

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

JCVI position statement on use of Bexsero[®] meningococcal B vaccine in the UK

March 2014

Introduction

JCVI is acutely aware of the burden and severity of meningococcal meningitis and septicaemia in the UK and has always recognised the need to fully explore the potential for its prevention through immunisation. This statement sets out the conclusions of the JCVI regarding its deliberations on the cost-effectiveness of using serogroup B meningococcal (MenB) vaccine in the UK, both routinely in infants and/or adolescents and in at risk groups. This statement follows extensive discussion, which the Committee believes was necessary to ensure the most robust conclusion possible was reached. The Committee is of the opinion that its deliberations have taken into account the views and comments received, and are based on the most up to date and complete scientific evidence on MenB disease and the MenB vaccine Bexsero[®]. The health economic analyses undertaken comply with the methodology of National Institute of Health and Care Excellence (NICE) and appropriate NICE guidance.

Background

In response to information supplied to JCVI in 2010 that a MenB vaccine was likely to reach the point of market authorisation in the coming years, JCVI convened a meningococcal sub-committee to conduct a comprehensive and detailed assessment of the evidence on the MenB vaccines in development and on the impact and cost effectiveness of a range of potential MenB immunisation strategies¹. In June 2013 the Committee received a request from the Secretary of State for Health for JCVI to provide him with a recommendation on the possible introduction of a routine meningococcal B immunisation programme².

The sub-committee met a total of five times (February 2011, July 2012, January 2013, April 2013 and September 2013^{3 4}), presenting its final conclusions to JCVI in October 2013. The sub-committee based its assessment on: evidence received through a call for evidence from interested parties issued in 2010; epidemiological analyses from UK health protection organisations; submissions from the vaccine manufacturers that addressed specific requests from the sub-committee for data on the safety and assessment of the potential efficacy of the vaccine; an impact and cost-effectiveness study on the use of Bexsero[®] in the UK⁵, and comments received on the interim statement from the Committee published in July 2013⁶. Unpublished data from other sources and published literature were also reviewed.

¹http://webarchive.nationalarchives.gov.uk/20120907090205/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@a_b/documents/digitalasset/dh_120659.pdf

²https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239394/SoS_letter_to_JCVI_Men_B_Vaccination_logo.pdf

³http://webarchive.nationalarchives.gov.uk/20120907090205/http://www.dh.gov.uk/ab/JCVI/DH_123529

⁴<https://www.gov.uk/government/policy-advisory-groups/joint-committee-on-vaccination-and-immunisation>

⁵ Christenson *et al* (2013). Introducing vaccination against serogroup B meningococcal disease: An economic and mathematical modelling study of potential impact. *Vaccine* 28;31(23):2638-46

⁶https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224896/JCVI_interim_statement_on_meningococcal_B_vaccination_for_web.pdf

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Impact and cost-effectiveness analysis

A key component of the assessment undertaken by JCVI was a study on the impact and cost-effectiveness of different vaccination strategies using Bexsero[®] conducted by the University of Bristol and London School of Hygiene and Tropical Medicine. This study was undertaken to investigate the impact and cost effectiveness of routine infant and / or adolescent immunisation programmes with and without catch-up campaigns, and a routine toddler immunisation programme. It included a cohort model to assess the direct impact of vaccination, and also a transmission dynamic model to assess the direct and indirect impacts of vaccination. The study followed the methodology of the NICE to estimate cost effectiveness. It included sensitivity analyses to assess the influence of key and uncertain parameters including: vaccine efficacy against meningococcal carriage; vaccine coverage against meningococcal strains; the incidence of invasive meningococcal disease (IMD); the quality of life losses from IMD; the rate of medically attended fever following vaccination; vaccine price; and discounting rates.

The analysis was first considered by the meningococcal sub-committee in February 2011, where the sub-committee agreed the study indicated that the use of Bexsero[®] in infant and / or adolescent vaccination programmes was likely to be cost-effective. However, during this meeting and the subsequent meetings held in July 2012 and January 2013, the Committee advised a number of changes be made to increase the robustness of the model. The model was revised based on the expert opinion of the sub-committee, the latest MenB epidemiology, and the best evidence available on the impact of invasive MenB disease (IMD). The revised study⁷ was presented to the sub-committee in April 2013, where the Committee agreed that the study had been well conducted and had taken into account the advice of the sub-committee. On the basis of this second iteration of the model, the meningococcal sub-committee concluded that use of the vaccine in infants was unlikely to be cost-effective, although the vaccine was close to demonstrating cost-effectiveness in some scenarios modelled.

