Boosting or not boosting: what may we learn from vaccine case studies ?

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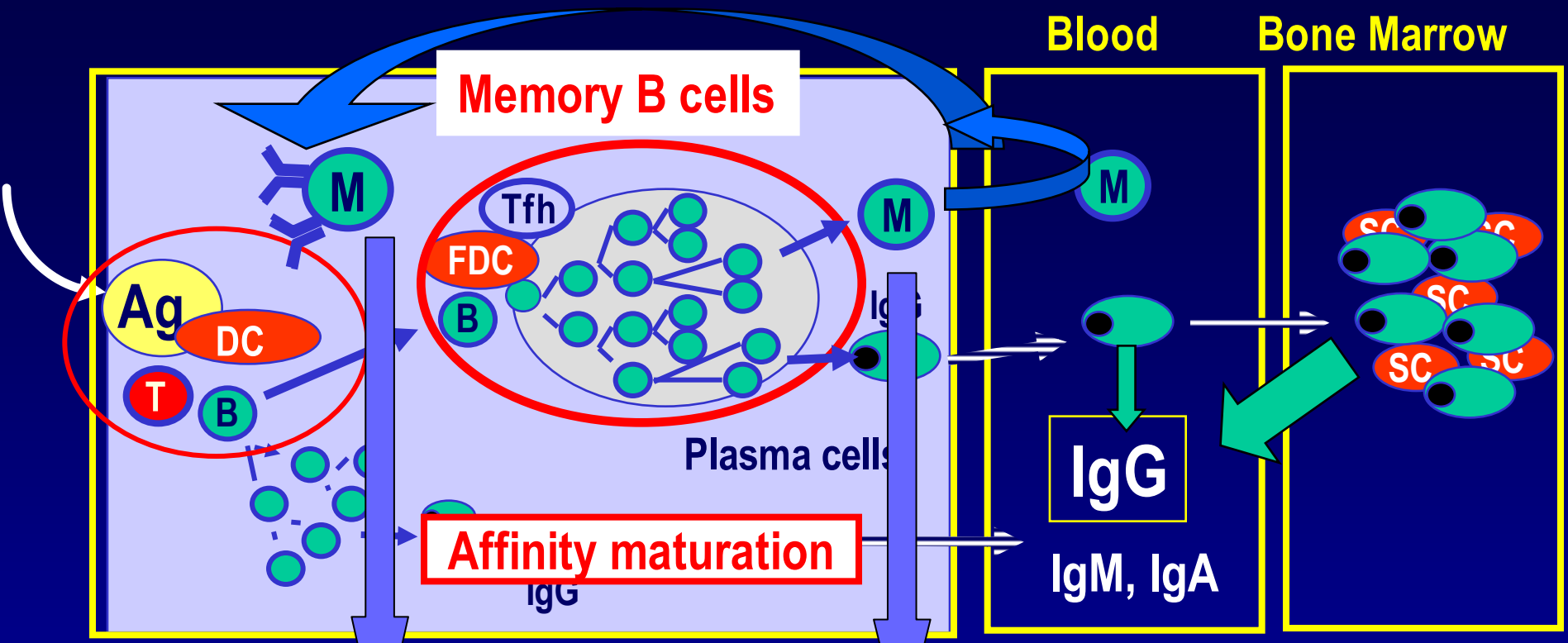
0 -1- 6 : the “classical” immunization schedule !



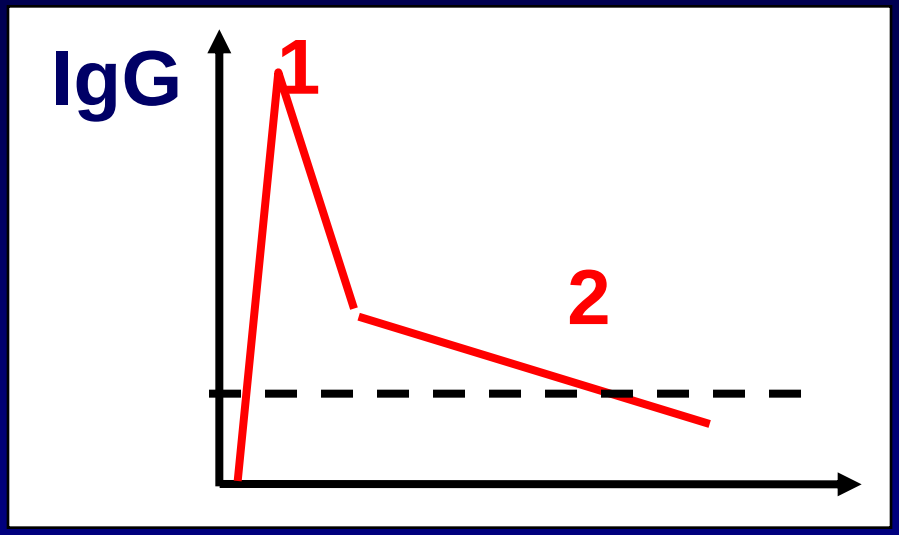
1(-2) doses for priming

Affinity maturation and clonal selection of the fittest B cells

1 booster dose to reactivate memory cells

≥ *4 months*

Memory B cells are resting cells which do not protect: when and why do we need to boost ?



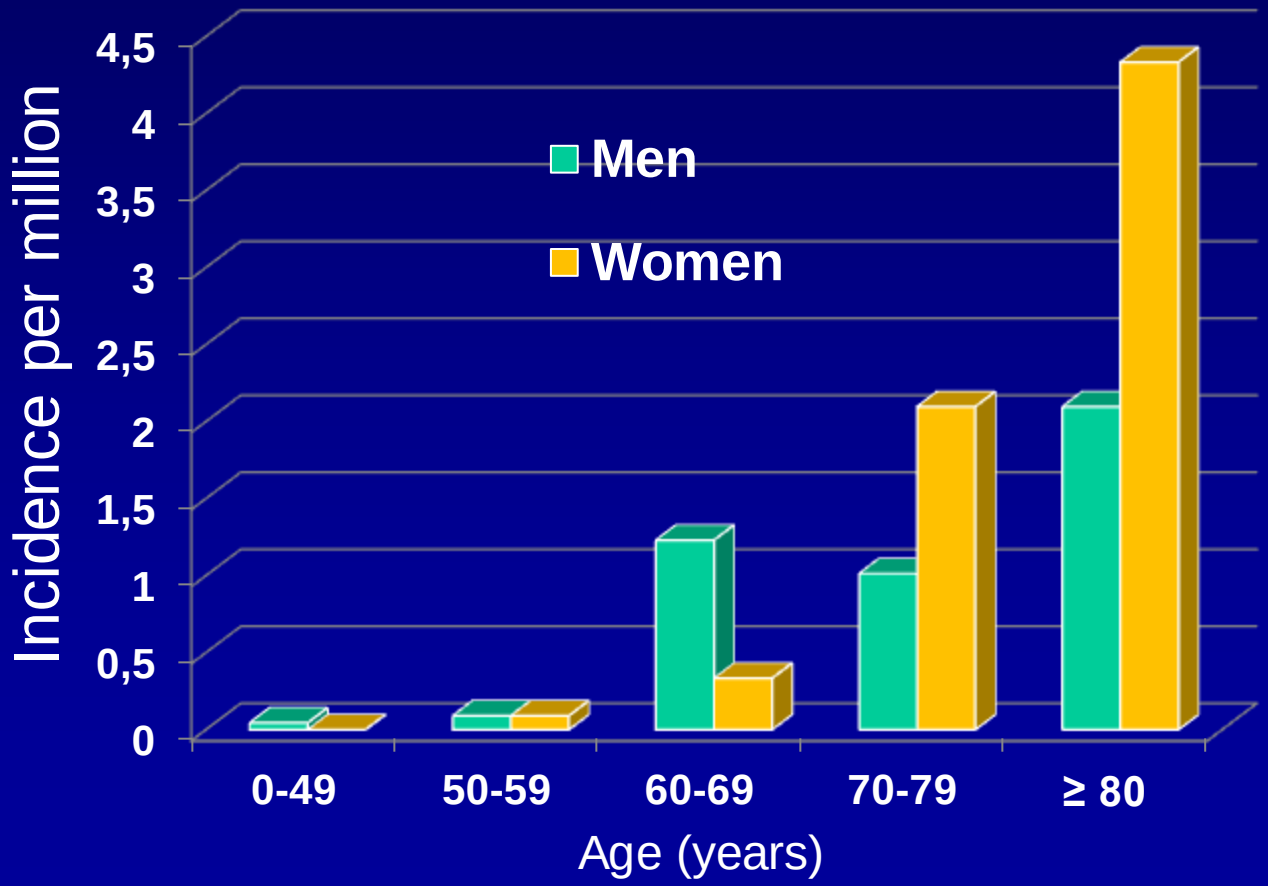
1. Induction of long-lived bone-marrow plasma cells

