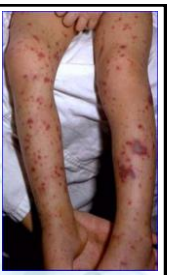
Brussels, 5 December 2014

Prevention of meningococcal disease – what has been achieved?



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Vaccine Research Center
University of Tampere
Tampere, Finland

Academic Expertise in Vaccine Research

Vaccine Research Center
UNIVERSITY OF TAMPERE
Finland

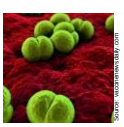
Disclosure / Timo Vesikari

Principal Investigator of studies on MenACWY vaccines by Novartis and GSK

and

MenB vaccines by Novartis and Pfizer

Meningococcal vaccines



Polysaccharide vaccines
MenA ⟶ MenACWY

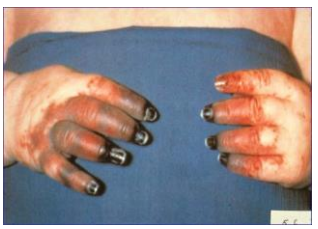
Polysaccharide-protein conjugate vaccines
Men C ⟶ MenACWY

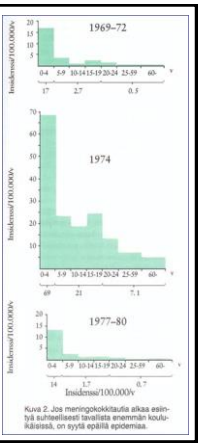
Protein-based MenB vaccines

Last MenA outbreak in Europe:

1974–1976

687 cases in Finland (pop. 5 million)

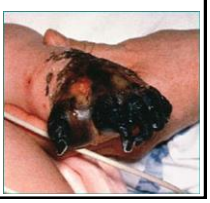




MenA outbreak and vaccination in Finland 1975

- A 10-fold increase in meningococcal disease compared to background years
- Mass vaccination in Finland in 1975 with Group A Meningococcal polysaccharide vaccine

  >1.2 million persons <20 years of age vaccinated
- It is not clear how much vaccination contributed to cessation of the outbreak



Incidence rates (per 100.000) of meningococcal disease in Europe 1999

Finland*	0.9 / 100.000
Europe	1.9 / 100.000
England and Wales	9.0 / 100.000
Ireland	13.0 / 100.000

*Finland had and has a low background rate of meningococcal diseases

Clonal expansion of MenC (sequence type 11) in the UK

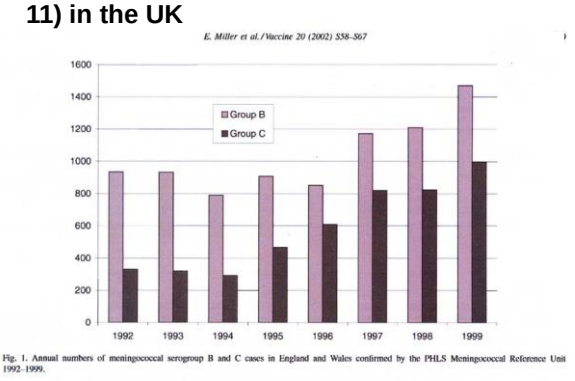


Fig. 1. Annual numbers of meningococcal serogroup B and C cases in England and Wales confirmed by the PHLS Meningococcal Reference Unit 1992–1999.

Deaths associated with meningococcal disease by age in UK 1994–1999

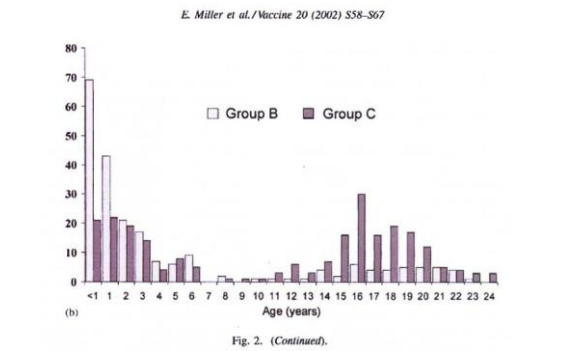


Fig. 2. (*Continued*).

