

# Modelling the spatio-temporal spread of infectious pathogens using metapopulations

18 February 2022

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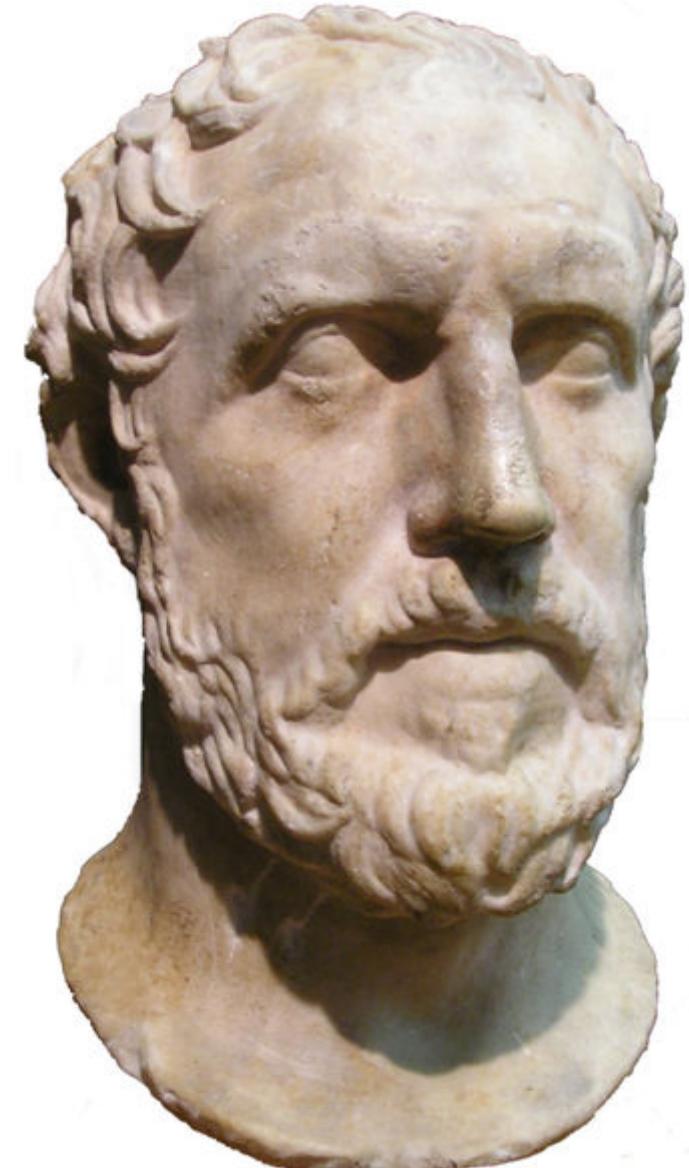
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\* The University of Manitoba campuses are located on original lands of Anishinaabeg, Cree, Oji-Cree, Dakota and Dene peoples, and on the homeland of the Métis Nation.

## Pathogens have been mobile for a while

It first began, it is said, in the parts of **Ethiopia** above Egypt, and thence descended into **Egypt** and **Libya** and into most of the King's country [**Persia**]. Suddenly falling upon Athens, it first attacked the population in **Piraeus**—which was the occasion of their saying that the Peloponnesians had poisoned the reservoirs, there being as yet no wells there—and afterwards appeared in the **upper city**, when the deaths became much more frequent.



Thucydides (c. 460 BCE - c. 395 BCE)  
[History of the Peloponnesian War](#)

# Outline

- Mobility and the spread of infectious diseases
- Waves of COVID-19
- Metapopulation epidemic models
- Basic mathematical analysis
- $\mathcal{R}_0$  is not the panacea - An urban centre and satellite cities
- Problems specific to metapopulations
- Numerical investigations

# **Mobility and the spread of infectious diseases**

# Mobility is complicated and drives disease spatialisation

Mobility is complicated:

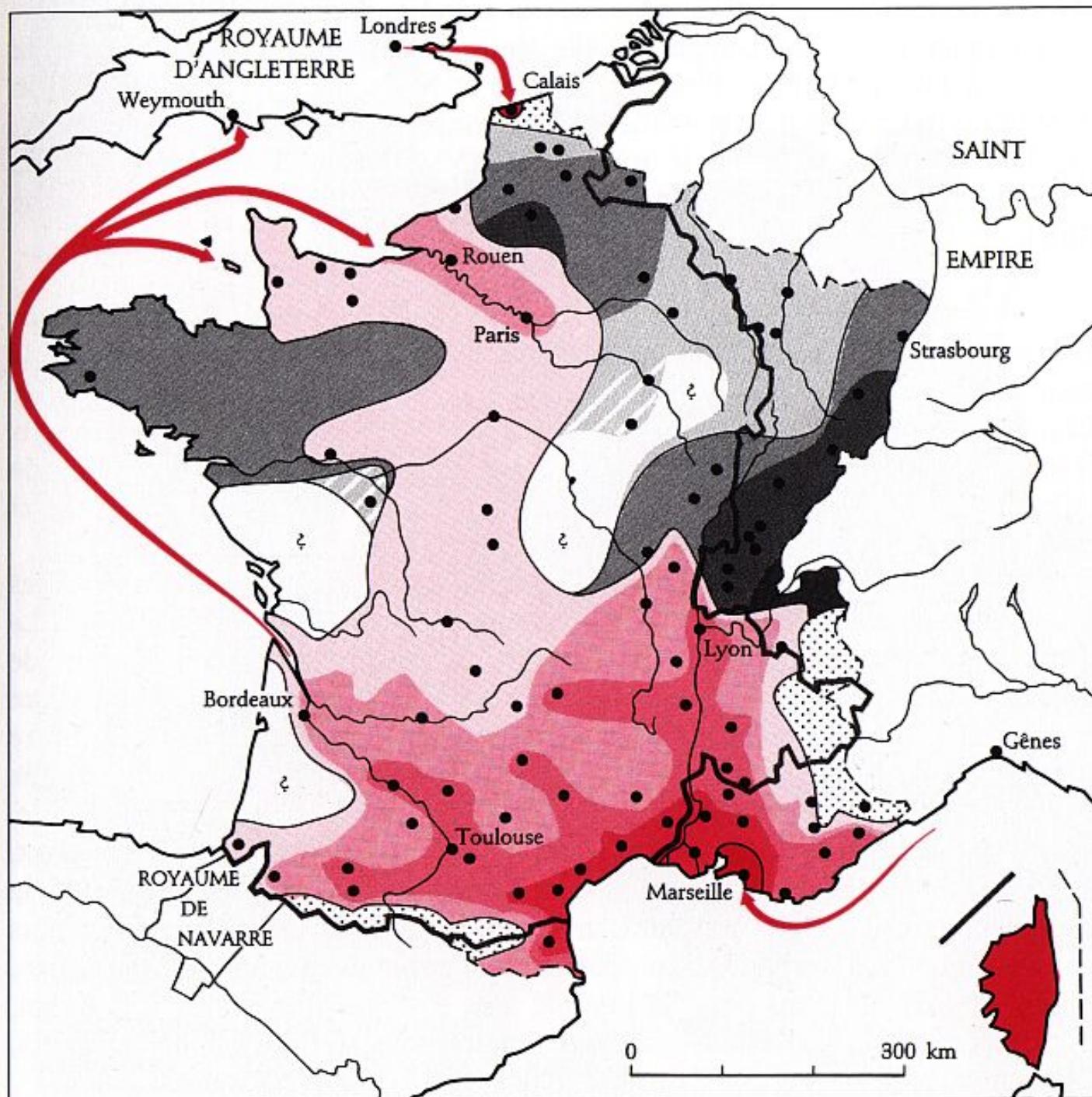
- Multiple modalities: foot, bicycle, personal vehicle, bus, train, boat, airplane
- Various durations: trip to the corner shop  $\neq$  commuting  $\neq$  multi-day trip for work or leisure  $\neq$  relocation, immigration or refugee seeking
- Volumes are hard to fathom

And yet **mobility drives spatio-temporal spread**:

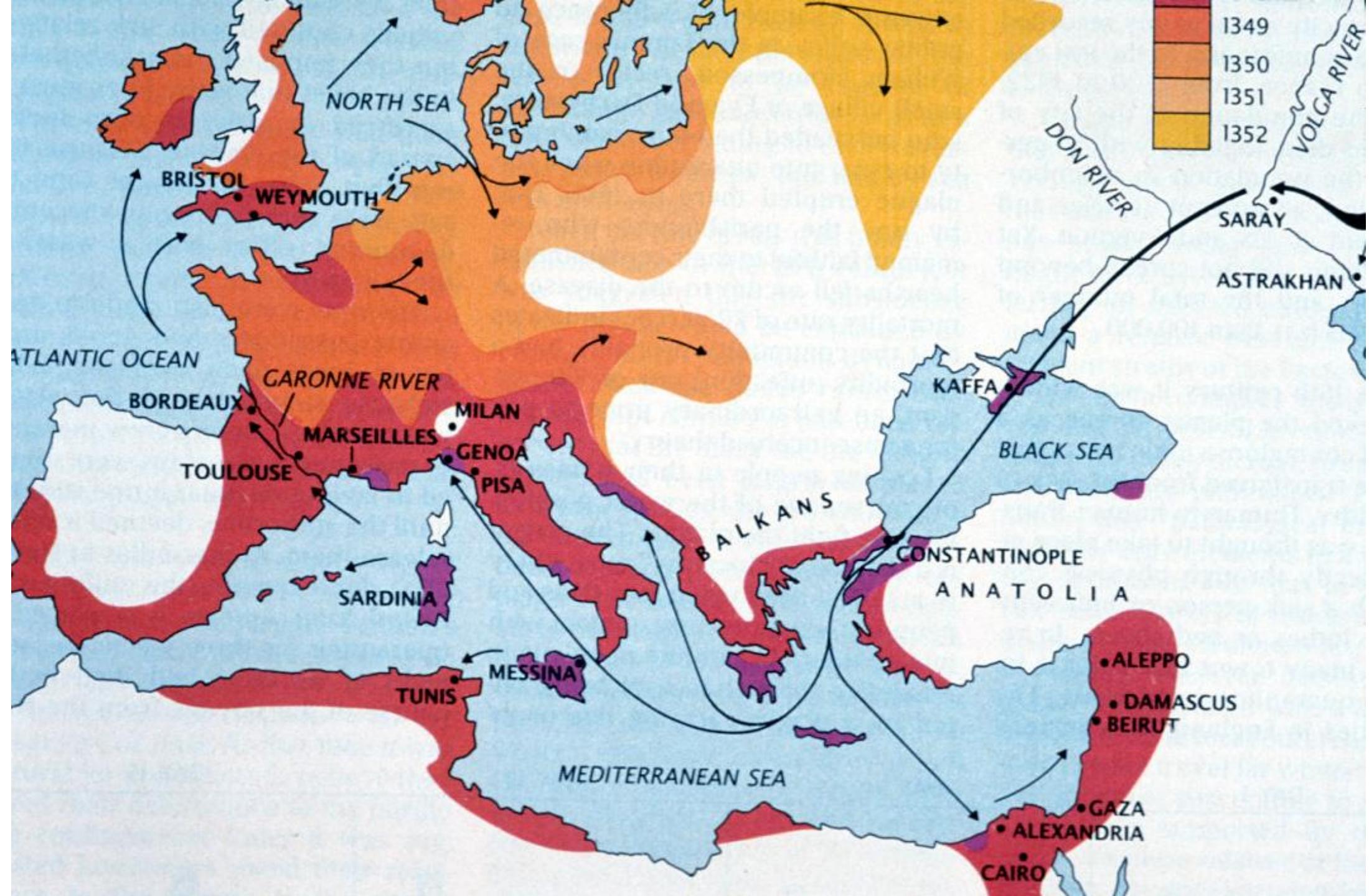
- Black Death 1347-1353 arrived in Europe and spread following trade routes
- SARS-CoV-1 spread out of HKG along the GATN
- Khan, Arino, Hu *et al*, [Spread of a novel influenza A \(H1N1\) virus via global airline transportation](#), *New England Journal of Medicine* (2009)

A.D.1212





- lieux éprouvés
- propagation de la peste par voie maritime
- avance de la peste en :
- 1347
- 4<sup>e</sup> trimestre
- 1348
- 1<sup>er</sup> trimestre
- 2<sup>e</sup> trimestre
- 3<sup>e</sup> trimestre
- 4<sup>e</sup> trimestre
- 1349
- 1<sup>er</sup> trimestre
- 2<sup>e</sup> trimestre
- 3<sup>e</sup> trimestre
- 4<sup>e</sup> trimestre
- 1350 à 1352
- 4<sup>e</sup> trimestre
- pays non touchés
- ? sans données précises
- frontières de la France au XIV<sup>e</sup> siècle
- - - frontières actuelles



# The Black Death: quick facts

- First of the middle ages plagues to hit Europe
- Affected Afro-Eurasia from 1346 to 1353
- Europe 1347-1351
- Killed 75–200M in Eurasia & North Africa
- Killed 30-60% of European population





