Contagion: Modelling Infectious Diseases

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2 MERS patients die in South Korea

By Ashley Fantz, K.J. Kwon and Catherine E. Shoichet, CNN
Updated 0459 GMT (1159 HKT) June 2, 2015

June 2, 2015

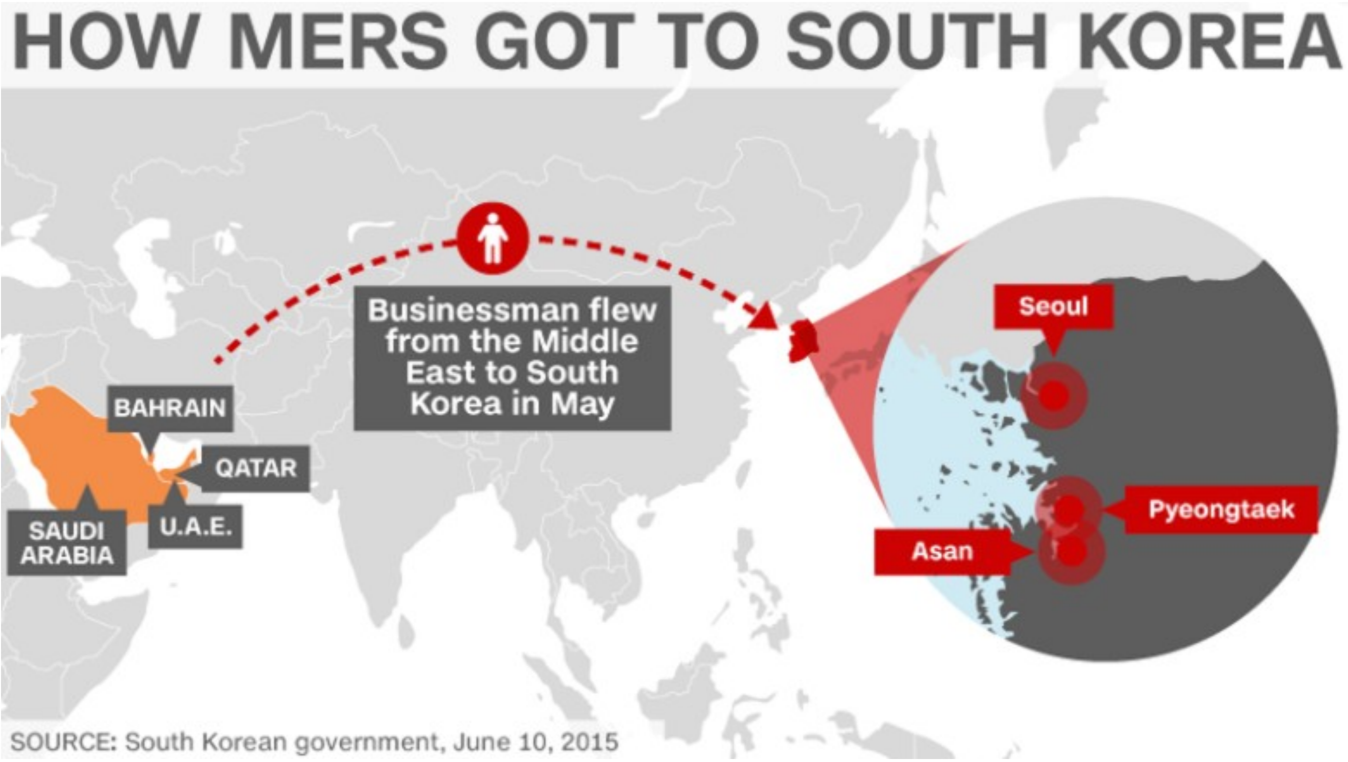
Almost 700 under quarantine after MERS outbreak 02:19

Story highlights

(CNN)—Two MERS patients have died in South Korea,

Middle Eastern Respiratory Syndrome, or MERS, is a disease

A 68 year old South Korean man, who traveled widely in the middle East, was the first case



SOURCE: South Korean government, June 10, 2015

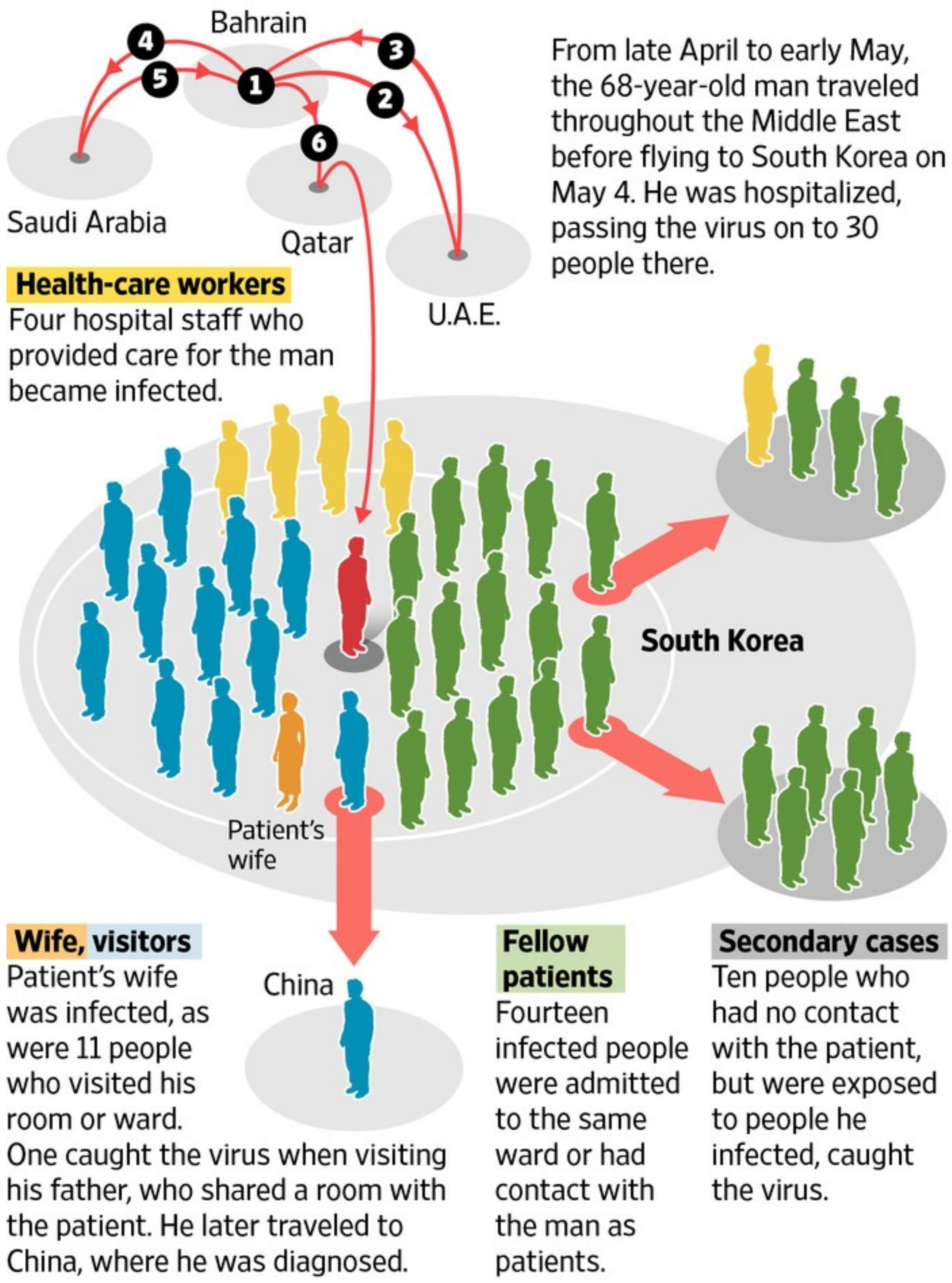
http://i2.cdn.turner.com/cnnnext/dam/assets/150611100255-mers-graphic-lo-res-exlarge-169.jpg

He reached S. Korea on 4 May and fell ill by 11 May

Went to 4 hospitals to be treated, but disease wasn't diagnosed early

Before being isolated, he infected several others

What we now know about how the disease spread from the first patient



From late April to early May, the 68-year-old man traveled throughout the Middle East before flying to South Korea on May 4. He was hospitalized, passing the virus on to 30 people there.

Health-care workers
Four hospital staff who provided care for the man became infected.

Wife, visitors
Patient's wife was infected, as were 11 people who visited his room or ward.
One caught the virus when visiting his father, who shared a room with the patient. He later traveled to China, where he was diagnosed.

Fellow patients
Fourteen infected people were admitted to the same ward or had contact with the man as patients.

Secondary cases
Ten people who had no contact with the patient, but were exposed to people he infected, caught the virus.

http://online.wsj.com/media/MERS_NDesktop.jpg

Why aren’t these head-line worthy?

(I made them up ..)

2 T patients die in South Korea

By Ashley Fantz, K.J. Kwon and Catherine E. Shoichet, CNN
Updated 0459 GMT (1159 HKT) June 2, 2015

20 Malaria patients die in India

By Ashley Fantz, K.J. Kwon and Catherine E. Shoichet, CNN
Updated 0459 GMT (1159 HKT) June 2, 2015

Why was so much trouble take to track down everyone the patient came into contact with?

Why are diseases like MERS special?

Because MERS is untreatable - no vaccine, no drug

2 MERS patients die in South Korea

By Ashley Fantz, K.J. Kwon and Catherine E. Shoichet, CNN

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Story highlights

(CNN)—Two MERS patients have died in South Korea,

It is often fatal. Patients die within a matter of days, often when their kidneys fail

Because MERS can be transmitted from person to person

It is an infectious disease, with pandemic potential (can spread around the world)

MERS originated in Saudi Arabia, which also has the most cases (2014 & 2015)

http://a.abcnews.com/images/Health/mers_coronavirus_world_map_140502_v12x5_12x5_992.jpg

Why should this worry us, in particular?

In September 2015, Saudi Arabia will see among the largest annual gatherings in human history (~6 million)

2014

After the Hajj, pilgrims will return to their countries, around 188 of them

http://hajjvoyage.com/wp-content/uploads/2014/04/HajjAndUmrah_456px1.jpg

How do we ensure that they don’t carry MERS back with them, triggering a pandemic?

How do diseases arise?

Diseases can be ..

Infectious

(Communicable)

Caused by a bacterium, a virus or a parasite + ..

worms, misfolded proteins

Other people can get them from you

Non-infectious

(Non-communicable)

From genetic causes, deficiencies, life-style + ..

combinations of these

Other people can't get them from you

Infectious

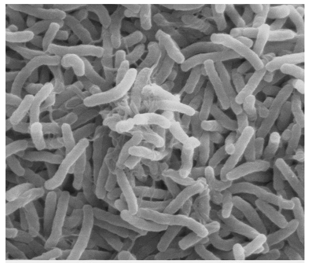
- Cholera (B)
- H1N1 (V)
- Dengue (V)
- Malaria (P)
- HIV-AIDS (V)
- Chicken pox (V)
- Influenza (Flu) (V)
- Tuberculosis (B)
- MERS (V)

Non-infectious

- Diabetes
- Scurvy
- Anaemia
- Hypertension
- Cancer
- Arthritis
- Cardio-vascular disease
- Obesity

(B) = from a bacterium, (V) = from a virus (P) = from a parasite http://www.bacteriamicroscopes.com/images/bacteria1.jpg

Bacteria



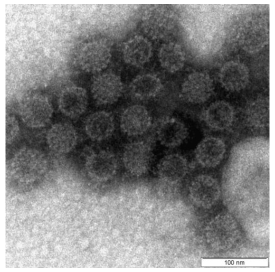
Bacteria are living organisms, multiply rapidly in a nutrient rich background

Once in the body, release chemicals (toxins) that make you feel sick. (Only for bacteria that make you ill, not all of them.)

Antibiotics (drugs) attack bacteria or halt their growth

http://www.imaging-git.com/sites/imaging-git.com/files/images/special/7667789__original.jpg

Viruses

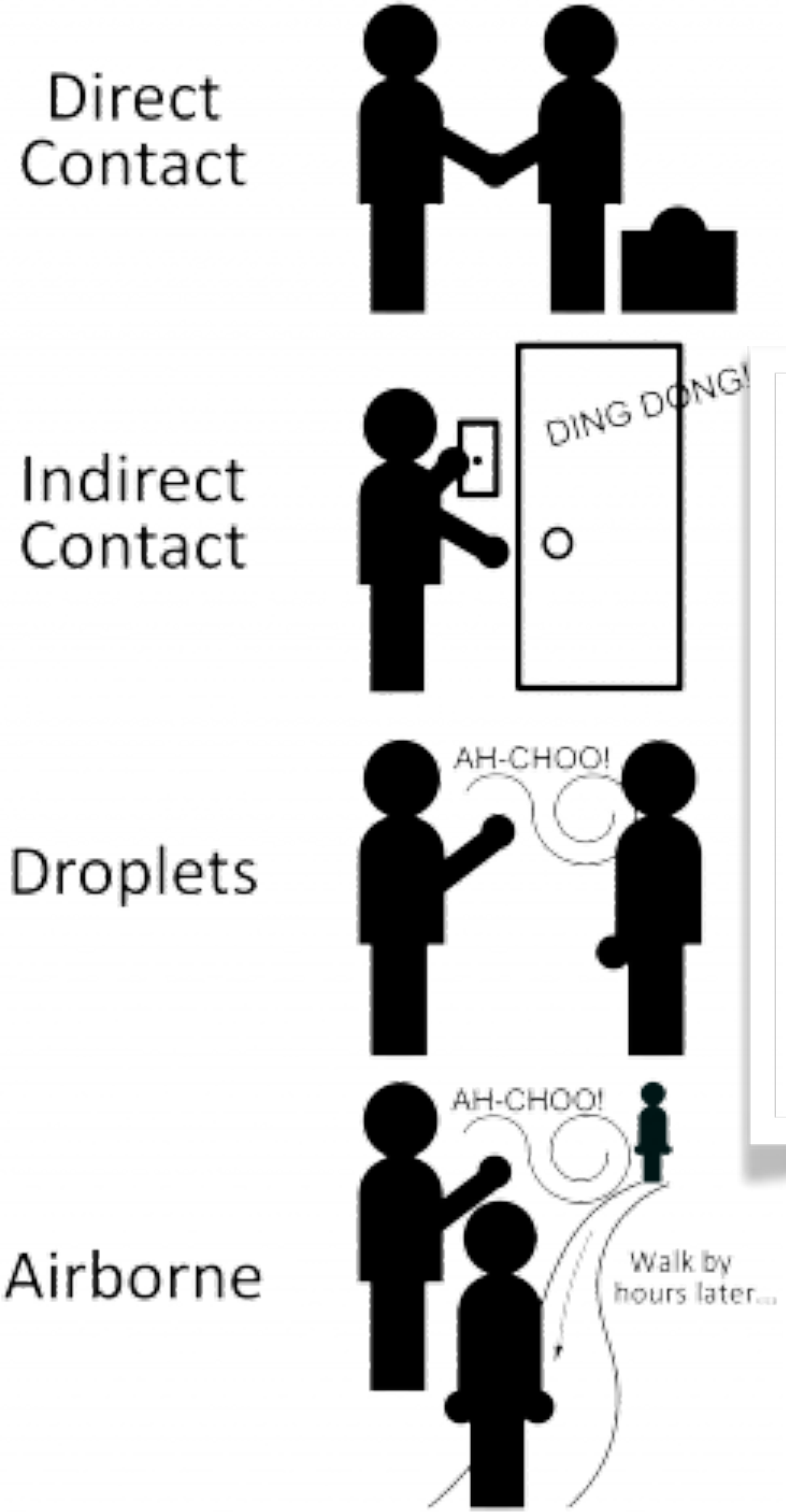


Viruses multiply inside cells, not outside. Straddle the living-non-living divide

