Pertussis Vaccination Schedules

Evidence in support/against various primary vaccination schedules

Liz Miller,
Member of the Pertussis Working Group
(Chair until February 2014)

SAGE Meeting
14-16 April 2015

Methods and evidence reviewed (1 of 3)

- **Overview of the current DTP schedules and vaccines** in use based on the 2014 UNICEF/WHO Joint Reporting Form (data for 2013).
- **Actual age of vaccination and age-specific coverage**: review of Demographic Health Surveys (DHS) & Multiple Indicator Cluster Surveys (MICS).
- **Review of age distribution of pertussis, diphtheria, and tetanus** (neonatal and non-neonatal) in the pre and post vaccine eras.

Methods and evidence reviewed (2 of 3)

- **Systematic literature review** (using Cochrane methodology) **of RCTs and observational studies** (cohort and case control) with data on the comparative efficacy/effectiveness, immunogenicity and reactogenicity of:

  -Different wP and aP primary schedules in children under 18 months of age.

  -Different booster vaccination schedules with wP or aP vaccines among children <5 years

World Health Organization

Methods and evidence reviewed (3 of 3)

- **Using comparative efficacy/effectiveness data from the systematic review, the direct impact of 2p+1 and 3p schedules on pertussis deaths <5 years was modelled**
  - 2p+1 (6w,10w, 9 m or 6w,14w, 9 m)
  - 3p (6w,10w,14w)
  - Primary schedules starting later than 6 weeks (eg. 2,4,6 m) not modelled because the WG considered that to prevent pertussis deaths vaccination should start as early as possible >= 6 weeks (see later slides)
- **Impact modelled in settings with different age distributions of pertussis deaths and different age-specific coverage rates for DTP1, DTP3 and measles** (as a proxy for a 9 month DTP3 coverage)
- Preliminary results presented to the WG at its August 2014 meeting. WG provided feed-back on the model parameters, following which further adjustments were made to the model

World Health Organization

Variation in DTP vaccination schedules

World Health Organization

Pertussis immunization schedules by WHO region

87 different schedules among 194 member states

WHO regions (N of countries)		Number of doses for <7 years			>7 years or adult doses	N of countries using aP	N of countries using aP in primary doses
		3	4	5			
AFR	*(47)*	40	7	0	0	2	2
AMR	*(35)*	2	9	24	12	12	6
EMR	*(21)*	5	8	8	2	6	6
EUR	*(53)*	0	35	18	23	42	41
SEAR	*(11)*	6	3	2	0	0	0
WPR	*(27)*	9	13	5	7	13	13
Total	***(194)***	**62**	**75**	**57**	**44**	**75**	**68**

4th dose administered between 11 months and 9 years
5th administered from 45 months

Source: WHO/IVB database, March 2015

World Health Organization

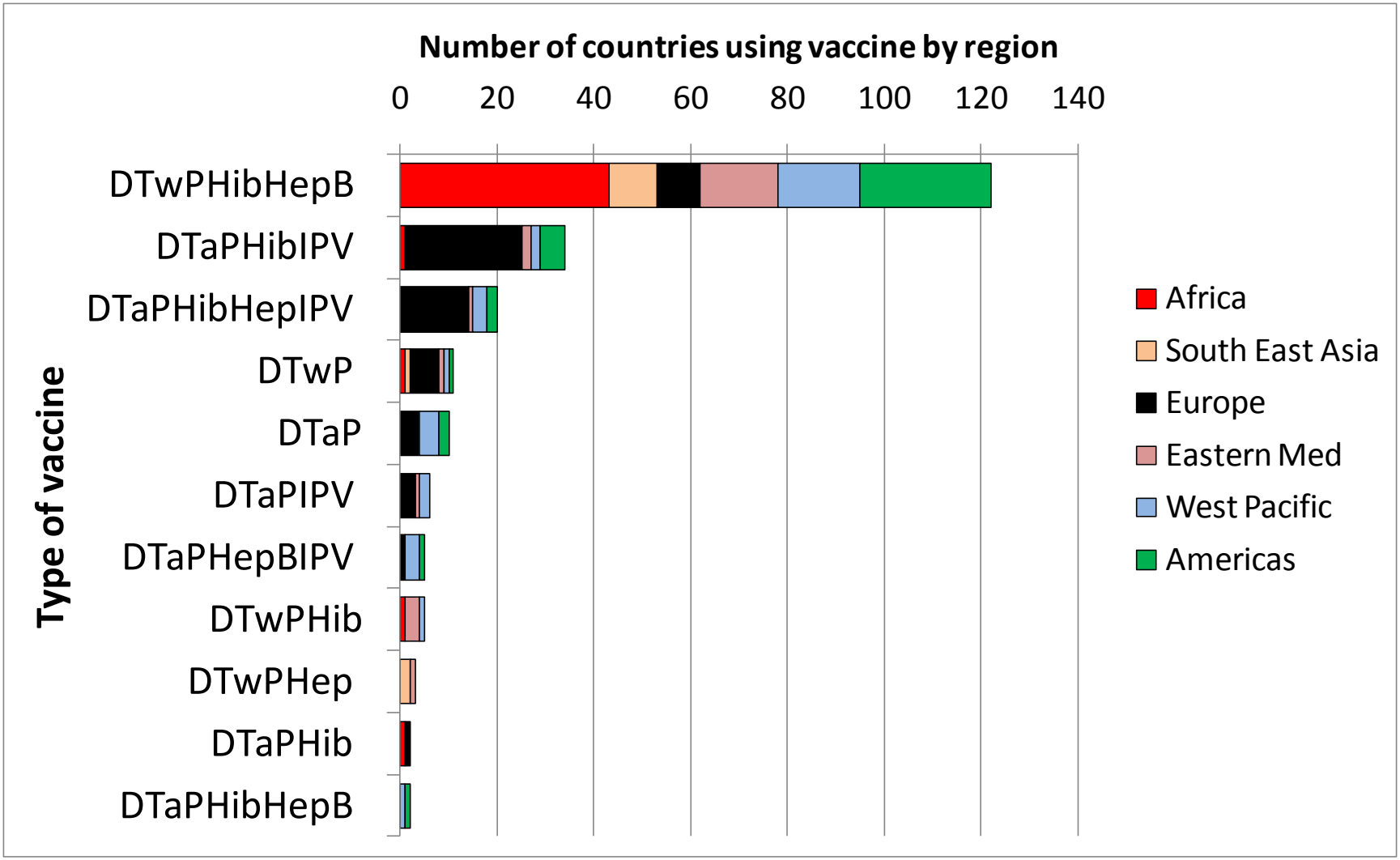
Age of administration of the primary doses of pertussis vaccines by WHO region

WHO regions (N of countries)		2, 3, 4 months	2, 4, 6 months	6, 10, 14 weeks	other with all 3 doses given <=6M	2p+1 schedule	**other**
AFR	*(47)*	2	2	39	4	0	0
	(35)	0	29	1	4	0	1
EMR	*(21)*	1	11	6	3	0	0
EUR	*(53)*	10	18	0	15	9	1
SEAR	*(11)*	1	4	6	0	0	0
WPR	*(27)*	2	5	11	9	0	0
Total	***(194)***	**16**	**69**	**63**	**35**	**9**	**2**

