Nordita Workshop 2023

Role of epidemic models in public health policy support

Mirjam Kretzschmar

UMC Utrecht

Topics

- Historical remarks
- What can models do/ not do?
- What type of model to use
- What can we offer to public health?
- Challenges for future pandemics

INTERVIEW | Mathematikerin warnt

"Die vierte Welle lässt sich kaum aufhalten"

HOME > LOCAL NEWS

COVID-19 modelling predicts York Region will avoid fourth wave this summer

Covid-19 modelling suggests we will be able to hit the 'four tests' and lift restrictions on 19 July

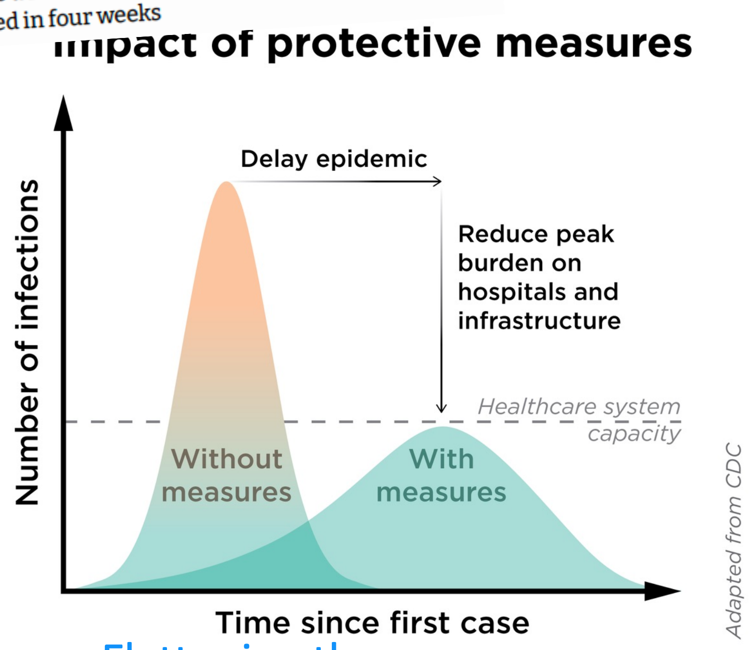
Modelling suggests it is a reasonably robust conclusion that restrictions can be lifted in four weeks

MODELLING THE PANDEMIC

The simulations driving the world's response to COVID-19. By David Adam

2. April 2021, 10:12 Uhr / 1.513 Kommentare /

Wie viele Menschen sich in den kommenden Wochen mit Corona infizieren, hängt davon ab, ob weitere Maßnahmen getroffen werden oder nicht. Manche Modelle zeigen: Die dritte Welle könnte die bislang höchsten Fallzahlen bedeuten. © Annick Ehmann für ZEIT ONLINE



Flattening the curve

New COVID-19 modelling shows pandemic improving outdoor activities 'encouraged'

BY NEWS STAFF
POSTED MAY 20, 2021 1:13 PM EDT LAST UPDATED MAY 20, 2021 AT 2:20 PM EDT

NI could see 1,000 plus Covid cases a day by end of summer, modelling projects

The central projection of the virus's trajectory in the coming months was outlined by the Department of Health.

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First model with public health impact

Do we really need modelling in epidemiology?

"As a matter of fact all epidemiology, concerned as it is with variation of disease from time to time or from place to place, must be considered mathematically (…), if it is to be considered scientifically at all. (…) And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand."

Sir Ronald Ross
in *The Prevention of Malaria*, 1911

1857-1932

- Discovered lifecycle of malariaparasites
- 1902 Nobelprice Medicine
- Ross developed one of the first mathematical models in
- infectious disease epidemiology.

Public health impact: use of vector control to fight malaria

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Pioneers in mathematical epidemiology

W.O. Kermack, A.G. McKendrick
A contribution to the mathematical theory of epidemics **115** *Proc. R. Soc. Lond. A,* 1927

SIR model

W.O Kermack
1898-1970
biochemist

A.G. McKendrick
1876-1948
physician

A Contribution to the Mathematical Theory of Epidemics.

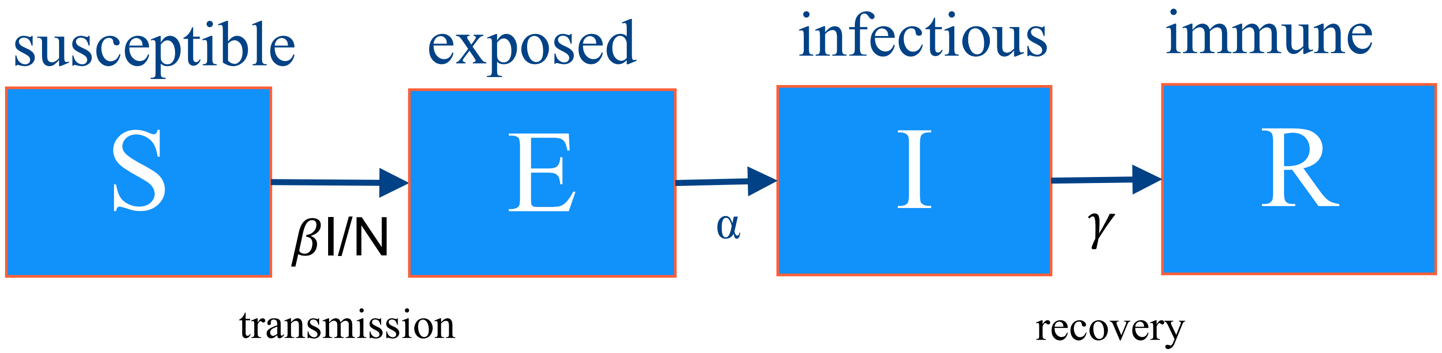
By W. O. Kermack and A. G. McKendrick.

(Communicated by Sir Gilbert Walker, F.R.S.—Received May 13, 1927.)

(From the Laboratory of the Royal College of Physicians, Edinburgh.)

SEIR model for COVID-19

Includes an exposed state: persons who are infected, but not yet infectious



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

$$\frac{dE}{dt} = \beta S \frac{I}{N} - \alpha E$$

$$\frac{dI}{dt} = \alpha E - \gamma I$$

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

Basic reproduction number $R_0 = \frac{\beta}{\gamma}$

Transmission rate x duration infectious period

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Deterministic compartmental models

Properties and assumptions => limitations

- Homogeneous mixing
- Constant infectivity
- Exponentially distributed time in compartments
- Large numbers in every compartment, no stochasticity

Advantages: mathematical tools available; flexibility

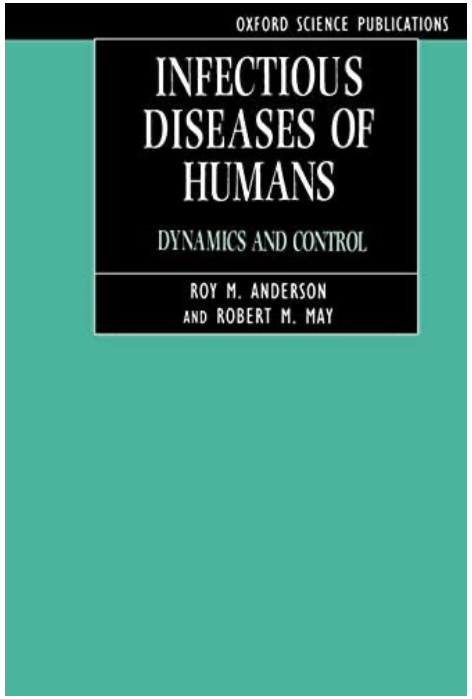
Many variants of SIR-type models have been developed

Hethcote HW. A thousand and one epidemic models.
In Frontiers in mathematical biology 1994 (pp. 504-515). Springer

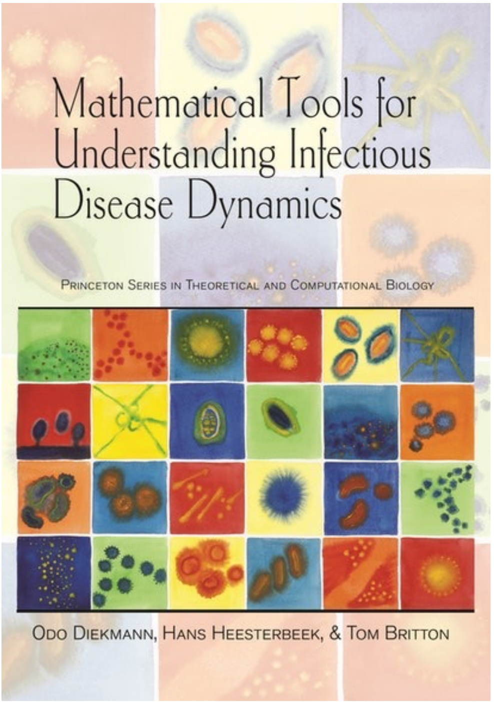
Important contributions

- Norman Bailey
- Klaus Dietz
- Roy Anderson, Bob May
- Odo Diekmann

1957



1991



2012

Role of modelling for public health?

BY SWITCHING TERMS IN HER EQUATIONS, MARJORIE FOUND SHE COULD REVERSE THE WEST NILE VIRUS EPIDEMIC.

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Smallpox modelling

A new situation:
Contingency planning has to rely on historical data for the analysis of control options in present society.

Weaponised smallpox virus could infect thousands in major cities

By Anne Gulland, GLOBAL HEALTH SECURITY CORRESPONDENT
15 March 2018 • 11:39am

A vial of smallpox vaccine used for military personnel in the US | CREDIT: Brenda McDermid/Reuters

Planning for smallpox outbreaks
Neil M. Ferguson, Matt J. Keeling, W. John Edmunds, Raymond Gani, Bryan T. Grenfell,
Roy M. Anderson and Steve Leach
Nature 425; 16 Oct 2003

Model answers to bioterror threat

Modelling has influenced research agendas and policies

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Institute of Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov

FOR IMMEDIATE RELEASE
Tuesday, June 9, 2009

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NIAID Leaders Outline Research Agenda for Universal, Voluntary HIV Testing and Treatment

2009

2011

90-90-90
An ambitious treatment target to help end the AIDS epidemic

UNAIDS

2014

The inspiration for the research agenda outlined by NIAID Director Anthony S. Fauci, M.D., and the Director of NIAID's Division of AIDS, Carl Dieffenbach, Ph.D., is a mathematical modeling study published by scientists from the World Health Organization (WHO) in *The Lancet* in January 2009. The model by Granich et al. predicts that within 10

