Public Health England

Protecting and improving the nation's health

Meningococcal B vaccine. Is vaccine effectiveness confirmed?

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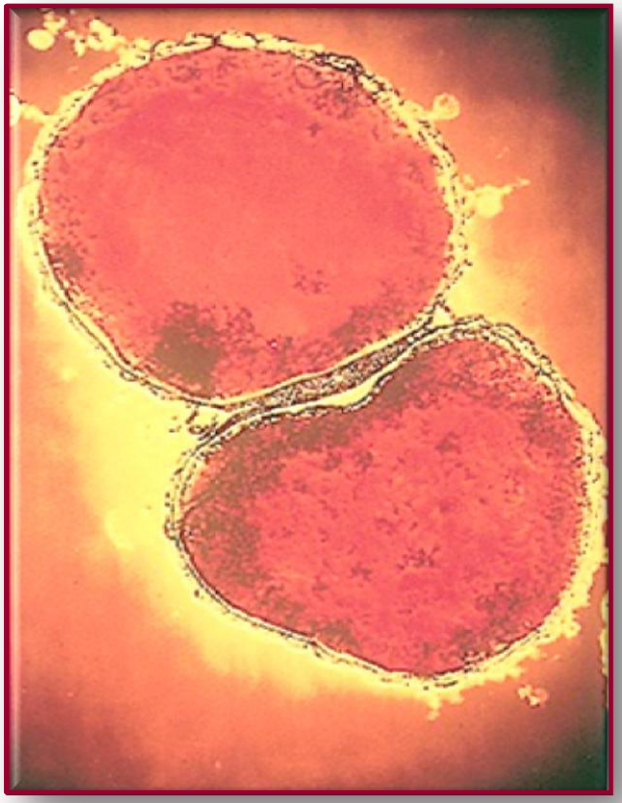
Meningococcal serogroups

- The polysaccharide capsule is used to classify into 12 distinct serogroups, 5 main serogroups cause the majority (95%) of all meningococcal disease around the world – A, B, C, W and Y.

- Polysaccharide vaccines were licensed for serogroups A, C, W and Y in the 1970s.
- Conjugate vaccines from 1999.
- Serogroup B vaccines licensed from 2013.



N. meningitidis, Gram-negative diplococci: magnification x20,000 at 35 mm size. Reproduced with permission from Science Photo Library http://www.sciencephoto.com

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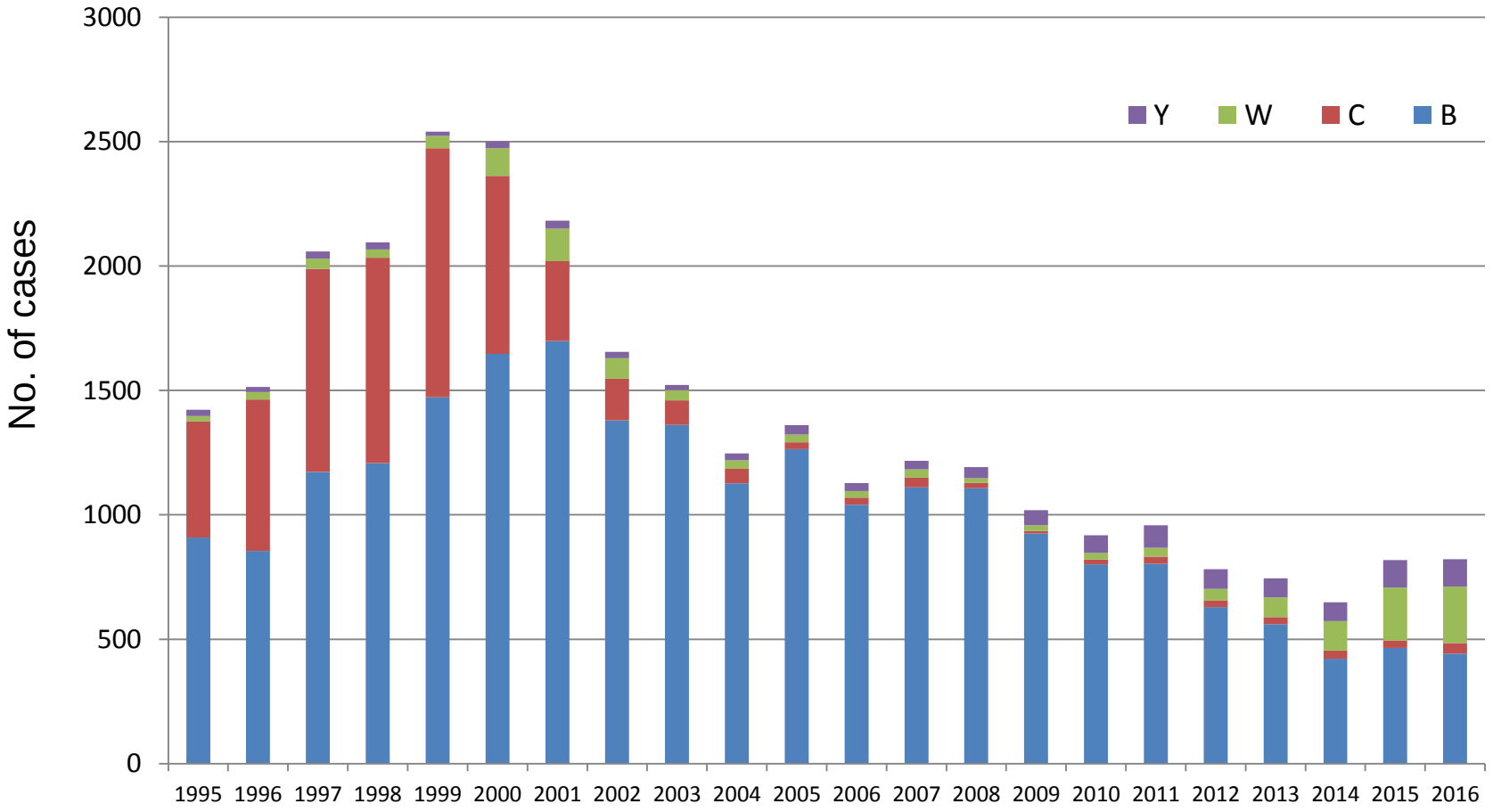
Laboratory confirmed cases of meningococcal disease in England & Wales, 1995 to 2016



