Immunisation against meningococcal B disease for infants aged from two months

Acknowledgement:

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Background

In 2010, the Joint Committee on Vaccination and Immunisation (JCVI)[1] convened a meningococcal sub-committee to conduct a comprehensive and detailed assessment of the evidence on the meningococcal B vaccine development and impact and cost-effectiveness of potential meningococcal B immunisation strategies. In June 2013, the Committee received a request for JCVI to provide a recommendation on the possible introduction of a routine meningococcal B immunisation programme.

Since 2013 the JCVI continually reviewed all the available evidence on the disease epidemiology, vaccine efficacy and safety and cost effectiveness of a meningococcal group B immunisation programme in the UK. In March 2014, the JCVI recommended the introduction of a routine infant meningococcal B immunisation programme following a 2+1 schedule at 2,4 and 12-13 months of age.

What is meningococcal disease?

Meningococcal disease is caused by invasive infection with the bacterium Neisseria meningitidis, also known as the meningococcus. There are 12 identified serogroups of which groups B, C, W and Y were historically the most common in the UK. Since the introduction of the routine MenC vaccination programme, cases of invasive meningococcal disease (IMD) in the UK due to capsular group C have reduced significantly. In 2014, there were 47 confirmed cases of meningococcal disease in Wales, including 36 caused by MenB. Three quarters of all MenB cases in Wales in 2014 occurred in children aged 5 years or younger and more than half were in children aged two years or younger. MenB cases were diagnosed in children in Wales as young as 1 month and peaked at 8 to 12 months of age. Invasive meningococcal disease most commonly presents as either meningitis or septicaemia, or a combination of both.

Meningococci colonise the nasopharynx of humans and are mostly harmless commensals. Between 5% and 11% of adults and up to 25% of adolescents carry the bacteria without any signs or symptoms of the disease. In infants and young children, the carriage rate is low.

The meningococci are transmitted by respiratory aerosols, droplets or by direct contact with the respiratory secretions of someone carrying the bacteria. The incubation period is from two to seven days and the onset of disease ranges from acute with severe and overwhelming features, to insidious with mild prodromal symptoms.

Who does it affect?

Meningococcal disease can affect all age groups, but the rates of disease are highest in children under two years of age. In 2014, 75% of all cases of meningococcal group B disease in Wales occurred in children under 5 years of age. Meningococcal B cases increase from birth, incidence peaks at five months before declining gradually until 24 months. Cases remain low until 12 years of age and then gradually increase to a smaller peak at 18 years before declining again.

Individuals with asplenia, splenic dysfunction or complement disorders are at an increased risk of invasive meningococcal disease and should be immunised in accordance with the schedule for immunisation of individuals with underlying medical conditions; green book chapter 7.

The Meningococcal B immunisation programme

What is the purpose of the programme?

The aim of the routine infant meningococcal B immunisation programme is to reduce the burden and severity of invasive meningococcal disease caused by *Neisseria meningitidis* capsular group B in the UK by protecting those at increased risk of disease.

Who is the vaccine recommended for?

The JCVI recommended the routine immunisation of infants at 2, 4 and 12-13 months of age, following a 2+1 schedule.

Routine cohort

Starting on the 1st September 2015 all infants born on or after the 1st July 2015 will be eligible for the meningococcal B vaccine which will be administered together with the other primary immunisations at 2 months, 4 months and 12-13months.

Catch up cohort

There will also be a catch-up programme for infants attending at age 3 and 4 month for routine immunisations. This will be for infants born from 1st May 2015 to the 30th June 2015. The JCVI agreed that these infants would be offered an altered schedule with the meningococcal B vaccine added to their primary immunisation appointments which they are due to attend from 1st September 2015. Infants born on or after 1 May 2015 presenting for their first, second or third routine primary immunisations from 1st September 2015 are eligible to receive the vaccine as outlined below.

Routine cohort

		Age of infant		
	DOB (born on or after)	**Priming dose**	**Priming dose**	**Booster**
Routine cohort	01/07/2015	8 weeks (2 months)	16 weeks (4 months)	52-56 weeks (12-13 months)

Catch–up cohort eligibility

All eligible children born from 1st May 2015 will be appointed by the child health system.

