Extensive swelling of the vaccinated limb (ELS) and administration of the DaPT-IPV vaccine at 4 years of age (switch from Infanrix-IPV® to Boostrix polio®) - update

Introduction

In the course of 2017, in the National Vaccination Program (RVP) Infanrix-IPV®, the DaPT-IPV (Diphtheria, Acellular Pertussis, Tetanus and Polio) booster vaccine at the age of 4 years was replaced by Boostrix-Polio® [1]. After replacing of the vaccine, the reporting rate of the total number of spontaneous reports dropped from 49.7 to 14.7 per 10,000 vaccinated children. In particular, the reporting rate of extensive swelling of the vaccinated limb (ELS) dropped from 10.6 to 1.0 per 10,000 vaccinees, but also the reporting rate of injection site inflammation, fever and other AEFIs decreased [2].
This decrease may be related to the differences in the composition of the vaccines. The vaccines differ in the amount of diphtheria, tetanus and pertussis antigens. Infanrix IPV® contained15 times more diphtheria toxoid, 3 to 10 times more pertussis antigens and 2 times more tetanus toxoid compared to Boostrix Polio®. The vaccines differ also in type of adjuvant. Infanrix-IPV® contains exclusively aluminium hydroxide and Boostrix Polio® a combination of aluminium phosphate and aluminium hydroxide [3-4].

Because the published signal from 2018 was based on a follow-up duration of up to 8 months after replacing Infanrix-IPV with Boostrix Polio, the Netherlands Pharmacovigilance Centre Lareb repeated the study with a longer follow-up duration, on request of the Medicine Evaluation Board (CBG-MEB) (date discussion 20-12-2018).

Reports, Reporting Rate and the Rate Ratio

In the Lareb database, spontaneous reports were selected after the administration of DaPT-IPV booster vaccine around the fourth year of life (3 to 5 years), which were received in the period from 1 January 2016 to 31 July 2019. The children concerned were vaccinated during this period. Since priming differences at infant age due to vaccine differences can influence the number of reports and type of reports after the 2nd booster vaccination at the age of 4, reports from before 2016 were excluded to prevent possible disruptions due to priming [5]. Four-year-old children vaccinated before 2016, have been vaccinated at infant age with Pediacel and after 2016 with Infanrix hexa. All reports in this overview relate to children who have been vaccinated with Infanrix hexa® at the infant age of 2, 3, 4 and 11 months.
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 reaction, 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 until over the adjacent joint and / or circular around the vaccinated arm. Injection site reaction is defined by Lareb as any other AEFI at the injection site other than ELS. 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) has been reported. Other AEFI is defined if the reported AEFI does not meet the criteria of ELS, injection site reaction 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, the RIVM was requested for an overview of all DaPT-IPV vaccines administered around 4 years of age between 1 January 2016 and 31 July 2019, broken down by type of vaccine, brand name and batch number. Table 1 gives an overview of the number of

vaccines administered. The RIVM information was used to calculate the reporting rate per 10,000 vaccinated persons and the Rate Ratio (RR).

Table 1. Overview of the number of booster DaPT-IPV vaccines, administered to children around 4 year of age between 1 January 2016 and 31 July 2019 based on data from 'Praeventis' (Praeventis)

Vaccination year	Infanrix IPV®	Boostrix Polio®	DaPT-IPV unknown / other*	Total**
2016	160,774	12	1,769	162,555
2017	40,193	118,849	1,314	160,356
2018		161,819	1,443	163,262
2019		95,374	384	95,758
Total	200,967	376,054	4,910	581,931

*For instance Infanrix hexa® without HIB-component

** 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.

Between 1 January 2011 and 31 July 2019, Lareb received 1448 spontaneous reports on AEFIs following the administration of a DaPT-IPV vaccine at the age of 4 years. All reports related to Infanrix-IPV® or Boostrix Polio®. Table 2 provides an overview of all reports and a breakdown per category: ELS, injection site reaction, fever and other AEFIs. The vast majority concerns reports of injection site reaction (n=960) and reports of ELS (n=246) whether or not in combination with fever. The number of reports of fever without injection site reaction / ELS (n=151) and other AEFIs (n=164) is limited.

Reporting Rate

After replacing Infanrix-IPV® with Boostrix Polio®, the reporting rate of the total number of reports dropped from 38.3 (range 35.5 – 49.5) to 18.0 (range 14.7 – 19.8) per 10,000 vaccinated children. In particular, the reporting rate of ELS dropped from 9.4 (range 9.1 – 10.7) to 1.5 (range 1.1 – 2.4) per 10,000 vaccinees. The reporting rate for injection site reaction dropped from 24.5 (range 22.0 – 34.3) to 12.4 (range 10.1 – 14.0), fever from 13.1 (range 12.9 – 14.9) to 6.7 (range 5.8 – 7.3) and other AEFIs from 3.9 (range 3.0 – 4.0) to 2.3 (range 1.4 – 2.9). See table 2.

Table 2. Overview of the number of spontaneous reports after administration of a DaPT-IPV booster vaccine at 4 years of age, broken down by type of AEFI and an overview of the number of vaccines administered according to the type of vaccine in the period from 1 January 2016 to 31 July 2019. The numbers between ( ) is the reporting rate per 10,000 administered vaccines

	2016*		2017*		2018		2019		Total	
vaccine	inf. IPV	Boostr. P	inf. IPV	Boostr. P	inf. IPV	Boostr. P	inf. IPV	Boostr. P	inf. IPV	Boostr. P
Administered vaccines	160,774	12	40,193	118,849	0	161,819	0	95,374	200,967	376,0542
Total N reports	570 (35.5)	1	199 (49.5)	175 (14.7)	1	321 (19.8)	0	181 (19.0)	770 (38.3)	678 (18.0)
Total N ELS	146 (9.1)	0	43 (10.7)	13 (1.1)	0	21 (1.3)	0	23 (2.4)	189 (9.4)	57 (1.5)
ELS with fever	*51 (3.2)*		*20 (5.0)*	*3 (0.3)*		*4 (0.2)*		*5 (0.5)*	*71 (3.5)*	*12 (0.3)*
ELS without fever	*95 (5.9)*		*23 (5.7)*	*10 (0.8)*		*17 (1.1)*		*18 (1.9)*	*118 (5.9)*	*45 (1.2)*
Total N injection site reaction**	354 (22.0)	1	138 (34.3)	120 (10.1)	1	227 (14.0)	0	119 (12.5)	493 (24.5)	467 (12.4)
Inj. S. React. with fever	*118 (7.3)*	*0*	*26 (6.5)*	*41 (3.4)*	*0*	*66 (4.1)*		*30 (3.1)*	*144 (7.2)*	*137 (3.6)*
Inj. S. React. without fever	*236 (14.7)*	*1*	*112 (27.9)*	*79 96.6)*	*1*	*161 (9.9)*		*89 (9.3)*	*349(17.4)*	*330 (8.8)*
Total N fever	207 (12.9)	0	57 (14.9)	69 (5.8)	0	118 (7.3)	0	64 (6.7)	264 (13.1)	251 (6.7)
Fever and ELS	*51 (3.2)*		*20 (5.0)*	*3 (0.3)*		*4 (0.2)*		*5 (0.5)*	*71 (3.5)*	*12 (0.3)*
Fever and Inj. S. React.	*118 (7.3)*		*26 (6.5)*	*41 (3.4)*		*66 (4.1)*		*30 (3.1)*	*144 (7.2)*	*137 (3.6)*
Fever without ELS and Inj. S. React.	*38 (2.4)*		*11 (2.7)*	*25 (2.1)*		*48 (3.0)*		*29 (3.0)*	*49 (2.4)*	*102 (2.7)*
Total N other AEFIs	64 (4.0)	2	12 (3.0)	28 (2.4)	2	47 (2.9)	0	13 (1.4)	78 (3.9)	90 (2.4)

- * The numbers in the table may differ slightly from the published signal in 2018, because the Lareb database is a living database
- ** In the published signal in 2018, injection site inflammation was shown in the table. In this signal injection site reaction.

Rate Ratios

For all reports and separately for ELS, injection site reaction, fever and other AEFIs, the Rate Ratio of Infanrix-IPV® was calculated in comparison with Boostrix Polio® and the corresponding 95% confidence interval. Table 3 provides an overview of the Rate Ratios. All Rate Ratios are significant.

Table 3. Rate ratios in the Lareb database

ATC5/7	MedDRA Preferred term	Rate Ratios [CI]	A	B	C	D
	All reports	2.12 (1.91-2.35)	770	200.967	678	376.054
	ELS	6.20 (4.61-8.34)	189	200.967	57	376.054
	Injection site reaction	1.97 (1.74-2.24)	493	200.967	467	376.054
	Fever	1.97 (1.65-2.34)	264	200.967	251	376.054
	Other AEFIs	1.62 (1.20-2.20)	78	200.967	90	376.054

A= N reported AEFI with Infanrix IPV
B= N children vaccinated with Infanrix IPV
C= N reported AEFI with Boostrix Polio
B= N children vaccinated with Boostrix Polio

Other sources of information

SmPC

The vaccines Triaxis Polio®, Infanrix-IPV® and Boostrix Polio® differ in the amount of diphtheria, tetanus and pertussis antigens [3,4,8]. Addendum 1 provides an overview of the composition of the 3 vaccines. Infanrix-IPV® in particular contains more antigens than the other two booster vaccines. The amount of diphtheria toxoid of Infanrix-IPV is 15 times higher compared to the other vaccines, the amount of tetanus toxoid is twice as high and for the pertussis component it differs a factor of 3 to 10 per component and per vaccine. In addition, the booster vaccines differ in the used adjuvants; TriaxisPolio® exclusively contains aluminium phosphate, Infanrix-IPV® exclusively aluminium hydroxide and Boostrix Polio® a combination of aluminium phosphate and aluminium hydroxide. In addition, the total amount of aluminium varies from 0.33 mg with Triaxis-Polio® to 0.5 mg with Infanrix-IPV® and Boostrix Polio®.

Literature and mechanism

In the second half of 2008, the RIVM noticed a sharp increase in the number of reports of local reactions after administration of DaPT-IPV vaccine (Infanrix-IPV®) at 4 years of age. The vast majority of these reports involved severe local reactions (diameter > 5 cm), sometimes extending over the shoulder and / or elbow [6,7]. In literature these extensive local reactions that extend to beyond the adjacent joint are also referred as ELS. This sharp increase in the number of serious local reactions / ELS corresponded in time period with the replacement of Triaxis Polio® in the RVP with Infanrix-IPV®.

On the basis of latency time and course, it is assumed that ELS is not an acute allergic reaction or infection [7]. It is generally assumed that it is a severe inflammatory reaction. On the one hand the literature assumes that the sharp increase in the number of strong local reactions /ELS is related to the switch from the administration of whole cell pertussis vaccine (wP) to an acellular pertussis vaccine (aP) at infant age. Children who have had a complete primary immunization series with aP-containing vaccines at infant age have a higher chance of developing pronounced local reactions/ELS after booster vaccination with an aP-containing vaccine at 4 years of age than children vaccinated at infant age with a full series of wP-containing vaccine or with a mixed series consisting of a wP and aP vaccine [7,9]. The underlying immunological mechanism for this is unknown. It is possible that cellular immunity plays a role in this, in which in aP primed children after administration of an aP booster vaccine at the age of 4 years there is a shift of the Th1 response in the direction of Th2 and Th17 response, and the associated cytokines [10,11,12].

In addition to pertussis specific T-cell differences, higher concentrations of 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 wP-containing vaccine [13]. Existing high tetanus specific Th2 cytokine concentrations are associated with an increased risk of local AEFIs [13]. In children with AEFIs after administration of a DaPT-IPV vaccine, the concentrations of pertussis specific IgE antibodies before and after administration of the booster vaccine were increased compared to children without AEFis [12]. Some studies show that aP primed children also have higher concentrations of pertussis specific IgE after administration of an aP containing booster at 4 years of age and ELS. Since ELS does not respond to antihistamines and this reaction appears only after 1 to 2 days, this could indicate a delayed-type hypersensitivity reaction caused by T cells and macrophages [12,14,15]. Another theory is that pronounced local reactions / ELS after booster vaccination at 4 years of age are related to the level of the diphtheria component in the booster vaccine [16,17].

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.[15] 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 aluminium 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 [16].

Knuf et al. [16] found during a comparison study of 9 candidate DTaP vaccines that the number of local reactions by DTaP booster vaccines in the second year of life can be reduced by reducing the amount of antigens without affecting immunogenicity. Every change in the composition of the vaccine must, according to the authors, be followed by a complete evaluation of the new product [18]. Lareb previously published an overview of reports of extensive swelling of the vaccinated limb after DT-IPV NVI® vaccine in 2014. Lareb concluded that in the evaluation of the causes of ELS the child's vaccination history, the role of the carrier protein, the adjuvant, and other vaccine components must be involved [19].

