The impact of vaccination on the epidemiology of infectious diseases

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- Basic epidemiological principles.
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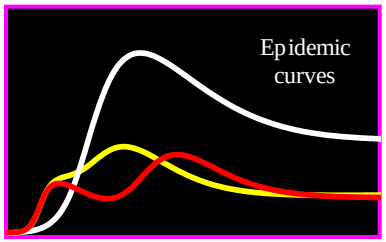
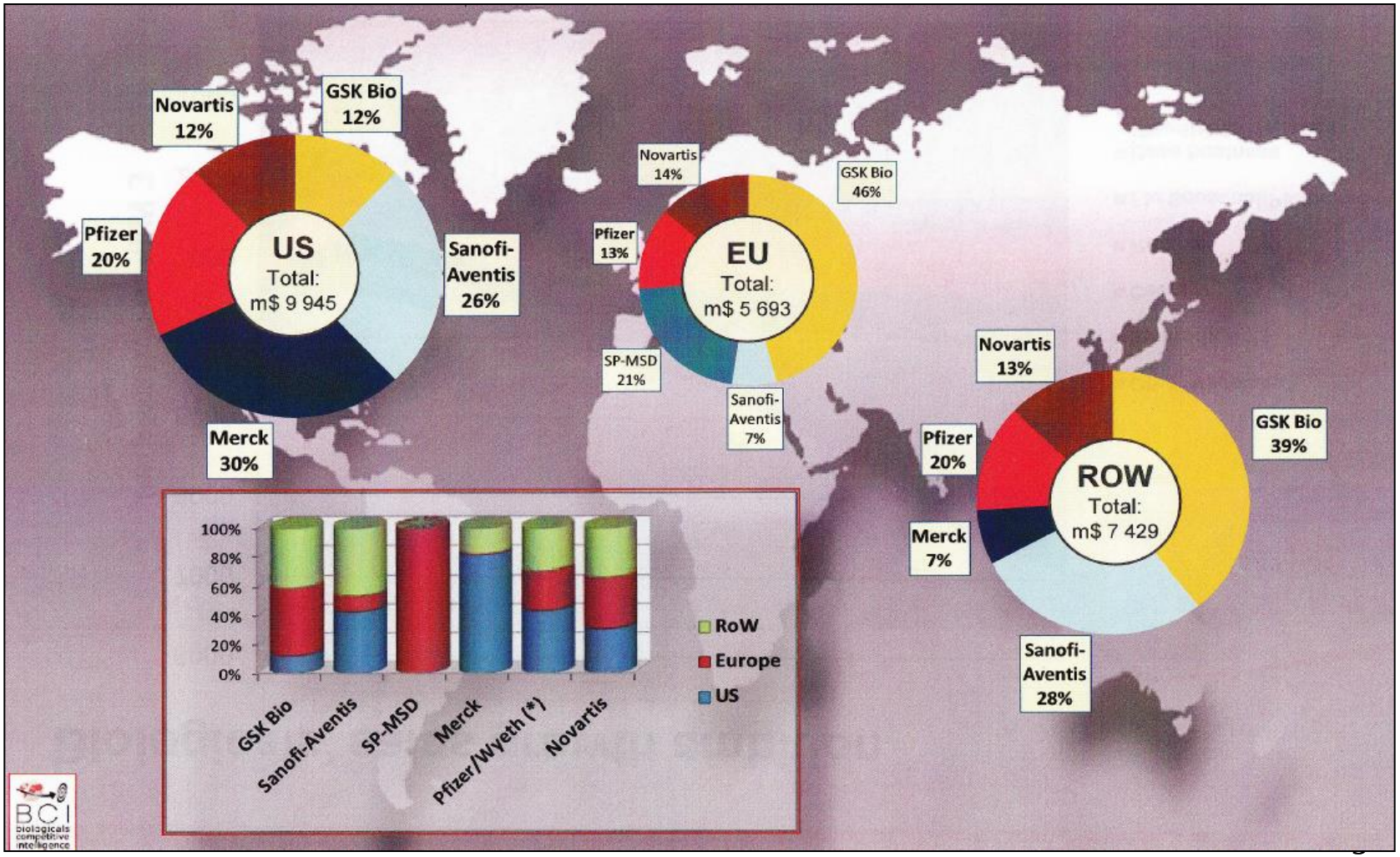
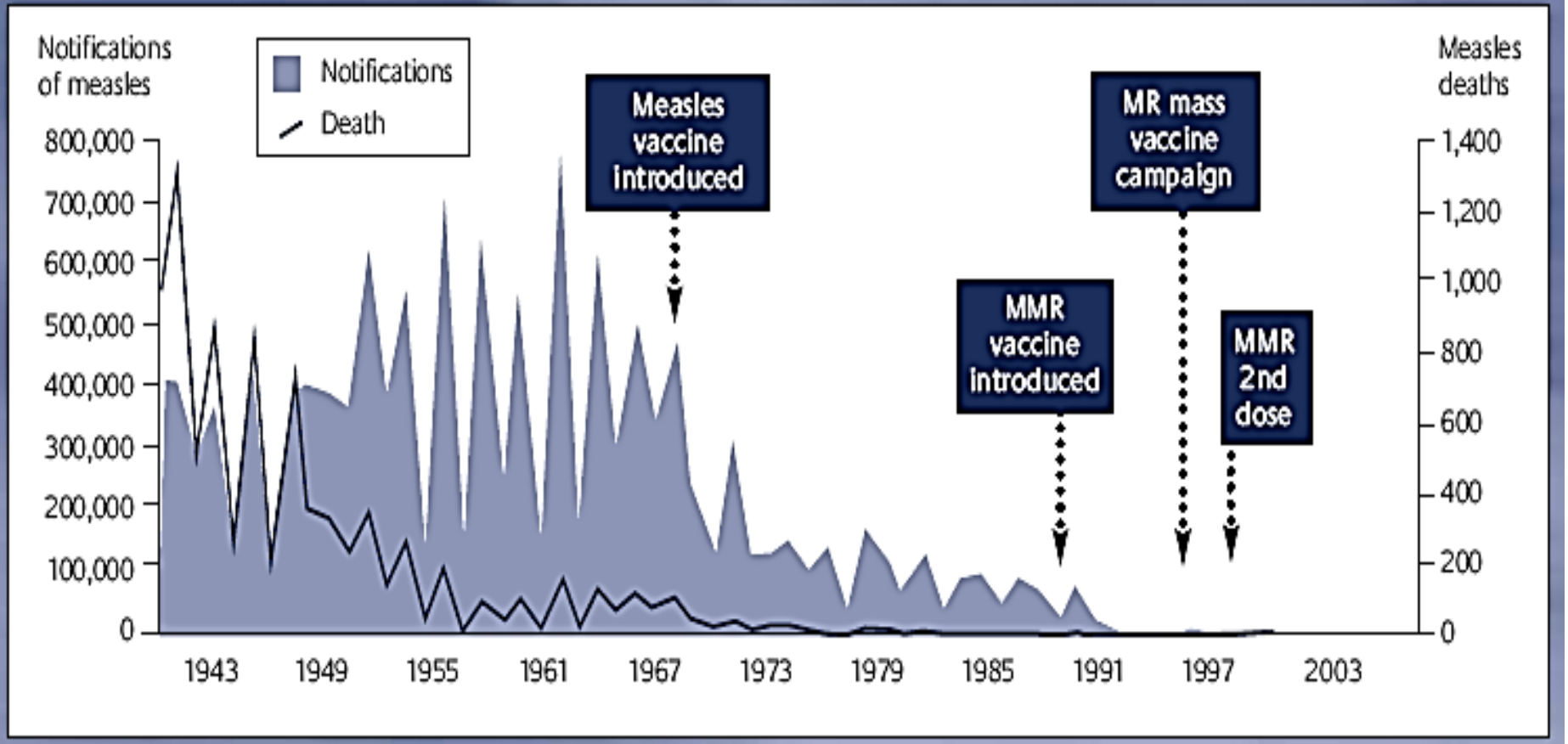


Geographical distribution of vaccine market share 2012-13



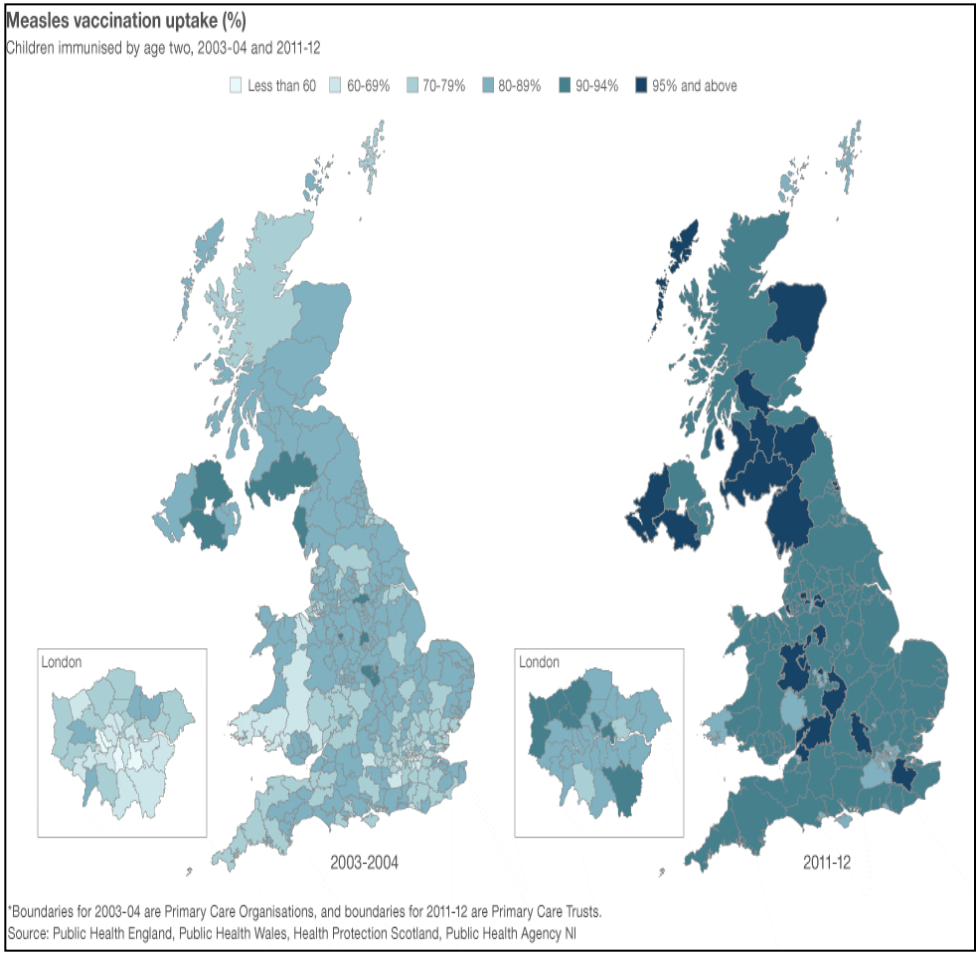
Great success - Measles – England & Wales

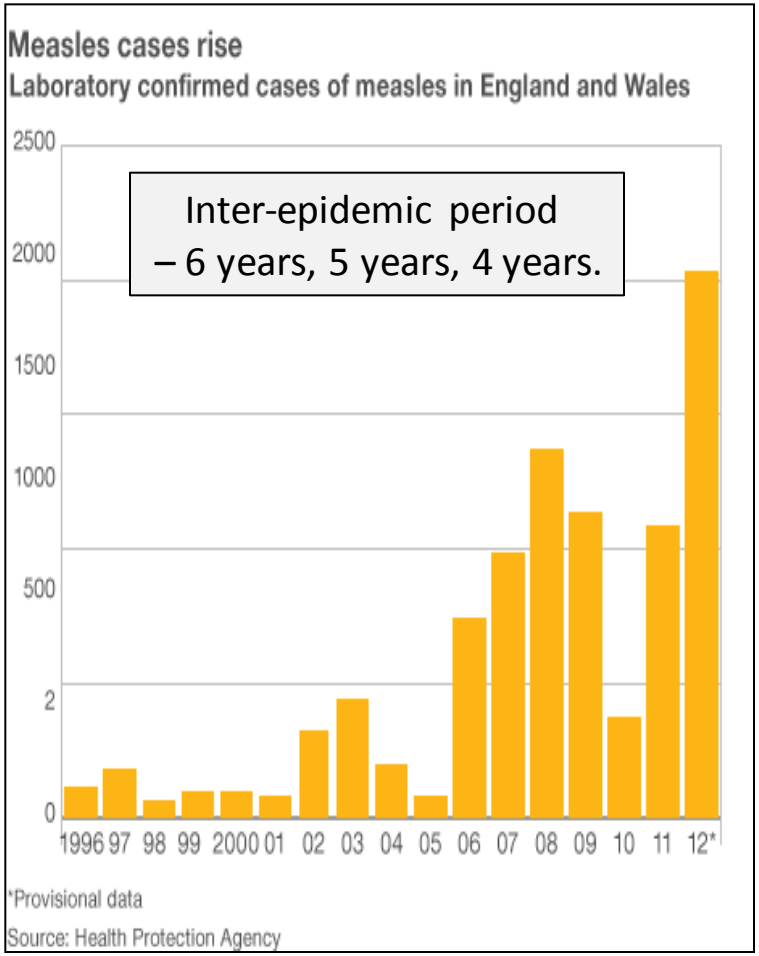
FIGURE-18 Notifications and deaths from measles in England & Wales, 1940-2002. Source: registrar General's Annual returns, ONS, CfI



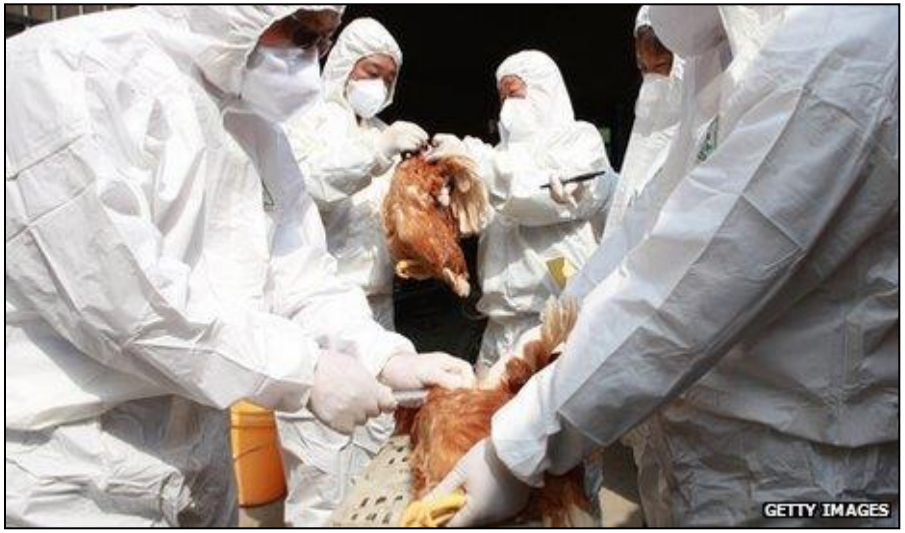
Measles epidemic in the UK - 2013

The media furore - started by a controversial paper published in the Lancet in 1998 (Wakefield et al) which raised fears about a link with autism (which has since been comprehensively discredited) - led to panic among parents



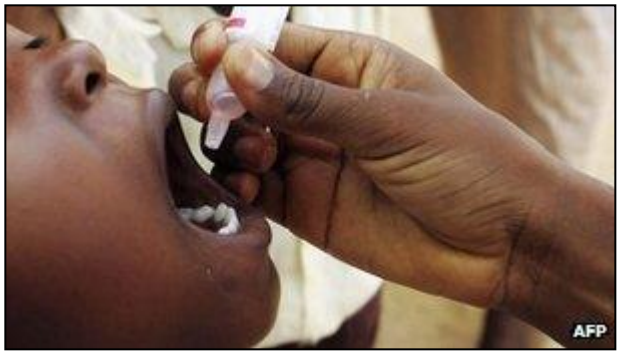


Events:- 2013-14



The new strain of bird flu H7N9 in China has infected more than 128 people in just over one month and killed 26 of those.

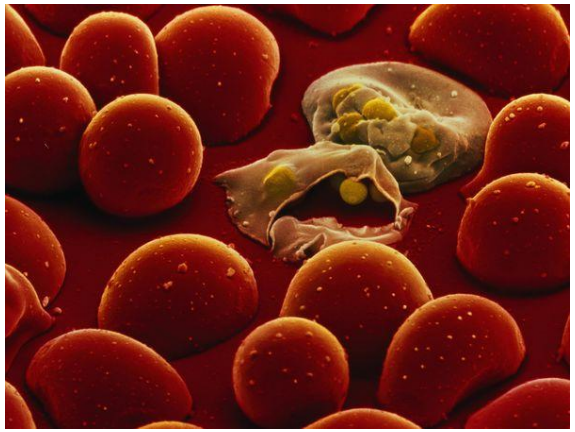
The H7N9 virus has not yet proved able to spread between people, but it has displayed two of the five mutations required for that to happen, making it a small step closer to becoming a pandemic than any previous flu variant.



polio vaccinators shot dead in Kano, Nigeria and Pakistan

Nigeria is one of only three countries (Pakistan and Afghanistan are the others) where polio is still endemic Nine female polio vaccinators have been killed in two shootings at health centres in northern Nigeria

Malaria vaccine (RTS,S) candidate reduces disease over 18 months of follow-up in late-stage study of more than 15,000 infants and young children



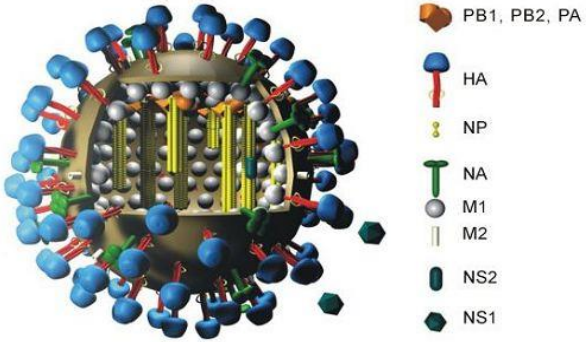
Results from ongoing Phase III clinical trial announced

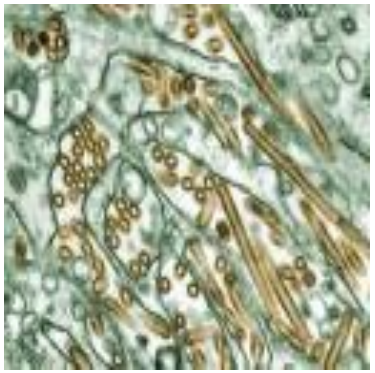
Further results from the Phase III efficacy trial of the RTS,S malaria vaccine candidate were presented on Tuesday, 8 October 2013, at the 6th Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference in Durban, South Africa. These latest results demonstrated that over 18 months of follow-up, RTS,S was shown to almost **halve** the number of malaria cases in young children (aged 5-17 months at first vaccination) and to reduce by around **a quarter the malaria cases in infants** (aged 6-12 weeks at first vaccination) in a study of 15,000 children and infants.

Health and Economic Impact of Seasonal Influenza A vaccination programme in England

Vaccine 30 May 2012 3459-62 Baguelin, Miller and Edmonds

Seasonal influenza vaccination impact was assessed with a transmission model. Vaccination is substantially reduce disease burden. The current programme is cost-effective when the vaccine is well matched

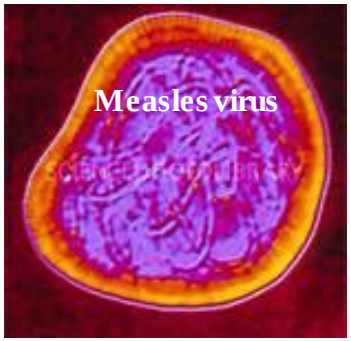




Conclusion

The current seasonal influenza vaccination programme appears to substantially reduce disease burden and provides good value for money.