Virus multiplication kills cells, bursts them open. so they can escape and infect other cells

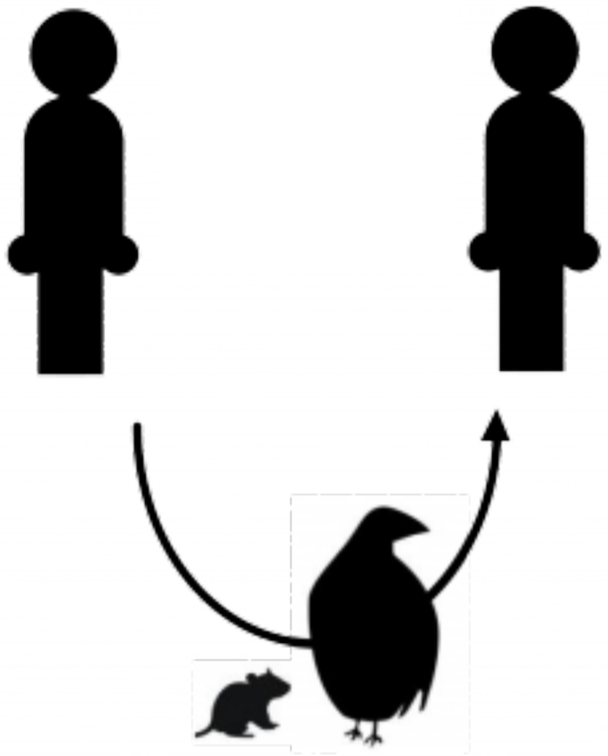
Antibiotics are useless against viruses. Finding drugs for viral diseases is hard

Some ways in which disease-causing bacteria and viruses are transmitted between humans



Also through wind (airborne) or contaminated water e.g. cholera.

Can also transmit disease via intermediate animals, called vectors, e.g. mosquitos (Malaria), fleas (Plague)



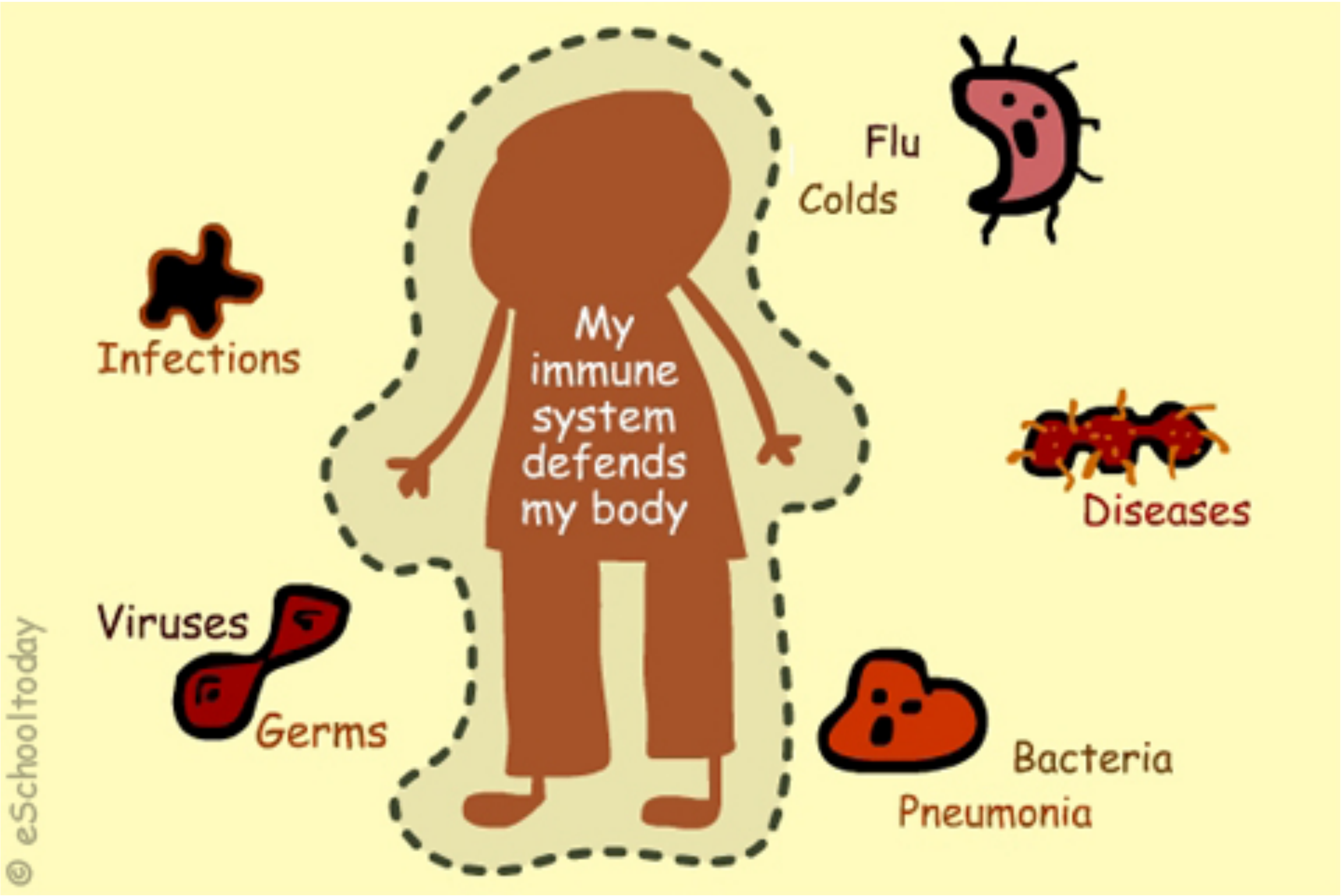
http://fsb.zedge.net/

Some diseases come to us from animals that are their normal hosts, e.g. Rabies

MERS likely originated in bats and camels

Why aren’t we constantly falling ill?

Our immune system usually protects us



Prior contact with the virus or bacterium helps the immune system recognise the invader

Vaccinations help do this

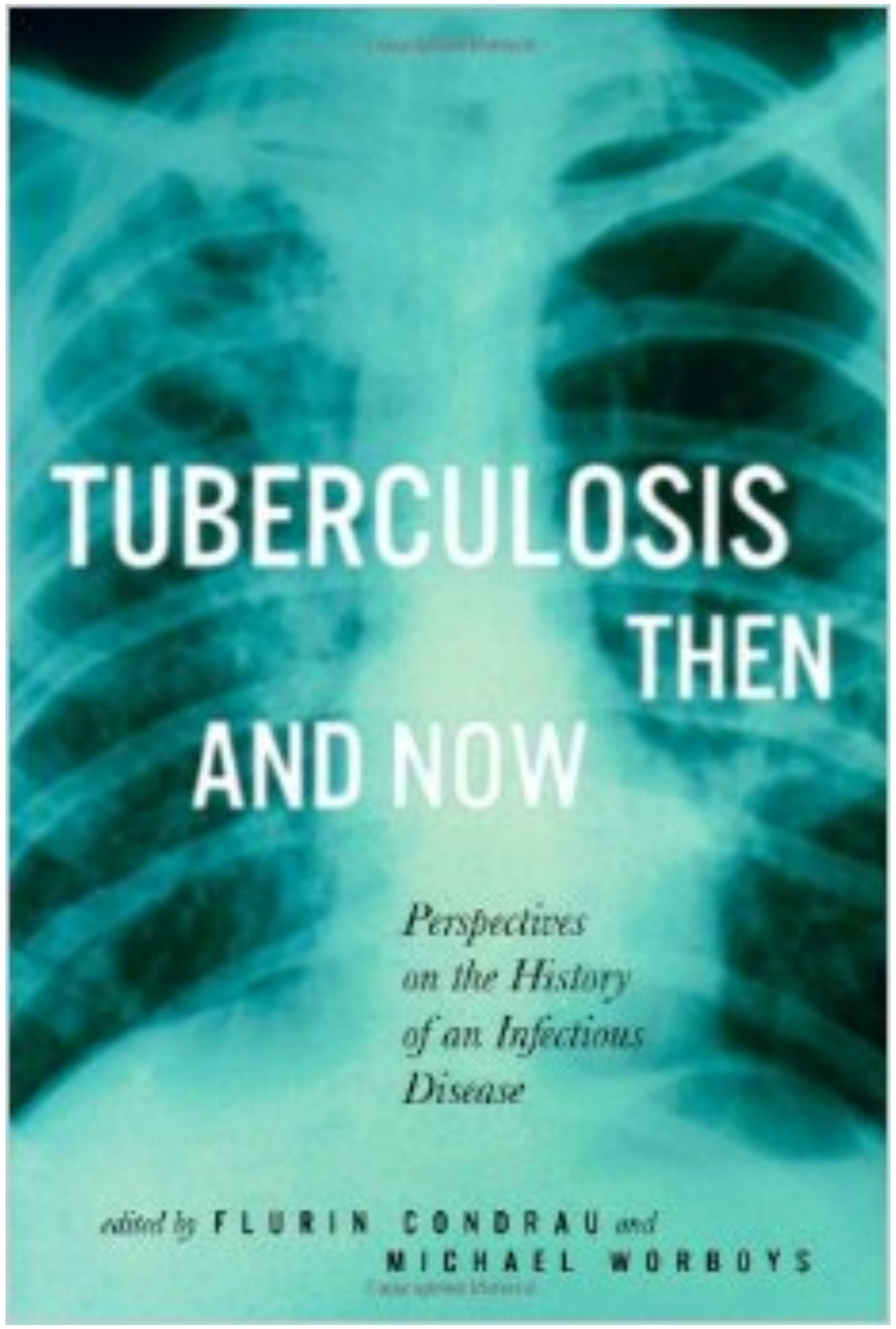
Some history of infectious disease

Infectious agents have probably always caused disease in humans.

Smallpox described in ancient Egyptian and Chinese writings.

(May have been responsible for more deaths than all other infectious diseases combined.)

Malaria, leprosy and polio have existed since ancient times.



Ancient Greece and Egypt: Epidemics of smallpox, leprosy, tuberculosis, diphtheria

Plague, measles and smallpox led to end of Roman empire

1347 - 1351: Plague killed 3 Europeans out of 10. This was called the Black Death

http://ssmckay.weebly.com/uploads/2/5/3/0/25308514/6913718_orig.jpg

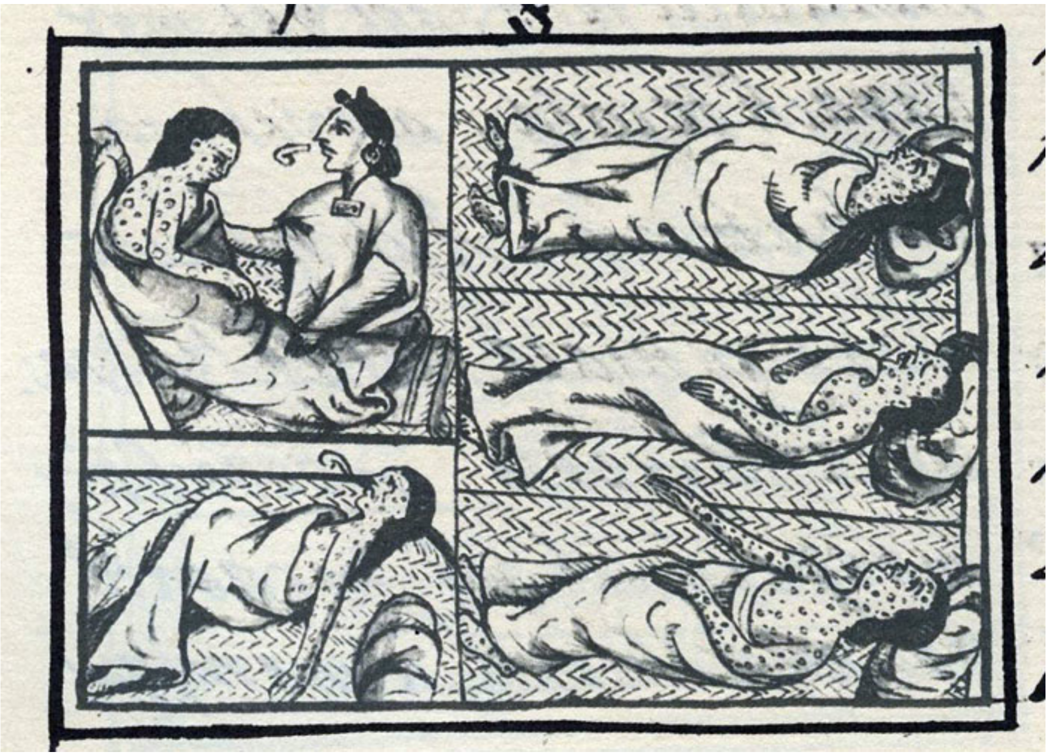
https://s-media-cache-ak0.pinimg.com/736x/f3/72/3e/f3723eab709971e3069f5726636c0f63.jpg