Reactivation of resting memory B cells

+Ag

Protection against tetanus

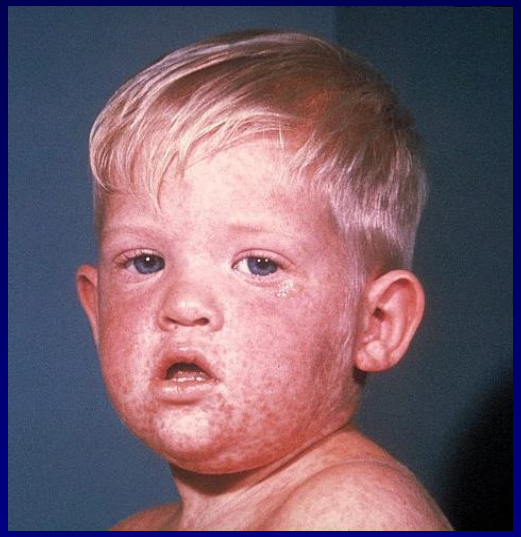
Surveillance of tetanus in France 2002-2004 :
67 cases



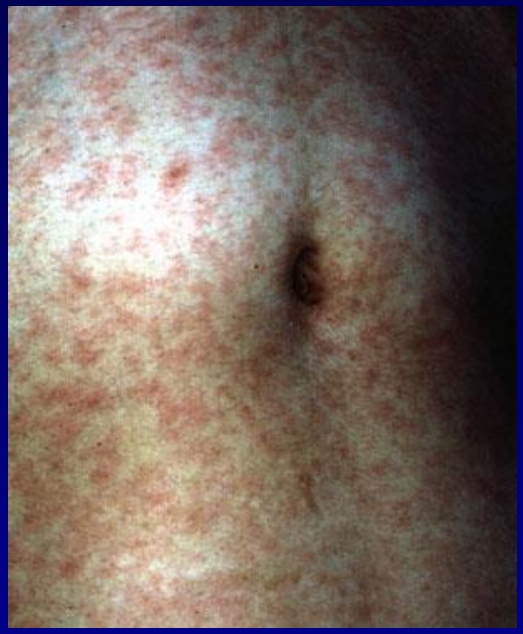
What ?

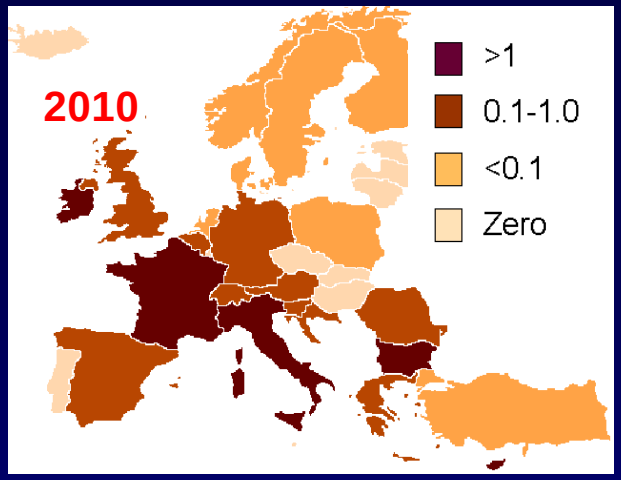
BEH 7/2006

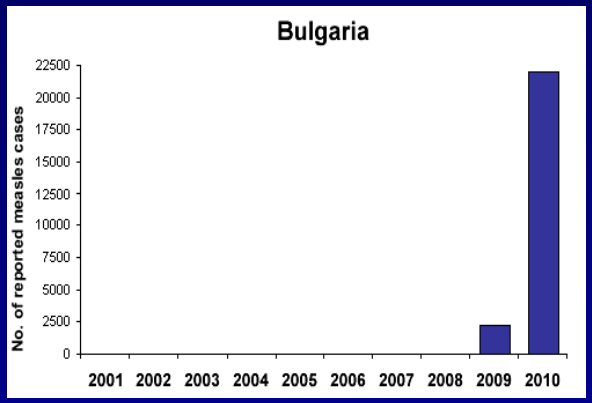
Failure of vaccine prevention in Europe !

