Barriers To New Vaccines

Vaccines are complicated!

- In this lecture we will go beyond the immunology to discuss the other challenges associated with new vaccine implementation

Learning Objective:

To understand some of the broader issues affecting vaccine uptake including delivery, acceptability and economic

New Vaccines

Barriers to (future) vaccines

- **Scientific Challenges** (e.g. HIV/Malaria/RSV/TB...)
- **Development Issues**
  - **Time**: 8 yrs in 1960s; 15 yrs now
  - **Cost** of vaccine development grows @ 12% per year (3x general inflation) Now costs $1,000,000,000 per vaccine
- **Injection Safety**
- **Logistics/ Cold Chain**
- **Cost of the product**
- Public expectation of **risk-free** vaccines
  - **'Precautionary principle':** even the theoretical possibility of harm leads to withdrawal
  - **Post-licensure monitoring**: can add ~25% to cost, leading to economic failure of a product

Development Issues

From me having a brilliant Idea to the bedside is a long (expensive) and winding road

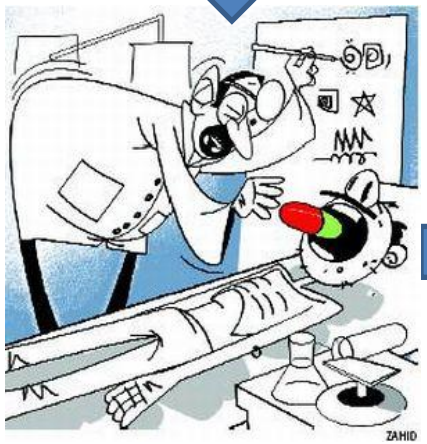
Pre-clinical

Formulation:
Stability
Acceptability
Dose/ volume
Cost per dose

Regulators
MHRA: UK
EMEA: EU
FDA; US

GMP Quality material

Toxicology



Clinical Trials

Sales and Marketing

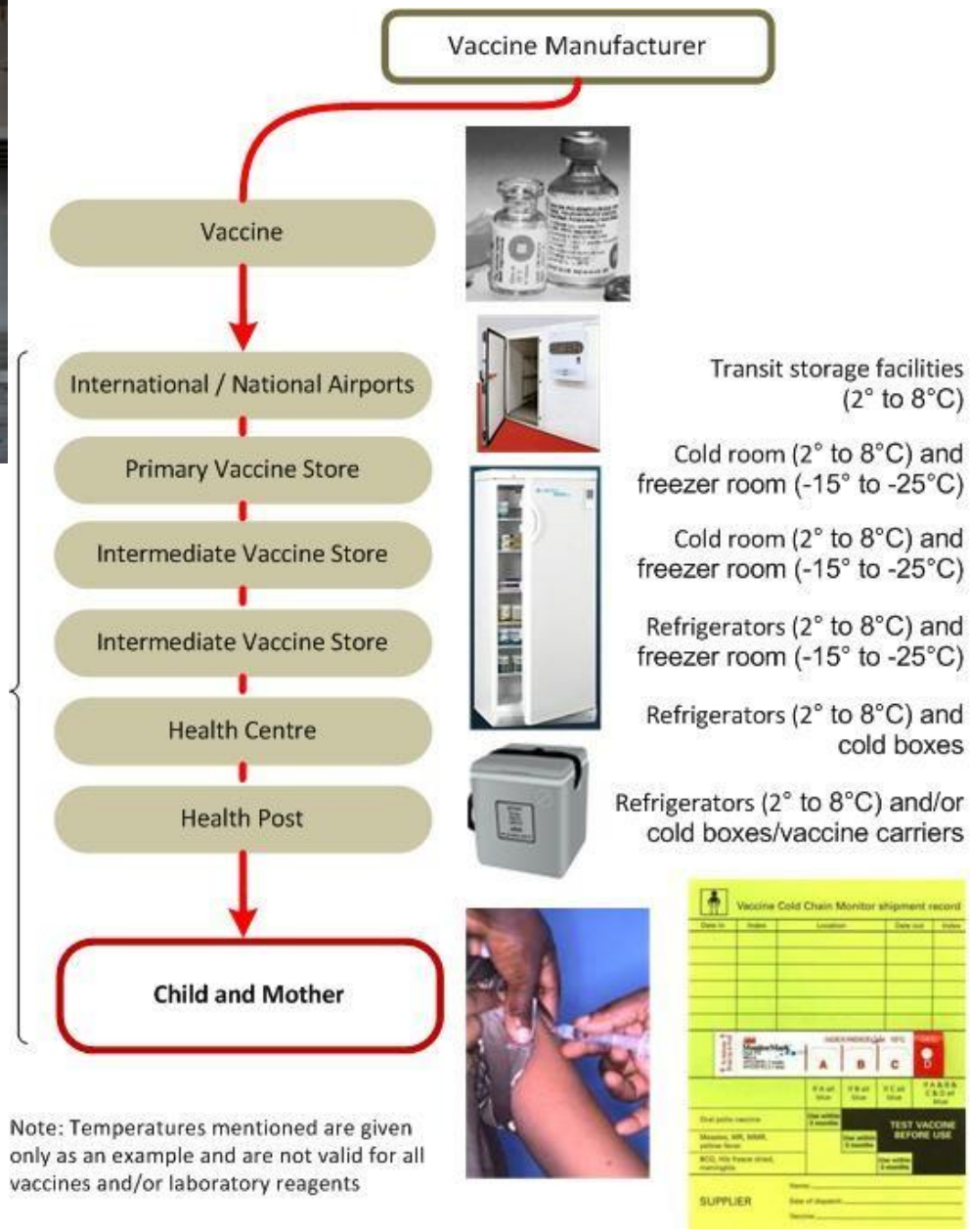
Large Scale
Manufacture

Injection safety

- Major problem in the developing world
  - Transmission of blood borne viruses via needles or syringes
  - Needlestick injuries for clinic staff
- Believed to be a significant contributor to Hep B and Hep C worldwide
- Role in HIV/AIDS unclear (Rumours)
- Sterilizing of used needles and syringes no longer recommended
- Auto-destruct technologies used increasingly in vaccination programs
- An alternative is to develop needle free vaccines

Logistics/ Cold chain

- Keep vaccine cool (2-6ºC) from place of manufacture to place of use
- Developed in an environment of vaccines that were very heat labile (esp. measles)
- In fact freezing of liquid vaccines is a much bigger problem
  - Can occur around the edges of UNICEF top-opening refrigerators
  - Results in inactive vaccine and sterile abscesses
  - Detected by shake-test, Freezewatch indicators



Cost of the product

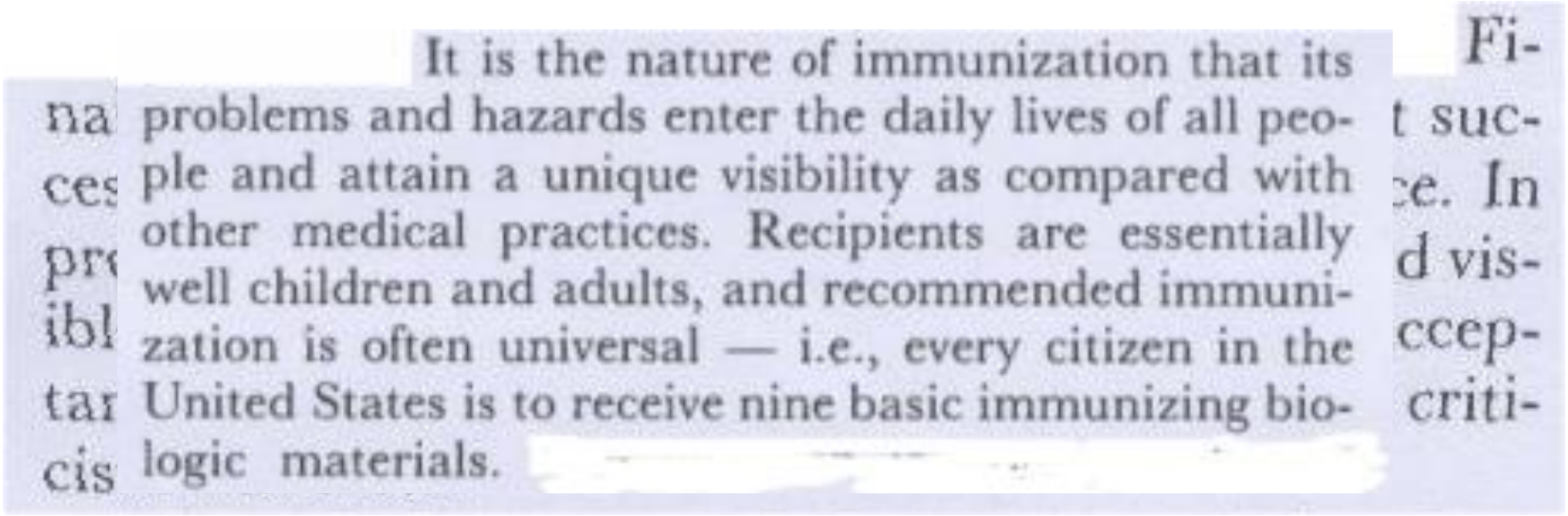
- Single shot of vaccine varies between $10 to $100 per dose (CDC figures Sept 10 2012 www.cdc.gov)
- Varies
  - with age of product e.g. Tetanus/ BSC/ OPV are all cheap, HPV is expensive
  - And complexity – Combination vaccines e.g. DTaP-Hib-IPV or polysaccharide
- Developing world costs $20 per child for BCG, DTP, measles, and OPV – prevents 2 million deaths, Adding hep b, Hib, and yellow fever would raise cost to $40 per child and prevent a further 1 million deaths
- Notably ~ 2005 there were only 4 big pharma making vaccines, now all of them have a vaccine arm

