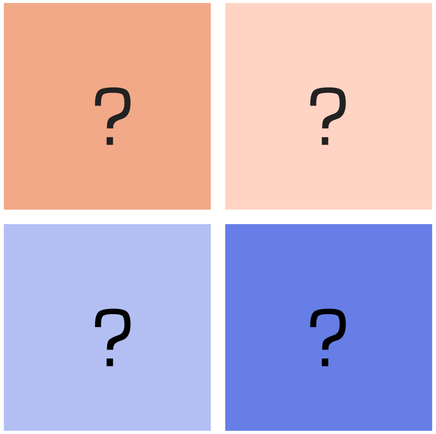


going beyond (2): population classes

population profile

- ?
- ?

mixing



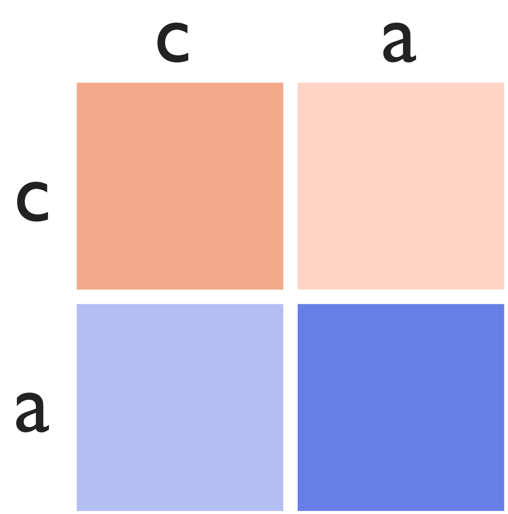
going beyond (2): population classes

e.g.: flu

population profile

- children
- adults

mixing: **contacts**



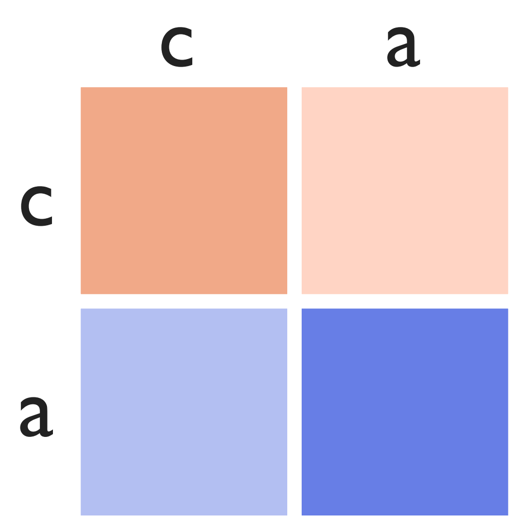
going beyond (2): population classes

e.g.: HIV

population profile

- female
- male

mixing: **transmissibility**



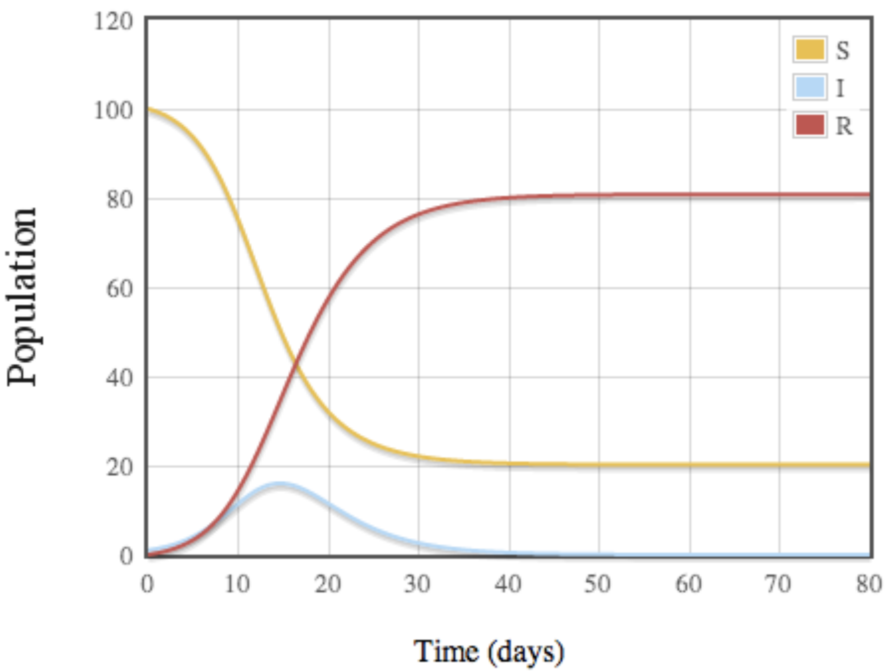
going beyond (3): frequency vs. density

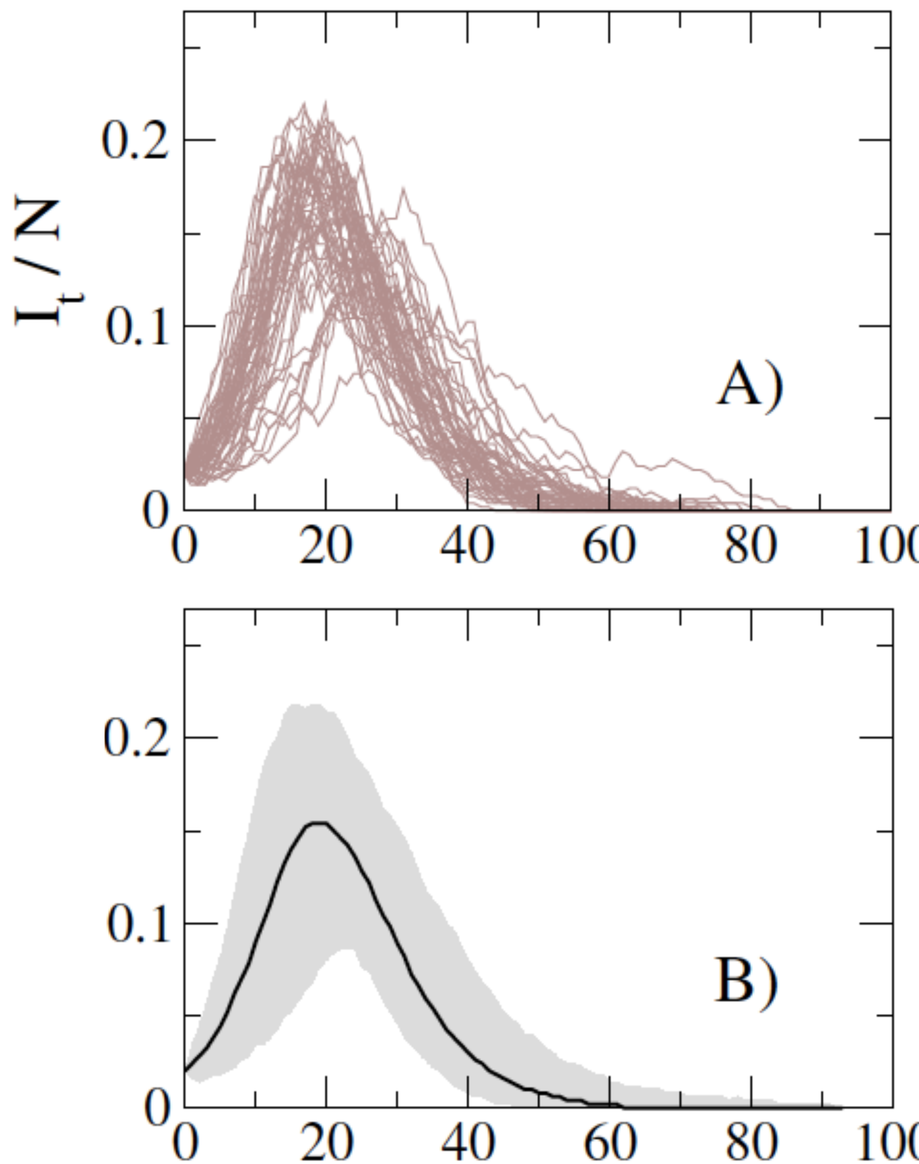
FD transmission: $$\frac{dI}{dt} = \beta S \frac{I}{N} - \mu I$$

DD transmission: $$\frac{dI}{dt} = \beta S I - \mu I$$

going beyond (3): frequency vs. density

going beyond (4): stochasticity





going beyond (5): *I am legend*

1. zombies (=infectious) work together to actively increase the number of zombies

going beyond (5): *I am legend*

1. zombies (=infectious) work together to actively increase the number of zombies

$$\frac{di}{dt} = \beta s \sqrt{i} - \mu i$$

going beyond (5): *I am legend*

1. zombies (=infectious) work together to actively increase the number of zombies

$$\frac{di}{dt} = \beta s\sqrt{i} - \mu i$$

2. zombies do not recover and stop infecting only when destroyed by a susceptible; susceptibles destroy as many zombies as they can.

going beyond (5): *I am legend*

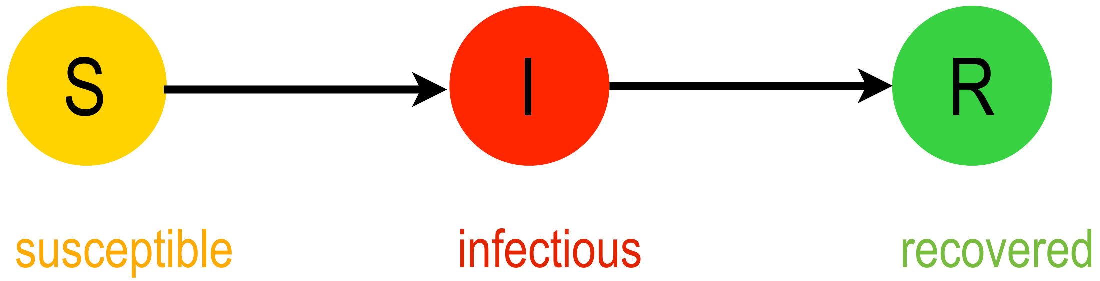
1. zombies (=infectious) work together to actively increase the number of zombies

$$\frac{di}{dt} = \beta s\sqrt{i} - \mu i$$

2. zombies do not recover and stop infecting only when destroyed by a susceptible; susceptibles destroy as many zombies as they can.

