Continued control of pneumococcal disease in the UK – the impact of vaccination

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Streptococcus pneumoniae, also known as the pneumococcus, is an important cause of morbidity and mortality in the developed and developing world. Pneumococcal conjugate vaccines were first introduced for routine use in the USA in 2000, although the seven-valent pneumococcal conjugate vaccine (PCV7) was not introduced into the UK’s routine childhood immunization programme until September 2006. After its introduction, a marked decrease in the incidence of pneumococcal disease was observed, both in the vaccinated and unvaccinated UK populations. However, pneumococci are highly diverse and serotype prevalence is dynamic. Conversely, PCV7 targets only a limited number of capsular types, which appears to confer a limited lifespan to the observed beneficial effects. Shifts in serotype distribution have been detected for both non-invasive and invasive disease reported since PCV7 introduction, both in the UK and elsewhere. The pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV, Synflorix; GlaxoSmithKline) and 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar 13; Pfizer) have been newly licensed. The potential coverage of the 10- and 13-valent conjugate vaccines has also altered alongside serotype shifts. Nonetheless, the mechanism of how PCV7 has influenced serotype shift is not clear-cut as the epidemiology of serotype prevalence is complex. Other factors also influence prevalence and incidence of pneumococcal carriage and disease, such as pneumococcal diversity, levels of antibiotic use and the presence of risk groups. Continued surveillance and identification of factors influencing serotype distribution are essential to allow rational vaccine design, implementation and continued effective control of pneumococcal disease.

Introduction

Streptococcus pneumoniae is a Gram-positive encapsulated bacterium. Currently 46 serogroups and 93 serotypes have been documented, the latest additions being serotype 6C (Park et al., 2007b), serotype 6D (Jin et al., 2009) and serotype 11E (Calix & Nahm, 2010). Capsular polysaccharides are highly immunogenic and are the main target for pneumococcal vaccines. However, the bacterium is capable of transformation, the horizontal exchange of genetic information, at both the intra- and interspecies level. This recombination of genetic material can result in subtle changes, which impact on the disease biology of strains and can also allow capsular switch to occur (Silva et al., 2006). This phenomenon results from recombination of heterologous DNA at the capsular locus. As a consequence, clonal isolates, as determined by multilocus sequence typing, can express different polysaccharide capsules (serotype). Isolates of the same serotype can also be of different sequence type (ST) (Coffey et al., 1998). The polysaccharide capsule is a key component of virulence, and serotypes differ in their association with invasive disease, antibiotic resistance and outbreak potential (Brueggemann et al., 2003; Magee & Yother, 2001; Weinberger et al., 2009).

The pneumococcal niche

Humans are the major reservoir of S. pneumoniae, carrying the bacteria asymptomatically in the nasopharynx (Hussain et al., 2005). Within the human population, young children are the key source of pneumococci. Prior to the seven-valent polysaccharide conjugate vaccine (PCV7) introduction in the UK, a carriage rate of 45 % had been reported in children under 2 years old, compared to only 8 % in those older than 18 (Hussain et al., 2005).

Despite being part of the respiratory commensal flora, the pneumococcus is also responsible for significant morbidity...
and mortality in the UK and worldwide (Melegaro et al., 2006; Mulholland, 2007). Pneumococcal disease ranges from acute otitis media (AOM) through to pneumonia and invasive disease (IPD) such as meningitis and septicaemia. Certain populations are at high risk of IPD and other pneumococcal diseases. These include infants under 2 years old, for whom a UK pre-PCV7 study estimated 15 pneumococcal meningitis cases per 100 000 (Melegaro et al., 2006). The elderly are also at risk, with approximately 45 cases of IPD per 100 000 occurring pre-PCV7 in persons over 65 years in Scotland (Kyaw et al., 2003). Additional risk groups for serious pneumococcal infection include children between 2 and 5 years old and the immunocompromised (Burman et al., 1985; Kyaw et al., 2003).

