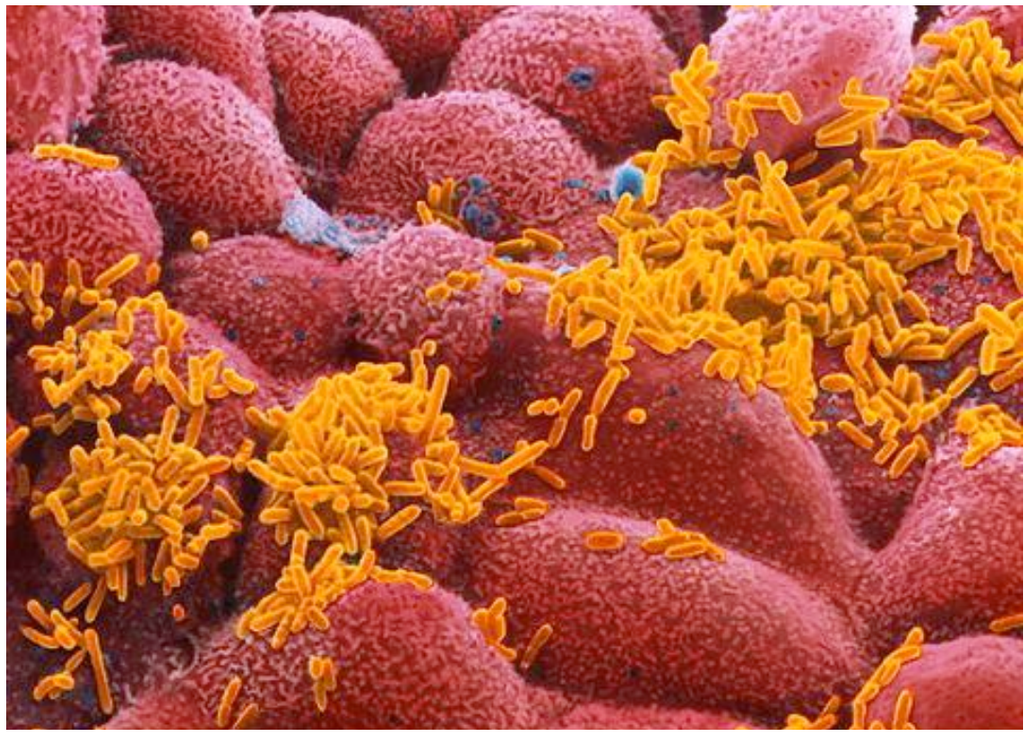
Optimizing Haemophilus influenzae type b immunization schedules

What evidence is available on: the number of doses, age at administration, interval between doses, duration of protection & combination vaccines ?



Rana Hajjeh, MD

National Center for Immunization and Respiratory Diseases

US Centers for Disease Control and Prevention

Today's Questions

- **What are the optimal schedules for Hib vaccines for children living in different epidemiological settings?**

1.How many primary doses, and is there a need for a booster dose?

- **Interval between doses?**
- **Duration of protection?**

2.Does the type of vaccine influence the choice of schedule?

- **Effect of type of Hib vaccine on effectiveness**
- **Effect of wP and aP on Hib vaccine effectiveness**

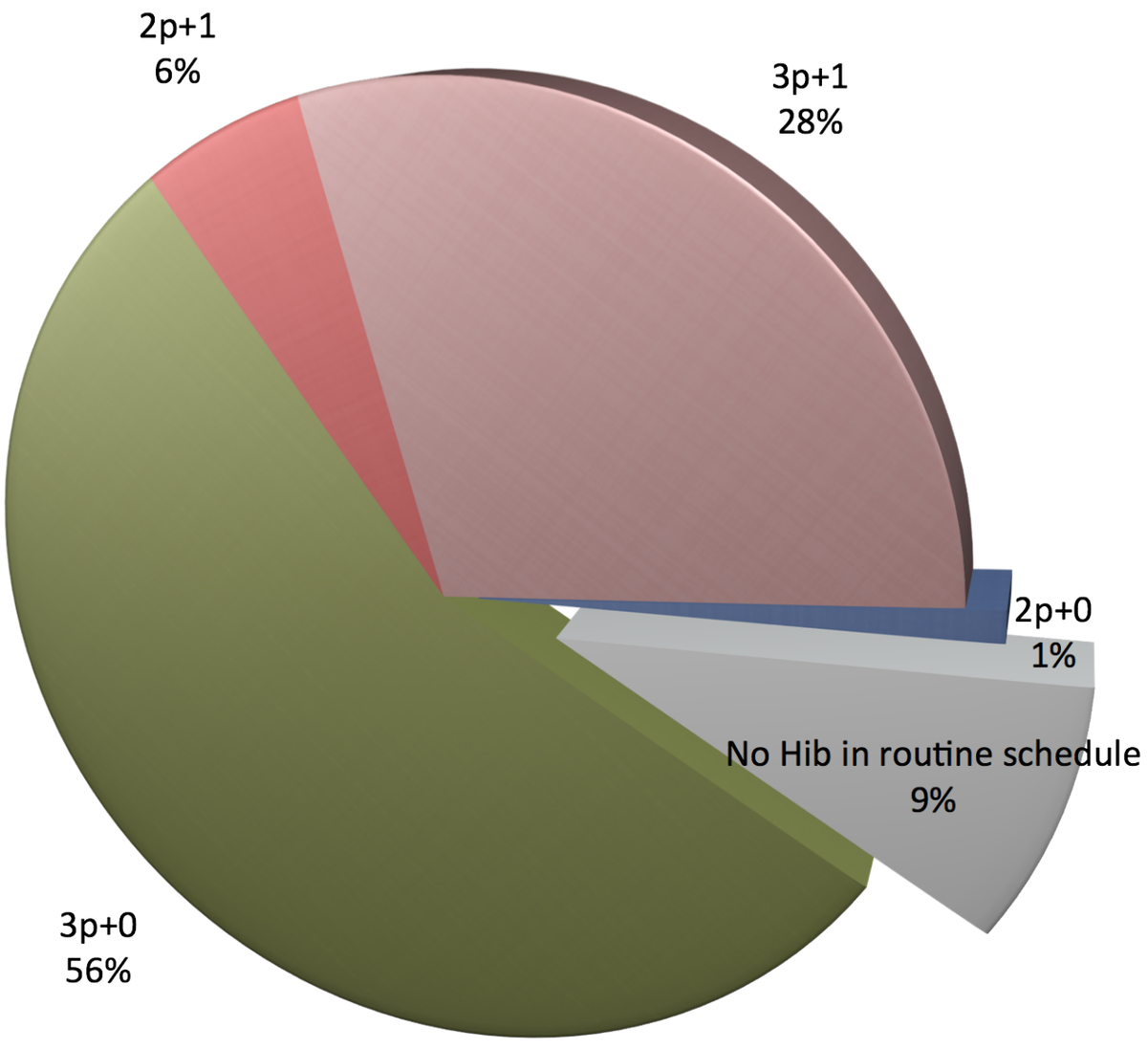
Current WHO recommendation for Hib vaccines

Age at 1st dose	Doses in primary series	Interval between doses		Considerations
		1st to 2nd	2nd to 3rd	
6 weeks (min) with DTP1, 24 mos (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3	Single dose if > 12 mos of age. Delayed/ interrupted schedule.

No recommendation for booster, but acknowledgement that some countries are using a booster dose

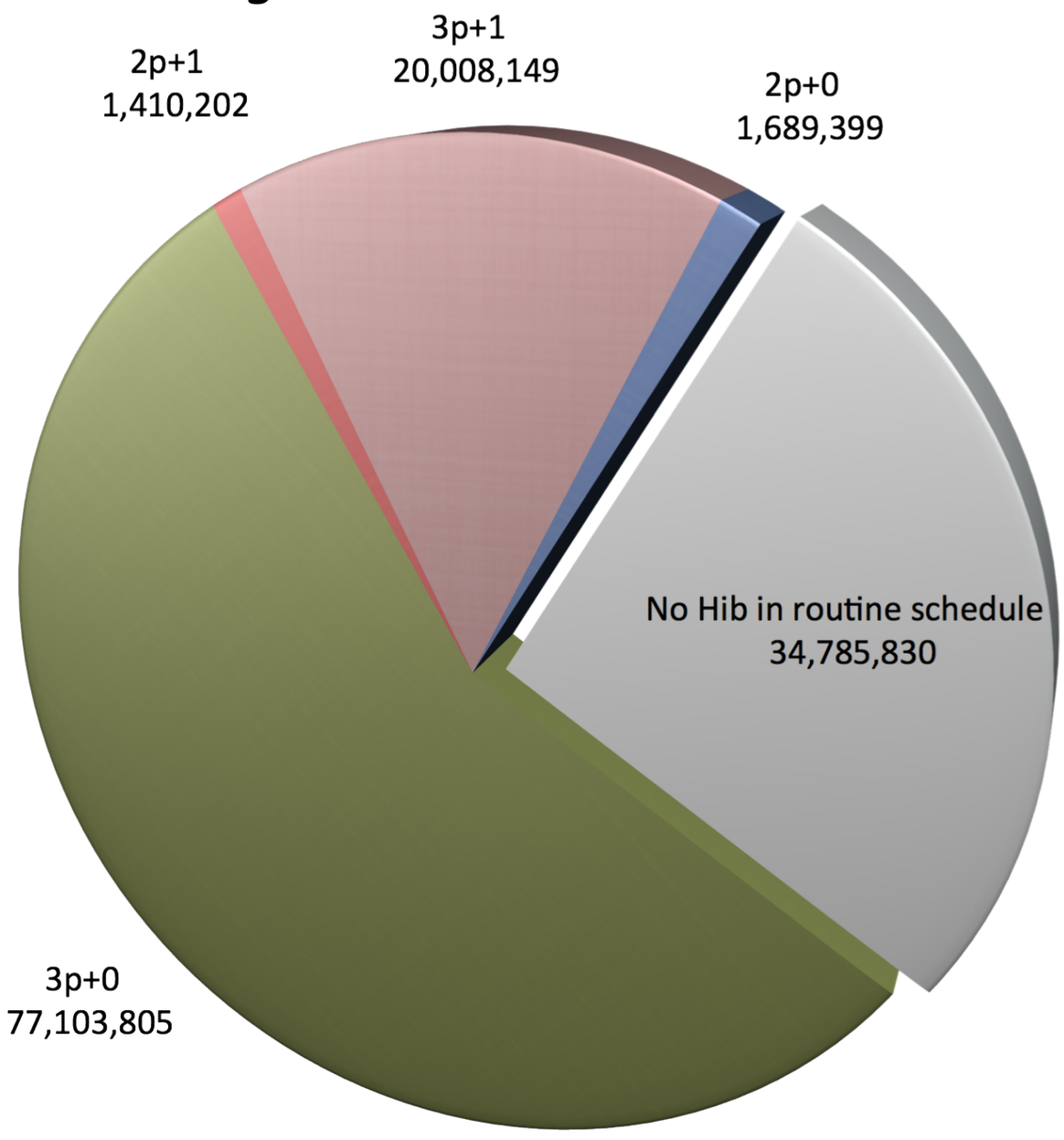
Status of Hib vaccine introduction and schedules currently in use worldwide

By percentage of countries



N= 194 countries

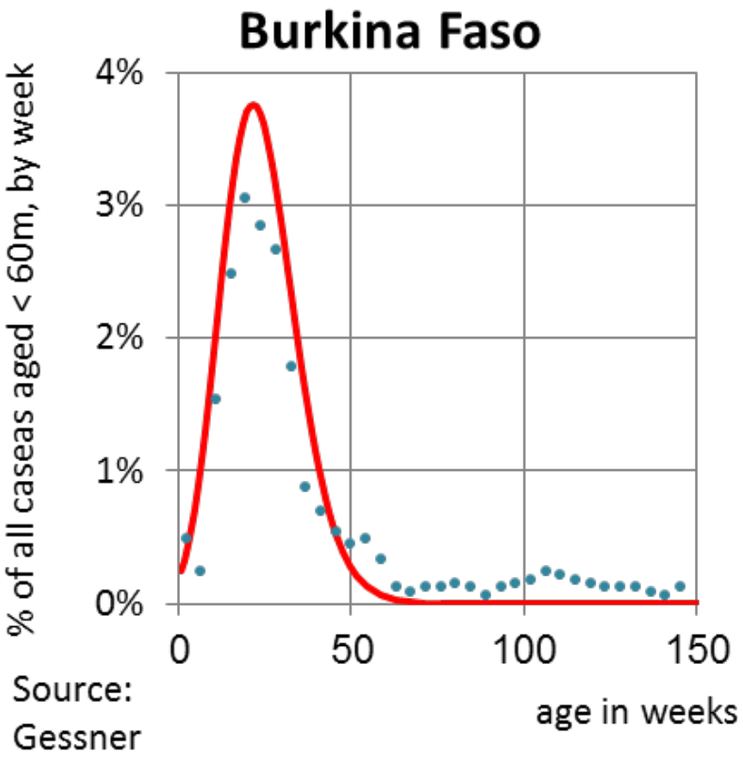
By number of infants



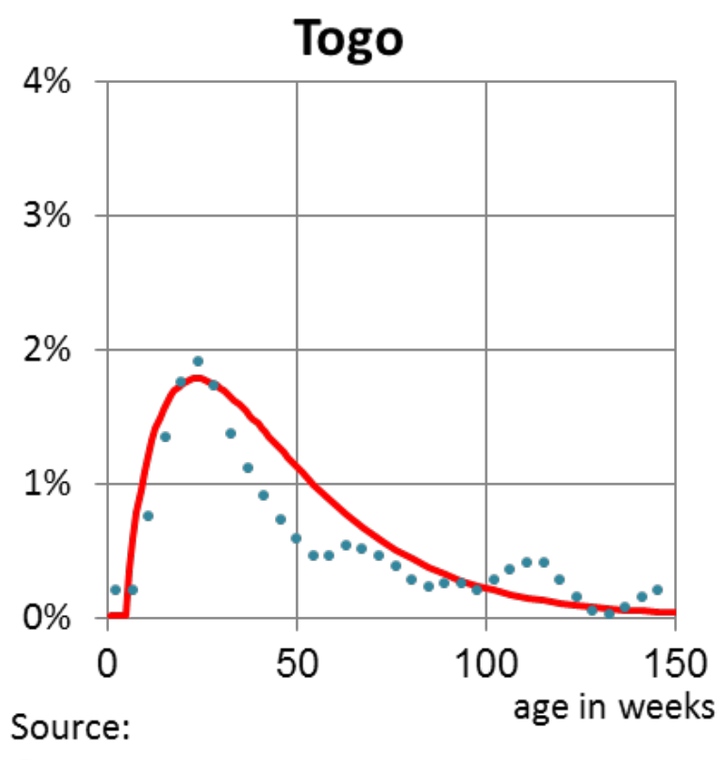
N= 134,997,385 newborns

Source: as reported in the JRF, data as at 31st December 2011

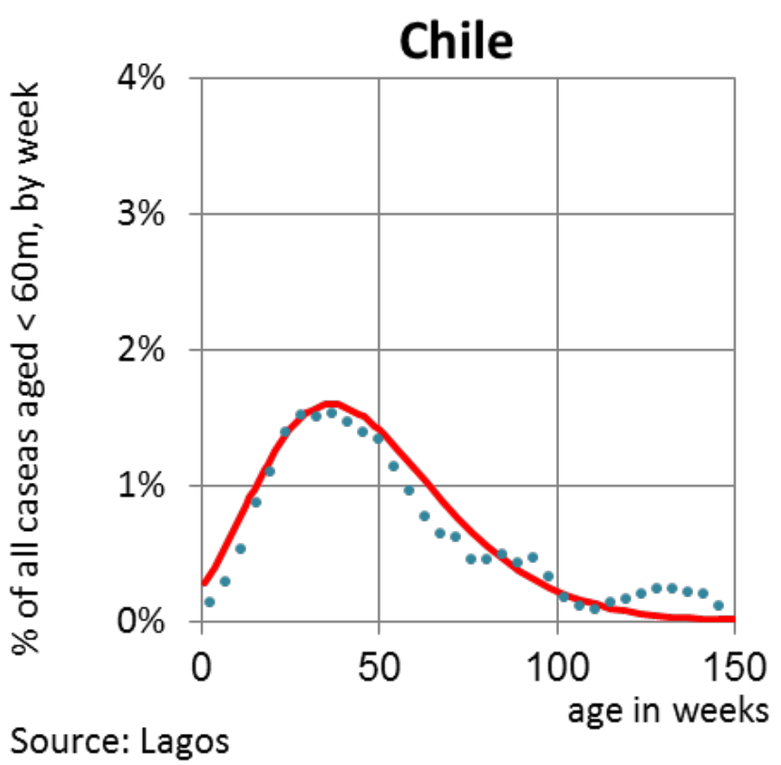
Onset age at Hib meningitis/invasive disease



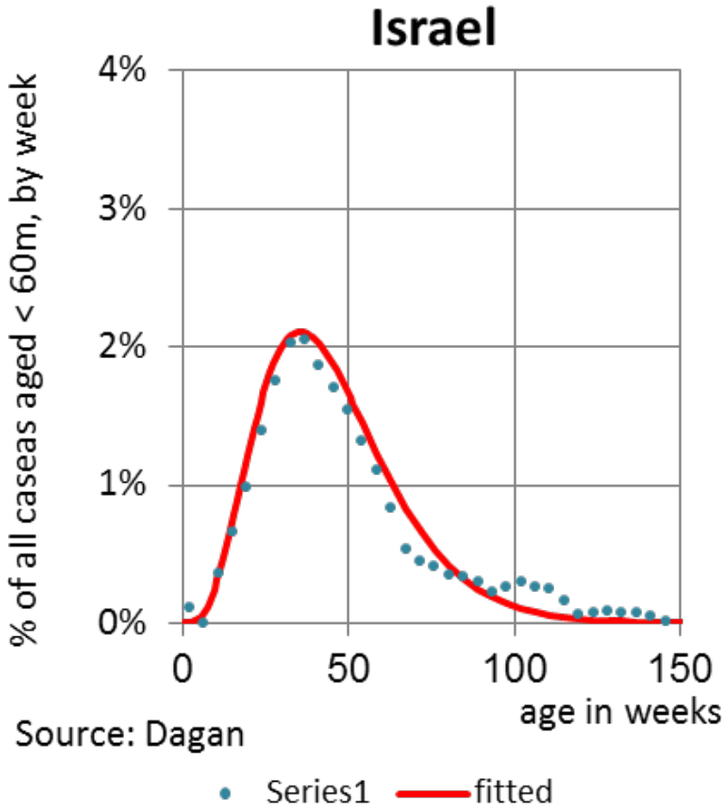
Source: Gessner



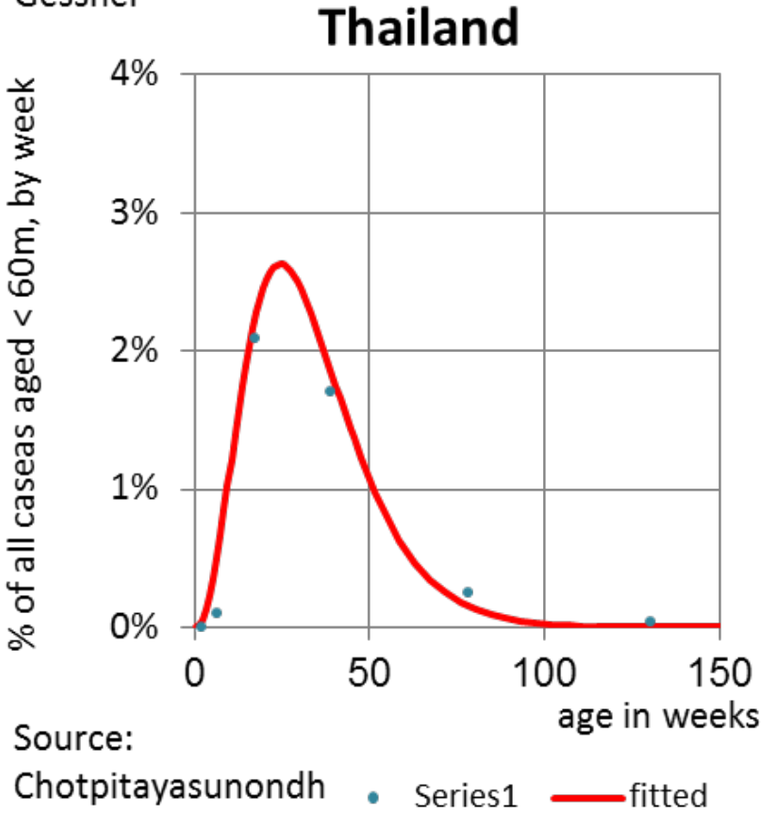
Source: Gessner



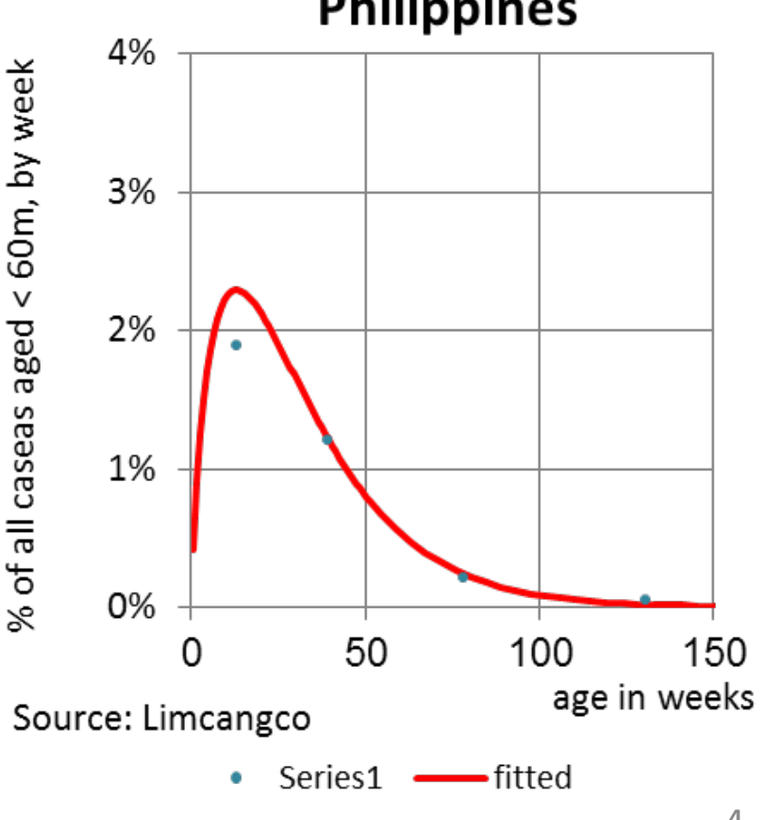
Source: Lagos



Source: Dagan



Source: Chotpitayasunondh



Source: Limcangco

Main sources of evidence

- **3 systematic reviews on Hib schedules**
- **1 systematic review on combination Hib vaccines**
- **35 countries data on long- term impact: using Hib vaccine in routine for ≥ 6 years & data on Hib disease pre & post introduction**
- **1 descriptive review of Hib disease & vaccination in the UK**
- **1 global review of age distribution of Hib disease cases**

How many primary doses?

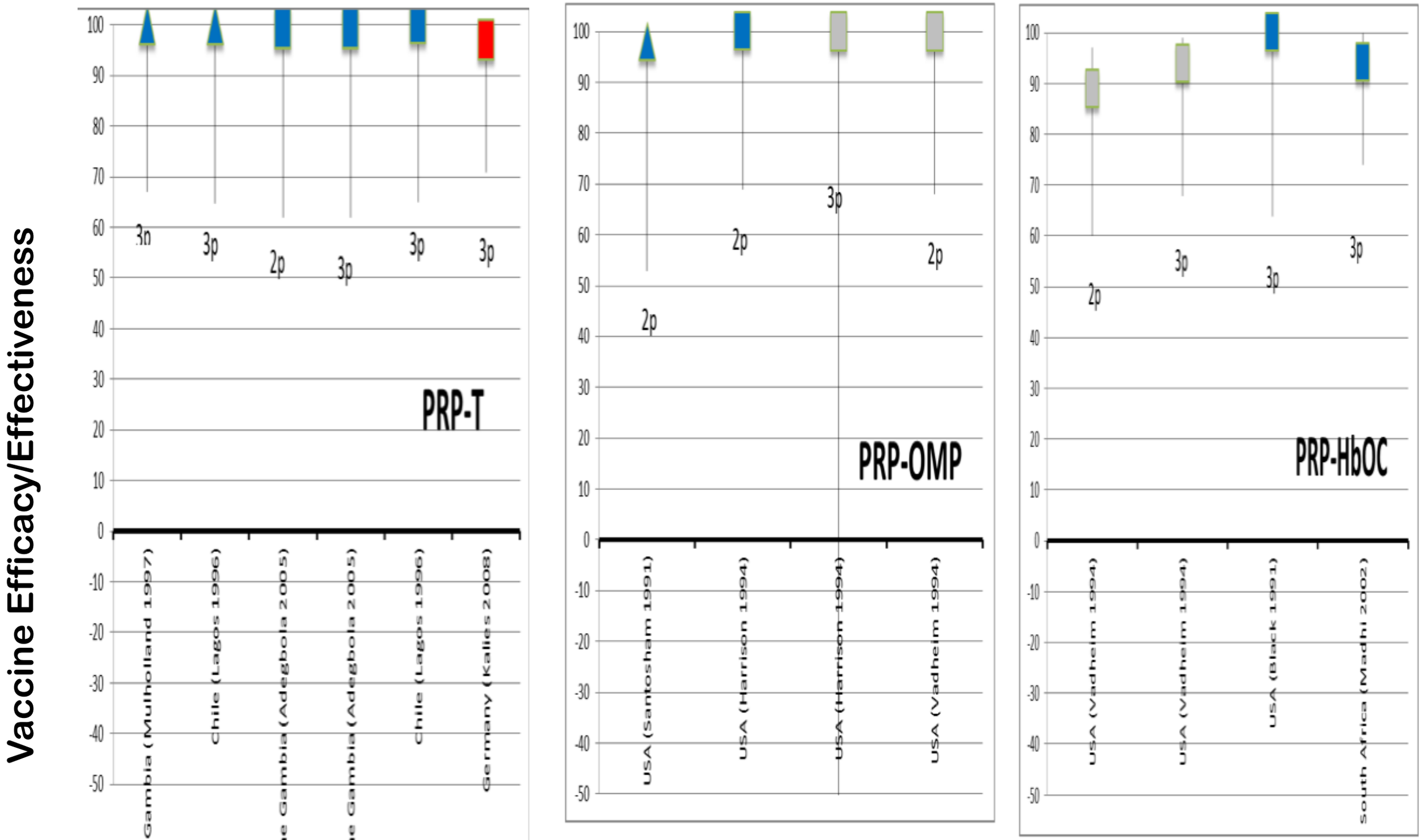
3p or 2p

Where did we gather the evidence to answer this question ?

WHAT WE LOOKED FOR	WHAT WE FOUND	
	Disease outcomes	Immunological outcomes
Studies directly comparing 3p schedule vs 2p schedule	RCTs- none Observational - none	RCTs - 6 Observational - none
Studies comparing 2p or 3p vs no Hib vaccination	RCTs- 6 Observational- 15	RCTs- none Observational - 3
Data on duration of protection	RCTs- none Observational - 5 plus studies from the UK	RCTs - 13 Observational - none plus studies from UK & unpublished data from Kenya
Data from long term impact in countries	Industrialized countries - 14 Non-industrialized countries - 21 countries	_____

Hib vaccine efficacy/effectiveness against invasive Hib disease

Studies comparing various schedules versus no vaccination

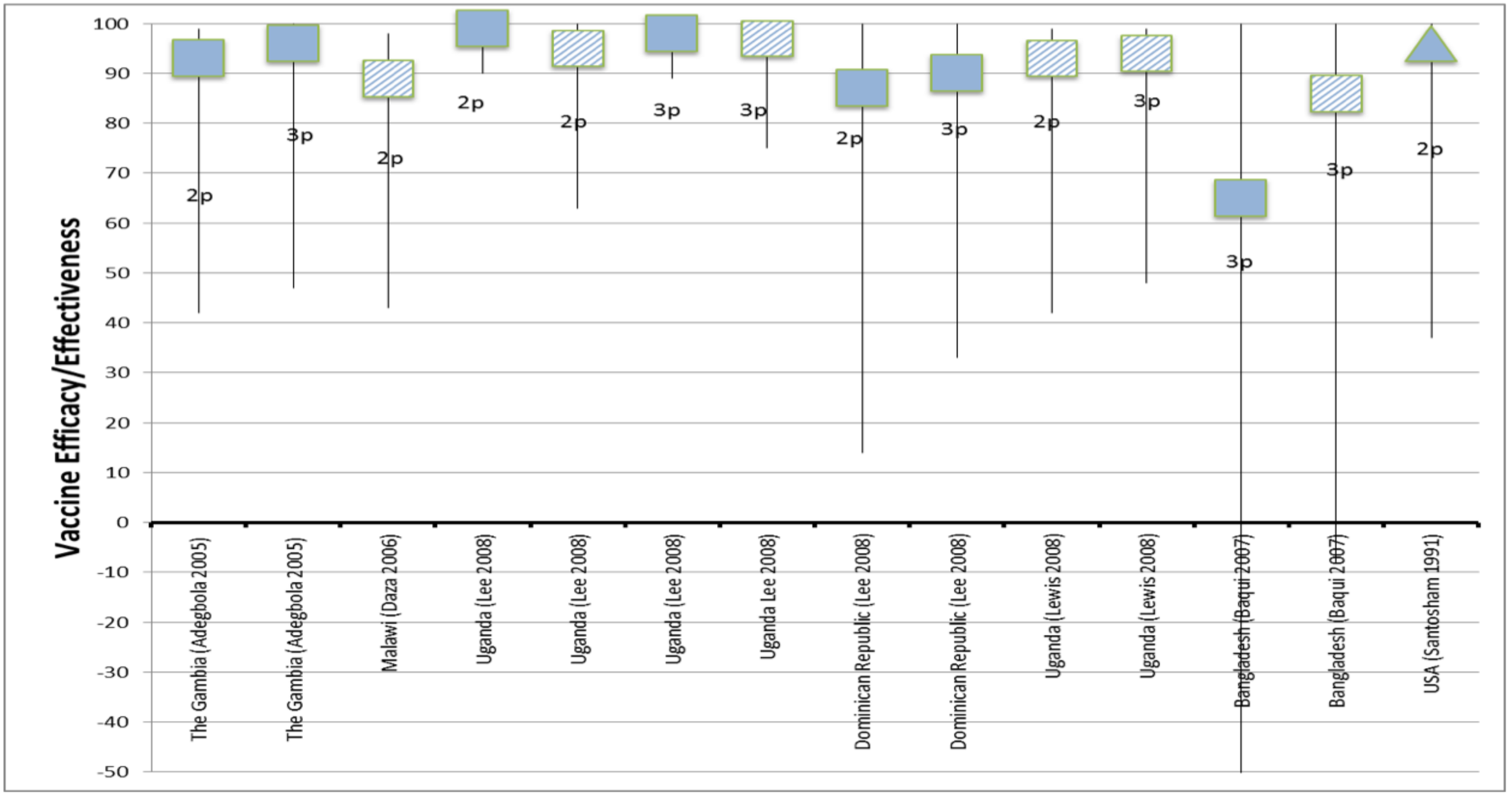


Triangle = RCT, Square = Observational study

Blue = wP; Red = aP; Grey = not stated

Hib vaccine efficacy/effectiveness against Hib Meningitis

Studies comparing various schedules versus no vaccination



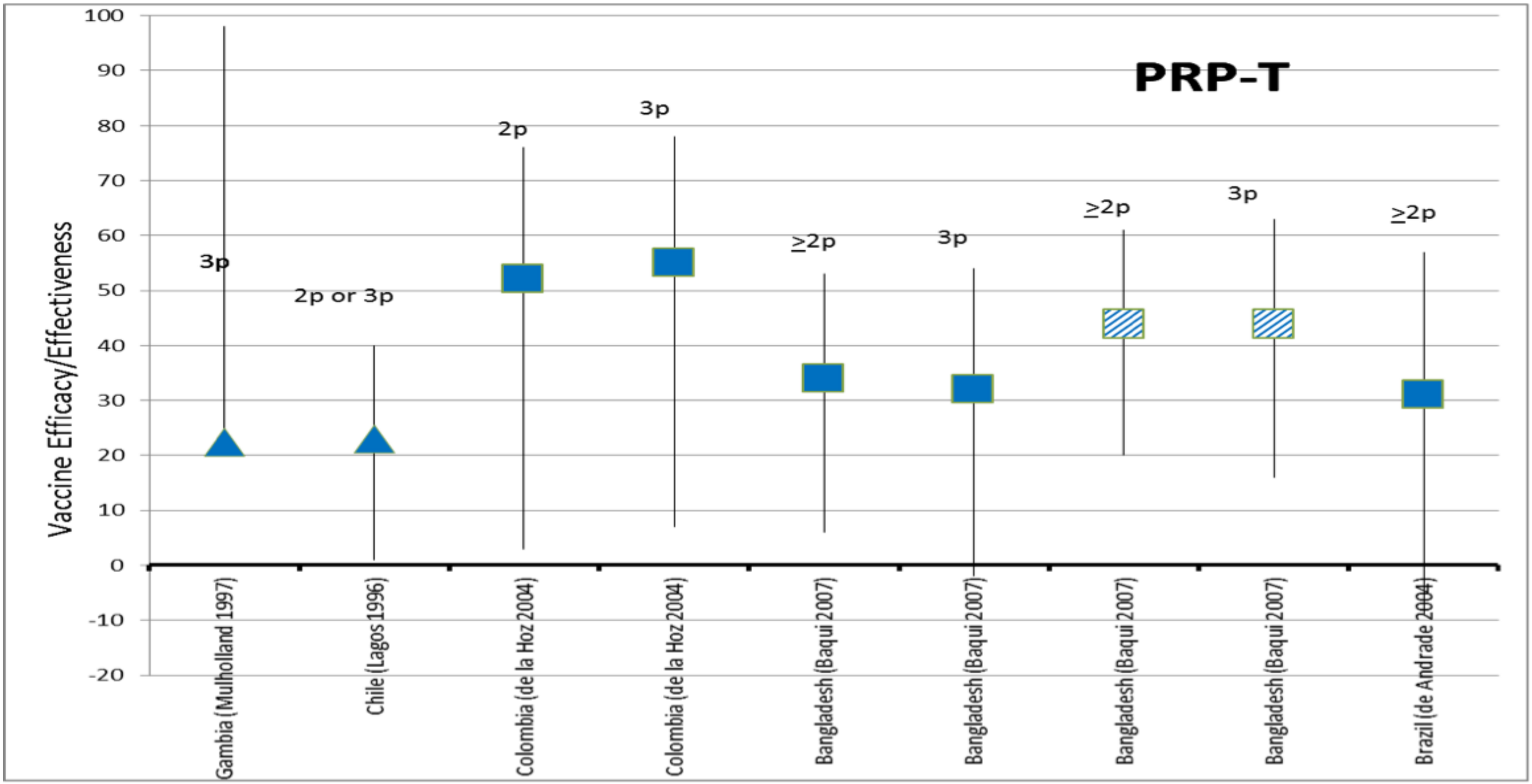
All studies used PRP-T conjugate combined with wP except the USA-Santosham 1991, that used monovalent Hib with PRP-OMP

Triangle = RCT, Square = Observational study,

solid= community control, hatches= hospital control

Hib vaccine efficacy/effectiveness against radiologically confirmed pneumonia

Studies comparing various schedules versus no vaccination



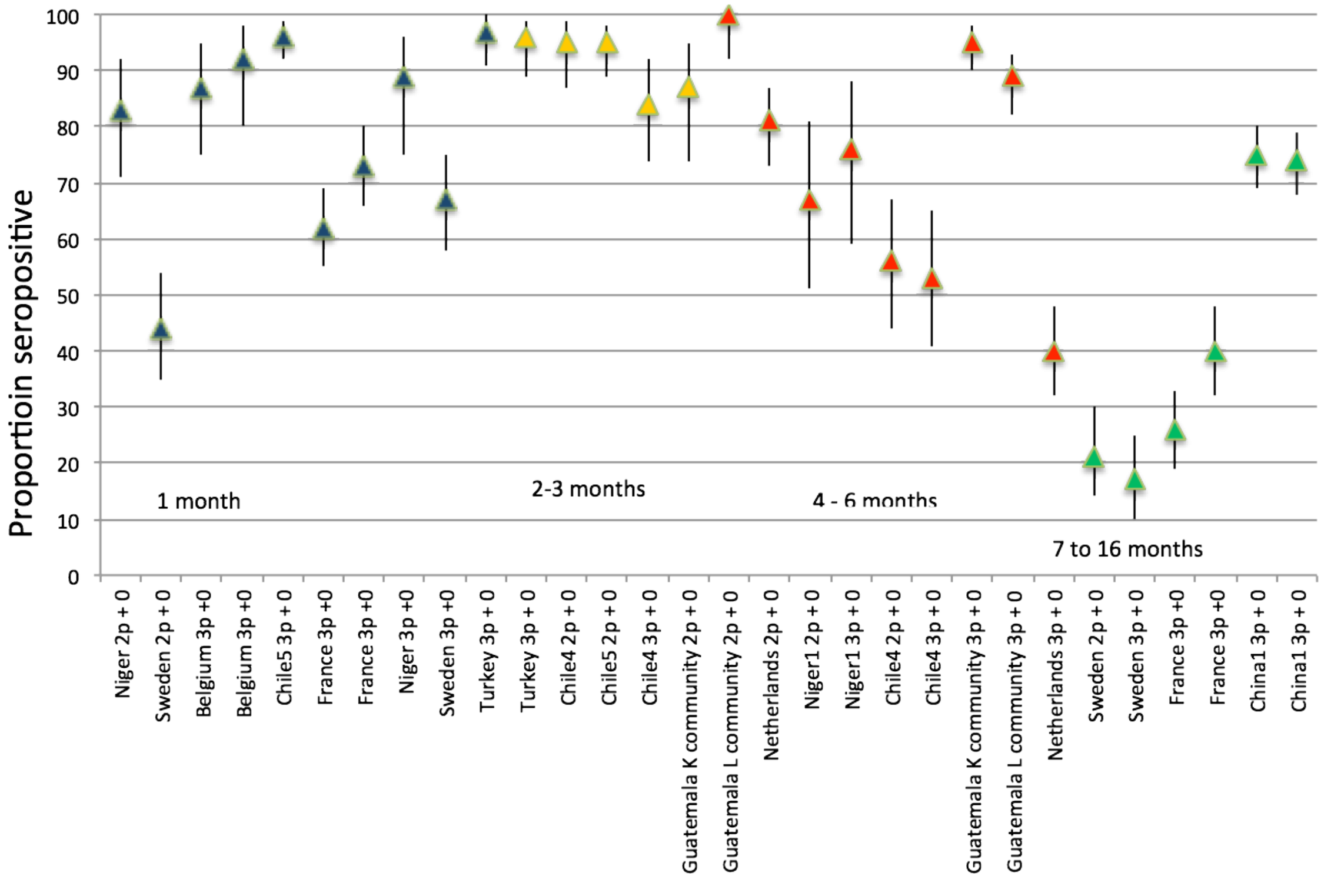
All studies used PRP-T conjugate combined with wP except the Colombia-De la Hoz 2004 that used monovalent PRP-T and Brazil-de Andrade 2004 which used monovalent PRP-HbOC vaccine

