



# Maternal immunization

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# Maternal immunization – why vaccinate during or after pregnancy?

- › To protect the newborn baby
- › To protect the mother
- › Because it is a time when women contact the health service



# Logical maternal immunization targets

- › To protect the newborn...
  - Group B Streptococcus
  - Tetanus
  - Pertussis
  - Pneumococcus
  - Influenza
  - Respiratory Syncytial Virus
  
- › To protect the mother...
  - Influenza
  - Malaria
  - Hepatitis E



# Maternal immunization targets

## 1. Tetanus



Photo courtesy Dr. M. Weber



# Large trial of cholera vaccine, Bangladesh, 1974

- › 93,000 persons randomized to receive cholera or Td vaccine
- › Analysis of women who delivered up to 32 months following vaccination:
  - CT: 262 deaths/4386 births (NMR 60)
  - TT1: 54 deaths/1265 births (NMR 43)
  - TT2: 119 deaths/2990 births (NMR 40)

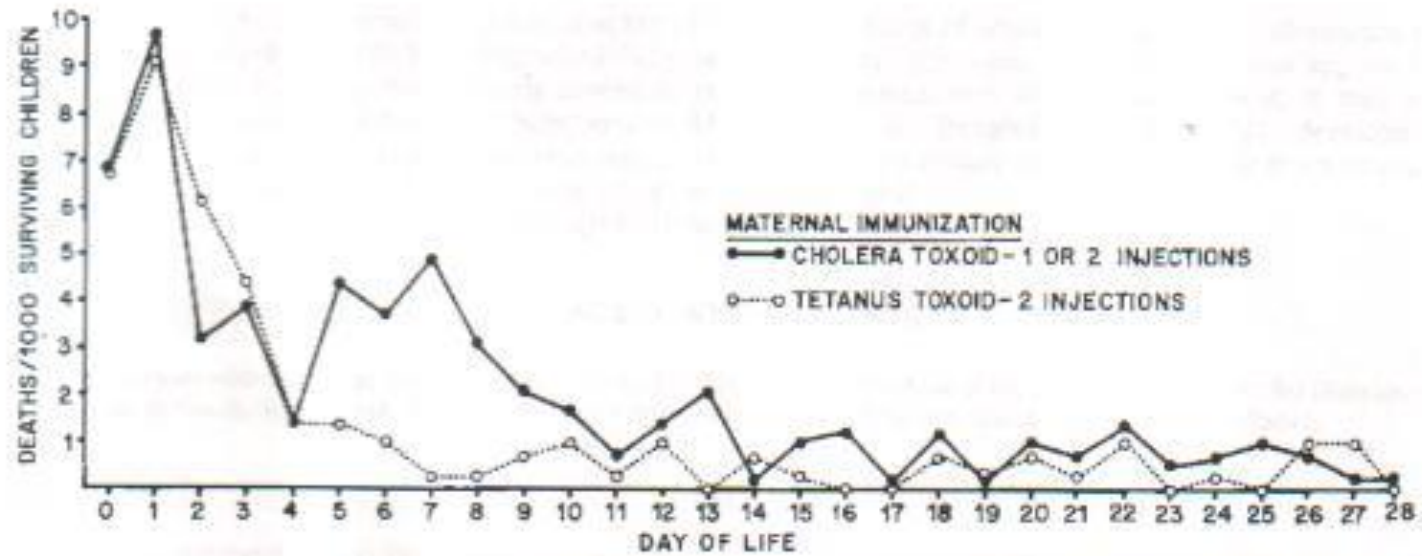


Fig. 1 Neonatal death rates by age of death following maternal immunization with one or two doses of cholera or two doses of tetanus/diphtheria toxoids.

