Case study

Introduction of vaccines to prevent an uncommon infectious disease in children – invasive meningococcal disease

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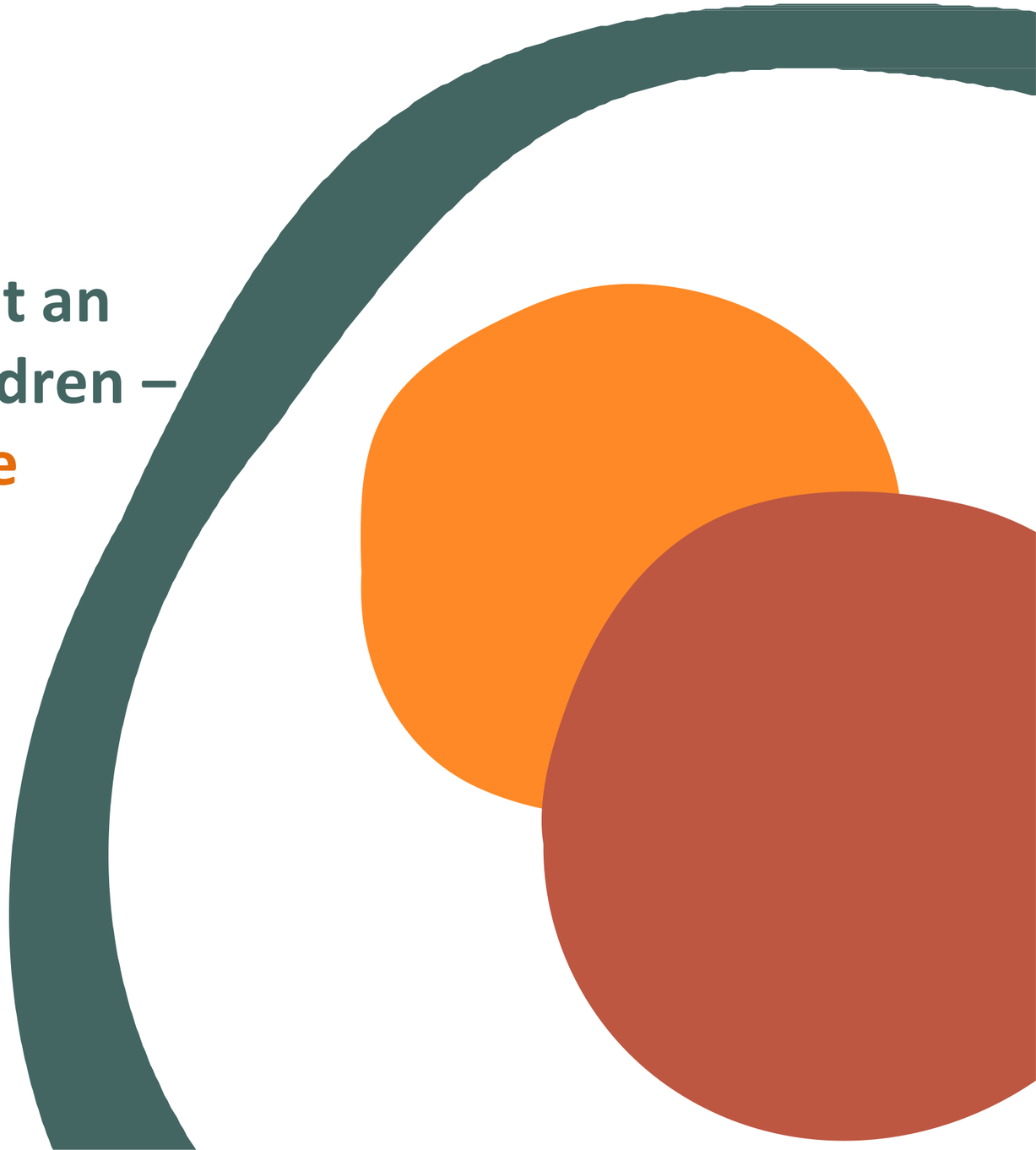


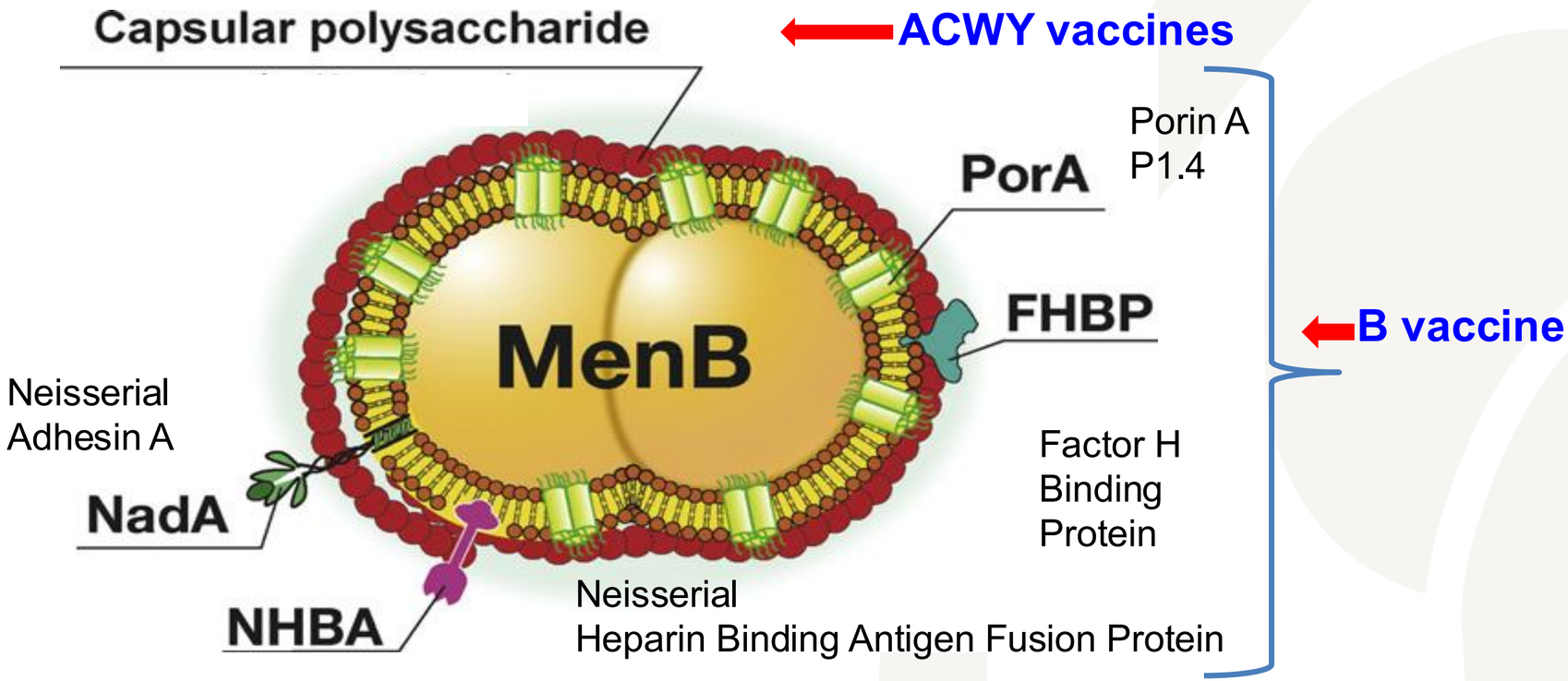
Invasive meningococcal disease

- *Neisseria meningitidis* causes sepsis and meningitis with highest rates in infants and adolescents
- 5-10% case fatality rate
- ~40% of children have life-long disability – blindness, deafness, mobility from limb amputation
- 5 of 13 known serogroups cause most disease (A,B,C,W,Y), majority of cases (85%) in Australia are due to group B
- Accidental pathogen: 5-10% of adolescents carry the meningococcus in their oropharynx and transmit it through coughing, kissing
- Seasonal variation in incidence, with higher rates in winter/spring

1. Marshall et al. Int J Evidence-Based Healthcare 2016:14:3-14. Marshall et al. NEJM 2020;382(4):318-327.

Microbiology → meningococcal vaccine development

- 13 serogroups
  - distinguished by differences in surface polysaccharides
  - common serogroups causing invasive disease: A,B,C,W,Y



http://f1000.com/prime/reports/m/3/16/fig-002

Conjugate meningococcal vaccine development

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Development of meningococcal vaccines

Early meningococcal vaccine development (1982)

- Polysaccharide meningococcal vaccines were derived from capsular polysaccharide which is a virulence factor for the bacteria and helps prevent immune-mediated bacterial killing
- Monovalent and multivalent
- Ineffective in young children < 2 years
- No herd immunity effect

Conjugate meningococcal vaccine development

- Capsular polysaccharides are conjugated to a carrier protein to induce a T-cell-dependent response, making these vaccines immunogenic from early infancy.
- Monovalent as well as multivalent vaccines
- Herd immunity impact

Clinical trial development of meningococcal conjugate vaccines

Several conjugate vaccines have been developed using different carrier proteins including – MenACWY-TT, MenACWY-CRM, MenACWY-Dip

MenC and MenACWY conjugate vaccines are immunogenic in infants and adolescents

Table 2. Non-inferiority of the proportion of meningococcal vaccine-naïve participants who achieved hSBA vaccine seroprotection[a] at Day 30 with MenACYW-TT compared with MCV4-TT (PPAS)

	MenACYW-TT (*N* = 293)		MCV4-TT (*N* = 296)		MenACYW-TT – MCV4-TT	
Serogroup	*n*	% (95% CI)	*n*	% (95% CI)	Difference, % (95% CI)	Non-inferiority[b]
A	266	90.8 (86.9–93.8)	264[c]	89.5 (85.4–92.7)	1.3 (–3.6–6.2)	Yes
C	291	99.3 (97.6–99.9)	240[c]	81.4 (76.4–85.6)	18.0 (13.6–22.8)	Yes
W	245	83.6 (78.9–87.7)	247	83.4 (78.7–87.5)	0.2 (–5.9–6.2)	Yes
Y	273	93.2 (89.7–95.8)	271	91.6 (87.8–94.5)	1.6 (–2.8–6.0)	Yes

CI, confidence interval; *n*, number of participants with seroprotection[a]; *N*, number of participants with available data for the endpoint.
95% CI of the single percentage calculated from the exact binomial method.
95% CI of the difference calculated from the Wilson Score method without continuity correction.
[a]Seroprotection defined as hSBA titre ≥1:8.
[b]The overall non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the difference is >–10% for all four serogroups.
[c]Data available for 295 participants.

van der Vliet D et al. (2021). Epidemiology and Infection 149, e50, 1–10.