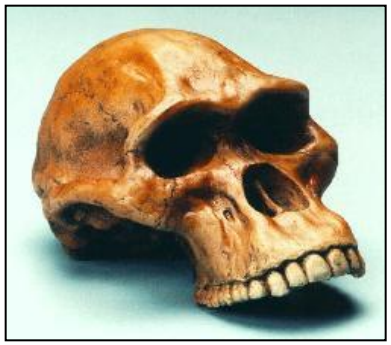
Genetic variation spectrum of pathogens

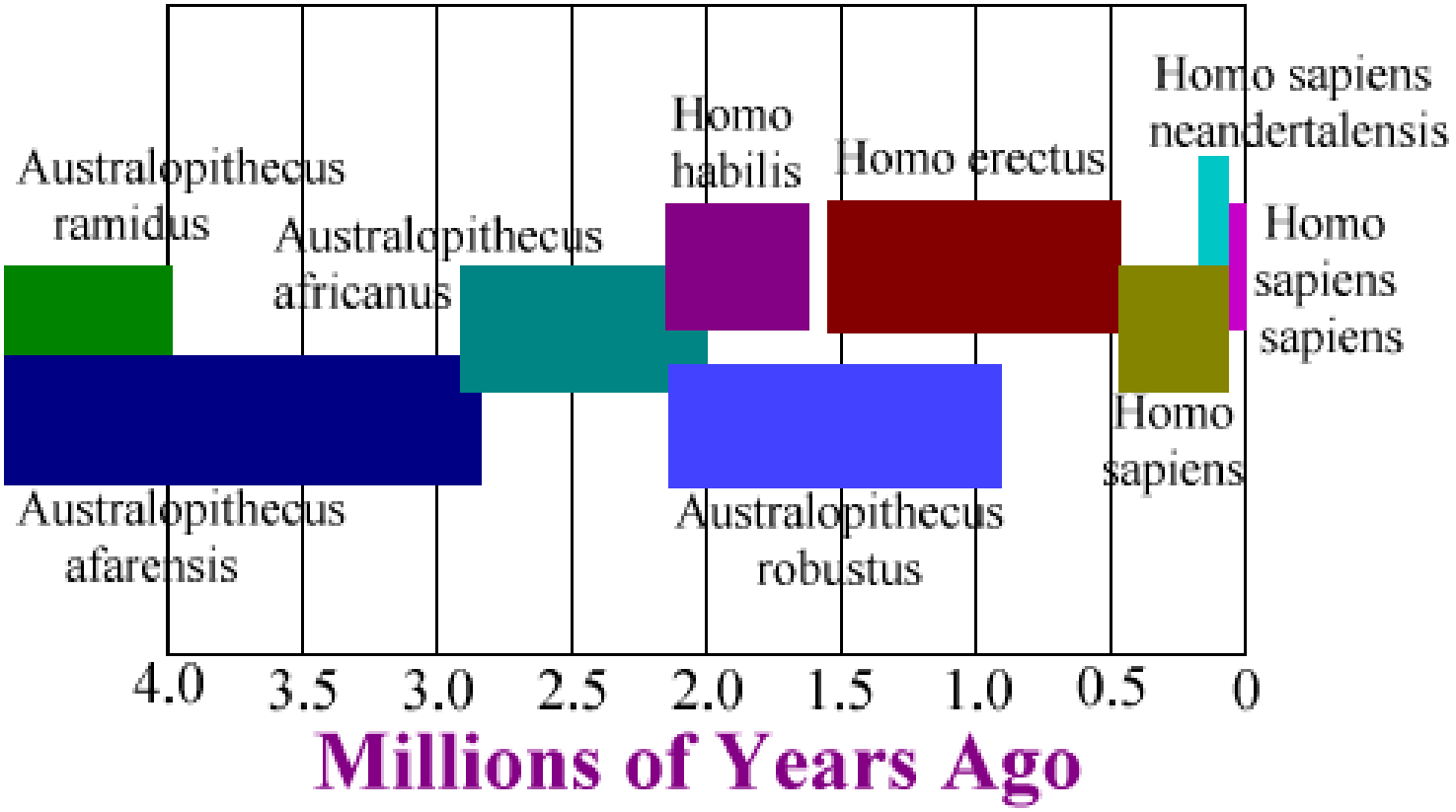


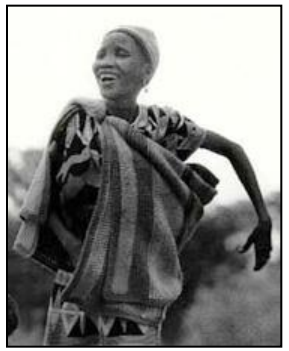
Relatively homogeneous ***Great heterogeneity***

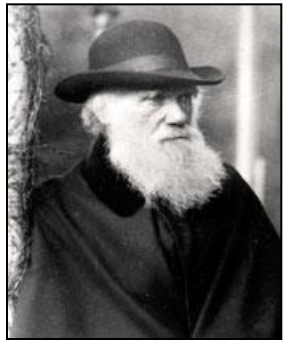
Measles virus	Bordetella	Dengue	Pneumococcal	HIV
Mumps virus			RSV	Malaria
Rubella virus			Rotavirus	
			HPV	
			Influenza A & B	

Human evolution

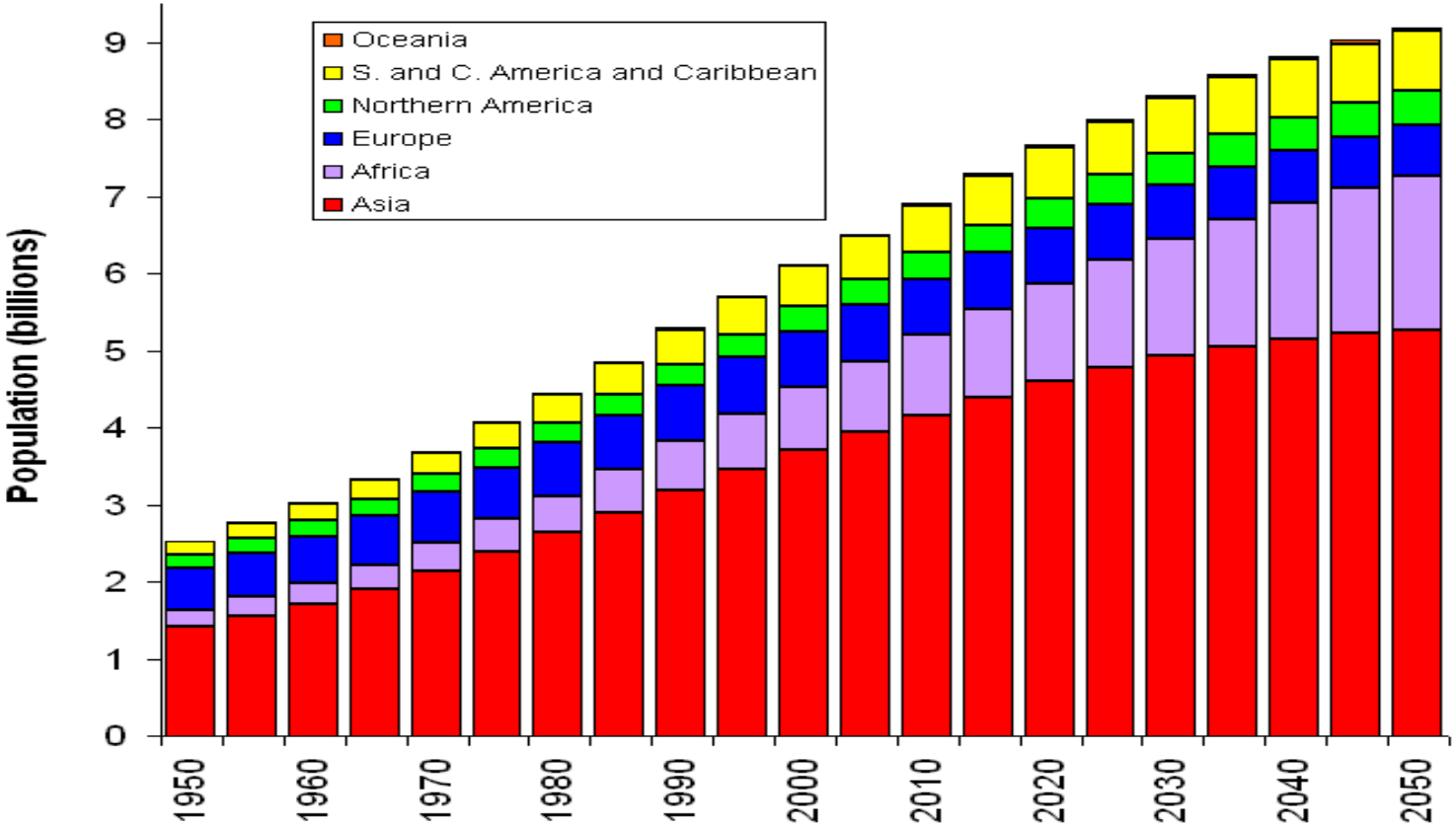






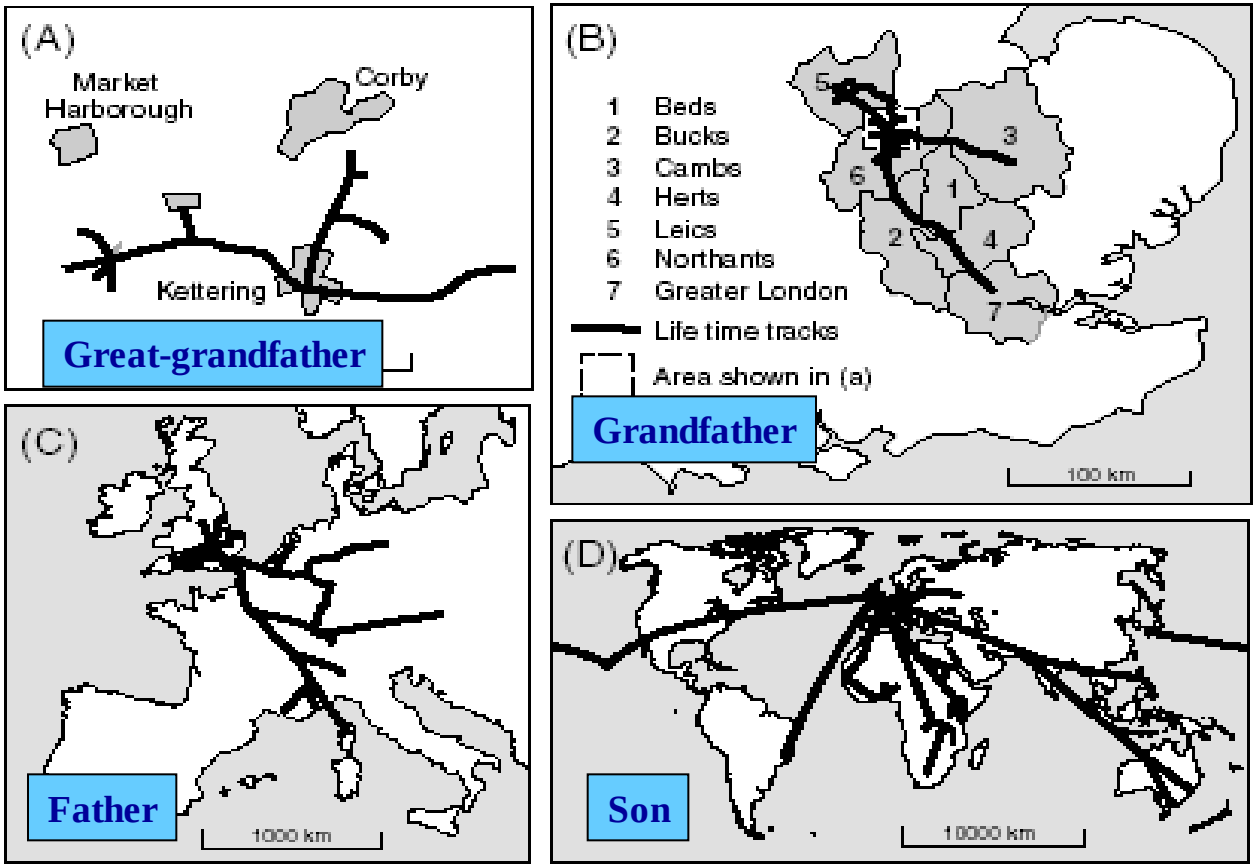


World population growth by continent: past and predicted



Record of increasing travel over four male generations of the same family.

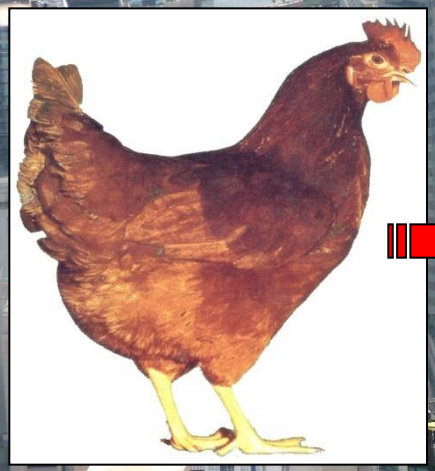
(A) Great-grandfather. (B) Grandfather. (C) Father. (D) Son. Each map shows in a simplified manner the individual's 'life-time tracks' in a widening spatial context, with the linear scale increasing by a factor of 10 between each generation (Bradley, 1994 Geog. Ann. 76:91-104).

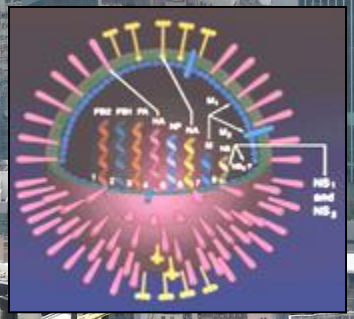


Air traffic flow – world picture - 2009

Hong Kong

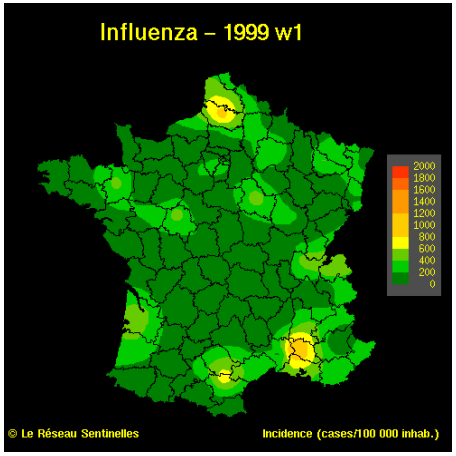
Re-assortment of bird and human influenza viruses

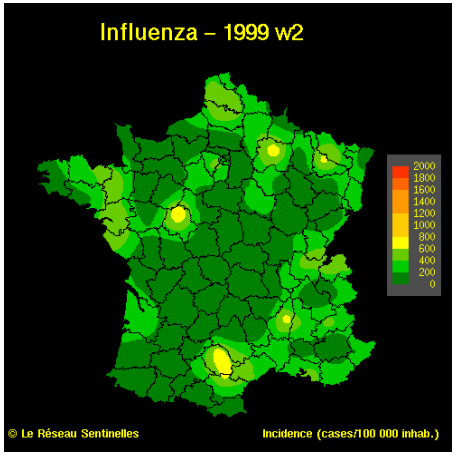


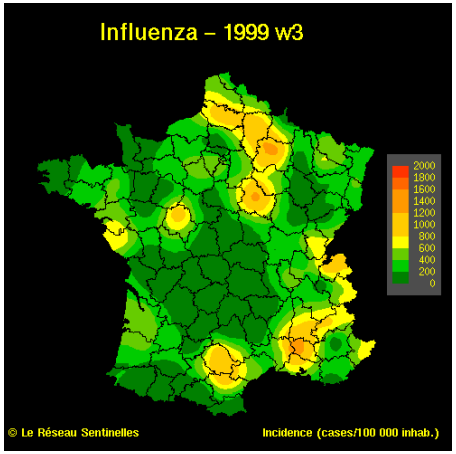


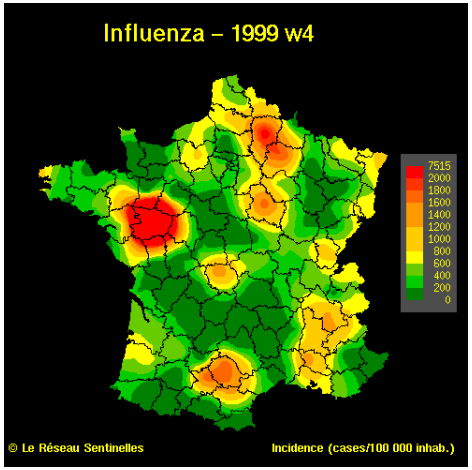
Less Developed Regions	1970	1994	2000	2015
Africa	0	2	2	3
Asia	2	10	12	19
Latin America	3	3	4	5
More Developed Regions				
Europe	2	2	2	2
Japan	2	2	2	2
North America	2	2	2	2

Surveillance - spatial dynamics of influenza A in France









http://www.b3e.jussieu.fr/ sentiweb/en/sommaire.html

French sentinel system for influenza case reporting.

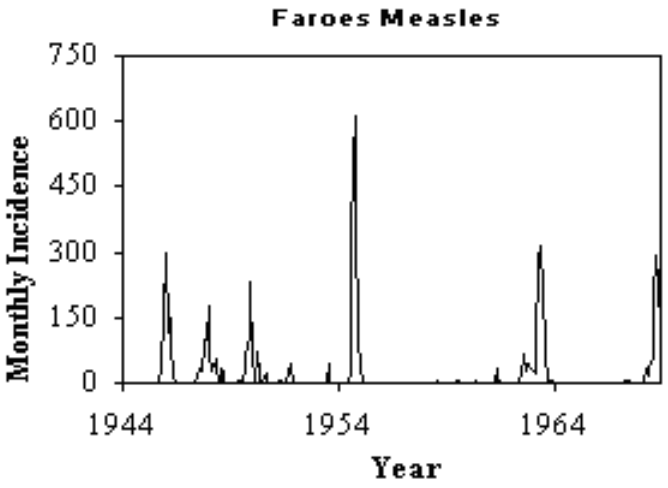
Very rapid spread seen over a period of 4 reporting weeks.

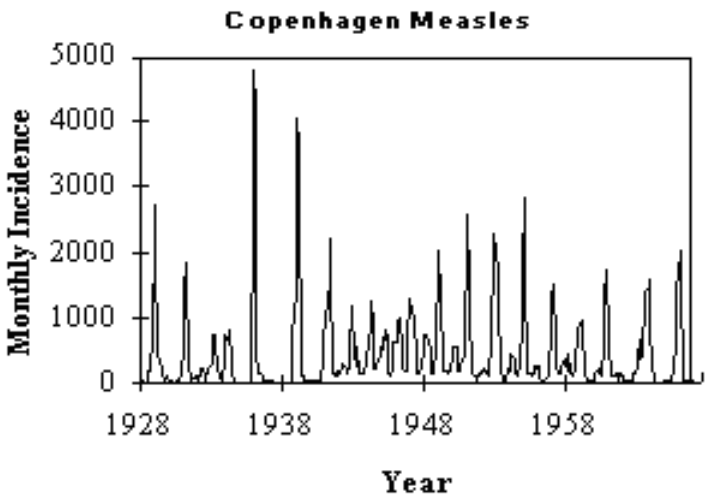
Daniel Bernoulli - 1700 to 1782

D. Bernoulli (1760)
used a simple mathematical model to evaluate the effectiveness in reducing mortality of variolation to protect against smallpox.

Daniel Bernoulli was one of a number of early mathematicians who turned their skills to probability problems raised by gamblers - at the card tables in Monte Carlo!
(e.g. C. Huyghens 1657).

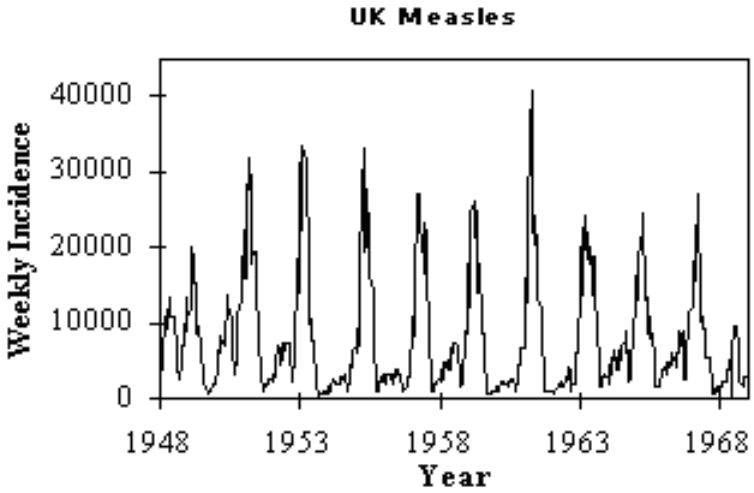
Stochasticity & persistence





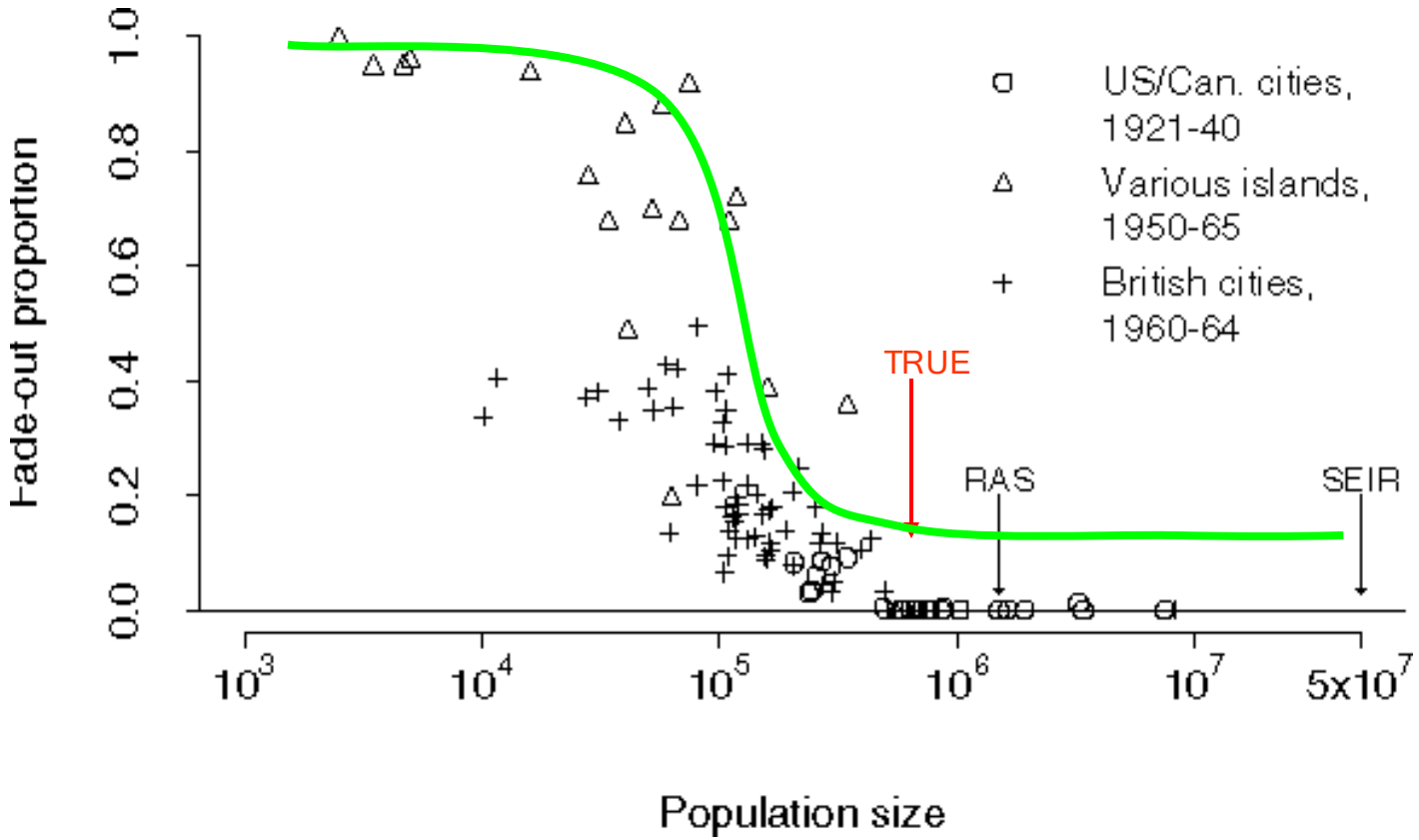
Disease extinction likely by chance when number of infectives falls to very low numbers.

- so extinction more frequent as population size decreases and cycle amplitudes increase.