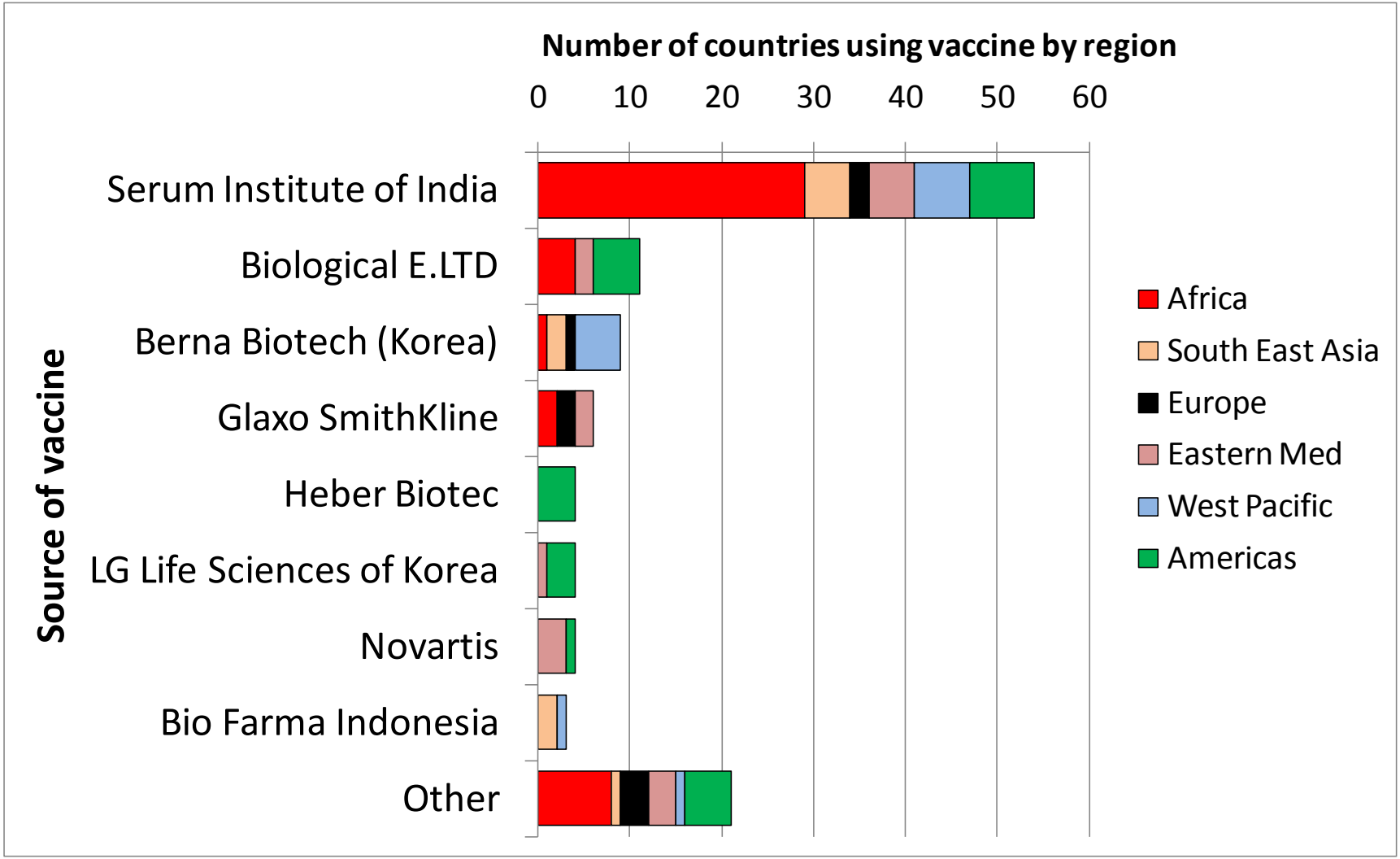
Source: WHO/IVB database, March 2015

World Health Organization

Number of countries using each type of DTP combination, grouped by region

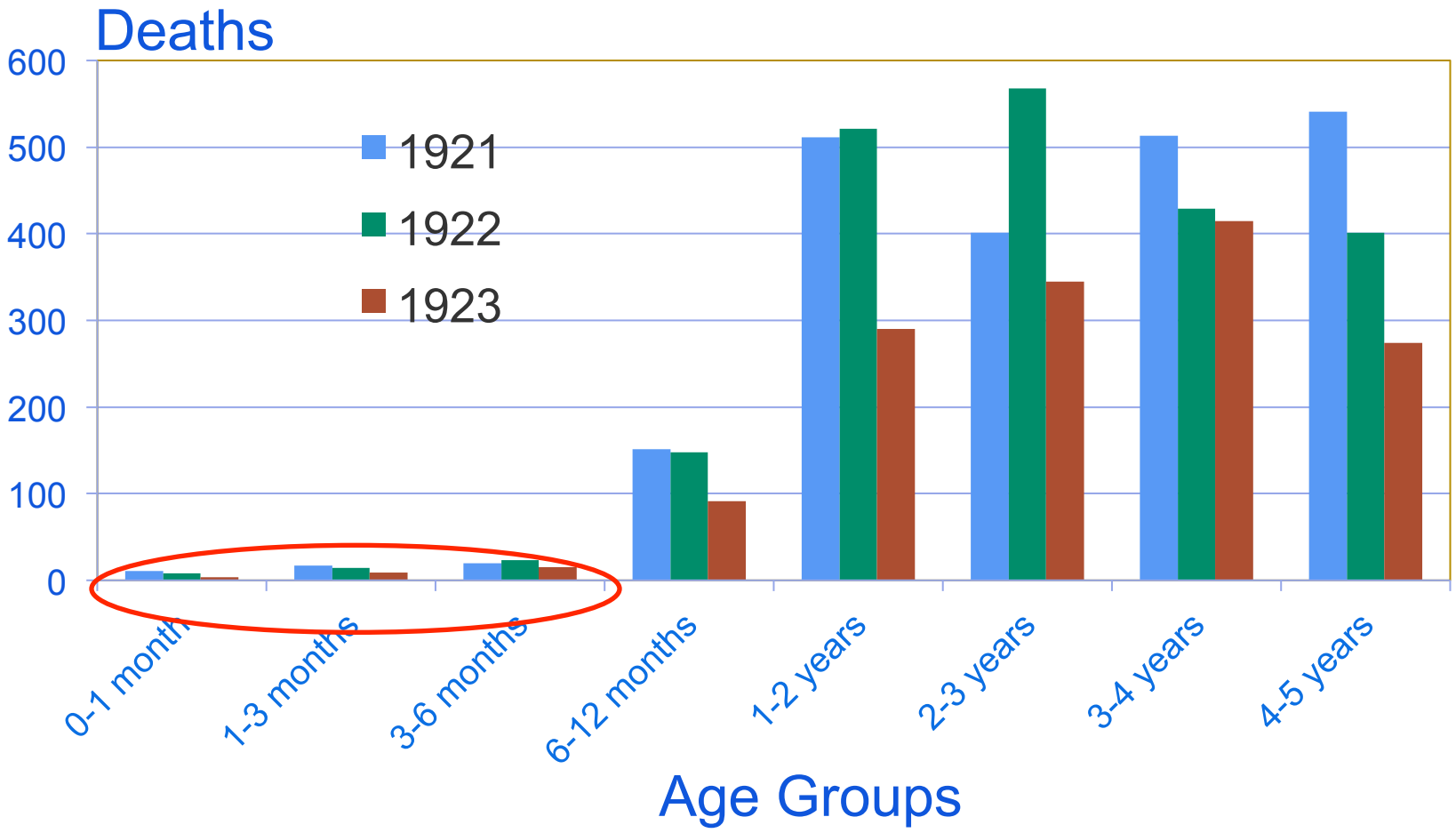


Number of countries using each type of DTwPHibHepB brand, grouped by region



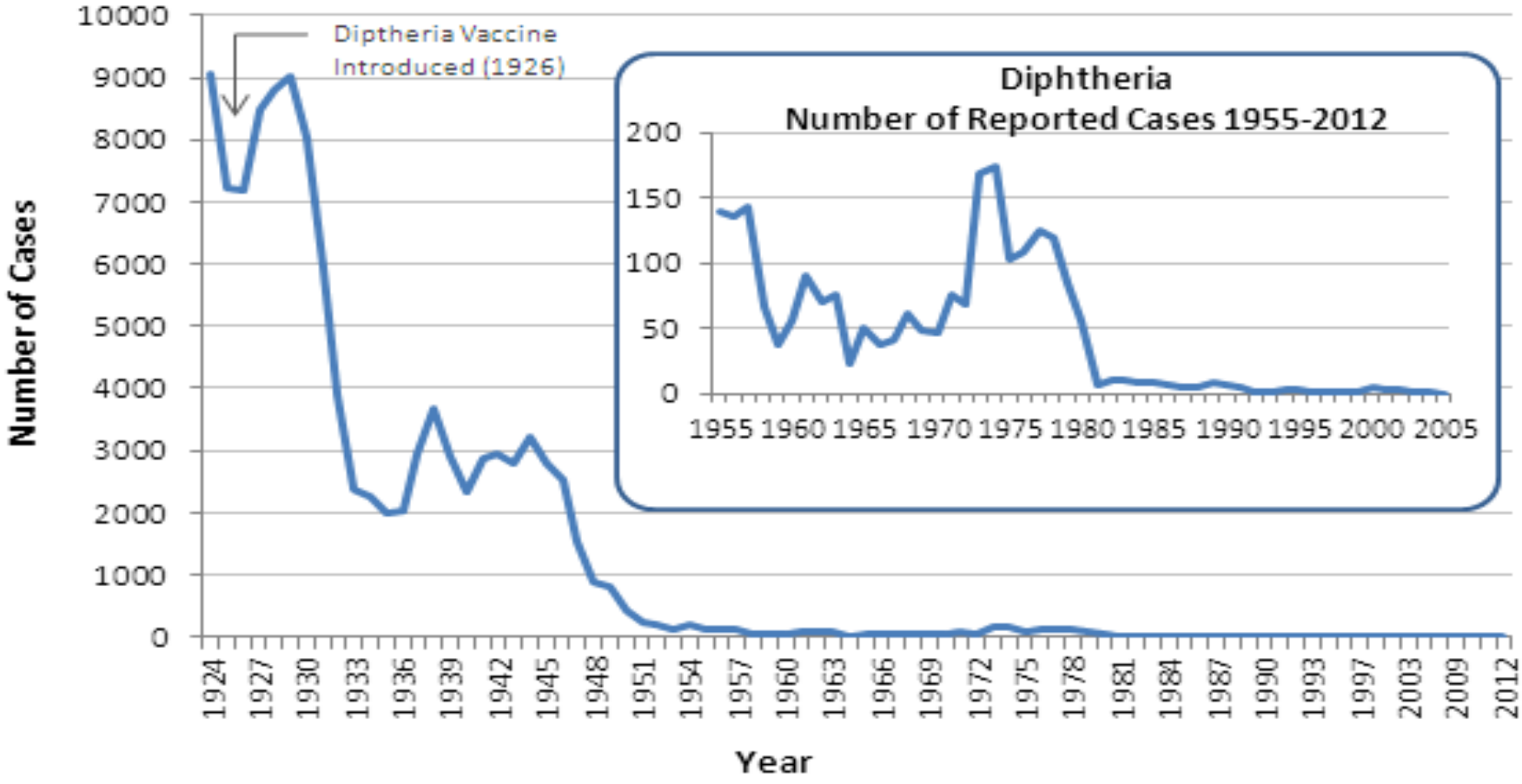
Review of evidence for diphtheria and tetanus

Prevaccine era: number of diphtheria deaths England and Wales by age and year , 1921-23



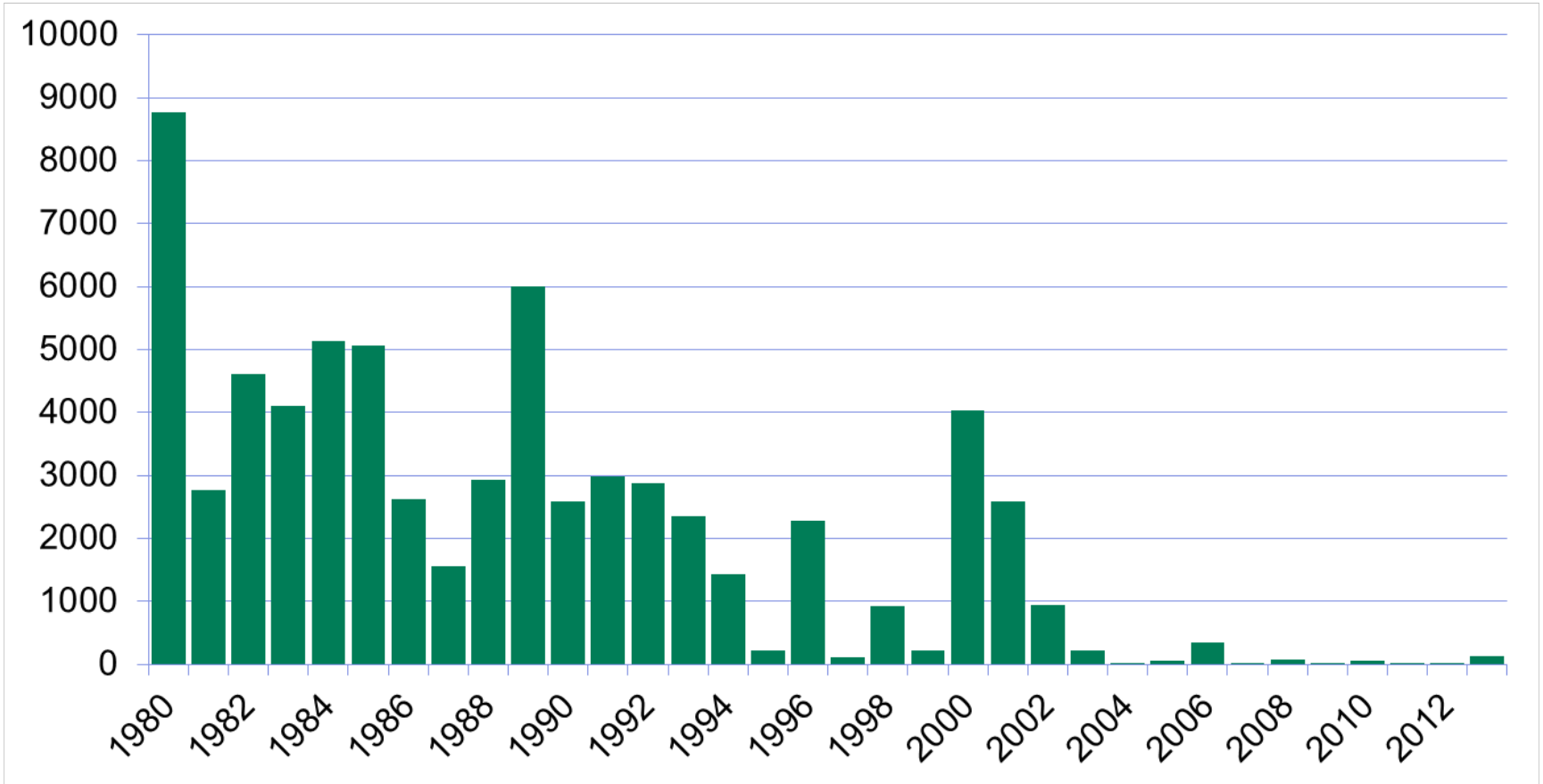
World Health Organization

Reported cases of diphtheria, Canada, 1924 – 2012



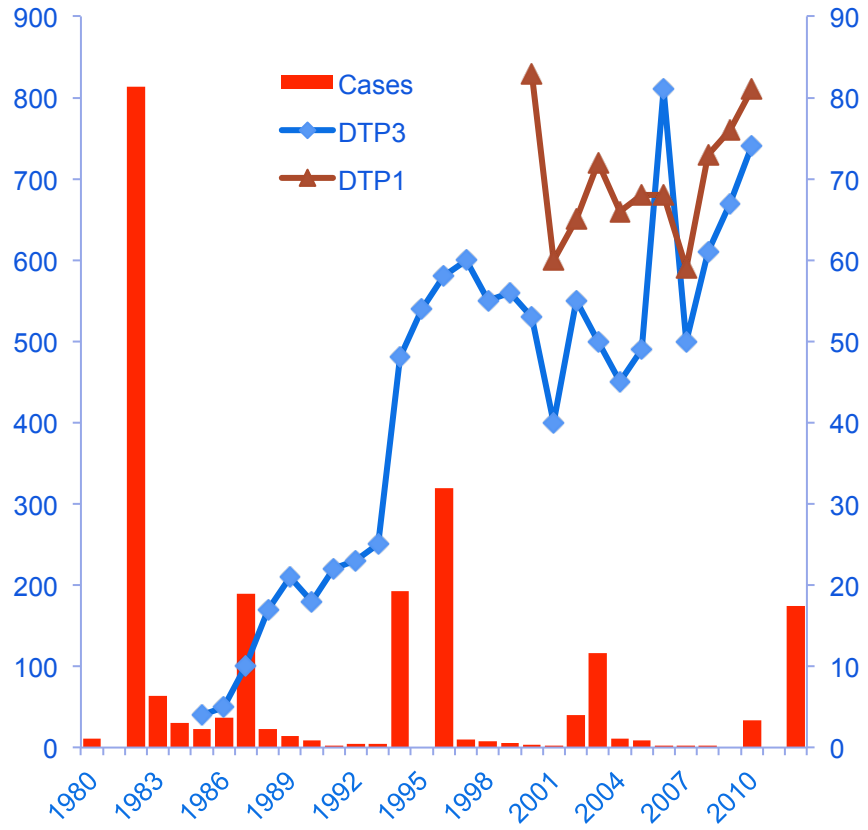
World Health Organization

Diphtheria cases reported from the African Region (AFR)

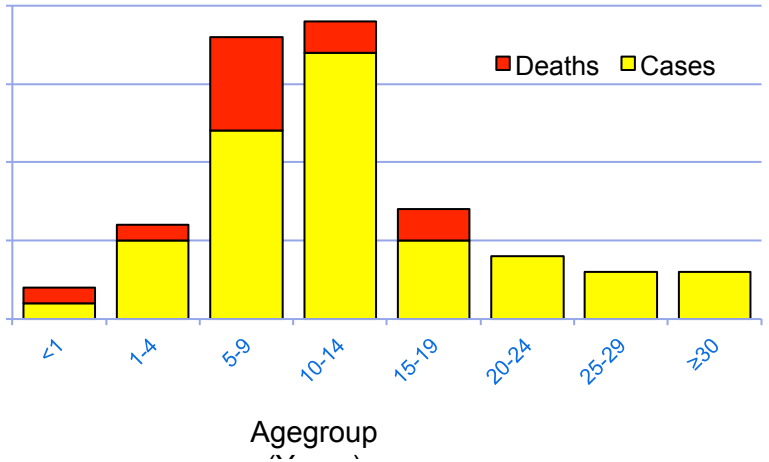


World Health Organization

Diphtheria in Lao PDR, 1980 -2012
Recent outbreaks Xiengkhouang 2010, Huoaphan 2012



http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tscoveragedtp3.htm



Lao PDR/CDC : Unpublished Data

World Health Organization

Age distribution of diphtheria in the pre and post vaccine area

- The incidence of diphtheria was high in the pre-vaccine era in many countries and it affected young children but spared very young infants.
- With routine childhood immunization diphtheria notifications steadily declined to record lows in 2012.
- Recent outbreaks in populations with low vaccination coverage
  - Children <15 years old but rates low in <1 year olds
- In industrialized countries sporadic cases occur in older individuals mainly related to importations of diphtheria disease, e.g. in Australia.

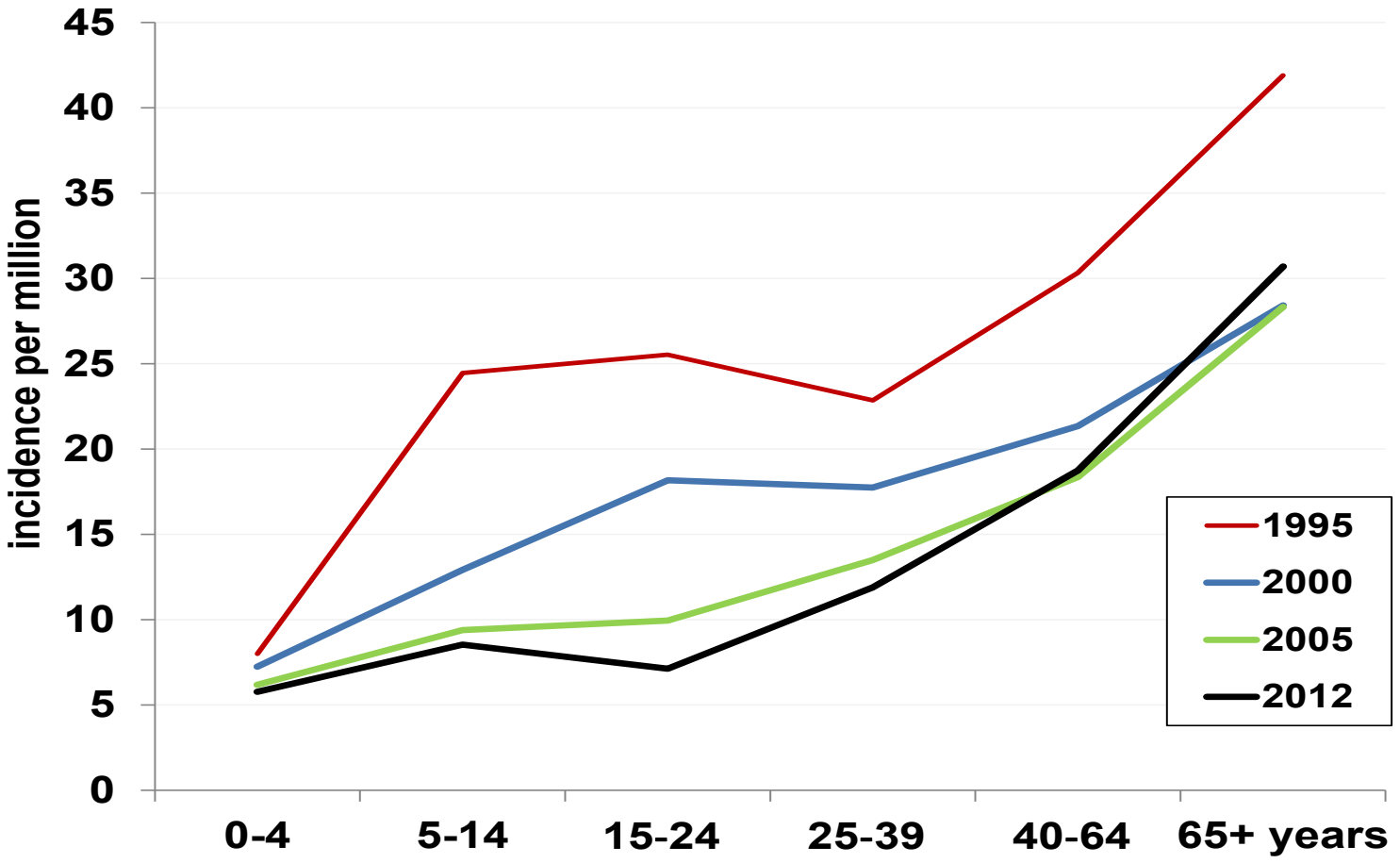
➢ **Prevention of diphtheria does not require immunization to be initiated early in infancy, though high coverage in infants important for disease control.**

Non-neonatal tetanus (nNT) in the pre-vaccine era

- High income countries – data on nNT trends and rough estimates of national totals available
- LMIC – limited data
- Children (29 days – 10 years) were most affected; rates typically highest in 5-9 year olds
- Post-neonatal tetanus in infancy (29 days – 1 year):
  - Very uncommon (≤ 1% of all nNT now)
  - England & Wales 1938-47: 0.8% of tetanus deaths[1]
  - US 1972-2002: 0.7% of reported cases[2]
  - Philippines 2010-2013: 0.5-0.9% of reported cases[3]

1. Conybeare ET. BMJ 1951; 1(4705):504-8
2. US CDC, unpublished data
3. Philippines MOH_NEC, unpublished data.

Tetanus in the post vaccine era – lower income countries: age-specific nNT incidence – Philippines 1995 - 2012



World Health Organization

Summary of age distribution of tetanus in the pre and post vaccine area

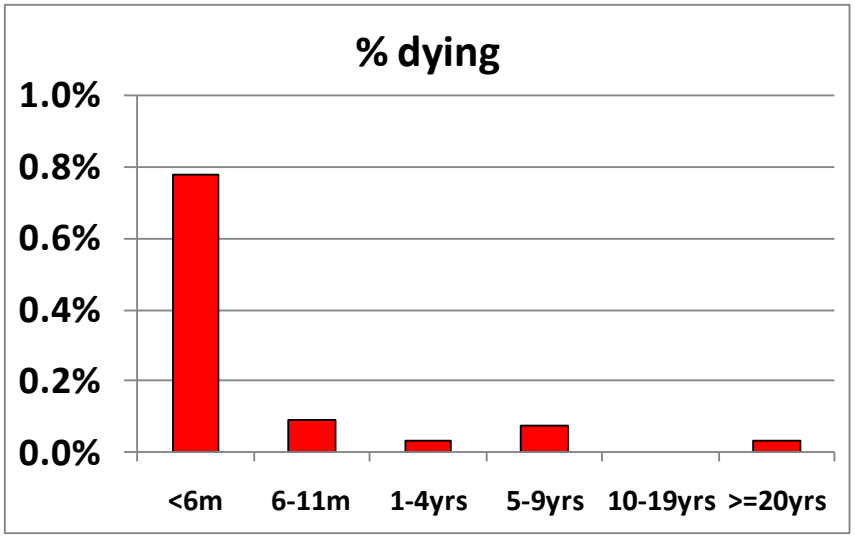
- **Limited data** : passive surveillance only; in many LMIC, nNT is not notifiable.
- **In the pre-vaccine era**:
  - The highest burden of tetanus occurred in neonates followed by children ≤15 years of age.
  - In industrialized countries, incidence of tetanus already **declined before vaccination** in association with urbanization, higher living standards, modern concepts of hygiene and other factors unrelated to vaccination.
- **In the post-vaccine era** (infant DTP and TT in adult women):
  - Tetanus has become increasingly rare
  - An upward age shift is observed: pediatric tetanus is very rare and usually occurs in unvaccinated children. The numbers of cases, incidence and mortality are all highest in older adults. Post neonatal tetanus in infancy is very uncommon.
  - **Current susceptibility to tetanus is in those who are inadequately immunized with TTCV, mainly adolescents and adult males in LMIC.**

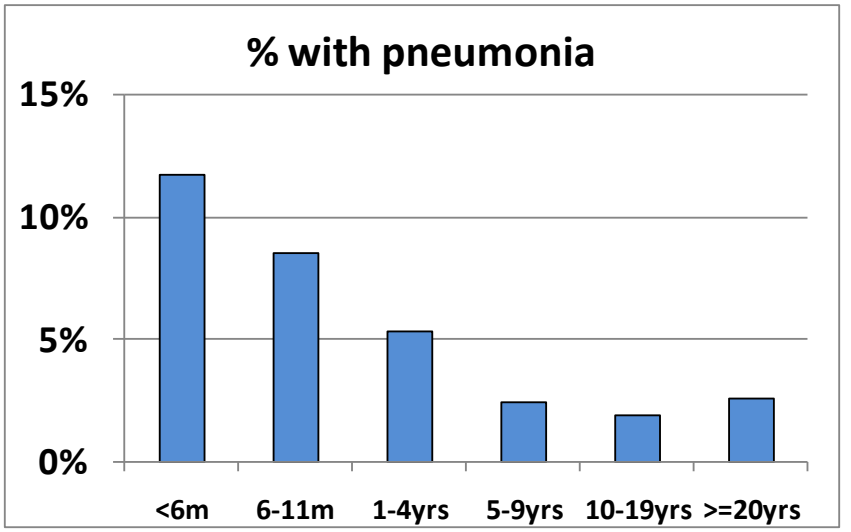
Review of evidence for pertussis

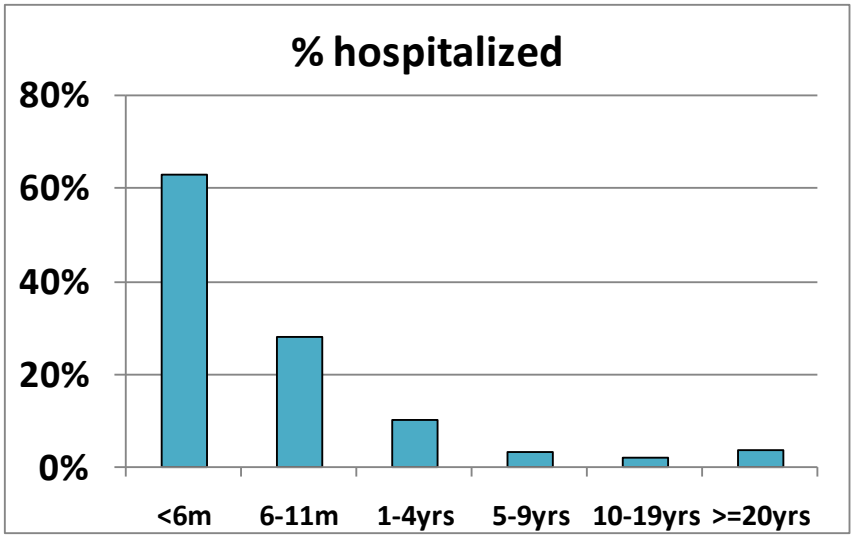
Age distribution of pertussis in the pre and post vaccine area

World Health Organization

Greater severity generally in younger infants: outcomes of 28,187 pertussis cases (USA, 1997-2000)

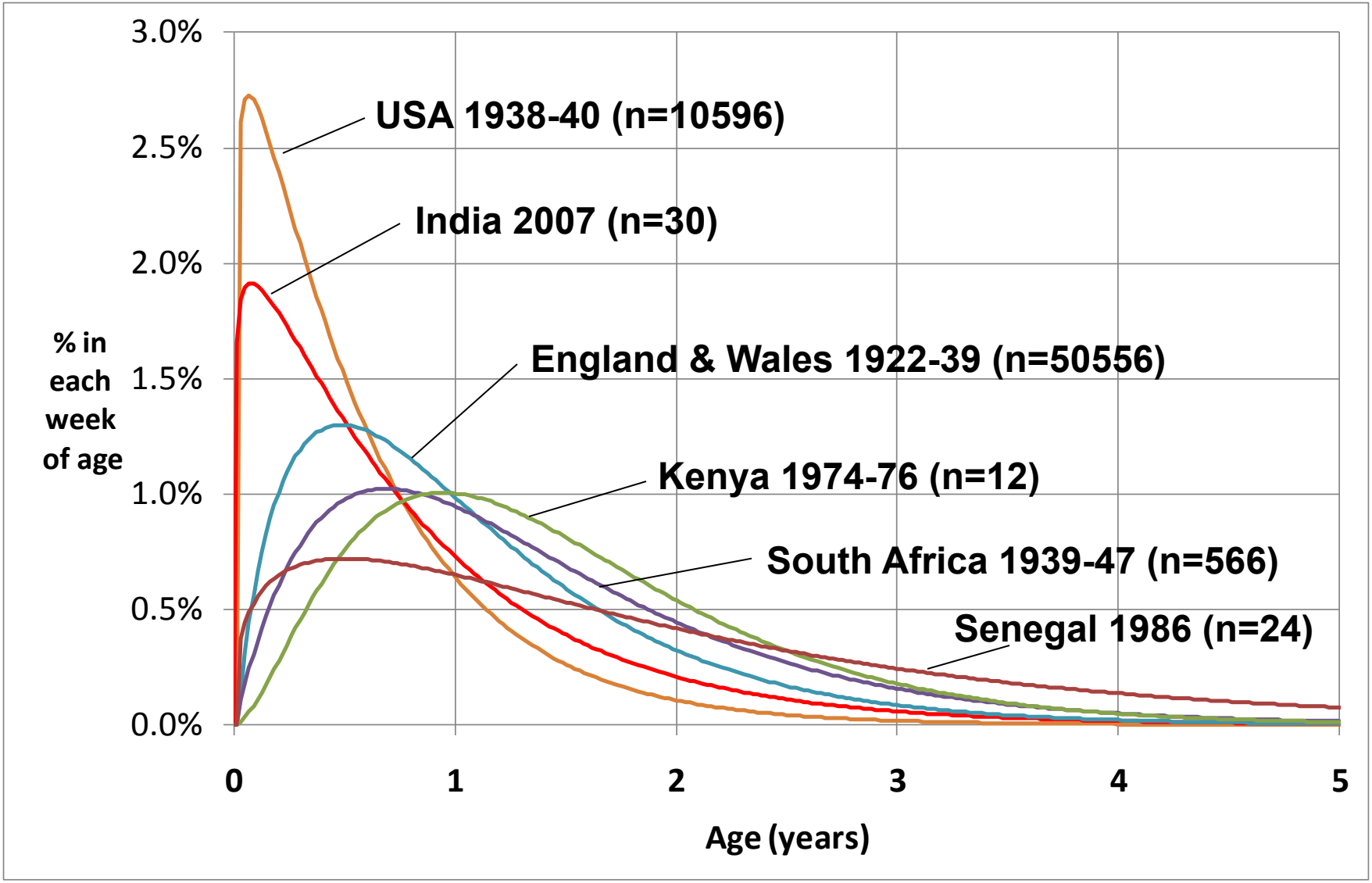






Source: Zanardi et al, MMWR, February 1, 2002 / 51(04);73-6. CDC. National Electronic Transmittal System for Surveillance (NETSS). *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5104a1.htm*

Variation in the age distribution of pertussis deaths <5yrs in the pre-vaccine era: curves fitted to available datasets

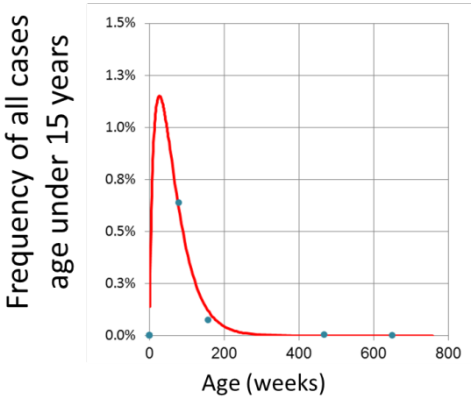


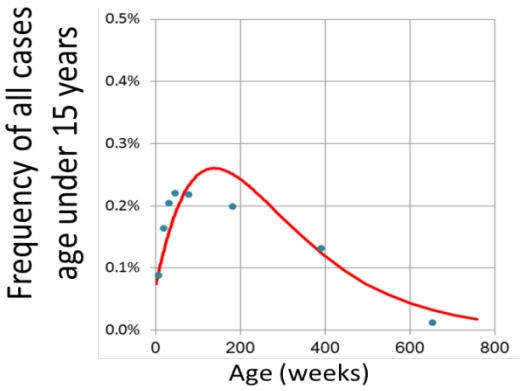
PRE-VACCINE

POST-VACCINE

UK

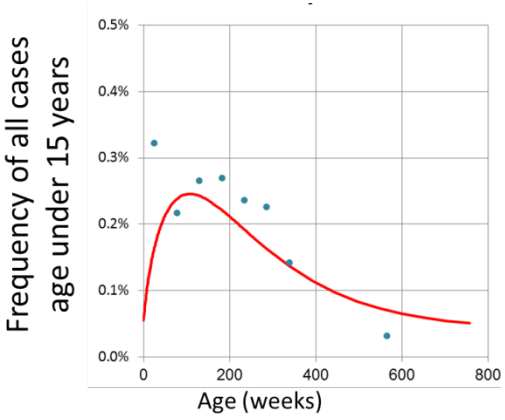
Pre-vaccine estimated total cases (1922-1925) are from reported CFRs and deaths; post-vaccine (1975-1979).

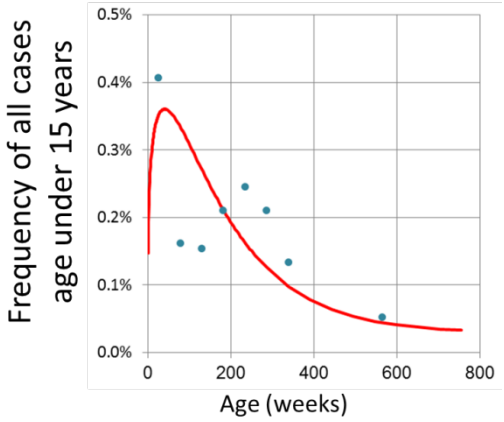




KENYA

Total reported cases are 918 in 1974-1976 (pre-vaccine). Post-vaccine data is from a follow-up from the same pre-vaccine data RCT.





Summary: Age distribution of pertussis in the pre and post vaccine area

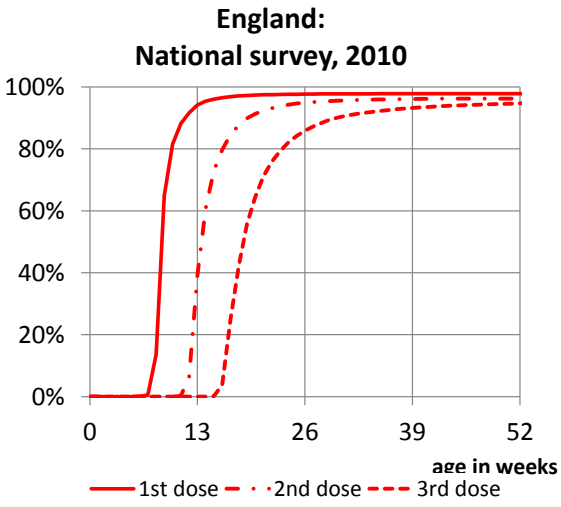
- Limited data on the distribution of recognised pertussis in unvaccinated (pre-vaccine) populations indicate that **most individuals were infected in childhood,** with > 50 % exhibiting classical disease. For developing countries **case fatality rates were high, particularly in infancy**.
- The introduction of effective infant vaccination with high coverage resulted in **steep decline in pertussis cases and deaths in children worldwide**, and **an upward shift in age distribution**, particularly in industrialized countries.
  - Age shifts may, in part, result from increased recognition of less typical disease in older subjects, and more sensitive surveillance and laboratory testing.
- **The prevention of infant pertussis is a key driver requiring DPT immunization to be initiated as early as possible in life.**

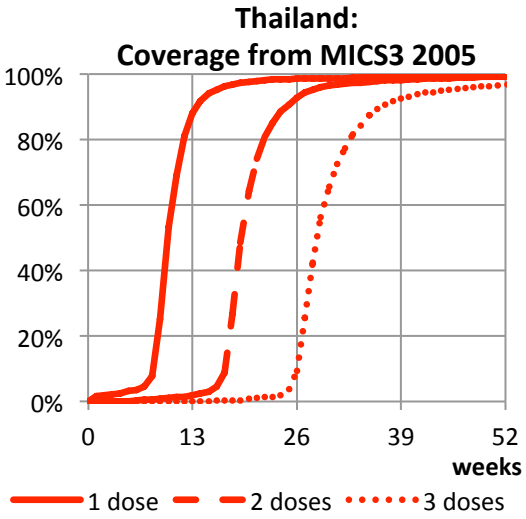
Review of evidence for pertussis

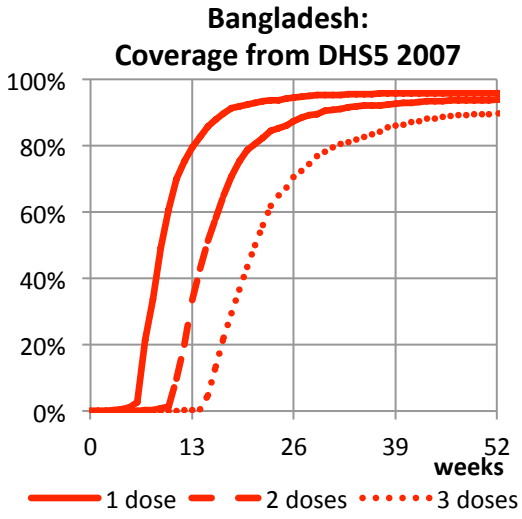
Variation in national estimates of vaccine coverage and timeliness by dose

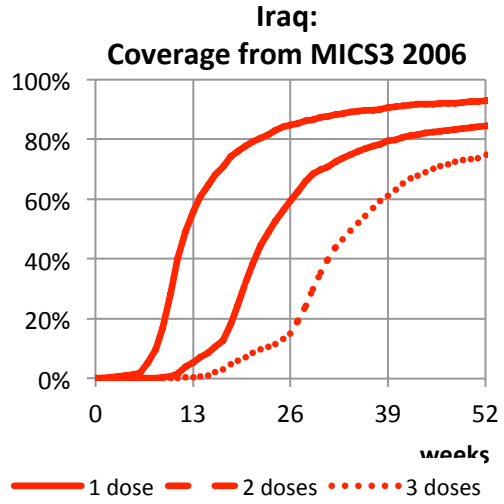
World Health Organization

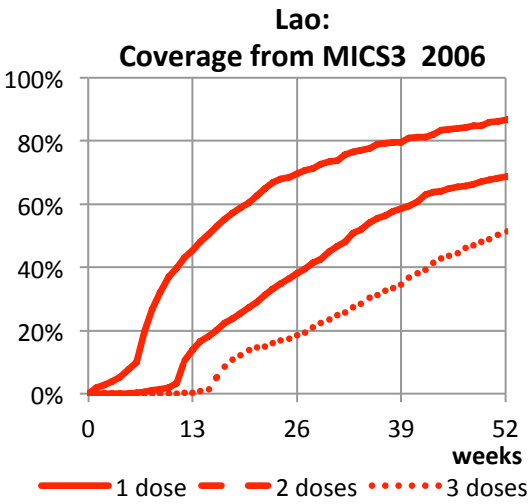
Variation in national estimates of vaccine coverage and timeliness by dose

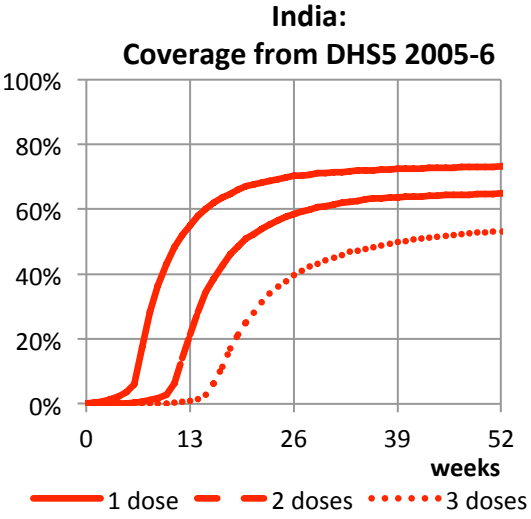












Available for 65+ countries, Sanderson DHS/MICS analysis, 2014

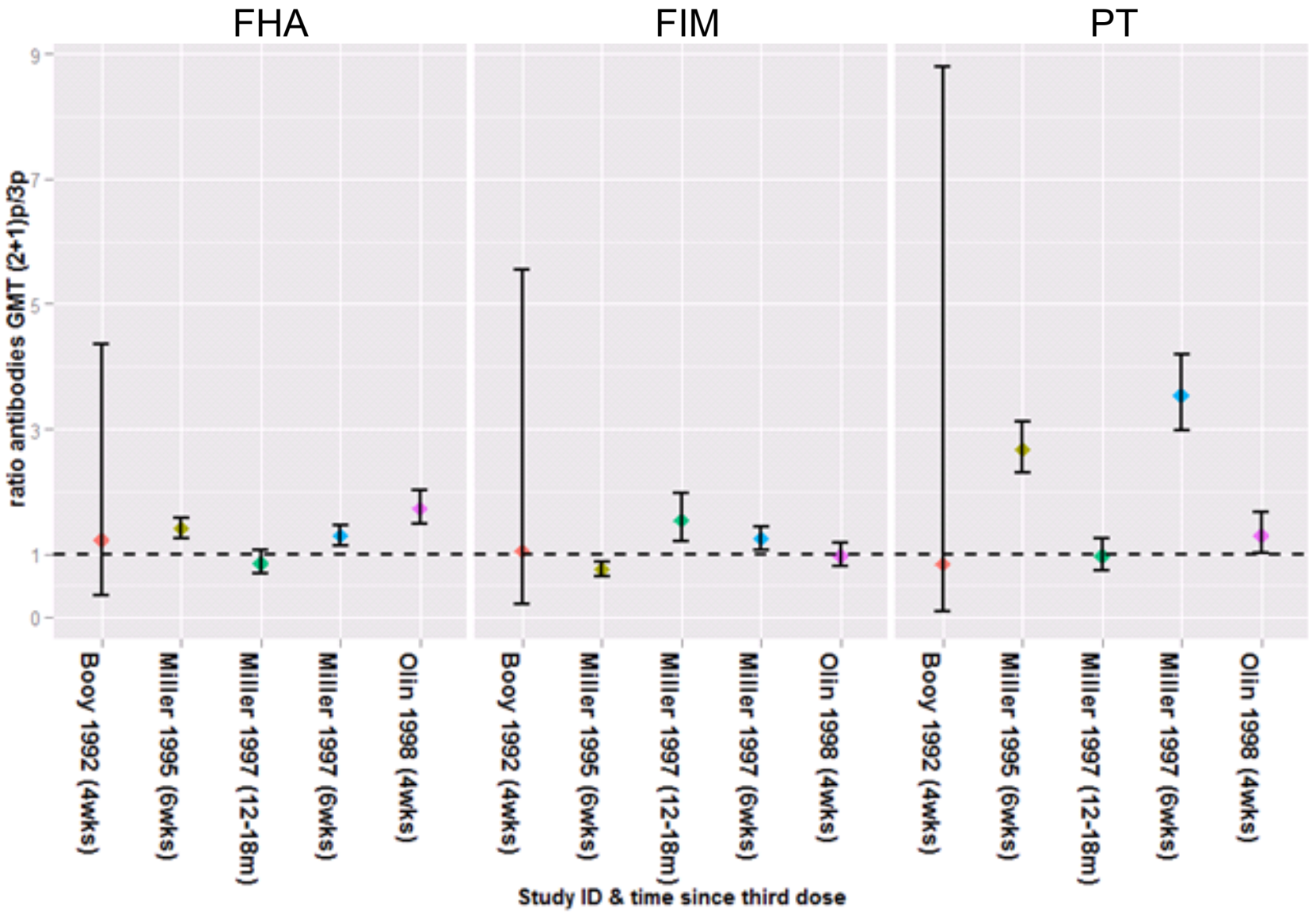
Review of evidence for pertussis

Vaccine immunogenicity, efficacy and effectiveness for different schedules: results of the systematic review

1. Immunogenicity of whole-cell vaccines under different schedules

World Health Organization

Ratio of some anti-pertussis antibodies GMT by vaccination schedule (2p+1 vs 3p)



Immunogenicity conclusions

- Some pertussis antigens in wP in some studies show **better immunogenicity with a 2p+1 type schedule than a 3p type** when titres are compared at the same time point after the last dose

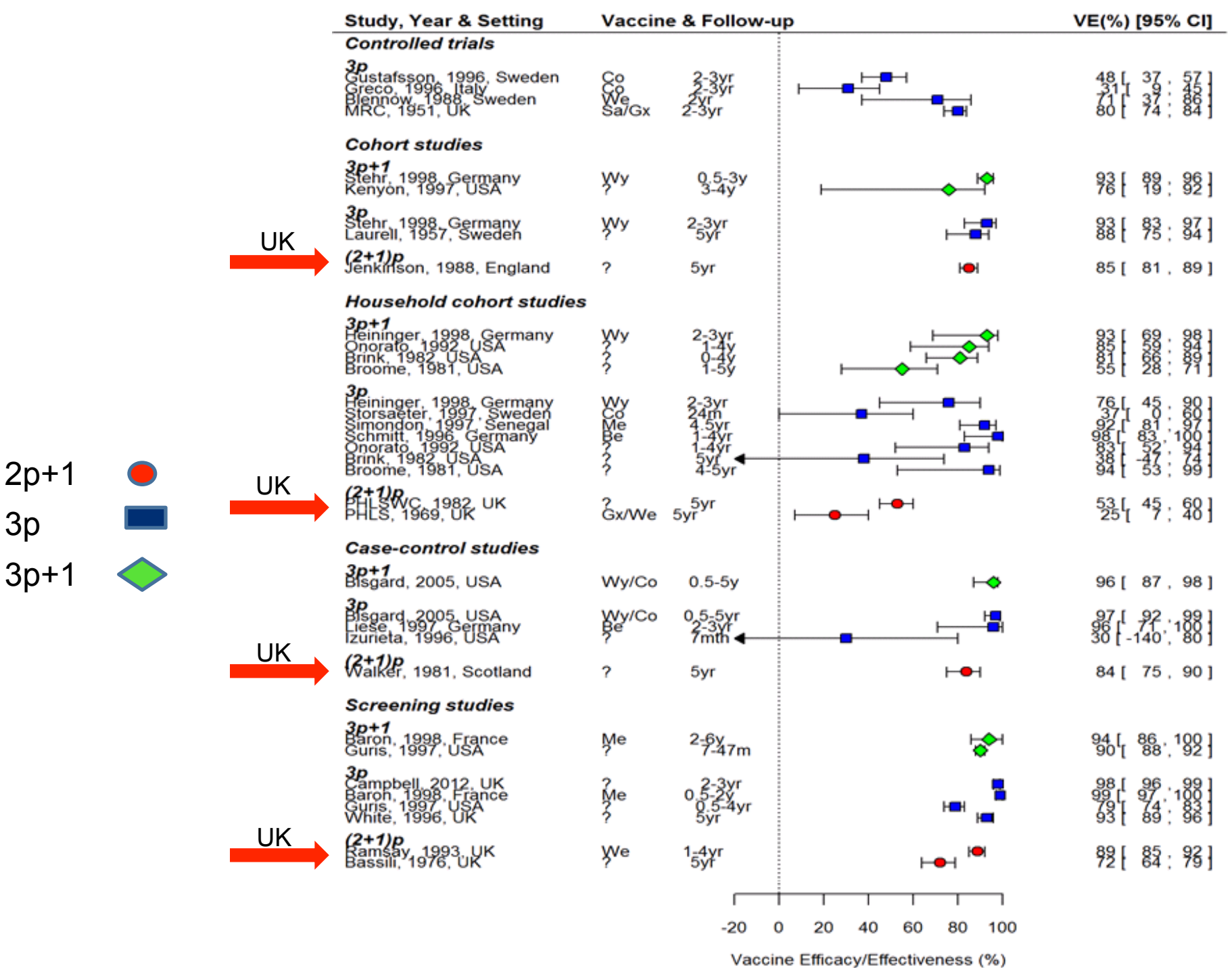
- **Lack of a good correlate of protection for the various pertussis antigens precludes direct translation of immunogenicity into efficacy.**

