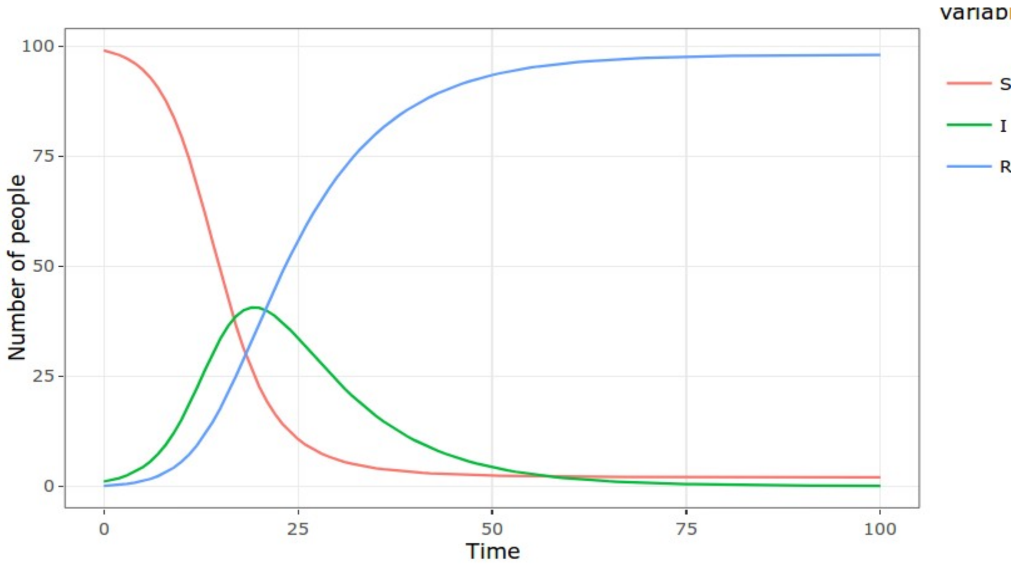
Introduction to Epidemiology



What is Epidemiology?

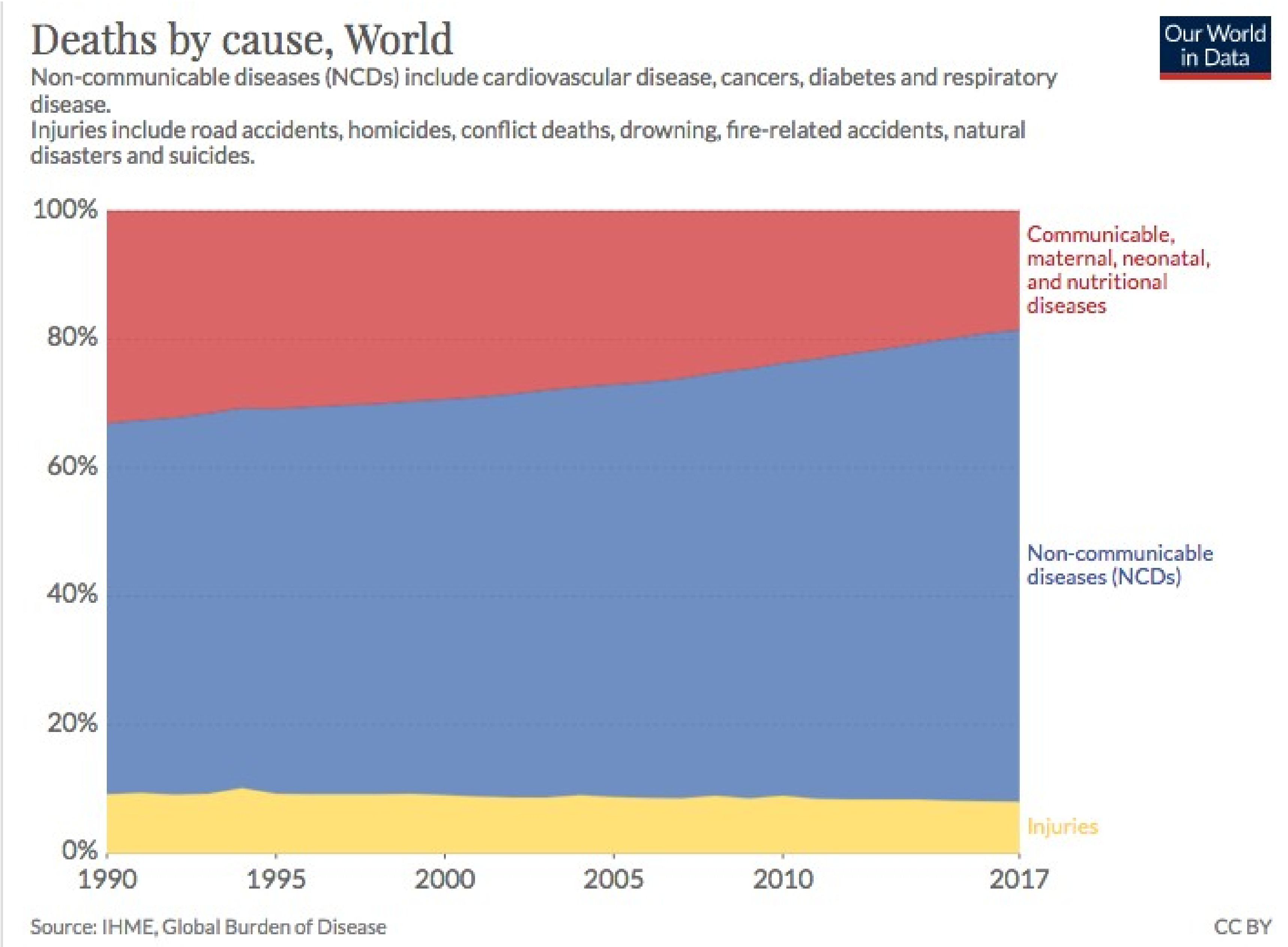
- The word is derived from two Greek components
- “Epi” = Upon
- “Demos” = Population (e.g. Democracy)
- So … Epidemiology is the study of something that acts upon populations

Epidemiology and parasitology

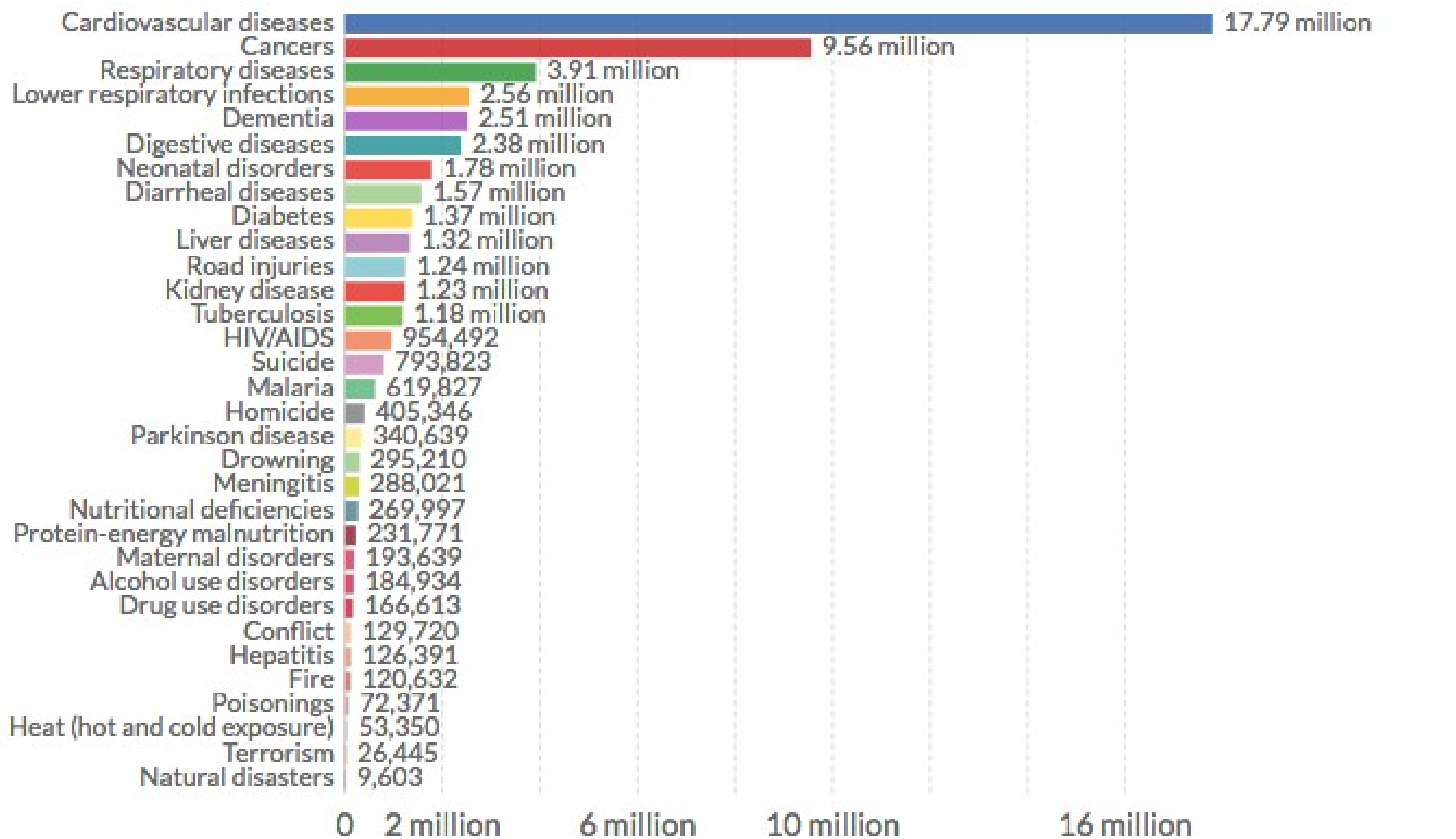
- **Epidemiology** places the focus on the population affected by the disease.
- **Parasitology** tends to focus on the parasite causing disease
- Historically bacteria and viruses were not treated as classic parasites (due partly to their **invisibility**)
- Bacteria and viruses tend to have **simpler life histories,** although they may still occur in multiple hosts
- Modern epidemiology also looks at **non transmissible** illnesses associated with **life style** and **environment**.
- Epidemiology provides guidance for **Public health** policy

What do people die of ?

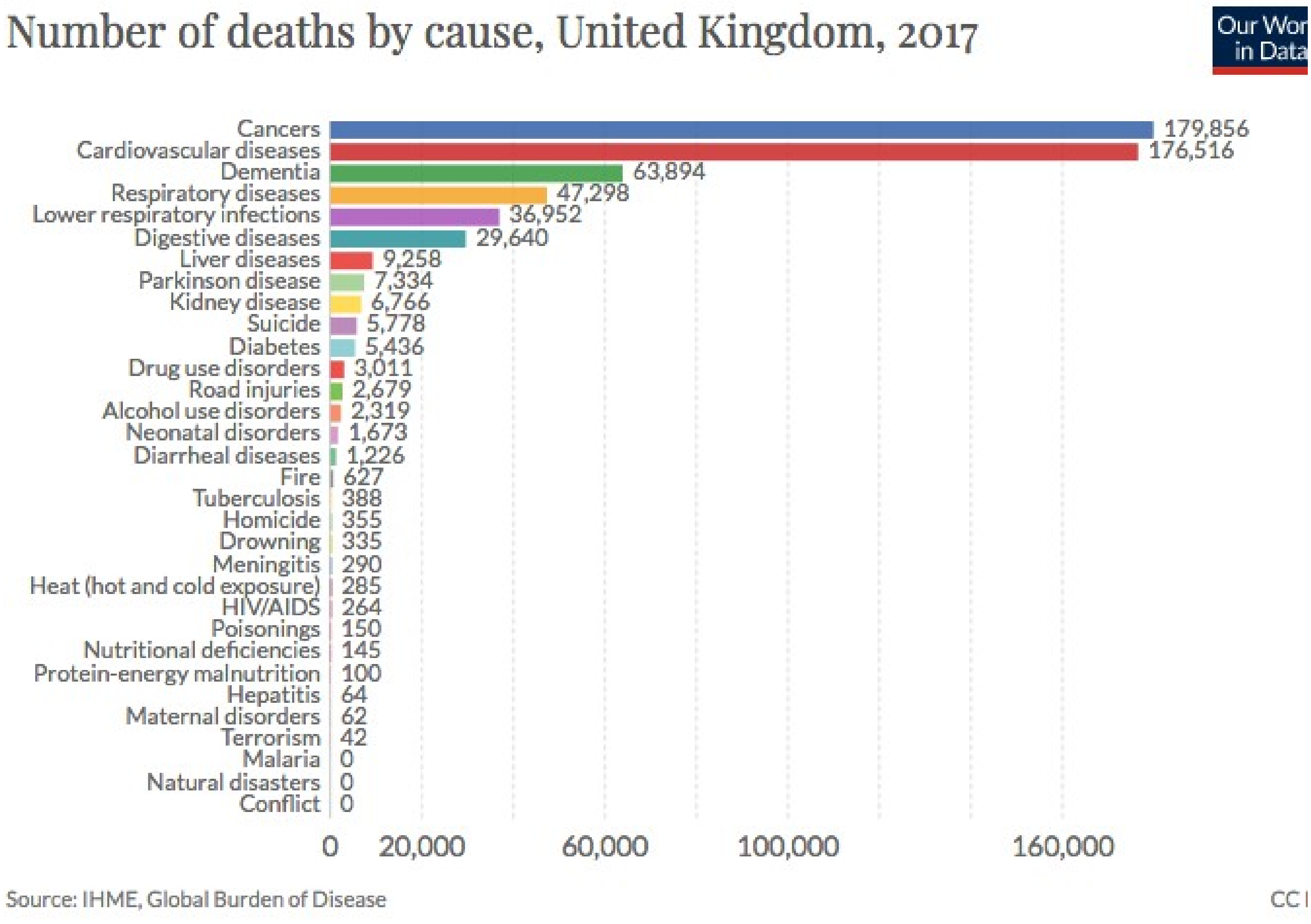
- In a typical year death as a direct result of a communicable illness has become relatively uncommon in the UK
- The most common causes of death are cardiovascular illnesses and cancer
- So .. many pubic health measures now concern altering life styles associated with risks of non communicable illnesses (smoking, obesity, lack of exercise)
- However …. as we have now been reminded … communicable diseases **can** have very major societal impacts
- They can cause epidemics/pandemics