# St Kilda 1886





# St Kilda 1886

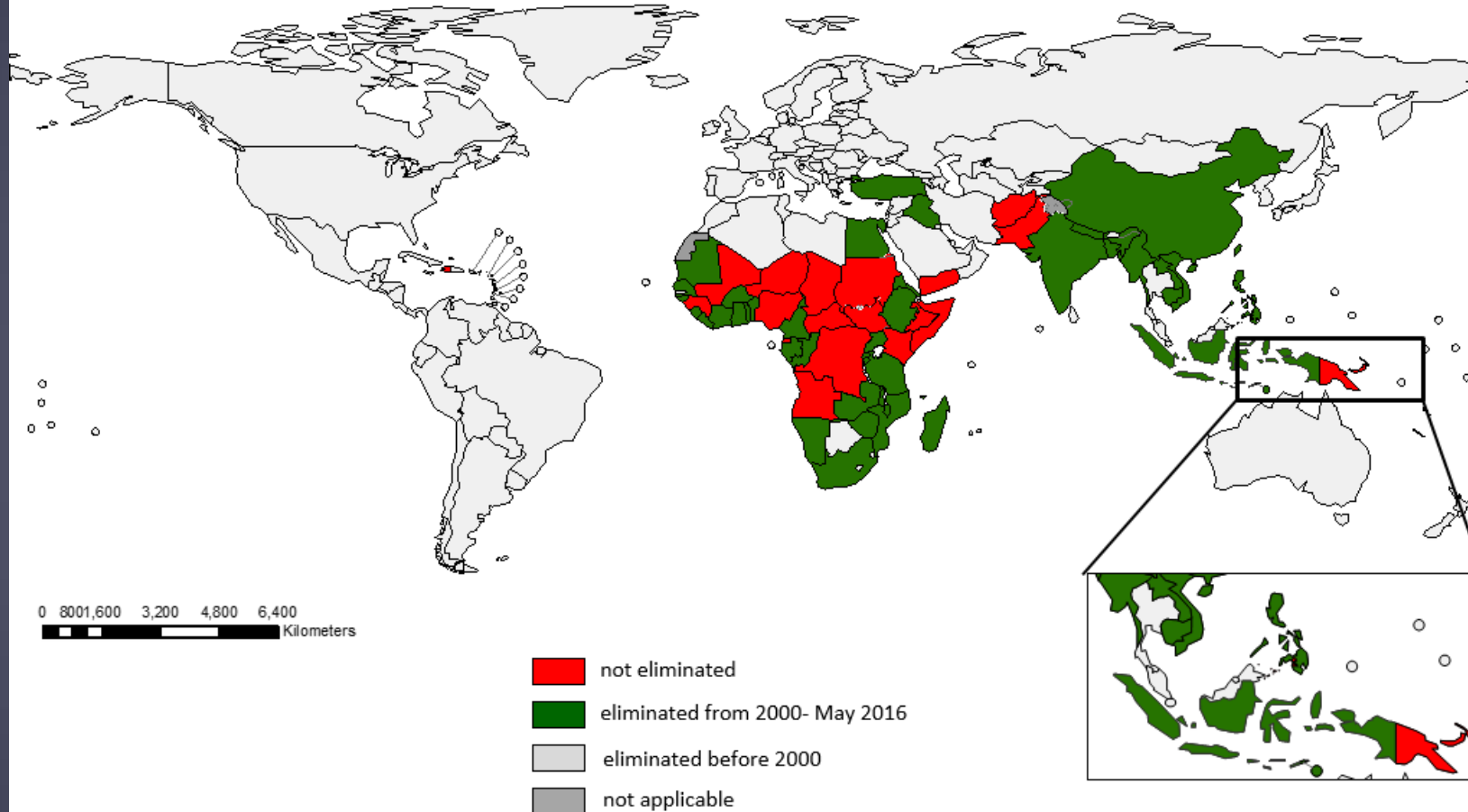


## St Kilda Island (UK)

- › Prior to 1892 NMR was 500/1000 live births
- › “8 day sickness” = neonatal tetanus
- › Management of the cord with bird droppings
- › Resistant to outside interventions
- › Only corrected when a man took over the midwifery in 1892

# 39 Countries eliminated MNT between 2000 & May 2016

\*(Plus Ethiopia except Somali region and 16 regions out of 17 in Philippines) leaving 20 countries yet to eliminate MNT



Source: WHO/UNICEF Database  
Date of slide : 19 May 2016  
Map production: Immunization Vaccines and  
Biologicals, (IVB), World Health Organization

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Elimination = <1 case per 1000 live births



# Maternal immunization targets

1. Tetanus
2. Influenza





# Maternal influenza vaccination

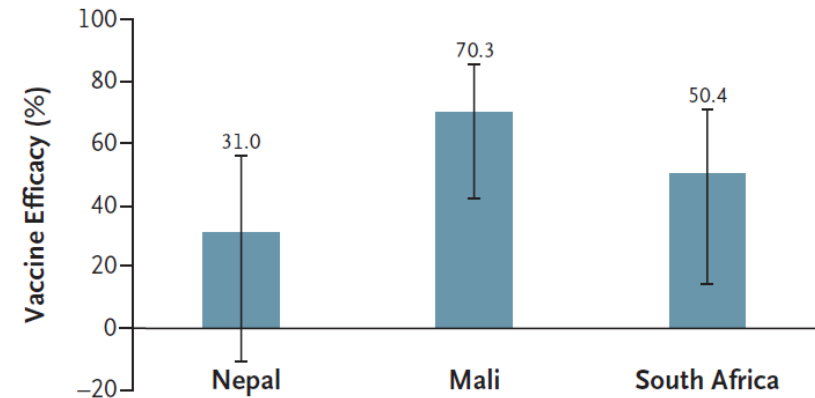
- › Recommended for pregnant women in US since 1960s due to risk of severe influenza
  - Vaccinate any time in pregnancy
  - Safety not questioned
  - Risk is small, but worse in pandemics
  - Infant influenza also an issue
- › Many countries have recommendations since 2012 WHO recommendation
  - Variable uptake

# Maternal influenza studies in LMICs

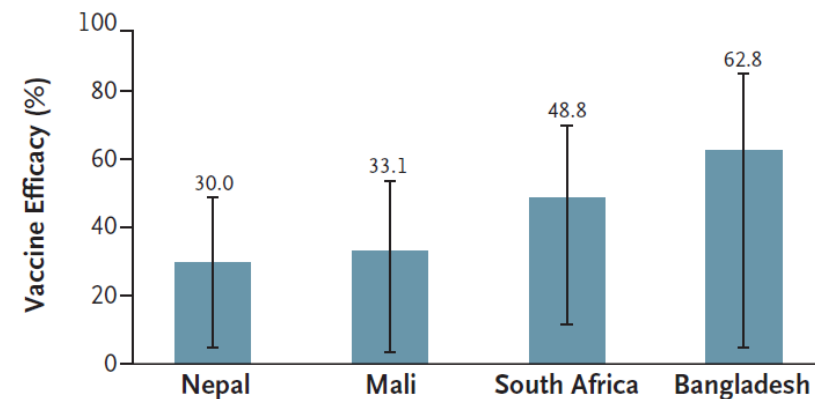
- › Mali, Sth Africa, Bangladesh, Nepal
  - Prevented 30-63% of influenza in infants (mild febrile illnesses)
  - Reduced incidence of low birth weight (Nepal, B'desh only)
    - › Mainly during influenza season in Nepal
    - › Nepal vaccinated 17-34 weeks (others 3<sup>rd</sup> trimester)

N Engl J Med 2017;376:1256-67.  
DOI: 10.1056/NEJMr1509044

**A** Laboratory-Confirmed Influenza in Mothers



**B** Laboratory-Confirmed Influenza in Infants



**Figure 2.** Estimated Efficacy of Influenza Vaccination during Pregnancy for Preventing Laboratory-Confirmed Influenza in Infants and Mothers.



