9th National Seminar on Travel Medicine

17 November 2011

Conjugate or polysaccharide quadrivalent meningococcal vaccine : no easy answer

15.15-15.35

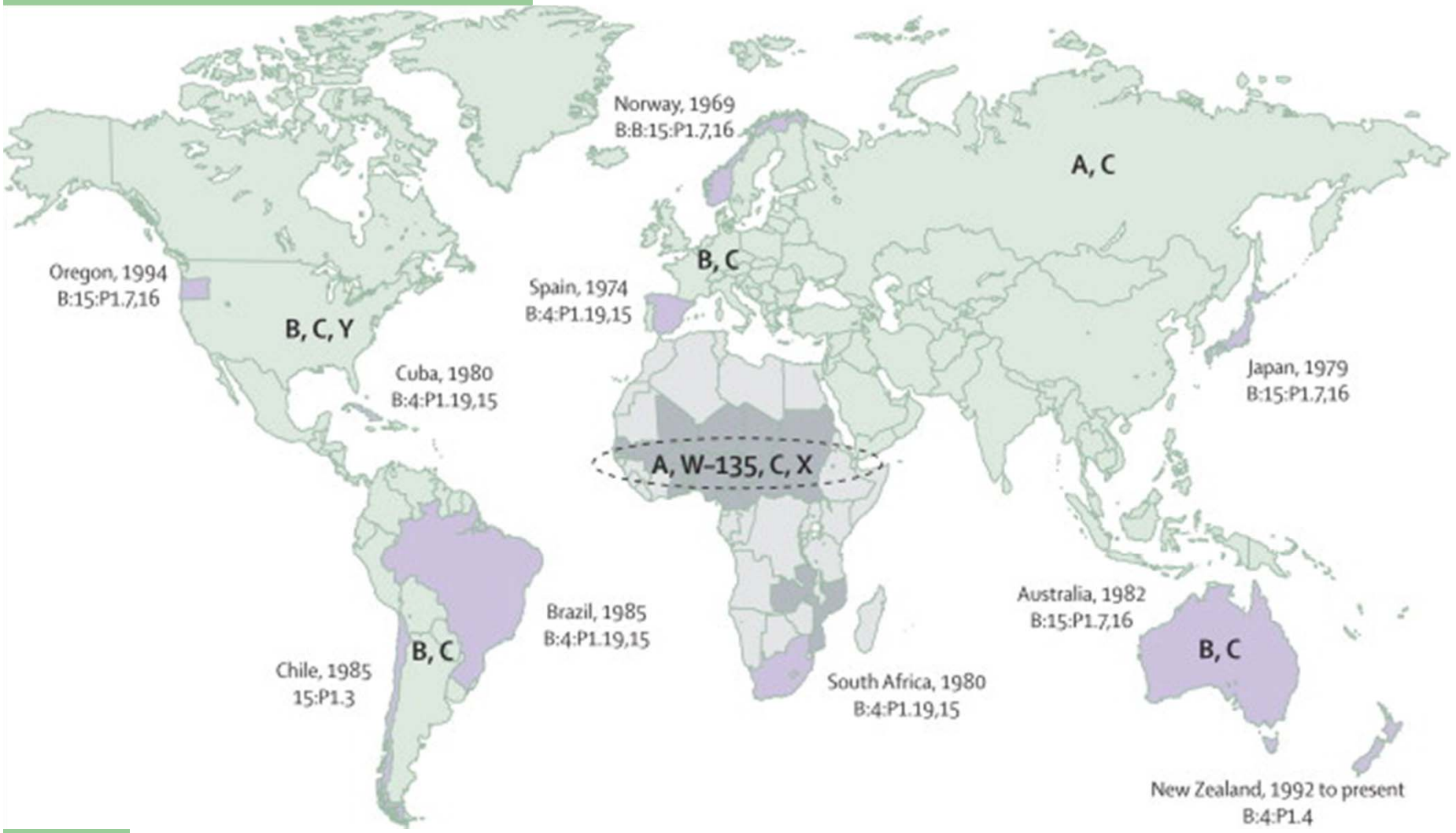
Conjugate or polysaccharide quadrivalent meningococcal vaccine : no easy answer

Pr. B. Vandercam, UCL Brussels & Pr. F. Van Gompel, ITG Antwerp

Conjugate or polysaccharide quadrivalent meningococcal vaccine : no easy answer ?

F. Van Gompel - B. Vandercam

Novembre 2011



Worldwide distribution of major meningococcal serogroups and of serogroup B outbreaks by serotype (shaded in purple). Lancet 2007, 369

Asymptomatic carriage : 10-20 %

- Non epidemic period, « normal » families
  - 18 % carriage in 32-months period
  - 19-38 % adult men (highest carriage)
  - Mean duration : 9 months (days to months)

- Immunologic process :
  - AB production within 2 weeks
  - Persistant > 4-6 months even with non groupable meningococci (± cross reacting AB)
  - Military camps : veterans lower carriage and disease

JID 1971 - J Exp Med 1969

Transmission : person to person

- By aerosol droplets
  Respiratory secretion
  Saliva
- New infection : invasive MD
  - Culture + : 4 days before (5/36)
  - Culture - : 1 day before (4/36)

SHORT INCUBATION PERIOD : 1-14 DAYS
NO TIME FOR NATURAL OR
VACCINE BOOSTER ?

Neisseria meningitidis
Risk factors for invasive disease

- Host factors
  - Terminal complement pathway deficiency (C5 – C9, properdine, facteur H ou D)
  - HIV infection : probably ?
  - Functionnal or anatomic asplenia
  - Genetic risk factors : polymorphisms for mannose-binding lectin and TNF
- Exposure factors
  - Household exposure
  - Concurrent upper respiratory tract infection
  - Demographic and socioeconomic factors and crowding (nightclub, alcohol, africans-americans)
  - Active and passive smoking
  - Microbiologists

Travlrs risk of MD

Like general population

- Dormitories
- Educationnal or military institution
- Refugee camps
- Sporting events
- Discotheque
- School bus

Risk variable

- Destination
- Mode of transport
- Type of accomodation
- Travel activities
- Duration of stay

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bacterial Meningitis in the United States, 1998–2007

Michael C. Thigpen, M.D., Cynthia G. Whitney, M.D., M.P.H., Nancy E. Messonnier, M.D., Elizabeth R. Zell, M.Stat., Ruth Lynfield, M.D., James L. Hadler, M.D., M.P.H., Lee H. Harrison, M.D., Monica M. Farley, M.D., Arthur Reingold, M.D., Nancy M. Bennett, M.D., Allen S. Craig, M.D., William Schaffner, M.D., Ann Thomas, M.D., Melissa M. Lewis, M.P.H., Elaine Scallan, Ph.D., and Anne Schuchat, M.D., for the Emerging Infections Programs Network