Granich et al. Lancet 2009

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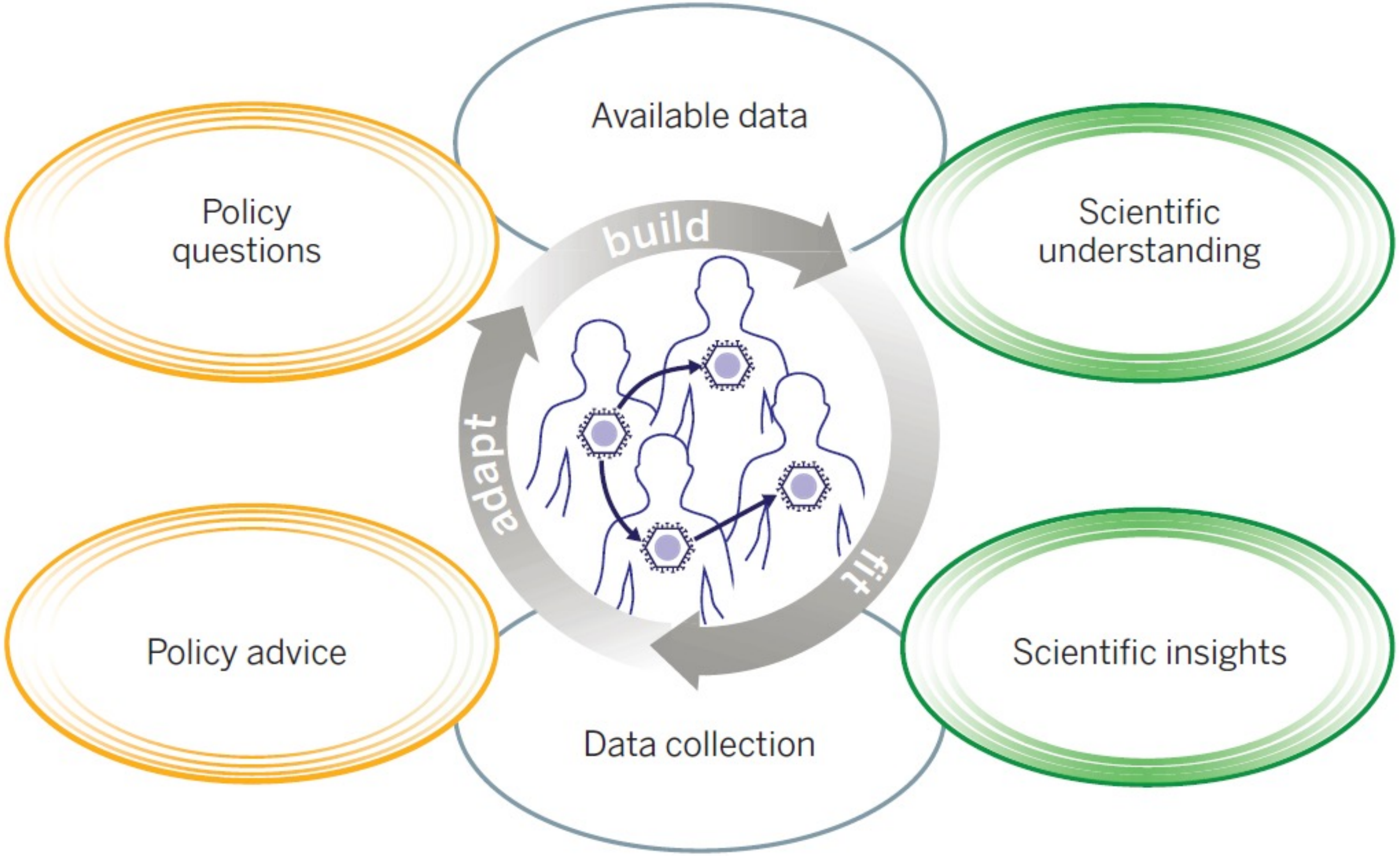
Cycle of model development



Modeling for public health. Policy questions define the model's purpose. Initial model design is

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Heesterbeek et al. Science 2015

Endemic versus epidemic infectious diseases

Endemic disease:

- Prevention/vaccination/screening
- Compare different strategies
- (Long term) Effect on prevalence
- Cost effectiveness

Long time scale

Epidemic disease:

- Predict future course
- Estimate parameters from outbreak data
- Assess intervention impact
- Monitoring

Short time scale

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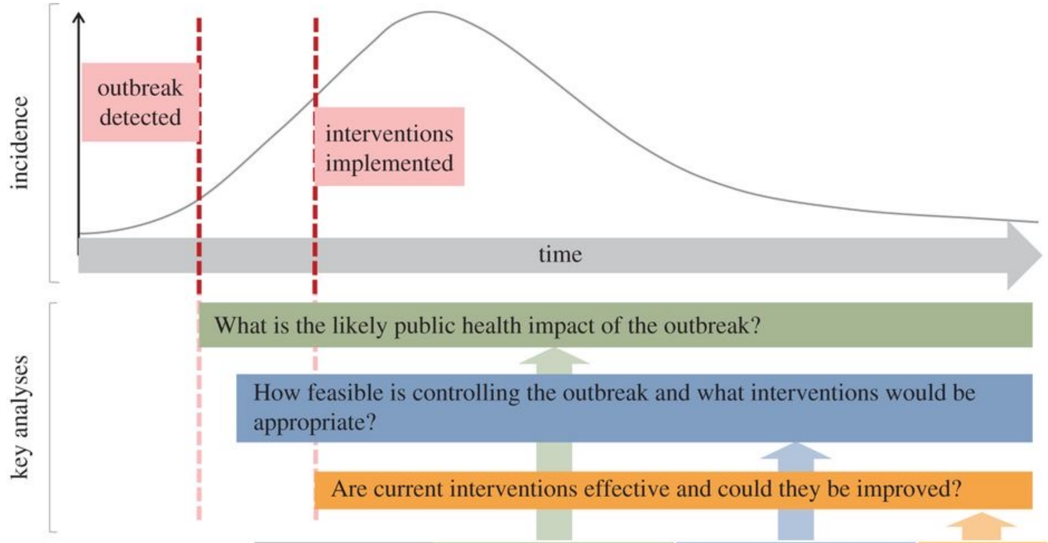
Data needs

Cori et al 2017
Key data for outbreak evaluation



data requirements

Where do the data come from?	data	assessing impact				feasibility of control				improving inter-ventions
		severity (CFR)	severity heterogeneities	short-term projections	long-term projections	transmissibility	transmission heterogeneities	delay distributions	intervention assessment	reassess all previous analyses
surveillance	aggregate case counts			Y	Y	Y	Y*		Y	Y
lab results; case records	case line-list	Y	Y				Y	Y		
case records; contact tracing; genetic studies	pairs infector/infected				Y	Y	Y	Y	Y	Y
genetic studies	sequence data						Y		Y	Y
census	population sizes across demographics and space				Y		Y		Y	Y
serology	immunity levels				Y		Y		Y	Y
centralized systems	health-care facilities								Y	Y
centralized systems	intervention scale		Y							Y
trials	individual effectiveness of interventions								Y	Y

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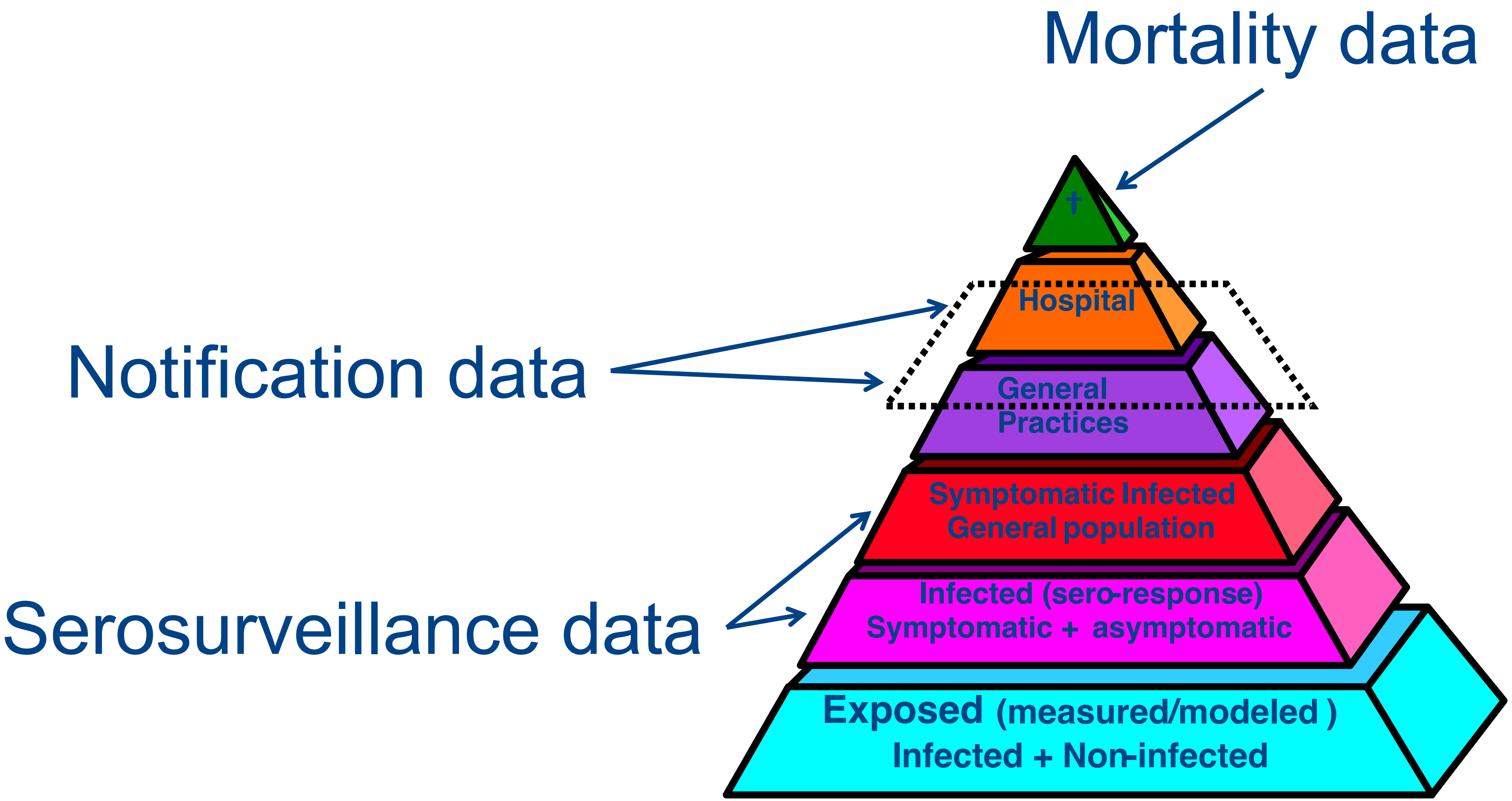
Interpreting surveillance data



Can we predict the course of an outbreak?

INFECTIOUS DISEASE

Estimating the Ebola epidemic

Modelers of infectious diseases strive to predict spread of the virus—and how to stop it

Science 5 Sept 2014

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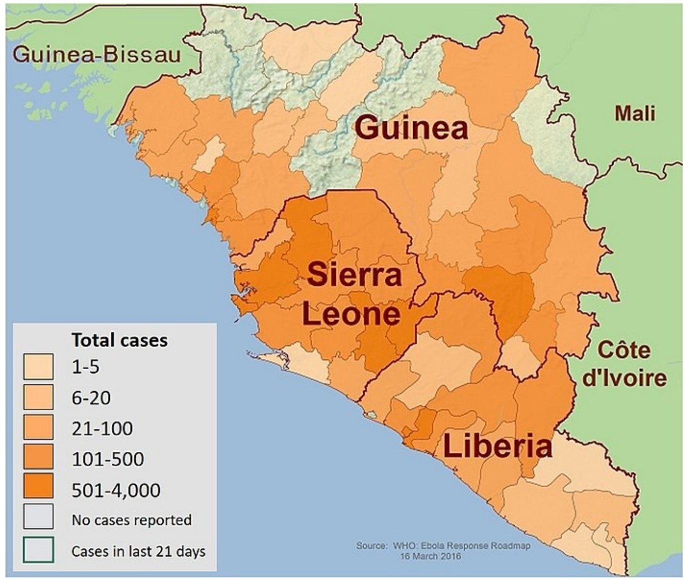
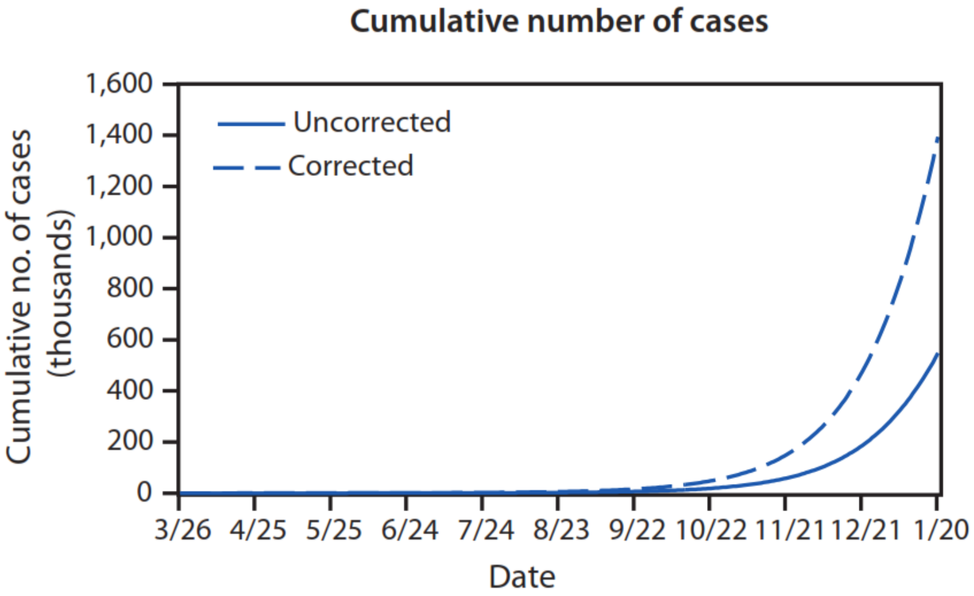
Ebola outbreak