The Problem with People

The problem with Vaccines/ People

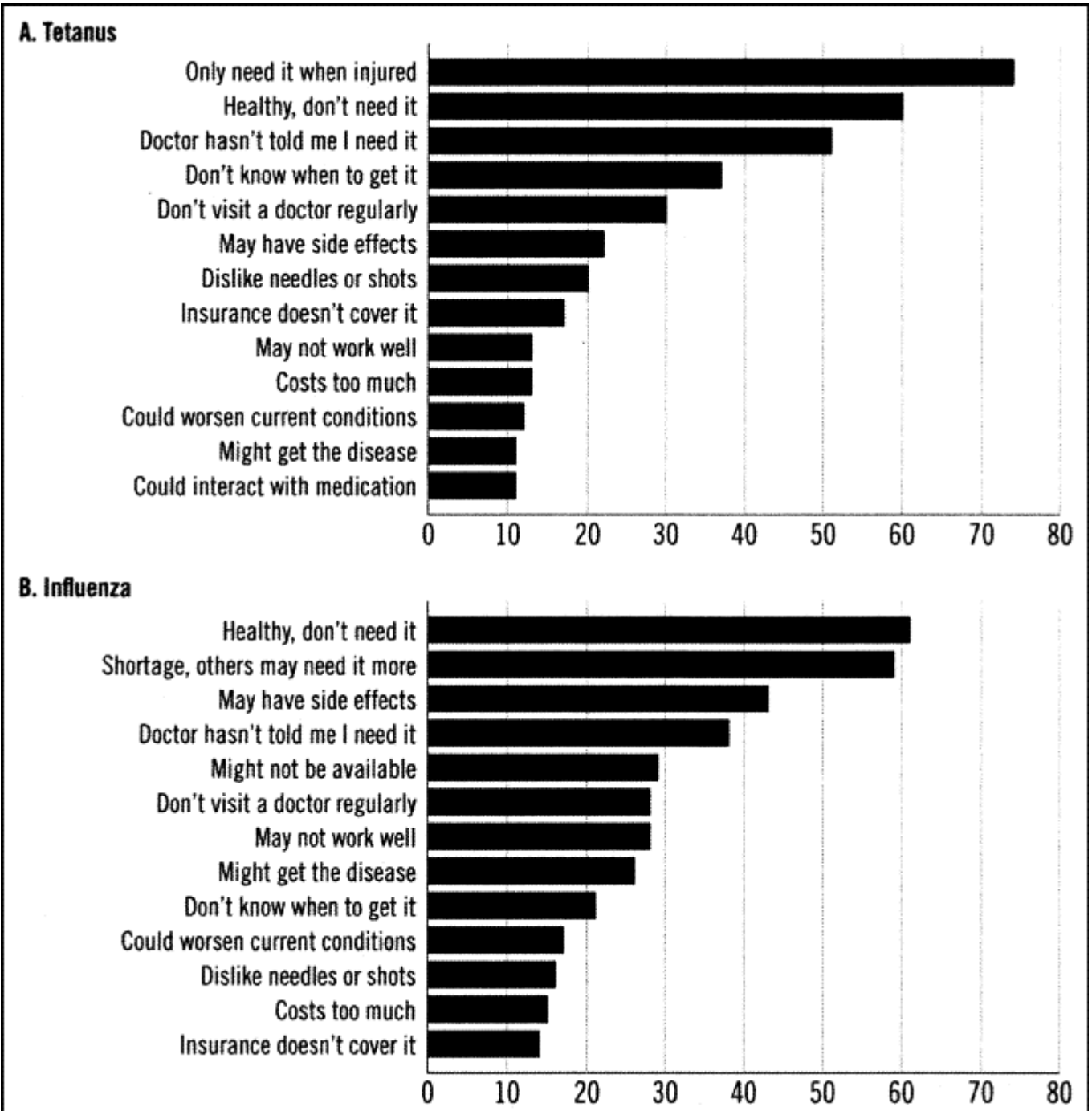
1. People don’t like needles
2. Trust in scientists is declining
3. The success of vaccines in removing diseases especially childhood ones
4. Cost/ recouping costs
5. Game theory and herd immunity
6. Badly informed population
7. Political Manipulation

A Contemporary View?



It is the nature of immunization that its problems and hazards enter the daily lives of all people and attain a unique visibility as compared with other medical practices. Recipients are essentially well children and adults, and recommended immunization is often universal — i.e., every citizen in the United States is to receive nine basic immunizing biologic materials.

Aug 4 1977



Why don't you get vaccinated?

Johnson et al 2008 AJM

Vaccines have been blamed for:

- Increased disease severity (RSV, measles)
- Insulin dependent diabetes
- Childhood epilepsy
- Cerebral palsy
- Autism
- Sudden infant deaths (SIDS)
- Asthma
- Inflammatory bowel disease
- Sterility
- ….etc, etc, etc

Vaccine Alert 1:
The Cutter Incident

A technician at the Cutter labs inspecting the filters

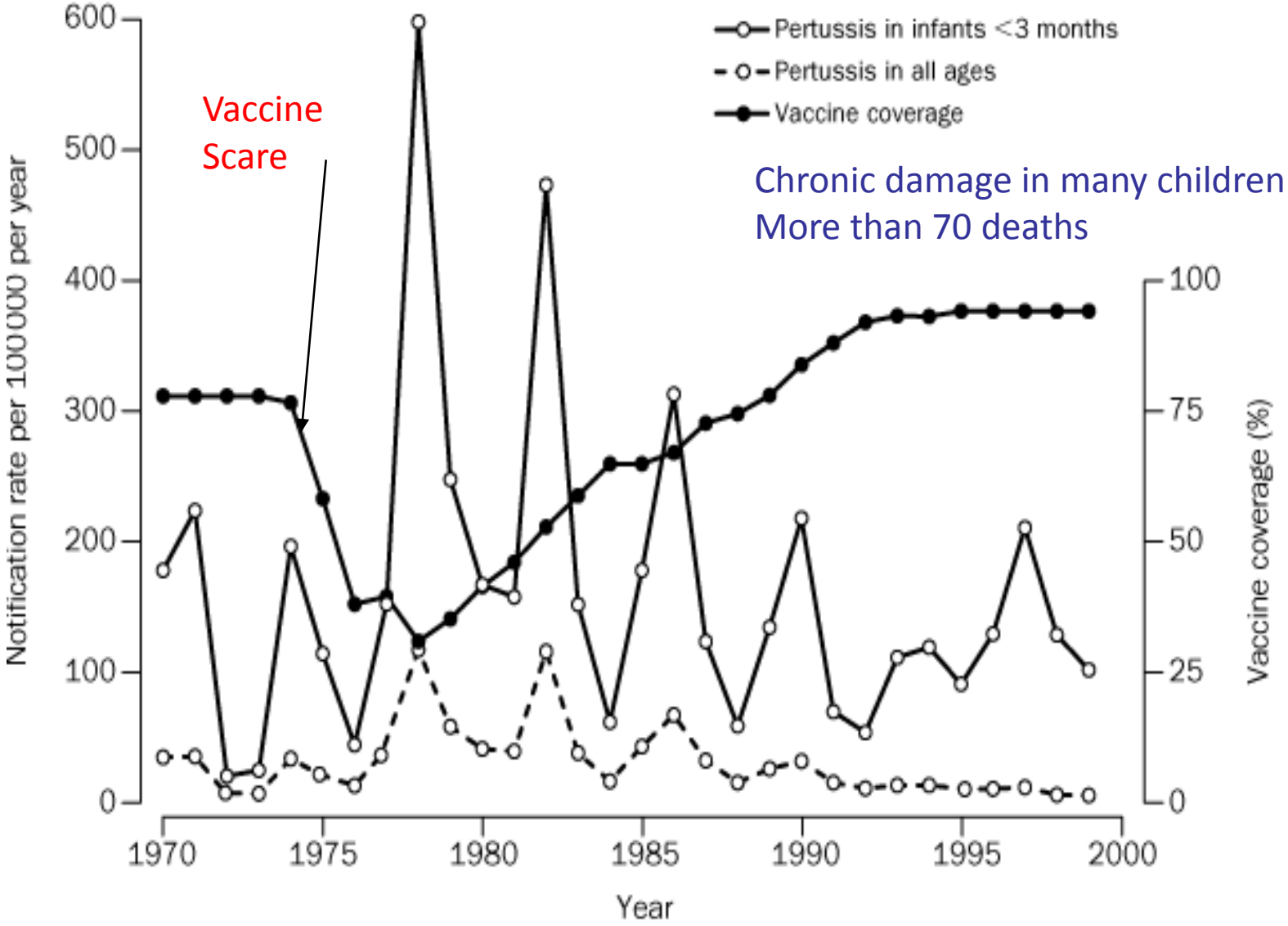
- Live inactivated polio virus (made by cutter labs)
- In 1955 Live virus included in some of the batches
- Abortive polio developed in 40,000 children
- 51 were permanently paralyzed and 5 died
- Cell debris during production prevented formalin inactivation