JCVI considered the advice of the meningococcal sub-committee in June 2013 and agreed with the views of the sub-committee. The Committee however felt that this decision was of such importance, and because the cost-effectiveness of the vaccine was very sensitive to a number of inputs that had potential to vary the results around the cost-effectiveness threshold, that the conclusions reached should be made open to consultation with those who had provided evidence to the Committee. The Committee therefore published an interim statement for consultation in July 2013, which indicated that the vaccine was highly unlikely to demonstrate cost-effectiveness at any vaccine price (i.e. even at £0 per dose the vaccine was unlikely to be cost-effective). During August 2013, a number of detailed comments were received and then considered by the meningococcal sub-committee and JCVI in September and October 2013 respectively. The submissions received included references to new and recently published evidence and information on additional parameters, such as litigation costs to the NHS associated with MenB disease, which had not been included in the first or second iterations of the analysis. Such parameters, whilst not routinely included in such analyses, are permitted under the NICE methodology, and both

⁷ Christenson *et al* (2013). Introducing vaccination against serogroup B meningococcal disease: An economic and mathematical modelling study of potential impact. *Vaccine* 28;31(23):2638-46

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

the sub-committee and JCVI concluded that further analyses were necessary to respond fully and take these factors into account.

The changes requested by the Committee were generally, but not exclusively positive towards the impact of the vaccine, the Committee considered it important these were modelled to ensure the robustness of the model. The changes made were:

- Revision of quality of life losses to include additional quality of life losses associated with the short term phase of IMD
- Inclusion in the base case model of a quality of life adjustment factor agreed by the JCVI in June 2013 (as opposed to this being accounted for in an additional analysis as had been done previously)
- An increased incidence of disease, considered by the Committee more representative of average incidence over a longer period
- Inclusion of new data on the rate of minor and severe sequelae following IMD
- Inclusion of a proportion of litigation costs associated with meningococcal disease in the NHS
- Inclusion of quality of life losses to family members.

The final analysis was received by JCVI in January 2014⁸, and was reviewed by the Committee during a two day meeting held on 11 and 12 February 2014. This statement sets out the findings of the Committee following that meeting.

Considerations of the Committee

Epidemiology

JCVI noted that in the last decade, the incidence of IMD in England and Wales had decreased by about one half to around 25 confirmed cases of IMD per 100,000 children aged less than one year and to less than 2 confirmed cases per 100,000 people across all ages combined (see Figure 1). Over this period, serogroup B meningococcus accounted for around 80% of IMD⁹ (see Figure 2) and there were 613 laboratory confirmed cases and 33 deaths from IMD arising from serogroup B meningococcus infection in epidemiological year 2011/2012¹⁰. The epidemiology of IMD from serogroup B meningococcus is similar in Scotland and Northern Ireland. A UK study suggests that around a tenth of survivors of IMD from serogroup B meningococcus have major physical and/or neurological disabilities, including amputation, deafness, epilepsy and/or learning difficulties and around one third of cases result in less severe physical and/or neurological disabilities¹¹.

⁸ Christenson *et al* (Unpublished). Introducing vaccination against serogroup B meningococcal disease: An economic and mathematical modelling study of potential impact.

⁹ http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136087064

¹⁰ <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/MeningococcalDisease/EpidemiologicalData/>

¹¹ Viner R *et al* (2012). Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol* 11:9, 774-783.

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Figure 1 – Incidence of invasive meningococcal disease in England and Wales 2002/03 to 2011/12 (data provided by Public Health England)¹²