# Maternal immunization targets

1. Tetanus
2. Influenza
3. Pertussis

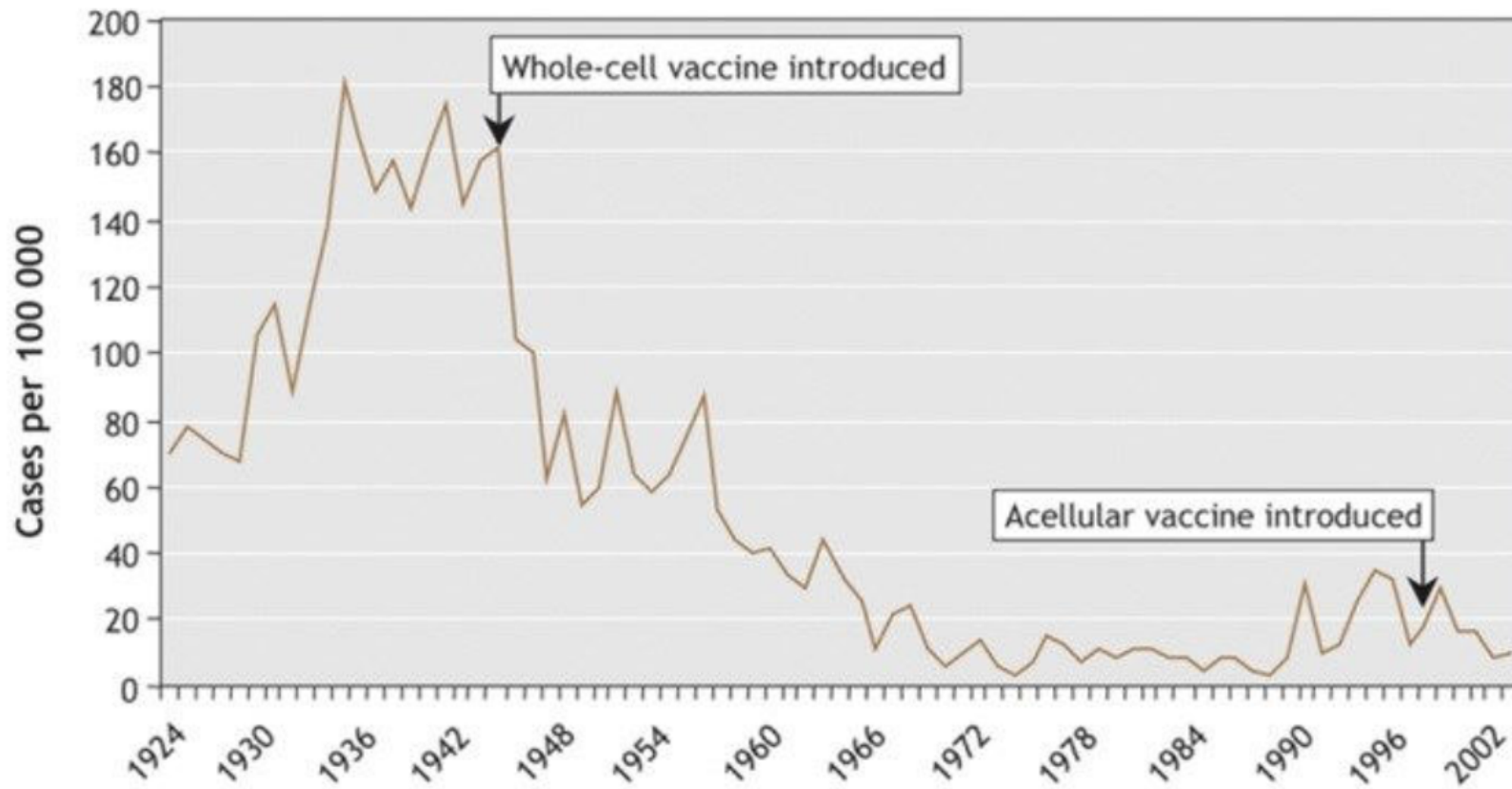
# Maternal pertussis immunization

- › New York 1942
- › 170 pregnant women given 6 doses of pertussis vaccine during 3rd trimester
- › Follow-up 1st 6 mths :
  - 100 vaccinees, 8 exposures, no cases
  - 100 controls, 6 exposures, 3 cases

Cohen P, Scadron SJ. J Pediatrics 1946;29:609-619.



Figure 3. The incidence of pertussis in Canada, 1924-2002.(5)

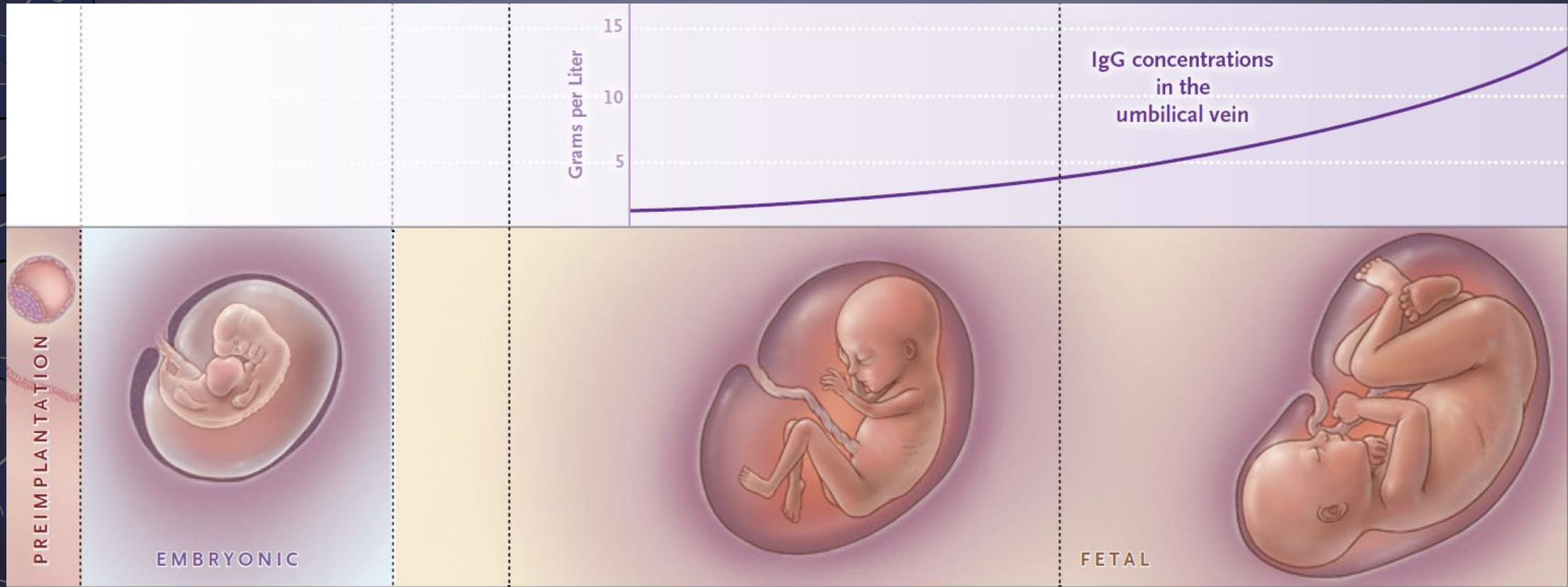




# Maternal pertussis immunization

- › Recommended in US, UK, Australia since 2012
- › Administered as DTaP
- › Usually recommended for third trimester
  - UK now recommends 2<sup>nd</sup> trimester

