Control of measles in England 1968-2009 and update on post-exposure prophylaxis

Mary Ramsay

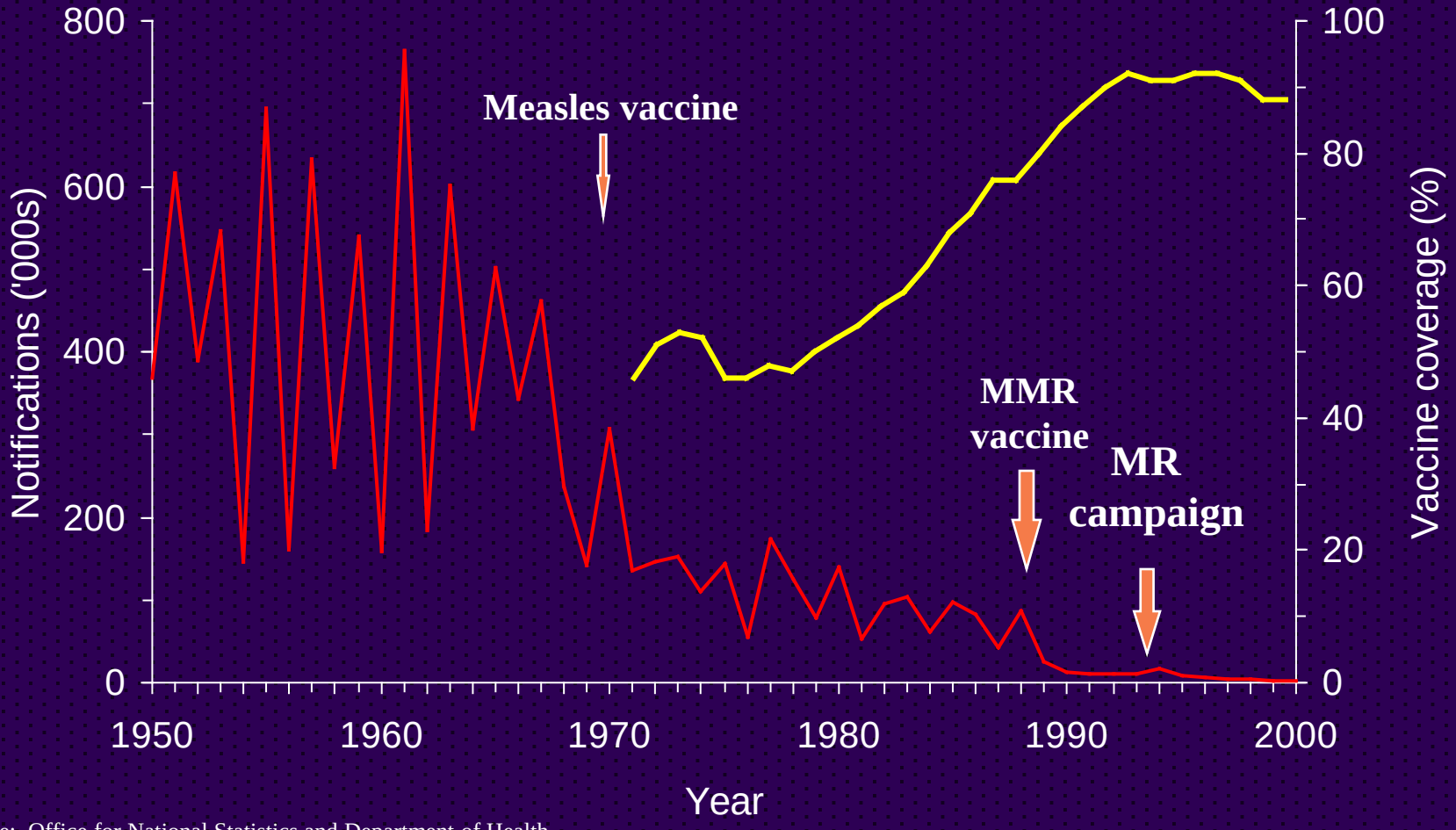
HPA Centre for Infections

History of measles epidemiology in the UK

- Prior to the use of measles vaccine
  - Large epidemics of measles every second year year
  - Up to 800,000 cases reported in each epidemic year
  - Most cases in pre-school children
  - Almost all adults immune from natural infections
- Measles vaccine introduced in 1968
  - Poor coverage until late 1980s
  - Epidemic cycles continued to occur
  - Most infections still occurring in young children

Annual measles notifications & vaccine coverage

England and Wales 1950-2000



Source: Office for National Statistics and Department of Health

History of measles vaccination

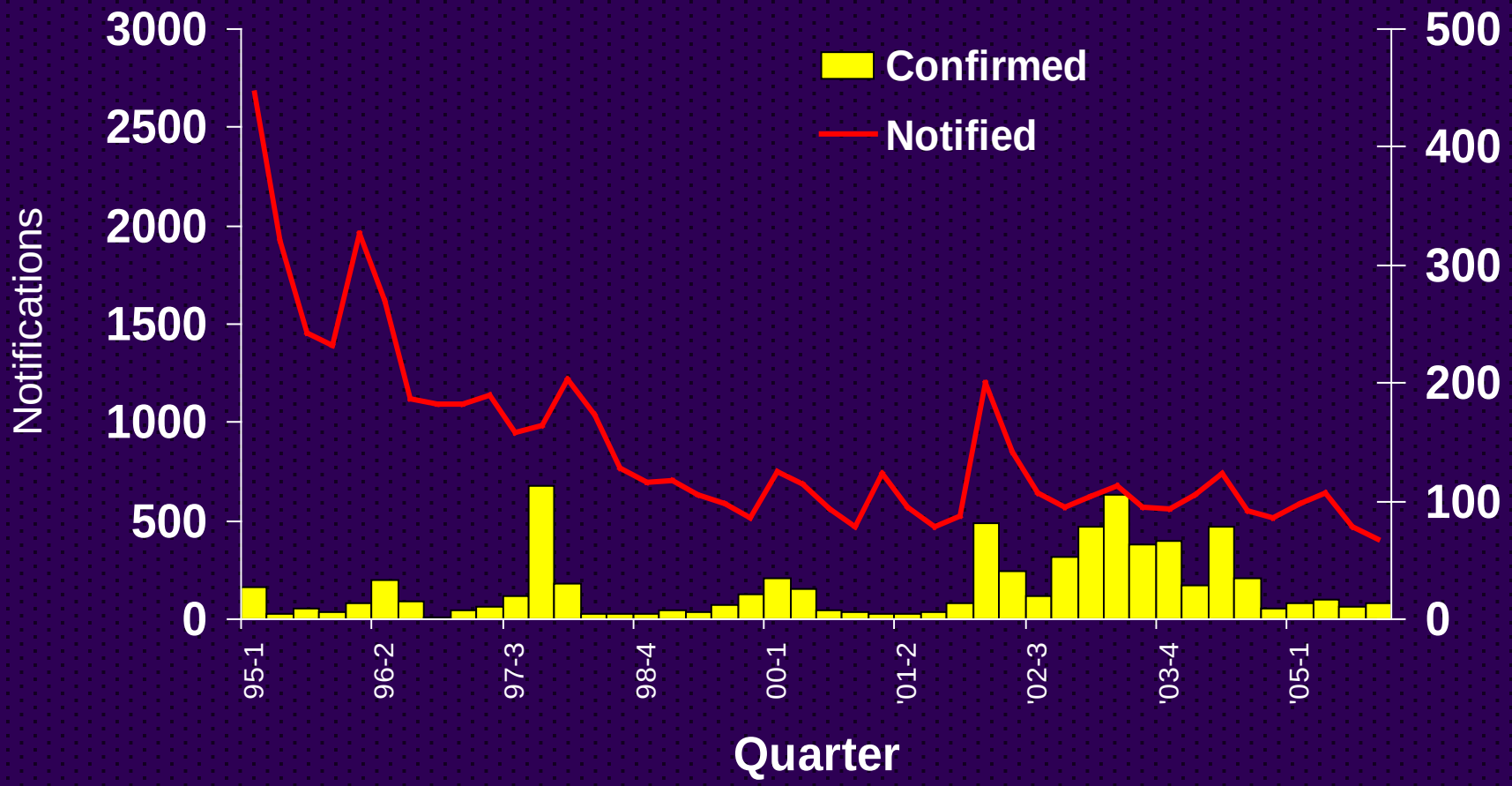
- In 1988, change to MMR vaccine
  - More popular, increase in coverage to 92%
  - Epidemic cycles interrupted
  - Between 1988 to 1993 cases fell to all time low
- During the “honeymoon” period
  - Unvaccinated children not exposed to natural infection
  - Accumulation of older susceptibles
  - Inevitable increase in cases in older children and adults
- In 1994, measles-rubella campaign for all children 5-16 years
  - Coverage of 92% achieved

