What is Science?

Brian Williams

South African Centre for Epidemiological Modelling and Analysis

DAIDD, Florida, October 2016

E-mail: williamsbg@me.com
Web site: www.sacema.org
Epi update: www.sacemaquarterly .com

Gary Trudeau

Donald Trump

Albert Einstein

The object of all science, whether natural science or psychology, is to co-ordinate our experiences into a logical system.

The Meaning of Relativity (1922) (Chapman & Hall, London, 1978) p. 1.

A very brief history of science…

Babylon and Ancient Greece (2000 BC – 300 BC)

Geometry and Number theory

Romans (500 BC – 500 AD)

Engineers who despised mathematics

Chinese (1000 BC – 1000 AD)

Invented everything but never ‘general theories’

Hindus (1000 BC – 1000 AD)

Arithmetic, algebra, trigonometry

Islamic philosophers (800 AD – 1400 AD)

Collected and investigated all the ideas of the ancient world

Europe (1400 AD – ?)

General laws that will explain everything

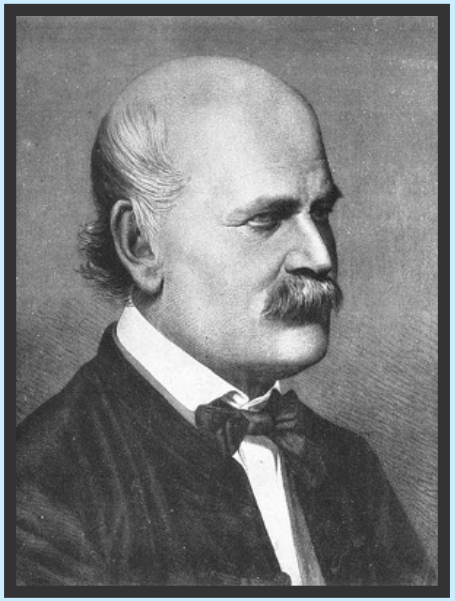
Newton, Darwin, Maxwell, Einstein, Planck

I can’t tell you what science is, I can only tell you what science does.

You can learn a language by studying the rules of grammar and syntax and the meanings of particular words. But if you really want to learn a language you have to just do it.