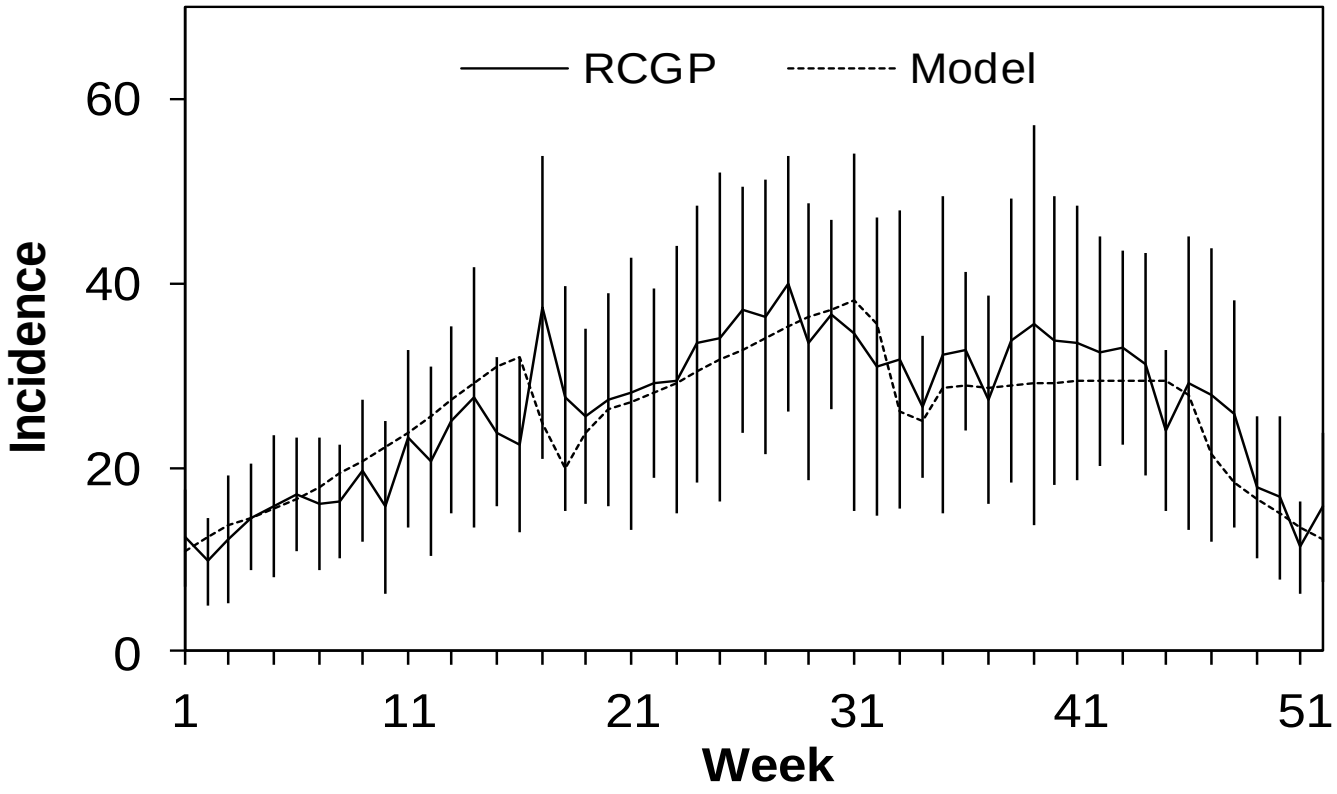


Critical community size

Minimum population size at which measles fadeouts (proportion of weeks with no cases) become rare.

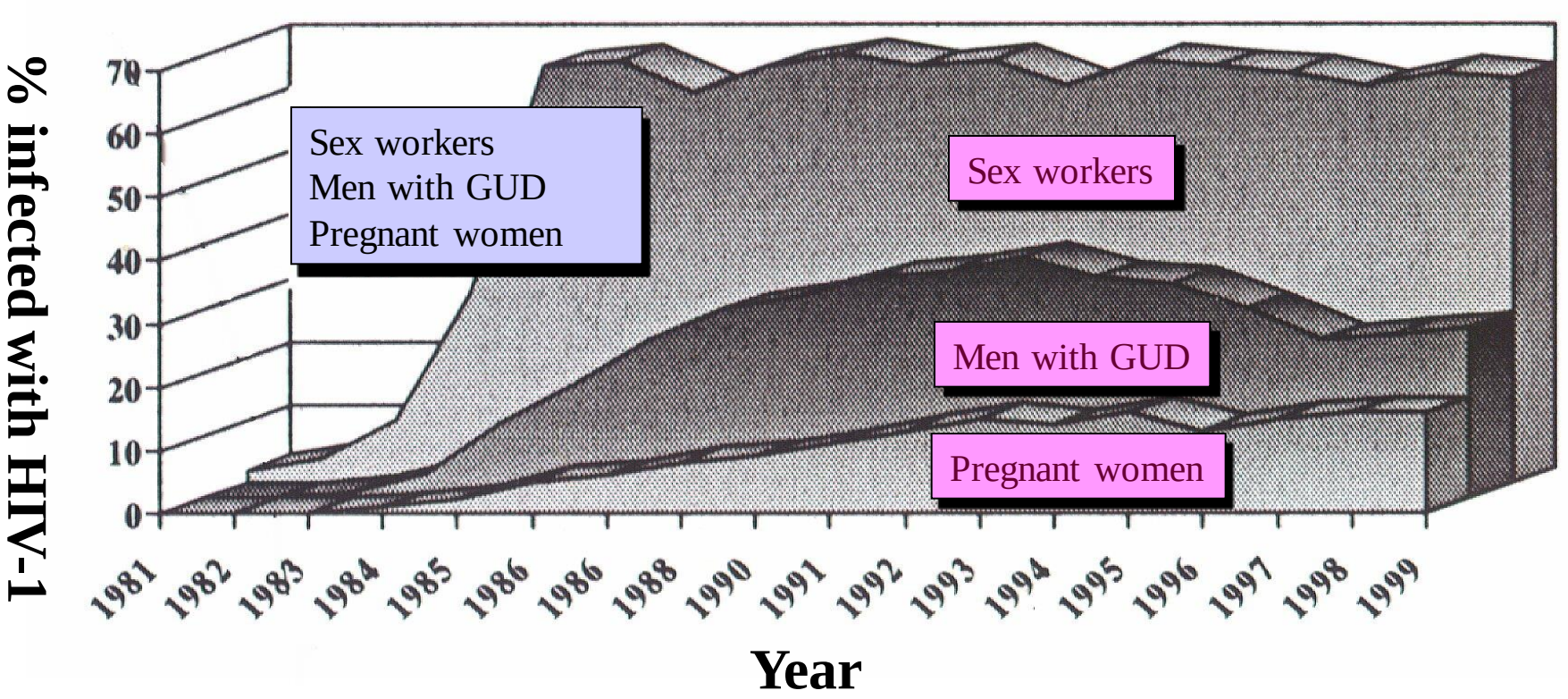


Seasonality in transmission of measles – school holidays



Confidence bar

HIV-1 prevalence in Nairobi, Kenya 1981-1999 – stratified by risk group



Basic principles in Infectious Disease Epidemiology

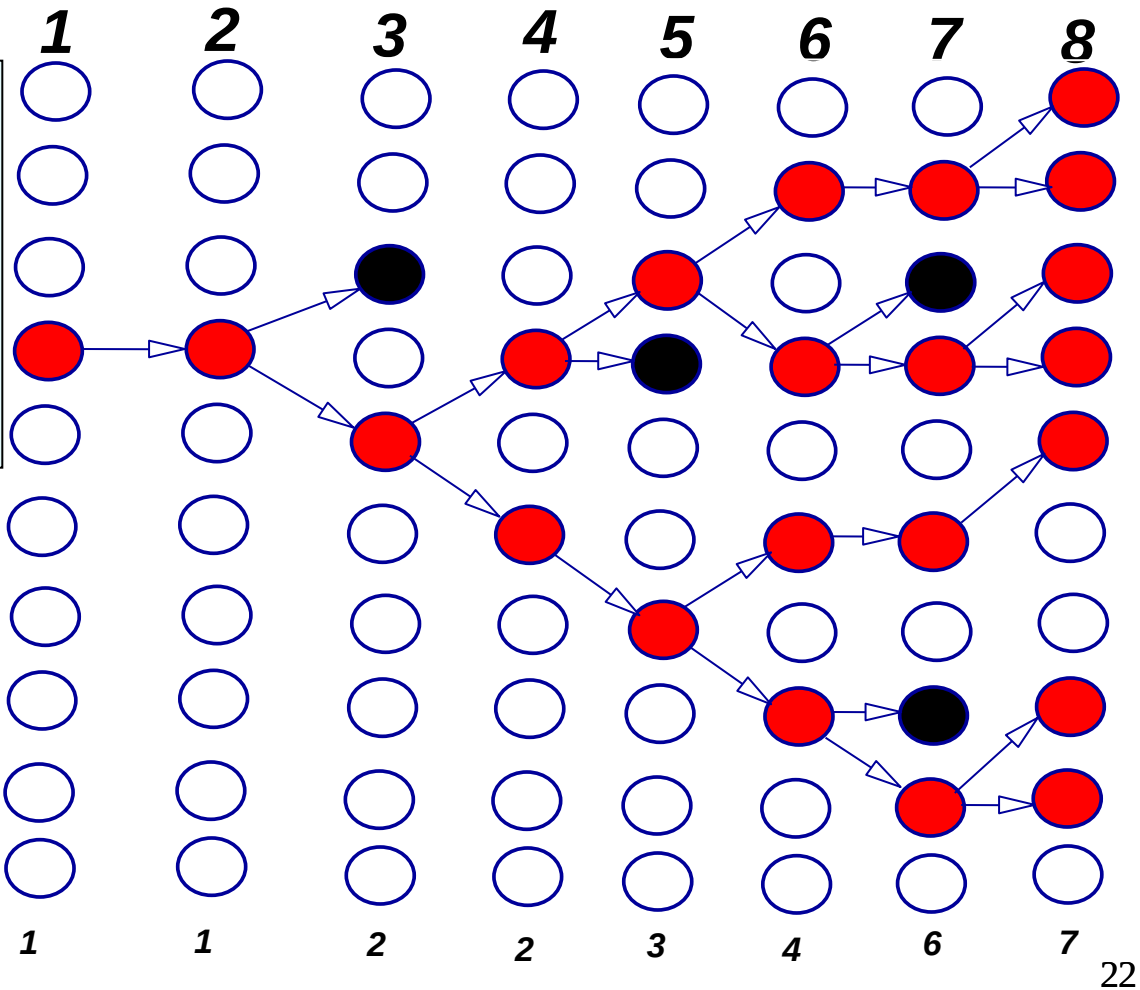
- The key determinant of incidence and prevalence of infection is the basic reproductive number $\mathbf{R_o}$.

- $\mathbf{R_o}$ measures the average number of secondary cases generated by one primary case in a susceptible population

- Many factors determine its magnitude, including those that influence the typical course of infection in the patient and those that determine transmission between people.

Basic Reproductive number, R_o

Chains of transmission between hosts

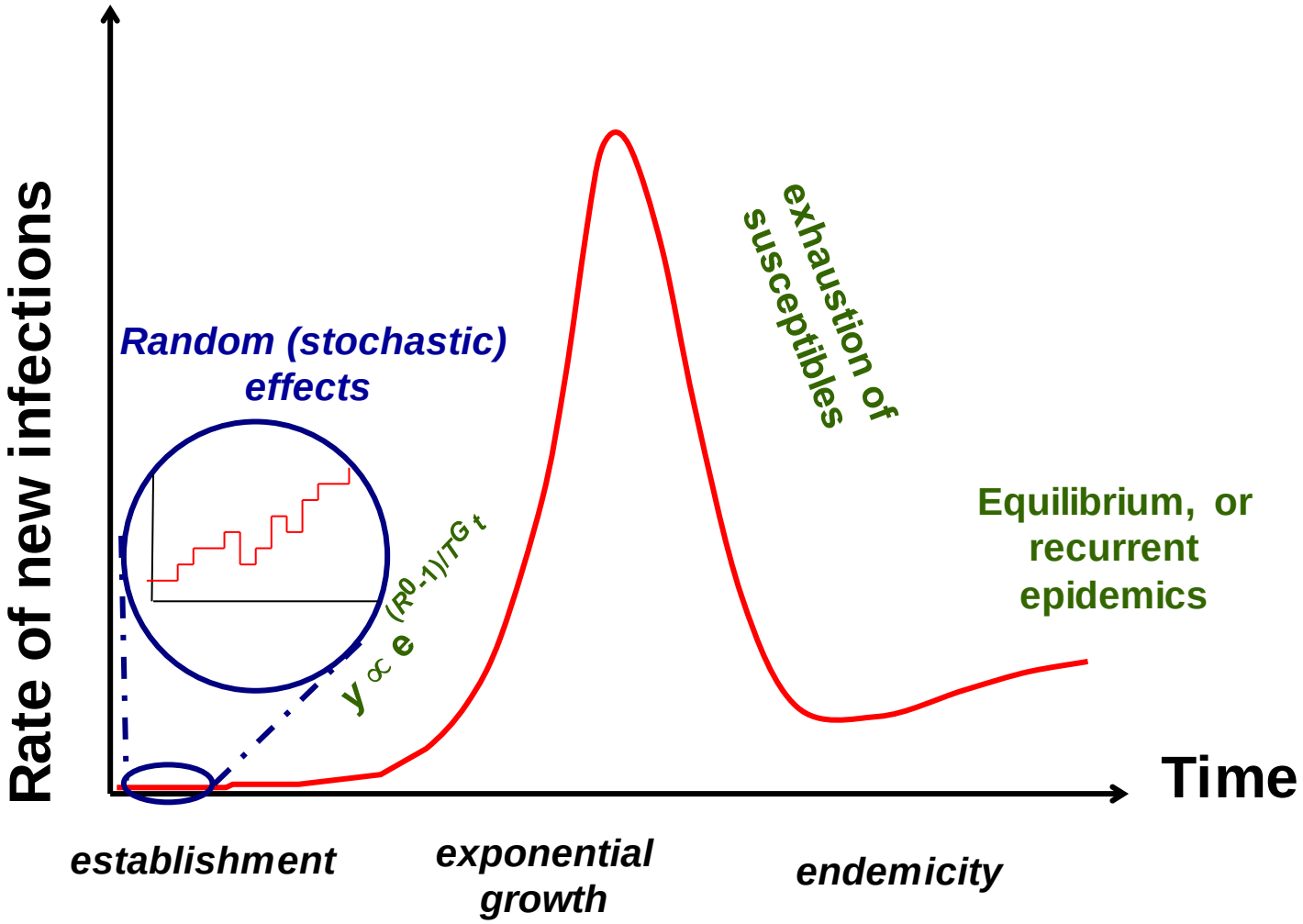


R_0 Basic reproduction number average no. of secondary cases generated by 1 primary case in a susceptible population

R_t Effective reproduction number number of infections caused by each new case occurring at time, *t*

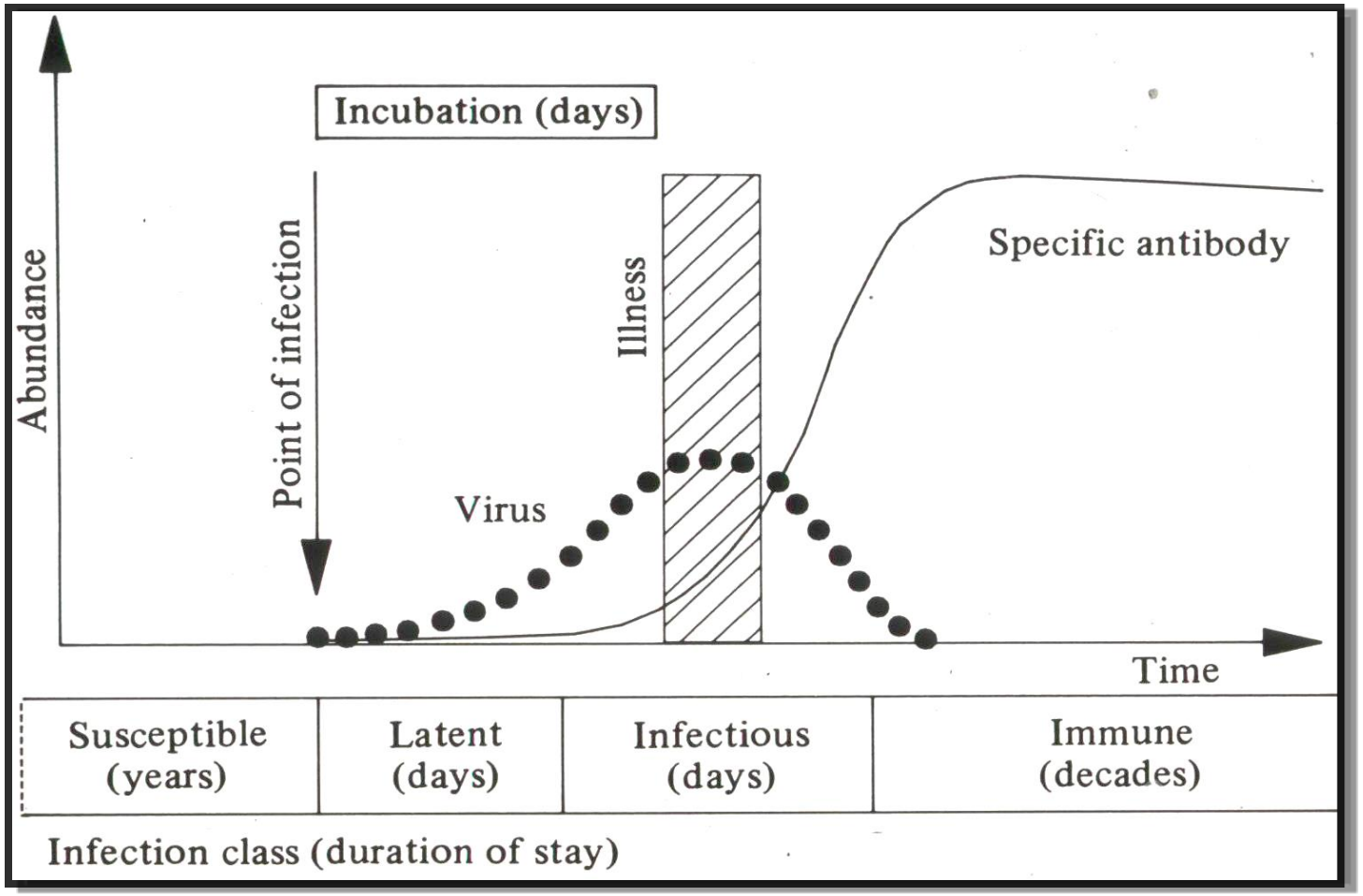
- The key determinant of incidence and prevalence of infection is the basic reproductive number R_o.
- Many factors determine its magnitude, including those that influence the typical course of infection in the patient and those that determine transmission between people.

The epidemic curve



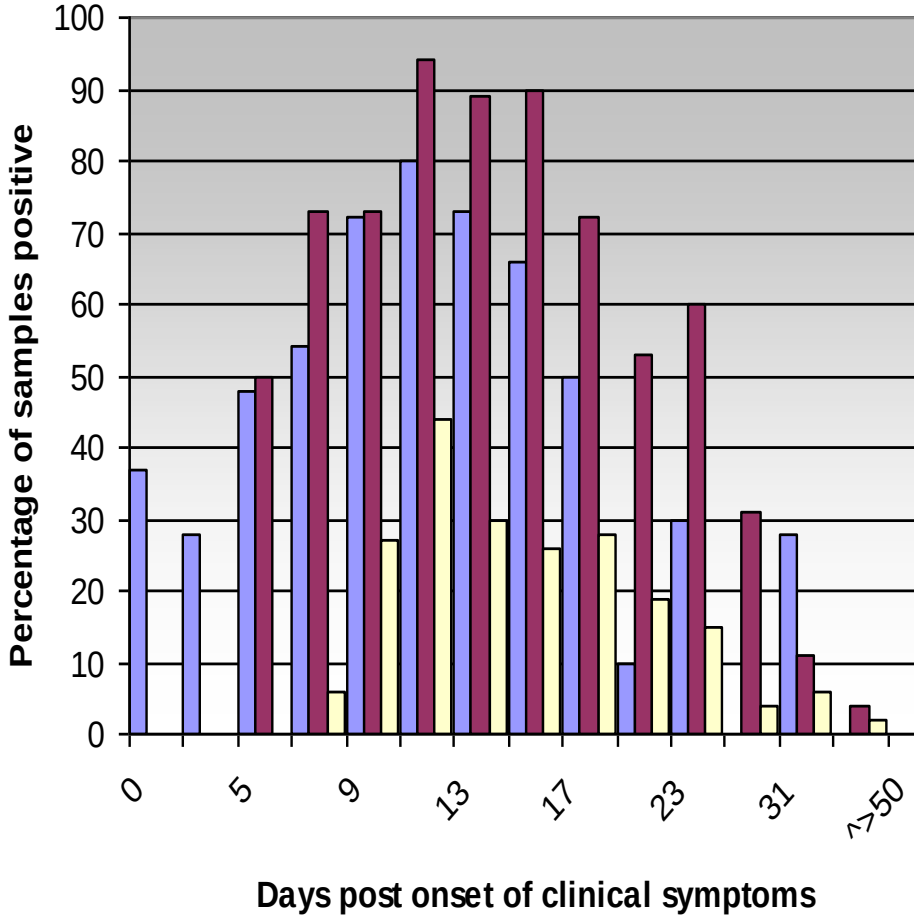
Typical course of infection within the host

Estimation of average latent & infectious periods plus distributions



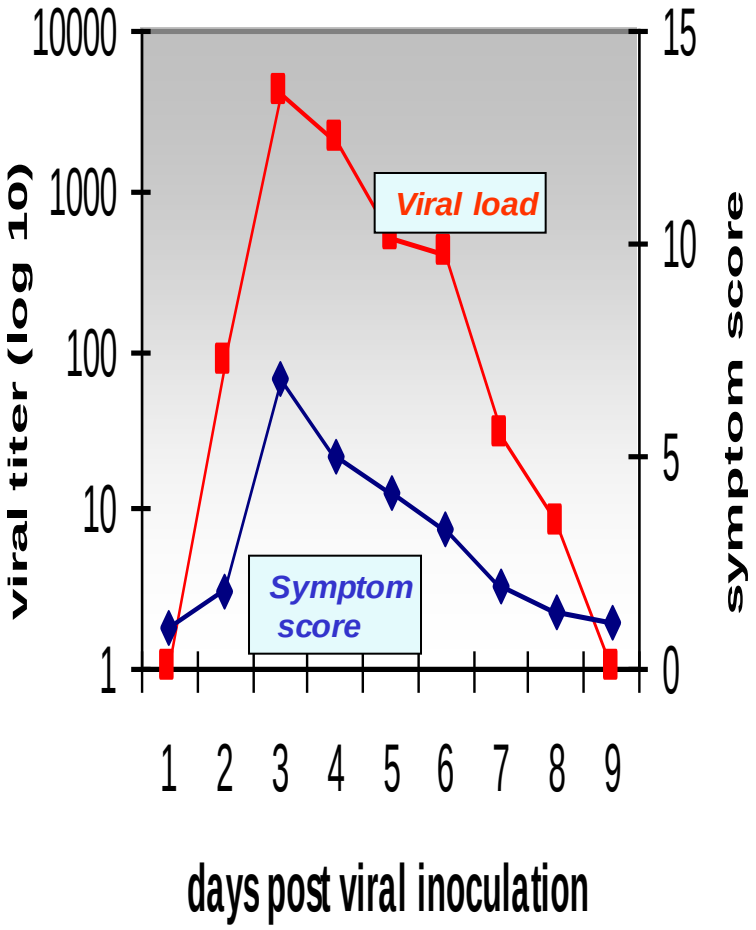
The typical course of infection

SARS CoV



Peiris et al (2003)

Influenza A



* Hayden et al. (1998) *J. Clin Invest* 101 p643
Experimental human influenza A/Texas/36/91 (H1N1) intranasal inoculation 10^5 dose

Transmission - directly transmitted viral and bacterial respiratory tract infections

For a directly transmitted viral infection that induces long lasting immunity post recovery R_o is given by; $R_o = \beta XD$

Where β is the probability of transmission on contact between infected and susceptible individuals, **X** is susceptible population density(influenced by the net birth rate and vaccine coverage) and **D** is the average duration of infectiousness.

