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REVIEW

The introduction of the meningococcal B (MenB) vaccine (Bexsero®) into the national infant immunisation programme — New challenges for public health

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Summary The United Kingdom is the first country to introduce Bexsero® (GSK Biologicals), a multicomponent, protein-based vaccine against meningococcal group B (MenB), into the national infant immunisation programme. This vaccine is like no other licensed vaccine and poses a number of implementation and surveillance challenges in England. From 01 September 2015, UK infants were offered a reduced two dose primary immunisation schedule at 2 and 4 months followed by a booster at 12 months. Because of high rates of fever post-vaccination, parents were advised to give their infants three doses of prophylactic paracetamol, with the first dose given as soon as possible after the primary MenB vaccination dose. Since the vaccine only protects against 73–88% of MenB strains causing invasive disease in England, clinical isolates and PCR-positive samples will require extensive characterisation by the Meningococcal Reference Unit (MRU) at Public Health England (PHE) in order to monitor vaccine effectiveness and identify potential vaccine failures. PHE is also conducting detailed clinical and epidemiological surveillance to assess the impact of the MenB immunisation programme on the morbidity and mortality associated with invasive meningococcal disease in infants and young children.

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Introduction

In September 2015, the United Kingdom was the first country to introduce Bexsero® (GSK Biologicals), a novel, multicomponent vaccine against meningococcal group B (MenB) disease, into the national infant immunisation programme. Bexsero® was licensed in Europe in January 2013 and, in March 2014, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended the introduction of an infant programme if the vaccine could be procured at a cost-effective price (https://www.gov.uk/government/publications/meningococcal-b-vaccine-jcvi-position-statement). In March 2015, the Health Secretary Jeremy Hunt announced that an agreement had been reached with the manufacturers and the programme began on 01 September 2015. Full details of the programme are available at: https://www.gov.uk/government/collections/immunisation.

Epidemiology

Neisseria meningitidis (the meningococcus) is a major global cause of bacterial meningitis and septicaemia in young children and adolescents. The infection develops rapidly and is associated with significant fatality along with serious long-term sequelae among survivors, including limb amputations, sensorineural deafness, epilepsy and cerebral palsy. Consequently, efforts to control the disease have focussed on prevention through vaccination. In the UK, as in most industrialised countries, MenB is responsible for the vast majority of invasive meningococcal disease (IMD) cases, especially in children and adolescents. MenB cases, however, have also been declining since the early 2000s, most likely because of secular trends.[1] In 2014, there were 628 laboratory-confirmed IMD cases and 32 deaths in England, including 400 MenB cases and 15 deaths. In <5 year-olds, there were 220 MenB cases, including 106 in infants (<1 year-olds) and 114 in toddlers (1–4 year-olds). While the current numbers are low, local and national MenB outbreaks can occur rapidly if a new virulent strain is introduced into the population, as currently occurring with MenW in England.[2]

The vaccine

The MenB capsular polysaccharide is structurally similar to human neural-cell adhesion molecules and, therefore, poorly immunogenic. Consequently, a novel approach using reverse vaccinology was used to identify highly conserved antigens on the surface of meningococci that were able to elicit bactericidal antibodies.[3] The most promising antigens were then combined with the outer membrane vesicle (OMV) of a New Zealand MenB outbreak strain and this new vaccine was found to be highly immunogenic in clinical trials.[3] Using Meningococcal Antigen Typing System (MATS), a unique vaccine antigen-specific ELISA which detects qualitative and quantitative differences in antigens, along with PorA genotyping information, Bexsero® is estimated to protect against 73% of circulating MenB strains in the UK.[4] When assessing serum bactericidal antibody (SBA) activity, however, a higher proportion of MenB strains (88%) were killed by vaccine-induced antibodies.[5]

Since licensure, more than a million Bexsero® doses have been administered across all age groups without any safety concerns. In particular, more than 17,000 adolescents attending Princeton University received Bexsero® to control a recent MenB outbreak, while in the Québec's Saguenay-Lac-Saint-Jean region, more than 45,000 infants, young children and adolescents were vaccinated with Bexsero® because of significantly higher local IMD incidence compared to the rest of the country.