Defeat of Aztecs by Spaniards (smallpox), 1519-1520

1919 pandemic flu, 60 to100 million deaths, end of World War I

More recently: SARS, Bird flu, Ebola, chikungunya, dengue

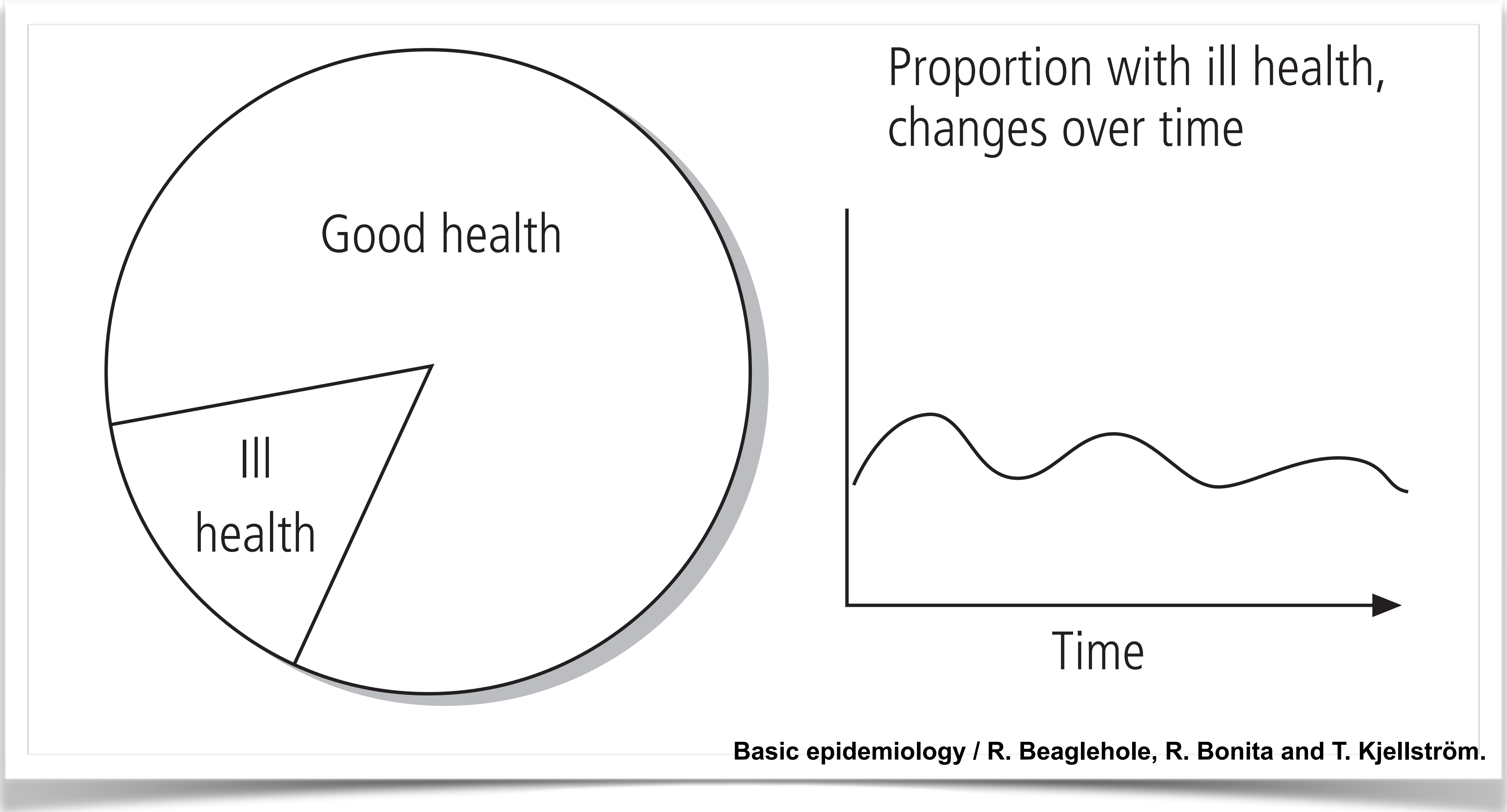
http://www.nlm.nih.gov/nativevoices/assets/timeline/000/000/236/236_w_full.jpg



http://photos1.blogger.com/blogger/6532/1726/1600/aztec%20empire%20map.gif

Wikipedia

How do infectious diseases affect populations - the field of epidemiology



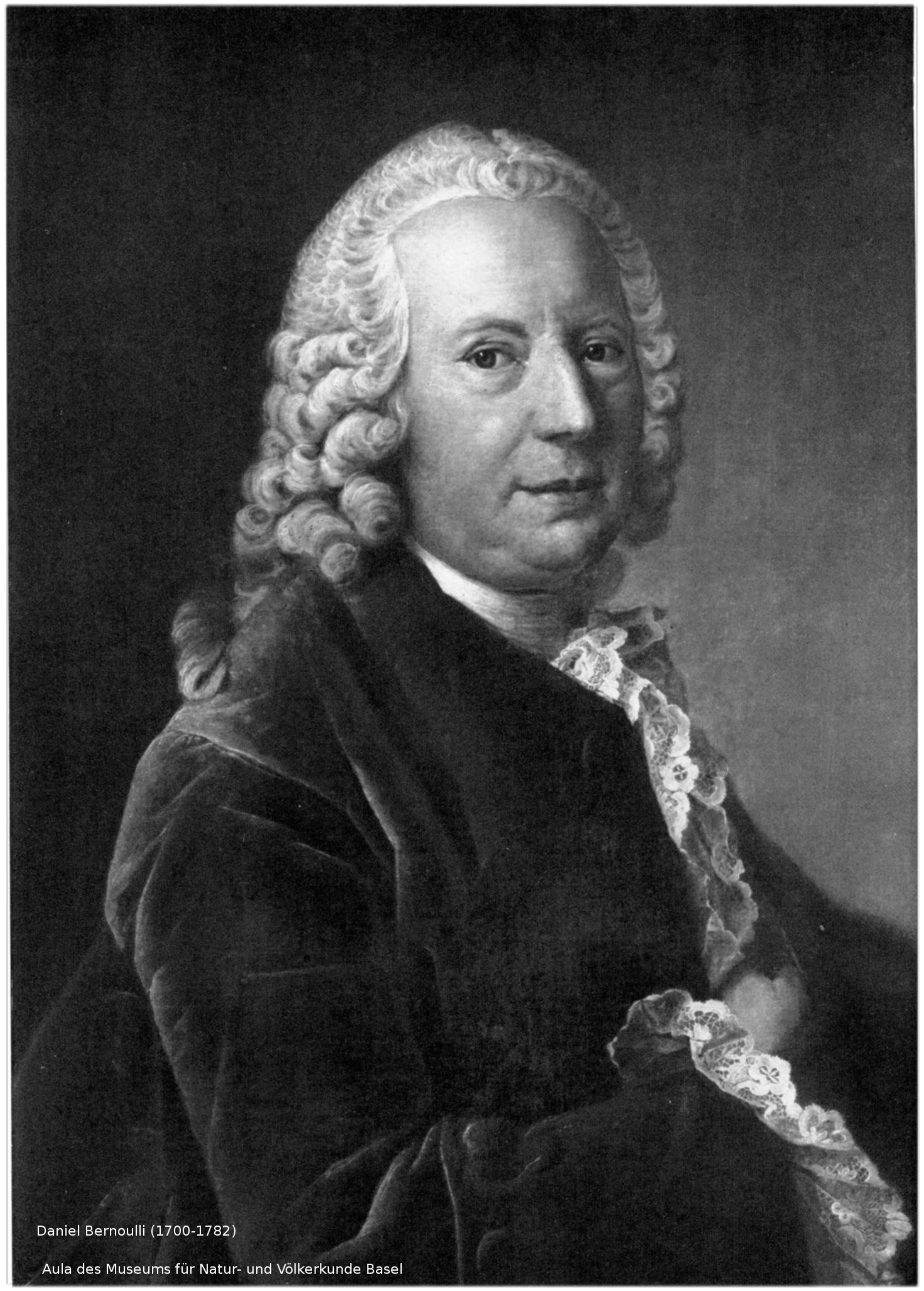
Basic epidemiology / R. Beaglehole, R. Bonita and T. Kjellström.

Mathematical epidemiology refers to the mathematical models which guide this field

Daniel Bernoulli (1700-1782) First mathematical model of disease spread, inoculation against smallpox

Bernoulli came from a family of eminent mathematicians, but trained as a physician

Bernoulli's model is a simpler case of a general model which we'll describe



Daniel Bernoulli (1700-1782)

Aula des Museums für Natur- und Völkerkunde Basel

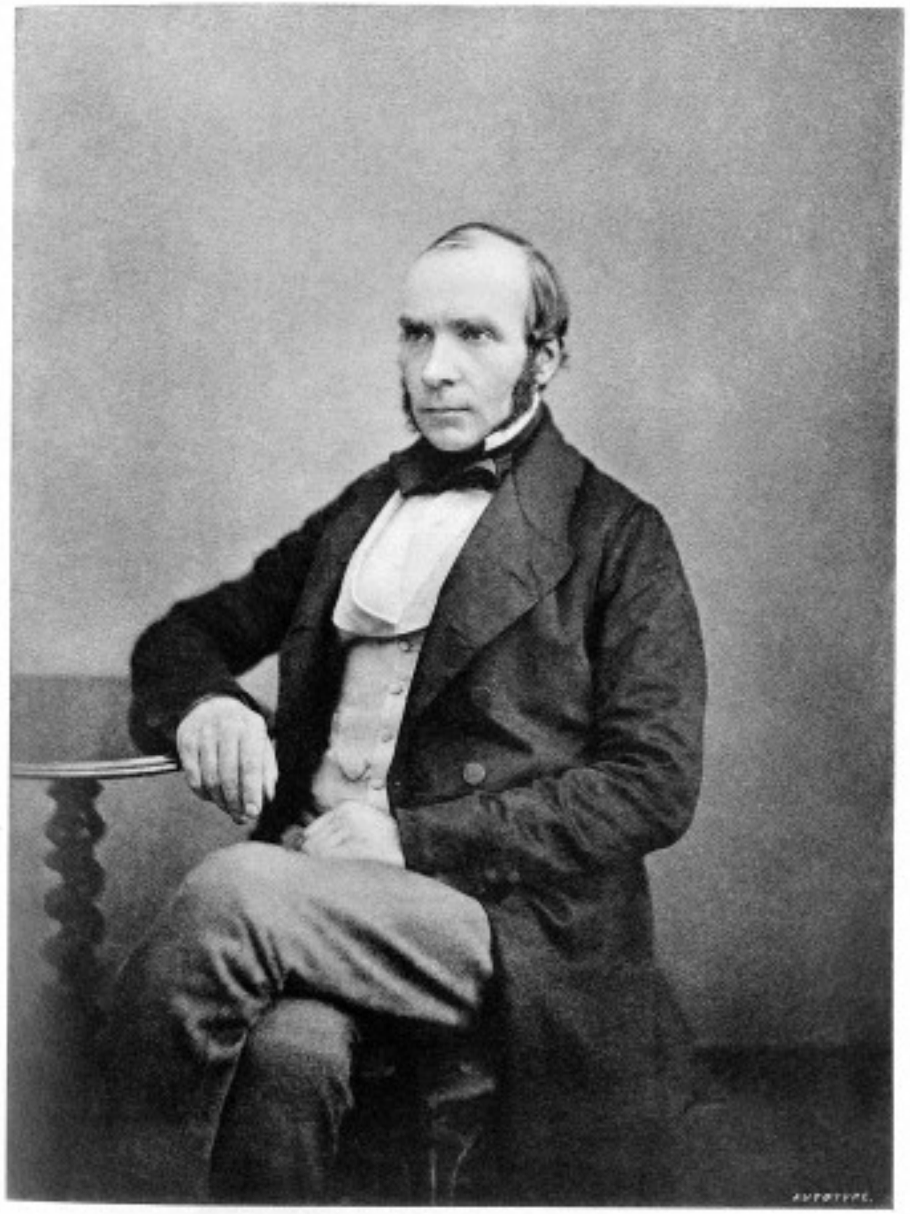
http://www.ub.uni-heidelberg.de/helios/fachinfo/www/math/homo-heid/bilder/Bernoulli-Aula.jpg

John Snow 1854: Cholera outbreak study.

Son of a coal-yard labourer, became a doctor.