$$\frac{di}{dt} = \beta si - \mu s$$

going beyond (6): heterogeneous contacts

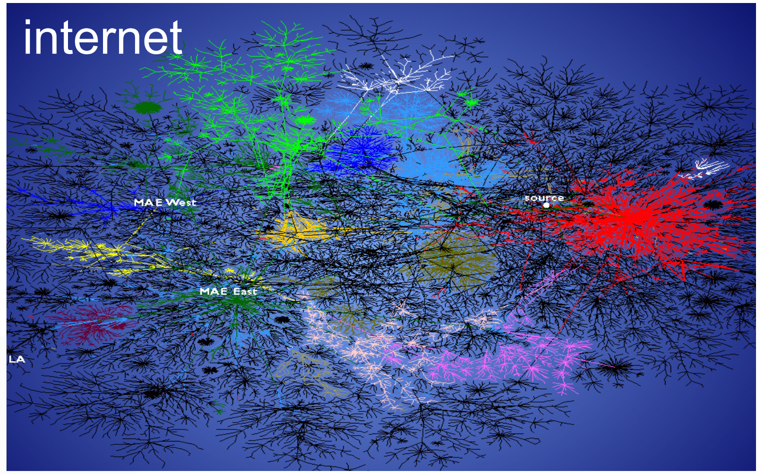


we neglect:

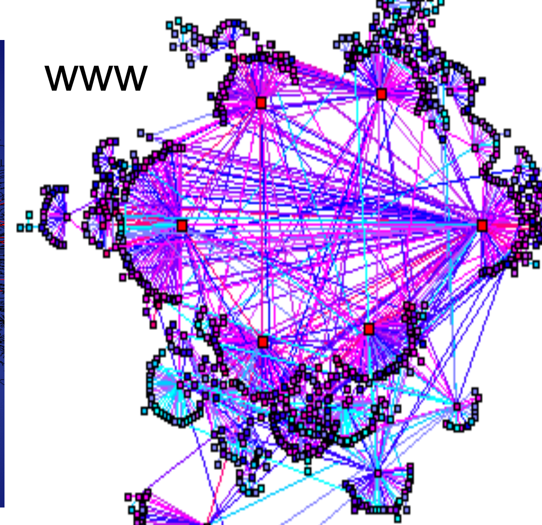
- age
- gender
- health
- job
- severity of disease
- environment
- social status
- latency
- susceptibility
- **contact heterogeneity**

