Increase in the number of reports of AEFIs after administration of Infanrix-IPV at 4-years of age in 2015 –possible relation with the primary vaccine given at infant age

Introduction

In the multi-annual summary 2011-2017 of the number of reports after administration of Infanrix-IPV at 4 years of age, an increase in the number of reports since 2015 can be seen [1]. Up to 1 August 2011, Pediacel® was used for the primary series in the National Immunisation Program (RVP). This vaccine was then replaced by Infanrix hexa® and used from 1 August 2011 until now. The question is whether the increase in the number of reports after administration of Infanrix-IPV® booster vaccine at 4 years of age can be related to differences in the primary series at infant age.

Reports, Reporting Rate and the Rate Ratio

In the Lareb database, spontaneous reports were selected after the administration of Infanrix-IPV® around the fourth year of life, which were received in the period from 1 January 2011 to 31 December 2017. The children concerned had to be vaccinated during the same period. Information about the brand name of the administered vaccine, batch number, vaccination date, date of birth, age, gender and the reported AEFIs were collected from these reports.
The AEFIs were classified as Extensive Limb Swelling (ELS), injection site inflammation, fever and other AEFIs. ELS is defined by Lareb as an extensive local reaction of the injection site with redness, swelling and/ or induration, reaching over the adjacent joint and / or circular around the arm. Injection site inflammation is defined by Lareb as a reaction containing at least 2 symptoms of redness, heat, pain and swelling at the injection site Fever is defined when an increase in body temperature (37.5-38 degrees Celsius), fever (body temperature not measured), pyrexia (38-<40.5 degrees Celsius), hyperpyrexia (40.5-≤42 degrees Celsius) or hyperthermia (>42 degrees Celsius) is coded in the report. Other AEFI is defined if the reported AEFI does not meet the criteria of ELS, injection site inflammation or fever.

In the Netherlands, all vaccinations, administered within the framework of the RVP, are recorded at child level in 'Praeventis', the central register of the Dutch National Institute for Public Health and the Environment (RIVM). When parents give their permission, the batch number is routinely requested from the RIVM when assessing spontaneous reports and the batch number is added to the report. For this analysis, a total overview of the number of children who received an Infanrix IPV around 4 years of age between 1 January 2011 and 31 December 2017, broken down by date of birth before and after 1-8-2011, was requested from RIVM. It was assumed that children born before 1-8-2011 were vaccinated with Pediacel® at infancy and after 1-8-2011 with infanrix hexa®, in accordance with the RVP schedule. Table 1 gives an overview of the number of vaccines administered. The RIVM information is used for calculating the reporting rate per 10,000 vaccinated persons and the Rate Ratio (RR).

Table 1. Overview of the number of children vaccinated with Infanrix-IPV at 4 years of age between 1 January 2011 and 31 December 2017 based on data from Praeventis of the RIVM, broken down to administered primary infant vaccine (Pediacel® - Infanrix hexa)*)* (Praeventis 4 April 2018)

Vaccination year	Pediacel®	Infanrix hexa®	Total***
2011	172,983	0	172,983
2012	172,618	0	172,618
2013	171,418	0	171,418
2014	170,623	0	170,623
2015	79,701	86,087	165,788
2016	0	158,231	158,231
2017**	0	39,473	39,473
Total	767,343	283,791	1,051,134

* It was assumed that everyone who received a booster at 4 years of age received the primary infant series. This assumption gives a small overestimation of the totals, because some children have settled in the Netherlands at a later age and have followed an alternative scheme.

** In 2017 Infanrix-IPV was replaced by Boostrix Polio
*** Due to stricter definition criteria used by the National Institute for Public Health and the Environment (RIVM) in calculating vaccination coverage, the number of vaccinated persons may differ slightly from the numbers published in the RIVM overviews.

Table 2 gives an overview of all reports, and a breakdown per category: ELS, injection site inflammation, fever and other AEFIs. The vast majority concerns reports of injection site inflammation (n = 1260) and reports of ELS (n = 715), whether or not in combination with fever. The number of reports of fever without injection site inflammation / ELS (n = 230) and other AEFIs (n = 285) is limited.