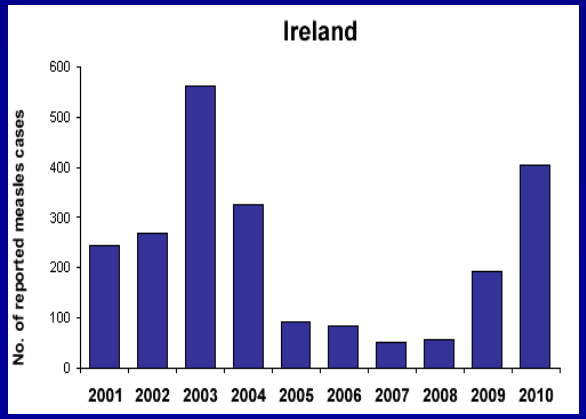


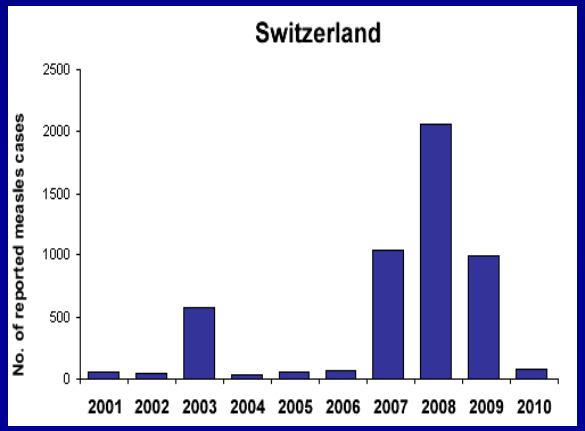
Source : Euvac.net

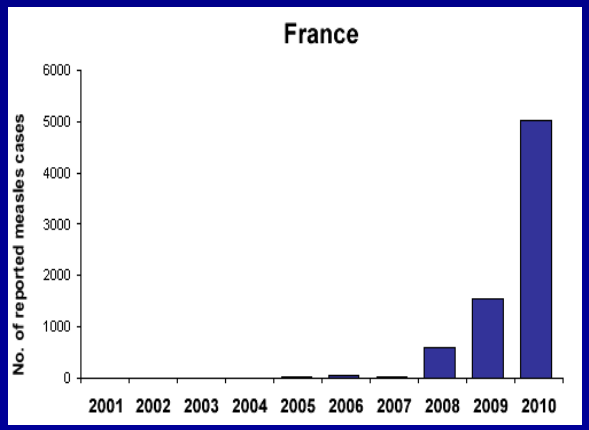






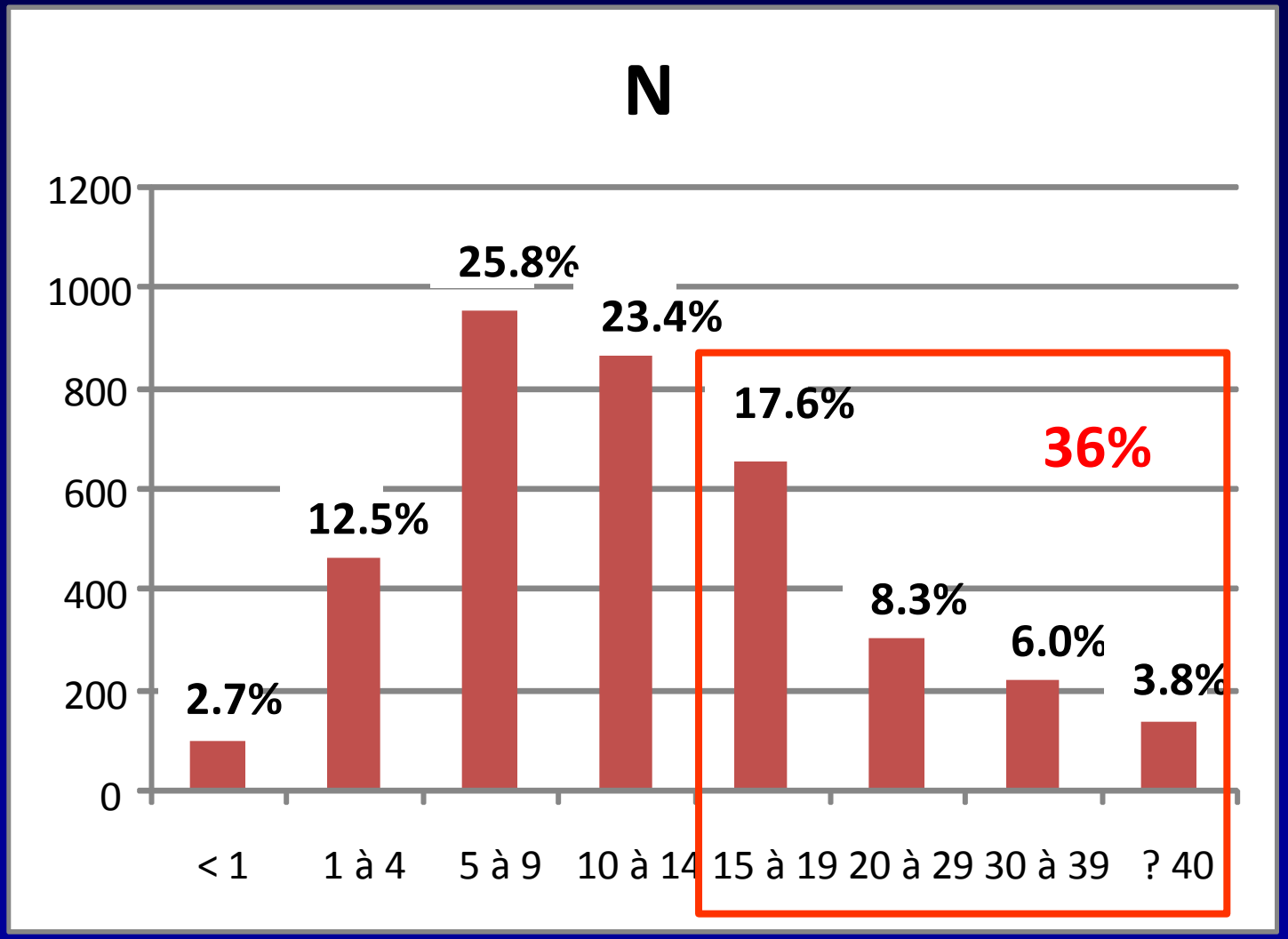






Measles in Switzerland (n = 2772) :
Age distribution

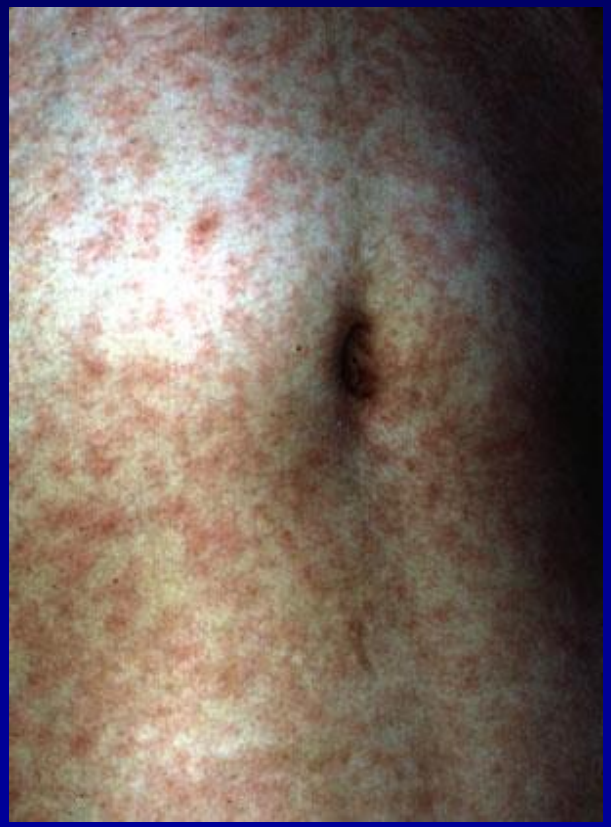
What?
Why?

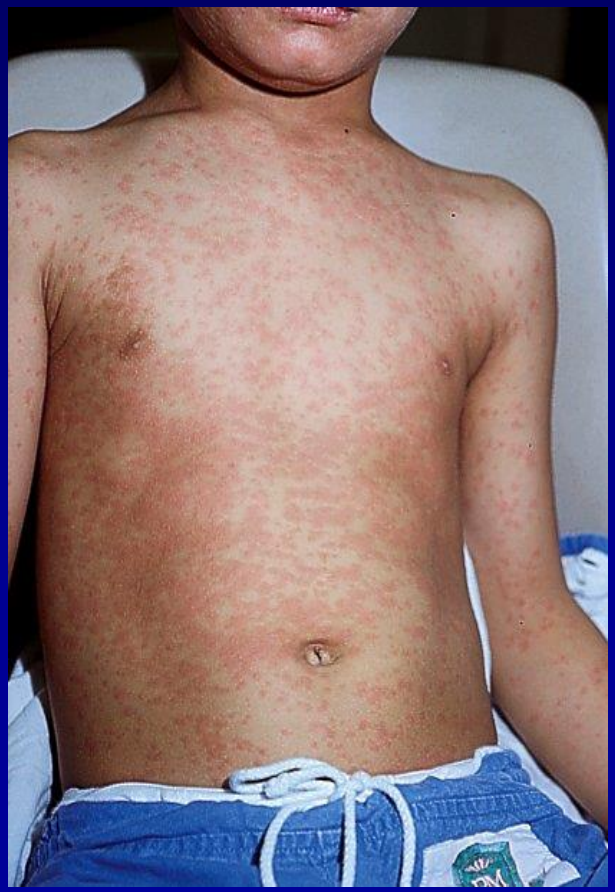


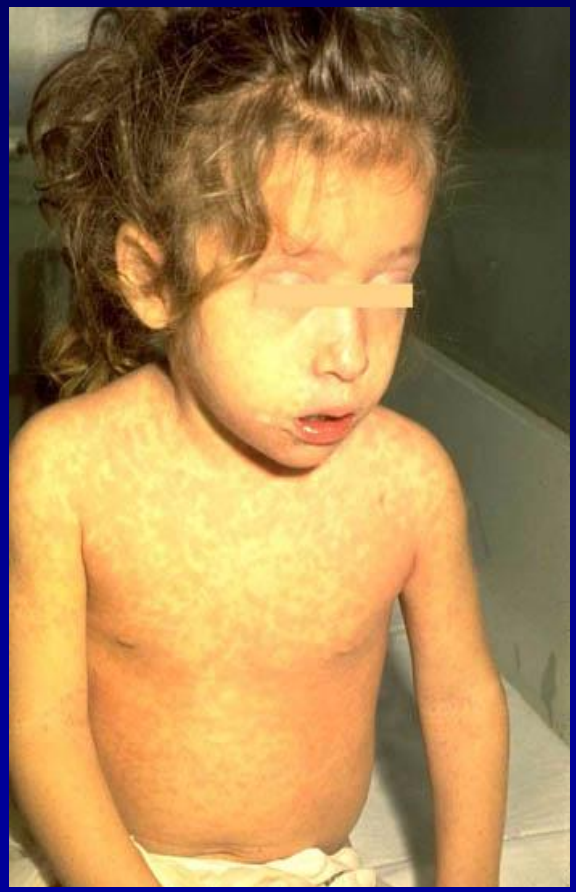
3267 cases (immuniz. records) :

- 3049 (93%) non immunized
- 133 (4.1%) 1 dose
- 63 (1.9%) 2 doses
- 22 (0.7%) ? dose(s)

Failure to have been immunized !





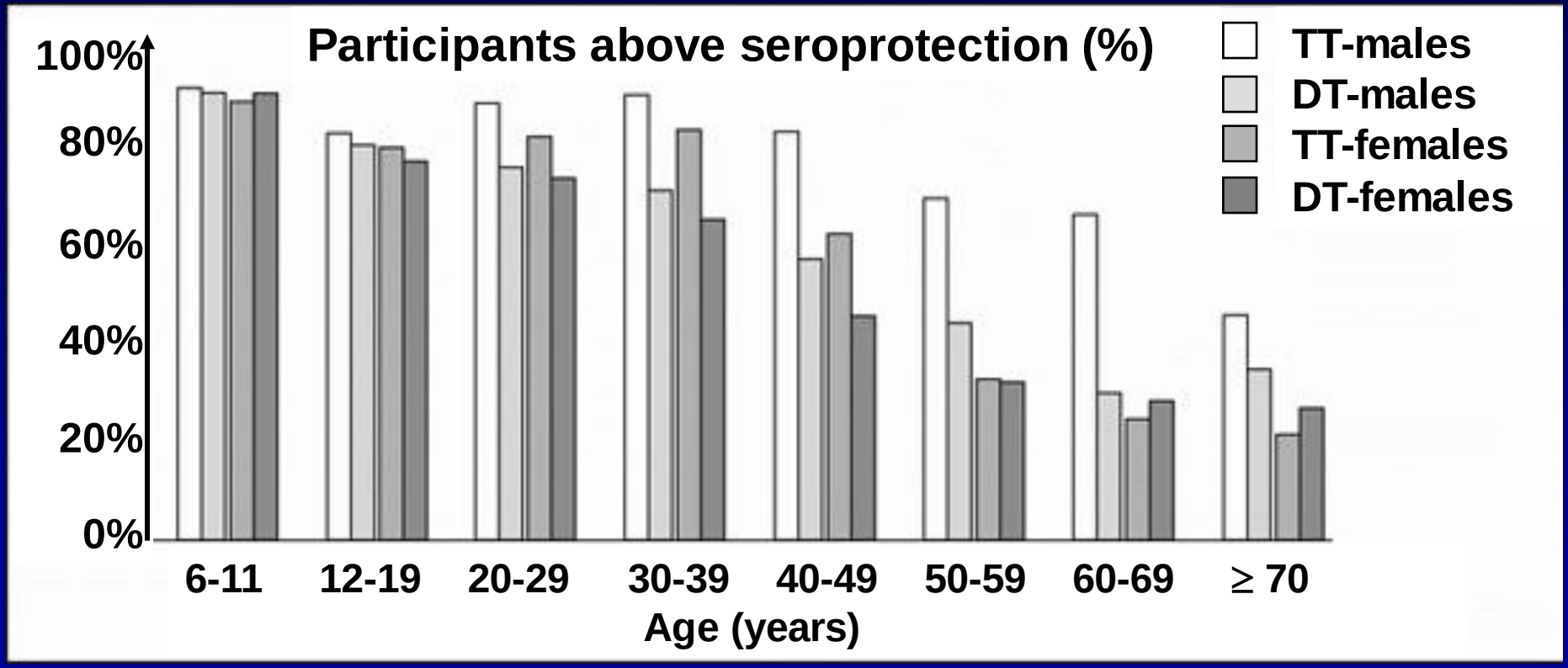


A few lessons from vaccine case studies

- **The most frequent vaccine failure is the failure to have been immunized !**

Distribution of protective levels of anti-diphtheria and tetanus antibodies in the US

McQuillan GM, Ann Intern Med. 2002



What?