## Plague control measures

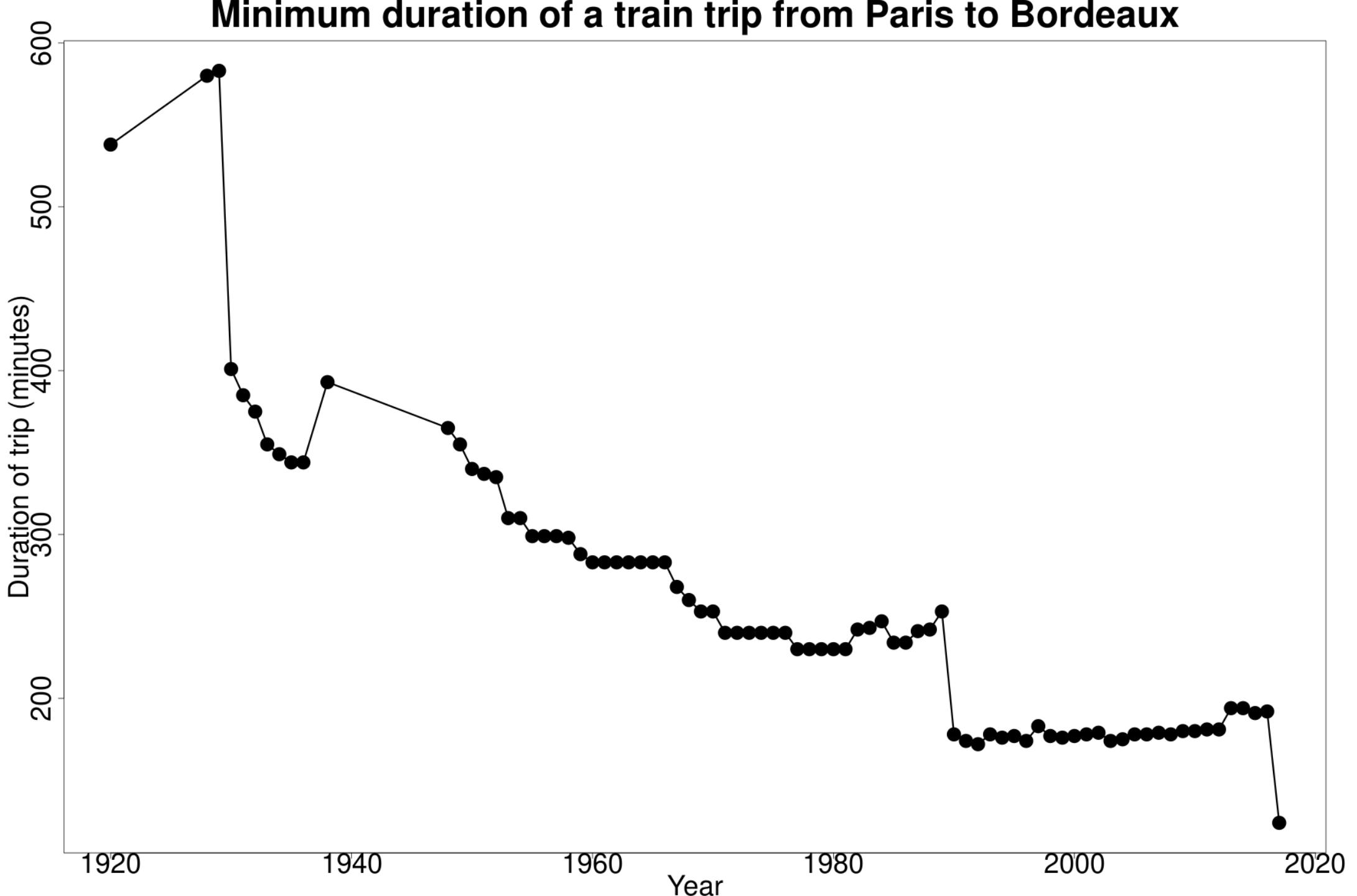
- Lazzarettos of Dubrovnik 1377 (30 days)
- Quarantena of Venice 1448 (40 days)

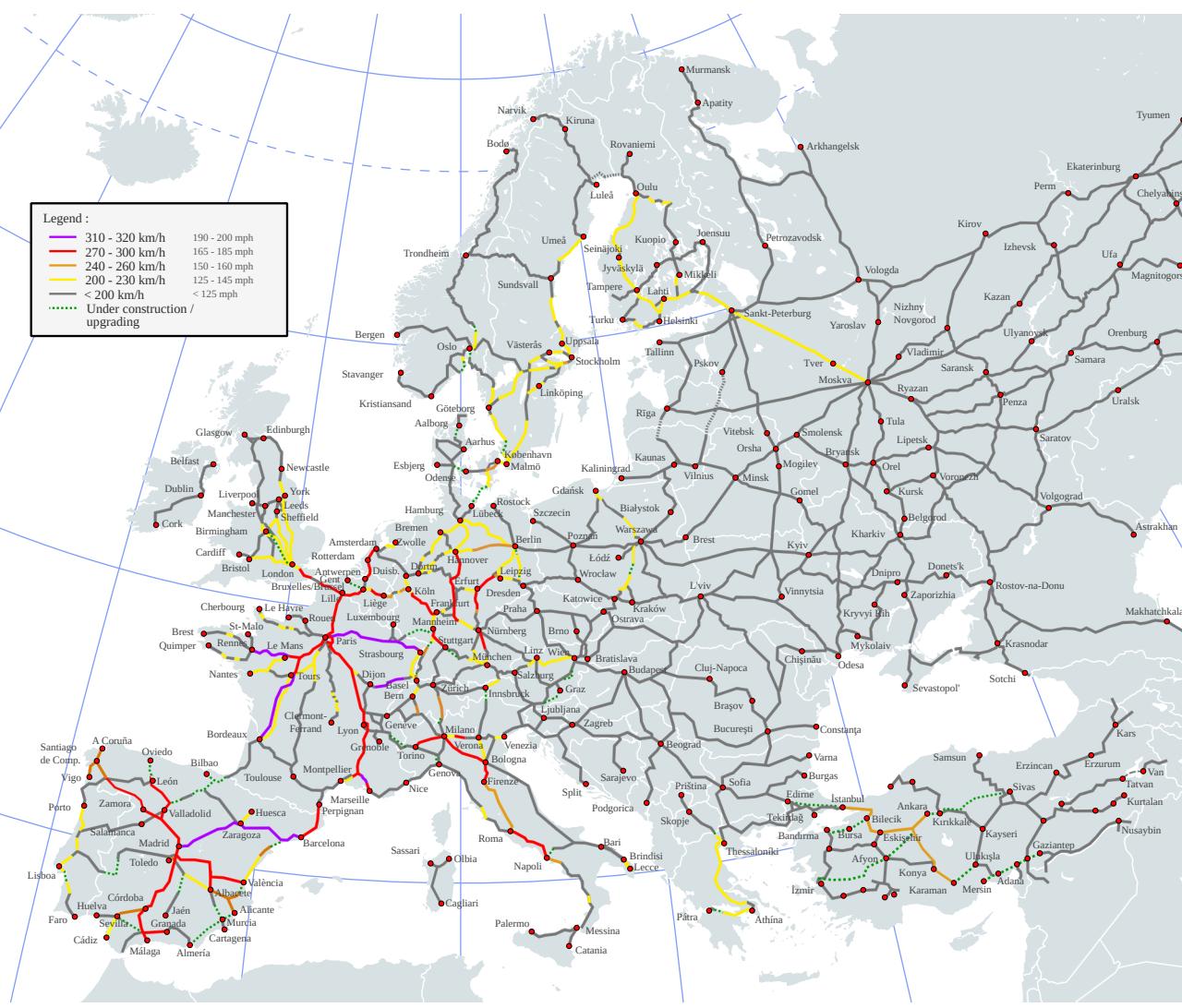
# **Pathogen spread has evolved with mobility**

Pathogens travel along trade routes

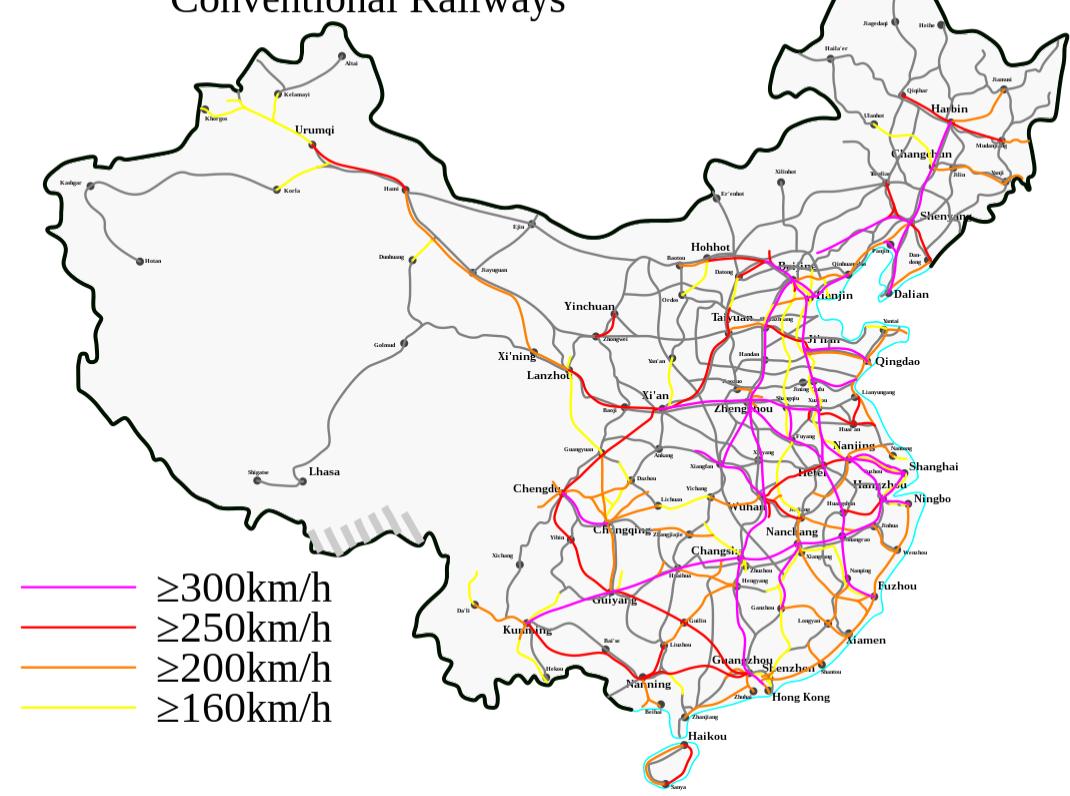
In ancient times, trade routes were relatively easy to comprehend

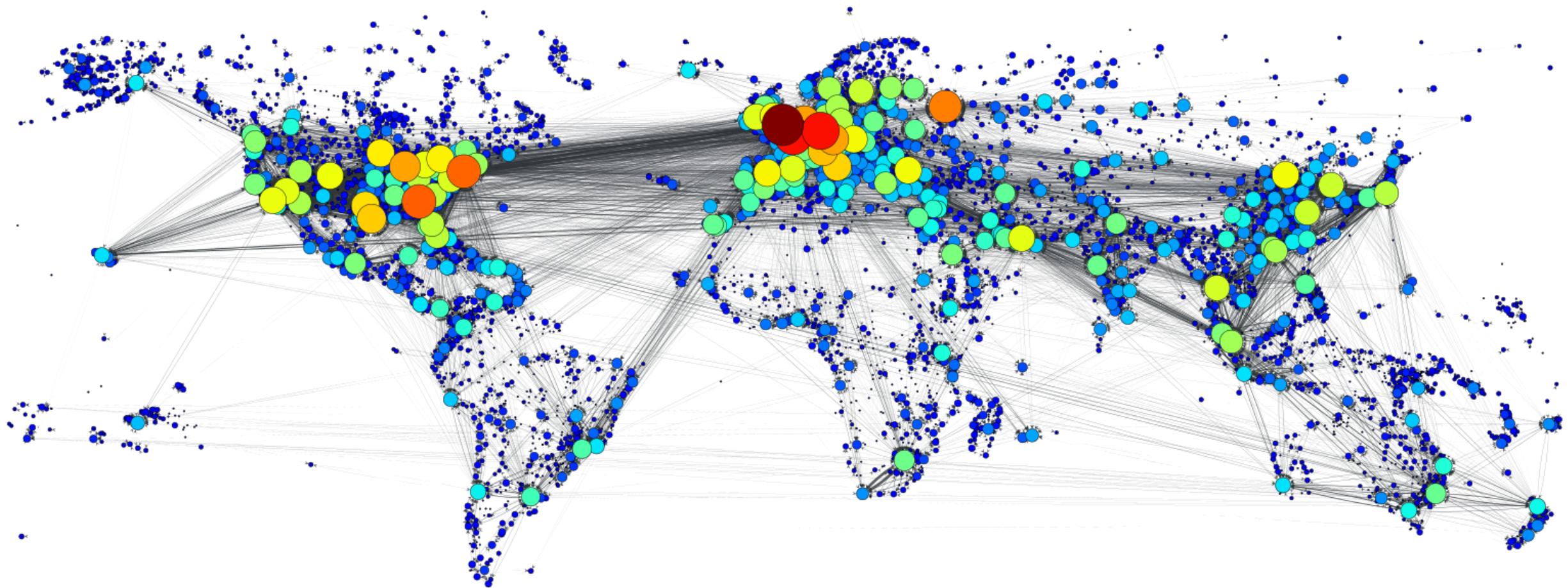
With acceleration and globalization of mobility, things change

