Optimising Immunisation Programmes

The Mathematics of Vaccination

Matt Keeling
University of Warwick

WARWICK

Basic Concepts

There is a strong history of using mathematical models to capture the spread of infectious diseases, dating back nearly 100 years.

Given that the natural history of infection is often relatively simple and humans mix fairly randomly, simple models give surprisingly good insights.

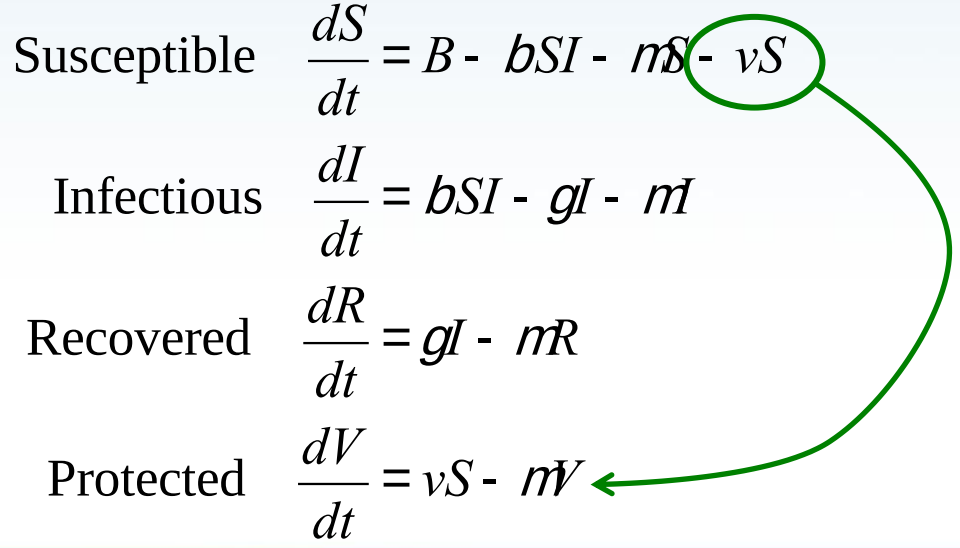
To these standard models we add immunisation by “moving” those successfully protected by vaccination to a separate class:

Susceptible $\frac{dS}{dt} = B - \beta SI - \mu S - \nu S$

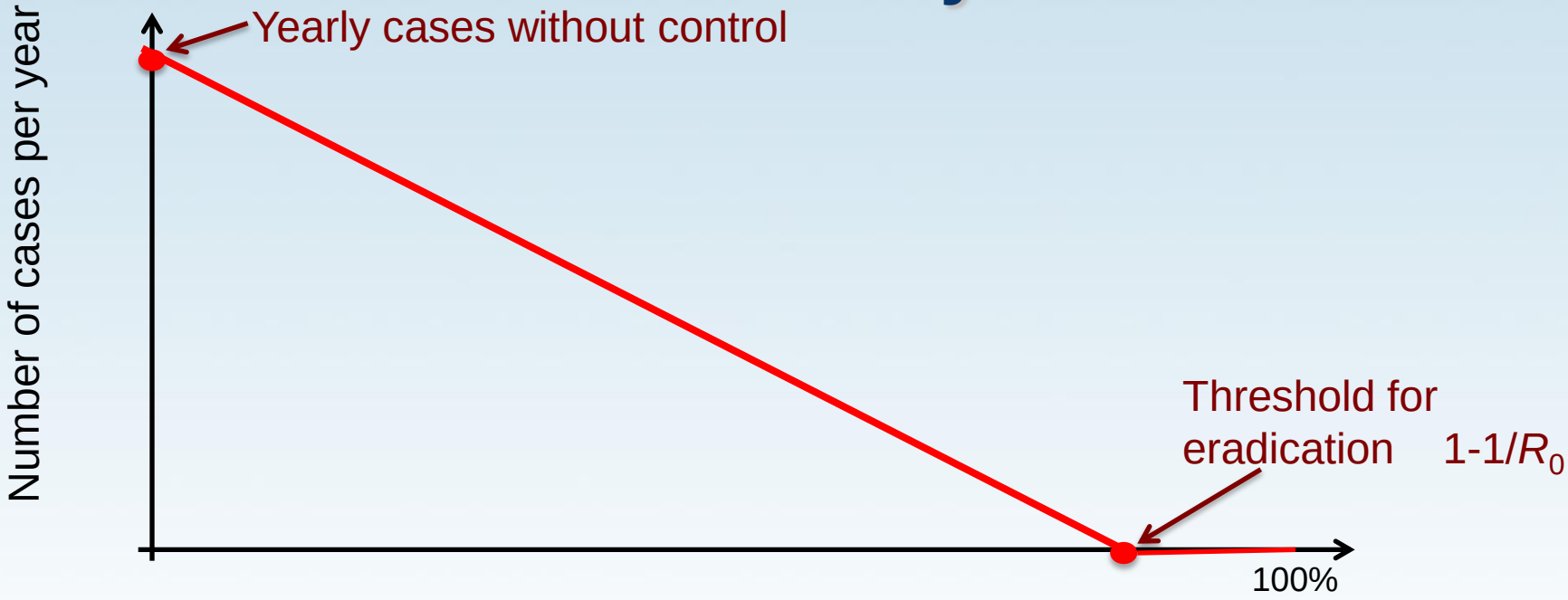
Infectious $\frac{dI}{dt} = \beta SI - \gamma I - \mu I$

