Cost-effectiveness of vaccines: assessment of the decision-making tools

John Edmunds

London School of Hygiene and Tropical Medicine

john.edmunds@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Overview

- Defining the scope
- Background to the models used in economic analyses of vaccination programmes
- A few examples
  - Predicting and quantifying the direct and indirect effect of vaccination programmes
- Summary of the literature
- Conclusions

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Broader economic impact of vaccination programmes

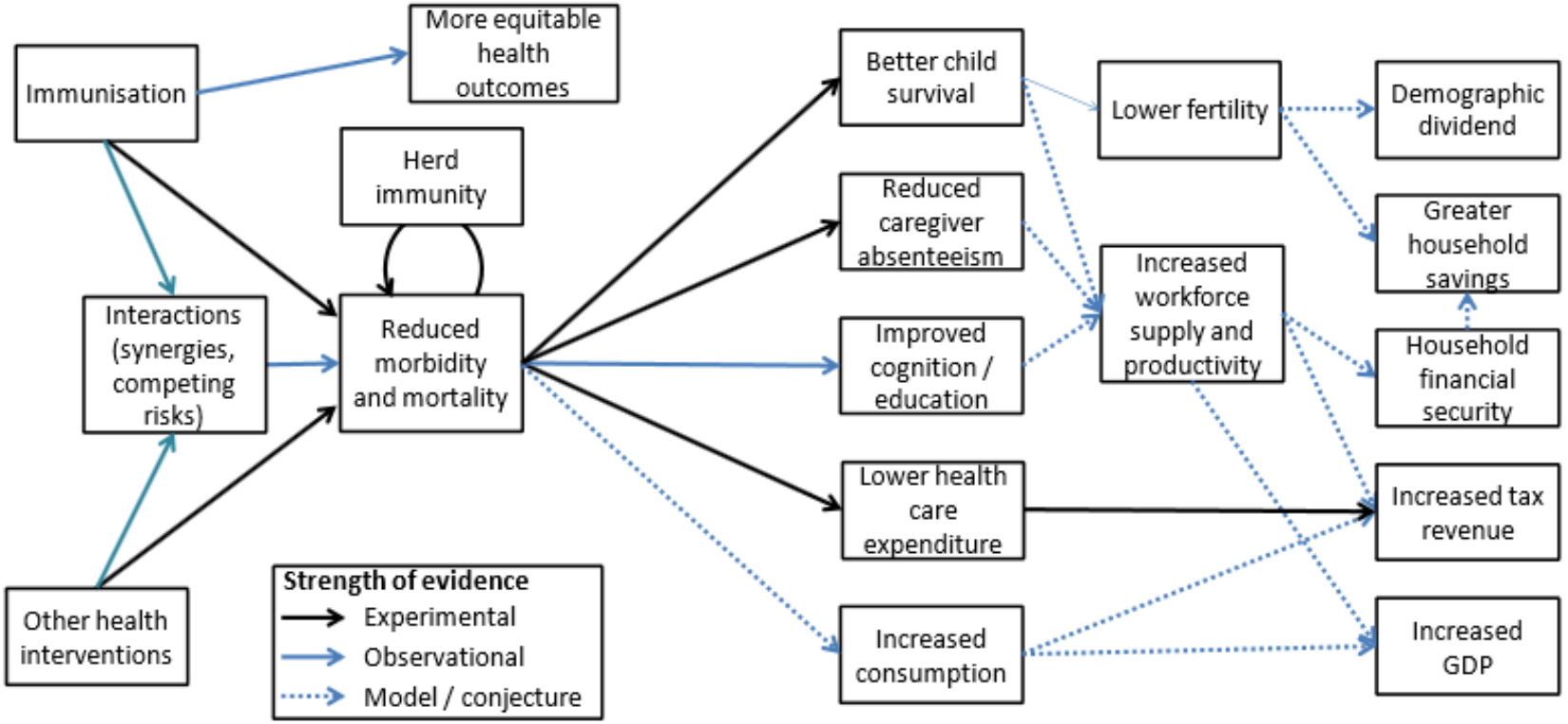


Figure 1 Conceptual pathways between indicators

Report on the WHO consultation on the broader economic impact on vaccines and Immunization programmes (BEIVIP) WHO (2012)

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Broader economic impact of vaccination programmes