September 2014

NEWS

Liberia and Sierra Leone could see 1.4 million Ebola cases by January



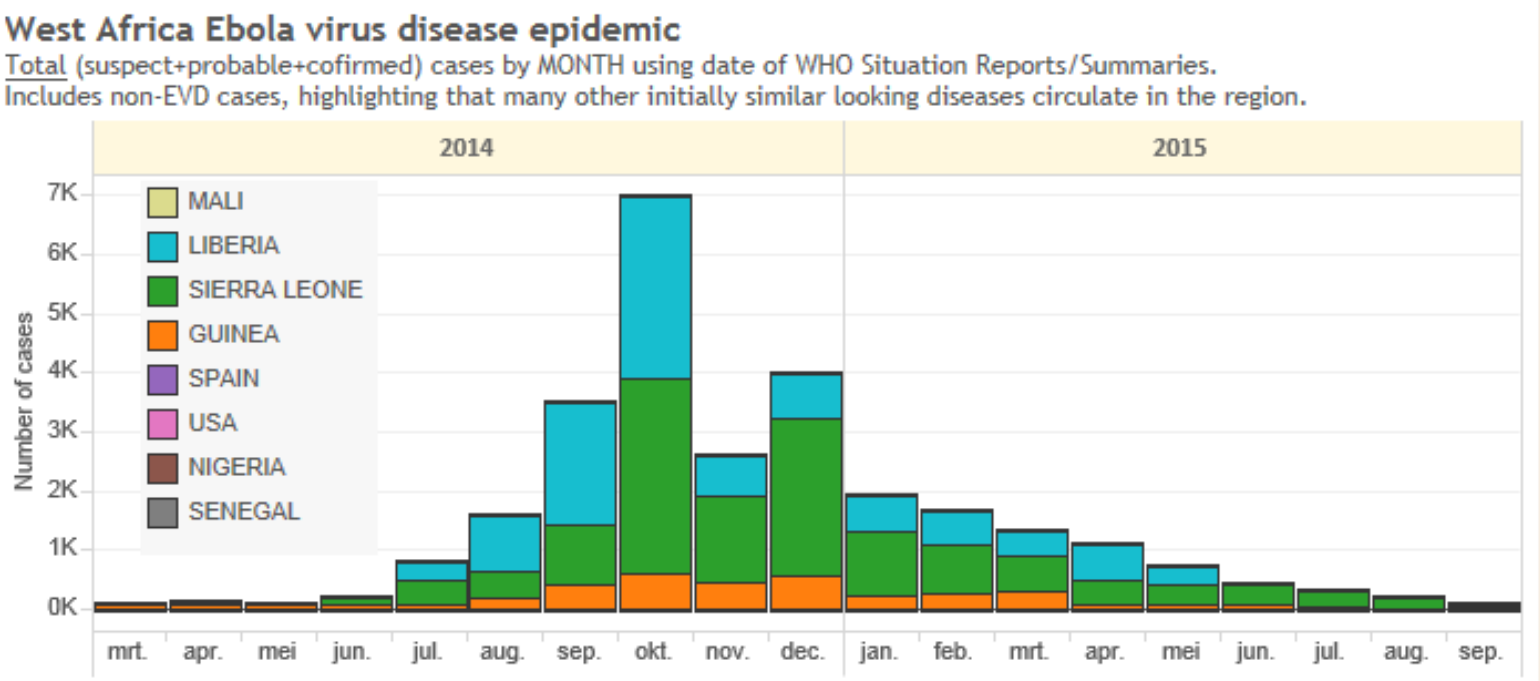


Ebola Epidemic Could Top a Million Victims If Not Contained, CDC Warns

U.S. officials unveil a computer model that shows infections could increase dramatically.

Meltzer MI, et al; Centers for Disease Control and Prevention (CDC). Estimating the future number of cases in the Ebola epidemic--Liberia and Sierra Leone, 2014-2015. MMWR Suppl. 2014 Sep 26;63(3):1-14.

Ebola epidemic curve



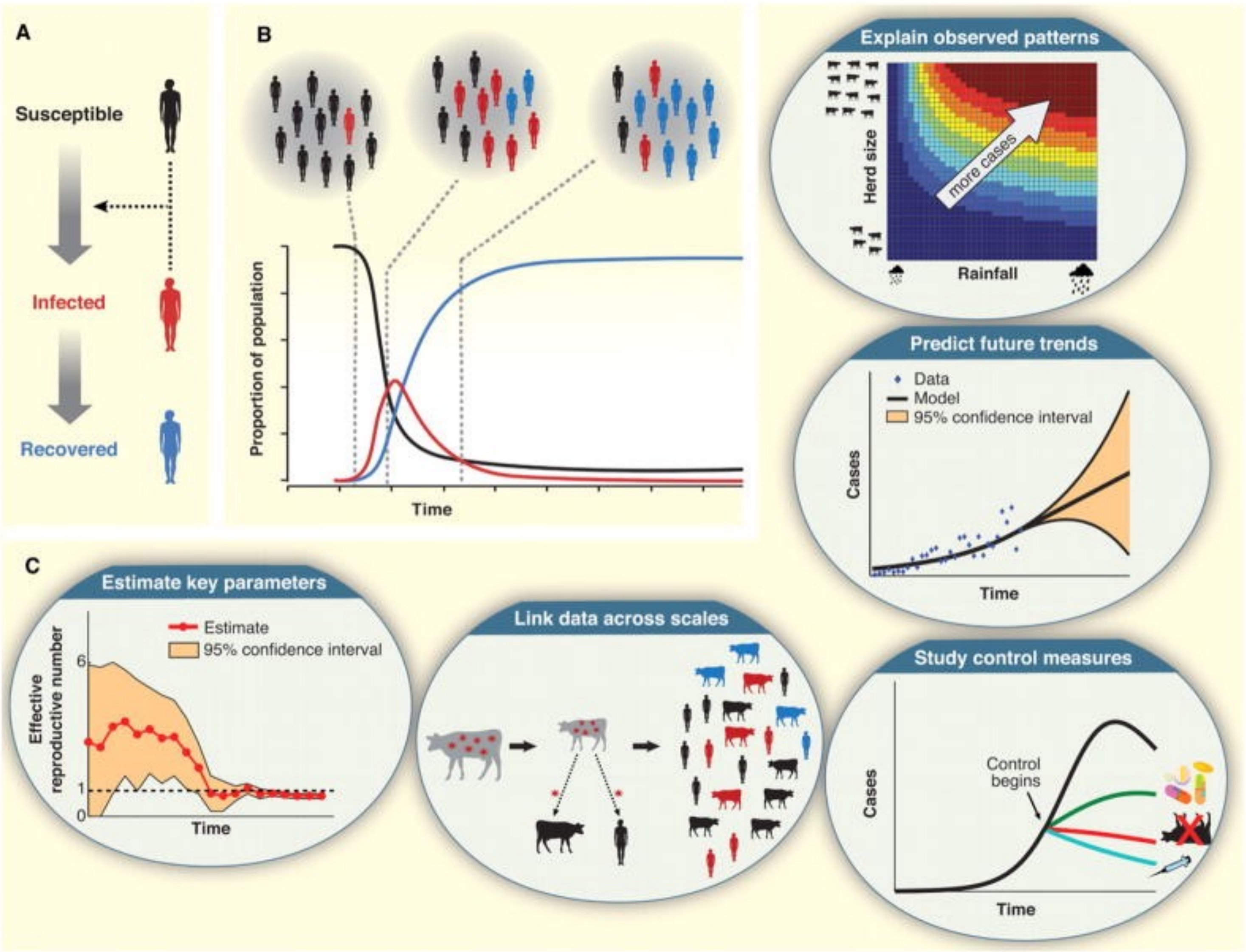
28.000 Ebola cases (suspected+probable+confirmed),
11.000 deaths

September 2015

WHO Situation report Sep 2015.

What can models do?

- Explain observations
- Compare interventions
- Estimate key quantities
- Link data from different sources
- Lead to testable hypotheses
- Help set up intervention trials



Lloyd-Smith et al. Science 2009

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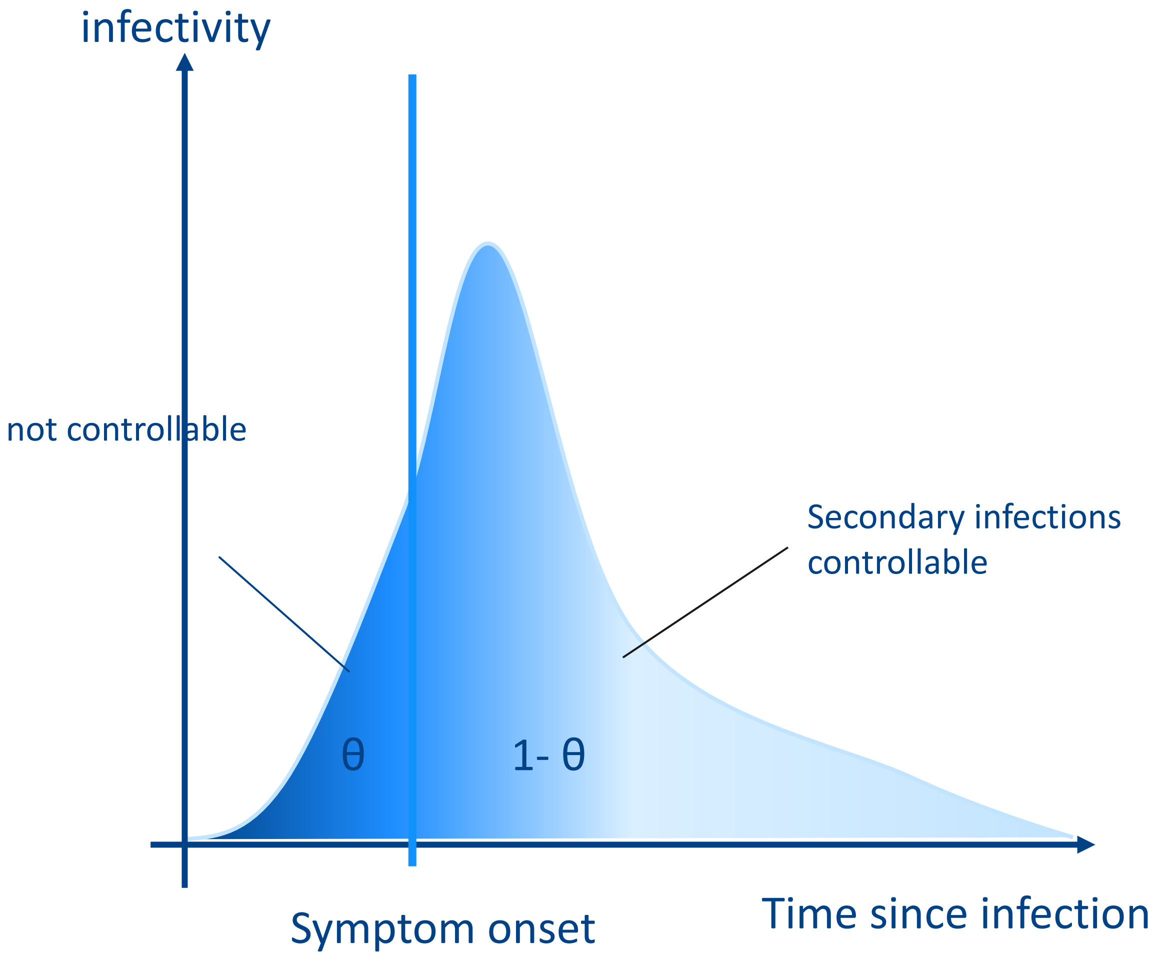
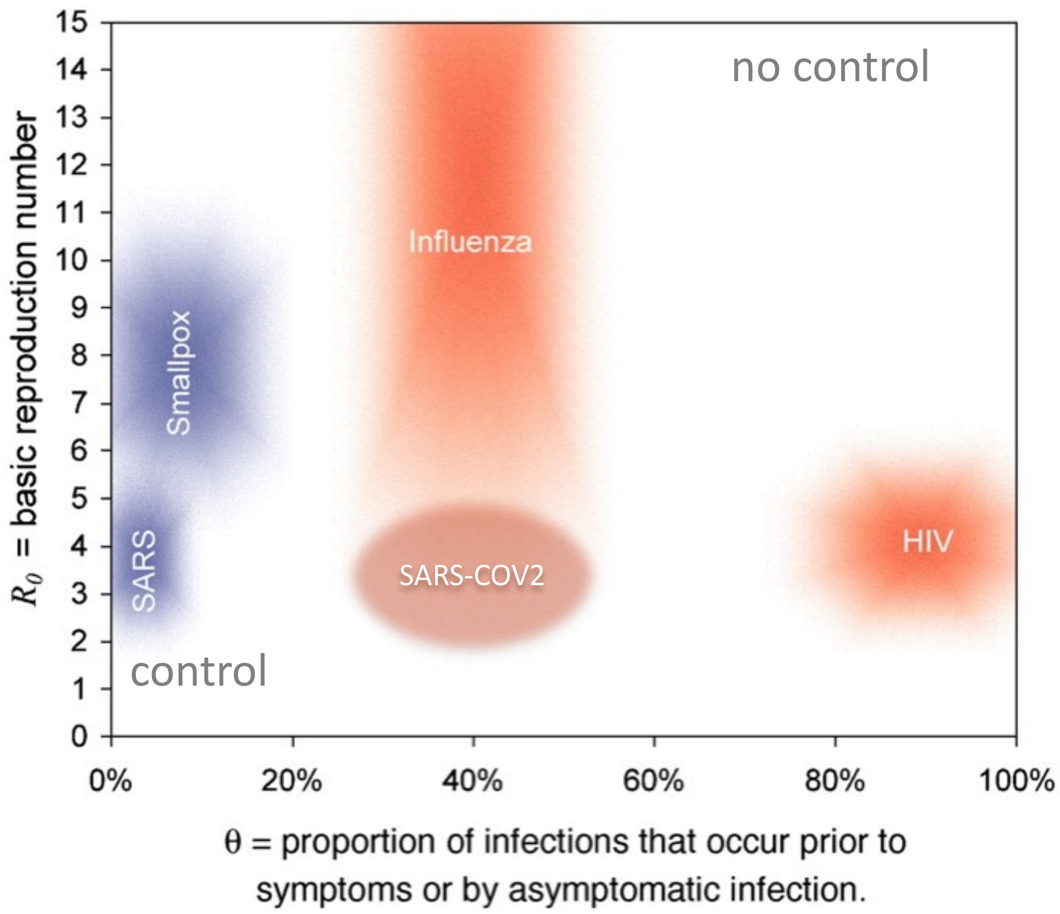
Infectivity and time of symptom onset

