PRZEGL EPIDEMIOL 2008; 62: 589 - 596

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COMPARISON OF ADVERSE EFFECTS FOLLOWING IMMUNIZATION WITH VACCINE CONTAINING WHOLE-CELL VS. ACELLULAR PERTUSSIS COMPONENTS

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The article presents comparative study of the incidence of adverse effects following vaccinations with whole cell and acellular pertussis vaccines, based on data collected in obligatory routine surveillance of AEFI in the period of 2001-2005 in Poland. Comparisons done in children less then 2 years old show in general about twice as high incidence of adverse effects following the whole-cell than the acellular vaccine. The biggest rate of proportions (RR=4,75) was observed for high pitch cry. There was no significant difference in incidence of the most severe reactions, including encephalopathy and nonfebrile seizures, and there was no significant difference in allergic reactions.

Słowa kluczowe: krztusiec, szczepienie,niepożądane odczyny poszczepienne, komponent pełnokomórkowy,komponent acelularny
Key words: pertussis, vaccination, adverse effect, whole cell, acellular

INTRODUCTION

Obligatory system of reporting adverse effects following immunization (AEFI) was introduced in Poland in 1996 (1,2). Analysis in this study is based on the data collected through the system. Frequency of AEFI reported during the period of 2001-2005 in children less then 2 years old, who received vaccines containing whole cell pertussis component, was compared with that of children who received acellular vaccines. Adverse effects following acellular vaccine were also compared between two different age groups: less then 2 years (first 4 doses) and at the age of 5 (fifth dose).

Vaccination program in Poland includes obligatory DTP (diphtheria, pertussis, tetanus) vaccination with first dose in the 6-8 week, second in the 3-4 month, third at the age of 5 months, with recommended 6 week periods between doses. Fourth dose is given in 16-18 month, and the fifth at the age of 5 years. Together with the first dose of DTP, the second dose of hepatitis B vaccine is given obligatorily. Second, third, and fourth doses of DTP are

accompanied by inactivated polio vaccine, and the fifth dose, at the age of five years, is given alongside the oral polio vaccine. Vaccinations against *Haemophilus influenzae* type b (Hib), which may have also accompanied DTP vaccination in 2001-2005, were given to a limited number of children, mostly at parent request and expense. Total number of children vaccinated against Hib in birth cohort 2001-2005 was 473408 out of 1793556 live births (26.4%).

Numerous publications provide comparative information on AEFI with whole cell and acellular pertussis vaccines (3-7). In most cases assessment of safety of those vaccines is based on samples analyzed in controlled clinical trials. Such a comparison provides reliable information about the most frequent effects, but may fail with effects which are rare.

Poland is a country of high vaccination coverage (>95%) for vaccines containing pertussis component. DTPw vaccine with the whole cell pertussis component is currently the most frequently used vaccination, but over last several years, increasing number of vaccine preparations combined with acellular pertussis component (DTPa) has been used at parental request and expense. Until 2002 four-dose schedule of vaccinations against pertussis was used. In 2003 obligatory fifth dose of DTPa was introduced for children at the age of 5.

The authors believe that population based comparisons of AEFI related to two different types of vaccines and to different ages at vaccination within this same population in the overlapping observation period provide new data not completely covered by existing studies based on another populations and reporting systems or performing analysis for whole cell and acellular vaccines in different observation periods (8,9).

MATERIAL AND METHODS

The data set for the study was obtained from routine, passive reporting of AEFI during the period of 2001-2005. Those reports provide information on the age of child, type of pertussis vaccine, the sequential number of the dose, information about all the other vaccines given simultaneously, and types of adverse effects in categories presented in the Table 1.