Deaths by cause, World
Our World in Data
Non-communicable diseases (NCDs) include cardiovascular disease, cancers, diabetes and respiratory disease.
Injuries include road accidents, homicides, conflict deaths, drowning, fire-related accidents, natural disasters and suicides.
100%
80%
60%
40%
20%
0%
1990
1995
2000
2005
2010
2017
Communicable, maternal, neonatal, and nutritional diseases
Non-communicable diseases (NCDs)
Injuries
Source: IHME, Global Burden of Disease
CC BY

Number of deaths by cause, World, 2017



Source: IHME, Global Burden of Disease


Number of deaths by cause, United Kingdom, 2017
Our World in Data
Cancers 179,856
Cardiovascular diseases 176,516
Dementia 63,894
Respiratory diseases 47,298
Lower respiratory infections 36,952
Digestive diseases 29,640
Liver diseases 9,258
Parkinson disease 7,334
Kidney disease 6,766
Suicide 5,778
Diabetes 5,436
Drug use disorders 3,011
Road injuries 2,679
Alcohol use disorders 2,319
Neonatal disorders 1,673
Diarrheal diseases 1,226
Fire 627
Tuberculosis 388
Homicide 355
Drowning 335
Meningitis 290
Heat (hot and cold exposure) 285
HIV/AIDS 264
Poisonings 150
Nutritional deficiencies 145
Protein-energy malnutrition 100
Hepatitis 64
Maternal disorders 62
Terrorism 42
Malaria 0
Natural disasters 0
Conflict 0
0
20,000
60,000
100,000
160,000
Source: IHME, Global Burden of Disease
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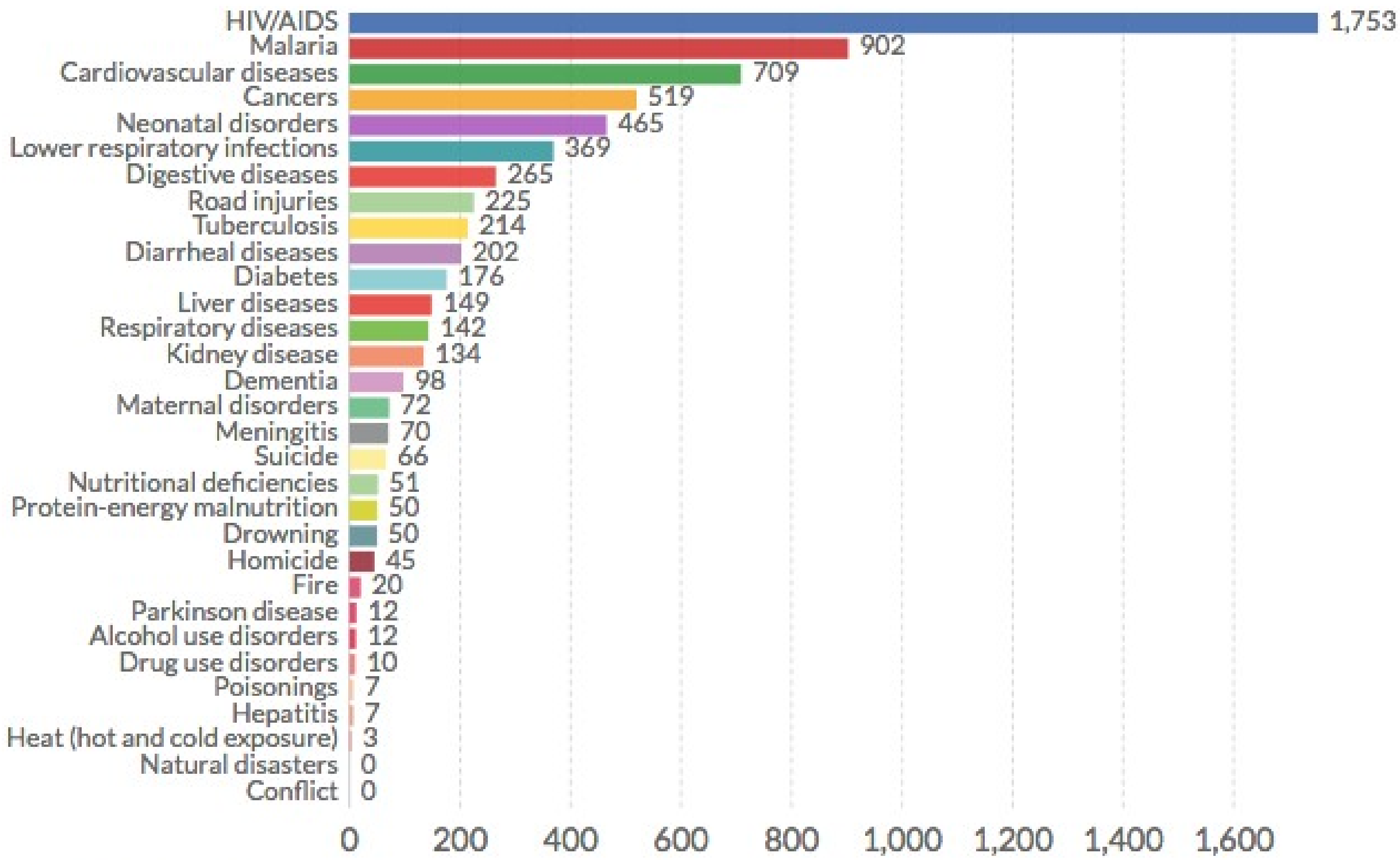
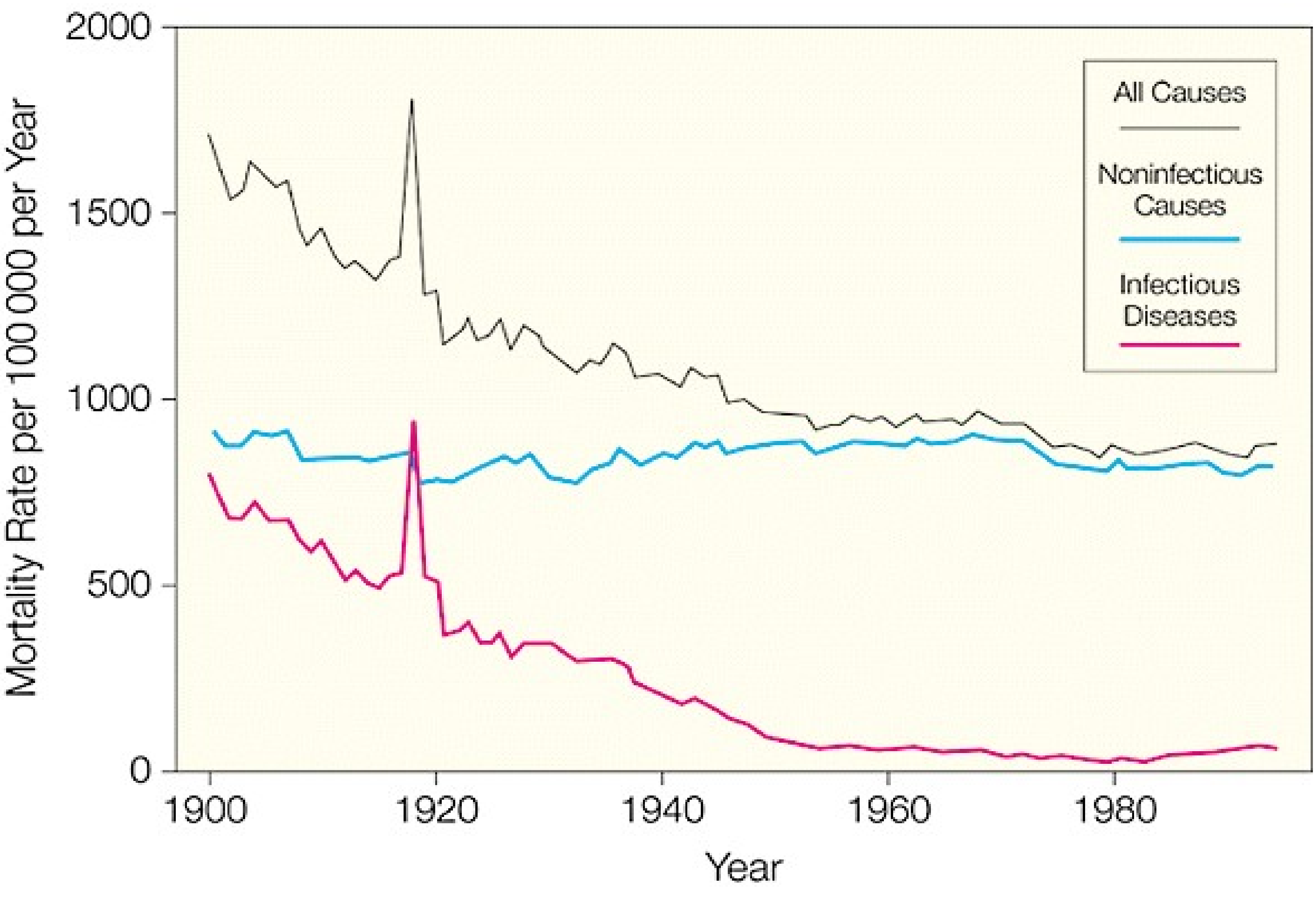
Number of deaths by cause, Equatorial Guinea, 2017



Percentage of human deaths attributed to communicable diseases

Deaths through communicable diseases in USA



Communicable illness and epidemics

- Transmittable (communicable) diseases pass from person to person, or organism to organism
- Contagious diseases spread within a population.
- A disease can be transmittable but not contagious, if the rate of spread is normally very low
- Not all communicable diseases lead to epidemics

Some terminology

- **Population at risk** : number of potential infections
- **Exposure:** contact with disease causing agent
- **Incidence** : number of new cases
- **Duration** : time that a case lasts
- **Prevalence** : Proportion of population affected
- **Morbidity:** Effects falling short of death
- **Mortality**: Death
- **Endemism**: Continuous presence in a population

Spatial scale

- The term epidemic applies when a contagious element spreads through any population at risk

- Outbreak: An epidemic that is limited to a defined **local** population at risk
- Pandemic: An epidemic that potentially impacts the entire **global** population

Origins of epidemiology as a science

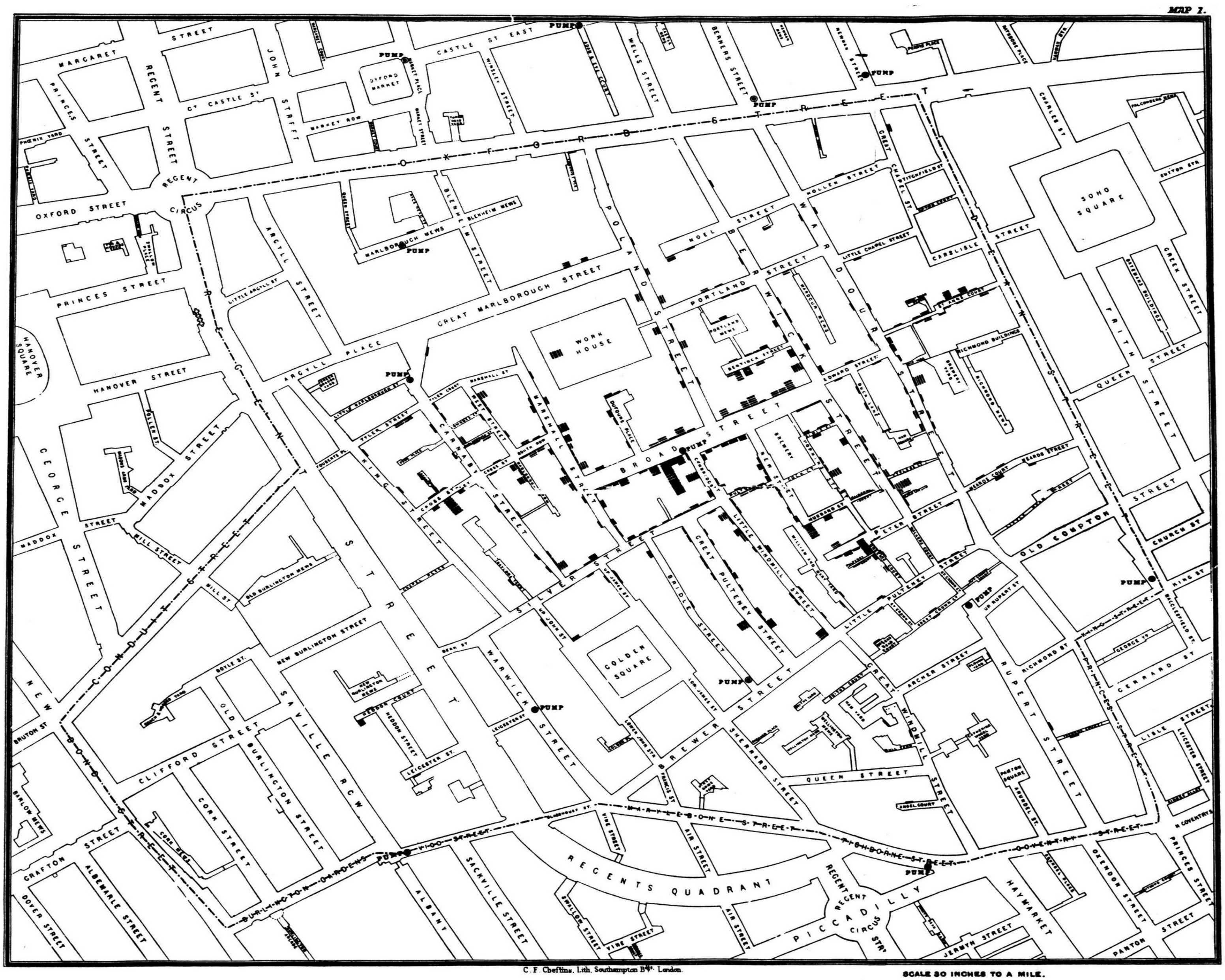
- The underlying cause of disease were not well understood until the 20th century
- Early epidemiologists aimed to understand the cause of incidence, prevalence and spread, rather than to study the agent
- The classic text book example: Cholera in London


RSC | Advancing the Chemical Sciences
National Chemical Landmark
Dr John Snow
(1813-1858)
Founding father of Epidemiology.
In 1854 his research linked
deaths to the water pump
near this site and thus
determined that cholera is
a water borne disease.
16 June 2008

Using spatial patterns to identify causes of disease

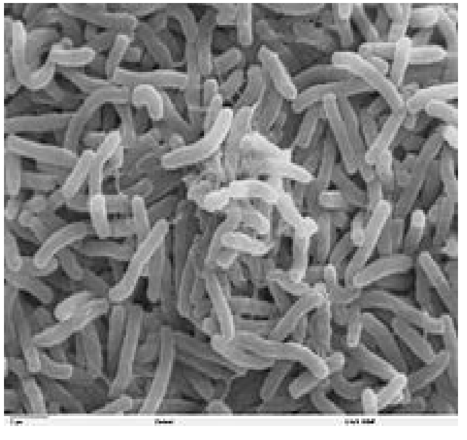
- Famous early example
- John Snow identified the origin of a cholera outbreak through mapping
- Studied a communicable (infectious/transmittable) disease
- Cholera first thought to be caused by a “miasma” in the air
- “The result of my inquiry is, that there has been no particular **outbreak** or **prevalence** of cholera in this part of London except among the persons who were in the habit of drinking the water of the Broad street pump”
- Cholera was eliminated in the UK through provision of sewage treatment.