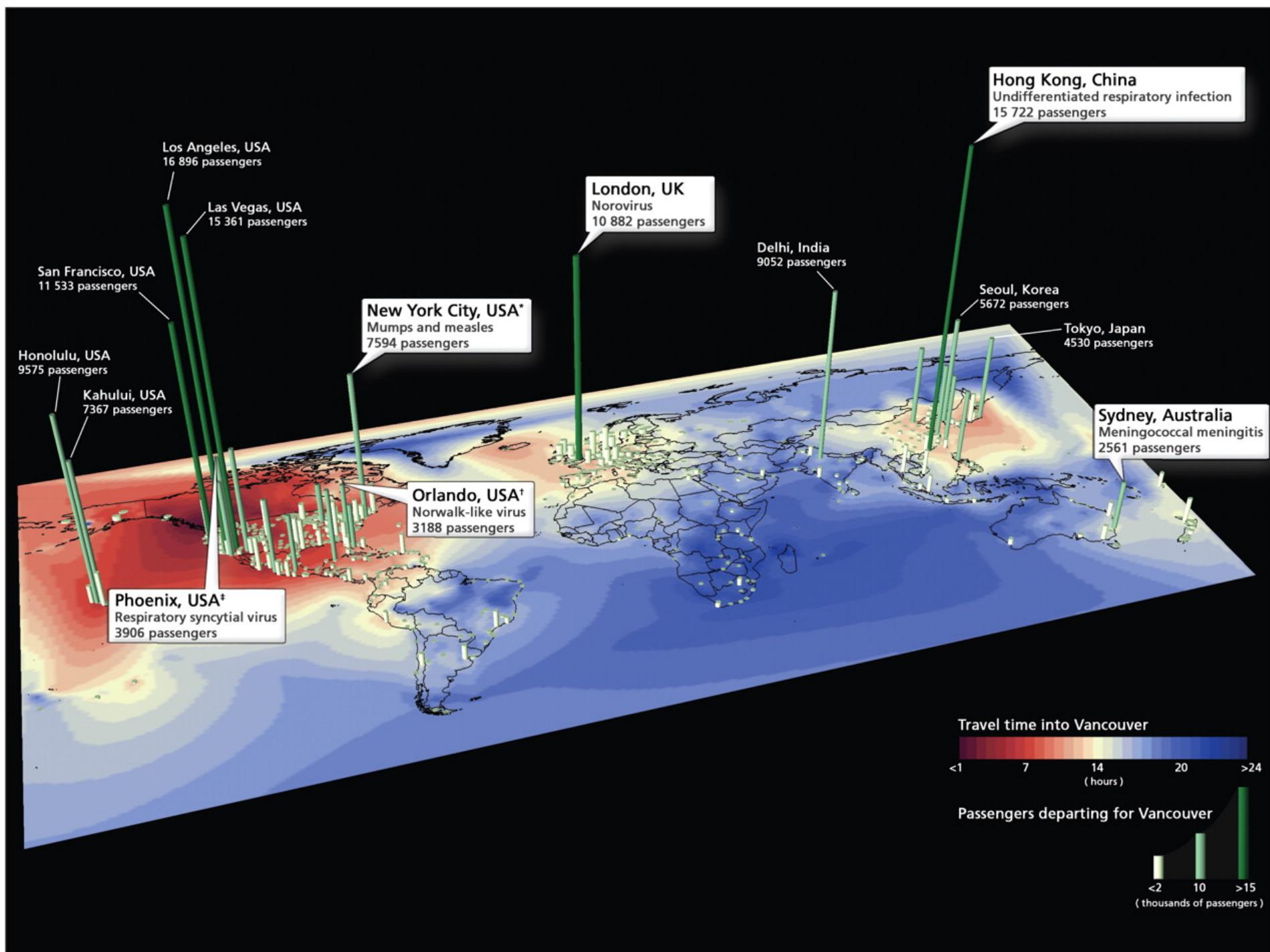




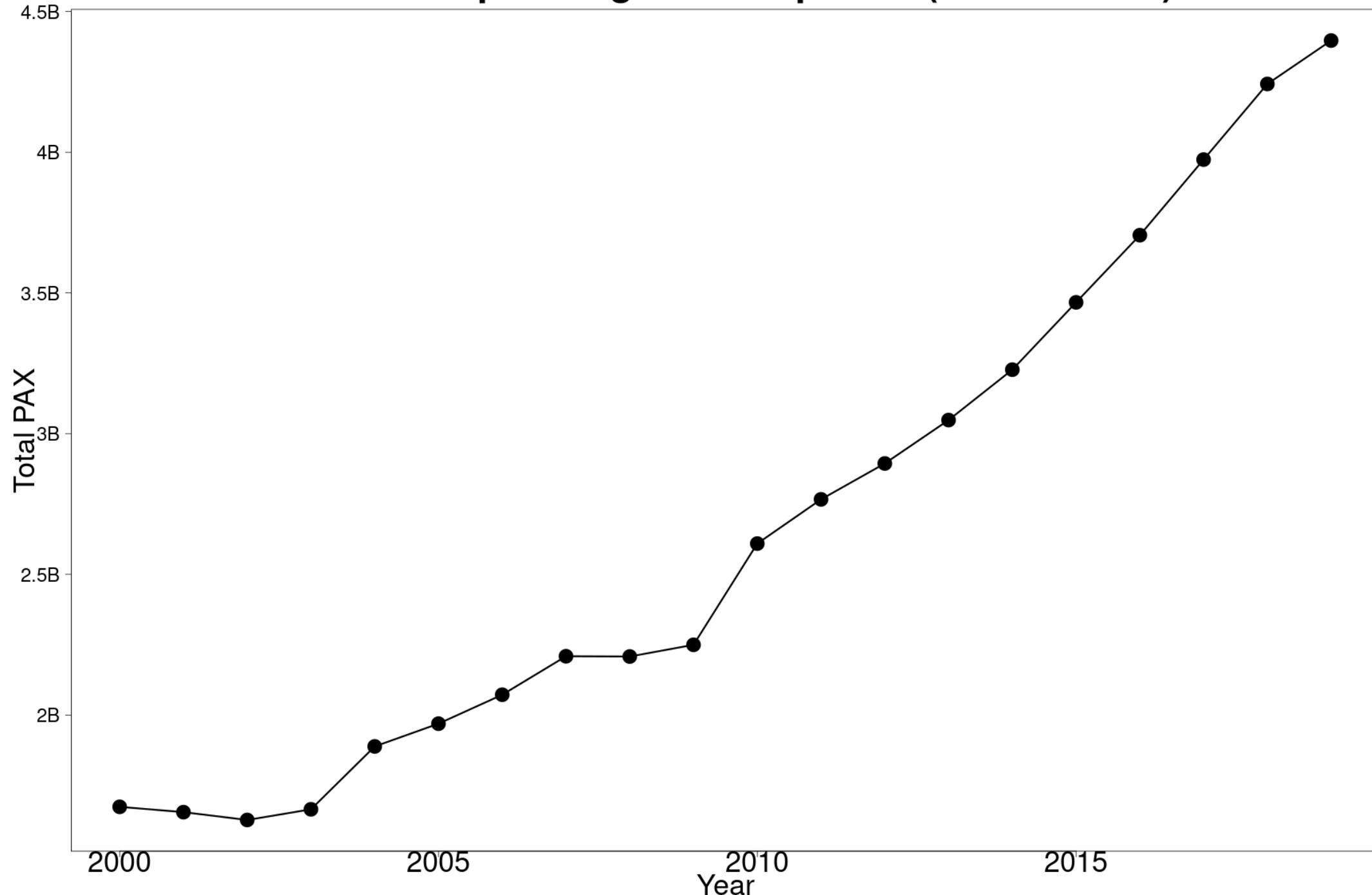
## Conventional Railways







# Number of passengers transported (all countries)



# Movement is fast but there is fragmentation

- Political divisions (jurisdictions): nation groups (e.g., EU), nations, provinces/states, regions, counties, cities..
- Travel between jurisdictions can be complicated or impossible
- Data is integrated at the jurisdictional level
- Policy is decided at the jurisdictional level
- Long range mobility is a bottom → top → top → bottom process

# Why mobility is important in the context of health

All migrants/travellers carry with them their "health history"

- latent and/or active infections (TB, H1N1, polio)
- immunizations (schedules vary by country)
- health/nutrition practices (KJv)
- treatment methods (antivirals)

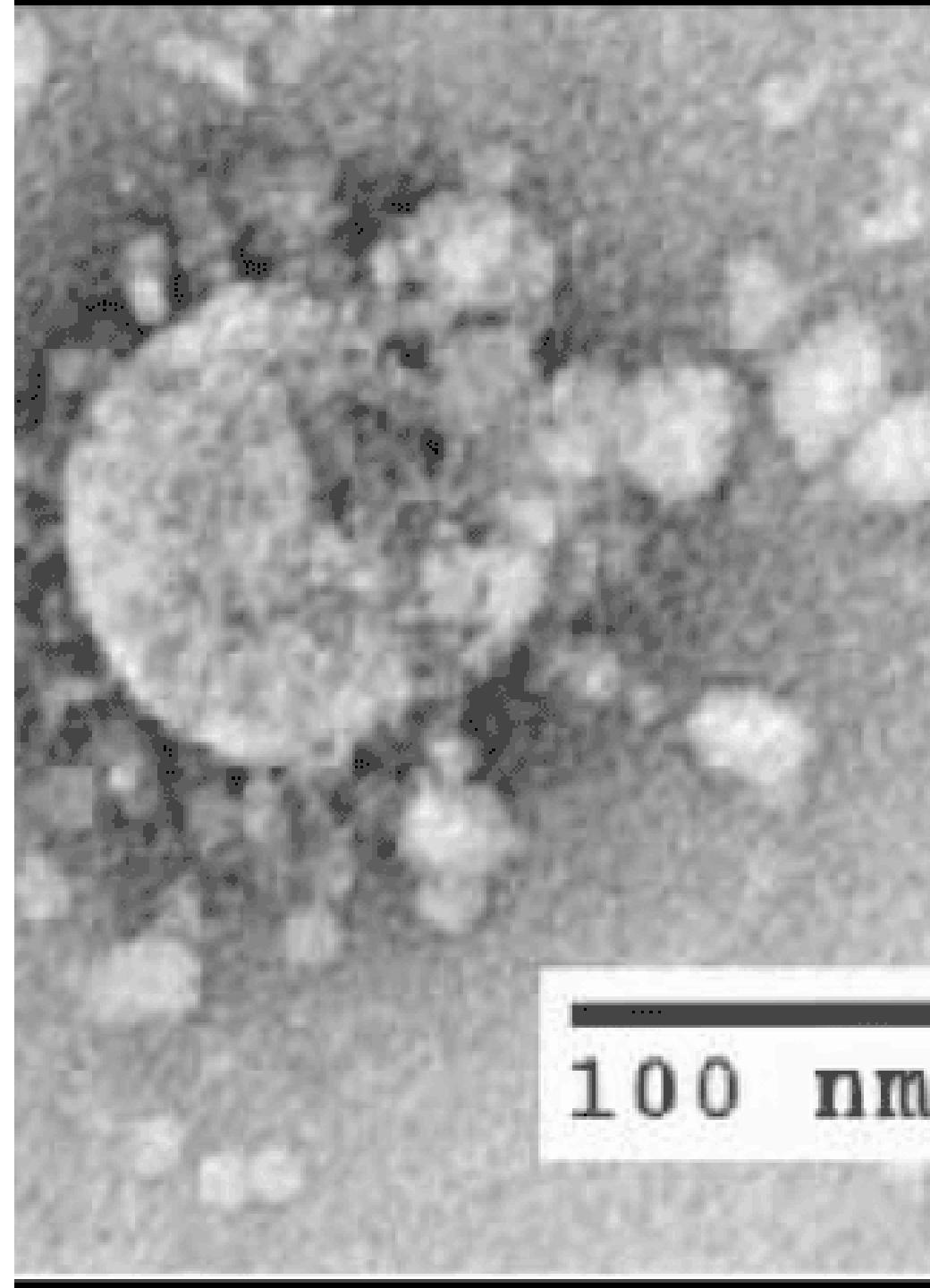
Pathogens ignore borders and politics

- antiviral treatment policies for Canada and USA
- SARS-CoV-2 anyone?

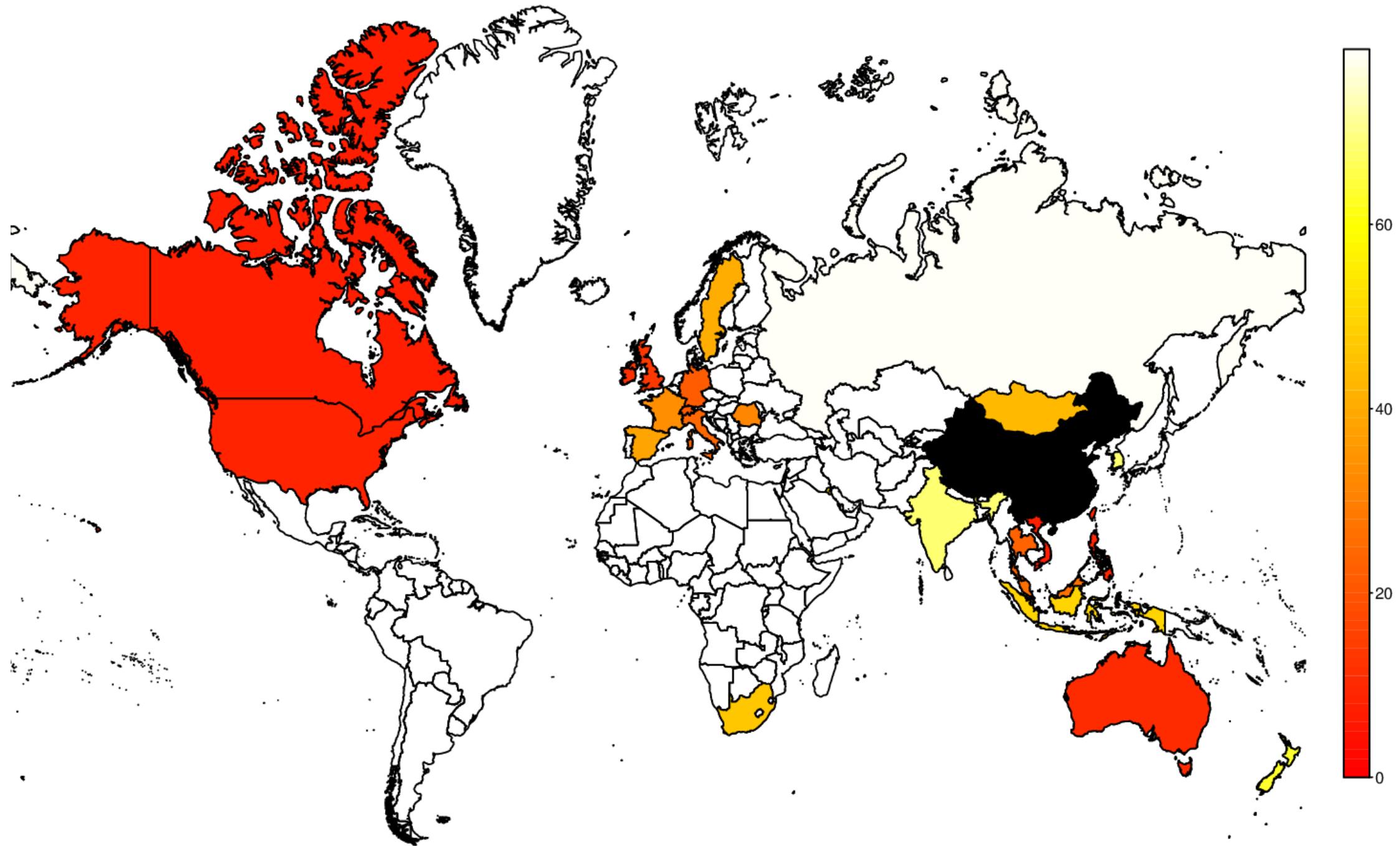
# SARS-CoV-1 (2002-2003)

## Overall impact

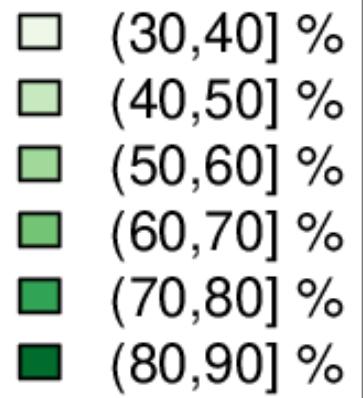
- Index case for international spread arrives  
HKG 21 February 2003
- Last country with local transmission  
(Taiwan) removed from list 5 July 2003
- 8273 cases in 28 countries
- (Of these cases, 1706 were HCW)
- 775 deaths (CFR 9.4%)



