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Pediatric and Adolescent Vaccines

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Overview

- Pediatric vaccine schedules
  - US
  - WHO
- Pneumococcal vaccines
  - Serotype replacement – a moving target
- Meningococcal vaccines
  - Vaccines for rare diseases
- Pertussis vaccines
  - A safer vaccine…with a trade off

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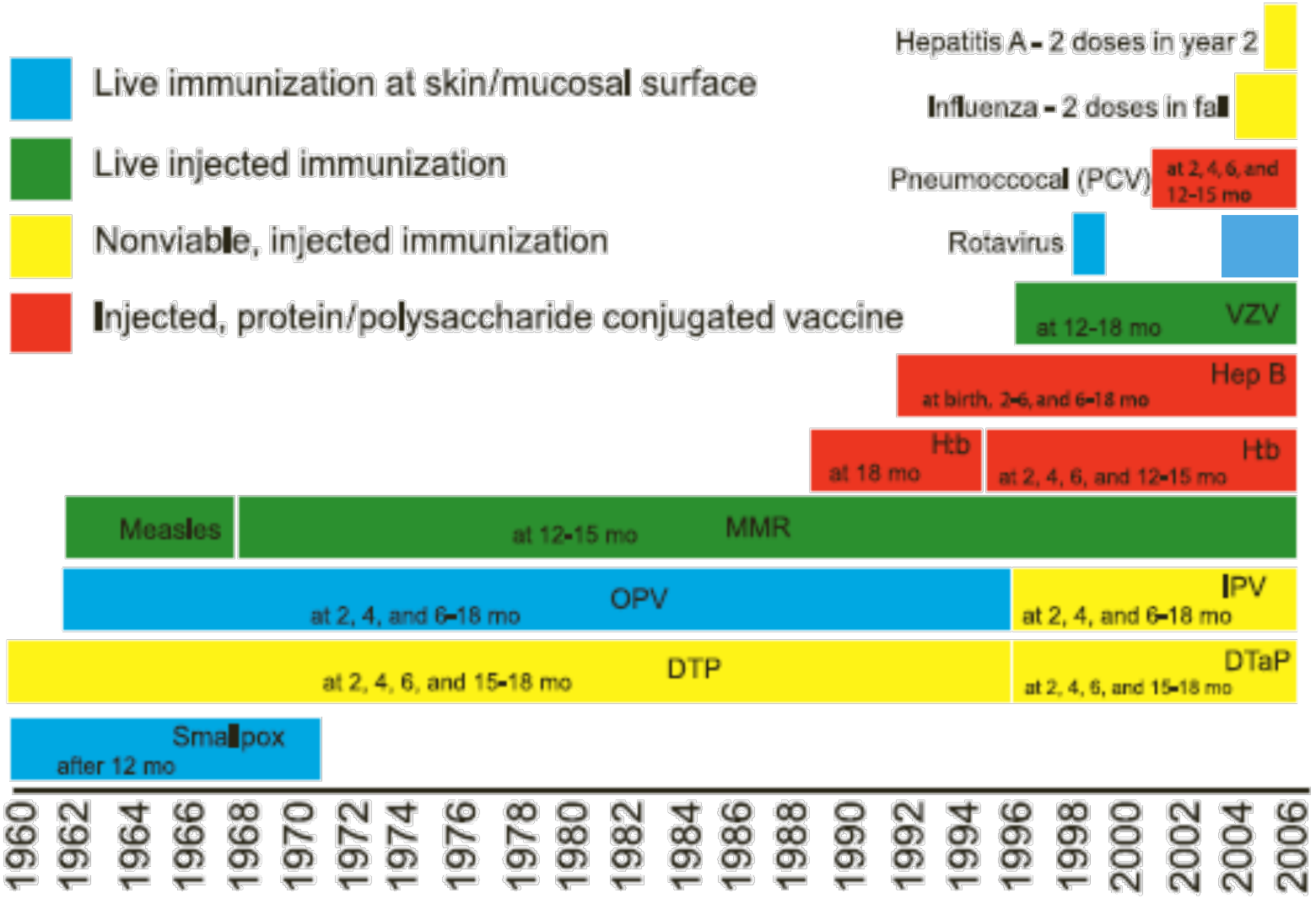
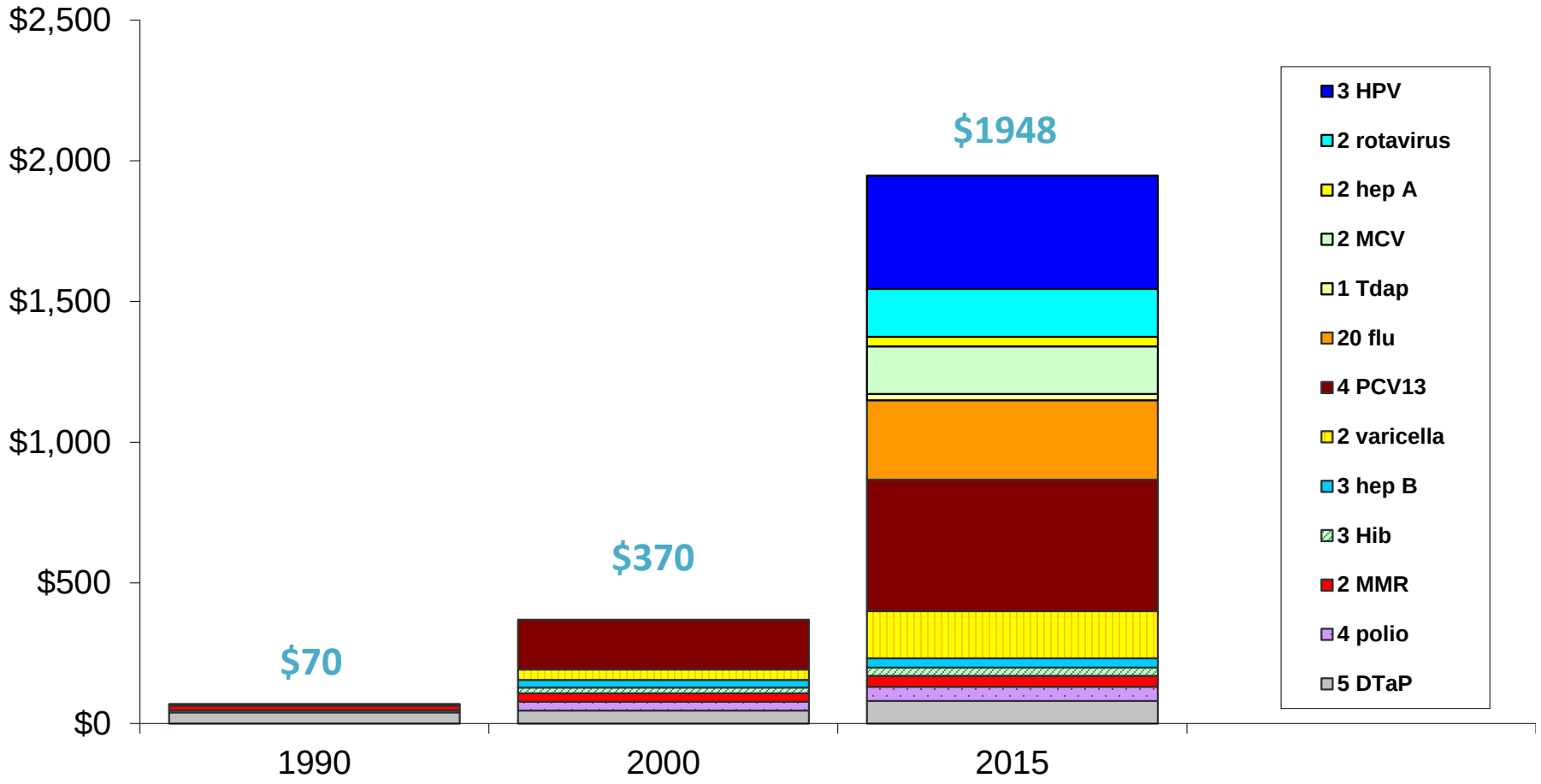
US Vaccines, age <2y



http://pediatrics.aappublications.org/cgi/reprint/119/1/222.pdf

Costs for Vaccines for One Child in the US



2015 represents minimum cost to vaccinate a child (birth through 18); exceptions are 1) no preservative pediatric influenza vaccine, and 2) HPV for males and females.

Federal contract prices as of February 1, 1990, September 27, 2000, and April 1, 2015.

K. Neuzil

Vaccines save lives and $$ in the US

- Costs of vaccination
  - $107 billion direct cost
  - $121 billion societal cost
- Averted cost for illnesses prevented by vaccination
  - $402 billion direct cost
  - $1.5 trillion societal cost
- Vaccines are costs saving!
  - $295 billion direct cost
  - $1.38 trillion societal cost

TABLE. Estimated number of illnesses, hospitalizations, and deaths prevented by routine childhood immunization for selected vaccine-preventable diseases among children born during the Vaccines for Children era — United States, 1994–2013

	Cases prevented (in thousands)		
Vaccine-preventable disease*	Illnesses	Hospitalizations	Deaths
Diphtheria	5,073	5,073	507.3
Tetanus	3	3	0.5
Pertussis	54,406	2,697	20.3
Haemophilus influenzae type B	361	334	13.7
Polio	1,244	530	14.8
Measles	70,748	8,877	57.3
Mumps	42,704	1,361	0.2
Rubella	36,540	134	0.3
Congenital rubella syndrome	12	17	1.3
Hepatitis B	4,007	623	59.7
Varicella	68,445	176	1.2
Pneumococcus-related diseases†	26,578	903	55.0
Rotavirus	11,968	327	0.1
Total	**322,089**	**21,055**	**731.7**

* Vaccines were considered as preventing disease for birth cohorts born in all years during 1994–2013 except for the following, which were only in use for part of the 20-year period: varicella, 1996–2013; 7-valent and 13-valent pneumococcal conjugate vaccines, 2001–2013; and rotavirus, 2007–2013.
† Includes invasive pneumococcal disease, otitis media, and pneumonia.

MMWR 2014: 63(16)

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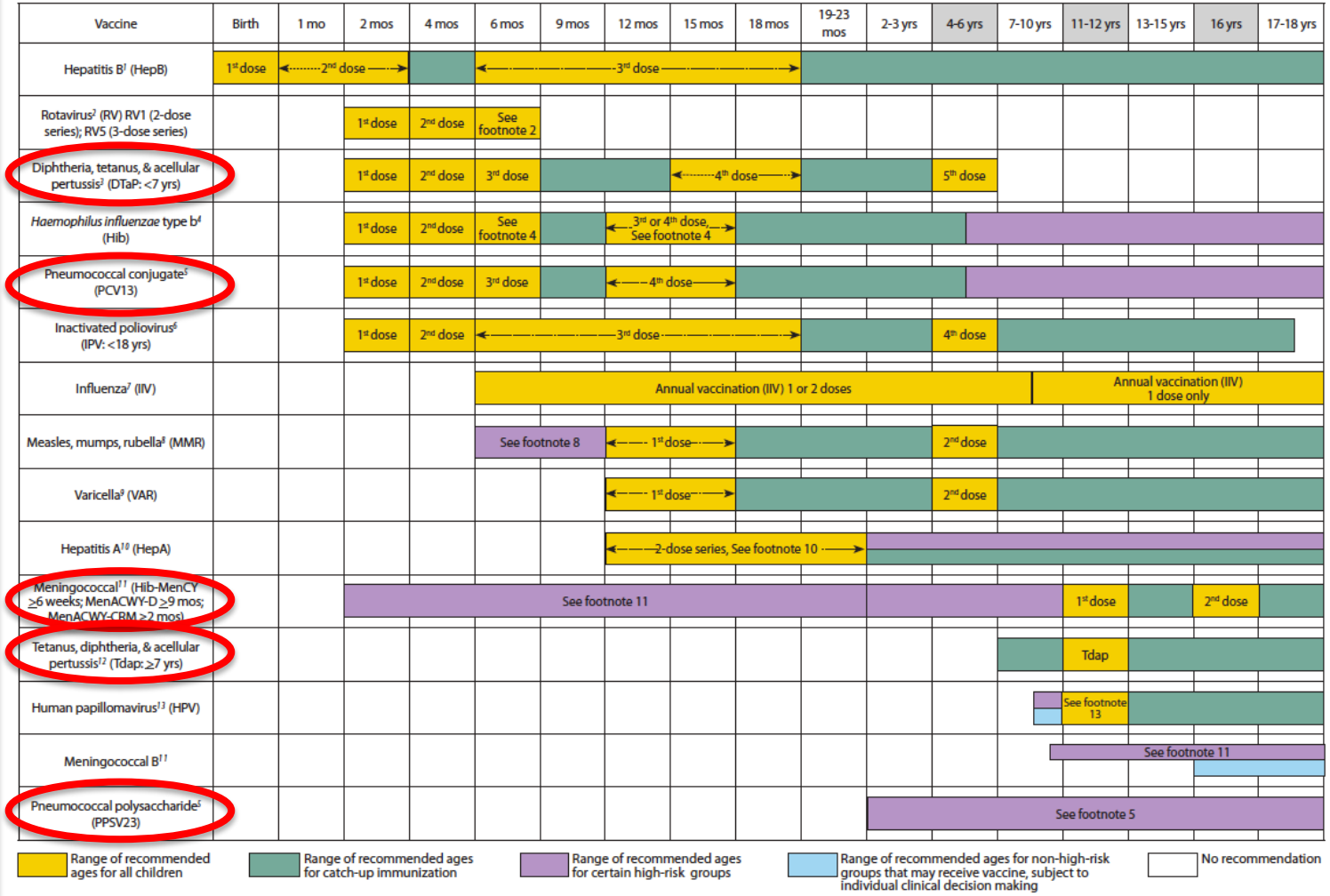
2017 US Schedule

Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2017.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 2]).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.



NOTE: The above recommendations must be read along with the footnotes of this schedule.