Recovered $\frac{dR}{dt} = \gamma I - \mu R$

Protected $\frac{dV}{dt} = \nu S - \mu V$



Basic Theory



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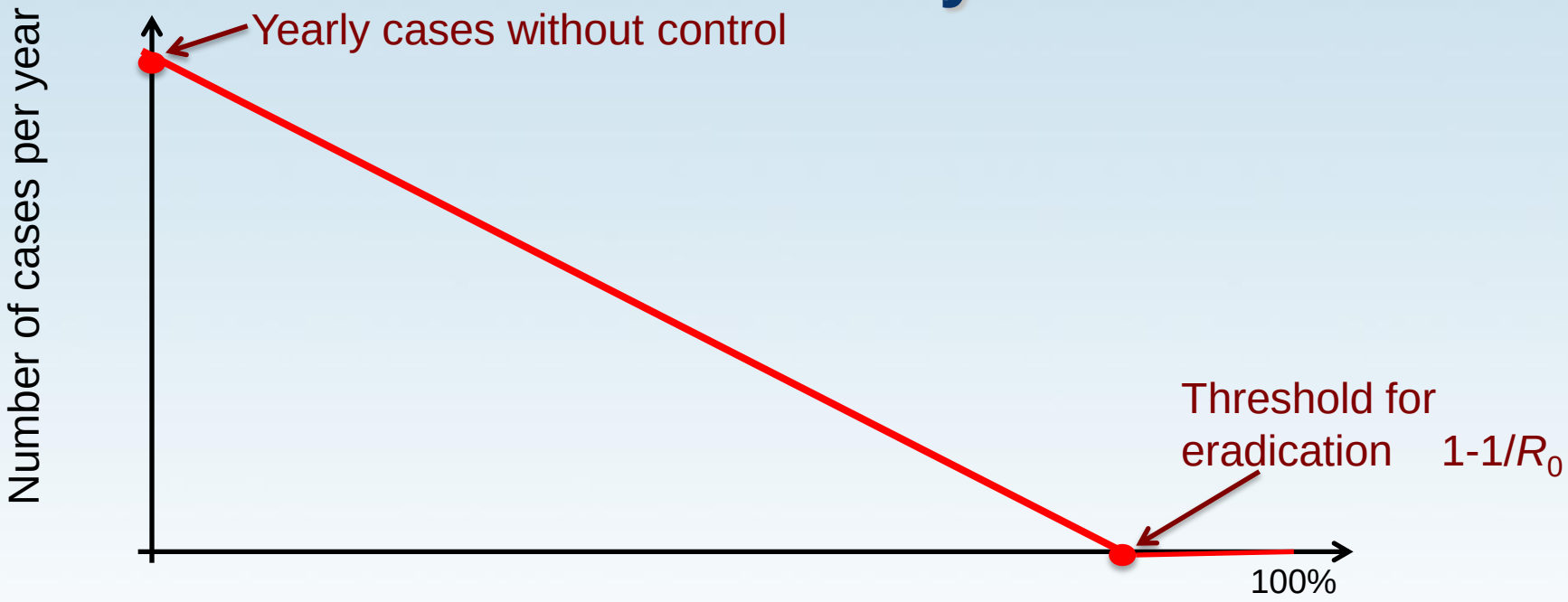
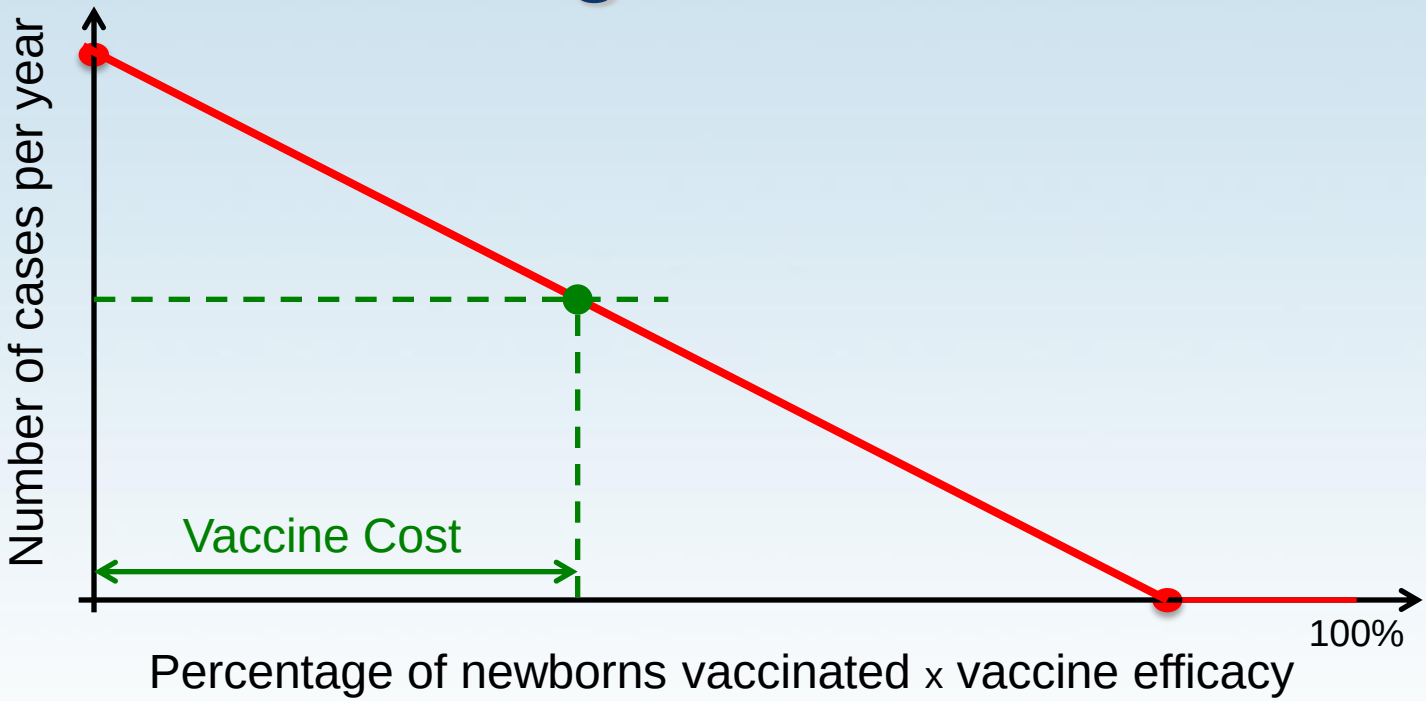


