22

Meningococcal

MENINGOCOCCAL MENINGITIS AND SEPTICAEMIA NOTIFIABLE

The disease

Meningococcal disease occurs as a result of a systemic bacterial infection by *Neisseria meningitidis*.

Meningococci are gram-negative diplococci, divided into antigenically distinct capsular groups. They are classified according to characteristics of the polysaccharide capsule into capsular group, and of outer membrane proteins into type and subtype. Further characterisation, undertaken by sequencing several other regions of the chromosomal DNA, defines the sequence type (ST).

There are to date 12 identified capsular groups, A, B, C, E, H, I, K, L, W, X, Y, and Z, of which groups B, C, W and Y were historically the most common in the UK. However, since the introduction of the routine meningococcal C conjugate vaccination programme, cases of invasive meningococcal disease in the UK due to capsular group C have reduced dramatically, with capsular group B accounting for around 80% of cases. Since 2009, capsular group W infections have been forming an increasing proportion of cases.

Meningococci colonise the nasopharynx of humans and are frequently 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 (Christensen *et al*., 2010). It is not fully understood why disease develops in some individuals but not in others. Age, season, smoking, preceding influenza A infection and living in 'closed' or 'semi-closed' communities, such as university halls of residence or military barracks, have been identified as risk factors for disease (Cartwright, 1995).

Transmission is by aerosol, droplets or direct contact with respiratory secretions of someone carrying the organism. Transmission usually requires

either frequent or prolonged close contact. There is a marked seasonal variation in meningococcal disease, with peak levels in the winter months declining to low levels by late summer.

Figure 22.1 The 'glass' test (picture courtesy of Meningitis Research Foundation)

Meningococcal infection most commonly presents as either meningitis or septicaemia, or a combination of both. Less commonly, individuals may present with pneumonia, myocarditis, endocarditis, pericarditis, arthritis, conjunctivitis, urethritis, pharyngitis and cervicitis (Rosenstein *et al*., 2001).

The incubation period is from two to seven days and the onset of disease varies from fulminant with acute and overwhelming features, to insidious with mild prodromal symptoms. Early symptoms and signs are usually malaise, pyrexia and vomiting. Headache, neck stiffness, photophobia, drowsiness or confusion and joint pains may variably occur. In meningococcal septicaemia, a rash may develop, along with signs of advancing shock and isolated limb and/or joint pain. The rash may be non-specific early on but as the disease progresses the rash may become petechial or purpuric and may not blanch. This can readily be confirmed by gentle pressure with a glass (the 'glass test') when the rash can be seen to persist (Figure 22.1). In young infants particularly, the onset may be insidious and the signs may be non-specific without 'classical' features of meningitis.

Health professionals should be alert to the possibility of meningococcal infection in a young child presenting with vomiting, pyrexia and irritability and, if still patent, raised anterior fontanelle tension. Clinical deterioration may be very rapid with poor peripheral perfusion, pallor, tachypnoea, tachycardia and the emergence of the meningococcal rash. In severe cases, patients may present with hypotension or in coma.

The incidence of meningococcal disease is highest in children under five years of age, with a peak incidence in those under one year of age. There is a secondary peak in incidence in young people aged 15 to 19 years of age.

Overall, the case-fatality ratio in the UK fell from an historic average of 10% to 5% by 2011 following the routine conjugate vaccination against capsular group C disease (Ramsay *et al*., 1997; Goldacre *et al*., 2003; Ladhani *et al*., 2012). The case-fatality ratio is higher in individuals with septicaemia than in those with meningitis alone (Stanton *et al*., 2011), increases with age, and is higher in individuals with capsular group C than capsular group B disease (Ramsay et *al*., 1997). Some strains of *N. meningitidis* appear to be associated with higher case fatality ratios, even after controlling for age (Trotter *et al*., 2002; Goldacre *et al*., 2003). Studies in paediatric intensive care settings have indicated that prompt and active management may reduce fatality (Thorburn *et al*., 2001; Booy *et al*., 2001). In those who survive capsular group B infection, up to 36% may develop long-term deficits in physical, cognitive, and psychological functioning, including 9% with major disabling deficits (Viner *et al*., 2012). The most severe long-term complications include hearing loss, severe visual impairment, communication problems, limb amputation(s), seizures and brain damage.

History and epidemiology of the disease

In the UK, large epidemics of meningococcal disease, probably caused by capsular group A infections, coincided with each of the two world wars (Jones, 1995). After the Second World War, disease levels declined from a maximum of over 12,000 notifications of meningococcal disease in England and Wales per year. However, between 1972 and 1975, incidence increased temporarily, associated with a capsular group B serotype 2a strain. In 1985, another hyperendemic period began, associated with increased circulation of a hypervirulent ST32, B15:P1.16 strain. A further hyperendemic period started in 1995–96, associated with an increased proportion of disease due to ST11 capsular group C serotype 2a infection. There was a shift in age distribution towards teenagers and young adults, among whom case fatality rates are particularly high. This period ended with the introduction of MenC vaccination in the UK from November 1999. The annual incidence of invasive

meningococcal disease across all age groups is currently around 2 per 100,000 (Ladhani *et al*., 2012). An increase in indigenous cases of an ST11 capsular group W has been seen in the UK since 2009, and may herald a new hyper-endemic period (Ladhani *et al*., 2015).

Meningococcal disease occurs in all countries. In the 'meningitis belt' of sub-Saharan Africa, the incidence of meningococcal infection rises sharply towards the end of the dry, dusty season when disease spreads rapidly, resulting in large epidemics within very short periods. These are predominantly due to capsular group A, but recent outbreaks have included capsular groups W, X and C. Increasing numbers of countries in sub-Saharan Africa have already introduced Group A meningococcal conjugate vaccine into routine and catch-up vaccination campaigns.

Large epidemics of meningococcal disease have been linked to the annual Hajj pilgrimage to Mecca in Saudi Arabia, resulting in importations into a number of countries, including the UK. These were initially caused by capsular group A infection and immunisation against group A became a requirement for entry to Saudi Arabia. In 2000 and 2001, an increase in capsular group W infections followed the Hajj with a number of cases in UK pilgrims and their families (Hahne *et al*., 2002). Evidence of receipt of quadrivalent vaccine (capsular groups A, C, Y, W) became an entry requirement in 2002.

The development of conjugate meningococcal vaccines

Meningococcal vaccines based solely on the capsular polysaccharide (often called 'plain' polysaccharide vaccines) provide only short-term protection to older children and adults and do not protect infants. In the mid-1990s, therefore meningococcal C (MenC) conjugate vaccines were developed to provide longer-term protection and to be effective in infants. As the rate of meningococcal capsular group C infections continued to rise, the development of the new vaccines was accelerated.

In November 1999, MenC conjugate vaccine was introduced into the UK routine immunisation programme along with a catch-up campaign for older children, adolescents and young adults up to 18 years. In January 2002, the campaign was extended to include adults under 25 years of age.

Following the MenC vaccine campaign, the number of reported and laboratory-confirmed capsular group C cases fell by over 90% in all age groups immunised (Figures 22.2 and 22.3) (Campbell *et al*., 2010; Miller *et al*., 2001; Trotter *et al*., 2004). Cases in other age groups fell by approximately two-thirds as a result of reduced carriage rates (Maiden *et al*., 2002) and reduced risk of exposure (Trotter

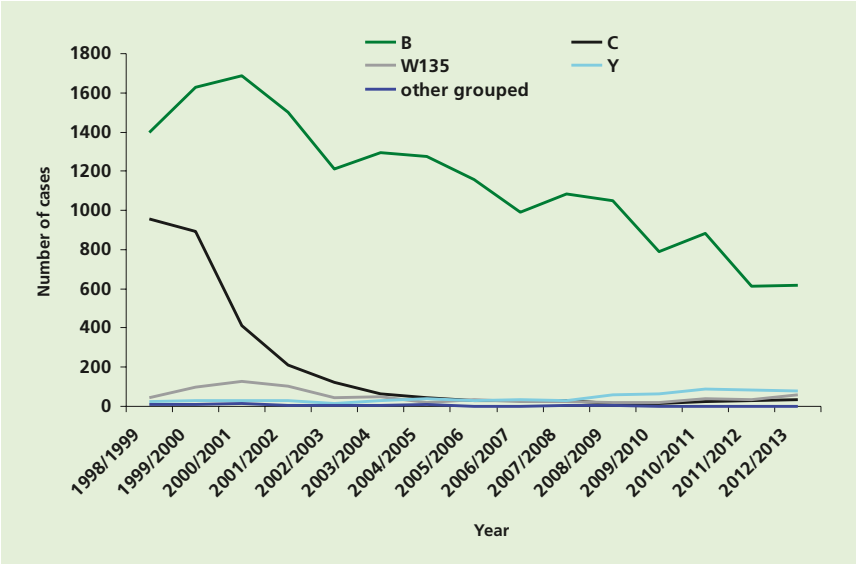

Figure 22.2 Cases of invasive meningococcal disease by epidemiological year, England and Wales 1998-2013. Source PHE Meningococcal Reference Unit Manchester.

