New and under-utilised vaccines: meningococcal disease

VACFA Conference

Cape Town

November 2014

Dr Beverley Cowper

BScHonsMScMBBCh (Wits)

SANOFI PASTEUR

Agenda

1. Meningococcal disease has life altering consequences:
   a. The disease and the organism
   b. Populations at risk: when, where, why….
2. Epidemiology of meningococcal disease: South Africa and Africa
3. Meningococcal vaccines:
   a. Non capsular: Men B
   b. Capsular:
      i. Plain polysaccharide vaccines
      ii. Conjugate vaccines
4. Meningococcal vaccines: recommendations for use
5. Conclusions

1. Meningococcal disease has life-altering consequences

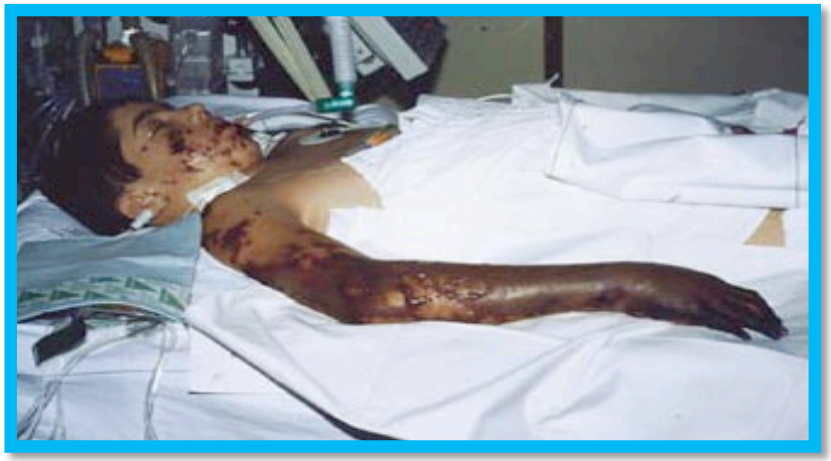

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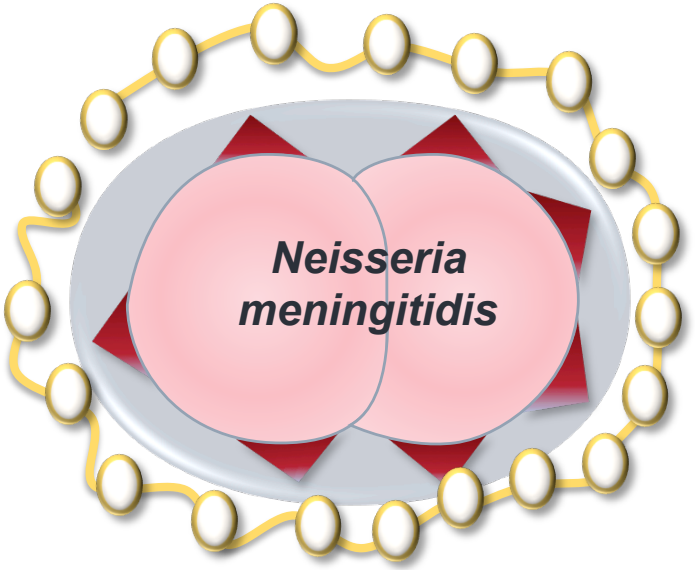
Image obtained with permission from: CharlotteCleverleyBisman.com

[92]Photo reprinted with permission from Schoeller T, Schmutzhard E. *N Engl J Med*. 2001;344(18):1372

1a. The disease and the organism..

Causative Agent: *Neisseria meningitidis* (meningococcus in invasive disease)

- Meningococci are diplococcal bacteria surrounded by a polysaccharide capsule[6]
  - The polysaccharide structure determines the pathogen's serogroup (SG)[6]
  - Six (A, B, C, Y, X, and W*) of 12 known SGs account for the majority of meningococcal infections worldwide[7,8]



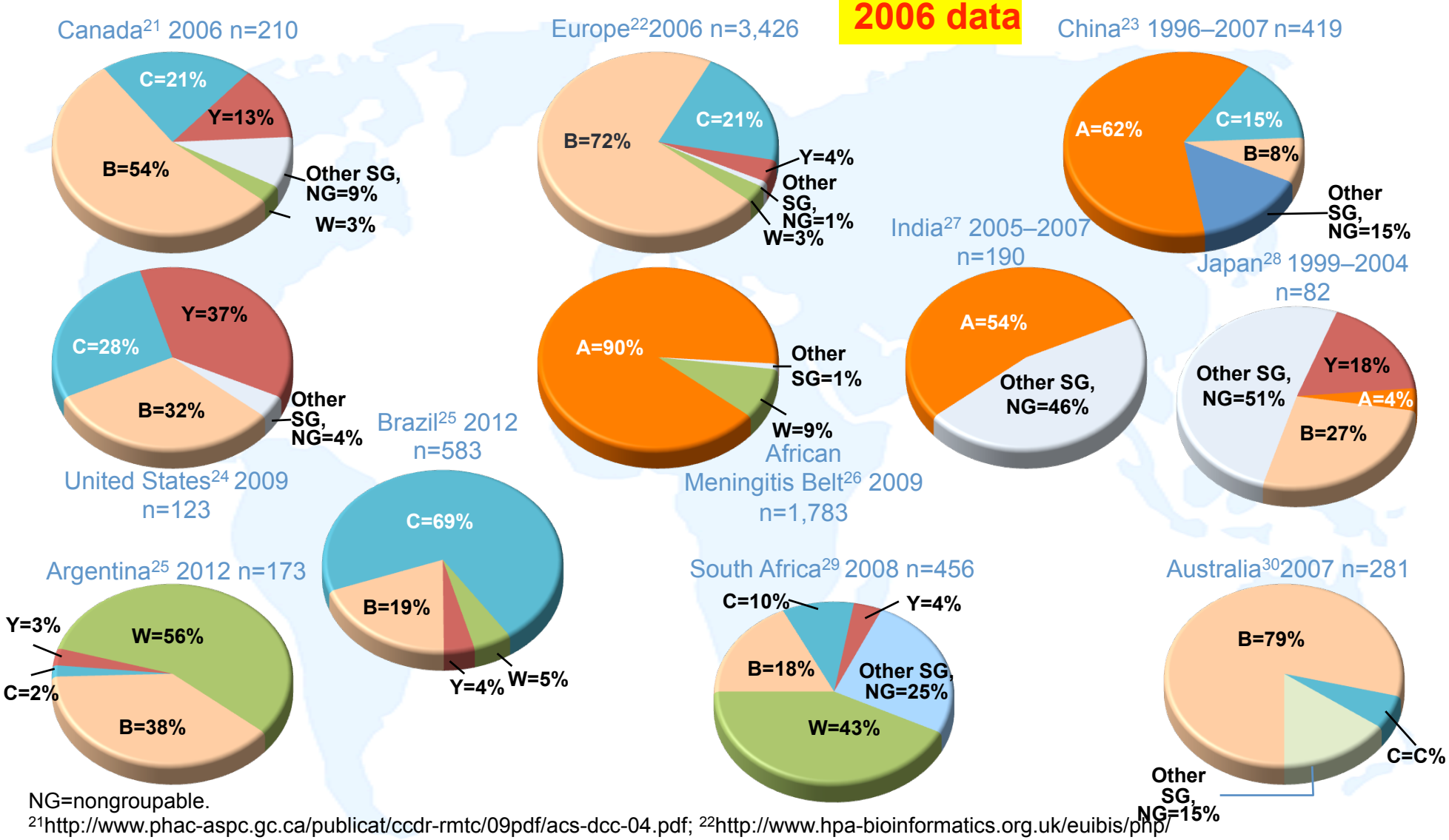
Polysaccharide capsule[6,9]

*W-135 has been replaced with W per new nomenclature.[11]

[6]Pollard AJ. In: *Harrison's Principles of Internal Medicine*. 18th ed. 2012;chapter 143; [7]Harrison LH. *Clin Infect Dis*. 2010;50(Suppl 2);S37. [8]http://www.who.int/mediacentre/factsheets/fs141/en/; [9]Image adapted from Criss AK. *Nat Rev Microbiology*. 2012;10(3):178; [11]Harrison OB. *Emerg Infect Dis.* 2013;19(4):566.

Meningococcal SG distribution varies geographically

2006 data

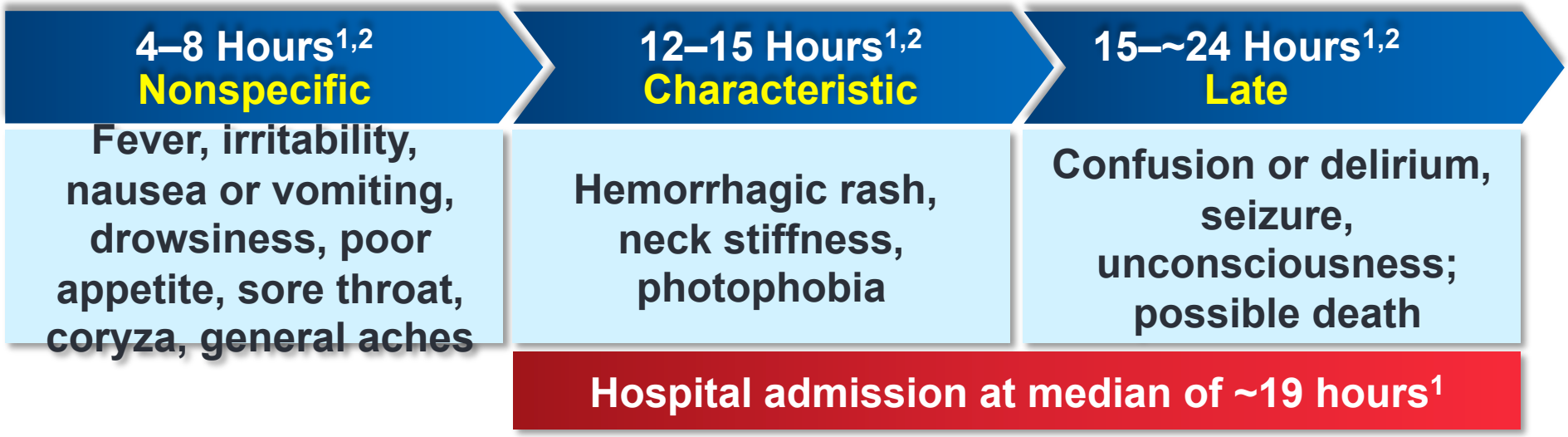


NG=nongroupable.

[21]http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09pdf/acs-dcc-04.pdf; [22]http://www.hpa-bioinformatics.org.uk/euibis/php/meningo_stack_chart.php?item=serogroup&year=2006; [23]Lin M. *Zhongguo Ji Hua Mian Yi*. 2009;15(1):58; [24]http://www.cdc.gov/abcs/reports-findings/survreports/mening09.pdf; [25]http://www.paho.org/hq/index.php?option=com_content&view=category&layout=blog&id=3609&Itemid=3953&lang=es; [26]http://www.who.int/csr/disease/meningococcal/BulletinMeningite2009_S27_31.pdf; [27]Sinclair D. *Trop Med Int Health*. 2010;15(12):1421; [28]Infectious Disease Surveillance Center. *IASR*. 2005;26(2):33; [29]http://www.nicd.ac.za/assets/files/CommDisBullMarch09_Vol0701.pdf; [30]The Australian Meningococcal Surveillance Programme. *Commun Dis Intell*. 2009;33(1):1.

Invasive meningococcal disease is difficult to diagnose and rapidly lethal

- Flu-like nature of early symptoms makes a definitive diagnosis challenging[1]
- Rapid progression, with death in as little as 24 hours[1,2]



[1]Thompson MJ, et al. *Lancet*. 2006;367:397; [2]Branco RG, et al. *J Pediatr (Rio J)*. 2007;83(2 suppl):S46.