Dates of birth	Recommended immunisation schedule
*1 May to 30 June 2015.	If third routine primary immunisation appointment at 4 months (16 weeks) is due on or after 1 September then follow this schedule: 4 months and 12-13 months (1+1)
	If second routine primary immunisation appointment at 3 months (12 weeks) is due on or after 1 September then follow this schedule: 3, 4 and 12-13 months (2+1)

*There are a small number of children (DOB 1–7 July and 1– 12 May) who may have already received their primary immunisations before 1 September and these children will be called for their Men B vaccines after 1 September 2015.

Infants born before the 1 May 2015 are not eligible to receive the meningococcal B vaccine.

What is the recommended vaccine for the programme?

Bexsero® is the recommended vaccine for the routine infant immunisation programme and is the **only** market authorised meningococcal B vaccine in the UK.

Bexsero® is a multi-component inactivated vaccine made from three *Neisseria meningitidis* proteins produced by recombinant DNA technology (*Neisseria meningitidis* group B NHBA fusion protein, *Neisseria meningitidis* group B NadA protein, *Neisseria meningitidis* group B fHbp fusion protein) **and** a preparation of *Neisseria meningitidis*

capsular group B outer membrane vesicle (OMV) *Neisseria meningitidis* group B strain NZ98/254).

Bexsero® can be ordered from the Immform website which supply other childhood vaccines.

What are the contraindications for receiving Bexsero®?

There are very few infants who cannot receive meningococcal vaccines. Where there is doubt, appropriate advice should be sought from your local health protection team or immunisation co-ordinator rather than withholding immunisation.

Bexsero® should **not** be administered to those who have had:

1. A confirmed anaphylaxis to a previous dose of the vaccine OR
2. A confirmed anaphylaxis to any constituent or excipients in the vaccine

For the composition and full list of excipients, please refer to the manufacturer's Summary of Product Characteristics (SPCs).

What adverse reactions are commonly associated with the administration of Bexsero®?

In clinical vaccine trials, the most common adverse reactions observed in infants and children under two years of age was a higher rate of fever (≥38°C) when Bexsero® was administered at the same time as other routine childhood vaccines than when Bexsero® was administered alone.

Other most common adverse reactions observed in infants and children (up to the age of 10 years) are tenderness at the injection site (including severe tenderness defined as crying when moving injected limb), rash, swelling or induration at the injection site, irritability, change in feeding/eating, sleepiness and unusual crying.

Bexsero® is a newly licensed vaccine and is subject to additional monitoring under the **black triangle (▼)** labelling scheme by the Medicines and Healthcare Regulatory Agency (MHRA). All suspected adverse reactions should be reported to the MHRA using the Yellow Card scheme .

The manufacturer's Summary of Products Characteristics (SPCs) states infants were at an increased risk of fever when Bexsero® was administered at the same time as other routine childhood vaccines. How common is fever and can it be prevented?

In one clinical trial, fever (≥38^{o}C) was reported in 51% - 62% of infants receiving Bexsero® and routine vaccines administered together, although high fever (≥39^{o}C) was less common (6%-12%).Six of the 1,885 recruited infants attended hospital because of fever within 2 days after vaccination with Bexsero®.

In a subsequent study, 70% of infants receiving Bexsero® had fever ≥38.5 °C at least once in the first 3 days after any primary dose. However, fever was less common (39%) in infants receiving prophylactic paracetamol just before or at the time of vaccination followed by 2 further administrations at 4–6 h intervals by parents/guardians. Of note, only around 5% of infants receiving paracetamol had fever ≥39^{o}C and the frequency of medically attended fever within 3 days of vaccination was less than 2% for any vaccination visit, irrespective of whether the Bexsero® was administered alone or together with the routine vaccinations.

That study was also important because it showed that serological responses to Bexsero® and the routine vaccinations were not affected by administering prophylactic paracetamol at the time of vaccination.

In another vaccine study[2] that did not include Bexsero®, infants receiving three doses of paracetamol (at vaccination and at 6-8 hour intervals) were half as likely to develop any post-vaccination fever, and also half as likely to develop high fever (>39 ^{o}C), compared with infants receiving two later doses of paracetamol (first dose at 6-8 hours after vaccination and another 6-8 hours later). Thus, the greatest benefit in reducing

post-vaccination fever appears to be come from the paracetamol dose give around the time of vaccination.

