

# 25

## Pneumococcal

### PNEUMOCOCCAL MENINGITIS NOTIFIABLE

#### The disease

Pneumococcal disease is the term used to describe infections caused by the bacterium *Streptococcus pneumoniae* (also called pneumococcus).

*S. pneumoniae* is an encapsulated gram-positive coccus. The capsule is the most important virulence factor of *S. pneumoniae*; pneumococci that lack the capsule are normally not virulent. Over 90 different capsular types have been characterised. About 66% of the serious infections in adults and about 80% of invasive infections in children are caused by eight to ten capsular types (Health Protection Agency, 2003).

Some serotypes of the pneumococcus may be carried in the nasopharynx without symptoms, with disease occurring in a small proportion of infected individuals. Other serotypes are rarely identified in the nasopharynx but are associated with invasive disease. The incubation period for pneumococcal disease is not clearly defined but it may be as short as one to three days. The organism may spread locally into the sinuses or middle ear cavity, causing sinusitis or otitis media. It may also affect the lungs to cause pneumonia, or cause systemic (invasive) infections including bacteraemic pneumonia, bacteraemia and meningitis.

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 seasonal variation in pneumococcal disease, with peak levels in the winter months.

Invasive pneumococcal disease is a major cause of morbidity and mortality. It particularly affects the very young, the elderly, those with an absent or non-functioning spleen and those with other causes of impaired immunity. Recurrent infections may occur in association with skull defects, cerebrospinal fluid (CSF) leaks, cochlear implants or fractures of the skull.

#### History and epidemiology of the disease

Currently, the pneumococcus is one of the most frequently reported causes of bacteraemia and meningitis. During 2005, 6207 laboratory isolates from blood,

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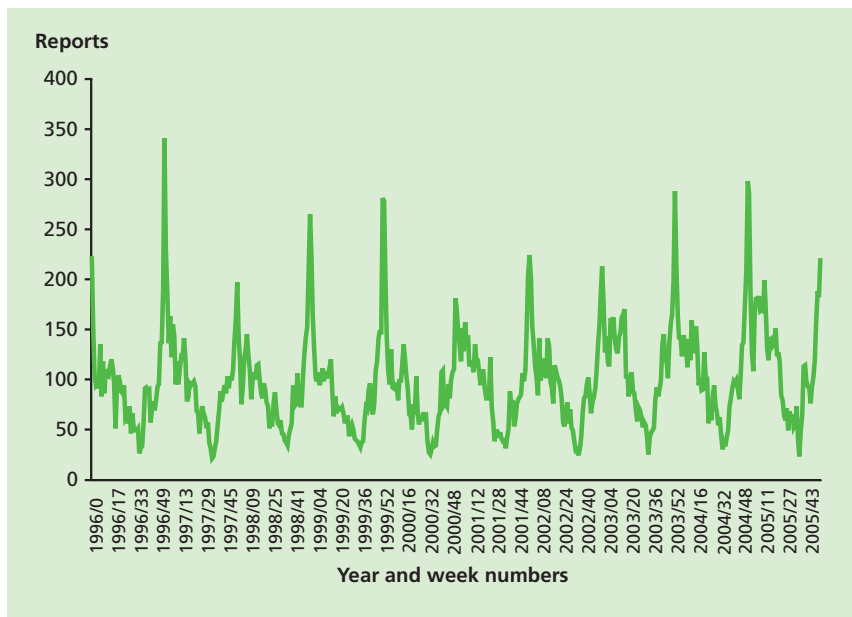


Figure 25.1 Weekly number of invasive pneumococcal disease cases in England and Wales (1996–2005)

CSF or other normally sterile sites were reported to the Health Protection Agency Centre for Infection (HPA CfI) from laboratories in England and Wales (Health Protection Agency, 2006). Figure 25.1 shows the weekly number of invasive pneumococcal disease cases in England and Wales between 1996 and 2005. The pneumococcus is also the commonest cause of community-acquired pneumonia (Bartlett and Mundy, 1995). Pneumococcal pneumonia is estimated to affect one in a thousand adults each year and has a case fatality ratio of 10 to 20% (World Health Organization, 1999).

Antimicrobial resistance among pneumococci occurs and susceptibility to macrolide antimicrobials, penicillin and cephalosporin can no longer be assumed. In 2000, 13% of invasive isolates in England and Wales reported to the HPA CDSC were resistant to erythromycin and 7% showed full or intermediate resistance to penicillin (George and Melegaro, 2001, 2003). An increase in pneumococcal antibiotic resistance has been reported worldwide (Appelbaum, 1992; Butler *et al.*, 1996; Davies *et al.*, 1999).

Since 1992, pneumococcal polysaccharide immunisation (see below) has been recommended for people with medical conditions for whom pneumococcal infection was likely to be more common or serious.

In recent years, the pneumococcal recommendations have undergone a number of changes:

- in 2002, a pneumococcal conjugate vaccine (see below) became available and was recommended for immunisation of at-risk groups under the age of two years
- in 2003, pneumococcal polysaccharide immunisation was recommended for all people aged 65 and over
- in 2004, the conjugate vaccine policy was extended to at-risk children under five years of age
- in 2006, pneumococcal conjugate vaccine was added to the routine childhood immunisation programme.

## The pneumococcal vaccination

There are two types of pneumococcal vaccine:

- pneumococcal polysaccharide vaccine (PPV) contains purified capsular polysaccharide from each of 23 capsular types\* of pneumococcus
- pneumococcal conjugate vaccine (PCV) contains polysaccharide from seven common capsular types.† These are conjugated to protein (CRM<sub>197</sub>) using similar manufacturing technology to that for *Haemophilus influenzae* type b (Hib) and meningococcal C conjugate vaccines.

The pneumococcal polysaccharide and pneumococcal conjugate vaccines do not contain thiomersal. The vaccines are inactivated, do not contain live organisms and cannot cause the diseases against which they protect.

## Pneumococcal polysaccharide vaccine (PPV)

Most healthy adults develop a good antibody response to a single dose of PPV by the third week following immunisation. Antibody response may be reduced in those with immunological impairment and those with an absent or dysfunctional spleen. Children younger than two years of age show poor antibody responses to immunisation with PPV.

It is difficult to reach firm conclusions about the effectiveness of PPV, but overall efficacy in preventing pneumococcal bacteraemia is probably 50 to 70% (Mangtani *et al.*, 2003; Fedson, 1999; Fine *et al.*, 1994; Butler *et al.*, 1993;

\* 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F

† 4, 6B, 9V, 14, 18C, 19F, 23F

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Melegaro and Edmunds, 2004). Current evidence suggests that PPV is not effective in protecting against non-bacteraemic pneumococcal pneumonia (Jackson *et al.*, 2003). It does not prevent otitis media or exacerbations of chronic bronchitis. The vaccine is relatively ineffective in patients with multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma (especially during treatment) and chronic alcoholism.

The vaccine does not protect against pneumococcal infection due to capsular types not contained in the vaccine, but the 23 types included account for about 96% of the pneumococcal isolates that cause serious infection in the UK (Health Protection Agency, 2003).

The length of protection is not known and may vary between capsular types. Post-immunisation antibody levels usually begin to wane after about five years, but may decline more rapidly in asplenic patients and children with nephrotic syndrome (Butler *et al.*, 1993).

There is no evidence of effectiveness of PPV in children under two years of age (Fedson *et al.*, 1999).

## Pneumococcal conjugate vaccine (PCV)

The antibody response in young children can be improved by conjugating the polysaccharide to proteins such as CRM<sub>197</sub>. The conjugated vaccine is immunogenic in children from two months of age. Data on efficacy comes from pre- and post-licensing studies in the US in which children were vaccinated at two, four and six months of age, with a fourth dose at 15 months. At the time of the pre-licence study, the serotypes included in the vaccine accounted for 89% of invasive pneumococcal infections in the US. The serotype-specific efficacy was 97% after the fourth dose had been given. The vaccine protects against pneumococcal meningitis, bacteraemia, pneumonia and otitis media (Black *et al.*, 2000; Black *et al.*, 2002).

