Review

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

R. A. Gladstone,[1] J. M. Jefferies,[1,2,3] S. N. Faust[1,3,4] and S. C. Clarke[1,2,3]

Correspondence
S. C. Clarke
S.C.Clarke@soton.ac.uk

[1]Division of Infection, Inflammation and Immunity, University of Southampton School of Medicine, UK

[2]Health Protection Agency, Southampton, UK

[3]Southampton NIHR Respiratory Biomedical Research Unit, Division of Infection, Inflammation and Immunity, Southampton University School of Medicine, UK

[4]Wellcome Trust Clinical Research Facility, Southampton University Hospitals Trust, Southampton, UK

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 has 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 CRM_{197}, 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 – 4, 6B, 9V, 14, 18C, 19F and 23F – were selected as 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 $\leqslant$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' (McEllistrem *et al.*, 2003). This was predicted to be mirrored in the UK (Spratt & Greenwood, 2000).

Table 1. Approximate number of IPD reports in those $<$5 years old by week 20 of 2006, 2007 or 2010

Data adapted from Current Epidemiology of Invasive Pneumococcal Disease (IPD) graphs, HPA website (www.hpa.org.uk).

Year	In PCV7	Not in PCV7	Total cases
2006	400	150	550
2007	275	175	450
2010	25	375	400
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 7F 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.

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

Rank	2006*	2009†
1	14 (26)	7F (50)
2	1 (8)	1 (35)
3	19F (5)	8 (32)
4	6A (5)	3 (30)
5	6B (5)	19A (24)
6	9V (5)	22F (24)

*Our unpublished data.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

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.

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 *et al.*, 2001; Prymula *et al.*, 2006); additionally the incidence has been shown to decrease in the US post-PCV7 (Black *et al.*, 2004; Block *et al.*, 2004; Eskola *et al.*, 2001; Prymula *et al.*, 2006). US cases of otitis media due to NVTs were also seen to increase in incidence in the post-PCV7 era, a 10 % rise in NVTs was reported by one study (Block *et al.*, 2004), along with observations of capsular switch events (McEllistrem *et al.*, 2003). Serotype data for AOM in the UK and Europe are scarce (Rodgers *et al.*, 2009), although data from the US suggest that serotype replacement, capsular switch 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.

Vaccine	Manufacturer	Serotypes	UK status
PCV7 (Prevenar)	Pfizer	4, 6B, 9V, 14, 18C, 19F, 23F	Licensed
PHiD-CV (Synflorix)	GlaxoSmithKline	**1**, 4, **5**, 6B, **7F**, 9V, 14, 18C, 19F, 23F	Licensed
PCV13 (Prevenar 13)	Pfizer	**1**, **3**, 4, **5**, **6A**, 6B, **7F**, 9V, 14, 18C, **19A**, 19F, 23F	Licensed in use

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 IPD 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.

Acknowledgements

Part of the work described in this review was funded by an investigator-led unrestricted research grant from Wyeth Vaccines.

References

Bättig, P., Hathaway, L. J., Hofer, S. & Mühlemann, K. (2006). Serotype-specific invasiveness and colonization prevalence in *Streptococcus pneumoniae* correlate with the lag phase during in vitro growth. *Microbes Infect* **8**, 2612–2617.

Black, S., Shinefield, H., Fireman, B., Lewis, E., Ray, P., Hansen, J. R., Elvin, L., Ensor, K. M., Hackell, J. & other authors (2000). Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* **19**, 187–195.

Black, S. B. M., Shinefield, H. R. M., Ling, S. M. M., Hansen, J., Fireman, B. M., Spring, D. M., Noyes, J. M., Lewis, E. M., Ray, P. M. & other authors (2002). Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J* **21**, 810–815.

Black, S., Shinefield, H., Baxter, R., Austrian, R., Bracken, L., Hansen, J., Lewis, E. & Fireman, B. (2004). Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. *Pediatr Infect Dis J* **23**, 485–489.

Block, S. L., Hedrick, J., Harrison, C. J., Tyler, R., Smith, A., Findlay, R. & Keegan, E. (2004). Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. *Pediatr Infect Dis J* **23**, 829–833.

Brueggemann, A. B., Griffiths, D. T., Meats, E., Peto, T. E., Crook, D. W. & Spratt, B. G. (2003). Clonal relationships between invasive and carriage *Streptococcus pneumoniae* and serotype- and clone-specific differences in invasive disease potential. *J Infect Dis* **187**, 1424–1432.

Brueggemann, A. B., Peto, T. E., Crook, D. W., Butler, J. C., Kristinsson, K. G. & Spratt, B. G. (2004). Temporal and geographic stability of the serogroup-specific invasive disease potential of *Streptococcus pneumoniae* in children. *J Infect Dis* **190**, 1203–1211.

Burman, L. A., Norrby, R. & Trollfors, B. (1985). Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. *Rev Infect Dis* **7**, 133–142.

Calix, J. J. & Nahm, M. H. (2010). A new pneumococcal serotype, 11E, has a variably inactivated *wcjE* gene. *J Infect Dis* **202**, 29–38.

Cao, J., Chen, D., Xu, W., Chen, T., Xu, S., Luo, J., Zhao, Q., Liu, B., Wang, D. & other authors (2007). Enhanced protection against pneumococcal infection elicited by immunization with the combination of PspA, PspC, and ClpP. *Vaccine* **25**, 4996–5005.

Cao, J., Li, D., Gong, Y., Yin, N., Chen, T., Wong, C. K., Xu, W., Luo, J., Zhang, X. & other authors (2009). Caseinolytic protease: a protein vaccine which could elicit serotype-independent protection against invasive pneumococcal infection. *Clin Exp Immunol* **156**, 52–60.

Carter, R. J. F. (2006). Infants too young to receive pneumococcal conjugate vaccine benefit from herd immunity. *Thorax* **61**, 610.

Casey, J. R., Adlowitz, D. G. & Pichichero, M. E. (2010). New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J* **29**, 304–309.

CDC (2005). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease – United States, 1998–2003. *MMWR Morb Mortal Wkly Rep* **54**, 893–897.

CDC (2009). Pneumonia hospitalizations among young children before and after introduction of pneumococcal conjugate vaccine – United States, 1997–2006. *MMWR Morb Mortal Wkly Rep* **58**, 1–4.

Clarke, S. C., Jefferies, J. M., Smith, A. J., McMenamin, J., Mitchell, T. J. & Edwards, G. F. S. (2006). Potential impact of conjugate vaccine on the incidence of invasive pneumococcal disease among children in Scotland. *J Clin Microbiol* **44**, 1224–1228.

Coffey, T. J., Enright, M. C., Daniels, M., Morona, J. K., Morona, R., Hryniewicz, W., Paton, J. C. & Spratt, B. G. (1998). Recombinational exchanges at the capsular polysaccharide biosynthetic locus lead to frequent serotype changes among natural isolates of *Streptococcus pneumoniae*. *Mol Microbiol* **27**, 73–83.

Committee on Infectious Diseases (2000). Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics* **106**, 362–366.

Dagan, R., Givonâ-Lavi, N., Leibovitz, E., Greenberg, D. & Porat, N. (2009). Introduction and proliferation of multidrug-resistant *Streptococcus pneumoniae* serotype 19A clones that cause acute otitis media in an unvaccinated population. *J Infect Dis* **199**, 776–785.

Department of Health (2006). Important changes to the childhood immunisation programme, PL/CMO/2006/1.

Department of Health (2010). Introduction of Prevenar 13® into the Childhood Immunisation Programme. Department of Health, Gateway reference: 13581.

Eskola, J., Kilpi, T., Palmu, A., Jokinen, J., Haapakoski, J., Herva, E., Takala, A., Kayhty, H., Karma, P. & other authors (2001). Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* **344**, 403–409.

Grijalva, C. G., Nuorti, J. P., Arbogast, P. G., Martin, S. W., Edwards, K. M. & Griffin, M. R. (2007). Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet* **369**, 1179–1186.

Haber, M., Barskey, A., Baughman, W., Barker, L., Whitney, C. G., Shaw, K. M., Orenstein, W. & Stephens, D. S. (2007). Herd immunity and pneumococcal conjugate vaccine: a quantitative model. *Vaccine* **25**, 5390–5398.

Hamel, J., Charland, N., Pineau, I., Ouellet, C., Rioux, S., Martin, D. & Brodeur, B. R. (2004). Prevention of pneumococcal disease in mice immunized with conserved surface-accessible proteins. *Infect Immun* **72**, 2659–2670.