Basic principles in Infectious Disease Epidemiology

- The magnitude of $\mathbf{R_o}$ varies according to location and population - it is strongly influenced by birth rate, population density and behavioural factors.

- The magnitude of $\mathbf{R_o}$ can be ascertained by cross sectional serological surveys.

What is Herd Immunity?

- The impact of the fraction immune in the community on the per capita rate of transmission of an infectious agent.
- The level of herd immunity can be measured by reference to the magnitude of reduction in the value of R_o.

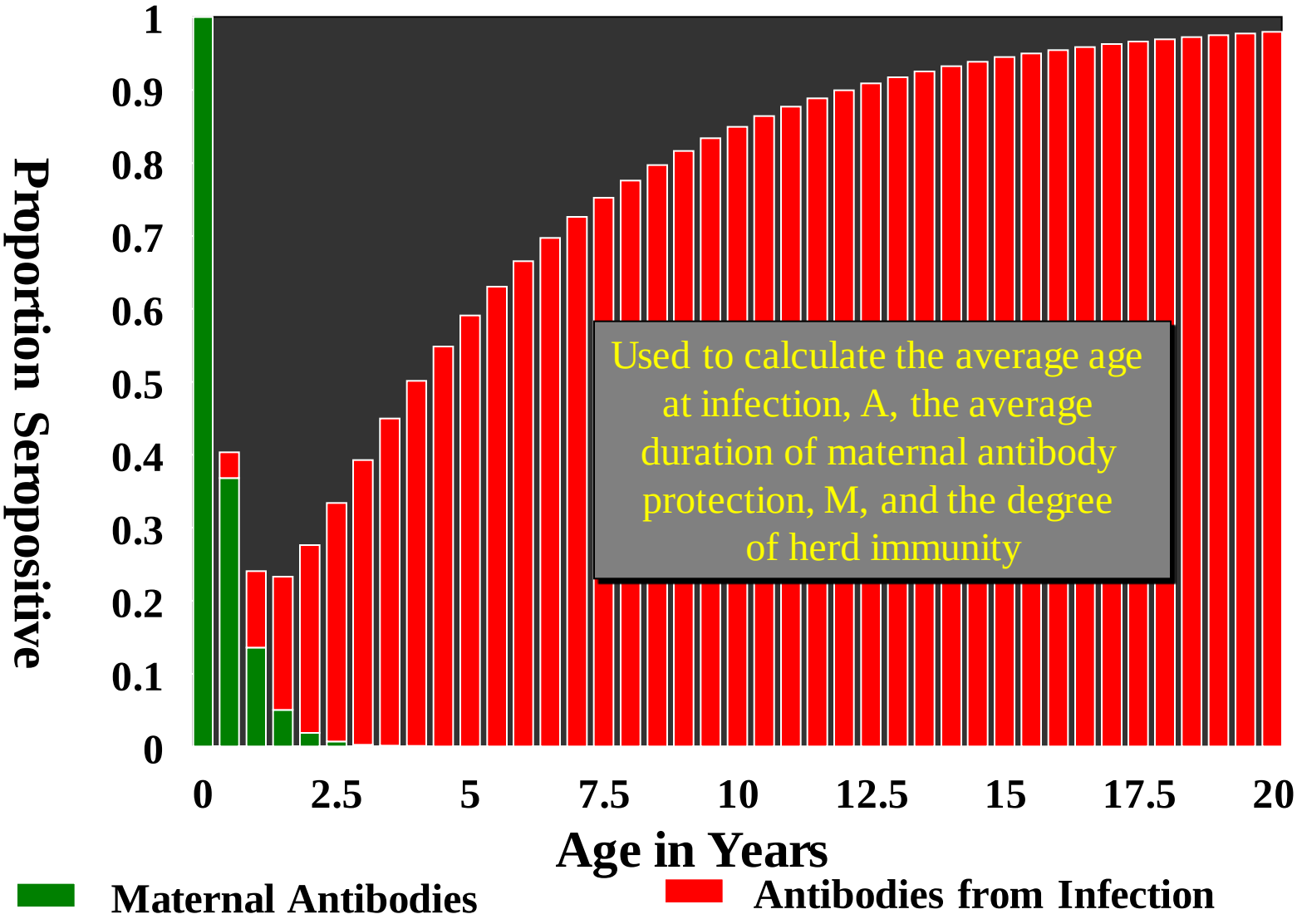
How can the degree of herd immunity and the magnitude of R_o be assessed?

- Cross-sectional and longitudinal serological surveys.
- Serum and saliva (viral infections).
- Activated T cells (bacteria and protozoa)?
- Quantitative assays.

Scientific methods in the study of herd immunity

- **Immunological** and **Disease Surveillance** methods provide the empirical base for analysis and interpretation.
- **Mathematical & statistical** methods play an important role in the analysis of infectious disease transmission and control.
- They help to define both what needs to be measured, and how best to measure define epidemiological quantities.

Age-specific serology - measles



Average age, A, at infection prior to immunisation

Infection	*Average age at infection, A*	*Location/time period*
Measles virus	5-6 years 2-3 years	USA 1955-58 Bangkok, Thailand 1967
Rubella virus	9-10 years	Sweden 1965
Varicella virus	6-8 years	USA 1921-28
Polio virus	12-17 years	USA 1920-60
Mumps virus	7-8 years	England & Wales 1975
Smallpox virus	10-15years	Bangladesh 1940

The calculation of the magnitude of R_o

A series of simple relationships exist between key epidemiological, demographic and vaccination programme related parameters.

The magnitude of $\mathbf{R_o}$ and the average at infection prior to mass vaccination, **A**, plus life expectancy in the population are related as follows

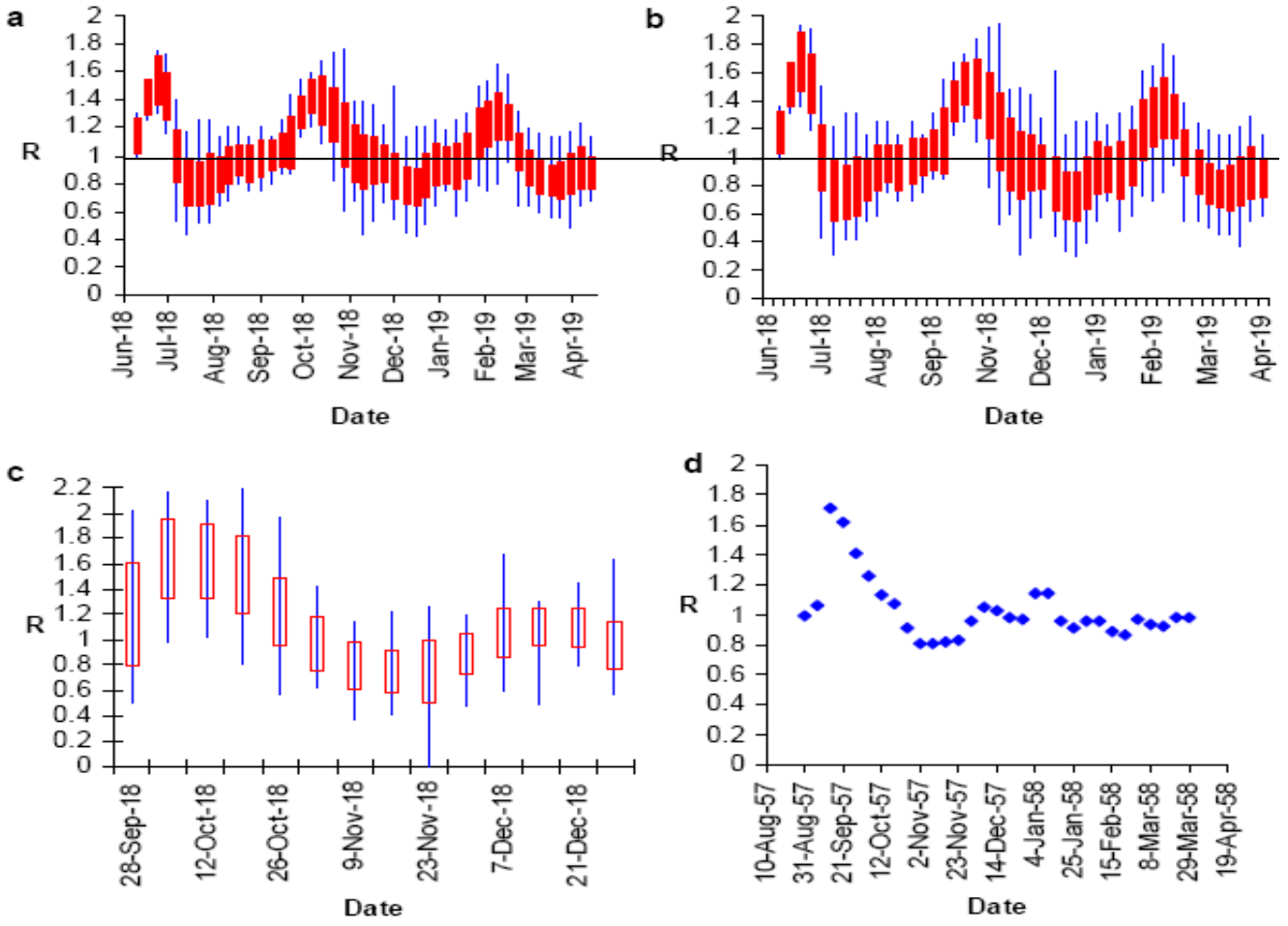
$$R_0 \cong (L - A)/(A - M)$$

Here, **M** is the average duration of maternal antibody protection (6 months) and **L** is life expectancy

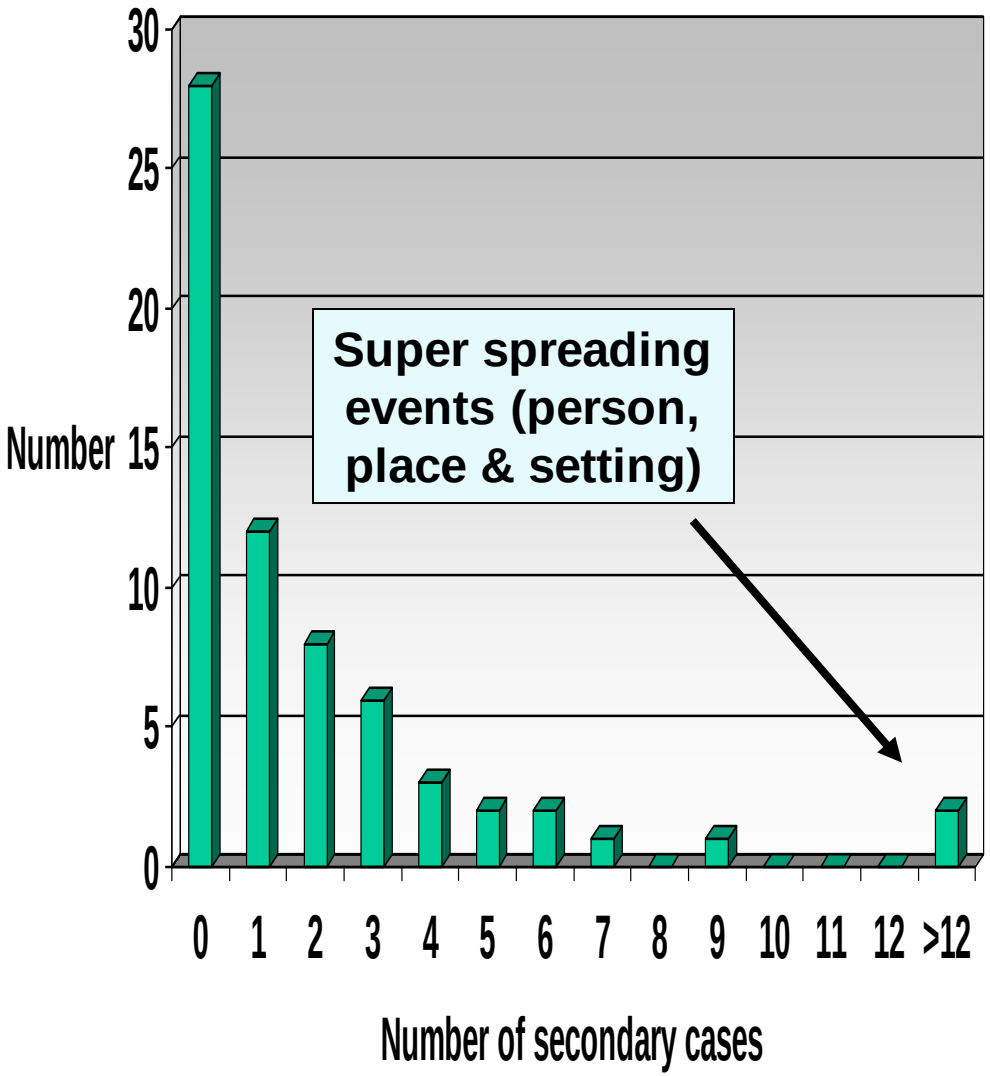
Estimates of the basic reproductive number, R_o

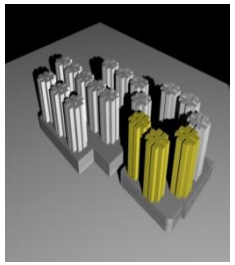
Infection	*Location*	*Time period*	R_o
Measles	England Canada	1947-50 1912-13	13-15 11-13
Varicella	USA	1943	7-8
Mumps	Netherlands	1970-80	11-14
Rubella	West Germany	1970-79	6-7
Polio	USA	1955	5-6
HIV-1	Nairobi, Kenya (sex workers)	1981-85	11-12
Smallpox	Bangladesh	1940	4-6
Influenza A (H1N1)	England	2010	1-1.5

Estimation of R_0 from past influenza A epidemics

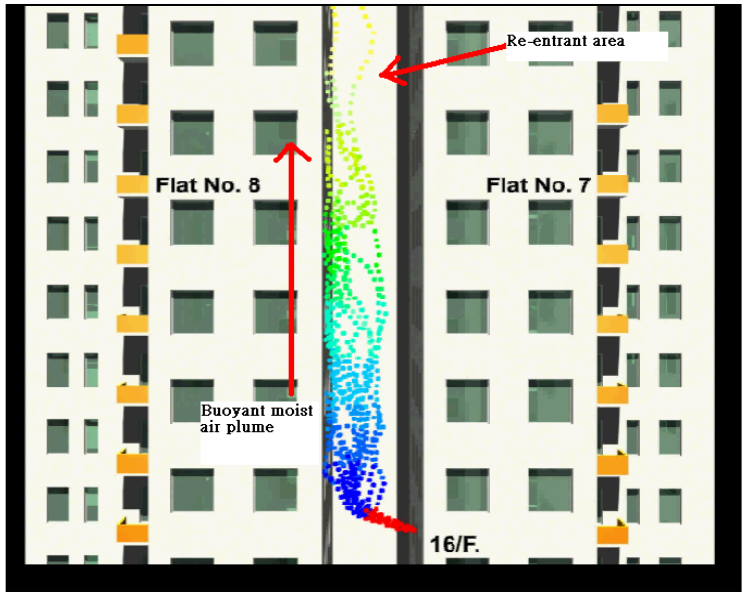


SARS - distribution of R

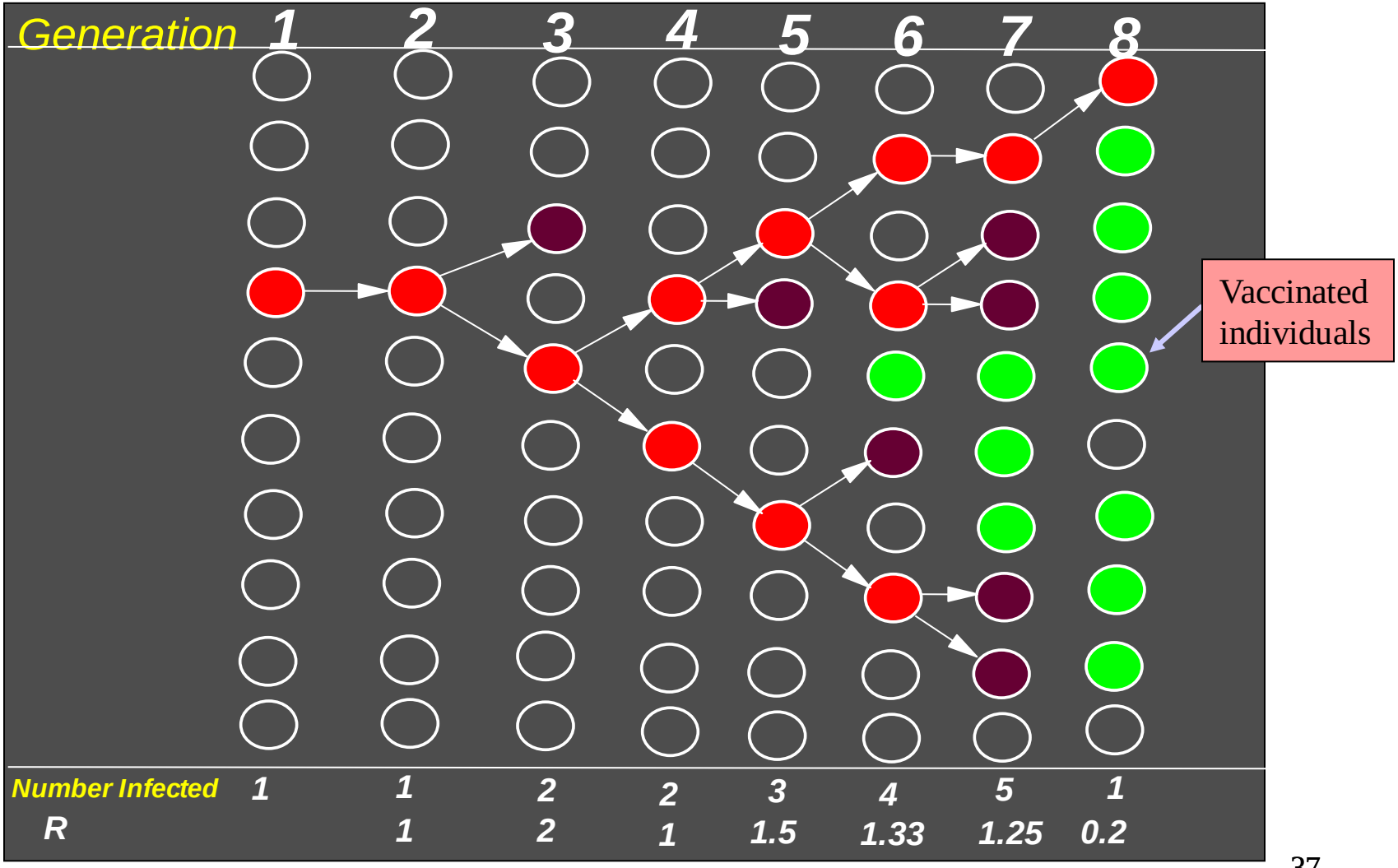




Rapid SARS Virus Spread in Flats 7 and 8, Block E Amoy Garden, Hong Kong. 1st March 2003 –
292 people infected by one index case



The generation of secondary cases with vaccination



Basic principles in Infectious Disease Epidemiology

The magnitude of $\mathbf{p_c}$, the fraction of each birth cohort that must be immunised to block transmission is given by the following simple expression:,

$$p_c \cong [L - A]/[L - b]/\varepsilon$$

The parameter **b** is the average age at first vaccination, **L** is life expectancy (related to the net birth rate), and **A** is the average age at infection prior to mass immunisation. Vaccine efficacy = ε, ranging from 0-1.

