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Heptavalent Pneumococcal Conjugate Vaccine (PCV7): French Survey of Serious Adverse Reactions

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Abstract – Purpose. Previous study did not reveal any particular heptavalent pneumococcal conjugate vaccine (PCV7) related risk. However, french drugs agency (Afssaps) requested the continuation of its surveillance. **Methods.** All serious PCV7-related adverse drug reactions spontaneously reported between October 1, 2004 and December 31, 2007 to the French pharmacovigilance centers or to Wyeth Pharmaceutical France were included. Vaccine failure was defined as an invasive pneumococcal infection due to vaccine serotype which occurs at least 15 days after the third dose of vaccine. Incidence rates were estimated according to the doses number except for vaccine failure estimated according to the vaccinated children number. **Results.** During the 39-month follow-up period, 154 serious adverse drug reactions were spontaneously reported: convulsions (17%), fever (13%), hypotonia (10%), sudden death (7%) and thrombopenic purpura (6%). Evolution was recovery in 72% of cases. PCV7 was the only suspect medication in 28% of cases. The median age was 4 months (range 1-108), and the children's sex was male in 53%. The adverse drug reaction recurred after a subsequent injection in six cases. Among the 24 pneumococcal infections PCV7 failure was certain in 4 cases. The incidences of serious adverse drug reactions did not differ from our previous survey, except the incidence of thrombopenic purpura and of PCV7 failure which seems to be increasing. **Conclusions.** This new study confirms the risk of vascular purpura, raises the thrombopenic purpura issue, and the emergence of PCV7 failures which will need a strict monitoring of the future 13 valences vaccine.

Mots clés :
vaccin conjugué heptavalent contre le pneumocoque ; PCV7 ; effets indésirables médicamenteux ; enfant ; infection à pneumocoque

Résumé – Vaccin heptavalent conjugué contre le pneumocoque (PCV7) : surveillance française des effets indésirables graves. Introduction. Deux études n'ont pas mis en évidence un risque particulier associé au vaccin conjugué heptavalent contre le pneumocoque (PCV7). Cependant, la poursuite de la surveillance des effets graves a été souhaitée par l'Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps). **Matériel et méthode.** Tous les effets indésirables (EI) graves associés au PCV7 notifiés entre le 1er octobre 2004 et le 31 décembre 2007 aux Centres régionaux de Pharmacovigilance ou à Wyeth Pharmaceutical France ont été inclus. Un échec vaccinal était défini par une infection due à un sérotype vaccinal et survenant au moins 15 jours après la troisième dose de PCV7. Les taux d'incidence ont été calculés en fonction du nombre de doses vendues sauf pour les échecs rapportés au nombre d'enfants vaccinés. **Résultats.** Durant les 39 mois de suivi, 154 EI graves ont été notifiés : convulsions (17 %), fièvre (13 %), hypotonie (10 %), mort subite (7 %) et purpura thrombopénique (6 %). L'évolution a été une guérison dans 72 % des cas. Le PCV7 était le seul médicament suspect dans 28 % des cas. L'âge médian était de 4 mois (extrêmes 1-108), et le sexe était masculin dans 53 % des cas. L'EI a récidivé lors d'une injection suivante dans six cas. Parmi les 24 infections à pneumocoque, un échec du PCV7 est certain dans 4 cas. Les incidences des EI graves sont proches de celles estimées lors de notre étude précédente, excepté celle du purpura thrombopénique et des échecs du PCV7 qui ont tendance à augmenter. **Conclusion.** Cette nouvelle étude confirme le risque de purpura vasculaire, pose le problème d'un risque de purpura thrombopénique et soulève la question de l'émergence d'échecs du PCV7 qui nécessitera une surveillance particulière du futur vaccin conjugué à 13 valences contre le pneumocoque.