Surveillance of measles

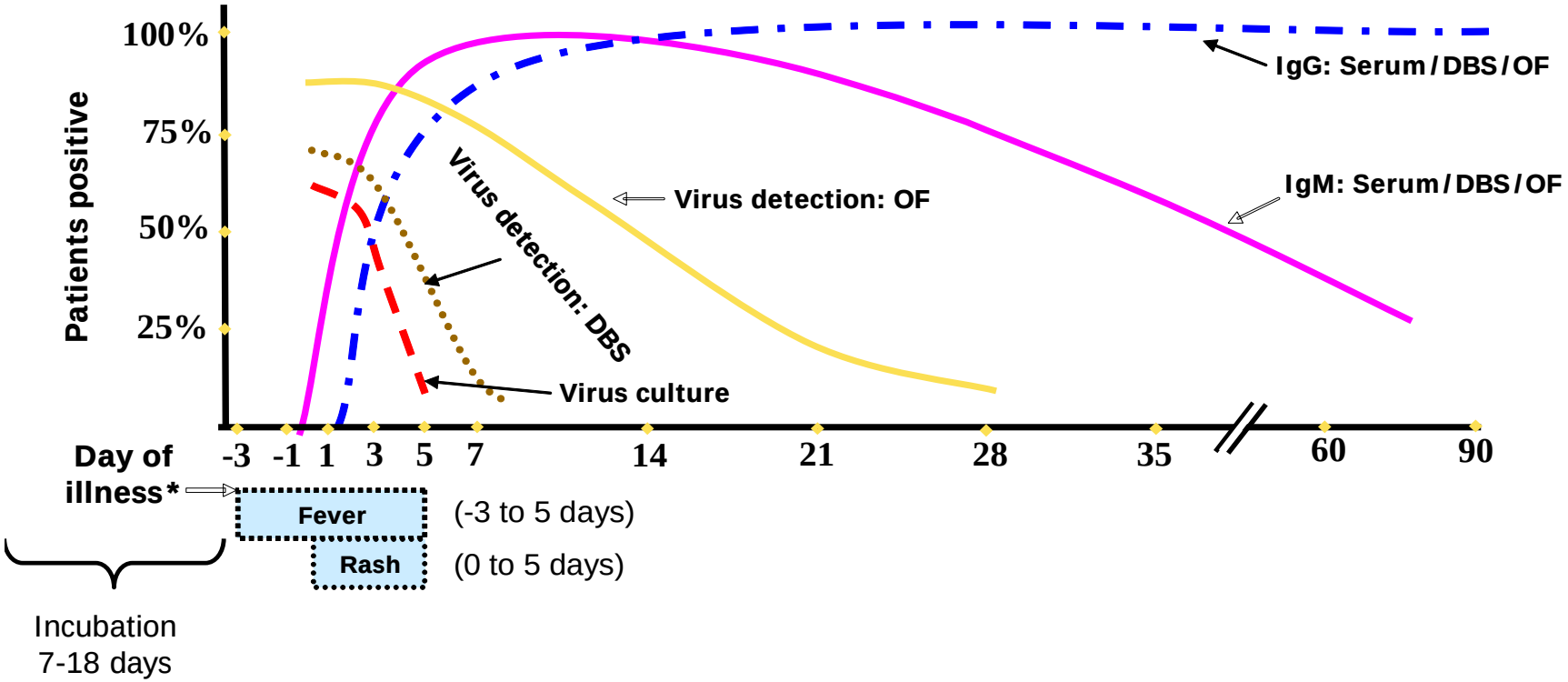
- Previously relied on clinical reports via statutory notification system
  - Predictive value high when incidence was high
- During 1991-1994
  - IgM blood spot testing only 40% confirmed
  - Also showed sensitivity of oral fluid testing > 90%
- Since late 1994, oral fluid testing follows all notifications of measles, mumps and rubella

