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Vaccination Schedules Past, Present and Future

Is there some rationale?

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Associate Director Center for Global Health

ADVAC 2014

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Conflict of Interest and disclosures

- **Research and consulting support**
  - Presiding a DSMB for sanofi-Pasteur, Inviragen and member of PATH and Novartis DSMB
  - Conducted public health vaccine studies sponsored by Bill and Melinda Gates Foundation
  - Consultacy for Takeda Vaccines
- **Other membership biases**
  - PAHO-WHO advisor on vaccine safety
  - International Committee of Pediatric Infectious Diseases Society

Definition of immunization schedule

A **vaccination schedule** is a series of vaccinations, including the timing of all doses, which may be either recommended or compulsory, depending on the country of residence.

"An immunization schedule is a schematic of the ideal timing of administration of one or more vaccines, based on the best opportunity to provide protection and minimize risk in the prevention of vaccine preventable diseases."

[Fom The Merck Manual, Eighth Edition, published 1950]

ROUTINE IMMUNIZATION PROCEDURES

Optional pediatric immunization schedules and timetables for the administration of booster or re-immunization doses are presented. A table outlining the use of human serum immune (gamma) globulin also is included. Although many pertinent details are given, actual dosage must be regulated according to individual circumstances and to the instructions accompanying packages of the various immunizing agents. (For special immunization procedures against such diseases as typhoid fever, yellow fever, cholera, plague, and other conditions not ordinarily included in pediatric practice, *see* the respective chapters.)

BASIC IMMUNIZATION

OPTIONAL SCHEDULE NO. 1

Age	Agent
3 months	Pertussis Vaccine (Alum Precipitated)
4 "	" " " "
5 "	" " " "
6 "	Diphtheria-Tetanus Toxoid (Alum Precipitated)
6 "	Smallpox Vaccine
7 "	Diphtheria-Tetanus Toxoid (Alum Precipitated)
11 "	Schick Test
11 "	Pertussis Vaccine (Alum Precipitated)

OPTIONAL SCHEDULE NO. 2

Age	Agent
As soon as umbilicus is healed and baby is thriving	Smallpox Vaccine
3 months	Diphtheria-Tetanus-Pertussis (Alum Precipitated or Aluminum Hydroxide Adsorbed)
4 "	Diphtheria-Tetanus-Pertussis (Alum Precipitated or Aluminum Hydroxide Adsorbed)
5 "	Pertussis Vaccine (Alum Precipitated)
7 "	Diphtheria-Tetanus-Pertussis (Alum Precipitated or Aluminum Hydroxide Adsorbed)
11 "	Schick Test

BOOSTER DOSES AND RE-IMMUNIZATION

(This schedule applies only when basic immunization has been previously accomplished.)

Age and Indication	Agent
2 years	Diphtheria-Tetanus-Pertussis (Alum Precipitated or Aluminum Hydroxide Adsorbed)
5 "	Diphtheria-Tetanus-Pertussis (Alum Precipitated or Aluminum Hydroxide Adsorbed)
5 "	Schick Test
Every 2 years	Smallpox Vaccine
Every 5 years or upon exposure to smallpox, or during threatened smallpox epidemic	Tetanus Toxoid (Alum Precipitated)
Any age, upon possible exposure to tetanus	Smallpox Vaccine
Any age, upon exposure to diphtheria	Fluid Tetanus Toxoid
Any age, upon exposure to pertussis	Fluid Diphtheria Toxoid
	Pertussis Vaccine (N.B., in Isotonic Saline)

Immunization Schedules in the United States and Great Britain -1967-68

TABLE 1. Recommended schedules for routine immunization

United States*					England and Wales†					
Age	DTP	OPV	M	SP	Age	DTP	OPV	M	SP	BCG
2–3 months	X	X			3–6 months	X	X			
3–4 months	X									
4–5 months	X	X			5–8 months	X	X			
12–18 months	X	X	X		9–14 months	X	X			
12–24 months				X	12–24 months			X	X	
School entry (3–6 years)	X	X		X	School entry (3–6 years)	Td	X		X	
					10–13 years					X
Every 10 years	Td			X‡	School leaving	Td	X		X	

DTP, Diphtheria–tetanus–pertussis vaccine; OPV, oral poliovaccine; M, measles vaccine; SP, smallpox vaccine; Td, tetanus-diphtheria toxoid, adult type.

* Adopted from United States Public Health Service (1967): *Immunization Against Disease* 1966–67 (National Communicable Disease Center publication).

† Adopted from Ministry of Health (1968a, b).

‡ For high risk groups, i.e. health personnel and overseas travel—every 3 years.

Karzon, DT. *Postgrad Med J* 45; 147: 1969

1961 – 1st Schedule Published by WHO

(Report of the technical discussions at the Thirteenth WHA)

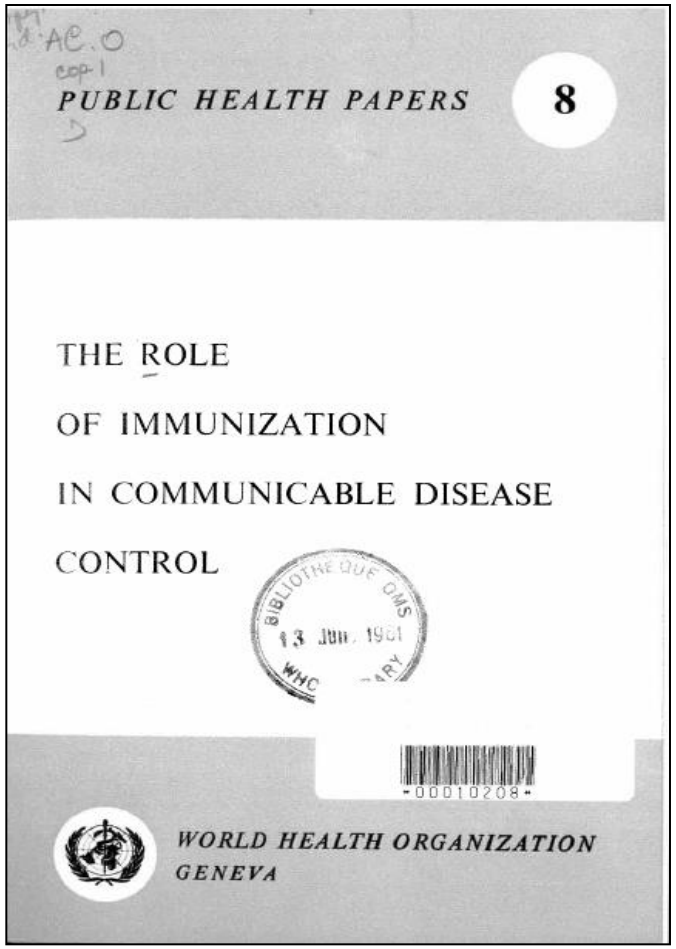

TABLE 2. SUGGESTED SCHEDULE OF IMMUNIZATION IN AREAS WITH INADEQUATE MEDICAL SERVICES; TO BE MODIFIED AS REQUIRED TO SUIT LOCAL CONDITIONS

Age	Vaccination	Visit
0-4 weeks	(1) BCG vaccination	1st
3-9 months	(2) Smallpox vaccination (3) Diphtheria-pertussis-tetanus (triple vaccine with alum): 2 doses at an interval of one month The first injection could be given at the time of smallpox vaccination. Smallpox vaccination is verified at the second visit. Failures of smallpox vaccination are revaccinated.	2nd and 3rd
School entry or soon thereafter	(4) Diphtheria/tetanus booster (plain or with alum) (5) TAB vaccination (where necessary): 2 doses at an interval of one month (6) Smallpox revaccination: at the time of second TAB injection	4th and 5th
10-14 years	(7) BCG revaccination (in tuberculin-negative reactors) (8) Smallpox revaccination (9) TAB booster	6th and 7th

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Courtesy of P. Duclos, WHO

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Expanded Program of Immunization

1974 — World Health Organization — **1980**

Founded by WHA27.57

- DTP3 @ 5%
- No schedule
- Program and personnel support

- DTP3 @ 20%
- Primary health care based

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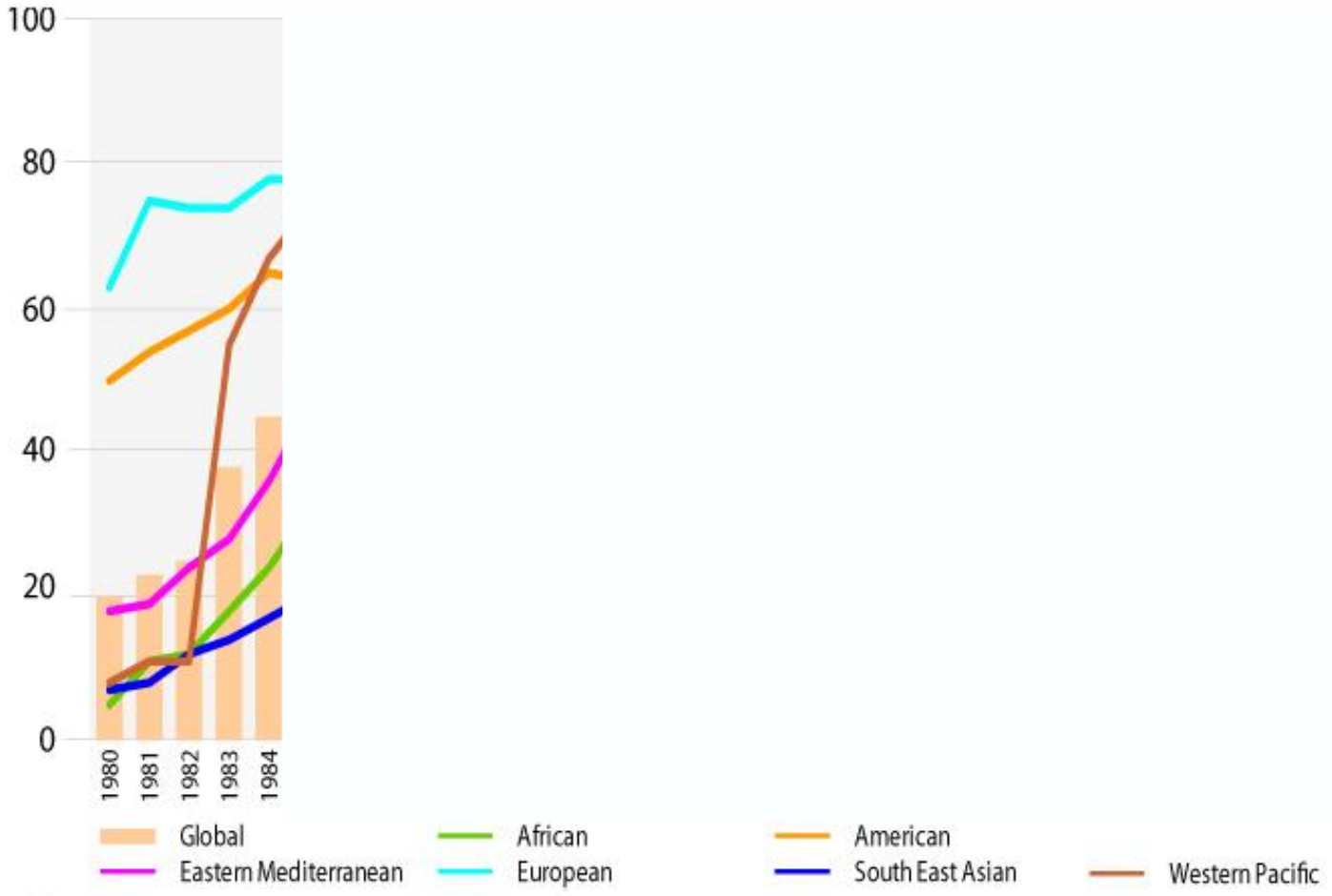
World Health Organization

Diphtheria-tetanus-pertussis (DTP3) immunization coverage (%) Global and by WHO region, 1980–2012



Source: WHO/UNICEF coverage estimates 2012 revision. July 2013.

Why are schedules important?

- **Programmatic:** framework for delivery of vaccines to target population
- **Evaluation of coverage**

Expanded Program of Immunization

World Health Organization

Founded by WHA27.57

- DTP3 @ 5%
- No schedule
- Program and personnel support

- DTP3 @ 20%
- Primary health care based

- DTP3 @ 41%
- >20 schedules
- Revision of evidence needed

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1984: Review of the Evidence on DTP and OPV Immunization Schedules

Goals:

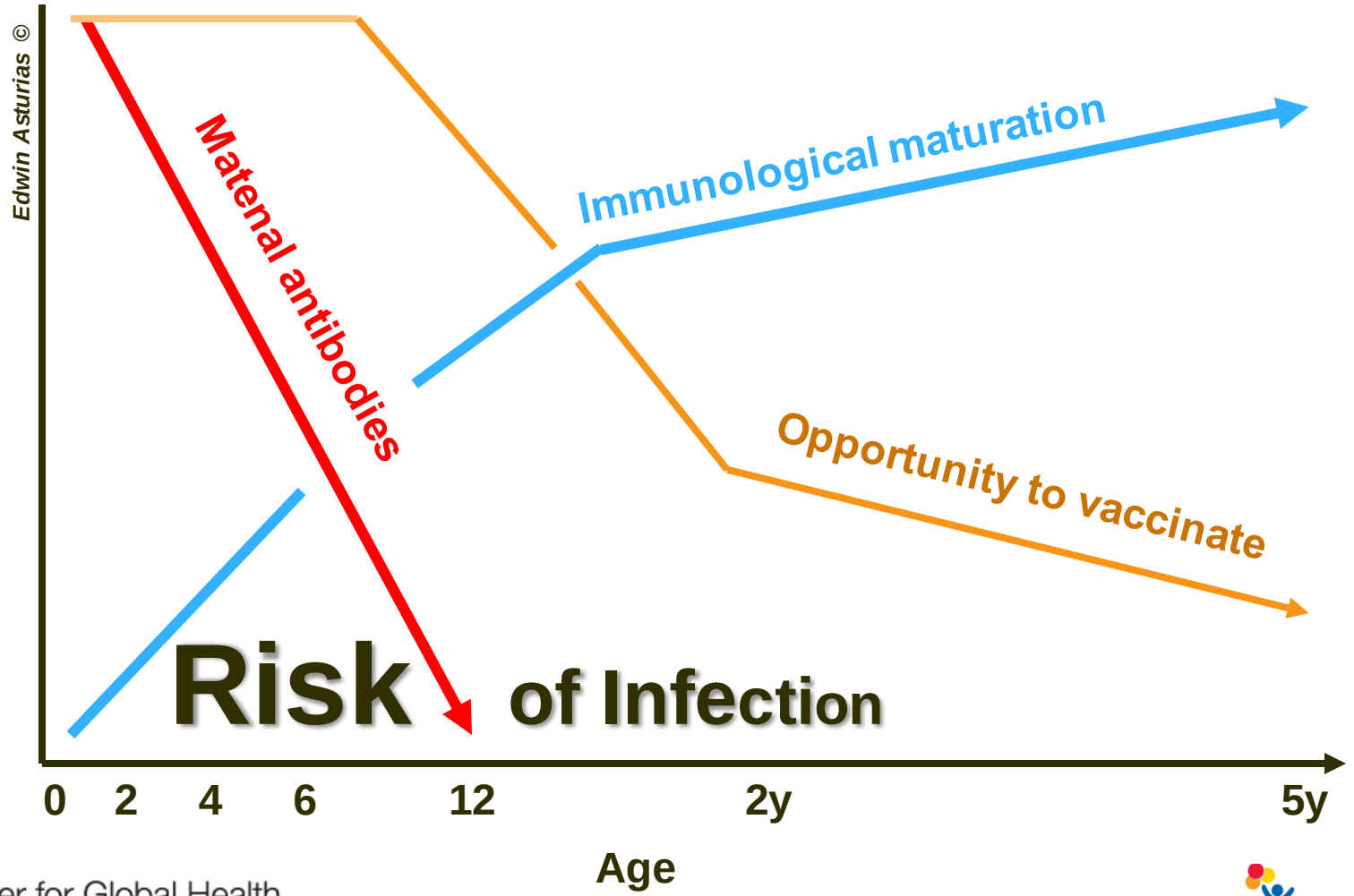
① Complete primary series as early as possible to increase coverage