# Countries with SARS cases (WHO/Dec 2003)



# Measles cases in the USA



Mali

Niger

Chad

Burkina Faso

Nigeria

Ivory Coast

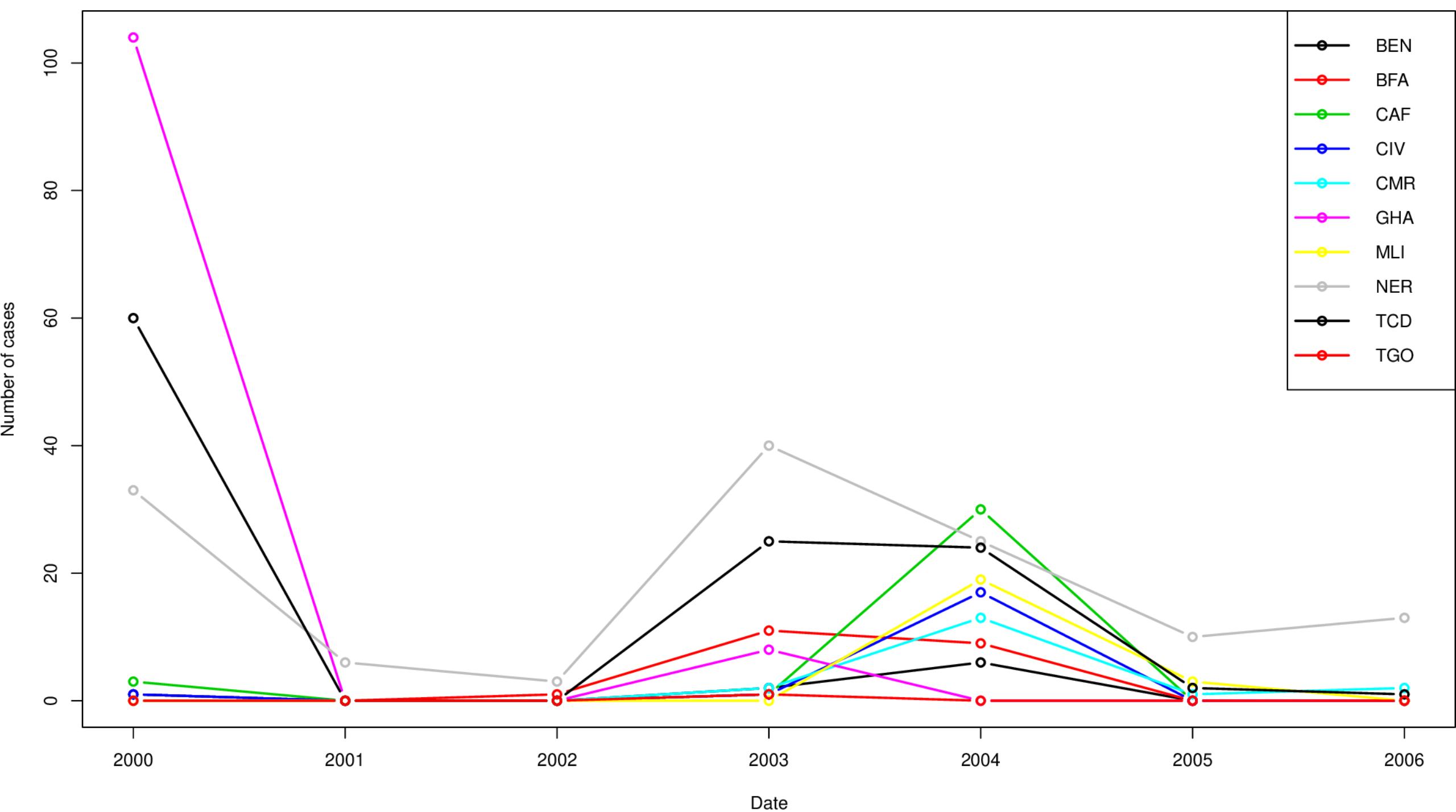
Benin

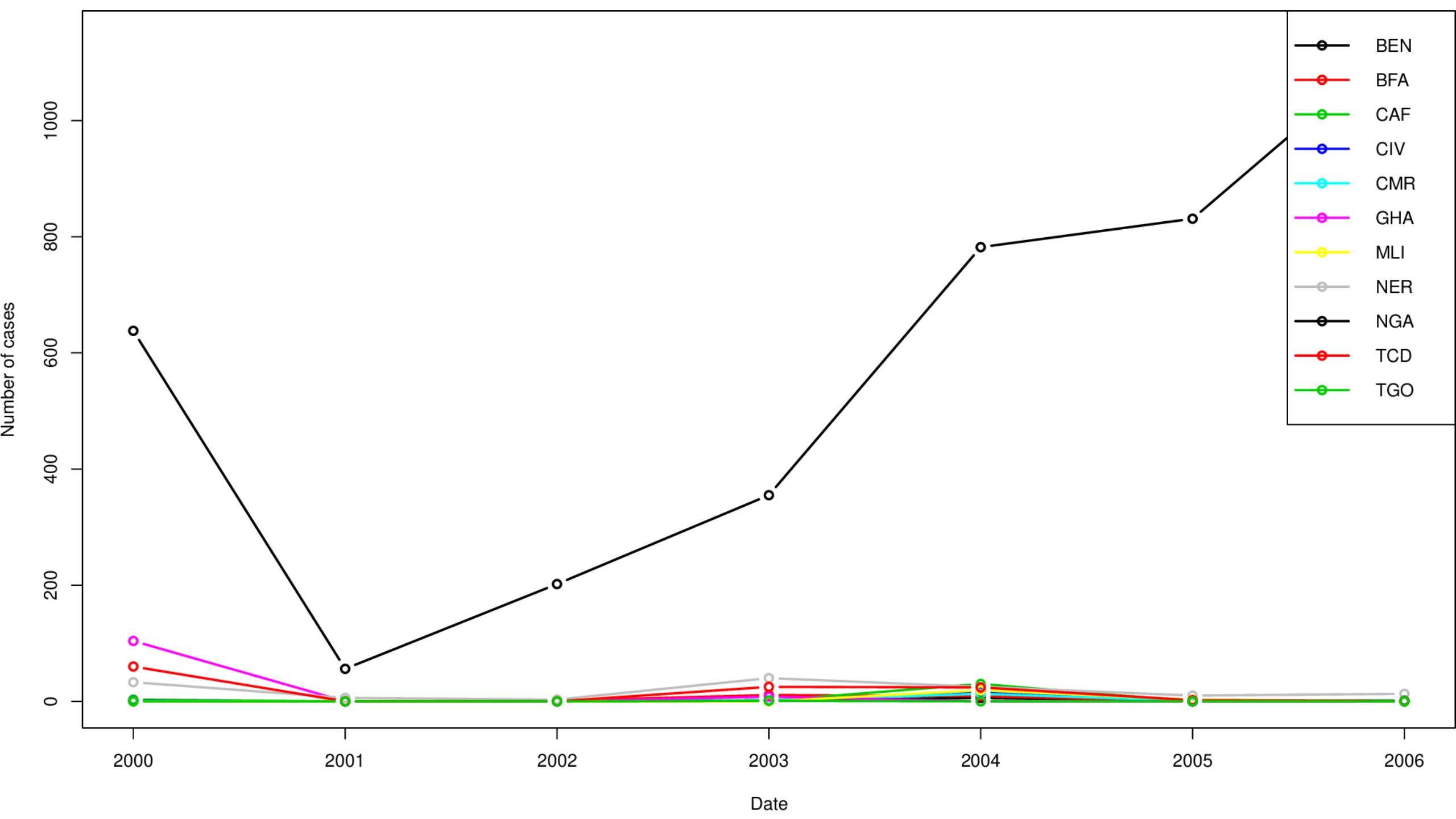
Central African Republic

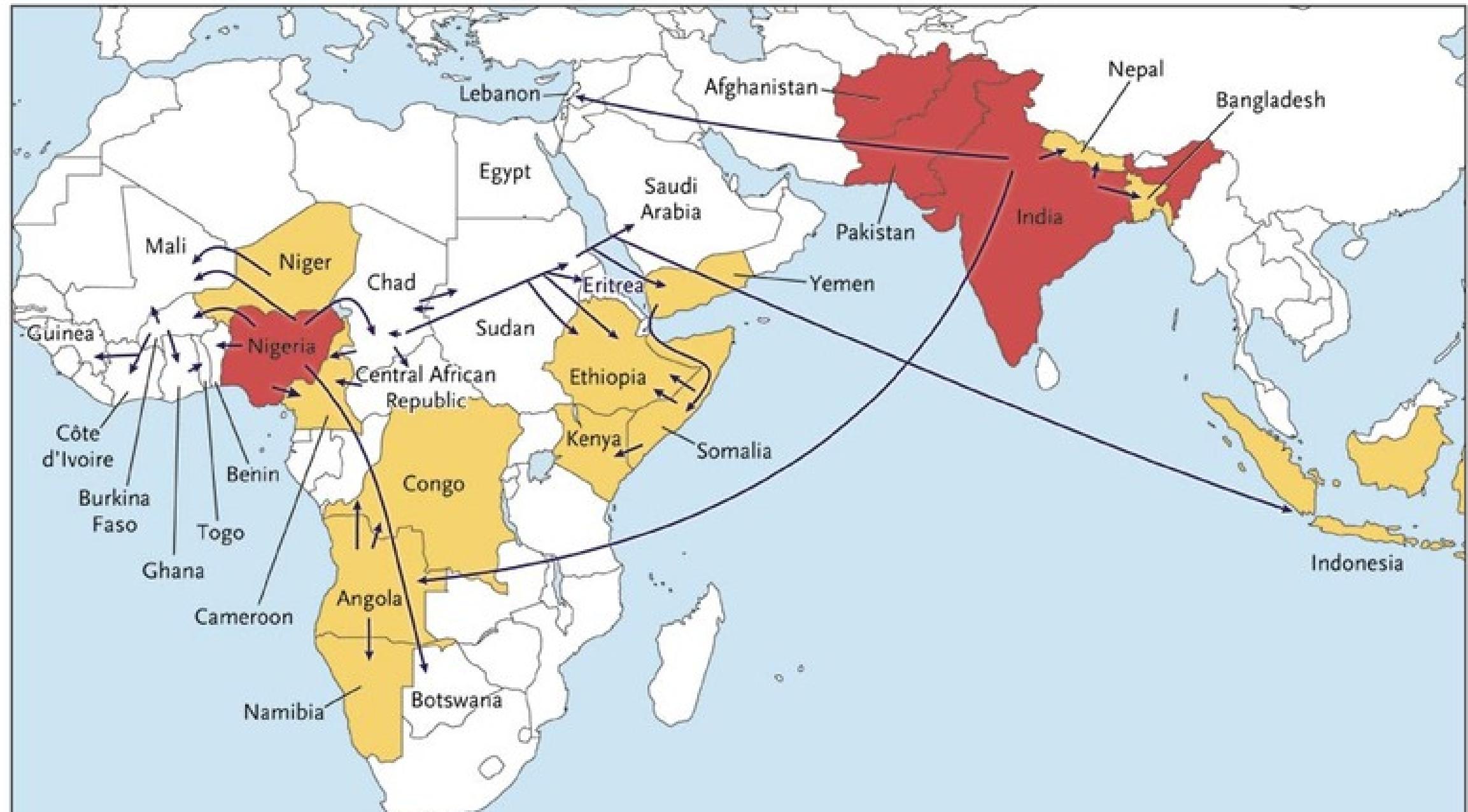
Ghana

Togo

Cameroon







Polio spread 2002-2006. Pallansch & Sandhu, N Engl J Med 2006; 355:2508-2511

# Waves of COVID-19

JA. Describing, modelling and forecasting the spatial and temporal spread of COVID-19 - A short review. *Fields Institute Communications* **85**:25-51 (2022)

# Amplification in Wuhan (Hubei province)

- Details of emergence and precise timeline before amplification started unknown
- Amplification in Wuhan
  - Cluster of pneumonia cases mostly related to the Huanan Seafood Market
  - 27 December 2019: first report to local government
  - 31 December 2019: publication
  - 8 January 2020: identification of SARS-CoV-2 as causative agent
- ~ 23 January 2020: lockdown Wuhan and Hubei province + face mask mandates

By 29 January, virus was found in all provinces of mainland China

# First detections outside China

Date	Location	Note
13 Jan.	Thailand	Arrived 8 Jan.
16 Jan.	Japan	Arrived 6 Jan.
20 Jan.	Republic of Korea	Airport detected on 19 Jan.
20 Jan.	USA	Arrived Jan. 15
23 Jan.	Nepal	Arrived 13 Jan.
23 Jan.	Singapore	Arrived 20 Jan.
24 Jan.	France	Arrived 22 Jan.
24 Jan.	Vietnam	Arrived 13 Jan.
25 Jan.	Australia	Arrived 19 Jan.
25 Jan.	Malaysia	Arrived 24 Jan.

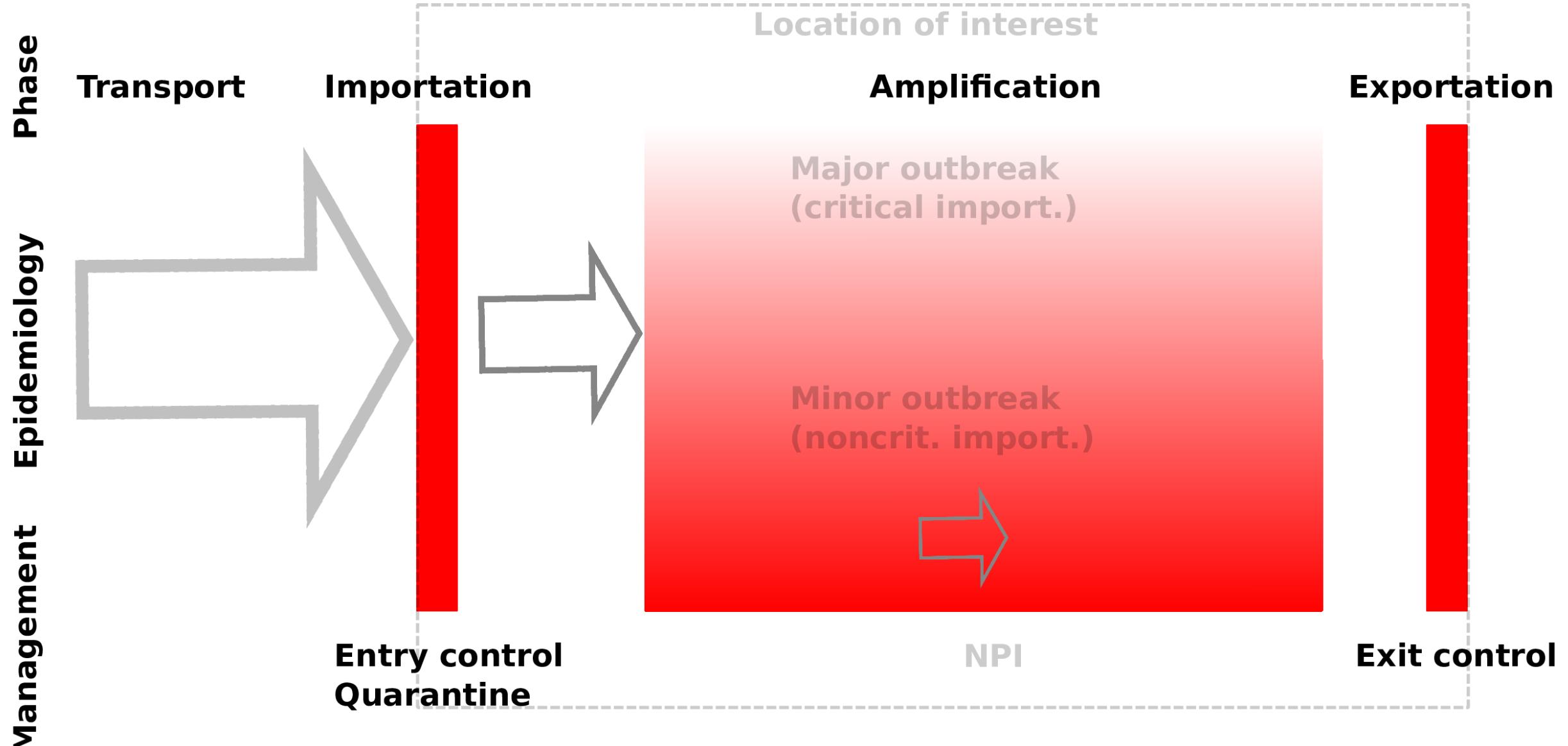
## Caveat : evidence of earlier spread

- Report to Wuhan authorities on 27 December 2019
- First export detections in Thailand and Japan on 13 and 16 January 2020 (with actual importations on 8 and 6 January)

