Ce que fait … et ne fait pas le vaccin méningococcique B

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JOURNEE DU GROUPE VACCINATION PREVENTION DE LA SPILF
Vendredi 12 Mai 2023

Liens d'intérêt

- **Travaux scientifiques à l'Institut Pasteur en collaboration et financement par GSK, Pfizer et Sanofi Pasteur.**
- **Conférences et advisory Boards pour GSK, Pfizer et Sanofi Pasteur.**
- **Financement des travaux de recherche par la Fondation TOTAL**
- **Brevet Bexsero *Neisseria meningitidis* X (Novartis/GSK).**
- **Brevets des tests rapides de diagnostic de *Neisseria meningitidis.***
- **Crédit institutionnel pour réaliser des formations internationales sur la méningite (Pfizer).**
- **Président de l'European Meningococcal and Haemophilus Disease Society (EMGM).**
- **Membre du Global Meningococcal Initiative (GMI)**
- **Membre du Task Force de l'OMS pour « Defeating meningitis by 2030).**
- **Pas de rémunération personnelle pour ces acticitvtés**

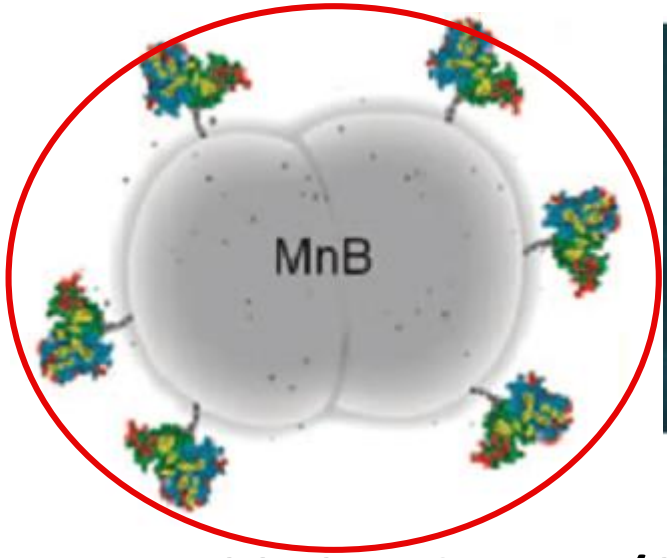
Current vaccines against meningococci

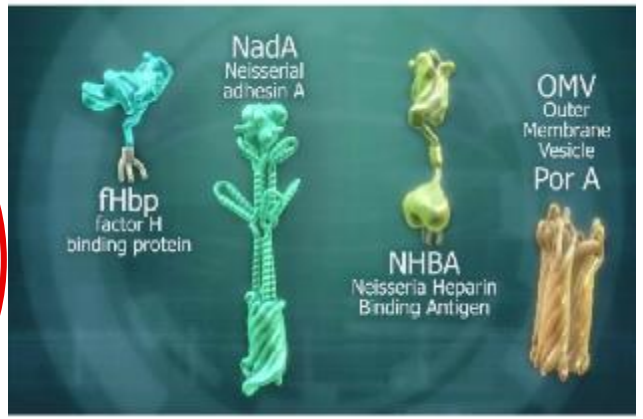
Capsular polysaccharide-based conjugate vaccines:

Monovalent: A ou C

Tetravalent ACWY

Pentavalents ACWYX and (underdevelopment)





2013: 4CMenB (2 months)

50 µg each
25 µg of OMV NZ98/254,
1.5 of mg aluminum hydroxide

Recommandations en 2013 et en 2021

2017: Bivalent MenB-FHbp (10 years old)

60 µg of each fHBP variant (lipidated)
0.25 mg aluminum phosphate

Recommandations en 2021

Pentavalents ABCWY (underdevelopment)

Conjugate capsular polysaccharide-based vaccines

- Impact on carriage
- Persistence of the immune response

IMD: The correlate of protection

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

Goldschneider et al., 1969 J Exp Med

Three values are considered for vaccine licensure:

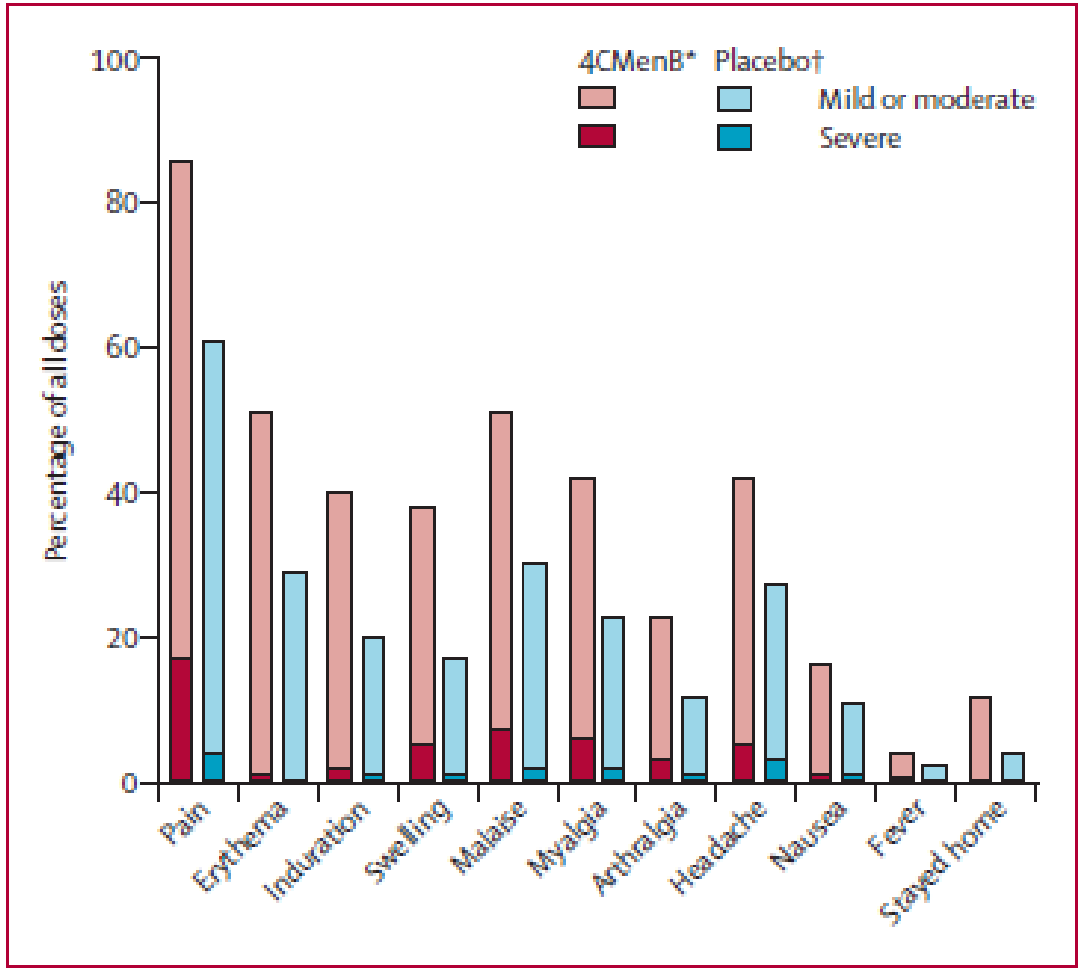
% of subjects with a titer ≥4

% of subjects with a four-fold increase in bactericidal titer

The geometric mean of titers of all subjects

4CMenB vaccine

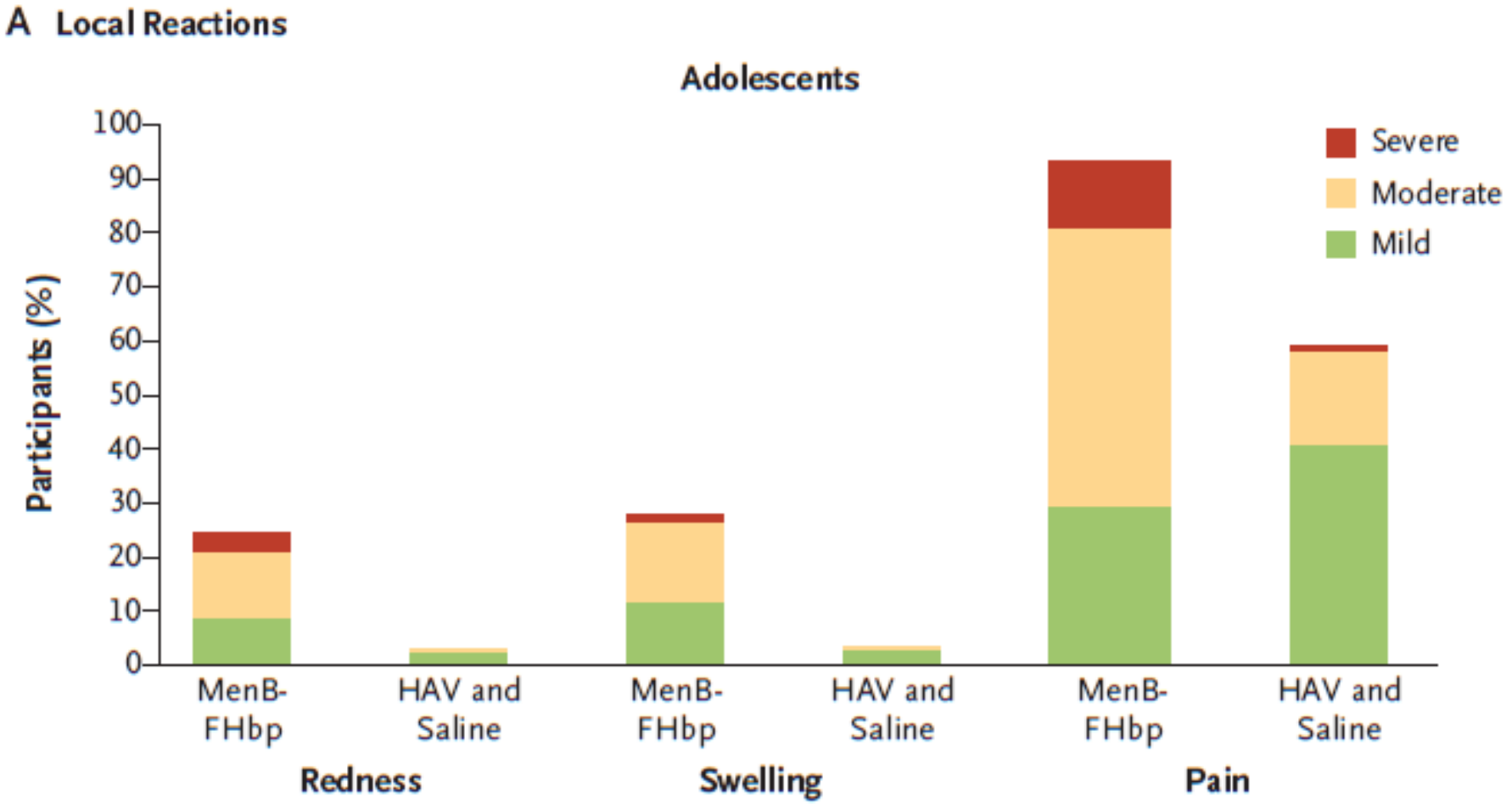
Healthy adolescents (11 to 17 years) Chile
2 doses or three doses. Follow-Up to 7 days
phase 2b/3, randomized, observer-blind study June 2008-December 2010:



90%-91%
≥1 AE

Santolaya et al., 2012 Lancet Infect Dis

Injection-Site Reactions Occurring after any Dose of the bivalent MenB-FHbp



Ostergaard et al., 2017 NEJM

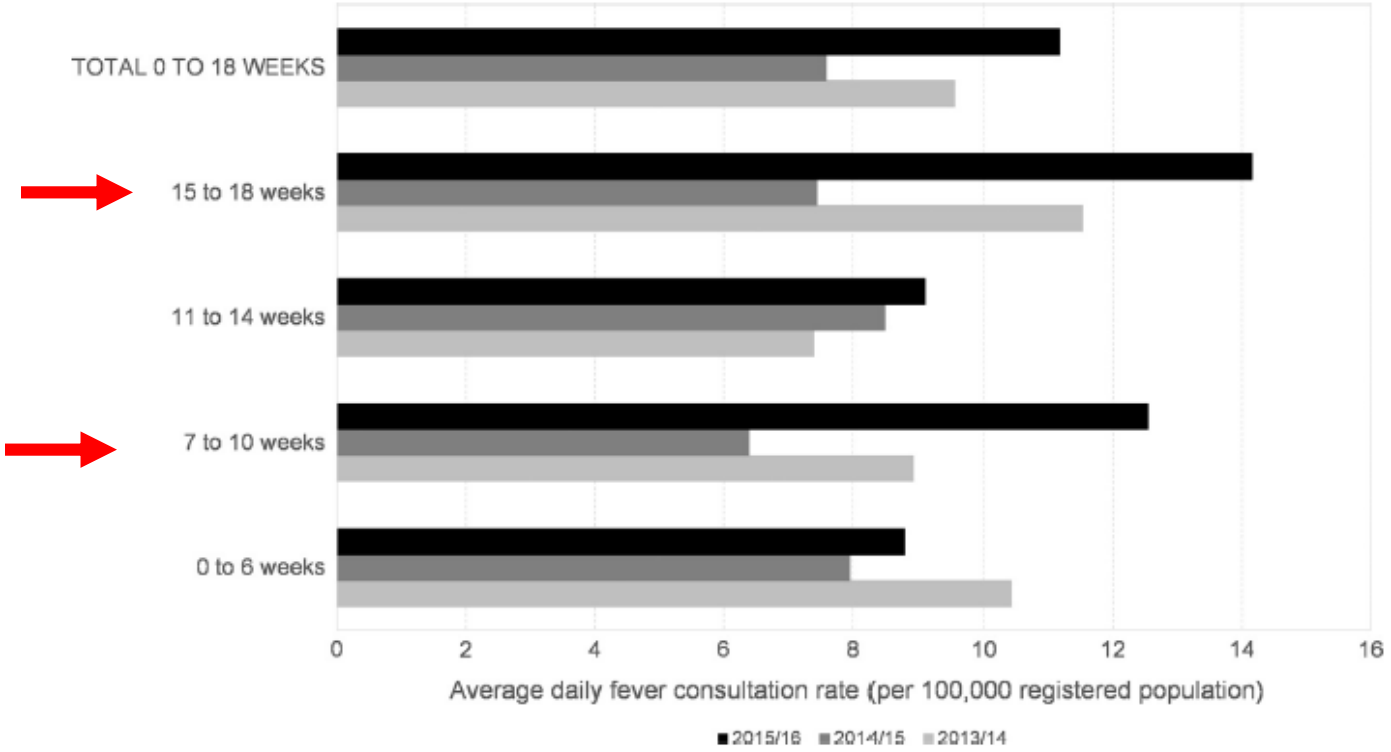
Safety of 4CMenB in routine infant immunisation in the UK

Fever consultations were identified using Read (CTV3) codes, a clinical coding system used by UK GPs

Twelve month periods (September to August) 2013-2015

Second dose
1.5-fold increase
(IRR 1.47,
95% CI 1.17 to 1.86,
p < .05)

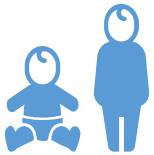
First dose
1.6-fold increase
(IRR 1.58,
95% CI 1.22 to 2.05,
p < .05)

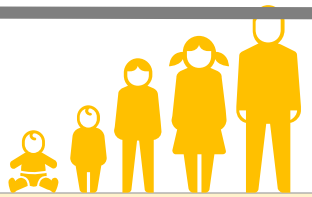


A small but significant difference in all-cause fever consultation rates in vaccine eligible infants who would have received 4CMenB with other vaccines.

Harcourt et al., Vaccine 2018

Impacts of the 4CMenB in infants





England[1]	Italy[2]	Portugal[3]
Infant	Infant	Infant+ ≥ 1y (2 doses)
80% vaccine effectiveness	**>90% vaccine effectiveness**	**79% vaccine effectiveness**
1 case averted every 4 days		
Three doses VE: 80.1% (95% CI: 70.3, 86.7%)	Tuscany VE: 93.6% (95% CI: 55.4, 99.1%) Veneto VE 91% (95% CI: 59.9, 97.9%)	VE: 79% (95% CI: 45 to 92%) from case–control study in individuals aged 2 months to 18 years

1. Ladhani SN *et al. N Engl J Med* 2020;382:309–317; 2. Azzari C *et al. Vaccines* 2020;8:E469; 3. Rodrigues FMP *et al. JAMA* 2020;324:2187–2194

Vaccine effectiveness of Bexsero against MenB disease, in England between 1st Sept 2015 and 30th June 2016 (10 months)

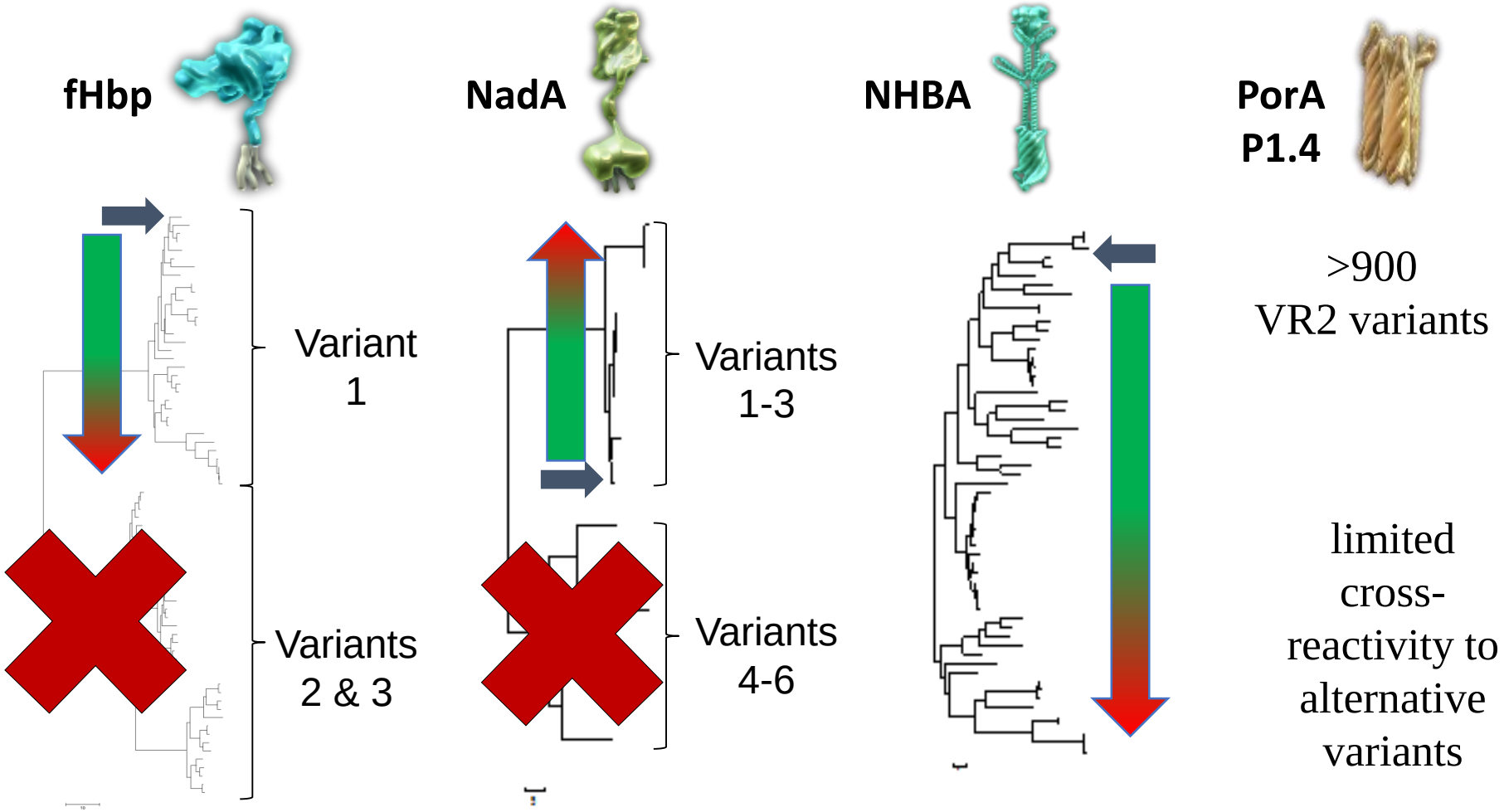
Doses	Cases in vaccinated / total cases	Average matched vaccine coverage	VE (95 %CI)
2+0	9/13 (69%)	92.9%	82.9% (24 % to 95.2%)

- **Based on assumption that 100% MenB cases are preventable by Bexsero.**
- **If re-calculate on basis that 88% of MenB cases preventable; VE = ~94%**

- VE calculated using the screening method.
- Cases in infants born on or after 1st May 2015 with MenB disease diagnosed between 01/09/15 and 30/06/16.
- Dose discounted if disease diagnosed <14 days after vaccination.

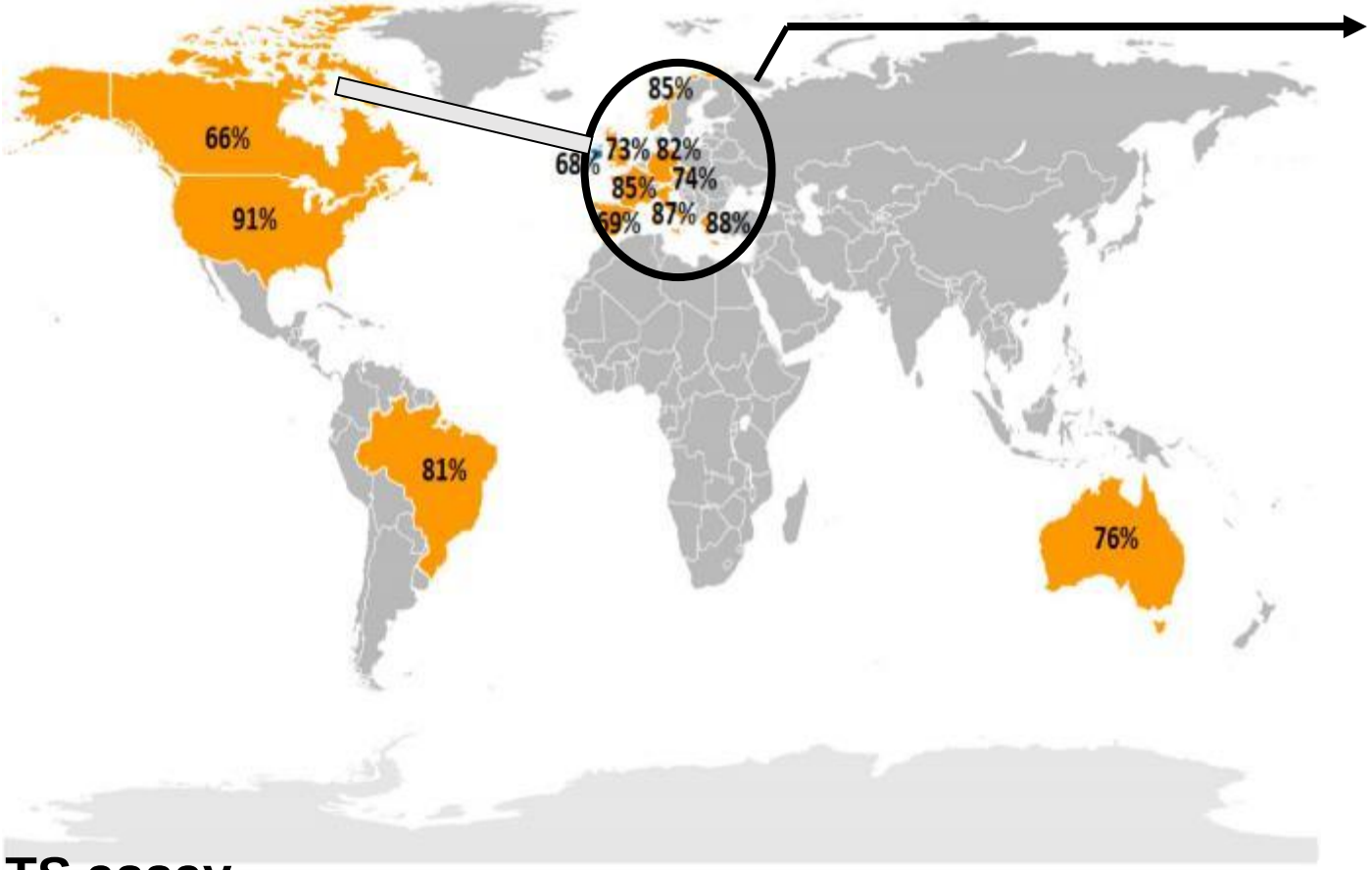
Parikh SR et al. Lancet 2016; 388:2775-82.

4CMenB: Antigen diversity and cross-reactivity of induced antibody



Vogel U *et al., Lancet Infect Dis* 2013;13:416-25,
Slide courtesy Professor Ray Borrow .