In the period from 2011-2015 all children were vaccinated at infant age with Pediacel® and at the age of 4 years with infanrix IPV® (Pediacel®-cohort) The reporting rate of the total number of reports after administration of infanrix IPV® in the Pediacel®-cohort varies from 15.1 per 10,000 vaccinated children to 23.6 per 10,000 vaccinees. In the period 2016-2017 all children were vaccinated at infant age with Infanrix hexa® and at the age of 4 years with infanrix IPV® (Infanrix hexa®-cohort The reporting rate of the total number of reports after administration of infanrix IPV® in the Infanrix hexa®-cohort varies from 35.9 per 10,000 vaccinated children to 49.7 per 10,000 vaccinees. In particular, the number of reports of injection site inflammation after infanrix IPV® in the Infanrix hexa cohort is greater compared with vaccination with Pediacel® cohort. This also applies to reports of fever and to a lesser extent to ELS and other AEFIs.

Table 2. Overview of the number of spontaneous reports after administration of Infanrix-IPV® around age 4, broken down by type of AEFI and an overview of the number of administered vaccines broken down by type of vaccine administered during the primary series at infant age. The numbers between () is the reporting rate per 10,000 administered vaccines.*

booster vaccine Infanrix-IPV	2011	2012	2013	2014		2015	2016	2017	
priming vaccine infant age	PEDIACEL®	PEDIACEL®	PEDIACEL®	PEDIACEL®	PEDIACEL®	Infanrix hexa®	Infanrix hexa®	Infanrix hexa®	total
Administered vaccines	172983	172618	171418	170623	79701	86087	158231	39473	
Total N reports	290 (16.8)	407 (23.6)	334 (19.5)	268 (15.7)	120 (15.1)	309 (35.9)	565 (35.7)	196 (49.7)	2490
Total N reports ELS	101 (5.8)	152 (8.8)	98 (5.7)	73 (4.3)	36 (4.5)	71 (8.2)	142 (9.0)	42 (10.6)	715
ELS with fever	25	36	27	18	10	29	52	20	217
EIS without fever	76	116	71	55	26	42	90	22	498
Total N reports Inj. S. inflammation	110 (6.4)	165 (9.6)	168 (9.8)	112 (6.6)	58 (7.3)	195 (22.7)	329 (20,8)	122 (30.9)	1260
Inj. S. Inflammation with fever	27	26	40	28	14	55	110	24	324
Inj. S. Inflammation without fever	83	139	128	84	44	140	219	98	936
Total N reports fever	77 (4.5)	100 (5.8)	103 (6.0)	88 (5.2)	38 (4.8)	99 (11.5)	209 (13,2)	57 (14.4)	771
ELS with fever	25	36	27	18	10	29	52	20	217
Inj. S. Inflammation with fever	27	26	40	28	14	55	110	24	324
fever without ELS and Inj. S. Inflammation	25	38	36	42	14	15	47	13	230
Other AEFIs	54 (3.1)	52 (3.0)	32 (1.9)	41 (2.4)	12 (1.5)	28 (3.3)	47 (3,0)	19 (4.8)	285

* From spring 2017, Infanrix-IPV® has been replaced by Boostrix Polio®. In this overview children who have been vaccinated with Boostrix Polio and the spontaneous reports relating to Boostrix Polio® are not taken into account.

Rate ratios

To investigate whether possible differences in the number of reports of ADRs following Infanrix-IPV® are associated with applied primary vaccines on infant age, Rate Ratios were calculated and the corresponding 95% confidence interval (CI) for all reports and for ELS, injection site inflammation, fever and other AEFI (Table 3 and *Addendum 1* for methodology).
Based on our data; Children who had a primary series with Infanrix hexa® on infant age seem more likely to report AEFIs after administration of Infanrix-IPV® booster vaccine than children who had a primary series with Pediacel®. This applies to both the total number of reports and reports of ELS, injection site inflammation, fever and other AEFIs.

Table 3. Rate Ratios (95% CI) for primary series with Infanrix hexa® vs primary series with Pediacel® for all reports and for ELS, injection site inflammation, fever and other AEFI

ATC5/7	Preferred term	Rate Ratios [CI]	A	B	C	D
	Total N reports	2.0 (1.89-2.21)	1070	282721	1420	**765923**
	ELS	1.5 (1,29-1.75)	255	283536	460	**766883**
	Inj. S inflammation	2.8 (2.55-3.18)	646	283145	614	**766729**
	Fever	3.0 (2.61-3.47)	406	283385	365	**766978**
	Other AEFIs	5.5 (4.29-7.04)	191	283600	94	767249

A= N children vaccinated with Infanrix IPV and primed with Infanrix hexa® with AEFI
B= N children vaccinated with Infanrix IPV and primed with Infanrix hexa® without AEFI
C= N children vaccinated with Infanrix IPV and primed with Pediacel® with AEFI
B= N children vaccinated with Infanrix IPV and primed with Pediacel® without AEFI

Other sources of information

SmPC

Pediacel® and Infanrix hexa® given in the primary series at infant age do not differ in the type of Pertussis component (*see Addendum 2*) [2,3]. Both vaccines are acellular Pertussis vaccines. Infanrix hexa® contains fewer Pertussis antigens compared to Pediacel® (Fimbriae type 2 and 3 are missing in Infanrix hexa®), but instead contains slightly more Pertussis toxoid, Filamentous Hemagglutinin and Pertactin. The biggest difference between the two vaccines is the addition of an extra vaccine component in Infanrix hexa®, the Hepatitis B surface antigen. Furthermore, Infanrix hexa® contains slightly more conjugated tetanus toxoid in the Haemophilus influenzae component and both vaccines differ in the adjuvant. In Pediacel® only $AlPO_4$ is used, total aluminum 0.33 mg. In Infanrix hexa® a combination of $AlPO_4$ and $Al(OH)_3$, total Al^{3+} 0.82 mg is used.

Literature and mechanism

The fact that the primary vaccination series can influence the number of local and systemic AEFIs after booster vaccine administration has been previously described [4,5]. Research showed that the number of pronounced local AEFIs and systemic AEFIs is significantly higher after administration of an aP (acellular Pertussis) booster vaccine in children with a primary infant formula with an aP containing vaccine compared to children with a primary series with a wP (whole cell Pertussis) containing vaccine [4,5]. Furthermore, it has been shown that children with a primary series with an aP-containing vaccine have higher numbers of T-helper 2 (Th2) cells than children with a primary series with a wP-containing vaccine, suggestive of Th2 skewing [5]. In addition to pertussis specific T-cell differences, higher pertussis specific IgG, IgG4 and IgE antibodies were also demonstrated in children with a primary series containing aP-containing vaccine compared to children with a primary series with a wP-containing vaccine [5-7]. Existing high tetanus specific Th2 cytokines are associated with an increased risk of local AEFIs and in children with AEFIs pertussis specific IgE antibodies before and after DaPT booster vaccines are higher compared to children without AEFIs [8].

Furthermore, previous research showed that despite decreasing IgG antibody levels in children 4 years of age, three years after primary vaccination, higher T-cell responses were measurable in children with a primary series containing an aP-containing vaccine compared to children with a primary series of a wP-containing vaccine, in which children with a primary aP series had more Th2 cells and in a wP series more Th1 cells [9].

A shift of a Th1 response towards a Th2 and Th17 response and the associated cytokines was seen in the aP primed group after administration of an aP booster vaccine at the age of 4 [4]. It is possible that this shift contributes to the increase in the number of injection site reactions after administration of aP containing booster vaccines at 4 years of age. Studies further showed that aP-containing vaccines in the primary series lead to higher concentrations of Pertussis specific IgE and a higher incidence of ELS after administration of an aP-containing booster vaccine. Since ELS does not respond to antihistamines and only appears after 1 to 2 days, this could indicate a delayed-type hypersensitivity reaction caused by T cells and macrophages [4,10,11].

Since aP-containing vaccines not only contain purified proteins, but also adjuvant that stimulates the immune system to a Th2 response, both the nature of the vaccine, the adjuvant and the vaccine intervals should be involved in the evaluation of the efficacy and safety of aP-containing vaccines. Not only the height of the antibody response should be considered, but also the cellular response [6].

The chance of developing a local reaction after administration of a DTaP vaccine increases with each subsequent vaccination. In a study by Rennels et al.[12] there was a significant linear association between the rates of entire thigh swelling after dose 4 and diphtheria toxoid content in the DTaP products. Lesser degrees of swelling (>50 mm but less than entire limb) correlated with pertussis toxoid content after dose 4 and aluminum content after dose 5. No relationship was established between levels of serum antibody to diphtheria, tetanus, or pertussis toxin and rates of swelling of the whole thigh [12].

