Antigen Surveillance: from Evolution to Immune Escape

Neisseria meningitidis: virulence, immune evasion and cross-reactivity

25 March 2026

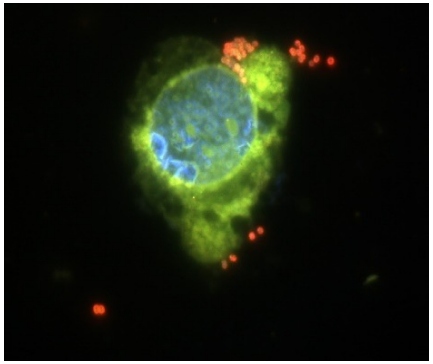
Muhamed-Kheir Taha

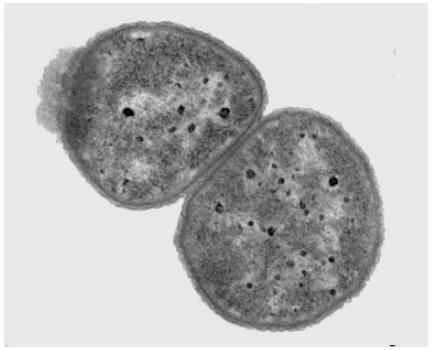
Institut Pasteur, Paris, France

Question 1. Neisseria meningitidis is:

Neisseria meningitidis

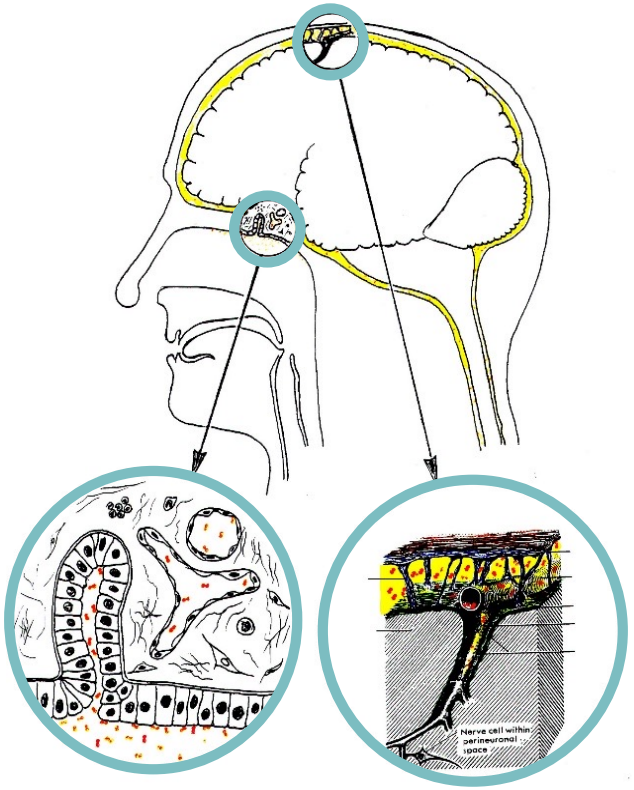
12 serogroups
A, B, C, Y, W and X[1,2]





Taha MK

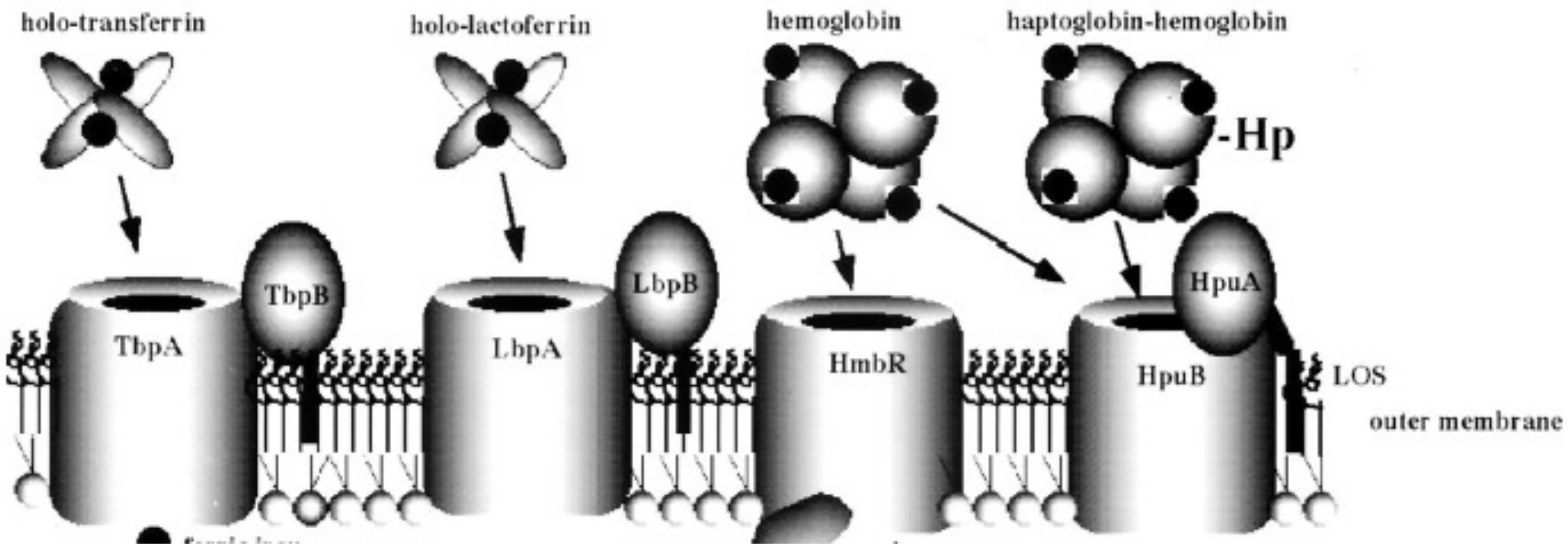
- Encapsulated bacterium (serogroups)[1,2]
- Only encountered in humans[2]
- Inter-human transmission (respiratory, but also, sexual transmission)[1-3]
- Dynamic and unpredictable epidemiology (transformation and recombination)[4,5]
- Frequent asymptomatic carriage (10%)[2,4]
- Invasive infections:
- Even treated, IMD still has a fatality rate around 10%[2,4]
- Invasive infections (mandatory reporting):
- Sporadic forms: Europe, America[2,6] Incidence 0.11–2 per 100,000 (Europe)[2]
- Epidemic forms: Africa (meningitis belt) Incidences up to 1000 per 100,000 [1]



Taha MK

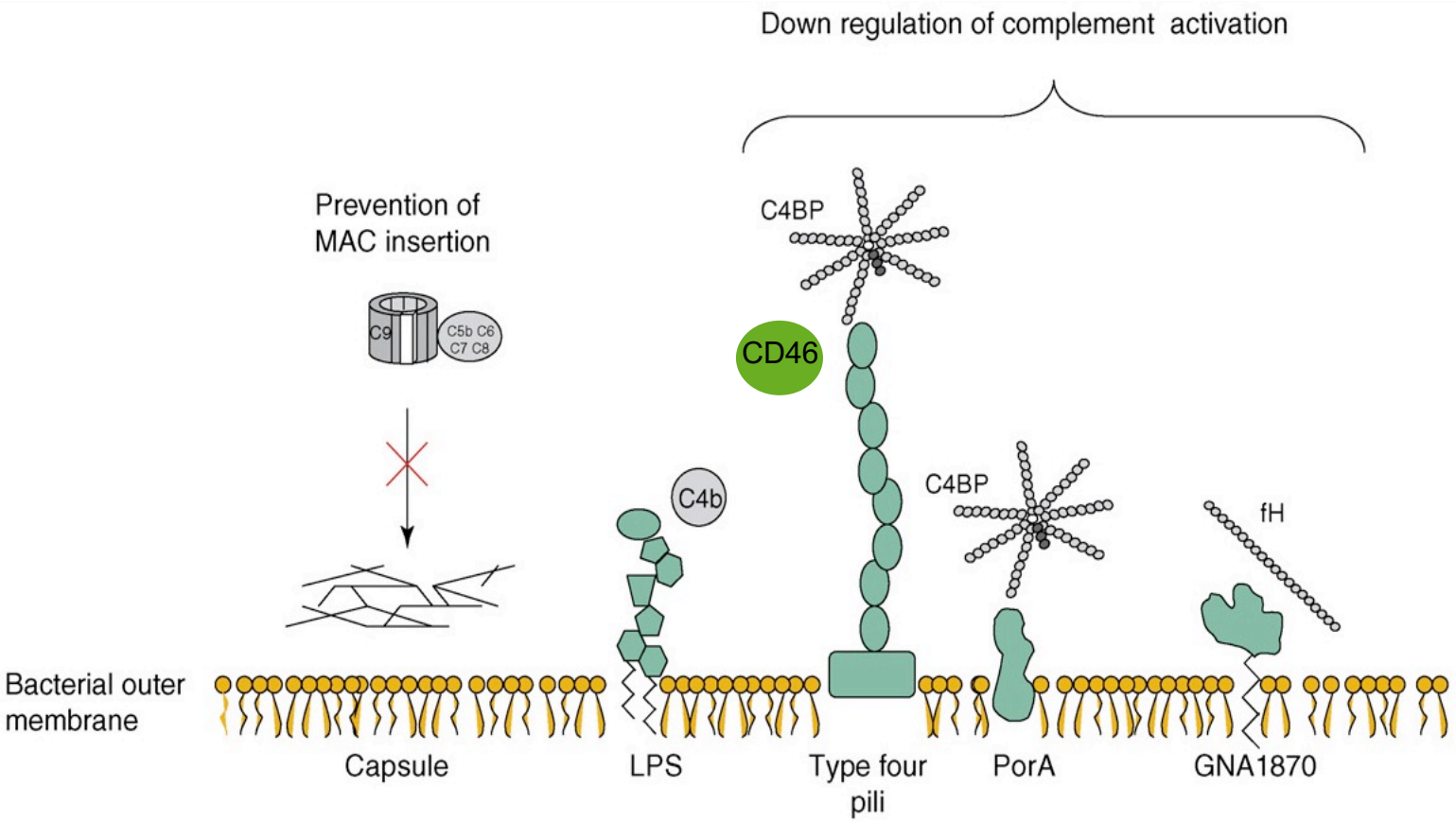
1. World Health Organization (WHO). Meningococcal Meningitis. Available at https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/meningococcal-meningitis. [Accessed August 2022]. 2. European Centre for Disease Prevention and Control (ECDC). Factsheet about meningococcal disease. Available at https://www.ecdc.europa.eu/en/meningococcal-disease/factsheet [Accessed August 2022]. 3. Ladhani SN, et al. Lancet. 2020;395(10240):1865-1877. 4. Stuart JM. Bacterial Meningitis-Epidemiology and Vaccination. Special edition of Microorganisms. 2021. 5. Booy R, et al. Hum Vaccin Immunother. 2019;15(2):470-480. 6. Centers for Disease Control and Prevention (CDC). Meningococcal Disease Surveillance. Available at https://www.cdc.gov/meningococcal/surveillance/ [Accessed August 2022].