**Control of pneumococcal disease**

The 23-valent polysaccharide vaccine (PPV, Pneumovax; Merck) has been available for over 25 years. This vaccine is used today to vaccinate at-risk adults and the elderly. Unfortunately, immunization with PPV and the recently been found to be largely unsuccessful in the UK elderly population (Joint Committee on Vaccination and Immunisation, 2009). In addition, PPV is known to elicit a T-cell-independent immune response, which is underdeveloped in those under 2 years old (Stein, 1992). Conjugate vaccines were designed to improve efficacy in those under 2 years old.

PCV7 Prevenar (Pfizer, previously Wyeth) was first recommended for use in the US in the year 2000 (Committee on Infectious Diseases, 2000). The vaccine contains the capsular polysaccharide of seven serotypes, conjugated to CRM197, a non-toxic diphtheria variant carrier protein (Eskola et al., 2001). This immunogenic protein increases the vaccine efficacy in the young by inducing a T-cell-dependent response (Black et al., 2000; Rennels et al., 1998). The seven serotypes included in the vaccine were 4, 6B, 9V, 14, 18C, 19F and 23F – they caused the majority of invasive disease in the US (Hausdorff et al., 2000). These serotypes are also associated with high antibiotic resistance (Hicks et al., 2007; Tyrrell et al., 2009).

**PCV7 impact in the UK**

PCV7 vaccination in the UK was predicted to result in a decrease in pneumococcal disease incidence (Clarke et al., 2006), as described in the US (CDC, 2005), where PCV7 also resulted in a reduction in pneumococcal antibiotic non-susceptibility (Richter et al., 2009). In September 2006, PCV7 was added to the UK routine childhood immunization programme to help reduce the burden of pneumococcal disease (Department of Health, 2006).

Serotype surveillance data for IPD in England, Wales and Scotland since PCV7 vaccine introduction are being continuously collected (www.hpa.org.uk, www.hps.scot.nhs.uk). Current data for England and Wales (Kaye et al., 2009) show a 41% decrease in the number of IPD cases in those aged 5 years and under between 2005–2006 (797 cases) and 2007–2008 (470 cases). This is primarily a result of a dramatic decrease in the number of IPD cases caused by vaccine types (VTs) in children ≤ 5 years old. This decrease can also be clearly seen when comparing the cumulative total of cases reported in the under 5s by week 20 of 2006, 2007 and 2010 (Table 1). VT disease, previously accounting for 70% of cases in this age group during 2005–2006, reduced to only 24% in 2007–2008. These overall trends have also been observed in Scotland (Shakir et al., 2009).

In addition to the decrease in IPD in the vaccinated population, herd immunity to VT pneumococci has been induced in the UK population as an indirect effect of infant PCV7 immunization. A decrease in VT IPD incidence has been seen in children over the age of 5 and adults, who are largely unvaccinated (Kaye et al., 2009). The level of herd immunity has been suggested to increase with the number of doses given (Haber et al., 2007). Prior to this observation, surveillance carried out in the US demonstrated a 42% fall in the incidence of IPD in infants <90 days old (Carter, 2006), indicating that herd immunity can also extend to those not yet old enough to be vaccinated or to have completed the vaccination course. A US model also predicted that even incomplete coverage and/or limited dose schedules would still confer herd immunity (Haber et al., 2007). Herd immunity, primarily due to reduced exposure through decreased carriage and transmission from the vaccinated population, contributes extensively to the overall impact and cost-effectiveness of vaccination (CDC, 2005; Melegaro & Edmunds, 2004). Without such effects, the PCV7 introduction may not have been considered economically viable in the UK (Melegaro & Edmunds, 2004).

**Serotype replacement**

Following PCV7 introduction in the US, a shift in the prevalent serotypes circulating in the population and causing disease was observed, termed ‘serotype replacement’ (McEllisterem et al., 2003). This was predicted to be mirrored in the UK (Spratt & Greenwood, 2000).