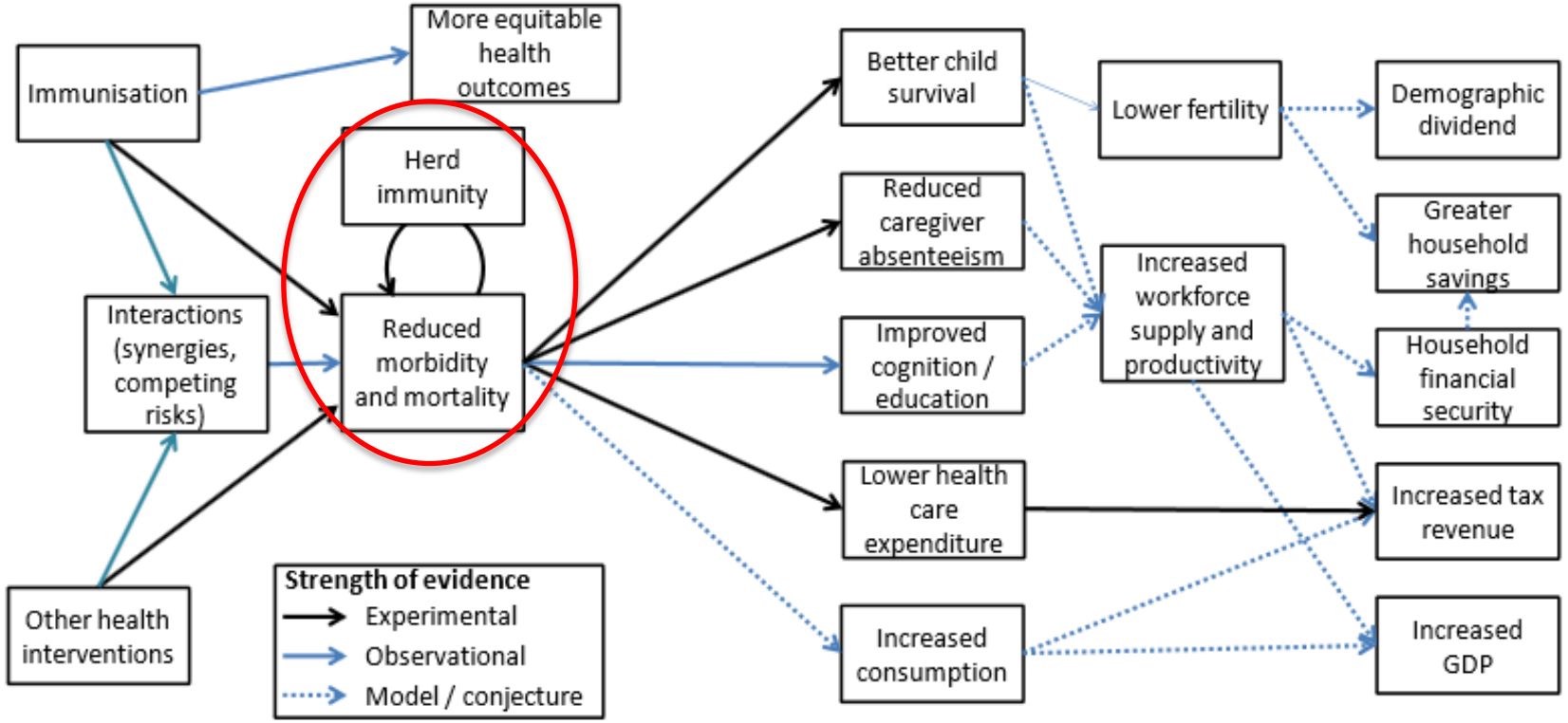


Figure 1 Conceptual pathways between indicators

Report on the WHO consultation on the broader economic impact on vaccines and Immunization programmes (BEIVIP) WHO (2012)

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Models used to evaluate C/E of programmes

- Static or decision analysis models (also used for non-infectious diseases)

– **Constant force of infection (fixed risk) models**

- Decision analysis models
- Markov models

– Attack rate (force of infection) is fixed parameter(s)

λ = fixed

- Dynamic models (only infectious)

– **Risk depends on the number infectious individuals**

– Force of infection depends on # infectious individuals at time t

$\lambda(t) = \beta I(t)$

– Population incidence is FOI multiplied by number susceptibles

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Dynamic models (e.g. the SIR model)

- Incidence in susceptibles depends on the # infectious individuals at a point in time
- Indirect protection included
  - Age-structured models can be used to predict future changes in the average age at infection
- Model infection (not disease)
  - Link infection (and infectiousness to disease)
- All other aspects same as static models
  - E.g. progression to disease, death etc.
- Usually run over multiple cohorts
  - Vaccination programmes run for many years
  - Indirect effects take time to build up

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Static: general scheme

Step 1

- Estimate the incidence
  - From literature or data
- Apply this incidence to the population of interest in the model

Step 2

- Estimate vaccine efficacy against disease (usually from Phase 3 trial)
- Assume coverage

Step 3

- Reduce incidence in cohort accordingly:
- Incidence in Vaccinated = Incidence * (1- (Coverage * efficacy))
- E.g.
  - Coverage = 0.9
  - Efficacy = 0.9
  - Incidence in vaccinated cohort is reduced by 81%

Step 4

- Estimate cost per case, cost of vaccination, QALYs lost per case etc.
- Integrate into economic analysis

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Dynamic: general scheme

Step 1

- Estimate the incidence
  - From literature or data
- Estimate the force of infection (per susceptible incidence)

Step 2

- Estimate or assume underlying direct/indirect contact patterns

Step 3

- Summarise host-pathogen relationships and estimate appropriate parameters
  - Natural immunity to infection and disease
  - Duration of infectiousness, latency, immunty etc
  - Probability of transmission given contact
- Calibrate model to baseline (pre-vaccination) data

Step 4

- Estimate vaccine efficacy against infection (and disease)
- Assume coverage

Step 5

- Run model with / without vaccination and calculate impact of programme in the population and how this changes over time

Step 6

- Estimate cost per case, cost of vaccination, QALYs lost per case etc.
- Integrate into economic analysis

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Comparing models:
chickenpox vaccination (Brisson & Edmunds, 2003)