For the Bexsero® programme, the JCVI has recommended three doses of paracetamol to be given to infants receiving Bexsero® with their routine primary immunisations at 2 and 4 months or as part of the catch up programme at 3 and 4 months.

Guidance around the use of prophylactic paracetamol suspension with Bexsero® vaccine

The JCVI has recommended the use of prophylactic paracetamol at the time of immunisation with Bexsero®. This is because fever has been a common adverse reaction in clinical vaccine trials and there are concerns that an increase in fever could adversely impact on the uptake of future immunisations. It could also increase avoidable demand for medical attention at Emergency Departments, GP practices or Out of Hours Services/ Parents. Healthcare professionals need to be informed and educated about the change in advice regarding the use of prophylactic paracetamol and the reactogencity of Bexsero® when administered at the same time with other routine childhood immunisations to clarify this new recommendation.

Prophylactic use of antipyretics was previously not routinely recommended as there was evidence at that time that antipyretics lowered the immunological response to some vaccines. Additionally, it was felt that a low grade fever was a normal immunological response following immunisation and such a response was an indication that the vaccine was effective. The latter fact remains true. However, the risk of fever greater than 38.0°C when Bexsero® is administered at the same time as other childhood vaccines is greatly increased and there is new evidence that antipyretics do not lower the immune response to other routine childhood vaccines.

For the MenB programme, the JCVI has therefore recommended three doses of paracetamol to be given to infants receiving Bexsero® at age less than 12 months with their routine primary immunisations. In the main infants will receive the first dose of paracetamol (60mg given as 2.5 ml of 120mg/5ml suspension) at the same time as their immunisation or as soon as possible after the vaccines are administered. Parents

should then be advised to give two further 60mg (2.5mls) paracetamol doses at **4-6 hours intervals**. Detailed written instructions will be provided on how to administer paracetamol suspension, the dose that is required and the timing of the doses.

Table: Dosage and timing of infant paracetamol suspension (120mg/5ml) for use after primary MenB vaccinations (usually at two and four months of age)

Age of baby	Dose 1	Dose2	Dose 3
Up to 6 months (usually at 2 and 4 months)	**One 2.5ml (60mg) dose as soon as possible after vaccination**	**One 2.5ml (60mg) dose 4-6 hours after 1st dose**	**One 2.5ml (60mg) dose 4-6 hours after 2nd dose**

For very premature babies (born before 32 weeks gestation), paracetamol should be prescribed according to the infant's weight at the time of vaccination.

Healthcare professionals should provide parents with the meningococcal B vaccine leaflet before their 2 month primary vaccination appointment, for example when the parents register their baby at the practice or when they have a birth visit by the Heath visitor or they attend the 6-8 week check. This will alert parents to the need to buy liquid paracetamol suspension in preparation for the 2 month immunisation appointment.

Practices will be able to order paracetamol suspension sachets and accompanying syringes via ImmForm. The paracetamol will come in a box of 12 sachets with 12 syringes and NHS branded leaflets in English. The leaflets are not those produced by Welsh Government, those will be available by emailing: hplibrary@wales.nhs.uk or telephoning 08456 064050.

Sachet/s of paracetamol can be offered to parents who do not have timely access to over-the-counter paracetamol. The paracetamol leaflet should be provided to the parent or guardian at the time of immunisation. Note the advice to administer a minimum of three doses of paracetamol to infants less than three months of age differs from the information contained in the summary of product characteristics, patient information leaflet and labelling on over the counter paracetamol products, including

the sachets supplied. The recommendation to use a minimum of three doses was made by JCVI and has been endorsed by the Commission on Human Medicines (CHM)[3]. The use of paracetamol for up to 48 hours post immunisation with MenB is supported where it is required to manage post-immunisation fever including in infants

between two and three months old where it is likely that the fever is due to immunisation. This recommendation does not extend to fever at any other time. In all cases if an infant is otherwise unwell parents should be advised to trust their instincts and not delay seeking medical attention. It is hoped that infant paracetamol suspension manufacturers will update product packaging and literature in due course. GPs and independent prescribers can also prescribe infant paracetamol. Most local pharmacies, supermarkets and many local stores stock liquid paracetamol suspension.