Timing of pediatric vaccines

- Immaturity of infant immune system
- Interference of maternal antibody
- Minimum studied intervals
- Convenience

WHO Guidelines

- Typical schedule:
  - Birth
  - 6,10,14 weeks
  - 9, 18 months
  - 6, 12 years
- Additional vaccines:

  Japanese encephalitis, yellow fever, tick-borne encephalitis, typhoid, cholera, meningococcous, hepatitis A, Rabies, Dengue (CYD-TDV), mumps, seasonal influenza, varicella

Table 2: Summary of WHO Position Papers - Recommended Routine Immunizations for Children

Antigen		Age of 1st Dose	Doses in Primary Series	Interval Between Doses			Booster Dose	Considerations (see footnotes for details)
				1st to 2nd	2nd to 3rd	3rd to 4th		
Recommendations for all children								
BCG [1]		As soon as possible after birth	1					Exceptions HIV
Hepatitis B [2]	Option 1	As soon as possible after birth (<24h)	3	4 weeks (min) with DTP1	4 weeks (min) with DTP3			Premature and low birth weight Co-administration and combination vaccine High risk groups
	Option 2	As soon as possible after birth (<24h)	4	4 weeks (min) with DTP1	4 weeks (min) with DTP2	4 weeks (min),with DTP3		
Polio [3]	bOPV + IPV	6 weeks (see footnote for birth dose)	4 (IPV dose to be given with bOPV dose from 14 weeks)	4 weeks (min) with DTP2	4 weeks (min) with DTP3			bOPV birth dose Transmission and importation risk criteria
	IPV / bOPV Sequential	8 weeks (IPV 1st)	1-2 IPV 2 bOPV	4-8 weeks	4-8 weeks	4-8 weeks		
	IPV	8 weeks	3	4-8 weeks	4-8 weeks		(see footnote)	IPV booster needed for early schedule (i.e. first dose given <8 weeks)
DTP [4]		6 weeks (min)	3	4 weeks (min) - 8 weeks	4 weeks (min) - 8 weeks		1-6 years of age (see footnote)	Delayed/ interrupted schedule Combination vaccine; maternal immunization
Haemophilus influenzae type b [5]	Option 1	6 weeks (min) 59 months (max)	3	4 weeks (min) with DTP2	4 weeks (min) with DTP3		(see footnote)	Single dose if >12 months of age Not recommended for children > 5 yrs Delayed/ interrupted schedule Co-administration and combination vaccine
	Option 2		2-3	8 weeks (min) if only 2 doses 4 weeks (min) if 3 doses	4 weeks (min) if 3 doses		At least 6 months (min) after last dose	
Pneumococcal (Conjugate) [6]	Option 1	6 weeks (min)	3	4 weeks (min)	4 weeks		(see footnote)	Vaccine options Initiate before 6 months of age Co-administration HIV+ and preterm neonates booster
	Option 2	6 weeks (min)	2	8 weeks (min)			9-15 months	
Rotavirus [7]	Rotarix	6 weeks (min) with DTP1	2	4 weeks (min) with DTP2				Vaccine options Not recommended if > 24 months old
	Rota Teq	6 weeks (min) with DTP1	3	4 weeks (min) - 10 weeks with DTP2	4 weeks (min) with DTP3			
Measles [8]		9 or 12 months (6 months min, see footnote)	2	4 weeks (min) (see footnote)				Combination vaccine; HIV early vaccination; Pregnancy
Rubella [9]		9 or 12 months with measles containing vaccine	1					Achieve and sustain 80% coverage Combination vaccine and Co-administration; Pregnancy
HPV [10]		As soon as possible from 9 years of age (females only)	2	6 months (min 5 months)				Target 9-13 year old girls Pregnancy Older age ≥ 15 years 3 doses HIV and immunocompromised

Refer to http://www.who.int/immunization/documents/positionpapers/ for table & position paper updates.

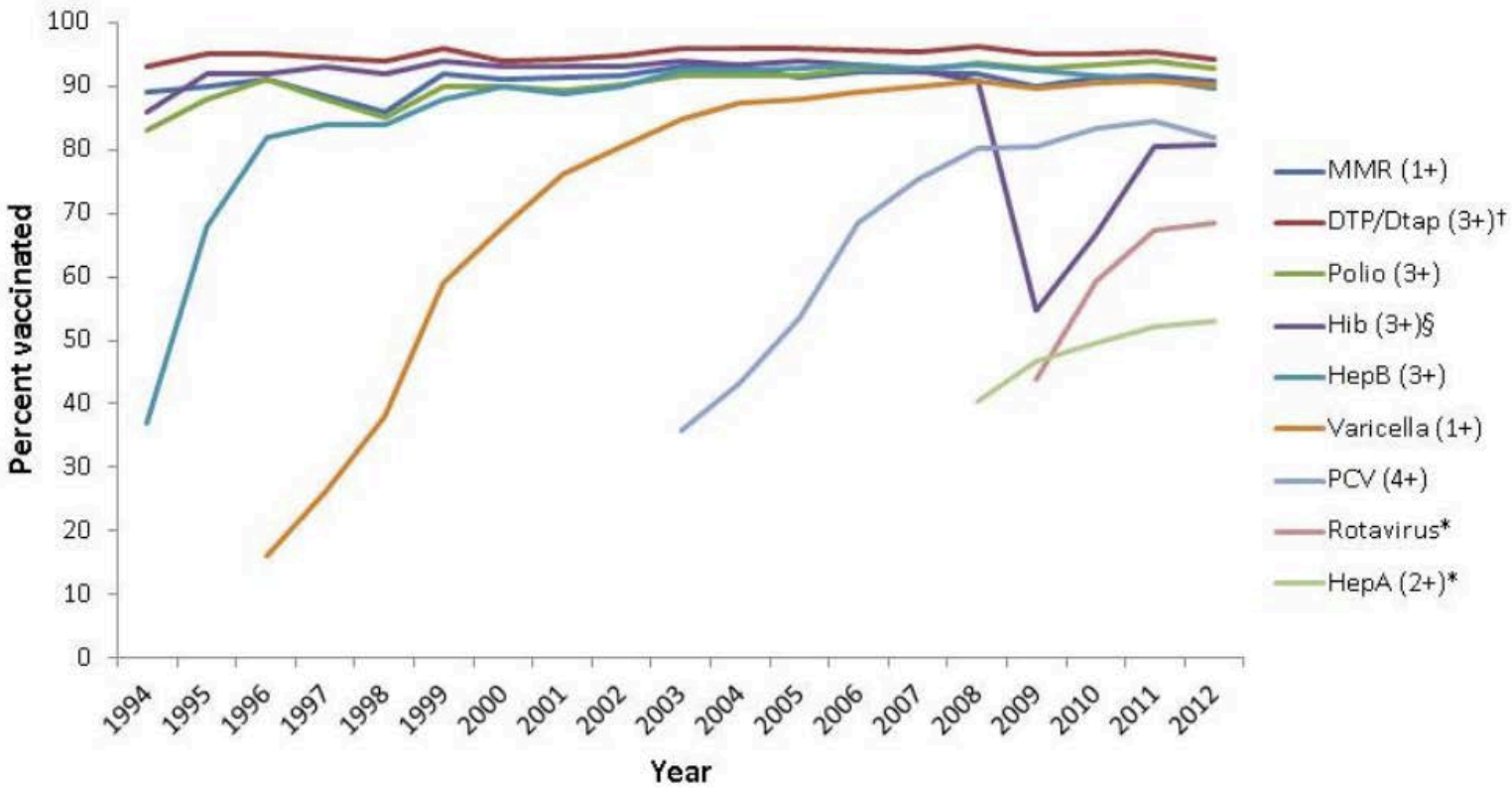
This table summarizes the WHO vaccination recommendations for children.The ages/intervals cited are for the development of country specific schedules and are not for health workers.

National schedules should be based on local epidemiologic, programmatic, resource & policy considerations. While vaccines are universally recommended, some children may have contraindications to particular vaccines.

Differences between US schedule & WHO guidance

- Schedule vs. Guidance
- Different vaccines
  - Cost
  - Disease prevalence
- Timing
  - Earlier vaccination in WHO guidance
    - Disease prevalence
  - Fever encounters in WHO guidance
    - Resource limitations

Vaccine-specific coverage among children 19-35 months



* The *Healthy People 2020* target for coverage is 90% for all vaccines with the exception of rotavirus (80%) and HepA (85%).

† DTP (3+) is not a Healthy People 2020 objective. DTaP (4+) is used to assess Healthy People 2020 objectives.

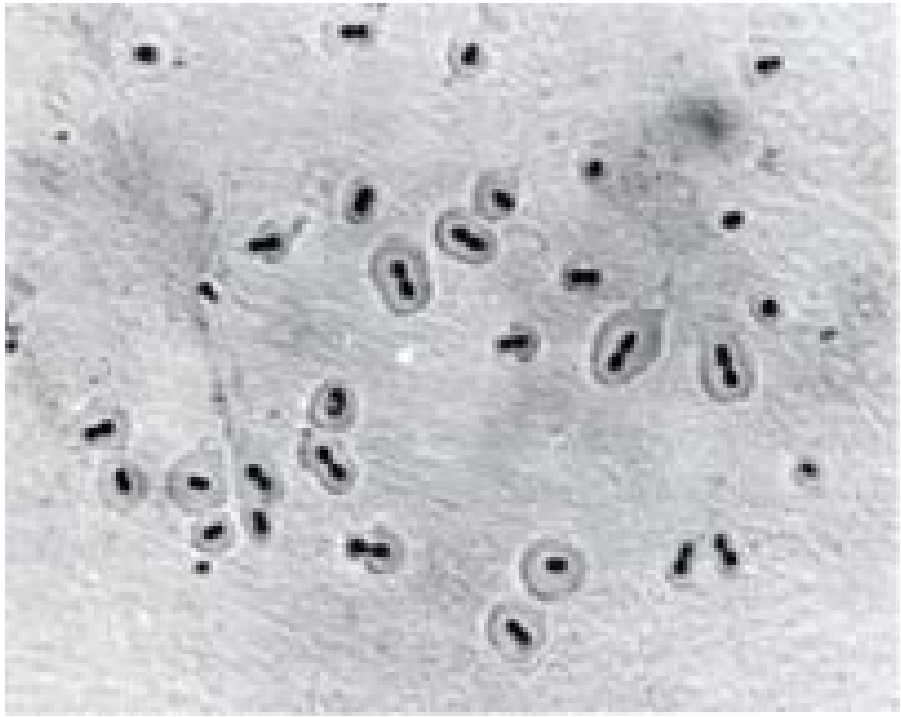
§ Reflects 3+ doses through 2008, and Full Series (3 or 4 doses depending on type of vaccine received) 2009 and later.

Pneumococcal Vaccines

Serotype replacement – a moving target

Streptococcus pneumoniae

- Gram positive diplococcus
- Capsule is the main virulence factor
  - Prevents phagocytosis
  - Anti-capsular antibodies are protective
- >90 serotypes
  - Some strains are more virulent than others



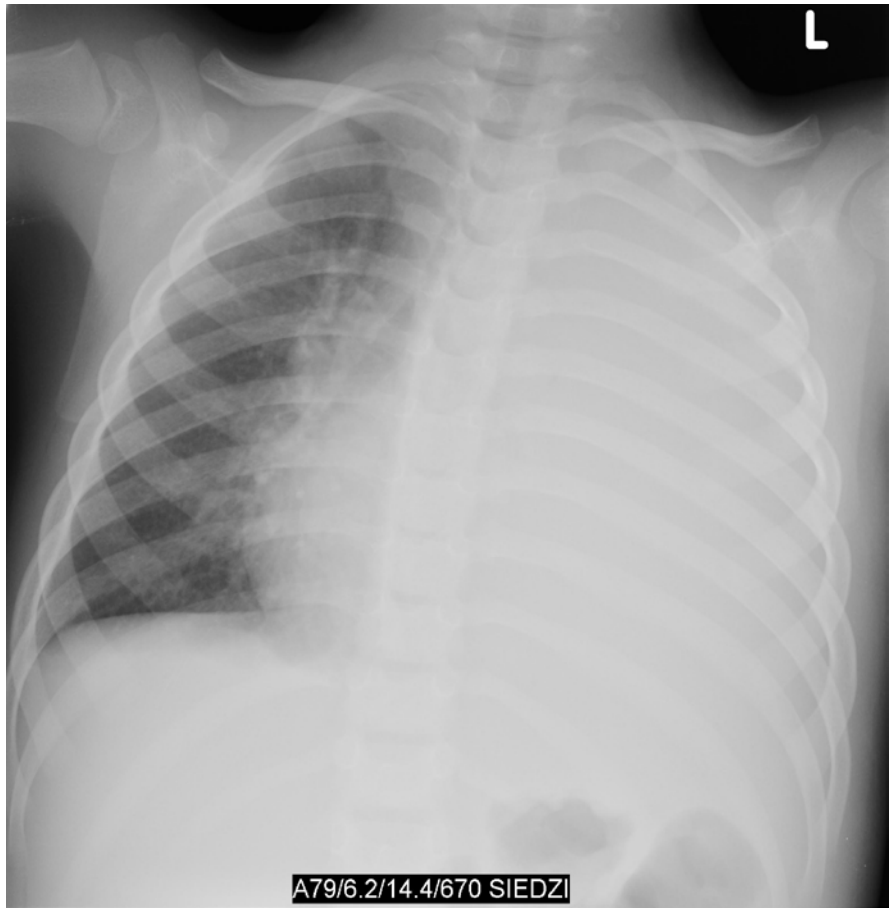
http://textbookofbacteriology.net

Quellung reaction

- capsular swelling caused by antibody binding to the capsule
- used for serotyping

Streptococcus pneumoniae

- Nasopharyngeal colonization
- Respiratory tract disease
  - Sinusitis, otitis media, pneumonia
- Invasive pneumococcal disease
  - Isolation of *S. pneumo* from normally sterile site (blood, CSF, pleural fluid, *etc.*)
- Affected populations
  - Infants, elderly, chronic pulmonary disease, immunosuppressed including asplenia