② Identify earliest starting age

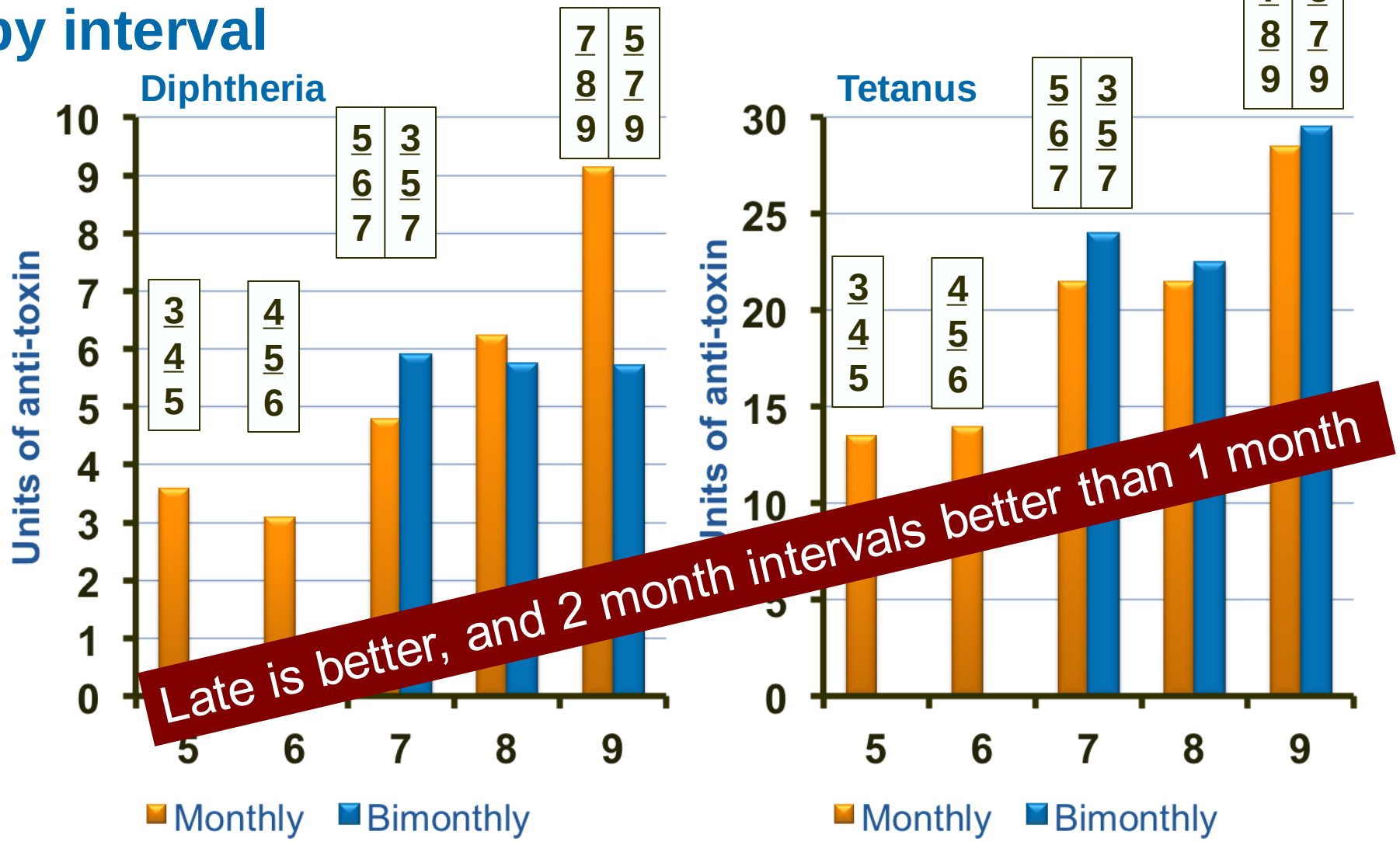
③ Define shortest effective intervals between doses

Halsey NA, Galazka A. The efficacy of DPT and oral poliomyelitis immunization schedules initiated from birth to 12 weeks of age. *Bull WHO; 63:1151-69, 1985*

Determinants of vaccination schedules in children…



GMC responses to diphtheria and tetanus in children receiving 3 doses of DTwP-IPV by interval



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Modified from
Brown GC et al AJPH 1964;79 (7):585

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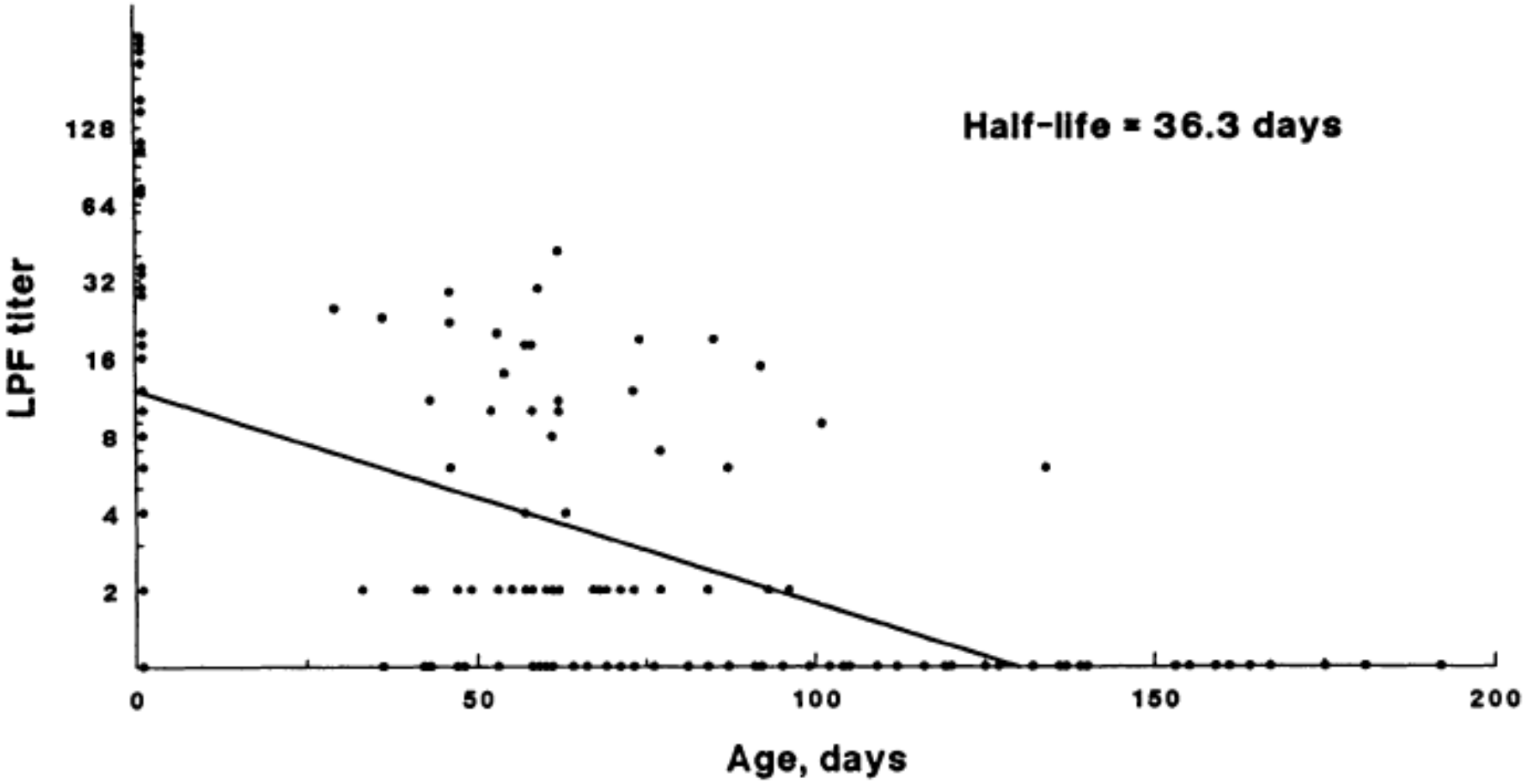
Antibodies to PT (LPF) antigen in unimmunized infants (ELISA units/mL)



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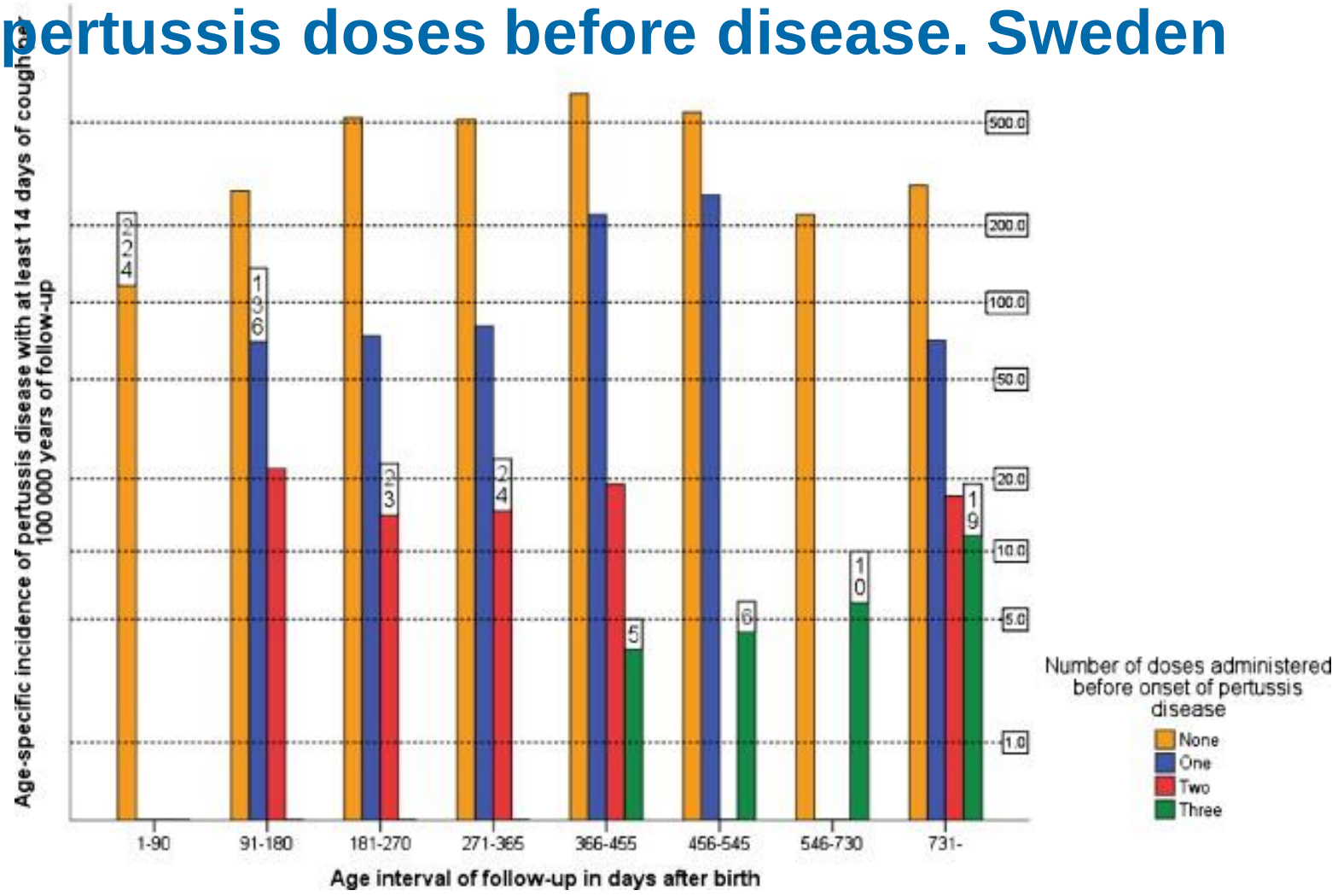
Van Savage J. J Infect Dis. 1990 Mar;161(3):487-92.

Age-specific incidence of lab-confirmed pertussis for infants born 1996 & 2007 by pertussis doses before disease. Sweden



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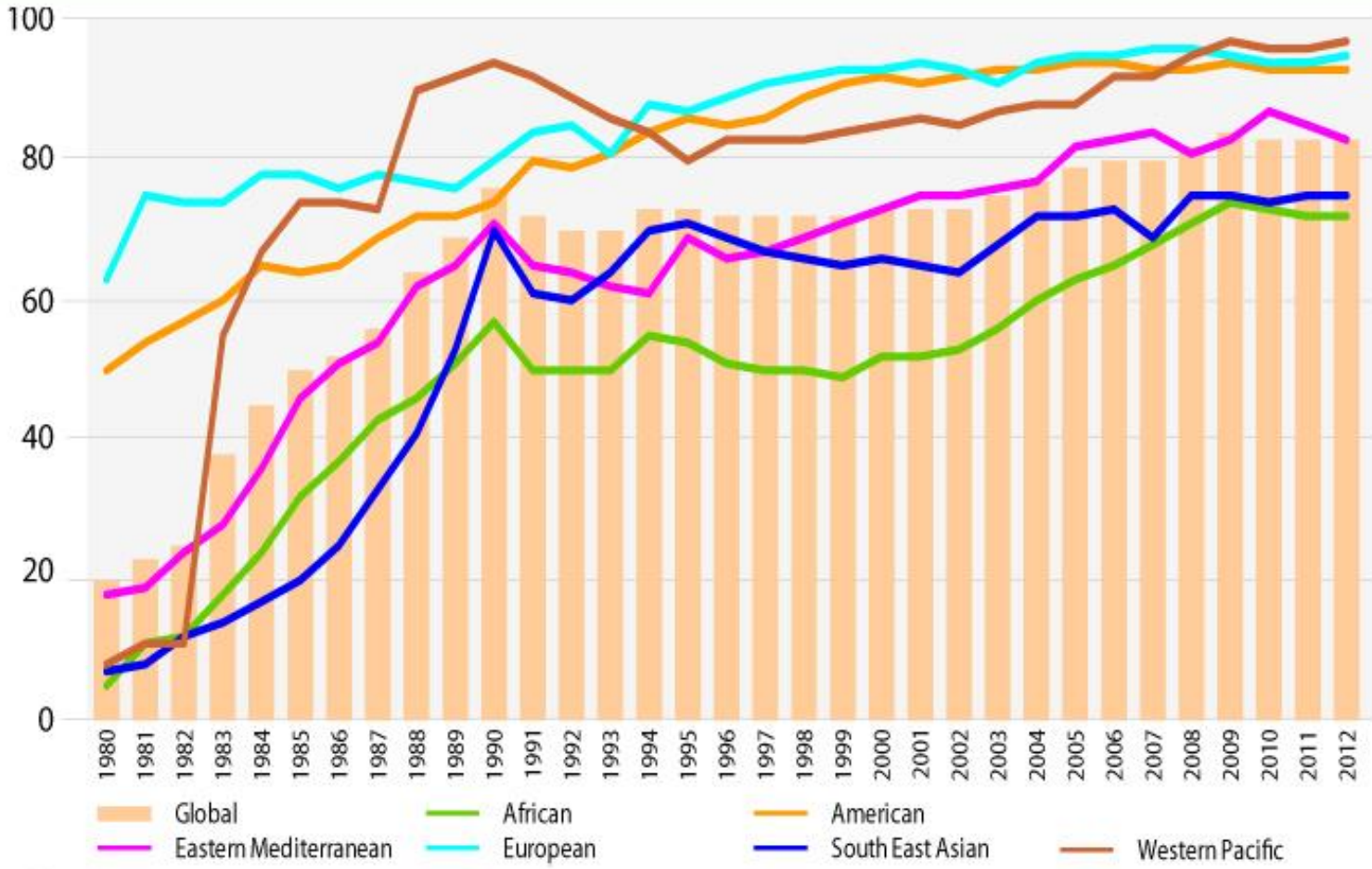
Diphtheria-tetanus-pertussis (DTP3) immunization coverage (%) Global and by WHO region, 1980–2012



Source: WHO/UNICEF coverage estimates 2012 revision. July 2013.