Vaccine efficacy

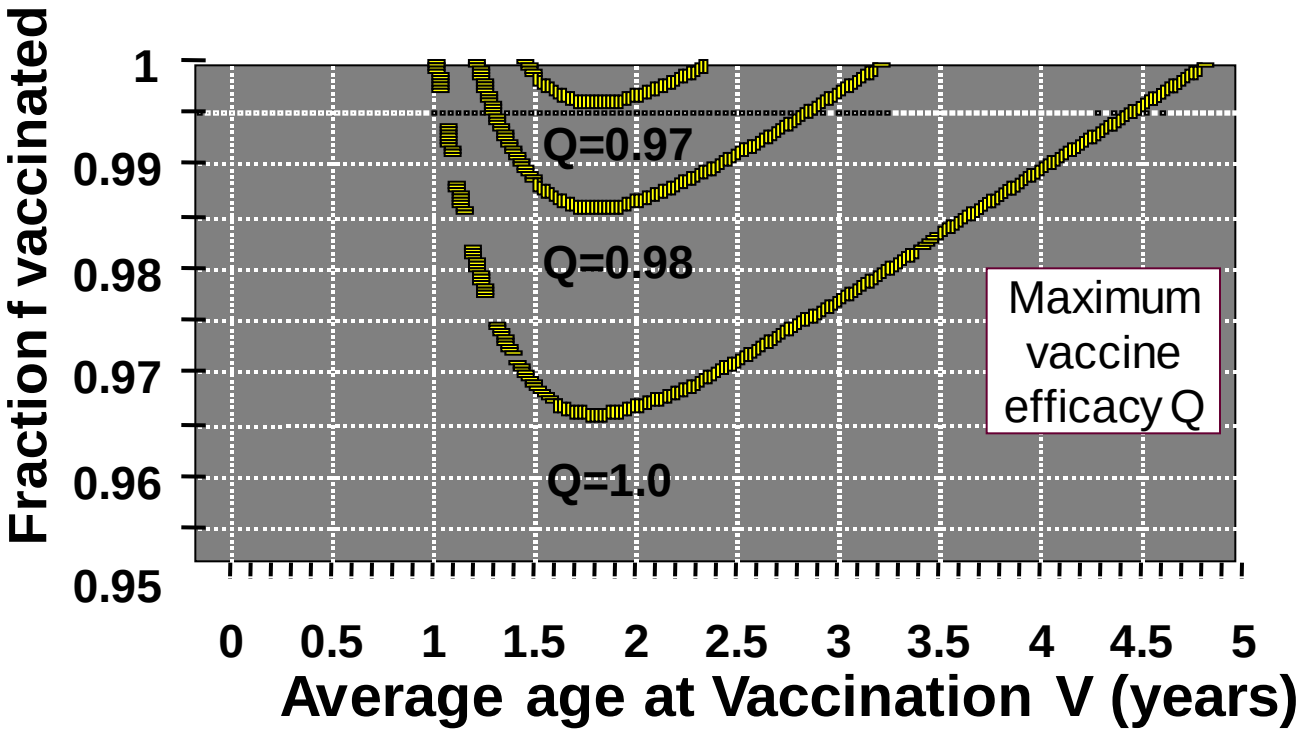
(Christensen & Bottiger,1991; Clarkson & Fine,1987; Ramsey et. al.,1994)

MEASLES	90%-95%
MUMPS	72%-88%
RUBELLA	95%-98%

Mass vaccination

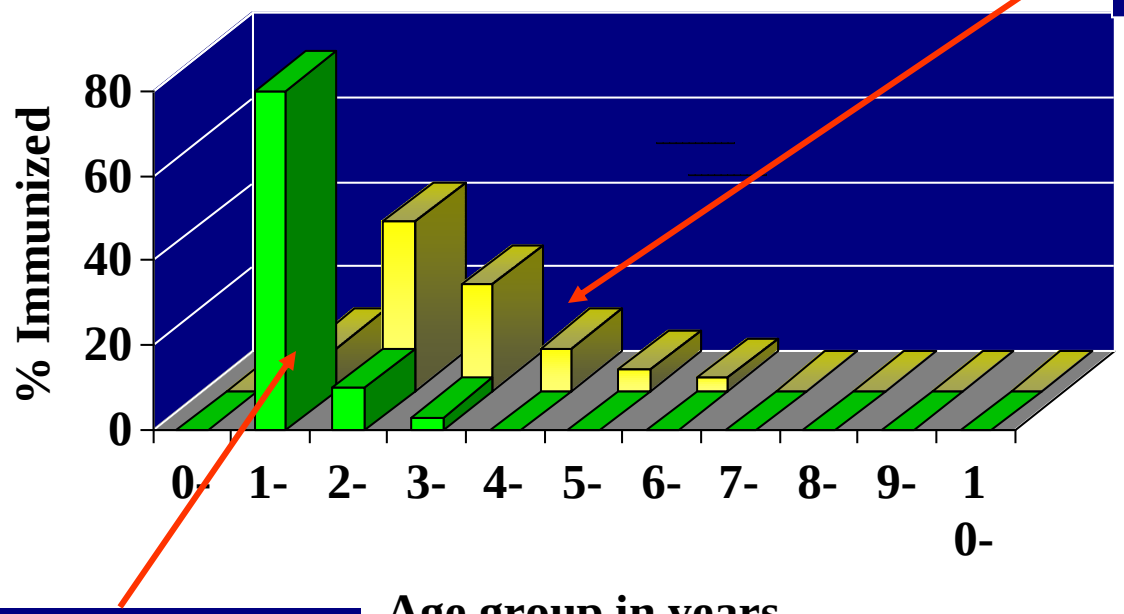
Anderson, et al (1998) Lancet 350:1466-1470

Fraction that must be vaccinated to block transmission (A=5 years) - measles



Vaccine efficacy changes with age due to presence of maternal antibodies

Age at vaccination - good and bad patterns

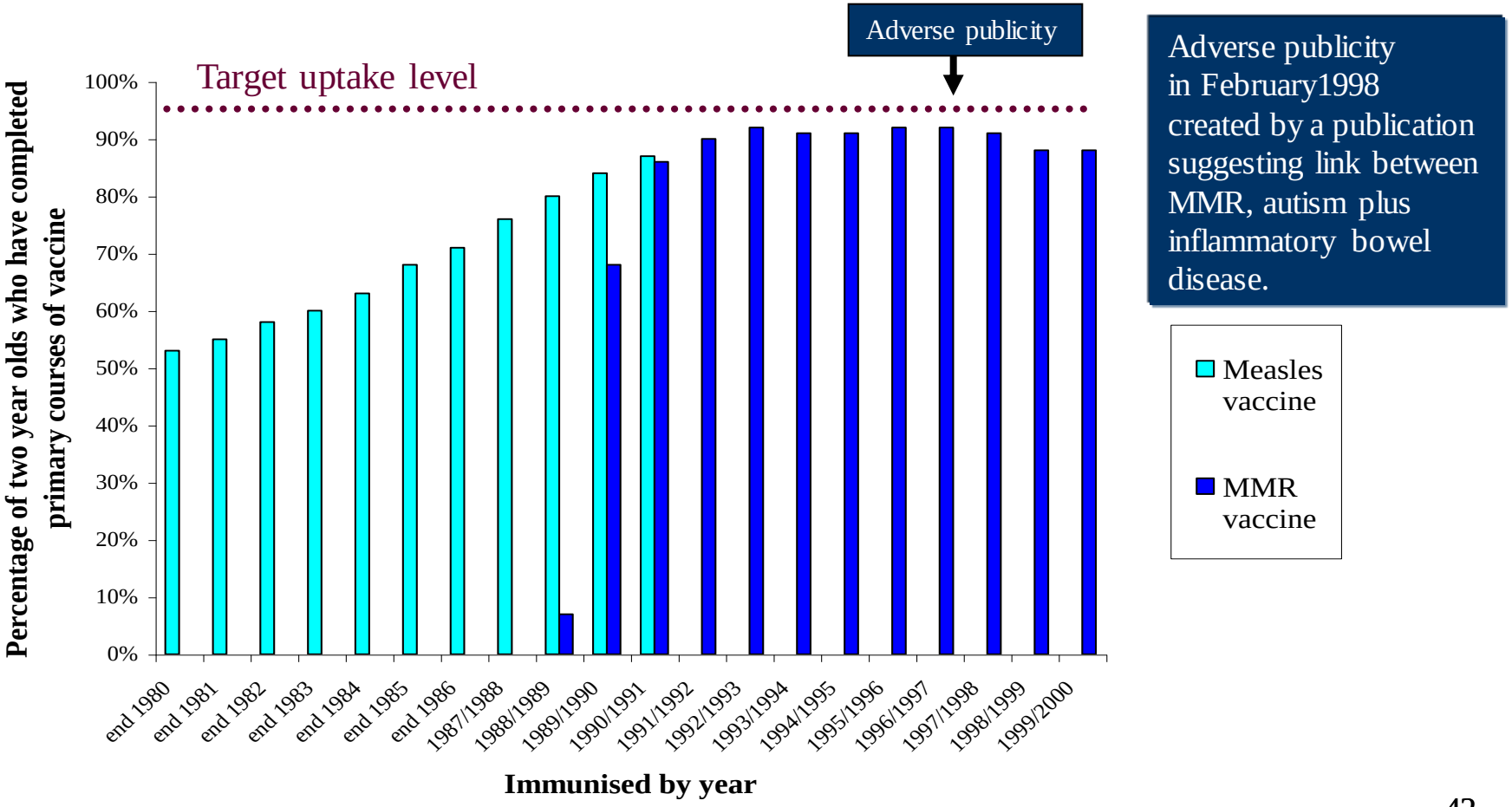


Poor pattern - spread to the right side of the optimal age

Good pattern - clustered around the optimal age

Percentage of children who had completed the primary course of measles or MMR vaccine at two years of age, Great Britain, 1980 - 2000

[Source: Department of Health, Statistics Division]

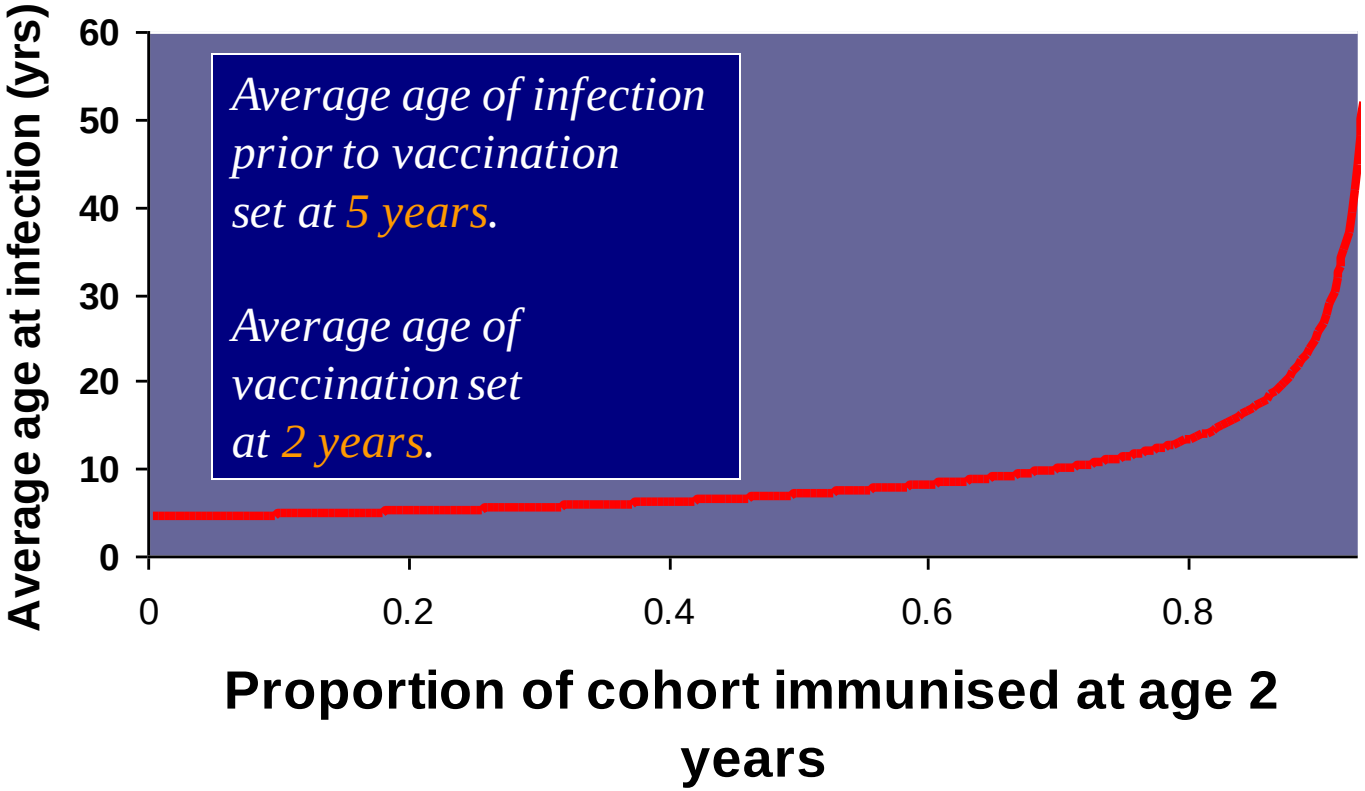


Adverse publicity in February1998 created by a publication suggesting link between MMR, autism plus inflammatory bowel disease.

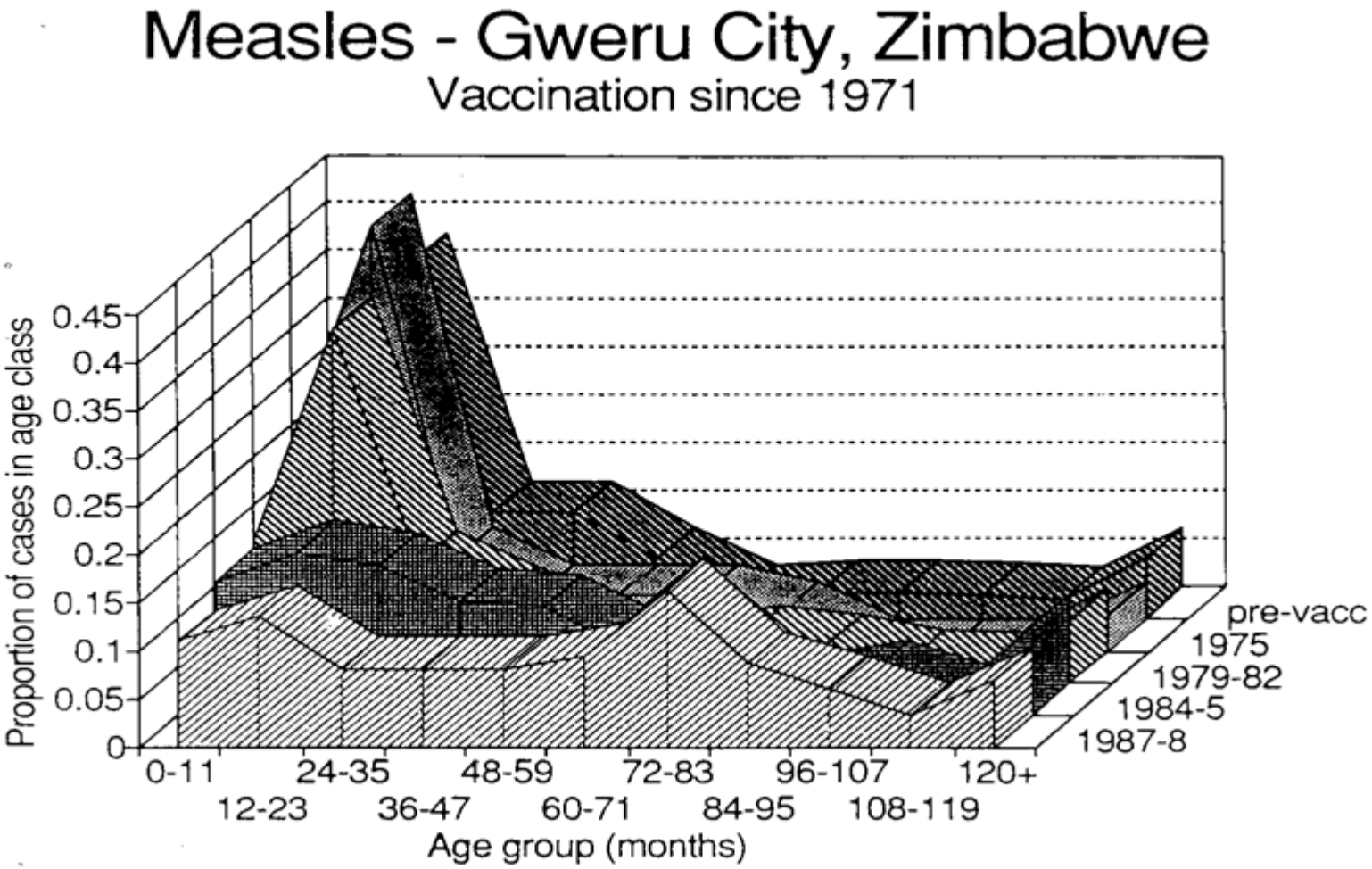
Predictions based on mathematical models of transmission and the impact of mass vaccination

1) Increase in average age at infection
2) Increase in the inter-epidemic period
3) Toughs in susceptibility in the herd immunity profile
4) Changes in the age distribution of infection and serious disease
5) Non-linear relationship between the incidence of infection and disease and vaccine uptake

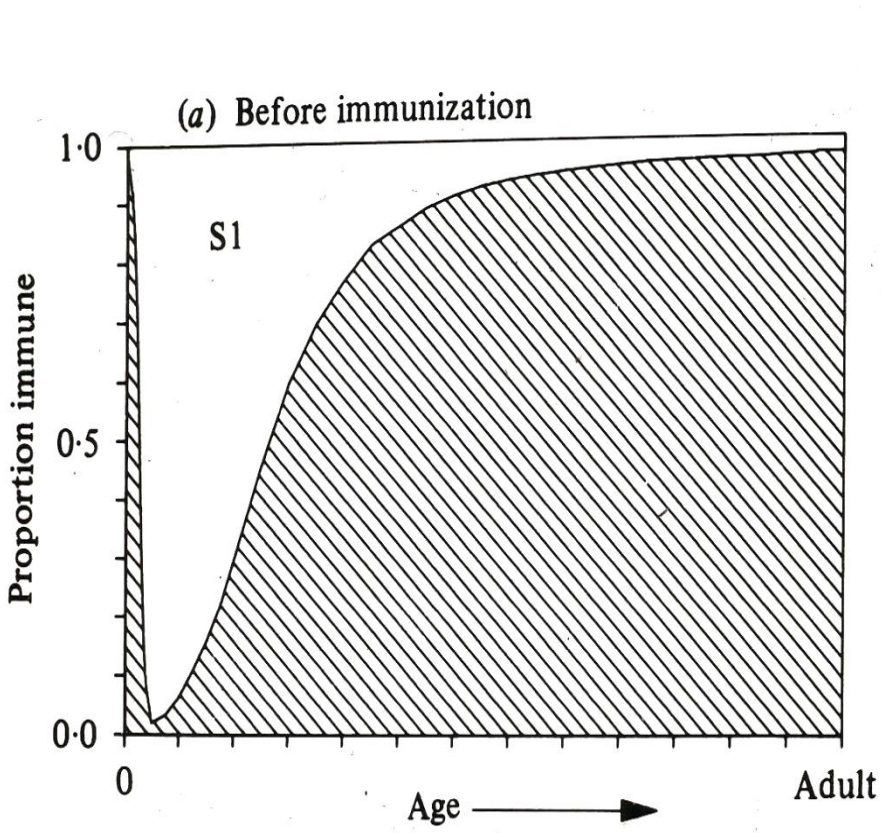
Average age of infection - the impact of vaccination