CONCLUSIONS

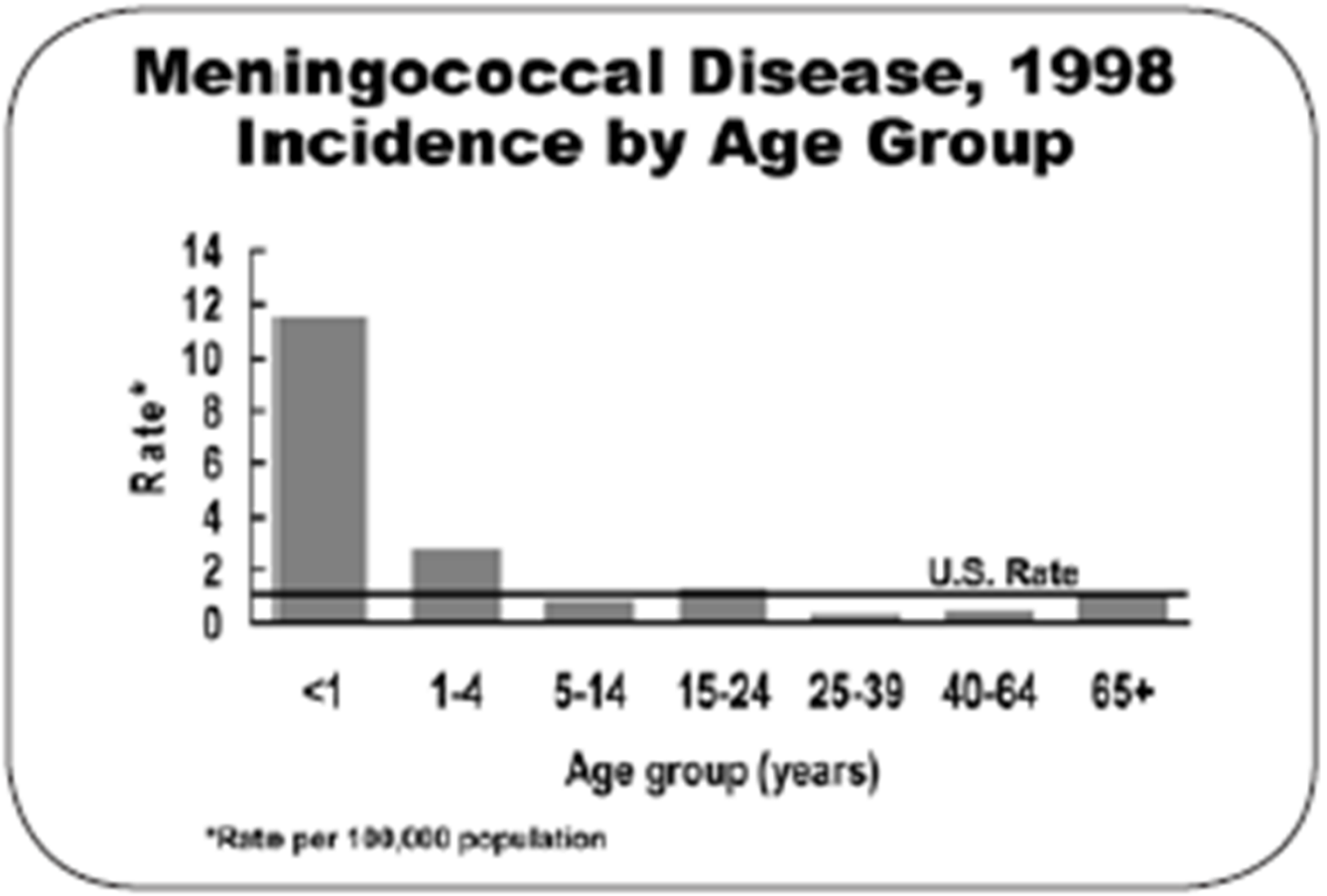
The rates of bacterial meningitis have decreased since 1998, but the disease still often results in death. With the success of pneumococcal and Hib conjugate vaccines in reducing the risk of meningitis among young children, the burden of bacterial meningitis is now borne more by older adults. (Funded by the Emerging Infections Programs, Centers for Disease Control and Prevention.)

Neisseria meningitidis in the US 1998-2007

- Older children, young adults : major cause (40 %)
- Absence of underlying diseases : ± 50 %
  (other pathogens 25 – 30 %)
- Outbreaks : < 5 % of reported cases
- Case fatality rate
  - Pediatric 3,8 % (N = 107)
  - Adult 10,4 % (N = 125)
- Permanent sequellae : 1/5 survivors

NO CHANGE IN CASE FATALITY RATE

NEJM 2011, 364:2016-2025



CDC, Pink Book 2011

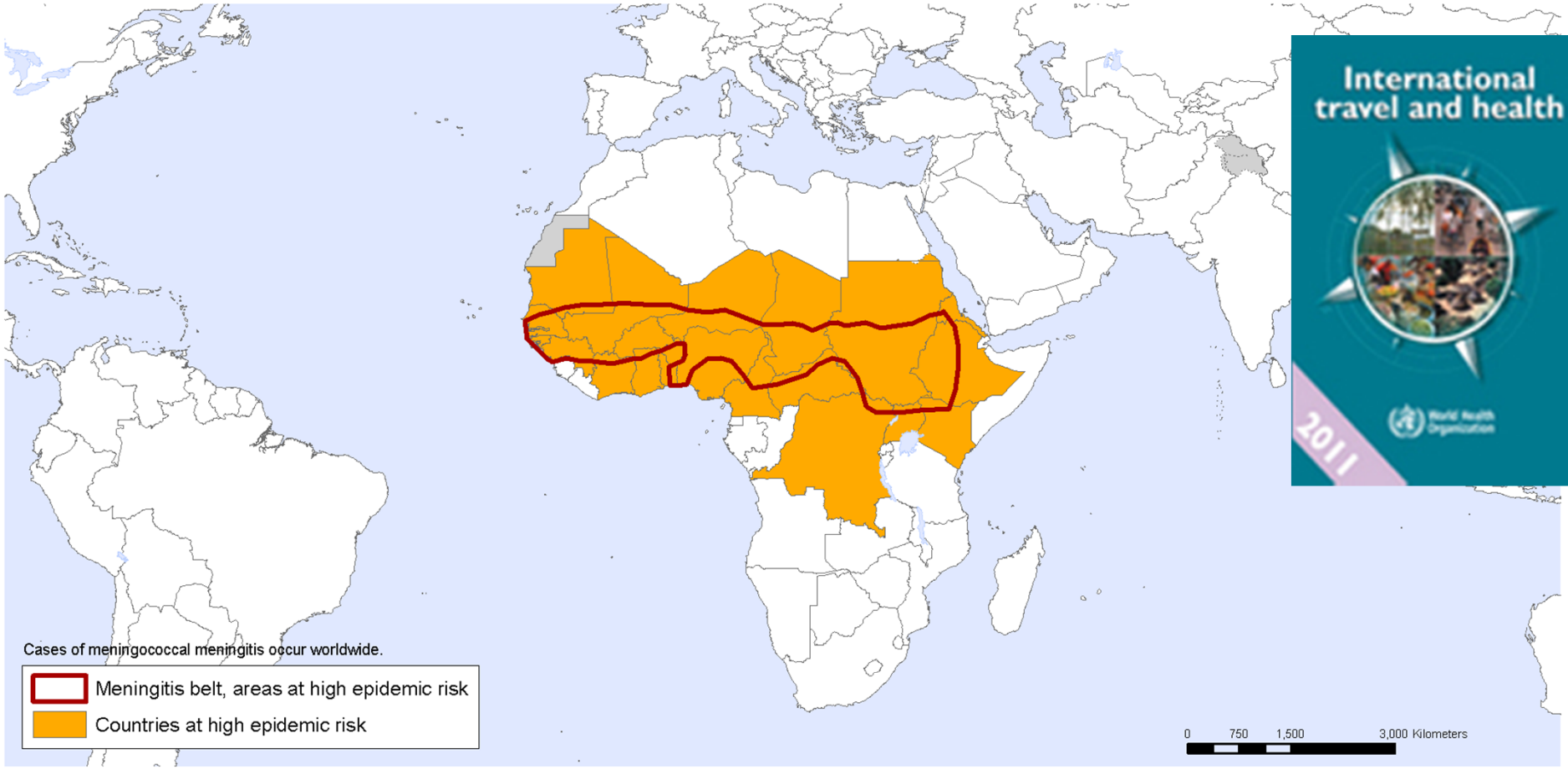
Annual estimated national burden of Meningococcal disease (per 100 000 population)