Predicted Coverage of 4CMenB Vaccine



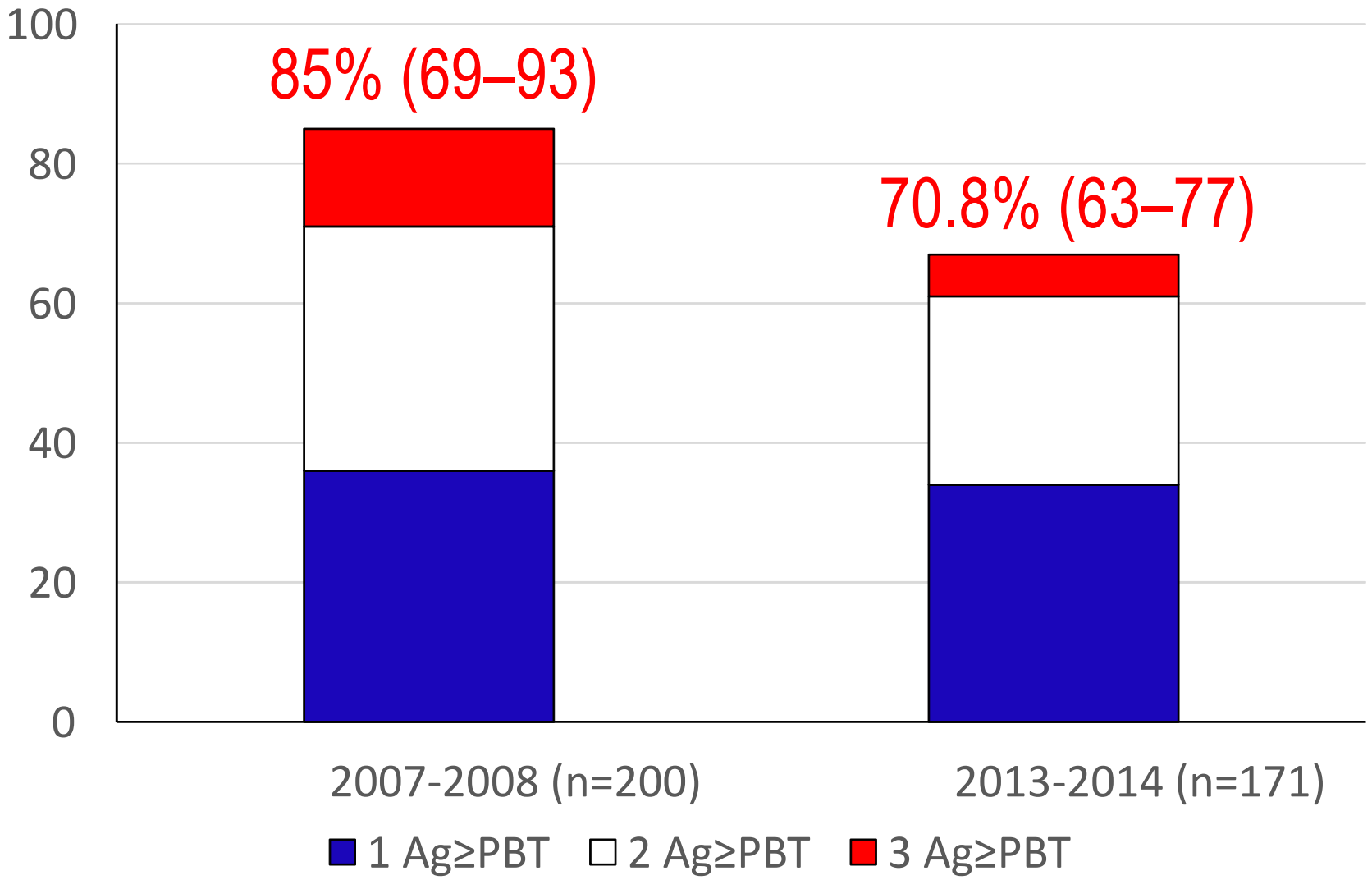
	Predicted coverage (95% CI)
England & Wales	73% (57–87)
France	85% (69–93)
Germany	82% (69–92)
Italy	87% (70–93)
Norway	85% (76–98)
Czech Republic	74% (58–87)
Spain	69% (48–85)
Greece	89% (64-99)
Poland	84% (79-91)
Combined*	78% (63–90)

MATS assay
Meningococcal Antigen Typing System

*Excludes Czech Republic, Greece and Poland and Spain

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

Evolution of coverage prediction



Vogel *et al.*, 2013, *Lancet Infect Dis*; Hong et al., Hum Vacc Immunother 2021

Evolution of strain coverage by 4CMenB vaccine in France

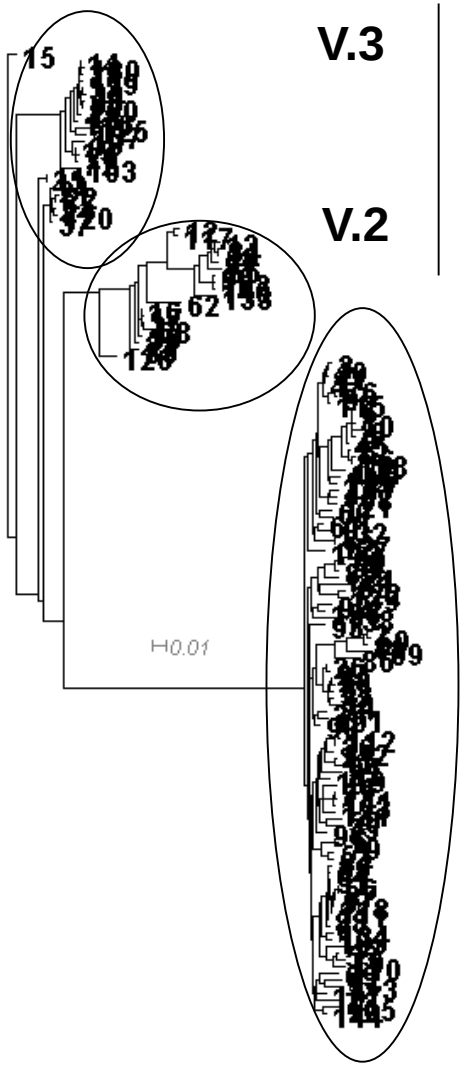
		2013-2014		2018-2019		
Age band	Number	gMATS	MenDeVAR	Number	gMATS	MenDeVAR
		%Coverge	%Coverge		%Coverge	%Coverge
<1y	35	61	59	34	69	62
1-4y	26	77	71	22	68	55
5-9y	6	100	92	6	75	58
10-14y	9	94	89	6	83	58
15-19y	28	79	71	10	100	75
20-24y	12	96	83	8	81	63
≥ 25y	52	76	73	49	63	51
Total	168	79	72	135	71	57

85% (69–93)

70.8% (63–77)

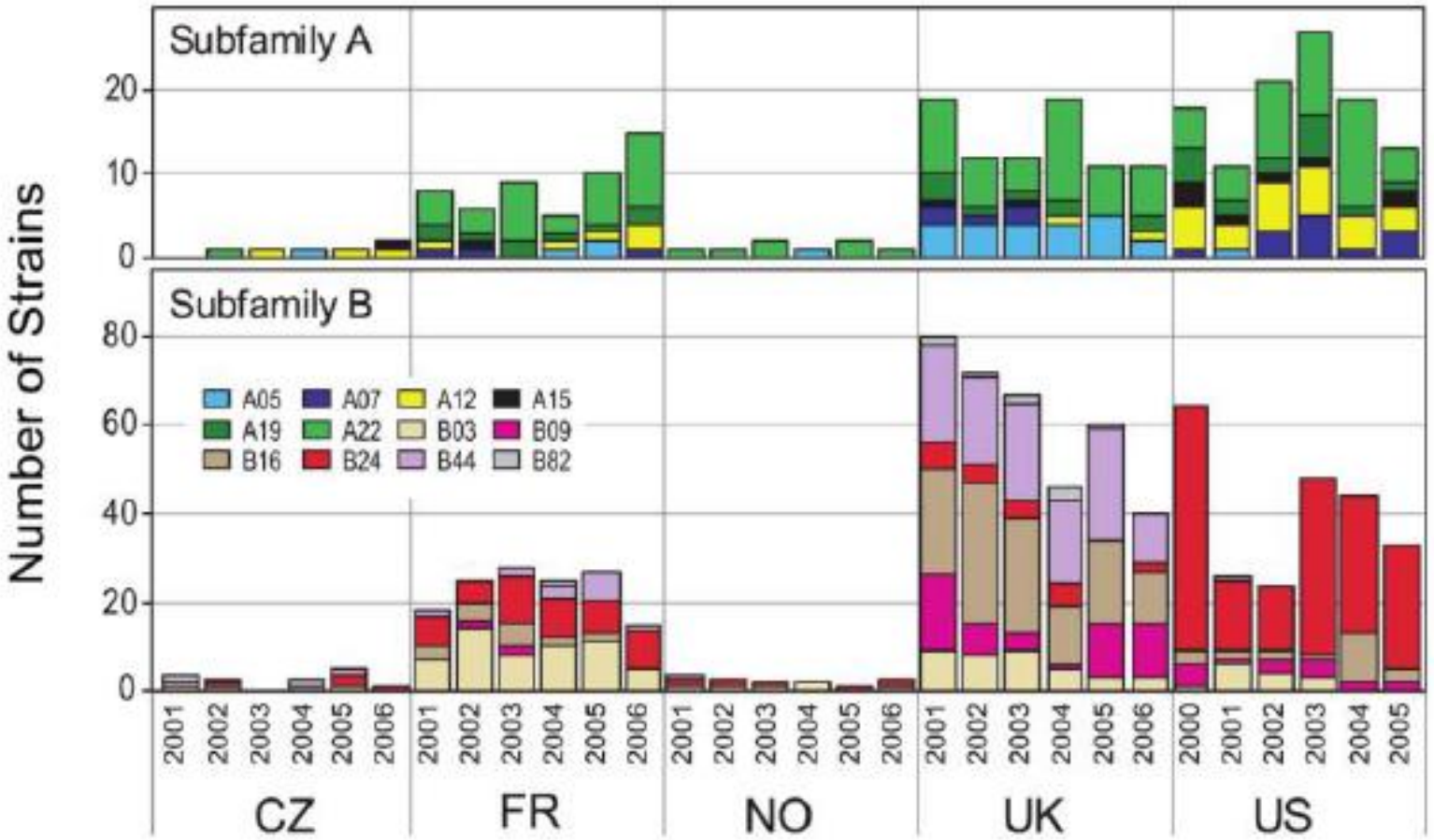
Hong et al., Hum Vacc Immunother accepted Nov2021

Diversity of fHbp



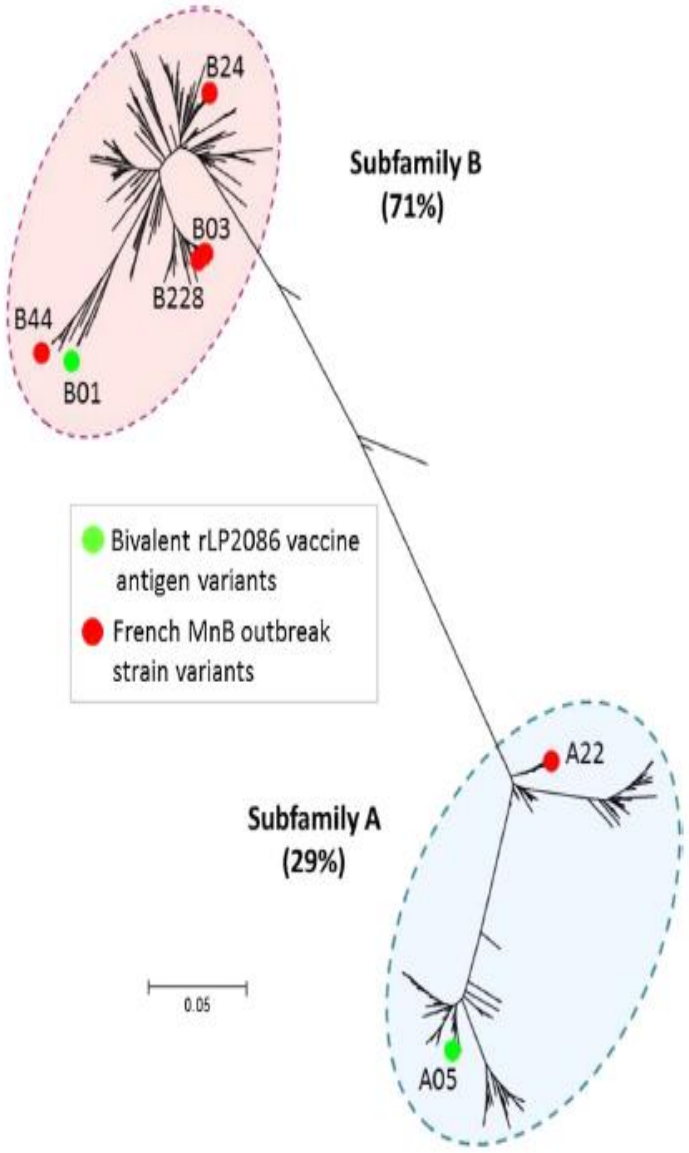
Subfamily A

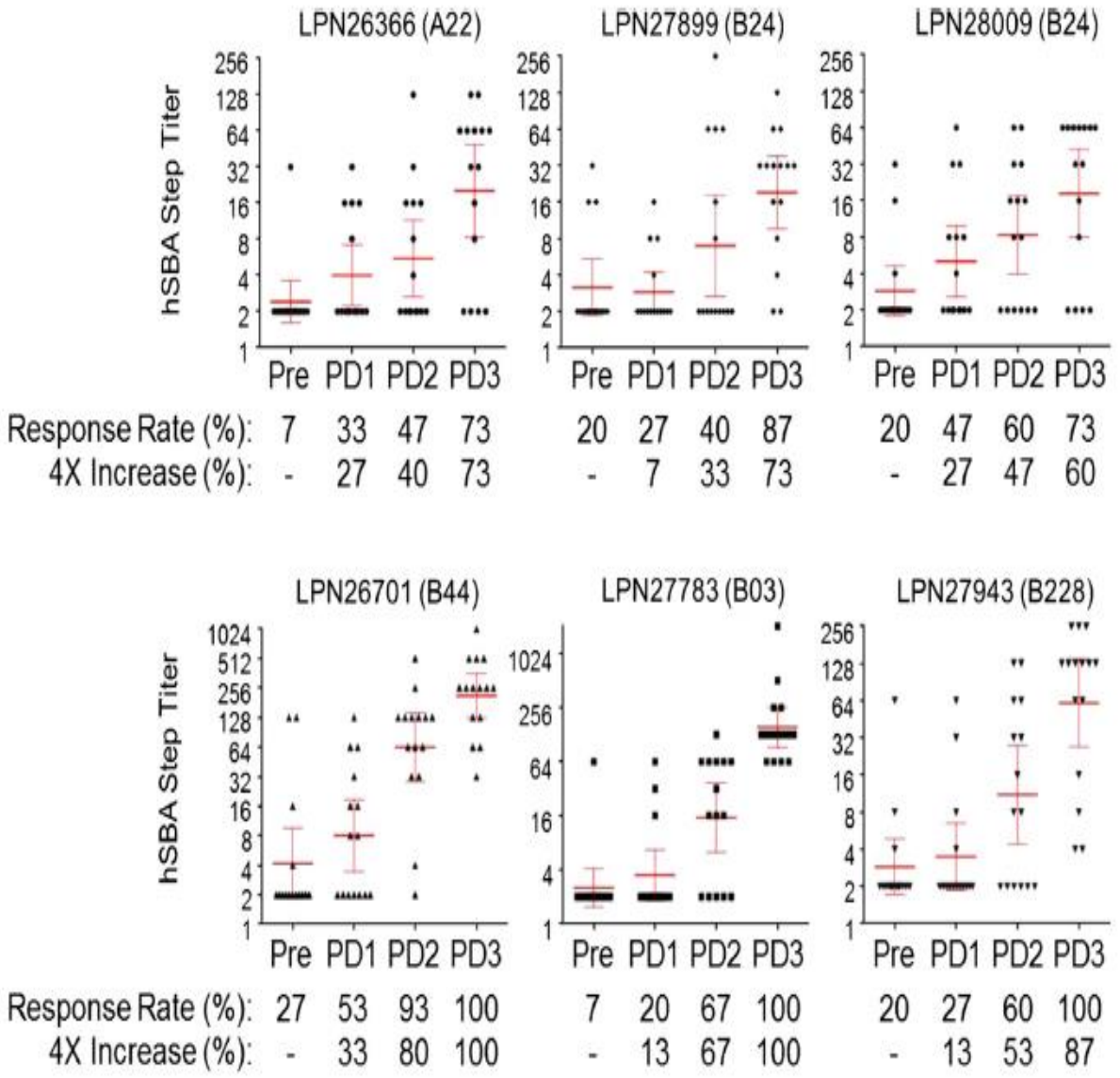
Subfamily B



Murphy et al., 2009 JID; Hoiseth et al., 2013PIDJ; Vogel et al., 2013 Lancet Infect Dis

SBA of sera from adolescents vaccinated with MenB-FHbp vaccine: outbreaks isolates

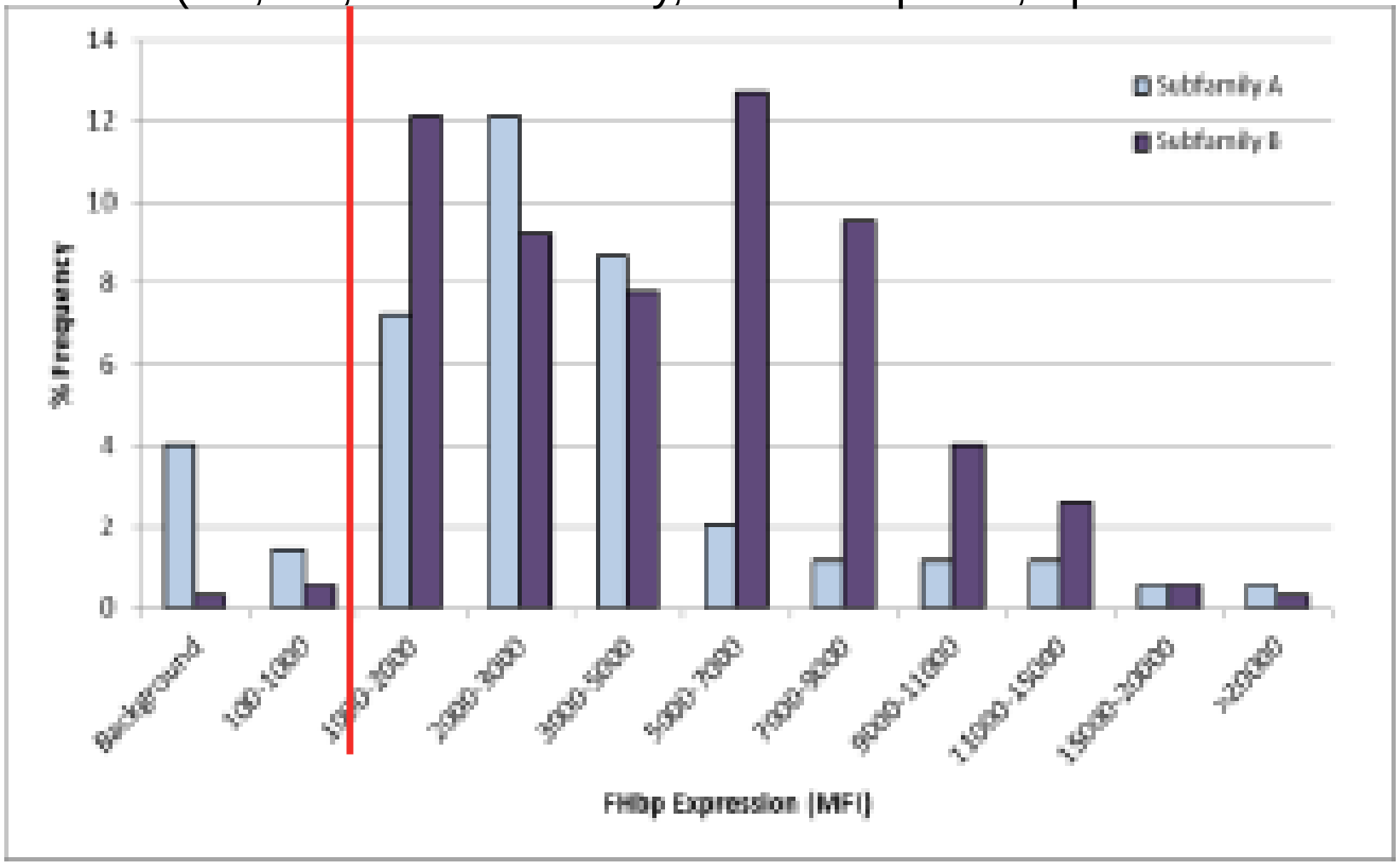




Taha et al., 2017 Vaccine

Predicted Coverage by the bivalent MenB-FHbp Vaccine

MEASURE (Meningococcal Antigen Surface Expression) assay
1923 isolates (US, UK, France Norway, Czech Republic, Spain and Germany)



91% predicted coverage

McNeil et al., 2018 MBio

Meningococcal carriage: the dilemma of 4CMenB vaccine

www.thelancet.com Vol 384 December 13, 2014

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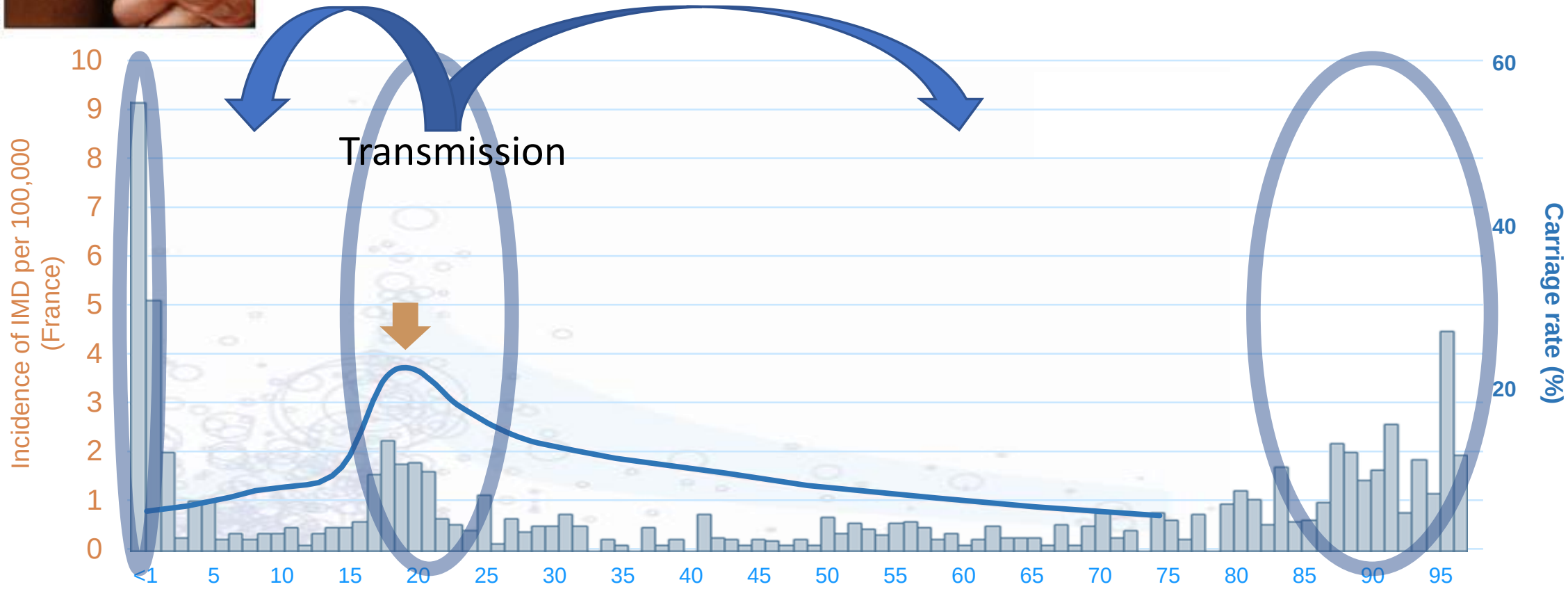


https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-a-prevention-vaccinale/infections-invasives-a-meningocoque/documents/bulletin-national2/les-infections-invasives-a-meningocoque-en-france-en-2019 [

Christensen H, et al., Lancet Infect Dis. 2010;10(12):853-861.

No effect of the 4CMenB vaccine on meningococcal carriage

Outcome	Vaccination Group (N=12,746)	Control Group (N=11,523)	Odds Ratio (95% CI)†
	no. (%)		
Carriage of disease-causing genogroup	326 (2.55)	291 (2.52)	1.02 (0.80–1.31)‡
Carriage of any *N. meningitidis*	547 (4.29)	561 (4.87)	0.85 (0.70–1.04)
Carriage of genogroup B	164 (1.29)	135 (1.18)	1.10 (0.81–1.47)
Carriage of genogroup Y	117 (0.92)	131 (1.13)	0.81 (0.56–1.18)
Carriage of genogroup W§	17 (0.16)	18 (0.18)	0.89 (0.43–1.85)
Carriage of genogroup C§	12 (0.11)	7 (0.07)	1.87 (0.63–5.55)
Carriage of genogroup X§	8 (0.07)	1 (0.01)	7.59 (0.98–58.83)¶
Acquisition of any *N. meningitidis*	430 (3.38)	427 (3.70)	0.91 (0.73–1.13)
Acquisition of disease-causing genogroup	272 (2.13)	238 (2.07)	1.03 (0.79–1.34)

- April 2016-June 2017.
- 24,269 students (15-18 years).
- South Australia.

Marshall et al., 2020 NEJM

No effect of the 4CMenB vaccine on meningococcal carriage

	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)

Autumn 2010; 2954 participants aged 18- 24 years. UK

987 control group; carriage rate 31%

979 4CMenB group; carriage rate 33%

Read et al., 2014, The Lancet

Meningococcal carriage after bivalent MenB-FHbp vaccine Rhode Island, 2015

20%–24% of participants carried any meningococcal bacteria and 4% carried group B

- 71% remained noncarriers,
- 8% cleared carriage,
- 5% remained carriers,
- 7% acquired carriage.

Ten students acquired serogroup B carriage: 3 after 1 MenB-FHbp dose, 4 after 2 doses, and 3 after 3 doses.

➔ MenB-FHbp vaccine did not reduce meningococcal carriage or prevent serogroup B carriage acquisition

Soeters et al., 2017 CID

Impact on non-B isolates: 4CMenB

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

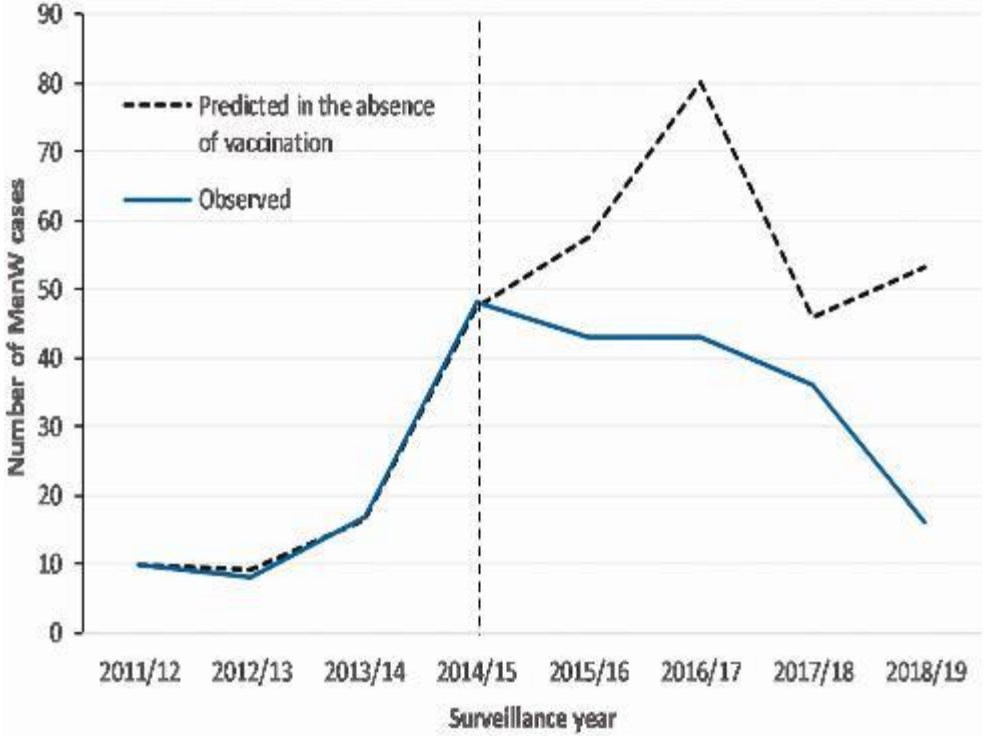
Shamez N. Ladhani, Marzia Monica Giuliani, Alessia Biolchi, Mariagrazia Pizza, Kazim Beebeejaun, Jay Lucidarme, Jamie Findlow, Mary E. Ramsay, Ray Borrow

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

Impacts of the 4CMenB infant immunization program on MenW disease

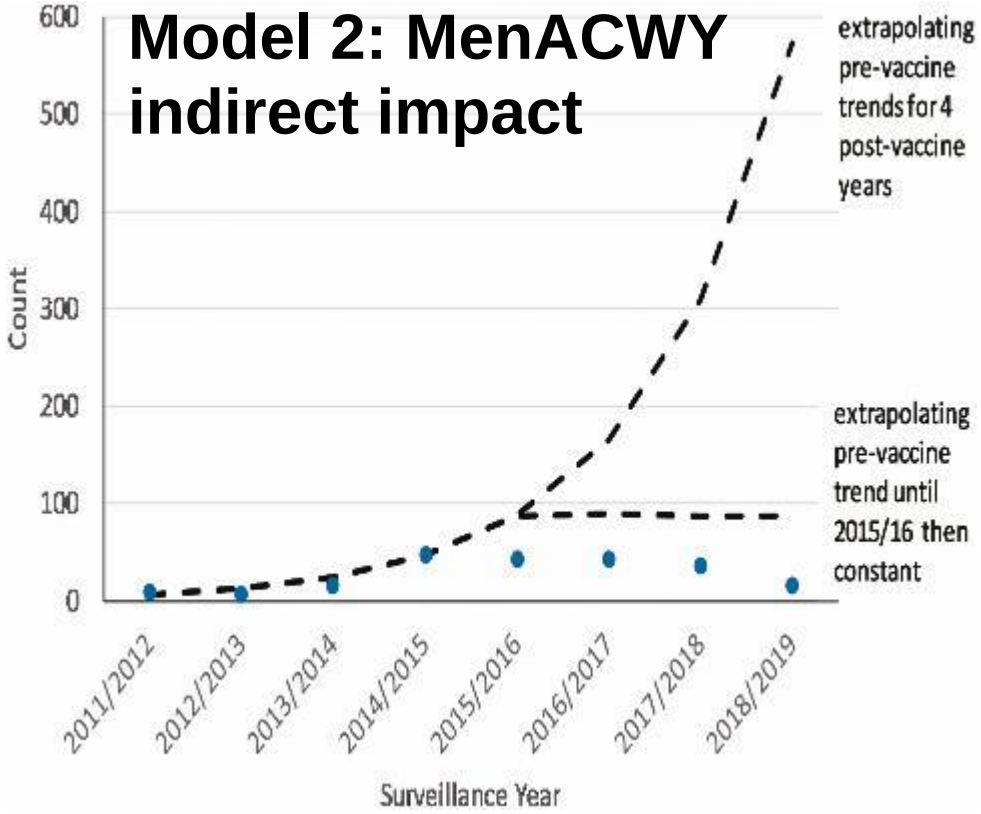
Data <5 year-old

Model 1: 4CMenB direct impact of on MenW



4CMenB directly prevented 98 cases

Model 2: MenACWY indirect impact



MenACWY program indirectly prevented an additional 114 (conservative) to 899 (extreme) cases over 4 years

Ladahani et al., Clinical Infectious Diseases 2021;73(7):e1661–8

Effectiveness of 4CMenB in Children (B and non-B)

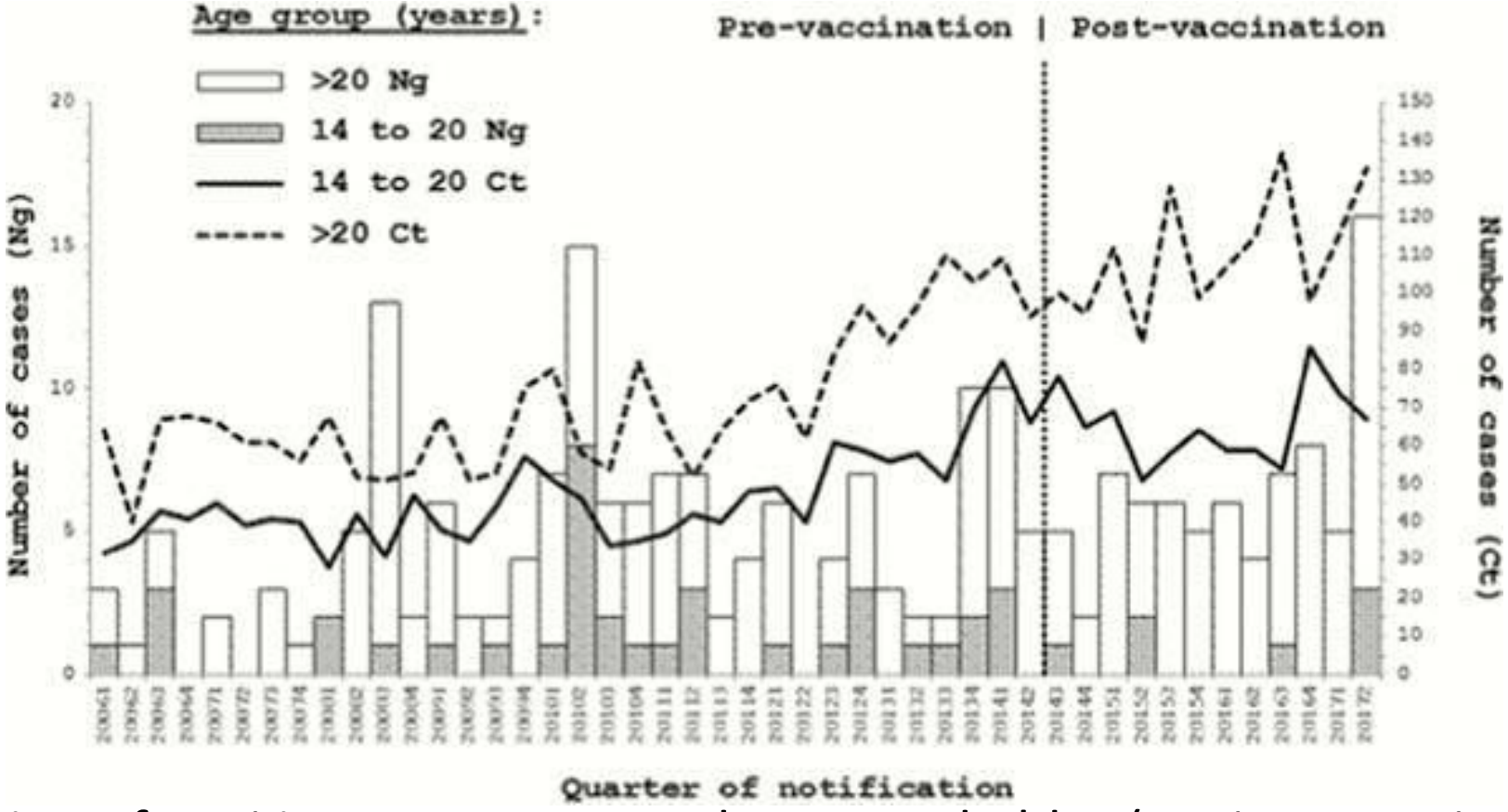
Characteristics		
N	306 cases IMD	1224 controls
vaccinated 4CMenB (at least one dose) N, (%)	35 (11.4%)	298 (24.3%)
% IMDB N (%)	243 (79.4%)*	
Effectiveness against MenB (at least 2 doses)	71% (95% CI, 45-85)	
Effectiveness against all groups (at least 2 doses)	76% (95% CI, 57-87)	
Effectiveness against MenB (at least 1 dose)	64% (95% CI, 41 to 78)	
Effectiveness against non-MenB (at least 1 dose)	82% (95% CI, 21 to 96)	

*Of which 44 cases due to isolates predicted to be covered by the 4CMenB but none of corresponding patients had been vaccinated.

Castilla et al., 2023 Feb 2;388(5):427-438.

Possible Impact of 4CMenB on gonorrhea incidence rates in Quebec, Canada

vaccination campaign of individuals aged 6 months to 20 years



Ng risk reduction of 59% in 14-20 compared to 21 and older (95% CI: −22% to 84%; *P* = 0.1).

Chlamydia trachomatis infections increased among persons of both age groups

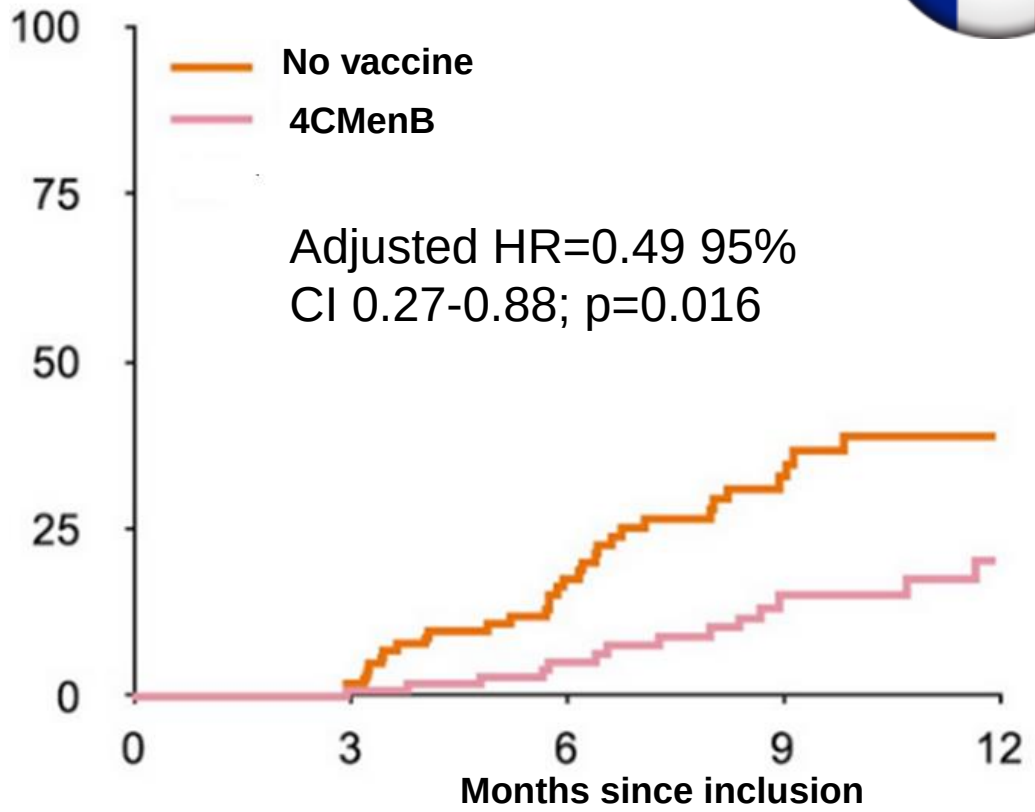
Longtin et al., et al., Open Forum Infect Dis. 2017 Fall; 4(Suppl 1): S734–S735.

Impact of 4CMenB on gonococcal infections

720 MSM under PEPr

+ or - DoxyPrEP 2:1)
- Doxy PrEP 200 mg within the 72h post sexual relation
- No PEPr

+ or – 4CMenB 1:1
- 2 doses 4CMenB M0 and M2
- No vaccine



- After M3, incidence of a first episode of gonococcal infection:
  - The group vaccinated (17 cases) and an incidence of 9.8 per 100 person-years
  - The non-vaccinated group (32 cases) 19.7 per 100 person-years
  - (51% reduction).

Molina et al., CROI 2023 –et al., abstr. 119,

MenB vaccines

	Two MenB vaccines	
Vaccines	**4CMenB**	**Bivalent rLP2086**
composition	***4 components*** fHbp variant 1 (subfamily B) (50 µg) NadA (50 µg) NHBA (50 µg) PorA P1.4 (25 µg)	***2 variants of fHbp*** fHbp variant 1 (subfamily B) (60 µg) fHbp variant 3 (subfamily A) (60 µg)
Licensure	**EMA (2013) : ≥ *2 mo* FDA (2015) : ≥ 10 y**	**FDA (2015) /EMA (2017) : ≥10 y**
Schemes	**> 2 Mo: 2+1** **> 2 y: 2 doses (0-2mo)** **> 10 y: 2 doses (0-1mo)**	**> 10 y : 2 doses (0-6mo) or 3 doses (0-1/2-6mo)**
acquisition of carriage	**No**	**No**
Cross-protection	**Expected against non-B meningococci and even against other *Neisseria***	**Expected against non-B meningococci**
Strain coverage	**Varies temporally and geographically**	**Varies temporally and geographically**