Discussion and conclusion

In the second half of 2008, the RIVM noticed an unexpected increase in the number of reports of strong local reactions / ELS after administration of DaPT-IPV booster vaccine at 4 years of age [6,7]. Since the transfer of the task of monitoring AEFIs to Lareb in 2011, Lareb notes that a relatively large number of reports of AEFIs are reported after administration of Infanrix-IPV® at the age of 4 compared to the other vaccination moments of the National Immunisation Programm. The majority of these reports concern reports of injection site reaction and ELS. After the switch from Infanrix-IPV® to Boostrix Polio® in 2017, Lareb notes a sharp decrease in the number of reports. The reporting rate per 10,000 vaccinated children decreased from 38.3 to 18.0. The decrease is most pronounced in the category ELS-reports, where the reporting rate per 10,000 vaccinated children decreased from 9.4 to 1.5, but there is also a decrease in reporting rate in the categories of injection site reaction, fever and other AEFIs.

The exact cause for the increase in the number of strong local reactions / ELS after administration of DaPT-IPV booster vaccine at 4 years of age in 2008 has never been elucidated. One theory is that the increase in local reactions / ELS is related to the transition of wP vaccines to aP vaccines at infant age [7,9]. This theory is not supported by our finding of the decrease in the number of reports of local reactions/ELS in 2017, since all children were vaccinated with the same DaPT-IPV-Hib-HepB vaccine at infant age, but differ in the administered second booster DaPT-IPV vaccine at the age of 4 years.

In retrospect, the observed increase in local response / ELS in 2008 may also be related to the replacement of Triaxis Polio® with Infanrix-IPV® in RVP in 2008, in addition to the previously described effect of priming differences on infant age (replacement of wP vaccine by aP vaccine at infant age [20].The increase in reports on AEFIs in 2008 after the switch from Triaxis Polio® to Infanrix IPV® and the decrease in 2017 after replacement of Infanrix IPV® by Boostrix Polio® probably related to differences in composition of the 3 vaccines [3,4,8].

Vaccine comparison shows that the amount of diphtheria toxoid in Infanrix-IPV® is 15 times higher compared to Boostrix Polio® and Triaxis Polio®, for tetanus toxoid this is twice as high and for the pertussis components it is a factor of 3 to 10 higher depending on the pertussis component. This finding is in line with suggestions from the literature that the level of the antigen component of the booster vaccine contributes to the emergence of strong local reactions and ELS.

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This signal has been raised on March 11, 2020. 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

11/03/2020

Addendum 1 Comparison of the 3 DaPT vaccines used

	Triaxis-Polio®	**Infanrix-IPV®**	**Boostrix-Polio®**
antigen	Diphtheria toxoïd not less than 2 IE* (2Lf)	Diphtheria toxoïd not less than 30 IE	Diphtheria toxoid not less than 2 IE (2,5 Lf)
	Tetanus toxoïd not less than 20 IE* (5 Lf)	Tetanus toxoïd not less than 40 IE	Teatnus toxoid not less than 20 IE (5 Lf)
	Pertussis antigens	Pertussis antigens	Bordetella pertussis antigens
	Pertussis toxoid 2.5 micrograms	Pertussis toxoid 25 micrograms	Pertussis toxoid 8 micrograms
	Filamentous hemagglutinin 5 micrograms	Filamentous hemagglutinin 25 micrograms	Filamentous hemagglutinin 8 micrograms
	Pertactin 3 microgram	Pertactin 8 microgram	Pertactin 2.5 microgram
	Fimbrial agglutinogen 2 and 3 micrograms		
	Inactivated polio vaccine**	Inactivated polio vaccine**	Inactivated polio vaccine**
	Type 1 40 D antigen units	Type 1 (Mahoneystam) 40 D antigen units	Type 1 (Mahoneystam) 40 D antigen units
	Type 2 8 D antigen units	Type 2 (MEF-1 stam) 8 D antigen units	Type 2 (MEF-1 stam) 8 D antigen units
	Type 3 32 D antigen units	Type 3 (Sauketstam) 32 D antigen units	Type 3 (Sauketstam) 32 D antigen units
adjuvant	Aluminum phosphate 1.5 mg	Aluminum hydroxide (Al (OH) 3)	adsorbed on hydrolyzed aluminum hydroxide and aluminum phosphate
	(0.33 mg as aluminum)	total Al^{3+} 0.5 milligram	total Al^{3+} 0.5 milligram
emulsifier	Polysorbate 80		
Preservatives and residues	Phenoxyethanol		
	Formaldehyde	sodium chloride	sodium chloride
	Glutaraldehyde	Medium 199 (amino acids, mineral salts, vitamins)	Medium 199 (as a stabilizer with amino acids, mineral salts, vitamins and other ingredients)
	streptomycin neomycin polymyxin B bovine serum albumin		Water for injection
stopper	latex free		