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Meningococcal Protein Vaccines
- where next?

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“a pain you cannot describe”

RESEARCH ARTICLE

Short-term changes in the health state of children with group B meningococcal disease: A prospective, national cohort study

Iain T. R. Kennedy[1], Albert J. van Hoek[1,2], Sonia Ribeiro[1], Hannah Christensen[3], W. John Edmunds[4], Mary E. Ramsay[1], Shamez N. Ladhani[1,5]*

Conclusions: The magnitude of Quality of Life loss is staggering, with the reported health state being at, or close to, the worst possible outcome imaginable.

… a state worse than death ....

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PLOS ONE | https://doi.org/10.1371/journal.pone.0177082 May 18, 2017

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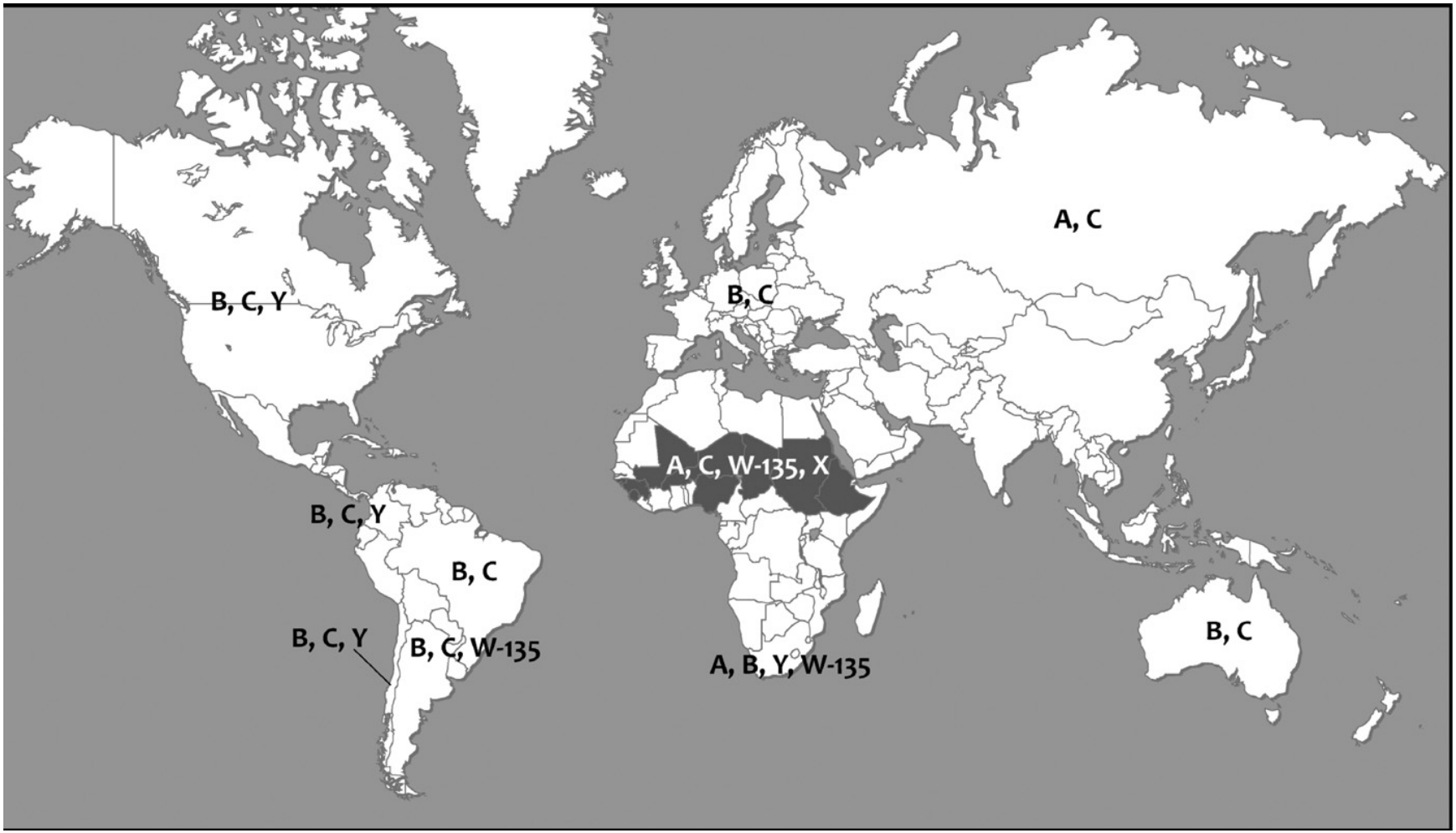
Worldwide distribution of major meningococcal serogroups



Harrison LH et al. Vaccine 2009;27S:B51–B63.

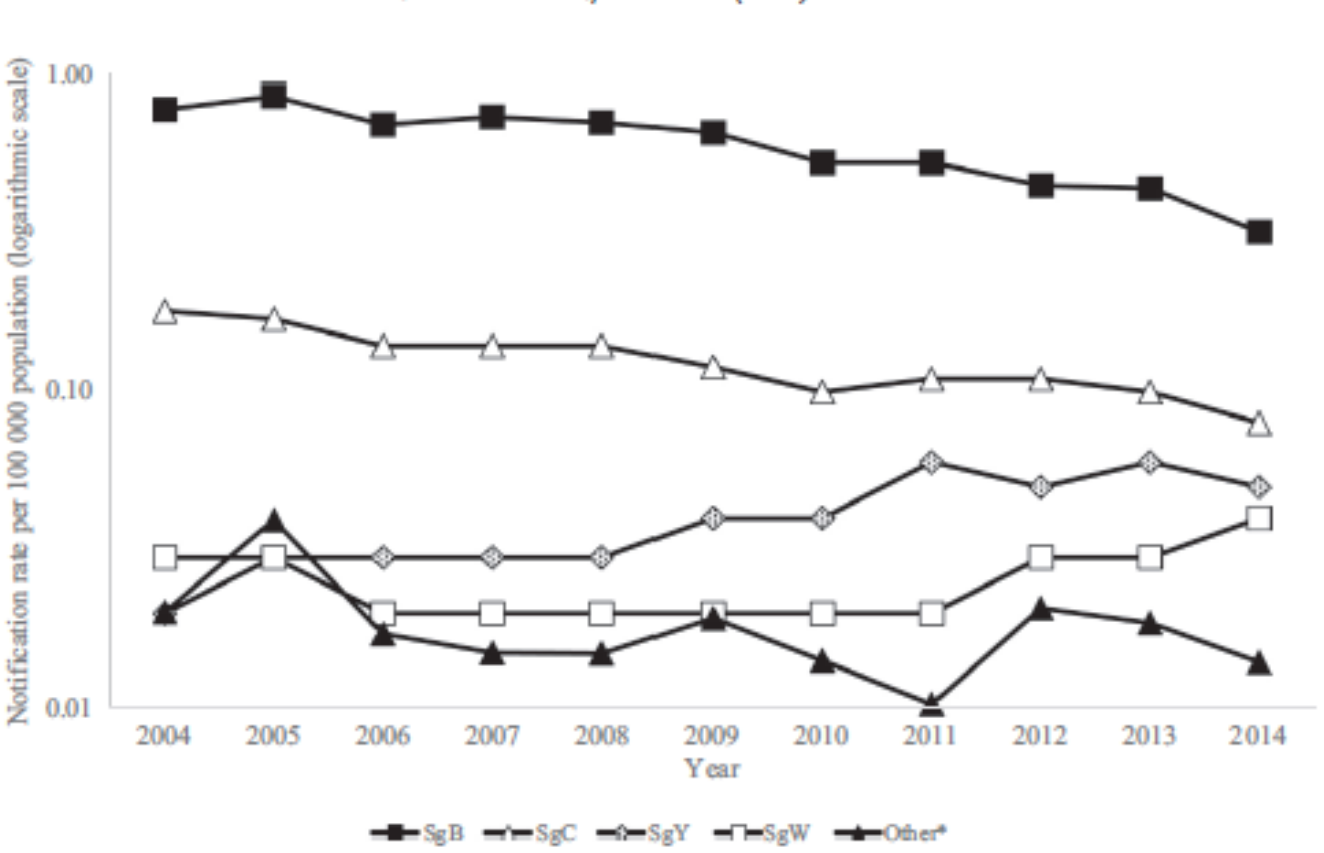
the ECDC network members for invasive meningococcal disease [1,2]

The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004–2014

Robert Whittaker [a,*], Joana Gomes Dias [a], Miriam Ramliden [a,b], Csaba Ködmön [a], Assimoula Economopoulou [a,c], Netta Beer [a], Lucia Pastore Celentano [a], the ECDC network members for invasive meningococcal disease [1,2]

The e EU/EEA count

Robert dmön [a],



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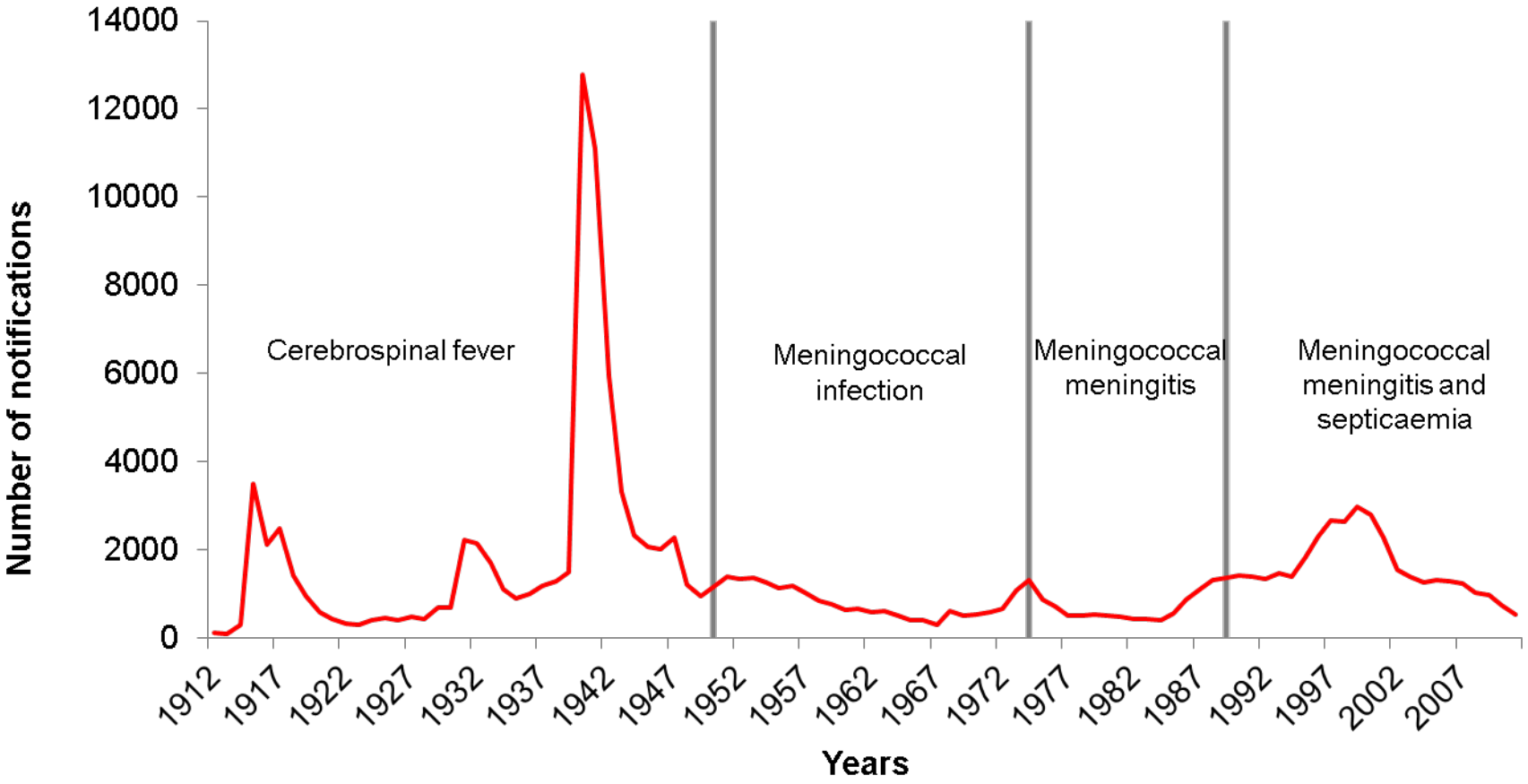
Long term trends in notified meningococcal disease, England and Wales



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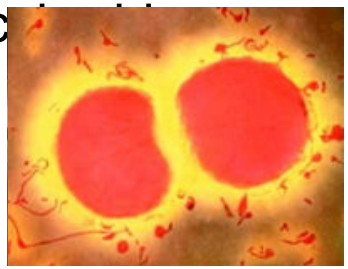
Vaccines against MenB

- MenC and MenACWY conjugate vaccines target the polysac[illegible] capsules – no cross-protection



- MenB polysaccharide is a polysialic acid - identical to found on surface of human foetal neuronal cells.
- Consequently;

  (i) Poorly immunogenic.

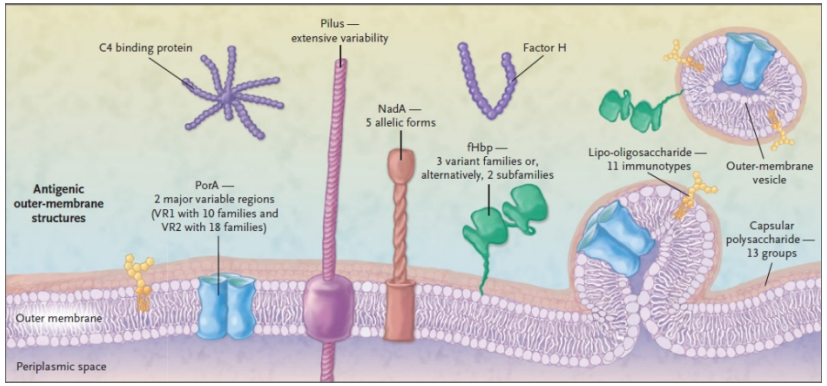
  (ii) Potential to induce an autoimmune response

- Use subcapsular antigens, which:

  (i) are Surface-exposed

  (ii) are Conserved

  (iii) induce Bactericidal activity



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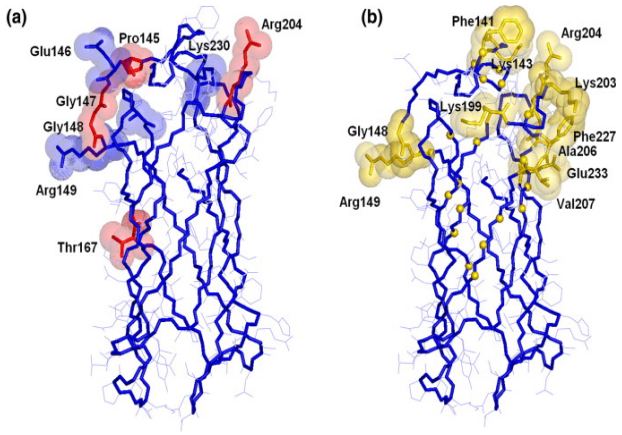
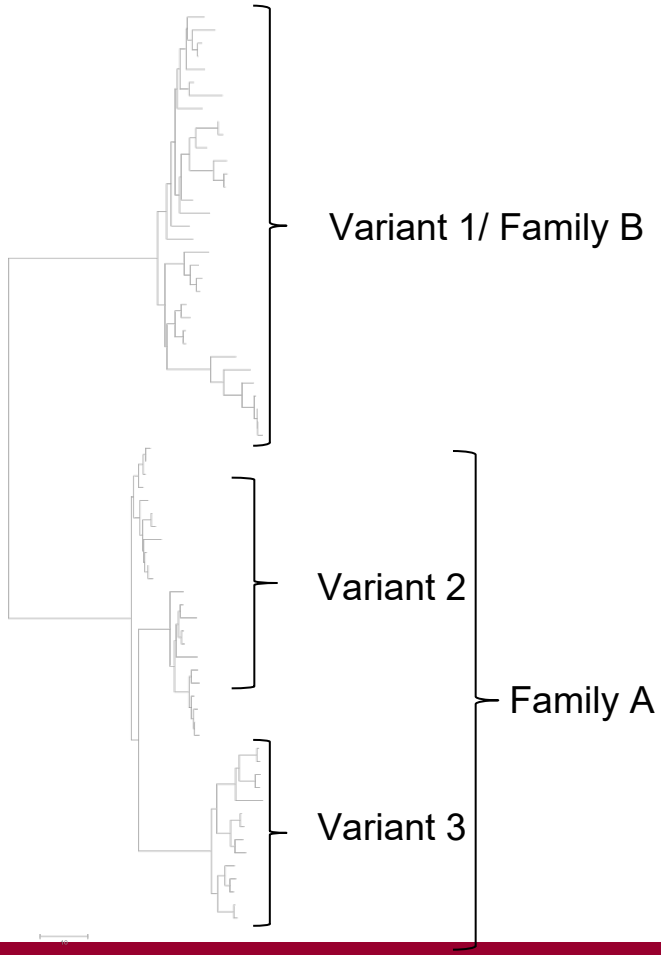
Bivalent rLP2086 Men-fHbp Vaccine





***Variant or family groups*:**

Novartis	**Pfizer**
Variant 1	Family B
Variants 2 & 3	Family A

Intra-family cross-reactivity good.

Inter-family cross reactivity poor.

*

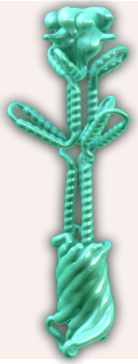
BEXSERO® Consists of 4 Antigenic Components Chosen to Achieve Broad Protection

fHbp: factor H binding protein

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

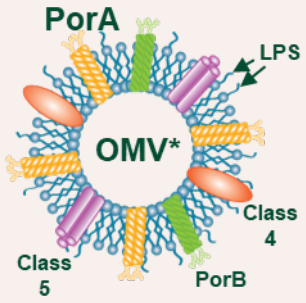
NHBA: neisseria heparin-binding antigen

- 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]

Combining antigens that target different steps of meningococcal pathogenesis is likely to help optimize MenB vaccine effectiveness

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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Predicted meningococcal strain coverage in Europe

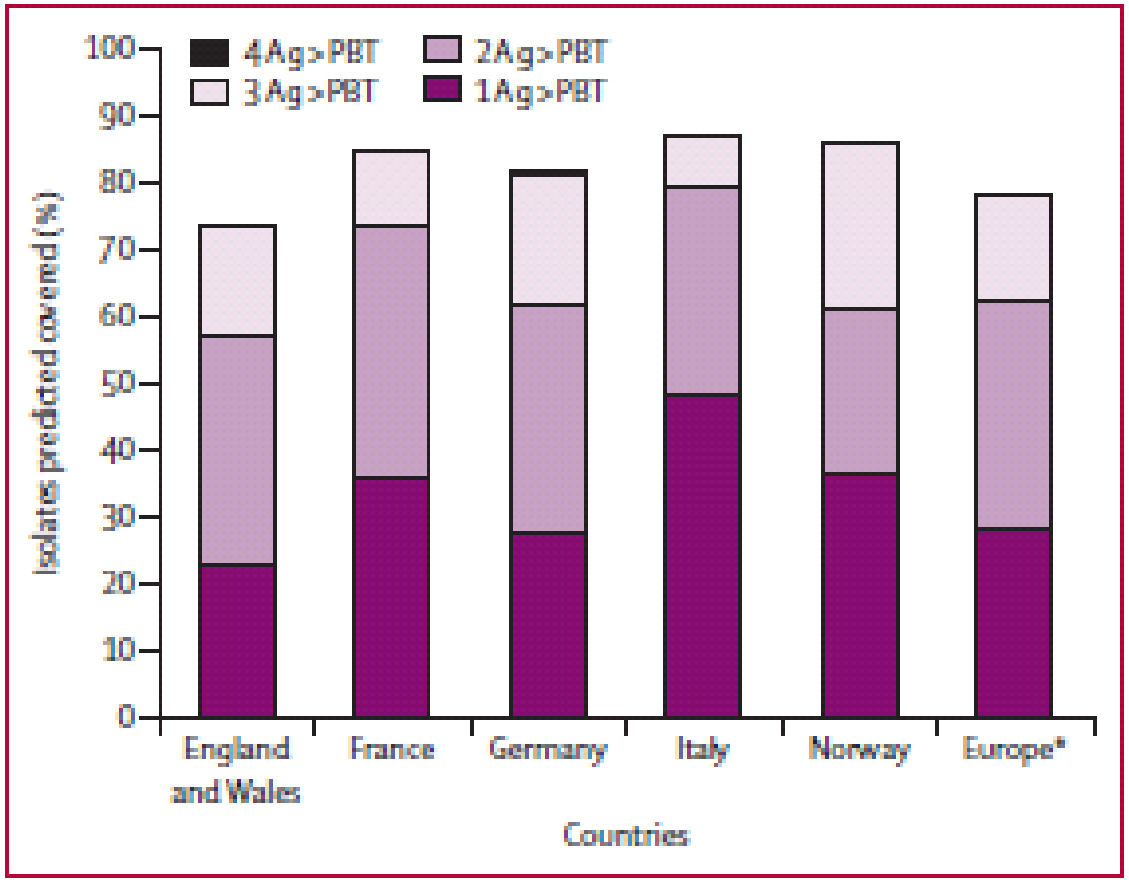

Figure 1: Percentages of isolates predicted by the meningococcal antigen typing system to be covered, and number of antigens, overall and by country

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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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4CMenB Impact

(3 Years)

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Cases: summary

- 01 September 2015 – 31 August 2018 (3 years)
- 361 lab-confirmed IMD cases in <2 year-olds
- Capsular Group Distribution
  - MenB: 246 cases (68%)
  - MenC: 22 cases (6%)
  - MenW: 73 cases ((20%)
  - MenY: 13 cases (4%)
  - Other: 7 cases (2%)
- MenB cases: 140 culture-confirmed (57%)

*

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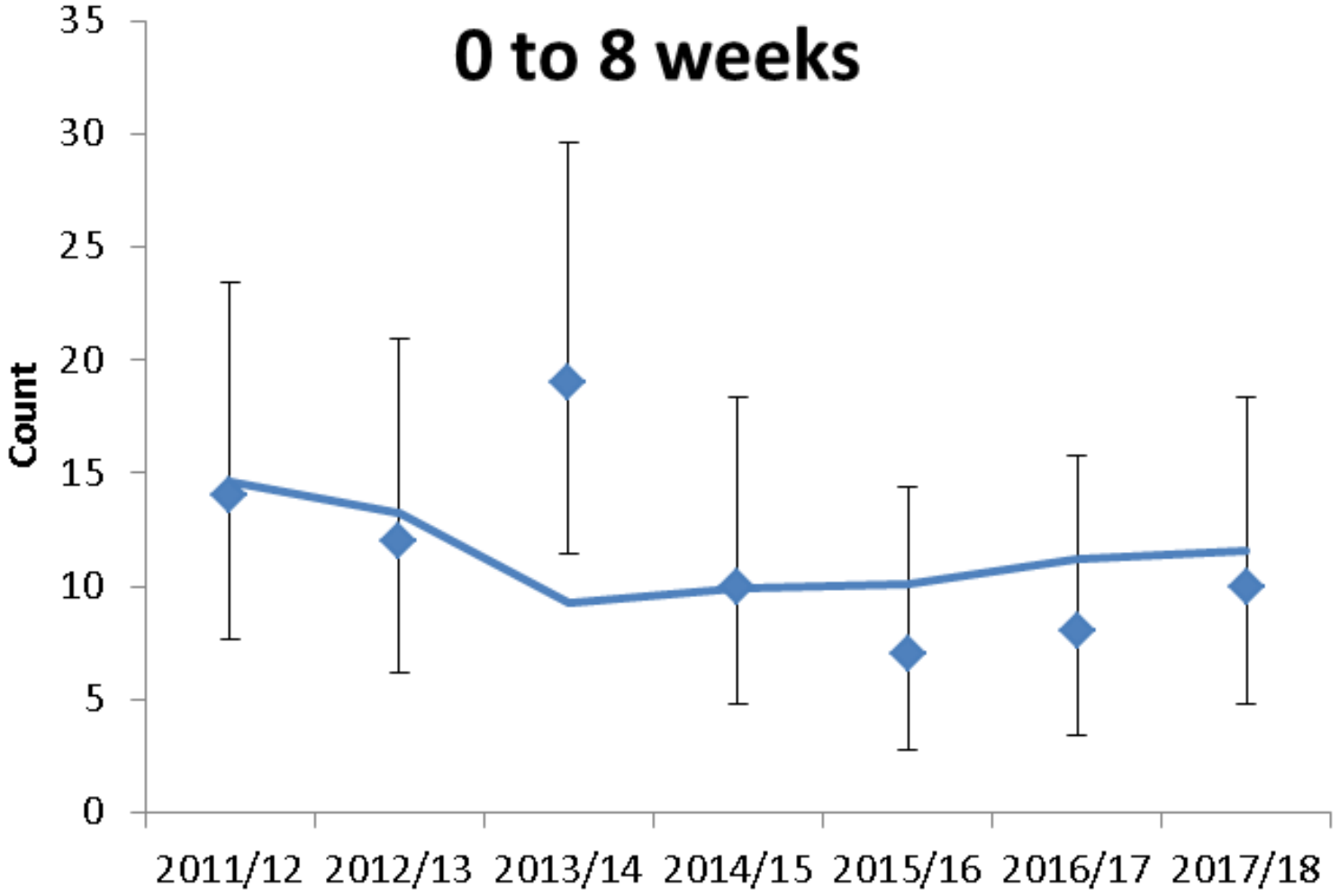

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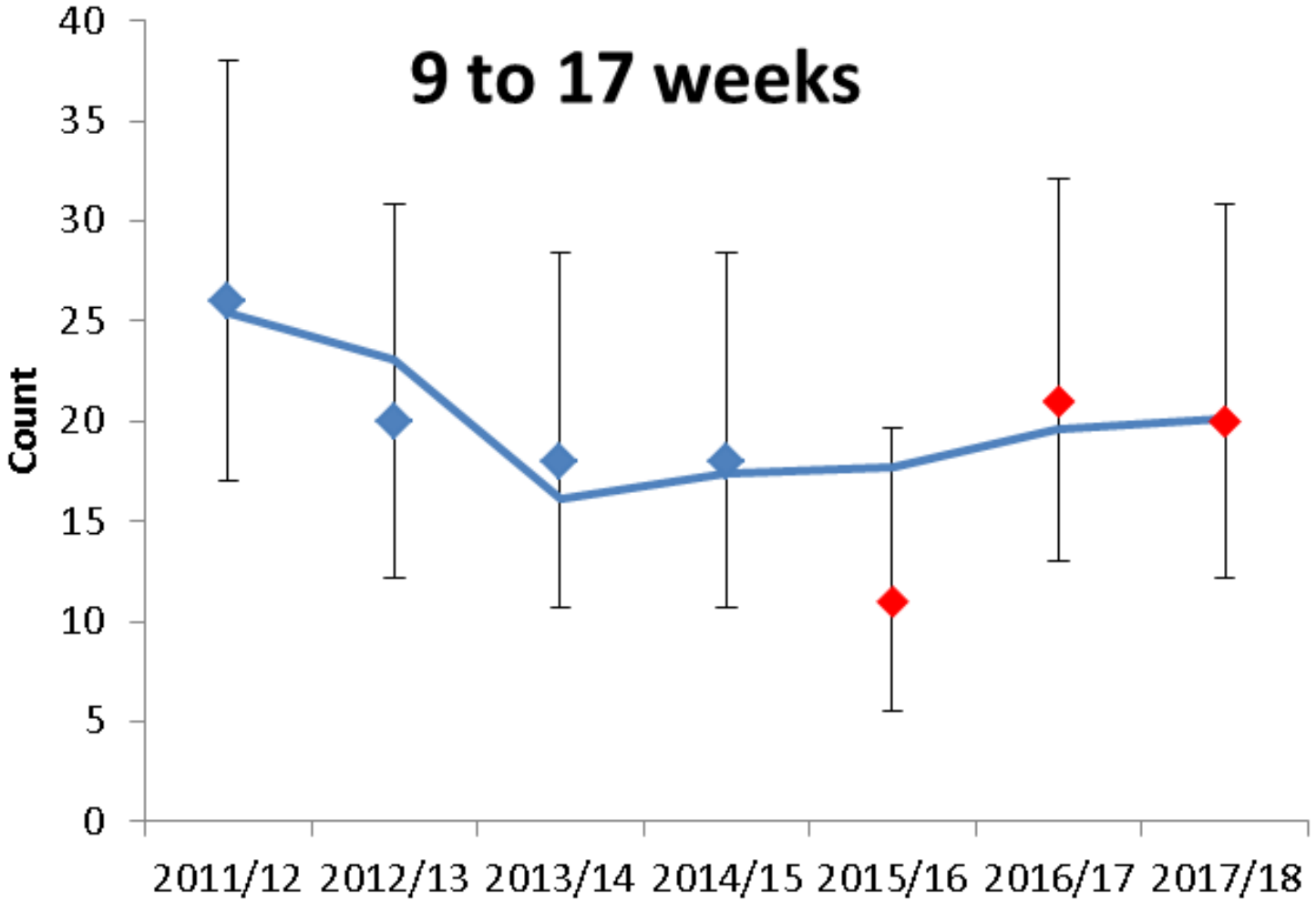

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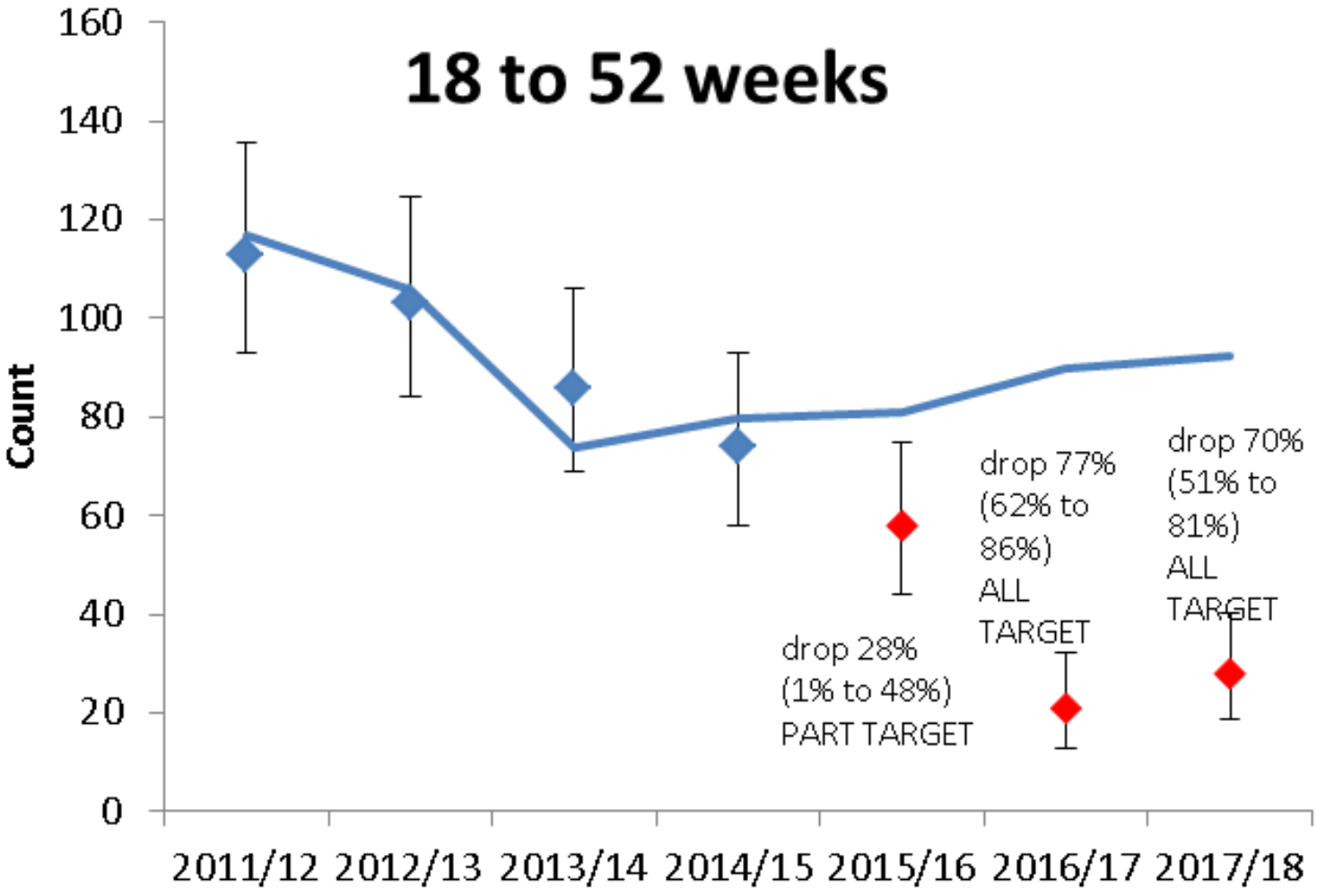

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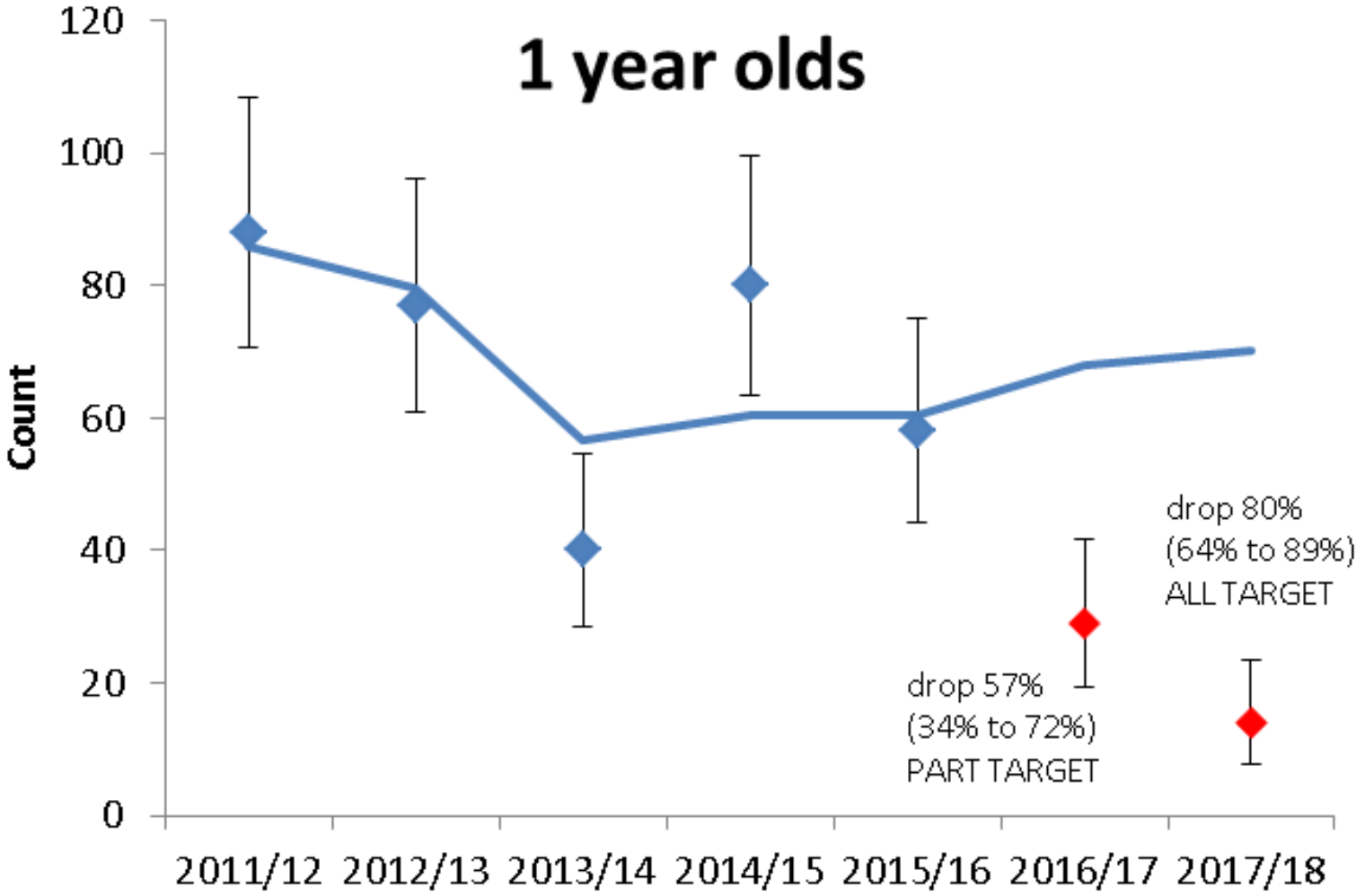

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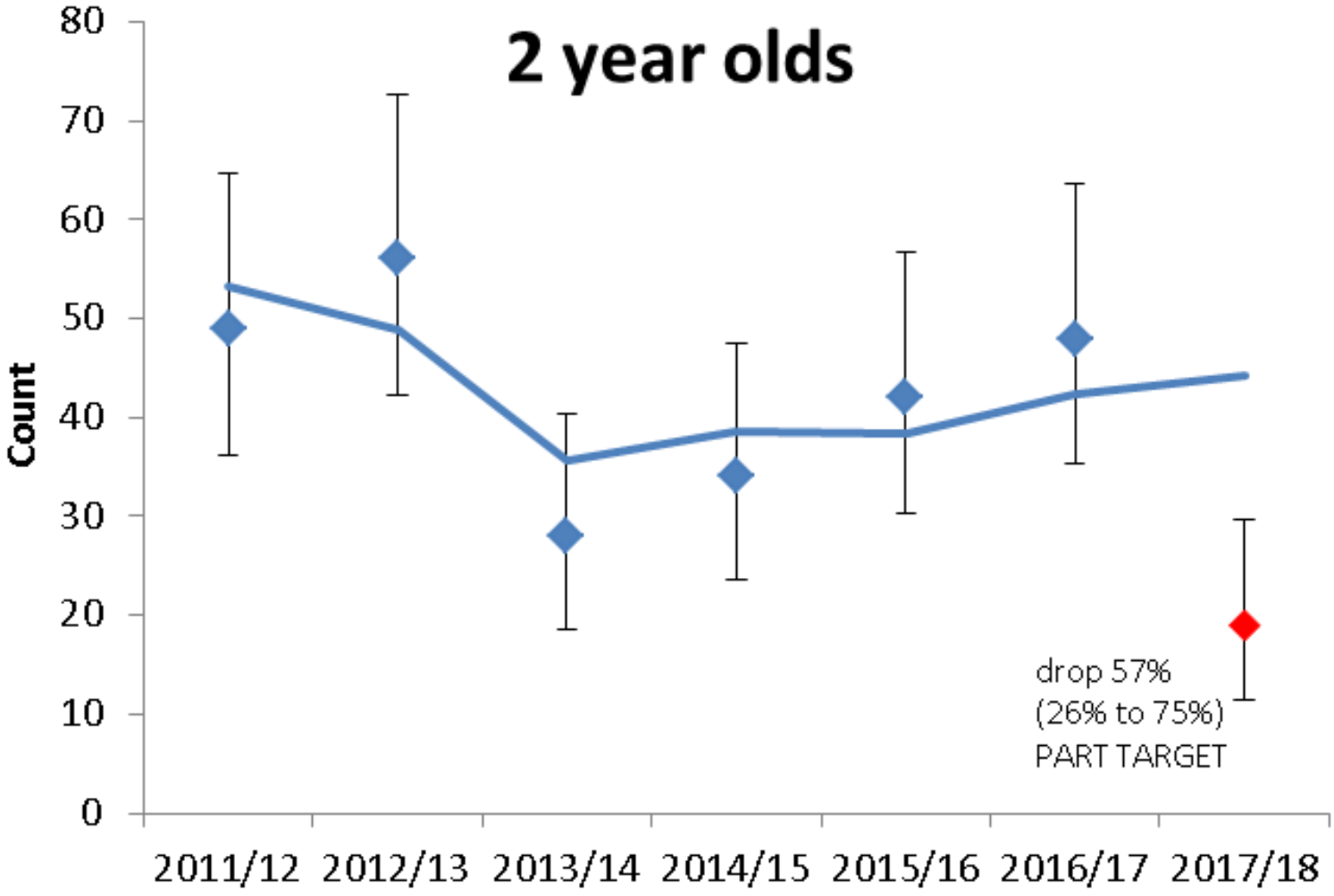

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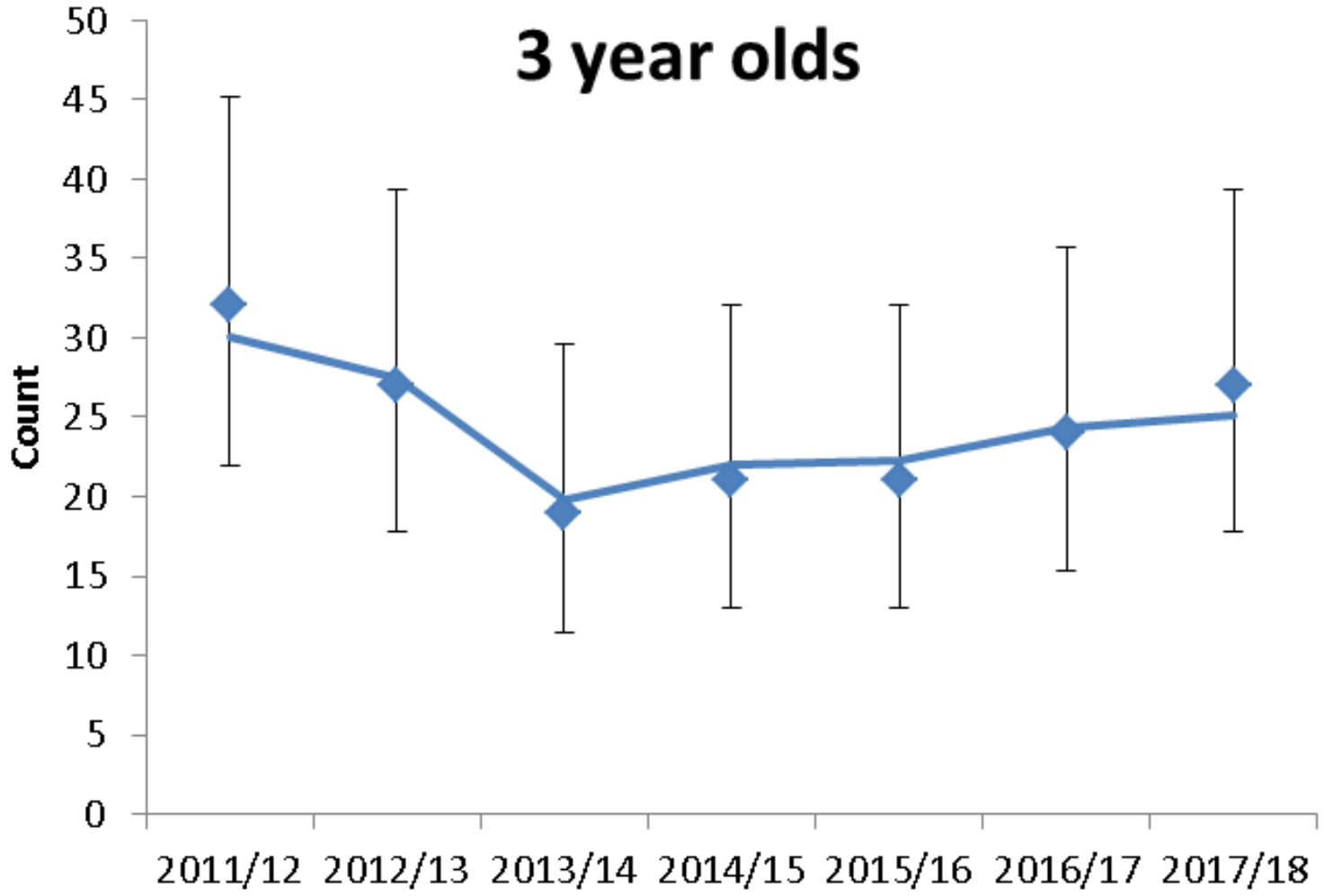

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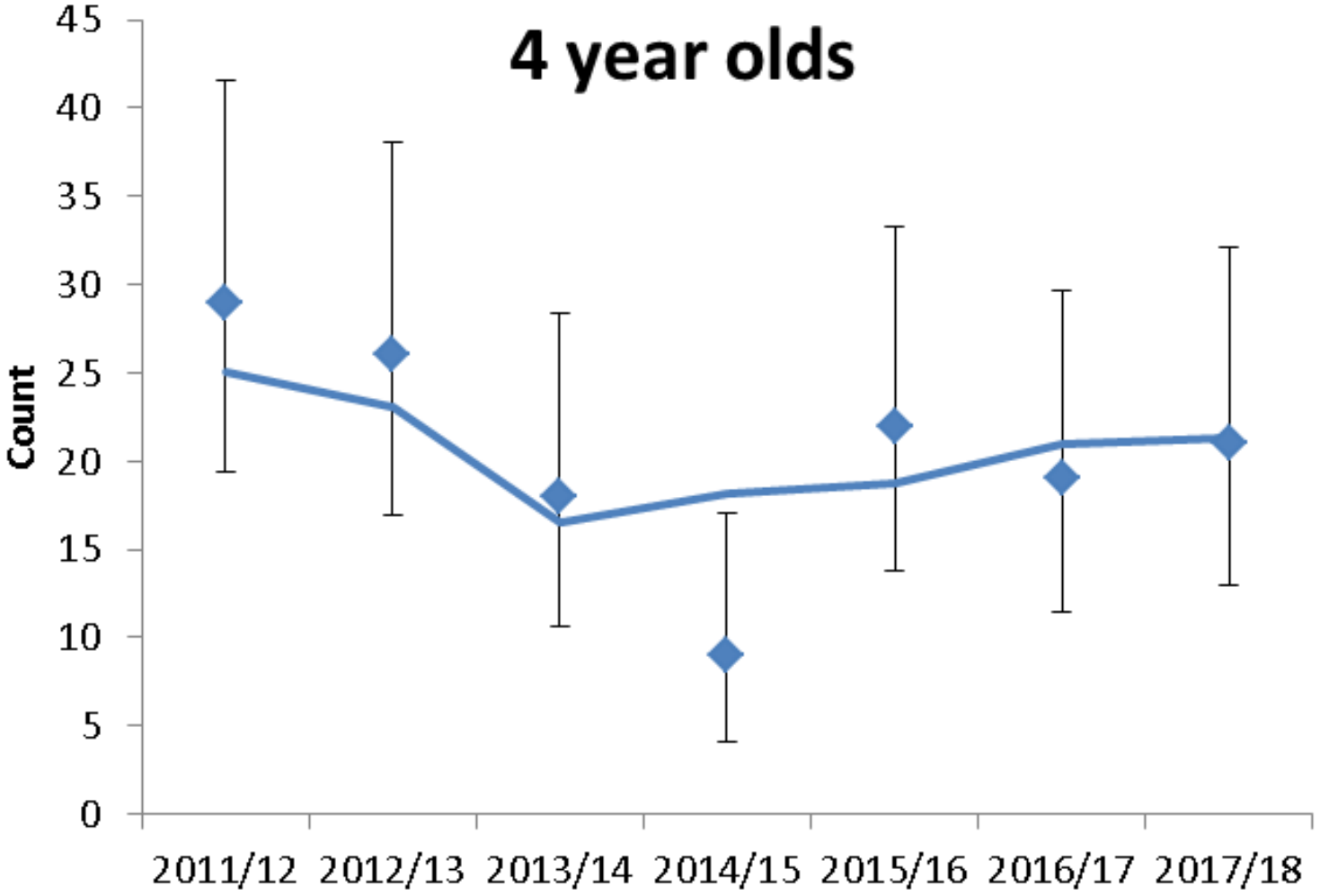

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4CMenB Safety
(3 million doses)

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Vaccine Safety: UK data

- So far, 3 million doses given to children so far
- Concerns before vaccine introduction
  - ? Kawasaki Disease – very rare in <6m, no evidence of increase
  - ? Seizures – no evidence of increase in any kind of seizure
  - ? Less likely to have subsequent vaccination – no evidence (97-98% return for their subsequent vaccines)
- Primary care consultations for fever
  - 1.5-fold increase in infants attending GP for fever post-vaccination with 4CMenB
- Secondary care consultations for fever
  - 3-4 fold increase in infants attending the ED for fever post-vaccination
- Hospitalisations for fever
  - Around half the infants attending the ED have septic screens +/- antibiotics
  - ? Did the parents give prophylactic paracetamol as recommended?

*

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Summary

- 4CMenB introduced into the UK infant programme in September 2015
- Overall, 169 cases confirmed and 277 cases prevented in the vaccine -eligible cohort after 3 years, irrespective of
  - *Vaccine coverage in the population*
  - *Number of vaccines doses received by the infants*
  - *MATS coverage of the MenB strains causing IMD cases*
  - *Vaccine effectiveness against invasive MenB disease*
- Significant reductions in infants for 3 consecutive years following a reduced 2-dose priming schedule
- 2+1 schedule protects for at least 2 years (i.e. 1 & 2 year-olds)
- So far, no major safety concerns after 3 million doses

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The way forward ….

1. Duration of protection after vaccination in children

   Rapid waning of vaccine-induced antibodies…?

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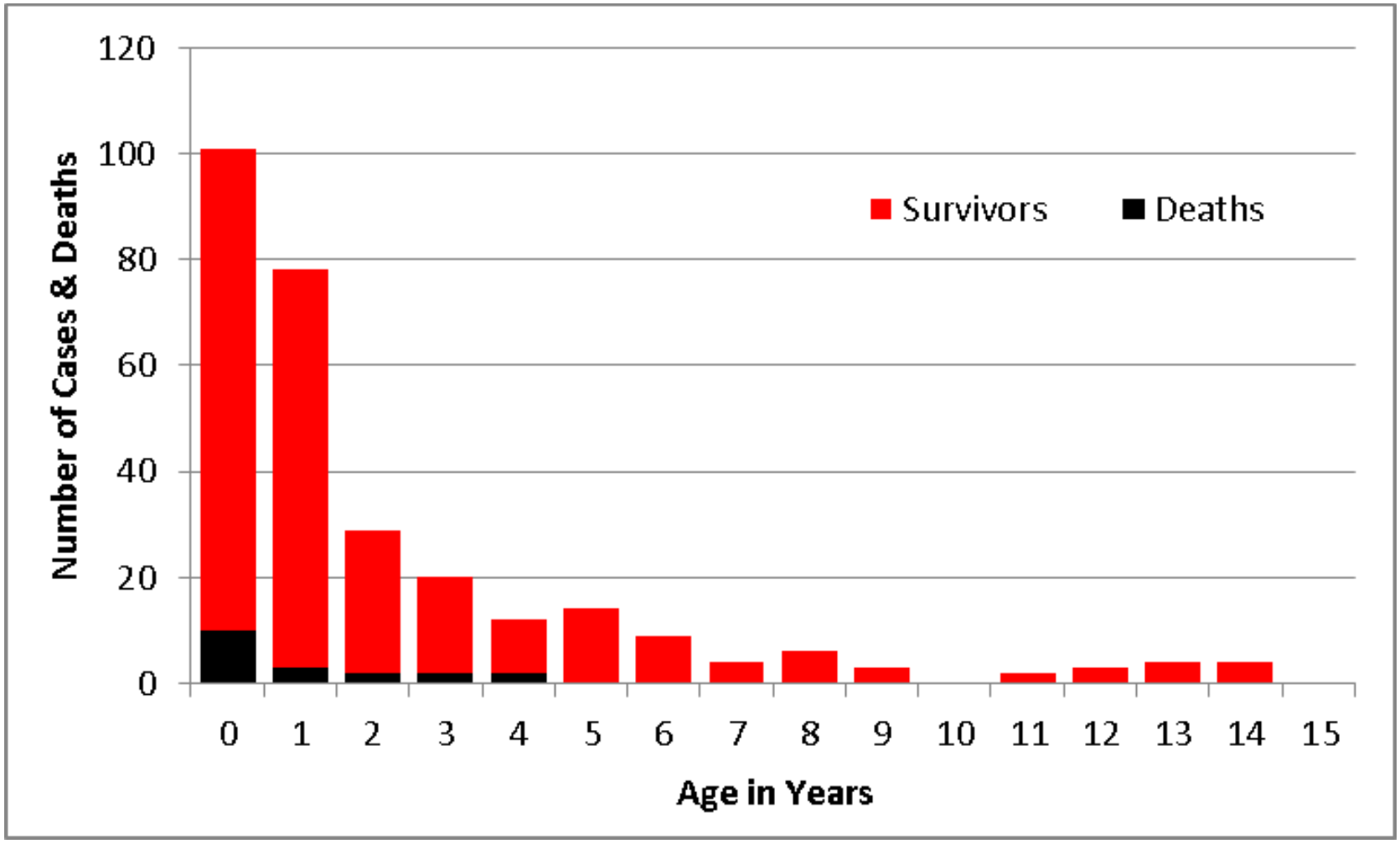
MenB cases/deaths, England 2014/15



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The way forward ….

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2. Impact on Carriage

   South Australia: teenage carriage study

   UK carriage study: 4CMenB vs. MenB-fHbp

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SA Health, University of Adelaide roll out meningococcal B vaccine trial

By Tom Fedorowytsch

Updated 13 Dec 2016, 3:24am

South Australian teenagers will be given free vaccines for meningococcal B as part of a "nation-leading" trial.

Up to 60,000 students in years 10, 11 and 12 will be offered the vaccine by the University of Adelaide and SA Health in 2017.

The organisations are examining the impact of immunising large community groups against the disease.

Meningococcal B has been in the spotlight this year with several cases in South Australia causing serious illness and even death

PHOTO: Jack Klemich died in 2009 at the age of 18, after contracting meningococcal B. (Supplied: Klemich family)

TOP STORIES

- Massive earthquake sparks tsunami off Mexico, leaves at least five dead
- Investors, staff, Matthew Hayden dudded in boutique whisky collapse
- Trio of hurricanes in Atlantic Ocean baffles weather scientists
- Second woman charged over botched breast surgery 'simply following directions'
- Grattan: Turnbull's rush for energy 'announceable' sows confusion
- 40 million forced to rebuild lives after devastating South Asia floods
- Florida sheriff warns sex offenders not welcome at Hurricane Irma shelters
- **SPORT** Stephens outmuscles Venus in one of the more brutal US Open semi-finals you'll see
- Same-sex marriage survey vote put up for auction on eBay

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The way forward ….

1. Duration of protection after vaccination in children

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   South Australia: teenage carriage study

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3. Protection against other serogroups

   MenW:cc11? Other serogroups?

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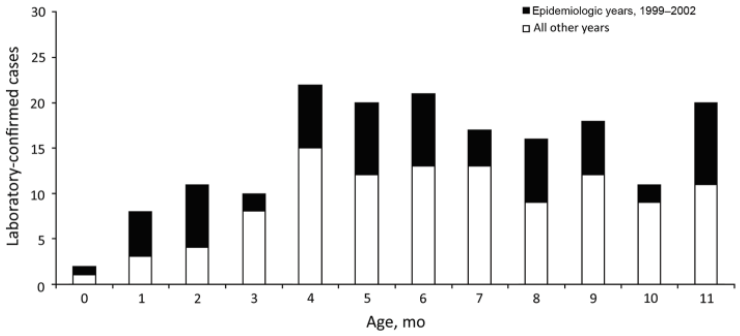
4CMenB → MenW:cc11

Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent *Neisseria meningitidis* W Strain, England

Shamez N. Ladhani, Marzia Monica Giuliani, Alessia Biolchi, Mariagrazia Pizza, Kazim Beebeejaun, Jay Lucidarme, Jamie Findlow, Mary E. Ramsay, Ray Borrow

Serum samples from children immunized with a meningococcal serogroup B vaccine demonstrated potent serum bactericidal antibody activity against the hypervirulent *Neisseria meningitidis* serogroup W strain circulating in England. The recent introduction of this vaccine into the United Kingdom national immunization program should also help protect infants against this endemic strain.



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The way forward ….

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   - *Rapid waning of vaccine-induced antibodies…?*
2. Impact on Carriage
   - *South Australia: teenage carriage study*
   - *UK carriage study: 4CMenB vs. MEnB-fHbp*
3. Protection against other serogroups
   - *MenW:cc11? Other serogroups?*
4. Universal meningococcal vaccine?

*

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MenABCWY Vaccine

Immunogenicity and safety of investigational vaccine formulations against meningococcal serogroups A, B, C, W, and Y in healthy adolescents

Xavier Saez-Llorens[1], Diana Catalina Aguilera Vaca[2], Katia Abarca[3], Emmanuelle Maho[4], Maria Gabriela Graña[5], Esther Heijnen[4], Igor Smolenov[4,*], and Peter M Dull[6]

RESEARCH PAPER

OPEN ACCESS Check for updates

Four-year antibody persistence and response to a booster dose of a pentavalent MenABCWY vaccine administered to healthy adolescents and young adults

Xavier Sáez-Llorens[a], Johnny Beltran-Rodriguez[b], Jose M. Novoa Pizarro[c], Ilhem Mensi[d], Pavitra Keshavan[d], and Daniela Toneatto[e]

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The way forward ….

1. Duration of protection after vaccination in children
   - *Rapid waning of vaccine-induced antibodies…?*
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   - *South Australia: teenage carriage study*
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3. Protection against other serogroups
   - *MenW:cc11? Other serogroups?*
4. Universal meningococcal vaccine (MenABCWY)
5. Effectiveness against *Neisseria gonorrhoea*

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Protection against Gonorrhoe

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

- *Retrospective analysis after New Zealand MenB outbreak*
- *Estimated VE = 31% (95% CI, 21-39%)*
- *Needs validating …. 4CMenB also has the NZ OMV component ...*

➔ *the next teenage vaccine?*

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Petousis-Harris et al. Lancet 390 (10102), p1603–1610, 30 September 2017

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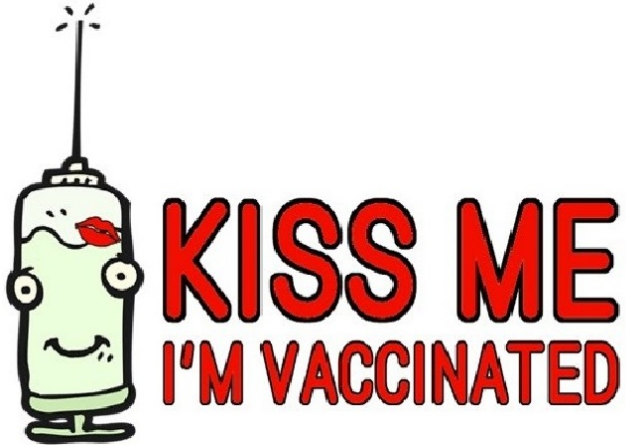
Acknowledgements

- Mary Ramsay,
- Ray Borrow, Jay Lucidarme and team
- Joanne Yarwood and team
- Phil Bryan and the MHRA team
- Vanessa Saliba
- Helen Campbell
- Sydel Parikh
- Kazim Beebeejaun
- MenB/ACWY Project Board



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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


Thank you

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Vaccine Effectiveness

- **Screening Method**: If 4CMenB was protecting infants from MenB disease, then the proportion of vaccinated cases would be lower than the proportion of infants vaccinated in the whole population.
- Adjusted VE after 1 dose: 24.1% (95% CI, -37.6% to 58.2%) based on 58 cases with dose74 cases and 16 unvaccinated cases
- Adjusted VE after 2 doses: 52.7% (95% CI, -33.5% to 83.2%) based on 37 cases with 2 doses and 4 unvaccinated cases

  23 culture-confirmed, 13 (56.5%) MATS-positive.

  Estimated VE against vaccine-preventable MenB strains: 66.3%.
- Adjusted VE after 2+1 schedule: 58.9% (95% Ci, -31.5 to 87.1%) based on 25 cases with 3 doses and 4 unvaccinated cases

  12 culture-confirmed cases, 5 subjected to MATS, 3 (40%) positive.

  Estimated VE against vaccine-preventable MenB strains: 70.5%.

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