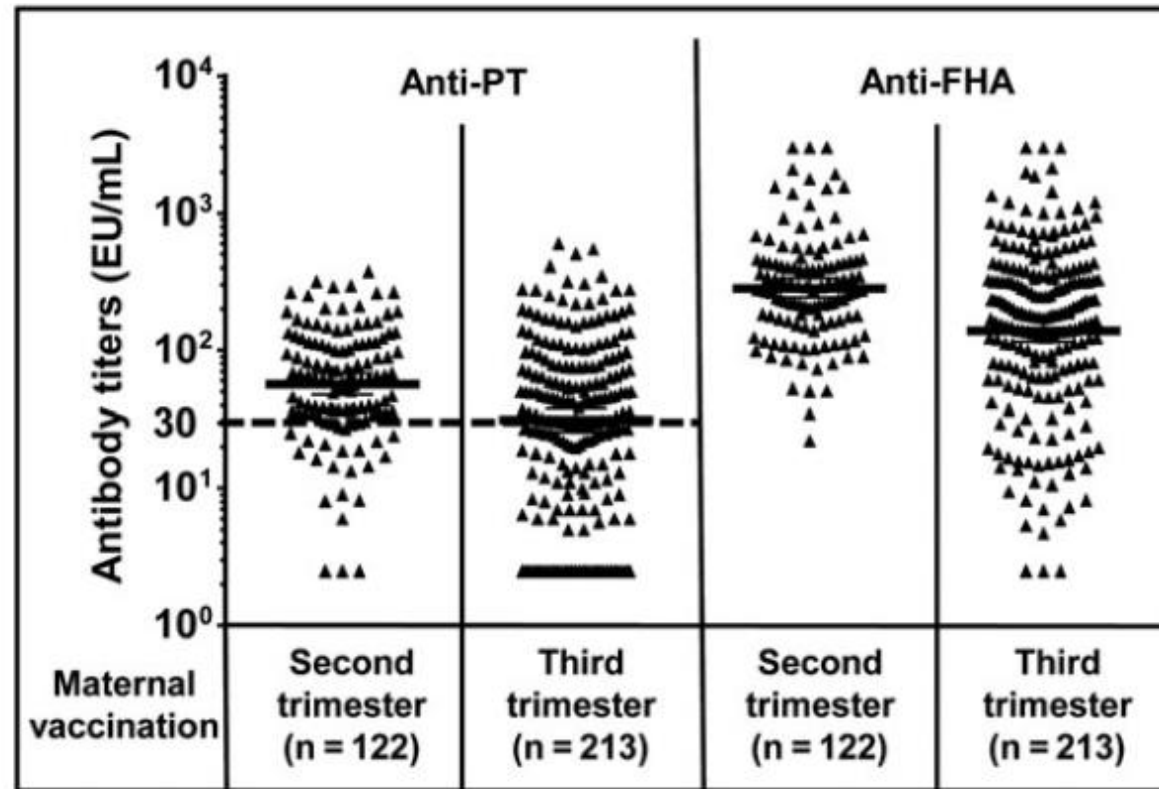
# When to vaccinate?



1<sup>st</sup> Trimester

2nd Trimester

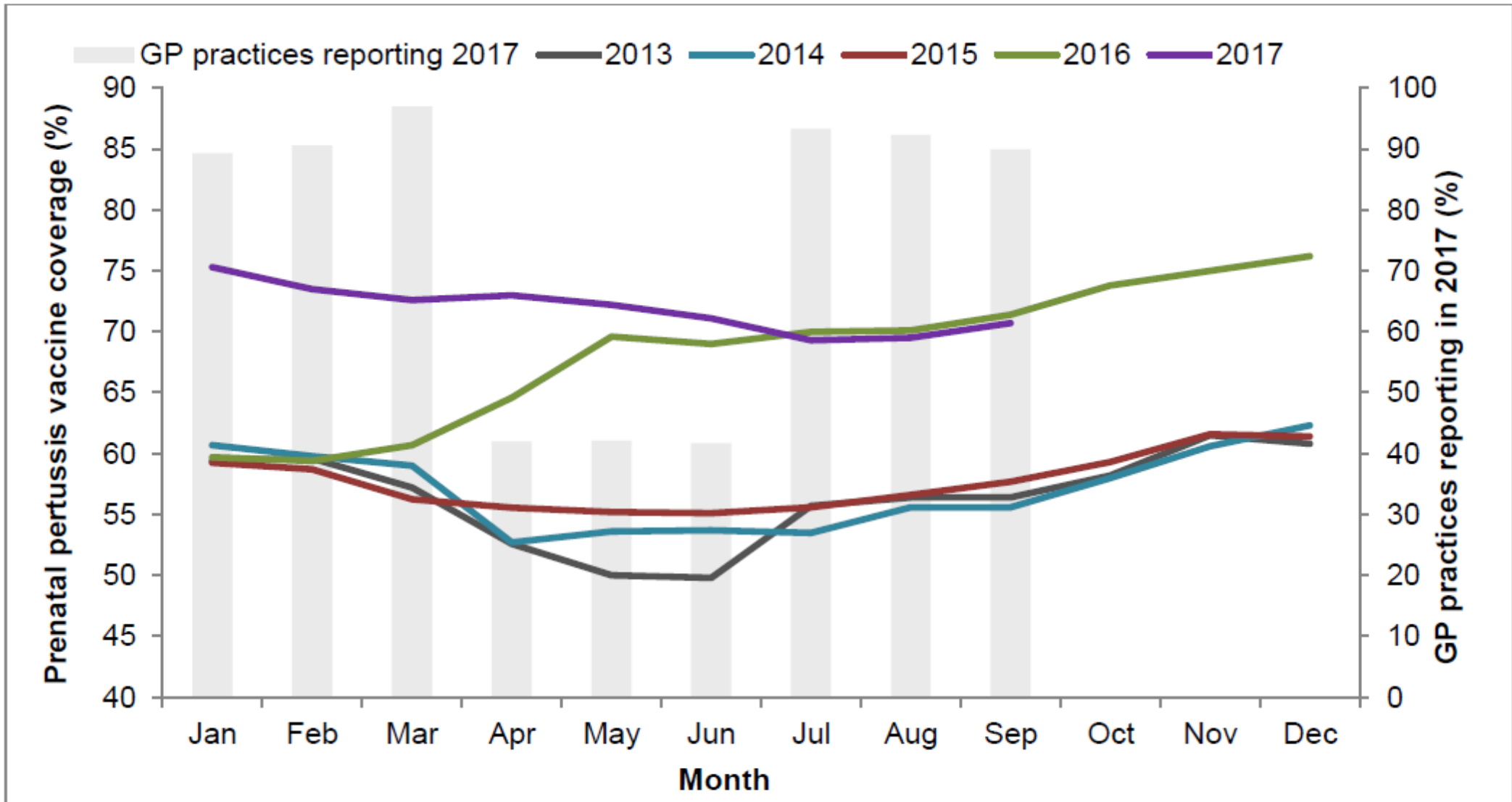
3rd Trimester



**Figure 1.** Anti-pertussis toxin (PT) and anti-filamentous hemagglutinin (FHA) cord blood antibody concentrations by trimester of maternal immunization. Individual anti-PT and anti-FHA antibody concentrations in newborns of mothers vaccinated with tetanus-diphtheria-acellular pertussis during the second or the third trimester; each point corresponds to 1 patient. Geometric mean concentrations and 95% confidence intervals are indicated. The dotted line indicates the cutoff for expected infant seropositivity (anti-PT = 30 enzyme-linked immunosorbent assay units [EU]/mL).