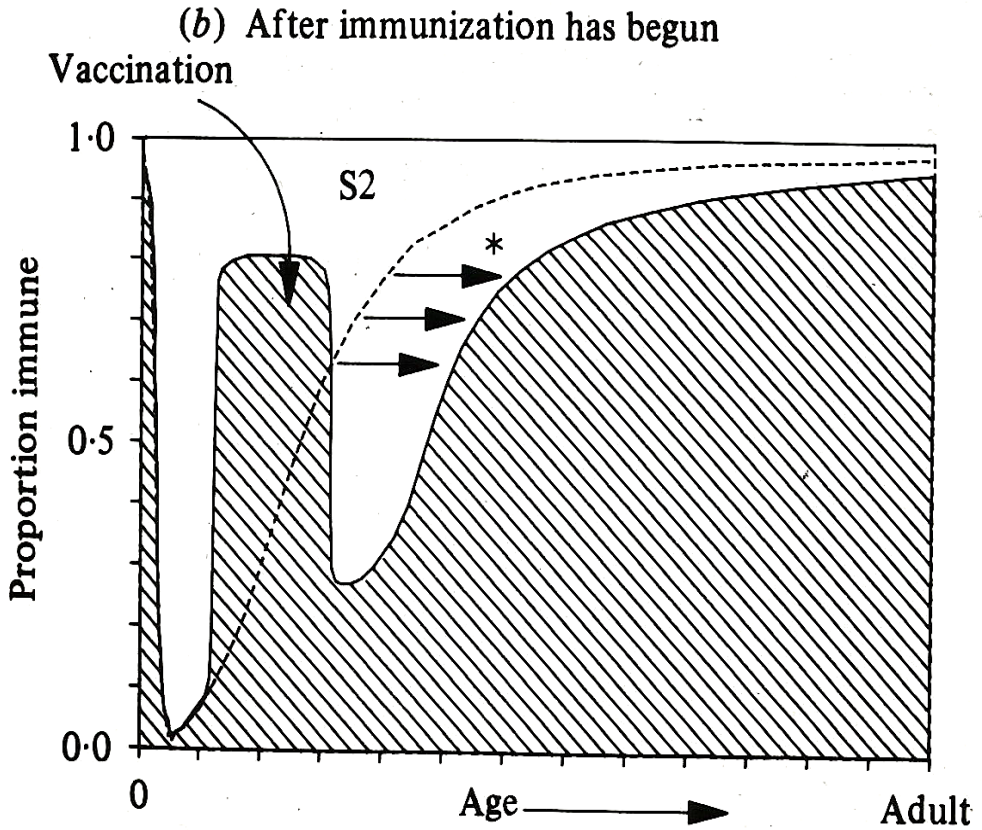


Vaccination - and the age distribution of infection



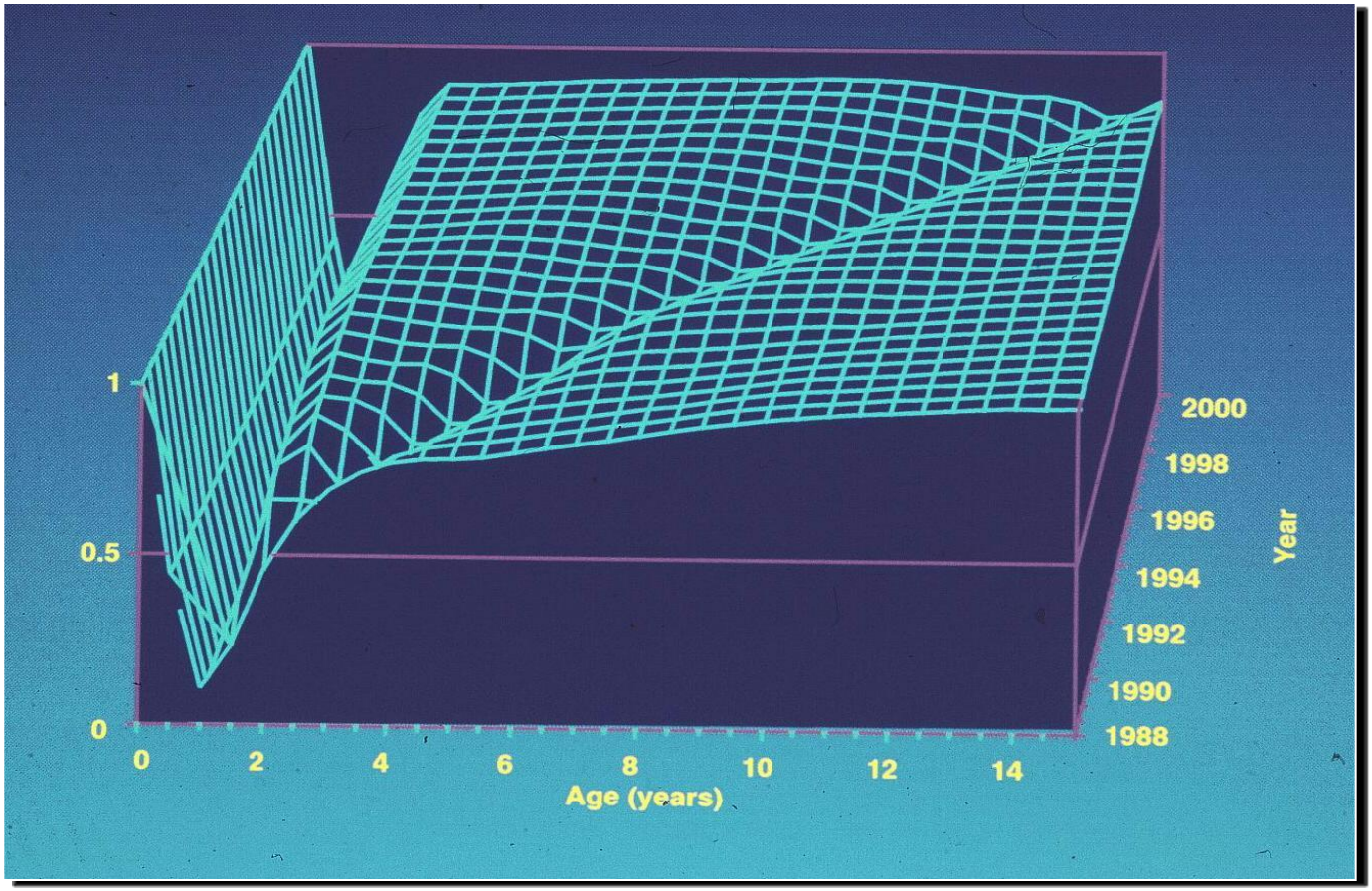
Impact of vaccination on serology





Herd immunity profile - across age classes and through time

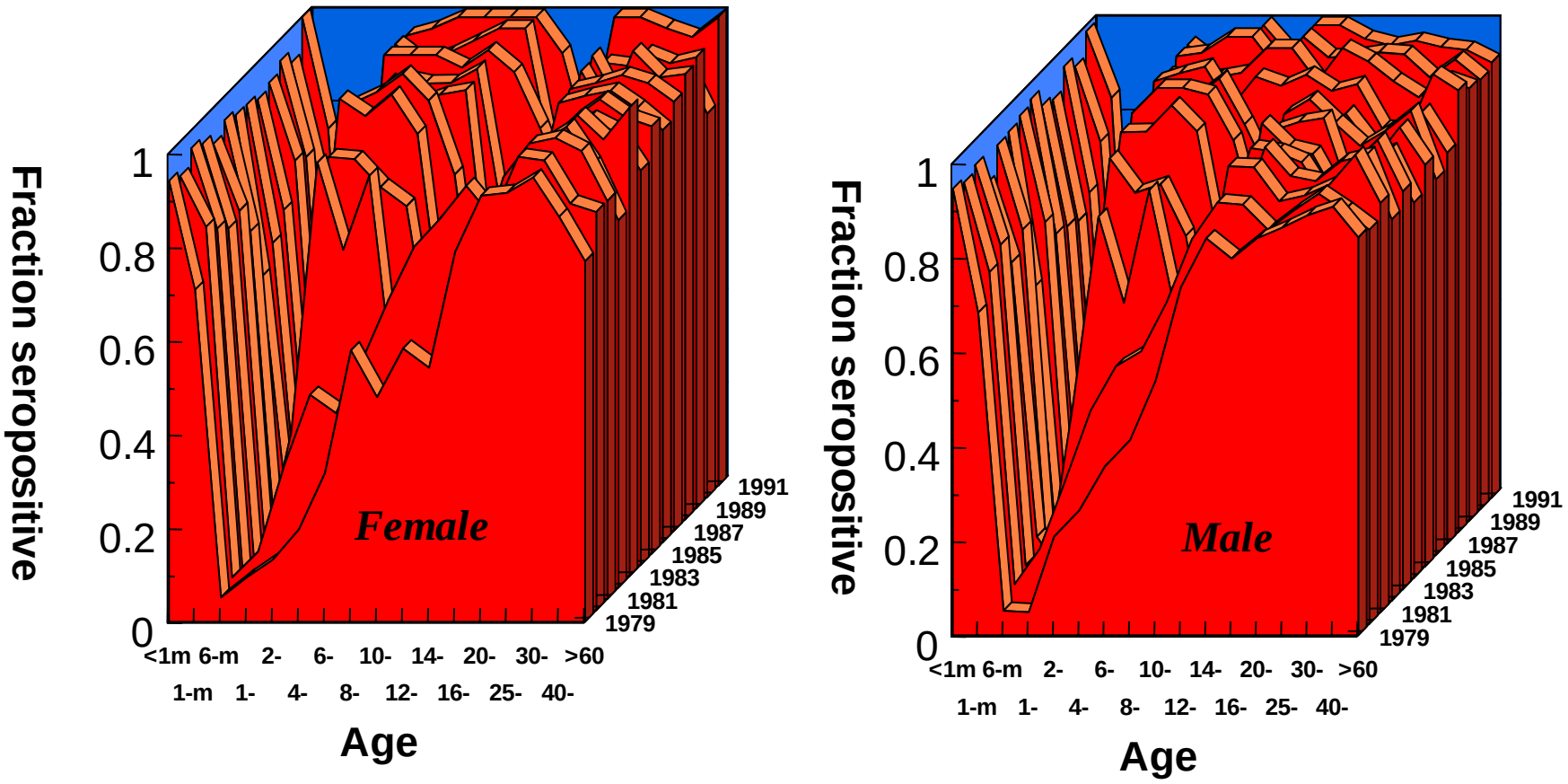
(Anderson and May, 1982; *Science* 215:1053-60).



Measles - serology post the introduction of a cohort based vaccination programme

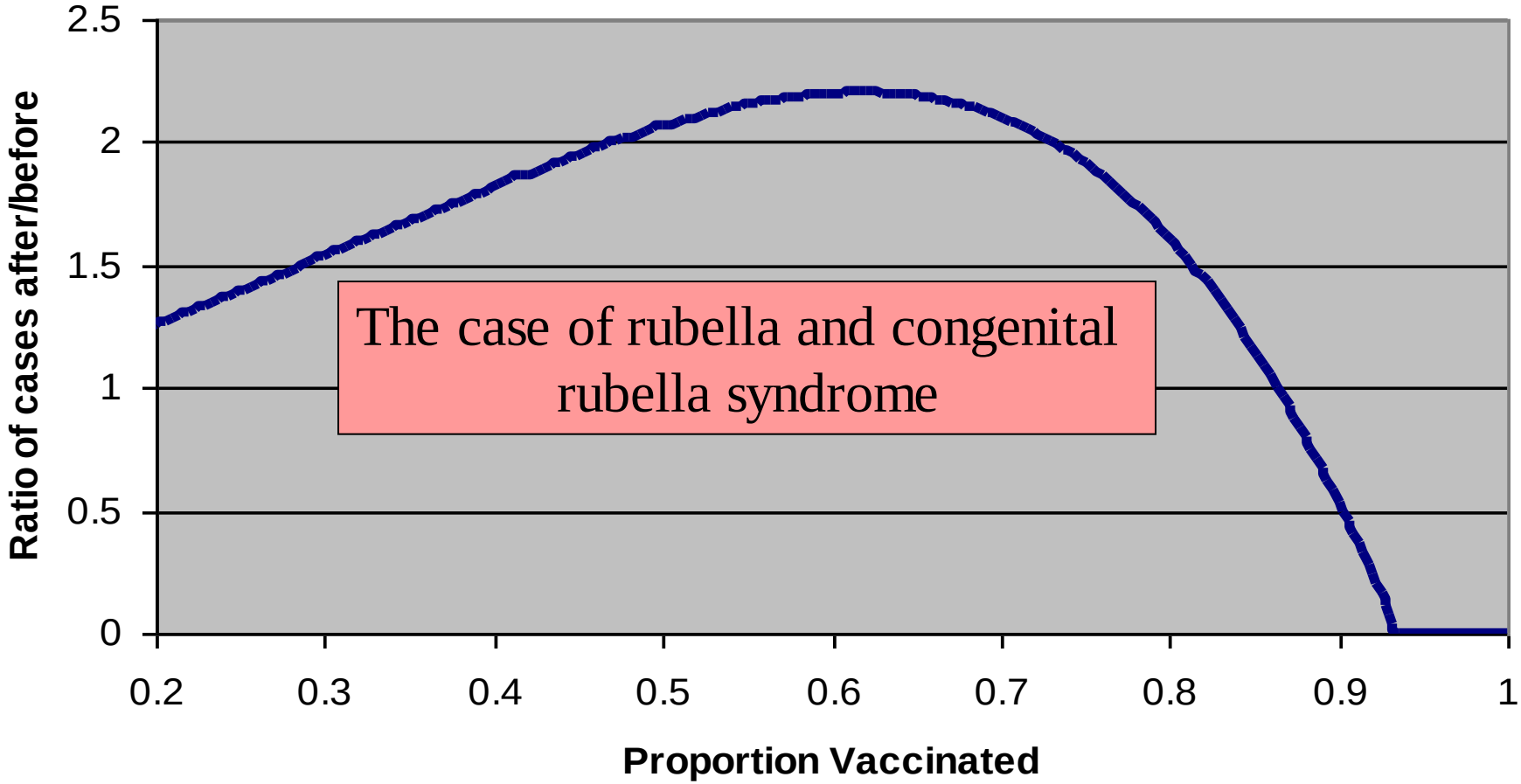
Age stratified & longitudinal serology for Rubella antibodies. Finland 1979-91

(Ukkonen et al, 1995)

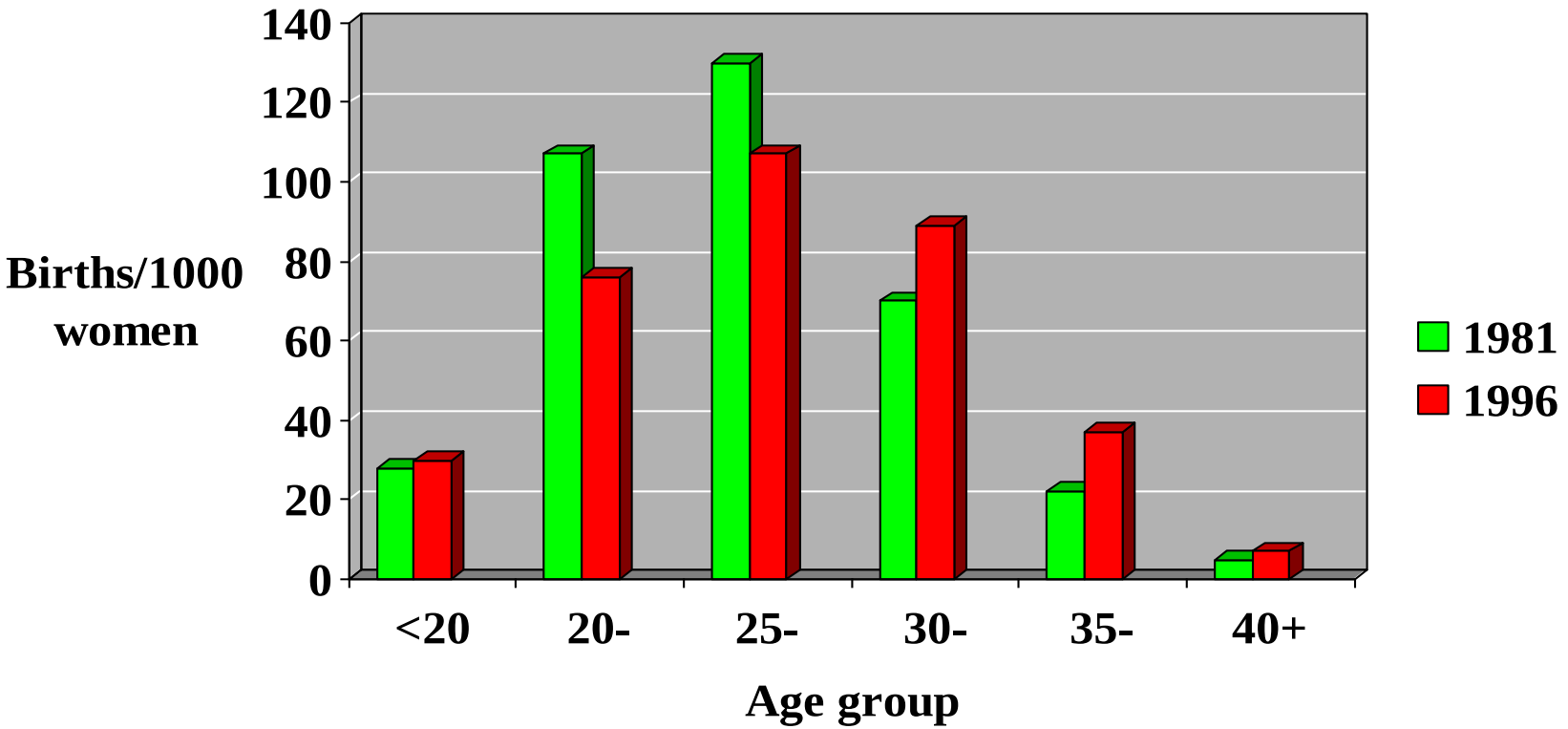


Mass vaccination can increase the incidence of serious disease if the likelihood rises with age per case of infection

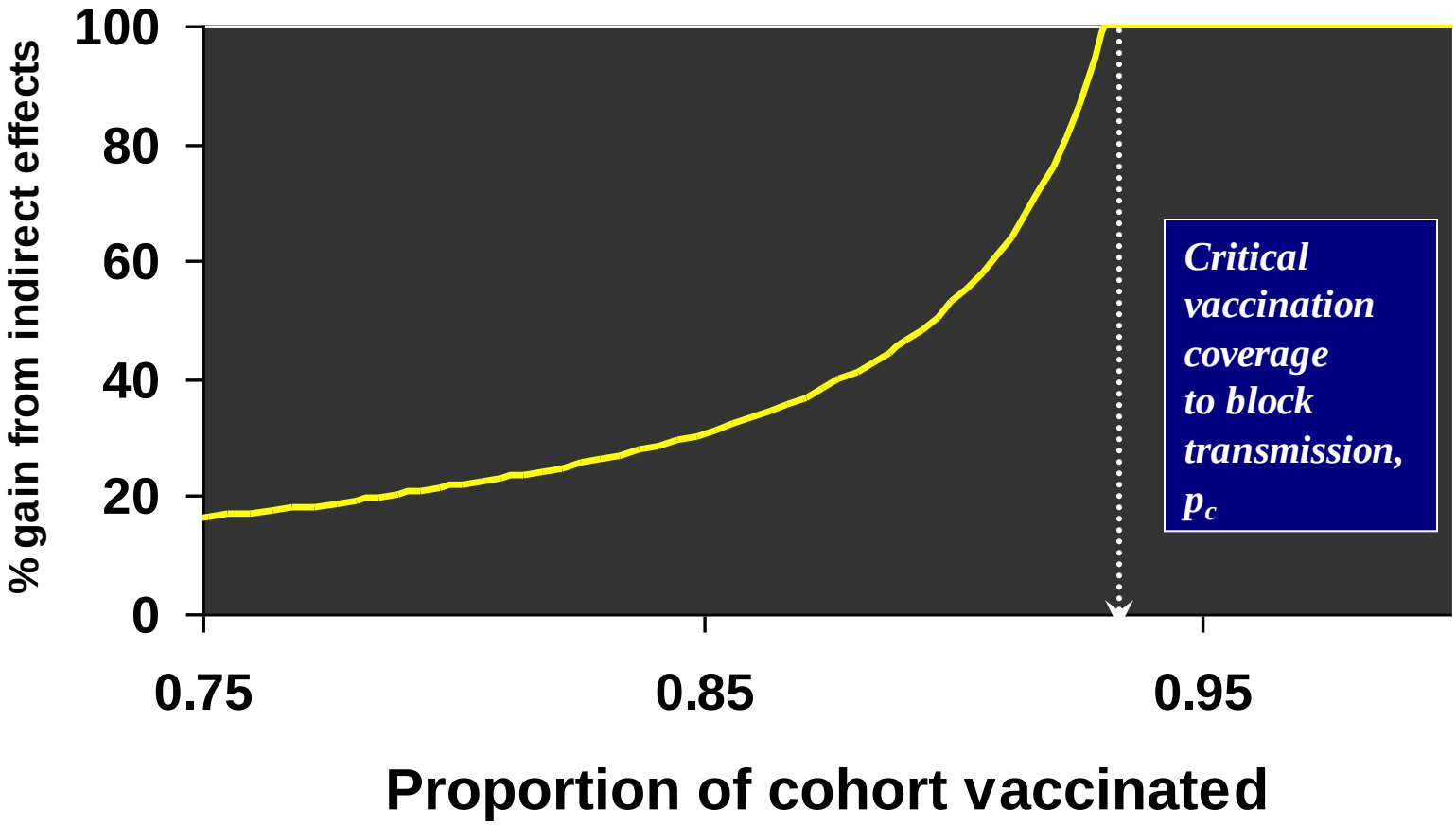
(Anderson & May, 1983; *J. Hygiene* 90:259-325)



Demography - age specific birth rates in the UK 1981 & 1996: Rubella immunization

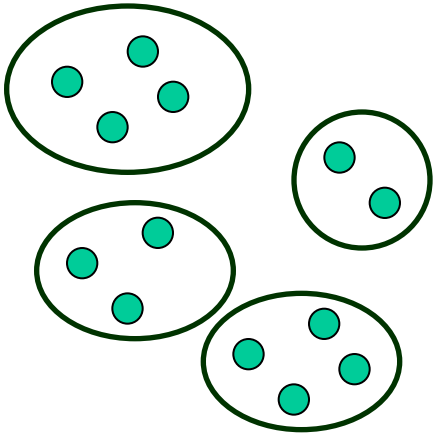


Percentage gain from the indirect effects of herd immunity

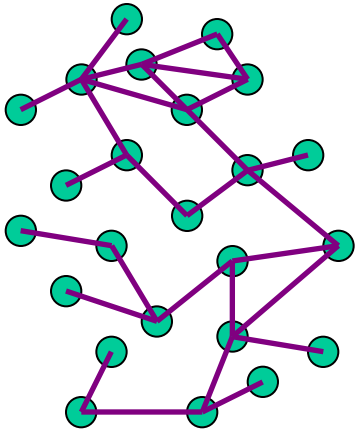


Model design for individual based stochastic simulations

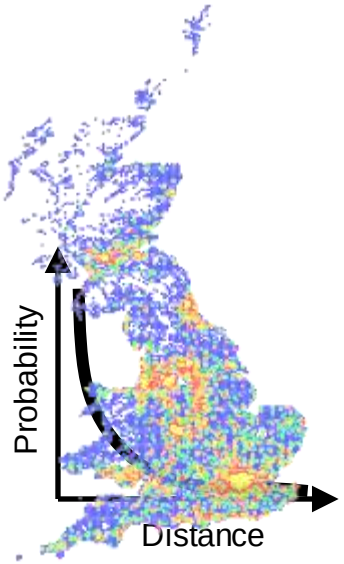
- High performance, object-oriented code. Intended to be scaleable to allow 000s of model simulations of 60 million population to be performed.
- Computationally intensive (>5GB memory use for 60 million).
- Three levels of population structure:



Household



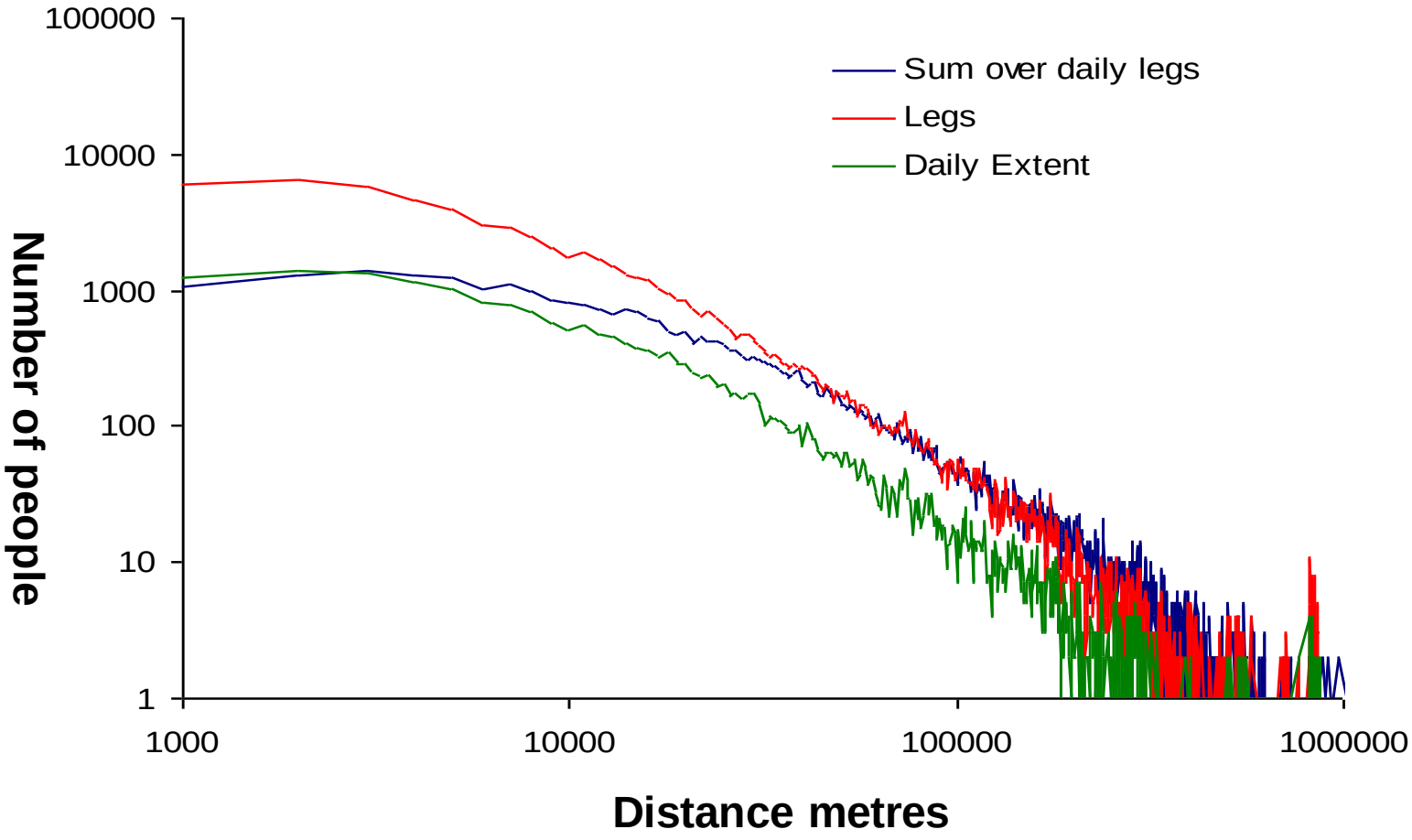
Network
(disease specific)



Spatial

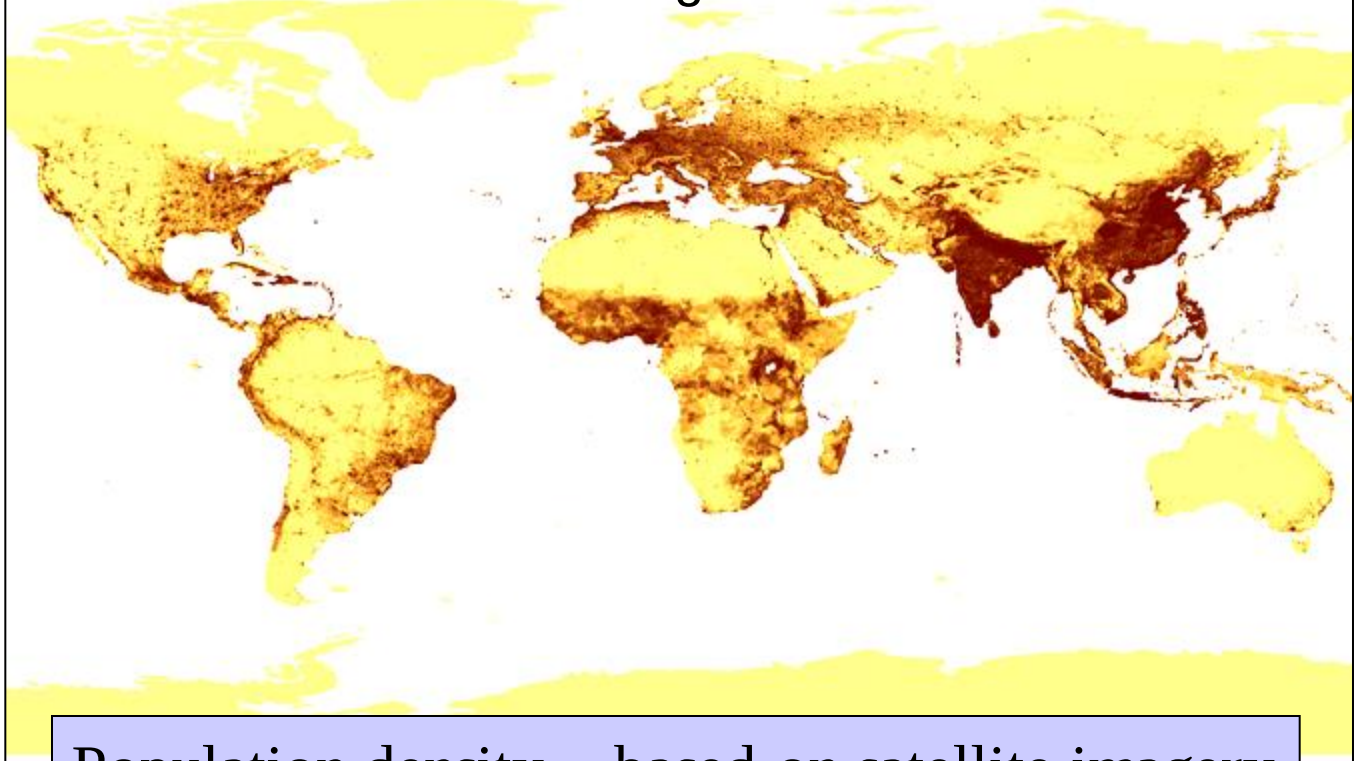
- Flexible modelling of disease biology (arbitrary distributions, number of disease stages), and interventions (ring vaccination, mass vaccination, quarantine, anti-viral treatment, movement constraints).