Percentage of newborns **successfully** immunised

= percentage of newborns vaccinated x vaccine efficacy

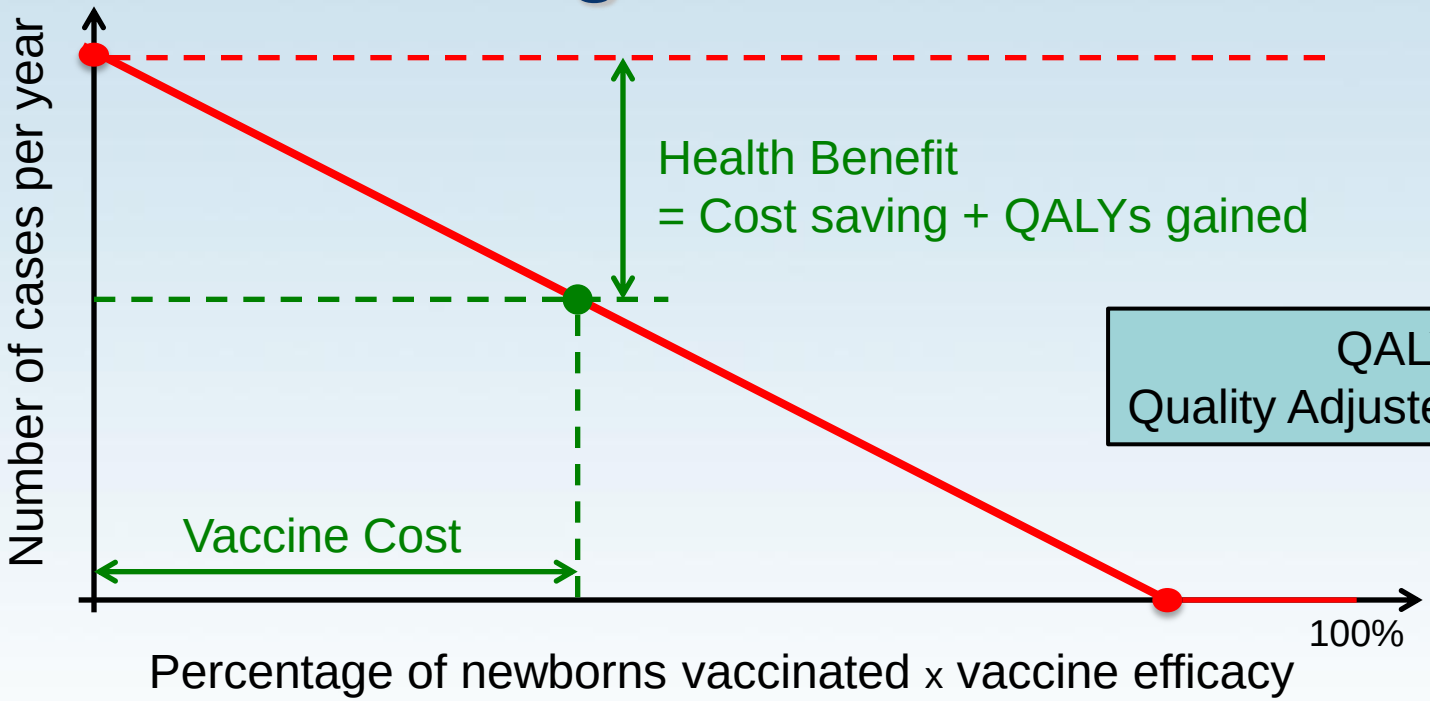
Calculating Costs & Benefits



Yearly Vaccine Costs = (cost of vaccine + cost of administration) x Number of doses per year.

= (vaccine + admin) x yearly births x proportion vaccinated.