IRON acquisition & transport in meningococci



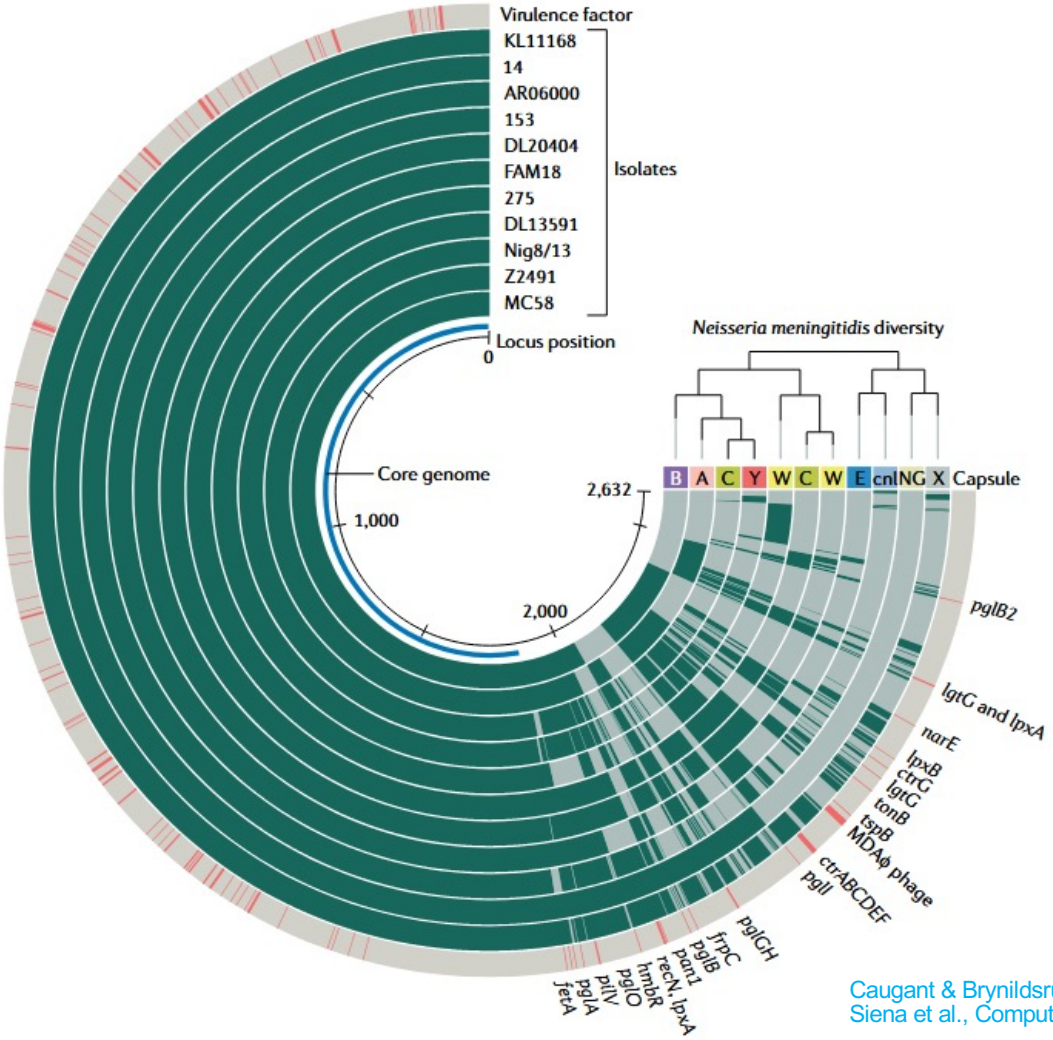
Perkins-Balding et al., 2004,

Resistance of *Neisseria meningitidis* against complement-mediated killing



Schneider et al., 2007 Trends Microbiol. 2007

Variability of Virulence Factors as a Potential Driver of Invasive Meningococcal Disease



pan-genome content o. The presence (dark green) and absence (light green) of genes encoding virulence factors

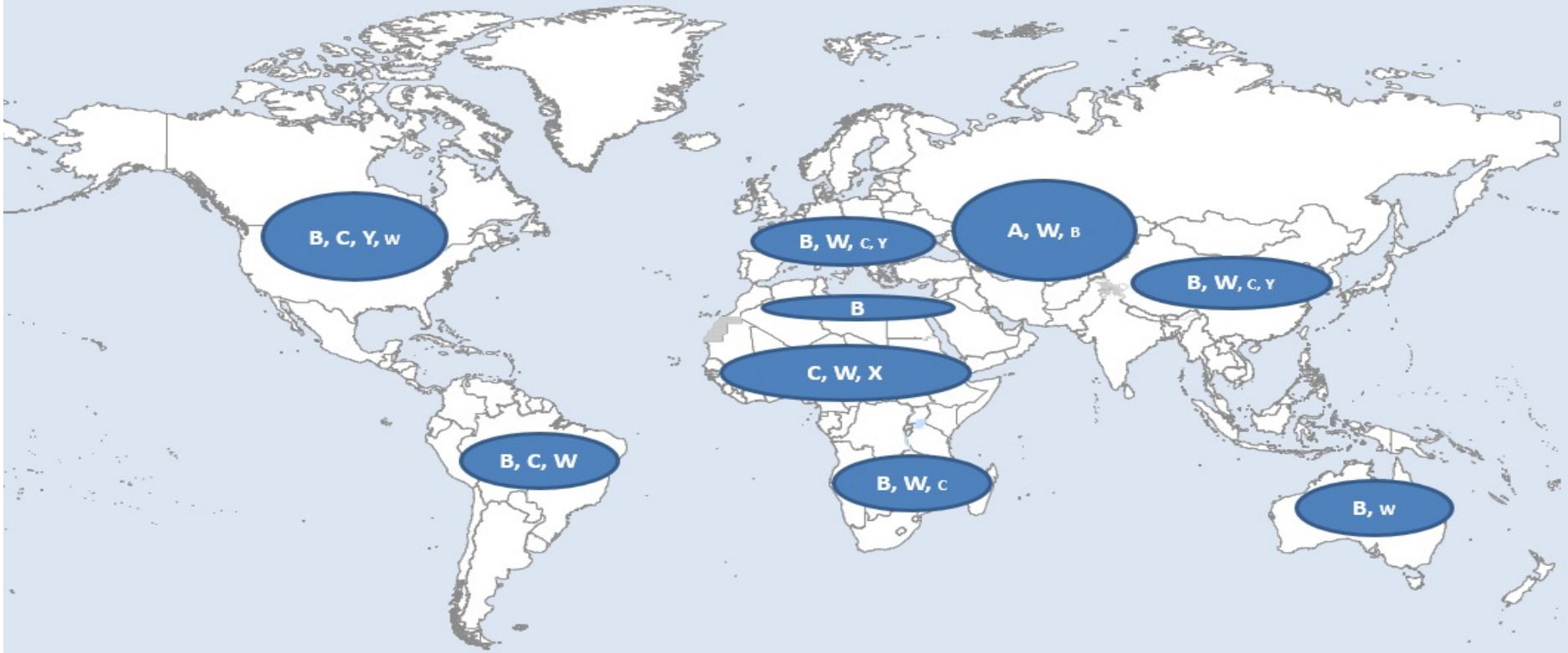
Caugant & Brynildsrud *Nat Rev Microbiol* **18**, 84–96 (2020). https://doi.org/10.1038/s41579-019-0282-6
Siena et al., Comput Struct Biotechnol J. 2018 Feb 15;16:61-69. doi: 10.1016/j.csbj.2018.02.002