Why?

Why no outbreaks ?

A few lessons from vaccine case studies

- The most frequent vaccine failure is the failure to have been immunized !
- **Herd immunity may mask / compensate for individual vaccine failures !**

Mumps Outbreak USA
May 2, 2006, > 2000 cases

- College students (median age 21 y)
- Parotitis: 66% reported cases
- Reported complications
  - orchitis
  - meningitis
  - encephalitis
  - deafness
  - oophoritis, mastitis, pancreatitis
- 25 hospitalizations
- No deaths

Cf wild-type mumps…

Similar observations elsewhere !

77% - 97% of students with 2 vaccine doses !!

Why ???

© Sonja Hutchins, CDC, 2006, www.acha.org/.../Mumps_in_the_Midwest_ACHAPresentation.ppt

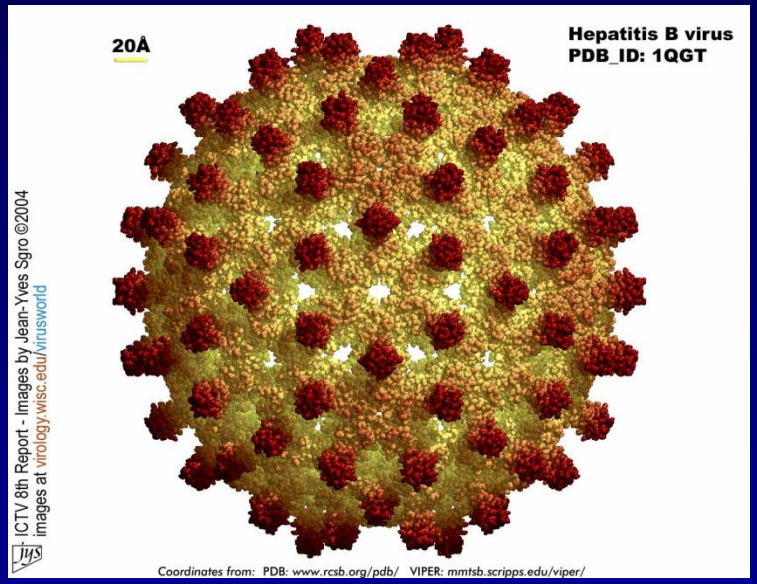
Potential explanations for vaccine failure after 2 mumps vaccine doses

- Primary vaccine failure √
- Secondary vaccine failure √
  - Loss of neutralizing Ab √
  - Loss of T cell immunity ?? √
- Mismatch between vaccine and outbreak strains (↓ neutralization) √ ?
- High viral load – close contacts (boarding schools) ?√

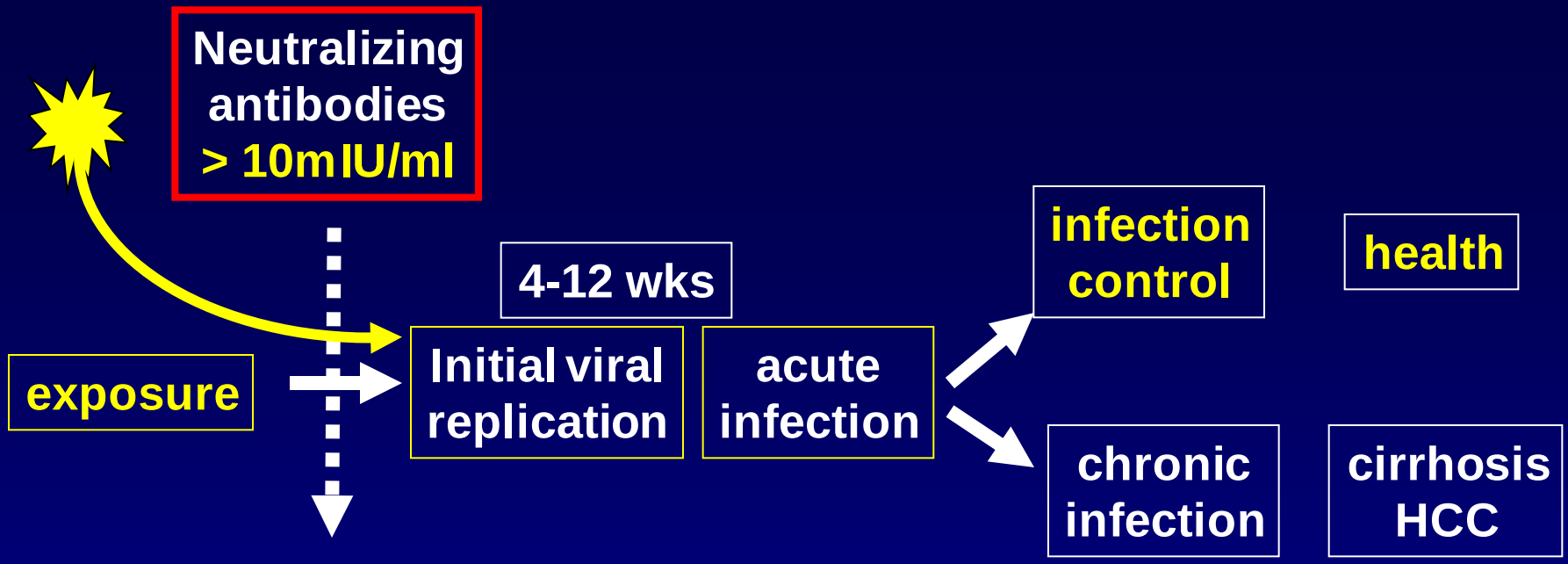
A few lessons from vaccine case studies

- The most frequent vaccine failure is the failure to have been immunized !
- Herd immunity may compensate for individual vaccine failures !
- **Live attenuated viral vaccines induce weaker responses than WT infections – these may persist for decades (measles, rubella) or wane more rapidly if vaccines are (too) highly attenuated (mumps, chickenpox) !**

Role of immune memory in vaccine-induced protection

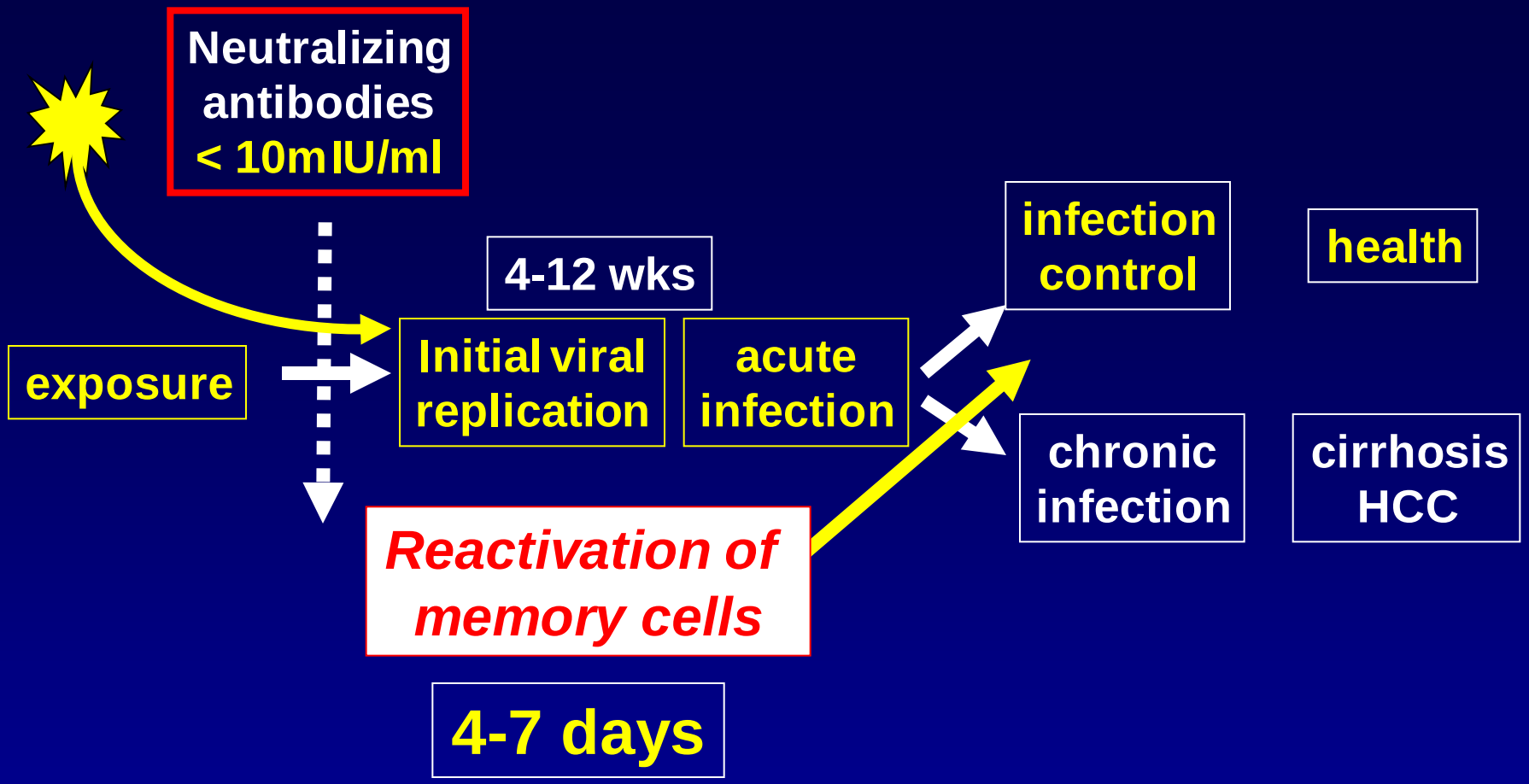


What is needed for protection against hepatitis B ?