Implementation

From 01 September 2015, infants born on or after 01 July 2015 in the UK were offered Bexsero® with their routine primary immunisations. All Bexsero® doses were recommended to be administered into the left thigh to monitor local reactions. Contrary to the licensed three-dose primary schedule, infants receive two doses at two and four months, followed by a 12-month booster. This decision was made because a recent, as yet unpublished, clinical trial found that nearly all infants achieved protective antibody thresholds after two doses given two months apart, which should protect them until their 12-month booster. A limited catch-up for infants born on or after 01 May 2015 and attending their three-month and four-month vaccination visits was also implemented whereby infants were offered Bexsero® at 3–4–12 and 4–12 months, respectively (http://www.nhs.uk/Conditions/vaccinations/Pages/meningitis-B-vaccine.aspx). The infant programme is unlikely to have any significant indirect (herd) impact across the population because meningococcal carriage rates are very low in young children.[6] Carriage rates increase rapidly in late adolescence; however, teenagers have not been targeted for vaccination because, although a reduction in MenB carriage was observed in adolescents receiving Bexsero®,[7] the size and duration of the effect on carriage and, therefore, any impact on disease at a population level, is uncertain.

Clinical trials in infants have identified high rates of fever (≥38 °C) in infants receiving Bexsero® with their routine immunisations (51–61%) compared to routine vaccinations alone (23%),[8] although medical attendance after vaccination and serious adverse reactions, such as febrile convulsions, were rare and did not correlate with the characteristic pattern of fever after Bexsero® vaccination.[8] In one of the Bexsero® trials, medical attendance for fever among infants receiving Bexsero® with their routine vaccination was substantially lower in the open-label subset compared with an observer-blind subset (1.4% vs. 5.3%),[9] indicating that providing parents with appropriate information at the time of vaccination could significantly reduce medical attendance rates.

In a subsequent randomised controlled trial, prophylactic paracetamol starting at the time of vaccination significantly reduced the incidence and intensity of post-vaccination fever and local reactions when Bexsero® was

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administered with routine infant vaccinations, without affecting immune responses to any of the vaccine antigens.[10] This finding is in contrast to a previous study where prophylactic paracetamol was associated with lower responses to multiple vaccine antigens, many of which persisted even after the boosters in the second year of life.[11] Interestingly, prophylactic ibuprofen does not prevent post-immunisation fever in infants.[12] Therefore, parents are advised to stock liquid infant paracetamol at home prior to the first immunisation appointment and give three doses of paracetamol at 4—6 hourly intervals with the first dose administered around the time of vaccination. However, some parents may decide not to give paracetamol and other infants may still experience breakthrough fever despite paracetamol. Clinicians should, therefore, ask about Bexsero® vaccination in the previous 48 h when assessing otherwise well infants presenting with fever in primary care or the Emergency Department. Fever after Bexsero® generally peaks at 6 h after vaccination and rarely persists beyond 48 h.

Surveillance

In England, Public Health England (PHE) has been conducting enhanced national surveillance of IMD for several decades. The provision by the PHE Meningococcal Reference Unit (MRU) of a national service for confirmation, grouping and characterisation of clinical meningococcal isolates alongside a free national PCR-testing service for patients suspected with IMD is critical for ensuring high case ascertainment, monitoring trends over time and emerging strains, as well as providing specialist advice for management of individual cases and outbreaks. This surveillance will play a vital role in evaluating, for the first time, Bexsero® effectiveness in a national programme.

Since the vaccine only protects against 73—88% of circulating MenB strains in England, all clinical isolates require additional testing using the meningococcal antigen typing system (MATS) at the MRU to assess whether the strain was potentially vaccine preventable and to estimate vaccine effectiveness. To achieve this aim, PHE Health Protection Teams are requesting microbiology laboratories to submit all meningococcal isolates (including throat swab isolates from probable IMD cases) to the MRU for confirmation and further characterisation, even if the diagnosis has been confirmed by PCR. The MRU is also attempting to characterise meningococcal strains in PCR-positive samples to provide additional information on whether they were likely to be vaccine-preventable. At the same time, PHE is working with clinicians and general practitioners to collect demographic, risk factor and vaccination histories for all confirmed cases. For children younger than five years with confirmed IMD, paediatricians are requested to complete clinical questionnaires for confirmed cases and to submit acute and convalescent sera to the MRU for assessing antibody responses. A detailed surveillance plan can be found here: https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis.

As the first country to introduce a national Bexsero® infant programme, England has a unique opportunity to demonstrate vaccine effectiveness and disease reduction, which could lead to other countries also adopting Bexsero® to protect their children against this devastating infection.

Contribution

All authors contributed equally to preparing, revising and approving the final version of manuscript.

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Conflicts of interest

None.

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