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EPI program success around the world

Vaccine Preventable Disease	Global cases (2011)	Estimated Global Deaths (2004)	Global Vaccine Coverage (2011)	% Reduction from reported peak
Diphtheria	4,880	5,000	84%	95.1%
Neo Tetanus	4,214	163,000	84%	86.8%
Pertussis	162,047	254,000	84%	91.8%
Polio	223[$]	<1000	84%	99.8%
Hepatitis B		600,000	75%	NA
Measles	354,820	*164,000	84%	80.5%

2008, [§] >90% coverage
[$] 2012

http://www.who.int/immunization_monitoring/diseases/en/

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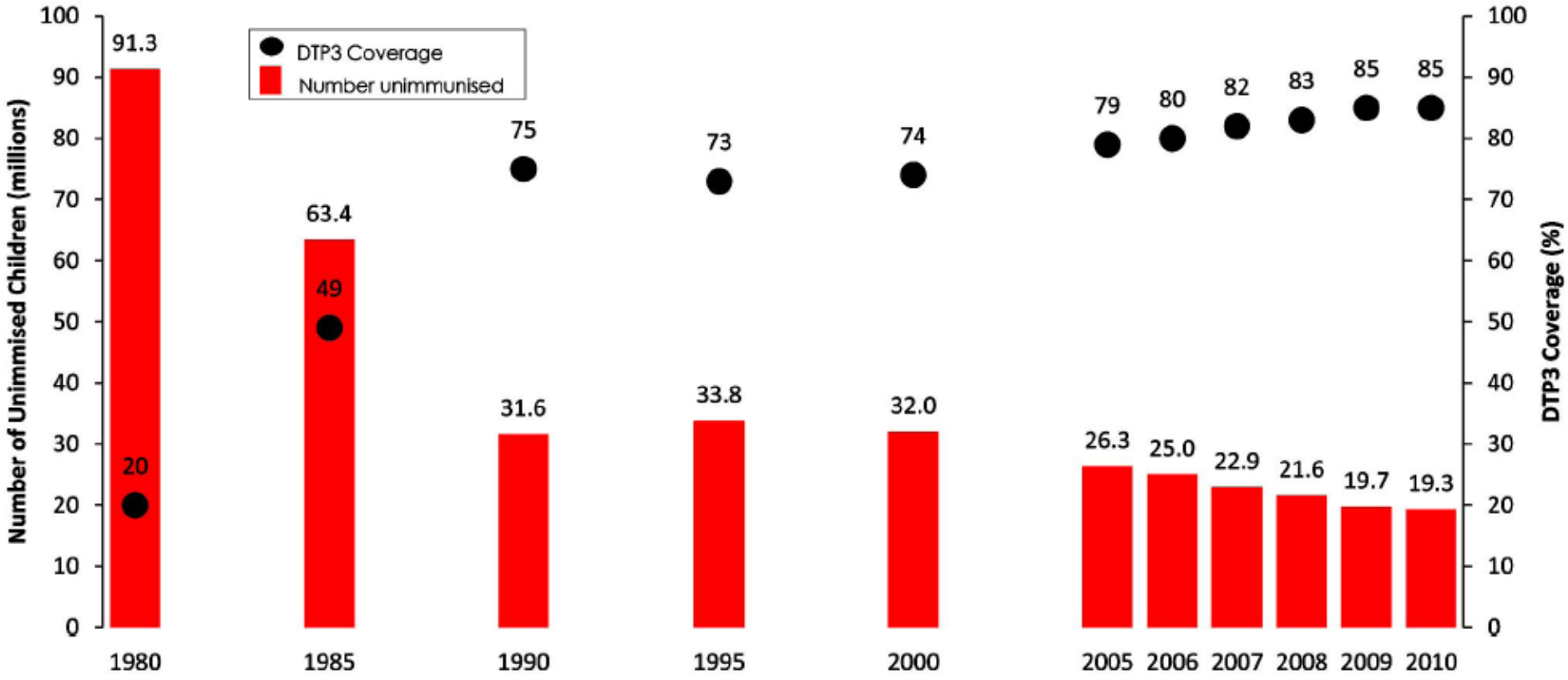
Prepared by E. Asturias

Global routine immunization coverage with 3 doses DTP and unimmunized surviving infants by year



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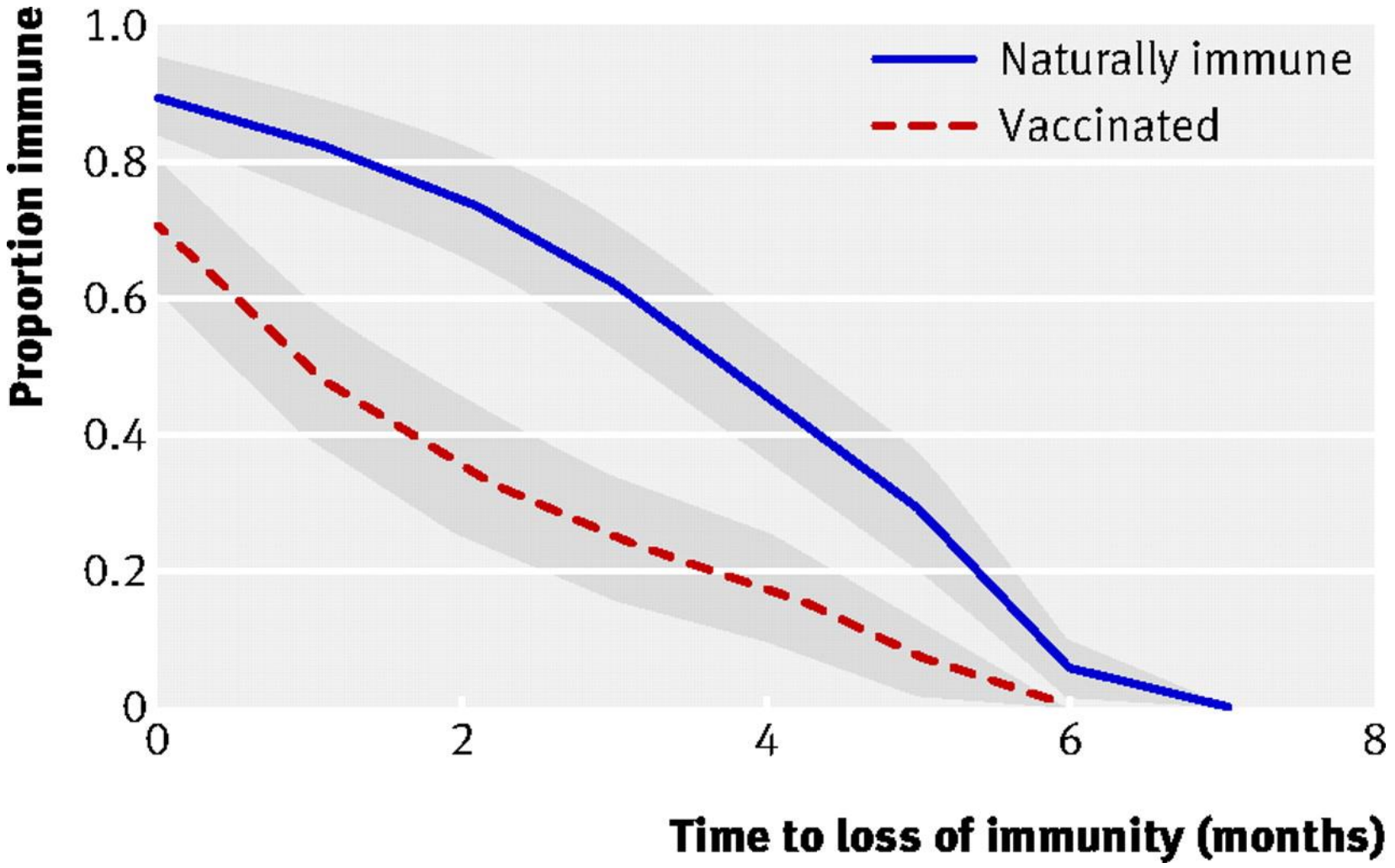
Brown DW. *Open ID Journal.* 2011 (5) 115

Seroconversion rates by age in developing countries after measles immunization

Country	Seroconversion (%) by age in months								Reference
	5	6	7	8	9	10	11	12	
Haiti		45	71	77	84	94	95	100	Halsey 1985
Ivory Coast			84				95		Breman 1975
Kenya	60	90	67	100	93			100	MoH 1977
Kenya	<50	40	93	90	93	94	100	100	EPI 1979
Latin America		58	69	82	85	92	89	92	PAHO 1982
Nigeria			64				89		Ruben 1973
Rhodesia		71			94				Burrowes 1976
South Africa		23	45	57	*86	71	*86	*80	Dick 1975

* Less than 10 children studied

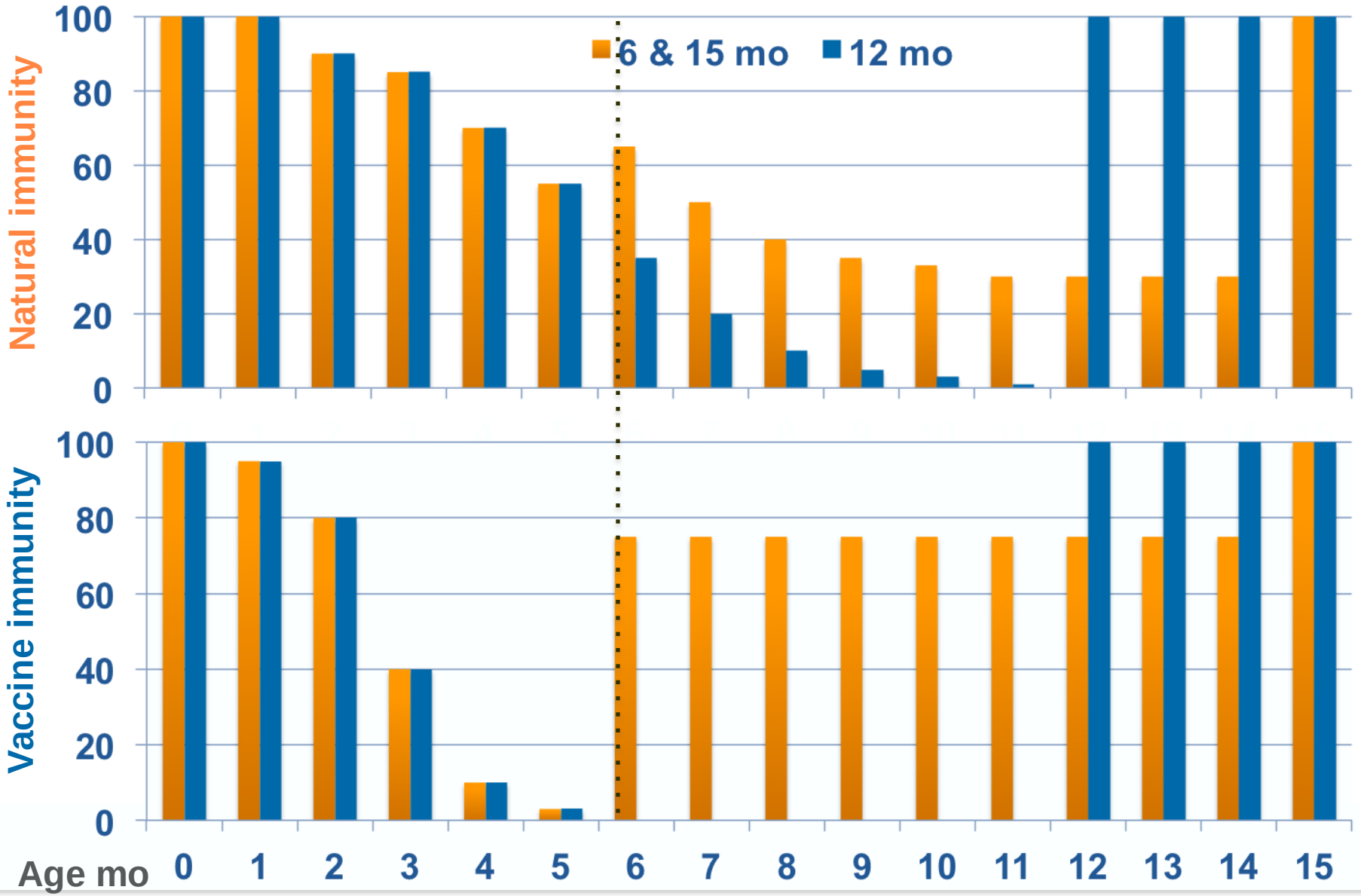
Early waning of maternal measles antibodies in era of measles elimination in Flanders, Belgium



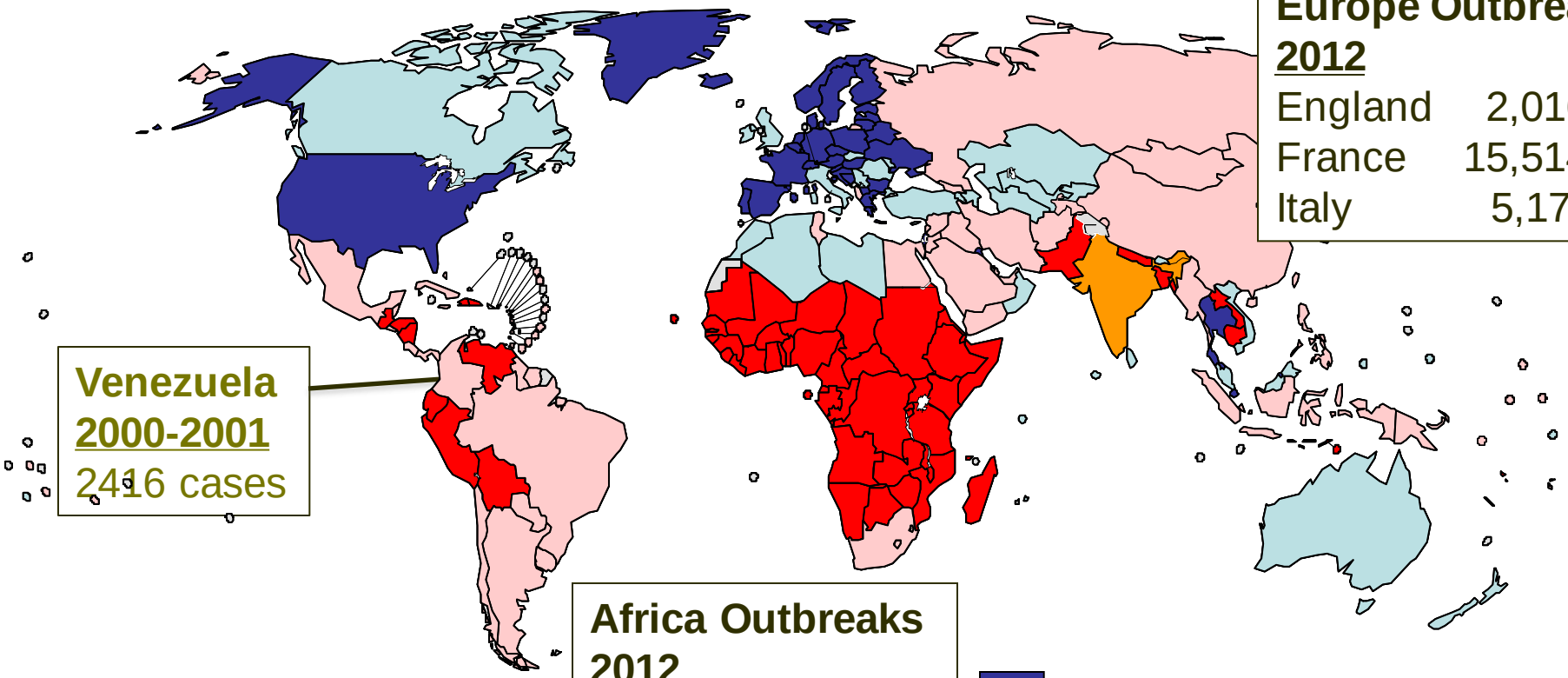
Leuridan E et al. BMJ 2010;340

Responses to 2 schedules of measles vaccine of infants from mothers with natural vs. vaccine induced immunity