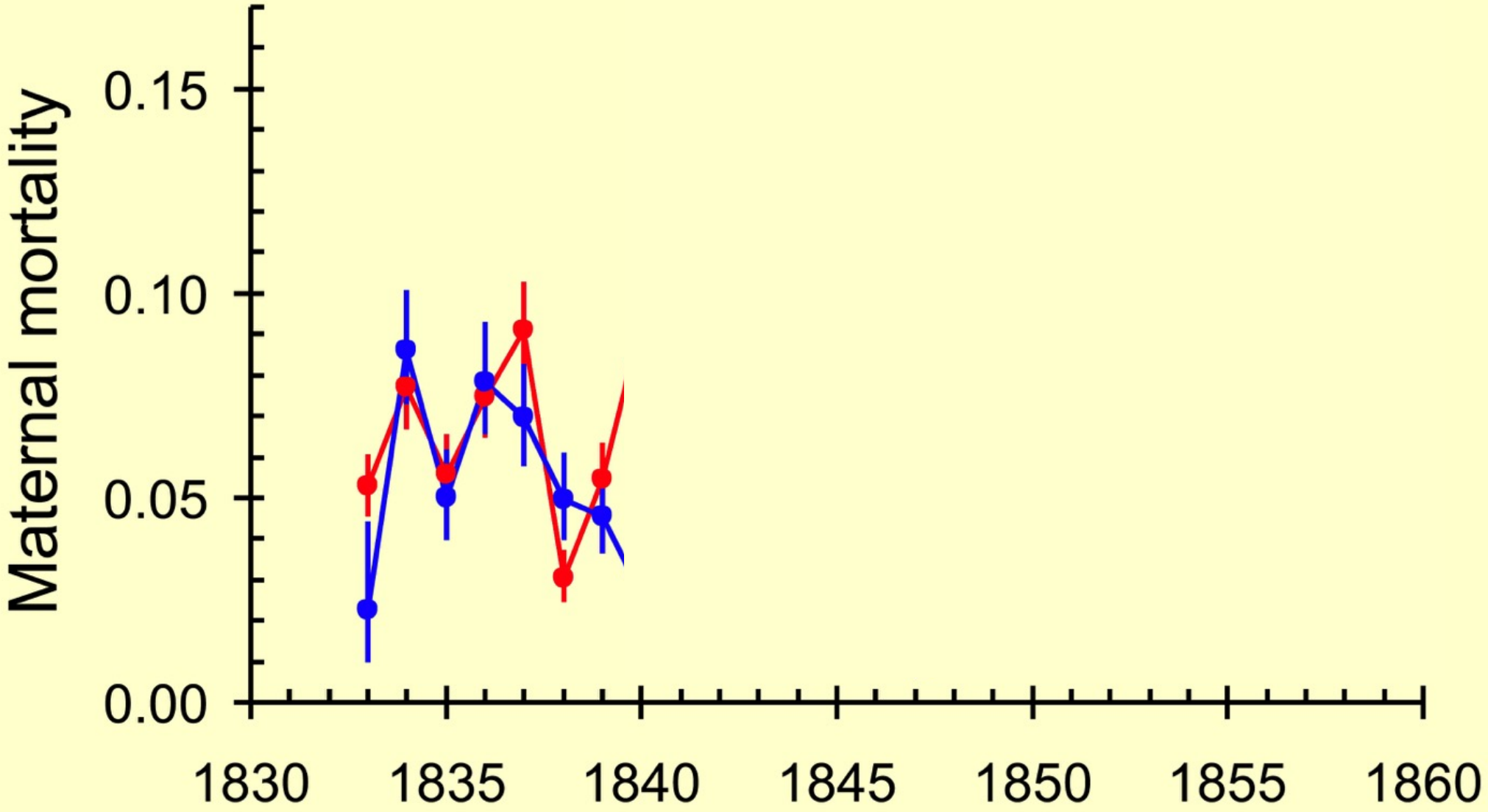
Why washing your hands matters

Ignaz Semmelweiss 1818–1865

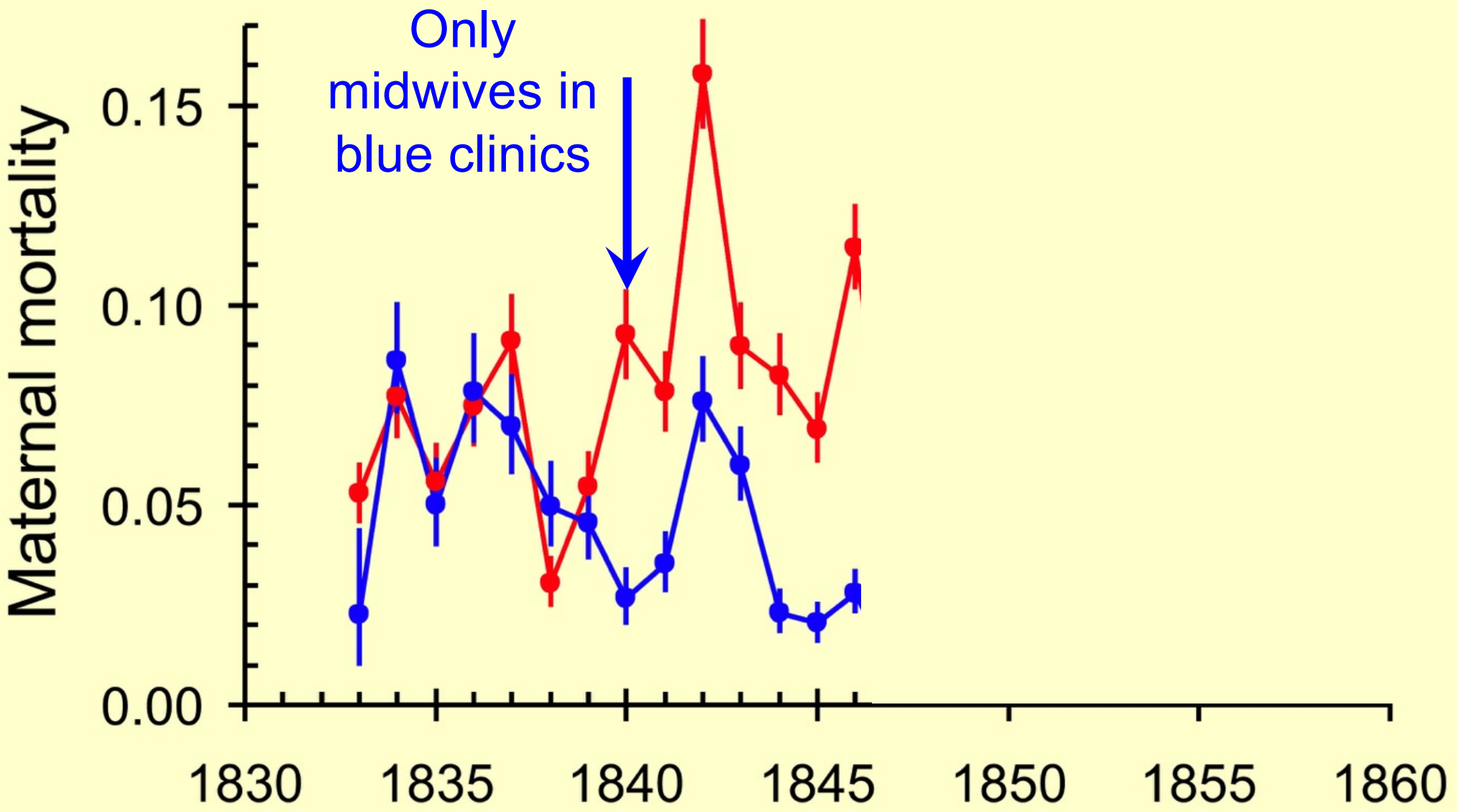


Junior doctor in Vienna General Hospital

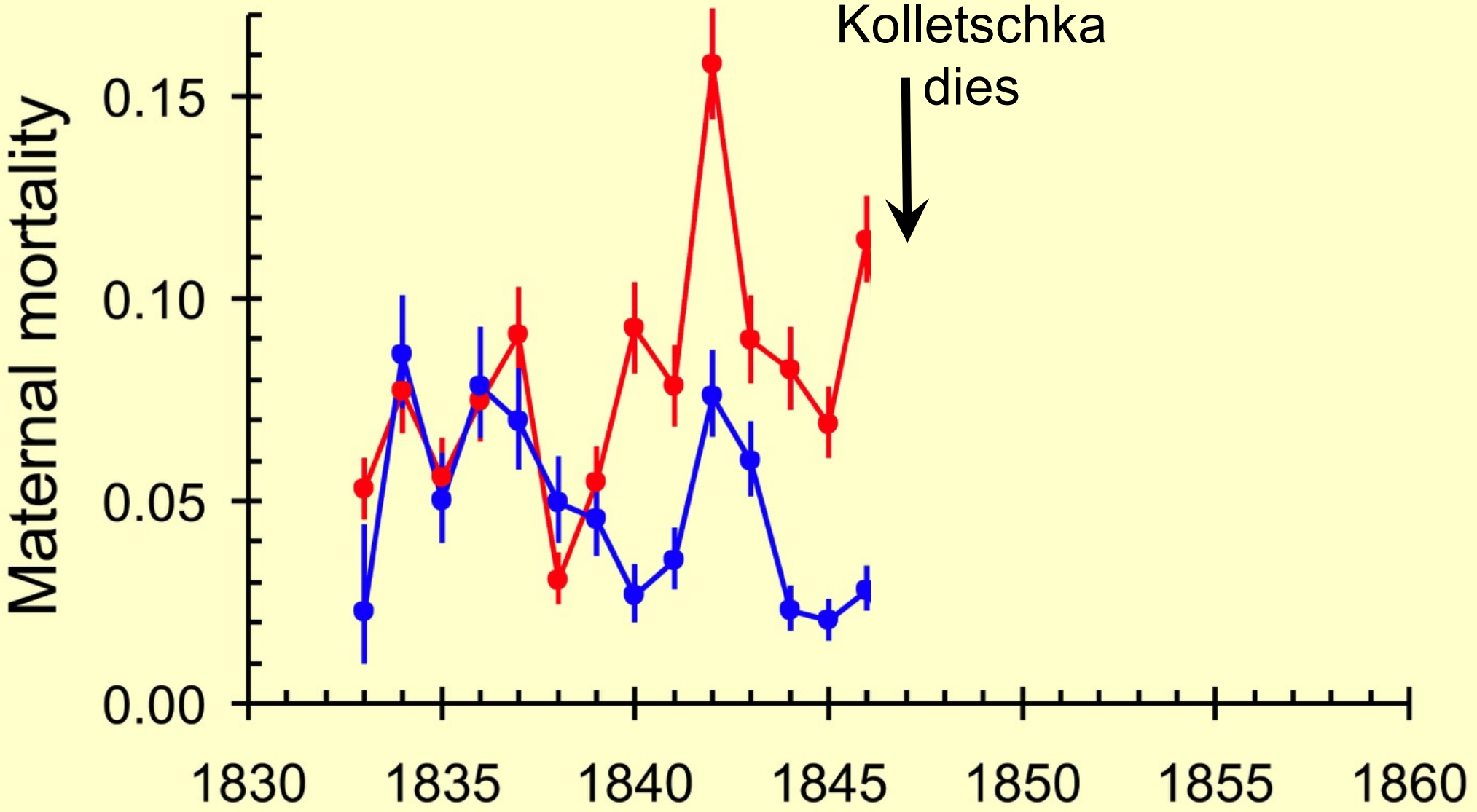
Puerperal fever and maternal mortality



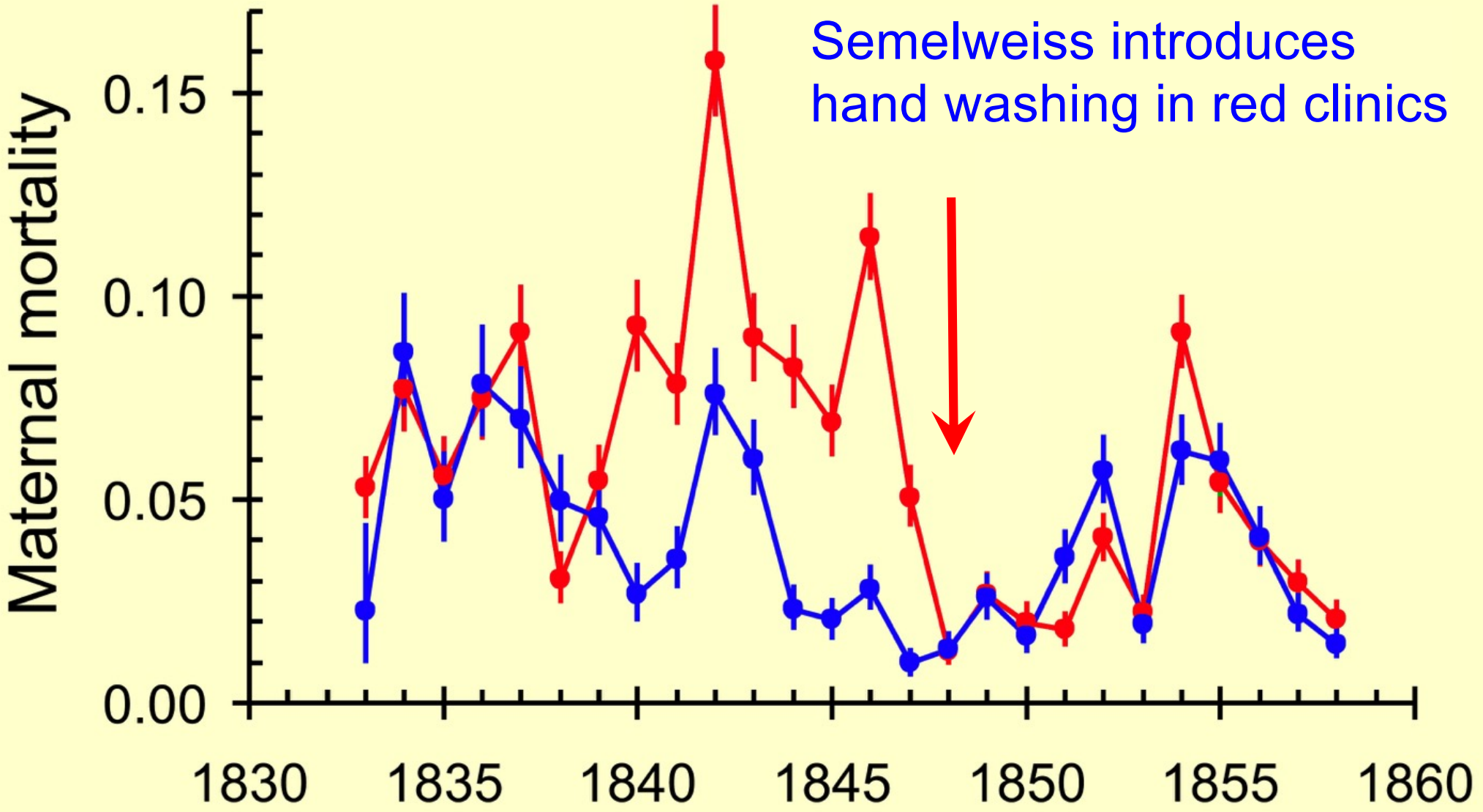
In the 1830s about 1 in 15 mothers were dying of puerperal fever in child birth in two clinics (red and blue)



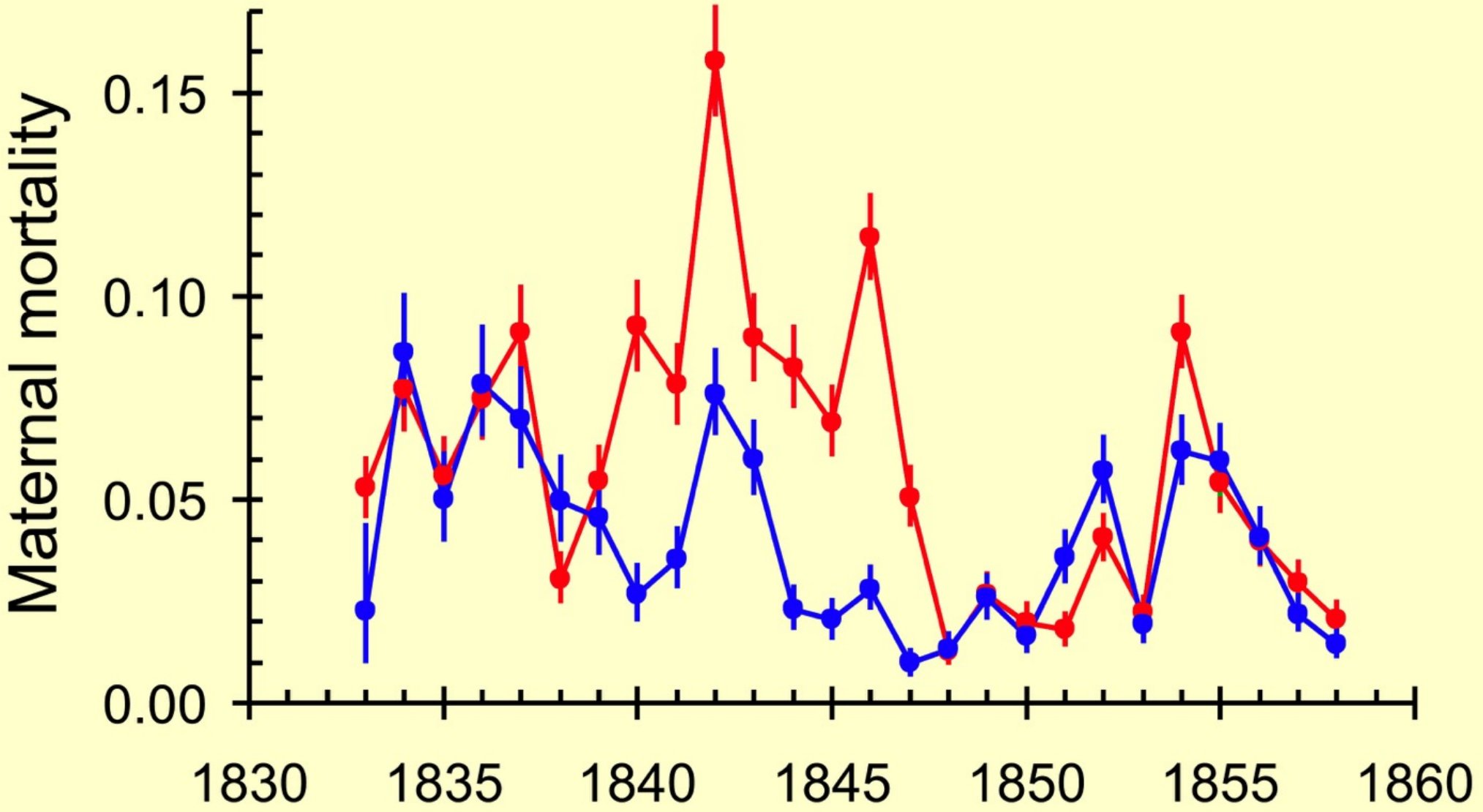
In 1840 maternal mortality in **blue** wards falls below **red** wards. Medical students were doing autopsies before delivering babies in **red wards** but stopped delivering in the **blue wards**.