Post-licensure surveillance, following introduction of PCV in the US in 1999 as part of a universal infant immunisation programme, has shown a large reduction in both invasive and non-invasive disease incidence due to vaccine serotypes in both vaccinated and older unvaccinated populations ('herd immunity'). This reduction in disease has also been accompanied by a fall in the rate of penicillin-resistant pneumococcal infections (Black *et al.*, 2004). However, a small increase in invasive disease due to non-vaccine serotypes (termed 'serotype replacement') has also been observed (Whitney *et al.*, 2003).

## 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 cannot be guaranteed for vaccines unless they have been 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.

## Presentation

Both PCV and PPV are supplied as single doses of 0.5ml.

### PCV

Storage can cause the vaccine to separate into a white deposit and clear supernatant. The vaccine should be shaken well to obtain a white homogeneous suspension and should not be used if there is any residual particulate matter after shaking.

### PPV

The polysaccharide vaccine should be inspected before being given to check that it is clear and colourless.

Vaccines must not be given intravenously.

## Dosage and schedule

### PCV

For children under one year of age:

- First dose of 0.5ml of PCV.
- Second dose of 0.5ml, two months after the first dose.
- A third dose of 0.5ml should be given at the recommended interval (see below).

Children over one year of age and under five years of age:

- A single dose of 0.5ml of PCV if indicated (see recommendations below).

### PPV

Adults over 65 years and at-risk groups aged two years or over:

- A single dose of 0.5ml of PPV.

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### Administration

Vaccines are routinely given into the upper arm in children and adults or the anterolateral thigh in infants under one year of age. This is to reduce the risk of localised reactions, which are more common when vaccines are given subcutaneously (Mark *et al.*, 1999; Diggle and Deeks, 2000; Zuckerman, 2000). However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

Pneumococcal vaccines can be given at the same time as other vaccines such as DTaP/IPV/Hib, MMR, MenC and influenza. The vaccines should be given at separate sites, preferably in different limbs. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records.

At the moment, there are no data on the administration of pneumococcal vaccination at the same time as the conjugate Hib/MenC vaccine (Menitorix ▼). Although there is no reason to think that this would cause any safety concerns, there is a theoretical possibility of reduced response from giving Hib/MenC at the same time as PCV. Therefore, as a precautionary measure, PCV should not be given routinely at the same time as the Hib/MenC booster. However, where rapid protection is required, for example those children under five years of age with splenic dysfunction, the two can be given on the same day or at any interval. As more data accumulate, this advice may be modified.

### Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper puncture-resistant 'sharps' box (UN-approved, BS 7320).

## Recommendations for the use of pneumococcal vaccine

The objective of the immunisation programme is to protect all of those for whom pneumococcal infection is likely to be more common and/or serious, i.e.:

- infants as part of the routine childhood immunisation programme
- those aged 65 years or over
- those aged two months and over in the clinical risk groups shown in Table 25.1.

Table 25.1 Clinical risk groups who should receive the pneumococcal immunisation

Clinical risk group	Examples (decision based on clinical judgement)
<b>Asplenia or dysfunction of the spleen</b>	This also includes conditions such as homozygous sickle cell disease and coeliac syndrome that may lead to splenic dysfunction.
<b>Chronic respiratory disease</b>	This includes chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema; and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD). Children with respiratory conditions caused by aspiration, or a neuromuscular disease (e.g. cerebral palsy) with a risk of aspiration. Asthma is not an indication, unless so severe as to require continuous or frequently repeated use of systemic steroids (as defined in Immunosuppression below).
<b>Chronic heart disease</b>	This includes those requiring regular medication and/or follow-up for ischaemic heart disease, congenital heart disease, hypertension with cardiac complications, and chronic heart failure.
<b>Chronic renal disease</b>	This includes nephrotic syndrome, chronic renal failure and renal transplantation.
<b>Chronic liver disease</b>	This includes cirrhosis, biliary atresia and chronic hepatitis.
<b>Diabetes</b>	Diabetes mellitus requiring insulin or oral hypoglycaemic drugs. This does not include diabetes that is diet controlled.
<b>Immunosuppression</b>	Due to disease or treatment, including asplenia or splenic dysfunction and HIV infection at all stages. Patients undergoing chemotherapy leading to immunosuppression. Individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age), or for children under 20kg, a dose of 1mg or more per kg per day. <i>However, some immunocompromised patients may have a suboptimal immunological response to the vaccine.</i>
<b>Individuals with cochlear implants</b>	<i>It is important that immunisation does not delay the cochlear implantation.</i>
<b>Individuals with cerebrospinal fluid leaks</b>	This includes leakage of cerebrospinal fluid such as following trauma or major skull surgery.

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Primary care staff should identify patients for whom vaccine is recommended and use all opportunities to ensure that they are appropriately immunised, for example:

- when immunising against influenza
- at other routine consultations, especially on discharge after hospital admission.

## Primary immunisation

### PCV

PCV is recommended for infants from two months of age as part of the routine childhood immunisation schedule and children under five years of age in a clinical risk group.

#### Infants under one year of age

The primary course of PCV vaccination consists of two doses with an interval of two months between each dose. The recommended age for vaccination is between two and four months. If the primary course is interrupted, it should be resumed but not repeated, allowing an interval of two months between doses. Although the currently available PCV is licensed for use as a three-dose primary course in infancy, evidence from UK immunogenicity studies shows that a two-dose primary immunisation course provides the same level of protection (Goldblatt *et al.*, 2006).

#### Children from one year to under two years of age

The primary course of PCV for this age group is one dose. If the primary course in children under one year was not completed, then a single booster dose of PCV should be given at least one month after the last dose to complete the course.

### PPV

#### Adults 65 years or over

A single dose of PPV should be administered.

## Risk groups

### Children under two years of age

At-risk children (Table 25.1) should be given PCV according to the schedule for the routine immunisation programme, at 2, 4 and 13 months of age. At-risk children who present late for vaccination should be offered two doses of PCV\*

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\* One month apart if necessary to ensure two doses are given before a dose at 13 months

Table 25.2 Vaccination schedule for those in a clinical risk group

Patient age at presentation	Vaccine given and when to immunise	
	7-valent PCV	23-valent PPV
At-risk children 2 months to under 12 months of age	Vaccination according to the routine immunisation schedule at 2, 4 and 13 months of age	One dose after the second birthday.
At-risk children 2 months to under 12 months of age who have asplenia or splenic dysfunction or who are immunosuppressed	Vaccination according to the routine immunisation schedule at 2, 4 and 13 months of age	One dose after the second birthday
At-risk children 12 months to under 5 years of age	One dose	One dose after the second birthday and at least 2 months after the final dose of PCV
At-risk children 12 months to under 5 years of age who have asplenia or splenic dysfunction or who are immunosuppressed	Two doses, with an interval of 2 months between doses	One dose after the second birthday and at least 2 months after the final dose of PCV
At-risk children aged over 5 years and at-risk adults	PCV is not recommended	One dose

before the age of 12 months, and a further dose at 13 months. At-risk children aged over 12 months who have either not been vaccinated or not completed a primary course should have a single dose of PCV.

For those children in this age group who have asplenia or splenic dysfunction, or who are immunocompromised and may have a sub-optimal immunological response to the first dose of vaccine, a second dose should be given two months after the first dose.

All at-risk children should be offered a single dose of PPV when they are two years of age or over (see below).

### Children aged two to five years of age

A single dose of PPV should be given, at least two months after the final dose of PCV.

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At-risk children under five years of age who have either not been vaccinated with PCV or not completed a primary course should have a single dose of PCV. For those children in this age group who have asplenia or splenic dysfunction, or who are immunocompromised and may have a sub-optimal immunological response to the first dose of PCV, a second dose should be given two months after the first dose. At-risk children under five years who have already received 23-valent PPV should receive a dose of PCV at least two months after the PPV.

Children between two and five years who have been fully immunised with PCV as part of the routine programme and who then develop splenic dysfunction or immunosuppression should be given an additional dose of PCV.

### Children aged over five years and adults

A single dose of PPV should be given, at least two months after the final dose of PCV.

## Reinforcing immunisation

### PCV

A reinforcing (booster) dose of PCV is recommended at 13 months of age for children who have received a complete primary course of two PCVs. It should be given one month after the Hib/MenC vaccine.

### PPV

Antibody levels are likely to decline rapidly in individuals with no spleen, splenic dysfunction or chronic renal disease (Giebink *et al.*, 1981; Rytel *et al.*, 1986) and therefore re-immunisation with 23-valent PPV is recommended every five years in these groups. Revaccination is well tolerated (Jackson *et al.*, 1999). Testing of antibody levels prior to vaccination is not required.

Although there is evidence of a decline in protection with time (Shapiro *et al.*, 1991), there are no studies showing additional protection from boosting individuals with other indications including age, and therefore routine revaccination is not currently recommended.

Individuals who have previously received 12- or 14-valent PPV or 7-valent PCV should be immunised with 23-valent PPV to gain protection from the additional serotypes.

## Individuals with unknown or incomplete vaccination histories

Unless there is a reliable history of previous immunisation, individuals should be assumed to be unimmunised. The full UK recommendations should be followed. A child who has not completed the primary course (and is under one year of age) should have the outstanding doses at appropriate intervals (see above). A child aged one and under two years of age should have a single dose of PCV.

## Children and adults requiring splenectomy or commencing immunosuppressive treatment

Previously unvaccinated children and adults requiring splenectomy or commencing immunosuppressive treatment may be at an increased risk of pneumococcal disease and should be vaccinated according to the schedule for this specific risk group. Children under five who have been fully immunised with PCV as part of the routine programme and who then develop splenic dysfunction more than one year after completing immunisation should be offered an additional dose of PCV.

Ideally, pneumococcal vaccine should be given four to six weeks before elective splenectomy or initiation of treatment such as chemotherapy or radiotherapy. Where this is not possible, it can be given up to two weeks before treatment. If it is not possible to vaccinate beforehand, splenectomy, chemotherapy or radiotherapy should never be delayed.

If it is not practicable to vaccinate two weeks before splenectomy, immunisation should be delayed until at least two weeks after the operation. This is because there is evidence that functional antibody responses may be better from this time (Shatz *et al.*, 1998). If it is not practicable to vaccinate two weeks before the initiation of chemotherapy and/or radiotherapy, immunisation can be delayed until at least three months after completion of therapy in order to maximise the response to the vaccine. Immunisation of these patients should not be delayed if this is likely to result in a failure to vaccinate.

## Contraindications

There are very few individuals who cannot receive pneumococcal 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 withholding the vaccine.

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The vaccines should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of the vaccines
- a confirmed anaphylactic reaction to any component of the vaccines.

Confirmed anaphylaxis is rare. Other allergic conditions, such as rashes, may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between true anaphylaxis and other events that are either not due to the vaccine or not life-threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and the circumstances in which they could be given. The risk to the individual of not being immunised must be taken into account.

## Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation should be postponed until they have fully recovered. 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

Pneumococcal-containing vaccines may be given to pregnant women when the need for protection is required without delay. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Plotkin and Orenstein, 2004).

## Premature infants

It is important that premature infants have their immunisation at the appropriate chronological age, according to the recommendation. There is no evidence that premature babies are at an increased risk of adverse reactions from vaccines (Slack *et al.*, 2001).

## Immunosuppression and HIV infection

Individuals with immunosuppression and HIV infection (regardless of CD4 count) should be given pneumococcal vaccines in accordance with the recommendations above. These individuals may not make a full antibody response, and so an additional dose of PCV is recommended. Specialist advice may be required.

Studies on the clinical efficacy of PPV in HIV-infected adults have reported inconsistent findings, including one study from the developing world where a higher risk of pneumonia was observed in vaccinees (Watera *et al.*, 2004). Observational studies in developed countries have not confirmed this finding, and most experts believe that the potential benefit of pneumococcal vaccination outweighs the risk in developed countries (USPHS/IDSA, 2001).

Further guidance is provided by the Royal College of Paediatrics and Child Health ([www.rcpch.ac.uk](http://www.rcpch.ac.uk)), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines ([www.bhiva.org/chiva](http://www.bhiva.org/chiva)).

## Adverse reactions

### PCV

Swelling and redness at the injection site and low grade fever are among the most commonly reported adverse reactions (10–20%) (Black *et al.*, 2000). No increased local or systemic reactions have been reported with repeated doses during the primary series, although a higher rate of transient tenderness has been reported after a fourth dose.

### PPV

Mild soreness and induration at the site of injection lasting one to three days and, less commonly, a low grade fever may occur. More severe systemic reactions are infrequent. In general, local and systemic reactions are more common in people with higher concentrations of antibodies to pneumococcal polysaccharides.

## Management of cases, contacts and outbreaks

### Cases of invasive pneumococcal disease (IPD)

Any case of invasive pneumococcal infection or lobar pneumonia believed to be due to *S. pneumoniae* should prompt a review of the patient's medical history to establish whether they are in a recognised risk group and whether they have been vaccinated. Patients with risk factors who have not previously been vaccinated should be given vaccination on discharge from hospital.

### Children under five years of age

All children under five years of age who have had IPD, for example pneumococcal meningitis or pneumococcal bacteraemia, should be given a dose of PCV irrespective of previous vaccination history. Children under

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13 months who are unvaccinated or partially vaccinated should complete the immunisation schedule.

These children should be investigated for immunological risk factors to seek a possible treatable condition predisposing them to pneumococcal infection. If they are found to fall into one of the risk groups in Table 25.1, they should continue vaccination as for other at-risk children (see section on Recommendations for the use of pneumococcal vaccine).

All new cases of IPD in children eligible for routine PCV will be followed up by the Health Protection Agency in England and Wales and Health Protection Scotland. These cases will be offered antibody testing against each of the seven vaccine serotypes and advice on clinical and immunological investigation (see [www.hpa.org.uk/infections/topics\\_az/vaccination/vacc\\_menu.htm](http://www.hpa.org.uk/infections/topics_az/vaccination/vacc_menu.htm)).

## Contacts

Close contacts of pneumococcal meningitis or other invasive pneumococcal disease are not normally at an increased risk of pneumococcal infection and therefore antibiotic prophylaxis is not indicated. Clusters of invasive pneumococcal disease should be discussed with local health protection teams.

## Outbreaks

Outbreaks of pneumococcal respiratory disease in hospitals and residential care homes need prompt investigation. Control measures including vaccination may be appropriate; these should be agreed in discussion with local health protection or infection control teams.

## Supplies

- 7-valent PCV (Prevenar™) is manufactured by Wyeth Vaccines (medical information: 01628 415330). It is supplied by Healthcare Logistics (Tel: 0870 871 1890) as part of the national childhood immunisation programme.
- 23-valent plain PPV (Pneumovax® II) is manufactured by Sanofi Pasteur MSD (Tel: 0800 085 5511) (Fax: 0800 085 8958).

In Northern Ireland, supplies should be obtained from local childhood vaccine-holding centres. Details of these are available from the regional pharmaceutical procurement service  
(Tel: 028 9055 2368).

A patient card and information sheet for asplenic and hyposplenic patients is available from:  
Department of Health Publications  
(Tel: 08701 555 455).  
(E-mail: [dh@prolog.uk.com](mailto:dh@prolog.uk.com)).

or in Wales from:  
Welsh Assembly Publications Centre  
(Tel: 029 2082 3683).  
(E-mail: [assembly-publications@wales.gsi.gov.uk](mailto:assembly-publications@wales.gsi.gov.uk)).

or in Scotland from:  
Chris Sinclair  
Public Health Division 1  
Health Department  
Scottish Executive  
Room 3ES  
St Andrew's House  
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(Tel: 0131 244 2241).  
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E-mail: [chris.sinclair@scotland.gsi.gov.uk](mailto:chris.sinclair@scotland.gsi.gov.uk)).

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