Spatial kernels – mobile phone data – frequency versus – distanced moved per defined time unit

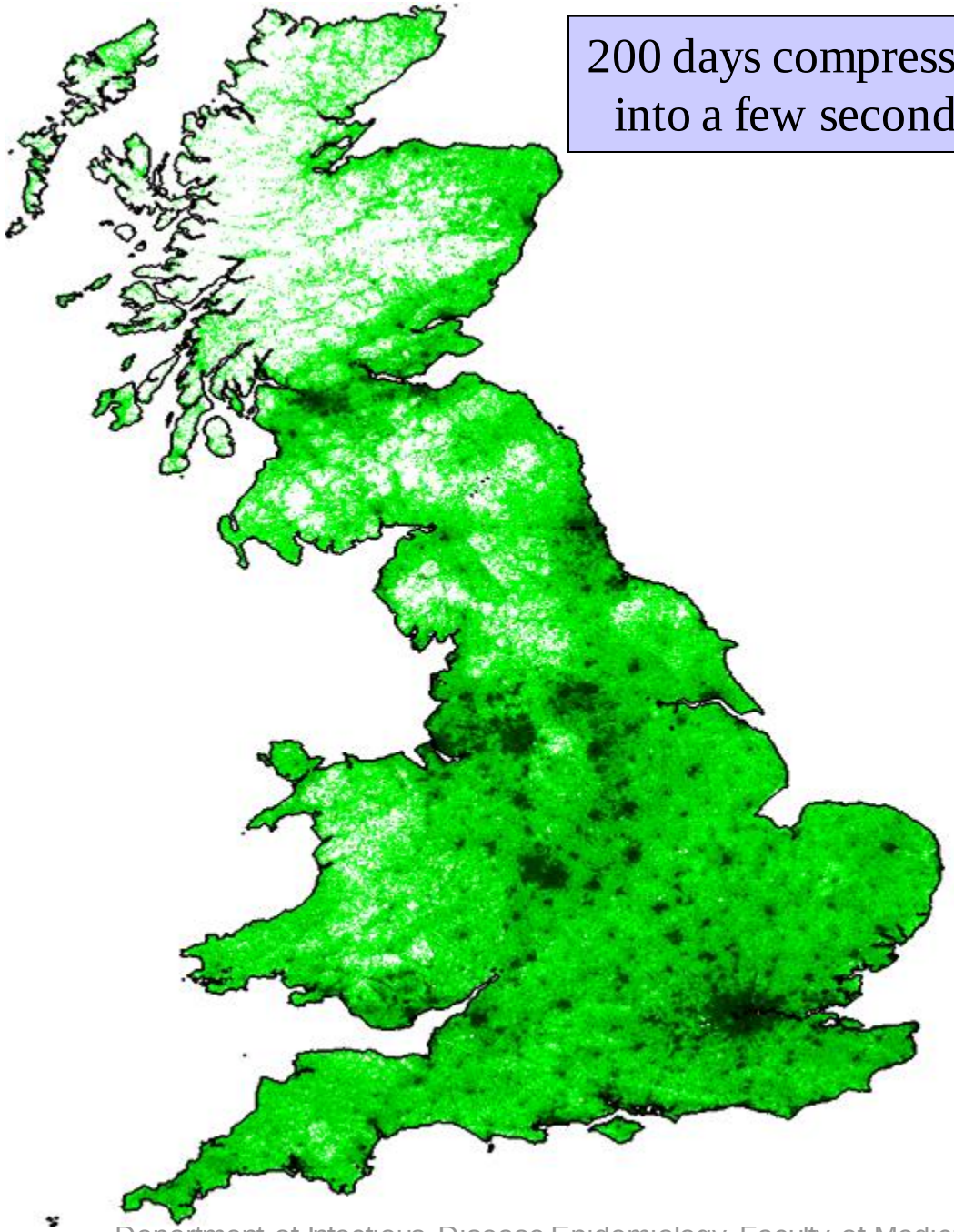


Data needs: detailed population data: *Landscan* (Oakridge Natl. Lab.)

Need both population data (density, age, household) and mixing/travel data.



Population density – based on satellite imagery



200 days compressed into a few seconds

Ferguson et al, 2006 – Nature - on line April 27th 2006

Individual based stochastic simulation model with three scales of mixing – extensive sensitivity analysis and analysis of past influenza epidemics

Imperfect vaccines

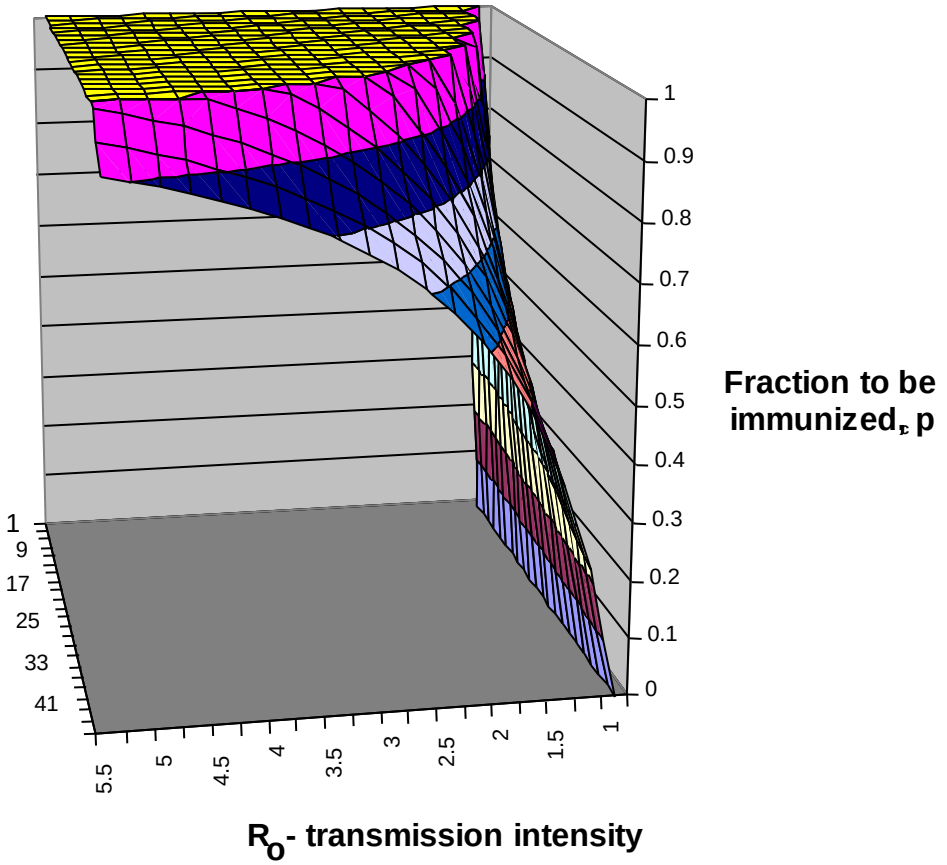
- Vaccinated individuals acquire infection but show slower progression to AIDS.
- Slower progression is linked to lower viral loads – especially in the primary HIV-1 infection phase.
- Lower viral load is linked to lowered infectiousness to susceptible sexual partners.
- Vaccination may be linked to increased risk behaviours.

Blocking transmission by mass vaccination

Protective vaccine – critical proportion to be immunized, p_c, to block transmission as a function of R_o and the duration of protection, V (efficacy, ε = 1).

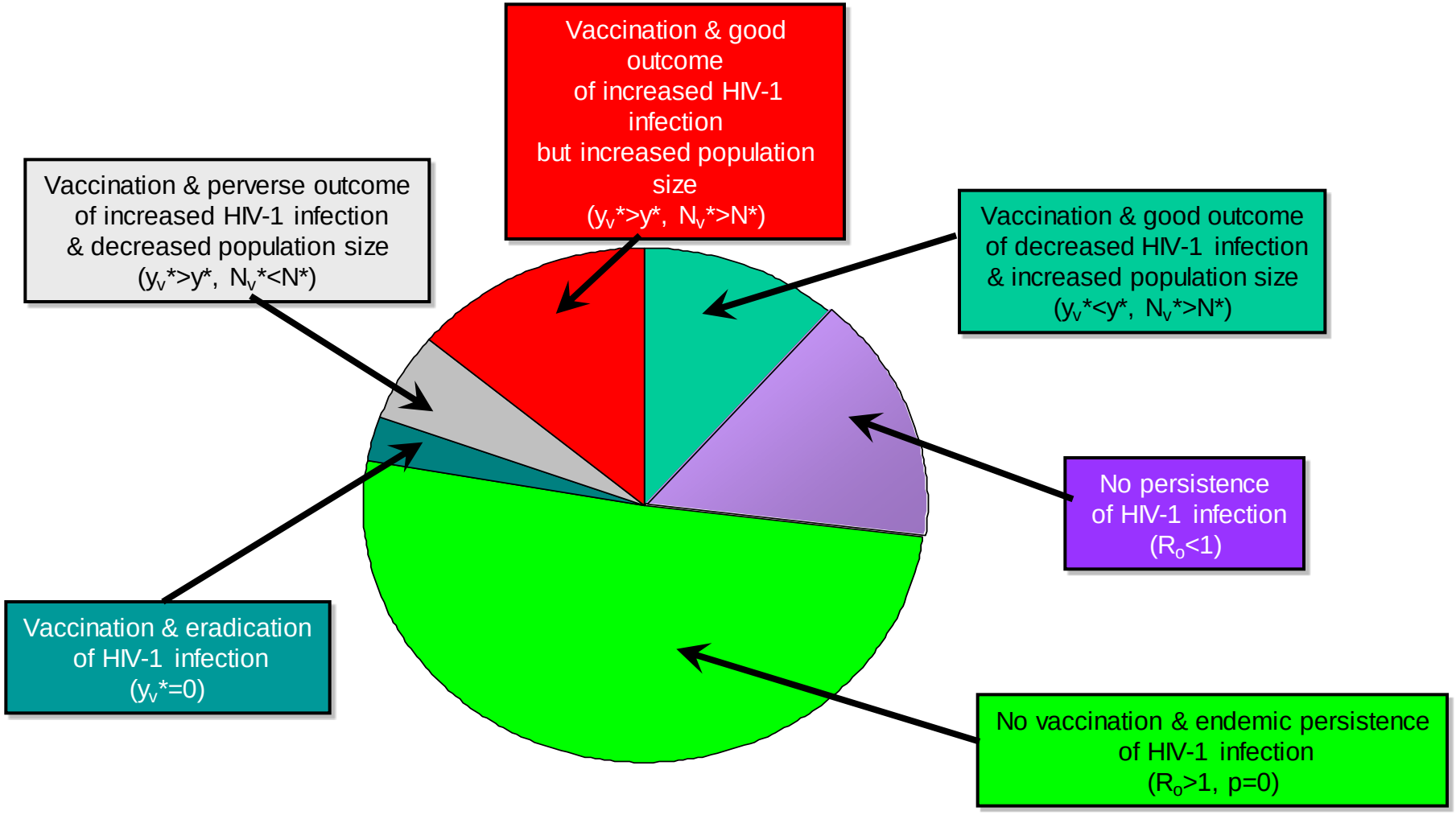
$$p_c = [1 - 1 / R_0] / \varepsilon$$

Vaccine efficacy = ε, ranging from 0-1
For influenza A …… if R_0=1.6 then p_c=37.5%.



Illustrative schematic diagram, in two dimensions, of a multidimensional parameter space denoting the six possible equilibrium states that can exist for different epidemiological and vaccine property related parameter combinations

(Anderson & Hanson, 2005, JID).



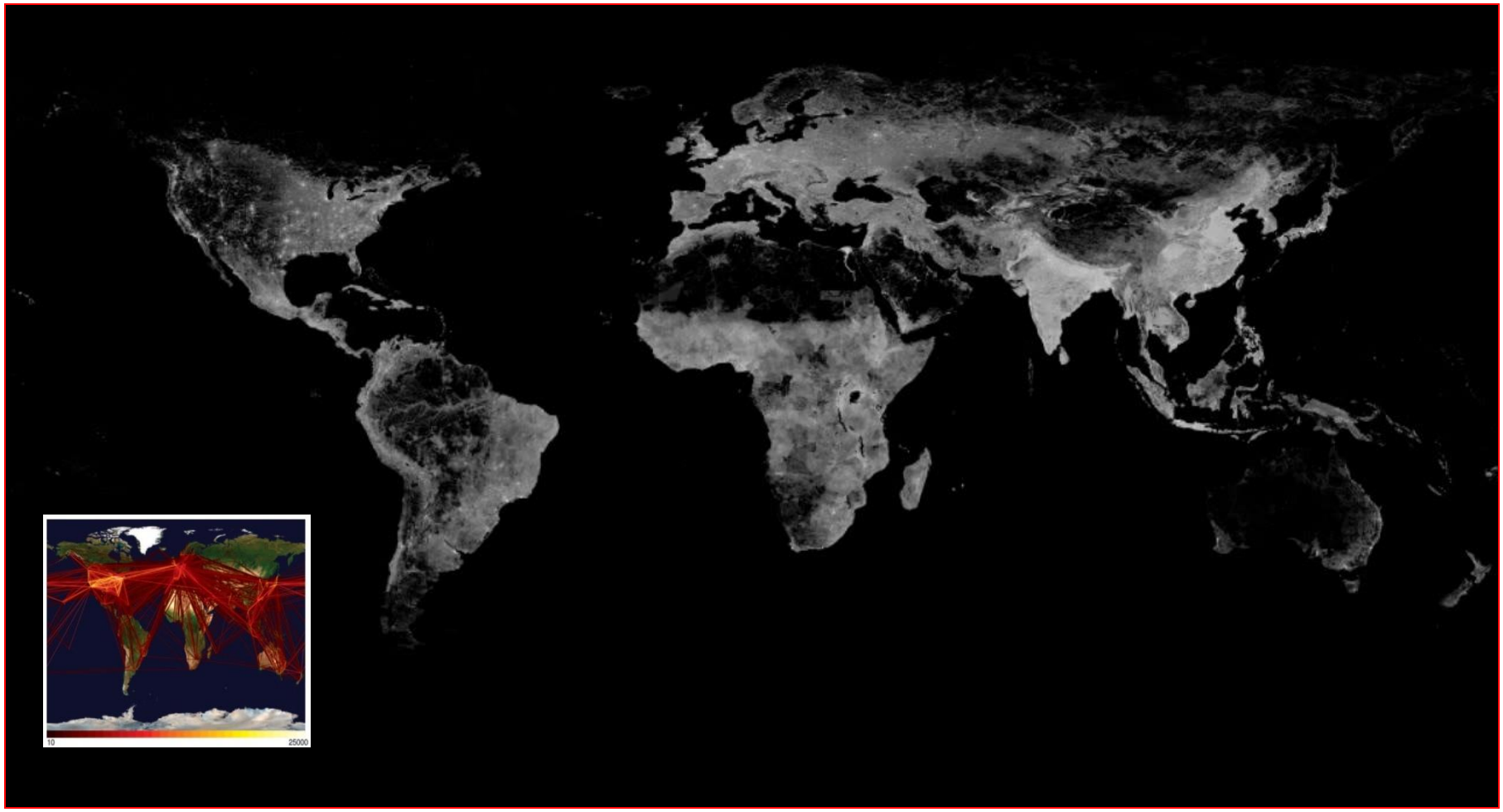
Conclusions

- Eradication difficult when R_o large and population density plus net birth rate high.
- Heterogeneity in population density and vaccine coverage important.
- Carrier state important as are reservoir hosts (if involved).
- Mathematical & computational methods permit analytical & simulation studies of potential impact of different strategies.
- Cost benefit studies need to take account of indirect effects of mass vaccination on transmission.
- Vaccine coverage must be maintained at high levels to avoid the immigration of infectives stimulating epidemics in susceptible pockets.
- Multi- strain systems – more research required – will new strains replace those targeted by a multi-valent vaccine?

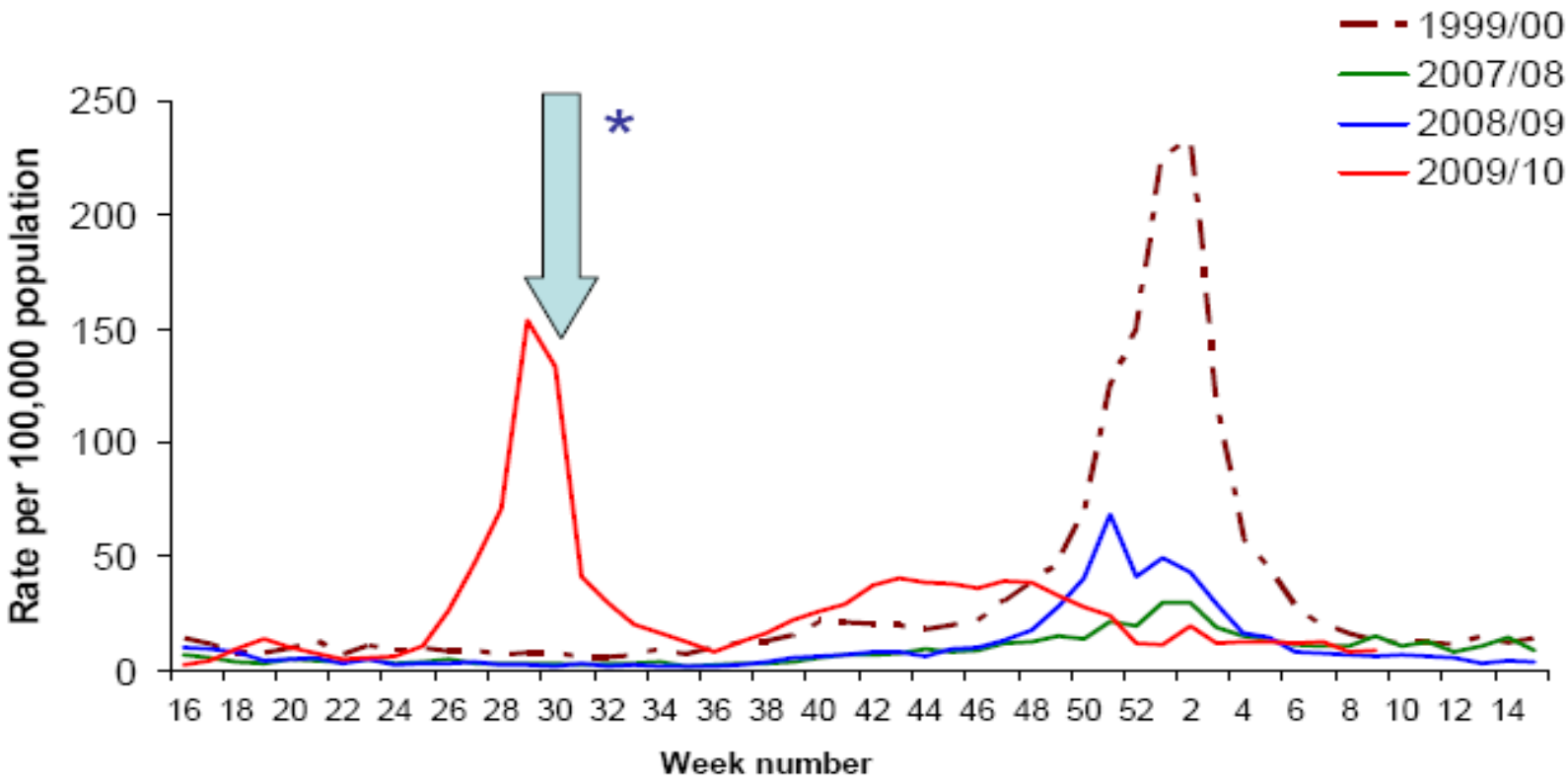
The End

Simulating global spread – Influenza A

(Ferguson et al, 2009)



H1N1 in England during the 2009-10 seasons – compared with previous years



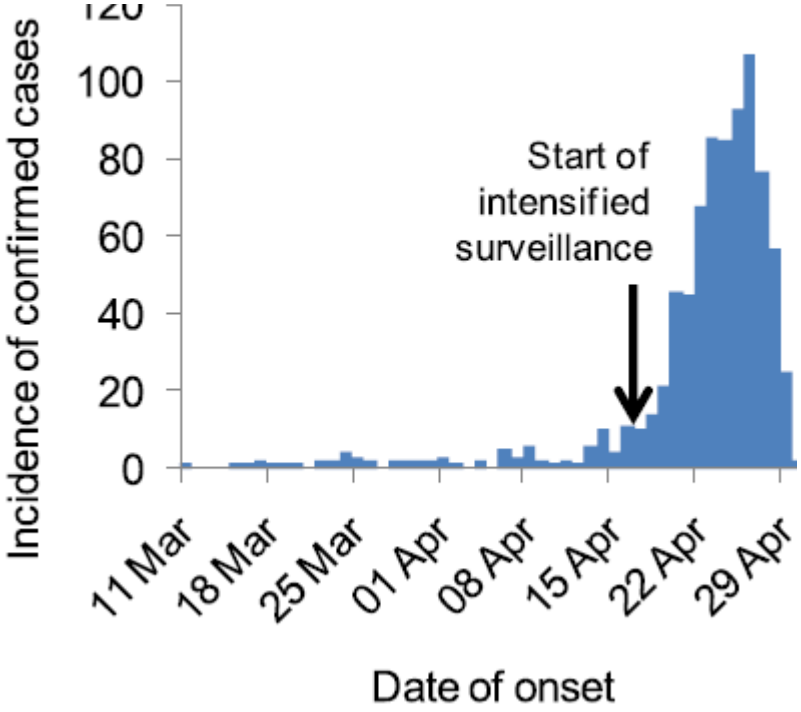
Week ending 28 February 2010: **9.0 consultations per 100,000 population**