⇒ amplification must have been occurring for a while longer

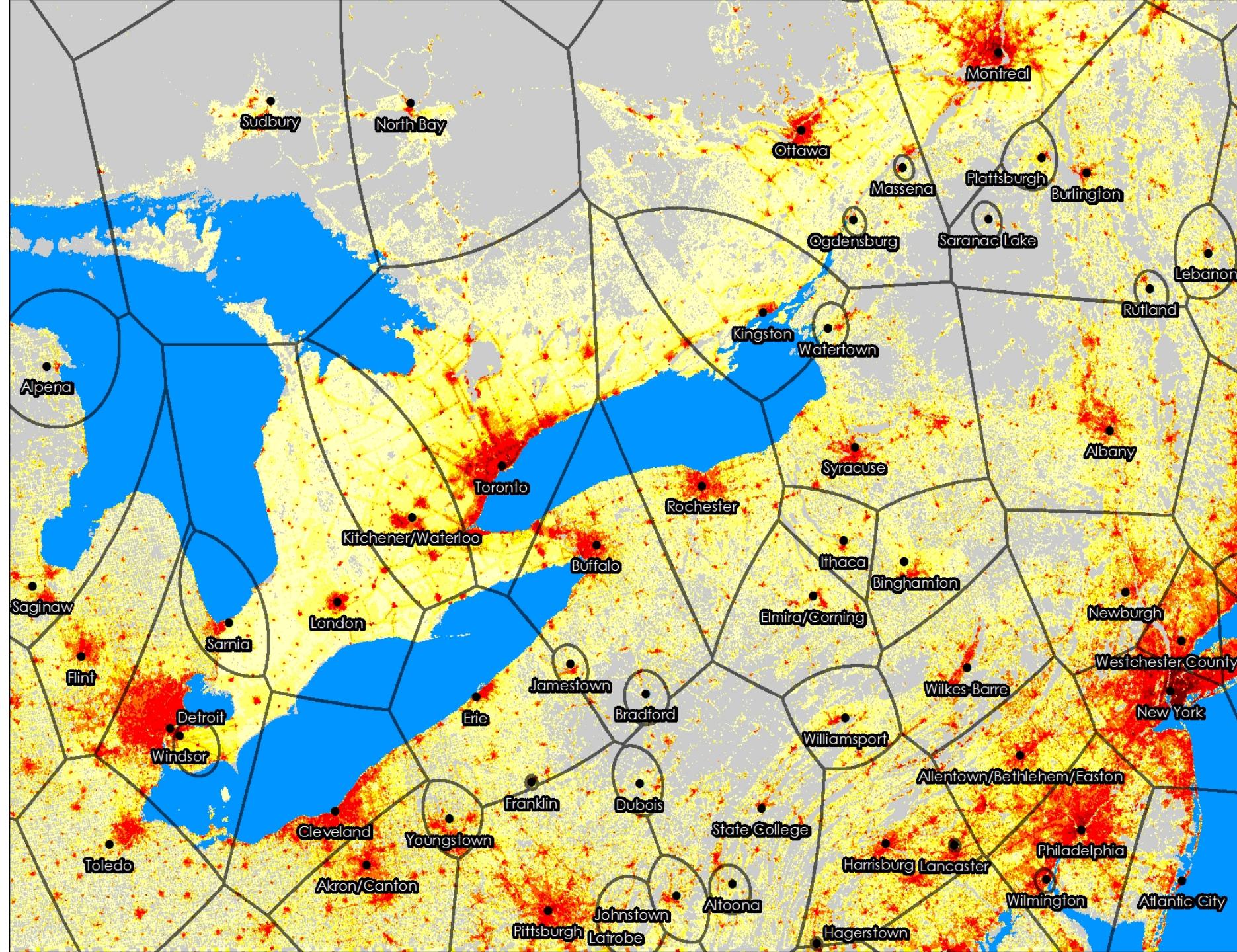
- France: sample taken from 42-year-old male (last foreign travel to Algeria in August 2019) who presented to ICU on 27 December 2019
- Retrospective studies in United Kingdom and Italy also showed undetected COVID-19 cases in prepandemic period

# Spread process in a jurisdiction-based world



# Metapopulation epidemic models

- JA & PvdD. Disease spread in metapopulations. *Fields Institute Communications* **48**:1-13 (2006)
- JA. Diseases in metapopulations. In *Modeling and Dynamics of Infectious Diseases*, World Scientific (2009)
- JA. Spatio-temporal spread of infectious pathogens of humans. *Infectious Disease Modelling* **2**(2):218-228 (2017)



# General principles (1)

- $|\mathcal{P}|$  geographical locations (*patches*) in a set  $\mathcal{P}$  (city, region, country..)
- Patches are vertices in a graph
- Each patch  $p \in \mathcal{P}$  contains **compartments**  $\mathcal{C}_p \subseteq \mathcal{C}$ 
  - individuals susceptible to the disease
    - individuals infected by the disease
    - different species affected by the disease
    - etc.

## General principles (2)

- Compartments *may* move between patches, with  $m_{cqp}$  rate of movement of individuals from compartment  $c \in \mathcal{C}$  from patch  $p \in \mathcal{P}$  to patch  $q \in \mathcal{P} \setminus \{p\}$
- Movement instantaneous and no death during movement
- $\forall c \in \mathcal{C}$ , defines a digraph  $\mathcal{G}^c$  with arcs  $\mathcal{A}^c$
- Arc from  $p$  to  $q$  if  $m_{cqp} > 0$ , absent otherwise
- $|\mathcal{C}|$  compartments, so each  $(p, q)$  can have at most  $|\mathcal{C}|$  arrows  $\rightarrow$  multi-digraph

# The underlying mobility model

## Simplest: explicitly move individuals around

$N_{cp}$  population of compartment  $c \in \mathcal{C}$  in patch  $p \in \mathcal{P}$

Assume no birth or death. Balance inflow and outflow

$$\begin{aligned} N'_{cp} &= \left( \sum_{q \in \mathcal{P} \setminus \{p\}} m_{cpq} N_{cq} \right) - \left( \sum_{q \in \mathcal{P} \setminus \{p\}} m_{cqp} \right) N_{cp} \\ &= \sum_{q \in \mathcal{P}} m_{cpq} N_{cq} \quad \text{with } m_{cpp} = - \sum_{q \in \mathcal{P} \setminus \{p\}} m_{cqp} \end{aligned}$$

# $|\mathcal{P}|$ -SLIRS model

$$S'_p = \mathcal{B}_p(N_p) + \nu_p R_p - \Phi_p - d_p S_p + \sum_{q \in \mathcal{P}} m_{pq}^S S_q$$

$$L'_p = \Phi_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{pq}^L L_q$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q \in \mathcal{P}} m_{pq}^I I_q$$

$$R'_p = \gamma_p I_p - (\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{pq}^R R_q$$

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \quad q_p \in \{0, 1\}$$

$L$  = "latently infected" (=E)

- JA & PvdD. Disease spread in metapopulations. *Fields Institute Communications* **48**:1-13 (2006)
- JA. Diseases in metapopulations. In *Modeling and Dynamics of Infectious Diseases*, World Scientific (2009)

# $|\mathcal{S}|$ $|\mathcal{P}|$ -SLIRS (multiple species)

$\mathcal{S}$  a set of species

$$S'_{sp} = \mathcal{B}_{sp}(N_{sp}) + \nu_{sp}R_{sp} - \Phi_{sp} - d_{sp}S_{sp} + \sum_{q \in \mathcal{P}} m^S_{spq} S_{sq}$$

$$L'_{sp} = \Phi_{sp} - (\varepsilon_{sp} + d_{sp})L_{sp} + \sum_{q \in \mathcal{P}} m^L_{spq} L_{sq}$$

$$I'_{sp} = \varepsilon_{sp}L_{sp} - (\gamma_{sp} + d_{sp})I_{sp} + \sum_{q \in \mathcal{P}} m^I_{spq} I_{sq}$$

$$R_{sp} = \gamma_{sp}I_{sp} - (\nu_{sp} + d_{sp})R_{sp} + \sum_{q \in \mathcal{P}} m^R_{spq} R_{sq}$$

$$\Phi_{sp} = \sum_{k \in \mathcal{S}} \beta_{skp} \frac{S_{sp} I_{kp}}{N_p^{q_p}}, \quad q_p \in \{0, 1\}$$

- JA, Davis, Hartley, Jordan, Miller & PvdD. [A multi-species epidemic model with spatial dynamics](#). *Mathematical Medicine and Biology* **22**(2):129-142 (2005)
- JA, Jordan & PvdD. [Quarantine in a multi-species epidemic model with spatial dynamics](#). *Mathematical Biosciences* **206**(1):46-60 (2007)

# $|\mathcal{P}|^2$ -SLIRS (residency patch/movers-stayers)

$$S'_{pq} = \mathcal{B}_{pq} (N_p^r) + \nu_{pq} R_{pq} - \Phi_{pq} - d_{pq} S_{pq} + \sum_{k \in \mathcal{P}} m_{pqk}^S S_{pk}$$

$$L'_{pq} = \Phi_{pq} - (\varepsilon_{pq} + d_{pq}) L_{pq} + \sum_{k \in \mathcal{P}} m_{pqk}^L L_{pk}$$

$$I'_{pq} = \varepsilon_{pq} L_{pq} - (\gamma_{pq} + d_{pq}) I_{pq} + \sum_{k \in \mathcal{P}} m_{pqk}^I I_{pk}$$

$$R'_{pq} = \gamma_{pq} I_{pq} - (\nu_{pq} + d_{pq}) R_{pq} + \sum_{k \in \mathcal{P}} m_{pqk}^R R_{pk}$$

$$\Phi_{pq} = \sum_{k \in \mathcal{P}} \beta_{qpk} \frac{S_{pq} I_{kq}}{N_p^{q_q}}, \quad q_q = \{0, 1\}$$

- Sattenspiel & Dietz. [A structured epidemic model incorporating geographic mobility among regions](#) (1995)
- JA & PvdD. [A multi-city epidemic model](#). *Mathematical Population Studies* **10**(3):175-193 (2003)
- JA & PvdD. [The basic reproduction number in a multi-city compartmental epidemic model](#). In *Positive Systems* (2003)

# General metapopulation epidemic models

Assume  $\mathcal{U} \subsetneq \mathcal{C}$  **uninfected** and  $\mathcal{I} \subsetneq \mathcal{C}$  **infected** compartments, with  $\mathcal{U} \cup \mathcal{I} = \mathcal{C}$  and  $\mathcal{U} \cap \mathcal{I} = \emptyset$

For  $k \in \mathcal{U}$ ,  $\ell \in \mathcal{I}$  and  $p \in \mathcal{P}$ ,

$$s'_{kp} = f_{kp}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{kpq} s_{kq}$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{\ell pq} i_{\ell q}$$

where  $S_p = (s_{1p}, \dots, s_{|\mathcal{U}|p})$  and  $I_p = (i_{1p}, \dots, i_{|\mathcal{I}|p})$

# Basic mathematical analysis

# Analysis - Toy system

For simplicity, consider  $|\mathcal{P}|$ -SLIRS with  $\mathcal{B}_p(N_p) = \mathcal{B}_p$

$$S'_p = \mathcal{B}_p - \Phi_p - d_p S_p + \nu_p R_p + \sum_{q \in \mathcal{P}} m_{Spq} S_q$$

$$L'_p = \Phi_p - (\varepsilon_p + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q$$

$$I'_p = \varepsilon_p L_p - (\gamma_p + d_p) I_p + \sum_{q \in \mathcal{P}} m_{Ipq} I_q$$

$$R'_p = \gamma_p I_p - (\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q$$

$$\Phi_p = \beta_p \frac{S_p I_p}{N_p^{q_p}}, \quad q_p \in \{0, 1\}$$

System of  $4|\mathcal{P}|$  equations

# Size is not that bad..

System of  $4|\mathcal{P}|$  equations !!!

However, a lot of structure:

- $|\mathcal{P}|$  copies of individual units, each comprising 4 equations
- Dynamics of individual units well understood
- Coupling is linear

⇒ Good case of large-scale system (matrix analysis is your friend)

# Behaviour of the total population

Consider behaviour of  $N_p = S_p + L_p + I_p + R_p$ . We have

$$\begin{aligned} N'_p &= \cancel{\mathcal{B}_p - \Phi_p} - d_p S_p + \cancel{\nu_p R_p} + \sum_{q \in \mathcal{P}} m_{Spq} S_q \\ &\quad + \cancel{\Phi_p} - (\cancel{\varepsilon_p} + d_p) L_p + \sum_{q \in \mathcal{P}} m_{Lpq} L_q \\ &\quad + \cancel{\varepsilon_p L_p} - (\cancel{\gamma_p} + d_p) I_p + \sum_{q \in \mathcal{P}} m_{Ipq} I_q \\ &\quad + \cancel{\gamma_p I_p} - (\cancel{\nu_p} + d_p) R_p + \sum_{q \in \mathcal{P}} m_{Rpq} R_q \end{aligned}$$

So

$$N'_p = \mathcal{B}_p - d_p N_p + \sum_{X \in \{S, L, I, R\}} \sum_{q \in \mathcal{P}} m_{Xpq} X_q$$

# Vector / matrix form of the equation

We have

$$N'_p = \mathcal{B}_p - d_p N_p + \sum_{X \in \{S, L, I, R\}} \sum_{q \in \mathcal{P}} m_{Xpq} X_q$$

Write this in vector form

$$\mathbf{N}' = \mathbf{b} - \mathbf{d}\mathbf{N} + \sum_{X \in \{S, L, I, R\}} \mathcal{M}^X \mathbf{X}$$

where  $\mathbf{b} = (\mathcal{B}_1, \dots, \mathcal{B}_{|\mathcal{P}|})^T$ ,  $\mathbf{N} = (N_1, \dots, N_{|\mathcal{P}|})^T$ ,  $\mathbf{X} = (X_1, \dots, X_{|\mathcal{P}|})^T \in \mathbb{R}^{|\mathcal{P}|}$ ,  $\mathbf{d}, \mathcal{M}^X$   $|\mathcal{P}| \times |\mathcal{P}|$ -matrices with

$$\mathbf{d} = \text{diag} (d_1, \dots, d_{|\mathcal{P}|})$$

# The movement matrix

$$\mathcal{M}^c = \begin{pmatrix} -\sum_{q \in \mathcal{P}} m_{cq1} & m_{c12} & m_{c1|\mathcal{P}|} \\ m_{c21} & -\sum_{q \in \mathcal{P}} m_{cq2} & m_{c2|\mathcal{P}|} \\ m_{c|\mathcal{P}|1} & m_{c|\mathcal{P}|2} & -\sum_{q \in \mathcal{P}} m_{cq|\mathcal{P}|} \end{pmatrix}$$

Consider a compartment  $c \in \mathcal{C}$ . Then the following hold true:

1.  $0 \in \sigma(\mathcal{M}^c)$  and corresponds to left eigenvector  $\mathbf{1}_{|\mathcal{P}|}^T = (1, \dots, 1)$
2.  $-\mathcal{M}^c$  singular M-matrix
3.  $0 = s(\mathcal{M}^c) \in \sigma(\mathcal{M}^c)$
4.  $\mathcal{M}^c$  irreducible  $\implies s(\mathcal{M}^c)$  has multiplicity 1

- JA, Bajeux & Kirkland. [Number of source patches required for population persistence in a source-sink metapopulation with explicit movement. \*Bulletin of Mathematical Biology\* 81\(6\):1916-1942 \(2019\)](#)

# The nice case

Recall that

$$\mathbf{N}' = \mathbf{b} - \mathbf{d}\mathbf{N} + \sum_{X \in \{S, L, I, R\}} \mathcal{M}^X \mathbf{X}$$

Suppose movement rates **equal for all compartments**, i.e.,

$$\mathcal{M}^S = \mathcal{M}^L = \mathcal{M}^I = \mathcal{M}^R =: \mathcal{M}$$

Then

$$\begin{aligned} \mathbf{N}' &= \mathbf{b} - \mathbf{d}\mathbf{N} + \mathcal{M} \sum_{X \in \{S, L, I, R\}} \mathbf{X} \\ &= \mathbf{b} - \mathbf{d}\mathbf{N} + \mathcal{M}\mathbf{N} \end{aligned}$$

$$\mathbf{N}' = \mathbf{b} - \mathbf{d}\mathbf{N} + \mathcal{M}\mathbf{N}$$

Equilibria

$$\begin{aligned}\mathbf{N}' = \mathbf{0} &\Leftrightarrow \mathbf{b} - \mathbf{d}\mathbf{N} + \mathcal{M}\mathbf{N} = \mathbf{0} \\ &\Leftrightarrow (\mathbf{d} - \mathcal{M})\mathbf{N} = \mathbf{b} \\ &\Leftrightarrow \mathbf{N}^* = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}\end{aligned}$$

given, of course, that  $\mathbf{d} - \mathcal{M}$  (or, equivalently,  $\mathcal{M} - \mathbf{d}$ ) is invertible.. Is it?

# "Perturbations" of movement matrices

$\mathcal{M}$  a movement matrix and  $D$  a diagonal matrix. The following hold true:

1.  $s(\mathcal{M} + d\mathbb{I}) = d$  for all  $d \in \mathbb{R}$
2.  $s(\mathcal{M} + D) \in \sigma(\mathcal{M}^c + D)$  and is associated with an eigenvector  $\mathbf{v} > \mathbf{0}$ . If, additionally,  $\mathcal{M}$  irreducible, then  $s(\mathcal{M}^c + D)$  has multiplicity 1 and is associated with  $\mathbf{v} \gg \mathbf{0}$
3.  $\text{diag}(D) \gg \mathbf{0} \implies D - \mathcal{M}$  nonsingular M-matrix and  $(D - \mathcal{M})^{-1} > \mathbf{0}$
4.  $\mathcal{M}$  irreducible and  $\text{diag}(D) > \mathbf{0} \implies D - \mathcal{M}$  irreducible nonsingular M-matrix and  $(D - \mathcal{M}^c)^{-1} \gg \mathbf{0}$

- JA, Bajeux & Kirkland. Number of source patches required for population persistence in a source-sink metapopulation with explicit movement. *Bulletin of Mathematical Biology* 81(6):1916-1942 (2019)

## Nonsingularity of $\mathcal{M} - \mathbf{d}$

From theorem on movement matrix,  $0 \in \sigma(\mathcal{M})$  and  $\tau(\mathcal{M}) = 0$

So, using spectral shift,

$$\tau(\mathcal{M} - \mathbf{d}) = - \min_{p \in \mathcal{P}} d_p$$

This gives a constraint: for total population to behave well (in general, we want this), we must assume all death rates are positive

Assume they are (in other words, assume  $\mathbf{d}$  nonsingular). Then  $\mathcal{M} - \mathbf{d}$  is nonsingular and  $\mathbf{N}^* = (\mathbf{d} - \mathcal{M})^{-1} \mathbf{b}$  unique

## Behaviour of the total population Equal movement case

$\mathbf{N}^* = (\mathbf{d} - \mathcal{M})^{-1}\mathbf{b}$  attracts solutions of

$$\mathbf{N}' = \mathbf{b} - \mathbf{d}\mathbf{N} + \mathcal{M}\mathbf{N} =: f(\mathbf{N})$$

Indeed, we have

$$Df = \mathcal{M} - \mathbf{d}$$

Since we now assume that  $\mathbf{d}$  is nonsingular, we have (spectral shift & properties of  $\mathcal{M}$ )  
 $\tau(\mathcal{M} - \mathbf{d}) = -\min_{p \in \mathcal{P}} d_p < 0$

# Behaviour of total population Depends on reducibility of movement

$\mathcal{M}$  irreducible  $\rightarrow \mathbf{N}^* \gg 0$

Assume that the movement matrix  $\mathcal{M}$  is reducible. Let  $a$  be the number of minimal absorbing sets in the corresponding connection graph  $\mathcal{G}(\mathcal{M})$ . Then

1. The stability modulus  $\tau(\mathcal{M}) = 0$  has multiplicity  $a$
2. Associated to the stability modulus  $\tau(\mathcal{M})$  is a nonnegative eigenvector  $v$ , with the following characteristics:
  - $v_i > 0$  if  $i$  is a vertex in a minimal absorbing set
  - $v_i = 0$  if  $i$  is a transient vertex

Recall that

$$\mathbf{N}' = \mathbf{b} - \mathbf{d}\mathbf{N} + \sum_{X \in \{S, L, I, R\}} \mathcal{M}^X \mathbf{X}$$

Suppose movement rates are **similar for all compartments**, i.e., the zero/nonzero patterns in all matrices are the same but not the entries (movement digraphs match, not necessarily the rates of movement)

Let

$$\underline{\mathcal{M}} = \left[ \min_{X \in \{S, L, I, R\}} m_{Xpq} \right]_{pq, p \neq q}$$

$$\overline{\mathcal{M}} = \left[ \max_{X \in \{S, L, I, R\}} m_{Xpq} \right]_{pq, p=q}$$

and

$$\overline{\mathcal{M}} = \left[ \max_{X \in \{S, L, I, R\}} m_{Xpq} \right]_{pq, p \neq q}$$

$$\overline{\mathcal{M}} = \left[ \min_{X \in \{S, L, I, R\}} m_{Xpq} \right]_{pq, p=q}$$

Then

# Cool, no? No!

We have

$$\mathbf{b} - \mathbf{d}\mathbf{N} + \underline{\mathcal{M}}\mathbf{N} \leq \mathbf{N}' \leq \mathbf{b} - \mathbf{d}\mathbf{N} + \overline{\mathcal{M}}\mathbf{N}$$

Me, roughly every 6 months: *Oooh, a linear differential inclusion!*

Unfortunately, roughly 10 minutes after that previous statement:  *$\underline{\mathcal{M}}$  and  $\overline{\mathcal{M}}$  are made from movement matrices but are not movement matrices (in particular, their column sums are not all zero)*

So no luck there

# Disease free equilibrium (DFE)

Assume system at equilibrium and  $L_p = I_p = 0$  for  $p \in \mathcal{P}$ . Then  $\Phi_p = 0$  and

$$0 = \mathcal{B}_p - d_p S_p + \nu_p R_p + \sum_{q \in \mathcal{P}} m_{pq}^S S_q$$
$$0 = -(\nu_p + d_p) R_p + \sum_{q \in \mathcal{P}} m_{pq}^R R_q$$

Want to solve for  $S_p, R_p$ . Here, it is best (crucial in fact) to remember some linear algebra. Write system in vector form:

$$\mathbf{0} = \mathbf{b} - \mathbf{d}\mathbf{S} + \nu\mathbf{R} + \mathcal{M}^S\mathbf{S}$$
$$\mathbf{0} = -(\nu + \mathbf{d})\mathbf{R} + \mathcal{M}^R\mathbf{R}$$

where  $\mathbf{S}, \mathbf{R}, \mathbf{b} \in \mathbb{R}^{|\mathcal{P}|}$ ,  $\mathbf{d}, \nu, \mathcal{M}^S, \mathcal{M}^R$   $|\mathcal{P}| \times |\mathcal{P}|$ -matrices ( $\mathbf{d}, \nu$  diagonal)

Recall second equation:

$$\mathbf{0} = -(\nu + \mathbf{d})\mathbf{R} + \mathcal{M}^R\mathbf{R} \Leftrightarrow (\mathcal{M}^R - \nu - \mathbf{d})\mathbf{R} = \mathbf{0}$$

So unique solution  $\mathbf{R} = \mathbf{0}$  if  $\mathcal{M}^R - \nu - \mathbf{d}$  invertible.

Is it?

We have been here before.. 0 is an eigenvalue of  $\mathcal{M}^R$  and  $\tau(\mathcal{M}^R) = 0$ .

So  $(\mathcal{M}^R - \nu - \mathbf{d})\mathbf{R} = \mathbf{0}$  has only the solution  $\mathbf{R} = \mathbf{0}$

From spectrum shift,  $\tau(\mathcal{M}^R - \nu - \mathbf{d}) = -\min_{p \in \mathcal{P}}(\nu_p + d_p) < 0$

So, given  $\mathbf{L} = \mathbf{I} = \mathbf{0}$ ,

$$\lim_{t \rightarrow \infty} \mathbf{R}(t) = \mathbf{0}$$

and DFE has  $\mathbf{L} = \mathbf{I} = \mathbf{R} = \mathbf{0}$

# **S at the DFE**

DFE has  $\mathbf{L} = \mathbf{I} = \mathbf{R} = \mathbf{0}$  and  $\mathbf{b} - \mathbf{d}\mathbf{S} + \mathcal{M}^S \mathbf{S} = \mathbf{0}$ , i.e.,

$$\mathbf{S} = (\mathbf{d} - \mathcal{M}^S)^{-1} \mathbf{b}$$

Recall:  $-\mathcal{M}^S$  singular M-matrix. From previous reasoning,  $\mathbf{d} - \mathcal{M}^S$  has **instability modulus** shifted right by  $\min_{p \in \mathcal{P}} d_p$ . So:

- $\mathbf{d} - \mathcal{M}^S$  invertible
- $\mathbf{d} - \mathcal{M}^S$  nonsingular M-matrix

Second point  $\implies (\mathbf{d} - \mathcal{M}^S)^{-1} > 0 \implies (\mathbf{d} - \mathcal{M}^S)^{-1} \mathbf{b} \gg 0$

So DFE makes sense with

$$(\mathbf{S}, \mathbf{L}, \mathbf{I}, \mathbf{R}) = ((\mathbf{d} - \mathcal{M}^S)^{-1} \mathbf{b}, \mathbf{0}, \mathbf{0}, \mathbf{0})$$

# Computing basic reprod. number $\mathcal{R}_0$

Use next generation method with  $\Xi = \{L_1, \dots, L_{|\mathcal{P}|}, I_1, \dots, I_{|\mathcal{P}|}\}$ ,  $\Xi' = \mathcal{F} - \mathcal{V}$

$$\mathcal{F} = (\Phi_1, \dots, \Phi_{|\mathcal{P}|}, 0, \dots, 0)^T$$

$$\mathcal{V} = \begin{pmatrix} (\varepsilon_1 + d_1) L_1 - \sum_{q \in \mathcal{P}} m_{1q}^L L_q \\ \vdots \\ (\varepsilon_{|\mathcal{P}|} + d_{|\mathcal{P}|}) L_{|\mathcal{P}|} - \sum_{q \in \mathcal{P}} m_{|\mathcal{P}|q}^L L_q \\ -\varepsilon_1 L_1 + (\gamma_1 + d_1) I_1 - \sum_{q \in \mathcal{P}} m_{1q}^I I_q \\ \vdots \\ -\varepsilon_{|\mathcal{P}|} L_{|\mathcal{P}|} + (\gamma_{|\mathcal{P}|} + d_{|\mathcal{P}|}) I_{|\mathcal{P}|} - \sum_{q \in \mathcal{P}} m_{|\mathcal{P}|q}^I I_q \end{pmatrix}$$

Differentiate w.r.t.  $\Xi$ :

$$D\mathcal{F} = \begin{pmatrix} \frac{\partial \Phi_1}{\partial L_1} & \cdots & \frac{\partial \Phi_1}{\partial L_{|\mathcal{P}|}} & \frac{\partial \Phi_1}{\partial I_1} & \cdots & \frac{\partial \Phi_1}{\partial I_{|\mathcal{P}|}} \\ \vdots & & \vdots & \vdots & & \vdots \\ \frac{\partial \Phi_{|\mathcal{P}|}}{\partial L_1} & \cdots & \frac{\partial \Phi_{|\mathcal{P}|}}{\partial L_{|\mathcal{P}|}} & \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_1} & \cdots & \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}} \\ 0 & \cdots & 0 & 0 & \cdots & 0 \\ \vdots & & \vdots & \vdots & & \vdots \\ 0 & \cdots & 0 & 0 & \cdots & 0 \end{pmatrix}$$

Note that

$$\frac{\partial \Phi_p}{\partial L_k} = \frac{\partial \Phi_p}{\partial I_k} = 0$$

whenever  $k \neq p$ , so

$$D\mathcal{F} = \begin{pmatrix} \text{diag} \left( \frac{\partial \Phi_1}{\partial L_1}, \dots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial L_{|\mathcal{P}|}} \right) & \text{diag} \left( \frac{\partial \Phi_1}{\partial I_1}, \dots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}} \right) \\ 0 & 0 \end{pmatrix}$$

# Evaluate $D\mathcal{F}$ at DFE

If  $\Phi_p = \beta_p S_p I_p$ , then

- $\frac{\partial \Phi_p}{\partial L_p} = 0$
- $\frac{\partial \Phi_p}{\partial I_p} = \beta_p S_p$

If  $\Phi_p = \beta_p \frac{S_p I_p}{N_p}$ , then

- $\frac{\partial \Phi_p}{\partial L_p} = \beta_p \frac{S_p I_p}{N_p^2} = 0$  at DFE
- $\frac{\partial \Phi_p}{\partial I_p} = \beta_p \frac{S_p}{N_p}$  at DFE

In both cases,  $\partial/\partial L$  block is zero so

$$F = D\mathcal{F}(DFE) = \begin{pmatrix} 0 & \text{diag} \left( \frac{\partial \Phi_1}{\partial I_1}, \dots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}} \right) \\ 0 & 0 \end{pmatrix}$$

## Compute $D\mathcal{V}$ and evaluate at DFE

$$V = \begin{pmatrix} \text{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L & 0 \\ -\text{diag}_p(\varepsilon_p) & \text{diag}_p(\gamma_p + d_p) - \mathcal{M}^I \end{pmatrix}$$

where  $\text{diag}_p(z_p) = \text{diag}(z_1, \dots, z_{|\mathcal{P}|})$ . Inverse of  $V$  easy ( $2 \times 2$  block lower triangular):

$$V^{-1} = \begin{pmatrix} (\text{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L)^{-1} & 0 \\ \tilde{V}_{21}^{-1} & (\text{diag}_p(\gamma_p + d_p) - \mathcal{M}^I)^{-1} \end{pmatrix}$$

where

$$\tilde{V}_{21}^{-1} = (\text{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L)^{-1} \text{diag}_p(\varepsilon_p) (\text{diag}_p(\gamma_p + d_p) - \mathcal{M}^I)^{-1}$$

# $\mathcal{R}_0$ as $\rho(FV^{-1})$

Next generation matrix

$$FV^{-1} = \begin{pmatrix} 0 & F_{12} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \tilde{V}_{11}^{-1} & 0 \\ \tilde{V}_{21}^{-1} & \tilde{V}_{22}^{-1} \end{pmatrix} = \begin{pmatrix} F_{12}\tilde{V}_{21}^{-1} & F_{12}\tilde{V}_{22}^{-1} \\ 0 & 0 \end{pmatrix}$$

where  $\tilde{V}_{ij}^{-1}$  is block  $ij$  in  $V^{-1}$ . So

$$\mathcal{R}_0 = \rho\left(F_{12}\tilde{V}_{21}^{-1}\right)$$

i.e.,

$$\mathcal{R}_0 = \rho \left( \text{diag} \left( \frac{\partial \Phi_1}{\partial I_1}, \dots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}} \right) \left( \text{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L \right)^{-1} \right. \\ \left. \text{diag}_p(\varepsilon_p) \left( \text{diag}_p(\gamma_p + d_p) - \mathcal{M}^I \right)^{-1} \right)$$

# Local asymptotic stability of the DFE

Define  $\mathcal{R}_0$  for the  $|\mathcal{P}|$ -SLIRS as

$$\mathcal{R}_0 = \rho \left( \text{diag} \left( \frac{\partial \Phi_1}{\partial I_1}, \dots, \frac{\partial \Phi_{|\mathcal{P}|}}{\partial I_{|\mathcal{P}|}} \right) (\text{diag}_p(\varepsilon_p + d_p) - \mathcal{M}^L)^{-1} \right. \\ \left. \text{diag}_p(\varepsilon_p) (\text{diag}_p(\gamma_p + d_p) - \mathcal{M}^I)^{-1} \right)$$

Then the DFE

$$(\mathbf{S}, \mathbf{L}, \mathbf{I}, \mathbf{R}) = ((\mathbf{d} - \mathcal{M}^S)^{-1} \mathbf{b}, \mathbf{0}, \mathbf{0}, \mathbf{0})$$

is locally asymptotically stable if  $\mathcal{R}_0 < 1$  and unstable if  $\mathcal{R}_0 > 1$

# $\mathcal{R}_0$ is not the panacea

An urban centre and satellite cities

JA & S Portet. [Epidemiological implications of mobility between a large urban centre and smaller satellite cities](#). *Journal of Mathematical Biology* **71**(5):1243-1265 (2015)

# Context of the study

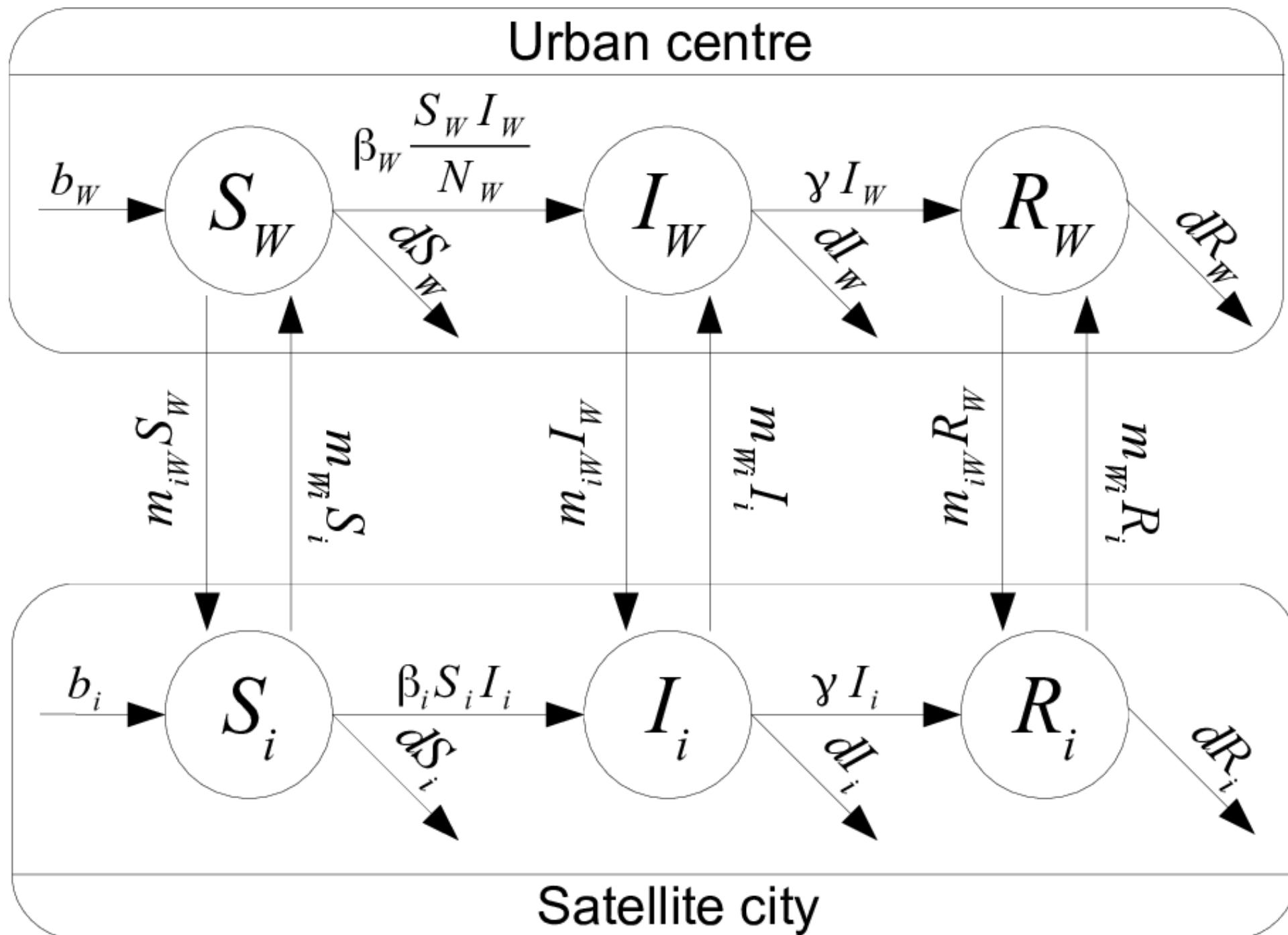
Winnipeg as urban centre and 3 satellite cities close to Winnipeg as smaller cities:  
Portage la Prairie, Selkirk and Steinbach

Manitoba ideal for this study

- population density low to very low outside of Winnipeg
- road network connecting Winnipeg to nearby cities simple and well studied: U of Manitoba Transport Infrastructure Group (UMTIG) releases yearly vehicle counts at hundreds of locations around the province

# **Estimated number of trips and related quantities**

<b>City</b>	<b>Pop.</b>	<b>Dist.</b>	<b>Avg. trips/day</b>
Winnipeg (W)	663,617	-	-
Portage la Prairie (1)	12,996	88	4,115
Selkirk (2)	9,834	34	7,983
Steinbach (3)	13,524	66	7,505



# Estimating movement rates

Consider city  $x$  and its population  $N_x$ . Assume rate at which individuals leave city  $x$  to go to city  $y$  is  $m_{yx}$ . *Ceteris paribus*,  $N'_x = -m_{yx}N_x$ , so  $N_x(t) = N_x(0)e^{-m_{yx}t}$ . Therefore, after one day,  $N_x(1) = N_x(0)e^{-m_{yx}}$ , i.e.,

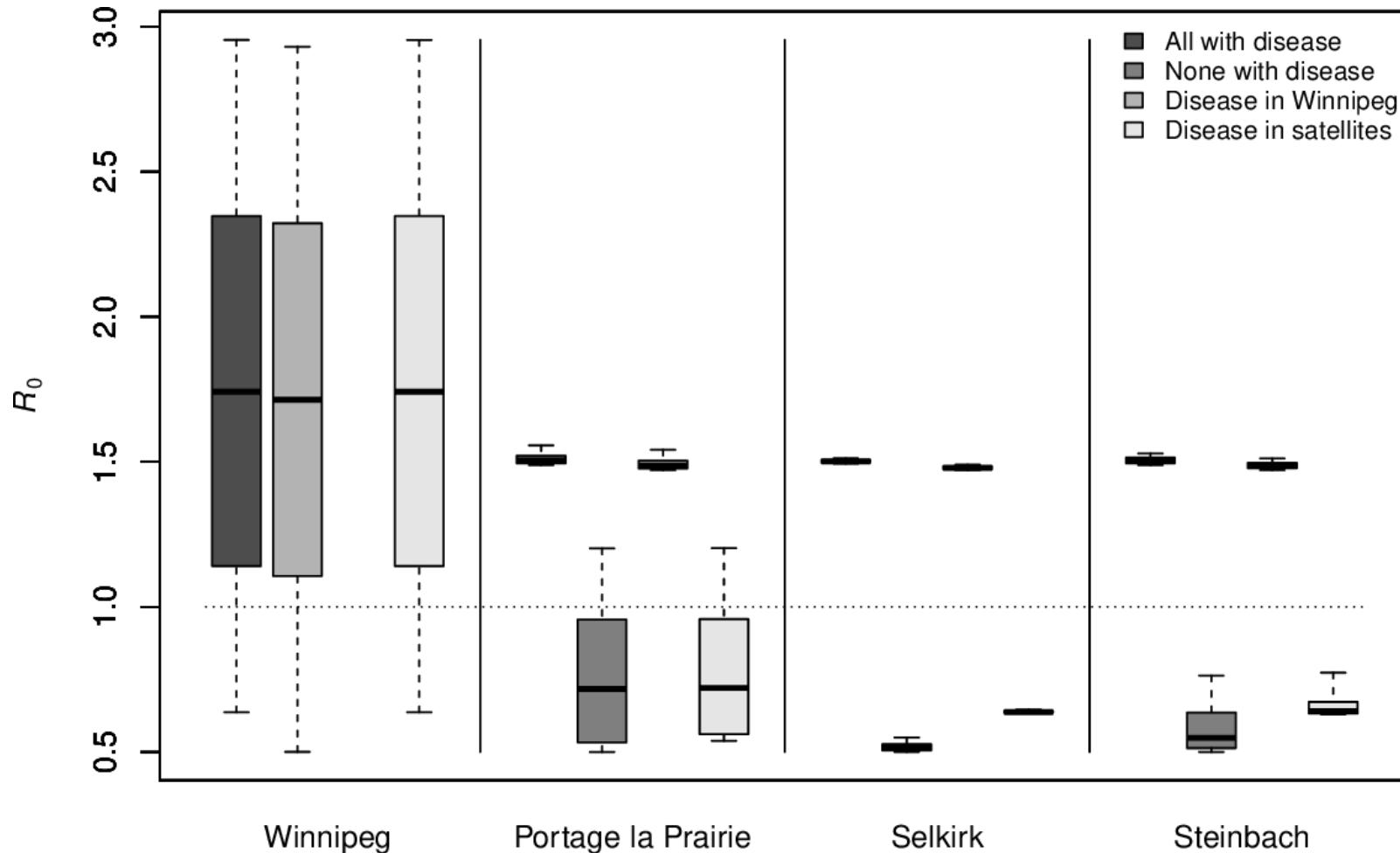
$$m_{yx} = -\ln \left( \frac{N_x(1)}{N_x(0)} \right)$$

Now,  $N_x(1) = N_x(0) - T_{yx}$ , where  $T_{yx}$  number of individuals going from  $x$  to  $y$  / day. So

$$m_{yx} = -\ln \left( 1 - \frac{T_{yx}}{N_x(0)} \right)$$

Computed for all pairs  $(W, i)$  and  $(i, W)$  of cities

# Sensitivity of $\mathcal{R}_0$ to variations of $\mathcal{R}_0^x \in [0.5, 3]$



with disease:  $\mathcal{R}_0^x = 1.5$ ; without disease:  $\mathcal{R}_0^x = 0.5$ . Each box and corresponding whiskers are 10,000 simulations

## Lower connectivity can drive $\mathcal{R}_0$

PLP and Steinbach have comparable populations but with parameters used, only PLP can cause the general  $\mathcal{R}_0$  to take values larger than 1 when  $\mathcal{R}_0^W < 1$

