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From Science to Real World Results

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Conflict of Interests

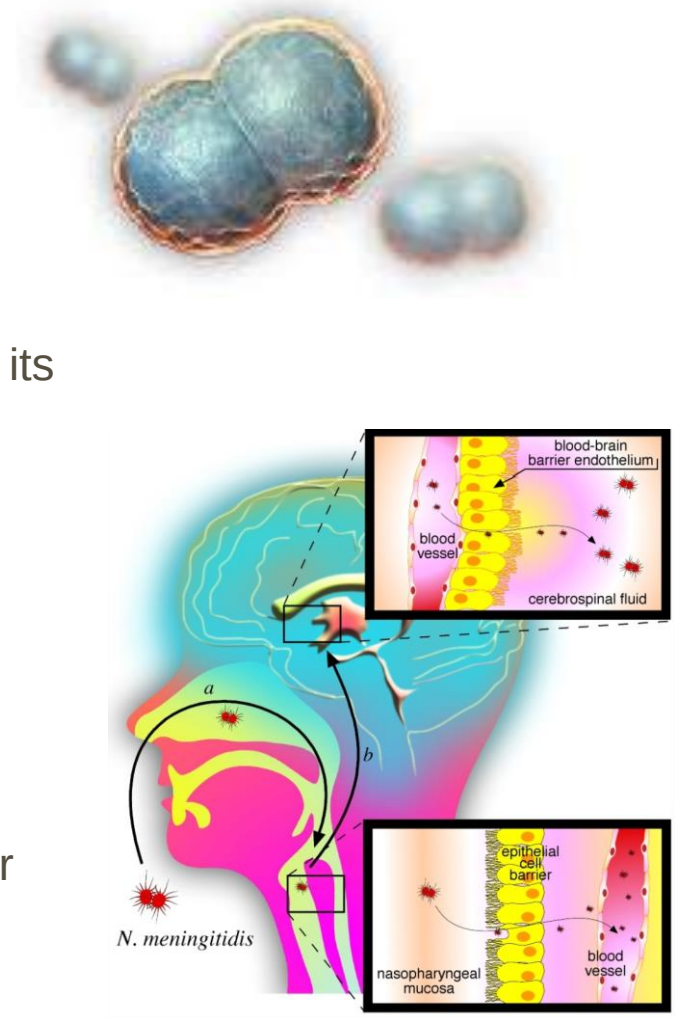


I'm a GSK employee.

Neisseria meningitidis and meningococcal disease



- Encapsulated, aerobic, Gram-diplococcus¹
- Strictly human pathogen¹
- Asymptomatic carriage is common¹
- Meningococcal disease (IMD) is characterized by its rapid onset and progression to meningitis and/or sepsis²
- Despite antibiotic treatment³
 - case fatality rate 10-25%
 - 10 - 20% have serious sequelae
- >90% of total cases of IMD are caused by 5 major serogroups: A, B, C, Y and W³

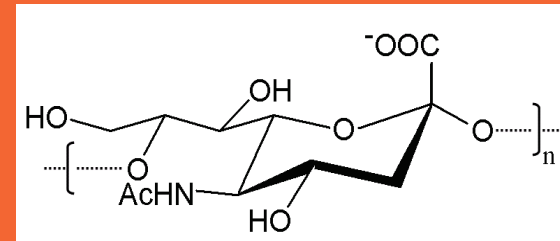
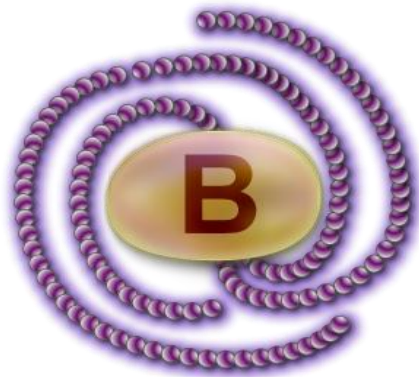


Meningococcus B capsule is a self antigen^{1,2}

Cannot be used for vaccination



- Serogroup B capsular polysaccharide structurally identical to polysialic acid units in fetal neural tissue^{1,2}
 - Poorly immunogenic^{1,2}
 - Potential risk of autoimmunity^{1,2}

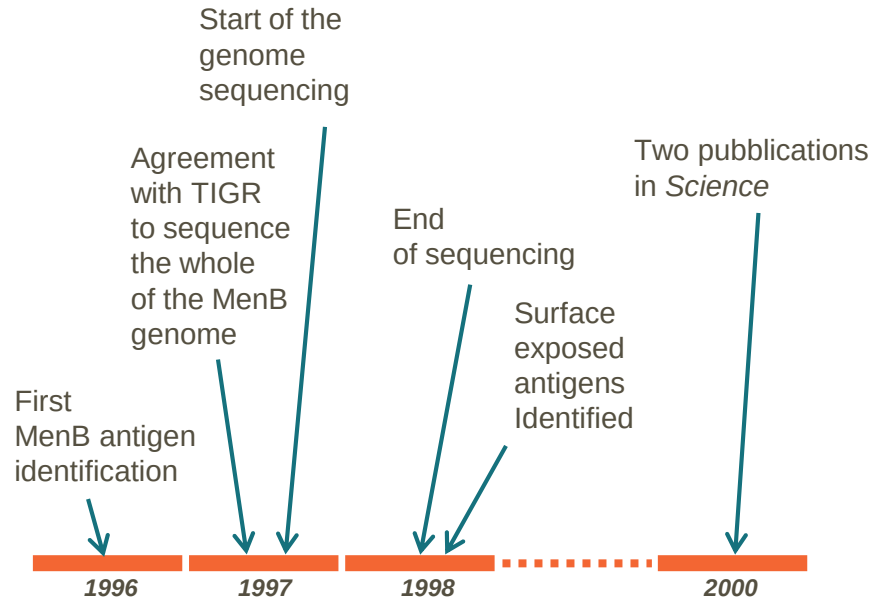


MenB

→8)- α -D-Neu5Ac-(-2→

Image adapted from Rappuoli R. The challenge of developing universal vaccines.
F1000 Medicine Reports 2011;3:16, with permission from Faculty of 1000 Ltd

The development steps of the MenB vaccine

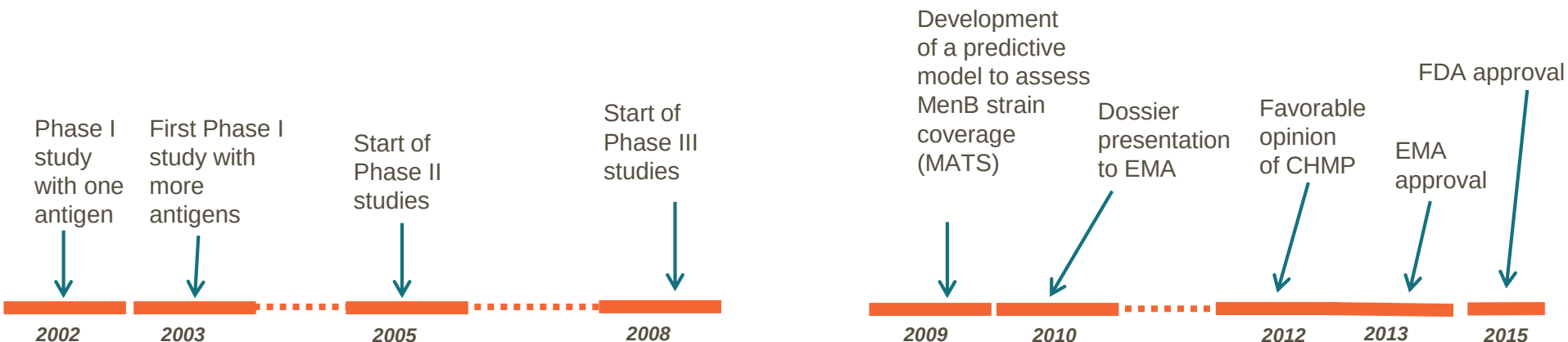


Research:

- 6 months for the complete genome
- 12 to identify protective antigens, never previously discovered by traditional approaches

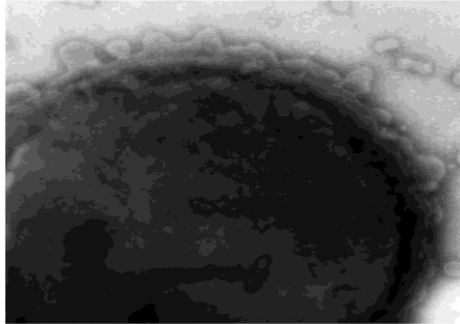
Clinical Development:

- 9 years to complete the dossier including infants, children, adolescents and adults

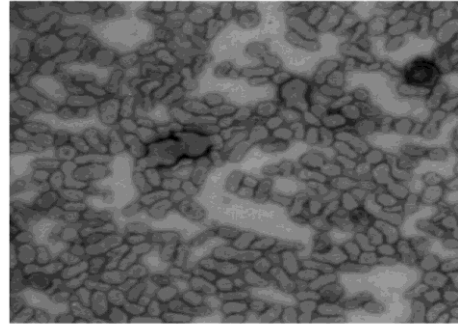


*The Institute for Genomic Research, Publications sciences: Tettelin H et al, Science 287 1809-1815, 2000; Pizza M et al, Science 287: 1816-1820, 2000

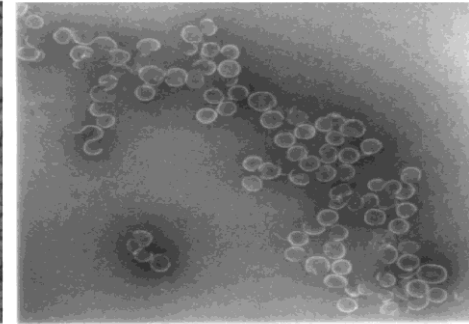
Tailor-made vaccines to specific MenB strains have been developed



"Blebbing" meningococcus

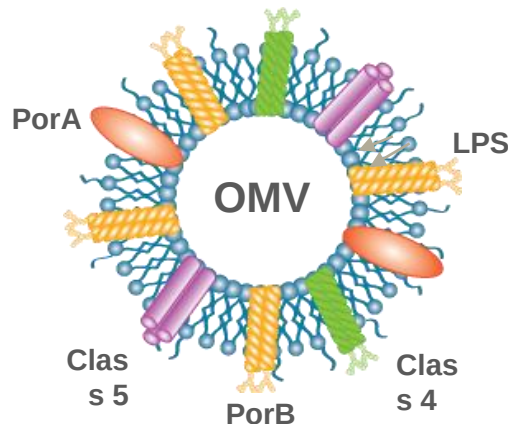


Extracted OMV vesicles

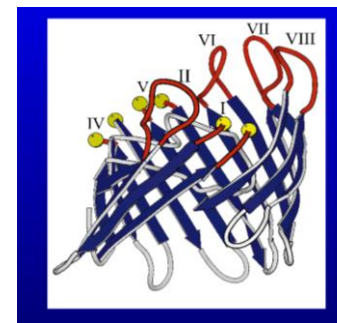


Purified LPS-depleted OMV

OMV-based serogroup B vaccines have been used in countries with outbreaks (e.g., New Zealand, Cuba, Norway), which tend to be caused by a single strain



PorA

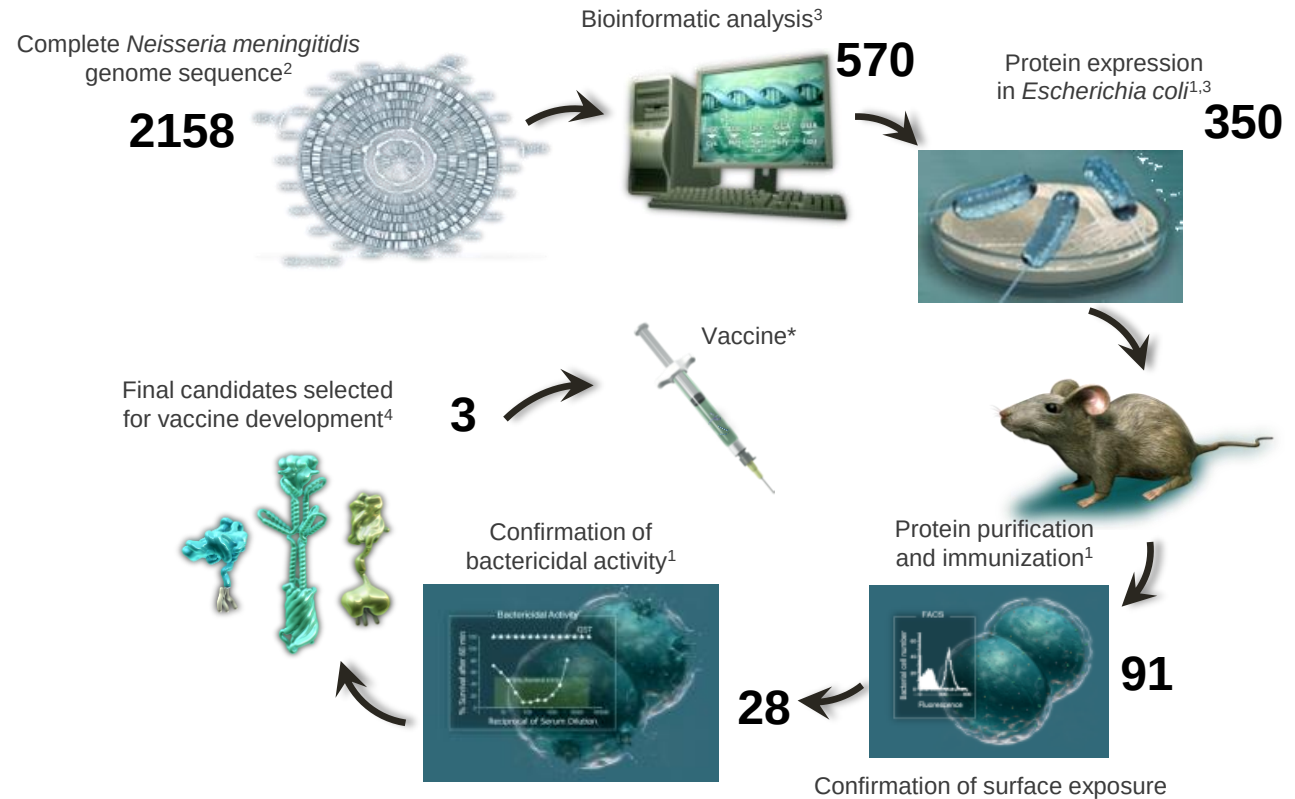


Reverse Vaccinology

A genomic-based approach to vaccine development



- Reverse vaccinology uses whole genome sequences to identify potential protein antigens that are likely to induce bactericidal antibodies¹
- Reverse vaccinology allows for the rapid identification of promising vaccine candidates that may not be discovered by traditional means¹



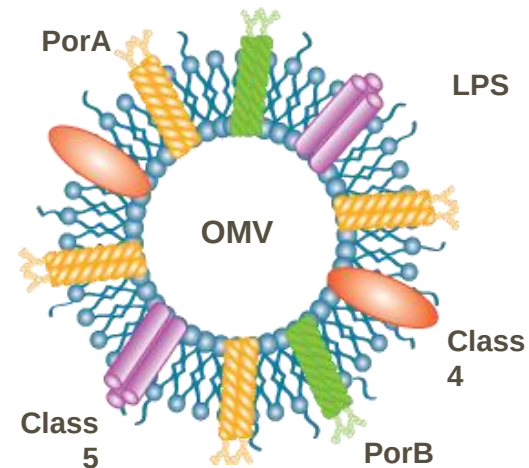
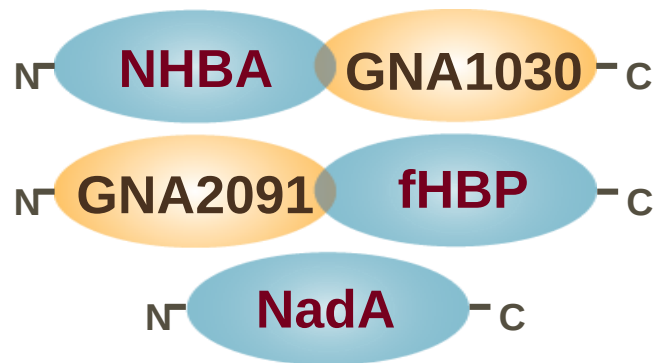
*Final candidates selected through reverse vaccinology were combined with PorA 1.4 to yield BEXSERO®.⁵

1. Serruto D, et al. *J Biotechnol.* 2004;113:15-32; 2. Tettelin H, et al. *Science.* 2000;287:1809-1815; 3. Pizza M, et al. *Science.* 2000;287:1816-1820; 4. Giuliani M, et al. *PNAS.* 2006;103:10834-10839; 5. Donnelly J, et al. *Proc Natl Acad Sci U S A.* 2010;107:19490-19495; Images are ©Hurd Studios, 2011 and 2012.

MenB vaccine composition



- Three protein antigens (two fusion proteins and one single polypeptide)^{1,2}
- Outer Membrane Vesicle (OMV) component (NZ PorA is P1.4)¹



➤ BEXSERO is a suspension for injection¹

Dose	NHBA-GNA1030	fHBP-GNA2091	NadA	OMV [¥]	Al ³⁺
0.5ml	50 µg	50 µg	50 µg	25 µg	0.5 mg

[¥]From *Neisseria meningitidis* serogroup B strain NZ98/254 measured as amount of total protein containing the PorA P1.4.

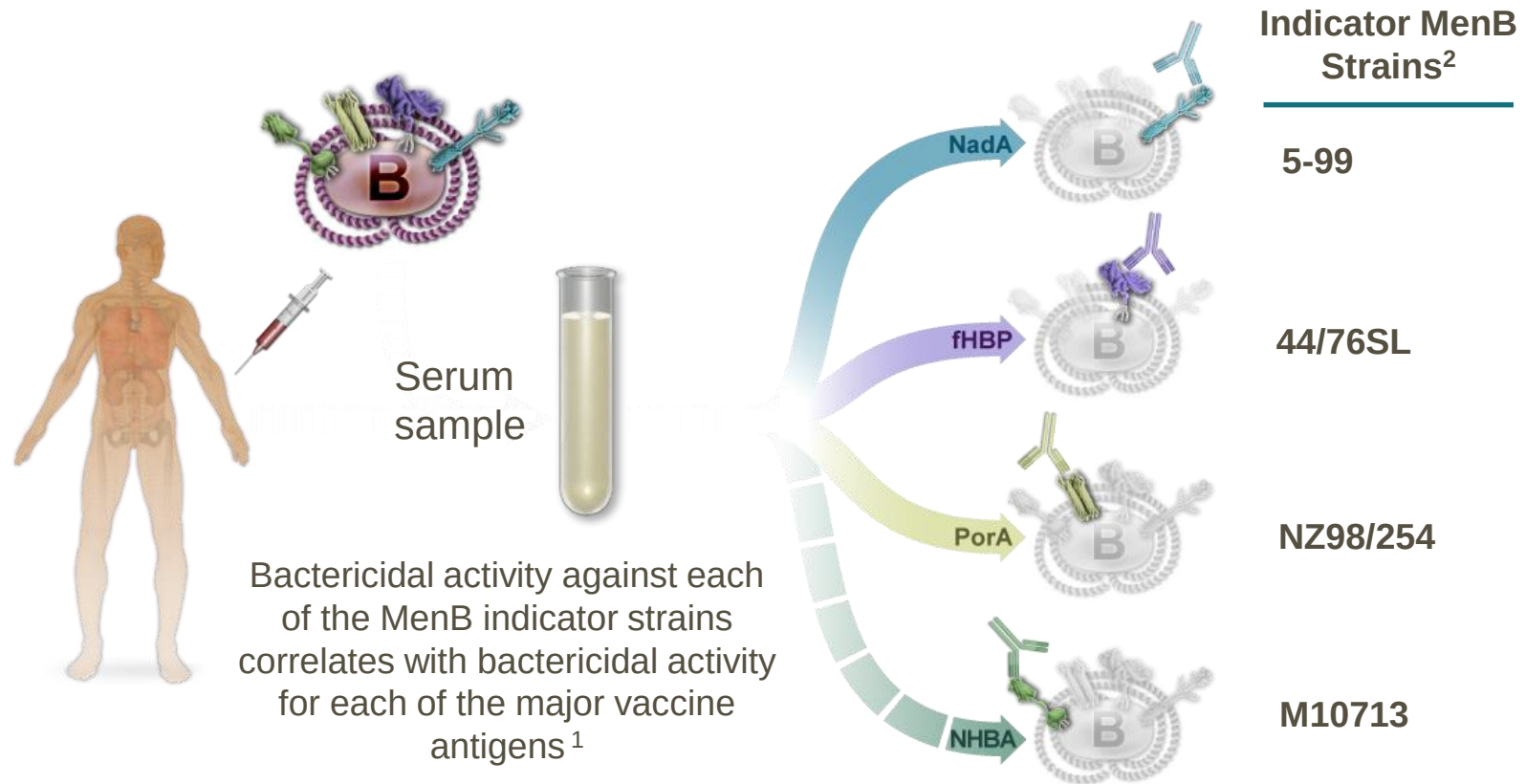
MenB, meningococcal serogroup B

4CMenB is the generic name of the 4-component recombinant meningococcal serogroup B vaccine which brand name is BEXSERO.