Comparative study of incidence frequency was done on selected, most common types of adverse effects. For comparison purposes three categories were selected, according to age and type of pertussis component: First, children below the age of 2 who received whole cell component; second, children below the age of 2 who received acellular component; and third, children at the age of 5 who received acellular component. Incidence of adverse effects was calculated as a fractions of the estimated numbers of doses given. Comparison of relative incidence frequency of different adverse effects between categories was done with the normal approximation test for binomial proportions, and if the proportions were not suited for this test, the Fisher exact test was used. For all the proportions, the relative risk (RR), p value and 95% CI (confidence interval) of RR were also calculated. All statistical calculations were done with the statistical analysis system SAS.

For acellular pertussis vaccines in children below the age of 2, the numbers of vaccinations were obtained from the numbers of sold doses of vaccines at the time of the study. For the whole cell vaccines, the numbers of doses given were obtained from obligatory reports of vaccination coverage minus the numbers of acellular doses obtained from sales data as mentioned above. The number of vaccinations of children at the age of 5 came directly from vaccination coverage reports, since at this age only acellular pertussis vaccine is permitted

Table I. Adverse effects following vaccinations with whole cell and acellular pertussis vaccines reported in Poland in 2001 - 2005

Tabela I. Niepożądane odczyny poszczepienne po szczepieniach szczepionkami pełnokomórkowymi i bezkomórkowymi zgłoszone w Polsce w latach 2001-2005

AEFI	Whole cell, age < 2		Acellular age < 2		Acellular age 5	
	Number	%	Number	%	Number	%
Local effects: total	329	36,8	58	53,2	113	96,6
Diameter >10 cm	123	13,8	42	38,5	76	65,0
Extended over joint	66	7,4	8	7,3	30	25,6
Bacterial abscess	2	0,2	-	-	-	-
Sterile abscess	43	4,8	1	0,9	1	0,9
Enlarged lymph nodes	32	3,6	4	3,7	16	13,7
Systemic effects: total	773	86,5	75	68,8	43	36,8
Fever: total	454	50,8	40	36,7	35	29,9
Including fever >39o C	222	24,8	19	17,4	4	3,4
Seizures: total	108	12,1	6	5,5	1	0,9
including						
first episode of febrile seizures	35	3,9	1	0,9	-	-
first episode of afebrile seizures	37	4,1	3	2,8	1	0,9
Allergic response: total	99	11,1	18	16,5	12	10,3
including: urticaria	90	10,1	16	14,7	12	10,3
Quincke's edema	8	0,9	1	0,9	1	0,9
laryngospasm	2	0,2	1	0,9	-	-
asthmatic reaction	1	0,1	1	0,9	-	-
lacrimation/running nose	6	0,7	-	-	-	-
serum sickness	-	-	-	-	-	-
Anaphylactic shock	1	0,1	-	-	-	-
Hyporeactive hypotonic episode: total	193	21,6	17	15,6	3	2,6
including						
with loss of consciousness or apnea	34	3,8	4	3,7	-	-
Persistent crying	326	36,5	13	11,9	-	-
Arthralgia	-	-	-	-	-	-
Guillain-Barre syndrom	-	-	-	-	-	-
Meningitis	2	0,2	-	-	-	-
Acute encephalopathy	11	1,2	2	1,8	-	-
Encephalitis	2	0,2	-	-	-	-
Brachial palsy	14	1,6	1	0,9	-	-
Sepsis	1	0,1	1	0,9	-	-
Thrombocytopenia	1	0,1	1	0,9	-	-

in Poland. The AEFI were classified as serious if they involved death, a life threatening illness, or permanent disability. Hospitalization was not identified as serious because of the generally low threshold for hospitalization of children with AEFI in Poland.

Whole cell pertussis preparation used in Poland has been produced by Biomed SA, Kraków. Children who were vaccinated with acellular vaccines could obtain preparation of any of the following brands Infanrix, Tripacel, Pentaxin. Adverse effects were not attributed in the analysis to the brand name of the vaccine.