Age group	Serogroup B – C – Y		N° of deaths
	Incidence	**Case fatality rate**	
< 1 year	5,38/10^5	6 %	13/215
1 year	1,47	3,4 %	2/59
2-4 years	0,90	4,8 %	5/105
5-13 years	0,36	10 %	14/132
14-24 years	0,75	11,5 %	41/337
25-64 years	0,28	12,8 %	**55/429**
≥ 65 years	0,69	23,8 %	**59/248**

CID 2010, USA

2009 = 2010 = 2011

Meningococcal meningitis, countries or areas at high risk, 2009



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Meningitis belt

- Majority serogroup A
- Dry season : december – june (dust wind, upper RTI)
- Baseline incidence 5-10-20/10^5/year (population displacement, market, overcrowding ...)
- Explosive epidemics : attack rate 1000/10^5
  - 2009 : 78 000 cases, 4000 deaths

Not a single case in travlrs (vax, social distancing)

Travlrs risk of MD

- 1986-1989 13 cases (survey)
- 1996-2008 11 cases (case reports)
  6 geosentinel
  $0,4/10^6$/month

$0,5/10^5$/year

Rare among travlrs

Same risk industrial countries

No risk O

All parts of the world/all age group/all types of travelers

JTM 2010, 17:9-17

Table 1 Anecdotal cases of meningococcal disease in travelers, 1996 to 2008[10–15]

Traveler		Infection	
Type	Origin	Location	Outcome
Children	UK, Germany	Majorca, Spain (2 children died in same hotel)	2 died, 2 recovered
Student	Swiss/French	Germany	1 died, 1 recovered
Athlete	Unknown (1,500 athletes from 43 countries)	Jaca, Spain	Recovered
Tourist	Swiss	Tirol, Austria	Died
Journalist	UK	Morocco >Japan> Singapore	Recovered
Business	Italy	India	Recovered from serogroup A disease

JTM 2010, 17:9-17

Travlrs risk of MD

- Hajj pilgrims (2.10^6)
  - Attack rate $640/10^5$ 1987 group A
  - Attack rate $25\text{-}30/10^5$ 2001 group W135
  - No exportation > 2004
  - Serogroup B in the future ?

JTM 2010, 17:9-17

Travlrs risk of MD and air flight

1 investigation/6 weeks CDC

2 reports of inflight transmission

- LA → Sidney 14 h (B)
- USA → Frankfurt 11h (B)

JTM 2010, 17:9-17

Quadrivalent polysaccharide vaccine (MPS4)

- 50 µg of each poly-s $ACYW_{135}$
- Dilution sterile water
- No preservative
- Subcutaneous

Quadrivalent meningococcal conjugate vaccine (MCV4)

- **Menactra** (*Sanofi Pasteur*) 4 µg of poly-S $ACWY_{135}$
  + 48 µg of diphteria toxoid (detox by formaldehyde) protein carrier
- **Menveo** (*Novartis*) 10 µg poly-S group A & 5 µg poly-S serogroup C, Y, W_{135}
  + CRM 197 non toxic mutant of diphteria toxin
- No preservative, no thiomersal
- No adjuvant
- IM

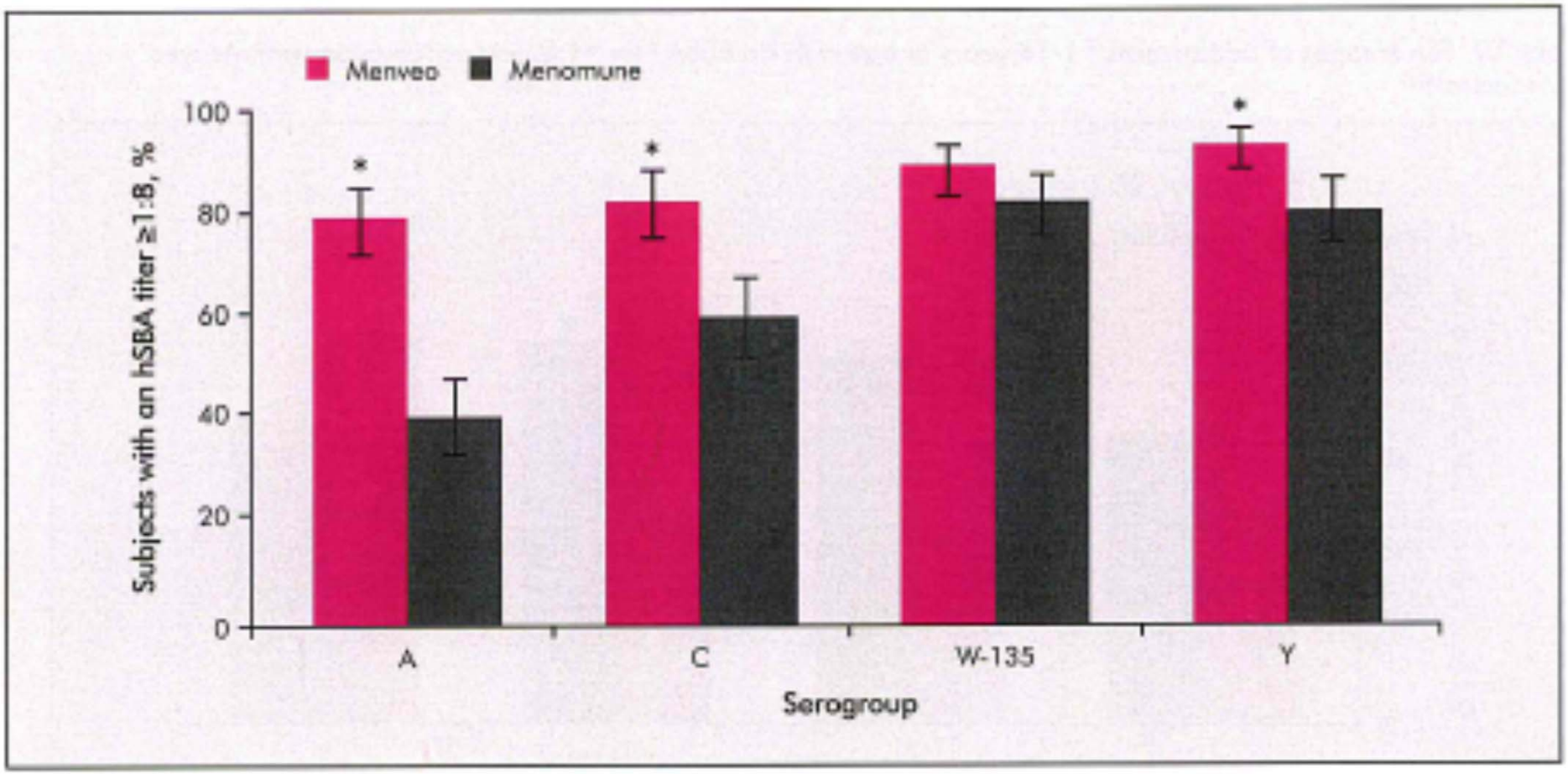
Meningococcal vaccines: a neglected topic in

Table 3. Comparison of meningococcal polysaccharide and conjugate vaccine properties.

Property	Polysaccharide	Conjugate
Immunogenic in infants	No*	Yes
Immune memory	No	Yes
Prolonged duration of protection	No	Yes‡
Booster effect	No§	Yes
Reduction of carriage	No	Yes
Contributes to herd effect	No	Yes
Hyporesponsiveness with repeated dosing	Yes	No

*Immunogenic for serogroup A.
‡Duration of protection is not known but is expected to be longer than that for polysaccharide vaccine.
§Booster effect for repeated doses.
Data taken from [43].

Figure 17. Proportion of adolescents 11-17 years of age with an hSBA titer ≥1:8 at 1 month post-vaccination with Menveo or Menomune[15]



*P<0.001

hSBA, serum bactericidal assay using human complement

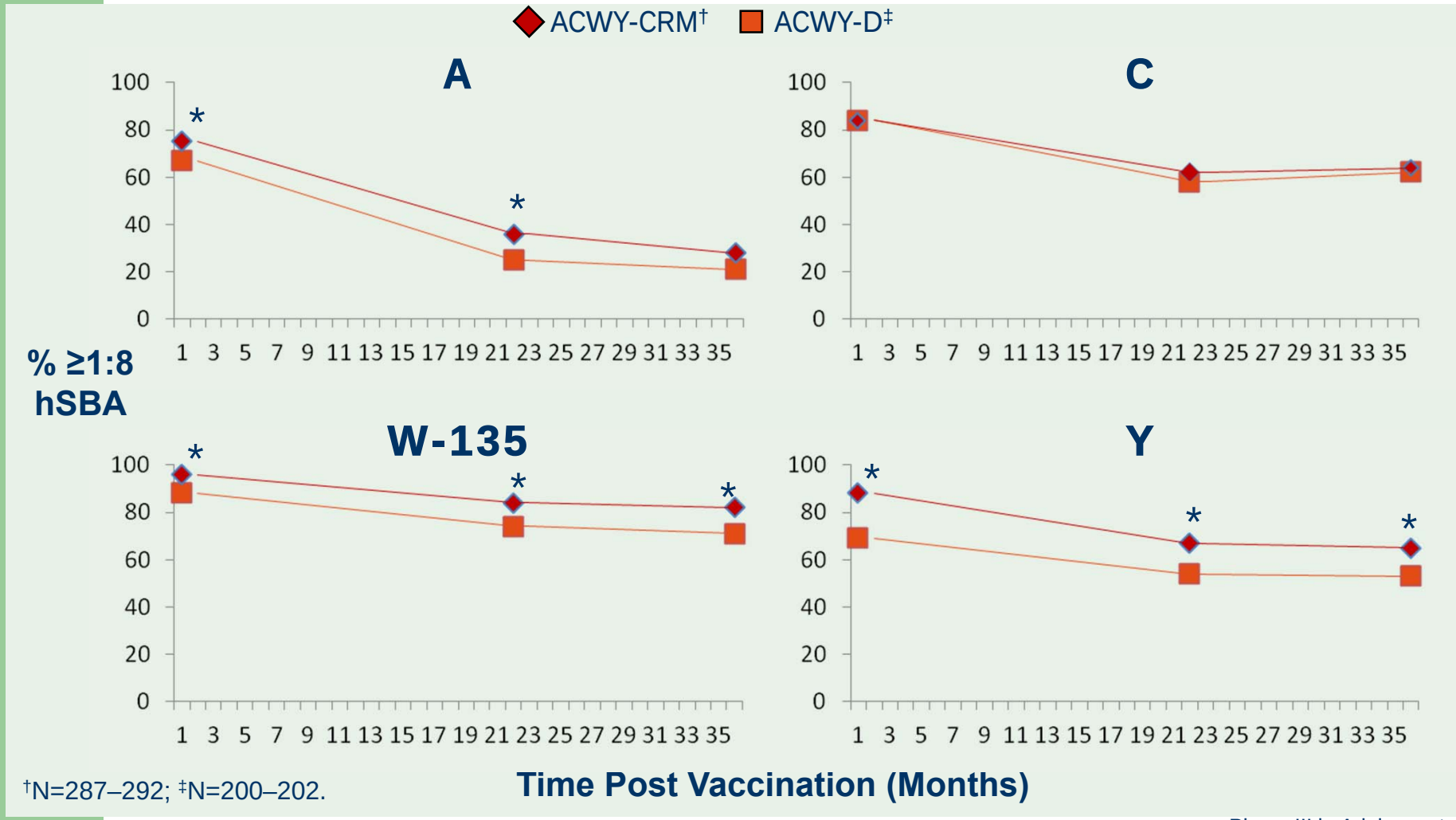
Jackson PIDJ 2009

Immunogenicity of MenACWY-CRM in phase III studies in adolescents and adults

Study	Age group (years)	Population site	Vaccine	Subjects with HSBA titers > 8, 1 month post vaccination, % (95 % confidence interval)			
				A	C	W-135	Y
Stambou-lian et al (2010)	19-55	2831	Men ACWY-CRM	81	88	98	88
	56-65		Men ACWY-CRM	87	90	94	88
			MPSV4	63	83	95	68

Int JID 2010

Persistence of Protective Immune Responses 36 months after a priming dose in Adolescence was evaluated using human complement Serum Bactericidal Assay (hSBA)



†N=287–292; ‡N=200–202.

*Statistically significant difference.

Jackson LA, et al. *Clin Infect Dis*. 2009;49:e1-e10; Gill C, et al. *Human Vaccines*. 2010;6:881–887; Presented at Pediatric Academic Society (PAS) 2011; Denver, CO.

Phase III in Adolescents
Study V59P13 US

Meningococcal disease in persons vaccinated with conjugate vaccine

- 12 reports
- Mean age : 18 (16 - 22)
- Mean time since vaccination : 3,25 year (1,5 - 4,5)
- Underlying condition : 5/12

PS

Already described with SBA satisfactory before vaccination era

J Infect 1987 - JID 1981 - MMWR
28 jan 2011

TABLE 2. Human complement serum bactericidal assay (hSBA) antibody responses after a booster dose MenACWY-CRM* administered 3 years after a single dose of MenACWY-D† or MenACWY-CRM in persons who received the first dose at age 11–18 years

	Proportion hSBA titer ≥8				Geometric mean titer			
	MenACWY-D† » MenACWY-CRM		MenACWY-CRM » MenACWY-CRM		MenACWY-D » MenACWY-CRM		MenACWY-CRM » MenACWY-CRM	
Serogroup	No.	(%)	No.	(%)	Titer	(95% CI)	Titer	(95% CI)
A	70	(100)	71	(100)	493	(366–664)	356	(256–495)
C	70	(100)	71	(100)	626	(435–901)	703	(473–1,044)
W-135	69	(99)	71	(100)	883	(610–1,278)	987	(656–1,485)
Y	70	(99)	71	(100)	459	(313–671)	679	(447–1,033)

Abbreviation: CI = confidence interval.
* Menveo, Novartis Vaccines and Diagnostics.
† Menactra, Sanofi Pasteur.

MMWR, aug 2011 (ACIP)

Meningococcal conjugate vaccine

- Significant decline in antibody 3 to 5 years after vaccination

  Few cases of MD among vaccinated persons

  → **Revaccination for persons at risk**

- Vaccination with a single dose not sufficient in complement deficiency, asplenia, HIV, young children

  → **2 doses 2 months apart**

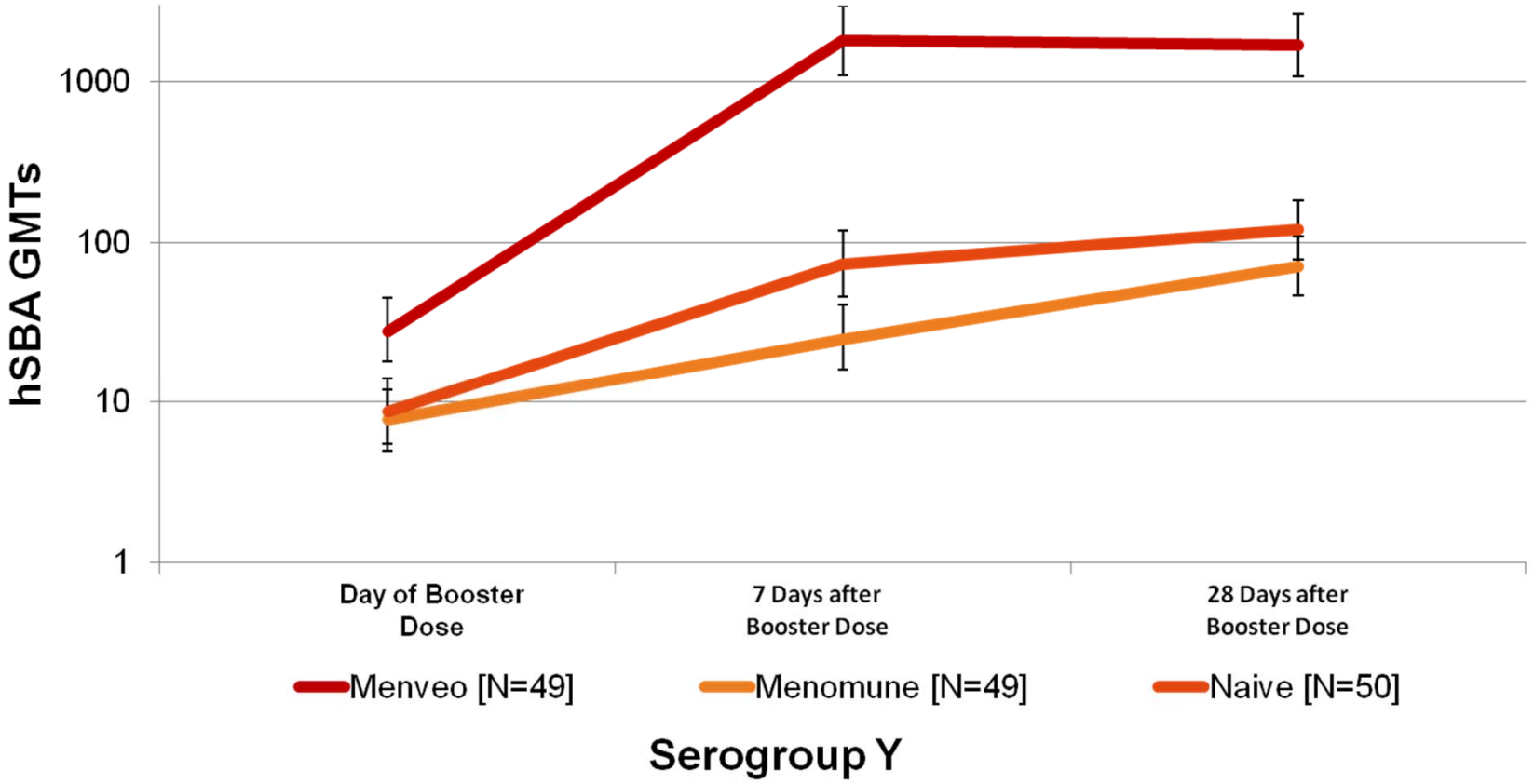
MMWR, jan 2011

MCV-4 booster 3 years after initial vaccination : convenience sample from MCV-4 and PSV-4 groups with vaccine-naive comparison

Geometric mean serum bactericidal antibody titers		
Day 28		
Serogroup	MCV-4	PSV-4
A	4326	3270
C	8192	665
Y	5846	2327
W-135	4612	1577

H. Keyserling, Arch Pediatr Adolesc Med 2005 (Menactra)

MENVEO was shown to be able to be used as a booster vaccine after both Plain Polysaccharide MenACWY vaccine or a Priming Dose of MENVEO



Jackson L, et al. Presented at Pediatric Academic Society (PAS) 2011; Denver, CO.

Data on file. Novartis Vaccines & Diagnostics.

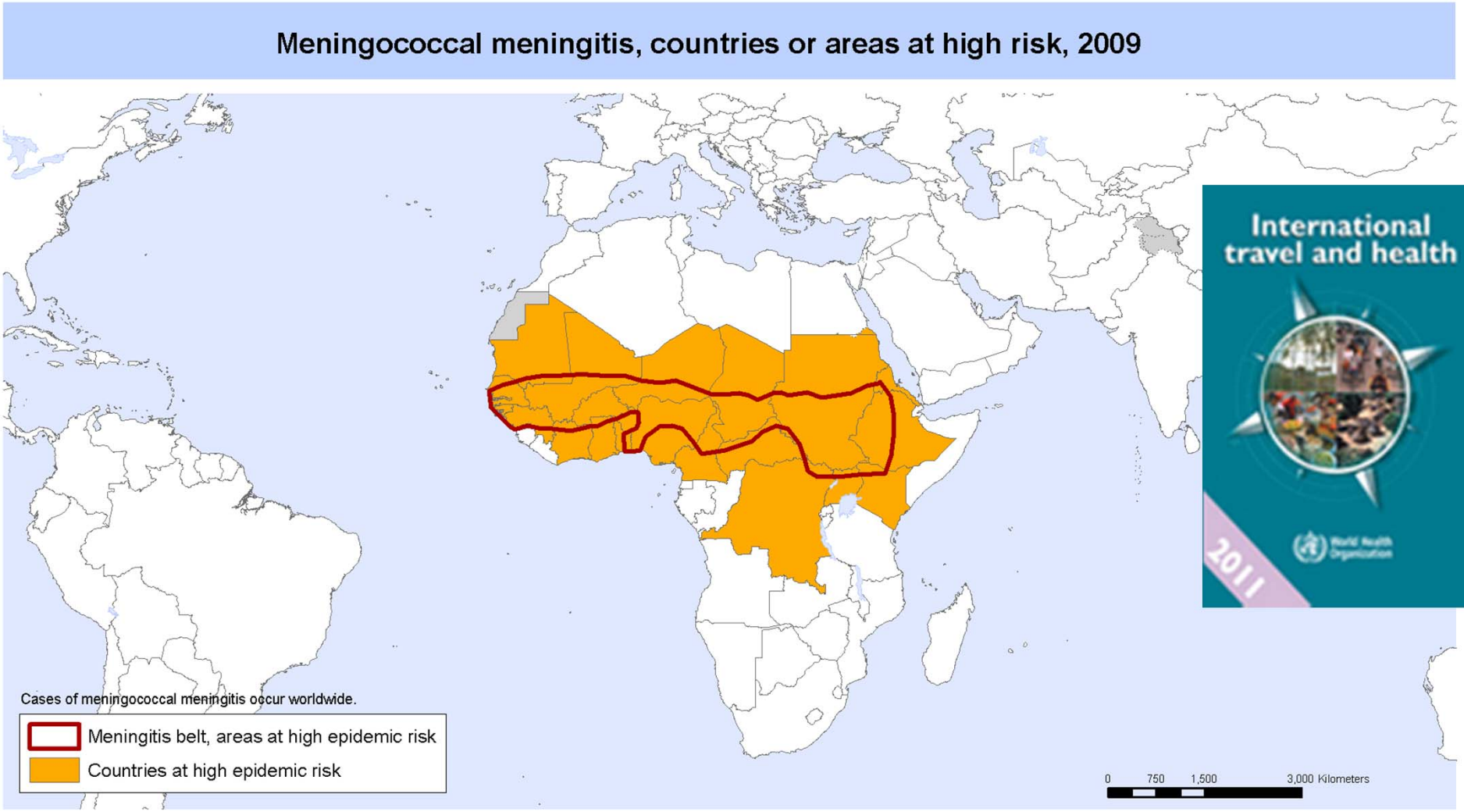
Update november 2011

BELGIAN CONSENSUS MEETING on TRAVEL MEDICINE June 20, 2011

Belgian Scientific Study Group on Travel Medicine

Pr. A. Van Gompel (ITG)
Pr. F. Jacobs (Hôp. Erasme, ULB)
Pr. P. Lacor (UZ-Brussel)
Dr. Ph. Leonard (CHU-ULg)
Pr. W. Peetermans (U.Z. - K.U.Leuven)
Dr. S. Callens (UZ.- U.Gent)
Dr. S.Quoilin (iph.fgov.be)
Dr.P. Soentjens (Belgian Army)
Pr. B. Vandercam (CHU. St. Luc, UCL)
Pr. Y. Van Laethem (CHU. St. Pierre, ULB)

2009 =2010= 2011



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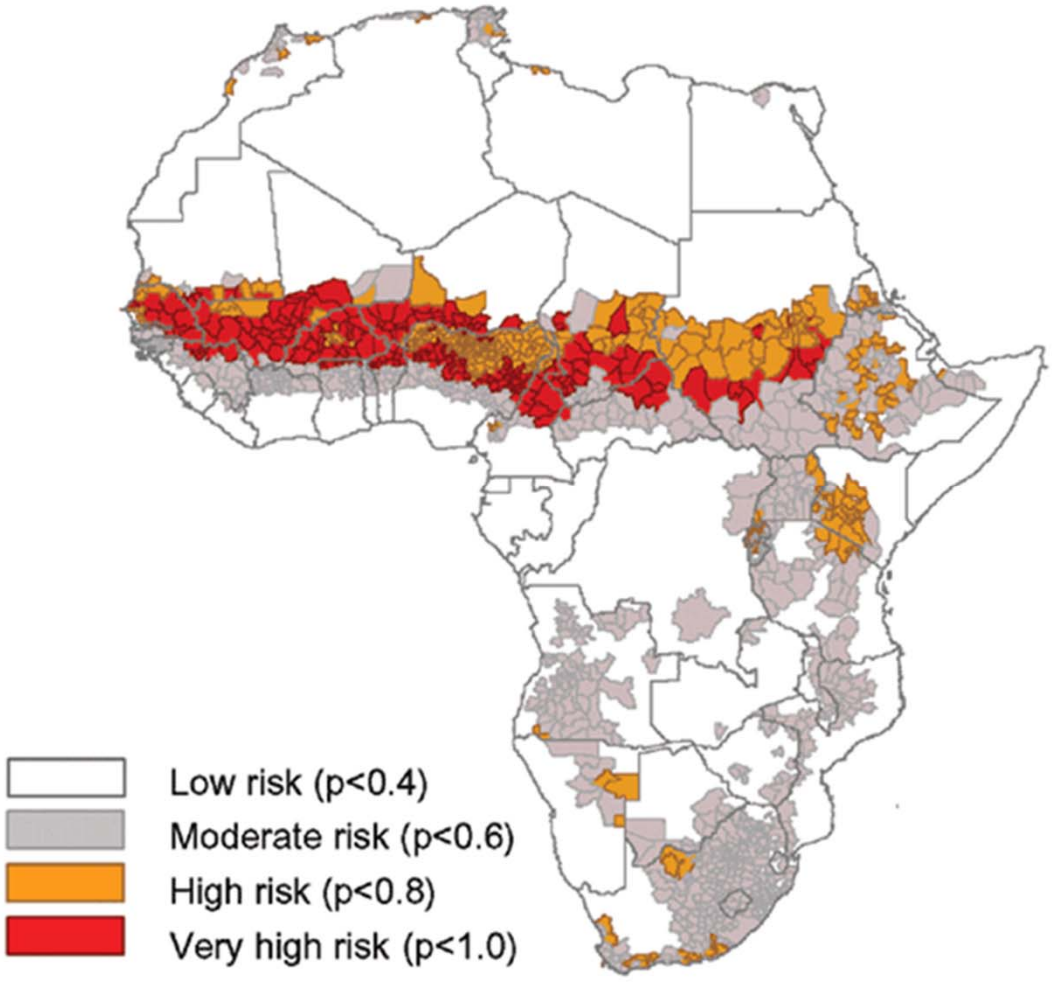
http://www.**cdc**.gov/ncidod/EID/vol9no10/03-0182-G2.htm



EID

Volume 9, Number 10, October 2003

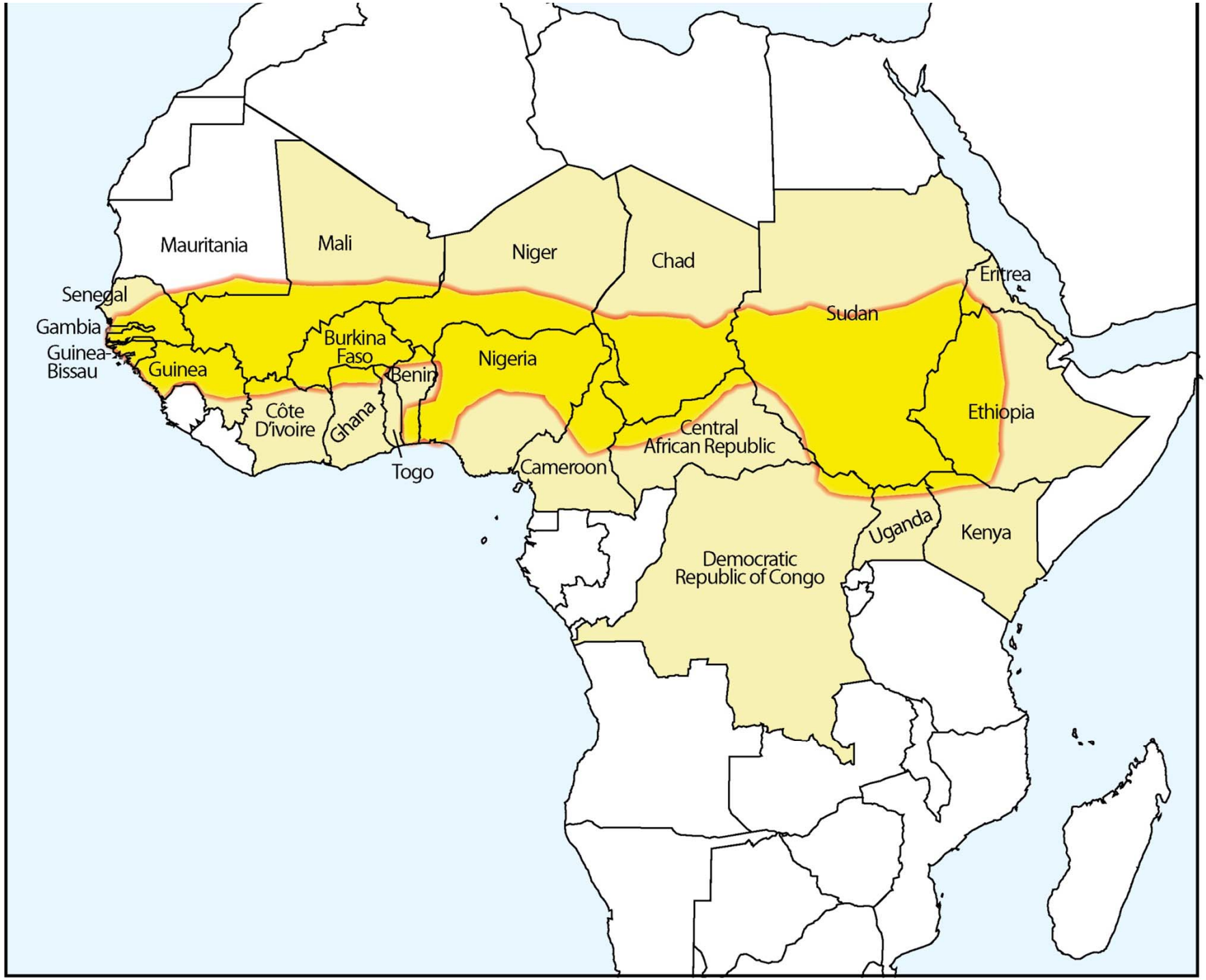
EXPERT REVIEWS

Meningococcal vaccines: a neglected topic in travel medicine?

Expert Rev. Vaccines 8(10), 1343–1350 (2009)

Table 2. Incidence of invasive meningococcal disease in different populations.

Population	Incidence per 100,000	Ref.
Travelers to developing countries (data from 1986 to 1989)	0.48	[2]
General US population:		
– 1989	1.3	[61]
– 2007	0.34	[106]
Meningitis belt epidemics	100–800	[103]
1987 Hajj pilgrims (USA)	640	[3]
2000 Hajj pilgrims (UK and Singapore)	25–30	[62]
Contacts of pilgrims (Singapore)	18–28	[63]


Mauritania
Mali
Niger
Chad
Eritrea
Senegal
Gambia
Guinea-Bissau
Guinea
Burkina Faso
Nigeria
Benin
Sudan
Ethiopia
Côte D'ivoire
Ghana
Togo
Cameroon
Central African Republic
Uganda
Kenya
Democratic Republic of Congo

8. Meningococcal vaccine: Mencevax or Menveo

- Since this year we have two meningococcal vaccines commercially available:
  - the polysaccharide vaccine Mencevax (33euro)
  - the new conjugated vaccine Menveo (52,6 euro).
- Menveo has the advantage that
  - antibody titers remain longer and that immune memory is installed.
  - It also eradicates carriership.
- It is not clear at this point at which time point a booster dose for the conjugated vaccine has to be given (3 or 5 or 10 years ?).

8. Meningococcal vaccine: Mencevax or Menveo

- The risk for carriership after Hajj is very low because every pilgrim coming from endemic countries receives eradicating antibiotic treatment on arrival in Saudi Arabia. For these reasons, the consensus conference expresses no priority for either vaccine.
- Mencevax® can be used when the travelers says that he only need the vaccine once (e.g; for Hajj).
- Menveo® is preferred for repetitive exposition such as expats and frequent travelers to countries of the meningitis belt.
- In the **UK** it is allowed to give Menveo from the age of 2 months

Meningococcal vaccines: a neglected topic in

Table 3. Comparison of meningococcal polysaccharide and conjugate vaccine properties.

Property	Polysaccharide	Conjugate
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Immune memory	No	Yes
Prolonged duration of protection	No	Yes‡
Booster effect	No§	Yes
Reduction of carriage	No	Yes
Contributes to herd effect	No	Yes
Hyporesponsiveness with repeated dosing	Yes	No

*Immunogenic for serogroup A.
‡Duration of protection is not known but is expected to be longer than that for polysaccharide vaccine.
§Booster effect for repeated doses.
Data taken from [43].

UK Green Book 2010 Chapter 22 *pages 230 & 242*

Although the vaccine is not yet licensed for infants, data show a better antibody response to all serogroups after two doses of conjugate vaccine (Snape *et al.*, 2008; Perrett *et al.*, 2009) than seen with the plain polysaccharide vaccine (Borrow, 2009); the response to serogroup C is comparable with that seen with the monovalent MenC conjugate vaccine (Southern *et al.*, 2008). Based on this and the experience with other conjugate vaccines, immunity is expected to be higher, longer-lasting and confer less risk of immunological tolerance than the plain vaccine. For this reason, conjugate vaccine is recommended in preference to plain vaccine in children under five years of age.

Quadrivalent (ACWY) conjugate vaccine

Children over two months of age and under one year:

- First dose of 0.5ml.
- Second dose of 0.5ml at least one month after the first dose.

A reinforcing dose of 0.5ml should be given 12 months after the primary course if the child continues to be at risk.

Children aged over one year of age and adults:

- Single dose of 0.5ml.

The need for, and timing of, a reinforcing dose has not yet been determined

UK Green Book 2010 Chapter 22

Age	Quadrivalent vaccine	
	Conjugate MenACWY (Menveo®)	Polysaccharide MenACWY (ACWY Vax)
Infants under one year*	'off label' • First dose of 0.5ml. • Second dose of 0.5ml one month after the first dose.	Not recommended
Children aged one year to four years	'off label' • Single dose of 0.5ml.	Not recommended
Children aged five years to ten years	'off label' (but preferred) • Single dose of 0.5ml.	• Single dose of 0.5ml.
Individuals aged 11 years and older	(preferred) • Single dose of 0.5ml.	• Single dose of 0.5ml.

* Replace the MenC vaccine with MenACWY conjugate vaccine if the infant requires MenACWY conjugate vaccine at the same time as the routine MenC vaccinations. If the infant has already had two MenC vaccinations then two MenACWY conjugate vaccines should also be given.

Menveo ®

Folia Pharmacotherapeutica maart 2011

- Voor vaccinatie tegen meningokokken van de serogroepen A, C, W en Y bestaat er in België nu

1. Mencevax® een polysacharidevaccin 33 euro
   met als voornaamste beperkingen
   – de geringe beschermingsduur (maximum 3 tot 5 jaar)
   – het beperkt immunogeen vermogen bij immuungedeprimeerde patiënten en jonge kinderen

2. Menveo® een met difterie-eiwit CRM-197 geconjugeerd polysacharidevaccin 52,60 Euro

- De vaccinatie bestaat uit één enkele intramusculaire injectie.

Menveo ®

Folia Pharmacotherapeutica mars 2011

- Pour la vaccination contre les méningocoques des sérogroupes A, C, W et Y, sont disponibles en Belgique

1. un vaccin polysaccharidique (Mencevax®) 33 euro dont les principales limites sont
   - sa durée de protection limitée (maximum 3 à 5 ans) et
   - son faible pouvoir immunogène chez les patients immunodéprimés et les jeunes enfants.

2. Un vaccin conjugué (à la protéine CRM-197 diphtérique) (Menveo®) 52,60 Euro

- La vaccination consiste en une seule injection intramusculaire.

Menveo ®

Folia Pharmacotherapeutica maart 2011

- Uit immunologische gegevens blijkt dat het geconjugeerd vaccin Menveo®
  - een iets meer uitgesproken immunogeen effect tegen bepaalde meningokokkenserotypes,
  - een langere beschermingsduur zou hebben – maar de preciese beschermingsduur op lange termijn is echter niet bekend, gezien er geen immunogeniciteitsstudies bestaan die langer dan één jaar duren.
- Voor bescherming op korte termijn (bv. bij een eenmalige reis naar een risicozone) werd geen klinische superioriteit aangetoond van het geconjugeerd vaccin tegen meningokokken A, C, W en Y, vergeleken met het polysacharidevaccin;
- bij risicopatiënten die een langdurigere immuniteit wensen, kan het geconjugeerd vaccin eventueel een voordeel bieden.

Menveo ®

Folia Pharmacotherapeutica mars 2011

- Des données immunologiques suggèrent que, par rapport au vaccin polysaccharidique, le vaccin conjugué
  - serait un peu plus immunogène contre certains sérotypes de méningocoques et
  - qu'il confèrerait une protection plus longue – mais la durée de protection à long terme n'est cependant pas connue étant donné qu'on ne dispose pas d'étude d'immunogénicité de durée supérieure à un an.
- Pour une protection à court terme (p. ex. lors d'un voyage dans une zone à risque), le vaccin conjugué contre les méningocoques A, C, W et Y n'a pas prouvé de supériorité clinique vis-à-vis du vaccin polysaccharidique;
- chez les personnes à risque qui souhaitent une immunité de plus longue durée, le vaccin conjugué peut éventuellement offrir un avantage.

CDC yellow book 2012

- CDC recommends routine vaccination of people with MenACWY (Menactra, Menveo) at age 11 or 12 years, with a booster dose at age 16 years.
- For adolescents who receive the first dose at age 13–15 years, a one-time booster dose should be administered, preferably at age 16–18 years.
- People who receive their first dose of MenACWY at or after age 16 years do not need a booster dose, **unless they remain at continued risk for meningococcal disease.**
- **Travelers** who were vaccinated previously and are **living in or returning to the meningitis belt** may need to be revaccinated.
- ACIP recommends that children previously vaccinated with MenACWY or MPVS4 at ages 2–6 years with a single dose who **remain at an increased risk for meningococcal disease** should receive an additional dose of MenACWY **3 years after** their previous meningococcal vaccine and **every 5 years thereafter, if at continued risk.**

Belgian Scientific Study Group on Travel Medicine

Mencevax

- Hadj
- Single voyage

Menveo

- Expatriates & their children
- Frequent travelers
- Immunodepressed
- Asplenia