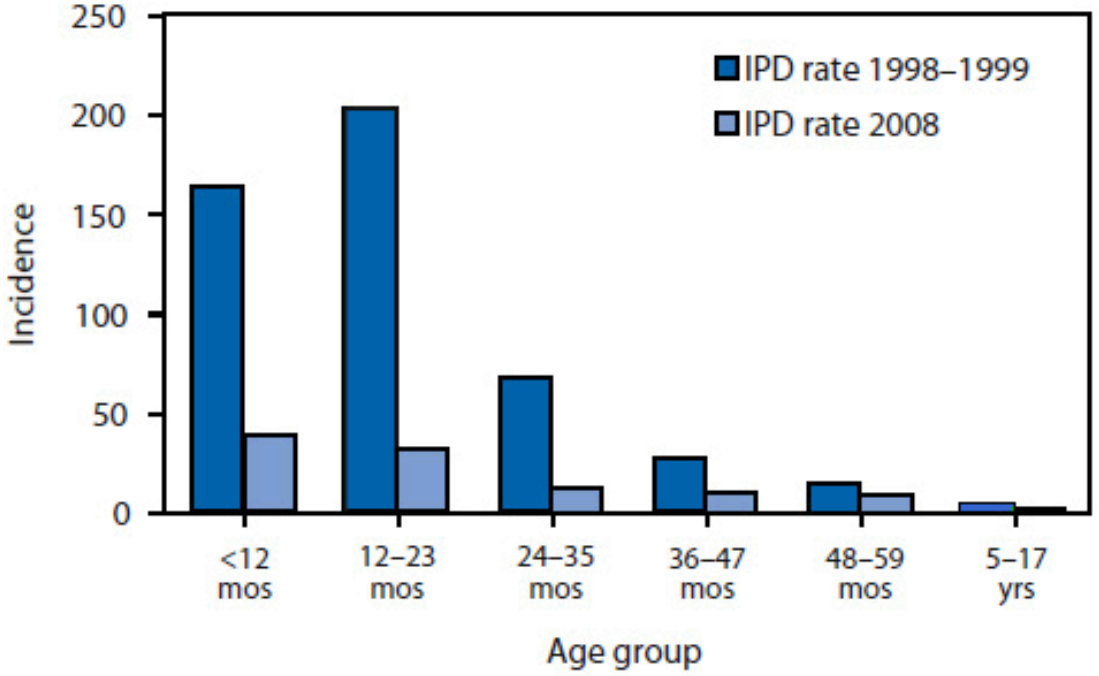


Respiratory Disease and Infection – A New Insight, ed. Bassam H. Mahboub

Pneumococcal vaccines in the US

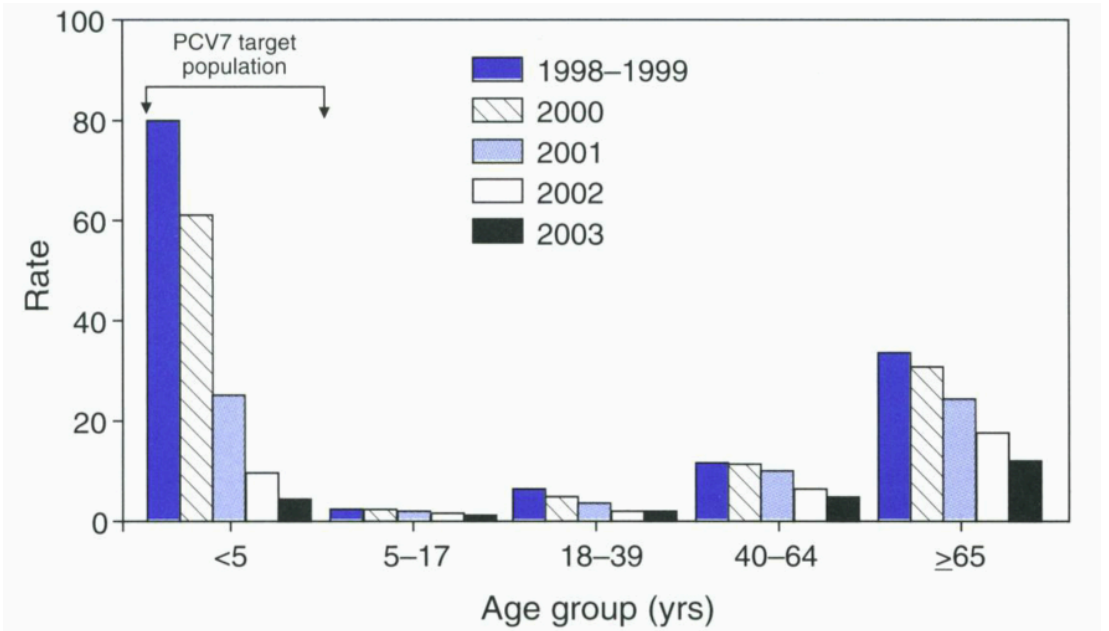
- Pneumovax (PPSV-23)
  - Purified polysaccharide
  - Licensed in 1983
    - replaced a 14-valent polysaccharide vaccine from 1977
- Prevnar 7 (PPV-7)
  - Added to routine pediatric schedule in 2000
  - Purified polysaccharide conjugated to CRM_{197}
- Prevnar 13 (PPV-13)
  - Replaced PPV-7 in 2010
  - 6 additional serotypes, including 19A

Effect of PCV 7 on invasive disease



*Per 100,000 population.

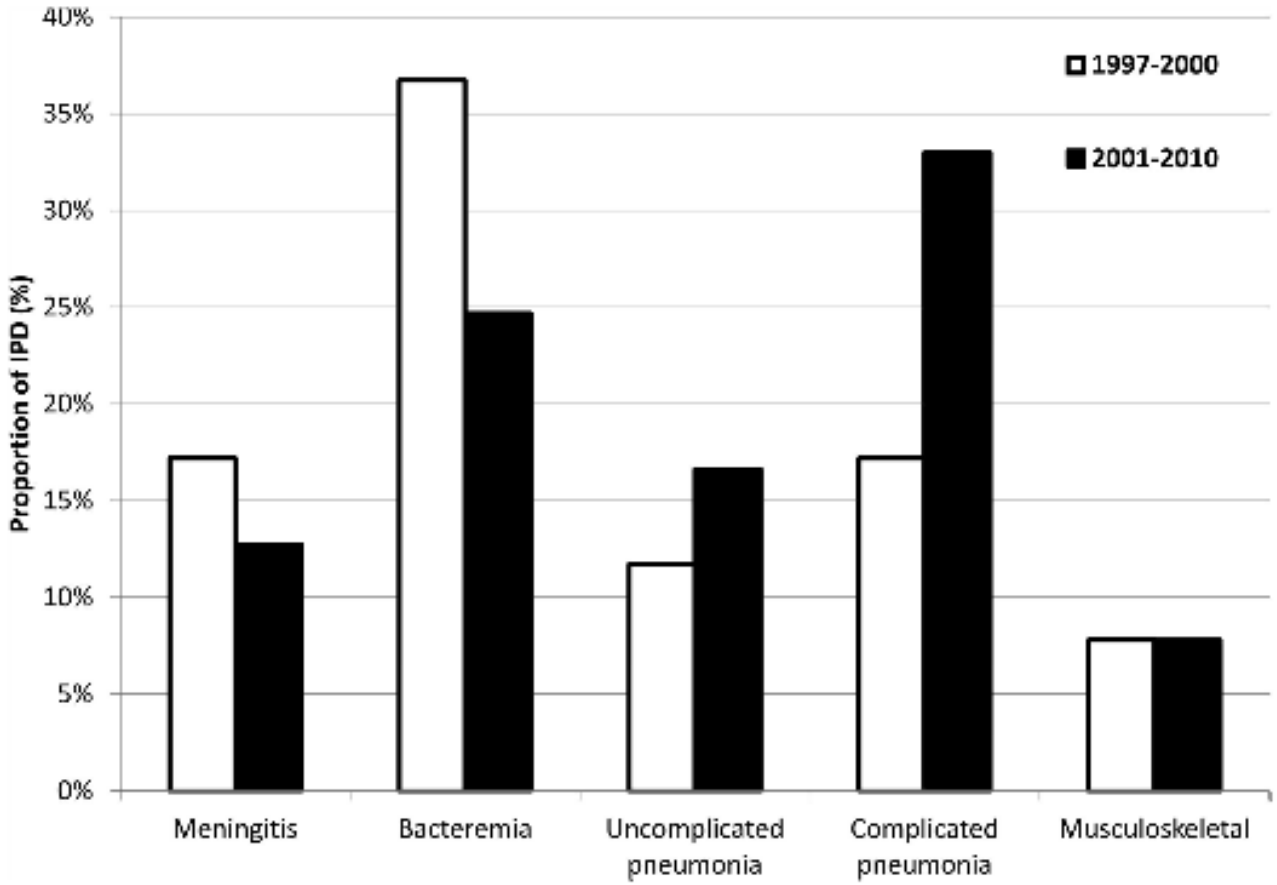
MMWR 2010: 59(RR11);1-18



* Per 100,000 population.
† For each age group, the decrease in VT IPD rate for 2003 compared with the 1998–1999 baseline is statistically significant ($p<0.05$).

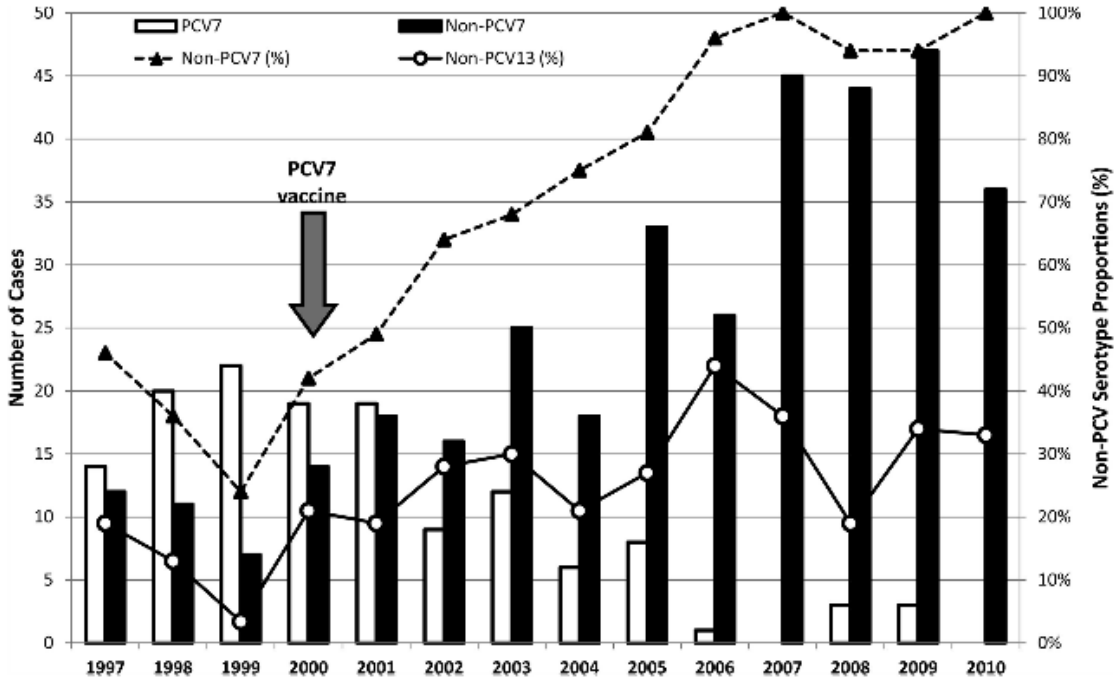
MMWR 2005: 54(36)

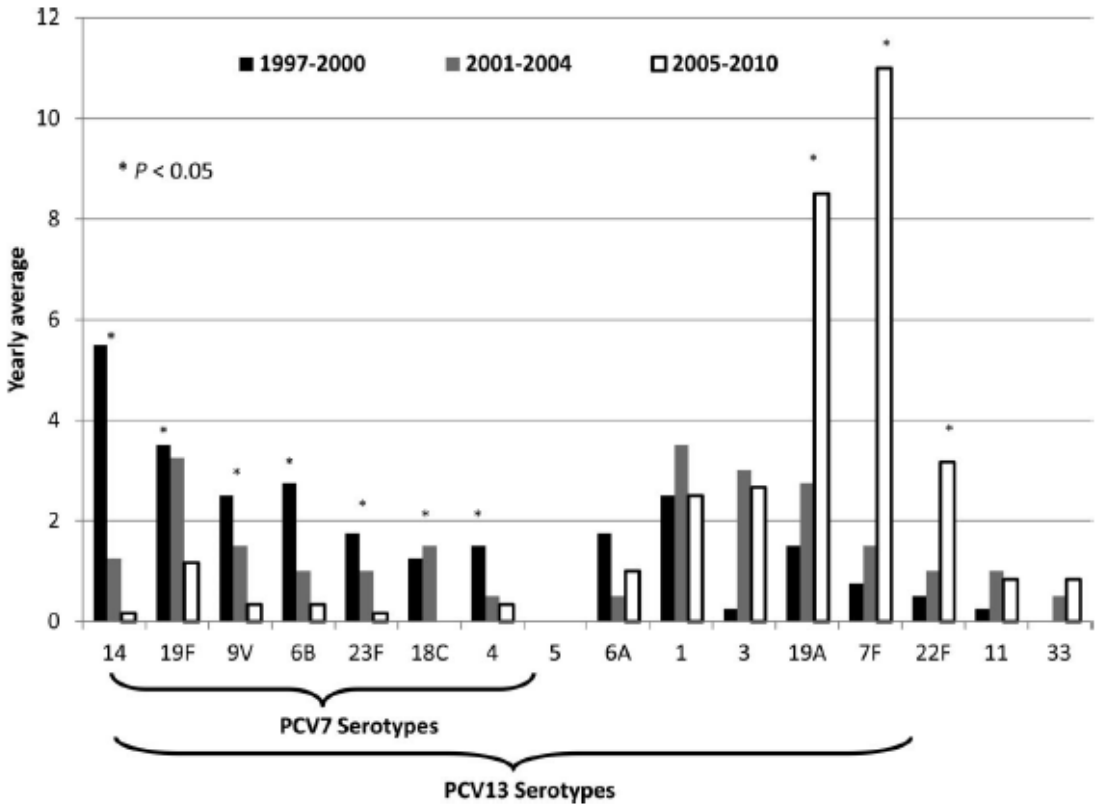
Effect of serotype replacement on clinical disease



Ampofo et al, PIDJ 2012; 31.

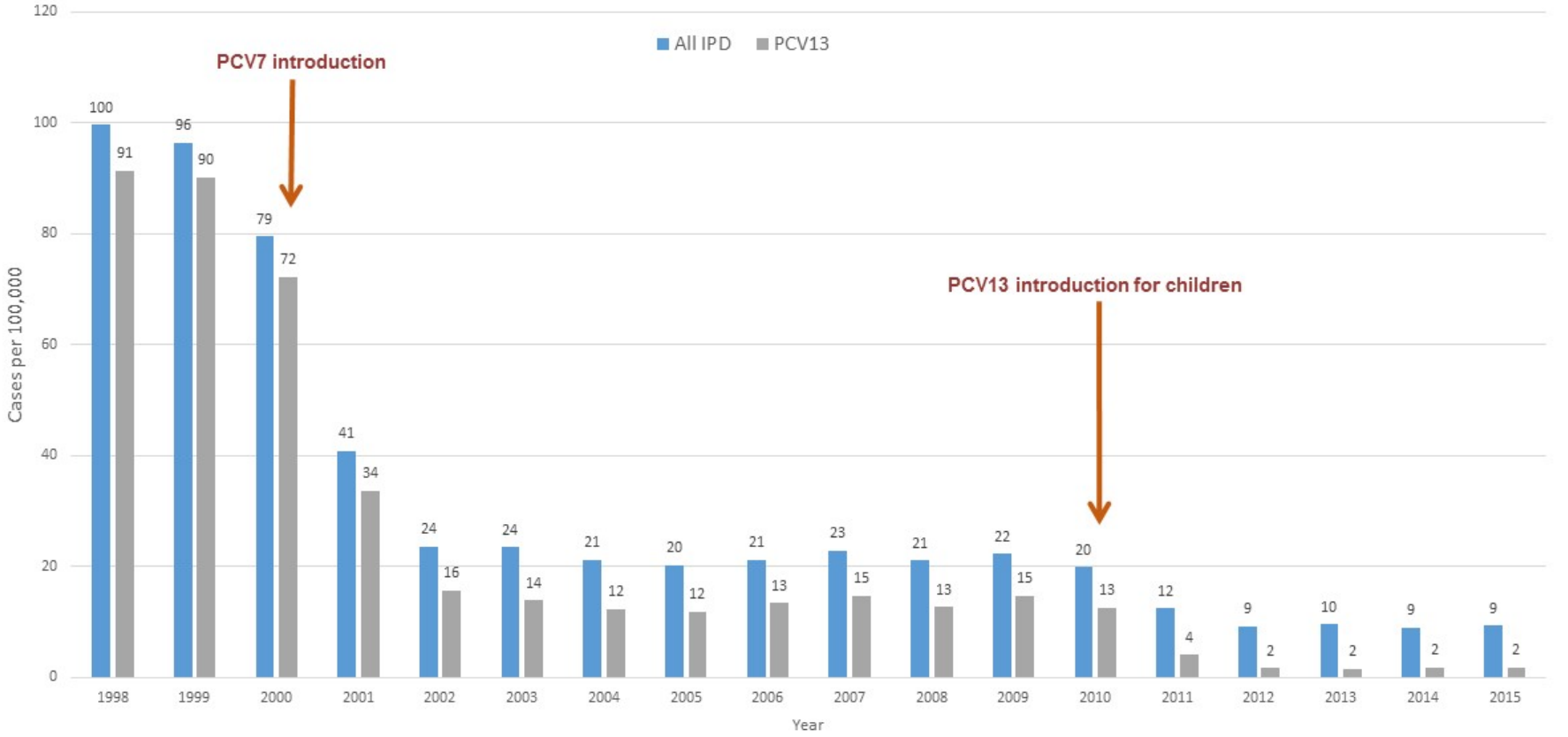
Effect of PCV7 on invasive disease serotype





Ampofo et al, PIDJ 2012; 31.

Trends in invasive pneumococcal disease, in children <5y



⁺PCV13 serotype: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F

Active Bacterial Core surveillance data, 1998–2015, unpublished

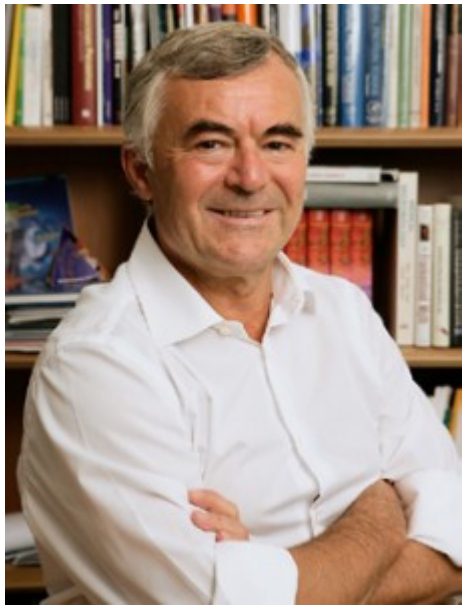
https://www.cdc.gov/vaccines/vpd/pneumo/public/index.html

Pneumococcal vaccine recommendations in children

- Prevnar 13
  - 4-dose primary series: 2m, 4m, 6m, 12-15m
  - Catch up for high-risk children
    - *HIV; immunosuppression; sickle cell disease; asplenia; DM; CSF leaks; cochlear implant; chronic cardiac, pulmonary, or renal disease*
- Pneumovax-23
  - High-risk children starting at age 2, at least 8 weeks after final dose of PCV13
  - 1 dose for most high-risk children
  - Booster dose, 5 years later, for children with immunocompromise, sickle cell disease, or asplenia.

Meningococcal vaccines

Vaccines for rare diseases



Neisseria meningitidis

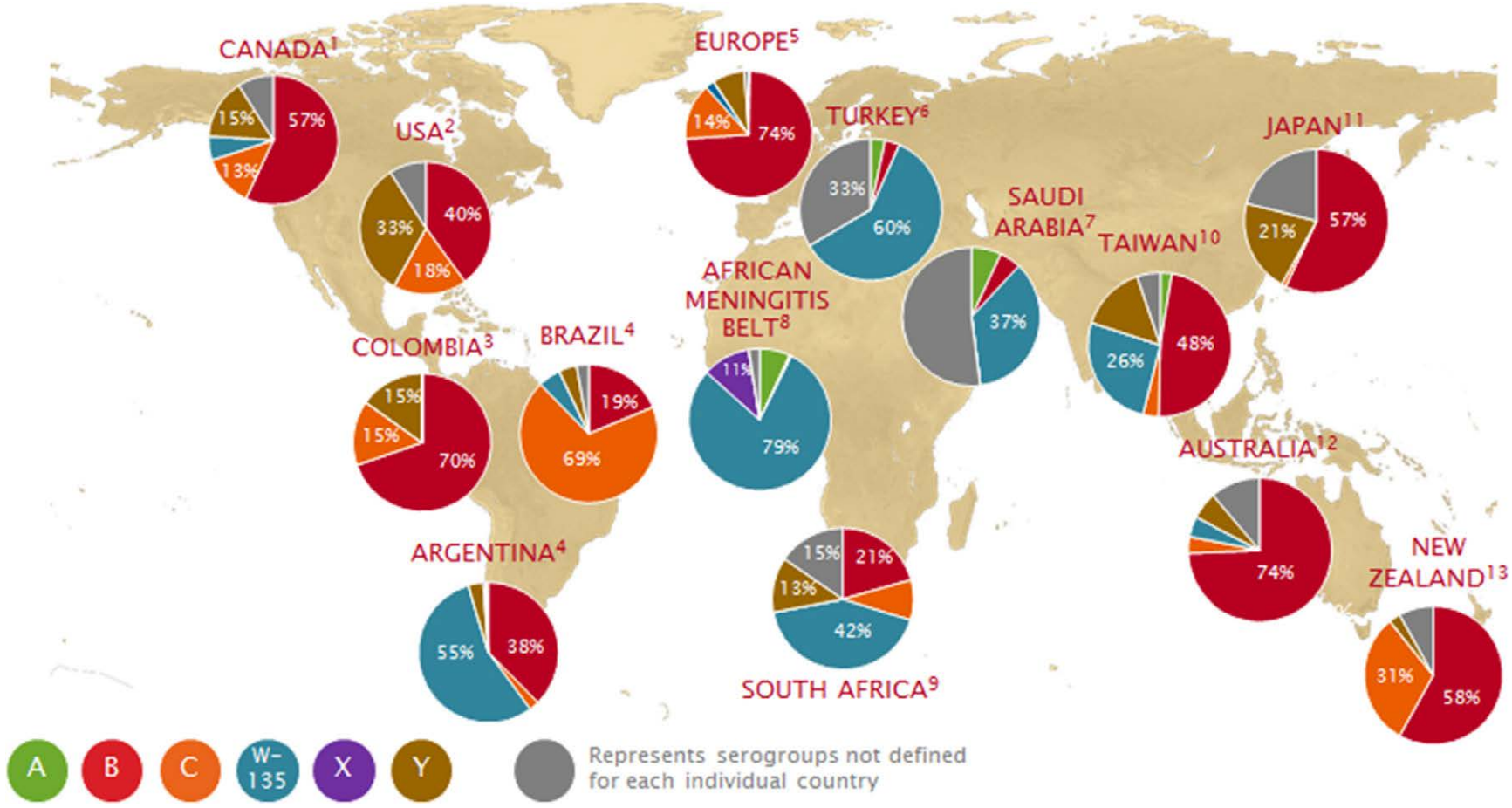
- Human nasopharynx is the only natural reservoir
  - 10% of population are carriers
  - **Meningitis, meningococcemia**, pneumonia, septic arthritis
- Affected populations
  - Infants, complement deficiency, asplenia, indoor crowding (college freshmen in dorms, Hajj)

weeklycontemporary.duerrhennersdorf.com

Purpura fulminans

- Mortality 10-15% (with antibiotics and critical care)

