Public Health England

Invasive Meningococcal Disease

- prevention through vaccination

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“a pain you cannot describe”

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“Two weeks of Hell”

Petition

Give the Meningitis B vaccine to ALL children, not just newborn babies.

All children are at risk from this terrible infection, yet the Government plan to only vaccinate 2-5 month olds. There needs to be a rollout programme to vaccinate all children, at least up to age 11. Meningococcal infections can be very serious, causing MENINGITIS, SEPTICAEMIA & DEATH.

▶ More details

Sign this petition

816,118 signatures

Show on a map

100,000

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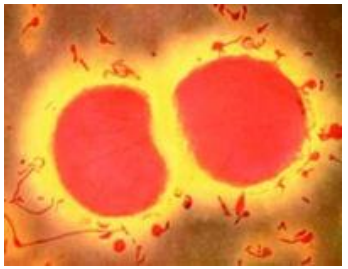
Vaccines against MenB

- MenC and MenACWY conjugate vaccines target the polysaccharide capsules – no cross-protection
- MenB polysaccharide is a polysialic acid - identical to that found on surface of human foetal neuronal cells.
- Consequently;

  (i) Poorly immunogenic.

  (ii) Potential to induce an autoimmune response

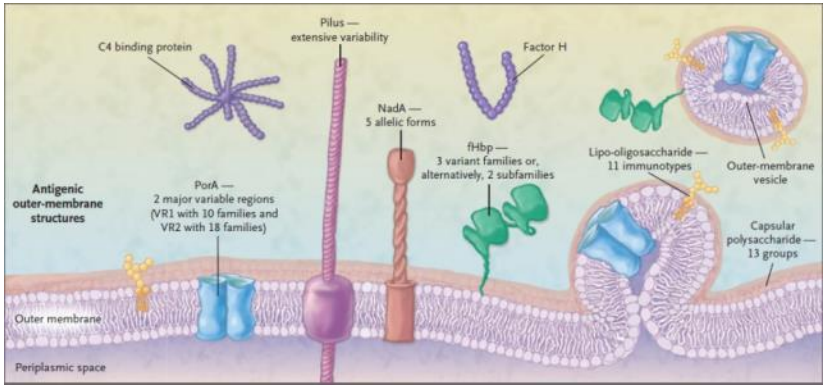


- Use subcapsular antigens, which:

  (i) are Surface-exposed

  (ii) are Conserved

  (iii) induce Bactericidal activity



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Predicted meningococcal strain coverage in Europe

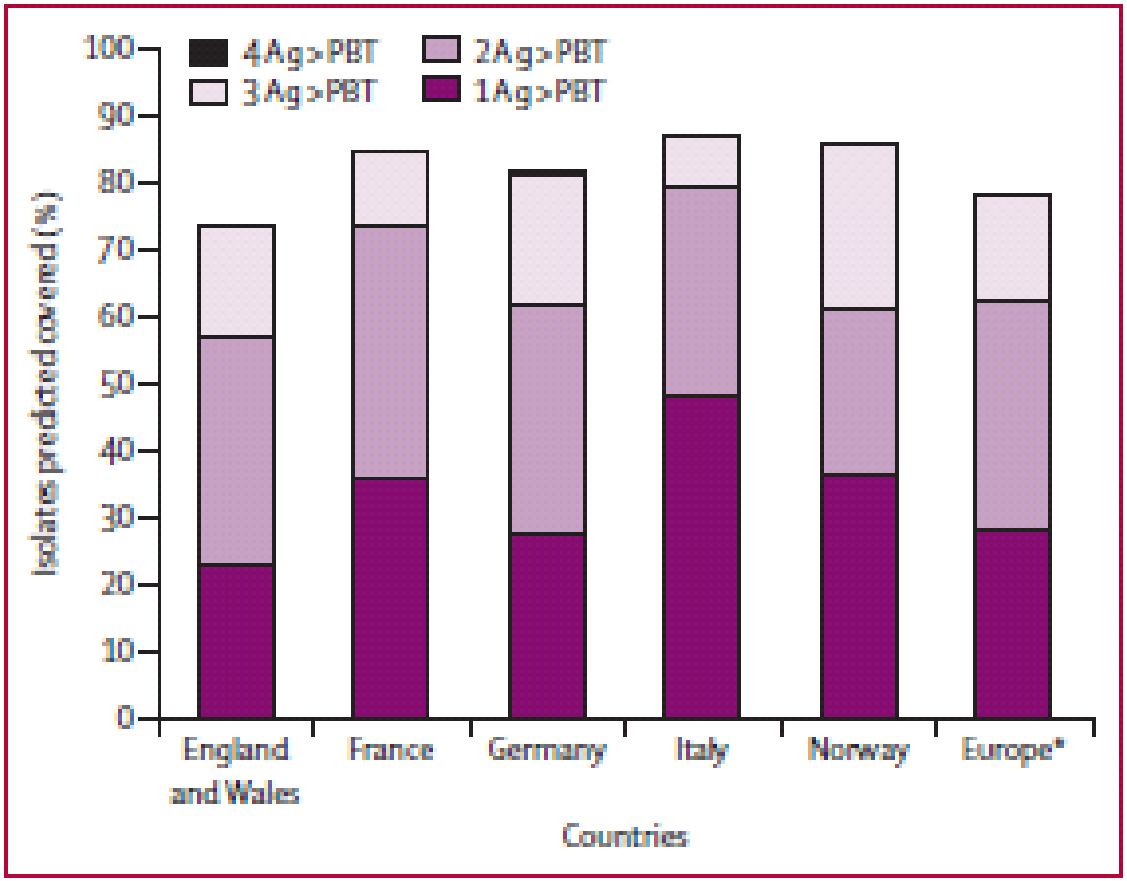

Figure 1: Percentages of isolates predicted by the meningococcal antigen typing system to be covered, and number of antigens, overall and by country

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Invasive Meningococcal Disease

England & Wales, 2008-14

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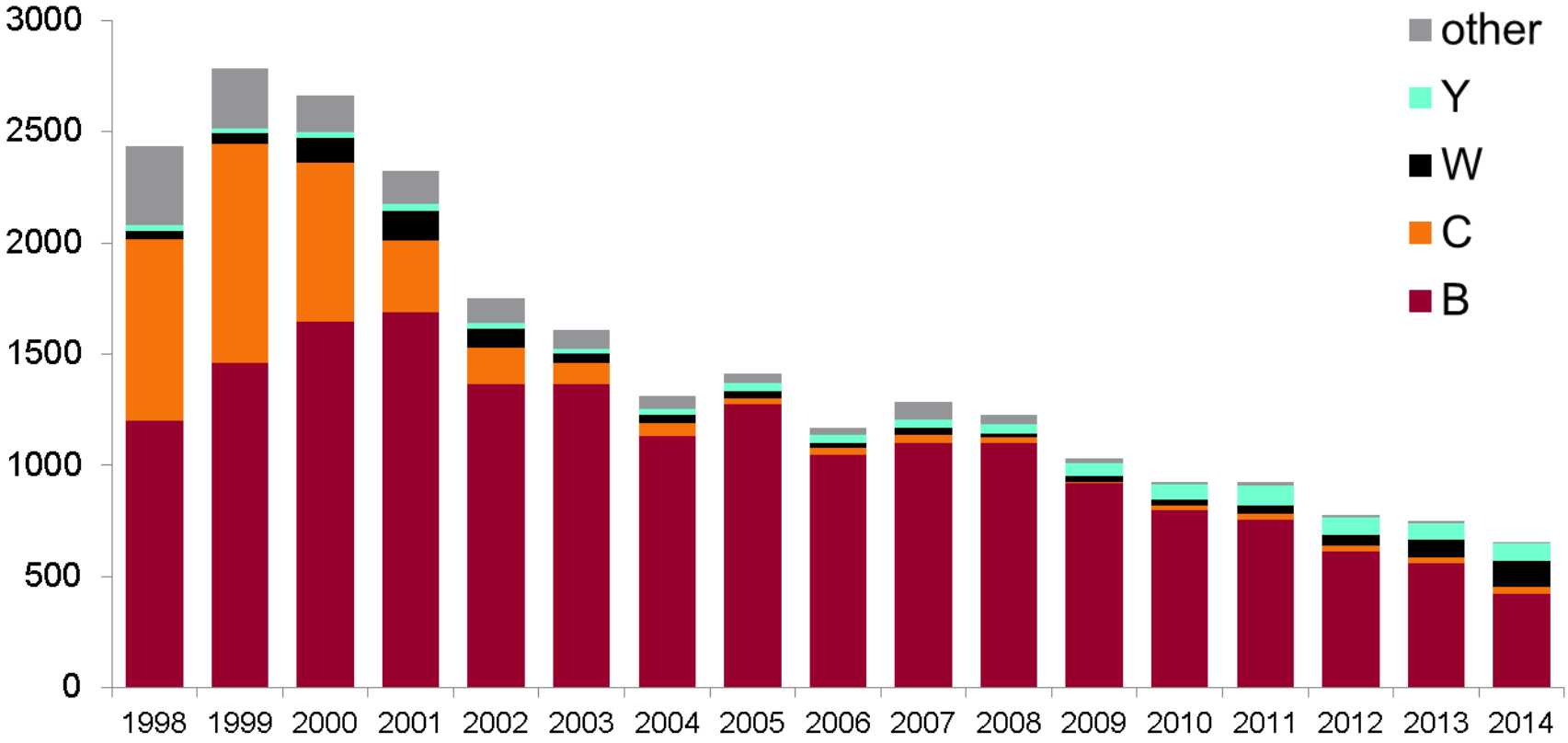
Laboratory confirmed cases invasive meningococcal disease

England and Wales



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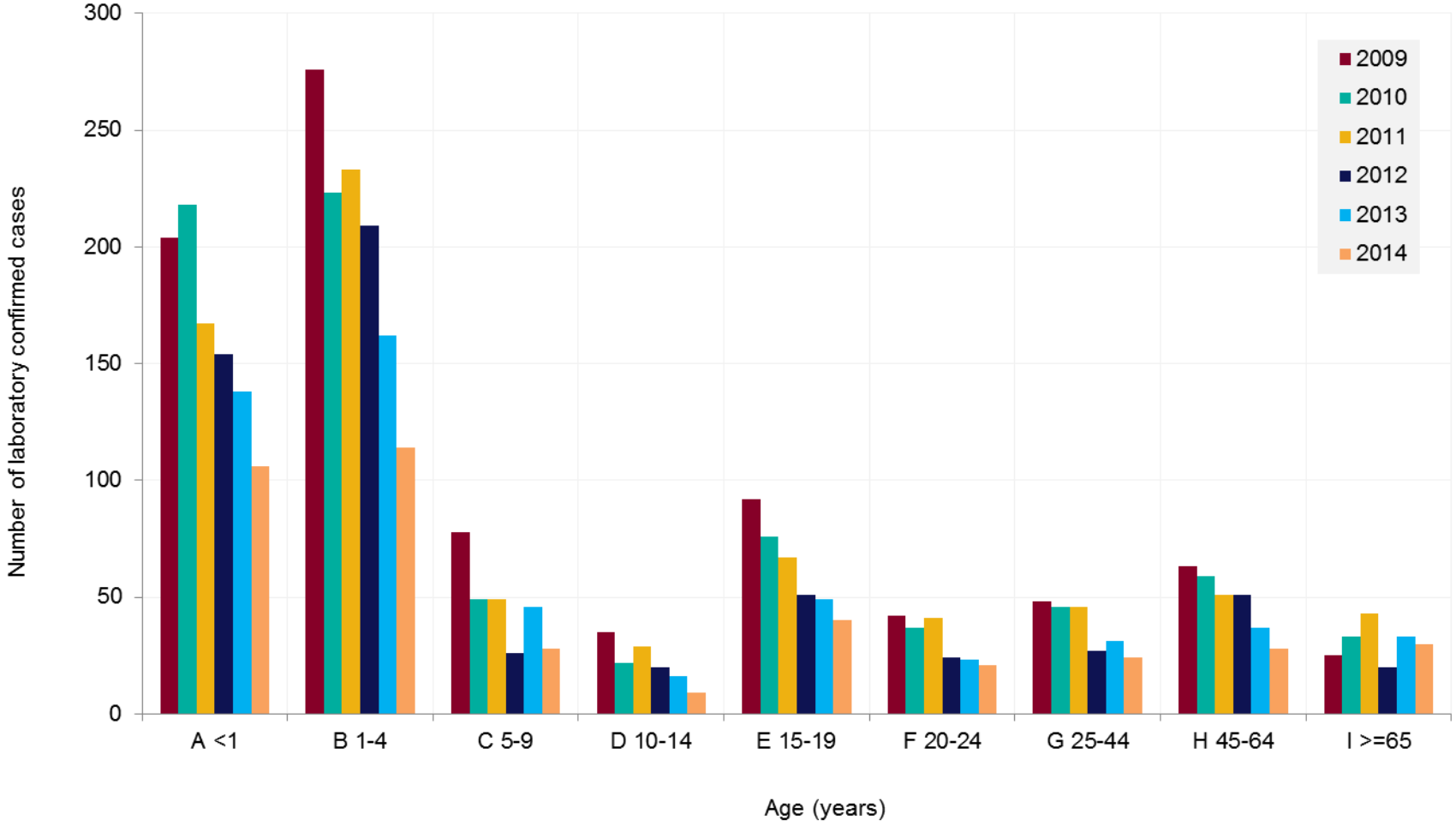
Laboratory confirmed cases of invasive meningococcal disease capsular group B (MenB) in England, calendar years 2009-2014