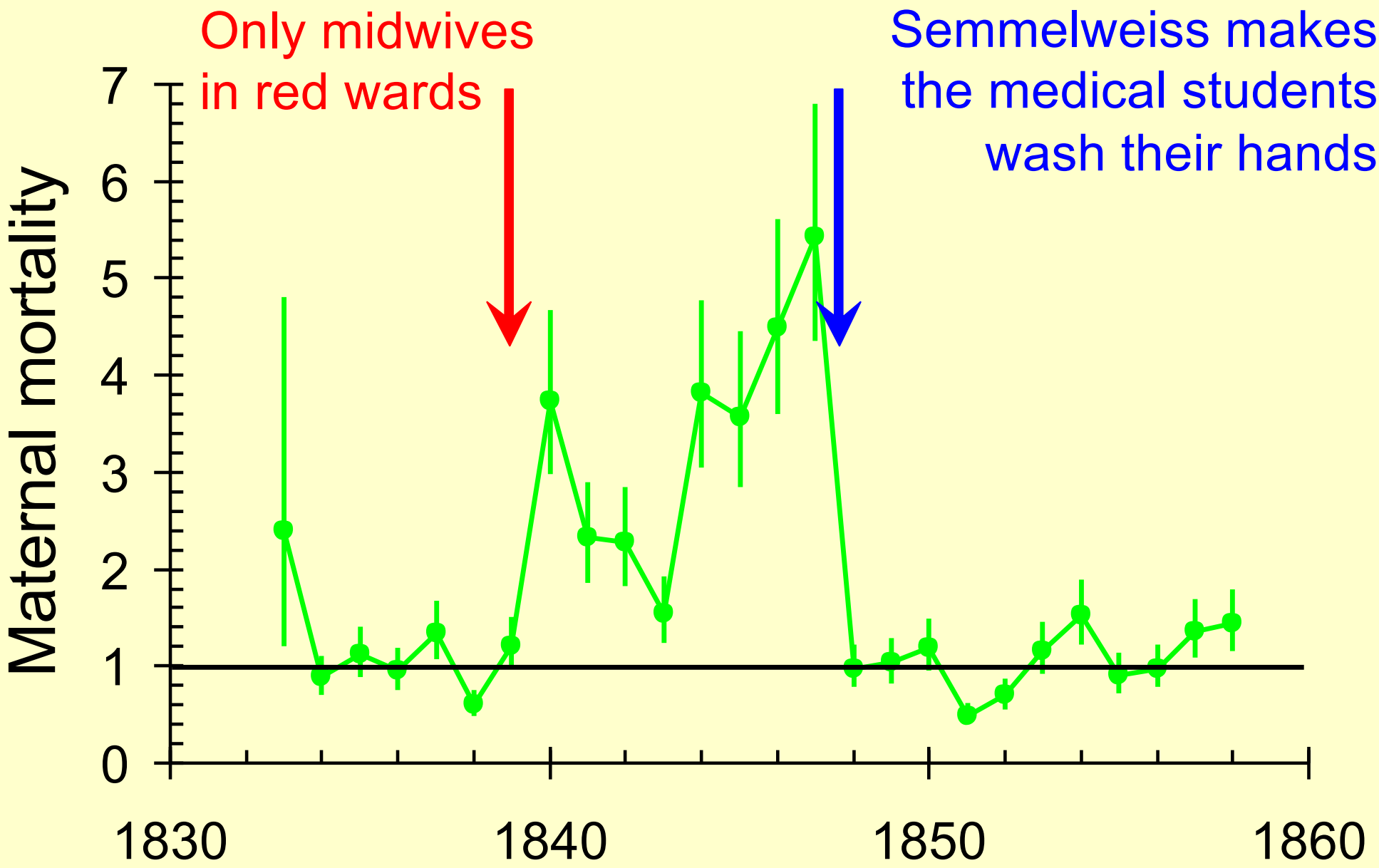
In 1847 Jakob Kolletschka is cut with a scalpel while performing a post-mortem and dies with a pathology similar to that of the mothers. Semelweiss makes a connection between the autopsies and the puerperal fever in women.



In 1848, aged 30 years, he makes medical students wash their hands in chlorinated lime before going to the maternity wards. Mortality in blue wards drops to the same level as in red wards.



Problem → Pattern in the data → Think of an explanation →
Do an intervention → See if it works → Fire the messenger



We can now work out odds-ratios comparing mortality in the blue and red wards and put confidence limits on the estimates.

Cholera
Air borne or Water borne?

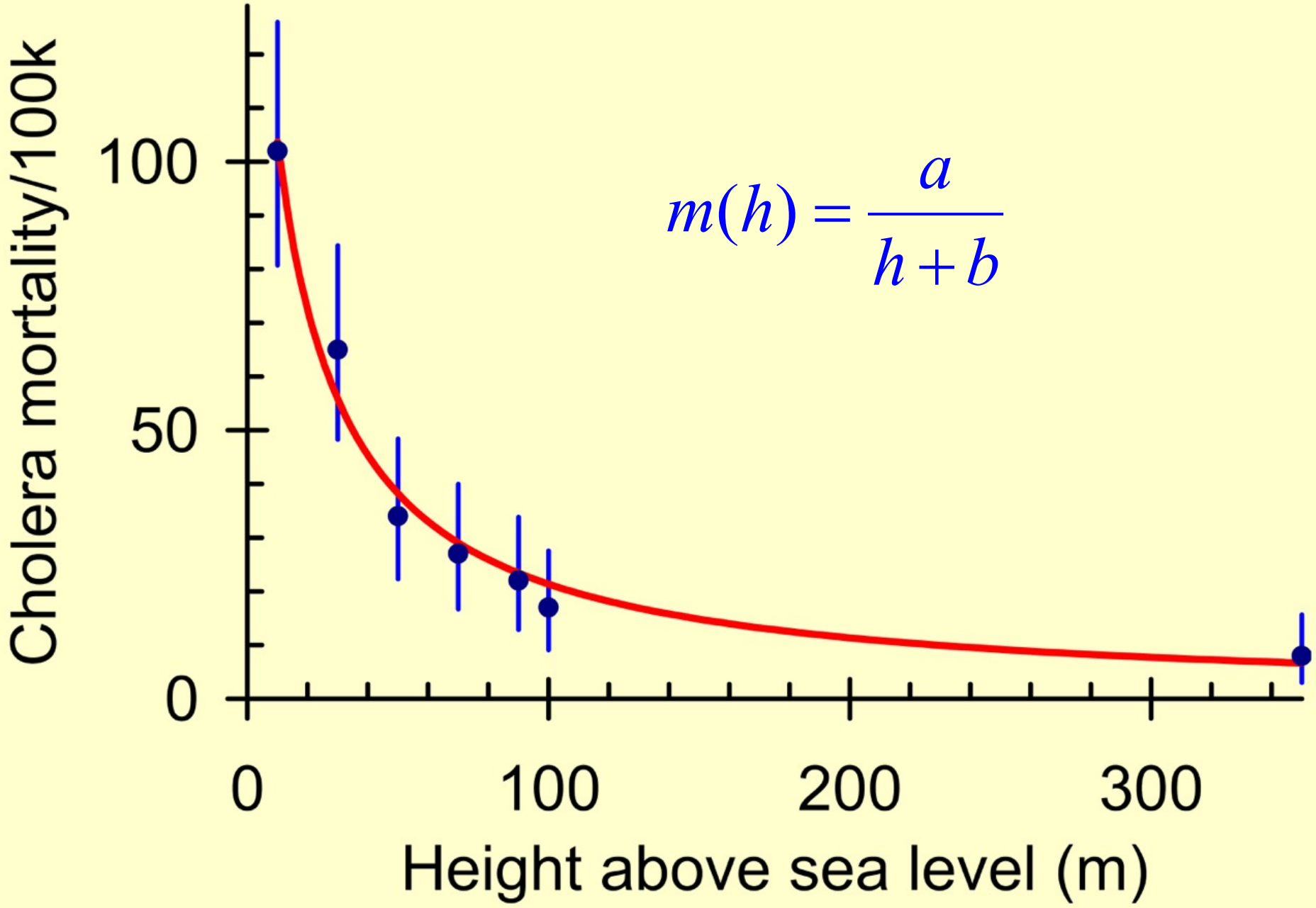
William Farr (1851)

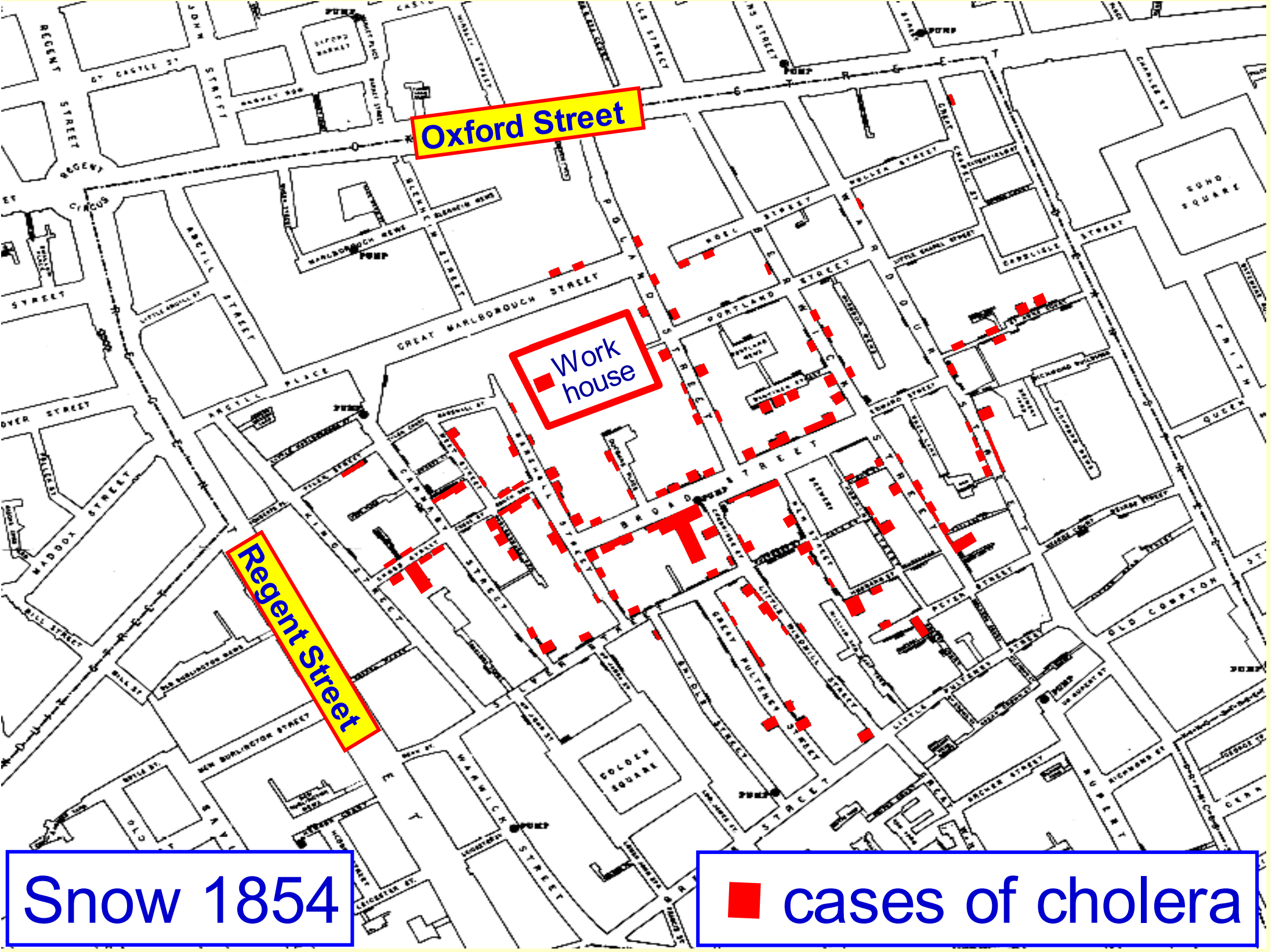
Miasma theory: Cholera is the result of breathing polluted air

