UK Vaccination Programme

Risk and Reward

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Measles explosion predicted

Twins stop breathing after jabs

Calls are being made for more information about the safety of vaccinations for premature babies after twin brothers nearly died

US plans to handle smallpox attack

MMR uptake still falling

Uptake of the all-in-one measles, mumps and rubella vaccine (MMR) in Scotland has fallen to its lowest level in eight years

Fresh Sars fears hit Asian markets

Doctors warn of bioterrorism risks

Doctors are warning about the dangers of bioterror attacks.

Terms of reference

"Our aim is to investigate, and hence stimulate informed debate and possible further studies, on the balance between risk and reward inherent in the current UK vaccination program from an independent statistically informed viewpoint. We do not aim to carry out any new investigations or studies but to interpret and assimilate existing data and studies. As part of our fact-finding we will try to discover whether any organisation currently monitors the trade-off between risk and reward, and what mathematical or statistical models are used."

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Agenda

- Introduction to vaccines
- Dynamics and control of infectious diseases
- Models
- Data
- Psychology of immunisation choices
- Case studies
- Conclusions

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Introduction to vaccines

How immunisation works

The natural immunity phenomenom...

- Under the threat of infection, the immune system attacks the invader and produces antibodies to destroy the organism
- The immune system "remembers" this destruction process, so that if the invader returns a repeat attack can be mounted faster
- Immunisation is the process of creating immunity artifically…

Source: BMA Family Health Encyclopedia. 1996

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How immunisation works, cont'd

- Can be passive or active:
  - Passive (short term) - injection with ready-made human antibodies.
  - Active (longer term) - vaccine containing living, weakened organisms, or inactivated organisms stimulates the immune system to produce its own particular antibodies

Source: BMA Family Health Encyclopedia. 1996

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Life Cycle of infection

- Latent period: from initial infection to the point at which the individual becomes infectious to others
- Incubation period: time from initial infection to the point where symptoms of the disease appear
- Infectious period: period during which the patient is infectious to others

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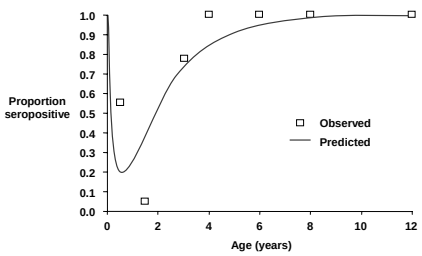
Proportion of children with anti-body to rubella virus



Source: Anderson and May

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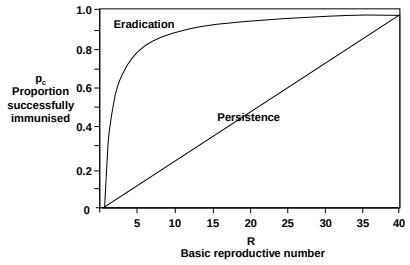
Dynamics and control of infectious diseases

Herd immunity



Source: Anderson and May

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Herd immunity – How is it achieved?

There are 2 effects of an immunisation programme:

- **Direct effect: those successfully immunised move into the immune class**
- **Indirect effect: more immune individuals mean fewer susceptibles to spread the infection so the force of infection is weaker**

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Herd immunity
Overall Criterion for Eradication (Anderson and May)

Define: **p** **proportion successfully immunised**
R **reproductive rate of parasite in the population**
R_0 **basic reproductive number (fully susceptible population)**

$R \leq R_0(1-p)$
If $R<1$ the infection cannot maintain itself

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

Where p_c is the critical proportion of the population successfully immunised to prevent spread of disease

$$R_0 \approx \frac{L}{A}$$

A = average age at infection
L = human life expectancy

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Relationship between R_0 and p_c