H.F Pabst. Vaccine 1999; 17:182



Countries given 1 vs. 2 doses of MCV in their routine immunization schedules (2010)



Europe Outbreaks 2012

England	2,016
France	15,514
Italy	5,178

Venezuela 2000-2001

2416 cases

Africa Outbreaks 2012

Congo	1,650
Ethiopia	3,552
Kenya	2,452
Zambia	13,150

- MCV1 & MCV2, no SIAs *(40 member states or 21%)*
- MCV1, MCV2 & one-time catch-up *(36 member states or 19%)*
- MCV1, MCV2 & regular SIAs *(57 member states or 28%)*
- MCV1 & regular SIAs *(59 member states or 31%)*
- Single dose *(1 member state or 1%)*

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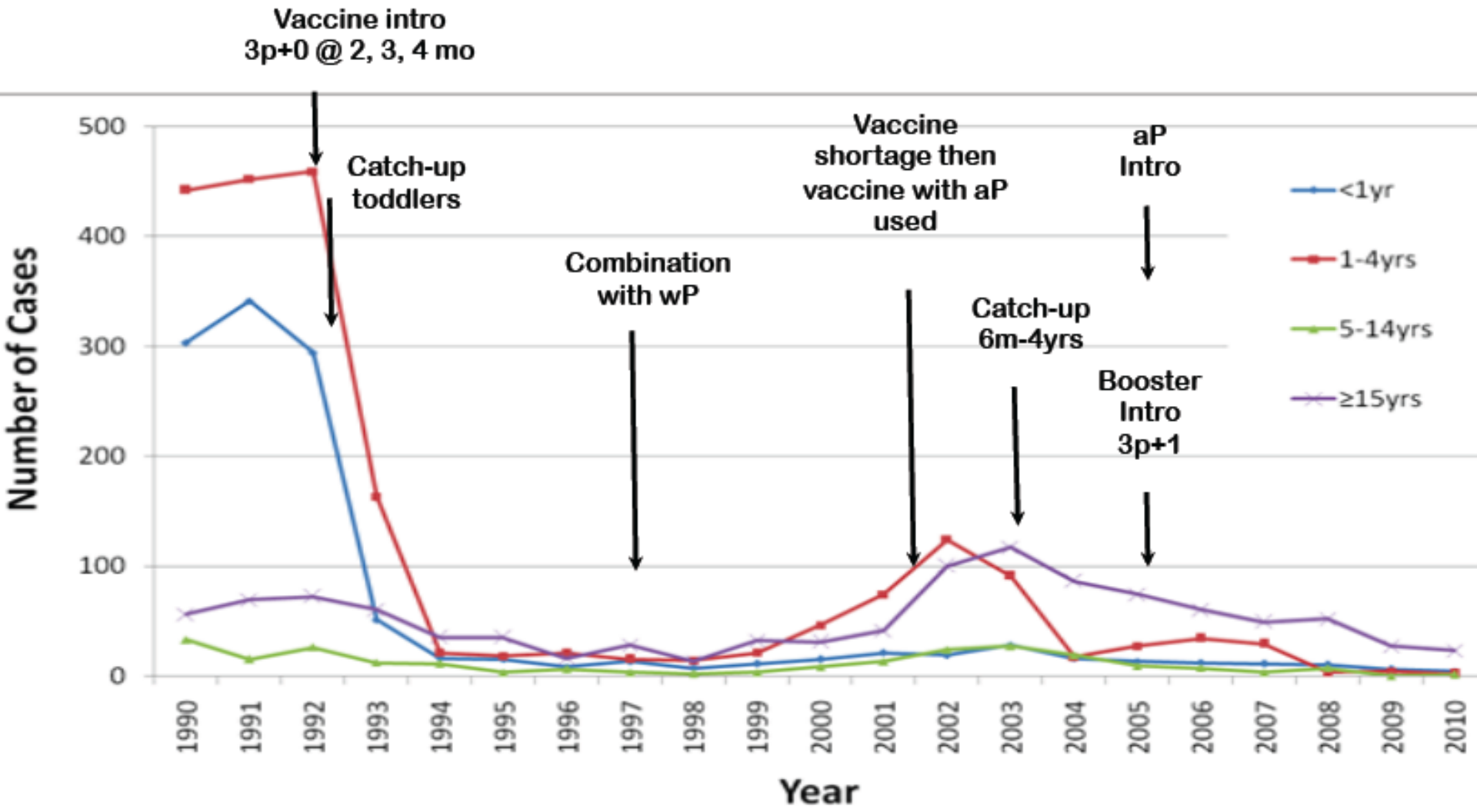
Incidence of Hib disease in the UK



http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HaemophilusInfluenzaeTypeB/

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Health Protection Agency

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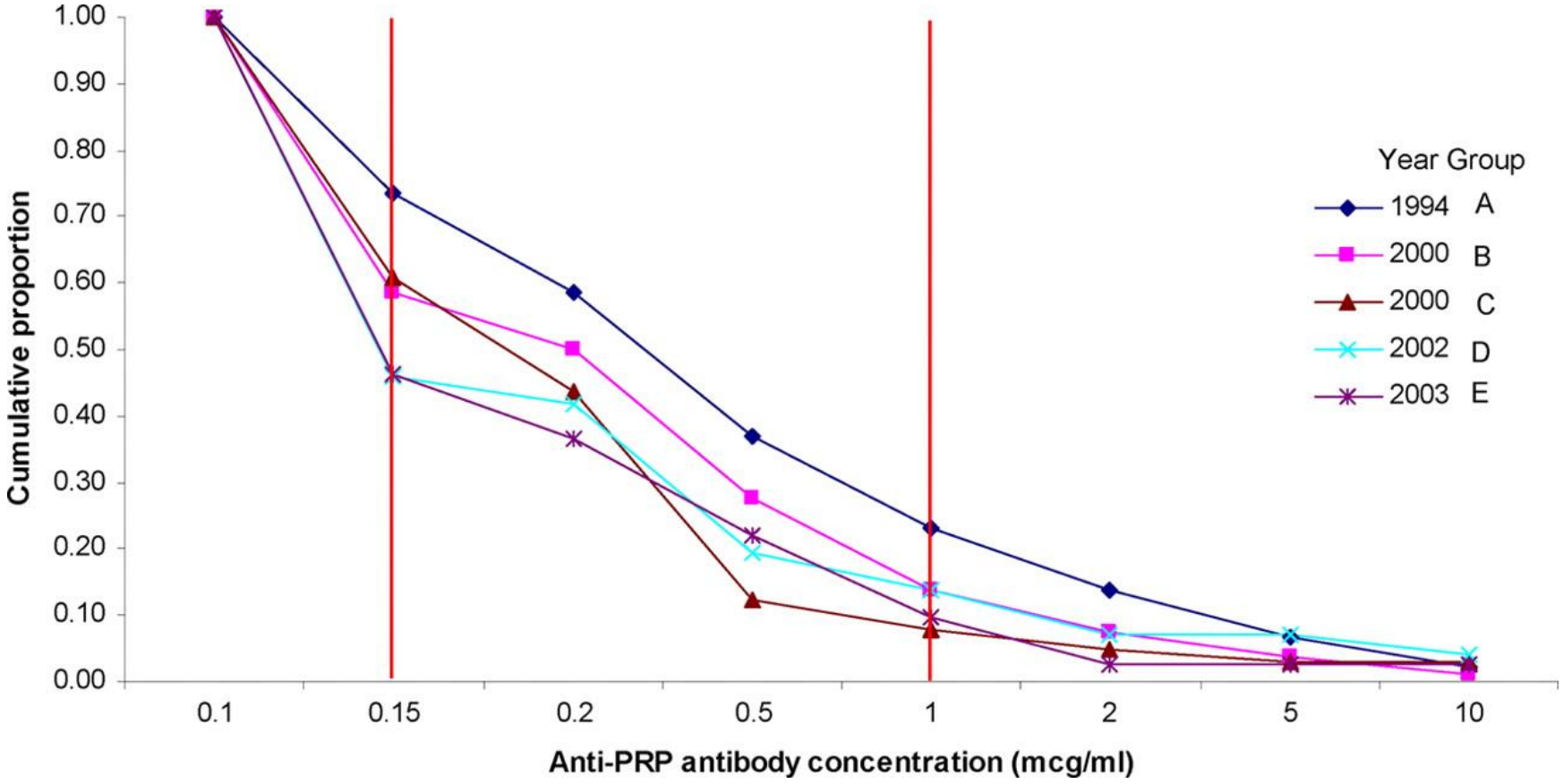
Reverse cumulative distribution of anti-PRP antibody concentrations (µg/ml) for groups of children whose sera were collected between 1994 and 2003.



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Kelly D F et al. Clin. Vaccine Immunol. 2009;16:246-252

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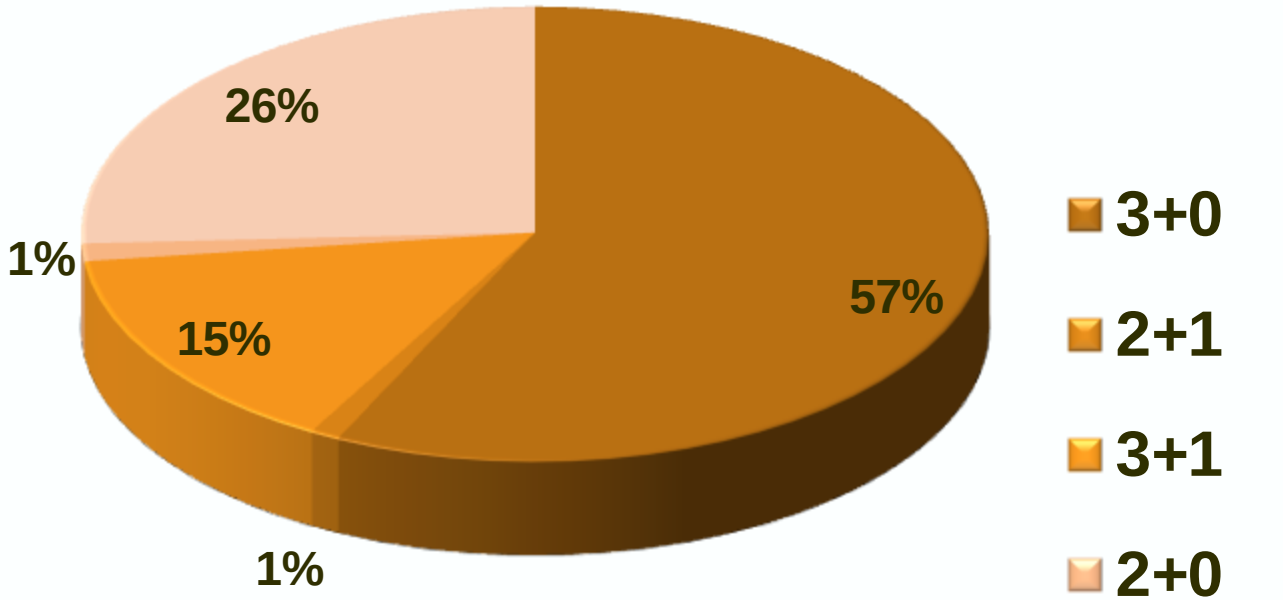
Countries having introduced Hib vaccine and infant Hib coverage, 2010

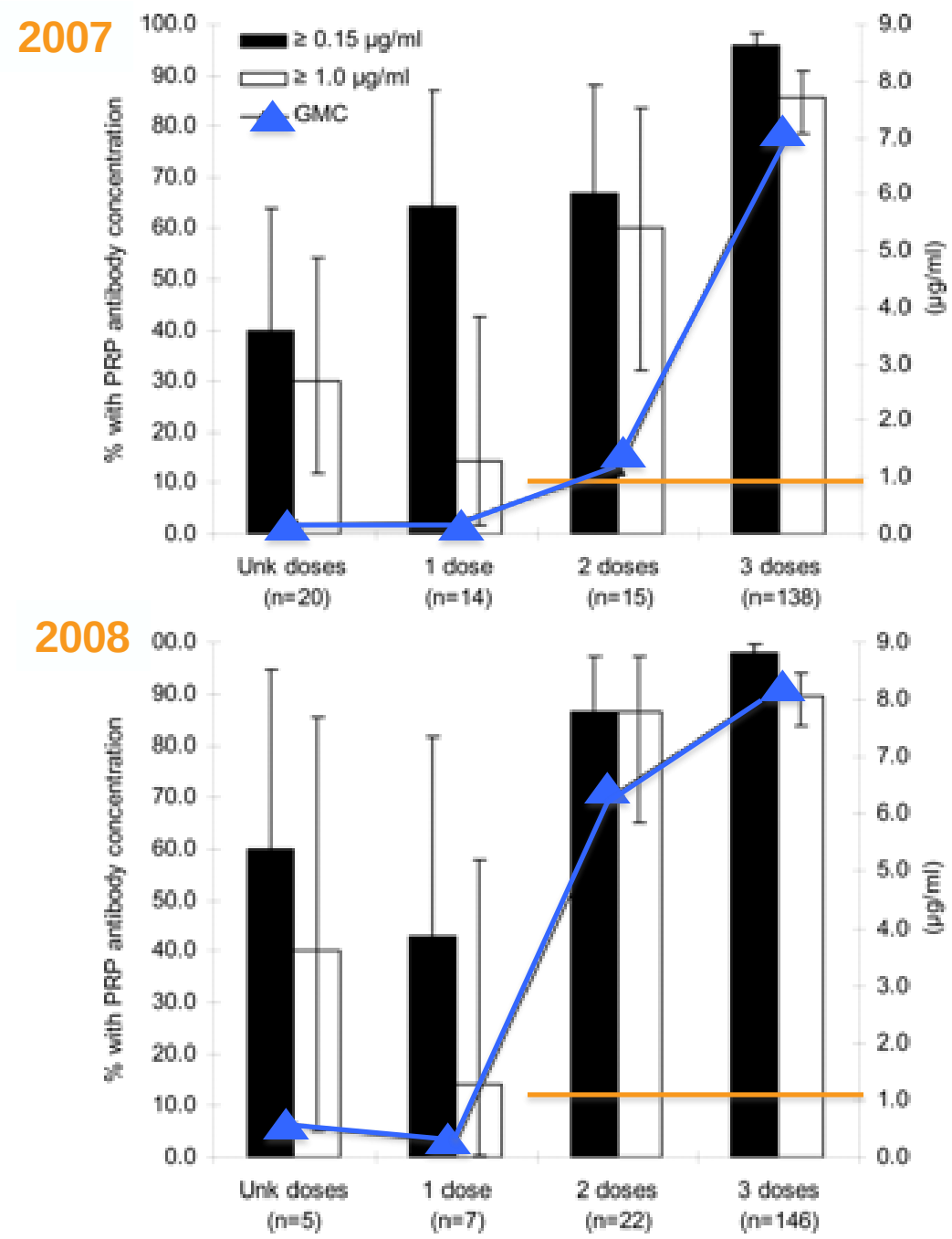
Percent of children by schedule globally



untries or 2%)

Hib vaccine not introduced (24 countries or 13%)

Percent of 6 to 7 month olds with serum anti-PRP concentrations in relation to the number of Hib vaccine doses received in Mali