infectious diseases: contact network models

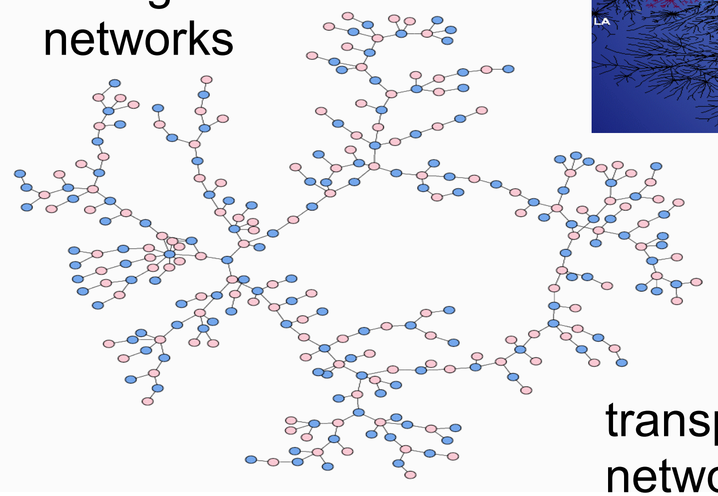
networks



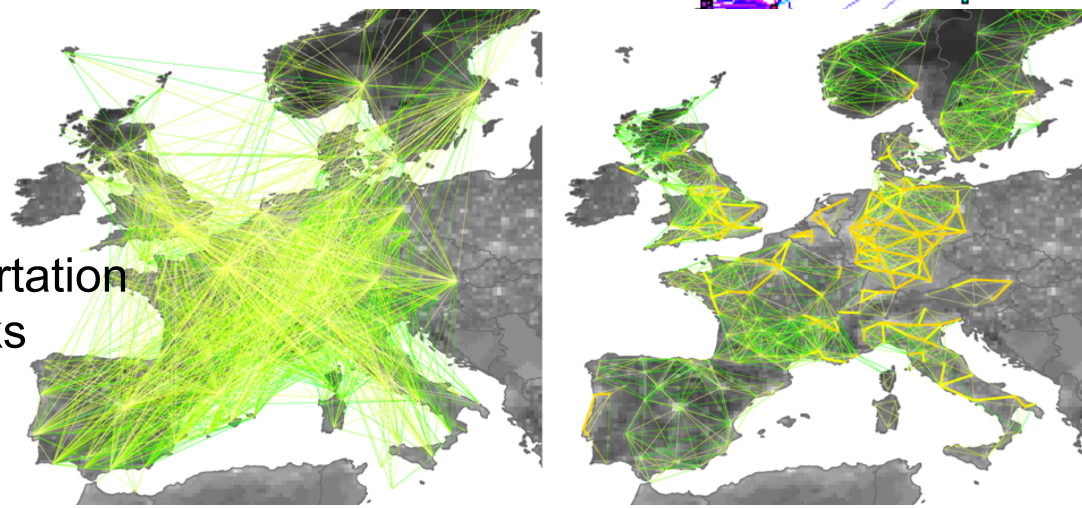
www



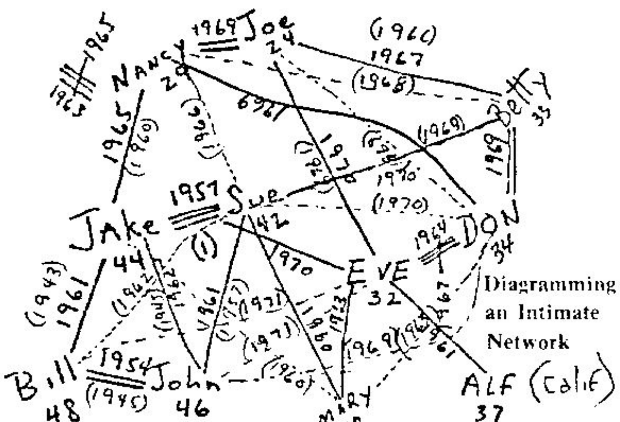
dating
networks

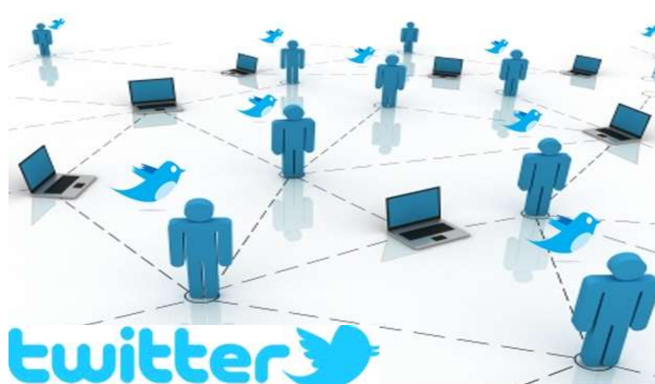


transportation
networks

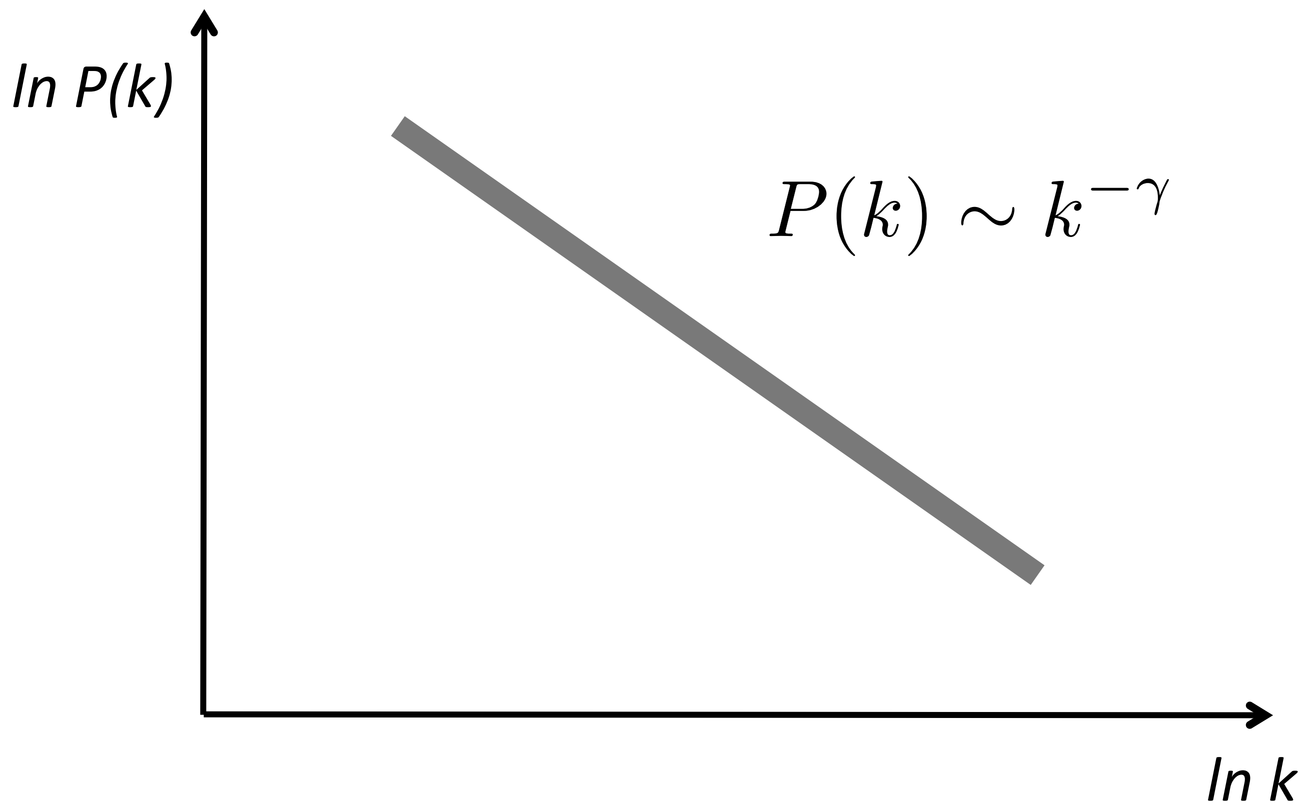


sexual
networks

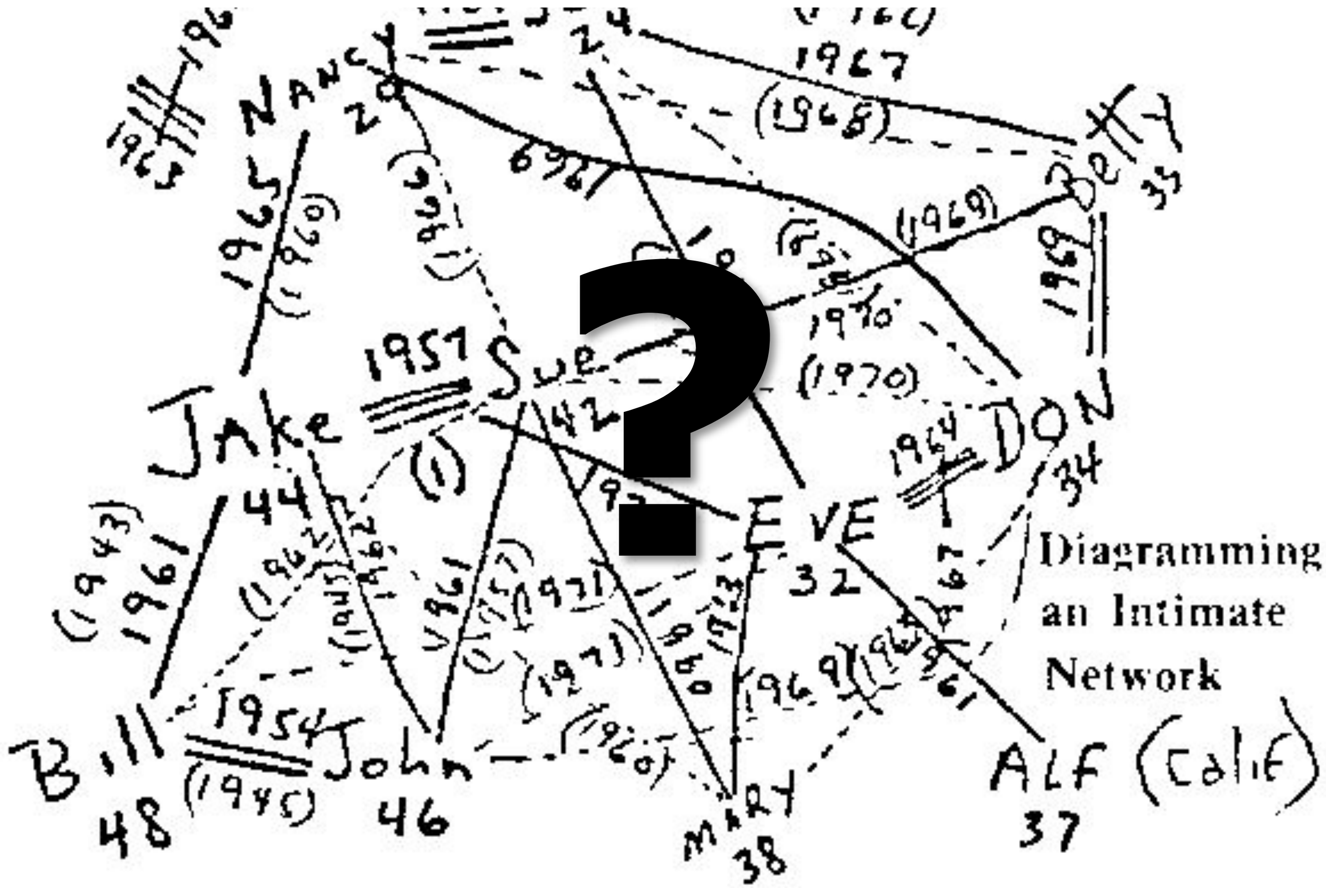




heterogeneous networks

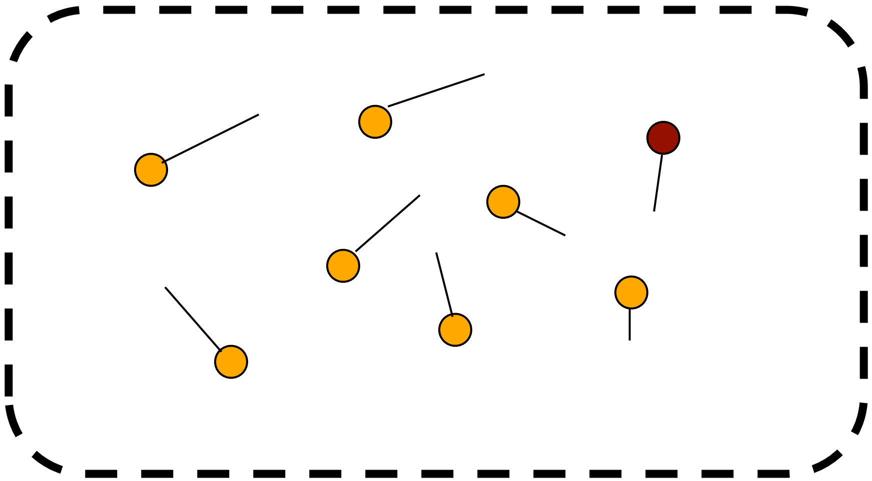


how to model?

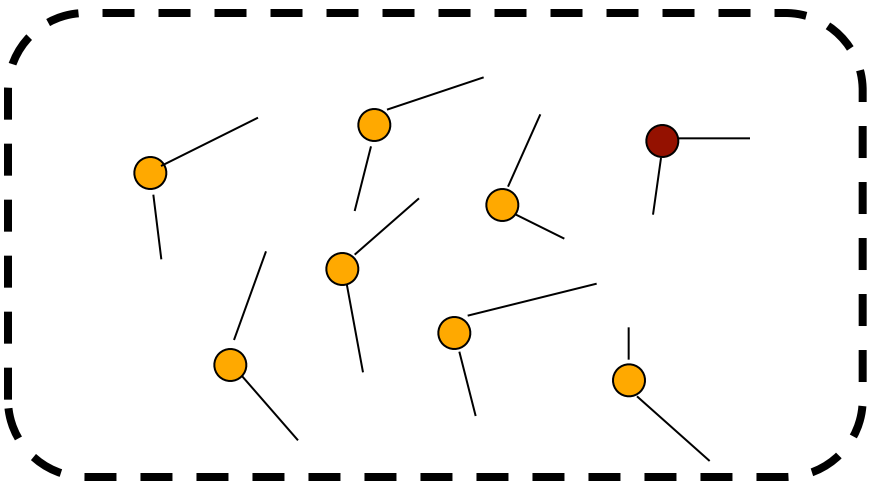


>> identification of relevant variables

degree-based representation or HMF



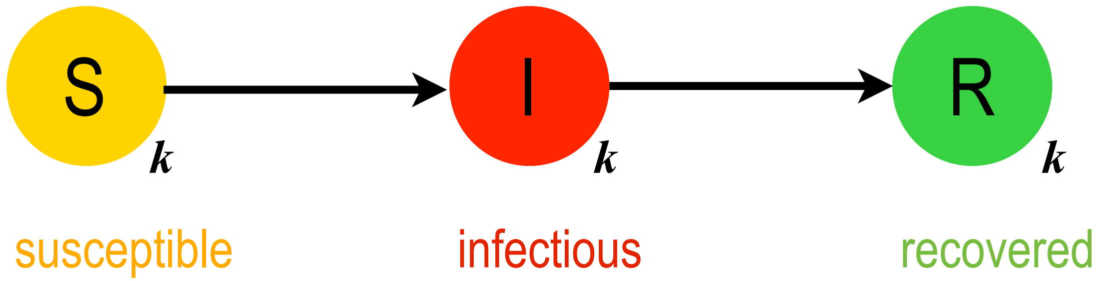
class of individuals with
degree k=1



class of individuals with
degree k=2

etc.