Evaluating BEXSERO Immunogenicity For Each of the 4 Antigenic Components



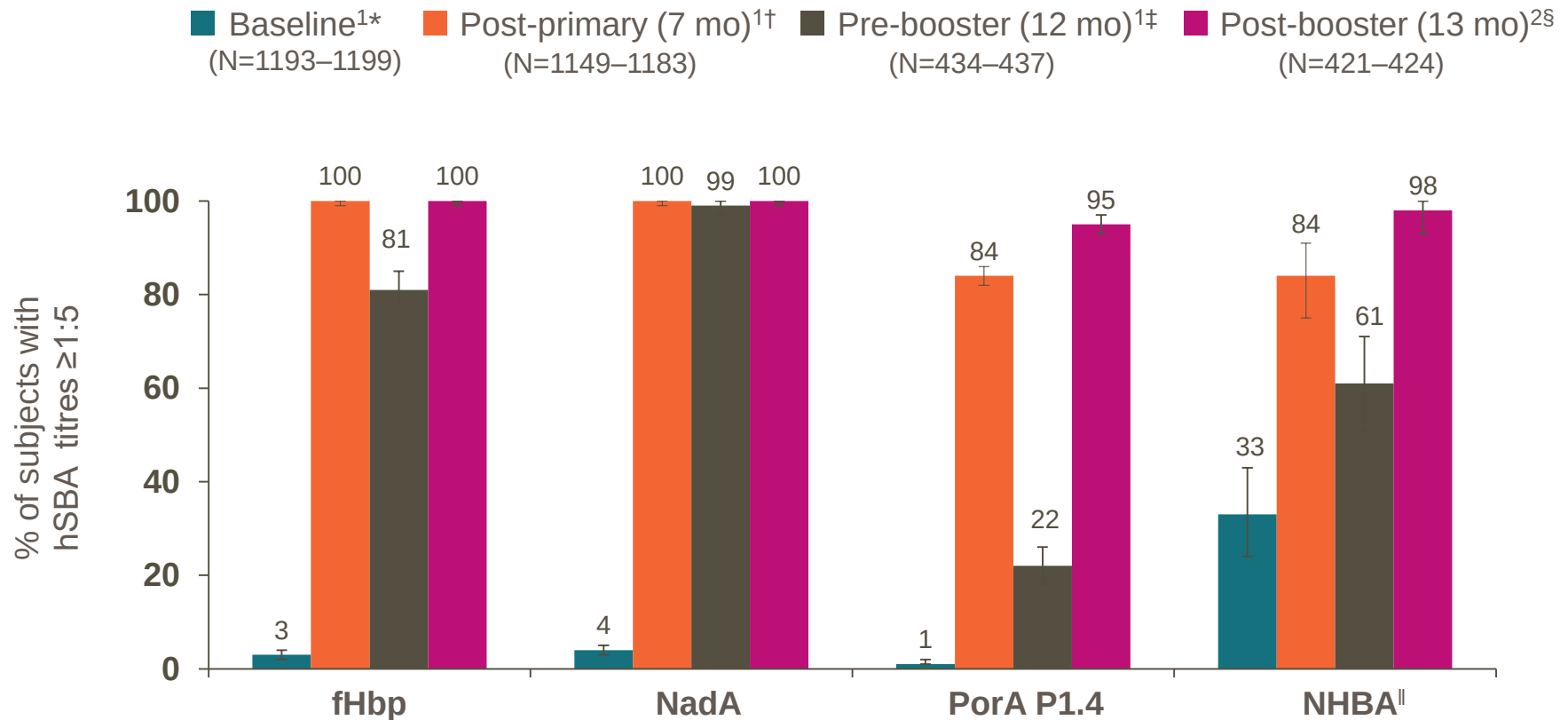
Ability of each major antigen component to induce bactericidal antibodies (surrogate for protective immunity)



MenB, meningococcal serogroup B

1. RCM BEXSERO, Settembre 2017; 2. European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Assessment Report: BEXSERO®. Updated 15 November, 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002333/WC500137883.pdf. Accessed 17Feb2016..

Immune response in infants following vaccination at 2-4-6-12 months with routine vaccines



*Blood drawn at 2 months; †Blood drawn at 7 months; ‡Blood drawn at 12 months; §Blood drawn at 13 months.

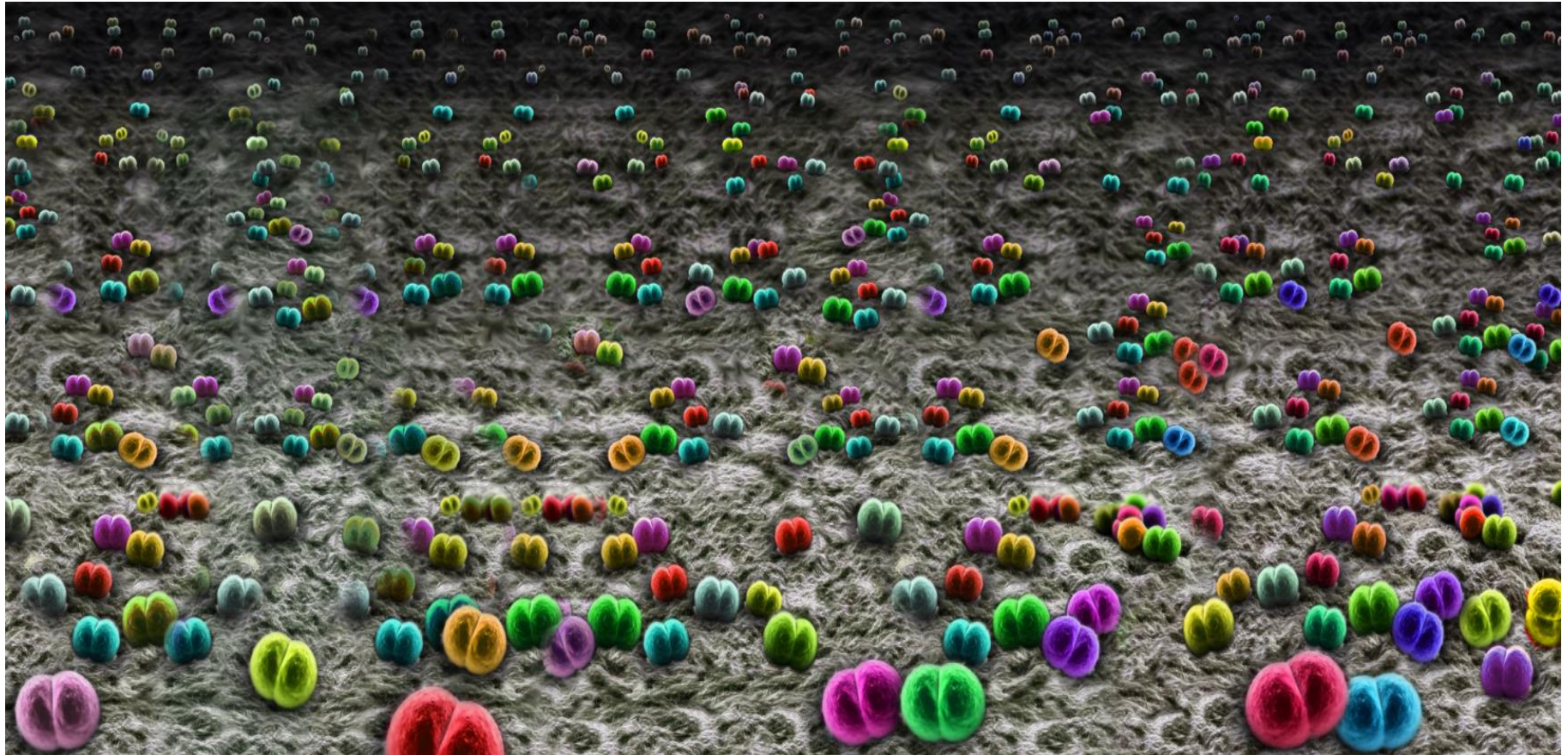
^{||}N=100 for NHBA; Numbers shown in parentheses are the number of infants across the three groups (fHbp, NadA, PorA P1.4).

Figure adapted and reprinted from *Lancet* 381, Vesikari T *et al*, Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomized trials, pages 825–835, Copyright (2013), with permission from Elsevier.

1. Vesikari T *et al*. *Lancet* 2013;381:825–835; 2. RCM BEXSERO Setembro 2017. 4CMenB is the generic name of the 4-component recombinant meningococcal serogroup B vaccine which brand name is BEXSERO.

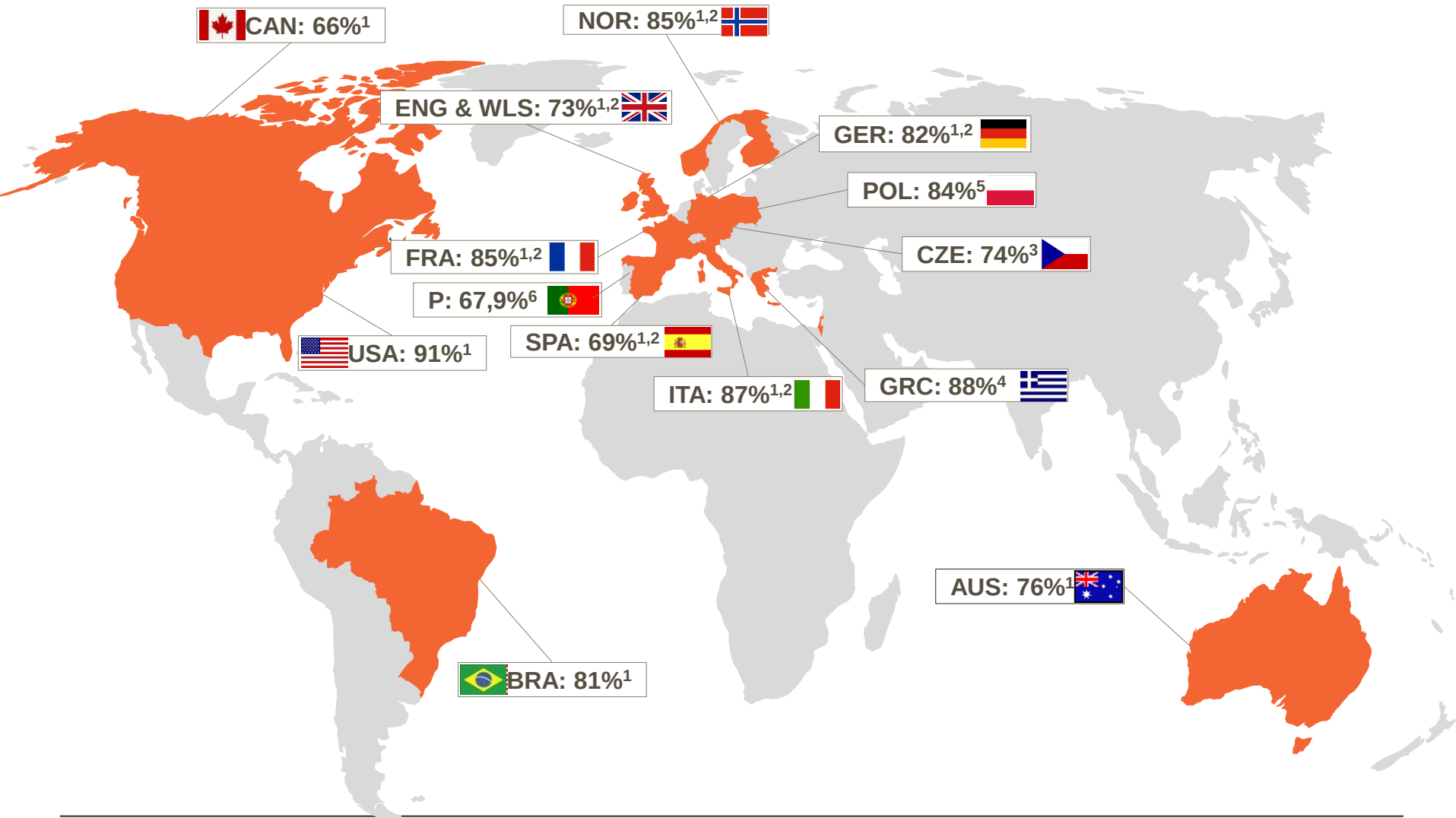
Is the vaccine able to cover diverse strains?

Meningococcal strains are very heterogeneous



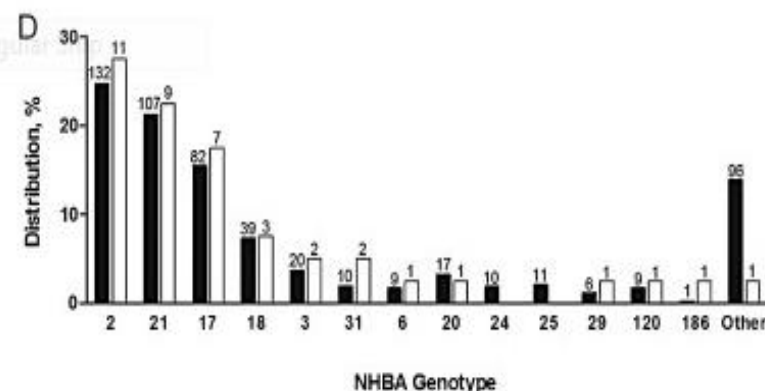
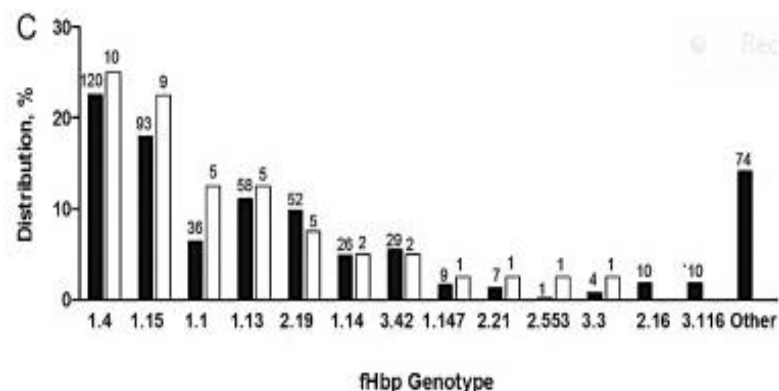
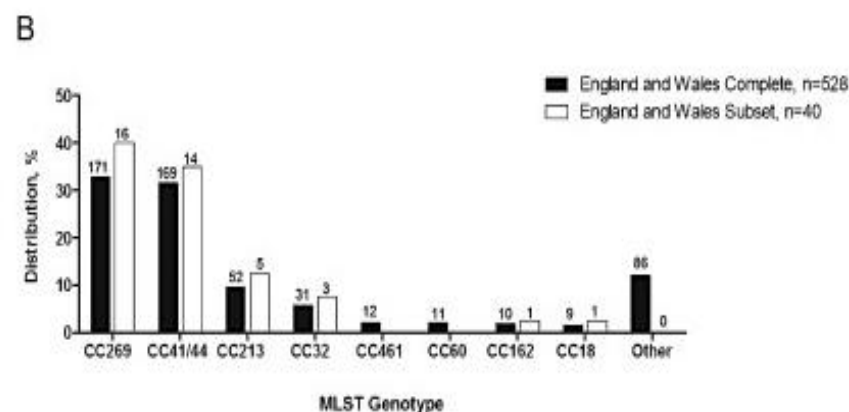
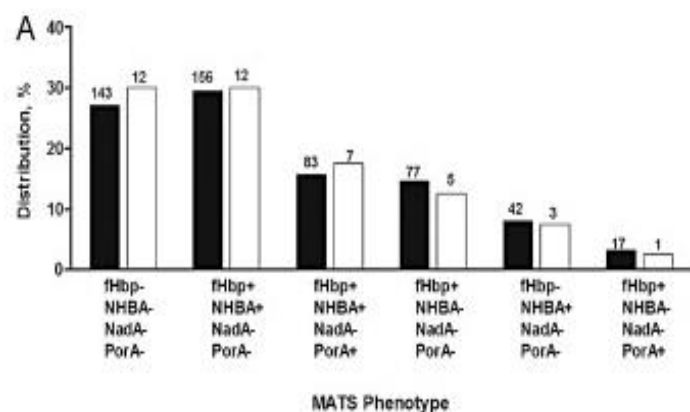
MATS coverage estimates

Meningococcal Antigen Typing System



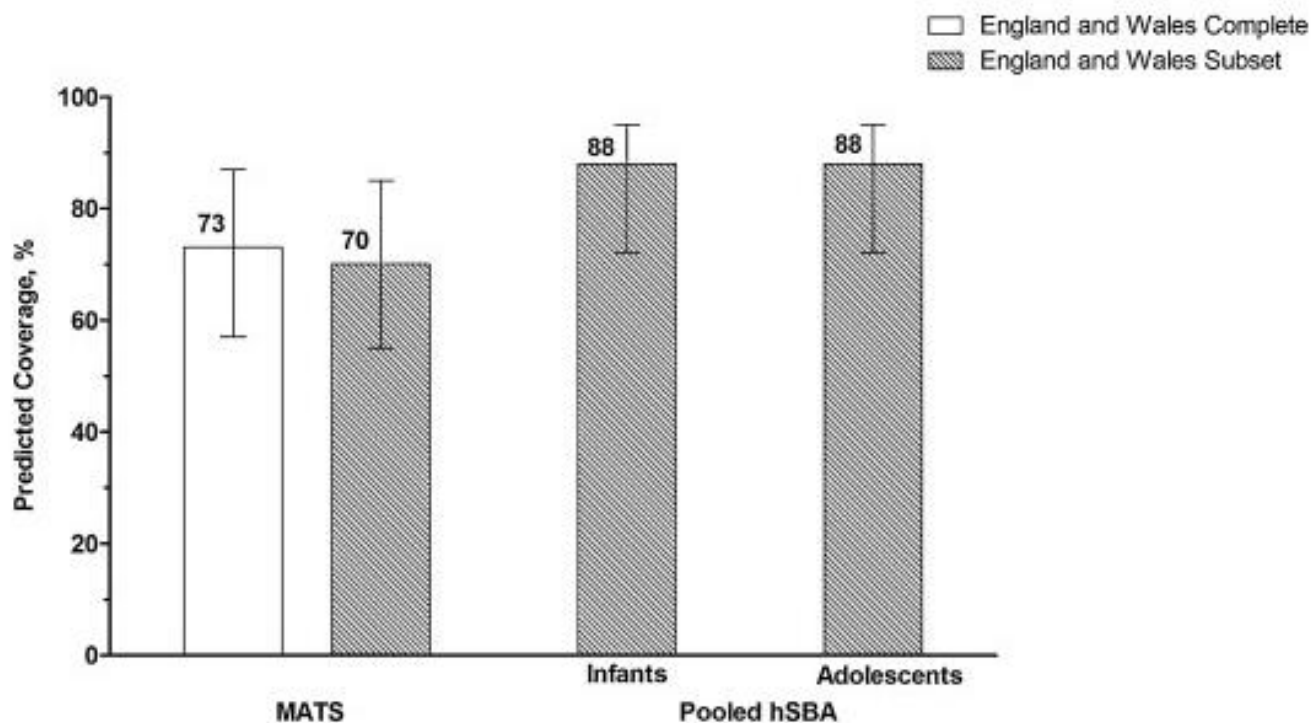
1. Medini D, et al. *Vaccine*. 2015;33:2629-2636; 2. Vogel U, et al. *Lancet Infect Dis*. 2013;13:416-425; 3. Křížová P, et al. *Epidemiol Mikrobiol Imunol*. 2014;63:103-106; 4. Tzanakaki G, et al. *BMC Microbiol*. 2014;14:111; 5. Wasko I, et al. *Vaccine*. 2016;34:510-515; 6. Simões MJ, Bettencourt C, De Paola R, Giuliani M, Pizza M, Moschioni M, et al. (2017) Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Portugal. *PLoS ONE* 12(5)

Selection of a representative panel of 40 MenB isolates from the overall panel of 535 England and Wales isolates (from July 2007 to June 2008)¹



MenB, meningococcal serogroup B

MATS is a conservative predictor of strain coverage by BEXSERO in infants and adolescents



83% effectiveness against all MenB disease, equivalent to 94% effectiveness against vaccine-preventable MenB disease¹

MATS - Meningococcal Antigen Typing System
MenB, meningococcal serogroup B

Post implementation results

National/regional immunization campaigns Aug-2015

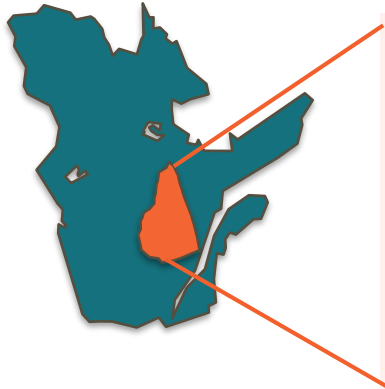


From protecting few to protecting hundreds of thousands

- **Canada**, Quebec, Saguenay-Lac-St-Jean region (completed – may be extended)¹⁻⁵
- **US**: Princeton and Santa Barbara Universities (completed)^{6,7}
- **Italy**: National Immunization Program (started in Jan 2017)^{8,9}
- **UK**: National Immunization Program (started on 01 Sep 2015)¹⁰

PIQ 2017. Édition 6. Santé et services sociaux Québec. <http://publications.msss.gouv.qc.ca/msss/fichiers/piq/chap10-3-2a.pdf>; 2. PIQ. 2017. List of updates. http://publications.msss.gouv.qc.ca/msss/fichiers/piq/piq_complet.pdf; 3. CIQ recommendations, 2014. http://www.meningitis.ca/en/Page/Files/9_Quebec%20will%20use%20new%20MenB%20Vaccine_apr_23_14.pdf; 4. Quebec Ministry of Health and Social Services. 2014. <http://publications.msss.gouv.qc.ca/msss/fichiers/2014/14-278-16W.pdf>; 5. INSPQ, 2014. Interim report. https://www.inspq.qc.ca/pdf/publications/1902_SerogroupB_Meningococcal_Vaccine.pdf; 6. CDC, 2013. <http://www.cdc.gov/meningococcal/downloads/interim-guidance.pdf>; 7. NMA 2016. <http://www.nmaus.org/disease-prevention-information/serogroup-b-meningococcal-disease/outbreaks/>; 8. PNPV 2017–2019. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf (accessed May 2017); 9. ANSA 2017. http://www.ansa.it/english/news/politics/2017/01/19/vaccine-plan-operational-in-a-few-weeks-2_16ee81fa-94c1-47c3-861b-f6ce34562e5f.html (accessed May 2017); 10. PHE, 2015. MenB vaccination: introduction from September 2015. <https://www.gov.uk/government/publications/menb-vaccination-introduction-from-1-september-2015>;

The MenB vaccination programme was implemented in Saguenay–Lac-Saint-Jean in May 2014¹



Saguenay–Lac-Saint-Jean, Quebec^{1,2}

- Targeted vaccination of **57,038** individuals residing, or attending an educational institution, in the region²
- Aged **≥2 months to ≤20 years**^{*1}
- BEXSERO® offered in schools and public health clinics¹
- Prophylactic antipyretics recommended in children aged ≤2 years to prevent fever¹

First dose¹

May to June 2014

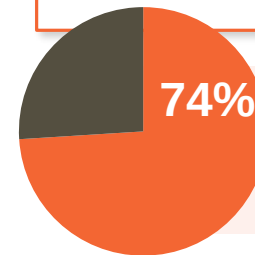
43,740 received one dose



Second dose²

As of latest press release (April 2015)

42,451 received at least two doses



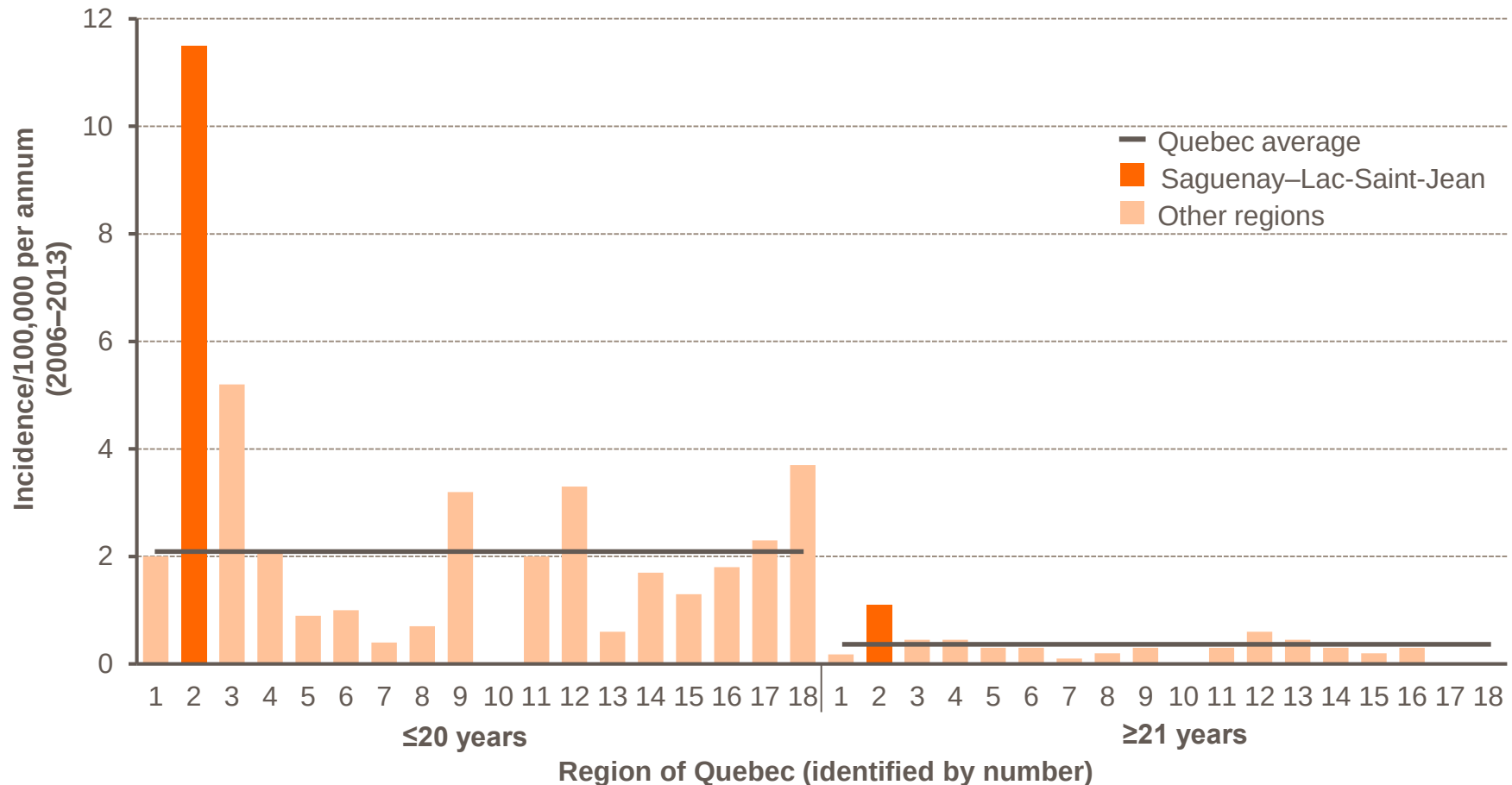
74% of target population²
(which is **97%** of total vaccine recipients) received ≥2 doses

*BEXSERO® has been approved in Canada from 2 months to 17 years of age;³ however, the upper age limit recommended by CIQ was ≤20 years of age.¹

1. INSPQ. Interim Safety Report. https://www.inspq.qc.ca/pdf/publications/1902_SerogroupB_Meningococcal_Vaccine.pdf. Accessed July 2016;

2. CIUSSS 2015 Press release. http://santesaglac.com/medias/documents/communiqués_presse/2015/COMMUNIQUE_meningoB__150415.pdf. Accessed July 2016;

In Quebec, incidence of MenB disease has been highest in the Saguenay–Lac-Saint-Jean region

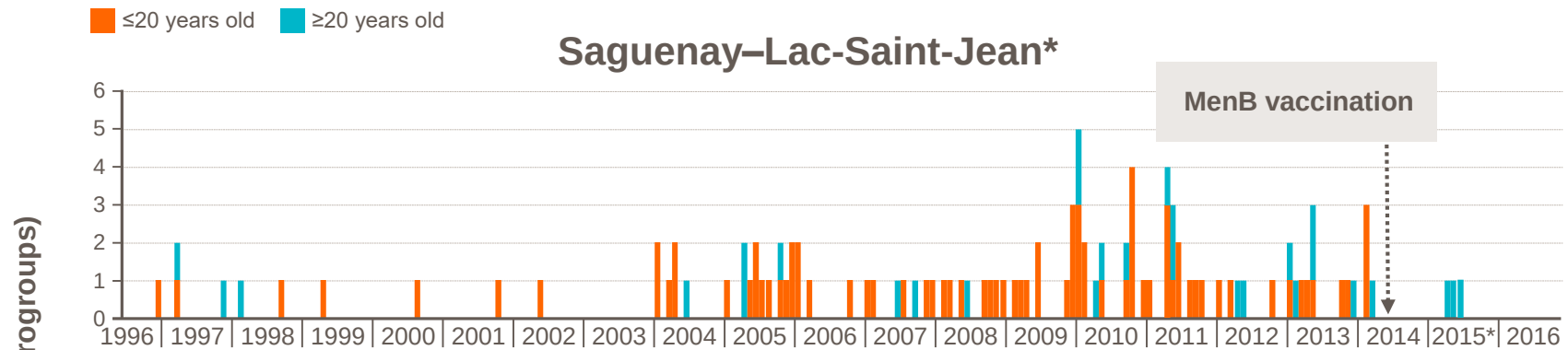


Region of Quebec:

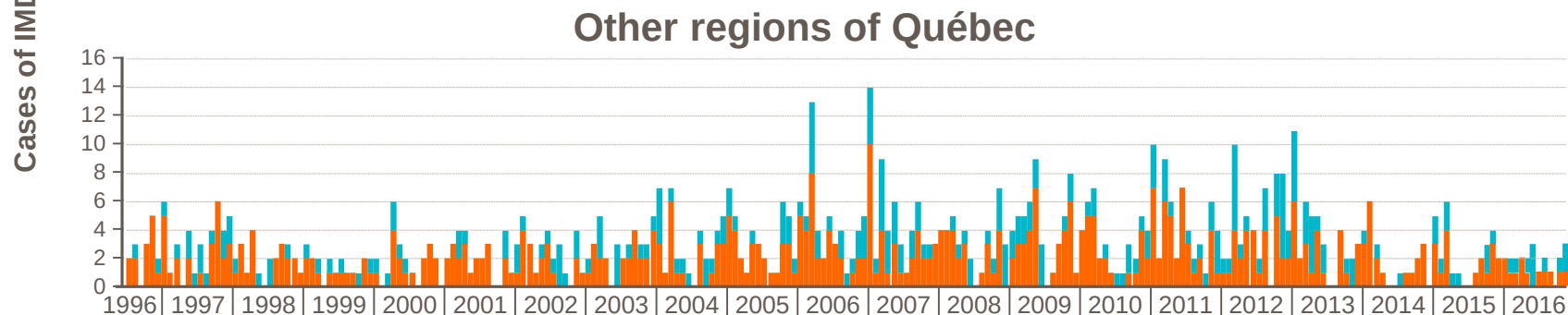
1. Bas-Saint-Laurent; 2. Saguenay–Lac-Saint-Jean; 3. Capitale-Nationale; 4. Mauricie-Bois-Franc; 5. Estrie; 6. Montréal; 7. Outaouais; 8. Abitibi-Témiscamingue; 9. Côte-Nord; 10. Nord-du-Québec; 11. Gaspésie-Îles-de-la-Madeleine; 12. Chaudière-Appalaches; 13. Laval; 14. Lanaudière; 15. Laurentides; 16. Montérégie; 17. Nunavik; 18. Terres-Cries-de-la-Baie-James

Figure adapted with permission from Institut national de santé publique du Québec (INSPQ), 2014. Avis sur la pertinence d'une intervention visant à contrôler une incidence élevée d'infections invasives à méningocoque de sérotype B dans l'Est du Québec. http://www.inspq.qc.ca/pdf/publications/1801_Infections_Invasives_Meningocoque.pdf (accessed July 2017)

No cases of IMD reported in Saguenay–Lac-Saint-Jean in vaccinated individuals after MenB vaccination was introduced (as of December 2016)



*Three cases occurred in unvaccinated individuals in March and April 2015 (one 13-year-old child and two adults)

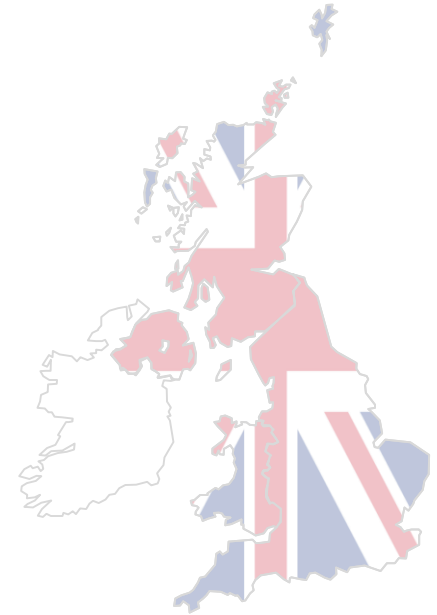


No IMD cases observed among the ~49,000 vaccinated residents
(aged 2 months to 20 years) more than 2 years after the start of the campaign*

*It was not possible to determine vaccine effectiveness; however, vaccination was associated with a significant decrease in disease risk (RR=0.22; 95% CI: 0.05–0.92; $P=0.04$); CI, confidence interval; IMD, invasive meningococcal disease; RR, relative risk

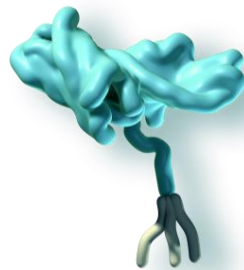
Figure adapted from De Wals P *et al.* Impact of an immunization campaign to control an increased incidence of serogroup B meningococcal disease in one region of Quebec, Canada. *Clin Infect Dis.* February 2017. DOI: 10.1093/cid/cix154, by permission of Oxford University Press

- As of May 2017, and following immunisation of at least **1.4 million children** (and administration of at least **3 million doses of Bexsero**)
- The vast majority of events related to **fever** (40%) and **localised reactions** (50%), the nature and severity of which were broadly as expected
- There was **no indication of an increase in convulsions** since the addition of Bexsero.
- No new safety signals were apparent amongst the other suspected ADRs reported, and the overall ADR reporting profile has reflected the expected reactogenicity of Bexsero.



Conclusion: Following significant exposure to Bexsero in the UK, **no unexpected safety concerns have arisen, and the expected higher rates of fever and local reactions do not appear to have had a negative impact on compliance with routine immunisation.**

Progressing
towards BEXSERO
antigens'
characterization



fHbp



NHBA

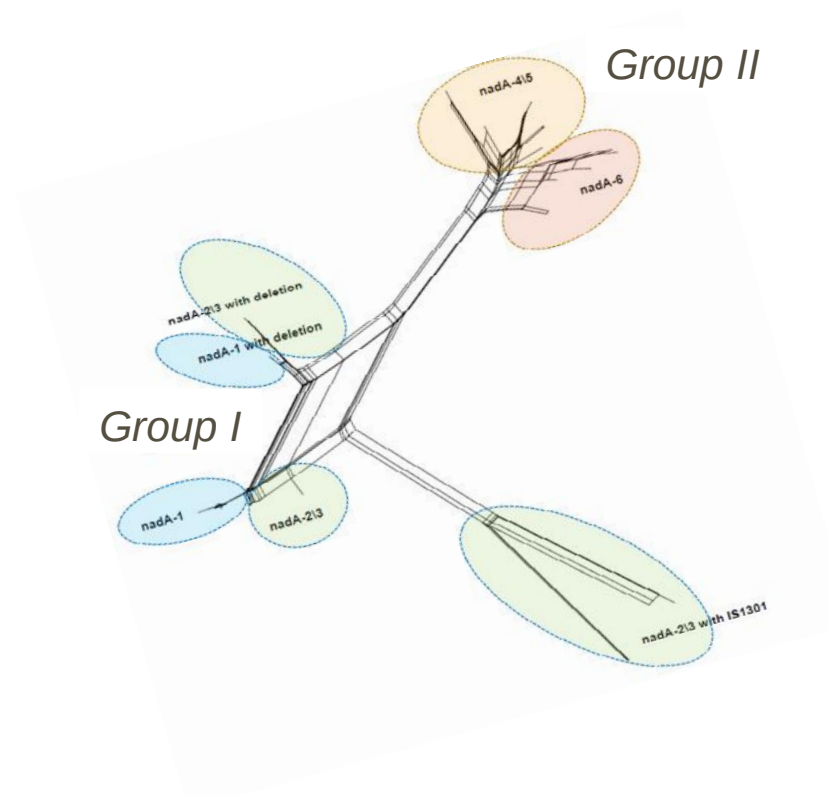


NadA

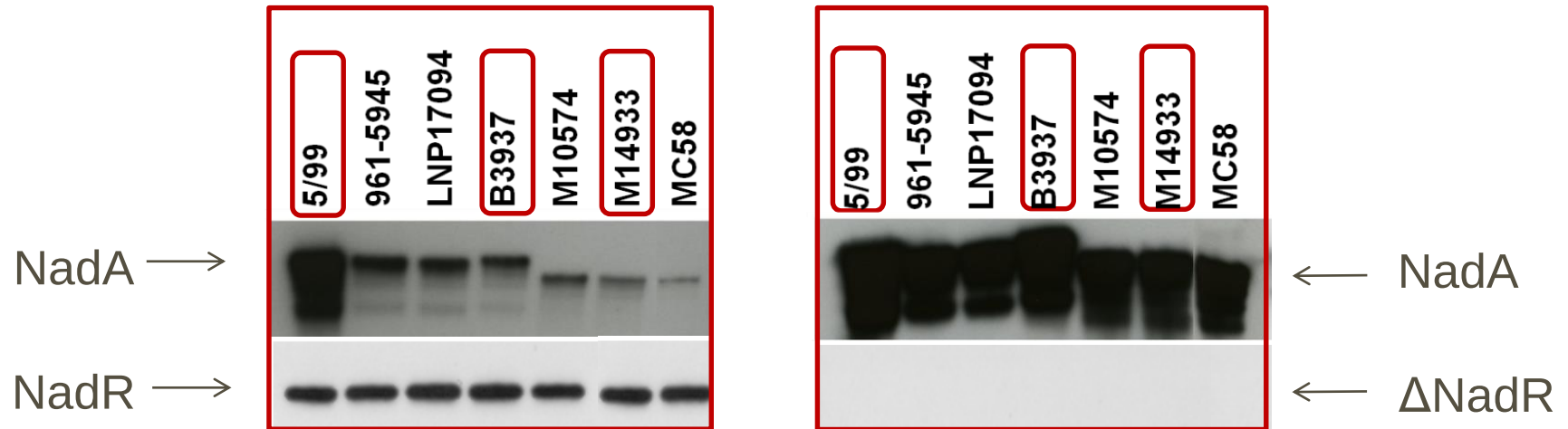
NadA (*Neisseria* adhesin A)



- NadA is a surface-exposed adhesin able to mediate adhesion and invasion of human cells^{1,2}
- *nadA* gene is not ubiquitous in meningococcal strains^{1,2}
 - Its frequency varies depending on country
- Classified into 2 main groups³
 - Group I includes the three main variants (1, 2 and 3), with cross-protective activity
 - Group II includes three more rare variants (4, 5 and 6)
- Structurally, it belongs to the class of oligomeric coiled-coil adhesins^{1,2}



NadA expression is variable among strains and influences hSBA results

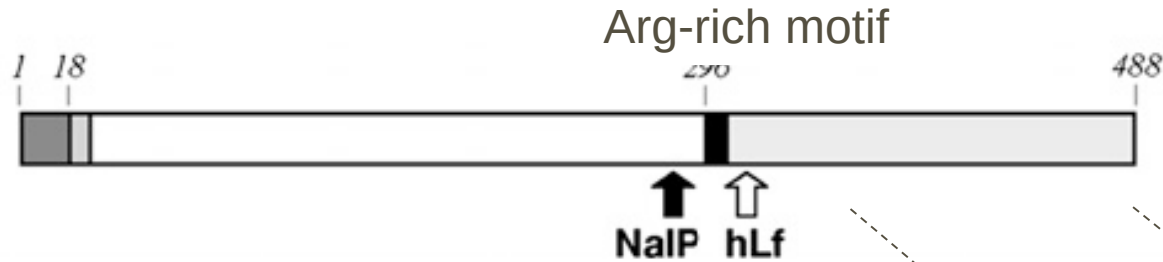


Strain	NadA expression	4CMenB pool infant sera	
		Pre	Post 4
5/99 wt	++++	4	>2048
M14933 wt	+	<2	32
B3937 wt	+	<2	<2