- Method
  - Assess the effectiveness of vaccination programmes using a:
  - Static model (only accounts for direct protection from vaccines)
  - Dynamic model (takes account of changes in risk of infection resulting from vaccination)
  - The two models are otherwise identical
    - Same (pre-vaccination force of infection)
    - Same risk of disease (age-specific) given infection

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

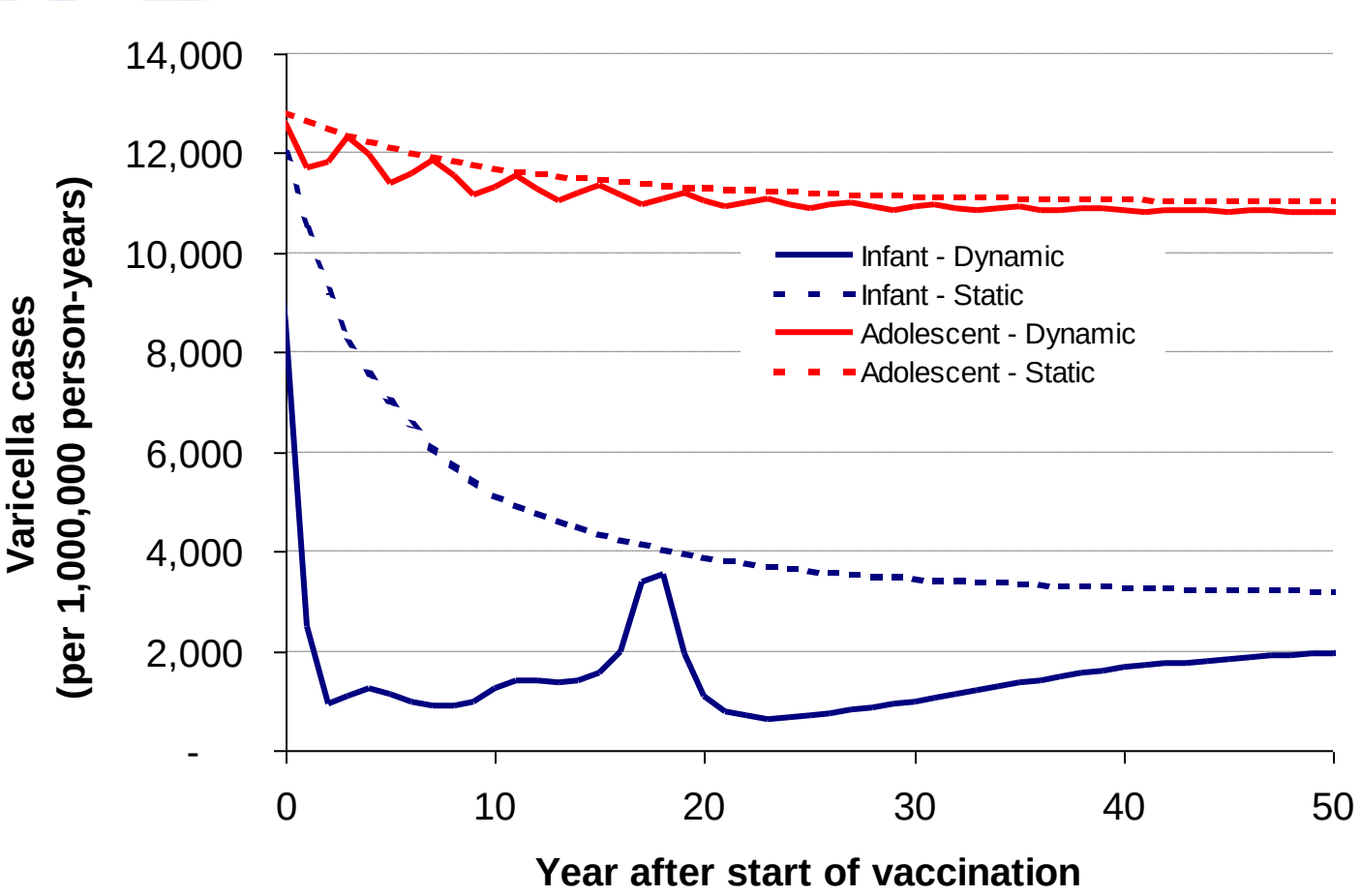
Comparing models:
chickenpox vaccination (Brisson & Edmunds, 2003)

- Universal infection usually of childhood
- Serious disease more common in adults
  - 30% hospitalisations and 50-85% of deaths in adults
- Assume:
  - Vaccine efficacy 100%
  - Coverage 80%
  - Population ~50 million, 75 year life-expectancy
- Compare:
  - Routine vaccination at 18 months (infant)
  - Routine vaccination at 11 years (adolescent)

- N.B. cut-down (toy) model, not very realistic!