1974: Vaccine Alert 2

- Anecdotal reports link whooping cough vaccine and brain damage

- In childhood, evidence of brain damage often appears at 1-5 yrs (i.e. at time of vaccination)

Whooping cough in England and Wales



Lancet 2000; **355:** 1553 - 1560 *Nigel J Gay, Elizabeth Miller (PHLS)*

1998: Vaccine Alert 3

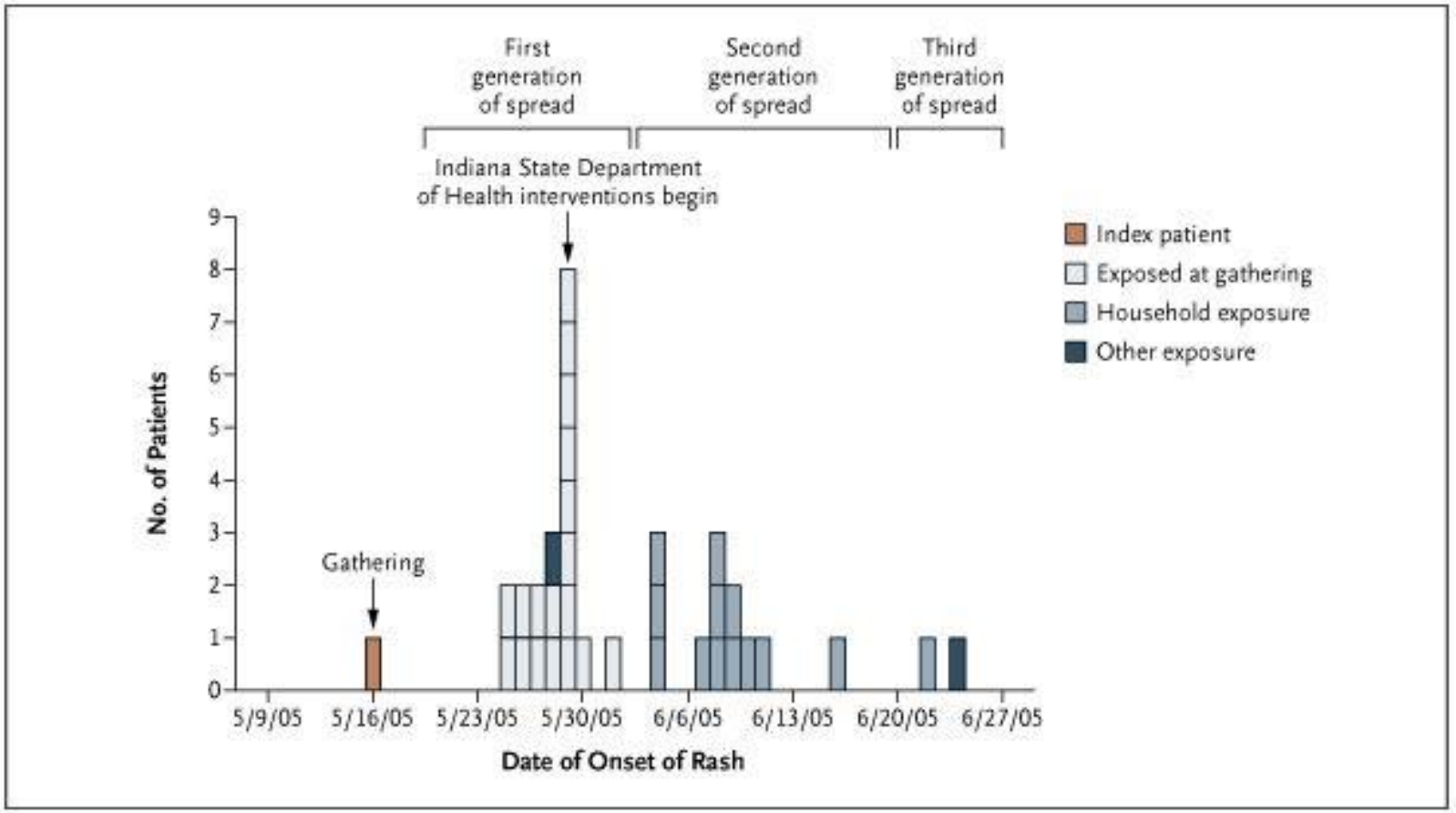
- Anecdotal link between MMR and autism

- In childhood, peak onset of overt autism is 1-5 yrs (i.e. at time of vaccination)

- Response: vaccine rates fell from 92% to 88%
  - Measles notifications rose
  - Chronic damage
  - Deaths

- National inquiry: no evidence of link

Measles in unvaccinated Children



Index case unvaccinated – went to Romanian orphanage
Came back to a church gathering where 50 others were unvaccinated.
Total cases 34
Health Care cost of this outbreak $167,685

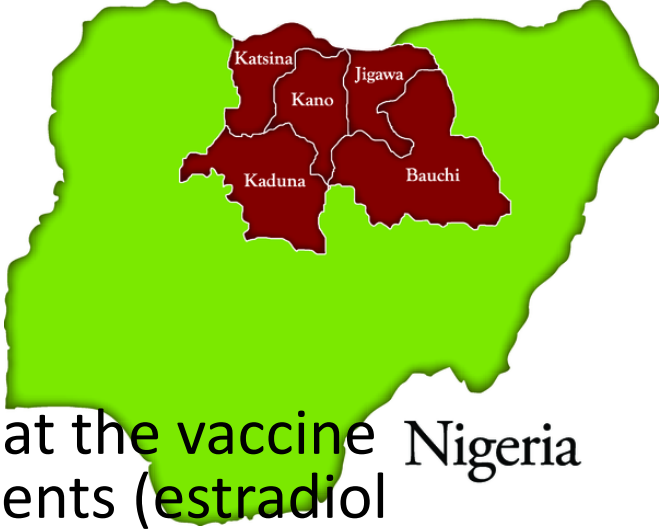
Washington Post June 2002

MMR in the news

Key Protagonist of Autism story: Dr Andrew Wakefield

1. Issues with funding of work and conflicts of interest
   – ‘received funding to see if there was any evidence to support possible legal action by a group of parents who claimed their children were damaged by the vaccine’
2. Paper disowned by the Lancet
3. Dr Wakefield has faced charges by the GMC and was struck off in 2010