Notified and confirmed measles

England and Wales 1995 – 2005

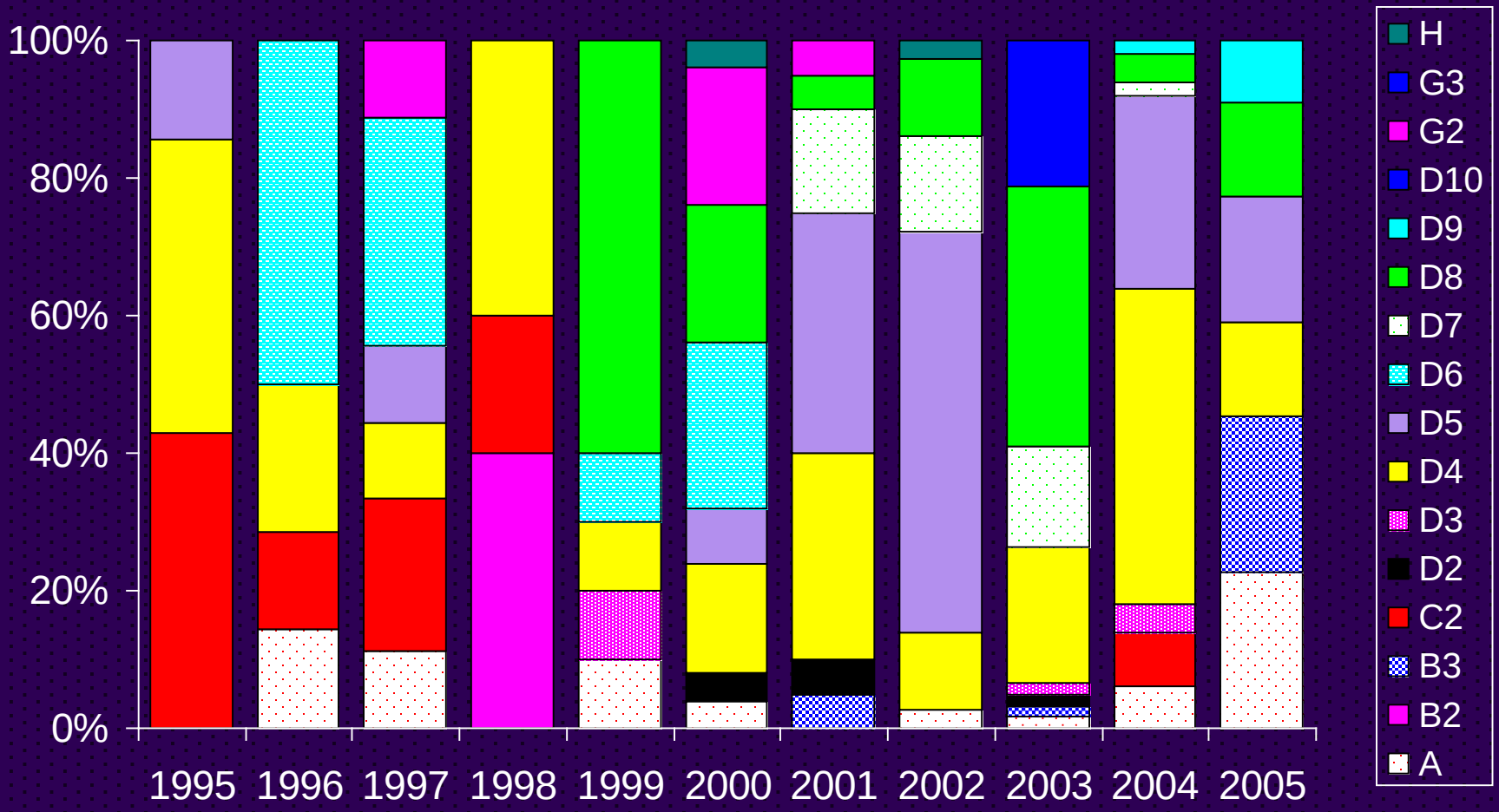


Investigation of measles virus infection



Manual for the laboratory diagnosis of measles and rubella virus infection
http://www.who.int/immunization_monitoring/LabManualFinal.pdf

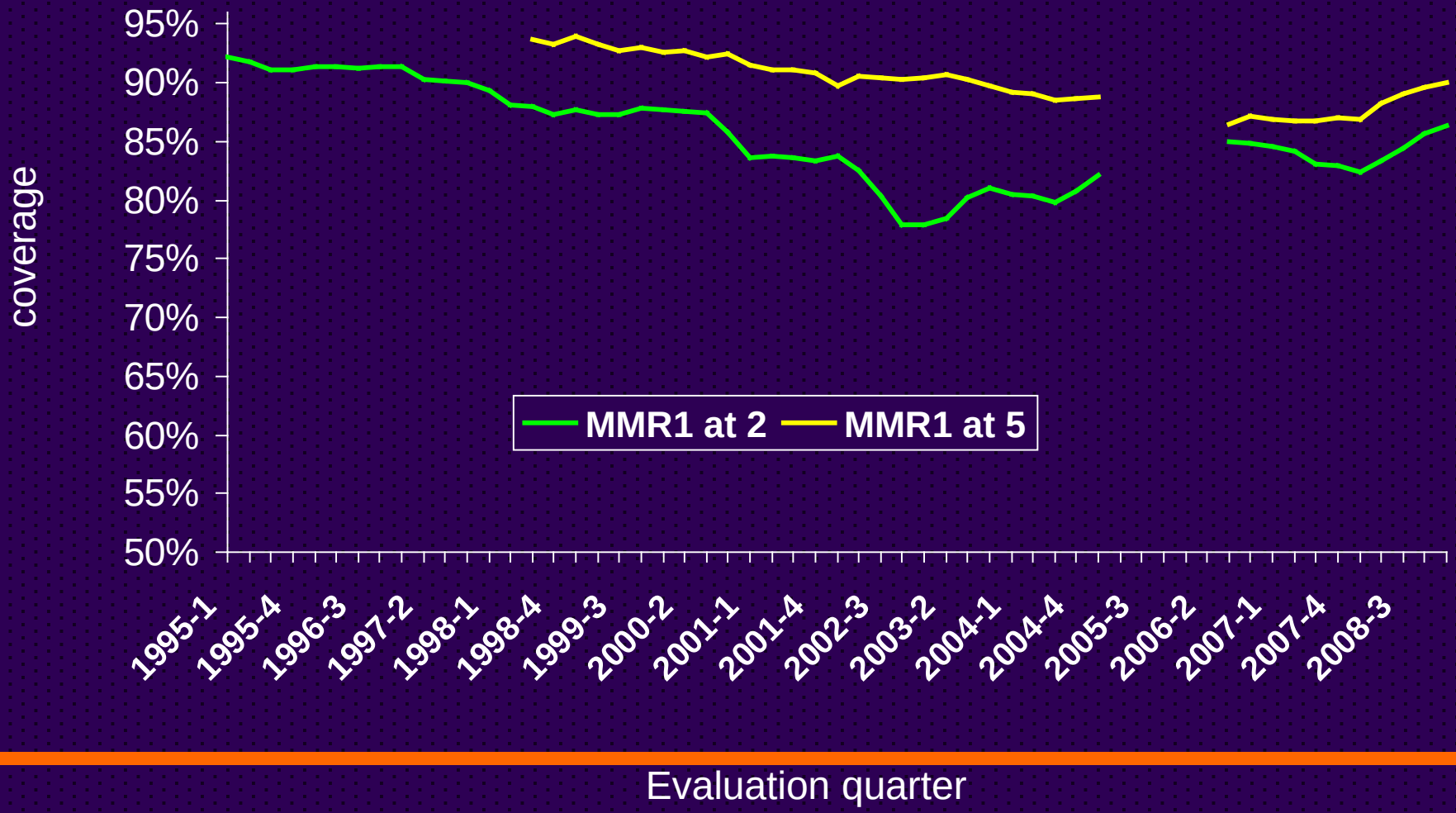
MEASLES GENOTYPES IN THE UK 1995-2005



Pattern of confirmed measles 1995-2005

- No relationship between notifications and confirmed cases
  - Proportion confirmed low, particularly in children
  - Increase in confirmed cases not reflected in notifications and vice versa
- Most cases in unvaccinated children and adults
  - only 7% had documented vaccination
  - Outbreaks in populations of low coverage (eg. Steiner)
- Many cases associated with importation
- Wide diversity of measles strains
  - Consistent with limited transmission from imported cases

MMR coverage at 24 months and 5 years England, 1995-2008



Trends in MMR coverage

- Decline in MMR coverage after 1998
- At 24 months
  - Fell from high of 92% to 79%, now 86.3%
- But more importantly, coverage of MMR1 at 5 years
  - Fell from 94% to 87% now 90.0%
  - Only 76% have had two doses

- Around 70,000 completely unvaccinated children start school each year

Measles epidemiology – how we can predict the future

- Each disease has it's own intrinsic transmissibility
  - Measles is one of the most highly infectious diseases known to man
- This is denoted by the reproduction number R_0
  - average number of secondary cases produced by a typical case in a totally susceptible population
  - For measles this is around 15-20
- How well a disease actually spreads is denoted by R – the effective reproduction number
  - the average number of secondary cases produced by a typical case in a real population setting