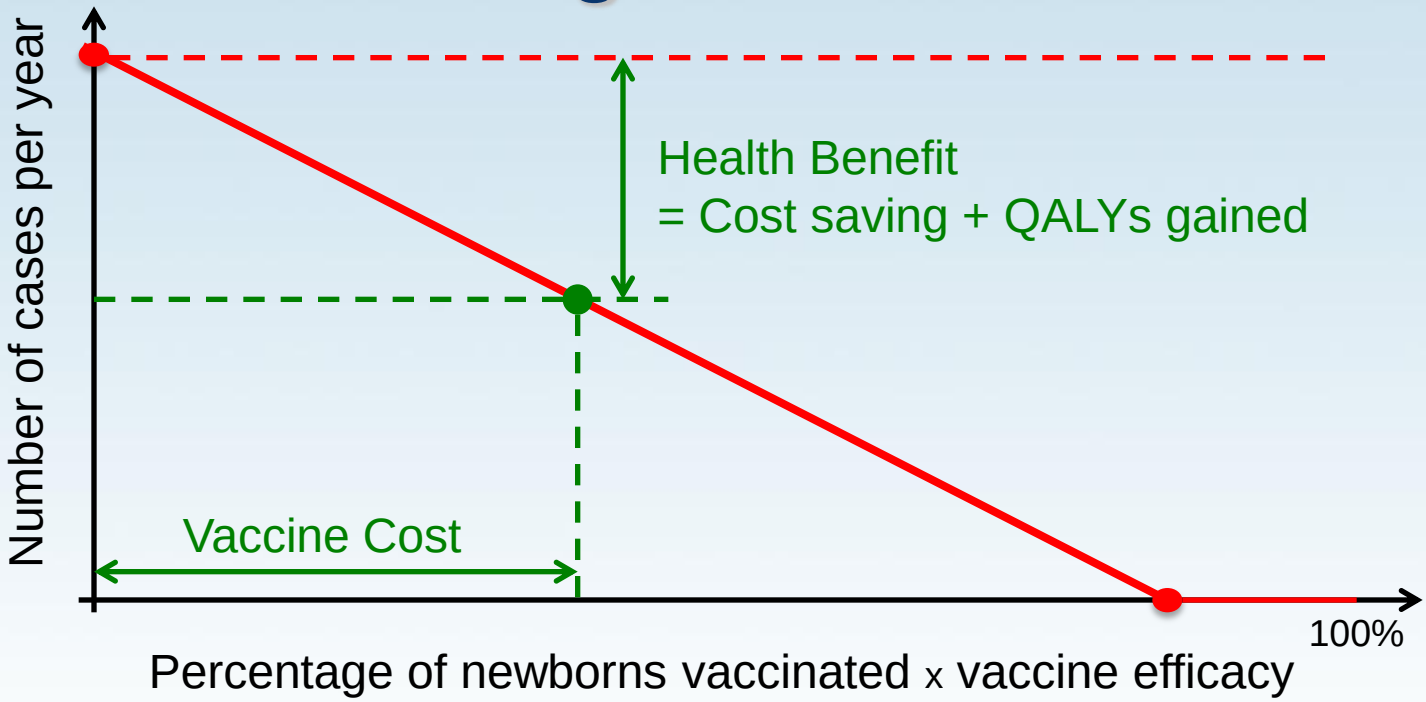
Calculating Costs & Benefits



Yearly Health Benefits = (average cost of treatment + average QALY loss) x Number of cases prevented per year.

Obviously, not all infections require treatment or result in a significant QALY loss

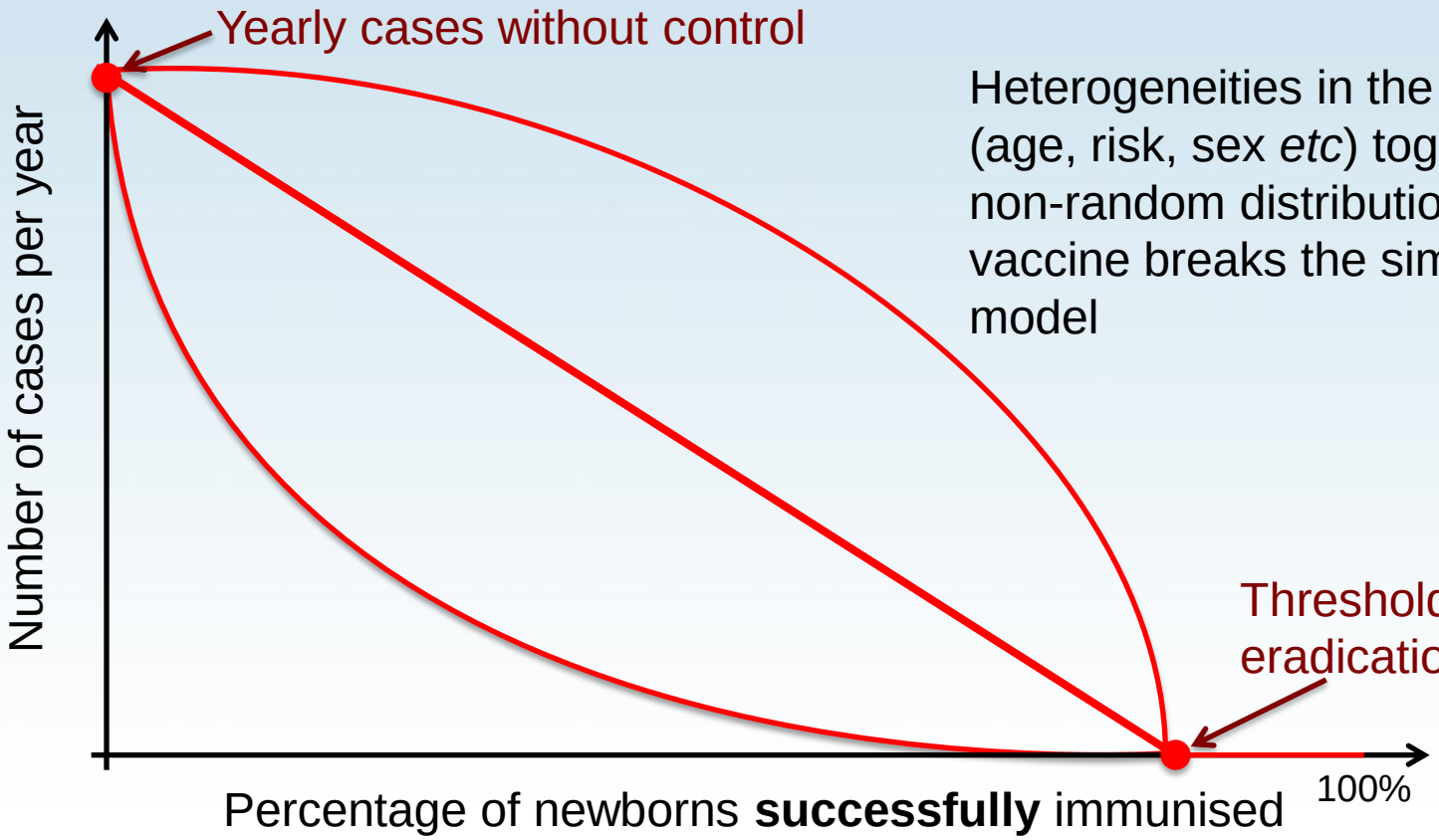
Calculating Costs & Benefits



In the UK we require that the QALYs gained cost less than £20,000-£30,000 each.

