Meningococcal Serogroup B Vaccine (Bexsero®)

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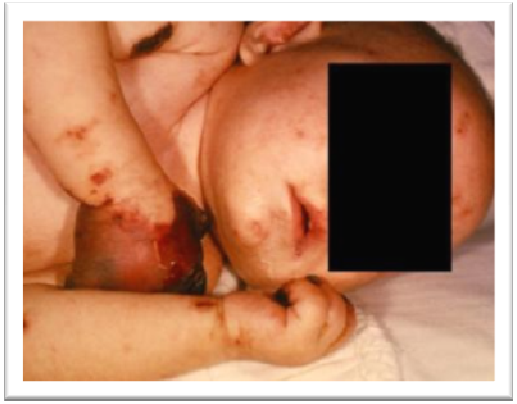
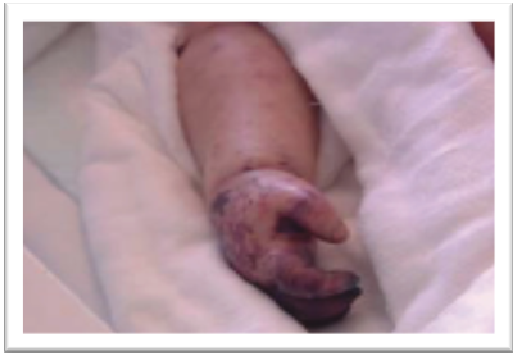
Meningococcal Serogroup B Disease Is a Serious, Often Severe, Illness in Infants

- Easily misdiagnosed[1]
  - Early signs and symptoms often resemble those of influenza or other common viral illnesses
- Rapid disease course
  - Progression from initial, nonspecific symptoms, such as fever and irritability, to death within 24 hours[1,2]
- Significant morbidity despite appropriate treatment
  - Up to 20% of survivors have significant sequelae[2,3]
  - ~1 in 10 MenB child survivors experience major sequelae[4]
  - Greater than one-third of MenB survivors experience minor deficits[4]
- Significant mortality despite appropriate treatment
  - ~10% of cases are fatal[1,3]





Top image: Courtesy of Centers for Disease Control and Prevention and Dr Gust. Bottom image: Courtesy of Meningitis Research Foundation UK. Available at www.meningitis.org.

1. Thompson MJ, et al. *Lancet*. 2006;367:397-403; 2. Meningococcal meningitis factsheet No 141. World Health Organization website. www.who.int/mediacentre/factsheets/fs141/en/index.html; 3. Rosenstein NE, et al. *N Engl J Med*. 2001;344:1378-1388; 4. Viner RM, et al. *Lancet Neurol*. 2012;11:774-783.

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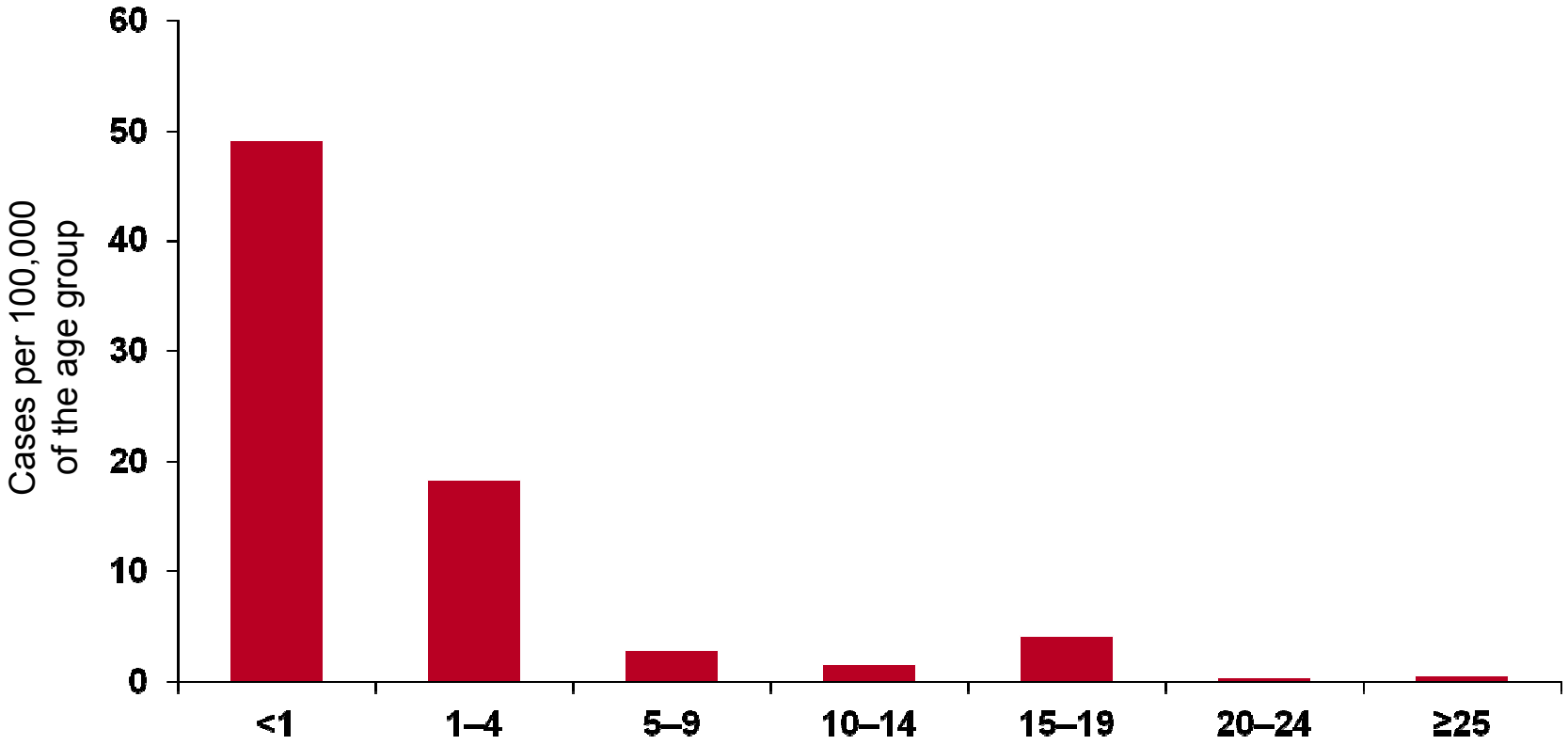
Incidence of Invasive Meningococcal Disease

Ireland, 2010



Health Protection Surveillance Centre. Meningococcal disease Annual Report 2010. Available at http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/BacterialMeningitis/Publications/AnnualReports/File,13119,en.pdf. Accessed Apr 2013

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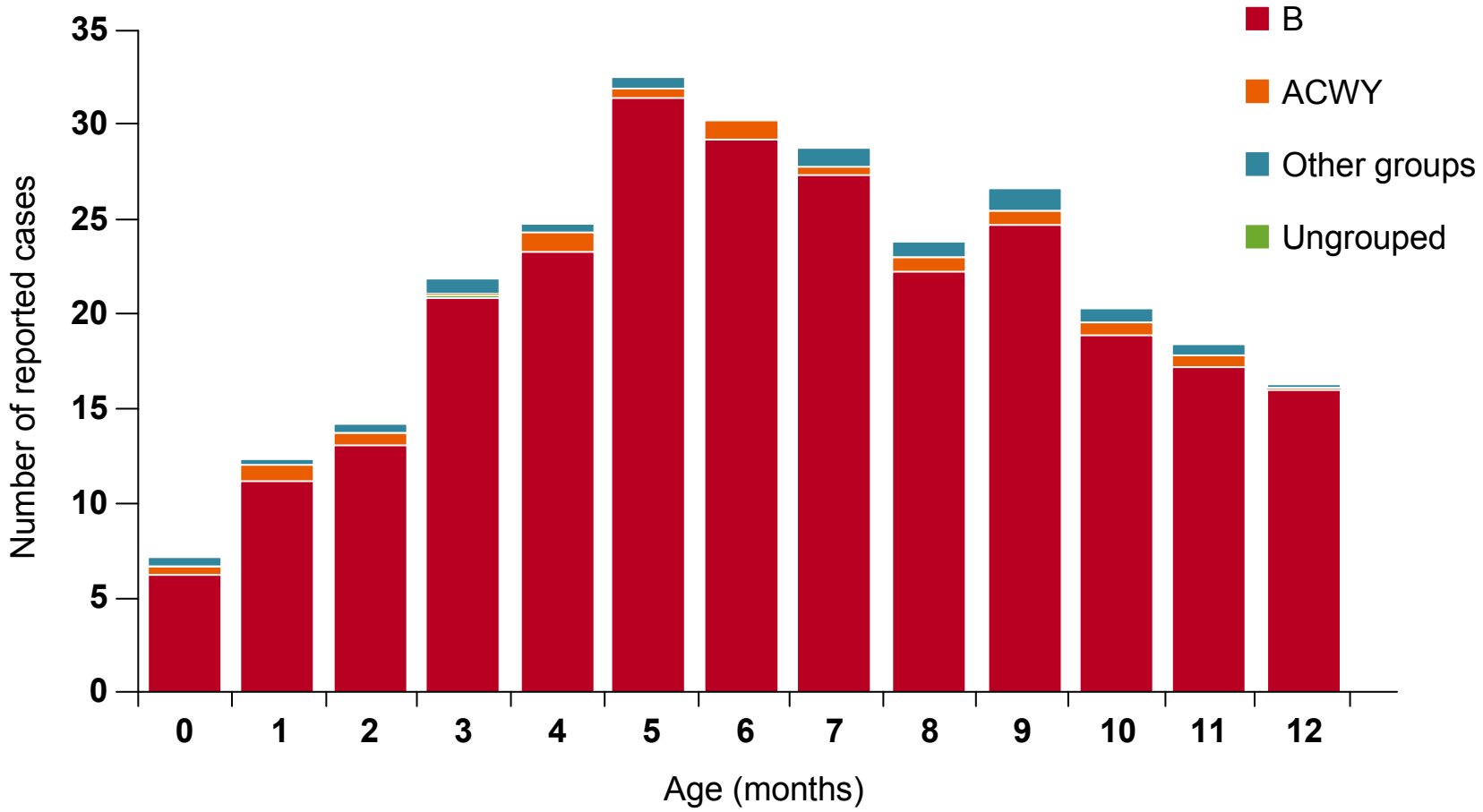
Cases of Meningococcal Disease in the First Year of Life

