4CMenB vaccine effectiveness: reasons for optimism

Published Online
October 27, 2016
http://dx.doi.org/10.1016/S0140-6736(16)32061-X

See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(16)31921-3

Preventing invasive meningococcal disease caused by the bacterial pathogen *Neisseria meningitidis* is of crucial public health importance in view of the sudden onset of symptoms, rapid progression to serious disease, and high risk of mortality even among previously healthy individuals.[1,2] The burden of invasive meningococcal disease has been reduced in many parts of the world through extensive public health efforts—most notably the introduction of conjugate group C vaccines in the UK in 1999,[3] and conjugate group A vaccines in the African meningitis belt beginning in 2010.[4] Yet, developing vaccines to protect against the diversity of disease-causing meningococcal B (MenB) strains has been challenging. The first vaccines designed to be broadly immunogenic against multiple MenB strains became available only recently,[5,6] with the 4CMenB vaccine (also known as Bexsero [GSK]) being licensed in Europe in 2013. The UK became the first country to introduce 4CMenB into a national infant immunisation programme in September, 2015. UK health authorities recommend a reduced two-dose priming schedule at 2 months and 4 months and a booster dose at 12 months of age for all infants born since July, 2015, plus an opportunistic catch-up programme for infants born in May or June, 2015.[7,8]

In *The Lancet*, Sydel Parikh and colleagues[9] report the first evidence of the effectiveness and impact of 4CMenB vaccine against laboratory-confirmed MenB disease. In this well-designed observational national cohort study, Parikh and colleagues applied the screening method to comprehensive UK surveillance data, comparing the proportion of vaccinated infant MenB cases to the proportion vaccinated among all eligible infants. Based on their careful analyses, two doses of 4CMenB showed 82·9% (95% CI 24·1–95·2) effectiveness against all cases of MenB disease among infants during the first year of life. By comparing the MenB incidence rate among vaccine-eligible infants to the incidence rate for the same age groups during the same time period in the 4 years before 4CMenB introduction, Parikh and colleagues found a significant 50% lower incidence among the cohort of infants eligible for 4CMenB in the first 10 months of the vaccination programme.

Previous evaluation of 4CMenB, as for meningococcal conjugate vaccines, had been based only on immunogenicity and safety studies. Because MenB disease is relatively rare, undertaking sufficiently powered clinical trials with disease endpoints to assess vaccine efficacy is not generally feasible. Clinical trials of 4CMenB showed that vaccination induced immunity against MenB reference strains.[10] However, evidence from the first use of 4CMenB in the USA in 2013 during a MenB outbreak showed that a third of adults vaccinated with two doses did not develop putatively protective immunity against the outbreak strain, thus raising questions about the breadth of the 4CMenB response.[11] Parikh and colleagues report high 4CMenB effectiveness against all laboratory-confirmed cases of MenB disease, irrespective of predicted strain coverage. These results highlight the key role of population-based epidemiological studies in providing essential evidence about the impact of newly developed vaccines and vaccination programmes. Such studies should be undertaken routinely to evaluate vaccines post licensure.

The results that Parikh and colleagues[9] report are encouraging and suggest that 4CMenB has the potential to significantly reduce the burden of MenB disease among infants. The authors identified high vaccine effectiveness and a significant impact of 4CMenB vaccine among infants vaccinated with a reduced two-dose priming schedule, rather than the three-dose priming schedule licensed in Europe, in the first 10 months after 4CMenB introduction, which is important to note. The infant priming schedule only

Dr P Marazzi/Science Photo Library

needs to provide protection until the 4CMenB booster dose is given at 12 months of age. Longer follow-up is needed to confirm these results in additional cohorts, to continue to assess safety, and to determine how long protection might last after the 12-month 4CMenB booster. The high vaccine uptake achieved in the UK, with 95·5% of eligible infants receiving at least one dose and 88·6% receiving both priming doses by 6 months of age, reflects public demand for, and acceptance of, new vaccines against MenB and the success of public health systems in the UK.

