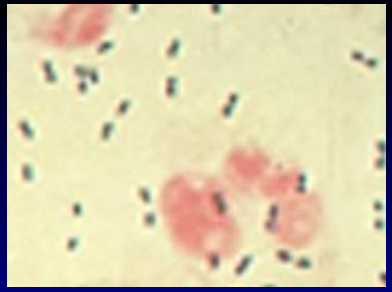
Vaccines against Polysaccharide Antigens: Pneumococcus and Meningococcus

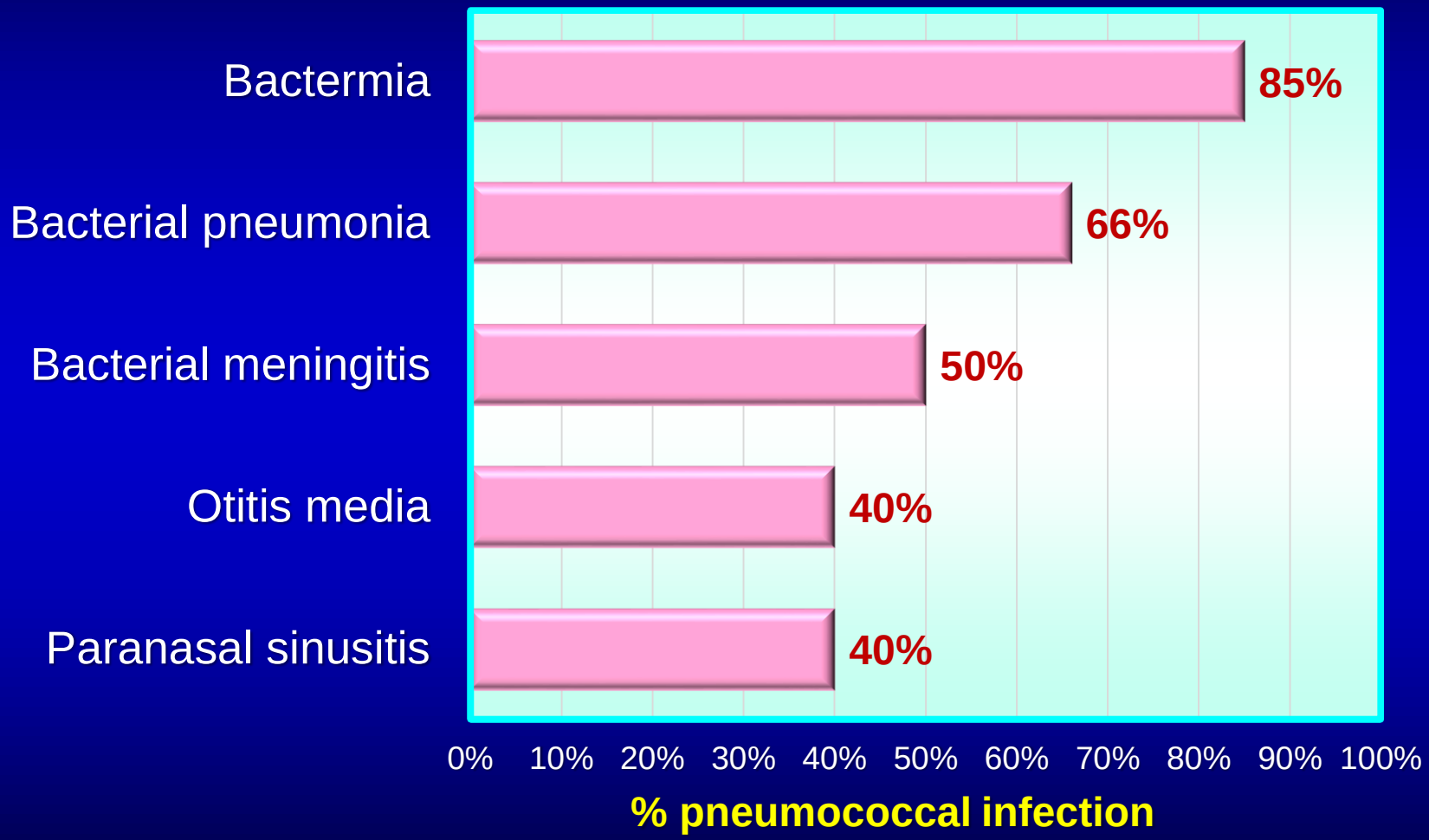
Ping-Ing Lee

National Taiwan University Children's Hospital

G.Q.

Bacterial diseases caused by *Streptoccus pneumoniae* in children





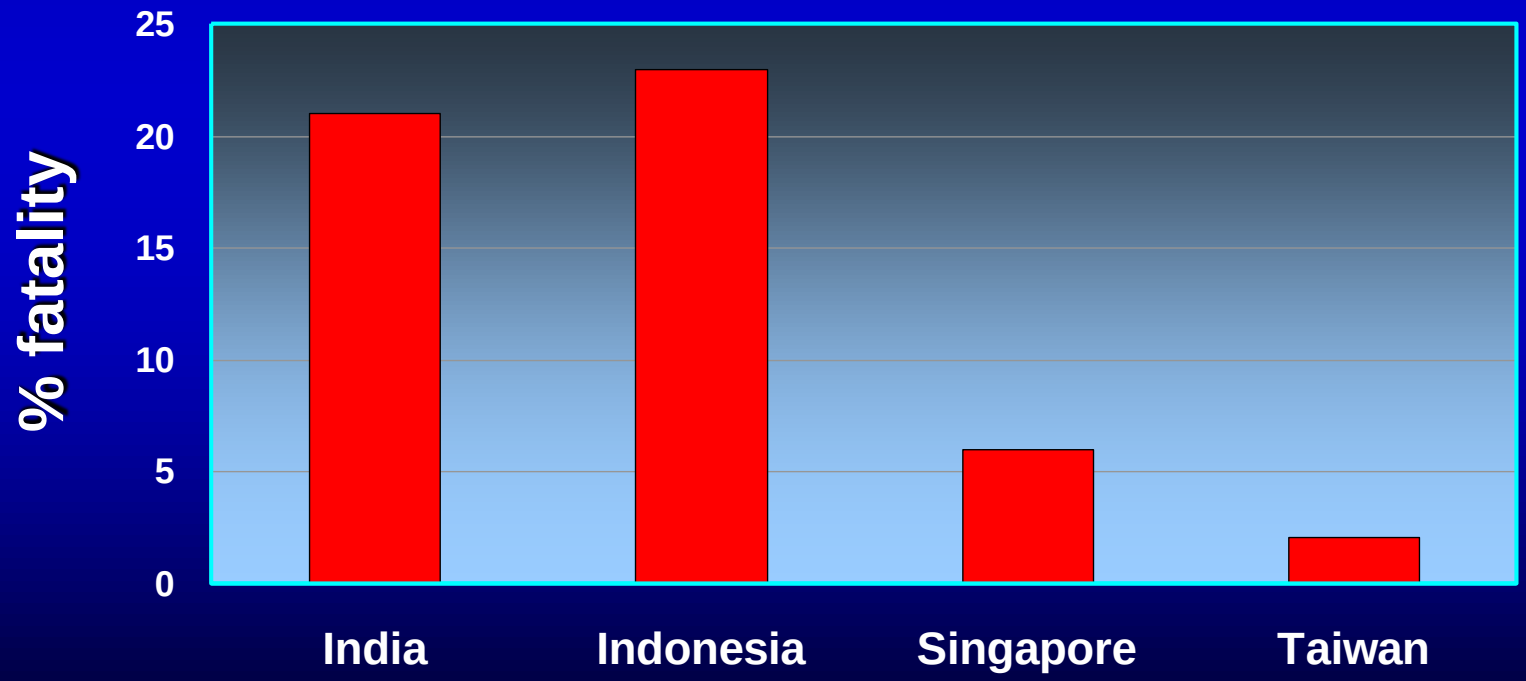
Eskola J, klein JO, Klugman KP, et al. Strategies for controlling pneumococcal disease. Monterey, Calif:Presented at the First international Pediatric infectious Disease conference; September 21-22, 1995;19-24

G.Q.

Disease burden of invasive pneumococcal disease in Asia

Asian Strategic Alliance for Pneumococcal Disease Prevention 2009

- A substantial disease burden, esp. for children < 5 yrs
- Sepsis, meningitis, pneumonia

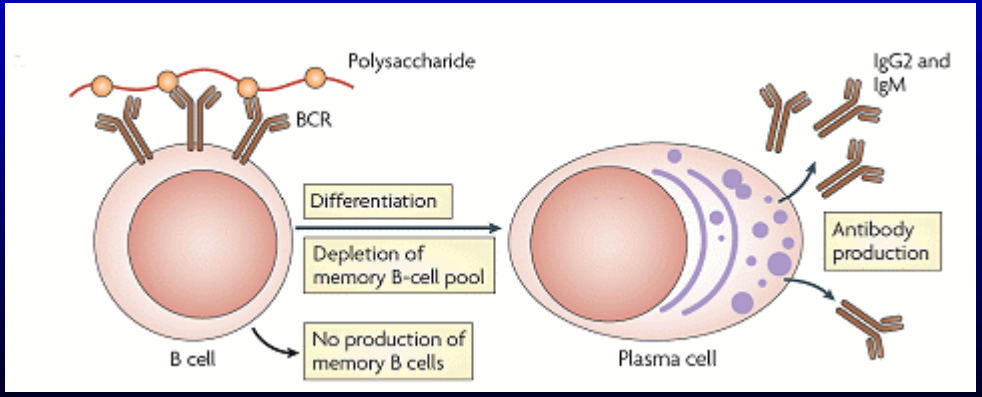


Overall case fatality rate due to IPD

G.Q.