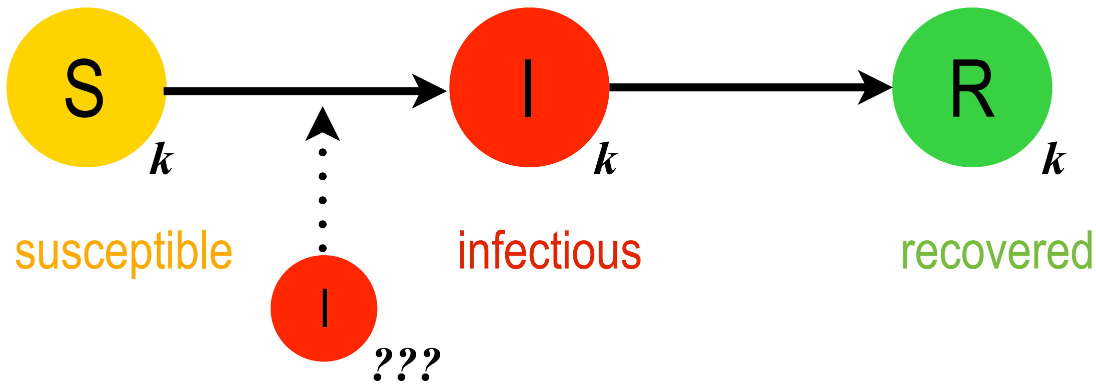
degree-based representation



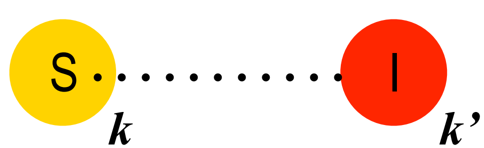
$$\frac{dI_k}{dt} = \boxed{\lambda \langle k \rangle \frac{I}{N}} S_k - \mu I_k$$

?

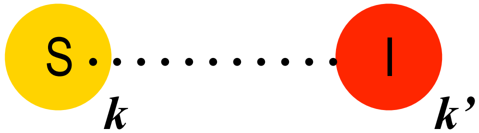
contagion process

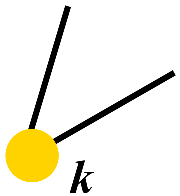


interaction with all possible classes k'

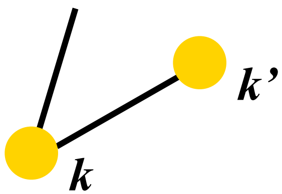


components

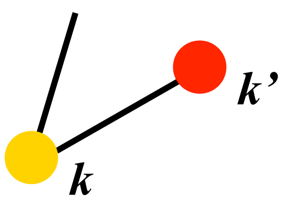




number of possible contacts: k

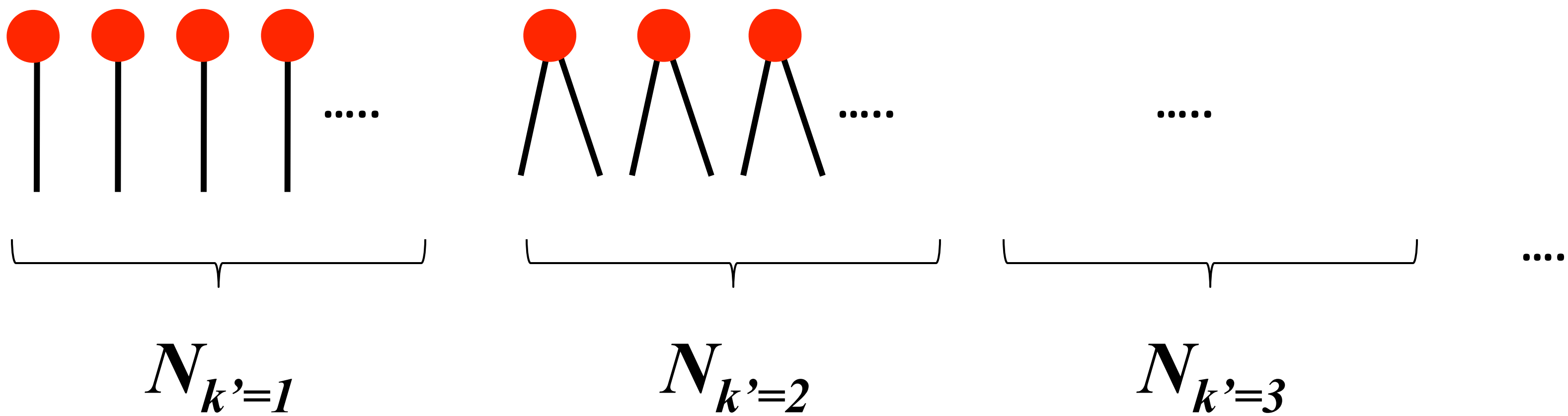


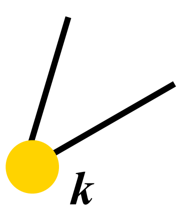
probability of contact with *k*': $P(k'|k)$



contact with *k*' is infectious: $I_{k'}$

probability that *k* points to *k'*

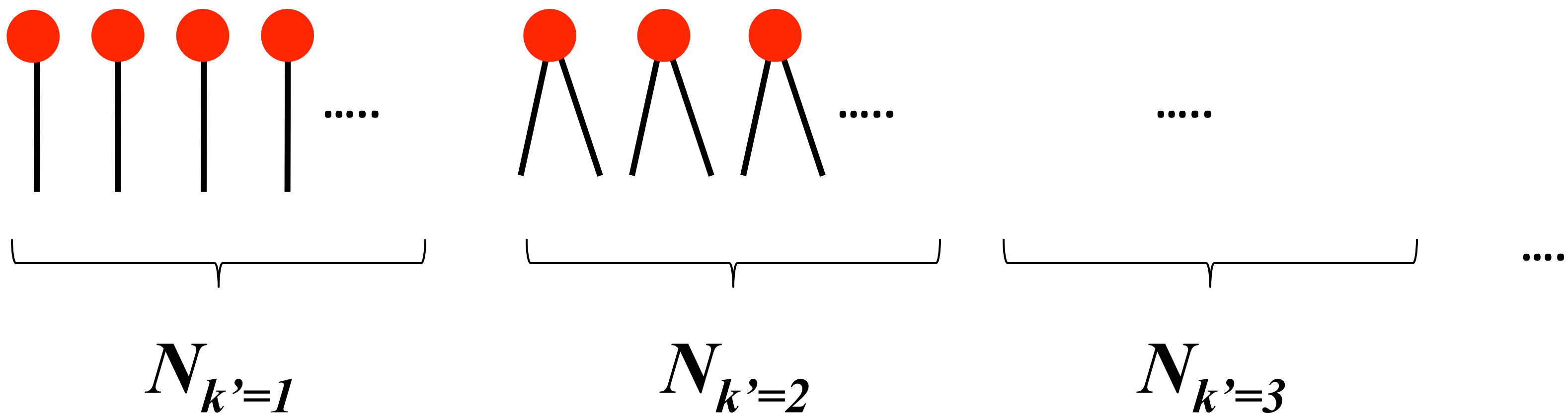


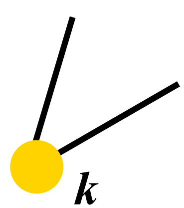


$$P(1\,|\,k) = \frac{1 \times N_1}{2E}$$

$$P(2\,|\,k) = \frac{2 \times N_2}{2E}$$

probability that *k* points to *k'*





$$P(k'|k) = \frac{k' N_{k'}}{N\langle k\rangle} = \frac{k' P(k')}{\sum_{k'} k' P(k')} = \frac{k' P(k')}{\langle k\rangle}$$

assumption: *uncorrelated* network

SIR on complex networks

$$\frac{dI}{dt} = \lambda k S_k \sum_{k'} P(k'|k) I_{k'} - \mu I_k$$

$$\frac{dI}{dt} > 0 \quad \Leftrightarrow \quad \boxed{\lambda > \lambda_c = \frac{\mu \langle k \rangle}{\langle k^2 \rangle - \langle k \rangle}}$$

epidemic threshold in heterogeneous networks

Cohen et al, PRL 2000
Pastor-Satorras et al, PRL 2001
Newman PRE 2002

$$\boxed{\lambda > \lambda_c = \frac{\mu}{\langle k \rangle}}$$

epidemic threshold in homogeneous mixing

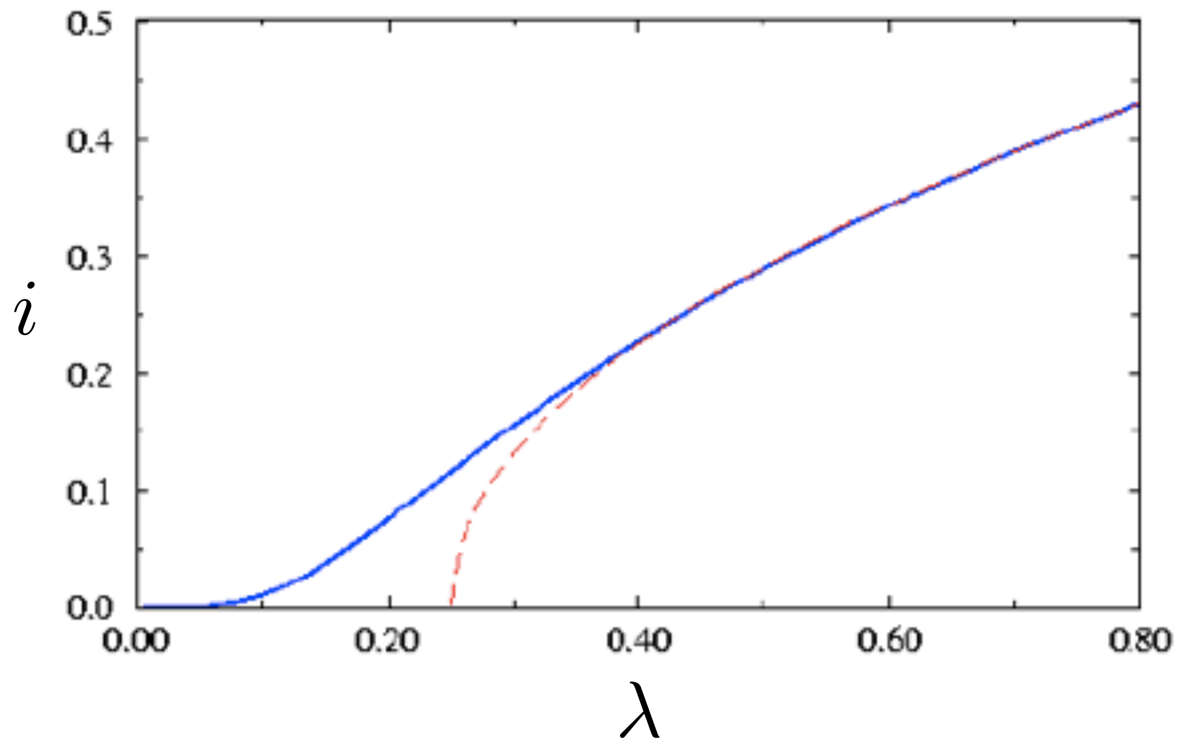
vanishing epidemic threshold

$$\lambda > \lambda_c = \frac{\mu \langle k \rangle}{\langle k^2 \rangle - \langle k \rangle}$$