Invasive Meningococcal Disease – Serogroup distribution, 2019

World Health Organization

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Map date: January 2020



SEROGROUP Most frequent

SEROGROUP Less frequent

Data Source: World Health Organization
Map Production: WHO Health Emergencies Programme

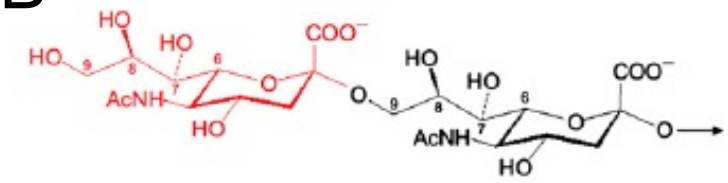
Vaccines currently available against Neisseria meningitidis:

Licensed meningococcal vaccines

Serogroup	Type	Brand	PS (µg)	Carrier	Use
A	Conjugate monovalent	MenAfriVac® Serum Institute of India	10	TT	• 1-29 y (catch-up ≥ 9 months
C	Conjugate monovalent	Neisvac ® (PFIZER)	10	TT	• ≥ 2 months
		Menjugate ® (GSK)		CRM-197	
ACWY	Conjugate tetravalent	Menveo® (GSK)	10, 5, 5, 5	CRM-197	• ≥ 2 y
		Nimenrix® (PFIZER)	5 ,5, 5, 5	TT	•≥ 6 weeks
		Mencatra® SANOFI PASTEUR	4, 4, 4, 4	Diphtheria toxoid	US 9 months- 55 y
		MenQuadfi® SANOFI PASTEUR	10, 10, 10, 10	TT	≥ 1 y
ACWYX	Conjugate pentavalent	NmCV-5 Serum Institute of India	5, 5, 5, 5, 5	TT (A, X) CRM-197 (CWY)	1-29 y

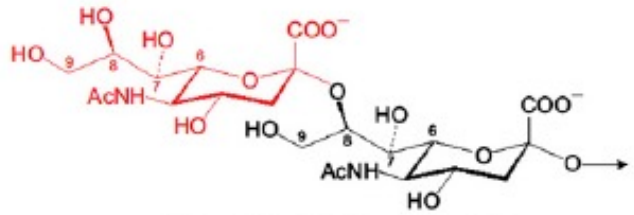
Issues in developing capsule-based vaccine against MenB

B

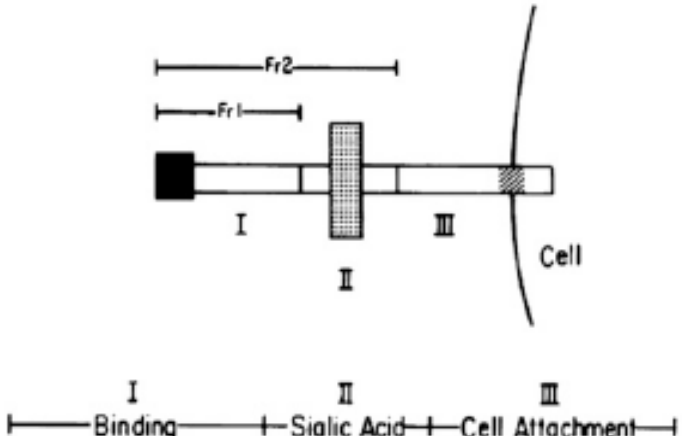


α-Neu5Ac-(2,9)-α-Neu5Ac

C



α-Neu5Ac-(2,8)-α-Neu5Ac



The insertion of (2→8)-α-(Neu-5Ac) into the peptide of N-CAM,

- Self antigen Poorly immunogenic
- Autoimmunity risk if modified

Robbins, et al., *Proc Natl Acad Sci U S A* **108**, 17871 (Nov 1, 2011).

Vaccines against meningococci

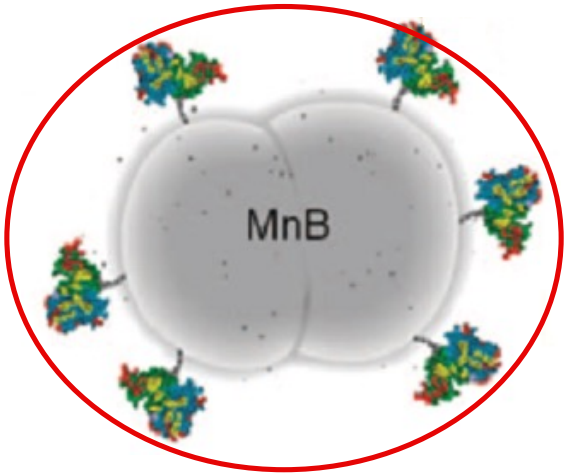
Capsular polysaccharide-based vaccines:

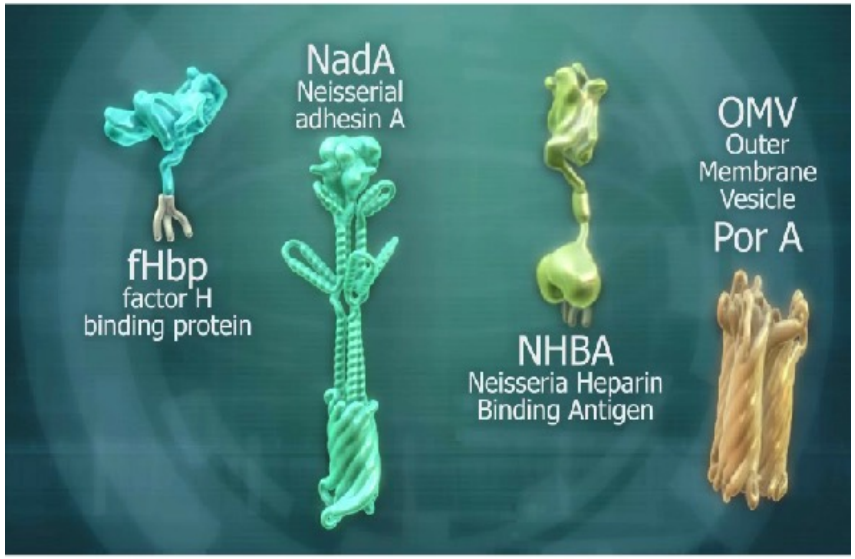
Monovalent: A, C

Tetravalent ACWY

Pentavalents ACWYX and ABCWY

(underdevelopment)





Conjugate capsular polysaccharide-based vaccines
•Impact on carriage
•Persistence of the immune response

4CMenB (2 months)
50 µg each
25 µg of OMV NZ98/254,
1.5 of mg aluminum hydroxide

Bivalent MenB-FHbp (10 years old)
60 µg of each fHBP variant
0.25 mg aluminum phosphate

Vaccines against N. meningitidis are licensed on the basis of:

Correlate of protection

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

Three values are considered for vaccine licensure:

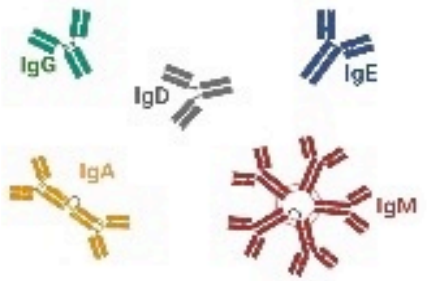
% of subjects with a titer ≥4

% of subjects with four-fold increase of bactericidal titer

Geometric mean of titers of all subjects

Goldschneider et al., *J Exp Med* 129, 1307 (Jun 1, 1969).

Classical serum bactericidal assay

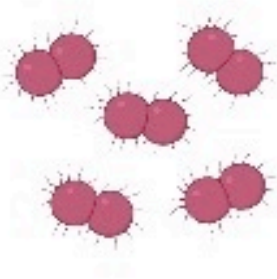


Serum samples

+

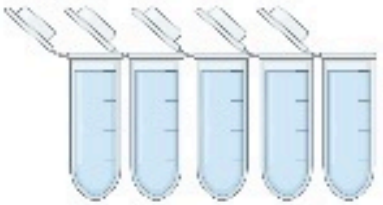
Exogenous source of complement

+



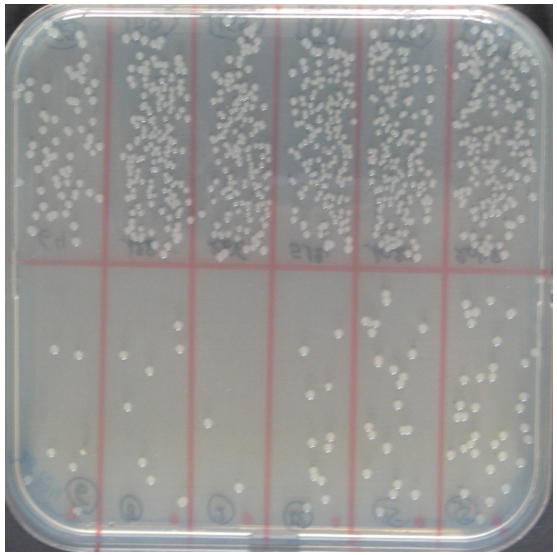
Bacteria

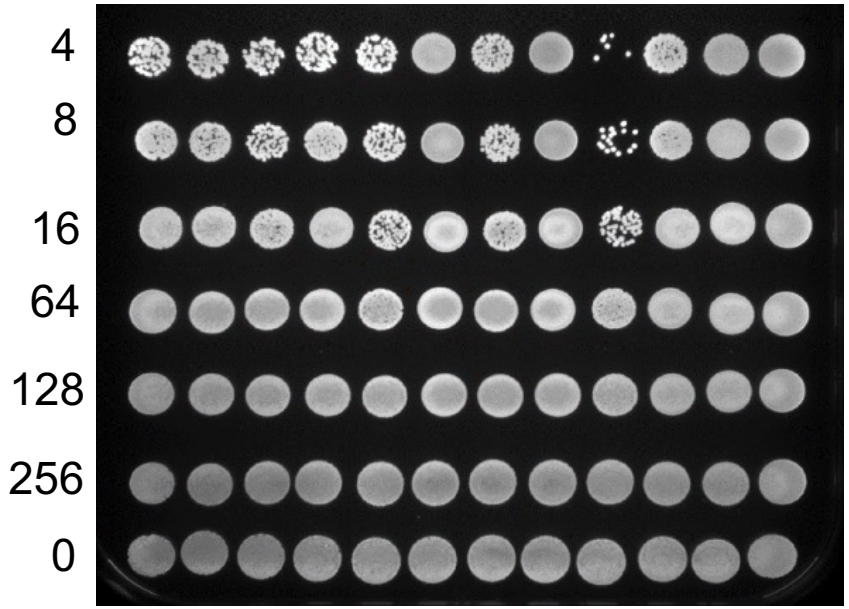
a)



No serum

+ serum
(X2 dilutions)





Fantoni, et al., *Microorganisms* **13**, (Mar 4, 2025).

Protein-based versus capsule-based vaccines

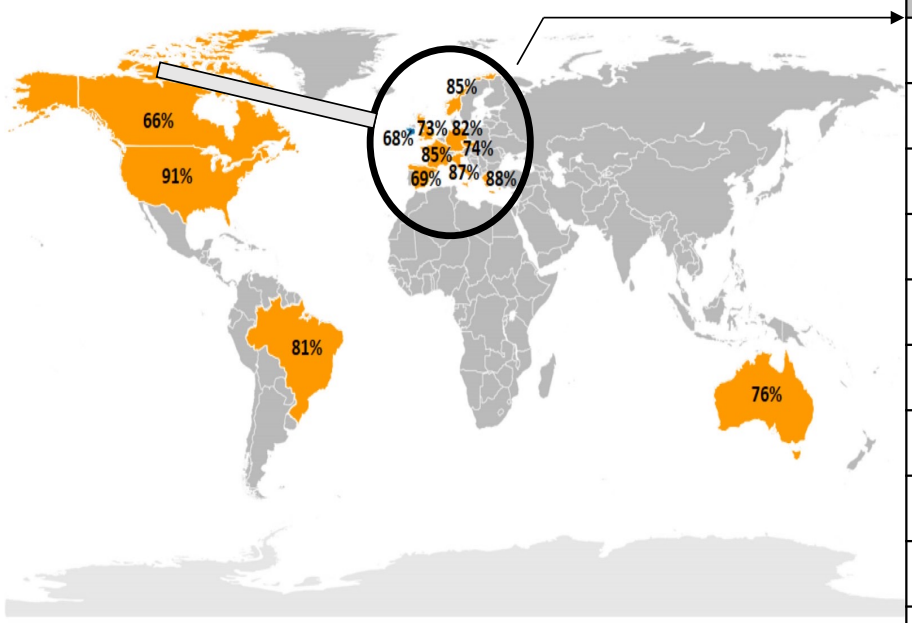
- Unlike capsular polysaccharide-based vaccines, MenB vaccines are composed of variable proteins.

- For capsular polysaccharide-based vaccines, coverage is straightforward and based on the presence or absence of the polysaccharide capsule (serogrouping).

- Coverage of isolates by MenB vaccines requires more sophisticated methods that involve determining the presence, homology, surface exposure, and levels of proteins in MenB isolates in relation to the proteins in the vaccine.

Vaccines agiast meningococci B cover all B isolates

MATS-Predicted Coverage of 4CMenB Vaccine



MATS assay
Meningococcal Antigen Typing System

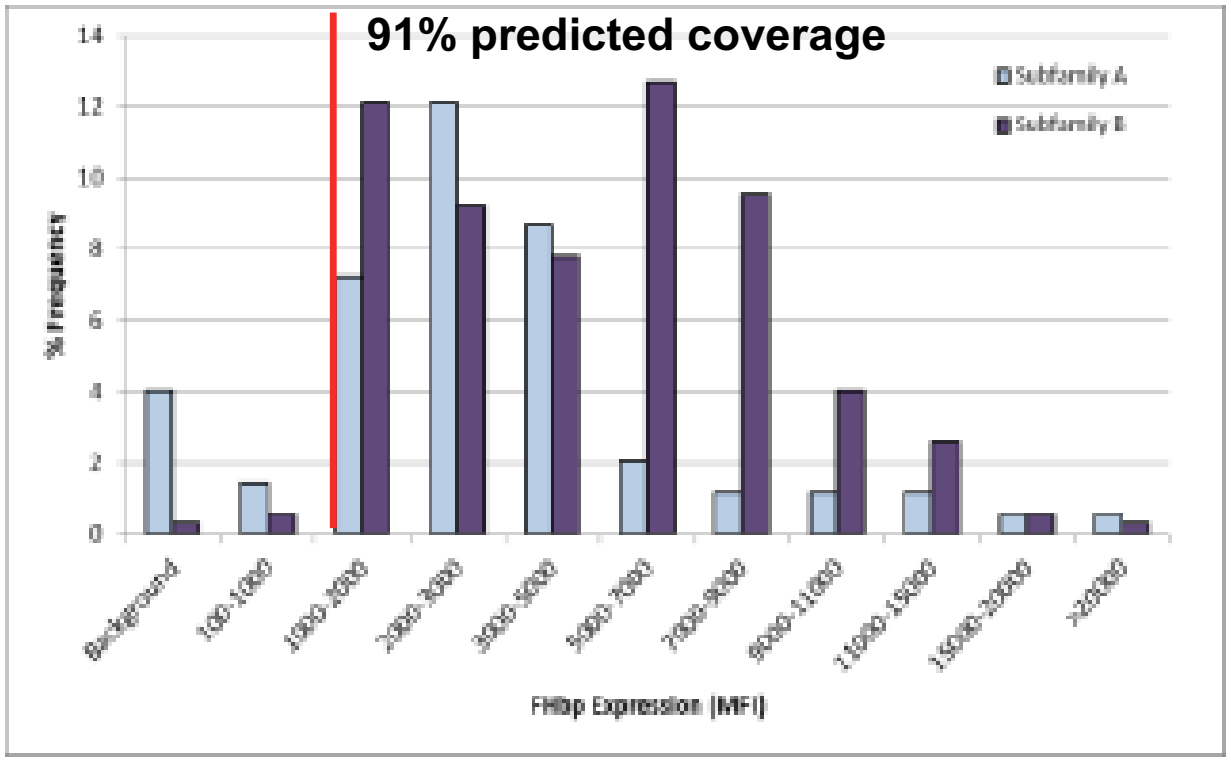
	Predicted coverage (95% CI)
England & Wales	73% (57–87)
France	85% (69–93)
Germany	82% (69–92)
Italy	87% (70–93)
Norway	85% (76–98)
Czech Republic	74% (58–87)
Spain	69% (48–85)
Greece	89% (64-99)
Poland	84% (79-91)
Combined*	78% (63–90)

*Excludes Czech Republic, Greece and Poland and Spain

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 by MenB-FHbp Vaccine

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

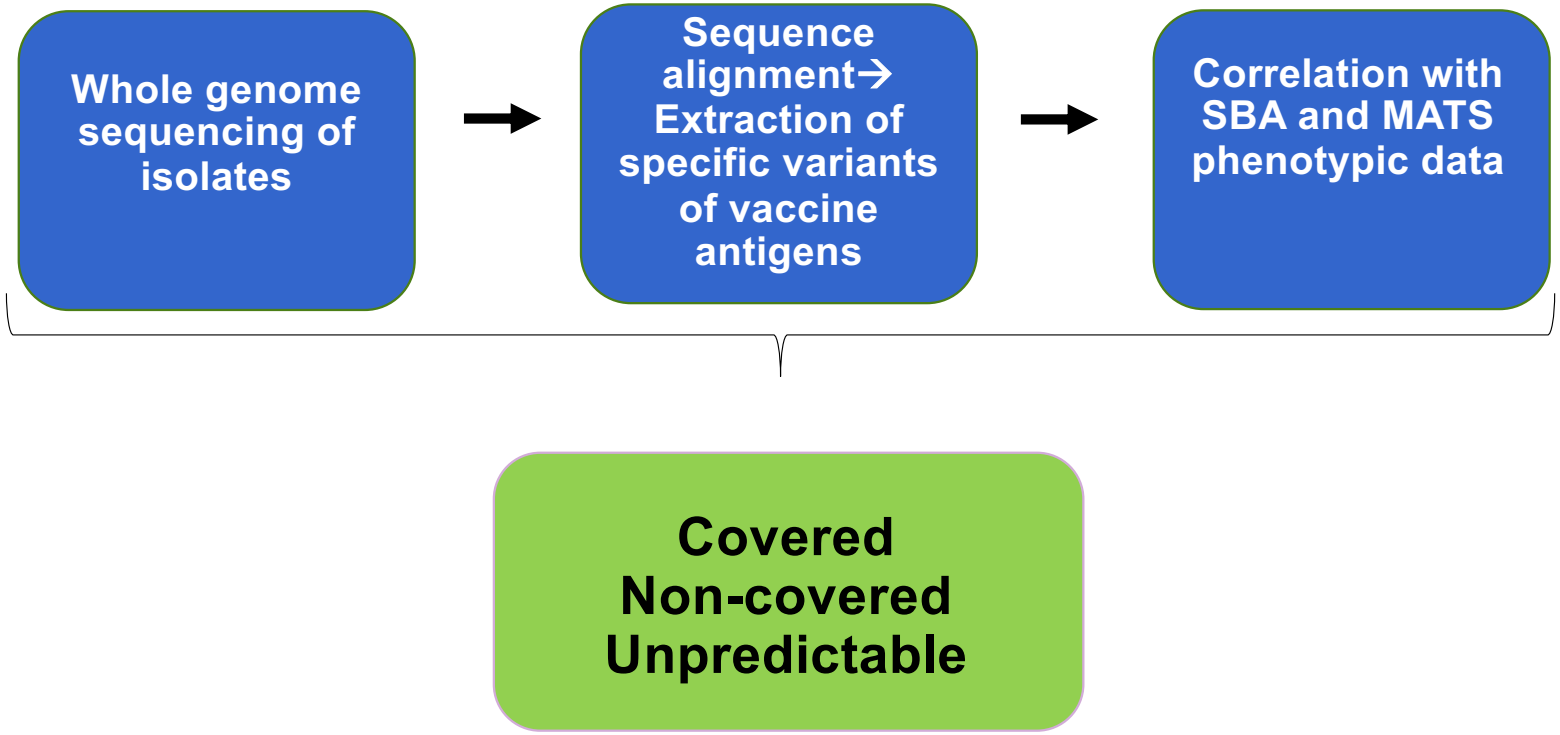


McNeil, et al. MBio. 2018;9(2). Epub 2018/03/15. doi: e00036-18 [pii] 10.1128/mBio.00036-18
.

Pros and Cons

Method	Pros	Cons
SBA	Gold Standard Bactericidal titers of sera (before and after vaccination) against isolates	Time consuming, source of complement, difficult to apply on all isolates
MATS/MEASURE Meningococcal Antigen Typing System/Meningococcal Antigen Surface Expression assay	Phenotypic: sequences and level of expression and surface exposition of antigens included in the vaccine	Time consuming, require viable bacteria. Specific for the corresponding vaccine

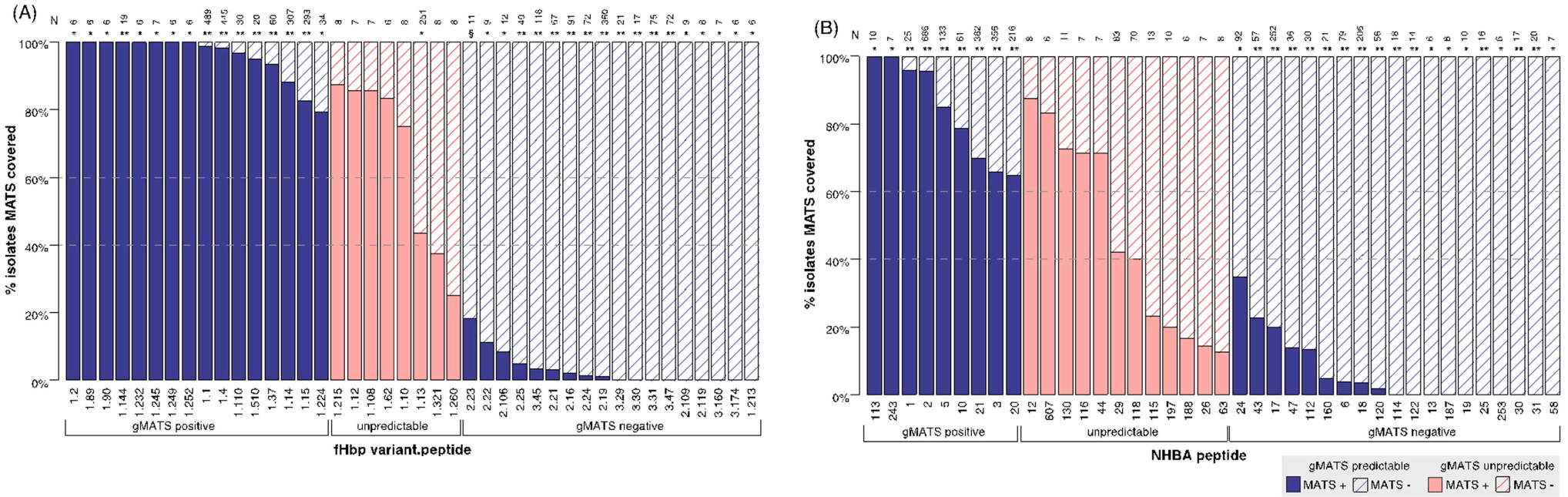
Genome-based methods for Estimation of strain coverage by MenB vaccines



BAST-based predicted coverage: Switzerland

Year of isolation	Number of samples per year	Exact 4CMenB	Exact 4CMenB (%)
2010	15	7	46.7
2011	26	8	30.8
2012	14	4	28.6
2013	23	9	39.1
2014	13	2	15.4
2015	13	1	7.7
Total	104	31	29.8

Leo et al. Vaccine 38 (2020) 5324–5331https://doi.org/10.1016/j.vaccine.2020.05.071



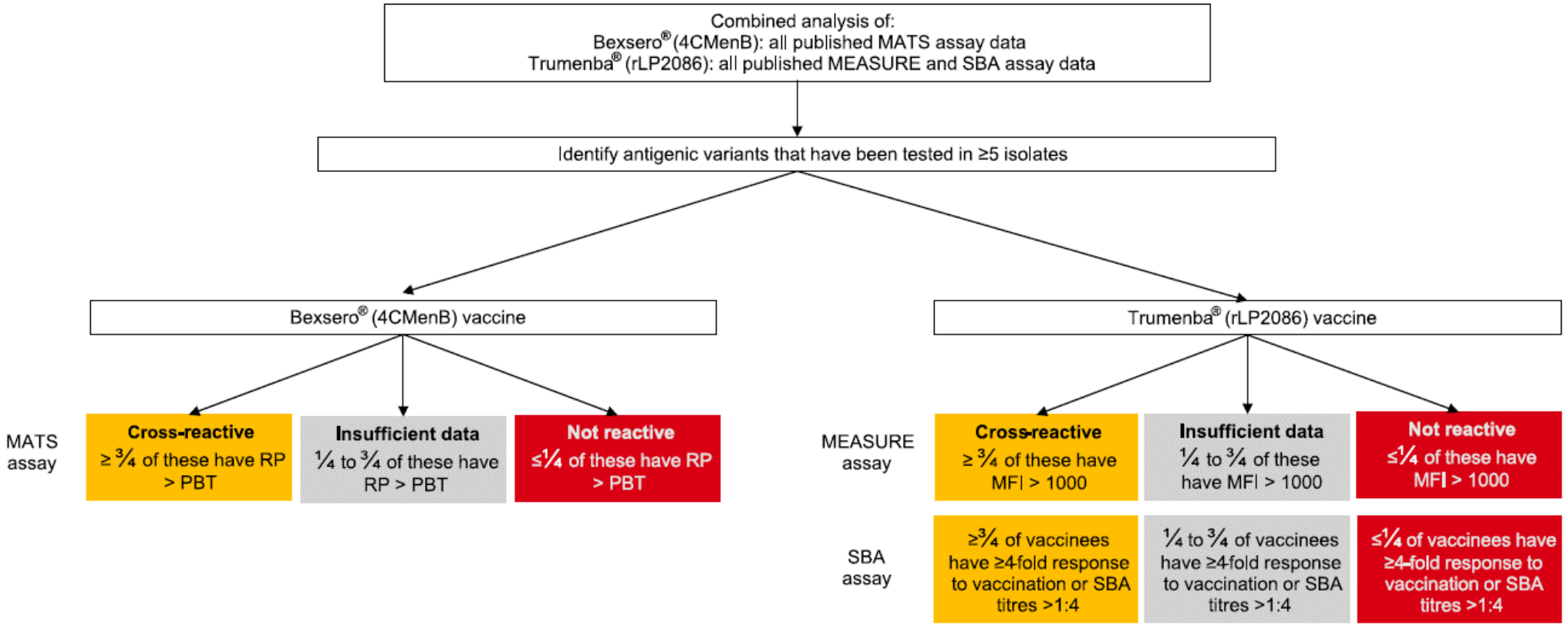
- Covered: Peptide IDs for which the percentage of MATS-covered Isolates >60%
- Non-covered: Peptide IDs for which the percentage of MATS-covered Isolates >40%
- A test of proportions rejected 50% as null hypothesis.

- Unpredictable Peptide IDs for which the percentage of MATS-covered Isolates ≥40 and ≤60
- 50% of unpredictable are considered covered

Muzzi et al. Vaccine. 2019;37(7):991-1000. doi: S0264-410X(19)30032-5 [pii] 10.1016/j.vaccine.2018.12.061

Meningococcal Deduced Vaccine Antigen Reactivity (MenDeVAR)

Online tool on PUBMLST.org



Rodrigues et al. J Clin Microbiol. 2020;59(1). doi: 10.1128/JCM.02161-20.

BAST-based predicted coverage: Switzerland

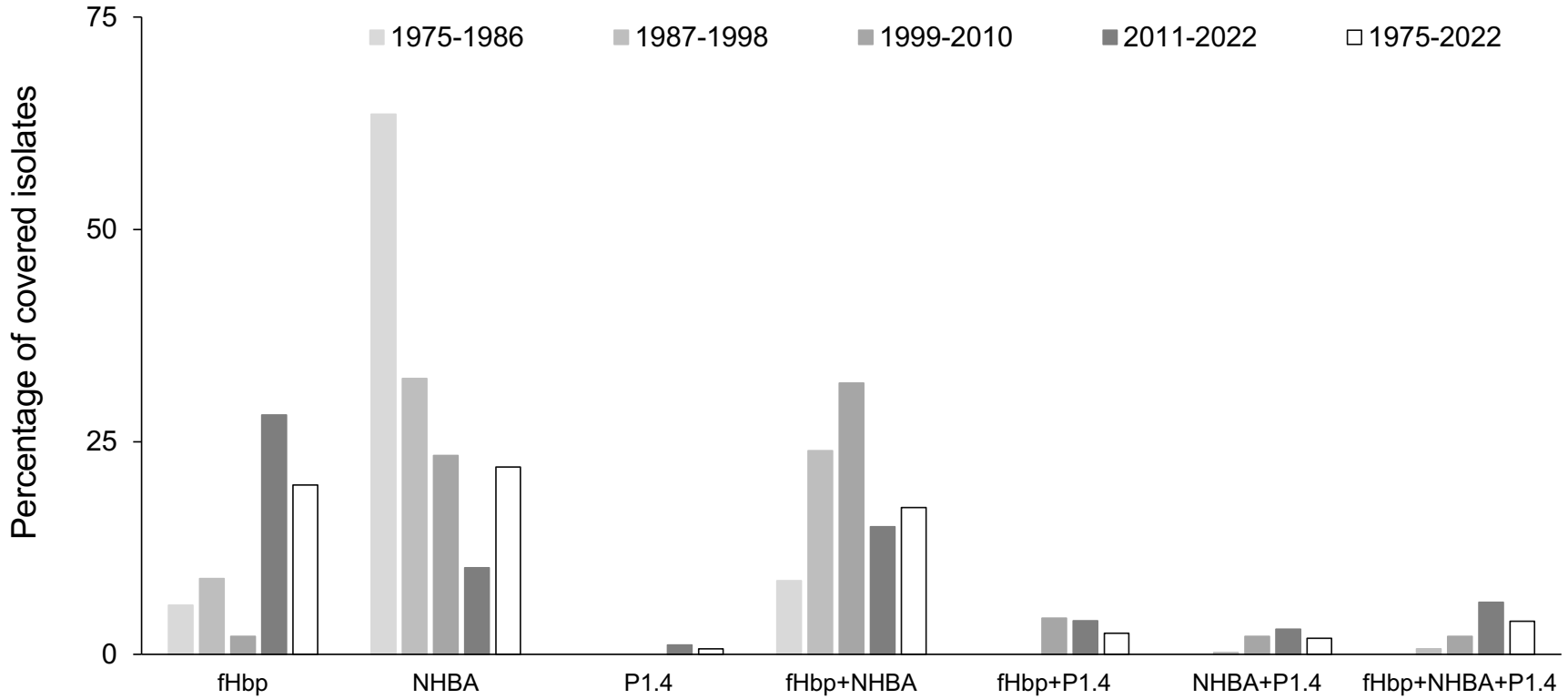
Year of isolation	Number of samples per year	Exact 4CMenB	Exact 4CMenB (%)
2010	15	7	46.7
2011	26	8	30.8
2012	14	4	28.6
2013	23	9	39.1
2014	13	2	15.4
2015	13	1	7.7
Total	104	31	29.8

gMATS → 67.8%

Leo et al. Vaccine 38 (2020) 5324–5331https://doi.org/10.1016/j.vaccine.2020.05.071

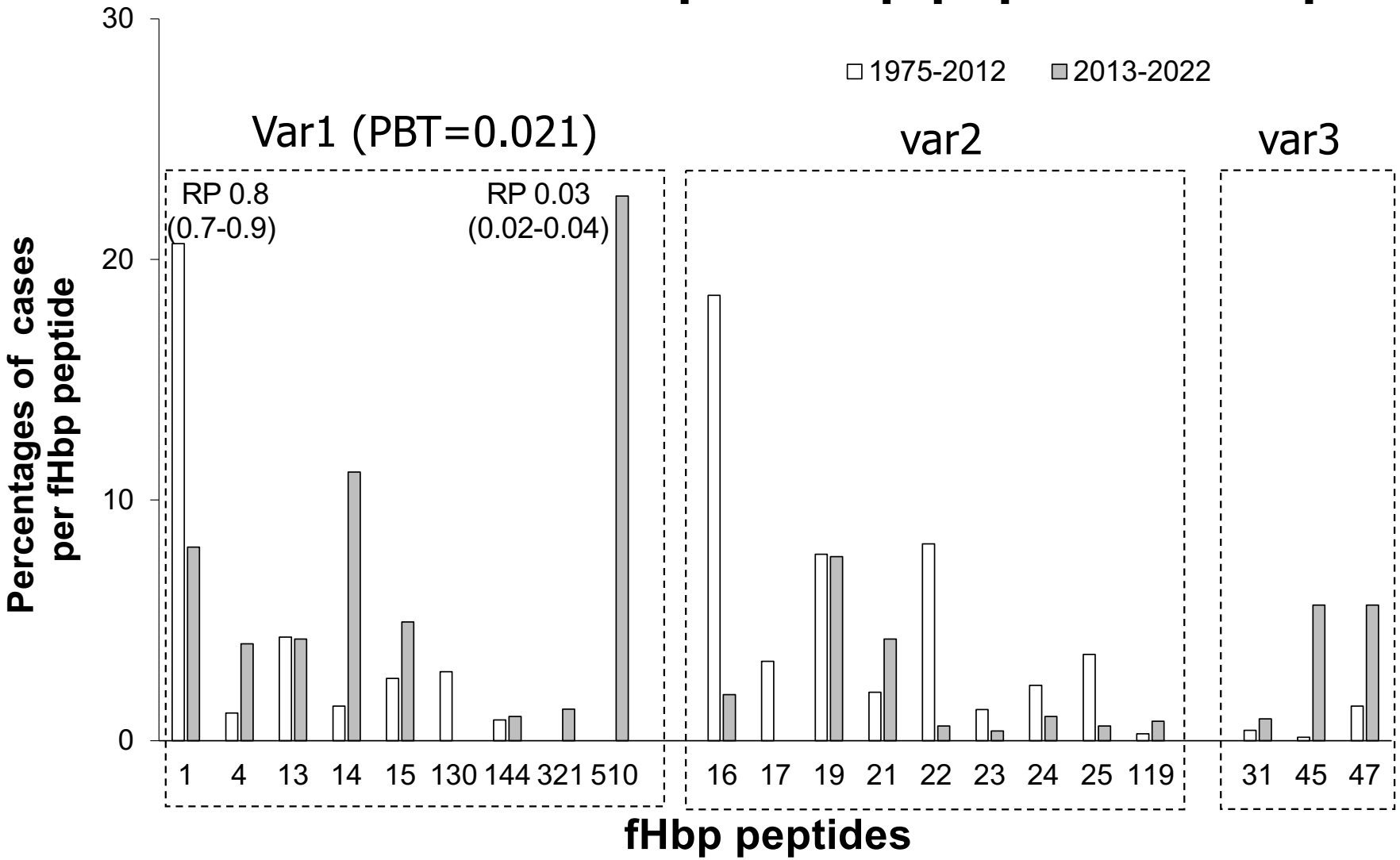
Fluctuations in serogroup B meningococcal vaccine antigens prior to routine MenB vaccination in France

	1975-1986	1987-1998	1999-2010	2011-2022	1975-2022
All	85.0 (78.0-91.9)	76.3 (66.2-86.3)	74.5 (66.0-83.0)	76.7 (67.5 -85.9)	77.4 (68.2-86.5)



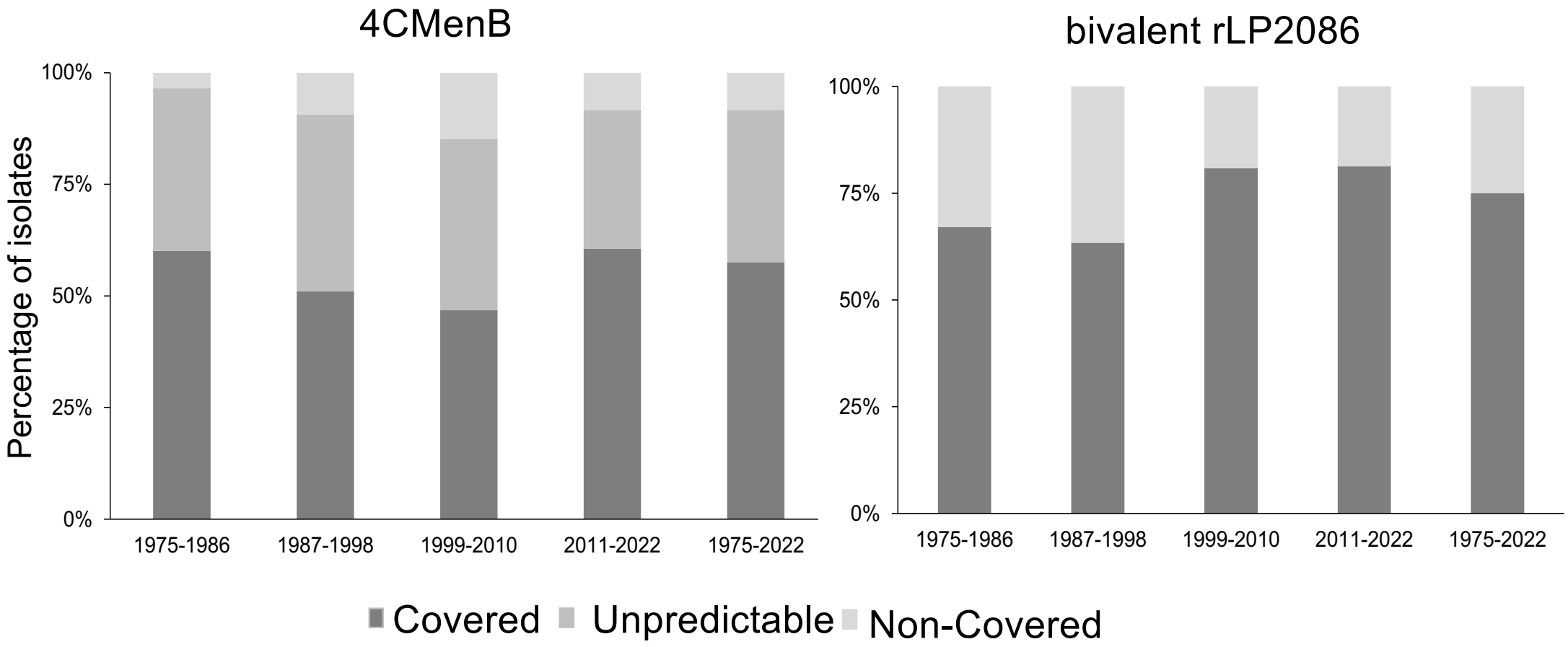
Falguière et al., 2025 communications medicine https://doi.org/10.1038/s43856-025-00800-2

Distribution of IMDB cases per fHbp peptides and per period



Falguière et al., 2025 communications medicine https://doi.org/10.1038/s43856-025-00800-2

Fluctuations in strain coverage of serogroup B meningococcal vaccine antigens in France MenDeVar



Falguière et al., 2025 communications medicine https://doi.org/10.1038/s43856-025-00800-2

Method	Pros	Cons
gMATS	Simple and portable. Nonculture	Only Bexsero (gMATS). Alignment-based method. but can not predict coverage for new alleles, cannot predict actual expression. Regulatory sequences (e.g. gene promoters) are not included in the analysis
MenDeVAR	Simple and portable. Both Bexsero and Trumenba. Nonculture	

npj | Vaccines

www.nature.com/npjvaccines

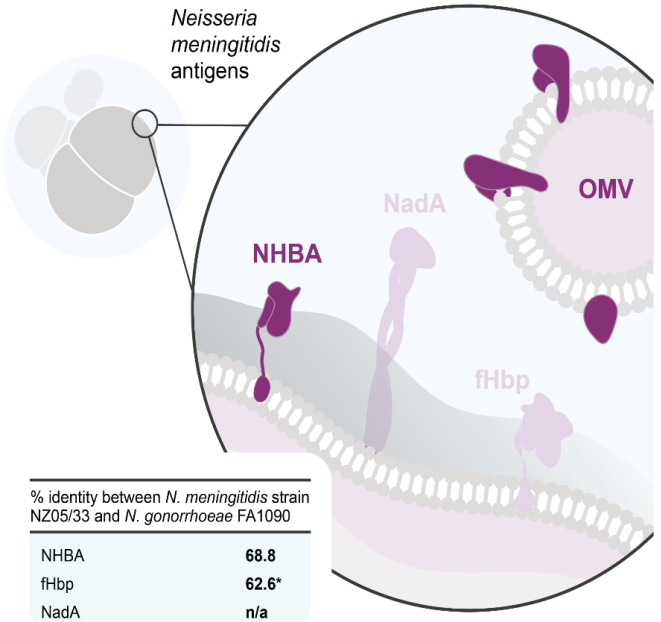
REVIEW ARTICLE OPEN

Check for updates

Looking beyond meningococcal B with the 4CMenB vaccine: the *Neisseria* effect

Yara Ruiz García[1]✉, Woo-Yun Sohn[1], Kate L. Seib[2], Muhamed-Kheir Taha[3], Julio A. Vázquez[4], Ana Paula S. de Lemos[5], Kumaran Vadivelu[6], Mariagrazia Pizza[6], Rino Rappuoli[6] and Rafik Bekkat-Berkani[1]

No correlate of protection against Ng

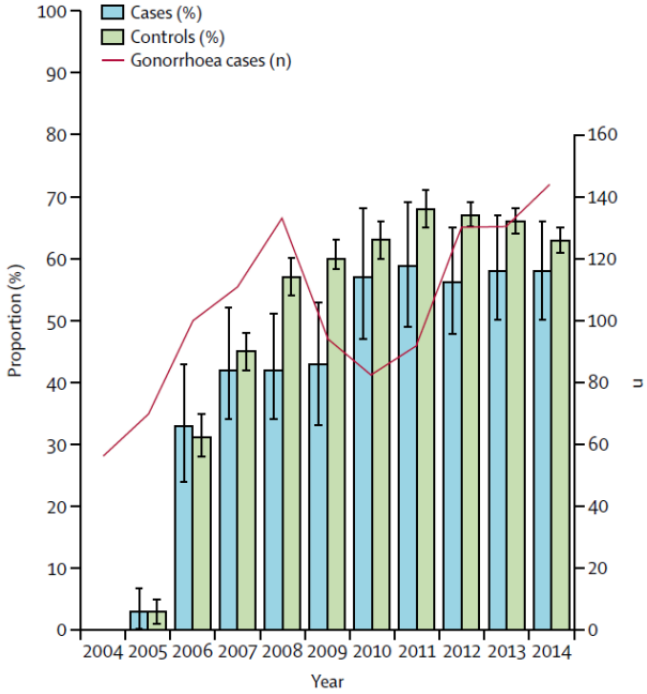


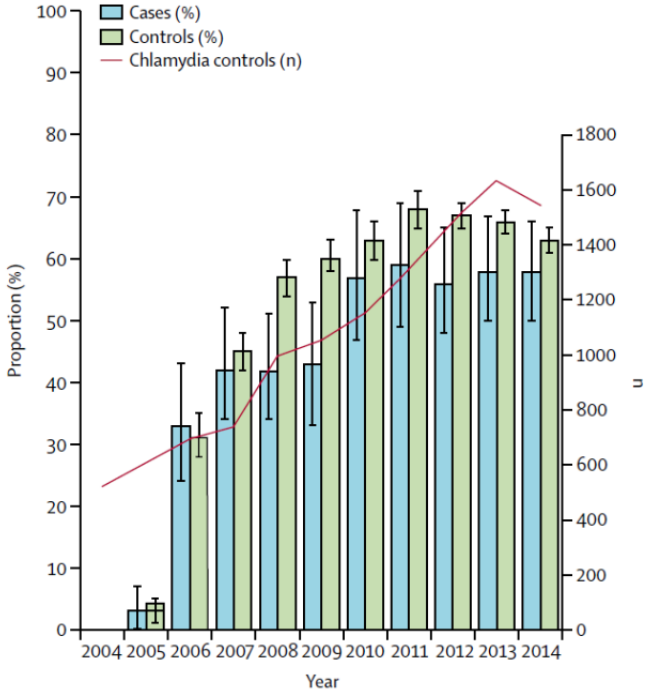
% identity between *N. meningitidis* strain NZ05/33 and *N. gonorrhoeae* FA1090	
NHBA	68.8
fHbp	62.6*
NadA	n/a

OMV proteins % identity between *N. meningitidis* strain NZ05/33 and *N. gonorrhoeae* FA1090	
FbpA	99.1
MafA adhesin	98.8
Antioxidation AhpC TSA family glutaredoxin	98.5
FkpA	97.8
TonB-dependent receptor (NMB0964)	96.9
MtrE	96.4
Hypothetical protein	96.3
TonB-dependent receptor (NMB1497)	96.1
OMP85	95.0
FrpB	94.3
Putative lipoprotein NMB1126/1164	94.2
OMP P1	94.0
Tbp1	93.7
NspA	93.7
RmpM	93.4
PilQ	91.4
LptD	89.8
LysM peptidoglycan -binding domain containing protein	88.7
PorB	67.3
OpcA	43.8
PorA	n/a
LbpA	n/a

A retrospective case-control study: New Zealand

- **Vaccinated individuals were significantly less likely to be cases than controls (OR 0.69 [95% CI 0.61–0.79]; p<0.0001).**





	Crude OR (95% CI)	Adjusted OR* (95% CI)	Vaccine effectiveness (95% CI)
Cases have gonorrhoea, and controls have chlamydia (co-infected excluded)			
Vaccinated *vs* unvaccinated 2004–14	0·65 (0·57–0·72)	0·69 (0·61–0·79)	31% (21–39)

OR=odds ratio. *Adjusted for ethnicity, sex, age group, deprivation, and geographical location.