Hanage, W. P., Kaijalainen, T. H., Syrjanen, R. K., Auranen, K., Leinonen, M., Makela, P. H. & Spratt, B. G. (2005). Invasiveness of

serotypes and clones of *Streptococcus pneumoniae* among children in Finland. *Infect Immun* **73**, 431–435.

Hanage, W. P., Huang, S. S., Lipsitch, M., Bishop, C. J., Godoy, D., Pelton, S. I., Goldstein, R., Huot, H. & Finkelstein, J. A. (2007). Diversity and antibiotic resistance among nonvaccine serotypes of *Streptococcus pneumoniae* carriage isolates in the post-heptavalent conjugate vaccine era. *J Infect Dis* **195**, 347–352.

Hausdorff, W. P., Bryant, J., Paradiso, P. R. & Siber, G. R. (2000). Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin Infect Dis* **30**, 100–121.

Hausdorff, W. P., Dagan, R., Beckers, F. & Schuerman, L. (2009). Estimating the direct impact of new conjugate vaccines against invasive pneumococcal disease. *Vaccine* **27**, 7257–7269.

Hicks, L. A., Harrison, L. H., Flannery, B., Hadler, J. L., Schaffner, W., Craig, A. S., Jackson, D., Thomas, A., Beall, B. & other authors (2007). Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. *J Infect Dis* **196**, 1346–1354.

Hussain, M., Melegaro, A., Pebody, R. G., George, R., Edmunds, W. J., Talukdar, R., Martin, S. A., Efstratiou, A. & Miller, E. (2005). A longitudinal household study of *Streptococcus pneumoniae* nasopharyngeal carriage in a UK setting. *Epidemiol Infect* **133**, 891–898.

Jefferies, J. M., Smith, A. J., Edwards, G. F. S., McMenamin, J., Mitchell, T. J. & Clarke, S. C. (2010). Temporal analysis of invasive pneumococcal clones from Scotland illustrates fluctuations in diversity of serotype and genotype in the absence of pneumococcal conjugate vaccine. *J Clin Microbiol* **48**, 87–96.

Jin, P., Kong, F., Xiao, M., Oftadeh, S., Zhou, F., Liu, C., Russell, F. & Gilbert, G. L. (2009). First report of putative *Streptococcus pneumoniae* serotype 6D among nasopharyngeal isolates from Fijian children. *J Infect Dis* **200**, 1375–1380.

Joint Committee on Vaccination and Immunisation (2009). *Minutes of the Pneumococcal Subgroup on Tuesday 15th January*. Department of Health.

Kaye, P., Malkani, R., Martin, S., Slack, M., Trotter, C., Jit, M., George, R. & Miller, E. (2009). Invasive pneumococcal disease (IPD) in England & Wales after 7-valent conjugate vaccine (PCV7); potential impact of 10 and 13-valent vaccines. *Presented at The 27th Annual Meeting of the European Society for Paediatric Infectious Diseases*, 9–13 June 2009, Brussels.

Kieninger, D. M., Kueper, K., Steul, K., Juergens, C., Ahlers, N., Baker, S., Giardina, P., Gruber, W. & Scott, D. (2008). Safety and immunologic non-inferiority of 13-valent pneumococcal conjugate vaccine compared to 7-valent pneumococcal conjugate vaccine given as a 4-dose series with routine vaccines in healthy infants and toddlers. *Presented at The 48th Annual ICAAC/IDSA 46th Annual Meeting*, 25–28 October 2008, Washington DC.

Kirkham, L.-A. S., Jefferies, J. M. C., Kerr, A. R., Jing, Y., Clarke, S. C., Smith, A. & Mitchell, T. J. (2006). Identification of invasive serotype 1 pneumococcal isolates that express nonhemolytic pneumolysin. *J Clin Microbiol* **44**, 151–159.

Kyaw, M. H., Christie, P., Clarke, S. C., Mooney, J. D., Ahmed, S., Jones, I. G. & Campbell, H. (2003). Invasive pneumococcal disease in Scotland, 1999–2001: use of record linkage to explore associations between patients and disease in relation to future vaccination policy. *Clin Infect Dis* **37**, 1283–1291.

Lee, H., Nahm, M. H., Burton, R. & Kim, K. (2009). Immune response in infants to the heptavalent pneumococcal conjugate vaccine against vaccine-related serotypes 6A and 19A. *Clin Vaccine Immunol* **16**, 376–381.

Lucero, M. G., Dulalia, V. E., Nillos, L. T., Williams, G., Parreno, R. A., Nohynek, H., Riley, I. D. & Makela, H. (2009). Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. *Cochrane Database Syst Rev* CD004977.

Magee, A. D. & Yother, J. (2001). Requirement for capsule in colonization by *Streptococcus pneumoniae*. *Infect Immun* **69**, 3755–3761.

McEllistrem, M. C., Adams, J., Mason, E. O. & Wald, E. R. (2003). Epidemiology of acute otitis media caused by *Streptococcus pneumoniae* before and after licensure of the 7-valent pneumococcal protein conjugate vaccine. *J Infect Dis* **188**, 1679–1684.

Melegaro, A. & Edmunds, W. J. (2004). Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. *Vaccine* **22**, 4203–4214.

Melegaro, A., Edmunds, W. J., Pebody, R., Miller, E. & George, R. (2006). The current burden of pneumococcal disease in England and Wales. *J Infect* **52**, 37–48.

Morsczeck, C., Prokhorova, T., Sigh, J., Pfeiffer, M., Bille-Nielsen, M., Petersen, J., Boysen, A., Kofoed, T., Frimodt-Møller, N. & other authors (2008). *Streptococcus pneumoniae*: proteomics of surface proteins for vaccine development. *Clin Microbiol Infect* **14**, 74–81.

Mulholland, K. (2007). Perspectives on the burden of pneumonia in children. *Vaccine* **25**, 2394–2397.

Nahm, M. H., Lin, J., Finkelstein, J. A. & Pelton, S. I. (2009). Increase in the prevalence of the newly discovered pneumococcal serotype 6C in the nasopharynx after introduction of pneumococcal conjugate vaccine. *J Infect Dis* **199**, 320–325.

Ogunniyi, A. D., Grabowicz, M., Briles, D. E., Cook, J. & Paton, J. C. (2007). Development of a vaccine against invasive pneumococcal disease based on combinations of virulence proteins of *Streptococcus pneumoniae*. *Infect Immun* **75**, 350–357.

Park, I. H., Park, S., Hollingshead, S. K. & Nahm, M. H. (2007a). Genetic basis for the new pneumococcal serotype, 6C. *Infect Immun* **75**, 4482–4489.

Park, I. H., Pritchard, D. G., Cartee, R., Brandao, A., Brandileone, M. C. C. & Nahm, M. H. (2007b). Discovery of a new capsular serotype (6C) within serogroup 6 of *Streptococcus pneumoniae*. *J Clin Microbiol* **45**, 1225–1233.

Pichon, B., Beasley, L., Slack, M., Efstratiou, A., Miller, E. & George, R. (2008). Effect of the introduction of the pneumococcal conjugate vaccine in the UK childhood immunisation scheme on the genetic structure of paediatric invasive pneumococci. In *The 6th International Symposium on Pneumococci and Pneumococcal Diseases*, 8–12 June 2008, Reykjavik, Iceland.

Pillai, D. R., Shahinas, D., Buzina, A., Pollock, R. A., Lau, R., Khairnar, K., Wong, A., Farrell, D. J., Green, K. & other authors (2009). Genome-wide dissection of globally emergent multi-drug resistant serotype 19A *Streptococcus pneumoniae*. *BMC Genomics* **10**, 642.

Pletz, M. W., Maus, U., Krug, N., Welte, T. & Lode, H. (2008). Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. *Int J Antimicrob Agents* **32**, 199–206.

Prymula, R., Peeters, P., Chrobok, V., Kriz, P., Novakova, E., Kaliskova, E., Kohl, I., Lommel, P., Poolman, J. & other authors (2006). Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study. *Lancet* **367**, 740–748.

Rennels, M. B., Edwards, K. M., Keyserling, H. L., Reisinger, K. S., Hogerman, D. A., Madore, D. V., Chang, I., Paradiso, P. R., Malinoski, F. J. & other authors (1998). Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. *Pediatrics* **101**, 604–611.

Richter, S. S., Heilmann, K. P., Dohrn, C. L., Riahi, F., Beekmann, S. E. & Doern, G. V. (2009). Changing epidemiology of antimicrobial-resistant *Streptococcus pneumoniae* in the United States, 2004–2005. *Clin Infect Dis* **48**, e23–e33.

Rodgers, G. L., Arguedas, A., Cohen, R. & Dagan, R. (2009). Global serotype distribution among *Streptococcus pneumoniae* isolates causing otitis media in children: potential implications for pneumococcal conjugate vaccines. *Vaccine* **27**, 3802–3810.

Sá-Leão, R., Nunes, S., Brito-Avô, A., Frazão, N., Simões, A. S., Crisóstomo, M. I., Paulo, A. C. S., Saldanha, J., Santos-Sanches, I. & other authors (2009). Changes in pneumococcal serotypes and antibiotypes carried by vaccinated and unvaccinated day-care centre attendees in Portugal, a country with widespread use of the seven-valent pneumococcal conjugate vaccine. *Clin Microbiol Infect* **15**, 1002–1007.

Scott, D. A., Komjathy, S. F., Hu, B. T., Baker, S., Supan, L. A., Monahan, C. A., Gruber, W., Siber, G. R. & Lockhart, S. P. (2007). Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. *Vaccine* **25**, 6164–6166.

Shakir, E., Cameron, C., Denham, B. & McMenamin, J. (2009). Respiratory and immunisation quarterly report. *HPS Wkly Rep* **43**, 407–408.

Silva, N. A., McCluskey, J., Jefferies, J. M. C., Hinds, J., Smith, A., Clarke, S. C., Mitchell, T. J. & Paterson, G. K. (2006). Genomic diversity between strains of the same serotype and multilocus sequence type among pneumococcal clinical isolates. *Infect Immun* **74**, 3513–3518.

Sjöström, K., Spindler, C., Ortqvist, A., Kalin, M., Sandgren, A., Kühlmann-Berenzon, S. & Henriques-Normark, B. (2006). Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. *Clin Infect Dis* **42**, 451–459.

Smith, T., Lehmann, D., Montgomery, J., Gratten, M., Riley, I. D. & Alpers, M. P. (1993). Acquisition and invasiveness of different serotypes of Streptococcus pneumoniae in young children. *Epidemiol Infect* **111**, 27–39.

Spratt, B. G. & Greenwood, B. M. (2000). Prevention of pneumococcal disease by vaccination: does serotype replacement matter? *Lancet* **356**, 1210–1211.

Stein, K. E. (1992). Thymus-independent and thymus-dependent responses to polysaccharide antigens. *J Infect Dis* **165**, S49–S52.

Tocheva, A. S., Jefferies, J. M. C., Christodoulides, M., Faust, S. N. & Clarke, S. C. (2010). Increase in serotype 6C pneumococcal carriage, United Kingdom. *Emerg Infect Dis* **16**, 154–155.

Tyrrell, G. J., Lovgren, M., Chui, N., Minion, J., Garg, S., Kellner, J. D. & Marrie, T. J. (2009). Serotypes and antimicrobial susceptibilities of invasive *Streptococcus pneumoniae* pre- and post-seven valent pneumococcal conjugate vaccine introduction in Alberta, Canada, 2000–2006. *Vaccine* **27**, 3553–3560.

Väkeväinen, M., Eklund, C., Eskola, J. & Käyhty, H. (2001). Cross-reactivity of antibodies to Type 6B and 6A polysaccharides of *Streptococcus pneumoniae*, evoked by pneumococcal conjugate vaccines, in infants. *J Infect Dis* **184**, 789–793.

Weinberger, D. M., Trzcinski, K., Lu, Y., Bogaert, D., Brandes, A., Galagan, J., Anderson, P. W., Malley, R. & Lipsitch, M. (2009). Pneumococcal capsular polysaccharide structure predicts serotype prevalence. *PLoS Pathog* **5**, e1000476.

Wysocki, J., Tejedor, J. C., Grunert, D., Konior, R., Garcia-Sicilia, J., Knuf, M., Bernard, L., Dieussaert, I. & Schuerman, L. (2009). Immunogenicity of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) when coadministered with different *Neisseria meningitidis* serogroup C conjugate vaccines. *Pediatr Infect Dis J* **28**, S77–S88.

Zhang, Q., Choo, S. & Finn, A. (2002). Immune responses to novel pneumococcal proteins Pneumolysin, PspA, PsaA, and CbpA in adenoidal B cells from children. *Infect Immun* **70**, 5363–5369.