1b. Populations at risk, where, why…

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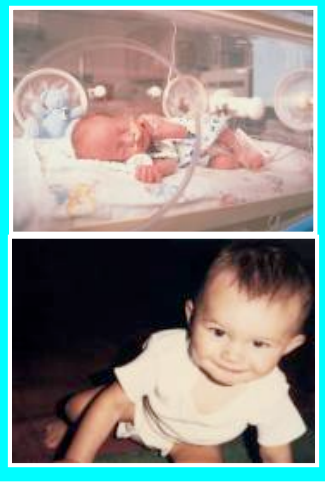
Meningococcal disease
Risk Factors for Meningococcal Disease

Lack of Serum Bactericidal Antibodies[1]	Impaired Immune System[2,3]	Nasopharyngeal Irritation[3]	Social Factors[3,4]

▪ Infants
▪ Other age groups
 
	▪ Complement deficiency
	▪ Humoral immune deficiency states
	▪ Asplenia
	▪ HIV/AIDS
		▪ Smoking
		▪ Respiratory tract infection
		 
			▪ Close contact with a case
			  ▪ Health Care Workers
			  ▪ Family
			▪ Crowding
			  ▪ Students
			  ▪ Recruits
			  ▪ Pilgrims
			▪ Kissing
			▪ Pubs/discos
			▪ MSM

Most cases of meningococcal disease occur in previously healthy persons without identified risk factors.

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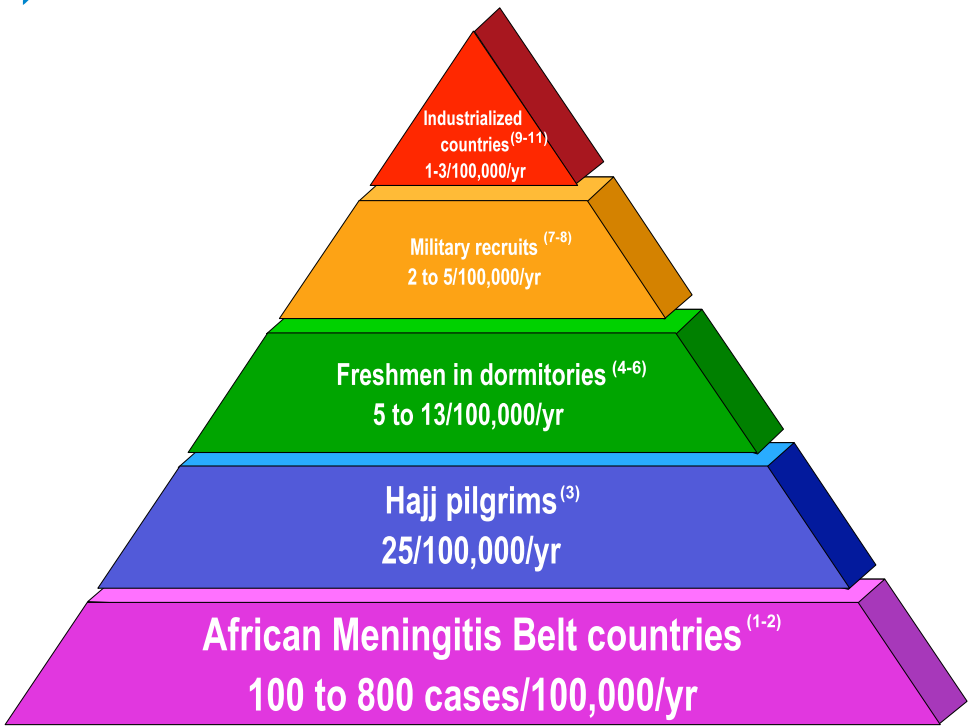
Different populations have widely varying incidence rates of invasive meningococcal disease (IMD)



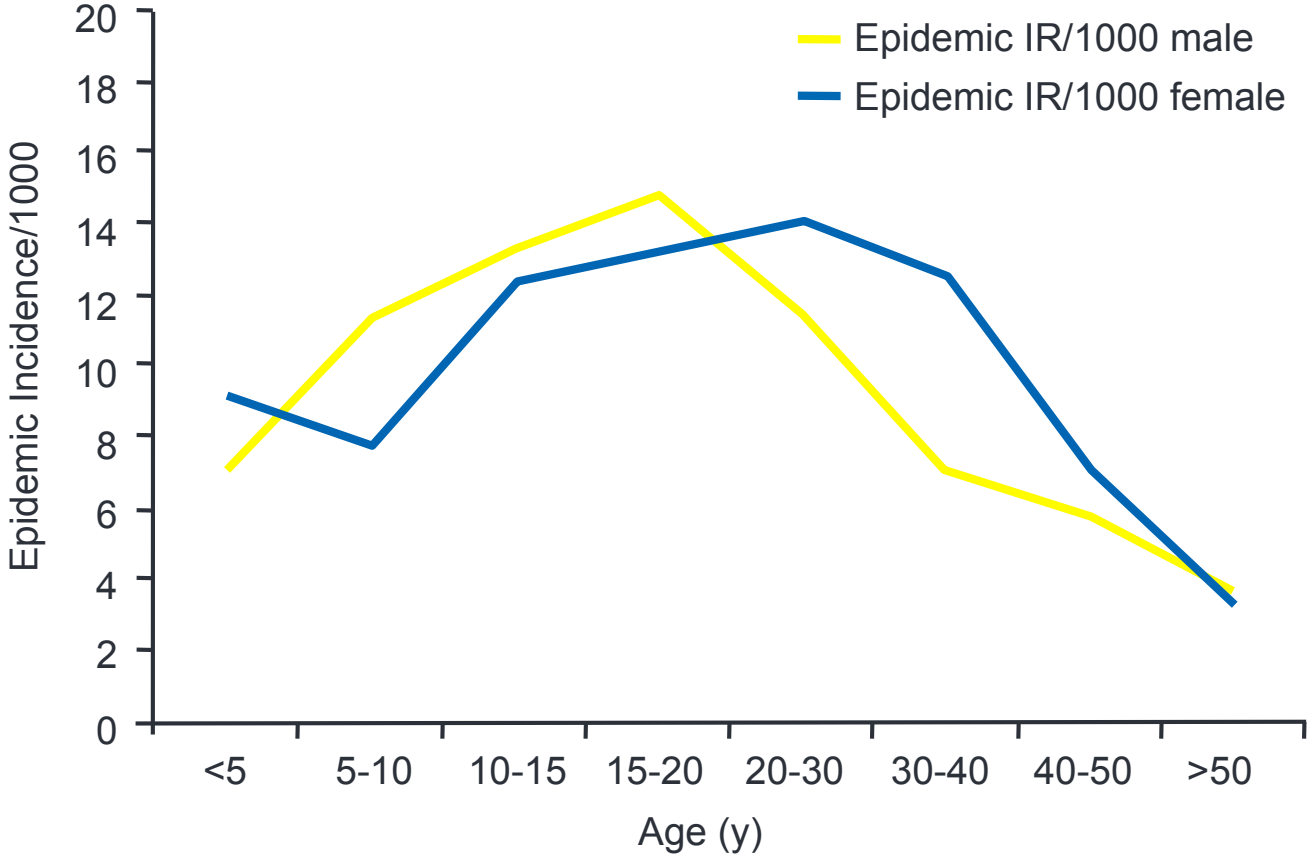
[1] World Health Organization. Control of Epidemic Meningococcal Disease. WHO Practical Guidelines. WHO/EMC/BAC/98.3. 2nd ed. Geneva, Switzerland, World Health Organization, 1998. Available at: http://www.who.int/emc-documents/meningitis/whoemcbac983c.html. Accessed April 12, 2005. [2] WHO. Wkly Epidemiol Rec 2003;78:294-6; [3] Wilder-Smith A, et al. Clin Infect Dis 2003;36:679-83; [4] Harrison LH, et al. JAMA 2001;286:694-9; [5] CDC. MMWR Recomm Rep 2000;49(RR-7):11-20; [6] Neal KR, et al. Epidemiol Infect 1999;122:351-7; [7] Brundage, JF, et al. Clin Infect Dis 2002;35:1376-81; [8] Spiegel A, et al. Santé 1996;6:383-8; [9] CDC. MMWR Morbid Mortal Wkly Rep 2004;51(53):1-84; [10] Squires SG, et al. Can Commun Dis Rep 2004; 30:17-28; [11] European Union Invasive Bacterial Infection Surveillance network. Invasive *Neisseria meningitidis* in Europe 2002. Dec 2003. Available at http://www.euibis.org/documents/2002_meningo.pdf. Accessed April 12, 2005.

Age groups at risk

- Globally:
  - Highest incidence of meningococcal disease occurs in infants under 1 year of age
  - Followed by children ages 1 to 4
    - CFR for all children below 15 is 5 to 15 %
  - Third highest incidence is in adolescents and young adults aged 15 to 24 years: can have the highest case fatality rate
    - CFR in the range of 23 %
  - Also, adults > 65 years
- South Africa shows a similar pattern although CFR in older age groups is higher

Age-specific incidence rates

In the African Meningitis Belt, invasive meningococcal disease incidence remains high from birth until early adulthood



Leimkugel J, et al. *PLOS Med*. 2007;4(3):e101.

2. Epidemiology of meningococcal disease: South Africa and Africa

Epidemiology

- Incidence rates: per 100 000 population per year
  - Developed countries 0.05-5/100 000
  - Developing countries 5-50/100 000
  - South Africa 1-5/100 000
- DURING EPIDEMICS - RATES INCREASE DRAMATICALLY – exceed 1000/100 000

CDC chapter 3 Infectious diseases related to travel accessed 10/11/2014

2a. Meningococcal disease in South Africa

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GERMS SOUTH AFRICA

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Thank you to all participating patients, laboratory, clinical and administrative staff for submitting case reports and isolates

NICD

CED: Anthony Smith, Bolele Disenyeng, Florah Mnyameni, Husna Ismail, Jack Kekana, Mimmy Ngomane, Mzikazi Dickmolo, Nomsa Tau, Rosah Mabokachaba, Tshegofatso Ntshabele, Kingdom Mncube.
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DPHSR: Bulelwa Zigana, Emily Dloboyi, Judith Tshabalala, Martha Bodiba, Mbali Dube, Portia Mogale, Thembi Mthembu, Tsakane Nkuna.