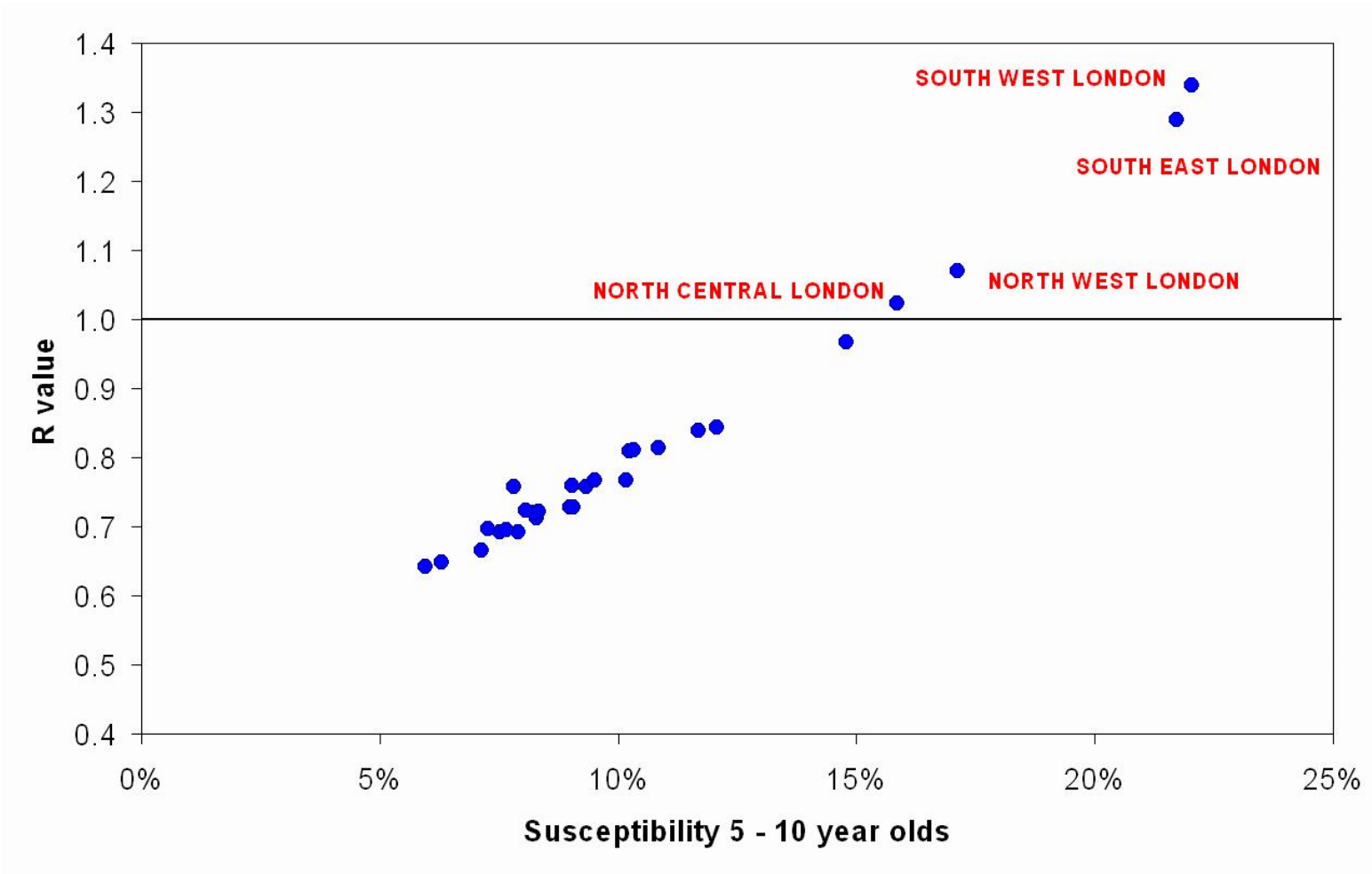
Maintaining measles control

- Effective reproduction number (R) depends on
  - R_0 - transmissibility of the infection
  - population contact rates
  - susceptibility of the population
- If R>1, the number of cases increases
- If R<1, the number of cases decreases
- To avoid an epidemic, R must be less than 1
  - A certain threshold level of susceptibility is necessary for epidemics to occur
  - Actual level required depends upon the contact rates in that age group

Estimating susceptibility using COVER data

- Historic coverage data for children now aged 5-17 years
- Assume 100%, 10% and 1% of unvaccinated, one dose and two dose MMR children are susceptible
- Apply to age specific mixing models
- Sensitivity analysis of impact of under-estimating coverage
  - Proportion of those recorded as unvaccinated who had received one dose of vaccine assumed to be 10%, 20%, 30%, 40% and 50%

R level by StHA in 2004/5



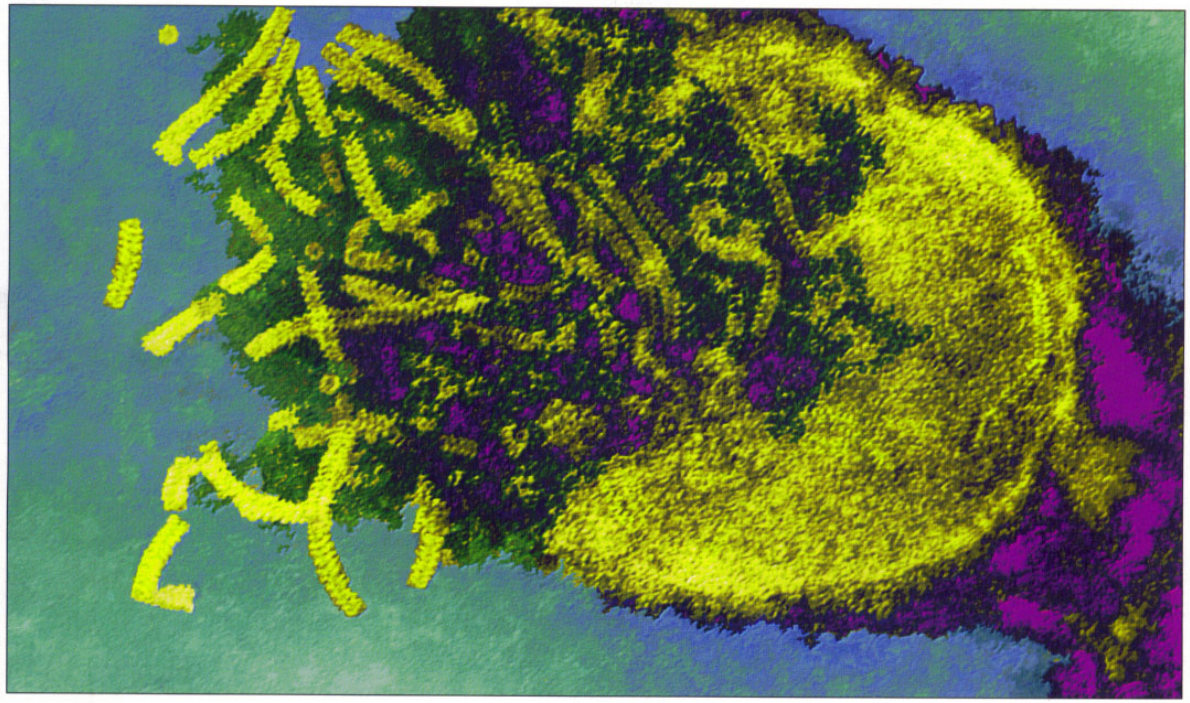
Predictions of outbreak sizes (in 000s) in 2007/08