Response to the MenC outbreak in UK in 1999

1. Licensure of MenC conjugate vaccine(s) on the basis of immunogenicity only
2. Start of a vaccination campaign in November 1999 involving infants, children and young people from 2 months to 19 years of age

- infants 3 doses at 2, 3 and 4 months
- between 6 and 12 months 2 doses
- 13 months to 19 years 1 dose

Teenagers and young adults had high rate of colonization and were the primary source of transmission in the community

Decline of MenC disease in the UK after vaccinations

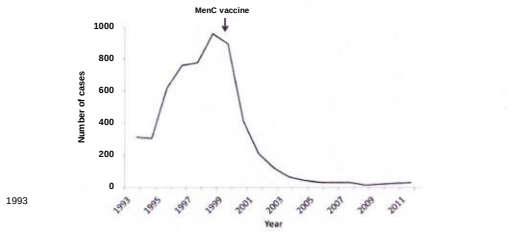


Figure 2 Number of laboratory confirmed cases of invasive serogroup C meningococcal disease in England and Wales between July 1993 and June 2012, before and after introduction of MenC vaccine into the UK routine immunisation schedule in 1999. Based on data from Gray *et al*[3] and http://www.hpa.org.uk (accessed 29 Nov 2012).[6]

Pollard AJ, *et al*. *Arch Dis Child* April 2013 Vol 98 No 4

Lessons from the MenC vaccine experience in the UK

1. Serum bactericidal antibody (rather than immunological memory) required for clinical protection and eradication of the carriage leading to interruption of transmission
2. High levels of MenC bactericidal antibodies were induced by MenC-conjugate vaccine, but the levels waned rapidly

Pollard AJ, et al. Arch Dis Child April 2013 Vol 98 No 4

MenC booster vaccination programmes in the UK

2006–2013 booster at 12 months
→ antibody levels decline rapidly after booster

2013 → "trimmed back" infant immunization at 3 months
booster at 12 months
booster at 13–15 years

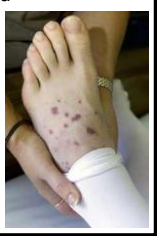
Adolescent booster induces high level of bactericidal MenC antibody, which protects infants and children through herd immunity

Pollard et al. adc.bmj.com January 21, 2014

Meningococcal A, C, W, Y conjugate vaccines

Men C conjugate vaccine and the UK programme model for development

Globally about 500 000 cases annually caused by various serogroups, but MenC is a local problem (www.who.int)



Men A conjugate vaccine

- In use in sub-Saharan Africa

Men ACWY tetravalent conjugate vaccines are intended to cover all four serogroups for more universal use

Meningococcal disease global serogroup distribution

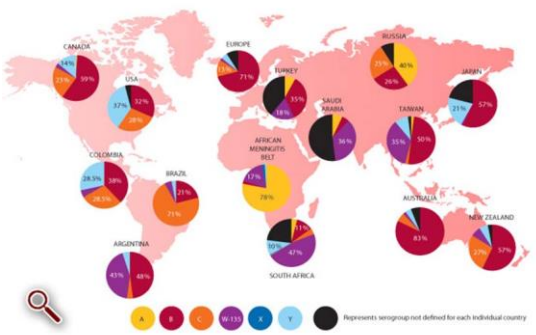


Figure 8. Global Distribution of Invasive Meningococcal Disease by Serogroup[5-17]

(www.meningitsinfo.com)

The "Meningitis Belt"

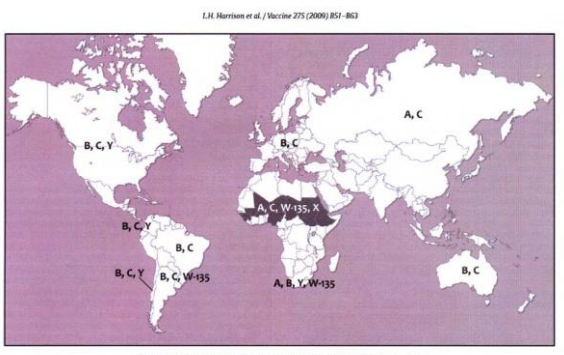


Fig. 1. Worldwide distribution of major meningococcal serogroups. See text for details.

MenA conjugate vaccine MenAfriVac

Manufactured by Serum Institute of India

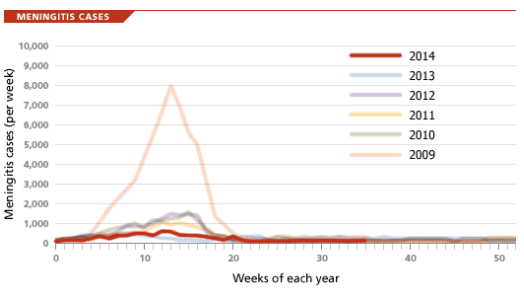
Vaccination in meningitis belt countries in Africa started in 2009

Target population 315 million people aged 1–29 years

153 million vaccinated

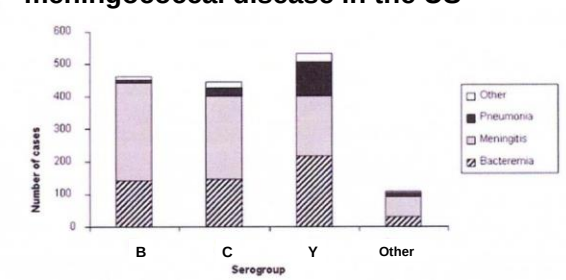
No cases in vaccinated subjects

Weekly cases of meningitis



WHO/IST. WHO Surveillance Bulletins. http://www.meningvax.org/epidemic-updates.php

Serogroup distribution of meningococcal disease in the US



Cohn AC, et al. CID 2010;50:184-191.

Meningococcal serogroup Y emergence in Europe

Update 2011

Michael Brüker,[1,*] Susanne Jacobsson,[2] Markku Kuusi,[3] David Pace,[4] María J. Simões,[5] Anna Skoczynska,[6] Muhamed-Kheir Taha,[7] Maija Toropainen[8] and Georgina Tzanakaki[9]

[1]Novartis Vaccines and Diagnostics GmbH, Marburg, Germany; [2]Örebro University Hospital, Örebro, Sweden; [3]National Institute for Health and Welfare, Helsinki, Finland; [4]Mater Dei Hospital, Msida, Malta; [5]Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisboa, Portugal; [6]National Reference Centre for Bacterial Meningitis, National Medicines Institute, Warsaw, Poland; [7]Institut Pasteur, Invasive Bacterial Infections Unit, Paris, France; [8]National Meningitis Reference Laboratory, National School of Public Health, Athens, Greece

Country	Number of serogroup Y cases, 2011	Relative proportion 2011	Relative proportion 2010
Austria	3	4.4%	5%
Czech Republic	2	3.1%	6%
Estonia	0	0%	0%
Greece	0	0%	0%
Hungary	0	0%	0%
Iceland	0	0%	0%
Ireland	1	1.2%	0%
Lithuania	0	0%	0%
Luxemburg	ND	ND	ND
Poland	2	0.7%	2%
Scotland	2	3.7%	2.3%
Spain	4	0.9%	1%
Belgium	4	4.2%	4.2%
Denmark	5	5.9%	0%
England & Wales	91	9.8%	7.5%
France	43	8.7%	5.5%
Germany	20	7%	7%
Finland	7	20.6%	38%
Italy	16	16.9%	10%
Malta	3	27%	0%
Netherlands	15	17%	8%
Norway	21	55%	31%
Portugal	7	10.4%	0%
Slovakia	2	12.5%	0%
Sweden	31	51%	39%
Switzerland	13	22%	21%

Figure 1. Relative proportion of N. meningitidis serogroup Y in various European countries in 2011. The figure is based on data communicated by the scientists listed in the Acknowledgment and/or published in web pages of national public institutes.[9] The data for 2011 are compared with data from 2010, which have been communicated earlier.[1] Color coding refers 2011 data. For Luxemburg, two IMD cases were reported in 2011, of which the serogroups were not determined (ND). Data were not available to the authors for countries shown in white.

Licensed MenACWY conjugate vaccines

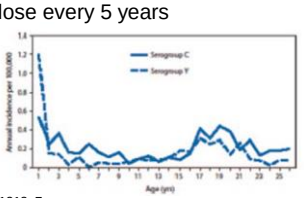
MenACWY-TT: *Nimenrix*™ (GlaxoSmithKline Vaccines), EU license from 12 months of age and Canada/Australia license from 12 months–55 years of age (1 dose)

MenACWY-DT: *Menactra*™ (Sanofi Pasteur), US/Canada/Gulf Cooperation Council countries license from 2–55 years of age (1 dose) and from 9–23 months of age (2 doses)

MenACWY-CRM$_{197}$: *Menveo*™ (Novartis), EU/Australia license from 2 years of age, US/Canada license from 2–55 years of age (1 dose) and recently in US from 2–23 months of age (2 or 4 doses)

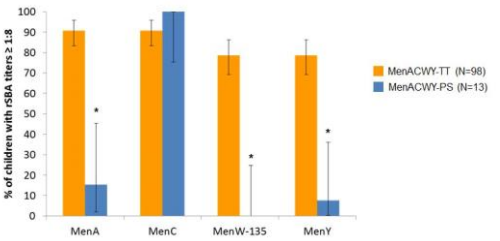
AAP Meningococcal conjugate vaccine (MenACWY) Recommendations (abbreviated)

1. Adolescents should be routinely immunized at 11–12 years with a booster at 16
2. A two-dose primary series 2 months apart for those at increased risk for meningococcal disease (e.g. C5-C9, properdin, factor H, factor D deficiency) Booster dose every 5 years



Pediatrics 2011;128:1213–7

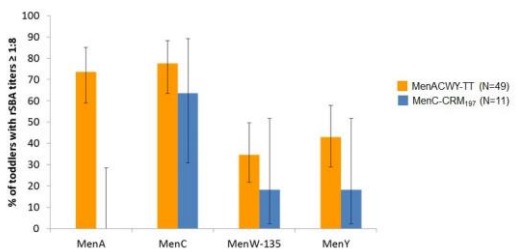
Observed rSBA titers ≥1:8 5 years after MenACWY (Nimenrix) vaccination of children



N = number of subjects in each group (ATP cohort for persistence at Year 5)
*statistically significant difference between MenACWY-TT and MenACWY-PS groups (exploratory analysis)

Ref. Vesikari, EMGM 2013, Bad Loipersdorf, Austria, 17–19 September 2013??

Observed rSBA titers ≥1:8 5 years after MenACWY (Nimenrix) vaccination of toddlers



N = number of subjects in each group (ATP cohort for persistence at Year 5)

Ref. Vesikari, EMGM 2013, Bad Loipersdorf, Austria, 17–19 September 2013??

Men ACWY vaccination Recommendations?

A decline of protective immunity happens over time, but optimal timing of booster is not known

Perhaps UK model for MenC vaccination will be the model for recommendations for MenACWY vaccination if used in a universal programme

3 months

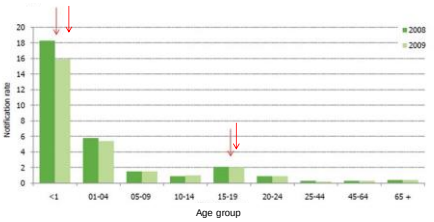
12 months

13–15 years

Incidence of invasive meningococcal disease in Europe

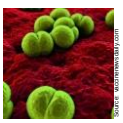
Serogroup B dominant throughout Europe

Notification rates of invasive meningococcal disease per 100 000 population by age group in Europe



European Centre for Disease Prevention and Control. Surveillance of invasive bacterial diseases in Europe 2008/2009. Stockholm: ECDC; 2011

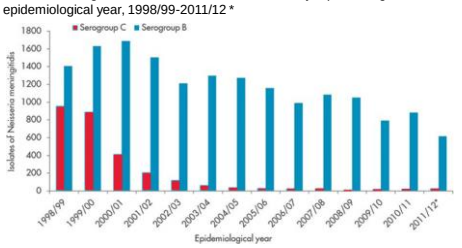
MenB protein vaccines



2-component vaccine (Pfizer)

4-component vaccine (Bexsero®, Novartis)

Invasive meningococcal B and C infections laboratory reports, England and Wales by epidemiological year, 1998/99-2011/12 *



* 2011/12 are provisional data

Source: http://www.bexsero.co.uk/healthcare-professional/about-meningitis-b-2.htm

Bivalent Factor H Binding Protein MenB Vaccine (Pfizer)

- fHbp is a key virulence protein of meningococci, binds complement faxtor H
- Bactericidal Antibody test (SBA) is based on this property
- Two subfamilies, A and B different geographical distribution investigational
- Pfizer MenB vaccine contains the two subfamilies
- Recombinant protein rLP2086 in E.coli
- Targeted at adolescents

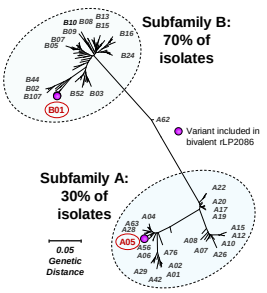
Background

LP2086, a factor H binding protein (fHBP), is a conserved, surface-exposed meningococcal virulence factor

- *fhbp* identified in all 1837 MenB strains obtained from the US, Europe, New Zealand, and South Africa, examined in a recent analysis
- 2 fHBP subfamilies (A and B) identified
- fHBP expressed in nearly all isolates

Subfamily B without lipid component included in Bexsero (Novartis)

Distribution in systemic MenB infections



Pfizer's MenB vaccine

factor H binding protein fHBP, rLP2086

Bivalent vaccine containing

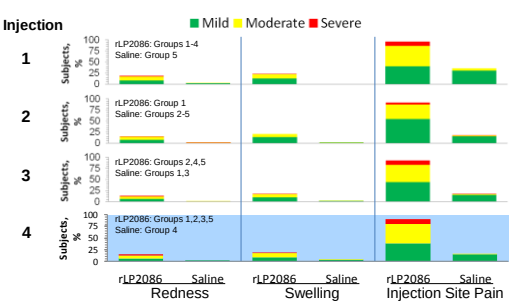
Subfamily A	60 µg
Subfamily B	60 µg

Immunogenicity in age group 11–18 years

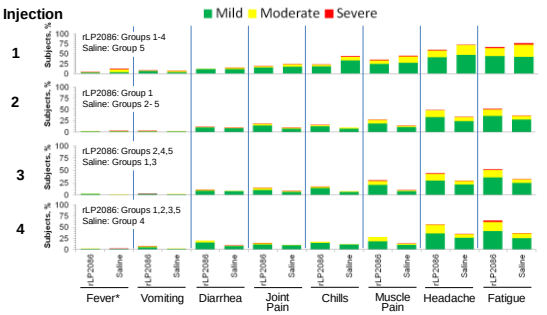
	hSBA ≥1:8	
	2 doses	**3 doses**
Subfamily A	**91–100 %**	**92–99 %**
Subfamily B	**70–81 %**	**86–89 %**

Vesikari et al. Meningitis and Septicaemia in Children and Adults 2013. November 5–6, 2013, London, UK.

Local Reactogenicity (Recorded by E-diary)



Systemic Reactogenicity (Recorded by E-diary)



29 October 2014 FDA approved TRUMENBA® MenB vaccine

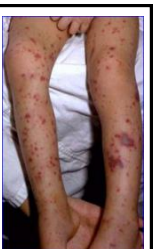
FDA's Breakthrough Therapy Designation and Priority Review programs

Persons 10–25 years of age

3 dose series

0, 2 and 6 months

Multicomponent vaccine 4cMenB



Licensed in EU in 2013
(Bexsero®, Novartis)

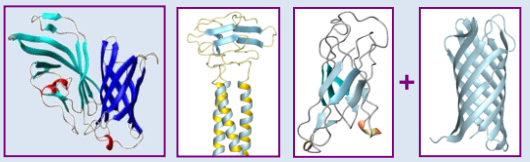
Protein antigens
- factor H binding protein (fHbp) subfamily B
- Neisseria adhesin A (Nad A)
- Neisseria heparin binding antigen (NHBA)

Outer membrane vesicle OMV, New Zealand strain 98/254

Rationale for OMV
- contains Porin antigen PorA 1.4
- increased overall immunogenicity
- strain 98/254 used to control MenB outbreak in New Zealand

4CMenB Vaccine (Bexsero^{R}, Novartis)

Conserved surface antigens selected to induce bactericidal antibody response in a broad number of strains



fHbp variant 1
Subfamily B

NadA

NHBA

PorA 1.4 (presented as part of the NZ98/254 OMV)

Pizza M, et al. *Science.* 2000;287(5459):1816-1820; Giuliani MM, et al. *Proc Natl Acad Sci US.* 2006;103(29):10834-10839; Cantini F, et al. *J Biol Chem.* 2009;284(14):9022-9062; Data on File, Novartis Vaccines.

Expected coverage of 4CMenB vaccine in the US and Europe

1801 strains of meningococci studied by SBA

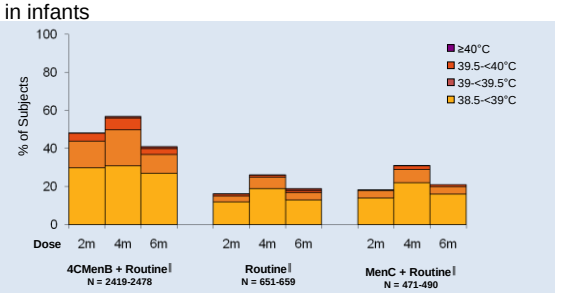
Antigen	Present in strains
NHB A	100 %
fHbp var. 1 (subfamily B)	68 %
Nad A	33 %
PorA 1.4	13 %

74 % of the strains had 2 antigens and 40 % had 3 antigens contained in 4CMenB

MATS typing
Predicted coverage of 4CMenB 77.5 %
(lowest UK 72.9 %, highest Italy 86.8 %)

Phase III Study V72P13 in Infants
Fever Profile of Bexsero in Infants

More reactogenic than any other routine immunization in infants



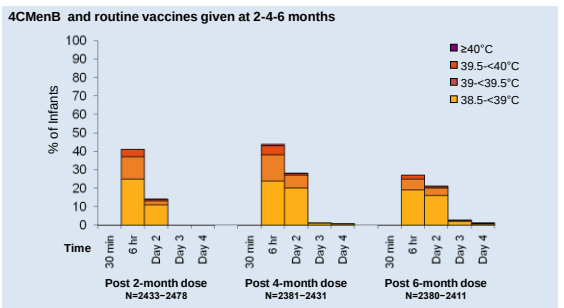
Routine vaccines: Infanrix-Hexa™; Prevenar™.

Vesikari T, et al. Lancet 2013;381:825-35.

Phase III in Infants
Study V72P13 in EU Countries

Phase III Study V72P13 in Infants
Fever Profile of 4CMenB in Infants After Each Dose

More reactogenic than any other routine immunization in infants



*Routine vaccines: PCV7 and DTPa-HPV-IPV/Hib.

Esposito S, et al. Presented at IPNC. Banff, Canada. Sept 11-16, 2010, Poster #182.??

Phase III in Infants
Study V72P13 in EU Countries

4cMenB vaccine associated reactions in adolescents

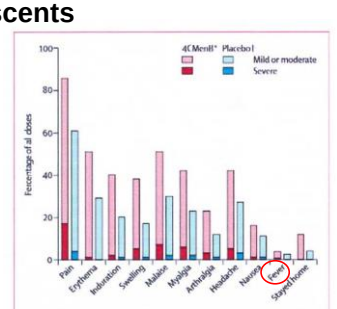


Figure 3: Cumulative reactions for all doses of 4CMenB and placebo injections
*Number of doses 3330. †Number of doses 2739.

Santolaya et al. Lancet 2012;379:617–624.

4cMenB reactogenicity with and without OMV

Fever rates ≥39°C		fHbp response
Men B + OMV	39 %	100
Men B + ½ OMV	30 %	113
Men B + ¼ OMV	23 %	113
Men B No OMV	8 %	60
Men B OMV + paracetamol	13 %	100

Esposito et al, submitted Human Vac & Immunother.

4cMenB Bexsero®

Safety summary
Infants
•unusually high reactogenicity (fever)
•potential (not confirmed) association with Kawasaki Disease

Toddlers & adolescents
•moderate reactogenicity
→ could be used in age groups 12 months to 17 years (as MenC vaccine in the UK)

Effect of MenB vaccine (Bexsero®) on meningococcal carriage

English university students, 2 doses of vaccine

Men ACWY-CRM (Menveo®) (N=956)
Men B (Bexsero®) (N=932)
Placebo (N=947)

Primary analysis one month after vaccination: no difference in meningococcal carriage between groups

Secondary analysis: Cumulative carriage at 1 year: Reduction in carriage of B, C, W, Y genogroups combined by 26% in Bexsero recipients

Reac RC, et al. Meningitis Research Foundation Conference, London, November 2013. Abstract. http://www.meningitis.org/conference2013

Prevention of secondary cases

Preventing secondary cases of invasive meningococcal capsular group B (MenB) disease using a recently-licensed, multi-component, protein-based vaccine (Bexsero®)

Shamez N. Ladhani [a,b,*], Rebecca Cordery [c], Sema Mandal [a], Hannah Christensen [d], Helen Campbell [a], Ray Borrow [e], Mary E. Ramsay [a], the PHE VaPIBI Forum Members

JID 2014;69:470–80

Conclusion: Early protection offered after a single dose of Bexsero® is likely to be low

Bexsero® in UK, Chapter I

England and Wales, JCVI position July 2013 (selected items)

- •Vaccine not cost-effective (“highly unlikely”)
- •Efficacy not established
- •Strain coverage may be overestimated
- •Effect on carriage not known
- •High fever rates could adversely effect acceptance of routine immunization programme
- •Bexsero® could be offered to selected target groups

Bexsero® in UK, Chapter II

21 March 2014

- Following further review, JCVI recommends routine vaccination of infants against MenB
- UK will introduce a nationwide campaign as soon as possible (July 2014)
- The recommendation depends on securing a cost-effective price for Bexsero
- News on reactogenicity in infants awaited

Men ABCWY vaccine (Novartis) – universal meningococcal vaccine

Polysaccharide conjugates for Men ACWY

Protein antigens for MenB

Reduced amount of OMV

The combination may be more than sum of the above

- MenB fHbp may cross protect against other meningococci

Clinical trial V102_15 in adolescents ongoing

Thank you!