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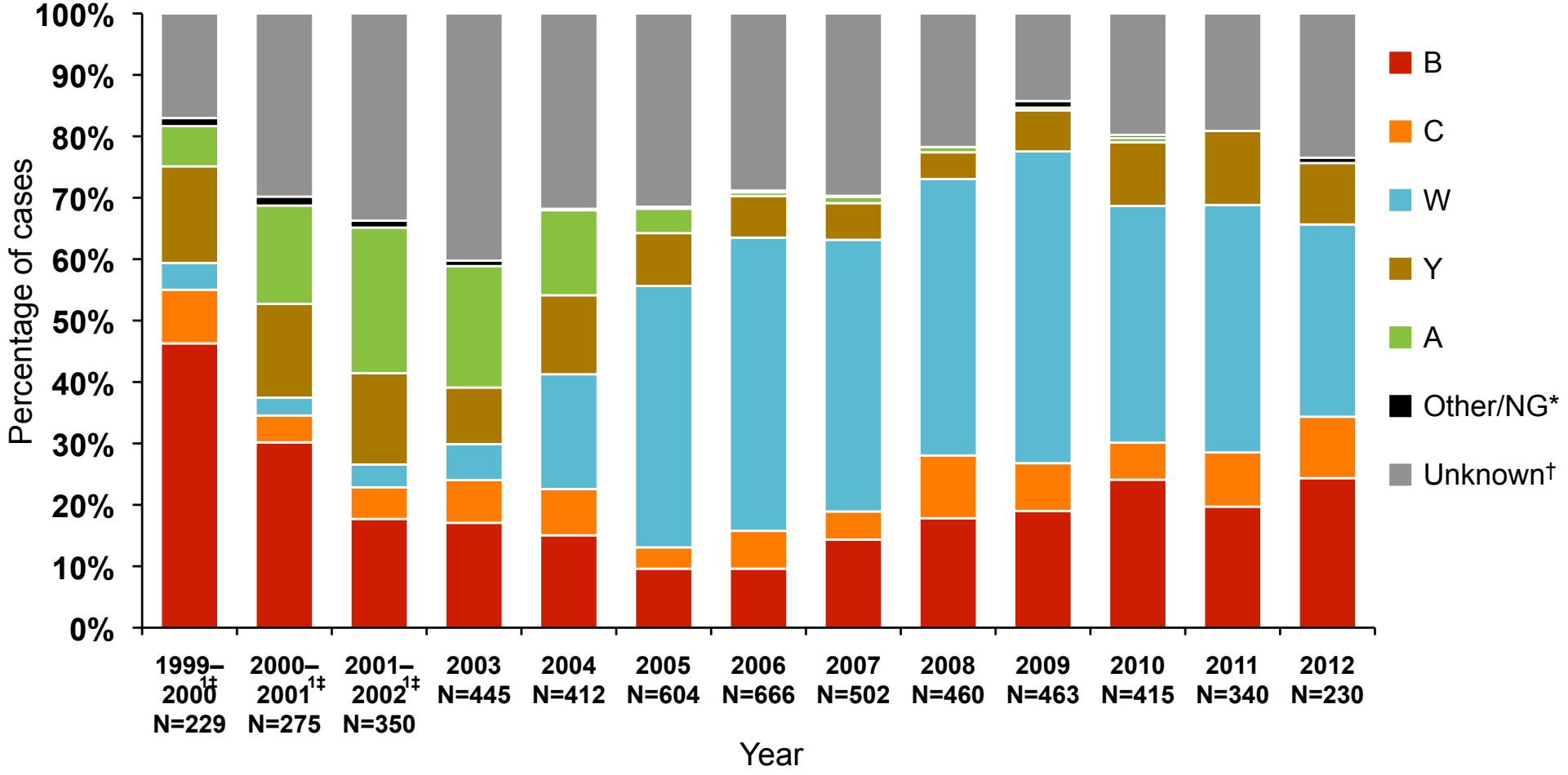
GERMS-SA: Carel Haummann, Patricia Hanise, Pieter Ekermans; Sandeep Vasaikar (EC); Anwar Hoosen, Dominique Goedhals, Justyna Wojno, Madeleine Pieters (FS); Alan Karstaedt, Caroline Maluleka, Charl Verwey, Charles Feldman, Jeannette Wadula, Kathy Lindeque, Maphoshane Nchabeleng, Nicolette du Plessis, Norma Bosman, Ranmini Kularatne, Ruth Lekalakala, Sharona Seetharam, Theunis Avenant, Trusha Nana, Vindana Chibabhai (GA); Asmeeta Burra, Fathima Naby, Halima Dawood, Koleka Mlisana, Lisha Sookan, Praksha Ramjathan, Prasha Mahabeer, Romola Naidoo, Sumayya Haffejee, Yacoob Coovadia (KZN); Andries Dreyer, Ken Hamese (LP); Greta Hoyland, Jacob Lebudi (MP); Dhamiran Naidoo, Eunice Weenink; Riezaah Abrahams (NC); Ebrahim Variava, Eduard Silberbauer (NW); Catherine Samuel, Preneshni Naicker (WC); Adrian Brink, Charlotte Sriruttan, Inge Zietsman, Maria Botha, Peter Smith, Suzy Budavari, Xoliswa Poswa (AMPATH); Chetna Govind, Keshree Pillay (LANCET); Marthinus Senekal (PathCare); Cynthia Whitney, Jennifer Verani, Stephanie Schrag (CDC); Keith Klugman (Emory); Ananta Nanoo, Anne von Gottberg, Arvinda Sooka, Cecilia Miller, Cheryl Cohen, Claire von Mollendorf, Karen Keddy, Linda de Gouveia, Linda Erasmus, Mmakgomo Rakhudu, Marshagne Smith, Melony Fortuin-de Smidt, Nazir Ismail, Nelesh Govender, Nevashan Govender, Olga Perovic, Penny Crowther-Gibson, Ruth Mpembe, Sarona Lingana, Sonwabo Lindani, Susan Meiring, Vanessa Quan (NICD).

GERMS-SA work has been supported by NICD/NHLS and the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (CDC) under the terms of [5U2GPS001328]. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NICD/NHLS or CDC.

MenW has become the predominant cause of meningococcal disease

South Africa, 1999–2012

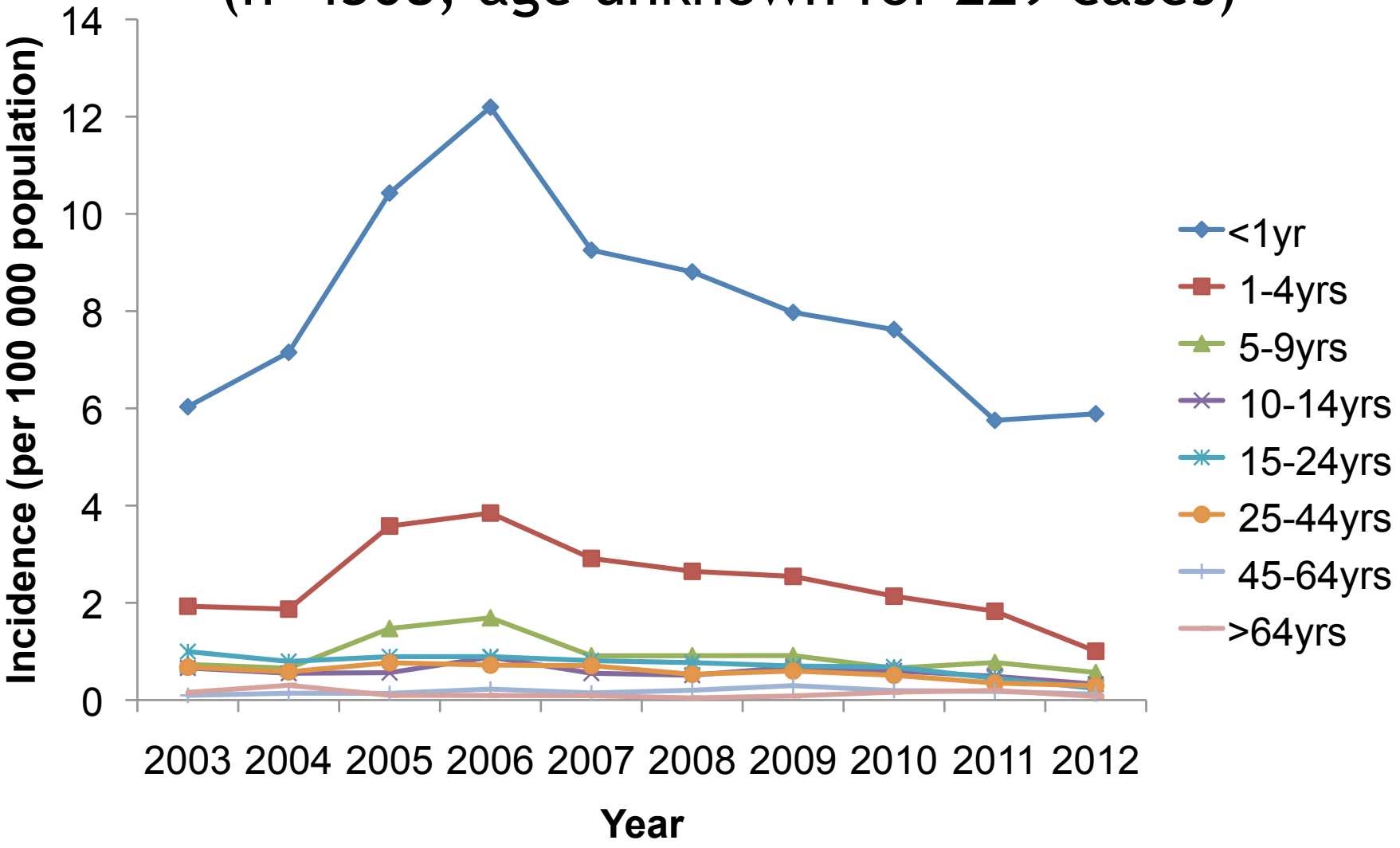


*May include serogroups e.g., X, E, Z, or non-groupable; †Serogroup not identified; ‡Year spans August through July.
Serogroup data from viable isolates and PCR results

1. Coulson GB, et al. Meningococcal Disease in South Africa, 1999–2002 *Emerg Infect Dis*. 2007;13:273-281; 2003-2012 data from GERMS-SA national surveillance, NICD, NHLS

Slide adapted from Novartis

Incidence of **invasive meningococcal disease** by age category, South Africa, 2003 to 2012 (n=4308, age unknown for 229 cases)



2b. Meningococcal disease in the African Meningitis Belt

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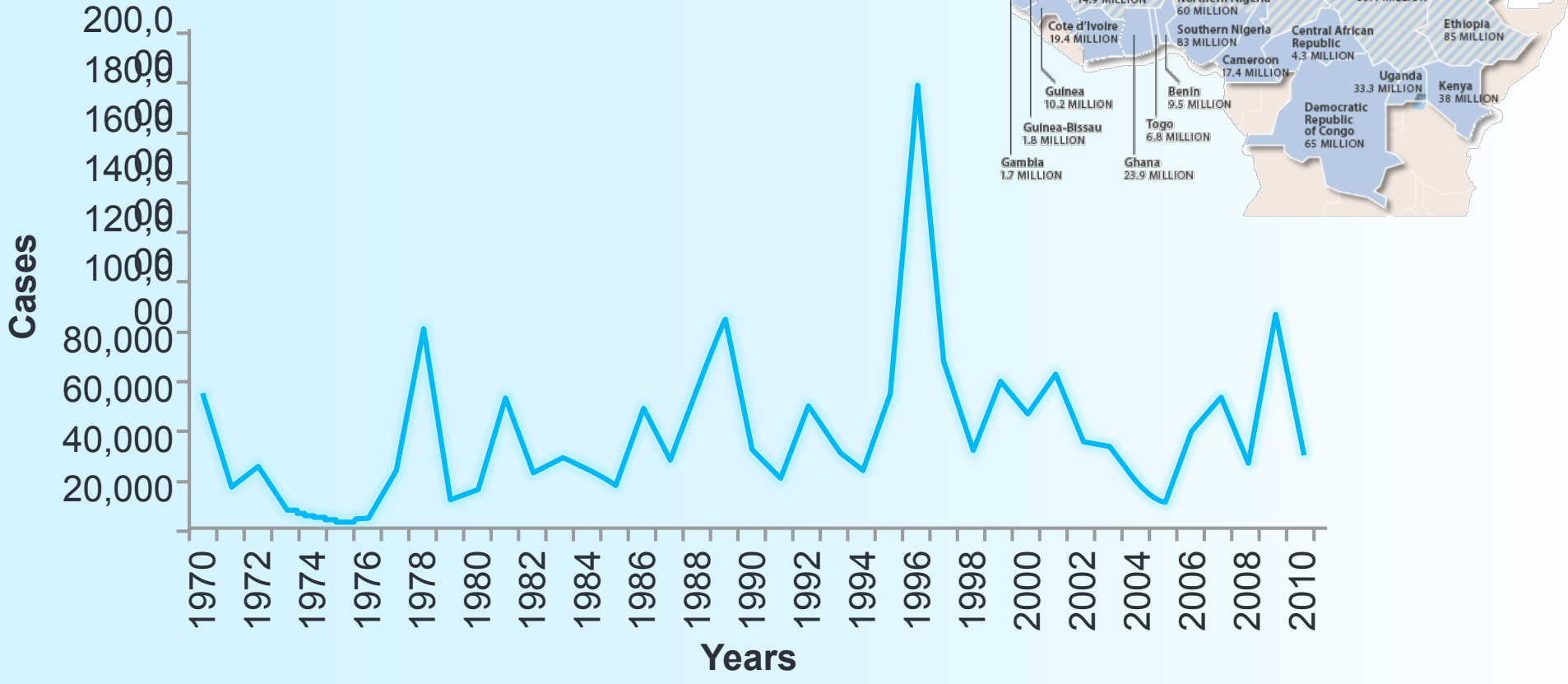
Every year bacterial meningitis epidemics affect more than 400 million people living in the 21 countries of the “African Meningitis Belt”