Discussion and conclusion

In the multi-year summary of spontaneous reports of AEFIs after administration of Infanrix-IPV® at 4 years of age, there has been an increase in the number of reports per 10,000 vaccinees since 2015. This increase mainly concerns an increase in the number of reports of injection site inflammation and fever and to a lesser extent ELS and other reports. Based on our data, this increase may appear to be related to differences in the administered vaccine during the primary infant infancy series. Infants who are vaccinated with infanrix hexa® at infancy are more likely to report AEFI after administration of Infanrix-IPV® at 4 years of age than infants who were primary vaccinated with Pediacel®.
In the investigated period there was also a change in needles used. On 1 January 2015 a compensation was also made available to switch to another type of needles in the RVP due to ARBO-technical reasons. The implementation took place gradually in 2015/2016. Due to the decentralized implementation, the needle thickness could vary between organizations. To check whether the implementation of the different needles contributed to the reporting rate differences between the period 2011-2015 and the period after 1 January 2015, information is required about the time of transition to the safe needles and the needle selection per organization. This information is missing in the Lareb database and is also not available at the RIVM. Since the implementation of the change in needles concerns all vaccination moments of the NIP and the increase in the number of reports is limited to the number of reports after administration of the booster vaccination at 4 years of age, it is less likely that the observed increase is related to the change in needles, but a possible effect cannot be completely excluded.
In conclusion, further research could be aimed at the possible relationship between the primary vaccination series at infant age and AEFIs after DaPT-IPV booster vaccination at 4 years of age, where the research must focus on all vaccine components.

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Addendum 1.

Berekening Reporting Rate (RR) voor de overgang van Infanrix hexa naar Boostrix Polio over de periode 2016 en 2017

	Melding bijwerking	**geen melding**	**totaal**
Infanrix hexa	1070	282721	283791
Pediacel	1420	765923	767343
totaal	2490	1048644	
RR	2,0		
95% CI	1,89-2,21		
	ELS	**geen ELS**	**totaal**
Infanrix hexa	255	283536	283791
Pediacel	460	766883	767343
	715	1050419	
RR	1,5		
95% CI	1,29-1,75		
	Injectieplaats ontsteking	**geen Injectieplaats ontsteking**	**totaal**
Infanrix hexa	646	283145	283791
Pediacel	614	766729	767343
	1260	1049874	
RR	2,8		
95% CI	2,55-3,18		
	koorts	**geen koorts**	**totaal**
Infanrix hexa	406	283385	283791
Pediacel	365	766978	767343
	771	1050363	
RR	3,0		
95% CI	2,61-3,47		
	overige bijwerking	**geen overige bijwerking**	**totaal**
Infanrix hexa	191	283600	283791
Pediacel	94	767249	767343
	285	1050849	
RR	5,5		
95% CI	4,29-7,04		

Addendum 2 Comparison of the two primary vaccines used for infants in the RVP since 2005

	Pediacel®	**Infanrix hexa®**
antigeen		
Difterie	Difterietoxoïd niet minder dan 30 IE	Difterietoxoïd niet minder dan 30 IE
Tetanus	Tetanustoxoïd niet minder dan 40 IE)	Tetanustoxoïd niet minder dan 40 IE)
Pertussis	Bordetella pertussis antigenen	Acellulair pertussis antigenen
	Pertussistoxoïd 25 microgram	Pertussistoxoïd 20 microgram
	Filamenteus hemagglutinine 25 microgram	Filamenteus hemagglutinine 20 microgram
	Pertactine 8 microgram	Pertactine 3 microgram
	Fimbriale agglutinogenen 2 en 3 5 microgram	
Hepatitis B		Hepatitis-B-oppervlakte antigeen 10 microgram (geproduceerd in gistcellen Sacharomyces cerevisiae)
Polio	Poliovirus (geïnactiveerd) (geproduceerd in verocellen) Type 1 40 D-antigeeneenheden	Poliovirus (geïnactiveerd) (geproduceerd in verocellen) Type 1 40 D-antigeeneenheden
	Type 2 8 D-antigeeneenheden	Type 2 8 D-antigeeneenheden
	Type 3 32 D-antigeeneenheden	Type 3 32 D-antigeeneenheden
Heamophilus influenzae	Haemophilus influenzae type b polysacharide (polyribosylribitol fosfaat) 10 microgram geconjugeerd aan tetanustoxoïd (PRP-T) 20 microgram	Haemophilus influenzae type b polysacharide (polyribosylribitol fosfaat) 10 microgram geconjugeerd tetanusyoxoïd ongeveer 25 microgram
adjuvans	Aluminiumfosfaat 1,5 mg (0,33 mg als aluminium)	Gehydrateerd aluminiumhydroxide (Al(OH)3) 0,5 milligram Al3+ aluminiumfosfaat (AlPO4) 0,32 miligram Al3+
emulgator	Polysorbaat 80	
conserververmiddelen	Fenoxyethanol	formaldehyde
reststop		NaCL
		Medium 199 (aminozuren, mineraalzouten en vitamines)
		streptomycine
		neomycine
		polymyine B
stopper	broombutyl	butyl

This signal has been raised on December 20, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl