Theory and Practice of Vaccination

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Lecture plan

- Review the basic theory of vaccination.
- The effect of vaccination on endemic disease in a population.
- The effect of vaccination on the disease dynamics.
- Rubella vaccination: perverse outcomes.
- Vaccination in practice: an example of a successful and an unsuccessful vaccination implementation.
- Pertussis vaccination.
- Vaccination in practice: Vaccine Impact Modelling Consortium

Review of the theory of vaccination

Vaccination is the generation of immunity to a pathogen in an individual through administering an appropriate antigen.

To prevent the spread of disease within a population, it's necessary to vaccinate enough individuals to achieve **herd immunity**.
With herd immunity, each infectious individual infects only 1 other, on average.

R_0 is mean number of infections generated by an infectious individual in a *susceptible* population.

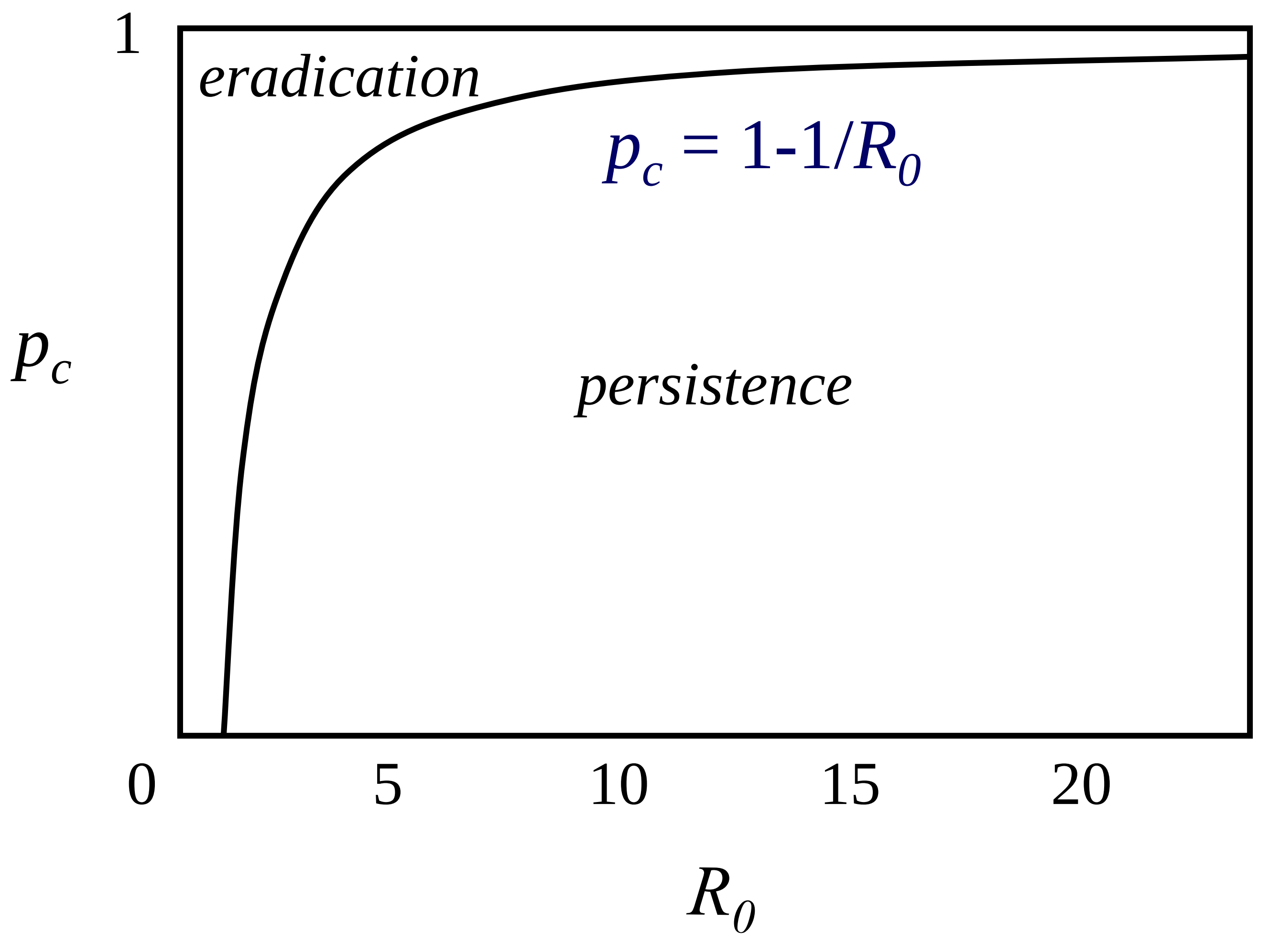
For vaccination coverage *p* of the whole population, effective reproductive number:

$$R = (1 - p)R_0$$

The minimum vaccination coverage for eradication is

$$R = 1 \Rightarrow p_c = 1 - 1/R_0$$

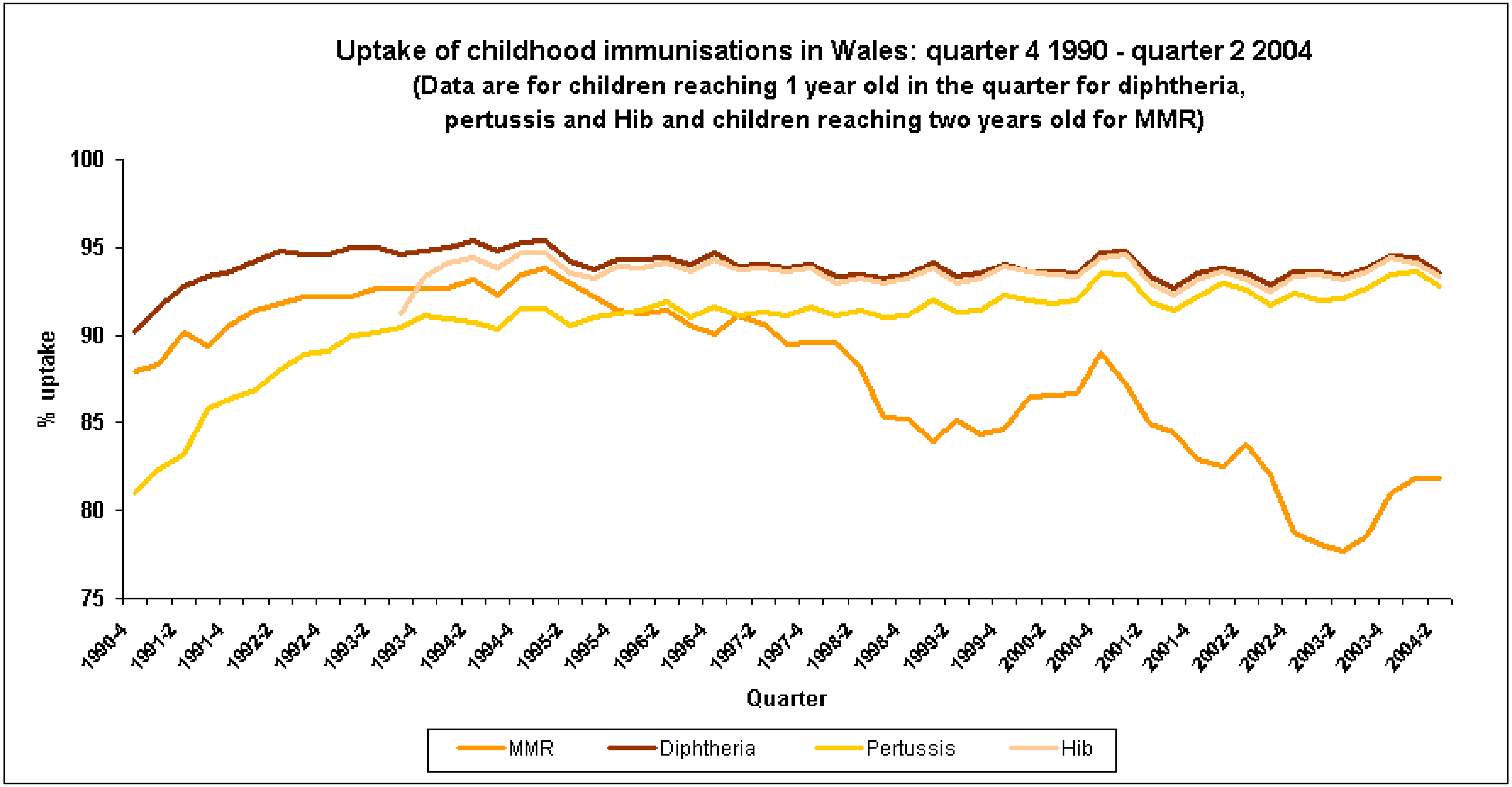
Review of the theory of vaccination



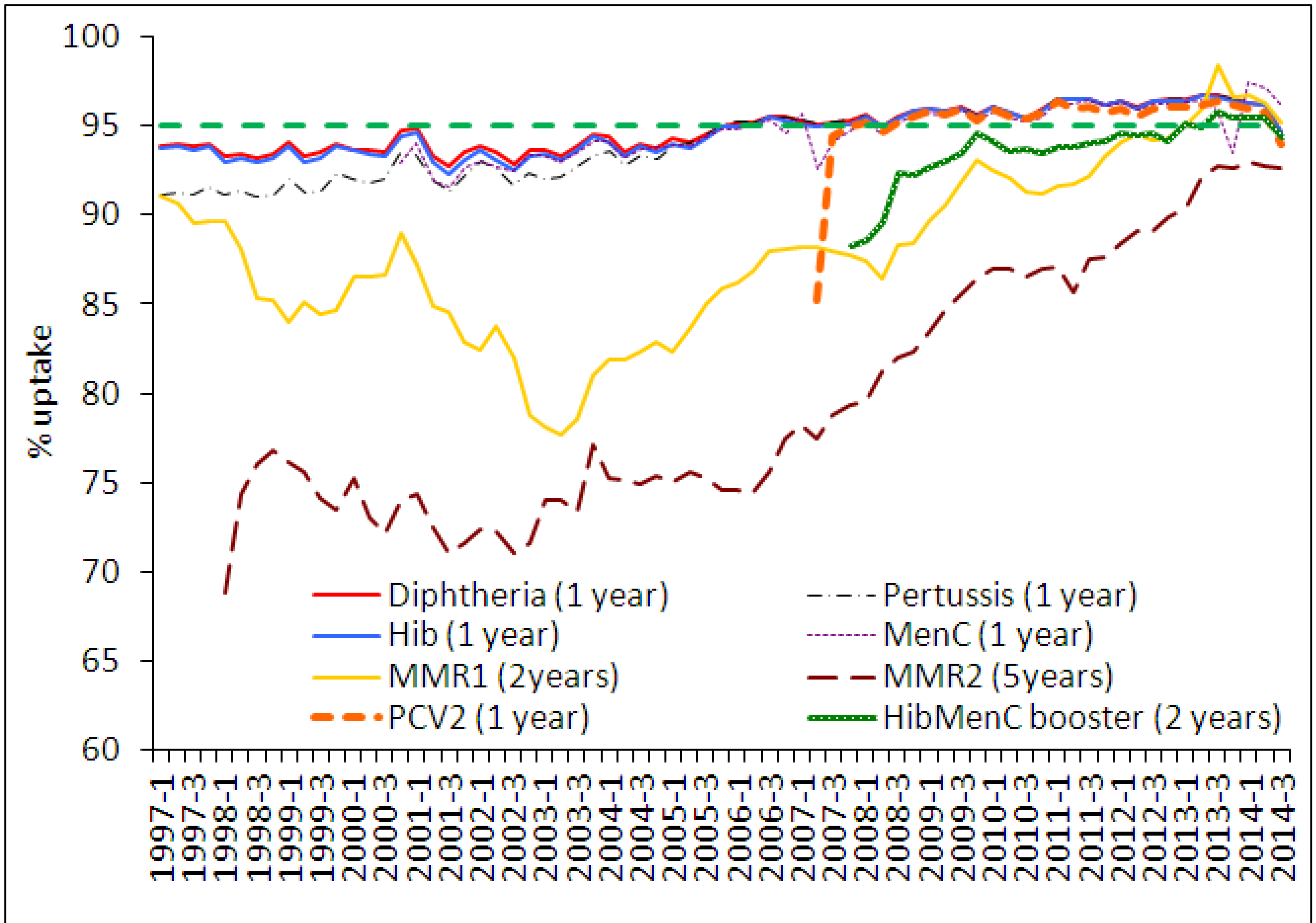
Pre-vaccination R_0 estimates for England and Wales

Infection	R_0	p_c
Measles	16-18	94-96%
Mumps	11-14	91-93%
Rubella	6-7	83-87%
Pertussis	16-18	94-96%

Vaccine coverage in Wales, 1990-2004



Vaccine coverage in Wales, 1997-2014

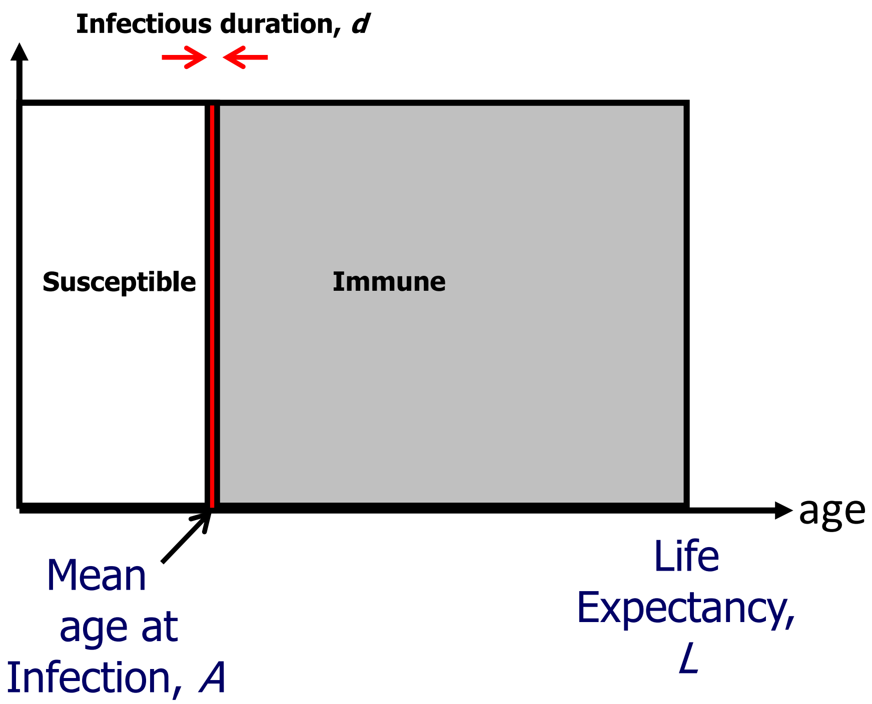


Endemic disease in an unvaccinated population

Consider a population in a stable endemic state with a disease that confers lifelong immunity.

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

Disease prevalence $= \dfrac{d}{L}$

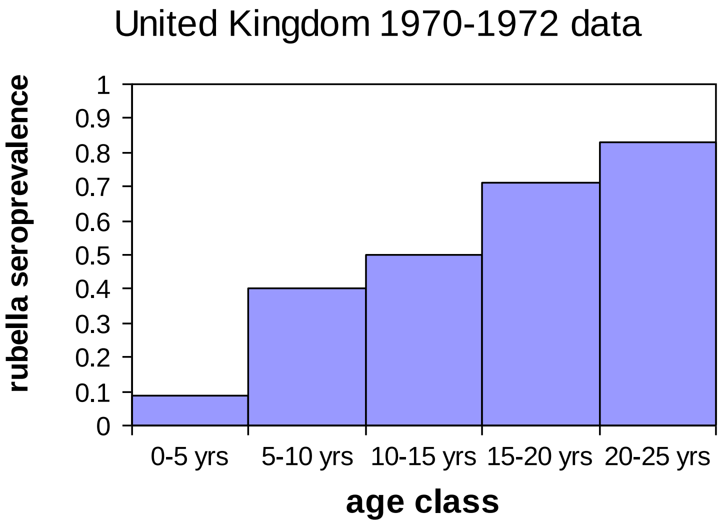


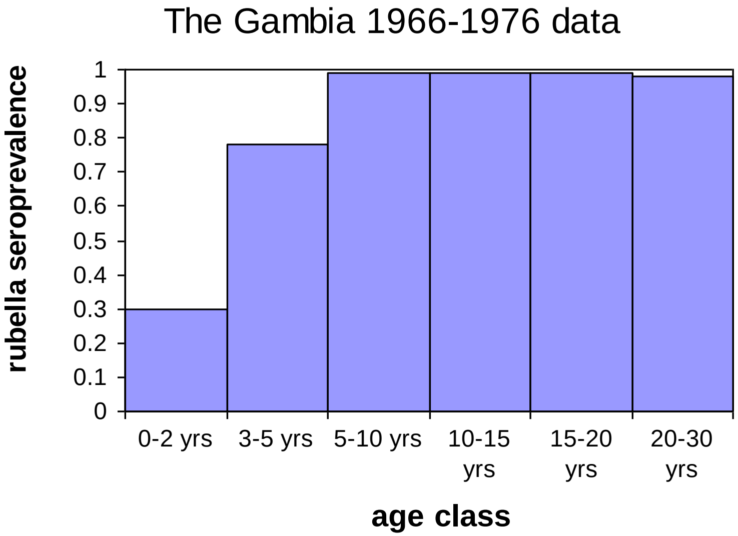
A is closely related to **force of infection**, the probability per unit time of an individual becoming infected:

$$\text{Force of infection, } \lambda = 1/A$$

R_0 and the mean age at infection A

Rubella sero-prevalence by age





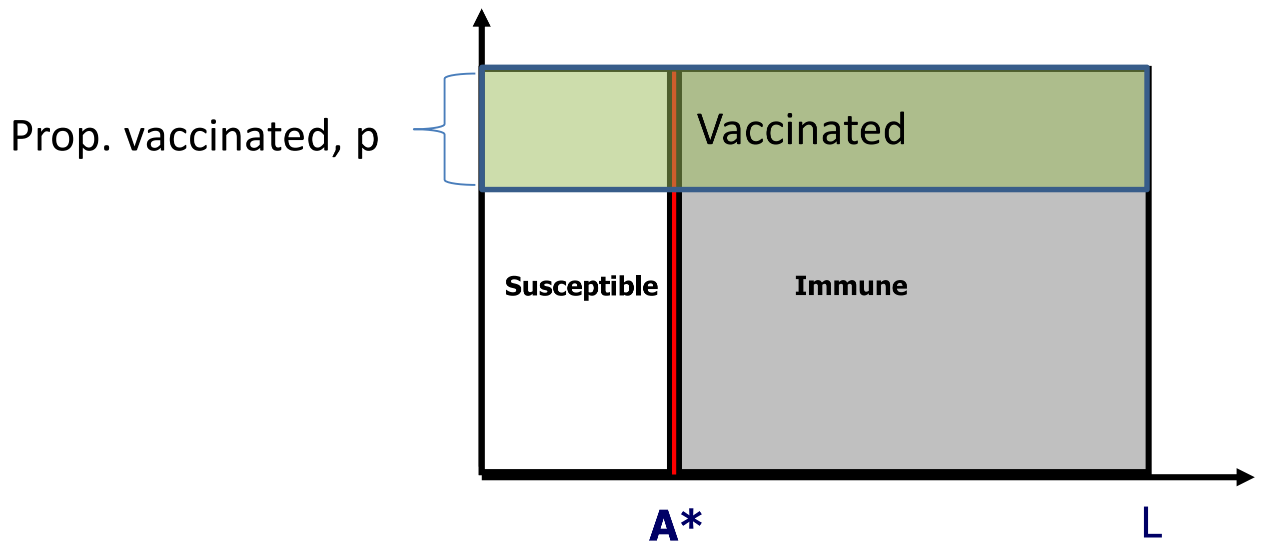
A_{UK}= 9-10 yrs

A_{Gambia}= 2-3 yrs

Force of infection = 1/A

Endemic disease in a vaccinated population

Consider same population with a proportion p vaccinated, insufficient for eradication. It now has average age of infection, A*.

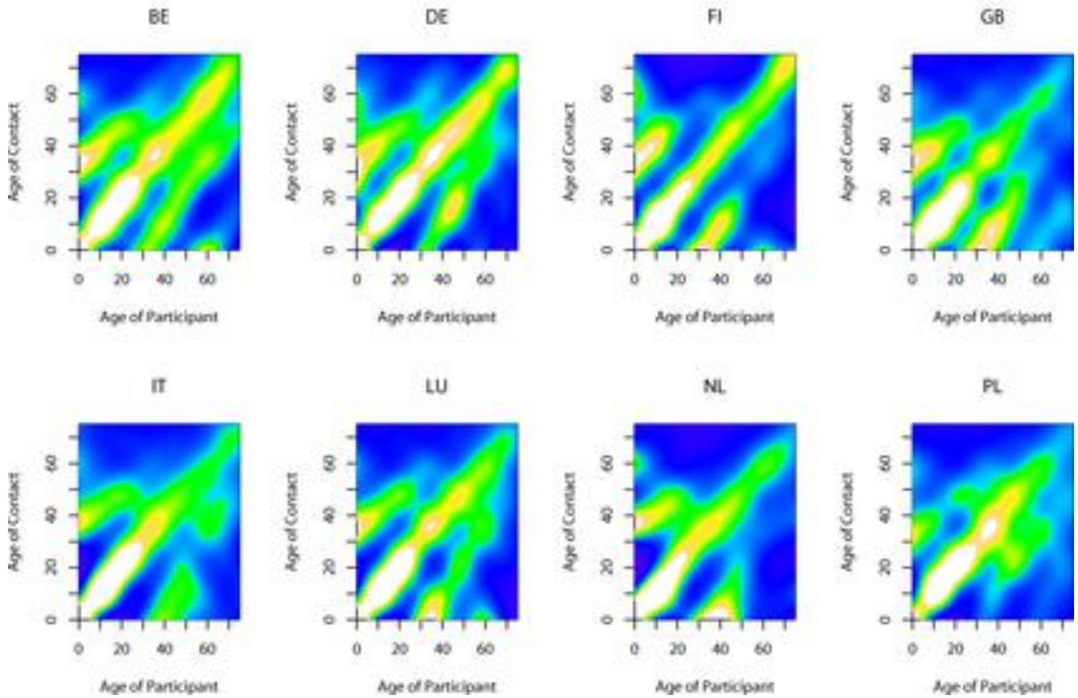


Proportion of pop^n susceptible is now $\dfrac{A^*(1-p)}{L}$ $\Rightarrow$ $R_0 \dfrac{A^*(1-p)}{L} = 1$

Comparing to the unvaccinated case: $\boxed{A^* = \dfrac{A}{(1-p)}, \text{prevalence} = \dfrac{(1-p)d}{L}}$

Realistic infectious contacts

Real patterns of contact between individuals are strongly correlated with age. Figure shows intensity of contact as a function of ages of participants:



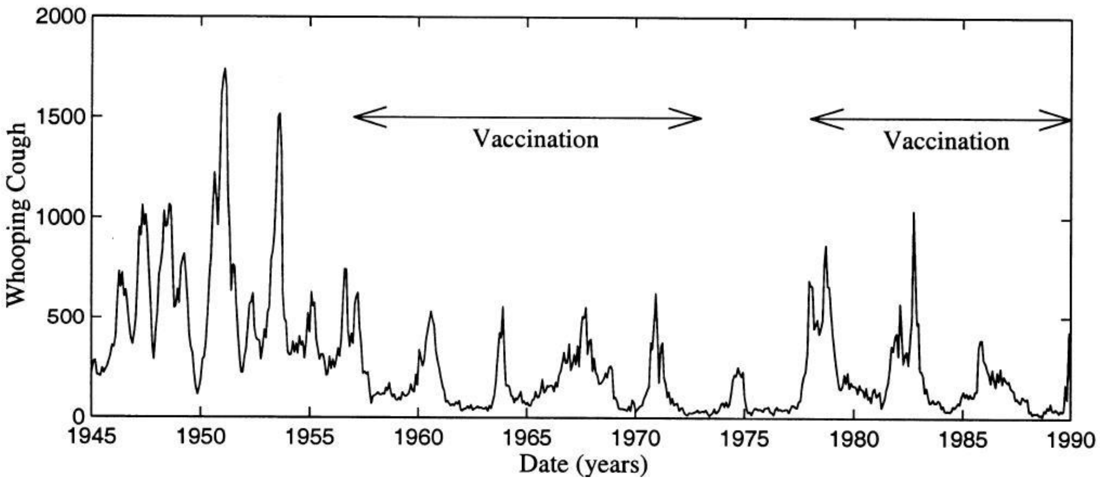
•Contact strongest between people of similar age.
•Contact most intense between school children.
•Note contacts between children and parents and also grandparents.

Mossong et al, 2008, PLoS Med., 5, p74

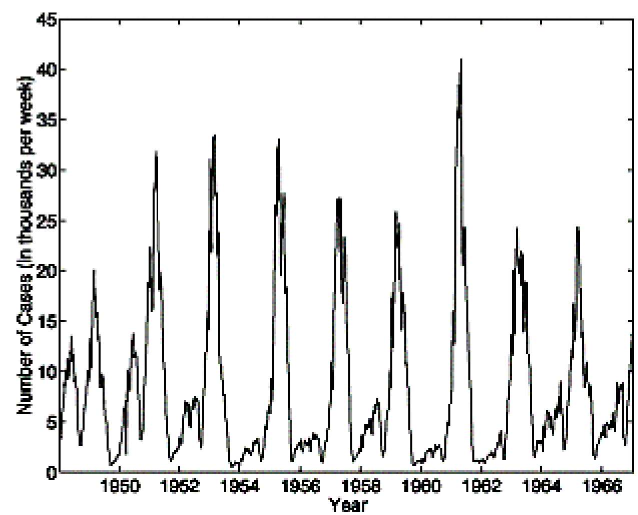
Periodicity in incidence

- Infectious diseases are often characterised by periodicity in incidence rates.
- The degree of annual variability can be extremely high.
- Period can be annual, biannual, three or four yearly or highly variable.

London pertussis notifications



Measles, UK



Seasonality in transmission

Seasonal variation in incidence is mainly generated by annual cycles in transmissibility between individuals.

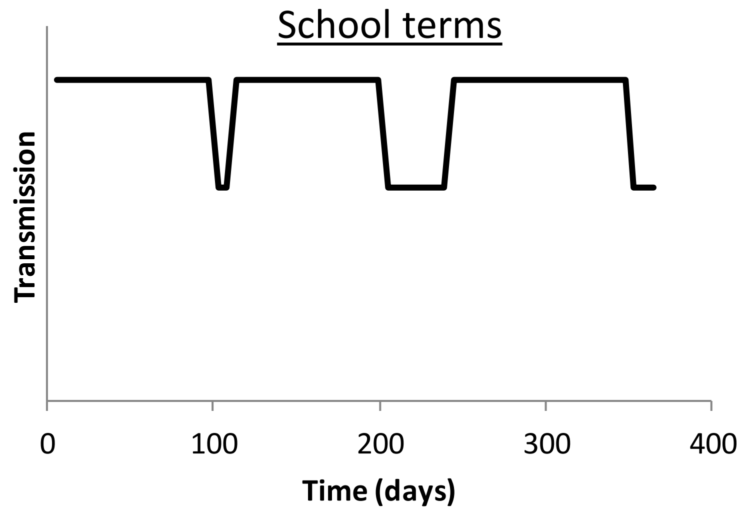
The possible mechanisms of variation are:

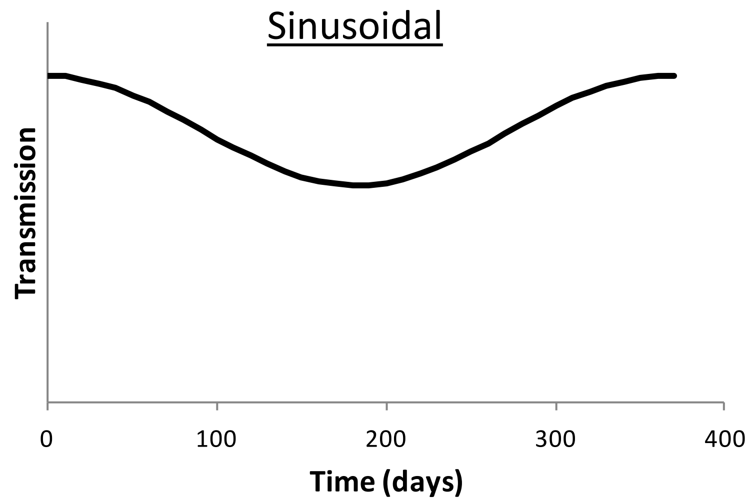
•Social distance: people spend more time indoors in winter, increasing the frequency and strength of contacts.

•School terms: Children in school experience more transmission in school than during holidays.

•Absolute humidity: drier air during winter facilitates aerosol transmission of disease (influenza).

•Vitamin D levels: Lower winter light levels leads lower Vitamin D levels which increase susceptibility





Effect of vaccination on disease dynamics

The periodicity of disease incidence depends on:

- Mean age of infection.
- Birth rates in the population
- Seasonality of contact rates

with a period approximately given by

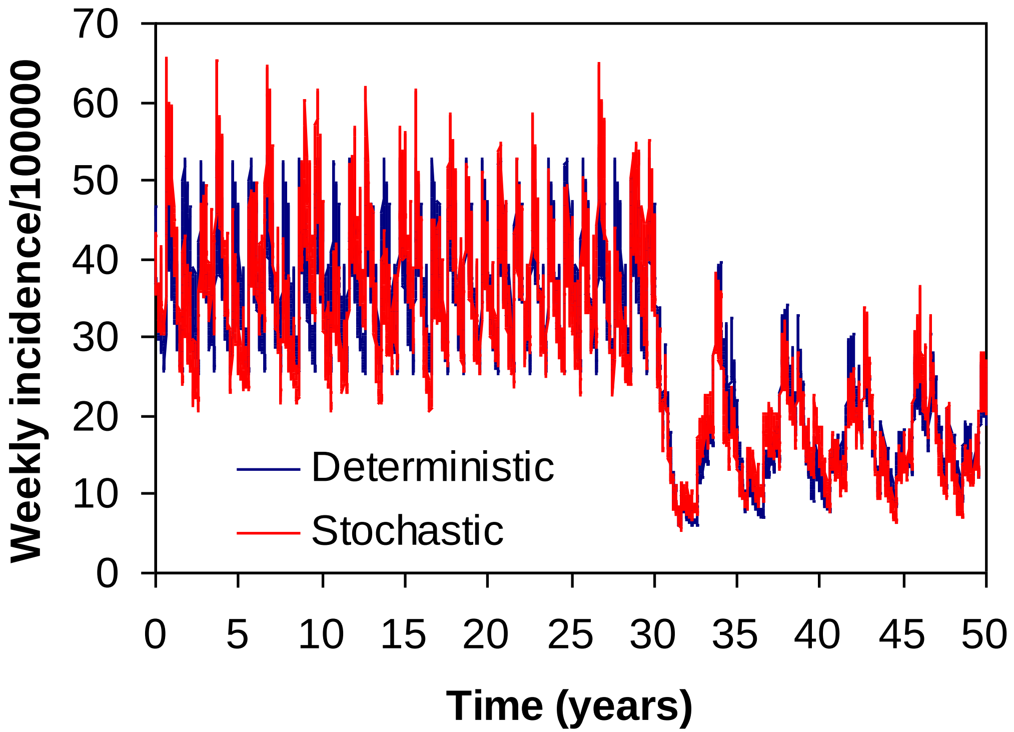
$$T \simeq 2\pi\sqrt{Ad} = 2\pi\sqrt{\frac{d}{\lambda}}$$

The altered mean age of infection under vaccination gives a new longer period:

$$T \simeq 2\pi\sqrt{\frac{Ad}{(1-p)}}$$

Simulating the impact of vaccination

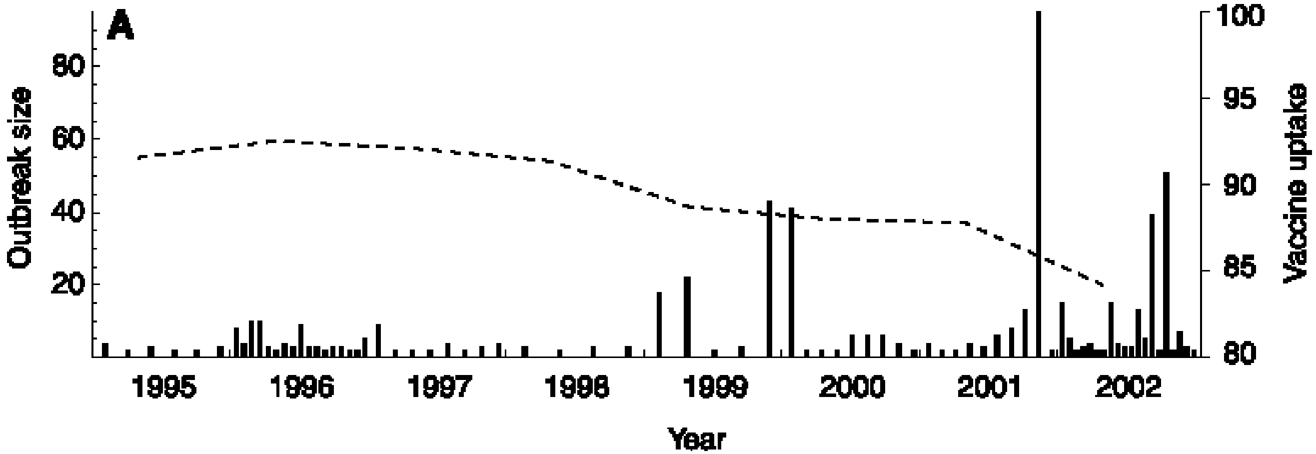
- Simple SEIR model, modeling 70% vaccination (at birth) with 85% efficacy.
- Assume vaccination reduces infectiousness.
- Switch from predominantly annual to 4-5 year cycles.
- Stochastic model somewhat more realistic.



The impact of reduced MMR uptake

• The current concern about MMR uptake levels makes predicting the likelihood of a large measles outbreak a priority.

• Can data on the current small outbreaks seen in the last few years tell us anything?



[Jansen, V.A.A. et al, Science (2002), 301:804]

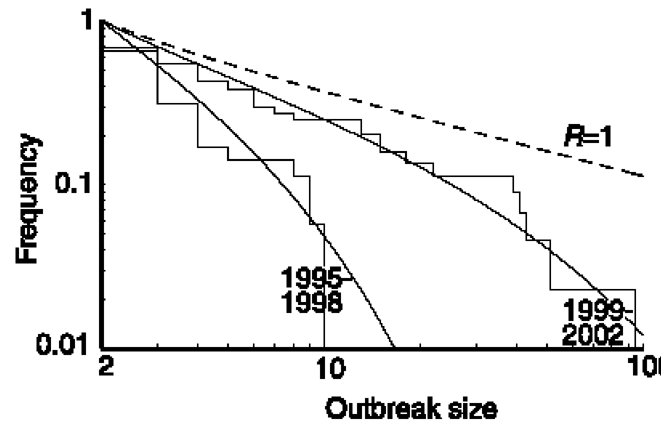
Inferring *R* from outbreak size distributions

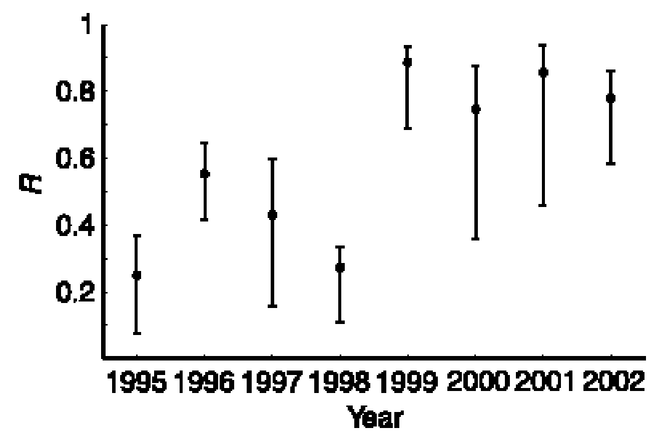
• For sub-critical transmission, possible to estimate *R* from the distribution of outbreak sizes (*m*=2/(1-R), where *m* is mean outbreak size).

• This analysis shows a significantly increased level of transmission in the period 1999-2002 compared with 1995-98.

• *R* is now dangerously close to 1 – meaning a major measles outbreak is due any time.

• This is an intrinsically stochastic analysis – since outbreak size is a random variable.





Introduction to rubella and CRS

Rubella infection

- Virus, directly transmitted
- Mild fever
- Rash (punctate and maculopapular)
- Transmission to foetus possible ($p>0.25$) when acquired during 1st trimester of pregnancy

Congenital rubella infection

- causes Congenital Rubella Syndrome in about 80% of cases
- CRS: deafness, blindness, heart defects

Epidemiology of CRS in the United Kingdom

years	71-75	76-80	81-85	86-90	91-95	96-00
CRI only	40	34	61	25	2	1
CRS	201	172	140	88	19	16
Total CRI/CRS births	241	206	201	113	21	17
Terminations for rubella (EW only)	3709	2002	759	268	43	17

Vaccination policies in the UK

1970- 1988: selective immunisation: all schoolgirls, susceptible adult women
1988- now: MMR in second year of life
1996: schoolgirl immunisation program ceased

Vaccination: a possible perverse outcome

The existence of an important risk group (women of child-bearing age) outside the usual age-range of infection can lead to unexpected effects.

- Pre-vaccination, most women are already immune to rubella by child-bearing age.
- Introducing vaccination will increase A, and hence the number of susceptibles in the risk group, S_α.
- However, vaccination also decreases the force of infection, λ_α, experienced by the risk group.

United Kingdom 1970-1972 data

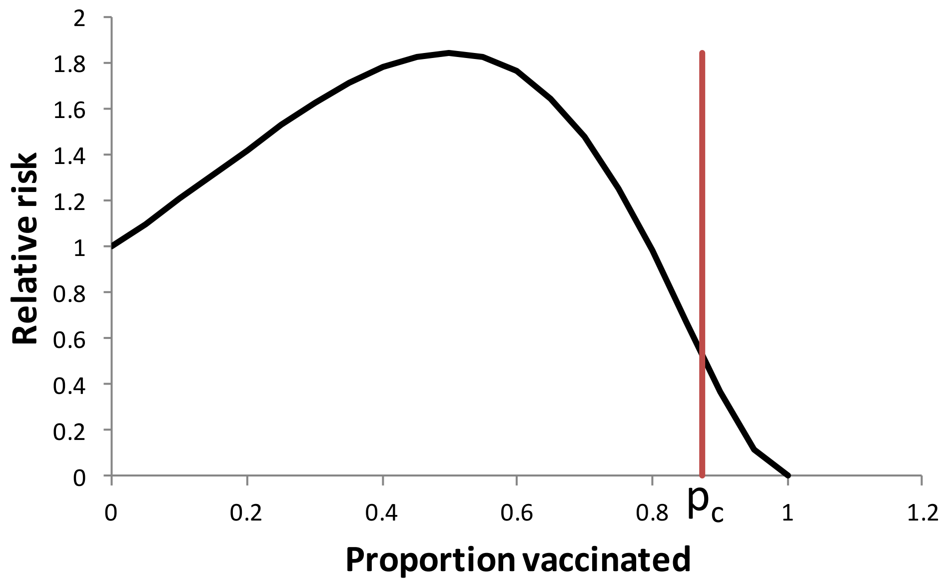
- *A* = 9-10 yrs

Case rate in the risk group is given by $S_\alpha \lambda_\alpha$, so:

$$\text{If } \lambda_\alpha \downarrow \text{ and } S_\alpha \uparrow \text{ then } \lambda_\alpha S_\alpha \downarrow \text{ or } \uparrow ?$$

Prediction of a simple model

A very simple model, based on vaccination at birth and uniform mixing shows an equilibrium increase in relative risk for a risk group at age 30. Risk increases with age and R_0.



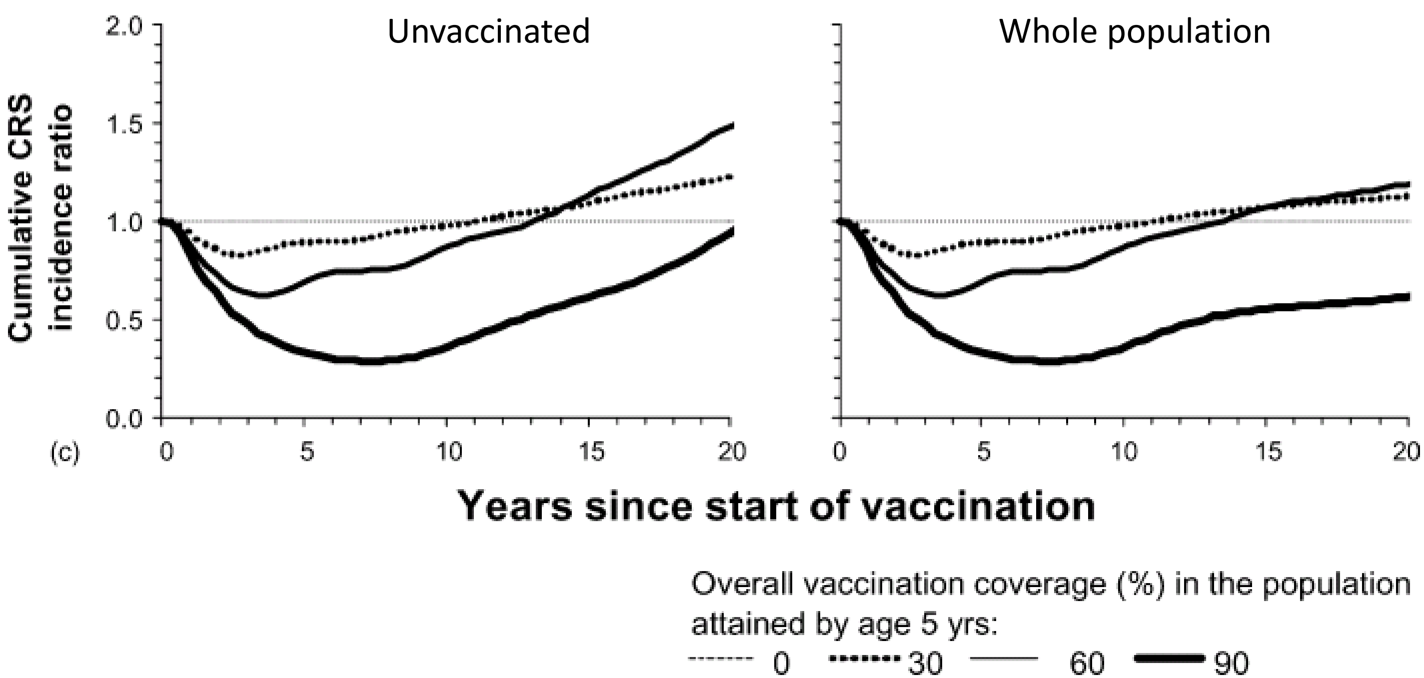
Is this effect seen in reality and, if so, how should vaccination programs be implemented to avoid it?

CRS: partially vaccinated populations – short term

- MMR is recommended vaccine, but relatively expensive.
- In many countries, availability is through private healthcare and hence covers only a fraction of the population.

Vaccinated group pushes FOI down. What happens to unprotected in short and long term?

Short term:



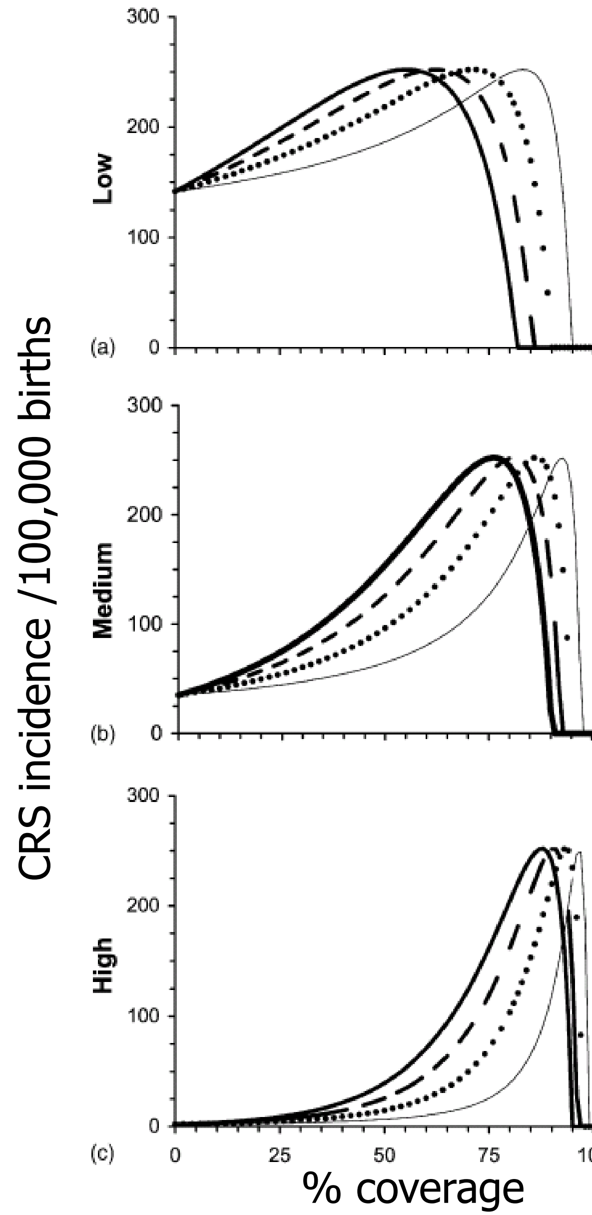
CRS: partially vaccinated populations – long term

Long term effects:

- Vaccination always increases CRS incidence in unvaccinated group.

- Incidence increases with coverage, up to a point.

- For medium-high pre-vaccination FOI, there is increase in the population as a whole.



Vaccination in Greece

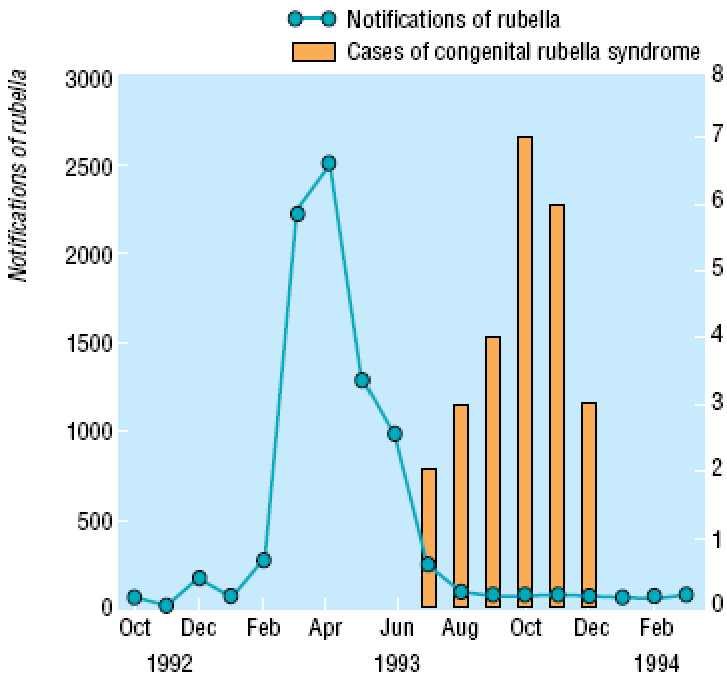
- Rubella vaccination in Greece started in ’77; not compulsory and mainly in private sector.
- Aimed primarily at young children (indirect strategy).
- Compulsory MMR for 1 year-olds from 1989.
- Poor assessment of vaccine uptake and notification of rubella cases. However, coverage probably <<50% for children up to 1989.

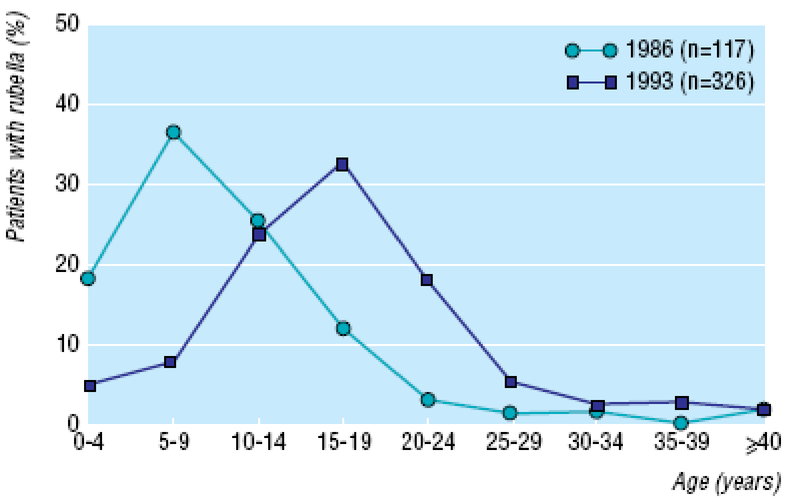
Susceptibility in risk group

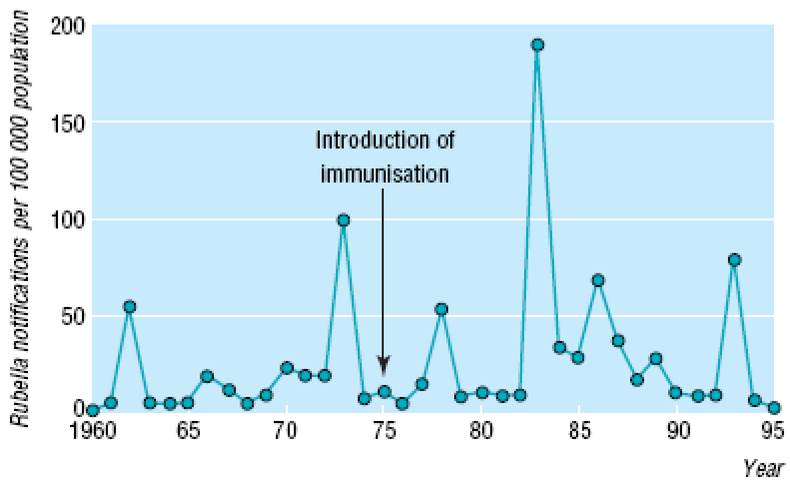
Year	% pregnant women susceptible
1971-5	12%
1980	11%
1981	17%
1984-9	24%
1990-1	36%

Rubella and CRS in Greece

- In 1993, a major rubella epidemic occurred in Greece, resulting in 25 confirmed CRS cases.
- Note shift in age distribution of rubella cases.
- CRS incidence matches outbreak, shifted by 7 months.



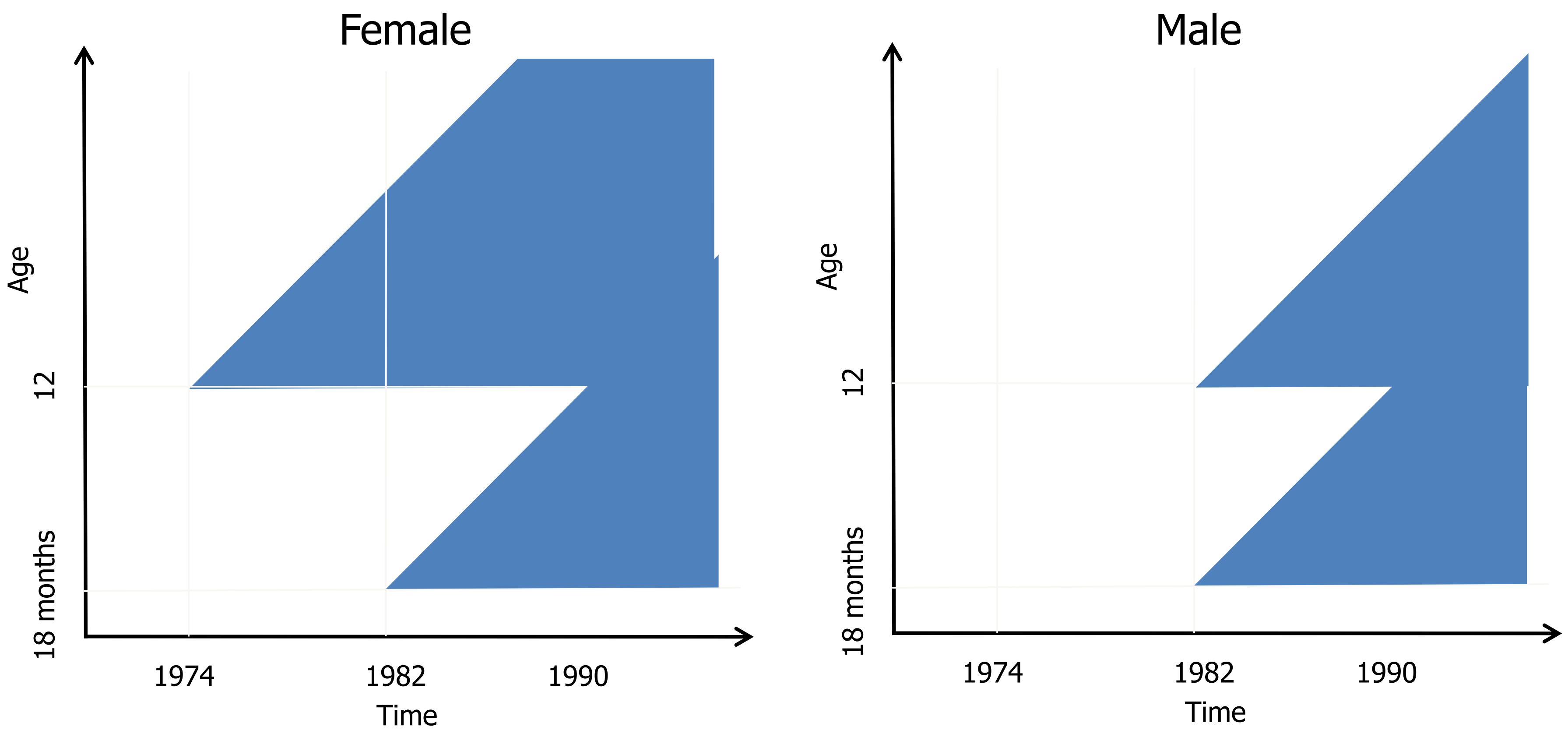




Implementation of vaccination in Sweden

'Standard' vaccination strategy (as used in UK, USA):

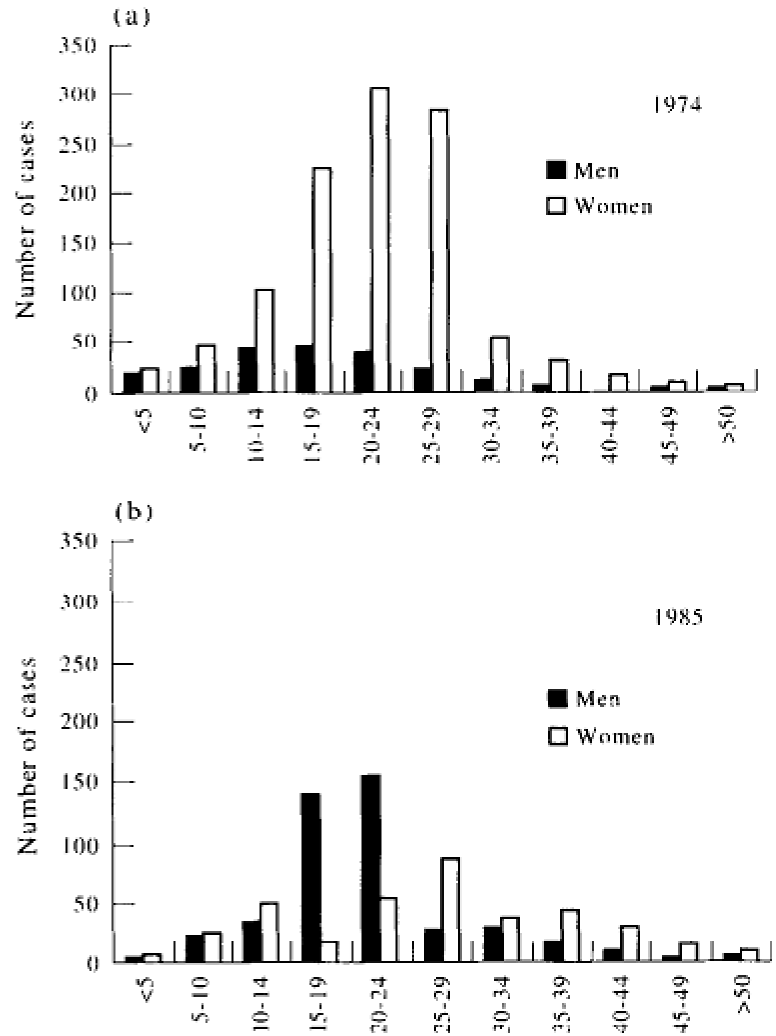
- 1974: direct phase. Vaccination of girls at 12 years. Also women, post-partum, if susceptible.
- 1982: indirect phase. vaccination of all 12-year-olds and children at 18 months.
- Coverage of target groups approximately 90% and increasing.



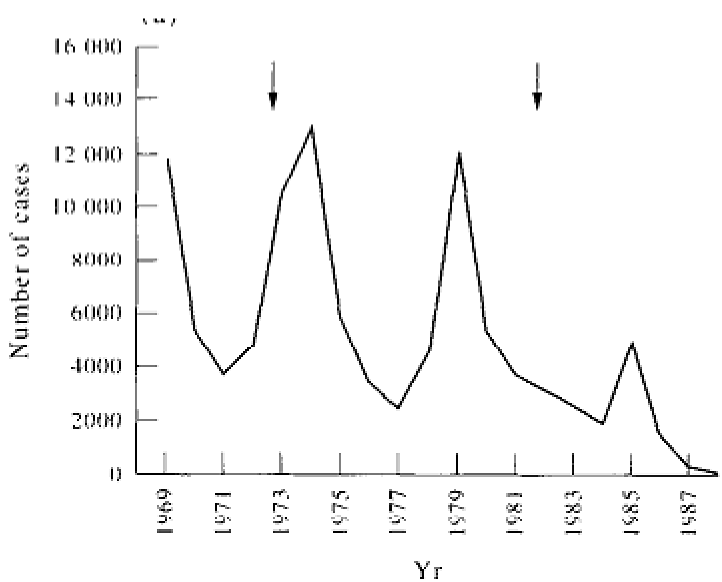
Effect of vaccination in Sweden

Effect of vaccination strategy:

- Rubella effectively eradicated since mid-90s.
- CRS: since 1973 53 severe cases, since 1985, none.
- Pregnant women: 12% susc. -> 3% by ’87.
- Changing coverage reflected in gender distribution of cases.
- Note gender-specific reporting bias.

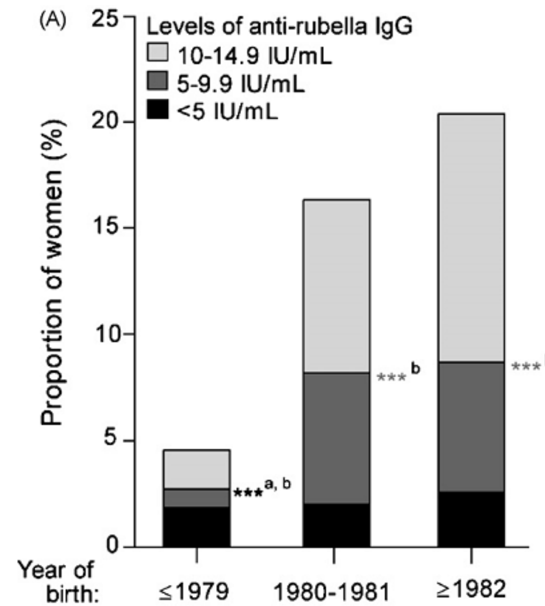


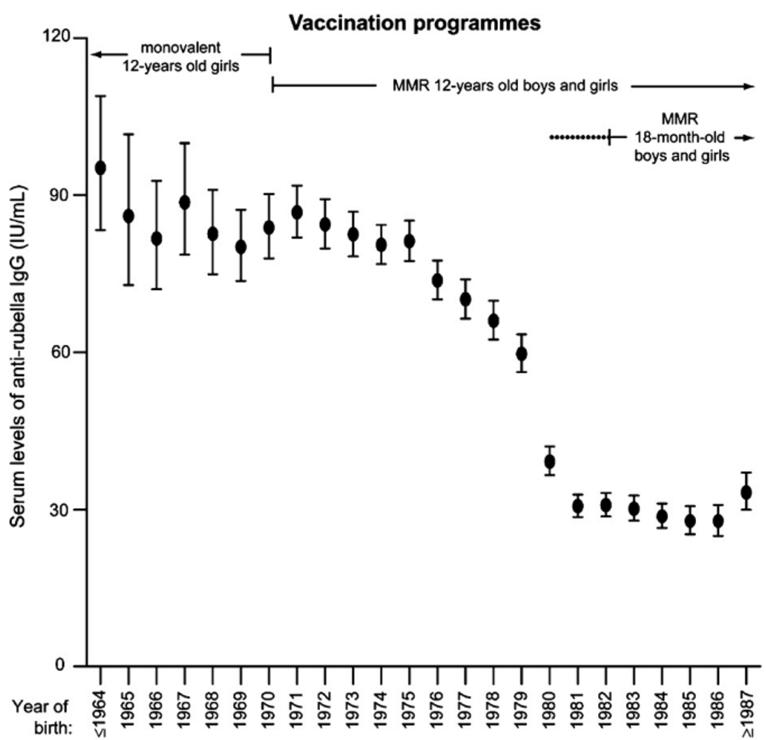
Lab-confirmed cases

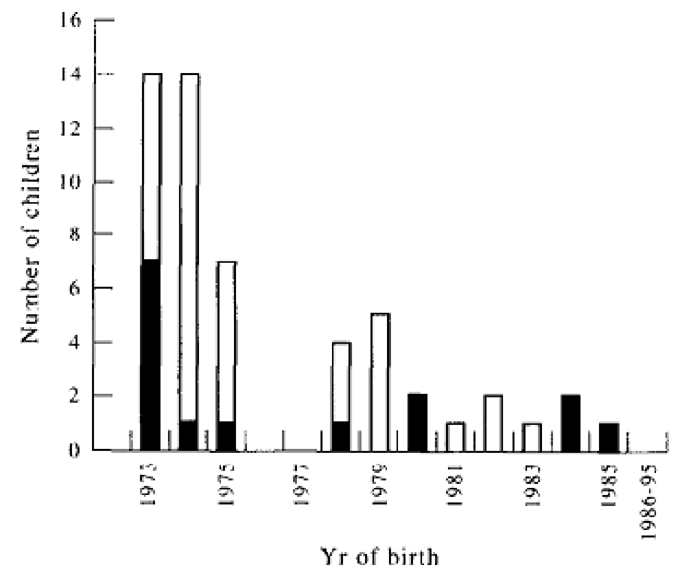


Serology in post-vaccination Sweden

Antenatal sera from primapara women:
- 95% of pregnant women protected.
- Serum IgG levels strongly depend on year of birth.
- Weaker protection for those born after ~1980.
- 'Natural' immunity stronger? Frequent challenge?
- Possible sub-clinical infections…







Pertussis

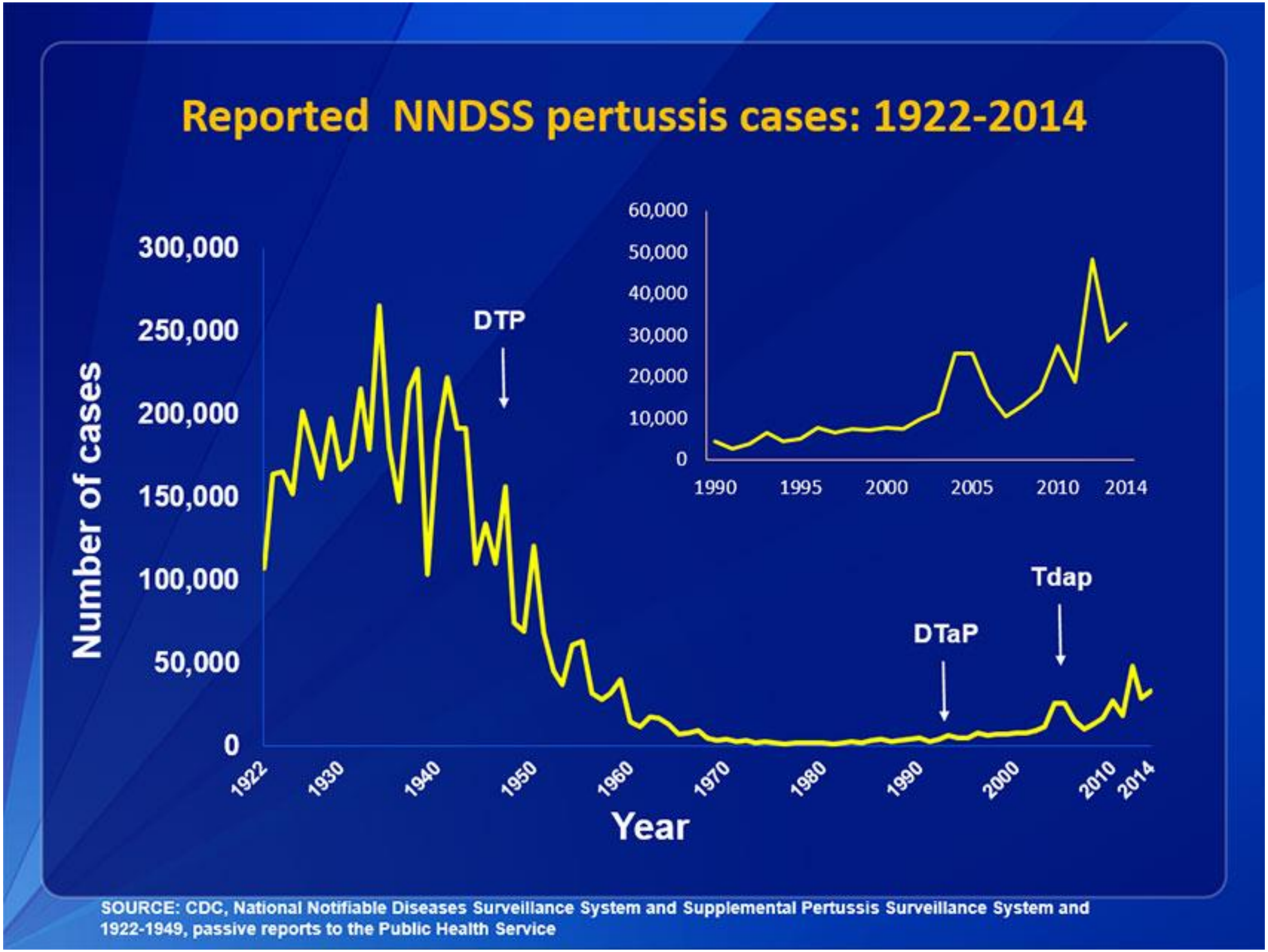
Aetiologic agent: Bordetella pertussis, a gram-negative coccobacillus.

Transmission: Highly transmissible ($R_0 \approx 16$), via direct contact with discharges from respiratory mucous membranes of infected persons.

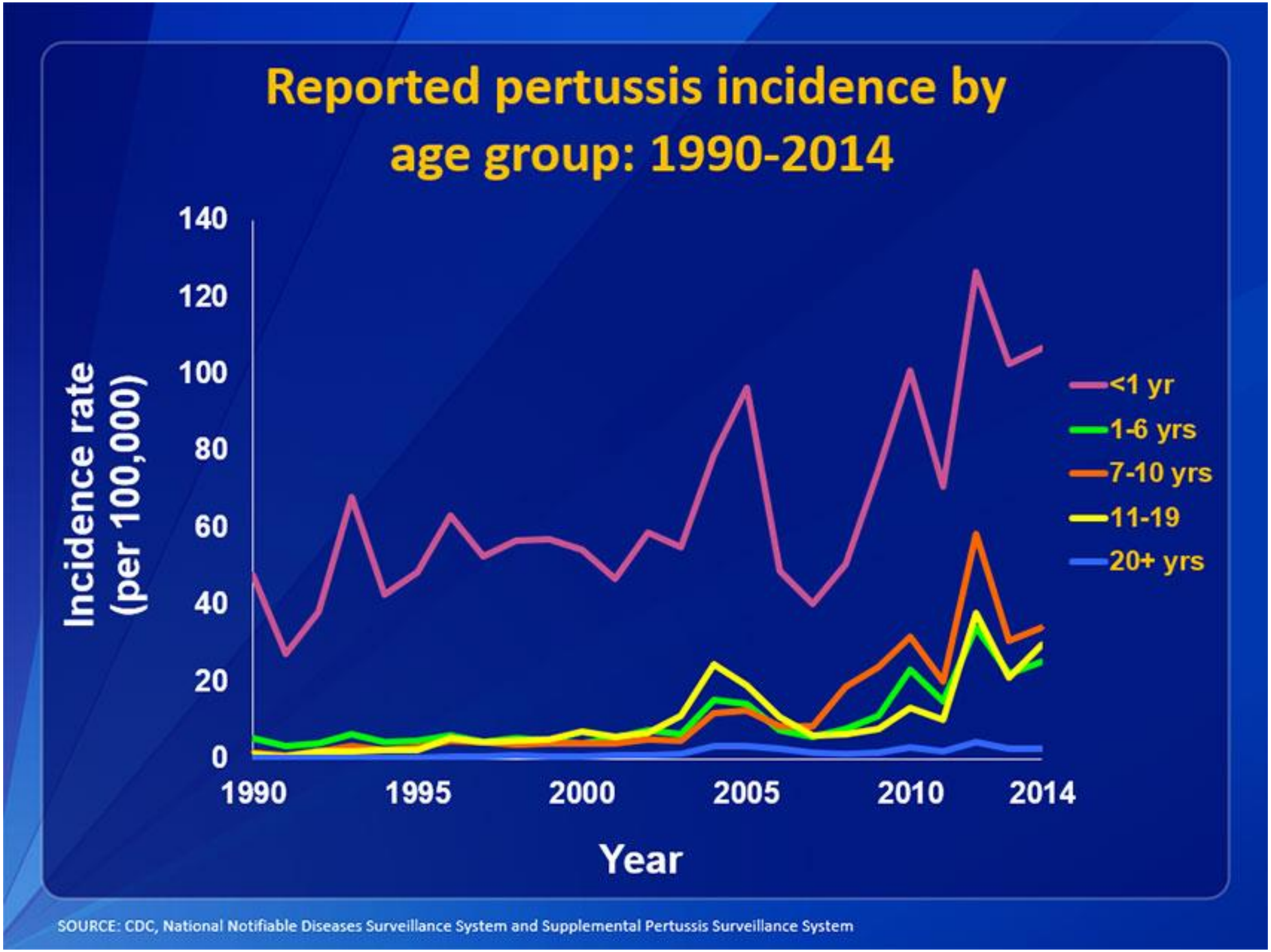
Clinical Features: Highly communicable, vaccine-preventable disease that lasts for many weeks – can result in very severe coughing, whooping, and post-tussive vomiting.

Major complications: most common in infants and young children and include hypoxia, apnea, pneumonia, seizures, encephalopathy, and malnutrition. High mortality in developing world.