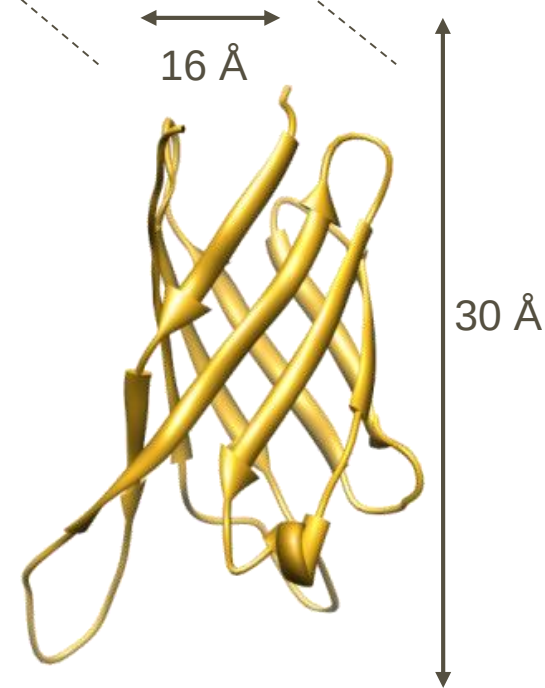
NHBA Neisseria Heparin Binding Antigen (GNA2132)



Features of the protein



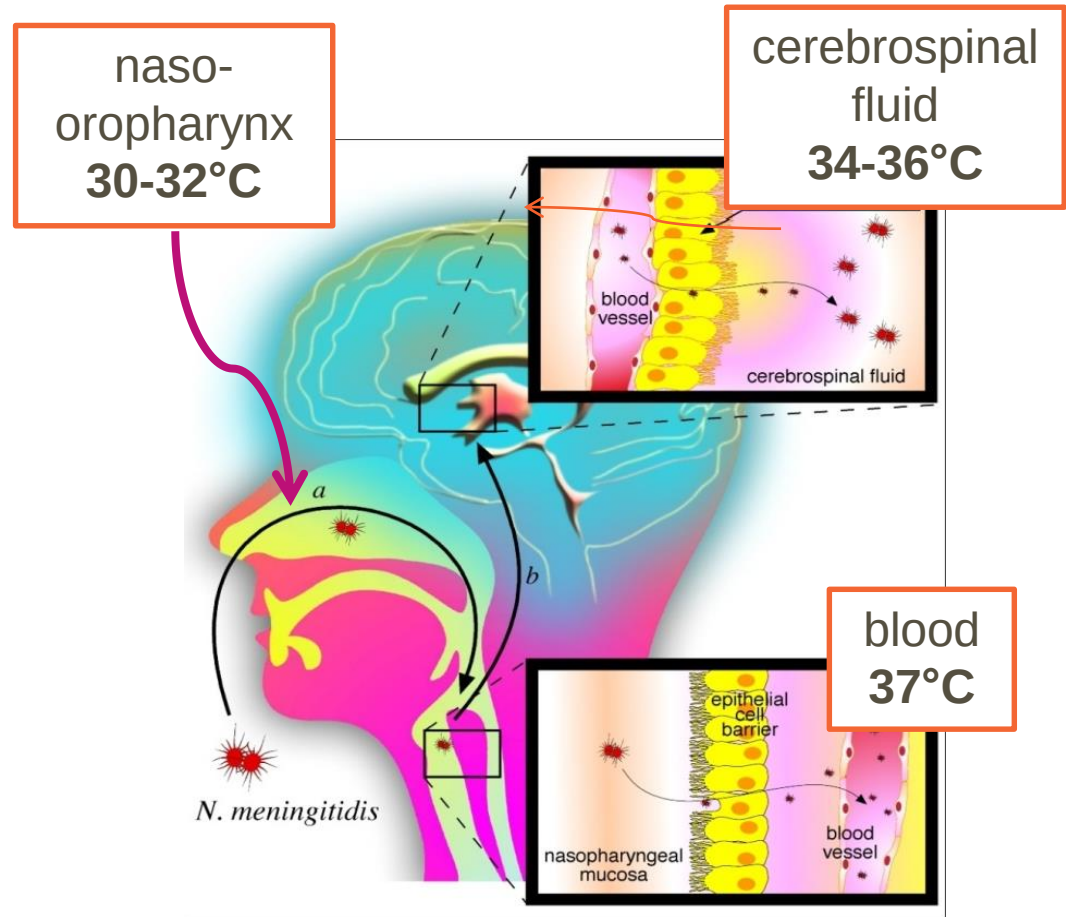
- Surface exposed lipoprotein
- It is ubiquitous in meningococci and other Neisserial species
- It is target of NalP and hLf protease activities
- It binds Heparin-like molecules through an Arg-rich motif
- C-term is a Beta-barrel domain
- It acts as an adhesin and could have a potential role in adhesion



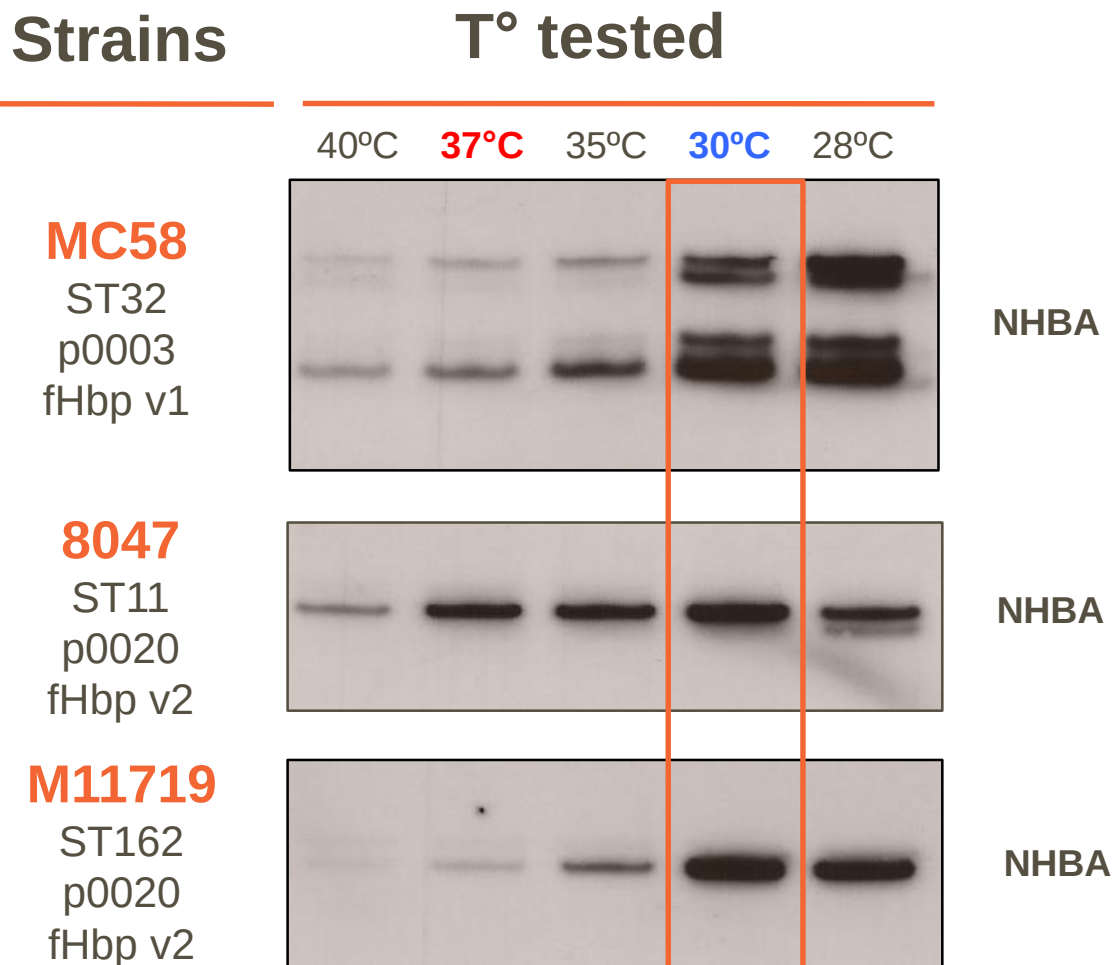
Nm encounters different temperatures during colonization and disease



Nm growth in the lab
37°C



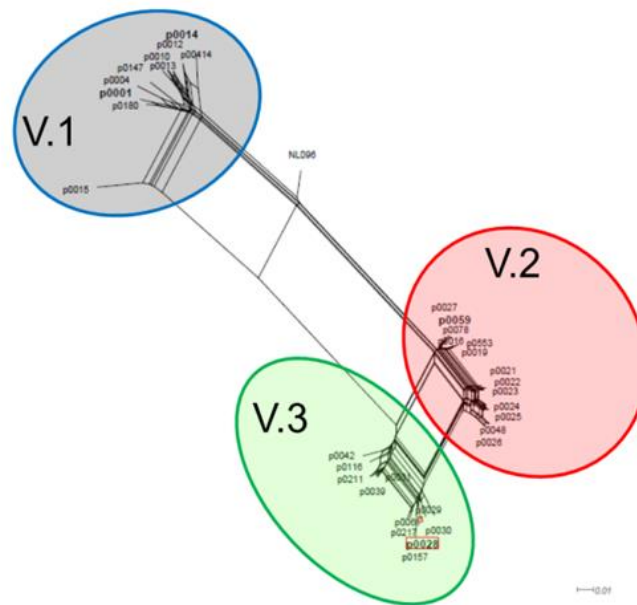
NHBA expression is maximal at ~30°C, a temperature detected in the upper respiratory tract