Sow S. *Am J Trop Med Hyg* 2009 vol. 80 no. 6 1033-1038

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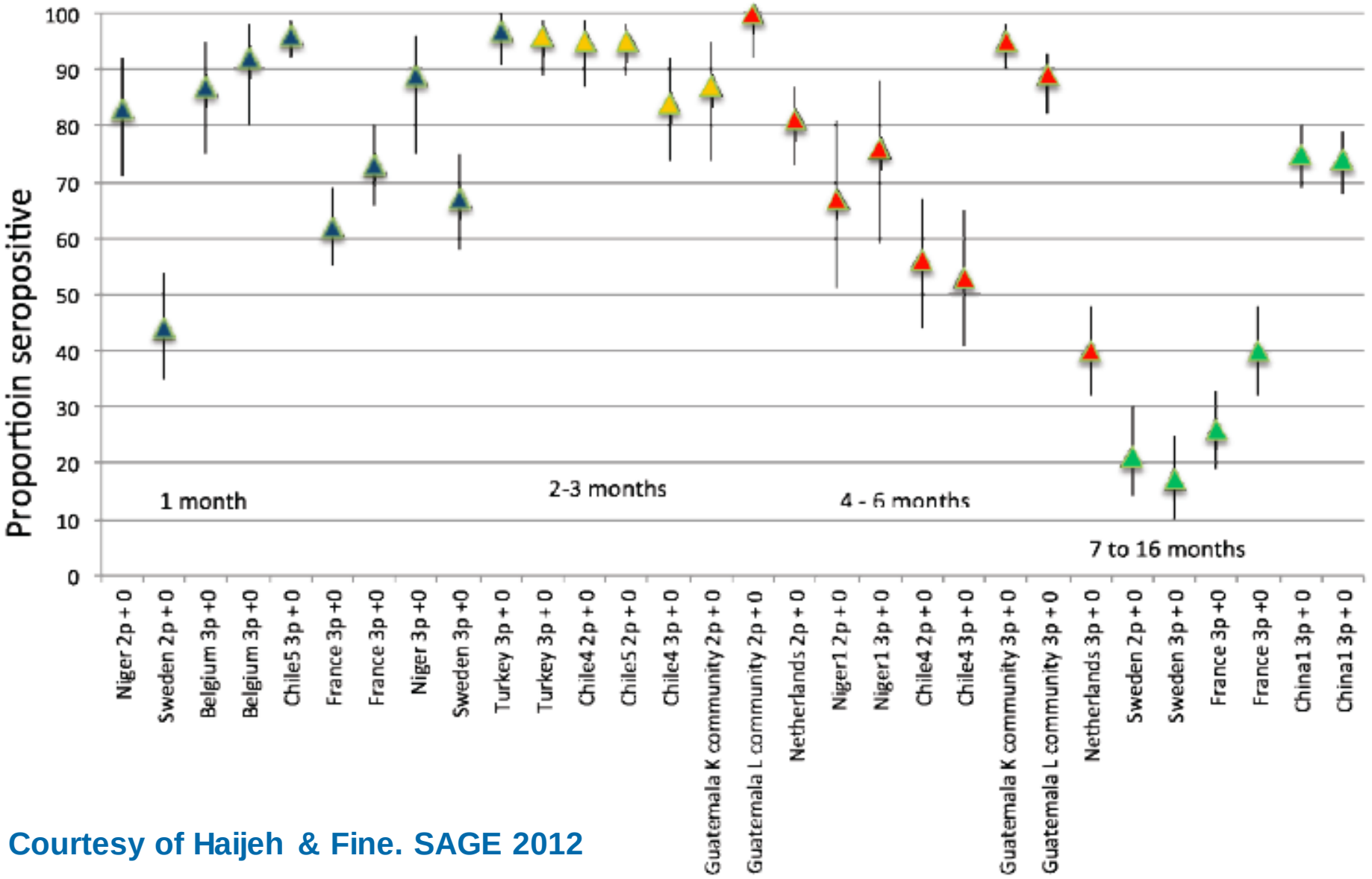
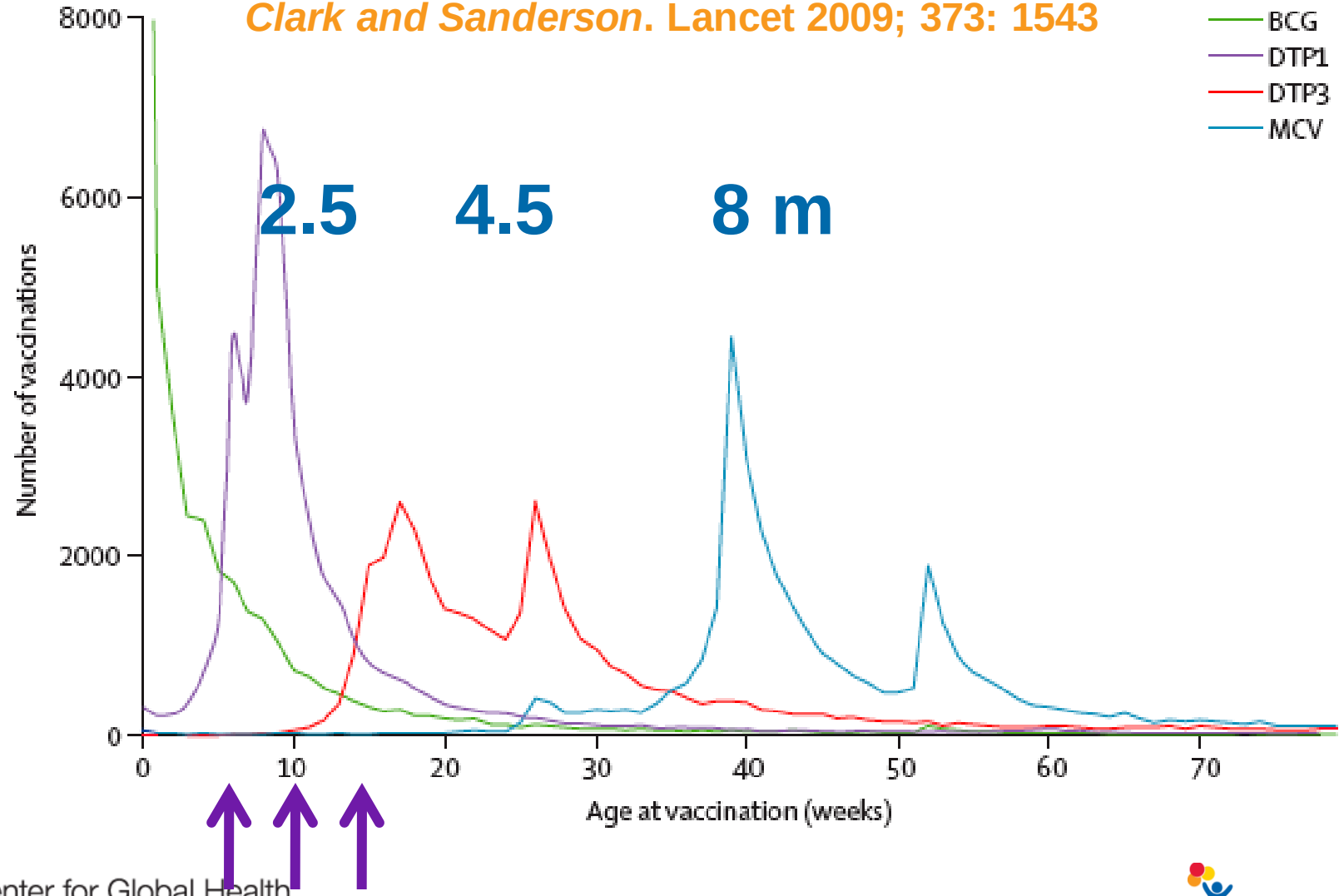
Duration of serologic responses to Hib (anti-PRP ≥ 1 mcg/mL in different countries with different schedules



Courtesy of Haijeh & Fine. SAGE 2012

Age distributions for administration of EPI vaccines in children aged 18–35·9 months

Clark and Sanderson. Lancet 2009; 373: 1543



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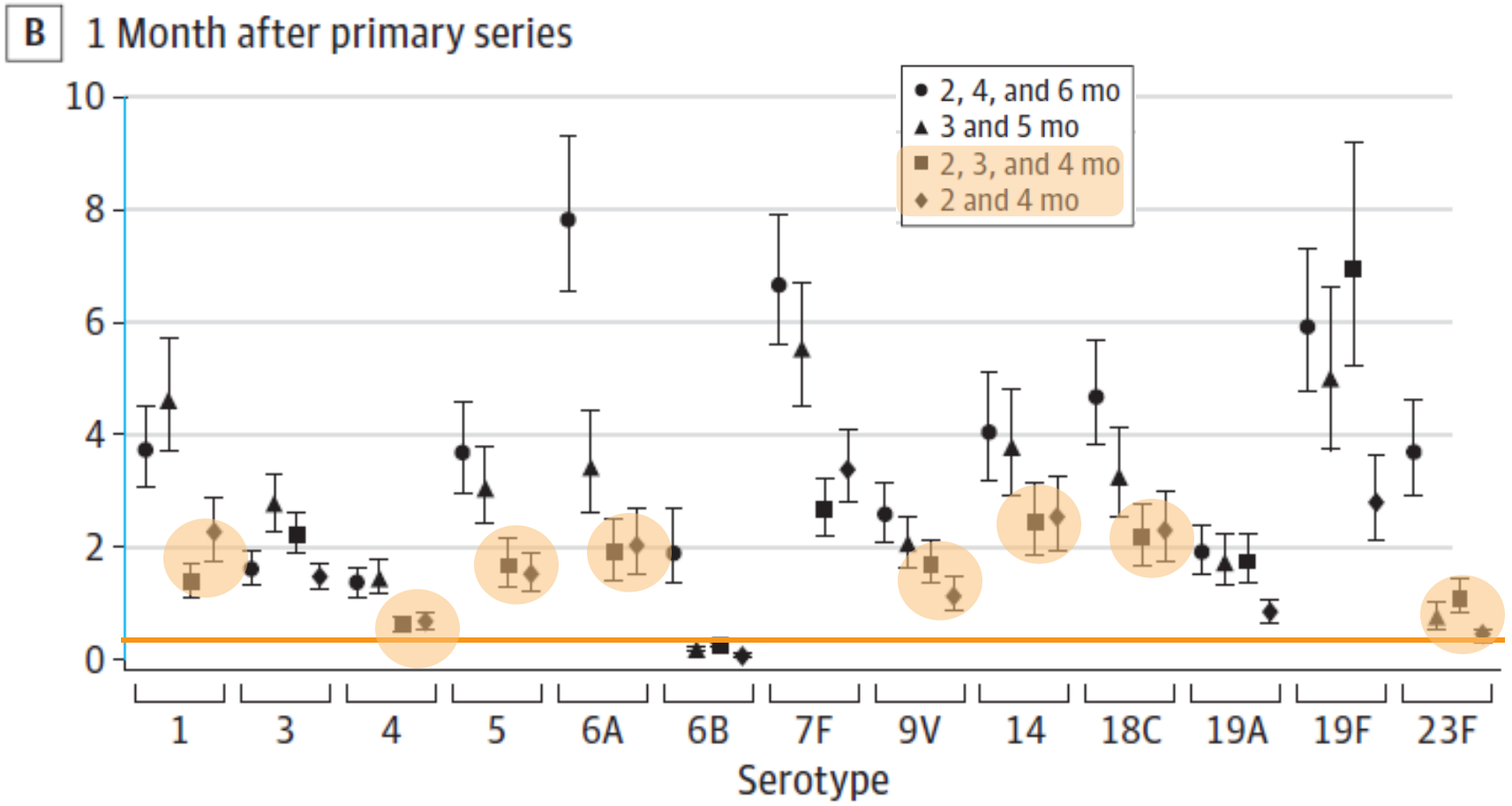
Pneumococcal Serotype-Specific Antibody GMCs Measured at 4 different Time Points (95% CI) in 4 different schedules in Netherlands



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Spijkerman et al JAMA. 2013;310(9):930-937.

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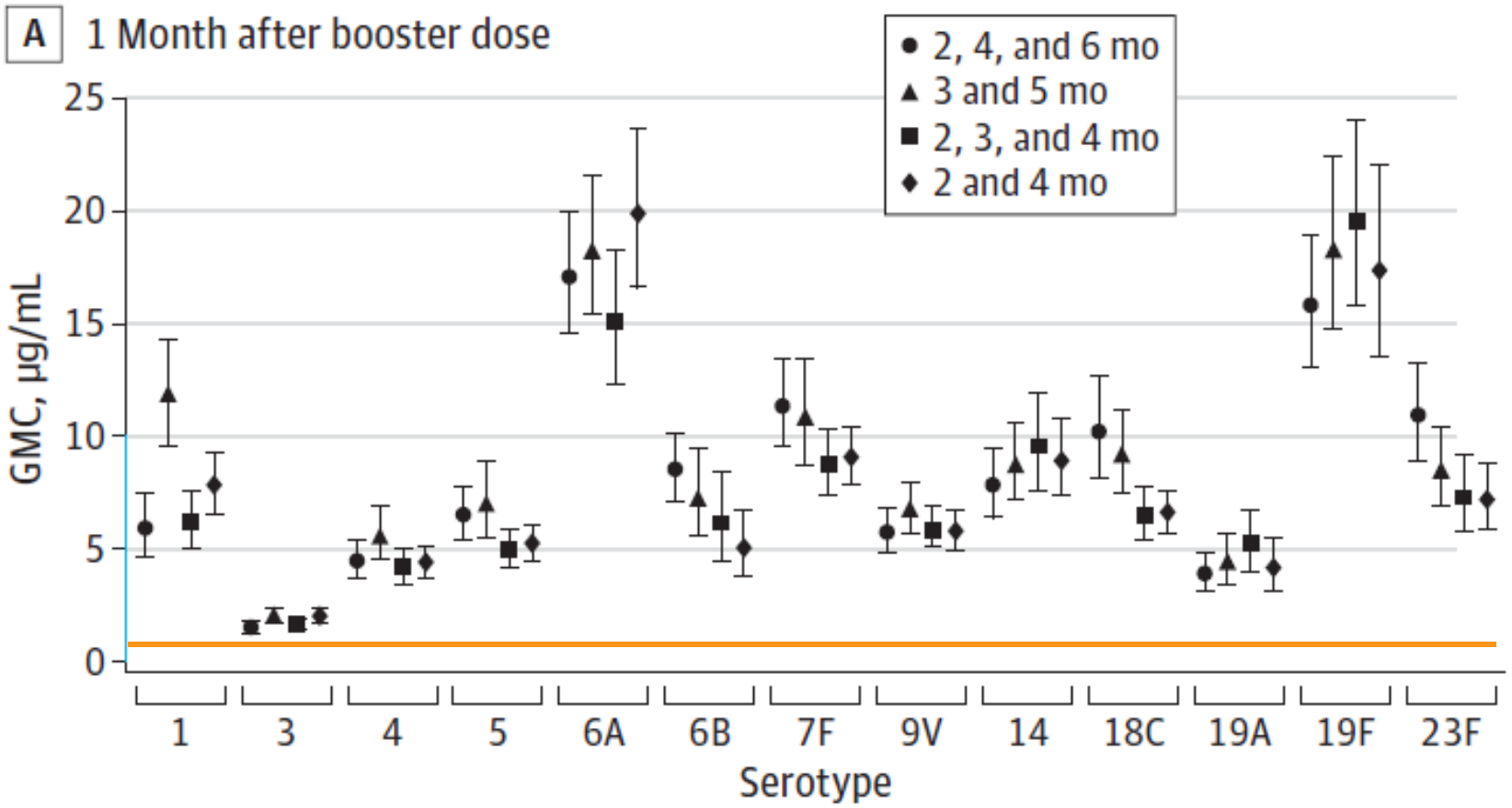

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Spijkerman et al JAMA. 2013;310(9):930-937.

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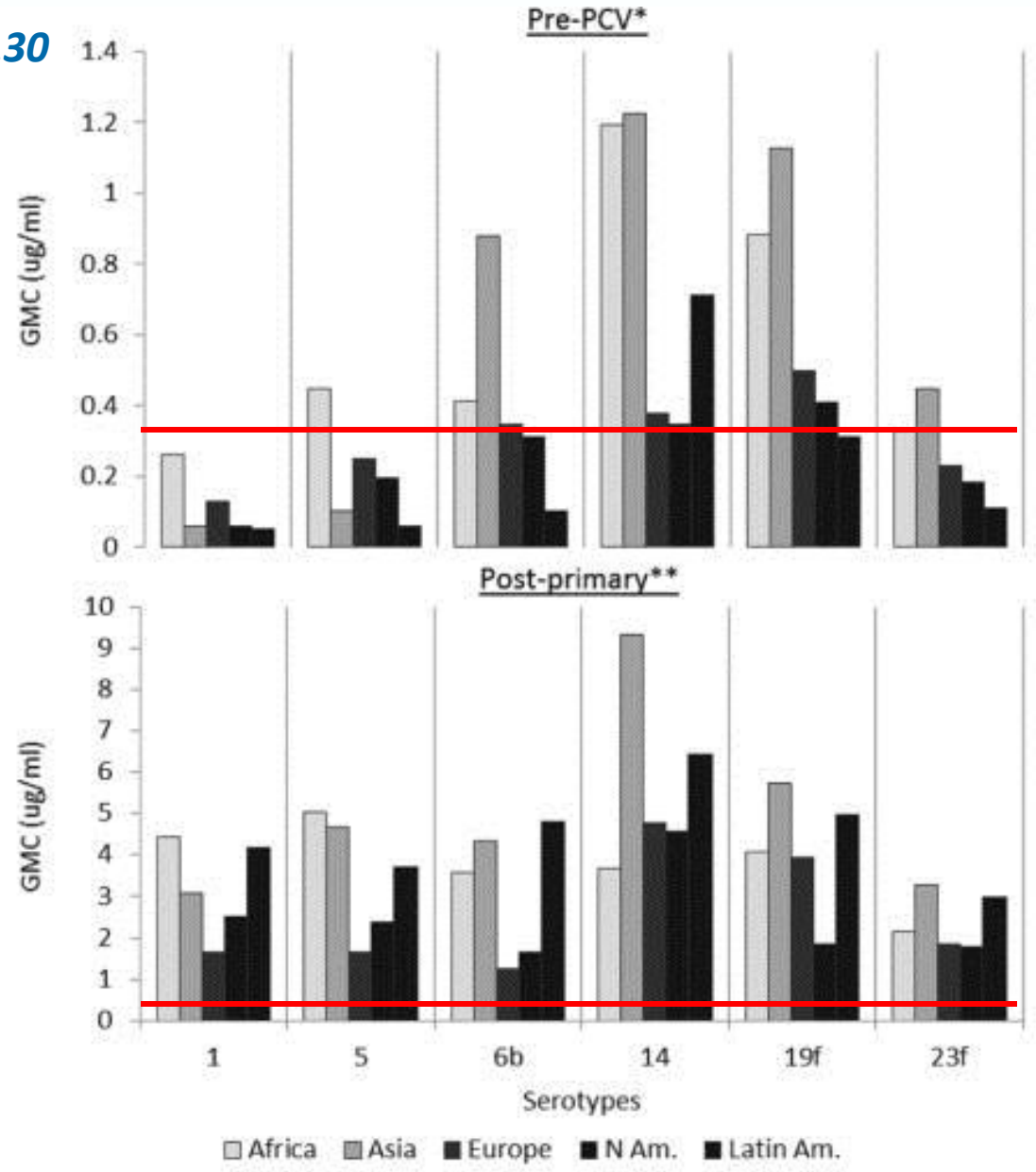
Average pre- and post-PCV pneumococcal IgG GMC in children by ST and geographic region 1994-2010

Park, Daniel; PIDJ 2014; 33 S130



* Children < 3 m

** Post 3 doses

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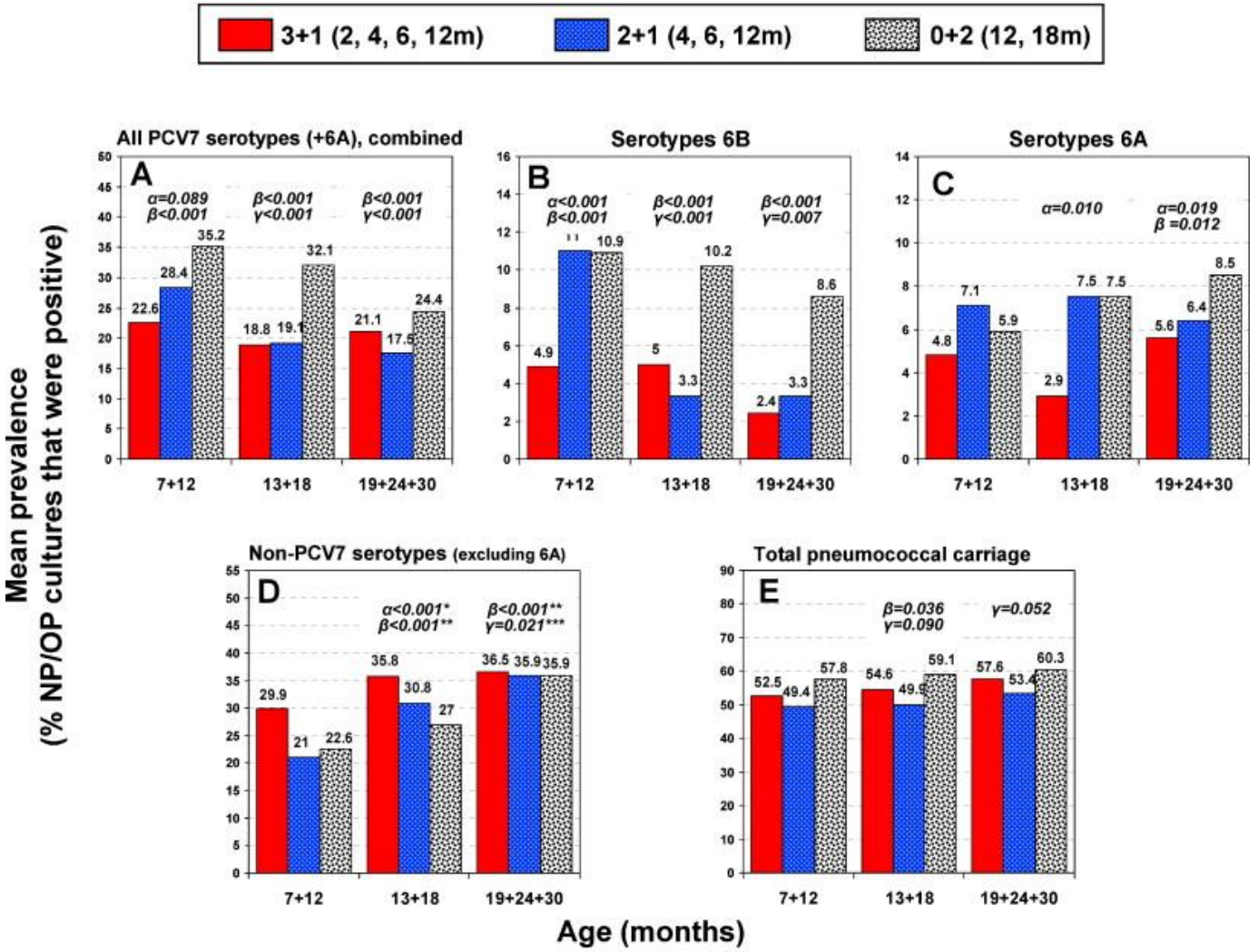
Prevalence of carriage by age and PCV serotypes by different schedules in Israel 2012



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Dagan R; Vaccine, (30) 34, 2012, 5132 - 5140

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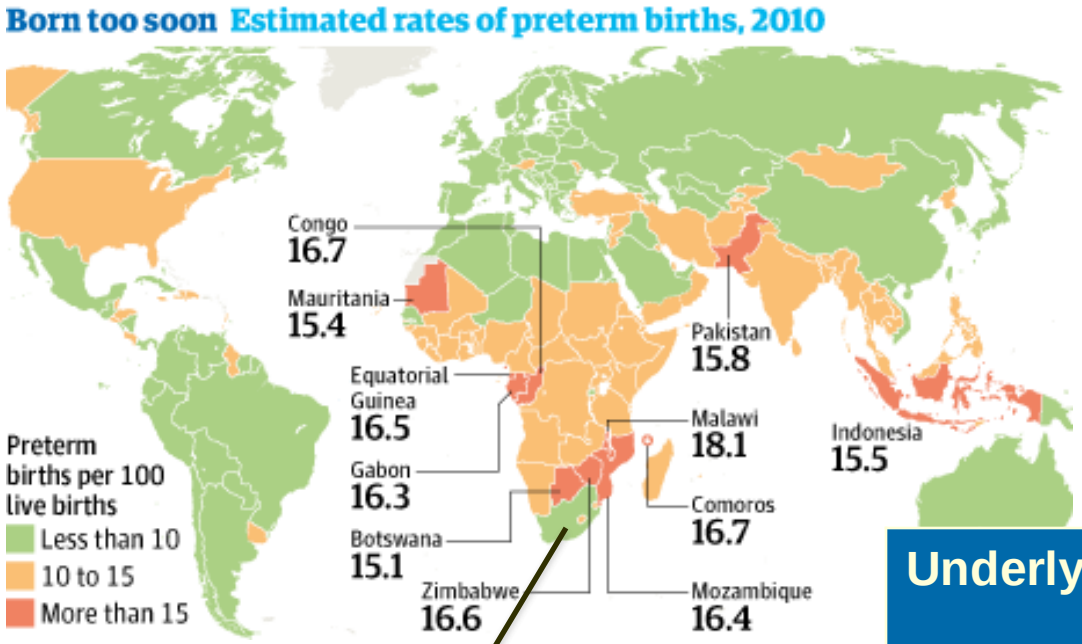
Special considerations for conjugate vaccine schedules (Hib & PCVs)



South Africa

Hib<5 years from 0.7 to 1.3/100,000 (2003 to 2009).
51% "vaccine failures"
HIV (+) in 34%

Risk Factors for Hib vaccine Failure in 12 EU countries (IBIS-EU)

Underlying condition	UK n=220	Other n=38
Prematurity (<37wk)	6	18
Malignancy	4	4
Congenital	5	5
Other	3	8
Total	**16**	**32**

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von Gottberg A (GERM-SA) Vaccine. 2012;30(3):565-71
Ladhani S. Clin Microbiol Infect. 2010;16(7):948-54

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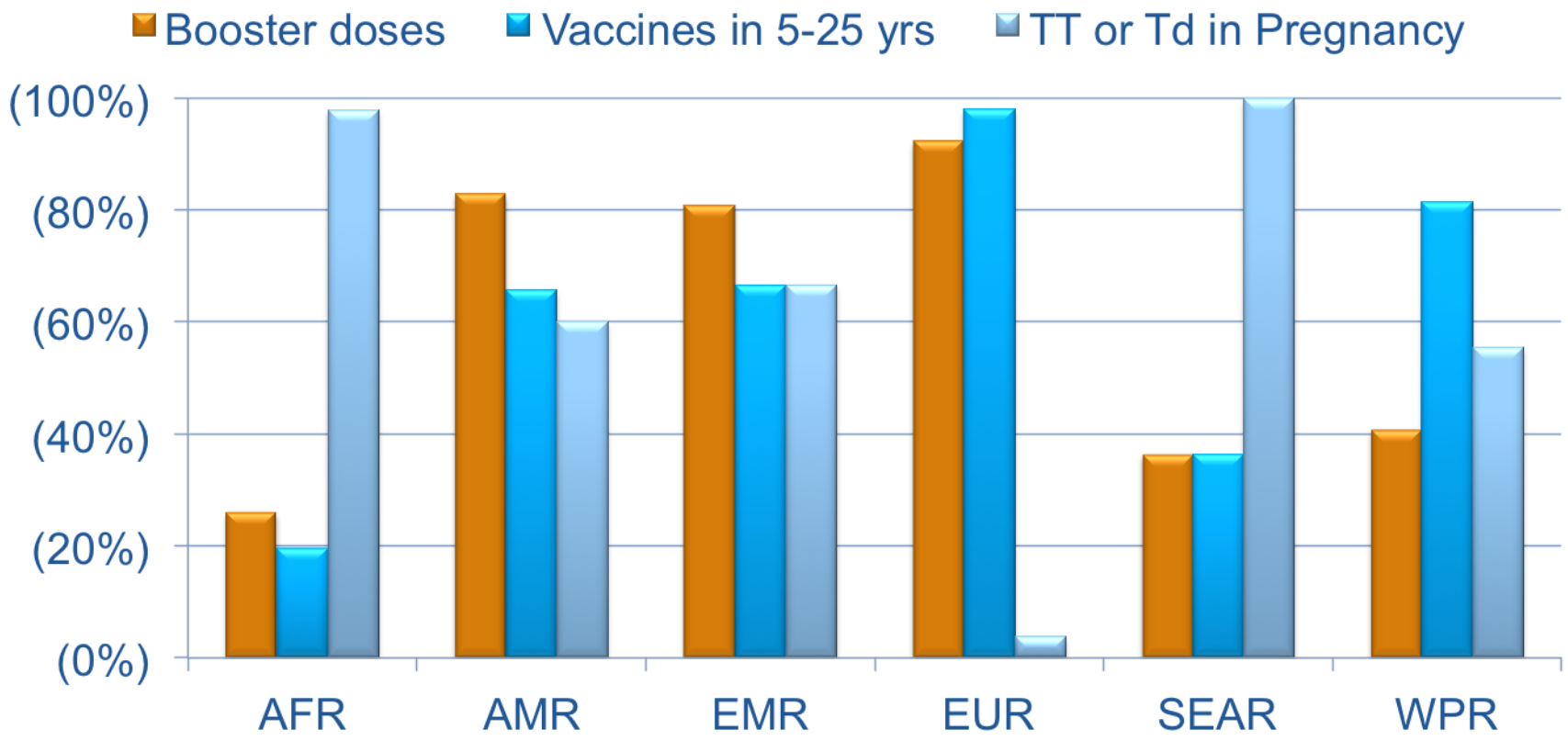
Vaccination after 12 months by WHO regions



* Includes DTP, DT, Td, Measles, MR,MMR, P, HepB or Hib

** Any vaccine given between age 5 and 25 (excluding TT for pregnant women)

Source: WHO IVB database, October 2005

Serologic Response to Inactivated Poliovirus Vaccine: A Randomized Clinical Trial Comparing 2 Vaccination Schedules in Puerto Rico

Gustavo H. Dayan,[1] Margaret Thorley,[2] Yasuhiro Yamamura,[5] Nayra Rodríguez,[5] Steve McLaughlin,[2] Lourdes M. Torres,[6] Antonio Seda,[5] Marcia Carbia,[5] Lorraine N. Alexander,[3] Victor Caceres,[4] and Mark A. Pallansch[1]

- Maternal antibodies interfere with response in early and short interval schedule at 6, 10,14 wk
- 2, 4 and 6 month schedule preferable

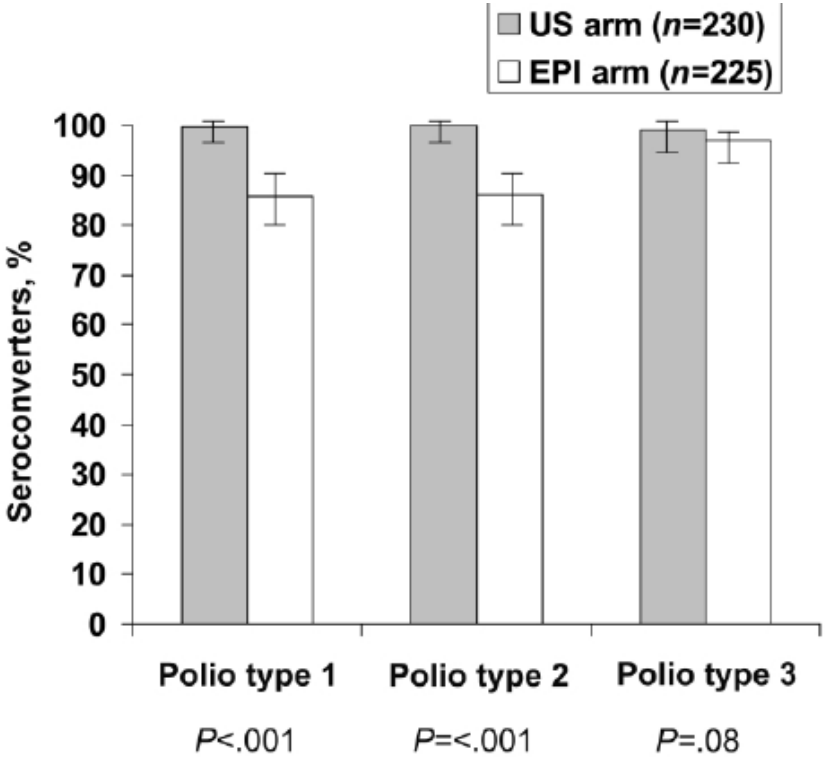
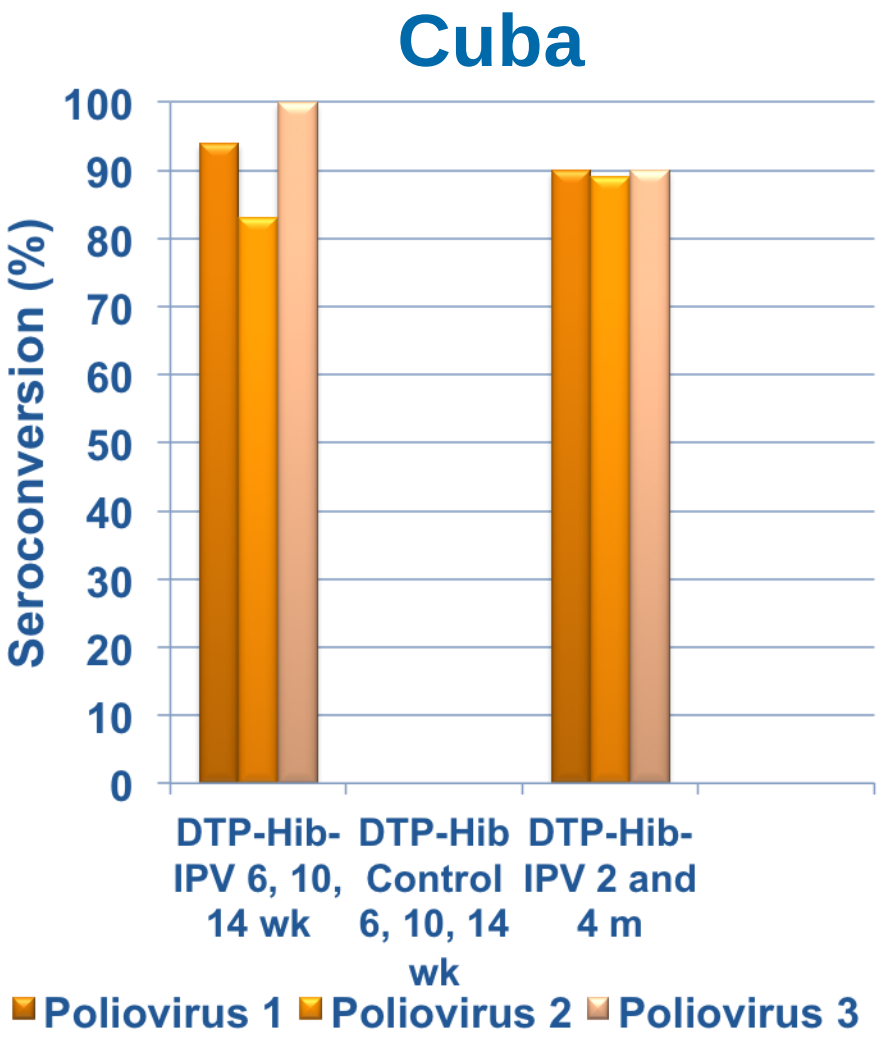
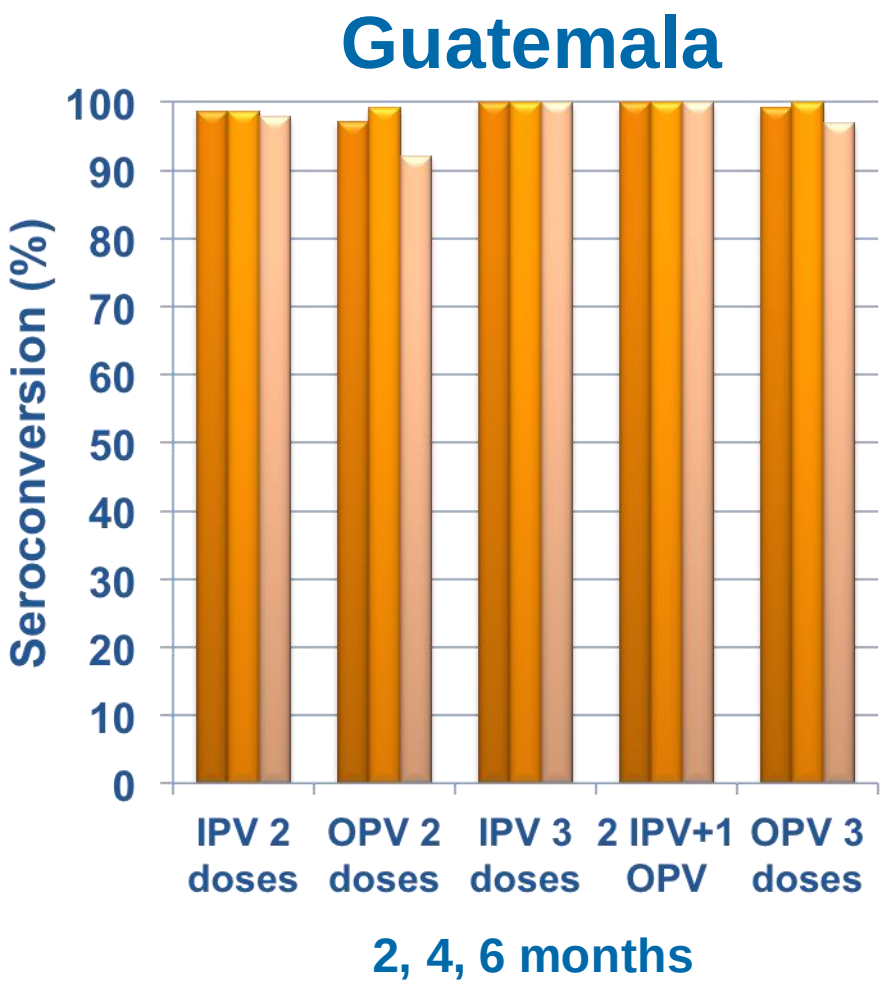


Figure 2. Seroconversion rates for poliovirus types 1, 2, and 3 after 3 doses of inactivated poliovirus vaccine, by study arm, Puerto Rico. EPI

Seroconversion to IPV vaccine to different doses and schedules in the Americas 2007





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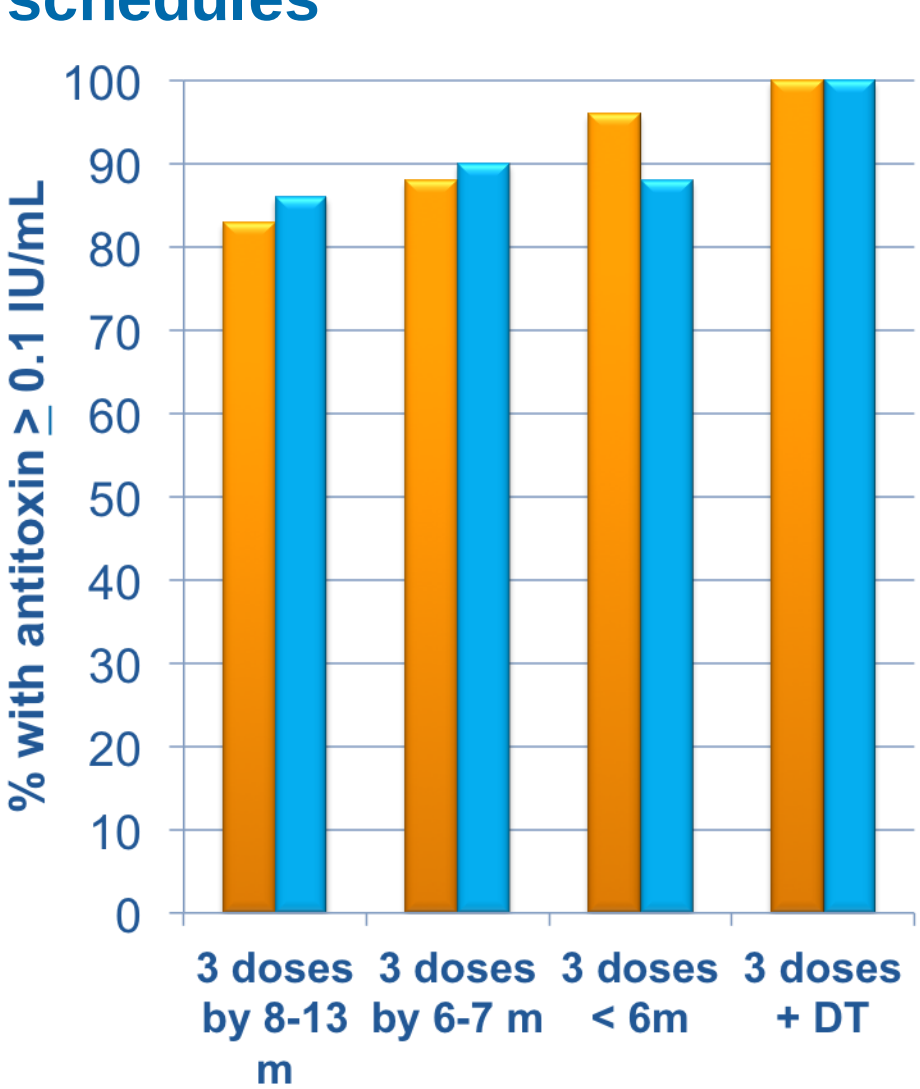
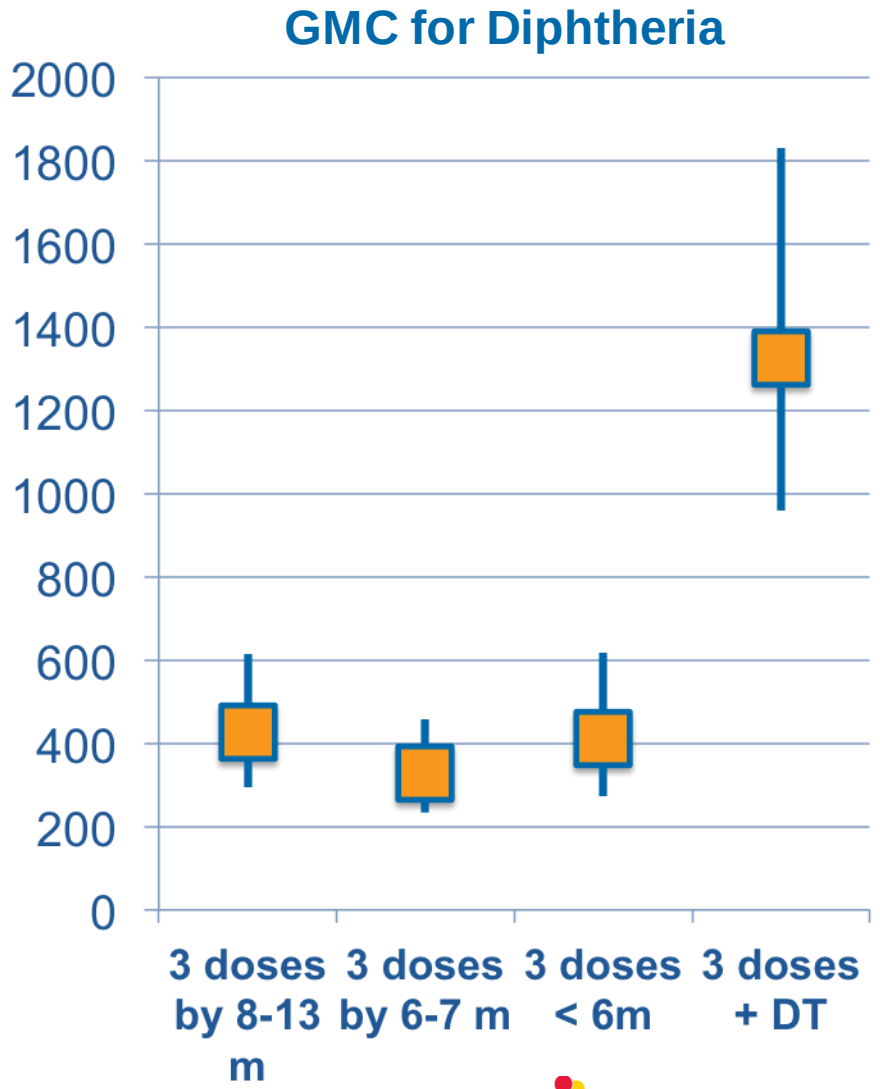
Cuba IPV Study Group *N Engl J Med.* 2007;356:1536-44.
Asturias EJ. *J Infect Dis*. 2007;196 (5):692-698

Diphtheria and tetanus anti-toxin concentrations in 129 children by 4 years of age from London after different DPT schedules





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Ramsay ME et al. *BMJ (302)* 1991

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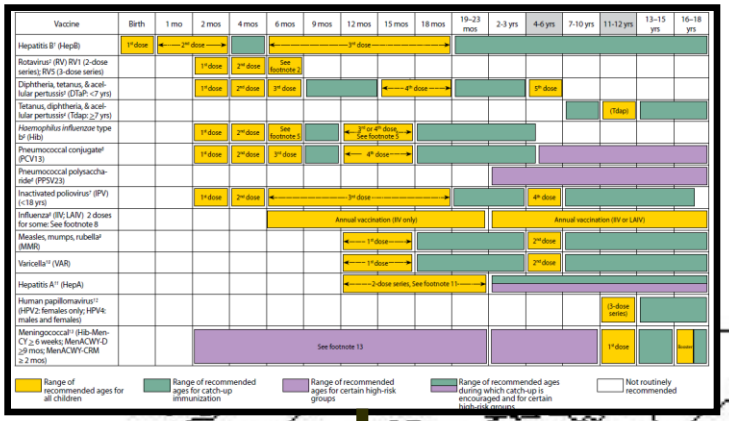
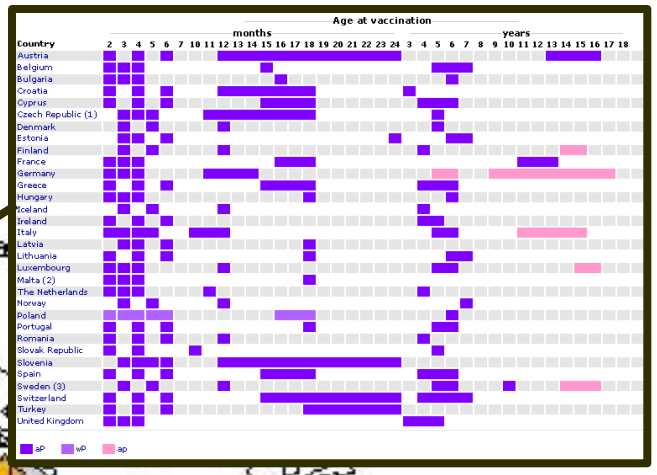
Country and Regional Schedules around the world by 2014





2, 4 ,6 ± booster

DTP recommended at 6, 10 and 14 weeks

WHO

Source: WHO IVB database, October 2005

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Courtesy F. Cutts

WHO Summary of Recommended Routine Immunization

Antigen		Children (see Table 2 for details)		Adolescents	Adults	Considerations (see footnotes for details)
Recommendations for all						
BCG[1]		1 dose				Exceptions HIV
Hepatitis B[2]		3-4-doses (see footnote for schedule options)		3 doses (for high-risk groups if not previously immunized) (see footnote)		Birth dose Premature and low birth weight Co-administration and combination vaccine Definition high-risk
Polio[3]		3 doses, with DTP				OPV birth dose Transmission and importation risk criteria Type of vaccine
DTP[4]		3 doses	Booster (DTP) 1-6 years of age	Booster (Td) (see footnote)	Booster (Td) in early adulthood or pregnancy	Delayed/interrupted schedule Combination vaccine
Haemophilus influenzae type b[5]		3 doses, with DTP				Single dose if 12-24 months of age Delayed/interrupted schedule Co-administration and combination vaccine
Pneumococcal (Conjugate)[6]	Option 1	3 doses, with DTP				Vaccine options Initiate before 6 months of age Co-administration HIV+ and preterm neonates booster
	Option 2	2 doses before 6 months of age, plus booster dose at 9-15 months of age				
Rotavirus[7]		Rotarix: 2 doses with DTP RotaTeq: 3 doses with DTP				Vaccine options
Measles[8]		2 doses				Combination vaccine; HIV early vaccination; Pregnancy
Rubella[9]		1 dose (see footnote)		1 dose (adolescent girls and/or child bearing aged women if not previously vaccinated; see footnote)		Achieve and sustain 80% coverage Combination vaccine and Co-administration Pregnancy
HPV[10]				3 doses (girls)		Vaccination of males for prevention of cervical cancer is not recommended at this time

http://www.who.int/immunization/policy/immunization_tables/en/

Why are schedules important?

- **Programmatic:** framework for delivery of vaccines to target population
- **Evaluation of coverage**
- **Research and development:** Parameters for vaccine studies (harmonization with existing vaccine schedules…)
- **Public information and guidance**

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

1ST FEBRUARY 2013, 88th YEAR / 1er FÉVRIER 2013, 88e ANNÉE
No. 5, 2013, 88, 49–64
http://www.who.int/wer

Contents

Rotavirus vaccines

WHO position paper January 2013

Although early immunization is still favoured, the manufacturers' conventional age restrictions on the first and last dose of rotavirus vaccines may have prevented vaccination of many vulnerable children in settings where the DTP doses are given late (i.e. after 15 weeks for DTP1 or after 32 weeks for DTP 2 or DTP3). By allowing infants to receive rotavirus vaccine together with DTP regardless of the time of vaccination, immunization programmes will be able to reach children who were previously excluded from the benefits of rotavirus vaccines. Because of the typical age distribution of RVGE, rotavirus vaccination of children >24 months of age is not recommended.

	Rotavirus Deaths Averted	Intussusception Deaths
15 week age restriction	-150,500 (63,500 to 197,000)	221 (146 to 328)*
No age restriction	-200,000 (98,500 to 264,000)	499 (329 to 741)*
No age restriction (vs. age restriction)	49,500 additional rotavirus deaths averted	278 additional IS events caused

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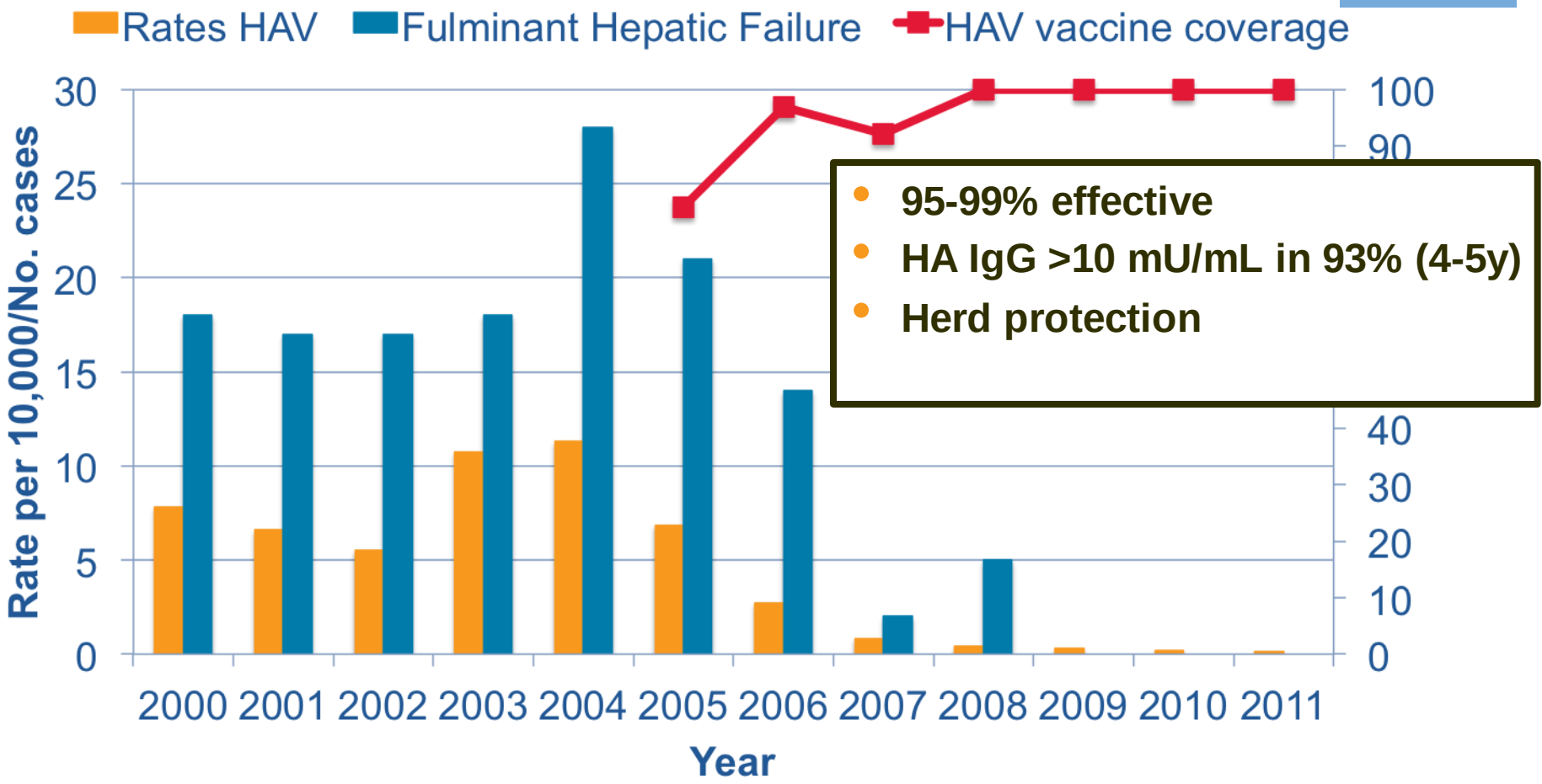
Trend of Hepatitis A incidence rates and cases of hepatic failure due to HAV in Argentina pre and post 1 dose HAV program



Modified from
Vizzotti C. Ministry of Health Report to SAGE
Republic of Argentina

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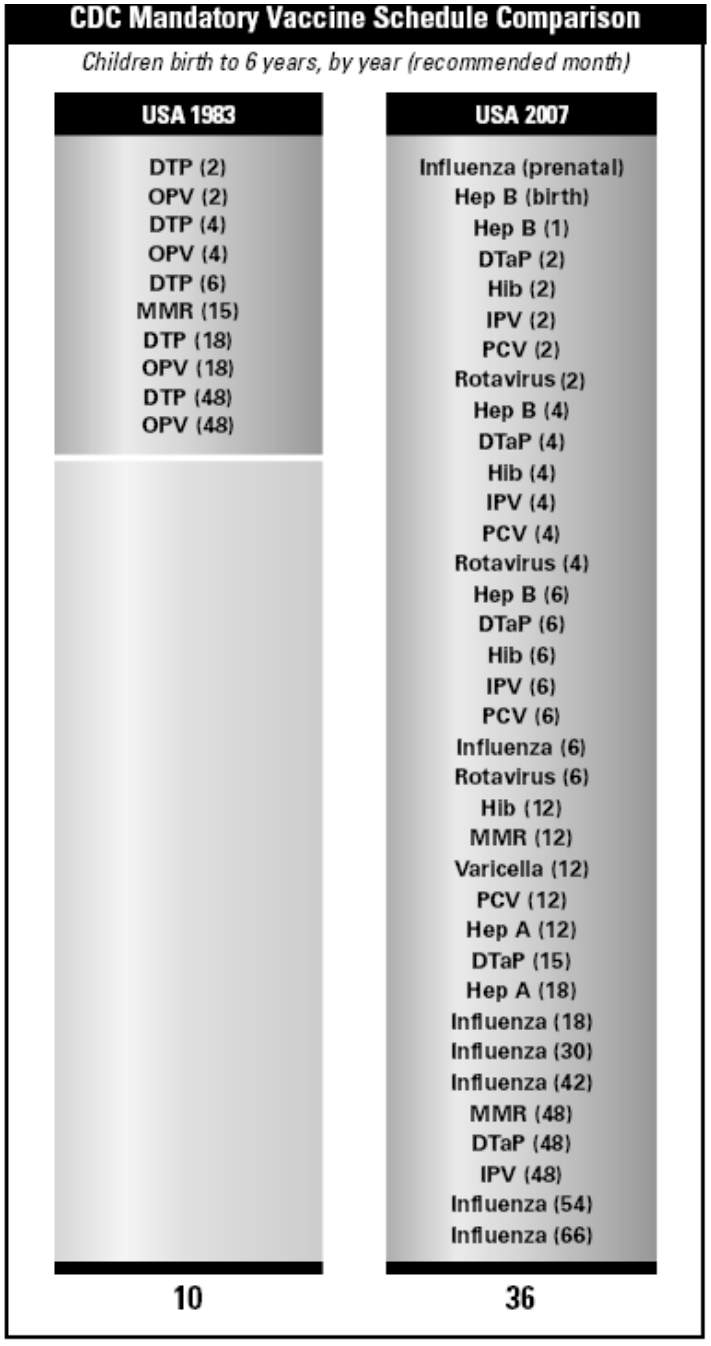
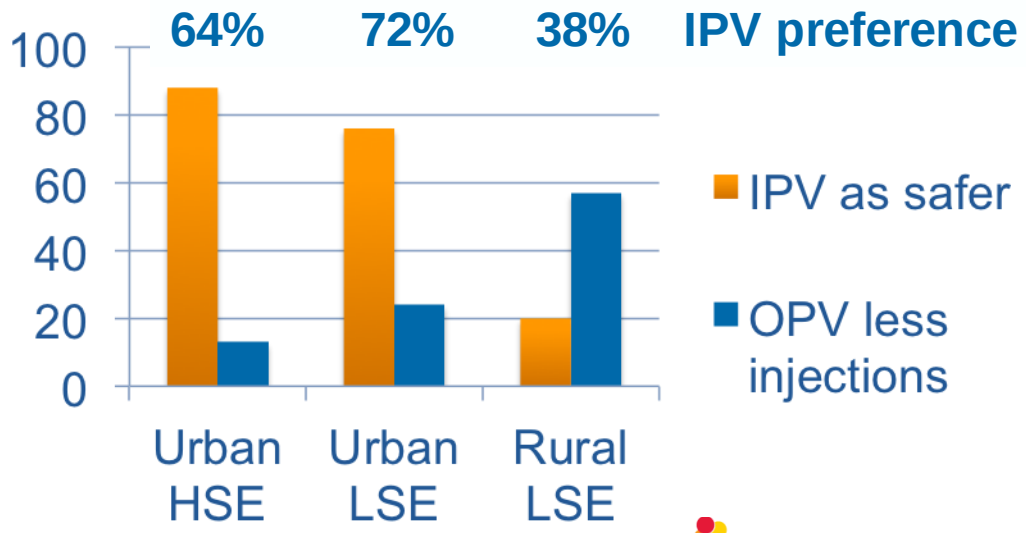


Parent's concerns HIC

- Crowding of schedule
- Immune "overload"
- Best age for immunity

Parent's preference for IPV vs. OPV Guatemala (*n*= 270)



Asturias EJ, unpublished. 2009

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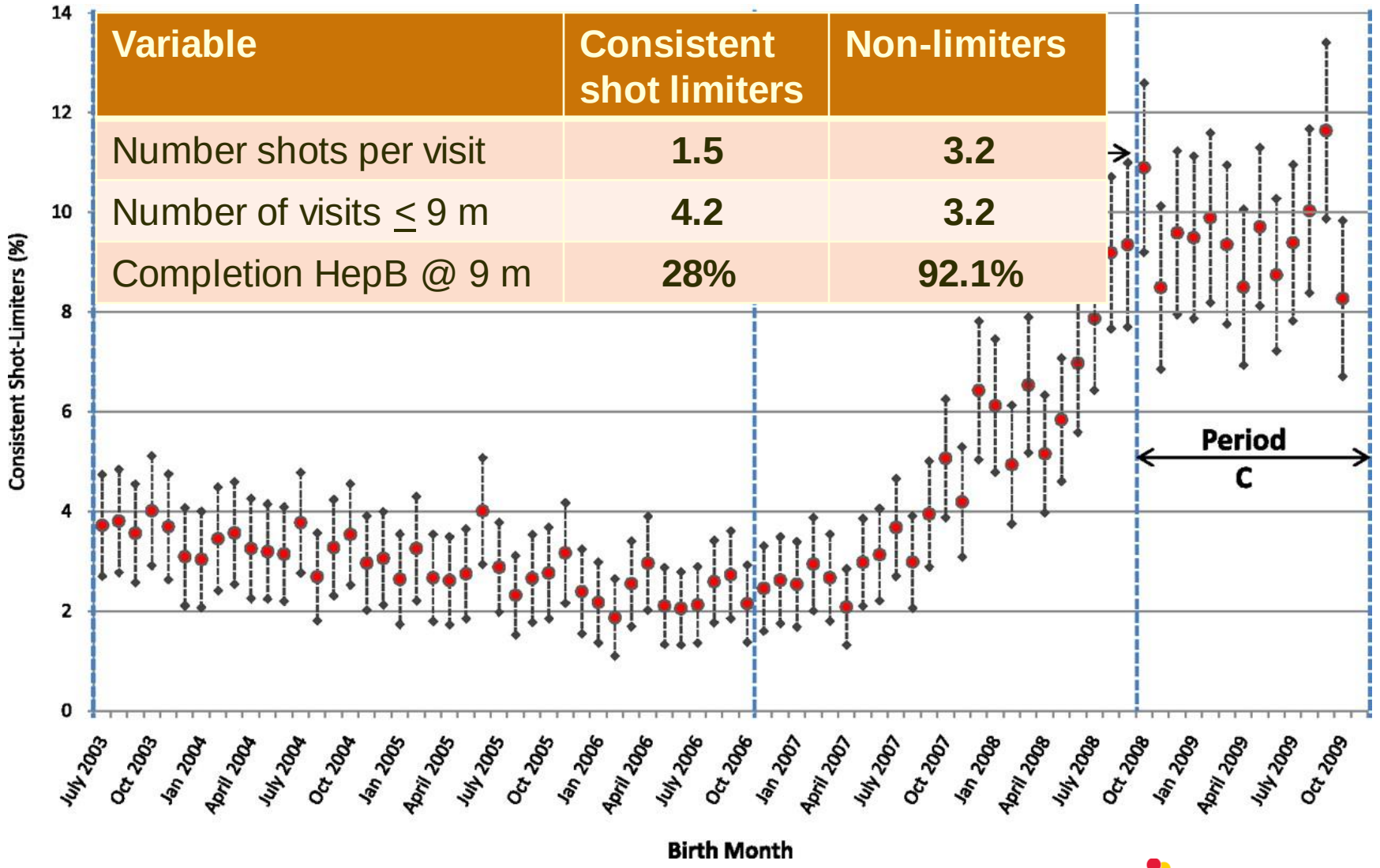
Rates of consistent users of alternate schedules according to birth month, 2003-2009, Oregon, USA

Variable	Consistent shot limiters	Non-limiters
Number shots per visit	**1.5**	**3.2**
Number of visits ≤ 9 m	**4.2**	**3.2**
Completion HepB @ 9 m	**28%**	**92.1%**



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Robison S G et al. *Pediatrics* 2012;130:32-38

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Next 10 years of the EPI Schedule…?

Vaccine	0-1 year	1-2 yrs	2-5 yrs	5-15 yrs
BCG	1 dose			
DPT	3 doses (2?)	1 dose		
Polio (IPV and bOPV)	3 doses (2?)			
Hib	3 doses (2?)	1 dose		
PCV	3 doses (2?)	1 dose		
Rotavirus	2-3 doses			
Measles-Rubella		1 dose	1 dose	
HPV				2-3 doses
Meningococcal	2-3 doses			
Malaria	3 doses			
Dengue		3 doses		
Influenza	1 dose	1 dose/yr	1 dose/yr	

From Tradition to Best Practice

- Need **primary series consistent with practice**
  - Ages for best immunological fit
  - **2 doses in the first year** probably sufficient
  - **Boosters ≥ 12 months** are key for long term and indirect protection
- Schedules will need to address **safety and crowding** for upcoming vaccines and confidence
- **Best timing for prevention!**

Thank you!

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Lake Atitlan - Guatemala

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