Cholera epidemic (1848-49), London

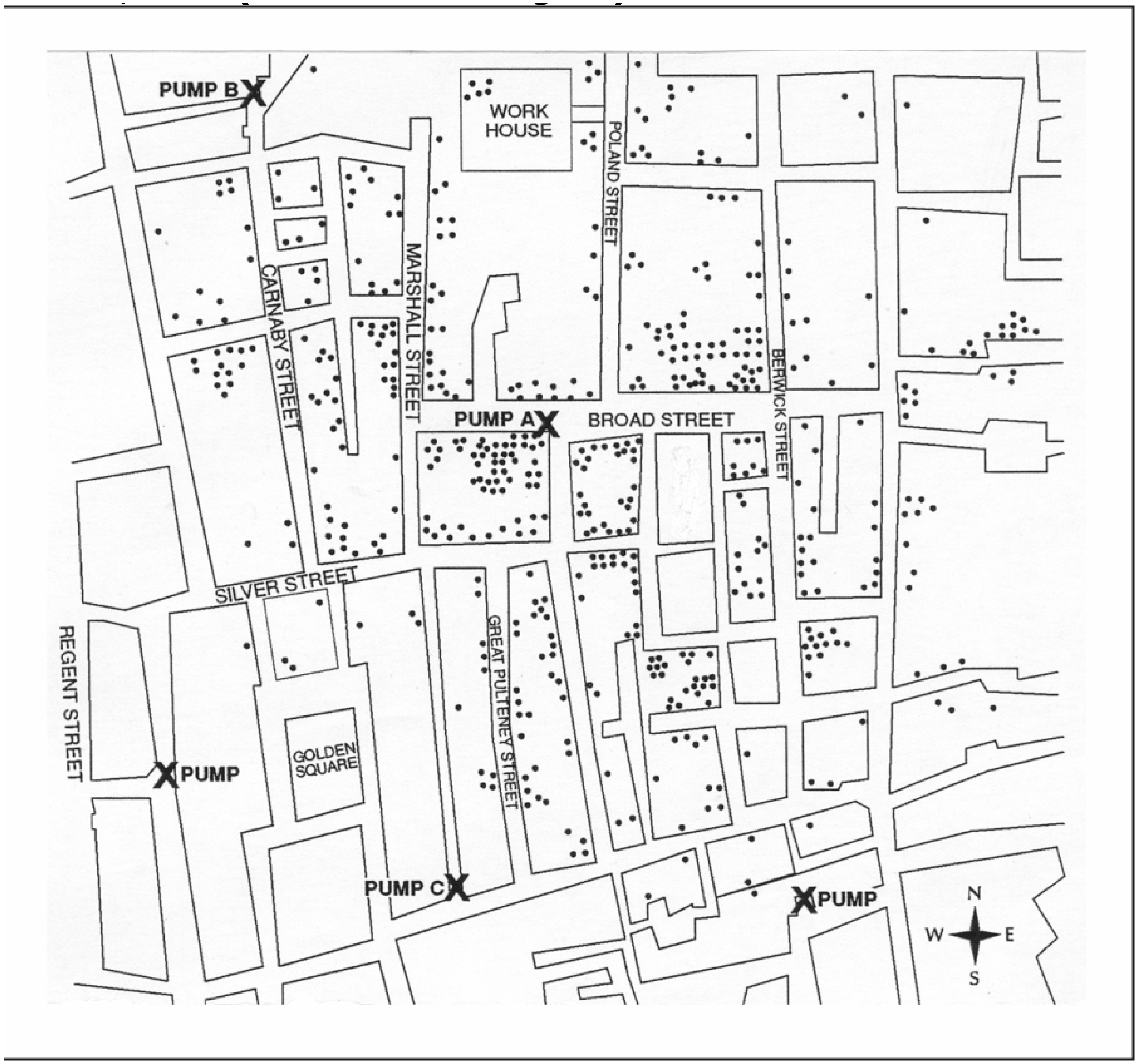
Water pumps as sources for cholera



John Snow

(Autotype from a Presentation Portrait, 1856, and Autograph facsimile.—B. W. R.)

Wellcome Images



Source: Snow J. Snow on cholera. London: Humphrey Milford: Oxford University Press; 1936.

More cases clustered around A, than B or C

Concluded Broad Street pump source primary source of infection with cholera

2 blocks unaffected. Had own source of water

Pump removed, outbreak ended

Source: Snow J. Snow on cholera. London: Humphrey Milford: Oxford University Press; 1936.

No knowledge of bacteria or viruses, but identified water as vehicle for transmission.

Florence Nightingale(1820-1910), the founder of modern nursing, was a statistician of repute.

Applied her methods to investigate causes of mortality and disease

http://spartacus-educational.com/00knighten.jpg

A "..pioneer in the graphical representation of statistics"

First female member of the Royal Statistical Society.

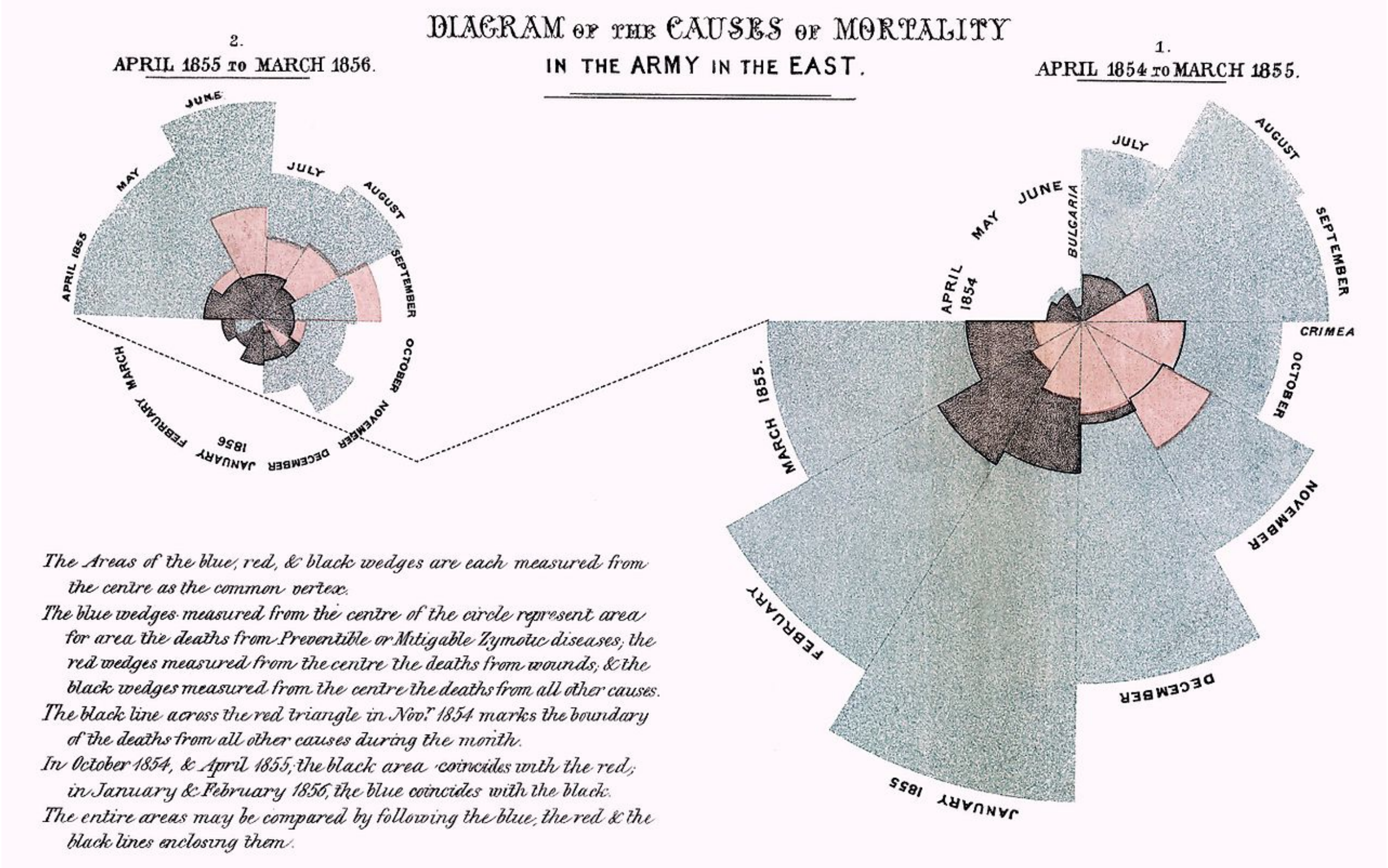


DIAGRAM OF THE CAUSES OF MORTALITY
IN THE ARMY IN THE EAST.

The Areas of the blue, red, & black wedges are each measured from the centre as the common vertex.

The blue wedges measured from the centre of the circle represent area for area the deaths from Preventible or Mitigable Zymotic diseases; the red wedges measured from the centre the deaths from wounds; & the black wedges measured from the centre the deaths from all other causes.

The black line across the red triangle in Nov.r 1854 marks the boundary of the deaths from all other causes during the month.

In October 1854, & April 1855, the black area coincides with the red; in January & February 1856, the blue coincides with the black.

The entire areas may be compared by following the blue, the red & the black lines enclosing them.

Wikipedia

Some Indian connections to models of infectious disease

These cities have a special place in the history of mathematical epidemiology

.. and there lies a story, actually several of them

Kasauli

Almora

Mumbai

Kolkata

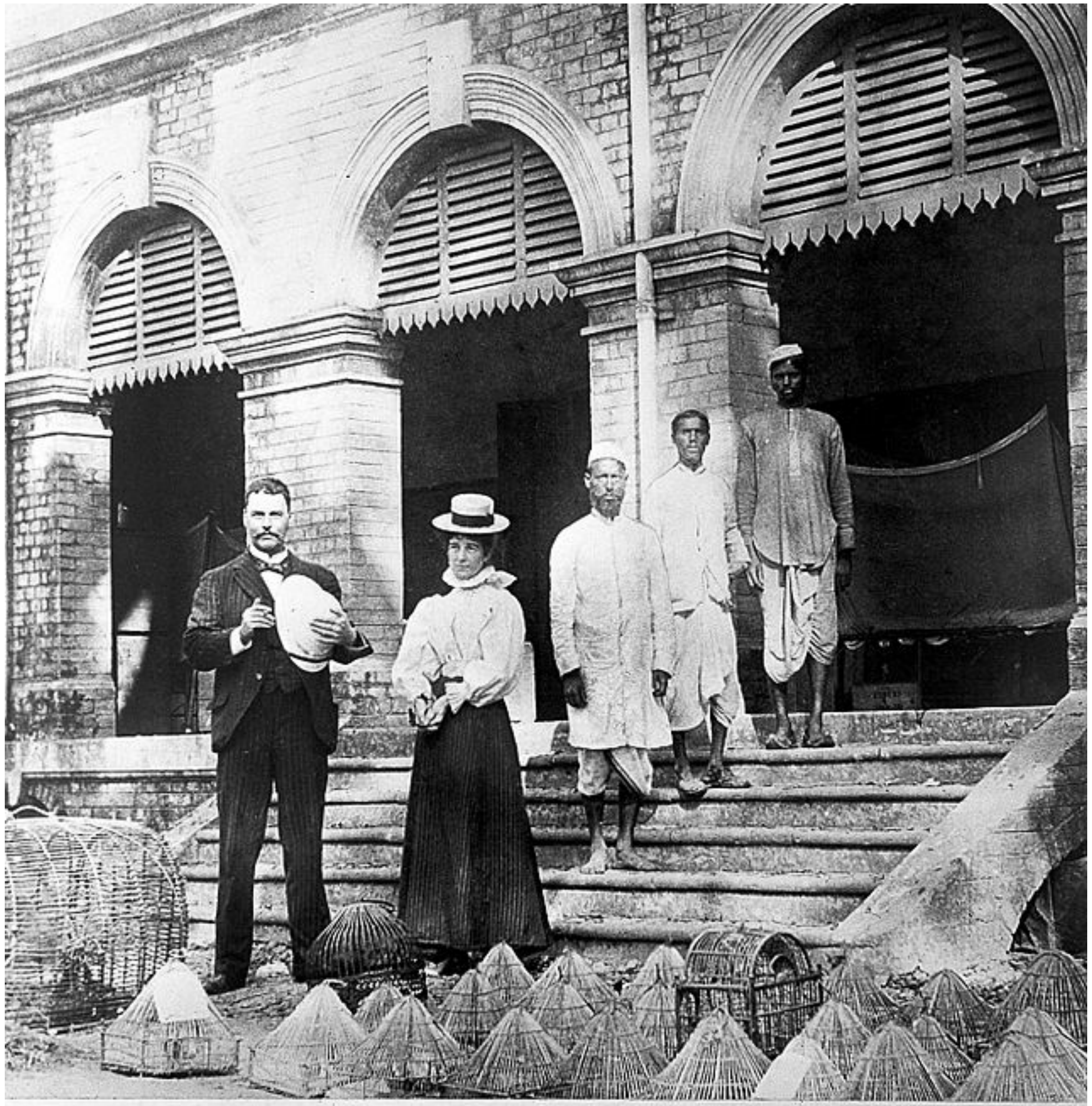
Bangalore

Ronald Ross (1857-1932), Nobel prize in 1902 for discovery of life-cycle of malarial parasite

Considered his work in mathematical epidemiology to be more important

Born in Almora, educated in England, joined Indian Medical Service in 1881, worked in Bombay and Kolkata

Posted in Bangalore, notes connection between water and mosquito control. In1895, observes first stages of growth of malarial parasite in mosquito



LABORATORY AT CALCUTTA. SURGEON-MAJOR ROSS, MRS. ROSS, MAHOMED BUX AND LABORATORY ASSISTANTS, 1898.

http://www.cdc.gov/malaria/images/history/ross_laboratory.jpg

Ross initiated mathematical models for malaria epidemiology.

But the work of Bernoulli, Ross and many others is largely subsumed in the model first developed by two Scottish mathematicians, one of whom had an Indian connection

This is the most famous model of infectious diseases today and has guided all later work, although it was not adequately recognised for many years

It is called the SIR model

A G McKendrick

Born in Scotland, trained as a doctor, joined Indian Medical Service. Director of Pasteur Institute in Kasauli

Returned to England in 1920. Superintendent of Royal College of Physicians Laboratory from 1920 to 1941

"Although an amateur, he was a brilliant mathematician, with a far greater insight than many professionals."

Wrote a set of three articles from 1927, 1932, and 1933

A.G.McKendrick

1876-1948

Wikipedia

W.O.Kermack

1898-1970

Wikipedia

W O Kermack

Trained as a mathematician, worked as a chemist for 28 years at the Royal College of Physicians Laboratory.