Snow's original map



Cholera

- Caused by bacteria *Vibrio cholerae*
- Occurs naturally in brackish and freshwater at low densities
- Shellfish in contaminated water concentrate bacteria found in plankton
- Transmitted through fecal/oral route



Cholera

- Causes vomiting and watery diarrhoea
- Many cases (up to 90%) asymptomatic or mild
- Around **100 million** bacteria needed to initiate symptoms caused by infection of small intestine
- Severe cases lead to death through dehydration
- One person can produce 10 litres of highly infectious diarrhoea in one day
- Cholera **outbreaks** often associated with natural disasters (hurricanes, floods, earthquakes)
- No risk of a modern cholera pandemic

Cholera

- Treated with antibiotics (although resistant strains increasingly common)
- Vaccination also available
- Oral rehydration usually prevents death
- Most effective control measure is **prevention of spread** through **public** health measures
- Focus is on the **population at risk**, not on the individual cases.

Epidemics that changed human history

- Black death: Led to the end of the feudal system
- “Guns germs and steel”: Diseases (particularly smallpox) introduced to the new world led to the collapse of the Mayan, Aztec and Inca empires,
- Spanish flu: Could have produced some of the social conditions that led to the second world war.

Historical pandemics

- 1334-1347: Black Death devastates Europe Three-quarters of the population possibly killed.
- 1348 Black death reached England and killed around 30% of the population
- 1563: Bubonic plague in London. One-half to one-third of London population die.
- 1665: The Great Plague of London. 20% of the London population (100,000) die.

Historical pandemics

- 1817-23: First global cholera pandemic.
- 1857-59: Worldwide influenza pandemic.
- 1863-79: Fourth global cholera pandemic.
- 1881-96: Fifth cholera pandemic.
- 1889-90: 'Russian flu' pandemic. Estimated 250,000 die in Europe
- 1918: 'Spanish flu' pandemic. 20m-40m die worldwide, more than were killed in the first world war. **The worst pandemic in history.**

The black death

Plague

- Rod shaped bacteria *Yersinia pestis*
- Leads to pneumonic, septicaemic and bubonic plague
- Usually transmitted between rodents and fleas. Fleas then transmit the disease to humans
- Pneumonic form spread between humans by coughing and sneezing
- Streptomycin effective modern cure in most cases (there is some resistance)
- Now only a few thousand cases per year (Asia, Madagascar). Some transmission from prairie dogs in USA. No human to human transmission in developed countries

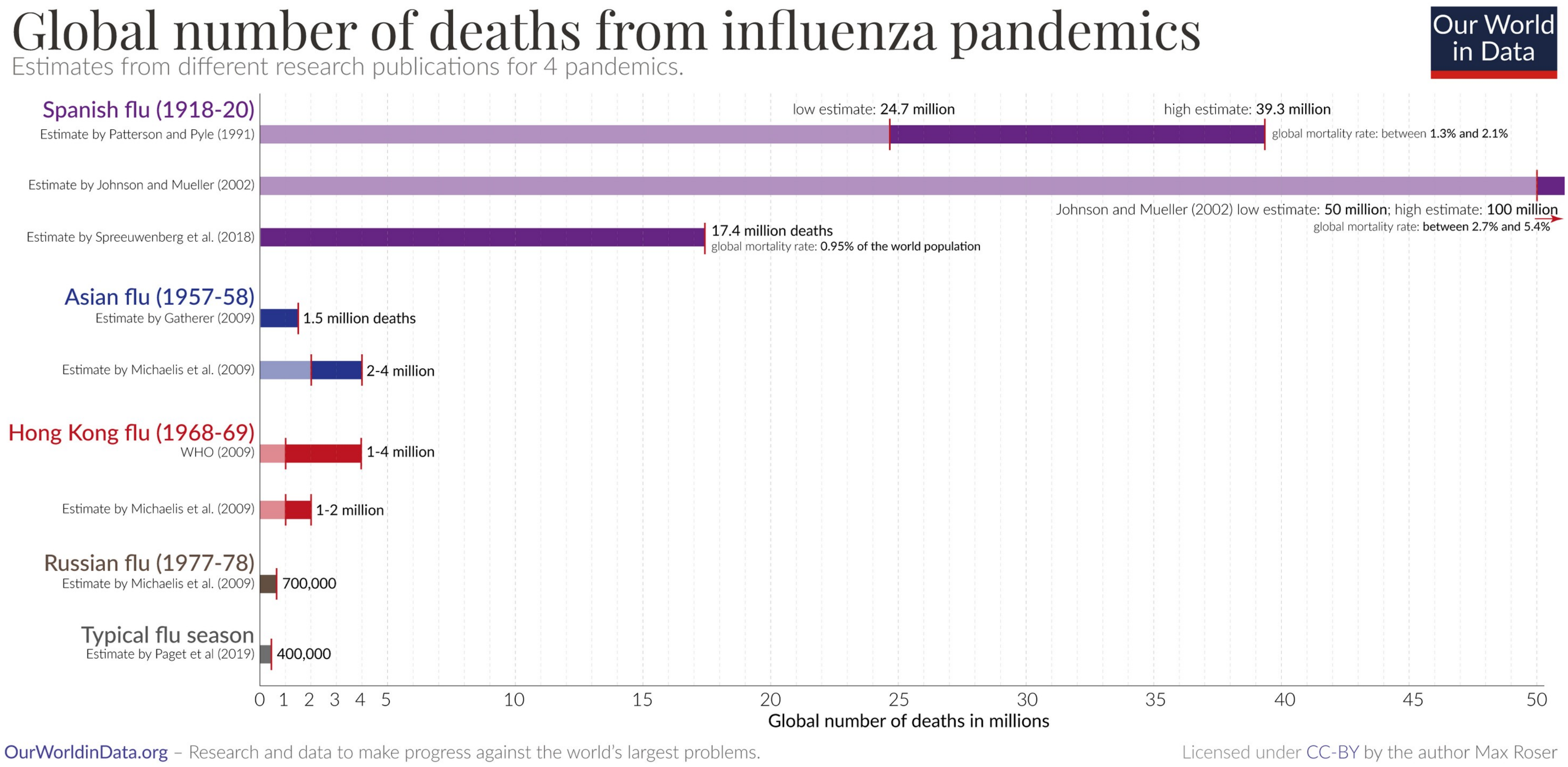
The fall of the Aztecs

- Smallpox introduced to MesoAmerica at beginning of 16th century
- Spread to Tenotichlan (Mexico city) prior to arrival of Cortes
- Reduced the population by up to 80%

Smallpox

- Caused by two viruses *Variola major* and *Variola minor*
- Eradicated in 1980 as a result of vaccination first discovered by Jenner (1798) developed from cowpox (Vaccine from vacca, latin for cow)
- Transmitted person to person, mainly through direct contact
- Infectious stage short in duration
- Natural acquired immunity in populations where smallpox endemic
- No immunity initially in the unexposed populations of the New World

Influenza pandemics



“Spanish flu”

- Estimate of 50 million: 2.7% of the world population at the time.
- Could have been 100 million (5.4%)
- Russian flu pandemic (1889-1894) is believed to have killed 1 million people
- https://ourworldindata.org/spanish-flu-largest-influenza-pandemic-in-history
-

“Spanish” flu

- Epidemics often mistakenly named after country of supposed origin.
- Spanish flu may actually have begun in New York (Olson et al 2006)
- Young people were at greater risk than the older population, which is not the usual pattern.
- This could have been due to acquired immunity of the older population exposed to the “Russian” flu

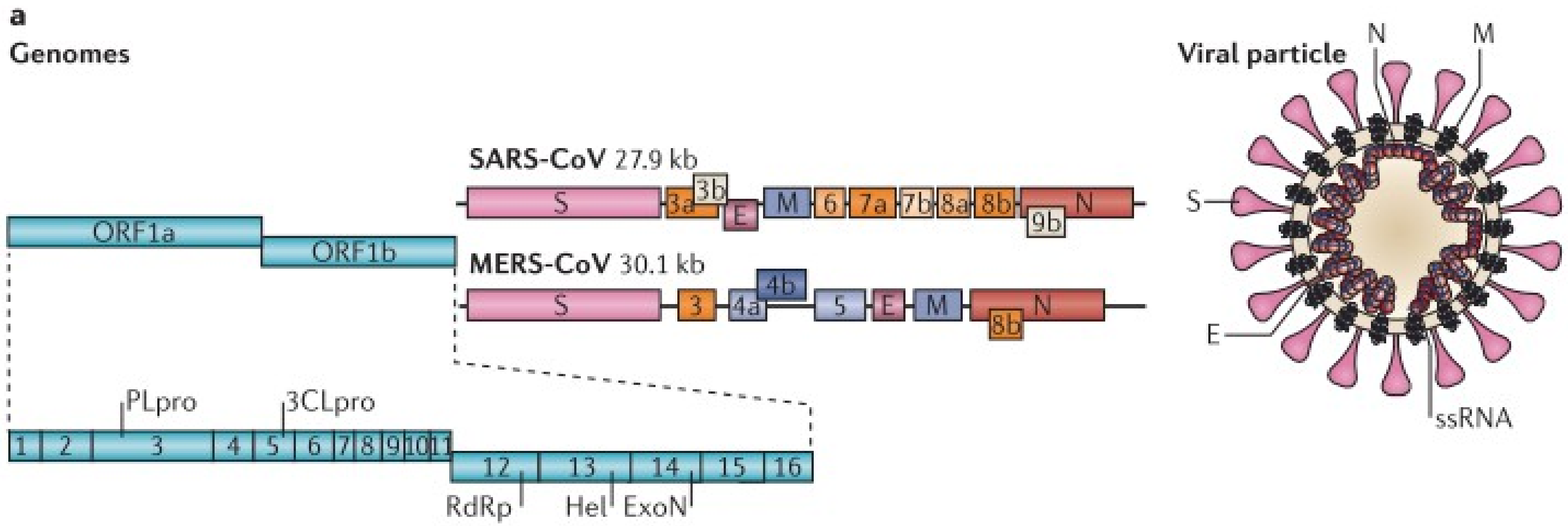
2009 “swine flu”