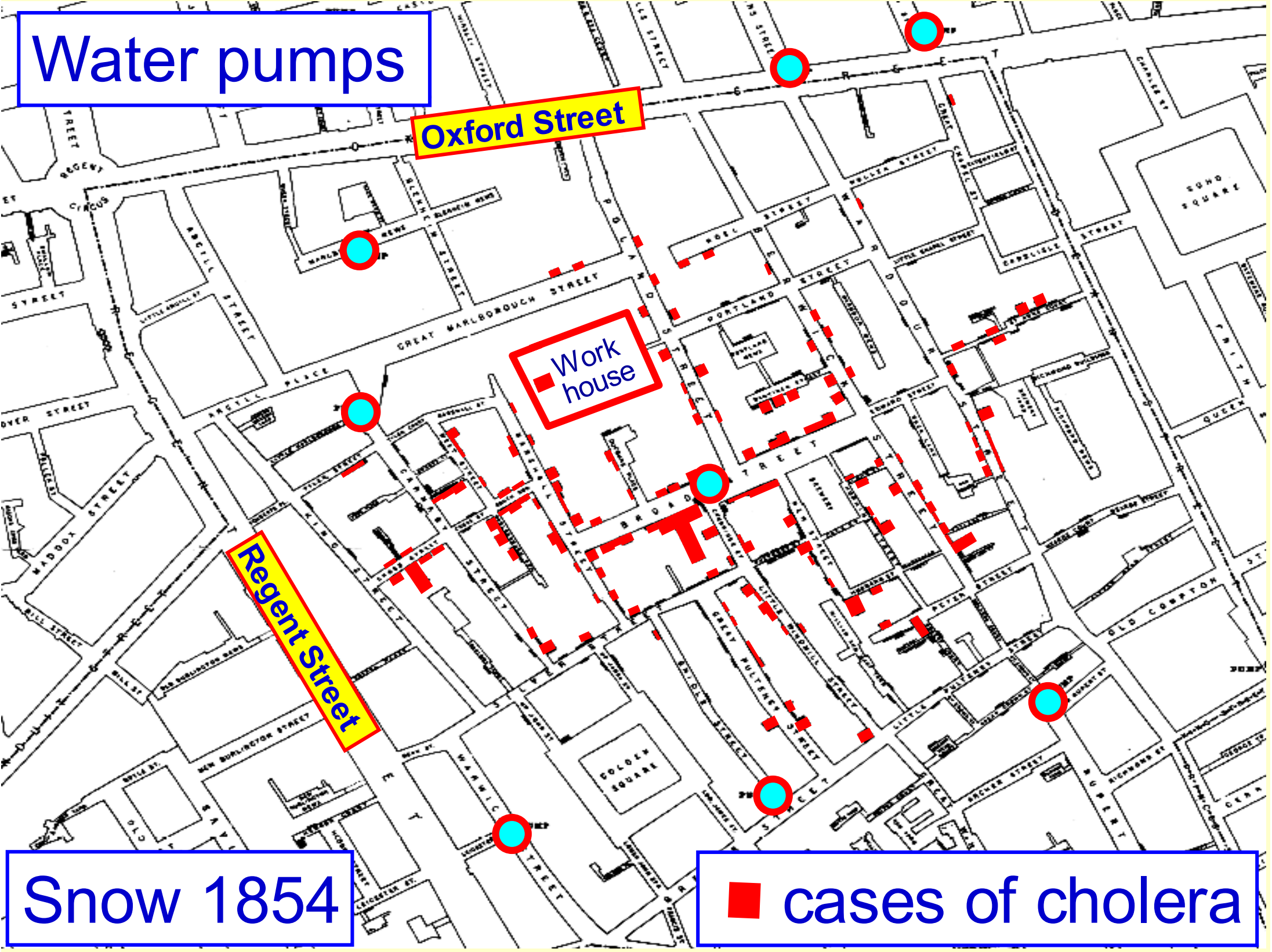
John Snow (1854)

Water borne: Cholera is the result of drinking contaminated water

Cholera mortality in London: 1849




Oxford Street
Work house
Regent Street
Snow 1854
cases of cholera


Water pumps
Oxford Street
Work house
Regent Street
Snow 1854
cases of cholera

Beware of false associations!

- You need data
- You need models
- The model must fit the data
- But the model is the realization of a theory and the theory must make biological sense!

Treating Cholera

In 1849 cholera killed 10% of the population of St. Louis: case fatality rate = 50%.

In 1991 cholera killed 1% of the population of Peru: case fatality rate < 1%.

The basis for this … is …oral rehydration therapy [which] requires only water, sugar and salt.

Barua, D. and Greenough, W.B. 'Cholera' *Curr. Top. in Inf.* Dis. (Plenum; 1992)

The WHO policy of DOTS
(Directly Observed Therapy, Short course)

WHO: Short course chemo-therapy for TB is a sterilizing cure (2000)

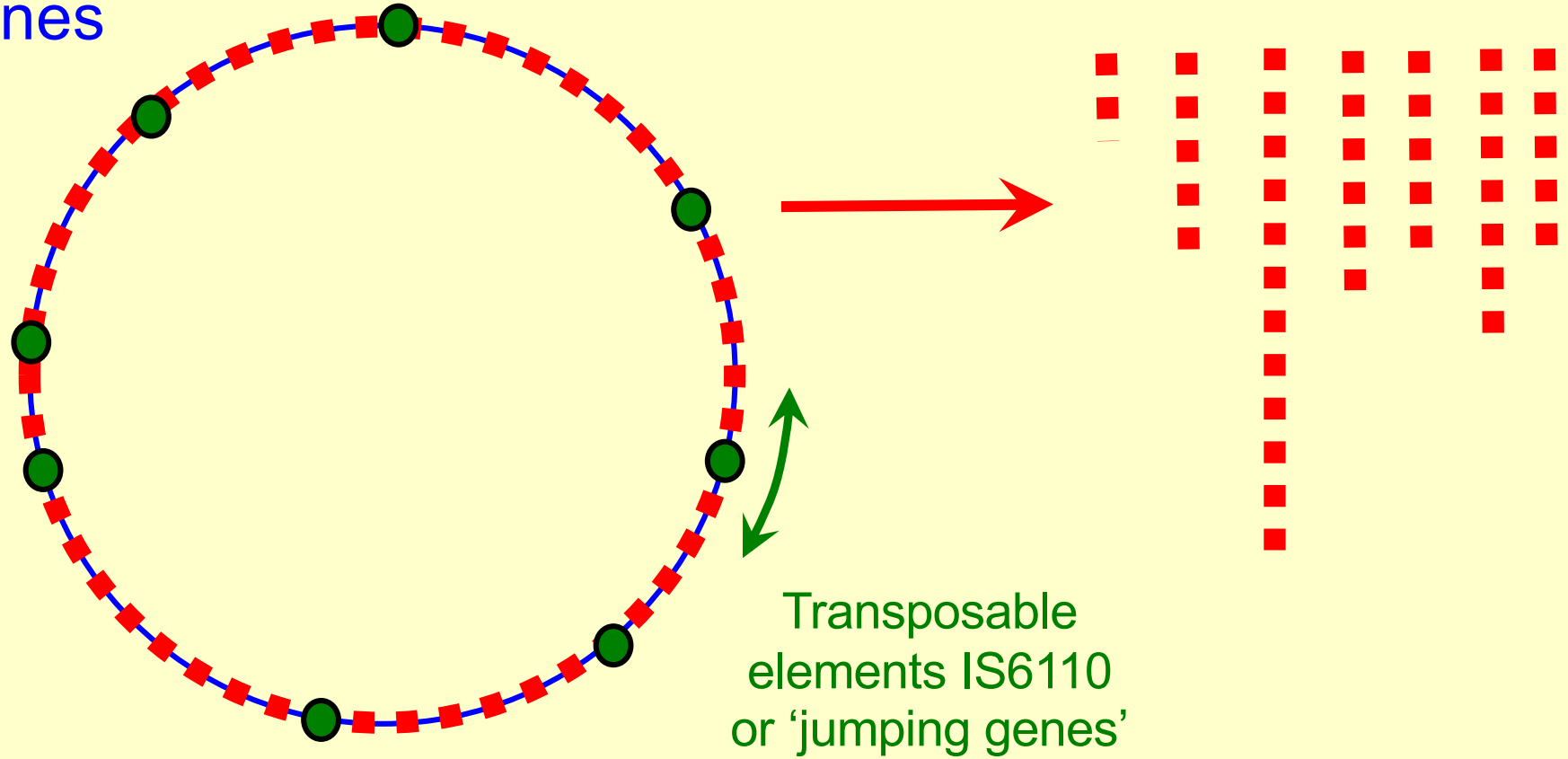
Tony Davies: TB is an inherently relapsing disease (1965)

But: Are recurrent cases relapses or reinfections?

The Eradication of TB in Rhodesia. Davies, C.J.A. MPH, London School of Hygiene and Tropical Medicine 1965. http://tinyurl.com/BGW-TonyDavies

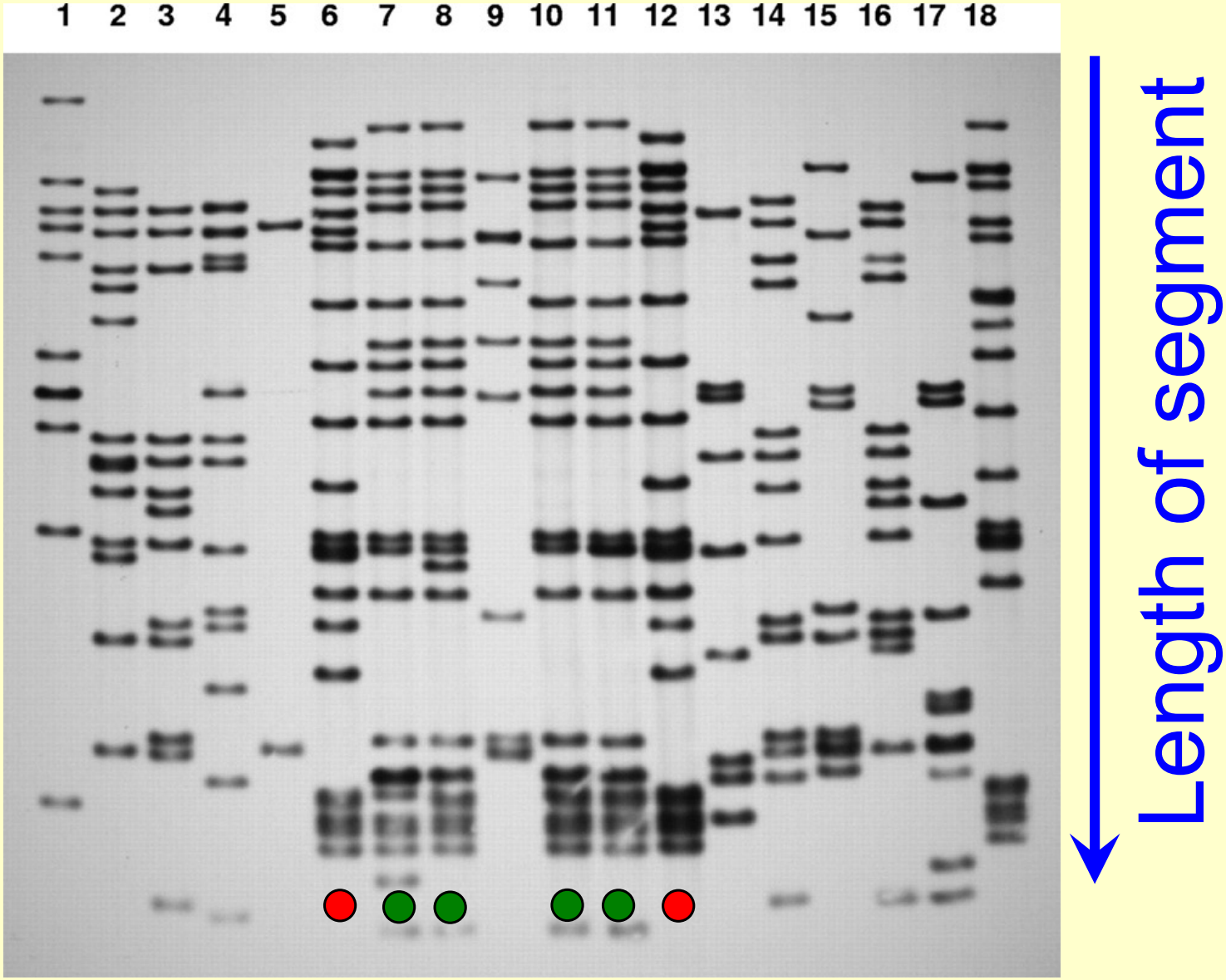
Chromosome of *Mycobacterium Tuberculosis*