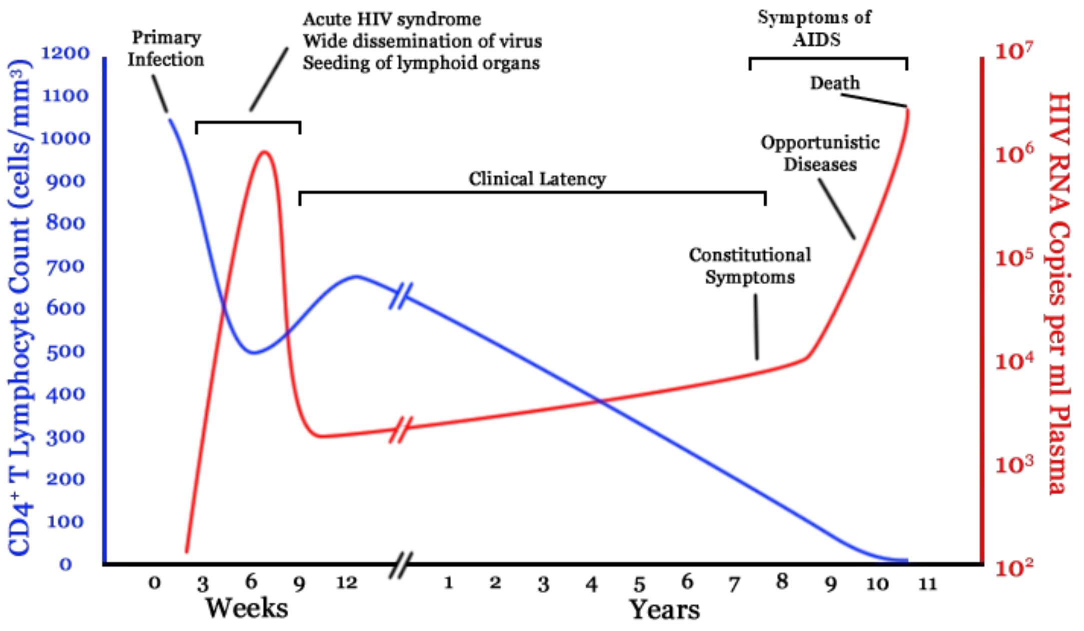




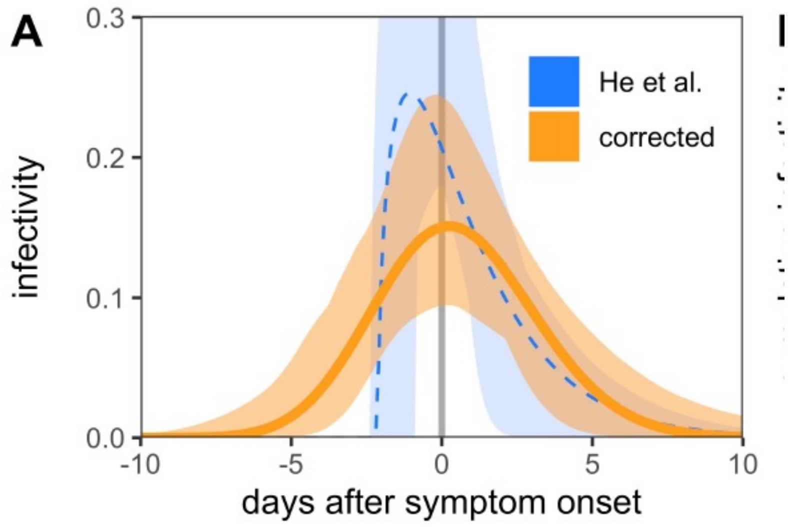
Fraser et al, PNAS 2004

Variable infectivity and transmission before symptom onset

HIV



SARS-CoV2



Ashcroft et al 2020

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Basic reproduction number R0

Definition

R_0 is the average number of new cases of an infection caused by one case in a population of susceptibles

Determined by

- Duration infectious period
- Contact rate
- Transmission probability per contact

Threshold value

$R_0 > 1$: infected person causes more than one new infection:
$\Rightarrow$ epidemic outbreak

$R_0 < 1$: less than one new infection $\Rightarrow$ epidemic stops

Time dependent reproduction number R(t)

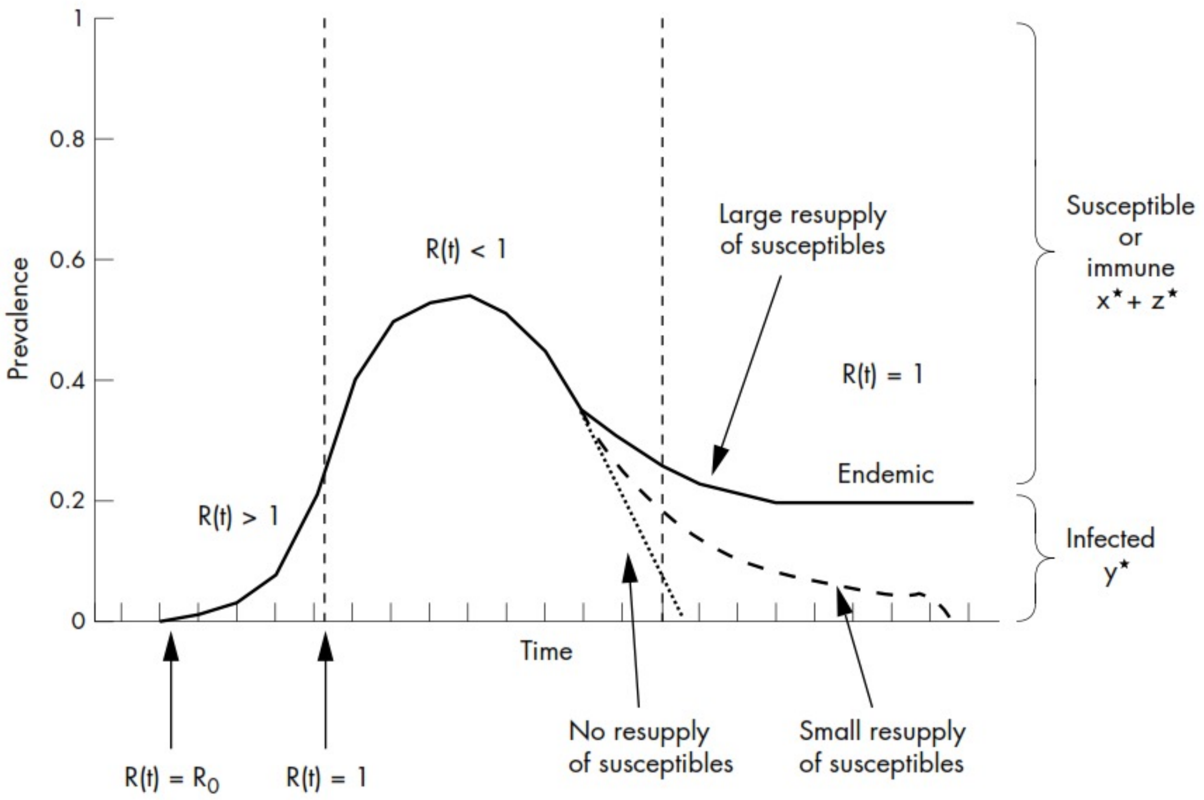

Figure 1 The course of an epidemic in a homogeneous population. The schematic illustration shows the initial growth and decline of an epidemic, as measured by the prevalence of infection, and the related values of the reproductive number, R_t, which initially equals the basic reproductive number, R_0. For the endemic steady state the reproductive number is 1, which is only possible if there is a steady supply of new susceptible individuals. If there is no resupply of susceptible individuals, infection will certainly die out. Additionally, if the replenishment of the susceptible pool is slow infection may die out by chance.

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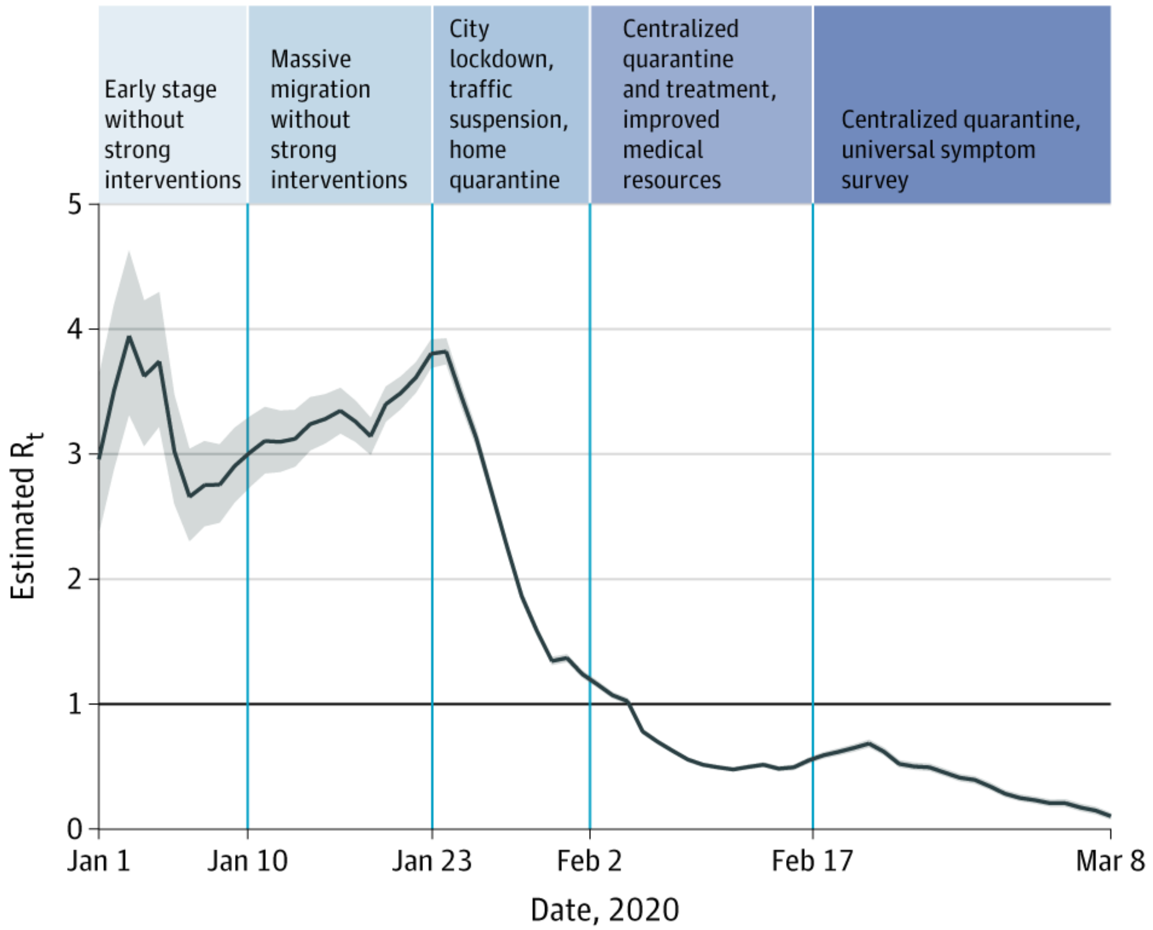
Garnett STI 2002

Use of R(t) to monitor impact of interventions

Estimate R_t from incidence and generation time distribution



From: **Public Health Measures and the Reproduction Number of SARS-CoV-2**

JAMA. 2020;323(21):2186-2187. doi:10.1001/jama.2020.7878

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Use of R_0 to estimate critical vaccination coverage

What vaccination coverage is needed for elimination?

