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

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

July 2013

JCVI has asked for comments on this interim position statement from stakeholders who provided evidence to JCVI and its meningococcal sub-committee. JCVI and the sub-committee will consider the responses before finalising this statement.

Background

1. JCVI convened, in 2010, a meningococcal sub-committee to conduct a comprehensive and detailed assessment of the evidence on the meningococcal B vaccines in development and on the impact and cost effectiveness of a range of potential meningococcal B immunisation strategies[1].

2. The sub-committee met on four occasions[2] [3] [4] [5] to review: the evidence received from a call for evidence from interested parties issued in 2010[6], epidemiological analyses from UK health protection organisations and 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. Unpublished data from other sources and published literature were also reviewed.

3. Bexsero®, a four component protein-based meningococcal vaccine manufactured by Novartis was authorised for use by the European Medicines Agency in January 2013[7] [8]. Since no other meningococcal B vaccine has completed clinical development and been authorised, the sub-committee's assessment was focussed on that vaccine.

4. The sub-committee also considered a study on the impact and cost-effectiveness of different vaccination strategies using Bexsero® that was conducted by the University of Bristol and London School of Hygiene and Tropical Medicine. This study, which was developed to take into account advice from the sub-committee, investigated 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 impacts of vaccination, and also a transmission dynamic model to assess the direct and indirect impacts of vaccination.

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[1] Minute of JCVI meeting held on 16 June 2010
[2] Minute of JCVI Meningococcal sub-committee meeting held on 18 February 2011
[3] Minute of JCVI Meningococcal sub-committee meeting held on 13 July 2012
[4] Minute of JCVI Meningococcal sub-committee meeting held on 23 January 2013
[5] Minute of JCVI Meningococcal sub-committee meeting held on 19 April 2013
[6] JCVI meningococcal sub-committee call for evidence - 26 October 2010
[7] European Medicines Agency Press Release on Bexsero®
[8] Bexsero® Summary of Product Characteristics

The study followed the methodology of the National Institute of Health and Care Excellence (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. This independent study has not yet been published but an earlier version of the study (before modification to take into account advice from the sub-committee) has been published[9]. The sub-committee also considered additional sensitivity analyses that looked at higher quality of life loss from IMD produced by the Department of Health's Health Protection Analytical Team that was based on the findings of the independent study. The sub-committee also compared the independent study with an unpublished cost effectiveness study provided by Novartis.

5. JCVI considered, in June 2013, the sub-committee's conclusions and advice on the use of Bexsero® together with the independent study on the impact and cost effectiveness of meningococcal immunisation programmes along with 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 programme[10].

Consideration

Epidemiology of IMD

6. 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, meningococcal serogroup B accounted for around 80% of IMD (see Figure 2)[11] and there were 613 laboratory confirmed cases and 33 deaths from IMD arising from meningococcal serogroup B infection in epidemiological year 2011/12[12]. A UK study suggests that around a tenth of survivors of IMD from meningococcal serogroup B result in 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 disabilities[13]. The epidemiology of IMD is similar in Scotland and Northern Ireland.

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[9] 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

[10] JCVI Minute of 12 June 2013 meeting

[11] http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136087064

[12] http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/MeningococcalDisease/EpidemiologicalData/

[13] 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.

Figure 1 – Incidence of invasive meningococcal disease in England and Wales 2002/03 to 2011/12 (data provided by Public Health England)[14]

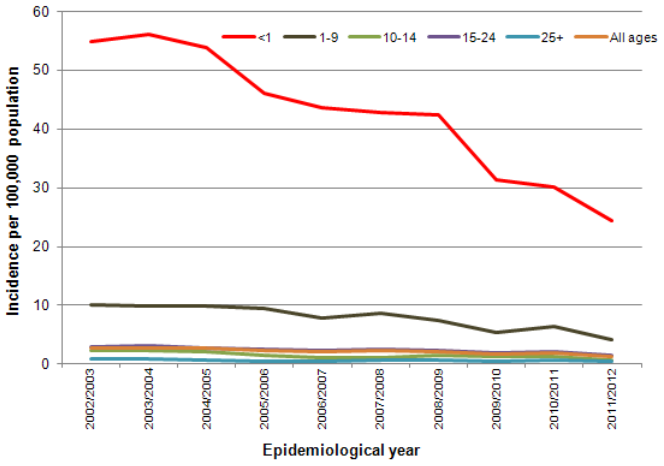
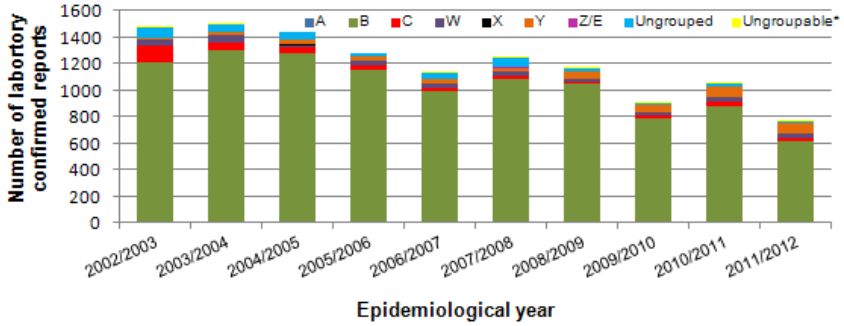


Figure 2 – Invasive meningococcal disease in England and Wales by capsular group 2002/03 to 2011/12 (data provided by Public Health England[15]



7. JCVI considered that, although the declining incidence of IMD may continue, particularly if other public health programmes to reduce the population exposure to cigarette smoke and influenza which are both risk factors for IMD have an impact, it is possible the incidence could rise again. Historically the incidence of IMD had fluctuated for reasons that are not well understood. Thus, the future incidence of IMD remains uncertain.