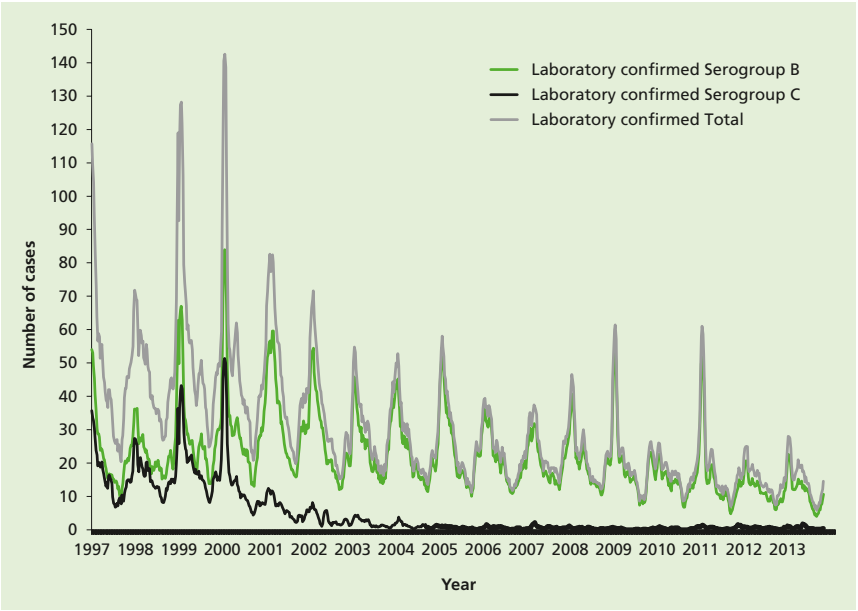

Figure 22.3 Laboratory-confirmed cases of meningococcal disease, England and Wales, five weekly moving averages 1997-2013. Source PHE Meningococcal Reference Unit Manchester.

et al., 2003). This indirect (herd) protection contributed to the number of cases continuing to fall across all age groups and now remaining at very low levels.

In 2006, following studies that showed that protection against meningococcal capsular group C waned during the second year of life (Trotter *et al*., 2004), a booster dose (combined with Hib vaccine as Hib/MenC vaccine) was introduced at one year of age and the infant programme was reduced from three doses (at age 2, 3 and 4 months) to two doses (at age 3 and 4 months).

In 2013, despite continuing excellent disease control, increasing evidence showed that vaccination against meningococcal capsular group C disease in early childhood provides short-term protective immune responses (Borrow *et al*., 2010; Kitchin *et al*., 2009; Perret *et al*., 2010), that vaccination later in childhood provides higher levels of antibodies that persist for longer (Snape *et al*., 2008a), and that meningococcal capsular group C vaccination significantly reduces nasopharyngeal carriage leading to indirect or herd protection (Ramsay *et al*., 2003; Maiden *et al*., 2008). This evidence led the Joint Committee on Vaccination and Immunisation (JCVI) to consider a further amendment to the schedule to sustain long term control by ensuring high antibody levels are maintained in the age groups at which meningococcal carriage becomes more common. An adolescent booster dose at age 13-14 years was added to the schedule.

At the same time, JCVI considered a study that showed a single dose of some varieties of MenC vaccines at three months of age would be sufficient to prime infants against meningococcal capsular group C disease, and provide protection for the first year of life (Findlow *et al*., 2012). Therefore in 2013, the second dose of MenC at 4 months of age was removed from the routine schedule.

Since Men C vaccine was introduced in 1999, overall levels of invasive meningococcal disease have decreased and capsular group B strains have accounted for around 80% of laboratory-confirmed cases submitted to the Public Health England (PHE) Meningococcal Reference Unit and the Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory (SHLMPRL) in this century. An increase in capsular MenW has been noted in England since 2009, with cases almost doubling in 2013 (from 46 to 78) and 2014 (to 119). Based on this increase, in October 2014 JCVI advised replacement of the adolescent MenC dose with quadrivalent ACWY conjugate vaccine. In February 2015, JCVI further advised an emergency catch-up programme with the MenACWY vaccine for children in the higher school years (JCVI, February 2015). In August 2015 a MenACWY catch-up programme began for all children aged 14-18 years of age and those less than 25 years of age attending university for the first time.

In January 2013, a four component meningococcal B (4CMenB) protein vaccine was authorised for use by the European Medicines Agency. In a European phase III trial of 1885 infants, 4CMenB was shown to be immunogenic and produced minimal interference with the response to routine vaccines when given at the same time (Gossger *et al*., 2012). The vaccine may provide protection against infection caused by up to 88% of meningococcal group B strains in England and Wales (Frosi *et al*., 2013).

In 2015 4CMenB was added to the routine UK immunisation schedule, and the MenC conjugate vaccine provided at around 14 years of age was replaced with MenACWY conjugate vaccine.

During 2016 the dose of MenC at 3 months of age is being phased out of the UK national programme, following JCVI advice. The MenC programme introduced in 1999 has been successful in reducing invasive MenC disease to a very small number of cases. The vaccination of adolescents against MenC since 2013 should sustain good herd protection and ensure that the risk to infants remains low. The dose of combined Hib/MenC offered at one year of age will provide good protection to toddlers. In addition, the introduction of Bexsero® (i.e. MenB vaccine) in to the infant programme may provide a degree of protection against some cases of invasive MenC disease.

The meningococcal vaccines

Different types of meningococcal vaccine are licensed; vaccines containing conjugated polysaccharides against serogroups A, W, C and/or Y and a multicomponent protein vaccine. These vaccines are detailed in Table 22.1. All licensed meningococcal vaccines are inactivated, do not contain live organisms and, therefore, cannot cause the diseases against which they protect.

Table 22.1 The meningococcal vaccines

Vaccine type	Protects against	Licensed vaccines
Conjugate vaccine (MenC conjugate)*	Meningococcal capsular group C	NeisVac-C® and Menjugate Kit®
Conjugate vaccine (Hib/MenC)	*Haemophilus influenzae* type b/meningococcal capsular group C	Menitorix®
Quadrivalent conjugate vaccine (MenACWY conjugate)	Meningococcal capsular groups A, C, W and Y	Menveo® and Nimenrix®

Vaccine type	Protects against	Licensed vaccines
Multicomponent protein vaccine (MenB)	Meningococcal capsular group B (may protect against other capsular groups)	Bexsero®

MenC conjugate vaccines

The MenC conjugate vaccines are made from capsular polysaccharide that has been extracted from cultures of capsular group C *Neisseria meningitidis*. The polysaccharide is linked (conjugated) to a carrier protein, according to the manufacturer's method. In the UK, MenC vaccines have been used that have been conjugated with either CRM197 (a non-toxic variant of diphtheria toxin) or tetanus toxoid. The conjugation increases the immunogenicity, especially in young children in whom the plain polysaccharide vaccines are less immunogenic. MenC vaccine confers no protection against other meningococcal capsular groups.

Hib/MenC conjugate vaccine

The Hib/MenC conjugate vaccine is made from capsular polysaccharides of *Haemophilus influenzae* type b and *Neisseria meningitidis* capsular group C, which are both conjugated to tetanus toxoid. The vaccine has been shown to elicit booster responses to both Hib and MenC when given in the second year of life to children who were primed in infancy with Hib and MenC conjugate vaccines.

Quadrivalent (ACWY) conjugate vaccines

The MenACWY conjugate vaccines are made from capsular polysaccharides that have been extracted from cultures of capsular group A, C, W and Y *Neisseria meningitidis*. The polysaccharides are conjugated to a carrier protein. In the UK, MenACWY vaccines are conjugated with either CRM197 or tetanus toxoid. In teenagers, both vaccines produce high levels of bactericidal antibodies to all four serogroups. In particular, response to MenC is good, regardless of the MenC vaccine received as a child (Ishola D, 2015). The response is strictly capsular group-specific and confers no protection against group B organisms..

Although neither of the available vaccines is licensed for use in infants, data show a good antibody response to all capsular groups after two doses of Menveo® conjugate vaccine (Snape *et al*., 2008b; Perrett *et al*., 2009). As there are some data on the use of Menveo® in children below one year of age Menveo® is preferred for use in this age group.

4CMenB protein vaccine (Bexsero®, GSK)

The multicomponent 4CMenB protein vaccine (Bexsero®) is made from three *N. meningitidis* proteins produced by recombinant DNA technology (Neisseria heparin binding antigen (NHBA), Neisserial adhesion A (NadA), factor H binding protein (fHbp)) and a preparation of *N. meningitidis* capsular group B outer membrane vesicles (OMV). The 4CMenB vaccine is immunogenic in young infants (Findlow *et al*., 2010) and adolescents (Santolaya *et al*., 2012) and is licensed for use from two months of age. Laboratory-based studies suggest that 4CMenB may protect against up to 88% of circulating meningogoccal B strains in England and Wales (Frosi *et al*., 2013), but its effectiveness in preventing disease in a population has yet to be established. 4CMenB may also protect against infection by capsular groups other than group B.

Storage

Vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness of vaccines may be impaired if not stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents. For further information on storage see **Chapter 3**.

Presentation

MenC conjugate

The MenC conjugate vaccine is available either as a lyophilised powder for reconstitution with a diluent or as a suspension in a syringe. After reconstitution of the lyophilised suspension, the vaccine must be used within one hour.

Discard any vaccine that is unused one hour following reconstitution. Note: the diluent must not be frozen.

Hib/MenC conjugate

Hib/MenC is supplied as a vial of white powder and 0.5ml of solvent in a pre-filled syringe. The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe to the vial containing the powder. After addition of the solvent, the mixture should be shaken well until the powder is completely dissolved. After reconstitution, the vaccine should be administered promptly or allowed to stand between +2˚ and +8˚ and be used within 24 hours.

Quadrivalent (ACWY) conjugate vaccine

Menveo is supplied as a powder in a vial and 0.5ml solution in a pre-filled syringe. The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe (containing MenCWY solution) to the vial containing the powder (MenA). Nimenrix is supplied as a powder in a vial (MenACWY) and 0.5ml solvent in a pre-filled syringe. The vaccine must be reconstituted by adding the entire contents of the pre-filled syringe to the vial containing the powder. After reconstitution of either vaccine, the entire 0.5ml should be drawn up into the syringe and used immediately, but Menveo® is stable at or below 25°C for up to eight hours, and chemical and physical in-use stability has been demonstrated for eight hours at 30°C for Nimenrix®.

4CMenB protein vaccine

4CMenB protein vaccine is supplied as a white opalescent liquid suspension (0.5ml) in a pre-filled syringe (single pack size) for injection. One dose (0.5ml) contains 50 micrograms each of NHBA, NadA and fHbp and 25 micrograms of OMV.

Dosage and schedule

See Table 22.2 in the 'Recommendations for the routine use of the meningococcal vaccines' section below.

For information on use of meningococcal vaccines in children and adults with asplenia, splenic dysfunction or complement disorders and in the management of suspected cases and contacts see the relevant sections below and **Chapter 7**.

Administration

All meningococcal-containing vaccines are given intramuscularly into the upper arm or anterolateral thigh. This is to reduce the risk of localised reactions, which are more common when the vaccine is given subcutaneously (Mark *et al*., 1999; Zuckerman, 2000; Diggle *et al*., 2000). However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding. When administering 4CMenB vaccine, it is important to note the information on fever and the administration of paracetamol (see 'Adverse reactions' section below).

Meningococcal vaccines can be given at the same time as other vaccines such as pneumococcal, measles, mumps and rubella (MMR), diphtheria, tetanus, pertussis, polio and Hib. The vaccines should be given at a separate site, preferably in a separate limb. If given in the same limb, they should be given at

least 2.5cm apart (American Academy of Pediatrics, 2006). The site at which each vaccine is given should be noted in the child's clinical record.

Disposal

For disposal of equipment used for vaccination, including used vials, ampoules, syringes or partially discharged vaccines please see Chapter 3.

Recommendations for the routine use of meningococcal vaccines

The objective of the routine immunisation programme is to protect directly or indirectly those at greatest risk of meningococcal disease.

Immunisation schedule

The routine immunisation schedule, as revised in 2016, is set out in Table 22.2.

Table 22.2 Meningococcal routine vaccination schedule*

Age	Primary/Booster	Dose
Two months	Primary**	One dose – 4CMenB vaccine†
Four months	Primary**	One dose – 4CMenB vaccine†
One year	Primary (MenC) & Booster (Hib)	One dose - Hib/MenC conjugate vaccine
	Booster	One dose – 4CMenB vaccine
Around 14 years	Booster	One dose - MenACWY conjugate vaccine

† Prophylactic paracetamol is advised where 4CMenB is administered to infants concomitantly with other routine vaccinations at 2 and 4 months – see 'Adverse Reactions' section below

* The 12 week old dose of MenC is being phased out of the routine programme during 2016.

** Although the summary of product characteristics for 4CMenB states that three doses should be given in those less than one year of age, the Joint Committee on Vaccination and Immunisation have advised that the provision of two doses of 4CMenB 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

Individuals with unknown or incomplete vaccination histories

When a child born in the UK presents with an inadequate immunisation history, every effort should be made to clarify what immunisations they may have had (see Chapter 11). Children coming to the UK who have a history of immunisation in their country of origin may not have been offered protection

with all the antigens currently used in the UK, and they may not have received any meningococcal-containing vaccines.

http://apps.who.int/immunization_monitoring/globalsummary/schedules

Children coming from developing countries, from areas of conflict, or from hard-to-reach population groups may not have been fully immunised. Where there is no reliable history of previous immunisation, it should be assumed that they are unimmunised and the full UK recommendations should be followed (see **Chapter 11**).

Infants younger than 12 months should receive the first dose of 4CMenB and a second dose of 4CMenB two months later. They should also receive the one year old Hib/MenC dose and 4CMenB booster, ensuring at least a two month interval between the 4CMenB doses.

Children born after June 30th 2015 aged one year to less than two years who received less than 2 doses in the first year of life should receive two additional doses of 4CMenB at least two months apart.

Children aged one year to less than ten years should receive a single dose of a MenC containing vaccine. Since single MenC will no longer be supplied for the UK programme, combined Hib/MenC vaccine should be used.

Additional information is available at **https://www.gov.uk/government/publications/vaccination-of-individuals-with-uncertain-or-incomplete-immunisation-status**

Children and young adults aged 10 years to less than 25 years (including students up to 25 years attending university for the first time) may also be eligible, or will shortly become eligible, for the teenage MenACWY conjugate vaccine. Those in this group who have never received a MenC-containing vaccine should be offered a single dose of the MenACWY conjugate vaccine. No further vaccination is then required.

Children and adults with asplenia, splenic dysfunction or complement disorders (including those on complement inhibitor treatment)

Children and adults with asplenia or splenic dysfunction may be at increased risk of invasive meningococcal infection. Such individuals, irrespective of age or interval from splenectomy, may have a sub-optimal response to the vaccine (Balmer *et al*., 2004). Children and adults with complement disorders (Figueroa *et al*., 1991), or on Eculizumab therapy (a humanized monoclonal

antibody that inhibits the terminal complement pathway), may be at increased risk of invasive meningococcal infection.

Given the increased risk, additional vaccinations against meningococcal disease are advised for individuals with asplenia or splenic dysfunction or when a complement disorder is diagnosed depending on age and vaccination history.

Meningococcal vaccination schedule for children and adults with asplenia, splenic dysfunction or complement disorders

A practical schedule for immunising individuals at increased risk of meningococcal disease is summarised in **Chapter 7,** depending on the age at which their at-risk condition is diagnosed. These at-risk individuals may require additional doses of meningococcal vaccines (Hib/MenC, Men ACWY and 4CMenB).

Where an opportunity arises, and depending on the individual patient's circumstances, children and adults who have never received 4CMenB or MenACWY conjugate vaccine should be offered these vaccines.

Individuals who are to receive Eculizumab therapy should be vaccinated at least two weeks prior to commencement of therapy (Summary of Product Characteristics for Soliris®, Alexion Europe, 2012). This advice applies to all newly diagnosed patients.

Reinforcing immunisation for children and adults with asplenia, splenic dysfunction or complement disorders

Meningococcal ACWY conjugate vaccine.

Booster doses of MenACWY conjugate vaccine in at-risk individuals are currently not recommended because the need for, and the timing of, boosters has not yet been determined.

Meningococcal B vaccine.

The need for, and the timing of, a booster dose of 4CMenB vaccine in at-risk individuals has not yet been determined.

Individuals who are travelling or going to reside abroad

All travellers should undergo a careful risk assessment that takes into account their itinerary, duration of stay and planned activities. In some areas of the world, the risk of acquiring meningococcal infection, particularly of developing capsular group A disease, is much higher than in the UK. Individuals who are particularly at risk are visitors who live or travel 'rough', such as backpackers,

and those living or working with local people. Large epidemics of both capsular group A and W meningococcal infection have occurred in association with Hajj pilgrimages, and proof of vaccination against A, C, W and Y capsular groups is now a visa entry requirement for pilgrims and seasonal workers travelling to Saudi Arabia.

Epidemics, mainly of capsular group A and more recently capsular group W infections, occur unpredictably throughout tropical Africa but particularly in the savannah during the dry season (December to June). Immunisation is recommended for long-stay or high-risk visitors to sub-Saharan Africa, for example, those who will be living or working closely with local people, or those who are backpacking.

From time to time, outbreaks of meningococcal infection may be reported from other parts of the world. Where such outbreaks are shown to be due to vaccine-preventable capsular groups, vaccination may be recommended for certain travellers to the affected areas.

Country-specific recommendations and information on the global epidemiology of meningococcal disease can be found on the following websites:

www.nathnac.org

www.travax.nhs.uk

Note: MenC conjugate vaccine protects against capsular group C disease only. Individuals travelling abroad (see above) should be immunised with an appropriate quadrivalent (ACWY) vaccine, even if they have previously received the MenC conjugate vaccine. There are currently no recommendations for 4CMenB vaccination for individuals who are travelling or going to reside abroad.

Table 22.3 Recommendations for the use of quadrivalent meningococcal ACWY vaccines for travel

Age	ACWY schedule
Birth to less than one year*	• First dose of 0.5ml • Second dose of 0.5ml one month after the first dose.
From one year of age (including adults)	• Single dose of 0.5ml

* If an infant has already had two MenC vaccinations then two MenACWY conjugate vaccines should also be given.

Contraindications

There are very few individuals who cannot receive meningococcal vaccines. When there is doubt, appropriate advice should be sought from a consultant paediatrician, immunisation co-ordinator or consultant in communicable disease control, rather than withhold immunisation. The vaccines should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of the vaccine, or
- a confirmed anaphylactic reaction to any constituent or excipient of the vaccine.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have recovered fully. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

Pregnancy and breast-feeding

Meningococcal vaccines may be given to pregnant women when clinically indicated. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated virus or bacterial vaccines or toxoids (Granoff *et al*., 2008). In cases where meningococcal immunisation has been inadvertently given in pregnancy, there has been no evidence of harm to the foetus.

Premature infants

It is important that premature infants have their immunisations at the appropriate chronological age, according to the schedule. The occurrence of apnoea following vaccination is especially increased in infants who were born very prematurely.

Very premature infants (born $\leq$ 28 weeks of gestation) who are in hospital should have respiratory monitoring for 48-72 hrs when given their first immunisation, particularly those with a previous history of respiratory immaturity. If the child has apnoea, bradycardia or desaturations after the first immunisation, the second immunisation should also be given in hospital, with respiratory monitoring for 48-72 hrs (Ohlsson *et al*., 2004; Pfister *et al*., 2004; Schulzke *et al*., 2005; Pourcyrous *et al*., 2007; Klein *et al*., 2008).

As the benefit of immunisation is high in this group of infants, immunisation should not be withheld or delayed.

Immunosuppression and HIV infection

Individuals with immunosuppression and human immunodeficiency virus (HIV) infection (regardless of CD4 count) should be given meningococcal vaccines in accordance with the routine schedule. These individuals may not make a full antibody response. Re-immunisation should be considered after treatment is finished and recovery has occurred. Specialist advice may be required.

Further guidance for the immunisation of HIV-infected individuals is provided by the Royal College of Paediatrics and Child Health (RCPCH; **http://www.rcpch.ac.uk/**), the British HIV Association (BHIVA; **http://www.bhiva.org/vaccination-guidelines.aspx**) and the Children's HIV Association (CHIVA; **http://www.chiva.org.uk/guidelines/immunisation/**).