Date source: PHE Meningococcal Reference Unit. Surveillance by PHE Immunisation Department – Last Update August 2015
Please see link for more information and data https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis

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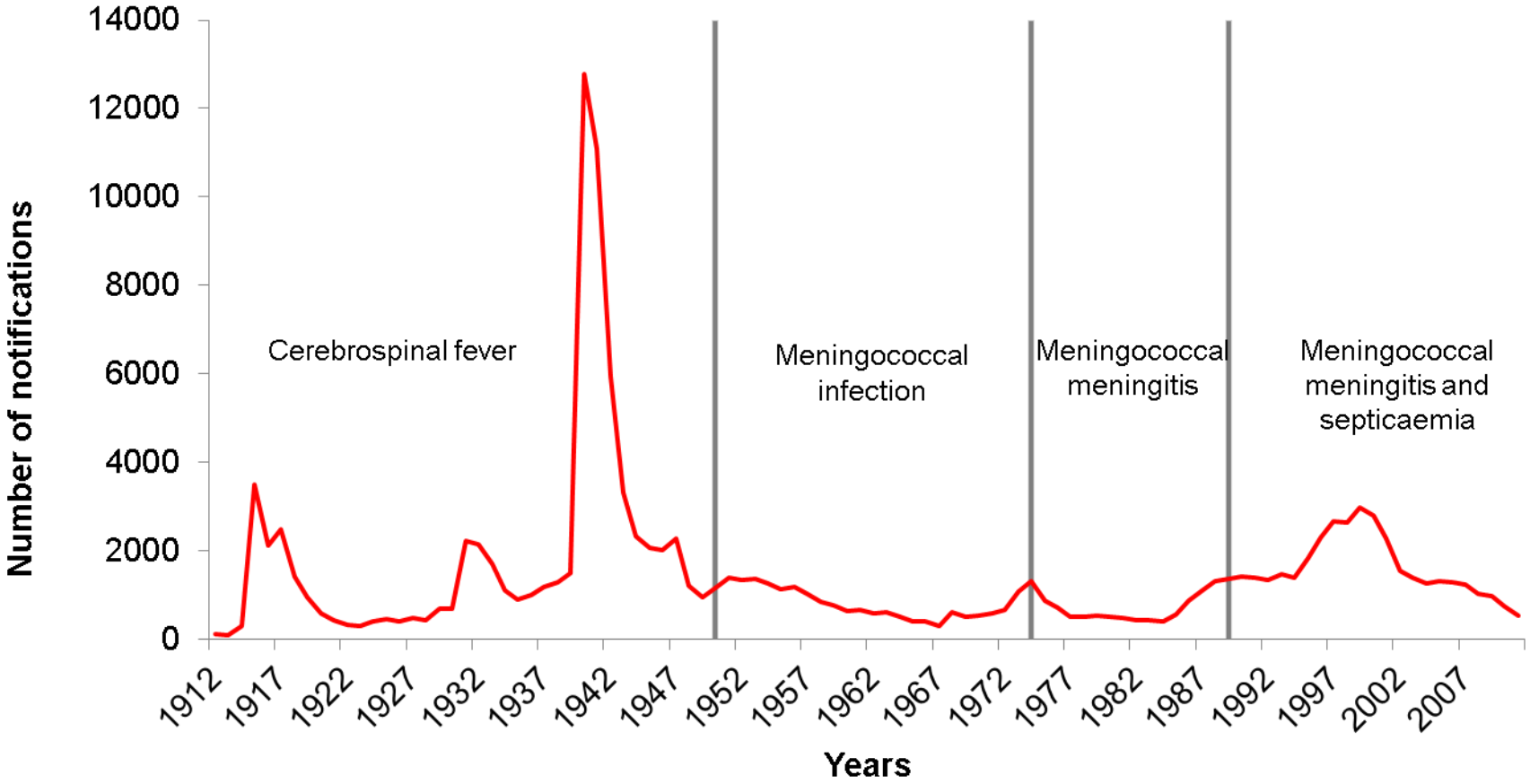
Long term trends in notified meningococcal disease, England and Wales



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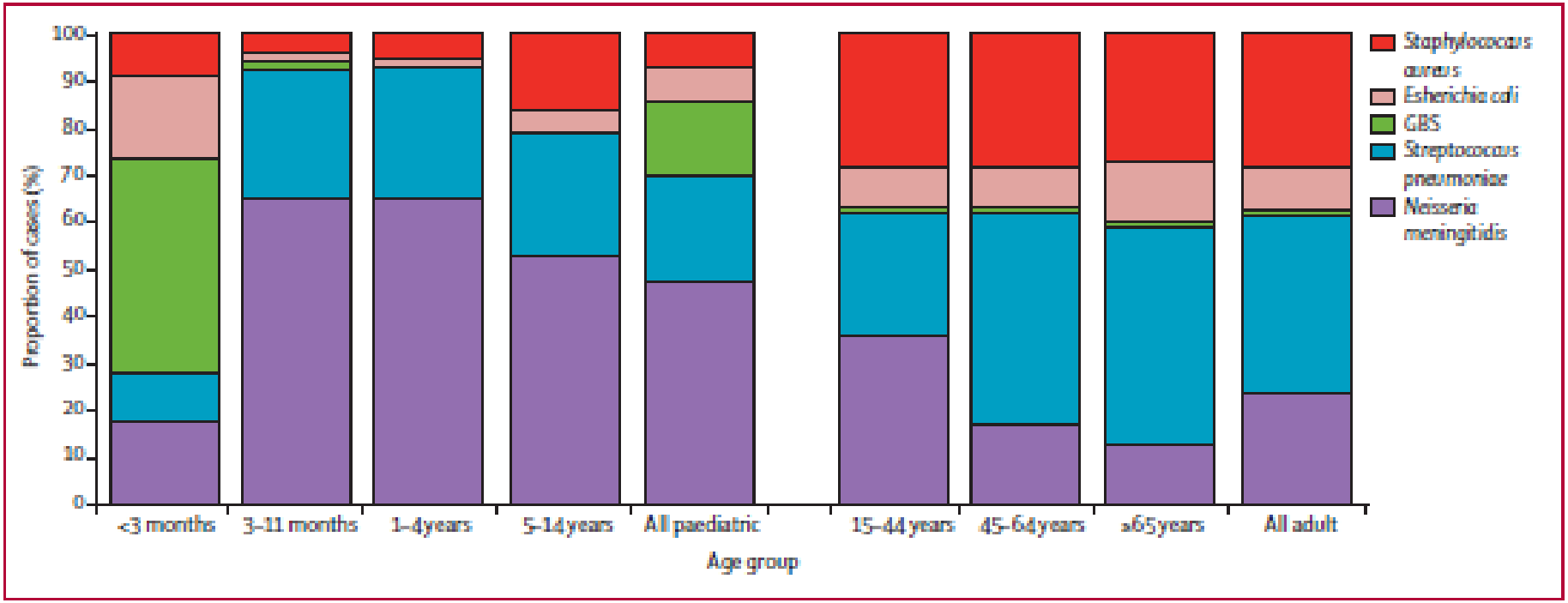
Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004–11: an observational study

Ifeanichukwu O Okike, Sonia Ribeiro, Mary E Ramsay, Paul T Heath, Mike Sharland, Shamez N Ladhani



Lancet Infect Dis 2014
Published Online
February 7, 2014

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UK MenB programme

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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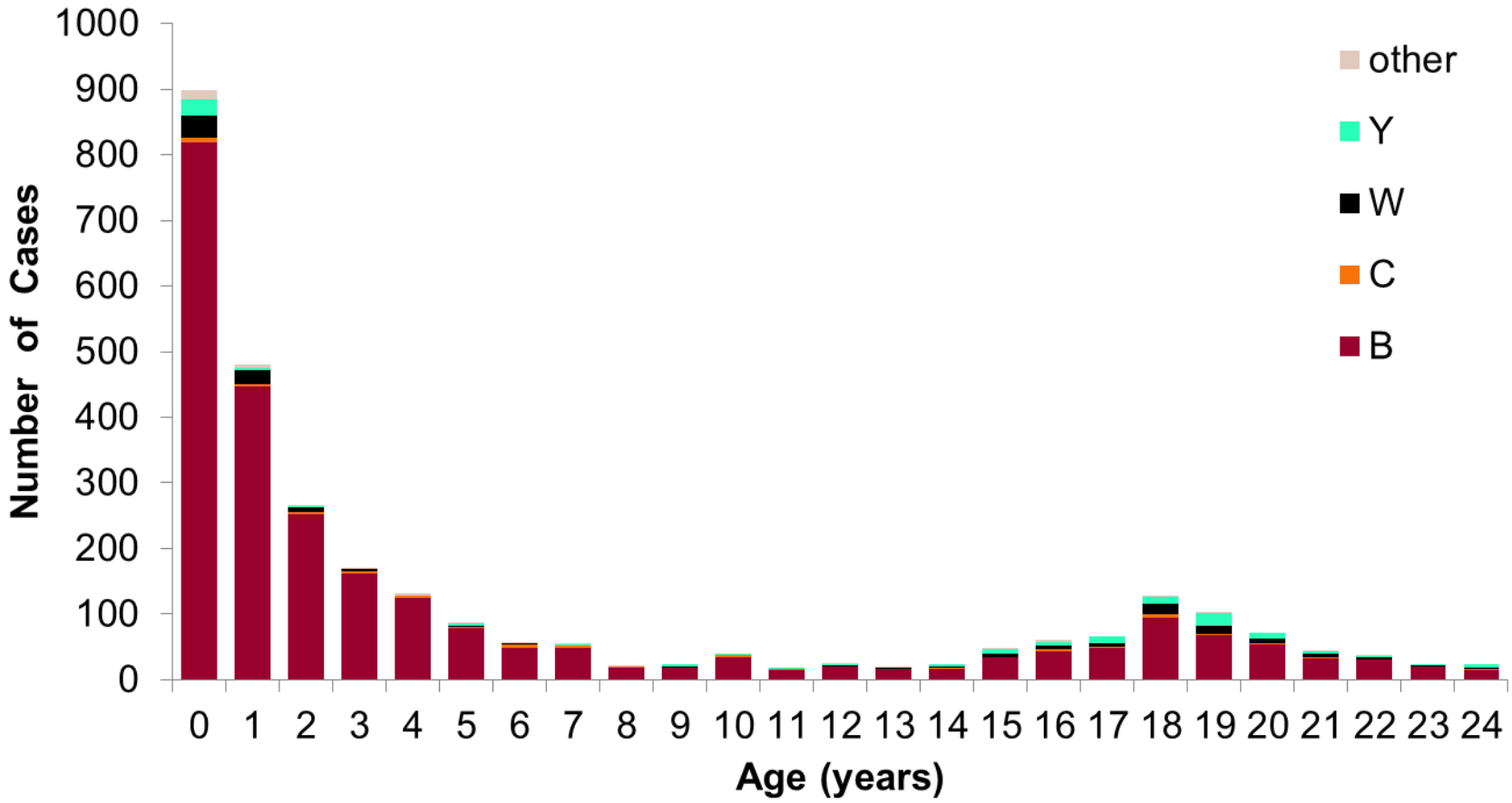
Laboratory confirmed IMD by group and age (2010-2014)