Vaccinate fraction p at birth $\Rightarrow$ fraction $(1 - p)$ still susceptible
$\Rightarrow R_p = R_0(1 - p)$

Control successful if

$$R_p < 1 \quad \Rightarrow \quad p > 1\text{-}1/R_0$$

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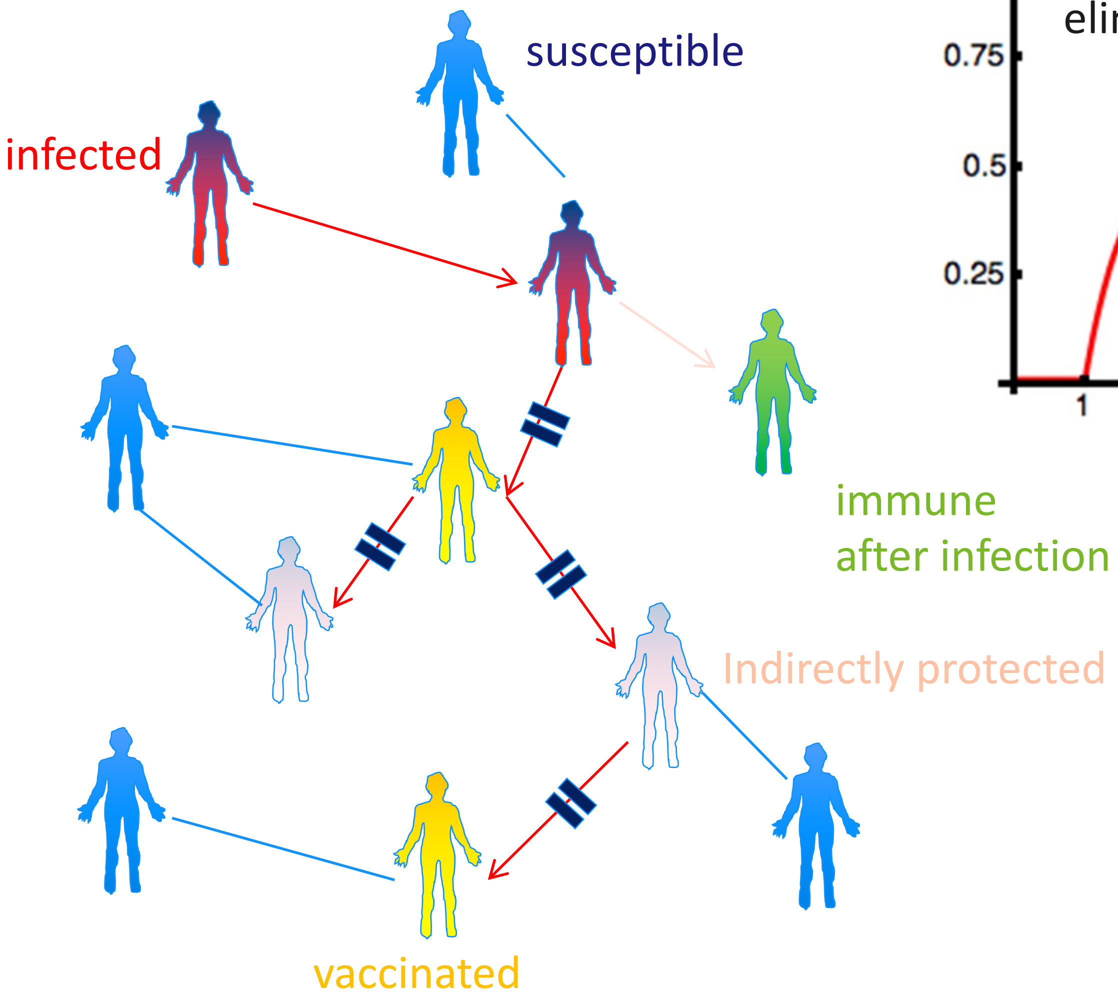
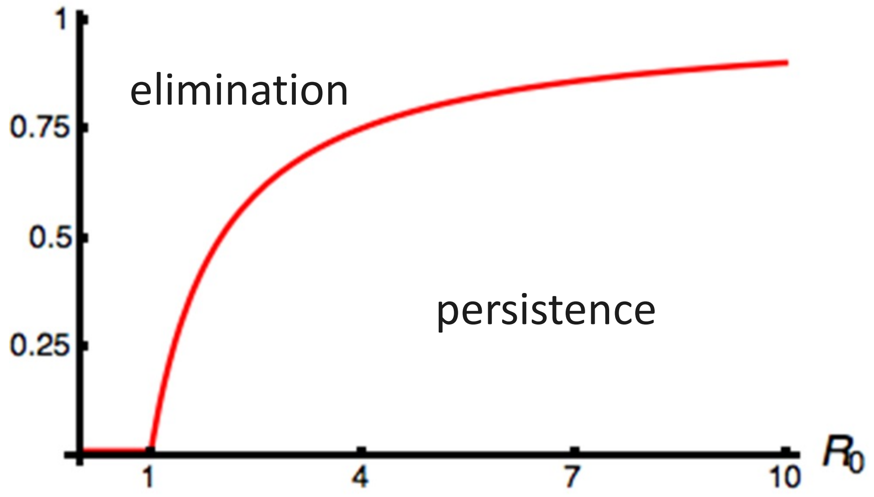
Herd immunity



Breaking transmission chains

Critical vaccination fraction p



$$p > 1 - \frac{1}{R_0}$$

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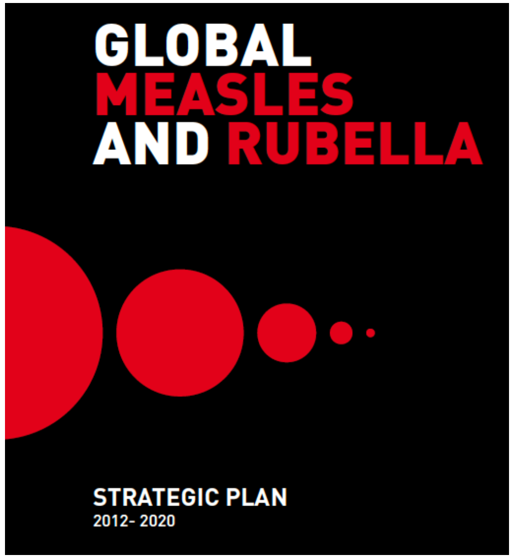
Examples

Measles:

R_0=18

$$p > 1 - \frac{1}{18} = 94.4\%$$



WHO strategic goal:
Measles elimination by 2020

Smallpox:

R_0=5

$$p > 1 - \frac{1}{5} = 80\%$$

Smallpox successfully
eradicated

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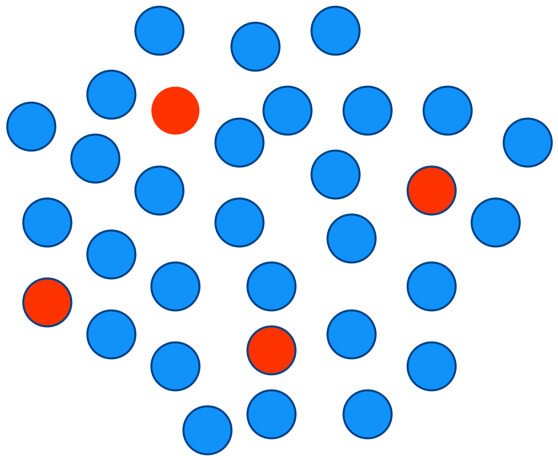
Herd immunity

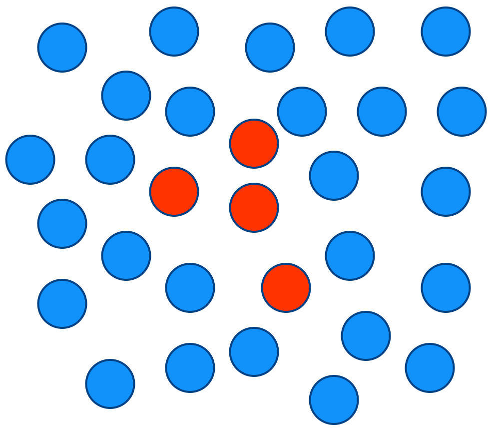
Measles in NL: $R_0 \approx 18$
$p > 94\%$

vaccination coverage $\approx 95\%$

If well-mixed, susceptibles protected by herd immunity

In NL susceptibles clustered
Outbreaks every 5-6 years





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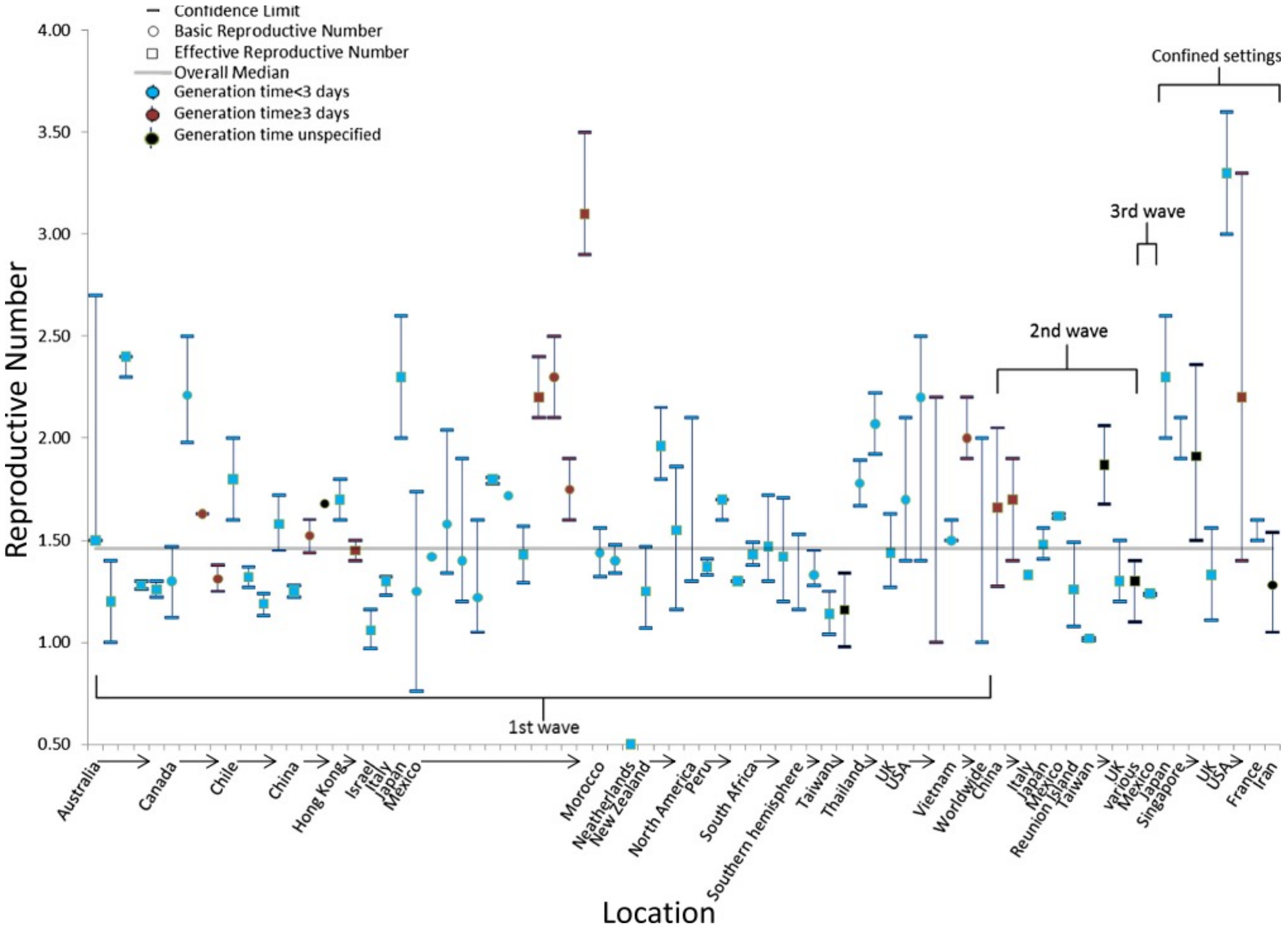
Estimates of R_0 for 2009 influenza



Biggerstaff BMC Inf Dis 2014

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Estimates of R_0 for SARS-CoV-2 Wuhan strain

Yousef Alimohamadi, et al.