$\langle k^2 \rangle \to \infty$
$\gamma \leq 3$

$\lambda_c \to 0$

thermodynamic limit



the infection pervades the system whatever spreading rate

the healthy phase does not exist

Cohen et al, PRL 2000
Pastor-Satorras et al, PRL 2001
Newman PRE 2002

immunization in heterogeneous networks

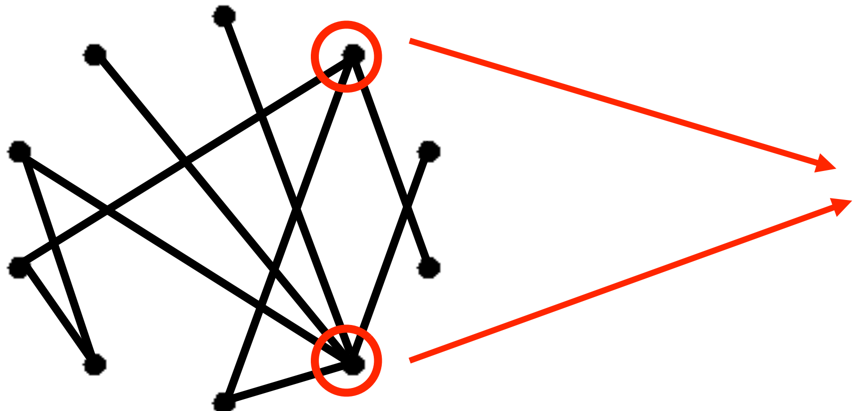
epidemic is controlled if $\lambda(1-v) \leq \lambda_c$

but in infinite-size heterogeneous networks $\lambda_c = 0$ $\Rightarrow$ $\boxed{v_c = 1}$

immunization threshold !!!

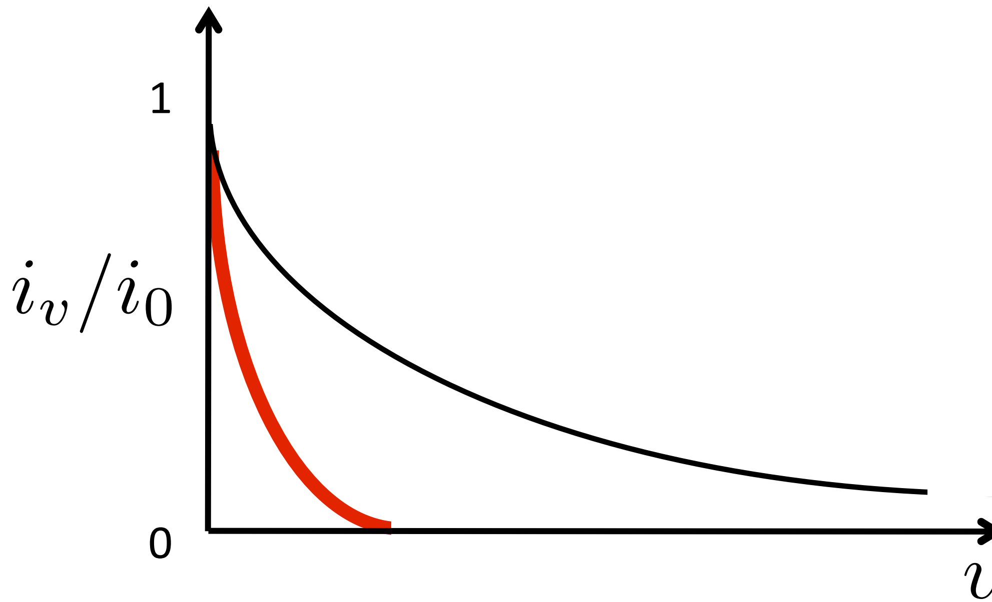
random immunization is *ineffective*... then what???

targeted immunization strategy



progressive immunization of crucial nodes: hubs

epidemic threshold is reintroduced

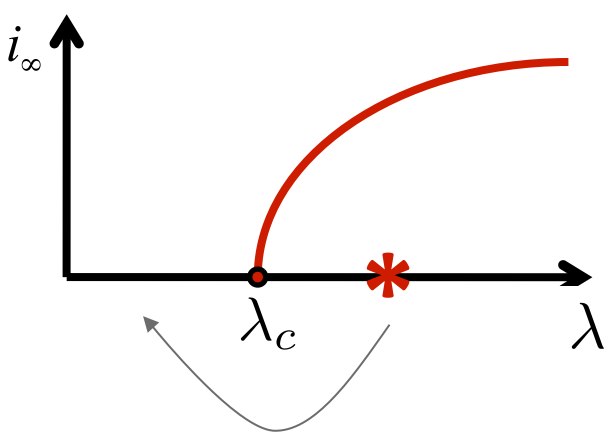


Pastor-Satorras & Vespignani, PRE 65, 036104 (2002)
Dezso & Barabasi cond-mat/0107420; Havlin et al. preprint (2002)

SIR: homogeneous mixing vs. heterogeneous networks

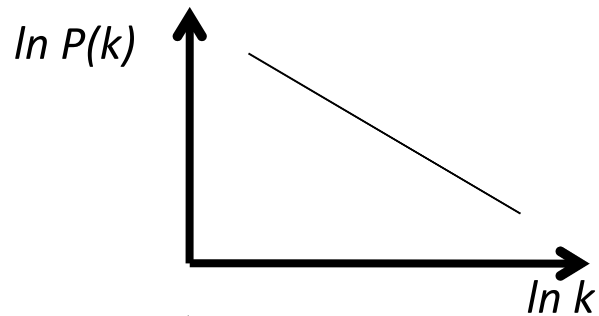
homogeneous mixing

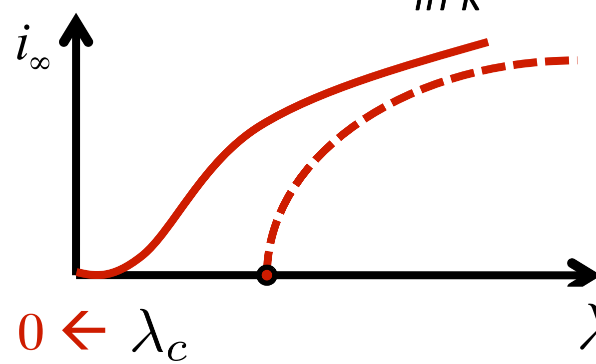
$$k \simeq \langle k \rangle$$



epidemic threshold:
active phase & healthy phase
immunization threshold

heterogeneous contact pattern





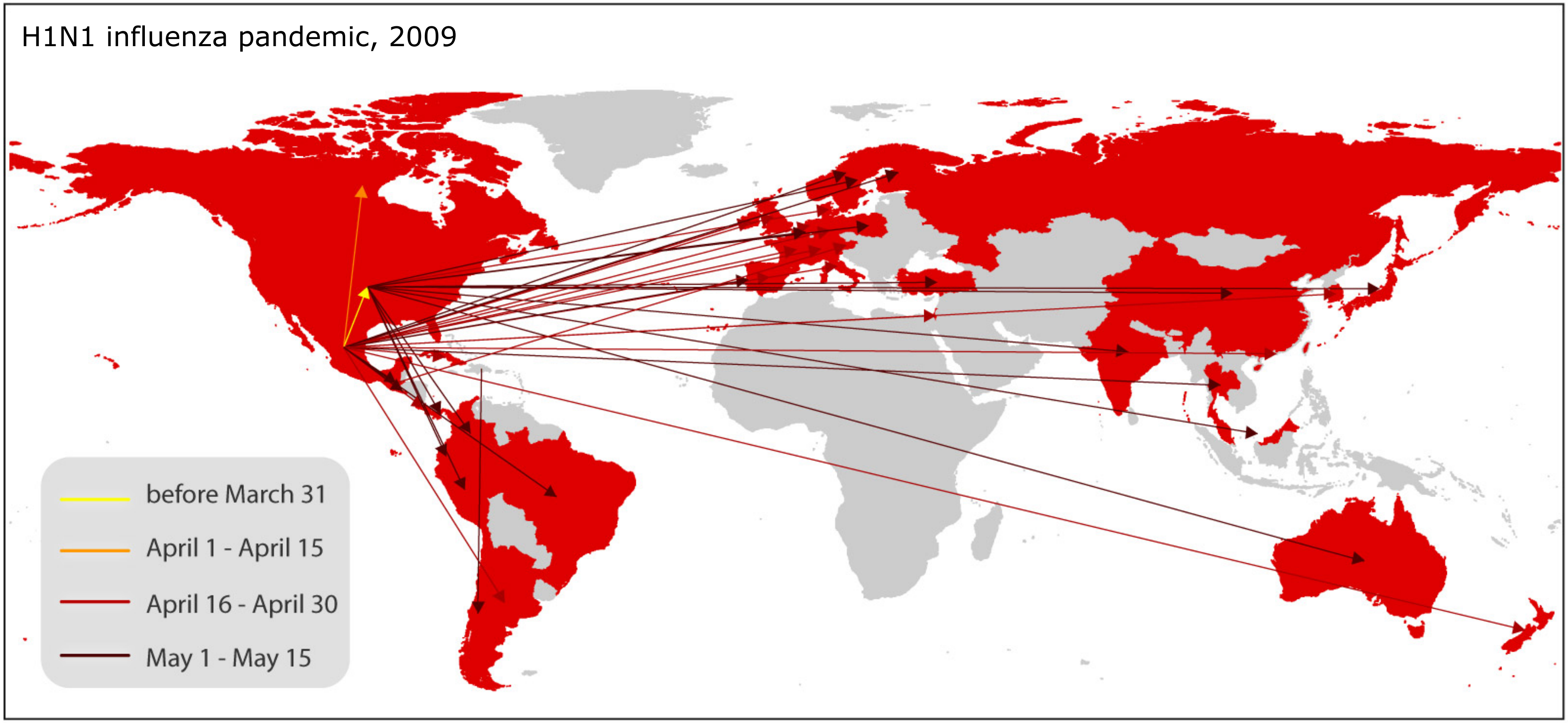
vanishing epidemic threshold:
healthy phase does not exist
targeted immunization