Nigerian Polio Boycott



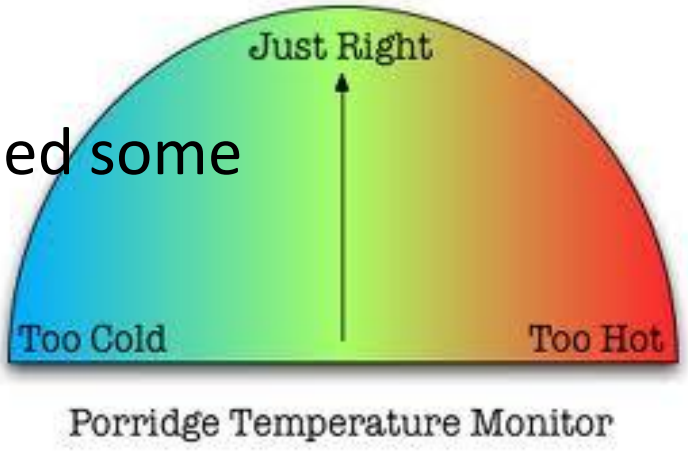
- 2003 Leaders in 3 Nigerian States argued that the vaccine could be contaminated with anti-fertility agents (estradiol hormone), HIV, and cancerous agents. (driver was backlash from 9/11 and Iraq war)
- 2004 Federal government demonstrated its safety, but was rejected by local groups
- Deadlock broken through dialogue – vaccine now manufactured by Indonesian company
- Fresh Polio Outbreak in October 2003
- Nigeria still one of the countries where Polio not erradicated (80% of global polio burden in 2006)
- Spread to surrounding countries but also to Yemen, Saudi Arabia, and Indonesia (due to Hajj or migrant oil-workers)
- Local politics – global consequences!

Freeloaders

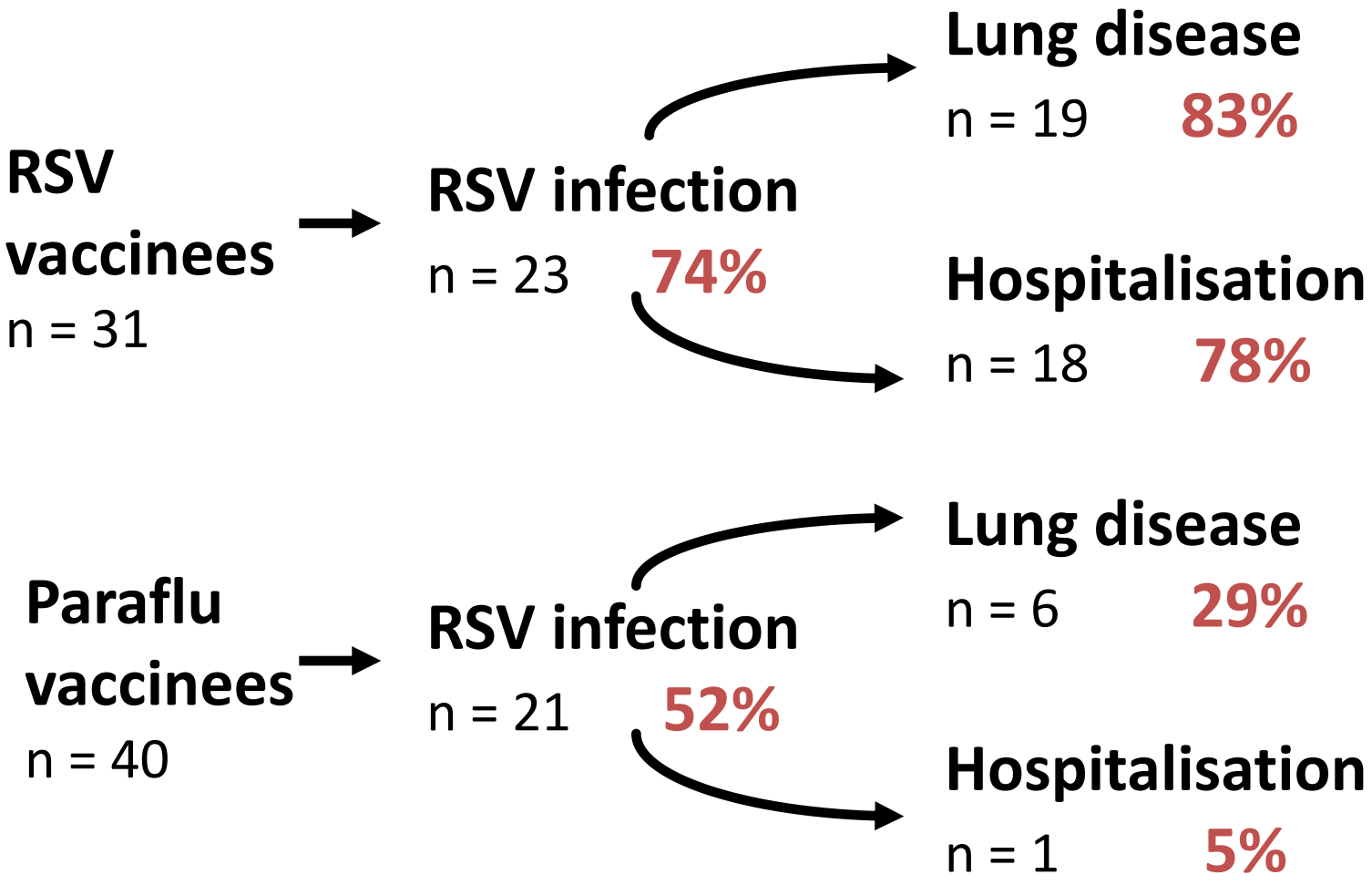
- Vaccination comes with costs to individuals - side effects, time, money, inconvenience.
- A high level of vaccine uptake in the community may mean that the chance of contracting an infection is close to 0.
- the ideal (selfish) strategy is that *everyone else* should be directly protected by vaccination
- when coverage is close to p_c, or when vaccination is perceived to carry a risk ≥ infection, incentive to get vaccinated is less
- E.g. MMR vaccination/ pertussis vaccinations
- Complex risk benefit calculation with limited information

When good vaccines go bad

- There are examples of vaccines that have either not been licensed or been revoked after license
- Vaccines work by artificially boosting the immune memory to an infection
- However the immune response generated may be in excess of that which is required to clear infection
- 2 Areas of concern for vaccines
  - acute responses
  - Chronic complications
- In order to get a response you do need some inflammation (goldilocks!)



Vaccine-augmented disease
Formalin-Inactivated RSV



Still not tested animals in 1965!

Merck STEP HIV

- Adenovirus 5 (Ad5) based vaccine
- 3,000 healthy uninfected volunteers with three rAD5 vectors- Ad5-gag, Ad5-pol, and Ad5-Nef
- Issues AdV specific antibody
- Possibly increased susceptibility – increasing the number of target Cells (CD4) in the target area – though the stats are based on v small numbers:
  - 24 Positive in Vaccinated
  - 21 Positive in Unvaccinated
  - But 5.2% in High Ad5 seropositive males compared to 2.2% in seronegative

Rotavirus

- RotaShield – rotavirus vaccine (Wyeth)
- Licensed in 1998, withdrawn 1999
- Potentially Increased risk of Intussusception (OR 21.7) after first dose
- Withdrawn in
- New vaccines licensed in 2006
- Potentially the withdrawal led to 1.4-3.2 million additional deaths

Narcolepsy and H1N1 vaccine

- Swedish Medical Products Agency (March 11) risk 4x higher in vaccinated than unvaccinated
- Absolute risk at 3 in 100,000
- Similar effect in Finland and Iceland
- Vaccine was Pandemrix (GSK) adjuvanted with MF59
- Narcolepsy strongly linked to (HLA) DQB1*0602 genotype, 100% of Finnish cases have this genotype
- Pandemrix no longer recommended for <20 yr olds

Fluvax (CSL)

- In the 2010 batches of virus high rates of febrile convulsions
- 3.3 per 1,000 doses (200x greater than US rate)
- Fluvax lead to high cytokine release
- Possibly linked to the strain in the virus 2009 was H1N1 Brisbane, 2010 had H1N1 California, but B strain incorporated is important
- Also use a slightly different manufacturing process
- Effect Heat Labile – probably a protein

Dengue – watch this space

- Large scale Dengue vaccine trial by Sanofi – 3% infected in vaccine group compared to 4% in placebo (30%) effective
- However Dengue Hemoraggic Fever (DHF) has been associated with incomplete cross serotype protection (immuno-pathology)
- If Dengue vaccine provides immune memory but incomplete protection, it may increase DHF

Implementing Vaccine Policy

Steps in the Implementation of a vaccination policy

Choose policy - mass or selective

- Examples of Mass Campaigns
- Examples of Selective Campaigns

Publish recommendations ('green book': *Immunisation Against Infectious Disease*)

License vaccine

Purchase vaccine

Media campaign

Start giving vaccinations

How it happens in the UK

- Recommendations for vaccine policy
  - Joint Committee on Vaccination and Immunisation
- Vaccine policy decisions
  - Department of Health
- Licensing of vaccine
  - Medicines and Healthcare products Regulatory Agency (MHRA)
- Purchase of vaccine
  - Department of Health from pharmaceutical companies
- Control of vaccine (including batch release)
  - National Institute for Biological Standards and Control

To Design a vaccine program from scratch

- What considerations are there?
  - Aim
  - Need
  - Scheduling with other vaccines
  - Availability
  - Cost
  - Population accessibility
  - Cultural attitudes and practices
  - Facilities available for delivery

Aim

- **Eradication -** Disease and its causal agent have been removed worldwide e.g. small pox
- **Elimination -** Disease has disappeared from one WHO region but remains elsewhere e.g. polio
- **Containment -** The point at which the disease no longer constitutes a 'significant public health problem' e.g. Hib

Is there a need?