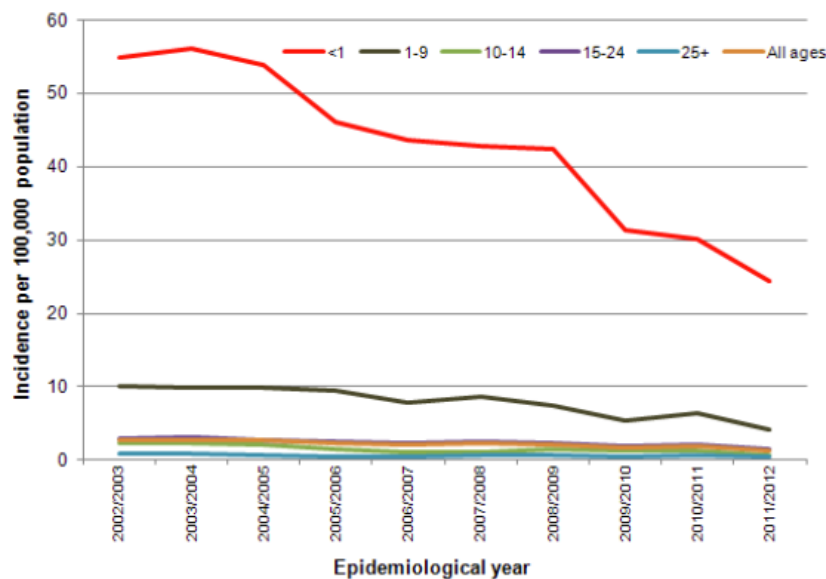
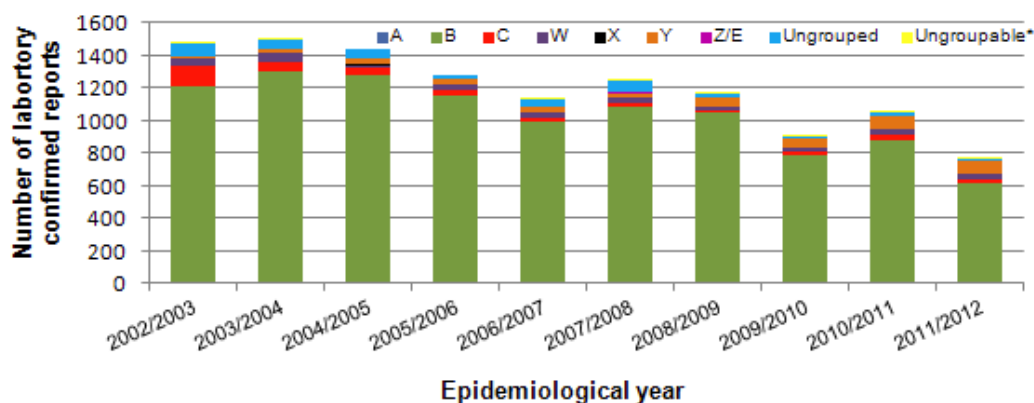


Figure 2 – Invasive meningococcal disease in England and Wales by capsular group 2002/03 to 2011/12 (data provided by Public Health England)¹³



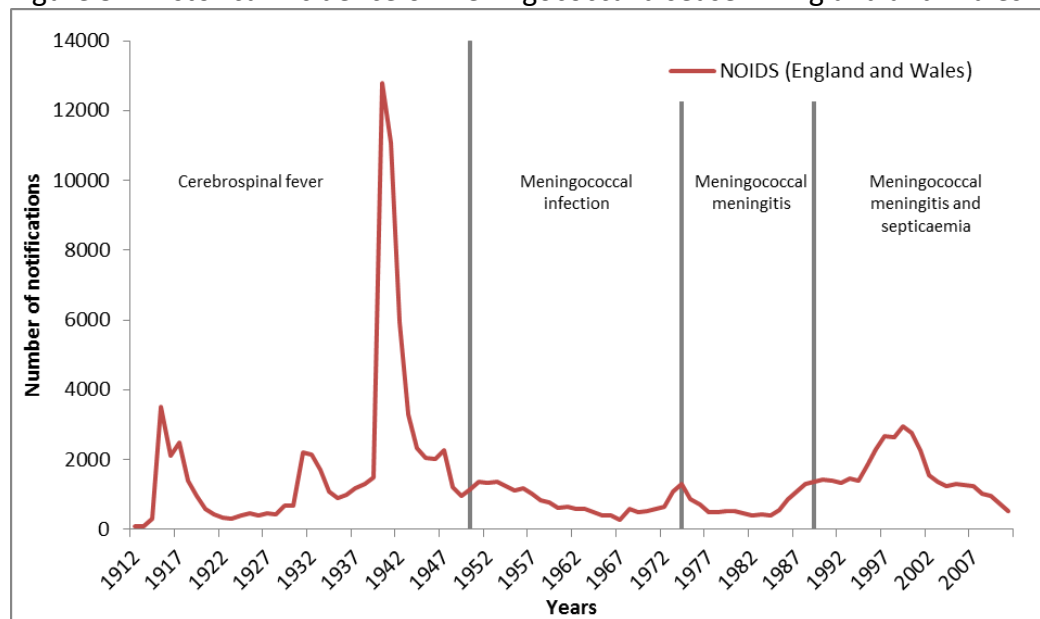
JCVI considered that, although the declining incidence of IMD may continue it was possible the incidence could rise again. Historically the incidence of IMD had fluctuated for reasons that are not well understood. The only long term data on incidence comes from NOIDs data (see Figure 3). Notifications of Infections Disease (NOIDs) data have included both meningitis and septicaemia since 1989 but is also prone to under-reporting. Hospital Episode Statistics (HES) data, which are felt to be more complete, are not available over the very long term, but was used as a basis for the cost-effectiveness model. The Committee agreed that while the future incidence of IMD remains uncertain the final iteration of the model should include a slightly higher incidence of disease based on HES data over a longer period; to better represent the historic fluctuations of the disease.