4 M base pairs
4 k genes



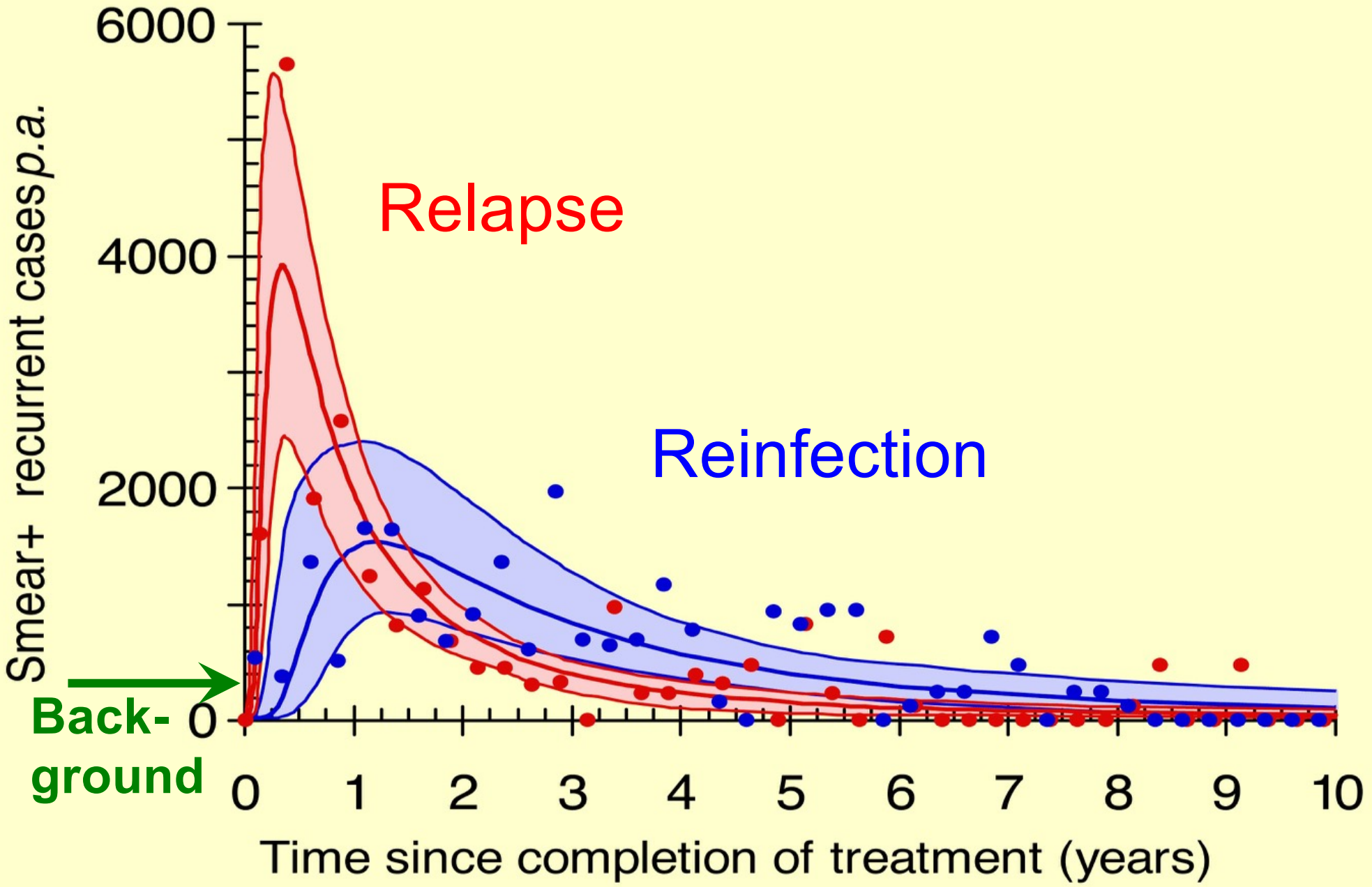
If you cut the chromosome at the sites of IS6110 you have lots of pieces of different lengths

IS6110 DNA fingerprints of clinical *M. tuberculosis* isolates



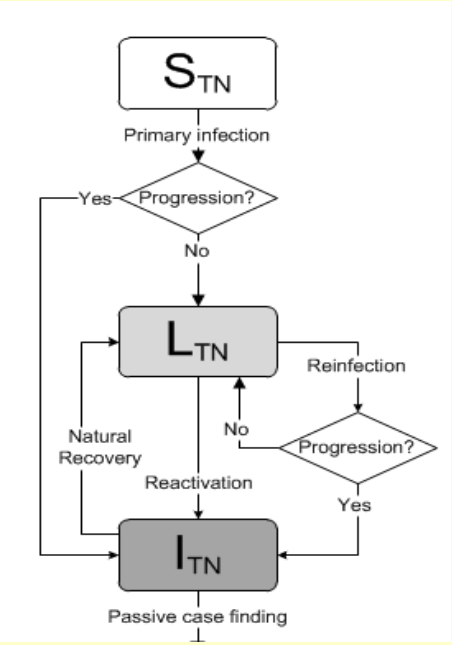
Warren, R. et al. J. Clin. Microbiol. (2006)

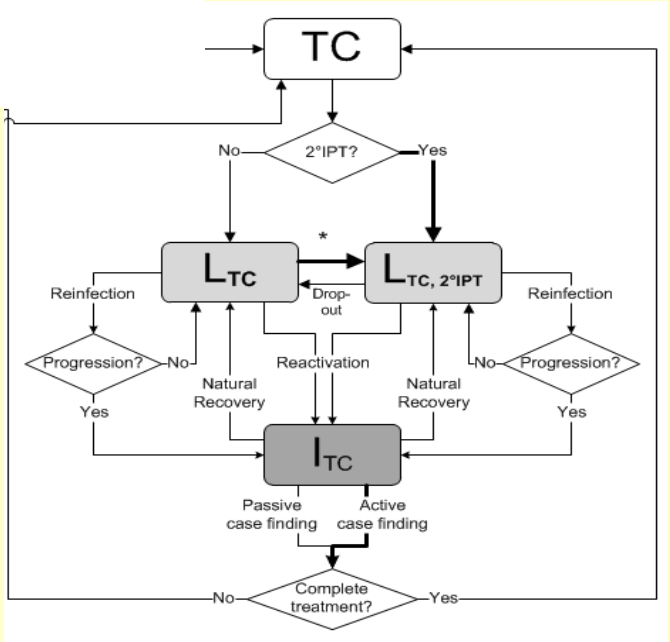
TB: recurrence after treatment

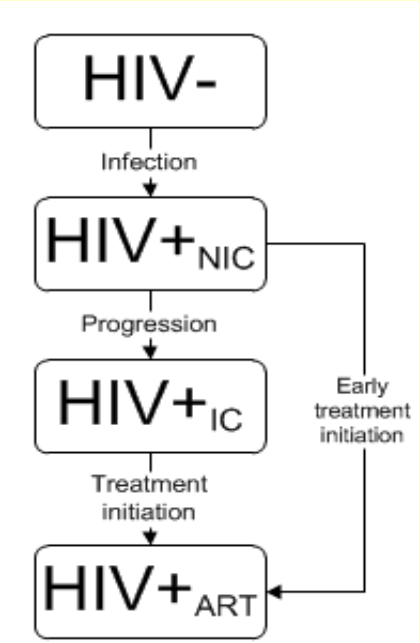


Marx, F.M., et al., Clin. Inf. Dis. (2014). Verver, S., et al., Am J Respir Crit Care Med, (2005)

