Control of pneumococcal disease in the United Kingdom – the start of a new era

Stuart C. Clarke
Hampshire and Isle of Wight Health Protection Unit, Oakley Road and Molecular Microbiology Group, Division of Infection Inflammation and Repair, University of Southampton Medical School, Southampton, UK

In 2000, a multi-valent pneumococcal conjugate vaccine, known as Prevnar, was licensed for use in infants and young children in the USA. The subsequent introduction of the vaccine into the childhood immunization schedule in that country led to a significant decrease in pneumococcal disease. The vaccine is effective against invasive and non-invasive pneumococcal infection, can be used in young children as well as adults and, like all conjugate vaccines, provides long-lasting immunity. Moreover, it reduces the incidence of antibiotic resistance because a number of resistant serotypes are targeted by the vaccine. Prevnar, also known as Prevenar, has since been licensed in numerous countries, including the UK. On 8 February 2006, the Departments of Health in England, Scotland and Wales announced the inclusion of Prevenar in the childhood immunization schedule. This announcement has important implications for pneumococcal infection, disease surveillance and immunization policy in the UK.

The pneumococcus

Streptococcus pneumoniae (the pneumococcus) is a Gram-positive bacterium and is classified into more than 90 pneumococcal serotypes in 46 serogroups (Henrichsen, 1995). However, the majority of invasive and non-invasive disease is associated with a much smaller number of serotypes. The pneumococcus is one of a number of bacterial pathogens that are highly promiscuous; it is able to exchange DNA with members of its own and other related species by transformation. This means that genes encoding virulence factors, including the polysaccharide capsule, can be exchanged, leading to the existence of capsule switch (Jefferies et al., 2004; Spratt & Greenwood, 2000). This is important as, at present, available pneumococcal vaccines and some of those that are under development are based on pneumococcal capsular polysaccharide.

Pneumococcal disease

Pneumococcal infection remains a major cause of otitis media, pneumonia, septicaemia and meningitis in the UK (Kyaw et al., 2003; Miller et al., 2000). It causes substantial morbidity and mortality, especially in the young and old. Otitis media is particularly common and is the leading indication for the administration of antibiotics in children in developed countries (McCaig et al., 2002). Both invasive pneumococcal disease (IPD) and non-invasive pneumococcal disease have a significant impact on the quality of life of children, adults and the elderly (Brouwer et al., 2005; Zimmerman, 2005). They result in absence from school or work, require attendance at the general practitioner or hospital and necessitate medication. They therefore also have an impact on the general economy due to the costs involved (De Graeve & Beutels, 2004).

Importantly, pneumococci have a carrier state; pneumococci are harboured in the nasopharynx from a young age and the carriage rate can be as high as 40 % (Long, 2005). A number of studies have found a link between colonization of the nasopharynx with pneumococci and an increased risk of acute and recurrent otitis media (Dhooge et al., 1999; Marchisio et al., 2003; Syrjanen et al., 2001). It is from the nasopharynx that the pneumococcus can also enter the bloodstream to cause septicaemia or meningitis. Certain risk factors make individuals prone to pneumococcal infection, including diabetes, asplenia, chronic lung disease, alcohol abuse, cancer and HIV/AIDS (Kyaw et al., 2003, 2005).

Surveillance of IPD has improved substantially throughout the UK in recent years due to interest in the potential for new pneumococcal vaccines (George & Melegaro, 2001; Kyaw et al., 2003; McChlery et al., 2005). There remains a considerable burden of IPD in the UK, particularly during the winter months, despite the availability of antibiotics and pneumococcal polysaccharide vaccines (PPVs) (George & Melegaro, 2001; Kyaw et al., 2003). In England and Wales, the overall incidence of IPD is 8·6 per 100 000 population (George & Melegaro, 2001), the highest burden being amongst the very young and elderly, with an incidence in excess of 30 per 100 000 (George & Melegaro, 2001; Miller et al., 2000; Sleeman et al., 2001). In Scotland, the overall incidence of IPD is 11 cases per 100 000 population, although the incidence rises to 51 cases per 100 000 in those 1 year of age and 45 cases per 100 000 in those aged over
The ten most common pneumococcal serogroups associated with IPD in Great Britain are shown in Table 1.

Antibiotic resistance in the pneumococcus
The pneumococcus has been controlled, to some degree, through the use of antibiotics. However, antibiotic resistance amongst pneumococci is an emerging problem in the UK. Macrolide resistance is a particular problem because one of the two major serotype 14 clones is resistant (Clarke et al., 2004a). Rates of macrolide resistance amongst invasive pneumococci in the UK are as high as 20% (Clarke et al., 2004a, 2005; George & Melegaro, 2001). Moreover, for England and Wales, penicillin non-susceptibility is around 7% (George & Melegaro, 2001) and, in Scotland, the incidence of penicillin non-susceptible isolates increased from 4.2% in 1992 to 12% in 1999 (Kyaw et al., 2000, 2002).

Pneumococcal vaccines
The prevention of IPD by immunization is an attractive proposition. Whilst antibiotics may currently be effective against most pneumococcal infections, increasing resistance may mean that such an approach cannot be relied upon in the future. Although pneumococcal vaccines have been available for some time, their effectiveness in the elderly and at-risk groups has been questioned. In addition, they were not effective in young children and hence were not introduced into the childhood immunization schedule.

Pneumococcal polysaccharide vaccines
The currently available PPV, namely Pneumovax (Merck), is inexpensive and safe (Artz et al., 2003). Pneumovax contains the polysaccharides of 23 different serotypes (Table 2) and has >90% serotype coverage in the UK and elsewhere (Clark et al., 2004b; George et al., 1997; Kyaw et al., 2000). However, controversy over the efficacy of the 23-valent PPV has continued for many years and is still not fully resolved (Ament et al., 2000; Melegaro & Edmunds, 2004b). Although data from randomized studies have failed to show that the PPV is effective in preventing pneumococcal pneumonia or death in adults, there is evidence from non-randomized studies to suggest that the PPV is effective in reducing IPD amongst adults and the elderly (Dear et al., 2003). Certain patient cohorts respond poorly to immunization with PPV and only a T-cell-independent response is elicited. The PPV is therefore wholly ineffective in those less than 2 years of age. In addition, the PPV has no effect on nasopharyngeal carriage of pneumococci (Ledwith, 2001).

Pneumococcal conjugate vaccines
Often, antibiotics do not eradicate carriage of an organism. This is the case for antibiotic treatment of otitis media and the eradication of nasopharyngeal carriage. Conjugate vaccines, however, have a good record of eradicating carriage as well as protecting against disease (Heath & McVernon, 2002; Maiden & Stuart, 2002) because they evoke a T-cell-dependent response. They are also efficacious in children less than 2 years of age. The new multi-valent pneumococcal vaccine is of the conjugate type. Named Prevenar (Prevnar in the USA) and manufactured by Wyeth, it also provides a moderate amount of protection against ear infections in children under 3-5 years of age (Fireman et al., 2003) and significantly reduces the risk of pneumonia, particularly in those aged less than 1 year (Black et al., 2002). Prevenar contains the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to a non-toxic diphtheria variant carrier protein (CRM197). As mentioned earlier, Prevenar was licensed in 2000 for use in infants and young children in the USA (Centers for Disease Control and Prevention, 2000). It was also licensed in the UK in 2001 for use in children under 5 years of age within certain at-risk groups (Department of Health, 2002).

Table 1. The most common serogroups/types of pneumococci causing invasive disease in Great Britain

<table>
<thead>
<tr>
<th>Country</th>
<th>Serogroup/type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>England and Wales</td>
<td>14, 9, 6, 19, 23, 8, 1, 4, 18 and 7</td>
<td>George &amp; Melegaro (2001)</td>
</tr>
<tr>
<td>Scotland</td>
<td>14, 8, 9V, 1, 3, 22F, 23F, 6B, 18C and 19F</td>
<td>McChlery et al. (2005)</td>
</tr>
</tbody>
</table>

Table 2. Serotypes represented in the 23V-PPV and multi-valent PCVs

<table>
<thead>
<tr>
<th>Vaccine*</th>
<th>Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovax (Merck)</td>
<td>1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F</td>
</tr>
<tr>
<td>Prevenar (Wyeth)*</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
</tr>
<tr>
<td>Streptorix (GlaxoSmithKline)*†</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F</td>
</tr>
<tr>
<td>PCV13 (Wyeth)*†</td>
<td>1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F</td>
</tr>
</tbody>
</table>

†These vaccines remain under development and are not yet licensed.
Initial studies have been carried out to assess the molecular epidemiology of the pneumococcus in the USA prior to vaccine administration (Gertz et al., 2003) and to compare this following vaccine administration (Black et al., 2001, 2002; Lexau et al., 2005; Whitney et al., 2003). These studies reveal that the use of Prevnar has significantly reduced the burden of pneumococcal disease in young children (Black et al., 2001, 2002; Whitney et al., 2003). From 1998/99 to 2003, the incidence of IPD associated with serotypes contained within Prevnar decreased by 94 %, and decreased by 75 % overall (Centers for Disease Control and Prevention, 2005). The indirect effect of the vaccine, known as herd immunity, has also reduced disease amongst older adults (Lexau et al., 2005). In addition, a substantial proportion of disease caused by antibiotic non-susceptible pneumococci has been prevented, leading to a reduction in the incidence of antibiotic-resistant pneumococci (Byington et al., 2002; McEllistrem et al., 2005; Stephens et al., 2005; Whitney et al., 2003).