Factor H binding protein



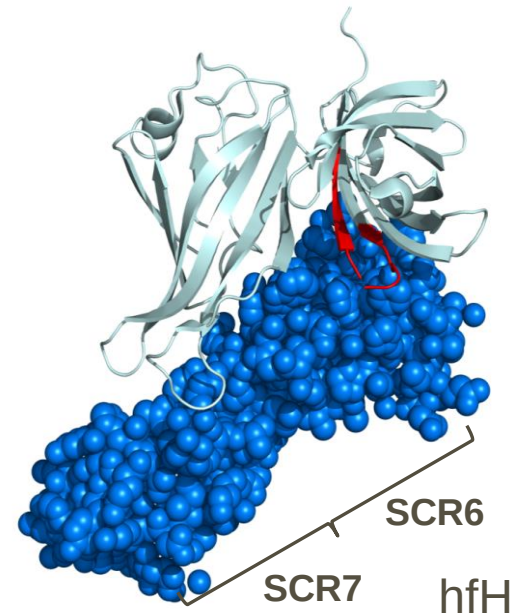
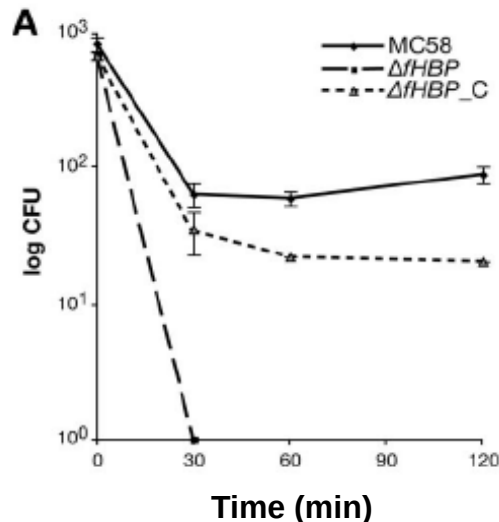
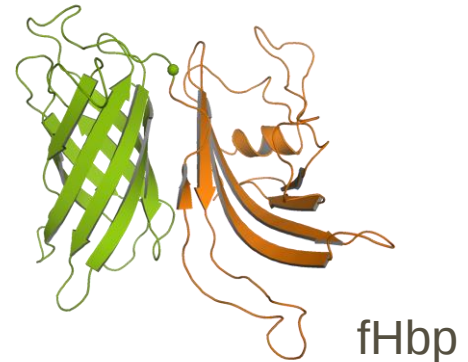
- fHbp gene is present in most meningococcal strains
- fHbp exists in 3 different genetic and immunogenic variants (v1, v2, v3), also referred to as subfamilies (A and B)



fHbp is a surface exposed lipoprotein which binds the human complement regulatory protein factor H (fH)



- Binding to fH enables bacterial survival in the bloodstream
- fH binding site is spread along the fHbp sequence
- Antibodies against fHbp can block the binding of fH and increase the susceptibility to killing by the complement alternative pathway
- Several mAbs against fHbp have been generated

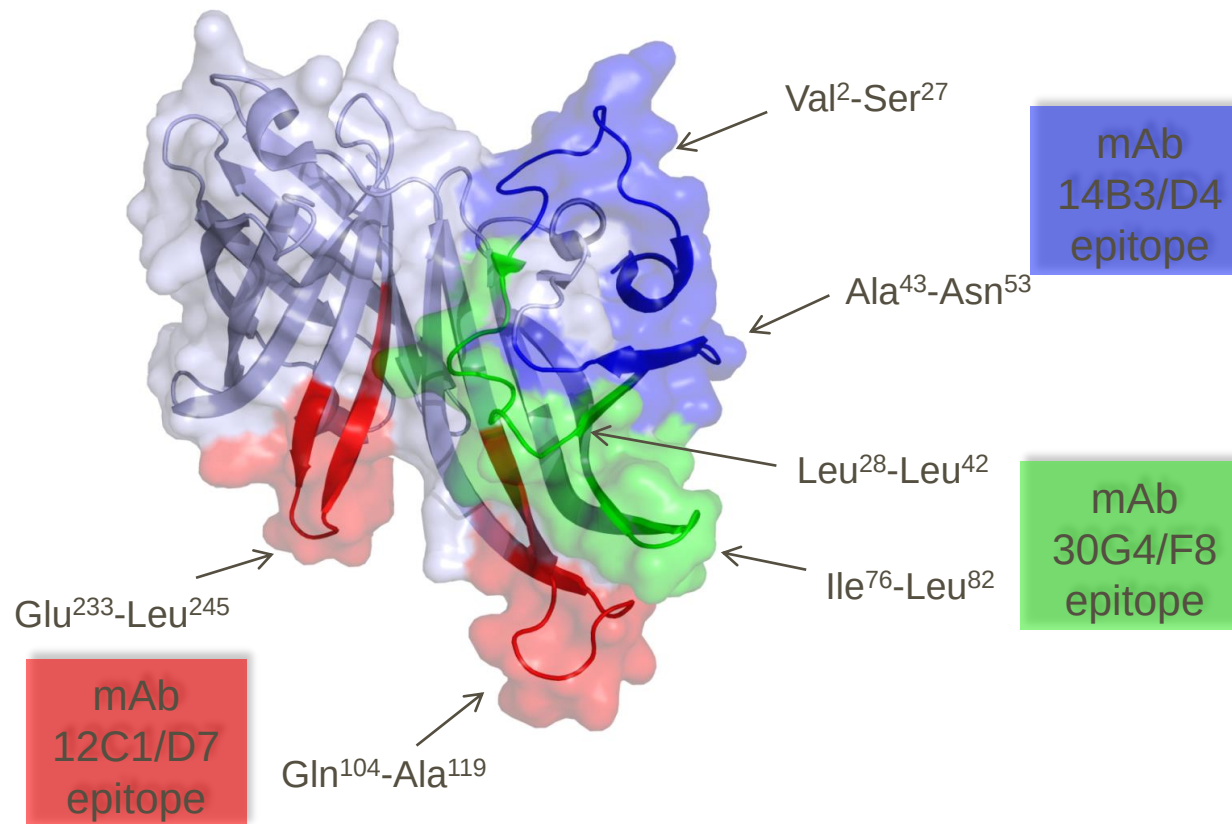


Different Mabs recognize different portions of fHbp

Mapping performed by Hydrogen Deuterium Exchange (H/DX)

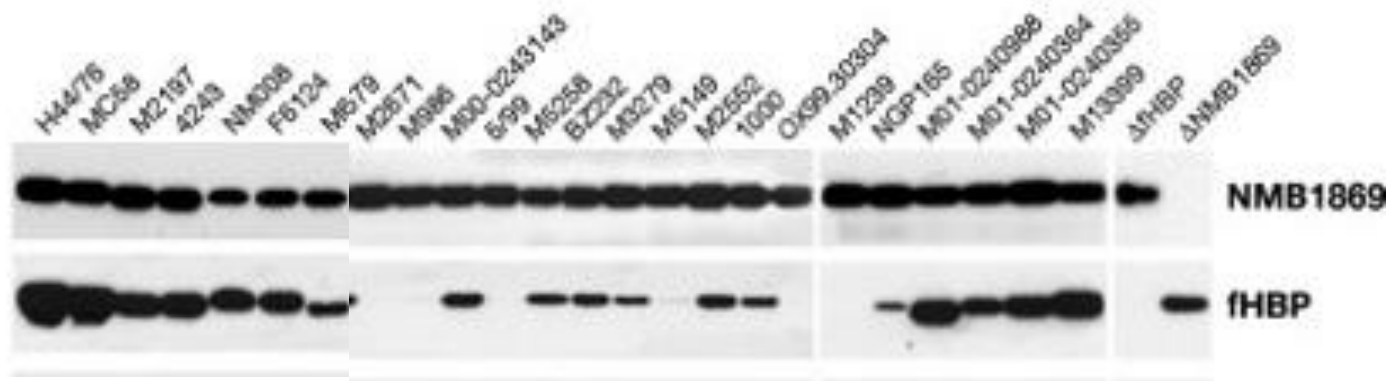


- Epitopes mainly on variable regions and this could explain the lack of cross-protection between fHbp variants



fHbp is variable in sequence and in expression level

- fHbp expression is variable among strains
 - Level of fHbp greatly influences strains' susceptibility to killing

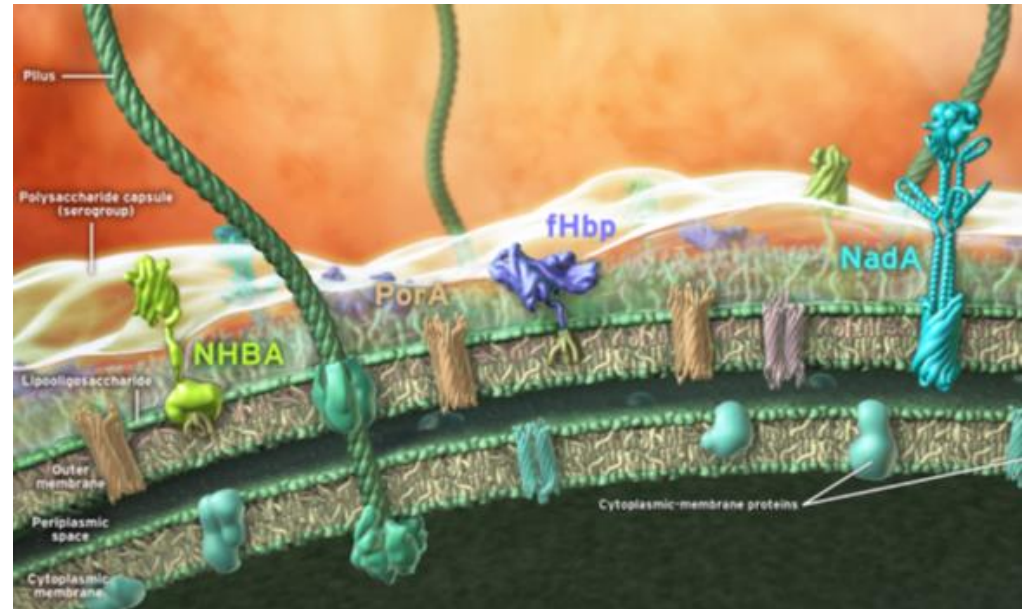


- Methods currently used for antigen quantification (FACS, WB, MATS) are based on antibodies and therefore they measure a combination of antigen quantity and antigen diversity
- Strains with frameshift mutations in fHbp have been recently identified.

BEXSERO Antigenic Components Are Important for Meningococcal Survival, Function, or Virulence



- **fHbp: factor H binding protein**
 - Binds factor H, which enables bacterial survival in the blood^{1,2}
- **NadA: neisserial adhesin A**
 - Promotes adherence to and invasion of human epithelial cells³⁻⁵
 - Antibodies could interfere in colonization⁴
- **NHBA: neisserial heparin-binding antigen**
 - Present in virtually all strains⁶⁻⁷
 - Binds heparin and heparan sulfate PGs via the Arg-rich region⁶
 - Binding increase the serum resistance
 - Mediate adhesion
- **NZ PorA 1.4: porin A**
 - Major outer membrane vesicles protein – induces strain specific bactericidal response⁸



A vaccine based on multiple antigens has the ability to protect also against strains expressing low amount of an antigen or very diverse in sequence and decrease the risk of immune evasion^{9,10}



Towards a meningitis free world

Questions?

Mariagrazia Pizza

Senior Scientific Director Bacterial Vaccines

GSK Siena, Italy

BEXSERO Medicamento Sujeito a Receita Médica

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