EXPERT REVIEWS

Current knowledge regarding the investigational 13-valent pneumococcal conjugate vaccine

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The introduction of a 7-valent pneumococcal conjugate vaccine (PCV-7) into the routine childhood vaccination schedule has been shown to be effective in preventing invasive pneumococcal disease (IPD), pneumonia, otitis media and meningitis in infants and young children as determined by epidemiological surveillance studies. There has been a rise in IPD due to nonvaccine serotypes; however, this rise is small compared with the overall reduction in IPD. Non-PCV-7 serotypes and vaccine-related serotypes, such as serotypes 1, 5, 7F, 6A and 19A, have also been reported to cause IPD in some parts of the world where morbidity and mortality from pneumococcal disease are higher. An investigational 13-valent pneumococcal conjugate vaccine (PCV-13) uses CRM_{197} as a carrier, similar to the current PCV-7, and covers serotypes 1, 3, 5, 6A, 7F and 19A, in addition to the serotypes of PCV-7 (serotype 4, 6B, 9V, 14, 18C, 19F and 23F). PCV-13 is safe and well tolerated with other pediatric vaccines in infants according to clinical trials. IgG anticapsular polysaccharide-binding concentrations and opsonophagocytic assay responses are similar and noninferior between PCV-13 and PCV-7 and, according to immunogenicity studies, PCV-13 has more potential to protect against pneumococcal diseases with the additional six serotypes. With the addition of these new serotypes, it could be possible to cover potential pneumococcal serotypes causing IPD throughout the world. The cost of the vaccine, its length of duration, optimal scheduling, combination and boosting with PCV-7 are still unresolved issues. Assessment of the vaccine's effectiveness and efficacy following potential licensure will require carefully designed cohort and case–control studies that can assess the indirect effects of PCV-13.

KEYWORDS: 13-valent pneumococcal conjugate vaccine • pneumococcal vaccine • 7-valent pneumococcal conjugate vaccine

While our ability to prevent pneumococcal infections is constantly increasing with new vaccines, *Streptococcus pneumoniae* is still a major cause of morbidity and mortality worldwide. Globally, pneumococcal diseases have been estimated to account for approximately 1 million deaths annually in children under 5 years of age. *S. pneumoniae* is the most common cause of invasive bacterial disease in children, including bacteremia, meningitis and bacteremic pneumonia [1]. At the time of its approval in 2000, the 7-valent pneumococcal conjugate vaccine (PCV-7) included seven of the most common serotypes (i.e., serotype 4, 6B, 9V, 14, 18C, 19F and 23F) causing pediatric invasive pneumococcal disease (IPD) in the USA. By May 2009, 35 countries had introduced PCV-7 into their national immunization program. Recently, the first Global Alliance for Vaccines and Immunization (GAVI)-eligible country, Rwanda, introduced PCV-7 to its national immunization program [2].

With the introduction of PCV-7 into routine childhood vaccination schedules in the USA, its efficacy in preventing IPD, pneumonia and otitis media in infants and young children has been demonstrated by epidemiological surveillance studies [3–6]. Rates of pneumococcal meningitis have decreased among children and adults since the introduction of PCV-7 [7]. However, although small compared with the overall reduction, there has been a rise in IPD cases due to nonvaccine serotypes in this postvaccine era in the USA [8]. With the demand for universally

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applicable serotype composition, studies for second-generation pneumococcal conjugate vaccines (PCVs) are ongoing. There are currently two new conjugated vaccines: 10-valent pneumococcal vaccine, which uses protein D from the nontypeable *Haemophilus influenzae* protein (PHiD-CV; GlaxoSmithKline; currently approved by the EMEA as of January 2009, including serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and an investigational 13-valent PCV (PCV-13; containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) [2]. We have evaluated recent data regarding the immunogenicity, safety and reactogenicity of PHiD-CV [Dinleyici EC, Yargic ZA; Manuscript submitted] and PCV-13. In addition, we have evaluated recent pneumococcal seroepidemiology from different geographical areas in order to further determine potential vaccine coverage. We extensively reviewed the major medical literature, including Index Medicus, PubMed, the Science Citation Index, Scopus and Google Scholar, in addition to the proceedings of recent major infectious disease and vaccine congresses, and the abstract book of the 6th International Symposium on Pneumococci and Pneumococcal Diseases, which was held in Iceland in 2008.

Vaccine composition

Investigational PCV-13 uses the same protein carrier (nontoxic diphtheria toxin cross-reactive material 197 [CRM_{197}]) as PCV-7. In addition to the coverage of all PCV-7 serotypes, PCV-13 includes six additional serotypes: 1, 3, 5, 6A, 7F and 19A. PCV-13 consists of polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, individually covalently conjugated onto a common carrier protein, CRM_{197}. The vaccine is formulated to contain 2 µg of each saccharide, except for 6B (4 µg), with a total nominal dose of 29 µg CRM_{197} per 0.5-ml dose. The final formulation contains 5 mmol/l succinate buffer, 0.02% polysorbate 80 and 0.125 mg of elemental aluminum per 0.5-ml dose.

Vaccine immunogenicity & noninferiority trials

Scott *et al.* conducted a Phase I clinical trial of PCV-13 in 30 healthy adults aged 18–49 years in Kansas, USA [9]. The study group had not received prior pneumococcal immunization and was randomized to receive a single intramuscular dose of either PCV-13 (n = 15) or a 23-valent protein polysaccharide vaccine (PPV-23; n = 15). The immunogenicity of PCV-13 was evaluated with pneumococcal serotype-specific anticapsular polysaccharide IgG for each serotype by ELISA using both C-polysaccharide and 22F serotype capsular polysaccharide absorption and functional opsonophagocytic antibodies (OPAs). The results showed that PCV-13 was more immunogenic than PPV-23 for most of the shared serotypes in the two vaccines. Point estimate geometric mean concentrations of pneumococcal serotype-specific antibodies were higher in the PCV-13 group compared with the PPV-23 group for 11 out of 12 matching serotypes (except serotype 4). Similarly, point estimate OPA geometric mean titers (GMTs) in the PCV-13 group exceeded those in the PPV-23 group for 11 out of 12 matching serotypes (except serotype 7F). For serotype 6A, which was not included in PPV-23, the PCV-13 group's IgG geometric mean concentration (GMC) and OPA GMT were greater than those for the PPV-23 group.

