

The clinical and ecological impact of childhood pneumococcal vaccination

Routine childhood vaccination against *Streptococcus pneumoniae* with PCV7 has reduced the incidence of pneumococcal disease as a result of the vaccine serotypes. However, it has also resulted in the emergence of serotypes not included in the vaccine, offsetting, but not yet overcoming, the benefits of vaccination.

Before pneumococcal vaccination, *Streptococcus pneumoniae* caused the majority of cases of pneumonia in the UK (Lim et al, 2001), most cases of bacterial meningitis in the USA (Durand et al, 1993) and was the third commonest isolate from blood cultures in England and Wales (Parsons and Dockrell, 2002). The World Health Organization estimated that pneumococcal infections accounted for the deaths of 476 000 children under 5 years of age worldwide in 2008 (World Health Organization, 2012).

There is substantial diversity in the capsular polysaccharide structure of pneumococci, generating greater than 90 serotypes (Henrichsen, 1995). As all vaccines use capsular polysaccharide antigen this serotype diversity has led to the development of multivalent vaccines, providing immunity to several serotypes. A quadrivalent and a hexavalent pneumococcal polysaccharide vaccine (PPV) were developed in the 1940s, followed by a 14-valent PPV in 1977 and 23-valent PPV in 1983 (Grabenstein and Klugman, 2012); PPV23 continues to be used in adults in the UK. However, the relatively poor immunogenicity of polysaccharide antigens means that children under 2 years of age, who are at particular risk of invasive pneumococcal disease, do not mount an adequate immune response to PPV23.

Conjugation of the pneumococcal polysaccharides to a carrier protein (e.g. diphtheria toxoid) enhances the polysaccharide-specific antibody response. This led to the development of a heptavalent pneumococcal conjugate vaccine (PCV7), licensed in 2000, which provides protective immunity in children under 2 years of age (Knuf et al, 2011). PCV7 has since been used as part of the routine infant vaccination schedule in many countries to prevent invasive pneumococcal disease in children. PCV7 was introduced to the UK childhood vac-

ination schedule in September 2006, and was replaced by a 13-valent conjugate vaccine (PCV13) in 2010 (Miller et al, 2011).

While PCV7 has had a significant impact on the prevalence of invasive pneumococcal disease in vaccinated and unvaccinated children and in adults, there has been considerable variation in the reduction in invasive pneumococcal disease achieved through vaccination in different regions. This review examines the reasons for this and evaluates the clinical and ecological impact of the routine vaccination of children with PCV7, as well as the clinical impact of the changing serotype ecology.

The clinical impact of PCV7

Vaccination of children with PCV7 leads to reduced nasopharyngeal colonization with vaccine-type pneumococci (Huang et al, 2005). As nasopharyngeal colonization is an essential step in the transmission of pneumococci and in the development of invasive infection, reducing colonization decreases both transmission and the risk of developing invasive pneumococcal disease (Muñoz-Almagro et al, 2009). Accordingly, vaccination with PCV7 has resulted in dramatic reductions in invasive pneumococcal disease as a result of vaccine-type pneumococci in vaccinated children, but also in all other age groups as a result of herd immunity (Pilishvili et al, 2010; Leal et al, 2012).

In England and Wales, vaccination with PCV7 has resulted in a reduction in invasive pneumococcal infection with vaccine-type pneumococci in children, with a 98% reduction in invasive pneumococcal disease caused by vaccine-type pneumococci in children under 2 years of age. However, it has also had a marked impact on the incidence of pneumococcal pneumonia caused by vaccine-type pneumococci in older adults, with an 81% reduction in vaccine-type pneumococcal pneumonia in individuals over 65 years of age, preventing 3070 hospital admissions caused by pneumococcal disease per year in people of all ages (Miller et al, 2011). PCV7 could potentially prevent up to 57% of cases of adult community-acquired pneumococcal pneumonia (Bewick et al, 2012).

The lesser impact of PCV7 in reducing invasive pneumococcal disease in older adults than in children proba-

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bly partly reflects the higher incidence of infection with less invasive, non-vaccine-type with increasing age and comorbidity (Bewick et al, 2012). In addition to reducing cases of pneumonia, PCV7 has also resulted in a reduction in cases of acute otitis media (Grijalva et al, 2006) and in cases of pneumococcal meningitis (Van der Linden et al, 2012).