Vaccine efficacy

8. JCVI considered that data from clinical trials show Bexsero® to be immunogenic in infants, children, adolescents and adults. When given with other routine childhood vaccinations there is little impact on the immunogenicity of Bexsero® or the other vaccines[16] [17]. However, not all the data available relate directly to the new UK routine

[14] http://www.hpa.org.uk/hpr/archives/2013/hpr18-2213.pdf
[15] http://www.hpa.org.uk/hpr/archives/2013/hpr18-2213.pdf
[16] 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
[17] Bexsero® Summary of Product Characteristics

immunisation schedule. Thus the full range of immune responses if Bexsero was incorporated into the UK immunisation schedule has not been completely assessed.

9. JCVI noted that clinical trials show that the antibody responses provided by the primary infant schedule of Bexsero® wane rapidly and differ between the four vaccine components complicating assessment of the duration of protection. Data on the persistence of the antibody responses following subsequent boosting and also from primary toddler or adolescent immunisation are more limited.

10. JCVI noted that the efficacy of Bexsero® against disease has not been established. Whilst there is evidence of efficacy of the Outer Membrane Vesicle (OMV) component of the vaccine in response to an IMD epidemic[18], there are no data on the efficacy of the other components. Efficacy had been assumed using Serum Bacteriocidal Activity (SBA), the usual surrogate for meningococcal vaccine efficacy. A functional antibody assay has been used to predict the effective coverage of the vaccine against meningococcal strains. This assay suggests that Bexsero® could be effective against around three quarters of strains present in the UK, although there is unpublished evidence to suggest this assay may underestimate effective coverage. However, efficacy is likely to depend on the number and level of vaccine antigens expressed by each strain and the antibody levels at the time of exposure. Thus, strain coverage and efficacy could be overestimated given antibody waning, particularly following primary infant immunisations before boosting when the burden of disease is high, but also potentially in the years following toddler or adolescent immunisations.

11. JCVI agreed that the impact of Bexsero® on the acquisition of, or on existing, meningococcal carriage was a key determinant of the indirect population protection that might be provided. However, the committee considered that the evidence available did not support definitive conclusions about the efficacy of Bexsero® against the acquisition of meningococcal carriage, although the vaccine appears to have little, if any, impact on existing carriage[19]. Thus, the potential indirect population protection that might be provided by routine immunisation with or without catch up campaigns cannot be readily assessed.

Vaccine safety

[18] 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.

[19] 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. http://www.abstractserver.com/espid2013/planner/index.php?go=abstract&action=abstract_iplanner&print=0&absno=1472&

12. JCVI noted that data from clinical trials suggest that the frequency of fever following routine infant immunisations would be expected to substantially increase if Bexsero® is given with other routine infant immunisations[20]. However, concomitant administration of prophylactic paracetamol reduces fever rates without significantly reducing immunogenicity[21] [22], in contrast to a study of concomitant paracetamol with routine infant immunisations (excluding Bexsero®)[23].

13. JCVI considered that, although some limited attitudinal research suggested that there would be high parental acceptance of routine meningococcal B immunisation programme[24], the increased fever rates expected if Bexsero® was added to the routine infant immunisation schedule could potentially adversely affect parental acceptance of the routine infant immunisation programme. There may also be the potential for clinicians to misdiagnose fever in infants due to infection, if seen shortly after immunisation. These risks would need to be managed if Bexsero® was routinely used in infants in the UK.

14. Whilst thousands of infants and older children had been given Bexsero®[25], JCVI noted that data are too limited to identify rare reactions to the vaccine.

Impact and cost-effectiveness of vaccination programmes

15. JCVI considered that the study by the University of Bristol and London School of Hygiene and Tropical Medicine was well conducted, was based on appropriate and accepted methodology and had included reasonable assumptions and appropriate sensitivity analyses. The study, therefore, provided a suitable and robust basis for informing immunisation policy. Nevertheless, there is large uncertainty about many key parameters.