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Herd immunity (external benefit)



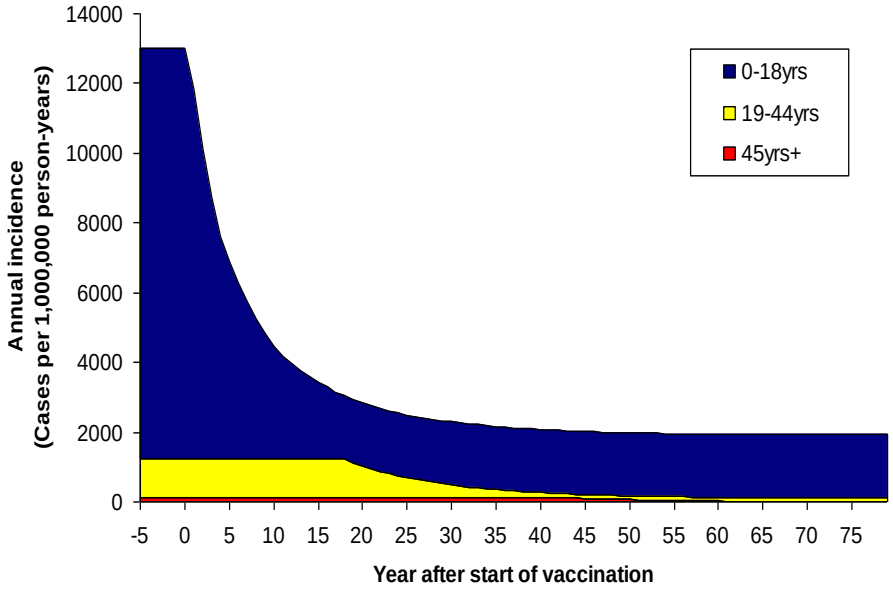
Diff = 10m over 80 yrs

- Size of indirect effect depends on reduction in incidence (i.e. how many immunised)

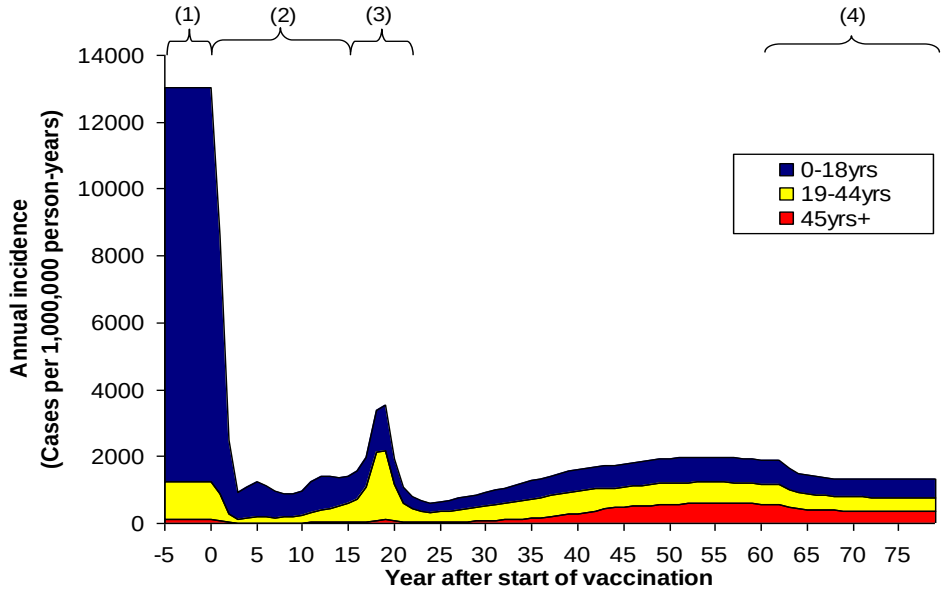
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Comparison of models:
age distribution after infant vaccination