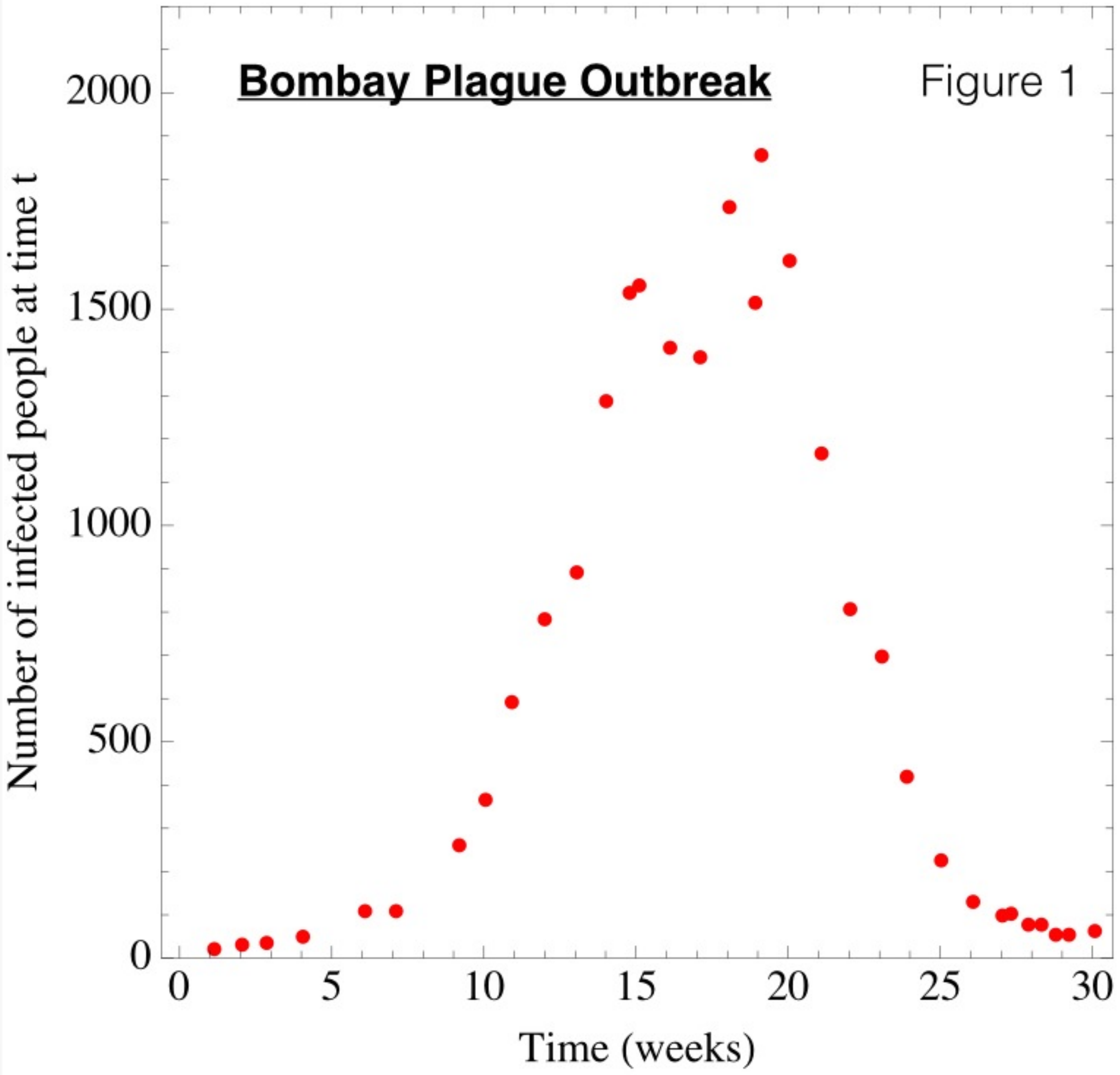
Continued research after being totally blinded from a chemistry experiment in 1924. Started a fruitful collaboration with McKendrick

He had an ‘altogether exceptional sense of algebraic form, in addition to [a] penetrating sense of mathematical significance’, with the blind Kermack ‘doing all the working in his head’

Data from a plague outbreak in Bombay in 1905, showing estimates of the number of infected people over time.

Once the outbreak was over (at week 30, which was July 21, 1906) a certain fraction of the population had been infected.

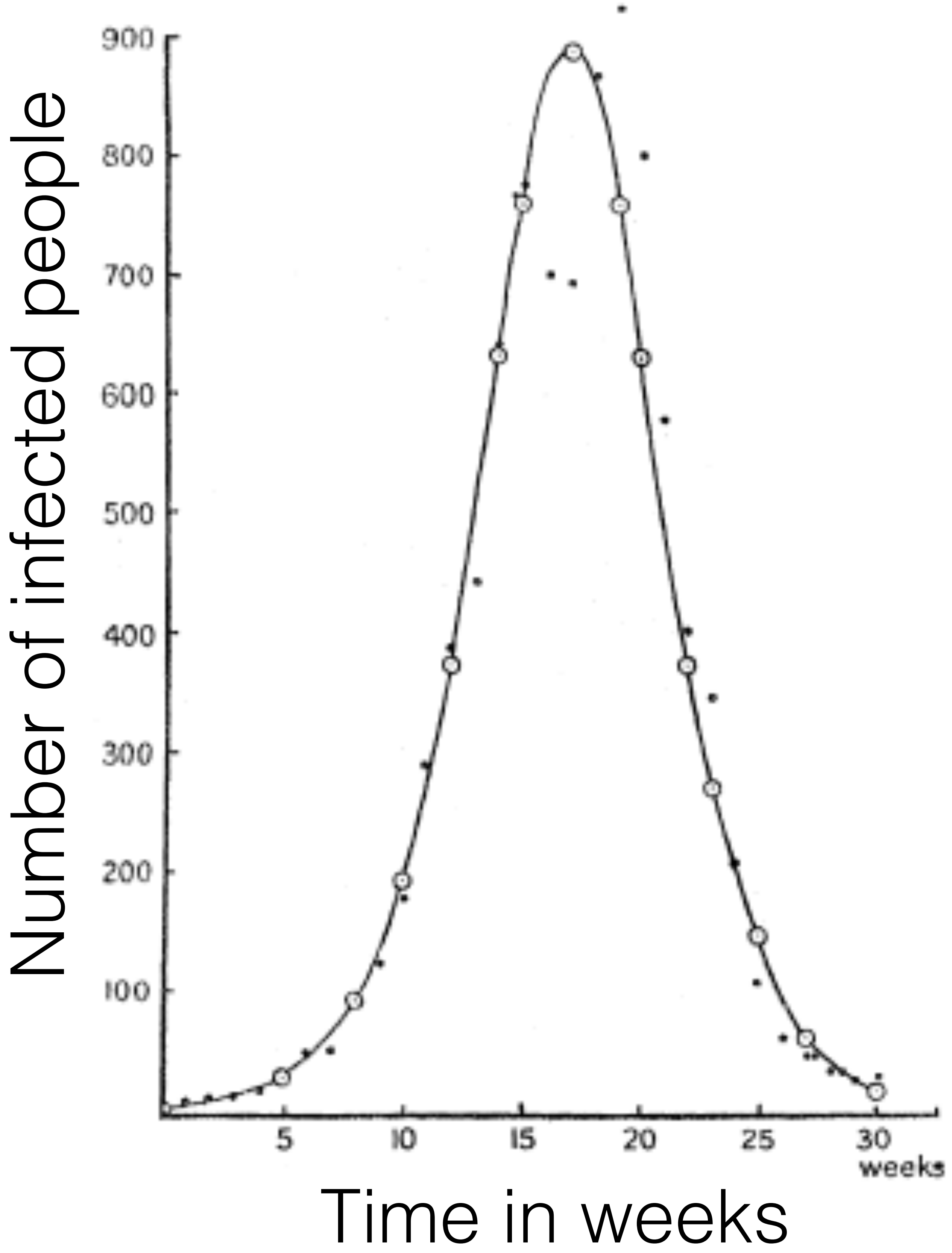
http://static.cdn-seekingalpha.com/uploads/2014/9/7379991_14110535248341_rld6.png



Kermack and McKendrick compared the data to their theory

This is the most reproduced figure in books on mathematical epidemiology.

It is justly famous



http://static.cdn-seekingalpha.com/uploads/2014/9/7379991_14110535248341_rld6.png

So what does the model of Kermack and McKendrick (the SIR model) contain?

Susceptible

Infected

A person can be either susceptible, infected or recovered, with respect to the disease

Recovered

Susceptible

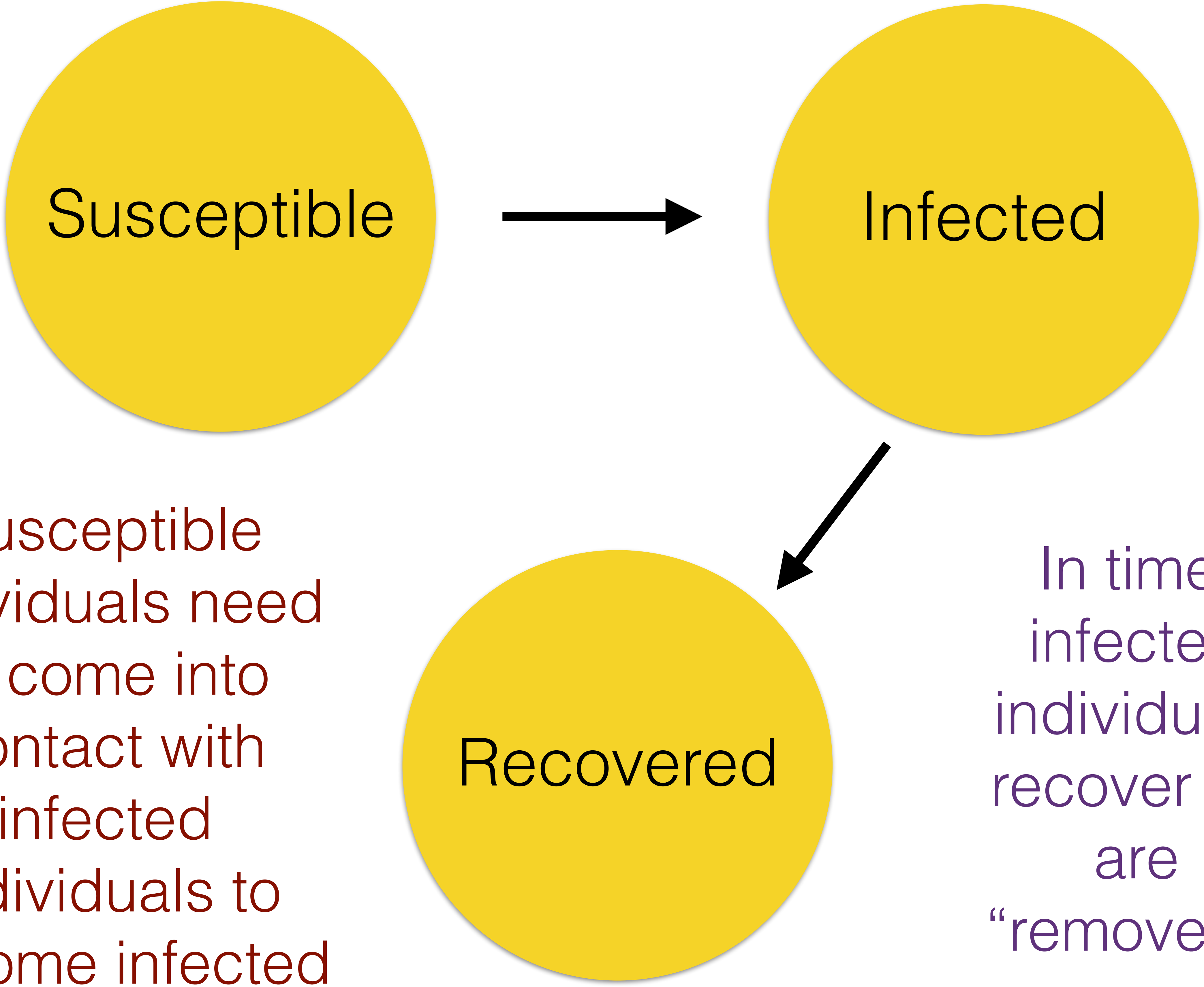
Infected

Each individual assigned to a compartment

People move between these compartments as they fall ill and get cured

Recovered

Someone who is susceptible can become infected and then recover



Susceptible

Infected

Recovered

Susceptible individuals need to come into contact with infected individuals to become infected

In time, infected individuals recover (or are “removed”)

Immunized

Exposed

Someone who has been exposed to infection but does not manifest symptoms of disease

Someone who is not susceptible to infection because they have been vaccinated

Susceptible

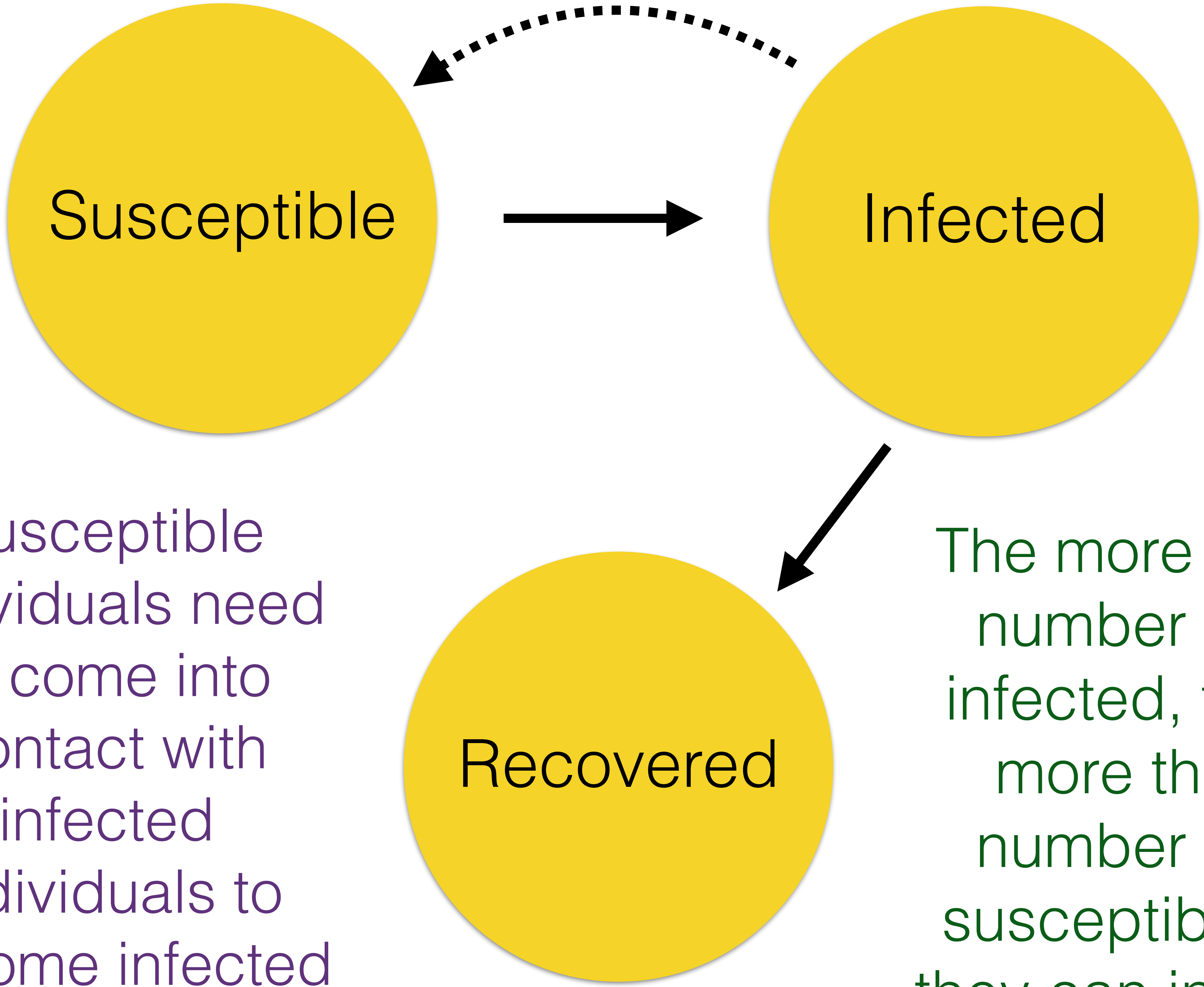
Infected

Someone who has been hospitalised because of infection

Could have more compartments

Recovered

Hospitalized



Susceptible

Infected

Recovered

Susceptible
individuals need
to come into
contact with
infected
individuals to
become infected

