World Health Organization
Global Vaccine Safety,
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
PNEUMOCOCCAL VACCINE

June 2012

The Vaccines

Pneumococcal vaccines are characterised by the number of *Streptococcus pneumoniae* serotype antigens that they contain and whether or not these antigens are conjugated to a protein carrier. The older pneumococcal vaccines are unconjugated (also called polysaccharide vaccines - PPSV) whilst the newer vaccines are conjugated (also called conjugated vaccines - PCV).

Currently available PPSV contain 23 purified capsular polysaccharide antigens of *Streptococcus pneumoniae,* serotypes. PCV consists of protein-polysaccharide combinations and contain a variable number (7, 10 or 13) of capsular polysaccharides antigens bound to a protein carrier (non-toxic diphtheria toxin CRM_{197}, or D-protein of *Haemophilus influenzae*). PCVs induce immunological memory in children less than 2 years of age. PCV13 is also approved for use in adults 50 and older.

Types of vaccines

	Vaccine antigens	Excipients
Unconjugated (PPSV)	*Pneumococcal 23-valent vaccine* - consists of 25 µg of each capsular polysaccharide antigens from the following serotypes - 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.	Dissolved in isotonic saline solution with phenol (0.25%) or thiomersal (0.01%) added as preservative.
Conjugated (PCV)	*Pneumococcal conjugate 7-valent vaccine* – consisting of 2-4 µg of capsular polysaccharide antigens from the following serotypes - 4, 6B, 9V, 14, 18C, 19F, 20, and 23F conjugated to non-toxic diphtheria toxin (CRM197). *Pneumococcal conjugate 13-valent vaccine* – consisting of 2 – 4 µg polysaccharides of the capsular antigens of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to a nontoxic diphtheria CRM197). *Pneumococcal conjugate 10-valent vaccine* – consisting of 1 microgram of polysaccharide for serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 micrograms of serotypes 4, 18C and 19F.	Aluminium phosphate No preservatives PCV13 also contains polysorbate 80, and succinate buffer.

Adverse events

Mild adverse events

Pneumococcal polysaccharide vaccine (unconjugated) - is considered very safe. Most common adverse events were reported in >10% of subjects vaccinated with Pneumococcal 23-valent vaccine include injection-site (IS) pain (soreness, tenderness) (60%), local swelling or induration (20.3%), headache (17.6%), local erythema (16.4%), asthenia and fatigue (13.2%) and myalgia (6.1%). Less than 1% developed a fever or more severe local reactions. Typically, local reactions are resolved within 5 days following vaccination (CDC Vaccine Information Statement, 2009). In a meta-analysis of nine randomized controlled trials of pneumococcal vaccine efficacy, local reactions were observed among approximately one third of 7531 patients receiving the vaccine (Fine, 1994, Burwen et al., 2007, Jackson 2008).

Pneumococcal vaccine (conjugated) - injection site reactions (erythema) occur in approximately 10% of vaccine recipients and there may be an increase in milder injection site reactions with subsequent doses and in older age groups (12-15 months of age) (Destefano S et al., 2008, Black S et al., 2008). Generalised reactions such as high fever are quite rare.

In studies most reactions after PCV13 were mild. They were similar to reactions reported after PCV7 which has been in use since 2000. Reported reactions varied by dose and age but on average about half of children were drowsy after the shot, had temporary loss of appetite. 1 in 5 had injection site swelling or redness or tenderness where the shot was given. About 1 in 3 had swelling where the shot was given. About 1 in 3 had mild fever and about 1 in 20 had high fever (over 39 C). About 1 in 7 was irritable. Life-threatening allergic reactions from vaccines are very rare. If they do occur, it would be within a few minutes to a few hours after vaccination (CDC Vaccine Information Statement, 2009).

In adults, commonly reported solicited adverse reactions include pain at injection site in about half of reactions, fatigue (1 in 3), headache or muscle pain (1 in 5). One in 10 had joint pain or decreased appetite or injection site redness or injection site swelling, limitation of arm movement. Chills or rash occurred in one in 20.

Pre-licensure data showed that after each dose of PCV administered concurrently with DTP-HbOC or DTaP, fever (≥38.0C) was reported more frequently compared to the control group within 48 hours of a vaccine dose. Concurrent administration with DTaP resulted in fever rates among recipients of Pneumococcal 13-valent conjugate vaccine from 15% to 34%, with higher rates after the 2nd dose. Other reported systemic events included fussiness, drowsiness, and decreased appetite. The percentage of subjects for each adverse reactions varied by age group and dose. Urticaria-like rash was reported in 0.4 to 1.4% of children within 48 hours of immunization with PCV administered concurrently with other routine childhood vaccines. Hypotonic-hyporesponsive episodes may also occur following the concurrent administration of Pneumococcal 13-valent conjugate vaccine and DTP vaccinations and seizures also following the concurrent administration of Pneumococcal 13-valent conjugate vaccine and either DTP or DTaP.

Post-marketing surveillance studies showed also an association between fever and PCV administration. PCV was associated with only mild reactions: up to about 1 infant out of 4 had redness, tenderness, or swelling where the shot was given. Up to 1 out of 3 had a fever greater than 38°C and up to 1 in 50 had a higher fever (over 39°C). Some children also became fussy or drowsy or had loss of appetite. No severe reaction has been associated with this vaccine. In analyses of secondary safety outcomes, the adjusted relative risk of hospitalization for reactive airways disease was 1.23 (95% CI = 1.11;1.35). Extended follow up of subjects originally enrolled in the NCKP efficacy trial revealed no increased risk of reactive airway disease among PCV recipients.

Severe adverse events

Pneumococcal vaccine (unconjugated) - Severe systemic adverse effects (e.g. anaphylactic reactions) have been reported rarely after administration (CDC, 1989). A meta-analysis which included 7531 patients did not report severe febrile or anaphylactic reactions (Fine, 1994). No neurological disorders (e.g. Guillain–Barré syndrome) have been reliably associated with administration of pneumococcal vaccine.

Pneumococcal vaccine (conjugated) - Increased risk of hospitalisation within 60 days of receiving a 7-valent pneumococcal conjugate vaccine (PCV7) for asthma and otitis media has been reported in pre-licensure studies (Eskola et al., 2001). Wheezing within 2 months of vaccination- also showed a twofold increased risk in PCV vs. meningococcal C conjugate recipients (Black, 2000) In addition, hospitalisation for physician-diagnosed reactive airway disease or asthma beyond 31 days has also been reported more frequently in recipients of a 9-valent pneumococcal conjugate vaccine – relative risk 1.79 (P=0.009) (Klugman, 2003). In this same study of 19,922 vaccine recipients and 19914 subjects who received a placebo vaccine hospitalisation for viral-associated pneumonia within 8 days of vaccination (in non-HIV infected children) was more frequent (30 vs. 15 cases, P=0.03).

Other safety issues

Multiple doses of pneumococcal unconjugated vaccine - Early studies have indicated that local reactions (i.e. Arthus type reactions) among adults receiving the second dose of discontinued 14-valent vaccine within two years after the first dose are more severe than those occurring after initial vaccination (CDC, 1989; Borgono et al., 1978). Subsequent studies have suggested that revaccination after intervals of >4 years is not associated with an increased incidence of adverse side-effects (CDC, 1989; Mufson, 1984; Rigau-Perez, 1983). For subjects aged 65 years or older, the local adverse reaction rate is higher following revaccination (79.3%) than following initial vaccination (52.9%). The proportion of subjects reporting local discomfort that interfered with or prevented usual activity or local induration ≥4 inches is higher following revaccination (30.6%) than following initial vaccination (10.4%). For subjects 50-64 years, the local adverse reaction rate for revaccinees and initial vaccines is similar (79.6% and 72.8% respectively). The rate of systemic adverse events is similar among both the initial vaccines and revaccinees within each age group. The rate of vaccine-related systemic reaction is higher following revaccination (33.1%) than following initial vaccination (21.7%) in subject 65 years or older, but similar in 50-64 years of age (37.5% in revaccinees and 35.5% in initial vaccines).

Studies evaluating multiple doses of vaccines from various bacteria containing polysaccharide have shown an altered immune response to subsequent polysaccharide challenge. It is not clear from the efficacy data of human vaccine regimens whether these observations have important clinical implications and if so, to what degree any hypo-responsiveness might affect clinical disease prevention (O'Brien KL et al., 2007). One study showed an increased rate in local reactions of large dimension in those receiving more than one dose of the vaccine (Snow et al., 1995). An evaluation of 1,000 elderly Medicare enrollees who received a second dose of PPSV23 showed that they were not significantly more likely to be hospitalized in the 30 days after vaccination compared to approximately 66,000 persons who received their first dose of vaccine (Snow et al., 1995). No data are available to allow estimates of adverse reaction rates among persons who received more than two doses of pneumococcal vaccine.

HIV infection – Minor or severe adverse reactions do note seem to be more likely in HIV infected children and adults (DeStefano S et al., 2008)

Sickle cell disease, adult renal transplant patients and premature infants – do not have an increased risk of adverse reactions following vaccination with pneumococcal vaccines. (DeStefano S et al., 2008)

Drug interactions:

PPSV23: Drug interactions: In a randomized clinical study, a reduced immune response to live zoster vaccine as measured by gpELISA was observed in individuals where vaccines were concurrently administered compared with individuals who received vaccines 4 weeks apart. Administrating of these vaccines should be considered to be separated by at least 4 weeks.

PCV13: In adults, antibody responses to Pneumococcal 13-valent conjugate vaccine are diminished when given with inactivated Influenza Virus Vaccine.

Summary of mild and severe adverse events

Nature of Adverse event	Description	Rate/doses
Mild	Injection site reactions Unconjugated vaccine (PPSV) Conjugated vaccine (PCV) Generalized reactions Both vaccines – fever . 39C	 50 per 100 10 per 100 < 1 per 100
Severe	None proven to date	

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such (Plotkin et al., 2008; Institute of Medicine of the National Academies 2011) and from data derived from a literature search on Pubmed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomised controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: **http://www.who.int/vaccine_safety/vaccrates/en/index.html**

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