	R_o Basic reproductive number	p_c Critical proportion of the population to be immunised for eradication
Malaria		99%
Measles	16 – 18	90 – 95%
Whooping Cough	16 – 18	90 – 95%
Chicken Pox	10 – 12	85 – 90%
Mumps	11 – 14	85 – 90%
Rubella	6 – 7	82 – 87%
Poliomyelitis	6 – 7	82 – 87%
Smallpox	4 – 7	70 – 80%

Source: Anderson and May

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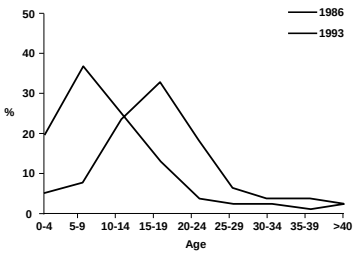
Age distribution of patients with rubella attending outpatient departments of general hospitals in greater Athens 1986 and 1993



Source: Panagiotopoulos et al 1996

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Models

Models

- Static
  λ Constant
- Dynamic
  λ (t) = ƒ (no infectious individuals in the population at time t)
- Where
  λ = force of infection (instantaneous per capitata rate at which individuals acquire infection)

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Modelling chickenpox and shingles

VZV ⇒ chickenpox ⇔ shingles
15-20%

- Chickenpox generally mild
- Shingles severe morbidity (.07% case fatality)
- Continued chickenpox exposure may boost immunity to shingles

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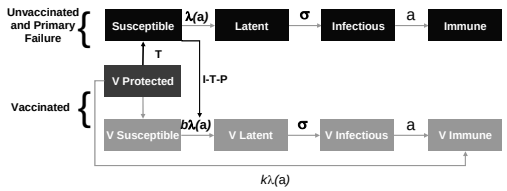
Modelling impact of VZV immunisation



Source: Brisson et al

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Commentary

- **Incidence of infection and morbidity will be reduced by mass vaccination**
- **However if exposure to chickenpox prevents shingles, then shingles will increase**
- **Intermediate coverage (40%–70% results in a long-term increase in chickenpox morbidity (due to increase in average age at which infection is acquired)**

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Cost-benefit model for measles

- **Model examines costs of:**
  - **Complications**
  - **Adverse events**
- **Measles is highly infectious. Prior to immunisation most people caught it**
- **Generally mild but can have serious complications e.g. pneumonia, encephalitis**

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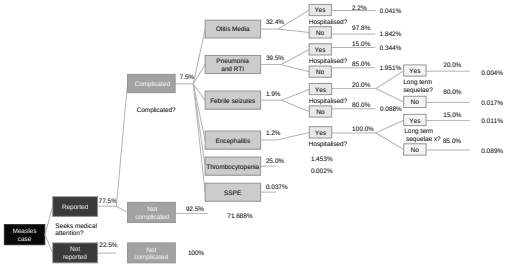
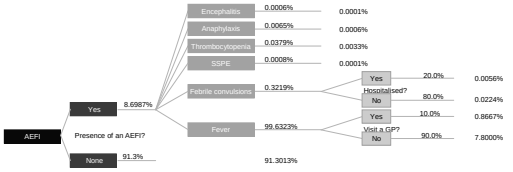
Cost benefit model for measles



Source: BMC Public Health

Cost benefit model for measles



Decision trees. a) measles cases and b) Adverse Event Following Immunisation (AEFI) with measles vaccines.

Legend: This graph shows the proportion of cases with each symptom, complication, sequelae or hospitalisation. A circle corresponds to a chance node (defined by the probability of the event occurring), a diamond represents an end node. The number at the top of each branch shows the proportion of each event occurring at that point in the tree. The total proportion of cases in each group per measles case is written at the right of each branch.