- Disease incidence
- Age distribution of disease
- Disease trends
- Disease complications
- Mortality
- Population / cultural attitudes
- Cost and benefit
- Political expenditure
- Vaccine efficacy and side effects
- Availability and validity of delivering
- Provision of trained primary care providers
- Vaccine type

babycards
www.babycardsnow.co.uk

Vaccination wall planner

2 months (Apr 2011)

DTaP/IPV/Hib vaccine:
protects against diphtheria, tetanus, pertussis (whooping cough), polio and Haemophilus influenzae. (First dose) ☐

Pneumococcal vaccine:
protects against pneumococcal infection, which can cause diseases such as pneumonia, septicaemia and meningitis. (First dose) ☐

3 months (May 2011)

DTaP/IPV/Hib vaccine:
protects against diphtheria, tetanus, pertussis (whooping cough), polio and Haemophilus influenzae. (Second dose) ☐

MenC vaccine:
protects against Meningococcal group C, a type of bacteria that can cause meningitis and septicaemia. (First dose) ☐

4 months (Jun 2011)

DTaP/IPV/Hib vaccine:
protects against diphtheria, tetanus, pertussis (whooping cough), polio and Haemophilus influenzae. (Third dose) ☐

MenC vaccine:
protects against Meningococcal group C, a type of bacteria that can cause meningitis and septicaemia. (Second dose) ☐

Pneumococcal vaccine:
protects against pneumococcal infection, which can cause diseases such as pneumonia, septicaemia and meningitis. (Second dose) ☐

12-13 months (Mar 2012 - Apr 2012)

Hib/MenC booster vaccine:
protects against Haemophilus influenzae type b (Hib) and Meningitis C. (Booster dose) ☐

MMR vaccine:
protects against measles, mumps and rubella. (First dose) ☐

Pneumococcal vaccine:
protects against pneumococcal infection, which can cause diseases such as pneumonia, septicaemia and meningitis. (Third dose) ☐

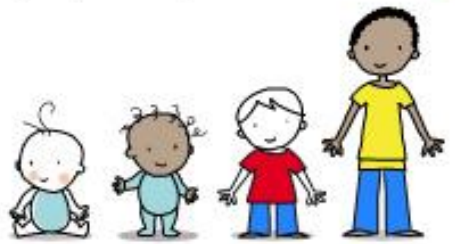
40 months (Jun 2014)

DTaP/IPV booster vaccine:
tops up the protection against diphtheria, tetanus, pertussis (whooping cough) and polio. (Booster dose) ☐

MMR vaccine:
protects against measles, mumps and rubella. (Second dose) ☐

13-18 years (Feb 2024 - Feb 2029)

Td/IPV booster vaccine:
tops up the protection against tetanus, diphtheria and polio. (Booster dose) ☐



All information in this chart is correct as of December 2010. The recommendations made are based on what you have told us and do not constitute medical advice. You should always talk to an appropriate health professional about immunisation. If your child has a long term chronic condition or has no spleen, they may need extra immunisations. As a result this schedule only applies to those who need routine immunisation. In other cases you should consult your doctor or nurse directly.

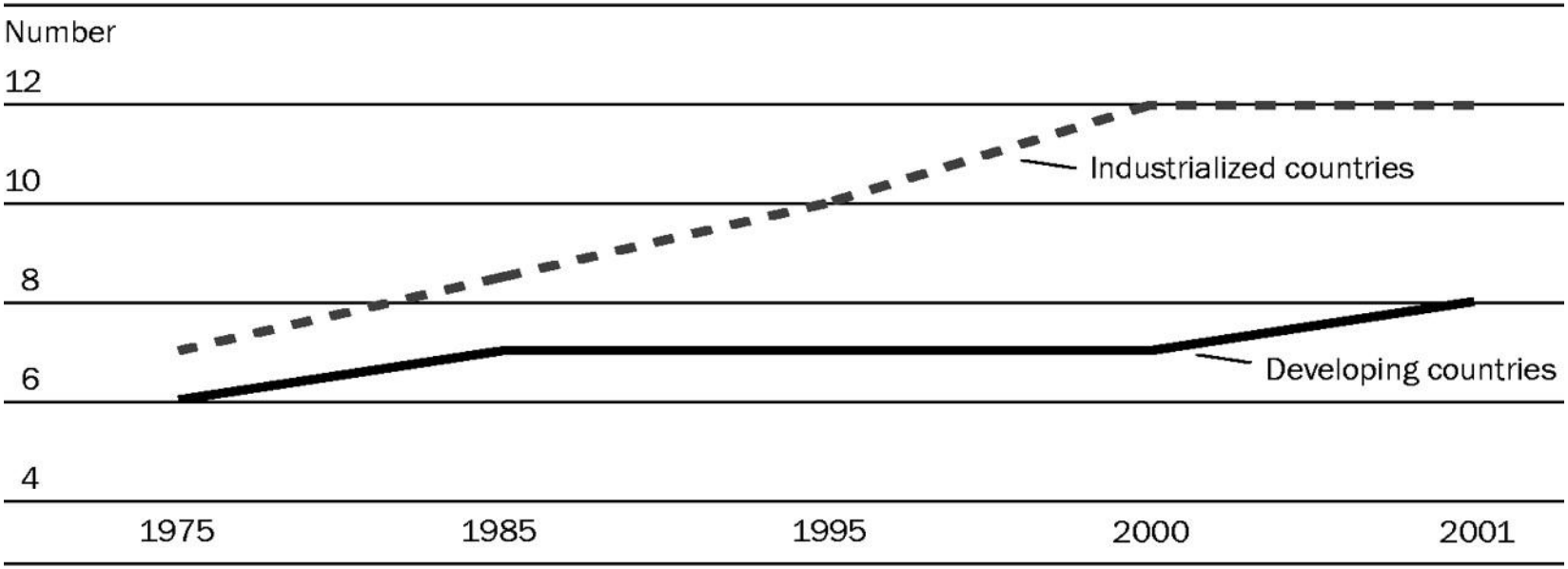
For more information visit www.nhs.uk/vaccination

NHS choices

Trends Over Time In The Number Of Vaccine Antigens Given To The Average Child In Developing And Industrialized Countries, Selected Years 1975–2001.

EXHIBIT 3

Trends Over Time In The Number Of Vaccine Antigens Given To The Average Child In Developing And Industrialized Countries, Selected Years 1975–2001



SOURCE: Amie Batson, World Bank, personal communication, 11 November 2004.