Safety of meningococcal conjugate vaccines

MenC and MenACWY vaccines are

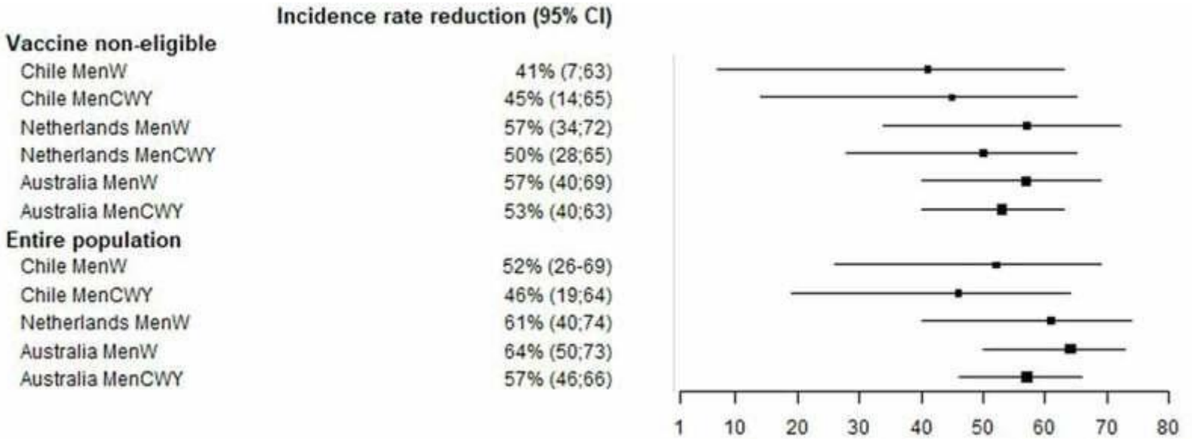
- safe to use in all age groups
- ~10% of infants may develop a temp. >38.5°
- Safely be administered concomitantly with other vaccines including meningococcal B vaccines

Table 2 Incidence of solicited local and general symptoms after each vaccination. The population analyzed was the total vaccinated cohort (all subjects who received a dose of vaccine)

Adverse event	Age (months)	Proportion reporting event (95% confidence interval)		
		Group 1 (MenACWY6/ MenACWY12)	Group 2 (MenACWY12)	Group 3 (MenC12/ MenACWY18)
Erythema	6	41% (29–54)	-	-
	12	41% (28–55)	45% (32–59)	44% (30–59)
	18	-	-	39% (25–55)
Induration	6	28% (18–41)	-	-
	12	36% (24–50)	36% (24–50)	32% (20–47)
	18	-	-	25% (13–40)
Tenderness	6	22% (13–34)	-	-
	12	32% (21–45)	43% (30–57)	26% (15–40)
	18	-	-	52% (36–67)
Changed eating habits	6	31% (20–44)	-	-
	12	22% (12–35)	21% (11–34)	28% (16–43)
	18	-	-	26% (14–42)
Sleepiness	6	42% (30–55)	-	-
	12	34% (22–48)	36% (24–50)	24% (13–38)
	18	-	-	39% (25–55)
Irritability	6	73% (60–83)	-	-
	12	58% (44–71)	52% (38–66)	58% (43–72)
	18	-	-	66% (50–80)
Vomiting	6	9% (3–19)	-	-
	12	5% (1–14)	11% (4–22)	8% (2–19)
	18	-	-	7% (2–19)
Diarrhea	6	9% (3–19)	-	-
	12	14% (6–26)	20% (11–33)	14% (6–27)
	18	-	-	11% (4–24)
Fever ≥38°C	6	5% (1–14)	-	-
	12	5% (1–14)	13% (6–25)	4% (0–14)
	18	-	-	23% (12–38)

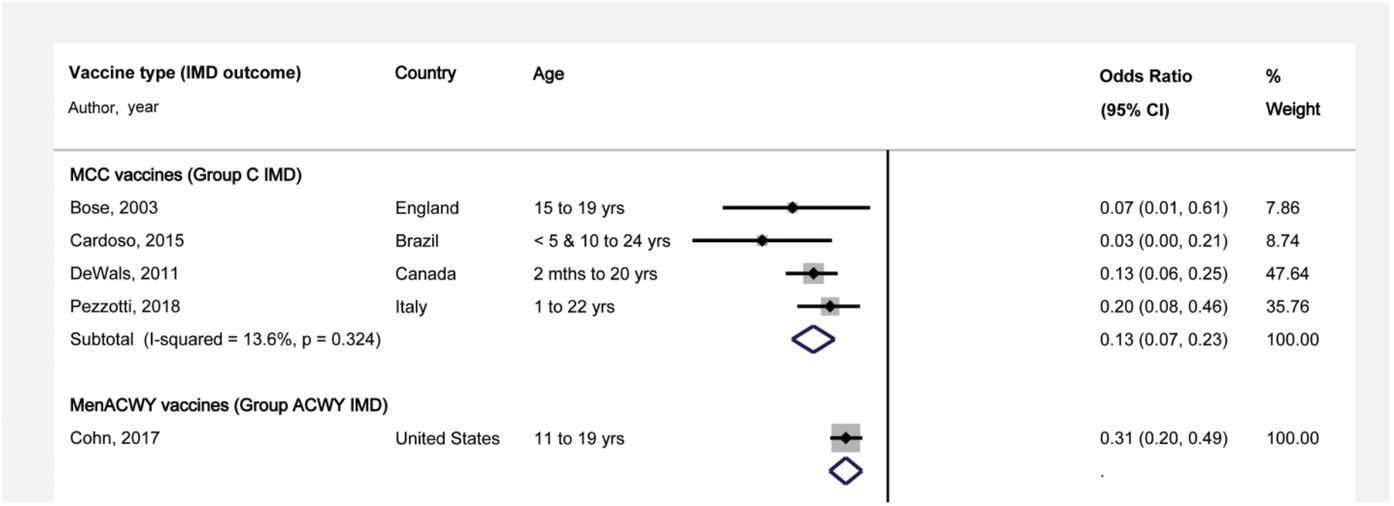
Halperin S. et al. Eur J Clin Microbiol Infect Dis (2010) 29:259–267

Conjugate meningococcal ACWY vaccines are highly effective in reducing disease



MenACWY included on the NIP
- 12 months
- 14-16 years

- Medical risk conditions



1. Villena R et al. Hum Vaccin Immunother. 2023;19(2):2251825. 2. McMillan et al. Clinical Infectious Diseases 2021;73(3):e609–19

Meningococcal B vaccine development

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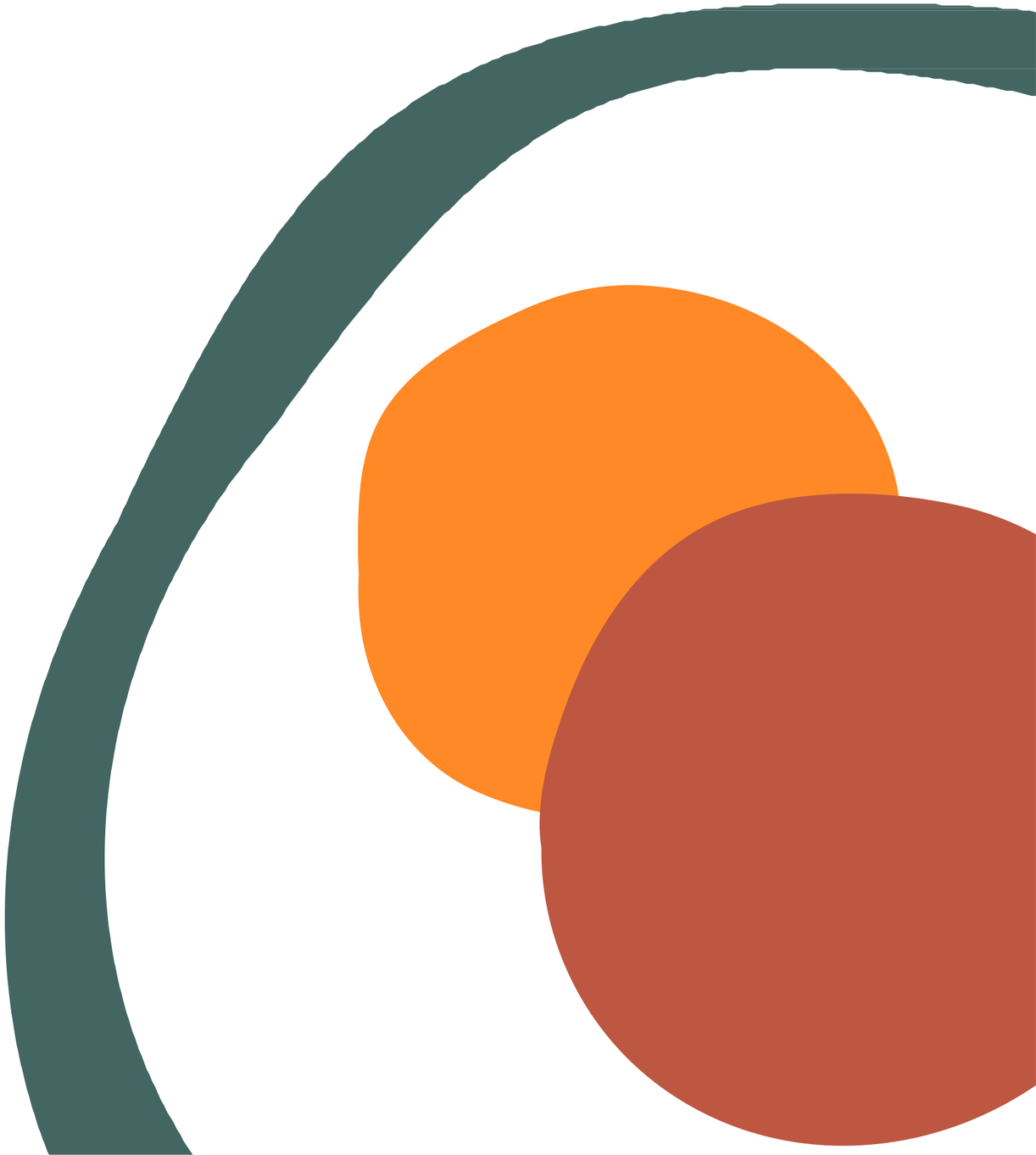