Another Phase I study was conducted in healthy Japanese adults aged 20–50 years in Hawaii [10]. This was an open-label, block-randomized (15 subjects in the PCV-13 group and 14 subjects in the PPV-23 group), active-controlled study. Both vaccines were immunogenic for all common serotypes, and PCV-13 was also immunogenic for 6A, which was not included in PPV-23. In this study, both vaccines were administered subcutaneously, and this was found to induce IgG antibody responses to all 13 serotypes included in the vaccine that were generally superior or at least comparable with the responses induced by PPV-23, although without statistical differences [10].

A WHO technical report was subsequently produced to define the criteria for the production and control of new PCVs. Current recommendations published in the WHO technical report series 927 continue to provide a solid basis for the evaluation of PCVs and may be referred to when assessing new vaccines for licensure and prequalification. The WHO has published guidelines for the clinical evaluation and licensure of new PCVs, proposing that the evaluation of newer formulations of PCVs be based on the demonstration of noninferiority in a head-to-head comparison with the existing PCV-7 in the proportion of subjects developing antibody concentrations above a defined threshold (0.35 µg/ml) at 4 weeks following a primary series of vaccination [11,12]. Additional criteria include the demonstration of functional antibodies measured with OPA after three doses and a test of immune memory, such as avidity or the ability to induce a booster response. OPA titers were available from two of the three studies, and analysis of the data showed that antibody concentrations in the range of 0.20–0.35 g/ml correlated best with an opsonophagocytic antibody titer of 1:8, which in turn correlated best with protective efficacy. In addition to the proportion of subjects who reach predefined antibody concentrations (by ELISA) or OPA titers, the geometric mean antibody concentrations (derived from ELISA data) or titers (derived from OPA data) and reverse cumulative distribution curves should all be determined for new PCVs [12].

Bryant *et al.* evaluated the immunogenicity of a fourth dose (dosing at 2, 4 and 6 months and a fourth dose given at 12–15 months) of PCV-13 in healthy toddlers [13]. Infants were randomized to receive PCV-13 (n = 86) or PCV-7 (n = 103) at 2, 4 and 6 months of age with diphtheria–tetanus–acellular pertussis (DTaP), inactivated polio virus (IPV), hepatitis B and *Haemophilus influenzae* type B (Hib) conjugate vaccines and received a fourth dose of the same vaccine at the age of 12–15 months concurrent with the Hib conjugate vaccine. All PCV-13 serotypes were immunogenic, with 92–100% of vaccinated toddlers achieving antibody concentrations of 0.35 µg/ml for for common serotypes with PCV-7 and additional serotypes. Post-toddler-dose GMCs were higher than pre-dose GMCs for all serotypes. According to these results and WHO recommendations, PCV-13 is immunogenic for all 13 serotypes when administered as three primary doses and one booster dose.

Grimprel *et al.* conducted a Phase III, randomized, active-controlled, double-blind, multicenter study to evaluate the safety, tolerability and immunogenicity of PCV-13 when given at 2, 3 and 4 months of age with routine pediatric vaccinations in France [14]. Three doses of PCV-13 induced a substantial response to all 13 pneumococcal serotypes in the vaccine. They concluded that the proportion of responders with antipolysaccharide IgG binding concentrations of 0.35 µg/ml or greater (at least 72.5% for all serotypes and 98% for serotype 19A) supported PCV-13 as an effective measure in preventing pneumococcal disease caused by the vaccine serotypes.

A study by Kieninger *et al.* compared the safety and noninferiority of four doses of PCV-13 with PCV-7 given at 2, 3, 4 and 12–15 months of age along with other routine pediatric vaccines in Germany [15]. The study included 604 subjects who were randomly assigned to receive either PCV-13 or PCV-7 [10]. IgG anticapsular polysaccharide binding concentrations and OPA responses were similar and noninferior between recipients of PCV-13 and PCV-7 for seven common serotypes, and binding antibody and OPA responses increased following the toddler dose. For the six additional serotypes, the functional OPA responses were ten- to 100-fold higher in the PCV-13 group, and functional antibody responses to serotype 6A were nearly tenfold greater than in the PCV-7 group. The proportion of responders for serotype 19A was 99%. Kieninger *et al.* concluded that PCV-13 would be as effective as PCV-7 for the seven common serotypes and would also provide additional potential protection against IPD caused by the additional six serotypes (serotypes 1, 3, 5, 6A, 7F and 19A) [15]. The percentage of responders (those in whom the postimmunization antibody concentration was above the threshold) for PCV-13 was shown to be noninferior. A head-to-head comparison of the shared serotypes is shown in Table 1.

Table 1. Head-to-head comparison of the percentage of subjects reaching the threshold of 0.35 µg/ml using PCV-13 and PCV-7 1 month after the primary dose series.

Serotype	PCV-13 (%)	PCV-7 (%)
4	98.2	98.2
6B	77.5	87.1
9V	98.6	96.4
14	98.9	97.5
18C	97.2	98.6
19F	95.8	96
23F	88.7	89.5
1	96.1	1.4
3	98.2	6.3
5	93.0	31.6
6A	91.9	31.6
7F	98.6	4.0
19A	99.3	79.2

PCV-7: 7-valent pneumococcal conjugate vaccine; PCV-13: 13-valent pneumococcal conjugate vaccine.
Data taken from [15].

The immunogenicity of the PCV-13 vaccine was assessed by Gadzinowski *et al.* in Poland [16]. They compared vaccine produced on a manufacturing scale with vaccine produced on a pilot scale. Three doses of PCV-13 were given at 2, 3 and 4 months of age. The proportions of responders with 0.35 µg/ml or more and GMCs were very similar between the manufacturing-scale and pilot-scale groups. According to this study, the final manufacturing scale and formulation should be effective in preventing pneumococcal disease caused by the vaccine serotypes.

Klinger *et al.* performed a study of the immunogenicity and safety of PCV-13 in infants in the UK [17]. The study enrolled 278 healthy infants aged 6–14 weeks who received PCV-13 or PCV-7 at 2 and 4 months along with other scheduled vaccines. According to this study, PCV-13 was immunogenic when given as part of the UK infant vaccine course. The percentage of participants achieving the thresholds of response for the concomitant antigens was comparable between the PCV-13 and PCV-7 groups. PCV-13 vaccination at 2 and 4 months resulted in 78.5–96.3% of vaccinated infants achieving the correlate of protection (≥0.35 µg/ml) for IPD for the six additional serotypes not contained in PCV-7. Among the PCV-13 recipients, 91% achieved the threshold of protection against Serotype 19A [17]. It must be noted, however, that over 50% of participants in the PCV-13 group achieved IgG of 0.35 µg/ml or higher for serotype 6B; less than 80% reached this threshold for serotype 23F, but more than 90% reached it for all remaining serotypes. In other studies evaluating the 1-month immunogenicity response after a three-dose primary series [14–16], the percentage of participants in the PCV-13 group achieving IgG above 0.35 µg/ml for serotypes 6B and 23F was also lower than other serotypes included in PCV-13; however, the percentage of responders was higher than compared with the study of Klinger *et al.*, which evaluated immunogenicity after a two-dose primary series of PCV-13 given at 2 and 4 months [17].