Age group	Assumed level of under-estimation in vaccine coverage			
	20%	30%	40%	50%
Outside of London	**19**	**8**	**1**	**0**
Inside of London	**106**	**62**	**30**	**6**
Total	**125**	**70**	**31**	**6**

28 October 2006

BMJ

333:867–926 No 7574 28 OCTOBER 2006 *Clinical research* ISSN 0959-8138



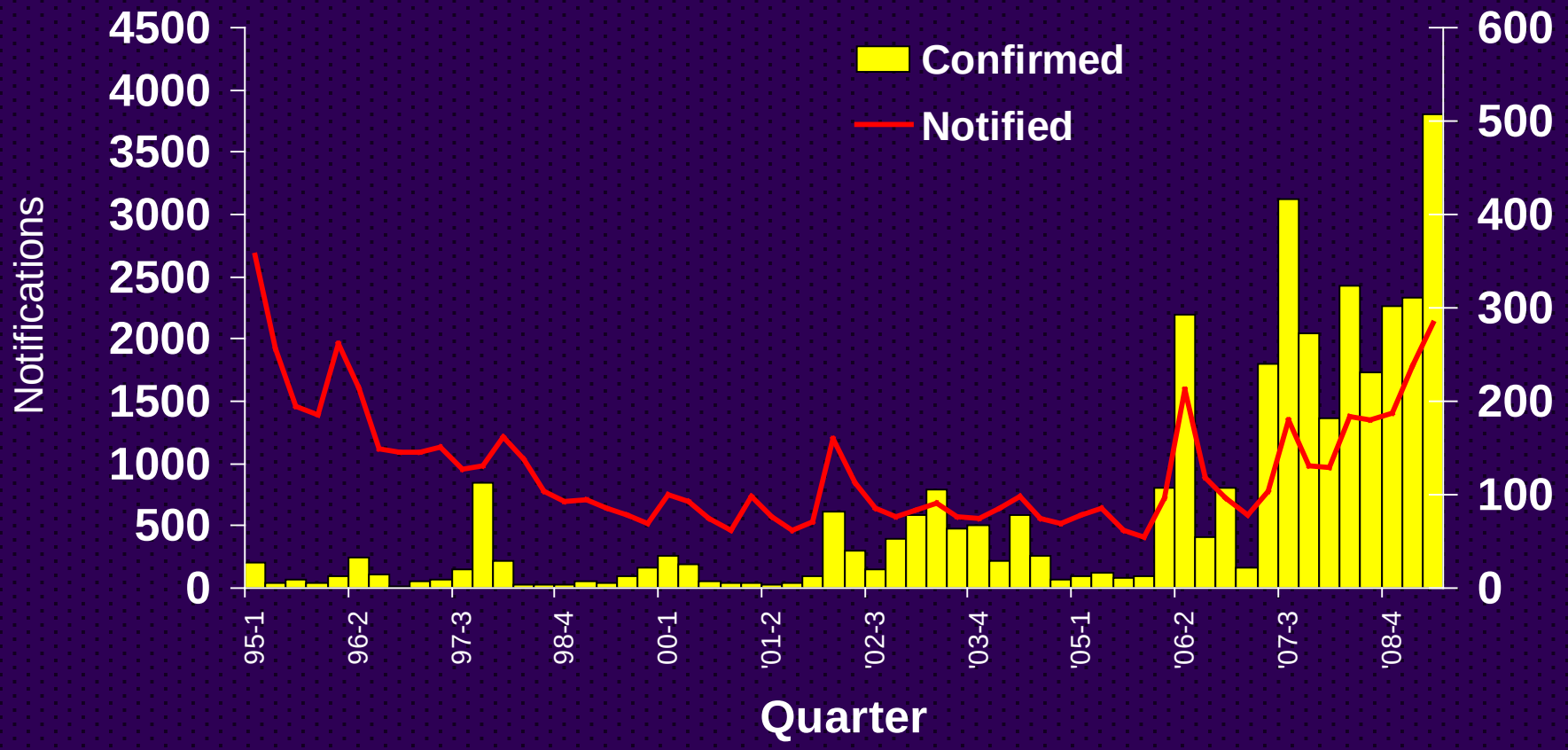
Measles is back in the UK

Pattern of confirmed measles 2006-2008

- Large outbreak in Irish travelling families in 2006
  - Associated with single strain (B3)
  - Limited spread to general community
  - International spread
  - One death (immunosuppressed teenager with lung disease)
  - Cases declined during late 2006
- New outbreak started in Irish travellers in 2007
  - Many cases in general community and outside of London