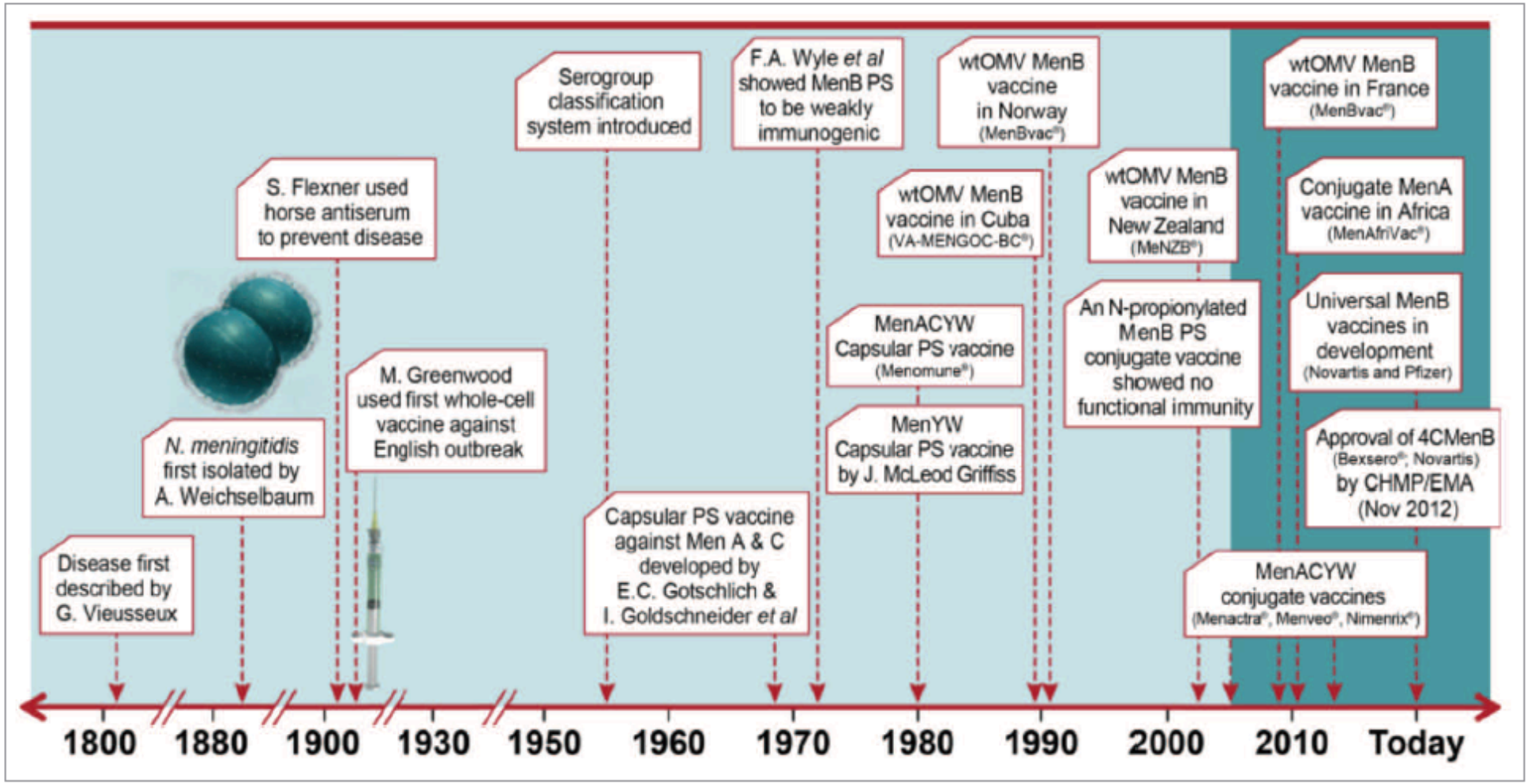
Trends of Epidemic Meningitis Disease in the African Belt, 1970-2010



[97]http://www.who.int/gho/epidemic_diseases/meningitis/en/; [98]http://www.path.org/menafrivac/meningitis-belt.php.

3. Meningococcal vaccines …

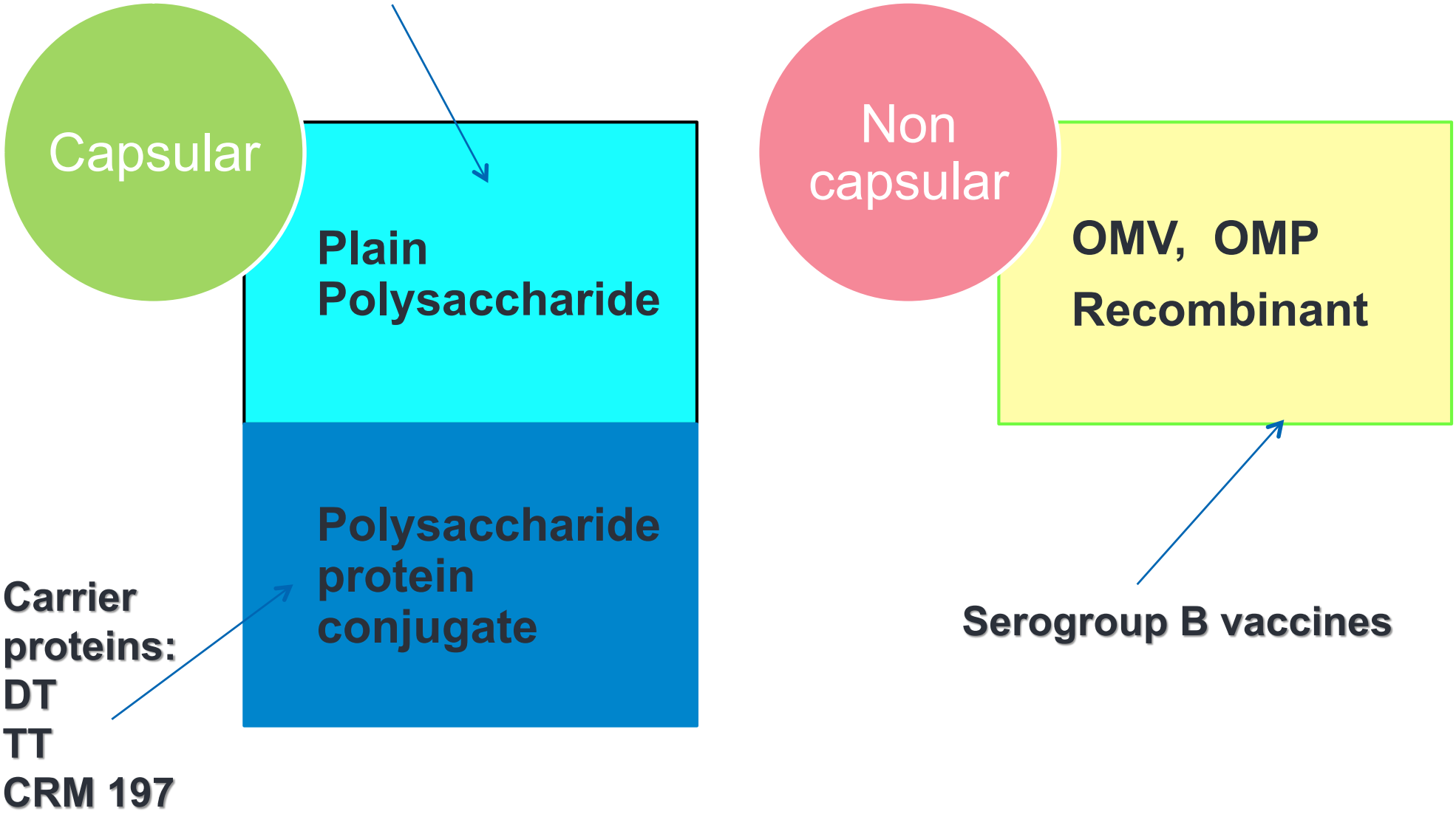
Meningoccocal vaccine development – time line



Holst et al. Human Vaccines & Immunotherapeutics 9:6, 1241–1253; June 2013 (courtesy Prof G Hussey)

Vaccine types

mono-, bi-, tri-, tetra-valent vaccines against Serogroups A, C, Y, W



Meningococcal vaccines

- No randomised controlled clinical trials to evaluate clinical efficacy because of the low incidence of meningococcal disease
- Because efficacy cannot be measured, immunogenicity data are used as a surrogate for efficacy for licensure
- Post licensure observational data also collected to assess vaccines and safety

MMWR 2013 62/ (RR02);1-22 accessed 8/11/2014

3a. Non capsular meningococcal vaccines …

Meningococcal B disease

- Can account for up to 50 % of cases in USA and Europe
- Serogroup can cause prolonged epidemics eg 1980s in Cuba and Norway; more recently, New Zealand
- High proportion of cases in children <5 yrs
- High morbidity and mortality
- Control of meningococcal disease could not be achieved without an effective vaccine against Men B

http://cid.oxfordjournals.org/content/50/supplement2 accessed on 10/11/2014

Serogroup B meningococcal vaccines

- The B capsular polysaccharide is an auto antigen:
  - not a suitable vaccine target
  - expressed by a number of host tissues and also poorly immunogenic in humans even when conjugated to a protein carrier
- Focus of vaccine development: non capsular antigens such as OMVs (outer membrane vesicles) and recombinant proteins
- Various OMV vaccines developed: safe, efficacious
  - 5 studies, children>4 and young adults: 2 doses, efficacy 57% to 83 % ; NZ, 3 doses, 2 months to 20 years, efficacy 73 % but 80 % for 6 months to 5 years
  - Porin protein A specific: antigenically variable
- Requirement for 'genome mining' to identify other suitable antigens

http://cid.oxfordjournals.org/content/50/supplement2 accessed on 10/11/2014

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January 22, 2013 07:44 CET

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Novartis receives EU approval for Bexsero®, first vaccine to prevent the leading cause of life-threatening meningitis across Europe

- *Bexsero is indicated to help protect all age groups against meningococcal serogroup B (MenB) disease, including infants who are the most vulnerable[1]*
- *MenB disease is associated with a high human toll for families and communities, as it can be fatal or may cause serious, life-long disabilities in survivors[2],[3]*
- *Novartis is working with health authorities to provide access to Bexsero as soon as possible*

Basel, June 17, 2014 - Novartis announced today the submission of a Biologic License Application (BLA) to the US Food and Drug Administration (FDA) for marketing approval for the use of Bexsero® (Multicomponent Meningococcal Group B Vaccine [recombinant, adsorbed]) to help protect against invasive meningococcal disease caused by serogroup B (meningitis B) in adolescents and young adults from 10 years through 25 years of age. This submission initiates a rolling submission process for Bexsero to the FDA, following the receipt of a Breakthrough Therapy designation in April.

(courtesy Prof G Hussey)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- Bexsero

meningococcal group B vaccine (rDNA, component, adsorbed)

This is a summary of the European public assessment report (EPAR) for Bexsero. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Bexsero.

- **What is Bexsero?**

Bexsero is a vaccine which is available as a suspension for injection in a pre-filled syringe. It contains parts of the bacteria *Neisseria meningitidis (N. meningitidis)* group B.

What is Bexsero used for?

Bexsero is used to protect individuals from the age of two months against invasive meningococcal disease caused by one group of the bacterium *N. meningitidis* (group B). Invasive disease occurs when the bacteria spread through the body causing serious infections such as meningitis (infection of the membranes that surround the brain and spine) and septicaemia (blood infection). Bexsero should be used according to official recommendations.

The medicine can only be obtained with a prescription.

- **How is Bexsero used?**

Bexsero is given by deep injection into a muscle, preferably into the shoulder muscle, or into the thigh muscle in children under two years old. In adults and adolescents aged 11 and over, two injections are given (at an interval of at least one month). In younger children, two injections are given (at an interval of at least two months), except in infants aged between two and five months who receive three injections (at intervals of at least one month). Children under two years old also receive an additional booster dose (at a time point determined by age).

This minute will remain draft until ratified by JCVI at its next meeting

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

Minute of the meeting on Tuesday 11 and Wednesday 12 February 2014

Recommendation

99. JCVI recommended a programme for use of the MenB vaccine with the NHS immunisation schedule at 2, 4, 12 months of age (2+1) in a carefully planned programme. Given the vaccine only demonstrated cost-effectiveness at a low price, plans for implementation should anticipate a sustainable and cost-effective programme.

(courtesy Prof G Hussey)

Meningococcal Disease

Meningococcal Home
About the Disease +
Meningococcal Vaccination
Surveillance
Meningococcal Outbreaks −
About Meningococcal Outbreaks
Serogroup B Meningococcal Vaccine & Outbreaks
Clinical Information
Laboratory Information
Meningococcal Disease in Other Countries

CDC > Meningococcal Home > Meningococcal Outbreaks

Princeton University Meningococcal Disease Outbreak

Recommend Tweet Share

Q. A.

This page was last updated March 18, 2014

On this Page

- Reasons to Get the Vaccine
- Vaccine Recommendations
- Getting the Vaccine

Princeton University is experiencing a prolonged outbreak of serogroup B meningococcal disease, with eight cases reported. CDC, the New Jersey Department of Health (NJDOH), Princeton University officials, and local health authorities have been working closely together since the first case of meningococcal disease associated with Princeton University was reported in March 2013. A serogroup B meningococcal vaccine, which is licensed for use in Europe, Canada, and Australia, is being used at Princeton University. More than 5,000 Princeton University students received the first dose of the vaccine in December 2013; more than 4,700 students received the second dose in February 2014. To date, there have been no unusual patterns or occurrence of serious reactions associated with the

Learn more about the serogroup B meningococcal

University of California, Santa Barbara Meningococcal Disease Outbreak

Recommend Tweet Share

Q. A.

This page was last updated March 11, 2014

On this Page

- Vaccine Recommendations
- Getting the Vaccine
- Reasons to Get the Vaccine

The University of California, Santa Barbara (UCSB) is experiencing an outbreak of serogroup B meningococcal disease, with four confirmed cases reported during November 2013. The Santa Barbara County Public Health Department (SBCPHD), the California Department of Public

Princeton University, New Jersey
strain has killed a student at Drexel University in Philadelphia, according to health officials. March 18, 2014.

(courtesy Prof G Hussey)

Pfizer's new MenB vaccine targeting adolescents

Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial

Peter C Richmond, Helen S Marshall, Michael D Nissen, Qin Jiang, Kathrin U Jansen, Maria Garcés-Sánchez, Federico Martinón-Torres, Johannes Beeslaar, Leszek Szenborn, Jacek Wysocki, Joseph Eiden, Shannon L Harris, Thomas R Jones, John L Perez, on behalf of the 2001 Study Investigators

Summary

Background *Neisseria meningitidis* serogroup B is a major cause of invasive meningococcal disease, but a broadly protective vaccine is not currently licensed. A bivalent recombinant factor H-binding protein vaccine (recombinant lipoprotein 2086) has been developed to provide broad coverage against diverse invasive meningococcus serogroup B strains. Our aim was to test the immune response of this vaccine.

Lancet Infect Dis 2012; 12: 597–607

Published Online May 7, 2012 http://dx.doi.org/10.1016/

USA FDA – breakthrough therapy designation

(courtesy Prof G Hussey)

Approved by the FDA October 30 th 2014

3bi. Meningococcal plain polysaccharide vaccines…

Meningococcal plain polysaccharide vaccines

- Available since the 1960s
- Purified capsular polysaccharide
- A/C, A/C/W-135, A/C/Y/W-135
- Serogroup specific
  - Control of outbreaks of serogroup C eg college students
  - Control of outbreaks in children due to serogroup A
- MPSV4 effectiveness data was supported by clinical efficacy data from studies with monovalent A and C vaccines and bivalent A/C vaccines
- T cell independent mechanism

Plain polysaccharide vaccines

	Serogroups	Manufacturer	Age indications
Bivalent			
AC vax	A&C	GSK	No longer available
Mengivac	A&C	SP	No longer available
	A&C	Bio-Manguinhoss & Finlay Institute	
Trivalent			
	A, C & W-135	GSK	No longer available
	A,C &W -35	Bio-Manguinhoss & Finlay Institute	
Quadrivalent			
Mencevac	A, C, W-135 & Y	GSK	2 yrs and older
Memomune	A, C, W-135 & Y	SP	2 -55 yrs old
NmVac4	A, C, W-135 & Y	JN Int Med Corp	2 yrs and older


WHO prequalification


1997


2007


TM 2013

(courtesy Prof G Hussey)

Meningococcal plain polysaccharide vaccines

- A and C vaccines:
  - good efficacy in older children and adults:
    - efficacy of serogroup C vaccine in US military recruits found to be 89.5 %
    - effectiveness of serogroup C vaccine aged 2 to 29 years in the USA found to be 85 %
    - efficacy of a serogroup A vaccine in school going children in Egypt was 89 %

Pichichero, M Expert.Opin.Biol.Ther.(2005)5(11):1475-1489

Meningococcal plain polysaccharide vaccines

- No impact on carriage
- Repeated vaccinations: immunological hypo -responsiveness with subsequent doses
- Duration of response: waning immunity in adults and children over time
- Excellent safety profile: local injection site pain and erythema are common but mild and systemic reactions like fever occurs in < 5 % of vaccinees
- Severe adverse reactions are rare

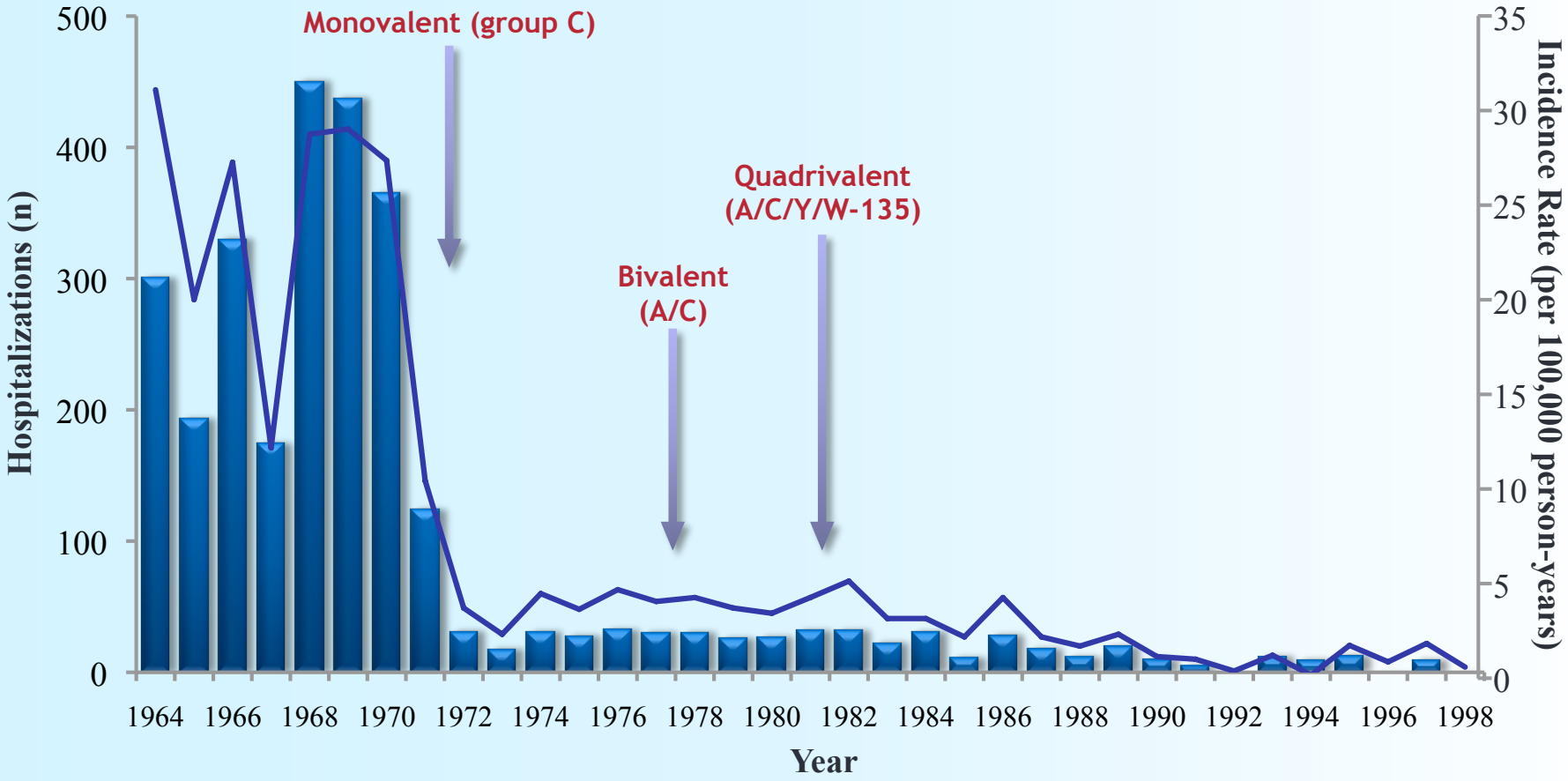
Pichichero, M Expert.Opin.Biol.Ther.(2005)5(11):1475-1489

Serogroup A and C polysaccharide vaccines

- Estimated clinical efficacies of > 85 % amongst school aged children and adults in outbreaks
- Multiple doses of PCV A and C can cause immunological hypo-responsiveness
- Can be partially overcome by giving conjugate vaccines

MMWR 2013/62(RR02);1-22 accessed 8/11/2014

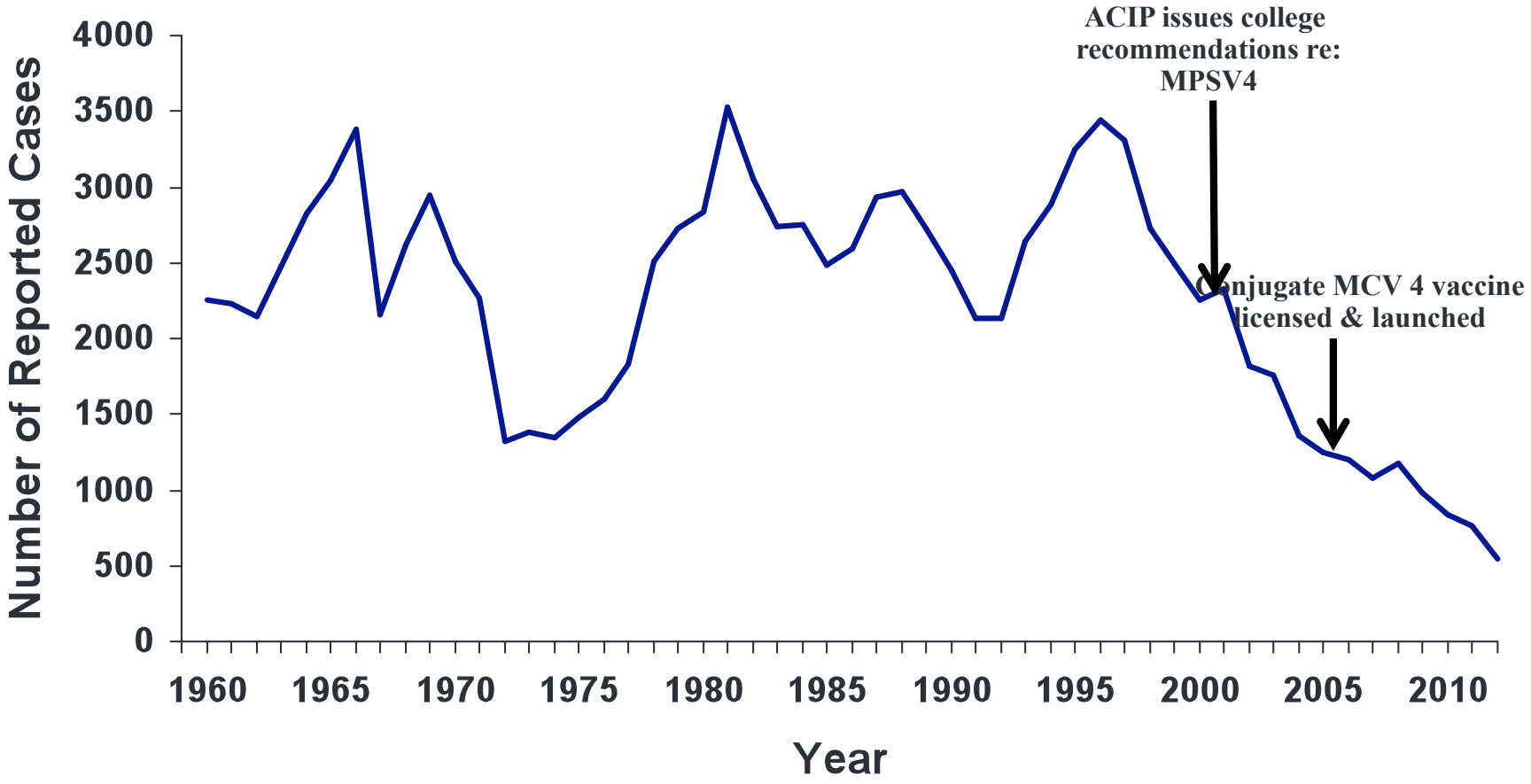
Vaccinating US military recruits since 1971 has reduced the incidence of meningococcal disease by >90% [66,67]



Bars indicate hospitalization frequencies; line indicates rates

[66]Adapted from Defraites RF. *MSMR*. 2000;6:2; [67]Broderick MP. *Emerg Infect Dis*. 2012;18(9):1430.

Reported Cases of Meningococcal Disease—United States, 1960–2012



References: **1.** CDC. Summary of notifiable diseases – US, 1993. MMWR 1993;42(53) **2.** CDC. Summary of notifiable diseases – US, 2011. MMWR 2011;60(53). **3.** CDC. Final 2012 Reports of Nationally Notifiable Infectious Diseases. MMWR 2013;62(33).

3bii. Meningococcal conjugated vaccines …

Differences between polysaccharide and conjugate meningococcal vaccines

Property	Polysaccharide	Conjugate
Effective 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

[19]Khatami A. *Expert Rev Vaccines*. 2010;9(3):285; [61]Granoff DM. In: *Vaccines*. 6th ed. 2013: chapter 21.

Meningococcal conjugate vaccines

- The inherent limitations of polysaccharide meningococcal vaccines prompted the development of conjugate vaccines
- Can be used in all ages, including infants
- Polysaccharide is chemically conjugated to a protein carrier – induces T cell dependent responses and primes immunological memory
- Produces long lasting immunity
- Impacts on nasopharyngeal carriage, afford herd immunity
- Effectiveness inferred by comparing SBA responses of the new vaccine against the antibody responses of MPSV4 vaccines
- Can be given with other paediatric vaccines on the schedule: refer to PI per vaccine type

Pichichero, M Expert.Opin.Biol.Ther.(2005)5(11):1475-1489

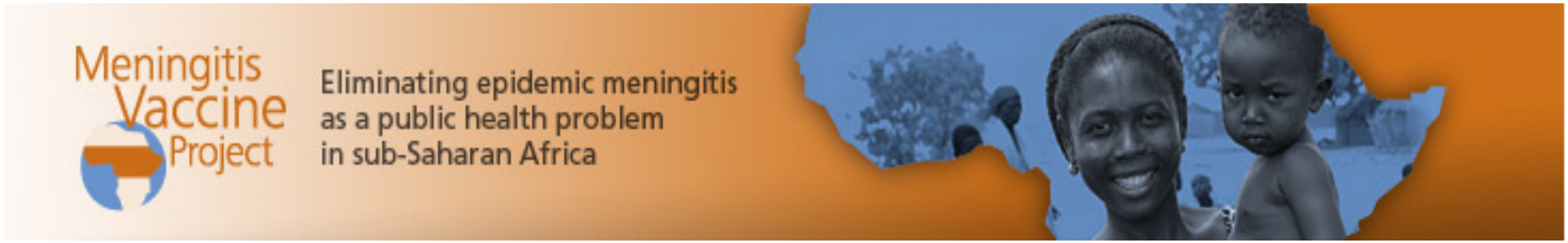
Worldwide Available Meningococcal Polysaccharide and Conjugate Vaccines[a]

Conjugate Vaccines		Carrier Protein[46-53,86]
Menjugate®	MenC	CRM197
Meningitec®	MenC	CRM197
NeisVac-C®	MenC	TT
Menitorix®	MenC-Hib	TT
MenAfriVac®	MenA	TT
Menactra®	MenACYW	DT
Menveo®	MenACYW	CRM197
Nimenrix™	MenACYW	TT
MenHibrix®	MenCY-Hib	TT

Polysaccharide Vaccines[54-56]	
Meningo A+C®	MenAC
Mencevax®	MenACWY
Menomune®	MenACWY

[a]Not all vaccines are licensed for use in every country

[46]Menjugate® [PI]. Novartis Vaccines; 2013; [47]Meningitec® [PI]. Pfizer; 2011; [48]NeisVac-C® [PI]. GlaxoSmithKline Inc; 2010; [49]Menitorix® [PI]. GlaxoSmithKline Australia; 2013; [50]MenAfriVac® [PI]. Serum Institute of India Ltd; [51]Menactra® [PI]. Sanofi pasteur; 2013; [52]Menveo® [PI]. Novartis Vaccines; 2013; [53]Nimenrix® [PI]. GlaxoSmithKline UK; 2013; [54]Meningo A+C [Public assessment report]. Sanofi Pasteur; 2013; [55]Mencevax® [PI]. GlaxoSmithKline Australia; 2010; [56]Menomune® [PI]. Sanofi pasteur; 2012; [86]MenHibrix® [PI]. GlaxoSmithKline; 2013.



Menafrivac:

- Developed post the epidemic of 1996-1997 in the meningitis belt; TT-conjugated serogroup A specific vaccine available from 2010
- The Meningitis Vaccine Project: a partnership between PATH, the WHO and other collaborators with funding by the BMGF
- Ongoing surveillance activities in 12 countries in Africa: duration of response, safety, serogroup replacement
- Under a $ a dose, protects people age 1 to 29 years of age
- Reduced meningitis incidence by 94 %, carriers of serogroup A reduced by 97 % post mass single dose vaccination (Chad)

www.gavi.org/library/news accessed 10/11/2014

Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community trial

D M Daugla, J P Gami, K Gamougam, N Naibei, L Mbainadji, M Narbé, J Toralta, B Kodbesse, C Ngadoua, M E Coldiron, F Fermon, A-L Page, M H Djingarey, S Hugonnet, O B Harrison, L S Rebbetts, Y Tekletsion, E R Watkins, D Hill, D A Caugant, D Chandramohan, M Hassan-King, O Manigart, M Nascimento, A Woukeu, C Trotter, J M Stuart, M C J Maiden, B M Greenwood

Summary

Background A serogroup A meningococcal polysaccharide–tetanus toxoid conjugate vaccine (PsA–TT, MenAfriVac) was licensed in India in 2009, and pre-qualified by WHO in 2010, on the basis of its safety and immunogenicity. This vaccine is now being deployed across the African meningitis belt. We studied the effect of PsA–TT on meningococcal meningitis and carriage in Chad during a serogroup A meningococcal meningitis epidemic.

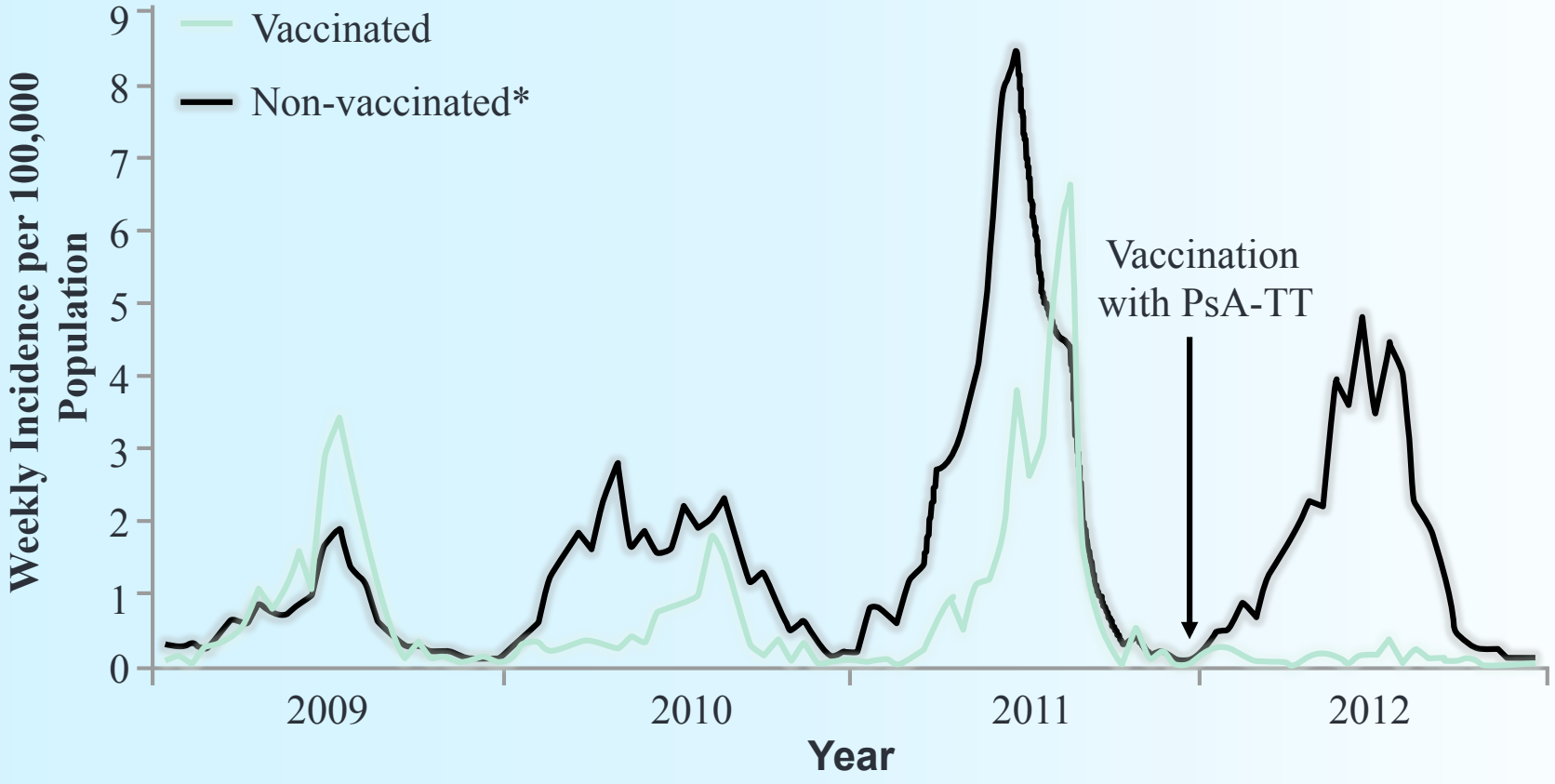
Published Online
September 12, 2013
http://dx.doi.org/10.1016/S0140-6736(13)61612-8

See Online/Comment

(courtesy Prof G Hussey)

Introduction of SG A meningococcal conjugate vaccine (PsA-TT) in Chad has strongly reduced disease incidence and carriage

Incidence of Reported Cases of Meningitis in Chad, 2009-2012



*Non-vaccinated: incidence of reported cases of meningitis in districts of epidemic alert in Chad that did not receive the vaccine.

[99]Daugla DM. *Lancet*. 2014;393(99-11):40.

WHO Global Alert and Response (GAR) report June 2013

- “From 1 January to 12 May 2013 (epidemiologic week 19), 9 249 suspected cases of meningitis, including 857 deaths, with a case fatality ratio of 9.3 percent, have been reported from 18 of the 19 African countries under enhanced surveillance for meningitis. The number of cases reported so far are the lowest recorded during the epidemic season in the last ten years”
- The decrease in the number of cases of meningitis is thought to be due to the progressive introduction of the newly developed Men A conjugate vaccine since 2010
- Immunization of > 100 million people in 10 countries between 2010 and 2012
- Large scale epidemics occur every 4 to 10 years in the meningitis belt: close surveillance required

http://www.meningvax.org accessed 10/11/2014

MenAfriVac® breaks the cold chain barrier!

19 February 2014—A study published online today in the journal *Vaccine* shows that removing the pioneering vaccine from constant refrigeration is not only safe but could extend vaccination coverage to the remotest regions in sub-Saharan Africa.

A second study published in the *Bulletin of the World Health Organization* shows that cutting out the cold chain could halve storage and vaccine transportation costs.

MenAfriVac®, which is manufactured by Serum Institute of India Ltd., is the first vaccine allowed to travel outside of the cold chain in Africa. As shown in the above photograph, there are no ice packs in the vaccine box, and a peak threshold indicator tells the vaccinators if the vaccine has reached its limit and needs to be discarded.

NEWS AND EVENTS

Study shows dramatic impact of MenAfriVac® in sub-Saharan Africa

Read the September 12, 2013, article in *The Lancet* »

Number of meningitis cases in Africa's meningitis belt at the lowest level in ten years

The decrease is thought to be due to the introduction of MenAfriVac®, the meningococcal A conjugate vaccine developed by the MVP.

Read the WHO report of June 6, 2013 »

Listen to Channel Africa Radio's interview with Dr. Marie-Pierre Préziosi »

Meningococcal disease in the African meningitis belt, 2012

On March 22, 2013, the World Health Organization published a summary of the meningitis situation in Africa in 2012.

Read the report »

MenAfriVac vaccination campaign in Chad

Read the MVP statement of January 10, 2013 »

Read the Chad Ministry of Health statement of January 21, 2013 (in French) »

Read the English translation »

100 millionth person receives MenAfriVac, the lifesaving vaccine developed by the MVP

The milestone took place early December in Nigeria.

Read the announcement »

Safety profile of Men A vaccine

- **GACVS WHO Committee report extract: 2009**

  - Initially 4 studies to evaluate reactogenicity and safety with 2 ongoing
  - Phase I studies; conducted in India 18 to 34 year olds
  - Phase II/III; 1 to 29 year olds in Africa and India
  - Local reactions; serious reactions also documented
  - No safety concerns or safety signals identified
  - Requirement for ongoing monitoring and surveillance

Success of Men C conjugate vaccines in the UK

- Programme initiated between 1999 and 2001:
  - A 64 % to 98 % reduction of serogroup C invasive disease in targeted groups
  - Substantial impact on herd immunity in the unvaccinated population
  - A 67 % reduction in nasopharyngeal carriage of serogroup C meningococci noted in adolescents compared before and 1 year after immunisation
  - Attack rates among unvaccinated children and adolescents dropped substantially by 66 % to 80 %
  - Overall vaccine effectiveness 90 % to 93 %
  - Annual deaths dropped from 67 to 5 between 1999 to 2001

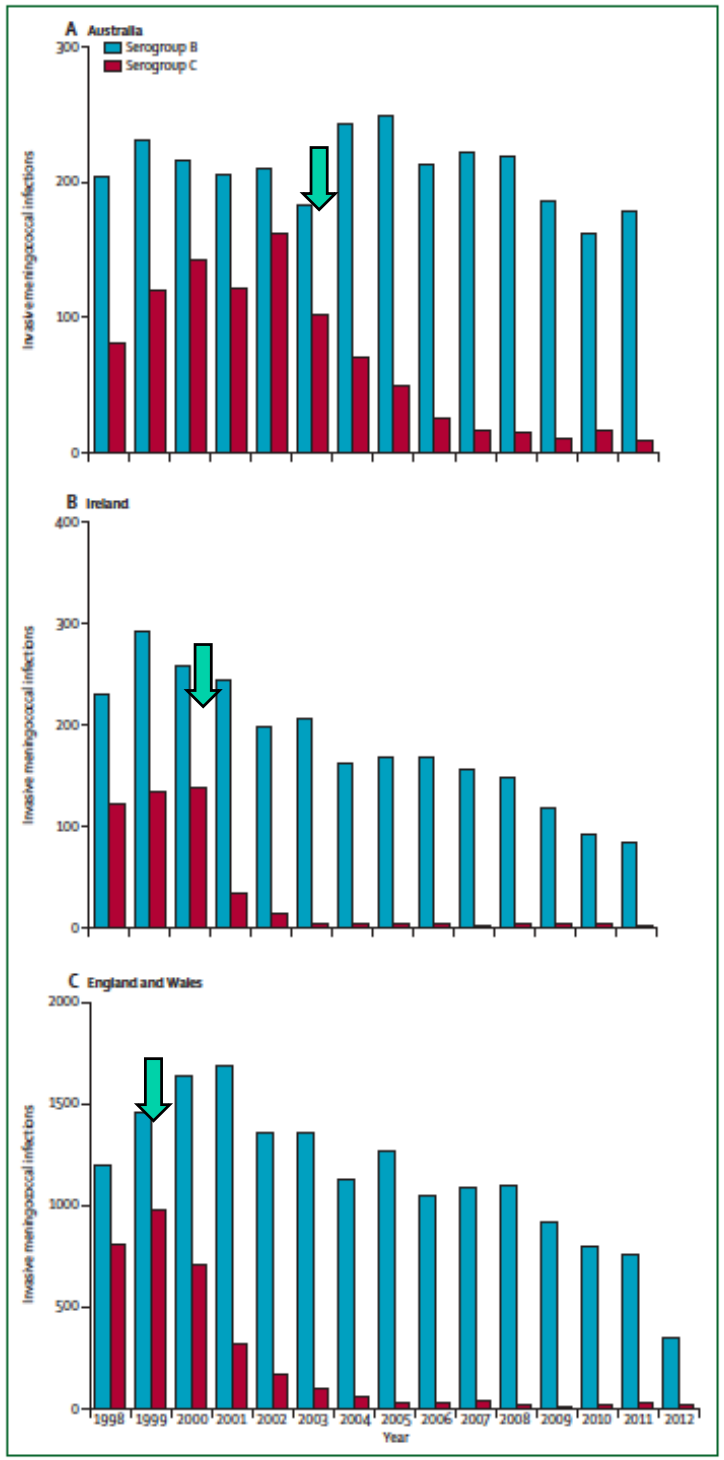
Pichichero, M Expert.Opin.Biol.Ther.(2005)5(11):1475-1489

Men C Conjugate

Australia – MenC in 2003, with a catch-up campaign between 2003 and 2007 for all children aged 1 -19 years.
July 2013, NIP - Hib & MenC at 12 mths.

Ireland – MenC in 2000; infants were given three doses before 1 year of age, with a catch-up programme in adolescents.
2013, NIP – 3 doses: 3 months (MenC), 12–13 months (Hib & MenC), and 14–15 years (Men C)

England and Wales - MenC introduced in 1999, with a catch up campaign in children up to 19 years of age.
NIP - two dose schedule at 3 and 12 months of age.

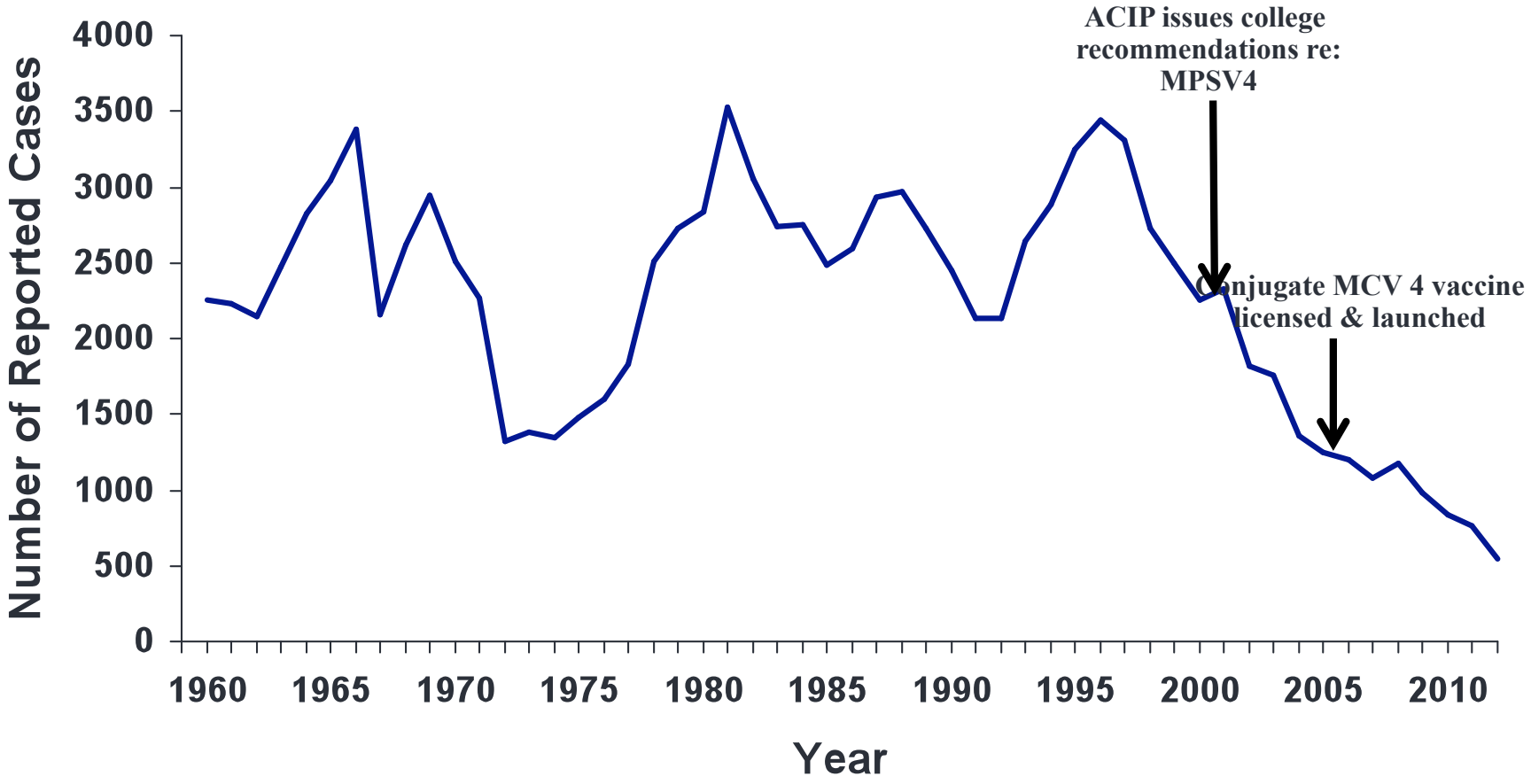


Andrews & Pollard - LID2014;14: 426–34

Meningococcal quadrivalent conjugate vaccines

- ACYW conjugate first licensed in the USA in 2005:
  - Conjugated to diphtheria
  - Safety and immunogenicity data in various age groups, many studies with the comparator being a polysaccharide meningococcal vaccine
  - Seroconversion rates were > 98 % for all subgroups
  - Safety profiles comparable; slightly more local reactions with the conjugated vaccine
  - Durable immunological response > 3 years with the conjugate vaccine
  - Induce herd immunity

Reported Cases of Meningococcal Disease—United States, 1960–2012



References: **1.** CDC. Summary of notifiable diseases – US, 1993. MMWR 1993;42(53) **2.** CDC. Summary of notifiable diseases – US, 2011. MMWR 2011;60(53). **3.** CDC. Final 2012 Reports of Nationally Notifiable Infectious Diseases. MMWR 2013;62(33).

TABLE. Summary of recommendations for meningococcal vaccination of children aged 2–23 months at increased risk for meningococcal disease — Advisory Committee on Immunization Practices, 2013

Vaccine	Age of primary vaccination	Booster doses*	Indicated for infants who:	Not indicated for:
MenACWY-CRM (Menveo)	2, 4, 6, and 12 months	• 1st booster 3 years after primary series • Additional boosters every 5 years	• Have complement component deficiencies • Have functional or anatomic asplenia (including sickle cell disease) • Are in the risk group for an outbreak for which vaccination is recommended • Are traveling to or residing in regions where meningitis is epidemic or hyperendemic	
MenACWY-D (Menactra)	9 and 12 months†	• 1st booster 3 years after primary series • Additional boosters every 5 years	• Have complement component deficiencies • Are in the risk group for an outbreak for which vaccination is recommended • Are traveling to or residing in regions where meningitis is epidemic or hyperendemic	• Infants with functional or anatomic asplenia (including sickle cell disease)§
Hib-MenCY-TT (MenHibrix)	2, 4, 6, and 12–15 months	• 1st booster (using MenACWY-CRM or MenACWY-D¶) 3 years after primary series	• Have complement component deficiencies	• Infants traveling internationally to regions where meningitis is epidemic or hyperendemic
		• Additional boosters (using MenACWY-CRM or MenACWY-D¶) every 5 years	• Have functional or anatomic asplenia (including sickle cell disease) • Are in the risk group for an outbreak for which vaccination is recommended	• Booster dose in children aged >18 months

* If the most recent dose was received before age 7 years, a booster dose should be administered 3 years later.
† For infants aged 9–23 months, 2 doses of MenACWY-D should be administered 12 weeks apart. For infants receiving the vaccine before travel, the second dose may be administered as soon as 8 weeks after the first dose (additional information at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm).
§ Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 years to prevent immune interference with 13-valent pneumococcal conjugate vaccine (PCV13).
¶ Hib-MenCY-TT should not be used for booster doses. A quadrivalent meningococcal vaccine (MenACWY-CRM or MenACWY-D) should be used for booster doses.

Meningococcal conjugate vaccines

- Other considerations:
  - Vaccine effectiveness ranges
  - Evaluation of the persistence of antibodies post vaccination is critical to monitor the duration of protection
    - determination of requirement for boosting or not
    - may be age and risk specific
  - Long term safety evaluations
  - Interchangeability? not evaluated
  - Requirements for special populations eg HIV, complement deficiencies, etc

Guillain-Barré Syndrome (GBS)

- February 2008: 26 confirmed GBS cases detected out of 15 million distributed doses[119]
  - CDC unable to determine whether Menactra® contributed to GBS risk
- The risk of GBS following receipt of Menactra® vaccine was evaluated in a large US retrospective cohort of individuals 11 to 18 years[51]
  - Fifteen percent, or ~1.5 million of these individuals had received the Menactra® vaccine
  - None of the 72 confirmed GBS cases were vaccinated with Menactra®
    within 42 days of symptom onset
  - Estimation of the attributable risk of GBS ranged from 0 to 5 GBS cases per 1,000,000 vaccines

[51]Menactra® - A/C/Y/W-135 [PI]. sanofi pasteur; 2013; [119]http://www.cdc.gov/vaccinesafety/Vaccines/gbsfactsheet.html.

4. Meningococcal vaccines: recommendations for use …

Meningococcal vaccine recommendations

- South Africa:
  - Local DoH/NICD Guidelines
  - ? Local additional vaccine Guideli
- WHO recommendations
- ACIP recommendations

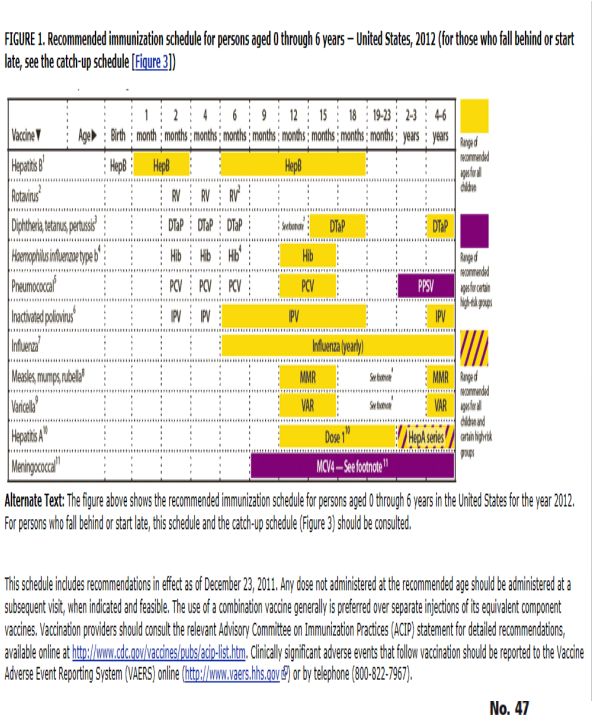
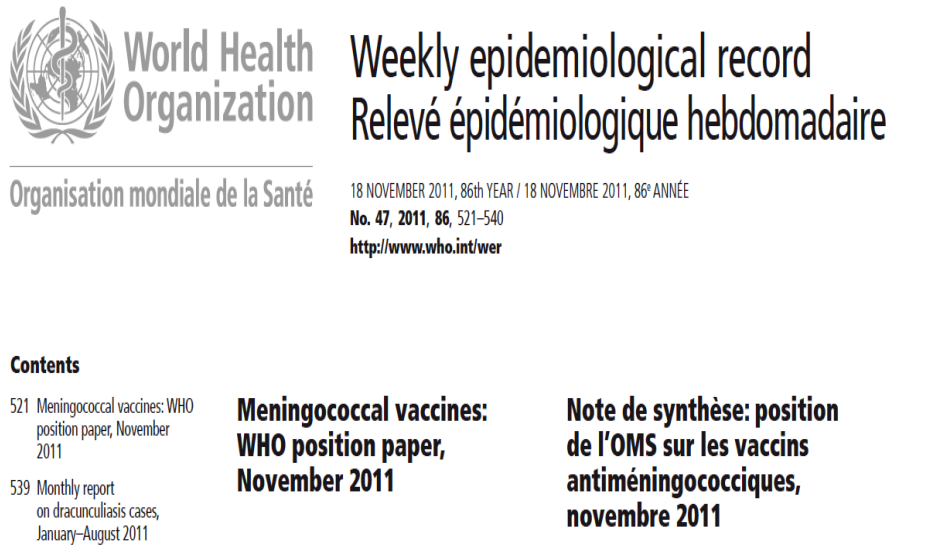


FIGURE 1. Recommended immunization schedule for persons aged 0 through 6 years – United States, 2012 (for those who fall behind or start late, see the catch-up schedule [Figure 3])

Alternate Text: The figure above shows the recommended immunization schedule for persons aged 0 through 6 years in the United States for the year 2012. For persons who fall behind or start late, this schedule and the catch-up schedule (Figure 3) should be consulted.

This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).



2011, 86, 521–540 No. 47

World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

18 NOVEMBER 2011, 86th YEAR / 18 NOVEMBRE 2011, 86e ANNÉE
No. 47, 2011, 86, 521–540
http://www.who.int/wer

Contents

Meningococcal vaccines: WHO position paper, November 2011

Note de synthèse: position de l'OMS sur les vaccins antiméningococciques, novembre 2011

ACIP Recommendations for Meningococcal Conjugate Vaccines in Adolescents[1]

- Routine vaccination with MenACWY is recommended at 11 or 12 years of age
- A booster dose is recommended at 16 years of age
- For adolescents who received first dose at age 13-15 years, booster dose should be given at age 16-18 years
- Persons who receive their first dose at or after 16 years of age do not need a booster dose
- Unvaccinated persons 11-18 years of age should be vaccinated at "the earliest possible health-care visit"

Note: Some of the current ACIP recommendations are inconsistent with the currently labeled indications for meningococcal conjugate vaccines.

Reference: 1. CDC. *MMWR*. 2013;62(RR-2):1-28.

ACIP recommendations for meningococcal conjugate vaccines: definition of persons at increased risk

- Persistent complement deficiencies, asplenia
- Lab workers exposed to meningococcal strains
- Travellers going to countries where meningitis is endemic or hyperendemic

- Reason this was defined in ACIP Guidelines: recommendations to revaccinate were made because of the limited data on the duration of protection against invasive meningococcal disease

ACIP recommendations for meningococcal conjugate vaccines in others[1]

- An unvaccinated college freshman who lives in a dormitory should be vaccinated with meningococcal conjugate vaccine
- Adults up to the age of 55 who are at increased risk of meningococcal disease should be vaccinated with a meningococcal conjugate vaccine
- Lab technicians, military recruits, travellers going to the meningitis belt, pilgrims going to the Hajj and those patients with certain diseases or conditions that predispose to bacterial infections eg complement deficiencies

2011 WHO Recommendations*

- Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection and their increased immunogenicity, particularly in children <2 years of age.

- Both conjugate and polysaccharide vaccines are efficacious and safe when used in pregnant women.

- When using conjugate vaccines, one recommended approach is initial mass vaccination of all children and adolescents aged from 9 months to 18 years followed by inclusion of the vaccine in the routine childhood immunization programme.

- The possible need for booster doses is not yet established for this vaccine.

* WHO position paper November 2011-11-28

2011 WHO Recommendations*

- High epidemic rates (>10 cases/100 000 population/year) IMD
- Intermediate endemic rates (2–10 cases/100 000 population/year)
- In countries where the disease occurs less frequently (<2 cases per 100 000 population/year), meningococcal vaccination is recommended for defined risk groups
  - Children and young adults in closed communities, e.g. boarding schools or military camps.
  - Laboratory workers at risk of exposure to meningococci
  - Travelers to high-endemic areas should be vaccinated against the prevalent serogroup(s).
- Meningococcal vaccination should be offered to all individuals suffering from
  - immunodeficiency, including asplenia, terminal complement deficiencies, or advanced HIV infection.

* WHO position paper November 2011-11-28

5. Conclusions …

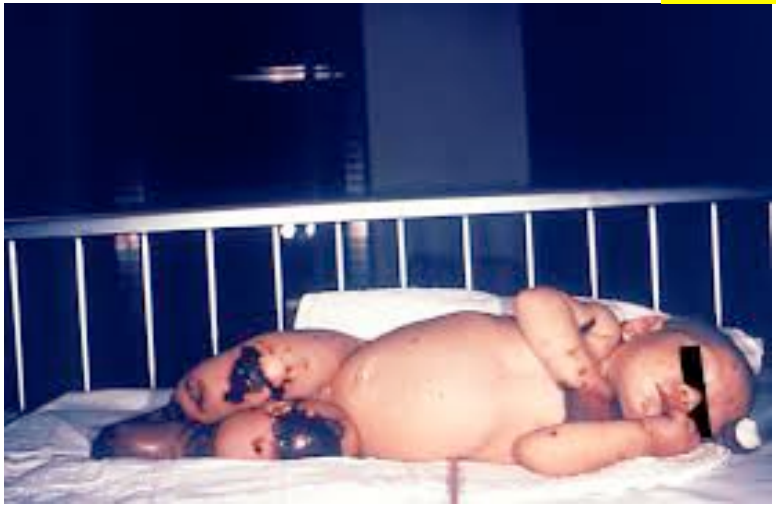
Conclusions

- Meningococcal disease is unpredictable and devastating; all ages potentially affected
- Different vaccine options: great strides, many options
  - Plain polysaccharide vaccines : well tolerated and efficacious
  - Conjugate meningococcal vaccines address ‘gaps’ eg infant and toddler vaccination, duration of response and hyporesponsiveness; they are also well tolerated, immunogenic and effective
- Recent meningococcal B vaccines – look promising
- The way vaccines are given are product specific (eg age and indication)

Conclusions

- Successful national immunisation programmes are many, conducted globally; key success factors include:
  - understanding disease in the different countries
  - vaccination of the most appropriate group depending on disease
- Recommendations per country depend on disease incidence and other risk factors: assessments essential

Meningococcal disease is a vaccine preventable disease



Refer to full prescribing information for product information

Acknowledgement of slides: Prof G Hussey, NICD GERMS team

Back up slides