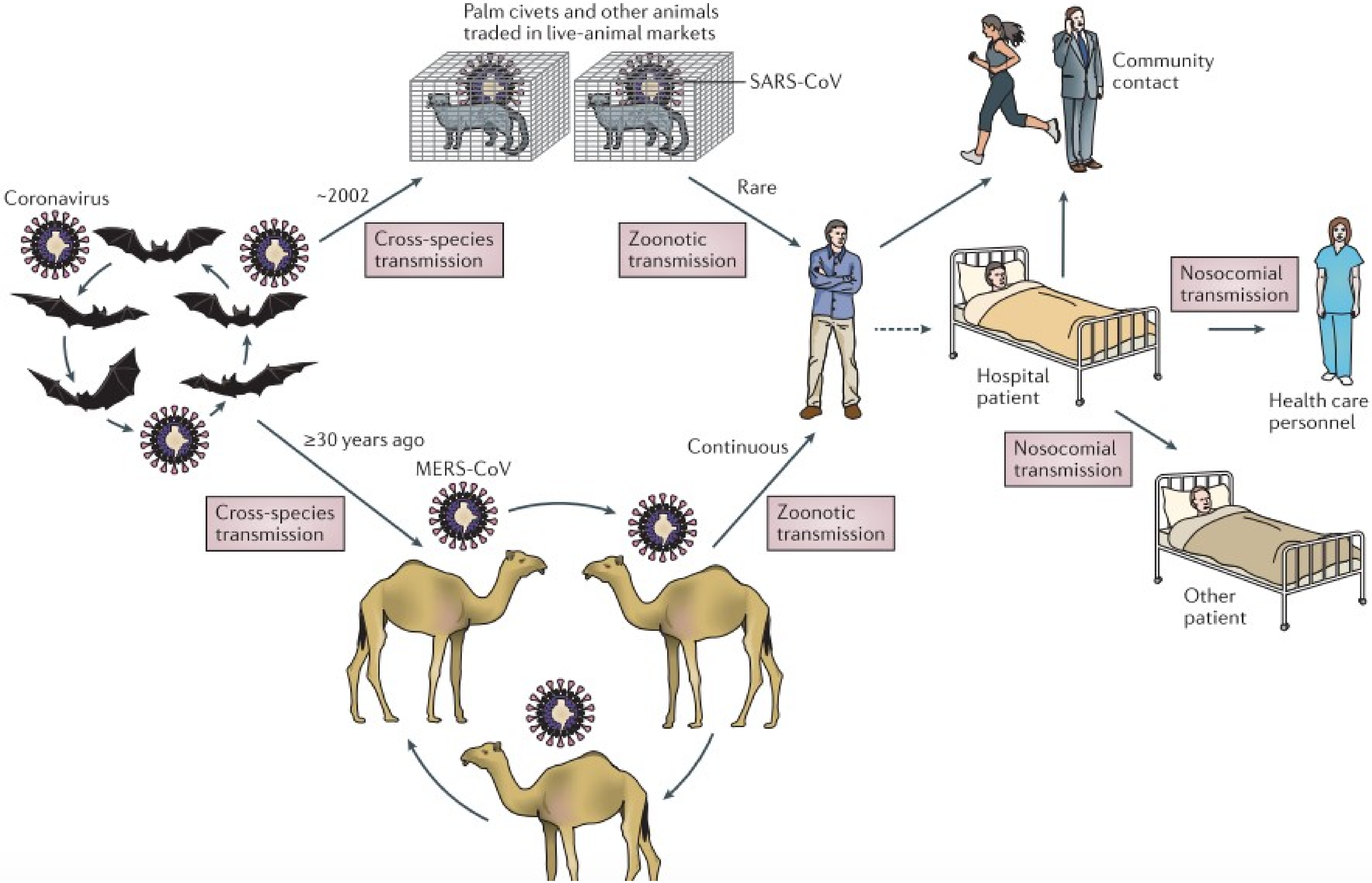
- Typical seasonal epidemics of influenza dominated by A/H3N2 strains
- March 2009: New swine-origin influenza virus (S-OIV), A (H1N1), emerged in Mexico and the USA.
- The virus quickly spread worldwide through human-to-human transmission
- June 11: WHO raised the influenza pandemic alert to the highest level (level 6)
- Hindsight showed that the strain had in fact very low virulence (only 0.02% to 0.1% fatality rates)

SARS and MERS

- Severe Acute Respiratory Syndrome and Middle Eastern Acute Respiratory Syndrome
- April 2003: SARS coronavirus (SARS-CoV) identified by researchers
- July 2003:   8,096 reported cases, including 774 deaths in 27 countries
- No more infections were detected after July
- June 2012: MERS-CoV identified in Saudi Arabia
- Led to 1,728 confirmed cases and 624 deaths

SARS and MERS





Palm civets and other animals traded in live-animal markets
SARS-CoV
Community contact
Coronavirus
~2002
Rare
Cross-species transmission
Zoonotic transmission
Nosocomial transmission
Hospital patient
Health care personnel
≥30 years ago
Continuous
Nosocomial transmission
MERS-CoV
Cross-species transmission
Zoonotic transmission
Other patient

Modelling epidemics

- Wide range of modelling techniques
- Spatial monitoring a key element in determining response
- Real time data can be very difficult to interpret
- Pandemics result in data sources that vary between countries

Modelling epidemics

- The government’s response to the current covid-19 pandemic is being guided by epidemiological modelling.
- “*All models are **wrong**. But some are useful*”
- Models are based on sets of simplifying assumptions regarding how the system that is being modelled works.
- Model parameterisation relies on good data
- If parameters are unknown then models **can** still be used. However the uncertainty in model parametrisation **must** be propagated through the model and be reflected in uncertainty regarding predictions.
- Modellers seek to avoid producing GIGO models. A model can be deliberately wrong, For example. unlikely worst case scenarios enhance preparedness.

Modelling epidemics

”Development of strategies for mitigating the severity of a new influenza pandemic is now a top global public health priority.

- Influenza prevention and containment strategies can be considered under the broad categories of
  - antiviral,
  - vaccine and
  - non- pharmaceutical measures … case isolation, household quarantine, school or workplace closure, restrictions on travel .
- Mathematical models are powerful tools for exploring this complex landscape of intervention strategies and quantifying the potential costs and benefits of different options.”

Ferguson, N. M. *et al.* (2006) ‘Strategies for mitigating an influenza pandemic’, *Nature*, 442(7101), pp. 448–452.

Assumptions made by Ferguson *et al* in 2006

- Assumed …..
  - 30% of transmission occurs within the household
  - 33% in the general community
  - 37% in schools and workplaces
  - Per capita contact rates are assumed to be double in schools than workplace

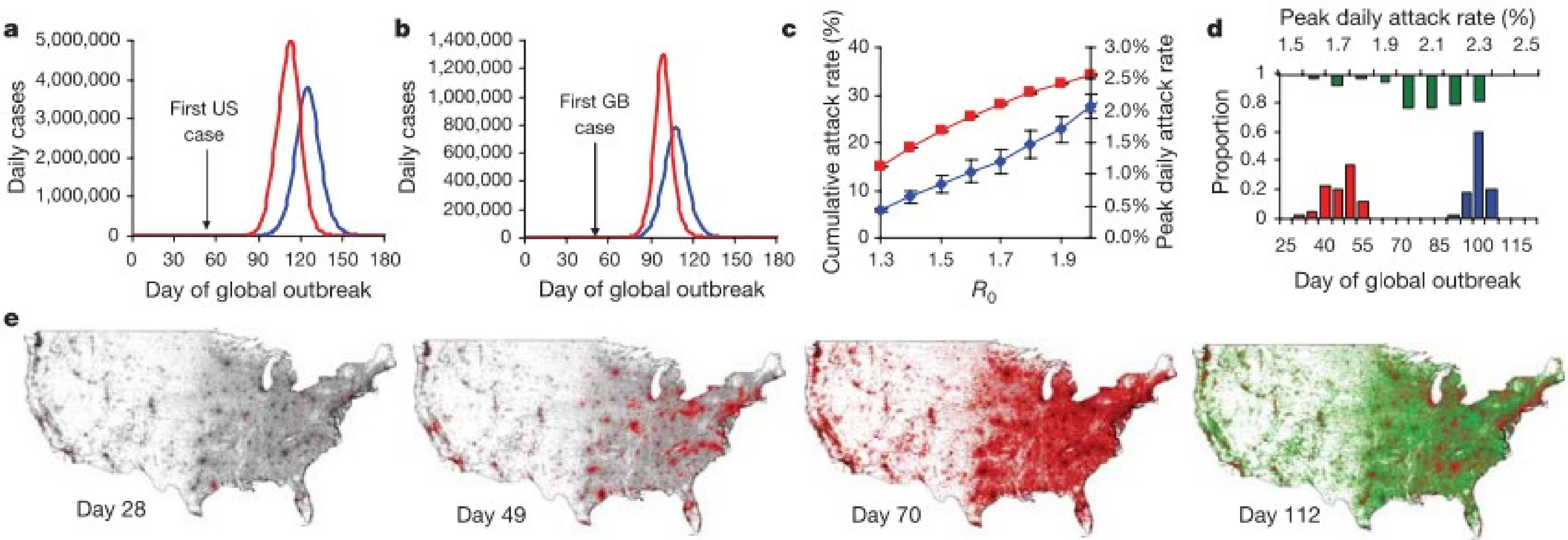
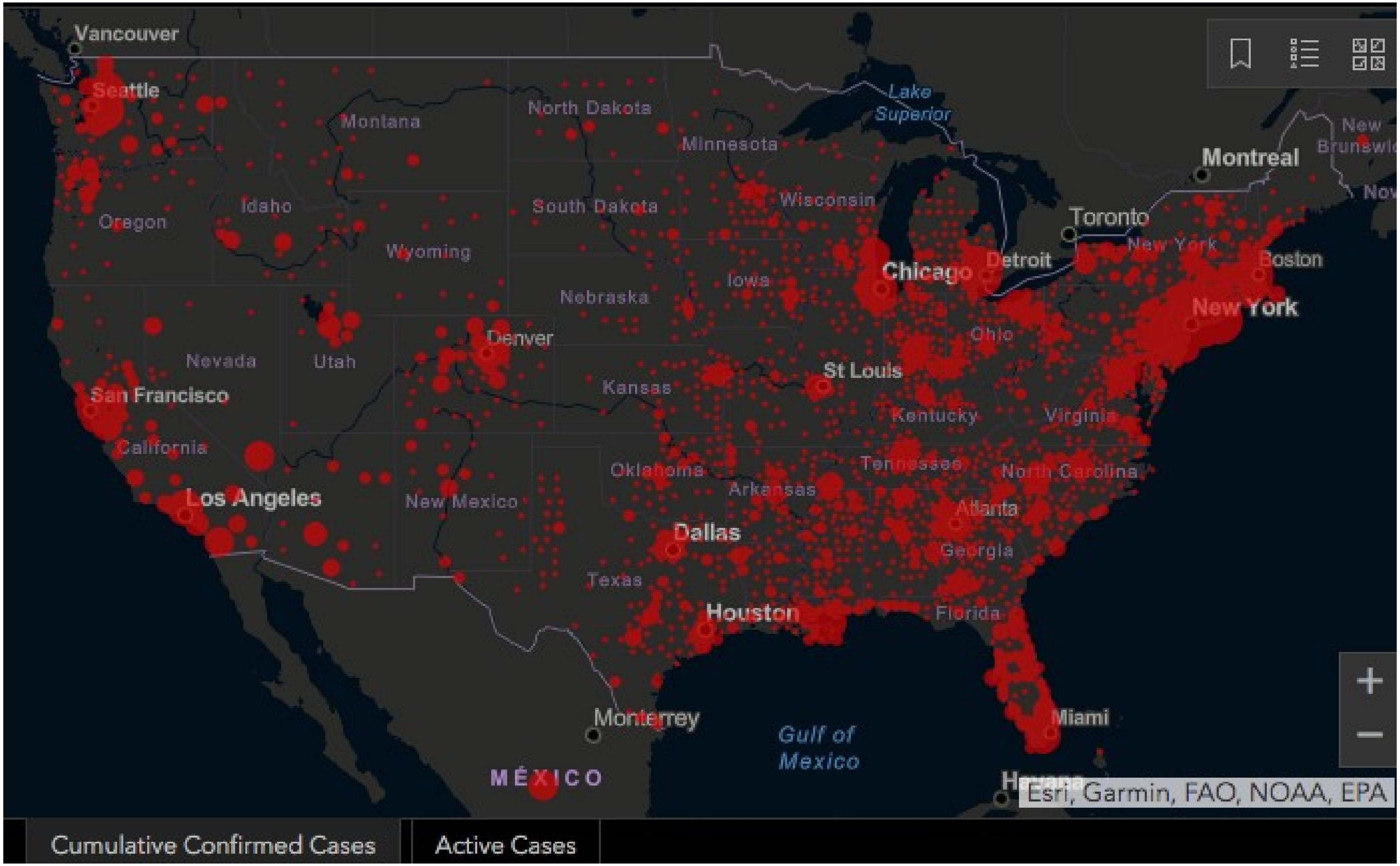


Figure 1 | Baseline pandemic dynamics. **a**, Clinical case incidence per day for the US pandemic (single realization shown) for high (red) and moderate (blue) transmissibility scenarios, assuming a generation time of 2.6 days, and that 50% of infected people are ill enough to be classified as clinical cases. Infection is seeded in the country as a function of the expected importation of infection from overseas derived from a simple global model of pandemic spread and available travel data (see Supplementary Information). Assumed population size of the United States was 300 million. Timing is shown both as days from the first case globally, and as days from the first case in the country. **b**, As **a**, but for Great Britain (modelled population size 58.1 million). **c**, Cumulative (red) and peak daily (blue) clinical attack rates as a function of R_0 for Great Britain, averaged over 40 model realizations. Error bars show standard deviations. **d**, Histogram showing stochastic variability (across 40 model realizations) in timing of initial case (red), peak of epidemic (blue) and peak attack rate (green) for Great Britain ($R_0 = 2.0$). **e**, Snapshots of the extent of spread of the US pandemic (moderate transmissibility) at four time points. Greyscale indicates population density; red indicates areas with infective cases; and green indicates areas where the pandemic is over. See Supplementary Information for full parameter and model details.