Modelling active follow-up



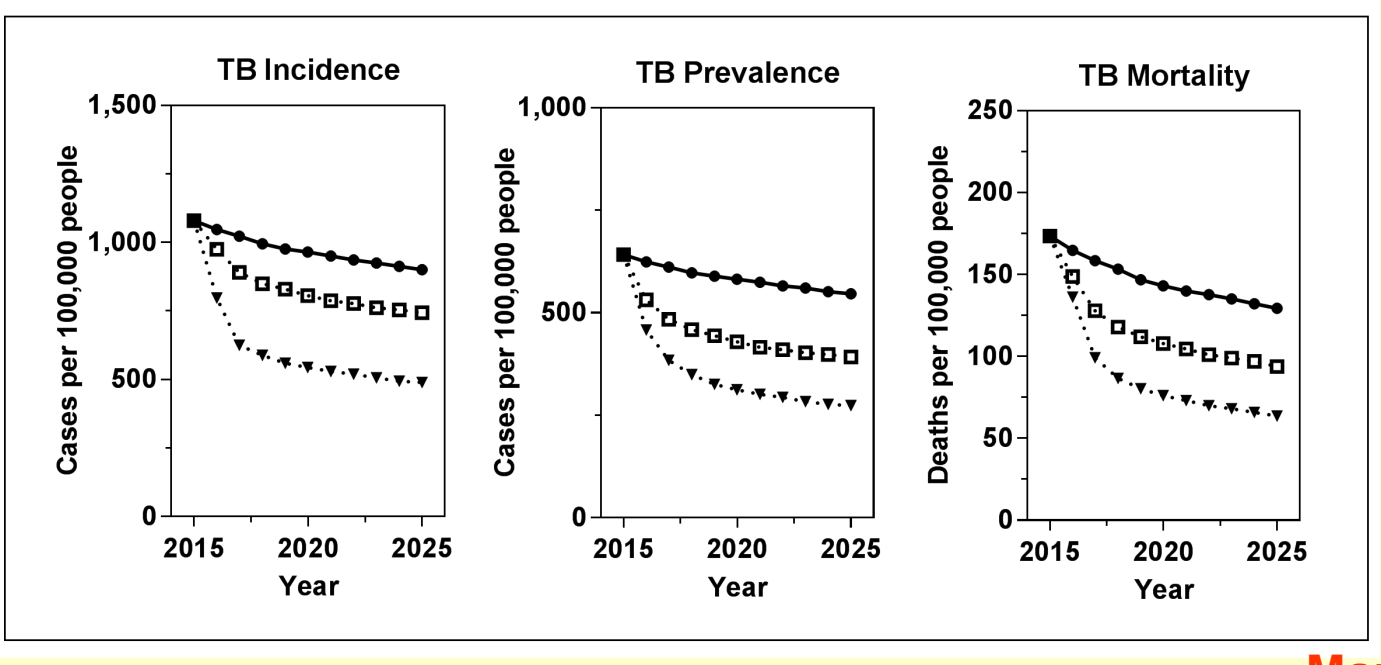




Passive case-finding

Active follow-up

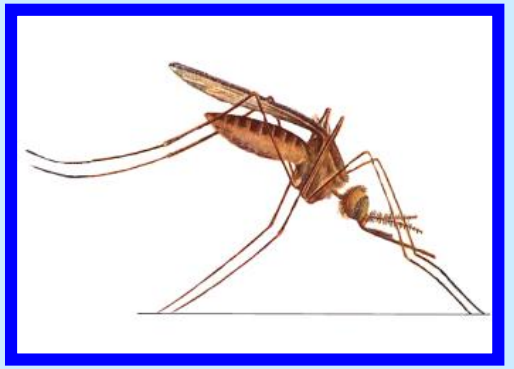
HIV



Current
+ follow-up
+ IPT

Marx, F.M., et al., (2016) In Press.

Always question the conventional wisdom



Malaria

Ross and MacDonald

1897 1954

To control malaria is it better to kill larvae or to kill adults?

To kill larvae you pour oil on water puddles where they breed.

To kill adults you spray insecticide on walls where the adults settle or on bed nets.

People get infected by mosquitoes and recover

$$\frac{dp}{dt} = am(1-p) - \rho p$$

Mosquitoes get infected by people and die

$$\frac{dm}{dt} = bp(1-m) - \delta m$$

$$R_0 = \frac{ab}{\rho\delta}$$ ← Generate new cases

← Lose infected cases

People carry parasites for ~ 3 months ρ : 0.011/ day

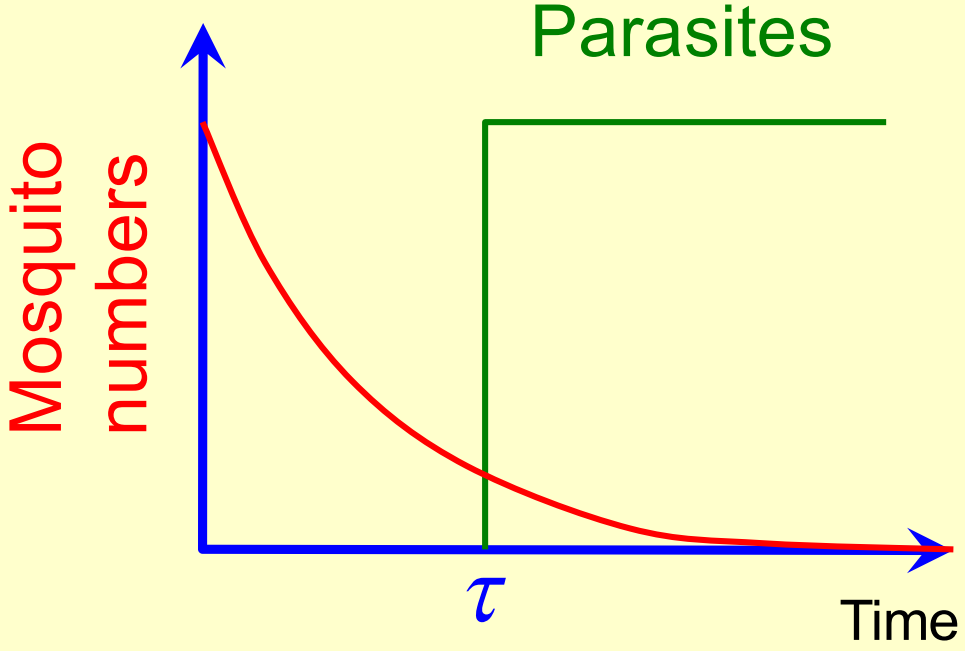
Mosquitoes live for ~ 6 days δ : 0.17 / day

People get bitten ~ twice a week

$$R_0 = \frac{ab}{\rho\delta} = \frac{0.14 \times 014}{0.011 \times 0.17} : \ 40$$

$$R_0 = \frac{ab}{\rho\delta}$$

But parasites take time to mature!



$$a \rightarrow a \frac{\int_{\tau}^{\infty} e^{-\delta t}}{\int_{0}^{\infty} e^{-\delta t}} = a\, e^{-\delta\tau}$$

$$R_0 = \frac{ab}{\rho\delta} e^{-\delta\tau}$$

$$= 40 \times 0.3 : \ 12$$

$$\delta \rightarrow 3\delta \,; R_0 = 1.1$$

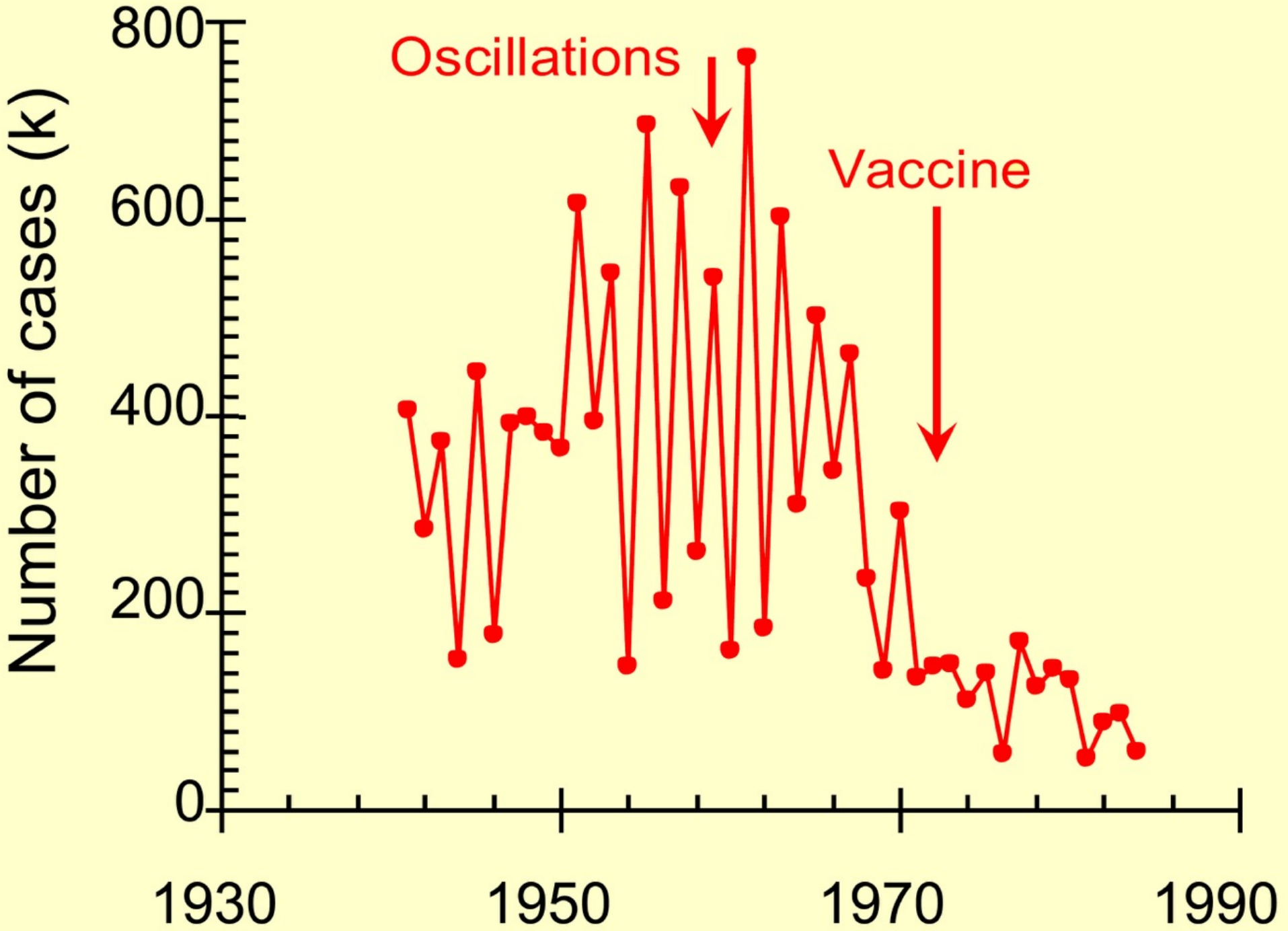
Smith *et al.* PLoS (2012) 8 e1002588

If you really understand the problem you no longer need the model!

Models force you to think clearly, force yo to quantify your assumptons, they help you to avoid self-deception, but at the end of the day they should be redundant

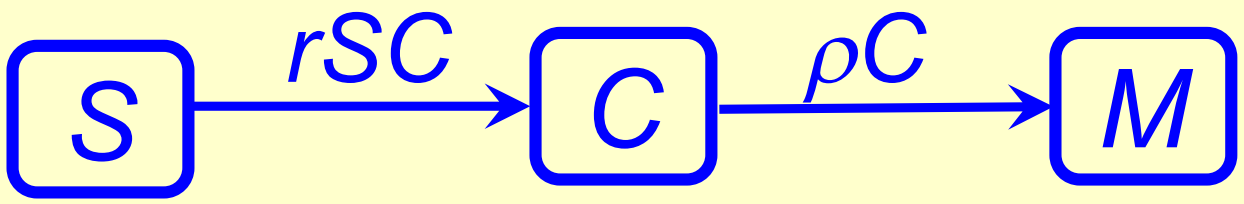
Measles

Measles in England and Wales



Measles

Incubation period 10 days; infectious period 7 days. Time step = 10+7/2 days = 2 weeks.