Journal of Preventive Medicine & Public Health

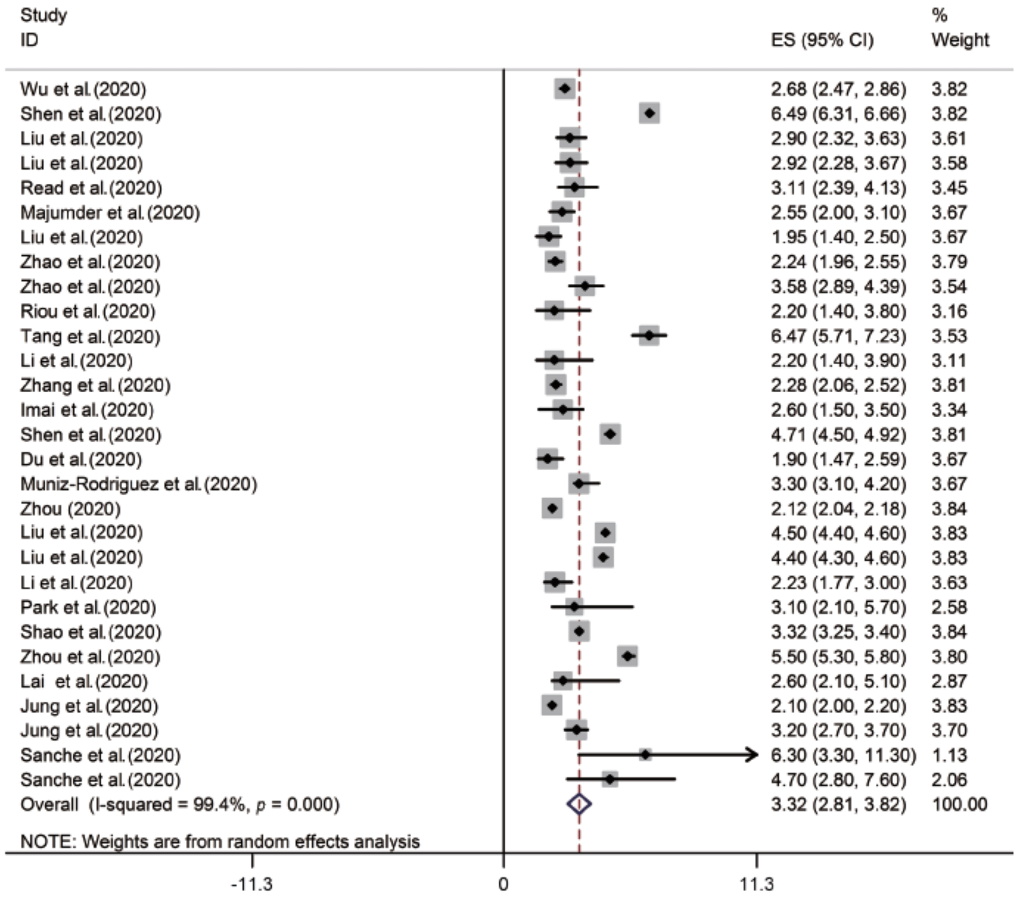

Figure 2. Forest plot of the estimated basic reproduction number of coronavirus disease 2019. ES, effect size; CI, confidence interval.

Based on data from China

Other estimates in the literature have similar range between 2.3 and 3.5

Pooled estimate: R_0=3.32 (CI 2.81, 3.82)

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Netherlands: introduction of conjugate vaccine against pneumococcal infections into NIP

Health Council advice 2002:

"De commissie concludeert dat de kosten van vaccinatie tegen pneumokokken bij de huidige vaccinprijs en vergeleken met andere programma's voor primaire preventie hoog zijn".

=> pneumococcal vaccine not cost effective

Health Council advice 2005

Persbericht

Gezondheidsraad

Health Council of the Netherlands

Datum : 25 oktober 2005

Vaccineren tegen pneumokokken bewezen effectief bij vier prikken

Verder blijkt dat een nieuwe raming van de kosten en baten van het bewezen effectieve vierprikkenschema een veel gunstiger beeld oplevert dan in 2002.

=> pneumococcal vaccine cost effective

What happened in between?

Sustained Reductions in Invasive Pneumococcal Disease in the Era of Conjugate Vaccine

Tamara Pilishvili,[1] Catherine Lexau,[8] Monica M. Farley,[3,4] James Hadler,[5] Lee H. Harrison,[6] Nancy M. Bennett,[7] Arthur Reingold,[9] Ann Thomas,[10] William Schaffner,[11] Allen S. Craig,[12] Philip J. Smith,[2] Bernard W. Beall,[1] Cynthia G. Whitney,[1] and Matthew R. Moore,[1] for the Active Bacterial Core Surveillance/Emerging Infections Program Network[a]

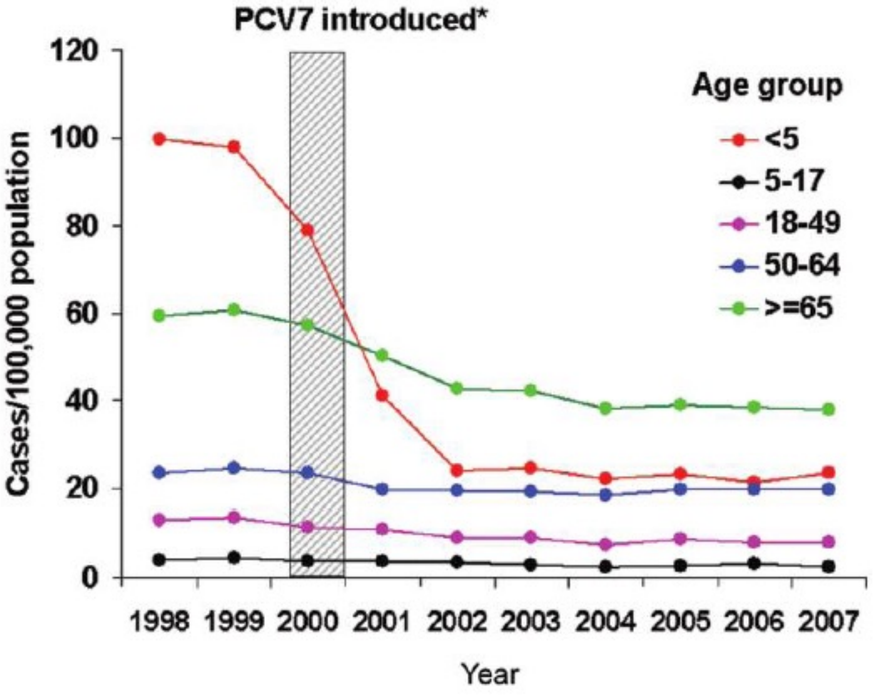

Figure 1. Changes in overall invasive pneumococcal disease (IPD) incidence rates by age group, 1998–2007. *Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine use among young children and infants in the second half of 2000.

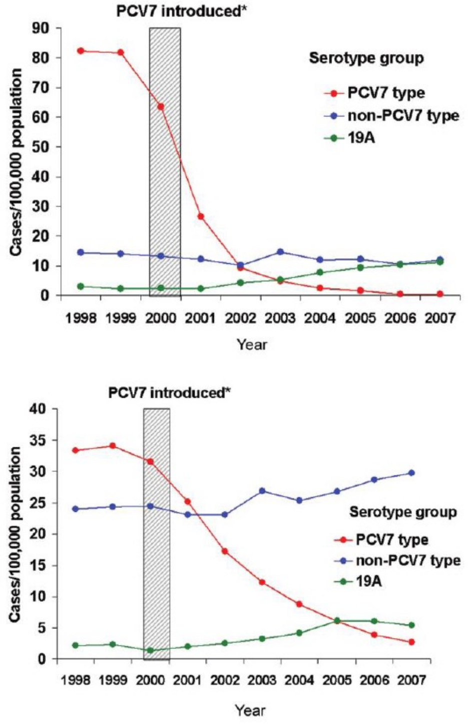

Figure 2. Changes in invasive pneumococcal disease (IPD) incidence by serotype group among children aged <5 years *(A)* and adults aged ≥65 years *(B)*, 1998–2007. *Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine use among young children and infants in the second half of 2000.

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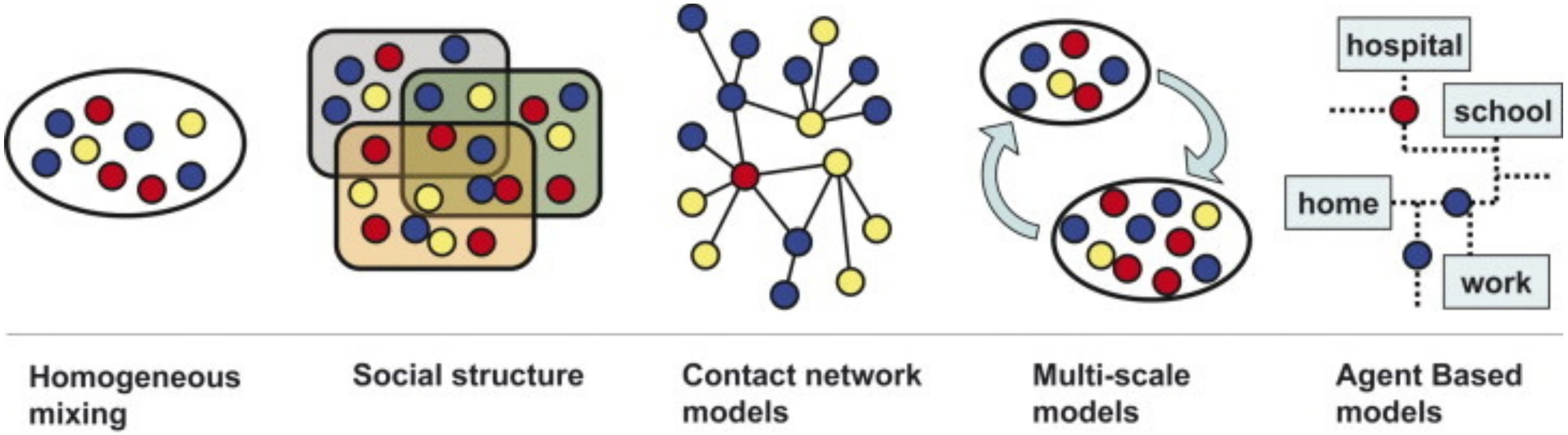
Modelling approaches

- Deterministic compartmental models (SEIR model)
- Compartmental models with heterogeneity (e.g. age), metapopulations
- Network models
- Within-host between-host models
- Agent based models



From Colizza et al 2007

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Areas of application of modelling

Modelling applications at RIVM

- Transmission modelling
- Risk assessment foodborne diseases
- Exposure modelling
- Dose response modelling
- Spatial spread and risk mapping
- Multicriteria decision analysis
- Disease burden estimation
- Economic impact assessment