Static



Dynamic

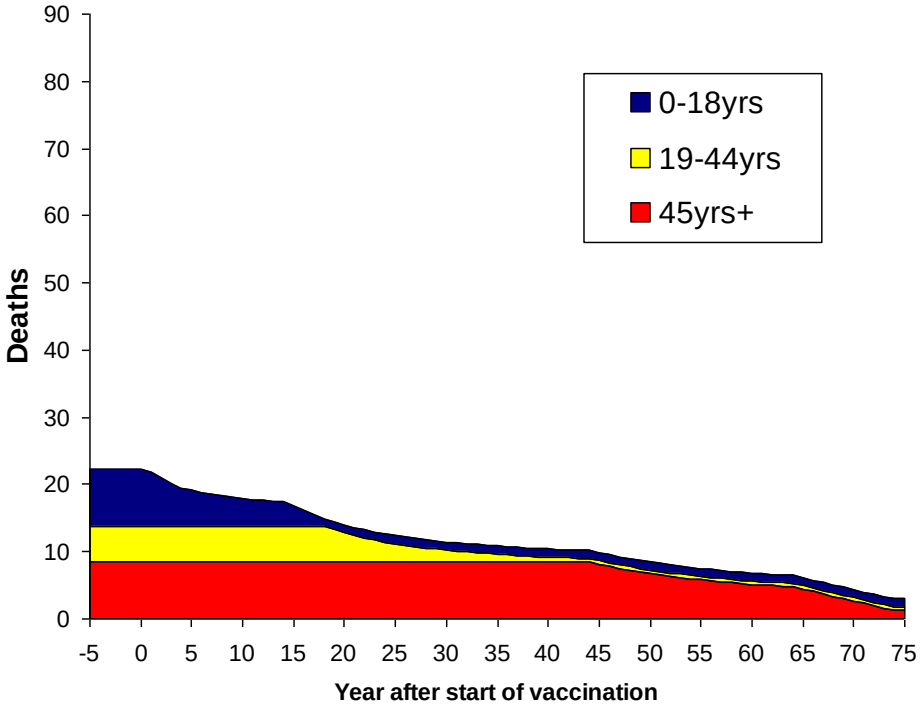


LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

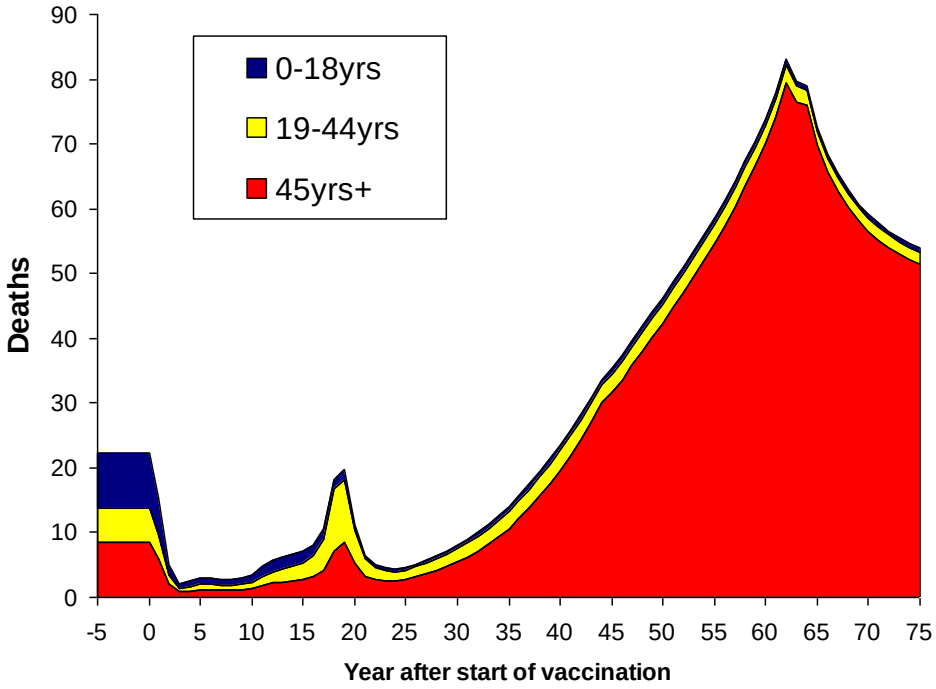
Brisson & Edmunds (2003) MDM *23 (1): 76-82*

Comparison of models: deaths

Static



Dynamic



N.B toy model! Results of more complicated model not as extreme.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Summary of chickenpox example

- Indirect protection (reduced risk of infection following mass immunisation) results in many extra cases prevented
- Reduced risk of infection following mass vaccination also:
  - Increases the average age at infection
    - Can have positive (e.g. pertussis) or potentially negative effects on health (e.g. chickenpox, rubella, HAV)
- Reduced throughput of susceptibles increases the inter-epidemic period
  - May well have a honey-moon period (relatively long period of low incidence after implementation of vaccination at high coverage
- Static models cannot take account of any of these things
- [Or elimination, or changes in return to scale with changes in coverage (see Brisson and Edmunds 2003)]

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Other indirect effects

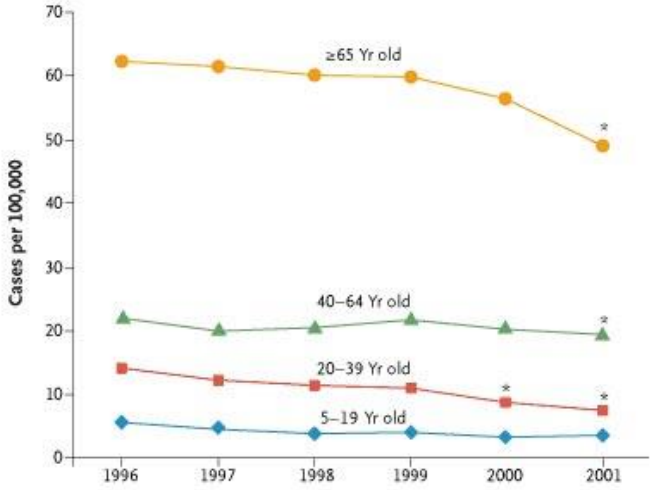
- Indirect protection and a concomitant increase in the average age at infection, time between epidemics, etc. are effects common to many vaccine preventable diseases
  - Particularly the “childhood” diseases that stimulate relatively long-term immunity
- However, there are also a range of vaccine (disease)-specific effects, e.g.:
  - transmission of OPV
  - Serotype replacement following pneumococcal conjugate vaccination (PCV)

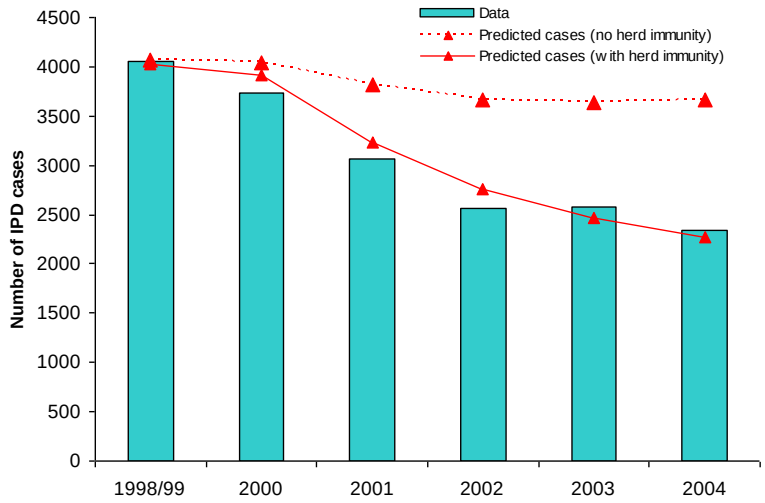
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Direct and indirect effects of PCV vaccination

- Vaccination offers direct protection to those immunised
  - Measured in Phase 3 trials
- Also lowers risk of infection to others, as vaccine offers protection against carriage
  - Need data on protection against carriage to model this

Reduction in IPD in US
Whitney et al. NEJM, 2003



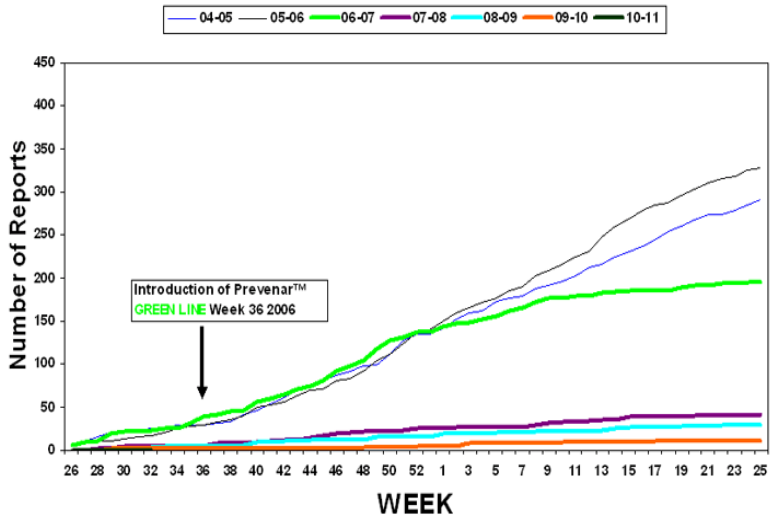


Herd immunity and serotype replacement in UK

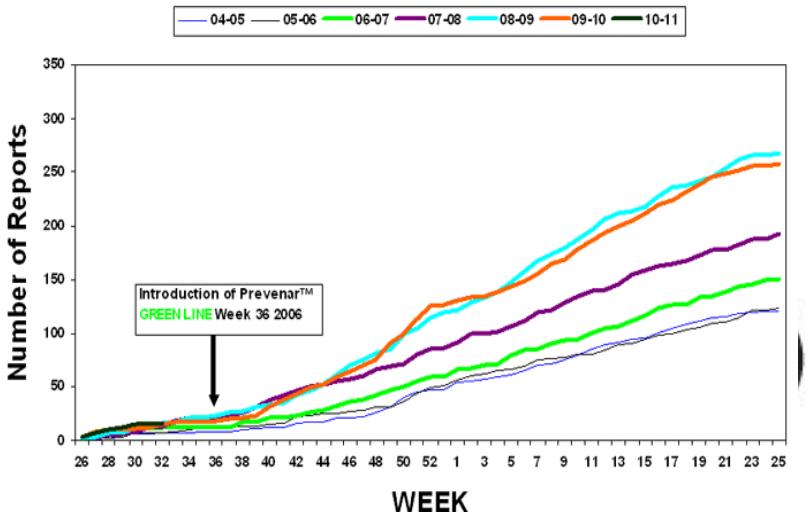
- Reduction in carriage with vaccine types can also lead to an increase of carriage with non-vaccine types if carriage of type A inhibits carriage with type B
- Could reduce the impact of the programme
- Level of replacement carriage depends on competition between VT & NVT
- Level of replacement disease depends on pathogenicity of NVT

IPD incidence E&W, HPA

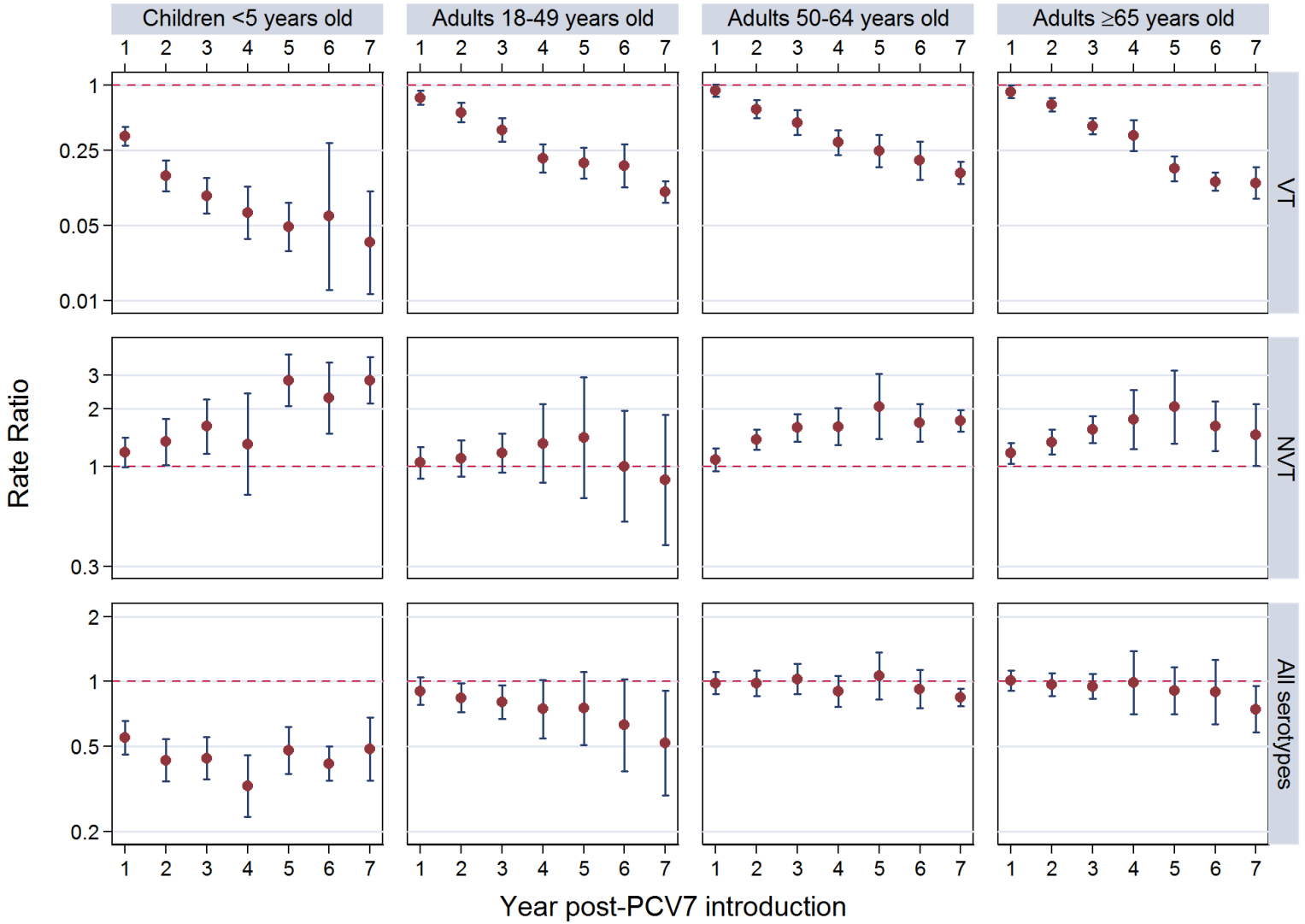
Serotypes in PCV7, <2 yrs



Serotypes NOT in PCV7, <2 yrs



Herd immunity & serotype replacement: impact on IPD



Feikin D *et al*. PLoS Med (2013)

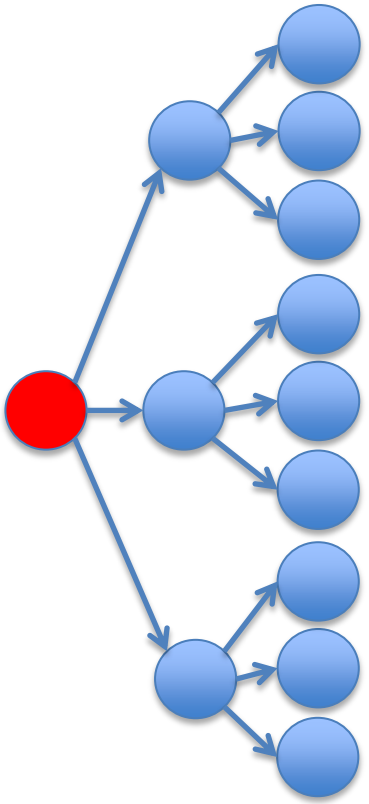
Summary of PCV

- Indirect effects are much larger than direct (on overall health)
- Herd immunity reduces infection in age groups not included in the vaccine
- Serotype replacement tempers beneficial impact of programme
- Reduction in vaccine types also makes wider immunisation less attractive
  - E.g. vaccination of the elderly, or risk groups (e.g. Rozenbaum et al. BMJ 2012)
- Models predicted serotype replacement likely (Lipsitch EID 1999) but the scale of the effect was difficult to predict before implementation
- Herd immunity and serotype replacement not captured by static models

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Outbreaks & timing of vaccination

- At outset of epidemic reproduction number is highest
  - Greater than 1
- Indirect effects (herd) maximal
  - Chains of transmission avoided