epidemic threshold for SIS

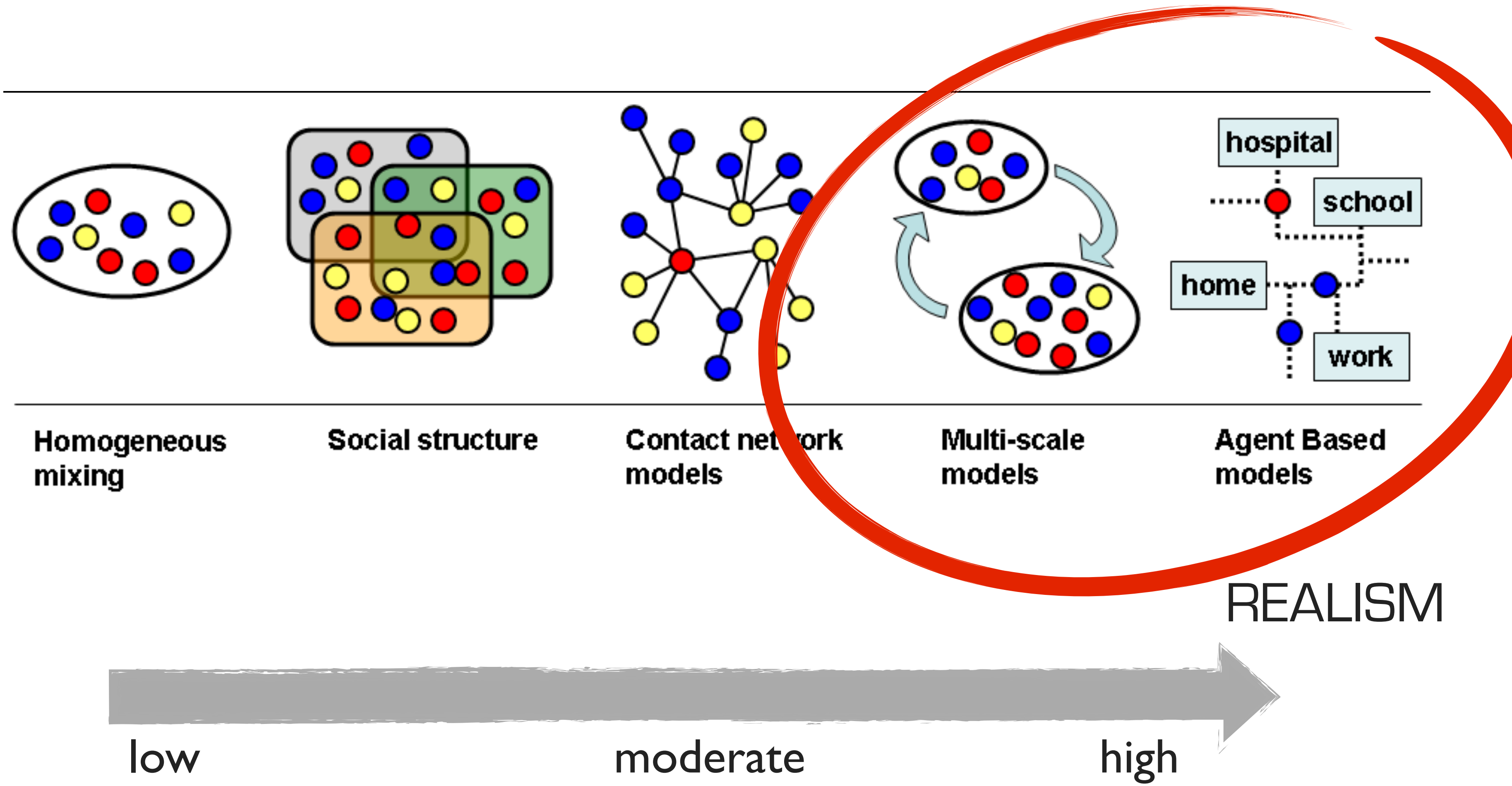
see: http://arxiv.org/pdf/1010.1646.pdf
http://arxiv.org/pdf/1105.5545.pdf
http://arxiv.org/pdf/1206.6728.pdf
http://arxiv.org/pdf/1305.4819.pdf

infectious diseases: space & metapopulation models

population & space

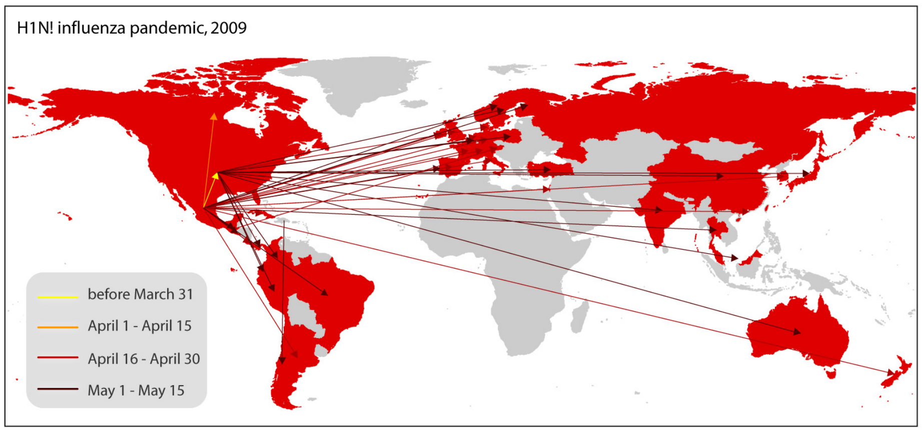


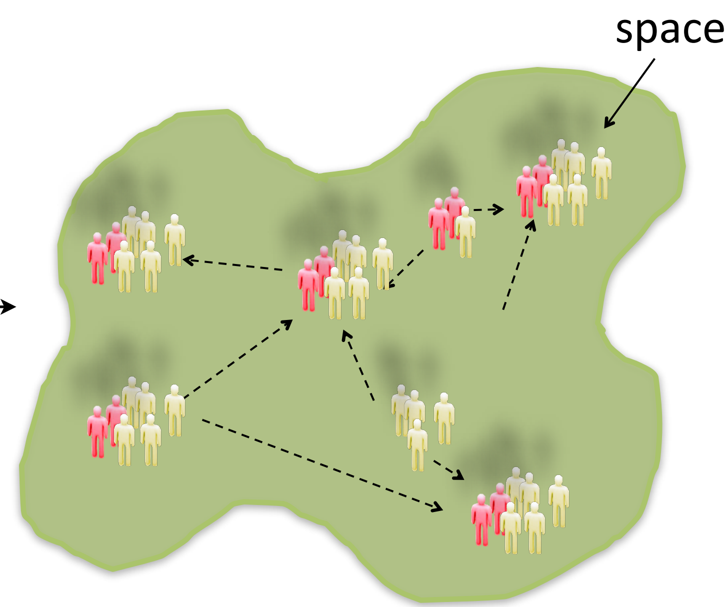
models' complexity



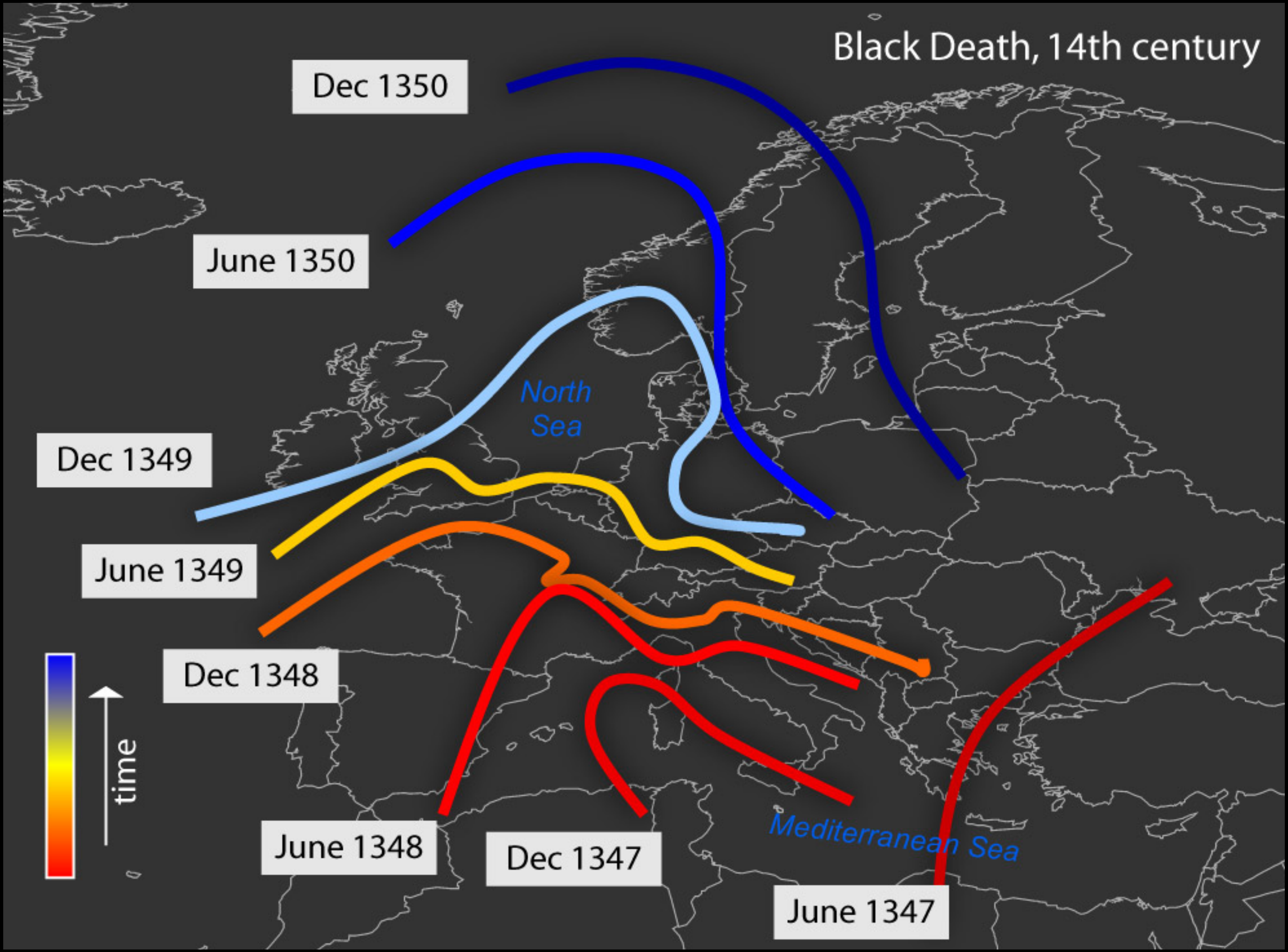
>> DATA...