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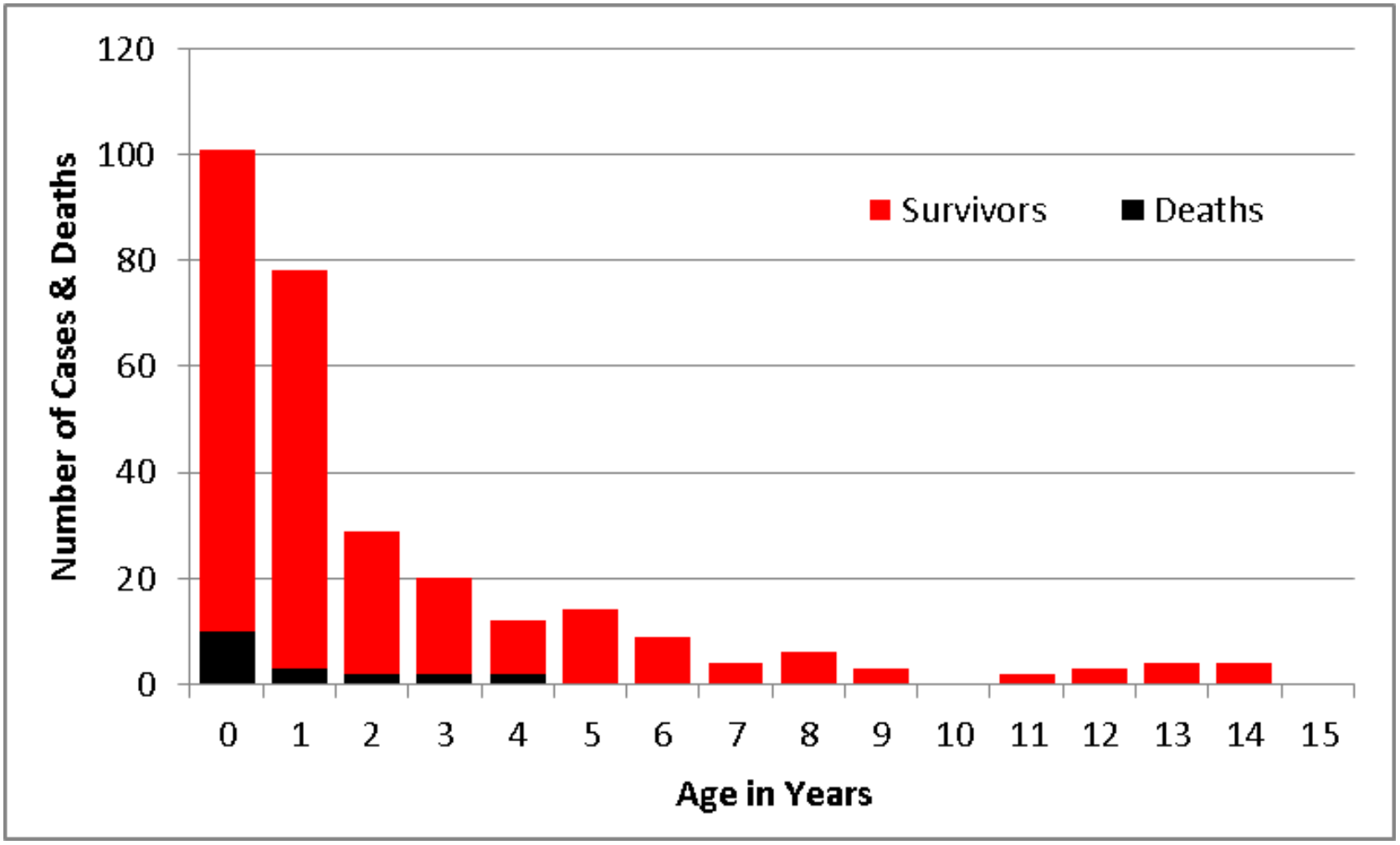
MenB cases/deaths, England 2014/15



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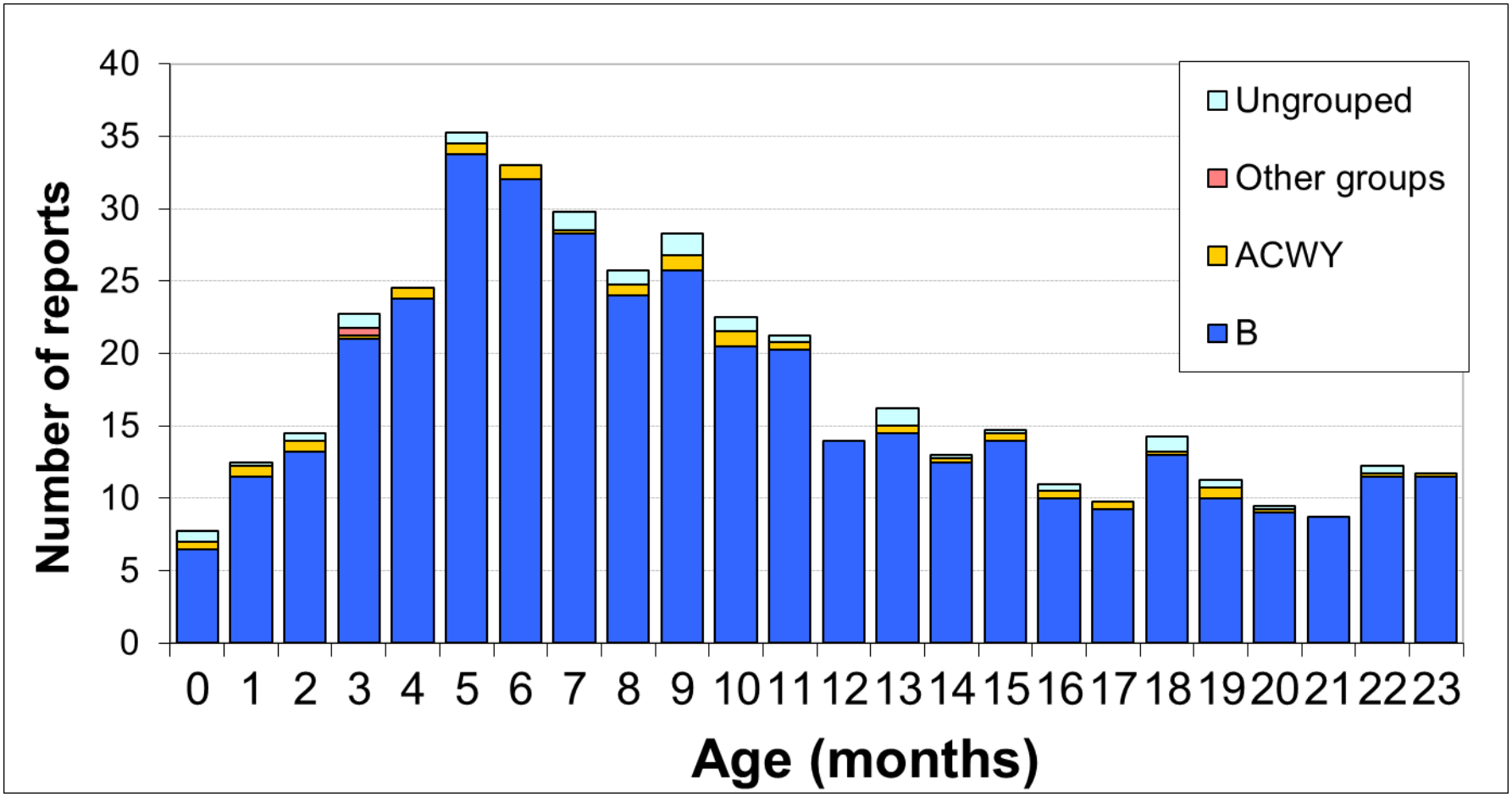
IMD in <2 year-olds

England & Wales (2006/07-2010/11)



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Proportion of children with bactericidal antibody (GMT) to specific strains at different schedules

Study	Schedule	44/76 fHBP	5/99 NadA	NZ 98/254 OMV
Findlow (≥1:4 hSBA)	2, 4, 6 m After third dose	95% (30)	95% (126)	85% (19)
	2, 4 m After second dose	87% (28)	100% (104)	74% (6.6)
Gossger (≥1:5 hSBA)	2, 3, 4 m	99.3% (82)	100% (323)	81% (11)

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Adverse reactions to 4CMenB

Bexsero® is associated with higher rates of local and systemic reactions when give with other routine infant vaccinations

- similar to those seen with whole cell pertussis vaccines

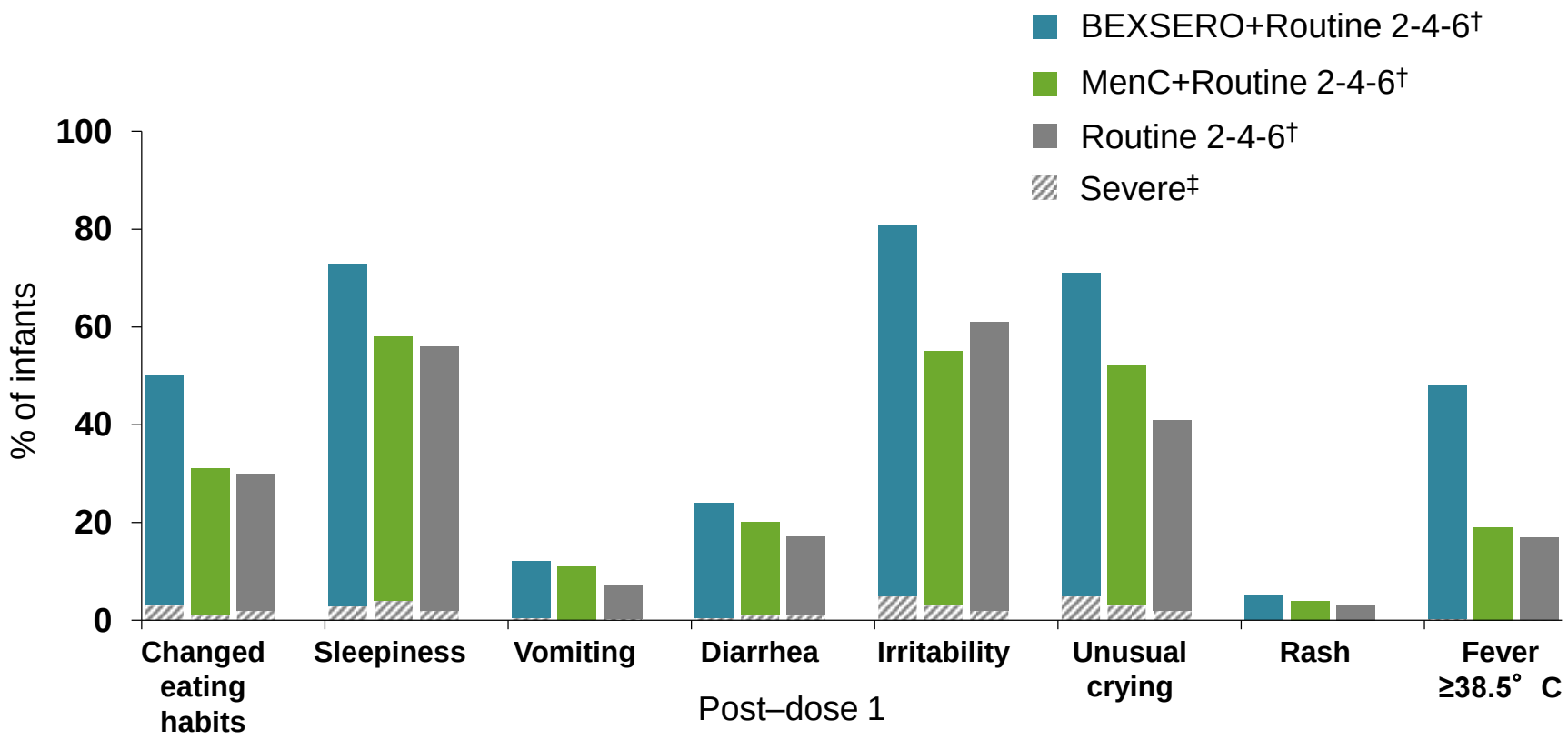
Systemic effects tend to be additive when given with other vaccines