16. JCVI noted that the study suggested that, assuming high vaccine efficacy against three quarters of meningococcal strains in the UK, routine infant immunisation with Bexsero® may prevent *directly* around a quarter of cases over the lifetime of each single vaccinated birth cohort. With the addition of catch-up campaigns of increasing size more cases could be prevented. By comparison, a routine toddler immunisation programme may prevent fewer cases. However, the committee concluded that routine infant immunisation is highly unlikely to be cost effective at any vaccine price, based on

[20] Bexsero® Summary of Product Characteristics
[21] 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;
[22] Bexsero® Summary of Product Characteristics
[23] 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
[24] Solutions Research Ltd attitudinal research (unpublished)
[25] Bexsero® Summary of Product Characteristics

the accepted threshold for cost effectiveness used in the UK and on an assessment of the results from a wide range of sensitivity analyses to explore ranges for uncertain parameters including the impact of the vaccine on IMD, the incidence of IMD, and the quality of life losses as well as different discount rates.

17. JCVI noted that the study suggested that routine immunisation of infants and adolescents might reduce *directly and indirectly* the annual number of cases by a total of more than one third to one half in around 10 years depending on assumptions made about vaccine efficacy against acquisition of meningococcal carriage. Disease reductions would occur more quickly if adolescent catch-up campaigns were also introduced. Again, however, the committee concluded that, based on the accepted threshold for cost effectiveness used in the UK and the results of a wide range of sensitivity analyses, routine infant immunisation on its own or combined with adolescent immunisation is highly unlikely to be cost effective at any vaccine price. However, the committee noted that under some scenarios a cost effective price might be established for routine adolescent with or without catch up campaigns if the vaccine has high efficacy against the acquisition of meningococcal carriage, which is highly uncertain. However, reductions in disease would accrue much more slowly from adolescent only immunisation compared with programmes that include routine infant immunisation.

18. JCVI noted that an unpublished cost effectiveness study by Novartis had come to different conclusions. Whilst the study used a similar model and methods to the independent study, there were key differences in a number of important parameters including assumed treatment costs of cases and in the quality of life losses of survivors of IMD. The independent study had based quality of life losses on data from a case-control of the quality of life losses of IMD arising from meningococcal serogroup B[26] considered by the committee to be the best and most relevant evidence available. The Novartis study had assumed a higher incidence of IMD and had based quality of life losses on data extrapolated from studies on IMD including a high proportion of IMD from other serogroups or on other infections or conditions.

Recommendation and advice

19. JCVI concluded that, on the basis of the available evidence, routine infant or toddler immunisation using Bexsero® is highly unlikely to be cost effective at any vaccine price based on the accepted threshold for cost effectiveness used in the UK and could not be recommended. Similarly if the vaccine had little or no impact on the acquisition of meningococcal carriage, adolescent immunisation is also highly unlikely to be cost effective at any vaccine price. However, the efficacy of the vaccine against meningococcal carriage is highly uncertain and under some scenarios routine adolescent

[26] 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.

immunisation might be cost effective. However, current evidence is insufficient to support a recommendation for the introduction of a routine adolescent immunisation programme using Bexsero®.

20. JCVI noted that its assessment had been challenging given that Bexsero® had been authorised in the absence of key data to support an assessment of effectiveness and cost effectiveness. However, JCVI is concerned about the potential adverse impact of its negative recommendation on the future of this vaccine and other meningococcal B vaccines, noting that large uncertainties remain about the potential impact of Bexsero® against IMD. However, only through use of the vaccine in large populations could the impact on the acquisition of carriage and the duration of protection and efficacy of the vaccine against IMD be evaluated and the cost effectiveness of routine immunisation be assessed more precisely.

21. JCVI notes that a population based evaluation of Bexsero® in adolescents is required, as the key uncertainty that influences cost effectiveness is the impact of the vaccine on the acquisition of meningococcal carriage in adolescence. The infrastructure and expertise available in the UK would make the UK an ideal setting for such an evaluation. Evaluation of the vaccine in adolescents would avoid potential adverse impacts on routine infant immunisations. However the impact of routine infant immunisation could also be evaluated in a large cohort, which would enable effectiveness against disease to be assessed relatively quickly. Bexsero® has been authorised for use by the European Medicines Agency who had concluded that the potential benefits of the vaccine are greater than the known risks. Whilst there are uncertainties about the efficacy and, as with any new vaccine or medicine, knowledge of the safety profile of the vaccine was limited to the size of the clinical trials, these trials suggested that there would be benefits to the vaccinated population. The infrastructure and expertise available in the UK would allow the impact on carriage and the impact on IMD, as well as the acceptability and safety of the vaccine to be assessed. Data could be accrued relatively quickly depending on the design of the evaluation and the size, age and number of cohorts offered the vaccine.

22. JCVI also considered the selective vaccination of certain groups and concluded that once Bexsero® is available it should be offered selectively to the same high risk groups for IMD that are offered meningococcal ACWY conjugate vaccine currently (excluding where used as a travel vaccine).[27] Since there are no data on the cost effectiveness of these immunisations, this advice is based on clinical judgement. Bexsero® could also be

[27] The Green Book: Immunisation Against Infections Disease, Chapter 22 – Meningococcal

offered to laboratory workers who are at high risk of occupational exposure to meningococcal serogroup B.

23. JCVI also supports plans for Public Health England to produce guidance on the use of Bexsero® for close contacts of cases in outbreaks of IMD associated with meningococcal serogroup B.