Source: BMC Public Health

Methodology

- **Decision trees built based on published data**
- **Distribution defined of the parameter estimates**
- **Model run 10,000 times — Monte Carlo simulation**
- **Provides outcome distribution for the cost of average measles case**
- **Mean at 95% credibility**

Results

- Three most influential variables were
  - Average no. of work days lost
  - Proportion seeking medical attention
  - Proportion of encephalitis cases developing sequelae leading to residential care

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Commentary

- Didn't include unproven side effects, notably autism
- Transaction costs of vaccinating not included i.e. parental time off work and Calpol

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Other models we looked at

Evaluating Cost-effectiveness of Vaccination Programmes, a Dynamic Perspective
Edmunds, Medley & Nokes, 1999

Predicting the Impact of Measles Vaccination in England and Wales
Babad et al, 1994

Modelling Forces of Infection for Measles, Mumps and Rubella
Farrington 1990

Modelling Rubella in Europe
Edmunds et al, 2000

Economic Evaluation of Options for Measles Vaccination Strategy n a Hypothetical Western European Country
Beutels and Gay, 2002

The Effect of Vaccination on the Epidemiology of VZV
Edmunds and Brisson, 2002

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Models: conclusion

- Highly complex issue to model
- Sophisticated models, some simplifications
  - Mortality
  - Vaccines provide lifelong immunity
- Sensitivity testing is critical even extremes

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Data

Key sources of data

Disease	ADRs
PHLS (HPA)	Yellow cards Clinical trials

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Data issues (1)

- **Finding data which is:**
  - **Relevant to the UK today**
  - **Sufficient sample size**
  - **Not affected by age shifts**
  - **Takes into account:**
    - **Medical advances**
    - **Changes in social conditions**

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Data issues (2)

- **Interpreting data on ADRs**
  - **Causality**
  - **Assessing level and clinical seriousness**

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Data issues: measles example

Serious effects of the disease vs reaction to MMR

Condition	Children affected after the natural disease	Children affected after the first dose of MMR
Convulsions	1 in 200	1 in 1000
Meningitis or encephalitis	1 in 200 to 1 in 5000	Less than 1 in a million
Conditions affecting blood clotting	1 in 3000 (rubella) 1 in 6000 (measles)	1 in 22,300
SSPE (delayed complication of measles that causes brain damage and death)	1 in 68000 (children under 2)	0
Deaths	1 in 2500 to 1 in 5000 (depending on age)	0

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Data: conclusion

- Data is critical
  - GIGO
- Data is complex
  - Causality
  - Relevant (times, geographical)

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Psychology of immunisation choices

The risk reward dilemma

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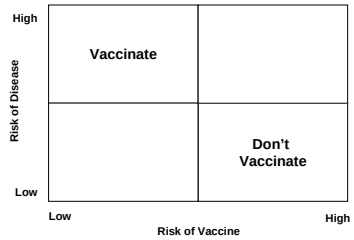
Vaccination risk reward matrix



Notes:
Risk of disease = severity x rate of infection
Risk of vaccine = severity x rate of adverse reaction, including infection

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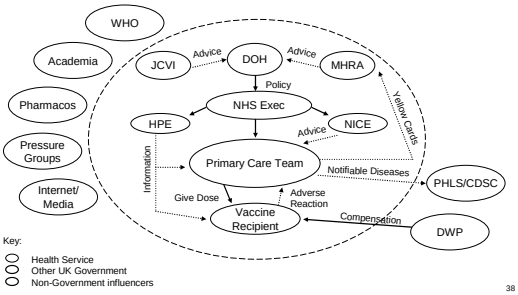
Who assess risk and rewards?



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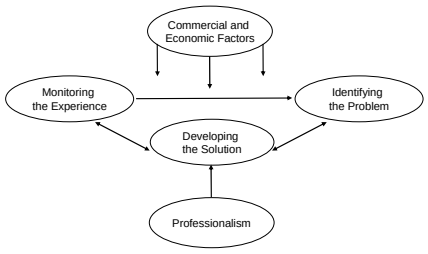
Vaccination Programme Control Cycle



