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4CMenB Vaccine Effectiveness: Reasons for Optimism

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Preventing invasive meningococcal disease (IMD) caused by the bacterial pathogen *Neisseria meningitidis* is of critical public health importance given 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 IMD has been reduced in many parts of the world through extensive public health efforts, most notably following the introduction of conjugate group C vaccines in the United Kingdom (UK) in 1999³, and conjugate group A vaccines in the African meningitis belt beginning in 2010⁴. 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]) licensed in Europe in 2013. The UK became the first country to introduce 4CMenB into a national infant immunization program in September 2015. UK health authorities recommend a reduced 2-dose priming schedule at 2- and 4-months and a booster dose at 12 months of age for all infants born since July 2015, plus an opportunistic catch-up program for infants born in May or June 2015^{7,8}.

In *The Lancet*, Sydel R. Parikh and colleagues report the first evidence of the effectiveness and impact of 4CMenB vaccine against laboratory-confirmed MenB disease⁹. 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 robust 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 four years prior to 4CMenB introduction, Parikh *et al.* found a significant 50% lower incidence among the cohort of infants eligible for 4CMenB in the first 10 months of the vaccination program.

Prior evaluation of 4CMenB, as for meningococcal conjugate vaccines, had been based solely on immunogenicity and safety studies. Because MenB disease is relatively rare, conducting sufficiently powered clinical trials with disease endpoints to assess vaccine efficacy is typically not feasible. 4CMenB clinical trials demonstrated that vaccination induced immunity against MenB reference strains¹⁰. However, evidence from the first use of 4CMenB in the US in 2013 during a MenB outbreak showed that one 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 response¹¹. Parikh and colleagues report high 4CMenB effectiveness against all laboratory-confirmed cases of MenB disease, regardless of predicted strain coverage. These results highlight the key role of population-based epidemiologic studies in providing essential evidence about the impact of newly developed vaccines and vaccination programs. Such studies should be undertaken routinely to evaluate vaccines post-licensure.

The results that Parikh *et al.* report are encouraging and suggest that 4CMenB has the potential to significantly reduce the burden of MenB disease among infants. That Parikh *et al.* found high vaccine effectiveness and a significant impact of 4CMenB vaccine among infants vaccinated with a reduced 2-dose priming schedule, rather than the 3-dose priming schedule licensed in Europe, in the first 10 months following 4CMenB introduction is important to note. The infant priming schedule only needs to provide protection until the 4CMenB booster dose is administered 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 may 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 six 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 programs. Evidence of high vaccine effectiveness, along with high vaccine uptake, should be reassuring to health authorities who are considering whether to introduce vaccine programs against MenB disease. In addition, cost-effectiveness analyses played a central role in the decision to introduce 4CMenB in the UK¹². 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 vaccination program costs could affect the impact of MenB vaccines.

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

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