Estimate vaccine effectiveness against gonorrhoea 31% (95% CI 21–39).

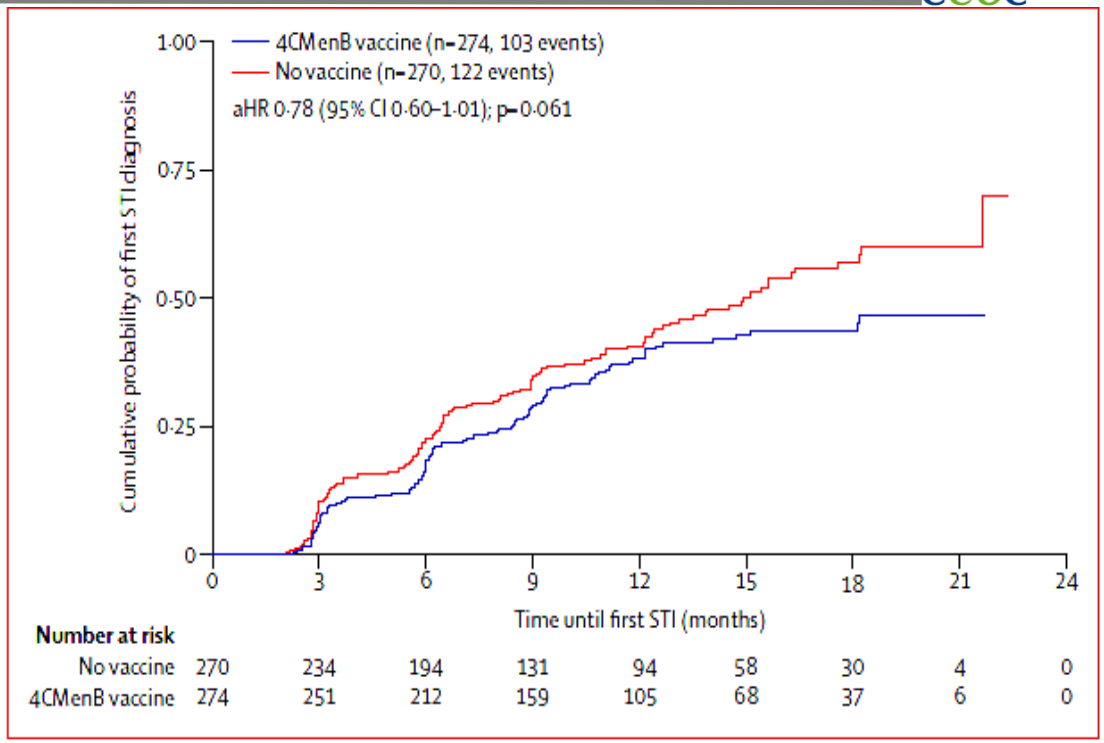
Petousis-Harris et al Lancet 2017

Impact of 4CMenB on gonococcal infections

544 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 gonorrhoea,
- 58.3 per 100 person-years (103 events in 274 participants) in the 4CMenB vaccine group
- 77.1 per 100 person-years (122 events in 270 participants) in the (no vaccine) group
- (aHR 0.78 [95% CI 0.60–1.01; p=0.061)

Molina et al., Lancet Infect Dis 2024 2024 https://doi.org/10.1016/S1473-3099(24)00236-6

Cross-protection of meningococcal B vaccines against gonorrhea: Meta-analysis

Georgiadis et al.,. *Vaccine* ***2025, 56, 127180, doi:10.1016/j.vaccine.2025.127180.***

Study (Year)	Design	Population	Comparator	Vaccine	**Case definition**	Effect Size (ES)	VE % (95% CI)
Abara 2022	Retrospective Case-control	18099 NG cases, 124876 CT controls (USA, 16–23y)	Unvaccinated	4CMenB (≥1dose)	Reported gonorrhea diagnoses by the STI	aPR 0.60 (0.47–0.77)	40% (23-53)
Abara 2024	Retrospective Case-control	10638 NG cases, 53393 CT controls (USA, 15–30y)	Unvaccinated	4CMenB (≥1dose)	Gonorrhea and chlamydia cases, using NAAT.	aPR 0.99 (0.79-1.25)	1% (-25-21)
Wang, 2023	Case-control	823 NG cases, 4935 CT controls (Australia)	Unvaccinated	4CMenB (2 doses)	Gonorrhea Notification by the surveillance system	aOR 0.72 (0.55–0.93)	28% (7-45)
Moulina 2024	RCT	274 vaccinated and 270 unvaccinated (France, 34-48y)	Unvaccinated	4CMenB (2 doses)	PCR test from at least one site (throat, urine, or anus)	aHR 0.78 (0.60-1.01)	22% (-1-40)
Raccagni 2023	Retrospective Case-control	103 cases, 948 controls) MSM with HIV (Italy, 37-51y)	Unvaccinated	4CMenB (2 doses)	Cultures or NAAT	aOR 0.56 (0.35–0.91)	44% (9-65)
Petousis-Harris 2017	Retrospective Case-control	14730 cases and controls (New Zealand, 15-30y)	Unvaccinated	MeNZB (≥1dose)	Cultures or NAAT	aOR 0.71 (0.62–0.80)	29% (20,38)
Bruxvoort 2023	Retrospective Cohort	6641 4CMenB and 26471 ACWY (USA, Mean age 18.8y)	MenACWY	4CMenB (≥1dose)	Cultures or NAAT	HR 0.54 (0.34–0.86)	46% (14-66)
Robison 2023	Retrospective Cohort	30,972 adolescents (USA, 18-20y)	MenB-FHbp (non-OMV)	4CMenB (≥1dose)	Mandatory reporting	RR 0.53 (0.32–0.86)	47% (13,68)
Lebate 2024	RetrospectiveCohort	51 PLWH (Italy, 25-39y)	Unvaccinated	4CMenB (≥1dose)	Cultures or NAAT	aOR 0.71 (0.11-71)	72% (29-89)

- **Pooled effect size (ES):** 0.70 (95% CI: 0.61–0.81, $p < 0.001$)
- **Pooled VE: 30% (95% CI: 19–39%**

Virulence of meningococci results from:

In summary

- *N. meningitidis* is a highly divers bacterium through horizontal DNA exchanges within the genus *Neisseria*
- Antigens can be shared across species of the genus *Neisseria*
- High antigen diversity leading to a high number of variants
- Variants can display variable:
  - virulence
  - antibiotic susceptibility
  - vaccine coverage

Further reading

- Borrow R, Alarcón P, Carlos J, et al; Global Meningococcal Initiative. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines 2017; 16:313–2
- Caugant, D.A., Brynildsrud, O.B. *Neisseria meningitidis*: using genomics to understand diversity, evolution and pathogenesis. *Nat Rev Microbiol* **18**, 84–96 (2020). https://doi.org/10.1038/s41579-019-0282-6
- Siena, E., Bodini, M. & Medini, D. Interplay between virulence and variability factors as a potential driverof invasive meningococcal disease. *Comput. Struct.Biotechnol. J.* **16**, 61–69 (2018).
- Lucidarme, J. et al. Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. J. Infect. 71, 544–552 (2015).
- Klughammer, J. et al. Comparative genome sequencing reveals within-host genetic changes in Neisseria meningitidis during invasive disease. PLOS ONE 12, e0169892 (2017).
- Brynildsrud, O. B. et al. Acquisition of virulence genes by a carrier strain gave rise to the ongoing epidemics of meningococcal disease in West Africa. *Proc. Natl Acad. Sci. USA* **115**, 5510–5515 (2018).

Acknowledgements

The creation of this training material was commissioned by ECDC to <Organisation1 (and organisation 2, if applicable)> with the direct involvement of <alphabetically ordered list of contributors>

The revision and update of this training material was commissioned by ECDC to <Organisation 3> with the direct involvement of <alphabetically ordered list of contributors>