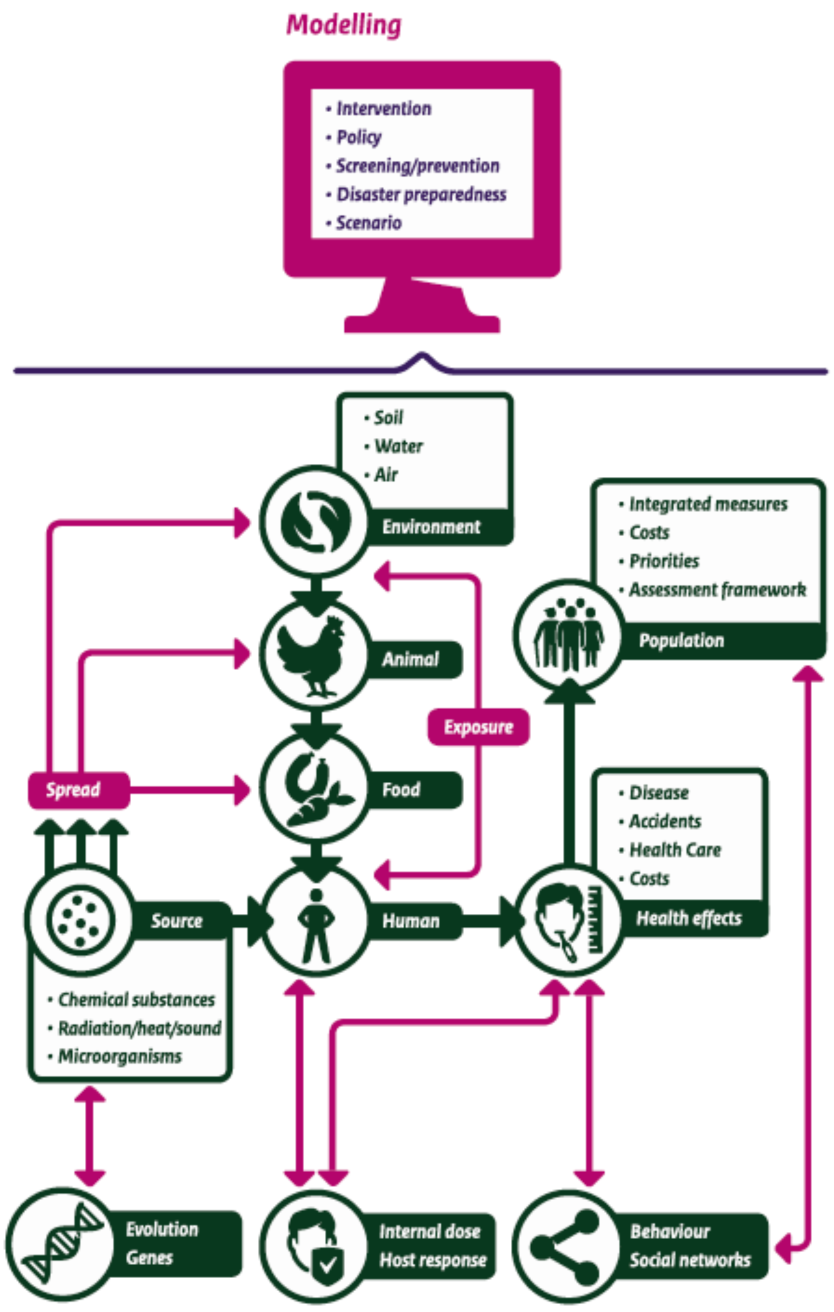

Fig. 1 Applications of mathematical modeling

Kretzschmar. J Publ Health Policy 2020

Burden of infectious disease in the Netherlands

Since 2014 Annual report

"State of infectious diseases in the Netherlands"

→ Estimation disease burden >32 diseases

6 sexually transmitted infections
11 vaccine-preventable infections
11 foodborne diseases
4 respiratory diseases

PLOS | ONE

RESEARCH ARTICLE

Disease Burden of 32 Infectious Diseases in the Netherlands, 2007-2011

Alies van Lier[1☯], Scott A. McDonald[1☯*], Martijn Bouwknegt[1], EPI group[1¶], Mirjam E. Kretzschmar[1,2], Arie H. Havelaar[3], Marie-Josée J. Mangen[1,2], Jacco Wallinga[1], Hester E. de Melker[1]

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Summary measure of population health

Disability Adjusted Life Years (DALYs) to express the burden of disease

$$DALY = YLL + YLD$$

YLL: Years of life lost due to mortality

$$= \Sigma\,(\mathbf{d} \times \mathbf{e})$$

d – sum of all fatal cases
e – remaining life expectancy at age of death

YLD: Years of healthy life lost due to disability

$$= \Sigma\,(\mathbf{n} \times \mathbf{t} \times \mathbf{w})$$

n – number of cases
t – duration of illness
w – disability weight

Introduced by Murray & Lopez 1997: Global Burden of Disease Study

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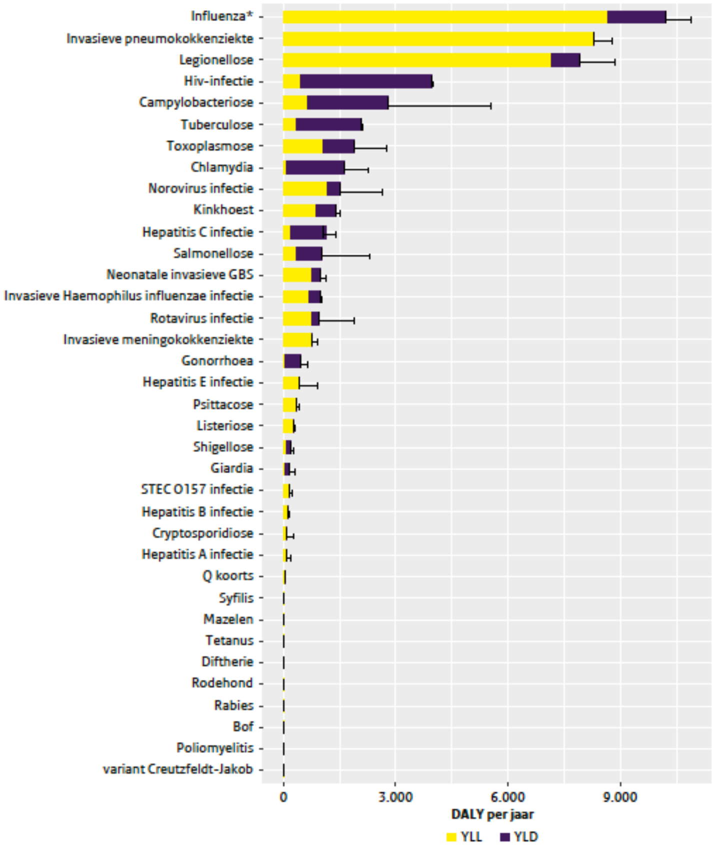
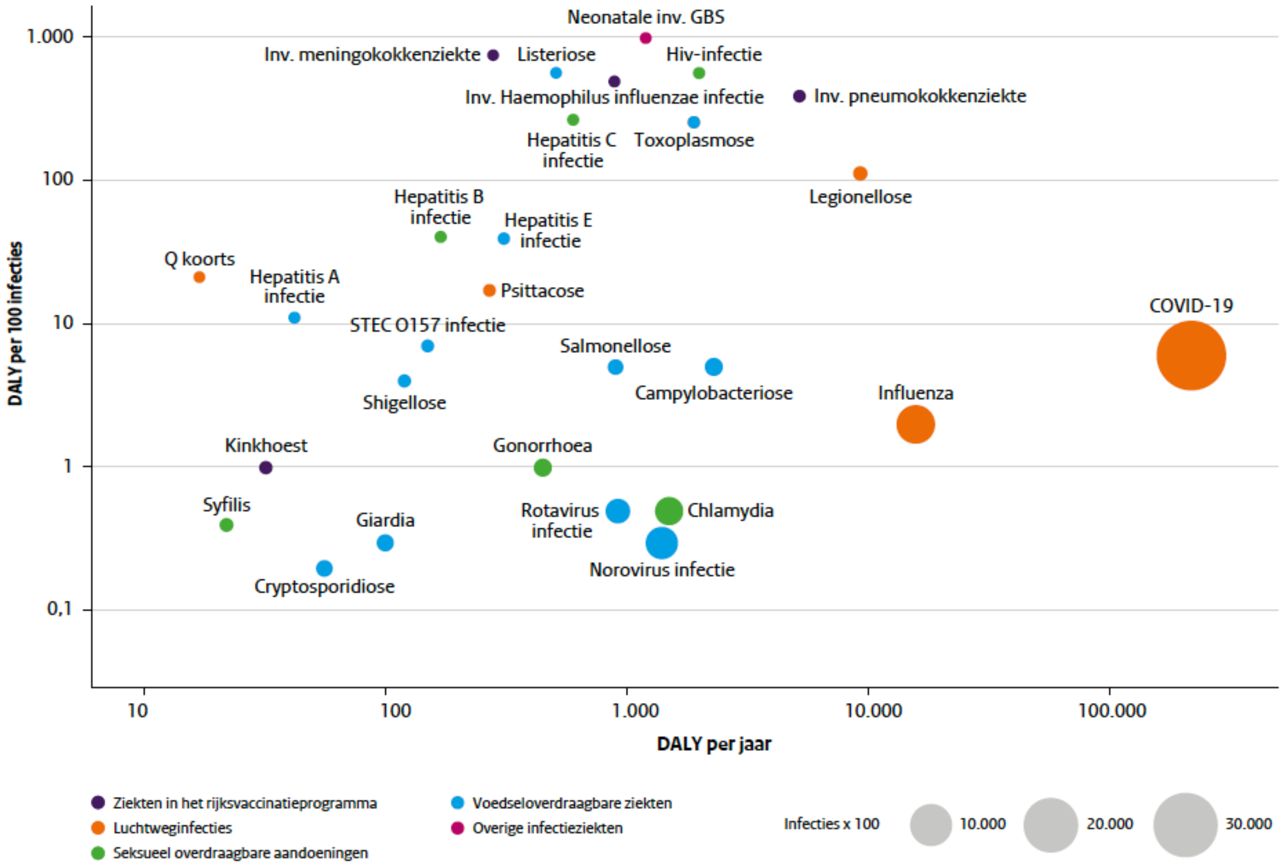
Average burden of infectious diseases 2017 - 2020

Figuur 3.2 Gemiddelde jaarlijkse ziektelast in DALY in Nederland in de periode 2017-2021 (2017-2020 voor chlamydia, gonorroe, syfilis, 2017 voor Lyme borreliose, en 2017/2018 – 2021/2021 voor influenza, uitgezonderd 2020/2021), uitgesplitst naar YLD en YLL





For Covid-19 the burden is for 2021

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Covid modelling work done in Utrecht

- Impact of self imposed measures and awareness on epidemic spread
- Effectiveness of contact tracing and isolation/quarantine
- Effects of school closure on epidemic spread
- Effects of universal testing strategies
- Impact of loss of adherence to measures during vaccination rollout
- Testing and quarantine measures at schools to reduce transmission
- Effectiveness of corona pass for reducing transmission

Communication to members of advisory team for ministry of health
Communication to media

Challenges

Isaac Newton Institute for Mathematical Sciences

What's On Visitors Documents Outreac

Home > What's On > Programmes & Workshops

Infectious Dynamics of Pandemics: Mathematical and statistical challenges in understanding the dynamics of infectious disease pandemics

IDP

5 May 2020 to 18 December 2020

Epidemics 38 (2022) 100546

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

ELSEVIER

Challenges for modelling interventions for future pandemics

Mirjam E. Kretzschmar [a,*], Ben Ashby [b], Elizabeth Fearon [c,d], Christopher E. Overton [e,f,g], Jasmina Panovska-Griffiths [h,i], Lorenzo Pellis [e,f,j], Matthew Quaife [k], Ganna Rozhnova [a,l], Francesca Scarabel [e,f,m], Helena B. Stage [e,f,n,o], Ben Swallow [p,q,1], Robin N. Thompson [f,r,s], Michael J. Tildesley [f,r,s], Daniel Villela [t]

Special issue Epidemics:
https://www.sciencedirect.com/journal/epidemics/special-issue/10DM7ZPJKM9

Translating modelling theory about pathogen evolution into epidemic-specific interventions that limit the risk of variants of concern emerging