Pertussis incidence trend: US

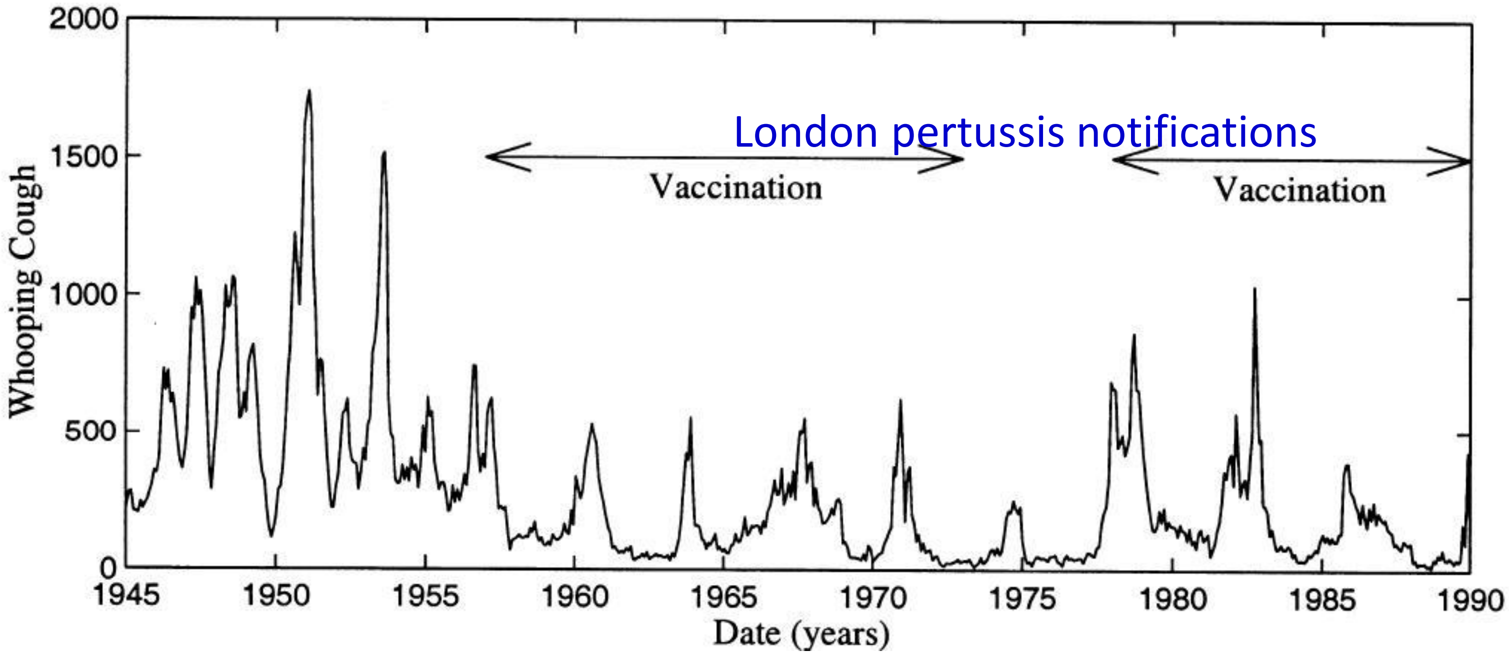


Pertussis incidence trend: by age



Dynamics

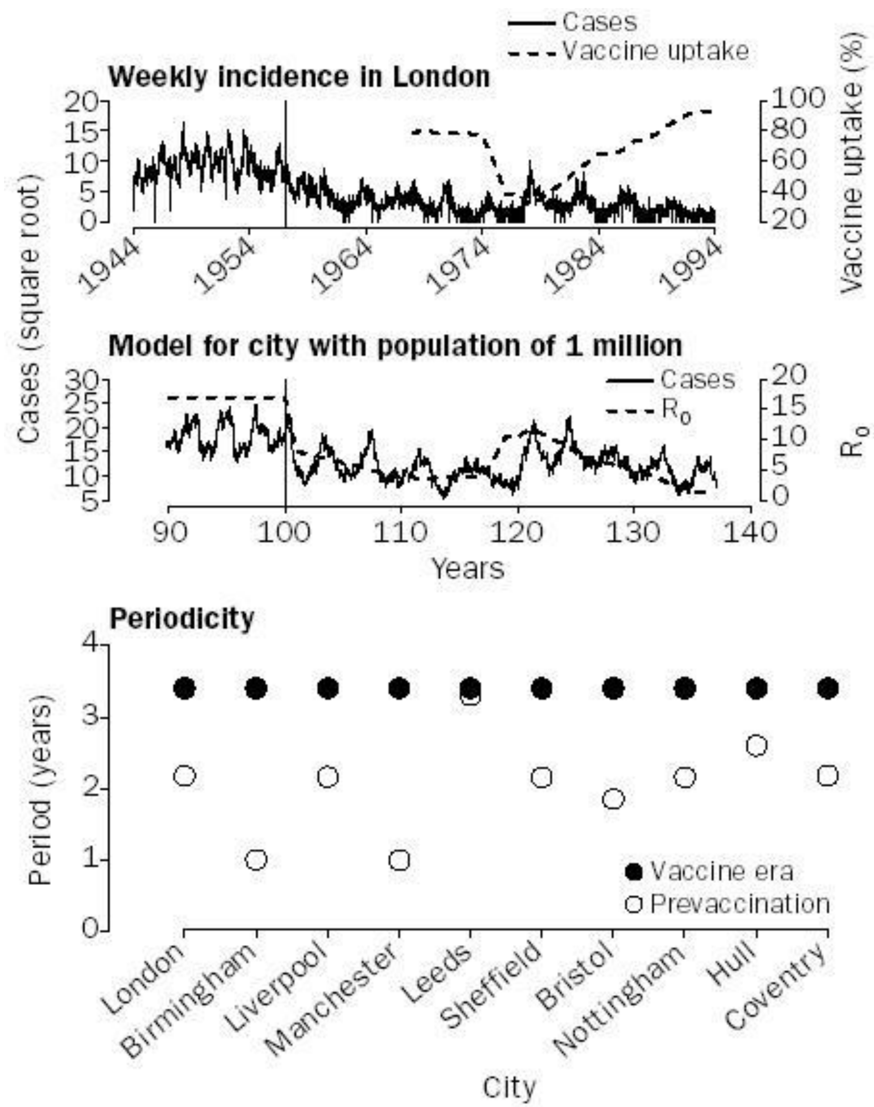
- Pre-vaccination dynamics show irregular annual epidemic cycles.
- Post-vaccination epidemics show ~4 year oscillations.

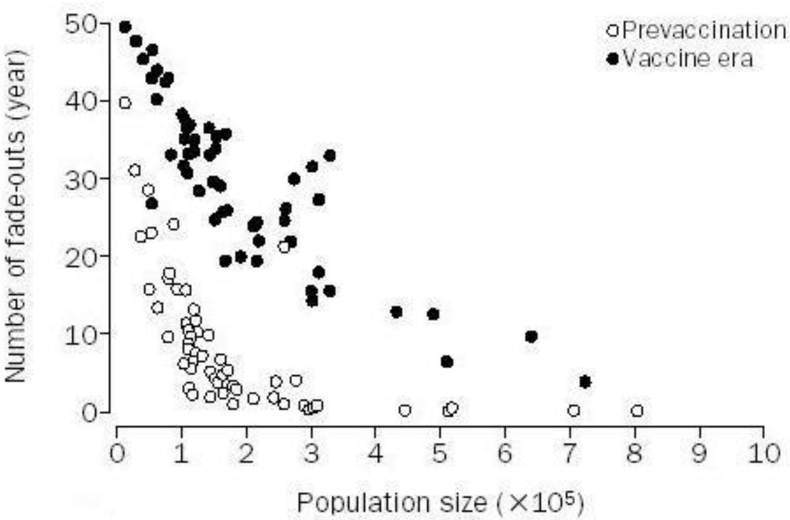


$$T \simeq 2\pi\sqrt{Ad} = 2\pi\sqrt{\frac{d}{\lambda}}$$

Does vaccination reduce transmission?

- Since whole cell vaccine is live, perhaps it contributes to asymptomatic infection?
- Can look for signatures of decline in temporal dynamics.

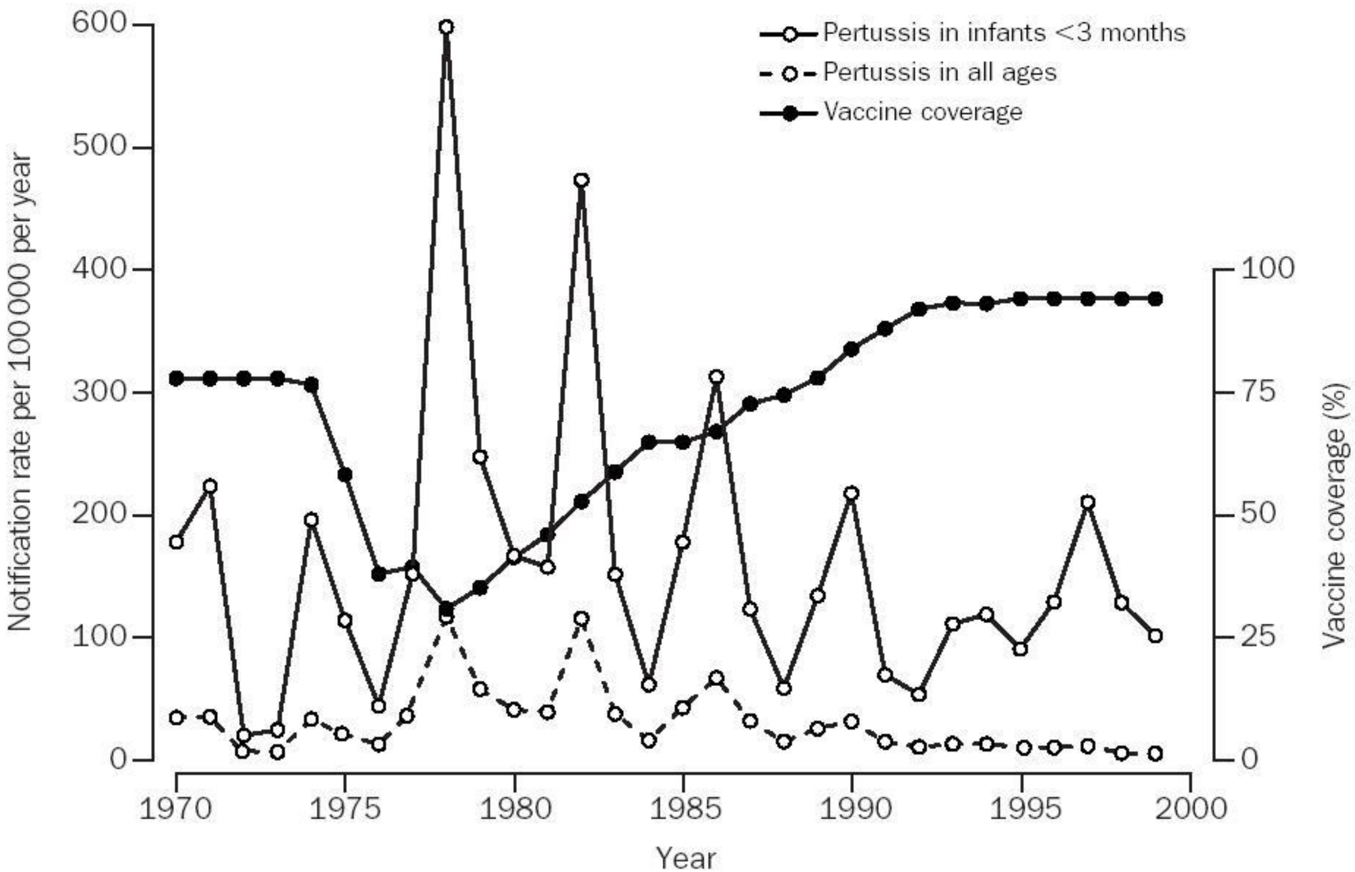




from *Rohani et al, Lancet (2000) 355:285-6*

Does vaccination reduce transmission?

- Possibly simpler method is to look at age-related patterns of infection.
- In particular, look at reported case in infants <3 months (prior to vacc.)



from *Gay & Miller, Lancet (2000) 355:1553*

Global vaccination programmes

- EPI – enhanced programme for immunization
  - Routine immunization in early childhood for a number of well established vaccines to prevent or reduce endemic disease burden
  - Which vaccines included, and at which ages differs between countries
- Vaccination campaigns
  - To increase population-level vaccination coverage quickly
  - To address gaps from low coverage of routine programmes

VACCINE IMPACT
MODELLING CONSORTIUM

- New initiative (since Jan 2017, www.vaccineimpact.org)
- Aim:
  - to quantify the impact of vaccination in low- and middle income countries globally
  - Impact = deaths and cases averted over the lifetime of vaccinated birth cohorts
  - Focussing on established vaccines (currently 10 antigens)
- Funded by Gavi, the Vaccine Alliance, and the Gates foundation
  - Impact estimates used to inform their investments, and to track progress against targets.

- Consortium approach:
  - Various modelling groups provide disease-specific estimates
  - These are then combined by the secretariat at Imperial College
  - Impact evaluated by estimating burden:
    - Assuming “best estimate” of vaccination coverage
    - Counterfactual scenario of no vaccination
    - Impact = difference in burden with and without vaccine

Conclusions

- Vaccination protects individuals directly, but also indirectly through the effect of herd immunity.

- Vaccination reduces the force of infection in the population and this has indirect effects on the mean age of infection and the age distribution of sero-positive individuals.

- Vaccination strategies can have unexpected consequences, developing over many years to produce a negative outcome.

- In situations, in which the risk group and population driving the infection differ, great care is needed in designing vaccine interventions.

References

Kakoulidou, M., Forsgren, M., Lewensohn-Fuchs, I., & Johansen, K. (2009). Serum levels of rubella-specific antibodies in Swedish women following three decades of vaccination programmes. *Vaccine*, *28*(4), 1002-1007.

