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Meningococcal B vaccination: policies and effectiveness data in Europe

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WHOcc for Meningitis

Conflicts of interest

- **Have undertaken contract research on behalf of the Institut Pasteur, Paris, France, for GSK, Novartis, Pfizer and Sanofi Pasteur.**

- **Patent: Bexsero & *Neisseria meningitidis* X (Novartis/GSK)**

- **Have acted as a consultant (conferences and advisory Boards): GSK, Novartis, and Pfizer and Sanofi Pasteur.**

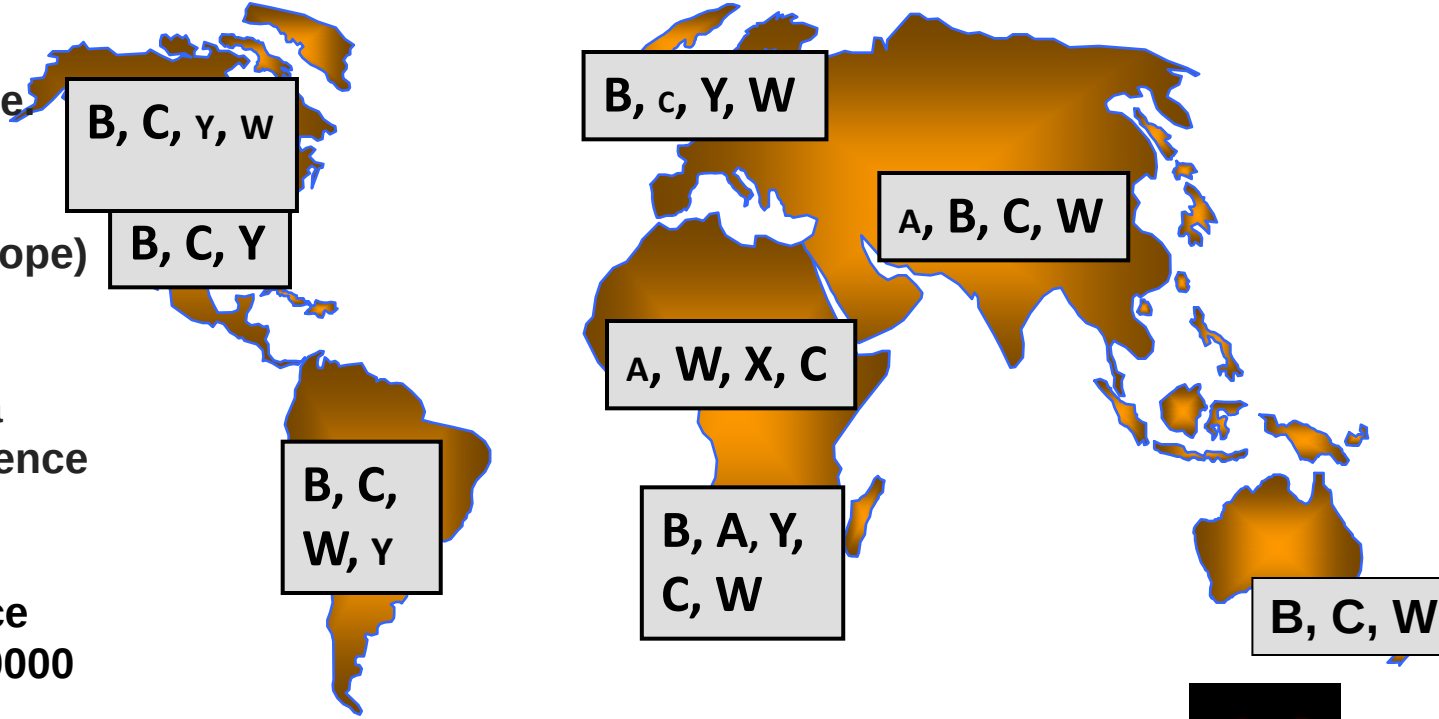
- **Research Funding from Fondation TOTAL**

Global serogroup distribution

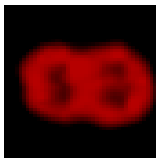
Sporadic forms: Europe, America
Incidence
0.11-2 per 100 000 (Europe)
<1 per 100 000 (US)

Epidemic forms: Africa (meningitis belt). Incidence up to 1000 per 100 000

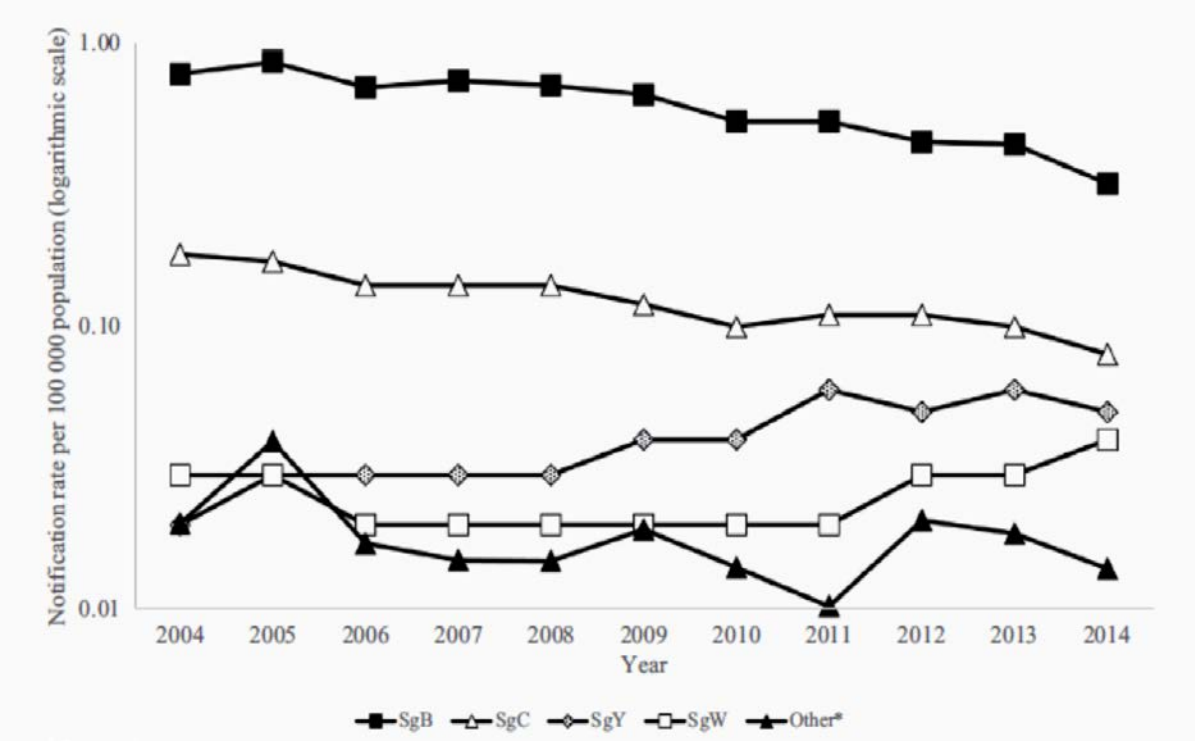
China: global incidence 1.84 (0.91-3.37) per 100000



Neisseria meningitidis Gram- capsulated bacteria

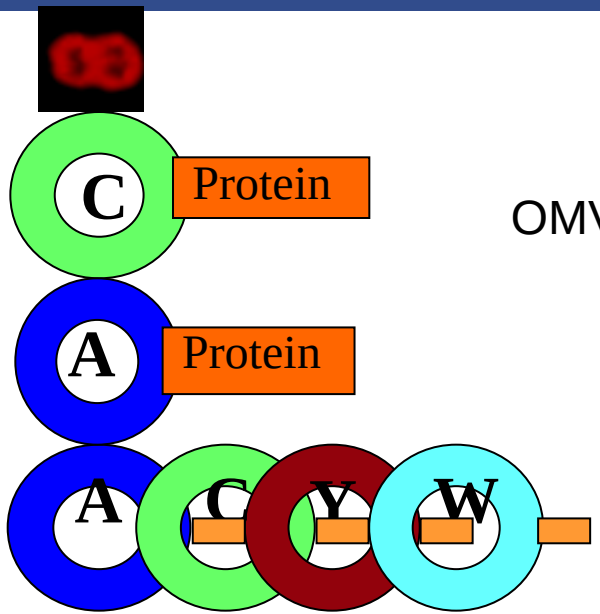


Annual notification rate per 100,000 Europe, 2004–2014



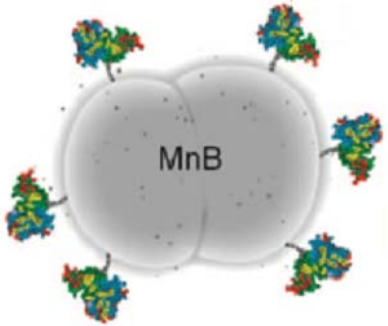
Whittaker et al., 2017 Vaccine

Anti-meningococcal vaccines



OMV-based vaccines

Recombinant vaccines



➔**Serogroup specific Immunity**

➔***No vaccine against serogroup B: self homologue (NCAM)***

Bexsero® 4CMenB licensed (2013) ≥ 2 months European Union, Canada, Australia, and United States.

Trumenba® Bivalent rLP2086, approved in the United States in individuals 10 to 25 years of age. Positive opinion CHMP 23 Mars 2017: ≥ 10 years

Vaccine components

fHbp (factor H Binding Protein)

- Binds specifically human fH downregulation of complement on Nm surface.

NHBA (Neisserial Heparin Binding Antigen)

- Binds glycosaminoglycans (eg, heparan sulfate) on the surface of host cells
- Increases bacterial serum resistance.

NadA (Neisserial adhesin A)

- Induced by 4-hydroxyphenylacetic acid (4HPA), secreted in human saliva, and 3-Cl-4-hydroxyphenylacetic acid (3Cl-4HPA), produced during inflammation.

PorA

- Major porin
- Increases bacterial serum resistance by binding 4CBp

Anti-meningococcal vaccines and the basis of the correlate of protection

	Bactericidal titer ≥4		*P*
	Group Cases	Group Control	
Bacterial strain tested	3/54 (5,6%)	444/540 (82%)	<0.001

% of subjects with a titer ≥4

% of subjects with four-fold increase of bactericidal titer

Geometric mean of titers of all subjects

Goldschneider et al., 1969 J Exp Med

Immunogenicity of 4CMenB vaccine: 11-17y

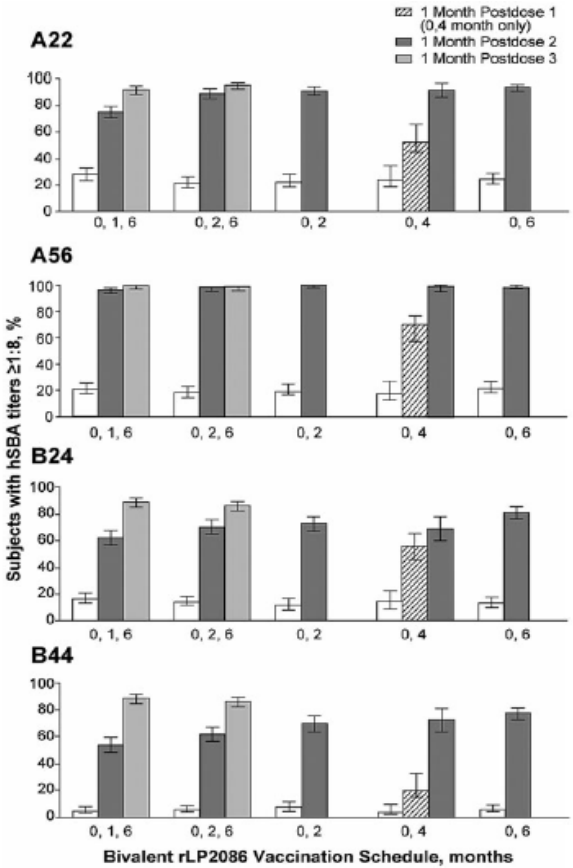
% of hSBA≥ 1:4

Strain 44/76SL (fHbp)								
	One dose		Two doses			Three doses		
Schedule (months)	**0**	**6**	**0,1**	**0,2**	**0,6**	**0,1,2**	**0,1,6**	**0,2,6**
Baseline	105/223 47% (40–54)	53/116 46% (36–55)	88/231 38% (32–45)	108/232 47% (40–53)	47/112 42% (33–52)	155/334 46% (41–52)	46/113 41% (32–50)	41/110 37% (28–47)
Month 1	206/223 **92%** (88–95)	50/115 43% (34–53)	214/231 **93%** (88–96)	214/232 **92%** (88–95)	103/112 **92%** (85–96)	316/333 **95%** (92–97)	107/113 **95%** (89–98)	99/110 **90%** (83–95)
Month 2	196/213 92% (88–95)	54/109 50% (40–59)	222/222 **100%** (98–100)	196/219 89% (85–93)	95/108 88% (80–93)	306/307 100% (98–100)	108/108 100% (97–100)	92/105 88% (80–93)
Month 3	182/208 88% (82–92)	52/108 48% (38–58)	214/215 100% (97–100)	215/215 **100%** (98–100)	90/107 84% (76–90)	302/303 **100%** (98–100)	104/105 99% (95–100)	104/104 **100%** (97–100)
Month 6	136/188 72% (65–79)	46/100 46% (36–56)	183/198 92% (88–96)	196/201 98% (94–99)	76/100 76% (66–84)	270/278 97% (94–99)	93/100 93% (86–97)	96/99 97% (91–99)
Month 7	123/173 71% (64–78)	88/95 **93%** (85–97)	167/186 90% (85–94)	170/179 95% (91–98)	86/86 **100%** (96–100)	243/255 95% (92–98)	95/95 **100%** (96–100)	91/91 **100%** (96–100)

Santolaya et al., 2102 The Lancet

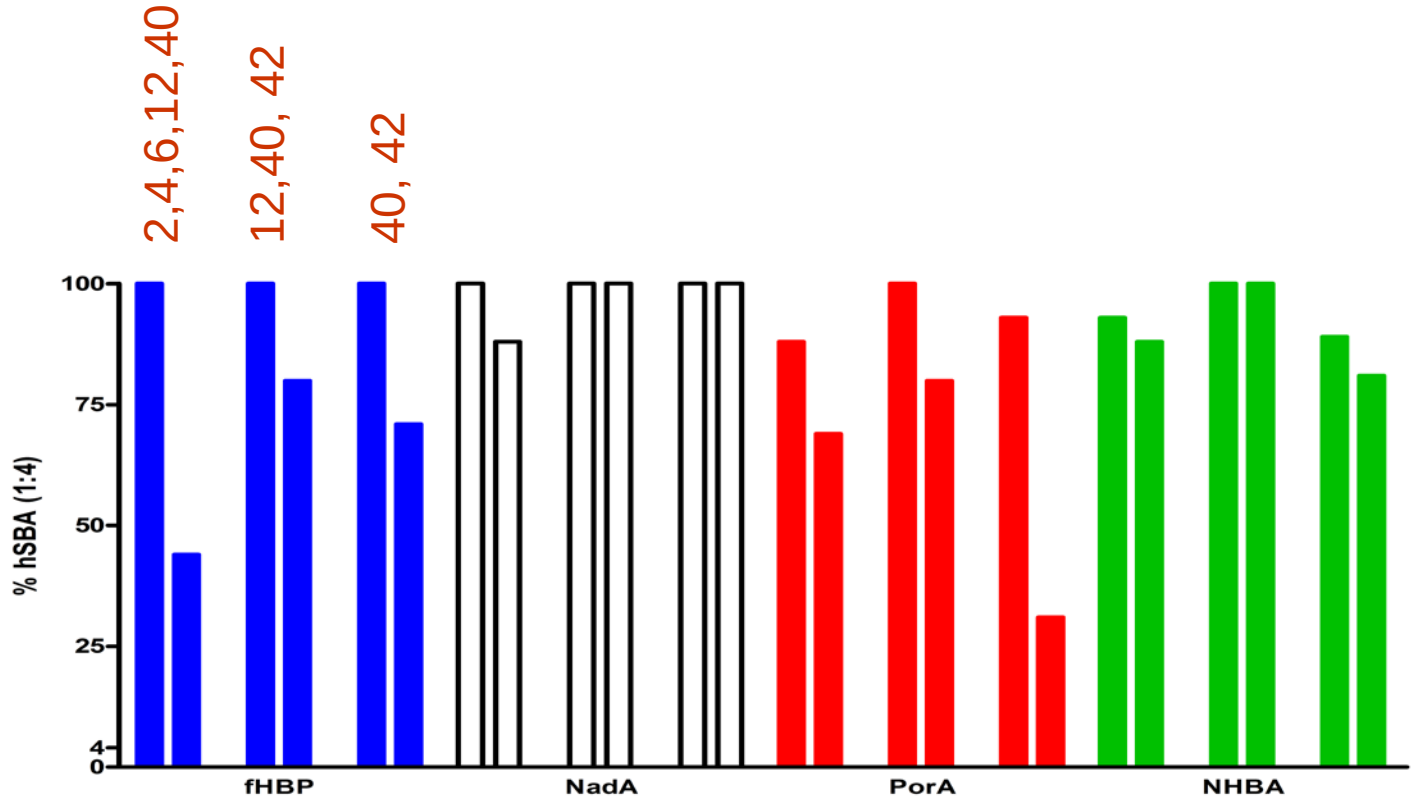
Immunogenicity of rLP2086 bivalent vaccine :11-18y

% of hSBA≥ 1:8



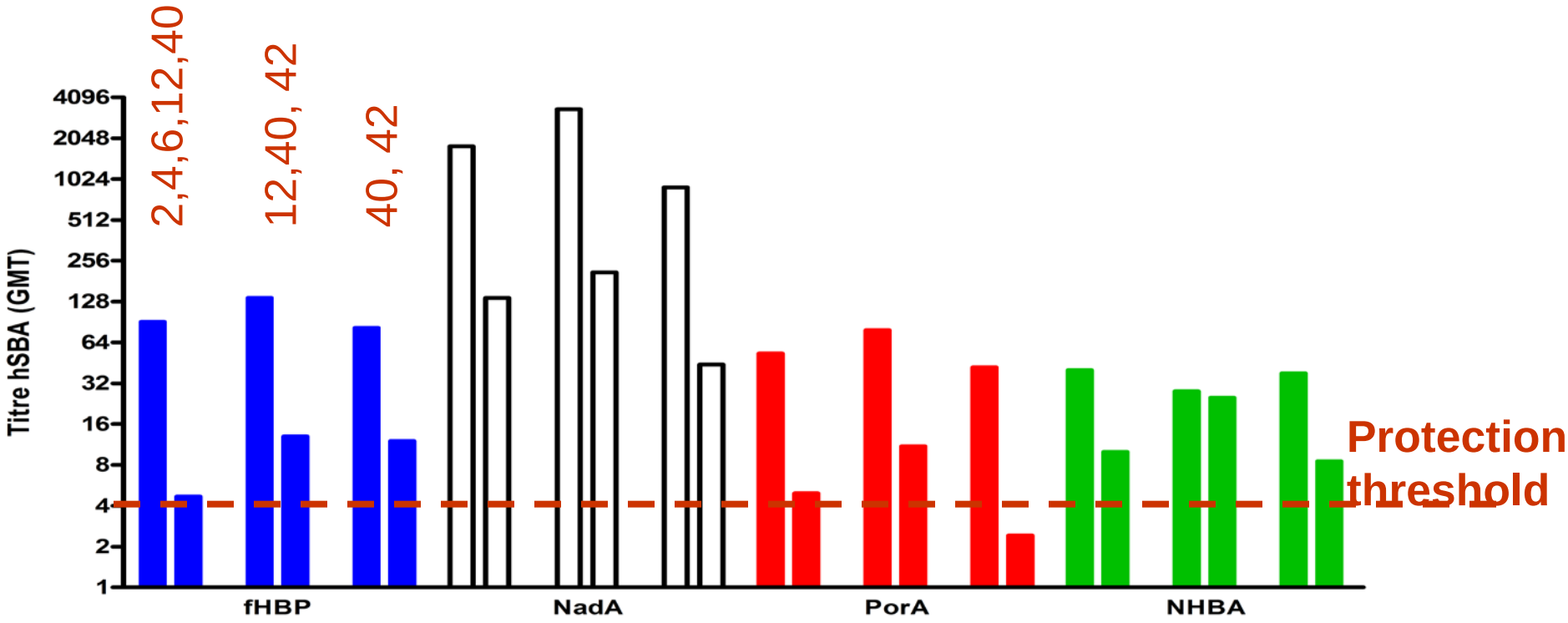
Vesikari et al., 2015 JPIDS

4CMenB: Persistence of hSBA (hSBA ≥ 1:4)



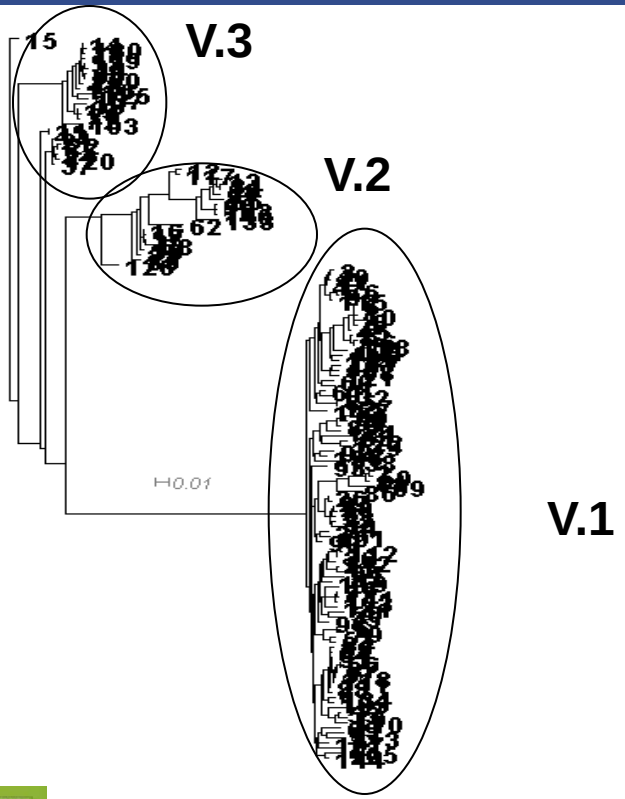
McQuaid et al., CMAJ 2015

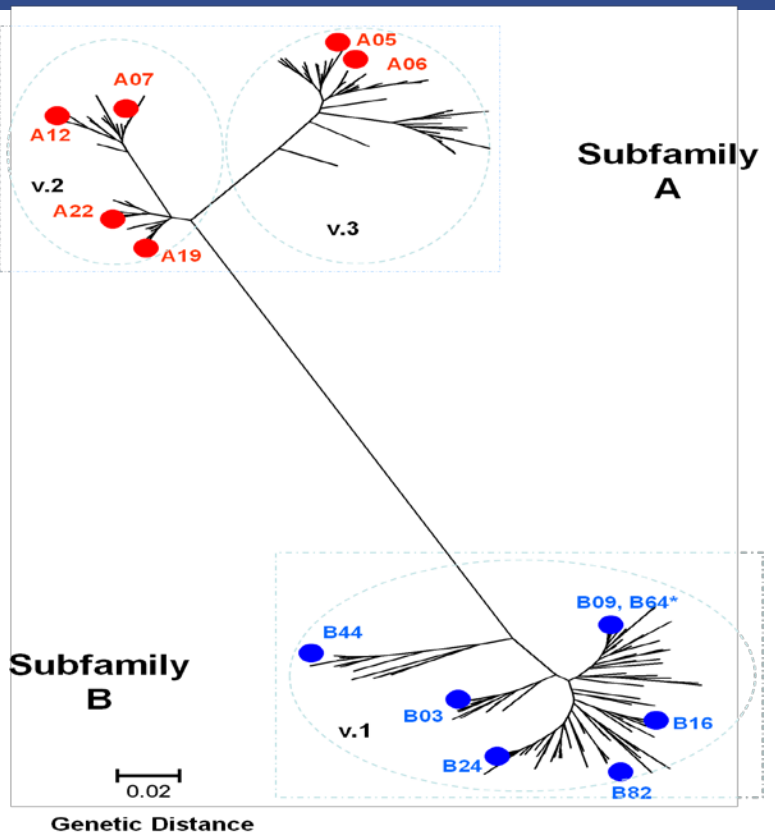
Persistence of hSBA (GMT)



McQuaid et al., CMAJ 2015

Diversity of fHBP





Murphy et al., 2009; Hoiseth et al., 2013, Vogel et al., 2013

Strain coverage

Are any of the vaccine components in the targeted isolate:

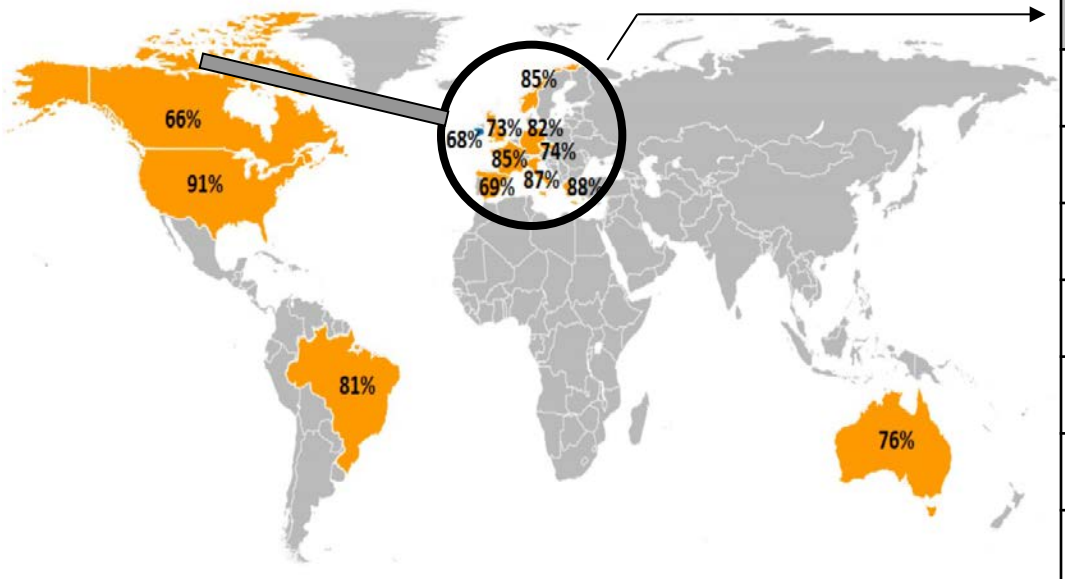
(i) Similar enough to the antigens in the vaccine such that the antibodies generated by the vaccine will kill the bacteria?

and

(ii)Expressed to a sufficient degree?

For an isolate to be ‘covered’, at least one antigen must be greater than a threshold that predicts killing by sera from vaccinated subjects

Predicated Coverage of 4CMenB Vaccine



Vogel *et al.,* 2013 Lancet Infect Dis
Bettinger et al., 2013 Vaccine Tzanakaki et al.,2014 BMC Microbiol
Wasko et al., 2016 Vaccine

	Predicted coverage (95% CI)
England & Wales	73% (57–87)
France	85% (69–93)
Germany	82% (69–92)
Italy	87% (70–93)
Norway	85% (76–98)
Czech Republic	74% (58–87)
Spain	69% (48–85)
Greece	89% (64-99)
Poland	84% (79-91)
Combined*	78% (63–90)

*Excludes Czech Republic, Greece and Poland and Spain

Outbreak Princeton University

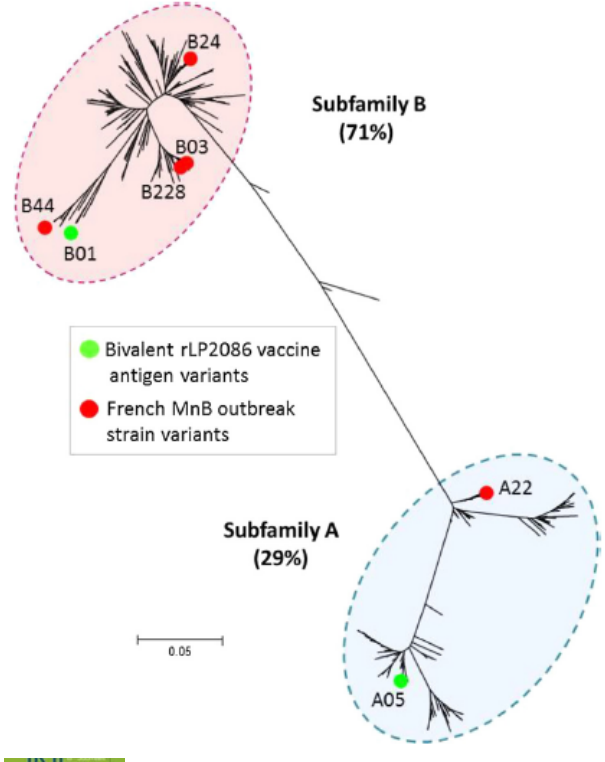
ST 409 [cc41/44/lineage3], PFGE 429, PorA P1.5-1,2.2, fHbp 1.276, NHBA p0002, and NadA^{-}

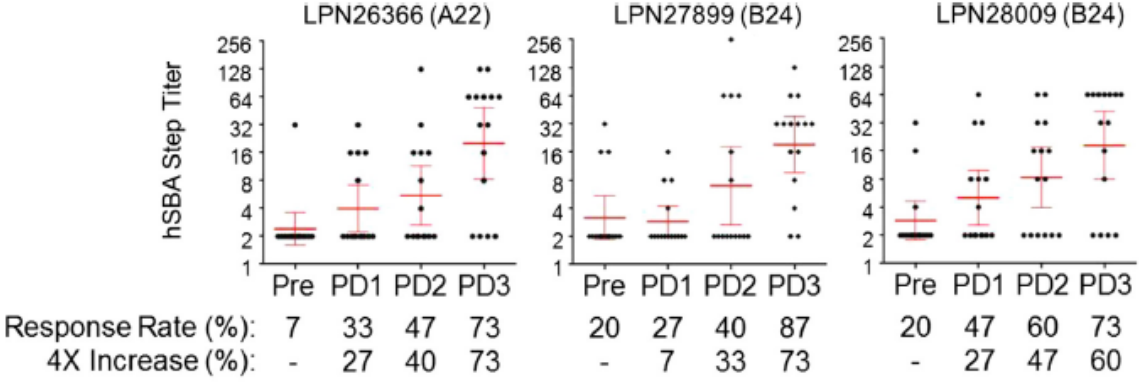
MATS+ (fHbp and NHBA)

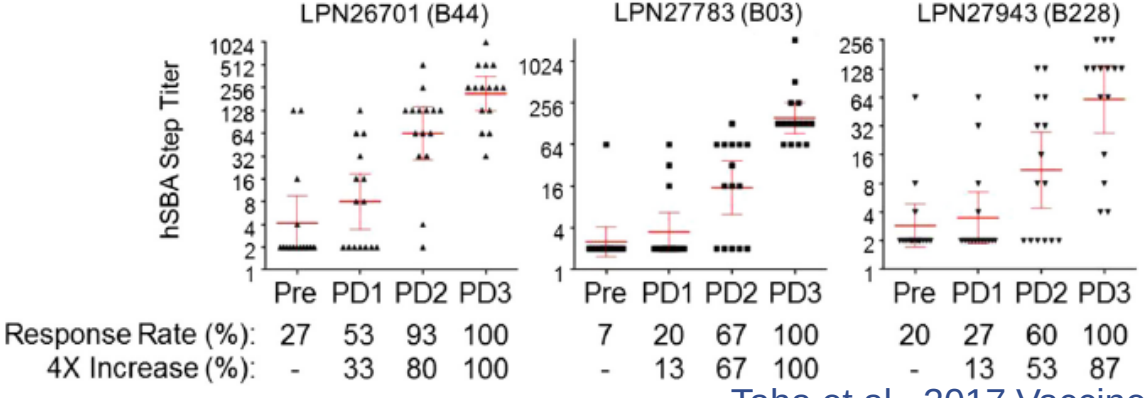
Eight weeks after the second dose of the 4CMenB vaccine was administered, there was no evidence of an hSBA response against the outbreak strain in 33.9%

Basta et al., 2016, NEJM

SBA of sera from adolescents vaccinated with bivalent rLP2086: Isolates from outbreaks







Taha et al., 2017 Vaccine

Effect of 4CMenB vaccine on meningococcal carriage

Autumn 2010; 2954 participants aged 18–24 years
987 control group ; carriage rate 31%
979 4CMenB group ; carriage rate 33%
988 MenACWY-CRM group; carriage rate 34%

carriage prevalence compared to control

	Odds ratio (95% CI)	Carriage reduction, (95% CI)
All NmB	**0·8 (0·6–1·1)**	**15.6% (-11·0 to 35·9)**
Disease associated MenB	**0·9 (0·7–1·2)**	**12·6% (-15 to 34·1)**
BCWY	**0·7 (0·6–0·9)**	**26·6% (10·5 to 39·9)**
CWY	**0·7 (0·5–0·9)**	**29·6% (8·1 to 46·0)**

Read et al., 2014, The Lancet

Impact on non-B isolates

Could the multicomponent meningococcal serogroup B vaccine (4CMenB) control *Neisseria meningitidis* capsular group X outbreaks in Africa?

Eva Hong[a], Marzia Monica Giuliani[b], Ala-Eddine Deghmane[a], Maurizio Comanducci[b], Brunella Brunelli[b], Peter Dull[b], Mariagrazia Pizza[b], Muhamed-Kheir Taha[a,*]

Vaccine 31 (2013) 1113–1116

Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent *Neisseria meningitidis* W Strain, England

Shamez N. Ladhani, Marzia Monica Giuliani, Alessia Biolchi, Mariagrazia Pizza, Kazim Beebeejaun, Jay Lucidarme, Jamie Findlow, Mary E. Ramsay, Ray Borrow

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 2, February 2016

4CMenB: UK

Meningitis B vaccine to be introduced in UK after U turn on its cost effectiveness

BMJ 2014;348:g2327 doi: 10.1136/bmj.g2327 (Published 24 March 2014)

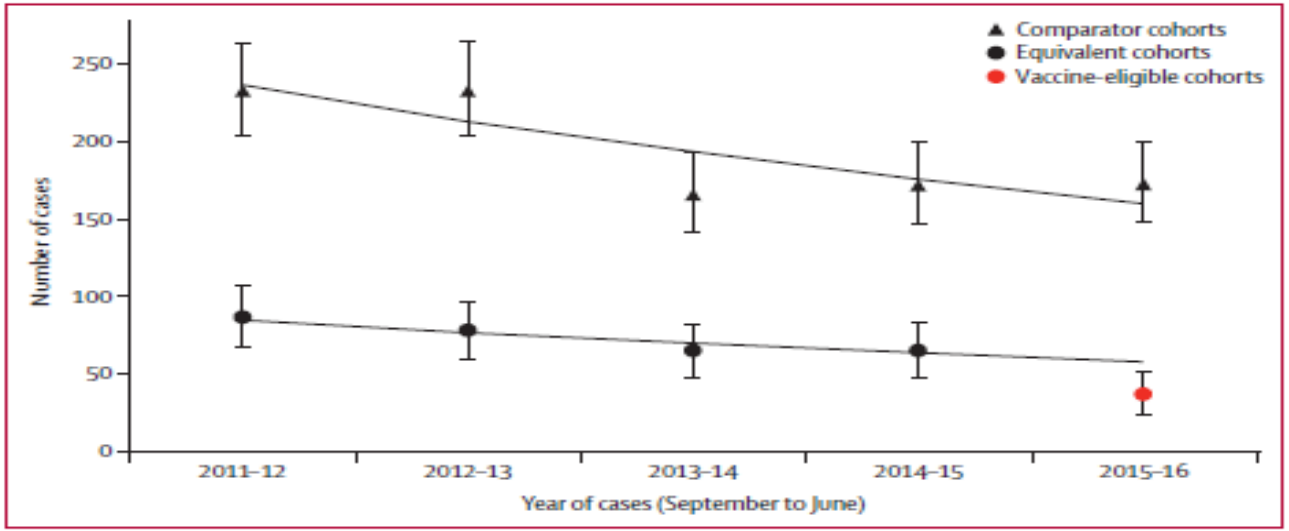
Jacqui Wise

•An abbreviated schedule was likely to be sufficiently immunogenic →cost-effectiveness could be improved by using a three-dose (2+1) schedule (2, 4, and 12 months).

- Provision of prophylactic paracetamol at the time of or shortly after vaccination, with a further 2 doses every 4-6 hours thereafter
- Reduce likelihood or intensity of fever without diminishing immune response

Impact of 4CMenB on MenB IMD in the United Kingdom

- **September, 2015 2 doses at 2 months and 4 months + an opportunistic catch-up for 3 month and 4 month olds.**
- **Coverage: 95·5% for one dose and 88·6% for two doses**
- **Cases diagnosed between Sept 1, 2015, and June 30, 2016**



vaccine effectiveness 94·2%

Ladhani et al., 2016, The Lancet

SURVEILLANCE AND OUTBREAK REPORTS www.eurosurveillance.org

A prolonged outbreak of invasive meningococcal disease in an extended Irish Traveller family across three Health Service Executive (HSE) areas in Ireland, 2010 to 2013

L O'Connor (lois_oconnor@hotmail.com)[1], M Ward[1], D Bennett[2], R Mulhall[2], P O'Lorcain[3], R Cunney[2,3], R McDermott[1], E Neville[4], J Heslin[4], R FitzGerald[5], K Meyler[2], M Conlon[1], A Clarke[1], B Corcoran[6], G Fitzpatrick[1], B O'Connor[4], P Flanagan[3], D O'Flanagan[3], S Cotter[3]

Article submitted on 09 July 2014 / published on 28 May 2015

- March 2010-November 2013 eight laboratory-confirmed cases of serogroup B, invasive meningococcal disease (IMD) were identified in an extended Irish Traveller family

- B:P1.7-2,4:cc41/44

- 4CMenB vaccine was administered to family members aged 2months to 23 years

4CMenB: France

Haut Conseil de la santé publique

AVIS

relatif à l'utilisation du vaccin Bexsero®
(Novartis Vaccines and Diagnostics)

25 octobre 2013

- **At risk subjects**
- **Outbreak control**

(http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=386).

The low/lack of impact, on the acquisition of meningococcal carriage.

- The decline in antibody production after vaccination.
- The reactogenicity (especially fever) of the vaccine when co-administered with other early childhood vaccines.
- Unfavorable cost-effectiveness.

Use of 4CMenB in Beaujolais Region in France

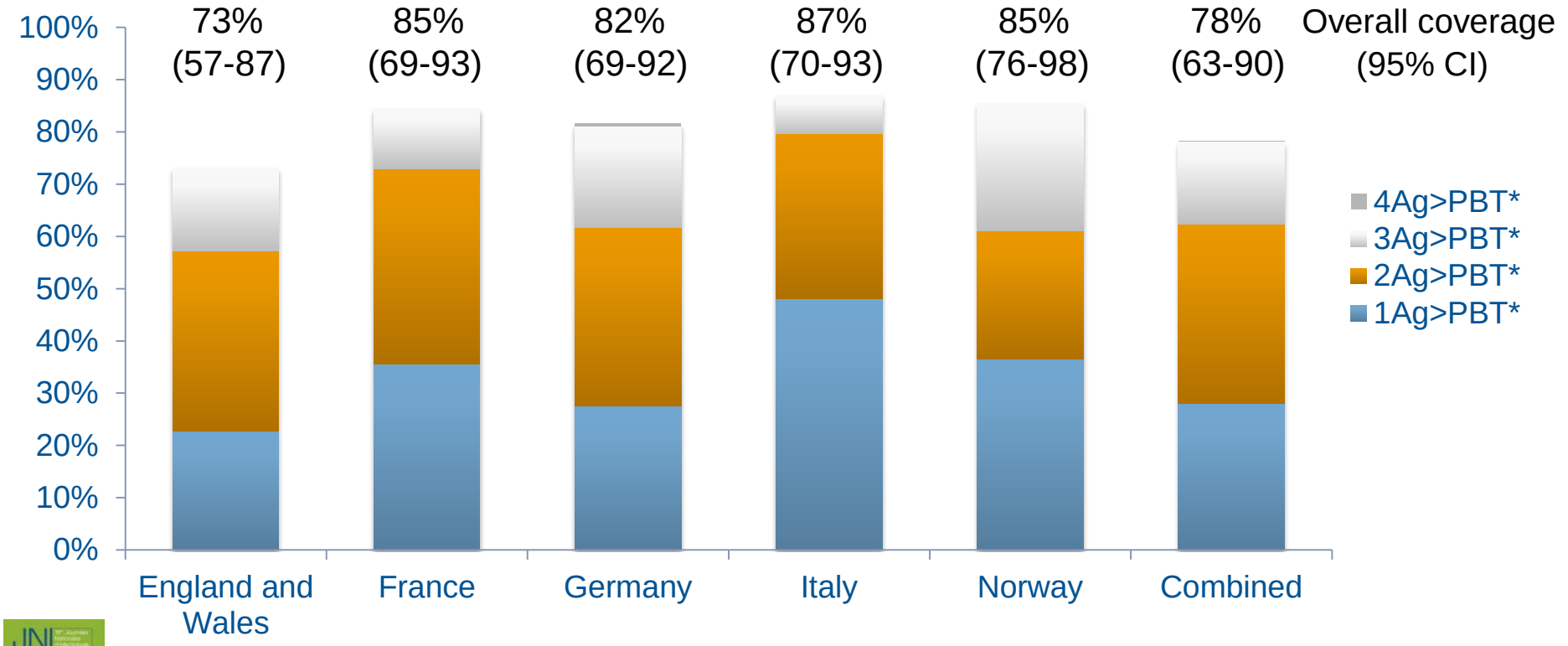
Background	• 4 cases of MenB IMD reported in February/March 2016 • Serotype: B:P1.19.15:F4-28:cc32
Vaccination	• 2 doses of 4CMenB vaccination • Recommended for all persons aged 2 months to 24 years (4338 subjects) in 12 municipalities in affected region
Outcomes	• No new cases reported • Alert lifted August 2016, surveillance continues

Data SPF, ARS and NRCM

Conclusions

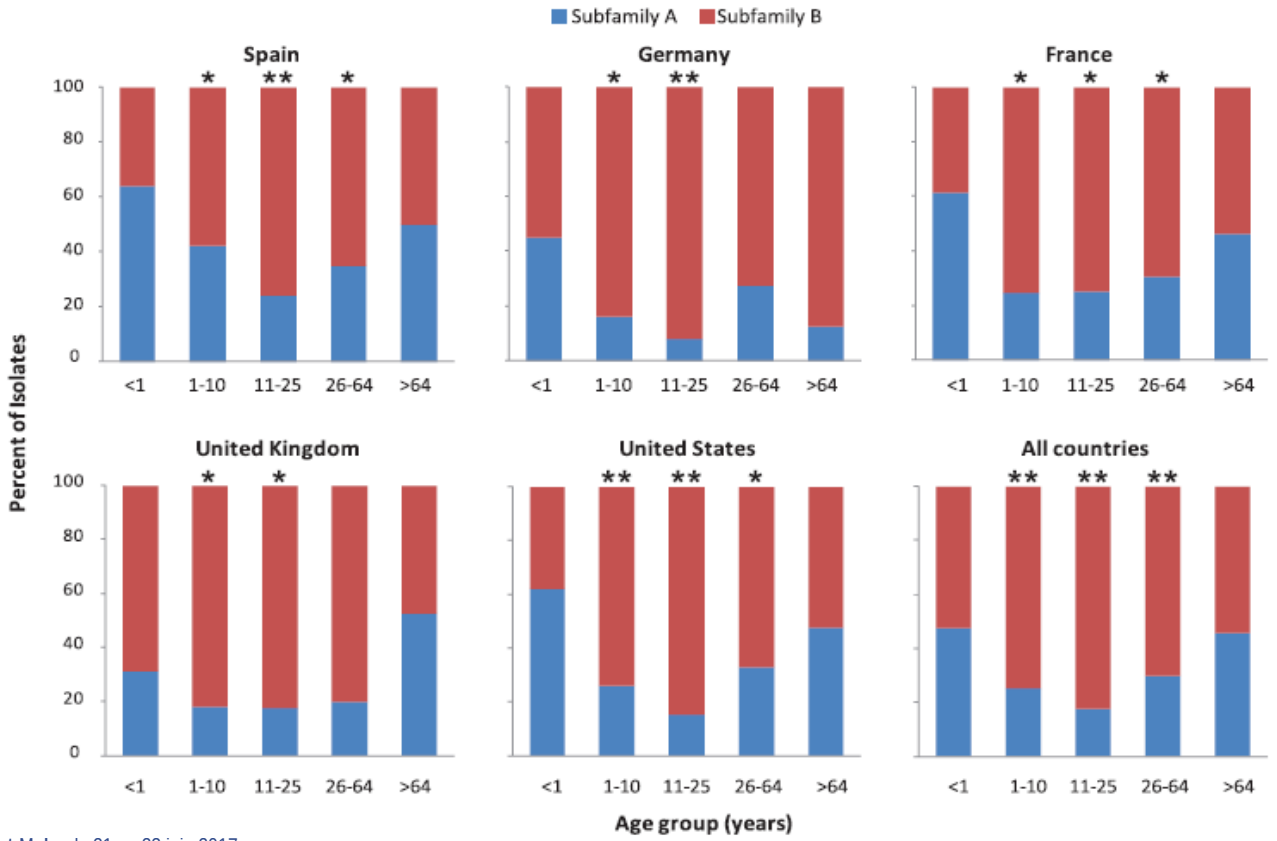
- **Vaccines targeting MenB can be developed on the basis of sub-capsular structures.**
- **Re-evaluate the impact on carriage acquisition.**
- **Explore the “universality” of these recombinant vaccines.**
- **Needs for boosters? When and frequencies?**
- **Vaccine strategies should consider:**
- **Local epidemiology & coverage of isolates**
- **Cost-effectiveness (criteria?)**
- **direct protection and herd immunity**

MATS predicted coverage of MenB isolates by 4CMenB vaccine



Vogel *et al.*, 2013 Lancet Infect Dis

Difference in epidemiology of fHBP subfamilies in different age groups



Hoiseth et al., 2013 Pediatr Infect Dis J

Outbreak isolates: France

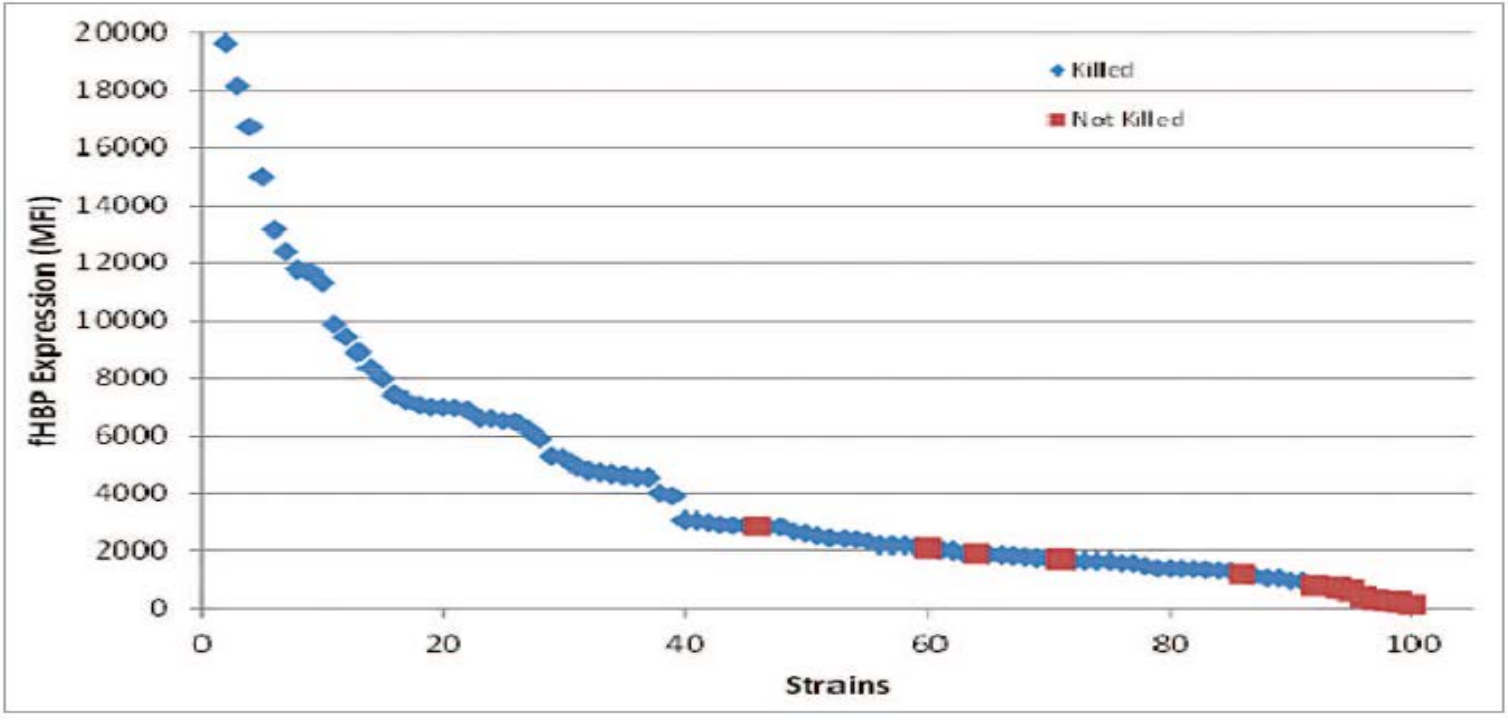
Neisseria meningitidis serogroup B outbreak strains from France: genotype and FHbp expression.

Strain ID	FHbp variant	Amino acid sequence identity to bivalent rLP2086 vaccine antigen, %	MLST	Clonal complex	PorA VR1/VR2	PorB	FHbp expression, MFI	FHbp median surface expression level[a] (25th–75th percentile), MFI
LNP26366	A22	88.9	1163	269	22/9	3–25	4214	2519 (1769–3425)
LNP26701	B44	91.6	269	269	19–1/15–11	3–25	8305	14,378 (11,047–18,848)
LNP27783	B03	90.8	UA	41/44	7–2/13–2	3–71	1309	2907 (1815–3948)
LNP27899	B24	86.2	32	32	7/16	3–324	4747	7518 (5583–10,229)
LNP27943	B228	90.8	4954	UA	19/15–1	3–14	4114	None
LNP28009	B24	86.2	32	32	7–2/16	3–36	3425	7518 (5583–10,229)

Taha et al., 2017 Vaccine

fHBP surface expression correlates with strain susceptibility in the SBA

Invasive MnB strains (n = 100) tested using the MEASURE assay



Zlotnik et al., 2014 Human Vaccines

Persistence of immune response of 4CMenB in laboratory workers

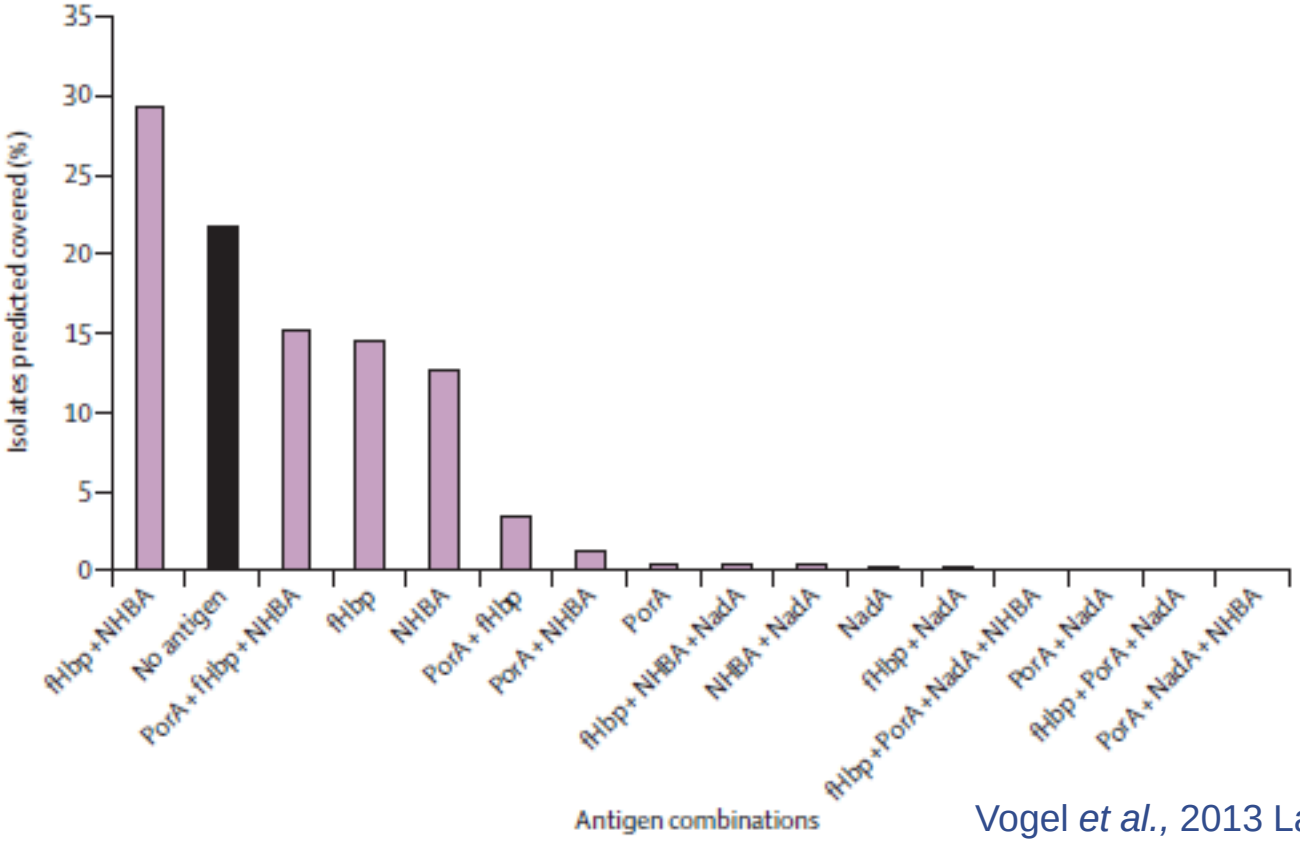
Individual serum				
	H44/76	NGH38	5/99	LNP24349
hSBA titer range (GMT)				
Baseline (n=8)	2-16 (3.084)	2-32 (5.187)	2-8 (3.364)	2-8 (3.668)
6 weeks after dose 2 (n=8)	16-256 (69.79)	2-256 (32.0)	256 (256)	16-128 (38.05)
pvalue (reference baseline)	0.0078	0.0156	0.0078	0.0078
1 year after dose 2 (n=7)	2-16 (4.0)	2-16 (4.876)	2-256 (35.33)	2-8 (4.0)
pvalue (reference 6w after dose 2)	0.0156	0.0313	0.0625	0.0156
number of people with ≥4 (%)				
Baseline (n=8)	3 (38%)	4 (50%)	4 (50%)	4 (50%)
After dose 2 (n=8)	8 (100%)	7 (88%)	8 (100%)	8 (100%)
1 year after dose 2 (n=7)	4 (57%)	4 (57%)	6 (86%)	5 (71%)

Pooled serum						
	LNP27783	LNP27896	LNP27899	LNP27931	LNP27942	LNP27943
hSBA titer with Bexpool*						
pre-vaccination	2	2	2	4	8	8
post-vaccination	8	16	8	16	32	32

* pool of sera from patients who received 2 doses schedule

Hong et al., 2016 Hum Vaccin Immunother

Percentages of isolates covered by specific antigen combinations



Vogel *et al.*, 2013 Lancet Infect Dis

Immunogenicity against non-B isolates

Isolate	Positive control (rabbit polyclonal)	Adults sera		Adolescents sera		Infant sera		
	Anti MenX	PI	Post 3rd	PI	Post 2nd	PI	Post 3rd	Post 4th
LNP13407	>4096	4	>128	<4	128	<4	32	64
LNP14354	2048	16	>128	4	>128	<4	>64	>64
LNP14355	2048	8	64	4	>128	<4	>64	>64
LNP14964	2048	<4	>128	<4	>128	<4	32	>64
LNP15038	1024	16	>128	<4	>128	<4	>64	>64
LNP15075	128	4	128	<4	32	<4	16	16
LNP15877	2048	4	>128	8	>128	<4	>64	>64
LNP23557	2048	<4	128	<4	64	<4	16	32
LNP23558	>4096	16	>128	<4	>128	<4	16	64
LNP24196	128	<4	4	<4	4	<4	<4	<4
LNP24287	1024	<4	4	<4	8	<4	<4	<4

Table. Bactericidal antibody titers in pooled serum samples from infants vaccinated with Bexsero and adolescents immunized with Menveo against 6 invasive clinical *Neisseria meningitidis* serogroup W isolates in England and Wales, UK, during 2011–2012*

Isolate	Adolescents receiving Menveo		Infants receiving Bexsero				
	Positive control†		Negative control‡	Pool 1§	Pool 2¶	Pool 3#	Pool 4**
	Before	After					
M11–240417	<16	256	<2	64	128	>128	>128
M11–240427	<16	128	<2	32	32	64	64
M11–240802	<16	512	<2	32	>64	>64	>64
M12–240016	<16	256	<2	32	32	64	128
M11–240798	<16	512	<2	>64	>64	>64	>64
M12–240754	<16	256	<2	64	64	>64	>64

Hong et al., 2013 Vaccine
Ladhani et al., 2016 Emrg Infect Dis

MATS underestimates 4CMenB vaccine strain coverage

- MATS predictions and hSBA results were significantly associated (P = 0.022).

- MATS predicted coverage of 70% (95% CI, 55–85%) was largely confirmed by 88% killing in the hSBA (95% CI, 72–95%). MATS had 78% accuracy and 96% positive predictive value against hSBA.

Contingency table for MATS coverage vs. hSBA coverage comparison.

MATS	hSBA[a]	
	Positive	Negative
Positive	27	1
Negative	8	4

Frosi et al., 2013 Vaccine