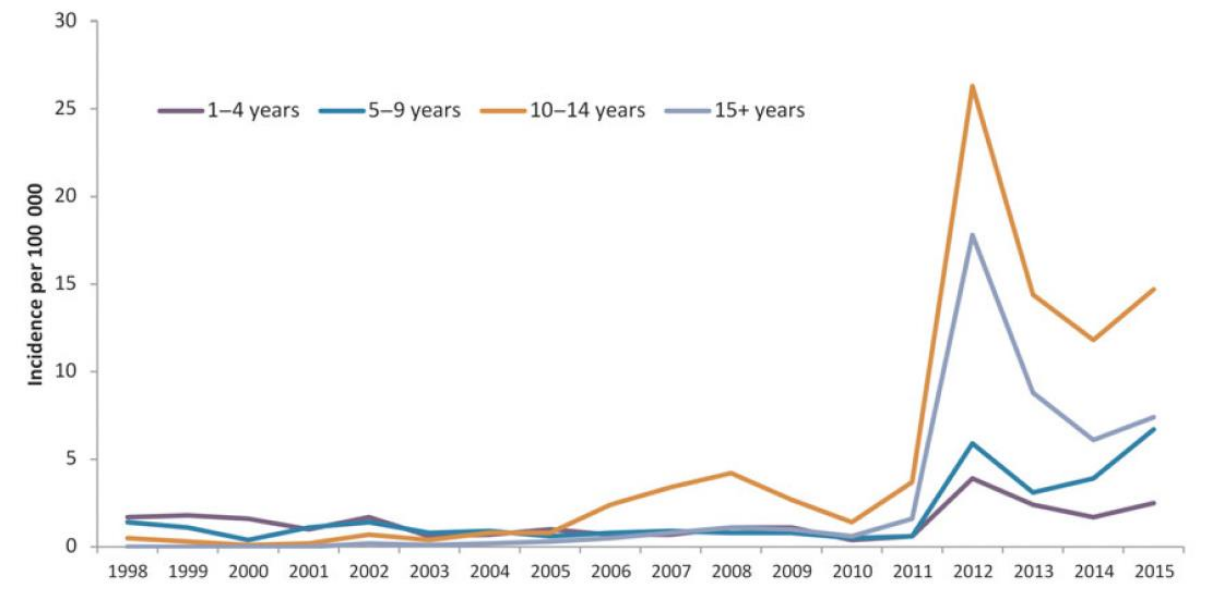
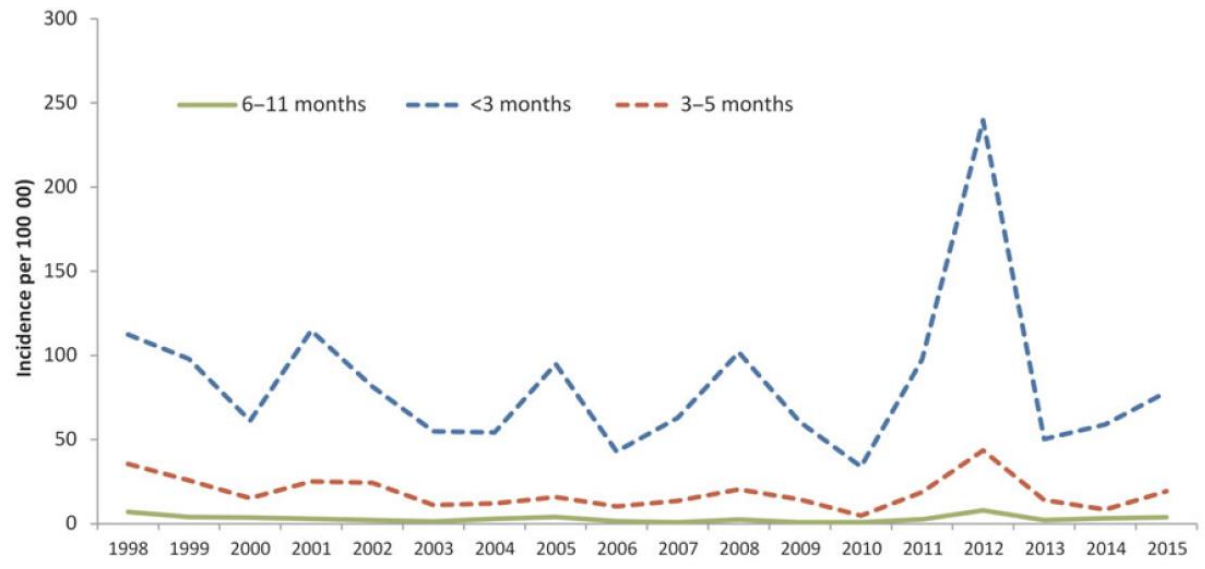
**Figure 1. Monthly pertussis vaccination coverage (%) in pregnant women: England, 2013-2017**





## Infant pertussis in UK

- › Maternal DTaP vaccination introduced October 2012
- › Pertussis in infants <3 months:
  - 2012 – 328
  - 2013 – 72
- › Effectiveness estimated to be over 90%, by screening method, based on 2012/2013 data, but...



**Figure 2.** Incidence of laboratory-confirmed pertussis, by year and age group, England only, 1998–2015.



# Maternal immunization targets

1. Tetanus
2. Influenza
3. Pertussis
4. Pneumococcal disease

PNEUMONIA IN PAPUA NEW GUINEA

A Study of the Effects of Western Medicine upon Disease in a  
Developing Country

by

Ian Douglas Riley

M.B., B.S. (Sydney), F.R.C.P. (Edinburgh), D.T.M. & H. (Liverpool)

Submitted as a thesis for the degree of Doctor of Medicine

at the University of Sydney

March, 1979.



Table 11.5 The effects of maternal vaccination during the Tari Vaccine trial.