United Kingdom, 2006–2010



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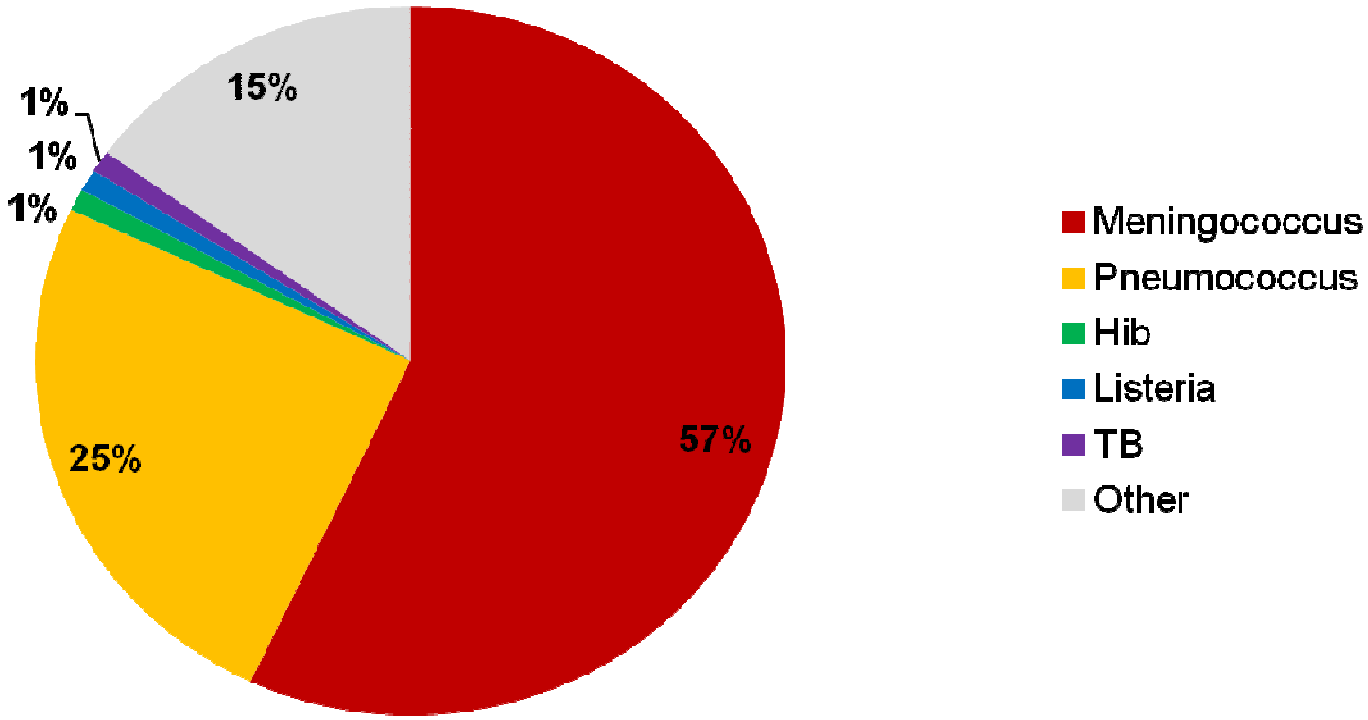
Adapted from Ladhani SN, et al. *Vaccine*. 2012;30:3710-3716.

Causes of bacterial meningitis in Ireland*



*5 year average 2007-2011

Adapted from: Health Protection Surveillance Centre (HPSC). Meningococcal disease annual and quarterly reports. Available at: www.hpsc.ie/hpsc/A-Z/VaccinePreventable/BacterialMeningitis/Publications/AnnualReports/ Accessed Jan 2013

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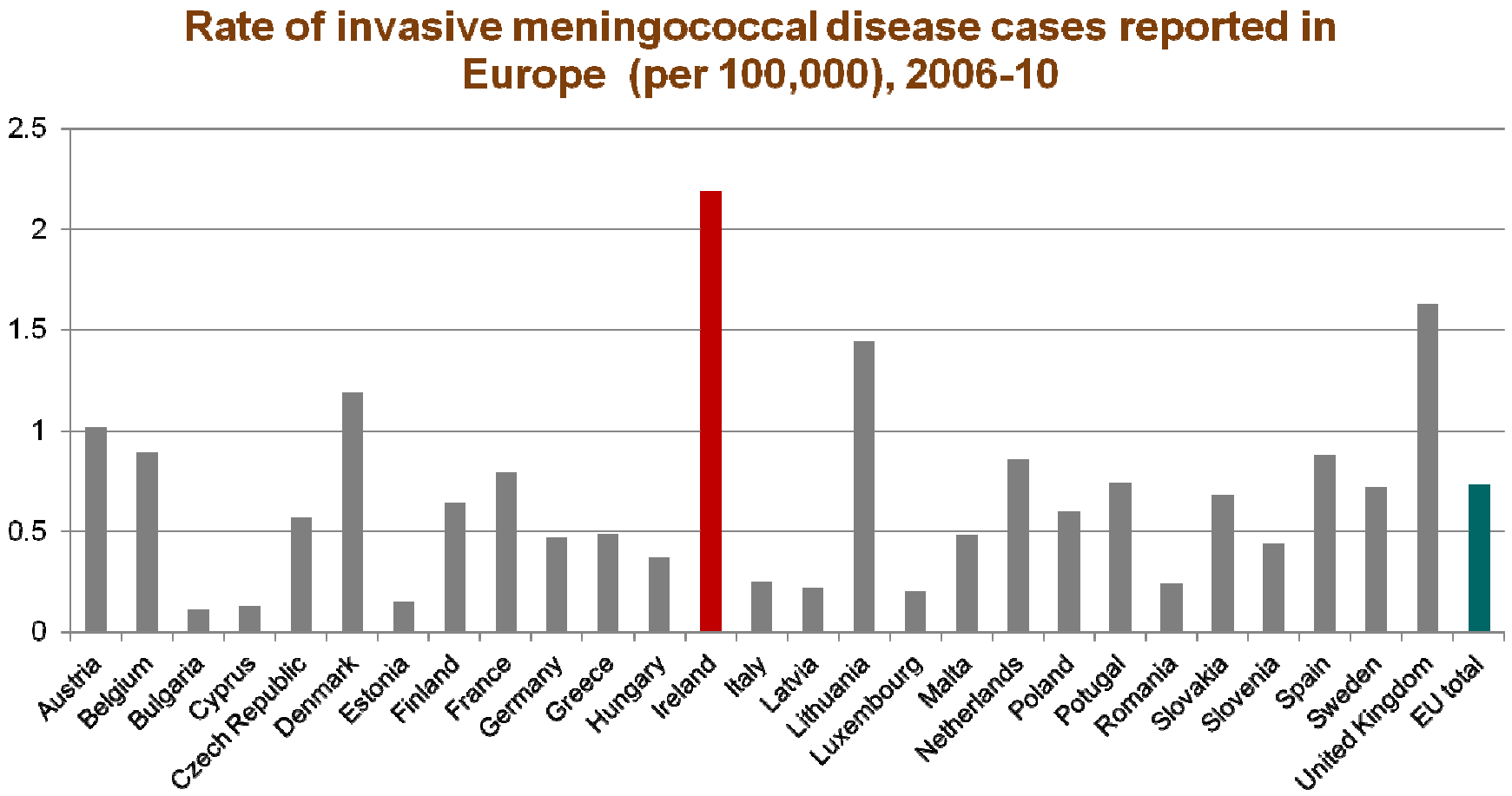
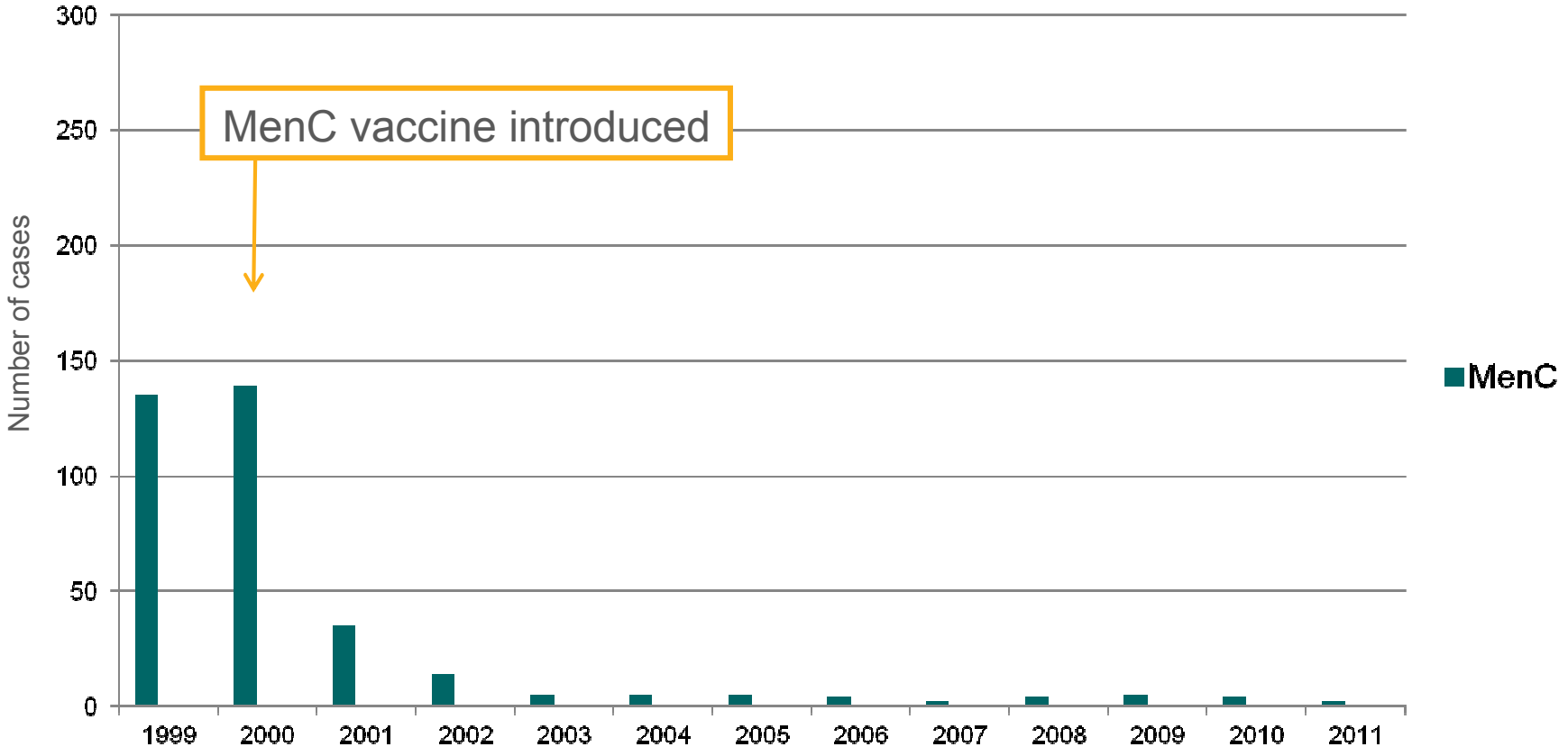
Meningococcal disease incidence across Europe



European Centre for Disease Prevention and Control. Table 2.5.3. Number and rate of invasive meningococcal disease cases reported in EU and EEA/EFTA, 2006–10. Annual epidemiological report 2012. Available at: http://ecdc.europa.eu/en/publications/Publications/Annual-Epidemiological-Report-2012.pdf Accessed Apr 2013.