$$\frac{\text{Vaccine Cost - Cost saving}}{\text{QALYs gained}} < £20,000$$

Complications: 1. Heterogeneity

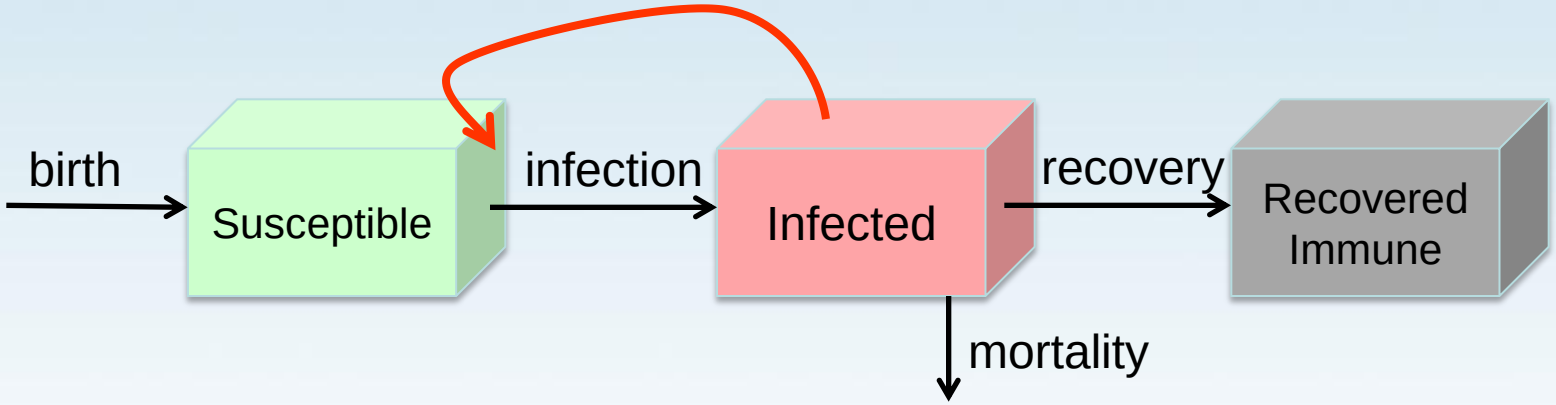


Heterogeneities in the population (age, risk, sex *etc*) together with non-random distribution of vaccine breaks the simple linear model

We need sophisticated mathematical models, that can capture the population-level spread of infection to predict the shape of this curve.

Complications: 1. Modelling Heterogeneity

We start with ‘boxes’ that describe the epidemiological state of an individual. Each person in the population must be in one (and only one) box.

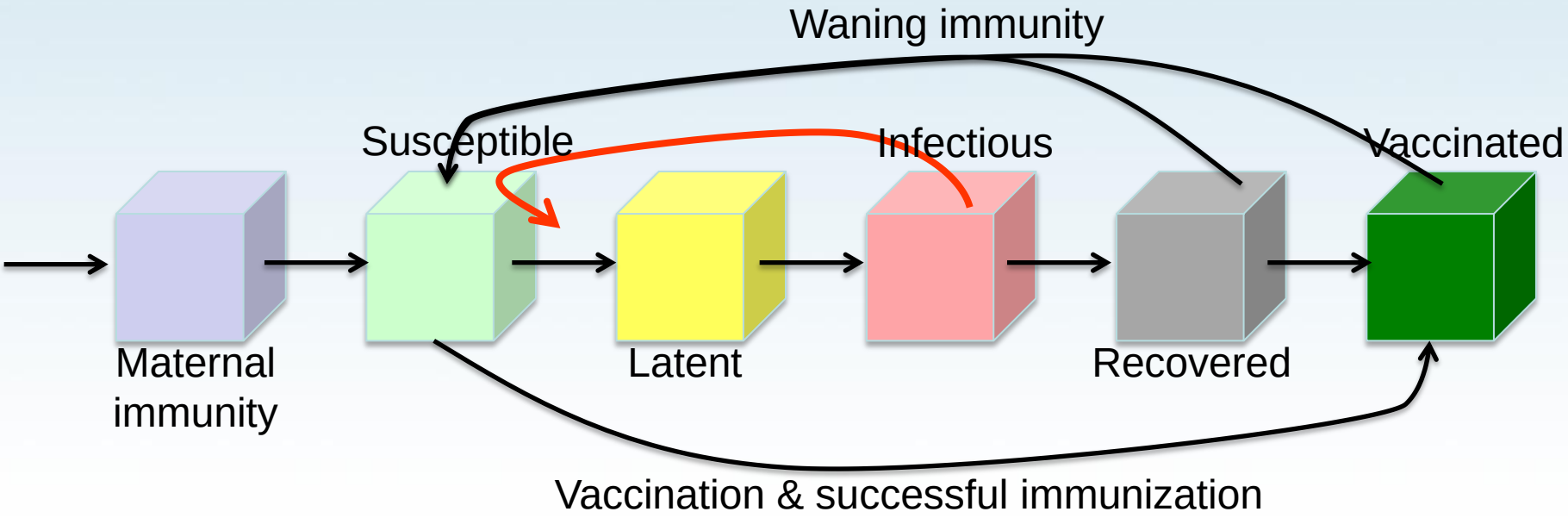


The flows (arrows) represent different processes, each with an associated rate.

Note that the risk of a susceptible individual being infected depends on the proportion of infected individuals in the population. It is this non-linear feed-back that makes the modelling complex.