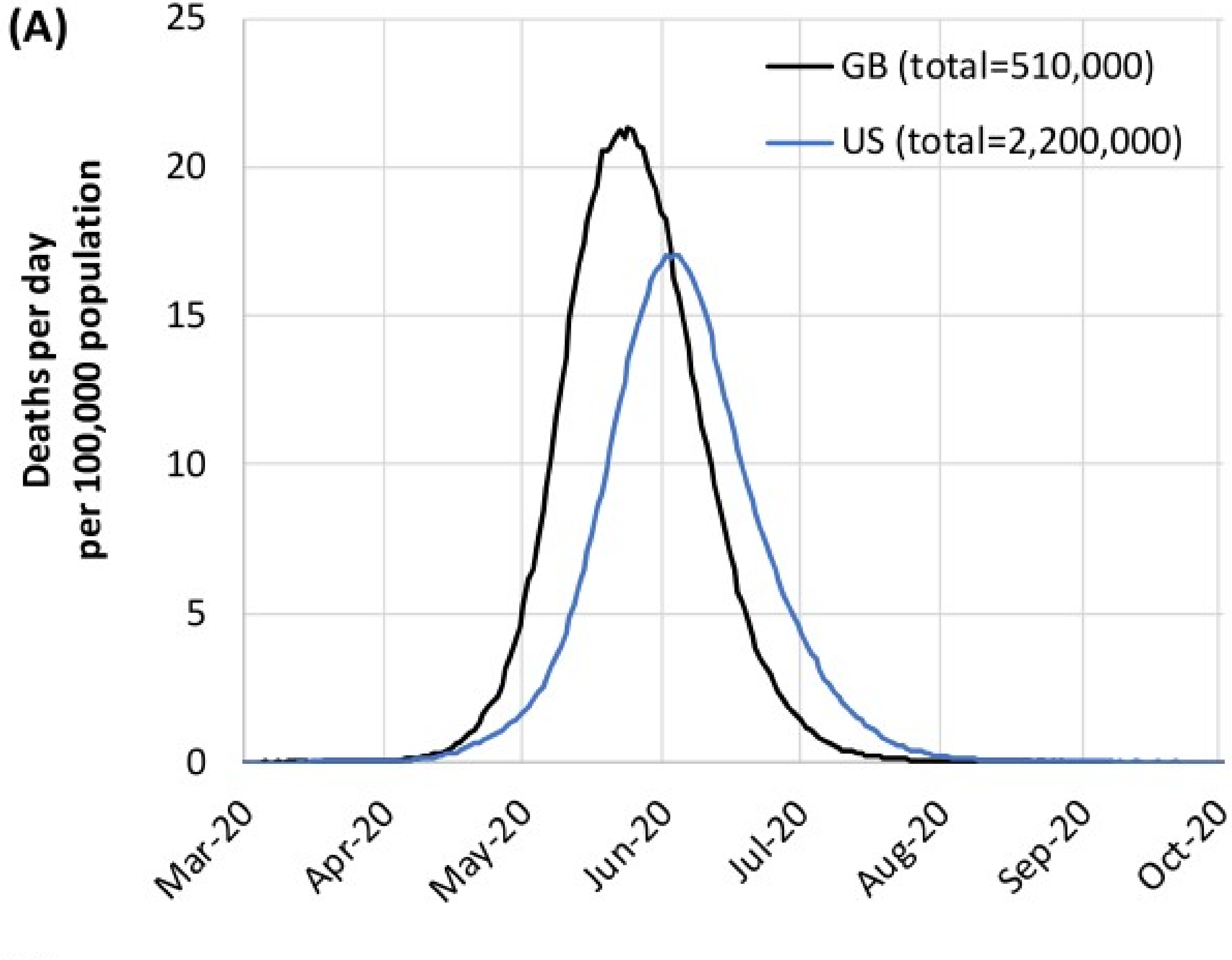
”In the United States, more structure is apparent: early spread is focal around seed infections (typically in urban centres) imported from overseas, but rapidly becomes almost homogenously distributed across the whole population”



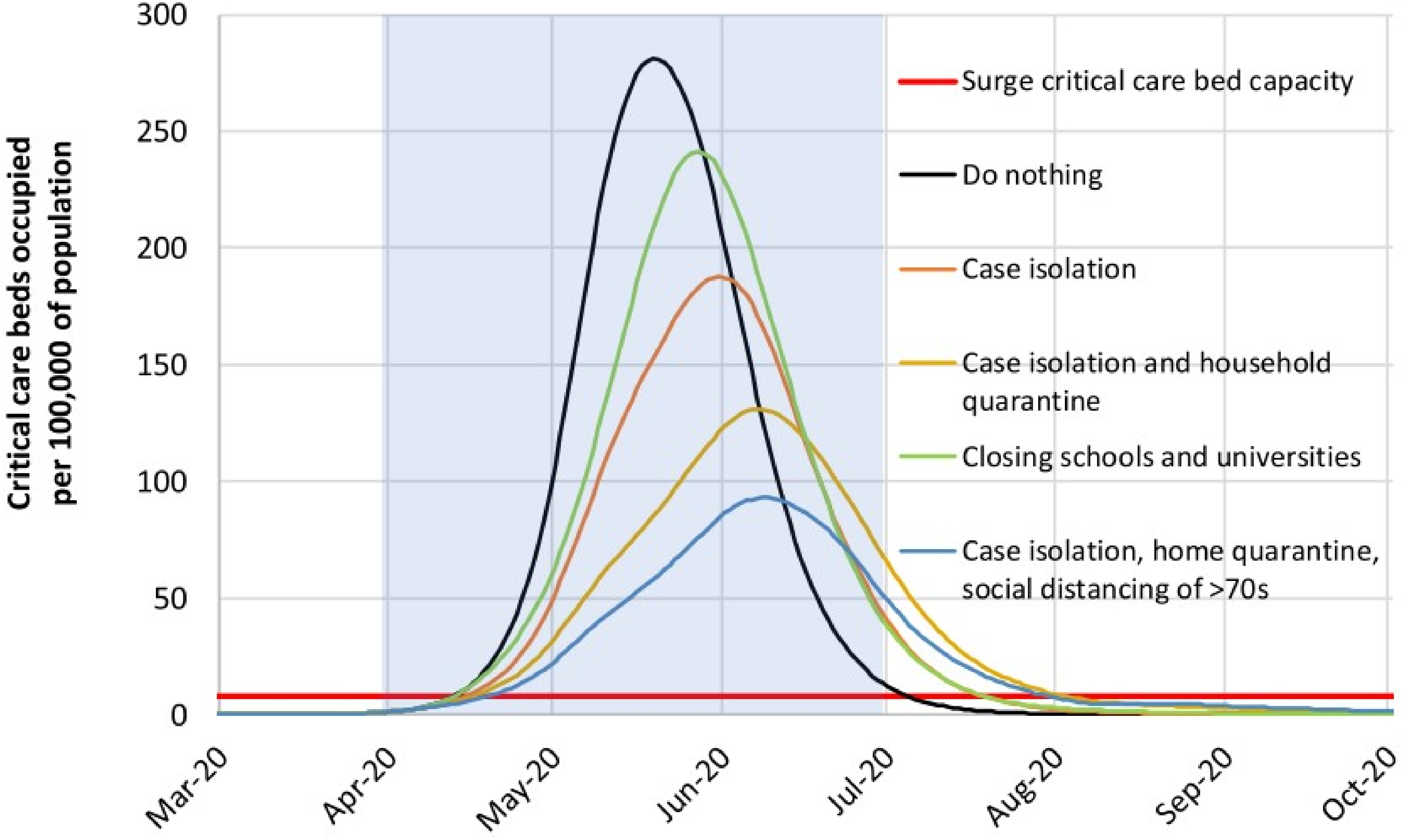
Modelling to advise government policy

- Ferguson, N. M. et al. (2020) ‘Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand’, (March), p. 20. doi: 10.25561/77482.
- The model predictions can be avoided

Predicted deaths



Predicted cases



Assumptions can differ

Lourenço, J. et al. (2020) ‘Fundamental principles of epidemic spread highlight the immediate need for large-scale serological surveys to assess the stage of the SARS-CoV-2 epidemic’, Unpublished report from the University of Oxford

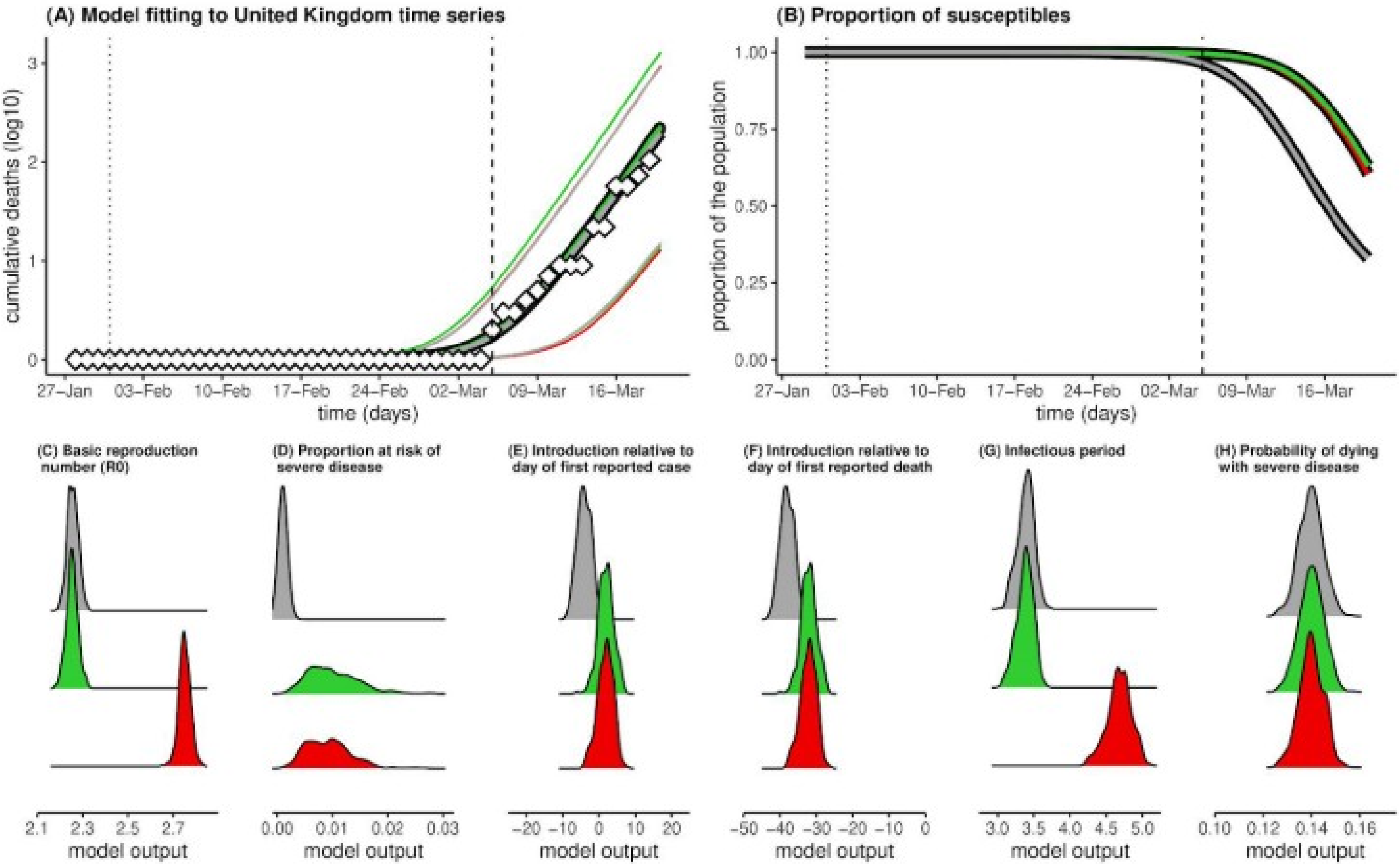


Figure 1. *Results for the United Kingdom for three scenarios:* $R_0 = 2.25$ *and* $\rho = 0.001$ *(grey),* $R_0 = 2.25$ *and* $\rho = 0.01$ *(green), and* $R_0 = 2.75$ *and* $\rho = 0.01$ *(red). MCMC ran for 1 million steps. Results presented are the posteriors (model output) using 1000 samples after a burnout of 50%* ***(A)*** *Model fits showing reported (diamonds) and model (lines) cumulative death counts. Deaths are log10 transformed for visualisation.* ***(B)*** *Mean proportion of the population still susceptible to infection (1-z, see Model).* ***(A-B)*** *Vertical lines mark the date of the first confirmed case (dotted) and date of first confirmed death (dashed).* ***(C)*** *Posteriors for* R_0, ***(D)*** *proportion of population at risk of severe disease (* ρ *).* ***(E)*** *Time of introduction relative to the date of the first*

Oxford model predictions not supported

- The Oxford model suggested that up to 30% of the population already had contact with Covid-19

Modelling epidemics

- The SIR model

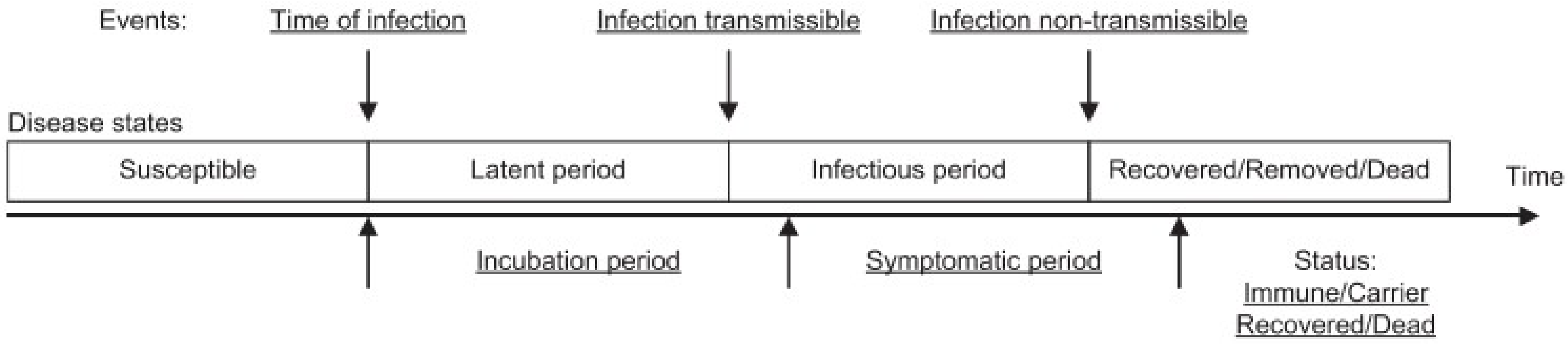
  Kermack and McKendrick

  - Susceptible (S)
  - Infected (I)
  - Removed (R)
- Compartment/flow model
- Set of differential equations representing rates

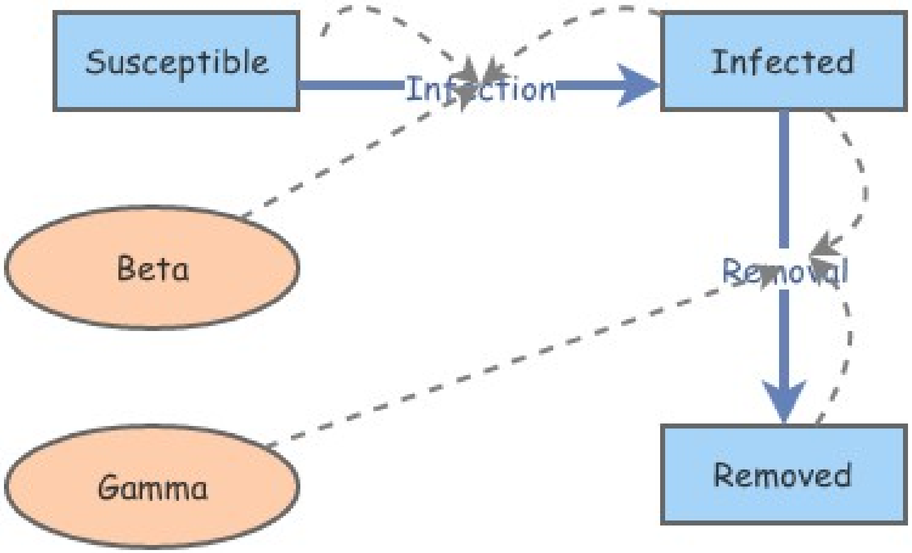
R_0

- The basic reproductive number is a key parameter when considering any epidemic
- R_0 is the average number of individuals infected by a single individual when all the population is susceptible
- If R_0 is below 1 then an epidemic cannot spread
- Understanding the SIR model will help In understanding R_0

Disease states



SIR model



https://insightmaker.com/insight/189276/SIR

SIR

- The starting point for the model is the susceptible compartment. This contains the proportion of the total population at risk that is susceptible to infection.
- As this is a proportion the value varies between 0 ... no one at risk because all are either infected or removed and 1 …. the whole population is at risk.
- To start a model run the compartment is set at 1 – the infected proportion.
- In this case if we seed the model with 1% infected the value for the proportion will be 0.99

SIR

Infection represents an outflow from the susceptible compartment.

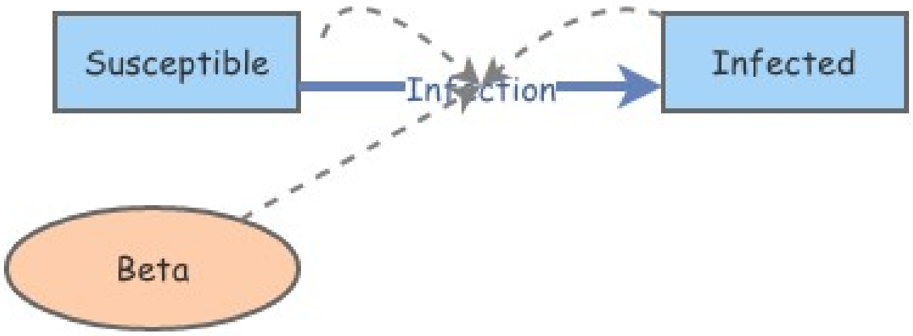
SIR

Susceptibles become infected through the process of infection. In this model it is assumed that a person who is infected is also infectious.

Infection takes place when infected(i.e. infectious) people come into contact with susceptibles. So the flow is influenced by both the proportion infected and the proportion susceptible.

At the start of an epidemic the number of contacts that result in transmission is low, as most contacts are between susceptible and susceptible individuals. .

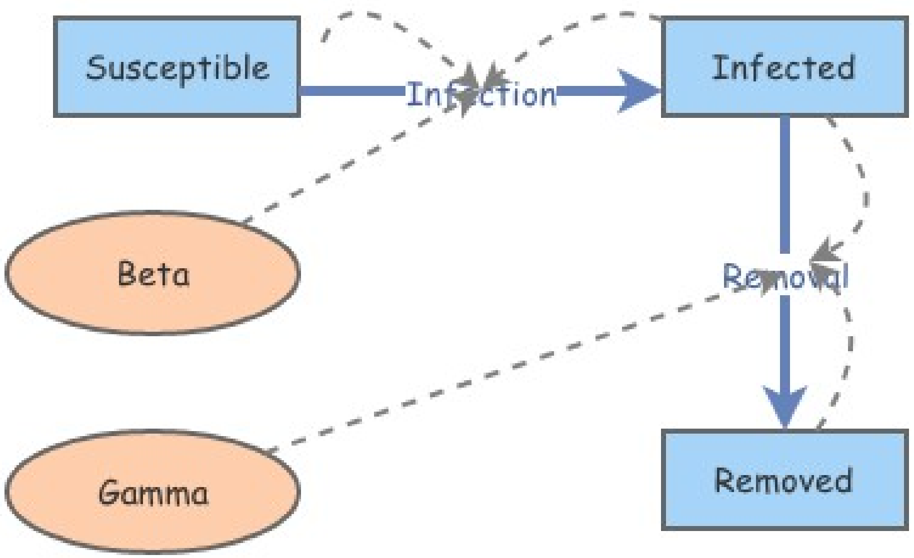
SIR



In the model the rate (flow) of infection is determined by multiplying P by I by beta.This makes beta a rather difficult parameter to understand intuitively.

- Beta is **not** the rate of transmission. That is a consequence of beta.
- Nor does beta represent the number of new infections per individual infected. That is an element of the model called R_0 (R zero or R nought).
- Beta is related to R_0 however.
- To see how this relationship works we need to continue to develop the model further. We will come back to this point.

SIR



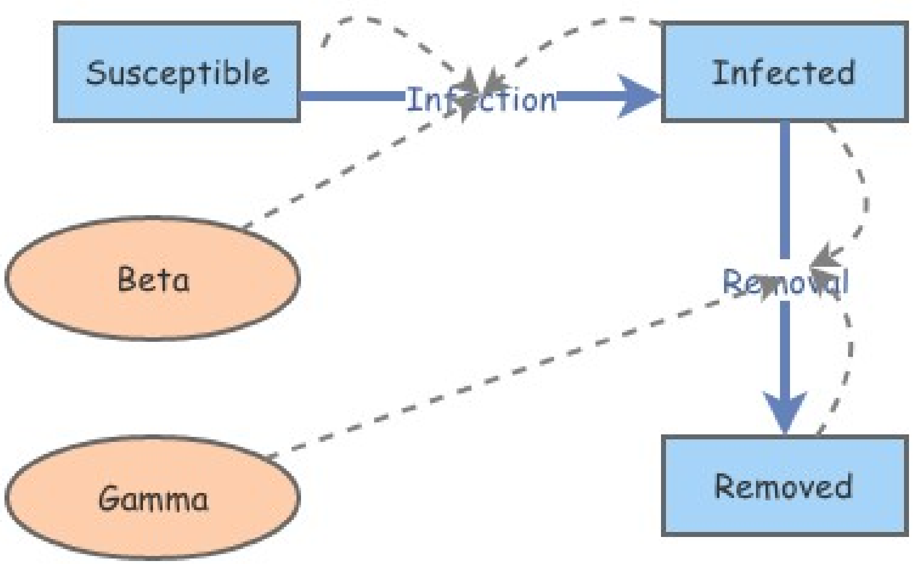
We now need to remove infected people from the infected compartment.

We can define a flow as a proportion of the content of the infected compartment that is removed during each time step.

The term **removed** is used in epidemic models to represent the proportion of the population that is no longer participating in the spread of the epidemic.

The most common forms of removal are through either **death** or **recovery with immunity.** Either of these outcomes results in the same effect on the overall progress of the disease. Clearly there is a major difference in these outcomes from the perspective of the overall consequences of the epidemic.

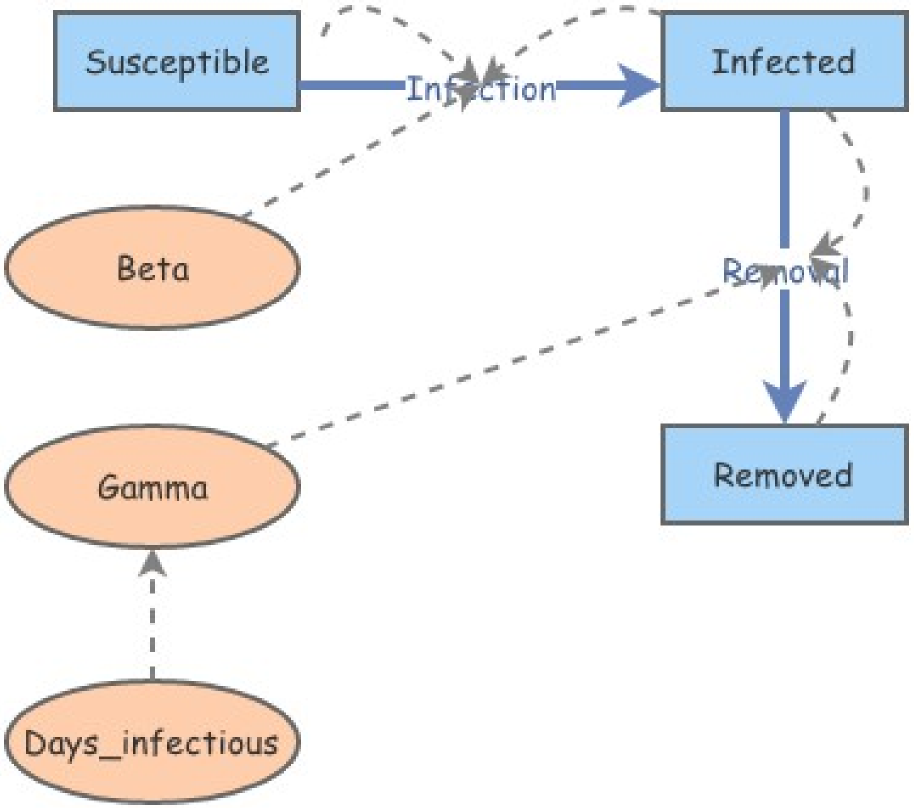
SIR



We need another parameter to control this flow. This is typically known as gamma.

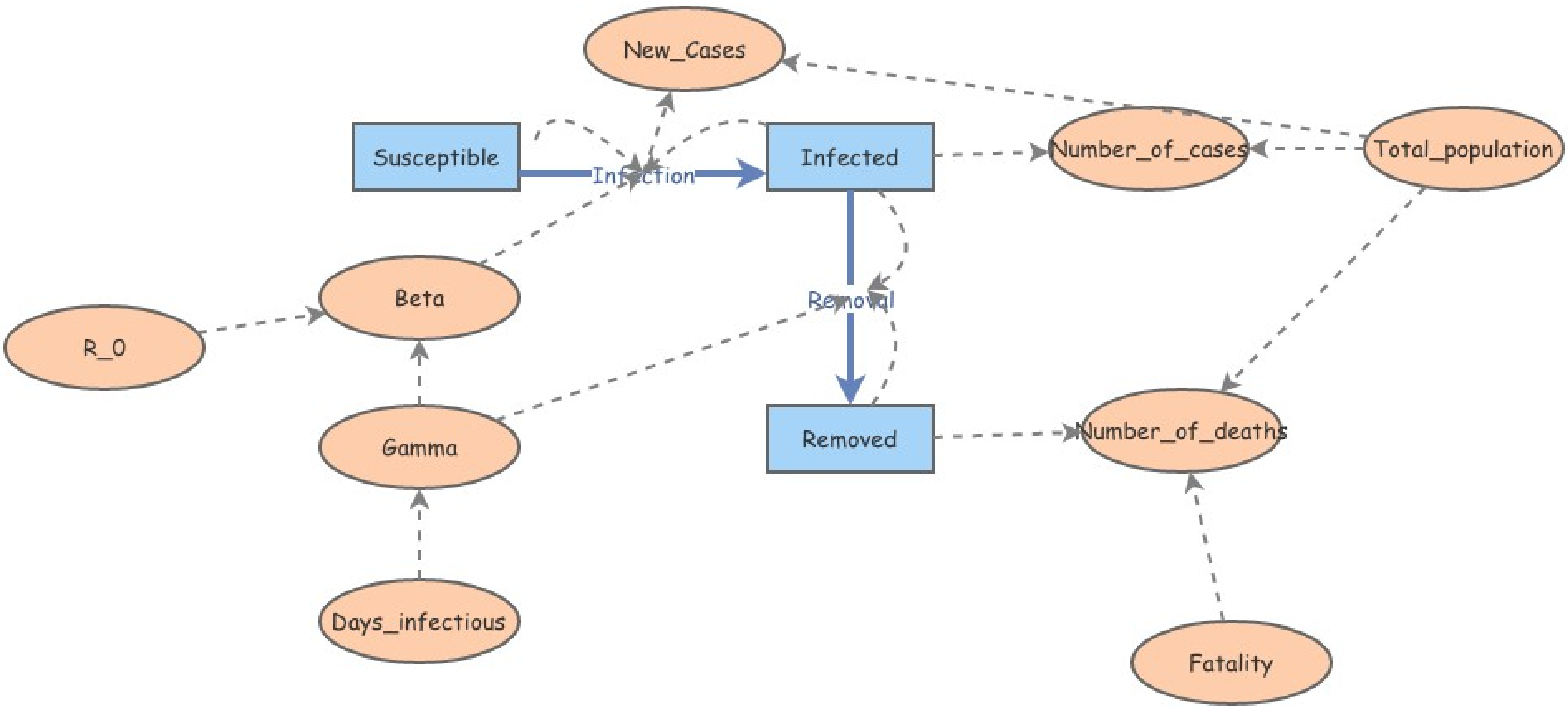
- **Gamma** is the proportion of the infected cases that are removed each time step.
- If the time step is one day and gamma is 0.1 then 10% of the cases are removed each day.
- This can be through death or recovery with immunity,

SIR



It is often more convenient to think of gamma in terms of its reciprocal (1/gamma),This represents the typical number of days that a person is infected.