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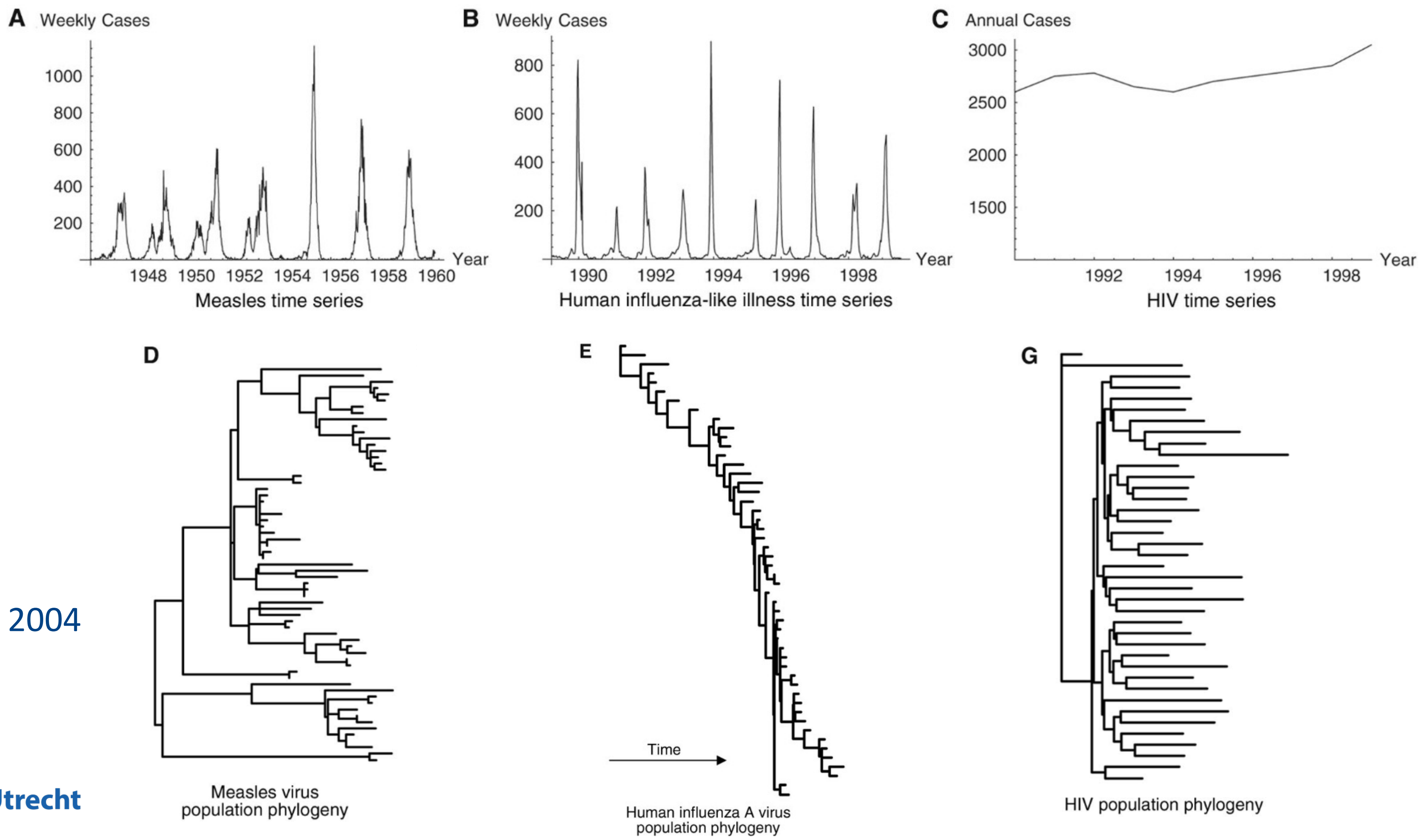
Interplay epidemiology and pathogen evolution



Grenfell et al 2004

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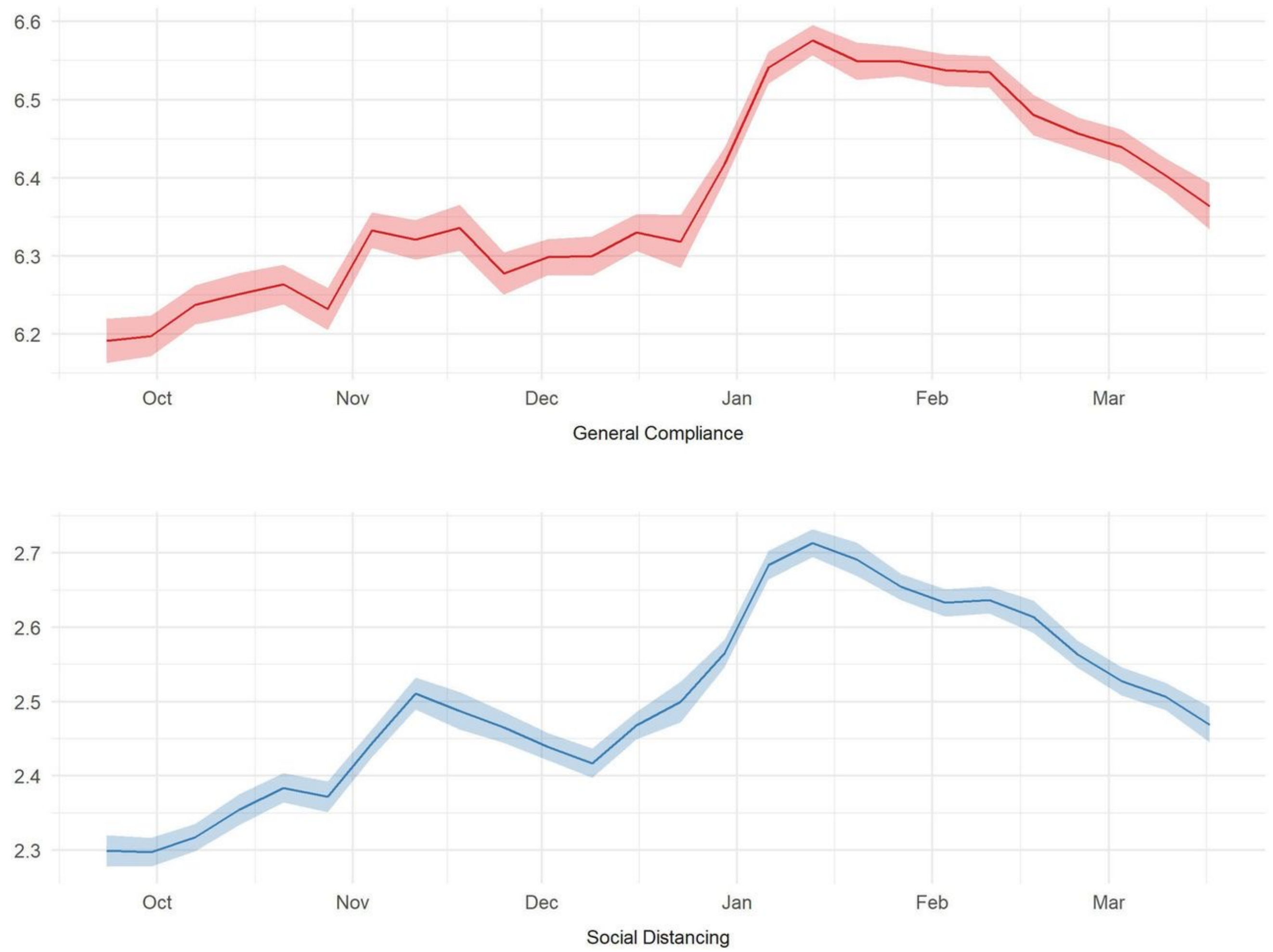
Changes in ~~behaviour~~ behaviour: difficult to include in model

Example:

Trends in compliance behaviours.

No difference observed between vaccinated and unvaccinated

Longitudinal study in UK



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Liam Wright et al. J Epidemiol Community Health
doi:10.1136/jech-2021-217179

JECH

SARS-CoV-2 in different countries

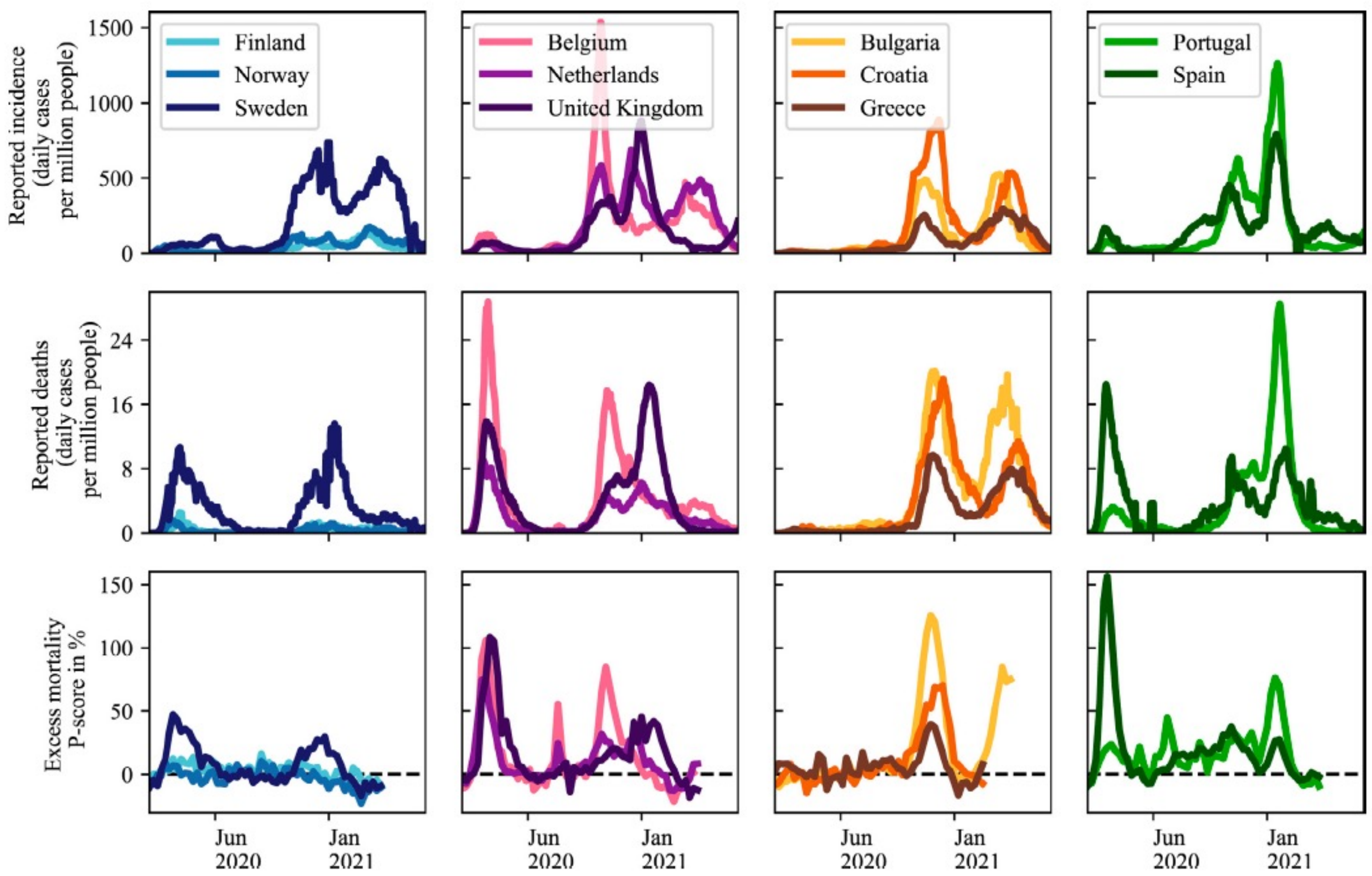

Fig. 2. Comparison of the COVID-19 pandemic in a selection of European countries grouped by geographical proximity. Many differences in reported incidence, reported deaths and excess mortality can be observed. Even though reported numbers are associated with wide uncertainty, the differences between countries and waves are evident. Data sources: https://ourworldindata.org/covid-cases and https://ourworldindata.org/excess-mortality-covid (Accessed: June 29, 2021).

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For discussion in this workshop

How can we contribute to support present and future public health policy?

- Enable more communication between modellers and policy makers
- Making advanced methods accessible
- Educating the public about aims other than prediction
- Develop ideas for translational research

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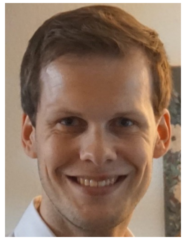


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