



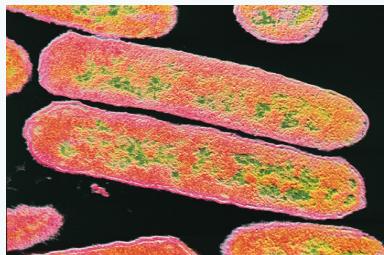
Review of GSK's meningitis vaccine portfolio: past, present and future

Jan T Poolman PhD Vice-President Bacterial Vaccine R&D

11 Nov 2009

Meningitis Research Foundation conference

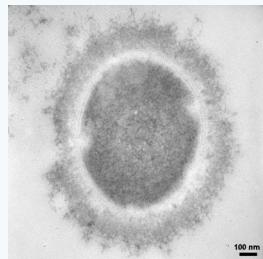
Haemophilus, Meningococcus, Pneumococcus...



Haemophilus influenzae

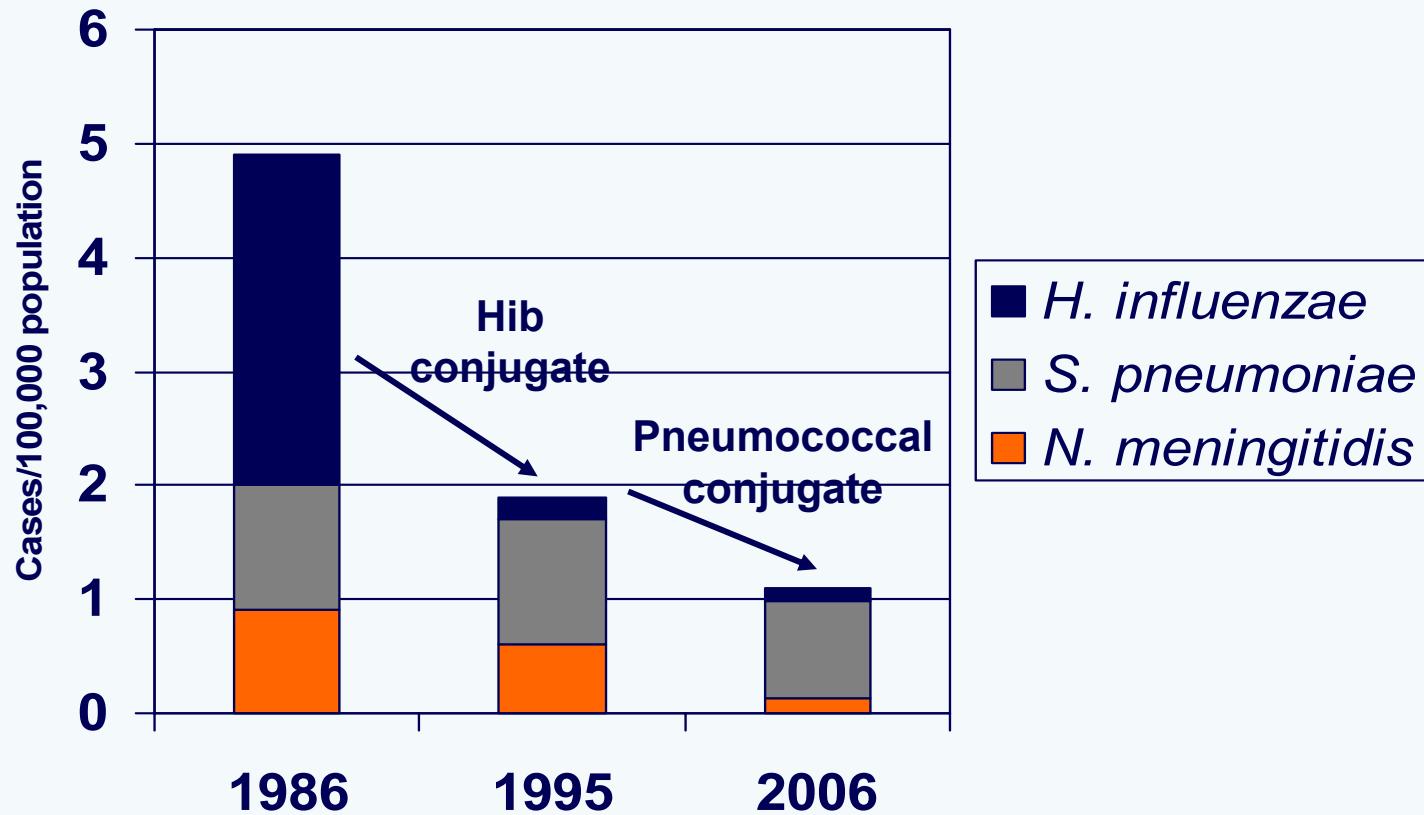


Neisseria meningitidis
(Meningococcus)



Streptococcus pneumoniae
(Pneumococcus)

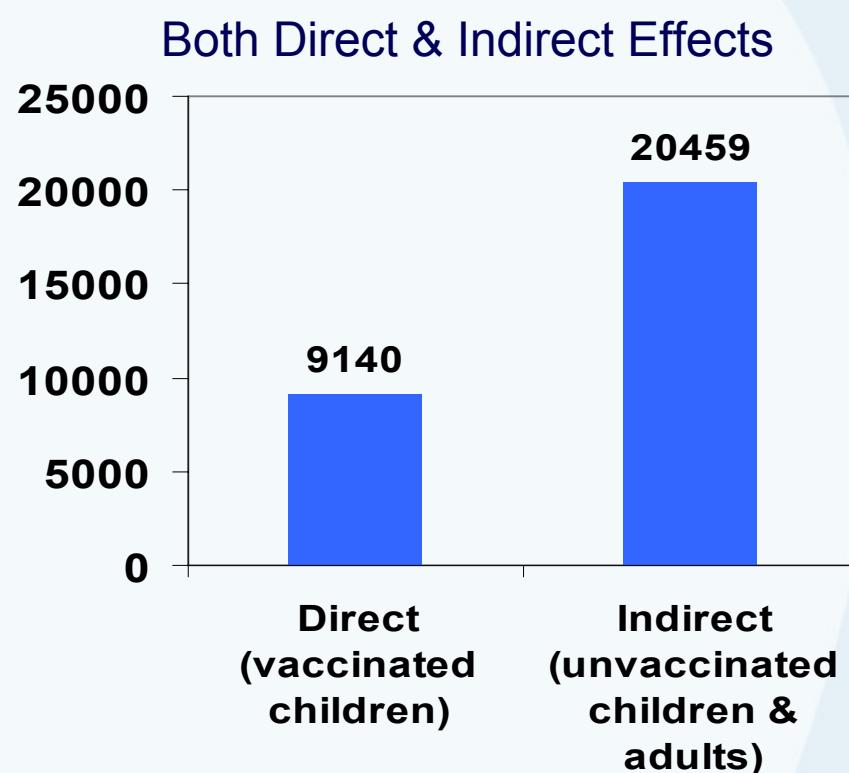
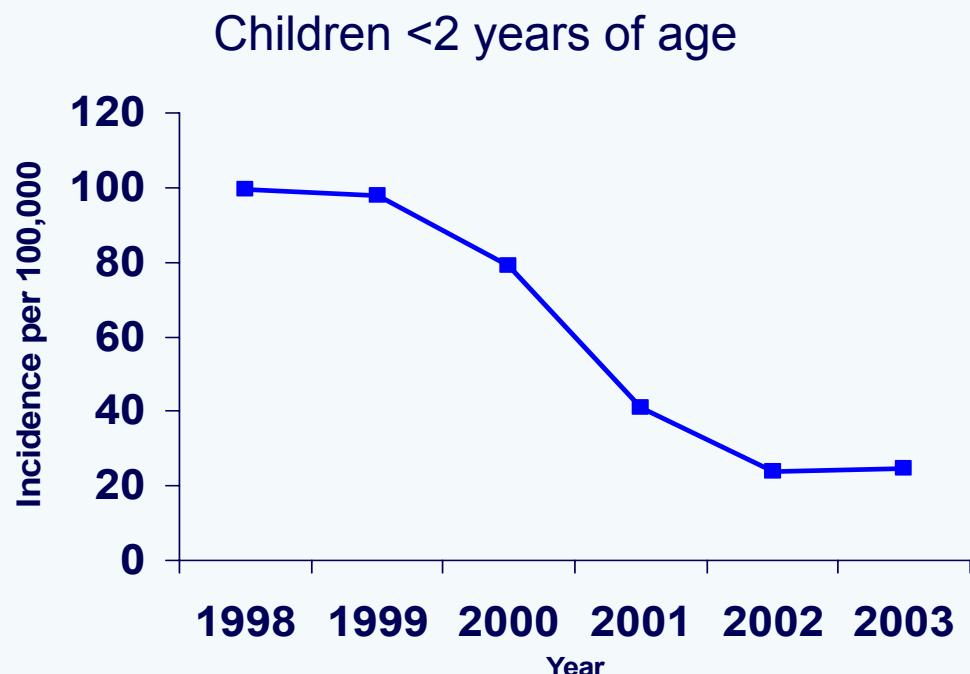
Trends in three pathogens causing paediatric bacterial meningitis, USA 1986-2006 after Hib and pneumo conjugate introductions



Source: Schuchat et al, NEJM 1997;337:970-6; 2006 estimates from CDC Active Bacterial Core Surveillance (www.cdc.gov/abcs)

Impact of pneumococcal conjugate vaccine - US

Effect of PCV7 on rates of IPD in US after introduction in 2000



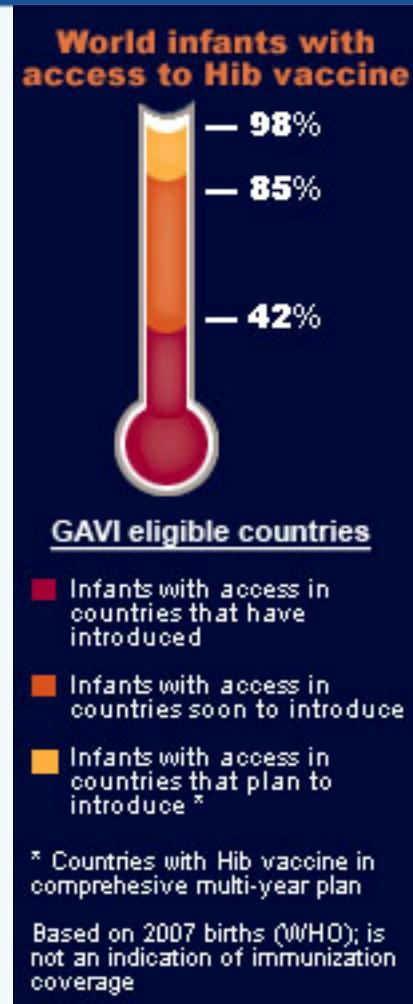
CDC ABCs surveillance
Kyaw MH et al 2006 NEJM 354 1455-63

CDC MMWR 2005;54; 893

GSK Conjugate milestones:1996-2009

1996	Hib monovalent	
1996	Combined DTPw HBV ± Hib	WORLD FIRST
1997	Combined DTPa/Hib and DTPa IPV	WORLD FIRST
1998	Combined DTPa IPV Hib vaccine	
2000	DTPa HBV IPV/ Hib (Hexa)	
2005	HibMenC	WORLD FIRST
2008	10-valent pneumo-NTHi conjugate	
2009	Hib monovalent licensed in USA	
2009	HibMenCY license application	WORLD FIRST

Hib implementation



Source: www.HibAction.org (The Hib Initiative)

European MenC monovalent conjugate vaccine schedules

Country	2m	3m	4m	5m	6m	12m	13m	14m	15m
UK									
Spain*									15-18
Ireland								13-24	
Canada									
Belgium									
Australia									
France (Apr 09)									
Netherlands									
Portugal									
Italy									
Greece									
Switzerland								12-15	
Germany								11-23	

Alberta
Province: 2,4,12

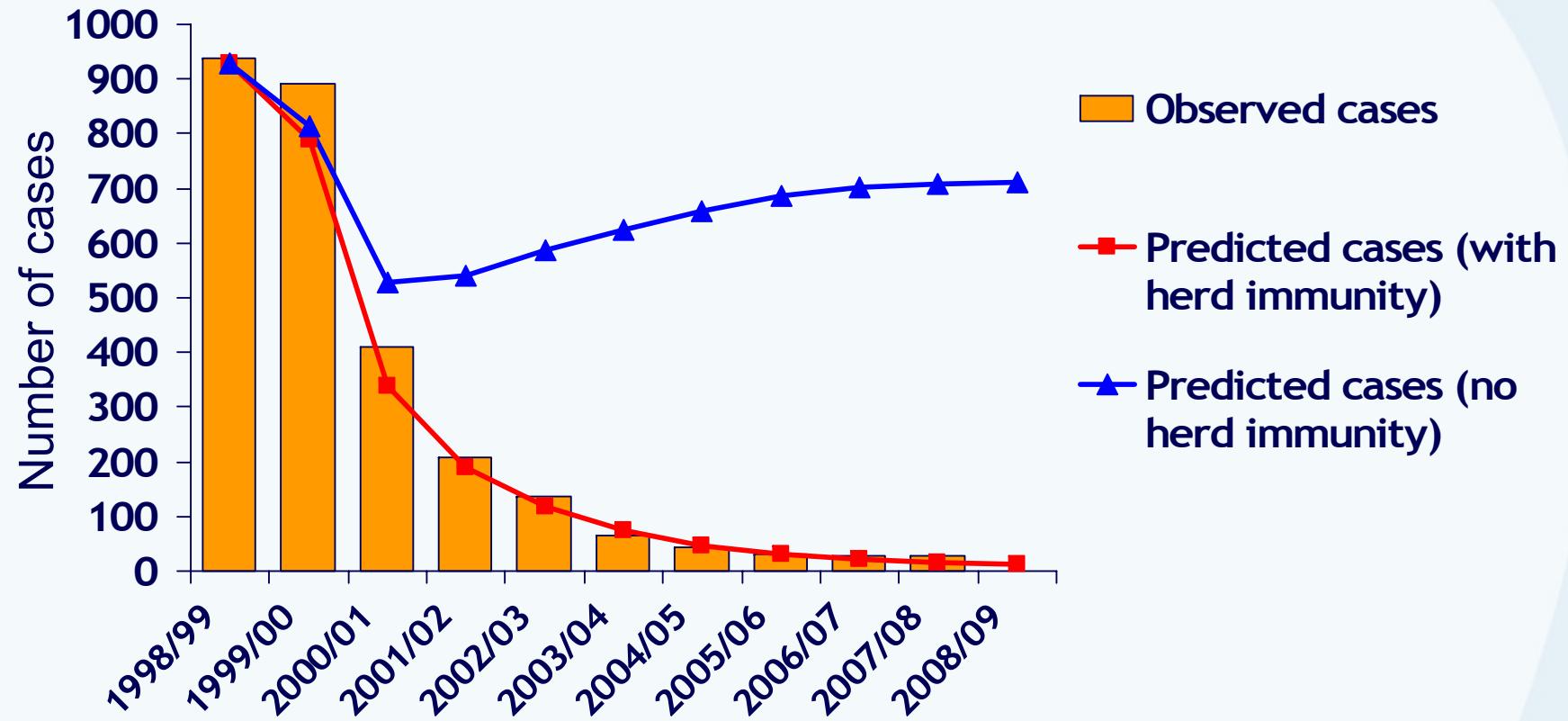
Together with
hexavalent vaccine
(DTPa-HBV-IPV-Hib)

2m/2y

USA: ACWY conjugate in teenagers

Cyprus: 2,4,6 at risk

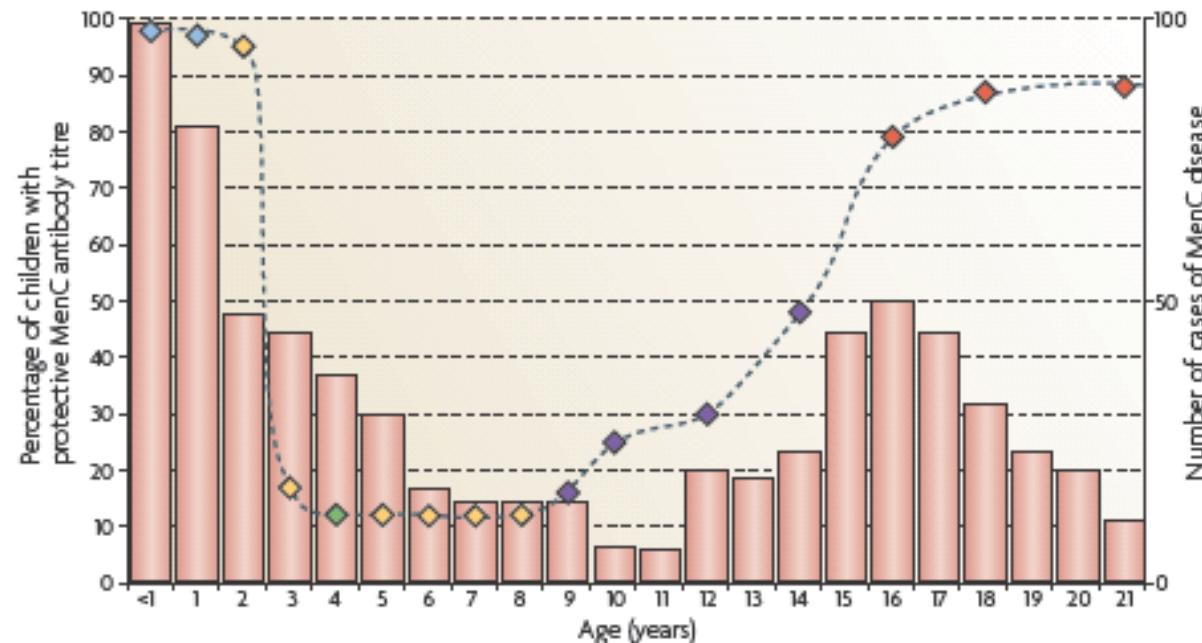
MenC vaccination in England & Wales Herd impact of conjugate immunization



Trotter, Edmunds, Med. Decis. Making. 2006; 26; 38-47.

HPA website: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859710351?p=1201094595391&printable=true

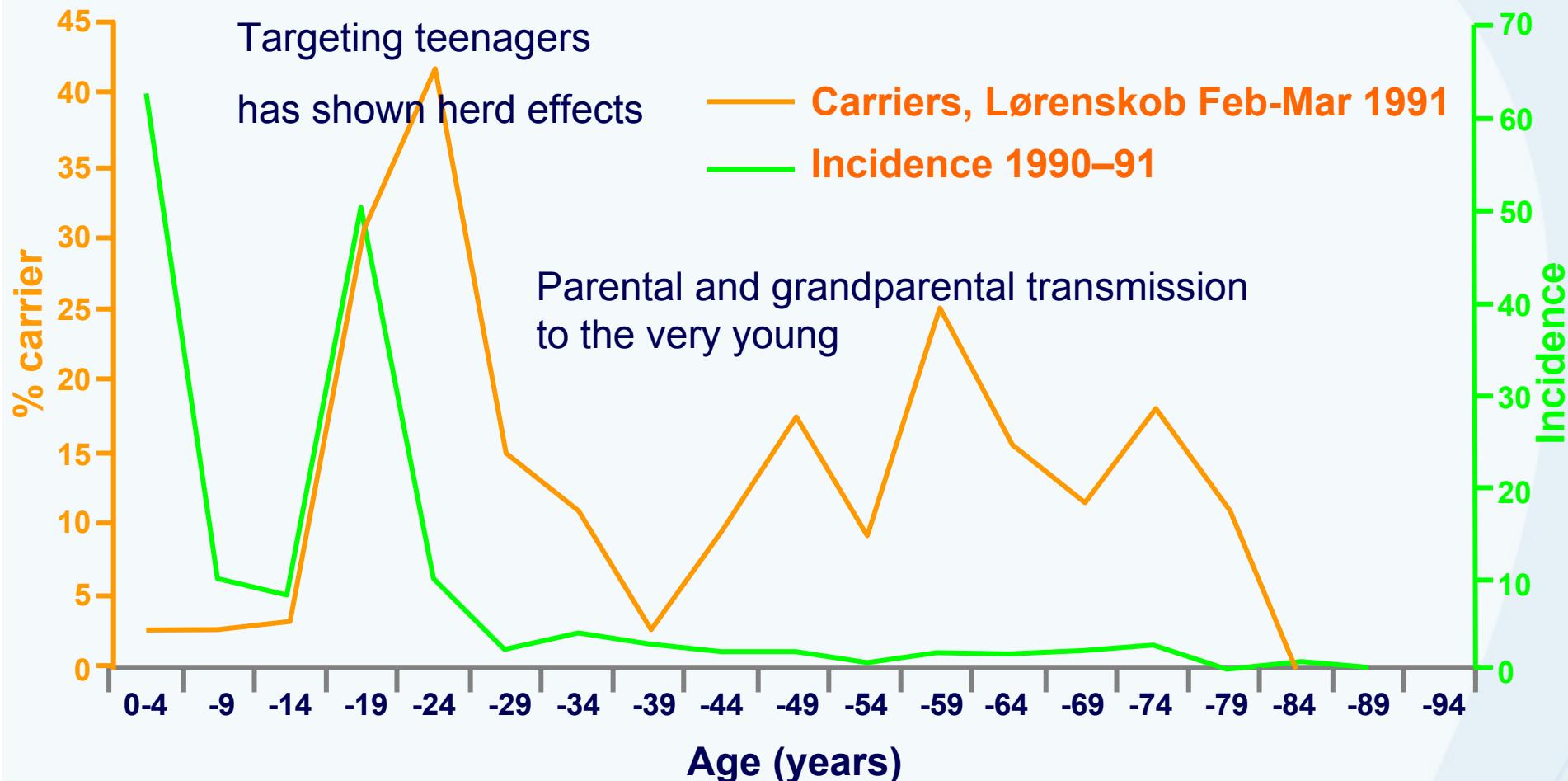
Persistence of bactericidal activity after MenC conjugate immunisation



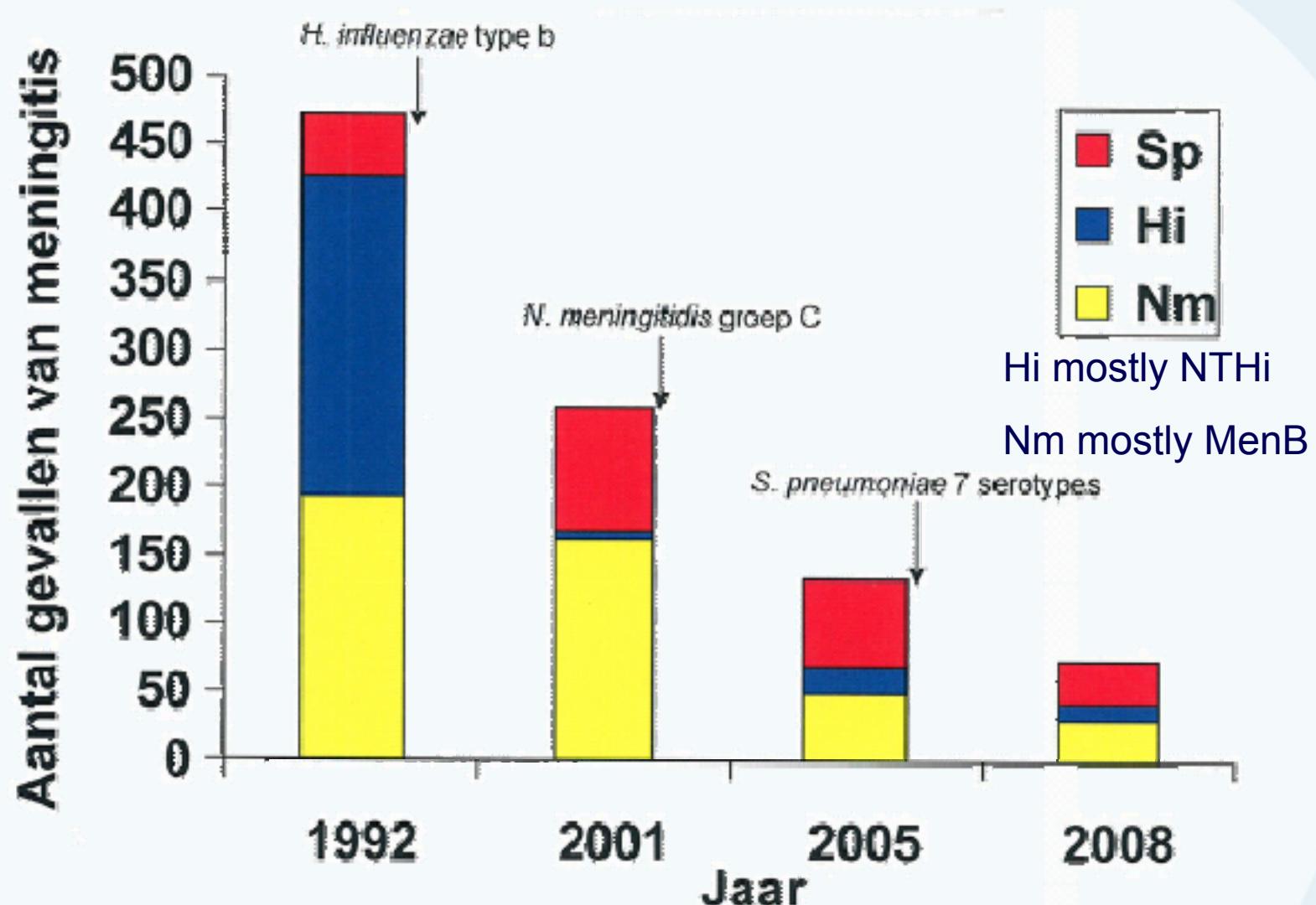
- ◆ Percentage of children with MenC SBA titre $\geq 1:4$ (human complement assay) after two doses of MenC vaccine (at 2 and 4 months of age) and one dose of MenACWY vaccine (at 12 months of age). Data are used to reflect the current UK schedule (although this uses MenC rather than MenACYW)
- ◆ Percentage of children with MenC SBA titre $\geq 1:8$ (rabbit complement assay) after three doses of MenC vaccine (at 2, 3 and 4 months of age)
- ◆ Percentage of children with MenC SBA titre $\geq 1:8$ (rabbit complement assay) after three doses of MenC vaccine (at 2, 3 and 4 months of age), two doses of vaccine (6–11 months of age) or one dose of vaccine (1–6 years of age)
- ◆ Percentage of children with MenC SBA titre $\geq 1:8$ (rabbit complement assay) after one dose of MenC vaccine (6–15 years of age)
- ◆ Extrapolated data from above studies

Age distribution of meningococcal carriage versus disease

Courtesy of Dominique Caugant



Impact of Hib,MenC and Spn in The Netherlands on bacterial meningitis 0-5 yrs



Dutch National Reference laboratory Bacterial Meningitis, personal communication Arie van der Ende

H.Influenzae invasive isolates 1988-2006 in the Netherlands

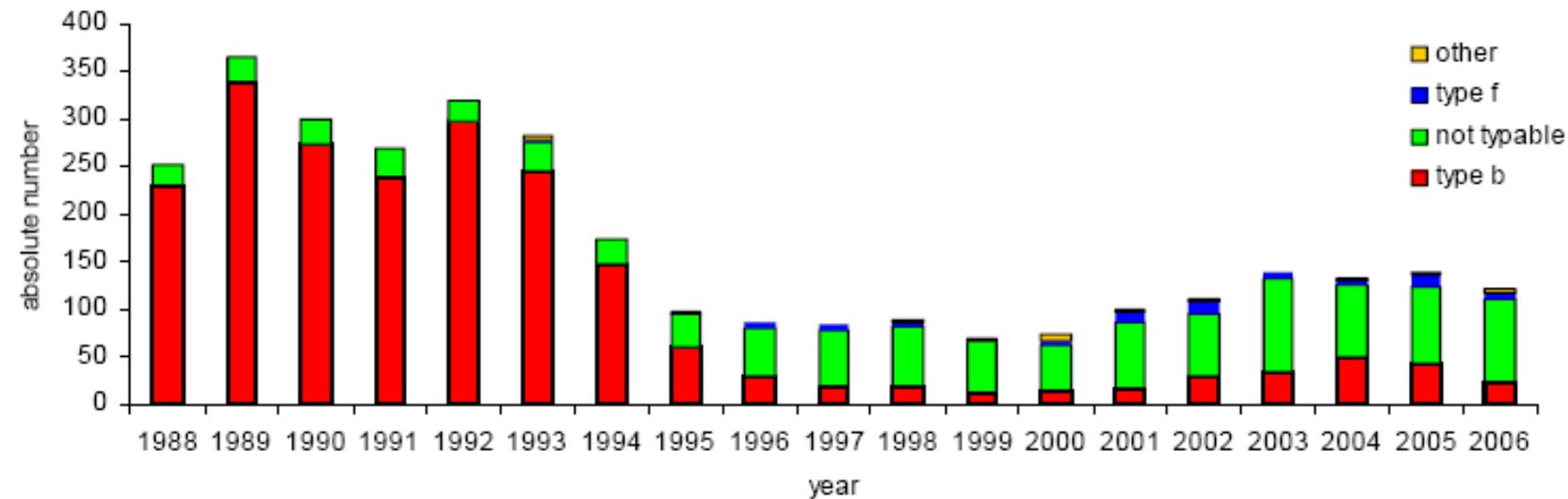


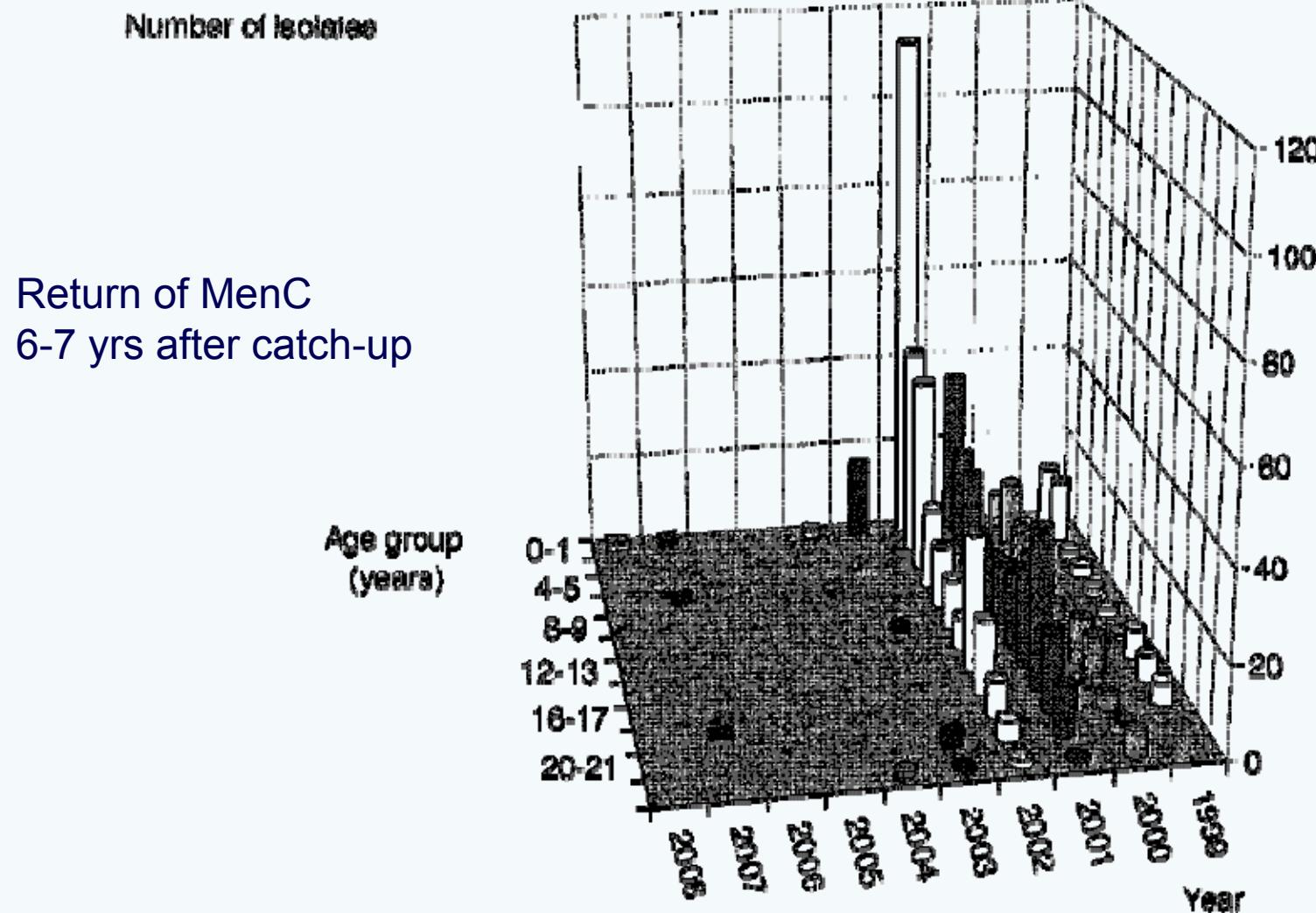
Figure 5 Absolute number of *H. influenzae* isolates by type, 1988-2006 (source: NRBM)

2007: 115 cases, 87 (75,7%) NTHi; 24 (20,9%) serotype b; 2 serotype f and 2 other serotypes (both 1,7%)

Lessons from Men C vaccination programme experience

- Mass vaccination with MenC conjugate vaccines are highly effective in preventing meningococcal serogroup C disease. UK experience.
- Men C conjugate vaccines show herd immunity effects
- Immunity wanes over time and a booster is required after primary vaccination of infants to provide prolonged protection
- Effectiveness of Men C conjugate vaccines has been subsequently confirmed in other countries, e.g. Spain, Australia, Belgium, Quebec, the Netherlands.
- Experience from Holland shows that 1 dose in toddlers plus catch-up campaign up to 18 years can control MenC disease, but ...

Age distribution serogroup C disease in the first 23 years of life (1999-2008)



GSK's meningitis vaccine portfolio

- DTPa(HB)IPVHib paediatric, primary + booster
- DTPwHBHib paediatric
- HibMenC, primary + booster ; as booster after DTPa(HB)IPVHib
- 10v Spneumo conjugate with PD from NTHi as carrier
- In late stage development: HibMenCY-TT for paediatric, prim + boost
- ACWY-TT for toddlers, adolescents & adults
- Men combinations for Africa, toddlers, adolescents & adults (incl. catch-up)

Options to introduce GSK's vaccines into a two-injection paediatric programme

Designed to avoid
interferences



or



+

Synflorix™

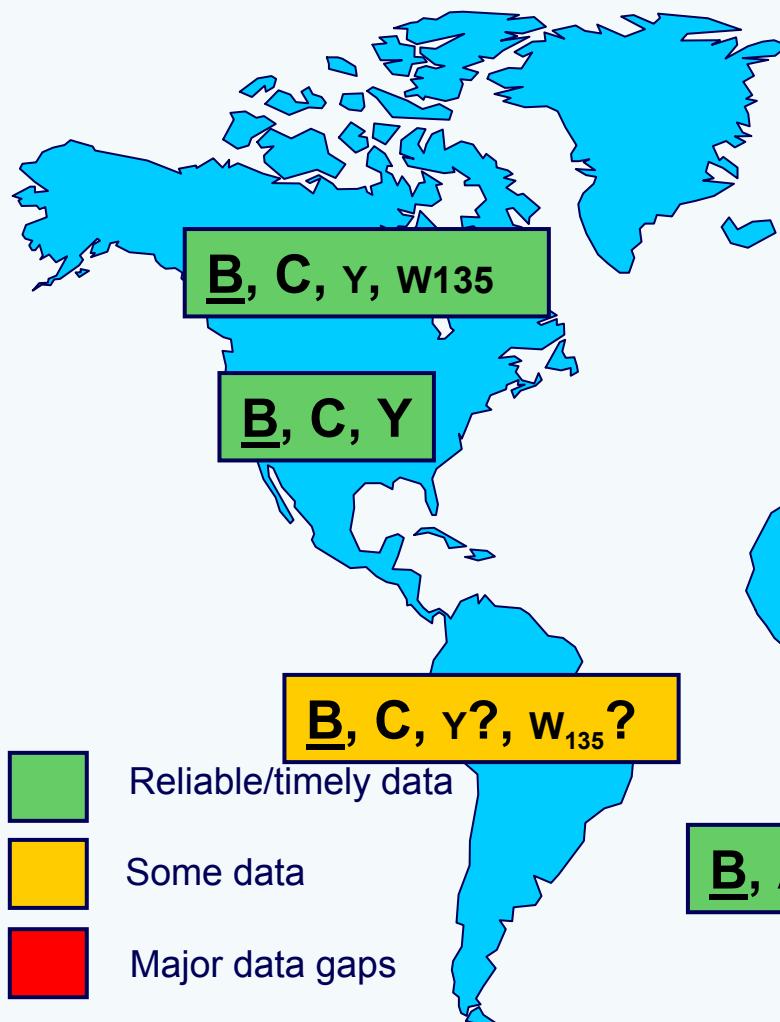
GSK's PHiD
conjugate vaccine



Examples of paediatric coadministration interferences

- DTPa2HBIPVHib + PCV7-CRM197 : stopped reduction of HB response
- DTPa3Hib + MenC-CRM197 : stopped reduction of Hib response
- DTPa3HBIPVHib + PCV7-CRM197 : OK reduction of Hib response, although acceptable
- DTPa5IPVHib + PCV7-CRM197 : OK reduction of Hib response, although acceptable
- DTPa5IPVHib + PCV11 DT-TT : stopped reduction of PCV-TT responses

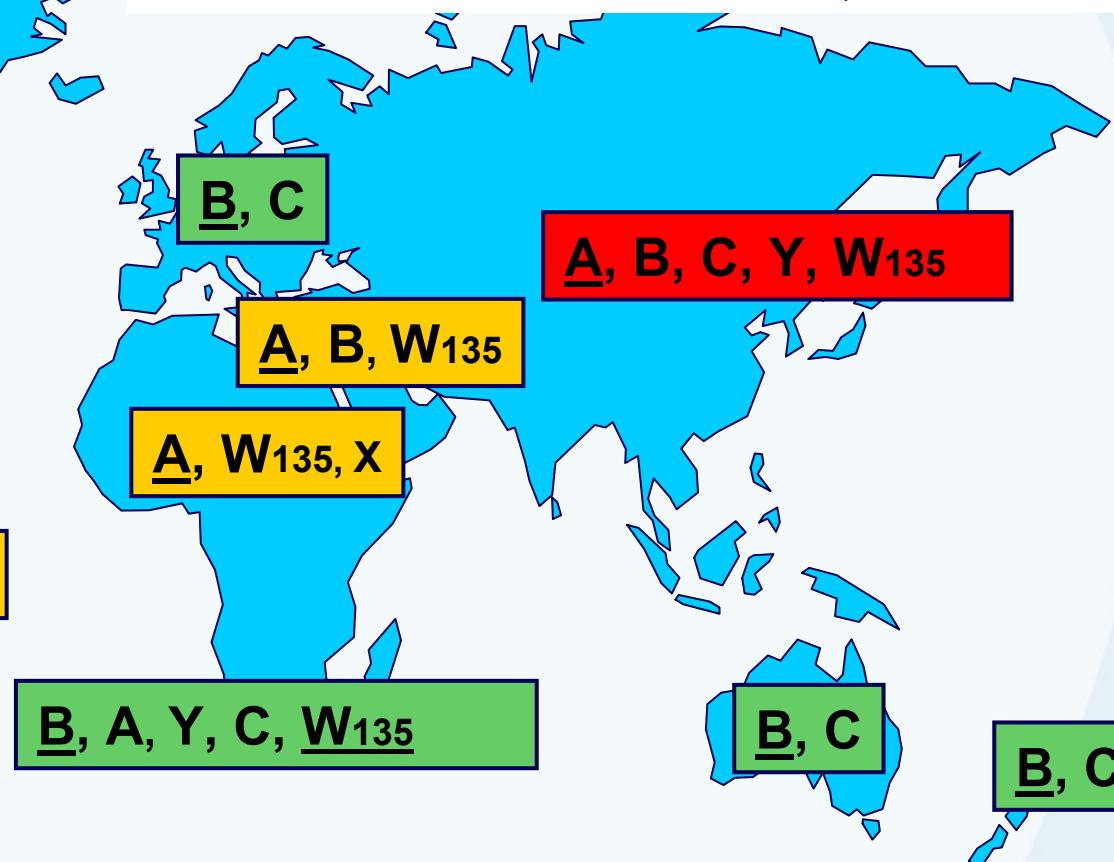
Global serogroup distribution of invasive meningococcal disease



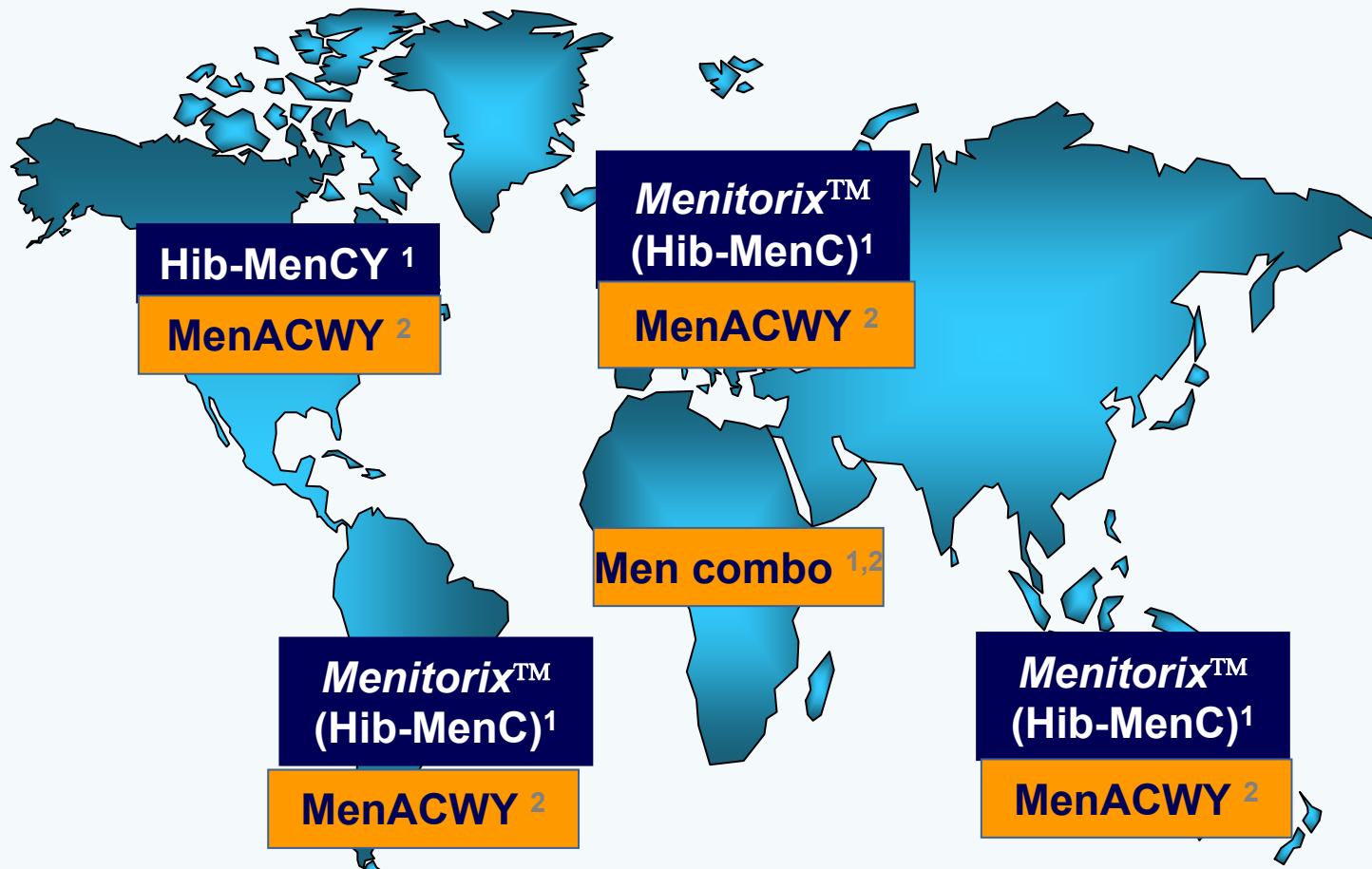
Incidence

Industrialised countries: ~1-10/100,000 (endemic)

African Meningitis Belt: large epidemics
~100-800/100,000



GSK's tailored offering: conjugate vaccines licensed or in clinical development

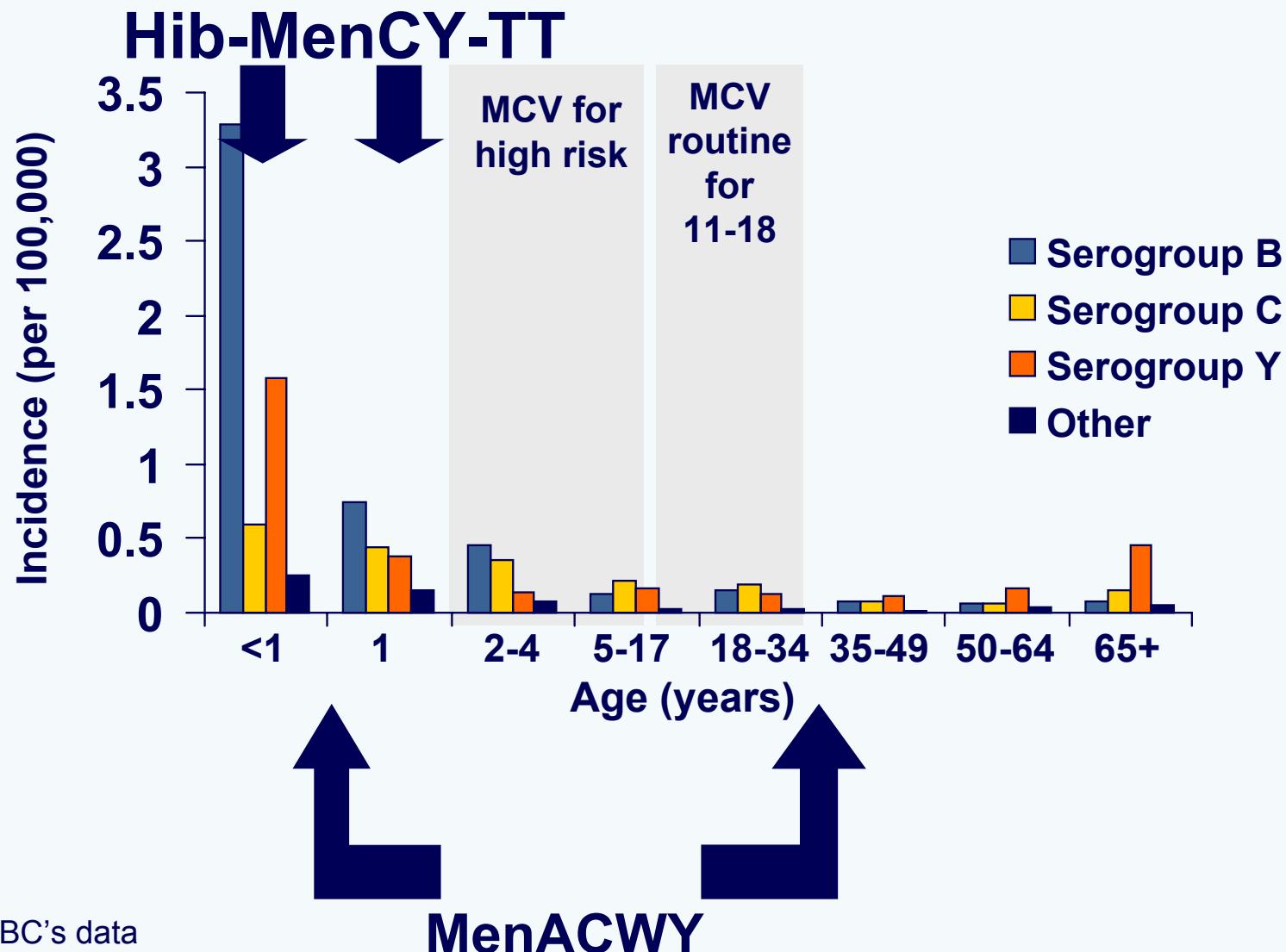


¹ infants, toddlers

² toddlers, adolescents, adults

GSK Meningococcal Vaccines for USA

Cases per 100,000 of *Neisseria meningitidis* (1997-2007)



Hib-MenCY-TT: Product Profile

- **Composition: per 0.5 ml dose:**

- 2.5 µg PRP conjugated to tetanus toxoid
- 5 µg PSC and 5 µg PSY conjugated to tetanus toxoid
- no aluminium
- no thiomersal, no phenoxy ethanol
- lyophilized, to be reconstituted with saline

- **Indication:**

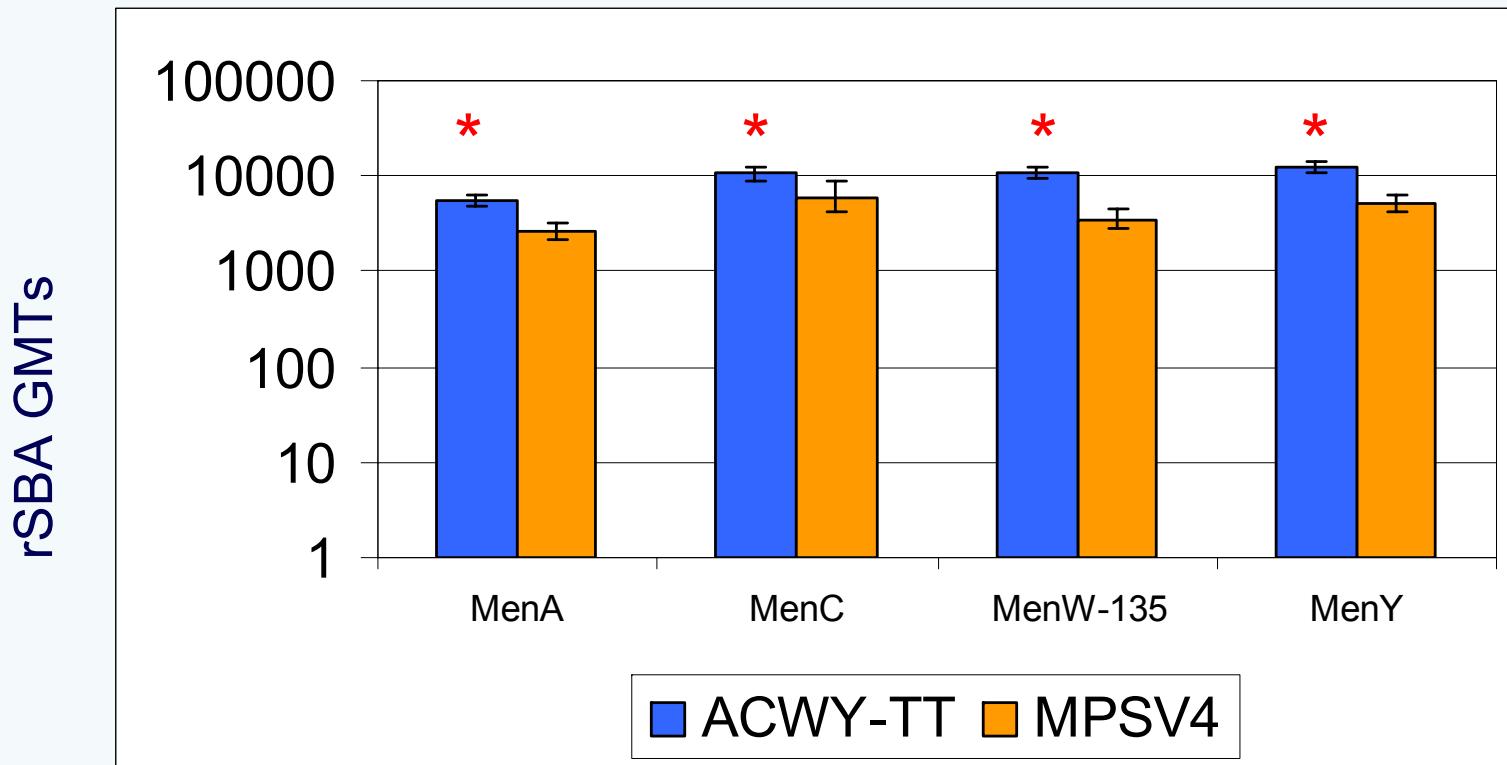
- 4-dose vaccination of children:
at 2, 4, 6 and 12-15 months of age

ACWY conjugates

- GSK-MenACWY-TT
 - *Neisseria meningitidis* serogroups A, C, W-135, and Y- tetanus toxoid conjugate vaccine (5 µg per conjugate)
 - Lyophilized formulation
 - No adjuvant
- Sanofi Pasteur- *Menactra*™
 - *Neisseria meningitidis* serogroups A, C, W-135, and Y- diphtheria toxoid conjugate vaccine (4 µg per conjugate)
 - Liquid formulation
 - No adjuvant
- Novartis- *Menveo*™
 - *Neisseria meningitidis* serogroups A, C, W-135, Y- CRM₁₉₇ conjugate vaccine (10 µg serogroup A; 5 µg for other serogroups)
 - Liquid C/W-135/Y conjugates reconstitute lyophilized A conjugate
 - Aluminum phosphate adjuvant in infant study by Snape, et al (but not in subsequent studies)

MenACWY-TT has Significantly Higher GMTs than MPSV4 (11-17 years)

rSBA GMTs in Subjects 11-17 years



*Statistically significantly higher rSBA GMT in MenACWY-TT vs. MPSV4

GSK MenACWY-TT vaccine - summary

- Over 7000 subjects already exposed to at least one dose of MenACWY-TT
- Safety and reactogenicity profile is clinically acceptable
- Non-inferiority to licensed monovalent MenC-CRM (Meningitec and Menjugate) in subjects 1-10 years
- Non-inferiority to licensed quadrivalent plain polysaccharide vaccine (Mencevax ACWY) in subjects 2-55 years
- Coadministrations to main paediatric and adolescents vaccines

Conclusions on meningococcal conjugate vaccines

- Thanks to the availability of MenA, MenC, HibMenC, HibMenCY, and ACWY conjugate vaccines, non-MenB meningococcal disease can be prevented
- Optimal schedules need to be agreed upon, it seems routine paediatric and adolescent immunisation best way forward
- Special attention needed for Africa, i.e. Men combinations for infants and catch-up
- Combination vaccines allow to reduce number of injections and increase compliance and easiness of vaccine programmes with special attention to avoid interferences

General Conclusions

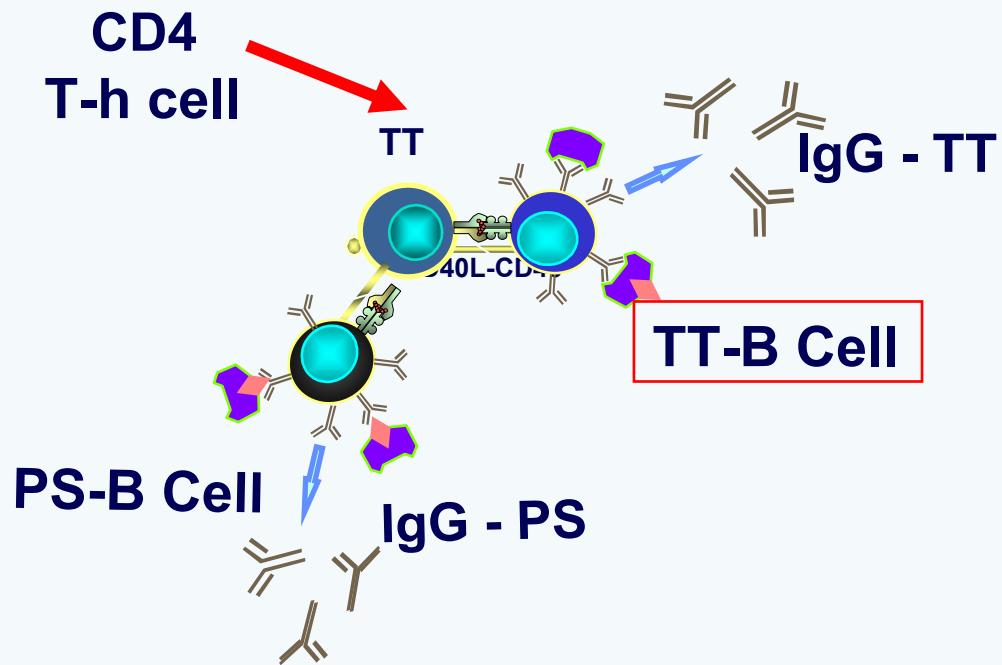
- One of the major successes of vaccinology in the last 2 decades was the introduction of conjugate vaccines : Hib, Spneumo, Men
- There are still unmet needs that need to be addressed
 - Expanded Spneumo (“close the door” incl. proteins)
 - NTHi
 - MenB
- Expanding the spectrum of pneumococcal coverage as well as adding NTHi is an innovative step in addressing invasive and respiratory bacterial diseases

The Future : Optimal combinations & schedules Hib,Spn,ACWY,NTHi & MenB

Thank you

Back-up

Carrier and other interferences



- B-cell competition
→inadequate help due to competition for T-help
- Ag capture by antibodies to carrier
- T-cell regulation ,may spread to combined antigens,ie bystander effect