However, Prevenar is the most expensive child vaccine routinely administered in the USA (Ray, 2002), accounting for more than 40 % of the total purchase price of vaccines within the childhood schedule. In this respect, the cost-effectiveness of Prevenar/Prevnar has been determined using hypothetical cohort models in the UK and USA (Lieu et al., 2000; Melegaro & Edmunds, 2004a). In both studies, the list price (approx. £30 and $58, respectively, per dose) meant that Prevenar/Prevnar would not be cost-effective. However, it was also reported that if the price was reduced it would bring cost-effectiveness within normally acceptable ranges (Lieu et al., 2000; Melegaro & Edmunds, 2004a). Recommendations for the implementation of Prevenar also take into account the absolute burden of disease, societal factors and the effect of herd immunity (De Graeve & Beutels, 2004; McIntosh, 2004). As such, Prevenar is considered cost-effective as reduced transmission of the organism within the community, after implementation of the vaccine in children, has benefited unvaccinated adults due to the indirect effect of the vaccine on carriage in the respiratory tract (Black et al., 2001; Lexau et al., 2005; Whitney et al., 2003).

**Pneumococcal vaccine policy in the UK**

In the UK, at present, the 23-valent PPV is recommended for use in the elderly and for certain high-risk groups, such as asplenics and those with HIV/AIDS (Department of Health, 2003, 2005). After expansion of the use of the 23-valent PPV for the elderly, the incidence of IPD in Scotland has declined for all older adults and as a proportion of all pneumococcal disease for those aged 65 and over (J. D. Mooney, A. Weir, J. McMenamin, L. Ritchie, T. McFarlane, C. R. Simpson, S. Ahmed and S. C. Clarke, unpublished data). However, it is unlikely that this will lead to any decrease of disease in children.

In 2002, Prevenar was recommended for use in those children under the age of 2 years who are at an increased risk of IPD (Department of Health, 2002). The Joint Committee on Vaccination and Immunisation recommended in late 2004 that there were no medical reasons not to offer the vaccine and that, in principle, it should be introduced into the childhood immunization schedule subject to further understanding of the number and timing of doses, the vaccine cost and guarantees of vaccine supply (Joint Committee on Vaccination and Immunisation, 2004). While this recommendation was under consideration, the use of Prevenar was extended in 2005 to include all those at increased risk under the age of 5 years (Department of Health, 2005).

**Introduction of the pneumococcal conjugate vaccine**

The introduction of Prevenar has been eagerly anticipated in the UK, and the Departments of Health in England, Scotland and Wales announced on 8 February 2006 that Prevenar will be introduced into the routine childhood immunization schedule during the summer of 2006. The vaccine coverage is likely to be 95 %, based on previous experiences with the *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup C (MenC) vaccines. The vaccine will be offered routinely to children at 2, 4 and 13 months of age. Studies in the UK suggest that serotype coverage for the vaccine will be around 76 % (Clarke et al., 2006a, b; Miller et al., 2000) but may approach 90 % for those aged 1 year (Clarke et al., 2006a). Using serotype coverage and estimates of vaccine efficacy and uptake, a study from Scotland has found that the potential reduction in disease for those aged more than 2 months, but less than 5 years, is estimated as 67·3 % (Clarke et al., 2006a). The results of that study should be able to be generalized to the rest of the UK. The introduction of Prevenar into the childhood immunization schedule will inevitably lead to a significant reduction in pneumococcal disease amongst children. Importantly, the epidemiology of IPD in the USA should be broadly mirrored in the UK, such that a decrease should occur in both invasive and non-invasive disease amongst children and adults due to the direct and indirect effects of the vaccine. The direct effects will affect those immunized with Prevenar, whereas the indirect effects, via herd immunity, will affect those not immunized. Older children, adults and the elderly will all benefit from herd immunity after the introduction of Prevenar.