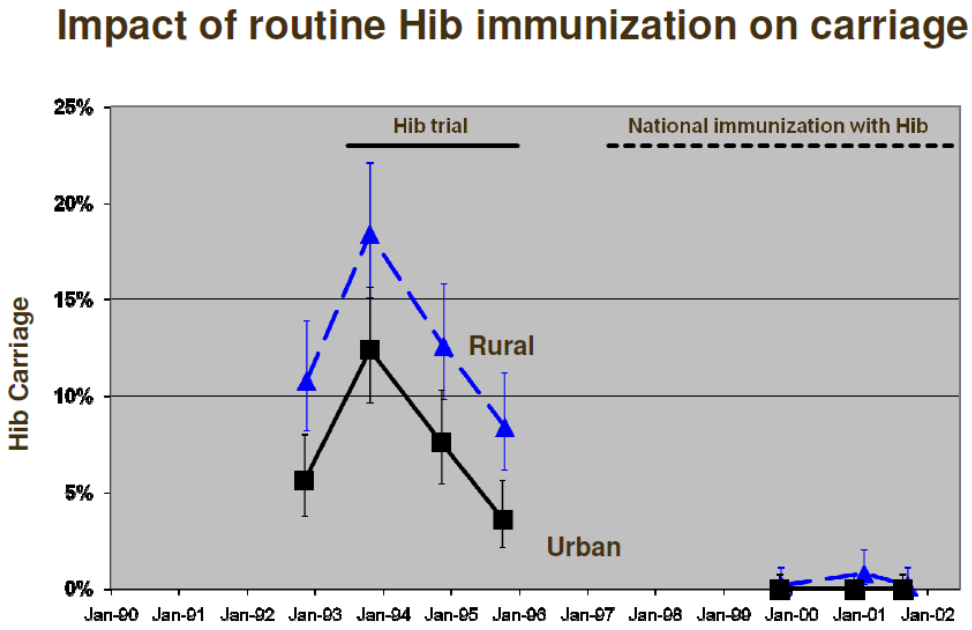
Lieu T A et al. Health Aff 2005;24:666-679

Issues with scheduling

1. Effect on Carriage
2. Effect on Carriage on Natural Immunity
3. Effect on Carriage on Natural Immunity On Maternal Antibody
4. Vaccine Interference
5. Evolutionary Effect - Influenza

Effect on Carriage

- Vaccines don't only protect the vaccinee but can also protect contacts
- Particularly when children are main carriers



Adegbola et al. Lancet 2005; 366:144-150

S-I-R-S

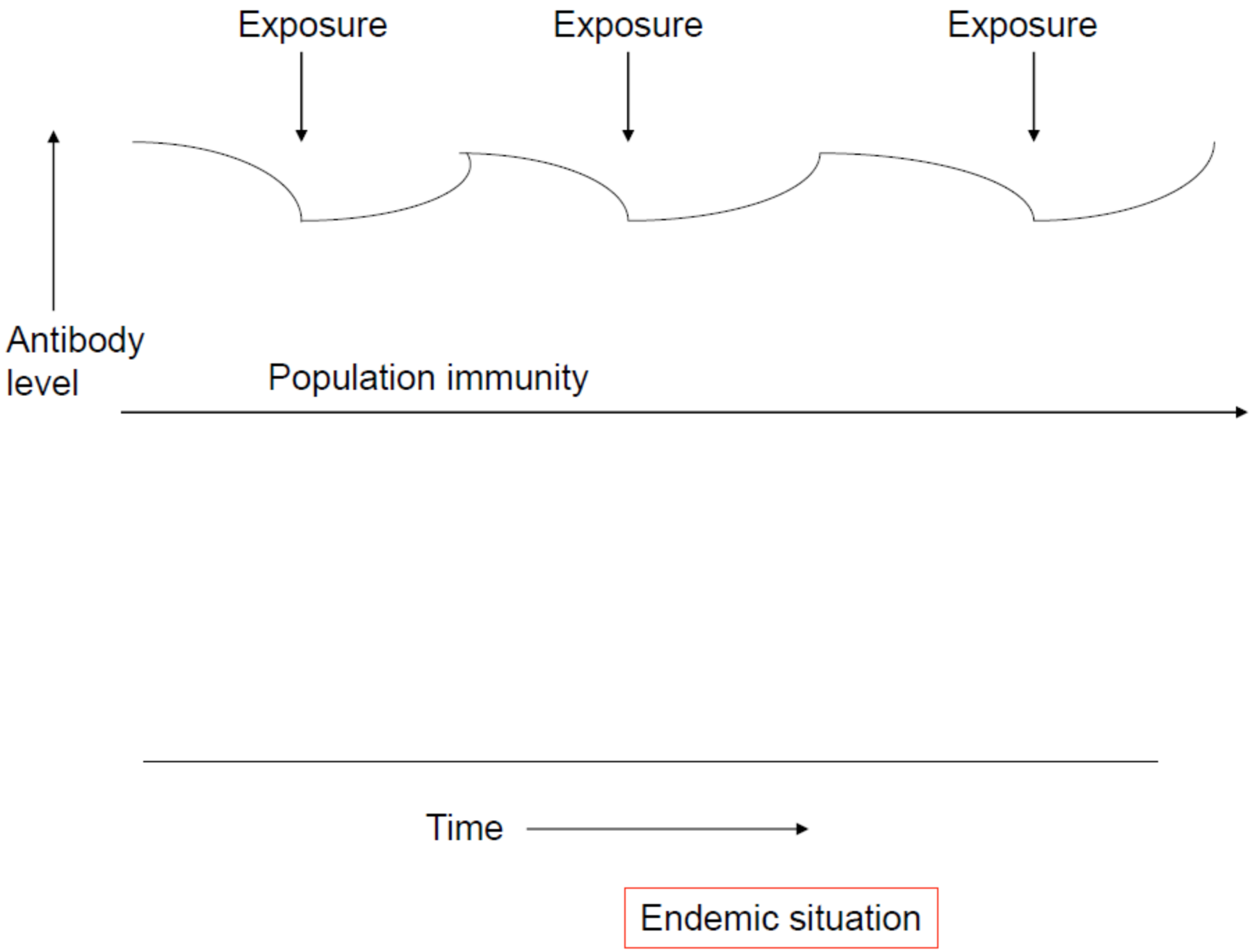
- UK experience was 8 years after intro of Hib vaccine rates were increasing
- UK schedule was 2,3,4 months with no booster
- Led to low antibody levels
- Vaccine failure – possibly also affected by combination in vaccine
- Vaccination also reduced community carriage – potentially affecting antibody
- Mathematical models suggested low antibody key correlate – leading to change in schedule and intro of a booster vaccine

	1992 [*n* (%)]		1994 [*n* (%)]		1997 [*n* (%)]		2002 [*n* (%)]	
(*a*) By year of collection and age								
Age (years)								
1–1·99	0/17	(0)	0/27	(0)	0/4	(0)	0/69	(0)
2–2·99	9/349	(2·58)	0/279	(0)	0/129	(0)	0/96	(0)
3–3·99	30/904	(3·32)	7/888	(0·79)	0/229	(0)	0/134	(0)
4–4·99	22/261	(8·43)	4/369	(1·08)	0/96	(0)	0/85	(0)
Total	61/1531	(3·98)	11/1563	(0·70)	0/458	(0)	0/384	(0)