¹² http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136087064

¹³ http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136087064

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Figure 3 – Historical incidence of meningococcal disease in England and Wales¹⁴



Vaccine Efficacy

JCVI considered that data from clinical trials show Bexsero[®] to be immunogenic in infants, children, adolescents and adults^{15 16 17}. There was however a lack of evidence on vaccine efficacy, since the vaccine had not yet been evaluated in an efficacy trial, and was not being used routinely in any country worldwide. Whilst evidence of effectiveness for one of the four main components of the vaccine (the OMV component) had been demonstrated at 73% during use in an outbreak in New Zealand, efficacy for the remaining components had not yet been studied.

JCVI agreed that the short term vaccine efficacy against disease of 95%, as used in the impact and cost-effectiveness model, was a plausible estimate of efficacy, given the impact of the OMV vaccine used in New Zealand, and immunogenicity of the other components in the vaccine. The Committee were also advised that if efficacy was slightly lower than the estimated value there would be only a modest impact on the cost-effectiveness of Bexsero[®] according to modelling undertaken.

As plausible variation of this parameter had only a limited effect on the cost-effective price of the vaccine, the Committee agreed that changes to vaccine efficacy within plausible confidence limits would not substantially alter the cost-effectiveness of the vaccine.

¹⁴ Christenson *et al* (Unpublished). Introducing vaccination against serogroup B meningococcal disease: An economic and mathematical modelling study of potential impact.

¹⁵ Gossger N *et al* (2012) Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. *JAMA* 307(6):573-82

¹⁶ Santolaya, M.E., *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(9816): p. 617-24. - See more at: <http://www.meningitis.org/menb-vaccine#sthash.cjHsk2SS.dpuf>

¹⁷ Bexsero[®] Summary of Product Characteristics

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Strain coverage

JCVI noted that earlier assessments of strain coverage for Bexsero[®] had been based on the MATS assay; however evidence considered by JCVI in October 2013 indicated the MATS assay underestimated the potential strain coverage of Bexsero[®]. The Committee noted that data on serum bactericidal antibody (SBA) activity, considered the gold standard for in-vitro assessment of a meningococcal vaccines correlate of protection, indicated the strain coverage of Bexsero[®] at 88%.¹⁸ The Committee concluded the best data for the strain coverage of Bexsero[®] would have come from SBA activity, and 88% should be used as the estimate of strain coverage.

JCVI agreed that the best evidence available on vaccine strain coverage was from SBA activity of the vaccine (the correlate of protection in the New Zealand study¹⁹), and that although uncertainty remained regarding the strain coverage, the Committee agreed that changes to this parameter within plausible confidence limits (down to 66% coverage) did not significantly alter the cost-effectiveness of the vaccine.

Duration of protection

JCVI agreed the duration of protection of the vaccine in infants included in the impact and cost-effectiveness model was consistent with the available data, although different antigens were likely to have different durations of protection (based on immunogenicity data)²⁰, although this variability was difficult to capture in an economic analysis. The Committee also noted that although uncertainty remained over how closely immunogenicity data would match duration of effectiveness in the field, the model parameters used for infants were the most plausible, and that variations of duration of protection in infants (set at 18 months) had only a limited impact on the cost-effective price of the vaccine for an infant programme.

The Committee noted that the changing duration of protection in adolescents (set at 10 years) had a significant impact on the cost-effective price, and as there was no evidence available on the duration of protection against both disease and carriage in adolescents there remains considerable uncertainty regarding the cost-effective price associated with an adolescent programme.