**Advantages and limitations of Prevenar**

The extent to which Prevenar will have an impact on IPD in the UK is of great interest and importance. Recent studies in the UK have characterized collections of pneumococci in an attempt to understand better its clonal distribution, population biology and invasive disease potential (Clarke et al., 2004b, 2006a, b; Jefferies et al., 2004; McChlery et al., 2005; Miller et al., 2000). Whilst these studies demonstrate a high serotype coverage rate for Prevenar, they make the assumption that all serotypes within the serogroups in Prevenar possess complete and equal immune cross-protection.
It is likely, in reality, that cross-protection is less than 100% for each vaccine-related serotype and that it also varies depending on the serotype. It is clear that a better understanding of cross-protection from vaccine-related serotypes is needed. However, as Prevenar includes serotypes 6B, 9V, 19F, 18C and 23F, it is possible that cross-protection may be afforded to vaccine-related serotypes and counteract any variation in individual vaccine serotypes. It is thought that, whereas such cross-protection may be variable between serotypes, it may be substantial (Long, 2005; O’Brien & Dagan, 2003).

However, more important is the fact that pneumococci are highly transformable. In a recent study, which looked at the genetic heterogeneity amongst 217 pneumococci isolated from invasive disease in children, 22 different serogroups/types were found (Clarke et al., 2006). These were further genotyped using multi-locus sequence typing (MLST) into 77 different sequence types. Although limited genetic heterogeneity was found amongst common serotypes, it highlights the possibility of an epidemiological shift in serotype distribution after the introduction of Prevenar. This is important, as pneumococci can change serotype (Coffey et al., 1998, 1999; Eskola et al., 2001; Meats et al., 2003; Nesin et al., 1998), as has also been observed in the meningococcus (Stefanelli et al., 2003; Swartley et al., 1997). The introduction of vaccines that contain only selected serotypes, as is the case with Prevenar, may promote capsule switch or capsule replacement (Crook, 2006; Jeferies et al., 2004; Spratt & Greenwood, 2000). Studies from the USA are already showing shifts in the epidemiology of pneumococcal disease after the introduction of Prevenar. Two recent reports describe the presence of related or identical clones with differing serotypes (Cordeiro et al., 2005; Pai et al., 2005). However, it may be that Prevenar provides vaccine-related serotype coverage for these clones, although this has not yet been confirmed. Another study has shown evidence of clonal replacement, although there was little clear evidence for capsule switching events driven solely by the selective pressure of Prevnar (Byington et al., 2005; Beall et al., 2006). There is also a limited understanding of the extent of simultaneous carriage of different serotypes at the same time (Chaves et al., 2003). Although this may initially be of less importance, because the secondary serotype is not as invasive and/or is not causing disease, it may provide an opportunity for capsule switch or replacement.

Even with these potential shortcomings, there are clear benefits of Prevenar. The vaccine is effective against non-invasive pneumococcal infection as well as IPD. The vaccine reduces carriage and therefore decreases the overall transmissibility of the pneumococcus. The vaccine can be used in young children as well as adults and, like all conjugate vaccines, provides long-lasting immunity. Moreover, the implementation of Prevenar should lead to a reduction, or at least a slowdown, in the incidence of macrolide and penicillin resistance. This is because the majority of antibiotic-resistant pneumococci are covered by Prevenar. Such a fall in antibiotic resistance has been seen in the USA (Whitney et al., 2003).

**Current and future issues**

Although the implementation of Prevenar, to accompany the MenC and Hib conjugate vaccines, is exciting, it is important to maintain the enhanced surveillance systems that have been put in place. Surveillance is required during and after the introduction of pneumococcal conjugate vaccines (PCVs). Such surveillance should include the monitoring of serotypes and sequence types causing invasive and non-invasive disease so that any indication of capsule switch or capsule replacement can be detected in a timely manner. In addition, surveillance should include the continued monitoring of disease caused by meningococci and *H. influenzae* but should also take into account the possibility of an increase in other bacterial pathogens that may fill the niche left by those covered by conjugate vaccines.

The development of new vaccines is an on-going process, such that 9- and 11-valent PCVs have already undergone trials. Although these trials led to them being dropped, 10- and 13-valent vaccines are now being developed. These will, depending on the vaccine, include serotypes within serogroups 1, 3, 5 and 7 (Hausdorff et al., 2001) (Table 2). However, these vaccines are still undergoing clinical trials and it may be some time before they are licensed for use. Beyond these vaccines, promising vaccine candidates are currently being studied that are not based on pneumococcal capsular polysaccharide. In years to come, these vaccines may provide universal protection against pneumococcal infection.

**Acknowledgements**

The author’s research makes use of the Multi Locus Sequence Typing website (http://www.mlst.net) developed by Man-Suen Chan and David Aanensen and funded by the Wellcome Trust. The author is a recipient of research funds from Wyeth, the manufacturer of Prevenar.

**References**