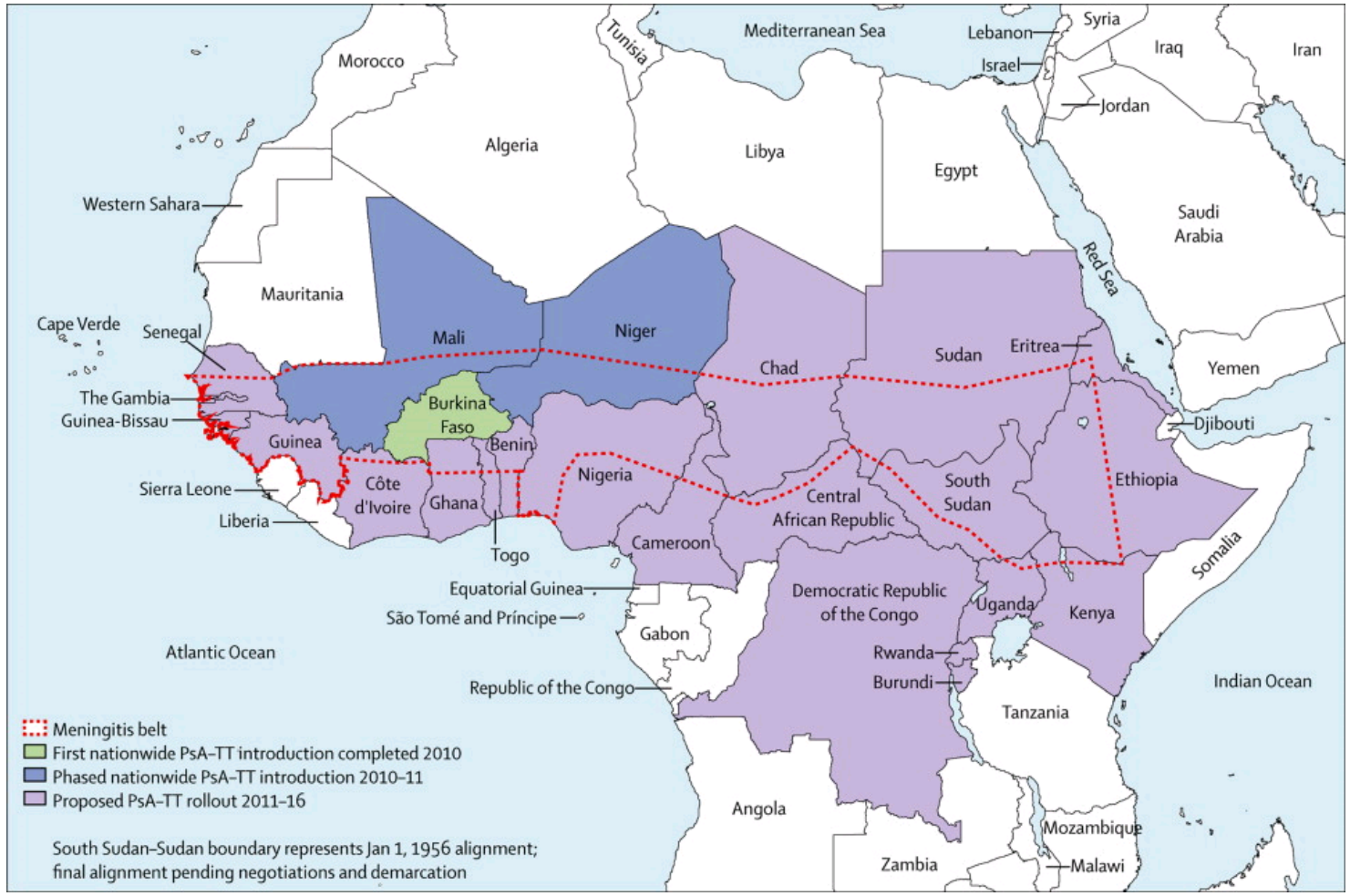
Meningococcal epidemiology



- 1.2 million cases annually
- >100,000 deaths

E. Oviedo-Orta et al. / Vaccine 33 (2015) 3628–3635

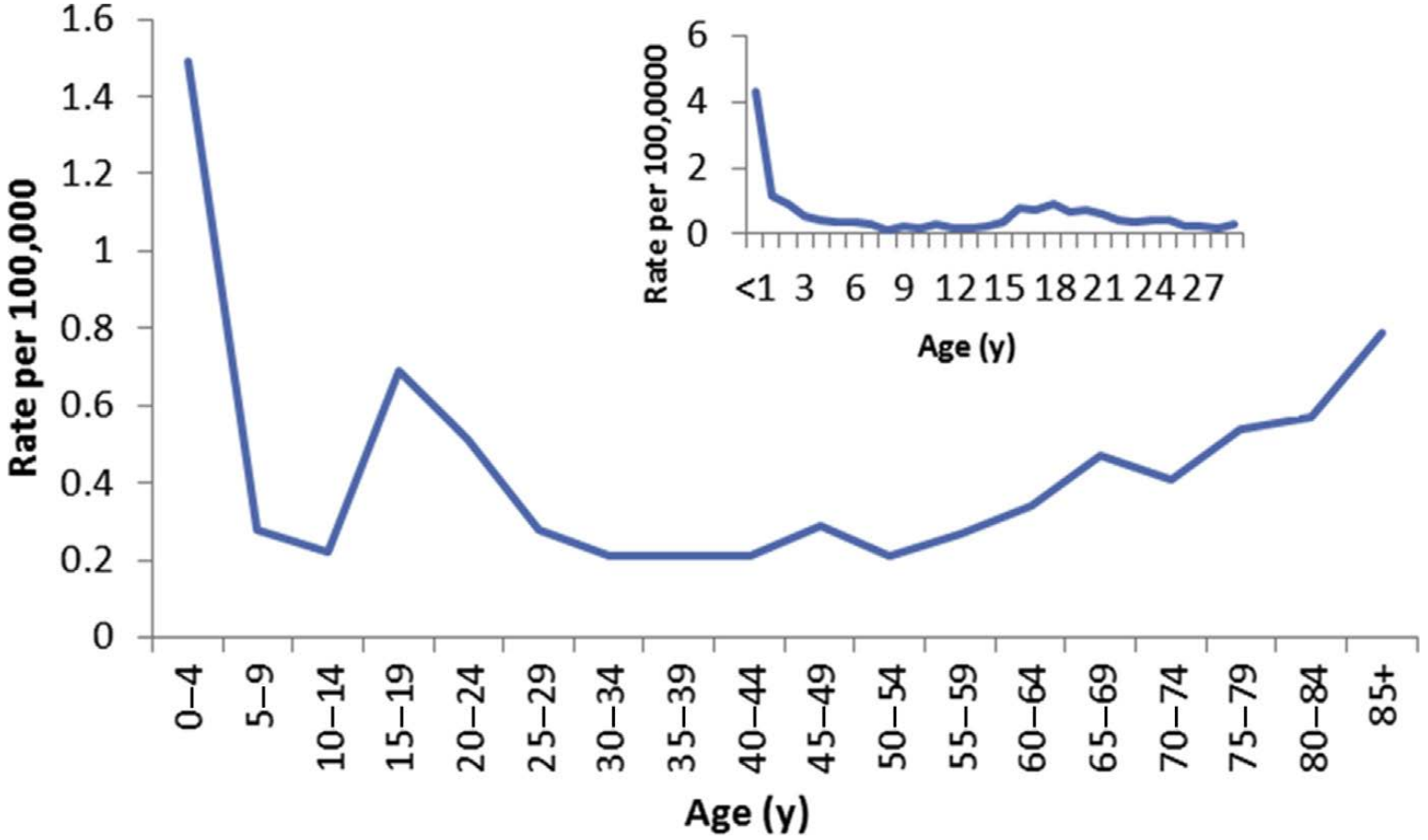
Meningitis belt



- "Usual" epidemic during the dry season
  - 10-100 cases/100,000
- "Explosive" epidemics every 8-12 years
  - 1000 cases per 100,000 (age <2y)

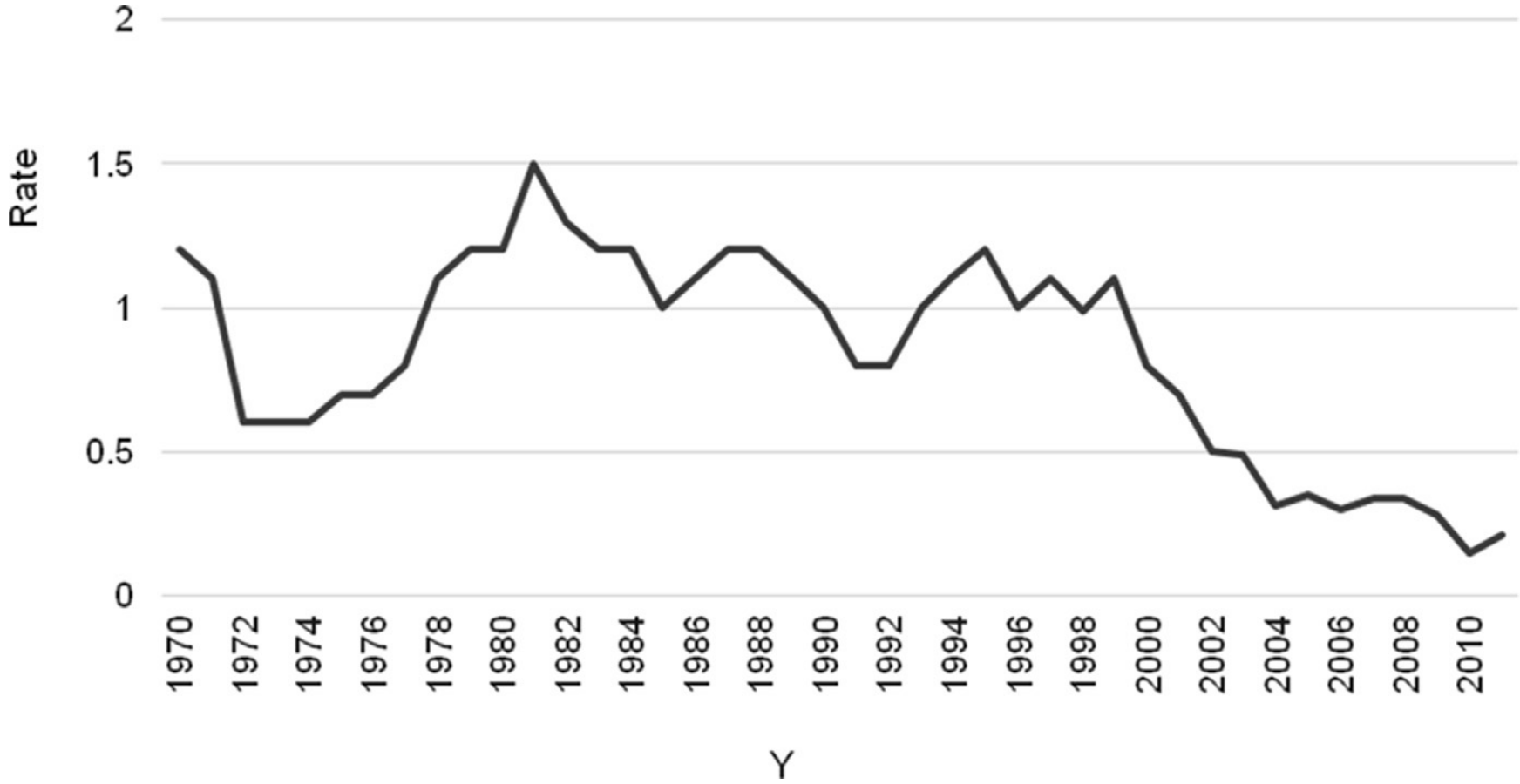
Novak et al, The Lancet Infectious Diseases 12(10) 2012

Epidemiology by age, US 2002-2011



MMWR 2013;662(RR-2):1-28

Deceasing meningococcal disease in US (not vaccine related)



MMWR 2013;662(RR-2):1-28

Polysaccharide and conjugate meningococcal vaccines in the U.S.

A, C, Y, W-135

Menveo

MCV4-CRM

GSK (prev. Novartis)

Conjugated to CRM-197

2010

Age 2m-55y

Menactra

MCV4-D

sanofi

Conjugated to DT

2005

Age 9m-55

Menomune

MPSV4

Sanofi

Polysaccharide

Age >2 y

CY

MenHibrix

Hib-MenCY

GSK

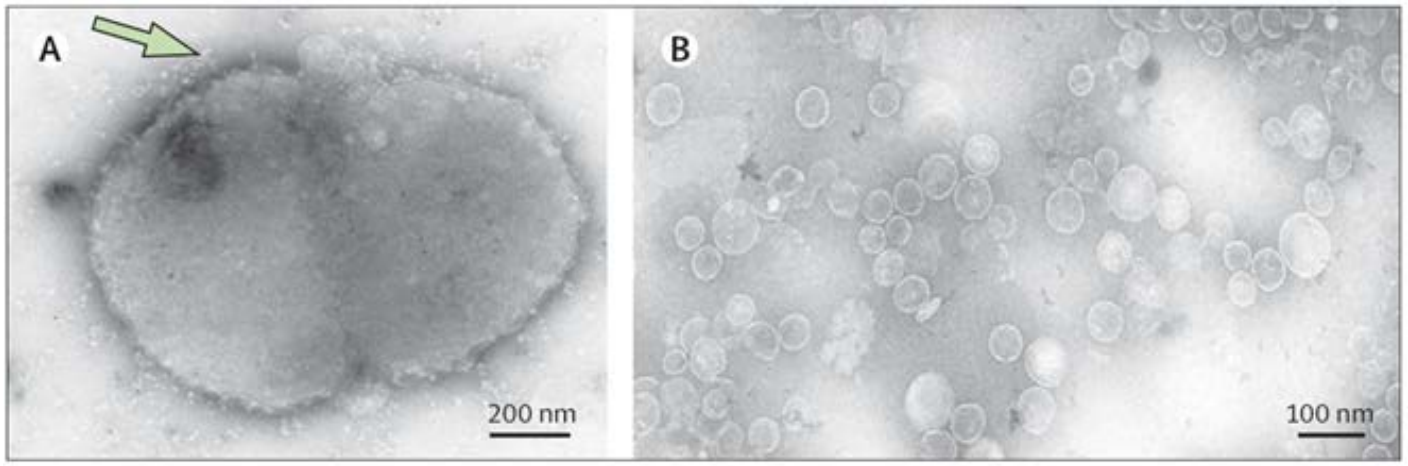
Conjugated to TT

2012

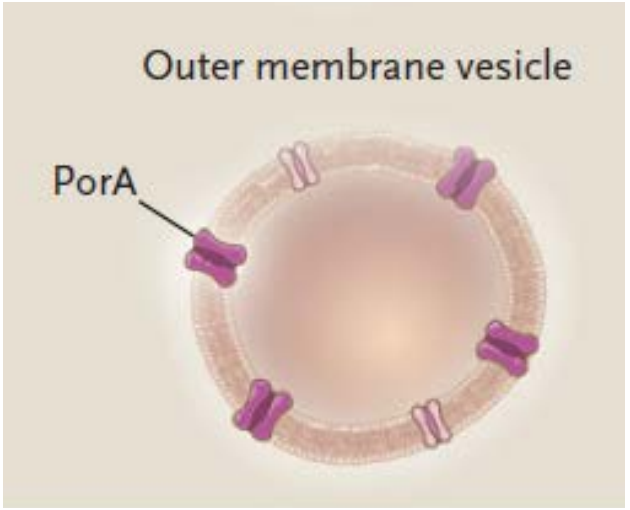
Age 6 wk – 18 months

Outer membrane vesicle Mening B vaccines

- Most antibodies directed to highly variable PorA
- Good outbreak vaccines
- Not very cross-protective
- Not very immunogenic in children



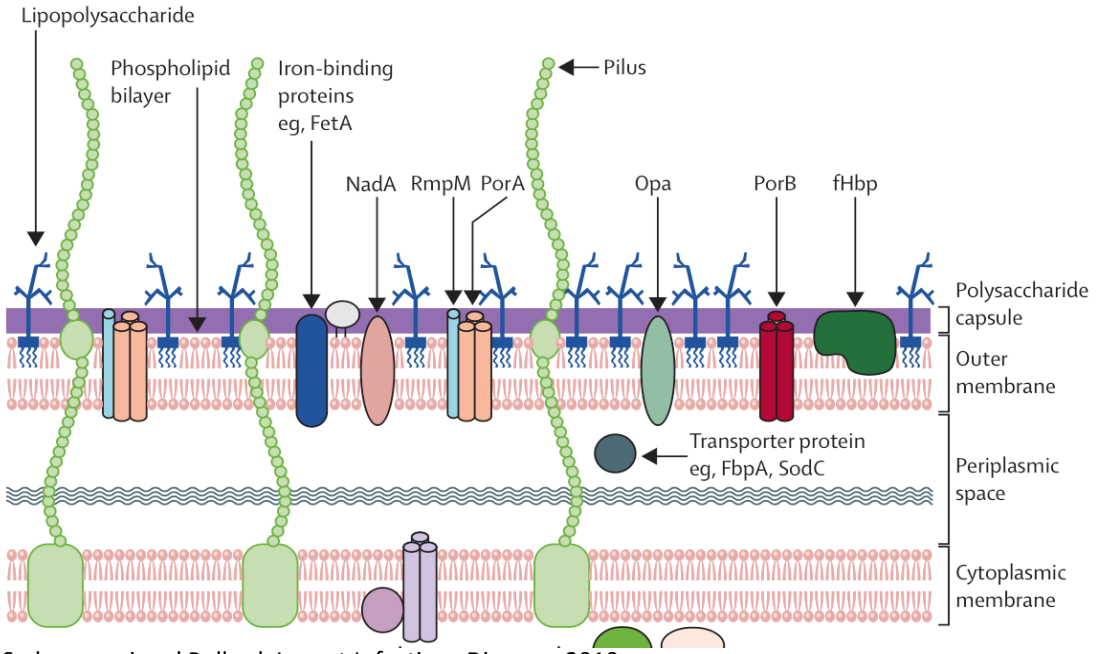
Sadarangani and Pollard, Lancet Infectious Diseases (2010)