Prevention of acute hepatitis B :
anti-HBsAg titer > 10mIU/ml at time of exposure

What happens if you have lost vaccine antibodies at time of exposure?



Acute hepatitis B infection (anti-HBc Abs)…

Reactivation of vaccine-induced memory cells protect against chronic hepatitis B !

A few lessons from vaccine case studies

- The most frequent vaccine failure is the failure to have been immunized !
- Herd immunity may compensate for individual vaccine failures !
- Live attenuated viral vaccines induce weaker responses than WT infection – and these may persist or wane more rapidly (chickenpox) !
- **Protection may persist after the disappearance of effectors (antibodies / T cells) : demonstrated role for immune memory !**

When is memory sufficient or not sufficient for protection ?

Sufficient

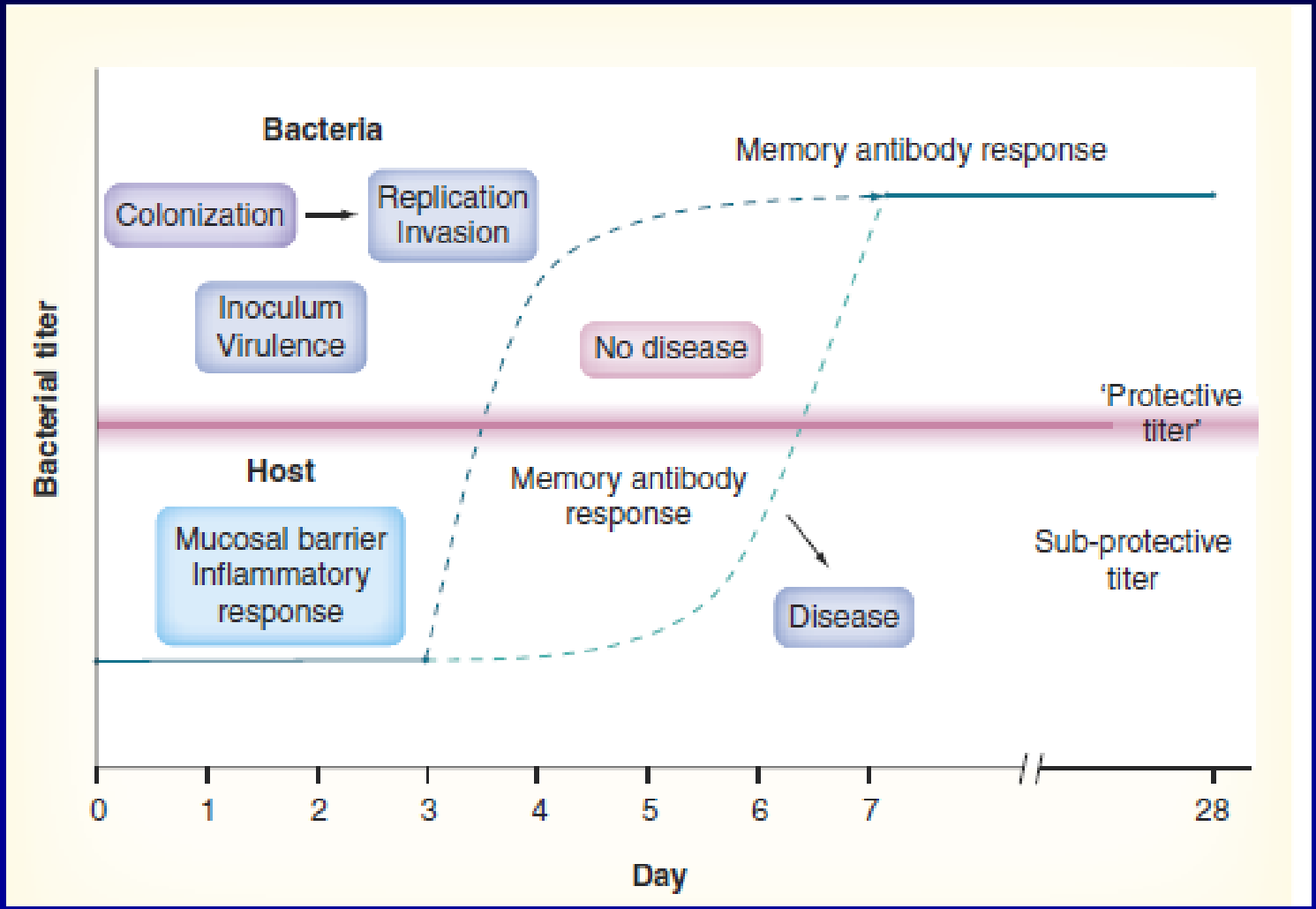
- …
- …
- …
- …
- …

Not sufficient

- …
- …
- …
- …
- …

And why ???

When is memory sufficient or not sufficient for protection ?



Jan Poolman[†1] and
Ray Borrow[2]

Expert Rev. Vaccines 10(3), 307–322 (2011)

Recalling memory responses before the bugs win the race…

Short incubation

- Hib
- Pneumococcus
- Meningococcus
- Influenza (Ab)

Prolonged incubation

- Hepatitis B
- Hepatitis A
- …

Mucosal only infections

- HPV !!
- Pertussis !!

Time for Ag to reach the LN and reactivate memory cells into Ag-producing cells

Insufficient memory !

Sufficient memory !

A few lessons from vaccine case studies

- The most frequent vaccine failure is the failure to have been immunized !
- Herd immunity may compensate for individual vaccine failures !
- Live attenuated viral vaccines induce weaker responses than WT infection – and these may persist or wane more rapidly (chickenpox) !
- Protection may persist after the disappearance of vaccine effectors: role for immune memory !
- **Persistence of immune memory may NOT be sufficient to confer protection…**

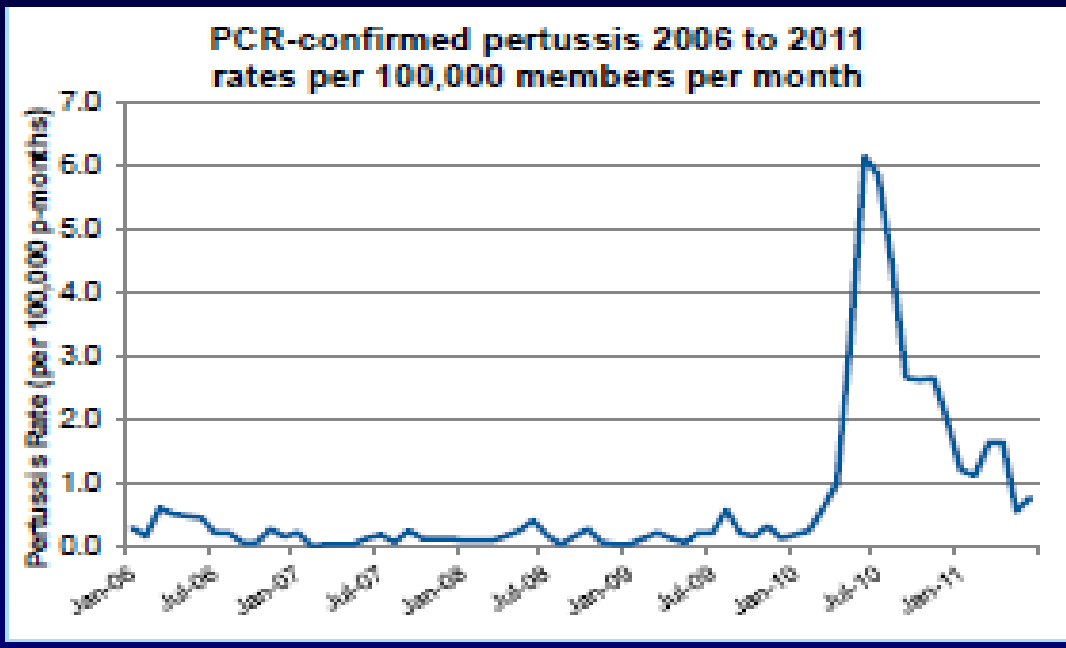
Does memory last forever?

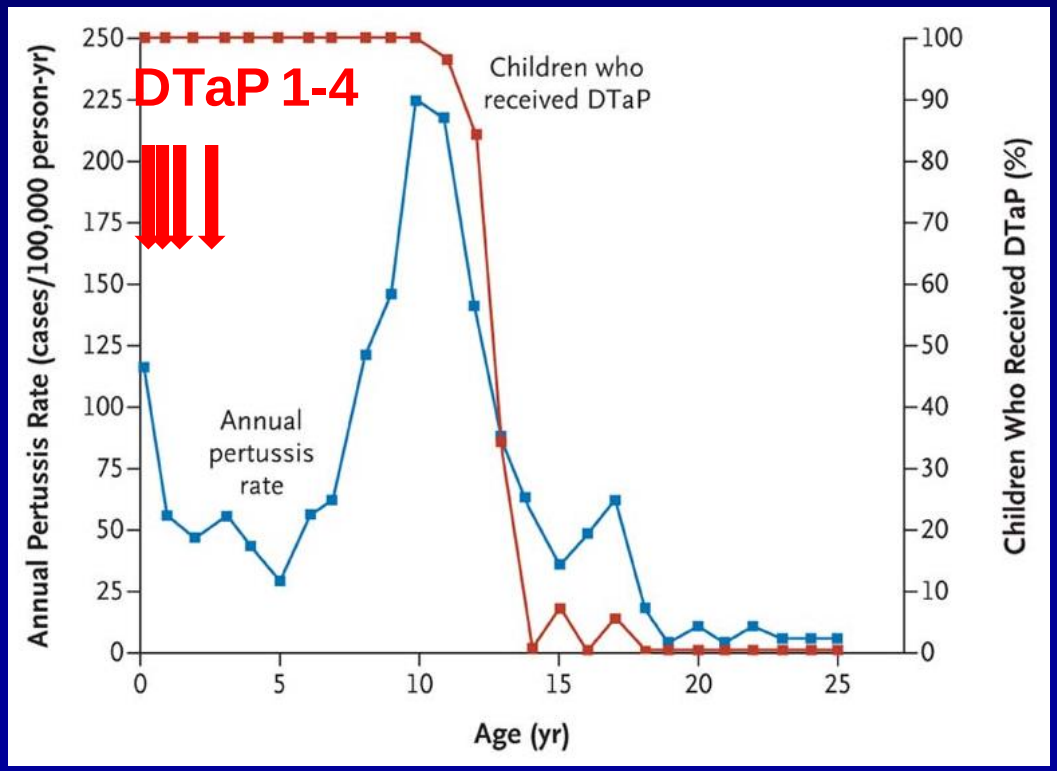
Pertussis outbreak, California 2010

Kaiser Permanente Vaccine Study Center

What ?

1. 0-5 years ?

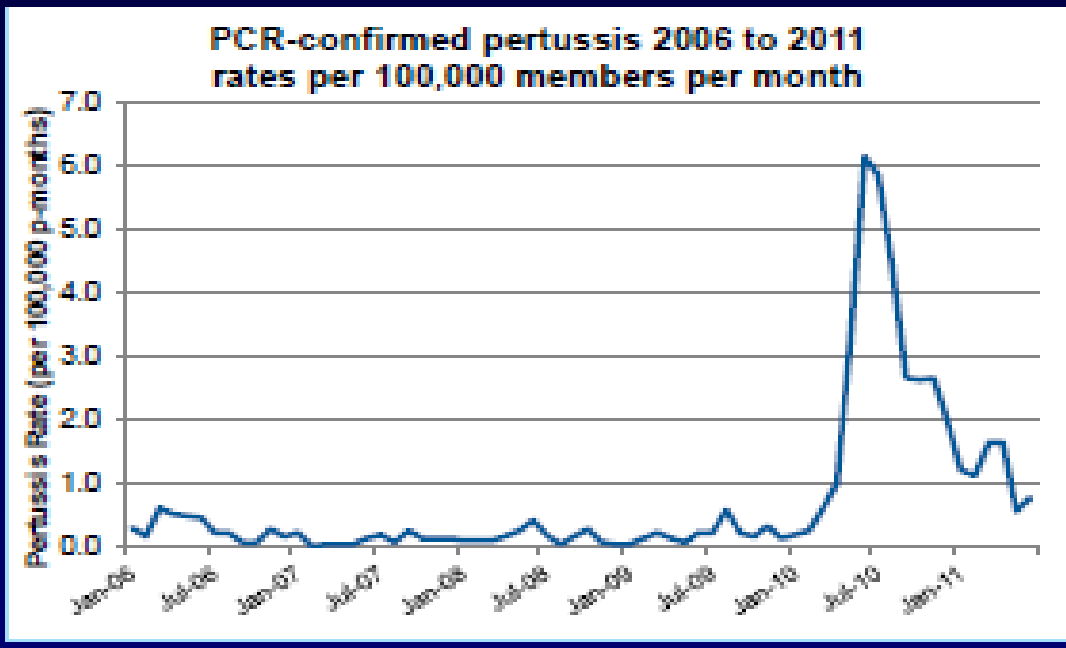




Klein NP et al. N Engl J Med 2012;367:1012-1019

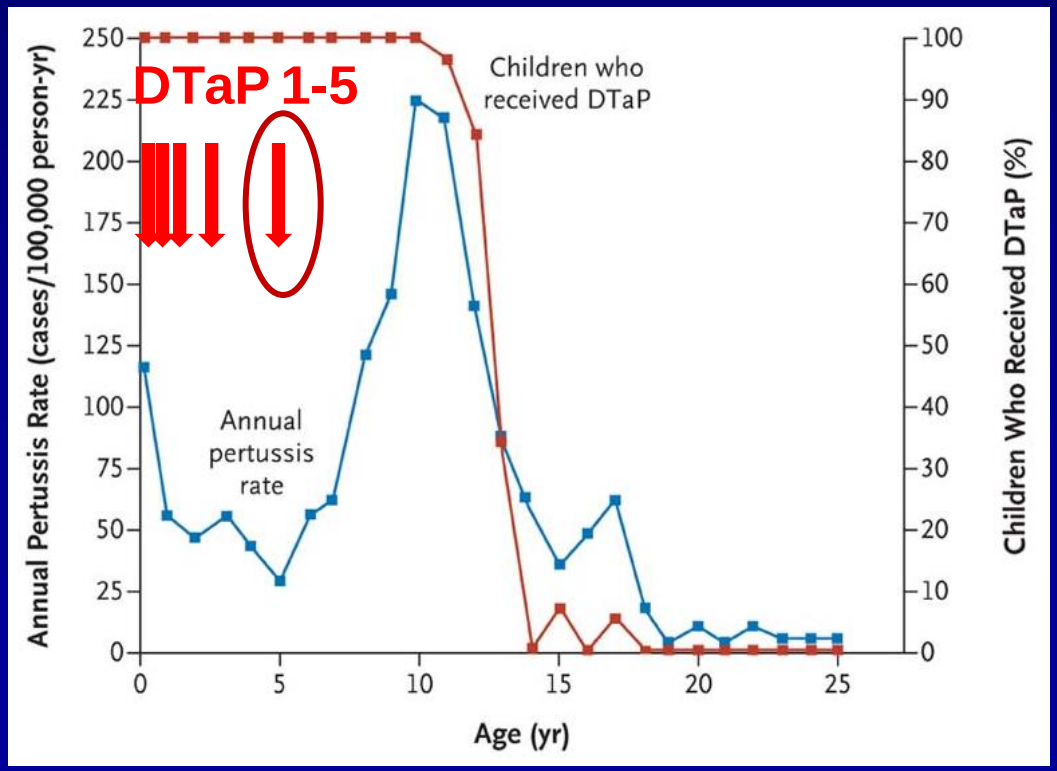
Pertussis outbreak, California 2010

Kaiser Permanente Vaccine Study Center



What ?

1. **0-5 years ?**
2. **5-10 years ?**



Which study design?

Klein NP et al. N Engl J Med 2012;367:1012-1019

Pertussis outbreak, California 2010

Kaiser Permanente Vaccine Study Center

Study Design

Using a case control design, we examined the relationship of vaccinations with the likelihood of a positive pertussis test. We looked at waning (time since last vaccine), effectiveness of Tdap, and the effect of delayed or missed vaccines.

Misegades LK JAMA 2012

Table 4. Odds Ratios for Pertussis Disease Associated With Receipt of 5 DTaP Doses and Estimated Vaccine Effectiveness for Each Year Following the Complete DTaP Series

	Primary Analysis[a]				Secondary Analysis[b]		
Estimated VE Model	Cases, No. (n = 682)	Controls, No. (n = 2016)	OR (95% CI)	Estimated VE, % (95% CI)	Controls, No.	OR (95% IE)	Estimated VE, % (95% IE)
Overall No. of doses							
0	53	19	1 [Reference]	1 [Reference]	11	1 [Reference]	1 [Reference]
5	629	1997	0.11 (0.06-0.21)	88.7 (79.4-93.8)	1018	0.13 (0.08-0.16)	87.2 (83.6-91.9)
Time since fifth dose, mo							
0 doses	53	19	1 [Reference]	1 [Reference]	11	1 [Reference]	1 [Reference]
<12	19	354	0.02 (0.01-0.04)	98.1 (96.1-99.1)	230	0.02 (0.01-0.02)	98.3 (97.8-98.9)
12-23	51	391	0.05 (0.02-0.09)	95.3 (91.2-97.5)	158	0.07 (0.04-0.09)	93.4 (91.1-96.0)
24-35	79	366	0.08 (0.04-0.13)	92.3 (86.6-95.5)	154	0.11 (0.06-0.14)	89.5 (85.7-93.7)
36-47	108	304	0.13 (0.07-0.24)	87.3 (76.2-93.2)	140	0.16 (0.10-0.20)	84.1 (80.1-90.4)
48-59	141	294	0.17 (0.09-0.31)	82.8 (68.7-90.6)	158	0.18 (0.12-0.24)	82.0 (75.8-88.4)
≥60	231	288	0.29 (0.15-0.54)	71.2 (45.8-84.8)	178	0.27 (0.17-0.35)	73.3 (65.1-83.0)

Abbreviations: IE, interval estimate; OR, odds ratio; VE, vaccine effectiveness.

[a] ORs and estimated VE, accounting for clustering by county and clinic.

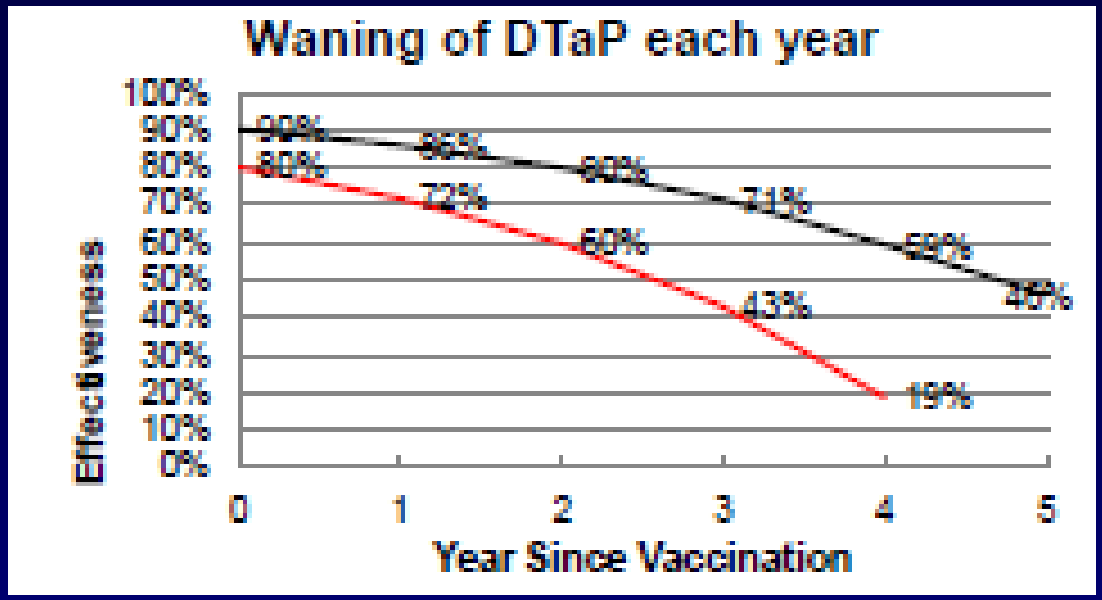
[b] Median and 95% IE based on 200 random, iterative samples of n=1029 controls and assuming an even distribution of controls in each age category from 4 to 10 years. When divided into "time since fifth dose" categories, the <12-month category captures a larger number of individuals (n=230) since the fifth dose can be administered at ages 4, 5, or 6 years.

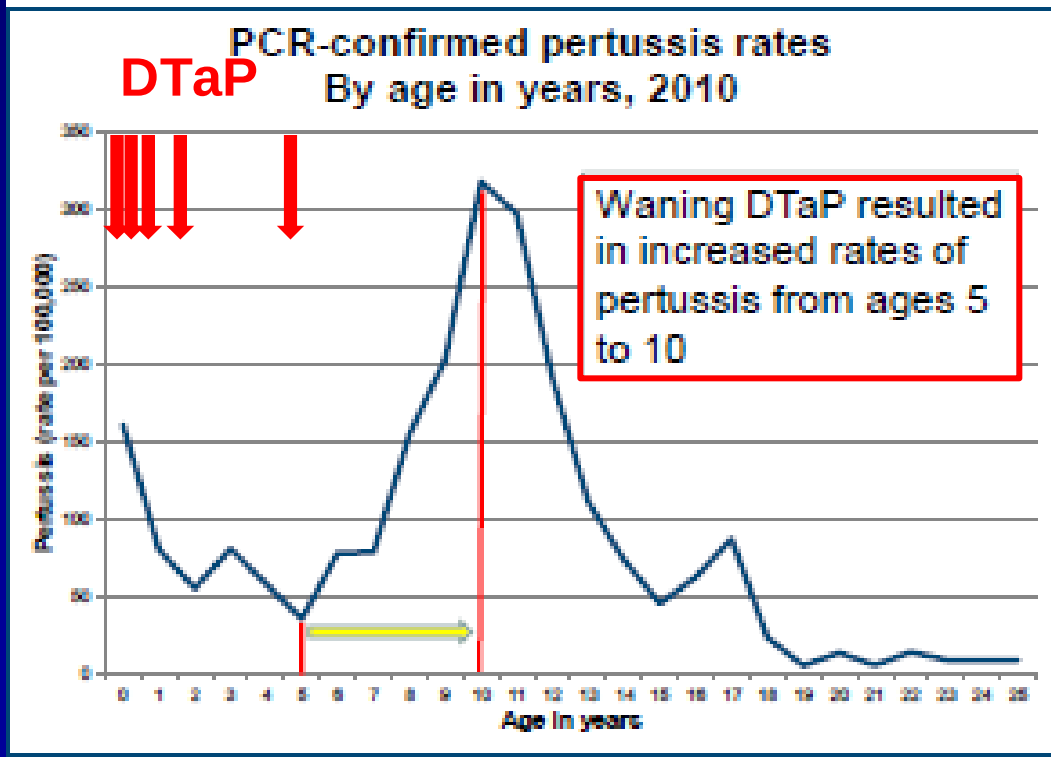
Pertussis outbreak, California 2010

Kaiser Permanente Vaccine Study Center

Case control study

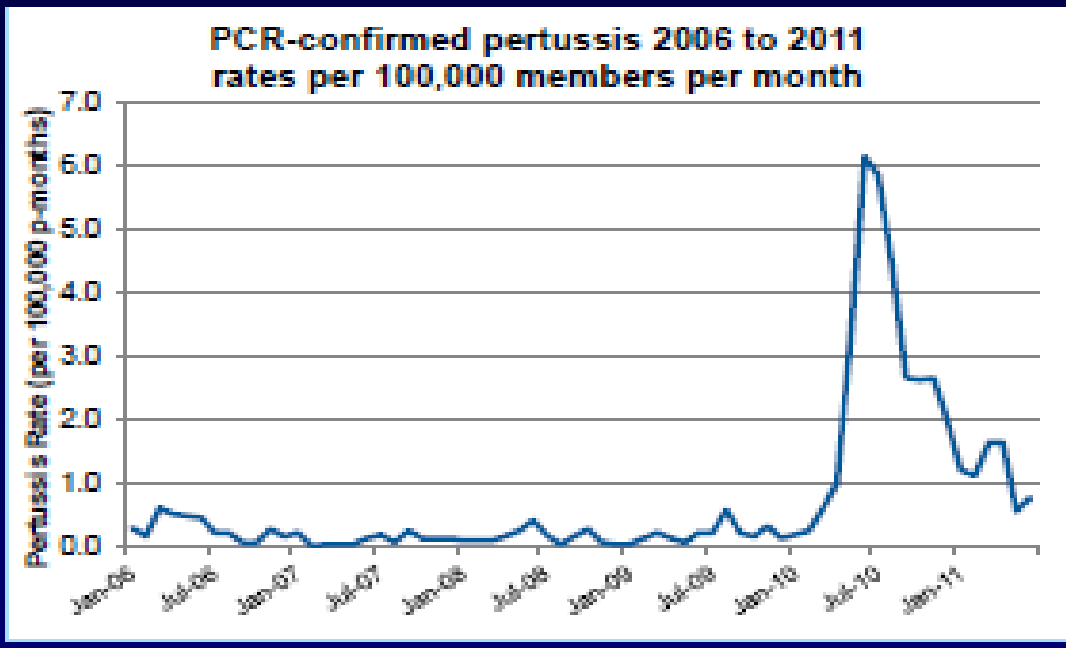
Rapid waning of immunity after DTaP5





Pertussis outbreak, California 2010

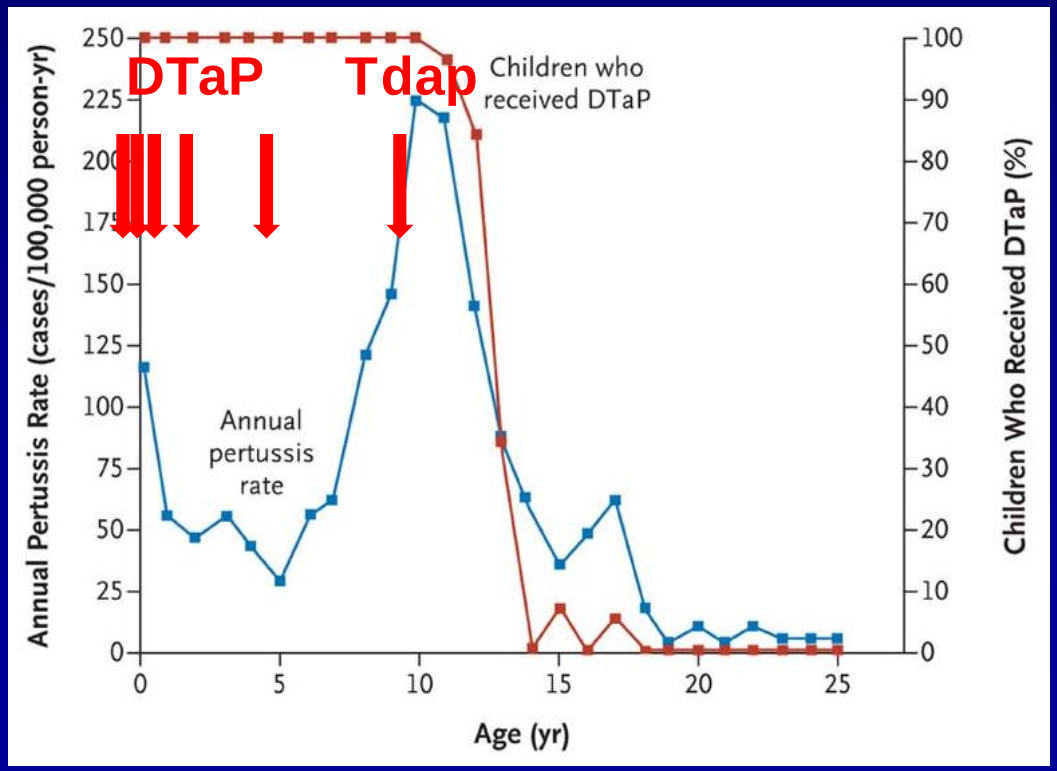
Kaiser Permanente Vaccine Study Center



What ?

1. **0-5 years ?**
2. **5-10 years ?**
3. **10-15 years ?**

Which design ?



Klein NP et al. N Engl J Med 2012;367:1012-1019

2. Tdap effectiveness (Presented elsewhere[2])

Table: Probability of a positive pertussis PCR test, based on vaccination with Tdap or not. (Effectiveness = (1 - Odds Ratio)

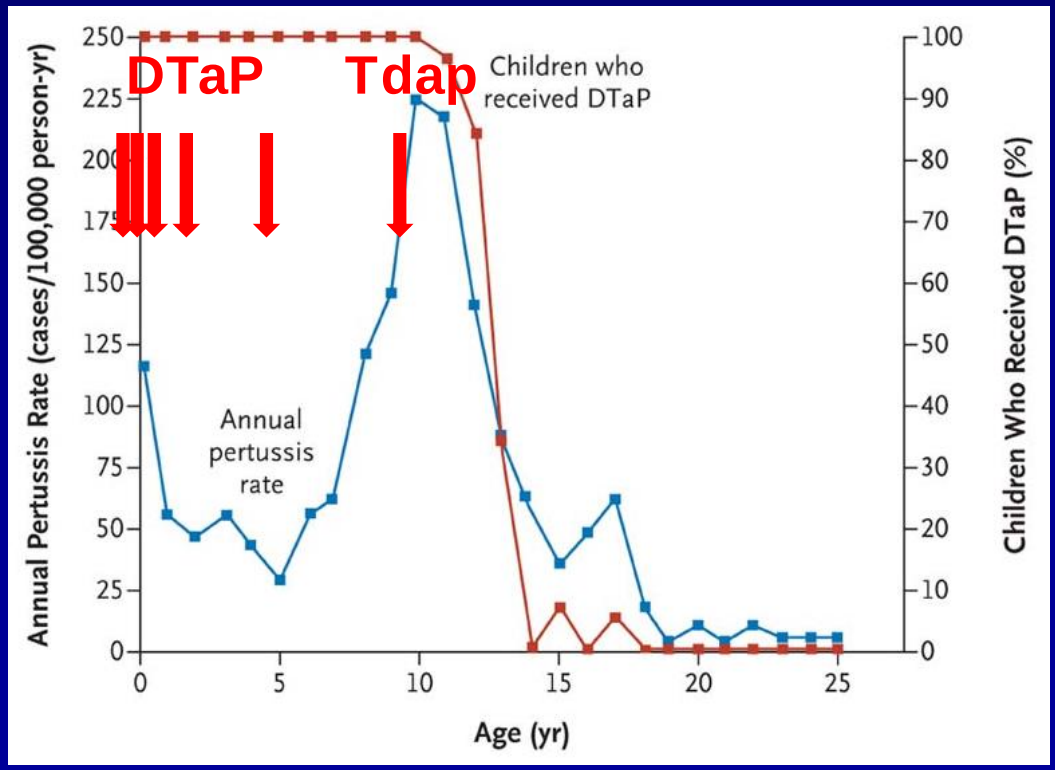
Control Type	Cases N	Controls N	Odds Ratio	95% CI	P-value
PCR Negative	566	9,166	0.448	0.359-0.559	<0.001
KPNC Pop	566	19,439	0.373	0.296-0.469	<0.001

➢Interpretation: Tdap is 55% effective at preventing PCR-confirmed pertussis

Case control study

Only 55% effectiveness of adolescent Tdap booster in DTaP-primed children !

Why is vaccine efficacy lower in adolescents than in infants ???



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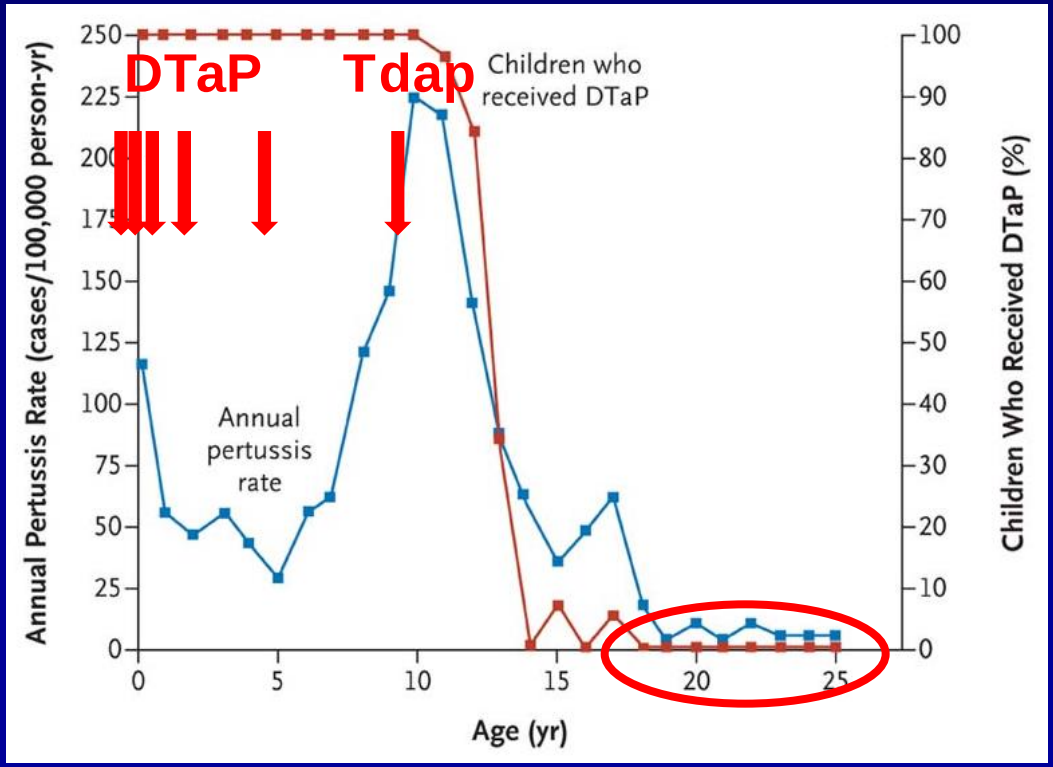
Few cases of pertussis in young adults > 18 years ?

What ?

1. **0-5 years ?**
2. **5-10 years ?**
3. **10-15 years ?**
4. **> 18 years ?**



Potential explanations for the failure of pertussis vaccines to confer sustained immunity

- Primary vaccine failures √ √ (aP >> wP)
- Secondary vaccine failures √ √ √ (aP >> wP)
  - Loss of vaccine Ab √ (rapid)
  - Loss of T cell immunity (Th17) √ (presumed)
  - Loss of « boostability » with ↑ number of aP doses (mech ?) √√ (aP)
  - Lack of timely natural boosting √√ (aP >> wP)
- Mismatch btwn vaccine and outbreak strains √ (?)
- Others ???

A few lessons from vaccine case studies

- The most frequent vaccine failure is the failure to have been immunized !
- Herd immunity may compensate for individual vaccine failures !
- Live attenuated viral vaccines induce weaker responses than WT infection – and these may persist or wane more rapidly (chickenpox) !
- Protection may persist after the disappearance of vaccine antibodies : role for immune memory !
- Persistence of immune memory may NOT always confer protection !
- **Immune memory may not be forever !**

A few lessons from vaccine case studies

- The most frequent vaccine failure is the failure to

Much remains to be studied !

  vaccine failures !
- Live attenuated viral vaccines induce weaker responses than WT infection – and these may persist or wane more rapidly (chickenpox) !
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