For example, **any fever** was seen following:

- 26-41% of Bexsero® doses when administered alone,
- 23-36% after routine vaccines given alone
- **51-61% after Bexsero® and routine vaccines administered together**

BEXSERO® Tolerability in Infants

Solicited systemic reactions when BEXSERO is given with routine vaccines—post–dose 1



*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=2478; MenC+Routine: N=490; Routine: N=659.

‡Fever was categorized as severe if temperature was ≥40˚ C. All other reactions were categorized as severe if subject was unable to perform normal daily activities.

1. Vesikari T, et al. *Lancet*. 2013;381:825-835; 2. Data on file, Novartis Vaccines and Diagnostics; 3. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; January 14, 2013.

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Vaccine acceptability and attitudes to vaccination

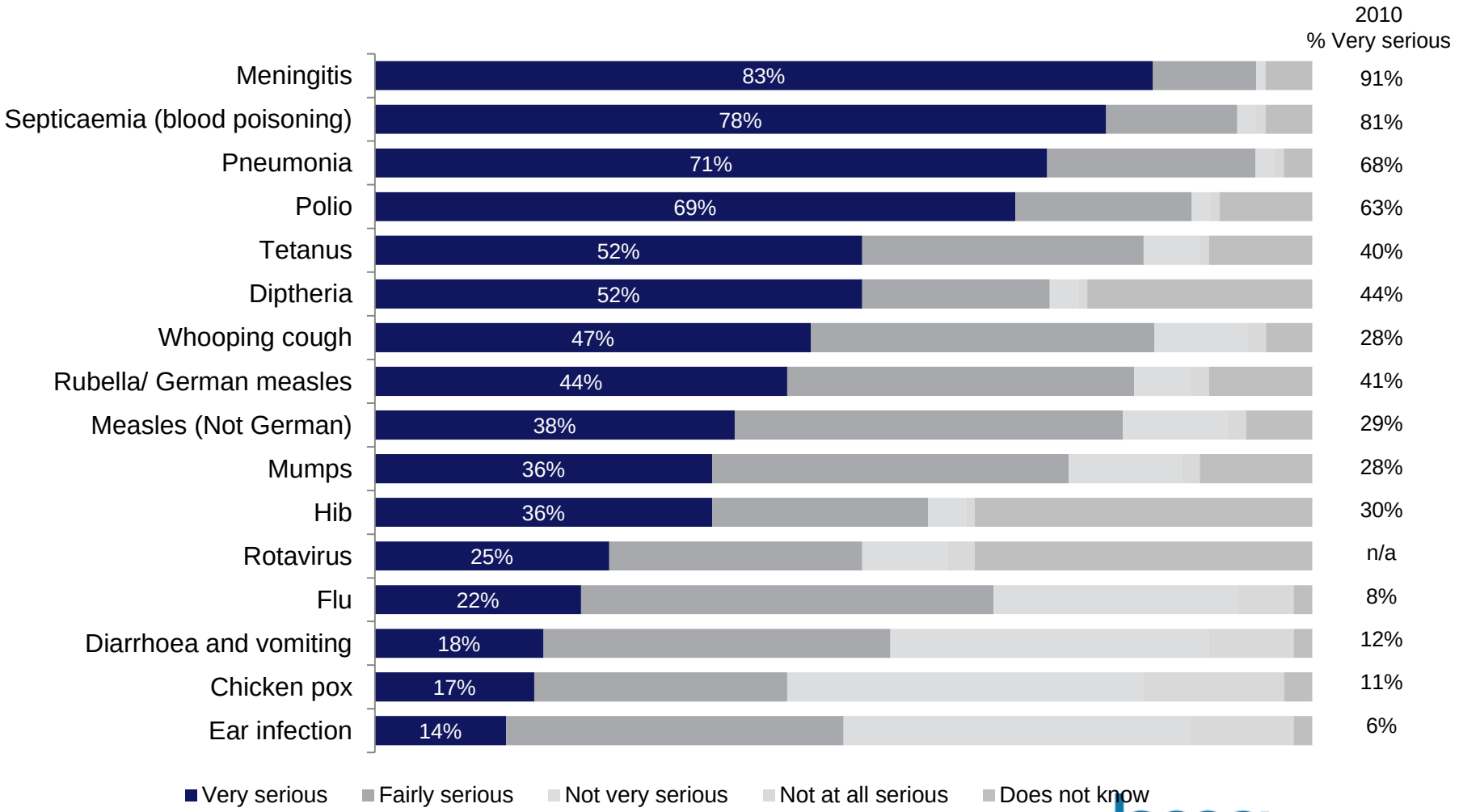
Regular survey of parents attitudes to vaccination

Last conducted in 2010

Resurrected in 2015!

Additional research on MenB commissioned in 2014

Could you please tell me how serious the consequences of children getting each disease would be?



bmg research Understanding People.

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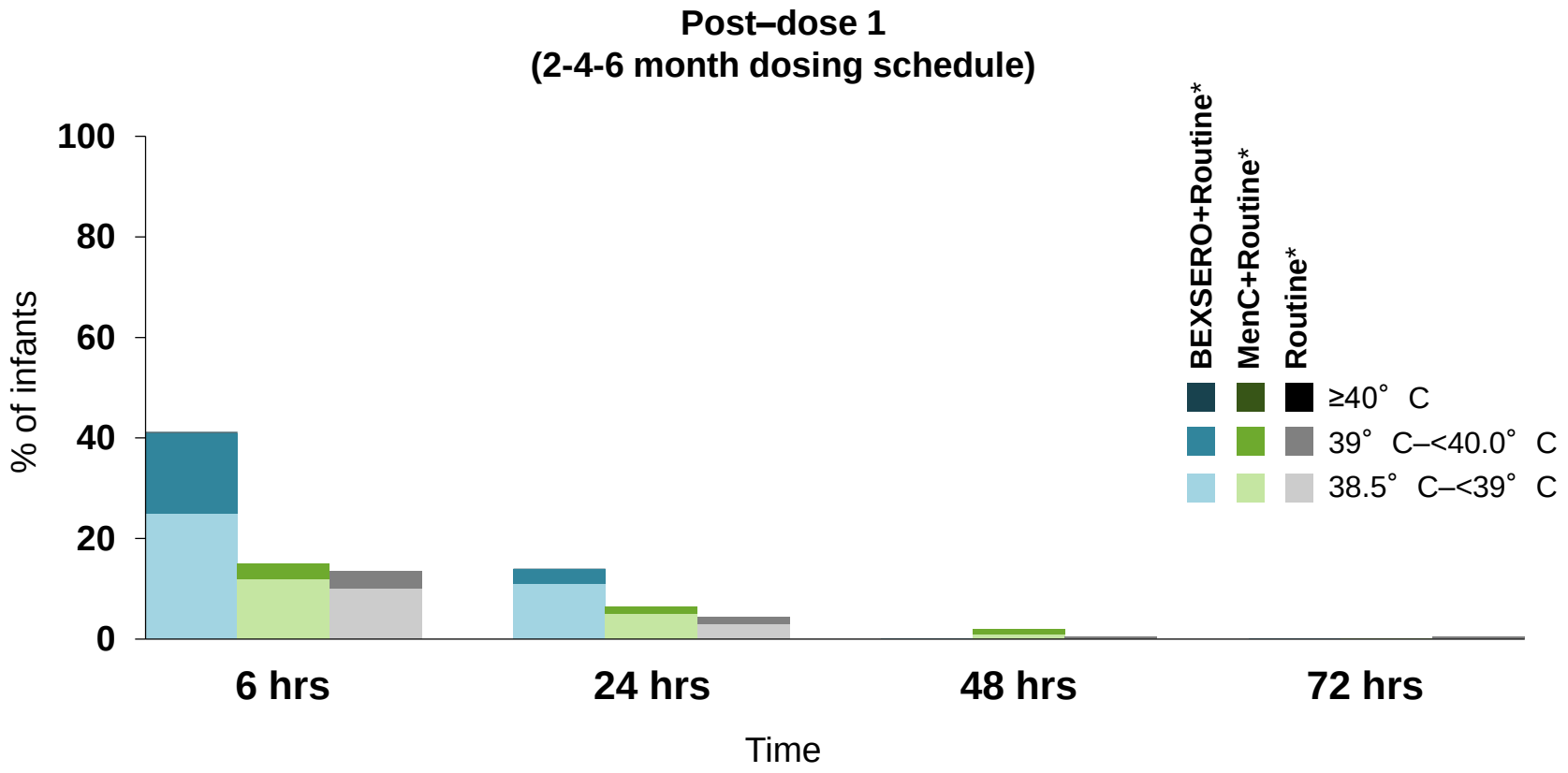
Specific research on MenB

Dr Cath Jackson, Valid Research
Dr Helen Bedford, UCL Institute of Child Health

- Most parents were unfamiliar with the term ‘meningococcal disease’ but had generally heard of ‘meningitis’
- Most parents had not heard of the MenB vaccine (whereas they knew that the schedule included a MenC vaccine)
- MenC programme is well established; information about MenB only needed because it’s a new vaccine
- Most parents liked leaflets in the Q+A format, some parents happy with the 2 minute guide, others preferred a longer version
- Parents worry about fever and consequences (in a 2 month old)
  - But better for child to have fever than meningitis
  - To some extent parents expect fever with immunisation.

When Fever Occurred, it Generally Followed a Predictable Pattern, With the Majority Resolving the Day After Vaccination

BEXSERO® given with routine vaccines—post–dose 1



*Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; BEXSERO+Routine: N=2433–2478; MenC+Routine: N=486–490; Routine only: N=643–659.
Fever was defined as rectal temperature ≥38.5° C.

1. Vesikari T, et al. *Lancet*. 2013;381:825-835; 2. Data on file, Novartis Vaccines and Diagnostics; 3. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; January 14, 2013.