NOVARTIS VACCINES AND DIAGNOSTICS

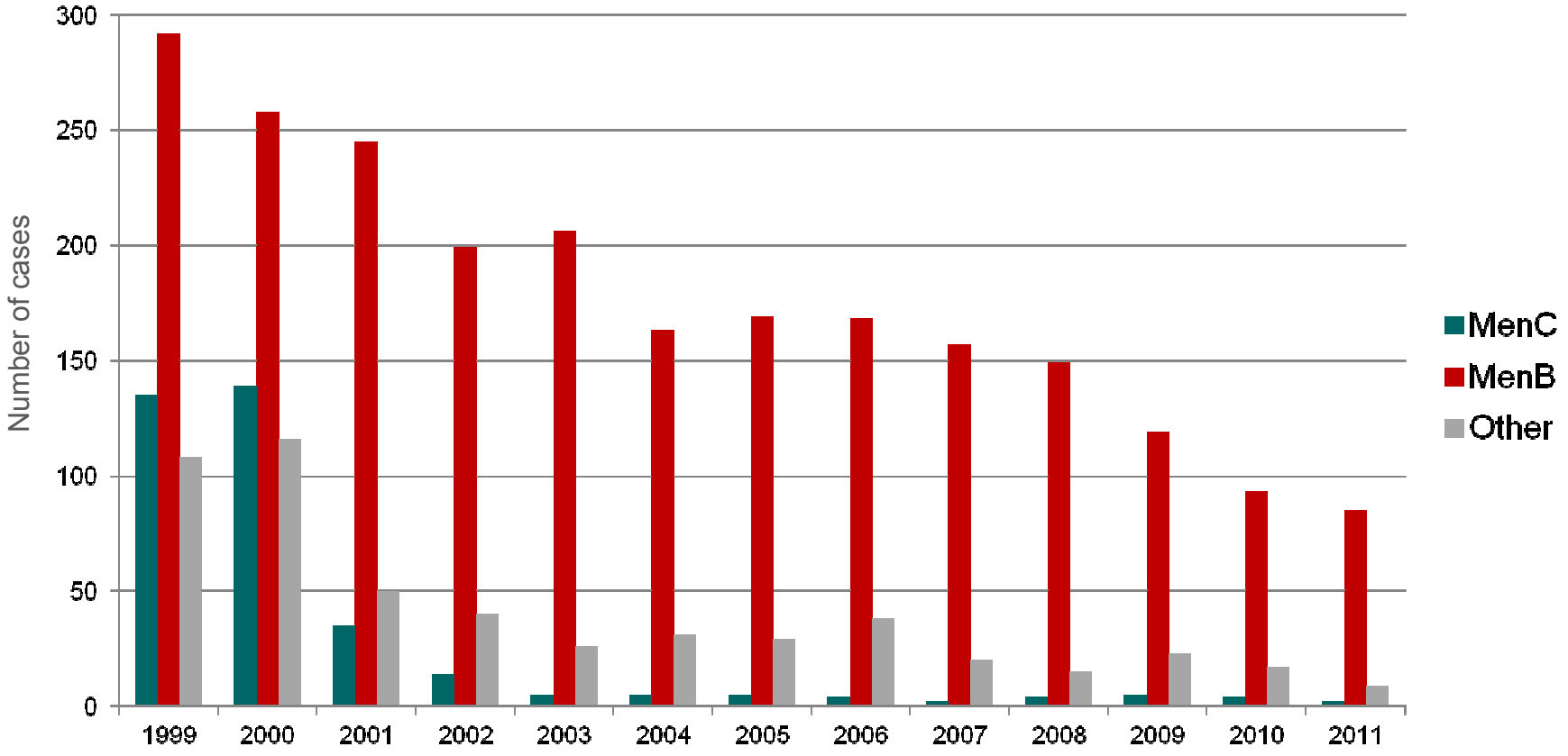
Cases of meningococcal serogroup C disease in Ireland, 1999-2011



Adapted from: Health Protection Surveillance Centre. Meningococcal disease annual and quarterly reports. Available at http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/BacterialMeningitis/Publications/. Accessed Apr 2013

NOVARTIS VACCINES AND DIAGNOSTICS

Cases of meningococcal disease in Ireland by serogroup 1999-2011



Adapted from: Health Protection Surveillance Centre. Meningococcal disease annual and quarterly reports. Available at http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/BacterialMeningitis/Publications/. Accessed Apr 2013

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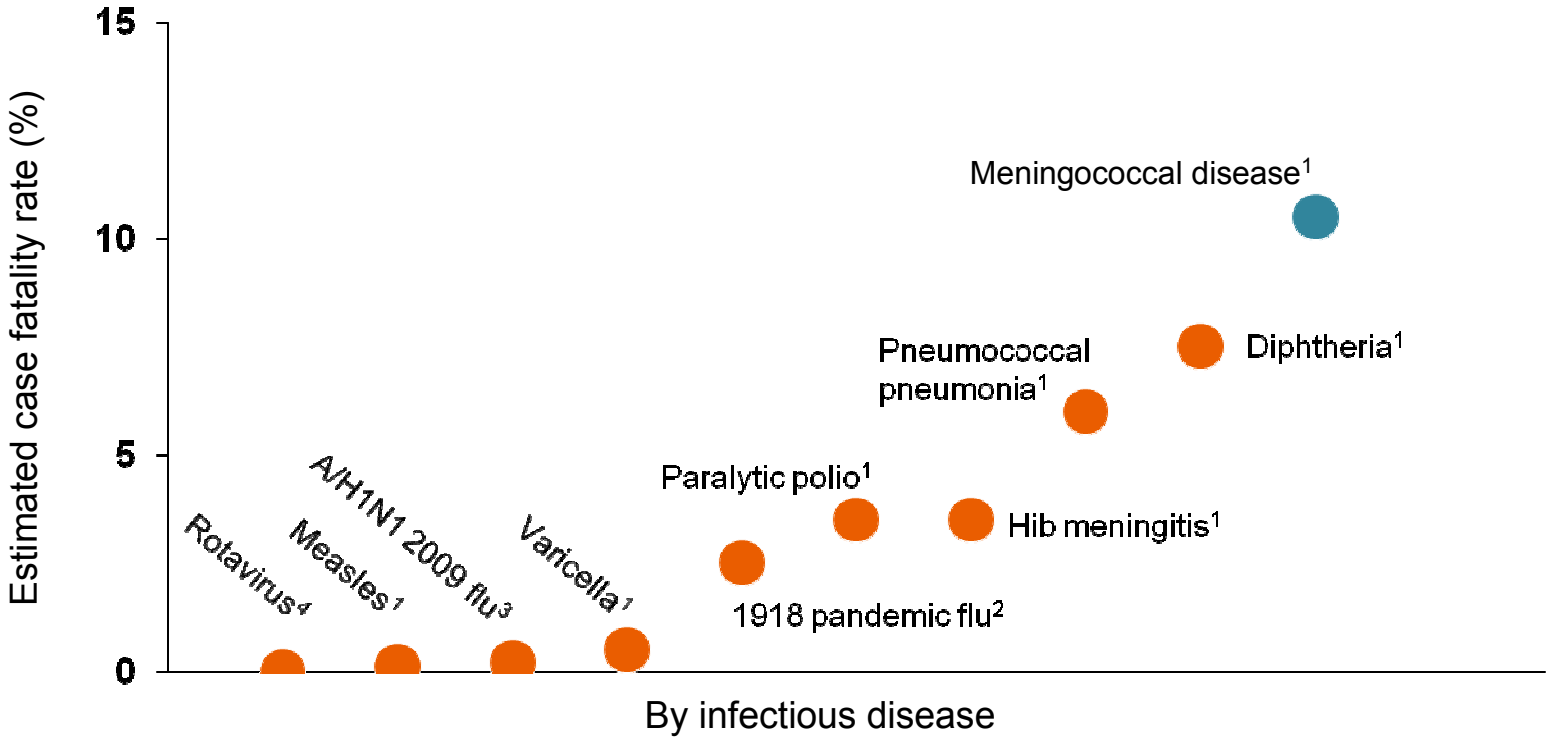
Meningococcal Disease Is Associated With Increased Case Fatality Compared With Many Other Vaccine-Preventable Diseases



Notes: Meningococcal disease and Hib meningitis: despite appropriate antimicrobial therapy; Paralytic polio: in children; 1918 pandemic flu: in young adults; Varicella: in children and adolescents; A/H1N1 2009 flu: worldwide; Measles: US. 1985-1992; Rotavirus: US general population.

1. Atkinson W, et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed. Washington, DC: Public Health Foundation; 2012. http://www.cdc.gov/vaccines/pubs/pinkbook/pink-chapters.htm; 2. Taubenberger JK, et al. *Emerg Infect Dis*. 2006;12:15-22; 3. Pandemic H1N1 2009 Overview. CIDRAP website. http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/biofacts/h1n1_panview.html; 4. Gerba CP, et al. *Wat Res*. 1996:30;2929-2940.