Bottinger, M., & Forsgren, M. (1997). Twenty years' experience of rubella vaccination in Sweden: 10 years of selective vaccination (of 12-year-old girls and of women postpartum) and 13 years of a general two-dose vaccination. *Vaccine*, *15*(14), 1538-1544.

Panagiotopoulos, T. et al., 1999. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. *BMJ (Clinical research ed.)*, 319(7223), pp.1462-7.

Vynnycky, E., Gay, N. J., & Cutts, F. (2003). The predicted impact of private sector MMR vaccination on the burden of Congenital Rubella Syndrome. *Vaccine*, *21*(21-22), 2708-2719.

Rohani, P., Earn, D. J., & Grenfell, B. T. (2000). Impact of immunisation on pertussis transmission in England and Wales. *Lancet*, *355*(9200), 285-6.

A good mathematical but also practical approach can be found in the early chapters of Infectious Diseases of Humans: Dynamics and Control. by Anderson and May.

Unused slides

The effect of vaccination on the age-susceptibility profile: a simple model calculation

In endemic equilibrium, prevalence only changes with age (not with time). Hence, for the susceptible population:

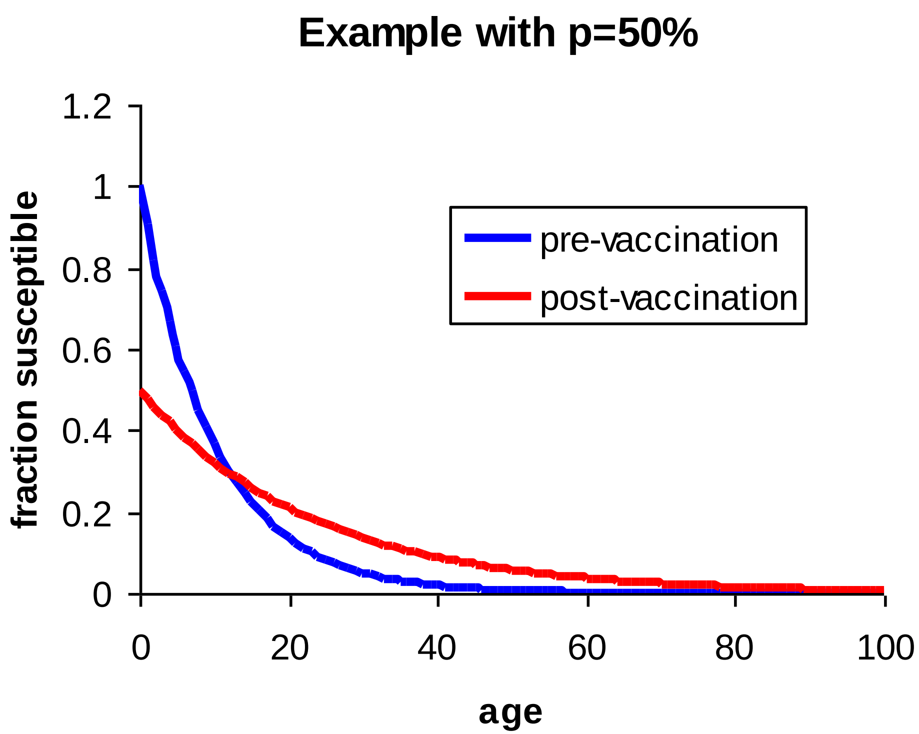
$$\frac{dX}{da} = -\lambda X - \mu X$$

	Pre-vaccination:	Post-vaccination:
Vacc.	$X(0) = 1$	$X(0) = (1 - p)$
FOI	$\lambda = \frac{1}{A} = R_0 \frac{1}{L} = R_0 \mu$	$\lambda^* = \frac{1}{A^*} = R_0 \frac{(1-p)}{L} = R_0 (1-p) \mu$

Vaccination and age-susceptibility profiles

Pre-vaccination: $$\text{Susc. fraction} = \exp(-(\mu R_0 + \mu)a)$$

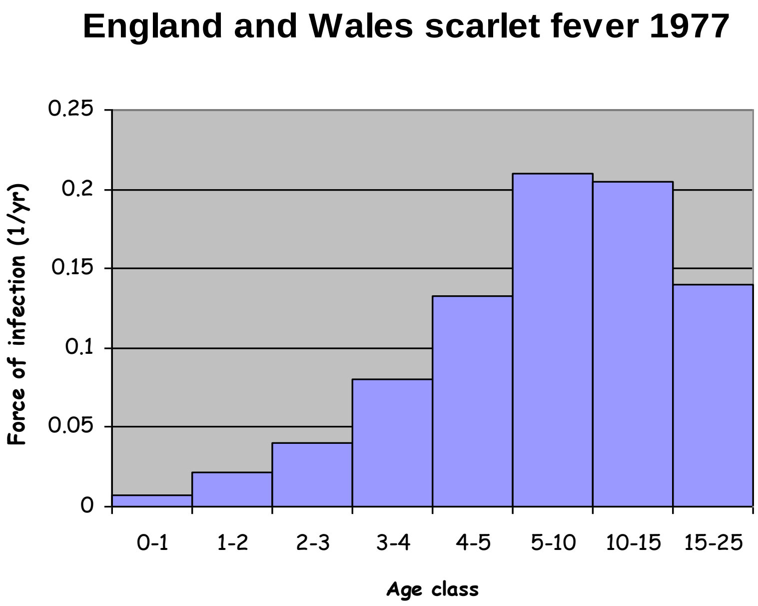
Post-vaccination: $$\text{Susc. fraction} = (1-p)\exp(-(\mu(1-p)R_0 + \mu)a)$$

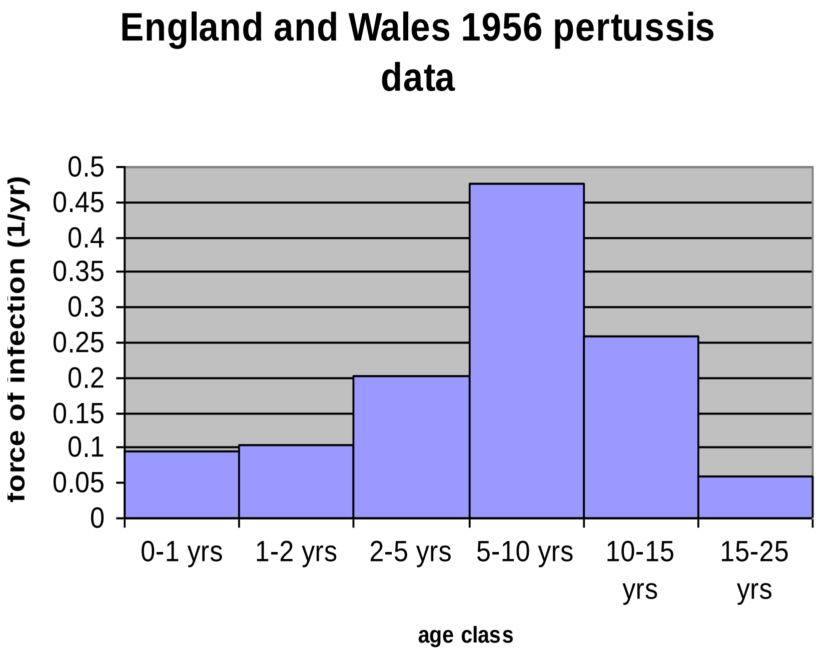


Ratio of risk =
$$(1-p)^2 \exp(\mu R_0 pa)$$

Empirical evidence for age heterogeneity

For childhood diseases, studies measuring the force of infection have shown that it is age-dependent





The effects of immunization programmes and other observed patterns cannot be reproduced with models without introducing age heterogeneity

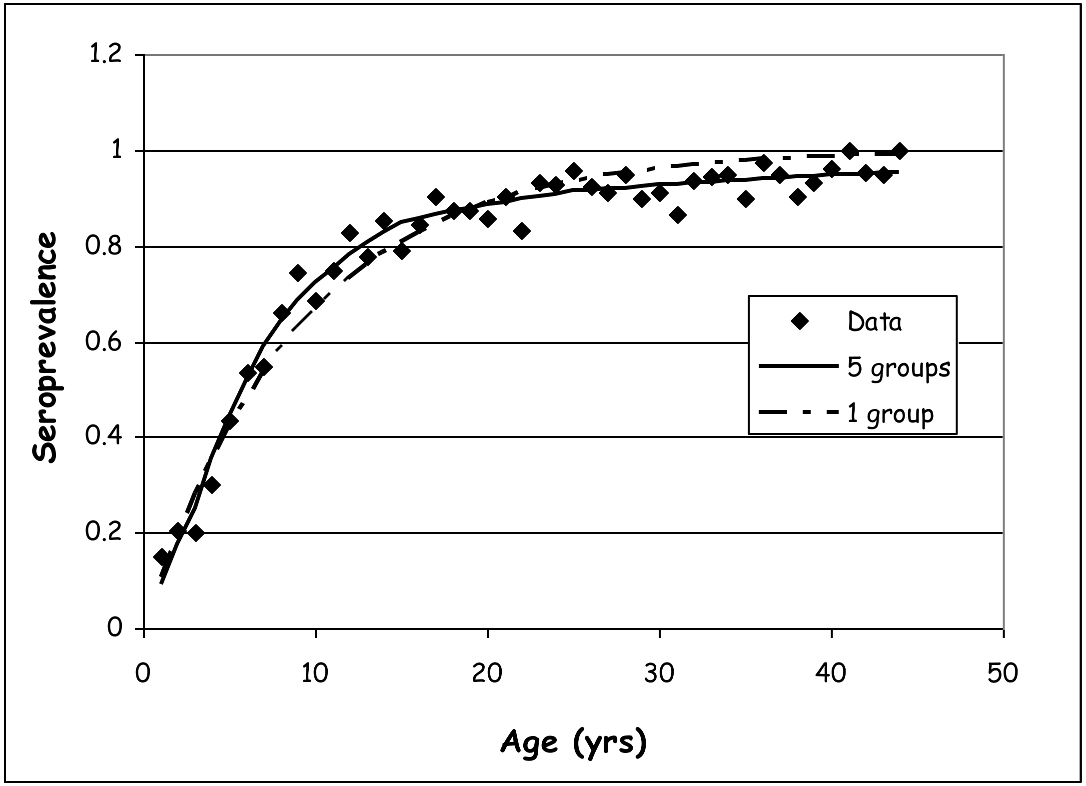
Example: Seroprevalence data by age for Rubella, 1987 (Farrington, 2001)

$$\bar{\lambda}(A_0, A_1) = \frac{1}{A_1 - A_0} \ln\left[\frac{1 - p(A_0)}{1 - p(A_1)}\right]$$

Results of fitting

Homogeneous mixing:
λ=0.11/yr

Heterogeneous mixing:
0-3 yrs: λ=0.098
3-8 yrs: λ=0.15
8-15 yrs: λ=0.12
15-25 yrs: λ=0.056
25+ yrs: λ=0.033

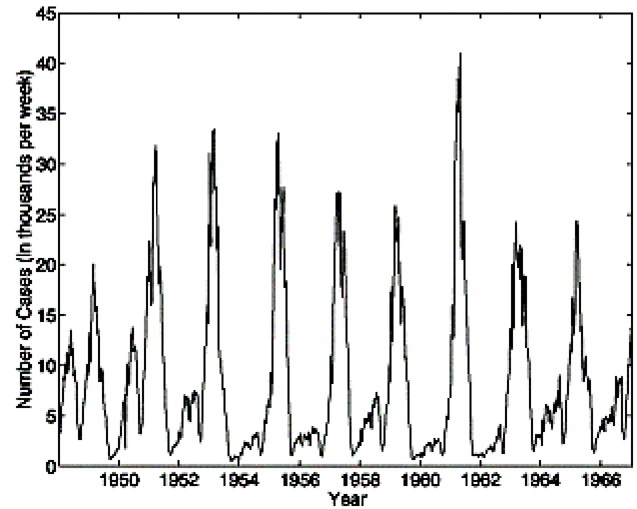


Steeper curve at younger ages and flatter at older ages reflects the stronger contact among children at school compared to adults.

Periodicity in incidence

- Incidence rates are usually highly variable over time.
- A range of periods are observed (annual, biennial, 3, 4, 5…)
- Behaviour often varies over longer time periods.
- Sometimes, behaviour appears random

Measles, UK



Mumps, Denmark