Protection against acquisition of carriage

The Committee noted that an independent analysis of data provided to the Committee by Novartis on the impact of Bexsero[®] on the acquisition of nasopharyngeal meningococcal carriage in adolescents²¹, had been completed²². The Committee concluded that the independent evaluation of the Novartis carriage study indicated that the impact of Bexsero[®] on prevention of acquisition of carriage was likely to be less than 30%, but was unlikely to be as low as zero. The Committee agreed that the vaccine probably had a positive impact on

¹⁸ [Frosi et al \(2013\). Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine* 31\(43\):4968-74.](#)

¹⁹ [Kelly C et al \(2007\). A prospective study of the effectiveness of the New Zealand meningococcal B vaccine. *Am. J. Epidemiol* 166\(7\): 817-823.](#)

²⁰ [Snape et al \(2013\). Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. *CMAJ* 185\(15\):E715-24.](#)

²¹ [Read R et al. Impact of a quadrivalent conjugate \(MenACWY-CRM\) or a serogroup B \(4CMenB\) meningococcal vaccine on meningococcal carriage in English university students. Poster abstract 31st annual meeting of the European Society of Paediatric Infectious Disease meeting 2013.](#)

²² Trotter et al (Unpublished)

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

carriage in adolescents but the size of the effect was such that it was not possible to predict accurately what would happen at the population level should the vaccine be used in adolescents. Therefore the Committee considered that considerable uncertainty remained regarding the cost-effectiveness of a routine adolescent programme in the UK. Impact on acquisition of carriage would have a limited impact on the cost-effectiveness of an infant programme as the impact would be driven by direct protection of the individual rather than herd immunity.

Discounting

A number of comments received during the consultation on the interim statement stated that the Committee should use a discounting rate of 1.5% for both costs and benefits in line with NICE Public Health Guidance²³. The Committee agreed that it would consider a 3.5% discounting rate for costs and benefits as the base case since this has been standard practice of the Committee for previous evaluations, according to NICE Health Technology Assessment Guidance²⁴, although it would consider and review the impact of a 1.5% rate for costs and benefits in the Committee's deliberations. The Committee has asked for a working group to be set up to examine and advise the Committee on the most appropriate discounting rate and QALY threshold to be used, which will also consider revised guidance from NICE, expected later in 2014.

Consideration of additional factors associated with implementation of an infant programme

Safety

JCVI considered safety data from clinical trials²⁵ totalling over 6000 participants, and reviewed the European Medicines Agency's (EMA) considerations of this data²⁶. As with any new vaccine or medicine, knowledge of the safety profile of the vaccine is limited to the size of the clinical trials, however the Committee in October 2013 agreed these trials suggested there would be benefits to the vaccinated population. Data from clinical trials suggest that the frequency of fever following routine infant immunisations would be expected to substantially increase if Bexsero[®] was given with other routine infant immunisations, however, concomitant administration of prophylactic paracetamol reduced fever rates without significantly reducing immunogenicity^{27 28}, in contrast to a study of concomitant paracetamol with routine infant immunisations (excluding Bexsero[®])²⁹. Data were too limited to identify rare adverse reactions to the vaccine, however the Committee agreed that the infrastructure and expertise available in the UK would allow the acceptability and safety of the vaccine to be assessed.

²³ <http://www.nice.org.uk/guidance/phg/>

²⁴ <http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf>

²⁵ Bexsero[®] Summary of Product Characteristics

²⁶ http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002333/WC500137883.pdf

²⁷ Prymula R, et al. Presented at: 29th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID); 7-10 June 2011; The Hague, The Netherlands; Poster #631;

²⁸ Bexsero[®] Summary of Product Characteristics

²⁹ Prymula R et al (2009). Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 17;374(9698):1339-50

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Impact of introducing a reactogenic vaccine into the infant programme

JCVI noted evidence of an increased risk of fever when Bexsero[®] was administered with other childhood immunisations in the UK schedule³⁰. Given this, and concerns of the Committee that this could lead to an increase in fever requiring medical attention, or lead to lower uptake of subsequent vaccinations it was agreed there would be a need to educate parents, and healthcare professionals on the potential reactogenicity of provision of Bexsero[®] concomitantly with other infant vaccinations. Good communications would reduce the impact of fever on the health service, and provision of prophylactic paracetamol at the time or shortly after vaccination, with a further two doses every four to six hours thereafter should reduce the likelihood or intensity of fever, without diminishing the immune response³¹.

Removal of the infant dose of meningococcal C vaccine

The Committee considered that as the MenB vaccine Bexsero[®] would likely provide some protection against other serogroups of meningococci, including serogroup C meningococci, that the dose of infant meningococcal C vaccine offered at three months of age could potentially be removed from the schedule. Furthermore, given the currently very good herd protection and the low level of meningococcal C carriage in the population, the need for the 3 month dose is uncertain, and the Committee noted that a number of countries have maintained control of MenC disease without any doses before 12 months of age. However, the Committee agreed that removal of the infant meningococcal C vaccine should only be undertaken once the programme of meningococcal C vaccination in adolescents was established, so that herd protection would be sustained by achieving high levels of antibody in adolescents in the future.