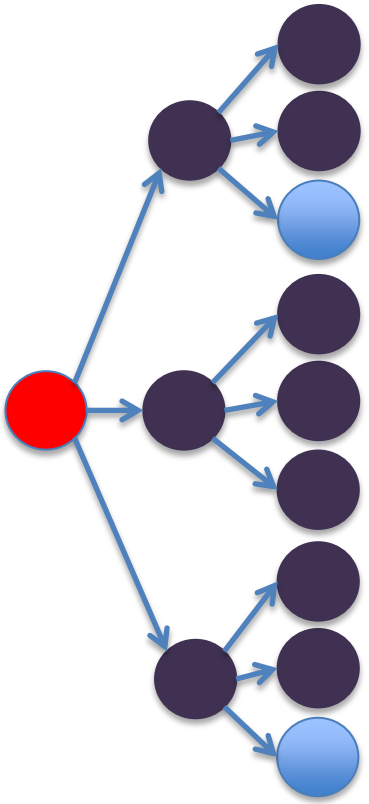
- In declining phase of an outbreak reproduction number is low
  - Less than 1
- Indirect effects small

- Cost-effectiveness of vaccination dependent on timing
- Static models not appropriate for outbreaks

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Outbreaks & timing of vaccination

- At outset of epidemic reproduction number is highest
  - Greater than 1
- Indirect effects (herd) maximal
  - Chains of transmission avoided



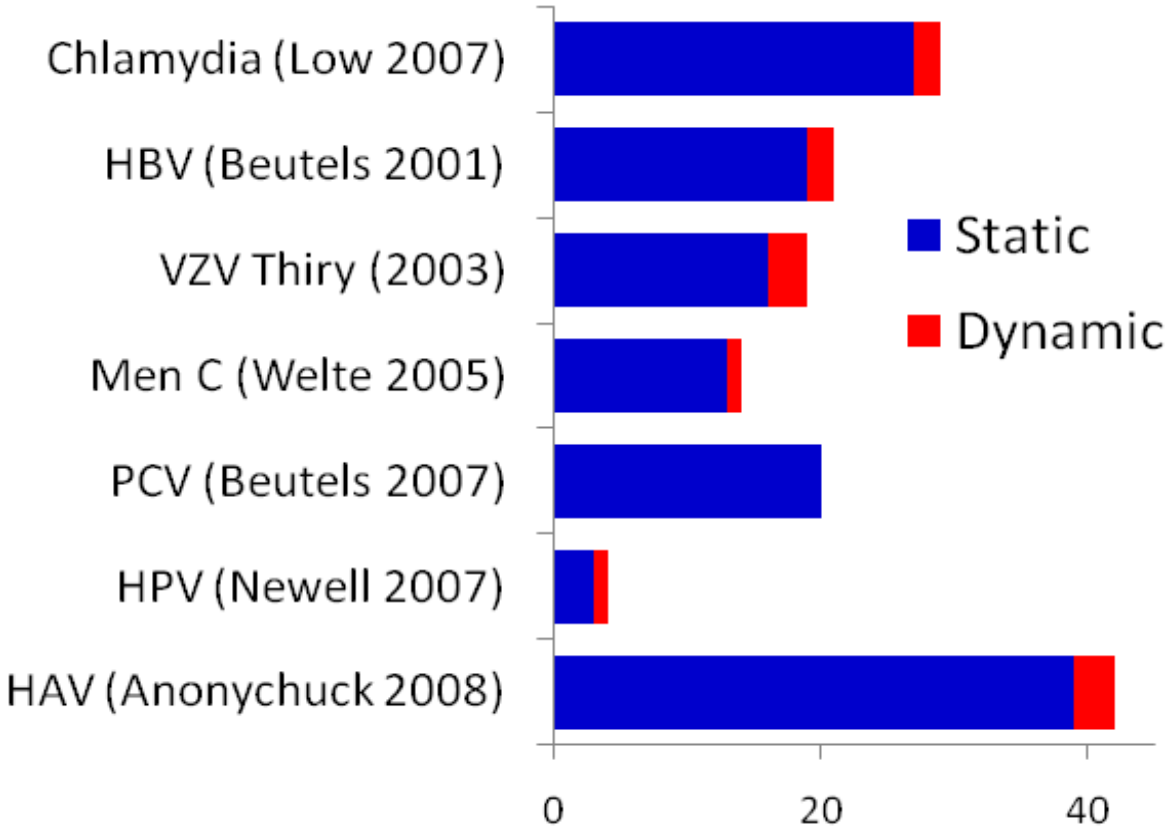
- In declining phase of an outbreak reproduction number is low
  - Less than 1
- Indirect effects small

- Cost-effectiveness of vaccination dependent on timing
- Static models not appropriate for outbreaks

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Types of models used in economic analyses

Systematic reviews of economic analyses



Kim & Goldie Pharmacoeconomics (2008)

23 dynamic

252 static

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Summary

- Indirect effects generally arise due to reduction in infectiousness
  - Not all vaccines/programmes likely to stimulate significant indirect effects, e.g.
    - PPV vaccination (doesn't protect against carriage)
    - Vaccination of adolescents against chickenpox/rubella (vaccinate at an age when most are already immune)
  - But most do
- Most indirect effects are beneficial to public health – greater numbers protected
- Not all are beneficial (e.g. age shifts, rubella, chickenpox; zoster)
- Affects distribution of disease in the population (+ve or -ve)
- Often influences optimal vaccination strategy (e.g. flu)
- Timing of vaccination has major impact on cost-effectiveness of outbreaks
- Indirect effects are rarely taken account in economic analyses
  - Poor decision making
- Investment in use of appropriate methods may well pay off

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE