**Clinical trials, network meta-analyses and real world data: growing evidence supporting 4CMenB effectiveness**

Dr Shamez N Ladhani,1 Professor Ray Borrow,2 Professor Nick J Andrews.3

1 *Immunisation Department*, 2 *Meningococcal Reference Unit*, 3 *Statistics, Modelling and Economics Department*, Public Health England, United Kingdom.

Corresponding author: Dr Shamez Ladhani, Immunisation Department, Public Health England, London, United Kingdom. Email: [shamez.ladhani@phe.gov.uk](mailto:shamez.ladhani@phe.gov.uk)

Competing interests: none

Meningococcal disease remains one of the most feared infectious diseases globally because of its sudden onset, rapid progression, high case fatality and severe neurodevelopmental sequelae among survivors. Of the 12 known meningococcal capsular groups, group B (MenB) is responsible for the most invasive cases in Europe, especially in young children.1 Unlike the highly effective polysaccharide-conjugate vaccines against groups A, C, W and Y, the development of a similar vaccine for MenB has been challenging because the MenB capsular polysaccharide is structurally identical to fetal neural cell adhesion molecules.2

Consequently, a novel, multi-component, protein-based meningococcal B vaccine with broad strain coverage (4CMenB, Bexsero®, GSK Biologicals, Belgium) was developed using reverse vaccinology and licensed in Europe in January 2013. 4CMenB is composed of three recombinant proteins—factor H-binding protein (fHbp), Neisserial heparin-binding antigen (NHBA), and Neisserial adhesin A (NadA)—and the outer membrane vesicles (OMV) from the New Zealand outbreak strain (NZ98/254), which incorporates the immunodominant Porin A (PorA) P1.4 protein. Because MenB disease is rare, the vaccine was licensed based on immunogenicity and safety studies only. Importantly, since these antigens may be present in any *Neisseria* spp., the vaccine is likely to protect against other meningococcal capsular groups,3 and also against gonococcal disease, as was recently reported with the New Zealand MenB OMV vaccine, which is incorporated into 4CMenB.4

In this issue, Dr Flaco and colleagues report the results of a systematic review along with head-to-head and network meta-analyses performed on the immunogenicity and safety of 4CMenB from 18 studies.5 The authors employed a comprehensive search strategy and bias assessment, as well as an array of meta-analyses on per-protocol and intention-to-treat (ITT). Reassuringly, the main findings of this review are consistent with the results of the individual clinical trials that led to vaccine licensure. The higher immunogenicity of 4CMenB compared to the original rMenB vaccine (without the OMV component) and controls (routine vaccinations without a MenB vaccine) is expected. After primary immunisation, nearly all infants had protective bactericidal antibody concentrations against the four test strains and, although antibodies waned subsequently, the subsequent booster after the first birthday restored the high seroconversion rates.

A limitation of these findings is that the vaccine-induced antibodies are tested against strains that that have been selected to closely match the vaccine antigens. Consequently, the extent of cross-protection, if any, against related-MenB strains that are likely to be encountered in the real world is not known. We also do not know whether bactericidal antibodies against any single vaccine antigen are sufficient to confer protection. Similarly, some vaccine antigens – or specific combinations of vaccine antigens – might provide additional or even synergistic protection against invasive disease.

Another important finding in the systematic review was that, whilst adolescents were able to maintain high bactericidal antibody concentrations up to 18 months after vaccination, immunity waned rapidly after the booster dose in infants. This finding suggests that the protection offered by the infant immunization programme may be short-lived. In the systematic review, data for geometric mean titres, unfortunately are not reported, which may have thrown more light on the observed rapid waning.

In September 2015, the UK became the first country to introduced 4CMenB into the national infant programme.6 Within 10 months, the vaccine was found to be 83% effective against all MenB cases in vaccine-eligible infants, equivalent to around 94% effectiveness against the 88% predicted vaccine-preventable MenB strains.6 Notably too, there was a nearly 50% reduction in cases in the vaccine eligible age-group and, reassuringly, this trend has continued for 1 year-olds who became eligible for the 12-month booster in May 2016.7 Continued surveillance will be critical to monitor the duration of protection offered by the UK infant 4CMenB programme, which utilised a reduced two-dose infant priming schedule instead of the 3+1 schedule licensed in Europe.

In the Saguenay-Lac-Saint-Jean region of Quebec, Canada, all children aged 2 months to 20 years were immunised in a one-off campaign in May 2014 (~43,000 vaccinated) to combat a local outbreak of disease due to a sequence type 269 clone, which has already led to a 78% reduction in MenB disease incidence.8 More recently, both the Republic of Ireland and Italy have implemented 4CMenB into their national infant immunization programmes at a reduced 2+1 and the licensed 3+1 schedules, respectively.

The authors of the systematic review also report on the safety of 4CMenB in the reported clinical trials. Consequently, the safety data are mostly limited to self-reported common vaccine-related reactions and uncommon serious adverse events, which are more frequent than for other vaccines. Such analyses, however, cannot assess the risk of rarer events of interest such as Kawasaki disease and febrile convulsions, which require post-licensure studies. Since 4CMenB implementation in the UK, for example, a small but significant increase in primary care and emergency department attendances for fever after vaccination has been observed.9 Reassuringly, though, the Medicine and Healthcare products Regulatory Agency (MHRA) has not identified any major safety concerns after the first 3 million doses administered to UK infants.

4CMenB and related next generation vaccines that are currently under development will play a vital role in protecting against both meningococcal and gonococcal disease. The results from such complex meta-analyses along with the real world data generated globally are invaluable for optimising the immunization schedule to offer maximum protection with minimal harm. As the authors rightly conclude, further studies are needed to determine the breadth of protection offered against related MenB strains and the persistence of protection in children who were immunised in infancy. Another important question is whether 4CMenB prevents meningococcal carriage; if this is confirmed, then an adolescent immunisation programme would become an attractive option for national immunisation programmes because, in addition to direct protection for adolescents who are known to have a higher risk of meningococcal disease, the vaccine could also induce population (indirect/herd) protection since teenagers are the main meningococcal carriers. Studies are currently underway to answer these important questions.

**REFERENCES**

1. Whittaker R, Dias JG, Ramliden M, Ködmön C, Economopoulou A, Beer N, Pastore Celentano L; ECDC network members for invasive meningococcal disease. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004 2014. Vaccine. 2017 ;35(16):2034-2041.
2. Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against *Neisseria meningitidis*. N Engl J Med. 2010;362(16):1511-20.
3. Ladhani SN, Giuliani MM, Biolchi A, Pizza M, Beebeejaun K, Lucidarme J, Findlow J, Ramsay ME, Borrow R. Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent Neisseria meningitidis W Strain, England. Emerg Infect Dis. 2016;22(2):309-11.
4. Petousis-Harris H, Paynter J, Morgan J, Saxton P, McArdle B, Goodyear-Smith F, Black S. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet. 2017;390(10102):1603-1610.
5. Flacco ME, Manzoli L, Rosso A, Marzuillo C, Bergamini M, Stefanati A, Cultrera R, Villari P, Ricciardi W, Ioannidis JPA, Contopoulos-Ioannidis DG. Immunogenicity and safety of the multicomponent meningococcal B vaccine (4CMenB): a systematic review and meta-analysis. Lancet Infectious Diseases 2017.
6. Parikh SR, Andrews NJ, Beebeejaun K, Campbell H, Ribeiro S, Ward C, White JM, Borrow R, Ramsay ME, Ladhani SN. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet. 2016 Dec 3;388(10061):2775-2782.
7. Public Health England. Meningococcal disease: guidance, data and analysis. Available at: <https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis>. Accessed: 21 November 2017
8. De Wals P, Deceuninck G, Lefebvre B, Tsang R, Law D, De Serres G, Gilca V, Gilca R, Boulianne N. Impact of an Immunization Campaign to Control an Increased Incidence of Serogroup B Meningococcal Disease in One Region of Quebec, Canada. Clin Infect Dis. 2017 May 1;64(9):1263-1267.
9. Ladhani SN,  Riordan A. [The yin and yang of fever after meningococcal B vaccination](http://adc.bmj.com/content/102/10/881). Arch Dis Child 2017; 102(10): 881