The more the
number of
infected, the
more the
number of
susceptibles
they can infect

S = Number of susceptibles
I = Number of infected
R = Number of recovered

N = S + I + R
The total population

To understand how epidemics spread, we need to understand how S, I and R change with time

Mathematicians call this a "dynamical system"

"A dynamical system is a concept in mathematics where a fixed rule describes how a point in a geometrical space depends on time.

Examples include the mathematical models that describe the swinging of a clock pendulum, the flow of water in a pipe, and the number of fish each springtime in a lake"

Wikipedia

Henri Poincare

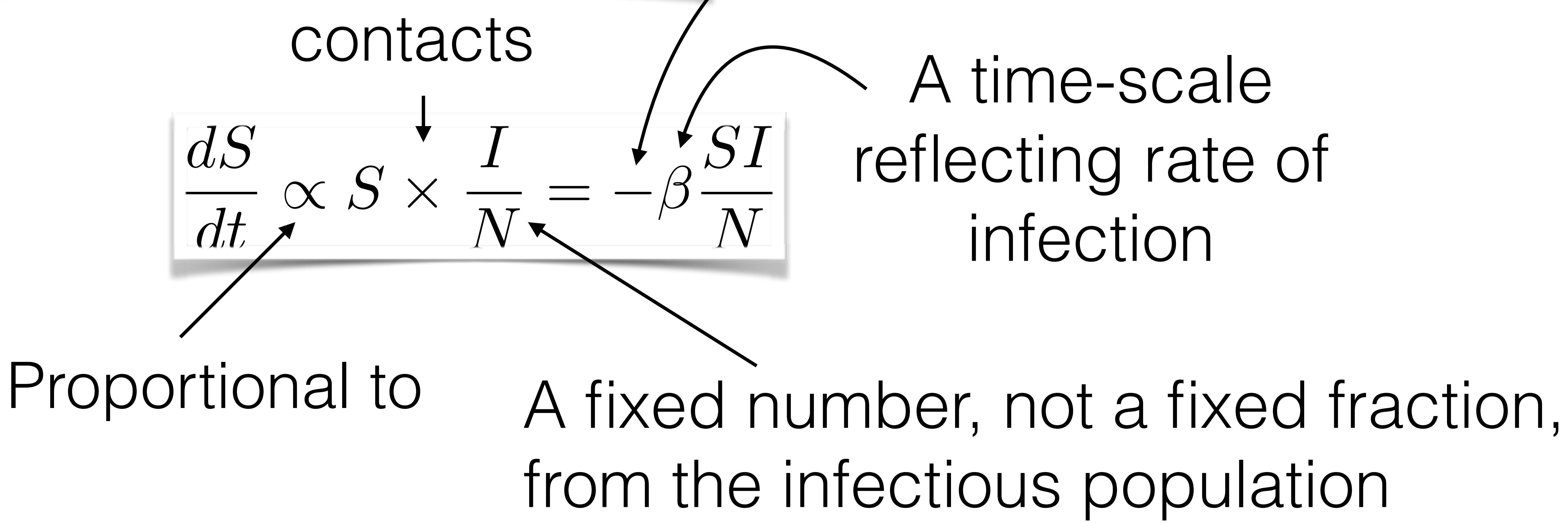
S = Number of susceptibles
I = Number of infected
R = Number of recovered

$$
\begin{aligned}
\frac{dS}{dt} &= F_1(S, I, R) \\
\frac{dI}{dt} &= F_2(S, I, R) \\
\frac{dR}{dt} &= F_3(S, I, R)
\end{aligned}
$$

What are the forms that the terms F_1, F_2 and F_3 can take?

Decide these by reasonable arguments

S = Number of susceptibles
I = Number of infected
R = Number of recovered



Number of susceptibles decreases

contacts

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

A time-scale reflecting rate of infection

Proportional to

A fixed number, not a fixed fraction, from the infectious population

---

Those infected, recover at some rate. Number recovering is proportional to the number infected

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

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

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

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

N = S + I + R
is constant

$$\frac{d(S + I + R)}{dt} = 0$$

This assumes that there are no births and deaths. The total number across each compartment remains constant

$$\text{Define } S = S/N, I = I/N, R = R/N, \text{ so } S + I + R = 1$$

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

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

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

The SIR Model

Note that S, I and R must all be less than or equal to 1

What do we want to know?

A given disease is characterised by the β and ɣ which appear in these equations

If a few infected persons are present initially, what determines if the disease will spread?

How many people will be infected as a result?

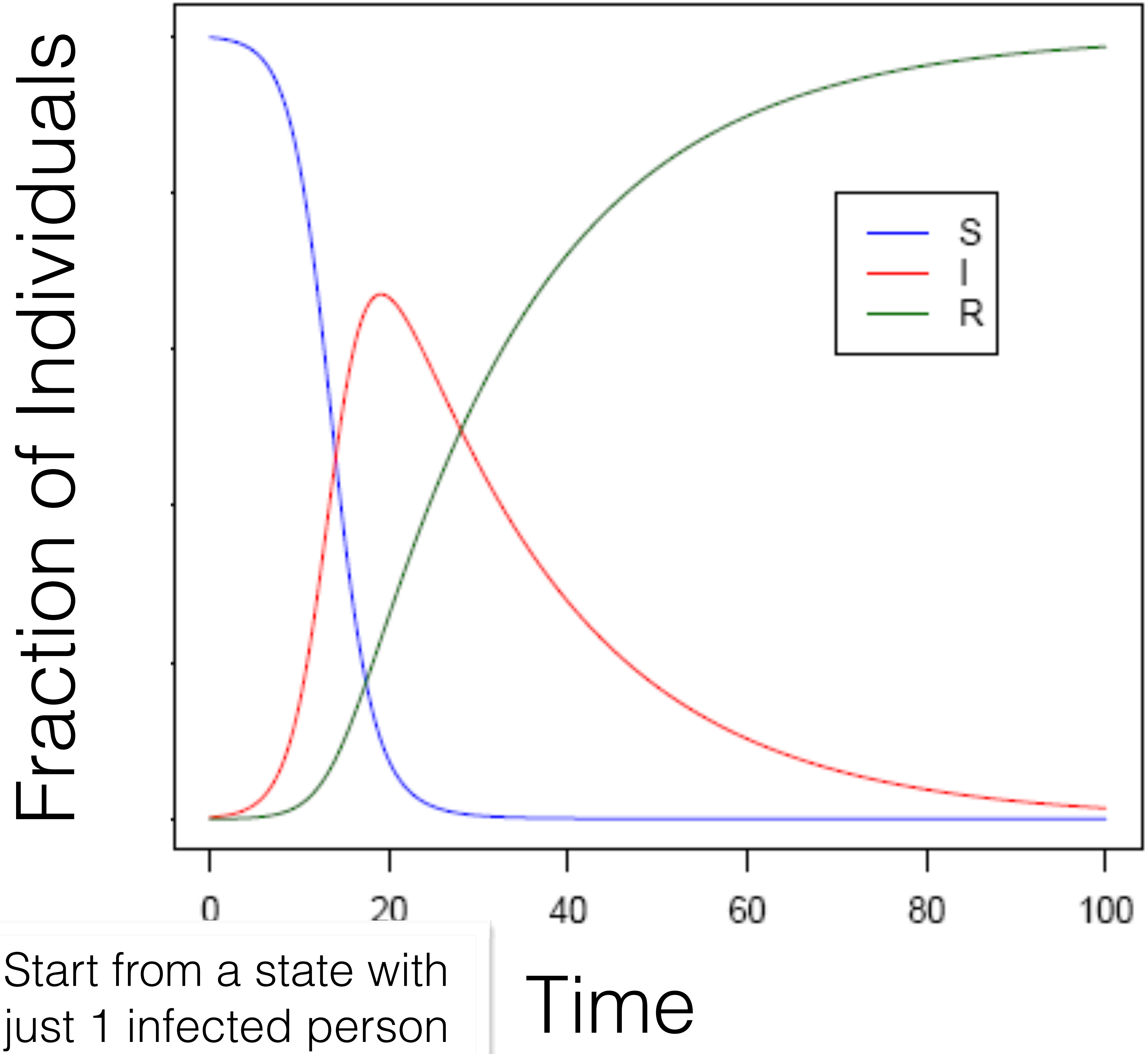
Can an infection recur in the population after dying out once?

What does immunisation do?

$$\frac{dS}{dt} = -\beta S I$$
$$\frac{dI}{dt} = \beta S I - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

The behaviour of S, I and R

Chris Myers lecture, Cornell web page

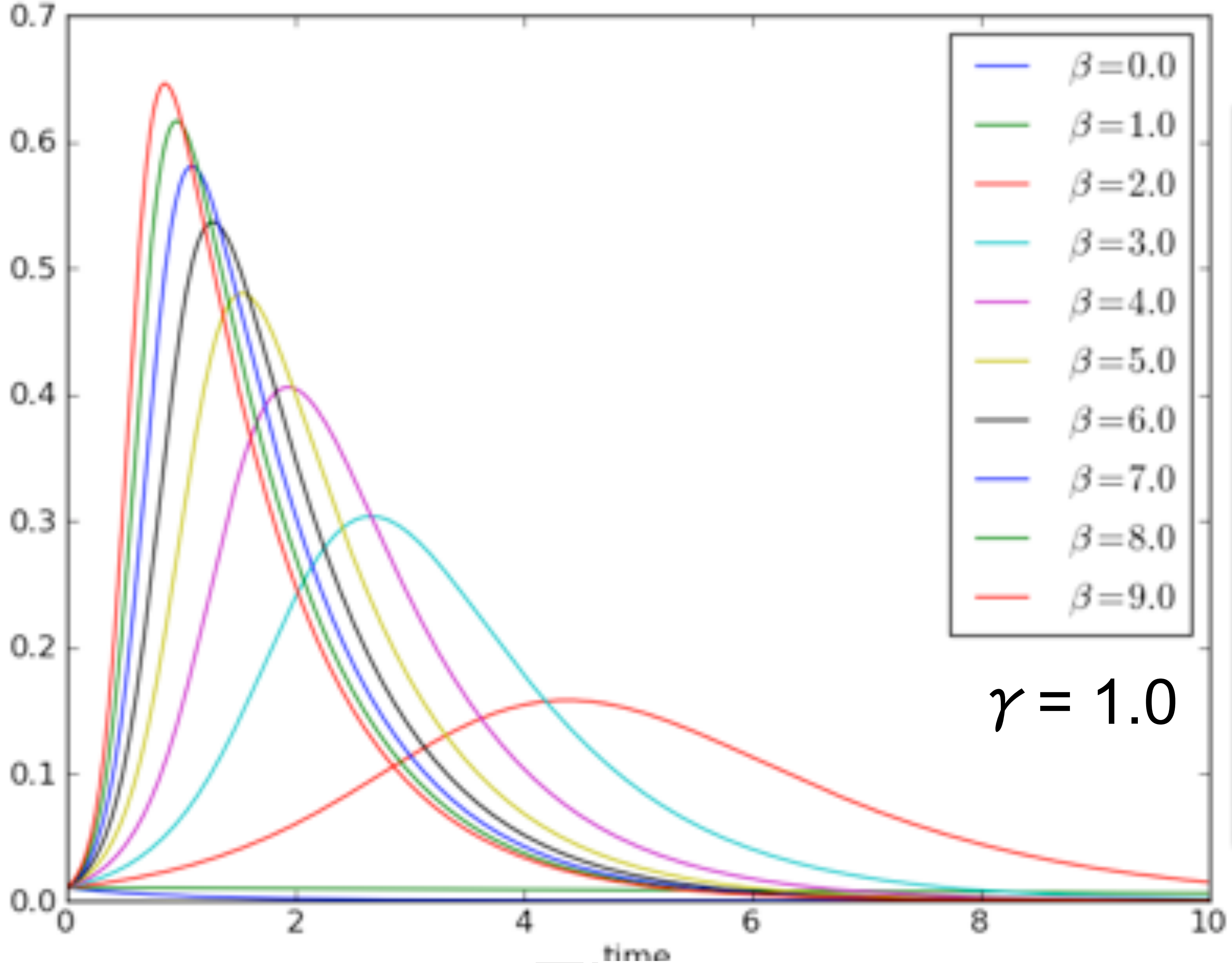


$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$

Can't solve these equations exactly in closed form, but can do them numerically

Start from a state with just 1 infected person

Chris Myers lecture, Cornell web page



Fraction Infected = I

Time

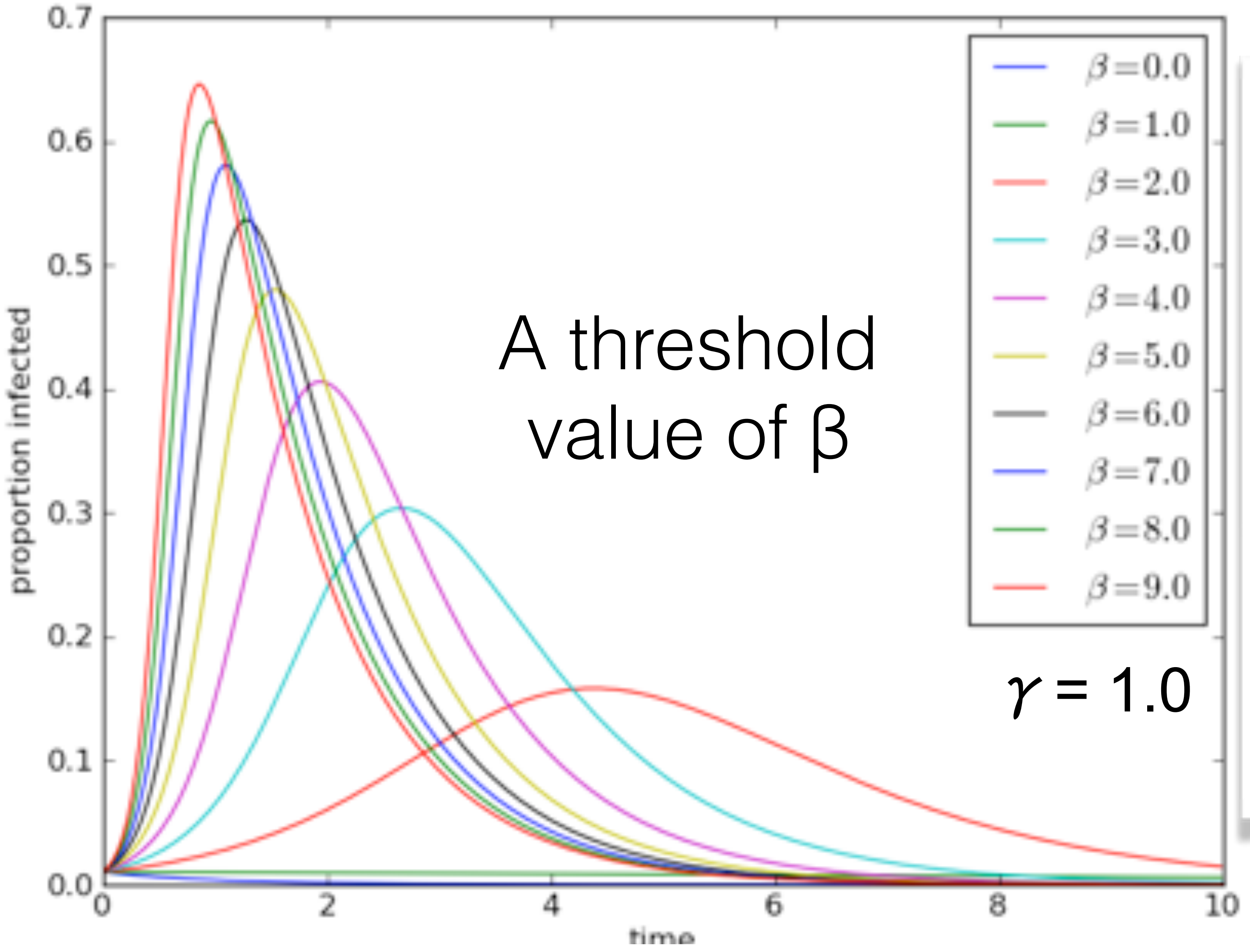
$$\frac{dS}{dt} = -\beta S I$$

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

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

Start from a state with just 1 infected person. Repeat for many β values

Chris Myers lecture, Cornell web page



Fraction Infected = I

Time

A threshold value of β

γ = 1.0

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

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

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

Above the threshold β, a disease infects more people before it dies out. Below it, it vanishes monotonically

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

$$\frac{dI}{dt} = (\beta S - \gamma)I$$

Assume S ≃ 1, add small number of infectious persons, I

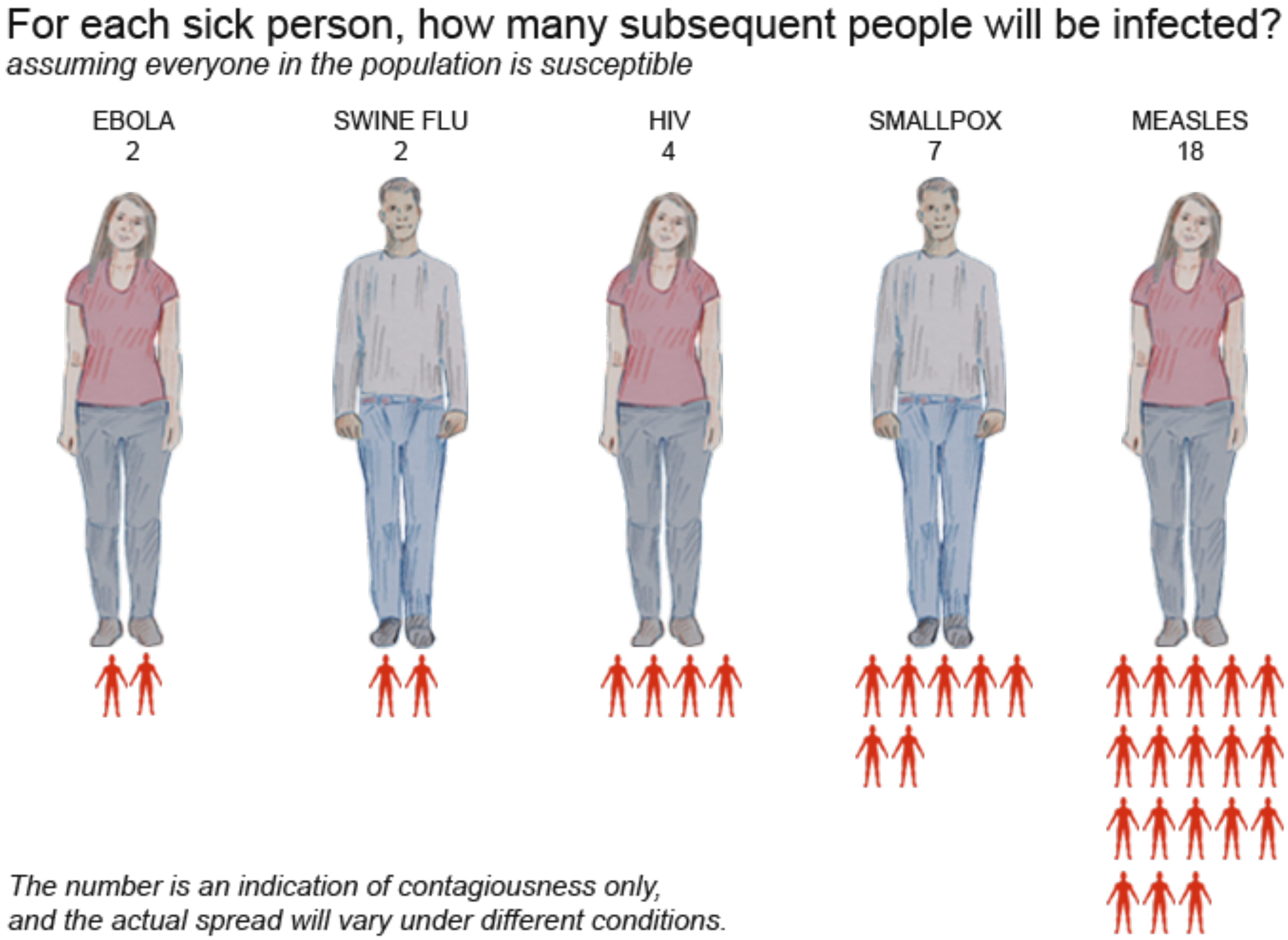
$$\frac{dI}{dt} = (\beta - \gamma)I$$

Whether I becomes bigger or not depends on the sign of $\beta - \gamma$

If $\beta/\gamma > 1$, the infected numbers grow. This ratio is so important, it has its own symbol, R_0, and its own name, the “Basic Reproductive Ratio”

The basic reproductive ratio, or R_0, has a particularly simple interpretation

The number of **people** that **one sick person** will infect (on average) is called R_0.



For each sick person, how many subsequent people will be infected?

assuming everyone in the population is susceptible

The number is an indication of contagiousness only, and the actual spread will vary under different conditions.

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

$$\frac{dS}{dR} = -\frac{\beta}{\gamma}S = -R_0 S$$

$$\frac{dS}{S} = -R_0\ dR$$

$$\ln S(t) - \ln S(0) = -R_0(R(t) - R(0))$$

$$S(t) = S_0 \exp\left[-R_0 R(t)\right]$$

Now because R(t) is always less than 1, S(t) can be bounded

$$S(t) \geq S_0 \exp\left(-R_0\right) > 0$$

Not everyone will be infected

Diseases die out because of the recovery (or death) of infected people, not because susceptibles run out

Why should we vaccinate against a disease?

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

Start with $\frac{dI}{dt} = (\beta S - \gamma)I$

$$\beta S - \gamma < 0$$
$$\beta S < \gamma$$
$$S < \frac{1}{R_0}$$
$$S \rightarrow S(1-p)$$
$$R_0^i = R_0 * (1-p)$$

For the disease not to propagate

Because $R_0 = \frac{\beta}{\gamma}$

Suppose we immunize a fraction of the susceptibles, this reduces R_0

Reduce R_0 below 1, defines a critical p, p_c

$$p_c = 1 - \frac{1}{R_0}$$

Herd immunity

1798	Smallpox
1882	Rabies
1890’s	Cholera and Typhoid
1920’s	BCG
1920’s	Diptheria
1950’s/ 1960’s	Polio
1960’s	Measles, Mumps and Rubella

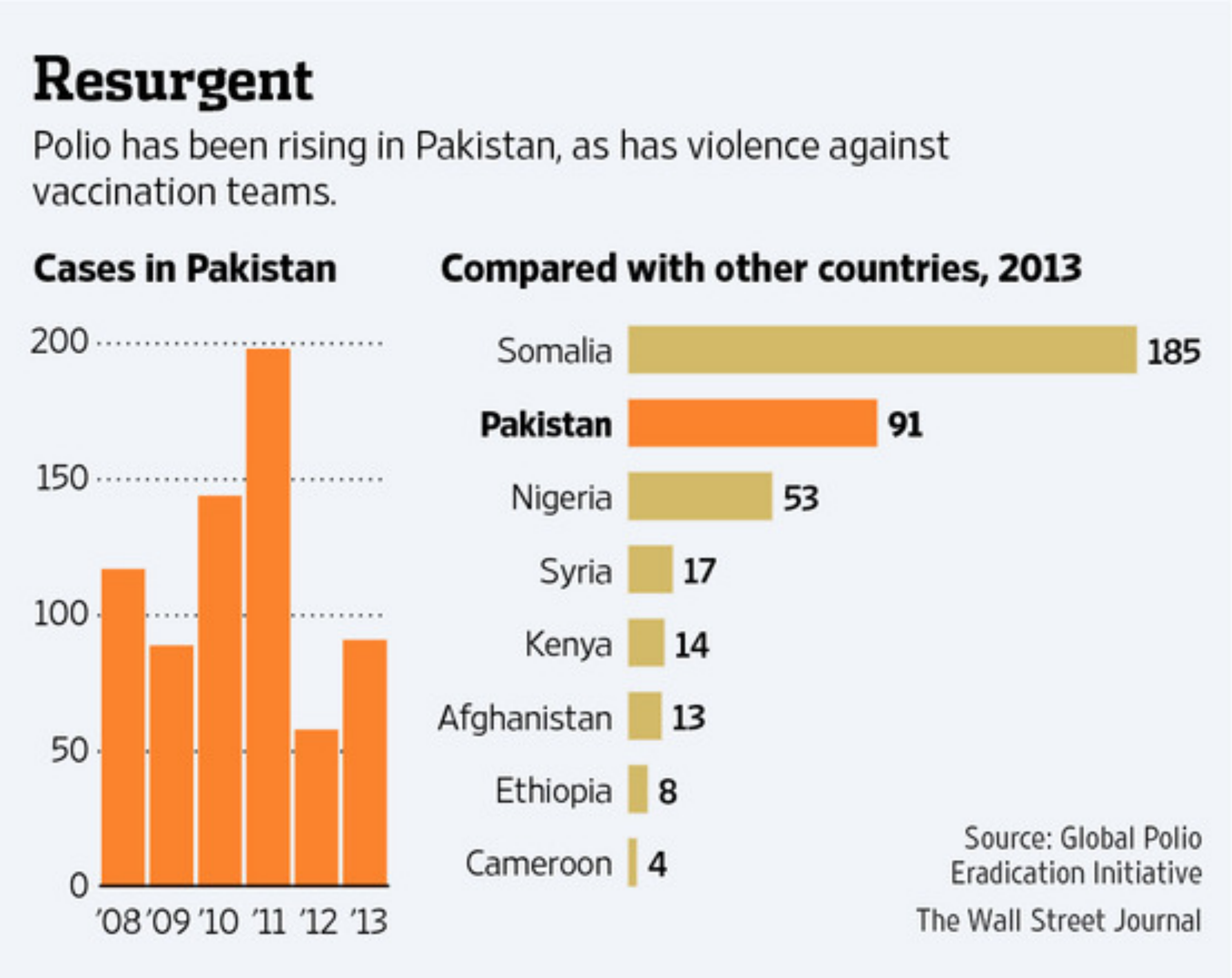
Vaccinating sufficient numbers in a population yields herd immunity

No AIDS vaccine yet

http://graphics8.nytimes.com/images/2012/04/16/blogs/16well-vaccination/16well-vaccination-tmagArticle.jpg

The effect of anti-vaccination campaigns

The return of polio is particularly worrying



Resurgent

Polio has been rising in Pakistan, as has violence against vaccination teams.