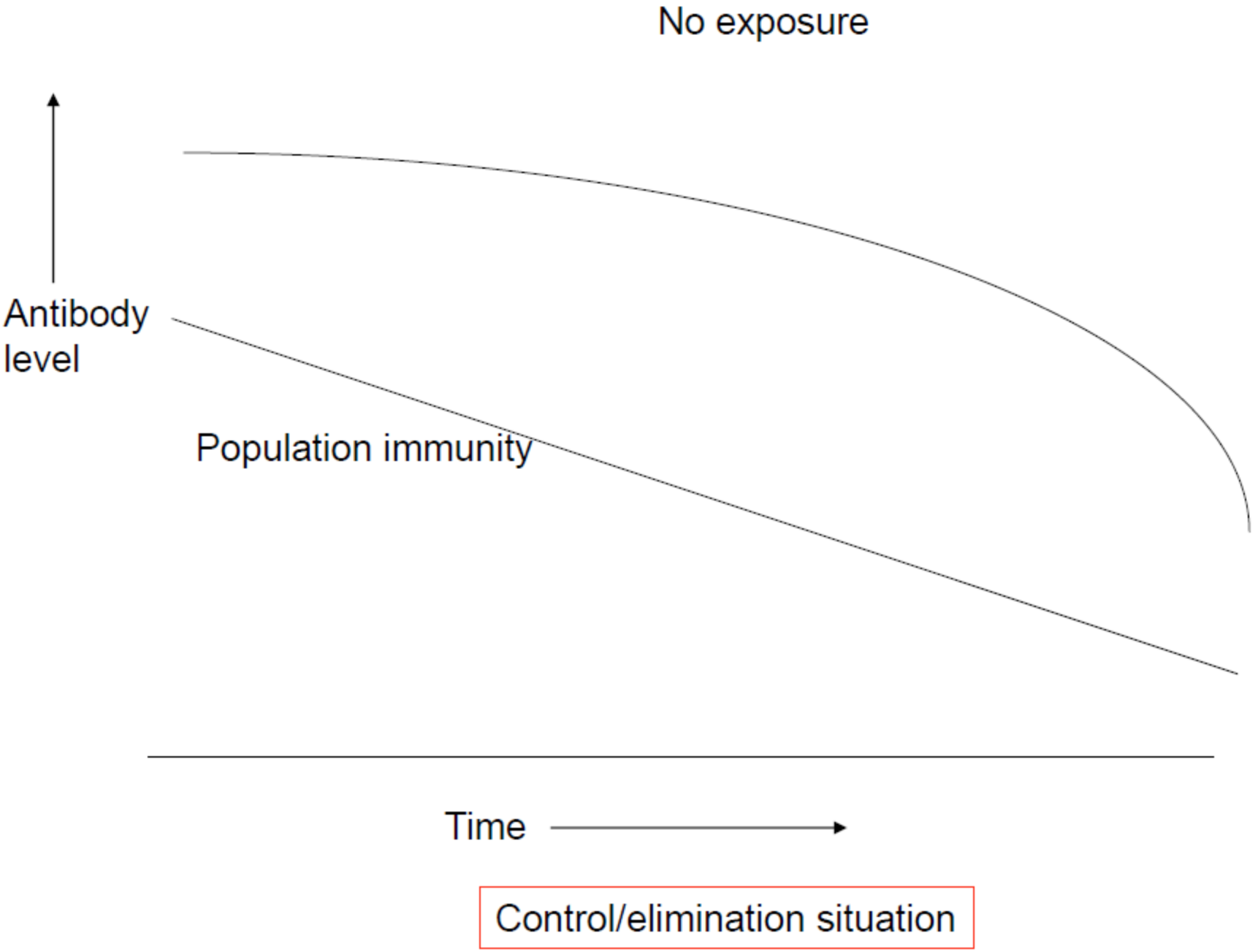
Effect on Carriage on Natural Immunity

Measles

- Good evidence that adult immunity is boosted by exposure to natural measles
- Control/elimination leads to loss of population immunity
- Outbreaks seen in adults –due to secondary vaccine failure
- Need for booster doses

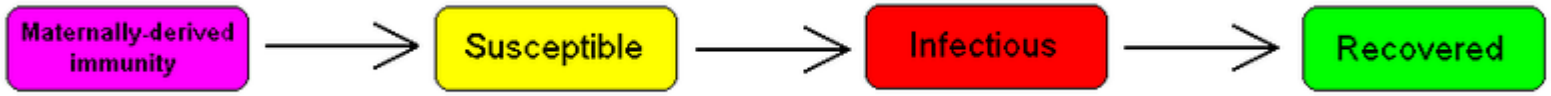


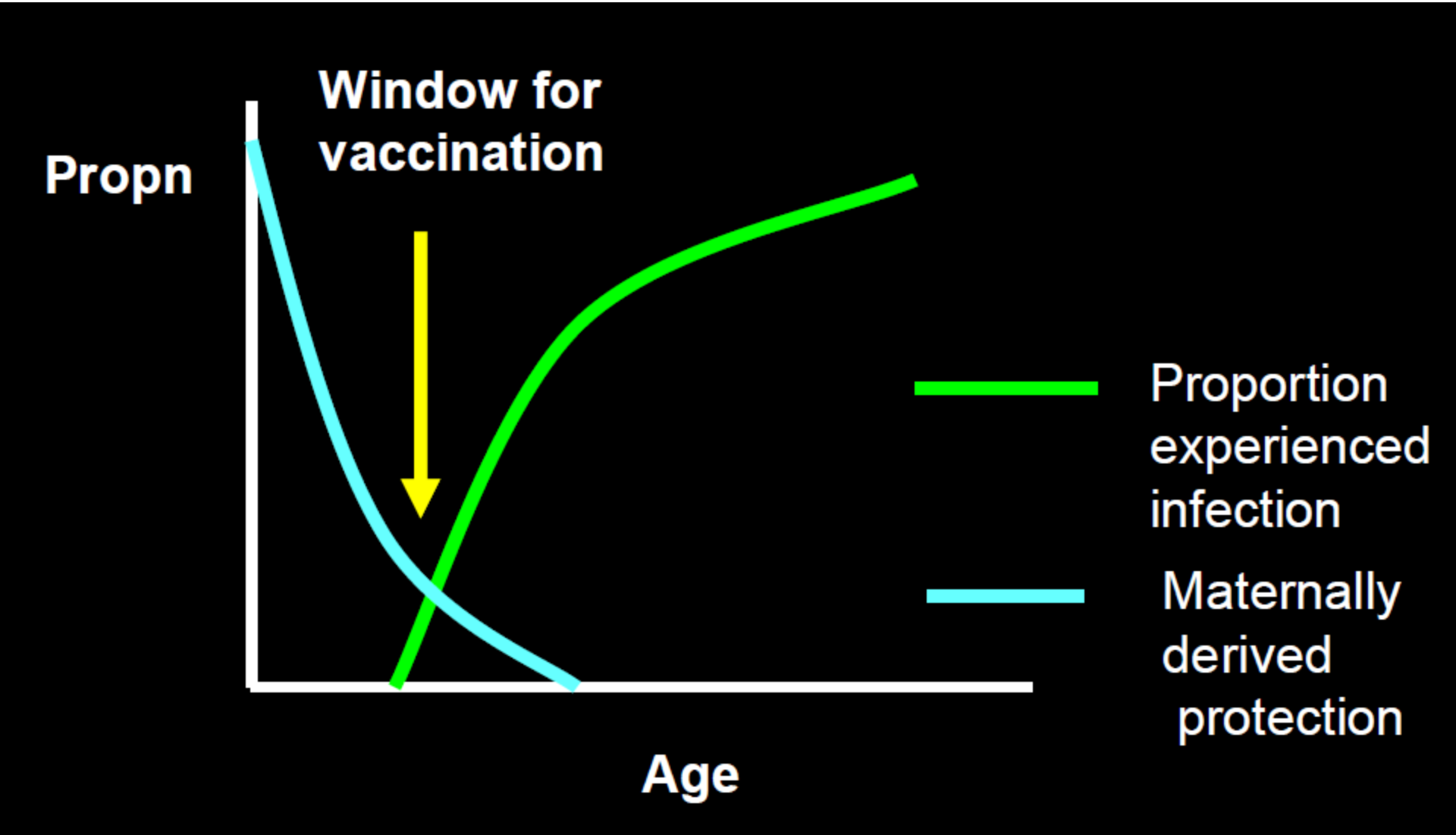
Endemic situation


No exposure
Antibody level
Population immunity
Time
Control/elimination situation

Effect on Carriage on Natural Immunity On Maternal Antibody

- Women of child bearing age are increasingly vaccinated rather than naturally infected
- This means that their levels of antibody are probably lower.
- Either way maternal immune status has a large impact on the response to vaccines in children
- Particulalry noted in Measles


Maternally-derived immunity
Susceptible
Infectious
Recovered


Window for vaccination
Propn
Age
Proportion experienced infection
Maternally derived protection

Why are responses to vaccines poor in infants?

Maternal Antibody

May prevent effective vaccination.

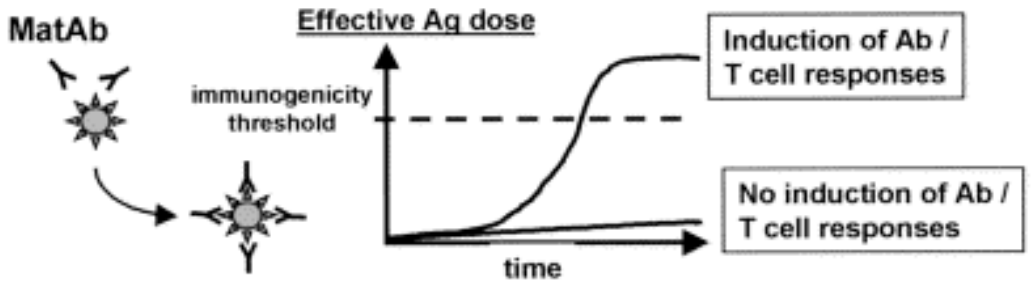
E.g. maternal antibody can block antibody production and therefore protection with measles - but not the development of T-cell memory, so this can be boosted later.

Sometimes higher doses or repeated vaccination can overcome.