Triangle = RCT, Square = Observational study,

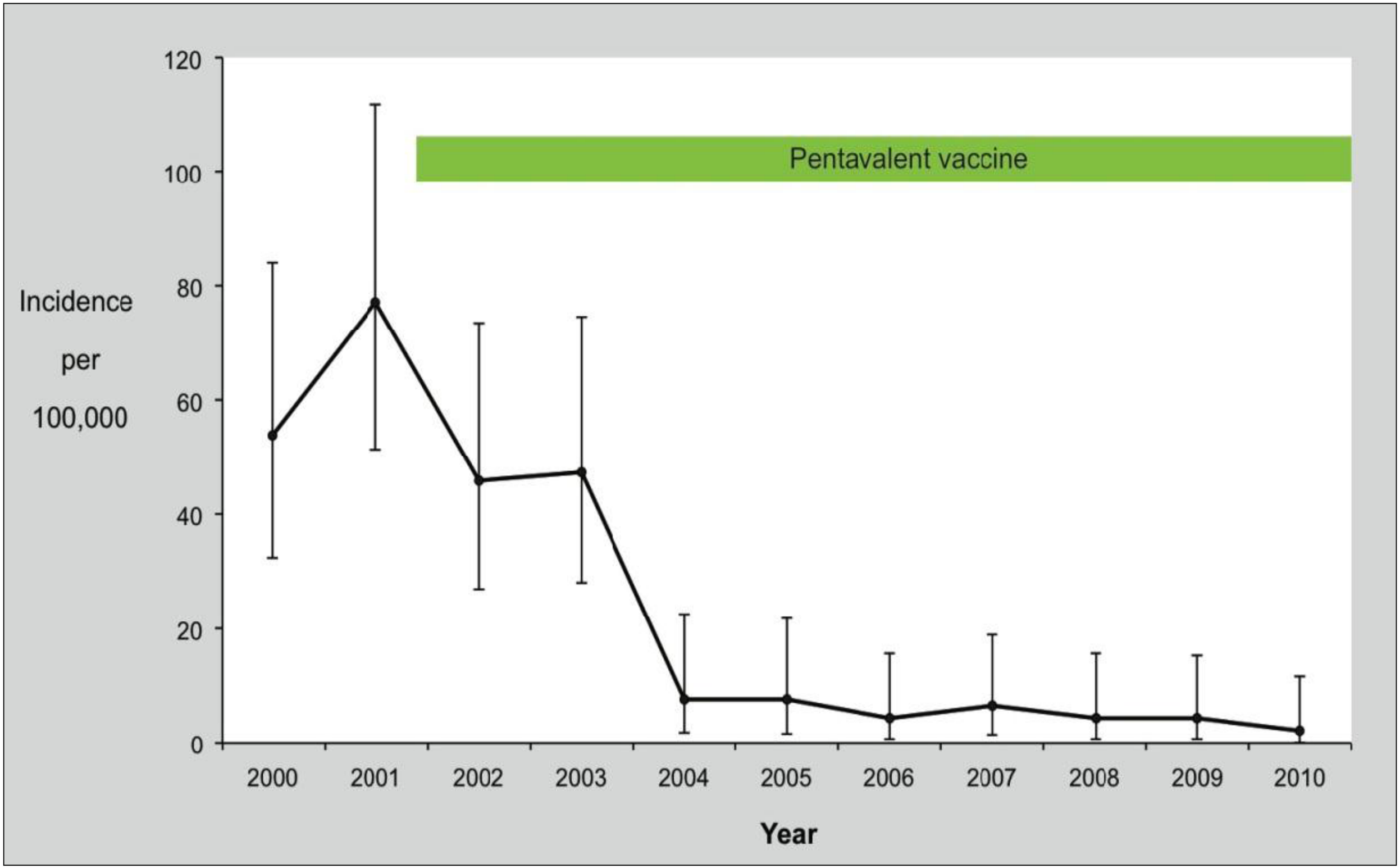
Blue = wP; Red = aP; Grey = not stated,

solid= community control, hatches= hospital control

Duration of serological response following Hib PRP-T conjugate vaccine (anti PRP antibodies ≥ 1.0ug/ml)

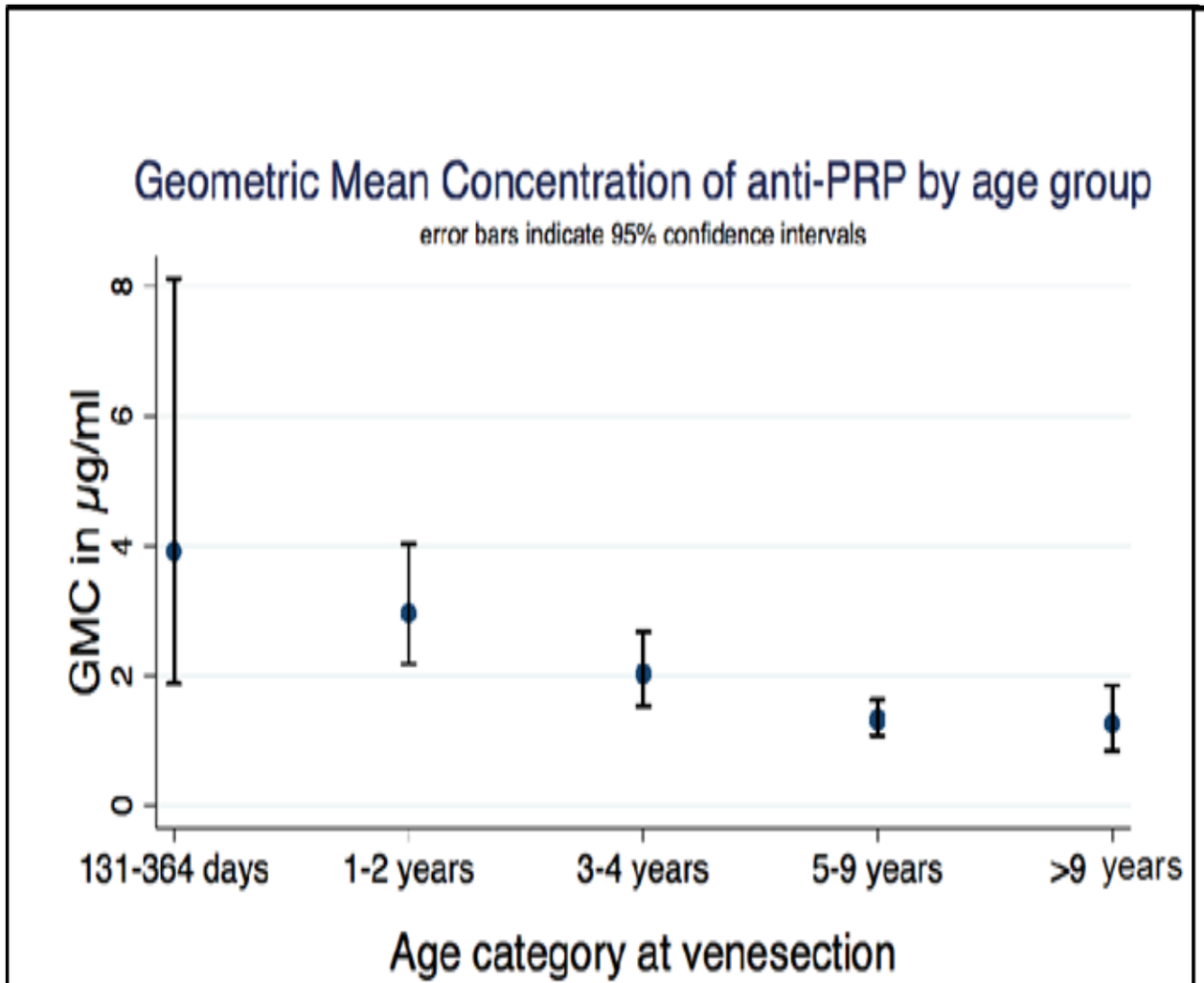


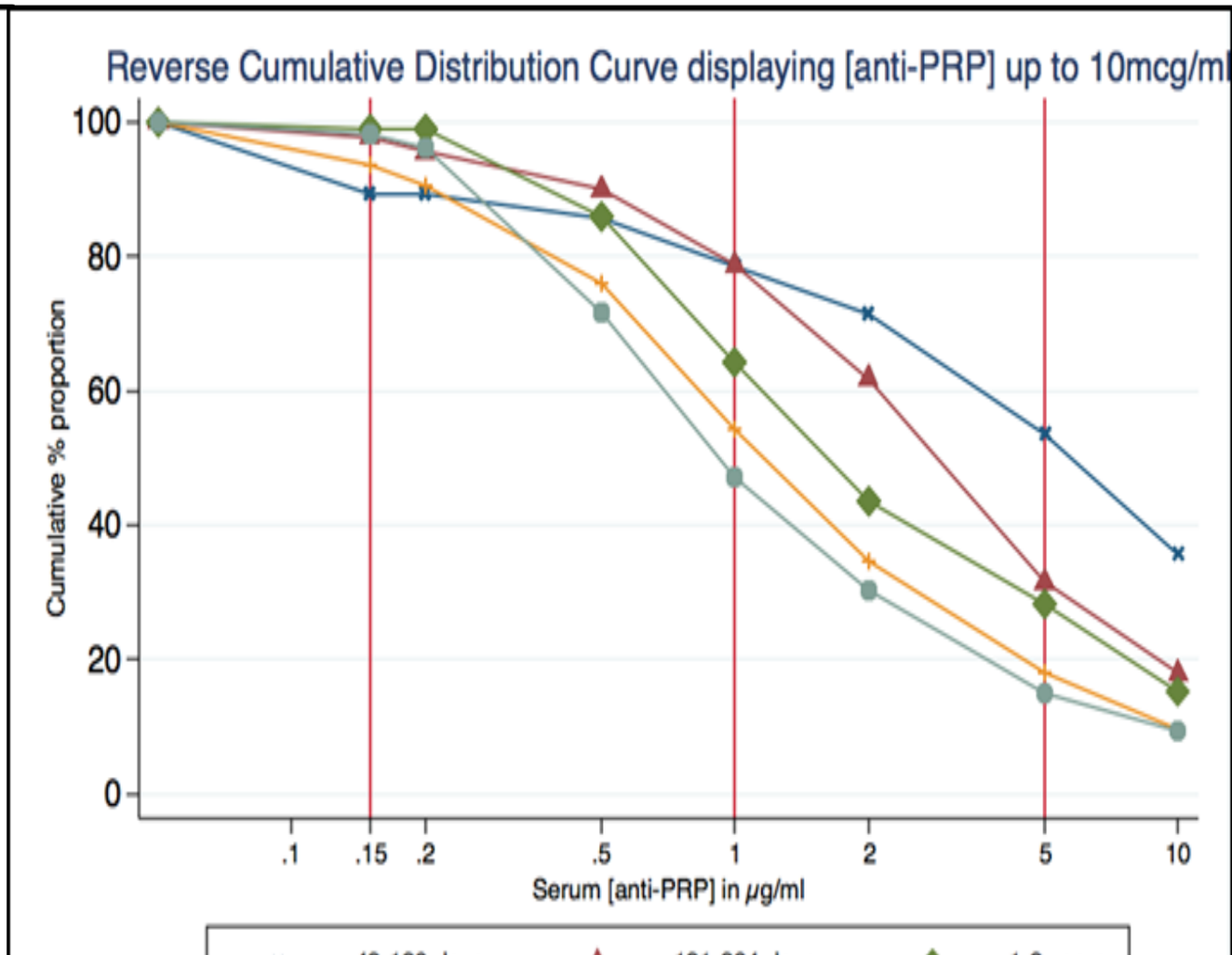
Effectiveness of Hib vaccine introduction into routine immunization in Kenya (Kilifi) (3p+0)



Source: A Scott personal communication

Effectiveness of Hib vaccine introduction into routine immunization in Kenya (3p+0)





Source: Figure courtesy of L Hammit, Goldblatt, and A Scott

Does using a 3p schedule results in greater immunogenicity or effect on disease than using a 2p schedule?

CONCLUSION

Data available do not favour a 3p+0 or 2p+0 schedule in terms of disease outcomes or immunogenicity for various Hib vaccine types.

Does using a 3p schedule results in greater immunogenicity or effect on disease than using a 2p schedule?

CAUTION

Vaccine efficacy from different trials cannot be compared directly as evidence of equivalence or superiority of one particular schedule.

Most of the evidence is from observational studies

The observational studies took place when the vaccine was in routine use and other children in the community may have received 3 or more doses.

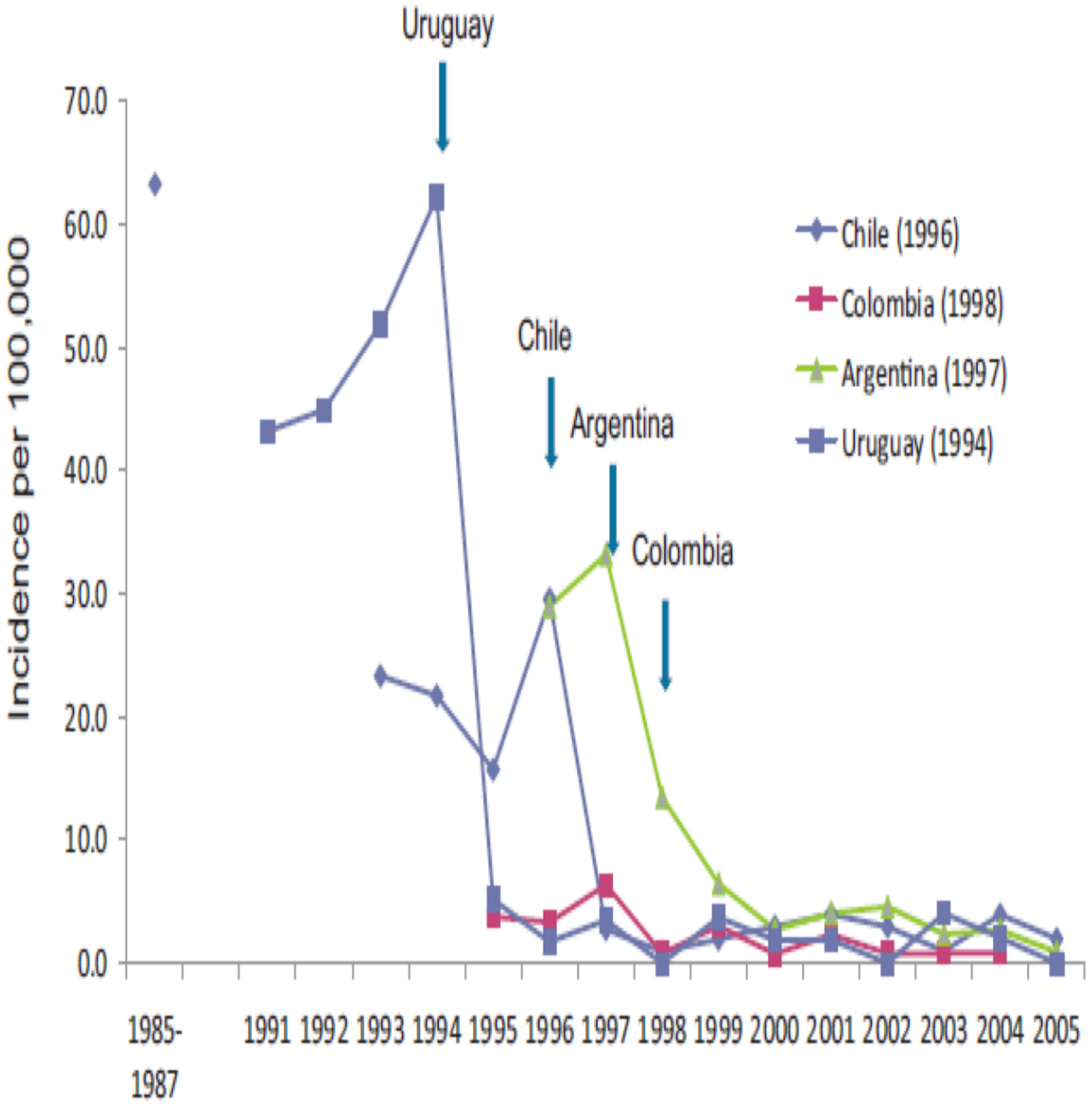
Is there a need for a booster dose?

Where did we gather the evidence to answer this question ?

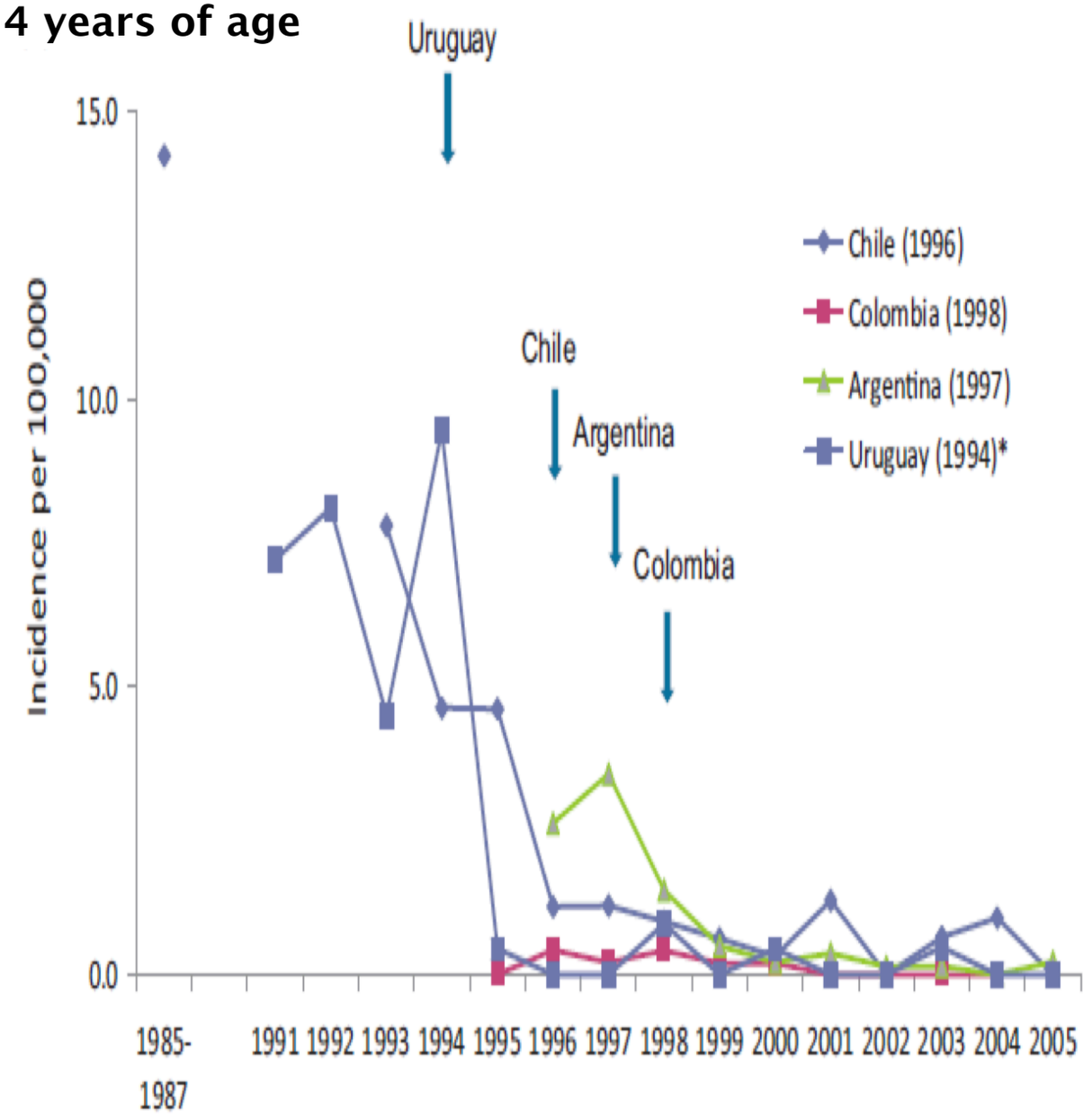
WHAT WE LOOKED FOR	WHAT WE FOUND	
	Disease outcomes	Immunological outcomes
Studies directly comparing 3p+0 vs 3p+1 or 2p+1 schedules	RCTs- none Observational - none	RCTs - 2 Observational - none
Studies comparing 3p+0 or 3p+1 or 2p+1 vs no vaccination	RCTs- 3 Observational- 2	RCTs- 6 Observational - 2
Data on duration of protection	RCTs- none Observational - 3 plus studies from the UK	RCTs - 8 Observational - none plus studies from UK & unpublished dat from Kenya
Data from long term impact in countries	Industrialized countries - 14 Non-industrialized countries - 21 countries	_____

Trends in Hib meningitis incidence in 4 South American countries after Hib vaccine introduction

Less than 1 year of age



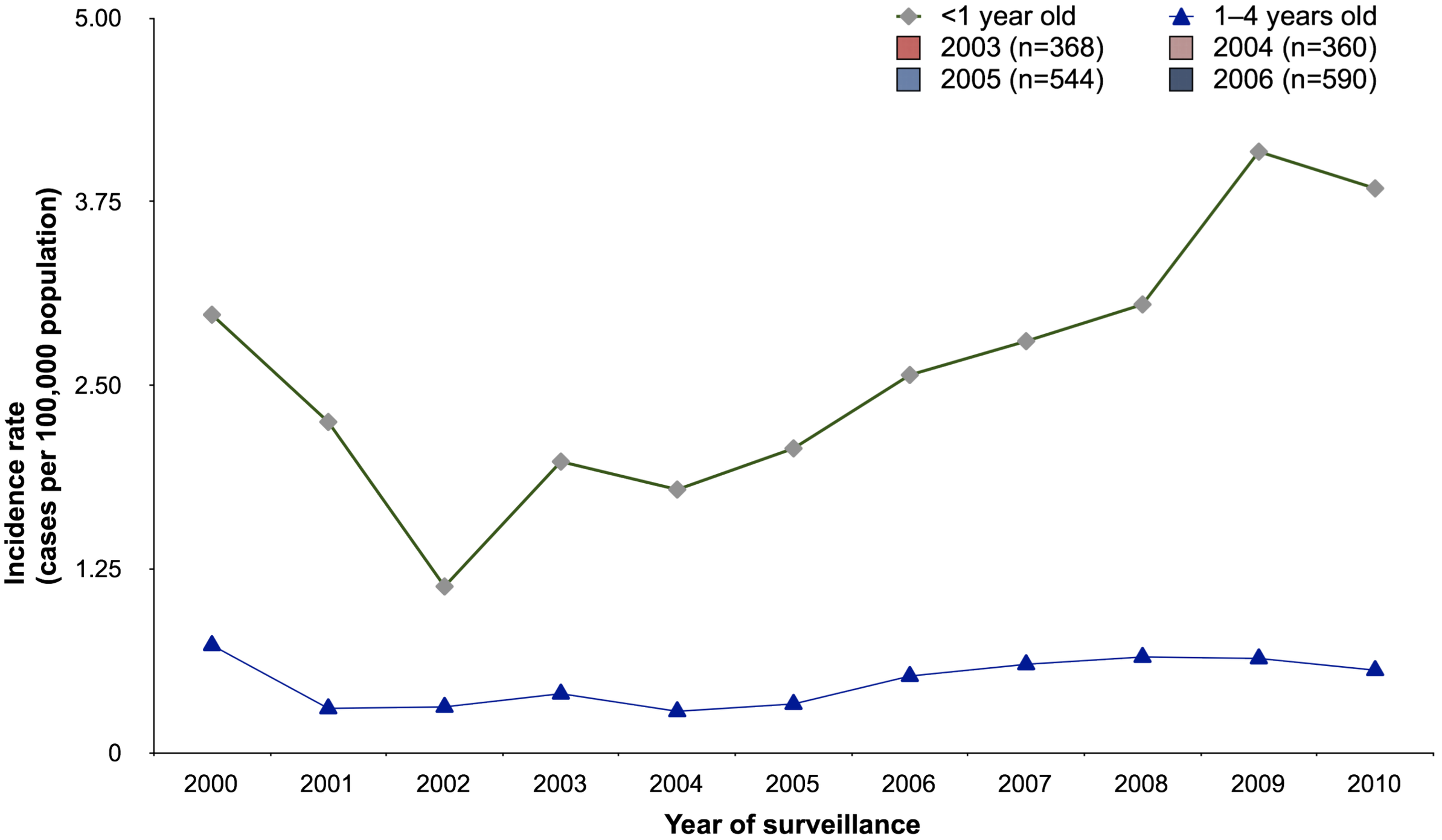
1-4 years of age



3p+0 (@ 2, 4, 6 mos) = Chile & Colombia
3p+1 (@ 2,4,6 & >b11 mo) = Uruguay & Argentina

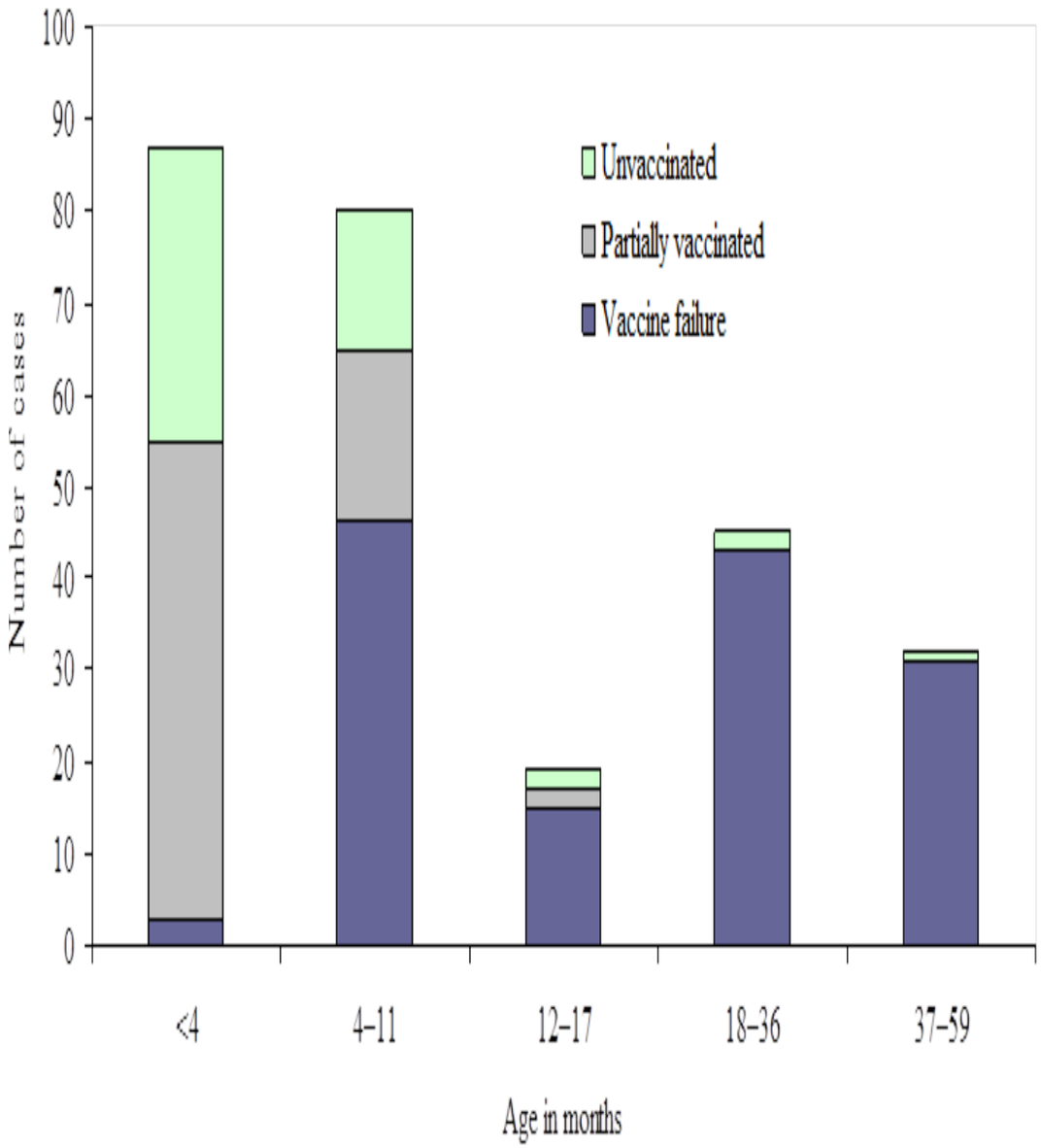
Source: Garcia S et al/Vaccine 30 (2012) 486-492

Incidence rates of laboratory-confirmed, Hib disease, in children <5 years old, South Africa, 2000-2010

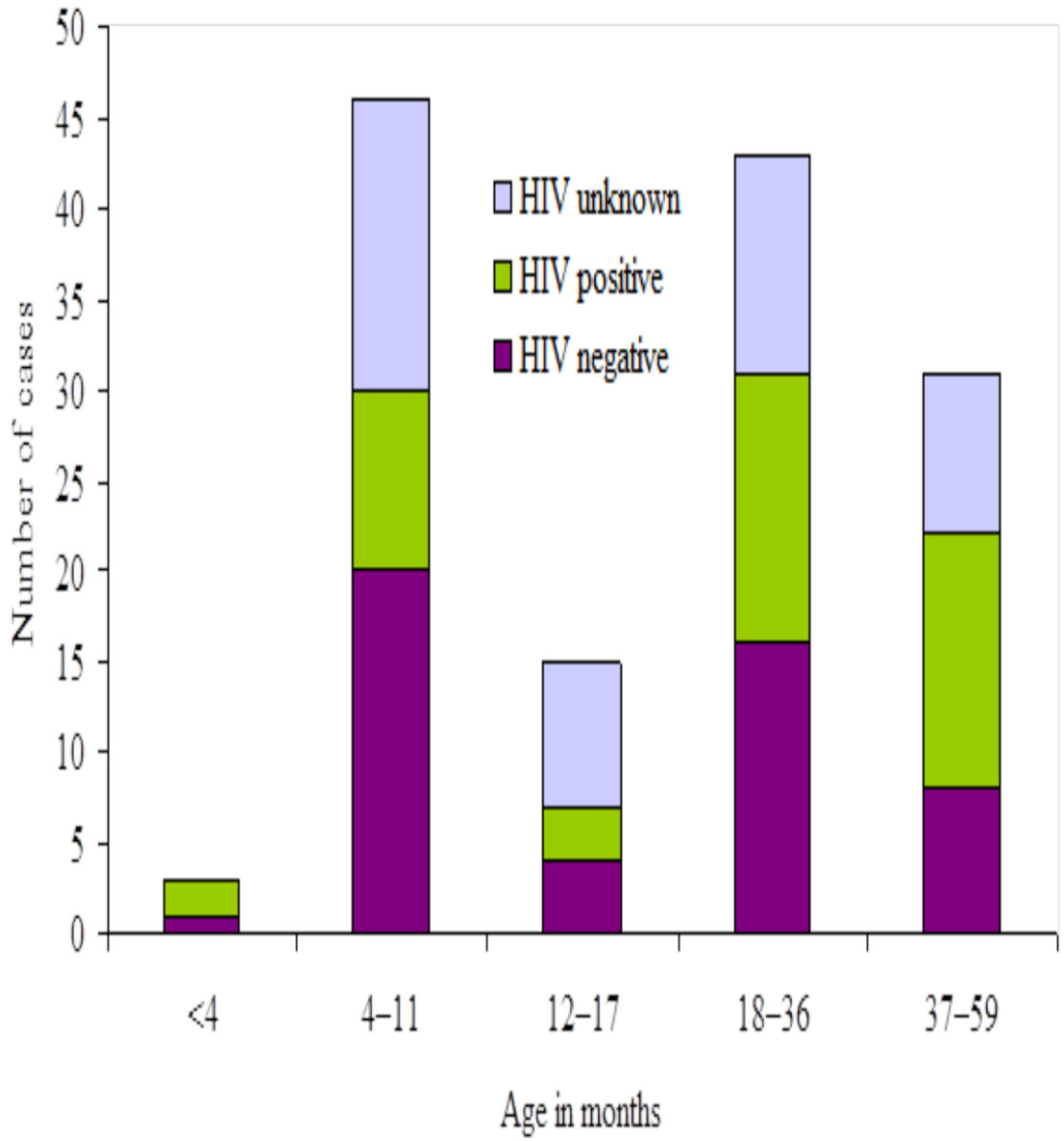


Source: Figure courtesy of A von Gottberg

Number of children with confirmed invasive Hib disease, reported by age and known vaccination status (n=263), South Africa, 2003-2009



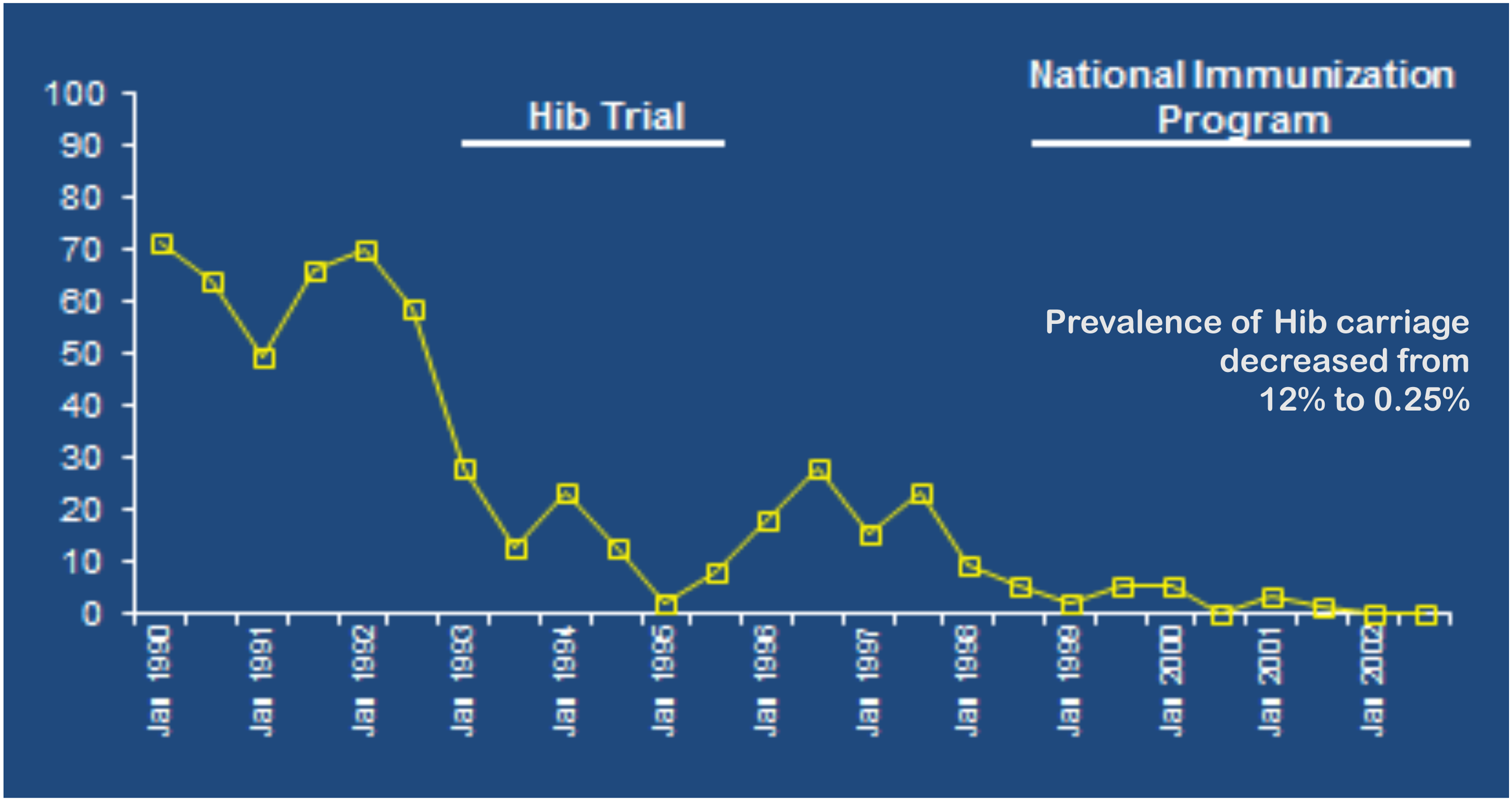
Number of Hib vaccine failures (n=138) by age and HIV infection, South Africa, 2003-2009



Source: Figure courtesy of A von Gottberg

Incidence of Hib meningitis in children < 5 years of age (cases per 100,000 per year) in The Gambia*

3p+0 @ 6,10, 14 weeks, PRP-T conjugate, Hib introduction 1997, penta since 2009



* using surveillance data from the Western Region

Source: Adegbola R et al 2005, updated courtesy of S Howie et al., MRC Gambia

Experience in The Gambia (3p+0)

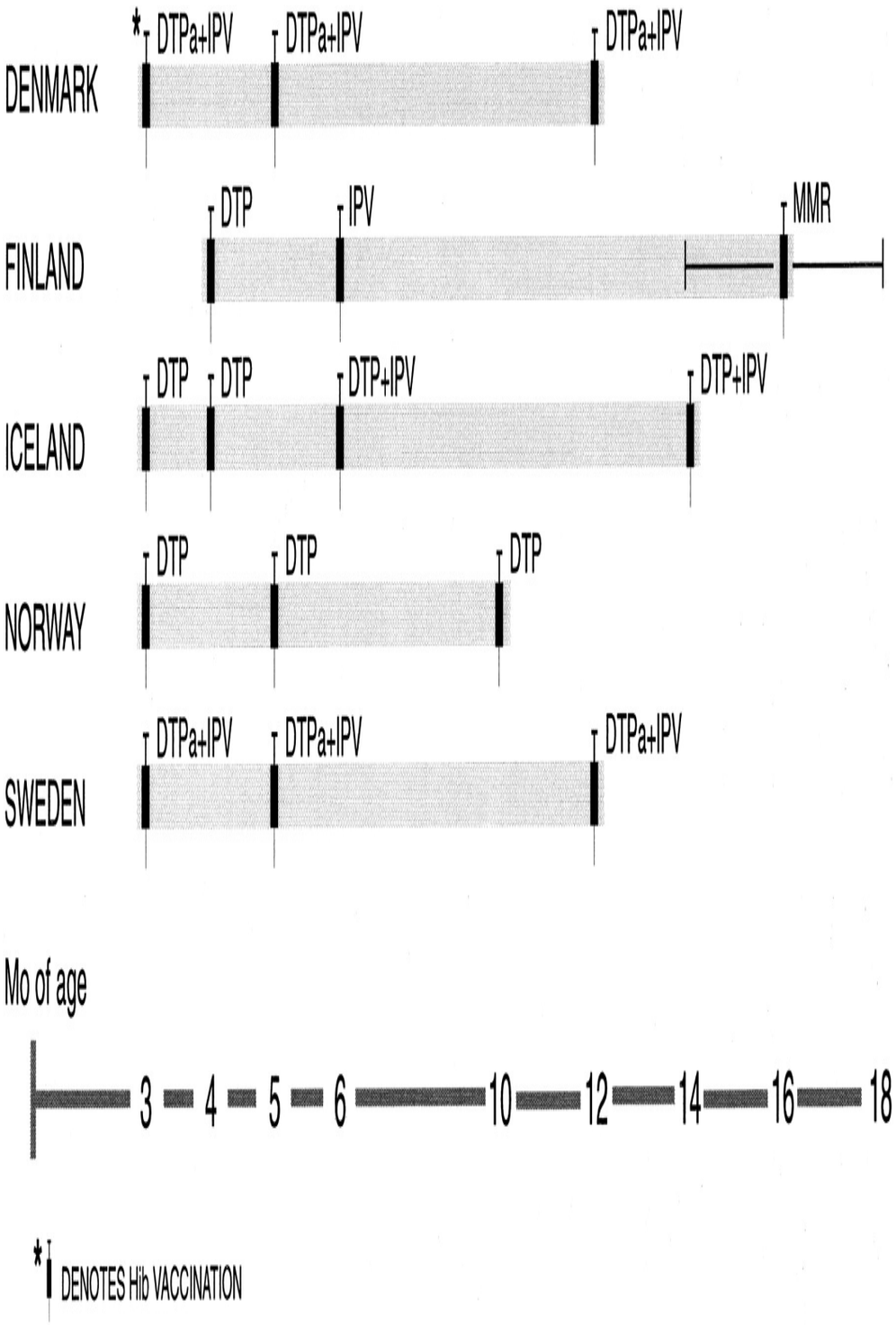
Summary courtesy of the MRC The Gambia

1997 Vaccine introduction

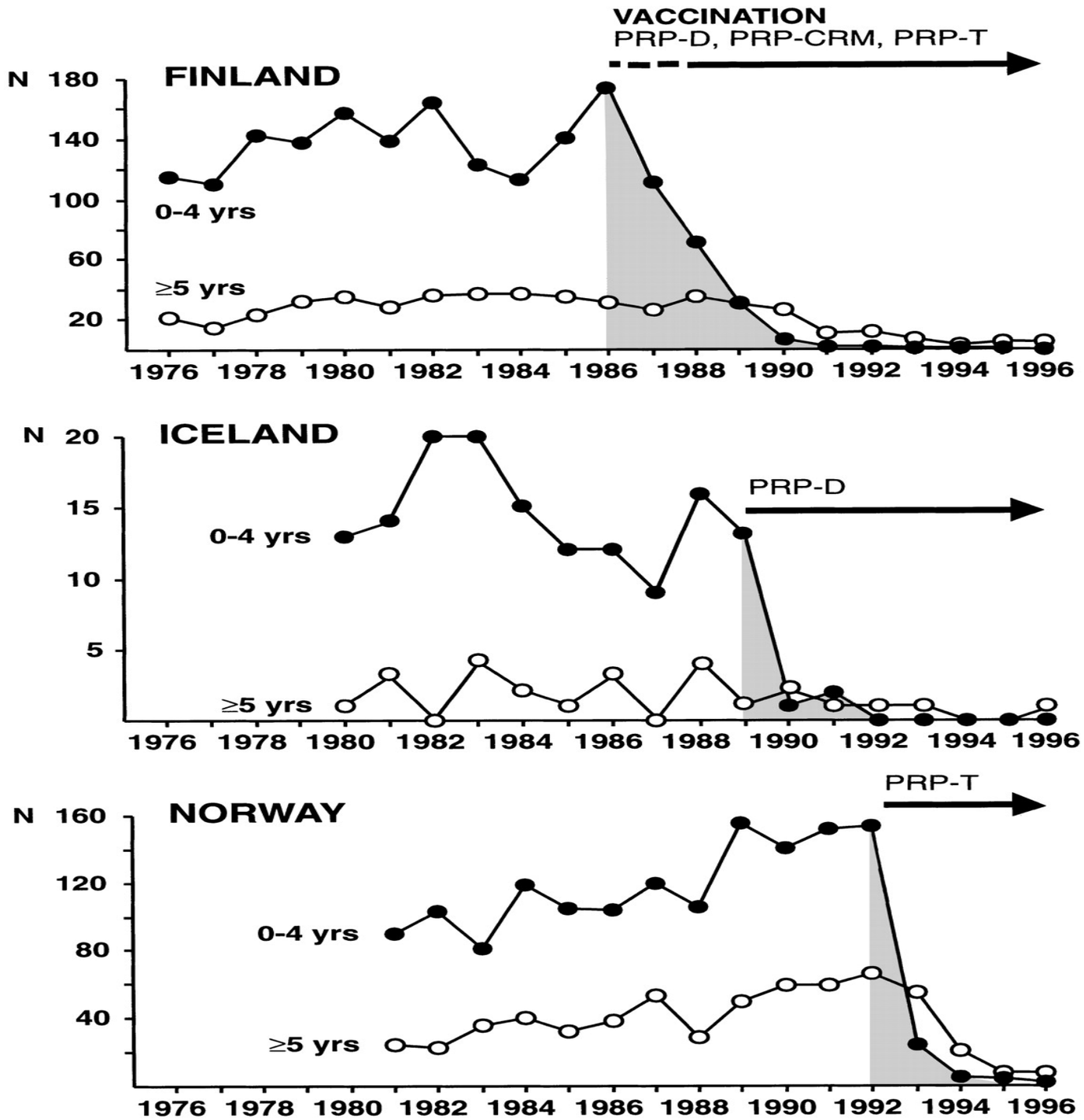
2009 Penta introduction

	Pre-1997	2002	2006	2007-10	2011-12*
Vaccine Coverage	Vaccine intro	3 doses=68%	-	3 doses=92%	-
Surveillance	Western Region formal surveill.	Western Region formal surv.	Western Region no formal surv. incidental case reports.	Western Region formal surv.	Western Region no formal surv. Eastern Region formal surv
Hib meningitis rate (100,000 < 5 yr)	70	0	5 cases	0.8 - 2.3	WR: few cases ER: > 20 cases
Age cases	80% < 12 mo	-	median age 15 months	-	50% < 12 mo 50% >2 doses
Carriage rate (1-2 yo)	12%	0.25%	-	0.9%	-

Hib vaccination schedule in the 5 countries of Scandinavia.

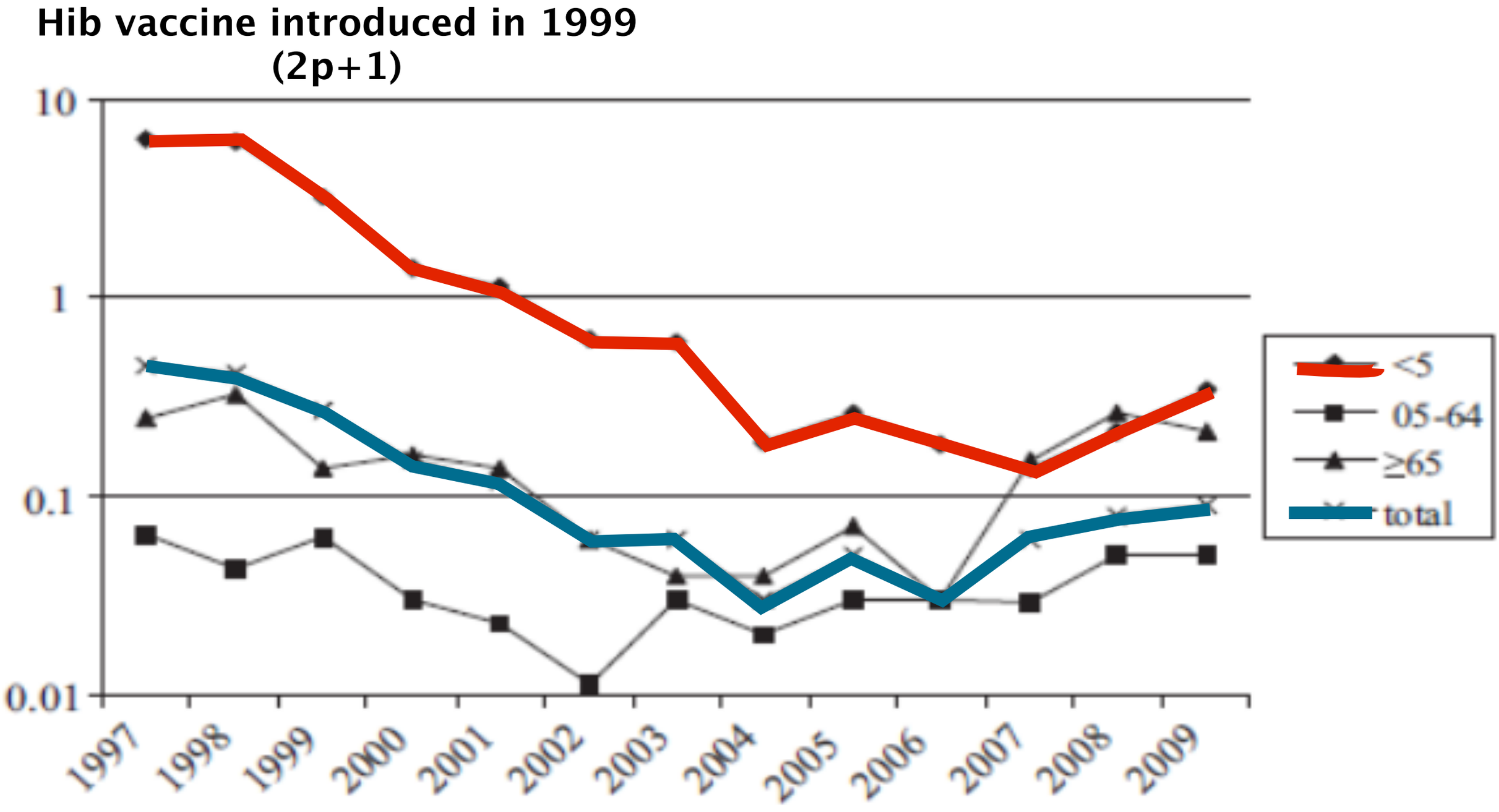


Sequence of starting vaccination and decline of classical Hib diseases in Finland, Iceland, and Norway.



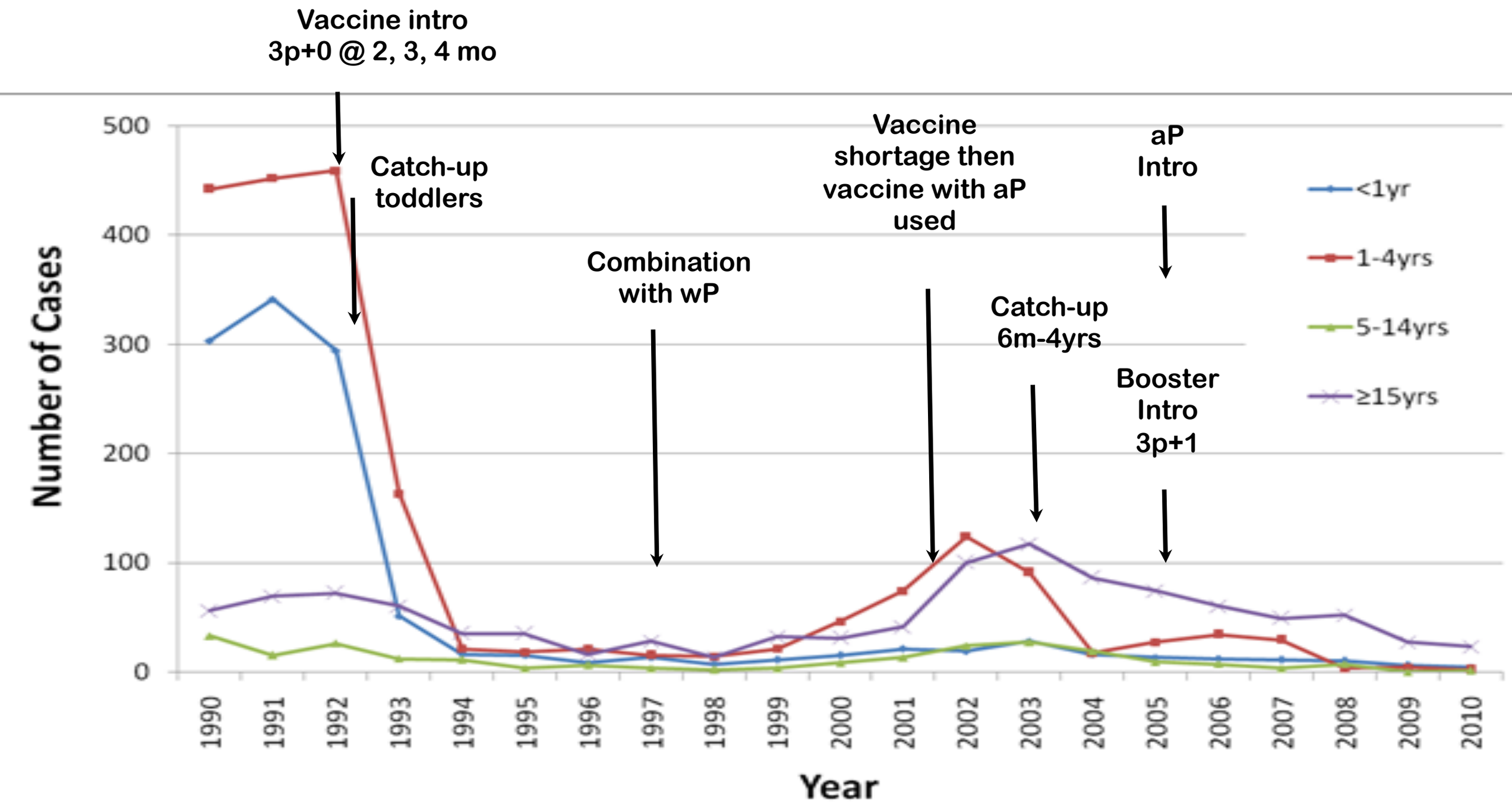
Peltola H et al. J Infect Dis. 1999;179:223-229

Age specific incidence rates (per 100,000 pop) for invasive disease caused by Hib in Italy, 1997-2009



Source: Giufre M et al 2011

Number of cases of invasive Hib disease in different age-groups diagnosed in England and Wales (1990-2010).



Source: Health Protection Agency Centre for Infection

- **Duration of protection**

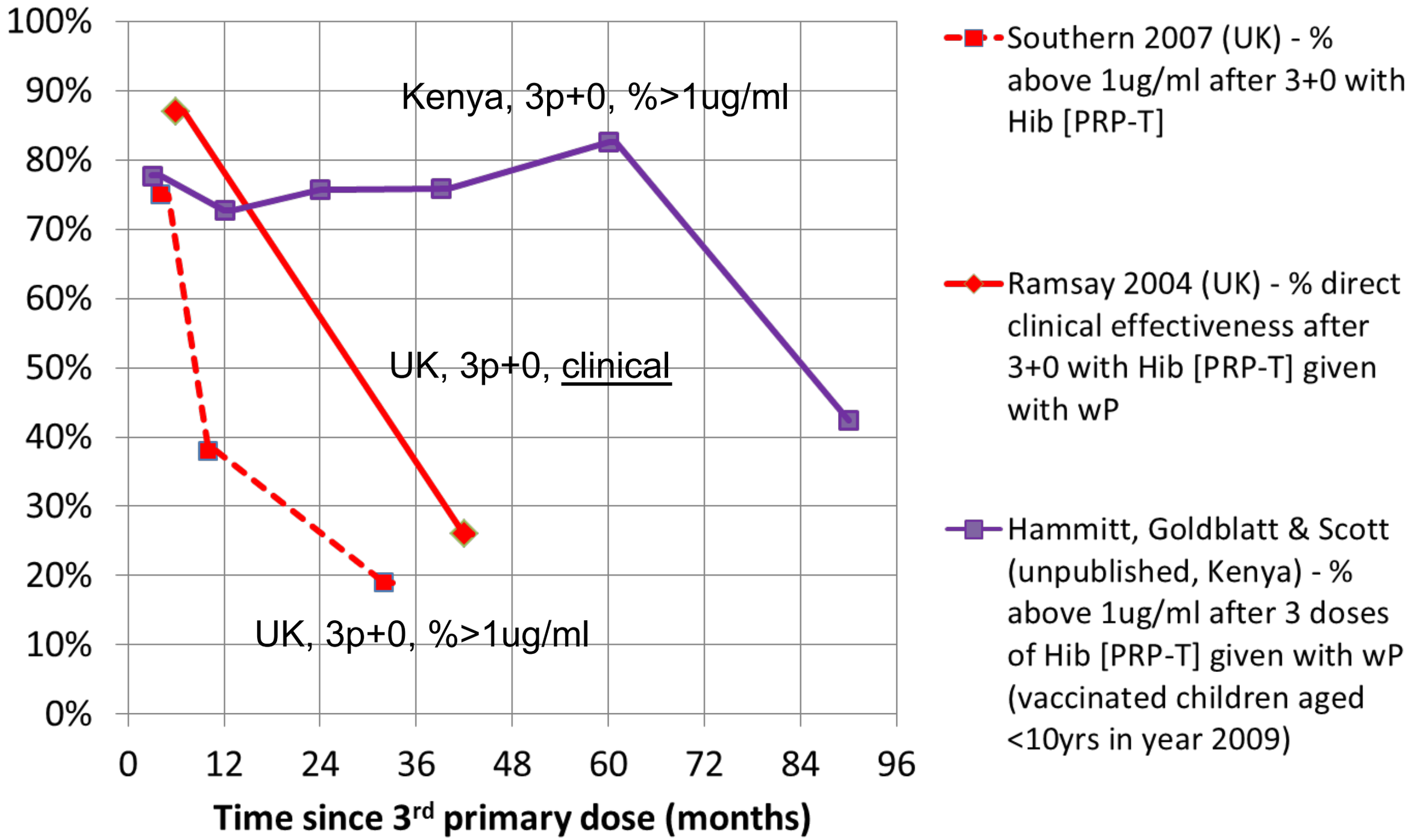
- **Although there is some evidence for decrease over time in the proportion above a set threshold there is limited evidence for this decline being associated with an increase in disease**

- **Example: two countries with good data**

- **Industrialised country (UK)**
- **Non-industrialized country (Kenya)**

Duration of seropositivity/protection after 3p+0:

% direct protection vs clinical disease in UK, % above 1ug/ml in the UK and Kenya



Does using a schedule with a booster results in greater immunogenicity or effect on disease?

CONCLUSION

In some countries, administering a booster dose during the child's second year of life has been deemed necessary to sustain overall disease control in population and direct protection of toddlers.

**The need for booster doses in non-industrialized countries
requires further evaluation.**

Does using 3 primary doses of Hib conjugate vaccine in infancy have a greater effect on disease or immunological outcomes than using two or three primary doses with a booster?

CAUTION

The situations in which a booster dose should be used remain unclear.

It would depend on various factors including local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Does using a Hib vaccine schedule with a longer interval between primary doses (e.g. ≥8 weeks) results in greater effect on Hib disease or immunogenicity than a schedule with a shorter interval (e.g. 4 weeks)?

The data we found showed no consistent or clinically relevant differences between shorter and longer intervals

- There were no RCTS or observational studies that compared various intervals and, types of vaccine conjugate and that reported effect on various disease outcomes.

- We did not find enough evidence on 2p+1 schedule at short intervals (i.e. 4 weeks).

- We dd not find strong evidence from observational studies for a difference in VE according to dosing interval.

- From long term impact studies, both 4 week and 8 week intervals have been used in a number of countries with good sustained impact.

Effect of combination vaccines

- Data do not suggest clinically relevant decreases in Hib efficacy or interference with other antigens with the use of combination vaccines compared with monovalent vaccines.

- There is some evidence of lower immunogenicity against Hib with the use of aP vaccines compared to wP vaccines, though little evidence of interference with other antigens in either combination.

- The clinical relevance of lower immunogenicity is unclear outside the UK, as is the necessity of a booster dose with the use of aP containing vaccines.

Herd immunity

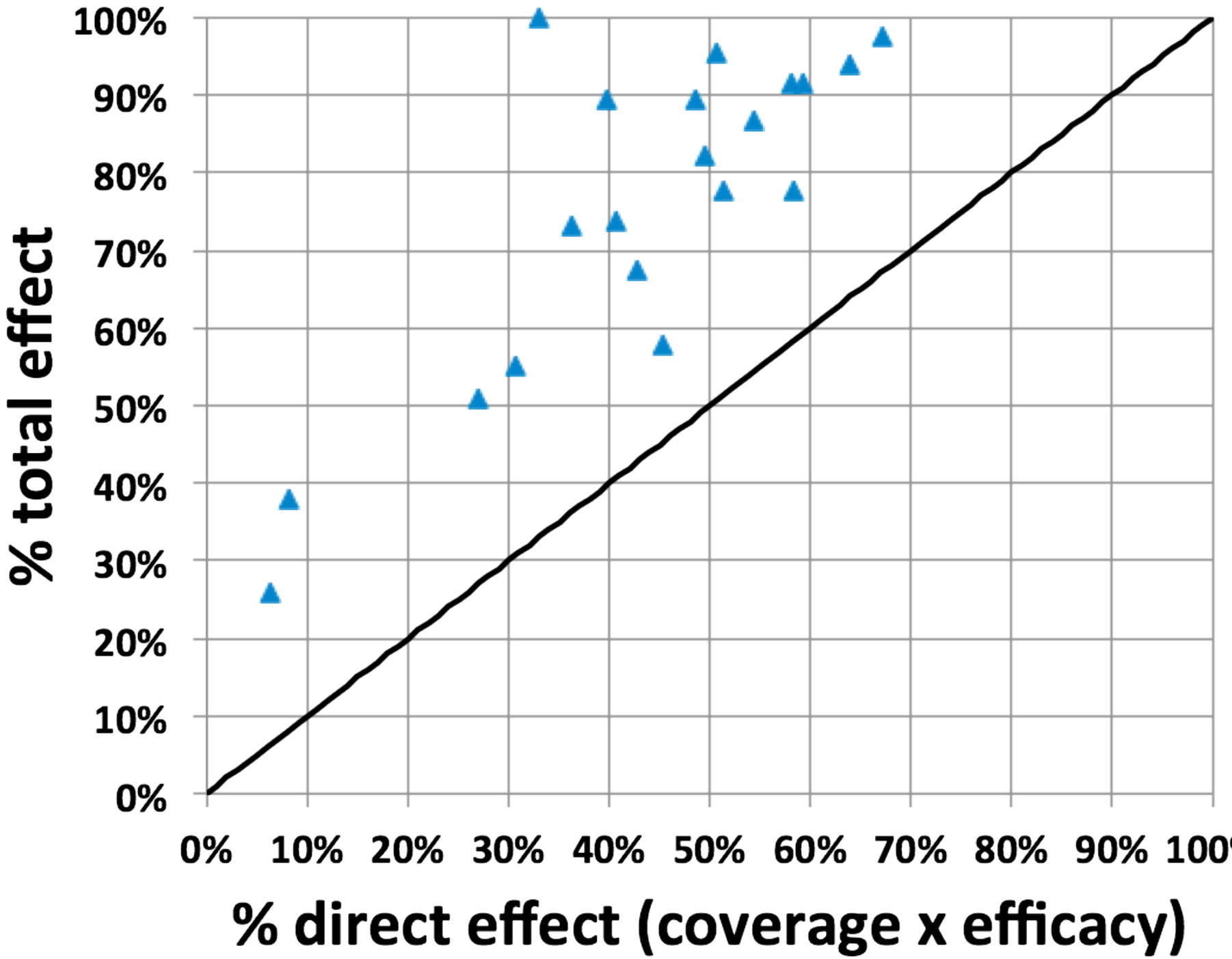
Systematic review of Hib vaccine herd effect <5yrs: total impact vs expected direct impact

- Observed total impact
  - % reduction in Hib meningitis/invasive disease <5yrs
- Expected direct impact
  - Hib dose 3 coverage x 93% efficacy (Griffiths et al, meta-analysis)
- Restricted to studies with weighted average of dose 3 coverage in under five population
  - 24 studies from 8 countries

Estimated herd effect <5yrs by comparing observed total impact with expected direct impact

24 data points

Australia = 2
Brazil = 12
Cuba = 1
France = 1
Kenya = 2
Senegal = 1
Spain = 3
Tonga = 2



Walker N et al, unpublished

Evidence gaps

- **Long term impact of Hib vaccine in developing countries**

- **Effect of various Hib schedules, especially in developing countries**

- **Effect of Hib vaccines administered in combinations containing aP**

Research priorities

- **Ongoing surveillance to monitor long term impact and possible disease resurgence in selected high quality surveillance sites.**
- **Evaluation of need for booster in HIV-infected children.**
- **Assessment of impact on Hib disease of switching to aP containing combinations**

Summary of Findings

- **Number of doses- at least 3 doses**
- **Either 3 or 2 primary doses (if part of a 2p+1 schedule)**

- **Need for booster - unclear**
- **Industrialized countries, most use boosters**
- **Developing countries, good impact demonstrated with 3p+0, need to further evaluate long term impact & need for booster**

- **Interval between doses- at least 4 weeks**

END