What should health professionals advise parents regarding the discrepancy between the paracetamol packaging and patient information leaflet (PiL) advising a maximum of 2 doses of paracetamol post immunisations for infants aged 2 months?

The Commission on Human Medicines (CHM)[3] has been consulted regarding the licensing restriction on Pharmacy (P) and General Sales List (GSL) paracetamol products which advise consulting a GP or pharmacist if more than 2 doses are required for a 2 month old infant post-immunisation. The reason for this licensing is to ensure early diagnosis of systemic bacterial infection. The CHM supported the JCVI recommendations for 3 doses of paracetamol post-immunisation with MenB and supported use of paracetamol for up to 48 hours post immunisations if required to manage post-immunisation fever in 2 month olds. This recommendation is based on the likelihood that fever is due to immunisation, it does not extend to fever at any other time and if the infant is otherwise unwell parents should trust their instincts and not delay seeking medical attention for the infant. Healthcare professionals are reminded that in some circumstances the recommendations regarding vaccines given in the Green Book chapters may differ from those in the Summary of Product Characteristics (SPC) for a particular vaccine. When this occurs, the recommendations in the Green Book are based on current expert advice received from the JCVI and should be followed.

What authorisation do nurses need to supply or administer liquid paracetamol to parents of infants receiving Bexsero®?

Despite liquid infant paracetamol being available to purchase from pharmacists and supermarkets, nurses and midwives can only supply or administer medicines using a recognised process as set out in the Nursing and Midwifery Council's Standards for Medicines Management[4] Nurses should familiarise themselves with these standards.

To enable nursing colleagues to practice in accordance with this standard, Public Health Wales (PHW) will make available a **Homely Remedy Protocol** for the supply of liquid infant paracetamol.

If a nurse assesses it would be helpful to show a parent how to measure the correct dose and administer the infant strength paracetamol, this can be done in the clinic. Each sachet contains 5mls, more than the recommended 2.5ml dose for babies aged under six months. So the correct dose should be measured and given to the baby. Any remaining paracetamol should be thrown away. The parent should be advised to get a further supply of paracetamol to give the second and third doses or if deemed necessary extra sachets to a maximum of three can be given to allow the parent time to get further paracetamol supplies. All doses supplied and administered must be recorded. The Homely Remedy Protocol will include all the relevant information and guidance for the correct supply and administration of paracetamol by a nurse it will be available on the Public Health Wales Vaccine Preventable Disease Programme intranet site.

Does liquid paracetamol need to be administered when children receive their 12-13 month booster dose of Bexsero®?

In clinical vaccine trials, the most common adverse reaction observed in infants and children under two years of age was a high rate of fever (>38°C) when Bexsero® was administered at the same time as other routine childhood vaccines. As a result, the JCVI recommended the use of prophylactic liquid paracetamol when infants receive Bexsero® at

the same time as other routine childhood vaccines such as DTaP/IPV/Hib at 2, 3 and 4 months of age. As these other vaccines are not administered as part of the 12-13 month

booster vaccines, there is no additional requirement to offer liquid paracetamol at the same time.

Can Ibuprofen be offered as an alternative to paracetamol to reduce post-vaccination fever after Bexsero® is administered with other routine vaccines?

In a head-to-head clinical trial of paracetamol versus ibuprofen to reduce post-vaccination fever[2], ibuprofen (two or three doses) did not reduce the rate or intensity of post-vaccination fever compared to the control arm where infants did not receive any anti-pyretic. This finding needs to be validated in further studies but does suggest that paracetamol should be the only recommended anti-pyretic to reduce post-vaccination fever in infants. Ibuprofen should, therefore, not be recommended as an alternative to paracetamol in this instance.

Should parents be worried about fever after vaccination?

Fever after vaccination with or without Bexsero® is common and nearly always mild (<39^{o}C). Fever is a normal and expected response of the immune system against the vaccine antigens and generally not harmful, but parents are often concerned about the risk of febrile convulsions or “fever fits.” Typically, febrile convulsions occur from 6 months to 5 years of age and are very uncommon in younger age groups. In clinical trials involving several thousand infants receiving their routine vaccinations (including Bexsero®), febrile convulsions are very rarely reported. In one of the largest Bexsero® trials, where 1885 infants were recruited and vaccinated at four different visits without paracetamol prophylaxis, only one infant developed a febrile convulsion two days after receiving Bexsero®[5]. In the subsequent study of 364 infants receiving Bexsero® with or without paracetamol[6], there was not a single case of febrile convulsion after any of the four vaccination visits.

What if a baby still has a fever after having had the three doses of paracetamol?

Some infants will still develop fever after vaccination, even after taking paracetamol. If an infant still has a fever after the first three doses of paracetamol but is otherwise well further paracetamol can be given. Always leave at least four hours between doses and never give more than four doses in 24 hours. Parents are advised to keep their child

cool by making sure they don't have too many layers of clothes or blankets on, and to give them plenty of fluids. If a parent is concerned about their baby at any time then parents should trust their instincts and speak to their GP or call NHS Direct Wales 0845 46 47**.** Paracetamol is recommended for the prevention and treatment of fever after immunisation as there is evidence that it is safe and effective. If 48 hours after vaccination a baby still has a fever parents should speak to their GP or call NHS Direct Wales 0845 46 47 for advice*.*

The advice in this question and answer sheet only applies to infants who have had the MenB vaccine. If an infant has a fever at any other time then parents should follow the instructions and dose advice on the product packaging and patient information leaflet.

What happens if the infant spits out the paracetamol suspension?

If the infant spits out or regurgitates at least half of the paracetamol suspension, then an additional age appropriate dose of liquid paracetamol should be administered.

Does liquid paracetamol affect the immune response to the oral rotavirus vaccine?

Ideally the rotavirus and paracetamol should be given at separate times, but the live vaccine virus should not be affected by close sequential administration of paracetamol syrup. A small volume of paracetamol is unlikely to add significantly to the volume or nature of the fluid present in the gut and therefore should not prevent the vaccine virus replicating to levels that provide a stimulus to the immune system*.*

Vaccine eligibility for the routine meningococcal B immunisation programme

Why is the national programme being routinely offered to infants aged 2 months?

Meningococcal B disease can affect all age groups, but the rates of disease are highest in the first two years of life. Cases increase from birth and peak around 5 months before declining. In considering the epidemiological and economic evidence as well as

vaccine safety and efficacy, the JCVI decided to prioritise young infants with the aim of providing optimal protection as early as possible.

How will the programme be delivered?

Bexsero® will be available through the routine immunisation programme from 1st September 2015. Infants attending for their routine primary immunisations at 2, and 4 months of age will be offered meningococcal B vaccine, and during the short initial catch up phase at 3 months of age as well. The vaccination schedule will be dependent on the child's age and eligibility at the start of the programme on the 1st September 2015.

The Child Health Computer system will schedule MenB vaccine at the primary immunisation appointments (2, 3 and 4 months of age) where possible. If MenB is not given at the primary immunisation appointments, the system will continue to call the infants for separate appointments. This means that all eligible infants born from 1st May 2015 will be called for appointments from 1st September 2015 onwards.

How effective is the vaccine

Bexsero® has been shown to be immunogenic in infants and toddlers. Vaccine-induced antibodies have been shown to be bactericidal (i.e. they kill the bacteria) against most meningococcal strains causing invasive disease in the UK. However, as yet there is no

evidence regarding the effectiveness of Bexsero® in preventing meningococcal disease in a population since the vaccine had not been implemented in any country.

A number of countries such as Cuba, Norway and New Zealand have previously used MenB vaccines, derived from outer membrane vesicles (OMVs) of specific MenB strains, causing large outbreaks in their respective

countries. A key limitation of these vaccines however, is that they mainly protect against specific MenB strains and do not provide broad cross-protection against other MenB strains causing invasive disease. In New Zealand, vaccine effectiveness for the OMV component of their vaccine was estimated to be 73%.

The cost-effectiveness model reviewed by the JCVI assumed that 88% of meningococcal B strains causing invasive disease in England would be covered by Bexsero® and the vaccine effectiveness against these strains would be 95%.

How many doses are required to ensure protection?

Clinical trials for Bexero® in infants initially included three doses followed by a booster in the second year of life. Recent studies, however, indicate that two Bexsero® doses given two month apart at 2 and 4 months will induce adequate levels of bactericidal antibodies against meningococcal B in nearly all infants. Vaccine responses will also be boosted after the 12-13 month dose. Vaccine responses in 3 month-olds receiving 2 priming doses a month apart and 4 month-olds receiving a single priming dose may be lower but will be boosted after the 12-13 month dose.

How long does protection last for?

The duration of protection following the recommended Bexsero® schedule has not been clinically established. Following a review of all the available evidence, the JCVI agreed the most plausible duration of protection is 18 months following a two dose primary course and 36 months following the additional booster dose administered at

12-13 months. Bexsero® should, therefore, protect infants and toddlers during their period of highest risk of MenB infection.

Does Bexsero® provide cross protection against other meningococcal serogroups, such as Men A, C, W and Y?

Bexsero® contains surface protein antigens that are highly conserved (present in most strains of meningococcal B) in all meningococci. However,

not all meningococci have all the vaccine antigens on their capsular surface. Although Bexsero® provides broad coverage against most meningococcal B strains causing invasive disease in the UK, it does not protect against all meningococcal B strains. Similarly, it is likely that Bexsero® will protect against some Men A, C, W and Y strains but it is currently not possible to accurately predict what proportion of meningococcal strains belonging to the different capsular groups would be covered by Bexsero®. Studies in this area are currently on-going. In the meantime, children requiring specific

protection against any of these capsular groups (Men A, C, W, Y) should receive the MenACWY conjugate vaccine (e.g. if travelling or if close contact of a confirmed case) and should not be assumed to be protected against these capsular groups even if they have received a complete course of Bexsero®. Infants will still be offered MenC vaccine as part of their routine schedule (3 months and 12-13 month booster).

Can the vaccine be offered to infants outside of the national programme?

Centrally procured stock should only be used for those eligible for immunisation as part of the national programme, as outlined above. Those in clinical risk groups with complement deficiencies or who have an absent or dysfunctional spleen should be immunised in accordance with the schedule for immunisation of individuals with underlying medical conditions; green book chapter 7. The vaccine is also recommended for laboratory workers working with meningococci under normal occupational health arrangements (Green Book Chapter 22).

Vaccine administration

How is Bexsero® administered?

Bexsero® will be supplied as a prefilled syringe in **packs of ten**, without needles, with a volume of 0.5mls. During storage, the contents of the syringe may settle with off-white deposits being noticeable. Before use, the pre-filled syringe must be shaken well so that any observable deposits are thoroughly mixed into the liquid forming a homogenous suspension that should be administered immediately.

The vaccine should not be administered where there are variations in physical appearance (i.e. not a homogenous suspension) or signs of foreign particulate are observed after shaking.

Where is Bexsero administered?

As Bexsero® is a newly licensed vaccine that is subject to additional monitoring under the black triangle labelling scheme by the Medicines and Healthcare Regulatory

Agency (MHRA), it is recommend that Bexsero® be administered intramuscularly (IM) in the **left thigh**, ideally on its own, so that any local reactions can be monitored more accurately and reported to the MHRA using the Yellow Card Scheme. If another vaccine needs to be administered in the same limb, then it must be given at least 2.5cm apart. **The sites at which each vaccine was given should be noted in the individual's health records.**

What is the shelf life of Bexsero®?

Bexsero® has a shelf life of two years when stored in its original packaging in a refrigerator at the recommended temperatures of +2°C and +8°C. Bexsero® should not be frozen. At the start of the programme the Bexsero® being supplied may have a shorter shelf life and expire in April 2016. Practitioners must check the expiry date of all vaccines being administered. It is recommended that health professionals only order what they need for a 2-4 week period rather than over-ordering.

Does Bexsero® contain latex?

Bexsero® will be supplied as a prefilled syringe in **packs of ten**, without needles. Note that the tip cap of the syringe may contain natural rubber latex. Although the risk for developing allergic reactions is very small, healthcare professionals should consider the benefit-risk prior to administering this vaccine to subjects with known history of hypersensitivity to latex if using these needles. For a full list of excipients, healthcare professionals should read the manufacturers Summary of Products Characteristics (SPCs).

Does Bexsero® contain any preservatives such as thiomersal?

No, Bexsero® does not contain thiomersal. For a full list of excipients, healthcare professionals should read the manufacturers Summary of Products Characteristics (SPCs).

Does Bexsero® contain any porcine gelatin?

No, Bexsero® does not contain porcine gelatin. For a full list of excipients, healthcare professionals should read the manufacturer's Summary of Products Characteristics (SPCs).

Should Bexsero® be administered separately to other vaccines?

Bexsero® can be given at the same time as the other vaccines administered as part of the routine childhood immunisation programme, including pneumococcal, measles, mumps and rubella (MMR), diphtheria, tetanus, pertussis, polio and Hib. It is recommend that Bexsero® be given in the **left thigh**, ideally on its own, so that any local reactions can be monitored more accurately. If another vaccine needs to be administered in the same limb, then it must be given at least 2.5cm apart. **The sites at which each vaccine was given should be noted in the individual's health records.**

Can Bexsero® be administered at the same time as MenC or MenACWY vaccines?

Two studies assessing protein-based meningococcal B vaccines given with the MenACWY vaccines reported similar vaccine responses with no significant adverse events. Preliminary results from an on-going, manufacturer-sponsored clinical trial in children receiving the meningococcal B vaccine co-administered with MenC conjugate vaccine in South America do not indicate any safety concerns. Since Bexsero® is a protein-based vaccine and both MenC and MenACWY are conjugate vaccines with no shared antigens, interference with vaccine responses is unlikely.

Therefore, currently available evidence indicates that Bexsero® can be safely co-administered with or at any time interval before or after MenC and MenACWY conjugate vaccines and other conjugate vaccines (pneumococcal, Hib) without affecting the immune response to either vaccines.

Why are infants in the 'catch-up' cohort being offered a different schedule (3, 4 and 12 -13 month or 4 and 12 -13 month) to that recommended for the routine cohort (2, 4 and 12-13 month)?

From the 1 September 2015, children born on or after 1 May 2015 will be offered at least one dose of Bexsero as part of their routine immunisations at 3 and 4 months of age. These children will also receive a booster dose of Bexsero as part of the 12 -13 months booster immunisations.

The aim of this JCVI recommendation is to extend protection to those infants who are most likely to benefit from the vaccine, before reaching an age when they are most at risk of meningococcal B disease, even if immunogenicity data for these modified schedules are limited. Additionally, children receiving a priming dose of Bexsero® in infancy should make a good response to the 12 months booster dose of Bexsero®.

The manufacturer's Summary of Product Characteristics (SPCs) states that infants under six months of age should receive three doses of Bexsero® with a minimum of one month interval in addition to the booster dose at 12-13 months of age. Why is Bexsero® only being recommended as a two dose schedule in infants aged under 6 months?

As yet unpublished findings of a clinical trial have shown that nearly all infants develop bactericidal antibodies against MenB following two doses of Bexsero® given two months apart and this finding formed the basis for the JCVI recommendation for a 2+1 schedule.

Healthcare professionals are reminded that in some circumstances the recommendations regarding vaccines given in the Green Book may differ from those in the Summary of Product Characteristics for a particular vaccine. When this occurs, the recommendations in the Green Book are based on current expert advice received from the JCVI and this advice should be followed.

Should infants aged 4 months on the 1 September 2015 who have already received their 3rd primary vaccine be recalled to receive Bexsero®?

If this does occur for any reason (e.g. Bexsero® was not available in the surgery at the visit or the immunisation nurse omitted the Bexsero® dose at the visit), then the patient should be called back and offered Bexsero® as soon as possible.

Are infants born before the 1 May 2015 going to be offered Bexsero® as part of a catch up programme?

The JCVI did not recommend a catch up programme for infants aged 5-12 months (born before the 1 May 2015) after reviewing the cost-effectiveness model. Since the vaccine was only found to be cost-effective at a very low price, a sustainable approach had to be followed for implementation. As meningococcal disease peaks around 5 months of age before declining, the priority of the meningococcal B immunisation programme is to ensure that Bexsero® is offered routinely to infants who are due to receive their routine primary immunisations on or after the 1 September (those born on or after 1 July 2015) with a limited catch up for those infants born from 1 May 2015 to

30 June 2015) which will provide protection to this most vulnerable group prior to the peak in incidence of disease at 5 months of age.

What should I do if I have inadvertently administered the second dose of Bexsero® at 3 months of age to an infant following the routine schedule (2, 4 and 12-13 months)?

In the event that the second dose of Bexsero® is administered one month earlier than recommended, infants should be offered an additional dose of vaccine at 4 months to ensure protection against meningococcal B disease.

As Bexsero® has been associated with an increase in fever when administered concomitantly with other routine childhood vaccines, infants inadvertently given Bexsero® at 3 months should be given liquid paracetamol as recommended following the 2-month or 4-month Bexsero® vaccination.

What should I do if an infant following the 1+1 catch-up schedule misses their first dose of Bexsero® at 4months?

Eligible infants who do not attend for their routine appointment at 4 months of age and consequently miss the first dose of Bexsero® should be offered the vaccine at the earliest opportunity or at their next visit to the practice. Infants born on or after 1 May 2015 are eligible to receive the Men B vaccine until 2 years of age. These infants should be managed according to the "*vaccination of individuals with uncertain or incomplete immunisation status*" to ensure they are up to date with all immunisations.

What should I do if the vaccine was administered at less than the recommended dose?

In the event that Bexsero® is administered at less than the recommended dose i.e. some of the vaccine is not injected, vaccination will need to be repeated because the dose that the infant received may not be sufficient to evoke a full immune response. Where possible, the dose of Bexsero® should be repeated on the same day or as soon as possible after.

As Bexsero® has been associated with an increase in rates of fever when administered concomitantly with other childhood vaccines, prophylactic paracetamol should be offered with this Bexsero® dose.

In the event that the additional dose of Bexsero® cannot be administered at the same visit or day, arrangements should be made to administer the additional dose as soon as possible, so as not to delay future doses.

Where should I administer Bexsero® if four vaccines need to be administered at the same time, i.e. at 12-13 month booster?

Infants attending for their routine booster immunisations at 12-13 months are likely to receive four vaccines that are required to be administered at the same time. It is recommended that Bexsero® should be administered in the **left thigh,** ideally on its own.

If another vaccine needs to be administered in the same limb, then it must be given at least 2.5cm apart. The sites at which each vaccine was given should be noted in the individual's health records.

What should I do if a parent is concerned about the number of vaccines being administered to their child in one session?

It is understandable that some parents may become concerned about the number of vaccines being administered in one session, particularly at 2 and 12-13 months of age when four vaccines are scheduled to be administered. Whilst these concerns are understandable, parents should be reassured by confident and knowledgeable healthcare professionals that immunisation and protection against harmful diseases at the very earliest opportunity is the absolute priority for their child. Studies have demonstrated that there are no harmful effects from administering multiple vaccines in one session and there is no evidence to support arguments of "overloading" the immune system. From the moment a child is born, they are continually being exposed to a wide number of bacteria and viruses on a daily basis that the immune system is able to cope with, and as a result become stronger[7]. Additionally, administering multiple vaccines in one session is a routine occurrence in most countries around the world with no evidence of harmful effects.

Where can I get further information?

Welsh Health Circular (WHC) 2015 040: Introduction of MenB immunisation for infants available at: http://gov.wales/docs/dhss/publications/150727whc040en.pdf. Accessed 3/8/15

Green Book https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Meningitis Now (charity) https://www.meningitisnow.org/

Meningitis Research Foundation (charity) http://www.meningitis.org/

NHS Immform https://www.immform.dh.gov.uk/ (log in required)

Information resources including leaflets and Q&As, available from NHS Direct Wales http://www.nhsdirect.wales.nhs.uk/immunisations

Information for health professionals – VPDP MenB programme page http://nww.immunisation.wales.nhs.uk/meningococcal-b-infant-vaccine-programme

References

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4. Nursing Midwifery Council: Standards for Medicines Management (2010) assessed June 30th 2015

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7. Centre for Disease Control (CDC) 2012. Frequently Asked Questions about Multiple Vaccinations and the Immune System. [internet] accessed 11 June 2015. http://www.cdc.gov/vaccinesafety/Vaccines/multiplevaccines.html

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