Kim JH, NEJM 2016:275;3

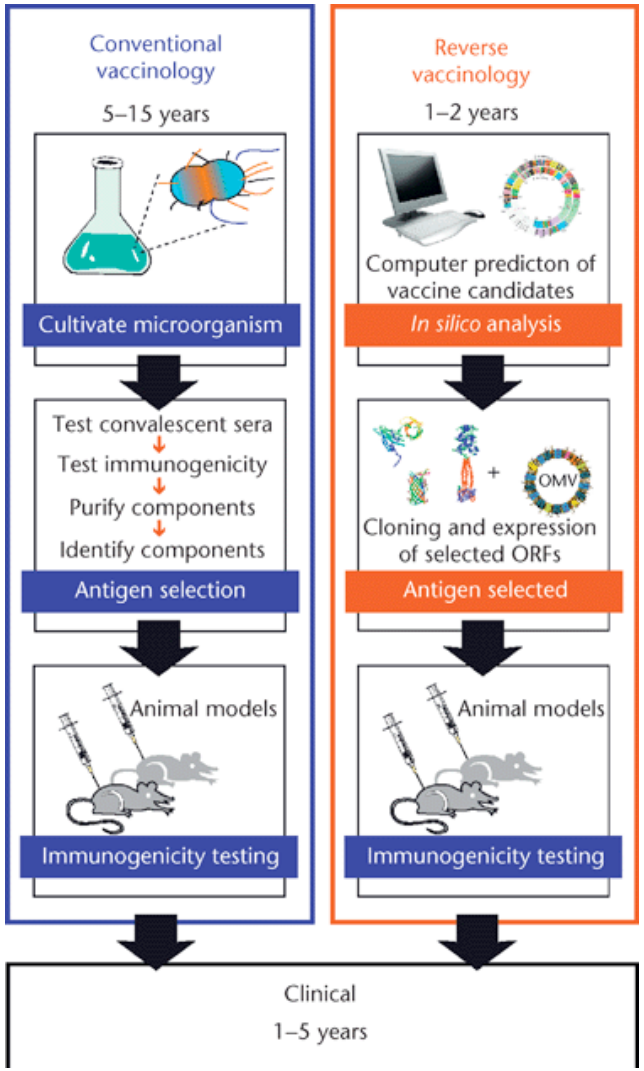
Cross-protective meningococcal B vaccines

- Group B polysaccharide is chemically identical to sugars on human neural cells
  - Poorly immunogenic
  - Risk of autoimmunity
- Therefore, search for other antigens

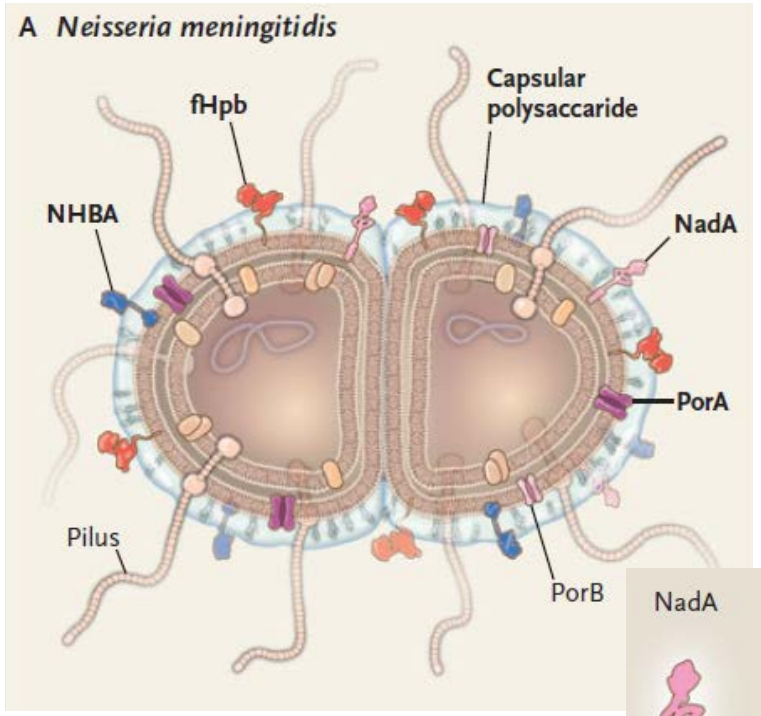


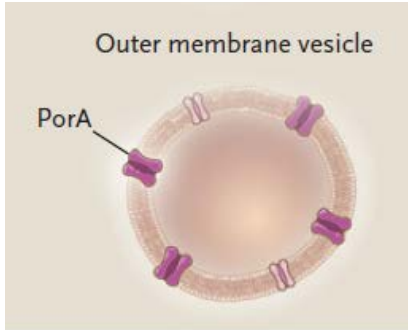
Sadarangani and Pollard, Lancet Infectious Diseases 2010

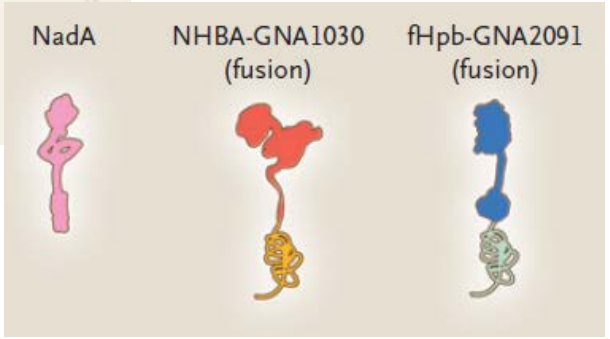
Reverse vaccinology and mening B vaccines



Rappuoli and Chiarot, www.els.net

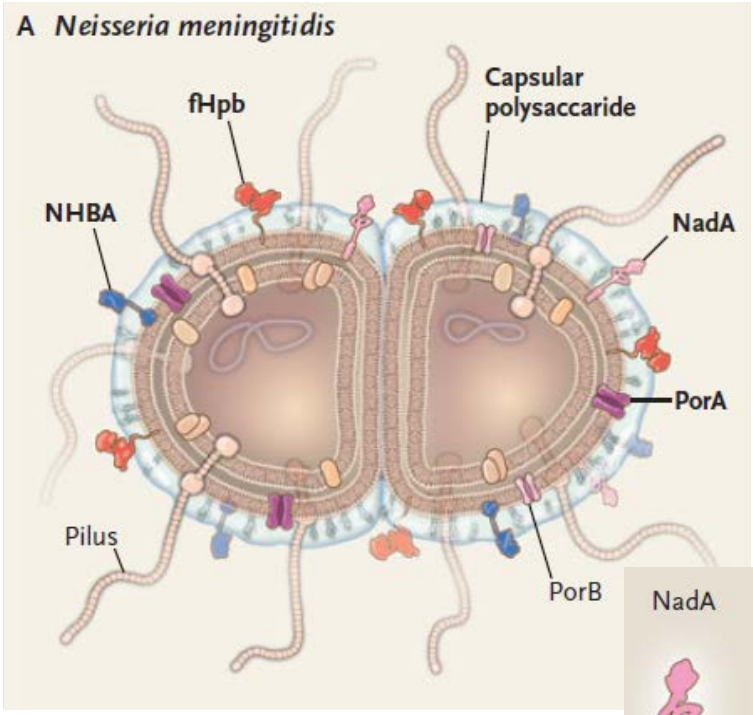


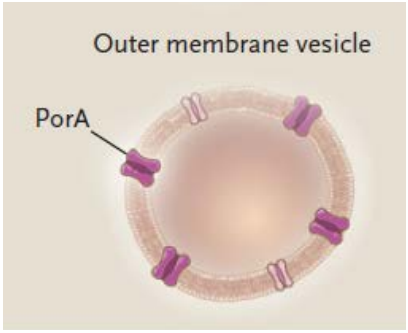


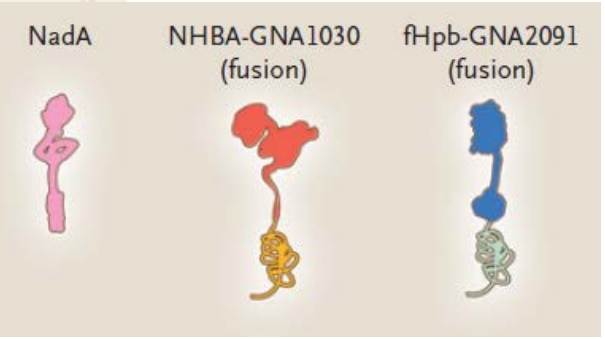


Reverse vaccinology and mening B vaccines

- NadA – neisserial adhesion A
- FHbp – factor H binding protein
  - 500 known amino acid sequence variants
  - 2 to 3 variant groups
- NHBA – neisserial heparin binding antigen
- OMVs – Outer membrane vesicles







Licensed MenB vaccines in the US

MenB-4C (Bexsero)

- GSK (prev. Novartis)
- NadA – neisserial adhesion A
- FHbp – factor H binding protein
- NHBA – neisserial heparin binding antigen
- OMVs – Outer membrane vesicles
- 0, 1 month schedule

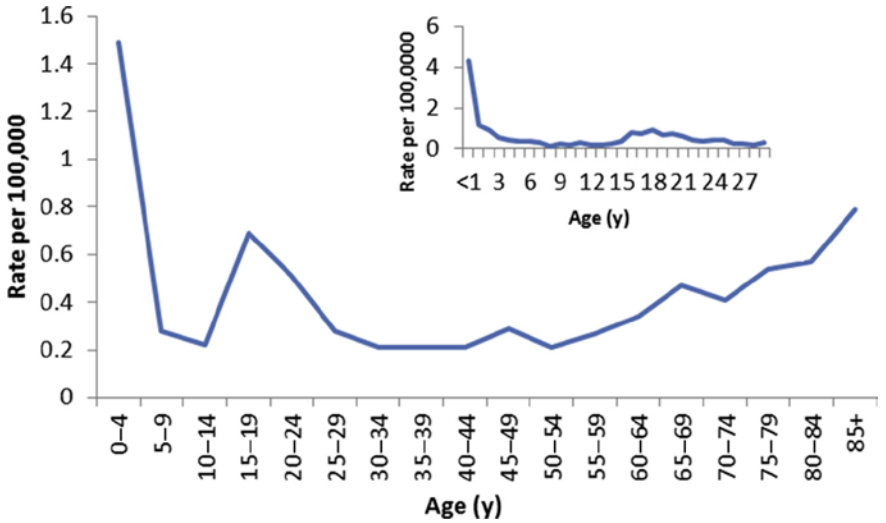
MenB-FHbp (Trumenba)

- Pfizer
- 2 purified recombinant lapidated factor H binding protein antigens
  - 1 antigen from 2 most common subfamilies
- 0, 2, 6 month schedule

Meningococcal vaccines and economics in the US

- 2007 ACIP meeting
  - Vaccination of 11-12 year olds recommended
  - Assumed: vaccine lasts 10 years
- 2008 ACIP meeting
  - 2-10 year olds have lower incidence of disease and more serogroup B disease than 11-19 year olds

1998-2007 Meningococcal disease		
Age	Incidence (per 100,000)	Cost per QALY saved
<2 y	3.9	-
2-10 y	0.68	$160,000
11-19 y	0.81	$90,000



MMWR 2013;662(RR-2):1-28

Meningococcal vaccines and economics in the US

- 2007 ACIP meeting
  - Vaccination of 11-12 year olds recommended
  - Assumed: vaccine lasts 10 years
- 2008 ACIP meeting
  - 2-10 y-olds have lower disease incidence and more group B disease than 11-19-y olds
  - Decision NOT to expand to 2-y olds
- 2010 ACIP meeting
  - Immunity wanes after 5 years
  - 2 approaches considered
    - Add a booster dose at age 16
    - Move the age of vaccination to age 14-15

1998-2007 Meningococcal disease		
Age	Incidence (per 100,000)	Cost per QALY saved
<2 y	3.9	-
2-10 y	0.68	$160,000
11-19 y	0.81	$90,000

Vaccination schedule	Lives/year saved
11-12 y (2010 policy)	9
14-15 y	14
11-12 y plus booster dose at age 16	24

Meningococcal B vaccine in healthy adolescents

- 2015 ACIP meeting - Discussion points
  - Safety
  - Immunogenicity
  - Cost-effectiveness
  - Individual testimony
- "Category B" recommendation – individual decision making
  - Coverage by ACA and VFC

TABLE 2. Potential cases and deaths prevented and cost-effectiveness of different strategies for MenB vaccination of adolescents and young adults, including college students, by age — United States

Age at MenB series	Cases prevented	Deaths prevented	NNV* to prevent case	NNV to prevent death	Cost per QALY (million $)
11 yrs	15	2	203,000	1,512,000	8.7
16 yrs	28	5	107,000	788,000	4.1
18 yrs	29	5	102,000	638,000	3.7
College student	9	1	368,000	2,297,000	9.4

Abbreviations: MenB = meningococcal B vaccine; NNV = number needed to vaccinate; QALY = quality-adjusted life years.
Sources: Unpublished data, ACIP meeting June 2015. Key model assumptions were presented at the June 2015 ACIP meeting. Methods described in Shepard CW, Ortega-Sanchez IR, Scott RD 2nd, Rosenstein NE. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. Pediatrics 2005;115:1220–32.