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1. Introduction

The heptavalent pneumococcal conjugate vaccine (PCV7), marketed in France since April 2001, is indicated for active immunization against infections (including invasive infections defined by a positive culture for *S. pneumonia* from the blood, pleural fluid or cerebrospinal fluid, but also pneumonitis and otitis media) caused by *Streptococcus pneumonia* due to the serotypes contained in the vaccine (4, 6B, 9V, 14, 19F, 23F and 18C). PCV7 is recommended by the "Haut Conseil de la Santé Publique" for all children under 2 years of age and for patients between 2 and 5 years at increased risk of pneumococcal disease.[1]

The vaccine has proven effective in reducing invasive infections due to serotypes contained in the vaccine,[2–5] and to a lesser extent reducing acute otitis media.[6–8] In France,[9] in all ages between the pre (2001/2002) and post vaccine periods (2007) the incidence of invasive pneumococcal infections (IPI) whatever the serotype increased (9.4% *versus* 10.2% per 100,000 *i.e.* +8%) particularly the bacteraemia. In children between 0 to 23 months, the incidence of IPI decreased (meningitis 8% *versus* 6% per 100,000 *i.e.* -26% and bacteraemia 22% *versus* 15% per 100,000 *i.e.* -32%). In this class of age there is a great reduction of IPI due to serotypes contained in the vaccine (meningitis -78% and bacteraemia -85%), but also a clear increase of IPI due to serotypes not contained in the vaccine (meningitis +95% and bacteraemia +82%).

Soon after commercialization of the vaccine in France, our working group conducted, on french drugs agency's (Afssaps or "Agence Française de Sécurité Sanitaire des Produits de Santé") request, a prospective study about tolerance of PCV7. Although this study concluded that the vaccine's safety profile did not differ from what was expected,[10] the French Pharmacovigilance Commission stated on November 29, 2005 that, surveillance of serious adverse drug reactions should be continued by the same team (Clinical Pharmacology Department/Regional Pharmacovigilance Center of Tours).

2. Material and method

All serious adverse drug reactions (ADRs) associated with PCV7, spontaneously reported in France between October 1, 2004 (the end of the preceding study) and December 31, 2007 to the 31 French Regional Pharmacovigilance Centers (RPVC) or to the manufacturer (Wyeth Pharmaceuticals France) were included. Serious ADRs were defined as "having required hospitalization, the prolongation of existing hospitalization, resulted in disability or death, or been life-threatening". Duplicate notifications to both the RPVC and the manufacturer were discarded. Each notification underwent semiological analysis by one of us (EAL) in order to attribute a principal diagnosis, signs associated with the ADR, or other potential ADRs. When several ADRs were observed in the same child, they were classified exclusively in a hierarchical order based on the severity of ADR. When several symptoms could be linked to the same ADR, the most pertinent and/or serious effect was considered, and others were deemed associated signs. For instance, when "apnoea, faintness, and hypotonia" were reported, apnoea was considered the principal diagnosis, while faintness and hypotonia were considered associated signs. Similarly, when "loss of consciousness, hypotonia, and pallor" were reported, loss of consciousness was considered the principal diagnosis, while hypotonia and pallor were considered associated signs. For each principal ADR, the characteristics of the child (age, sex), the vaccine (injection order), the ADR (delay of onset from time of vaccine injection, outcome), and the medications given concomitantly to PCV7, particularly other vaccines, were collected. Pneumococcal infections (including invasive infections, but also pneumonitis, otitis media and arthritis) due to vaccine serotypes or to unspecified serotype were separately analyzed. We considered as a vaccine failure (ADR) infections due to vaccine serotype which occurs at least 15 days after the third dose of vaccine. All principal ADRs were analyzed according to the French imputability method.[11] The incidence rates of notifications were estimated using PCV7 sales figures provided by the manufacturer considering every vaccine sold as an administered vaccine.

3. Results

During the 39-month follow-up period, 157 serious ADRs were spontaneously reported to the manufacturer (151) or to the RPVCs (73). Three were excluded from analysis because the diagnosis indicated that the vaccine was not likely involved [osteoma (1), congenital fibrosarcoma (1), muscular cancer (1)]. Among the remaining 154 ADRs, the most frequent were: convulsions 27 cases (17%), fever 20 cases (13%), hypotonia 16 cases (10%), sudden death 11 cases (7%) and thrombopenic purpura 10 cases (6%) [table I and table II]. Evolution was recovery (72%), unknown (15.8%), deaths (7.9% *i.e.* n=12 including the 11 sudden death) or consequences (4.6%). PCV7 was the only suspect medication in 44 cases (28%). It was associated with another vaccine in 99 cases [Pentavac® (41), Infanrixtetra® (23), Infanrixquinta® (23), other (12)], and with another drug in 21 cases [(paracetamol (7), lidocain/prilocain-gel (5), domperidone (4), other (5)]. The children's median age was 4 months (range 1-108), and was unspecified in four cases. The children's sex was male in 53.2%, female in 44.8%, and unspecified in 1.9%. The ADR occurred after the first (30.5%), the second (28.6%), the third (11%), or the fourth (3.9%) vaccine injection. The PCV7 injection order was

Table I. Incidence of serious PCV7-related adverse drug reactions (excluding pneumococcal infections) notified in France between October 1, 2004 and December 31, 2007 (39 months).

Unwanted event	Number (%)	Incidence/100,000 doses [CI 95%]
Seizures	**27 (17%)**	0.34 [0.24-0.46]
- Febrile	13	
- Apyretic	8	
- Unspecified	6	
Fever	**20 (13%)**	0.25 [0.16–0.37]
- ≥39 °C	16	
- ≥38<39 °C	1	
- Unspecified	3	
Hypotonia	**16 (10%)**	0.20 [0.12–0.31]
Sudden death	**11 (7%)**	0.14 [0.07–0.24]
Thrombocytopenic purpura	**10 (6%)**	0.13 [0.06–0.22]
Cutaneous	**9 (5.8%)**	0.11 [0.05–0.20]
- Urticaria	7	
- Other	2	
Vascular purpura	**6 (3.8%)**	0.07 [0.02–0.15]
Apnea	**5 (3.2%)**	0.06 [0.02–0.14]
Kawasaki disease	**4 (2.5%)**	0.05 [0.01–0.12]
Loss of consciousness	**3 (0.9%)**	0.03 [0.007–0.10]
Faintness	**3 (0.9%)**	0.03 [0.007–0.10]
Abnormal cries	**1 (0.06%)**	0.013 [0.0003–0.07]
Other	**39 (25%)**	
Total	**154**	

unspecified in 38 cases (24.7%). In six children the ADR recurred after a subsequent injection (number of vaccine re-administrations unknown): apnoea (1), febrile convulsions (1), fever (2), bronchiolitis (1) and localized edema (1).

Febrile convulsions occurred when the fever was between 38 °C and 38.9 °C (5 cases), between 39 °C and 39.9 °C (4 cases), superior to 40 °C (1 case) and unspecified (3 cases). Apyretic convulsions accompanied West syndrome in three of eight cases and partial epileptic seizures in one case. In the three children with West syndrome, the seizures persisted. Thrombopenic purpuras were most frequently associated with cutaneous and mucosal hemorrhages, and in one case with a cerebral hemorrhage. Platelets were between 1000 and 32 000/mm3 (mean 8 500/mm^3). A fever accompanied one case of vascular purpura (40 °C) and one case of loss of consciousness (39 °C).

The twenty four infections (table III) *i.e.* meningitis (14), pneumopathy (8), bacteraemia (1) and arthritis (1) were due to PCV7's vaccine serotype in five cases and to unspecified serotype in nineteen cases. Among the five infections due to PCV7 vaccine serotype, four occurred after a complete vaccination (two cases of meningitis, serotype 4 and 19F, one case of pneumopathy, serotype 18C, and one case of arthritis, serotype 19F) and are "certain" PCV7 failures. Among the nineteen infections due to an unspecified serotype, ten occurred after a complete vaccination and a vaccine failure cannot be excluded ("possible" PCV7 failures).

4. Incidence of unwanted events

The incidence of serious ADRs associated with PCV7 reported in France during the 39-month period between October 1, 2004 and December 31, 2007, as estimated using PCV7 sales figures during this period (7,836,151 doses), is listed in table I. If we assumed 4 doses per child (n=1 959 037 vaccinated children) the incidence of certain vaccine failure (n=4) is 0.2 per 100 000 vaccinated children [0.05-0.5] and the incidence of possible failure (n=10) is 0.5 per 100 000 [0.2-0.9].

5. Discussion

Our study was not designed to be exhaustive, but simply to detect by the spontaneous notification method any potential,

Table II. Characteristics of main serious PCV7-related adverse drug reactions (excluding pneumococcal infections) notified in France between October 1, 2004 and December 31, 3007 (39 months).

Adverse drug reaction	N	Injection order	Gender M/F	Median age [range]	Associated vaccine	Time to occurrence	Evolution
Febrile seizures	13	R1=5 R2=3 R3=1 R4=1 NP=3	5/8	16 months [1-36]	Infanrix®=3 Infanrix Quinta®=1 Pentavac®= 2 Priorix®= 2	<24 H=5 1-3 D=5 4-5 D=2 15 D=1	Recovery=13
Apyretic seizures	8	R1=3 R2=2 R4=1 NP=2	5/3	6.5 months [2-19]	Pentavac®= 3 Infanrix Quinta®= 4 US=1	<24 H=3 2-11 D=5	Recovery=5 Persistence=3
Hypotonia	16	R1=9 R2=4 NP=3	5/16	5.6 months [2-30]	Infanrix Quinta®=3 Pentavac®=5 Infanrix®=5	A few minutes- a few hours	Recovery=14 Persistence=1 US=1
Sudden death	11	R1=3 R2=2 R3=1 R4=1 NP=4	6/4 US =1	4 months [2-7]	Infanrix Quinta®=2 Pentavac®=5 Rotarix®/Infantrix Quinta® =1 US=3	Median=2 D [4 H–4 D] US=1	
Thrombocytopenic purpura	10	R1=1 R2=4 R3=2 R4=2 NP=1	4/10	19.25 months [3 months - 9 years]	Infanrix ®=2 Pentavac®=2 MMR=1	6 D [1-20]	Recovery=10
Vascular purpura	6	R2=2 R3=3 NP=1	4/2	7.2 months [4–15]	Infanrix Quinta®=1 Pentavac®=1 Infanrix®=1	1 D=2 12 D=1 US=1	Recovery=4 US=2
Apnea	5	R1=1 R2=2 NP=2	3/2	3 months [2–7]	Infanrix®=2 Infanrix Quinta®=2	<1 D=3 ≥1-≤2 D=2	Recovery=4 US=1
Kawasaki disease	4	R1=1 R2=3	3/1	11 months [4 – 21]	Pentavac®=2	Median 16.5 D [3–60 D]	Recovery=1 Coronary sequelae=2 US=1
Loss of consciousness	3	R1=1 R2=1 R3=1	2/1	3 months [2 – 5]	Infanrix Quinta®=2 Pentavac®=1	1 H=1 >1 H-<4 H=2	Recovery=1

D: day; **F**: female; **H**: hour; **M**: male; **N**: number; **R**: injection order; **US**: unspecified

Table III. Pneumococcal infections due to vaccine serotype or unspecified serotype notified in France between October 1, 2004 and December 31, 2007 (39 months).

	Included in PCV7	Unspecified	Total
	N	N	N
Meningitis	3	11	14
Pneumopathy	1	7	8
Bacteremia	0	1	1
Arthritis	1	0	1
Total	5 (21%)	19 (79%)	24

N: number

serious, ADR not previously identified. Owing to differences in methodology, the ADRs of our work cannot be compared with those reported in clinical trials or meta-analyses. However, our study results may be compared to those of a preceding research work using the same methodology, which dealt with 153 spontaneous, serious, or unexpected ADRs that were reported during a 42-month observation period.[10] This comparison is primarily based upon the incidences of reported ADRs, which takes into account the increase in the number of vaccinated children as evinced by the number of vaccine doses sold, which increased from 2 172 646 during a period of 42 months to 7 836 151 during a period of 39 months (table IV).

The incidence of certain serious ADRs (sudden death, Kawasaki disease, vascular purpura) is very similar in the two surveys. Taking into account the incidence of sudden infant death in France, which was estimated in 2005 at 32 for 100 000 children aged less than one year,[12] the expected number of sudden death cases during the week following the administration of 7 836 151 vaccine doses in France can be estimated at 48 cases. The 11 cases reported is inferior to the expected number, even taking into account a potential under-notification which, given the seriousness of the event, is probably low. The case of Kawasaki disease, reported in our previous survey, was not regarded as an alarming signal and the present data hold the same to be true. Taking into account the incidence of Kawasaki disease (1.5 cases for 100 000 children in Great Britain, unknown in France), the number of cases expected during the 2 months following the administration of 7 836 151 vaccine doses in France can be estimated at 20. The reported number (n=4) is inferior to the expected number, but the significance of the under-notification is not known. In the Kaiser database, the relative risk of Kawasaki disease is 2.2 [0.16-3.63] in 65 927 PCV7–vaccinated children, as compared to the 40 233 non-vaccinated control cases. However, after adjusting for potential confounding factors, only the Asian race is independently associated with Kawasaki disease.[13] The incidence of vascular purpura is stable. This ADR was also reported in the United States in the PCV7 post-marketing data,[14] which showed seven cases of vascularitis to be associated with PCV7 alone. The inclusion of this ADR in the SPC, which was proposed by the French Commission of Pharmacovigilance in 2005, was not yet accepted by the European working group. The incidence of thrombopenic purpuras, although still low, appears to be in progression as compared to the preceding study, increasing from 0.05 [0.001-0.26] to 0.13 [0.06-0.22] per 100 000 vaccinated children. This probably constitutes a signal, as PCV7 was associated with the ROR Vax® (which is known to be associated with thrombopenic purpura) in only one case, and the median delay of onset following the PCV7 injection (6 days) is compatible with the role of the vaccine. We reported four certain PCV7 failures. PCV7 failures was absent from our preceding survey but 4 were observed in a French study among 709 pneumococcal meningitis between 2001 and 2006.[15] We did not observe any PCV7-related respiratory disease, but a systematic review of 42 studies including safety evaluations of anti-pneumococcal vaccines revealed an increased risk for respiratory disease, such as bronchial asthma.[16] Based on the American Kaiser (Northern California Permanente) database, in 65 927 PCV7-vaccinated children compared to 35 549 non-vaccinated controls, there was no increased risk for diseases that may lead to hospitalization apart from a slightly increased risk (RR 1,23) for respiratory diseases, which remained significant after adjusting for confounding factors.[17] Because it was based upon spontaneous reporting our study has two main limitations. First its methodology do not allowed evaluating the emerging IPI by pneumococcal strains not included in the PCV7 vaccine, such as the 19A serotype. This risk identified in the United States[18–22] and in France between the pre and post vaccination periods[9] explains the need for the manufacturer to develop a 13 valences vaccine. The second limitation is the lack of data on children who received an other PCV7 dose after a serious ADR associated with a previous injection. Consequently, the pertinence of potential recommendations given by the manufacturer or the RPVC regarding re-administration cannot be properly analyzed. Recurrence of the ADR was observed in six cases, but the number of re-administrations is not known. This issue deserves further attention during the notification process, as this information would allow a better understanding of the causal relationship and to give recommendations based on strong evidences.

6. Conclusion

This new study did not detect any new serious PCV7- ADR. The study results raise the thrombopenic purpura issue, which requires further surveillance. Furthermore, it confirms the risk of vascular purpura, which should be mentioned in the SPC. It also raises the question of the PCV7 failure observed in four cases.

Table IV. Incidences of PCV7-related serious adverse drug reaction in France during two pharmacovigilance surveys.

	Incidence/100,000 vaccinations	
Period	First study	Present study
	April 2001 - September 2004	October 2004 – December 2007
Duration	42 months	39 months
Sales	2 172 646 doses	7 836 151 doses
- Sudden death	0.09 [0.0-0.3]	0.14 [0.07-0.24]
- Seizures	0.5 [0.3-1]	0.34 [0.24-0.46]
- Thrombocytopenic purpura	0.05 [0.001-0.26]	0.13 [0.06-0.22]
- Abnormal cries	0 [0-0.1]	0.01 [0-0.07]
- Kawasaki disease	0.05 [0.001-0.26]	0.05 [0.01-0.13]
- Vascular purpura	0.092 [0.011-0.29]	0.07 [0.02 – 0.15]
- Certain PCV7 failure	0 [0-0.1]	0.2 [0.05-0.5] /100,000 vaccinated children

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