<table>
<thead>
<tr>
<th>Year</th>
<th>In PCV7</th>
<th>Not in PCV7</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>400</td>
<td>150</td>
<td>550</td>
</tr>
<tr>
<td>2007</td>
<td>275</td>
<td>175</td>
<td>450</td>
</tr>
<tr>
<td>2010</td>
<td>25</td>
<td>375</td>
<td>400</td>
</tr>
</tbody>
</table>

Increase ↑/decrease ↓
Although there has been a dramatic reduction in VT IPD, the phenomenon of ‘replacement disease’ has occurred in the UK. Replacement disease is due to the increase in non-vaccine serotype (NVT) IPD cases, which has greatly offset the decrease in VT IPD (Table 1). The total number of IPD cases in those over 5 years of age did not change significantly between 2005–2006 (5514 cases) and 2007–2008 (5496 cases). Importantly, a recent increased incidence of IPD caused by PCV7 NVTs has been detected in all age groups, particularly involving serotypes 7F, 19A and 22F (Kaye et al., 2009). These NVTs have also been observed to cause an increased incidence of IPD in countries outside the UK using PCV7, such as in Portugal (Sá-Leão et al., 2009) and 19A and 22F in the US (Hicks et al., 2007). The post-PCV7 19A increase in the US was particularly associated with one multilocus sequence type, ST320, a clone which had high antibiotic resistance (Hanage et al., 2007; Pillai et al., 2009). This may have been the driving force in its increase (Dagan et al., 2009). However, the 19A clone increasing in the UK is predominantly ST199 (Pichon et al., 2008), not ST320, suggesting factors other than antibiotic resistance were involved in causing this increase.

Vaccine inclusion of related serotypes within a serogroup was previously assumed to confer some level of cross-protection (Hausdorff et al., 2000). However, serotype 19A IPD incidence has increased in the UK despite the fact that the related serotype 19F was included in the vaccine. The 19F polysaccharide is known to be the least immunogenic of the PCV7 VTs (Pletz et al., 2008), and in addition cross-reaction of antibodies for 19F to 19A has also been shown to be weak in vitro (Lee et al., 2009). In carriage, a significant increase in the prevalence of serotype 6C has been observed since PCV7 introduction in the UK (Nahm et al., 2009; Tocheva et al., 2010). This is despite the presence of the 6B polysaccharide in PCV7, which does provide protection against 6A (Väkeväinen et al., 2001). 6B cross-reactivity does not extend to 6C, therefore the PCV7 elicits negligible or no immune protection against this serotype (Park et al., 2007a). Serotypes related to the VTs have contributed to serotype replacement more than was perhaps first expected, potentially because they are in a prime position to fill the specific niche vacated by their counterpart in an environment under vaccine pressure. Replacement disease has dramatically reduced the effectiveness of PCV7 vaccination and is likely to be a major factor in the decision to replace PCV7 with PCV13 in April 2010.

The most common serotypes causing IPD can change rapidly. In Scotland, IPD-causing serotypes changed considerably from 2005/2006 to 2009 (Table 2). In 2009, 7F was reported to be the most common IPD-causing serotype in the under 5s, accounting for 12 % of cases (Kaye et al., 2009). Before the introduction of PCV7, this serotype caused little disease; in fact, 7F was not isolated from a single reported IPD case for children under 5 years old in Scotland during 2006 (unpublished data). Dramatic changes in serotype prevalence can occur over time. This demonstrates the importance of long-term epidemiological surveillance in allowing appropriate response and action to changes.

It must also be noted that serotype distribution can fluctuate substantially in the absence of vaccination. A highly significant increase in serotype 1 was observed within the UK prior to routine PCV7 immunization, highlighting that other factors are also involved in pneumococcal serotype dynamics (Jefferies et al., 2010; Kirkham et al., 2006).

Although not the only cause, PCV7 is likely to have been playing an important part in serotype fluctuations in the UK by reducing VTs and creating a niche, which is being filled by NVTs or other species of bacteria. Ongoing surveillance and research will help uncover the reasons why certain organisms appear better at filling this niche than others, and why some cause invasive disease while others cause little or none at all.

### Table 2. Serotypes (no. of cases) involved in IPD in Scotland: rank order of incidence in those ≤5 years old

<table>
<thead>
<tr>
<th>Rank</th>
<th>2006*</th>
<th>2009†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14 (26)</td>
<td>7F (50)</td>
</tr>
<tr>
<td>2</td>
<td>1 (8)</td>
<td>1 (35)</td>
</tr>
<tr>
<td>3</td>
<td>19F (5)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>4</td>
<td>6A (5)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>5</td>
<td>6B (5)</td>
<td>19A (24)</td>
</tr>
<tr>
<td>6</td>
<td>9V (5)</td>
<td>22F (24)</td>
</tr>
</tbody>
</table>

*Our unpublished data.
†Data from Shakir et al. (2009).

PCV7 coverage

Historically, PCV7 covered 90 % of the serotypes causing IPD in the US. Crucially, even before PCV7 introduction, the disease serotype coverage in the UK was much lower. In Scotland, only 76.5 % of all IPD cases in those aged under 5 years old were calculated to be covered by PCV7 (Clarke et al., 2006), whilst in the developing world coverage was suggested to drop as low as 45 % for IPD (Hausdorff et al., 2000).

Pneumococci are the primary causal agent for pneumonia. The impact of PCV7 on pneumonia is hard to quantify as confirmed pneumococcal pneumonia cases are difficult to define. Some result in IPD, while the majority probably do not. Despite this variation, studies have indicated that PCV7 efficacy for clinical and X-ray-defined pneumonia is between 5 % and 25 % (Black et al., 2002; Lucero et al., 2009). In addition, the incidence of pneumonia-related hospitalization has decreased by up to 39 % since PCV7 introduction in the US in children under 2 years old (Grijalva et al., 2007; CDC, 2009). All-cause pneumonia
cases remained stable during US PCV7 introduction, suggestive of other species contributing to disease replacement (CDC, 2009). Direct UK data regarding the impact of PCV7 on lower respiratory tract infection are not available, although it is likely that serotype replacement is occurring for pneumococcal pneumonia, as has been reported for IPD.

*S. pneumoniae* is also a leading cause of AOM. This non-invasive disease is a particular issue in young children and has a high economic burden worldwide (Melegaro et al., 2006). Pneumococcal conjugate vaccines have been shown to offer some protection against AOM (Eskola, 2006). Pneumococcal conjugate vaccines have been shown to decrease in the US post-PCV7 (Black et al., 2006). Direct UK data regarding the impact of PCV7 on lower respiratory tract infection are not available, although data from the US suggest that serotype replacement, strain switching, and species replacement may limit the effectiveness of pneumococcal vaccination against otitis media in the UK. *Haemophilus influenzae* is also an important cause of AOM, specifically, non-typable *H. influenzae* (NTHi) AOM, which was seen to increase by 15% following widespread PCV7 vaccination in the US (Casey et al., 2010). Increases in NTHi may also be filling part of the niche left by pneumococcal VTs in the UK.

Over time, PCV immunization will continue to impact on serotype prevalence and affect the incidence of pneumococcal disease. This impact will reduce current vaccine efficacy, confirming the need for ongoing vaccine development to ensure control of pneumococcal disease.

### Vaccine progression

PHiD-CV and PCV13 are now both licensed in the UK, with Prevenar 13 having replaced Prevenar in the UK immunization programme. These vaccines target additional serotypes that are important to current disease incidence and are not well targeted by PCV7 (Table 3).

The PHiD-CV developed by GlaxoSmithKline includes two capsular polysaccharide types conjugated to either diphtheria (serotype 19F) or tetanus (serotype 18C) toxoid, and eight others (1, 4, 5, 6B, 7F, 9V, 14, 23F) conjugated to NTHi protein D (Wysocki et al., 2009). This is said to give PHiD-CV the extra ability of providing some protection against AOM caused by NTHi and therefore may influence the impact and cost-effectiveness of this vaccine (Wysocki et al., 2009). Originally, the GlaxoSmithKline experimental vaccine included 11 serotypes, yet the inclusion of serotype 3 was rejected due to a lack of inducible immunogenicity during clinical trials (Prymula et al., 2006). The PCV13 developed by Wyeth (now Pfizer) targets the same pneumococcal serotypes as the PHiD-CV plus three additional serotypes, all conjugated to the immunogenic diphtheria toxoid (Scott et al., 2007). Notably, 22F is not targeted by the PHiD-CV or PCV13, and this serotype has dramatically increased in IPD prevalence in children under 2 years of age in England and Wales (Kaye et al., 2009). 22F is also now ranked sixth in Scotland for IPD in children under 5 (Table 2).