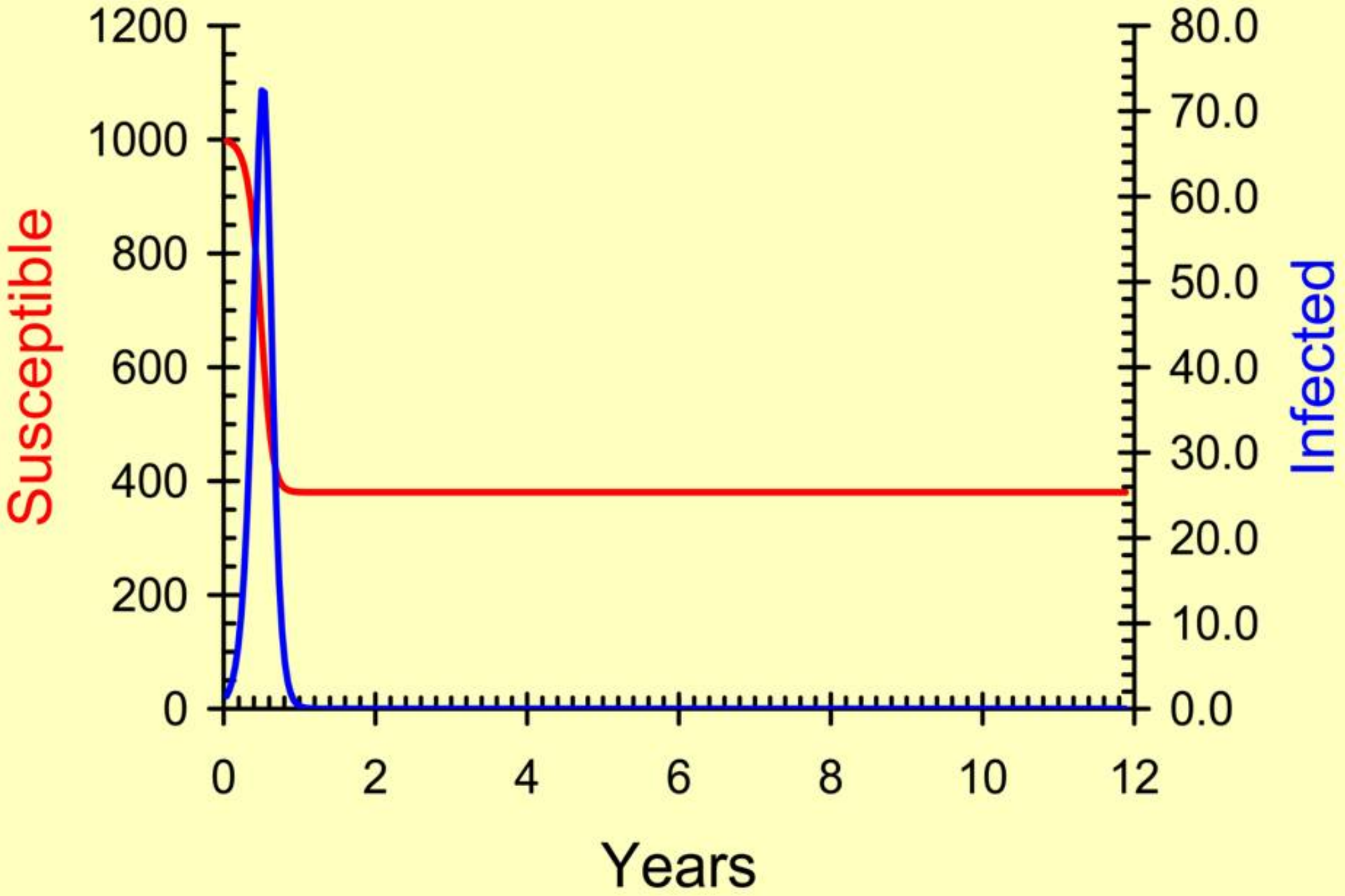
$$S_{t+1} = S_t - C_{t+1}$$

$$C_{t+1} = R_0 C_t \frac{S_t}{S_t + C_t + M_t}$$

$$M_{t+1} = M_t + C_{t+1}$$

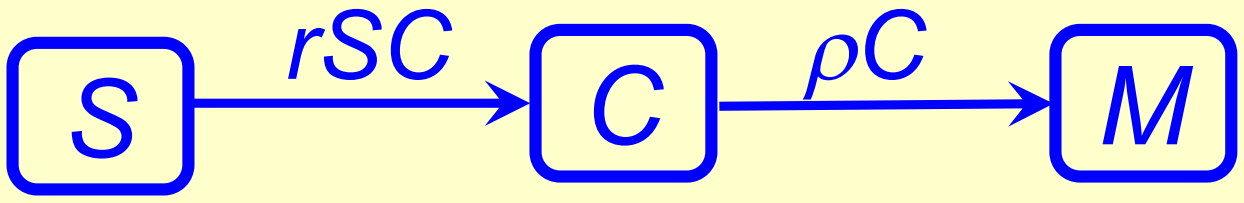
Fine, P. and Clarkson, J.A. (1982) Measles in England and Wales 1: An a analysis of factors underlying seasonal patterns, 2: The impact of the measles vaccination programme on the distribution of immunity in the population 3: Assessing published predictions of the impact of vaccination on incidence' *International Journal of Epidemiology* 11:514; 11:1525; 12:332.

$R_0 = 2$ $\beta = 1\%$ p.a.


Susceptible
Infected
Years
1200
1000
800
600
400
200
0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
2
4
6
8
10
12

Measles

Incubation period 10 days; infectious period 7 days. Time step = 10+7/2 days = 2 weeks.