Complications: 1. Modelling Heterogeneity

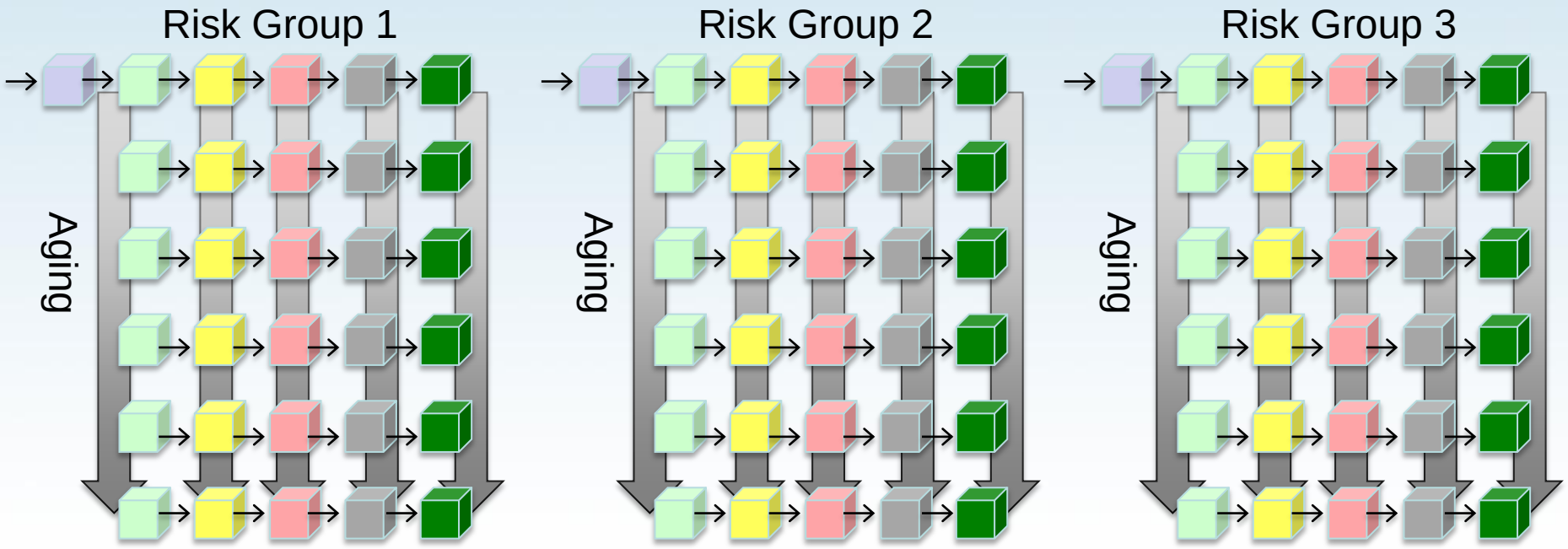
Real models often need more boxes (more epidemiological states) and more arrows (more transitions).



Again it is the proportion of infectious people in the population that drives generation of new cases.

Complications: 1. Modelling Heterogeneity

Real models also need to recognise that people are different; we therefore divide the population based on age and other risk factors.



Infection can now be driven by interactions between and within risk-groups and ages.

The main problem is now determining the rates of interaction and the parameters that determine the rates of transition which can be different for each group and age

Complications: 2. Temporal Effects

For various practical and economic reasons, future costs and benefits must be 'discounted' – it is better to save one life now than one life in 50 years time. This reflects the public's natural values.

The current discounting rate is set at 3.5%, so 100 lives now are worth 96.5 lives next year or about 17 lives in 50 years time.

This focus on the now has two main implications:

1) The dynamics following the introduction of the vaccine are important (we can't just look at the long-term behaviour).

2) Infections that require vaccination while young but cause disease later in life (rubella, HPV) have a lower intrinsic worth.

This can often mean that we are trying to model large changes in temporal dynamics when the data comes from a (relatively) static picture.

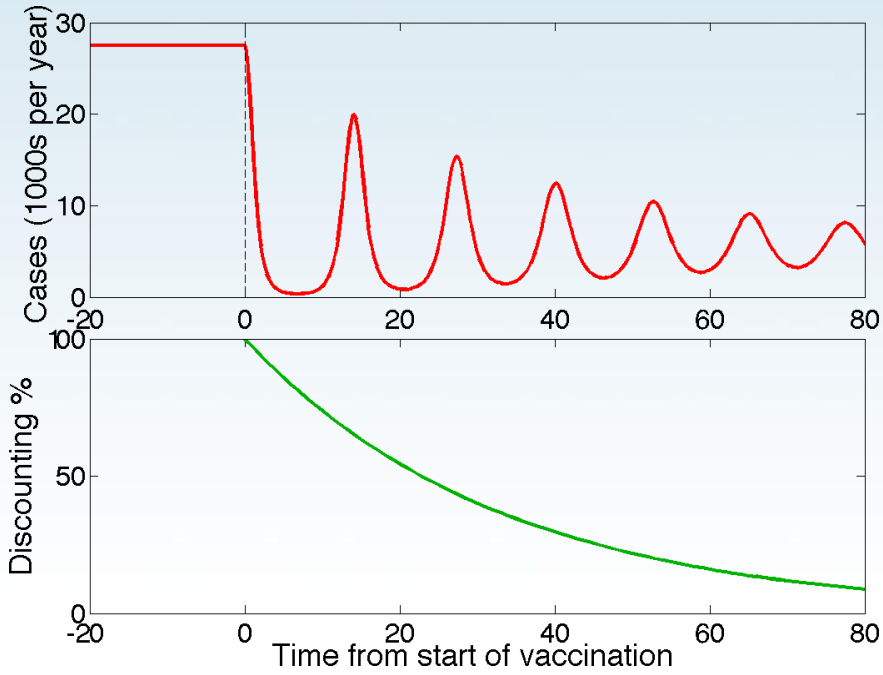
Complications: 2. Temporal Effects

1) The dynamics following the introduction of the vaccine are important (we can't just look at the long-term behaviour).

Here we are looking at a typical model of childhood infection.

Following the sudden onset of a vaccination program the infection may go through a 'honeymoon' period where the cases are pushed much lower than there long-term average.

This low trough is weighted more due to the discounting compared to the long-term mean.