Meningococcal vaccine recommendations in the US

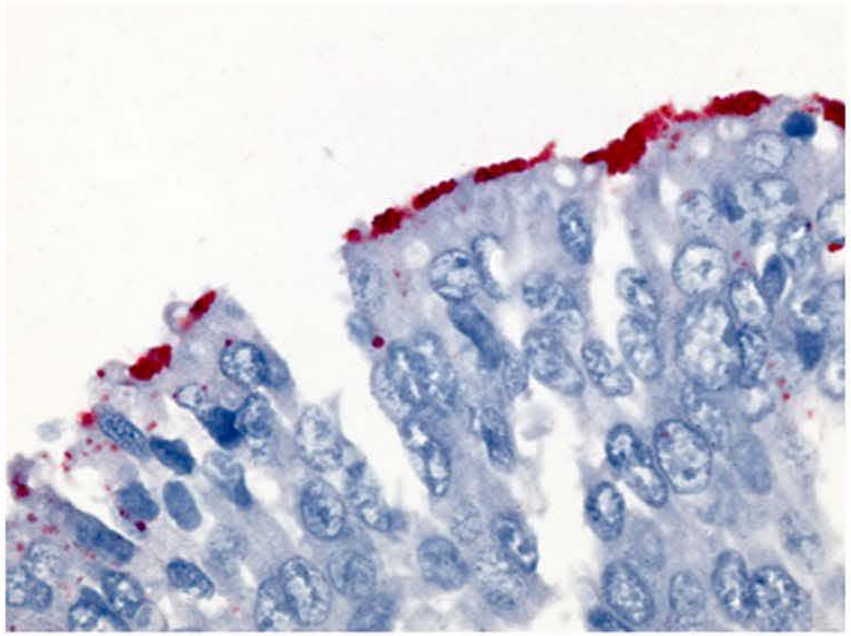
- Healthy adolescents
  - MenACWY, 2 doses: 11-12 y and after16y
  - MenB, 2 or 3 dose series: consider after age 16 y
- Infants at risk
  - MenACWY-CRM or Hib-MenCY, 3 doses plus booster, beginning at 2 months
  - Boost after 3 years, and then every 5 years
- Children at risk
  - 1-2 doses MenACWY, boost every 5 years
- Children at risk, age $\geq$ 10y
  - MenB 2 or 3 dose series

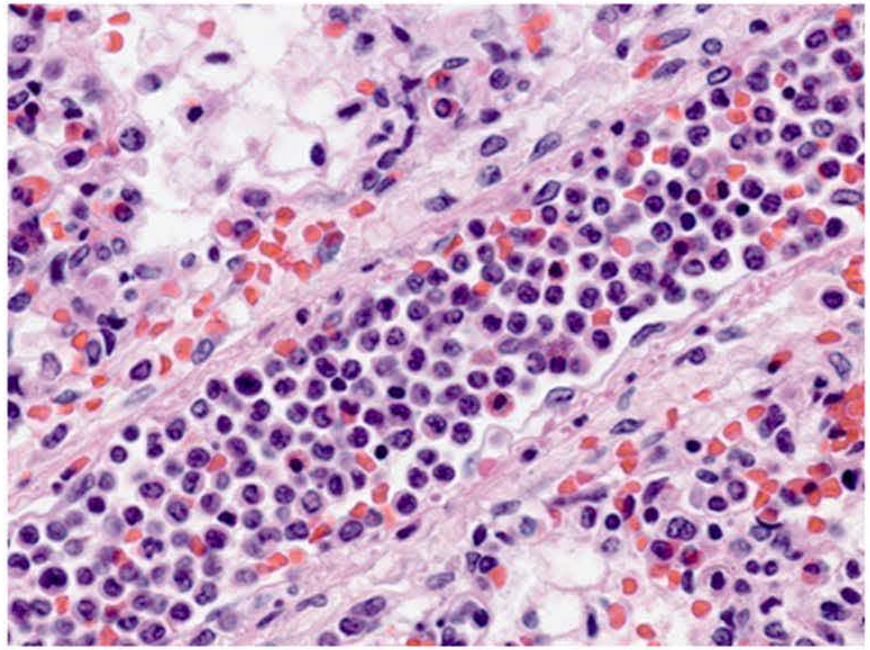
Pertussis vaccines

A safer vaccine…with a trade off

Bordetella pertussis

- Exclusively a human disease
- Gram negative coccobacillus, fastidious organism





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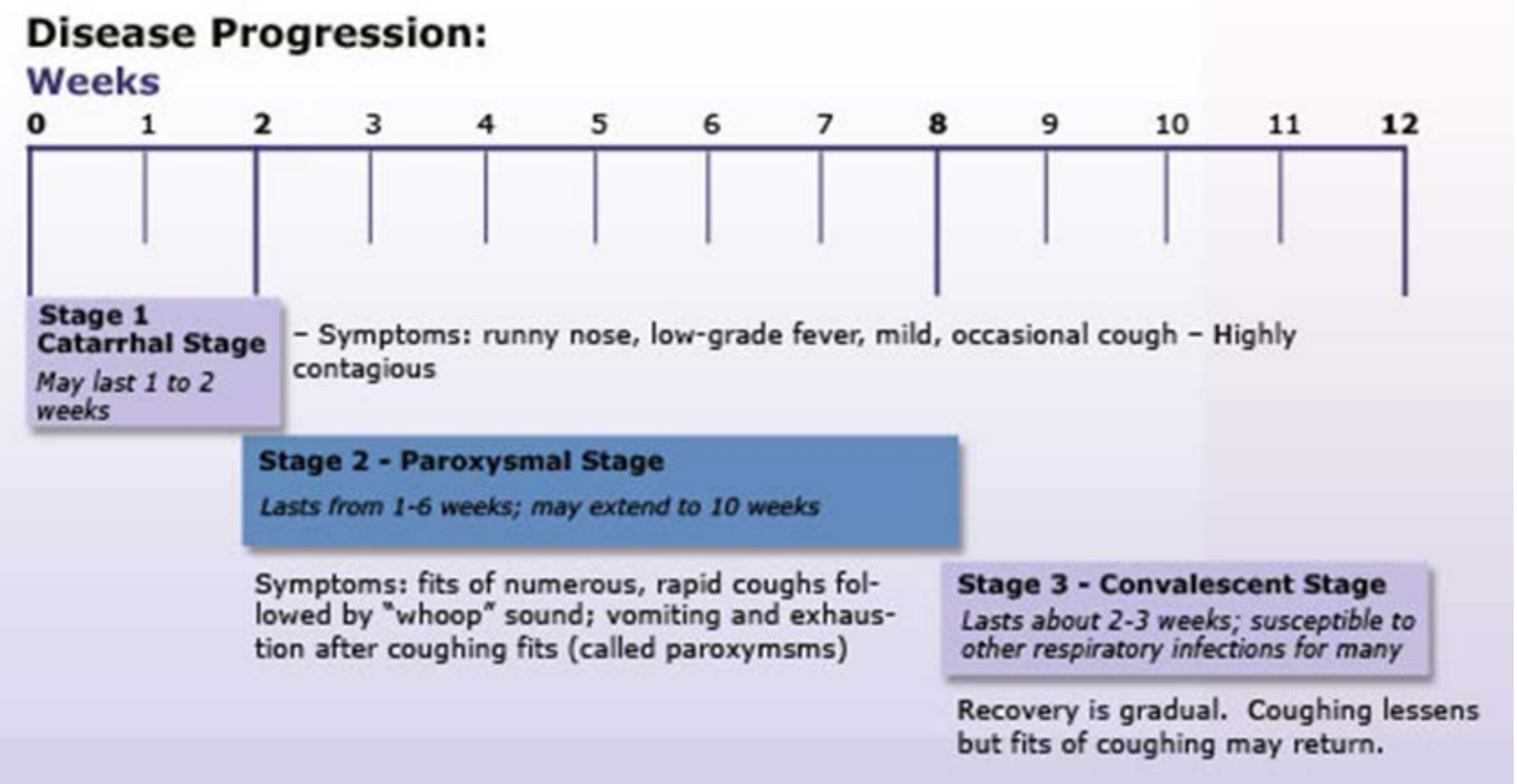
Pertussis clinical manifestations



- Almost all deaths among infants
- Natural immunity is limited

http://www.pkids.org/diseases/pertussis.html

Pertussis vaccines

DTP DTwP DTaP Tdap DT Td TT

Whole cell

- 1930's
- Inactivated, whole *B. pertussis*
- >3000 antigens, including endotoxins

Acellular

- 1980's (Japan), 1990's (US)
- Extractions from *B. pertussis* cultures
- 2 – 5 antigens
  - Detoxified pertussis toxin
  - Filamentous Hemagglutinin
  - Pertactin
  - Fimbriae Types 2 and 3

Pertussis vaccine reactogenicity

Whole cell

- Injection site reactions
- Fever >40.5˚C, 0.3%
- Inconsolable crying (≥3h), ≤1%
- Febrile seizures 1/1750
- Hypotonic-Hyporesponsive Syndrome 1/1750

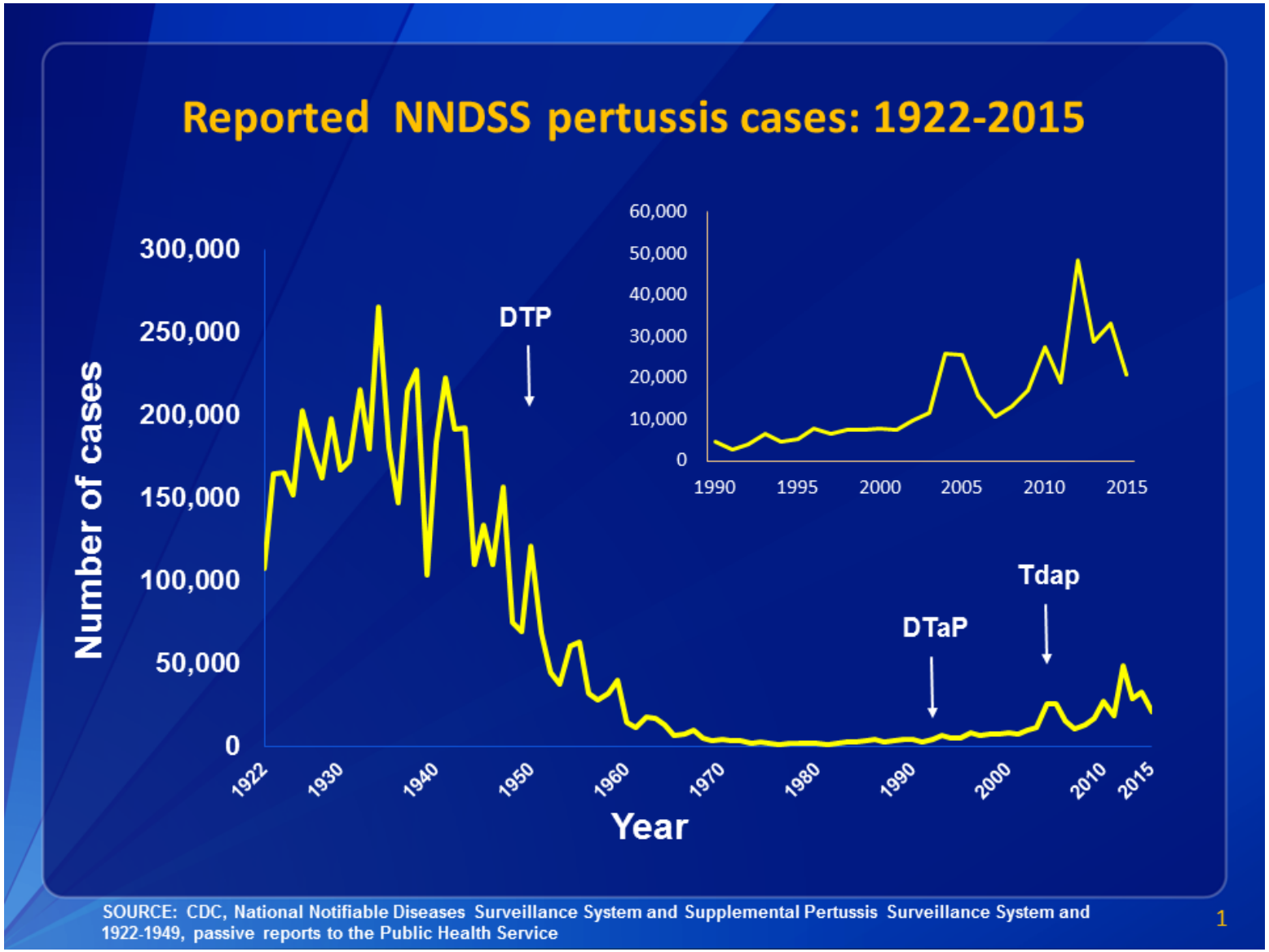
Acellular

- Many fewer than with Whole cell vaccine
- Injection site reactions
  - Extensive Limb swelling 2-3% after 4th + 5th doses