Reduced dose schedules

JCVI noted that immunologically, the age and the interval between doses would have a greater impact on antibody titres than the number of doses given. With infant vaccines, two doses given two months apart were likely to provide a similar antibody response after the second dose, to that provided after the third dose with a 2, 3, 4, 12 month schedule and may prime for a better response to the 12 month booster, as documented for other vaccines. Data available indicated that only minor differences between antibody titres for the recombinant protein components after two doses 2 months apart, as opposed to three doses one month apart, and that there was a small increase in antibody for the OMV component following the third dose³². It was further noted that the vast majority of vaccinations given in the UK were given on time, and the use of a 2, 4, 12 month schedule should provide protection from the second dose prior to the peak of incidence of disease at five months of age. The Committee agreed that evidence, knowledge of the immunology and experience with other vaccines indicated the provision of two doses in infancy at two and four months of age, with a booster dose at 12-13 months of age, would likely be sufficient to provide substantial protection against MenB IMD in infants and toddlers, and

³⁰ [Bexsero[®] Summary of Product Characteristics](#)

³¹ [Prymula R *et al* \(2009\). Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. Lancet. 17;374\(9698\):1339-50](#)

³² Novartis data (Unpublished)

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

agreed that in terms of effectiveness and cost-effectiveness this should be the schedule of choice for the UK.

The Committee further agreed where children attend for routine vaccination at three or four months of age, where they have not previously been offered Bexsero[®], a schedule of three months, four months, with a booster dose at 12-13 (3, 4, 12 schedule); or four months, with a booster dose at 12-13 (4, 12) would be acceptable and could be considered by DH and PHE in considerations of implementation of Bexsero[®] in the UK.

Cost-effectiveness of using Bexsero[®] in the UK immunisation schedule

JCVI considered, of the many scenarios modelled by the team from the University of Bristol, which scenario they considered the most plausible, i.e. which figures for impact against disease, impact against acquisition of carriage, and duration of protection were most likely, given the evidence available, to be closest to real world values.

For an infant programme JCVI agreed that the most plausible scenario included the parameters of 95% efficacy, 88% strain coverage, 18 and 36 month duration of protection after primary and booster doses, and 30% vaccine efficacy against acquisition of carriage. For both 2, 3, 4, 12 month and 2, 4, 12 month schedules, a cost-effective price for the vaccine existed for an infant programme. However, whilst a positive vaccine price existed, indicating cost-effectiveness, (as opposed to a 'negative vaccine price' i.e. where the supplier would have to make payment to the Department Of Health to make the programme cost-effective), the vaccine price was significantly lower than the list price for Bexsero[®].

For an adolescent programme the Committee agreed the most plausible scenario included parameter estimates of 95% efficacy, 88% strain coverage, 120 month duration of protection and 30% protection against acquisition of carriage, and using these parameters, agreed that a positive cost-effective price for the vaccine existed for a two dose adolescent programme. The price was again much lower than the list price for Bexsero[®]. However the Committee agreed there was considerable uncertainty pertaining to these parameters.

Uncertainty

As in the first two iterations of the model, the JCVI noted that the third and final iteration indicated that the cost-effectiveness of using Bexsero in an infant programme in the UK was close to the threshold of cost-effectiveness, with some scenarios modelled demonstrating cost-effectiveness, and some not. The Committee noted that uncertainty remained regarding a number of key parameters associated with the impact of the vaccine in infants and adolescents, including effectiveness against disease, strain coverage and duration of protection against disease, and as each of these factors affected the impact of the vaccine, they also affected the cost-effectiveness of the vaccine.

As in previous deliberations, the JCVI needed to assess not only whether the most plausible scenario given the available evidence was cost-effective, but also whether the level of uncertainty around this scenario meant that the Committee could be reasonably sure the vaccine would be cost-effective.

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

To assess this, the Committee considered a number of alternative scenarios, within the realms of plausibility, where the vaccine parameters were less favourable to the vaccine being cost effective. The Committee in particular considered a scenario where strain coverage was reduced from 88% to 66%, and the protection against acquisition of carriage reduced from 30% to 0%. This assessment followed the methodology for dealing with uncertainty recommended by the Working Group on Uncertainty and set out in the JCVI Code of Practice³³.

For infants this scenario did not indicate a significant risk of substantial adverse impact on the health of the population (i.e. healthcare budget diverted from a more cost-effective NHS intervention) if the vaccine could be procured for a very low price (as compared to the list price). The consensus of the Committee was that whilst uncertainty remained, and whilst in some scenarios the vaccine would not be cost-effective at a positive vaccine price, the results of the final iteration of the cost-effectiveness model indicated that for an infant programme, in the scenarios considered most plausible by the Committee, the vaccine was still cost effective (at a very low positive price) and did not therefore generate a substantial risk of displacing more health benefit (due to the cost of the programme) than it generated.