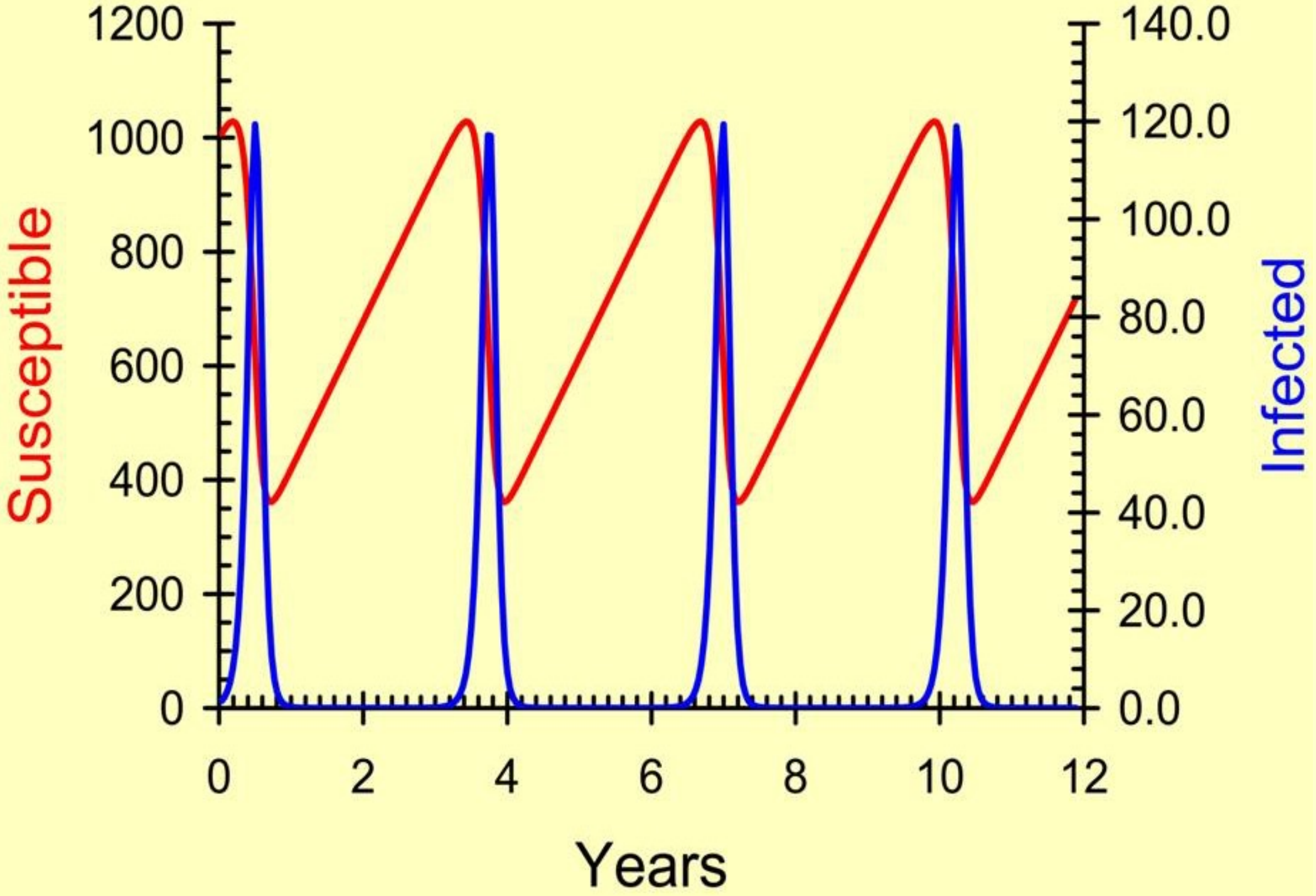
$$S_{t+1} = S_t - C_{t+1} + \beta N_t$$

$$C_{t+1} = R_0 C_t \frac{S_t}{S_t + C_t + M_t}$$

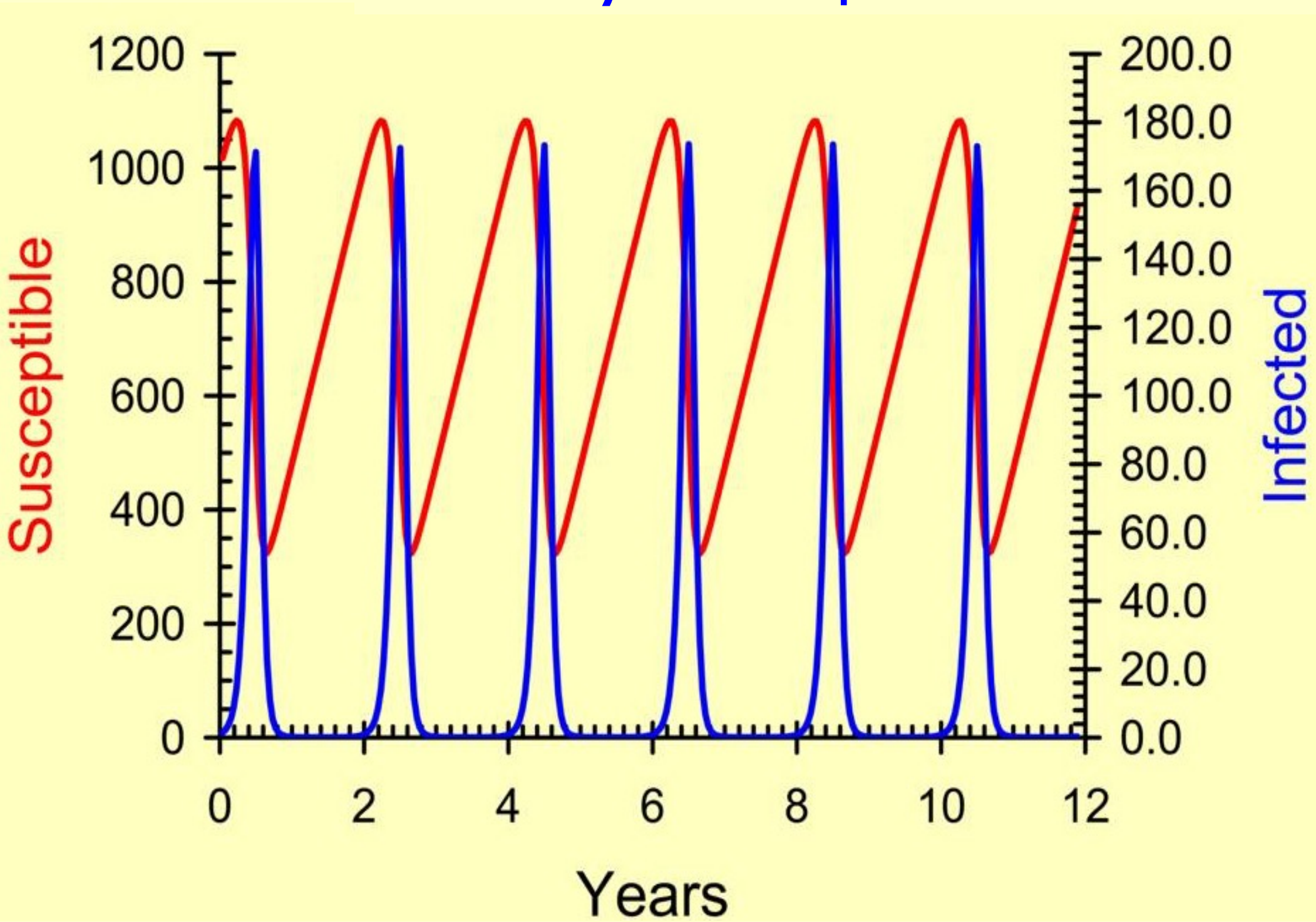
$$M_{t+1} = M_t + C_{t+1} - \beta N_t$$

Fine, P. and Clarkson, J.A. (1982) Measles in England and Wales 1: An a analysis of factors underlying seasonal patterns, 2: The impact of the measles vaccination programme on the distribution of immunity in the population 3: Assessing published predictions of the impact of vaccination on incidence' *International Journal of Epidemiology* 11:514; 11:1525; 12:332.

$R_0 = 2$ $\beta = 2\%$ p.a.


Susceptible
1200
1000
800
600
400
200
0
Infected
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
2
4
6
8
10
12
Years

$R_0 = 2$ $\beta = 1\%$ p.a.


Susceptible
1200
1000
800
600
400
200
0
Infected
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
2
4
6
8
10
12
Years

If you see oscillations or chaos think about time delays

Science in 2050…

Nearly all of the science that we now take for granted was done in the last 100 years

When I was born there were (almost) no vaccines, no antibiotics, anaesthesia was still very crude and there were no computers.

We are digital machines

Cure people born with inherited genetic disorders (cystic fibrosis)
China has just done the first attempt at gene editing
We will be able to create designer babies

Machines are increasingly alive

But if the machines can drive cars, fight our wars, do delicate surgery, manage our finances, solve our equations… what is left for us to do?

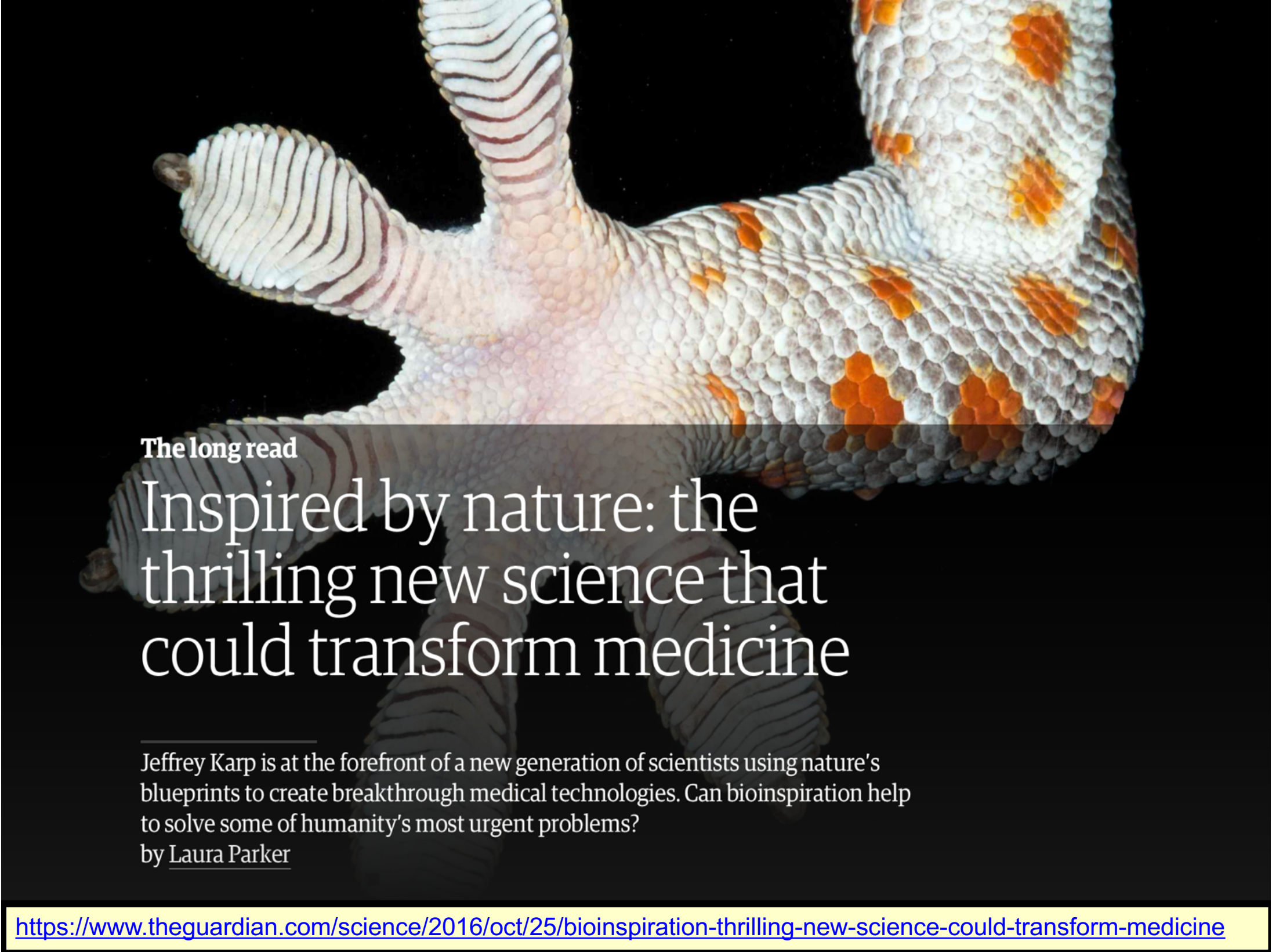
So you have to decide what you want to do…
You will surely need good computational skills
You won't need the level of analytical (in the mathematical sense) that my generation needed.

The problems are going to be concerned with complexity theory: how do many organisms or machines interact? What kind of emergent properties arise from the interactions of many simple units?

And you have to choose what to study…

Areas that I think are going to be important

1. Morphogenesis	Really tough
2. Immunology	Hard
3. Chronic diseases	Doable
4. Biomimicry	Fascinating



The long read

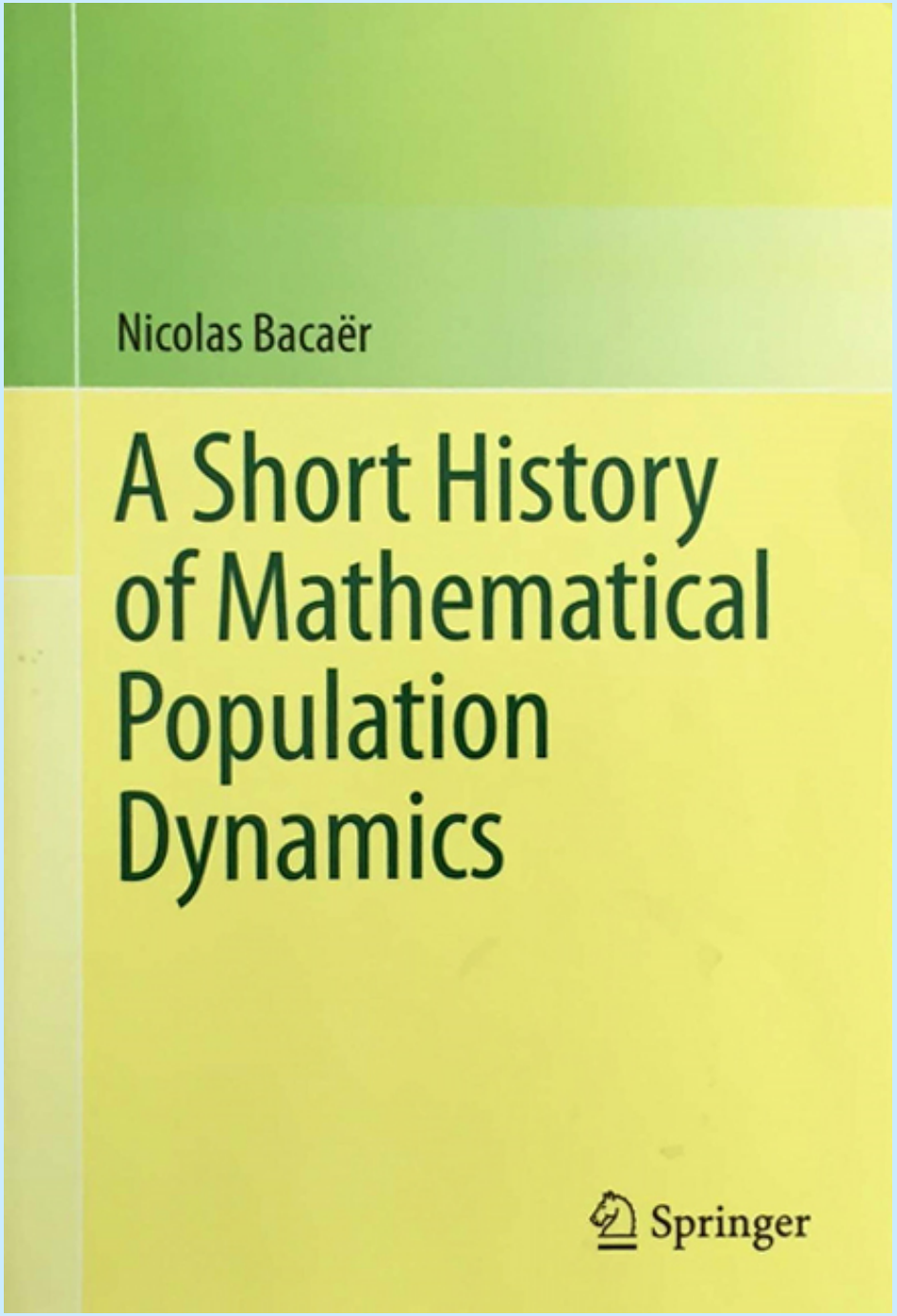
Inspired by nature: the thrilling new science that could transform medicine

Jeffrey Karp is at the forefront of a new generation of scientists using nature's blueprints to create breakthrough medical technologies. Can bioinspiration help to solve some of humanity's most urgent problems?

by Laura Parker

https://www.theguardian.com/science/2016/oct/25/bioinspiration-thrilling-new-science-could-transform-medicine

Where we are coming from



And where we may be going