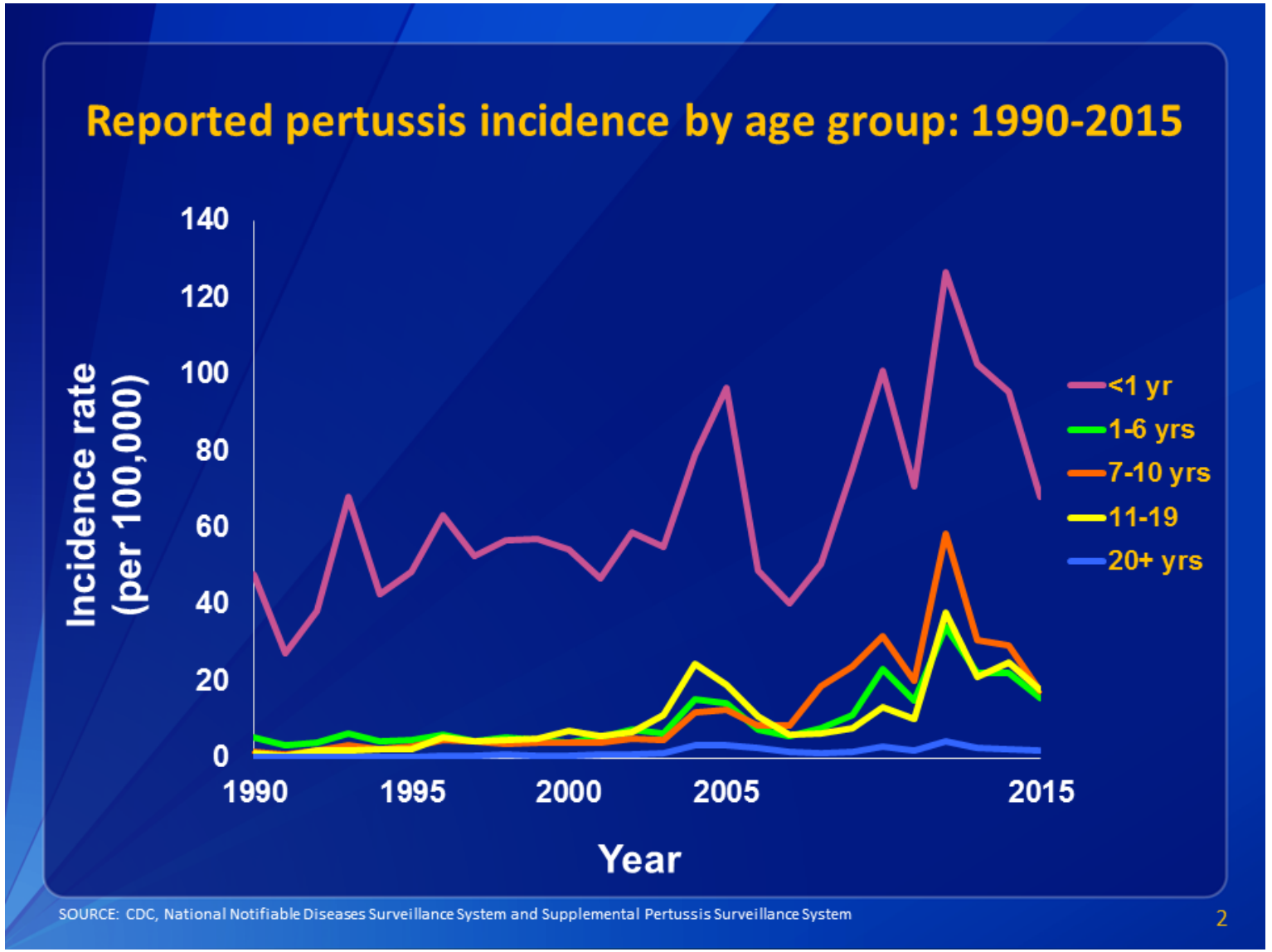
Marshall H S et al. Pediatrics 2006;118:1501-1509

Current pertussis vaccine recommendations in US

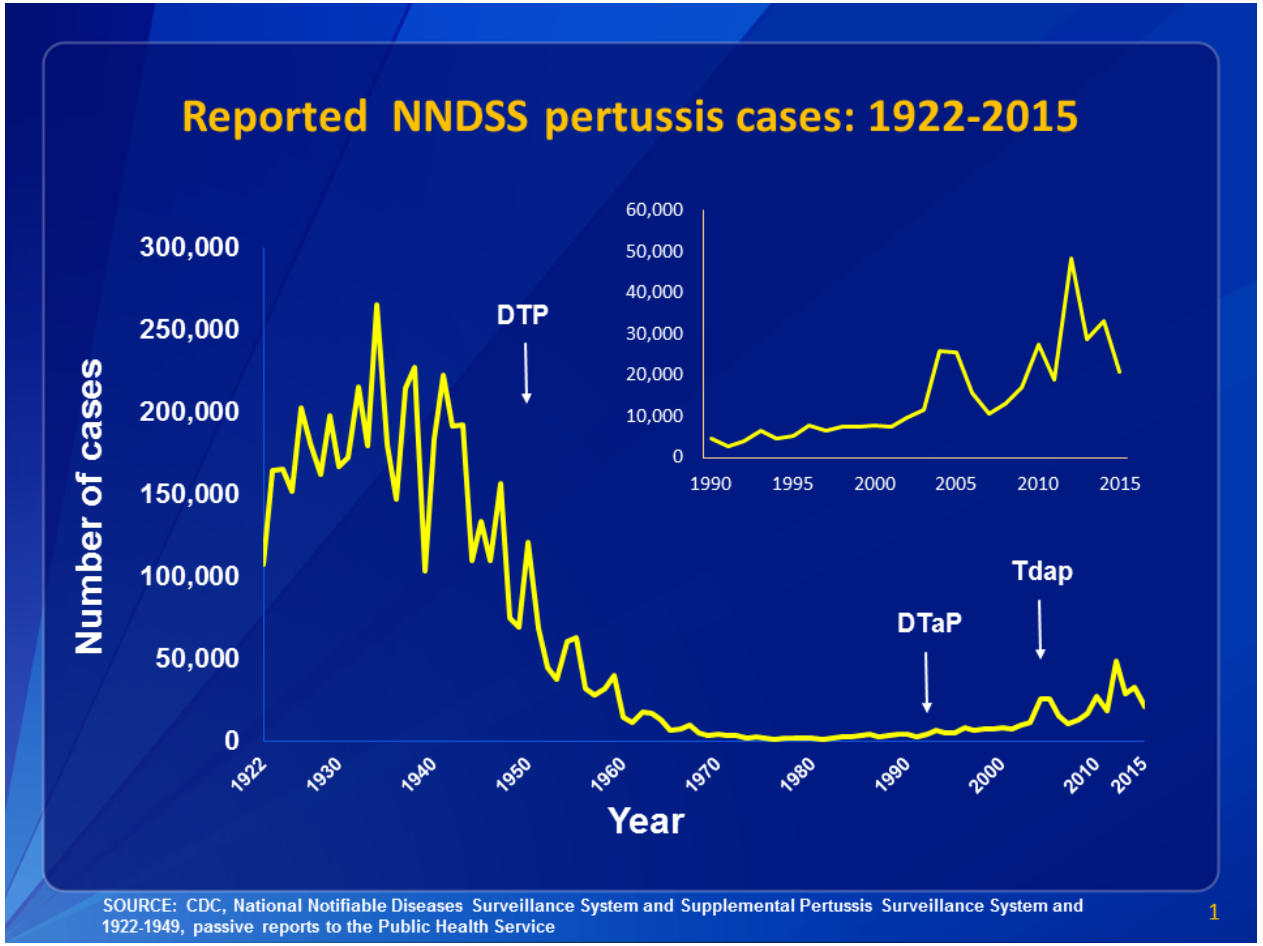
- DTaP for all children: 2, 4, 6m, 15-18m, 4-6y
- Tdap for all children: 11-12y
- All adults should get one dose of Tdap. No minimum interval between Td and Tdap.
- Tetanus boosters (Tdap or Td) are given every 10 years, especially if at increased risk (travel), post-exposure
- Pregnant women: 1 dose of Tdap during each pregnancy
  - 27^{th}-36^{th} week, earlier is preferred



- Cyclical epidemics every 2-5 years
- DTwP vaccine use was followed by a dramatic decrease in cases
- But, cases have been slowly rising since the 1970s


Reported pertussis incidence by age group: 1990-2015
Incidence rate (per 100,000)
140
120
100
80
60
40
20
0
1990
1995
2000
2005
2015
Year
<1 yr
1-6 yrs
7-10 yrs
11-19
20+ yrs
SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

Why has there been a resurgence of pertussis?



- Increased recognition and reporting
  - PCR diagnostic
- Genetic changes in *B. pertussis*
  - Increased virulence of strains
  - Strains with variant antigens
- Shortcomings of the DTaP vaccine
  - Waning immunity
  - "Linked epitope suppression"
    - Original antigenic sin
  - Presentation of fewer antigens allows for more vaccine escape
  - Change in T-cell priming

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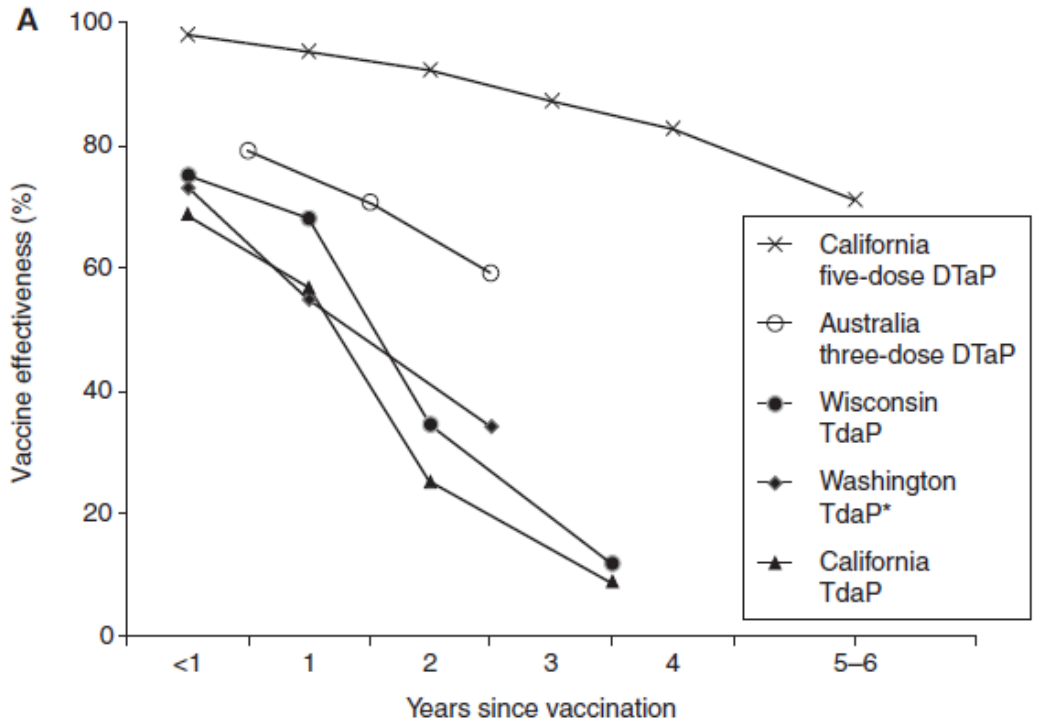
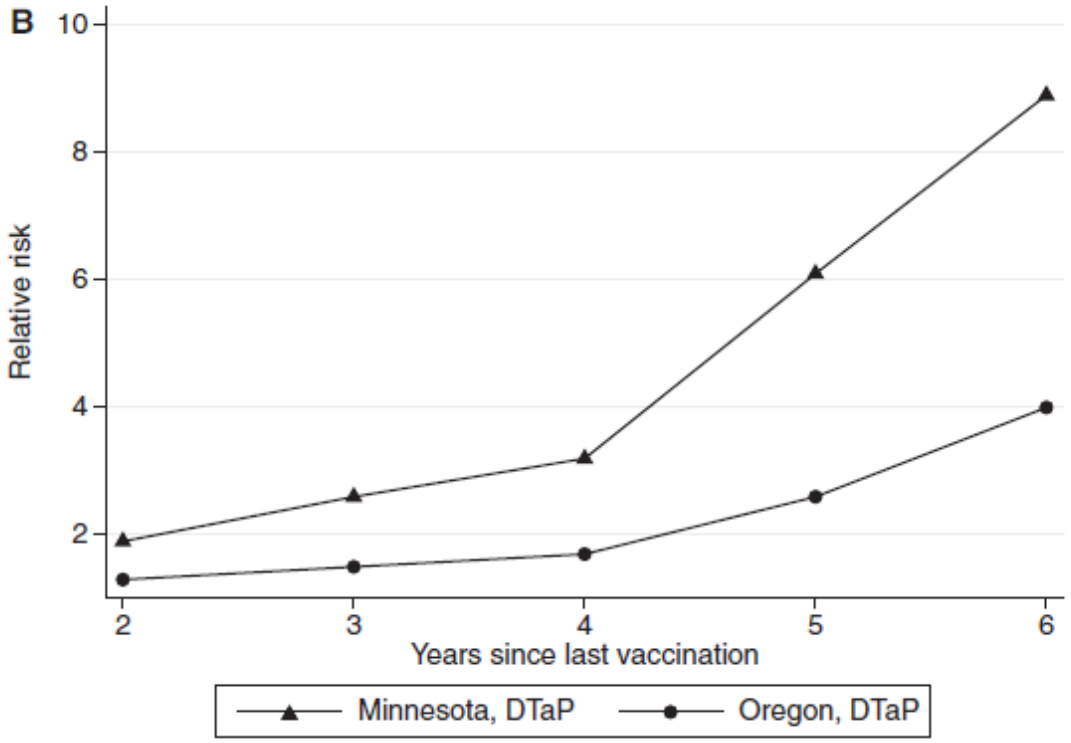
Waning pertussis immunity





Burdin et al, Cold Spring Harbor Perspectives in Biology, 2017

Strategies for preventing pertussis

- Adult booster
- Vaccination during pregnancy
- Cocooning
- New vaccines
  - Live-attenuated pertussis vaccines
  - New acellular vaccines
  - Safer whole cell vaccines

Resources

- Immunization Action Coalition
  - Immunize.org
- CDC, including the Pink Book
  - www.cdc.gov/vaccines/pubs/pinkbook/chapters.html
- Vaccine Education Center
  - www.chop.edu/centers-programs/vaccine-education-center