Safety profile of pneumococcal conjugate vaccines: systematic review of pre- and post-licensure data

Frank DeStefano,[a] Dina Pfeifer[b] & Hanna Nohynek[c]

Abstract A 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) was licensed in the United States of America in 2000, but no comprehensive postmarketing review of safety has been carried out. We conducted a systematic review of the safety of PCV7 and other pneumococcal conjugate vaccines. A total of 42 studies were included in the review. Reactogenicity data from some randomized trials suggest that PCV7 may result in more local reactions and fever than certain comparison vaccines. However, the reactions were mild and self-limited, and PCV7 did not carry an increased risk of severe injection-site reactions or high fever. Some, although not all, of the randomized trials in children found that mild local and systemic reactions associated with PCV7 may increase with the number of doses, at least over the three-dose primary series. In addition, PCV7 and other pneumococcal conjugate vaccines were found to have tolerable reactogenicity in Native American and African populations and in medically high-risk groups for which pneumococcal vaccination is recommended. Two of the largest studies of PCVs, one involving PCV7 and the other, PCV9, found a statistically significant increased risk of hospitalization for reactive airway disease, including asthma. Another large trial of PCV9, however, did not find an increased risk of asthma. In conclusion, this review of the evidence did not identify any major safety problems with PCV7 or any other pneumococcal conjugate vaccine, with the possible exception of reactive airway disease, which may bear further scrutiny as additional data become available.

Bulletin of the World Health Organization 2008;86:373–380.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Background

In February 2000, a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7; Prevnar®, Wyeth Lederle Vaccines) was licensed in the United States of America (USA). The vaccine is recommended for all children aged 2–23 months and for children aged 24–59 months who are at an increased risk of pneumococcal disease, for example, those with sickle-cell disease, human immunodeficiency virus (HIV) infection, or another immunocompromising or chronic medical condition. Healthy children receive a primary series of vaccinations at 2, 4 and 6 months of age followed by a booster dose at 12–15 months. The vaccine has been used most extensively in the USA, but it is also registered and recommended for universal infant use in 23 other countries, predominantly in North America and western Europe, and has been registered in 65 countries in which universal use recommendations have not been made.[1] In 2005, more than 26 million doses were sold globally, enough to fully vaccinate 6.5 million infants. Other pneumococcal conjugate vaccines has been developed, but none has yet been licensed.

The Global Advisory Committee on Vaccine Safety (GACVS) of WHO is responsible for ensuring that adequate and ongoing attention is paid to the safety of vaccines. GACVS regularly reviews the safety profile of vaccines using postmarketing surveillance data as the body of evidence and experience with vaccine use evolves. We conducted a systematic review of the evidence for a GACVS review of the safety of PCV7 and other pneumococcal vaccines.[2]

Methods

We sought any article with original data on adverse events associated with pneumococcal conjugate vaccines. Outcomes of interest included any adverse health condition reported as being possibly associated with pneumococcal vaccine administration.

Articles were identified from systematic searches of the PubMed and Cochrane Collaboration databases, reviews of bibliographic reference lists, and consultations with experts in the field. The literature search covered all years and there was no language or other restriction. PubMed was searched using the following algorithm containing medical subject heading (MeSH) terms combined with text words: ["pneumococcal vaccines/adverse effects" (MeSH) OR "pneumococcal vaccines/contraindications" (MeSH) OR "pneumococcal vaccines/toxicity" (MeSH)] OR [(pneumococcal vaccines) AND (erythema OR induration OR pain OR tenderness OR fever OR febrile OR death OR mortality OR SIDS OR seizure OR anaphylaxis OR allergic reaction OR rash OR urticaria OR vomiting OR diarrhoea OR serum sickness OR thrombocytopenia OR dyspnoea OR safety OR morbidity OR harm)].

The articles were independently reviewed by two epidemiologists and a senior medical epidemiologist using

[a] RTI International, Suite 119, 2951 Flowers Rd, Atlanta GA 30341, United States of America.
[b] Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland.
[c] National Public Health Institute (KTL), Helsinki, Finland.
Correspondence to Frank DeStefano (e-mail: fdestefano@rti.org).
doi:10.2471/BLT.07.048025
(*Submitted: 27 September 2007 – Revised version received: 14 December 2007 – Accepted: 6 February 2008*)

specially developed abstraction forms. The senior epidemiologist oversaw the work of the epidemiologists and resolved any questions.

The PubMed search identified 998 articles potentially involving pneumococcal vaccine safety. By reviewing just the titles and abstracts, we narrowed the list of potentially relevant articles to 149. Reading of texts resulted in 37 articles on pneumococcal conjugate vaccines being included in the review. References cited in reviewed articles identified three additional articles for inclusion. Suggestions of experts identified two conference abstracts and two United States Food and Drug Administration (FDA) product licensure applications. The FDA data[3,4] supplemented data reported in two published studies.[5,6] A summary of the design and other characteristics of the 42 published articles and two abstracts included in the review is available at: http://www.rti.org/files/PCV_Safety_Rev_App.pdf. We also obtained unpublished data from two pharmacovigilance systems, including the United States Vaccine Adverse Events Reporting System (VAERS)[7] and the system in Quebec, Canada.[8] Both are voluntary reporting systems that accept reports of adverse events that the person filing the report suspects may have been associated with vaccination.

Results

Reactogenicity

The reactogenicity of PCV7 vaccination, including injection-site reactions and fever, has been evaluated in several randomized clinical trials.[5,6,9–14] The findings of these trials are summarized in Table 1 (available at: http://www.who.int/bulletin/volumes/86/5/07-048025/en/index.html) for reactions of any level of severity and in Table 2 for more severe reactions.

According to dose and age

When mild reactions are included (Table 1), there is a suggestion that the prevalence of injection-site redness or fever may increase with the dose number over the first three primary PCV7 doses,[5,6,10,13,14] and several studies found the highest frequency of injection-site reactions and fever in the 12–15-month age group.[12,14,15] When the analysis was restricted to more severe reactions, however, the rates were substantially lower and there was little indication of a trend with dose number or age (Table 2).

Three observational studies or non-randomized trials also provided information on how reactogenicity varied with dose number and age (Table 3). The studies by Käyhty et al. and Shao et al. found more injection-site reactions as the dose number increased.[16–18] Käyhty et al. reported a similar trend for fever > 38 °C. Fernández et al. reported the only study in which healthy children aged over 24 months were vaccinated.[19]

None of the PCV7 studies used an immunization schedule compatible with the WHO Expanded Programme on Immunization schedule of 6, 10 and 14 weeks used for diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b (Hib) and oral polio vaccine. The studies that have been conducted using schedules similar to the WHO schedule all evaluated newer pneumococcal conjugate vaccines that are still under development and these studies reported little if any reactogenicity data. Reactogenicity data related to dose number were only reported by Obaro et al.[20] for PCV9 and Capeding et al.[21] for PCV11 (Table 4).

After primary doses and booster dose

In healthy children, a booster dose of PCV7 is recommended at 12–15 months of age, following a primary series of vaccinations at 2, 4 and 6 months. In the reported randomized clinical trials, the booster dose was found to be associated with a higher incidence of injection-site reactions and fever in some of the studies,[12,14,15] but not in others.[3–6,11,12]

A variety of approaches involving different schedules of PCV7 and 23-valent pneumococcal polysaccharide vaccine (PPV23), sometimes referred to as "prime-boost" if PCV7 is followed by PPV23, have been proposed, primarily to try to increase pneumococcal strain coverage and the antibody response. Nachman et al. studied a small number of children with HIV-1 infection and found few injection-site reactions with the administration of PPV23 at 24 months among children who had received the four main PCV7 vaccinations.[22] O'Brien et al. studied children with sickle-cell disease and compared a dose schedule of three PCV7 injections as a primary series followed by PPV23 at 24 months with a schedule of one PCV7 dose at 12 months followed by PPV23 at 24 months.[23] About half of each group experienced unspecified local reactions after the PPV23 dose. All published studies of primary immunization with PCV followed by a PPV booster in healthy individuals used investigational PCVs and most reported minimal safety data.[24–26] The study that reported the most complete safety data was a randomized trial in which infants received three doses of PCV11 followed by either PCV11 or PPV23 for the fourth dose; local reaction and fever rates were higher with PPV23.[27]

Vaccine safety

PCV7

The most comprehensive evaluation of PCV7 safety beyond short-term reactogenicity was carried out in the pre-licensure trial conducted by Kaiser Permanente of Northern California, USA.[3,5] Apart from injection-site reactions and fever, however, most adverse events occurred infrequently. Hospitalization for asthma within 60 days of vaccination was reported to be more frequent in the PCV7 group than the comparison group, but analyses of asthma diagnoses outside of the hospital setting did not reveal an association with PCV7.[3] A group-randomized trial of PCV7 conducted in Native American children reported few data on adverse reactions.[28] The one notable safety finding was that hospitalization for otitis media occurred more frequently in PCV7 recipients than in comparison vaccine recipients, which is puzzling given that another clinical trial found that PCV7 is effective in preventing otitis media.[6] No increased risk of death following PCV7 vaccination was found in the Northern Californian or any other study.[5,6,22,28]

Two retrospective cohort studies of adverse events requiring medical attention in the Northern California Kaiser Permanente population have been reported as abstracts. One study found a slight increase in reactive airway disease among infants vaccinated with PCV7 compared with a historical cohort of infants vaccinated with Hib.[29] A simi-

Table 2. **Reactogenicity of moderate or greater severity for PCV7 according to age at dose administration: randomized trials in healthy children under 2 years of age**

Reactogenicity[a]	Age at dose administration (months)	Study					
		Black et al.[5]	Eskola et al.[6]	Knuf et al.[12]	Scheifele et al.[13]	Schmitt et al.[14]	Tichmann-Schumann et al.[15]
PCV7 (*n*)	–	693	831	125	376	118	175
Comparison	–	Men C	Hep B	Hexa	No PCV	Other vaccines	Other vaccines
Redness (%)	2	0.3	0	0.8	1.2	0 (3 months)	–
	4	0	0.2	3.3	1.6	1.9	–
	6	0.2	0.4	3.4	1.6	0 (5 months)	–
	12–15	0.6	0.9	7.3		4.4	–
Swelling (%)	2	0.1	1.1	2.5	4.8	0 (3 months)	–
	4	0.4	1.0	5.0	1.2	1.0	–
	6	0.5	0.5	5.2	3.2	0 (5 months)	–
	12–15	0.6	1.3	8.1	–	2.2	–
Fever (%)	2	0.9	0.4	0.8	–	3.8 (3 months)	4.6
	4	2.5[b]	1.0	0.8	–	2.9	4.1 (3 months)
	6	1.7	2.0[b]	1.7	–	4.7 (5 months)	2.4 (4 months)
	12–15	1.3	1.6	2.7	–	8.3	11.2

Hep B, hepatitis B; Hexa, INFANRIX® hexa; Men C, meningitis C; PCV7, 7-valent pneumococcal polysaccharide-protein conjugate vaccine.
[a] Local reactions > 2.0 cm, > 2.4 cm or > 3.0 cm according to study; fever > 39 ºC.
[b] Significantly ($P < 0.05$) higher with PCV7 than comparison vaccination.

lar analysis of children with Kawasaki disease found a twofold increased risk which was not statistically significant after adjustment for sex, age, race and other factors.[30]

Individual case reports can serve as an early alert of a possible vaccine safety problem. An analysis of post-licensure voluntary reports to VAERS was conducted 2 years after the vaccine was licensed.[7] The majority of reports described minor adverse events. The proportion of reports involving serious events was similar to that for other vaccines. We obtained summary VAERS reports for PCV7 for the entire period of the vaccine's availability up to 31 August 2006. The updated data revealed safety profiles similar to those reported in the earlier review. The most frequently reported conditions continued to be fever, injection-site reactions, rashes (including urticaria), and irritability or agitation. We also obtained unpublished preliminary data on PCV7 adverse events reports from the pharmacovigilance system of the province of Quebec, Canada. The safety profile was similar to that observed in the VAERS reports; the most frequently reported adverse reactions in children under 5 years of age were fever, local reactions, allergic reactions and rash.

Other pneumococcal conjugate vaccines

A number of other PCVs with different numbers of strain antigens and different conjugate proteins have been developed, although none are being marketed currently. Randomized trial results have been reported for PCV4,[31] PCV5,[32] PCV8,[24] and PCV9.[20,33–37] Studies of PCV11 have also been reported.[21,27,38–40] Most of these studies have been relatively small and have reported limited data on acute injection-site reactions and systemic reactogenicity.

The largest trial of a pneumococcal conjugate vaccine was conducted in South Africa. It included 19 922 infants vaccinated with PCV9 at 6, 10 and 14 weeks and 19 914 infants who received placebo injections.[34] Seizures of any type occurred with a similar frequency in the vaccine (n = 44) and placebo (n = 40) groups. Among children without an HIV infection, hospitalization for viral pneumonia (mostly due to respiratory syncytial virus) within 8 days of vaccination was significantly more frequent in PCV9 recipients (n = 30) than in placebo recipients (n = 15). Beyond 31 days after vaccination, hospitalization for asthma or reactive airway disease was more frequent in the PCV9 group (n = 59) than in the placebo group (n = 33), with a relative risk of 1.79 (P = 0.009).

Another large efficacy trial of PCV9 was conducted in the Gambia. It included 8718 infants vaccinated with PCV9 and 8719 placebo recipients.[36] There was no difference in local reaction or fever rates between the groups. In PCV9 vaccinees, 110 serious adverse events (i.e. hospitalization or death) were observed within 7 days of vaccination, compared with 131 in placebo recipients. This included 12 deaths in the PCV9 group and 15 deaths in the placebo group. An increase in outpatient consultations after the first dose of PCV9 was reported to have been primarily related to nurses' clinical diagnoses of pneumonia (of unknown type). No increase in asthma was found.

Safety in special groups

Individuals with high-risk medical conditions

In a randomized trial of PCV7 vaccination in 30 HIV-1 infected infants, few severe injection-site or febrile reactions were detected; two children who received PCV7 and one placebo recipient died, but the deaths were not attributable to the vaccine.[22] Feikin et al.

studied different schedules of PCV7 and PPV23 vaccination in HIV-infected adults; no severe adverse reactions were detected.[41] In a randomized trial of PCV5 involving 18 HIV-infected infants and 17 infants without HIV, few infants in either group developed an injection-site reaction or fever.[32] The large South African PCV9 trial did not report safety data for HIV-infected children.[34]

In a study of children with sickle-cell disease vaccinated with PCV7, unspecified local reactions during the three-dose primary series occurred with a similar frequency in children with (52%) and without (57%) the disease; fever > 38 °C occurred in 7% of children with sickle-cell disease and in 19% of those without.[23]

Kumar et al. compared PCV7 and PPV23 in adult renal transplant recipients and found no difference in injection-site redness or pain.[42] Lin et al. found that injection-site pain was common in all groups in a study of different PCV7 and PPV23 immunization schedules among 25 children who were solid organ transplant recipients.[43]

Premature infants

In a subanalysis of the pre-licensure clinical trial in northern California, 1592 premature infants were compared with 10 402 full-term infants and found to have similar rates of local reactions and fever following vaccination with PCV7.[44] Another study compared 46 premature and 46 full-term infants immunized with PCV7; few local reactions or fevers > 39 °C occurred in either group.[45]

The elderly

Jackson et al. evaluated the reactogenicity of varying dosages of PCV7 in elderly individuals previously vaccinated with PPV23.[46] Injection-site reactions increased as the dosage volume increased, although even at the highest volume the local reaction rate was no higher than in the PPV23 revaccination group.

Table 3. **Reactogenicity of any severity for PCV7 according to age at dose administration: nonrandomized studies in healthy children under 3 years of age**

Reactogenicity	Age at dose administration (months)	Study		
		Fernández et al.[19]	Käyhty et al.[16]	Shao et al.[17,18]
PCV7 (*n*)	–	115	101	60
Comparison	–	none	DTaP-IPV/Hib	none
Redness (%)	2	–	1.0 (3 months)	17
	4	–	5.1 (5 months)	22
	6	–	–	28
	12–15	–	18.2	–
	17–19	–	–	50
	24–36	40.0	–	
Swelling (%)	2	–	5.9 (3 months)	17
	4	–	19.2 (5 months)	18
	6	–	–	25
	12–15	–	21.2	
	17–19	–	–	47
	24–36	32.2	–	–
Fever (%)	2	–	38 (3 months)	35
	4	–	54 (5 months)	48
	6	–	–	32
	12–15	–	62	–
	17–19	–	–	50
	24–36	7.0	–	–

DTaP-IPV/Hib, diphtheria, tetanus, pertussis (acellular antigens), inactivated polio vaccine and *Haemophilus influenzae* type b; PCV7, 7-valent pneumococcal polysaccharide-protein conjugate vaccine.

Discussion

The primary source of safety information on PCV7 comes from pre-licensure trials and a few other trials that have been reported after licensure. Reactogenicity data from randomized trials suggest that PCV7 may result in more local reactions and fever than comparison vaccines, such as hepatitis B or meningococcal C conjugate. However, the reactions were mild and self-limited; PCV7 does not appear to carry an increased risk of more severe injection-site reactions or high fever. Moreover, PCV7 and other pneumococcal conjugate vaccines have generally been found to have acceptable reactogenicity in special populations and high-risk groups, including premature infants and individuals with HIV infection, sickle-cell disease or organ transplants, as well as in Native American infants.

Data on longer-term safety and rare serious adverse events are more limited than short-term reactogenicity data. The large efficacy trials of PCV7 and PCV9 were most able to address safety and for the most part no major safety problems were identified. The possible exception is respiratory adverse events. In the Northern California Kaiser Permanente trial, hospitalization for asthma within 60 days of vaccination was increased, but no increase in the asthma rate was seen in outpatient settings. Preliminary results from a separate retrospective study in the population of northern California also suggested that there was a slight increase in the risk of reactive airway disease, including asthma, in infants vaccinated with PCV7. The finding in the large South African PCV9 trial of a nearly twofold increased risk of hospitalization for reactive airway disease and asthma suggests that reactive airway disease associated with pneumococcal conjugate vaccines may bear further monitoring. In a similar vein, large PCV9 trials in both the Gambia and South Africa found an indication that medical care visits for pneumonia had increased: hospital admissions for viral pneumonia in South Africa and nurse consultations for pneumonia of an unspecified type

in the Gambia both increased. The trial in the Gambia, however, did not find an increase in asthma. Results should be forthcoming from a recently completed large clinical trial of PCV11 conducted in the Philippines that may provide additional useful data on the risk of respiratory adverse events.[47]

Safety is an important consideration in making both individual and policy decisions on the use of a vaccine. Other factors, however, must also be taken into account. Foremost is the efficacy of the vaccine, which has been well established by clinical trials of PCV7.[3,6] In the USA, PCV7 was rapidly adopted; by 2005, the coverage level for the receipt of three or more doses among children aged 19–35 months was greater than 80%.[48] The effectiveness of the vaccine has resulted in a dramatic decrease in the incidence of invasive pneumococcal disease due to vaccine strains.[49]

Although it is not a safety issue, one potential concern is that pneumococcal strains which are not included in the vaccine will replace vaccine strains as a cause of invasive pneumococcal disease.[4] Surveillance in the USA has found significant increases in the rates of disease caused by non-vaccine serotypes.[49] However, this increase has been small compared to the decline in invasive disease due to vaccine serotypes, except in the native Alaskan population.[50] Replacement disease is not anticipated to result in an increase in the overall pneumococcal disease burden. However, it may reduce the anticipated benefit of introducing PCV. Surveillance to document the extent of this effect in developing countries will be required.

WHO regards the inclusion of PCV7 in national immunization programmes as a priority.[51] Mild local reactions and fever do occur, but we did not identify any major safety problem associated with pneumococcal conjugate vaccines, with the possible exception of reactive airway disease. Additional data on a possible association with this disease would be valuable. ■

Table 4. **Reactogenicity of PCV9 and PCV11 according to age at dose administration: schedules were compatible with the WHO Expanded Programme on Immunization**

Reactogenicity	Obaro et al.[20]		Capeding et al.[21]	
Vaccine (*n*)	PCV9 (104)		PCV11 (50)	
Comparison (*n*)	IPV (102)		DTwPHib (opposite thigh)	
Reaction	**Age at dose administration (months)**	**Percentage with reaction**	**Age at dose administration (weeks)**	**Percentage with reaction[a]**
Redness (> 2 cm)	2	–	6	0
	3	–	10	0
	4	–	14	0
Swelling[b]	2	ns	6	7.8
	3	6[c]	10	4.1
	4	8[c]	14	0
Tenderness	2	ns	6	–
	3	15[c]	10	–
	4	18[c]	14	–
Fever (> 38.7 °C)	2	–	6	8.0
	3	–	10	12.2
	4	–	14	8.5

DTwPHib, diphtheria, tetanus, pertussis (cellular antigens), and *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; ns, not significant; PCV9, nonavalent pneumococcal polysaccharide-protein conjugate vaccine.

[a] PCV11 site for local reactions.

[b] Obaro: > 5 mm; Capeding: > 2 cm.

[c] Significantly higher ($P < 0.05$) with PCV7 than IPV.

Acknowledgements

We thank Sarah Rosquist and Eric Gillis, RTI International, for assistance with the literature review; Cynthia Whitney, Centers for Disease Control and Prevention (CDC), for advice on the review and identification of relevant studies; Lynn Whitener, University of North Carolina at Chapel Hill, for guidance on the PubMed search; Penina Haber, CDC, for provision of VAERS data; Louise Ringuet, Laboratoire de Santé Publique du Quebec, for provision of Quebec pharmacovigilence data; and Thomas Cherian, Adwoa Bentsi-Enchill and Philippe Duclos, Department of Immunization, Vaccines and Biologicals, WHO, for support and guidance on the project.

Funding: Project funded by WHO (Contract No. HQ/06/188086).

Competing interests: None declared.

Résumé

Profil d'innocuité des vaccins antipneumococciques conjugués : revue systématique des données pré-autorisation et post-autorisation

Le vaccin antipneumocccique conjugué protéine/polyoside heptavalent (PCV7) a été autorisé aux Etats-Unis d'Amérique en 2000, mais aucune étude d'innocuité postcommercialisation complète n'a été effectuée. Nous avons mené une revue systématique concernant l'innocuité du PCV7 et d'autres vaccins antipneumococciques conjugués. Au total, 42 études ont été incluses dans la revue. Les données de réactogénicité de certains essais randomisés laissent à penser que le PCV7 peut entraîner davantage de réactions locales et de fièvre que certains des vaccins auquel il est comparé. Néanmoins, ces réactions sont bénignes et spontanément résolutives et le PCV7 ne présente pas de risque accru de réaction grave au site d'injection ou de forte fièvre. Certains des essais randomisés menés chez l'enfant, mais pas tous, ont observé que les réactions locales ou systémiques bénignes associées au PCV7 pouvaient augmenter avec le nombre de doses administrées, tout au moins sur la série de trois doses primaires. En outre, il a été constaté que le PCV7 et d'autres vaccins antipneumococciques conjugués présentaient une réactogénicité tolérable pour les populations amérindiennes et africaines et pour les groupes à haut risque médical, chez lesquels la vaccination antipneumococcique est recommandée. Deux études de grande ampleur sur les PCV, l'une consacrée au PCV7 et l'autre au PCV9, ont relevé une augmentation statistiquement significative du risque d'hospitalisation pour maladie réactive des voies aériennes, notamment pour une crise d'asthme. Un autre essai de grande ampleur sur le PCV9 n'a cependant pas constaté d'augmentation du risque d'asthme. En conclusion, cette revue des données n'a identifié aucun problème majeur de sécurité avec le PCV7, ni avec un autre vaccin antipneumococcique, à l'exception peut être des maladies réactives des voies aériennes, qui pourraient faire l'objet d'un examen plus approfondi lorsque des données supplémentaires seront disponibles.

Resumen

Perfil de seguridad de las vacunas antineumocócicas conjugadas: revisión sistemática de los datos anteriores y posteriores a la autorización

En 2000 se autorizó en los Estados Unidos de América una vacuna antineumocócica conjugada heptavalente de polisacáridos y proteínas (PCV7), pero no se ha llevado a cabo un análisis poscomercialización exhaustivo de su seguridad. Realizamos una revisión sistemática de la seguridad de la vacuna PCV7 y de otras vacunas antineumocócicas conjugadas, que abarcó en total 42 estudios. Los datos de reactogenicidad de algunos ensayos aleatorizados parecen indicar que la PCV7 puede provocar más reacciones locales y fiebre que algunas de las vacunas de comparación. Sin embargo, las reacciones fueron leves y de resolución espontánea, y la PCV7 no se asoció a un mayor riesgo de fiebre alta o de reacciones graves en el punto de inyección. En algunos, aunque no todos, de los ensayos aleatorizados realizados con niños se observó que las reacciones locales y sistémicas leves asociadas a la PCV7 tienden aparentemente a aumentar con el número de dosis, al menos en la serie primaria de tres dosis. Se observó además que la PCV7 y otras vacunas antineumocócicas conjugadas presentaban una reactogenicidad tolerable en las poblaciones africanas y de indios estadounidenses, así como en grupos de alto riesgo médico a los que se recomienda la vacunación antineumocócica. En dos de los mayores estudios realizados sobre las PCV, uno sobre la PCV7 y otro sobre la PCV9, se observó un aumento estadísticamente significativo del riesgo de hospitalización por enfermedades reactivas de las vías respiratorias, asma incluido. En otro importante ensayo sobre la PCV9, sin embargo, no se detectó un mayor riesgo de asma. En conclusión, en esta revisión de la evidencia disponible no se detectaron problemas relevantes relacionados con la seguridad ni con la PCV7 ni con otras vacunas antineumocócicas conjugadas, exceptuando quizá las enfermedades reactivas de las vías respiratorias, que pueden ser objeto de ulteriores investigaciones a medida que se obtengan nuevos datos.

ملخص

مرتسم السلامة للقاحات المكورات الرئوية المقترنة: مراجعة منهجية للمعطيات قبل وبعد الترخيص

في عام ألفين أجيز استخدام اللقاح السباعي التكافؤ المقترن للبروتين – عديد السكريد للمكورات الرئوية (PCV7) في الولايات المتحدة الأمريكية، إلا أنه لم تجر عليه مراجعة شاملة تالية للتسويق لتقرير مدى سلامته. وقد قام الباحثون بمراجعة منهجية لسلامة هذا اللقاح وغيره من اللقاحات المقترنة للمكورات الرئوية؛ وقد شملت المراجعة 42 دراسة. وتشير المعطيات الخاصة بمدى تفاعلية اللقاح في بعض التجارب المعشاة إلى أن لقاح المكورات الرئوية السباعي التكافؤ المقترن للبروتين – عديد السكري (PCV7) قد يؤدي إلى تفاعلات موضعية وحمى أكثر من لقاحات معينة مشابهة. إلا أن التفاعلات كانت بسيطة ومحدودة ذاتيا ولم يحمل هذا اللقاح خطراً زائداً لتفاعلات شديدة في موضع الحقن أو حدوث حمى مرتفعة. وقد أظهرت بعض الدراسات المعشاة التي أجريت على الأطفال، وليست جميعها، أن التفاعلات الموضعية والجهازية البسيطة المرافقة لهذا اللقاح قد تزيد بزيادة عدد الجرعات، وعلى الأقل إذا زادت على ثلاث جرعات في السلسلة الأولية. كما بينت الدراسات أن هذا اللقاح وغيره من لقاحات المكورات الرئوية الأخرى المقترنة هي لقاحات ذات قدرة تفاعل يمكن تحملها لدى الأمريكيين الأصليين، ولدى السكان المنحدرين من أصل أفريقي، ولدى المجموعات المعرضة لاحتمال خطر مرتفع، ويوصى بإعطائهم هذه اللقاحات . كما بينت اثنتان من أكبر تلك الدراسات، أجريت إحداهما على اللقاح السباعي التكافؤ المقترن للبروتين – عديد السكري للمكورات الرئوية (PCV7) والأخرى على اللقاح التساعي التكافؤ المقترن للبروتين عديد السكريد للمكورات الرئوية

(CPV9)، ارتفاع خطر الإدخال في المستشفى بشكل يعتد به إحصائياً بسبب أمراض تنفسية تفاعلية من بينها الربو. فيما لم يتبين من خلال دراسة أخرى على اللقاح التساعي التكافؤ المقترن للبروتين – عديد السكري للمكورات الرئوية CPV9 ازدياد خطر الإصابة بالربو. واستنتج الباحثون أن مراجعة البينات لم تسفر عن التعرف على أي مشكلات رئيسية تتعلق بالسلامة، لدى استخدام اللقاح السباعي التكافؤ المقترن للبروتين – عديد السكريد للمكورات الرئوية CPV7 أو أي لقاح مقترن غيره للمكورات الرئوية؛ مع احتمال استثناء الأمراض التنفسية التفاعلية والتي قد تحتاج لمزيد من التمحيص مع توافر المزيد من المعطيات.

References

1. *Pneumococcal vaccines accelerated development and introduction plan* (pneumoADIP). Available from: http://www.preventpneumo.org [accessed on 25 March 2008].
2. Global Advisory Committee on Vaccine Safety. 29-30 November 2006. *Wkly Epidemiol Rec* 2007;82:18-24. PMID:17236262
3. Clinical review of new product license application (PLA 92-0279), Prevnar seven valent pneumococcal conjugate vaccine. US Food and Drug Administration (FDA); February 2000. Available from: http://www.fda.gov/cber/products/prevnar.htm [accessed on 25 March 2008].
4. Clinical review of amendment to product license application (STN# 103905 10031). US Food and Drug Administration (FDA); June 2005. Available from: http://www.fda.gov/cber/review/pneuled100102r.pdf [accessed on 25 March 2008].
5. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, 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* 2000;19:187-95. PMID:10749457 doi:10.1097/00006454-200003000-00003
6. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al.; Finnish Otitis Media Study Group. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;344:403-9. PMID:11172176 doi:10.1056/NEJM200102083440602
7. Wise RP, Iskander J, Pratt RD, Campbell S, Ball R, Pless RP, et al. Postlicensure safety surveillance for 7-valent pneumococcal conjugate vaccine. *JAMA* 2004;292:1702-10. PMID:15479935 doi:10.1001/jama.292.14.1702
8. Addressing concerns regarding immunization and vaccines: questions, answers and issues. Division of Immunization, Laboratory Centre for Disease Control, Health Canada; 1996. Available from: http://www.hc-sc.gc.ca/hpb/lcdc/bid/di/mscn_6f.html [accessed on 25 March 2008].
9. Choo S, Seymour L, Morris R, Quataert S, Lockhart S, Cartwright K, et al. Immunogenicity and reactogenicity of a pneumococcal conjugate vaccine administered combined with a Haemophilus influenzae type B conjugate vaccine in United Kingdom infants. *Pediatr Infect Dis J* 2000;19:854-62. PMID:11001109 doi:10.1097/00006454-200009000-00009
10. Rennels MB, Edwards KM, Keyserling HL, Reisinger KS, Hogerman DA, Madore DV, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. *Pediatrics* 1998; 101:604-11. PMID:9521941 doi:10.1542/peds.101.4.604
11. Shinefield HR, Black S, Ray P, Chang I, Lewis N, Fireman B, et al. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. *Pediatr Infect Dis J* 1999;18:757-63. PMID:10493334 doi:10.1097/00006454-199909000-00004
12. Knuf M, Habermehl P, Cimino C, Petersen G, Schmitt HJ. Immunogenicity, reactogenicity and safety of a 7-valent pneumococcal conjugate vaccine (PCV7) concurrently administered with a DTPa-HBV-IPV/Hib combination vaccine in healthy infants. *Vaccine* 2006;24:4727-36. PMID:16616973 doi:10.1016/j.vaccine.2006.03.032
13. Scheifele DW, Halperin SA, Smith B, Ochnio J, Meloff K, Duarte-Monteiro D. Assessment of the compatibility of co-administered 7-valent pneumococcal conjugate, DTaP.IPV/PRP-T Hib and hepatitis B vaccines in infants 2-7 months of age. *Vaccine* 2006;24:2057-64. PMID:16356598 doi:10.1016/j.vaccine.2005.11.021
14. Schmitt HJ, Faber J, Lorenz I, Schmöle-Thoma B, Ahlers N. The safety, reactogenicity and immunogenicity of a 7-valent pneumococcal conjugate vaccine (7VPnC) concurrently administered with a combination DTaP-IPV-Hib vaccine. *Vaccine* 2003;21:3653-62. PMID:12922095 doi:10.1016/S0264-410X(03)00389-X
15. Tichmann-Schumann I, Soemantri P, Behre U, Disselhoff J, Mahler H, Maechler G, et al. Immunogenicity and reactogenicity of four doses of diphtheria-tetanus-three-component acellular pertussis-hepatitis B-inactivated polio virus-*Haemophilus influenzae* type b vaccine coadministered with 7-valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J* 2005;24:70-7. PMID:15665713 doi:10.1097/01.inf.0000148923.46453.48
16. Käyhty H, Ahman H, Eriksson K, Sörberg M, Nilsson L. Immunogenicity and tolerability of a heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 12 months of age. *Pediatr Infect Dis J* 2005;24:108-14. PMID:15702037 doi:10.1097/01.inf.0000151022.92222.be
17. Shao PL, Lu CY, Chang LY, Huang FY, Lee CY, Hsueh PR, et al. Safety and immunogenicity of heptavalent pneumococcal conjugate vaccine booster in Taiwanese toddlers. *J Formos Med Assoc* 2006;105:542-9. PMID:16877233
18. Shao PL, Lu CY, Chang LY, Huang FY, Wang CY, Yang CY, et al. Safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in Taiwanese infants. *J Formos Med Assoc* 2004;103:613-7. PMID:15340660
19. de Arístegui Fernández J, Cos Arregui B, Zurimendi Carril A, Alday Esteban MV, Alzua Ruiz J, De la Fuente Jausoro E, et al. Evaluation of the safety and immunogenicity of pneumococcal seven-valent conjugate vaccine (Prevenar) administered in previously unvaccinated Spanish children aged 24 to 36 months. *Vaccine* 2005;23:1917-22. PMID:15793941 doi:10.1016/j.vaccine.2004.10.024
20. Obaro SK, Adegbola RA, Chang I, Banya WA, Jaffar S, Mcadam KW, et al. Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM197 administered simultaneously but in a separate syringe with diphtheria, tetanus and pertussis vaccines in Gambian infants. *Pediatr Infect Dis J* 2000;19:463-9. PMID:10819345 doi:10.1097/00006454-200005000-00014
21. Capeding MZ, Puumalainen T, Gepanayao CP, Kayhty H, Lucero MG, Nohynek H. Safety and immunogenicity of three doses of an eleven-valent diphtheria toxoid and tetanus protein--conjugated pneumococcal vaccine in Filipino infants. *BMC Infect Dis* 2003;3:17. PMID:12908876 doi:10.1186/1471-2334-3-17
22. Nachman S, Kim S, King J, Abrams EJ, Margolis D, Petru A, et al.; Pediatric AIDS Clinical Trials Group Study 292 Team. Safety and immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants with human immunodeficiency virus type 1 infection. *Pediatrics* 2003;112:66-73. PMID:12837869 doi:10.1542/peds.112.1.66
23. O'Brien KL, Swift AJ, Winkelstein JA, Santosham M, Stover B, Luddy R, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle-cell disease. Pneumococcal Conjugate Vaccine Study Group. *Pediatrics* 2000;106:965-72. PMID:11061761 doi:10.1542/peds.106.5.965
24. Sigurdardottir ST, Ingolfsdottir G, Davidsdottir K, Gudnason T, Kjartansson S, Kristinsson KG, et al. Immune response to octavalent diphtheria- and tetanus-conjugated pneumococcal vaccines is serotype- and carrier-specific: the choice for a mixed carrier vaccine. *Pediatr Infect Dis J* 2002;21:548-54. PMID:12182380 doi:10.1097/00006454-200206000-00013
25. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. *J Pediatr* 1996;128:649-53. PMID:8627437 doi:10.1016/S0022-3476(96)80130-2
26. Blum MD, Dagan R, Mendelman PM, Pinsk V, Giordani M, Li S, et al. A comparison of multiple regimens of pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine and pneumococcal polysaccharide vaccine in toddlers. *Vaccine* 2000;18:2359-67. PMID:10738092 doi:10.1016/S0264-410X(00)00021-9

27. Nurkka A, Joensuu J, Henckaerts I, Peeters P, Poolman J, Kilpi T, et al. Immunogenicity and safety of the eleven valent pneumococcal polysaccharide-protein D conjugate vaccine in infants. *Pediatr Infect Dis J* 2004;23:1008-14. PMID:15545855 doi:10.1097/01.inf.0000143640.03214.18
28. O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski J, Brown L, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet* 2003;362:355-61. PMID:12907008 doi:10.1016/S0140-6736(03)14022-6
29. Black S, France EK, Center KJ, Hansen J, Lewis E, Graepel J, et al. Postmarketing assessment of uncommon events following Prevnar, 7-valent pneumococcal conjugate vaccine. *IDSA 44th annual meeting, October 2006, Toronto, Canada*.
30. Black S, France EK, Center KJ, Hansen J, Lewis E, Graepel J, et al. Kawasaki Disease (KD) following immunization: Case series from a large safety surveillance study of Prevnar, 7-valent pneumococcal conjugate vaccine. *IDSA 44th annual meeting, October 2006, Toronto, Canada*.
31. Dagan R, Melamed R, Zamir O, Leroy O. Safety and immunogenicity of tetravalent pneumococcal vaccines containing 6B, 14, 19F and 23F polysaccharides conjugated to either tetanus toxoid or diphtheria toxoid in young infants and their boosterability by native polysaccharide antigens. *Pediatr Infect Dis J* 1997;16:1053-9. PMID:9384339 doi:10.1097/00006454-199711000-00010
32. King JC Jr, Vink PE, Farley JJ, Smilie M, Parks M, Lichenstein R. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. *Pediatrics* 1997;99:575-80. PMID:9093301 doi:10.1542/peds.99.4.575
33. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999;180:1171-6. PMID:10479145 doi:10.1086/315009
34. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003;349:1341-8. PMID:14523142 doi:10.1056/NEJMoa035060
35. Obaro SK, Enwere GC, Deloria M, Jaffar S, Goldblatt D, Brainsby K, et al. Safety and immunogenicity of pneumococcal conjugate vaccine in combination with diphtheria, tetanus toxoid, pertussis and *Haemophilus influenzae* type b conjugate vaccine. *Pediatr Infect Dis J* 2002;21:940-7. PMID:12394817 doi:10.1097/00006454-200210000-00011
36. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005;365:1139-46. PMID:15794968 doi:10.1016/S0140-6736(05)71876-6
37. Buttery JP, Riddell A, McVernon J, Chantler T, Lane L, Bowen-Morris J, et al. Immunogenicity and safety of a combination pneumococcal-meningococcal vaccine in infants: a randomized controlled trial. *JAMA* 2005;293:1751-8. PMID:15827314 doi:10.1001/jama.293.14.1751
38. Dagan R, Kayhty H, Wuorimaa T, Yaich M, Bailleux F, Zamir O, et al. Tolerability and immunogenicity of an eleven valent mixed carrier *Streptococcus pneumoniae* capsular polysaccharide-diphtheria toxoid or tetanus protein conjugate vaccine in Finnish and Israeli infants. *Pediatr Infect Dis J* 2004;23:91-8. PMID:14872172 doi:10.1097/01.inf.0000109221.50972.53
39. Wuorimaa T, Käyhty H, Leroy O, Eskola J. Tolerability and immunogenicity of an 11-valent pneumococcal conjugate vaccine in adults. *Vaccine* 2001;19:1863-9. PMID:11228355 doi:10.1016/S0264-410X(00)00441-2
40. Wuorimaa T, Dagan R, Eskola J, Janco J, Ahman H, Leroy O, et al. Tolerability and immunogenicity of an eleven-valent pneumococcal conjugate vaccine in healthy toddlers. *Pediatr Infect Dis J* 2001;20:272-7. PMID:11303829 doi:10.1097/00006454-200103000-00011
41. Feikin DR, Elie CM, Goetz MB, Lennox JL, Carlone GM, Romero-Steiner S, et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. *Vaccine* 2001;20:545-53. PMID:11672921 doi:10.1016/S0264-410X(01)00347-4
42. Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. *J Infect Dis* 2003;187:1639-45. PMID:12721944 doi:10.1086/374784
43. Lin PL, Michaels MG, Green M, Mazariegos GV, Webber SA, Lawrence KS, et al. Safety and immunogenicity of the American Academy of Pediatrics-Recommended Sequential Pneumococcal Conjugate and Polysaccharide Vaccine Schedule in Pediatric Solid Organ Transplant Recipients. *Pediatrics* 2005;116:160-7
44. Shinefield H, Black S, Ray P, Fireman B, Schwalbe J, Lewis E. Efficacy, immunogenicity and safety of heptavalent pneumococcal conjugate vaccine in low birth weight and preterm infants. *Pediatr Infect Dis J* 2002;21:182-6. PMID:12005078 doi:10.1097/00006454-200203000-00003
45. Esposito S, Pugni L, Bosis S, Proto A, Cesati L, Bianchi C, et al. Immunogenicity, safety and tolerability of heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 11 months post-natally to pre- and full-term infants. *Vaccine* 2005;23:1703-8. PMID:15705475 doi:10.1016/j.vaccine.2004.09.029
46. Jackson LA, Neuzil KM, Whitney CG, Starkovich P, Dunstan M, Yu O, et al. Safety of varying dosages of 7-valent pneumococcal protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. *Vaccine* 2005;23:3697-703. PMID:15882530 doi:10.1016/j.vaccine.2005.02.017
47. Lucero MG. Effectiveness of an 11-valent pneumococcal conjugate vaccine for preventing radiographically confirmed pneumonia in children under 2 years of age: A randomized, double-blind, placebo-controlled trial in the Philippines. *12th International Society for Infectious Diseases, Lisbon, Portugal, June 2006*.
48. National, state, and urban area vaccination coverage among children aged 19-35 months – United States, 2005. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2006;55:988-93. PMID:16971887
49. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737-46. PMID:12724479 doi:10.1056/NEJMoa022823
50. Singleton RJ, Hennessy TW, Bulkow LR, Hammitt LL, Zulz T, Hurlburt DA, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *JAMA* 2007;297:1784-92. PMID:17456820 doi:10.1001/jama.297.16.1784
51. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. *Wkly Epidemiol Rec* 2007;82:93-104. PMID:17380597

Table 1. **Reactogenicity of any severity for PCV7 according to age at dose administration: randomized trials in healthy children under 2 years of age**

Reactogenicity	Age at dose administration (months)	Study								
		Black et al.[5]	Choo et al.[9]	Eskola et al.[6]	Knuf et al.[12]	Rennels et al.[10]	Scheifele et al.[13]	Schmitt et al.[14]	Shinefield et al.[11]	Tichmann-Schumann et al.[15]
PCV7 (*n*)	–	693	368	831	125	106	376	118	272	175
Comparison	–	Men C	No PCV	Hep B	Hexa	Other vaccines	No PCV	Other vaccines	DTP-Hib	Other vaccines
Redness (%)	2	10.0	–	14[a]	21.8	–	19.4	14.2 (3 months)	17.0	39.3
	4	11.6[a]	–	16	29.2	–	23.6	16.0	18.0[b]	42.4 (3 months)
	6	13.8[a]	–	20[a]	23.9	–	36.7	20.8 (5 months)	16.0	37.1 (4 months)
	12–15	10.9	–	15	32.1	–	–	31.9	9.1	51.4
Swelling (%)	2	9.8[a]	–	6[a]	24.4	–	27.0	6.6 (3 months)	10.0[b]	22.5[a]
	4	12	–	5	28.6	–	25.6	9.5	11.0[b]	29.1 (3 months)
	6	10.4[a]	–	5	21.3	–	27.7	0.8 (5 months)	9.0[b]	26.5 (4 months)
	12–15	12.1	–	6	36.9	–	–	9.9	6.4	37.0
Fever (%)	2	15.1[a]	2–4	14.3[a]	32.8	25	–	44.5 (3 months)	21.5	42.8[a]
	4	23.9[a]	2 (3 months)	18.4[a]	42.3	28	–	33.0	33.5	49.4[a] (3 months)
	6	19.1[a]	1–6 (4 months)	23.5[a]	28.3	38	–	29.0 (5 months)	29.6	33.5[a] (4 months)
	12–15	21	–	11.5[a]	50.0	22	–	48.2	11.0	48.6

DTP-Hib, diphtheria, pertussis, tetanus, and *Haemophilus influenzae* type b; Hep B, hepatitis B; Hexa, INFANRIX® hexa; Men C, meningitis C; PCV7, 7-valent pneumococcal polysaccharide-protein conjugate vaccine.

[a] Significantly ($P < 0.05$) higher with PCV7 than comparison vaccination.

[b] Significantly ($P < 0.05$) lower with PCV7 than comparison vaccination.