Adverse reactions

MenC conjugate vaccine

Pain, tenderness, swelling or redness at the injection site and mild fevers are common in all age groups. In infants and toddlers, crying, irritability, drowsiness, impaired sleep, reduced eating, diarrhoea and vomiting are commonly seen. In older children and adults, headaches, myalgia and drowsiness may be seen.

Neurological reactions such as dizziness, febrile/afebrile seizures, faints, numbness and hypotonia following MenC conjugate vaccination are very rare.

Hib/MenC conjugate

Mild side effects such as irritability, loss of appetite, pain, swelling or redness at the site of the injection and slightly raised temperature commonly occur. Less commonly crying, diarrhoea, vomiting, atopic dermatitis, malaise and fever over 39.5˚C have been reported.

Quadrivalent (ACWY) conjugate vaccine

For Menveo®, very common or common reported reactions included injection site reactions including pain, erythema, induration and pruritus. Other very common or common reactions include headache, nausea, rash and malaise. Reports of all adverse reactions can be found in the Summary of Product Characteristics for Menveo® (GSK, accessed 15/07/2016).

For Nimenrix®, very common or common reported reactions included injection site reactions including pain, erythema, and swelling. Other very common or common reactions include irritability, drowsiness, headache, nausea, and loss of appetite. Reports of all adverse reactions can be found in the Summary of Product Characteristics for Nimenrix® (Pfizer, accessed 15/07/2016).

4CMenB vaccine

For 4CMenB (Bexsero®), the most common local and systemic adverse reactions observed in adolescents and adults were pain at the injection site, malaise and headache. In infants and children up to ten years of age, injection site reactions, fever (≥38oC) and irritability were very commonly seen. Diarrhoea and vomiting, eating disorders, sleepiness, unusual crying and the development of a rash were commonly or very commonly seen in this age group. Reports of all adverse reactions can be found in the Summary of Product Characteristics for Bexsero® (GSK, 2013).

In infants and children under two years of age, fever ≥38°C (occasionally ≥39°C) was more common when 4CMenB was administered at the same time as routine vaccines (see **Chapter 11**) than when 4CMenB was given alone. The fever peaks at around 6 hours and has usually gone by 48 hours after vaccination. Prior to the introduction of 4CMenB, prophylactic paracetamol around the time of vaccination was not routinely recommended for preventing post-vaccination fever (see **Chapter 8**) because of concerns that it may lower antibody responses to some vaccines (Prymula *et al*., 2009); although this reduction is unlikely to be clinically significant (Das *et al*., 2014). The immunogenicity of both Bexsero® and the other routine vaccines in infants is not affected by giving paracetamol when such vaccines are co-administered with 4CMenB. (Prymula *et al*., 2011), and paracetamol has been shown to reduce fever and other symptoms associated with vaccination (Prymula *et al*., 2011, Das *et al*., 2014). JCVI have recommended, therefore, that paracetamol should be given prophylactically when 4CMenB is given with the routine vaccines in infants under one year of age. A 2.5ml dose of liquid paracetamol (infant paracetamol 120mg/5ml) should be given orally as soon as possible after vaccination, followed by a second 2.5 ml dose after 4-6 hours and a third 2.5 ml dose 4-6 hours after the second dose. Should fever persist following the third dose and provided that the child appears otherwise well, additional doses of paracetamol may be administered at intervals of four to six hours for up to 48 hours. Parents should be advised to seek medical advice if their child is noticeably unwell with a fever present, or if the fever occurs at other times. Ibuprofen appears to be less effective than paracetamol at controlling fever following vaccination and is not therefore recommended (Das *et al*., 2014).

Surveillance following use of 4CMenB in Quebec (INSPQ July 2014) and the UK has not identified any serious or unexpected health problems associated with use of the vaccine; however, because it is a newly licensed vaccine 4CMenB (Bexsero®) is subject to additional monitoring under black triangle labelling (see 'Reporting adverse events' below).

Reporting adverse events

Anyone can report a suspected adverse reaction to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (**www.yellowcard.gov.uk**).

All suspected adverse reactions to vaccines occurring in children or in individuals of any age after vaccination with vaccines labelled with a black triangle (▼), should be reported to the MHRA using the Yellow Card scheme. Serious suspected adverse reactions to vaccines in adults should be reported through the Yellow Card scheme.

Management of suspected cases and contacts

Current recommendations from NICE are that children and young people with suspected bacterial meningitis without non-blanching rash should be transferred directly to secondary care without giving parenteral antibiotics. If urgent transfer to hospital is not possible (for example, in remote locations or because of adverse weather conditions), antibiotics should be administered to children and young people with suspected bacterial meningitis.

For suspected meningococcal disease (fever with non-blanching rash or meningococcal septicaemia) parenteral antibiotics (intramuscular or intravenous benzylpenicillin) should be given at the earliest opportunity, either in primary or secondary care, but urgent transfer to hospital should not be delayed in order to give the parenteral antibiotics.

http://guidance.nice.org.uk/CG102/NICEGuidance/pdf/English

https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis

Management of contacts

For public health management of contacts of cases and outbreaks, advice must be sought from the local health protection team. Household contacts of cases of meningococcal infection are at increased risk of developing the disease. This risk is highest in the first seven days following onset in the index case

but persists for at least four weeks. Immediate risk can be reduced by the administration of antibiotic prophylaxis to the whole contact group.