SIR



New_Cases
Susceptible
Infection
Infected
Number_of_cases
Total_population
Beta
R_0
Removal
Gamma
Removed
Number_of_deaths
Days_infectious
Fatality

The SIR model

$$\frac{dS}{dt} = -\beta \frac{SI}{N}$$

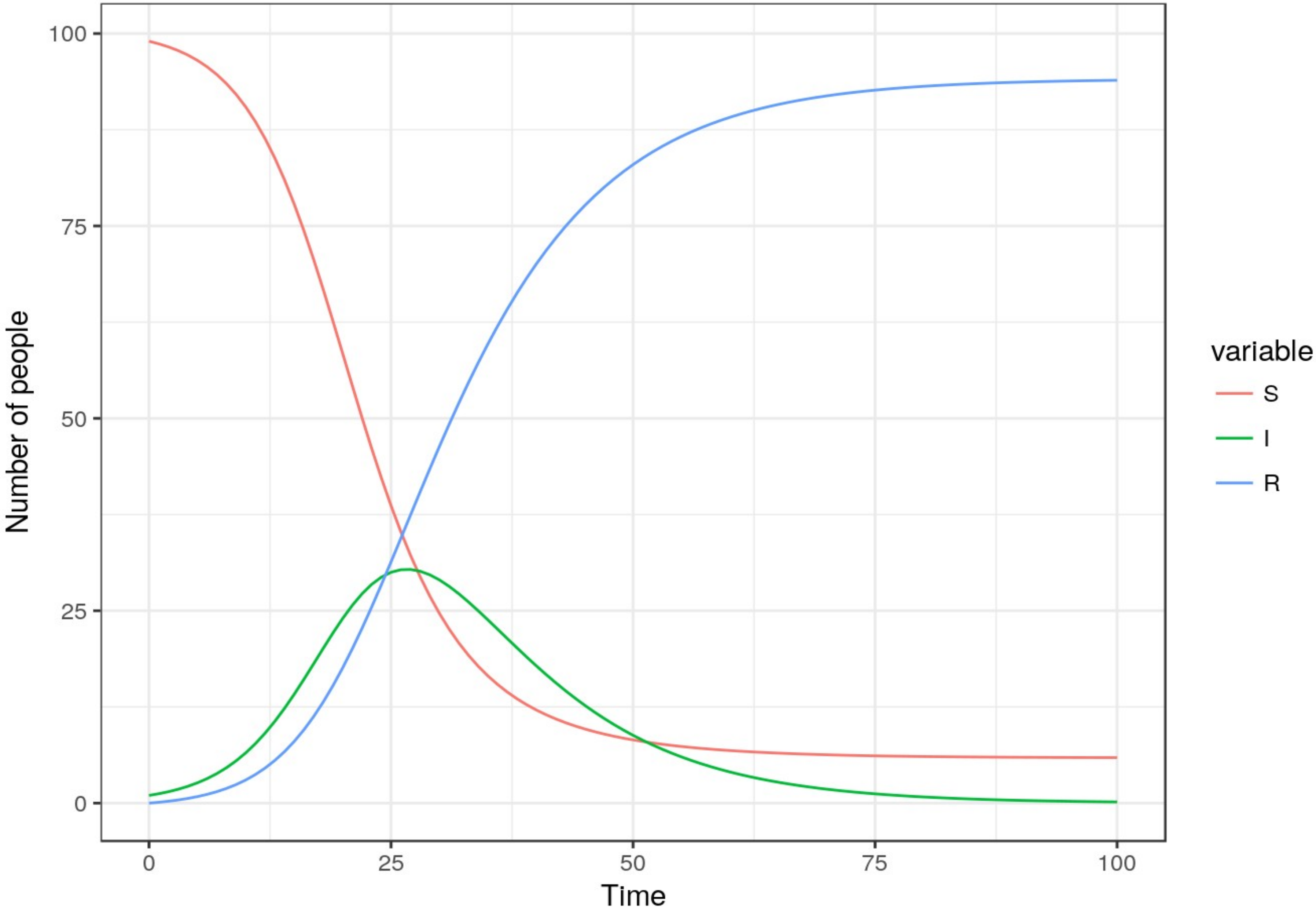
$$\frac{dI}{dt} = \beta \frac{SI}{N} - \gamma \frac{I}{N}$$

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

Peak rate of transmission

- Maximum rate of transmission occurs when half the population are infected, and half are susceptible. In a population at risk of 100 people
- 0.1 * (50 *50) / 100 = 2.48
- So around 25 new cases every ten days at peak transmission with beta = 0.1
- Compare with 1 new case every ten days at the outset
- Rate of transmission forms a parabola with a peak at p(S) = 0.5 and p(I) = 0.5
- This produces a sigmoid curve when integrated

SIR model



The basic reproductive number (R zero)

- The average number of new cases resulting from one infected individual at the beginning (time zero) of the outbreak
- This is approximately beta divided by gamma
- e.g if beta is 0.25 and gamma is 0.1 = 2.5

$$R_0 \approx \frac{\beta}{\gamma}$$

Consequences

- If $R_0 < 1$ the disease dies out
- If $R_0 > 1$ the disease spreads
- The actual value of R_0 depends on circumstances and potential actions taken that affect transmission and duration of the illness
- Can be very high (>10) for easily spread illness in a totally susceptible population (e.g. flu, common cold)
- Tends to be low for severe illness causing rapid mortality

Immunity

- Removal of individuals from the infected population as a result of immunity results in contacts that do not lead to new cases
- Immunity slows down the spread of the disease
- High levels of natural or induced immunity (vaccinations) lead to $R_0 < 1$
- “Herd immunity”

The herd immunity threshold

- Immunity will always slow the spread of disease, but it can also prevent spread entirely
- Mathematically it can be shown that spread becomes impossible when the proportion of the population that is immune = $1 – 1/R_0$
- Example: $R_0 = 3$
- Herd immunity threshold = 1 – 1/3 = 2/3 = 66%
- So, it is not necessary to vaccinate the entire population to prevent outbreaks

Freeloaders

- Vaccination can be risky
- Assume 1% death rate through vaccination, but 10% death rate if the disease is contracted.
- Vaccination of 66% of a population of 1000 would leads to around 7 deaths
- However failure to vaccinate could lead to 100 deaths
- “Freeloaders” refuse to take the 1% risk
- If freeloading exceeds herd immunity threshold an outbreak may occur

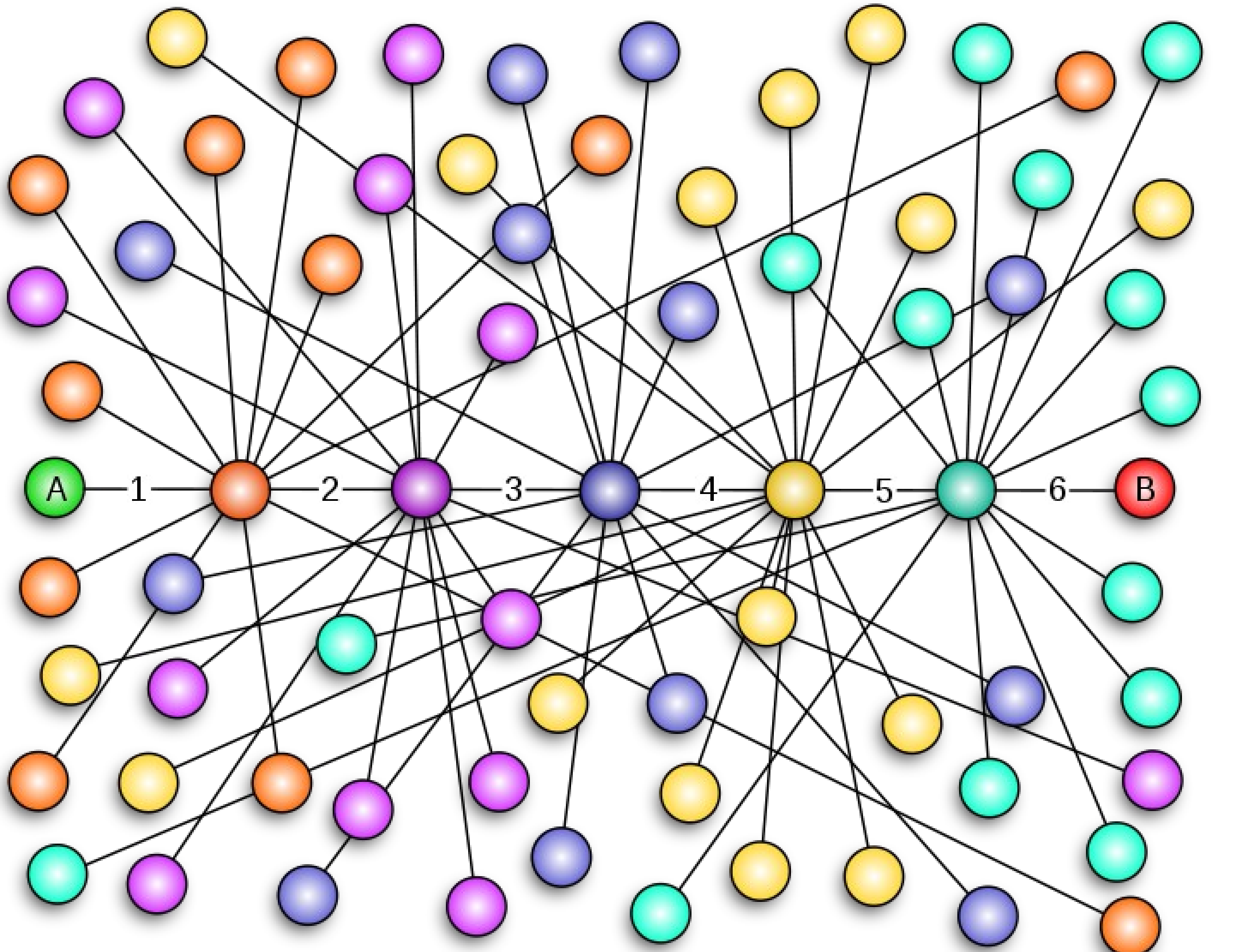
Ring vaccination

- Controls outbreak by vaccinating and monitoring the ring of people around each infected individual.
- Forms a buffer of immune individuals to prevent the spread of the disease.
- Used to control smallpox
- Smallpox was totally eliminated without ever reaching the full herd immunity threshold

Assumption of SIR model

- A key assumption of the SIR model is complete mixing
- Every member of the population at risk has an equal chance of infection
- This does not take into account spatial structure , clustering and networks of contacts
- Epidemics show spatial patterns, as John Snow pointed out

Six degrees of separation



Gurevich and Kochen (MIT)

- (In the US) ” It is practically certain that any two individuals can contact one another by means of at most two intermediaries. In a (socially) structured population it is less likely but still seems probable. And perhaps for the whole world's population, probably only one more bridging individual should be needed.”
- Social media and memes?

Animal and endemic disease

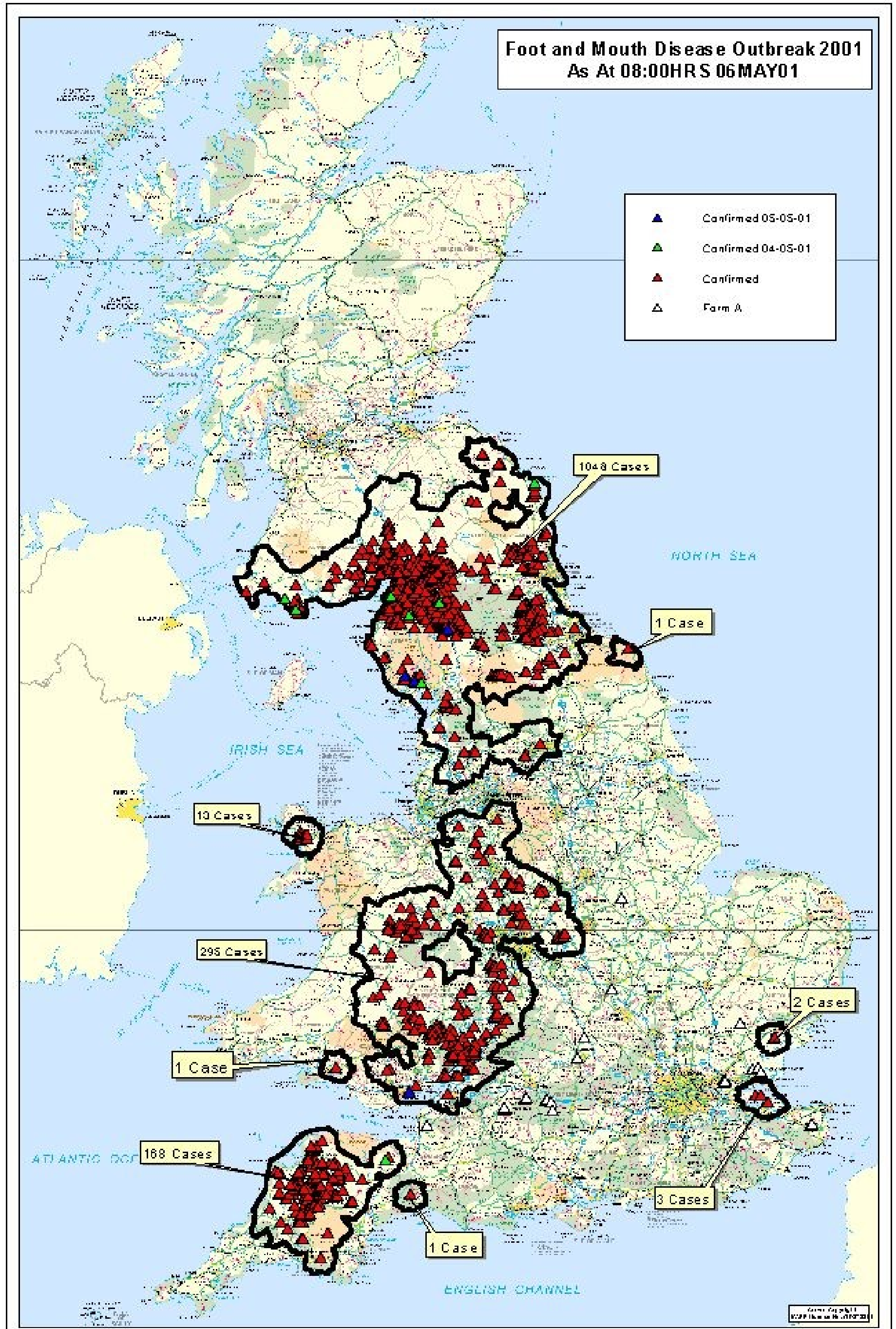
- Animal populations often affected by endemic diseases
- Constantly present at low levels with periodic outbreaks
- If the disease affects commercially important livestock intervention often used to control outbreaks