In general, the frequency of medically attended fever was low

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	5.3% (26/493)	2.8% (13/470)

		BEXSERO Vaccine + Routine Vaccines*	Routine Vaccines*
Open-Label Subset	Any dose	1.4% (28/1966)	1.8% (12/659)

Medical intervention less likely with knowledge of vaccine received

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

Vesikari T, et al. *Lancet*. 2013;381:825-835.

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NICE guidance on management of feverish illness in children under 5 years (2007/2013)

Use of antipyretic agents

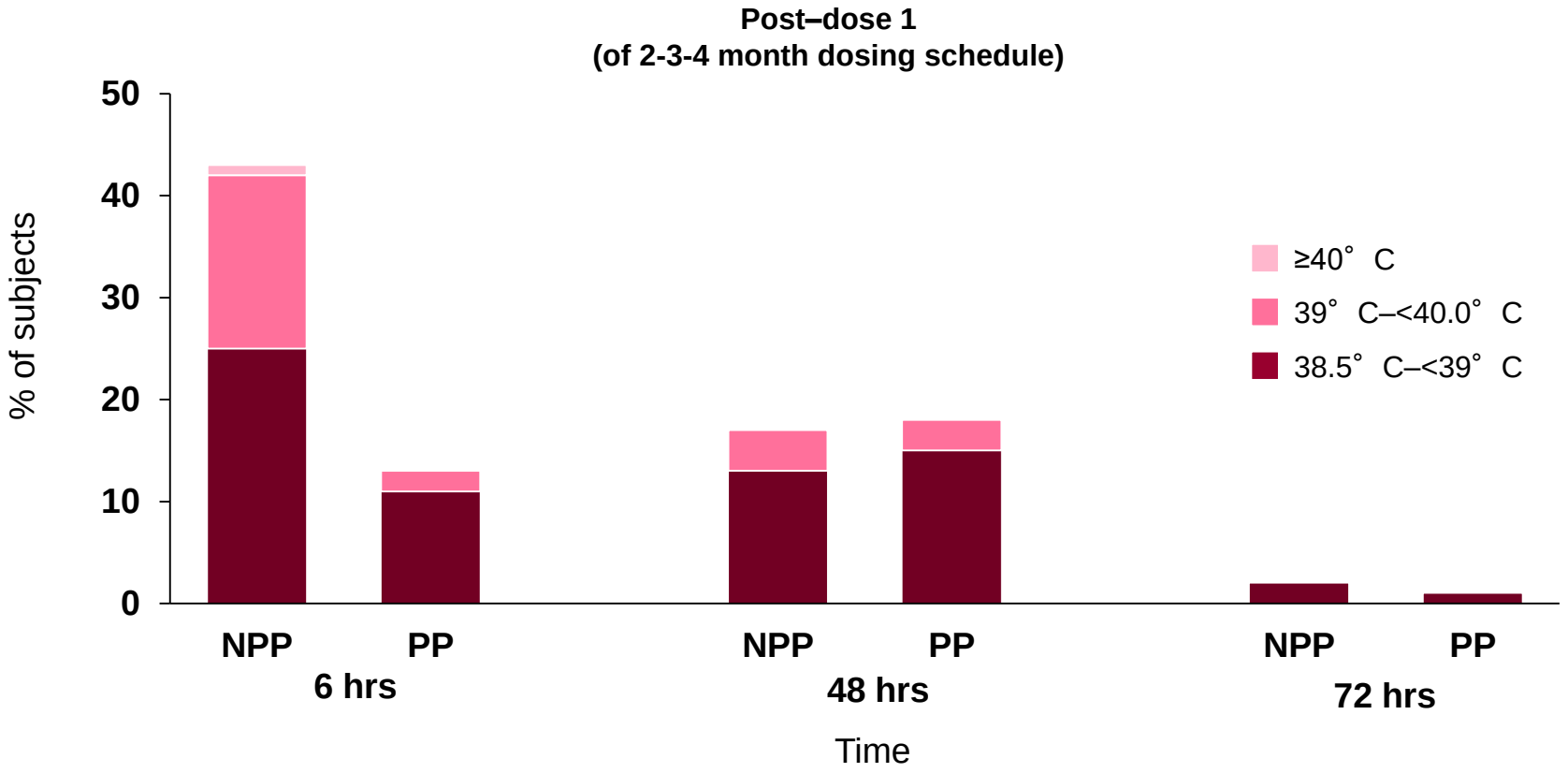
Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials

Roman Prymula, Claire-Anne Siegrist, Roman Chlibek, Helena Zemlickova, Marie Vackova, Jan Smetana, Patricia Lommel, Eva Kaliskova, Dorota Borys, Lode Schuerman

In 2010, JCVI recommended that paracetamol should not be routinely offered to infants to prevent fever because it may interfere with vaccine responses

Prophylactic Paracetamol at the Time of and Closely After Vaccination Reduced Fever

When BEXSERO® is given concomitantly with routine infant vaccines

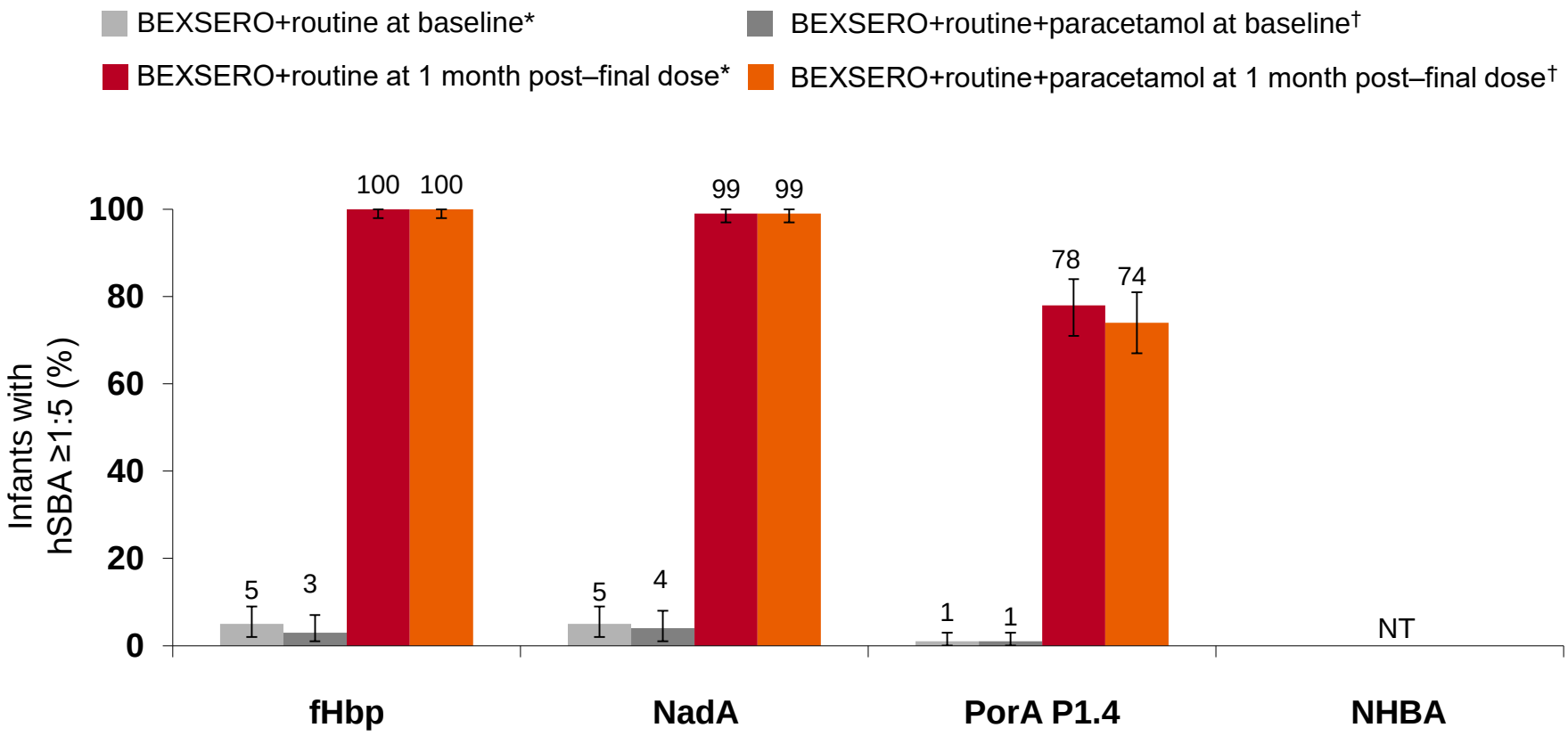


NPP: no prophylactic paracetamol (N=182); PP: with prophylactic paracetamol (N=178-179).
Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

1. Prymula R, et al. Presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID); June 7-10, 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.; January 14, 2013.

Prophylactic Paracetamol at the Time of and Closely After Vaccination Did Not Impact Immunogenicity of BEXSERO®

BEXSERO given concomitantly with routine infant vaccines
2-3-4 month schedule



*N=165–171; †N=160–169.
Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.
NT=not tested.

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.; January 14, 2013.

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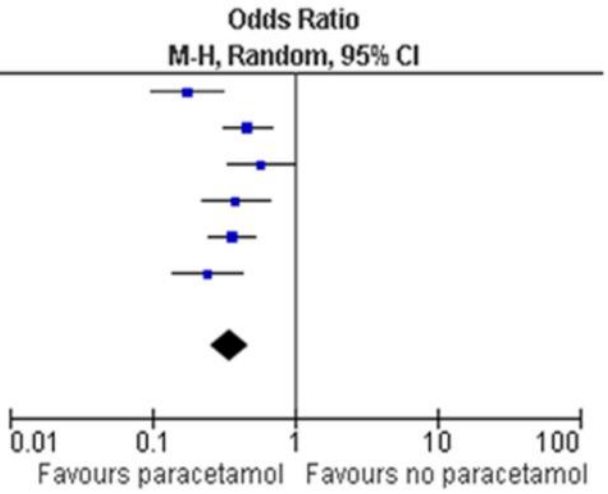
Systematic review in 2014

The effect of prophylactic antipyretic administration on adverse reactions and antibody response in children

Study or Subgroup	Paracetamol Events	Total	No paracetamol Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Hayat 2011	23	118	68	118	14.4%	0.18 [0.10, 0.32]
Ipp 1987	62	233	94	216	19.8%	0.47 [0.32, 0.70]
Jackson 2011	25	176	39	176	15.2%	0.58 [0.33, 1.01]
Lewis 1988	35	115	57	107	15.3%	0.38 [0.22, 0.66]
Prymula 2009	94	226	154	233	20.4%	0.37 [0.25, 0.53]
Rose 2013	43	100	95	126	14.9%	0.25 [0.14, 0.43]
Total (95% CI)		**968**		**976**	**100.0%**	**0.35 [0.26, 0.48]**
Total events	282		507			

Heterogeneity: Tau² = 0.09; Chi² = 12.01, df = 5 (P = 0.03); I² = 58%

Test for overall effect: Z = 6.54 (P < 0.00001)



Also reduction in

- Pain, swelling and redness at injection site
- Irritability, drowsiness, persistent crying and loss of appetite
- Although reduction in antibody was observed, size of reduction was considered unlikely to result in clinically significant reduction in protection

Das RR et al PLoS ONE 9(9): e106629. doi:10.1371/journal.pone.0106629

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Timing of paracetamol doses with other infant vaccines

	PCV13 + Infanrix Hexa + Paracetamol Twice Daily	PCV13 + Infanrix Hexa + Ibuprofen Twice Daily	PCV13 + Infanrix Hexa + Paracetamol Thrice Daily	PCV13 + Infanrix Hexa + Ibuprofen Thrice Daily	PCV13 + Infanrix Hexa
Number of Participants	149	157	147	155	187
Percentage of Participants Reporting Fever Within 4 Days:					
Fever ≥38 - ≤39 °C	32.9	45.2	18.4	34.2	41.7
Fever >39, ≤40 °C	1.4	1.4	0.7	0.7	1.2
Fever >40 °C	0.0	0.0	0.0	0.0	0.0