The Committee noted that considerable uncertainty remained regarding the duration of protection against disease and impact against acquisition of carriage afforded by Bexsero[®] in adolescents. Again, as each of these factors affected the impact of the vaccine, they also affected the cost-effectiveness of the vaccine. The level of uncertainty present in these parameters was considered significant as variance of these parameters within the range of plausible scenarios had a substantial effect on the cost-effectiveness of an adolescent programme, with less favourable scenarios being cost-ineffective. The scenarios considered by the Committee, representing its lower reasonable estimates of strain coverage and vaccine efficacy (95% efficacy, 66% strain coverage and no protection against acquisition of carriage), indicated a substantial risk of displacing more health benefit (due to the cost of the programme) than generated by the programme. The Committee therefore concluded that an adolescent programme, though plausibly cost effective at a suitably low vaccine price, posed too high a risk of producing less overall health benefit than other current health service interventions without further investigation, particularly of the vaccine efficacy against the acquisition of carriage.

Evaluation of the impact of Bexsero[®] in adolescents

JCVI noted that uncertainty regarding the duration of protection provided by Bexsero[®] in adolescents could not be resolved quickly. However, uncertainty around the impact of the vaccine on acquisition of nasopharyngeal meningococcal carriage could be reduced by undertaking a large targeted carriage study in adolescents with the endpoint being impact on carriage of relevant strains associated with invasive disease. The Committee discussed the importance of having a robust estimate of carriage impact in order to determine if there was, or if there definitely was not an impact on carriage.

³³https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/224864/JCVI_Code_of_Practice_revision_2013_-_final.pdf

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Consideration of an infant programme

JCVI noted that following the changes made to the model, as requested by the Committee in October 2013 in response to consultation comments and new evidence, a number of scenarios demonstrated cost-effectiveness at a price significantly lower than the list price for Bexsero[®], although there were no scenarios for an infant programme in which the vaccine was cost-effective at the list price. Variance of key parameters associated with the impact of an infant programme (efficacy, duration of protection and strain coverage) within plausible limits as determined by the Committee, whilst altering the cost-effective vaccine price still resulted in the vaccine being cost-effective.

JCVI noted that scenarios with relatively high strain coverage (88%) and efficacy against carriage (30%) were generally cost-effective for a four dose infant programme at a low vaccine price. In sensitivity analyses examining less favourable scenarios including the lower limits of strain coverage (66%), and without efficacy against carriage, the vaccine could be demonstrated as cost-effective where reduced dose schedules were used and/or an infant dose of MenC vaccine was removed. Adjusting the discounting rate to 1.5% led to an improvement in the cost-effectiveness of the vaccine when compared with the 3.5% rate which has been used as standard by JCVI.

JCVI concluded that with a low vaccine price, the vaccine was likely to be cost-effective in an infant programme even if the strain coverage was lower than expected. The cost-effective price of Bexsero[®] in an infant programme in the UK could be increased with a reduced dose schedule (2+1) and/or removal of an infant MenC dose from the current schedule. The vaccine was not cost-effective in any scenario at the list price for Bexsero[®].

Given the concerns of JCVI regarding uncertainty, and of members regarding the impact that introducing a reactogenic vaccine such as Bexsero[®] could have on the currently very successful infant programme, the Committee agreed that any implementation of Bexsero[®] should closely monitor:

- changes in the molecular epidemiology of MenB in the UK;
- duration of protection of the vaccine in infants;
- medically attended events following vaccination;
- coverage of other infant vaccines.

Conclusion

The rapid and severe nature of IMD, the burden of disease seen in infants and young children, and the value society places upon preventing disease in its youngest members were considered throughout the Committee's deliberations on the use of Bexsero[®] MenB vaccine in the UK. The Committee reaffirmed its position that the burden and severity of IMD in the UK made the need to explore the potential for its prevention through immunisation of vital importance.