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Case Studies

Polio
Measles

Polio – background

- An acute illness caused by 1 of the 3 types of polio virus
- Infection may be clinically apparent or range in severity from a non-paralytic fever to aseptic meningitis or paralysis
- Paralysis may occur i.e. 1 in a thousand infected adults and 1 in 75 children
- Paralysis may be mild but can be very severe and some people die, especially if their respiratory muscles are paralysed
- Infection rate in households can reach 100%

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Polio – background, cont´d

- Incubation 3 to 21 days
- Most infectious 7 to 10 days before and after the onset of symptoms
- Two main type of vaccines: Inactivated Polio Vaccine (IPV) and Live Oral Polio Vaccine (OPV)
- OPV can lead to vaccine-associated poliomyelitis

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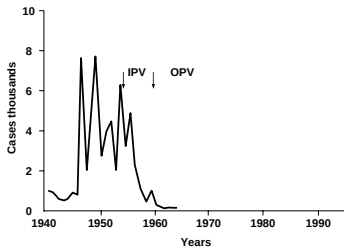
Poliomyelitis notified cases



Source: England and Wales (1940-1995)

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Polio – adverse reactions

Yellow Card	(1963 – 2003)
Total reactions	2,991 (serious 786)
Total reports	1,446 (serious 632)
Total fatalities	37 (26 SIDS)
Total Polio	17

DSS compensation scheme *	
Claims	1,675
Success	277

** Scheme started 1979, claims go back to NHS inception implies 80% disability*

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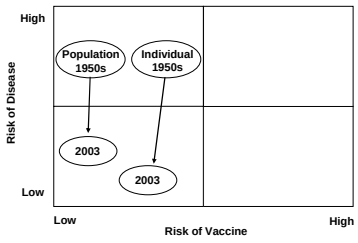
Dynamic risk reward matrix – Polio



Notes:
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Measles – background

- An acute viral illness transmitted via droplet infection
- Very infectious (R=16). Bi-annual epidemics pre-vaccination
- Incubation 10 days, with a further 2 to 4 days before the rash appears
- Complications include otitis media, bronchitis, pneumonia, convulsions and encephalitis

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Measles – background, cont'd

- Vaccine introduced in 1988
- Combined vaccination for measles, mumps, rubella
- Controversy over potential severe side-effects, particularly autism and Crohn's disease

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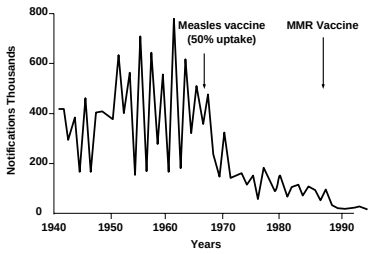
Measles notified cases



Source: Green Book

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ADRS – MMR

Yellow Card	(1998 – 2003)
Total reactions	6,191 (serious 1,554)
Total reports	3,715 (serious 1,350)
Total fatalities	17 (3 SIDS)
Total Measles	159

DSS compensation scheme	
Claims	579
Success	12

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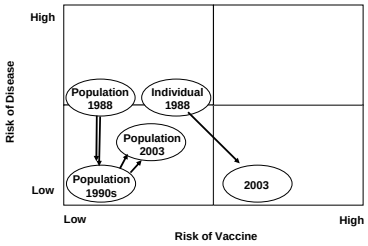
Dynamic risk reward mix – Measles



Notes:
Risk of disease = severity x rate of infection
Risk of vaccine = severity x rate of adverse reaction, including infection

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Conclusions

- **Vaccinations have historically reduced death and suffering**
- **UK does have a sophisticated surveillance system**
- **Existing statistics and epidemiological models and papers gives understanding of relative risk of vaccines and diseases**
- **Complex interaction between individual and herd immunity**

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Conclusions, cont'd

- Poorly implemented immunisation programme can be dangerous, since diseases tend to have more serious side effects as people get older
- Polio illustrates the dilemmas of success of a vaccine
- The MMR debate does matter because ongoing high coverage is required to prevent epidemics, and epidemics among older population can be more serious

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