Many other countries have been cautious about introducing MenB vaccines, in part due to questions about the breadth and duration of protection, and the cost-effectiveness of programmes. Evidence of high vaccine effectiveness, along with high vaccine uptake, should be reassuring to health authorities who are considering whether to introduce vaccine programmes against MenB disease. In addition, cost-effectiveness analyses played a central part in the decision to introduce 4CMenB in the UK.[12] To inform vaccination policies in other settings, additional epidemiological and cost-effectiveness studies are now needed to answer important remaining questions, including how differences in the age distribution of MenB cases, variation in the relative frequencies of disease-causing MenB strains, the potential impact of MenB vaccines on carriage among teenagers, and variation in the costs of vaccination programmes could affect the impact of MenB vaccines.

If the reductions in MenB disease that Parikh and colleagues observed among UK infants are sustained over time and replicated in other settings, then MenB vaccines could have a vital role in reducing the threat of meningococcal disease.

Nicole E Basta, Hannah Christensen
University of Minnesota, School of Public Health, Minneapolis, MN 55454, USA (NEB); and University of Bristol, School of Social and Community Medicine, Bristol, England, UK (HC)
nebasta@umn.edu

NEB is funded by the National Institutes of Health Early Independence Award from the Office of the Director (1DP5OD009162). NEB has collaborated with Ray Borrow and co-authored studies of meningococcal A and B vaccines using data from the USA and Africa. HC is funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in evaluation of interventions at the University of Bristol in partnership with Public Health England (PHE). HC has collaborated with PHE when developing mathematical and economic models predicting the impact of 4CMenB in the UK and has co-authored papers with PHE colleagues, including Article authors Shamez Ladhani, Helen Campbell, Ray Borrow, and Mary Ramsay, on preventing secondary cases of invasive meningococcal capsular group B (MenB) disease using Bexsero, but she had no involvement in the present Article. HC has received honoraria from Sanofi Pasteur, paid to her employer, and consultancy fees from IMS Health and AstraZeneca. The views expressed are those of the author(s) and not necessarily those of the NIH, NHS, the NIHR, the Department of Health, or Public Health England.

1 Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009; **27:** B51–63.
2 Khatami A, Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. *Expert Rev Vaccines* 2010; **9:** 285–98.
3 Campbell H, Borrow R, Salisbury D, Miller E. Meningococcal C conjugate vaccine: the experience in England and Wales. *Vaccine* 2009; **27:** B20–29.
4 Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* 2014; **383:** 40–47.
5 Esposito S, Principi N. Vaccine profile of 4CMenB: a four-component Neisseria meningitidis serogroup B vaccine. *Expert Rev Vaccines* 2014; **13:** 193–202.
6 Brendish NJ, Read RC. Neisseria meningitidis serogroup B bivalent factor H binding protein vaccine. *Expert Rev Vaccines* 2015; **14:** 493–503.
7 Ladhani SN, Campbell H, Parikh SR, Saliba V, Borrow R, Ramsay M. The introduction of the meningococcal B (MenB) vaccine (Bexsero®) into the national infant immunisation programme—new challenges for public health. *J Infect* 2015; **71:** 611–14.
8 Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child* 2016; **101:** 91–95.
9 Parikh SR, Andrews NJ, Beebeejaun K, et al. 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; published online Oct 27. http://dx.doi.org/10.1016/S0140-6736(16)31921-3.
10 Santolaya ME, O'Ryan ML, Valenzuela MT, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. *Lancet* 2012; **379:** 617–24.
11 Basta NE, Mahmoud AA, Wolfson J, et al. Immunogenicity of a meningococcal B vaccine during a university outbreak. *N Engl J Med* 2016; **375:** 220–28.
12 Christensen H, Trotter CL, Hickman M, Edmunds WJ. Re-evaluating cost effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study. *BMJ* 2014; **349:** g5725.