#### PHiD-CV and PCV13 coverage

Based on national (England and Wales) surveillance data, the percentage of serotypes causing cases of IPD covered by PCV7, PHiD-CV, and PCV13 was calculated (Kaye et al., 2009). In 2007–2008, only 24% of IPD cases in those under 5 years old were caused by serotypes covered by PCV7, in stark contrast to the 76.5% UK estimate based on IPD coverage in this age group prior to vaccine implementation (Clarke et al., 2006). The serotype coverage of IPD in children under 5 years of age for PHiD-CV and PCV13 was 53% and 74%, respectively, for 2007/2008, a dramatic decrease from the 81% and 92% 2005/2006 coverage. A fundamental observation is that the potential coverage of PHiD-CV and PCV13 had already decreased prior to implementation due to the routine use of PCV7 and the associated serotype replacement, as well as shifts in pneumococcal epidemiology caused by other non-vaccine factors.

Clinical trials and mathematical models offer a basis for prediction of vaccine impact. One study used an algorithm that suggested that the PHiD-CV will be at least as effective as PCV7 in protecting against pneumococcal invasive disease worldwide (Hausdorff et al., 2009), although the design of such an algorithm is complex and based on assumptions which may affect the model output. In clinical trials, the study population will naturally be exposed to multifaceted epidemiological factors that will affect vaccine

### Table 3. Serotypes included in the 7-, 10- and 13-valent PCVs

Data from Black et al. (2000), Scott et al. (2007) and Wysocki et al. (2009). Bold and underlined text indicates serotypes not included in PCV7.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Serotypes</th>
<th>UK status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7 (Prevenar)</td>
<td>Pfizer</td>
<td>4, 6B, 9V, 14, 18C, 19F, 23F</td>
<td>Licensed</td>
</tr>
<tr>
<td>PHiD-CV (Synflorix)</td>
<td>GlaxoSmithKline</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F</td>
<td>Licensed</td>
</tr>
<tr>
<td>PCV13 (Prevenar 13)</td>
<td>Pfizer</td>
<td>1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F</td>
<td>Licensed in use</td>
</tr>
</tbody>
</table>
Impact in the target population. A German clinical study, powered to show immunological non-inferiority, showed that PCV13 should be just as effective as PCV7 at protecting against the seven serotypes included within the PCV7, as well as inducing sufficient immunity for the further VTs (Kieninger et al., 2008). Importantly, PCV13 was shown to induce an opsonophagocytic activity to serotype 19A, which indicates that it will be efficient in preventing cases of serotype 19A invasive disease (Kieninger et al., 2008).

Both PHiD-CV and PCV13 are likely to be effective in reducing IPD and non-invasive disease. However, the relative effect of PHiD-CV compared to PCV13 immunization on the prevention of combined pneumococcal and NTHi invasive or all-cause disease has not yet been established. As well as the effect on invasive diseases, pneumococcal carriage in individuals and the population is affected by routine immunization of the population, and the serotype effects appear to differ from those seen in invasive disease (unpublished data).

Invasive potential

Pneumococcal serotypes are known to differ in their invasiveness (Smith et al., 1993). Traditionally the serotypes chosen for vaccine inclusion have been based on the rank order incidence of disease. These serotypes are often the most prevalent in carriage but they are not necessarily those with the highest potential for invasiveness (Brueggemann et al., 2003, 2004). By targeting the serotypes in rank order of disease incidence, any serotype replacement that occurs may result in increased prevalence of a particularly invasive serotype. Several studies have calculated the potential of an individual serotype causing a disease case, taking into account factors such as the prevalence in carriage (Bättig et al., 2006; Brueggemann et al., 2004; Hanage et al., 2005). One study highlighted that moderately prevalent NVT serotypes 3, 8, 33 and 38 all had similar potential to cause invasive disease as the VT 6B, 19F and 23F, previously responsible for a considerable proportion of disease cases in the pre-vaccine era (Brueggemann et al., 2004). If a shift in prevalence occurred, for example, reduced VT 23F with increased NVT 8, this could then potentially result in serotype 8 having a similar disease incidence as VT 23F previously. NVT 19A and 7F, which have recently increased as a cause of IPD in the UK (Kaye et al., 2009), have also previously been reported to be associated with invasive disease (Brueggemann et al., 2003; Sjöström et al., 2006). This may indicate that greater virulence of a serotype has been central to the rise in case numbers rather than an expansion of clones with these serotypes.

The presence of serotypes in PHiD-CV and PCV13 additional to those contained within PCV7 will, to some degree, help to protect against the emergence of some previously under-represented serotypes with significant invasive potential.

Future work

Data are only just becoming available on post-PCV7 pneumococcal carriage in the UK due to the time vaccine implementation has taken to translate into altered carriage and for the collection of comparable data. Further serotype data are also required for pneumonia and AOM, although these are not collected routinely by UK surveillance systems. A more detailed understanding of the dynamics of serotype prevalence is central to sustaining the control of pneumococcal disease.

Due to the global variation in serotype prevalence, vaccine design and use would preferably be specific to a geographical area, although this is unrealistic due to the time and cost involved in vaccine development. Future vaccines may have broader global application if design can employ more complex epidemiological models to simulate serotype replacement. One alternative is the use of vaccines based on highly conserved, immunogenic pneumococcal surface proteins that are involved in bacterial virulence. Current candidate proteins include pneumococcal surface protein A (PspA), pneumococcal surface protein C (PspC), pneumolysin (Ply) and caseinolytic protease (ClpP) (Cao et al., 2007; Hamel et al., 2004). Proteins could potentially be used in combination to maximize synergistic effects potentially providing protection from most, if not all, isolates of pneumococci (Cao et al., 2007; Morsczeck et al., 2008). Protein-based vaccines could potentially give broad protection from pneumococcal infection independent of serotype and invasiveness. However, such vaccines would also be predicted to have major effects on overall pneumococcal carriage with as yet unknown clinical significance of non-pneumococcal bacterial replacement. Establishing protection against otitis media and carriage would also ideally require stimulation of a mucosal antibody response (Zhang et al., 2002). If proven to be safe in both direct and indirect effects, additional advantages of protein-only vaccines could be the induction of T-cell responses and ease of vaccine formulation resulting in reduced production costs when compared to conjugate vaccines. At present, candidate proteins are being evaluated in murine models, including the demonstration of passive immunity from polyclonal antibodies against specific pneumococcal proteins (Cao et al., 2007, 2009; Morsczeck et al., 2008; Ogunniyi et al., 2007).

Summary

Four winters after PCV7 introduction to the UK routine infant immunization programme, the positive impact is clear. There has been a significant reduction in the incidence of PCV7 serotypes causing pneumococcal IPD in those under 5 years old, together with the induction of herd immunity. However, serotype replacement has occurred, such that IDP incidence in those under 2 years of age is now similar to that prior to PCV7 introduction.

Serotype replacement has been observed for invasive and non-invasive pneumococcal disease worldwide, and it is
evident that the overall effectiveness of PCV7 on the total pneumococcal disease burden has reduced. In April 2010, PCV13 replaced PCV7 in the UK infant immunization programme, and it is important to note that no older child catch-up campaign has been implemented (Department of Health, 2010). The presence of additional serotypes within PCV13 will help to combat the serotype replacement observed. Many additional factors will influence the serotype shifts in carriage and disease, including capsular switch events and presence of antimicrobial resistance. Nevertheless, pneumococcal vaccines based on a limited number of serotypes will continue to have a limited lifespan due to the selection pressure vaccines exert and the diversity of the bacteria. Increased vaccine coverage and control of pneumococcal disease is required worldwide, not only in the UK and other Western countries.

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References