Clinical Trials .gov: Study Assessing the Effect of Medications to Prevent Fever on Prevenar 13®
https://www.clinicaltrials.gov/ct2/show/NCT01392378?term=vaccine+paracetamol+ibuprofen&rank=2

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Summary of evidence on paracetamol

- Fever is common after Bexsero® and fever rates are additive to those normally seen after infant vaccines
  - Concern about high rate of medical attendance
  - Fever peaks at six hours after vaccine, uncommon after 48 hours
- Rates and intensity of fever reduced by prophylactic paracetamol
  - Immunogenicity of concomitant infant vaccines not reduced when given with paracetamol and Bexsero®
- Studies with other infant vaccines show
  - Paracetamol also reduces other systemic and local reactions
  - three doses of paracetamol starting immediately is better than two doses starting at 6 hours (suggests first dose is the most important)
  - Paracetamol superior to ibuprofen in preventing fever and symptoms

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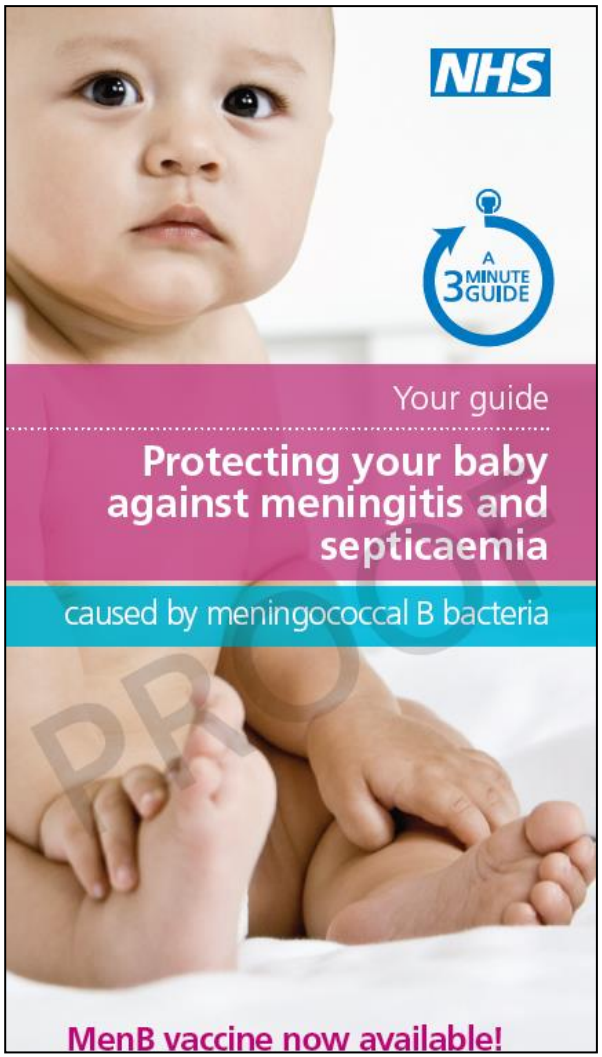

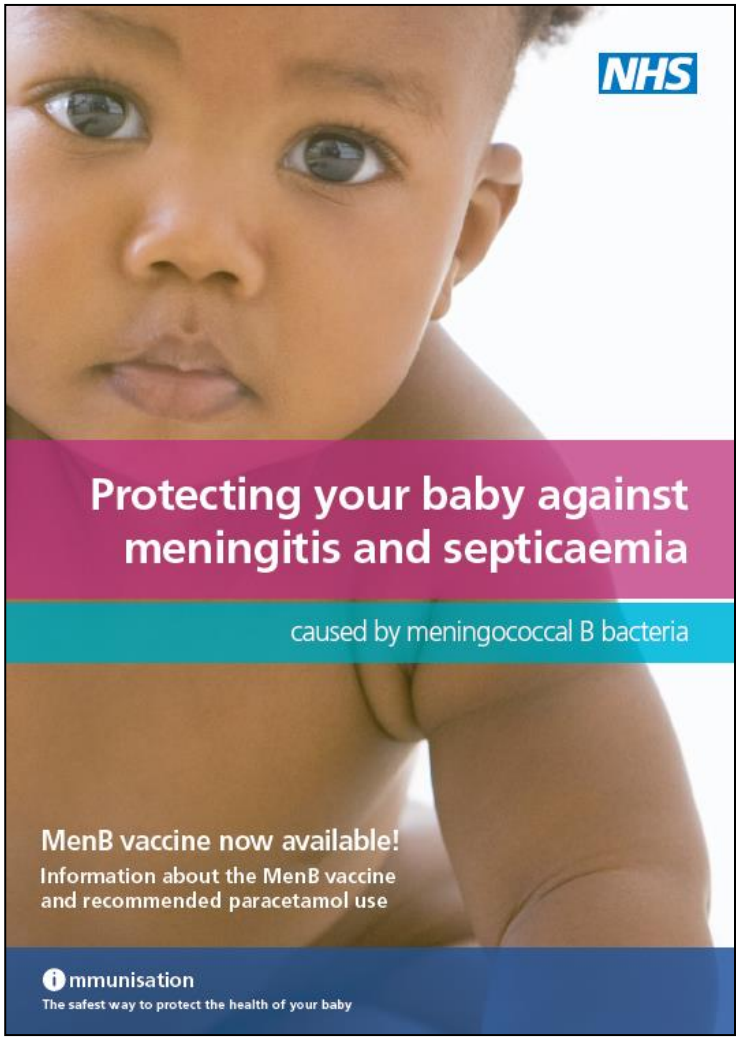

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Bexsero Vaccine Effectiveness

1. Too Early To Tell
2. Vaccine offered for only 8 months so far
3. Infants in the first 2 months of life (0-2 months) will not be protected
4. Only 70 cases in vaccine eligible infants in 2014/15 (pre-vaccine)
5. MenB cases falling naturally for past 15 years
6. Half the cases (50%) diagnosed by PCR only – limited strain info.
7. Culture-confirmed cases need MATS testing in reference laboratory – takes several weeks
8. So far, 400,000 babies immunised, 8 cases after 1 dose, 1 case after 2 doses

➔ *We are already seeing a greater-than-predicted reduction in MenB cases in the vaccine eligible infants and not in the other age groups*

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How has it gone?
Vaccine eligibility

- Children getting MenB “booster” at 12 months of age in absence of primary course
- Children born after 1st May who had already completed their primary course
  - Eligible under contract but not being actively called
- Confusion between catch-up cohorts and those in eligible cohort who present late (e.g. movements from abroad)
- Requests for children who had started private vaccinations
- Very few calls after first few weeks

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How has it gone?
Use of paracetamol

- Nurses wanting to administer during vaccination clinic
- Parents taking before come in to see the nurse
- How long to wait (could they wait to get cheaper product in local supermarket)
- Pharmacists refusing to sell because outside product license
- Premature and small for dates babies
  - Need individual prescription
  - Neonatal units refusing to give paracetamol
- Very few calls after first few weeks

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Conclusions

1. The UK is the first country to introduce routine MenB vaccine
2. Post marketing surveillance will be essential to provide international experience for other to build on
3. MenB implementation in the UK is built on successful infant programme in general practice
4. The vaccine should protect against 73-88% of MenB cases in vaccinated infants and toddlers
5. Recommending paracetamol prophylaxis has been challenging but, so far, successful
6. The programme is supported by range of communication materials
7. No significant concerns in the first 6 months of the programme

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PHE Website

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Resources for health professionals and patients

- PHE MenB Health Care Worker Q+A
- PHE MenB vaccine leaflet (long version)
- PHE MenB vaccine leaflet: 3 minute guide
- PHE MenACWY vaccination programme patient information leaflet and posters
- PHE MenACWY Health Care Worker Q+A
- PHE Paracetamol Patient Information Leaflet
- Training the trainer slide sets and animated voice over
- OVG video on parent consultation

- Meningitis Research Foundation: http://www.meningitis.org/
- Meningitis Now. https://www.meningitisnow.org/
- NHS Choices. http://www.nhs.uk/conditions/Meningitis/Pages/Introduction.aspx

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Acknowledgements

- Mary Ramsay
- MenB/ACWY Project Board
- Matthew Olley, Vanessa Saliba, Helen Campbell, Ray Borrow, at PHE
- Jim Wassil, Novartis Vaccines
- Phil Bryan MHRA
- Hannah Christensen, University of Bristol

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Controlling the increase in Meningococcal group W disease

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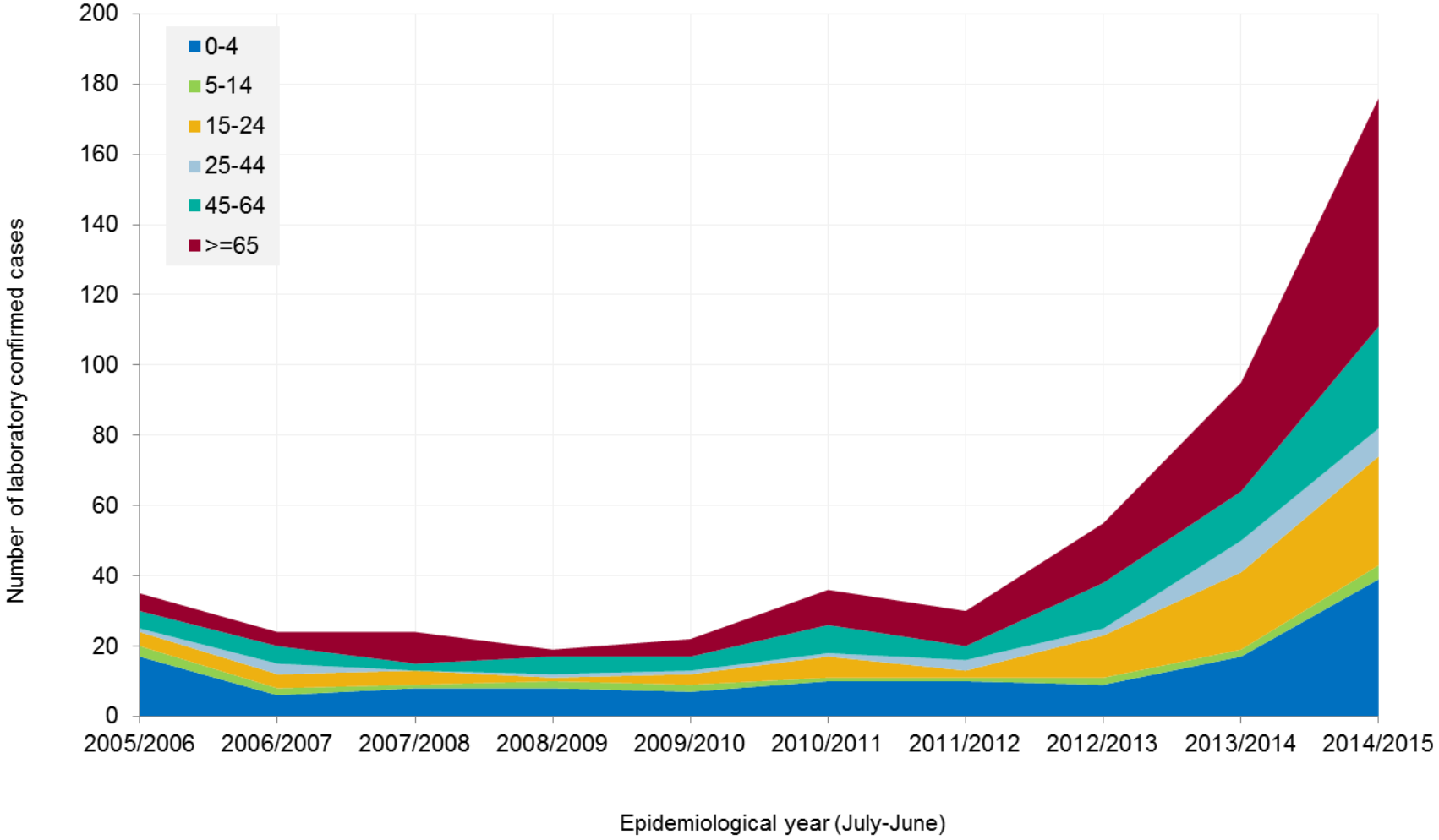
Laboratory confirmed cases of meningococcal group W (MenW) disease in England, 2005/06-2014/15