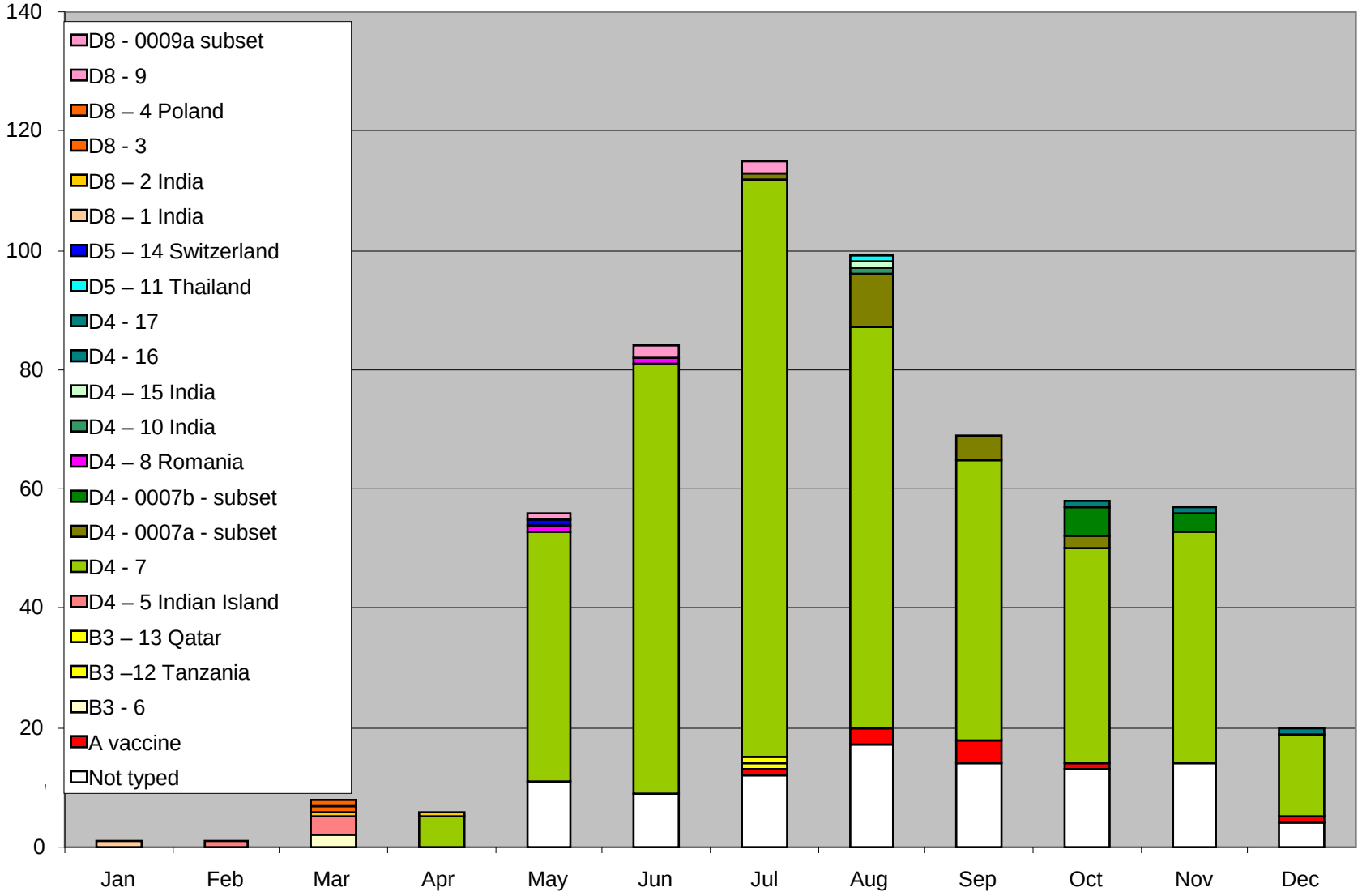
Notified and confirmed measles

England and Wales 1995 – Jun 2008



Measles genotypes 2007

Cluster analysis (>99.7% similarity)

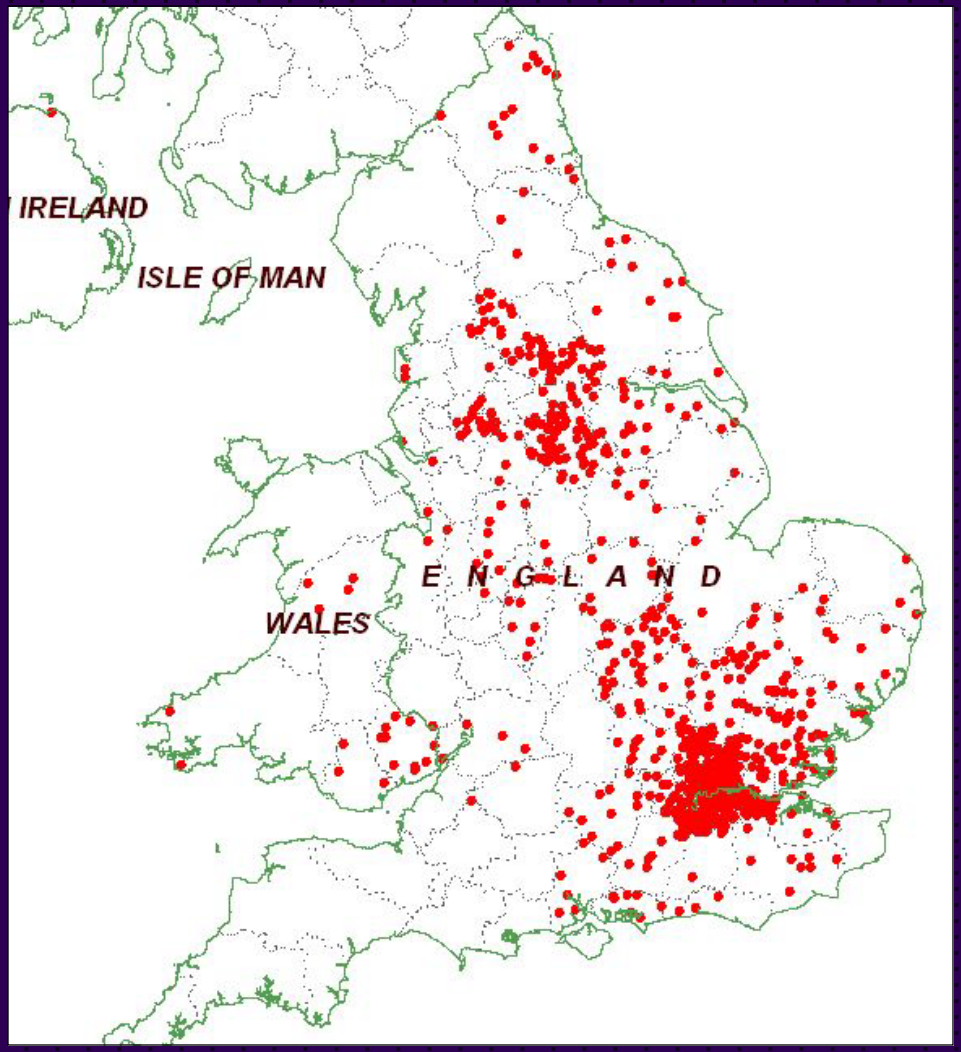


Distribution of D4 Enfield measles England and Wales, 2007-8

Initially in ‘Irish travellers’
Exported to Norway

Spread to Orthodox Jewish community
Exported to Israel
Exported to Antwerp
Exported to Germany
then to Ireland
Exported to Italy

