

09

Meningococcal Infection

Group C vaccine introduced 2000

NOTIFIABLE

Introduction

Meningococcal infection is the spectrum of disease caused by *Neisseria meningitidis* and includes meningitis, septicaemia and, less commonly, other invasive infections such as septic arthritis or endophthalmitis. The meningococci are gram-negative diplococci and are divided into at least 13 antigenically distinct serogroups; most disease-associated strains belong to serogroups A, B, C, Y or W₁₃₅. In Ireland serogroup B and C strains accounted for over 99% of all invasive disease prior to the introduction of the serogroup C conjugate vaccine in 2000.

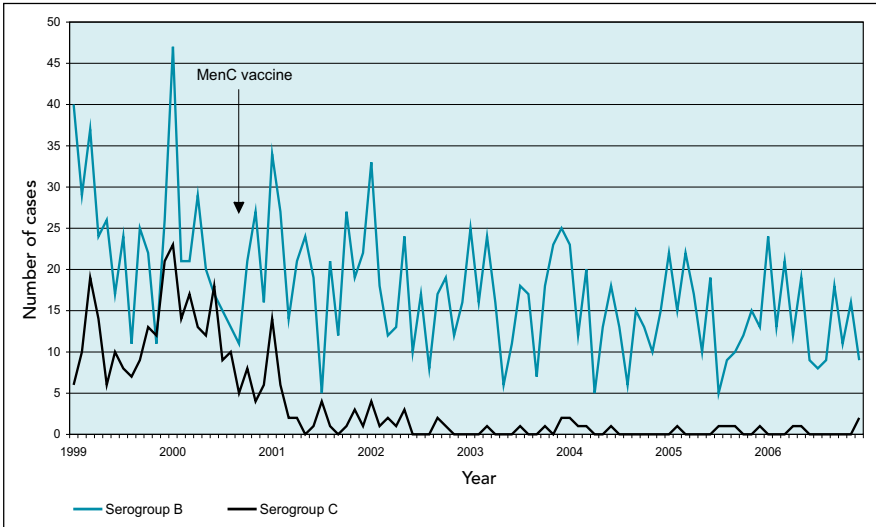
The significance of the meningococcus as a pathogen lies in the potential severity of the illness, the absence of effective vaccines against all individual meningococcal serogroups, the unique ability of the organism to cause outbreaks or epidemics, and the intense public anxiety that follows a case or outbreak. In Ireland the majority of cases of meningococcal infection are sporadic.

Epidemiology

N. meningitidis is a human-only pathogen and is carried in the nasopharynx. Overall approximately 10% of the population are asymptomatic carriers. Carriage is uncommon in infancy and early childhood with peak carriage rates (up to 25%) occurring in the 15-19 year age group. Transmission occurs from person-to-person by aerosol, respiratory droplets or direct mucosal contact with respiratory secretions of a person carrying the organism. Naturally acquired serum bactericidal antibodies to *N. meningitidis* result from carriage, the duration of immunity induced is unknown.

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Figure 9.1 Notifications of serogroup B and serogroup C meningococcal infection in Ireland, 1999-2006. Source: HPSC



A small minority of individuals who pick up *N. meningitidis* develop invasive infection after an incubation period which is typically 2-3 days. The reasons why invasive infection develops in some individuals but not in others are unclear. Factors that have been identified as increasing the risk of invasive infection include active or passive smoking, a preceding severe respiratory tract infection particularly influenza A, and living in closed or semi-closed communities such as military barracks or halls of residence. Individuals with late complement component (C5-C9), C3 or properdin deficiencies, or those with functional or anatomic asplenia, have an increased risk of invasive and/or recurrent meningococcal disease.

Invasive meningococcal disease occurs in all countries worldwide. The infection is endemic in Northern Europe, with a background incidence of 2-3 culture confirmed cases per 100,000. In Ireland the infection shows a seasonal variation, the majority of cases occurring in winter and early spring. Periodic upsurges in meningococcal activity resulting in hyperendemic disease occur, associated with increased circulation of distinct subtypes and/or a hypervirulent strain or strains.

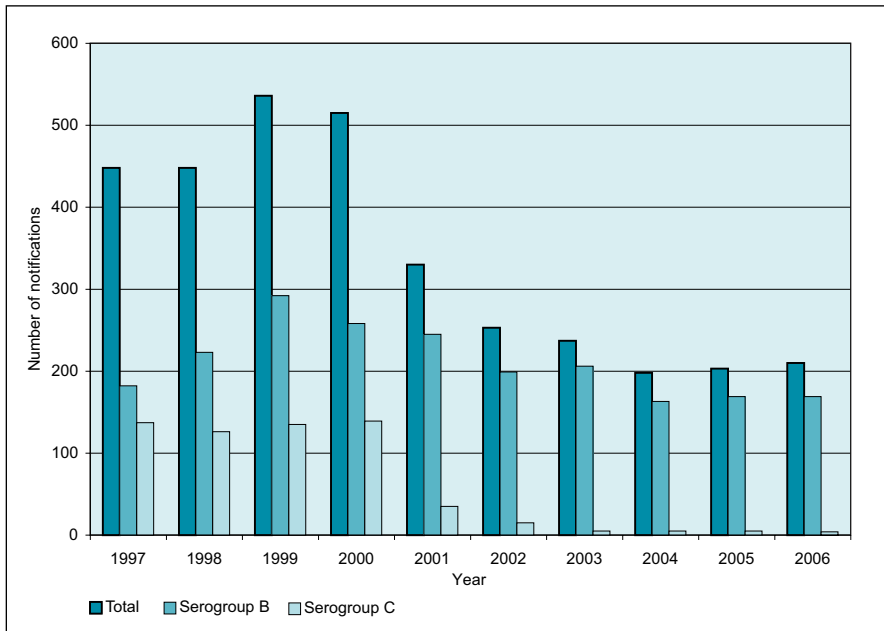
There have been many large epidemics of meningococcal disease following introduction and spread of hypervirulent strains. Epidemic disease is characterised by an increased case-attack rate and altered age distribution, with increased numbers of cases seen in adolescents

and adults. Examples include serogroup A epidemics in England and Wales that coincided with each of the two world wars, and large epidemics involving serogroup A or serogroup W₁₃₅ strains have occurred in association with the annual pilgrimage (Hajj) to Mecca, Kingdom of Saudi Arabia, with importation into other countries by returning pilgrims.

However, in the last 100 years, the highest burden of disease has been in the so-called 'meningitis belt' of sub-Saharan Africa, due mainly to serogroup A or less commonly, serogroup W₁₃₅ with attack rates of up to 1/1,000 and reported mortality rates of up to 40%. Epidemic disease with distinct serogroup B strains has also occurred, including a large epidemic in Norway in the 1970s and in New Zealand in the last 10 years.

Invasive meningococcal disease may occur at any age but is most common in endemic countries, in infancy and early childhood, with a second smaller peak of incidence in adolescents and young adults. In Ireland, the overall case-fatality rate is less than 5%. Serogroup C infection is typically associated with higher morbidity and mortality rates in adolescents and young adults than in other age groups. Overall, the mortality rates are higher in individuals with septicaemia than in those

Figure 9.2 Number of invasive meningococcal disease notifications in Ireland, 1997-2006. Source: HPSC



with meningitis alone. Survivors may have permanent morbidity including skin scarring, digit and/or limb amputation, seizures, hearing loss, and brain damage.

Impact of *N. meningitidis* serogroup C conjugate vaccine in Ireland

Since the introduction of the *N. meningitidis* serogroup C conjugate (MenC) vaccine into the Irish schedule in 2000, the incidence of serogroup C disease has shown a 96% reduction, from 132 culture and/or PCR confirmed cases in 1999 to 3 culture and/or PCR confirmed cases in 2006 (Figure 9.1 and Figure 9.2). In the same period the number of culture and/or PCR confirmed cases of serogroup B disease fell from 285 in 1999 to 161 in 2006.

Effects of meningococcal disease

The onset of disease may be fulminant, with abrupt onset of fever, prostration, shock, a rapidly progressing purpuric rash and death; or it may be insidious, with a mild upper respiratory prodrome of 2 or 3 days. In an infant or young child the common early symptoms (reluctance to feed, trivial fever and irritability) are non-specific. Clinical recognition of meningococcal disease in the initial phase of the illness is problematic. The patient's skin may appear blotchy or pale. A typical non-blanching petechial or purpuric rash may be present with meningococcal septicaemia; however, the rash may be very scanty and may initially be erythematous.

One review of the course of illness in children prior to admission to hospital found that most had only non-specific symptoms in the first 4-6 hours, with the classic features of haemorrhagic rash, meningism and impaired consciousness developing later (median onset 13-22 hours). In contrast, early symptoms of sepsis (leg pains, cold hands and feet, abnormal skin colour) were present in 72% at a median time of 8 hours. The signs and symptoms of meningococcal meningitis are indistinguishable from the signs and symptoms of bacterial meningitis caused by other pathogens, with the exception of the rash, which may be present in some 40% of patients.

Management of suspected cases, contacts, carriers and outbreaks

A Initial management of suspected cases

Primary care

In view of the often rapid progression and high mortality rate of meningococcal disease, early treatment of suspected cases with penicillin

may be life-saving. It is recommended that GPs carry supplies of this drug in an emergency bag.

Recommended dosage of Benzylpenicillin

Adults and children >10 years	1,200 mg
Children 1-9 years	600 mg
Children <1 year	300 mg

This should be given intravenously when possible. It can be given by the intramuscular route in shocked patients but is not as effective.

Penicillin should not be given if there is a history of penicillin anaphylaxis (which is extremely rare) and patients should go to hospital as quickly as possible.

Hospital care

Each acute hospital should have readily available guidelines in place for the management of suspected invasive meningococcal disease.

Advice should be sought from the local Department of Public Health for management of suspected outbreaks. The most up-to-date information on management of contacts is available from Departments of Public Health.

B Chemoprophylaxis

Close contacts are at increased risk of developing infection. This risk is highest in the first 7 days following onset of symptoms in the index case, and falls during the following weeks. Chemoprophylaxis should be given as soon as possible after identification of the index case, but can be given up to 1 month later if a contact is not immediately identified or traced. The aims of chemoprophylaxis are to eliminate carriage from recently colonised susceptible individuals in the period before invasive disease may develop, and to reduce spread of the organism.

The following persons should be given prophylaxis:

- 1 The index case, as soon as the patient can tolerate oral medication, unless treatment was with cefotaxime or ceftriaxone
- 2 Those who in 7 days prior to the onset of illness of the index case
 - shared living or sleeping accommodation with the patient; including child-minders and baby-sitters
 - had mouth kissing contact with the patient

- were in the same nursery/crèche as the patient, where the nature of nursery/crèche contact is similar to that for household contacts. This includes adult carers.
- 3 HCWs (including those present at autopsy) who did not wear a (surgical) mask and whose mouth or nose was directly exposed to infectious airborne droplets or secretions within one metre of a probable or confirmed case of meningococcal disease, who has not received at least 24 hours appropriate antibiotic treatment. *HCWs should wear surgical masks when in close contact with an infectious case for the first 24 hours after the initiation of effective antimicrobial treatment.*
 - 4 Chemoprophylaxis is not necessary for classmates of an index case unless a number of cases occur during the same term:
 - If two or more cases of infection with the same strain occur in one class all class members and staff should receive prophylaxis
 - If the cases occur in different classes, management is more difficult but should be guided by such considerations as
 - o the interval between the cases
 - o the size of the contact group
 - o the carriage rate in the school
 - o whether the cases are due to a vaccine-preventable strain
 - o the degree of public concern, particularly if a death has occurred
 - o the incidence of the disease in the wider community.*In such situations management should be discussed with a relevant Specialist.*
 - 5 Special consideration is needed when an index case has attended a house party in the preceding 7 days, especially if pre-school children were present. If chemoprophylaxis is appropriate it should be given to all attendees, both adults and children.
 - 6 Special consideration should be given to situations in which there is greater than usual interaction between members of the extended family and an index case, particularly where overcrowding or adverse environmental living conditions exist.
 - 7 Ideally chemoprophylaxis should be given to all contacts as soon as possible after notification of the index case. However, it can be given up to a month after identification of an index case, as carriage may persist for a long period.

It is not recommended that prophylaxis be given routinely to passengers on public transport, e.g. bus, train, where an index case has been identified.

Prophylactic antibiotics

Rifampicin

This is the drug of choice, and should be given promptly and preferably within 24 hours of diagnosis of the index case.

All close contacts should be advised that infection can occur even if prophylaxis is given. This is because the antibiotic may not be effective if the contact is incubating disease, or because the contact may become recolonised and then develop the disease. Contacts should be advised to seek medical advice should symptoms develop.

Dose of Rifampicin

Children 0-12 months	5 mg/kg 12 hourly for 2 days
Children 1-12 years	10 mg/kg 12 hourly for 2 days
Children over 12 years & adults	600 mg 12 hourly for 2 days

Side-effects

Rifampicin recipients should be informed about the following possible side-effects:

- interference with contraceptive pill
- interference with anticoagulants
- red coloration of urine, sweat and tears
- permanent discolouration of soft contact lenses

Precautions and contraindications to Rifampicin

Anaphylaxis to a previous dose, severe liver disease and pregnancy.

Alternative prophylaxis

- Ceftriaxone as a single intramuscular dose (250 mg in adults, 125 mg in children under 12 years).
- Although not licensed for this purpose a single dose of ciprofloxacin (500 mg orally for adults) has been shown to be effective.

Pregnancy

While no drug can be regarded as absolutely safe in pregnancy, harmful effects on the foetus have not been documented in relation to use of ceftriaxone.

C Meningococcal vaccine

Contacts of a case of infection with a vaccine-preventable strain should be immunised with the appropriate vaccine (see below). The aim of immunisation is to prevent late secondary cases.

(a) Meningococcal serogroup C conjugate vaccine (MenC)

The serogroup specific polysaccharide antigen is attached to a carrier protein. The conjugated vaccines induce a T-cell dependent memory response from 2 months of age.

Dose and route of administration

The dose at all ages is 0.5 ml, given by intramuscular injection in the anterolateral thigh or the deltoid region.

In patients with thrombocytopenia or bleeding disorders, MenC vaccine may be given subcutaneously (see Chapter 2).

Indications

Primary schedule

Infants under 12 months require 2 doses, generally at 4 and 6 months, with a booster in the second year of life. Those over 12 months need only 1 dose. The need for a later booster, e.g. in adolescence, has not yet been defined.

Contacts of cases

Close contacts of cases of meningococcal infection have an increased risk of developing the disease in subsequent weeks. If results of typing indicate a serogroup C strain, MenC vaccine should be given to all previously unimmunised close contacts (of all ages), in addition to chemoprophylaxis. Close contacts who are only partially immunised should complete the course of vaccine. Children who have not received a dose of MenC vaccine over 1 year of age, should be offered a booster.

Index Cases

If the index case has been previously vaccinated, a booster dose of MenC vaccine is recommended although recurrent serogroup C disease is rare.

MenC vaccine should also be offered to any unimmunised index cases (whatever the serogroup) under the age of 23 years. This policy ensures that persons in this age group are given equivalent protection to their age-matched immunised peers.

Local outbreaks

Immunisation has been shown to be effective in controlling outbreaks in institutions (e.g. schools) and communities, reducing the incidence of infection.

Meningococcal serogroup C vaccine has no role in the management of outbreaks of non-serogroup C infection.

Children and adults with asplenia or splenic dysfunction

Children and adults with asplenia or splenic dysfunction are believed to be at increased risk of invasive meningococcal disease. However, these individuals may have a sub-optimal response to meningococcal vaccines.

- These children, if under 1 year of age, should be immunised in accordance with the routine schedule.
- Children over 1 year of age, and adults, should be immunised with 2 doses of MenC vaccine (Hib/MenC if available), administered 2 months apart.
- Those who have been fully immunised as part of the routine infant immunisation programme and who subsequently have a splenectomy or develop splenic dysfunction, should be given an additional dose of MenC vaccine (usually as Hib/MenC).
- If travelling to a country where there is an increased incidence of serogroup A, W₁₃₅ or Y meningococcal disease, such individuals should be immunised with the quadrivalent (ACW₁₃₅Y) polysaccharide vaccine (see below). Note: When the quadrivalent conjugated polysaccharide ACW₁₃₅Y vaccine becomes available, this should be administered instead of the polysaccharide vaccine.

Contraindications

Anaphylactic reaction to a preceding dose or any of the constituents, including meningococcal serogroup C polysaccharide, or the carrier protein (either diphtheria toxoid or the CRM197 carrier protein is the carrier protein contained in the currently available MenC vaccines, and in Hib vaccine).

Precautions

Acute severe febrile illness, defer until recovery.

Pregnancy: There is no evidence of risk from immunising pregnant women or those who are breast-feeding, with inactivated viral or bacterial vaccines or with toxoids. Hence, MenC vaccine may be given when there is a high risk of the individual developing the disease.

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Adverse reactions

Local: Injection site reactions may occur, are generally mild and last for approximately 24-48 hours.

General: Generalised reactions are rare.

(b) Plain polysaccharide (PS) meningococcal vaccine

Quadrivalent A,C,W₁₃₅,Y meningococcal PS vaccine is effective against serogroup A C W₁₃₅ and Y meningococci. Immunity develops in more than 90% of recipients within 5-7 days of a single injection. However, young children respond less well than adults, with little response to the Group C polysaccharide before 24 months. Infants respond to serogroup A, polysaccharide from 2 months of age. However, the protection induced is short-lived.

Dose and route of administration

Primary immunisation

Those aged 2 months to 2 years of age. The primary course consists of 2 doses each of 0.5 ml, with an inter-dose interval of 3 months.

Children over 2 years and adults

A single dose of 0.5 ml is given by intramuscular injection.

Booster dose of vaccine

For those at continued risk, a reinforcing dose should be given every five years. Children who were immunised under the age of 5 years should receive an initial booster after 2-3 years if at ongoing risk.

Indications

Travel

ACW₁₃₅Y polysaccharide vaccine is indicated for immunisation of long-stay and high-risk travellers to areas where epidemics or hyperendemic disease with serogroup A, C or W₁₃₅ infection occur.

High-risk travellers are those who live or work with local people, and those who live or travel 'rough'. At present this recommendation includes travel to sub-Saharan Africa and the Kingdom of Saudi Arabia (for the latter, ACW₁₃₅Y vaccination is now a visa entry requirement).

From time to time, meningococcal disease outbreaks occur in various parts of the world. Where such outbreaks are due to vaccine-preventable strains, vaccination may be recommended for some groups of travellers to the affected areas. The advice of an appropriate Specialist should be sought.

Note: Visa entry requirements should be checked in good time prior to travel to individual countries.

Individuals with deficiencies in the complement pathway or properdin deficiency

Congenital complement deficiencies are rare. However, there is a strong association with susceptibility to meningococcal disease and deficiencies in the early complement components (C1, C4, C2 but especially C3) and the late lytic components (C5 – C9) of the complement pathway. C2 deficiency is the most common familial complement deficiency detected in Ireland.

- Individuals with C3 defects are at risk of severe infection with encapsulated bacteria including *N. meningitidis*.
- Meningococcal disease in individuals with deficiencies of late complement components (C5-C8) is almost always caused by serogroup W₁₃₅ and Y (serogroups B and C are less common).
- Recurrent meningococcal disease is typical in persons with C5-C8 deficiencies.

Individuals who have had recurrent meningococcal infection should be tested for complement deficiency; investigations should ideally be performed some weeks following infection.

Properdin deficiency is a very rare X-linked defect. Screening for properdin deficiency should be considered when there is a family history of meningococcal disease occurring in accordance with an X-linked pattern (many males affected).

Those individuals who are identified as having deficiencies of any complement component, or properdin deficiencies, should be immunised with the available meningococcal vaccines.

- These children, if under 1 year of age, should be immunised against *N. meningitidis* serogroup C in accordance with the routine schedule.
- Children over 1 year of age, and adults, should be immunised with 2 doses of MenC vaccine, administered 2 months apart.
- Those who have been fully immunised as part of the routine infant immunisation programme and who are subsequently found to have complement or properdin deficiency should be given an additional dose of MenC vaccine
- The quadrivalent polysaccharide ACW₁₃₅Y vaccine may be administered to those individuals in these groups who are over 2 years of age, and should be administered no less than 2 months after the final dose of MenC vaccine.

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Contacts of cases

For confirmed serogroup A infection, immunisation with quadrivalent (A,C,W₁₃₅,Y) polysaccharide vaccine should be offered to all close contacts over 2 months of age. For confirmed infections with serogroups W₁₃₅ or Y, all close contacts over 2 years of age should be offered quadrivalent (A,C,W₁₃₅,Y) polysaccharide vaccine.

Contraindications

Anaphylactic reaction to a preceding dose or any of the constituents.

Precautions

- 1 Severe reaction to a previous dose
- 2 Acute severe febrile illness, defer until recovery.

Adverse reactions

Local: Injection site reactions occur in approximately 10% of recipients and last for approximately 24-48 hours.

General: Generalised reactions are rare although pyrexia occurs more frequently in young children than in adults.

Pregnancy and breast-feeding. Meningococcal vaccines may be given to pregnant women when clinically indicated. There is no evidence that it is harmful to vaccinate pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or with toxoids.

Serogroup B vaccines

The serogroup B capsule is weakly immunogenic and also contains antigens that may cross-react with human neurological tissue. Hence it has not thus far been possible to develop serogroup B vaccines based on the capsule. In response to an epidemic of infection with a single serogroup B strain, a strain specific outer membrane vesicle (OMV) vaccine was developed in Norway. This vaccine did not go into general use because the epidemic came to an end as the vaccine became available.

The OMV technology was subsequently exploited to develop additional specific serogroup B vaccines, which have been successfully utilised to combat epidemic serogroup B disease in Cuba and New Zealand. Each of these 'designer' vaccines targets antigens that are specific to an individual strain and will not induce cross-protection against other serogroup B strains. In recent years throughout northern Europe,

including Ireland, many different serogroup B strains have been associated with disease. The Norwegian and Cuban strains are not found in Ireland and the New Zealand serogroup B vaccine would only give limited protection.

There is no available vaccine effective against the different serogroup B organisms circulating in Northern Europe, including Ireland.

Bibliography

American Academy of Pediatrics (2006). Report of the Committee on Infectious Diseases, *The Red Book 2006*, 27th ed. Elk Grove Village, IL:

Cartwright K (1995). Meningococcal carriage and disease. In: Cartwright K (ed.) *Meningococcal Disease*: pp 115-46. John Wiley & Sons; Chichester, UK.

Davison KL, Ramsay ME, Crowcroft NS, Lieftucht A, Kaczmarek E, Trotter CL, Gungabissoon U, Begg NT (2002). Estimating the burden of serogroup C meningococcal disease in England and Wales. *Commun Dis Public Health* 3:213-9.

Department of Health UK (2006). Immunisation against Infectious Disease (The Green Book). 3rd ed. London: The Stationery Office.

Goldschneider I, Gotschlich EC, Artenstein MS (1969). Human immunity to the meningococcus. II. Development of natural immunity. *J Exp Med* 129:1327-48.

Granoff DM, Feavers IM, Borrow R (2004). Meningococcal vaccines. In: Plotkin SA and Orenstein WA (eds.) *Vaccines*. 4th ed. WB Saunders Company, Philadelphia, pp 959-88,

Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, Harnden A, Mant D, Levin M (2006). Clinical recognition of meningococcal disease in children and adolescents. *Lancet*; 367:397-403.