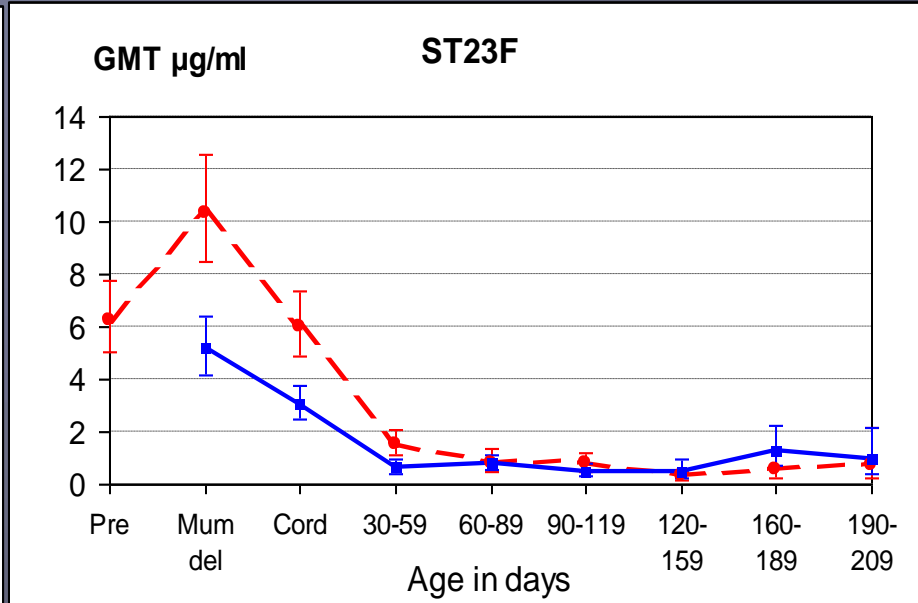
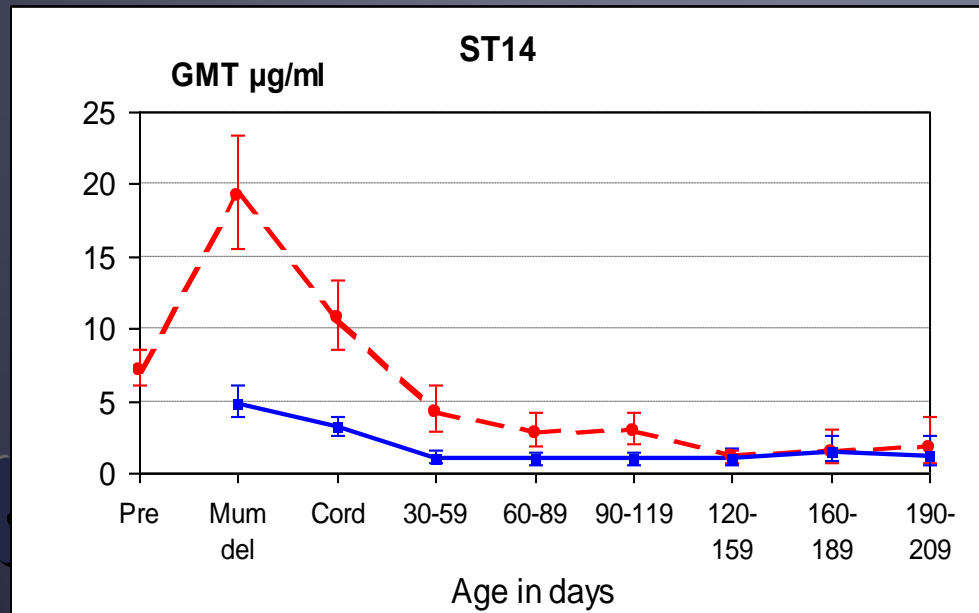
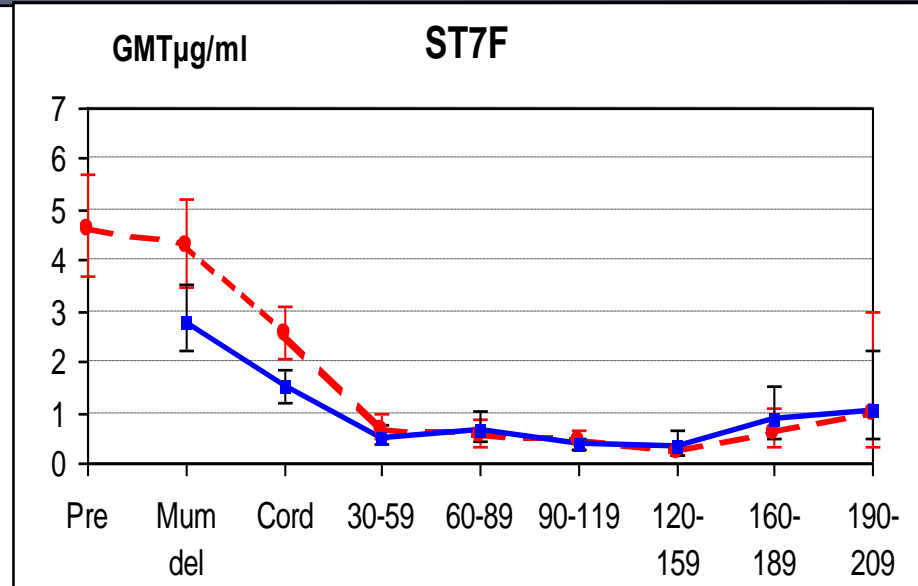
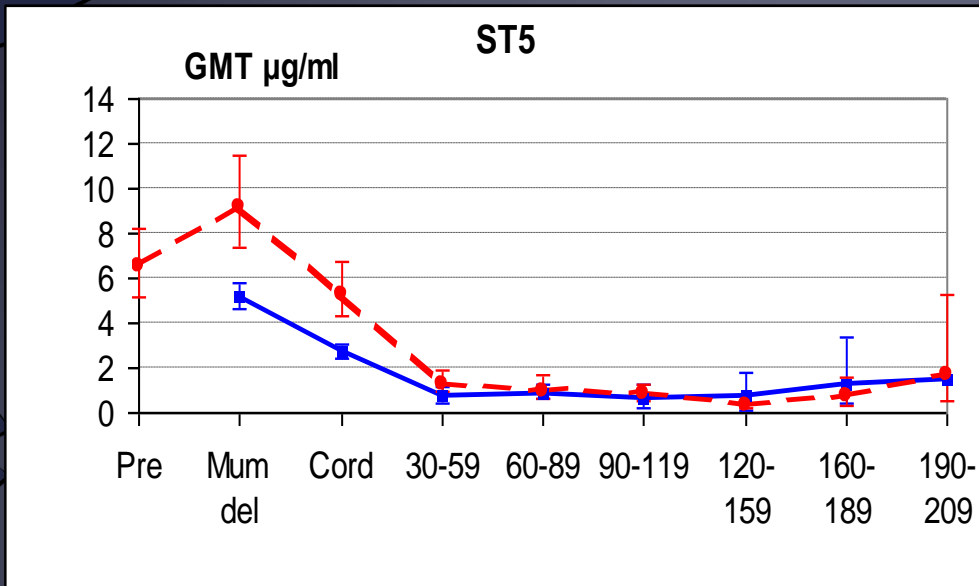
	VACCINE	PLACEBO	TOTAL
Number of pregnant women included in the vaccine trial	187	167	354
Abortions (under 28 weeks)	2	0	2
Congenital defects	1	2	3
Deformed left ear (vaccine)			
Diaphragmatic hernia - died (placebo)			
hydrocephalus - died (placebo)			
Stillborn (28 weeks and over)	6	4	10
Died during first week of life	2	1	3
Deaths during infancy and childhood	11	5	16
pneumonia	2	6	8
Other (includes septicaemia)			
TOTAL	24	18	42