Source: Global Polio Eradication Initiative

The Wall Street Journal

http://cf067b.medialib.glogster.com/media/1d/1d044859d4f13e00bfb35b984cde177d157d2ff76b1cbf594e47087d29a2d4cb/polio-child-jpg.jpg

Allowing births and deaths can maintain infectious diseases in the population (endemic)

Other variants of the model can give periodic behaviour, as recorded for measles, which used to recur yearly in the UK and Europe

There are many variants of the SIR model, each suiting a particular disease. Many contexts to studying them

The model is simple, yet general. This is what gives it its power

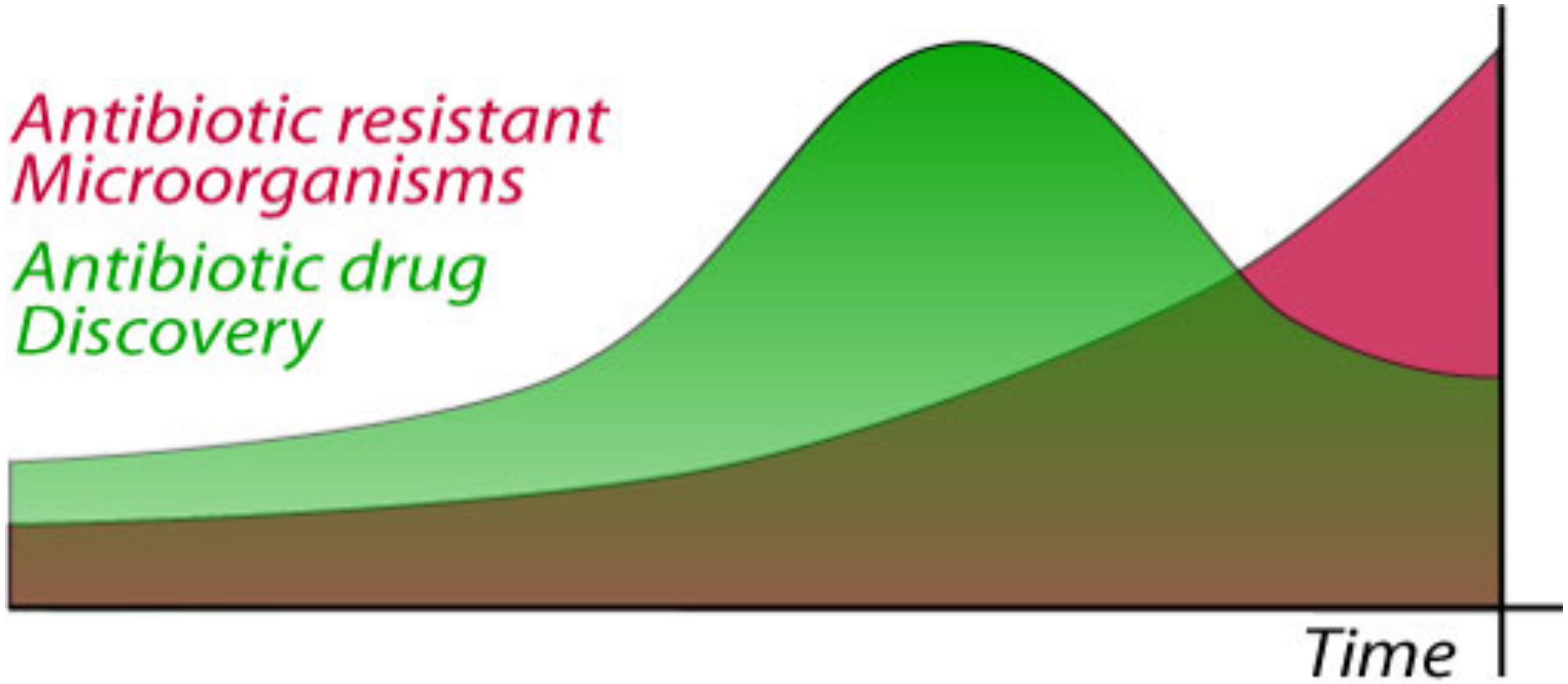
The human cost of infectious disease

In the 2001-2002 foot-and mouth disease epidemic affecting farm animals in the UK, between 6-10 million sheep and cattle were culled to prevent its spread.

This cost their farming industry between 800 million and 2.4 billion pounds.

The economic cost of infectious disease

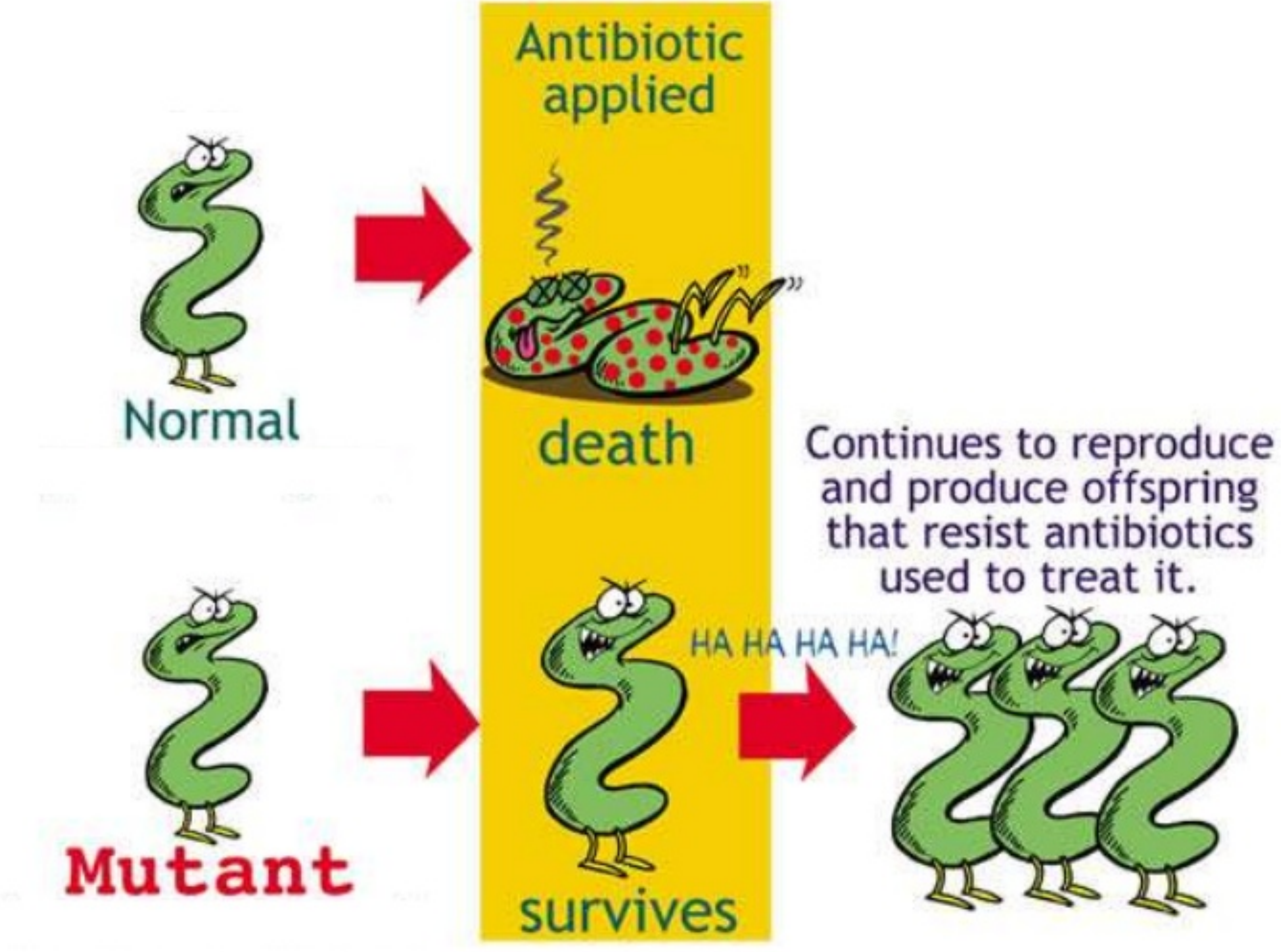
http://uc-care.ku.dk/english/images/graph_01.jpg



Antibiotic resistance is the biggest problem (a "ticking time bomb") in public health today. We are running out of antibiotics that work, because of overuse leading to drug-resistance, and not finding new ones

Why?

Bacteria keep mutating
Some mutations can resist antibiotics



http://sites.psu.edu/sci297bfa13/wp-content/uploads/sites/6052/2014/12/h-pylori.jpg

What can you do?

2 simple things ..

Cold or flu?

Antibiotics won’t help.

Taking them for a virus will **not** make you feel better or get you back to work faster.

If you have the flu or cold, don’t take an antibiotic.

These are viral diseases. It’s useless

Drink lots of water, eat fruit and stay at home

Wash your hands!

http://static.wixstatic.com/media/7fff19_23d3cfb2207f444eb0ac9521b0350736.gif

Summary

- Why study infectious diseases?
  - MERS, ancient and modern history, what is disease, bacteria and viruses
- History of disease modelling
  - Bernoulli, Snow, Ross, Kermack, McKendrick
- The SIR model, derivation
  - A dynamical system: Susceptible, Infected, Recovered
- The Reproductive Ratio
  - What gives a disease more or less pandemic potential
- Herd Immunity
  - Why vaccinate?
- Endemic diseases, periodicity
  - SIR model has many uses, many generalisations

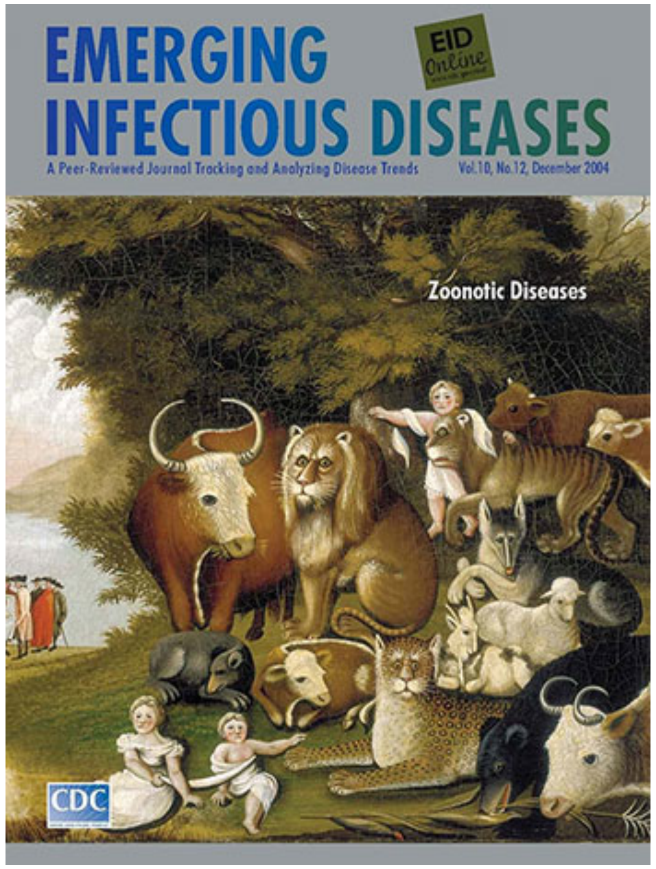
A last few points ..

Infectious diseases have always been with us

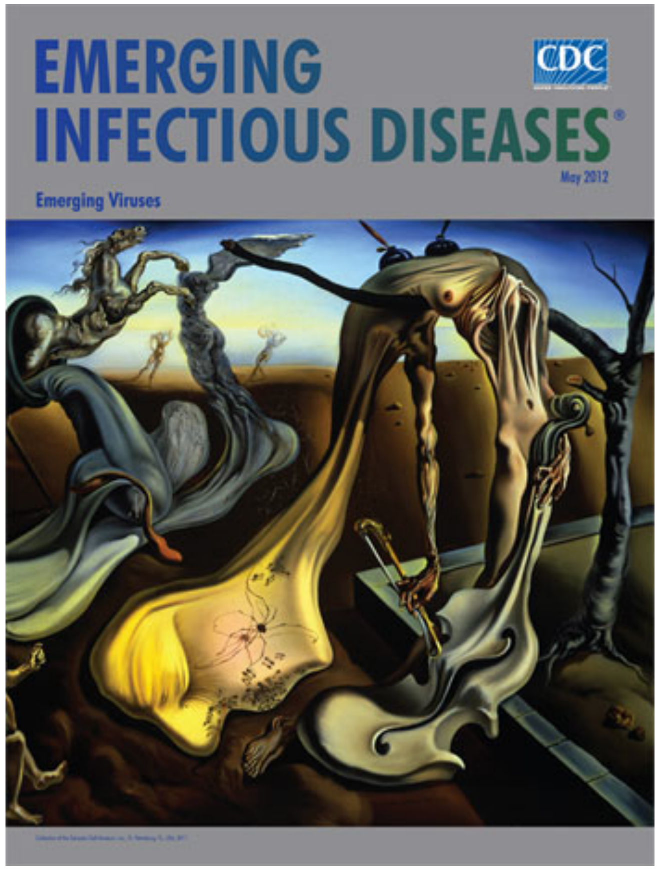
New infectious diseases, such as MERS, will also keep emerging

Apart from human costs, infectious diseases also inflict economic costs.

Can devastate a society



http://wwwnc.cdc.gov



The models I described are used to help public health officials decide what to do when faced with an epidemic

They can indeed save lives

http://i.telegraph.co.uk/multimedia/archive/03000/EBOLA02_3000930b.jpg

http://cdn.theatlantic.com/static/mt/assets/international/Pak%20vac%20article.jpg

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Dealing with such diseases relies on the selflessness and remarkable bravery of large numbers of people, most of whom will remain unknown. They are the true heroes of our times.