RESULTS

Table I presents an overview of the numbers of adverse effects in each reported category, following vaccinations in children who received either acellular or whole cell pertussis component. The most frequent local adverse effect was inflammatory reaction, swelling and redness at injection site. Among systemic reactions the most frequent in children less then 2 years old was fever, then unusual high-pitched cry and hypotensive hyporeactive episode

Table II. Frequency of AEFI following vaccinations against pertussis with whole cell and accellular vaccines in children > 2 years old in 2001 - 2005

Tabela II. Względna częstość występowania niepożądanych odczynów poszczepiennych po szczepionkach pełnokomórkowych i bezkomórkowych u dzieci w wieku poniżej 2 lat w latach 2001-2005

AEFI	Vaccine preparations whole cell					
	Whole cell dose 1 - 4	Frequency	Acellular dose 1-4	Frequency	p value	RR Whole cell/ Acelluar (95% Cl)
Number of vaccine doses	7 037 929		1 334 143			
Local effects: total	329	4,7 · 10-5	58	4,3 · 10-5	0,610	1,08 (0,81-1,42)
Systemic effects: total	773	1,1 · 10-4	75	5,6 · 10-5	<0,0001	1,95 (1,54-2,48)
Fever: total	454	6,5 · 10-5	40	3,0 · 10-5	<0,0001	2,15 (1,56-2,97)
Including fever >39^{o} C	222	3,2 · 10-5	19	1,4 · 10-5	0,001	2,22 (1,39-3,54)
Seizures: total	108	1,5 · 10-5	6	4,5 · 10-6	0,002	3,41 (1,50-7,76)
first episode of afebrile seizures	37	5,3 · 10-6	3	2,2 · 10-6	0,1935 (Fisher)	2,33 (0,72-7,58)
Allergic response: total	99	1,4 · 10-5	18	1,3 · 10-5	0,871	1,04 (0,63-1,72)
Hyporeactive hypotonic episode: total	193	2,7 · 10-5	17	1,3 · 10-5	0,002	2,15 (1,31-3,53)
with loss of consciousness or apnea	34	4,8 · 10-6	4	3,0 · 10-6	0,360	1,61 (0,57-4,54)
Persistent crying	326	4,6 · 10-5	13	9,7 · 10-6	<0,0001	4,75 (2,73-8,28)
Acute encephalopathy	11	1,6 · 10-6	2	1,5 · 10-6	0,9561 (Fisher)	1,04 (0,23-4,70)

(HHE). Also quite frequent were allergic reactions. Estimated reference numbers of DTP vaccine doses for each study group were as follows: 7 037 929 doses of DTPw given to children below the age of 2 years, 1 334 143 doses of DTPa given to children below age of 2 years, and 1 119 997doses of DTPa given to children at the age of 5 years.

Table II and III present comparisons of relative incidence frequencies (proportions) of the selected AEFIs. Table II compares adverse effects following vaccinations with vaccines containing whole cell vs. acellular pertussis component in children below the age of 2 years. Table III contains comparison of adverse effects following acellular pertussis vaccines in children less than 2 years old and in children 5 years old.

Table III. Frequency of AEFI following vaccinations against pertussis with accellular vaccines in different age groups in 2001 - 2005

Tabela III. Względna częstość występowania niepożądanych odczynów poszczepiennych po szczepionkach bezkomórkowych u dzieci w różnych grupach wieku w latach 2001-2005

AEFI	Acellular vaccines preparations					
	dose 1 - 4	Frequency	dose 5	Frequency	p value	RR dose 5/dose 1-4 (95% Cl)
Number of vaccine doses	1 334 143		1 119 997			
Local effects: total	58	4,3 · 10-5	113	1,0 · 10-4	<0,0001	2,32 (1,69-3,19)
Systemic effects: total	75	5,6 · 10-5	43	3,8 · 10-5	0,045	0,68 (0,47-0,99)
Fever: total	40	3,0 · 10-5	35	3,1 · 10-5	0,858	1,04 (0,66-1,64)
Including fever >39° C	19	1,4 · 10-5	4	3,6 · 10-6	0,007	0,25 (0,09-0,74)
Seizures: total	6	4,5 · 10-6	1	8,9 · 10-7	0,1350 (Fisher)	0,19 (0,02-1,65)
Allergic response: total	18	1,3 · 10-5	12	1,1 · 10-5	0,535	0,79 (0,38-1,65)
Hyporeactive hypotonic episode: total	17	1,3 · 10-5	3	2,7 · 10-6	0,006	0,21 (0,06-0,71)
with loss of consciousness or apnea	4	3,0 · 10-6	-	-	0,1307 (Fisher)	-
Persistent crying	13	9,7 · 10-6	-	-	<0,0001 (Fisher)	-
Acute encephalopathy	2	1,5 · 10-6	-	-	0,5038 (Fisher)	-

When acellular and whole cell pertussis components were compared in children below the age of 2, there was no statistically significant difference between proportions of local adverse effects. Statistically significant differences were observed between proportions of systemic adverse effects which occurred about twice as frequently among receivers of whole cell than acellular vaccine. None of the reactions was more frequent in children receiving acellular then whole cell pertussis vaccine. The highest rate of proportions (RR=4.75) was related to

high pitch cry. Febrile reactions were more than twice as frequent among children receiving whole cell vaccine. When both febrile and afebrile cases were counted, seizures were more then 3 times as frequent among children receiving DTPw, but if only first episodes of afebrile seizures were counted, rate of proportions was insignificant. Insignificant rates of proportions were also observed regarding total allergic reactions, acute encephalopathy and the most severe cases of HHE, marked by apnea or loss of consciousness. But the rate of proportions of all cases of HHE was 2.15, signaling higher frequency among DTPw receivers.

Comparison of selected adverse effects following acellular vaccines in children less then 2 years old and 5 years old is presented in table III. Local adverse effects were more frequent in children 5 years old and the rate of proportions was highly significant.

Rate of proportion regarding combined numbers of systemic effects was of low significance with 1,47 times higher occurrence among younger children. In children less then 2 years old significantly more frequent were also: high fever $>39^0$C and HHE. Some adverse effects, like severe HHE, high pitch cry and acute encephalopathy were not observed in 5 year old children.

DISCUSSION

The data presented here confirm general knowledge of higher incidence of systemic adverse effects after whole cell pertussis preparations than acellular ones. In most cases rate of proportions was close to 2 or slightly higher. The higher rate of seizures could be attributed mostly to higher rate of high fever after whole cell preparations since rate of proportions of first episodes of afebrile seizures was not significant.

Acute encephalopathy occurred very rarely in either group. It was reported only in two cases following acellular vaccine and in 11 after whole cell preparation. Rate of proportions was not significant. Encephalopathy is frequently brought as argument against vaccination by antivaccination movements. Although it follows injections with pertussis vaccines it is so rarely reported, that its occurrence seems to require some other special predisposing factors, which should be carefully investigated in all cases of reported post-vaccination encephalopathy (10-12).

Lack of significance in rates of allergic reactions appears surprising because the load of potential bacterial antigens in whole cell vaccine preparations is so much higher than in acellular ones. In general, the incidence of allergic reactions was low in both groups. It doesn't support the view that bacterial proteins are the main source of allergens in vaccine preparations.

The striking difference between both types of vaccine was in the incidence of high pitch cry, one of the most frequent reactions after whole cell preparation and quite rare after acellular one.

In most instances acellular vaccine is less reactogenic and more comfortable for children and their custodians. But severe and serious reactions are very rare after either type of preparation, and even if they are more frequent after whole cell vaccines, the rates were not significant.

