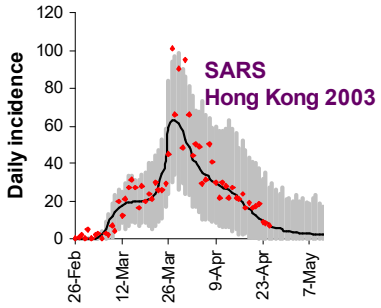
Mathematical modelling to support risk assessment and planning during emerging infectious disease epidemics

Simon Cauchemez
Mathematical Modelling of Infectious Diseases Unit
Institut Pasteur, Paris

Institut Pasteur

Motivating example 1: Early risk assessment during EID epidemics

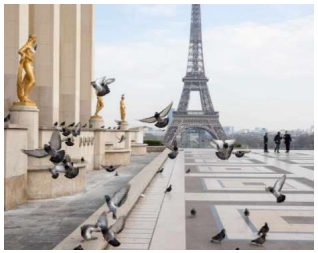
- Emerging infectious disease epidemics: SARS-CoV-2, SARS-CoV-1, pandemic influenza, Ebola, ZIKV…
- Key needs for evidence-based policy making:
  - ➢ Assess the epidemiological situation:
  - ➢ Interpret data:
    - ✓ Epidemiological characteristics of pathogen?
    - ✓ Transmission risk factors?
    - ✓ Impact of interventions?
  - ➢ Extrapolate / predict:
    - ✓ What should be expected?
    - ✓ What should be done?



Zika – the Americas



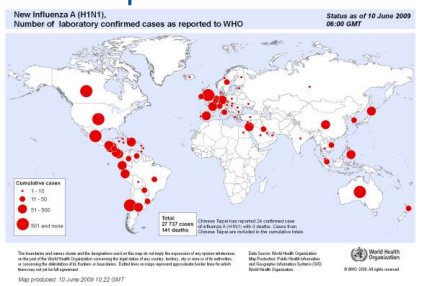
COVID-19



Ebola – West Africa



2009 flu pandemic – week 6



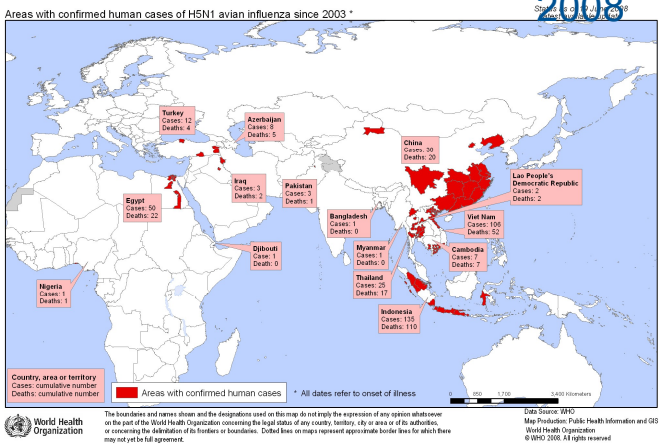
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Motivating example 2: Getting prepared for a severe influenza pandemic



Me (as a PhD student and postdoc in early 2000)

A new highly pathogenic avian influenza virus (H5N1)



Treatment



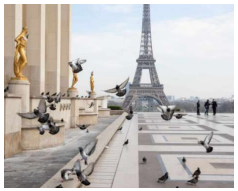
Vaccination



School closure



Social distancing



Masks



Contact tracing



- Questions:
  - What could be the impact of an influenza pandemic?
  - What measures could be implemented?

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Overview

- Key challenges for epidemic risk assessment.
- Key parameters to estimate:
  - Evaluating transmissibility.
  - Evaluating severity.
  - Can it be controlled?
- Mathematical models.
- Evaluating the impact of interventions.
- Preparing for a severe influenza pandemic.

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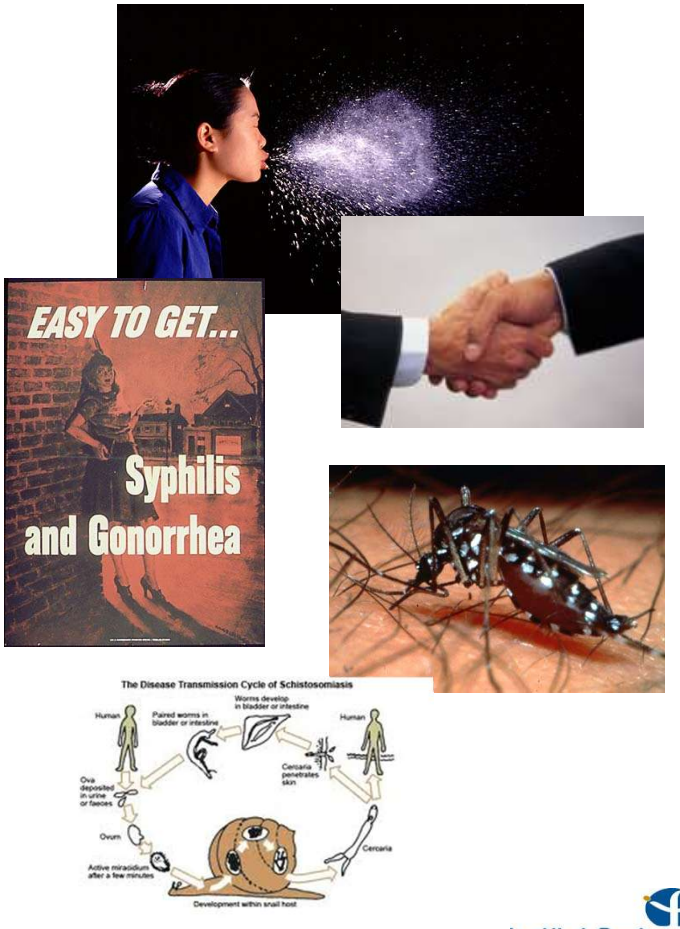
Challenges

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Challenge 1: Understanding complex epidemic dynamics

What do infectious diseases have in common? Transmission

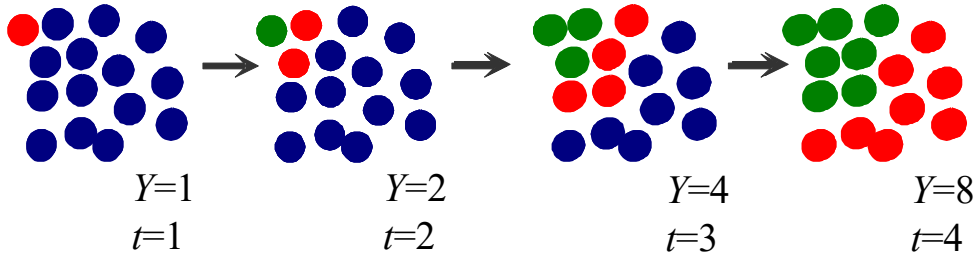
- Aerosol/droplets (measles, mumps, influenza, pertussis…).
- Sexual contact (HIV, gonorrhoea, syphilis, chlamydia, HBV).
- Intermediate hosts (schistosomiasis).
- Vectors (dengue, malaria, onchocerciasis, nosocomial infections…).

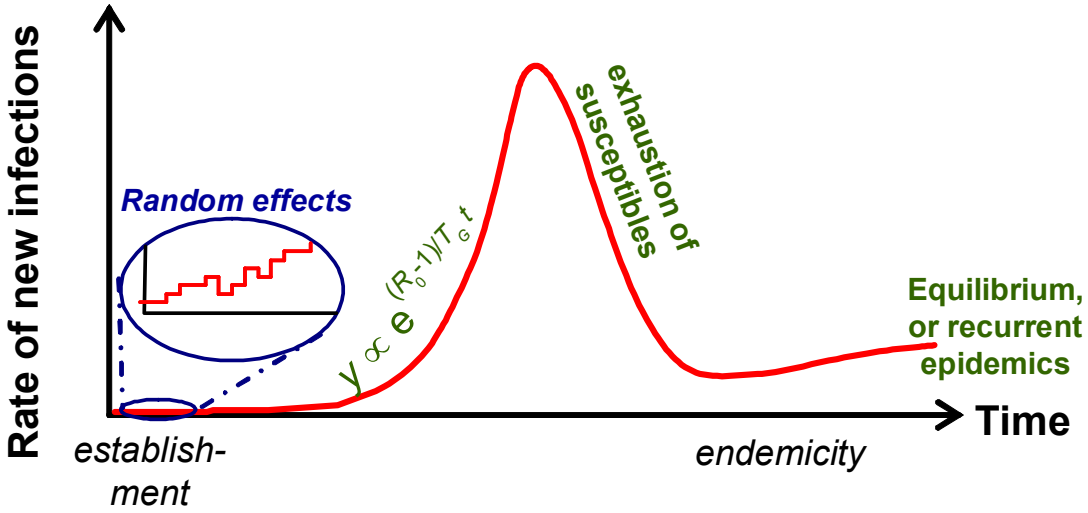


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Challenge 1: Understanding complex epidemic dynamics

- One person gets infected.
- That person infects others.
- They infect more.
- Giving a chain reaction.
- An *epidemic*.

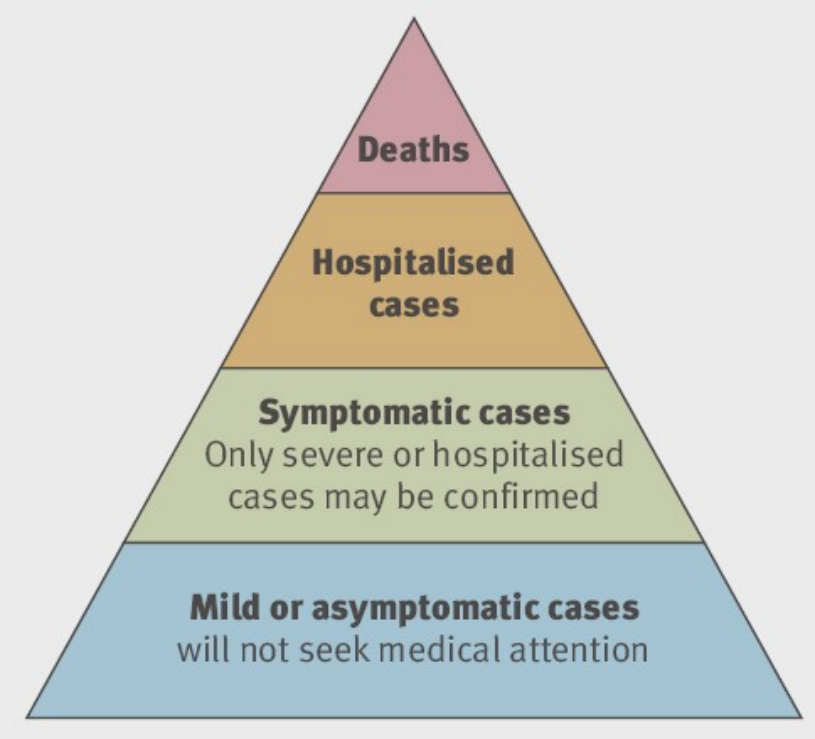




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Challenge 2: Addressing the issue of missing data

How much of the epidemic do we really see?

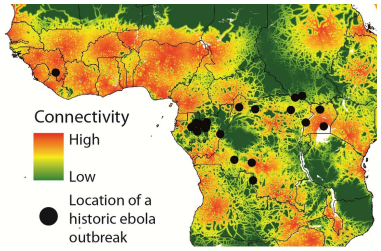


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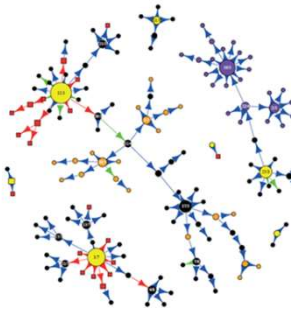
Challenge 3: Developping a multidisciplinary perspective on epidemics

Humans

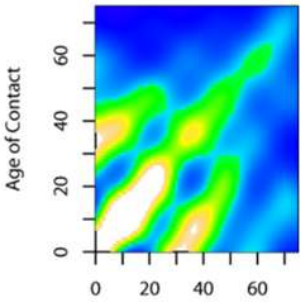
Mobility



Social networks

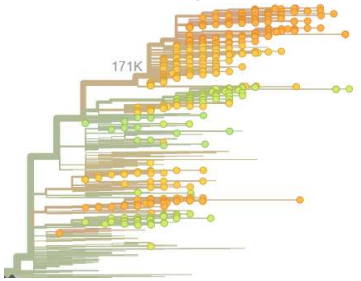


Contact patterns

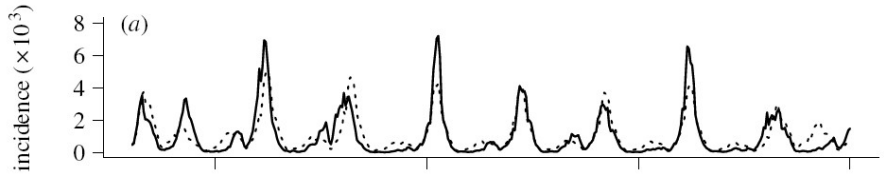


Viruses

Genetic sequences

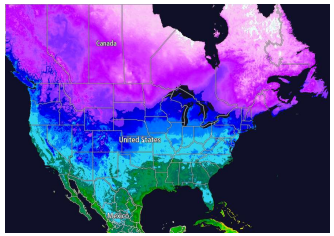


Epidemic dynamics



Climate data

Temperatures



Interventions



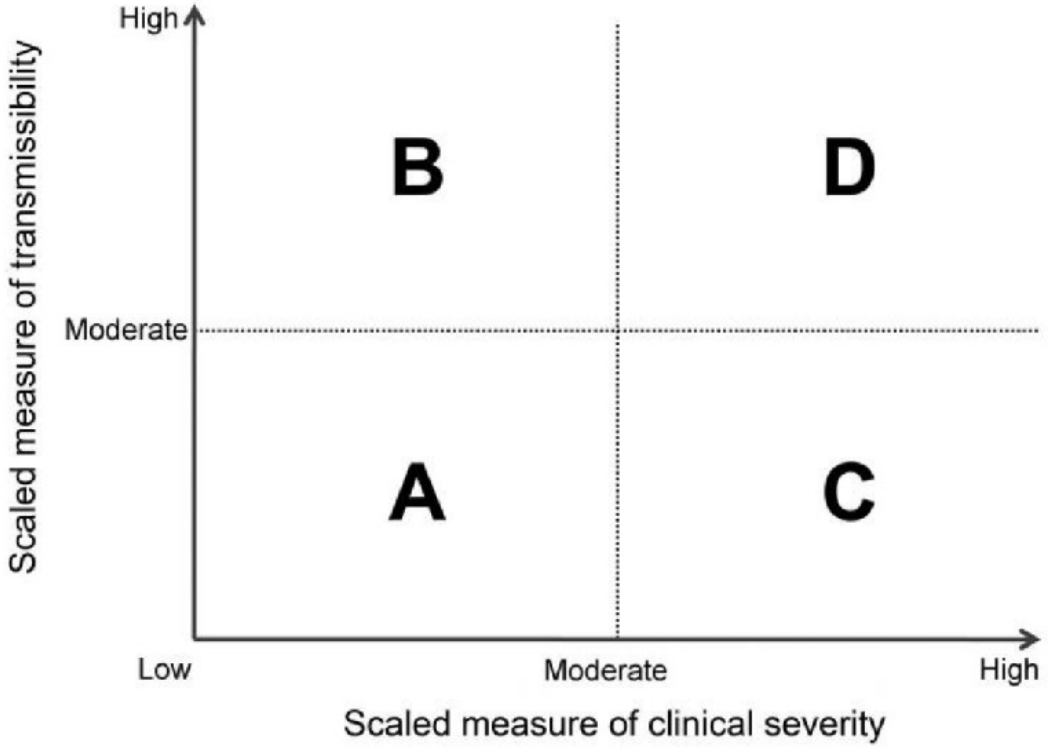
Clinical data



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Key quantities to assess pandemic impact

Transmissibility and severity



[Reed et al, MMWR 2013]

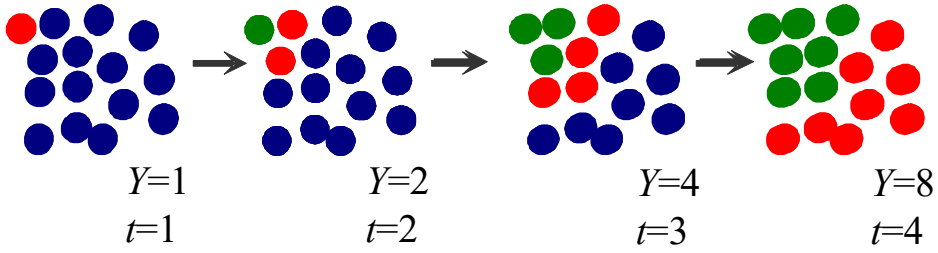
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Transmissibility

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Transmissibility

Reproduction number R - mean number of cases generated by a case.



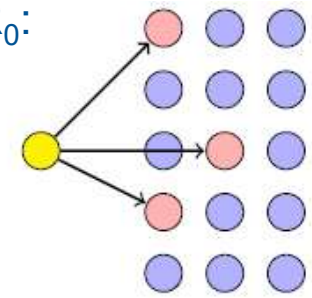
Policy questions

- Is the epidemic going to take off? Is it under control?
- What proportion of the population will be infected?
- What vaccination coverage is required to control epidemic?

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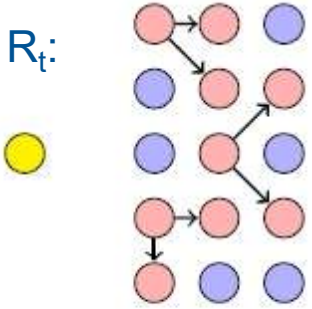
Two different reproduction numbers

Basic reproduction number R_0:
In a “theoretical” population with no immunity



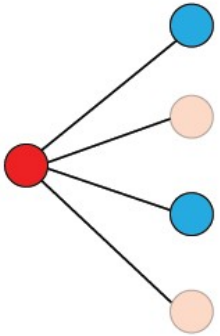
$R_0 = 3$

Effective reproduction number R_t:
At time t in epidemic



$R_1 = 2$

Susceptibility determines R_t



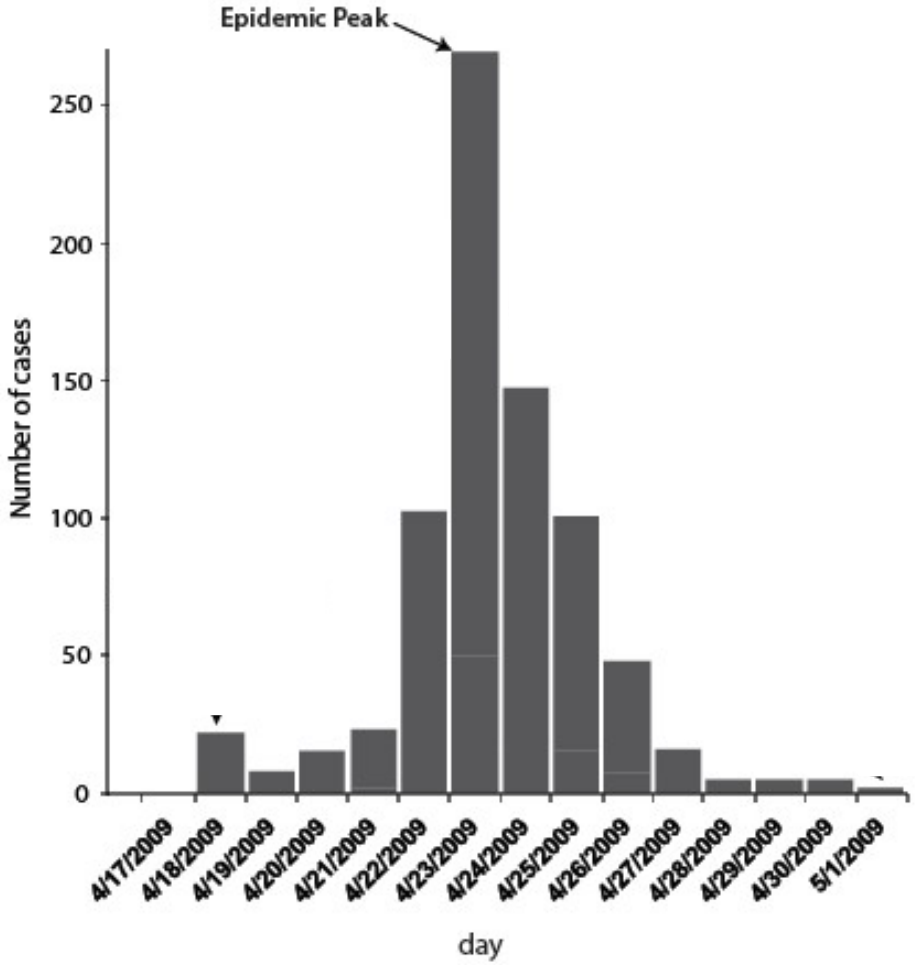
$R_t = s_t \cdot R_0$

where s_t is the proportion of susceptible

$R_t = (1-i_t) \cdot R_0$
where i_t is the proportion immunized

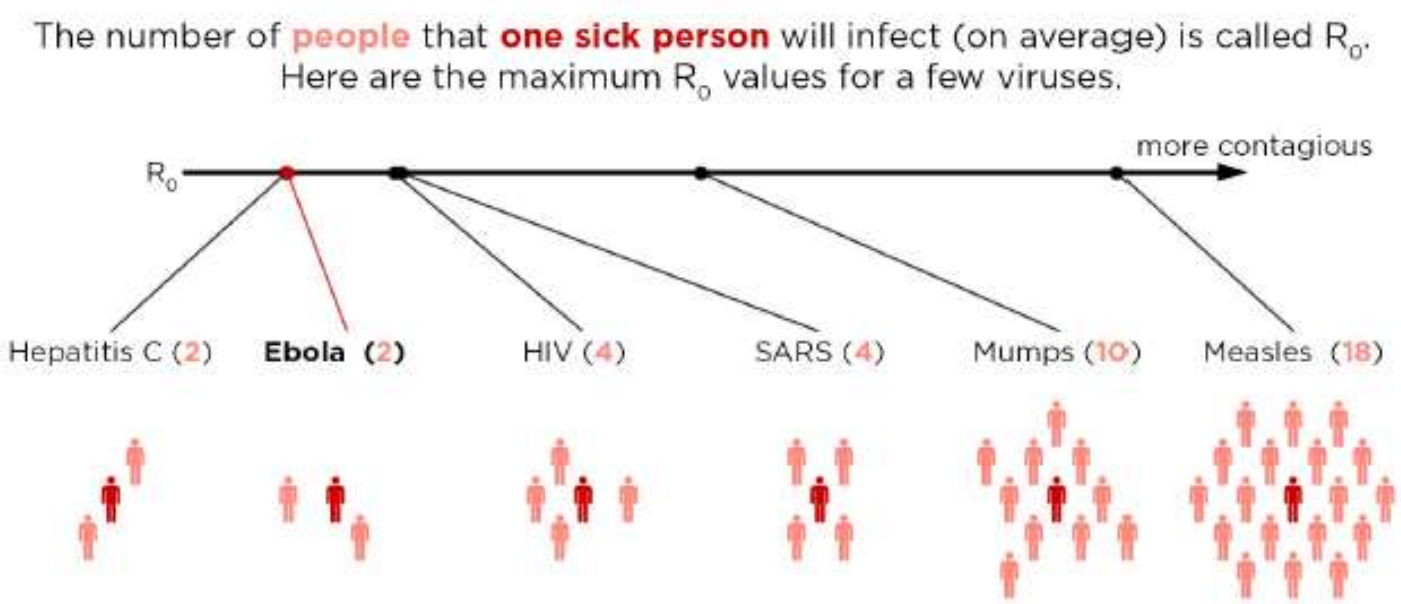
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R in the epidemic



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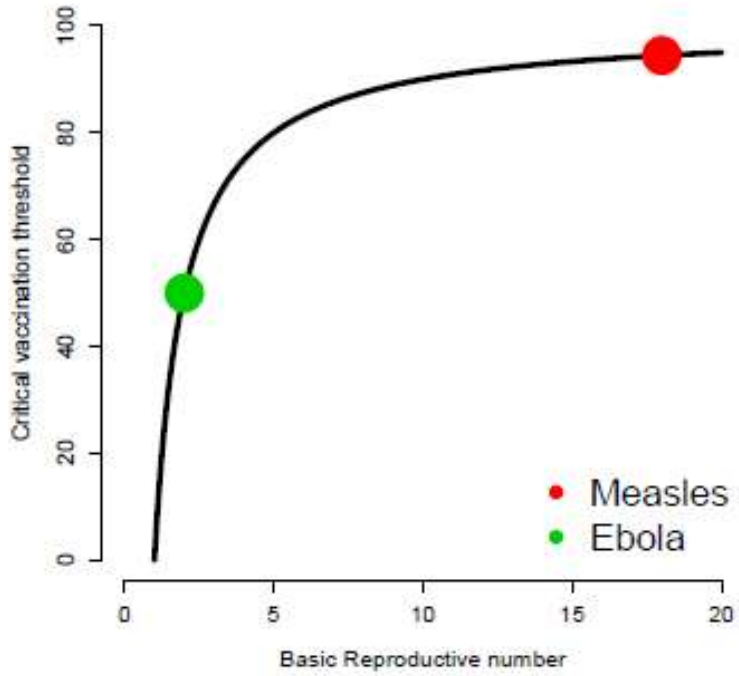
R_0 for different pathogens



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Herd immunity and the critical vaccination threshold

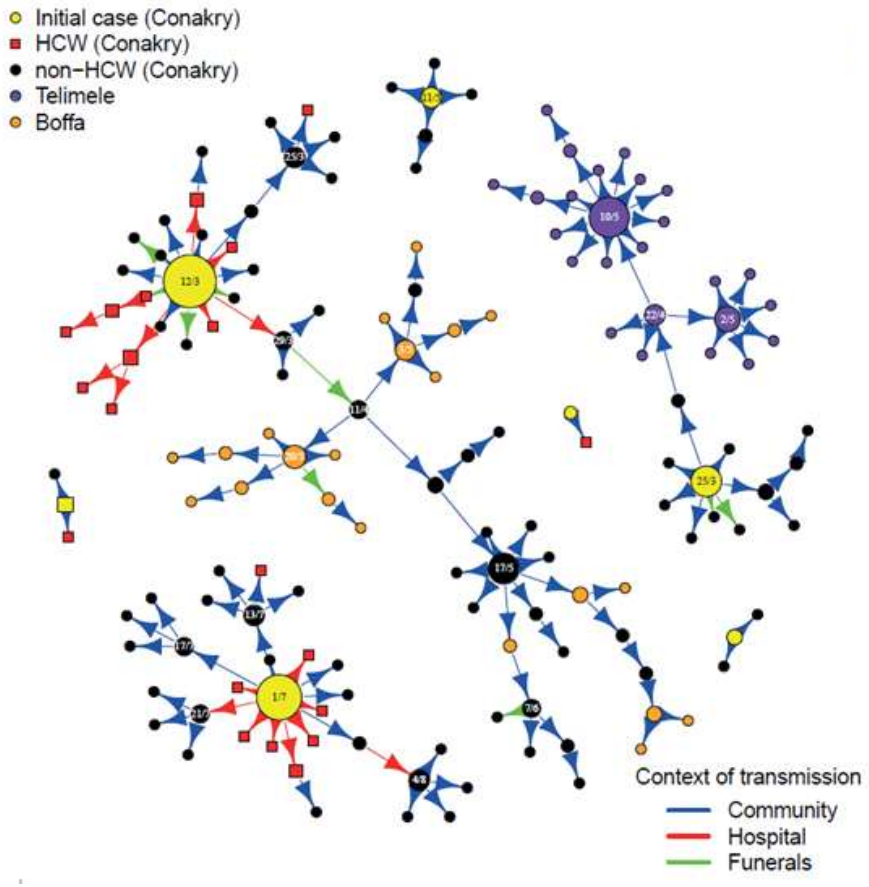
- We want R_t to drop below 1.
  $R_t = (1-i_t).\ R_0 \quad < 1 \quad$ where i_t is the proportion immunized
- The critical vaccination threshold is $V = 1 - 1/R_0$.

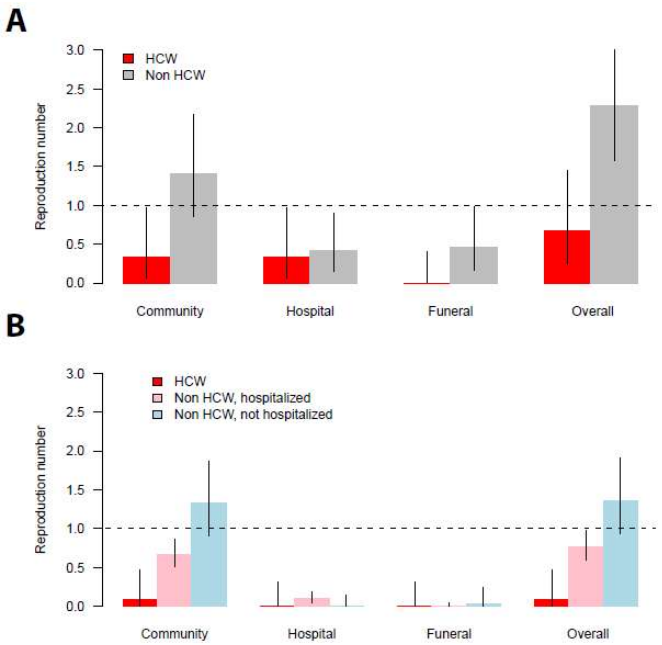


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How can we measure transmission?: Transmission trees

Chains of transmission of Ebola in Conakry, Guinea

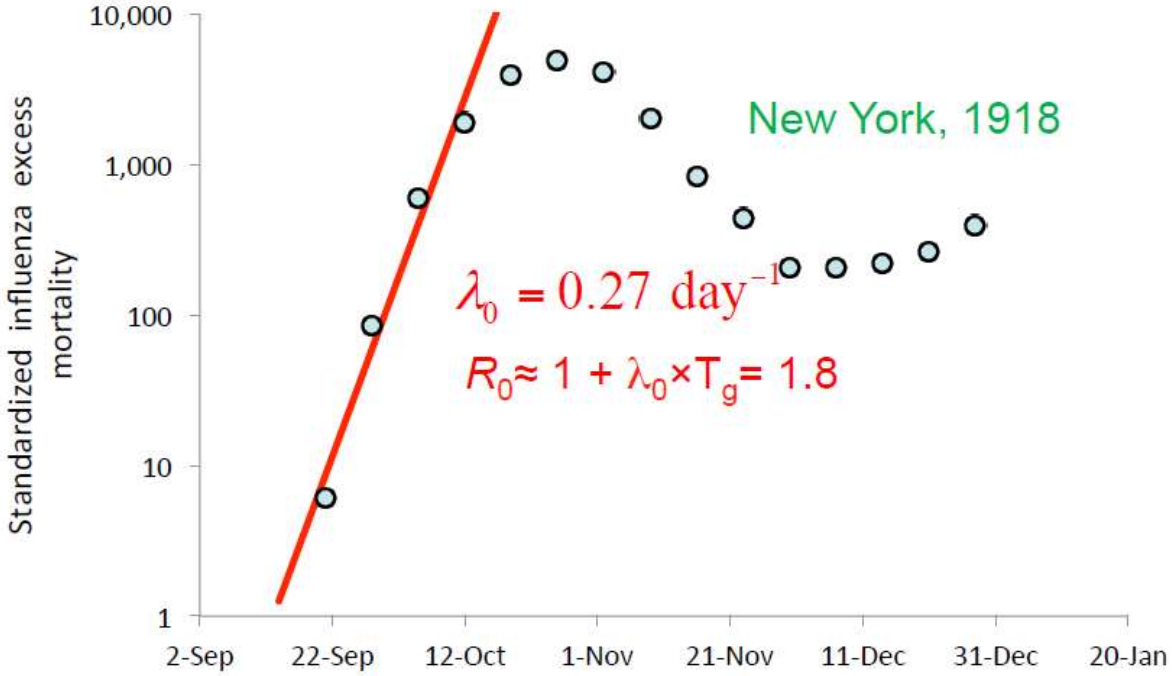


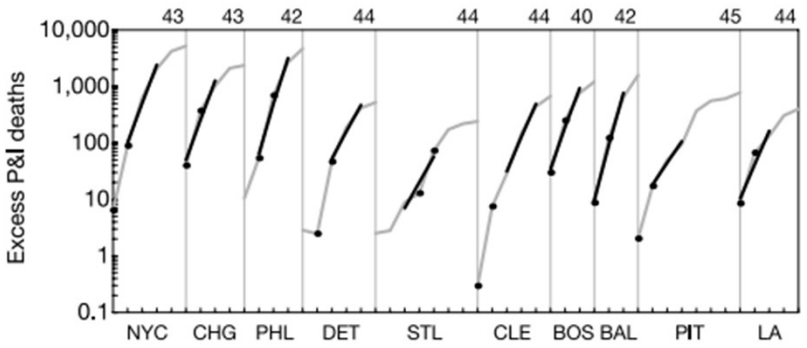


[Faye et al, Lancet ID 2015]

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How can we measure transmission?: Studying the growth in cases



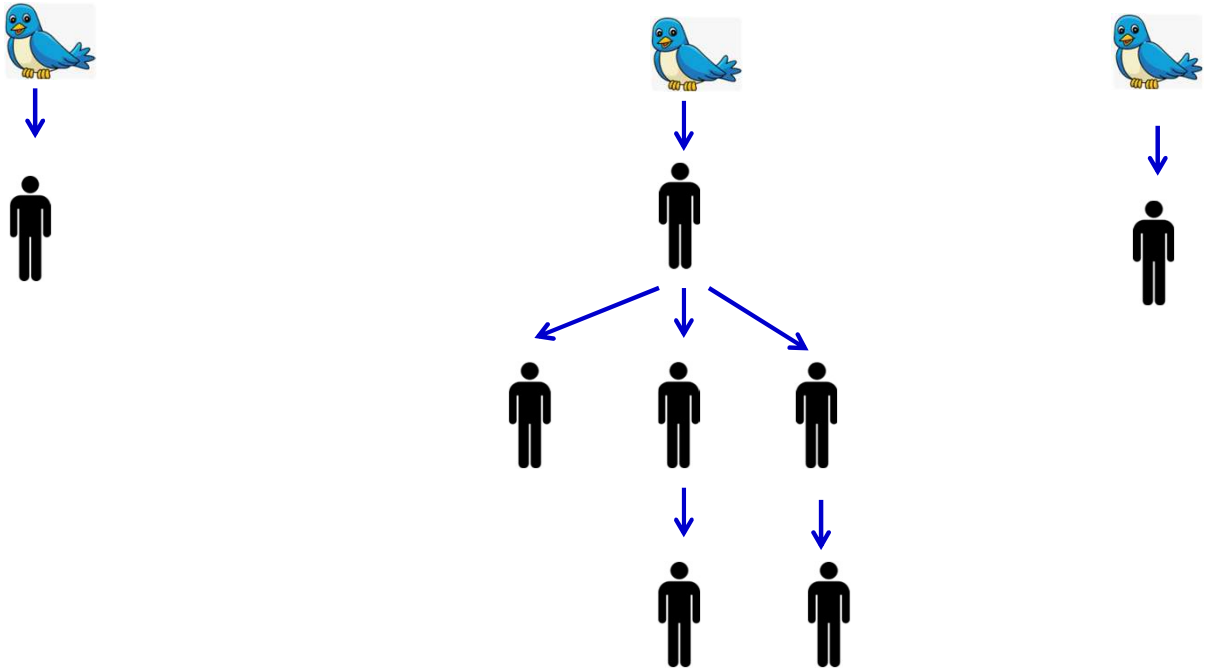


[Mills et al, Nature, 2004]

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How can we measure transmission?: Analysis of the size of human clusters

Outbreaks of zoonotic diseases such as avian influenza



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How can we measure transmission?: Analysis of the size of human clusters

Expected number of cases at different generations

	Gen. 1	Gen. 2	Gen. 3	Gen. 4 …
If R=2	1	2	4	8
General case	1	R	R^2	R^3
If R=0.5	1	0.5	0.25	0.125

Average cluster size= 1 + R + R^2 + R^3 + R^4 …

For R≥1

Infinite average cluster size

For R<1

Average cluster size=$\frac{1}{1-R}$

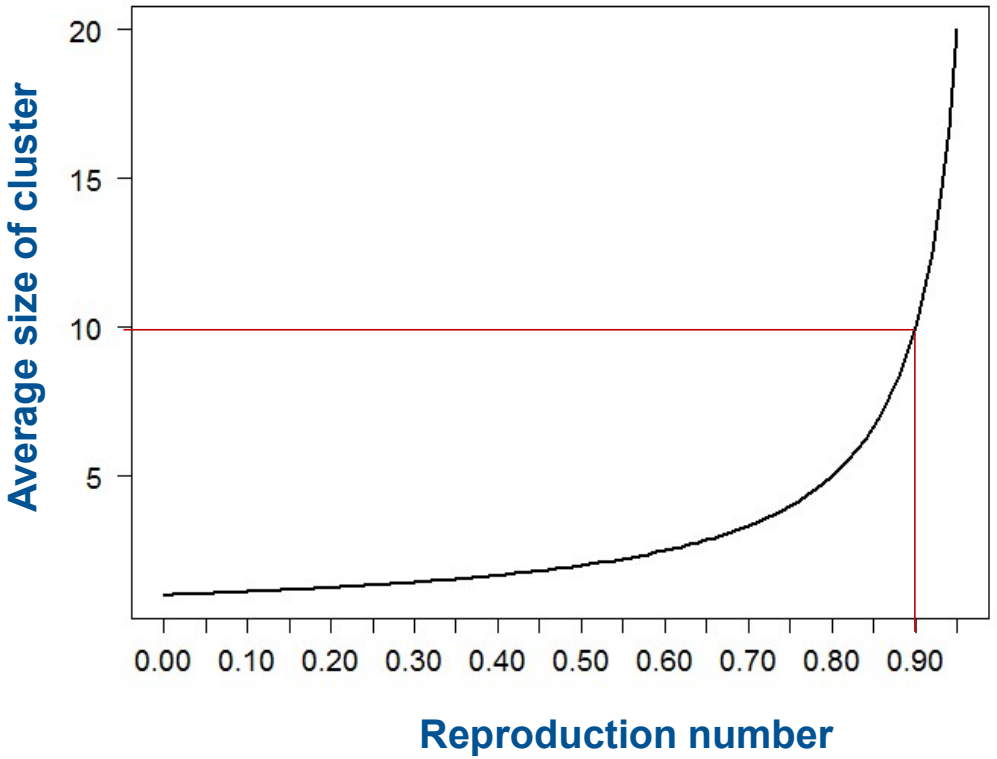
$$R = 1 - \frac{1}{s}$$

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Relationship between the average cluster size and the reproduction number

Average size S	R
2	0.5
3	0.66
4	0.75
5	0.8
10	0.9
20	0.95

$$R = 1 - \frac{1}{S}$$



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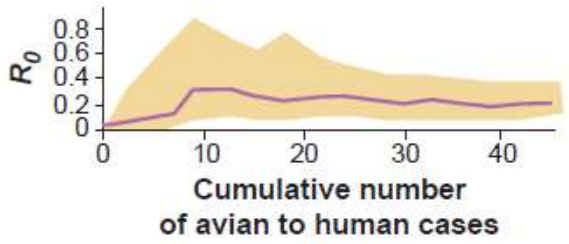
Monitoring cluster size distribution to detect changes in transmissibility

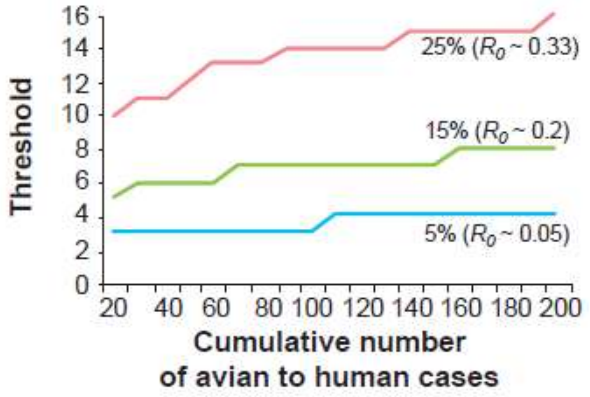
H5N1 avian influenza

POLICY FORUM

PUBLIC HEALTH

Public Health Risk from the Avian H5N1 Influenza Epidemic



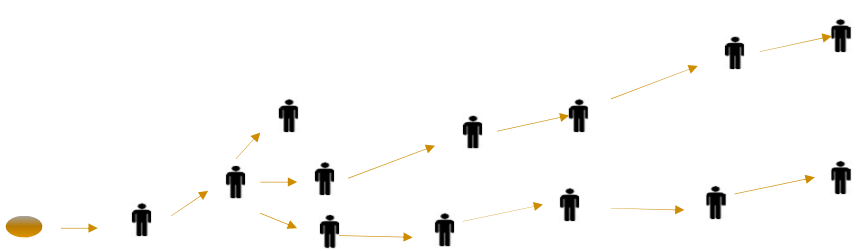


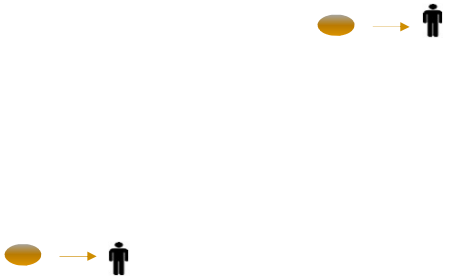
[Ferguson et al, Science, 2004]

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Limitations

- Selection bias:
  - Large clusters are more likely to be detected than small ones,
  - R may therefore be overestimated.





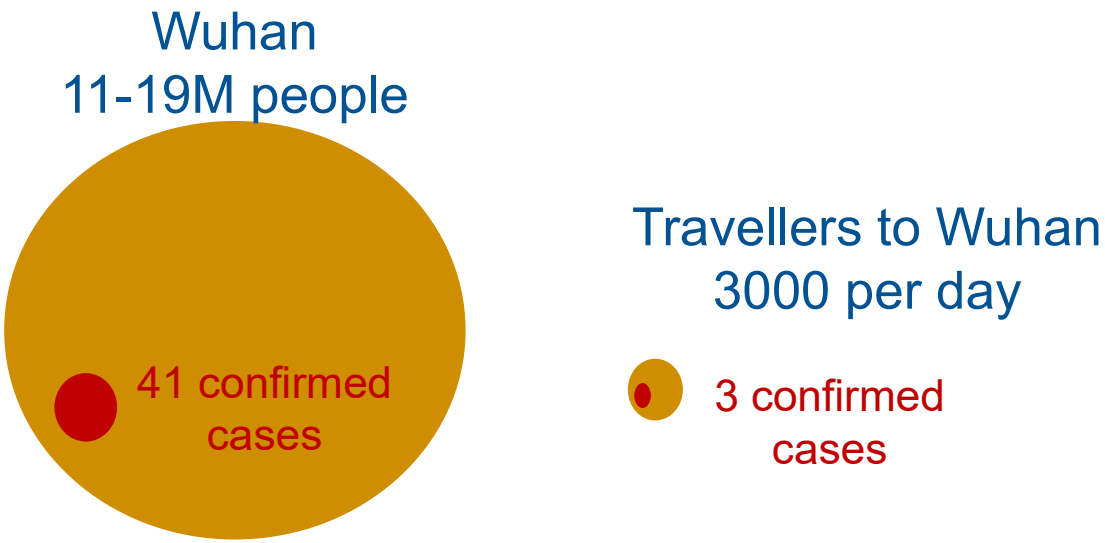
- It is not always possible to determine the cluster size
  - Possible to estimate R from proportion of cases infected in reservoir!

[Cauchemez et al, PLoS Med 2013]

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First assessments of the transmissibility of SARS-CoV-2

Jan 17th 2020



[Imperial College, Report 1]

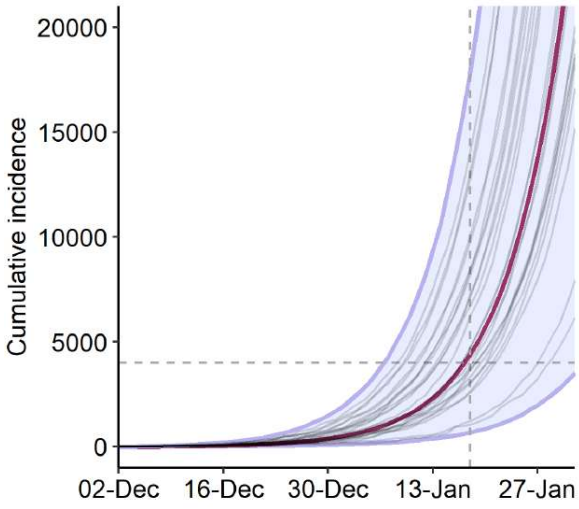
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First assessments of the transmissibility of SARS-CoV-2

Jan 22nd 2020

Imperial College

- Assumptions of 20-200 introductions from the reservoir in December
- What reproduction number R to get ~4000 cases by Jan 18th?

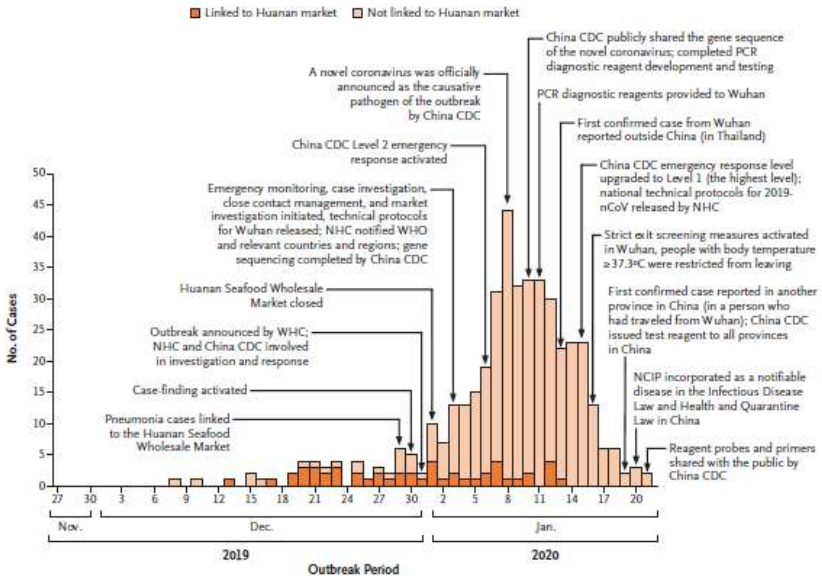


R ~2.6 [1.5-3.5]

High interhuman transmission v. likely

Jan 30th 2020

Hong Kong University



R ~2.2 [1.4-3.9]

[Li et al, NEJM 2020]

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Beyond reproduction numbers

- Reproduction numbers are an important measure of transmissibility… but it's just an average across the population.
- We need to understand who is contributing the most to transmission.
- Who is most at risk of getting infected? of transmitting if infected?

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Household transmission studies

- Households - A natural laboratory to study transmission:
  - High contact rates;
  - Well-defined and relatively small units.

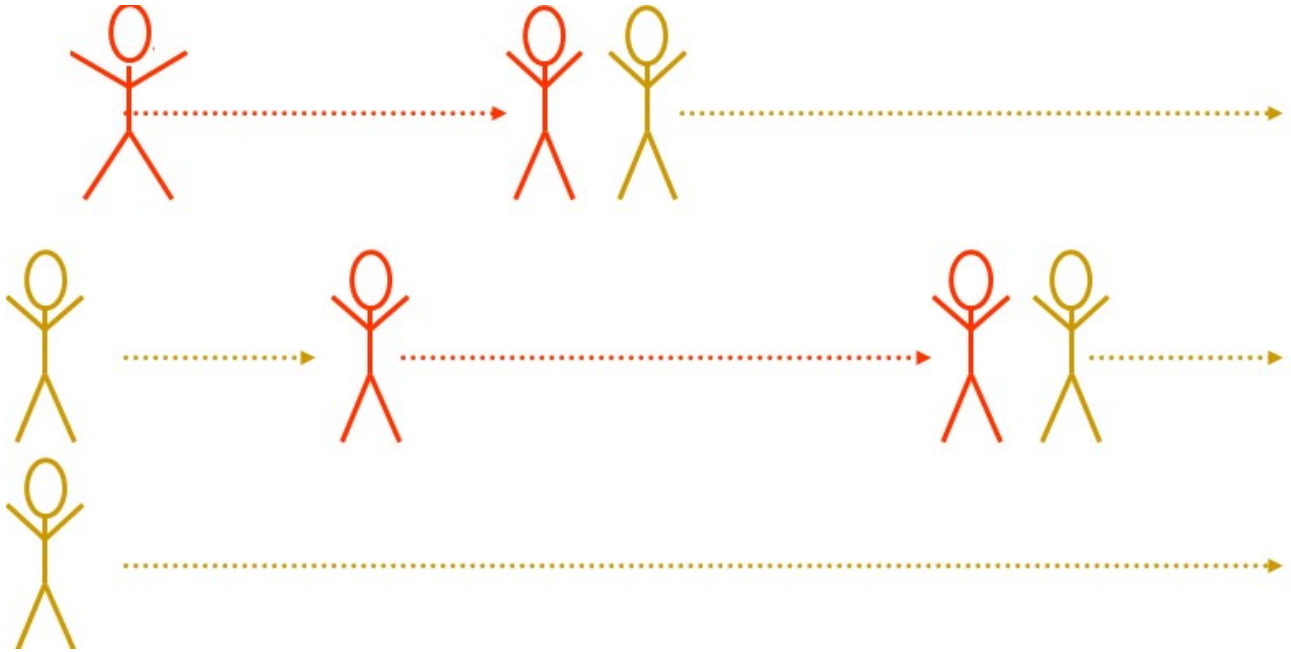
- Key source of information on key model parameters:
  - Generation times;
  - Household transmission rates;
  - Relative susceptibility/infectivity of different groups (e.g. children vs adults);
  - Impact of interventions on transmission (e.g. masks, antivirals).

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Influenza household transmission studies

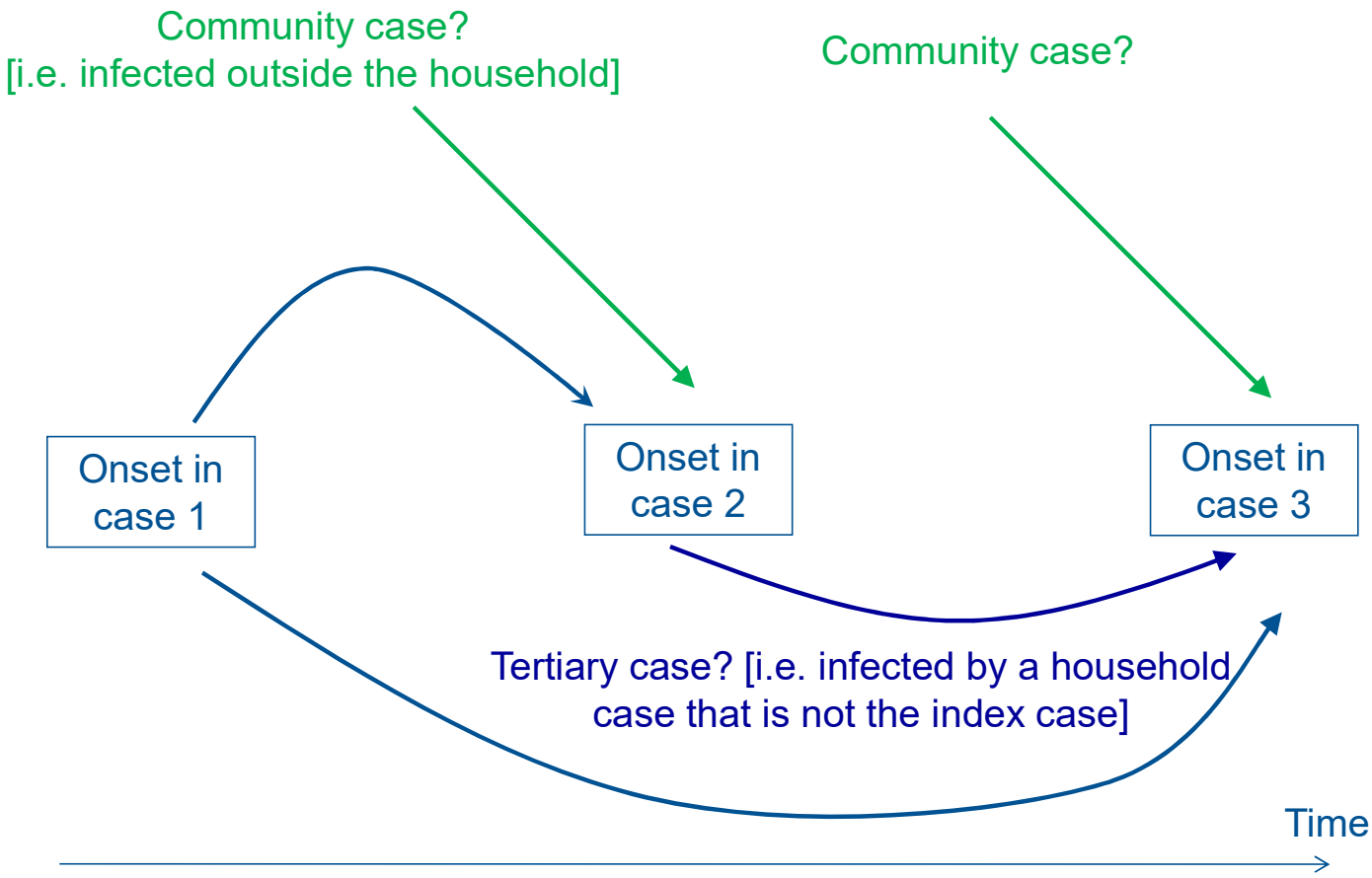
[Cauchemez et al, Stat Med, 2004; Ferguson et al, Nature 2005]

Follow-up of symptoms in 334 households for 15 days after onset in a confirmed index case



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Different routes of infection are possible…



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Modelling transmission within households

Risk of infection of individual s at time t in the household:

$$\lambda_s(t) = \alpha_s + \sum_{i \in I(t)} \beta_i$$

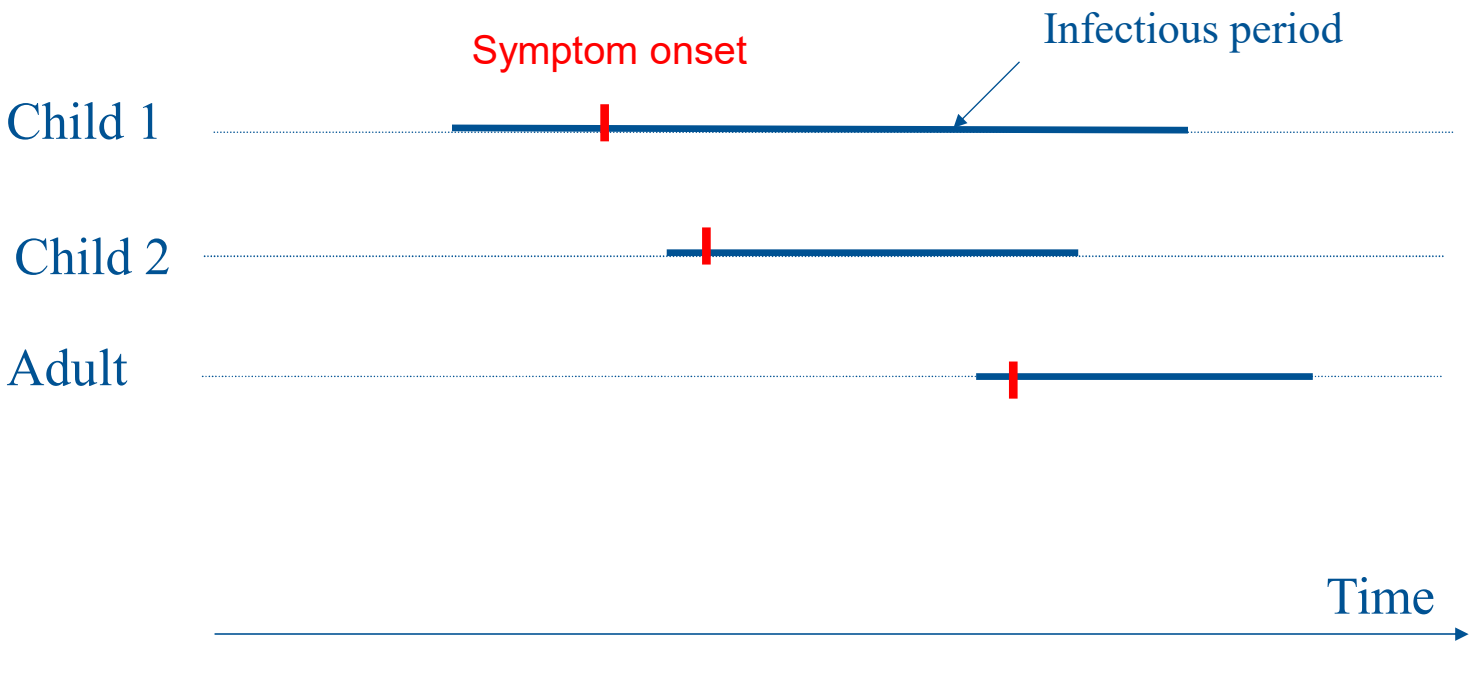
Risk of infection outside household

Risk of infection exerted by infectious household members

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Inference from incomplete data

- Infectious periods are unknown – we just observe dates of symptom onset;
- Explore trajectories consistent with data on symptoms onset.

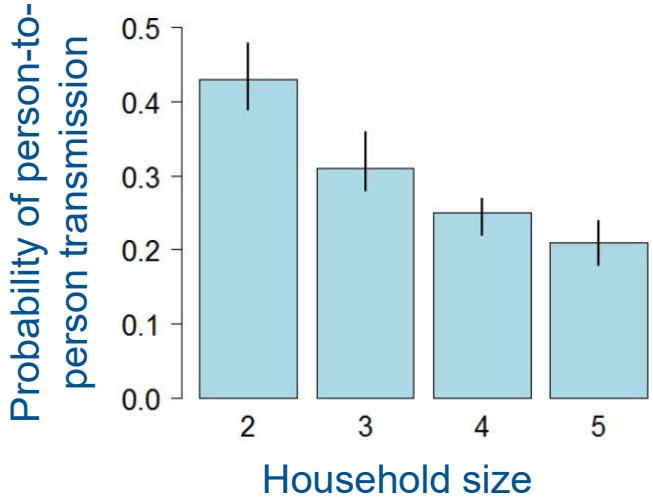


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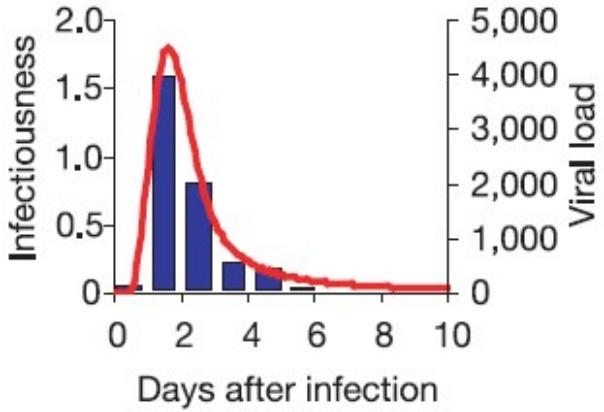
Transmission of seasonal influenza in French households

[Cauchemez et al, Stat Med, 2004; Ferguson et al, Nature 2005]

Household structure and transmission



Key transmission parameters: the generation time



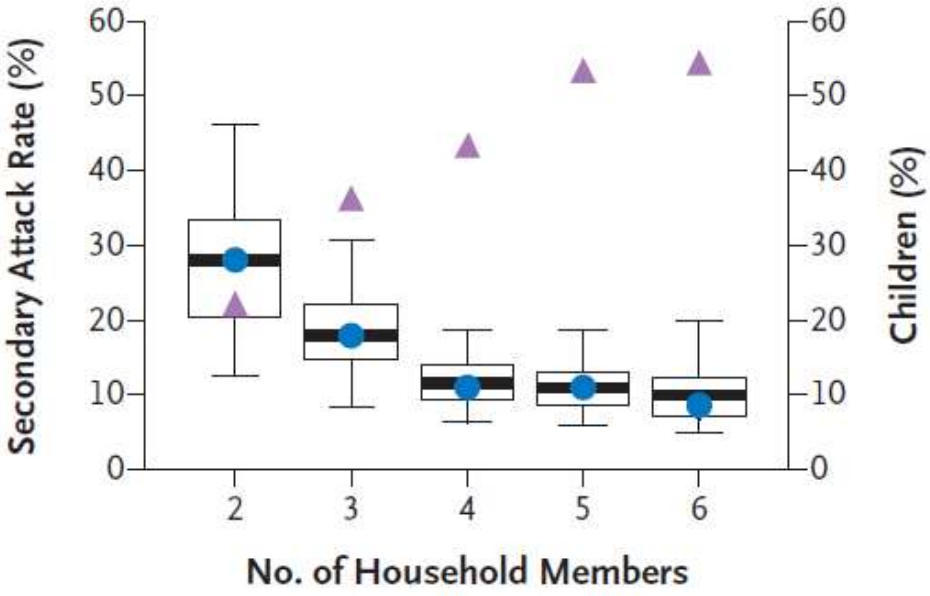
- Substantially shorter than initially thought (2.6 vs 4.1 days)
- Important implications for control

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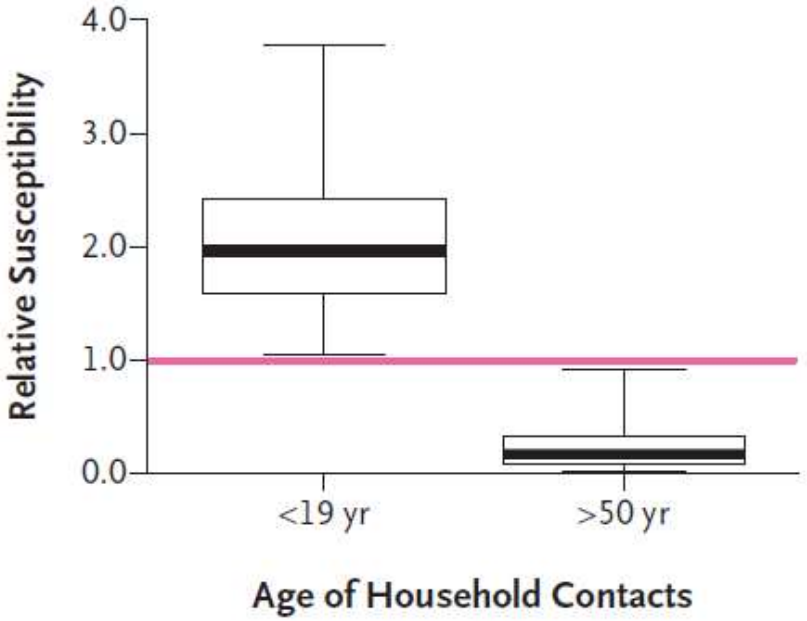
Household studies for early assessment during the 2009 H1N1 pandemic [Cauchemez et al, NEJM 2009]

Collaboration with CDC – Follow-up of 216 households for 7 days

Transmission risks within households

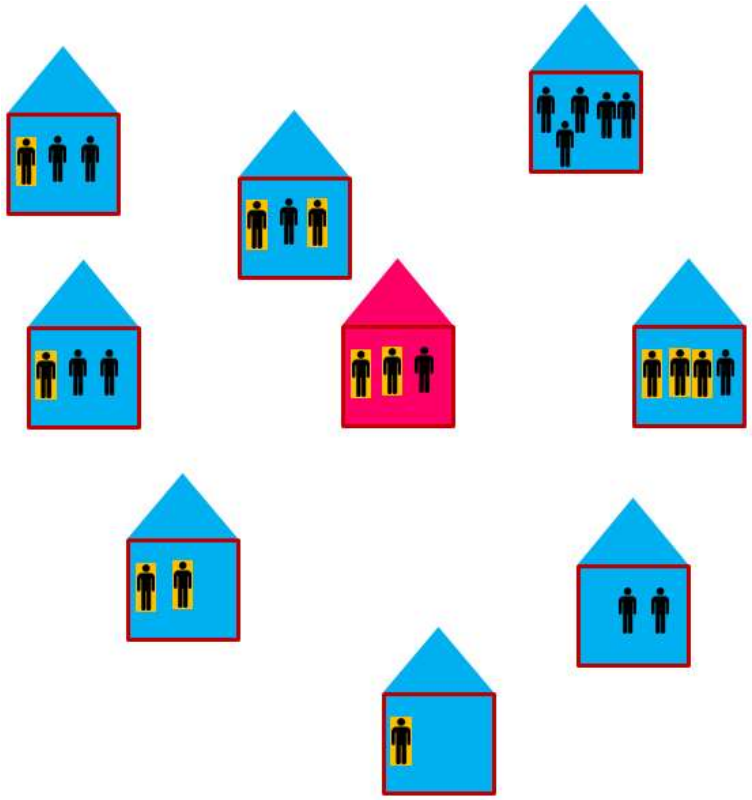


Children twice more susceptible than adults



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Households are not isolated from the rest of the world!

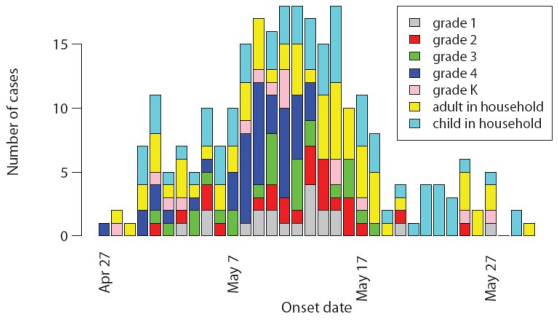


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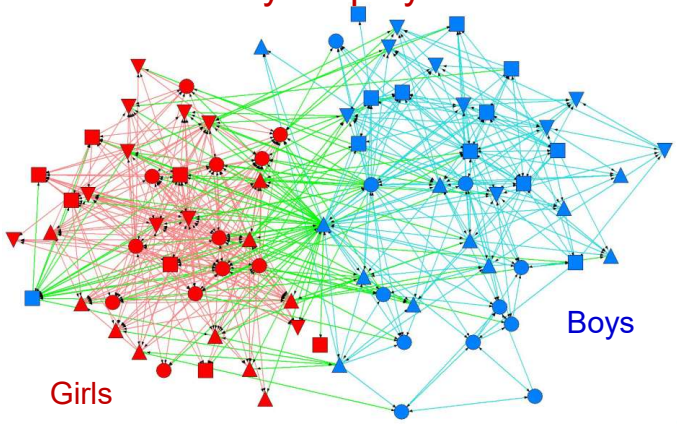
Transmission in other settings: A school outbreak of pandemic influenza in 2009 [Cauchemez et al, PNAS, 2011]

- Demographic & clinical information collected on students and their family members – 2 phone interviews:
  - 370 students,
  - 899 household members.
- Surveys in school for 4th graders:
  - Activities,
  - Seating charts,
  - Playmates.

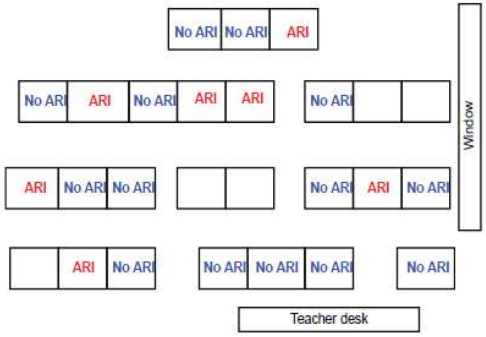
Epidemic curve



Social networks - Who are your playmates?

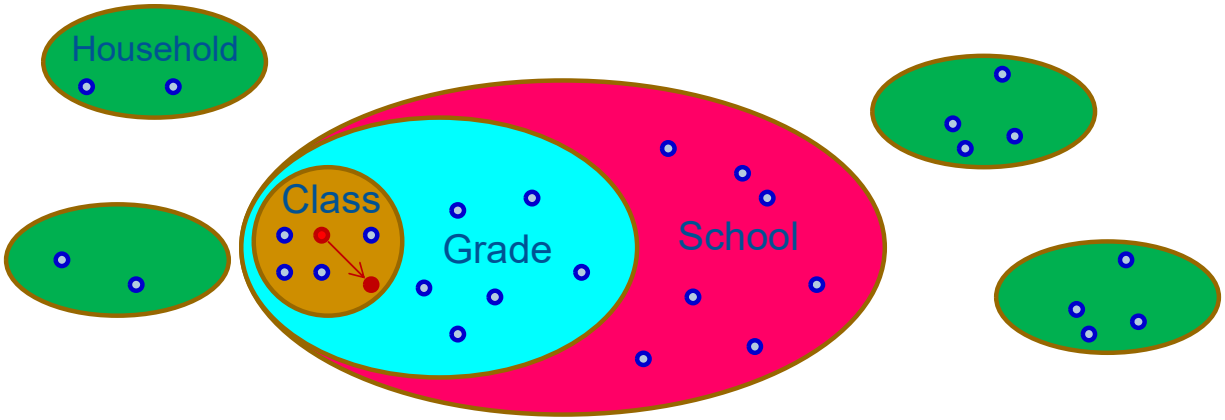


Seating charts



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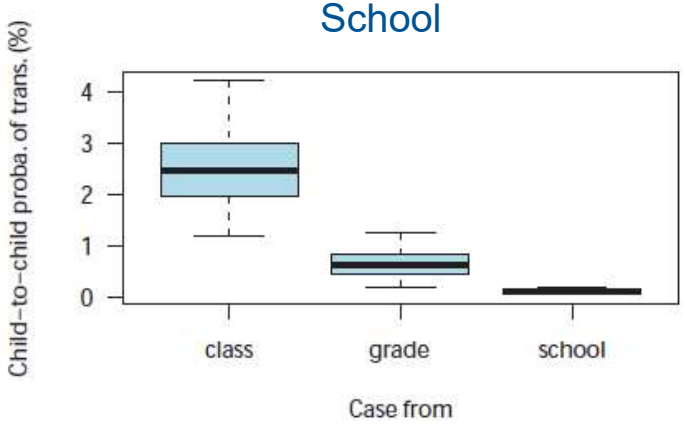
Statistical model



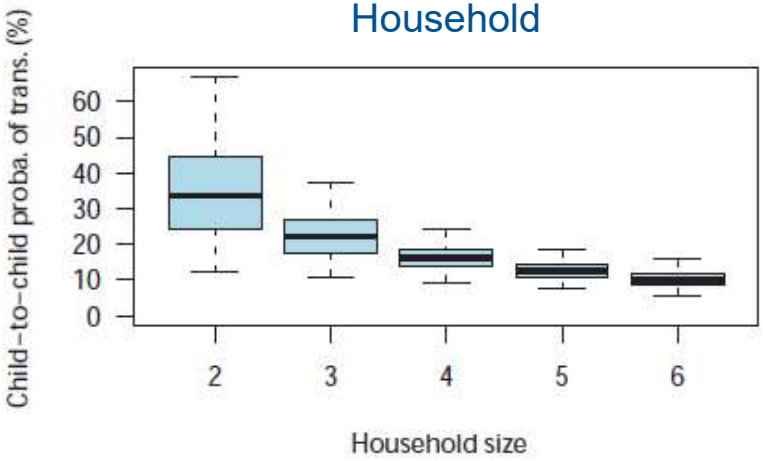
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Transmission rates in the school and in the household

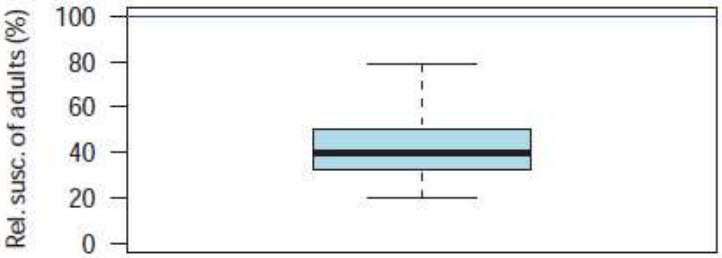
School



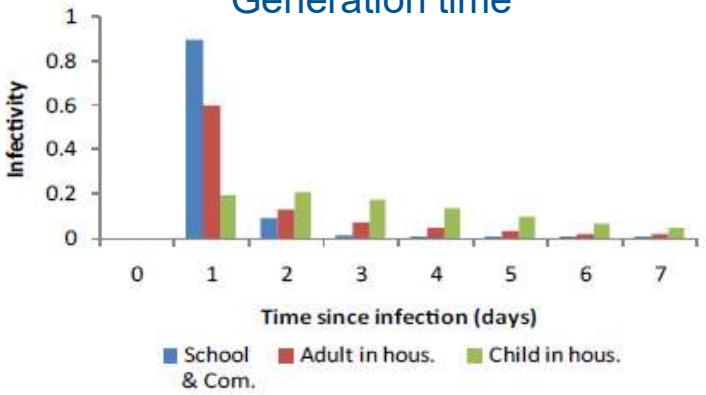
Household



Age dependent susceptibility



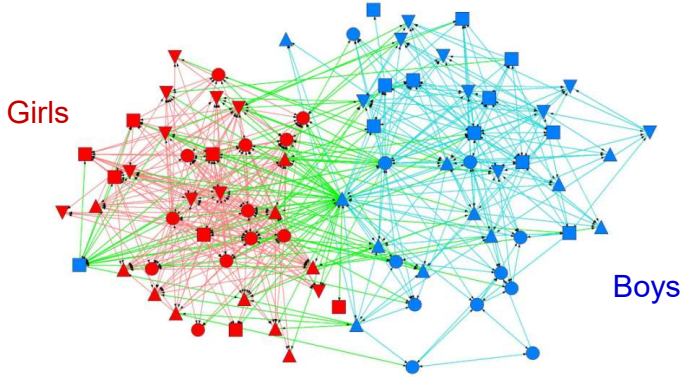
Generation time



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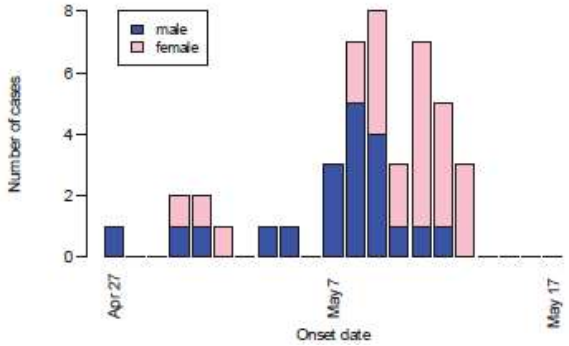
Gender-related mixing & transmission patterns

Social networks: Students are 4 times more likely to play with students of the same gender

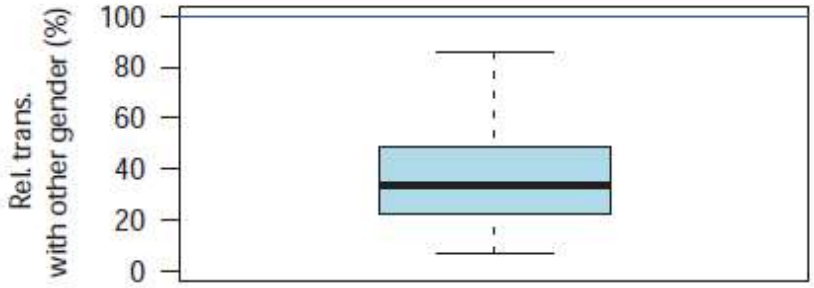


Evidence that this aspect of mixing patterns affected the transmission dynamics

i) Boys had onset before girls! (p=0.023)



ii) Bayes Factor for model with gender-effect: 8.0

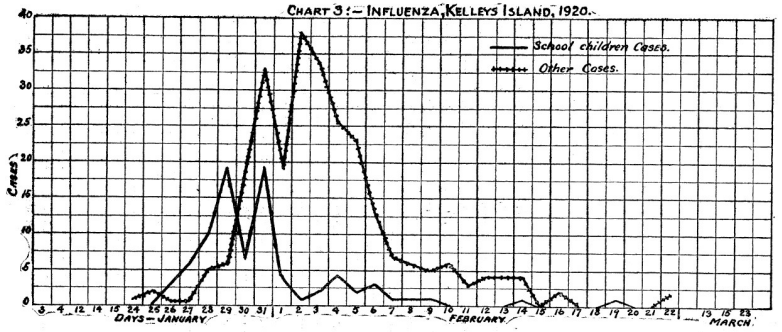


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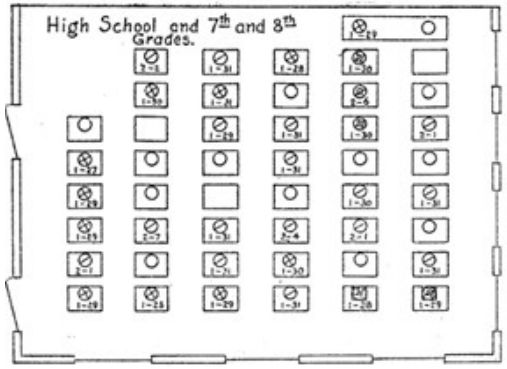
Was influenza transmission different 100 years ago? Pandemic flu in Kelly Island, 1920 (C. Armstrong)

- Isolated island, 689 inhabitants;
- Epidemic period: 24 Jan – 16 Feb 1920.
- Investigation begins 19 Feb 1920.
- Demographic, clinical and contact information collected on the 689 inhabitants of the island.

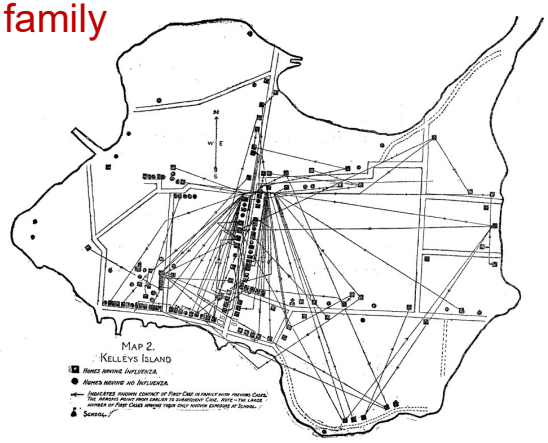
Epidemic curves



Seating charts



Known contact for first case in family



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Additional difficulty: Individual records have been destroyed

- No individual level records available, even after Armstrong's daughter examined his personal effects.
- However, some person specific, and a lot of marginal data available in the paper.
- Reconstructing individual data from aggregated data.

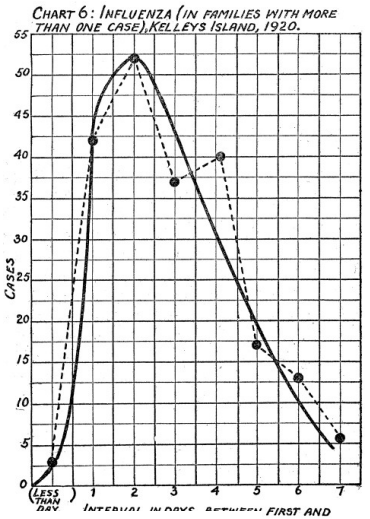
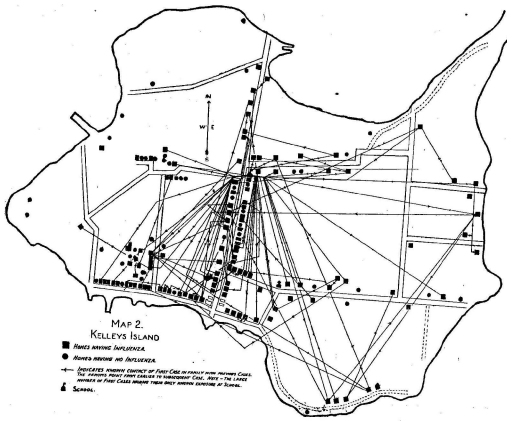
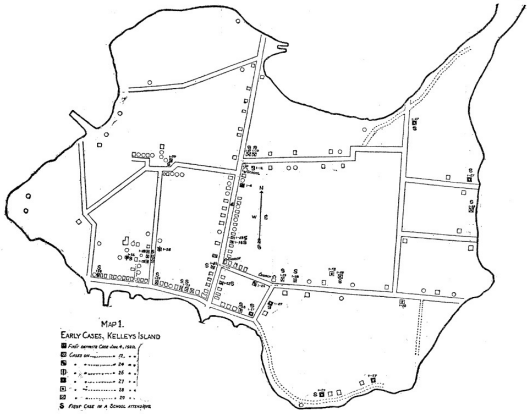


TABLE XIII.—*Summary of 27 known contacts followed by influenza, Kelleys Island, 1920.*

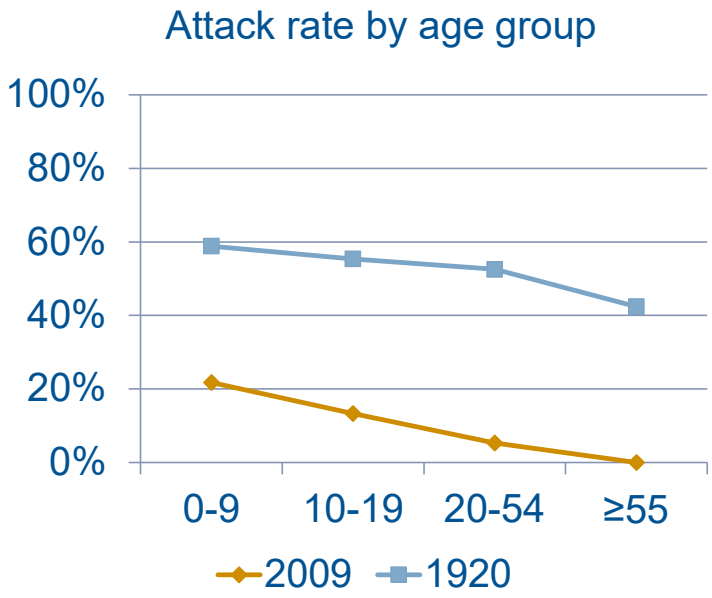
Home No.	Age.	Sex.	Date of exposure. From—	Date of exposure. To—	Date of onset.	Interval in days.	Day of illness of the case to which exposed.	Nature of contact.
2	46	F.	Jan. 28	.....	Feb. 1	4	1st.....	Visiting cases.
20	42	M.	Jan. 28	Jan. 29	Jan. 31	2-3	1st.....	Associated with ill persons at a dance.
21	66	F.	Feb. 2	.....	Feb. 4	2	2d, 3d, and 4th.	Visiting cases.
33	21	M.	Feb. 1	.....	Feb. 2	1	1st, 2d, and 3th.	Do.
35	70	F.	Jan. 31	Feb. 3	Feb. 3	0-3	1st, 2d, and 3d.	Caring for cases.
37	28	M.	Feb. 2	.....	Feb. 3	1	2d.....	Visiting cases.
41	24	F.	Jan. 29	.....	Jan. 31	2	1st.....	Associated with ill persons at a dance.
42	26	F.	Jan. 29	.....	Jan. 30	1	1st.....	Gave violin lessons to ill boy.
43	34	F.	Jan. 29	.....	Jan. 30	1	1st.....	Kissed and visited with ill nephew.
44	54	M.	Jan. 27	Jan. 29	Jan. 29	0-2	1st.....	Visiting cases.
45	19	M.	Jan. 29	.....	Feb. 2	4	1st and 2d...	Do.
46	22	F.	Jan. 29	.....	Feb. 1	3	1st.....	Associated with ill at a dance.
48	56	F.	Jan. 29	.....	Jan. 31	2	1st.....	Do.
51	36	M.	Jan. 31	Feb. 2	Feb. 3	1-3	1st.....	Visiting and caring for cases.
56	58	F.	Feb. 4	.....	Feb. 7	3	1st, 2d, and 3d.	Caring for cases.
76	34	M.	Jan. 29	.....	Feb. 1	3	1st and 2d...	Visiting cases.
79	32	F.	Jan. 30	.....	Jan. 31	1	1st, 2d, and 3d.	Caring for cases.
81	35	F.	Jan. 24	.....	Jan. 27	3	.....	Visiting cases.
82	34	M.	Jan. 18	Jan. 29	Jan. 31	2-3	1st.....	Visited and had refreshments at home of ill.
101	28	F.	Feb. 2	.....	Feb. 3	1	1st.....	Visited cases.
104	60	F.	Feb. 5	.....	Feb. 7	2	6th and 7th..	Do.
121	24	F.	Jan. 30	Feb. 1	Feb. 3	2-4	1st and 2d...	Caring for cases.
147	35	F.	Jan. 30	Feb. 3	Feb. 3	0-4	1st, 2d, 3d, and 4th.	Do.
152	37	F.	Feb. 3	.....	Feb. 4	1	1st, 2d, and 3d	Visiting cases.
154	24	F.	Jan. 31	Feb. 1	Feb. 2	0-1	1st.....	Husband returned from mainland ill.
156	25	M.	Feb. 14	Feb. 16	Feb. 16	0-2	1st, 2d, and 3d	Caring for cases.
160	43	F.	Feb. 2	.....	Feb. 3	1	2d.....	Visiting cases.



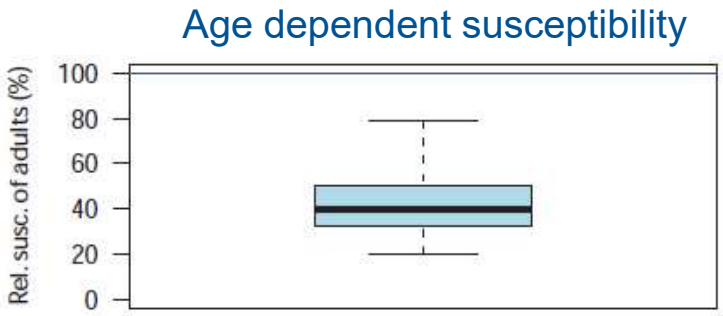


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Attack rates by age group



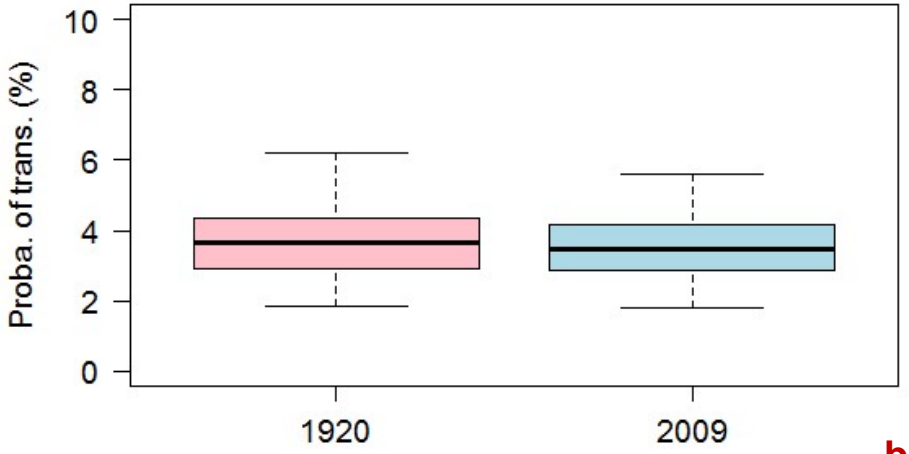
2009



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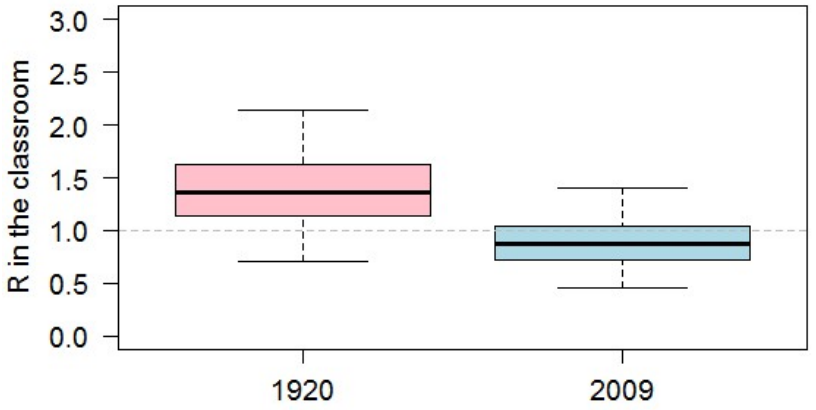
Probability of transmission in the classroom

Same probability of transmission…



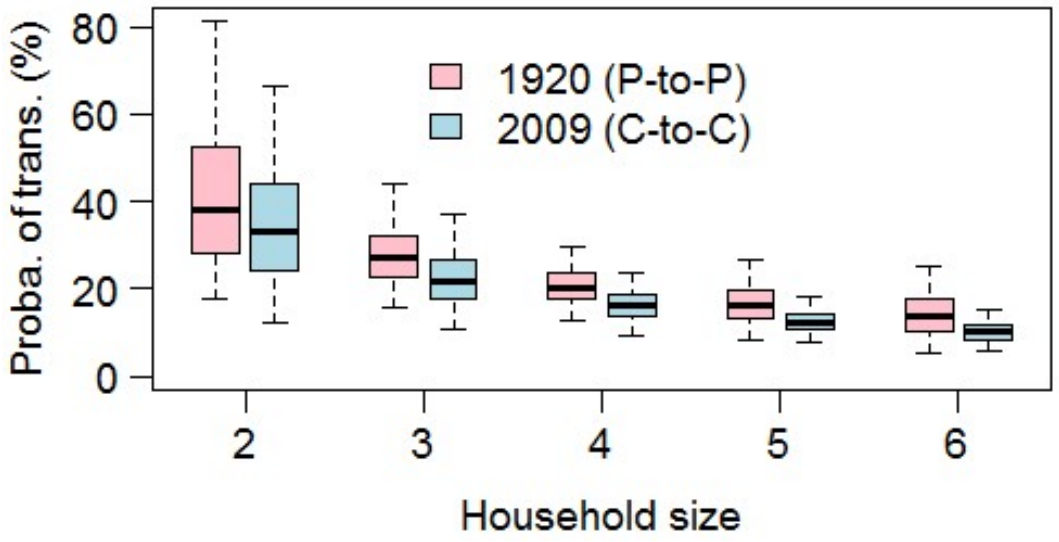
	Average number of children per class
1920	39
2009	25

… but more children per classroom



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Probability of transmission in the household



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Assessing transmissibility

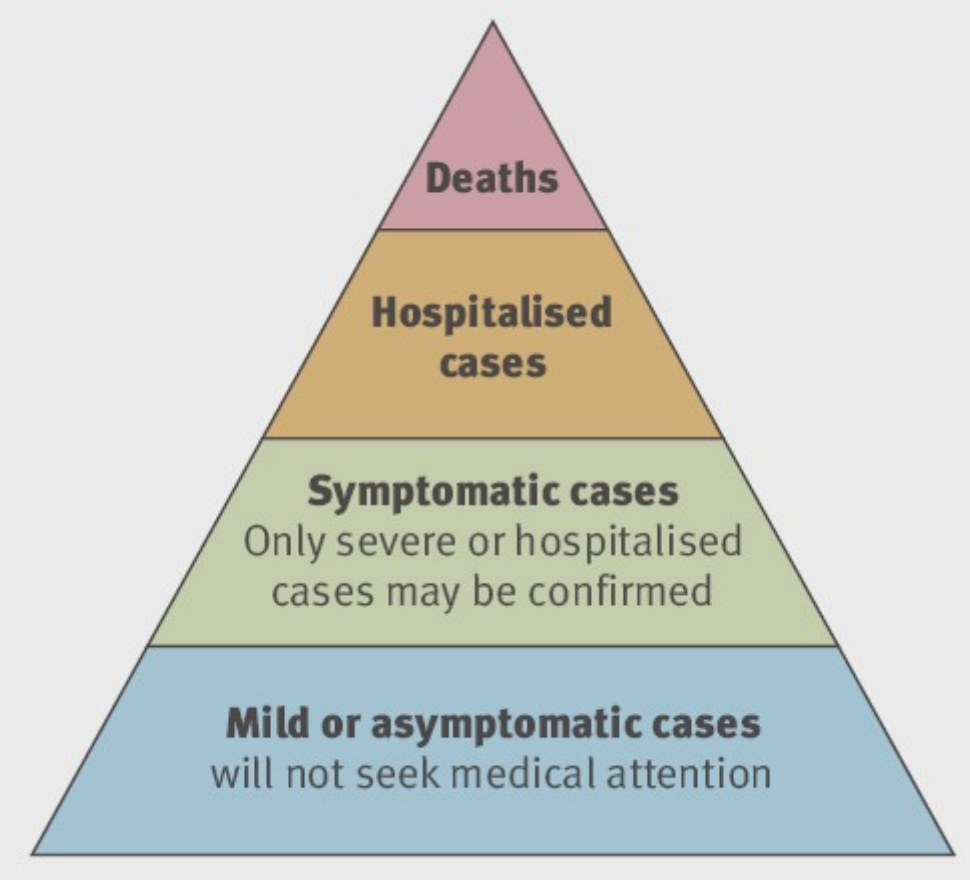
- Estimating reproduction numbers from
  - Chains of transmission (rarely)
  - Growth in cases
  - Cluster sizes
  - …
- Assessing key transmission characteristics from transmission studies in households and other environments:
  - Relative contribution of different groups to transmission
  - Generation times
  - …

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Severity

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The severity pyramid



At beginning of an emergence:

- We can usually quickly ascertain transmissibility.
- Biggest uncertainty is on severity.

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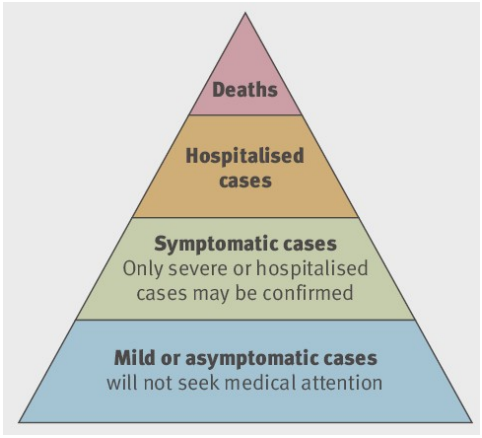
The 2009 H1N1pdm09 influenza pandemic: What was the severity of infection? [Fraser et al, Science 2009]

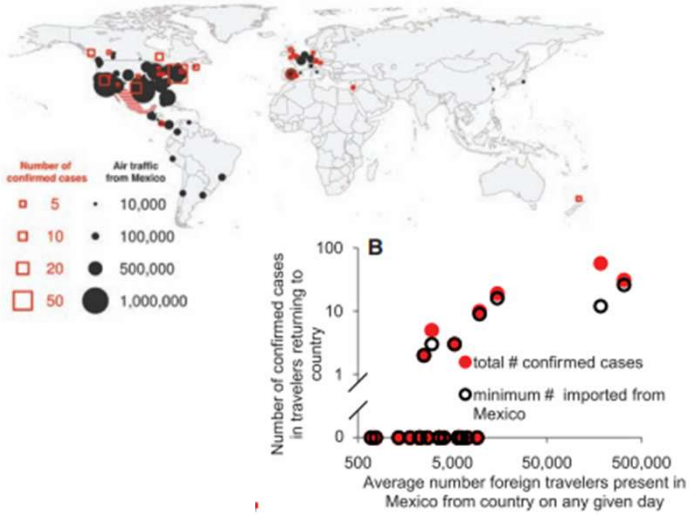
- Early Mexican data:
  - ~100 deaths
  - ~12,000 identified cases.

  → Naive Case Fatality Ratio~0.8-0.9%

- How many infections do we miss?

- Analysis of travellers data:
  - Cases in international travellers more likely picked up by surveillance.
  - Reconstructing true size of the epidemic in Mexico from the number of cases in travellers, passenger flows and durations of stay.
  - Assumption same risk of infection in travellers than in local population.
  - Estimated about ~26,000 local infections.
  - Still overestimated CFR…





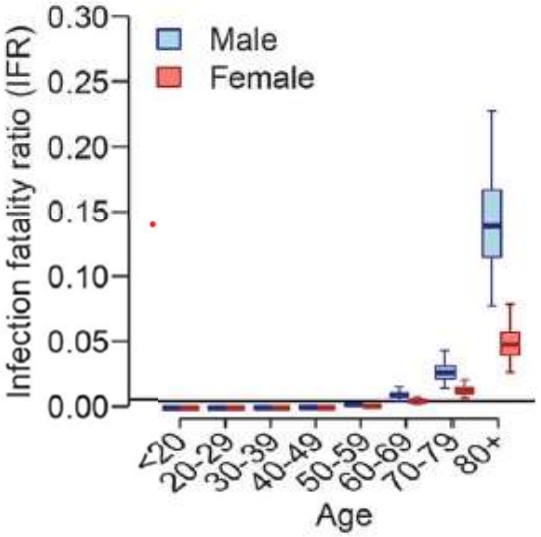
Population at-risk of severe outcome

Zika & microcephaly – Infants



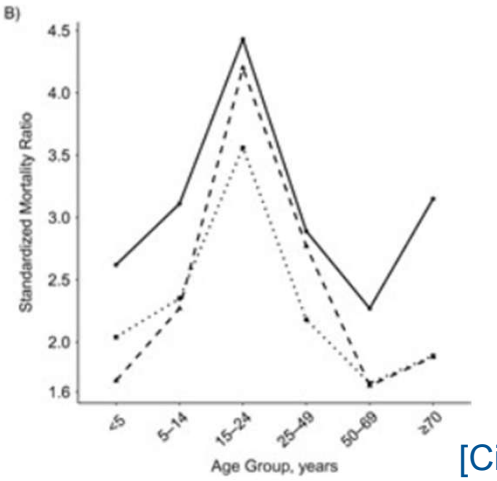
[Cauchemez et al, Lancet 2016]

COVID19 – Elderly people and people with comorbidities



[Salje et al, Science 2020]

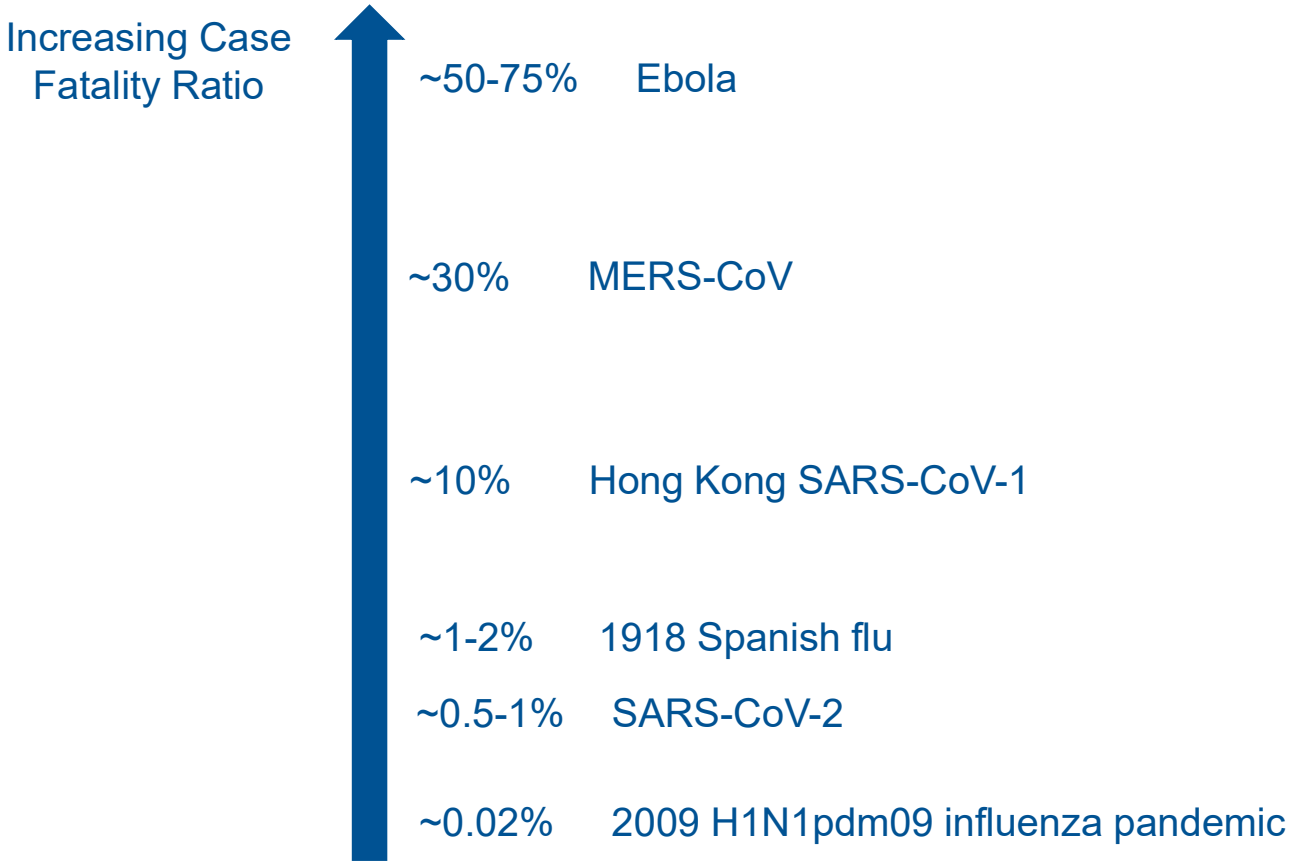
1918 influenza pandemic – young adults



[Cilek et al, AJE 2018]

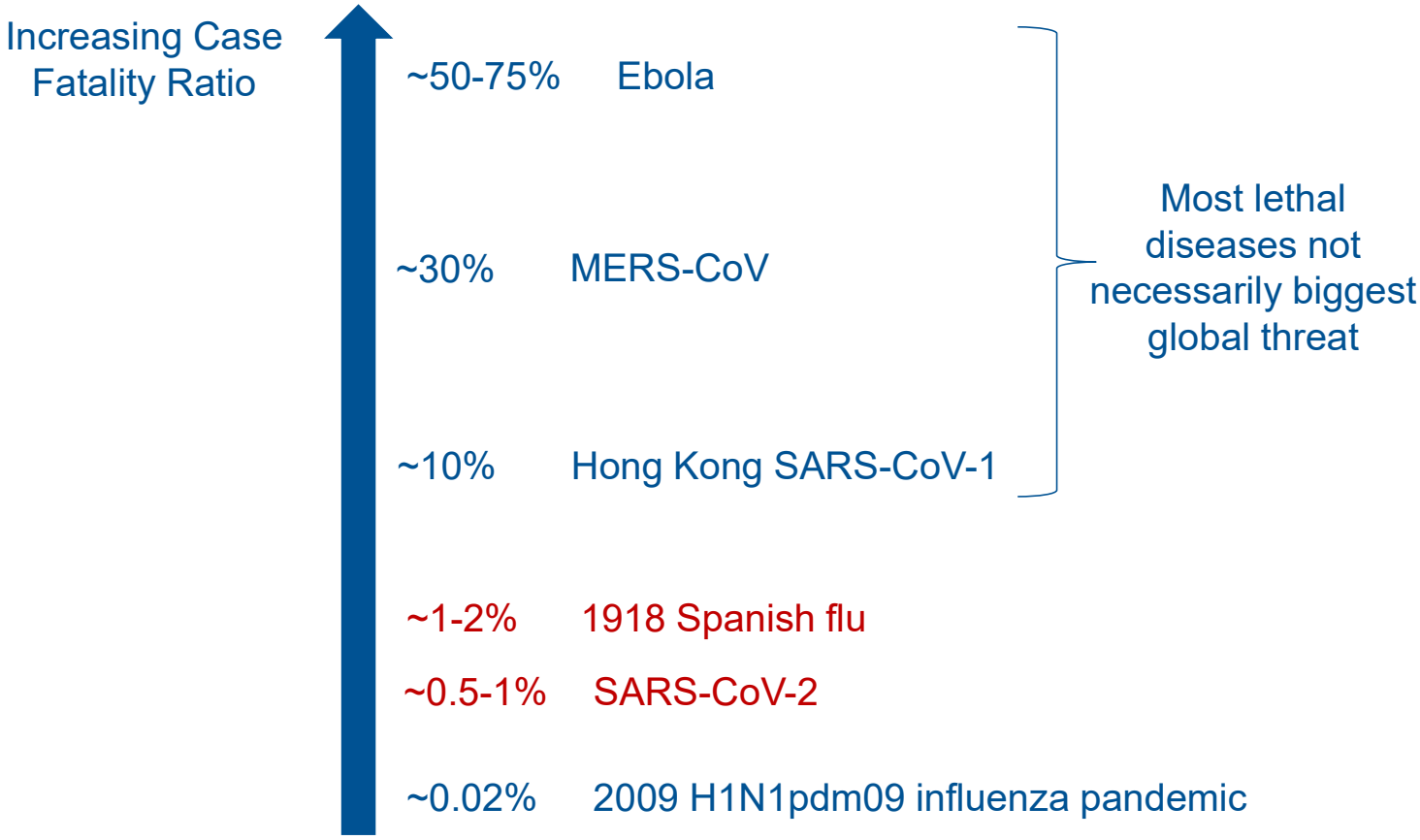
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The severity paradox



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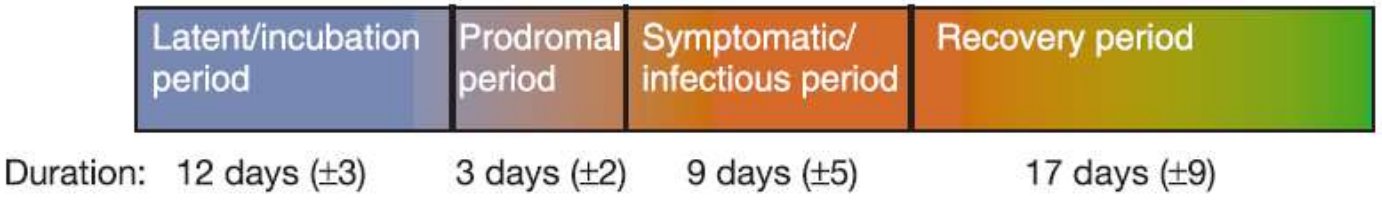
The severity paradox



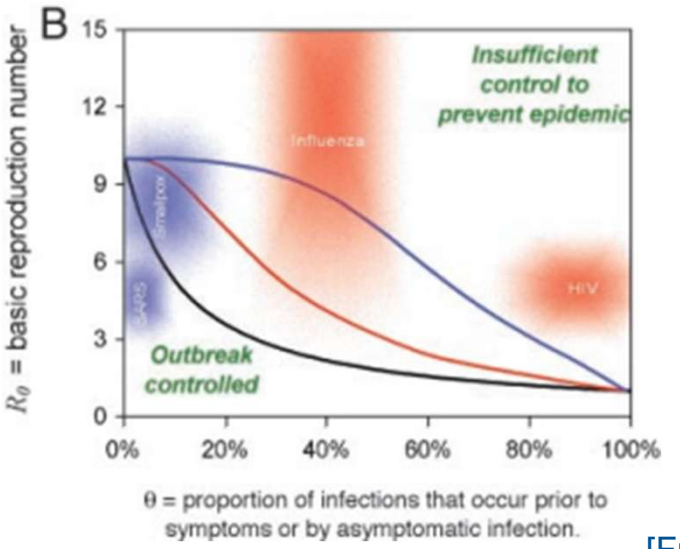
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What makes an infectious disease controllable?

The elimination of Smallpox







- **Are all infections symptomatic/severe?**
- **Can transmission occur before symptom onset?**
- **How fast is transmission?**

[Fraser et al, PNAS 2004]

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Mathematical models

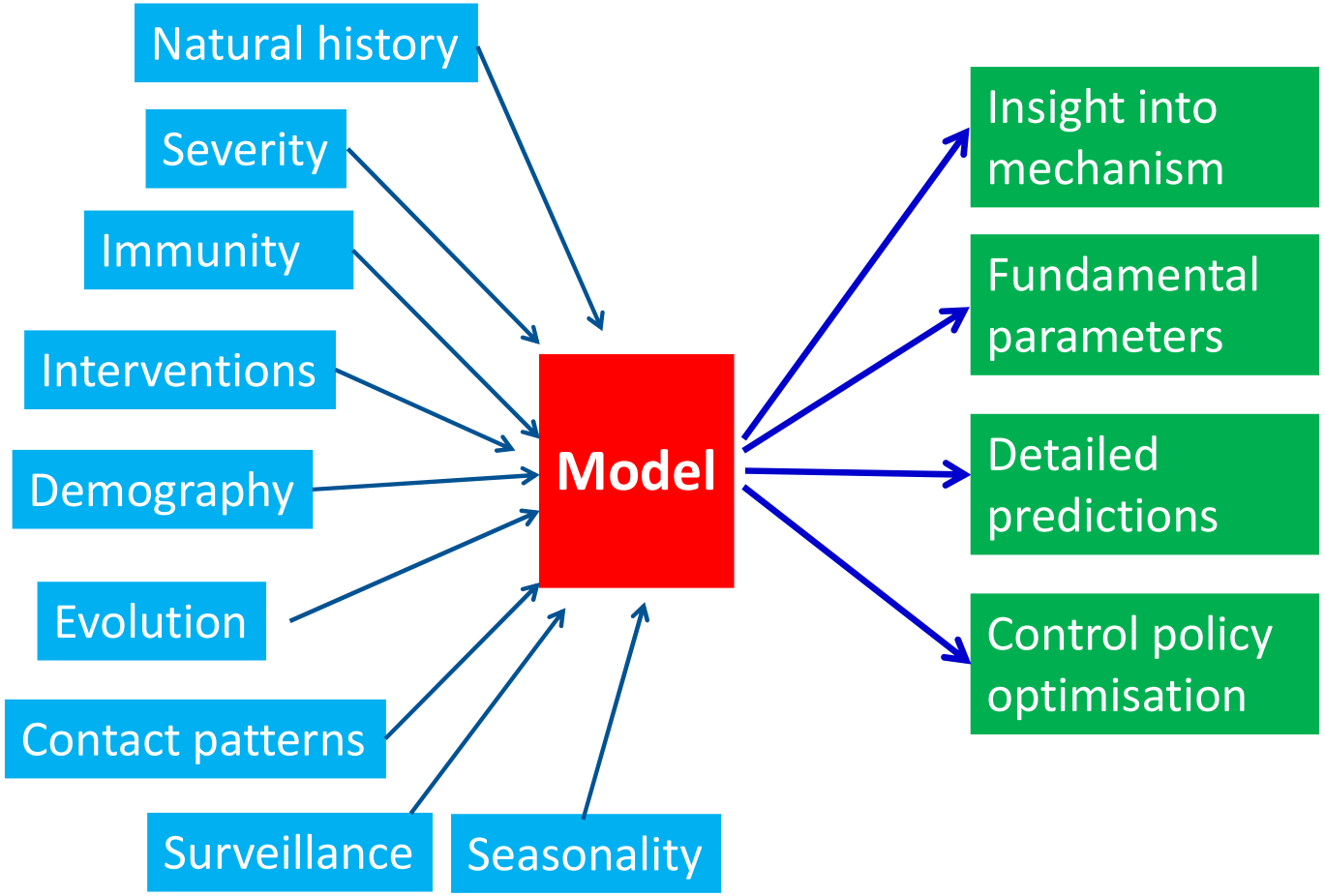
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Mathematical models

- *“All models are wrong, but some are useful”.* G.E.P. Box
- *“Describing complex, poorly-understood reality with a complex poorly understood model is not progress”.* J. Maynard Smith

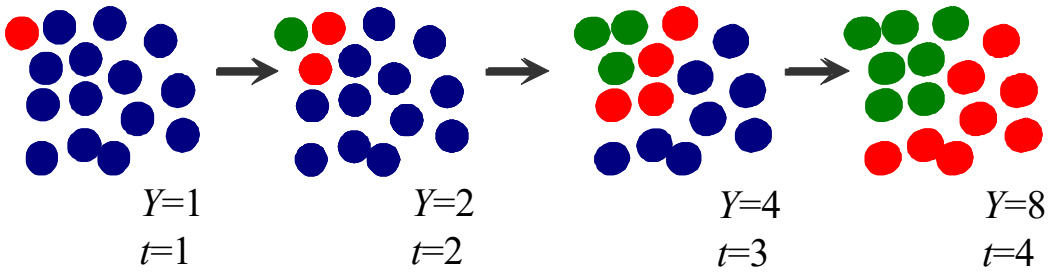
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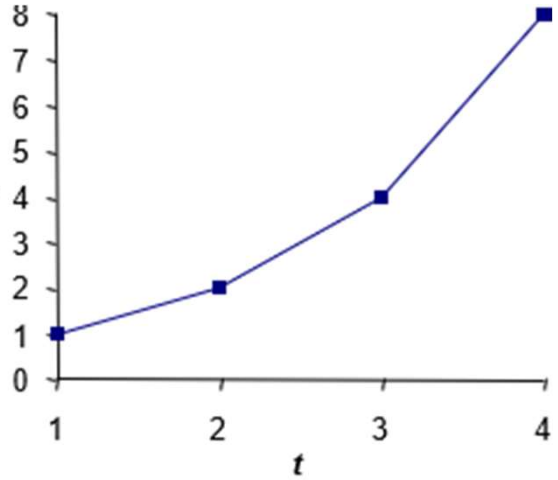
A tool to synthesize information and understand the interplay between the drivers of epidemics



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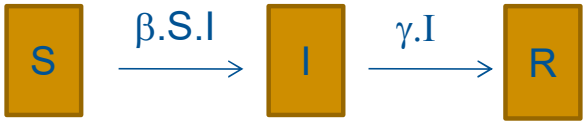
Early stages of an epidemic
- The branching process



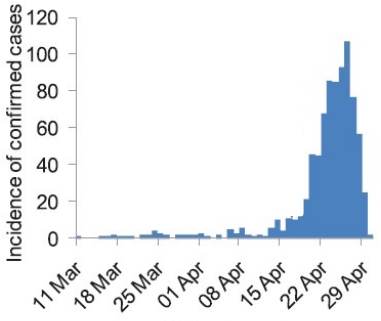


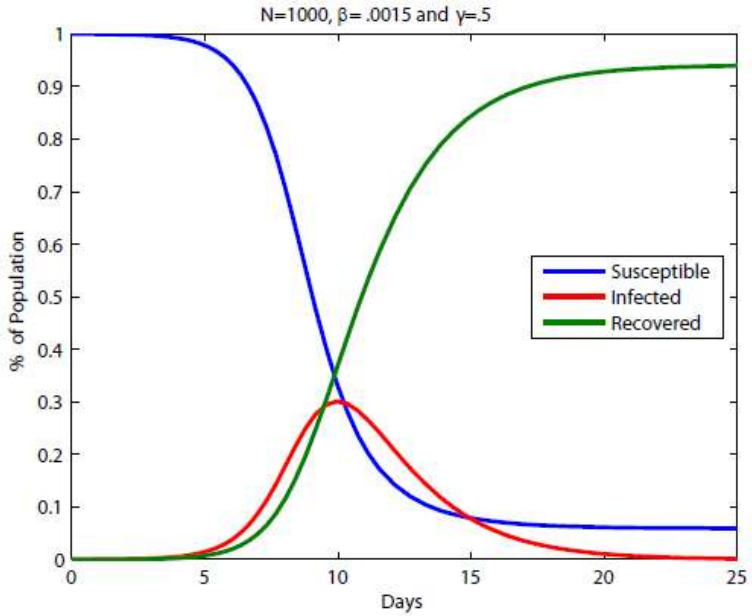
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Compartmental models: The Susceptible-Infectious-Removed SIR model



$$\begin{cases} \partial S/\partial t = -\beta.S.I \\ \partial I/\partial t = \beta.S.I - \gamma.I \\ \partial R/\partial t = \gamma.I \end{cases}$$

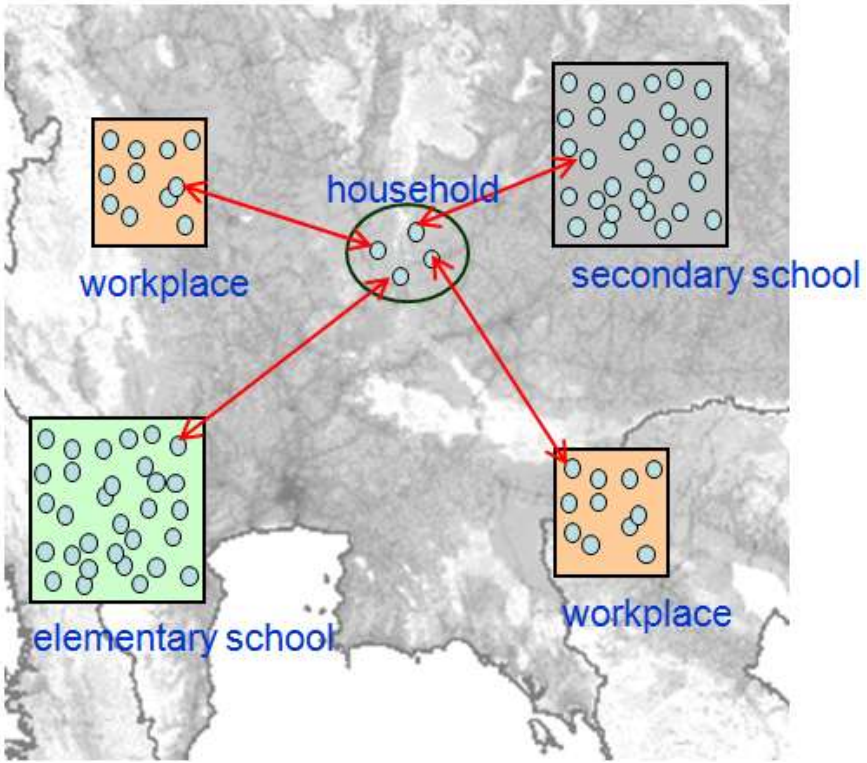




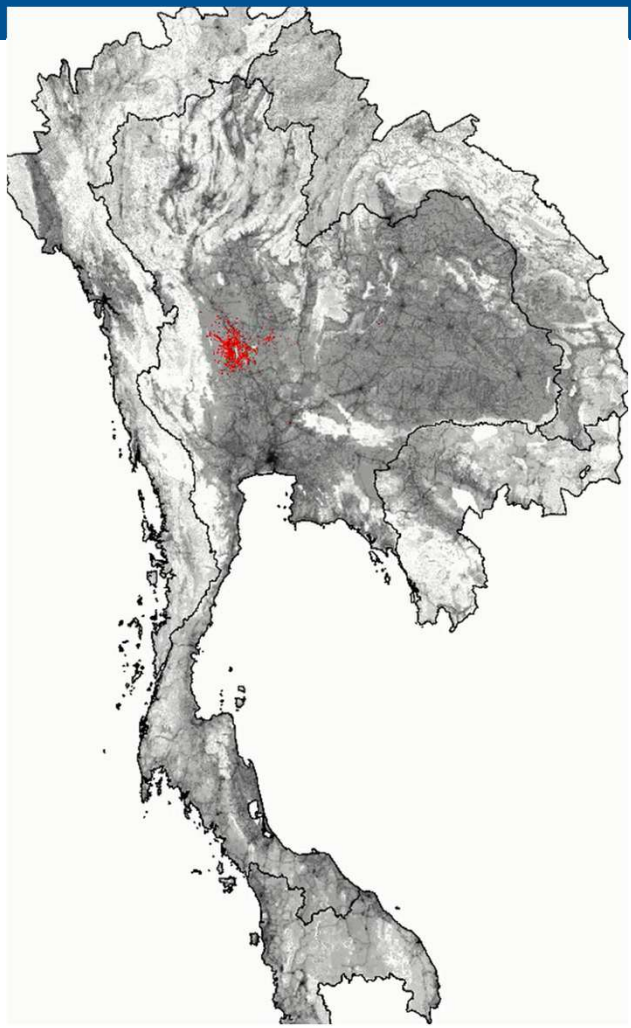
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Agent-based models

Intensive use of simulations



[Ferguson et al, Nature 2005]



What is the appropriate level of complexity in a model?

- Branching process?
- Compartmental model?
- Agent-based model?



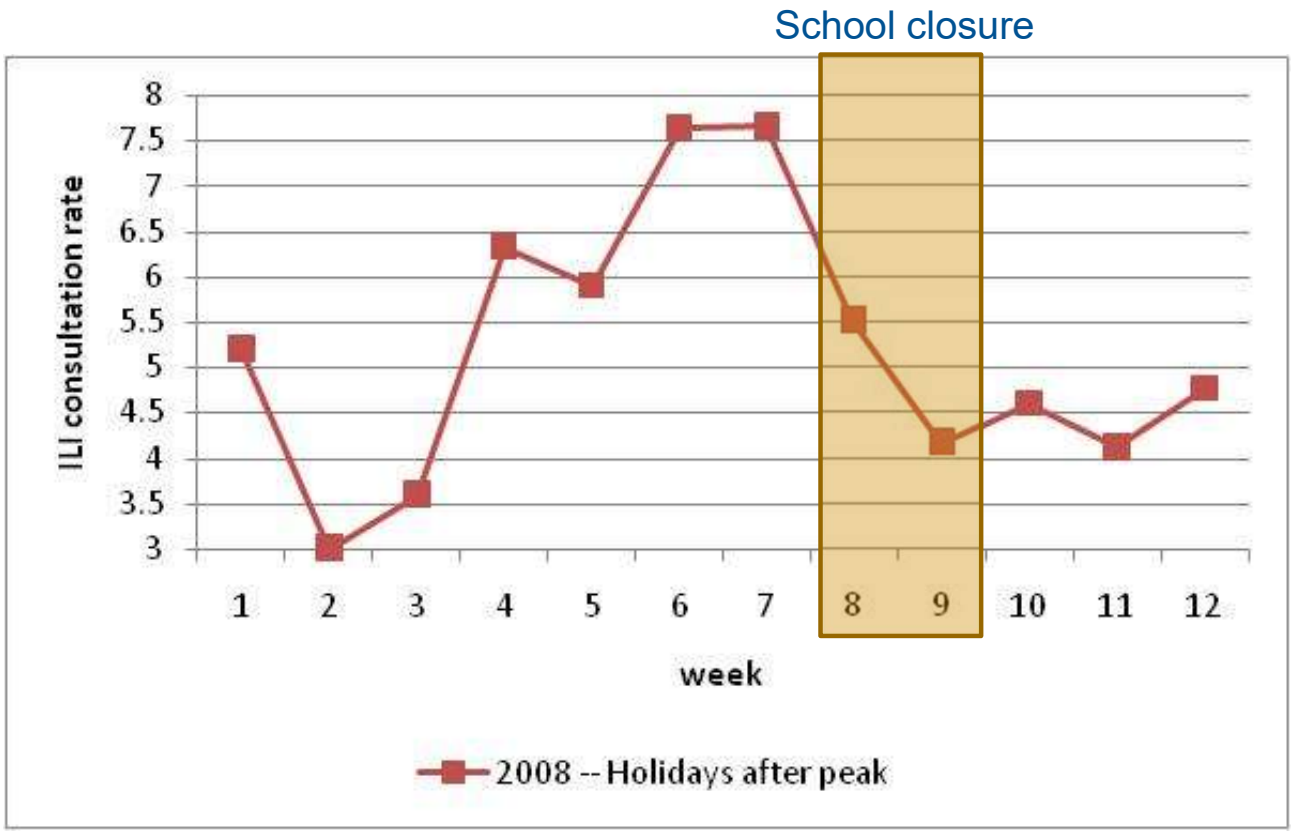
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Evaluating the impact of interventions

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School closure in Hong Kong, March 2008

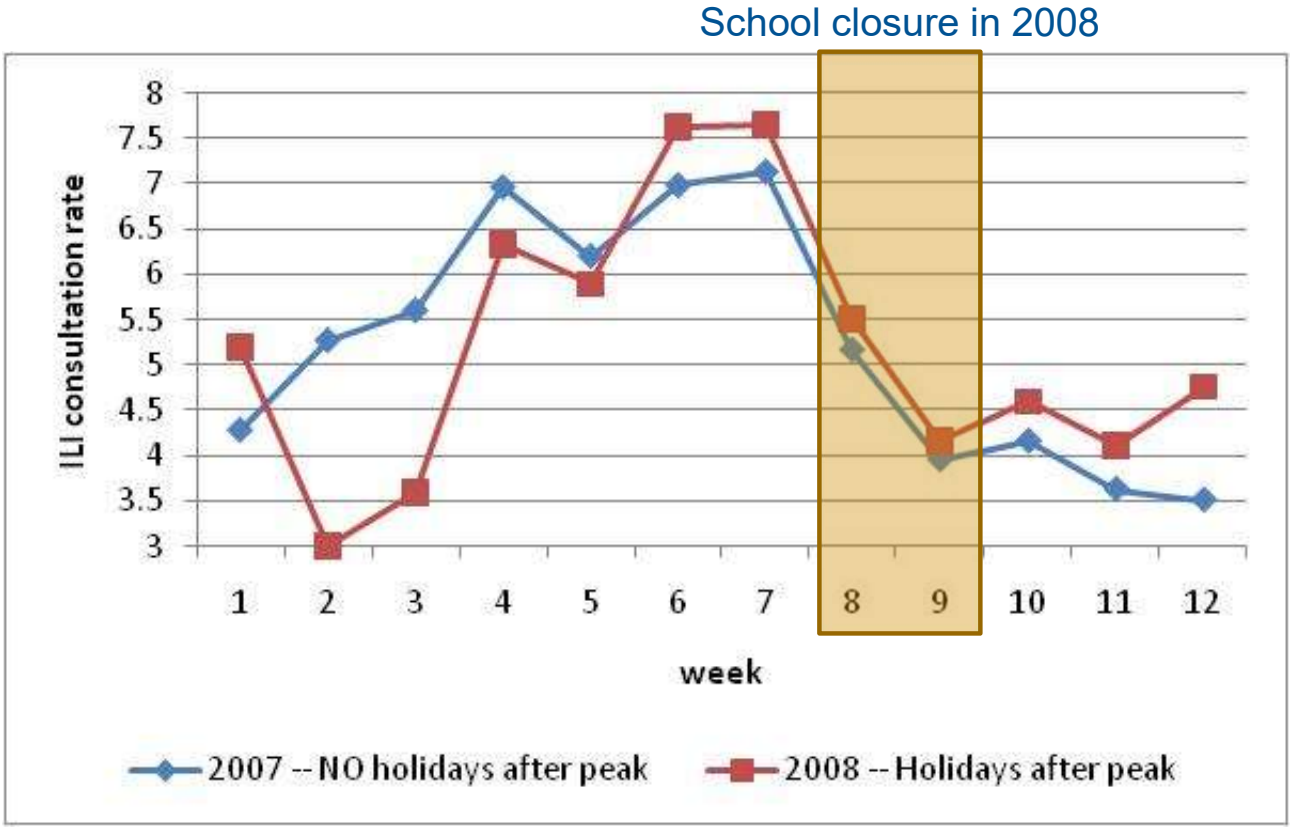
[Cowling et al., EID, 2008]



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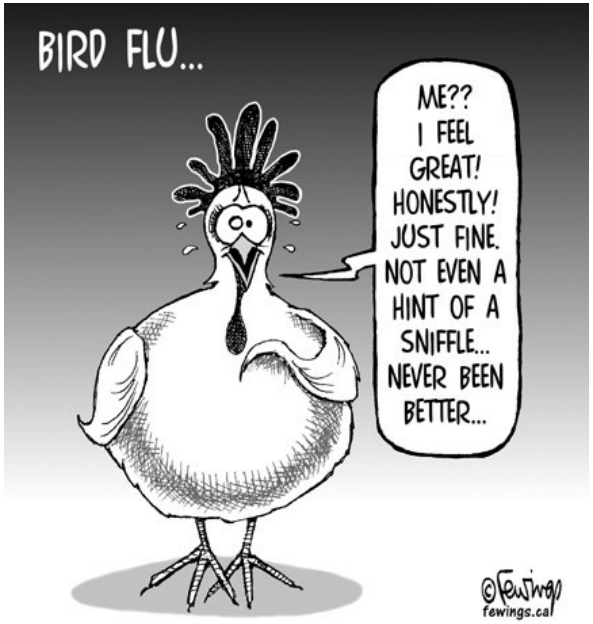
School closure in Hong Kong, March 2008

[Cowling et al., EID, 2008]



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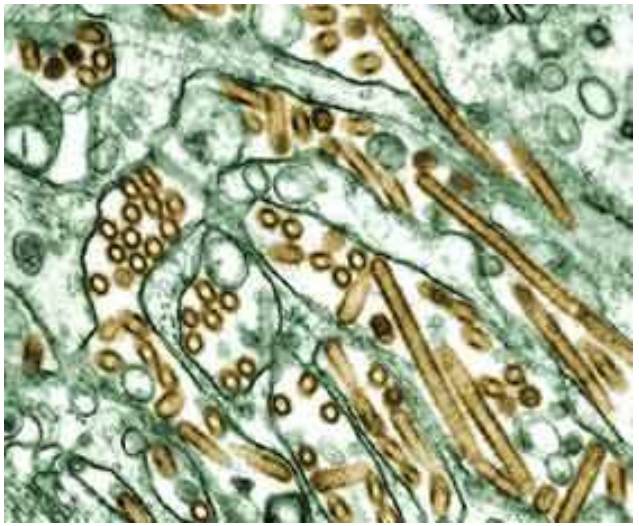
Planning for a severe influenza pandemic



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Planning for severe influenza pandemic

- What could it look like?
- What impact could it have?
- What could we do?

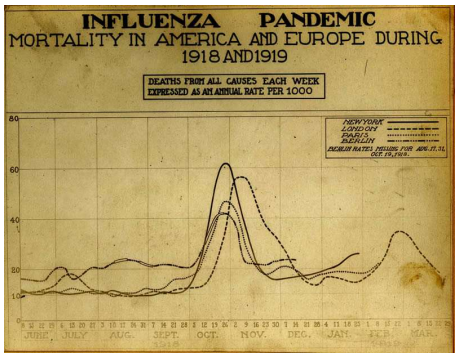


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Determining the transmission characteristics of pandemic influenza

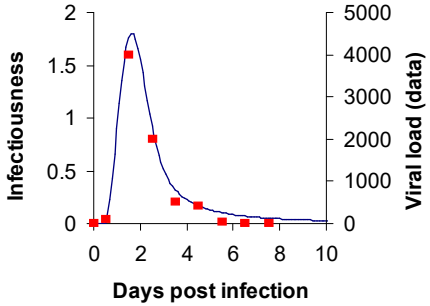
Huge efforts exploring historical archives to identify as much datasets as possible to better characterize the threat

Transmissibility in 1918 pandemic



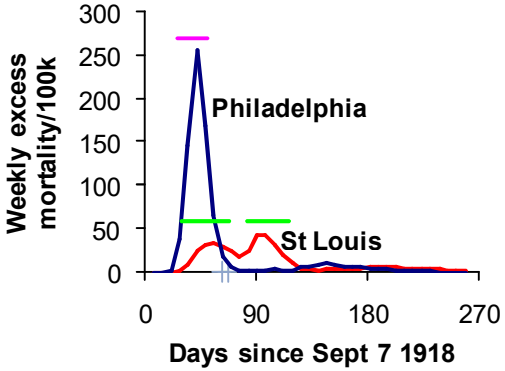
[Mill et al, Nature 2004]

Influenza challenge studies



[Carrat et al, AJE 2008]

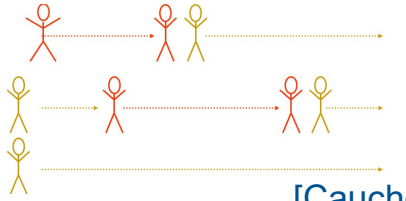
Impact of interventions in 1918 pandemic





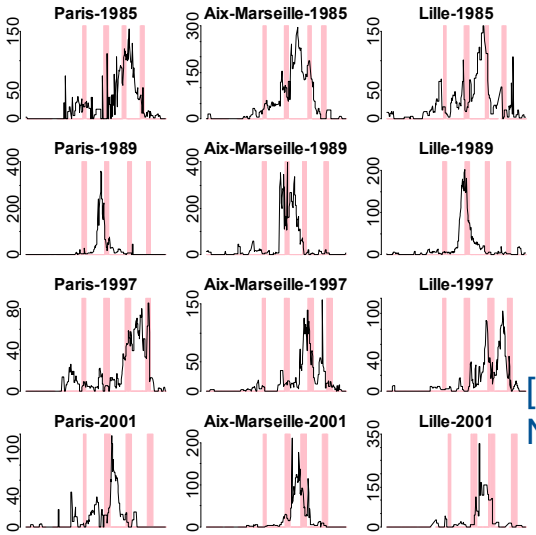
[Bootsma et al, PNAS 2007]

Household transmission studies – Seasonal influenza



[Cauchemez et al, Stat Med 2004]

Impact of school holidays – Seasonal influenza



[Cauchemez et al, Nature 2008]

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Pandemic control objectives and tools

1. Containing the initial outbreak.
2. Slowing international spread.
3. Local mitigation:
   - ➢ Minimizing mortality/morbidity.
   - ➢ Slowing spread until vaccine avail.
   - ➢ Preserving societal resilience.
   - ➢ Minimizing economic impact.



Tools: vaccines, antivirals, case isolation, household quarantine, 'Social distancing', travel restrictions, masks…

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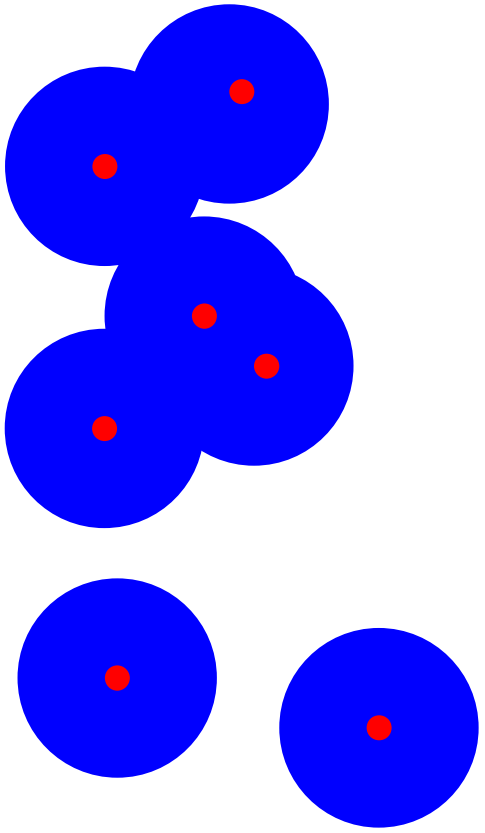
Policies to contain a pandemic at source

Containment = elimination of virus before spread is extensive.

Variety of options; e.g.:

- treatment of cases.
- prophylaxis of household members.
- prophylaxis of schools/workplaces of cases.
- blanket prophylaxis of affected areas.
- Closure of schools/workplaces.
- Reduce travel in and out of affected zones

Delays, detection thresholds and usage limits simulated.

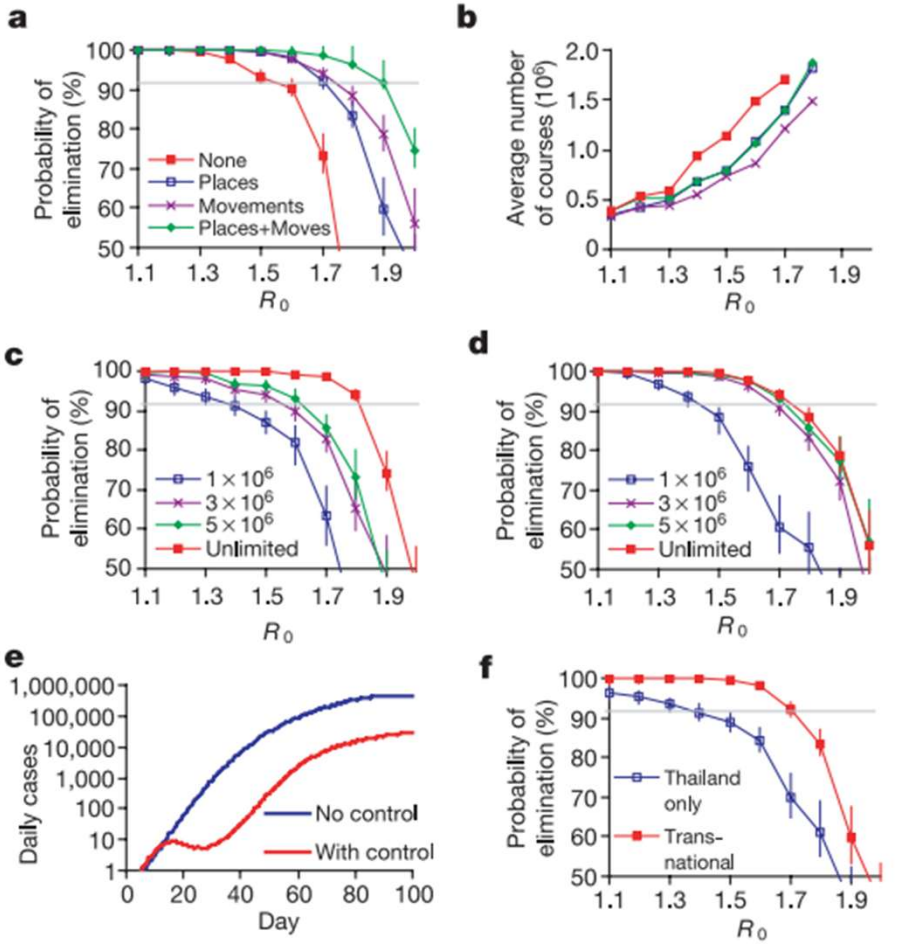


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Can we contain a pandemic?

[Ferguson et al, Nature 2005]

- Yes – for 1918 transmissibility and given 3m courses stockpile.
- BUT – extremely challenging. Need to detect outbreak at <50 cases, react to new cases in 2 days.
- Roche donated 3m courses to WHO for global stockpile.

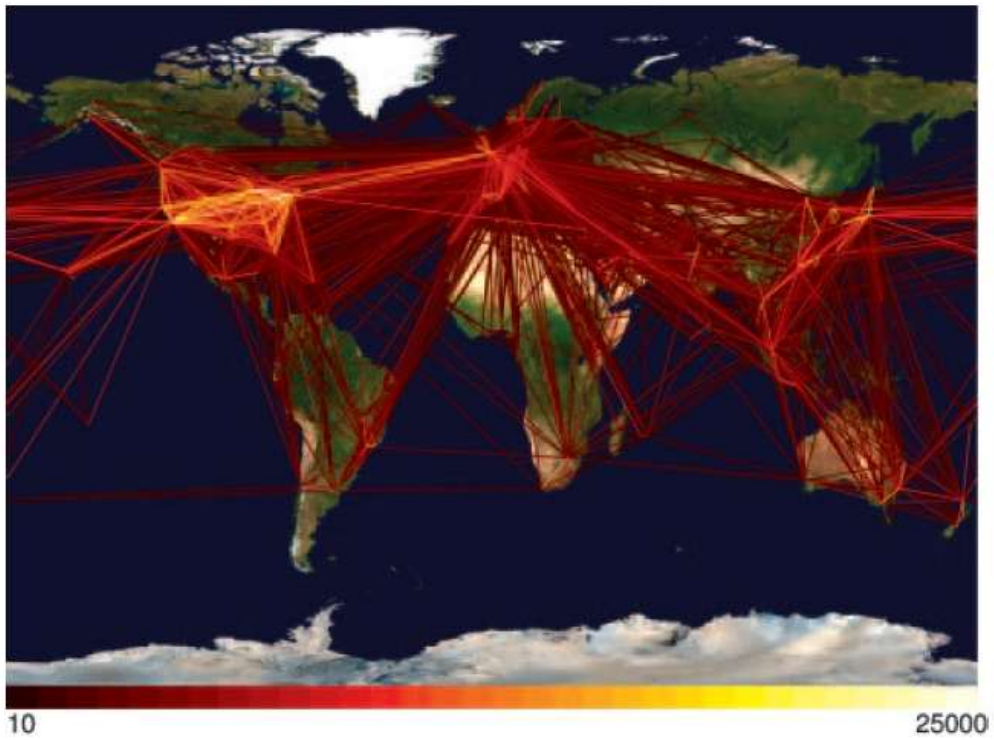


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Global spread and travel restrictions

[Hollingsworth et al, Nature 2006]

- 80% drop in travel to affected countries seen in SARS-CoV-1 epidemic – mostly spontaneous.
- Key problem is rate of increase in cases in flu pandemic – 10-fold in 7-14 days.
- Hence stopping 90% of infections getting in buys 1-2 weeks, 99% buys 2-4 weeks.



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Mitigating a pandemic once it started

[Ferguson et al, Nature 2006]



Treatment

Marginal effect on transmission and attack rates unless given just after symptoms onset (within 6 hours).

Prophylaxis

Household prophylaxis reduces attack rates by ~1/3, but need ~50% stockpile.



School closure

Reduce peak incidence by ~40%, but might also prevent 1/7 cases.



Vaccination

Difficult to predict efficacy – have to look at various efficacy scenarios.

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How should these assessments change today?

- What have we learnt during the COVID-19 pandemic?
- Impact of new treatments (Baloxavir marboxil) for pandemic mitigation?

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