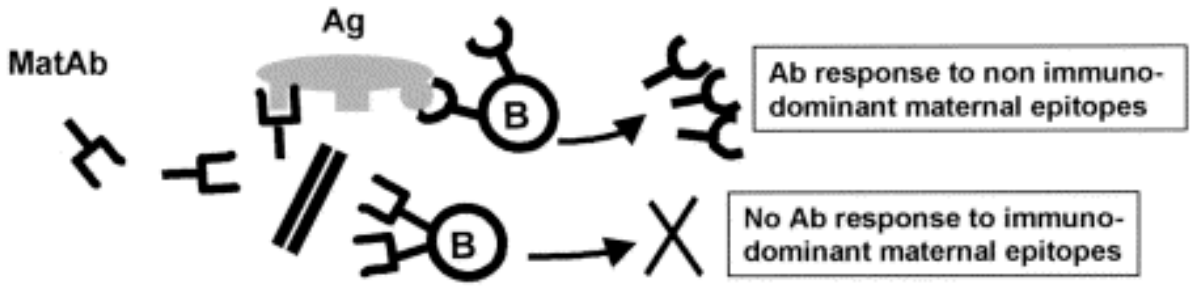
Immunity Gap - Maternal antibody titres are too low to protect, but are still enough to prevent effective vaccination.

Influence of passively transferred antibodies on induction of vaccine responses

1. Neutralisation of live vaccines, depending on MatAb / Ag load ratio



2. Epitope-specific B cell masking, preventing binding by epitope specific infant B cells



3. APC uptake of immune complexes, processing and Ag presentation

Siegrist CA *Vaccine* (2001) **19** : 3331-46

Vaccine interference

- Sometimes one vaccine may affect another when co-administered
- When 2 live vaccines are administered at staggered intervals, the immune response to one may prevent the other 'taking'
- Another example is the DTaP-Hib vaccine where antibody responses are lower to Hib polyribosylribitol phosphate antigen than when administered singly
  - This effect linked to pertussis formulation – effect only occurs for acellular pertussis (aP) but not whole cell pertussis (wP)
  - May have contributed to reduced Hib vaccine efficacy in UK
- Also a number of vaccines use the same carrier protein
- Finally if live viral vectors are used, pre-existing immunity to the vector may affect vaccine efficacy

Vaccine Driven Evolution

- Immunity drives Selection of Pathogens
- It may be that for pathogens with greater than one serotype vaccination may simply switch the main circulating agent (e.g. HPV)
- Or for respiratory bacteria may change the prevalence of the bacteria colonising the respiratory space
- Or it may be that universal pediatric flu vaccination lead to the switch from H3N2 to H1N1

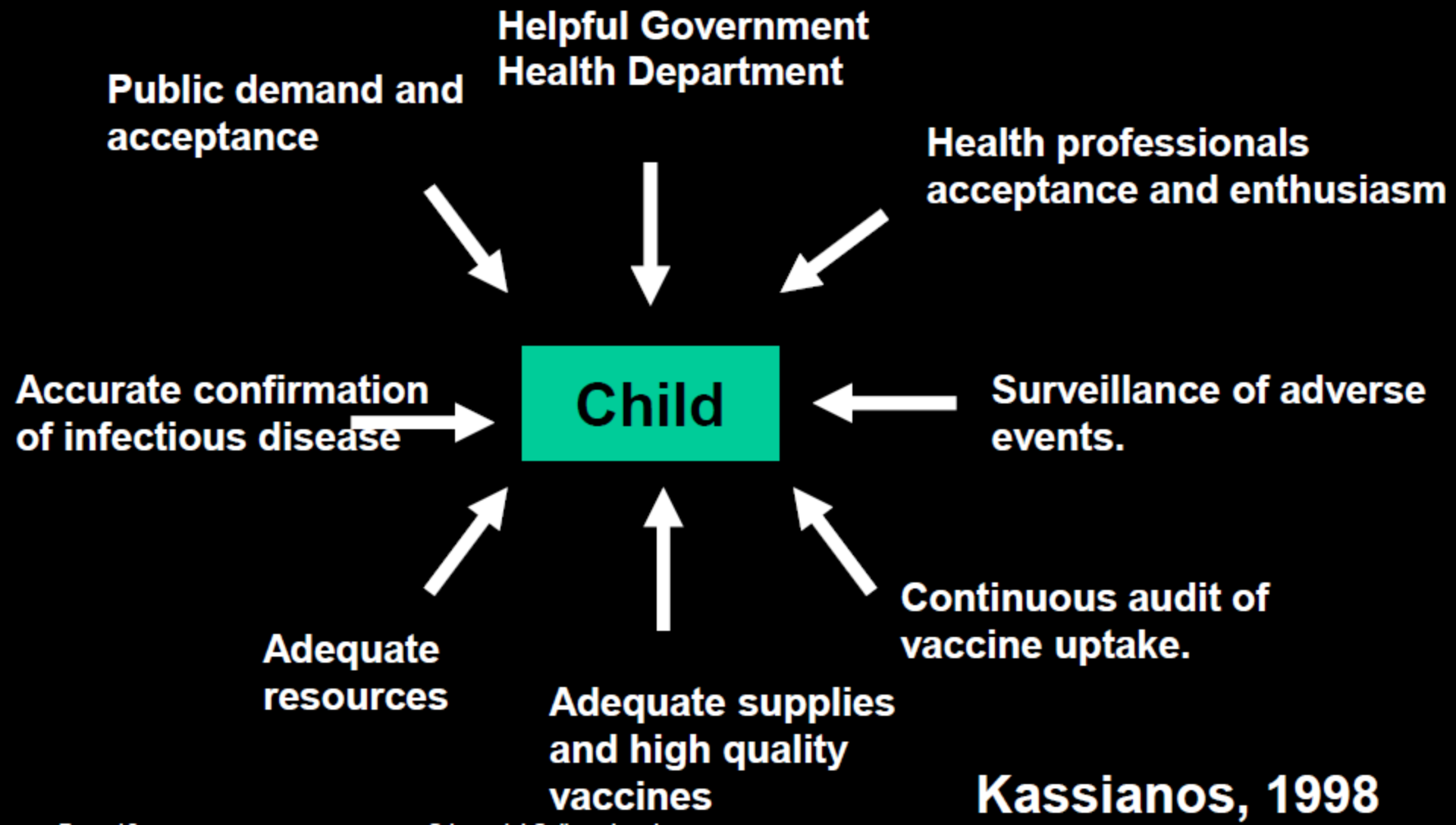
HPA Schedule considerations

- Vaccines are recommended for the youngest age group at risk of experiencing the disease for whom the vaccine's efficacy and safety have been demonstrated
- Recommendations for the age at which vaccines are administered are influenced by:
  - age-specific risks for disease
  - age-specific risks for complications
  - ability to respond to the vaccine according to age
  - potential interference with the immune response by passively transferred maternal antibody

HPA **Scheduling recommendations**

- There is no limit to the number of vaccines that can be administered at any one time
- -simultaneous administration is safe, advantageous and does not cause 'immune overload‘
- Live vaccines, if not given at same appointment, should be separated by a four week interval
- -shorter interval may result in a reduced immune response to the dose given 2nd because interferon produced in response to the 1st vaccine inhibits replication of the virus in 2nd vaccine
- 4 week interval recommended between administration of live viral vaccines and tuberculin testing
- -this can result in a false-negative test in tuberculin-positive individuals
- MMR should not be given for 3m following receipt blood transfusion or immunoglobulin
- -these may contain measles-specific antibody which could prevent vaccine virus replication

Factors influencing achievement of high immunization coverage



Kassianos, 1998

Efficacy

Two theoretical ways in which a vaccine fails

- **Failure to *Take* *failed sero-conversion/ immunogenicity. Efficacy = fraction fully protected.***
- **Failure against infectious challenge (infection) – challenge dose, cofactors, *Degree* –*Efficacy = number of challenges protected from.***
- ***This affects*** $p_c = \frac{(1 - 1/R_0)}{E}$

The future?

1. Big Pharma are now seeing vaccines as an area of profit – more investment more breakthroughs
2. Big Philanthropy are doing their best to focus on neglected tropical diseases

New Vaccines

- **Human Papillomavirus** cause of genital warts and associated with cervical cancer
- **Gardasil** (Merck): Quadravalent recombinant HPV 6, 11, 16, 18 vaccine (4 virus serotypes)
- Licensed in June 2006 by the FDA
- The role of the religious right!
  - **Gardasil** – the Merck vaccine is effective against warts and cancer
  - **Cervarix** – The GSK Vaccine is effective against cancer only
- **Rotavirus** New Vaccines released in 2006 Rotarix (GSK) and RotaTeq (Merck)
- Sanofi's **Dengue** Virus
- **HIV** RV144 trial

Conclusions