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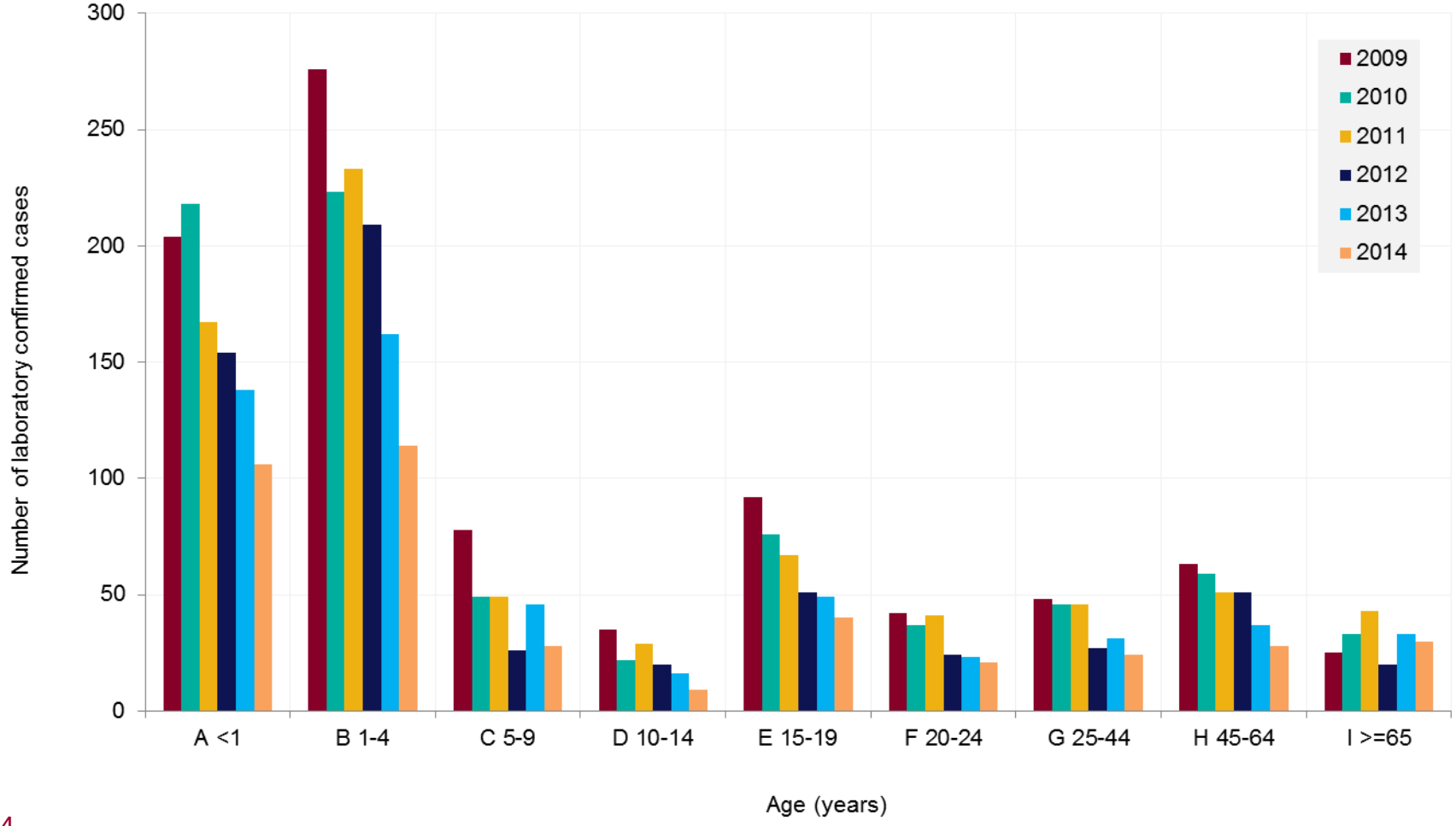
Laboratory confirmed cases of invasive meningococcal disease capsular group B (MenB) in England, calendar years 2009-2014



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Why is there no MenB polysaccharide vaccine?

- MenB polysaccharide is polysialic acid, a compound identical to that found on the surface of human neuronal cells.

- Consequently;

  (i) Poorly immunogenic.

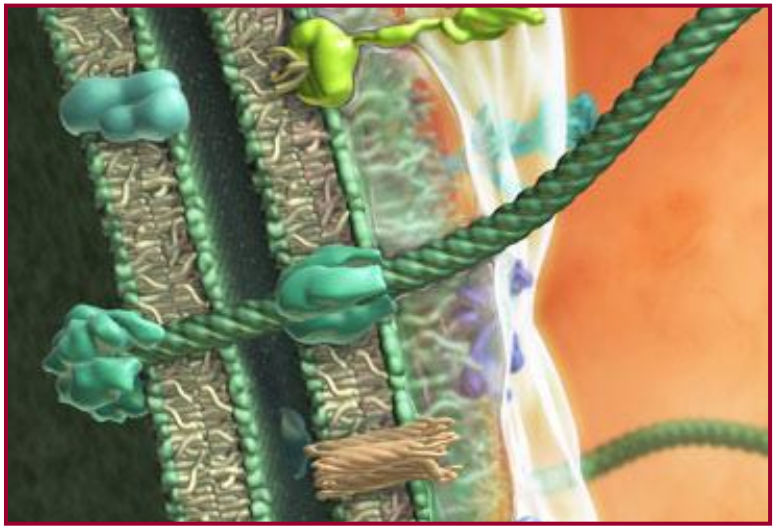
  (ii) Potential to induce an autoimmune response.

- Use subcapsular antigens, which are;

  (i) Surface exposed.

  (ii) Conserved.

  (iii) Induce bactericidal activity.



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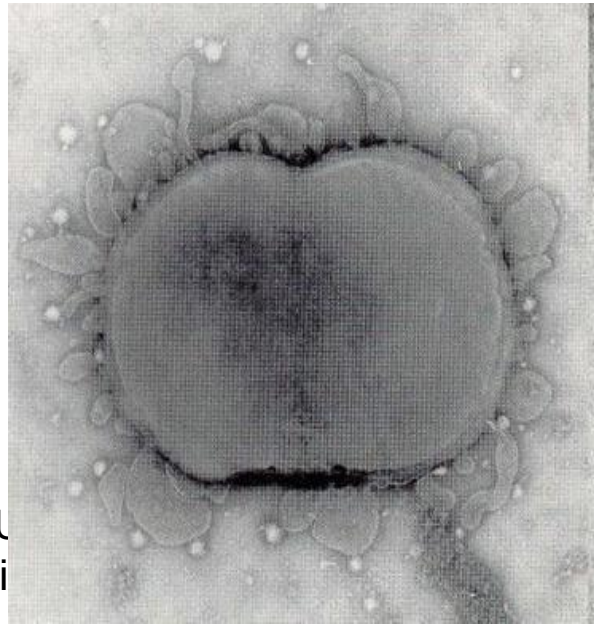
Subcapsular approaches

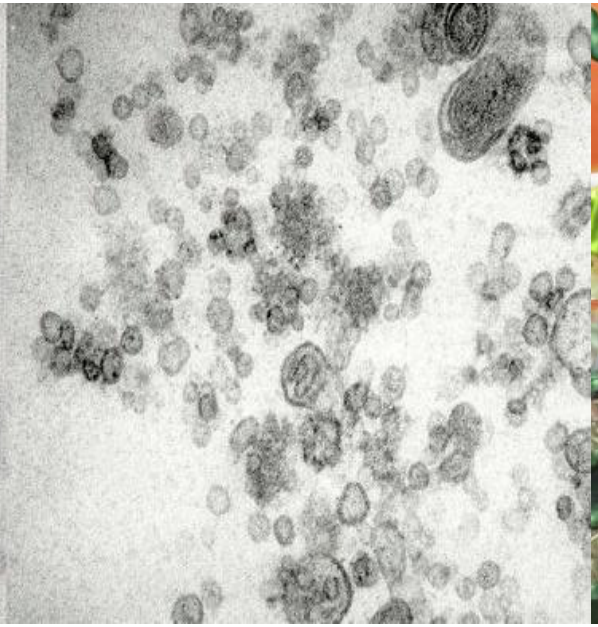
- Development of subcapsular antigen vaccines has broadly followed two pathways-

(i) Outer membrane vesicles (OMVs)

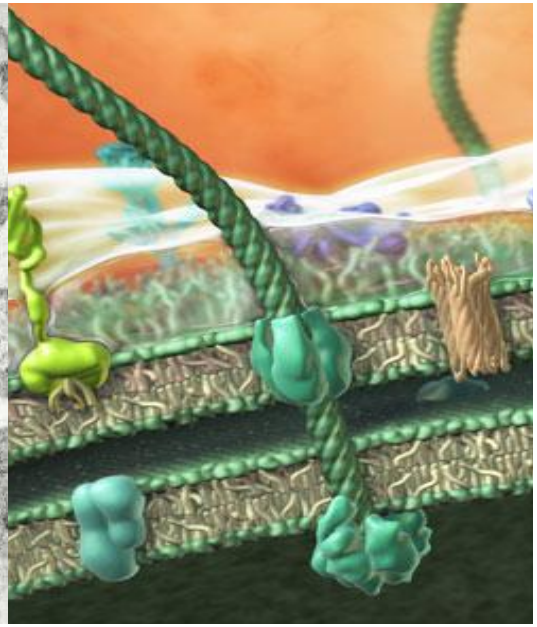
(ii) Individual proteins



Blebbing



Purified OMVs



OMV cross section

- U
epi

- Immune response is primarily directed against the PorA protein, resulting in limited cross-protection.

Purified or recombinant outer membrane proteins showing multiple antigens

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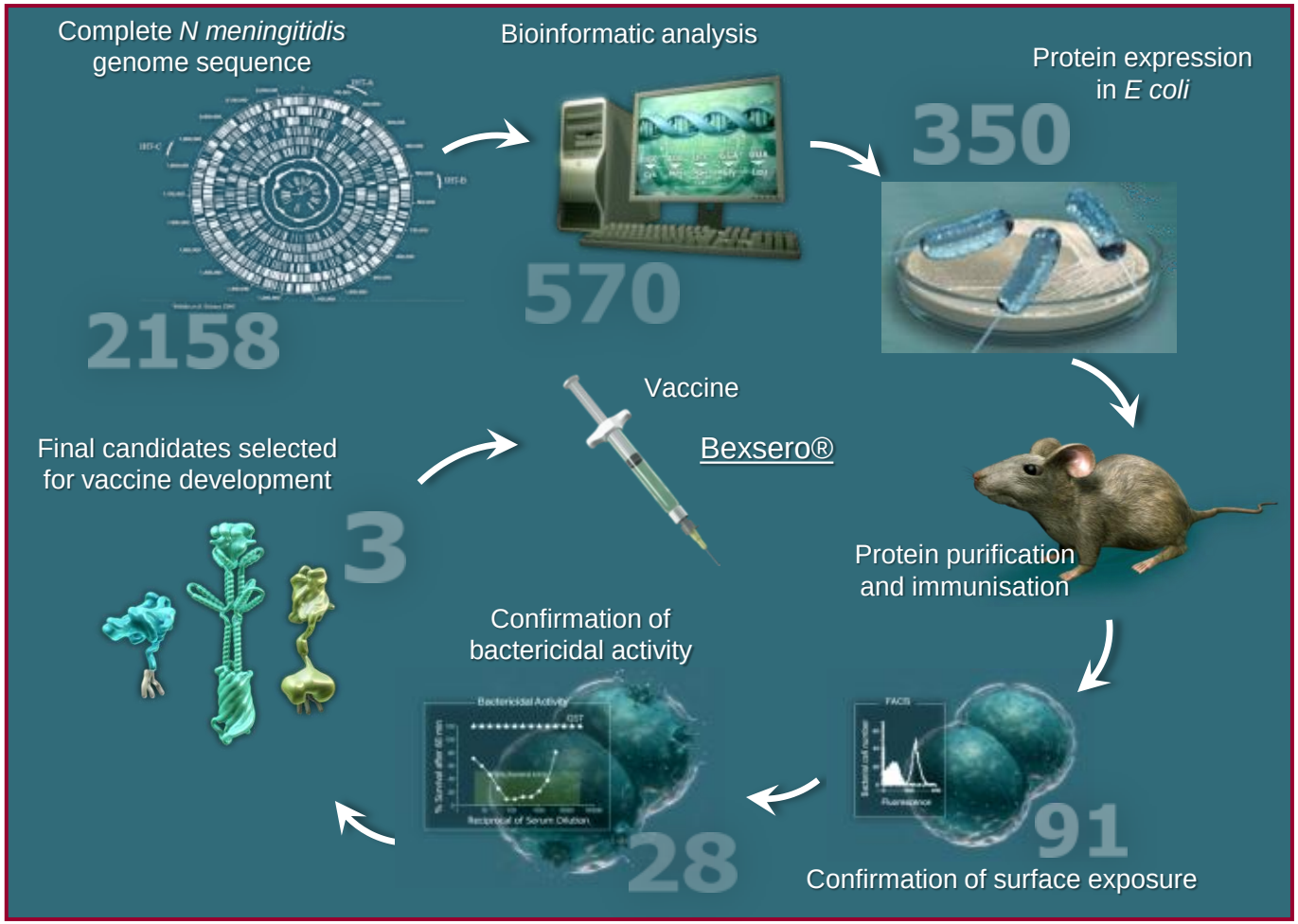
Reverse vaccinology- a genomic based approach to vaccine development

Reverse vaccinology uniquely allows rapid identification of promising vaccine candidates:

- Scan genome sequences
- Identify potential protein antigens
- Verify surface expression and bactericidal activity
- Vaccine candidates selected



1. Tettelin H, *et al., Science*. 2000;287:1809-1815; 2. Rappuoli R. *Vaccine*. 2001;19:2688-2691; 3. Pizza M, *et al., Science*. 2000;287:1816-1820.

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Bexsero (GSK) components

Three recombinant proteins discovered by reverse vaccinology

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

Bexsero® formulation

Dose	fHbp fusion protein	NadA protein	NHBA fusion protein	OMV	AL^{3+}
0.5 mL	50 µg	50 µg	50 µg	25 µg	0.5 mg

1.Donnelly J, et al. *Proc Natl Acad Sci U S A*. 2010;107:19490-19495;
2. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2014.

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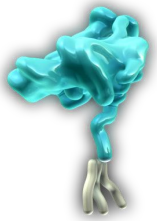
Bexsero, antigen diversity and cross-reactivity of induced antibody

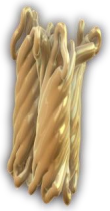
fHbp

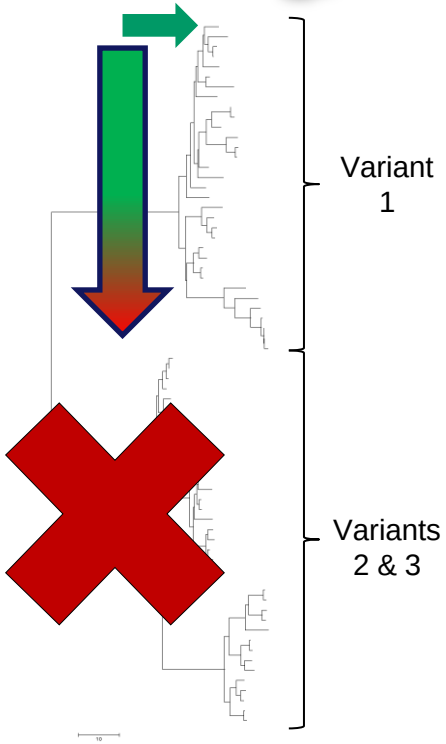


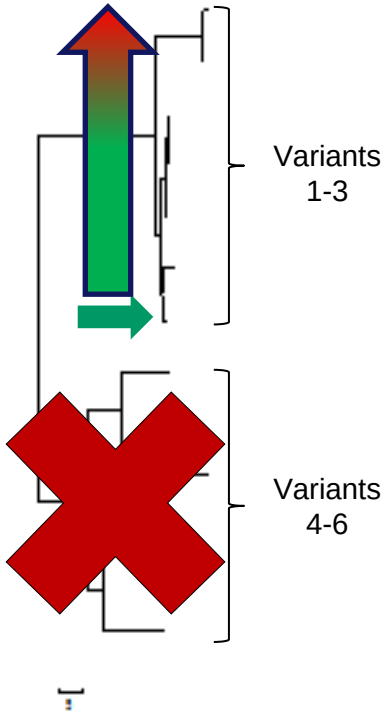
NadA

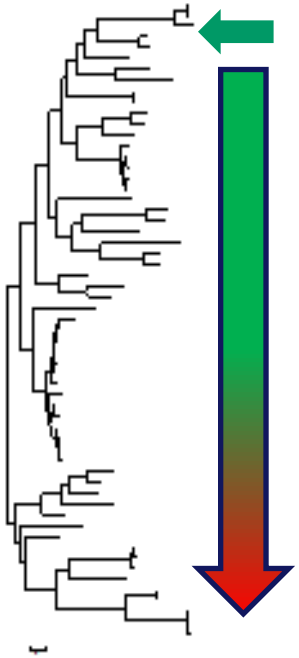
NHBA

PorA









785 VR2 variants[1]

limited cross-reactivity to alternative variants

Vogel U *et al.*, *Lancet Infect Dis* 2013;13:416-25.
Variant contained within vaccine.
[1]Pubmlst.org- last updated 10/10/2016.

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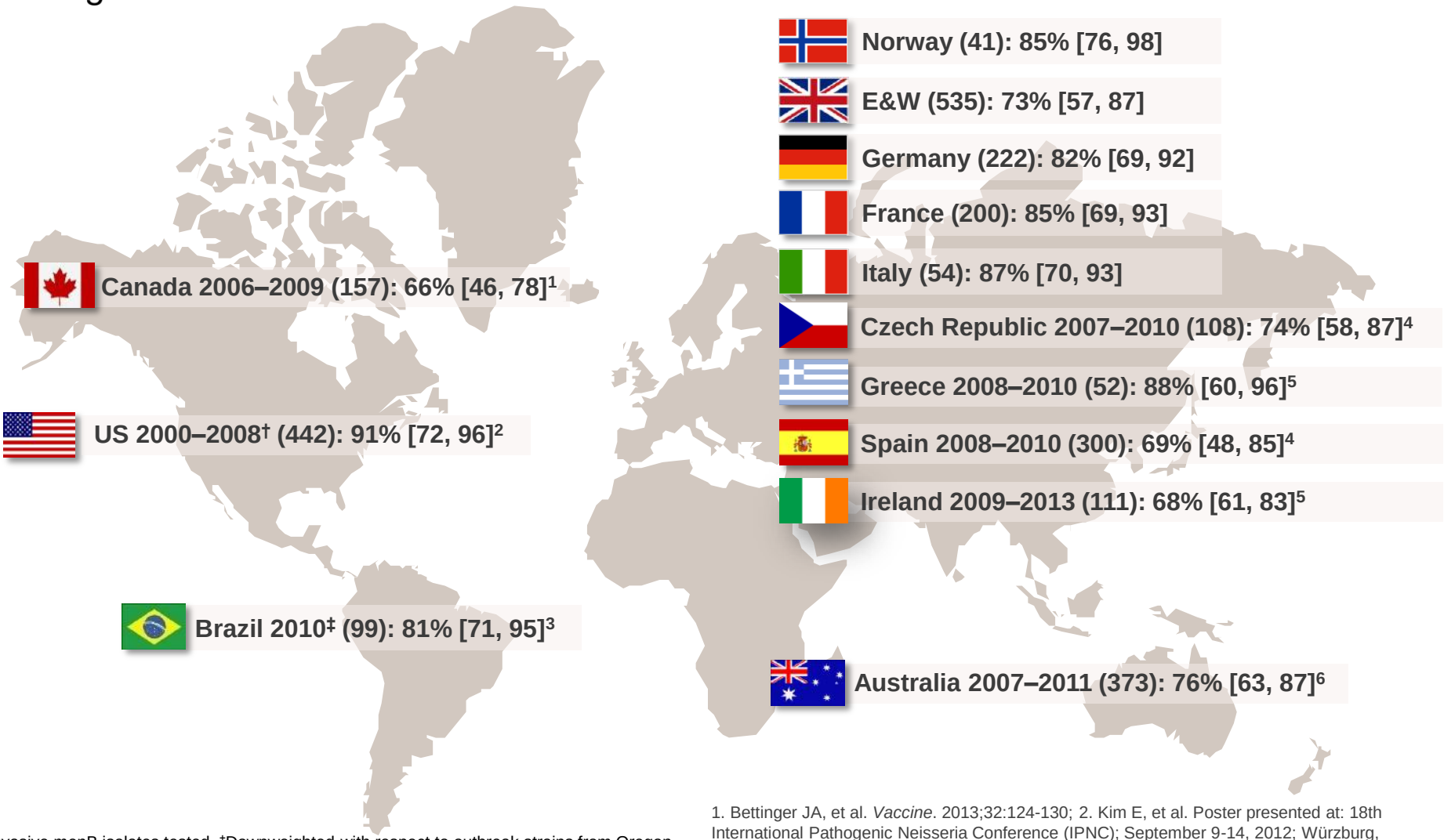
Strain coverage of Bexsero not universal - MATS predicted



Norway (41): 85% [76, 98]

E&W (535): 73% [57, 87]

Germany (222): 82% [69, 92]

France (200): 85% [69, 93]

Italy (54): 87% [70, 93]

Czech Republic 2007–2010 (108): 74% [58, 87][4]

Greece 2008–2010 (52): 88% [60, 96][5]

Spain 2008–2010 (300): 69% [48, 85][4]

Ireland 2009–2013 (111): 68% [61, 83][5]

Canada 2006–2009 (157): 66% [46, 78][1]

US 2000–2008† (442): 91% [72, 96][2]

Brazil 2010‡ (99): 81% [71, 95][3]

Australia 2007–2011 (373): 76% [63, 87][6]

*All invasive menB isolates tested. †Downweighted with respect to outbreak strains from Oregon. ‡Represents about 53% of capsular group B cases.

1. Bettinger JA, et al. *Vaccine*. 2013;32:124-130; 2. Kim E, et al. Poster presented at: 18th International Pathogenic Neisseria Conference (IPNC); September 9-14, 2012; Würzburg, Germany. Poster P270; 3. Lemos AP, et al. Poster presented at: 18th International Pathogenic Neisseria Conference (IPNC); September 9-14, 2012; Würzburg, Germany. Poster P272; 4. Vogel U, et al. *Lancet Infect Dis*. 2013;13:416-425; 5. Data on file, Novartis Vaccines and Diagnostics; 6. Tozer SJ, et al. Poster presented at: 27th International Congress of Pediatrics (ICP); August 24-29, 2013. Melbourne, Australia.

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Bexsero clinical program

- Phase I to III studies in infant, toddlers and adolescents complete.
  - Over 5000 infants/toddlers & 19,000 adolescents/adults vaccinated.
- Induces serum bactericidal antibody (SBA) against a range of MenB strains.
- Acceptable safety and tolerability profile in all age groups.
  - Most reactions mild to moderate but increased systemic reactogenicity when combined with routine infant vaccination.
- Co-administered infant vaccines elicit expected immune responses when given with Bexsero.
- Licensed by European Medicines Agency in January 2013.

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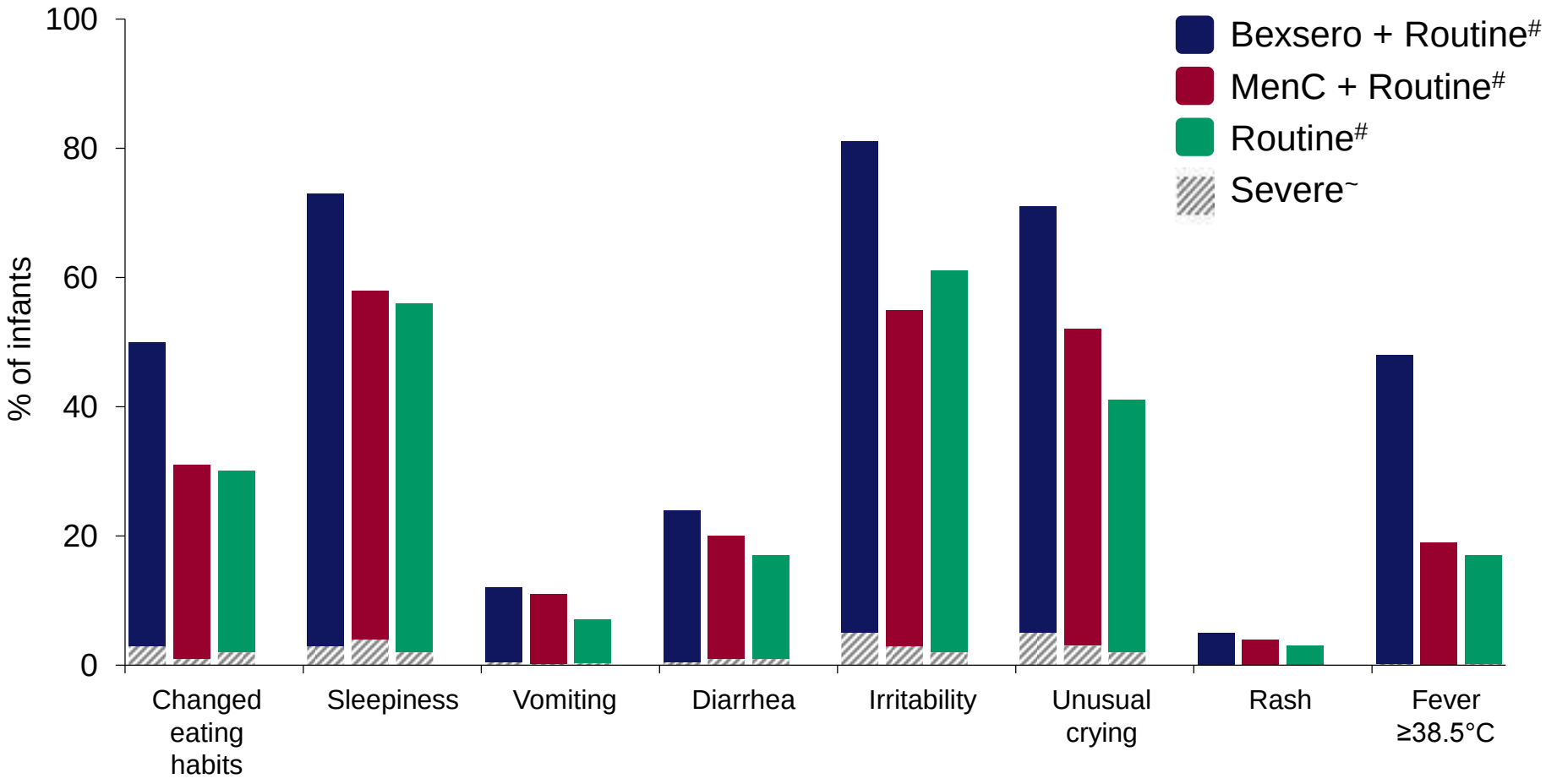
Solicited systemic reactions post-first dose of Bexsero* in infants when administered with routine vaccines



*No increase in the incidence or severity of the adverse reactions with subsequent doses.

#Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; Bexsero+Routine: N=2478; MenC+Routine: N=490; Routine: N=659.

~Fever categorised as severe if temperature ≥40°C. All other reactions categorised as severe if subject unable to perform normal daily activities.

Vesikari T, *et al., Lancet*. 2013;381:825-835;
Bexsero [summary of product characteristics].

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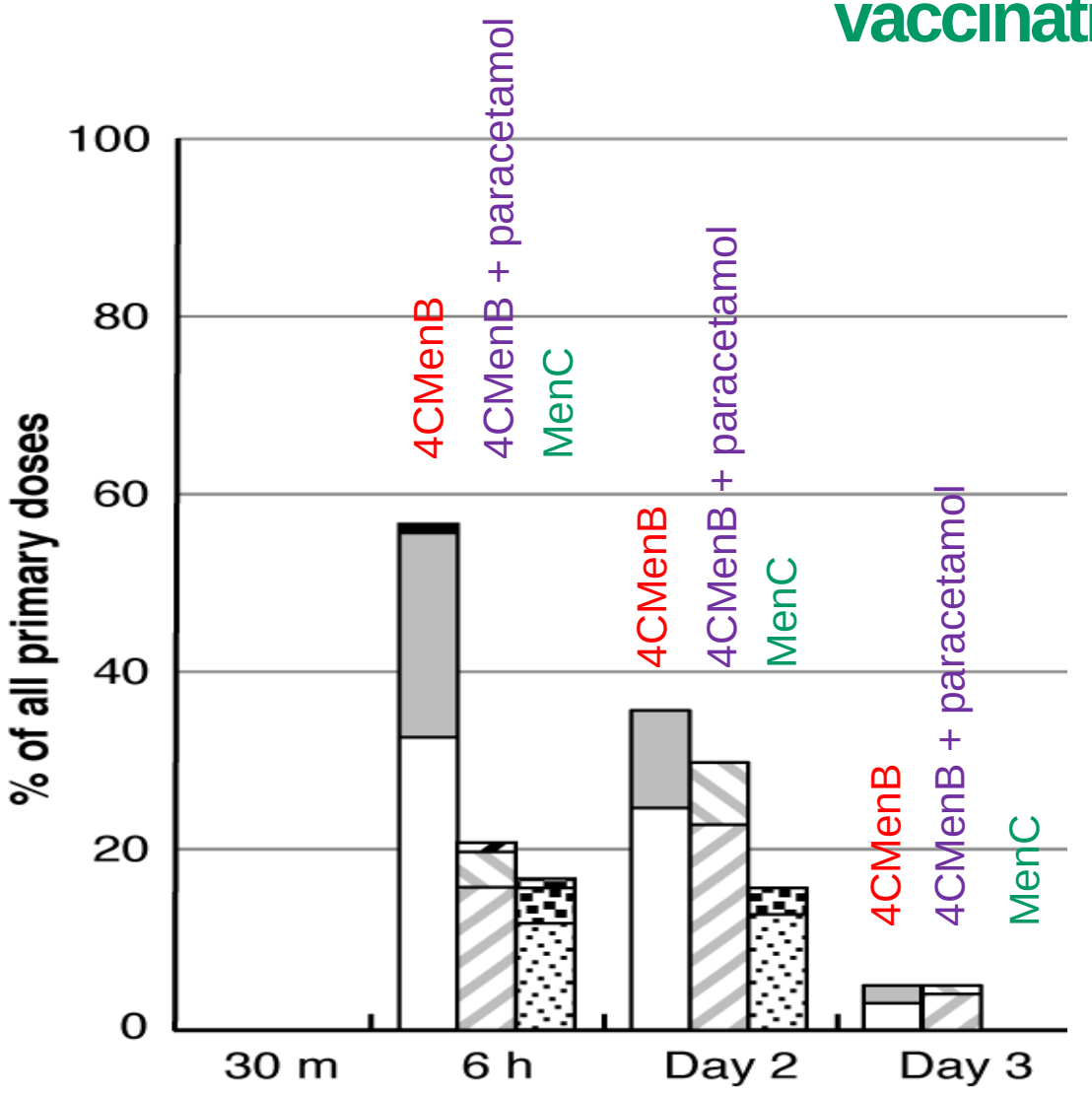
Proportions of infants, per vaccination group with temperatures ≥ 38.5 ° C, following primary vaccination



Oral paracetamol at the time of vaccination, with two subsequent doses at 4 to 6 hours intervals

Prymula *R et al.* Hum Vaccin Immunother 2014 Apr 24;10(7) 1993-2004.

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Bexsero- UK immunisation schedule

Licensed schedule (Summary of Product Characteristics)

Population	Age	Primary dose series	Booster recommended
Infants	2 to 5 months	3	Yes (12-23 months)
Unvaccinated infants	6 to 11 months	2	Yes (12-23 months)
Toddlers and above	≥12 months	2	-

Proportions of infants with SBA titres ≥4 following second /third infant priming dose[1]

	Antigen (SBA target strain)		
Schedule	fHbp (44/76-SL)	NadA (5/99)	OMV (NZ 98/254)
After three doses (at 2, 4 & 6 months of age)	95%	95%	85%
After two doses (at 2 & 4 months of age)	87%	100%	74%

[1]Findlow J *et al.* Clin Infect Dis 2010 Nov 15;51(10) 1127-37.

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Bexsero implementation in the UK

Negotiations to procure at cost-effective price were concluded in late March 2015

MenB vaccine given with routine immunisation appointments from 1st September 2015

Routine cohort: infants born on or after the **1 July 2015**

Schedule: 2, 4 and 12 months (2+1)

Catch-up cohort: infants born from **1 May to 30 June 2015**
Schedule: 3, 4 and 12 months (2+1)
Schedule: 4 and 12 months (1+1)

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Bexsero implementation in the UK

Bexsero given with routine immunisation appointments from 1st September 2015

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Cases: summary, first 10 months

- 01 September 2015 - 30 June 2016 (10 months)
- 55 lab-confirmed IMD cases in vaccine-eligible infants
  - born on or after 01 May 2015,
  - diagnosed on or after 01 September 2015
  - aged ≥10 weeks at diagnosis
- Capsular group distribution
  - 37 (67%) MenB,
  - 11 (20%) MenW,
  - 5 (9%) MenY
  - 2 (4%) ungrouped.

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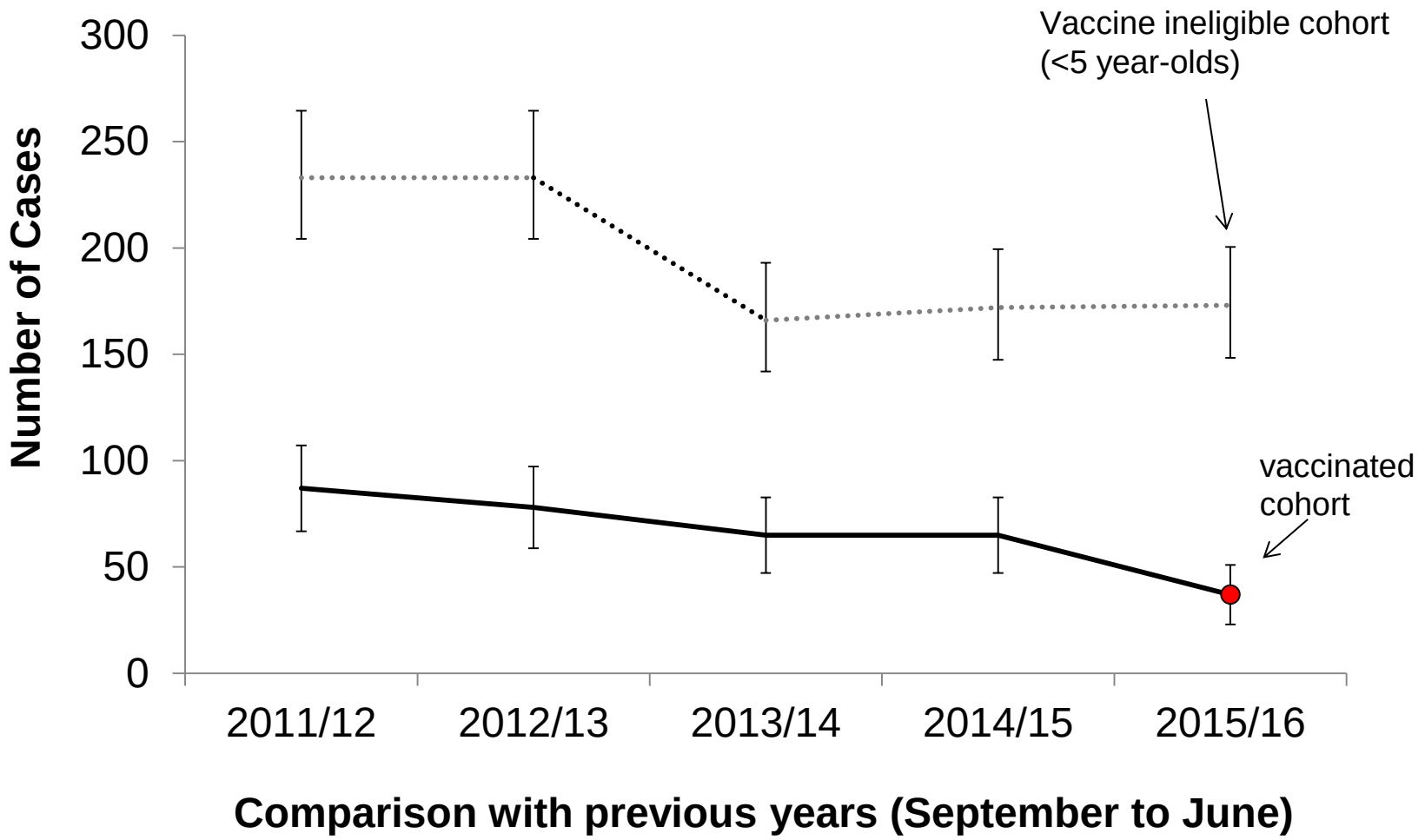
CASES: before and after



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Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study

Sydel R Parikh, Nick J Andrews, Kazim Beebeejaun, Helen Campbell, Sonia Ribeiro, Charlotte Ward, Joanne M White, Ray Borrow, Mary E Ramsay, Shamez N Ladhani

Summary

Background In September, 2015, the UK became the first country to introduce the multicomponent group B meningococcal (MenB) vaccine (4CMenB, Bexsero) into a publicly funded national immunisation programme. A reduced two-dose priming schedule was offered to infants at 2 months and 4 months, alongside an opportunistic catch-up for 3 month and 4 month olds. 4CMenB was predicted to protect against 73–88% of MenB strains. We aimed to assess the effectiveness and impact of 4CMenB in vaccine-eligible infants in England.

Methods Public Health England (PHE) undertakes enhanced surveillance of meningococcal disease through a combination of clinical, public health, and laboratory reporting. Laboratory-confirmed cases of meningococcal disease are followed up with PHE local health protection teams, general practitioners, and hospital clinicians to collect demographic data, vaccination history, clinical presentation, and outcome. For cases diagnosed between Sept 1, 2015, and June 30, 2016, vaccine effectiveness was assessed using the screening method. Impact was assessed by comparing numbers of cases of MenB in vaccine-eligible children to equivalent cohorts in the previous 4 years and to cases in vaccine-ineligible children.

Findings Coverage of 4CMenB in infants eligible for routine vaccination was high, achieving 95·5% for one dose and 88·6% for two doses by 6 months of age. Two-dose vaccine effectiveness was 82·9% (95% CI 24·1–95·2) against all MenB cases, equivalent to a vaccine effectiveness of 94·2% against the highest predicted MenB strain coverage of 88%. Compared with the prevaccine period, there was a 50% incidence rate ratio (IRR) reduction in MenB cases in the vaccine-eligible cohort (37 cases *vs* average 74 cases; IRR 0·50 [95% CI 0·36–0·71]; p=0·0001), irrespective of the infants' vaccination status or predicted MenB strain coverage. Similar reductions were observed even after adjustment for disease trends in vaccine-eligible and vaccine-ineligible children.

Interpretation The two-dose 4CMenB priming schedule was highly effective in preventing MenB disease in infants. Cases in vaccine-eligible infants halved in the first 10 months of the programme. While ongoing national surveillance will continue to monitor the longer-term impact of the programme, these findings represent a step forward in the battle against meningococcal disease and will help reassure that the vaccine protects against this deadly infection.

Funding Public Health England.

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See Online/Comment http://dx.doi.org/10.1016/S0140-6736(16)32061-X

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Introduction

In September, 2015, the UK became the first country to introduce the multicomponent, protein-based meningococcal vaccine (4CMenB; Bexsero, GSK, Rixensart, Belgium) into a national, publicly funded infant immunisation programme.[1] The vaccine was offered to all infants born since July 1, 2015, at 2 months, 4 months, and 12 months alongside their routine immunisations. Catch-up vaccination was also opportunistically offered to 3 month and 4 month olds attending their routine immunisation visits, who were eligible for a 3-4-12 month and 4-12 month schedule, respectively.

Before introduction of 4CMenB, the UK immunisation schedule had included the group C meningococcal (MenC) conjugate vaccine since 1999.[2] As an emergency response to a national outbreak of group W meningococcal (MenW) disease, 13–18 year olds and new university entrants have been offered the quadrivalent MenACWY conjugate vaccine since August, 2015.[3] These conjugate vaccines target the polysaccharide capsule of meningococci and do not offer cross-protection against other meningococcal capsular groups, such as group B (MenB), which remains responsible for most cases of invasive meningococcal disease in the UK, especially in young children.[1]

Development of an effective conjugate vaccine against MenB has not been possible because its polysaccharide capsule is structurally homologous to glycoproteins in fetal neural cell adhesion molecules, making them poorly immunogenic self-antigens.[4] 4CMenB is a novel vaccine composed of three recombinant proteins—factor H-binding protein (fHbp), Neisserial heparin-binding antigen (NHBA), and Neisserial adhesin A (NadA)—and the outer membrane vesicles (OMV) from the New Zealand outbreak strain (NZ98/254), which incorporates the immunodominant Porin A (PorA) P1.4 protein.[5] The vaccine was licensed in Europe in January, 2013, on the

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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.[illegible]% to 95.2%)
1+0	20/28 (71%)	76.2%	22.0% (-105% to 67.1%)
At least one	29/37 (78%)		

- **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.

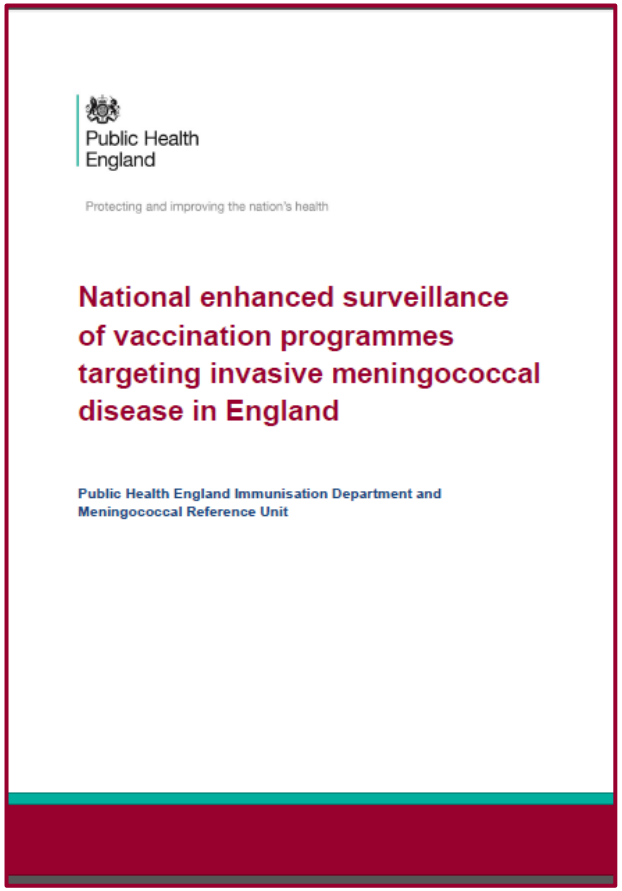
Ongoing enhanced surveillance

- Determined that there are no safety concerns so far…

- On-going surveillance is essential to continue to monitor impact, including post-12 month booster.

- Further work required into investigating the MenB breakthrough cases in terms of;
  - Using MATS to determine if disease isolate was ‘vaccine preventable’.
  - Underlying conditions in the patient.

- Investigating the impact of Bexsero on non-MenB disease.



https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457723/MeningoEnhancedSurveillancePlan_01092015_v1.1.pdf

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Bexsero – pharmacovigilance strategy

- UK first country to use Bexsero® in a national programme.
- Developed in advance of UK programme – endorsed by Commission on Human Medicines.
- Starting point :

  - Safety from clinical trial programme, post-marketing data outside of UK and the manufacturer's risk management plan.

- Underpinned by Yellow card Scheme (passive surveillance) & supported by ad hoc analysis of data from Clinical Practice Research Datalink (active surveillance/epi studies).

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Yellow Card (YCs) expectations

Planning assumptions:

- Expected ~120,000 routine doses/month, rising to 180,000 with boosters.
- Anticipated ~ 1 YCs per 1,000 doses (based on prior experience with major new vaccines eg MenC, HPV).
- Expected ~1.7m doses & 1,700 YCs by end Oct 2016
- What happened (as of Nov 2016)?

  Latest coverage ~1.5 to 1.8m doses given
  YCs 1,094
  ~1.6 per 1,000 doses - ~ half that expected

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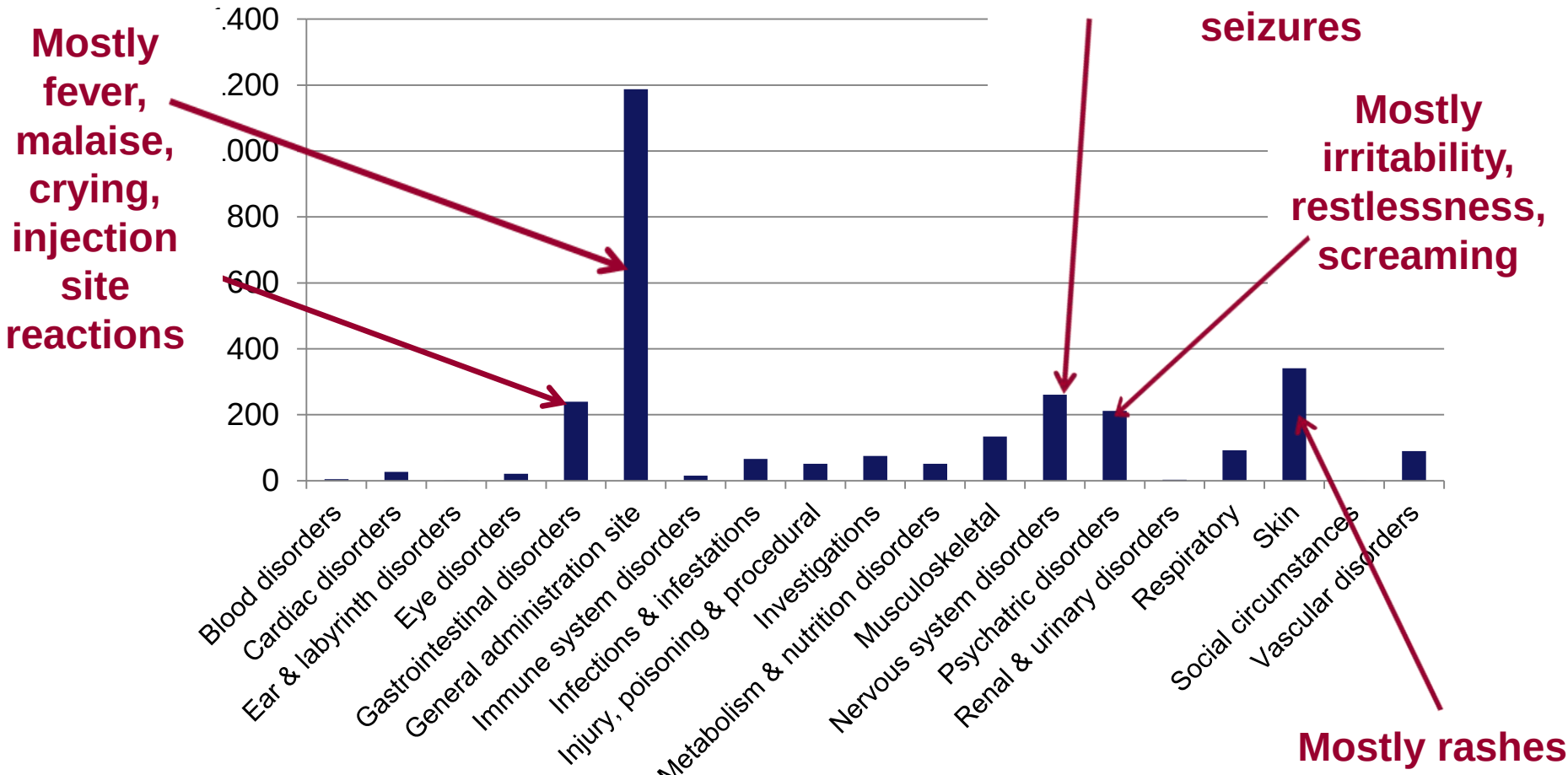
Number of events per System Organ Class



1,094 YCs include 2,845 event terms

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Fever

- Fever (inc related event terms); n = 391
- Severity not always reported, and information in Yellow Cards not able to determine impact of Paracetamol.
- A small proportion with A&E attendance/admission for observation and some with precautionary antibiotic treatment septic screen due to severity of fever (ie to rule out underlying infections).
- Given number of children immunised and expected fever rates, no indication of anything unexpected or unusual.

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Local reactions

- Wide range of event terms reported, n = ~ 600
- Isolated reports of extensive swelling, persistent local reactions and inability to use limb/bear weight
  - not unexpected
- ~ 100 reports refer to a nodule/mass (ie pea sized lump) under skin at injection site.
  - In several cases persisted for weeks/months.
  - In most cases, pain/redness/discomfort has not persisted, some report persistent itchiness.

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Bexsero®, safety summary

- Yellow Card – not proof of causal associations

  - except injection site events

- No serious, unexpected safety issues identified to date

  - nature of Yellow Cards largely as anticipated
  - number of Yellow Cards low compared to expectations

- More robust analysis of seizures & Kawasaki Disease in progress

- In context of efficacy, safety profile is so far acceptable and reassuring

- Safety will remain under review

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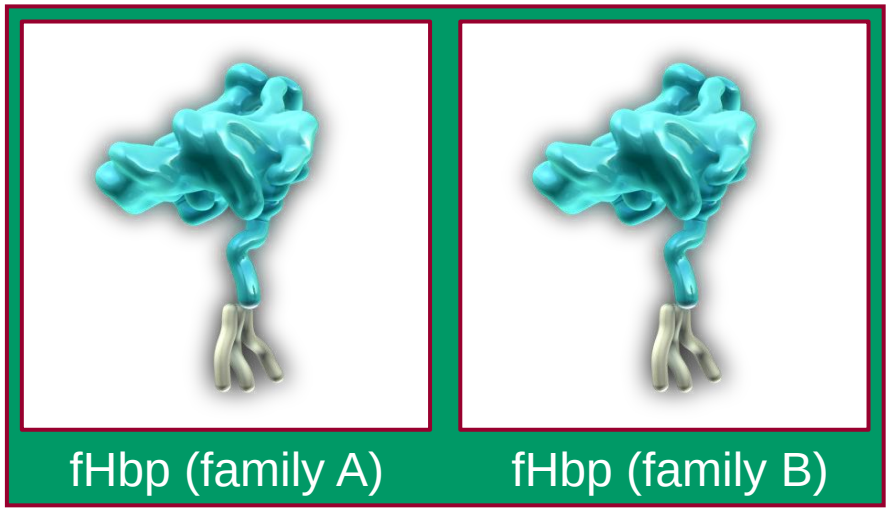
Trumenba® (Pfizer)



Bi-valent fHbp vaccine

- fHbp discovered by ‘traditional’ vaccinology.
- Licensed in the US on 29th October 2014.
- Licensed for 10-25 year olds
- Either: Three dose 0, 1-2, 6 months or
  Two dose 0, 6 months

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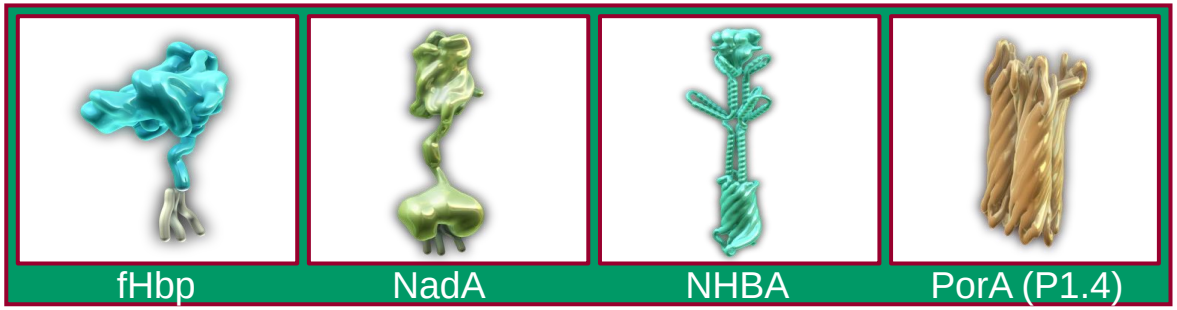
Summary

- Not been possible to produce a polysaccharide/conjugate MenB vaccine.
- Bexsero licensed in Europe in 2013.

Bexsero:



- Bexsero implemented into the UK infant schedule from 1st Sept 2015.
- Now have UK data for first 10 months of implementation;
  - Vaccine efficacy post-2nd dose against MenB disease is 83%.
  - No safety concerns.

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Acknowledgements

PHE Colindale:
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MHRA:
Phil Bryan and team

Meningitis Research Foundation

MRF MENINGOCOCCUS GENOME LIBRARY

(http://www.meningitis.org/research/genome).