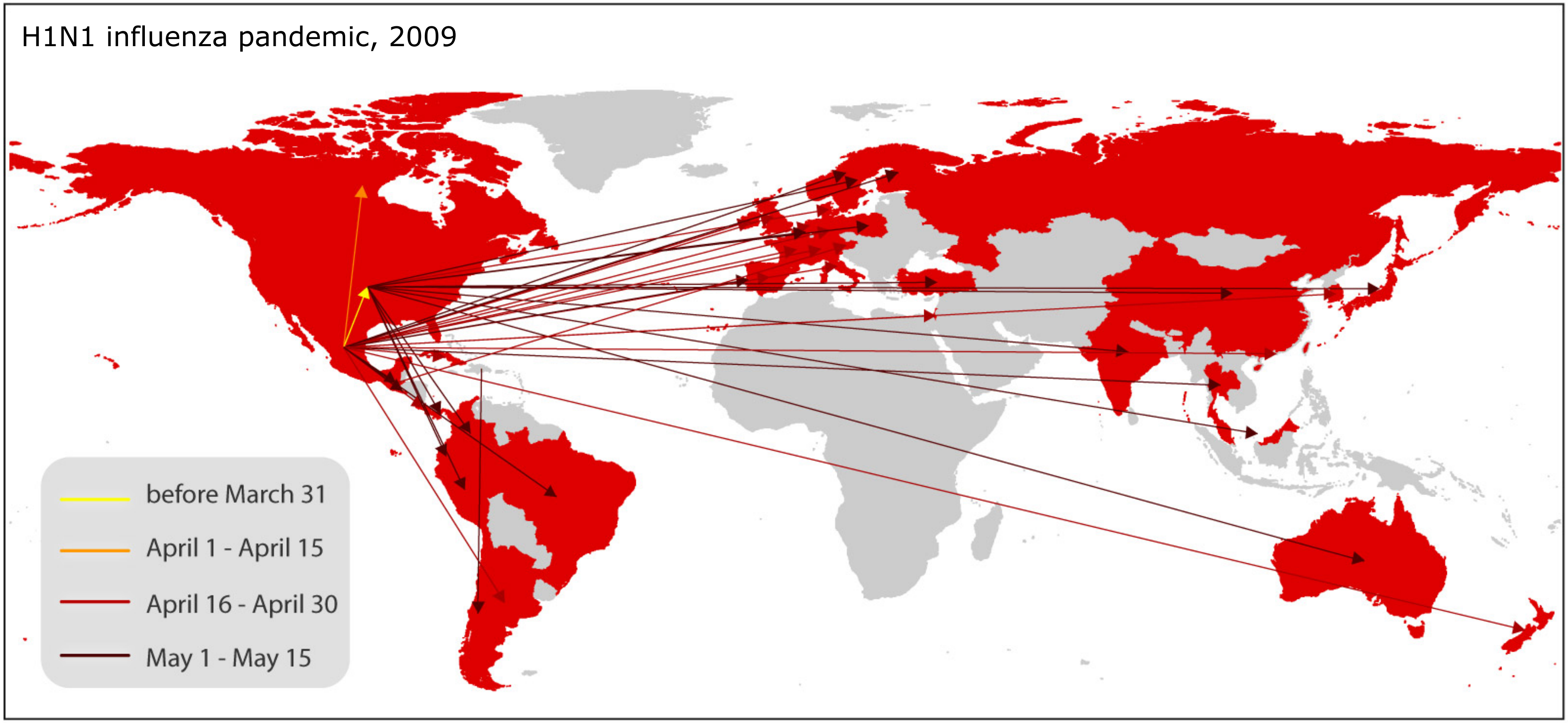
modeling spatial spread



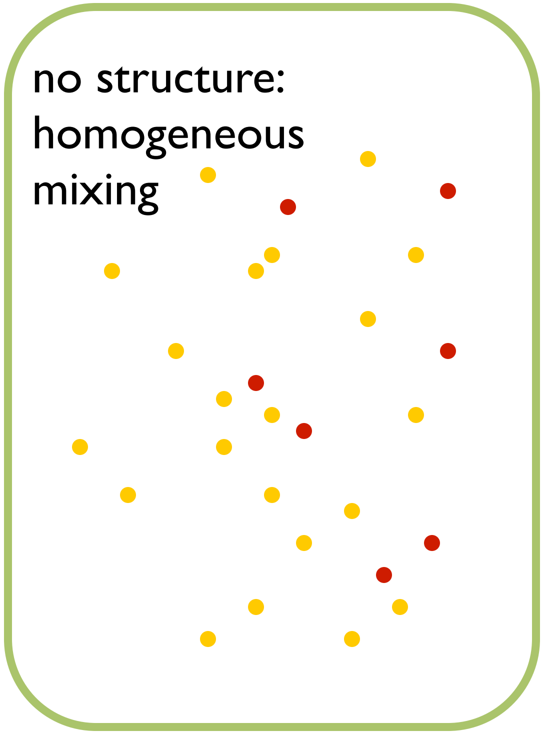


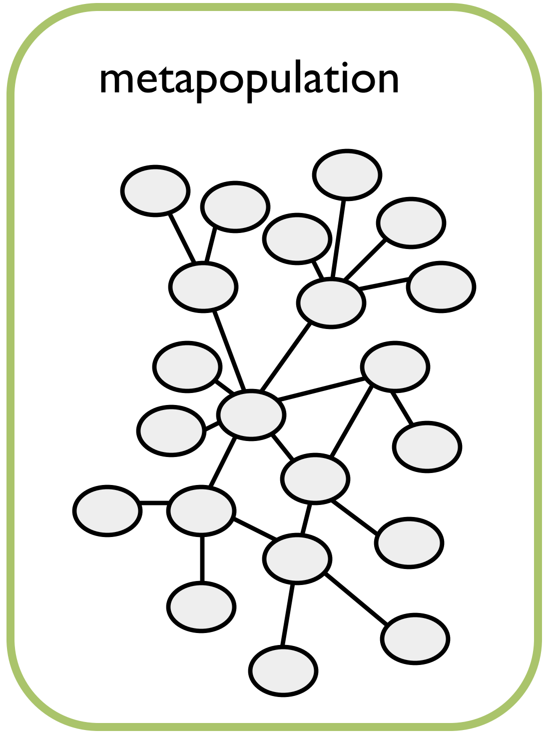
"Professional epidemiologists appear oblivious to where the epidemic is, asking only when numbers will appear along the time horizon."
geographer Peter Gould (1991)


Black Death, 14th century
Dec 1350
June 1350
Dec 1349
June 1349
Dec 1348
June 1348
Dec 1347
June 1347
North Sea
Mediterranean Sea
time


H1N1 influenza pandemic, 2009
before March 31
April 1 - April 15
April 16 - April 30
May 1 - May 15

metapopulation model: a compromise

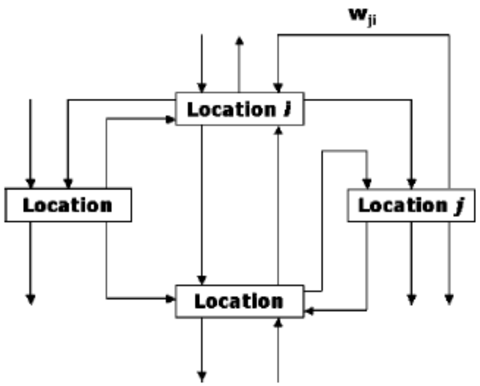




local populations:

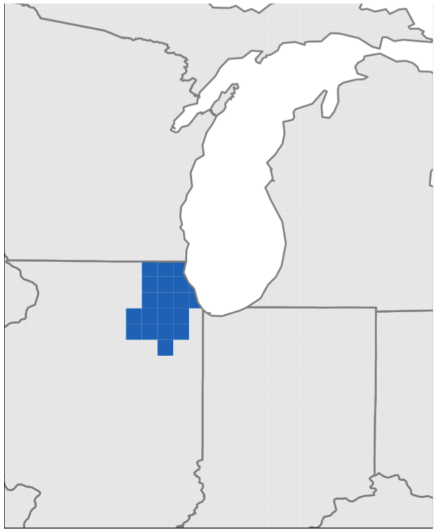
- discrete entities in space: *patches*
- interaction between populations : *coupling, flows*

patches & coupling



movement of people
between in-city locations

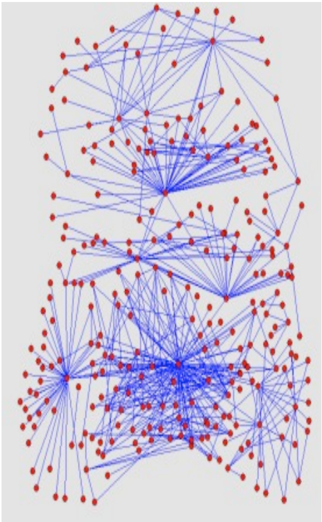
commuting patterns

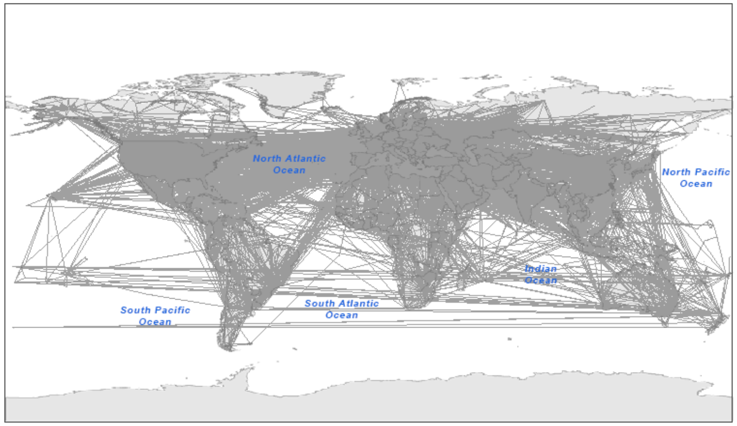


air travel

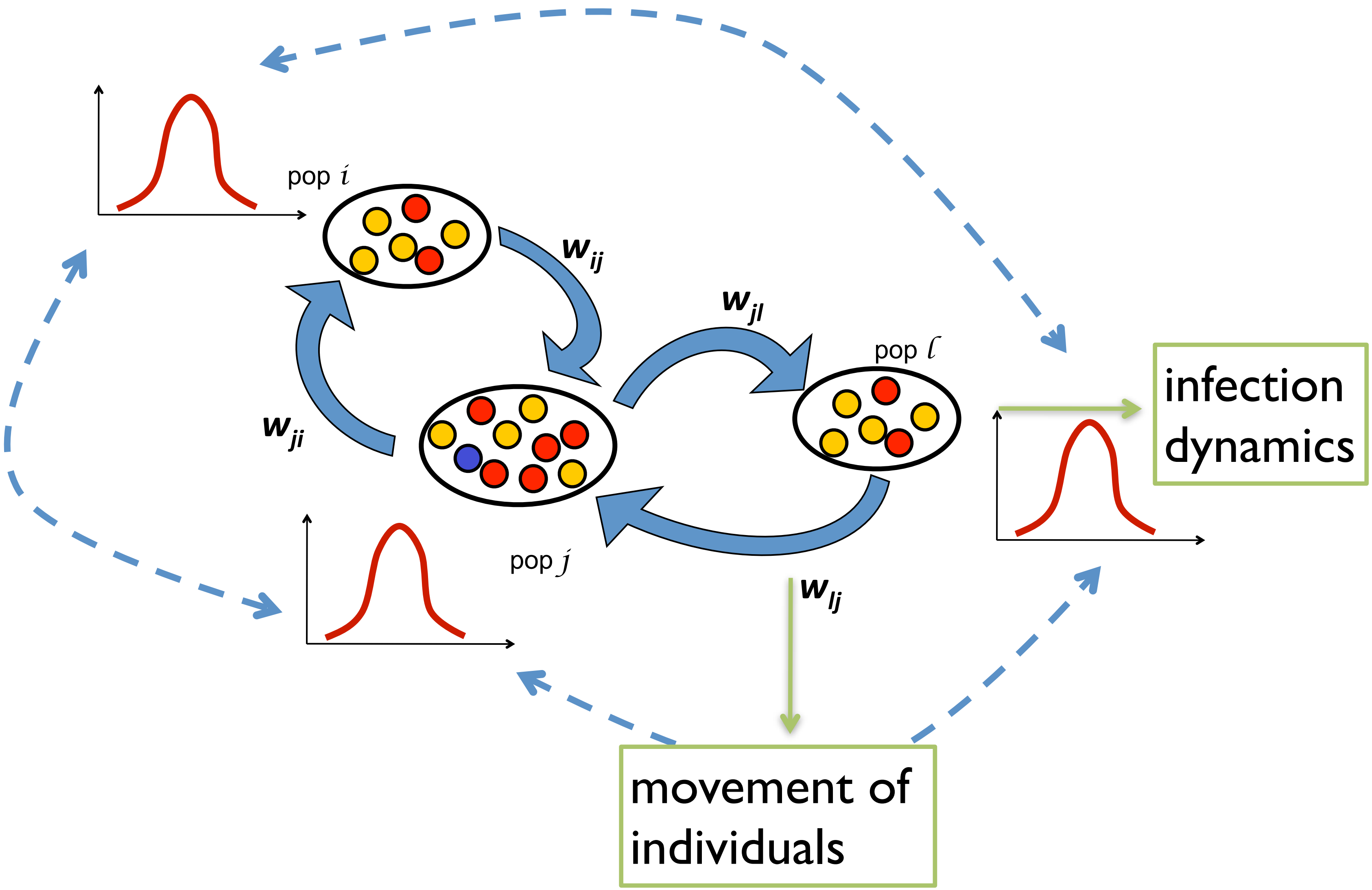
TABLE I. Sample section of a TRANSIMS activity file. In this example, person 115 arrives for a social recreational activity at location 33 005 at 19.25 o'clock and departs at 21.00 o'clock.

Person ID	Location ID	Arrival time	Departure time	Activity type
115	4225	0.0000	7.00	Home
115	49 296	8.00	11.00	Work
115	21 677	11.2	13.00	Work
115	49 296	13.2	17.00	Work
115	4225	18.00	19.00	Home
115	33 005	19.25	21.00	Social/rec
115	4225	21.3	7.00	Home
220	8200	0.0000	8.50	Home
220	10 917	9.00	14.00	School
220	8200	14.5	18.00	Home
220	3480	18.2	20.00	Social/rec
220	8200	20.3	8.6	Home





metapopulation models



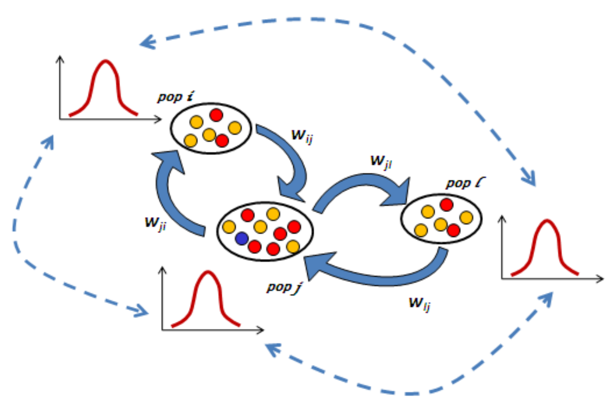
SIR metapopulation models

$$\frac{dS_i}{dt} = -\beta \frac{I_i(t)S_i(t)}{N_i} + \boxed{\Omega_i^S}$$

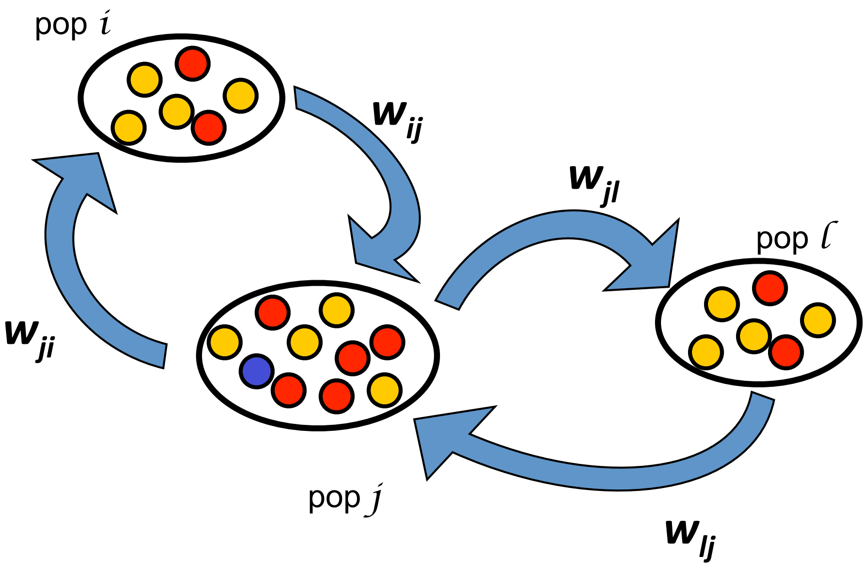
$$\frac{dI_i}{dt} = \beta \frac{I_i(t)S_i(t)}{N_i} - \mu I_i(t) + \boxed{\Omega_i^I}$$

$$\frac{dR_i}{dt} = \mu I_i(t) + \boxed{\Omega_i^R}$$

Ω_i^X Measure of *in-flow* and *out-flow* of people in compartment *X*



coupling



probability to travel from *i* to *j* ?

$$p_{ij} = p$$

$$p_{ij} = \frac{w_{ij}}{\sum_j w_{ij}}$$

$$p_{ij} = \frac{w_{ij}}{N_i}$$

- for all compartments
- for a subset of compartments