Pneumococcal polysaccharide vaccine

- *Streptococcus pneumoniae*: at least **92 serotypes**
- **23-valent pneumococcal capsular polysaccharide vaccine (1983):**
  - Serotypes: 1、2、3、4、5、6B、7F、8、9N、9V、10A、11A、12F、14、15B、17F、18C、19F、19A、20、22F、23F、33F
  - **T cell-independent immune response**
    - **Poor immune memory**
    - **Poor booster effect**
    - **Poorly immunogenic in children < 2 years**



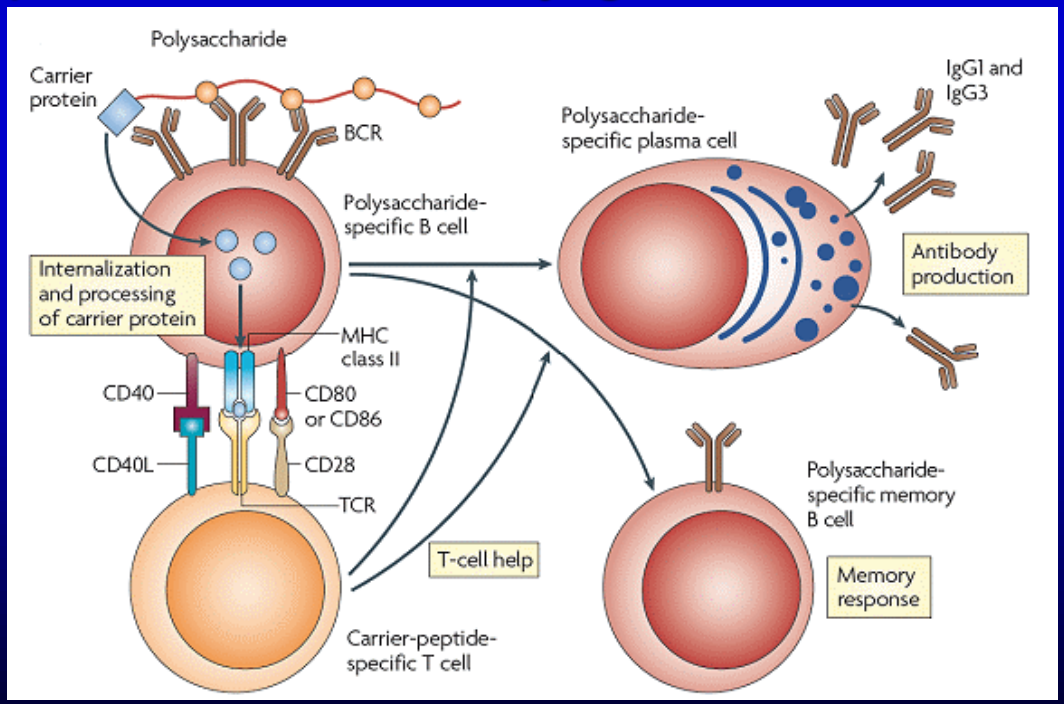
Pollard AJ. Nat Rev Immunol 2009;9:213.

G.Q.

Pneumococcal conjugate vaccine

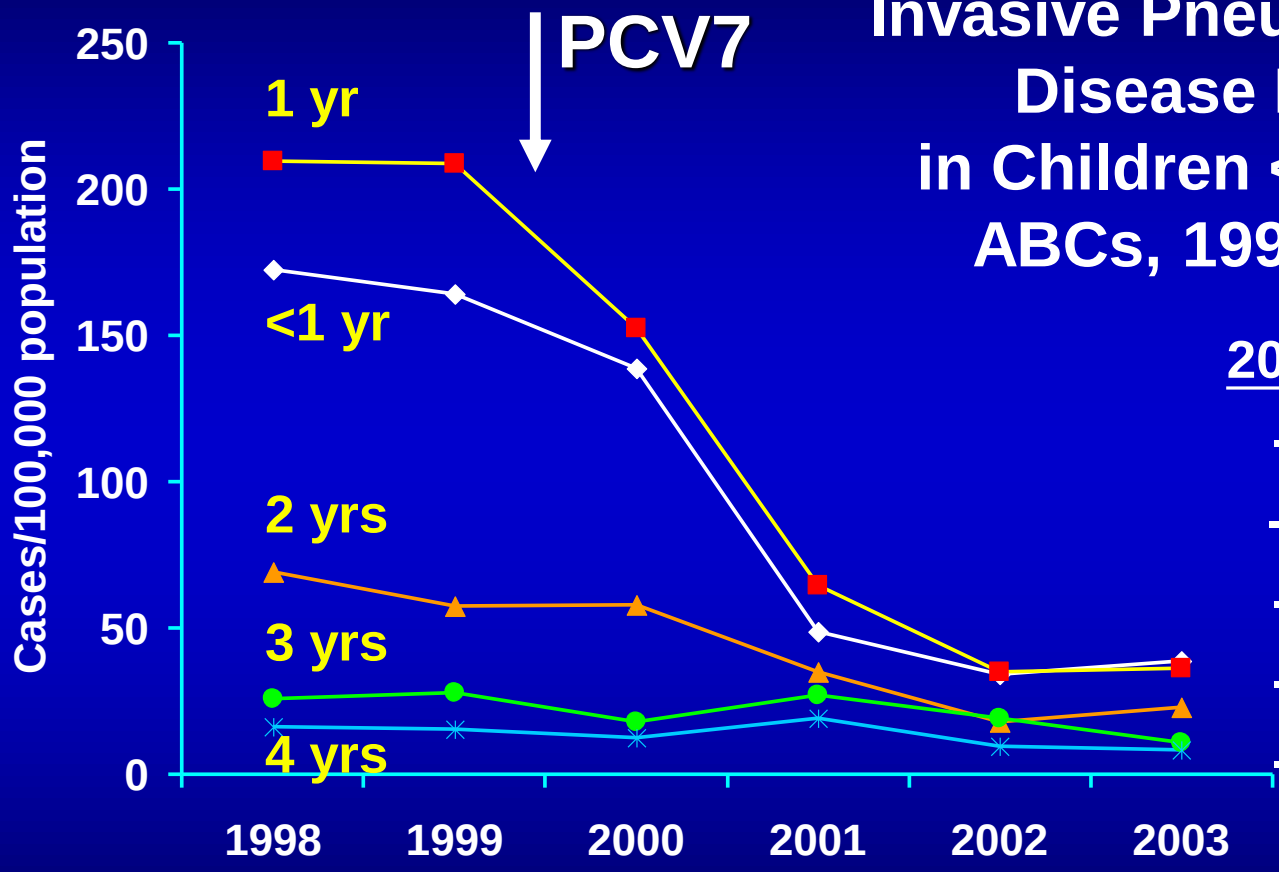
- **T cell-dependent immune response**
  - **Immune memory (+)**
  - **Booster effect (+)**
  - **Immunogenic in children < 2 years**
- *Haemophilus influenzae* type b conjugate vaccine

  ➔ pneumococcal conjugate vaccine



Pollard AJ. Nat Rev Immunol 2009;9:213.

Impact of pneumococcal conjugate vaccine on target age group



Invasive Pneumococcal Disease Rates in Children <5 Years, ABCs, 1998-2003

2003 vs baseline

- 77% (<1 yr)
- 83% (1 yr)
- 64% (2 yr)
- 60% (3 yr)
- 48% (4 yr)

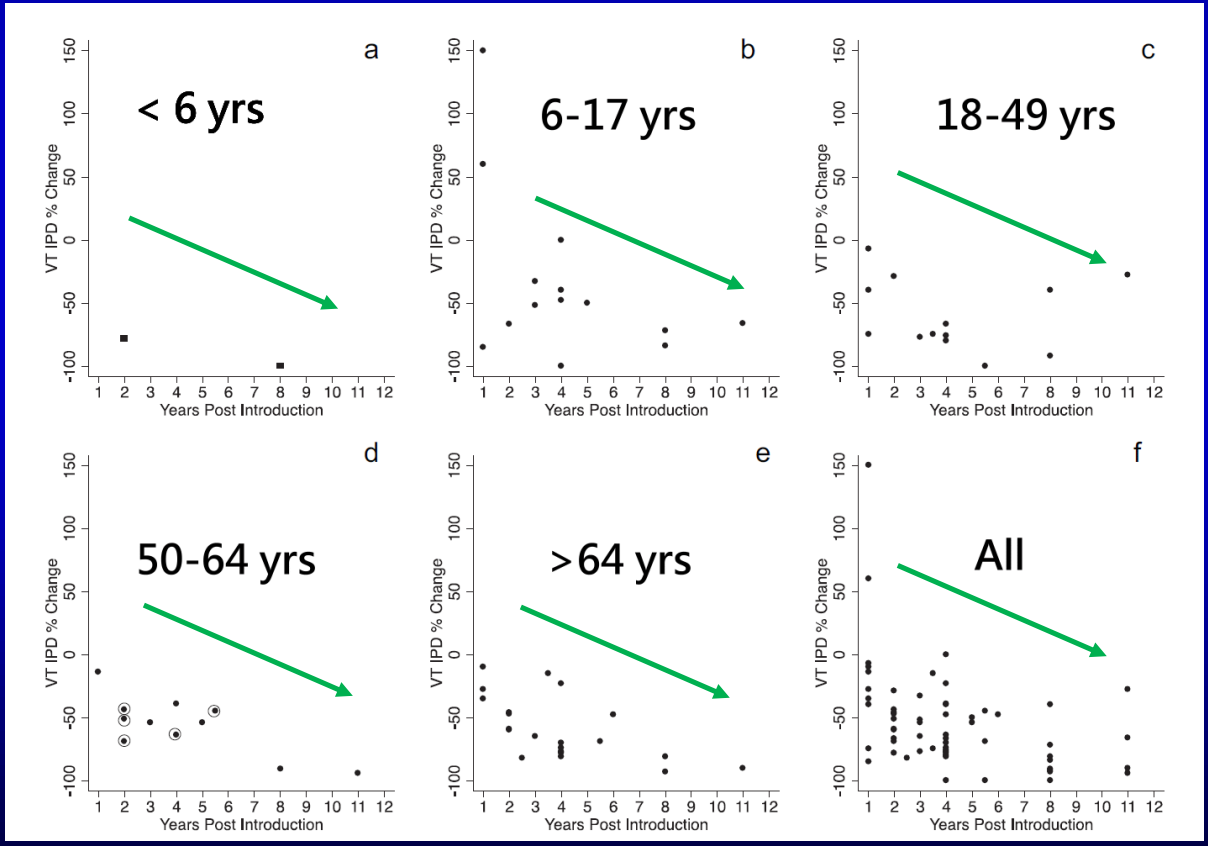
2003 data are preliminary

U.S. Centers for Disease Control & Prevention; Atlanta, GA, USA

G.Q.

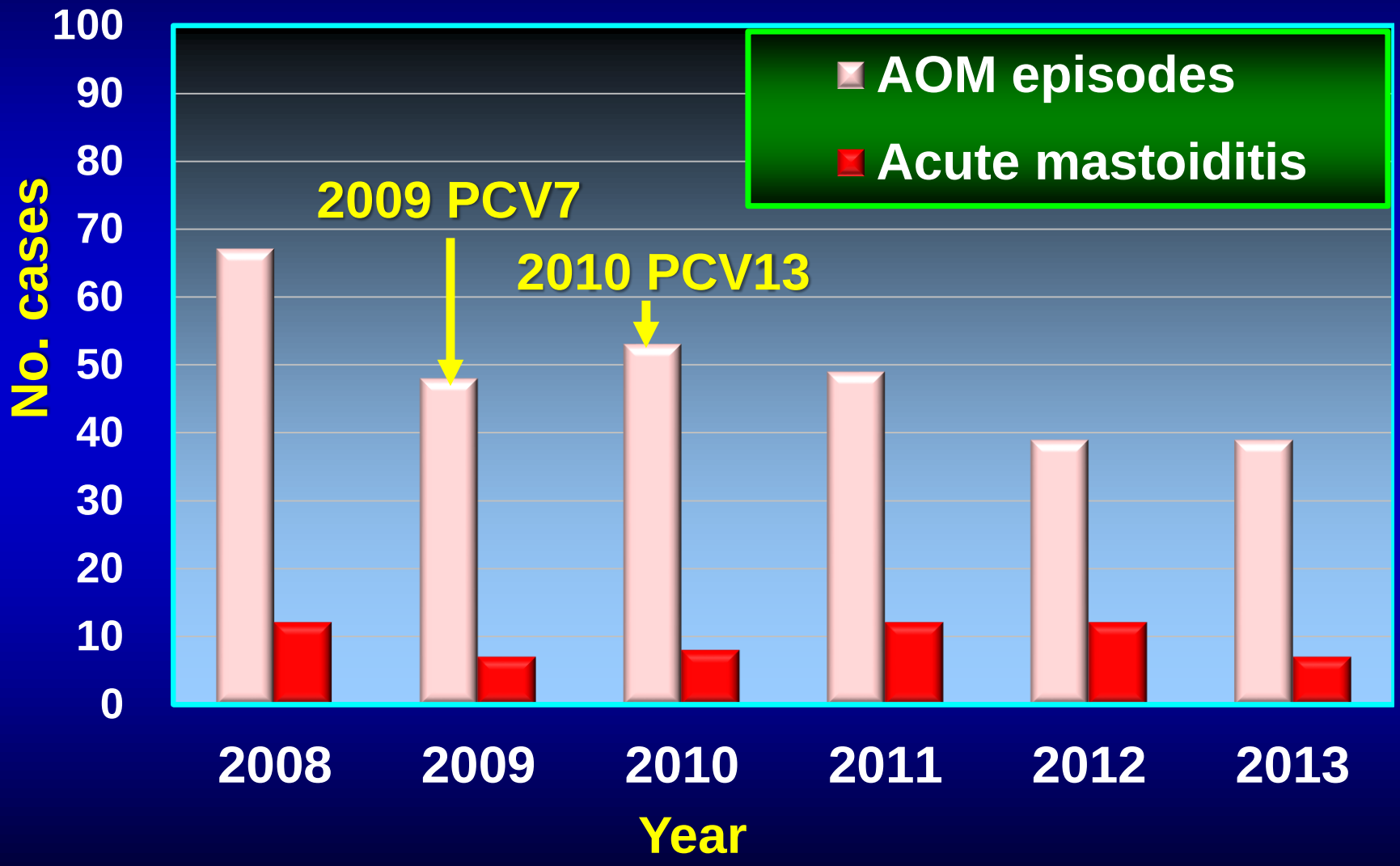
Herd protection against invasive pneumococcal diseases Meta-analysis, 2014

- Vaccine-type IPD in non-targeted populations consistently decreased after PCV introduction.



Davis SM. Vaccine. 2014;32(1):133.

Changing trends of acute otitis media bacteriology N=279, < 6 yrs, 2008-2010, Israel



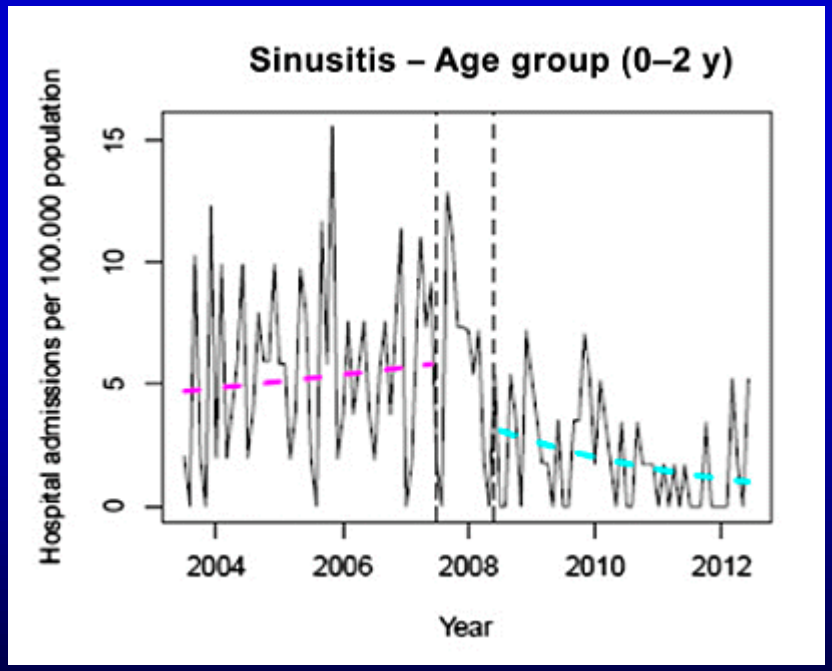
G.Q.

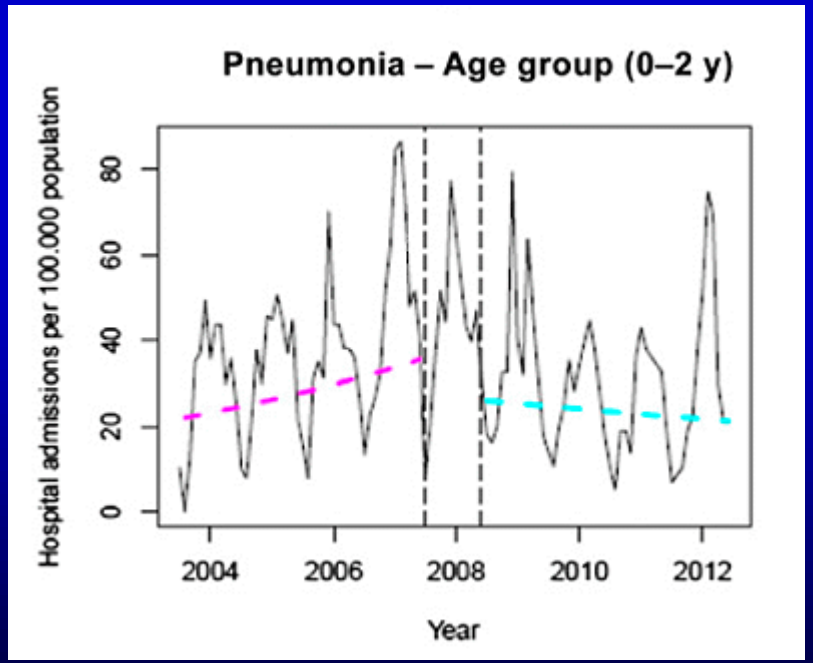
Tamir SO. Pediatr Infect Dis J 2015;34(2):195.

Sinusitis and pneumonia hospitalization in the PCV era < 2yrs, 2003-2012, Sweden

PCV7 and PCV13 vaccination

- **Sinusitis ↓ 66%**
- **Pneumonia ↓ 19%**





G.Q. Lindstrand A. Pediatrics 2014;134(6):e1528.

Decreasing resistance of *S. pneumoniae* after the use of PCV7 USA

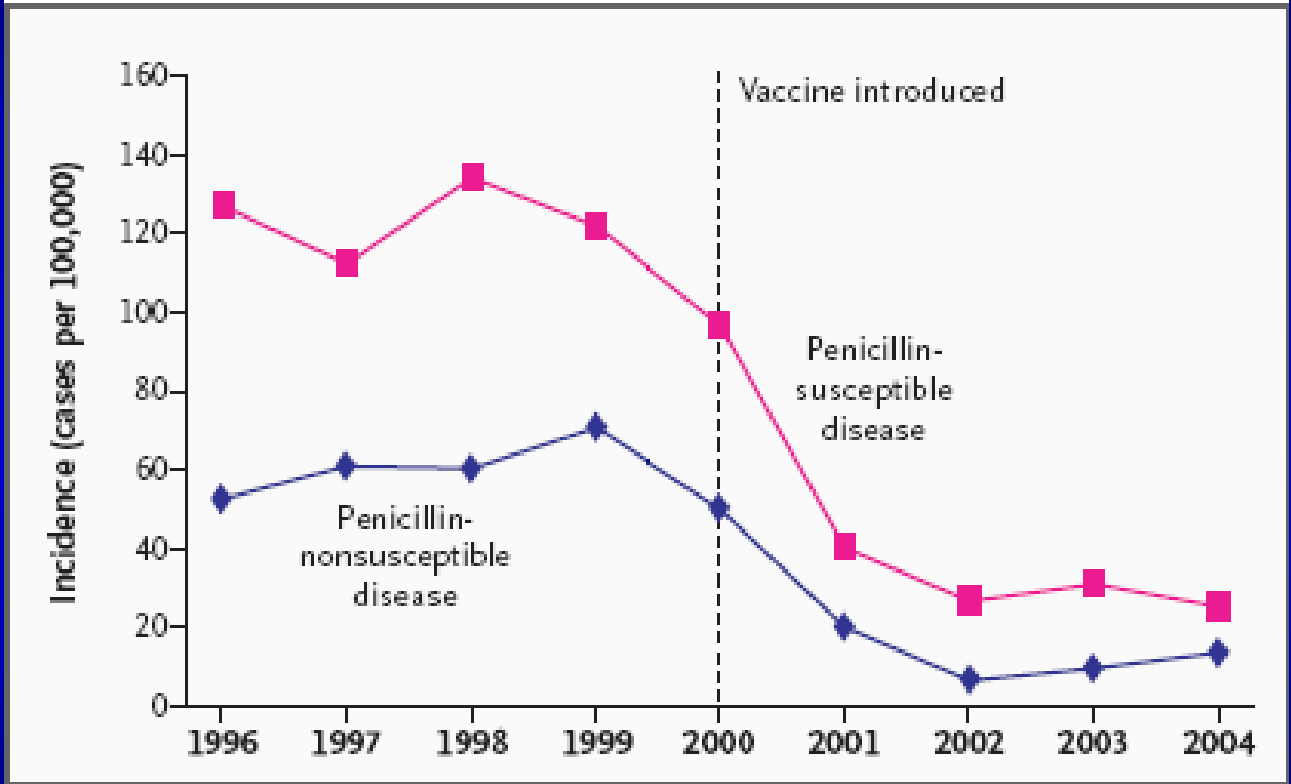
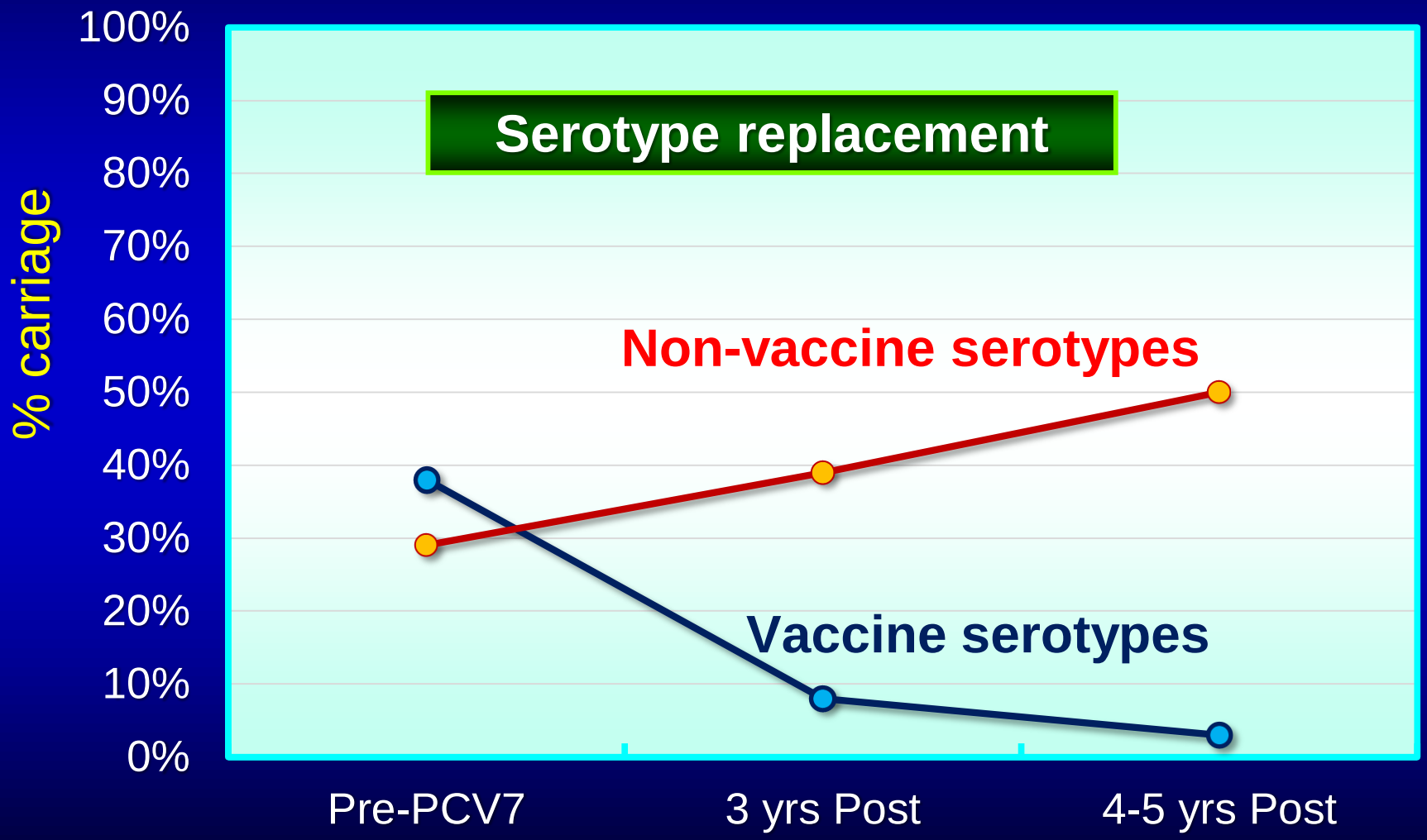


Figure 1. Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004.

G.Q.

Kyaw MH. N Engl J Med 2006;354:1455.

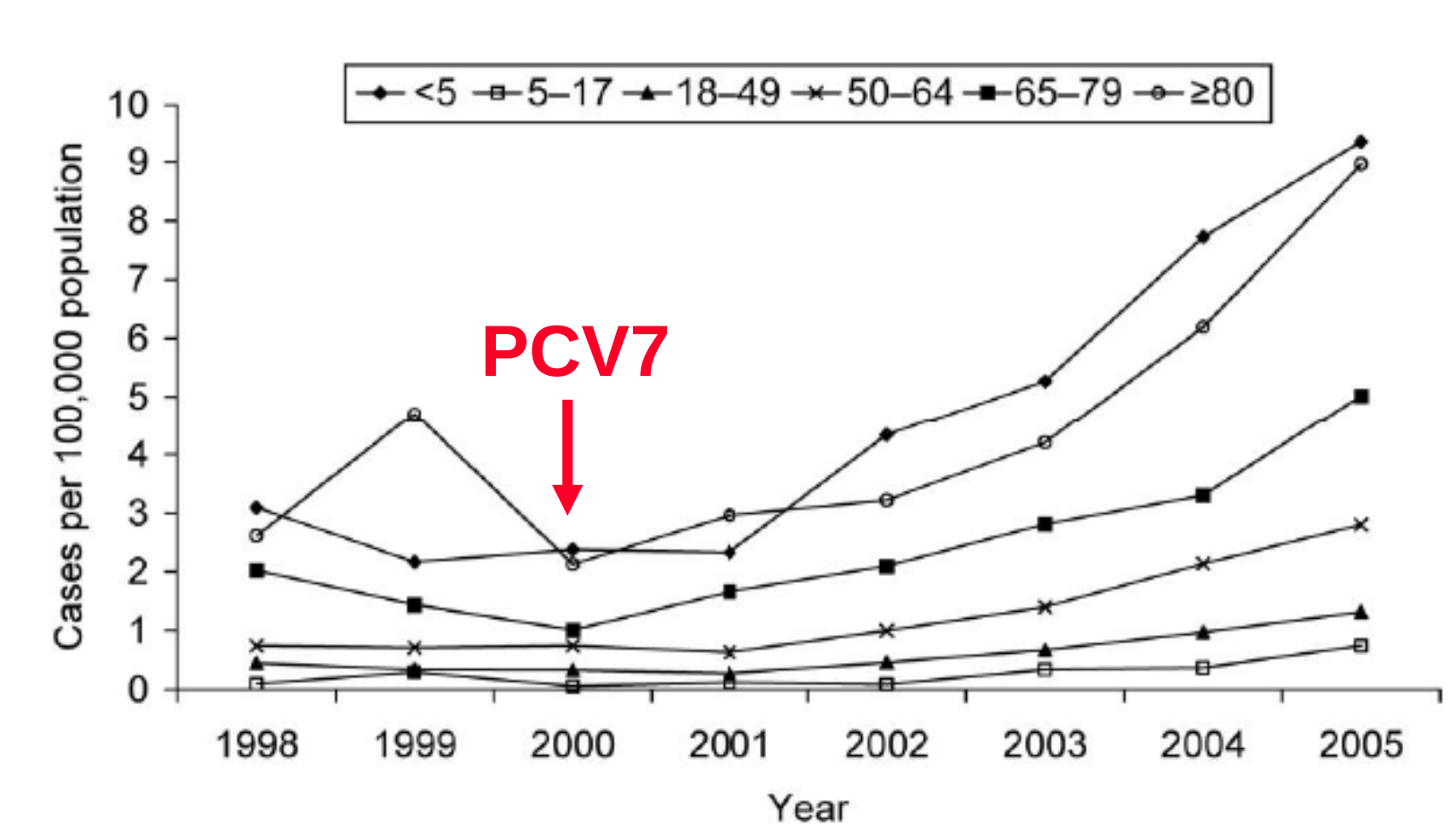
Effect of PCV7 on nasopharyngeal pneumococcus carriage N=330, 2012, Netherlands



G.Q.

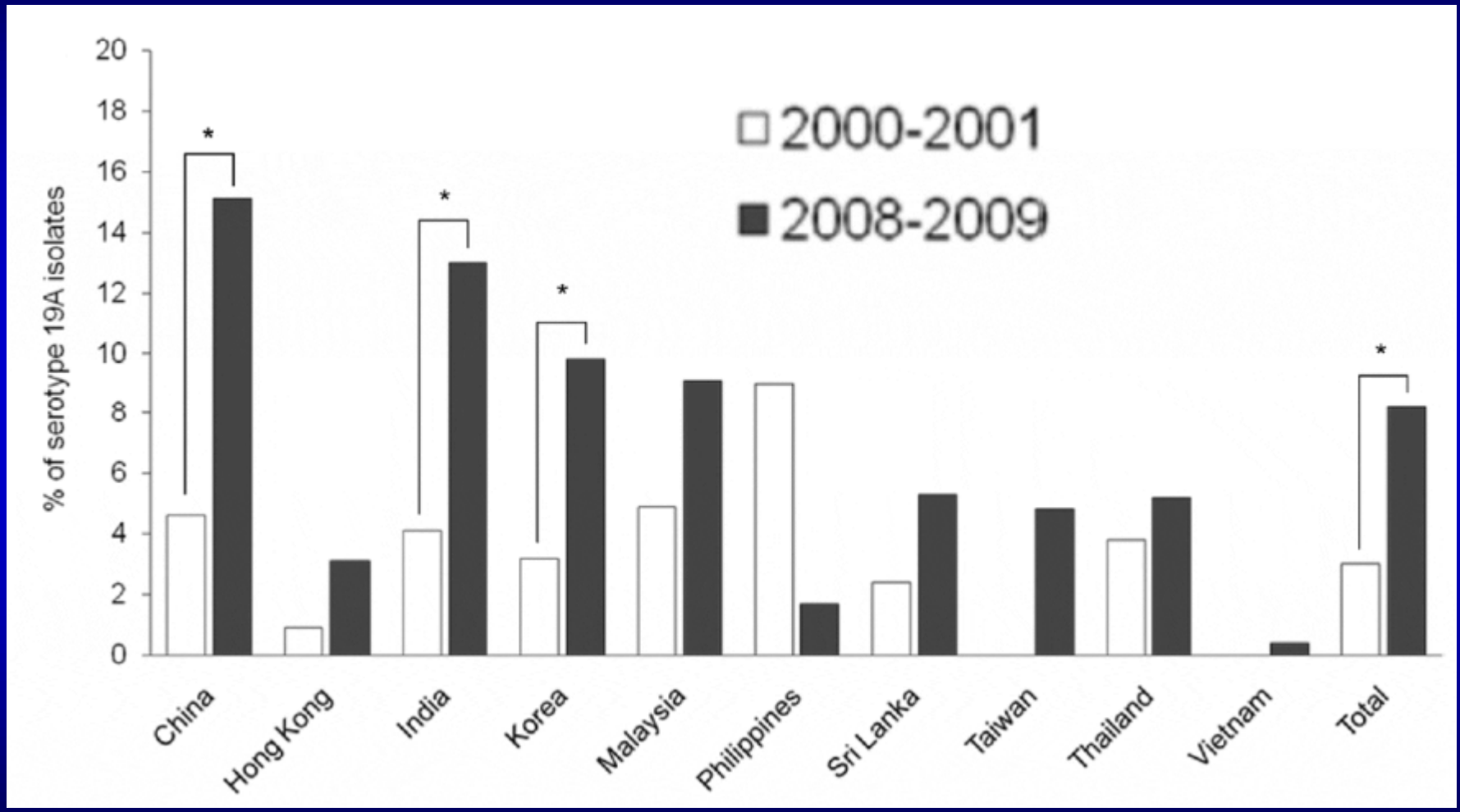
Spijkerman J. PLoS ONE 7(6): e39730.

Emerging 19A as a cause of IPD
1998-2005, CDC, USA



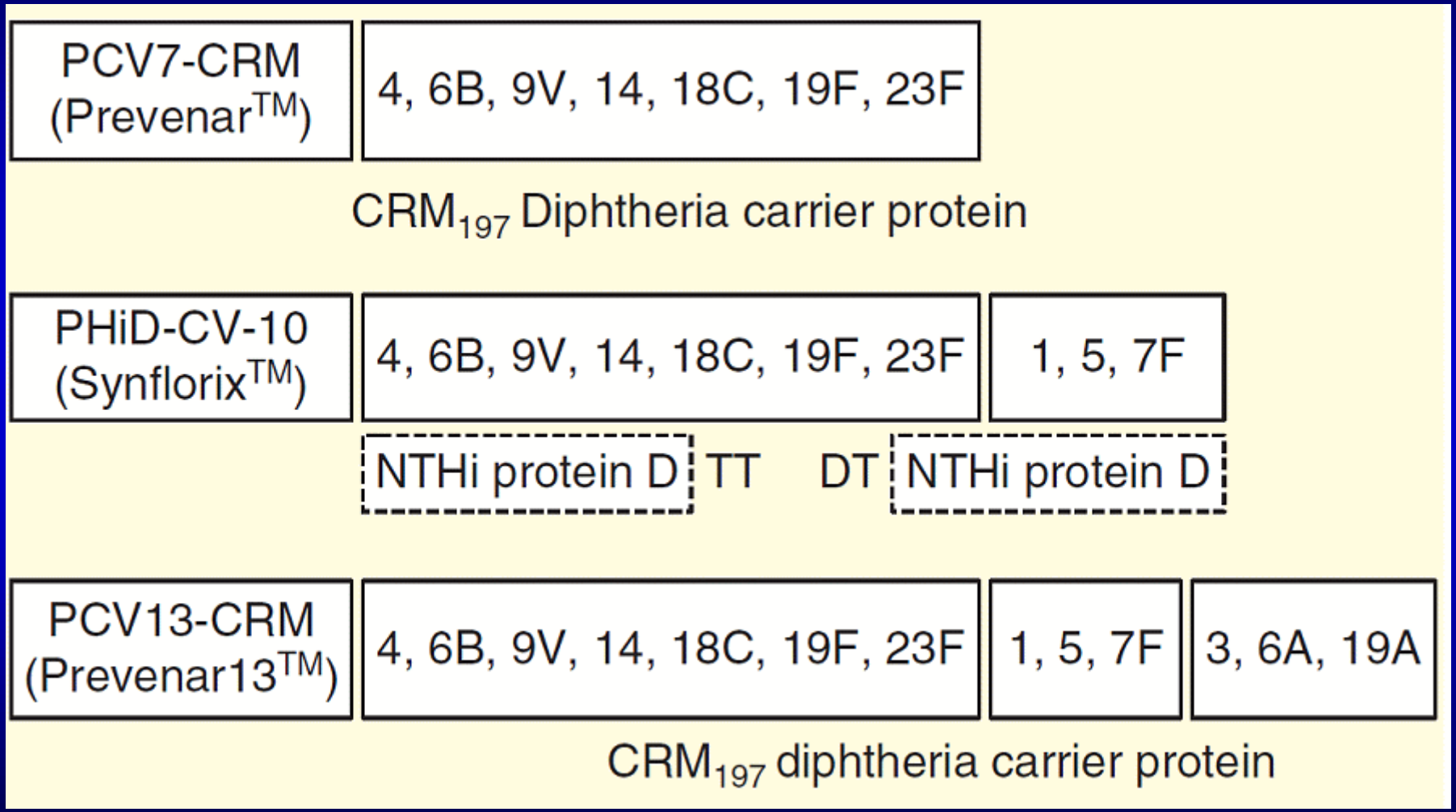
G.Q. Moore MR. J Infect Dis 2008;197:1016.

Increasing 19A in Asia Pacific, 2012



Kim SH. Antimicrob Agents Chemother 2012;56(3):1418.

Formulations of available pneumococcal conjugate vaccines



G.Q. Hausdorff WP. Expert Rev Vaccines 2015;14(3):413.

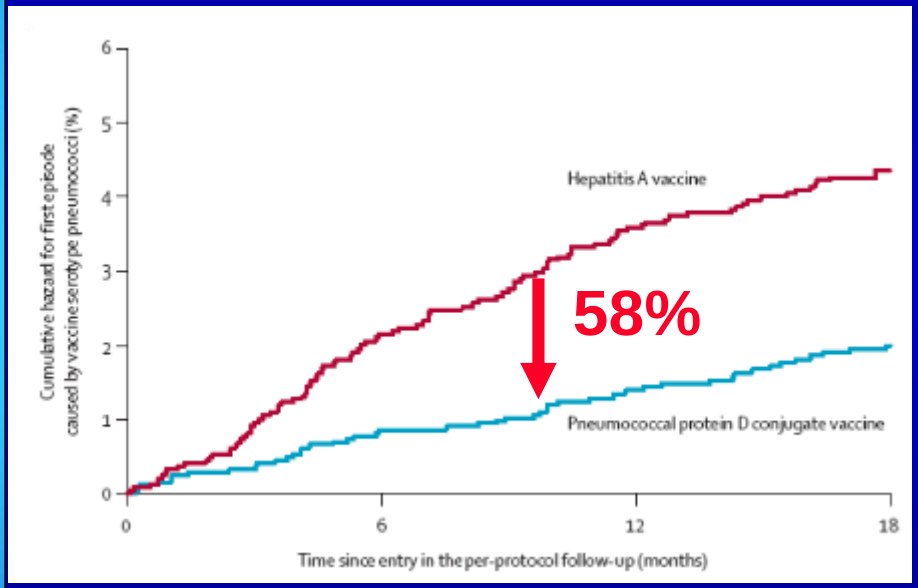
11-valent PCV

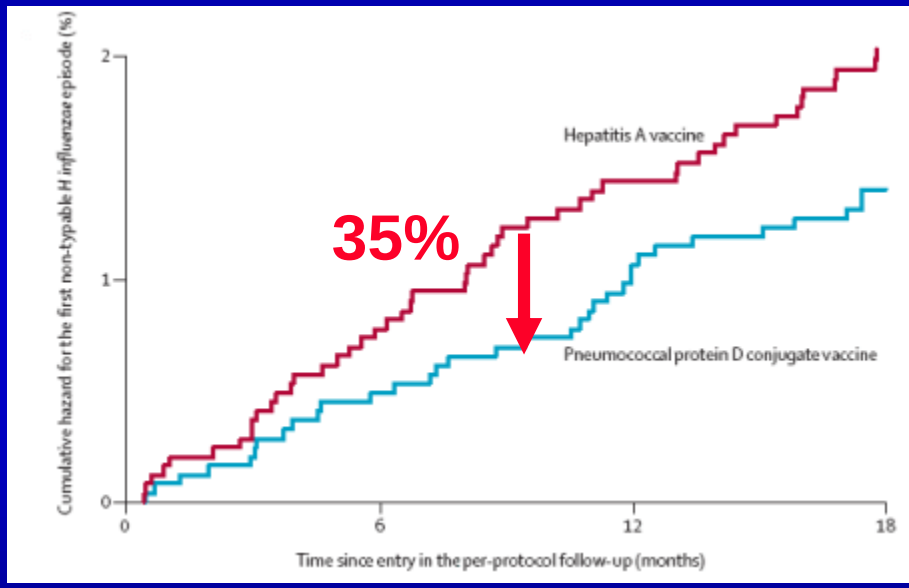
Protein D from nontypeable *Haemophilus influenzae*

Serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F)

Age: 3, 4, 5, 12-15 mo

N=4968, Czech/Slovakia



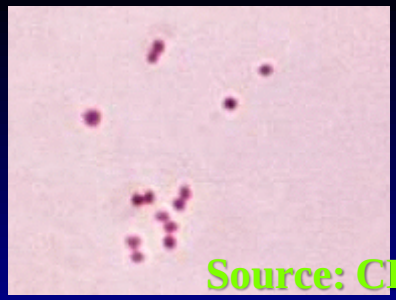


Otitis media by vaccine type pneumococcus

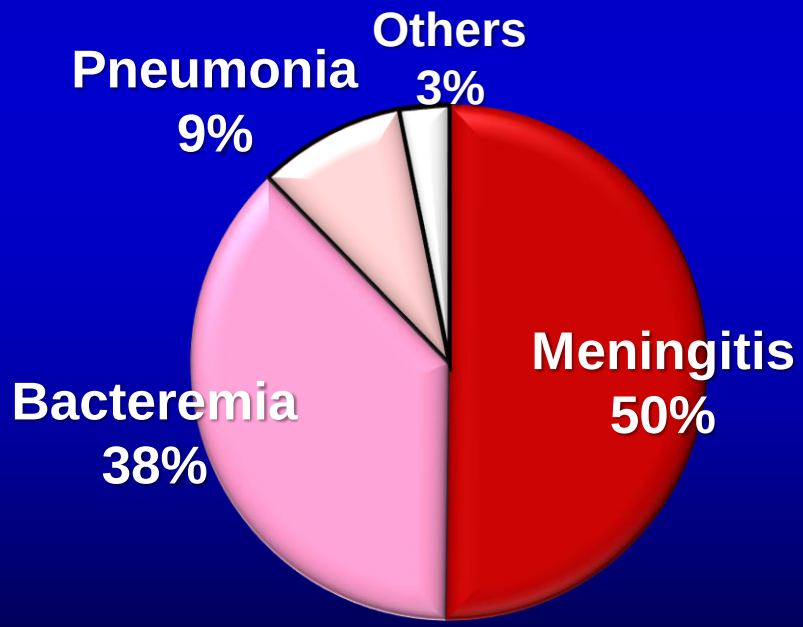
Otitis media by *Haemophilus influenzae*

G.Q. Prymula R. Lancet 2006;367:740.

Meningococcal disease



- Pathogen: ***Neisseria meningitides*, gram-negative diplococcus**
- Diseases: one of three syndromes - bacterial meningitis, bacteremia, pneumonia

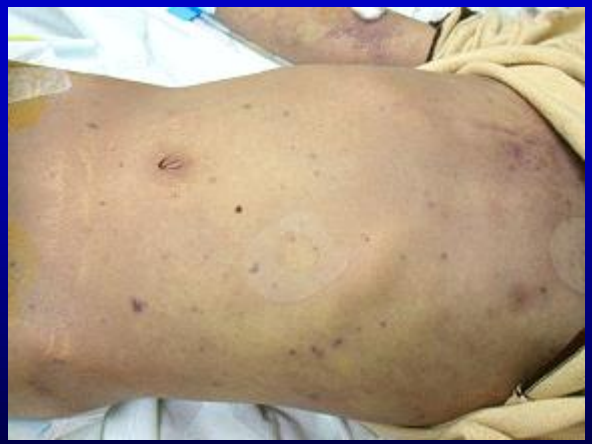


Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., 2015.
Cohn AC. Clin Infect Dis 2010;50:184–91.

G.Q.

Neisseria meningitides

- **13 serogroups**: A, B, C, D, E, H, I, K, L, W, X, Y, Z
- Invasive meningococcal diseases: **A, B, C, W, Y**
- **Nasopharyngeal carriage: 1-25%,** less than 1% to 5% of persons exposed develop invasive disease
- Morbidity: 11-19%
- **Mortality: 10%** in developed countries**, 20**% in developing world.

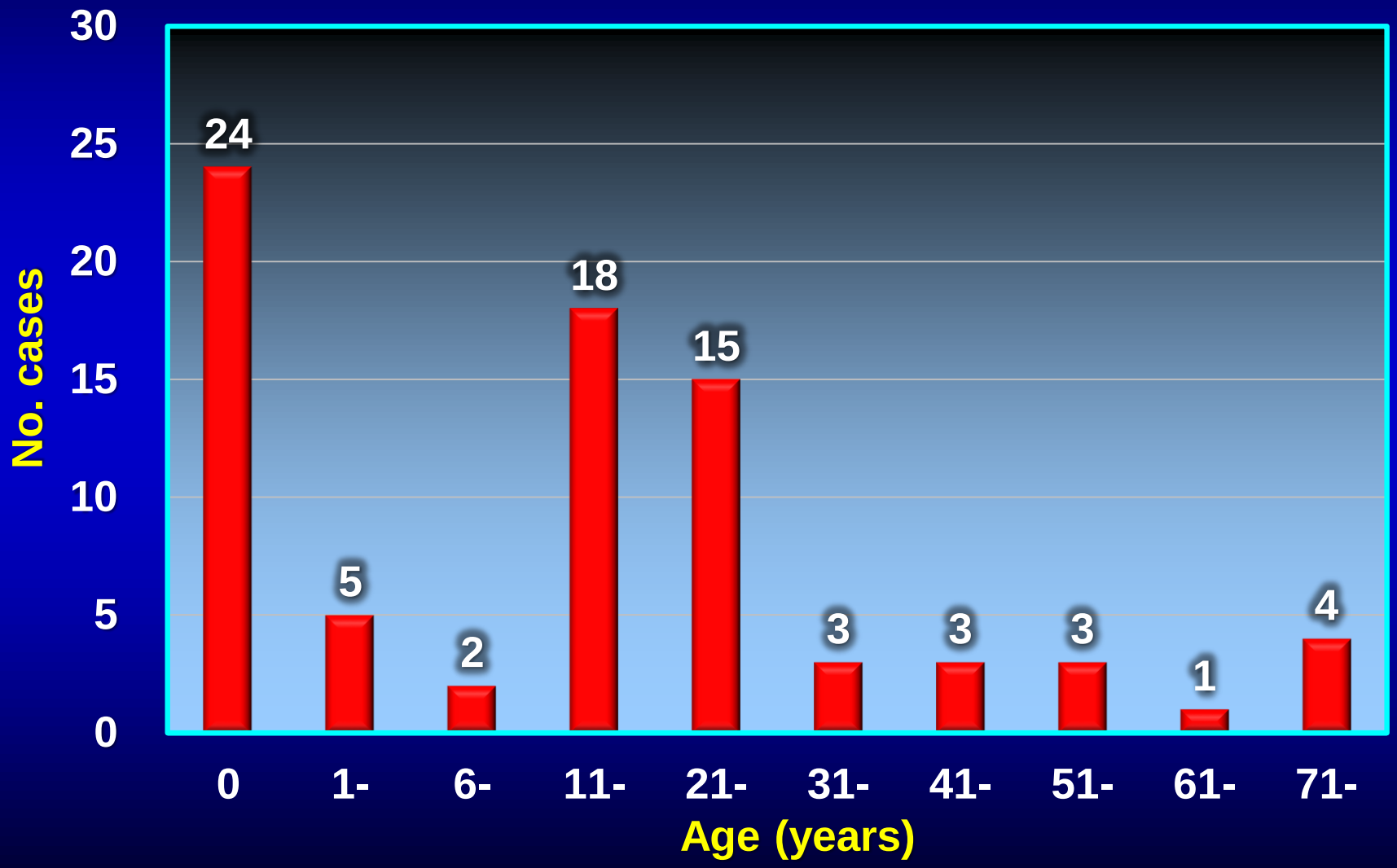


G.Q. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., 2015.

Epidemiology of meningococcal disease by serogroup

Papaevangelou V. Expert Rev Vaccines 2012;11(5):523.

Age distribution of invasive meningococcal disease N=78, 1998 - 2001, Taiwan



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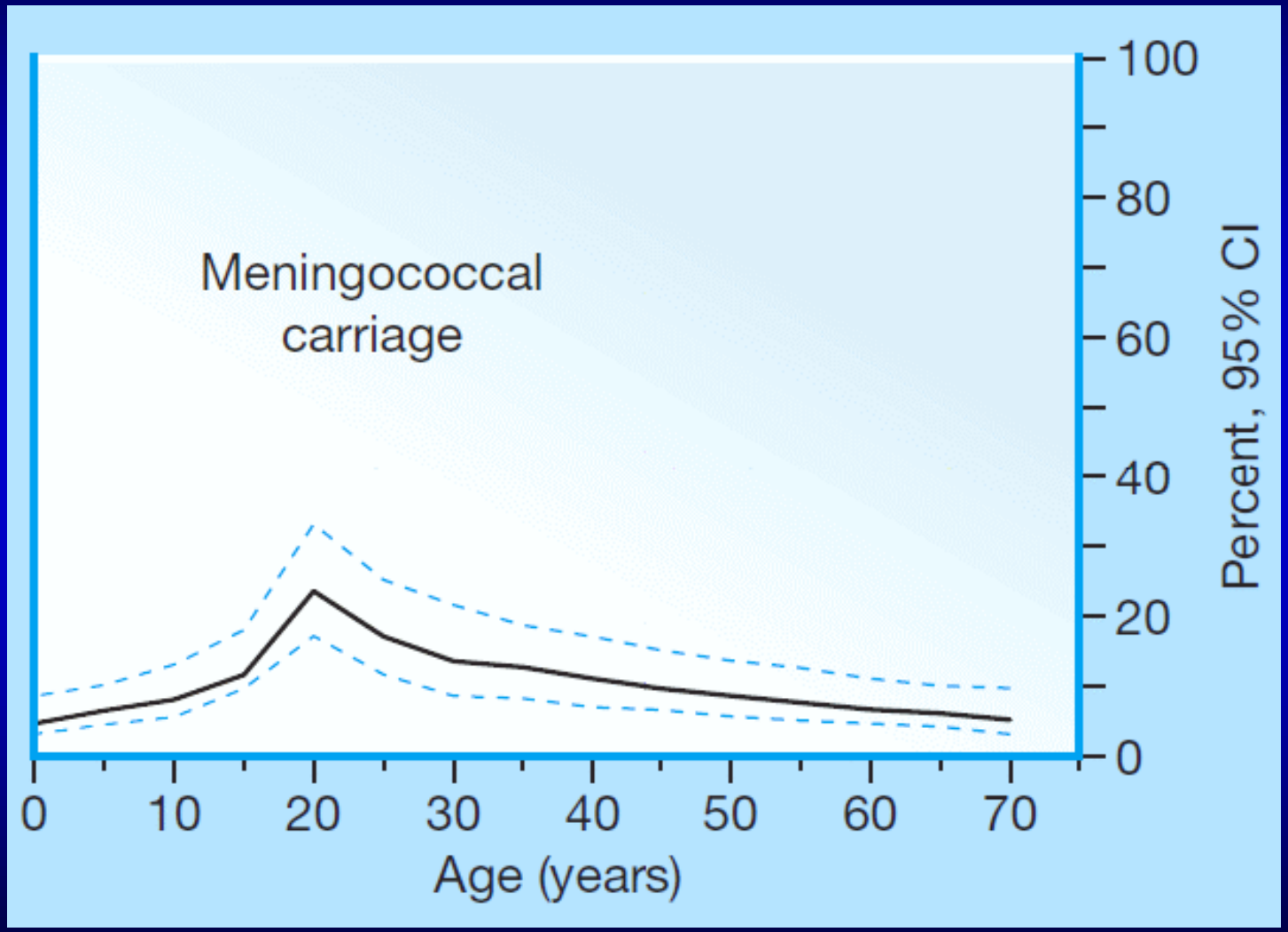
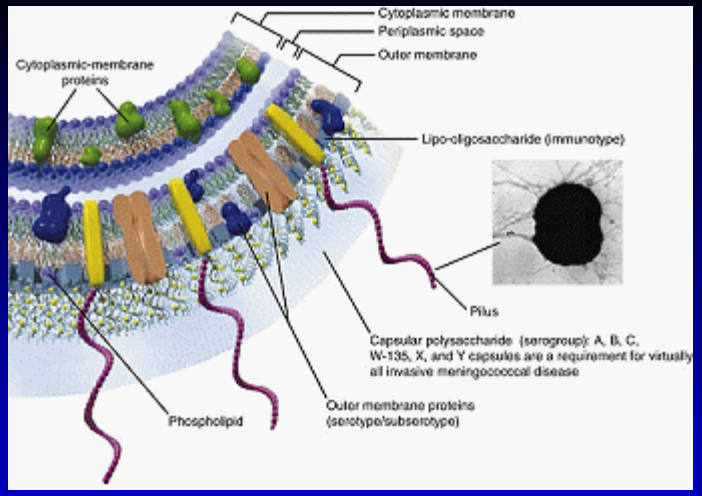
Meta-analysis of meningococcal carriage by age



Stanley Plotkin. Vaccines, 6th ed., 2013.

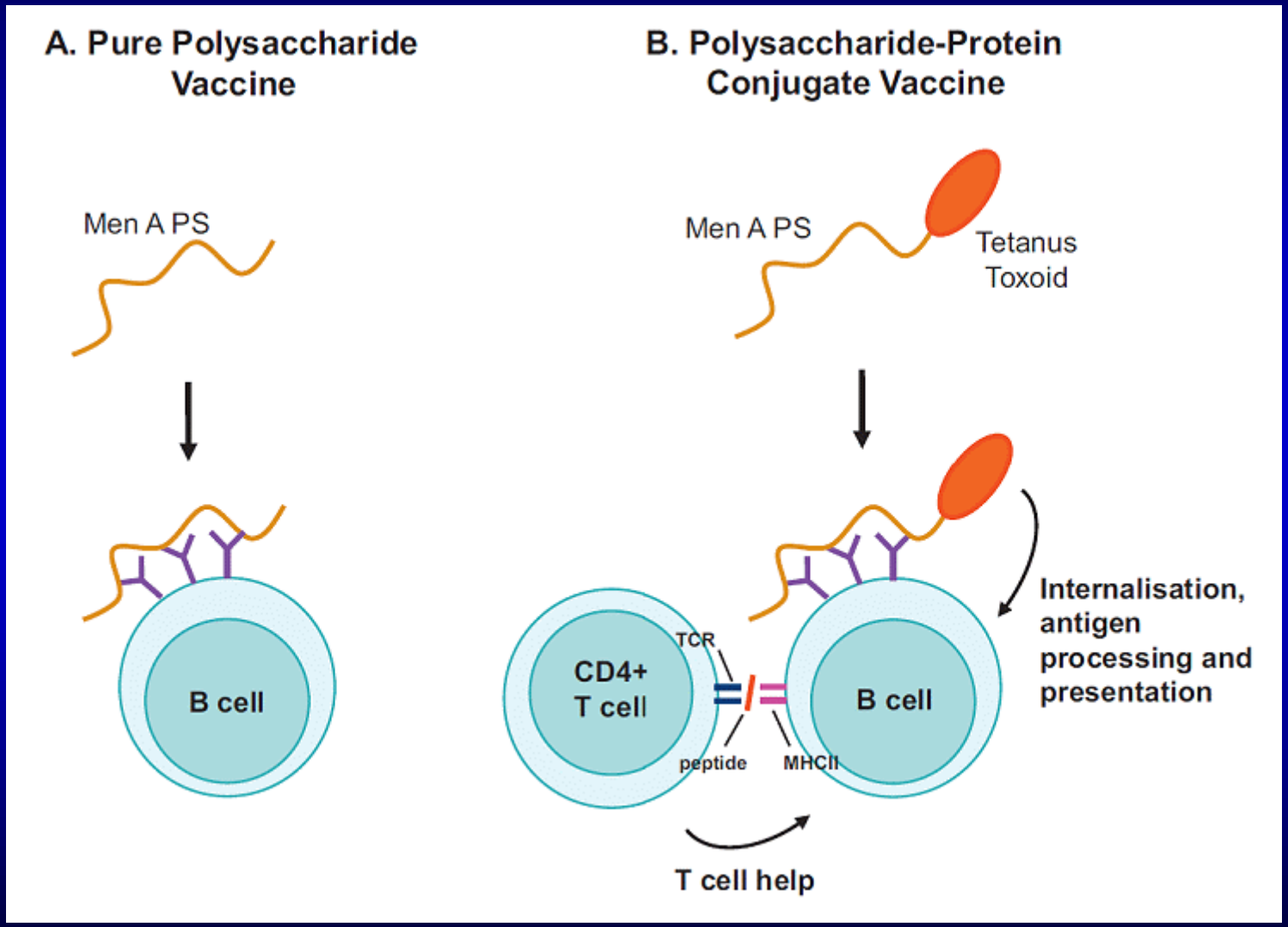
Meningococcal polysaccharide vaccines



- Serogroups **A, C, and later Y and W**: 1970s - 1980s.
- **Poor immune memory**
- **Transient protection** (3-5 years)
- **Poorly immunogenic** in children younger than **2 years**
- Immunologic hyporesponsiveness to repeat vaccinations of the polysaccharide.

G.Q. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., 2015.

Conjugate vaccine technology used in meningococcal vaccine



MacLennan CA. Semin Immunol 2013;25(2):114.

Vaccines for *Neisseria meningitidis* : United States, 2016

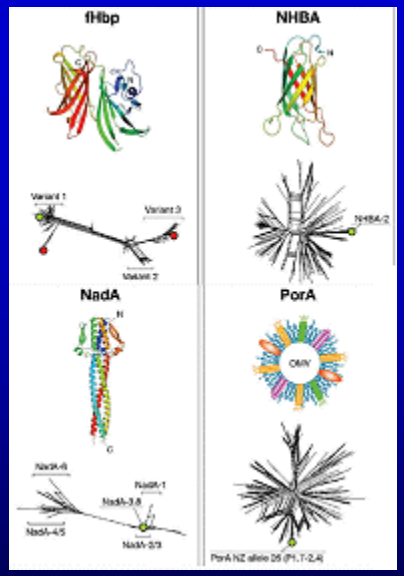
Menveo (GlaxoSmithKline)	Meningococcal (groups **A, C, Y, and W**) Oligosaccharide Diphtheria CRM197 Conjugate
Menactra (Sanofi Pasteur)	Meningococcal (groups **A, C, Y, and W**) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
Menomune (Sanofi Pasteur)	Meningococcal (groups **A, C, Y, and W)** polysaccharide (for ages 56 and older)
MenHibrix (GlaxoSmithKline)	Meningococcal groups **C and Y** and *Haemophilus* b Tetanus Toxoid Conjugate Vaccine
Bexsero (Novartis)	Meningococcal **group B** Recombinant Protein Vaccine
Trumenba (Pfizer)	Meningococcal **group B** Recombinant Protein Vaccine

G.Q.

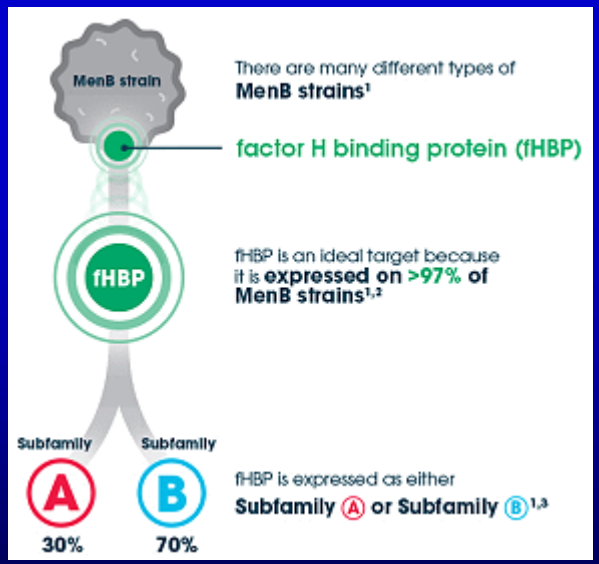
Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., 2015.

Meningococcal serogroup B vaccines

- **Serogroup B polysaccharide capsule:**
  - **Similar to human polysialic acid structures**, such as the neural cell adhesion molecule (NCAM).
  - **Poorly immunogenic** as an antigen in humans and animals.
- **Surface protein antigen**
  - **4CMenB (Bexsero):** reverse vaccinology, 4 proteins antigens
  - **rLP2086 (Trumenba):** 2 factor H binding proteins



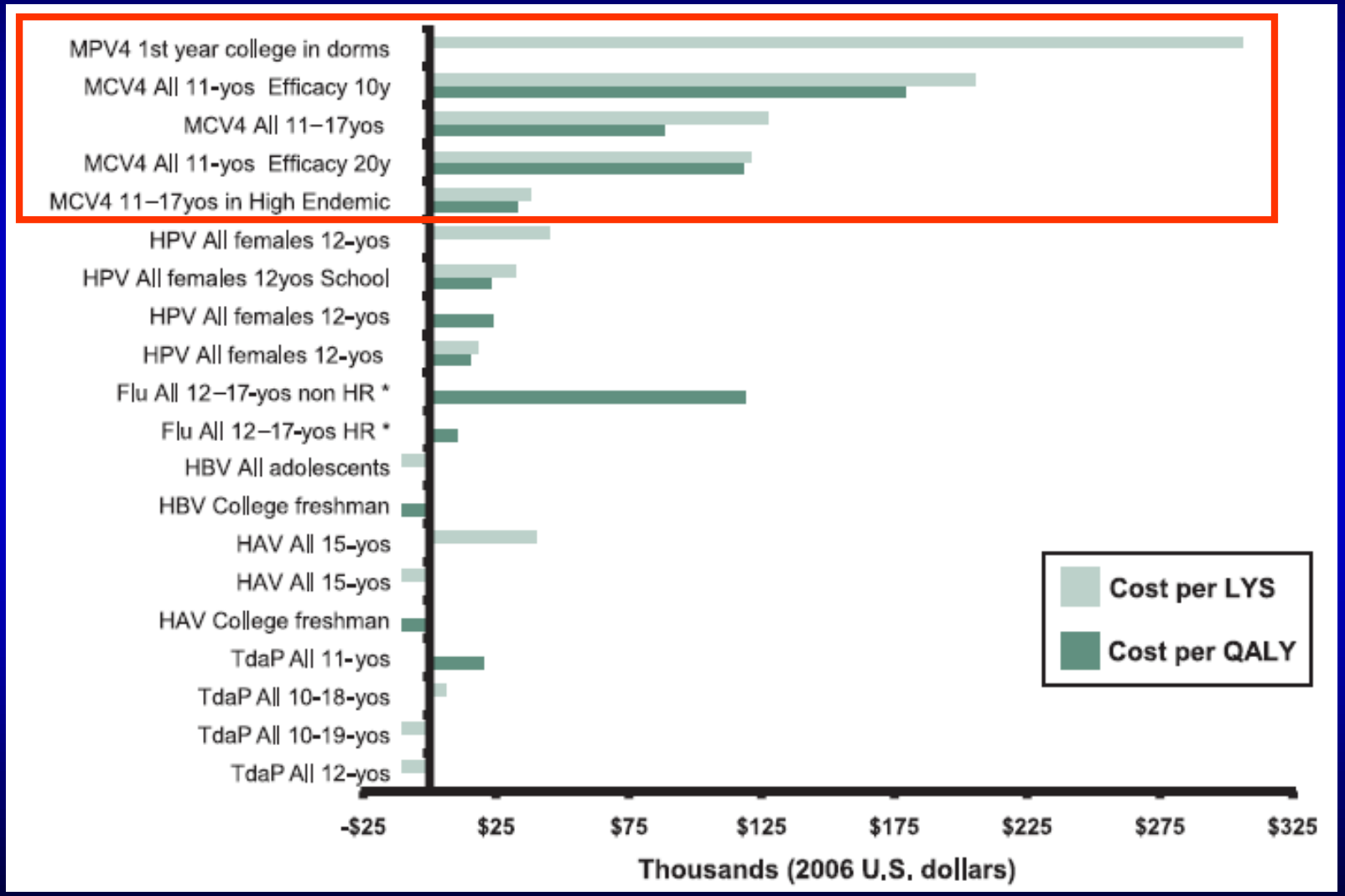
Toneatto D. Expert Rev Vaccines 2017;16(5):433.



https://www.pfizerpro.com/product/trumenba/

G.Q. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th ed., 2015.

Projected cost-effectiveness of new vaccines for adolescents USA



G.Q. Ortega-Sanchez IR. Pediatrics 2008;121:S63.

Meningococcal disease may create fear, anxiety, and panic

2001, Taiwan

- Sudden death of a 20-year-old girl (May, 2001)
  - Medical dispute
- Sudden death of a nurse (April, 2001):
  - Medical dispute
- Sudden death of a soldier in a military camp (June, 2001)
  - Military officers were sued and were judged to be guilty

PANIC!!!

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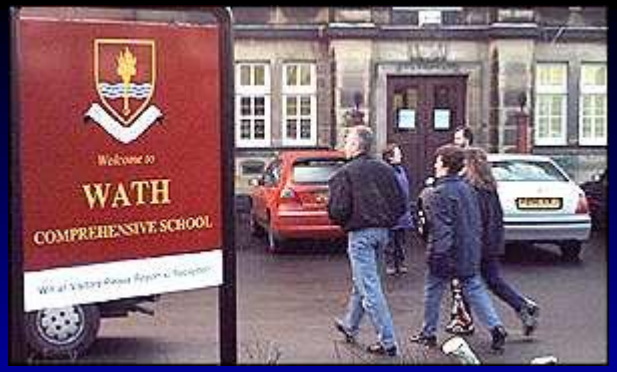
Meningitis: The 1999 panic

BBC News, Mar 9, 1999



- Throughout January **1999, a severe outbreak of meningitis in south Wales** took a prominent position in the headlines.
- As a **public health emergency** was declared, mass vaccinations were performed at schools in Pontypridd.
- Doctors did their best to calm **public fears** about the likelihood of infection, but parents were alarmed and marched to demand blanket vaccinations - regardless of whether their children attended the affected schools.

G.Q.

http://news.bbc.co.uk/2/hi/health/293501.stm

Use of meningococcal vaccine
ACIP, CDC, USA, 2013-2015

- **4-valent meningococcal conjugate vaccine** (A, C, Y, W-135):
  - **Routine** at **11–12 years** **and a booster at 16 years.**
  - Routine vaccination of persons aged ≥2 months at **increased risk** for meningococcal disease: Asplenia, complement deficiency, first-year college students living in residence halls, military recruits, occupational exposure, travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic
  - Vaccination of persons in **at-risk groups** to control outbreaks.
- **Serogroup B meningococcal vaccines** may be administered **to adolescents and young adults aged 16–23 years** to provide short-term protection

Cohn AC. MMWR Recomm Rep 2013;62(RR-2):1-28.
MacNeil JR. MMWR 2015;64(41):1171.

G.Q.

List of countries to have included meningococcal vaccines in routine immunization

Country	Ref.	Vaccine	Year introduced	Routine recommendations	Catch up program	Incidence rates
Africa (Burkina Faso, Niger, Mali) *	60	Serogroup A conjugate	2010	Still to be defined	Mass vaccination of 1–29 year old with a single dose	
Australia	67	Serogroup C conjugate	2003	Single dose at 12 months	All aged 1–19 years	3.5–7.9 pre-vaccine 1.4 post-vaccine
Belgium	68	Serogroup C conjugate	2002	Single dose at 12–14 months	Up to 19 years of age	3.69 pre-vaccine 0.8 post-vaccine
Canada	53,54,69	(1) Serogroup C conjugate (2) Quadrivalent conjugate including serogroups A, C, W, Y) approved in 2006.	2002	Most provinces use the MenC conjugate at 12 months while a few use the quadrivalent conjugate based on local epidemiology and/or children >2 years with primary antibody deficiencies		1.38 pre-vaccine 0.42 post-vaccine
China	68	(1) Serogroup A polysaccharide (2) Serogroups A/C polysaccharide	1982 2005	Vaccine at 6 and 18 months Vaccine at 3 and 6 years		
Cuba	69,70	Serogroup B OMV and Serogroup C polysaccharide	1991	Introduced into National Infant Immunization Program after epidemic incidence levels in 1980s		3.4–8.5 pre-vaccine <1 post-vaccine
Egypt	71	Serogroup A/C Polysaccharide	1992	School based vaccination program		
France	72	Serogroup C conjugate	2010	Age 12–24 months	Up to 24 years	
Germany	72,73	Serogroup C conjugate	2006	One dose in second year of life		
Iceland	66,73	Serogroup C conjugate	2002	6 and 8 months of age	Up to 19 years	7.58 pre-vaccine 1.3 post-vaccine
Ireland	74,75		2001	Part of routine immunization at 2, 4, and 6 months of age (now changed to 4, 6 months and booster in second year of life)	Up to 23 years	14.8 pre-vaccine 4.5 post-vaccine
Netherlands	55,65,76	Serogroup C conjugate	2002–3	Single dose at 12 or 14 months	Up to 18 years of age	4.51 pre-vaccine 1.1 post-vaccine
New Zealand	77,78	Serogroup B OMV Serogroup C conjugate	2004	Mass immunization for everyone aged between 6 months and 20 years. MeNZB routine use has now been terminated due to a marked decrease in the incidence of meningococcal B disease		17.4 pre-vaccine 2.6 post-vaccine
Portugal	79	Serogroup C conjugate	2001	3, 5, and 15 months of age	Up to 18 years	
Spain	66	Serogroup C conjugate	2001	Part of routine immunization at 2, 4, and 6 months of age (now changed to 2, 6, and booster at 15–18 months)	Up to 6 years in some regions, up to 19 in others. Later extended to 19 years in all Spanish regions)	3.74 pre-vaccine 1.3 post-vaccine
Switzerland		Serogroup C conjugate	2005	12–18 m	11–15 years	
UK	80,81	Serogroup C conjugate	1999	Part of primary immunization schedule at 2, 3, and 4 months of age. From 2006 at 3, 4, 12 months of age. From 2013 at 4, 12 months and 14 years of age.	Up to 18 years of age (1999–2000), up to 25 years (2001)	5.39 pre-vaccine 2.1 post-vaccine
USA	18,82	Serogroup A, C, Y, W conjugate (Serogroup A, C, Y, W polysaccharide alternative)	2005	Primary dose at age 11–12 years with a booster dose at age 16, people at increased risk as mentioned above	Adolescents aged 13–18 Booster dose at 5 years	0.8 pre-vaccine 0.28 post-vaccine

G.Q.

Ali A. Pathog Glob Health 2014;108(1):11.


Thanks!
Alishan
Taiwan