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13-valent pneumococcal conjugate vaccine (PCV13)

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The 13 valent pneumococcal conjugate vaccine (PCV13, Prevenar 13™) is the broader coverage successor to the highly effective seven valent vaccine (PCV7, Prevenar™) which has reduced rates of pneumococcal disease in many countries. Despite the success of PCV7, pneumococcal disease due to non-PCV7 serotypes remains a threat in many settings, in particular many developing countries with a high burden of pneumococcal disease where serotype 1 and 5 are among the most common serotypes. Disease due to certain non-PCV7 serotypes, in particular serotype 19A has also begun to increase in incidence in countries with widespread use of PCV7. PCV13 consists of 13 pneumococcal capsular polysaccharides individually conjugated to the diphtheria-derived protein carrier CRM₁₉₇. In addition to serotypes 4, 6B, 9V, 14, 18C, 19F and 23F included in PCV7, PCV13 also includes serotypes 1, 3, 5, 6A, 7F and 19A. PCV13 was licensed on the basis of non-inferiority trials and has proved to be at least as safe and effective as PCV7. PCV13 replaced PCV7 in the childhood immunization schedules of the US and UK in 2010 and is being rolled out to an increasing number of developing countries during 2011. Here we review the current literature regarding this vaccine, describing safety, efficacy, global serotype coverage and use and future directions.

Introduction

Conjugate vaccines which chemically combine polysaccharide and protein antigens have successfully reduced the incidence of a number of serious infectious diseases of early childhood including meningitis and sepsis. Conjugation of polysaccharides to a protein carrier elicits a T-cell dependent immune response resulting in effective immunization of children aged less than two years of age, who are a major reservoir for many opportunistic pathogenic bacteria.

One such pathogen *Streptococcus pneumoniae* (the pneumococcus) still causes a significant proportion of infections among young children. Invasive pneumococcal disease (IPD) such as meningitis and sepsis is responsible for the deaths of

approximately 735,000 children under 2 y of age every year.¹ *S. pneumoniae* is also one of the most commonly isolated pathogens from community acquired pneumonia and otitis media and has been estimated to be responsible for over 30% of all acute otitis media episodes.²

Pneumococci can be divided into 93 serotypes on the basis of the antigenic properties of their polysaccharide capsule. Geographically there are differences in serotype prevalence³ although, prior to the introduction of conjugate vaccines the majority of IPD globally was caused by around ten of these serotypes.⁴ Heptavalent pneumococcal vaccine containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23 F each conjugated to a diphtheria protein component, CRM₁₉₇ (Prevenar, PCV-7) was developed by Wyeth (now Pfizer) and proved both safe and effective in clinical trials⁵ and post-licensure studies.⁶ The US was the first country to add PCV to their routine childhood immunization schedule in 2000, the vaccine was recommended for all children aged 2–23 mo and for children aged 24–59 mo who are at an increased risk of pneumococcal disease. As of 2008, 91 countries had licensed PCV7 and 23 of these had incorporated the vaccine into their routine immunization schedules.⁷

PCV7 was designed to protect against the serotypes that caused the majority of IPD in North America and has proved remarkably successful at reducing mortality and morbidity from IPD in the US and elsewhere.^{8–11} After PCV7 implementation, data from the US reported a 94% decrease of invasive pneumococcal disease (IPD) among children under 5 y old from 1998–1999 to 2003,¹² a reduction of disease in unvaccinated individuals was also reported.¹³ Despite successfully combating pneumococcal disease in the developed world, the serotypes covered by PCV7 account for less than 60% of IPD in Africa, Asia and South America.¹⁴

Studies from the US showed that despite the success of PCV7, an increase in disease caused by non-vaccine serotypes was observed,^{15,16} this phenomenon is known as serotype replacement and can result from expansion of existing non-vaccine serotypes^{17,18} as well as from vaccine type pneumococci acquiring the polysaccharide capsule of a non-vaccine serotype¹⁹ (serotype switching). Both mechanisms of vaccine evasion have been observed in settings with widespread use of PCV7. In England and Wales epidemiological surveillance of IPD has shown that, disease due to serotypes included in PCV7 declined after PCV7 introduction but that non-vaccine serotype IPD have continued

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Table 1. Recommended immunization series for PCV13

Three-dose primary series	Two-dose primary series
The recommended immunization series consists of four doses, each of 0.5 ml. The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age.	When given as part of a routine infant immunization program, a series consisting of three doses, each of 0.5 ml, may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. The third (booster) dose is recommended between 11 and 15 months of age (see section 5.1).