While the incidence of invasive pneumococcal disease has declined in all countries following the introduction of PCV7 there has been wide variation in the extent of the observed reduction. The very significant reduction in total cases of invasive pneumococcal disease seen in the USA after the introduction of PCV7 has not been replicated in Europe, with a notably lesser reduction in invasive pneumococcal disease seen in Spain, the UK and the Netherlands (Miller et al, 2011; Horácio et al, 2012; Vergison and Hanquet, 2012). PCV7 was formulated to cover the serotypes most commonly causing invasive pneumococcal disease in North America (Jauneikaite et al, 2012) and the observed differences in the impact of PCV7 may reflect differences in the pre-vaccine serotype ecology.

In the pre-PCV7 era seven vaccine-type serotypes of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F and 23F) accounted for the large majority of invasive pneumococcal disease in the USA but there was considerable variation in the prevalence of certain serotypes between geographical regions; for example invasive pneumococcal disease caused by serotype 1 was more prevalent in Europe than the USA (Horácio et al, 2012) and overall vaccine-type pneumococci accounted for a lower proportion of invasive pneumococcal disease in Europe than the USA: 72% in Europe compared to >80% in the USA (Reinert et al, 2010). Although this difference of 8% is relatively small, it may partly account for why PCV7 has not been as effective in Europe as it has in the USA (Vergison and Hanquet, 2012).

The ecological impact of PCV7: serotype replacement

Probably the single most important reason for the relative lack of effectiveness of PCV7 on the overall incidence of *S. pneumoniae* infections in some countries is that vaccination is associated with changes in pneumococcal serotype ecology. As PCV7 protects against only seven of the many circulating pneumococcal serotypes concerns were raised that, following the introduction of vaccination, non-vaccine serotypes could increase in prevalence and reduce the benefits of vaccination (Weinberger et al, 2011). Indeed, although vaccination with PCV7 has resulted in a marked decrease in the carriage of vaccine-type among both vaccinated and unvaccinated children, there has been a proportional increase in the carriage of non-vaccine serotypes, leaving overall carriage rates unchanged (Huang et al, 2005). This effect on colonization is termed serotype replacement.

The extent of serotype replacement since the introduction of PCV7 has varied in different settings: only modest replacement has been observed in North America, while a greater level of serotype replacement has been seen in England and Wales (Pilishvili et al, 2010), and in some countries such as Spain, serotype replacement with non-vaccine serotypes has almost entirely offset the reduction in the incidence of invasive pneumococcal disease caused by vaccine serotypes (Muñoz-Almagro et al, 2009).

The variation in serotype replacement after the introduction of PCV7 could reflect differences in pre-vaccine serotype ecology; a greater incidence of non-vaccine serotypes before the introduction of vaccination may allow more rapid expansion of these serotypes in response to the elimination of vaccine type pneumococci. Even within populations there has been variation in serotype replacement; for example, while serotype replacement has been limited in most of the USA, in parts of Alaska populated mostly by indigenous peoples serotype replacement has almost completely negated the benefit of PCV7 (Wenger et al, 2010). These specific populations have very high rates of pneumococcal disease and colonization, with the potential to allow much more rapid expansion of non-vaccine serotypes after the introduction of routine vaccination with PCV. These data also highlight the potential role of living conditions and genetic factors, in addition to geography, in influencing serotype replacement.

Although the emergence of non-vaccine serotypes has varied in different settings, there has been a consistent increase in the prevalence of specific serotypes 1, 7F, 19A and 22F (Miller et al, 2011; Weil-Olivier et al, 2012), with serotype 19A becoming the dominant non-vaccine serotype in many different geographical areas (Horácio et al, 2012). This is perhaps surprising, as it was initially anticipated that the 19F component of PCV7 would provide some cross protection against 19A. The expansion of serotype 19A has been mostly driven by increased prevalence of existing 19A strains but strains expressing vaccine-type capsular serotypes have also undergone recombination events at the capsular polysaccharide biosynthesis (*cps*) locus, changing their capsular serotype to 19A. Interestingly, although serotype 19A vaccine escape capsular switch mutants have occurred on multiple occasions, a single strain has come to dominate and shown a rapid western spread across the USA from an origin on the Eastern seaboard (Golubchik et al, 2012).

Serotype prevalence is dynamic and shows considerable variation with both time and location (Grijalva et al, 2011), and serotype replacement cannot solely be attributed to vaccination. For example, in the UK there was expansion of serotype 1 before routine use of PCV7 (Trotter et al, 2010) and serotype 19A was increasing in several countries before the introduction to PCV7, perhaps one reason why this serotype has dominated sero-

type replacement since (Leal et al, 2012). However, the consistency of serotype replacement in diverse areas following the introduction of PCV7 supports a contributing role for vaccination (Weinberger et al, 2011), although only the emergence of certain serotypes, for example 7F and 19A, correlates with the level of vaccine coverage (Hanquet et al, 2010).

The clinical impact of changing serotype ecology

Serotype replacement in colonization is reflected in the incidence of invasive pneumococcal disease caused by non-vaccine serotypes, with invasive pneumococcal disease caused by vaccine serotypes falling markedly but with a corresponding increase in invasive pneumococcal disease caused by non-vaccine serotypes (Miller et al, 2011; Leal et al, 2012).

Pneumococcal serotype affects the prevalence and duration of nasopharyngeal colonization, ability to cause invasive disease, likelihood of causing pneumonia-associated empyema or septicaemia, and the probability of a severe outcome or mortality (Weinberger et al, 2010; Brown, 2012). The variation between serotypes in the likelihood of causing invasive disease per colonization event is very significant: for example, serotypes 1, 5 and 7 are sixty times more likely to cause invasive pneumococcal disease than 3, 6A or 15 (Brueggemann et al, 2004). Hence, an increase in nasopharyngeal carriage of non-vaccine serotypes would not necessarily result in an equivalent increase in invasive pneumococcal disease if the non-vaccine serotypes are less invasive than the vaccine type pneumococci they are replacing.

Furthermore a rise in the proportion of cases of invasive pneumococcal disease caused by non-vaccine serotype is partly attributable to the falling number of total cases since the introduction of PCV7. Accordingly, the incidence of invasive pneumococcal disease in the USA has remained lower than in the pre-vaccine era despite widespread serotype replacement in carriage (Weinberger et al, 2011). However, the changes in absolute numbers of disease caused by non-vaccine serotype demonstrate that serotype replacement disease can occur, resulting in non-vaccine serotypes causing an increasing number of cases of invasive pneumococcal disease especially in Europe. For example in England and Wales there has been a 68% increase in invasive pneumococcal disease caused by non-vaccine serotypes in children aged under 2 years of age, and a 48% increase in adults aged over 65 years. This has considerably diminished the overall impact of vaccination in reducing invasive pneumococcal disease: while there has been a 98% reduction in invasive pneumococcal disease caused by vaccine-types in children under 2 years of age the overall incidence of invasive pneumococcal disease has only been reduced by 56% because of the expansion in disease caused by non-vaccine serotypes.

Likewise, the reduction in invasive pneumococcal disease in adults over 65 years was 48% for vaccine-type pneumococci, but only 19% once the increasing incidence of invasive pneumococcal disease caused by non-vaccine serotypes is factored in (Miller et al, 2011). Interestingly, the increase in incidence of non-vaccine serotypes has been less significant in pneumococcal meningitis than in pneumococcal pneumonia (Van der Linden et al, 2012): although the proportion of cases caused by non-vaccine serotypes has increased this has made little impact on the reduction in incidence of pneumococcal meningitis (Bingen et al, 2008). This may reflect the lesser invasiveness of the non-vaccine serotypes compared to the vaccine serotypes included in PCV7.

The changing prevalence of individual pneumococcal serotypes could also impact on patterns of disease. In this context the rising prevalence of the highly invasive serotype 19A is of particular concern. Serotype 19A has caused an increasing burden of invasive pneumococcal disease in the post-PCV7 era (Moore et al, 2008), becoming the commonest cause of invasive pneumococcal disease in children in the USA (Kaplan et al, 2010). Infection with serotype 19A has been particularly associated with mastoiditis, invasive disease and complicated pneumonia, and there has been a significant increase in the incidence of empyema in children in the UK caused by pneumococci of serotype 19A, leading to considerable morbidity (Thomas et al, 2012). An increase in complicated pneumonia and empyema in children caused by the other emerging non-vaccine serotypes, particularly 1, 3 and 7F, has also been noted since the introduction of PCV7 (Ampofo et al, 2012; Brown, 2012; Leal et al, 2012).

Different pneumococcal serotypes also have different propensities to develop antibiotic resistance, and the emergence of non-vaccine serotypes has also been associated with rising levels of antibiotic resistance (Moore et al, 2008). Serotype 19A has a particularly high level of multidrug resistance, and there has been a rapid increase in the incidence of invasive disease caused by penicillin-resistant 19A in Asia (Song et al, 2012). Interestingly pneumococci of the antibiotic resistance genome sequence-type Spain23F-1, which previously expressed vaccine serotypes, have now been identified expressing the 19A serotype (Muñoz-Almagro et al, 2009). The emergence of antibiotic-resistant 19A cannot be solely attributed to vaccination, and countries with high levels of antibiotic usage have also experienced the greatest increases in the incidence of antibiotic-resistant 19A (Hausdorff et al, 2012).

The place of PCV13

PCV13, which expands serotype coverage to include most of the significant serotypes to have emerged as causes of invasive pneumococcal disease in children in the post-PCV7 era, including 1, 7F and 19A, has now

been introduced into the routine vaccination schedule in the UK and USA (Miller et al, 2011). By covering a larger range of serotypes, and including many of the prevalent serotype replacement strains, PCV13 may have a much stronger effect on the incidence of invasive pneumococcal disease than PCV7. However, a considerable proportion of cases of pneumonia in adults are caused by non-PCV13 serotypes and will therefore not be prevented, and there is likely to be further serotype replacement, especially if the non-conjugate polysaccharide vaccine PPV23 is replaced with PCV13 in the vaccination of adults. The significance and implication of this serotype replacement is difficult to forecast (Weinberger et al, 2011; Brown, 2012). Interestingly, in the UK after introduction of PCV7, adults have continued to be infected with pneumococcal serotypes included in PCV7; this suggests that infant carriage is not the only source of infection and that adult carriage could be significant and provide a reservoir for re-emergence of these serotypes should vaccine-induced immunity wain (Brown, 2012).

Conclusions

Routine childhood vaccination with PC7 has resulted in a significant, if variable, reduction in invasive pneumococcal disease, both through direct protection of the vaccinated children and, via herd immunity, to unvaccinated children and adults. The vaccine was formulated to contain those serotypes causing the greatest disease burden in the USA at the time of its formulation and the vaccine has had a lesser impact in other regions compared to the USA, most likely as a result of differences in prevailing serotype.

PCV7 has also exerted a great selection pressure on the pneumococcal population, resulting in the increasing significance of serotypes not included in the vaccine. Several non-PCV7 serotypes have emerged to become of considerable clinical significance, particularly 19A, which has increased in prevalence and is contributing to the rising incidence of complicated pneumonia and empyema in children. Serotype 19A is also associated with increasing levels of antibiotic resistance, particularly in settings of high antibiotic use. Fortunately most of the non-vaccine serotypes are currently of lower invasive potential than those included in PCV7, and while the increasing incidence of pneumococcal disease caused by non-vaccine serotypes has offset the benefit of vaccination, overall, PCV7 has resulted in a significant decrease in invasive pneumococcal disease. The widespread use of PCV13 will confer protection against several of these emerging and significant non-PCV7 serotypes. However, the serotype ecology will continue to change in response to vaccine selection pressures and there is evidence of pneumococci switching serotype to evade vaccine-induced immunity: vigilant surveillance is essential. **BJHM**

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KEY POINTS

- Vaccination with a capsular antigen conjugated to a protein significantly reduces the risk of invasive pneumococcal disease in children, and through herd immunity can also reduce the incidence of invasive pneumococcal disease in unvaccinated children and adults.
- The vaccine only protects against selected capsular serotypes of *Streptococcus pneumoniae*, and as a consequence its efficacy has been impaired by an increasing prevalence of non-vaccine pneumococcal serotypes.
- Some non-vaccine serotypes of *S. pneumoniae* are linked to a higher risk of complicated pneumonia and empyema, and to antibiotic resistance.
- Continuing surveillance will be essential to monitor the effects of vaccination on pneumococcal ecology and disease, and to ensure the vaccine formulation continues to prevent infection with the prevalent capsular serotypes.

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