For prophylaxis, the use of single dose ciprofloxacin is now recommended in preference to rifampicin, particularly because it is a single dose and is readily available in high street pharmacies. Ciprofloxacin as a single dose of 500mg may be given for adults (250mg for children aged five to 12 years and 125mg for those aged one month to four years). Alternative options are discussed at **https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis.**

For confirmed or probable MenC infection, a MenC-containing conjugate vaccine should be offered to all close contacts (of all ages) who were previously not immunised, partially immunised or vaccinated more than one year previously with a MenC conjugate containing vaccine.

For confirmed capsular group A, W or Y infections, vaccination with a MenACWY conjugate vaccine should be offered to all close contacts of any age (two doses one month apart if aged under one year; one dose in older individuals) who were previously not immunised or vaccinated more than one year previously with MenACWY conjugate vaccine.

Hib/MenC, MenACWY and/or 4CMenB vaccine should also be offered according to the recommended national schedule to any eligible unimmunised index cases. This policy ensures that persons in this age group are given equivalent protection to their age-matched immunised peers.

The 4CMenB vaccine is currently not routinely recommended for household contacts of an index case or for contacts in an educational setting. The decision to offer any meningococcal vaccine should not delay the administration of antibiotic chemoprophylaxis, which is the single most important intervention against further cases of meningococcal disease.

Any case provides an opportunity to check the vaccine status of the index case and contacts, and to ensure that eligible individuals have been fully immunised according to the UK schedule.

Management of meningococcal clusters and outbreaks

In addition to sporadic cases, outbreaks of meningococcal infections can occur particularly in closed or semi-closed communities such as schools, military establishments and universities. Advice on the management of such outbreaks should be obtained from the local Health Protection Team (HPT).

In a meningococcal cluster or outbreak, meningococcal vaccination with the appropriate meningococcal vaccine should be considered for the same group that would receive antibiotic chemoprophylaxis. For meningococcal B clusters, 4CMenB (Bexsero®) may be considered unless additional typing suggests that the cluster strain is not caused by a vaccine- preventable meningococcal B strain. Additional advice on the use of 4CMenB (Bexsero®) in this setting can be accessed here:

https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis

Advice on the use of meningococcal vaccines in outbreaks is available from: Public Health England, Colindale (Tel: 020 8200 6868), Health Protection Scotland (Tel: 0141 300 1100) and the Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory (Tel: 0141 201 8659).

Please contact the Immunisation Department at Public Health England Colindale if you experience any delay in obtaining meningococcal vaccines for household contacts or in case of an outbreak.

Supplies

Centrally purchased vaccines for the NHS as part of the national immunisation programme can only be ordered via ImmForm. Vaccines for use as part of the national childhood immunisation programme are provided free of charge. **Vaccines for private prescriptions, occupational health use or travel are NOT provided free of charge and should be ordered from the manufacturers**. Further information about ImmForm is available at **https://www.gov.uk/government/collections/immform**, from the ImmForm helpdesk at **helpdesk@immform.org.uk** or Tel: 0844 376 0040. For further information about vaccines available via ImmForm, please see ImmForm Helpsheet 13.

In Northern Ireland, supplies should be obtained under the normal childhood vaccines distribution arrangements, details of which are available by contacting the Regional Pharmaceutical Procurement Service on 028 9442 4089.

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Procurement, Commissioning & Facilities of NHS National Services Scotland (Tel: 0131 275 6725).

4CMenB, MenC/Hib and at least one MenACWY vaccine from the list below will be available at any one time:

- Bexsero® – (4CMenB) manufactured by GlaxoSmithKline
- Menitorix® – (Hib/MenC) manufactured by GlaxoSmithKline
- Menveo® – (MenACWY) manufactured by GlaxoSmithKline
- Nimenrix® – (MenACWY) manufactured by Pfizer

Vaccines for use outside of national programmes should be ordered directly from manufacturers:

- Bexsero® (4CMenB)) – manufactured by GlaxoSmithKline (Tel: 0808 100 9997)
- Menitorix® (Hib/MenC conjugate vaccine) – manufactured by GlaxoSmithKline (Tel: 0808 100 9997)
- Menjugate® (MenC conjugate vaccine) – manufactured by GlaxoSmithKline (Tel: 0808 100 9997)
- Menveo® (Quadrivalent conjugate ACWY vaccine) – manufactured by GlaxoSmithKline (Tel: 0808 100 9997)
- NeisVac-C® (Men C conjugate vaccine) – manufactured by Pfizer (01304 616 161)
- Nimenrix® (Quadrivalent conjugate ACWY vaccine) – manufactured by Pfizer (01304 616 161)

Vaccine for the national immunisation programme should not be used for the vaccination of contacts of confirmed cases and in outbreaks of MenACWY infection. Vaccine should be ordered from the manufacturers.

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