Review of evidence for pertussis

Vaccine immunogenicity, efficacy and effectiveness for different schedules: results of the systematic review

2. Effectiveness of whole-cell vaccines under different schedules

World Health Organization


Study, Year & Setting
Vaccine & Follow-up
VE(%) [95% CI]
Controlled trials
3p
Gustafsson, 1996, Sweden Co 2-3yr 48 [37 , 57]
Greco, 1996, Italy Co 2-3yr 31 [9 , 45]
Blennow, 1988, Sweden We 2yr 71 [37 , 86]
MRC, 1951, UK Sa/Gx 2-3yr 80 [74 , 84]
Cohort studies
3p+1
Stehr, 1998, Germany Wy 0.5-3y 93 [89 , 96]
Kenyon, 1997, USA ? 3-4y 76 [19 , 92]
3p
Stehr, 1998, Germany Wy 2-3yr 93 [83 , 97]
Laurell, 1957, Sweden ? 5yr 88 [75 , 94]
UK
(2+1)p
Jenkinson, 1988, England ? 5yr 85 [81 , 89]
Household cohort studies
3p+1
Heininger, 1998, Germany Wy 2-3yr 93 [69 , 98]
Onorato, 1992, USA ? 1-4y 85 [59 , 94]
Brink, 1982, USA ? 0-4y 81 [66 , 89]
Broome, 1981, USA ? 1-5y 55 [28 , 71]
3p
Heininger, 1998, Germany Wy 2-3yr 76 [45 , 90]
Storsaeter, 1997, Sweden Co 24m 37 [0 , 60]
Simondon, 1997, Senegal Me 4.5yr 92 [81 , 97]
Schmitt, 1996, Germany Be 1-4yr 98 [83 , 100]
Onorato, 1992, USA ? 1-4yr 83 [52 , 94]
Brink, 1982, USA ? 5yr 38 [-47 , 74]
Broome, 1981, USA ? 4-5yr 94 [53 , 99]
2p+1
UK
(2+1)p
PHLSWC, 1982, UK ? 5yr 53 [45 , 60]
PHLS, 1969, UK Gx/We 5yr 25 [7 , 40]
3p
3p+1
Case-control studies
3p+1
Bisgard, 2005, USA Wy/Co 0.5-5y 96 [87 , 98]
3p
Bisgard, 2005, USA Wy/Co 0.5-5yr 97 [92 , 99]
Liese, 1997, Germany Be 2-3yr 96 [71 , 100]
Izurieta, 1996, USA ? 7mth 30 [-140 , 80]
UK
(2+1)p
Walker, 1981, Scotland ? 5yr 84 [75 , 90]
Screening studies
3p+1
Baron, 1998, France Me 2-6y 94 [86 , 100]
Guris, 1997, USA ? 7-47m 90 [88 , 92]
3p
Campbell, 2012, UK ? 2-3yr 98 [96 , 99]
Baron, 1998, France Me 0.5-2y 99 [97 , 100]
Guris, 1997, USA ? 0.5-4yr 79 [74 , 83]
White, 1996, UK ? 5yr 93 [89 , 96]
UK
(2+1)p
Ramsay, 1993, UK We 1-4yr 89 [85 , 92]
Bassili, 1976, UK ? 5yr 72 [64 , 79]
-20
0
20
40
60
80
100
Vaccine Efficacy/Effectiveness (%)

Vaccine efficacy/effectiveness (VE) conclusions for wP vaccines

- Wide variation between wP products given under the same schedule - so drawing conclusions about relative efficacy of different schedules difficult.
- For the same product, VE varies with case definition.
- The wP vaccines with low efficacy (eg US Connaught vaccine, or UK vaccines prior to 1969) no longer used
- VE data for 2p+1 limited to the UK
- No VE data for the most often used wP vaccine (from the Serum Institute of India)

Modelling of impact of different wP schedules on pertussis mortality in different settings requires estimates of dose specific efficacy

- WG already provided estimates of VE of 1 and 2 doses of wP and aP from published and unpublished studies which they considered robust (presented to SAGE April 2014)
- Systematic review also provided dose-specific VE estimates

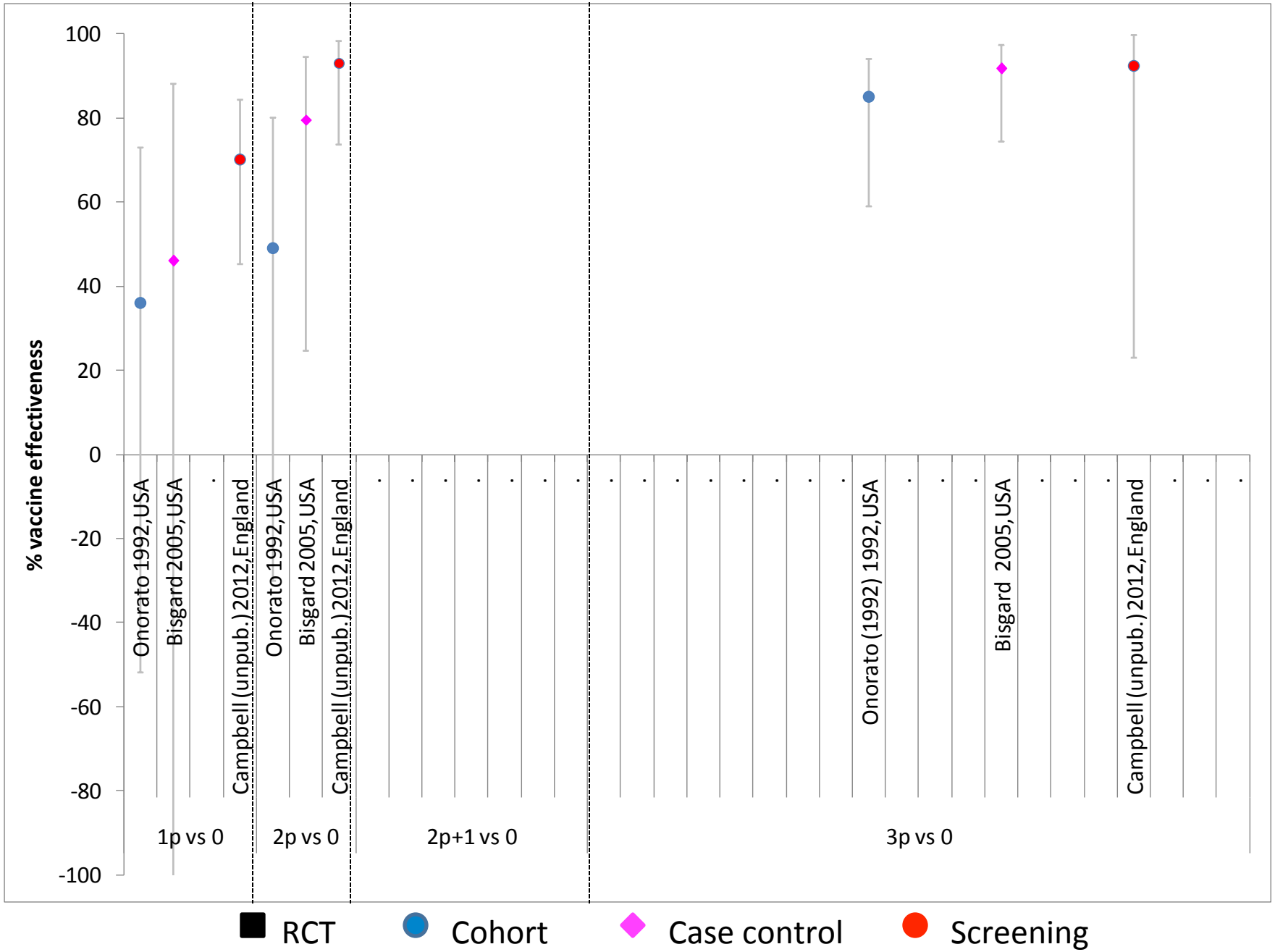
World Health Organization

1 or 2 dose effectiveness WG analysis

Country/ Vaccine	Single dose	Two doses
Australia (aP) Quinn et al (2014)	VE hospitalization: 55% (95%CI: 43-65)	VE hospitalization: 83% (95%CI: 70-90)
England (aP or wP) Campbell et al (2012)	VE against infant pertussis disease: 62% (95%CI: 53-69)	VE against infant pertussis disease: 85% (95%CI: 77-91)
France (wP) Briand et al (2007)	VE against infant pertussis disease: 58% (95%CI: 9-81)	VE against infant pertussis disease: 87% (95%CI: 2-98)
Germany (aP) Juretzko et al (2002)	VE hospitalization: 68% (95%CI: 46-81)	VE hospitalization: 91.8% (95%CI: 85-96)
USA (wP or aP) Bisgard et al. (2005)	VE against pertussis disease in ages 6-23mo: 51% (95% CI: -71-86)	VE against pertussis disease in ages 6-23mo: 80% (95% CI: 41-93)