Zootic examples

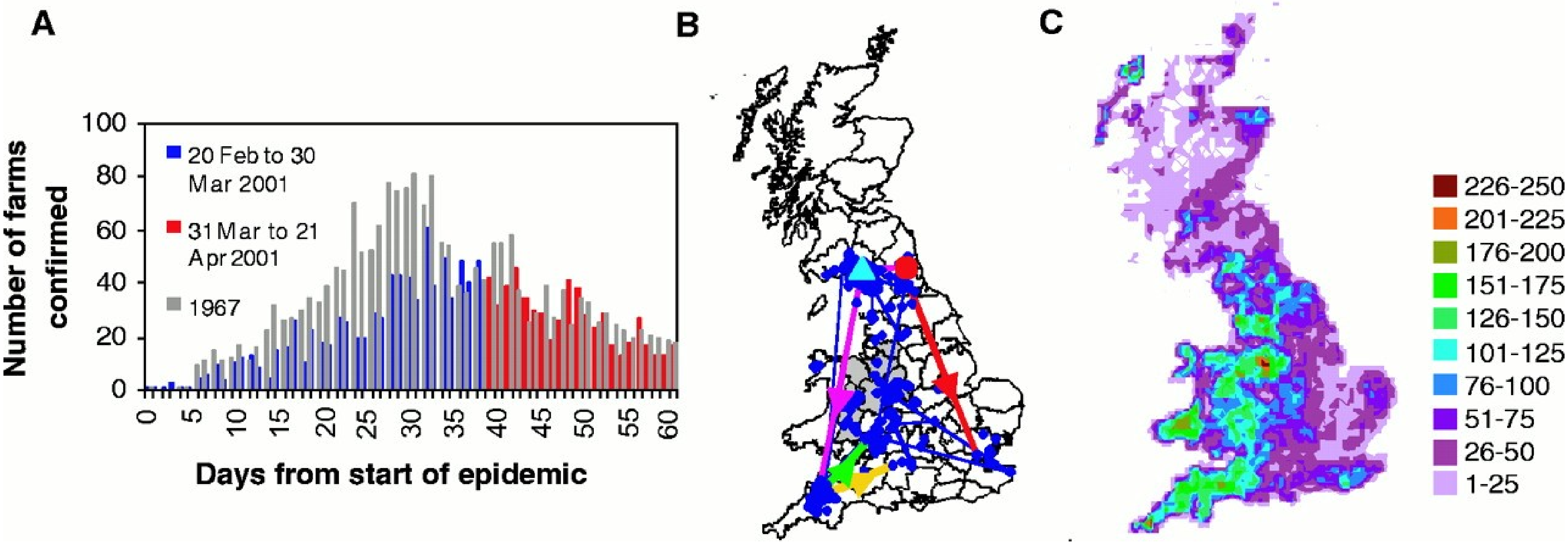
- Foot and mouth epidemic, UK 2001
- 2,026 farms with incidence of disease
- Over 6 million cows and sheep killed
- First case reported in Essex February 2001, traced to source in Northumberland
- By 31 March around 50 new cases per day
- Spread initially influenced by frequency of movement of animals around the country

Foot and mouth

- *Aphthae epizooticae* virus
- Infectious, but rarely fatal
- Symptoms include fever and blisters (on feet and mouths)
- Does not typically cause disease in humans
- Causes major economic impact as meat from animals infected and testing positive to antibodies cannot be sold or exported.

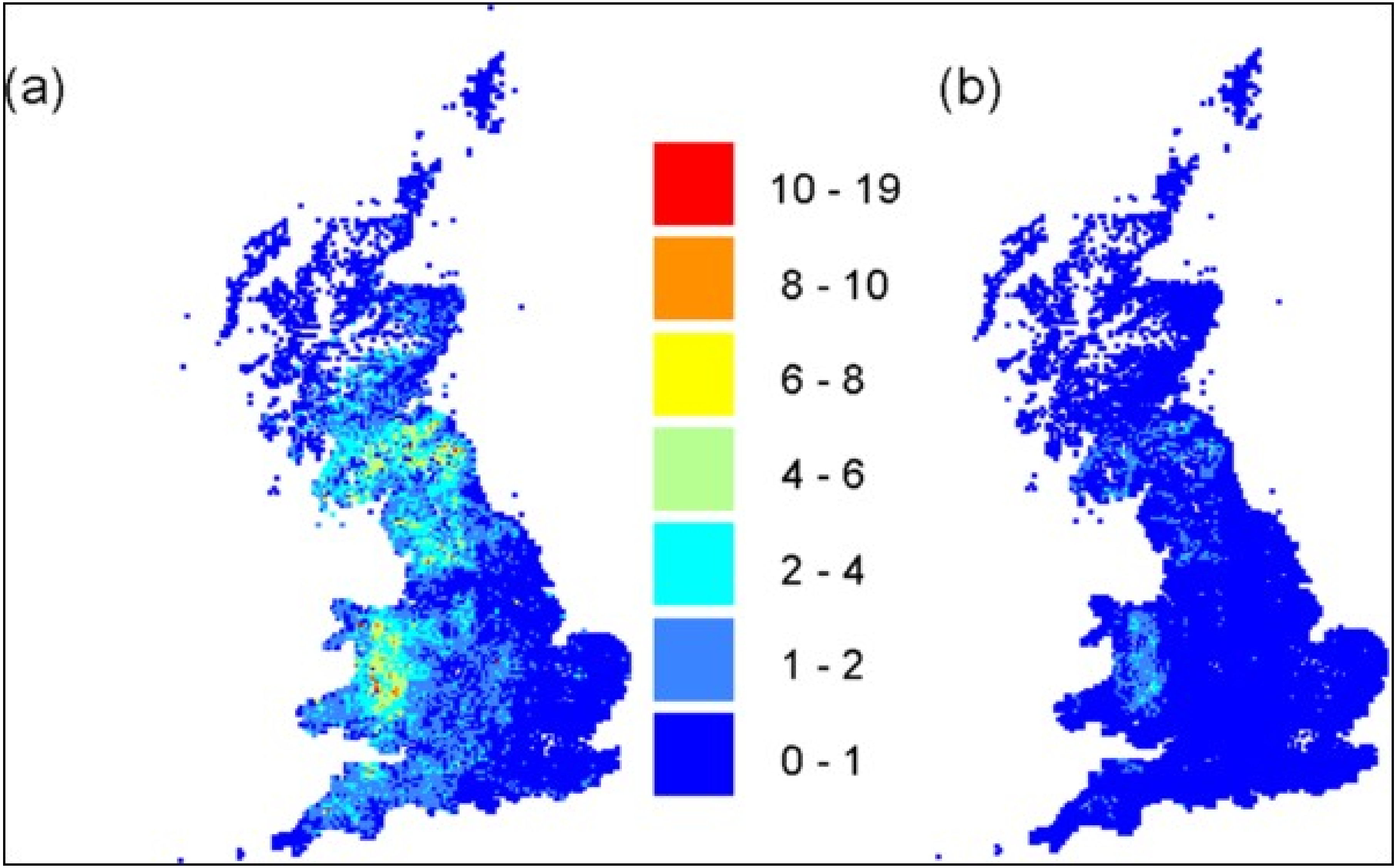

Foot and Mouth Disease Outbreak 2001
As At 08:00HRS 06MAY01
Confirmed 05-05-01
Confirmed 04-05-01
Confirmed
Farm A
1048 Cases
NORTH SEA
1 Case
IRISH SEA
13 Cases
295 Cases
2 Cases
1 Case
ATLANTIC
168 Cases
3 Cases
1 Case
ENGLISH CHANNEL

Comparison of the temporal and spatial patterns of the 1967–68 and 2001 FMD epidemics.



Neil M. Ferguson et al. Science 2001;292:1155-1160

Maps of transmission risk (potential R0) before 23rd February (a) and after (b) as predicted from the interaction model with time varying kernel conditioned on the first infection



Chis Ster I, Ferguson NM (2007) Transmission Parameters of the 2001 Foot and Mouth Epidemic in Great Britain. PLOS ONE 2(6): e502. https://doi.org/10.1371/journal.pone.0000502
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0000502

Combating foot and mouth

- All animals at infected farm killed
- Prevented spread through lowering 1/gamma i.e. time during which infectious animals were contagious
- All animals at neighbouring farms also killed
- Equivalent to ring vaccination

Myxomatosis

- Caused by the myxoma **virus**.
- First observed in Uruguay in laboratory rabbits in the late 19th century.
- Caused localized skin tumours in native host (non lethal)
- Introduced into Australia in 1950 in an attempt to control the rabbit population
- Affected rabbits develop skin tumours, blindness,fatigue, fever.
- Die within 14 days of contracting the virulent form of the disease.

Myxomatosis

- Spread by direct contact with an affected animal or by being bitten by fleas or mosquitoes that have fed on an infected rabbit.

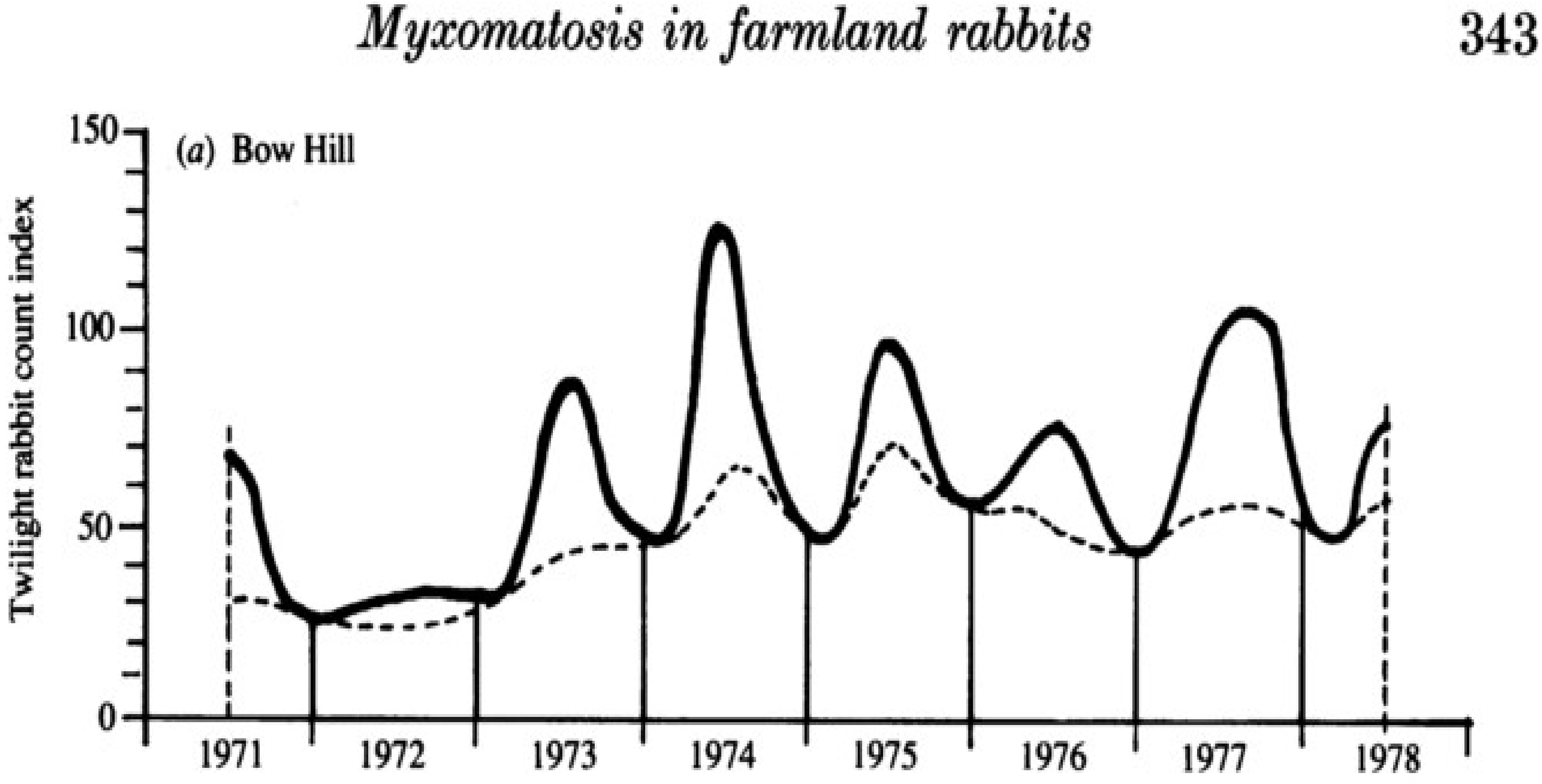
Myxomatosis

- First strain extremely virulent (high mortality)
- Killed rabbits very quickly (4 days)
- Reduced Australian rabbit population from 600 million to 100 million in two years.
- Genetic resistance in survivors
- Descendants of survivors acquired partial immunity in the first two decades.
- Resistance has been increasing slowly since the 1970s
- Now kills about 50% of infected rabbits.

Myxomatosis

- Strains with lower virulence may have been selected for
- Disease now endemic in most rabbit populations
- Outbreaks common, but do not control the population over the longer term
- Introduced to UK in in 1953. Killed up to 90% of rabbits in 1954
- Studies in the UK showed cyclical patterns of localised low intensity outbreaks from 1970's, that continue today

Myxomatosis



Ross, J. et al., 1989. Myxomatosis in farmland rabbit populations in England and Wales. Epidemiology and Infection, 103(2), pp.333–357.

Conclusion

- Epidemics of transmissible diseases display some potentially predictable dynamics
- Models can capture the general pattern of epidemics
- Consideration of key parameters of epidemic models can help predict patterns.
- Precise quantitative prediction rarely possible.
- However, many general patterns can be predicted using a few simple parameters.