Same strain in France and Spain



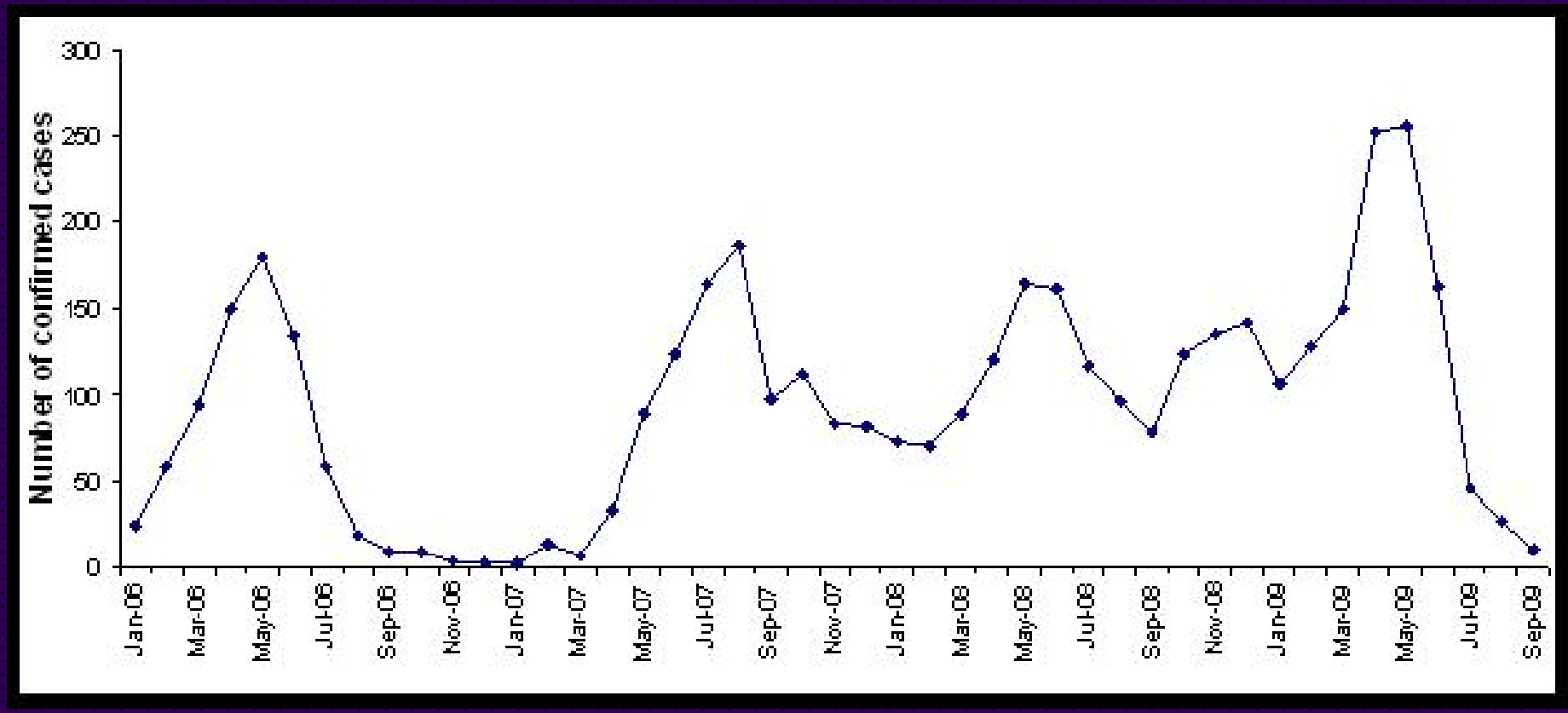
Pattern of confirmed measles 2006-2009

- Cases continued from 2007 into 2009
  - Total of 990 cases in 2007, 1370 cases in 2008
  - Death in 18yr old immunosuppressed individual
  - Age group most affected - primary school children
  - Less than 10% with history of vaccination
  - 1093 cases confirmed in England so far in 2009
- D4 Enfield strain has been circulating for more than one year
  - Meets the WHO definition of endemic transmission

Catch-up campaign

- London catch-up in 2005
- National catch up 2008-9
- Plan to vaccinate in priority order
  - Unvaccinated children under 18 years of age
  - Partially vaccinated primary schoolchildren
  - Partially vaccinated secondary schoolchildren
  - Teenagers going to higher education
- Ensure MMR offered at all appropriate opportunities (e.g. school leaving)
- Identify pockets of low coverage and plan specific interventions

Laboratory confirmed cases in England & Wales by month : Jan 2006 to September 2009



Could the worst be over?

- Outside of London modelling predicted between 1,000-8,000 cases
  - already had 2200 cases outside of London
- Number of cases has declined in summer 2009
  - No evidence of increase since schools have returned

- Risk in London still very unclear!
- Success of catch-up campaigns difficult to assess
- Still a high risk in low coverage / crowded settings
  - Travelling families
  - Boarding schools etc

What do we need to do to prepare for measles?

- Ensure high immunity amongst health care workers
  - Vaccinate and/or establish immune status
- Three recent SUIs
  - Outbreak of 6 cases in HCWs in Central Middlesex in 2006
  - Oncology SHO in May 2008
    - Just attended MRCP course
    - Known to be measles susceptible – DNA'd for vaccine!
  - A&E SHO in July 2008
    - Known to be measles susceptible, exposed to patient with measles and given post-exposure MMR
    - Continued to work and then developed measles – different strain from index case!

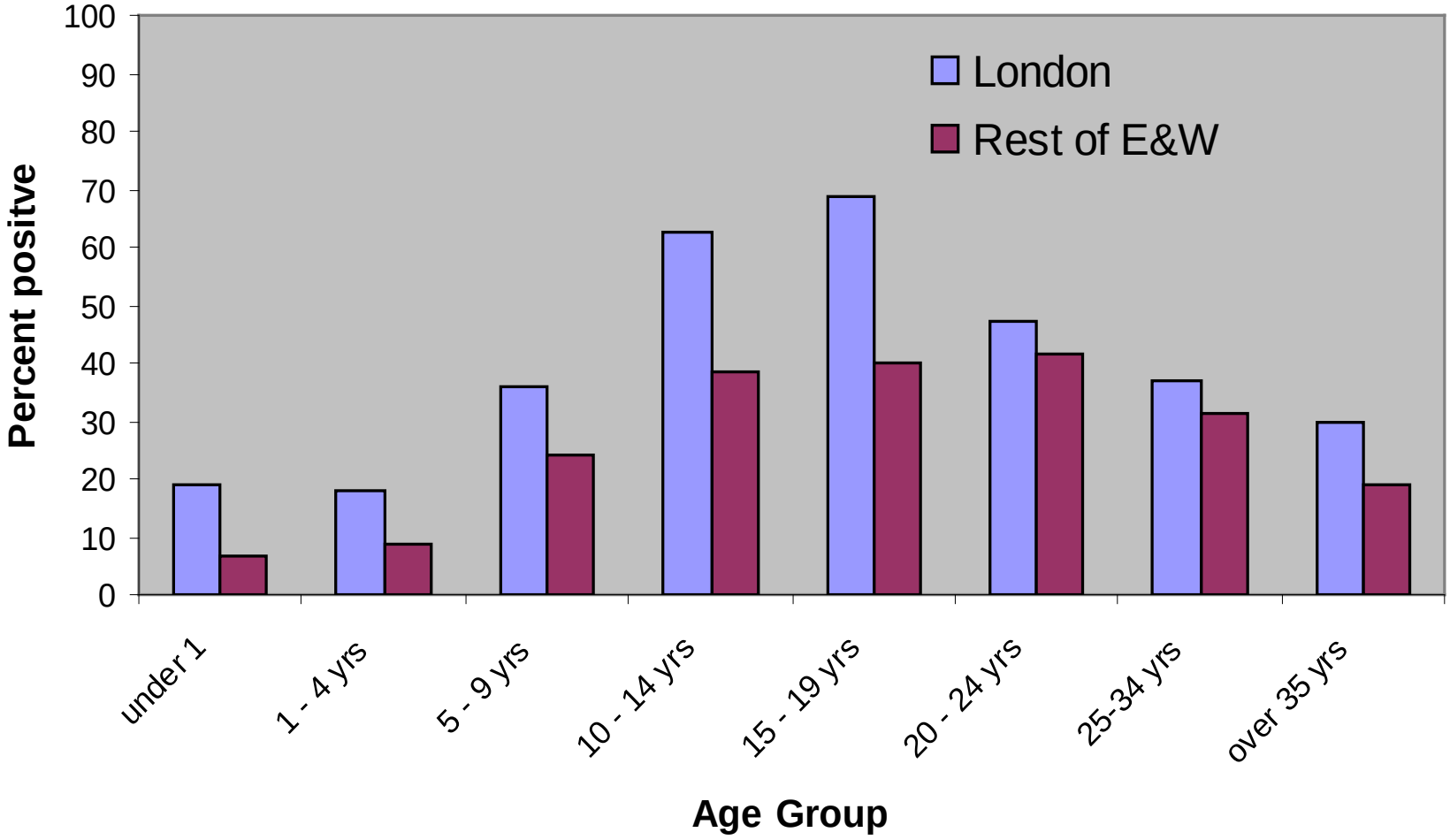
What do we need to do to prepare for measles?

- Protect immuno-suppressed individuals at high risk
  - establish their immunity status
  - make sure their family is protected
  - warn them about contact with measles
  - e.g. death in 2008
- Provide appropriate post-exposure prophylaxis
  - Response to suspected measles cases

Dealing with suspected cases

- Arrange confirmation
  - Oral fluid to CfI (no delay required)
  - Additional serum or other samples may be useful
- Urgent management of contacts required for confirmed, epidemiologically linked or cases assessed as “likely” by experienced HP specialist
  - Needs knowledge of local epidemiology

Proportion of notified measles with detectable IgM or viral RNA in oral fluid, 2008



Dealing with contacts of confirmed or “likely” measles cases

- Previous post-exposure prophylaxis with IM HNIG within six days was indicated for:
  - Immunosuppressed individuals
  - Infants under nine months
  - Pregnant women

- Previous dose of HNIG
  - Under 1 year 250mg (approx 1.5 mls)
  - 1-2 years 500mg (approx 3 mls)
  - Over 3 years 750mg (approx 4mls)
- Healthy contacts may be offered MMR within 3 days

Evidence for use of HNIG

- US trial in household contacts 4-5 days from exposure (1942)
  - Efficacy of 69%
  - Some suggestion of milder illness in controls
- Observational study in US outbreak 1990
  - HNIG given within 6 days of exposure (2 days of rash onset in index)
  - Efficacy of 8% (95% CI 0-59%)

Reason for declining efficacy

- HNIG made from “normal” pooled donor plasma
  - Antibody levels in vaccinated populations are lower than those naturally infected populations
  - Antibody levels are boosted temporarily by community exposure
  - Likely that recent HNIG has much lower measles titre

Testing of recent HNIG

Product	Manufacturer	Year	Number of lots tested	Measles antibody (IU/ml)	
				Mean	Range
Subgam®	BPL	2008	3	23	16-28
Vivaglobin 16%	CSL-Behring	2008	12	36	32-42
Subcuvia®	Baxter	2008	17	39	25-65

Based on single Japanese study – therapeutic dose of HNIG for average adult (75kg) 45mls!!!

Previous dose 4mls

Use of IVIG as an alternative to IM HNIG

- IV products contain variable amounts of measles antibody
  - those from US donors are lower than those from Europe
- Therapeutic dose with any of the products available in UK can be achieved with dose of 0.15g (approx 3mls) per kg
  - Can be infused over an hour or two
  - Will require admission to day unit or ward
- IVIG is in short supply (demand management)
  - Immunosuppressed patients only

Indications for measles PEP

- Immunosuppressed
  - High mortality
- Pregnant women
  - No evidence for congenital syndrome
  - Few controlled studies BUT data consistent with higher maternal morbidity and mortality AND high rate of fetal loss / premature delivery
- Infants
  - Higher rate of complications (pneumonia etc)
  - Higher risk of SSPE

Assessing measles susceptibility

- Need to avoid unnecessary HNIG
  - HNIG unlikely to offer any benefit to individuals with measureable antibody
- Need to assess
  - History of measles
  - History of vaccination
  - Measles IgG status

Avoiding unnecessary measles PEP

- High proportion of adults individuals are immune to measles
  - 99% of those born before 1970 (natural infection)
  - 90% of those born between 1970 and 1989 (either vaccine or natural exposure)
- Of those born since 1990, we expect that
  - 99% of those who have received two doses
  - 90% of those who have received one dose
  - 0% of those unvaccinated are immune to measles

Managing immunosuppressed contacts

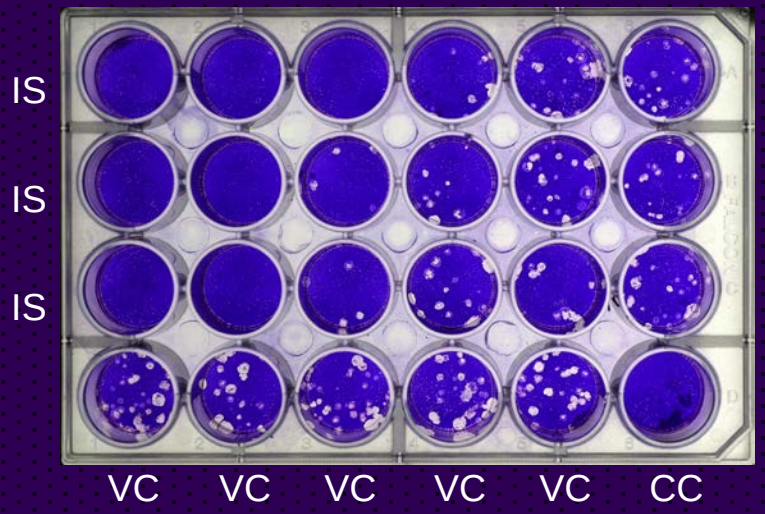
- Severely immunosuppressed, likely to lose measles antibody
  - Undertake urgent measles antibody test (regardless of past history or previous positive test)
- Less severe immunosuppression (those likely to have maintained measles antibody)
  - If not known to be antibody positive, management depends on age, past history or urgent measles antibody test
- If negative or equivocal admit for IVIG
- If testing not possible within 3 days of onset, give IVIG anyway

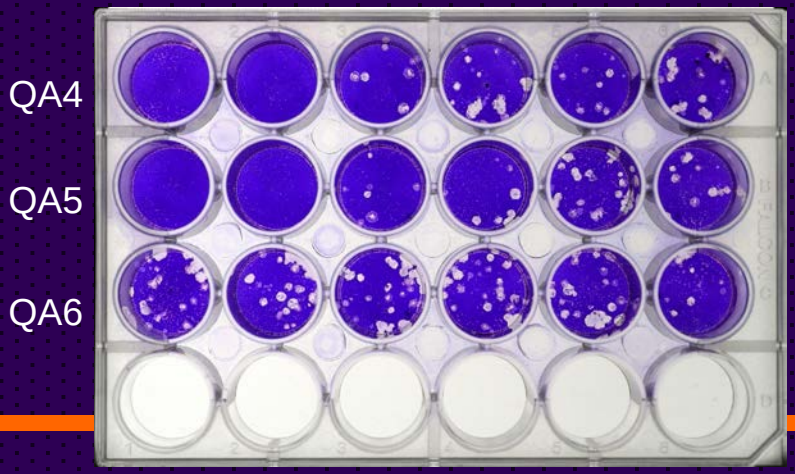
Pregnant women

- Not practical to admit large number of pregnant women for IVIG
- Assess susceptibility using age, history and/or urgent IgG

- Those found to be antibody negative or likely to be susceptible
  - Offer IM HNIG at higher dose than previous recommendation (3 vials)
- Aim to modify disease and reduce risk of maternal morbidity or fetal loss

What is a Protective Level of Measles Antibody?





120 mIU/mL Chen *et al*

Measuring IgG – correlate of protection?

- Based on US outbreak of measles in a group of blood donors by PRNT

Ab titre by PRNT	Clinical attack rate
≤ 120	8/9 clinical measles
> 120	0/71clinical measles

- Commercial assays
  - Wide variety of assays in use (VIDAS most common)
  - Probably sensitivity is low but specificity high
  - False negatives are most likely problem in UK population

Summary

- Measles is highly infectious and can spread with minimal contact (often unnoticed)
- The only way to effectively protect the population is by ensuring high levels of vaccination
- Post-exposure management is difficult and probably low effectiveness
- Important to limit use of PEP by IgG testing
- Importance of QA for measles IgG assays

Acknowledgements

- Staff at CfI Immunisation Department and Immunisation Diagnosis Unit
  - Particularly Kevin Brown, Antoaneta Bukasa
- Laboratory, child health staff and GPs who contribute to surveillance
- HPU staff who administer oral fluid surveillance and follow up cases and outbreaks