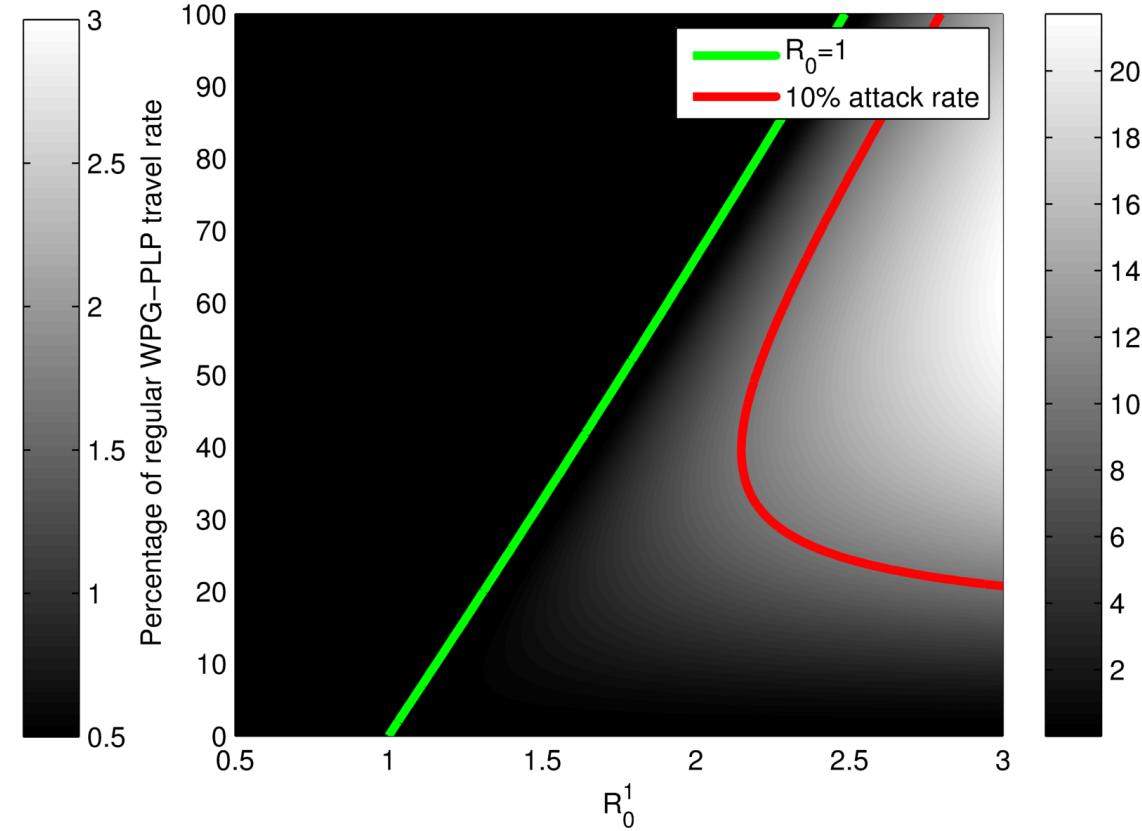
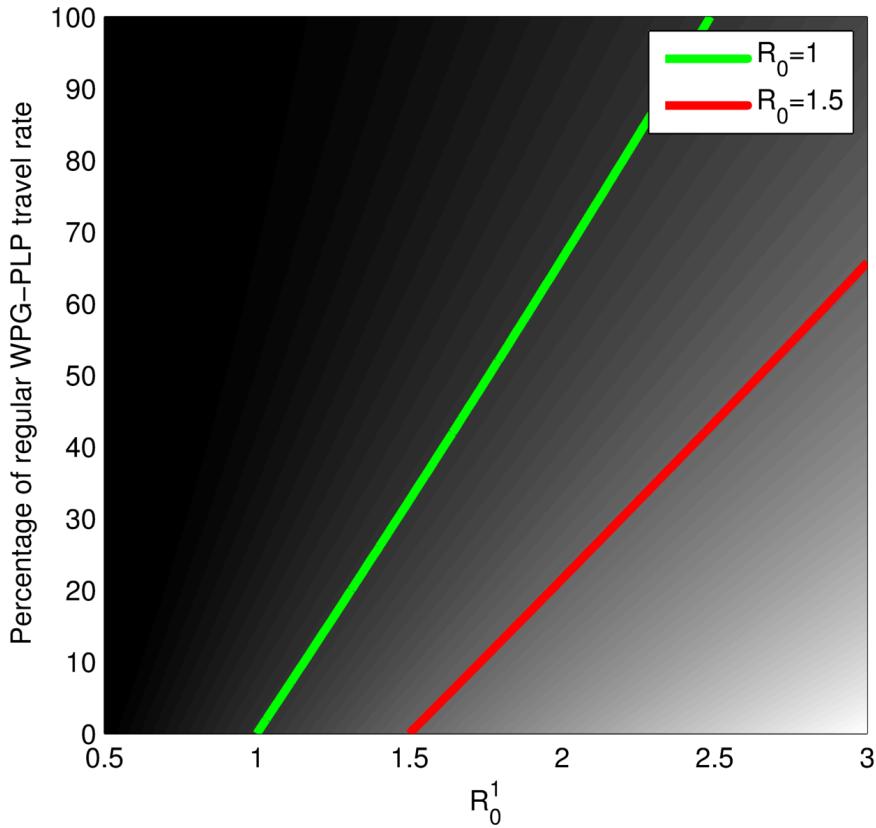
This is due to the movement rate: if  $\mathcal{M} = 0$ , then

$$\mathcal{R}_0 = \max\{\mathcal{R}_0^W, \mathcal{R}_0^1, \mathcal{R}_0^2, \mathcal{R}_0^3\},$$

since  $FV^{-1}$  is then block diagonal

Movement rates to and from PLP are lower  $\rightarrow$  situation closer to uncoupled case and  $\mathcal{R}_0^1$  has more impact on the general  $\mathcal{R}_0$

# $\mathcal{R}_0$ does not tell the whole story!



Plots as functions of  $\mathcal{R}_0^1$  in PLP and the reduction of movement between Winnipeg and PLP. Left: general  $\mathcal{R}_0$ . Right: Attack rate in Winnipeg

# Problems specific to metapopulations

# Inherited dynamical properties

Given

$$s'_{kp} = f_{kp}(S_p, I_p)$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p)$$

with known properties, what is known of

$$s'_{kp} = f_{kp}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{kpq} s_{kq}$$

$$i'_{\ell p} = g_{\ell p}(S_p, I_p) + \sum_{q \in \mathcal{P}} m_{\ell pq} i_{\ell q}$$

- Existence and uniqueness ✓
- Invariance of  $\mathbb{R}_+^\bullet$  under the flow ✓
- Boundedness ✓
- Location of individual  $\mathcal{R}_{0i}$  and general  $\mathcal{R}_0$ ?
- GAS?

## Mixed equilibria

Can there be situations where some patches are at the DFE and others at an EEP?

This is the problem of **mixed equilibria**

This is a metapopulation-specific problem, not one of inheritance of dynamical properties!

# Types of equilibria

**[Patch level]** Patch  $p \in \mathcal{P}$  at equilibrium is **empty** if  $X_p^* = 0$ , at the **disease-free equilibrium** if  $X_p^* = (s_{k_1 p}^*, \dots, s_{k_u p}^*, 0, \dots, 0)$ , where  $k_1, \dots, k_u$  are some indices with  $1 \leq u \leq |\mathcal{U}|$  and  $s_{k_1 p}^*, \dots, s_{k_u p}^*$  are positive, and at an **endemic equilibrium** if  $X_p \gg 0$

**[Metapopulation level]** A **population-free equilibrium** has all patches empty. A **metapopulation disease-free equilibrium** has all patches at the disease-free equilibrium for the same compartments. A **metapopulation endemic equilibrium** has all patches at an endemic equilibrium

# Mixed equilibria

A **mixed equilibrium** is an equilibrium such that

- all patches are at a disease-free equilibrium but the system is not at a metapopulation disease-free equilibrium
- or, there are at least two patches that have different types of patch-level equilibrium (empty, disease-free or endemic)

E.g.,

$$((S_1, I_1, R_1), (S_2, I_2, R_2)) = ((+, 0, 0), (+, +, +))$$

is mixed, so is

$$((S_1, I_1, R_1), (S_2, I_2, R_2)) = ((+, 0, 0), (+, 0, +))$$

Suppose that movement is similar for all compartments and that the system is at equilibrium

- If patch  $p \in \mathcal{P}$  is empty, then all patches in  $\mathcal{A}(p)$  are empty
- If patch  $p \in \mathcal{P}$  is at a disease free equilibrium, then the subsystem consisting of all patches in  $\{p, \mathcal{A}(p)\}$  is at a metapopulation disease free equilibrium
- If patch  $p \in \mathcal{P}$  is at an endemic equilibrium, then all patches in  $\mathcal{D}(p)$  are also at an endemic equilibrium
- If  $\mathcal{G}^c$  is strongly connected for some compartment  $c \in \mathcal{C}$ , then there does not exist mixed equilibria

Note that MSAC  $\rightarrow \mathcal{A}^c = \mathcal{A}$  and  $\mathcal{D}^c = \mathcal{D}$  for all  $c \in \mathcal{C}$

# Interesting (IMHO) problems

More is needed on inheritance problem, in particular GAS part (Li & Shuai, Kamgang & Sallet, and older stuff: Michel & Miller, \v{S}iljak)..

Incorporate travel time (delay) and events (infection, recovery, death ..) during travel

Cantrell & Cosner's islands (PDEs in the patches)

Nonlinear movement rates

Understand stochastic version better

# Numerical investigations

- JA. Spatio-temporal spread of infectious pathogens of humans. *Infectious Disease Modelling* **2**(2):218-228 (2017)
- JA. Mathematical epidemiology in a data-rich world. *Infectious Disease Modelling* **5**:161-188 (2020)
- github repo [modelling-with-data](#)

## Not very difficult

- As for the mathematical analysis: if you do things carefully and think about things a bit, numerics are not hard. Well: not harder than numerics in low-D
- Exploit vector structure

# Define the vector field

```
SLIAR_metapop_rhs <- function(t, x, p) {
  with(as.list(x), {
    S = x[p$idx_S]
    L = x[p$idx_L]
    I = x[p$idx_I]
    A = x[p$idx_A]
    R = x[p$idx_R]
    N = S + L + I + A + R
    Phi = p$beta * S * (I + p$eta * A)
    dS = S - Phi + p$M %*% S
    dL = Phi - p$epsilon * L + p$M %*% L
    dI = (1 - p$pi) * p$epsilon * L - p$gammaI * I + p$M %*% I
    dA = p$pi * p$epsilon * L - p$gammaA * A + p$M %*% A
    dR = p$gammaI * I + p$gammaA * A + p$M %*% R
    list(c(dS, dL, dI, dA, dR))
  })
}
```

# Set up parameters

```
pop = c(34.017, 1348.932, 1224.614, 173.593, 93.261) * 1e+06
countries = c("Canada", "China", "India", "Pakistan", "Philippines")
T = matrix(data =
  c(0, 1268, 900, 489, 200,
    1274, 0, 678, 859, 150,
    985, 703, 0, 148, 58,
    515, 893, 144, 0, 9,
    209, 174, 90, 2, 0),
  nrow = 5, ncol = 5, byrow = TRUE)
```

# Work out movement matrix

```
p = list()
# Use the approximation explained in Arino & Portet, JMB
# 2015.
p$M = mat.or.vec(nr = dim(T)[1], nc = dim(T)[2])
for (from in 1:5) {
  for (to in 1:5) {
    p$M[to, from] = -log(1 - T[from, to]/pop[from])
  }
  p$M[from, from] = 0
}
p$M = p$M - diag(colSums(p$M))
```

```
p$P = dim(p$M)[1]
p$idx_S = 1:p$P
p$idx_L = (p$P + 1):(2 * p$P)
p$idx_I = (2 * p$P + 1):(3 * p$P)
p$idx_A = (3 * p$P + 1):(4 * p$P)
p$idx_R = (4 * p$P + 1):(5 * p$P)
p$eta = rep(0.3, p$P)
p$epsilon = rep((1/1.5), p$P)
p$pi = rep(0.7, p$P)
p$gammaI = rep((1/5), p$P)
p$gammaA = rep((1/3), p$P)
```

# Set up IC and time

```
# Set initial conditions. For example, we start with 2
# infectious individuals in Canada.
L0 = mat.or.vec(p$P, 1)
I0 = mat.or.vec(p$P, 1)
A0 = mat.or.vec(p$P, 1)
R0 = mat.or.vec(p$P, 1)
I0[1] = 2
S0 = pop - (L0 + I0 + A0 + R0)
# Vector of initial conditions to be passed to ODE solver.
IC = c(S = S0, L = L0, I = I0, A = A0, R = R0)
# Time span of the simulation (5 years here)
tspan = seq(from = 0, to = 5 * 365.25, by = 0.1)
```

## Set up $\beta$ to avoid blow up

Let us take  $\mathcal{R}_0 = 1.5$  for patches in isolation. Solve  $\mathcal{R}_0$  for  $\beta$

$$\beta = \frac{\mathcal{R}_0}{S(0)} \left( \frac{1 - \pi_p}{\gamma_{Ip}} + \frac{\pi_p \eta_p}{\gamma_{Ap}} \right)^{-1}$$

```
for (i in 1:p$P) {  
  p$beta[i] = 1.5/S0[i] * 1/((1 - p$pi[i])/p$gammaI[i] + p$pi[i] *  
                           p$eta[i]/p$gammaA[i])  
}
```

```
# Call of the ODE solver
sol <- ode(y = IC, times = tspan, func = SLIAR_metapop_rhs, parms = p)
## DLSODA- At current T (=R1), MXSTEP (=I1) steps
## taken on this call before reaching TOUT
## In above message, I1 = 5000
##
## In above message, R1 = 117.498
##
# Put solution in an easier to use form
times = sol[, "time"]
S = sol[, p$idx_S]
L = sol[, p$idx_L]
I = sol[, p$idx_I]
A = sol[, p$idx_A]
R = sol[, p$idx_R]
N = S + L + I + A + R
```

# Sample plot

```
# Sample plot: number infected per 100,000 inhabitants
xlim = range(times)
ylim = c(0, max(I/N * 1e+05))
pdf(file = "FIGS/one_sim_5countries.pdf", width = 11, height = 8.5)
plot(0, xlim = xlim, ylim = ylim, xlab = "Time (days)",
      ylab = "Number infectious per 100,000")
for (i in 1:p$P) {
  lines(times, I[, i]/N[, i] * 1e+05, col = i)
}
legend("topright", legend = countries, col = 1:p$P, lty = 1)
dave <- dev.off()
```

# Epilogue / Postlude

# In conclusion

- Space is a fundamental component of the epidemic spread process and **cannot** be ignored, both in modelling **and** in public health decision making
- One way to model space is to use metapopulation models
- Metapopulation models are easy to analyse locally, give interesting problems at the global level and are easy to simulate
- Simulation (deterministic and stochastic) can be costly in RAM and cycles
- Metapopulation models are not the only solution

# To finish, let us circle back to Thucydides!

- [...] physicians [...] died [...] the most thickly, as they visited the sick most often
- No remedy was found that could be used as a specific; for what did good in one case, did harm in another
- those who had recovered from the disease [...] knew what it was from experience, and had now no fear for themselves; for the same man was never attacked twice—never at least fatally
- An aggravation of the existing calamity was the influx from the country into the city, and this was especially felt by the new arrivals. As there were no houses to receive them, they had to be lodged at the hot season of the year in stifling cabins, where the mortality raged without restraint
- *Supplications in the temples, divinations, and so forth were found equally futile*

**Merci / Miigwech / Thank you**