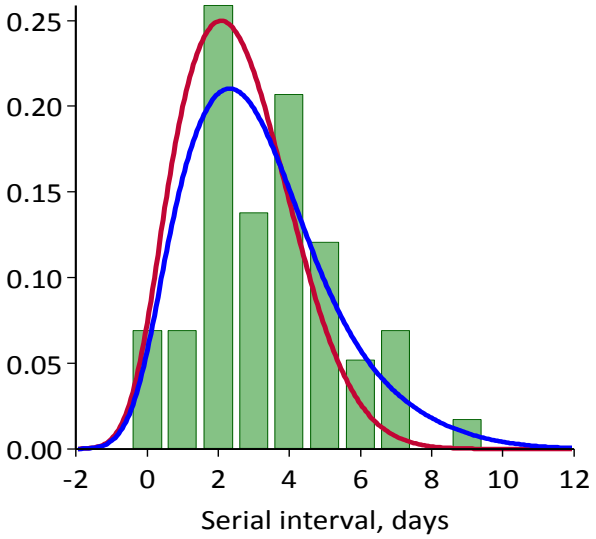
* Level reduced by availability of NPFS for 2009/2010 period but not earlier periods

Source: RCGP to 28 February 2010

R for Mexico in April-May

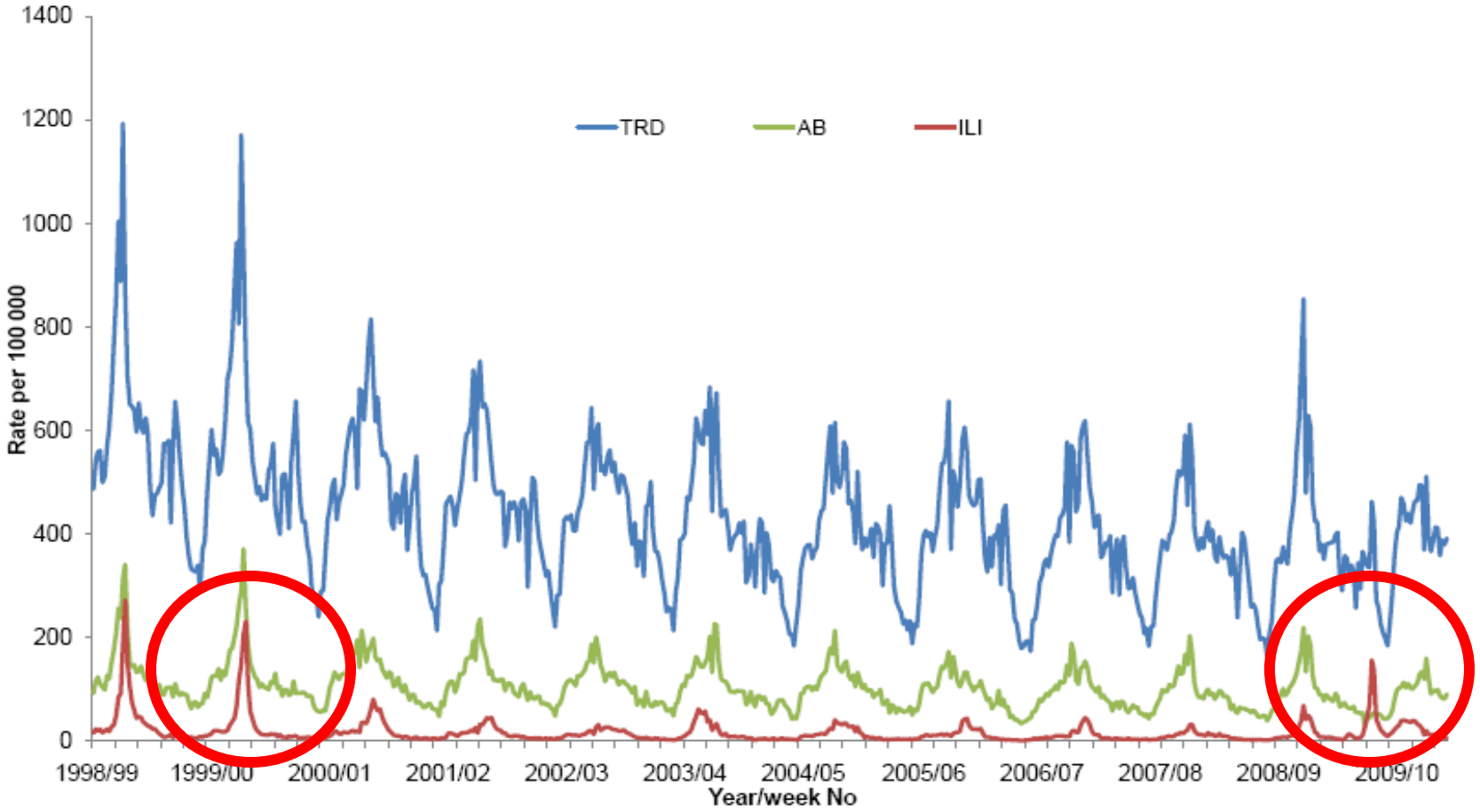
(Fraser et al, 2009 Nature)





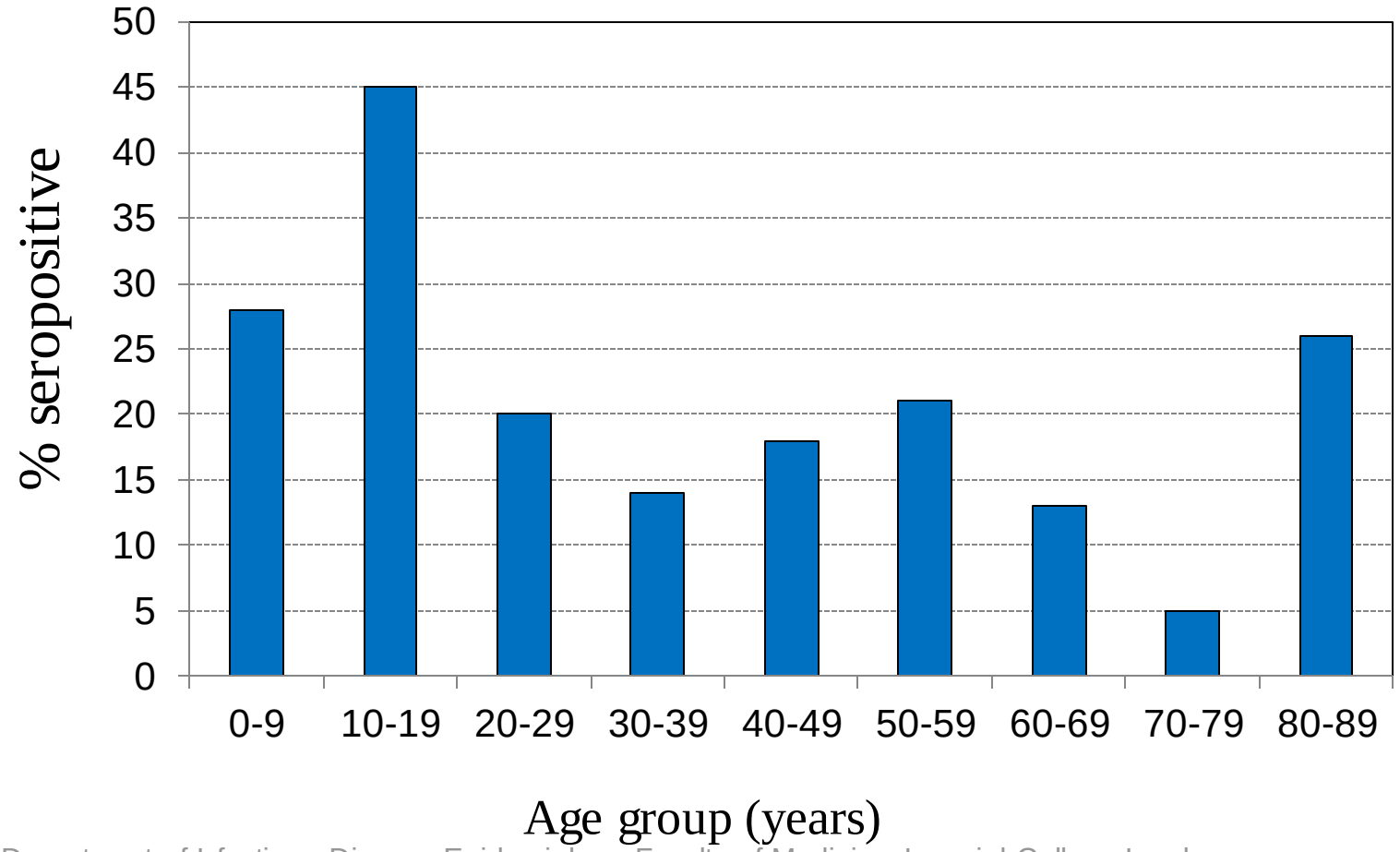
- *R*=1.5 (95% Cr.I.:1.2-1.9) from confirmed case epi curve.
- *R*=1.4 (95% Cr.I.:1.1-1.9) from spatial back-calculation.
- *R*=1.2 (95% Cr.I.:1.1-1.9) from sequence analysis.

England and Wales – RCGP consultation rates for Total Respiratory Disease (TRD), Acute Bronchitis (AB) & Influenza like illness (ILI)

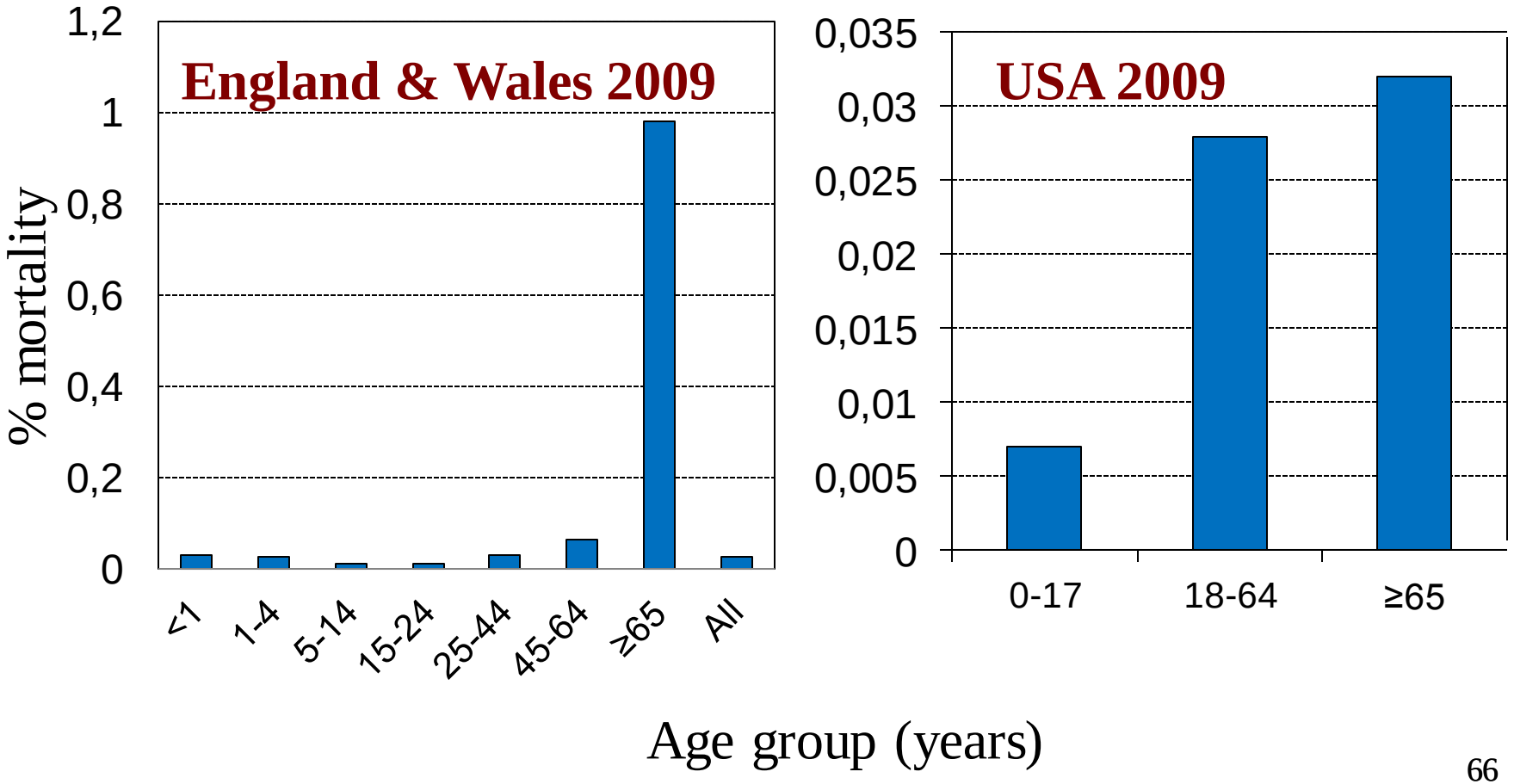


Seroprevalence following the second wave of pandemic 2009 H1N1 influenza

(University of Pittsburgh Medical Center's Presbyterian Hospital and the Children's Hospital of Pittsburgh from mid-November and early December 2009 – Ross et al Seroprevalence Following the Second Wave of Pandemic 2009 H1N1 Influenza. PLoS Curr Influenza. 2010 February 24: RRN1148).



Mortality in the UK by age group
H1N1 - 2009



Lessons learnt – H1N1

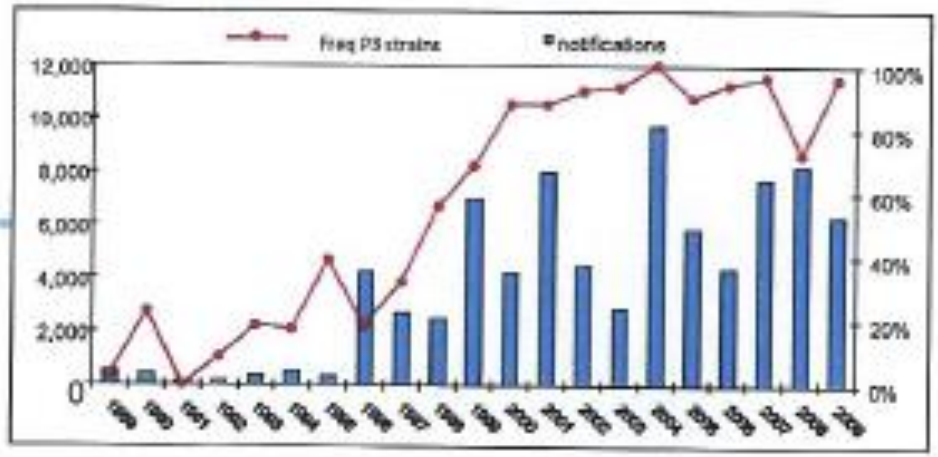
- Estimation of morbidity and mortality rates early in the epidemic.
- Serology as soon as possible – essential for estimation of case fatality (stratified by age and risk factors).
- Identify co-morbidities/risk factors as quickly as possible – first 500 cases.
- On the bases of R_0 and case fatality estimates – define policy objectives.
- Electronic capture of data and display real time.
- Logistics of antiviral delivery and policy of use.
- Policy on vaccine delivery to at risk groups.
- Vaccine uptake – reasons for refusal.

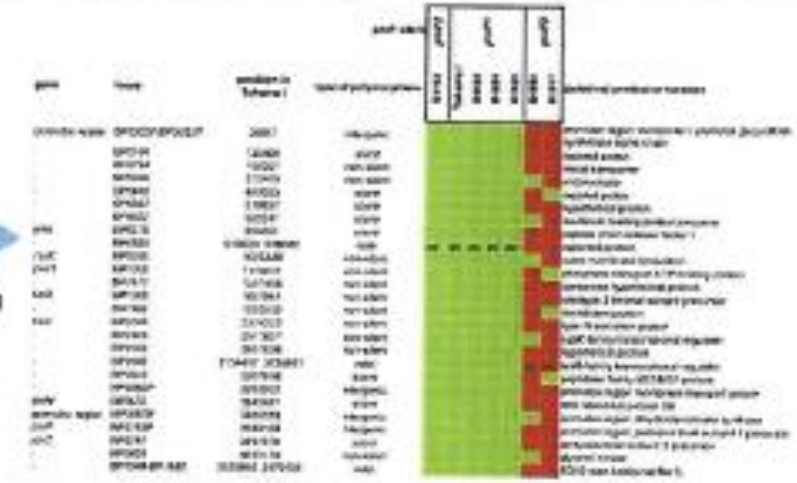
New era 2012-2020

- Escape mutants – mumps and pertussis.
- Immunotherapy – cancer vaccines.
- Vaccines that are partially effective – Malaria GSK trials.
- Low hanging fruit have been plucked

Emergence of P3 strains of Bordetella pertussis

Emergence of P3 strains of B. pertussis with increased pertussis toxin production





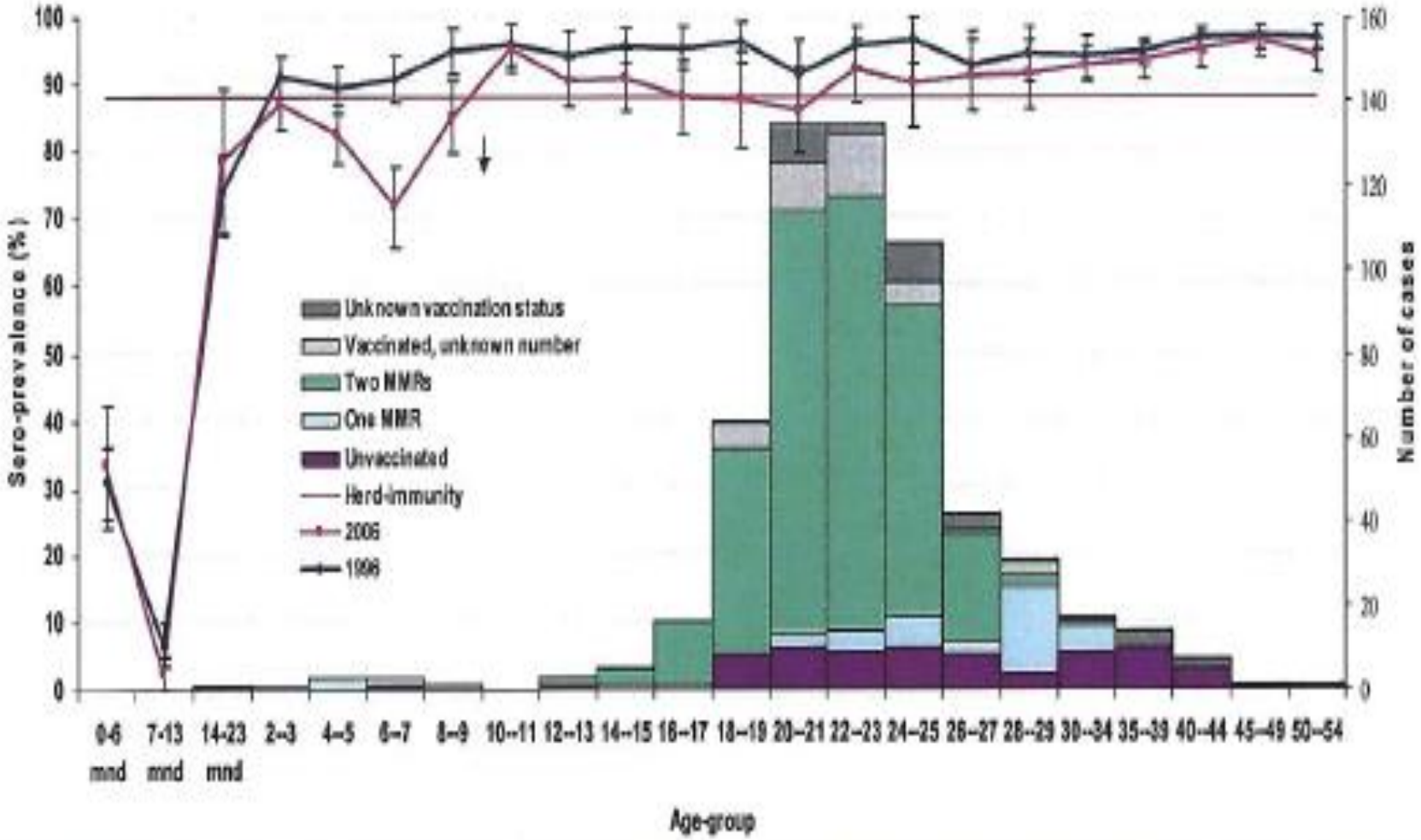
Characterisation of SNP's

New rapid SNP based typing Methods for monitoring of virulence variants

Mooi et al., 2009; Bart et al., 2010; van Gent et al., 2011

Sero-surveillance – mumps - Netherlands

- Pienter-I (1995/1996) and Pienter-II (2006/2007) IgG titers by age



HIV-1 vaccines

- At present, there are many ongoing HIV-1 vaccine trials and several pending for 2006, involving different vaccines (of which some are DNA-based, some use recombinant viral vectors, 4 are protein subunits and 3 are lipopeptide-based).
- Most are in Phase I, with VaxGen's two trials (in North America and Thailand) the only Phase III studies completed. Both Phase III trials were completed in 2003, with efficacy data revealing no difference in infection in treated and untreated arms.
- The majority use clade B strains, but a few candidates (especially among the newer ones in the pipeline) are based on clades A, C, D and E (http://www.iavi.org).

Eradication criterion – protective vaccines

$$p_c > \frac{[1 - 1/R_0][1 + L/V]}{\varepsilon}$$

p_c is the critical fraction of each cohort immunised, R_0 is the basic reproductive number, L is life expectancy, V is the duration of vaccine protection and ε is vaccine efficacy

Eradication criterion – imperfect vaccines

$$p_c > \frac{[1 - 1/R_0][1 + L/V]}{\varepsilon[1 - R_{0v}/R_0]}$$

p_c is the critical fraction of each cohort immunised, R_0 is the basic reproductive number for unvaccinateds, R_{0v} is the reproductive numbers for vaccinateds, L is life expectancy, V is the duration of vaccine protection and ε is vaccine efficacy