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Any assessment of a vaccine to prevent meningococcal meningitis and septicaemia warranted the most rigorous of consideration. Given the level of uncertainty associated with a new vaccine such as Bexsero[®], the complexities associated with modelling the impact of MenB vaccination, and the borderline cost-effectiveness of the vaccine under the currently accepted methodology for assessing cost-effectiveness accepted by Government, the Committee agreed that considerable work had been required in the development of advice and recommendations regarding use of Bexsero[®] in the UK. This work had been absolutely necessary to ensure any programme would increase the overall health of the population

After considering evidence on the meningococcal B vaccine Bexsero[®], the Committee agreed that the vaccine was likely to be effective in preventing a proportion of cases of IMD, and given the likely strain coverage of the vaccine a national implementation in infants in the UK would be likely to prevent a significant number of cases of IMD in that age group. The overall impact of an adolescent vaccination programme in the UK would be highly dependent on the impact and duration of protection of the vaccine against acquisition of meningococcal carriage, which remained highly uncertain.

Comments received during the stakeholder consultation, where appropriate, had been taken into account within the revised impact and cost-effectiveness model. Taking into account comments from stakeholders and revising the evidence base underpinning the model had increased the robustness of the model and demonstrated the importance of consultation by the Committee in the process of evaluating the use of vaccines in the UK. Revisions to the model had generally been positive towards the impact of the vaccine in the UK, and whilst the findings from the revision of the model considered in July could not indicate any cost-effective vaccine price for an infant schedule, plausible parameters for both infant and adolescent vaccination programmes under the revised model demonstrated cost effectiveness, albeit at a low vaccine price.

Taking into account the uncertainties associated with the impact of an infant vaccination programme using Bexsero[®], the Committee concluded that both a programme providing vaccinations at 2, 3, 4, and 12 month (3+1) schedule, and a programme providing vaccinations at 2, 4, and 12 months (2+1) schedule were likely to be both effective and cost-effective, albeit at a price significantly lower price than the list price for Bexsero[®]. Even in the most favourable of scenarios no infant programme could demonstrate cost-effectiveness at the list price for Bexsero[®]. The Committee agreed that a 2+1 schedule would be the preferred schedule for a UK programme.

Whilst a number of plausible scenarios for an adolescent programme demonstrated cost-effectiveness, the degree of uncertainty regarding duration of protection and protection against acquisition of meningococcal carriage meant the Committee was unable to form a recommendation on the use of Bexsero[®] in adolescents, as there was a significant risk such a programme would result in a net loss of health in the population through displacement of other interventions within the health service.

The advice of JCVI is made with reference to the UK immunisation programme and may not necessarily transfer to other epidemiological circumstances

Recommendation

JCVI recommended a programme for use of the MenB vaccine with the NHS immunisation schedule at 2, 4, 12 months of age (2+1) in a carefully planned programme. Given the vaccine only demonstrated cost-effectiveness at a low price, plans for implementation should anticipate a sustainable and cost-effective programme.

The JCVI did not recommend a 5-12 month catch up as it had not been specifically considered in the cost-effectiveness analysis. When assessing 1-4 year old catch-up, in view of the marginal cost-effectiveness of even the base programmes (i.e. without catch up), the JCVI considered that the priority should be the implementation of the primary immunisation programme. JCVI further advised that once a MenB vaccination programme was established in infants, and once the MenC vaccination programmes in adolescents and those entering university were established (programmes which would provide indirect protection of infants against MenC disease) that the infant dose of MenC currently given at three months of age should be removed from the schedule.

JCVI further advised that a targeted carriage study be undertaken in adolescents to assess the impact of Bexsero[®] on the acquisition of meningococcal carriage. Such a study should significantly reduce uncertainty associated with the impact of Bexsero[®] on the acquisition of meningococcal carriage in adolescents, and guide future decision making by the Committee on the impact and cost-effectiveness of an adolescent programme in the UK.

JCVI agreed to review the impact of an infant programme, (should a cost-effective price be agreed on); evidence on the impact of Bexsero[®] on carriage in teenagers; the cost-effectiveness of an adolescent programme; the MenC vaccination programme for teenagers; and the merits of reducing the number of doses of MenC vaccinations provided in infancy, within the next two years.

JCVI

21 March 2014

Notes

1. The Joint Committee on Vaccination and Immunisation (JCVI) is an independent Departmental Expert Committee and a statutory body constituted for the purpose of advising the Secretary of State on *"The provision of vaccination and immunisation services being facilities for the prevention of illness"*.
2. The JCVI's terms of reference as agreed by the UK health departments are - *"To advise UK health departments on immunisations for the prevention of infections and/or disease following due consideration of the evidence on the burden of disease, on vaccine safety and efficacy and on the impact and cost effectiveness of immunisation strategies. To consider and identify factors for the successful and effective implementation of immunisation strategies. To identify important knowledge gaps relating to immunisations or immunisation programmes where further research and/or surveillance should be considered."*