Date source: PHE Meningococcal Reference Unit. Surveillance by PHE Immunisation Department – Last Update August 2015
Please see link for more information and data https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis

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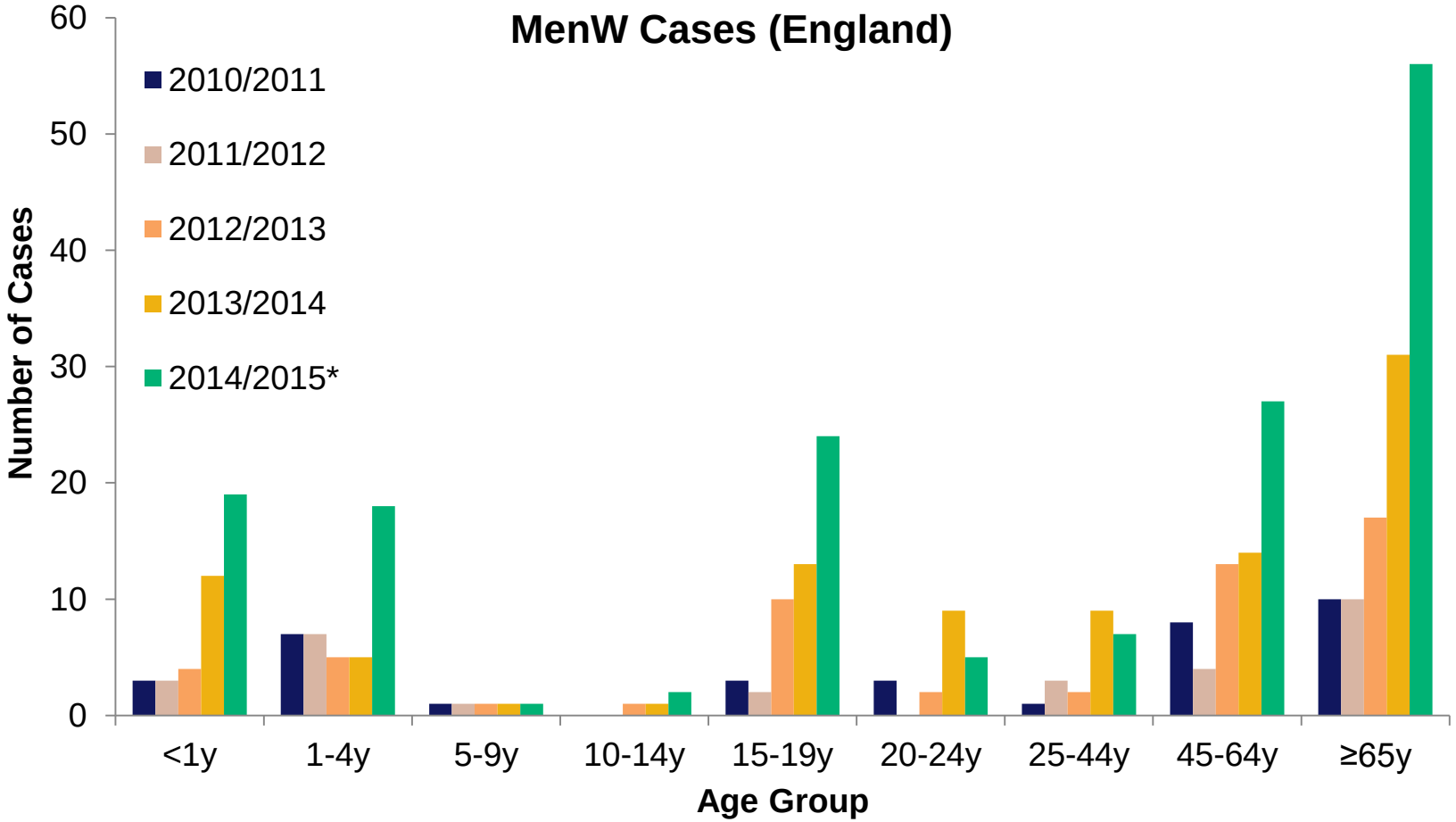
MenW cases by age group

England, 2010/11-2014/15*



** data available until end May 2015*

	Age group (years)					
	<5 n=32	5-19 n=21	20-44 n=12	45-64 n=26	≥65 n=38	All cases n=129
Recent Travel		1		1		2*
Risk						
Risk Factors	1 (3%)	-	2 (17%)	2 (8%)	7 (18%)	12 (9%)
Malignancy	1 (3%)	-	-	-	6 (16%)	7 (5%)
HIV-positive	-	-	1 (8%)	2 (8%)	-	3 (2%)
Immunosuppressive drug	-	-	1 (8%)	-	1 (2%)	2 (2%)
Comorbidities						
Other comorbidity	1 (3%)	2 (10%)	-	2 (8%)	7 (18%)	12 (9%)
Clinical Presentation						
Septicaemia	17 (53%)	9 (43%)	6 (50%)	12 (46%)	19 (50%)	63 (49%)
Septicaemia & Meningitis	6 (19%)	5 (24%)	3 (25%)	2 (8%)	5 (13%)	21 (16%)
Meningitis	4 (13%)	4 (19%)	2 (17%)	4 (15%)	2 (5%)	16 (12%)
Pneumonia	-	2 (10%)	-	6 (23%)	7 (18%)	15 (12%)
Septic arthritis	4 (13%)	1 (5%)	-	1 (4%)	3 (8%)	9 (7%)
Epiglottitis/supraglottitis	1 (3%)	-	1 (8%)	1 (4%)	2 (5%)	5 (4%)
ICU admission	11 (34%)	10 (48%)	6 (50%)	10 (38%)	11 (29%)	48 (37%)
Deaths						
All deaths	0	2	2	5	10	19 (15%)

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Presentation with gastrointestinal symptoms and high case fatality associated with MenW in teenagers

Sex	History and clinical features	Initial Assessment	IMD suspected	ITU	Outcome	Confirmation	Final Diagnosis
F	2 days D&V, stomach cramps lethargy, no rash	Saw GP on Day 1, Sudden deterioration Day 2, rapid progression in A&E: "? abdominal sepsis"				Blood culture	Septicaemia
M						PC	
F						PC	
F						Bloc	
F						PC	
F	1 day D&V, fever, headache	culture and CSF meningococcal PCR negative; b PCR sent later and was positive (12 days after on				PCR blood	Septicaemia
F							
M	Gen						
M	1 day						
F	2 h						
F	Fever						
F	3 days						
M	Fe						
M							
M	lethargy, lymphadenopathy; no fever, no rash	antibiotics					

7/15 cases (*6 females*) presented with D&V symptoms

4/7 cases seen by GP or A&E on the day of illness

IMD suspected in only 2/7 cases

5/7 died:
- 3 in A&E
- 2 in ITU (<24 hrs)

MenW isolated from blood (2 culture / 5 PCR) in all cases

Remaining 8/15 cases:
- 2 septicaemia, 1 died in A&E (MenW from 2 blood culture)
- 1 meningitis & septicaemia (MenW from CSF PCR)
- 2 septic arthritis (MenW from 2 blood culture, 1 PCR joint fluid)
- 2 pneumonia (MenW from 2 blood culture)
- 1 atypical presentation (No fever, Men W from blood culture)

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Strategy to control MenW

Wide age range affected

- Incidence highest in infants and adolescents
- Still high number of cases in older adults

Strategy in Chile of vaccinating children, only impacted on vaccinated age group

- Failed to control overall disease rates

Only feasible strategy is to target carriers with conjugate ACWY vaccine

- Plan to immunise adolescents
- vaccinating older cohorts in catch up will accelerate control

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JCVI recommendations: February 2015

- Even though the number of cases is low, JCVI considered this situation a public health emergency
  - rapid increase in virulent MenW
  - international experience (e.g. South America)

- The MenACWY programme will have direct impact on vaccinated teenage cohorts (second highest incidence group)
  - Excellent protection expected after a single dose

- Importance of completing catch-up quickly: to generate herd protection across the age range and slow the rate of increase

Public Health England

Serum bactericidal antibody killing of UK W cc11 strains by serum from infants immunised with Bexsero®

Lab number	Site	Type	Pre-	Pool1	Pool2	Pool3	Pool4 Post 4th
							>128
							64
							>64
							128
M11-240798	Blood	W:NT:P1.5,2 cc11	<2	>64	>64	>64	>64
M12-240754	Blood	W:NTP1.5,2 cc11	<2	64	64	>64	>64

This work suggests that children immunised with Bexsero may have some protection against the emerging strain of MenW

Public Health England

Recommended vaccines

- Menveo® is supplied in 5 dose pack (powder in a vial and solution in a vial = 10 vials per pack), no needles.

- Nimenrix® is supplied in single pack as a powder in a vial (MenACWY) and 0.5ml solvent in a pre-filled syringe. Two needles are included.

Public Health England

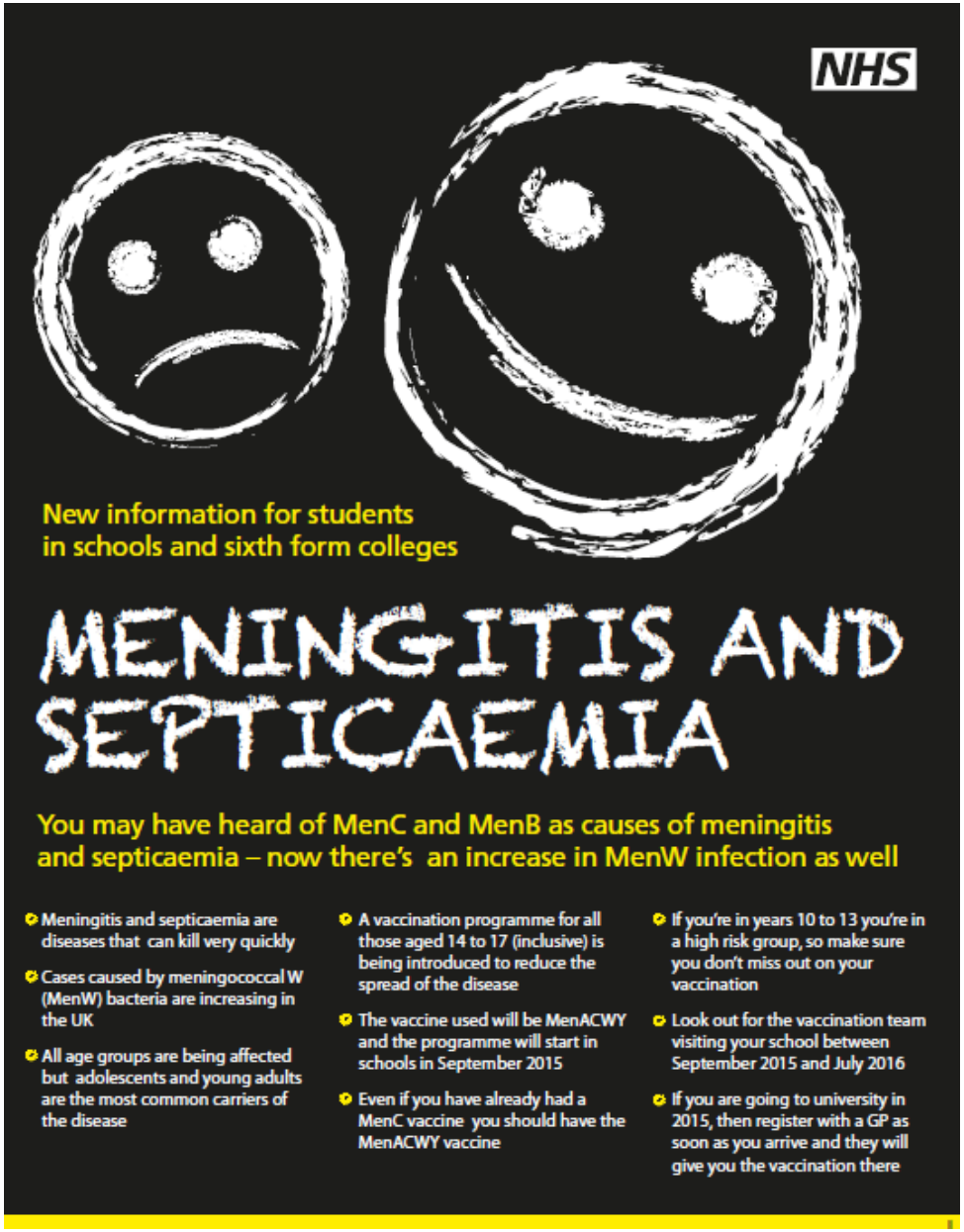
ACWY programme – planned roll-out

Birth cohort	2014/15 year - age	Academic year				
		2014/15	2015/16	2016/17	2017/18	2018/19
01/09/2003-31/08/2004	Y6 – 10/11				Y9 ACWY	
01/09/2002-31/08/2003	Y7 - 11/12			Y9 ACWY		
01/09/2001-31/08/2002	Y8 - 12/13		Y9 ACWY			
01/09/2000-31/08/2001	Y9 - 13/14		Y10 ACWY			
01/09/1999-31/08/2000	Y10 - 14/15	Y10 MenC		Y12 ACWY		
01/09/1998-31/08/1999	Y11 - 15/16			Y13 ACWY		
01/09/1997-31/08/1998	Y12 - 16/17		Y13 ACWY			
01/09/1996-31/08/1997	Y13 – 17/18	Y13 ACWY				

Key

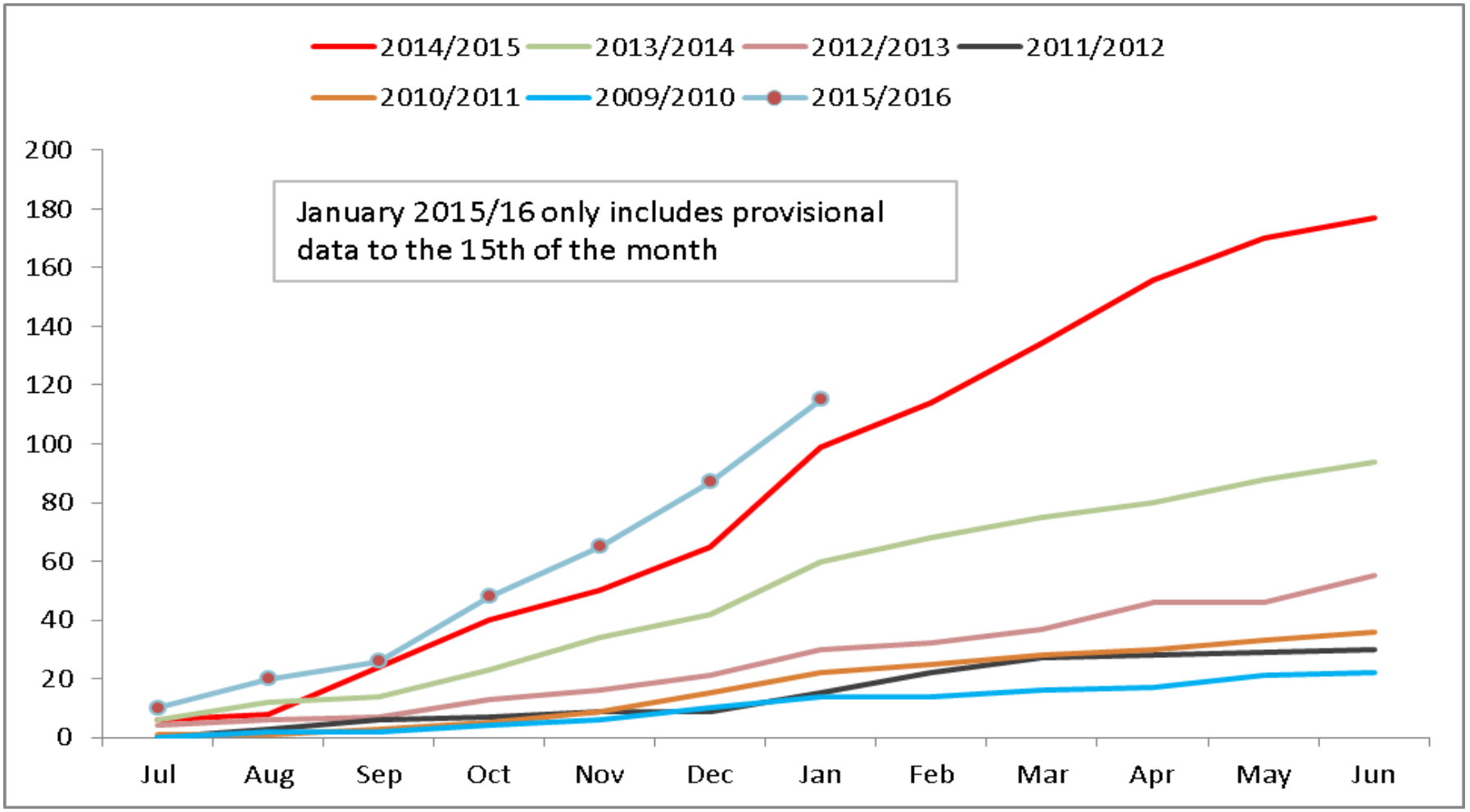
- Routine schedule MenC
- Routine schedule ACWY
- School based catch-up ACWY
- Primary care catch-up cohorts
- Delivery mechanism to be decided
- Completed

Public Health England



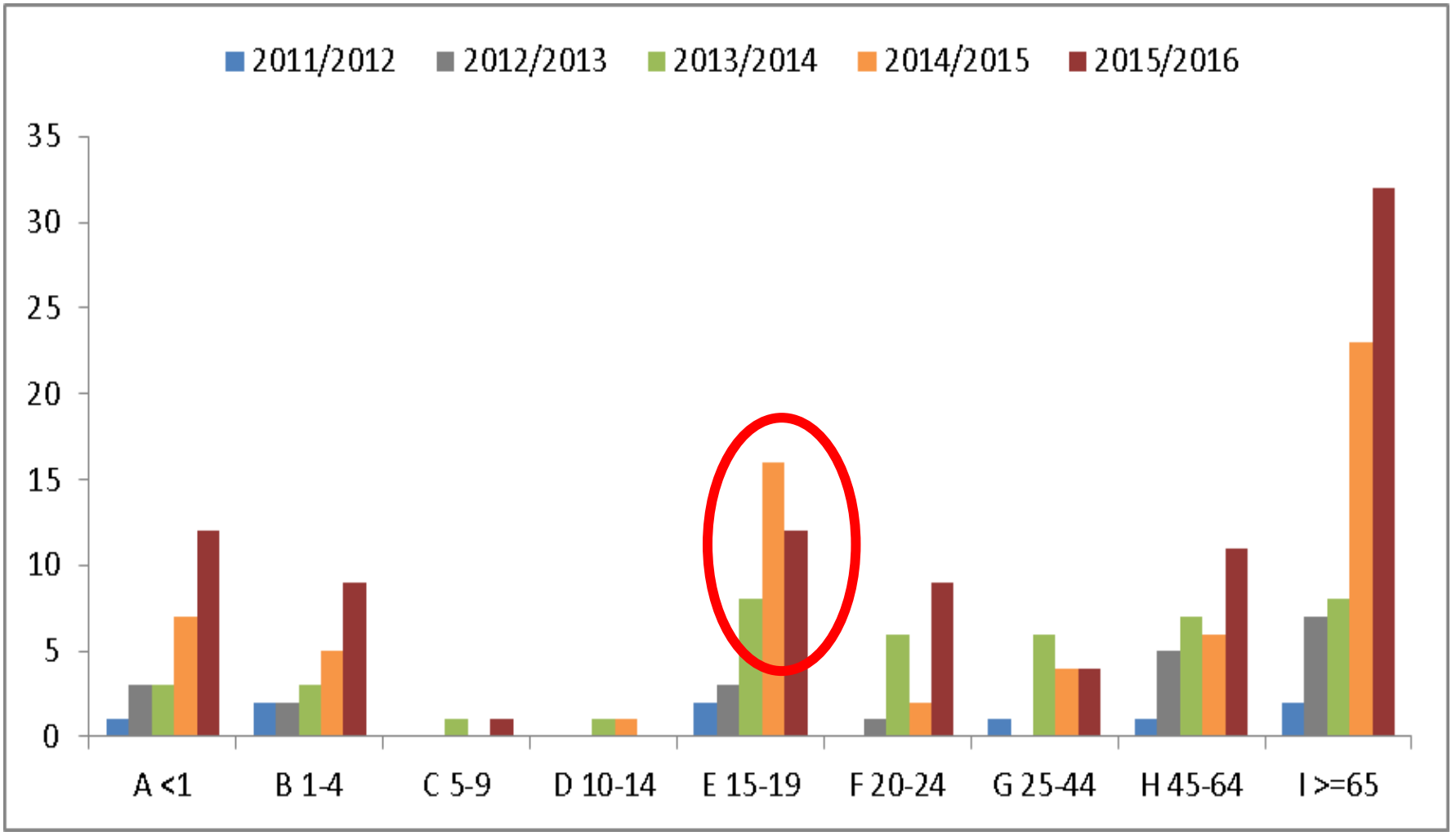
Public Health England

Cumulative MenW cases by epidemiological year (July to June) in England



Public Health England

Confirmed MenW cases to 31 December, last 5 epi years by age group, England



Public Health England

Summary

Two major programmes to vaccinate the UK population against meningococcal disease were launched in 2015

The UK will be the first country to introduce routine MenB vaccine

Post marketing surveillance will be essential to provide international experience for other to build on

Vaccines are expected to be largely acceptable to parents and health care staff

MenB implementation will build on successful infant programme in general practice

ACWY programme is likely to less successful in older age groups, due to low awareness and concern

Programmes are supported by range of communication materials

Public Health England

Resources for health professionals and patients

- PHE MenB Health Care Worker Q+A
- PHE MenB vaccine leaflet (long version)
- PHE MenB vaccine leaflet: 3 minute guide
- PHE MenACWY vaccination programme patient information leaflet and posters
- PHE MenACWY Health Care Worker Q+A
- PHE Paracetamol Patient Information Leaflet
- Training the trainer slide sets and animated voice over
- OVG video on parent consultation

- Meningitis Research Foundation: http://www.meningitis.org/
- Meningitis Now. https://www.meningitisnow.org/
- NHS Choices. http://www.nhs.uk/conditions/Meningitis/Pages/Introduction.aspx

Public Health England

PHE Website

Public Health England

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