Taken from Wyeth (now Pfizer), Summary of Product Characteristics.

to rise;²⁰ similar observations have been made in other European countries.²¹

Expanded valency PCVs have the potential to address both the global variation in serotype distribution and may at least initially offset phenomenon of serotype replacement. PCV9 (Wyeth, now Pfizer) was shown to be effective against 50% of all-serotype IPD in a large clinical trial performed in the Gambia,²² however this vaccine was not developed further. Instead, a further six serotypes (1, 3, 5, 6A, 7F and 19A) were added to PCV7 to create a more comprehensive 13-valent vaccine (Pneumovax 13, PCV13). This vaccine was first licensed in Chile in 2009 and in Europe and the US in 2010 and replaced PCV7 in the US²³ and UK²⁴ in 2010. A 10-valent PCV (PCV10, Synflorix) was developed by GSK and gained WHO pre-qualification in 2009.²⁵

Here we review the current literature describing PCV13.

Vaccine Formulation

The 13-valent pneumococcal conjugate vaccine Prevnar-13 (also known as Prevnar-13, PCV13) is composed of pneumococcal capsular serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F each conjugated to CRM₁₉₇ carrier protein. PCV13 is indicated for infants and children from six weeks of age.

Schedule. Immunization is usually recommended through national immunization programs. Two potential schedules recommended for children between 6 weeks and 6 mo old are either a three-dose primary series or a two-dose primary series (Table 1).^{26,27}

Catch Up Programs

Children who began on PCV7 in countries where PCV13 became available before completing a course with the 7-valent vaccine would have been recommended to take part in a catch up program. The UK recommendation for PCV13 has been to immunize children who had received one or two doses of PCV7 with PCV13 for the remaining doses of their schedule. Children aged under two at risk of pneumococcal disease (defined as those with diabetes, chronic respiratory, heart, kidney or liver disease or cerebrospinal fluid leaks and those with asplenia, splenic dysfunction, HIV infection or any other immunosuppressive condition or who are receiving immunosuppressive therapeutics²⁶) who have already completed a course with 3 doses of PCV 7 may be offered a single dose of PCV13.²⁶ In the US catch up has been implemented in a similar manner, the Advisory Committee on immunization practices (ACIP) recommended that infants and children who have received 1 or more doses of PCV7 should

complete the immunization series with PCV13 and that children aged 12–23 mo who have received 3 doses of PCV7 before age 12 mo should receive 1 dose of PCV13, given at least 8 weeks after the last dose of PCV7. No additional PCV13 doses are recommended for children aged 12 to 23 mo who received 2 or 3 doses of PCV7 before age 12 mo and at least 1 dose of PCV13 at age ≥12 mo. In addition a single supplemental dose of PCV13 is recommended for all children aged 14–59 mo who have received 4 doses of PCV7 or another age-appropriate, complete PCV7 schedule and for children aged 6 to 18 y who are at increased risk for IPD.²⁷

Use of PCV13 in Pediatric Risk Groups

Although not on national schedules, UK pediatric infectious diseases and immunology consensus opinion is that children with HIV should receive pneumococcal conjugate vaccine as PCV13 (2 doses at least 1 mo apart if they have not previously been immunized with this vaccine).²⁸ PCV13 (previously PCV7) has also replaced polysaccharide-only vaccine for the protection of “at risk” children in pediatric infectious diseases and immunology clinics. Trials evaluating PCV13 in pediatric risk groups such those with HIV and cancer are ongoing, as are trials designed to assess the effect of PCV13 vaccination on pneumococcal carriage (Table 2).

Safety and Immunogenicity

The safety and immunogenicity of PCV13 has been studied in comparison to its predecessor, PCV7^{29–31} and also in conjunction with other vaccines that would be expected to be administered concurrently as a part of a routine, national, childhood immunization program such as: DTaP, HBV and IPV/Hib.³² Following a WHO consultation in June 2009, it was decided that evaluation of immunogenicity of pneumococcal vaccines should be undertaken by demonstration of immunological non-inferiority to PCV7 and that all relevant immunological data should be taken into account when comparing new pneumococcal conjugate vaccines, including IgG titers and functional measurements by use of opsonophagocytosis assay (OPA).³³

Immune responses against all 13 serotypes were elicited in phase III clinical trials, and did not interfere with the immune responses to other routine child immunizations.^{29,30,32,34} Yeh and colleagues performed a double-blind randomized control non-inferiority trial comparing infant immune responses to PCV7 and PCV13 after 3 and 3 + 1 doses in US infants. Serum IgG responses to serotypes 6B, 9V and 3 after three infant doses

Table 2. Current trials of PCV-13 in children*

Study title	Trial number	Trial status
Safety and Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine (13vPnC) in HIV-Infected Subjects 6 Years of Age or Older Who Are Naive to Pneumococcal Vaccine	NCT00962780	Recruiting
Study Evaluating the Impact of a 13-valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Colonization in Healthy Infants	NCT00508742	Active
Study Evaluating 13-valent Pneumococcal Conjugate Vaccine (13vPnC) in Children With Sickle Cell Disease	NCT00918580	Recruiting
Trial Evaluating a 13-valent Pneumococcal Conjugate Vaccine Given With Diphtheria, Tetanus, and Acellular Pertussis Vaccine (DTaP) in Healthy Japanese Infants	NCT01200368	Active
Study to Evaluate 13 Valent Pneumococcal Conjugate Vaccine (13vPnC) Vaccine Followed by 23-valent Pneumococcal Polysaccharide Vaccine (23vPS) Vaccine in Allogeneic Hematopoietic Stem Cell Transplant Recipients	NCT00980655	Recruiting
Investigating the clinical use of 13-valent pneumococcal conjugate vaccine (Prevenar) in childhood acute lymphoblastic leukaemia	ISRCTN12861513	Ongoing
Broader Protection Against Pneumococcal Disease	ISRCTN21841117	Completed

Data taken from www.clinicaltrials.gov or www.controlled-trials.com (accessed 12.05.2011).

did not meet the pre-defined non-inferiority criterion (difference in percentage of infants achieving an IgG serum concentration of $>0.35 \mu\text{g/ml}$) one month after the third dose of PCV13. However the level of functional antibody as defined by an opsonophagocytosis assay (OPA) titer of $>1:8$ was met for all 13 serotypes. Following the fourth (booster) dose, responses to serotype 3 still failed to reach the non-inferiority criterion but again, OPA titers indicated the presence of functional antibodies to all 13 serotypes.^{34,35} PCV13 was generally well tolerated with an adverse event and safety profile similar to that of PCV7.^{29,34}

Efficacy and Effectiveness

PCV13 has been in use in the US and UK since 2010, and while it is too early to assess long-term effects, surveillance data from the Health Protection Agency suggests that in England and Wales, routine use of PCV13 has reversed the previous increasing trend of IPD caused by serotypes not included in PCV7 but included in PCV13.²⁰ Data from a number of countries suggests that there is potential for further serotype replacement, with non-PCV13 serotypes 6C, 8, 11A, 11C, 12F, 22F, 15B/C and 35B reported as increasing in prevalence in a number of carriage and disease studies.³⁶⁻⁴⁰ The propensity of these formerly less common serotypes for carriage and/or disease is an area that requires further study.

Indirect Benefits

Indirect benefits resulting from the use of PCV13 such as herd immunity (the indirect protection of unvaccinated individuals) and herd protection (an overall decrease in pneumococcal disease in children targeted for vaccination) will be important factors in the evaluation of PCV13 effectiveness. Use of PCV7 prevented more than twice as many cases of IPD through indirect effects on pneumococcal transmission than through its direct effect of protecting vaccinated children.⁴¹

In July 2010, representatives from Australia, Canada, England and Wales, South Africa, and the US presented epidemiological surveillance data to a panel of World Health Organization (WHO) experts illustrating the impact of implementing pneumococcal vaccine into a routine national schedule.⁴² All representatives reported evidence of herd protection and herd immunity.⁴²

Prior to PCV7 introduction the majority of antibiotic-resistant pneumococci were of common pediatric serotypes (6A, 6B, 9V, 14, 19A, 19F and 23F).⁴³ An indirect effect of PCV7 in the US was a reduction in IPD caused by antibiotic resistant pneumococci.^{44,45} However, an increase in antibiotic resistant non-PCV7 serotype pneumococci in carriage and IPD was also observed,⁴⁶⁻⁴⁸ particularly serotype 19A.^{49,50} PCV13 is effective against this serotype and is therefore expected to positively impact upon pneumococcal antibiotic resistance in countries such as the US where non-susceptible serotype 19A pneumococci are now among the most prevalent. It should however be noted that antibiotic resistant pneumococci of serotypes 15A and 35B which are not covered by PCV13 have also increased in prevalence in the US since PCV7 introduction.^{51,52} Hanquet and colleagues have suggested that emergence of non-vaccine type pneumococci following PCV is likely due to the interplay of several factors including but not limited to vaccine uptake rates, temporal trends in serotype distribution and antibiotic prescribing practices.²¹ The effectiveness of PCV13 in further reducing rates of resistance among pneumococci may therefore differ in settings according to population based factors.

Cost Effectiveness

Rozenbaum and colleagues reported in 2010 that implementing a 4 dose (3 + 1) PCV7 schedule in the Netherlands was no longer considered to be cost effective;⁵³ the incremental cost effectiveness ratio (ICER) compared with no vaccine was calculated to be 113,891 Euro/QALY. The authors concluded that this decreased cost effectiveness from earlier estimates of 20,000 Euro/QALY

was due to increases in IPD caused by non-vaccine serotypes. The study also used the model to predict ICER of a shift from PCV7 to PCV13 and resulted in an ICER of 50,042 Euro/QALY, falling to 35,743 Euro/QALY when a 3 dose (2 + 1) schedule was used to populate the model. Further reductions were seen when the price of PCV13 was reduced to that of PCV7 and when this reduced cost vaccine was combined with the 2 + 1 schedule (31,250 Euro/QALY and 21,654 Euro/QALY respectively).

Rubin and colleagues⁵⁴ have modeled the impact of infant vaccination in the US with PCV13 vs. PCV7 on pneumococcal disease incidence and mortality as well as the incremental benefit of a serotype catch-up program and their model predicted that PCV13 would be more effective than PCV7 at preventing IPD and would also result in cost savings. Zimmerman and coworkers at the University of Pittsburgh modeled the impact of PCV13 in adults and predicted that use of PCV13 would be highly cost-effective in 50 y olds when compared with current US PPV23 recommendations.⁵⁵ The UK JCVI pneumococcal sub-committee reviewed data regarding clinical risk groups for IPD in December 2010.⁵⁶ At this meeting an immunization schedule of two doses of PCV13 two months apart followed one dose of PPV23 at four months later for individuals in such risk groups was discussed. It was noted that there was no evidence to recommend two doses of PCV13 over a single dose and that two doses could divert healthcare expenditure away from other inventions. The absence of any cost-effectiveness data led the committee to agree that further consideration was required on the cost-benefit of one vs. two doses of PCV13 for the immunosuppressed risk groups.⁵⁶

Continuing Public Health Efforts

Use of PCV13 in adult populations at risk of pneumococcal disease. Currently all PCVs are licensed only for use in children, however certain groups of adults are at increased risk of pneumococcal infection and could arguably benefit from such vaccines. In February 2009 the UK Joint Committee on Vaccines and Immunization (JCVI) suggested that adults over the age of 65 and certain other adult populations could benefit from PCV vaccination but that more evidence was required.⁵⁷ These groups include individuals with HIV, people with chronic renal disease and those who have had bone marrow transplants. In 2011 the JCVI advised that the PPV23 program was no longer effective at preventing pneumococcal disease in adults over 65 and should be ceased, however this guidance also stated that following review of unpublished data from Pfizer that the committee noted there was currently no conclusive evidence that PCV13 would be more effective in older adults.⁵⁸

Phase 3 trials of PCV13 in adults are currently underway in a number of settings (Table 3), recently Pfizer reported that the safety, tolerability of a single dose of PCV13 was comparable to PPV23 in the 50 to 64 y age range. Immunogenicity elicited by PCV13 was at least that invoked by PPV23 in 60–64 y olds and functional antibody responses were higher for the majority of serotypes included in both vaccines after vaccination with PCV13 than following PPV23 vaccination. A second trial which

administered PCV13 one year after either PPV23 or PCV13 in adults aged 70 y and above demonstrated comparable safety and tolerability of PCV13 when compared with a single dose of PPV23 and reported that when a second dose of PCV13 was administered to subjects who had received a first dose of PCV13, this was at least as immunogenic as the initial dose of PCV13 for all 13 serotypes; however, when PCV13 was administered after an initial dose of PPV23, functional antibody responses were less robust compared with a single dose of PCV13 for the majority of serotypes.^{59–61}

GAVI initiative. PCV13 is likely to be more effective than PCV7 in Africa, Asia and South America due to the higher incidence of serotypes 1, 5 and 7F.^{62–64} The Global Alliance for Vaccines and Immunization (GAVI) is an alliance of organizations set up to increase access to immunization in resource-poor countries (those with a per capita gross national income of less than US\$ 1,000) and works as a public-private partnership to provide vaccines in these countries. GAVI initiatives have implemented pneumococcal conjugate vaccines in 19 GAVI-eligible countries via a unique and innovative Advance Market Commitment (AMC) mechanism which ensures that vaccine is available to developing countries at an affordable price, with the country making a small per-dose co-payment. Eight countries (Nicaragua, Honduras, Guyana, Sierra Leone, Kenya, Democratic Republic of Congo, Mali and Yemen) have introduced PCV13 during 2010 and 2011.⁶⁵

Future Prospects—New Approaches to Pneumococcal Vaccines

PCV-13 is safe and effective against the IPD caused by vaccine serotypes, and (based on the results of PCV7 implementation) is expected to reduce rates of carriage and pneumonia due to these serotypes. However, serotype replacement in both IPD and carriage has been well documented following widespread use of PCV7 and despite the broader protection offered by PCV13 there is still potential for further replacement. PCV13 contains pneumococcal capsular polysaccharides corresponding to the serotypes currently causing over 70% of IPD worldwide.⁶⁶

As PCV7 has been superseded by PCV13 could further serotypes be added to increase the range of protection offered by PCV13? Higher valency PCVs are not likely to be developed due to the high costs of development and the complexity of ensuring adequate immunogenicity for each serotype.⁶⁶ However, Merck have reported that following vaccination with either PCV7 or a 15-valent PCV containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F conjugated to CRM₁₉₇, antibody responses in infant rhesus monkeys were comparable.⁶⁷ In addition, data suggests that there may be a reduction in the ability of some children to respond to certain common serotypes when vaccinated with PCV13 compared vaccination with PCV7.⁶⁸

The development of effective conserved pneumococcal protein vaccines (CPPV) that would not target the polysaccharide capsule and therefore would prevent pneumococcal disease and carriage without resulting in the selective pressure that is thought to drive serotype replacement as well as negating the need for

Table 3. Current and completed trials of PCV-13 in adults*

Study title	Trial number	Trial status
Study Comparing a 13-valent Pneumococcal Conjugate Vaccine With 23-valent Pneumococcal Polysaccharide Vaccine in Adults	NCT00427895	Recruiting
Safety and Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine (13vPnC) in HIV-Infected Subjects 6 Years of Age or Older Who Are Naive to Pneumococcal Vaccine	NCT00962780	Active
Study to Evaluate a 13-valent Pneumococcal Conjugate Vaccine in Elderly Subjects	NCT00269672	Completed
Study Evaluating a 13-valent Pneumococcal Conjugate Vaccine in Elderly Subjects	NCT00500357	Completed
Study Evaluating a 13-Valent Pneumococcal Conjugate Vaccine (13vPnC) in Adults	NCT00744263	Active
Study Evaluating Safety and Immunogenicity of 13-Valent Pneumococcal Conjugate Vaccine With Influenza Vaccine in Adults	NCT00492557	Completed
Study Evaluating 13 Valent Pneumococcal Conjugate Vaccine With Trivalent Inactivated Influenza Vaccine	NCT00521586	Active
Study Evaluating Safety of 13-Valent Pneumococcal Conjugate Vaccine in Healthy Elderly Subjects	NCT00500266	Completed
Study Evaluating 13-valent Pneumococcal Conjugate Vaccine in Healthy Japanese Adults Aged ≥ 50 Years	NCT00562354	Completed
Safety & Immunogenicity of 13vPnC in HIV-Infected Subjects Aged 18 or Older Who Were Previously Immunized With 23vPS	NCT00963235	Recruiting
Study Evaluating Persistence Of Antibody Response Elicited By 13vPnC In Healthy Adults Previously Vaccinated	NCT01025336	Completed
Study to Evaluate 13 Valent Pneumococcal Conjugate Vaccine (13vPnC) Vaccine Followed by 23-valent Pneumococcal Polysaccharide Vaccine (23vPS) Vaccine in Allogeneic Hematopoietic Stem Cell Transplant Recipients	NCT00980655	Recruiting
Lenalidomide and Vaccine Therapy in Treating Patients With Early-Stage Asymptomatic Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	NCT01351896	Not yet recruiting

Data taken from www.clinicaltrials.gov or www.controlled-trials.com (accessed 12.05.2011).

costly conjugation processes. A single antigen, conserved in all pneumococci has proved elusive due to the inherent heterogeneity of the pneumococcal pan-genome, however a number of combinations of conserved proteins including PspA, PspC, PhtB and PhtE,⁶⁹ and [PspC and PspA] have shown promising results in animal models. Intercell is developing a triple antigen vaccine, based on the antigens StkP, PcsB and PsaA^{66,70} and in 2010 reported results from the first in-human phase I trials in 32 subjects confirming immunogenicity, safety and tolerability of the vaccine.⁷¹ Other CPPV vaccines, including inactivated whole cell vaccine, common protein vaccines and fusions of pneumolysin toxoid to other protein antigens are in pre-clinical trials.⁶⁶

A recent study by Webster and colleagues set out to assess the views of a group of international experts regarding priority setting for interventions against pneumonia;⁶⁶ this study found that there was a higher level of optimism for low-cost PCVs than for low-cost CPPVs. Reasons for this were concerns over low-cost CPPV development costs and the likelihood of CPPVs becoming available for implementation within a 10 y time period.

Concluding Remarks

PCV13 has been demonstrated to be safe and immunogenic in children and adults. It currently has high global serotype coverage (>70%) and increased coverage of serotypes causing the majority of IPD and pneumonia in Africa, Asia and Latin America. PCV13 has been approved for use in more than 40 countries worldwide and, due to the pioneering GAVI initiative, is the first vaccine to be implemented in developed and developing countries in the same year.

Although this vaccine is expected to greatly reduce the burden of pneumococcal disease worldwide, data regarding serotype prevalence in many developing countries is lacking therefore robust estimates of effectiveness cannot be made. Additionally, the potential for further serotype replacement in addition to that observed following PCV7 implementation should not be ignored. Good quality pre- and post-vaccine surveillance is required in order to understand the effects of PCV13 on carried and disease-causing pneumococci.

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