	VACCINE	PLACEBO
<u>History of breathlessness</u>		
0-2 days		101
3-6 days	60	21
7 days +	18	7
Nil	2	4
	4	
<u>History of cough</u>		
0-2 days		82
3-6 days	51	29
7 days +	29	16
Nil	2	6
	2	
<u>Temperature</u>		
Less than 38°C		84
38°C +	54	58
Unknown	30	1
	0	
<u>Respiratory rate per minute</u>		
Less than 40	11	19
40-59	28	46
60 +	43	60
Unknown	2	8
<u>Intercostal indrawing</u>		
Present	42	66
Absent	32	51
Unknown	10	26
<u>Radiology</u>		
Bronchiolitis	1	8
Unisegmental pneumonia	6	11
Bronchopneumonia	4	4
No abnormality	21	23
Not done	52	87
	84	133
<u>Total attacks involved</u>		
	142	155
<u>Total persons at risk</u>		

## Impact of maternal immunisation with 14V pneumococcal polysaccharide vaccine on infant pneumonia Papua New Guinea 1973-1976

Age	Pneumonia episodes/ No. mothers		Efficacy	p
	Vaccine	Placebo		
<b>In utero</b> at time of maternal immunisation followed for <b>3 years</b>	57/84	73/93	14%	0.1
<b>Child age 1-17 months</b> at time of maternal immunisation followed over <b>next 5 months</b>	84/286	133/310	32%	0.003
<b>Child age 1-17 months</b> at time maternal immunisation followed over <b>next 3 years</b>	218/286	284/310	17%	0.02

# Anti-Pnc IgG antibody titres in serum



Vaccinated ----- Unvaccinated



Vaccine 2002;20-1837-45

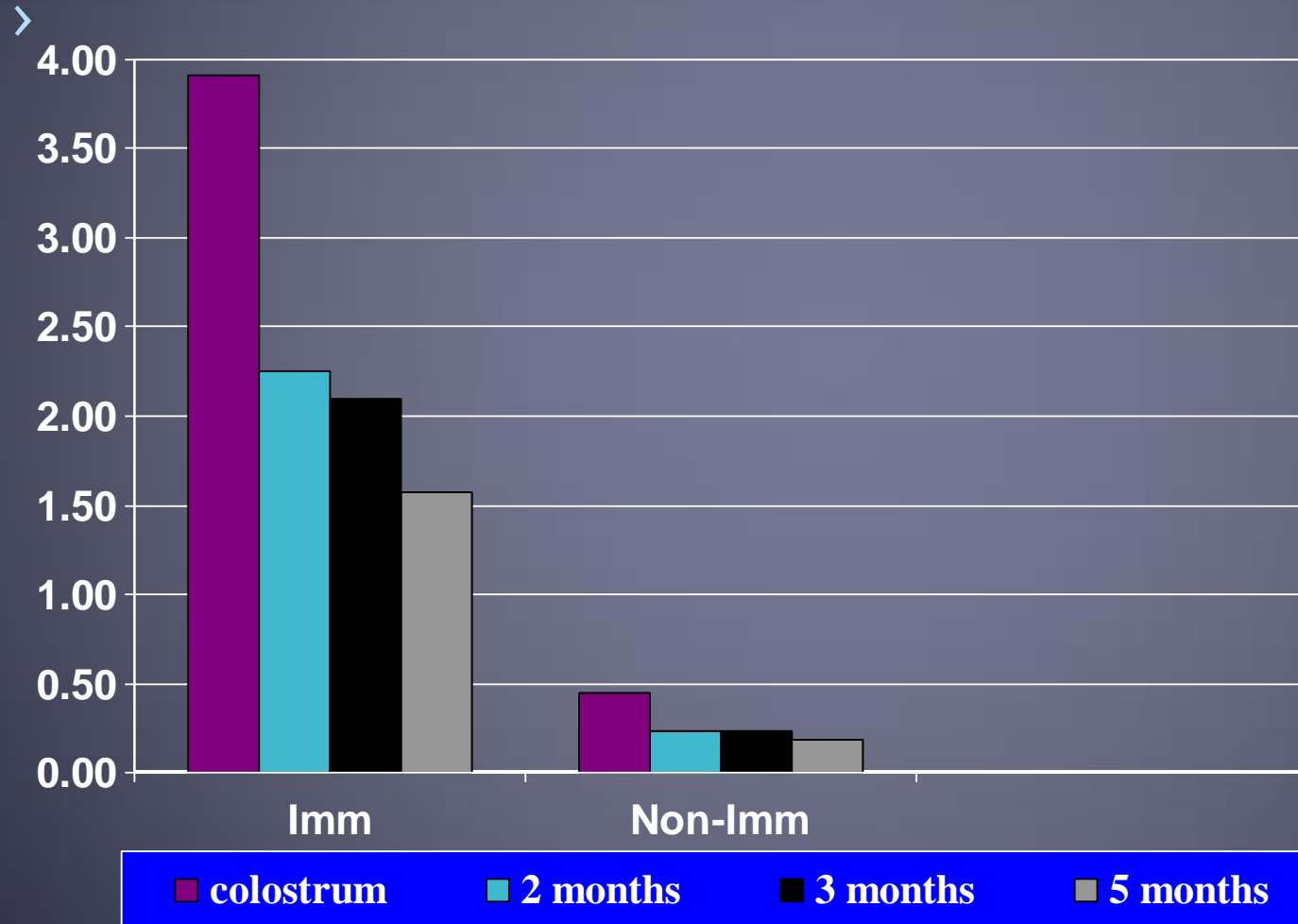


## Breast milk antibodies

- › Levels in vaccinees > levels in controls
- › Varies with serotype
  - 14, 19F produce high specific IgA titres
- › Elevation lasts 4-6 months in some studies



# Breast milk antibodies Hib vaccine (Gambia)





# Maternal immunization targets

1. Tetanus
2. Influenza
3. Pertussis
4. Pneumococcal disease
5. Respiratory Syncytial Virus (RSV)



## RSV disease

### › In infants

- Acute bronchiolitis (most cases due to RSV)
- Pneumonia
- Laryngotracheobronchitis (croup)
- Causes seasonal epidemics, every winter

### › Older children and adults

- Minor ARIs, sometimes with wheeze

### › Elderly

- More severe respiratory illness, maybe significant mortality

# Formalin Inactivated RSV vaccine

> 1967

## **History of FI-RSV Vaccine Enhanced Disease in Clinical Trials**

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**<1966 – Live and inactivated RSV given parenterally without benefit**