The systematic review did not add additional robust information

Dose-specific VE of wP: studies reporting on all 3 doses

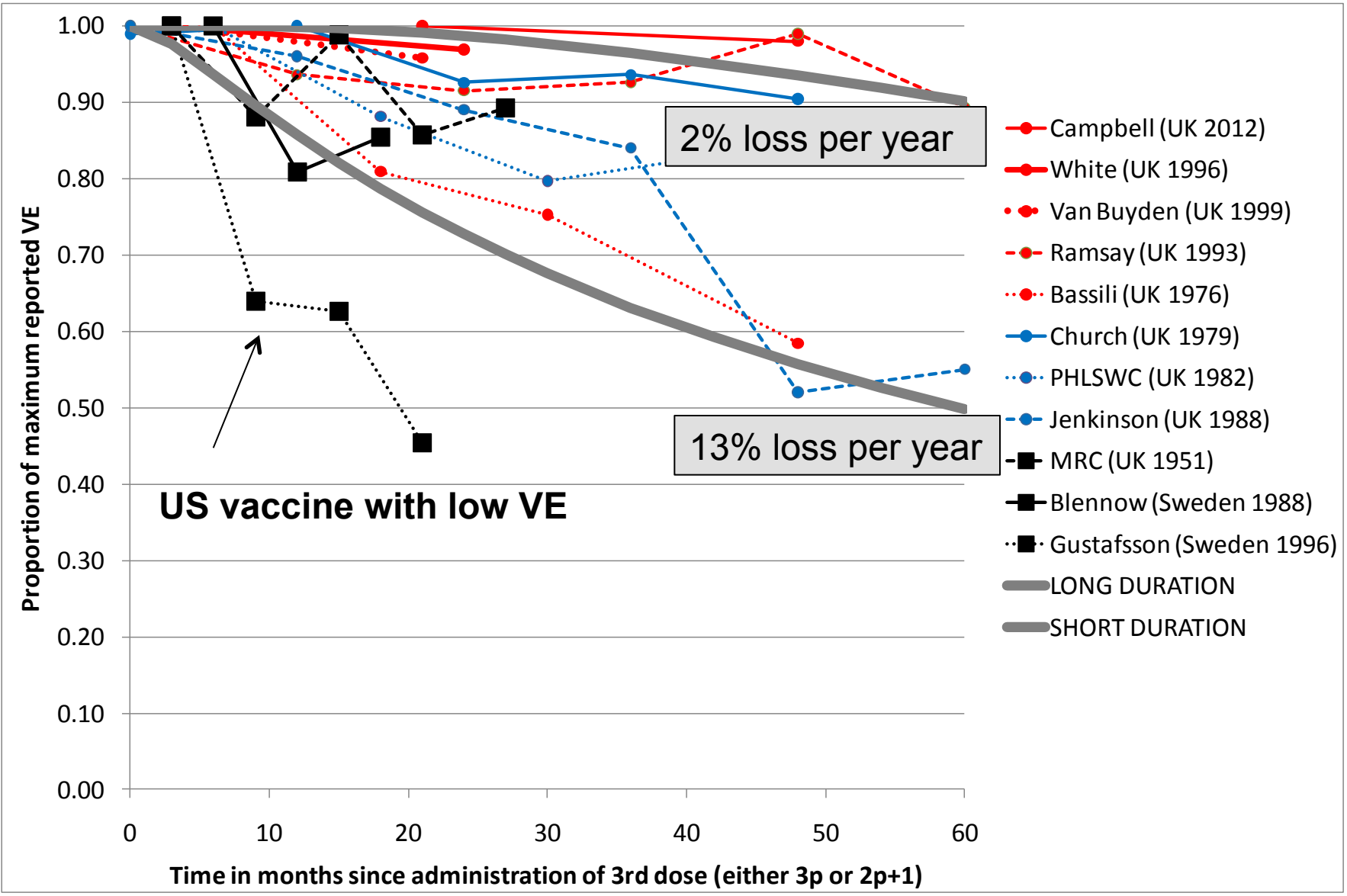


For related modelling work:

Duration of clinical protection afforded by whole-cell vaccines

Relative clinical protection by time since 3 doses of wP:

VE expressed as a proportion of the highest reported VE in studies with multiple follow-up points



wP vaccine: summary of effectiveness (1)

Obtaining robust estimates of dose-specific VE, impact of interval between doses and schedule is difficult because of differences in case definition, vaccine brand, study designs, and follow-up interval.

- **Robust studies with "good" wP vaccines show >40% VE with 1 dose and ≥ 80% with 2 doses**

- **Age at initiation of first dose:**
  - Data only available for schedules **initiated around 2-3 months**, not earlier.
  - No within study comparison of VE of similar regimens starting at 2 months vs later age. Between-study comparisons provide no evidence on whether wP vaccine efficacy is different when the 1st dose is given at 2 or 3 months.

- **Effect of interval between 1st and 2nd dose:**
  - No within-study data available. Limited evidence from between-study comparisons that VE is no different with 3p at monthly or 2-monthly intervals.
  - No data on interval other than 2-monthly between 1st and 2nd doses for 2p+1.

wP vaccine: summary of effectiveness (2)

- **3p versus 2p+1 schedule:**
  - Moderate quality evidence (including 4 controlled trials and 3 screening and 3 case-control studies) that **3p schedules** are effective in the first 5 years of life.
  - **Low grade evidence (no data from RCTs) that 2p+1 schedules are effective against pertussis at age 1-5 years** (protection in under 1year old not included). **Limited data on VE (none from LMIC) of 2 doses in infants under 1 years old.**
  - **Very limited data on direct comparison of 3p and 2p+1 schedules**; no convincing evidence for increased clinical protection with 2p+1 vs 3p after 3rd dose though immunogenicity may be higher
  - **Hence no direct evidence that either schedule is superior or inferior to the other.**
- **Studies do not suggest rapid waning of immunity after a 3p schedule**

World Health Organization

Acellular pertussis vaccines: schedules summary (1)

Good level of control of severe pertussis in children and good individual protection were achieved in different countries using different aP primary schedules *(i.e. different starting age, interval between doses i.e. 2p+1 versus 3p, and timing of booster doses)* **and different formulations**.

3p schedule:

- **The age of initiation and length of intervals of 3p schedule do not substantially impact on immunogenicity** *(Very low to moderate quality of evidence).*

3p versus 2p+1 schedules:

- **Only one RCT * compared a 3p type schedule (2,4,6 months) with a 2p+1 type schedule (3,5,12 months) : 2p+1 provided better clinical protection from 3rd dose on, unclear difference before 3rd dose**

- **2 vs. 3 primary doses likely result in lower clinical protection and titers until the 3rd dose is given** *(Very low to low quality of evidence).*

*Olin et al. Dev Biol Standard 1998

Acellular pertussis vaccines: schedules summary (2)

Booster doses

- **No serological impact of timing of booster between 15 and 18 months** (after 3 primary doses) was observed *(Moderate quality of evidence)*
- **Resurgence of pertussis observed in some countries some years after switching from wP to aP** - with an increased risk in unprotected infants.
  - Countries experiencing a resurgence had used different schedules / products to each other, preventing direct conclusions.

World Health Organization

Reactogenicity of pertussis containing vaccines in children with focus on comparative reactogenicity for different schedules

- DTwP:
  - The reactogenicity of DTwP is essentially driven by age at administration.
  - There is limited evidence that the risk of adverse events after the third vaccine dose is higher in children using the 2p+1 schedule than those using a 3p schedule.
  - There may be substantial differences between different wP products.

- DTaP:
  - There were no significant differences in reactogenicity between the accelerated and longer DTaP schedules.
  - For some of the time points for erythema/redness, swelling/nodule, any systemic symptoms, and irritability there was a lower risk of adverse events with the accelerated schedule.

World Health Organization

Session Overview

Evidence in support/against various primary DTP vaccination schedules

E. Miller, Member of SAGE pertussis vaccine working group (chaired the group until February 2014)

Modelling of impact of different DTP schedules

A. Clark, LSHTM

Summary and review of proposed recommendations

C. A. Siegrist, Chair of SAGE pertussis vaccine working group

Discussion

Influence of vaccine schedules on diphtheria and tetanus immunity

- There is **some evidence available** for all questions on DT primary or booster schedules, with **limited level of confidence**. **Only one study evaluated VE**.
- **Primary infant schedule (2p+1 vs 3p)**
  - Substantially lower mean antitoxin titers after 2 than 3 primary doses
  - Difference not persisting beyond the 1st year of life *(rapid antibody decline regardless of the number of primary doses)* or after boosting *(2 doses sufficient for priming)* and did not clearly translate into a difference in clinical protection (overall low quality of evidence).
- **Influence of age at boosting:**
  - A 6 months interval between 2nd and 3rd dose provides substantially higher antitoxin titers during 2nd year of life, though very low quality of evidence.
  - Boosters during the 2nd year of life after 3 primary doses substantially increases antitoxin titers.
  - Booster vaccination at age 18 months yields slightly higher antitoxin concentrations than earlier boosting, but no better protection (low quality evidence).

World Health Organization