Comparison of adverse events in different ages following acellular anti-pertussis vaccines shows no significant differences in febrile reactions, seizures and allergic reactions, which almost evenly occur in both age groups. Though some of the reactions like HHE and high pitch cry may be seen as characteristic for younger age group. They are very rarely, or not

at all, reported among 5 year old children. Two cases of acute encephalopathy were reported in children less the two years old and none in the older age group.

Proportions rate (RR=2.32) indicates more then double frequency of local reactions in older children. It is probably not related to the direct effect of vaccine, but rather to higher mobility and increased ability of older children to irritate the site of injection.

With different criteria of use of whole cell and acellular vaccines there is a possibility of selection bias of children vaccinated with each type of preparation. Most of the children below age of 2 received acellular pertussis vaccine at parental request. It is unlikely that such decision would be made on the basis of susceptibility to AEFI. In rare cases acellular pertussis vaccine was given on doctor's recommendation based on health condition of a child or due to adverse effect following previous dose of the whole cell preparation. But such cases with strong potential for bias should not exceed the total number of adverse effects reported. So they would amount to less then 1% of the instances in which acellular pertussis replaced whole cell preparation.

Pertussis component is never given alone. Other vaccines given simultaneously may be responsible for some adverse effects following those combined vaccinations. Most of those other vaccines are given obligatorily, and even if they are responsible for some fraction of adverse effects they create common background and do not differentially influence relative rates, which are the base for comparability of whole cell and acellular pertussis vaccine (10). The exception is the vaccine against Hib infections, which, being given at parental request, may be more frequently associated with acellular than with whole cell pertussis vaccines. Low reported rate of adverse effects following Hib vaccination and low vaccination coverage by this vaccine allow us to estimate that it would cause rather minor, differential increase of the numbers of adverse effects on the side of acellular vaccines, without significant distortion of presented data.

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PORÓWNANIE NIEPOŻĄDANYCH ODCZYNÓW POSZCZEPIENNYCH PO SZCZEPIONKACH PRZECIW KRZTUŚCOWI ZAWIERAJĄCYCH KOMPONENT PEŁNOKOMÓRKOWY I ACELULARNY

STRESZCZENIE

Artykuł zawiera wyniki porównawczego badania częstości występowania niepożądanych odczynów poszczepiennych (NOP) po pełnokomórkowych i bezkomórkowych szczepionkach przeciw krztuścowi. Badanie zostało oparte na danych rutynowego nadzoru nad niepożądanymi odczynami poszczepiennymi z lat 2001-2005. Dokonano porównania odczynów po podaniu preparatów zawierających komponent pełnokomórkowy oraz bezkomórkowy u dzieci poniżej 2 roku życia oraz po szczepionkach bezkomórkowych u dzieci poniżej 2 roku życia i w 5 roku życia. W przeciwieństwie do wcześniejszych badań , porównania te dokonane zostały w trym samym okresie czasu i na tej samej populacji. Porównywano odczyny poszczepienne w kategoriach, w jakich są one klasyfikowane w rutynowym nadzorze. W większości kategorii NOP częstość ich występowania po szczepionkach pełnokomórkowych jest ponad dwukrotnie wyższa niż po szczepionkach acelularnych. Największa wartość stosunku częstości NOP została odnotowana w przypadku nieutulonego płaczu (RR=4,75). Porównanie częstości NOP po szczepionkach bezkomórkowych u dzieci poniżej 2 roku życia i w wieku 5 lat nie wykazało różnic w większości kategorii z wyjątkiem wysokiej gorączki, nieutulonego płaczu i

epizodu hipotensyjno- hiporeaktywnego z bezdechem, który występował tylko u dzieci poniżej 2 roku życia, a nie był odnotowywany u dzieci w wieku 5 lat. Odczyny miejscowe były znamiennie częstsze u dzieci w wieku 5 lat, co może wiązać się z większą aktywnością ruchową tych dzieci i możliwością manipulacji w miejscu szczepienia.

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Otrzymano: 9.05.2008 r.

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