Meningococcal B vaccine development

Capsular polysaccharide Men B vaccines

- capsular based meningococcal B vaccines are poorly immunogenic
  - mimics neural cell adhesion molecule (PSA-NCAM) expressed on surface of human foetal neural tissue
- potential to induce auto-antibodies
- Phase 1 Men B vaccine study in adults, antibodies were non-functional

Vaccines to protect against **epidemic disease**

- Epidemic outbreaks in Cuba and New Zealand
- Outer membrane vesicles (immunodominant outer membrane protein, porin A (PorA))
- Strain specific response, unable to generate antibodies against heterologous strains
  - OMV VA-MENGOC-BC (Cuba)
  - OMV MeNZB (New Zealand)

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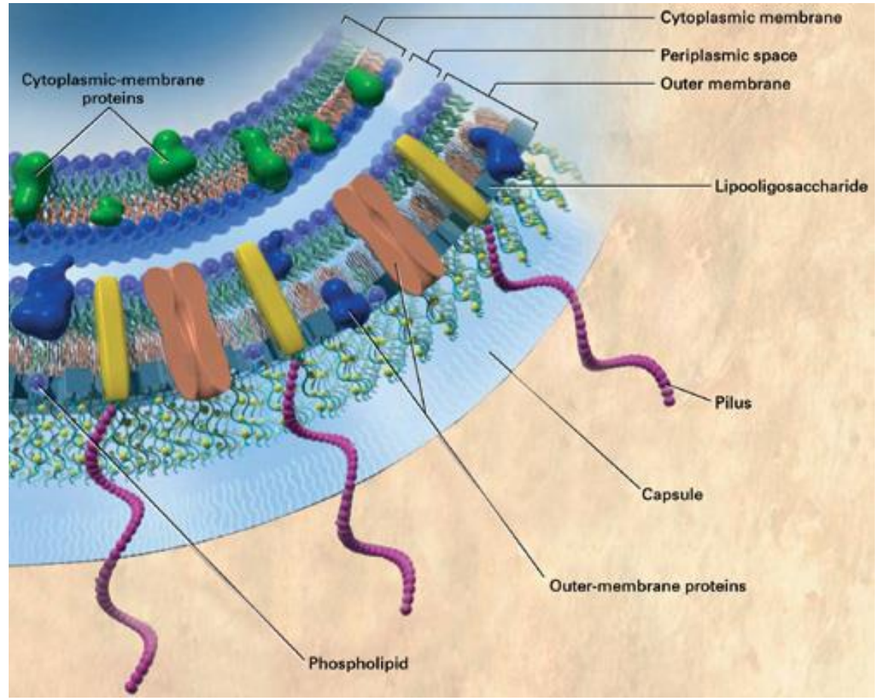
Immunologic Response of Man to Group B Meningococcal Polysaccharide Vaccines

F. A. Wyle,* M. S. Artenstein, B. L. Brandt, E. C. Tramont, D. L. Kasper, P. L. Altieri, S. L. Berman, and J. P. Lowenthal

From the Department of Bacterial Diseases and the Department of Biologics Research, Walter Reed Army Institute of Research, Washington, D.C.

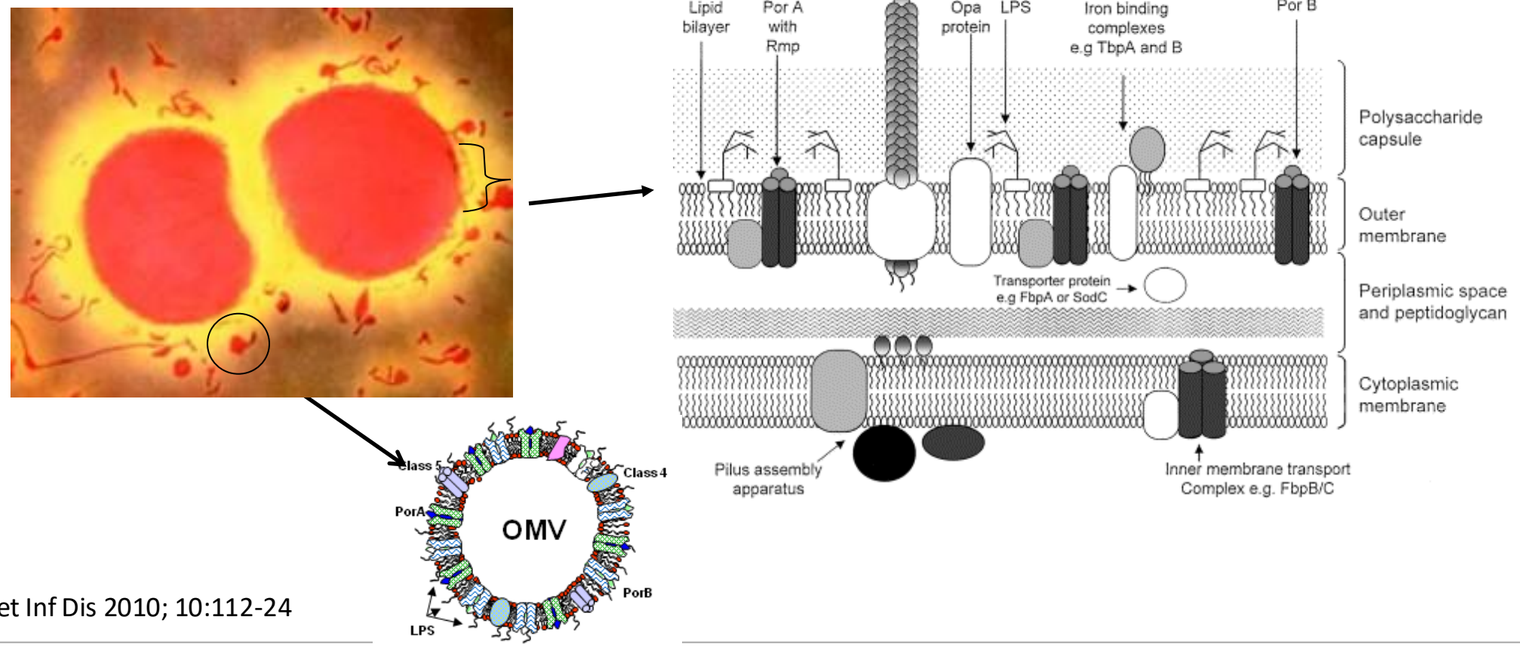


Wyle FA et al. I Infect Dis 1972;126:514-21

Development of broadly protective meningococcal B vaccines required a new approach – Reverse Vaccinology

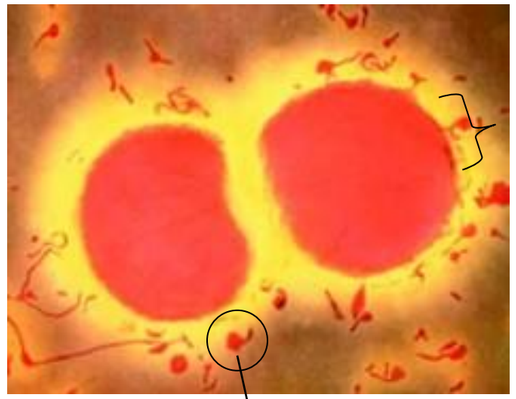
Vaccines to protect against **endemic disease**

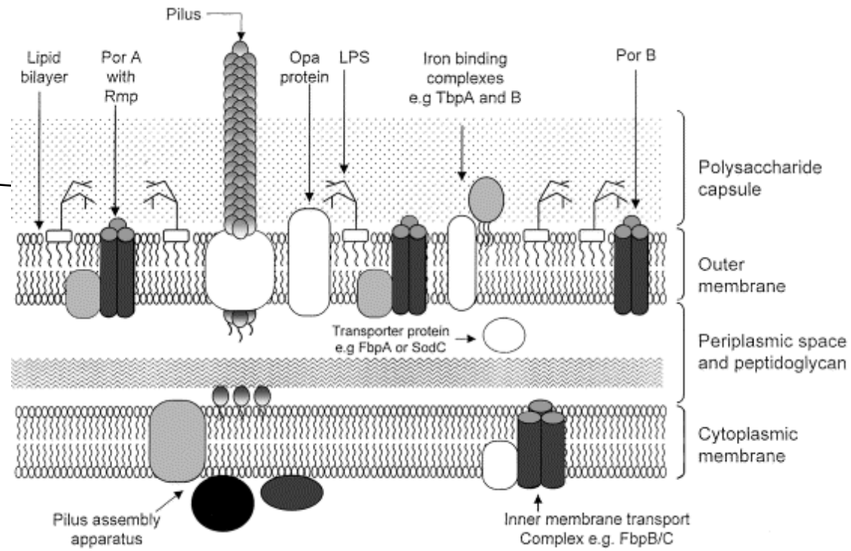
- Identification of outer membrane proteins that are **immunogenic, conserved and surface exposed** - Reverse vaccinology
- Subcapsular antigens for protection against endemic disease



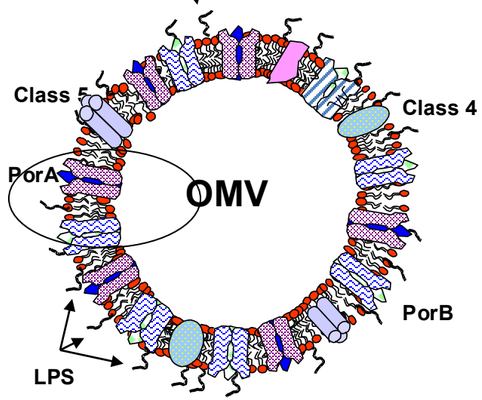
Sadarangani M and Pollard A, Lancet Inf Dis 2010; 10:112-24

Meningococcus Vaccine Targets identified through reverse vaccinology





Morley SL, Pollard AJ, Vaccine 2001

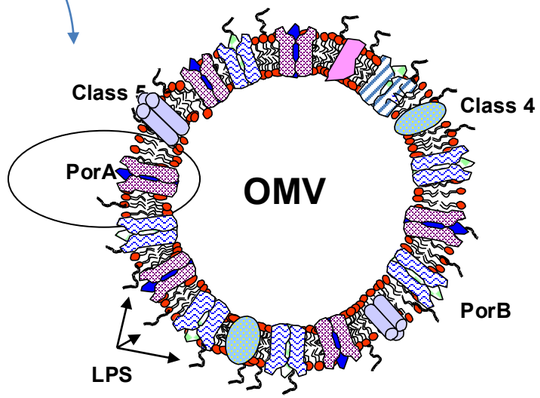


Strain specific MenB vaccines (MeNZB)

– Outer Membrane Vesicle

Broad protection - Multi-component vaccine '4CMenB'

- Factor H binding Protein
- NadA
- NHBA
- Outer Membrane Vesicle (PorA)



Sadarangani M and Pollard A, Lancet Inf Dis 2010; 10:112-24

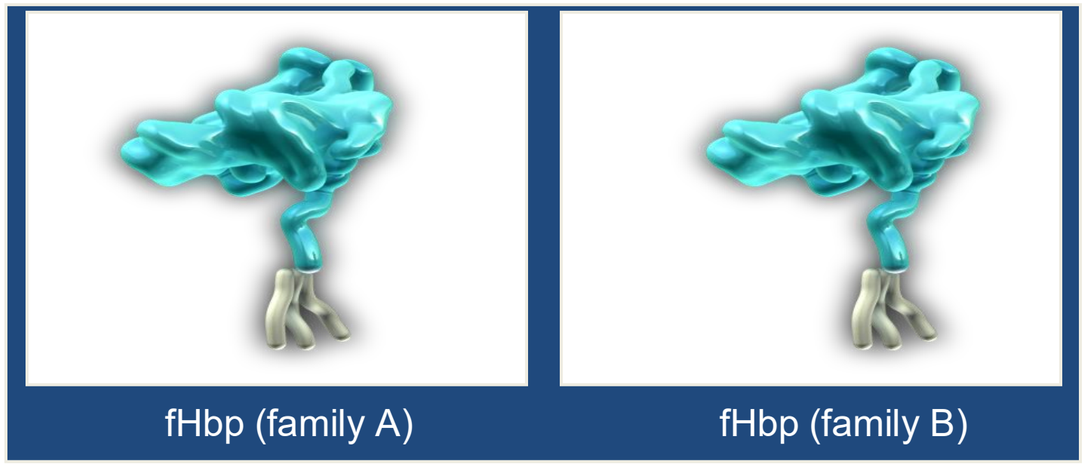
Meningococcal B vaccines: 4CMenB (Bexsero; GSK)

Three recombinant proteins discovered by reverse vaccinology

OMVs from the New Zealand strain (NZ 98/254)

Donnelly J, et al. *Proc Natl Acad Sci U S A*. 2010;107:19490-19495

Meningococcal B vaccines: MenB:fHbp (Trumenba; Pfizer)



= MenB:fHbp

recombinant lipidated factor H binding protein meningococcal serogroup B vaccine

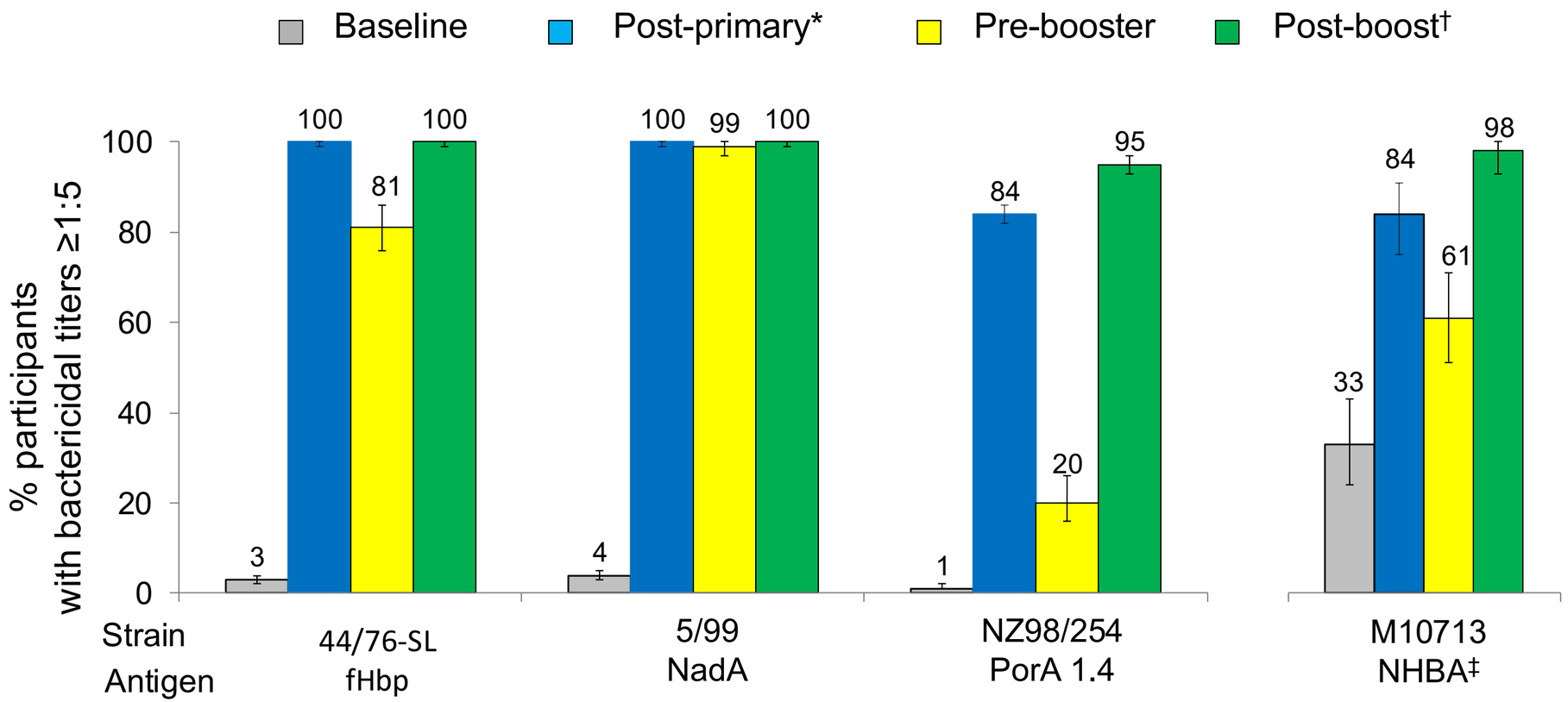
- 60 µg *Neisseria meningitidis* serogroup B factor H binding protein subfamily A
- 60 µg *Neisseria meningitidis* serogroup B factor H binding protein subfamily B

fHbp is a bacterial virulence factor

- Assists in bacterium evading complement mediated bacteriolysis

Immunogenicity of 4CMenB vaccine components assessed in phase III studies

4CMenB given at 2, 4, 6, and 12 months



Phase III in Infants and Toddlers

1. Vesikari T, et al. Presented at IPNC. Banff, Canada. Sept 11-16, 2010, Poster #180. 2. Vesikari T, et al. Present at: 29th ESPID Meeting, June 7–11, 2011. The Hague, The Netherlands.

Meningococcal B Vaccines

4CMenB

Licensed in the EU, Australia, Canada, USA

- Use from 6 weeks of age
- OMV + fHBP + NadA + NHBA
- clinical trials in adults, adolescents, toddlers and infants
- Immunogenic with acceptable safety profile in clinical trials

MenB:fHbp

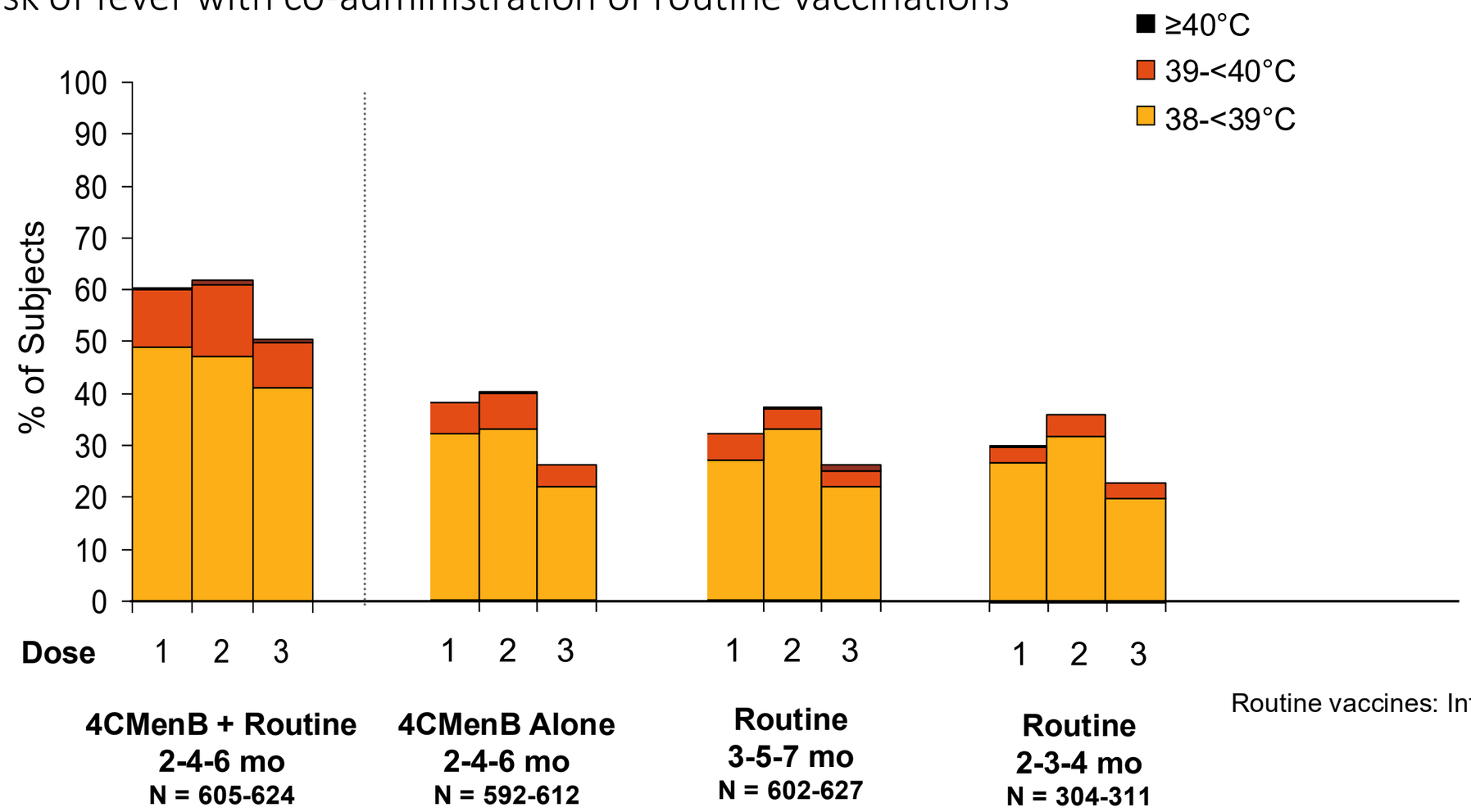
- Licensed in Australia, USA, EU, Canada for ≥ 10 years of age
- fHBP, subfamily A & subfamily B
- Clinical trials in adults, adolescents and toddlers (infant study discontinued)
- Immunogenic with acceptable safety profile in clinical trials

1. Snape M et al. PIDJ 2010;29:e71-9
2. Findlow J. CID 2010;51:1127-37
3. Santolaya ME et al. Lancet 2012;379(9816):617–624
4. Vesikari T et al. Lancet 2013;381(9869):825-35.
5. Gossger N et al. JAMA 2012;307(6):573-82.

1. Marshall et al. Lancet Infect Dis. 2017
2. Richmond P et al. Lancet Inf Dis 2012;12(8):597–607.
3. Marshall H et al. PIDJ 2012;31(10):1061-68.
4. Marshall H et al. Vaccine 2013;31(12):1569-75.
5. Nissen et al. PIDJ 2013; 32 (4):364-371
6. Martinon-Torres F et al. Vaccine 2014;32:5206-5211

Safety of 4CMenB vaccine in infants

Increased risk of fever with co-administration of routine vaccinations



Routine vaccines: Infanrix-hexa, Prevenar

Adapted from Gossger, Snape et al JAMA 2012;307(6):573–582.

4CMenB vaccine safety in infants in a population program

Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study

Philip Bryan, Suzie Seabroke, Jenny Wong, Katherine Donegan, Elizabeth Webb, Charlotte Goldsmith, Caroline Vipond, Ian Feavers

Summary

Background Safety data for the multicomponent meningococcal group B vaccine (4CMenB) has so far been limited to experience from clinical trials and isolated local outbreaks. Since the UK is the first country to implement a nationwide routine immunisation programme with 4CMenB (at age 8 weeks, 16 weeks, and then 1 year), we aimed to assess the safety of 4CMenB in this setting.

Methods In this prospective surveillance study, we assessed suspected adverse reactions of 4CMenB in children up to age 18 months reported in the UK Yellow Card Scheme and primary care records extracted from the Clinical Practice Research Datalink (CPRD). We proactively assessed reports of fever, local reactions, Kawasaki disease, seizures, and sudden death, and compared the number of spontaneous reports with the expected number of events based on background incidence and the number of children vaccinated. We also identified any unexpected adverse reactions and estimated compliance with subsequent doses of routine vaccinations.

Findings From Sept 1, 2015, to May 31, 2017, approximately 1·29 million children aged 2–18 months received about a combined 3 million doses of 4CMenB. 902 reports of suspected adverse reactions were received through the UK Yellow Card Scheme, of which 366 (41%) were related to local reactions and 364 (40%) related to fever. The only unexpected finding was that 160 reports of local reactions described a persistent nodule at the site of injection, usually without other local symptoms. There were 55 (6%) reports of seizures, with an age-adjusted observed-to-expected ratio of 0·13 (95% CI 0·10–0·17). Ecological analyses found similar rates of seizures within 7 days of

Lancet Child Adolesc Health 2018

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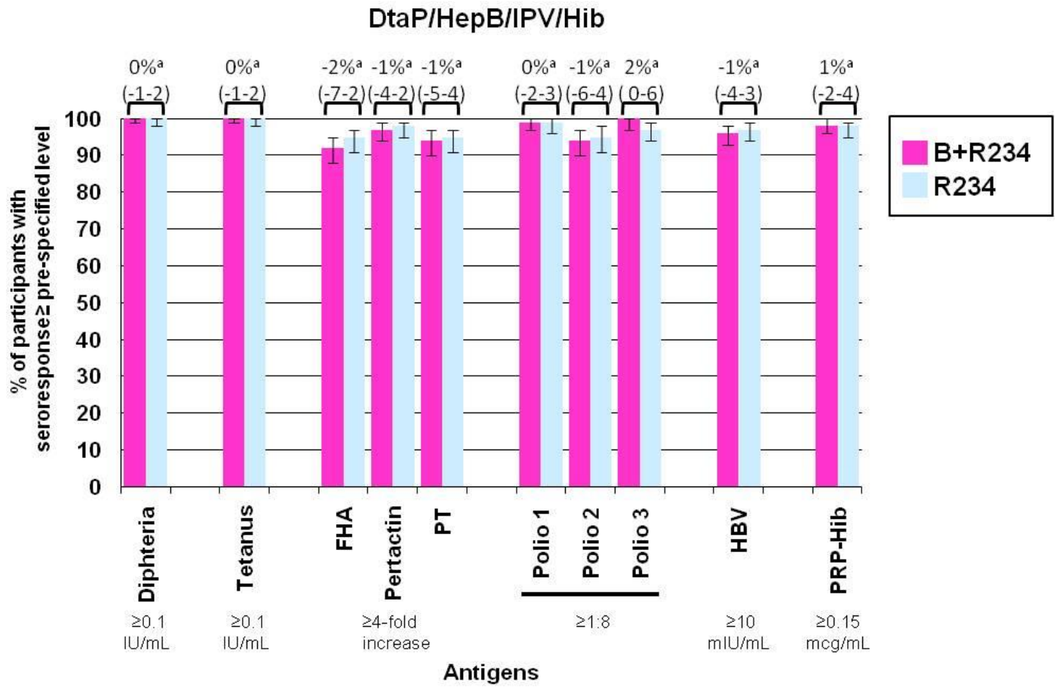
See Online/Comment
http://dx.doi.org/10.1016/S2352-4642(18)30135-4

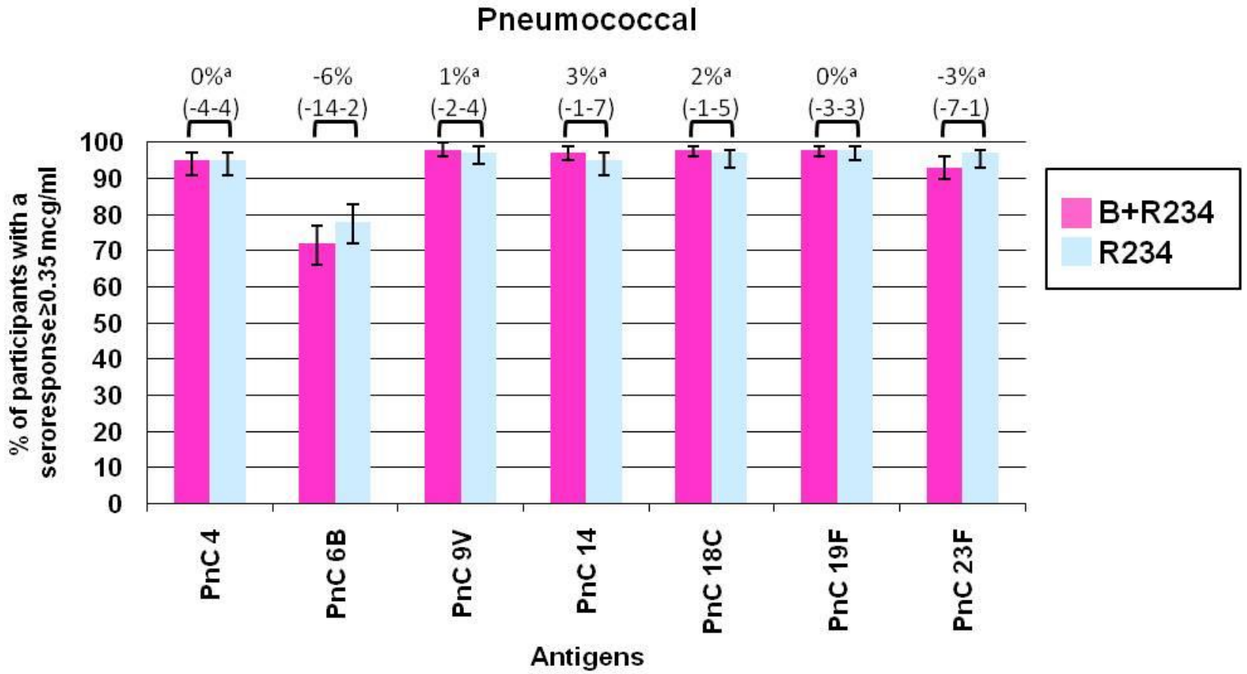
Vigilance and Risk Management of Medicines, Medicines and Healthcare Products Regulatory Agency, London, UK (P Bryan PhD, S Seabroke PhD, J Wong MSc, K Donegan PhD, E Webb BSc, C Goldsmith BSc); **and Division of Bacteriology, National Institute for Biological Standards and Control, Hertfordshire, UK** (C Vipond PhD, I Feavers PhD)

Prophylactic paracetamol prior to and following 4CMenB vaccination in infants < 2 years

Bryan P et al. The Lancet Child Adol 2018;2(6):395-403

Minimal interference when 4CMenB is administered with routine vaccines





Adapted from Gossger, Snape et al JAMA 2012;307(6):573–582.

4CMenB vaccine clinical program

Licensed

- EU, UK, USA, Australia, Brazil, Argentina
- Initially licensed in a 3+1 schedule for infants and 2 dose schedule for adolescents
- Alternative 2+1 schedule now used in most countries (UK, EU, Australia)
- Use of anti-pyretics (eg paracetamol) to reduce fever when administered to infants with routine immunisations

Population programs

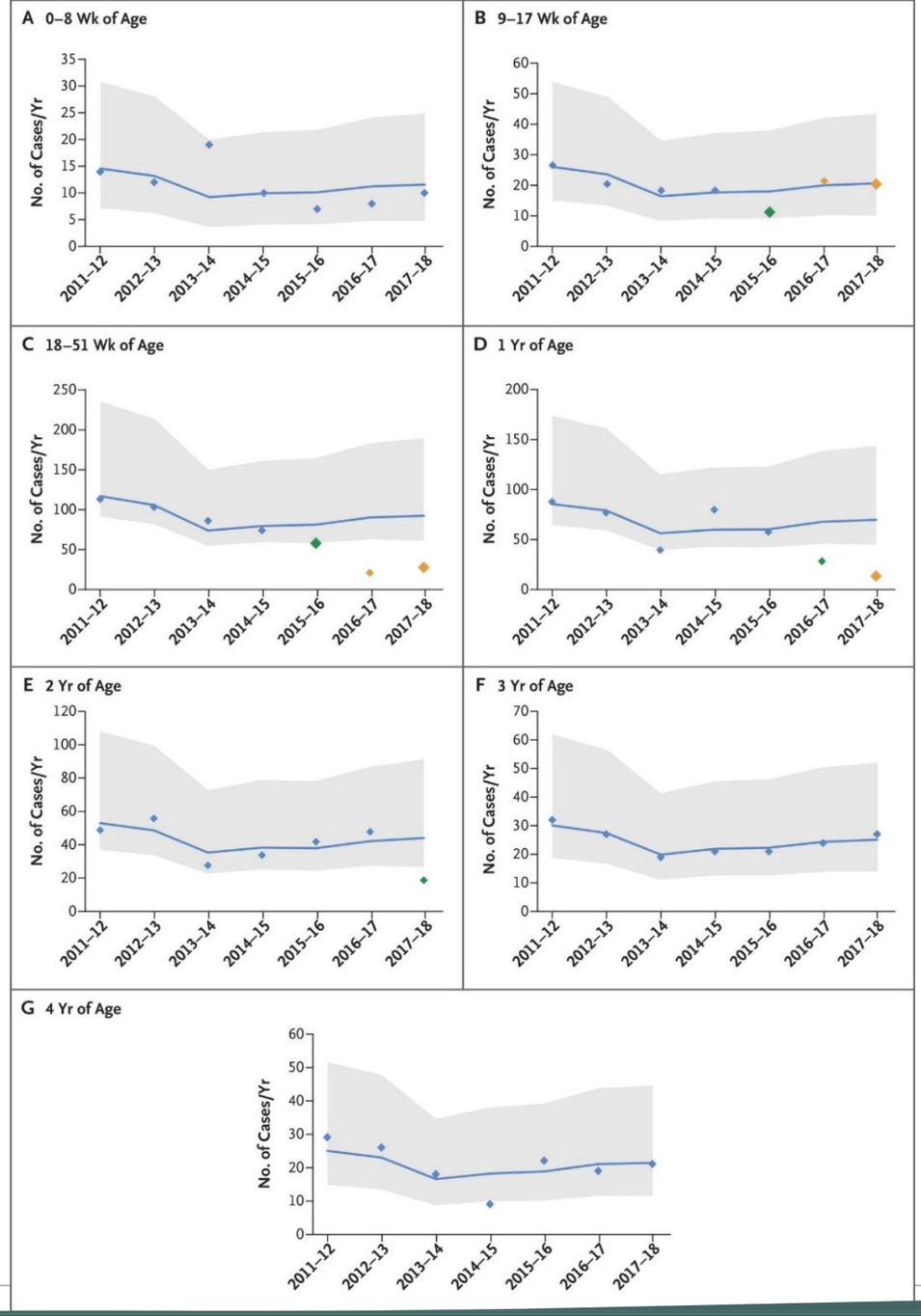
- UK, Italy, Ireland, Australia, NZ
- Australia
  - NIP for Aboriginal and Torres Strait Islander infants and medical risk conditions
  - State/Territory funded programs – SA, NT, Qld, Tas (to commence soon) for infants and adolescents

Vaccine impact and effectiveness in infants, UK; 4CMenB

Coverage
- 92.5% uptake of dose 1&2
- 87.9% uptake 3 doses by 2 years of age

Vaccine Impact
- 75% reduction in MenB disease in vaccine eligible cohort

Vaccine Effectiveness: 59.1% (95%CI -31.1, 87.2)



Ladhani SN et al. NEJM 2020;382(4):309-17

4CMenB vaccine effectiveness against diverse MenB strains

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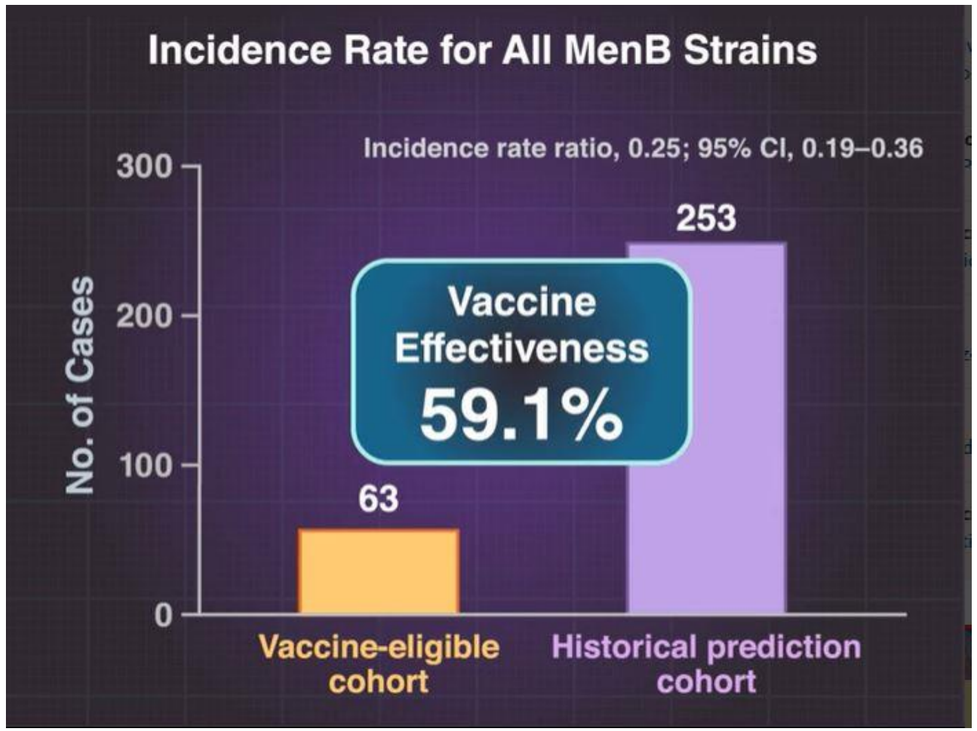
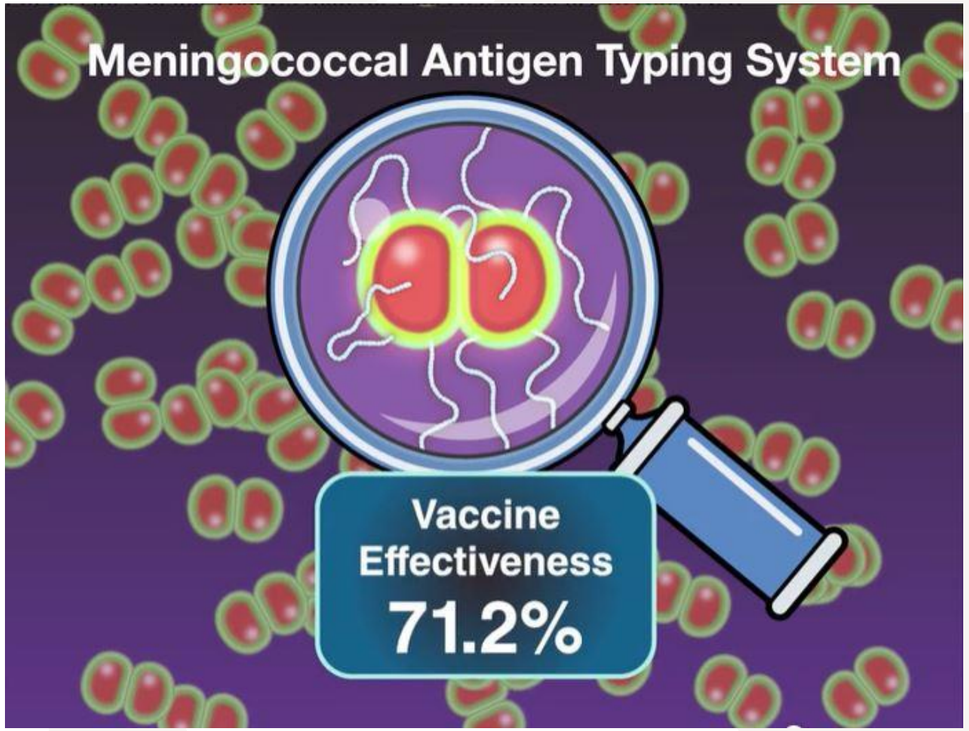
Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England

Shamez N. Ladhani, M.R.C.P.C.H.(U.K.), Ph.D., Nick Andrews, Ph.D., Sydel R. Parikh, M.Sc., Helen Campbell, Ph.D., Joanne White, B.Sc., Michael Edelstein, F.F.P.H., Xilian Bai, Ph.D., Jay Lucidarme, Ph.D., Ray Borrow, F.R.C.Path., Ph.D., and Mary E. Ramsay, F.F.P.H.

Meningococcal Antigen Typing System is a system for assessing panels of region specific meningococcal strains for presence of at least one expressed antigen sufficiently matched to allow killing by vaccine induced antibodies





4CMenB vaccine coverage predicted by MATS is variable by region

4CMenB coverage depends of epidemiology and diversity of MenB strains globally

Some strains may not express any of the proteins contained in the vaccine

Prediction based on a proprietary Meningococcal Antigen Typing System

Australia:~76% (95%CI 63–87%) preventable by 4CMenB

Varies by country

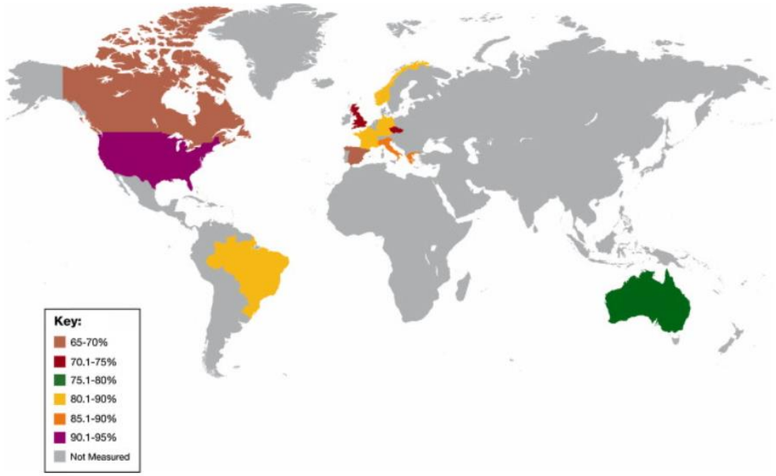


Fig. 4

Global MATS coverage estimates for 4CMenB.

Table 1. Strain coverage predicted by MATS and gMATS, overall and by year of sample collection, state/territory, and the patient's age group.

	N	MATS coverage, % (95% CI)	gMATS coverage, % (LL-UL)
Overall	**520**	**74.6 (61.1–85.6)**	**81.0 (75.0–86.9)**
By year			
2007	108	70.4 (57.4–83.3)	79.2 (74.1–84.3)
2008	119	81.5 (69.7–89.0)	82.8 (76.5–89.1)
2009	103	70.9 (58.2–81.5)	80.1 (75.7–84.5)
2010	93	77.4 (60.2–87.1)	87.6 (81.7–93.5)
2011	97	72.2 (58.8–86.6)	75.3 (67.0–83.5)
By state/territory			
New South Wales & ACT	156	71.8 (54.5–82.0)	78.5 (71.8–85.3)
Northern Territory	4	–*	62.5 (50.0–75.0)
Queensland	141	85.1 (73.0–94.3)	87.2 (84.4–90.1)
South Australia	40	90.0 (90.0–95.0)	93.8 (92.5–95.0)
Tasmania	9	–*	66.7 (66.7–66.7)
Victoria	118	73.7 (56.8–85.6)	80.9 (71.2–90.7)
Western Australia	52	51.9 (42.3–71.1)	65.4 (57.7–73.1)
By age group**			
<1 year	75	64.0 (53.3–74.7)	68.7 (58.7–78.7)
1–<2 years	28	71.4 (64.3–89.3)	76.8 (67.9–85.7)
2–<5 years	30	83.3 (66.7–90.0)	98.3 (96.7–100)
5–29 years	118	80.5 (66.1–91.5)	86.4 (82.2–90.7)
>29 years	68	75.0 (58.8–86.8)	77.9 (72.1–83.8)

MATS, meningococcal antigen typing system; gMATS, genetic MATS; 4CMenB, 4-component meningococcal serogroup B vaccine; N, number of tested isolates; CI, coverage interval; LL, lower limit; UL, upper limit; ACT, Australian Capital Territory.

Notes: * Not calculated, due to the small number of strains isolated.

** The age of the patient from whom the sample was collected was only documented for 319 of the total 520 strains.

1. Medini et al. *Vaccine* 2015;33:2629-2636 2. Tozer S et al. Human vaccines and immunotherapeutics 2021;17(9):3230-3238

4CMenB strain coverage against non-MenB strains due to expression of OMPs in other serogroups

Serogroup	No. of strains	Percentage (95% CI)
C	50	64.0 (46.0, 86.0)
W-135	27	63.0 (40.7, 92.6)
Y	30	36.7 (26.7, 43.3)

Australian meningococcal non-B strains expressing 4CMenB Antigens in MATS

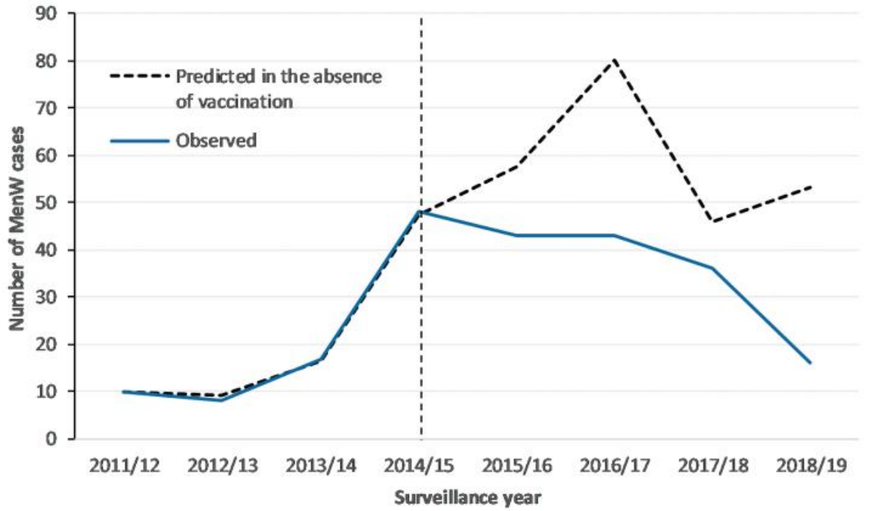


Figure 2. Observed MenW cases* in children under 5 years and predicted cases based on MenW disease trends in unvaccinated childhood cohorts aged ≤12 years in England during 2011/2012 to 2018/2019 surveillance years (September through August). *There were 679 000 children in each age group of 0, 1, 2, 3, and 4 years, so 10 cases would represent an incidence of 14.7 per million; similarly, there were 5.20 million children aged 5–12 years, so 10 cases would represent an incidence of 1.9 per million. Abbreviation: MenW, meningococcal group W.

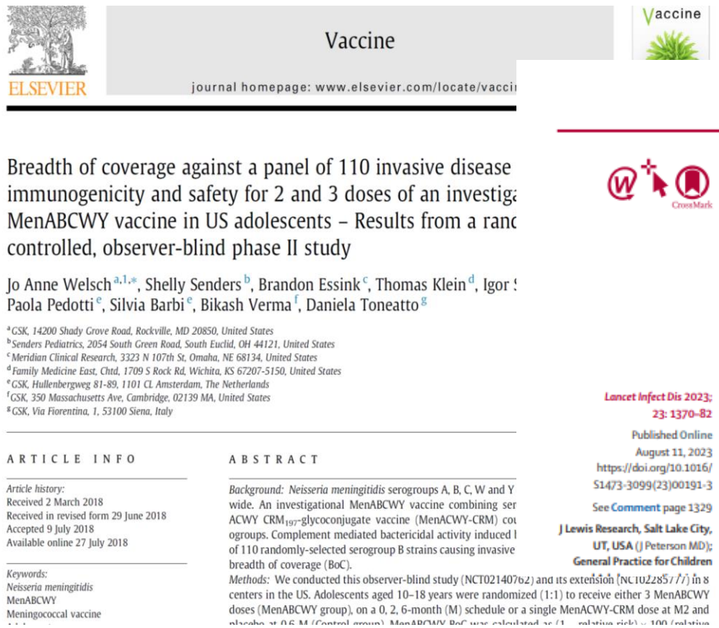
Impact of 4CMenB vaccine on serogroup W in the UK

1. Tozer S. et.al. IPNC Wurtzberg, Germany 2012 2. Ladhani et al Clinical Infectious Diseases 2021;73(7):e1661–8

Next generation pentavalent Men ABCWY vaccines

ABCWY – licensed in the US (Pfizer, GSK)

ACWYX – other potential pentavalent vaccines



Vaccine

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Breadth of coverage against a panel of 110 invasive disease immunogenicity and safety for 2 and 3 doses of an investig MenABCWY vaccine in US adolescents – Results from a ranc controlled, observer-blind phase II study

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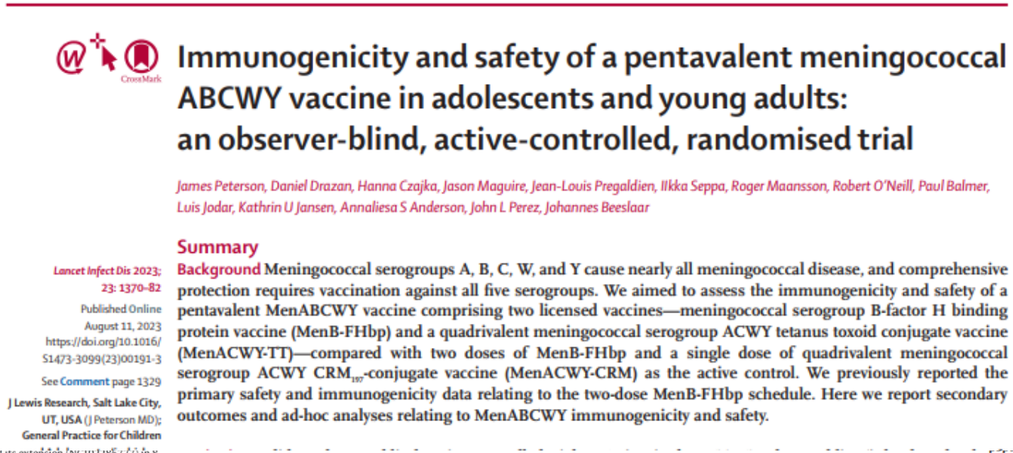
ABSTRACT

Background: *Neisseria meningitidis* serogroups A, B, C, W and Y wide. An investigational MenABCWY vaccine combining ser ACWY CRM_{197}-glycoconjugate vaccine (MenACWY-CRM) co ogroups. Complement mediated bactericidal activity induced l of 110 randomly-selected serogroup B strains causing invasive breadth of coverage (BoC).

Methods: We conducted this observer-blind study (NCT02140782) and its extension (NCT02278757) in 8 centers in the US. Adolescents aged 10–18 years were randomized (1:1) to receive either 3 MenABCWY doses (MenABCWY group), on a 0, 2, 6-month (M) schedule or a single MenACWY-CRM dose at M2 and placebo at 0.6 M (Control group). MenABCWY BoC was calculated as (1 – relative risk) × 100 (relative



Immunogenicity and safety of a pentavalent meningococcal ABCWY vaccine in adolescents and young adults: an observer-blind, active-controlled, randomised trial

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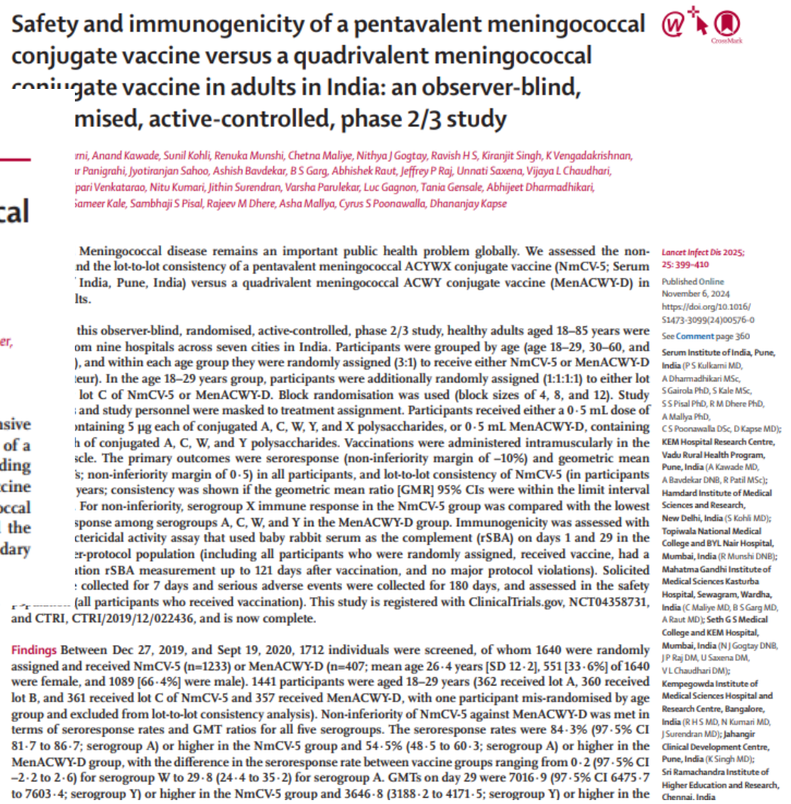
Summary

Background Meningococcal serogroups A, B, C, W, and Y cause nearly all meningococcal disease, and comprehensive protection requires vaccination against all five serogroups. We aimed to assess the immunogenicity and safety of a pentavalent MenABCWY vaccine comprising two licensed vaccines—meningococcal serogroup B-factor H binding protein vaccine (MenB-FHbp) and a quadrivalent meningococcal serogroup ACWY tetanus toxoid conjugate vaccine (MenACWY-TT)—compared with two doses of MenB-FHbp and a single dose of quadrivalent meningococcal serogroup ACWY CRM_{197}-conjugate vaccine (MenACWY-CRM) as the active control. We previously reported the primary safety and immunogenicity data relating to the two-dose MenB-FHbp schedule. Here we report secondary outcomes and ad-hoc analyses relating to MenABCWY immunogenicity and safety.



Safety and immunogenicity of a pentavalent meningococcal conjugate vaccine versus a quadrivalent meningococcal conjugate vaccine in adults in India: an observer-blind, mised, active-controlled, phase 2/3 study

rni, Anand Kawade, Sunil Kohli, Renuka Munshi, Chetna Maliye, Nithya J Gogtay, Ravish H S, Kiranjit Singh, K Vengadakrishnan, r Panigrahi, Jyotiranjan Sahoo, Ashish Bavdekar, B S Garg, Abhishek Raut, Jeffrey P Raj, Unnati Saxena, Vijaya L Chaudhari, pari Venkataraa, Nitu Kumari, Jithin Surendran, Varsha Parulekar, Luc Gagnon, Tania Gensale, Abhijeet Dharmadhikari, ameer Kale, Sambhaji S Pisal, Rajeev M Dhere, Asha Mallya, Cyrus S Poonawalla, Dhananjay Kapse

Meningococcal disease remains an important public health problem globally. We assessed the non- nd the lot-to-lot consistency of a pentavalent meningococcal ACYWX conjugate vaccine (NmCV-5; Serum India, Pune, India) versus a quadrivalent meningococcal ACWY conjugate vaccine (MenACWY-D) in lts.

this observer-blind, randomised, active-controlled, phase 2/3 study, healthy adults aged 18–85 years were om nine hospitals across seven cities in India. Participants were grouped by age (age 18–29, 30–60, and), and within each age group they were randomly assigned (3:1) to receive either NmCV-5 or MenACWY-D eur). In the age 18–29 years group, participants were additionally randomly assigned (1:1:1:1) to either lot lot C of NmCV-5 or MenACWY-D. Block randomisation was used (block sizes of 4, 8, and 12). Study and study personnel were masked to treatment assignment. Participants received either a 0·5 mL dose of ntaining 5 µg each of conjugated A, C, W, Y, and X polysaccharides, or 0·5 mL MenACWY-D, containing h of conjugated A, C, W, and Y polysaccharides. Vaccinations were administered intramuscularly in the scle. The primary outcomes were seroresponse (non-inferiority margin of –10%) and geometric mean s; non-inferiority margin of 0·5) in all participants, and lot-to-lot consistency of NmCV-5 (in participants years; consistency was shown if the geometric mean ratio [GMR] 95% CIs were within the limit interval For non-inferiority, serogroup X immune response in the NmCV-5 group was compared with the lowest sponse among serogroups A, C, W, and Y in the MenACWY-D group. Immunogenicity was assessed with ctericidal activity assay that used baby rabbit serum as the complement (rSBA) on days 1 and 29 in the r-protocol population (including all participants who were randomly assigned, received vaccine, had a ition rSBA measurement up to 121 days after vaccination, and no major protocol violations). Solicited collected for 7 days and serious adverse events were collected for 180 days, and assessed in the safety (all participants who received vaccination). This study is registered with ClinicalTrials.gov, NCT04358731, and CTRI, CTRI/2019/12/022436, and is now complete.

Findings Between Dec 27, 2019, and Sept 19, 2020, 1712 individuals were screened, of whom 1640 were randomly assigned and received NmCV-5 (n=1233) or MenACWY-D (n=407; mean age 26·4 years [SD 12·2], 551 [33·6%] of 1640 were female, and 1089 [66·4%] were male). 1441 participants were aged 18–29 years (362 received lot A, 360 received lot B, and 361 received lot C of NmCV-5 and 357 received MenACWY-D, with one participant mis-randomised by age group and excluded from lot-to-lot consistency analysis). Non-inferiority of NmCV-5 against MenACWY-D was met in terms of seroresponse rates and GMT ratios for all five serogroups. The seroresponse rates were 84·3% (97·5% CI 81·7 to 86·7; serogroup A) or higher in the NmCV-5 group and 54·5% (48·5 to 60·3; serogroup A) or higher in the MenACWY-D group, with the difference in the seroresponse rate between vaccine groups ranging from 0·2 (97·5% CI –2·2 to 2·6) for serogroup W to 29·8 (24·4 to 35·2) for serogroup A. GMTs on day 29 were 7016·9 (97·5% CI 6475·7 to 7603·4; serogroup Y) or higher in the NmCV-5 group and 3646·8 (3188·2 to 4171·5; serogroup Y) or higher in the

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