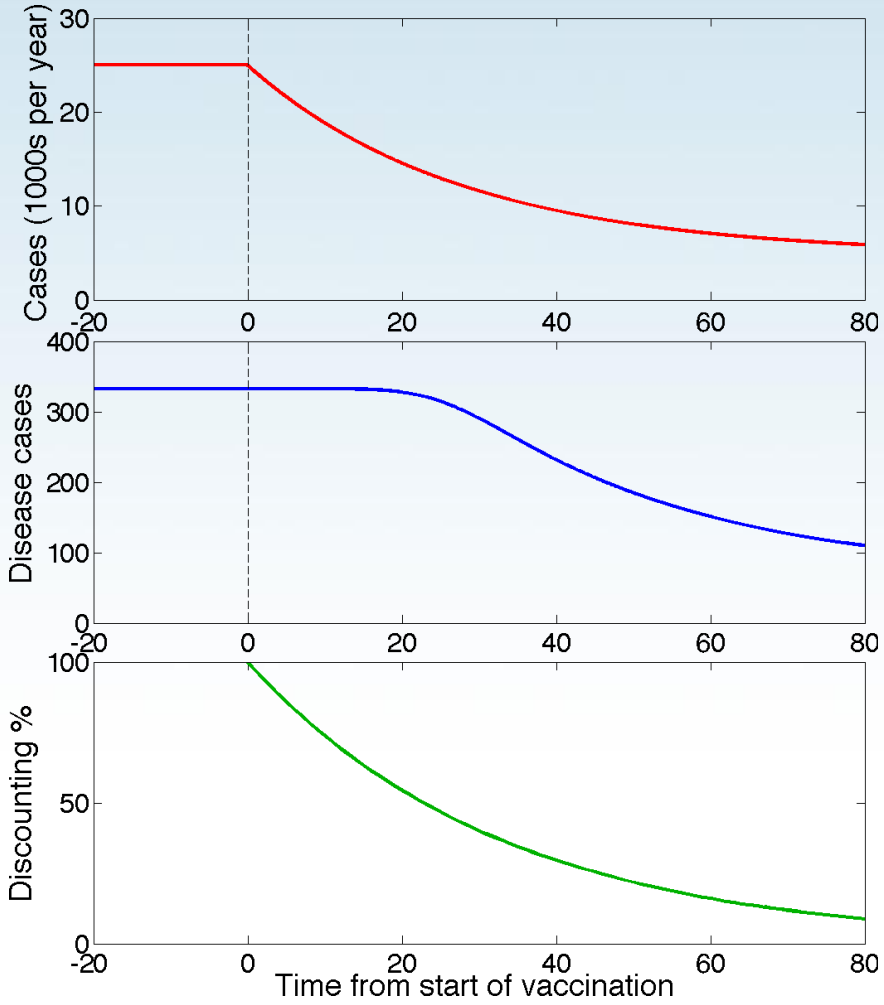
Complications: 2. Temporal Effects

2) Infections that require vaccination while young but cause disease later in life (rubella, HPV) are ‘disadvantaged’

Here looking at a typical STI we see that the drop in cases is much slower.

However if we are thinking about an infection such as HPV, then the delay before a reduction in disease might be 15-20 years.

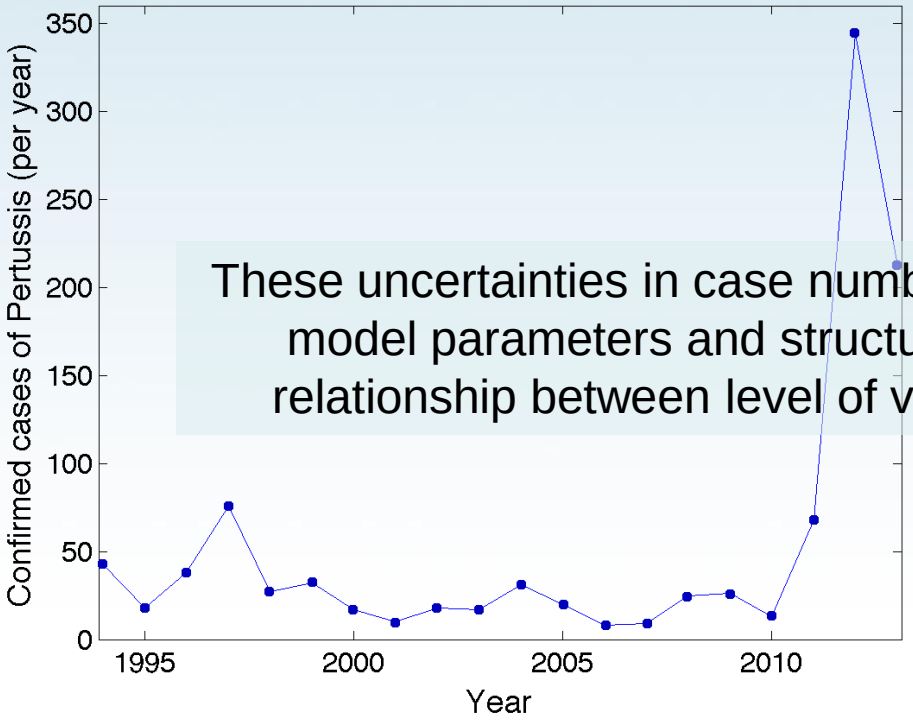
Such delays are penalised by discounting – we are spending now to save lives in the far future.

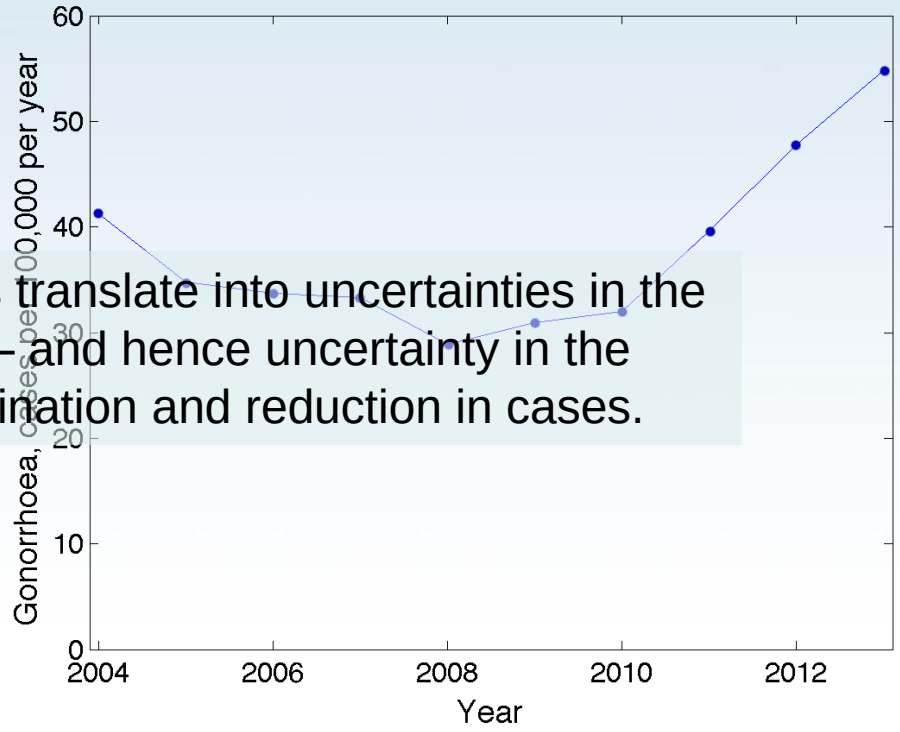


Complications: 3. Uncertainty

Unfortunately we are rarely certain about anything!