Vaccine safety

The results of the safety studies for PCV-13 are summarized in Table 2. According to these studies, PCV-13 was generally well tolerated, and the level of reactogenicity observed was well within the acceptable levels for routinely used vaccines. No adverse events were thought to be related to the study vaccine, and no serious adverse events were reported. By referencing the data and then focusing on key safety data, fever, local reaction and any other key differences, safety was assessed with Phase III trials and was found to be similar between PCV-13 and PCV-7. Based on the results of the clinical trials of PCV-13, it appears to be a safe and well-tolerated vaccine [9–10,13–17].

Coadministration with other pediatric vaccines

Grimprel *et al.* evaluated the safety, tolerability and immunogenicity of PCV-13 when administered with DTaP-Hib/IPV [14]. Immune responses to DTaP-Hib/IPV vaccine antigens using a three-dose infant series are comparable when administered with

Table 2. Summary of studies regarding the safety of investigational PCV-13.

Authors	Study design	Vaccine	Results	Ref.
Scott *et al.*	Phase I study Healthy adults 20–50 years	PCV-13 vs PPV-23 Subcutaneous	PCV-13 well tolerated Although a small number of local self-limiting reactions were classified as severe (erythema and/or swelling >7 cm or pain preventing usual activities), there were not any serious adverse events The higher percentage of local reactogenicity (e.g., injection site pain, erythema and induration) to PCV-13 in this study compared with PPV-23 might be associated with the formulation of PCV-13 with aluminum phosphate adjuvant and subcutaneous injection, which may produce more local reactions The level of reactogenicity observed in this trial was well within acceptable levels for routinely used vaccines	[10]
Scott *et al.*	Phase I study US adults	PCV-7 vs PPV-23	PCV-13 was generally well tolerated No fever >38°C between vaccination day and the subsequent 7 days One subject in the PCV-13 group reported induration at the injection site, while another reported redness All 15 subjects in the PCV-13 group reported injection site tenderness that interfered with limb movement No adverse events were thought to be related to the study vaccine, and no serious adverse events were reported during this trial	[9]
Bryant *et al.*	Phase II trial Healthy toddlers	PCV-13 vs PCV-7	Local and systemic reactions were similar between the PCV-13 and PCV-7 groups	[13]
Grimprel *et al.*	Phase III trial Randomized, active-controlled, double-blind, multicenter study France	PCV-13 vs PCV-7, with concomitant DTaP-Hib/IPV	The PCV-13 and PCV-7 groups showed comparable tolerability	[14]
Kieninger *et al.*	Phase III trial 604 subjects	PCV-13 vs PCV-7	The incidence of any induration, any erythema or mild erythema after dose one, and any induration, mild induration, any erythema and mild erythema after dose two was slightly higher in the PCV-13 groups than in the PCV-7 group The incidence of mild fever was slightly higher in the PCV-13 group after dose three	[15]
Gadzinowski *et al.*	Phase III Poland	PCV-13 vs PCV-7	The percentage of subjects reporting local reactions, systemic events and use of antipyretic medication was comparable between the PCV-13 and PCV-7 groups	[16]

DTaP-Hib: Diphtheria–tetanus–acellular pertussis–*Haemophilus influenzae* type b; IPV: Inactivated polio virus; PCV: Pneumococcal conjugate vaccine; PPV: Protein polysaccharide vaccine.

PCV-13 or PCV-7 and are well tolerated. Kieninger *et al.* showed noninferiority for immune responses to the selected Infanrix® hexa antigens (Hib, diptheria and hepatitis B) between recipients of PCV-13 and PCV-7 [15]. Klinger *et al.* also conducted a study including 278 healthy infants aged 6–14 weeks and found that PCV-13 at 2 and 4 months was immunogenic and well tolerated when given with serogroup C meningococcal vaccine at 2 and 4 months and DTaP–IPV–Hib vaccine at 2, 3 and 4 months [17].

Serotype coverage

The distribution of pneumococcal serotypes causing IPD, mucosal disease and nasopharyngeal (NP) carriage varies geographically [18–20]. Based on current global serotype project (GSP) data, theoretical vaccine coverage is summarized in Table 3. Data suggest that changing from PCV-7 to PCV-13 would increase the proportion of covered serotypes from 78.1 to 88% in North America, from 67.1 to 88% in Europe, from 39.3 to 76.9% in Africa, from 48 to 73.9% in Asia, from 54.4 to 83.4% in Latin America, and from 64.5 to 79.1% in Oceania [101].

After the PCV-7 era, despite the increase in the incidence of 19A infections, a much greater decrease in vaccine serotypes was observed in nearly all observational studies in the USA and European countries [2]. During the investigational phase of PCV-7, vaccine experts hoped to expand coverage against vaccine-related serotypes 6A and 19A; however, serotype 6B in PCV-7 produces only partial protection against serotype 6A, and serotype 19F in PCV-7 appears to produce poor protection against serotype 19A. Although small compared with the overall reduction in IPD, there has been an increase in serotype 19A IPD since the introduction of PCV-7 [8]. There are some variations between regions prevalent with serotypes 1, 3, 5, 6A, 7F and 19A [101]. For example, serotype 1 is the second most common serotype in Africa, although it does not rank in the top seven serotypes in North America and Oceania. In addition, serotypes 1 and 5 are among the top three ranked serotypes in GAVI-eligible countries and are among the top six ranked serotypes among children under 5 years of age in regions with the highest pneumococcal disease burden (e.g., Africa, Asia and Latin America). Investigational PCV-13 theoretically covers between 73.9 (Asia) and 88% (Europe and North America) of serotypes and could potentially reduce childhood morbidity and mortality in children under 5 years of age in Africa, Asia, Latin America and GAVI-eligible countries. Shouval *et al.* retrospectively evaluated 5497 isolates from children younger than 3 years of age between 1 January 2000 and 31 December 2004, and PCV-13 extended the coverage to 84, 79, 54 and 67% of IPD, acute otitis media (AOM), acute conjunctivitis, and NP carriage groups, respectively [21]. This was primarily due to coverage of serotypes 6A and 19A, which were common in all four studied groups. During the post-PCV-7 era in the USA, the annual incidence of IPD caused by penicillin-nonsusceptible *S. pneumoniae* (PNSP), erythromycin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* (MDRSP) in children younger than 2 years of age decreased between 1999 and 2004 [22], according to the Active Bacterial Core Surveillance. In parallel to the emergence of serotype 19A, there was a substantial increase in antibiotic resistance in serotype 19A, including PNSP, penicillin-resistant *S. pneumoniae* (PRSP) and MDRSP [23]. Most clinically significant drug resistance among *S. pneumoniae* is confined to seven serotypes: 6A, 6B, 9V, 14, 19A, 19F and 23F. PCV-13 covers all of these resistant serotypes, especially drug-resistant serotype 19A; however, no relevant data exist regarding investigational PCV-13 and antibiotic resistance. For otitis media, the calculated theoretical coverage of investigational PCV-13 would increase due to the high prevalence of serotypes 3, 6A and 19A as emerging otopathogens, and this would affect antibiotic resistance [24,25].

We will now attempt to summarize the current data regarding the additional serotypes of PCV-13.

Serotype 1

Serotype 1 is the second most common serotype in Africa and the fourth most common in Asia and Latin America, although it is not among the top seven serotypes in North America and Oceania [101]. Serotypes 1 and 5 cause more than 30% of IPD cases among all age groups combined in Gambia [26]. Serotype 1 has the potential to cause epidemics, and it was the cause of meningitis outbreaks in Burkina Faso and Northern Ghana [27]. In Chile, Lagos *et al.* reported that serotype 1 was the most frequently isolated serotype in children between 36 and 59 months of age and the second most frequent pathogen – after serotype 14 – among hospitalized children under 5 years of age [28]. In Italy, Montagnani *et al.* retrospectively evaluated a clinical analysis of 640 children who were hospitalized between 1992 and 2006 and showed that serotype 1 was the most prevalent invasive serotype (38.1%) [29]. Campbell *et al.* evaluated 2049 children in Mali, of whom 5% had an IPD, including 47 cases of meningitis and 44 bacteremic pneumonias, and found that 54% of the isolates were serotype 5 [30]. Although

Table 3. Theoretical serotype coverage of different pneumococcal conjugate vaccines from each geographical region.

PCV	Africa (%)	Asia (%)	Europe (%)	Latin America (%)	North America (%)	Oceania (%)
PCV-7	39.3	48	67.1	54.4	78.1	64.5
PHiD-CV	62.5	66.2	76.2	73.6	80.6	71.1
PCV-13	76.9	73.9	88	83.4	88	79.1

Calculated percentage of PCV-7 and PHiD-CV does not contain serotype 6A and 19A as vaccine-related serotypes.
PCV-7: 7-valent pneumococcal conjugate vaccine; PCV-13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal vaccine, which uses protein D from the nontypeable *Haemophilus influenzae* protein.
Serotype coverage calculated from theoretical GSP data from [101].

serotype 1 pneumococci are rarely isolated from carriers, Nunes *et al.* described the emergence and expansion of a single serotype 1 lineage among healthy carriers who attended daycare centers in Portugal [31]. They also found that the prevalence of serotype 1 strains among all pneumococci increased from 0% in 2001 and 2002, to 0.4% in 2003 and 3.1% in 2006.

The increase of serotype 1 has been related to the increase in pneumonia with pleural effusion and the increase in the proportion of childhood pneumonia cases that are complicated and the absolute number of pneumococcal empyema cases, especially in children older than 2 years of age [32,33]. Byington *et al.* reported that pleural effusion was most often caused by serotype 1 prior to and even after the introduction of PCV-7 [34]. Obando *et al.* evaluated 111 children with parapneumonic empyema due to *S. pneumoniae* and found that 48% were infected with serotype 1 [35]. Gupta *et al.* reported firsthand an outbreak of serotype 1 pneumococcal pneumonia among young children in a school in northeastern England and proposed that the introduction of a vaccine including the serotype 1 antigen should be considered if there is evidence that serotype 1 disease is an increasing public-health problem [36]. Goldbart *et al.* retrospectively evaluated the prevalence of pleural empyema complicating community-acquired pneumonia in Israel [37]. Their results showed that there was an increase in prevalence between 1990 and 2002, that *S. pneumoniae* was the most common pathogen and that 62.5% of these pneumococci were serotype 1.

Serotype 3

According to GSP data, the prevalence of serotype 3 ranges from 0.4% (Oceania) to 2.2% (Latin America) [101]. Richter *et al.* studied 1647 *S. pneumoniae* isolates (all specimens, all age groups) obtained from 41 US medical centers between 2004 and 2005 and found that serotype 3 was the second most common (11.2%), after serotype 19A (14.5%) [38]. Although serotype 3 is not a frequent cause of IPD, it was isolated as an otopathogen in children from Europe [24,25,39]. In the post-PCV-7 era, serotype 3 is the most frequent (13%) isolate from middle-ear fluid in children receiving two or four doses of PCV-7 with 19A and 19F [24]. Serotype 3 is the second most common serotype causing AOM in children aged over 24 months in Costa Rica [40]. Serotype 3 has also been an important cause of complicated pneumonia both before and after the PCV-7 era [41]. It should be noted that the only vaccine containing serotype 3 is the investigational PCV-13.

Serotype 5

According to GSP data, the prevalence of serotype 5 ranges from 0.4% (Europe) to 10.7% (Africa). Serotype 5 is the third most common serotype in Africa and Latin America [101].

Serotype 6A

It has been clearly shown that antibodies against serotype 6B can prevent IPD, AOM and NP carriage of serotype 6A [42]. On the other hand, it has been shown that the effect of PCV-7 on IPD caused by serotype 6A is not of the same order of magnitude as that on IPD caused by serotype 6B [4]. Following the introduction of PCV-7 in the USA, carriage and disease caused by serotype 6B, but not 6A, were markedly reduced in adults [41]. It is assumed that 6B conjugate vaccines (PCV-7 and PHiD-CV) provide cross-protection against 6A disease, but investigational PCV-13 covers serotype 6A and has been shown to be immunogenic and noninferior to PCV-7 [14,15,17].

Serotype 7F

Serotype 7F is another important serotype that is included in both PCV-13 and PHiD-CV. The distribution of serotype 7F ranges from 0.8% (Africa) to 3.2% (Europe). Despite the fact that serotype 7F is not among the top seven serotypes in different geographical areas [101], Rückinger *et al.* reported that it had the highest case–fatality rate (14.8%) [43]. Multivariate analysis in that study gave an odds ratio of 4.3 (1.3–14.7) for fatal outcome and 4.0 (1.6–10.4) for severe outcome when 7F was compared with all other serotypes.

Serotype 19A

It was hoped that IPD caused by vaccine-related serotype 19A would be reduced due to cross-protection from serotype 19F, which was included in PCV-7. Although there has been an overall increase in the incidence of IPD caused by serotype 19A, the observed increase is small compared with the overall decrease in IPD following the introduction of PCV-7 [8].

Serotype 19A is equally responsible for IPD, NP carriage and AOM [42]. In addition, it is currently the most important serotype causing pediatric IPD in the post-PCV-7 era in the USA [44–47]. Singleton *et al.* reported that serotype 19A was responsible for 28.3% of IPD in native Alaskan children under 2 years of age [8]. In addition, Richter *et al.* reported that most PRSP and MDRSP strains in the USA in 2004–2005 were serotype 19A (including all isolates and all age groups) [38]. Moore *et al.* reported that the age-specific incidence rate of serotype 19A IPD increased by 145–285% between the prevaccine baseline period and 2005, with the largest absolute rate increases seen among young children and older adults [44]. Among 393 isolates of *S. pneumoniae* from children, nonvaccine serotypes accounted for 89.1%, and 30.5% of all isolates were serotype 19A in the post-PCV-7 era in the USA [48].

The increased prevalence of infections caused by serotype 19A, however, cannot be explained by direct effects of PCV-7 on serotype distribution. According to surveillance data from South Korea between 1991 and 2006, serotype 19A isolates were increasingly recognized among clinical isolates before the introduction of PCV-7. According to this study, among 107 invasive isolates from children younger than 5 years of age, the proportion of serotype 19A increased from 0% in 1991–1994 to 26% in 2001–2003. From 2001 to 2003, serotype 19A was the most common serotype among IPD isolates from children younger than 5 years of age in South Korea. The authors suggest that this increase before the PCV-7 era was due to multidrug-resistant ST320 isolates containing *mef/erm* determinants for the expansion of serotype 19A [49]. In 2007, Song *et al.* reported an increase in serotype 19A in South Korea, accompanied by an increase in ST320, although it was not significance due to limited isolates [50]. The authors explained the

increase in serotype 19A in the post-PCV-7 era by expansion of the pre-existing ST320 clone. It should be noted that this study includes isolates from people of all ages.

In Alaska, the increase in serotype 19A colonization and IPD seems to be related to clonal complex (CC)172 clonal expansion [8]. Serotype 19A had become an important cause of IPD in Alaska in 2006 following the introduction of PCV-7 in 2001. Among Navajo children, the incidence of IPD-7 caused by serotype 19A has not increased. In Spain, on the other hand, the incidence of serotype 19A increased greatly after the vaccine introduction period; however, it is difficult to suggest that this increase was a consequence of vaccine pressure [51]. In Belgium, serotype 19A increased in frequency from 2.1 to 6.6% from 1997–1999 to 2001–2004, prior to the introduction of PCV-7 [52]. In France, serotype 19A became more frequent after the introduction of PCV-7; however, Mahjoub-Messai *et al.* reported clonal expansion of the preexisting penicillin-intermediate sequence type 276 [53].

Dagan *et al.* reported an increasing incidence of serotype 19A as an otopathogen in Israel before the introduction of PCV-7 [54]. Increased multidrug-resistant serotype 19A isolates were associated with the introduction and proliferation of two multidrug-resistant clones that were not previously associated with multidrug resistance. The authors explained this increase by the rapid increase in azithromycin use and the frequent use of oral cephalosporins.

In conclusion, diverse mechanisms are involved in the increased prevalence of serotype 19A: expansion of pre-existing predominant clones (e.g., CC199), capsular switching of vaccine serotypes [44,55], and the appearance of multiple unrelated multidrug-resistant CCs among serotype strains [46,56] and new clones of serotype 19A in the population [57]. Invasive and carriage isolates of serotype 19A are nonsusceptible to penicillin, and this provides an additional survival advantage for serotype 19A [47,58]. According to a study by Richter *et al.*, the clear increase in serotype 19A among the PCV-7-related serotypes suggested limited vaccine activity against serotype 19F [38]. PCV-13 includes serotype 19A and could be beneficial in problematic serotype 19A regions. The prevalence of 19A, as well as other emerging nonvaccine serotypes, needs to be tracked over time.

Expert commentary

According to reported phase trials, PCV-13 is safe, immunogenic and noninferior to PCV-7 based on the purposed WHO criteria for new PCVs. According to recent epidemiological data, investigational PCV-13 would cover 80% of IPD isolates worldwide with additional serotypes 1, 3, 5, 6A, 7F and 19A. Investigational PCV-13 would also be a better candidate for the prevention of otitis media and related conditions due to its coverage of serotypes 6A, 19A and 3, the primary otopathogens in both the pre- and post-PCV-7 eras. The limitations of the predictive capacity of prelicensure immunogenicity data strongly support the need for postmarketing studies, especially in developing countries with higher morbidity and mortality due to pneumococcal infections. Postlicensure (potential) surveillance in countries where PCV-13, if issued on a larger scale will give valuable information for a better understanding of public-health issues, including pneumonia, NP carriage and herd immunity. Head-to-head comparisons of antibody responses are useful for evaluating vaccine efficacy against IPD; however, they are unable to predict the effects on NP carriage, herd immunity, AOM and pneumonia. For PCV-13 and other PCVs, coherent vaccine efficacy for NP carriage, otitis media, pneumonia and herd immunity is still lacking (although it is expected to be higher than IPD) and needs to be evaluated and standardized with postsurveillance follow-up. Reactogenicity studies have been performed with some childhood vaccines, and PCV-13 seems to be safe and well tolerated. Reactogenicity studies for the combination of PCV-13 with rotavirus vaccine, BCG and hepatitis B vaccine, however, are still needed. The cost of PCV-13 is also a primary determinant of its widespread usage worldwide, especially in developing countries.

Strict comparisons and choosing between PCV-13 and PHiD-CV are still not possible with published immunogenicity and safety data. There are immunogenicity studies of both vaccines compared with PCV-7; however, different ELISA procedures were used for the comparisons. According to these data, PCV-13 is immunogenic and noninferior to PCV-7 for the shared serotypes and is also immunogenic for the additional serotypes according to WHO-confirmed noninferiority criteria [11–17]. In a head-to-head comparison trial between PHiD-CV and PCV-7, noninferiority of the immune response to PHiD-CV as measured by ELISA was demonstrated for all serotypes except 6B and 23F, with a difference between groups of more than 10%. Postprimary and postbooster dose geometric mean antibody concentrations and OPA titers were lower than PCV-7 for some shared serotypes [102]. This comparison showed the noninferiority to antibody for each serotype in potential vaccine as a desirable, but not absolute, requirement, and need to be evaluated on an individual level. However, we could not suggest these immunogenicity results for vaccine efficacy and these noninferiority criteria were not used for mucosal infections. Vaccine efficacy depends on serotype epidemiology at the country-based level, the status of PCV-7 introduction, the proportion of children receiving vaccine in the population (especially for herd immunity), antibiotic pressure and coexisting conditions (e.g., HIV status). PCV-13 includes an additional three serotypes (3, 6A and 19A) and would have an expanded coverage for IPD and otitis media worldwide. PHiD-CV includes serotype 1 and 5, which were main pathogens in Europe, Asia and Africa. Although PHiD-CV was designed to protect against AOM as well as IPD due to vaccine serotypes, PHiD-CV does not cover serotype 3 and 19A, which are emerging otopathogens. However, there are insufficient data that PHiD-CV is effective against nontypeable *Haemophilus influenza*, which is the one of the common etiological agents in the post-PCV-7 era, and potential efficacy following potential licensure will require carefully designed cohort and case–control studies that can assess effects. The main limitation of our review is the lack of published peer-reviewed randomized, controlled trials. We reviewed the abstracts and main body of immunogenicity and safety trials that were presented at important infectious disease and vaccine congress such as the Interscience Conference on Antimicrobial Agents and Chemotherapy or the International Symposium on Pneumococci and Pneumococcal Diseases. After publication of the upcoming trials, we could clearly compare immunogenicity and safety of

investigational PCV-13. Until potential approval of PCV-13, vaccine experts should compare the effectiveness of PHiD-CV and PCV-7. In addition, correlates of immune protection for potential new PCVs should be revised and standardized.

Five-year view

More than 35 countries have introduced PCV-7 to their national immunization programs. We need to see the results of a combination schedule of PCV-7 and PCV-13. In addition, children immunized will PCV-7 according to their national immunization program may be immunized with booster PCV-13 for protection against additional serotypes; however, this needs to be evaluated. Herd immunity effects have been one of the most important benefits of PCVs; however, this effect occurs due to reductions in NP carriage and transmission of vaccine type pneumococci after an increased proportion of children receive the vaccine. Assessment of vaccine effectiveness and efficacy following potential licensure will require carefully designed cohort and case–control studies that can assess the indirect effects of PCV-13. Therefore, new conjugate vaccines with a broader coverage are warranted for children and the PCV-13 designed for the prevention of pneumococcal infections in adults. In the next few years, we will see the results of randomized, controlled trial CAPITA [59] for the evaluation of vaccine efficacy against community-acquired pneumonia in adults. Owing to immunogenicity, it does not seem practical to added new serotypes to 13-valent vaccines in the future. At this point, we suggest introducing PCVs to immunization programs, especially in low-income countries, and trying to increase awareness about pneumococcal infections. Widespread use of current PCVs in developing countries could give us a chance to achieve one of the important Millennium Development Goals (2015): a two-third reduction in the mortality rate among children under 5 years of age.

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Key issues

- Investigational 13-valent pneumococcal conjugate vaccine (PCV-13) contains the serotypes in seven-valent pneumococcal conjugate vaccine (PCV-7) plus serotypes 1, 3, 5, 6A, 7F and 19A. It could be a potential vaccine where serotypes 1, 5, 6A and 19A are the main serotypes in the pre- or post-PCV-7 eras. PCV-13 has potential efficacy against PCV-7-related serotypes such as 6A and 19A.
- Data suggest that changing from PCV-7 to PCV-13 would increase the proportion of covered serotypes from 78.1 to 88% in North America, from 67.1 to 88% in Europe, from 39.3 to 76.9% in Africa, from 48 to 73.9% in Asia, from 54.4 to 83.4% in Latin America and from 64.5 to 79.1% in Oceania.
- For otitis media, the calculated theoretical coverage of investigational PCV-13 would increase due to the high prevalence of serotypes 3, 6A and 19A as emerging otopathogens, and this would affect antibiotic resistance.
- PCV-13 is immunogenic for all 13 serotypes. Following a primary series of vaccination for PCV-13, based on the demonstration of noninferiority in a head-to-head comparison with PCV-7 (the proportion of subjects developing antibody concentrations above a 0.35 µg/ml), immunogenicity results of PCV-13 were similar compared with PCV-7.
- PCV-13 is safe and well tolerated in children and when coadministered with routinely used pediatric vaccines.
- Issues of efficacy of duration, optimal scheduling, combination and boosting with PCV-7 remain unresolved issues.
- Assessment of vaccine effectiveness and efficacy following potential licensure will require carefully designed cohort and case–control studies that can assess the indirect effects of PCV-13.
- The WHO has recognized the priority of introducing PCV into the routine infant immunization schedule in all countries owing to the extremely high yearly mortality rate for pneumococcal diseases. Until licensure and marketing of new pneumococcal conjugate vaccines, PCV-7 will continue to be used.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Centers for Disease Control and Prevention (CDC). Progress in introduction of pneumococcal conjugate vaccine – worldwide, 2000–2008. *MMWR Morb. Mortal. Wkly Rep.* 57(42), 1148–1151 (2008).

2 Dinleyici EC, Yargic ZA. Pneumococcal conjugated vaccines: impact of PCV-7 and new achievements in the postvaccine era. *Expert Rev. Vaccines* 7(9), 1367–1394 (2008).

3 Black S, Shinefield H, Fireman B *et al.* Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr. Infect. Dis. J.* 19(3), 187–195 (2000).

4 Whitney CG, Pilishvili T, Farley MM *et al.* Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case–control study. *Lancet* 368(9546), 1495–1502 (2006).

5 Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet* 369(9568), 1179–1186 (2007).

6 Zhou F, Shefer A, Kong Y, Nuorti JP. Trends in acute otitis media-related health care utilization by privately insured young children in the United States, 1997–2004. *Pediatrics* 121(2), 253–260 (2008).

7 Hsu HE, Shutt KA, Moore MR *et al.* Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N. Engl. J. Med.* 360(3), 244–256 (2009).

8 Singleton RJ, Hennessy TW, Bulkow LR *et al.* Invasive pneumococcal disease caused by nonvaccine serotypes among alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA* 297(16), 1784–1792 (2007).

9 Scott DA, Komjathy SF, Hu BT *et al.* Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. *Vaccine* 25(33), 6164–6166 (2007).

•• **First Phase I results of the 13-valent pneumococcal conjugate vaccine (PCV-13).**

10 Scott D, Ruckle J, Dar M, Baker S, Kondoh H, Lockhart S. Phase 1 trial of 13-valent pneumococcal conjugate vaccine in Japanese adults. *Pediatr. Int.* 50(3), 295–299 (2008).

11 WHO. Recommendations for the production and control of pneumococcal conjugate vaccines. Technical Report Series, No. 927, 64–98. WHO, Geneva, Switzerland (2005).

12 Feavers I, Knezevic I, Powell M, Griffiths E; on behalf of the WHO Consultation on Serological Criteria for Evaluation and Licensing of New Pneumococcal Vaccines. Challenges in the evaluation and licensing of new pneumococcal vaccines, 7–8 July 2008, Ottawa, Canada. *Vaccine* 27(28), 3681–3688 (2009).

13 Bryant KA, Block SL, Scott DA. Safety and immunogenicity of a toddler dose of a 13-valent conjugated pneumococcal vaccine. Presented at: *6th International Symposium on Pneumococci and Pneumococcal Infections (ISPPD).* Rejkjavik, Iceland, 8–12 June 2008.

14 Grimprel E, Scott D, Laudat F, Baker S, Gruber W. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine given with routine pediatric vaccination to healthy infants in France. Presented at: *48th Annual ICAAC/IDSA 46th Annual Meeting.* Washington DC, USA, 25–28 October 2008.

• **Demonstrated the immunogenicity and safety of PCV-13 when coadministered with other pediatric vaccines.**

15 Kieninger DM, Kueper K, Steul K *et al.* 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: *48th Annual ICAAC/IDSA 46th Annual Meeting.* Washington DC, United States, 25–28 October 2008.

•• **Demonstrated the noninferiority of PCV-13 and comparable immunogenicity results with PCV-7 for shared serotypes.**

16 Gadzinowski J, Tansey S, Mellelieu T *et al.* A Phase 3 trial evaluating the safety, tolerability and immunogenicity of manufacturing scale 13-valent pneumococcal conjugate vaccine. Presented at: *48th Annual ICAAC/IDSA 46th Annual Meeting.* Washington DC, USA, 25–28 October 2008.

17 Klinger CL, Snape MD, John T *et al.* Immunogenicity of DTaP–IPV–Hib and MenC vaccines in the UK when administered with a 13-valent pneumococcal conjugate vaccine. Presented at: *48th Annual ICAAC/IDSA 46th Annual Meeting.* Washington DC, USA, 25–28 October 2008.

• **Demonstrated the immunogenicity of PCV-13 when coadministered with other pediatric vaccines.**

18 Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. *Lancet Infect. Dis.* 5(2), 83–93 (2005).

19 Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin. Infect. Dis.* 30(1), 100–121 (2000).

20 Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. *Clin. Infect. Dis.* 30(1), 122–140 (2000).

21 Shouval DS, Greenberg D, Givon-Lavi N, Porat N, Dagan R. Serotype coverage of invasive and mucosal pneumococcal disease in israeli children younger than 3 years by various pneumococcal conjugate vaccines. *Pediatr. Infect. Dis. J.* (2009) (In Press).

• **Demonstrated the serotype coverage of investigational PCV-13 and other pneumococcal conjugate vaccines of invasive and mucosal isolates in Israel.**

22 Kyaw MH, Lynfield R, Schaffner W *et al.* Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N. Engl. J. Med*. 354(14), 1455–1463. (2006).

23 Dagan R, Klugman KP. Impact of conjugate pneumococcal vaccines on antibiotic resistance. *Lancet Infect. Dis.* 8(12), 785–795 (2008).

24 Rodgers GL, Arguedas A, Cohen R, Dagan R. Global serotype distribution among *Streptococcus pneumoniae* isolates causing otitis media in children: potential implications for pneumococcal conjugate vaccines. *Vaccine* 27(29), 3802–3810 (2009).

•• **Excellent review of global serotype distribution of *Streptococcus pneunmoniae* causing otitis media.**

25 Levidiotou S, Vrioni G, Tzanakaki G *et al.* Serotype distribution of *Streptococcus pneumoniae* in north-western Greece and implications for a vaccination programme. *FEMS Immunol. Med. Microbiol.* 48(2), 179–182 (2006).

26 Adegbola RA, Hill PC, Secka O *et al.* Serotype and antimicrobial susceptibility patterns of isolates of *Streptococcus pneumoniae* causing invasive disease in The Gambia 1996–2003. *Trop. Med. Int. Health* 11(7), 1128–1135 (2006).

27 Leimkugel J, Adams FA, Gagneux S *et al.* An outbreak of serotype 1 *Streptococcus pneumoniae* meningitis in northern Ghana with features that are characteristic of *Neisseria meningitidis* meningitis epidemics. *J. Infect. Dis.* 192(2), 192–199 (2005).

28 Lagos R, Munoz A, San Martin O *et al.* Age- and serotype-specific pediatric invasive pneumococcal disease: insights from systematic surveillance in Santiago, Chile, 1994–2007. *J. Infect. Dis.* 198(12), 1809–1817 (2008).

29 Montagnani F, Fanetti A, Stolzuoli L *et al.* Pneumococcal disease in a paediatric population in a hospital of central Italy: a clinical and microbiological case series from 1992 to 2006. *J. Infect.* 56(3), 179–184 (2008).

30 Campbell JD, Kotloff KL, Sow SO *et al.* Invasive pneumococcal infections among hospitalized children in Bamako, Mali. *Pediatr. Infect. Dis. J.* 23(7), 642–649 (2004).

31 Nunes S, Sa-Leao R, Pereira LC, Lencastre H. Emergence of a serotype 1 *Streptococcus pneumoniae* lineage colonising healthy children in Portugal in the seven-valent conjugate vaccination era. *Clin. Microbiol. Infect.* 14(1), 82–84 (2008).

32 Hausdorff WP. The roles of pneumococcal serotypes 1 and 5 in paediatric invasive disease. *Vaccine* 25(13), 2406–2412 (2007).

33 Brueggemann AB, Spratt BG. Geographic distribution and clonal diversity of *Streptococcus pneumoniae* serotype 1 isolates. *J. Clin. Microbiol*. 41(11), 4966–4970 (2003).

34 Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. *Pediatr. Infect. Dis. J.* 25(3), 250–254 (2006).

35 Obando I, Muñoz-Almagro C, Arroyo L *et al.* Pediatric parapneumonic empyema, Spain. *Emerg. Infect. Dis.* 14(9), 1390–1397 (2008).

36 Gupta A, Khaw FM, Stokle EL *et al.* Outbreak of *Streptococcus pneumoniae* serotype 1 pneumonia in a United Kingdom school. *BMJ* 337(a2964), DOI: 10.1136/bmj.a2964 (2008) (Epub ahead of print).

37 Goldbart AD, Leibovitz E, Porat N *et al.* Complicated community acquired pneumonia in children prior to the introduction of the pneumococcal conjugated vaccine. *Scand. J. Infect. Dis.* 1–6, (2008).

38 Richter SS, Heilmann KP, Dohrn CL, Riahi F, Beekmann SE, Doern GV. Changing epidemiology of antimicrobial-resistant *Streptococcus pneumoniae* in the United States, 2004–2005. *Clin. Infect. Dis.* 48(3), e23–e33 (2009).

39 Prymula R, Peeters P, Chrobok V *et al.* 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(9512), 740–748 (2006).

40 Arguedas A, Dagan R, Guevara S *et al.* Middle ear fluid *Streptococcus pneumoniae* serotype distribution in Costa Rican children with otitis media. *Pediatr. Infect. Dis. J.* 24(7), 631–634 (2005).

41 Hammitt LL, Bruden DL, Butler JC *et al.* Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. *J. Infect. Dis.* 193(11), 1487–1494 (2006).

42 Shouval DS, Greenberg D, Givon-Lavi N, Porat N, Dagan R. Site-specific disease potential of individual *Streptococcus pneumoniae* serotypes in pediatric invasive disease, acute otitis media and acute conjunctivitis. *Pediatr. Infect. Dis. J.* 25(7), 602–607 (2006).

43 Rückinger S, von Kries R, Siedler A, van der Linden M. Association of serotype of *Streptococcus pneumoniae* with risk of severe and fatal outcome. *Pediatr. Infect. Dis. J.* 28(2), 118–122 (2009).

44 Moore MR, Gertz RE Jr, Woodbury RL *et al.* Population snapshot of emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005. *J. Infect. Dis.* 197(7), 1016–1027 (2008).

45 Hennessy TW, Singleton RJ, Bulkow LR *et al.* Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity. *Vaccine* 23(48–49), 5464–5473 (2005).

46 Pai R, Moore MR, Pilishvili T, Gertz RE, Whitney CG, Beall B; Active Bacterial Core Surveillance Team. Postvaccine genetic structure of *Streptococcus pneumoniae* serotype 19A from children in the United States. *J. Infect. Dis.* 192(11), 1988–1995 (2005).

47 Pelton SI, Huot H, Finkelstein JA *et al.* Emergence of 19A as virulent and multidrug resistant *Pneumococcus* in Massachusetts following universal immunization of infants with pneumococcal conjugate vaccine. *Pediatr. Infect. Dis. J.* 26(6), 468–472 (2007).

48 Critchley IA, Jacobs MR, Brown SD, Traczewski MM, Tillotson GS, Janjic N. Prevalence of serotype 19A *Streptococcus pneumoniae* among isolates from U.S. children in 2005–2006 and activity of faropenem. *Antimicrob. Agents Chemother.* 52(7), 2639–2643 (2008).

49 Choi EH, Kim SH, Eun BW *et al.* *Streptococcus pneumoniae* serotype 19A in children, South Korea. *Emerg. Infect. Dis.*14(2), 275–281 (2008).

50 Song JH, Baek JY, Cheong HS, Chung DR, Peck KR, Ko KS. Changes of serotype and genotype in *Streptococcus pneumoniae* isolates from a Korean hospital in 2007. *Diagn. Microbiol. Infect. Dis.* 63(3), 271–278 (2009).

51 Fenoll A, Granizo JJ, Aguilar L *et al.* Temporal trends of invasive *Streptococcus pneumoniae* serotypes and antimicrobial resistance patterns in Spain from 1979 to 2007. *J. Clin. Microbiol.* 47(4), 1012–1020 (2009).

52 Amrine-Madsen H, Van Eldere J, Mera RM *et al.* Temporal and spatial distribution of clonal complexes of *Streptococcus pneumoniae* isolates resistant to multiple classes of antibiotics in Belgium, 1997 to 2004. *Antimicrob. Agents Chemother.* 52(9), 3216–3220 (2008).

53 Mahjoub-Messai F, Doit C, Koeck JL *et al.* Population snapshot of *Streptococcus pneumoniae* serotype 19A isolates before and after introduction of seven-valent pneumococcal vaccination for French children. *J. Clin. Microbiol.* 47(3), 837–840 (2009).

54 Dagan R, Givon-Lavi N, Leibovitz E, Greenberg D, Porat N. Introduction and proliferation of multidrug-resistant *Streptococcus pneumoniae* serotype 19A clones that cause acute otitis media in an unvaccinated population. *J. Infect. Dis.* 199(6), 771–773 (2009).

55 Brueggemann AB, Pai R, Crook DW, Beall B. Vaccine escape recombinants emerge after pneumococcal vaccination in the United States. *PLoS Pathog.* 3(11), e168 (2007).

56 Munoz-Almagro C, Jordan I, Gene A, Latorre C, Garcia-Garcia JJ, Pallares R. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of 7-valent conjugate vaccine. *Clin. Infect. Dis.* 46(2), 174–182 (2008).

57 Klugman KP. The successful clone: the vector of dissemination of resistance in *Streptococcus pneumoniae*. *J. Antimicrob. Chemother.* 50(Suppl. S2), 1–5 (2002).

58 Hanage WP, Huang SS, Lipsitch M *et al.* Diversity and antibiotic resistance among nonvaccine serotypes of *Streptococcus pneumoniae* carriage isolates in the post-heptavalent conjugate vaccine era. *J. Infect. Dis.* 195(3), 347–352 (2007).

59 Hak E, Sanders EA, Verheij TJ *et al.* Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. *Neth. J. Med.* 66(9), 378–383 (2008).

Websites

101 Pneumococcal regional serotype distribution for pneumococcal AMC TPP www.vaccineamc.org/files/TTP_codebook.pdf

•• **Reviews all published and unpublished data about invasive pneumococcal isolates worldwide.**

102 Product characteristics http://ec.europa.eu/enterprise/pharmaceuticals/register/2009/2009033055611/anx_55611_en.pdf

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