**1966-7 – 4 independent studies using Pfizer lot 100 formalin-inactivated RSV did not protect and caused enhanced disease**

B Graham, WHO Consultation on RSV Vaccine Development March 23-24, 2015

# FI-RSV vaccine – enhanced disease

Vaccine	n	Infected (%)	Hospitalized (%)*	Deaths**
FI- RSV	31	20 (65)	16 (80)	2
FI-PIV-1	40	21 (53)	1 (5)	0

Kim et al. Am J Epidemiol 1969;89:422

- Vaccine produced binding antibody, non-functional
- Th2 biased immune response (II 4,5,10,14)
- Current view
  - New vaccines are at risk of enhanced disease if:
    - High levels of IL4 and/or IL14
    - Antibody is non-neutralizing

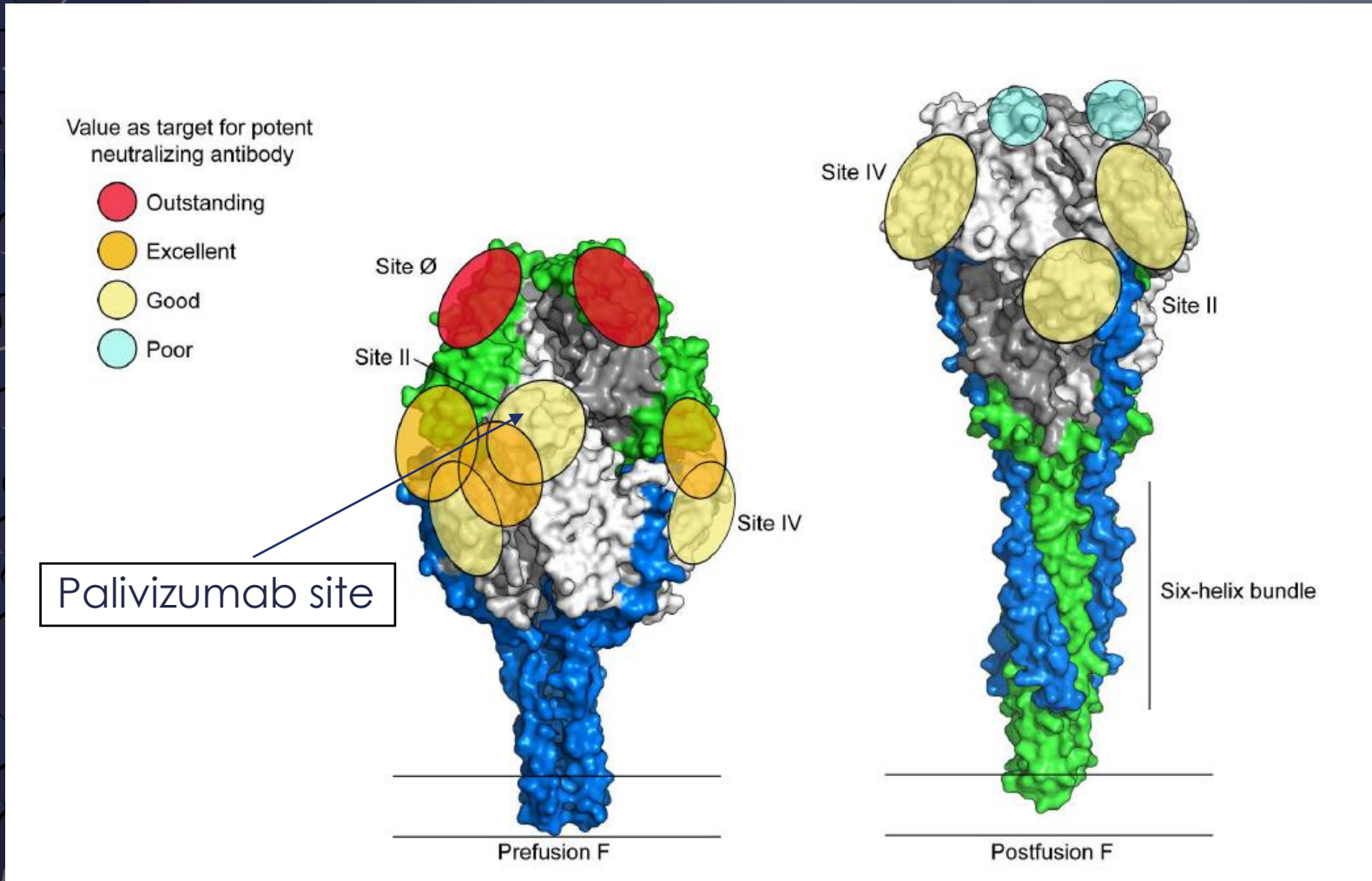




## Current RSV vaccine approaches

- › Passive protection with monoclonal antibody
  - Palivizumab – expensive, repeated injections needed
  - New long acting version under development
- › Live attenuated RSV vaccine
  - Previous problem with ARI symptoms
  - New candidate expressing ↑F-protein
- › F (fusion)-protein based vaccines

# F-protein – Pre and Post Fusion structure



B Graham, WHO Consultation on RSV Vaccine Development March 23-24, 2015

# F Protein vaccines

## Postfusion F

Developer	Phase	Populations (tested)	Populations (target)	Adjuvant
Novavax	2	18-49 y.o., elderly, pregnant women, children 24-71 mos.	elderly, pregnant women, children 24-71 mos.	Alum
MedImmune	1	elderly	elderly	GLA-Se
Novartis	1	18-45 y.o.	pregnant women, elderly?	Alum/MF59

## Prefusion F

Developer	Phase	Population (tested)	Population (target)	Adjuvant
GSK	1	men; women	pregnant women	Alum +/-
NIH/VRC	Preclinical → 1			

R Karron. WHO Consultation on RSV Vaccine Development March 23-24, 2015



# Post-Fusion F protein approaches

- › Novavax – F nano-particle vaccine
  - Only vaccine in Phase 3 trials –
    - › Adult immunization – protect the elderly
    - › Maternal immunization – protection against infant infection
  - Adult phase 3 trial results –
    - › No efficacy in elderly
    - › 28/5892 in vaccine recipients; 26/5917 in placebo recipients
  - Maternal immunization study –
    - › Trial underway in USA, Australia, New Zealand, South Africa, Chile, Philippines and other sites
      - Sample size 8618 over 4 years
    - › Endpoint – infant severe RSV+ LRTI
    - › Problem – only a fraction of cases can be prevented



# Conclusions

- › Effective approach for:
  - Tetanus
  - Pertussis
  - Influenza – LMICs need to judge preventable disease burden
- › May be effective for:
  - RSV
  - Group B Streptococcus
  - Also perhaps others such as Group A Streptococcus, malaria