Take the simplest measure – number of cases per year.





These uncertainties in case numbers translate into uncertainties in the model parameters and structure – and hence uncertainty in the relationship between level of vaccination and reduction in cases.

In these examples, could you really pin-point the expected number of cases per year?

Complications: 3. Uncertainty

Similarly, almost all other measures are uncertain.

Disease associated costs – these come from the relatively small number of infected individuals that need treatment. How should we include changes in treatment over time?

QALY loss due to infection – again this information comes from the small number of cases where there are serious complications.

Vaccine efficacy – this is generally based on immunological assays (rather than direct protection) and limited numbers of individuals.

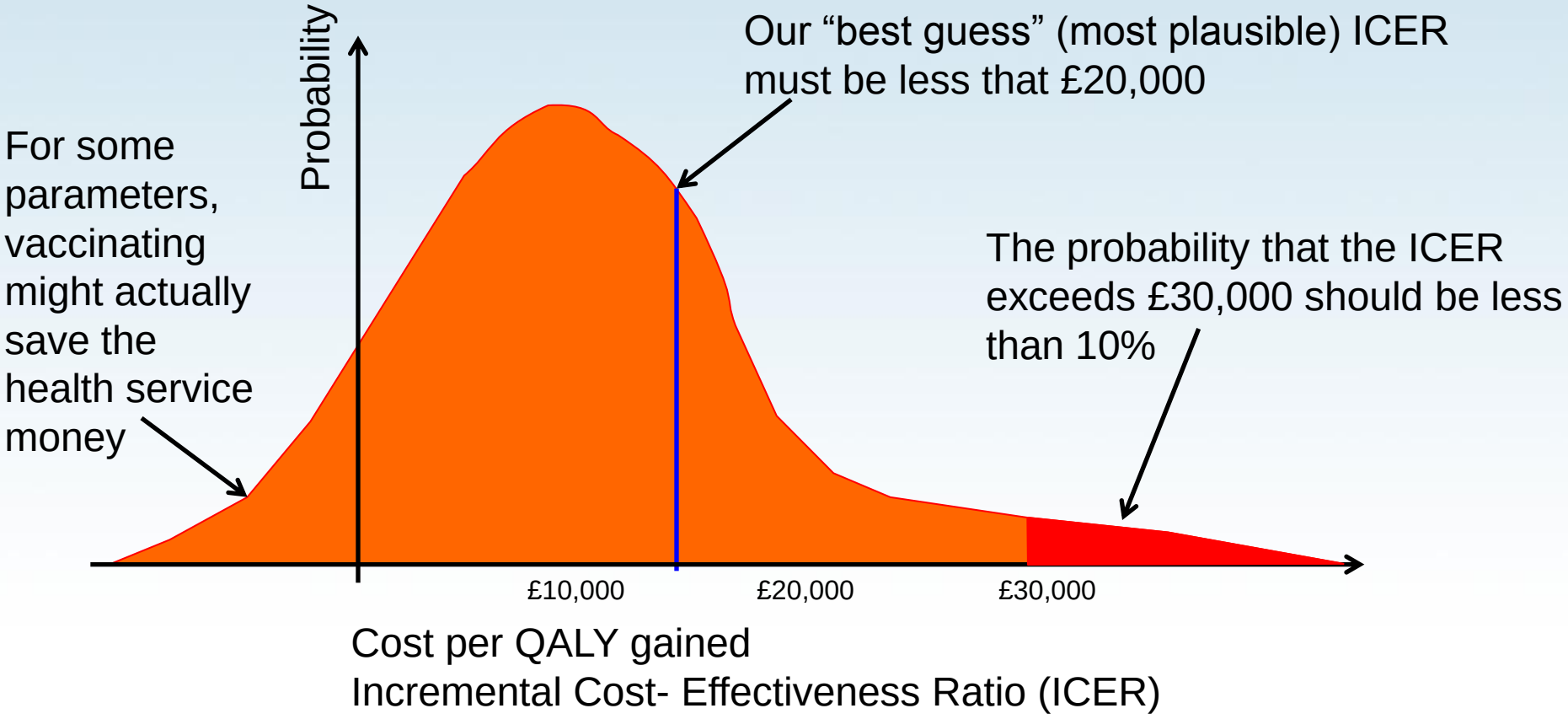
Epidemiological dynamics – for many infections the eradication threshold ($1-1/R_0$) is not readily determined and involves multiple interacting components.

Model structure – models are often built on a limited amount of data, and can only include a limited number of risk factors.

All this means that our predictions are subject to wide variability.

Complications: 3. Uncertainty

JCVI now has a set method of dealing with uncertainty.



We must believe ICER < £20,000 and be confident ICER < £30,000

Conclusions

- In the UK we are fortunate in having JCVI, which is one of the few bodies that has a rigorous means of determining if a vaccine should be recommended.
- Due to the interactions between heterogeneities, uncertainties and discounting, mathematical models are needed to produce robust predictions.
- Mathematical models have been amazingly successful, helping to shape UK vaccination policy. Similar models are now being applied to other infections and other countries.
- Predictive models are not the only consideration; immunological, medical, social, societal and ethical considerations are also vitally important.

The Future

The UK is the clear world-leader in the development of mathematical models for infectious disease, and the optimisation of control methods. However, several major challenges remain:

- Better statistical methods are required for fitting complex mathematical models to partial noisy data.
- Better optimisation methods are needed to determine the most effective distribution of vaccine across the population.
- Better within-host models are needed to link the action of a vaccine to the population-level protection.
- Better understanding of vaccine uptake is required to parameterise spatial heterogeneities.