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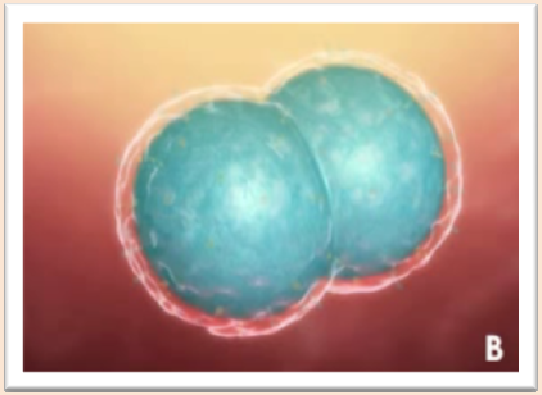
Challenges to Developing a Broadly Effective MenB Vaccine

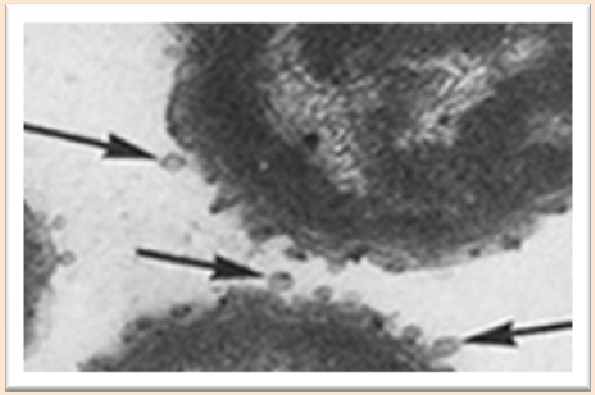
Capsular Vaccines

- Poorly immunogenic[1,2]
  - Structural homology between the B polysaccharide and human tissue, leading to immunological tolerance[1,2]



OMV-based Vaccines

- Immunogenic and proven effective for a **single** serogroup B strain[3,4]
- Limited in ability to help protect against different meningococcal serogroup B strains[3,4]
  - >8000 MenB strains exist[5]



Outer membrane “blebs” of *N meningitidis*[6]

1. Finne J, et al. *J Immunol*. 1987;138:4402-4407; 2. Wyle FA, et al. *J Infect Dis*. 1972;126:514-522; 3. Sadarangani M, et al. *Lancet Infect Dis*. 2010;10:112-124; 4. Tan LK, et al. *N Engl J Med*. 2010;362:1511-1520; 5. Neisseria Multi Locus Sequence Typing website. http://pubmlst.org/neisseria/; 6. Devoe IW, et al. *J Exp Med*. 1973;138:1156-1167.

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Bexsero: 4 Antigenic Components Chosen to Achieve Broad Protection

fHbp: factor H binding protein

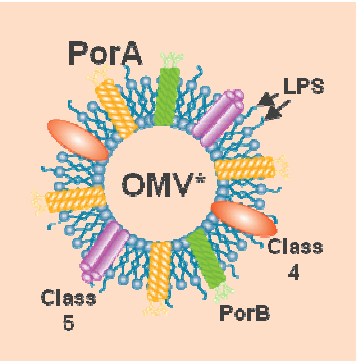
- Binds factor H, which enables bacterial survival in the blood[1,2]

NHBA: neisseria heparin-binding antigen

- Binds heparin, which may promote bacterial survival in the blood[7]
- Present in virtually all strains[6,7]

NadA: neisserial adhesin A

- Promotes adherence to and invasion of human epithelial cells[3-5]
- May be important for colonisation[4]



NZ PorA P1.4: porin A

- Major outer membrane vesicle protein—induces strain-specific bactericidal response[8]

Dose	**fHbp** fusion protein	**NadA** protein	**NHBA** fusion protein	**OMV***	**Al**$^{3+}$
0.5ml	50 mcg	50 mcg	50 mcg	25 mcg	0.5 mcg

*From *Neisseria meningitidis* serogroup B strain NZ 98/254 measured as amount of total protein containing the PorA P1.4.

1. Madico G, et al. *J Immunol*. 2006;177:501-510; 2. Schneider MC, et al. *Nature*. 2009;458:890-893; 3. Comanducci M, et al. *J Exp Med*. 2002;195:1445-1454; 4. Capecchi B, et al. *Mol Microbiol*. 2005;55:687-698; 5. Mazzon C, et al. *J Immunol*. 2007;179:3904-3916; 6. Serruto D, et al. *Proc Natl Acad Sci U S A*. 2010;107:3770-3775; 7. Bambini S, et al. *Vaccine*. 2009;27:1794-2803; 8. Martin DR, et al. *Clin Vaccine Immunol*. 2006;13:486-491.

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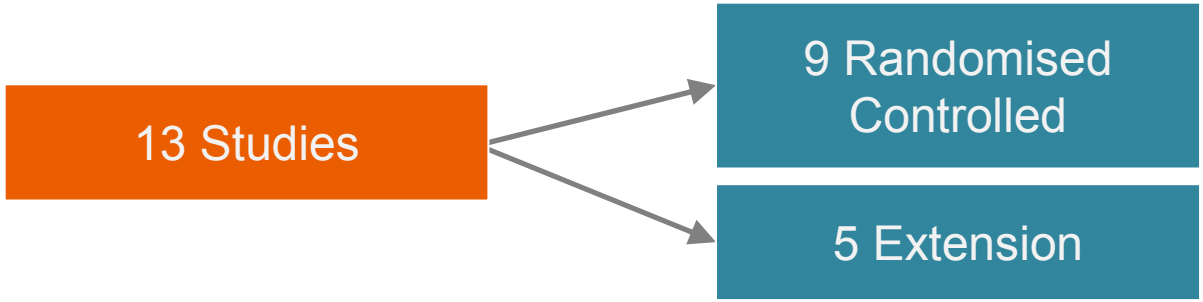
Bexsero: Clinical Development Programme for Immunogenicity Beginning in the Second Month of Life



7812 subjects (from 2 months of age) received at least 1 dose of the vaccine

Infants and children 2 months to <2 years of age

- 5850 received at least 1 dose of Bexsero
- 2949 received booster dose in second year of life

Children 2 to 10 years of age

- 250 were included

Adolescents and adults ≥11 years of age

- 1712 were included

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Data on file, Novartis Vaccines and Diagnostics.

Bexsero: Summary of Posology

	Age Group	Primary Immunisation	Intervals Between Primary Doses	Booster
Infants	Infants 2–5 months of age	3 doses each of 0.5 ml, with the first dose given at 2 months of age*	Not less than 1 month	1 dose between 12 and 23 months†
	Unvaccinated infants 6–11 months of age	2 doses each of 0.5 ml	Not less than 2 months	1 dose in second year of life; interval of at least 2 months between primary series and booster†
Children	Unvaccinated children 12–23 months of age	2 doses each of 0.5 ml	Not less than 2 months	1 dose with an interval of 12–23 months between primary series and booster†
	Children 2–10 years of age	2 doses each of 0.5 ml	Not less than 2 months	Need not established
Adolescents and Adults	Adolescents (from 11 years of age) and adults‡	2 doses each of 0.5 ml	Not less than 1 month	Need not established

*The first dose should be given at 2 months of age. The safety and efficacy of the vaccine in infants less than 8 weeks of age has not yet been established. No data are available.
†The need for, and timing of, further booster doses has not yet been determined.
‡There are no data in adults above 50 years of age.

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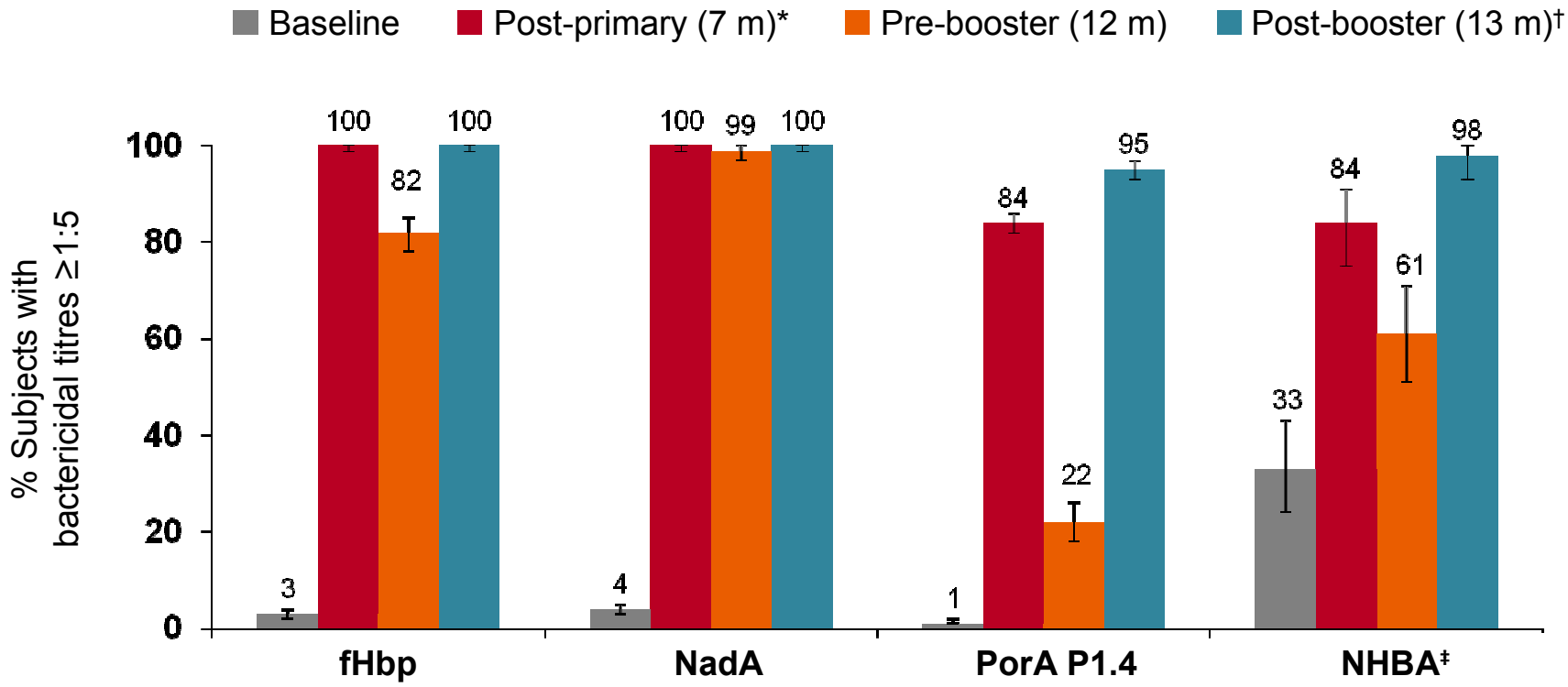
BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics; 2012.

Bexsero Immunogenicity in Infants

2-4-6-12 month dosing schedule with routine vaccines



*Blood drawn at 7 months, N=1149–1152.
†Blood drawn at 13 months, N=421–424.
‡N=100.

Phase III in Infants
Study V72P13 and
V72P13E1 in EU Countries

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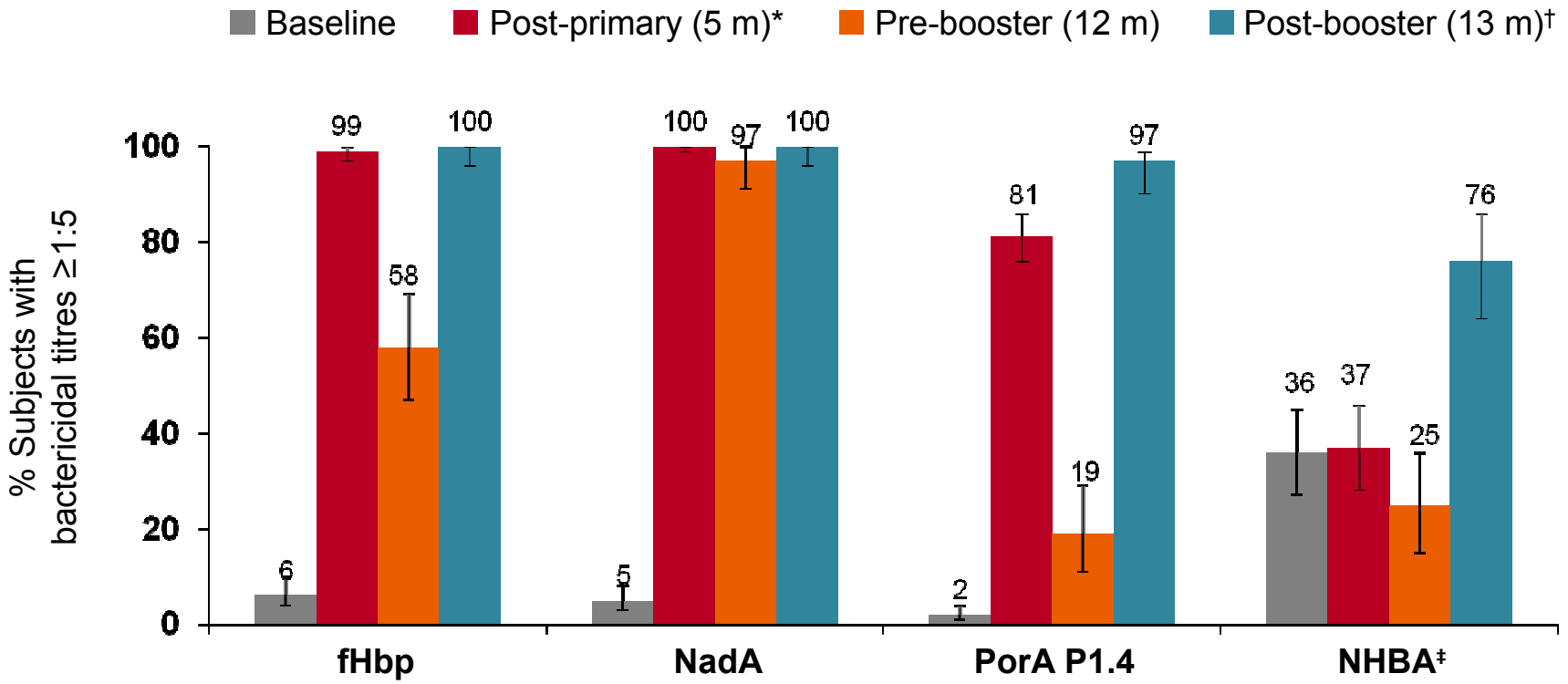
VACCINES AND DIAGNOSTICS

Vesikari T, et al. Lancet 2013;381(9869):825-35.
BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics; 2012.

Bexsero Immunogenicity in Infants

2-3-4-12 month dosing schedule with routine vaccines



*Blood drawn at 5 months, N=273–275.
†Blood drawn at 13 months, N=83–86.
‡Blood drawn at 5 months, N=112; blood drawn at 13 months, N=67.

Phase IIb in Infants
Study V72P12 in EU Countries

1. Gossger N, et al. JAMA. 2012;307:573-582; 2. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

NOVARTIS
VACCINES AND DIAGNOSTICS

Co-administration of Bexsero With Routine Vaccines

DTaP-HBV-IPV/Hib‡	Antigen	Lower limit for 95% CI for difference in seroresponders	Non-inferiority criteria met† (concomitant use with Bexsero)
	Diphtheria	–1	YES
	Tetanus	–2	YES
	Pertactin	–8	YES
	Pertussis toxin	–5	YES
	FHA	–8	YES
	Polio 1	–5	YES
	Polio 2	–11	NO*
	Polio 3	–4	YES
	Hepatitis B	–5	YES
	PRP-Hib	–3	YES

PCV7§	Antigen	Lower limit for 95% CI for difference in seroresponders	Non-inferiority criteria met† (concomitant use with Bexsero)
	Serotype 4	–4	YES
	Serotype 6B	–4	YES*
	Serotype 9V	–2	YES
	Serotype 14	–4	YES
	Serotype 18C	–3	YES
	Serotype 19F	–3	YES
	Serotype 23F	–8	YES

*Inconsistent results were seen across studies for responses to inactivated poliovirus type 2 (shown here) and pneumococcal conjugate serotype 6B (not shown) and lower antibody titres to pertactin were also noted, but these data do not suggest clinically significant interference.
†Criteria met for LL 95% CI for difference in seroresponders >–10%. Blood drawn at 7 months.
‡N=238–248; §N=242–243.

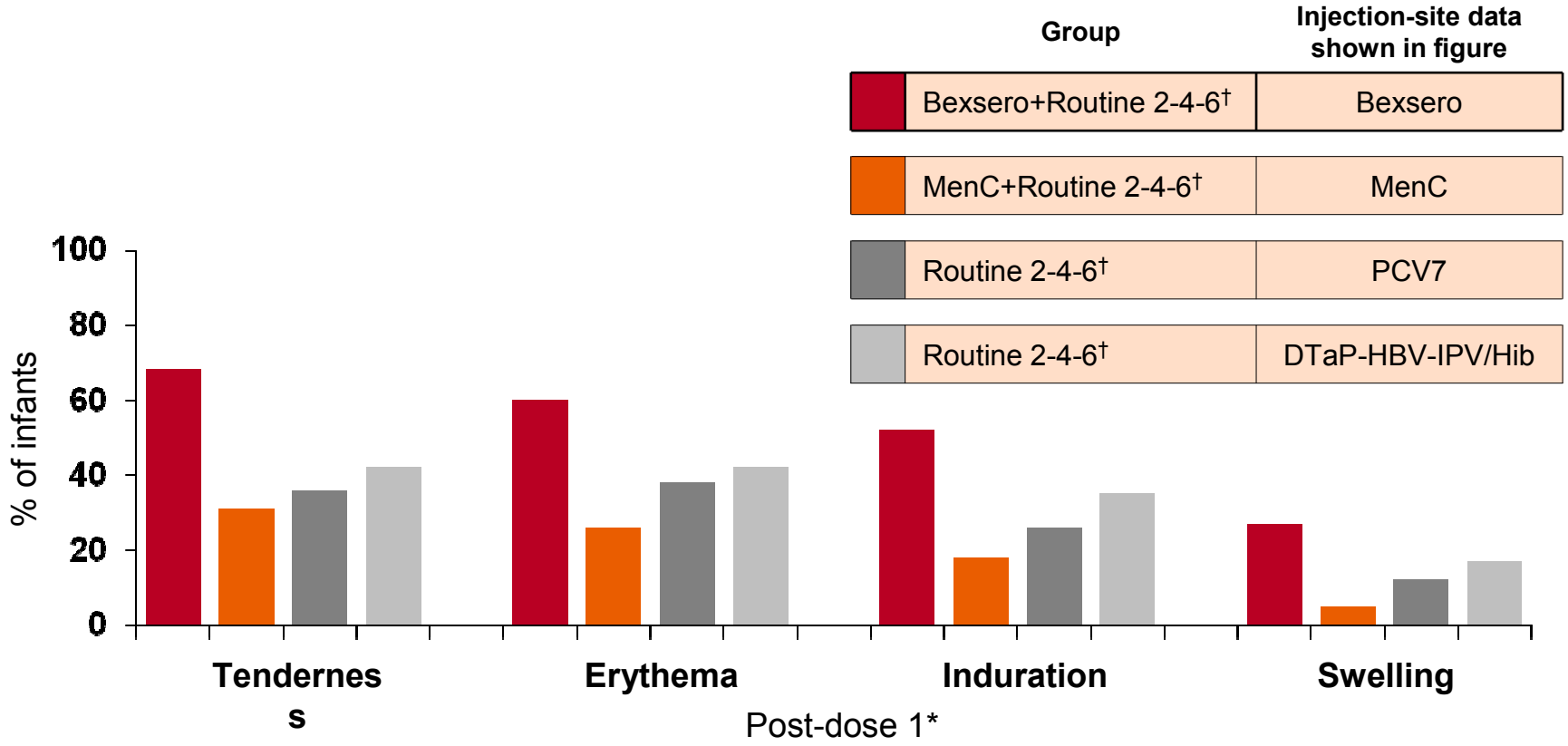
Phase III in Infants
Study V72P13 in EU Countries

1. Vesikari T, et al. Lancet 2013;381(9869):825-35; 2. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

NOVARTIS VACCINES AND DIAGNOSTICS

Bexsero Tolerability in Infants

Solicited local reactions



*No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series.

†Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; Bexsero+Routine: N=2477; MenC+Routine: N=490; Routine (PCV7): N=659; Routine (DTaP-HBV-IPV/Hib): N=659.

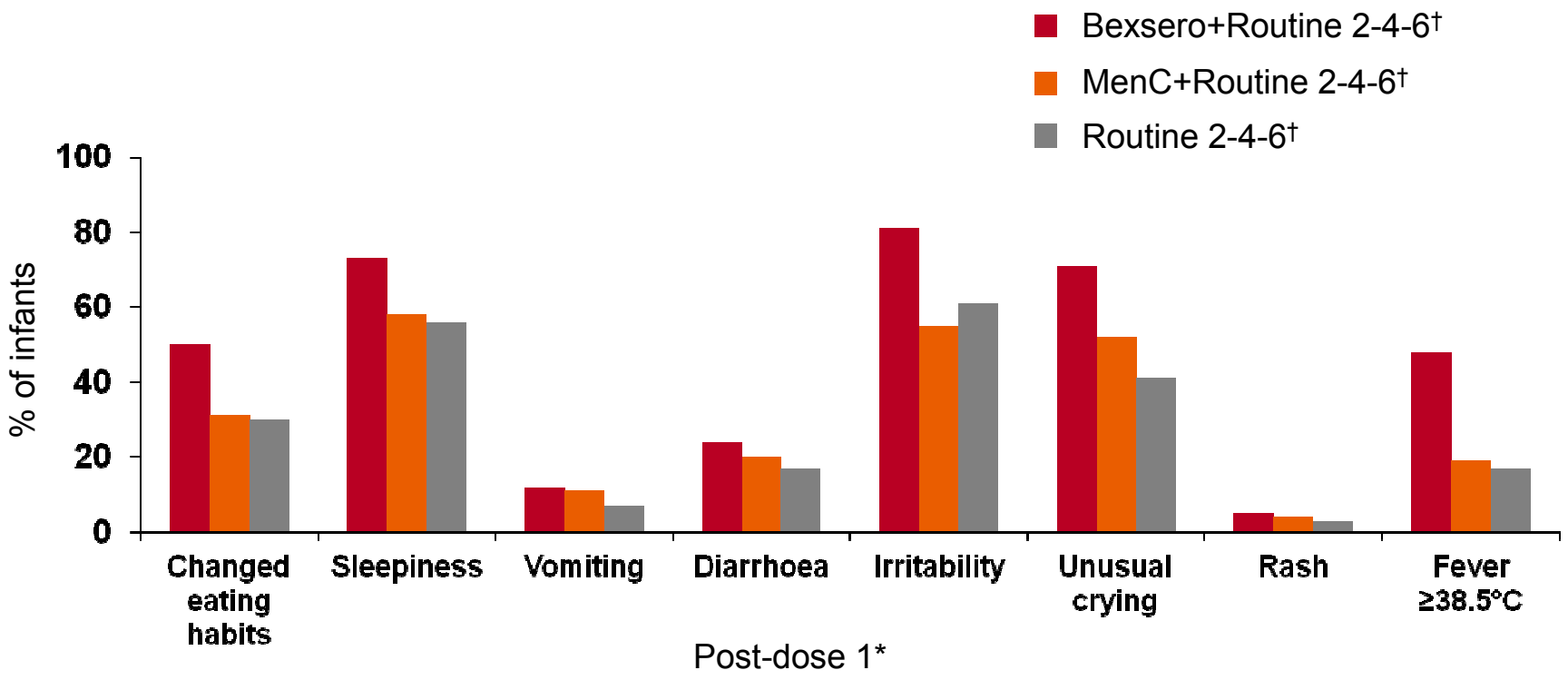
Phase III in Infants
Study V72P13 in EU Countries

1. Vesikari T, et al. Lancet 2013;381(9869):825-35 . 2. Data on file, Novartis Vaccines and Diagnostics; 3. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

NOVARTIS VACCINES AND DIAGNOSTICS

Bexsero Tolerability in Infants

Solicited general reactions



*No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series.

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Phase III in Infants
Study V72P13 in EU Countries

1. Vesikari T, et al. Lancet 2013;381(9869):825-35 ; 2. Data on file, Novartis Vaccines and Diagnostics; 3. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

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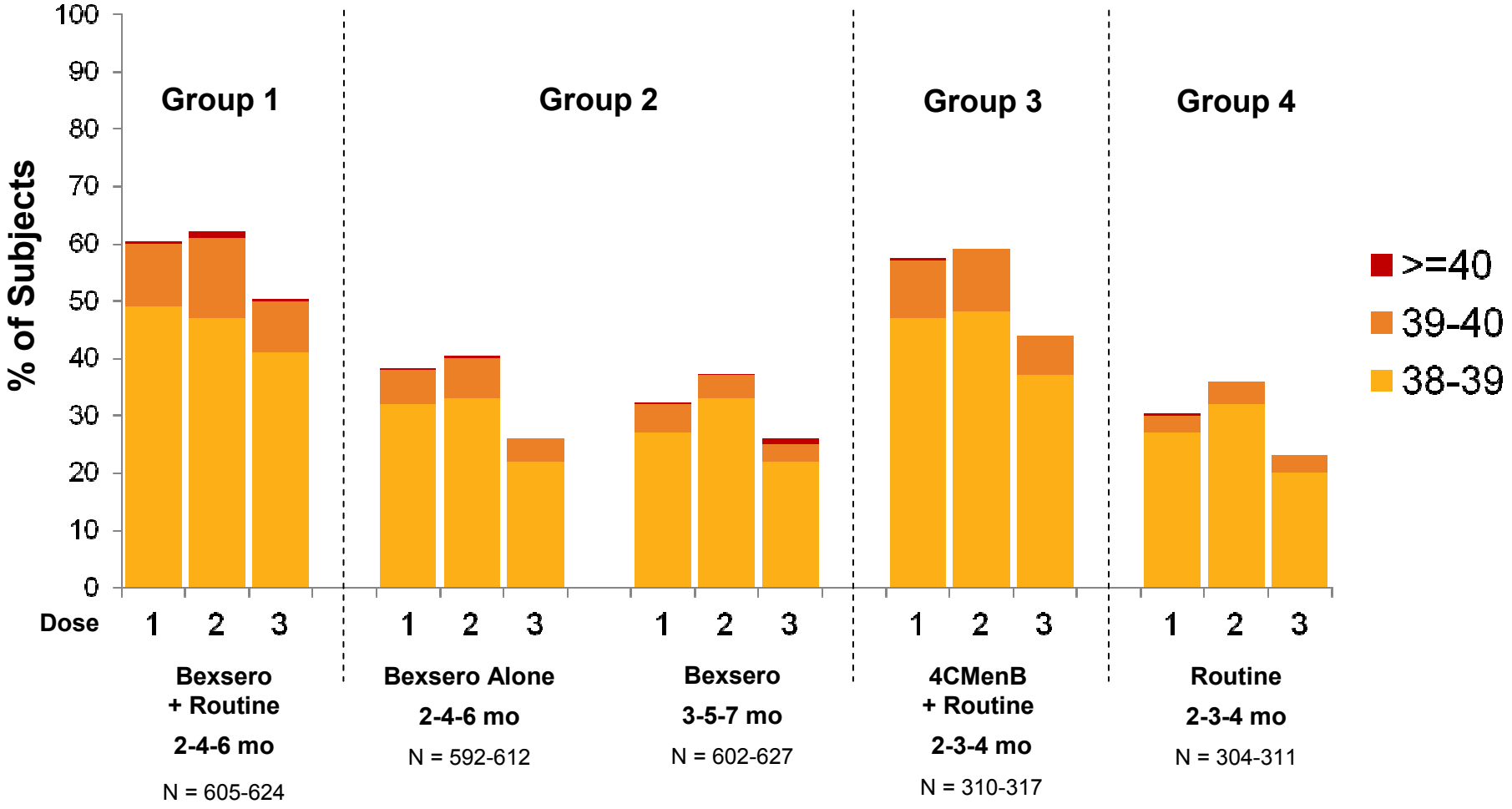
Fever Profile of 4CMenB in infants

*Daily fever rates according to 3 different vaccination schedules given 4CMenB vaccine ± routine vaccines or routine vaccines alone**



*Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

Phase III in Infants
Study V72P12 in EU Countries

NOVARTIS VACCINES AND DIAGNOSTICS

Gossger N, et al. Immunogenicity and tolerability of recombinant meningococcal serogroup B vaccine administered with or without routine infant vaccinations according to different immunisation schedules: A randomized controlled trial. *JAMA 2012;307:573-82.*

Medically Attended Fever After Any Dose

*Any fever for which a medical visit was sought**

Percentage of Subjects with Medically Attended Fever
(Number of Subjects with Medically Attended Fever/Total Number of Subjects)

		Bexsero® Vaccine + Routine Vaccines†	MenC+ Routine Vaccines†
Observer-Blind Subset	Any dose	5.27% (26/493)	2.77% 13/470)

		Bexsero Vaccine + Routine Vaccines†	Routine Vaccines†
Open-Label Subset	Any dose	1.42% (28/1966)	1.82% (12/659)

*Fever was defined as rectal temperature ≥38.5ºC or axillary temperature ≥38°C. Medically attended fever was any fever for which medical attention (a visit to or from medical personnel [medical doctor or nurse practitioner]) was sought.

†Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

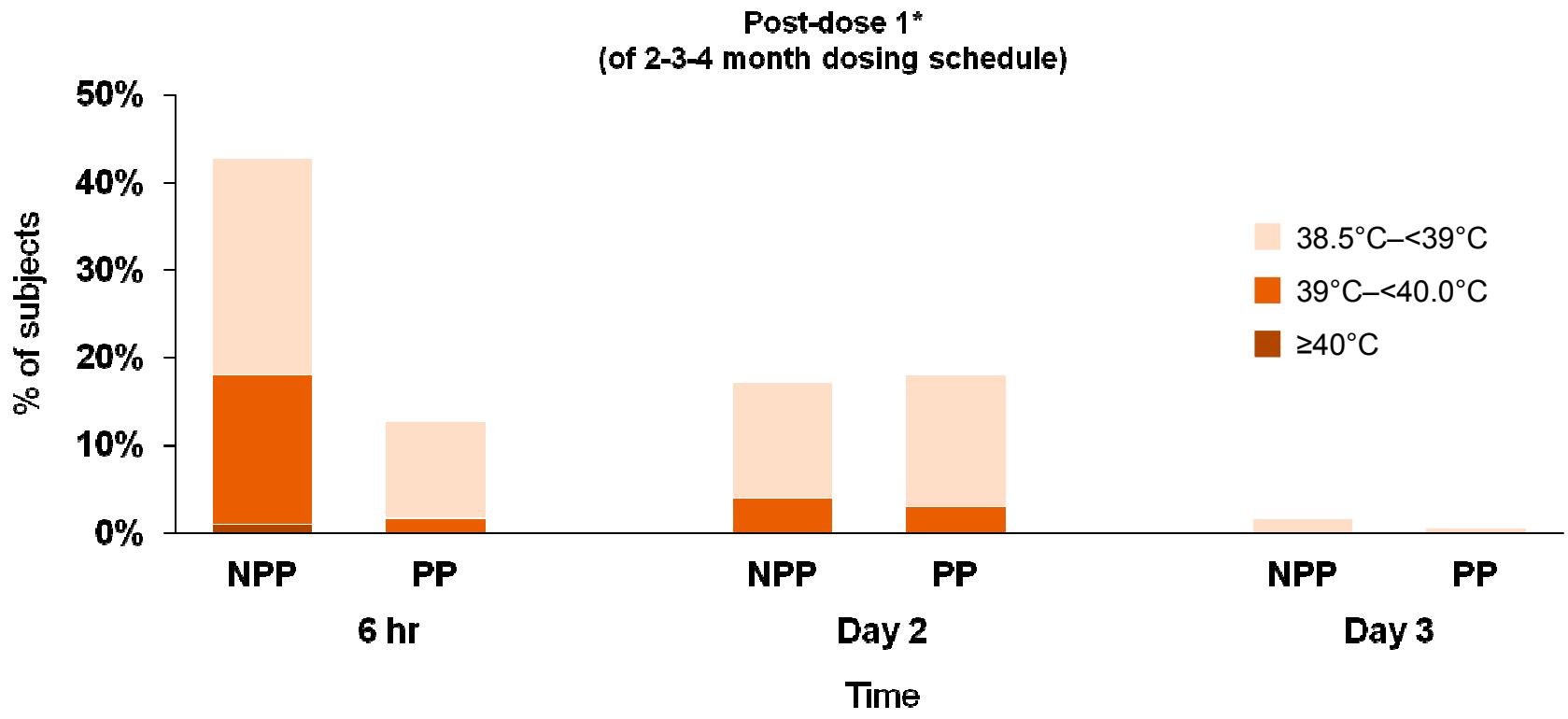
Phase III in Infants
Study V72P13 in EU Countries

NOVARTIS VACCINES AND DIAGNOSTICS

Vesikari T, et al. Lancet 2013;381(9869):825-35

Impact of Prophylactic Paracetamol on Reducing Fever

When Bexsero is given concomitantly with routine infant vaccines



*Similar results were observed with subsequent doses of the vaccination series.

NPP: no prophylactic paracetamol (N=182); PP: with prophylactic paracetamol (N=178-179).
Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

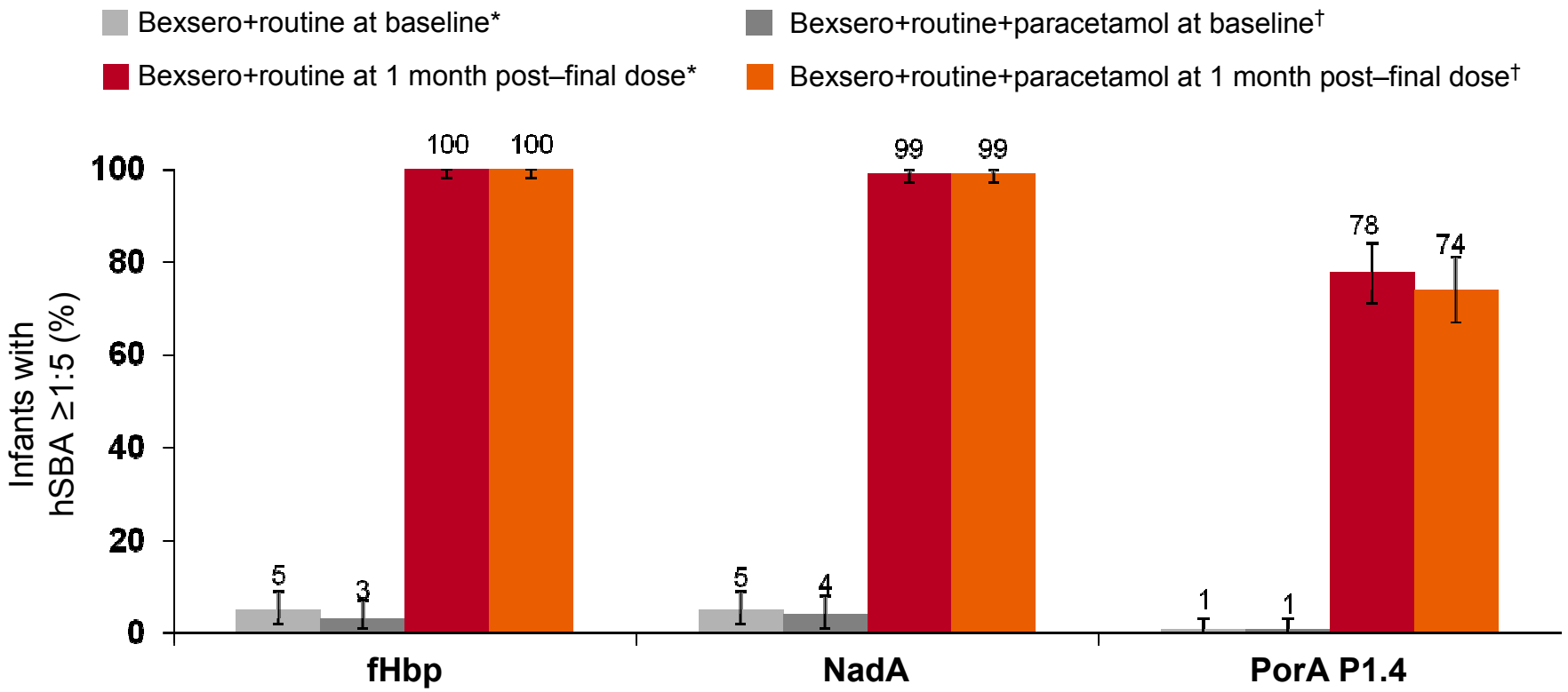
Phase II in Infants
Study V72P16 in EU and
LATAM Countries

1. Prymula R, et al. Presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID); 7-10 June 2011; The Hague, The Netherlands. Poster #631; 2. Data on file, Novartis Vaccines and Diagnostics; 3. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

NOVARTIS VACCINES AND DIAGNOSTICS

Co-administration of Bexsero and Routine Vaccines With or Without Paracetamol

Prophylactic paracetamol at the time of and closely after vaccination did not impact immunogenicity



*N=165–171; †N=160–169.

Each vaccine group followed a 2-3-4 month accelerated dosing schedule.

Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

Phase II in Infants
Study V72P16 in EU and LATAM Countries

1. Prymula R, et al. Presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID); 7-10 June 2011; The Hague, The Netherlands; Poster #631; 2. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

NOVARTIS VACCINES AND DIAGNOSTICS

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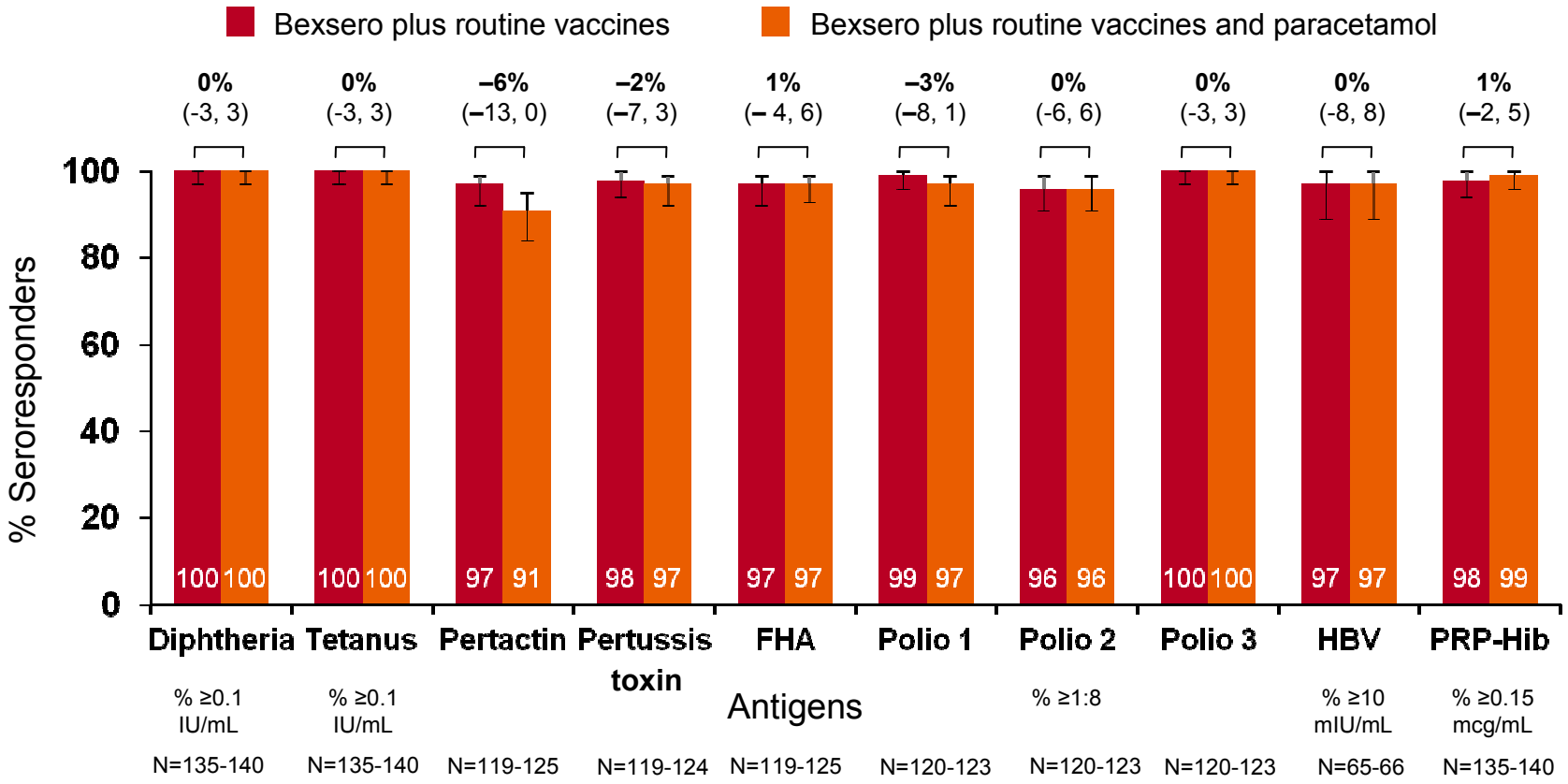

Each vaccine group followed a 2-3-4 month accelerated dosing schedule.
Blood draw at 5 months.
Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

Phase II in Infants
Study V72P16 in EU and LATAM Countries

1. Prymula R, et al. Presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID); 7-10 June 2011; The Hague, The Netherlands; Poster #631; 2. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2012.

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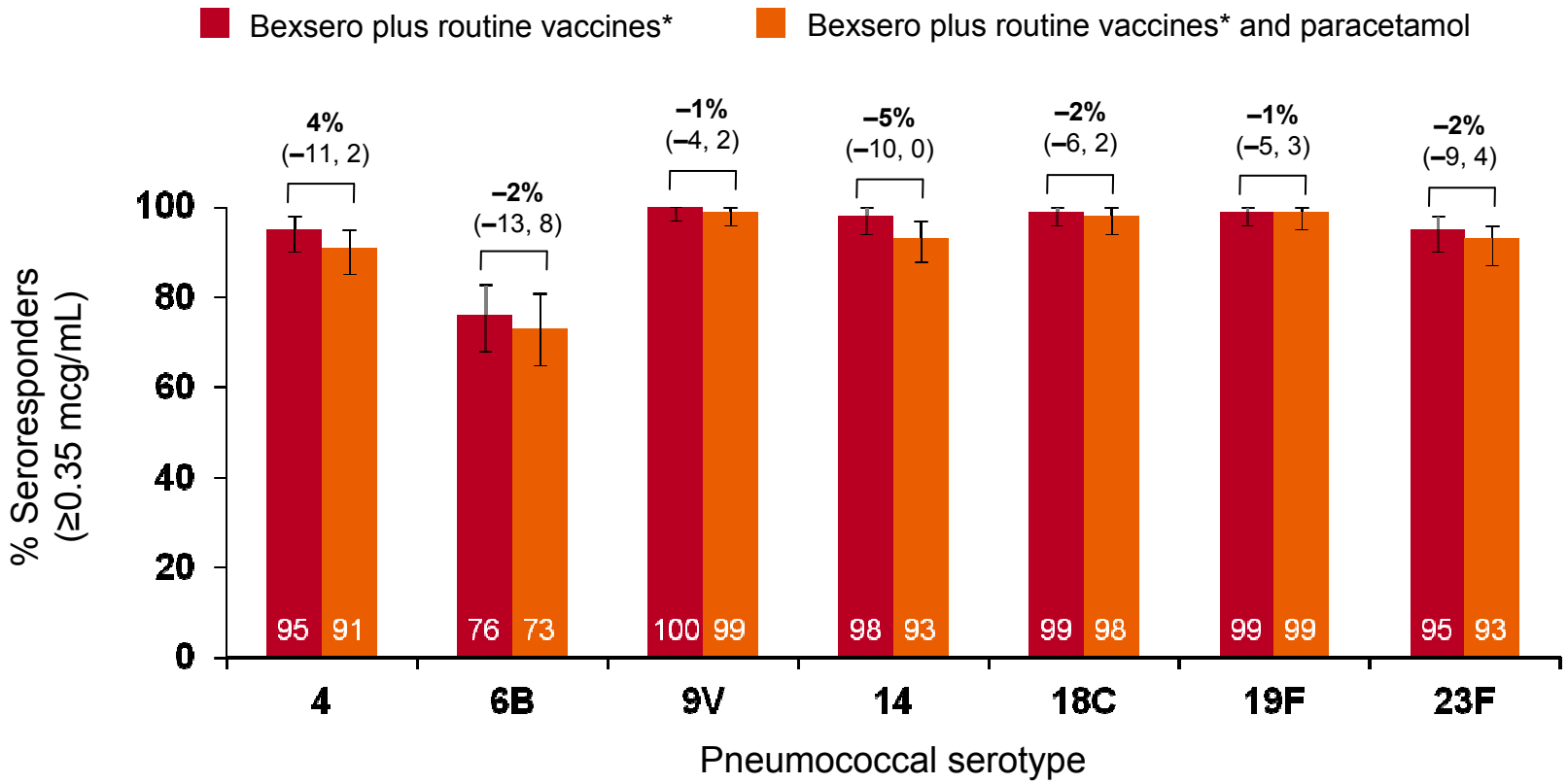

*N=135–140.
Each vaccine group followed a 2-3-4 month accelerated dosing schedule.
Blood draw at 5 months.
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Phase II in Infants
Study V72P16 in EU and LATAM Countries

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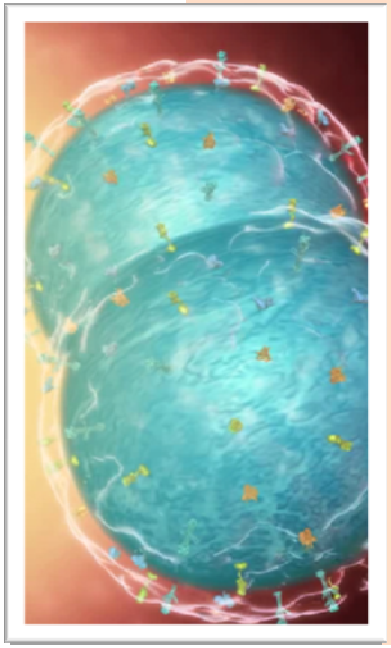
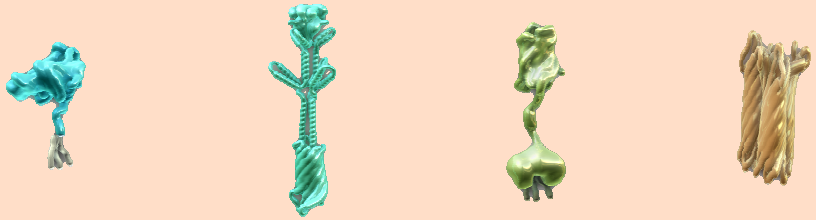
Coverage Estimates for Bexsero

The Meningococcal Antigen Typing System (MATS)





- Antigens used in Bexsero can be found in circulating strains
- For bacterial killing by antibodies induced by this vaccine, antigens have to be:
  - (i) Expressed to a sufficient degree*
  - (ii) Similar enough to the antigens in the vaccine*,†

such that the antibodies generated by the Investigational Multicomponent Men B Vaccine will kill the bacteria

MATS can predict the percentage of MenB strains in a region that are potentially covered by Bexsero

- MATS has been validated and standardised and is used by national reference laboratories around the globe to estimate predictive coverage of Bexsero

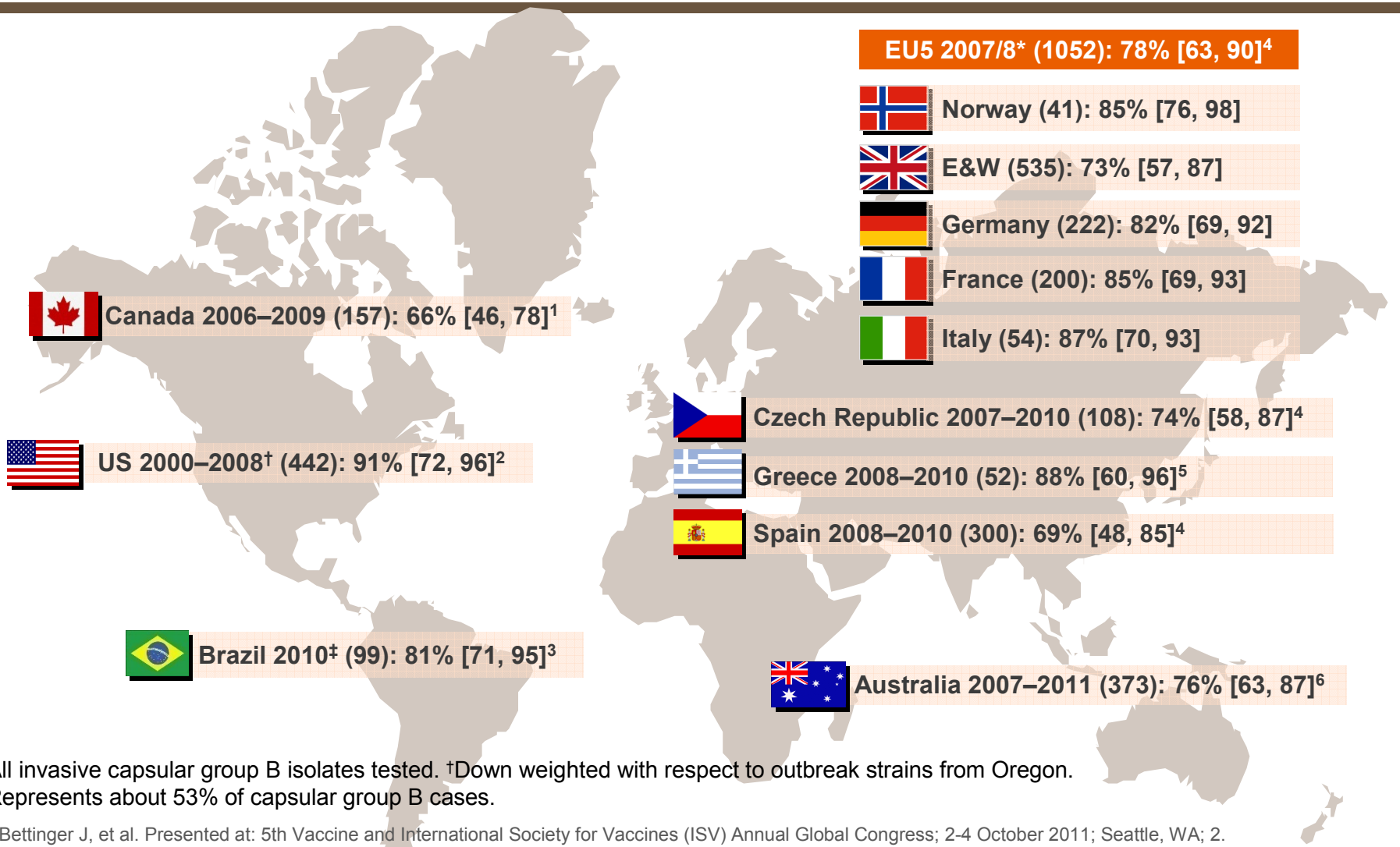
*fHbp, NHBA and NadA assessments use ELISA → PHENOTYPIC.

†PorA is prominent on the surface of the bacteria (ie, sufficiently expressed). Conventional PCR genotyping is used to determine the similarity of the PorA gene sequence in a particular strain to that in Bexsero.

NOVARTIS VACCINES AND DIAGNOSTICS

Donnelly J, et al. *Proc Natl Acad Sci U S A.* 2010;107:19490-19495.

MATS Predicts the Country-Specific Estimated Strain Coverage of Bexsero



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

1. Bettinger J, et al. Presented at: 5th Vaccine and International Society for Vaccines (ISV) Annual Global Congress; 2-4 October 2011; Seattle, WA; 2. Kim E, et al. Presented at: 19th International Pathogenic Neisseria Conference (IPNC). 9-14 September 2012. Würzburg, Germany. Poster P270; 3. Lemos AP, et al. Presented at: 19th International Pathogenic Neisseria Conference (IPNC). 9-14 September 2012. Würzburg, Germany. Poster P272; 4. Vogel U, et al. *Lancet Infect Dis*. 2012 [in press]; 5. Data on file, Novartis Vaccines and Diagnostics; 6. Nissen M, et al. Presented at: 19th International Pathogenic Neisseria Conference (IPNC). 9-14 September 2012. Würzburg, Germany. Poster P269.

NOVARTIS VACCINES AND DIAGNOSTICS

Summary

- Serogroup B affects mainly infants, is easily misdiagnosed, can kill within 24 hours of onset and may cause serious, lifelong disabilities despite appropriate treatment
- Vaccination is the best prevention against an aggressive disease that leaves little time for intervention
- Bexsero is a novel meningococcal serogroup B vaccine for active immunisation against invasive MenB disease caused by the majority of circulating pathogenic strains
- In clinical studies, Bexsero has demonstrated a protective immune response in infants, children, adolescents and adults with or without routine vaccines
- MATS results from 8 European countries, Australia, United States, Brazil and Canada on nearly 2590 MenB strains estimate that 66% to 91% would be covered by Bexsero
- Predicted coverage of MenB strains by Bexsero has the potential to impact the incidence of MenB disease in these regions